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The pH of the reaction controls the stereoselectivity of organocatalyzed direct aldol reactions in water

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ABSTRACT

The direct aldol reaction of 4-nitrobenzaldehyde and cyclohexanone, catalyzed by a protonated prolinamide catalyst in water, proceeds with the formation of aldol product that has high diastereoselectivity and enantioselectivity in an optimal pH range of 4–5.

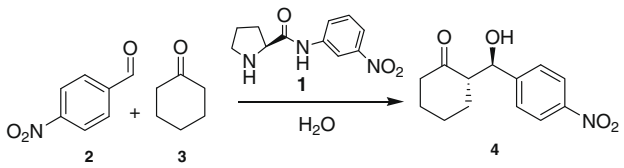
1. Introduction

The chemistry of organic reactions in water is undergoing rapid growth because of various potential advantages, such as alleviation of environmental problems associated with the use of organic solvents, industrial applications, unique reactivity, and selectivity.[1] However, the solubility of organic reactants offers a great challenge as most of these are insoluble in water. Due to their lesser solubility, organic reactions using water as solvent have been the subject of recent debate with regard to the use of terminology, and so have been classified as on water,[2] in water[3] or in the presence of water.[3c,4] Most recently, synthetic chemists have taken up the challenge of developing efficient aqueous phase small organic molecule-catalyzed processes.[5]

Asymmetric aldol reactions catalyzed by small organic molecules via enamine intermediates have emerged as useful carbon–carbon bond forming reactions providing aldol products with excellent enantioselectivities.[6] These reactions are typically performed in an organic solvent, but our group and others have reported that enamine-based organocatalytic direct asymmetric aldol reactions can be performed in water without the addition of any organic cosolvent.[7] The design of the organocatalyst that efficiently catalyzes an asymmetric aldol reaction in water consists of the following: a secondary amino group that serves as the catalytic site; an amide group bonded to a stereogenic center which provides stereoselective orientation in the transition state through hydrogen bonding; and finally, a hydrophobic group that contributes to hydrophobic interactions between the reactants and the catalyst. It was observed that a Bronsted acid additive not only provides greater solubility to the organocatalyst in water, but also enhances the enantioselectivity of the aldol product.[2b,8] We thought that since the Bronsted acid additive alters the pH of the aqueous reaction medium, the increase in the enantioselectivity may be due to the acidic aqueous reaction medium. We planned to systematically study the role of pH of the aqueous reaction medium on the enantioselectivity of a direct aldol reaction catalyzed by prolinamide catalysts. To the best of our knowledge, the effect of pH on an organocatalytic reaction in water has not been reported earlier. In this communication, we reveal the results of our study.

2. Results and discussion

A set of experiments were set-up to systematically study the effect of pH of the reaction mixture on the enantio- and diastereoselectivity of the aldol product. The experimental protocol consisted of stirring the catalyst **1** (20 mol %) in 2.5 mL of water, followed by the addition of the requisite amount of hydrobromic acid to attain the required pH of the solution. After the addition of cyclohexanone (5 mmol) and 4-nitrobenzaldehyde (1 mmol) to this solution, the reaction mixture was stirred for 24 h at 27 °C (Scheme 1). The results of these experiments show that diastereoselectivity increases with the lowering of the pH of the reaction mixture. At pH 6.41 the diastereoselectivity of **4** was 68:32 (*anti*:*syn*) (Table 1, entry 1). The highest diastereoselectivity of 97:3 (*anti*:*syn*) (Table 1, entry 12) was observed at pH 2.05, and a very small variation in the diastereoselectivity was observed in the pH range of 3.51–0.94 (Table 1).



Scheme 1. Direct asymmetric aldol reaction of cyclohexanone and *p*-nitrobenzaldehyde in water using catalyst **1**.

The enantioselectivity of the aldol product also increased with the decrease in pH of the reaction mixture, and this was maximum

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Table 1
Effect of pH on the enantioselectivity and diastereoselectivity of the aldol product[a]

Entry	pH	Yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] of *anti* (%)
1	6.41	92	68:32	71
2	6.26	91	73:27	88
3	6.01	92	77:23	88
4	5.70	92	84:16	89
5	5.36	90	90:10	92
6	5.03	91	91:9	95
7	4.54	92	92:8	96
8	4.09	92	93:7	95
9	3.51	91	95:5	93
10	3.08	90	95:5	93
11	2.45	88	96:4	92
12	2.05	81	97:3	94
13	1.51	76	94:6	93
14	0.94	20	94:6	93

[a] Reaction conditions: 1 mmol aldehyde, 5 mmol ketone, 20 mol % catalyst, 2.5 mL water, 27 °C.
[b] Isolated yield.
[c] Determined from ^{1}H NMR of crude reaction mixture.
[d] Determined by HPLC using chiral phase AS–H column.

between the pH range 4 and 5, being highest (ee 96%) at pH 4.54 (Table 1, entry 7). At a lower pH (beyond 2.05) the yield of the aldol product decreased. Thus this study establishes that the pH of the reaction mixture is important to obtain highly stereoselective catalysis of the direct aldol reaction by prolinamide catalysts.

We further envisaged exploring the role of the conjugate base of the acid on the stereoselective outcome of the reaction. The results of the direct aldol reactions of cyclohexanone with 4-nitrobenzaldehyde using catalysts **1a–g**, prepared by protonation with different protic acids, are summarized in Table 2. The results indicate that the protonating acid does have a large effect on the diastereo- and enantioselectivity of the aldol product. This can be correlated with the pK_a of the protonating acids and the pH of the reaction mixture. The catalysts protonated with acids having a higher pK_a value (Table 2, entries 1 and 2) catalyzed the aldol reaction less selectively whereas those with a lower pK_a (Table 2, entries 3–7) yielded aldol products in high diastereo- and enantioselectivity.

Table 2
Effect of protonating acids on the diastereoselectivity and enantioselectivity of the aldol reaction[a]

Entry	Catalyst	Acid	pK_a[b]	pH of solution	Yield[c] (%)	dr[d] (*anti*:*syn*)	ee[e] of *anti* (%)
1	**1a**	CH_3COOH	4.76	6.81	89	62:38	66
2	**1b**	CF_3COOH	0.26	5.30	82	85:15	88
3	**1c**	HNO_3	−1.30	4.07	85	94:6	92
4	**1d**	HCl	−8.00	4.37	89	92:8	92
5	**1e**	HBr	−9.21	4.01	92	94:6	95
6	**1f**	$ClSO_3H$	−10.43	1.90	69	92:8	91
7	**1g**	CF_3SO_3H	−13.00	1.57	51	92:8	91

[a] Reaction conditions: 1 mmol aldehyde, 5 mmol ketone, 20 mol % catalyst, 2.5 mL water, 27 °C.
[b] pK_a of acid measured in water.[10]
[c] Isolated yields.
[d] Determined from ^{1}H NMR of crude reaction mixture.
[e] Determined by HPLC using chiralphase AS–H column.

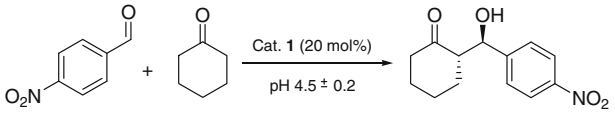
However, with chlorosulfonic acid and trifluoromethanesulfonic acid as protonating acids, the aldol product was obtained in low yield, which can be attributed to the inhibiting effect of the strong acids on the catalyst. Interestingly, the reaction was not completely inhibited by protonating acids with low pK_a values (Table 1, entries 6–7), unlike the observations made by the groups of Gryko and Najera where the acid additives with a pK_a value of less than zero inhibit the reaction completely.[8d,9] In aqueous conditions our catalysts are receptive to a broader range of acids. The pH of the reaction mixture, containing 20 mol % of protonated catalysts **1a–g**, varied with the pK_a of the acid (Table 2). Thus we suggest that the nature of the protonating acid has no effect on the stereoselective outcome of the aldol reaction; it is controlled by the pH of the reaction mixture.

Another observation made during this study pertains to the optimum pH range 4–5 (Table 1, entry 7) within which the enantioselectivity was found to be highest. We believe that an optimal equilibrium between the protonated and protonation free prolinamide catalyst in the aqueous medium (Eq. 1) is responsible for the high enantioselectivity.[7b]

$$RN^+H_3X^- \overset{H_2O}{\rightleftharpoons} RNH_2 + H^+ + X^- \quad (1)$$

This probably inhibits the general base catalysis of the aldol reaction, thus allowing the reaction to proceed through enamine catalysis. To further confirm the importance of pH in directing the stereoselectivity of the direct aldol reaction irrespective of the protonating acid we performed a set of aldol reactions of cyclohexanone with 4-nitrobenzaldehyde while maintaining the pH of the reaction mixture at 4.5 ± 0.2 using different acids (Table 3).

Table 3
Organocatalyzed direct aldol reaction at pH 4.5 ± 0.2[a]



2 3 4

Entry	Acid	Time (h)	Yield[b] (%)	dr[c] (*anti*:*syn*)	ee[d] of *anti*
1	Acetic acid	24	88	80:20	88
2	TFA	24	91	88:12	91
3	HBr	24	92	92:8	96
4	HCl	24	90	92:8	94
5	HNO_3	24	90	92:8	94
6	H_2SO_4	24	92	93:7	94
7	HBr/AcOH(33%)	24	90	93:7	96
8	$ClSO_3H$	24	87	95:5	94
9	CF_3SO_3H	24	86	96:6	93

[a] Reaction conditions: 1 mmol aldehyde, 5 mmol ketone, 20 mol % catalyst, 2.5 mL water, 27 °C.
[b] Isolated yield.
[c] Determined from ^{1}H NMR of crude reaction mixture.
[d] Determined by HPLC using chiral phase AS–H column.

The enantioselectivity was nearly similar. The yield of the aldol product **4**, obtained by using catalysts **1f** and **1g** increases (Table 3, entries 8 and 9) from that obtained at pH 1.9 (Table 2, entry 6) and pH 1.57 (Table 2, entry 7), respectively. This suggests greater reactivity of the catalysts in the optimal pH range.

3. Conclusion

In conclusion, we have demonstrated that high diastereoselectivity and enantioselectivity of the protonated prolinamide-catalyzed direct asymmetric aldol reaction in water are dependent on the pH of the reaction medium. In general, the acidic pH favors high stereoselectivity, whereas a pH range of 4–5 is optimum for excellent diastereoselectivity and enantioselectivity in water.

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