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Direct Asymmetric Intermolecular Aldol Reactions Catalyzed by Amino Acids and Small Peptides

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Abstract: In nature there are at least nineteen different acyclic amino acids that act as the building blocks of polypeptides and proteins with different functions. Here we report that α-amino acids, β-amino acids, and chiral amines containing primary amine functions catalyze direct asymmetric intermolecular aldol reactions with high enantioselectivities. Moreover, the amino acids can be combined into highly modular natural and unusual small peptides that also catalyze direct asymmetric intermolecular aldol reactions with high stereoselectivities, to furnish the corresponding aldol products with up to >99% *ee*. Simple amino acids and small peptides can thus catalyze asymmetric aldol reactions with stereoselectivities matching those of natural enzymes that have evolved over billions of years. A small amount of water accelerates the asymmetric aldol reactions catalyzed by amino acids and small peptides, and also increases their stereoselectivities. Notably, small peptides and amino acid tetrazoles were able to catalyze direct asymmetric aldol reactions with high enantioselectivities in water, while the parent amino acids, in stark contrast, furnished nearly racemic products. These results suggest that the prebiotic oligomerization of amino acids to peptides may plausibly have been a link in the evolution of the homochirality of sugars. The mechanism and stereochemistry of the reactions are also discussed.

Keywords: aldol reaction · amino acids · asymmetric catalysis · ketones · organocatalysis · peptides

Introduction

The direct asymmetric aldol reaction is one of the most important C–C bond-forming reactions in nature, and is catalyzed by aldolase enzymes with excellent stereocontrol.[1] The reaction is also believed to have been the key transformation for the prebiotic asymmetric formation of sugars.[2] The goal of controlling the stereochemistry of the asymmetric aldol reaction has inspired chemists and raised this transformation to prominence in the asymmetric assembly of complex natural products.[3,4] In particular, the development of catalytic stereoselective methods for asymmetric directed aldol reactions has recently been the subject of intense research:[5] the utilization of, for example, organometallic complexes and Lewis bases as catalysts has been highly successful in asymmetric Mukaiyama-type aldol reactions between activated silyl enol ethers and aldehydes,[6] whilst furthermore, enantioselective aldol reactions between unmodified ketones and aldehydes are catalyzed with excellent stereoselectivities by chiral organometallic complexes.[7] Another approach to the catalysis of direct asymmetric aldol reactions is the use of aldolase enzymes.[1,8]

Asymmetric organocatalysis is a fast-moving research field.[9] In this context, proline and its derivatives have proven to be efficient catalysts for direct intermolecular asymmetric aldol reactions.[10,11] In stark contrast with proline, linear amino acids are considered to be poor or no catalysts for intermolecular enantioselective aldol reactions between unmodified ketones and aldehydes,[11a–d] though intramolecular aldol condensations have been mediated by the utilization of stoichiometric equivalents of acyclic amino acids together with $HClO_4$ or camphorsulfonic acid.[10] Moreover, N-terminal prolyl peptides have been used as asymmetric catalysts for direct enantioselective intermolecular aldol reactions.[12] Oligopeptides and their derivatives have the advantage of allowing the generation of structural diversity and functionality and the employment of combinatorial techniques.[13,14] However, small peptides with acyclic

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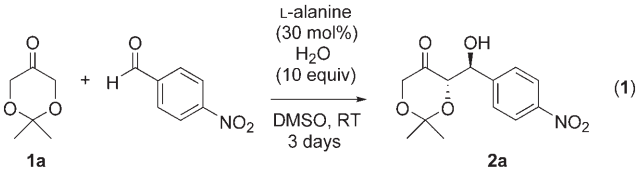
amino acid residues at their N-termini are not believed to catalyze asymmetric aldol reactions. A dramatic increase in potential catalyst structures would thus occur if acyclic amino acids and small modular peptides N-terminated with acyclic amino acids were indeed found to be able to catalyze direct intermolecular asymmetric aldol reactions between ketones and aldehydes. For example, there are 19 natural amino acids containing a primary amine function that can be combined to produce 19^2 (>361) and 19^3 (>6859) different di- and tripeptides, respectively. Moreover, proteinogenic acids, β-amino acids, and acyclic chiral amines could also be used to expand the structural variety further. Intrigued by this tremendous potential structural diversity and motivated by our interest in stereoselective organocatalysis,[15] we most recently found that acyclic amino acids and small modular peptides can catalyze direct intermolecular asymmetric aldol reactions with excellent stereoselectivities.[16] In addition, we also found that ancient oligopeptides catalyze the asymmetric formation of sugars under prebiotic conditions.[16b] Here we describe: 1) structure–activity relationships of acyclic amino acids, acyclic amino acid N-terminated peptides, and their derivatives, 2) the synthetic scope of catalysis by acyclic amino acids, acyclic chiral amines, and small modular peptides in direct asymmetric aldol reactions, 3) catalysis in aqueous media and water, and 4) studies concerning the reaction mechanism.

Results and Discussion

During our studies of amino acid catalyzed de novo synthesis of ketoses we most recently found that (*S*)-proline-mediated aldol reactions with dimethyl-1,3-dioxan-5-one (**1a**) were significantly accelerated by water,[11o] and so we decided to investigate asymmetric aldol reactions catalyzed by acyclic amino acids and modular small peptides in wet organic solvents. In an initial experiment, we investigated the reaction between the dihydroxyacetone phosphate mimetic **1a** (1.5 mmol) and *p*-nitrobenzaldehyde (0.5 mmol) in wet DMSO (2.0 mL + 90 μL H_2O) [Eq (1)].

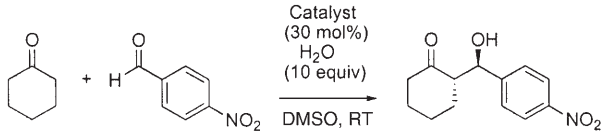


1a **2a** (1)

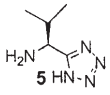
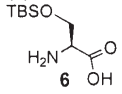
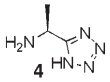
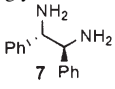
84% yield, 6:1 d.r., >99% *ee*

Remarkably, the desired aldol adduct **2a** was isolated in 84% yield with 6:1 d.r. and >99% *ee*. Inspired by the excellent stereoselectivity of this reaction, we decided to screen several acyclic amino acids and chiral amines for their ability to catalyze the direct aldol reaction between cyclohexanone (**1b**) and *p*-nitrobenzaldehyde in wet DMSO (Table 1).

Table 1. Asymmetric aldol reactions catalyzed by acyclic amino acids and chiral amines.



1b **2b**

Entry	Catalyst	Time [h]	Yield[a] [%]	d.r.[b]	*ee* [%][c]	Entry	Catalyst	Time [h]	Yield[a] (%)	d.r.[b]	*ee*[c] (%)
1	(*S*)-alanine	72	95	15:1	92	14	*N*-methyl-(*S*)-valine	92	trace	1:1	−14
2	(*S*)-α-aminobutyric acid	72	88	6:1	92	15	(*S*)-histidine	72	60	4:1	71
3	(*S*)-valine	72	98	37:1	>99	16	(*S*)-phenylalanine	48	70	3:1	73
4	(*S*)-norvaline	72	79	6:1	90	17	β-alanine	48	35	3:1	–
5	(*S*)-alaninol	72	91	1:2	46	18	(*S*)-threonine	53	80	8:1	98
6	(*S*)-arginine	72	62	1:1	4	19	(*S*)-tyrosine	53	45	3:1	31
7	(*S*)-aspartate	72	75	6:1	63	20	(*S*)-α-methylvaline	310	62	1:1	−4
8	 **3**	72	94	1:15	24	21	 **5**	23	70	16:1	98
9	(*S*)-isoleucine	72	82	10:1	>99	22	(*S*)-methionine	48	87	7:1	88
10	(*S*)-serine	72	88	7:1	80	23	 **6**	68	80	4:1	63
11	 **4**	8	60	10:1	92	24	((*S*)-cysteine)$_2$	16	95	2:1	32
12	(*S*)-leucine	51	60	10:1	92	25	glycine	72	90	10:1	–
13	(*S*)-lysine	48	74	1:1	84	26	 **7**	72	23	2:1	12

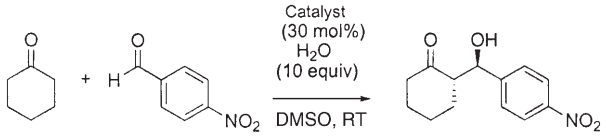
[a] Yield of isolated product yield after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR analysis of the crude product. [c] The *ee* of **2b** was determined by chiral-phase HPLC analyses.

To our delight, we found that several simple natural and nonproteinogenic amino acids catalyzed the reaction with excellent enantioselectivities, with alanine, valine, isoleucine, leucine, and threonine, for example, catalyzing the asymmetric assembly of β-hydroxyketone **2b** with >90% *ee*. The aromatic amino acids phenylalanine and histidine also mediated the asymmetric aldol reaction with good enantioselectivity, whereas tyrosine catalyzed the asymmetric formation of **2b** with low stereoselectivity. In stark contrast with the cysteine dimer, the sulfide-containing amino acid methionine mediated the asymmetric assembly of **2b** in high yield and with high enantioselectivity (Table 1, entries 22 and 24). The basic amino acid arginine catalyzed the formation of nearly racemic **2b**, whilst the acid-functionalized amino acid aspartate catalyzed the asymmetric formation of **2b** with good enantioselectivity (Table 1, entries 6 and 7). In addition, the asymmetric aldol reaction with lysine and serine as the catalysts furnished **2b** in high yields and with good *ee*s (Entries 10 and 13). The trend from our studies is that employment of small aliphatic α-amino acids as asymmetric catalysts gives high asymmetric induction. In addition, amino acids containing an acid functionality or a β-hydroxy group are good catalysts. Aromatic amino acids can also catalyze the stereoselective aldol reaction with high enantioselectivity and should therefore be considered as catalysts, whilst *N*-methylated valine was a poor catalyst under our reaction conditions, giving *ent*-**2b** with low enantioselectivity (Table 1, entry 14). The significant difference in reactivity and stereoselectivity between valine and *N*-methylated valine is plausibly due to steric effects in the enamine formation between the *N*-methylated amino acid and cyclohexanone **1b** and in the transition states.

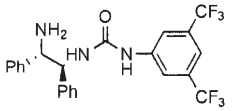
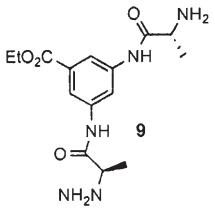
Moreover, the intermolecular aldol reaction was also mediated by linear amino alcohols and chiral amines, although the enantioselectivities were low. The simple chiral amine **3** mediated the stereoselective aldol reaction with excellent *syn* diastereoselectivity (Table 1, entry 8), indicating that simple acyclic chiral amines might be excellent catalysts for the development of *syn*-selective intermolecular aldol reactions. Notably, the strategy of converting the acid moieties of the amino acids into tetrazoles increased the reactivities and solubilities of the amino acids:[17] the primary amine tetrazoles **4** and **5**, for example, catalyzed the asymmetric formation of aldol product **2b** in 84% and 70% yields with >99% and 98% *ee*, respectively (Table 1, entries 11 and 21). β-Amino acids also catalyzed the direct intermolecular aldol reaction. Moreover, TBS-protected serine **6** also mediated the asymmetric aldol reaction with good stereoselectivity (Table 1, entry 23).

We also screened several simple small peptides and their analogues for their abilities to catalyze the direct aldol reaction between cyclohexanone (**1b**) and *p*-nitrobenzaldehyde in wet DMSO (Table 2).

Table 2. Direct asymmetric aldol reactions catalyzed by small peptides, dendritic peptides, urea peptides, pseudo peptides, and albumin.



1b **2b**

Entry	Catalyst	Time [h]	Yield[a] [%]	d.r.[b]	*ee* [%][c]	Entry	Catalyst	Time [h]	Yield[a] [%]	d.r.[b]	*ee*[c] [%]
1	(*S*)-ala-(*S*)-ala	24	73	8:1	91	12	$((S)\text{-ala})_4$	72	trace	1:1	67
2	(*S*)-ala-(*S*)-phe	24	70	2:1	93	13	$((S)\text{-ala})_5$	72	trace	1:1	6
3	(*S*)-ala-gly	48	46	4:1	81	14	(*S*)-ala-(*S*)-phenylalaninol	51	45	1:1	25 (52)[d]
4	(*S*)-ala-(*S*)-val	41	87	1:1	87	15	(*S*)-ala-(*S*)- alaninol	19	20	1:2	9
5	(*S*)-val-(*S*)-ala	48	92	1:1	98	16	(*S*)-val-(*S*)- phenylglycinol	51	30	1:12	34 (65)[d]
6	(*S*)-val-(*S*)-val	24	75	1:1	94	17	(*S*)-val-(*R*)- phenylglycinol	26	35	1:1	33 (55)[d]
7	(*S*)-ser-(*S*)-ala	24	55[e]	2:1	92	18	(*S*)-phe-(*S*)-phenylalaninol	19	19	1:2	0 (52)[d]
8	(*S*)-val-(*S*)-phe	24	72	2:1	96	19	albumin	48	65	2:1	10
9	gly-(*S*)-ala	48	65	2:1	11	20	 **8**	54	32	1:1	76
10	β-ala-β-ala	48	45	1:2	–	21	 **9**	57	62	2:1	62
11	(*S*)-ala-(*S*)-ala-(*S*)-ala	72	90	1:2	81						

[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR analysis of the crude product. [c] The *ee* of **2b** was determined by chiral-phase HPLC analyses. [d] The *ee* of the *syn* diastereomer as determined by chiral HPLC analyses. [e] 20 equivalents of H_2O were used.

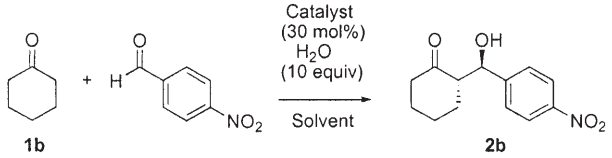
To our delight the efficiencies of the asymmetric aldol reactions improved (relative to those of those catalyzed by the parent acyclic amino acids) when simple dipeptides were used as the catalysts. Simple alanine- and valine-terminated dipeptides, for example, catalyzed the asymmetric formation of **2b** in high yields and with up to 98% *ee*. Peptides containing *N*-terminal glycine moieties also catalyzed the asymmetric aldol reaction, but with lower stereoselectivities than the corresponding peptides with *N*-terminal alanines. We also found that small peptides based on β-amino acids also catalyzed the direct intermolecular aldol reaction. The sizes of the small peptides were important, since the efficiency and stereoselectivity of the aldol reaction decreased with increased number of amino acid residues in the oligopeptide: the enantioselectivities of the asymmetric aldol reactions mediated by oligoalanine catalysts, for instance, were in the order ala-ala > ala-ala-ala > $(ala)_4$ > $(ala)_5$. Notably, the stereoselectivities of the asymmetric aldol reaction decreased dramatically when going from tetraalanine to pentaalanine, which catalytically assembled **2b** with 67% *ee* and 6% *ee*, respectively (Table 2, entries 12 and 13). Interestingly, albumin, a protein available off the shelf, was also able to catalyze the asymmetric aldol reaction and furnished **2b** in high yield and with 10% *ee* (Table 2, entry 19). Pseudo-dipeptides containing alcohol moieties also catalyzed the asymmetric formation of **2b**, though with lower efficiencies and stereoselectivities than the corresponding dipeptides. Notably, (*S*)-val-(*S*)-phenylglycinol catalyzed the reaction with high *syn* diastereoselectivity to give **2b** in moderate yield with 12:1 d.r. and 65% *ee* (Table 2, entry 16). Moreover, the urea-based peptide analogue **8** catalyzed the asymmetric formation of **2b** with high enantioselectivity but in low yield (Table 2, entry 20). Nevertheless, chiral urea derivatives containing catalytic primary amine residues deserve consideration in the design of novel organocatalysts for asymmetric C–C bond-forming reactions that proceed by a catalytic enamine mechanism. The dendritic peptide **9** catalyzed the asymmetric formation of **2b** in good yield and with good enantioselectivity (Table 2, entry 21), so amino acid derived dendrimers should be employable in the design of new interesting catalysts with multiple catalytic sites.

Asymmetric aldol reactions in different solvents: We next decided to employ the simple amino acids valine and alanine as catalysts for the asymmetric assembly of **2b** in different solvents (Table 3).

We found that valine catalyzed the asymmetric intermolecular aldol reaction with high enantioselectivity in all the wet organic solvents tested. The highest reaction rates were achieved in DMSO, NMP, and DMF. Notably, performing the valine- and alanine-mediated reactions in water gave the aldol product **2b** in low yield with less than 6% *ee* (Table 3, entry 12).[18] Sodium dodecylsulfate (SDS) was used as surfactant since it improves the solubilities of the organic substrates in water. However, a change of catalyst to the corresponding valine tetrazole **5** gave **2b** in moderate yield and with 67% *ee* in water (Table 3, entry 21). Notably, increasing the concentration accelerated the reaction and gave **2b** with 99% *ee* (Table 3, entry 22). Moreover, the amino acid-derived tetrazoles were more efficient than the parent amino acids in all the organic solvents tested. We also investigated simple alanine- and valine-derived dipeptides in different solvents (Table 4).

We found that ala-ala catalyzed the asymmetric aldol reaction with high enantioselectivities (89–94% *ee*) in wet polar solvents such as DMSO, MeOH, EtOH, NMP, and DMF. Notably, the dipeptide-mediated aldol reactions in dry DMSO gave **2b** with moderate enantioselectivities: ala-

Table 3. Solvent screen for aldol reactions catalyzed by acyclic amino acids and amino acid tetrazoles.

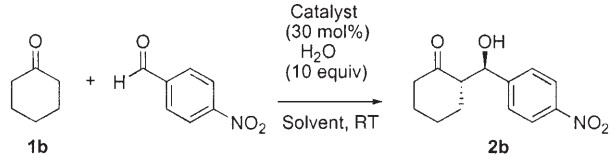


1b 2b

Entry	Catalyst	Solvent	Temp [°C]	Time [h]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	(*S*)-valine	DMSO[d]	RT	47	70	5:1	94
2	(*S*)-valine	DMSO	RT	72	98	37:1	>99
3	(*S*)-valine	$CHCl_3$	RT	147	20	6:1	95
4	(*S*)-valine	dioxane	RT	124	16	4:1	92
5	(*S*)-valine	MeOH	RT	28	25	6:1	95
6	(*S*)-valine	EtOH	RT	52	30	4:1	92
7	(*S*)-valine	NMP	RT	51	65	9:1	95
8	(*S*)-valine	DMF	RT	69	60	8:1	95
9	(*S*)-valine	EtOAc	RT	195	10	4:1	92
10	(*S*)-valine	CH_3CN	RT	144	25	8:1	95
11	(*S*)-valine	H_2O[e]	RT	240	5	2:1	33
12	(*S*)-valine	H_2O[f]	RT	41	20	1:1	-6
13	(*S*)-alanine	DMSO[d]	RT	92	50	3:1	83
14	(*S*)-alanine	DMSO	RT	72	95	15:1	92
15	(*S*)-alanine	DMSO	4	97	55	8:1	92
16	(*S*)-alanine	DMSO	4	24	21	15:1	95
17	(*S*)-alanine	H_2O[f]	RT	163	12	1:1	67
18	(*S*)-**4**	DMSO	RT	8	84	14:1	>99
19	(*S*)-**4**	$CHCl_3$	RT	96	15	6:1	95
20	(*S*)-**5**	DMSO	RT	23	70	16:1	98
21	(*S*)-**5**	H_2O[f]	RT	96	40	1:1	67
22	(*S*)-**5**	H_2O[g]	RT	7	30	11:1	99

[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^1H NMR analysis of the crude product. [c] The *ee* of **2b** was determined by chiral-phase HPLC analyses. [d] No water was added. [e] DMSO (10 vol%) no SDS added. [f] Sodium dodecylsulfate (SDS, 72 mg) added. [g] 5 equivalents of **1b** and 130 μL H_2O.

Table 4. Solvent screen for the simple peptide-catalyzed aldol reactions.



Entry	Catalyst	Solvent	Time [h]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	(*S*)-ala-(*S*)-ala	DMSO[d]	72	51	1:3	55
2	(*S*)-ala-(*S*)-ala	DMSO	24	73	8:1	91
3	(*S*)-ala-(*S*)-ala	MeOH	51	77	3:1	89
4	(*S*)-ala-(*S*)-ala	EtOH	51	72	4:1	92
5	(*S*)-ala-(*S*)-ala	NMP	52	84	3:1	93
6	(*S*)-ala-(*S*)-ala	DMF	48	74	3:1	94
7	(*S*)-ala-(*S*)-ala	DMSO/H_2O 1:1	23	80	3:1	86
8	(*S*)-ala-(*S*)-ala	DMF/H_2O 1:1	67	67	3:1	93
9	(*S*)-ala-(*S*)-ala	DMF/H_2O 1:5	116	25	2:1	70
10	(*S*)-ala-(*S*)-phe	DMF/H_2O 1:5	70	70	2:1	83
11	(*S*)-ala-(*S*)-phe	MeOH/H_2O 1:1	48	90	2:1	81
12	(*S*)-ala-(*S*)-ala	EtOH/H_2O 1:1	68	67	3:1	83
13	(*S*)-ala-(*S*)-ala	NMP/H_2O 1:1	22	56	3:1	87
14	(*S*)-ala-(*S*)-ala	H_2O[e]	68	22	2:1	70
15	(*S*)-val-(*S*)-val	H_2O[e]	76	40	2:1	67
16	(*S*)-val-(*S*)-phe	H_2O[e]	52	47	3:1	83
17	(*S*)-val-(*S*)-ala	H_2O[e]	96	30	2:1	70
18	((*S*)-alanine)$_3$	H_2O[e]	120	42	2:1	75
19	((*S*)-alanine)$_4$	H_2O[e]	72	trace	2:1	71
20	((*S*)-alanine)$_5$	H_2O[e]	72	trace	2:1	58
21	(*S*)-val-(*S*)-phe	H_2O[f]	52	48	3:1	86
22	(*S*)-val-(*S*)-phe	phosphate buffer[g]	120	27	2:1	85
23	(*S*)-val-(*S*)-phe	phosphate buffer[h]	120	27	2:1	85
24	albumin	H_2O[e]	67	27	1:1	9

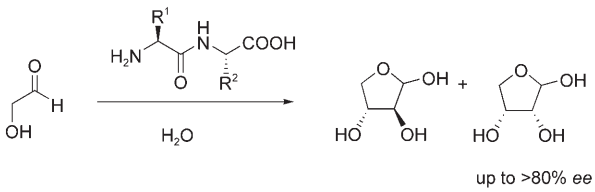
[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR of the crude product. [c] The *ee* of **2b** was determined by chiral-phase HPLC analyses. [d] No water added. [e] Sodium dodecylsulfate (SDS, 72 mg) added. [f] 1 equivalent of α-cyclodextrin added. [g] Phosphate buffer, 40 mM, pH 7.2, SDS. [h] NaOAc buffer, 0.1 M, pH 4.2, SDS.

ala catalyzed the formation of **2b**, for example, with 55% *ee* (Table 4, entry 1), so a small amount of water is important for achieving high enantioselectivity in the dipeptide-catalyzed asymmetric intermolecular aldol reaction. Interestingly, the enantioselectivity of the dipeptide-catalyzed aldol reaction was not affected by performing the reactions in buffered aqueous media, product **2b** being formed with high *ee*s. However, the efficiencies of the peptide-catalyzed asymmetric aldol reactions decreased at low pH.

The simple dipeptide val-phe catalyzed the asymmetric aqueous aldol reaction with the highest enantioselectivity of all the dipeptides tested. The enantioselectivities of the tetra- and pentaalanine-catalyzed aqueous asymmetric aldol reactions were also significantly improved (Table 4, entries 19 and 20): penta-(*S*)-alanine, for example, catalyzed the asymmetric formation of **2b** with 58% *ee* in water, in comparison with 6% *ee* in wet DMSO. The enantioselectivity of the albumin-catalyzed asymmetric aldol reaction was almost the same either in DMSO or in water (**2b**, 9–10% *ee*). Inspired by the pioneering work by Breslow and co-workers,[19] 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: (*S*)-val-(*S*)-phe, for instance, catalyzed the asymmetric assembly of **2a** with 3:1 d.r. and 86% *ee* under these reaction conditions (Table 4, entry 21).

Prebiotic significance: The remarkably large differences in enantioselectivity between the dipeptides and their corresponding parent acyclic amino acids in aqueous media could be important from a prebiotic perspective. In this context, we found that the simple peptides (*S*)-ala-(*S*)-ala and (*S*)-val-(*S*)-val furnished D-erythrose with 48 and 82% *ee*, respectively, under prebiotic conditions [Eq. (2)]. In comparison, (*S*)-ala and (*S*)-val furnished D-erythrose with 5 and 12% *ee*, respectively.[2c]

Oligopeptide formation may thus have played a role in the evolution of homochirality of sugars. For instance, we found that ancient amino acids that are oligomerized to peptides with the help of volcanic gas[20] catalyze the asymmetric aldol



(2)

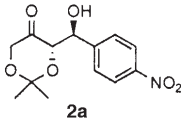
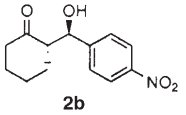
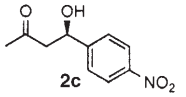
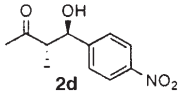
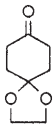
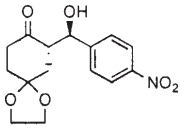
reaction with excellent stereoselectivity under these prebiotic conditions.[21] In a plausible scenario, extraterrestrial amino acids may perhaps have oligomerized to form oligopeptides that enabled the asymmetric formation of sugars with high optical activity.[22]

Substrate scope: We next investigated the substrate scope of asymmetric intermolecular aldol reactions catalyzed by acyclic amino acids and dipeptides in wet DMSO. We found that the (*S*)- and (*R*)-amino acids and their derivatives mediated the enantioselective aldol reactions with cyclohexanones as donors with excellent enantioselectivities, giving the corresponding aldol products **2a**, **2b**, and **2e** with 92–99% *ee* (Table 5).

Moreover, unsymmetrical ketones were good donors and the corresponding aldol products were furnished with excel-

Table 5. Asymmetric aldol reactions with different ketones, catalyzed by acyclic amino acids.

1 2

Entry	Catalyst	Ketone	Prod.	Time [h]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	(*S*)-alanine	**1a**	 **2a**	72	84	6:1	>99
2	(*S*)-valine	**1a**	**2a**	72	86	5:1	>99
3	(*S*)-**4**	**1a**	**2a**	72	70	3.1	>99
4	(*S*)-**5**	**1a**	**2a**	72	87	4:1	>99
5	(*S*)-valine	**1b**	 **2b**	72	98	37:1	>99
6	(*R*)-valine	**1b**	*ent*-**2b**	72	89	16:1	99
7	(*S*)-alanine	 **1c**	 **2c**	120	30[d]		56
8	(*S*)-valine	**1c**	**2c**	120	41[d]		54
9	(*S*)-alanine	 **1d**	 **2d**	72	56	3:1	75
10	(*S*)-alanine	 **1e**	 **2e**	71	80	16:1	92

[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR analysis of the crude product. [c] The *ee* of **2** was determined by chiral-phase HPLC analyses. [d] 5 equivalents of acetone were used. In all other cases 3 equivalents of donors **1** were used.

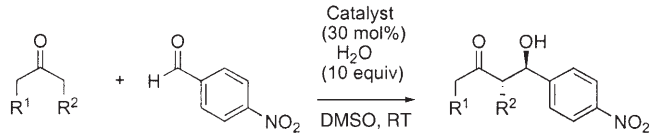
lent regioselectivities in moderate yields and with high enantioselectivities. (*S*)-Alanine, for example, catalyzed the asymmetric formation of **2d** as a single regioisomer in 56% yield with 3:1 d.r. and 75% *ee* (Table 5, entry 9), C–C bond-formation thus having occurred on the methylene carbon of the ketone. Reactions with acetone were slow, giving the corresponding aldol products in low yields but with good enantioselectivities after a reaction time of four days. Hence, cyclohexanones and substituted acyclic ketones are excellent and good donors, respectively, in asymmetric aldol reactions mediated by acyclic amino acids. Similar substrate specificities of the catalysts were observed in the dipeptide- and pseudo-peptide-catalyzed direct asymmetric aldol reactions (Table 6).

In particular, the dihydroxyacetone mimic **1a** was an excellent donor and all the tested di- and pseudo-peptides mediated the asymmetric formation of **2a** with excellent enantioselectivity. Moreover, the dipeptide-mediated asymmetric aldol reactions with hydroxyacetone and dihydroxyacetone proceeded with high enantioselectivities to furnish the aldol products **2f** and **2g** with 75 and 70% *ee*, respectively (Table 6, entries 10 and 11). Notably, the acyclic amino acids only furnished trace amounts of the dihydroxyacetone-derived aldol product **2g**,[18c] so structural complexity gives higher reactivity and stereoselectivity both in organic solvents and in aqueous media. This was also observed in the case of the aldol reactions with acetone, in which the corresponding product **2c** had been formed with high enantioselectivity but in low yield after 48 h. Moreover, small modular peptides catalyze the formation of aldol products **2** with high enantioselectivity in aqueous media under environmentally benign reaction conditions.[23]

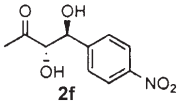
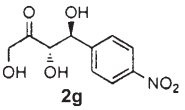
We also investigated direct intermolecular aldol reactions between ketones and different acceptor aldehydes catalyzed by alanine and by alanine tetrazole **4** (Table 7).

The aldol reactions mediated by alanine and by the tetrazole **4** proceeded smoothly, and the aldol products **2h**–**2n**—derived from the dihydroxyacetone mimic **1a** and cyclohexanone (**1b**)—were furnished with excellent enantioselectivities. Remarkably, a simple chiral methyl group is enough to reach the stereoselectivity of aldolase enzymes. The acyclic amino acid-catalyzed aldol reactions with acetone as the

Table 6. Dipeptide- and pseudo-peptide-catalyzed asymmetric aldol reactions with different ketones.

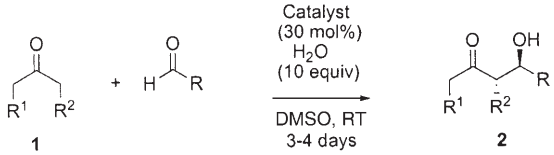


1 2

Entry	Catalyst	Ketone	Prod.	Time [h]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	(*S*)-ala-(*S*)-ala	**1a**	**2a**	48	73	3:1	99
2	(*S*)-ala-(*S*)-phe	**1a**	**2a**	48	88	5:1	99
3	(*S*)-val-(*S*)-phe	**1a**	**2a**	48	89	6:1	99
4	(*S*)-val-(*S*)-val	**1a**	**2a**	48	83	2:1	99
5	(*S*)-val-(*R*)-phealaninol	**1a**	**2a**	48	80	4:1	99
6	(*S*)-val-(*R*)-pheglycinol	**1a**	**2a**	48	82	4:1	99
7	(*S*)-val-(*S*)-phe	**1b**	**2b**	24	72	2:1	96
8	(*S*)-val-(*S*)-phe	**1c**	**2c**	24	25[d]		65
9	(*S*)-val-(*S*)-phe	**1c**	**2c**	48	20[d, e]		71
10	(*S*)-val-(*S*)-phe	 **1f**	 **2f**	48	93	1:1	75
11	(*S*)-val-(*S*)-phe	 **1g**	 **2g**	72	53[f]	1:1[f]	70[f]
12	(*S*)-val-(*S*)-val	**1g**	**2g**	72	67[f]	1:1[f]	51[f]

[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR analysis of the crude product. [c] The *ee* of **2** was determined by chiral-phase HPLC analyses. [d] 5 equivalents of acetone were used. [e] Reaction run in H_2O with SDS. [f] Reaction performed in DMSO/H_2O 1:1.

Table 7. Asymmetric aldol reactions catalyzed by alanine and by alanine tetrazole **4**.



1 2

Entry	Catalyst	Ketone	R	Prod.	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	(*S*)-alanine	**1a**	4-CNC_6H_4	**2h**	84	6:1	>99
2	(*S*)-alanine	**1a**	4-BrC_6H_4	**2i**	77[d]	6:1	97
3	(*S*)-alanine	**1a**	4-ClC_6H_4	**2j**	75[d]	5:1	98
4	(*S*)-alanine	**1a**	CH_2OBn	**2k**	41	>19:1	99
5	(*S*)-alanine	**1a**	Ph	**2l**	68	1:1	94
6	(*S*)-**4**	**1a**	4-CNC_6H_4	**2h**	68	12:1	99
7	(*S*)-**4**	**1a**	4-BrC_6H_4	**2i**	55	13:1	96
8	(*S*)-**4**	**1a**	4-ClC_6H_4	**2j**	50	9:1	95
9	(*S*)-alanine	**1b**	4-ClC_6H_4	**2m**	44	17:1	>99
10	(*S*)-alanine	**1b**	4-BrC_6H_4	**2n**	42	18:1	>99
11	(*S*)-**5**	**1b**	4-BrC_6H_4	**2n**	50[e]	13:1[e]	90[e]
12	(*S*)-alanine	**1c**	Ph	**2o**	39		50

[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR analysis of the crude product. [c] The *ee* of **2** was determined by chiral-phase HPLC analyses. [d] 5 equivalents of H_2O were used. [e] Reaction performed in water (130 μL) with 5 equivalents of **1b**.

donor were slow and furnished the corresponding aldol products in low yields but with good enantioselectivities. The dipeptide-catalyzed asymmetric aldol reactions between ketones **1a** and **1b** and different acceptor aldehydes were also investigated (Table 8).

The dipeptide-catalyzed reactions were more efficient than the alanine- and valine-catalyzed asymmetric aldol reactions, and the corresponding aldol products **2h–2p** were asymmetrically assembled with high enantioselectivity (71–99% *ee*). The peptides complement each other, suggesting that an ideal peptide catalyst for a given pair of substrates might be producible. Interestingly, the dipeptides were more soluble in wet DMSO than the acyclic amino acids.

Aldol reactions mediated by acyclic amino acids and by small peptides were also performed with substituted glyoxylate acceptors, generating aldol products containing *tetra*substituted carbon centers. We found, for example, that valine and valine tetrazole **5** catalyzed the reaction between cyclohexanone **1b** and phenylglyoxylate with excellent stereoselectivity (Table 9).

In particular, valine tetrazole **5** was an excellent catalyst, furnishing the corresponding tertiary aldol product **2q** in 78% yield with >19:1 d.r. and 98% *ee* (Table 9, entry 3). Interestingly, the diastereomer furnished—with excellent diastereoselectivity—by the primary amino acids is the opposite of that obtained when (*S*)-proline is used as the catalyst.[24] The acyclic amino acids and small peptides are also able to catalyze asymmetric self-aldol reactions with aldehydes to furnish the corresponding β-hydroxyaldehydes with moderate to high enantioselectivities [Eq. (2)]. Acyclic amino acids and highly modular peptides and their derivatives can also be employed as catalysts for other asymmetric C–C bond-forming reactions such as the one-pot three-component Mannich[25] [Eq. (3)] and nitro-Michael [Eq. (4)] reactions[26].

Mechanism: A plausible acid-mediated enamine mechanism of the acyclic acid- and dipeptide-catalyzed asymmetric

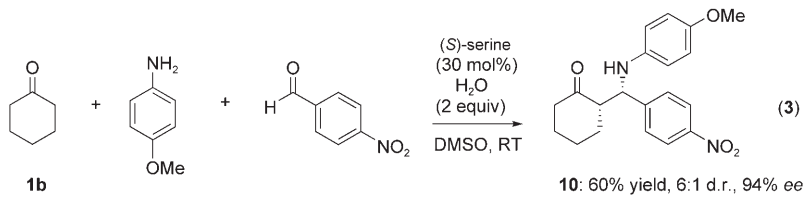
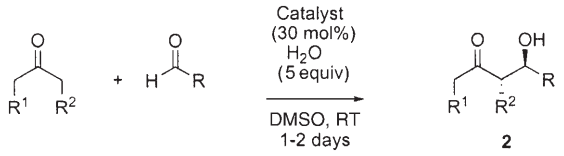


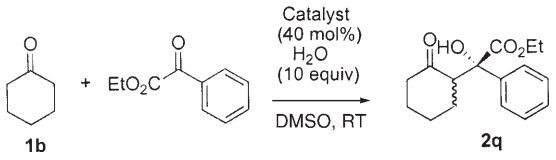
Table 8. Dipeptide-catalyzed asymmetric aldol reactions.



Entry	Catalyst	Ketone	R	Prod.	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	(*S*)-ala-(*S*)-ala	**1a**	4-CNC_6H_4	**2h**	64	13:1	99
2	(*S*)-ala-(*S*)-ala	**1a**	4-BrC_6H_4	**2i**	55	2:1	92
3	(*S*)-ala-(*S*)-ala	**1a**	4-BrC_6H_4	**2i**	48	2:1	78
4	(*S*)-ala-(*S*)-ala	**1a**	4-ClC_6H_4	**2j**	43	1:1	80
5	(*S*)-val-(*S*)-ala	**1a**	4-ClC_6H_4	**2j**	30	1:1	71
6	(*S*)-ala-(*S*)-ala	**1a**	*i*Pr	**2p**	50	2:1	97
7	(*S*)-ala-(*S*)-phe	**1b**	4-BrC_6H_4	**2n**	88	2:1	99
8	(*S*)-ala-(*S*)-ala	**1b**	4-BrC_6H_4	**2n**	86	2:1	96
9	(*S*)-ala-(*S*)-ala	**1b**	4-ClC_6H_4	**2m**	57	2:1	98

[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR analysis of the crude product. [c] The *ee* of **2** was determined by chiral-phase HPLC analyses.

Table 9. Organocatalytic asymmetric aldol reaction between cyclohexanone (**1b**) and phenylglyoxylate.

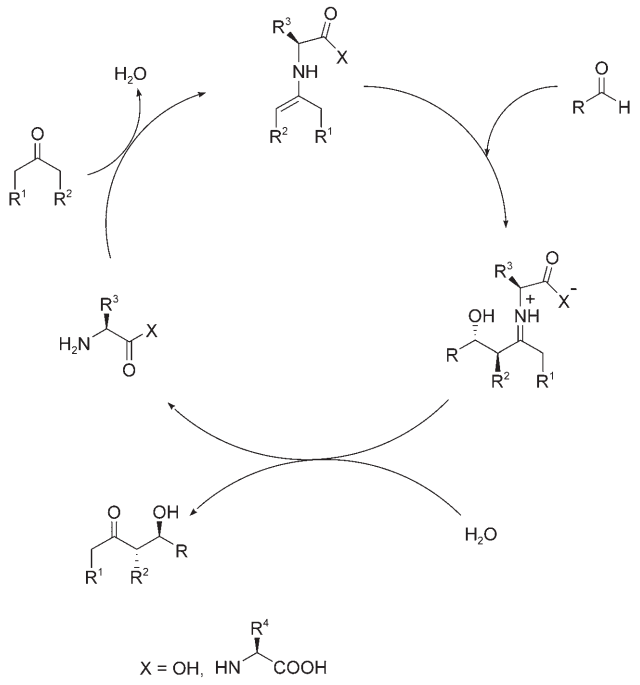


Entry	Catalyst	Time [h]	Yield [%][a]	d.r.[b]	*ee*[c]
1	(*S*)-valine	120	51	6:1	96
2	(*S*)-val-(*S*)-phe	120	60	2:1	68
3	(*S*)-**5**	78	78	>19:1	98

[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR analysis of the crude product. [c] The *ee* of **2p** was determined by chiral-phase HPLC analyses.

intermolecular aldol reaction is depicted in Scheme 1. The ketone donor reacts with the amino acid or dipeptide, resulting in a plausible enamine. Next, the acceptor aldehyde reacts with the chiral enamine to give (after hydrolysis) the enantiomerically enriched aldol product and the catalytic cycle can be repeated. Furthermore, the beneficial effect of water in the acyclic amino acid catalyzed and small peptide-catalyzed asymmetric aldol reaction is plausibly due to improved catalyst turnover due to faster hydrolysis of the intermediates of the enamine catalytic cycle, as well as to the suppression of catalyst inhibition.[27]

We did not observe significant nonlinear effects in the alanine- and valine-catalyzed reactions (Figure 1).[28] However, the reactions display a slightly positive effect at low *ee* of the catalyst and a slightly negative effect at higher *ee*, crossing the straight line. In fact, if a stoichiometric amount of amino acid was employed (100 mol%) the effect would become even higher and the curves would display a significant positive effect crossing the straight line of no linear effect (eutectic point)[29] to become negative again. This phenomenon is the result of the different solubility of the two-enantiomer crystals of the scalemic



Scheme 1. Mechanism of the acyclic amino acid- and dipeptide-catalyzed direct asymmetric aldol reaction.

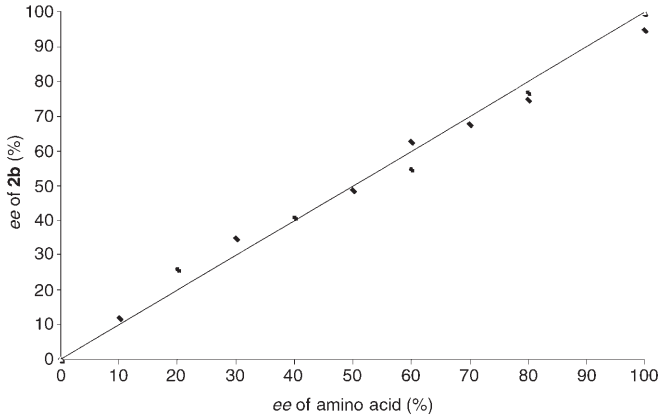


Figure 1. The enantiomeric excess of aldol product **2b** as a function of the enantiomeric excess of the direct asymmetric aldol reaction catalyzed by (*S*)-alanine (◆) and by (*S*)-valine (■).

amino acid catalyst mixture in wet DMSO. We thus believe that a single alanine and valine molecule is involved in the transition state and mechanism, acting as a molecular enzyme. Remarkably, in the case of (*S*)-serine we observed a significant positive nonlinear effect, caused by the different solubility of the two-enantiomer crystals of the scalemic serine catalyst mixture in wet DMSO (Figure 2).[30]

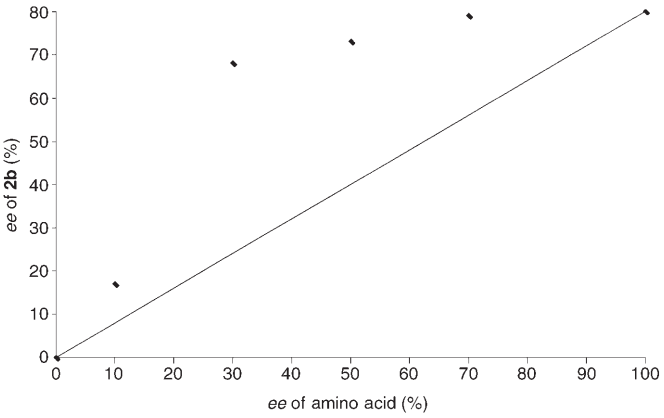


Figure 2. The enantiomeric excess of aldol product **2b** as a function of the enantiomeric excess of the (*S*)-serine-catalyzed (◆) direct asymmetric aldol reaction.

We did not observe any significant nonlinear effect in the (*S*)-ala-(*S*)-ala-catalyzed asymmetric aldol reaction (Figure 3). A single ala-ala molecule is thus involved in the transition state and reaction mechanism, acting as a small enzyme mimic. The higher solubility of the dipeptide relative to alanine and valine may explain the absence of significant nonlinear effects in Figure 2.

We also found that the aldol reaction can be reversible, depending on the catalyst and substrate: the enantioselectivity of the aldol product **2b** obtained with ala-ala catalysis, for example, decreased from 91% *ee* after 48 h to 83% *ee* after 120 h.

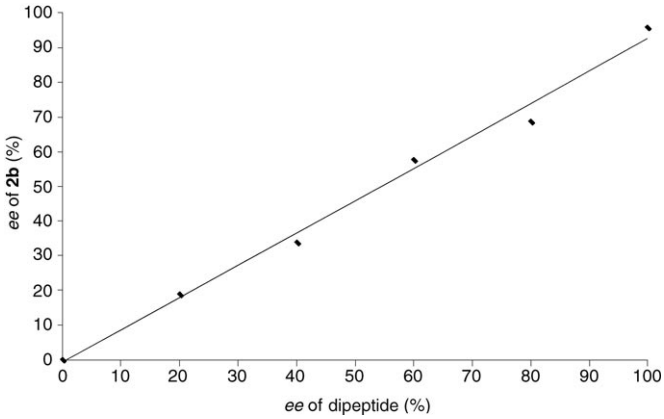
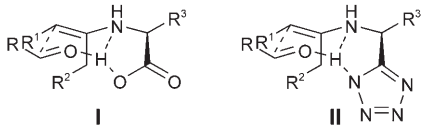


Figure 3. The enantiomeric excess of aldol product **2b** as a function of the enantiomeric excess of the (*S*)-ala-(*S*)-ala-catalyzed (◆) direct asymmetric aldol reaction ($y = 0.93x - 0.71$, $R^2 = 0.992$).

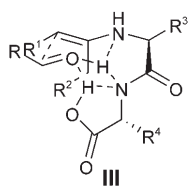
The stereochemistry of the aldol products **2** obtained through acyclic amino acid, primary amine, and peptide catalysis was *R* as determined by chiral-phase HPLC analyses, optical rotation, and comparison with the literature.[11–12,16,23,24] The relative stereochemistry of the cyclic aldol products **2** was *anti*, as determined by NMR analyses and comparison with the literature. From the relative and absolute stereochemistries of the aldol products **2**, we propose the six-membered chair-like transition states **I** and **II** to account for the stereochemical outcomes of the reactions catalyzed by the acyclic amino acids and the tetrazoles **4** and **5**, respectively.



I **II**

Thus, the *Re* face of the acceptor aldehyde is attacked by the *Si* face of the chiral enamine to give the *anti*-aldol product **2**. In addition, density functional theory (DFT) calculations for the alanine-catalyzed aldol reactions are in accordance with our suggested carboxylic acid catalyzed enamine mechanism and transition state **I** for the acyclic amino acid-mediated aldol reaction.[27,31] From the absolute and relative stereochemistries of the β-hydroxy ketones **2**, we propose transition state **III** to account for the stereochemical outcome of the dipeptide catalyzed reaction.

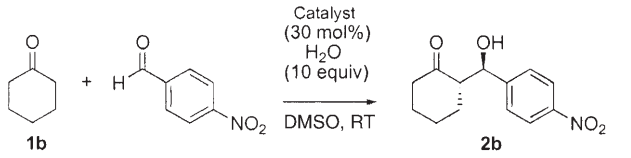
Transition state **III**, in which the *Re* face of the chiral enamine is approached by the *Si* face of the acceptor aldehyde, is also a plausible six-membered cyclic transition state in which the stabilization of the generated alkoxide of the product is accomplished by hydrogen bonding by the peptide



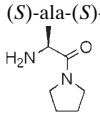
III

backbone and the formation of a charge relay system that increases the Brønsted acidity of the dipeptides. In fact, a charge relay system is very important in the enamine catalysis of aldolase enzymes.[32] In addition, we showed that proton transfer from the carboxy group and hydrogen bond activation, which is facilitated by the presence of a small amount of water, were important to achieve high asymmetric induction (Table 10, Figure 4). The higher enantioselectivities observed for the dipeptide-catalyzed reactions with acyclic ketones, relative to those seen with the parent amino acids, may be explained in terms of assistance by the peptide backbone in the stabilization of transition state **III**. Moreover, the stereochemistry of the dipeptide's two stereocenters affects the enantioselectivity of the reaction: gly-(*S*)-alanine, for example, catalyzed the asymmetric formation of **2b** with 11% *ee*. Thus, the stereocenter of the *N*-terminal acyclic amino acid influences and directs most of the stereochemistry. Nevertheless, the remote stereocenter of the *C*-terminal amino acid of the dipeptide can provide asymmetric induction in transition state **III**, which consequently gives optically active aldol products. Moreover, the change from (*S*)-ala-(*S*)-ala to (*S*)-ala-(*R*)-ala decreased the *ee* of **2b** from 91 to 77%, whilst the absence of an alkyl group at the second stereocenter also decreased the *ee* by 10%. The excellent enantioselectivity observed for reactions with cyclic ketones catalyzed by amino acids and small peptides can be explained by stabilization of transition states **I**, **II**, and **III**, respectively, by the rigidity of the cyclohexane ring. Thus, the reactions with cyclic ketones showed higher enantioselectivity than those with acyclic ketones.

Table 10. Peptide-catalyzed direct asymmetric aldol reactions.



1b 2b

Entry	Catalyst	Time [h]	Yield [%][a]	d.r.[b]	*ee* [%][c]
1	(*S*)-ala-(*S*)-ala	24	73	8:1	91
2	(*S*)-ala-(*R*)-ala	48	88	4:1	77
3	(*S*)-ala-gly	48	46	4:1	81
4	gly-(*S*)-ala	48	65	2:1	11
5	(*S*)-ala-(*S*)-ala-OEt	73	55	2:1	80
6		73	55	2:1	80

[a] Yield of isolated product after silica gel column chromatography. [b] Diastereoselectivity (d.r. = *anti*:*syn*) was determined by ^{1}H NMR analysis of the crude product. [c] The *ee* of **2b** was determined by chiral-phase HPLC analyses.

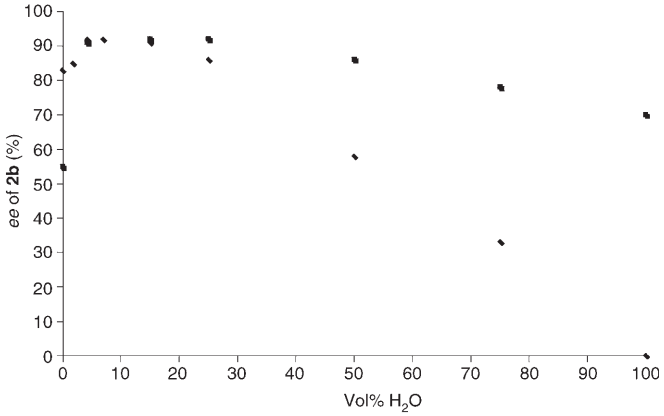


Figure 4. The dependence of the enantiomeric excess (*ee*) of **2b** derived from the asymmetric aldol reactions between cyclohexanone (**1b**) and *p*-nitrobenzaldehyde—catalyzed by (*S*)-alanine (◆) and by (*S*)-ala-(*S*)-ala (■)—as a function of the vol% H_2O in DMSO.

In the case of the alanine-catalyzed reaction, the enantioselectivity is improved by a small amount of water (4.3–15 vol%). We believe that the small amount of water increases the enantioselectivity by increasing the Brønsted acidity of the acyclic amino acid catalyst. Increasing the amount of water (>15 vol%) decreases the enantioselectivity of the aldol reaction, which gives support for hydrogen bonding as an essential feature of the transition state **I**. This is further supported by the finding that valine tetrazole **4**, which has a more acidic proton then alanine or valine, catalyzed the assembly of **2b** in an asymmetric fashion with good to excellent enantioselectivity in water, thus maintaining an ordered transition state **II** in aqueous media. The *ee* of aldol product **2b** obtained through (*S*)-ala-(*S*)-ala catalysis is also significantly improved by the addition of a small amount of water: the addition of 10 equivalents of H_2O, for instance, increased the *ee* of **2b** from 55% to 91%. In addition, the (*S*)-ala-(*S*)-ala-mediated asymmetric aldol reaction tolerates up to 40 and 50 vol% of water in DMSO and DMF, respectively, without the enantioselectivity of the reaction being affected. Notably, the dipeptide-mediated aldol reaction exhibited a high enantioselectivity in water. All these results provide precedent that hydrogen bonding from the acid moiety and the backbone of the peptide is very important in the transition state **III**, which allows a highly ordered transition state under aqueous conditions. The dramatic increase in the enantioselectivity of the asymmetric aldol reaction mediated by pentapeptide $(ala)_5$, which increases with a magnitude of 9.2 when organic solvent is changed to water may be explained in terms of a combination of improved hydrogen bonding and a more favored conformation (folding) of the pentapeptide.

Conclusion

In summary, we have shown that several natural and non-proteinogenic acyclic amino acids, and also chiral amines, can catalyze the asymmetric aldol reaction. Excellent enantioselectivities were achieved in several cases: the amino

acid-derived tetrazole catalysts **4** and **5**, for example, catalyzed the formation of aldol products **2** with up to >99% *ee*. We also showed that small highly modular peptides, pseudo-peptides, peptide-based dendrimers, and urea derivatives can also catalyze the direct asymmetric intermolecular aldol reaction with high enantioselectivities. Remarkably, simple amino acids and small peptides can catalyze the asymmetric aldol reaction with enzyme-like stereoselectivity to yield the corresponding aldol products with up to >99% *ee*. In addition, phenylglyoxylate can be utilized as an acceptor for the acyclic amino acid mediated asymmetric aldol reaction to yield the corresponding tertiary aldol product with high diastereo- and enantioselectivity. In addition, acyclic amino acids and dipeptides are able to catalyze other C–C bond-forming reactions with excellent stereoselectivities. Notably, the presence of a small amount of water both accelerated the reaction and improved the enantioselectivity, which suggests hydrogen bonding is of significant importance in the transition state. Unlike the acyclic amino acids, the small peptides catalyzed the asymmetric aqueous aldol reaction with high stereoselectivity: the di- and tripeptides, for instance, catalyzed the asymmetric formation of erythrose with high enantioselectivity in water. These results may be important for the evolution of homochirality of sugars and evolution of aldolase enzymes. The mechanism and the transition-state model have been discussed on the bases of the stereochemistry of the aldol products, structure, and activity, as well as enantiomeric excess relationships. In addition, our study shows that there is a plethora of readily available amino acids and their derivatives that can be utilized as highly selective organocatalysts for direct asymmetric aldol reactions. Nature's full structural variety can thus be employed in the design and combinatorial synthesis of nontoxic and simple organic catalysts.

Experimental Section

General methods: Chemicals and solvents were either purchased *puriss p. A.* from commercial suppliers or were purified by standard techniques. Silica gel plates (Merck 60 F254) were used for thin-layer chromatography (TLC), and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2 \cdot H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL), followed by heating, or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL), followed by heating. Flash chromatography was performed with silica gel (Merck 60, particle size 0.040–0.063 mm), ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian AS 400 instrument. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants (J) are given in Hz. The spectra were recorded in $CDCl_3$ as solvent at room temperature, with TMS as internal standard (δ = 0 ppm) for ^{1}H NMR and $CDCl_3$ as internal standard (δ = 77.0 ppm) for ^{13}C NMR. GC was carried out with a Varian 3800 GC instrument. Chiral GC-column used: CP-Chirasil-Dex CB 25 m × 0.32 mm. HPLC was carried out with a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter (δ = 589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix. The spectral data of chiral products **2a**–**2q** are known.[11,12,16,23,24]

Typical experimental procedure for direct asymmetric aldol reactions catalyzed by alanine and acyclic amino acids: A catalytic amount of (*S*)-amino acid or chiral amine (0.15 mmol, 30 mol%) was added to a vial containing acceptor aldehyde (0.5 mmol), donor ketone **2** (1.5 mmol), and H_2O (5 mmol, 90 μL) in DMSO (2 mL). After vigorous stirring at room temperature for the times shown in the tables the reaction mixture was poured into an extraction funnel containing brine (5.0 mL), diluted with distilled H_2O (5.0 mL), and EtOAc (15 mL). The reaction vial was also washed with EtOAc (2 mL), which was poured into the extraction funnel. The aqueous phase was extracted with EtOAc (2 × 15.0 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude aldol product was purified by silica gel column chromatography (EtOAc/pentane mixtures) to furnish the desired aldol product **2**. The *ee* values of the aldol products **2** were determined by chiral-phase HPLC analysis or chiral-phase GC analyses.

Typical experimental procedure for the direct asymmetric aldol reactions catalyzed by peptides, pseudo-peptides, dendrimer 9, and urea 8: A catalytic amount of di- or tripeptide (0.15 mmol, 30 mol%) was added to a vial containing acceptor aldehyde (0.5 mmol), donor ketone **2** (1.5 mmol), and H_2O (5 mmol, 90 μL) in DMSO (2 mL). After vigorous stirring at room temperature for the times shown in the tables the reaction mixture was poured into an extraction funnel containing brine (5.0 mL), diluted with distilled H_2O (5.0 mL), and EtOAc (15 mL). The reaction vial was also washed with EtOAc (2 mL), which was poured into the extraction funnel. The aqueous phase was extracted with EtOAc (2 × 15.0 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude aldol product was purified by silica gel column chromatography (EtOAc/pentane mixtures) to furnish the desired aldol product **2**. The *ee*s of the aldol products **2** were determined by chiral-phase HPLC analysis or chiral-phase GC analyses.

Compound 2a:[16] $[\alpha]_D^{25} = -131.1$ (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 3H; CH_3), 1.40 (s, 3H; CH_3), 3.9 (m, 1H), 4.13–4.50 (m, 3H), 5.01 (d, J = 7.8 Hz, 1H; C*H*OH), 7.70 (d, J = 8.4 Hz, 2H; ArH), 8.22 (d, J = 8.4 Hz, 2H; ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 23.4, 66.6, 71.7, 75.8, 101.4, 123.2, 127.9, 138.3, 146.5, 210.6 ppm; HPLC (Daicel Chiralpak AD, *iso*-hexanes/*i*-PrOH 96:4, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 52.12 min; minor isomer: t_R = 57.02 min.

Compound 2b:[11m] $[\alpha]_D$ = +12.8 (c = 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.52–2.14 (m, 6H), 2.33–2.52 (m, 2H), 2.59 (m, 1H), 3.15 (br s, 1H), 4.90 (d, J = 8.6 Hz, 1H), 7.49 (d, J = 8.7 Hz, 2H), 8.20 (d, J = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz): δ = 24.6, 27.6, 30.7, 42.6, 57.1, 73.9, 123.5, 127.8, 147.5. 148.4, 214.7 ppm; HPLC (Daicel Chiralpak AS, *i*-hexanes/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 53.57 min; minor isomer: t_R = 65.52 min; MALDI-TOF MS: 272.0897; calcd for $C_{13}H_{15}NO_4$ $[M+Na]^+$ 272.0899.

Compound 2c:[11m] $[\alpha]_D^{25}$ = +41.2 (c = 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.23 (s, 3H; CH_3), 2.83–2.87 (m, 2H; CHOHCH_2CO), 3.61 (s, 1H; OH), 5.26 (m, 1H; C*H*OH), 7.54 (d, J = 8.7 Hz, 2H), 8.21 (d, J = 8.7 Hz, 2H) ppm; HPLC (Daicel Chiralpak AS, *i*-hexanes/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 22.41 min; minor isomer: t_R = 30.31 min.

Compound 2e:[11m] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.53 (m, 1H), 1.69–1.76 (m, 2H), 1.97–2.05 (m, 1H), 2.42–2.48 (m, 1H), 2.66–2.75 (m, 1H), 2.94–3.01 (m, 1H), 3.86–3.89 (m, 2H), 3.92–3.95 (m, 2H), 4.04 (m, 1H), 4.92 (m, 1H), 7.49 (d, J = 8.6 Hz, 2H), 8.19 (d, J = 8.7 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.50, 37.9, 38.9, 53.4, 64.9, 65.2, 74.0, 107.2, 123.9, 128.0, 128.8, 148.4, 214.0 ppm; HPLC (Daicel Chiralpak AD, *iso*-hexanes/*i*-PrOH 80:20, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 35.71 min; minor isomer: t_R = 44.03 min.

Compound 2f:[16] ^{1}H NMR (400 MHz, $CDCl_3$) (*anti*:*syn* = 1:1 mixture): δ = 2.01 (s, 3H), 2.35 (s, 3H), 3.10 (br s, 1H; OH), 3.78 (br s, 1H; OH), 4.39 (m, 1H), 4.45 (d, J = 4.6 Hz, 1H), 5.07 (d, J = 4.5 Hz, 1H), 5.20 (m, 1H), 7.59 (d, J = 8.8 Hz, 4H), 8.20 (d, J = 8.8 Hz, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 28.0, 73.1, 74.6, 80.3, 80.9, 123.8, 123.9, 127.3, 127.5, 146.8, 147.7, 207.4, 208.0 ppm; HPLC (Daicel Chiralpak AD, *i*-hexanes/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm):

major isomer: t_{Ranti} = 38.5 min; minor isomer: t_{Ranti} = 36.1 min;): major isomer: t_{Rsyn} = 32.1 min; minor isomer: t_{Rsyn} = 34.0 min.

Compound 2g:[18c] ^{1}H NMR ($CDCl_3$, 400 MHz, 1:1 mixture of diastereoisomers): δ = 4.12 (d, J = 19.4 Hz, 1H), 4.25 (d, J = 5.8 Hz, 1H), 4.30 (d, J = 2.6 Hz, 1H), 4.44 (d, J = 19.4 Hz, 1H), 4.48 (d, J = 4.0 Hz, 2H), 4.86 (d, J = 5.9 Hz, 1H), 5.15 (d, J = 2.2 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H; ArH), 7.60 (d, J = 8.4 Hz, 2H; ArH), 8.12 (m, 4H; ArH) ppm; ^{13}C NMR (100 MHz): δ = 68.2, 68.3, 74.7, 75.4, 79.7, 80.7, 124.0, 124.1, 128.7, 129.3, 148.7, 148.9, 150.2, 150.9, 212.1, 212.6 ppm; HPLC (Daicel Chiralpak AD, *i*-hexanes/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 77.52 min; minor isomer: t_R = 80.23; major isomer: t_R = 88.52 min; minor isomer: t_R = 83.23 min. MALDI-TOF MS: 264.0491; calcd for $C_{10}H_{11}NO_6$ $[M+Na]^+$: 264.0484.

Compound 2h:[16a] $[\alpha]_D^{25}$ = −101.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 3H; CH_3), 1.37 (s, 3H; CH_3) 3.78 (brs, 1H), 4.06 (d, J = 17.3, 1H), 4.19–4.29 (m, 2H), 4.93 (d, J = 7.8 Hz, 1H; C*H*OH), 7.51 (d, J = 8.4 Hz, 2H; ArH), 7.63 (d, J = 8.4 Hz, 2H; ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 23.5, 66.6, 72.0, 76.0, 101.2, 128.2, 128.4, 133.7, 137.8, 210.9 ppm; HPLC (Daicel Chiralpak OJ, *i*-hexanes/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 34.50 min; minor isomer: t_R = 36.52 min.

Compound 2i:[16a] $[\alpha]_D^{25}$ = −110.9 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 3H; CH_3), 1.37 (s, 3H; CH_3), 3.78 (brs, 1H), 4.03 (d, J = 17.3 Hz, 1H), 4.19–4.29 (m, 2H), 4.93 (d, J = 7.8 Hz, 1H; C*H*OH), 7.52 (d, J = 8.4 Hz, 2H; ArH), 7.63 (d, J = 8.4 Hz, 2H; ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 23.5, 66.6, 72.0, 76.0, 101.2, 128.2, 128.4, 133.7, 137.8, 210.9 ppm; HPLC (Daicel Chiralpak AS, *i*-hexanes/*i*PrOH 97:3, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 24.10 min; minor isomer: t_R = 30.32 min.

Compound 2j: $[\alpha]_D^{25}$ = −178.8 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3H; CH_3), 1.36 (s, 3H; CH_3), 3.62 (brs, 1H), 4.03 (d, J = 17.4 Hz, 1H), 4.19–4.29 (m, 2H), 4.86 (d, J = 7.8 Hz, 1H; C*H*OH), 7.21–7.42 (4H; ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4, 23.7, 66.8, 72.1, 76.0, 101.6, 112.0, 119.0, 128.0, 132.0, 144.8, 210.8 ppm; HPLC (Daicel Chiralpak AS, *i*-hexanes/*i*PrOH 97:3, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 23.41 min; minor isomer: t_R = 28.9 min.

Compound 2k:[16a] $[\alpha]_D^{23}$ = −129.7 (c = 3.3, $CHCl_3$) [literature: $[\alpha]_D^{25}$ = −106.7 (c = 1.0, $CHCl_3$)];[33] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 3H), 1.48 (s, 3H), 3.16 (d, J = 4.2 Hz, 1H), 3.70–3.67 (m, 2H), 4.03 (d, J = 17.2 Hz, 1H), 4.21 (m, 1H), 4.27 (d, J = 17.2 Hz, 1H), 4.45 (d, J = 6.2 Hz, 1H), 4.56–4.63 (m, 2H), 7.27–7.37 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 24.2, 66.9, 69.9, 70.2, 73.7, 74.04, 101.1, 127.9, 128.5, 129.2, 138.1, 210.0 ppm; HPLC (Daicel Chiralpak AD, hexanes/*i*PrOH 96:4, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 46.02 min; minor isomer: t_R = 40.73 min; MALDI-TOF MS: 303.1211; calcd for $C_{15}H_{20}O_5$ $[M+Na]^+$: 303.1208.

Compound 2l:[11o] $[\alpha]_D^{25}$ = −95.69 (c = 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 3H), 1.36 (s, 3H), 3.63 (brs, 1H), 4.03 (d, J = 16.5 Hz, 1H), 4.22 (d, J = 16.5 Hz, 1H), 4.33 (d, J = 7.1 Hz, 1H), 4.90 (d, J = 7.9 Hz, 1H), 7.29–7.40 (m, 5H) ppm; ^{13}C NMR: δ = 23.3, 24.0, 66.9, 73.0, 76.5, 101.4, 127.3, 128.0, 128.3, 139.5, 211.1 ppm; HPLC (Diacel Chiralpak AD, *i*-isohexane/*i*PrOH 88:2, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_r = 36.05 min, minor isomer: t_r = 40.77 min.

Compound 2m: $[\alpha]_D$ = +21.6 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23–1.32 (m, 1H), 1.50–1.58 (m, 2H), 1.60–1.66 (m, 1H), 1.73–1.81 (m, 1H), 2.03–2.10 (m, 1H), 2.29–2.37 (m, 1H), 2.43–2.48 (m, 1H), 2.51–2.57 (m, 1H), 3.99 (d, J = 2.9 Hz, 1H), 4.74 (dd, J = 8.8, 2.8 Hz, 1H), 7.20 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H) ppm; ^{13}C NMR (100 MHz): δ = 24.9, 27.9, 31.0, 42.8, 57.5, 74.2, 128.6, 128.7, 133.7, 139.8, 215.4 ppm; HPLC (Daicel Chiralpak AS, *i*-hexanes/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, λ = 254 nm): major isomer: t_R = 22.04 min; minor isomer: t_R = 20.36 min.

Compound 2n: $[\alpha]_D$ = +20.5 (c = 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.23–1.32 (m, 1H), 1.49–1.58 (m, 2H), 1.61–1.69 (m, 1H), 1.75–1.81 (m, 1H), 2.03–2.10 (m, 1H), 2.30–2.41 (m, 1H), 2.43–2.48 (m, 1H), 2.50–2.59 (m, 1H), 3.99 (brs, 1H), 4.74 (d, J = 8.6 Hz, 1H), 7.18 (d, J = 8.3 Hz, 2H), 8.45 (d, J = 8.3 Hz, 2H) ppm; ^{13}C NMR (100 MHz): δ = 25.0, 28.0, 30.9, 42.8, 57.5, 74.3, 121.9, 128.9, 131.6, 140.3, 215.4 ppm; HPLC (Daicel Chiralpak AS, *i*-hexanes/*i*PrOH 90:10, flow rate 1.0 mL min^{-1}, λ = 254 nm): major isomer: t_R = 23.04 min; minor isomer: t_R = 21.22 min.

Compound 2o:[11m] $[\alpha]_D^{25}$ = +59.2 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (s, 3H), 2.87 (m, 2H), 3.32 (d, J = 3.0 Hz, 1H), 5.17 (m, 1H), 7.27–7.38 (m, 5H) ppm; ^{13}C NMR: δ = 28.8, 30.1, 36.1, 38.7, 41.4, 45.8, 47.6, 58.0, 112.0, 121.2, 129.4, 147.0, 213.1 ppm; the enantiomeric excess of the aldol was determined on the acetylated compound (CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.8 mL min^{-1}, t_i = 100 °C (35 min), t_f = 200 °C (5 °C min^{-1}): major isomer: t_R = 43.00 min; minor isomer: t_R = 42.80 min.

Compound 2p:[11m] $[\alpha]_D^{25}$ = −27.74 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.8 Hz, 3H; CH_3), 0.96 (d, J = 6.8 Hz, 3H; CH_3), 1.38 (s, 3H; CH_3), 1.43 (s, 3H; CH_3), 1.92–2.01 (m, 1H), 3.07 (d, J = 2.3 Hz, 1H), 3.64–3.67 (m, 1H), 3.97 (d, J = 17.3 Hz, 1H), 4.22 (dd, J = 1.5, 17.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 19.4, 23.8, 24.0, 28.7, 66.7, 74.1, 74.3, 101.1, 212.4 ppm; HPLC (Daicel Chiralpak AD, *i*-hexanes/*i*PrOH 95:5, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 15.21 min; minor isomer: t_R = 12.81 min.

Typical experimental procedure for the peptide- and amino acid-catalyzed direct asymmetric aldol reactions in water: A catalytic amount of (*S*)-amino acid, dipeptide, or oligopeptide (0.075 mmol, 30 mol %) was added to a vial containing acceptor aldehyde (0.25 mmol, 38 mg), cyclohexanone (**1b**) (0.75 mmol, 80 mL), and SDS (72 mg, 0.25 mmol) in H_2O (1 mL). After vigorous stirring of the reaction mixture for the time shown in the tables at room temperature it was directly loaded on a silica gel column. The crude aldol product was purified by silica gel column chromatography (EtOAc/pentane mixtures) to furnish the desired aldol product **2b**. The *ee*s of the aldol product **2b** were determined by chiral-phase HPLC analyses.

Typical experimental procedure for the peptide- and amino acid-catalyzed direct asymmetric aldol reactions in water and aqueous buffer: A catalytic amount of (*S*)-amino acid, dipeptide, or oligopeptide (0.075 mmol, 30 mol %) was added to a vial containing acceptor aldehyde (0.25 mmol) and cyclohexanone (**1b**, 0.75 mmol, 80 mL) in H_2O (0.25 mmol α-cyclodextrin, 1 mL) or aqueous buffer (1 equiv SDS, 1 mL). After 1–4 days of vigorous stirring at room temperature the reaction mixture was quenched by extraction with EtOAc (3×15 mL). In the latter case the combined organic phases were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldol product was purified by silica gel column chromatography (EtOAc/pentane mixtures) to furnish the desired aldol product **2b**. The *ee*s of the aldol products **2b** were determined by chiral-phase HPLC analyses.

Typical experimental procedure for the peptide- and amino acid-catalyzed direct asymmetric aldol reactions in aqueous media: A catalytic amount of (*S*)-amino acid, dipeptide, or tripeptide (0.075 mmol, 30 mol %) was added to a vial containing acceptor aldehyde (0.25 mmol, 38 mg) and donor ketone **1** (0.75 mmol), **1c** (1.36 mmol, 100 mL), or **1g** (dimeric form, 500 mg) in H_2O (1 equiv. SDS, 1 mL) or aqueous media (1 mL). After vigorous stirring at room temperature for the times shown in the tables the reaction mixture was quenched by extraction with EtOAc (3×15 mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldol products were purified by silica gel column chromatography (EtOAc/pentane mixtures) to furnish the desired aldol products **2**. The *ee* values of the aldol products **2** were determined by chiral-phase HPLC analyses.

Synthesis of alanine-tetrazole 4: NH_4HCO_3 (0.89 g, 1.26 equiv) was added to a solution of Boc_2O (2.5 g, 1.3 equiv) and Cbz-Ala (2.0 g) in MeCN (14 mL) and Py (2.2 mL, 3 equiv.) and the reaction mixture was stirred overnight at room temperature. The solvents were removed by evaporation and the residue was dissolved in EtOAc and washed with 2× 15 mL water. The water was reextracted with EtOAc and the combined volume of EtOAc was dried over $MgSO_4$, filtered, and concentrated. The crude product was weakly UV active and had an R_f = 0.42 (MeOH/CH_2Cl_2 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) of the crude Cbz-Alanine

amide: δ = 1.41 (d, J = 7.1 Hz, 3H), 4.29 (m, 1H), 5.17 (m, 2H), 5.39 (brs, 1H), 6.11 (brs, 1H), 7.27 ppm (m, 5H).

Next, $POCl_3$ (0.55 mL, 1.2 equiv in CH_2Cl_2 (5 mL)) was added dropwise at −10 °C to a solution of Cbz-alanine amide (1.1 g) in Py (10 mL), and the resulting mixture was stirred for 3 h. When the starting material was "depleted" by TLC (MeOH/CH_2Cl_2 1:9) the mixture was poured onto ice (≈30 g). The organic phase was separated and pyridine was removed by repeated washing with a not concentrated $CuSO_4$ solution. The organic phase was then pre-dried with brine and later dried over $MgSO_4$. Filtration and concentration afforded the crude product as an oil, TLC R_f = 0.51 (MeOH/CH_2Cl_2 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) of the crude Cbz-alanine nitrile: δ = 1.41 (d, J = 6.8 Hz, 3H), 4.65 (m, 1H), 5.17 (m, 2H), 5.39 (brs, 1H), 7.28 (m, 5H).

NaN_3 (300 mg, 1.1 equiv) and NH_4Cl (256 mg, 1.15 equiv.) were added simultaneously to a solution of crude Cbz-alanine nitrile (850 mg) in DMF (13 mL). The reaction was heated to 90–95 °C and kept at that temperature (3 h) until the TLC (HOAc/EtOA 1:99) spot at R_f = 0.63 did not increase in strength. The reaction mixture was poured onto ice (30 g), acidified to pH close to 2 with HCl (2 M), and extracted with $CHCl_3$ (3× 20 mL). The organic phase was washed with water (20 mL), then pre-dried with brine (20 mL), and finally dried over $MgSO_4$ before filtration and removal of solvent by evaporation. Traces of DMF were removed under reduced pressure. The crude product is a yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) of the crude Cbz-alanine tetrazole: δ = 1.59 (d, J = 6.9 Hz, 3H), 5.07 (m, 2H), 5.22 (m, 1H), 6.19 (brs, 1H), 7.28 (m, 5H) ppm.[34]

The Cbz-alanine tetrazole (825 mg) was dissolved in MeOH (10 mL) and a catalytic amount of Pd/C was added. After 17 h the catalyst was filtered off with celite and the solvent was removed under reduced pressure to give alanine tetrazole **3** quantitatively as a white solid. ^{1}H NMR (400 MHz, D_6-DMSO): δ = 1.41 (d, J = 6.8 Hz, 3H), 4.51 (m, 1H) ppm; ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 20.2, 44.4, 161.0 ppm.

Synthesis of valine-tetrazole 5: NH_4HCO_3 (0.89 g, 1.26 equiv) was added to a solution of Boc_2O (2.5 g, 1.3 equiv) and Cbz-L-valine (2.0 g) in MeCN (14 mL) and Py (2.2 mL, 3 equiv) and the reaction mixture was stirred overnight at room temperature. The solvents were removed by evaporation and the residue was dissolved in EtOAc and washed with water (2×15 mL). The water was reextracted with EtOAc and the combined volume of EtOAc was dried over $MgSO_4$, filtered, and concentrated. The crude product was weakly UV active and had an R_f = 0.42 (MeOH/CH_2Cl_2 1:9). ^{1}H NMR (400 MHz, $CDCl_3$) of the crude Cbz-valine amide: δ = 0.99 (dd, J = 6.8 Hz, 6H), 2.15 (m, 1H), 4.02 (m, 1H), 5.12 (s, 2H), 5.29 (brs, 1H), 5.39 (brs, 1H) 5.78 (brs, 1H), 7.30 ppm (m, 5H).

$POCl_3$ (0.55 mL, 1.2 equiv in CH_2Cl_2 (5 mL)) was added dropwise at −10 °C to a solution of Cbz-L-valine amide (1.1 g) in Py (10 mL) and the resulting mixture was stirred for 3 h. When the starting material was "depleted" by TLC (MeOH/CH_2Cl_2 1:9) the mixture was poured onto ice (≈30 g). The organic phase was separated and pyridine was removed by repeated washing with a not concentrated $CuSO_4$ solution. The organic phase was then pre-dried with brine and later dried over $MgSO_4$. Filtration and concentration afforded the crude product as an oil, TLC R_f = 0.51 (MeOH/CH_2Cl_2 1:9).

NaN_3 (300 mg, 1.1 equiv) and NH_4Cl (256 mg, 1.15 equiv) were added simultaneously to a solution of crude Cbz-valine nitrile (850 mg) in DMF (13 mL). The reaction was heated to 90–95 °C and kept at that temperature (3 h) until the TLC (HOAc/EtOAc 1:99) spot at R_f = 0.63 did not increase in strength. The reaction mixture was poured onto ice (30 g), acidified to pH close to 2 with HCl (2 M), and extracted with $CHCl_3$ (3× 20 mL). The organic phase was washed with water (20 mL), then pre-dried with brine (20 mL), and finally dried over $MgSO_4$ before filtration and removal of solvent by evaporation. Traces of DMF were removed under reduced pressure. The crude product is a yellowish solid.

The Cbz-valine tetrazole (825 mg) was dissolved in MeOH (10 mL) and a catalytic amount of Pd/C was added. After 17 h the catalyst was filtered off with celite and the solvent was removed under reduced pressure to give valine tetrazole **5** quantitatively as a white solid. ^{1}H NMR (400 MHz, D_2O): δ = 0.70 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 2.25(m, 1H), 4.38 (d, J = 7.6 Hz, 1H).

General procedure for the preparation of dipeptides: A stirred solution of Cbz-protected α-amino acid (10 mmol) in dichloromethane (30 mL) was cooled to −15 °C and neutralized with NMM (*N*-methyl morpholine, 10 mmol). Next, isobutyl chlorocarbonate (10 mmol) was added. After the mixture had been stirred for 20 minutes a solution of the salt of amino acid ester (10 mmol) and NMM (10 mmol) in dichloromethane (30 mL) was added. The mixture was stirred at −15 °C for 1 h and was next allowed to warm up to room temperature. The progress of the reaction was monitored by TLC (AMC stain). At completion, the reaction mixture was extracted with HCl (1 N, 3×20 mL), Na_2CO_3 (1 N, 3×20 mL), and brine (30 mL). The organic layer was dried with sodium sulfate. The dipeptide product was checked by TLC and NMR; in most cases it was pure enough for the next step. If not, the product was purified by silica gel column chromatography. Next, palladium on activated carbon (100 mg, 10 wt%) was added under argon to a solution of protected dipeptide (1 g) in methanol (20 mL). The reaction mixture was stirred under hydrogen (90 psi) for one day. The reaction was checked by TLC and NMR analyses. At the completion of hydrogenolysis, the Pd/C catalyst was removed by filtration on celite and washed with methanol and water. The combined filtrates were evaporated under reduced pressure. The dipeptide product was checked by NMR analyses and, if necessary, recrystallization was preformed in an appropriate solvent.

Typical experimental procedure for the direct asymmetric synthesis of tertiary aldol 2q catalyzed by valine tetrazole 5, valine, and dipeptide: A catalytic amount of catalyst (0.20 mmol, 40 mol%) was added to a vial containing acceptor aldehyde (0.5 mmol), donor ketone **2b** (5 mmol), and H_2O (5 mmol, 90 μL) in DMSO (2 mL). After vigorous stirring at room temperature for the time shown in Table 9 the reaction mixture was poured into an extraction funnel containing brine (5.0 mL), diluted with distilled H_2O (5.0 mL), and EtOAc (15 mL). The reaction vial was also washed with EtOAc (2 mL), which was poured into the extraction funnel. The aqueous phase was extracted with EtOAc (2×15.0 mL). The combined organic phases were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude aldol product was purified by silica gel column chromatography (EtOAc/pentane mixtures) to furnish the desired aldol product **2q**.

Compound 2q: Major diastereomer: $[\alpha]_D^{25}$ = −28.0 (c = 1.0, $CHCl_3$, 98% *ee*); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.2 Hz, 3H; CH_3), 1,55–1.88 (m, 5H), 1.90 (m, 1H), 2.06 (m, 1H), 2.29–2.44 (m, 2H), 3.18 (dd, J = 5.5, 12.7 Hz, 1H), 4.16 (s, 1H), 4.25 (q, J = 7.14, 7.12 Hz, 2H), 7.26–7.36 (m, 3H; ArH), 7.50 (d, J = 7.2 Hz, 2H; ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 25.6, 28.0, 30.8, 30.8, 43.2, 53.9, 62.1, 73.4, 125.8, 128.1, 128.5, 128.7, 140.6, 173.2, 212.7 Hz ppm; HPLC (Daicel Chiralpak AD, *i*-hexanes/*i*PrOH 95:5, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 25.60 min; minor isomer: t_R = 32.50 min. Minor diastereomer: $[\alpha]_D^{25}$ = +37.0 (c = 1.0, $CHCl_3$, 26% *ee*) [literature: $[\alpha]_D^{25}$ = −139.6 (c = 1.0, $CHCl_3$, 96% *ee*)];[24] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.2 Hz, 3H; CH_3), 1,52–1.75 (m, 5H) 1.87 (m, 2H), 2.07 (m, 1H), 2.31–2.45 (m, 2H), 3.40 (dd, J = 6.1, 12.9 Hz, 1H), 3.87 (s, 1H), 4.11–4.25 (m, 2H), 7.27–7.37 (m, 3H; ArH), 7.58 (d, J = 7.9 Hz, 2H; ArH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 25.1, 27.5, 27.8, 42.6, 59.0, 62.2, 77.8, 125.5, 127.9, 128.5, 139.2, 174.8, 213.0 Hz ppm; HPLC (Daicel Chiralpak AD, *i*-hexanes/*i*PrOH 90:10, flow rate 0.5 mL min^{-1}, λ = 254 nm): major isomer: t_R = 22.80 min; minor isomer: t_R = 30.60 min

Procedure for the ala-ala-catalyzed conjugate addition of ketone 1b to a nitroolefin: The relevant ketone (0.75 mmol) and nitroolefin (0.25 mmol) were added to a suspension of catalyst (30 mol%) in DMSO (0.5 mL), NMP (0.5 mL), and H_2O (45 μL, 10 equiv). The resulting mixture was stirred for 72 h, quenched with brine, and extracted with ethyl acetate (3×10 mL), and the combined organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, pentane/ethyl acetate 10:1–4:1) to give the Michael products. The *ee*s of the products were determined by chiral HPLC analysis.

Compound 11: a white solid (96.6% *ee*): $[\alpha]_D^{25} = +27.4$ ($c = 0.5$, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, 400 MHz): $\delta = 7.40–7.10$ (5H; m), 4.93 (dd, $J = 12.4$, 4.4 Hz; 1H), 4.64 (dd, $J = 12.4$, 9.6 Hz; 1H), 3.76 (dt, $J = 9.6$, 4.4 Hz; 1H), 2.78–2.72 (1H; m), 2.52–2.32 (2H; m), 2.15–2.05 (1H; m), 1.84–1.48 (4H; m), 1.30–1.18 (1H; m) ppm; ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): $\delta = 211.90$, 137.74, 128.93, 128.16, 127.77, 78.88, 52.53, 43.93, 42.73, 33.19, 28.51, 25.02 ppm. The *ee* of the product was determined by chiral HPLC analysis (Chiralpak AD column, *i*-hexane/*i*PrOH = 90/10, 0.5 mL min^{-1}, t_R (major) = 19.45 min, t_R (minor) = 22.82 min). MALDI-TOF MS: 270.1108; $C_{14}H_{17}NO_3$ calcd for $[M+Na]^+$ 270.1106.

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