Acyclic amino acid-catalyzed direct asymmetric aldol reactions: alanine, the simplest stereoselective organocatalyst†

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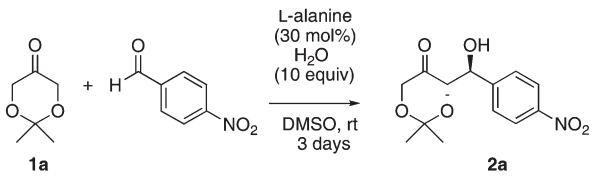
The linear amino acid-catalyzed direct asymmetric intermolecular aldol reaction is presented; simple amino acids such as alanine, valine, isoleucine, aspartate, alanine tetrazole 3 and serine catalyzed the direct catalytic asymmetric intermolecular aldol reactions between unmodified ketones and aldehydes with excellent stereocontrol and furnished the corresponding aldol products in up to 98% yield and with up to > 99% ee.

The direct asymmetric aldol reaction is one of the most important C–C bond-forming reactions in nature, and it is catalyzed by aldolase enzymes with excellent stereocontrol.[1] The enzyme's ability to control the enantioselectivity of the direct aldol reaction has inspired chemists and raised this transformation to prominence in the asymmetric assembly of complex natural products.[2,3] In particular, the development of catalytic stereoselective methods for the asymmetric directed aldol reaction has recently been the subject of intense research.[4] For example, the utilization of organometallic complexes and Lewis bases as catalysts has been highly successful for the asymmetric Mukaiyama-type aldol reaction between activated silyl enol ethers and aldehydes.[5a–g] Furthermore, the enantioselective aldol reaction between unmodified ketones and aldehydes is catalyzed by chiral organometallic complexes.[5h–k] Another approach to the catalysis of the direct asymmetric aldol reaction is the use of aldolase enzymes.[1,6]

Recently, organocatalysis has experienced a renaissance in asymmetric synthesis.[7] In this context, proline and its derivatives have proved to be the best catalysts for the direct intermolecular asymmetric aldol reaction.[8,9] In stark contrast to proline, linear amino acids are considered to be poor or no catalysts for the intermolecular enantioselective aldol reaction between unmodified ketones and aldehydes.[9a–d] However, intramolecular aldol condensations have been mediated by employment of stoichiometric equivalents of phenylalanine together with $HClO_4$ or camphorsulfonic acid.[8] Intrigued by these results and our interest in stereoselective enamine-catalysis,[10] we decided to investigate the possibility of employing linear amino acids as catalysts for the asymmetric aldol reaction between unmodified ketones and aldehydes. Moreover, most natural amino acids and their derivatives are acyclic, and therefore it would be of paramount interest as well as a conceptual advance to enable their use in enamine-catalyzed asymmetric transformations, thus allowing the full exploration of nature's diverse array of amino acids.

Herein, we show that linear amino acids catalyze the direct asymmetric aldol reaction between cyclic ketones and aldehydes with up to > 99% ee. Remarkably, nature's smallest and oldest chiral amino acid catalyzed the aldol reaction with a stereoselectivity that can match the ones of enzymes.[11]

In an initial experiment, we investigated the L-alanine-catalyzed reaction between dihydroxyacetone phosphate mimetic **1a** and *p*-nitrobenzaldehyde in wet DMSO (10 equiv. of water). (Equation 1).[12]



84% yield, 6:1 dr, >99 %ee (1)

To our delight, the desired aldol adduct **2a** was isolated in 84% yield with 6 : 1 dr and > 99% ee. Having achieved this extraordinary result, we decided to screen several natural amino acids for their ability to catalyze the direct aldol reactions in wet DMSO. Thus, cyclohexanone **1b** was allowed to react with *p*-nitrobenzaldehyde in the presence of a catalytic amount of different natural and unnatural linear amino acids (Table 1).

Notably, all the amino acids tested mediated the formation of the desired aldol products under the set reaction conditions and several of the amino acids exhibited excellent stereoselectivity for the transformation. For example, employing L-serine or L-valine as the catalysts for the aldol reactions with cyclohexanone **1b** enabled the isolation of aldol product **2b** in 80% yield with 6 : 1 dr and > 99% ee and 98% yield with 37 : 1 dr and > 99% ee, respectively. In comparison, L-proline furnishes aldol product **2b** with a dr of 2 : 1 and 89% ee.[9c] Importantly, tetrazole **3** derived from L-alanine was an excellent catalyst for the direct asymmetric aldol reaction and enabled the asymmetric formation of **2b** in high yield within 8 h with 14 : 1 dr and > 99% ee. Thus, the efficiency and solubility of the primary amino acids in organic solvents can be significantly improved by converting them to the corresponding tetrazoles.[9m] Moreover, simple chiral primary amino alcohols and amines did also catalyze the direct asymmetric aldol reaction with high *syn*-selectivity. Intrigued by the small size and simplicity of alanine, we decided to further investigate the L-alanine-catalyzed direct intermolecular aldol reaction between a set of different donor ketones **1** and *p*-nitrobenzaldehyde (Table 2). The L-alanine-catalyzed reactions proceeded smoothly and furnished

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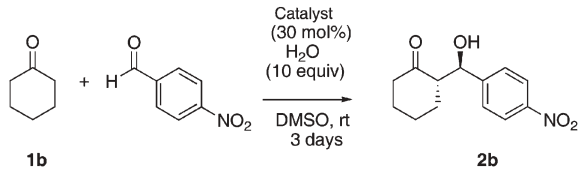
Table 1 Examples of screened catalysts for the direct asymmetric intermolecular aldol reaction between **1b** and *p*-nitrobenzaldehyde

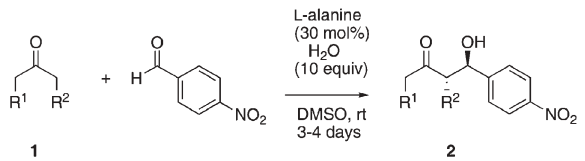


1b **2b**

Entry	Catalyst	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	L-Alanine	95	15 : 1	99
2	L-Aminobutyric acid	88	6 : 1	92
3	L-Valine	98	37 : 1	> 99
4	L-Norvaline	79	6 : 1	90
5	L-Alaninol	91[d]	1 : 2	46
6	L-Arginine	62	1 : 1	4
7	L-Aspartate	75	5 : 1	> 99
8	(*R*)-Methylbenzylamine	94[d]	1 : 15	24
9	L-Isoleucine	82	10 : 1	> 99
10	L-Serine	80	6 : 1	> 99
11	L-Alanine tetrazoles	84[e]	14 : 1	> 99

[a] Isolated yield after silica-gel column chromatography. [b] *anti* : *syn* ratio as determined by NMR analyses. [c] Determined by chiral-phase HPLC analyses. [d] Reaction time was 48 h. [e] Reaction time was 8 h.

Table 2 The alanine catalyzed direct intermolecular aldol reactions with different ketones



1 **2**

Entry	Ketone	Product	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	**1a**	**2a**	84	6 : 1	> 99
2	**1b**	**2b**	95	15 : 1	99
3	**1c**	**2c**	56	3 : 1	75
4	**1d**	**2d**	80	16 : 1	92

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

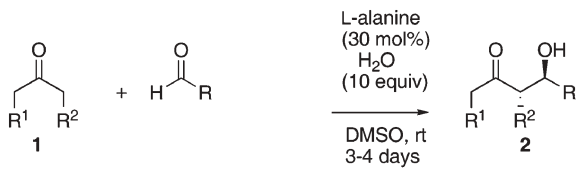
the desired aldol products **2a–d** in good yield with up to > 99% ee. In particular, the L-alanine mediated aldol reactions with cyclic ketones **1a–b** and **1d** as donors proceeded with high chemo-, diastereo- and enantioselectivity. Moreover, the L-alanine-catalyzed direct asymmetric aldol reactions with acyclic nonsymmetric ketone **1c** exclusively furnished regioisomer **2c** in 56% yield with 75% ee. The opposite enantiomer of the aldol products **2** was obtained by employing the acyclic D-amino acid as the catalyst. Furthermore, the reaction proceeded with excellent chemoselectivity and no elimination product was observed. The L-alanine-catalyzed asymmetric aldol reaction between different ketones and acceptor aldehydes was also investigated (Table 3).

The L-alanine-catalyzed asymmetric aldol reaction between unmodified ketones **1a** or **1b** and different aromatic aldehydes proceeded smoothly furnishing the desired aldol adducts **2** with up to > 19 : 1 dr and > 99% ee. For instance, ketone products **2e** and carbohydrate **2h** were isolated in 75% yield with 6 : 1 dr and > 99% ee and 41% yield with > 19 : 1 dr and 99% ee, respectively. These results demonstrate that a cyclic five-membered structural motif of the amino acid derivative is not essential to catalyze the direct asymmetric aldol reaction between ketones and aldehydes with high stereoselectivity.

The stereochemistry of the β-hydroxy group of the aldol adducts **2** derived by linear L-amino acid catalysis was *R* as determined by chiral-phase HPLC analysis, optical rotation and comparison with the literature.[9] The relative stereochemistry of the cyclic aldol products **2** was *anti* as determined by NMR spectroscopy and comparison with the literature.[9] Based on the absolute and relative configuration of aldol products **2**, we propose that the L-alanine and linear amino acid-catalyzed direct asymmetric aldol reactions between ketones and aldehydes occurred *via* a plausible six-membered chair-like transition-state **I**, where the *Re*-face of the catalytically generated chiral enamine is approached by the *Si*-face of the acceptor aldehyde (Fig. 1).[13]

Furthermore, the beneficial effect of water in the L-alanine and linear amino acid-catalyzed asymmetric aldol reaction is due to improved catalyst turnover *via* faster hydrolysis of the intermediates of the enamine catalytic cycle, as well as the suppression of catalyst inhibition.[14]

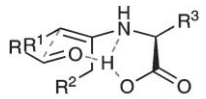
Table 3 Examples of different alanine-catalyzed direct asymmetric aldol reactions



1 **2**

Entry	Ketone	R	Product	Yield (%)[a]	Dr[b]	Ee (%)[c]
1	**1a**	4-CNC_6H_4	**2e**	75	6 : 1	> 99
2	**1a**	4-BrC_6H_4	**2f**	77[d]	6 : 1[d]	97[d]
3	**1a**	4-ClC_6H_4	**2g**	75[d]	5 : 1[d]	98[d]
4	**1a**	CH_2OBn	**2h**	41	> 19 : 1	99
5	**1b**	4-BrC_6H_4	**2i**	44	17 : 1	> 99
6	**1b**	4-ClC_6H_4	**2j**	42	18 : 1	> 99

[a] Isolated yield after silica-gel column chromatography [b] *Anti* : *syn* ratio as determined by NMR analyses [c] Determined by chiral-phase HPLC analyses [d] 5 equiv. water was used



I

Fig. 1 Plausible transition state **I** for the primary amino acid-catalyzed asymmetric aldol reactions between ketones and aldehydes.

In summary, we have demonstrated that linear amino acids and their derivatives can be of synthetic use as catalysts for the direct asymmetric intermolecular aldol reaction. For example, alanine, valine, aspartate, isoleucine, alanine tetrazole **3** and serine catalyzed the direct asymmetric aldol reactions with excellent stereoselectivity, and furnished the corresponding β-hydroxy ketones in high yield and up to > 99% ee. The linear amino acid- and amine-catalyzed reactions are accelerated by water, and are inexpensive, operationally simple and environmentally benign. Importantly, our study demonstrates that a cyclic five-membered ring motif in the amino acid catalyst is not essential for achieving high asymmetric induction of the aldol products. Thus, several simple linear natural and nonproteogenic amino acids and their derivatives can be used as catalysts for this important asymmetric reaction, which will dramatically expand the structural diversity that can be utilized in the design of novel organocatalysts. In fact, a simple α-methyl group of an amino acid is enough to reach the excellent stereoselectivity of natural aldolase enzymes. Further expansion of the use of linear amino acids and their derivatives in organocatalytic asymmetric C–C bond-forming reactions, mechanistic studies and density functional theory calculations is ongoing.

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