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Aqua-organocatalyzed direct asymmetric aldol reaction with acyclic amino acids and organic bases with control of diastereo- and enantioselectivity

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Abstract—An effective aqua-organocatalytic direct aldol reaction is described. Aromatic amino acids can be a bifunctional catalyst system, which demonstrate excellent reactivity, diastereoselectivity, and enantioselectivity (up to 96% ee) in water without the addition of organic solvents. Furthermore, the present study demonstrates that both diastereo- and enantioselectivity can be easily modulated by the appropriate combination of an organocatalyst together with an organic base as a co-catalyst.

1. Introduction

Reactions, in which water is used as the solvent, have attracted a great deal of attention because water is a desirable solvent with respect to environmental concerns, safety, and cost, and which avoids the problems of pollution that are inherent with organic solvents.[1] Although the development of enantioselective reactions in water is an extensively investigated topic,[2] it has long been considered as a realm of enzymes.

Water often inhibits the catalyst's activity or alters enantioselectivity by interfering in the transition states of the reactions. Thus, the development of small organic molecules that catalyze enantioselective reactions in water is currently a highly challenging goal in chemistry.

In Nature aldol condensations are promoted by two distinct classes of aldolases: Class I aldolases contain an active site lysine involved in the formation of a nucleophilic enamine intermediate, and Class II aldolases that contain an active site zinc co-factor facilitating enolate formation by coordinating to the carbonyl oxygen of the ketone donor.[3] Natural Class I aldolase enzymes and aldolase catalytic antibodies catalyze enantioselective aldol reactions in water, in a hydrophobic pocket.[4]

Recently, small chiral amines have become attractive and powerful organocatalysts for C–C bond forming reactions and yield aldol products with excellent enantioselectivities.[5] Proline and short peptides incorporating N-terminal proline residues are capable of catalyzing direct aldol reactions in organic solvents, such as DMSO or DMF, under mild conditions. Although several chiral organocatalysts provide aldols enantioselectively in aqueous organic solvents, they still require the use of an organic solvent, and large amounts of buffer or surfactant.[6]

More recently, the artificially designed organocatalysts **1** and **2** (Fig. 1) were found to be efficient for direct aldol reactions in water with high enantioselectivity.[7] These organocatalysts are based on proline with appropriate hydrophobic groups.

Natural amino acids can be divided in three different groups: hydrophobic, hydrophilic, and neutral. Six of them possess hydrocarbon-like side chains.[8] This results in a tendency for nonpolar groups to contact each other, with an accompanying decrease in their interactions with water, and engage in hydrophobic bonds.

Thus, we reasoned that such hydrophobic amino acid catalysts would balance the influence of hydrophobic interaction and hydrogen bonding in the transition state in water.[9]

Furthermore, the present study would assess the influence of such hydrophobic amino acids on a water-based

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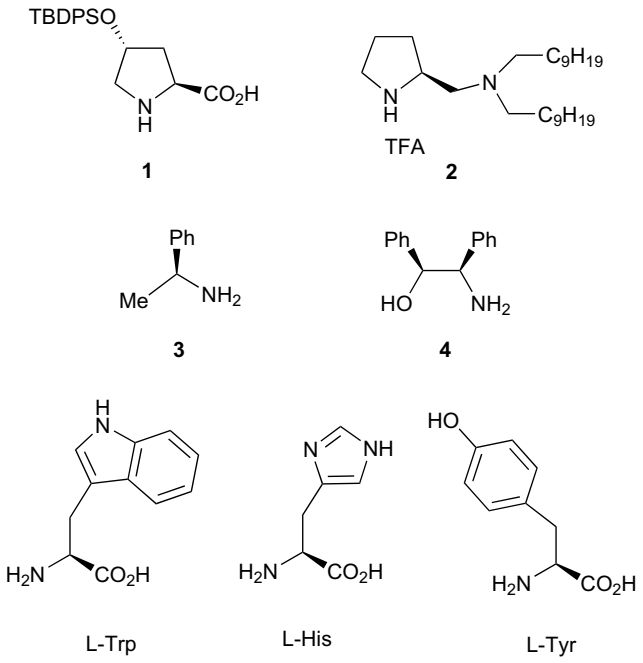


Figure 1.

prebiotic model of aldolase catalysis. Chiral amino acids were possibly present in the prebiotic period, either formed on earth or from an extraterrestrial origin. Amino acid catalysis may hold significant clues to the evolution of homochirality in aqueous prebiotic chemistry.[10]

Previously, we and others, have reported that the addition of organic bases significantly improves the rate of the direct aldol reaction in organic solvents.[11] In particular, we have shown that organic bases can be employed as co-catalysts to enforce *syn*-selectivity, while retaining a high level of enantioselectivity. In stark contrast, amino acids alone, and proline in particular, usually favor the formation of *anti*-aldol adducts.

This observation raises the possibility of modulating the *anti–syn* selectivity by the appropriate combination of an organocatalyst together with an organic base as a co-catalyst in water. Herein, we report a highly diastereo- and enantioselective aldol reaction promoted by hydrophobic amino acids in water and the influence of added organic bases on selectivities.

2. Results and discussion

To verify this assumption, the aldol reaction of cyclohexanone and 4-nitrobenzaldehyde to afford **5a** was performed in water, using several amino acid catalysts (20 mol %) in the presence or absence of additives. An examination of the ability of hydrophobic amino acids to catalyze the model reaction indicated that amino acids bearing an aromatic substituent gave better results, in terms of both yield and enantioselectivities as shown in Table 1. Reactions carried out with 0.2 M 4-nitrobenzaldehyde required the use of a 2-fold excess of cyclohexanone with a low conversion after 96 h. However, at higher concentration (0.5 M), higher conversion was achieved after 48 h. Further increase of the concentration to 1 M allowed the generation of an aldol adduct in high yield.

L-Valine and L-leucine are considered as very hydrophobic amino acids, however, little to no reaction progress was observed after 3 days in water (entries 1 and 2). As would be expected, neutral amino acids did not show any success in catalyzing the reaction either in water or in a buffered medium (entries 3–6).

Most notably, the reaction with aromatic amino acid L-phenylalanine led to an interesting result, the asymmetric aldol reaction proceeded efficiently in the presence of water and the *anti*-aldol product was obtained with excellent diastereoselectivity in a high enantioselectivity of 76% ee (entry 7). The effect of water as the reaction solvent is very important. Thus, reaction in a buffered aqueous medium resulted in a decrease in both diastero- and enantioselectivity for the *anti* aldol product, despite the rate acceleration (entry 8). The reaction scarcely proceeded with L-phenylalanine in the presence of sodium dodecylsulfate (SDS) in water, even at a high concentration of the catalyst (entries 9 and 10). L-Phenylglycine was unable to promote the aldol reaction.

L-Tryptophan, bearing a larger aromatic group, led to the best results in terms of yield, diastereo- and enantioselectivity in water. Thus, a smooth reaction proceeded in 62% yield to afford the *anti*-aldol as a major product with 88% ee (entry 16). Both L-Phe and L-Trp afforded excellent diastereoselectivities favoring the anti isomers (>18:2 dr).

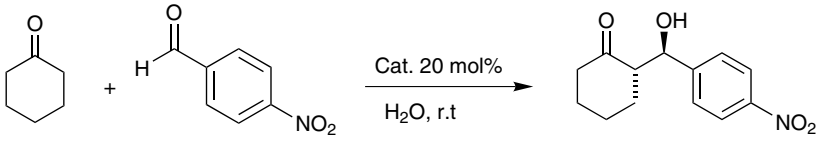
The major aldol isomer **5a** resulting from L-amino acid catalyzed reactions had a (2*S*,1′*R*)-absolute configuration. The observed stereoselectivity is in line with that of L-proline and its derived catalysts, thus favoring the *re*-facial attack on the aldehyde.[12]

Perhaps most interestingly, the reactions catalyzed by L-histidine led to a switch in the enantioselectivity, with the formation of equal amounts of *anti* and *syn* isomers (entries 12 and 13), although in a rather slow reaction. The major aldol products, both *anti* and *syn*, were generated with an absolute configuration opposite to that obtained with other L-amino acids as catalysts. A similar trend in the inversion of absolute stereochemistry was also observed for L-threonine in PBS, but with a lower reactivity (entry 15).

Simple primary amine (*S*)-phenylethylamine **3** and amino alcohol (1*S*,2*R*)-2-amino-1,2-diphenylethanol **4** were also tested as organocatalysts. Consequently, chiral primary amine **3**, lacking the hydroxy group adjacent to the stereogenic center, produced the *syn* aldol as the major product in 92% yield and with 22% ee (entry 17). However, catalyst **4** in water gave equal amounts of *anti* and *syn* aldol product in 90% yield and with low enantioselectivity (entry 18). The drop in selectivity may arise from competing general base catalysis of the aldol reaction.

L-Tryptophan was chosen for further studies of asymmetric aldol reactions with a variety of different aromatic

Table 1. Amino acid catalyzed aldol reaction of cyclohexanone and 4-nitrobenzaldehyde[a]



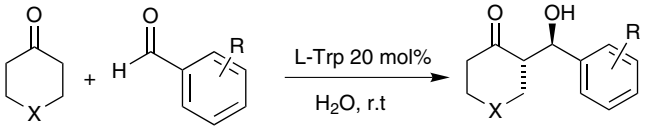
5a

Entry	Amino acid	Time (h)	Yields[b] (%)	*anti*:*syn*[c]	ee[d] *anti*:*syn* (%)
1	L-Val	72	0		
2	L-Leu	72	7	9:1	99:—
3[e]	L-Asp	72	0		
4	L-Asp	72	0		
5	L-Ser	110	0		
6[e]	L-Ser	21	<5		
7	L-Phe	72	52	19:1	76:—
8[e]	L-Phe	72	79	4:1	54:—
9[f]	L-Phe	48	0		
10[f,g]	L-Phe	55	<5		
11	L-Phg	48	<5		
12	L-His	72	60	1:1	*ent*- 62:*ent*- 84
13[e]	L-His	72	30	1:1	*ent*- 60:*ent*- 80
14	L-Thr	72	0		
15[e]	L-Thr	72	20	1:1	*ent*- 72:*ent*- 85
16	L-Trp	24	62	18:2	88:—
17	(*S*)-**3**	16	92	2:3	*ent*- 20:*ent*- 22
18	(1*S*,2*R*)-**4**	48	90	1:1	*ent*- 12:*ent*- 39
19	L-Tyr	24	<5		

[a] Unless otherwise stated, all reactions were carried out using 1.0 M aldehyde and 2.0 M ketone in the presence of 20 mol % catalyst in water.
[b] The yields are for isolated products.
[c] Determined by ^{1}H NMR of the crude product.
[d] The ee was determined by chiral HPLC analysis. The enantiomers were assigned by comparison to those obtained L-proline.
[e] Phosphate buffer at pH 7.1 was the solvent used.
[f] 1 equiv SDS was added.
[g] 50 mol % catalyst was used.

aldehydes under the optimized conditions for the model reaction. The reaction appears to be quite general with respect to aldehyde acceptor. Generally, excellent diastereo- and enantioselectivities were observed, as shown in Table 2. Typically, *anti*-aldol products are formed with enantioselectivities ranging from 53% to 96% ee. In contrast, a reaction with water miscible ketone provided aldol product with lower diastereo- and enantioselectivity (42% ee),

Table 2. L-Trp-catalyzed aldol reaction of cyclohexanone with aldehydes in water[a]



(2*S*,1′*R*)-**5**

Entry	Aldol product	R	X	Time (h)	Yield[b] (%) (*anti*:*syn*)[c]	ee *anti*[d] (%)
1	**5a**	4-NO_2	CH_2	24	62 (91:9)	88
2	**5b**	2-NO_2	CH_2	96	78 (92:8)	94
3	**5c**	4-CN	CH_2	48	82 (86:14)	70
4	**5d**	4-Cl	CH_2	66	87 (88:12)	87
5	**5e**	2-Cl	CH_2	66	83 (89:11)	84
6	**5f**	4-Br	CH_2	66	57 (90:10)	53
7	**5g**	4-CF_3	CH_2	72	64 (89:11)	96
8	**5h**	4-NO_2	O	96	74 (62:38)	42
9	**5i**	4-NO_2	S	48	0	—

[a] Unless otherwise stated, all reactions were carried out using 1.0 M aldehyde and 2.0 M ketone in the presence of 20 mol % catalyst in water.
[b] The yields are for isolated products.
[c] Determined by ^{1}H NMR of the crude product.
[d] The ee was determined by chiral HPLC analysis.

although with good yield (entry 8). However, the solid ketone tetrahydro-4-thiopyranone did not participate in the aldol reaction (entry 9).

The effectiveness of the aromatic amino acids as catalysts compared to proline and other acyclic amino acids can be attributed to the solubility of the catalysts. While prolines dissolve in water, aromatic and aliphatic amino acids are mainly hydrophobic and are only partially soluble in water, which results in heterogeneous mixtures.

Although Tyr did not display any catalytic property in the present study, an important implication of the cation–π interaction and the related 'polar–π' interactions is that Phe, Tyr, and Trp should not be considered simply 'hydrophobic' amino acids. They are in fact distinct from the conventional hydrophobic residues, such as Val, Leu, and Ile. Recent studies have shown that cation–π interactions, the electrostatically favorable attraction between a cation and a π-system, are not only quite strong in aqueous media but also commonly found in protein structures.[13]

We then turned our attention to histidine catalysis. The observed inversion of enantioselectivity with L-His as a catalyst in water, suggests the formation of the *Si*-face enamine intermediate approached by the *Re*-face of the acceptor (Fig. 2). The hydrogen bonding involving the imidazolium ring rather than the carboxylate group would facilitate this situation. In this case the imidazole ring functions as a base, which contributes to the deprotonation of the carboxylic acid. The participation of water—forming the first hydration shell—can be characterized in providing a proton shuffle through a hydrogen bond network that might enable proton transfer and aldehyde activation by the imidazolium.

As mentioned above, catalysis with histidine resulted in a slow reaction. We presumed that the addition of an organic base would facilitate enamine formation and thus accelerate the reaction. Interestingly, we have found that organic bases (DBU, DBN, TMG, or Imidazole) can be also employed to improve the rate of the reaction catalyzed by histidine with inversion of enantioselectivity. Perhaps most importantly, these organic bases promoted the aldol reaction by tryptophan. As shown in Table 3, a combination of histidine and one of the organic bases in 20 mol % of each allowed the addition of cyclohexanone to 4-nitrobenzaldehyde with *syn*-selectivity. In contrast, a similar combination with tryptophan catalyst favored the *anti*-selectivity.

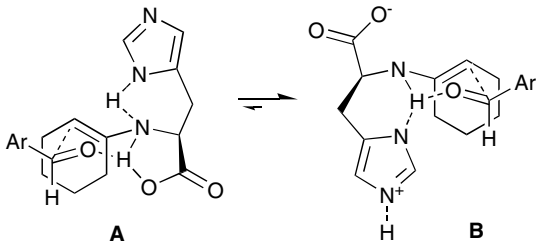
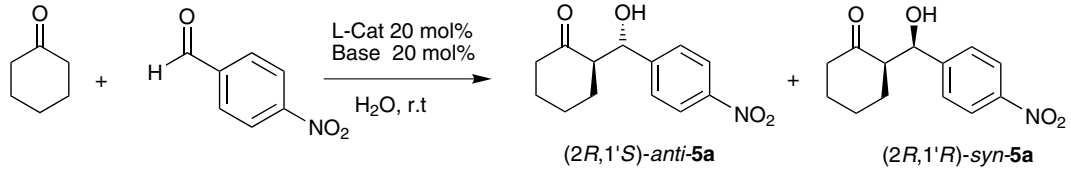


Figure 2. The proposed intermediates in the aldol reaction catalyzed by histidine in water. (A) Disfavored *Re*-facial attack on carbonyl. (B) Favored *Si*-facial attack on carbonyl.

Whereas similar enantioselctivities for the *syn*-aldol were provided with histidine or tryptophan, higher enantioselectivities were obtained for the *anti*-aldol in the presence of histidine.

In the case of histidine catalysis, participation of these organic bases can be characterized in providing assistance in the formation of an enamine. Thus, intermediate **B** (Fig. 2) still favored for the formation of aldol adduct: the lower enantioselectivity observed may be attributed to competing general base catalysis. On the other hand, deprotonation of the carboxylic group of tryptophan might in turn result in a *Si*-face enamine approaching the *Re*-face of the acceptor, probably activated by the protonated base.

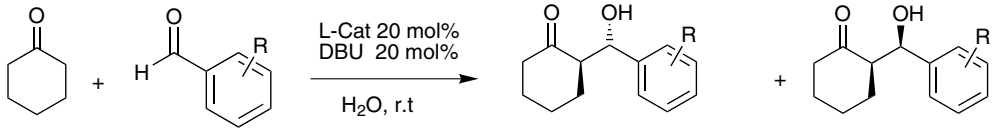
Table 3. Effect of added organic base on the L-Trp- and L-His-catalyzed aldol reaction of cyclohexanone with aldehydes in water[a]



Entry	Catalyst–base	Time (h)	Yields[b] (%)	*anti*:*syn*[c]	ee[d] (%) *anti*:*syn*
1	L-Trp–DBU	16	97	2:1	<5:60
2	L-Trp–DBN	16	95	2:1	<5:46
3	L-Trp–TMG	16	86	2:1	<5:—
4	L-Trp–Im	24	97	2:1	<5:65
5	L-His–DBU	24	66	1:1	31:48
6	L-His–DBN	24	91	1:1	31:50
7	L-His–TMG	24	89	1:2	30:52
8	L-His–Im	24	84	2:3	nd:56

[a] Unless otherwise stated, all reactions were carried out using 1.0 M aldehyde and 2.0 M ketone in the presence of 20 mol % catalyst and 20 mol % organic base in water.
[b] The yields are for isolated products.
[c] Determined by ^{1}H NMR of the crude product.
[d] The ee was determined by chiral HPLC analysis.

Table 4. Base assisted aldol reaction of cyclohexanone with aldehydes in water[a]



(2*R*,1'*S*)-*anti*-**5** (2*R*,1'*R*)-*syn*-**5**

Entry	R	Time (h)	Yield[b] (%) (*anti*:*syn*)[c]	ee[d] (%) *anti*:*syn*
1	4-NO_2	24	66 (1:1)	31:48
2	2-NO_2	24	66 (2:3)	39:50
3	4-CN	24	90 (2:3)	20:44
4	4-CF_3	24	92 (1:1)	46:30

[a] Unless otherwise stated, all reactions were carried out using 1.0 M aldehyde and 2.0 M ketone in the presence of 20 mol % catalyst and 20 mol % organic base in water.
[b] The yields are for isolated products.
[c] Determined by ^{1}H NMR of the crude product.
[d] The ee was determined by chiral HPLC analysis.

The scope of the aldol reaction, under these new conditions, has been examined. Similar trends were observed for the histidine–DBU catalytic system with respect to the enantioselectivities and yields when varying the structure of aromatic aldehydes (Table 4). Other aromatic aldehydes such as 2-chloro-, 4-chloro-, and 4-bromobenzaldehyde were also suitable for the present aldol reaction, however, enantioselectivities could not be determined.

3. Conclusion

In conclusion, we have developed an aqua-organocatalyzed asymmetric aldol reaction. Aromatic amino acids acting as a bifunctional catalyst system demonstrated excellent reactivity, diastereoselectivity, and enantioselectivity in water without the addition of organic solvents. Furthermore, conceptually, these results demonstrate that both diastereo- and enantioselectivity can be easily modulated by the appropriate combination of an organocatalyst together with an organic base as a co-catalyst. The present results suggest that aldol catalysis with aromatic amino acids under hydrophobic conditions could have provided a chiral influence in prebiotic chemistry.

Further investigations focusing on the full scope of this aqua-organocatalysis and related systems are currently underway and will be reported in due course.[14]

4. Experimental

4.1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Flash column chromatography was performed using 200–300 mesh silica gel. ^{1}H NMR spectra were recorded on a Varian Unity 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, m = multiplet), coupling constants (Hz), and integration.

^{13}C NMR spectra were recorded on Varian Unity 400 (100 MHz) with complete proton decoupling ($CDCl_3$: 77.23 ppm). Chiral HPLC was performed using a Varian 9012 pumping system and Varian 9050 UV detector series with a chiral column (Chiralcel OD, 0.46 cm (ϕ) × 25 cm, Daicel Chemical Ind., Ltd.). The racemic samples were prepared by either using racemic proline or pyrrolidine-acid as the catalyst. The major enantiomer was assigned by comparison of racemic aldol products with those reported in the literature using L-proline.

4.2. General procedure for the aldol reaction

The following procedure for the reaction of cyclohexanone with *p*-nitrobenzaldehyde in water is representative.

To a mixture of the bifunctional catalyst (0.2 mmol) and *p*-nitrobenzaldehyde (150 mg, 1.0 mmol) were added cyclohexanone (208 μL, 2.0 mmol) and water (0.8 mL) at room temperature under air (0.2 mmol of organic base was added, see Tables 3 and 4). The reaction mixture (emulsion) was stirred for 24–96 h. The water phase was extracted with ethyl acetate (3 × 2 mL), and the organic extracts dried over Na_2SO_4, filtered, and concentrated to give pure aldol adduct **5a** through flash column chromatography on silica gel (hexane/ethyl acetate (3:1)).

Diastereoselectivity and conversion were determined by ^{1}H NMR analysis of the crude aldol product after removal of the catalyst on a short pad of silica. The enantiomeric excess (ee) of **5a** was determined by chiral-phase HPLC analysis. The absolute configuration of aldol products **5** was extrapolated by comparison of the HPLC-data with the literature.

All compounds gave satisfactory analytical and spectral data. Compounds **5** are already known.[5a,7a] Characterization data for selected examples are given below:

2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclohexanone **5a**: Reaction time: 24 h; yield: 62%; *anti*:*syn* = 90:10. *anti*-diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.55–2.16 (m, 6H), 2.37–2.50 (m, 2H), 2.59 (m, 1H), 4.98 (d, $J = 8.4$ Hz, 1H), 7.49 (t, $J = 8.0$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 24.5, 27.5, 30.6, 42.5, 57.0, 73.8, 123.4, 127.8, 147.4, 148.4, 214.6; HPLC analysis Chiralcel OD (hexane/*i*-PrOH = 95:5, 1.5 mL/min, 254 nm, 20 °C) t_R (major) 12.8 min and t_R (minor) 16.4 min, ee: 88%.

Syn-diastereomer (determined only for reactions catalyzed by histidine and when organic bases are used as co-catalysts, see Tables 3 and 4) ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 8.20$ (2H, d, $J = 8.7$ Hz, ArH), 7.51 (2H, d, $J = 8.7$ Hz, ArH), 5.49 (1H, m, CHC*H*OH), 2.63 (1H, m, C*H*CHOH), 2.47–2.30 (2H, m, C*H*2C(O)), 2.13–1.36 (6H, m, chex-*H*). HPLC: Chiralcel-OD. Hexane/*i*-PrOH, 95:5, 1.5 mL min^{-1}, 254 nm: t_R (major) = 11.5 min; t_R (minor) = 12.4 min.

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