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Asymmetric aldol reactions catalyzed by the promiscuous aldo–ketoreductase enzyme

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ABSTRACT

The promiscuous aldo–ketoreductase (AKR) enzyme is used as a sustainable biocatalyst for the first time to catalyze asymmetric aldol reactions in aqueous medium. The reactions between aromatic aldehydes and cyclic/acyclic ketones give the corresponding products in moderate yields and enantioselectivities in the presence of water. The influence of solvents, the mole ratio of substrates, and enzyme concentration are investigated. The mechanism of the AKR1A1-catalyzed aldol reaction is also discussed.

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Biocatalysis has emerged as an elegant and green tool for modern organic synthesis due to its high efficiency, good selectivity, and environmental acceptability.[1] Although an enzyme is capable of catalyzing a specific reaction effectively, some unexpected experimental results have indicated that many enzymes are catalytically promiscuous.[2] Promiscuous enzymes have flourished as popular asymmetric biocatalysts for a range of organic reactions in recent years.[3–5] These types of enzymes can catalyze different chemical transformations of natural and non-natural substrates.[6–8] Promiscuous enzymes have been used to catalyze the formation of carbon–carbon and carbon–heteroatom bonds via classic and widely used organic reactions.[9] The aldol reaction is a fundamental organic reaction for the construction of C–C bonds, which has been seldom mentioned in published studies of promiscuous biocatalysts.[10–13] Generally, aldolases (class I and II) and aldolase antibodies (38C2 and 33F12) are the most common enzymes used in the catalysis of aldol reactions.[14] Promiscuous enzymes have frequently catalyzed Michael, Mannich and Markovnikov additions as well as aldol reactions.[15–19] Asymmetric aldol reactions between wet acetone and aromatic aldehydes catalyzed by a lipase enzyme were reported by Wang.[20] In 2003, Berglund reported the first aldol reaction catalyzed by CAL-B (lipase from *Candida antarctica*).[21]

In this study, we focused on an aldo–ketoreductase (AKR) enzyme in order to investigate its catalytic activity in asymmetric aldol reactions. To the best of our knowledge, aldo–ketoreductase has not been reported as an enzyme for catalyzing carbon–carbon bond-forming reactions. We therefore used commercially available AKR1A1 as an enzyme to catalyze the aldol reaction. There are important tetrad amino acids in the active site of AKR similar to the aldolase enzyme.[22] The positions of Asp 45, Lys80, Tyr50, and His113 in the active site pocket are somehow able to impart catalytic activity. Therefore, this similarity encouraged us to choose AKR as an enzyme for investigation of its catalytic activity in aldol reactions.

Initially, an aldol experiment was carried out in order to investigate the catalytic activity of the promiscuous AKR1A1 enzyme, focusing on its ability to catalyze the reaction between cyclohexanone and 4-nitrobenzaldehyde. The reaction was performed in a mixture of *i*-PrOH/phosphate–sodium buffer (1:1) using *p*-nitrobenzaldehyde (30 mg, 0.198 mmol, 1 equiv), cyclohexanone (23.3 mg, 0.99 mmol, 5 equiv), and AKR1A1 (10 mg). Generally, a higher pH tends to give the product in a better yield, but slightly acidic conditions were beneficial for improving the stereoselectivity.[22] The reactions catalyzed by AKR1A1 were conducted at different pHs (4.0 to 8.0). The results are summarized in Table 1. As expected, the pH had a significant influence on the

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yield and stereoselectivity. For pH = 5.0 and 5.5, the corresponding aldol product was obtained in moderate yield (entries 3 and 4, 51% and 60%) and moderate enantioselectivity (39% and 40% ee). At pH = 8.0, the reaction became almost a base-catalyzed process, therefore, extremely low enantioselectivity (entry 9, 4% ee) and a higher yield (95%) were obtained. Control experiments showed that in the absence of AKR1A1, at pH = 5.5, no reaction took place under these conditions (entry 10). Finally, a pH of 5.5 was chosen as the optimum pH in terms of the efficiency and selectivity of the AKR1A1-catalyzed process.

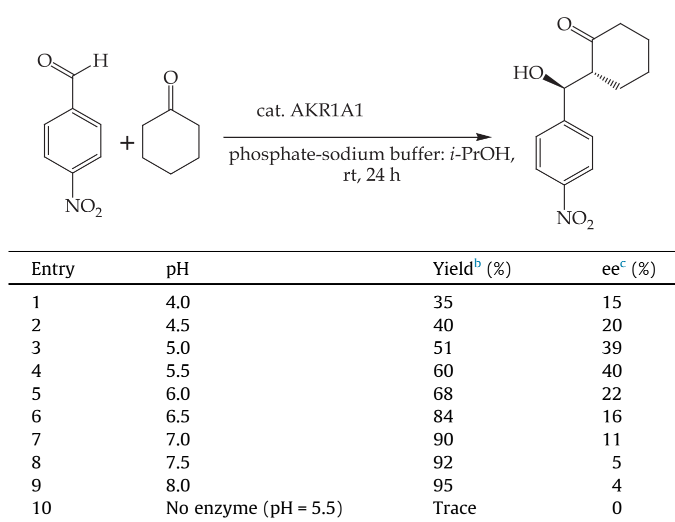
To further optimize the reaction conditions, the effect of the mole ratio of the substrates on the AKR1A1-catalyzed aldol reaction was investigated. The results indicated that this factor had a very significant impact on the yield and ee, but changes in the diastereoselectivity were less obvious (Table 2). Consequently, the mole ratio of substrates, 4-nitrobenzaldehyde/cyclohexanone = 1:5 (entry 4), was chosen as the optimum ratio for further exploration.

The influence of the catalyst loading on the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone was next investigated. The results showed that an increase in the AKR1A1 loading (from 2 mg to 20 mg) led to a rise in the yield (from 10% to 69%), with a slight increase in the selectivity (from 65:45 to 85:15 dr, and from 39% to 43% ee) (Table 3). Thus, an enzyme concentration of 10 mg/mL was chosen as the optimum for further investigation.

The reaction medium has been recognized to be one of the most important factors influencing enzymatic reactions. Thus, the aldol reaction in various solvents in the presence of a few drops of 1 M benzoic acid (BA) as an additive for adjustment of the pH was investigated. The results are shown in Table 4.

The results clearly indicated that the reaction medium significantly influenced the catalytic activity and stereoselectivity of AKR1A1. Generally, the aldol reaction in high polarity solvents such as DMF and NMP gave higher yields (entries 1 and 2) than those in low polarity solvents such as $CHCl_3$ (entry 4). Interestingly, $CHCl_3$ and *i*-PrOH produced very poor enantiomeric excesses and yields when they were used separately as the solvent. However, higher enantioselectivities and yields were obtained by adding an equal volume of H_2O to these two solvents (entries 6 and 7).

Table 1
Effect of pH on the aldol reaction catalyzed by AKR1A1 in phosphate–sodium buffer/*i*-PrOH[a]



Entry	pH	Yield[b] (%)	ee[c] (%)
1	4.0	35	15
2	4.5	40	20
3	5.0	51	39
4	5.5	60	40
5	6.0	68	22
6	6.5	84	16
7	7.0	90	11
8	7.5	92	5
9	8.0	95	4
10	No enzyme (pH = 5.5)	Trace	0

[a] Reaction conditions: *p*-nitrobenzaldehyde (0.198 mmol, 1 equiv), cyclohexanone (0.59 mmol, 3 equiv), AKR1A1 (10 mg), phosphate–sodium buffer/*i*-PrOH (1:1, 1 mL, pH = 4.0–8.0), rt, 24 h.
[b] Isolated yield after silica gel column chromatography.
[c] ee was determined by HPLC using a chiral OD-H column.

Table 2
Effect of the mole ratio of the substrates on the model aldol reaction[a]

Entry	Mole ratio[b]	Yield[c] (%)	dr[d] (*anti*:*syn*)	ee[d] (%) (*anti*)
1	1:1	15	82:18	20
2	1:2	55	84:16	33
3	1:3	60	85:15	40
4	**1:5**	**68**	**85:15**	**43**
5	1:10	66	86:14	43

[a] Reaction conditions: 4-nitrobenzaldehyde (0.1 mmol), cyclohexanone (0.1, 0.2, 0.3, 0.5, 1.0 mmol), AKR1A1 (10 mg), phosphate–sodium buffer/*i*-PrOH (1:1, 1.0 mL, pH = 5.5), rt, 24 h.
[b] Mole ratio of 4-nitrobenzaldehyde/cyclohexanone.
[c] Isolated yield.
[d] ee and dr were determined by HPLC using a chiral OD-H column.

Table 3
Effect of enzyme loading on the aldol reaction

Entry	Cat. loading[a] (mg)	Yield[b] (%)	dr[c] (*anti*:*syn*)	ee[c] (%), (*anti*)
1	0	NR	–	–
2	2	10	65:45	33
3	5	45	75:25	39
4	**10**	**68**	**85:15**	**43**
5	15	68	85:15	43
6	20	69	84:16	43
7	30	68	84:16	43

[a] Reaction conditions: 4-nitrobenzaldehyde (0.1 mmol), cyclohexanone (0.5 mmol), AKR1A1 (0, 2, 5, 10, 15, 20, 30 mg), phosphate–sodium buffer/*i*-PrOH (1:1, 1.0 mL, pH = 5.5), rt, 24 h.
[b] Isolated yield.
[c] ee and dr were determined by HPLC using a chiral OD-H column.

Table 4
Effect of the solvent on the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone catalyzed by AKR1A1[a]

Entry	Solvent	Yield[b]	ee[c] (%)	dr[d] (*anti*:*syn*)
1	NMP	50	39	82:18
2	DMF	50	39	82:18
3	MeCN	50	34	86:14
4	$CHCl_3$	20	20	73:27
5	*i*-PrOH	25	26	85:15
6	**$CHCl_3$:H_2O (1:1)**	**65**	**43**	**91:9**
7	*i*-PrOH/H_2O (1:1)	52	37	82:18

[a] Reaction conditions: 4-nitrobenzaldehyde (0.1 mmol), cyclohexanone (0.5 mmol), AKR1A1 (10 mg), solvent (1.0 mL, pH = 5.5), rt, 24 h.
[b] Isolated yield.
[c,d] ee and dr were determined by HPLC using a chiral OD-H column.

Among the surveyed solvents, the best result was obtained with a mixture of $CHCl_3$:H_2O (1:1, entry 6). In order to pursue asymmetric aldol reactions, $CHCl_3$:H_2O (1:1) was chosen as the reaction medium for further investigation.

Next, the substrate scope and limitations were investigated using different aromatic aldehydes and cyclohexanones in the AKR1A1-catalyzed asymmetric aldol reaction. The results are given in Table 5. It can be seen that a wide range of aromatic aldehydes reacted with cyclic and acyclic ketones under the optimized conditions. The electronic and steric effects of the substituents on the aromatic aldehydes were also investigated.

In general, the aldol products were obtained in higher yields when the ketone was reacted with aromatic aldehydes bearing an electron-withdrawing substituent (entries 1–7). In contrast, only a trace amount of product was obtained when 4-methoxybenzaldehyde bearing an electron-donating group was used (entry 8). This can be explained by the fact that electron-withdrawing groups enhance the electrophilicity of the carbonyl group, which

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