

Small organic molecule in enantioselective, direct aldol reaction “in water”†

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A small organic molecule, Pro-NH₂, catalyzing the enantioselective aldol reaction “in water” not merely “in the presence of water” with good enantioselectivity has been discovered for the first time.

Reactions using water as a reaction medium are attracting a great deal of attention,¹ because water possesses unique properties, including the ability to accelerate some organic reactions.² Most of organic reactions using water as a solvent are carried out “in the presence of water”, and the organic reagents and catalyst, when one is used, are not actually dissolved in water, the reaction proceeding in the organic phase. In particular, for the asymmetric catalytic aldol reaction, which is a key carbon-carbon bond forming reaction, creating β -hydroxy carbonyl compounds found in many natural products and drugs,³ there is a controversy whether they are really in “all wet”.^{4,5} As far as we are aware there is no example for which the reaction proceeds with high enantioselectivity “in water”, with all the reagents dissolved homogeneously in water and the reaction proceeding in the aqueous phase, catalyzed a small organic molecule. Thus, it has been a great challenge to develop a small organic molecule, promoting aldol reaction “in water” with suitable asymmetric induction.^{4,5} Here we report such a small molecule for the first time. We found that proline-amide, which may have been present on the early Earth, promotes the aldol reaction “in water”, generating the aldol product with good enantioselectivity.

Over the past few years there have been a number of reports on the asymmetric aldol reaction, a key process in organic synthesis, in water. Metal-based Lewis acids have been reported to catalyze the asymmetric Mukaiyama-type aldol reaction “in the presence of water” in combination with an organic solvent,⁶ while Zn-proline promotes the aldol reaction in aqueous media with moderate enantioselectivity (up to 56% ee).⁷ Organocatalysts have been reported to promote the enantioselective, direct aldol reaction in organic solvents,⁸ reactions which in some cases proceed with water present,⁹ though the organic solvent is still required. The first aldol reactions to use only water as solvent were reported independently by Barbas' and our groups. Barbas *et al.* used a diamine with a long alkyl chain and an acid as a co-catalyst, the reaction proceeding in an emulsion.¹⁰ Our group has developed a highly lipophilic siloxyproline catalyst,¹¹ and a combined

proline-surfactant organocatalyst,¹² both of which promote the asymmetric, direct aldol reaction with excellent enantioselectivity. Though our reactions are efficient “in the presence of a large amount of water”,^{12,13} they proceed in the organic phase. Recently we have reported the proline-mediated wet reaction.¹⁴ However further searches for a small organic molecule, capable of promoting the aldol reaction “in water” with high enantioselectivity, have led us to proline amide, the first such molecule.

The self-aldol reaction of propanal was selected as the model because it is a simple but fundamental aldol reaction important for the biosynthesis of carbohydrates and terpenes, and because propanal itself dissolves in water. The catalyst search was performed in the presence of six equivalents of water, using nineteen amino acids, of which Ala and Glu are non-racemic amino acids characterized from the Murchison meteorite.¹⁵ The reaction hardly proceeded at all in the presence of a catalytic amount of most of these amino acids. The exceptions were Met, Lys, and Arg which after 24 h afforded the products with low enantioselectivity (<20% ee). Some dipeptides promoted the reaction “in water”. Ala-Ala, which was reported to promote the aldol reaction of ketones and aldehydes in H₂O-EtOH (1 : 1) in an enantioselective manner,¹⁶ afforded the products with low enantioselectivity. Good enantioselectivity was obtained for the *anti*-isomer when Pro-Val was employed, while low ee was obtained for the *syn*-isomer. On the other hand, amino amides other than Glu-NH₂ were found to promote the reaction in reasonable yield. In the cases of Tyr-NH₂, Phe-NH₂ and Trp-NH₂, moderate enantioselectivity was obtained. Notable results were obtained when Pro-NH₂ was utilized: a moderate yield was obtained in short time (3 h) with good enantioselectivities (*syn*: 74% ee, *anti*: 78% ee), in which the reaction mixture became cloudy within 30 min.

Though a suitable catalyst was discovered, monitoring of the progress of the reaction was difficult because the reaction mixture became cloudy in a short reaction time. Moreover it is difficult to distinguish the reaction in water and that in the organic phase once the reaction mixture becomes cloudy. Thus, a detailed investigation was performed under more dilute conditions (2 mol L⁻¹), in which homogeneous reaction continues for a longer reaction time.‡ It was observed that propanal and Pro-NH₂ dissolved in water, generating a clear, homogeneous solution without forming a biphasic or an emulsion at the beginning. After stirring the aqueous propanal solution (2 mol L⁻¹) with a catalytic amount of Pro-NH₂ for 2.5 h at room temperature (Fig. 1), the aldol product was obtained in 40% yield with good enantioselectivity (Table 1, entry 20). From this time, formation of small, oily particles started, making the reaction mixture cloudy. This oily phase consisted of

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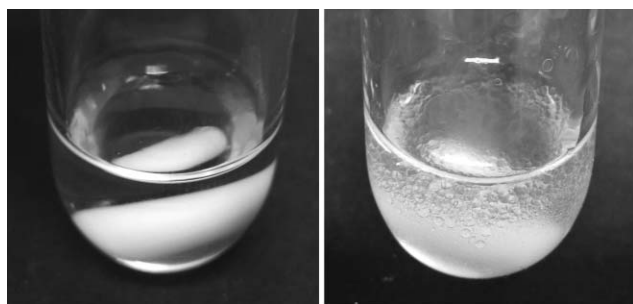


Fig. 1 Reaction mixture of the aldol reaction of propanal catalyzed by Pro-NH₂ after stirring for 2.5 h (left) and 24 h (right) at room temperature.

2-methylpent-2-enal, the dehydrated aldol adduct. After stirring for 24 h (Fig. 1), the aldol product was isolated in 29 and 9% yield from the water and the oily phase respectively, with lower enantioselectivity, while 2-methylpent-2-enal was isolated in 13 and 43% yield from the water phase and the oily phase, respectively (Table 1, entry 21). The reason why the yields of the aldol product at 2.5 h and 24 h are nearly the same is owing to this dehydration side reaction. The fact that enantioselectivities of the aldols at 24 h are low compared with those at 2.5 h indicates that racemization

Table 1 Effect of amino acid, amino amide, or dipeptide as catalyst of the self-aldol reaction of propanal in water^a

Entry	Catalyst	Time/h	Yield ^b (%)	Reaction		
				syn : anti ^c	ee 1 ^d (%)	ee 2 ^d (%)
1	L-Ala	24	<3	ND	ND	ND
2	L-Pro	24	<3	ND	ND	ND
3	L-Met	24	7	1.2 : 1	-14	-18
4	L-Lys	24	11	1 : 1	4	-10
5	L-Arg	24	15	1 : 1.8	-14	-8
6	L-Asn	24	<3	ND	ND	ND
7	L-Glu	24	<3	ND	ND	ND
8	L-Ala-L-Ala	24	15	1 : 1	3	18
9	L-Pro-L-Ala	24	<3	ND	ND	ND
10	L-Pro-L-Val	24	11	1 : 1	62	48
11	L-Ala-NH ₂	24	18	1.2 : 1	11	28
12	L-Phe-NH ₂	24	32	1.1 : 1	12	-56
13	L-Tyr-NH ₂	24	41	1.1 : 1	-13	-53
14	L-Glu-NH ₂	24	<3	ND	ND	ND
15	L-Trp-NH ₂	24	21	1 : 1	14	-52
16	L-Thr-NH ₂	24	32	1.5 : 1	9	13
17	L-His-NH ₂	24	29	1.1 : 1	8	-35
18	L-Val-NH ₂	24	21	1.7 : 1	46	-34
19	L-Pro-NH ₂	3	41	1.1 : 1	74	78
20 ^e	L-Pro-NH ₂	2.5	40	1.1 : 1	74	78
21 ^e	L-Pro-NH ₂	24	38 ^f	1.1 : 1	45	36

^a The reaction was conducted with 0.15 mmol of catalyst, 3.0 mmol of propanal, and 0.33 mL of water at room temperature, otherwise noted. ND indicates not determined. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC after conversion to the benzoyl ester. ^e The reaction was performed using 1.5 mL of water (2 mol L⁻¹), and see text. ^f 2-Methylpent-2-enal was generated in 56% yield, see text.

or kinetic resolution in the dehydration reaction proceeded. For the first 2.5 h, propanal is completely dissolved in D₂O, and was found by ¹³C NMR to exist together with its hydrated form in a ca. 1 : 1 ratio throughout the course of the reaction. The aldol product, however, is not hydrated. Therefore during this time all the reagents are dissolved in water homogeneously with the formation of only a small amount of hydrophobic 2-methylpent-2-enal. Thus, the aldol reaction of propanal proceeds “in water” and not “in the organic phase” at least for the first 2.5 h. This is the first such asymmetric aldol reaction, proceeding “in water” with good enantioselectivity.

Pro-NH₂ in water and Pro in DMF^{8c} afforded the aldol products with the same absolute configuration, indicating that an amide proton of Pro-NH₂ likely activates the carbonyl group in the same way as does the carboxylic acid proton of Pro. As the asymmetric aldol reaction due to Pro is thought to proceed *via* an enamine mechanism, the present Pro-NH₂ mediated reaction likely proceeds *via* the same manner.

Next the effect of concentration was examined (Table 2). The reaction scarcely proceeds when performed under neat conditions, indicating that the presence of water is essential. On the other hand, the yield was decreased when an excess amount of water (100 equiv.) was employed, because the reagents were diluted. This is also evidence that the reaction proceeds in the aqueous phase. A moderate yield was obtained in the presence of 50 equiv. of water. Good enantioselectivity was obtained regardless of the concentration. This is a marked contrast to the proline-mediated aldol reaction, in which the addition of water severely compromises the enantioselectivity.^{8b} It was suspected that the addition of an amine to an aqueous mixture leads to raising of pH, promoting the non-enantioselective aldol reaction by the general base mechanism, with the results of decreased enantioselectivity.⁴ The fact that the enantioselectivity is not affected by the amount of water would be a piece of evidence that the reaction in water proceeds by the enamine mechanism rather than by the general base mechanism.

Though it is known that aldehyde and amine can react to generate an enamine under aqueous conditions when an organic solvent is present, this is the first result showing that this can occur in a clear water solution without addition of any such solvent, and that the enamine generated can react with a further molecule of aldehyde with high enantioselectivity. Moreover, the present catalyst may have been present on the early Earth, generated from optically-enriched Pro and ammonia by a non-enzymatic reaction, and we have demonstrated that Pro of very high optical

Table 2 Effect of solvent and concentration on the self-aldol reaction of propanal^a

Entry	Solvent	Concentration	Yield ^b (%)	syn : anti ^c	ee 1 ^d (%)	ee 2 ^d (%)
1	Neat ^e		0			
2	Water	1 equiv. ^f	29	1.1 : 1	66	69
3	Water	5 equiv.	31	1.1 : 1	69	67
4	Water	20 equiv.	23	1.3 : 1	74	78
5	Water	50 equiv.	48	1 : 1	67	67
6	Water	100 equiv.	14	1 : 1	68	68

^a The reaction was conducted with 0.15 mmol of Pro-NH₂, 3.0 mmol of propanal, and water as indicated at room temperature for 3 h. ^b Isolated yield. ^c Determined by ¹H NMR. ^d Determined by chiral HPLC after conversion to the benzoyl ester. ^e The reaction was conducted without solvent. ^f The equivalents of water to propanal.

purity can be generated from Pro of very low optical purity under certain reaction conditions.¹⁷ The good enantioselectivity induced by Pro-NH₂ is remarkable when compared with the enantioselectivity (10–15%) catalyzed by the previously examined catalysts plausibly present in the prebiotic environment.^{14,18,19}

Though there is a room for the improvement in the yield, diastereo-, enantio-selectivities, and generality, the present reaction is the first example that a small organic molecule (MW = 66) can catalyze the asymmetric, direct aldol reaction “in water”.

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Notes and references

‡ Typical procedure of asymmetric self-aldol reaction of propanal (Table 1, entry 20).

To a 2 mol L⁻¹ propanal aqueous solution (1.5 mL, 3.0 mmol) was added L-proline carboxamide (17 mg, 0.15 mmol) at room temperature. After stirring the reaction mixture for 2.5 h, the reaction mixture was cooled at 0 °C and MeOH (3 mL) and NaBH₄ (284 mg, 7.5 mmol) were added. The reaction mixture was stirred for 1 h at 0 °C. The reaction was quenched with pH 7.0 phosphate buffer solution and the organic materials were extracted with ethyl acetate three times and the combined organic extracts were dried over anhydrous Na₂SO₄, and concentrated *in vacuo* after filtration. Purification by silica gel column chromatography (ethyl acetate–hexane = 1 : 2 → 1 : 1) gave (2*R*,3*R*)-2-methylpentane-1,3-diol and (2*R*,3*S*)-2-methylpentane-1,3-diol (diastereomer ratio = 1.1 : 1, 73 mg, 0.6 mmol) in 40% yield.

Enantiomeric excess was determined by HPLC analysis with a Chiralpak IA column (100 : 1 hexane : 2-propanol, λ = 254 nm), 1.0 mL min⁻¹; major enantiomer (*syn*) *t*_r = 24.6 min, minor enantiomer (*syn*) *t*_r = 29.9 min, major enantiomer (*anti*) *t*_r = 31.5 min, minor enantiomer (*anti*) *t*_r = 34.4 min, after conversion to their mono benzoyl esters.

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