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N-Primary-Amine-Terminal *β*-Turn Tetrapeptides as Organocatalysts for Highly Enantioselective Aldol Reaction

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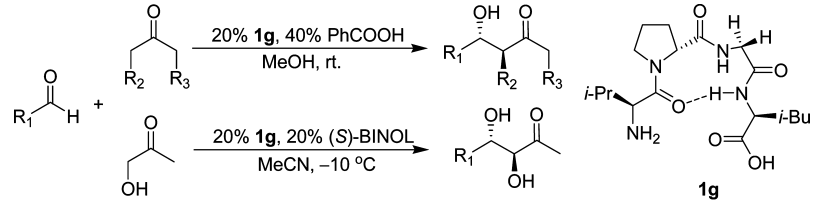

R_2, R_3 = H, H; H, *i*-Bu; $-(CH_2)_2-$; $-(CH_2)_3-$. Yield up to 99%, ee up to 96%

Tetrapeptides, containing a terminated primary amine and conformationally restricted D-Pro-Gly or D-Pro-Aib (2-aminoisobutanoic acid) segment as a strongly *β*-turn-nucleating element, were designed and synthesized with condensation of *N*-module dipeptides with *C*-module dipeptides in solution. They were first applied to catalyze aldol reactions, and were found to be effective catalysts for the transformations. The tetrapeptide Val-D-Pro-Gly-Leu-OH (**1g**) was the optimal organocatalyst. It was shown that the intensive *β*-turn conformation, indicated by CD and NOESY spectra, contributed to the (*R*)-aldol and high enantioselectivity of the reaction of acetone in MeOH, whereas the sharply varied conformation should contribute to the low enantioselectivity and (*S*)-product of the reaction in 1,2-dichloroethane (DCE). The asymmetric induction in the reaction of hydroxyacetone was not affected by solvents, and predominant *anti* products were achieved by **1g** in MeCN with the additive (*S*)-BINOL.

Introduction

The asymmetric aldol reaction, which forms C−C bonds and generates chiral carbons, is a key reaction in organic synthesis, with remarkable biological and prebiological significance,[1] and thus has been at the center of research.[2] And simple small molecules as efficient chiral organocatalysts in this reaction are currently very interesting for chemists and have shown fruitful results.[3]

There has recently been an increase in the application of peptides as catalysts for asymmetric reactions.[4] Benefiting greatly from advances in the understanding of enzyme-mediated biosynthesis, biomimetic synthesis has been a new field of extensive research.[3a,5] Synthetic peptides as interesting and important artificial enzymes are attractive because structural modifications can easily be introduced and used for fine-tuning of the catalytic properties. Unlike structurally simple and small molecular organocatalysts, higher structural artificial peptidic enzymes are more structurally similar to enzymes. The successful application experiences of synthetic peptidic catalysts in organic reactions will return to greatly contribute to the

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development of research on enzyme-mediated synthesis. Now, researchers have concentrated on two classes of peptides in the asymmetric aldol reaction. One type is the peptide of *N*-terminal proline. The application of *N*-prolyl peptides has indeed proven to be a fertile ground for the development of the peptide-catalyzed asymmetric reaction.[6] Another type is the peptide of *N*-terminal primary amino acids, which is more interesting because *N*-terminal primary amine is the catalytic function group in the active center of natural aldolases.[2h−j] In the earlier works, however, the enantioselective results of the asymmetric aldol reactions catalyzed by peptides bearing primary amines were far inferior to the *N*-prolyl peptides, especially the reaction of acetone with aldehydes.[4c,7] This result might be attributed to the less successful enantioselective outcomes of primary amine organocatalysts in the asymmetric aldol reaction than that of secondary amine organocatalysts. Recently, the research of primary amine organocatalysts has been improved remarkably.[8] It would greatly contribute to the highly efficient primary amine peptides in the reaction. The former successful primary amine peptides were mainly applied to the aldol reaction of cycloketones and the aldol dimerization of glycoaldehyde to D-erythrose or D-threose,[9] nevertheless, they had unattractive behavior in reactions of methyl alkyl ketones.[7,10]

Just as enzymes, some functional groups, which are far away from each other in the primary structure, are close enough to each other in the rigid space to form the active center and work synergistically. However, only a few reports have been disclosed that the higher structure of peptides, which are certainly essential topics for the artificial polypeptidic enzyme mimics,[11] could contribute to high activity and enantioselectivity in this reaction. Colonna and co-workers disclosed that PLL (polyleucine) with secondary α-helix structure,[12] which have been an excellent catalyst for the asymmetric Juliá−Colonna epoxidation reaction of electron-deficient ketenes,[13] was an effective catalyst for the aldol reaction of cyclohexanone with less than 76% ee as well. The β-turn, a fundamental element of the β-hairpin, is a common feature within proteins and enzymes, encompassing on average 25% of the residues.[14] And some synthetic β-turn peptides as effective chiral catalysts have been successfully reported in several asymmetric catalytic reactions.[15] However, there are only two disclosed successful examples in the asymmetric aldol reaction catalyzed by β-turn peptides to date. Wennemers' group suggested that a turn-like conformation of a *N*-prolyl tripeptide was important for orienting the two functional groups into close vicinity, which was crucial for efficient catalysis of acetone with up to 91% ee.[6b] And it was then rechecked by Reiser and co-workers, using aminocyclopropane carboxylic acids to stabilize the secondary structure of their *N*- and *C*-prolyl α/β-tripeptide.[16] Thus, research on high-efficiency and higher-structure peptidic organocatalysts is greatly challenging and eagerly desired on account of biomimetic catalysis in this reaction. It is clear that there is no β-turn tetrapeptides with a *N*-terminal primary amine group, which is also one of the key function groups in the active center of natural aldolases, as organocatalysts have been disclosed in this reaction to date. Hererin we report our reults on this topic.

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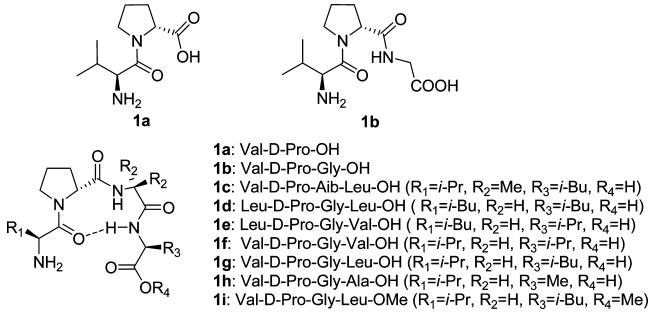

FIGURE 1. Peptidic organocatalysts.

Results and Discussion

The dipeptides D-Pro-Gly and D-Pro-Aib have been proved to greatly nucleate tight β-turn or β-hairpin secondary structures even in short peptides.[17] Therefore, as well as the di- and tripeptides (Figure 1, **1a** and **1b**) for comparison purposes, a series of tetrapeptide catalysts (Figure 1, **1c**−**i**) bearing *N*-terminal primary amines with these central segments were designed.

The peptides **1b**−**g** were synthesized by condensation of two dipeptidic modules via a routine mixed anhydride procedure (Scheme 1).[18] The dipeptides **4a**−**c** with *N*-terminal bulky amino acids, such as valine, were synthesized with the DIC-HOBt (DIC: diisopropylcarbodiimide; HOBt: *N*-hydroxybenzotriazole) condensation method,[19] whereas the dipeptides **4d**−**e** without *N*-terminal bulky amino acids were prepared by using the mixed anhydride procedure. The *N*-terminal modules **5a**,**b** and *C*-terminal modules **5c**−**e** were achieved from **4a**,**b** and **4c**−**e** after partial deprotection of Boc and Bn with TFA and catalytic hydrogenation, respectively. These modules were directly condensed with each other without further purification, using the mixed anhydride procedure, to give the protected peptides. Removal of the whole protective groups from **4a** and **6a**−**g**, or the Boc group from **6h**, afforded the peptidic organocatalysts **1a**−**i**.

Initially, 10 mol % of **1g** was tested in the model reaction of 4-nitrobenzaldehyde with acetone at room temperature (Table 1). Screening a variety of solvents indicated that methanol was optimal, with ee up to 66% (entry 2). Particularly noteworthy was that the peptide catalyst generated aldol products with opposite configurations despite the fact that there was no difference but for the polarity of solvents. The configuration of the product would be *R* when the reaction was carried out in strongly polar solvents (entries 1−8), whereas it would be *S* in both weakly polar and apolar solvents (entries 9−16). And among apolar solvents, DCE (1,2-dichloroethane) gave the highest ee with 40% (entry 14). It was speculated that the different solvents, because of the hydrogen competition, might have different impact on the secondary structure of the peptide, and then change its catalytic activity and inductive direction.

Then we experimented on a series of additives with a gradient pK_a to increase the enantioselectivity. Interestingly, it seemed that the pK_a of additives greatly influenced the enantioselectivity. Apparently, the acidic additives with pK_a between 3.0 and 5.0, except for DNP (2,4-dinitrophenol), bahaved better than others in the enantioselectivity. PhCOOH (pK_a 4.19) could mostly improve the enantioselectivity from 66% up to 83% ee (entry 22). Too strong acidic additives such as trifluoroacetic acid (TFA) gave no product at all (entry 27).

Then the enantioselective catalytic activities of the catalysts **1a**−**h** were investigated. The results demonstrated that the tetrapeptides with stable β-turn structure produced higher enantioselectivities than di- and tripeptides. The dipeptide **1a** and tripeptide **1b** nearly gave the same enantioselectivity as each other. This result indicated that linkage of a further achiral Gly to *C*-terminus of the dipeptide **1a** did not contribute to the higher enantioselecitivty. In current amino acid sequences, peptides with a central D-Pro-Gly segment revealed better enantioselectivities than that of peptide **1c** with a central D-Pro-Aib segment (entries 22 and 28−34). The tetrapeptide **1g** turned out to be the most effective. Application of the tetrapeptide **1i**, the methyl ester of **1g**, afforded the sharply decreased enantioselectivity and declined reactivity (entry 35). It indicated that the free *C*-terminal carboxyl acid of the peptide played a crucial role in the enantioselectivity and reactivity. Further optimizing experiments showed that increasing the amount of catalyst to 20 mol % could improve its enantioselectivity up to 91% (entry 36). While increasing the additive loading to 40 mol %, excellent enantioselectivity (95%) was harvested (entry 37). Notably, this value is the highest ee in the reaction of acetone with *p*-nitrobenzaldehyde catalyzed by *N*-primary-amine-terminal peptidic catalysts to date.

The optimal protocol was expanded to aldol reactions of acetone with a variety of aromatic aldehydes (Table 2). Generally, the electron-withdrawing group on the aldehyde facilitated the reaction proceeding to completion. High enantioselectivities (up to 96% ee) but moderate yields were obtained with electron-deficient aldehydes. It appeared that para-substituted aromatic aldehydes, such as 4-nitrobenzaldehyde, 4-(trifluoromethyl)benzaldehyde, and 2,4-dichlorobenzaldehyde, could give good yields and high enantioselectivities (entries 1, 4, and 7). When 1-naphthaldehyde and 2-naphthaldehyde were used as electron acceptors, excellent enantioselectivities but poor conversions to the aldol product were observed (entries 8 and 9). Actually, the severe dehydration made the reaction unable to give high yields, especially for electron-donating aryl aldehydes. And alkylaldehydes failed to give aldol products. The reaction between methyl isobutyl ketone and *p*-nitrobenzaldehyde also gained a high enantioselectivity (93% ee, entry 10), but a poor yield due to low activity. The peptide (**1g**) was subsequently tested in the aldol reactions of representative cyclic ketones (Table 2, entries 11−13). The reactions were observed to give high yields (up to 87%) and enantioselectivities (up to 86% ee) but poor diastereoselectivities.

It was interesting that no effects of solvents on the configuration of aldol product could be observed likewise when replacing acetone with hydroxyacetone, and each solvent gave predominantly (*S*,*S*)-aldol (Table 3). Therefore, the similar great influence of the peptide secondary structure on this reaction could not surprisingly be investigated as the former reaction of acetone. Apparently, the hydroxy group of the ketone abstracted the different impact of these solvents on the configuration and

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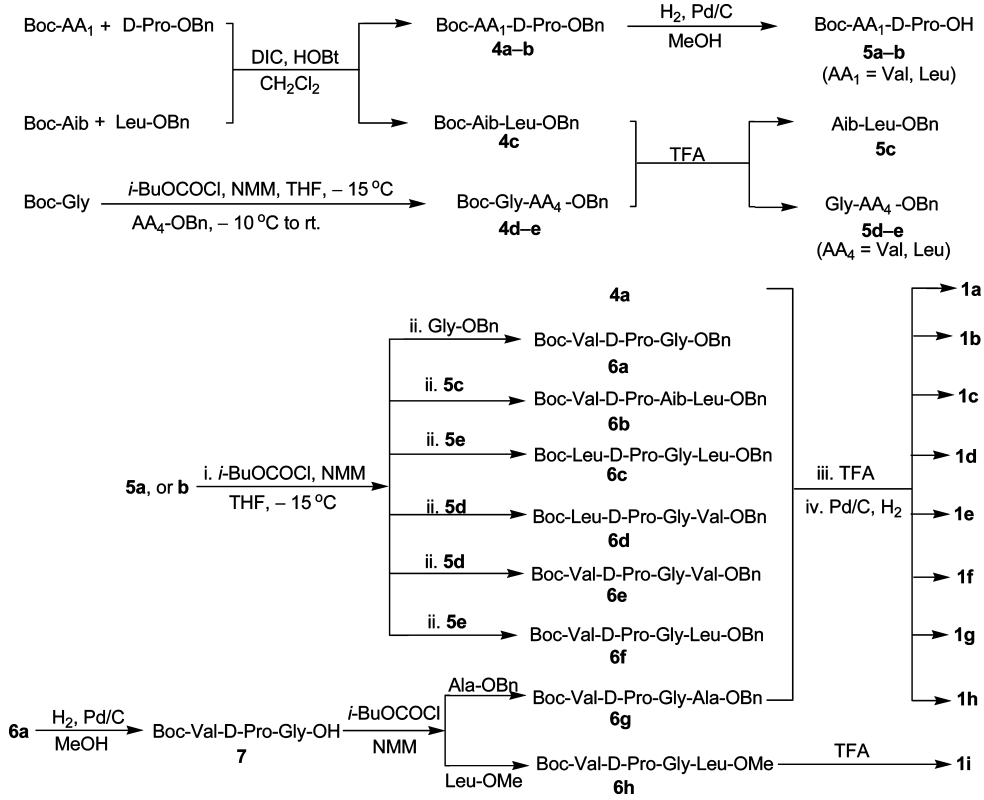
SCHEME 1. Synthesis of Peptidic Organocatalysts 1a−h



strongly made the tetrapeptide **1g** only achieve the (*S*)-hydroxy product. But the distinct effect on their enantioselectivities could be observed, and MeCN was the optimal one. The results of additives indicated that (*S*)-BINOL was the best selection (entry 11). Decrease on both enantioselectivity and diastereoselectivity in the absence of the additive denoted the crucial role of (*S*)-BINOL in this reaction (entry 12). Without tetrapeptide **1g**, however, only (*S*)-BINOL itself did not push the reaction in its process at all (entry 13). Furthermore, it was notable that the configuration of the additive BINOL could not impact the asymmetric outcome of the reaction, whether (*S*)- or (*R*)-BINOL as an additive afforded the same configuration of aldol product in nearly identical enantioselectivities (entries 11 and 14), just as Shan and co-worker had found in their research.[20] This observation indicated that BINOL functioned as an effective cocatalyst to assist the tetrapeptide catalyst **1g** to enhance the activity and enantioselectivity of the asymmetric transformation. An interesting phenomenon was that the predominant *syn* products were achieved when PhCOOH was used as an additive whereas *anti* products were principally obtained when other additives were introduced in the reaction. Further improvements of enantioselectivity and diastereoselectivity were achieved under a lowered temperature at the cost of decreased reactivity (entries 15−17). To our delight, the catalyst **1g** was very active in this reaction. The reaction between hydroxyacetone and *p*-nitrobenzaldehyde was accomplished in 1.5 h at room temperature (entry 11). Even at −10 °C, 30 h were enough to complete the reaction (entry 16).

So a variety of aromatic aldehydes with hydroxyacetone were examined in the presence of 20 mol % of **1g** in CH_3CN and 20 mol % of (*S*)-BINOL as an additive (Table 4). It is noteworthy that *anti*-1,2-diols with high enantioselectivities (up to 91% ee, entry 5) were obtained in the reactions, while *syn*-1,2-diols were very easy to generate in most cases.[21] And this is the first successful case of branched isomeric products of hydroxyacetone catalyzed by peptidic organocatalysts.[6c] Different from reactions of acetone, it seemed that reactions of hydroxyacetone and ortho-substituted aromatic aldehydes could give higher enantioselectivities, such as 2-nitrobenzaldehyde and 2-trifluoromethylbenzaldehyde (entries 5 and 7).

It is more interesting that the same peptidic catalyst generated different enantioselectivity and configuration in the identical reaction of acetone with 4-NO_2PhCHO in different solvents, such as methanol and DCE, although the nucleated D-Pro-Gly segment strongly induced the type II β-turn structure. And the remarkable catalytic properties of peptide **1g** in methanol suggested the existence of privileged conformations in which the *C*- and *N*-termini should be close to each other. The end-capped tetrapeptide Ac-Val-D-Pro-Gly-Leu-NMe_2 has been reported to fold largely into the β-hairpin comformation.[17b] To address the question whether peptide **1g** also created the β-turn structure, CD (circular dichroism) and NOESY spectra of tetrapeptide **1g** were made.

It can be observed from the CD spectra (see Figure S1 in the Supporting Information) that tetrapeptide **1g** in methanol and ethanol have very similar performance. This clearly indicates a strong negative band at <195 nm, a highly intensive positive band at 200 nm, and a weak band at 210 nm, suggesting the presence of the β-turn structure of the peptide in alcohols.[22] Compared with strongly polar organic solvents, however, the CD curve flattens in water. The spectrum of **1g** in DCE shows

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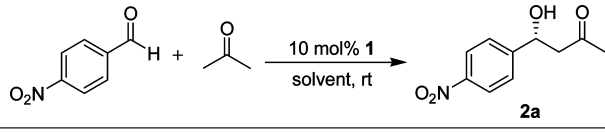
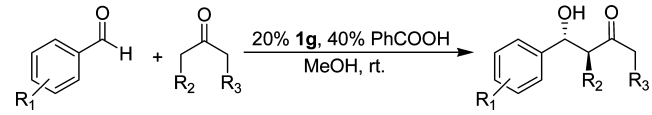
TABLE 1. Screening of Catalysts and Optimization of Conditions



entry	peptide[a]	solvent	additive (pK_a)[b]	ee (%)[c]
1	**1g**	H_2O		13 (*R*)
2	**1g**	MeOH		66 (*R*)
3	**1g**	EtOH		20 (*R*)
4	**1g**	*i*-PrOH		17 (*R*)
5[d]	**1g**	MeOH/THF		46 (*R*)
6	**1g**	DMF		0
7	**1g**	DMSO		15 (*R*)
8[e]	**1g**	DMSO/H_2O		18 (*R*)
9	**1g**	acetone		25 (*S*)
10	**1g**	CH_3CN		25 (*S*)
11	**1g**	toluene		31 (*S*)
12	**1g**	THF		5 (*S*)
13	**1g**	CH_2Cl_2		28 (*S*)
14[f]	**1g**	DCE		40 (*S*)
15	**1g**	Et_2O		13 (*S*)
16	**1g**	n-hexane		6 (*S*)
17	**1g**	MeOH	Et_3N	20 (*R*)
18	**1g**	MeOH	DIPEA	32 (*R*)
19	**1g**	MeOH	NMM	54 (*R*)
20	**1g**	MeOH	PNP (7.15)	55 (*R*)
21	**1g**	MeOH	AcOH (4.75)	60 (*R*)
22	**1g**	MeOH	PhCOOH (4.19)	83 (*R*)
23	**1g**	MeOH	DNP (3.96)	50 (*R*)
24	**1g**	MeOH	HCOOH (3.75)	74 (*R*)
25	**1g**	MeOH	salicylic acid (2.98)	45 (*R*)
26	**1g**	MeOH	$ClCH_2COOH$ (2.82)	10 (*R*)
27	**1g**	MeOH	TFA (0.23)	
28	**1a**	MeOH	PhCOOH	30 (*R*)
29	**1b**	MeOH	PhCOOH	31 (*R*)
30	**1c**	MeOH	PhCOOH	13 (*R*)
31	**1d**	MeOH	PhCOOH	47 (*R*)
32	**1e**	MeOH	PhCOOH	60 (*R*)
33	**1f**	MeOH	PhCOOH	58 (*R*)
34	**1h**	MeOH	PhCOOH	73 (*R*)
35	**1i**	MeOH	PhCOOH	19 (*R*)
36[g]	**1g**	MeOH	PhCOOH	91 (*R*)
37[h]	**1g**	MeOH	PhCOOH	95 (*R*)

[a] 10 mol % of peptide was used unless noted otherwise. [b] 10 mol % of additive was used. PNP = *p*-nitrophenol. [c] Determined by chiral HPLC. [d] MeOH/THF 1:1 (v/v). [e] DMSO/H_2O 100/1 (v/v). [f] DCE = 1,2-dichloroethane. [g] 20 mol % of catalyst and 20 mol % of additive were used. [h] 20 mol % of catalyst and 40 mol % of additive were used.

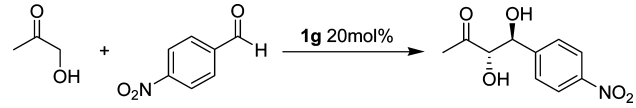
TABLE 2. Reaction of Acetone and Cyclic Ketones with Aldehydes[a]



entry	R_1	R_2,R_3	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	4-NO_2	H,H	78	58		95
2	3-NO_2	H,H	70	29		87
3	2-NO_2	H,H	66	55		61
4	4-CF_3	H,H	72	44		93
5	2-CF_3	H,H	120	20		81
6	2-Cl	H,H	94	30		85
7	2,4-di-Cl	H,H	72	47		91
8	1-Naph	H,H	144	12		94
9	2-Naph	H,H	144	10		96
10[e]	4-NO_2	H,^{i}Bu	240	24		93
11	4-NO_2	$-(CH_2)_3-$	76	87	36/64	86(51)[f]
12	2-NO_2	$-(CH_2)_3-$	72	60	53/47	37(81)[f]
13	4-NO_2	$-(CH_2)_2-$	36	84	2/1	73(81)[f]

[a] Entries 1−9, MeOH/acetone 3:2 (v/v); entry 10, MeOH/methyl isobutyl ketone, 3:2 (v/v); entries 11 and 12, MeOH/cyclohexanone, 3/2 (v/v); entry 13, MeOH/cyclopentanone, 3/2 (v/v). [b] Isolated yields. [c] Determined (*anti/syn*) by chiral HPLC. [d] Determined by chiral HPLC. [e] Linear isomer determined by ^{1}H NMR. [f] Ee of *anti* isomer; ee in parentheses is of the *syn* isomer.

TABLE 3. Optimization of Aldol Reaction of Hydroxyacetone[a]



entry	solvent[b]	additive (mol %)	time (h)	*anti/syn*[c]	ee (%)[d]
1	MeOH	PhCOOH (40)	7	40/60	42
2	DMF	PhCOOH (40)	2	42/58	32
3	THF	PhCOOH (40)	2	41/59	38
4	CH_2Cl_2	PhCOOH (40)	2	47/53	38
5	CH_3CN	PhCOOH (40)	1.5	42/58	51
6	CH_3CN	4-NO_2PhCO$_2$H (20)	1	56/44	75
7	CH_3CN	2-NO_2PhCO$_2$H (20)	1.5	56/44	73
8	CH_3CN	4-NO_2Phenol (20)	1	61/39	76
9	CH_3CN	3-NO_2Phenol (20)	2	62/38	78
10	CH_3CN	2-naphthnol (20)	1.5	58/42	76
11	CH_3CN	(*S*)-BINOL (20)	1.5	63/37	81
12	CH_3CN		2	43/57	49
13[e]	CH_3CN	(*S*)-BINOL (20)	24		
14	CH_3CN	(*R*)-BINOL (20)	1.5	67/33	79
15[f]	CH_3CN	(*S*)-BINOL (20)	14	66/34	80
16[g]	CH_3CN	(*S*)-BINOL (20)	30	74/26	87
17[g]	CH_3CN	(*S*)-BINOL (40)	30	73/27	85

[a] 0.2 mmol reaction at room temperature unless noted otherwise. [b] Hydroxyacetone/solvent 2/3 (v/v). [c] Determined by chiral HPLC. [d] Ee of *anti* isomer, determined by chiral HPLC. [e] No peptide was used as catalyst. [f] Reaction at 0 °C. [g] Reaction at −10 °C.

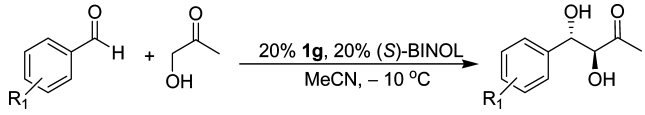
an obvious red-shifted and higher positive absorbance curve from 215 to 225 nm in comparison with similar spectra in methanol and ethanol. Thus, it could be conceivable that higher conformations or secondary structures of this series peptidic catalysts should be intensively solvent dependent. The intensive secondary β-turn structure of **1g** formed in methanol would contribute to high enantioselectivity and (*R*)-configuration, whereas the greatly varied secondary structure of **1g** in DCE should contribute to the low enantioselectivity and (*S*)-configuration. Moreover, it can be clearly observed that addition of benzoic acid greatly enhanced the ellipticity of **1g** in methanol but did not cause any shift of the curve in the wavelength. This intensified absorbance should contribute well to the much higher enantioselectivity of **1g** in methanol with the additive benzoic acid.

The NOE experiments (see Figures S2 and S3 in the Supporting Information) in methanol indicate the presence of a type II β-turn structure that is in good accord with the investigation on the CD curves. The β-turn for tetrapeptide **1g** is supported by the observation of the strong NH (Gly)-NH (Leu) NOE and the C$^{\alpha}$H (Pro)-NH (Leu) NOE. In addition, a type II β-turn can result from the characterized strong C$^{\alpha}$H (Pro)-NH (Gly) NOE.[22a,23] A similar tendency with benzoic acid (**1g**: PhCOOH = 1:2) as the additive can also be observed. And the main difference between the spectra with and without benzoic acid in methanol is that the strong signals from benzoic acid in the benzene ring region made the spectra more confusing. It is surprising that no cis rotamer was noted in the NMR.

(22) (a) Imperiali, B.; Fisher, S. L.; Moats, R. A.; Prins, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 3182. (b) Brahms, S.; Brahms, J. *J. Mol. Biol.* **1980**, *138*, 149. (c) Dutt, A.; Dutta, A.; Mondal, R.; Spencer, E. C.; Howard, J. A. K.; Pramanik, A. *Tetrahedron* **2007**, *63*, 10282.

(23) (a) Raghothama, S. R.; Awasthi, S. K.; Balaram, P. *J. Chem. Soc., Perkin Trans. 2* **1998**, 137. (b) Morikis, D.; Roy, M.; Sahu, A.; Troganis, A.; Jennings, P. A.; Tsokos, G. C.; Lambris, J. D. *J. Biol. Chem.* **2002**, *277*, 14942.

TABLE 4. Aldol Reaction of Hydroxyacetone with Aromatic Aldehydes[a]



entry	R_1	time (h)	yield (%)[b]	anti/syn[c]	ee (%)[d]
1	4-NO_2	30	>99	74/26	87
2	3-NO_2	72	89	47/53	62
3	2-NO_2	72	85	63/37	91
4	4-CF_3	42	57	63/37	68
5	2-CF_3	72	42	63/37	81
6	2-Cl	60	56	60/40	73

[a] 0.2 mmol reaction in 0.6 mL of CH_3CN and 0.4 mL of hydroxyacetone at −10 °C. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Ee of *anti* isomer, determined by chiral HPLC.

In summary, several *N*-primary-amine-terminal tetrapeptides with β-turn nucleating segments were designed and synthesized, and were first applied to catalyze the asymmetric aldol reaction. Tetrapeptide **1g**, based on the conformationally highly restricted sequence D-Pro-Gly, was an efficient organocatalyst when it formed a stable β-turn secondary structure in methanol. It could catalyze the highly enantioselective reactions of acetone with aldehydes in the addition of benzoic acid. The solvents not only influenced the enantioselectivity but also the asymmetric induction of the reaction. A strongly polar solvent such as MeOH could give the (*R*)-aldols, whereas apolar and weakly polar solvents such as DCE afforded the (*S*)-aldols. Both of the CD and NOESY spectra showed the presence of the clear β-turn secondary structure in MeOH, which should contribute to (*R*)-aldols and high enantioselectivity. In the aldol reaction of hydroxyacetone, however, the solvents only affected the values of the enantioselectivities but not the asymmetric inductions. Therefore secondary structures of the tetrapeptide which are greatly dependent upon the varied solvents could not surprisingly have effects on the asymmetric induction on account of the strong behavior of hydroxyacetone in the reaction. The peptide **1g** harvested (*S*,*S*)-aldols in MeCN with the additive BINOL, and achieved the highest enantioselectivity of the branched isomeric products of hydroxyacetone with peptidic organocatalyts. Interestingly, the same peptidic catalyst was used to catalyze the reactions of different ketones, acetone and **hydroxy**acetone, but afforded different configuration aldols.

Experimental Section

General Procedure for Synthesis of Peptides 4a−c.[24] Boc-Val-OH (1.8 g, 8.27 mmol) was stirred with HOBt (1.36 g, 9.1 mmol) and DIC (1.41 mL, 9.1 mmol) in THF (25 mL) at 0 °C for 0.5 h. A mixture of D-Pro-OBn·HCl (2 g, 8.27 mmol) and NMM (1 mL, 9.1 mmol) in DMF (4 mL) was added, and the reaction was stirred for another 48 h. The insoluble byproduct was filtered off and the filtrate evaporated to dryness. The remaining oily residue was dissolved in EtOAc, and extracted successively with saturated aqueous $NaHCO_3$ solution, water, aqueous HCl (1.0 M), and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was recrystallized with petroleum ether and ethyl acetate to give the dipeptide **4a** as a white crystal (2.5 g, 75%). Mp 109 °C; $[\alpha]^{20}_D$ +47 (*c* 0.76, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.39 (m, 5H), 5.23−5.25 (d, *J* = 10.8 Hz, 1H), 5.11−5.20 (m, 2H), 4.47−4.50 (dd, *J* = 3.2 Hz, *J* = 8.8 Hz, 1H), 4.33−4.36 (dd, *J* = 6.4 Hz, *J* = 9.2 Hz, 1H), 3.85−3.89 (m, 1H), 3.53−3.59 (m, 1H), 2.06−2.22 (m, 2H), 1.93−2.04 (m, 3H), 1.39−1.48 (m, 9H), 0.96−0.98 (d, *J* = 6.8 Hz, 3H), 0.90−0.92 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 170.9, 155.7, 135.7, 128.6, 128.5, 128.2, 128.0, 79.4, 66.7, 58.9, 56.8, 47.1, 31.5, 29.1, 28.3, 24.6, 19.6, 17.3; ESI-MS calcd for $[C_{22}H_{32}N_4O_5 + H^+]$ 405.2, found 405.2, and calcd for $[C_{22}H_{32}N_4O_5 + Na^+]$ 427.2, found 427.2.

General Procedure for Synthesis of Peptides 4d−e.[25] To a solution of Boc-Gly-OH (2 g, 11.4 mmol) in THF (40 mL) was added NMM (1.26 mL, 12.54 mmol) dropwise at −15 °C, followed by *i*-BuOCOCl (1.64 mL, 12.54 mmol). After 3−5 min, a mixture of Leu-OBn·TOSOH (4.48 g, 11.4 mmol) and NMM (1.26 mL, 12.54 mmol) in DMF (6 mL) was added dropwise. The mixture was stirred at −15 °C for 30 min and then for 4 h at room temperature. The insoluble byproducts formed were filtered off and the filtrate was evaporated to dryness. The remaining oily residue was dissolved in EtOAc and extracted successively with saturated aqueous $NaHCO_3$, water, aqueous HCl (1.0 M), and brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo, to provide **4e** as an oil (4.34 g, 100%). $[\alpha]^{20}_D$ −4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.39 (m, 5H), 6.78−6.80 (d, *J* = 7.2 Hz, 1H), 5.36−5.38 (t, *J* = 4.8 Hz, 1H), 5.15 (m, 2H), 4.68 (m, 1H), 3.81−3.85 (dd, *J* = 5.2 Hz, *J* = 11.2 Hz, 2H), 1.50−1.67 (m, 3H), 1.45 (s, 9H), 0.90−0.91 (m, 6H); ESI-MS calcd for $[C_{20}H_{30}N_2O_5 + H^+]$ 379.2, found 379.3, and calcd for $[C_{20}H_{30}N_2O_5 + Na^+]$ 401.2, found 401.3.

General Procedure for Synthesis of Peptides 6a−f. Debenzylation was carried out by dissolving **4a** (2 g, 4.95 mmol) in MeOH, successively introduced with Pd/C (10 m%, 200 mg). Stirring under H_2 atmosphere continued for 2 h. After this period the Pd/C residue was filtered and the collected solvent was evaporated to provide **5a** (1.56 g, quantitative). This compound was directly used in the next synthetic step with no further purification.

To the dipeptide **4e** (2 g, 5.29 mmol) was added a solution of TFA (5.3 mL) in CH_2Cl_2 (5.3 mL) at 0 °C. After 2 h of stirring the acid was removed under reduced pressure. The remaining oily residue was dissolved in CH_2Cl_2, and then adjusted to about pH 10.0 with aqueous NaOH (1.0 M). The organic layer was separated, and the aqueous layer was re-extracted three times with CH_2Cl_2. Then the combined organic layers were washed with a little brine, dried with anhydrous Na_2SO_4, and condensed to dryness in vacuo to afford **5e** as an oil (1.40 g, 95%). This compound was directly used in the next synthetic step with no further purification.

To a solution of **5a** (1.56 g, 4.95 mmol) in THF (20 mL) was added NMM (0.60 mL, 5.45 mmol) dropwise under an argon atmosphere at −15 °C, followed by *i*-BuOCOCl (0.71 mL, 5.45 mmol). After 5 min, a mixture of **5e** (1.38 g, 4.95 mmol) and NMM (0.60 mL, 5.45 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at the same temperature for 30 min successively at room temperature for 4 h. The insoluble byproducts formed were filtered off and the filtrate evaporated to dryness. The remaining oily residue was dissolved in EtOAc and extracted successively with saturated aqueous $NaHCO_3$, water, aqueous HCl (1.0 M), and saturated brine and then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was recrystallized with petroleum ether and ethyl acetate to give the desired product **6f** as a white crystal (2.05 g, 72%). Mp 123.5−125.5 °C; $[\alpha]^{20}_D$ −15 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.36 (m, 5H), 7.23−7.24 (m, 1H), 5.32−5.34 (d, *J* = 6.8 Hz, 1H), 5.13−5.20 (dd, *J* = 12.4 Hz, *J* = 14.8 Hz, 2H), 4.59−4.64 (m, 1H), 4.47−4.50 (t, *J* = 6.0 Hz,1H), 4.14−4.20 (dd, *J* = 7.2 Hz, *J* = 16.8 Hz, 1H), 4.07 (m, 1H), 3.94−3.98 (m, 1H), 3.56−3.65 (m, 2H), 2.16−2.21 (m, 2H), 1.99−2.09 (m, 2H), 1.90−1.95 (m, 1H), 1.61−1.76 (m, 3H), 1.40 (s, 9H), 1.00−1.01 (d, *J* = 6.8 Hz, 3H), 0.95−0.97 (d,

(24) Larroque, A.-L.; Dubois, J.; Thoret, S.; Aubert, G.; Chiaroni, A.; Guéritte, F.; Guénard, D. *Bioorg. Med. Chem.* **2007**, *15*, 563.

(25) Marshall, G. R.; Beusen, D. D.; Kociolek, K.; Redlinski, A. S.; Leplawy, M. T.; Pan, Y.; Schaefer, J. *J. Am. Chem. Soc.* **1990**, *112*, 963.

J = 6.8 Hz, 3H), 0.88−0.92 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.7, 169.0, 156.9, 135.7, 128.4, 128.0, 127.8, 80.3, 66.4, 61.0, 58.2, 50.7, 47.6, 43.1, 40.7, 30.1, 29.2, 28.1, 24.6, 23.4, 22.8, 21.7, 19.1, 18.8; ESI-MS calcd for [$C_{30}H_{46}N_4O_7$ + H^+] 575.3, found 575.3.

General Procedure for Synthesis of Peptides 6g,h.[26] Compound **7** was quantitatively prepared according to the same procedure as peptide **5a** and directly used in the next step without further purification. To a solution of **7** (803 mg, 2.38 mmol) in THF (10 mL) was added NMM (0.29 mL, 2.62 mmol) dropwise under an argon atmosphere at −15 °C, followed by *i*-BuOCOCl (0.34 mL, 2.62 mmol). After 5 min, a mixture of Ala-OBn·TOSOH (834 mg, 2.38 mmol) and NMM (0.29 mL, 2.62 mmol) in DMF (2 mL) was added dropwise. The mixture was stirred at the same temperature for 30 min successively at room temperature for 4 h. The insoluble byproducts formed were filtered off and the filtrate was evaporated to dryness. The remaining oily residue was dissolved in EtOAc and extracted successively with saturated aqueous $NaHCO_3$, water, aqueous HCl (1.0 M), and brine and then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was recrystallized with petroleum ether and ethyl acetate to give the desired product **6g** as a white crystal (734 mg, 58%). Mp 129−131 °C; $[\alpha]^{20}_D$ −3 (c 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.41 (m, 6H), 5.33−5.35 (d, J = 6.4 Hz, 1H), 5.11−5.17 (m, 2H), 4.56−4.61 (m, 1H), 4.50−4.52 (m, 1H), 3.96−4.15 (m, 3H), 3.65−3.70 (dd, J = 6.0 Hz, J = 17.6 Hz, 1H), 3.56−3.62 (dd, J = 8.0 Hz, J = 17.2 Hz, 1H), 1.91−2.22 (m, 5H), 1.44−1.46 (d, J = 7.2 Hz, 3H), 1.38−1.40 (m, 9H), 1.00−1.02 (m, 3H), 0.95−0.97 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 172.6, 171.7, 168.8, 155.8, 135.6, 128.5, 128.2, 127.9, 80.4, 66.6, 61.0, 58.3, 48.1, 47.7, 43.1, 30.3, 29.1, 28.3, 28.2, 24.7, 19.2, 18.8, 17.9; ESI-MS calcd for [$C_{27}H_{40}N_4O_7$ + H^+] 533.3, found 533.2, and calcd for [$C_{27}H_{40}N_4O_7$ + Na^+] 555.3, found 555.2.

General Procedure for Synthesis of Peptides 1a−h. To the tetrapeptide **6f** (1.93 g, 3.37 mmol) was added a solution of TFA (3.4 mL) in CH_2Cl_2 (3.4 mL) at 0 °C. After 4 h of stirring, the acid was removed under reduced pressure. The remaining oily residue was dissolved in CH_2Cl_2, and then adjusted to about pH 10.0 with aqueous NaOH (1.0 M). The organic layer was separated, and the aqueous layer was re-extracted three times with CH_2Cl_2. Then the combined organic layers were washed with a little brine, dried with anhydrous Na_2SO_4, and condensed to dryness in vacuo (1.47 g, 3.10 mmol, yield 92%). The remaining residue was dissolved in MeOH, introduced with Pd/C (10 mol %, 147 mg). Stirring under H_2 atmosphere was continued for 2 h. After this period, Pd/C was filtered and the collected solvent was evaporated. The obtained white solid was refluxed in ether for 10 min, then filtered immediately to provide **1g** (1.06 g, 89%). Mp 152−154 °C; $[\alpha]^{20}_D$ +58 (*c* 0.85, H_2O); FT-IR (solid) 3248, 2956, 2866, 1690, 1650, 1558, 1516 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 4.30−4.33 (m, 1H), 4.06−4.09 (d, J = 8.7 Hz, 2H), 3.81 (s, 1H), 3.62−3.72 (m, 2H), 3.51−3.59 (m, 1H), 2.13−2.22 (m, 2H), 1.86−1.93 (m, 3H), 1.40−1.55 (m, 3H), 0.91−0.93 (d, J = 6.9 Hz, 3H), 0.83−0.85 (d, J = 6.9 Hz, 3H), 0.73−0.75 (d, J = 5.1 Hz, 3H), 0.69−0.71 (d, J = 5.1 Hz, 3H); ^{13}C NMR (75 MHz, D_2O) δ 179.0, 174.3, 170.3, 169.0, 61.1, 57.1, 53.5, 48.0, 42.3, 40.5, 29.2, 28.6, 24.5, 24.2, 22.4, 20.4, 17.9, 15.9; ESI-MS calcd for [$C_{18}H_{32}N_4O_5$ + H^+] 385.2, found 385.2, calcd for [$C_{18}H_{32}N_4O_5$ + Na^+] 407.2, found 407.2; HRMS calcd for [$C_{18}H_{32}N_4O_5$ + H^+] 385.2445, found 385.2438.

General Procedure for Synthesis of Peptides 1i. To the tetrapeptide **6h** (0.5 g, 1 mmol) was added a solution of TFA (1 mL) in CH_2Cl_2 (1 mL) at 0 °C. After the mixture was stirred for 4 h, the acid was removed under reduced pressure. The remaining residue was dissolved in CH_2Cl_2, then the pH was adjusted to 10.0 or so with aqueous ammonia (2.0 M). The organic layer was separated, and the aqueous layer was re-extracted three times with CH_2Cl_2. Then the combined organic layers were washed with a little brine, dried with anhydrous Na_2SO_4, and condensed to dryness in vacuo to give the desired product **1i** (0.35 g, yield 87%). $[\alpha]^{20}_D$ +48 (*c* 1.0, $CHCl_3$); FT-IR 3297, 3068, 2958, 2874, 1744, 1668, 1626 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.57 (m, 1H), 7.42−7.44 (d, J = 7.2 Hz, 1H), 4.49−4.55 (m, 1H), 4.42−4.46 (m, 1H), 4.21−4.27 (dd, J = 7.6 Hz, J = 17.2 Hz, 1H), 3.81−3.87 (m, 1H), 3.69 (s, 3H), 3.64−3.65 (d, J = 5.2 Hz, 1H), 3.54−3.60 (m, 1H), 3.27−3.28 (d, J = 6.8 Hz, 1H), 2.46 (br, 2H), 1.98−2.46 (m, 4H), 1.85−1.90 (m, 1H), 1.69−1.82 (m, 2H), 1.59−1.64 (m, 1H), 0.90−0.99 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 174.0, 171.9, 169.5, 61.0, 58.9, 52.1, 50.7, 47.4, 42.7, 40.4, 31.9, 29.0, 24.8, 24.7, 22.9, 21.6, 19.8, 17.5; HRMS calcd for [$C_{19}H_{34}N_4O_5$ + H^+] 399.2602, found 399.2604.

General Procedure for Asymmetric Aldol Reaction of Acetone and Aldehydes. Tetrapeptide **1g** (0.04 mmol) and benzoic acid (0.08 mmol) were added into a mixture of aldehyde (0.2 mmol) and dry ketone (0.4 mL) in MeOH (0.6 mL). The reaction was stirred to completion monitored by TLC, and then saturated aqueous NH_4Cl (2 mL) was added to quench the reaction. Subsequently, the mixture was extracted with EtOAc three times. The organic layers were combined, dried with anhydrous Na_2SO_4, concentrated in vacuo, and purified by preparative TLC or column to yield the desired aldol product.

(*R*)-4-Hydroxy-4-(4-nitrophenyl)butan-2-one (2a):[6,8] yield 58%; 95% ee; $[\alpha]^{20}_D$ +45 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16−8.23 (m, 2H), 7.52−7.58 (m, 2H), 5.24−5.30 (m,1H), 3.60 (br, 1H), 2.84−2.88 (m, 2H), 2.23 (s, 3H); ee was determined by HPLC with a AS-H column (hexane:2-propanol = 95:5), 1.0 mL/min, t_R = 13.48 min for (*R*)-enantiomer (major) and 18.97 min for (*S*)-enantiomer (minor).

General Procedure for Asymmetric Aldol Reaction of Hydroxyacetone and Aldehydes. Peptide **1g** (0.04 mmol) and (*S*)-BINOL (0.04 mmol) were added to a solution of aldehyde (0.2 mmol) in CH_3CN (0.6 mL). After the mixture was cooled to −10 °C, hydroxyacetone (0.4 mL) was added. The reaction was stirred to completion monitored by TLC, and then saturated aqueous NH_4Cl (2 mL) was added to quench the reaction. Subsequently, the mixture was extracted with EtOAc three times. The organic layers were combined, dried with anhydrous Na_2SO_4, concentrated in vacuo, and purified by preparative TLC or column to yield the desired aldol product.

(3*S*,4*S*)-4-(4-Nitrophenyl)-3,4-dihydroxybutan-2-one (3a):[21] yield 99% (*anti* and *syn*); *anti*/*syn* 74/26; 87% ee (*anti*); $[\alpha]^{20}_D$ −12 (*c* 2.0, MeOH); **(*anti*-3a)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.26 (m, 2H), 7.61−7.63 (d, J = 8.4 Hz, 2H), 5.10−5.11 (d, J = 3.2 Hz, 1H), 4.48 (m, 1H), 3.75−3.76 (d, J = 4.0 Hz, 1H), 3.14 (s, 1H), 2.03 (s, 3H); **(*syn*-3a)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.26 (m, 2H), 7.61−7.63 (d, J = 8.4 Hz, 2H), 5.24 (s, 1H), 4.42 (s, 1H), 3.78−3.79 (d, J = 4.4 Hz, 1H), 2.93−2.94 (d, J = 7.2 Hz, 1H), 2.38 (s, 3H); diastereomeric ratio and enantiomeric excess determined by HPLC with a AD-H column (hexane:2-propanol = 70:30), 1.0 mL/min, t_R = 5.41 (major for *S*,*S* isomer) and 5.96 (minor for *R*,*R* isomer) min for the *anti* isomers, 6.55 and 8.10 min for the *syn* isomers.

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Supporting Information Available: CD spectra, 2D NMR (NOESY), characterization of compounds, and spectra (^{1}H NMR, ^{13}C NMR, and HPLC). This material is available free of charge via the Internet at http://pubs.acs.org.

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