The Effectiveness of Proteinogenic Amino Acids in the Asymmetric Aldol Reaction in DMSO and Aqueous DMSO

Yujiro Hayashi,* Takahiko Itoh, Norio Nagae, Masahiro Ohkubo, Hayato Ishikawa

Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan
Fax +81(3)52614631; E-mail: hayashi@ci.kagu.tus.ac.jp

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Abstract: The effects of twenty proteinogenic amino acids have been investigated in the aldol reaction of aldehyde and ketone in DMSO and aqueous DMSO (in the presence of three equivalents of water). Not only proline but also other amino acids promote the aldol reaction enantioselectively. The effect of water varies with amino acid, and water does not affect the enantioselectivity in most cases, the exceptions being Pro, Ser and His. In the case of Pro, large positive effects on diastereo- and enantioselectivities were observed in the reaction of α-substituted methyl ketone, while no effect was observed in that of methyl ketone.

Key words: asymmetric synthesis, aldol reactions, organocatalyst, amino acids, water

The aldol reaction is one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1] In 1997, Shibasaki and co-workers reported the first highly enantioselective, direct, catalytic aldol reaction based on an organometallic catalyst.[2] In 2000, List, Barbas and Lerner discovered the proline-mediated direct, asymmetric, catalytic intermolecular aldol reaction.[3] Since this seminal discovery, many kinds of organocatalysts have been developed for the enantioselective aldol reaction.[4,5]

Reactions using water as a solvent have attracted a great deal of attention because water possesses unique properties and is a safe medium, avoiding the problems of pollution inherent with organic solvents.[6] Several aldol reactions have been reported to proceed by the use of organocatalysis in aqueous conditions, and increases in diastereo- and enantioselectivities have been reported.[7,8] In spite of the many endeavors to perform the aldol reaction in the presence of water without organic solvent,[9] there had been no highly enantioselective examples until our[10] and Barbas'[11] groups developed such a reaction at the end of 2005. We have reported that siloxyproline is an effective organocatalyst, which promotes the enantioselective aldol reaction even in the presence of a large amount of water. Recently we also found that the aldol reaction of ketone and aldehyde proceeds catalyzed by proline under wet conditions (in the presence of three equivalents of water), and that the 'wet' conditions are essential, because the enantioselectivity decreases without water, while the yield decreases when a larger amount of water (18 equiv) is employed.[12] In these reactions, water plays an essential role by increasing the diastereo- and enantioselectivities.

Except for MacMillan's[13] and Maruoka's[14] catalysts, most of the organocatalysts developed for the asymmetric aldol reactions have been based on the proline skeleton. Is proline special? In the seminal paper of 2000[3] it was reported that proline promotes the enantioselective aldol reaction of acetone and *p*-nitrobenzaldehyde in DMSO, while His, Val, Tyr and Phe do not. However, there are reports that other amino acids can promote the aldol reaction, and in some cases, excellent enantioselectivity has been achieved. For instance, Cordova and co-workers examined the aldol reaction of *p*-nitrobenzaldehyde and cyclohexanone using 13 of the 20 proteinogenic amino acids and discovered that excellent enantioselectivity was obtained when either Val or Ile was used as the catalyst under aqueous conditions, with ten equivalents of water employed in DMSO.[7l] Lu examined seven amino acids in the same reaction in the presence of water without using organic solvent and found that Trp afforded the aldol product in 96% ee.[8a] He also reported that the aldol reaction of cyclohexanone and benzaldehyde does not proceed in the presence of water with any of five amino acids, Ser, Thr, Val, Leu, and Ile, but that siloxythreonine is an effective catalyst.[8e] These reactions were performed in aqueous DMSO or in the presence of water. Is the water essential? Does water increase the diastereo- or enantioselectivity? A thorough comparison of the reactions in organic solvent and aqueous solvent in the presence of each amino acid is necessary. As no systematic study has been made of all the proteinogenic amino acids in the aldol reaction in organic solvent and aqueous solvent, we have investigated the reaction in detail, with the results we describe in this paper.

We chose *p*-nitrobenzaldehyde and cyclohexanone for our model reaction. The reaction was performed at room temperature in water-free DMSO,[15] or in aqueous DMSO containing three equivalents of water, with the results summarized in Table 1. The reaction proceeded with all the proteinogenic amino acids except Cys, and aldol products were obtained enantioselectively except with Gly. The yield and diastereo- and enantioselectivity were dependant on the amino acid. With the exceptions of Phe, Lys, Arg, Asp, and Gln, in most cases the diastereoselectivity increased when the reaction was performed in aqueous DMSO. A marked increase in the diastereoselectivity was observed when Pro was employed: An excellent de

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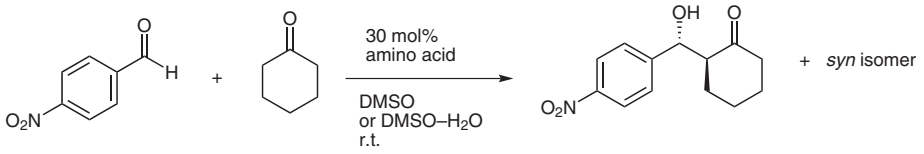
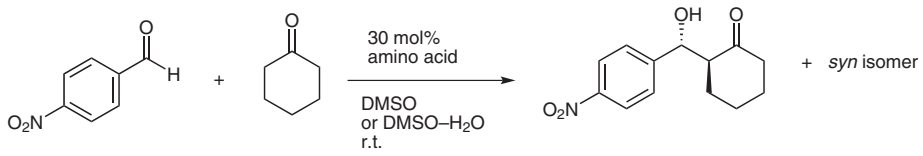
(*anti*:*syn* = 10.3:1) was obtained in aqueous DMSO in spite of the low de (1.5:1) in DMSO. For most of the amino acids the enantioselectivity was the same for the reactions in water-free and aqueous DMSO. Only when Pro, Ser and His were employed did water have a positive effect, increasing the enantioselectivity. For Pro the reaction was faster compared with other amino acids, but over-reaction (dehydration) occurred, giving the dehydrated α,β-unsaturated ketone as a side product. Thus, we quenched the reaction within two hours and the yield was low in DMSO (entry 15), while a good yield of 79% was obtained in aqueous DMSO (entry 16, vide infra).

Table 1 The Effectiveness of Amino Acids for the Aldol Reaction in DMSO and in Aqueous DMSO[a,16]



Entry	Amino acid	Solvent	Time (h)	Yield (%)[b]	*anti*:*syn*[c]	ee (%)[d]
1	Gly	DMSO	30	73	1.7:1	0
2	Gly	aq DMSO	30	75	5.7:1	0
3	Ala	DMSO	12	74	4.5:1	90
4	Ala	aq DMSO	12	72	13.7:1	90
5	Val	DMSO	6	79	5.6:1	93
6	Val	aq DMSO	6	65	15.1:1	96
7	Leu	DMSO	16	73	4.1:1	94
8	Leu	aq DMSO	16	83	10.6:1	95
9	Ile	DMSO	24	84	5.4:1	96
10	Ile	aq DMSO	24	84	13.0:1	97
11	Phe	DMSO	11	57	2.1:1	70
12	Phe	aq DMSO	11	70	2.8:1	69
13	Trp	DMSO	7	78	2.5:1	79
14	Trp	aq DMSO	7	81	3.8:1	81
15	Pro	DMSO	2	41	1.5:1	84
16	Pro	aq DMSO	2	79	10.3:1	96
17	Ser	DMSO	48	79	1.8:1	75
18	Ser	aq DMSO	48	84	5.3:1	91
19	Thr	DMSO	12	78	3.9:1	92
20	Thr	aq DMSO	12	80	9.8:1	96
21	Tyr	DMSO	24	76	1.8:1	85
22	Tyr	aq DMSO	24	84	4.6:1	82
23	Cys	DMSO	48	<5	nd[e]	nd[e]
24	Cys	aq DMSO	48	<5	nd[e]	nd[e]
25	Met	DMSO	9	70	2.6:1	84
26	Met	aq DMSO	9	79	8.2:1	84
27	His	DMSO	24	80	2.7:1	59

Table 1 The Effectiveness of Amino Acids for the Aldol Reaction in DMSO and in Aqueous DMSO[a,16] (continued)



Entry	Amino acid	Solvent	Time (h)	Yield (%)[b]	*anti*:*syn*[c]	ee (%)[d]
28	His	aq DMSO	24	82	3.7:1	67
29	Lys	DMSO	30	75	2.2:1	75
30	Lys	aq DMSO	30	76	2.8:1	79
31	Arg	DMSO	18	29	0.9:1	–24
32	Arg	aq DMSO	18	47	0.8:1	–18
33	Asp	DMSO	44	77	2.1:1	77
34	Asp	aq DMSO	44	77	2.7:1	69
35	Asn	DMSO	3	65	4.3:1	89
36	Asn	aq DMSO	3	47	6.6:1	91
37	Glu	DMSO	12	73	2.2:1	88
38	Glu	aq DMSO	12	89	8.7:1	71
39	Gln	DMSO	48	77	5.5:1	88
40	Gln	aq DMSO	48	78	5.9:1	87

[a] Reaction conditions: *p*-nitrobenzaldehyde (0.4 mmol), cyclohexanone (2.0 mmol), amino acid (0.12 mmol), DMSO (400 μL), with or without H_2O (22 μL), r.t.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Enantiomeric excess of the major *anti* isomer as determined by chiral phase HPLC analysis.
[e] Not Determined.

In the reaction using proline, a marked increase in enantioselectivity was observed. Is this a general phenomenon with proline? Excellent enantioselectivity was also obtained by the use of Val and Ile. Are Val and Ile also effective in other aldol reaction? We next examined the aldol reaction catalyzed by Pro, Val and Ile in detail using other combinations of ketone and aldehyde. The reaction using proline was fast at room temperature, causing overreaction (vide supra), and so testing was performed at lower temperature (4 °C), whereas the reaction was carried out at room temperature in the cases of valine and isoleucine. These results are summarized in Tables 2 and 3.[17]

First, proline was examined as a catalyst. As expected, a clean reaction proceeded without the formation of dehydrated product. Even under these conditions, the enantioselectivity of the product obtained in DMSO was low, while an excellent result was obtained in aqueous DMSO. These results indicate that any kinetic resolution at the dehydration stage can be ruled out. In the case of both *p*-nitro- and *o*-chlorobenzaldehyde, water exhibited a positive effect on diastereo- and enantioselectivities. In contrast to these positive effects, when acetone was employed as the nucleophilic ketone, water either decreased or did not affect the moderate enantioselectivity that was observed (Table 2, entries 5–8). We further investigated the reaction of other acyclic ketones such as methyl ethyl ketone,[7k,m,8d] for which interesting results were obtained (Table 3, entries 1 and 2): Two regioisomers were formed and the effect of water was different for each of these. Water had a positive effect on the reaction in which the ethyl side of the ketone reacted, while no effect was observed with the other pathway, i.e. reaction on the methyl side. Thus, while adding water led to an increase in enantioselectivity for an α-substituted methyl ketone, no such effect was observed in the unsubstituted case (Figure 1).

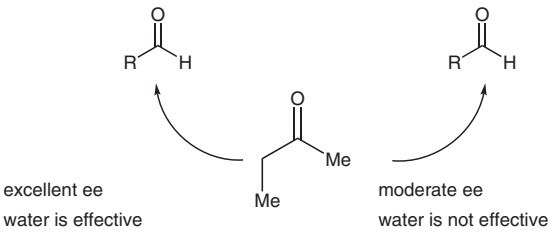
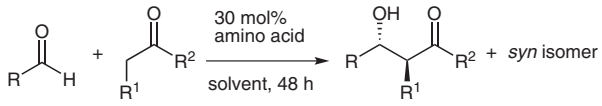
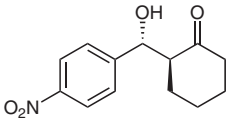
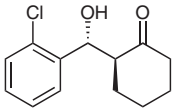
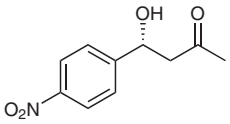
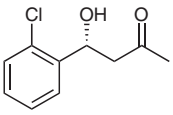


Figure 1 Difference in reactivity between methyl and ethyl substituents in the proline-mediated aldol reaction

Table 2 The Effect of Ketone in the Amino Acid Mediated Aldol Reaction in DMSO and Aqueous DMSO[a,16]

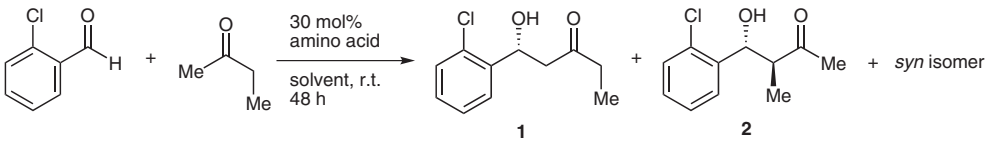


Entry	Product	Amino acid	Solvent	Temp. (°C)	Yield (%)[b]	*anti*:*syn*[c]	ee (%)
1		Pro	DMSO	4	61	5.8:1	80[d]
2		Pro	aq DMSO	4	79	15.9:1	93[d]
3		Pro	DMSO	4	65	6.4:1	82[d]
4		Pro	aq DMSO	4	76	>20:1	98[d]
5		Pro	DMSO	4	63		75[e]
6		Pro	aq DMSO	4	72		61[e]
7		Pro	DMSO	4	75		68[e]
8		Pro	aq DMSO	4	82		67[e]
9		Val	aq DMSO	23	26		40[e]
10		Ile	aq DMSO	23	34		47[e]

[a] Unless otherwise noted, the reaction conditions were as follows: aldehyde (0.4 mmol), ketone (2.0 mmol), amino acid (0.12 mmol), DMSO (400 μL), with or without H_2O (22 μL), indicated temperature, 48 h.
[b] Isolated yield.
[c] Determined by ^1H NMR.
[d] Enantiomeric excess of the major *anti* isomer as determined by chiral phase HPLC analysis.
[e] Enantiomeric excess determined by chiral phase HPLC analysis.

Next valine and isoleucine were employed in aqueous DMSO (Table 2, entries 9 and 10; Table 3, entries 3 and 4). Although the reaction was performed at room temperature, the reaction was slow, affording the aldol products in low yield. Both in the reaction of acetone and methyl ethyl ketone, low enantioselectivity was observed. In the reaction of methyl ethyl ketone, *anti*:*syn* ratio was also low. These results indicate that Val and Ile, which gave excellent results in the aldol reaction of cyclohexanone, are poor catalysts in the reaction of acyclic ketones in terms of the reactivity, diastereoselectivity and also enantioselectivity.

Table 3 The Effect of Pro, Val and Ile in the Aldol Reaction of 2-Butanone[a]



			1		**2**		
Entry	Amino acid	Solvent	Yield (%)[b]	ee (%)[c]	Yield (%)[b]	*anti*:*syn*[d]	ee (%)[e]
1	Pro	DMSO	45	65	16	2.6:1	89
2	Pro	aq DMSO	46	69	25	>20:1	98
3	Val	aq DMSO	9	55	14	2.8:1	74
4	Ile	aq DMSO	11	59	15	2.9:1	63

[a] Reaction conditions: aldehyde (0.4 mmol), ketone (2.0 mmol), amino acid (0.12 mmol), DMSO (400 μL), with or without H_2O (22 μL), r.t., 48 h.
[b] Isolated yield.
[c] Enantiomeric excess determined by chiral phase HPLC analysis.
[d] Determined by ^1H NMR.
[e] Enantiomeric excess of the major *anti* isomer as determined by chiral phase HPLC analysis.

In summary, we have investigated use of all the proteinogenic amino acids in the aldol reaction of aldehyde and ketone in DMSO and aqueous DMSO, and found that most of them promote the aldol reaction of cyclohexanone enantioselectively. A positive water effect on diastereoselectivity has been observed with some of the amino acids, while water afforded a positive effect on enantioselectivity only when Pro, Ser or His were employed. For the proline-mediated aldol reaction, a large positive effect on diastereo- and enantioselectivities was observed in the reaction of α-substituted methyl ketone, while no effect was observed in that of methyl ketone. Whereas valine and isoleucine afforded excellent results in the aldol reaction of cyclohexanone, they are not suitable catalysts in the reaction of acyclic ketones.

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(16) **Typical Experimental Procedure (Table 1)**: To a DMSO solution (0.40 mL) or aq DMSO solution (DMSO: 0.40 mL; H_2O: 22 μL) of amino acid (0.12 mmol) were added *p*-nitrobenzaldehyde (60.5 mg, 0.4 mmol) and cyclohexanone (207 μL, 2.0 mmol) under an argon atmosphere at r.t. When the reaction was complete, it was quenched with pH 7.0 phosphate buffer solution. The organic materials were extracted with EtOAc (3 ×) and the combined organic extracts were dried over anhyd Na_2SO_4, and concentrated in vacuo after filtration. The residue was purified by flash chromatography to give an aldol product.

Diastereoselectivity was determined by ^{1}H NMR (400 MHz). Enantiomeric excess was determined by HPLC analysis with a Chiralpak AS-H column (hexane–2-propanol = 10:1, λ = 231 nm), 1.0 mL/min; major enantiomer t_R = 11.5 min, minor enantiomer t_R = 18.7 min.

(17) All compounds are known: (a) 2-(Hydroxy-4-nitrophenylmethyl)cyclohexanone: Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (b) 2-(2-Chlorophenylhydroxymethyl)cyclohexanone: Chen, J.; Lu, H.; Li, X.; Cheng, L.; Wan, J.; Xiao, W. *Org. Lett.* **2003**, *5*, 4369. (c) 4-Hydroxy-4-(4-nitrophenyl)-2-butanone: Rodriguez, B.; Bruckmann, A.; Bolm, C. *Chem. Eur. J.* **2007**, *13*, 4710. (d) 4-(2-Chlorophenyl)-4-hydroxy-2-butanone: Maya, V.; Raj, M.; Singh, V. K. *Org. Lett.* **2007**, *9*, 2593. (e) 1-(2-Chlorophenyl)-1-hydroxy-3-pentanone and 4-(2-chlorophenyl)-4-hydroxy-3-methyl-2-butanone: Luo, S.; Xu, H.; Li, J.; Zhang, L.; Cheng, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 3074.