The small peptide-catalyzed direct asymmetric aldol reaction in water†

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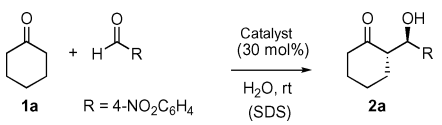
Simple modular di- and tripeptides with a primary amine at the *N*-terminus catalyze the aqueous asymmetric aldol reaction between unmodified ketones and aldehydes to furnish the corresponding β-hydroxy ketones with up to 86% ee in water and 99% ee in aqueos media.

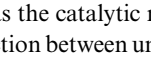
The asymmetric aldol reaction is a powerful method for forming carbon–carbon bonds.[1,2] In Nature, there are two types of aldolase enzymes that catalyze the direct aldol reaction with excellent stereocontrol: class I aldolases employ chiral enamines whereas class II aldolases utilizes chiral Zn enolates as nucleophiles for the stereoselective addition of dihydroxyacetone phosphate (DHAP) to aldehydes.[1] Water is the reaction media for most enzymatic reactions in living systems. Thus, the stereoselective aldol reaction plausibly evolved in aqueous media along with the evolution of aldolase enzymes. In organic synthesis, there are several methods for achieving directed catalytic stereoselective aldol reactions.[2,3] However, methods for catalyzing enantioselective aldol reactions in water are rare.[4] For example, chiral organometallic complexes have been developed that catalyze the asymmetric Mukaiyama-type aldol reaction between activated silyl enol ethers and aldehydes in aqueous media.[5] Moreover, biocatalysts mediate the direct asymmetric aldol reaction with high stereoselectivity in aqueous buffers.[1,6,7] Organocatalysis is an active research area.[8] In this context, proline and its derivatives are excellent catalysts for the direct asymmetric aldol reaction in organic solvent.[9] However, proline and other chiral pyrrolidine derivatives furnish nearly racemic products in water.[10] Moreover, amino acids catalyze the asymmetric dimerization of glycol aldehyde to furnish tetroses with low ees in water.[11] This has led to speculation that amino acid catalysis is a plausible mechanism for the origins of homochirality. We recently found that acyclic amino acids[12a] and small linear peptides[12b] catalyze the direct intermolecular asymmetric aldol reaction with high stereoselectivity in organic solvents. We therefore wanted to expand this concept to water or aqueous media providing for the asymmetric assembly of aldol products under environmentally benign reaction conditions. Moreover, the lessons learnt from these studies would give important information on a molecular level about the evolution of homochirality and catalysis of aldolase enzymes. Herein, we report that small peptides with a primary amine as the catalytic residue, catalyze the asymmetric aqueous aldol reaction between unmodified ketones and aldehydes to furnish the corresponding aldol products with high ees (up to 86% in H_2O, up to 99% in aqueous media). In stark contrast, natural amino acids catalyzed the formation of nearly racemic aldol products, which implies that peptide bond-formation is important for the evolution of high asymmetry in water.

In initial experiments, we screened a variety of natural amino acids, di- and tripeptides for their ability to catalyze the asymmetric aldol reaction between cyclohexanone **1a** (0.75 mmol) and *p*-nitrobenzaldehyde (0.25 mmol) in water (1 mL) and sodium dodecyl sulfate (SDS, 0.25 mmol) (Table 1).

We found a remarkable high difference in stereoselectivity between the small peptide- and amino acid-catalyzed direct aldol reactions: All the peptides tested catalyzed the asymmetric formation of the desired aldol product **2a** with 39–83% ee whereas the simple amino acids catalyzed the formation of small amounts of **2a** with <5% ee. For example, L-valL–L-phe and $(L\text{-ala})_3$ mediated the asymmetric assembly of product **2a** in 47% yield with 3 : 1 dr and 83% ee and 42% yield with 2 : 1 dr and 75% ee, respectively. Moreover, the tripeptide $(L\text{-ala})_3$ catalyzed the asymmetric assembly of **2a** with a higher ee as compared to the dipeptide $(L\text{-ala})_2$ showing the beneficial effect of structural complexity in water. In addition, valine tetrazole **3** catalyzed the asymmetric formation of **2a** with 1 : 1 dr and 67% ee. Hence, converting amino acids to tetrazole derivatives can have a beneficial effect in water as well

Table 1 Examples of screened catalysts for the direct asymmetric intermolecular aldol reaction between **1a** and *p*-nitrobenzaldehyde in water



Entry	Catalyst	Time/h	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	L-val–L-val	76	40	2 : 1	67
2	L-val–L-phe	52	47	3 : 1	83
3	L-val–L-phe	70[d]	70	2 : 1	83
4	L-val–L-ala	96	30	2 : 1	71
5	L-val–L-ala	68	22	2 : 1	70
6	L-val–L-val	68	45	2 : 1	56
7	L-ala–L-ala–L-ala	120	42	2 : 1	75
8	L-ser–L-ala	73	80	2 : 1	39
9	 **3**	96	40	1 : 1	67
10	L-valine	41	20	1 : 1	<5
11	L-proline	42	10	1 : 1	<5
12	L-alanine	163	12	1 : 1	0

[a] Isolated yield after silica-gel column chromatography. [b] *anti* : *syn* ratio as determined by NMR analyses of the crude product. [c] Determined by chiral-phase HPLC analyses. [d] 20 vol% DMF and no SDS.

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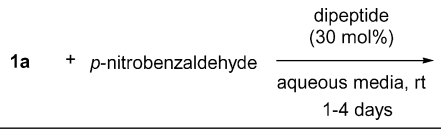
Table 2 The peptide-catalyzed direct intermolecular aldol reaction in different aqueous media



Entry	Catalyst	Solvent	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	L-val–L-phe	Phosphate buffer[d]	48	2 : 1	83
2	L-val–L-phe	NaOAc buffer[e]	27	2 : 1	85
3	L-val–L-phe	H_2O[f]	47	3 : 1	83
4	L-val–L-phe	H_2O[g]	48	3 : 1	86
5	L-val–L-phe	H_2O–DMF, 5 : 1	70	2 : 1	83
6	L-val–L-ala	H_2O–DMF, 1 : 1	67	3 : 1	93
7	L-ala–L-ala	H_2O–EtOH, 1 : 1	72	3 : 1	83
8	L-ser–L-phe	H_2O–MeOH, 1 : 1	90	2 : 1	81
9	L-ala–L-ala	H_2O–NMP, 1 : 1	56	3 : 1	87
10	L-ala–L-ala	H_2O–DMSO, 1 : 1	80	3 : 1	86

[a] Isolated yield after silica-gel column chromatography. [b] *anti* : *syn* ratio as determined by NMR analyses of the crude product. [c] Determined by chiral-phase HPLC analyses. [d] Phosphate buffer, 40 mM, pH 7.2, SDS. [e] NaOAc buffer, 0.1M, pH 4.2, SDS. [f] 1 equiv. SDS. [g] 1 equiv. α-cyclodextrin added.

as in organic solvent.[9o] The addition of a small amount of DMF (20 vol%) instead of SDS increased the yields and ees of **2a**. Thus, we also investigated the peptide-catalyzed direct asymmetric aldol reaction in different aqueous buffer and media (Table 2).

The enantioselectivity of the dipeptide-catalyzed aldol reaction was not affected by performing the reactions in buffered aqueous media and product **2a** was formed with high ees. However, the efficiency of the peptide-catalyzed asymmetric aldol reactions decreased at low pH. Inspired by the pioneering studies of Breslow and co-workers,[13] we also investigated whether the addition of α-cyclodextrin to the peptide-catalyzed asymmetric aldol reaction in water (no SDS) would improve the enantioselectivity by creating a hydrophobic environment (entry 4). In fact, L-val–L-phe–L-ala catalyzed the asymmetric assembly of **2a** with 3 : 1 dr and 86% ee under these reaction conditions. The dipetide-catalyzed direct asymmetric aldol reaction proceeded smoothly in aqueous media and product **2a** was isolated in high yield with 3 : 1 dr and up to 93% ee. Encouraged by these results we also investigated the peptide-catalyzed aqueous asymmetric aldol reaction for a set of different ketones and aldehydes in aqueous media (Table 3).

To our delight, the simple linear peptides catalyzed the asymmetric aldol reactions with DHAP mimetic **1b** and ketones **1** as the donors with high enantioselectivity and furnished the corresponding aldol products **2b**–**e** in 51–83% yield with up to 99% ee. Notably, the small peptides catalyzed the first enantioselective aldol reactions with dihydroxy acetone (DHA) as the donor. For instance, L-val–L-phe catalyzed the asymmetric assembly of aldol product **2e** in 53% yield with 1 : 1 dr and 70% ee (entry 6). In comparison, proline and valine catalyzed the formation of trace amounts of **2e** (<10% ee). Thus, small peptides should be considered for the development of direct asymmetric aldol reactions with DHA as the donor.

Our recent density functional theory (DFT) calculations have shown that the primary amino acids utilize a carboxylic acid-catalyzed enamine mechanism (Fig. 1, **I**).[14]

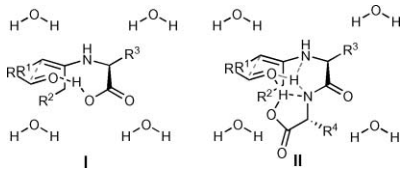
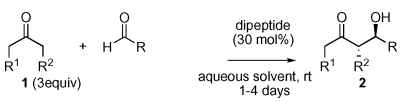


Fig. 1 Plausible transition states I and II for the primary amino acid–dipeptide-catalyzed asymmetric aldol reactions.

The generation of nearly racemic aldol products **2** by amino acid catalysis in water indicates that the H_2O molecules prevent

Table 3 Examples of dipeptide-catalyzed direct intermolecular aldol reactions between different ketones aldehydes in aqueous media



Entry	Dipeptide	Ketone	R	Product	Conditions	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	L-val–L-phe	 1b	4-$NO_2C_6H_4$	 2b	H_2O–DMSO, 1 : 1	51	15 : 1	99
2	L-val–L-phe	**1b**	4-$NO_2C_6H_4$	**2b**	H_2O–MeOH, 1 : 1	83	2 : 1	99
3	L-val–L-val	**1b**	4-$NO_2C_6H_4$	**2b**	H_2O–DMSO, 1 : 1	52	1 : 1	99
4	L-val–L-phe	**1a**	4-ClC_6H_4	 2c	H_2O–MeOH, 1 : 1	65	1 : 1	86
5	L-val–L-phe	**1a**	4-BrC_6H_4	**2d**	H_2O–MeOH, 1 : 1	66	1 : 1	63
6	L-val–L-phe	 1c	4-$NO_2C_6H_4$	 2e	H_2O–DMSO, 1 : 1	53	1 : 1	70
7	L-val–L-val	**1c**	4-$NO_2C_6H_4$	**2e**	H_2O–DMSO, 1 : 1	67	1 : 1	51

[a] Isolated yield after silica-gel column chromatography. [b] *anti* : *syn* ratio as determined by NMR analyses of the crude product. [c] Determined by chiral-phase HPLC analyses.

efficient stabilization of the six-membered transition state by the chiral enamine, which lowers the energy difference between the possible transition states. In contrast, the high enantioselectivity of the small peptide-catalyzed aldol reactions in water suggests that the peptide bond of the natural catalyst is crucial in preserving a stabilized transition state structure, were the *Re*-face of the chiral enamine is approached by the *Si*-face of the acceptor aldehyde (Fig. 1, **II**). This is plausibly accomplished by stabilization of the generated alkoxide of the product by hydrogen bonding by the peptide backbone and the formation of a charge relay system that increases the Brønstedt acidity of the di- and tri-peptides. In fact, a charge relay system is very important in the enamine catalysis of aldolase enzymes.[15]

In summary, we present that small peptides with a catalytic primary amino acid residue at the *N*-terminus catalyze the asymmetric intermolecular aldol reaction between unmodified ketones and aldehydes with high stereoselectivity in water. For example, simple di- and tripeptides catalyzed the asymmetric assembly of the corresponding β-hydroxy ketones in up to 86% ee in water and 99% ee in aqueous media. The high modularity of the small peptides should enable the construction of several novel catalysts by combinatorial techniques for the aqueous asymmetric aldol reaction. The remarkably high difference in stereoselectivity between the peptide and amino acid-catalyzed aqueous aldol reactions suggest that peptide bond-formation was an important step towards the evolution of asymmetric catalysis and homochirality. Moreover, the small peptide-catalyzed aqueous aldol reaction may be of biological significance.[16,17] Further development of environmentally benign asymmetric C–C bond-forming reactions, mechanistic studies and DFT calculations are ongoing.

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