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Primary amine catalyzed direct asymmetric aldol reaction assisted by water

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Abstract—L-Valine was found to be an active catalyst in the asymmetric direct aldol reaction. The aldol reaction of a variety of aromatic aldehydes with acetone was catalyzed by 20 mol % of L-valine at 35 °C with the aldol products obtained in moderate to good yields (48–83%) and enantiomeric excesses (42–72%). The reaction was more efficient catalytically with best results observed in the presence of 1 mol equiv of water, with respect to the aldehyde, in either DMSO or DMF as solvent. The effect of water concentration on the reaction rate and enantioselectivity was also investigated. Thus, with increasing water concentration in DMSO there was decreasing enantioselectivity. However, the reaction in the presence of L-phenylalanine showed a lower level of reactivity and enantioselectivity to afford the aldol in 25% with 31% ee. In marked contrast, reaction with L-phenylglycine resulted in the negligible formation of the aldol (<5%). Our results, suggest a new strategy in the design of new bioorganic catalysts for direct asymmetric aldol reactions.

1. Introduction

The asymmetric aldol reaction is one of the most powerful methods for the construction of complex chiral polyol architectures. Early developments in asymmetric direct aldol reactions catalyzed by heterobimetallic complexes were reported by Shibasaki et al. and Trost et al.[1] Recent finding by Barbas et al. and List et al. proved L-proline to be a powerful catalyst in the asymmetric intramolecular direct aldol reaction and paved the way for the development of the concept of small organic molecules as catalysts.[2] However, screens of catalysts have so far only yielded closely related five-membered proline derivatives.[3] Conversely, it has long been known that except where the secondary enamine form is stabilized by further conjugation, the equilibrium is usually almost completely in favor of the imine form. Despite the thermodynamic instability, this possibility of enamine formation could be employed in reactions with electrophilic reagents in process, which have always required the isolation of the enamine.[4] In this context there is a need for catalytic direct aldol reactions using aliphatic amino acids. Aliphatic amino acids are also thought to be involved in the origin of homochirality in the synthesis of building blocks such as sugars during the prebiotic world.[5]

In a recent report by Wong et al., a hydrogen-bonded water molecule was found to participate in a proton relay in the DERA catalyzed effective tautomerization of acetaldehyde imine to its enamine, allowing for the aldol reaction in a hydrophobic pocket.[6] Computational studies suggested that hydrogen-bond donors, such as water itself, are able to provide carbonyl compounds with two hydrogen bonds.[7] Based on these observations, we wondered whether water might participate in a proton relay that could allow for enamine formation involving primary amines in organic solvents.[8] Since the imine–enamine equilibrium is strongly solvent dependent, these solvents must have high polarity and propensity for hydrogen bond accepting because of their ability to stabilize transition states.[9]

2. Results and discussion

Aliphatic amino acids were initially observed to be ineffective in catalyzing the direct aldol reaction, yielding less than 10% aldol adduct at room temperature.[2c] We began our investigation by the evaluation of the conditions that would allow the aldol reaction to take place.

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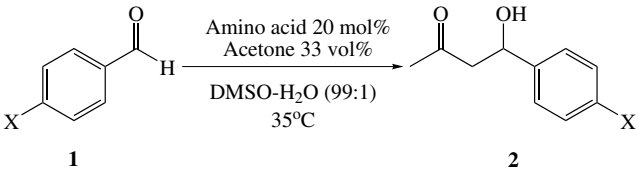
No reaction was observed when reacting 4-nitrobenzaldehyde with acetone in the presence of 20 mol % of L-valine in pure DMSO. In contrast, when the reaction mixture was stirred at 35 °C for 24 h, aldol product was obtained in 30% yield. Also L-valine appeared to catalyze the aldol reaction at higher temperatures, which has not been reported previously.

However, when the reaction was performed in DMSO containing 1 vol % water and in the presence of 20 mol % L-valine, an acceleration of the reaction was observed with the aldol product obtained in 58% yield and 53% ee after 24 h (Scheme 1 and Table 1).[10]



Scheme 1.

With these results in hand, we next tried to evaluate the reactivity of different aliphatic amino acids under the same reaction conditions and at the same concentration of catalyst with respect to substrate. However, the reaction in the presence of L-phenylalanine showed a lower level of reactivity and enantioselectivity to afford the aldol in 25% after 20 h with 31% ee. In marked contrast, the reaction with L-phenylglycine resulted in the negligible formation of the aldol (<5% after 20 h).

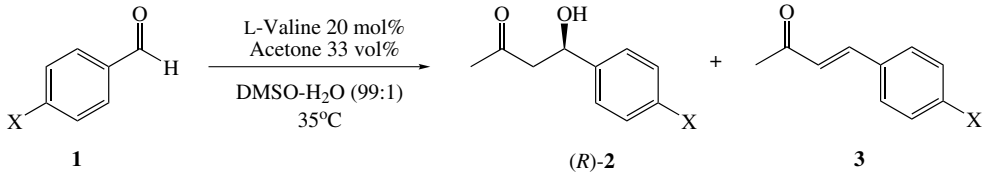
Table 1. Amino acid-catalyzed aldol reaction of acetone and 4-nitrobenzaldehyde

Amino acid	X	Time (h)	Yields (%)	Ee aldol (%)
L-Valine	NO_2	24	58	53
L-Phenylalanine	NO_2	20	25	31
(D)-Phenylglycine	NO_2	20	<5	—
L-Aspartic acid	NO_2	24	35	40
L-Glutamic acid	NO_2	24	36	18
L-Histidine	NO_2	24	25	12
L-Threonine	NO_2	24	37	42

Comparison of acidic aspartic and glutamic amino acids with L-valine resulted both in low reactivity and enantioselectivity. An even lower reactivity was observed with the basic L-histidine. Interestingly, neutral L-threonine gave comparable results with L-aspartic acid, probably resulting from hydrogen bonds with the acidic proton on the side chain. These preliminary results show that valine is the most suitable primary amine containing catalyst for the aldol reaction.

The generality of L-valine in catalyzing the direct aldol reaction was evaluated with a variety of different aromatic aldehydes under optimal conditions. The aldol reaction of aldehydes **1** with acetone was catalyzed by 20 mol % of L-valine at 35 °C with aldol products **2** obtained in good yields (48–83%) and enantiomeric excesses (42–72%) as shown in Table 2. In general,

Table 2. Direct asymmetric aldol reactions catalyzed by L-valine

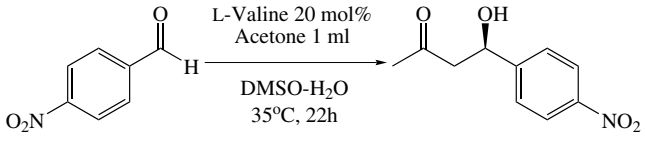


1a, X = H
1b, X = Cl
1c, X = Br
1d, X = NO_2
1e, X = CN

X	Entry	Solvent–H_2O (99:1)	Yields[a] (%)		Time (h)	Ee **2**[b] (%)
			Aldol **2**	Cond. **3**		
H	1	DMSO	48	47	46	62[c]
	2	DMF	50	42	72	72[c]
Cl	3	DMSO	51	41	46	48
	4	DMF	79	19	63	56
Br	5	DMSO	52	41	48	49
	6	DMF	68	30	63	62
NO_2	7	DMSO	58	—	24	53
	8	DMF	87	—	63	42
CN	9	DMSO	82	—	40	62
	10	DMF	83	—	63	60

[a] The yields were determined by ^1H NMR spectroscopy.
[b] The ee was determined by chiral HPLC analysis using a Kromasil TBB-CHI (see Ref. 12).
[c] The ee was determined by chiral GC analysis using a Chrompack Chirasil-CB Dex. The major enantiomer was assigned to be (*R*) by cross comparison of racemic aldol products with those reported in the literature using L-proline (Ref. 2c).

reactions using benzaldehyde, 4-chloro- and 4-bromobenzaldehydes **1a–c** afforded aldol products together with considerable amounts of dehydration product **3**. Improved enantioselectivities were observed when reactions in DMF–H_2O were performed (99:1) as solvent under similar reaction conditions although appreciable condensation did still occur. Unfortunately in this case, the rate of the reaction was much slower than in DMSO–H_2O (99:1). Interestingly, 4-nitro- and 4-cyanobenzaldehydes **1d** and **1e** reacted smoothly in presence of valine in DMSO–H_2O (99:1) to yield aldols **2d** and **2e** as the sole reaction products (Scheme 2). A similar reactivity was observed in DMF–H_2O (99:1) although at a slower rate and lower enantioselectivity.



1d (*R*)-**2d**

Scheme 2.

The effect of water concentration on the reaction rate and enantioselectivity of the aldol reaction was also investigated (Table 3). This showed that by increasing water concentration in DMSO, enantioselectivity decreased. Such an observation has previously been reported for proline catalyzed aldol reactions.[2c]

Table 3. Effect of water concentration on aldol reaction

Entry[a]	Amount of H_2O		Yield (%)	Ee (%)
	vol %	mmol		
1	1	1.1	58	53
2	2	2.2	60	44
3	4	4.4	60	42

[a] Reactions were run using 2 mL solvent. Acetone (1.0 mL), 4-nitrobenzaldehyde (1.0 mmol), and L-valine (0.2 mmol).

More intriguing is the fact that when performing the aldol reaction in the presence of water at different concentrations, it appears that 1.1 mmol, that is, 1 mol equiv of water with respect to aldehyde gave the best ee (Table 3, entry 1). Similar results were observed when varying the concentration of reagents (Table 4). Comparison of entries 1 and 2 in Tables 3 and 4, respectively, show clearly the importance of water concentration. Remarkably, the addition of either more or substoichiometric amounts of water both resulted in lower ees, while maintaining good reaction rates.

Table 4. Effect of reaction solution concentration on aldol reaction

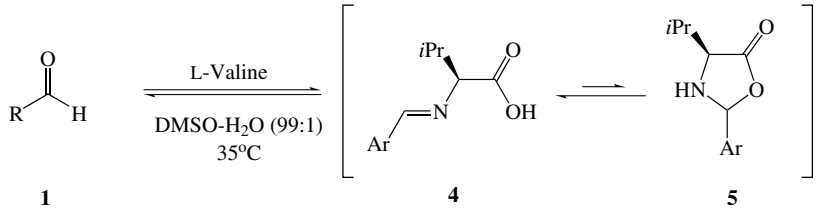
Entry	Solution volume[a] (mL)	H_2O (mmol)	Yield (%)	Ee (%)
1	1	0.55	78	42
2	2	1.1	58	53
3	3	1.6	58	50
4	4	2.2	54	48

[a] Reactions were run in DMSO–H_2O (99:1). Acetone (1.0 mL), 4-nitrobenzaldehyde (1.0 mmol), and L-valine (0.2 mmol).

From the findings above, it is clear that water plays a critical role in the reaction. Thus, preliminary NMR investigations were performed for the purpose of examining the water effect and for a better understanding of the efficiency of valine. It is well known that amino acids can condense with aliphatic and aromatic aldehydes to form oxazolidinones and other compounds, including products of self-aldolization. In particular aromatic aldehydes react with acyclic amino acids in DMSO to produce the corresponding imine.[11]

In a ^1H NMR study of valine catalyzed aldol reaction of acetone with 4-nitrobenzaldehyde in DMSO-d_6–H_2O (99:1), under standard conditions, we observed the coexistence of an aldehyde along with a compound displaying a single resonance at δ 8.49, and two doublets at δ 8.31 and 8.03 ppm. The latter ^1H NMR peaks were attributed to an imine resulting from the condensation of valine with aldehyde as already suggested.[11] Similarly and in the absence of acetone, the ^1H NMR experiment in DMSO-d_6–H_2O (99:1) showed that imine **4** was easily formed at rt, as outlined in Scheme 3. However, although oxazolidinone is the major adduct in the case of proline, we were unable to observe any formation of oxazolidinone **5**.[11]

The formation of the imine could be regarded as a parasitic equilibrium, which results in the poisoning of the catalyst thus causing lower reaction rates (Scheme 3). At the same time, water effects shift this equilibrium to the formation of the aldehyde and regeneration of the amino acids that still allow for catalysis. This might also explain why phenylalanine was still producing aldol adduct besides the imine, although in a much lower rate when compared to valine. Conversely, the lower enantioselectivity of phenylalanine may be attributed to



1 **4** **5**

Scheme 3.

racemization during imine formation as previously reported.[11a] Although not observed, the carbinolamine, enamine, and hydrate could also be formed at lower concentrations.

Furthermore, participation of water at low concentration, that is, hydrophobic conditions, can be characterized in providing a proton shuffle through a hydrogen bond network that might enable imine–enamine tautomerization and aldehyde activation. This situation is facilitated by polar and hydrogen bond acceptors DMSO or DMF.

3. Conclusion

In summary, we have demonstrated that water participates in the efficient catalysis of aldol reactions using primary amino groups of amino acids. This suggests a new strategy in the design of new bioorganic catalysts for direct asymmetric aldol reactions. The results herein suggest that water plays a more intricate role. Further investigations of the solution structures in order to identify the factors that facilitate the imine–enamine tautomerization of primary amines, are currently in progress in our laboratory.

Acknowledgements

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