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Highly Modular Dipeptide-like Organocatalysts for Direct Asymmetric Aldol Reactions in Brine

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Xiao-Mu Hu,[a] Dong-Xu Zhang,[a] Sheng-Yong Zhang*[a] and Ping-An Wang*[a]

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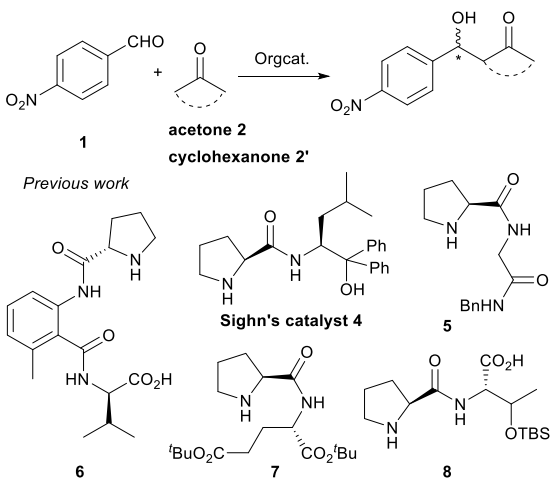
A novel series of dipeptide-like organocatalysts derived from proline, amino acids and primary amines have been prepared for direct asymmetric aldol reactions between various aromatic aldehydes and acetone to afford aldol products in good yields (up to 82%) and moderate enantioselectivities (up to 67% *ee*) with only 1 mol% of catalyst-loading in brine. Under the same conditions, the direct asymmetric aldol reactions of aromatic aldehydes and cyclohexanone give aldol products with high yields (up to 91%) and moderate to good enantioselectivities (up to 88% *ee*) and excellent diastereoselectivities (up to 99% dr). These organocatalysts are easily synthesized from commercially available materials in multi-gram scale with high modularity in their structural and stereogenic properties.

Introduction

The direct aldol reaction is one of most fundamental reactions for carbon-carbon bond formation.[1,2] Many efforts are devoted to develop highly efficient asymmetric version of this important reaction both in metal[3] or metal-free catalytic conditions.[4] Since the prominent achievements of List and Barbas III on proline catalysis,[5] a large number of organocatalysts have been prepared and applied in direct aldol reactions between various aldehydes and ketones to achieve excellent yields and enantioselectivities.[6-19]

Peptides are common bio-molecules and constituents in living organisms, and play vital roles in variously biological activities. In modern organic synthesis, small peptides can be used as catalysts and ligands for enantioselective transformations[20] such as acylation,[21] epoxidation,[22] and cyclopropanation.[23] Undoubtedly, the research of organic synthesis in or on aqueous medium is attractive to chemists by its environmentally benign property and easily handled process.[24] Since Janda's[25] pioneering work on direct asymmetric aldol reactions in water, Barbas III,[26] Hayashi,[27] and Singh[28] *et al.* have independently developed enantioselective aldol reactions in aqueous media to achieve excellent results. Small peptides are also utilized as organocatalysts for direct asymmetric aldol reactions in water or brine to afford aldols in good yields and enantioselectivities,[29] and some elegant examples[30] are listed in Figure 1. However, the high catalyst-loading (usually 10~30 mol%) and additives are necessary to ensure good yields and enantioselectivities in most cases, and the low-loading organocatalysts without any additive for the direct asymmetric aldol reactions under aqueous conditions are rare.



Substrate	Conditions	Yield(%)	*ee*(%)	ref.
2	0.5mol% **4**, brine, -5°C, 10-16h	78	86	[28]
2'	same as above conditions	88	86	[28]
2	20mol% **5**, brine, r.t., 48h	75	60	[30a]
2'	same as above conditions	100	92	[30a]
2	10mol% **6**, 5mol% TFA, DMSO, 5.5eq. H_2O, 4°C	55	87	[30b]
2'	same as above conditions	76	99	[30b]
2	20mol% **7**, 20mol% 4-NBA, r.t., MeCN/H_2O(10/1, V/V)	100	73	[30c]
2'	20mol% **7**, 20mol% 4-NBA, r.t., brine	100	87	[30c]
2	20mol% **8**, H_2O, r.t.	35	31	[30d]

Figure 1. Typical small peptides catalysed direct aldol reactions.

In this paper, we have presented the preparation and application of a novel class of highly modular dipeptide-like organocatalysts derived from proline, amino acids and primary

amines for direct aldol reactions between various aromatic aldehydes and ketones in brine to provide aldol products in excellent yields and moderate to good enantioselectivities with only 1 mol% of catalyst-loading (Figure 2). Different amino acid tethered proline-skeletons were compared and their catalytic behaviour was also evaluated in this study.

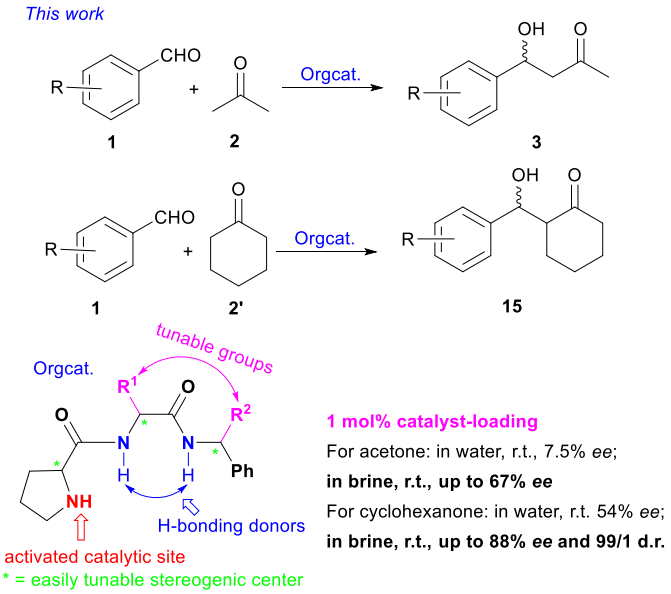
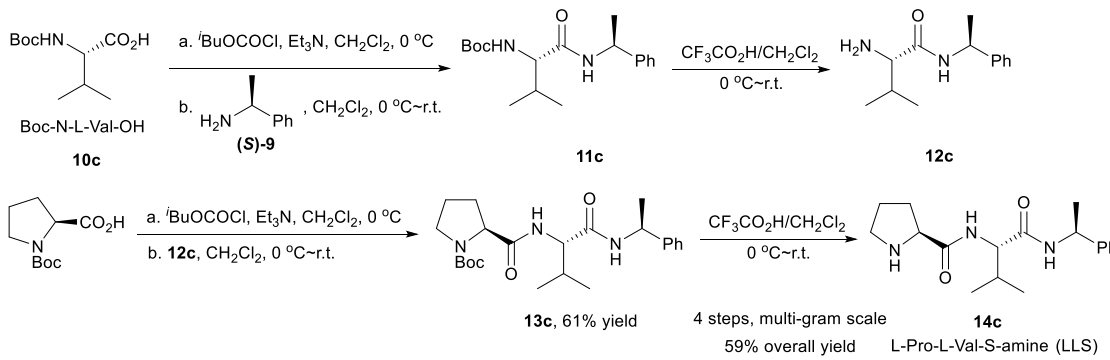


Figure 2. Dipeptide-like organocatalysts in this study.

Synthesis of Dipeptide-like Organocatalysts

The synthesis of these dipeptide-like organocatalysts is very straightforward and shown in Scheme 1. The coupling of the chiral (or achiral) primary amines **9** with different Boc-protected amino acids **10** under the mixed-anhydride conditions provides the intermediates **11** in high yields which directly followed the deprotection of Boc-group to afford the amines **12**. The connection of **12** with Boc-proline can produce **13** which undergo the deprotection to yield the final dipeptide-like organocatalysts **14** (Figure 3). Only one column chromatographic purification of the intermediates **13** needed in the third step. The organocatalysts **14b-e** derived from L-proline and (*S*)-methylbenzylamine but containing different amino acid motifs in the middle part of the structures, are prepared for the detection of the steric effect on their chiral induction abilities in the direct aldol reactions. The family of **14f-h** are synthesized from chiral methylbenzylamine, valine and proline but with different configurations to investigate the effect of the tunably stereogenic centers on aldol reactions. The organocatalyst **14i** with the ending group of benzylamine is used in the direct aldol reaction to show the necessity of the chiral or achiral primary amine group in these dipeptide-like analogues. The catalyst **14a** [from L-Proline and (*S*)-methylbenzylamine] are used as catalysts for the comparison with the peformace of the above dipeptide-like organocatalysts **14b-i** in the direct aldol reactions.

Results and discussion



Scheme 1. The synthetic route to **14c**

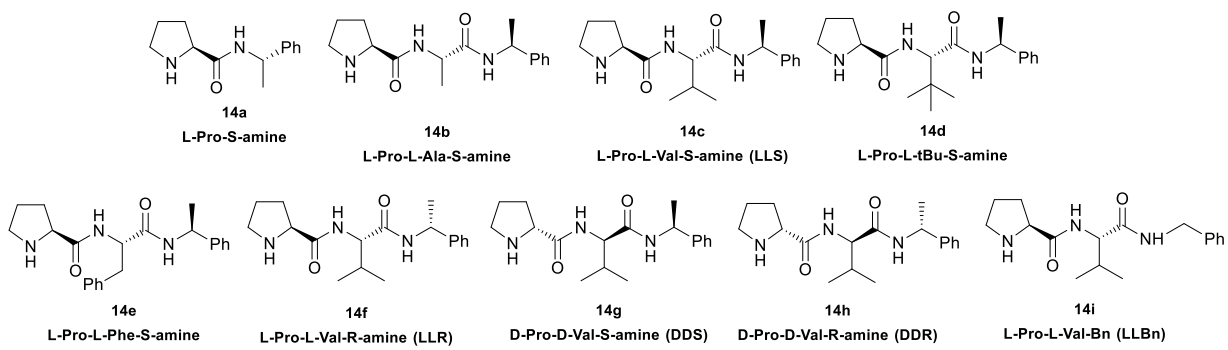


Figure 3. The structures of organocatalysts **14a-i**.

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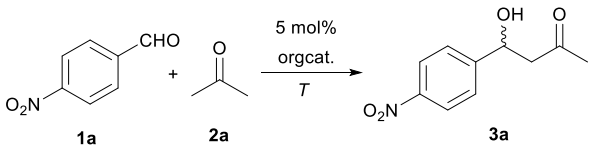
Direct Aldol Reactions by Using Dipeptide-like Organocatalysts

With these above dipeptide-like organocatalysts **14b-i** in hand, the direct aldol reaction of 4-nitrobenzyaldehyde and acetone was chosen as the model reaction for the test of the activities of catalysts. Initially, the reaction was performed under neat conditions at room temperature (r.t.) with catalysts L-proline (30 mol%), and **14a-e** (5 mol% respectively), and the results are shown in the Table 1. From the Table 1, it was found that L-proline was the effective catalyst to give moderate yield (76%) and relatively good enantioselectivity (67% *ee*) of aldol product (Table 1, entry 1) but with a large amount of catalyst-loading. The catalyst **14a** with slightly positive result of aldol reaction has good yield (87%) but with very low enantioselectivity (Table 1, entry 2, 20% *ee*). The catalyst **14b** from L-proline, L-alanine and (*S*)-methylbenzylamine (L-Pro-L-Ala-*S*-amine) gives 82% yield and 37% *ee* of aldol product (Table 1, entry 3). With the increase of the steric hindrance of the middle part of the catalysts, the yield and the enantioselectivity of aldol adduct is also significantly increased (Table 1, entries 3, 4 and 5). To our surprise, the most hindered *t*-Bu in the middle part of catalyst **14d** affords lower yield and enantioselectivity than the catalyst **14c** (L-Pro-L-Val-*S*-amine, LLS, Table 1, entry 4 vs 5). The catalyst **14e** with L-Phe in the midde part results the lower enantioselectivity than **14c** (Table 1, entry 6 vs 4). When the reaction is performed at -40 ^{o}C in neat acetone, the yield of aldol product is decreased but with the increase of the enantioselectivity (Table 1, entry 6 with **14c**, 75% *ee* vs 57% *ee*) and the sacrifice of reaction time (up to 3 days).

In order to investigate the effect of the tunable stereogenic centers of catalysts on aldol reactions, **14f** (L-Pro-L-Val-*R*-amine, LLR), **14g** (D-Pro-D-Val-*S*-amine, DDS), **14h** (D-Pro-D-Val-*R*-amine, DDR) and **14i** (L-Pro-L-Val-Bn, LLBn) were prepared respectively. The direct aldol reactions of 4-nitrobenzyaldehyde and acetone under neat condition at r.t. or at -40 ^{o}C were performed by using these above catalysts. It was found that the configuration of the chiral carbon atom in the terminal amine of catalysts is changed from (*S*)- to (*R*)-, the enantioselectivity of aldol product is slightly increased from 75% (r.t., with catalyst **14c**) to 80% *ee* (-40^{o}C, with catalyst **14f**, Table 1, entry 4 vs 7). Switching the configuration of proline motif of catalysts from L- to D-, the configurations of aldol product are also changed to be their opposite configurations (Table 1, entries 4, 7 vs 8, 9). When the terminal amine is achiral (catalyst **14i**), the enantioselectivity of aldol product is decreased (Table 1, entry 10). These results indicate that the different stereogenic centers in these dipeptide-like catalysts can produce the obviously different enantioselective inductions and **14f** is the best choice both at r.t. and -40 ^{o}C on the direct aldol reactions.

Table 1. The direct aldol reactions catalyzed by dipeptide-like organocatalysts **14** under neat conditions.

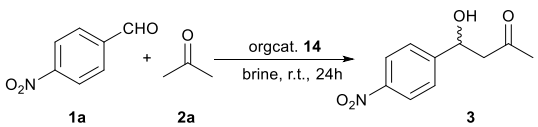


1a **2a** **3a**

		r.t.[b]		-40 ^{o}C[c]	
entry[a,b]	orgcat.	yield(%)	*ee*(%)[d]	yield(%)	*ee*(%)[d]
1[e]	L-pro	76	67(*R*)	-	-
2	**14a**	87	20(*R*)	67	39(*R*)
3	**14b**	82	37(*R*)	62	59(*R*)
4	**14c**	92	57(*R*)	68	75(*R*)
5	**14d**	84	45(*R*)	65	61(*R*)
6	**14e**	84	41(*R*)	67	57(*R*)
7	**14f**	**92**	**55(*R*)**	**63**	**80(*R*)**
8	**14g**	94	57(*S*)	57	53(*S*)
9	**14h**	93	57(*S*)	61	49(*S*)
10	**14i**	90	49(*R*)	59	47(*R*)

a. 0.5 mmol of aldehyde **1a** in 1.0 mL of acetone for every entry. b. The reaction time is 24 h. c. The reaction time is 3 days. d. The enantiomeric excess (*ee*) of aldol product was determined by chiral HPLC with Chiralpak AS-H column. e. 30 mol% of L-proline was used in entry 1.

Table 2. The direct aldol reactions in brine.



1a **2a** **3**

entry[a]	orgcat.(mol%)	yield(%)	*ee*(%)[b]
1	**14c**(5)	79	44(*R*)
2	**14f**(5)	80	45(*R*)
3	**14g**(5)	83	45(*S*)
4	**14h**(5)	82	45(*S*)
5	**14i**(5)	89	35(*R*)
6	**14f**(10)	85	23(*R*)
7	**14f(1)**	**80**	**45(*R*)**
8[c]	**14f**(1)	77	7.5(*R*)

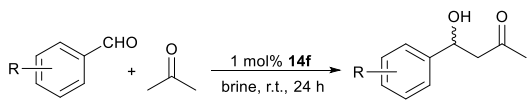
a. 0.5 mmol of aldehyde **1a** and 0.5 mL of acetone in 1.0 mL of brine for every entry. b. The enantiomeric excess (*ee*) of aldol product was determined by chiral HPLC with Chiralpak AS-H column, the configuration of aldol product was assigned by comparison to the literature data. c. The reaction was performed in water.

To the environmental benign concern, the direct aldol reaction was undertaken in brine at r.t. with the catalysts **14c**, **14f-i**. There is a decrease of at least 10 % *ee* for every entry when changing from neat conditions to brine (Table 2, entries 1-5). The catalyst-loading is also investigated. Interestingly, the

enantioselectivity of aldol product is obviously decreased to be 23% *ee* with 10 mol% of catalyst-loading of **14f** (Table 2, entry 6 vs entry 2), and this may due to the reaction switching from kinetic-control to thermodynamic-control.[31] To our delight, when the amount of **14f** is reduced to be 1 mol%, the aldol product is afforded in slightly lower yield (80%) but with relatively stable enantioselectivity (45% *ee*) comparison to 5 mol% of catalyst-loading (Table 2, entry 7 vs entry 2). However, when the reaction was performed in water with 1mol% of catalyst **14f**, the enantioselectivity is decreased dramatically to 7.5% *ee* (Table 2, entry 8 vs entry 7).This shows that these dipeptide-like organocatalysts are highly efficient for the direct aldol reactions in brine but with very poor performance in water.

By using only 1 mol% of dipeptide-like organocatalyst **14f**, the direct aldol reactions of acetone and various aromatic aldehydes (Table 3) with electron-withdrawing or electro-donating group are suitable to brine medium at r.t. to produce aldol adducts in good yields (up to 82%) and moderate enantioselectivities (up to 67% *ee*).

Table 3. The direct aldol reactions between various aromatic aldehydes and acetone in brine with 1 mol% of catalyst **14f**.



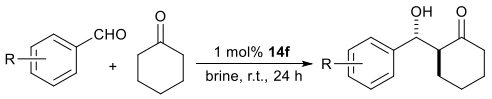
1a-i **2a** **3a-i**

entry[a]	substrate	product	yield(%)	ee(%)[b]
1	**1a** R = 4-NO_2	**3a**	80	45(*R*)
2	**1b** R = 2-NO_2	**3b**	82	60(*R*)
3	**1c** R = 3-NO_2	**3c**	80	56(*R*)
4	**1d** R = 4-Br	**3d**	75	51(*R*)
5	**1e** R = 3-Br	**3e**	78	52(*R*)
6	**1f** R = H	**3f**	60	54(*R*)
7	**1g** R = 2,4-dichloro	**3g**	67	41(*S*)
8	**1h** R = 4-Me	**3h**	61	54(*R*)
9	**1i R = 3-OMe**	**3i**	**65**	**67(*R*)**
10	**1j** R = 3,4,5-$(OMe)_3$	**3j**	78	47(*R*)

a. 0.5 mmol of aldehyde **1** and 0.5 mL of acetone in 0.5 mL of brine for every entry. b. The enantiomeric excess (*ee*) of aldol products **3a-j** was determined by chiral HPLC with Chiralpak AD-H, OD-H and AS-H columns, the configuration of aldol product was assigned by comparison to the literature data.

The direct aldol reaction of 4-nitrobenzyaldehyde and cyclohexanone (Table 4, entry 1) in water with 1 mol% of **14f** afforded **15a** in excellent diastereoselectivity (dr > 98%) and moderate enantioselectivity of anti-product (54% *ee*). However, switching the reaction solvent of water to brine, the enantioselectivity of **15a** is significantly increased to 88% *ee* (Table 4, entry 2). The direct aldol reactions between various aromatic aldehydes **1a-k** and cyclohexanone in brine with 1 mol% of catalyst **14f** were smoothly performed at r.t. to furnish aldols **15a-k** with moderate to good enantioselectivities (except benzyaldehyde **1f**, entry 7, 28% *ee*) and excellent diastereoselective ratios (Table 4, entries 2-12).

Table 4. The direct aldol reactions between various aromatic aldehydes **1a-k** and cyclohexanone in brine with 1 mol% of catalyst **14f**.



1a-k **15a-k**

entry[a]	substrate	product	yield(%)	anti:syn	ee(%)[d]
1[b]	**1a**	**15a**	81	98:2	54
2	**1a**	**15a**	**82**	**96:4**	**88**
3	**1b**	**15b**	89	99:1	68
4	**1c**	**15c**	92	99:1	65
5	**1d**	**15d**	85	98:2	77
6	**1e**	**15e**	86	99:1	76
7	**1f**	**15f**	72	98:2	28
8	**1g**	**15g**	87	99:1	78
9	**1h**	**15h**	76	95:5	84
10	**1i**	**15i**	81	97:3	67
11	**1j**	**15j**	80	89:11	66
12[c]	**1k**	**15k**	91	91:9	81

a. 0.5 mmol of aldehyde **1** and 0.5 mL of acetone in 0.5 mL of brine for entries 2 to 12. b. The reaction was performed in 0.5 mL of acetone with 0.5 mL of water for entry 1. c. For entry 12, the substrate **1k** is 4-chlorobenzyaldehyde. d. The enantiomeric excess (*ee*) of aldol products **15a-k** was determined by chiral HPLC with Chiralpak AD-H column, the configuration of aldol product was assigned by comparison to the literature data.

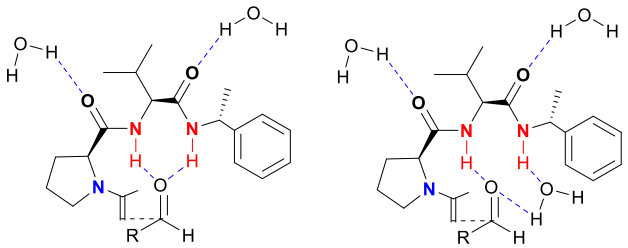


Figure 4. The proposed transition states in brine and in water.

From the above reaction results, we have noticed that not only acetone but also cyclohexanone react with various aromatic aldehydes in brine to afford aldol adducts with superior enantioselectivities to those in water (Table 2, entry 7 vs entry 8; Table 4, entry 2 vs entry 1). This observation may due to the "salting-out effect" increasing "hydrophobic effect" which was found in the previous reports by Barbas III,[26] Hayashi[27] and Singh[28] *et al.*. The OH groups of the surface water molecules in brine may form the proper amount of additional hydrogen bonds with two amide oxygen atoms to make the amidic NH more acidic resulting in a tight transition state in hydrophobic micro-surroundings to ensure the good enantioselectivity. When the aldol reaction was performed in water, a large amount of hydrogen bonds might form not only with two amide oxygen atoms but also with amidic NH groups to deteriorate the stable transition state leading to poor enantioseletivity. The proposed transition states are shown in Figure 4.

In summary, we have prepared a novel series of dipeptide-like organocatalysts for the direct asymmetric aldol reactions of various aromatic aldehydes and acetone in brine with only 1 mol% of catalyst-loading to provide aldol products in good yields (up to 82%) and moderate enantioselectivities (up to 67% *ee*). Additionally, under the same reaction conditions, the direct asymmetric aldol reactions of various aromatic aldehydes with cyclohexanone afford the corresponding aldol adducts in high yields (up to 91%) and moderate to good enantioselectivities (up to 88% *ee*) with excellent diastereoselectivitives (d.r. up to 99%). These dipeptide-like organocatalysts are easily synthesized in multi-gram scale with high tunability in their structural and stereogenic properties. The more complex dipeptide-like organocatalysts with multi-hydrogen bonding sites are investigated in due course.

Experimental

General

Melting points are uncorrected and expressed in ℃ by MRS-2 Melting point apparatus from Shanghai Apparatus Co., Ltd. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$, solution on a Bruker AV-400 spectrometer using TMS as an internal reference. Coupling constant (*J*) values are given in Hz. Multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High-resolution mass spectra were performed on a Bruker microTOF-Q II Mass Spectrometer with ES ionization (ESI). All commercially available reagents were used as received. Thin-layer chromatography on silica (with GF254) was used to monitor all reactions. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured on a Perkin Elmer 343 polarimeter. Chiral High Performance Liquid Chromatography (HPLC) analyses were performed using an Agilent 1200 Series apparatus and Chiralpak AD-H, OD-H and AS-H columns purchased from Daicel Chemical Industries. The configuration of the products has been assigned by comparison to the literature data or assigned by analogy. All reactions involving air- or moisture-sensitive species were performed in oven-dried Schlenk tubes under an inert atmosphere.

Typical synthetic procedure for preparation of dipeptide-like organocatalyst 14c

A solution of Boc-L-Val-OH (**10c**, 2.17g, 10 mmol), Et_3N (1.52g, 15 mmol) and isobutyl chloroformate (1.57mL, 10 mmol) in dichloromethane (DCM, 25 mL) at 0 ^{o}C was stirred for 30 min, after which the (*S*)-(-)-1-Phenylethylamine **9** (11 mmol) was added and stirred at this temperature for 2 h after which it was warmed to room temperature along with stirring overnight. The reaction was monitored by TLC, and then quenched with sat. aq. NH_4Cl (25 mL), and successively washed with H_2O, and brine. Aqueous phase extracted with dichloromethane (3 × 25 mL). The organic layers were dried over Na_2SO_4, filtered, and concentrated to give the crude **11c** as light yellow glue which was directly deprotected by using trifluoroacetic acid (TFA, 4 mL, 52 mmol, 6 equiv.) in 30 mL of DCM to afford the crude product **12c** without further purification. The coupling of Boc-L-Pro-OH (1.72g, 8 mmol) with crude **12c** was performed following the same procedure of the connection of **10c** with **9** to yield the crude **13c** as yellow wax. This crude **13c** was directly undergone the deprotection of Boc-group via TFA (4 mL, 52 mmol) in anhydrous DCM (30 mL) produced the crude product **14c** which was purified by a flash column chromatography (*n*-hexane/ethyl acetate/Et_3N = 1/5/0.05, V/V) to provide the final dipeptide-like organocatalyst **14c** (1.87g, total yield 59% based on Boc-L-Val-OH).

(*S*)-*N*-((*S*)-1-phenylethyl)pyrrolidine-2-carboxamide[32] (14a)

Compound **14a** was prepared from Boc-L-Pro-OH and (*S*)-(-)-1-Phenylethylamine. The same procedure as described above for the preparation of compound **14c** was used.
Yield 72%; white solid; mp 145-147 ^{o}C; $[\alpha]^{25}_D$ = -91.8^o (c = 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 1H), 7.36-7.34 (m, 5H), 5.11 (dd, *J* = 7.2, 1.6 Hz, 1H), 3.75 (dd, *J* = 5.6, 3.6 Hz, 1H), 3.07-3.01 (m, 1H), 2.96-2.90 (m, 1H), 2.21-2.12 (m, 2H), 1.99-1.92 (m, 1H), 1.78-1.50 (m, 2H),1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.95, 143.52, 128.59, 127.18, 126.15, 60.58, 48.03, 47.24, 30.74, 26.16, 22.17; HRMS(ESI$^+$) Calcd. for $C_{13}H_{19}N_2O$ $[M+H]^+$ = 219.1497, Found: 219.1498.

(*S*)-*N*-((*S*)-1-oxo-1-(((*S*)-1-phenylethyl)amino)propan-2-yl)pyrrolidine-2-carboxamide[29f] (14b)

Compound **14b** was prepared from Boc-L-Pro-OH, Boc-L-Ala-OH and (*S*)-(-)-1-Phenylethylamine. The same procedure as described above for the preparation of compound **14c** was used.
Yield 52%; white solid; mp 155-157 ^{o}C; $[\alpha]^{25}_D$ = -216.7^o (c = 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 1H), 7.37-7.26 (m, 5H), 6.96 (d, *J* = 7.2 Hz, 1H), 5.07 (t, *J* = 7.2 Hz, 1H), 4.44 (t, *J* = 7.2 Hz, 1H), 3.78-3.73 (m, 1H), 3.05-3.01 (m, 1H), 2.95-2.91 (m, 1H), 2.15-1.91 (m, 2H), 1.90 (br, 1H), 1.77-1.67 (m, 2H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.36 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.62, 171.26, 143.34, 128.64, 127.23, 126.05, 60.39, 48.90, 48.50, 47.27, 30.69, 26.21, 22.13, 17.73; HRMS(ESI$^+$) Calcd. for $C_{16}H_{24}N_3O_2$ $[M+H]^+$ = 290.1869, Found: 290.1871.

(*S*)-*N*-((*S*)-3-methyl-1-oxo-1-(((*S*)-1-phenylethyl)amino)butan-2-yl)pyrrolidine-2-carboxamide[22a] (14c, LLS)

Compound **14c** was prepared from Boc-L-Pro-OH, Boc-L-Val-OH and (*S*)-(-)-1-Phenylethylamine. Yield 59%; white solid; mp 141-142 ^{o}C; $[\alpha]^{25}_D$ = -98.2^o (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.8 Hz, 1H), 7.34-7.26 (m, 5H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 4.18 (t, *J* = 8.2 Hz, 1H), 3.77 (dd, *J* = 4.8, 4.4 Hz, 1H), 3.08-3.02 (m, 1H), 2.97-2.91 (m, 1H),

2.19-2.10 (m, 3H), 1.97-1.89 (m, 1H), 1.76-1.69 (m, 2H), 1.47 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.36, 170.37, 143.26, 128.61, 127.27, 126.14, 60.48, 58.47, 48.92, 47.31, 30.98, 30.68, 26.16, 21.92, 19.48, 18.12; HRMS(ESI$^+$) Calcd. for $C_{18}H_{28}N_3O_2$ $[M+H]^+$ = 318.2182, Found: 318.2188

(*S*)-*N*-((*S*)-3,3-dimethyl-1-oxo-1-(((*S*)-1-phenylethyl)amino) butan-2-yl)pyrrolidine-2-carboxamide (14d)

Compound **14d** was prepared from Boc-L-Pro-OH, 3-Me-Boc-L-Val-OH and (*S*)-(-)-1-Phenylethylamine. The same procedure as described above for the preparation of compound **14c** was used. Yield 62%; white solid; mp 86-88 ^{o}C; $[\alpha]^{25}_D$ = -80.3^o (c = 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 10.0 Hz, 1H), 7.37-7.26 (m, 5H), 6.94 (d, *J* = 5.6Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 4.31 (d, *J* = 10.0 Hz, 1H), 3.85 (br, 1H), 3.11-2.97 (m, 2H), 2.21-2.11 (m, 1H), 1.97-1.72 (m, 2H), 1.49-1.47 (m, 2H), 1.46 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.43, 169.67, 143.43, 128.52, 127.19, 126.32, 60.48, 60.12, 58.40, 48.96, 47.20, 34.98, 30.96, 26.60, 26.04, 21.89, 18.44; HRMS(ESI$^+$) Calcd. For $C_{19}H_{30}N_3O_2$ $[M+H]^+$ = 332.2338, Found: 332.2337.

(*S*)-*N*-((*S*)-1-oxo-3-phenyl-1-(((*S*)-1-phenylethyl)amino) propan-2-yl)pyrrolidine-2-carboxamide (14e)

Compound **14e** was prepared from Boc-L-Pro-OH, Boc-L-Phe-OH and (*S*)-(-)-1-Phenylethylamine. The same procedure as described above for the preparation of compound **14c** was used. Yield 53%; white solid, mp 107-109 ^{o}C; $[\alpha]^{25}_D$= -15.4^o (c = 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.30-7.12 (m, 10H), 6.64 (d, *J* = 29.3, 7.5 Hz, 1H), 5.02 (t, J = 7.2 Hz, 1H), 4.60 (q, *J* = 8.0 Hz, 1H), 3.64 (dd, *J* = 4.0, 5.2 Hz, 1H), 3.20-2.77 (m, 4H), 2.07-2.02 (m, 2H), 1.75-1.68 (m, 1H), 1.64-1.49 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.71, 169.81, 143.26, 137.21, 129.28, 128.56, 127.17, 126.78, 126.02, 60.23, 58.42, 48.81, 47.09, 30.65, 25.92, 21.97, 18.44; HRMS(ESI$^+$) Calcd. for $C_{22}H_{28}N_3O_2$[M+H]$^+$ = 366.2182, Found: 366.2179.

(*S*)-*N*-((*S*)-3-methyl-1-oxo-1-(((*R*)-1-phenylethyl)amino)butan-2-yl)pyrrolidine-2-carboxamide (14f, LLR)

Compound **14f** was prepared from Boc-L-Pro-OH, Boc-L-Val-OH and (*R*)-(+)-1-Phenylethylamine. The same procedure as described above for the preparation of compound **14c** was used. Yield 67%; white solid, mp 132-133 ^{o}C; $[\alpha]^{25}_D$= -23.5^o (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 9.2 Hz, 1H), 7.28-7.20 (m, 5H), 6.90 (d, *J* = 8.0 Hz, 1H), 5.11 (t, *J* = 7.2 Hz, 1H), 4.23 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.59 (dd, *J* = 4.8, 4.4 Hz, 1H), 3.03-2.97 (m, 1H), 2.94-2.89 (m, 1H), 2.23-2.05 (m, 2H), 1.94-1.86 (m, 2H), 1.73-1.66 (m, 2H), 1.49 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.58, 170.28, 143.18, 128.58, 127.15, 126.11, 60.41, 58.22, 48.73, 47.26, 30.95, 30.68, 26.17, 22.07, 19.52, 18.23; HRMS(ESI$^+$) Calcd. for $C_{18}H_{27}N_3O_2$[M+H]$^+$ = 318.2182, Found: 318.2182.

(*R*)-*N*-((*R*)-3-methyl-1-oxo-1-(((*S*)-1-phenylethyl)amino)butan-2-yl)pyrrolidine-2-carboxamide (14g, DDS)

Compound **14g** was prepared from Boc-D-Pro-OH, Boc-D-Val-OH and (*S*)-(-)-1-Phenylethylamine. The same procedure as described above for the preparation of compound **14c** was used. Yield 53%; white solid; mp 122-123 ^{o}C; $[\alpha]^{25}_D$ = +23.9^o (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.2 Hz, 1H), 7.30-7.20 (m, 5H), 6.93 (d, *J* = 8.0 Hz, 1H), 5.11 (t, J = 7.2 Hz, 1H), 4.23 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.61 (dd, *J* = 5.2, 4.0 Hz, 1H), 3.04-2.98 (m, 1H), 2.94-2.90 (m, 1H), 2.23-2.05 (m, 3H), 1.93-1.85 (m, 1H), 1.70 (t, *J* = 6.8 Hz, 2H), 1.50 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.38, 170.23, 143.15, 128.57, 127.16, 126.11, 60.37, 58.34, 48.79, 47.24, 30.74, 26.12, 22.07, 19.51, 18.24; HRMS(ESI$^+$) Calcd. for $C_{18}H_{28}N_3O_2$ $[M+H]^+$ = 318.2182, Found: 318.2187.

(*R*)-*N*-((*R*)-3-methyl-1-oxo-1-(((*R*)-1-phenylethyl)amino)butan-2-yl)pyrrolidine-2-carboxamide (14h, DDR)

Compound **14h** was prepared from Boc-D-Pro-OH, Boc-D-Val-OH and (*R*)-(+)-1-Phenylethylamine. The same procedure as described above for the preparation of compound **14c** was used. Yield 56%; white solid; mp 141-143 ^{o}C; $[\alpha]^{25}_D$ = +98.8^o (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 9.2 Hz, 1H), 7.35-7.25 (m, 5H), 7.02 (d, *J* = 7.6 Hz, 1H), 5.10 (t, *J* = 7.2 Hz, 1H), 4.24 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.74 (dd, *J* = 4.8, 4.4 Hz, 1H), 3.07-3.01 (m, 1H), 2.96-2.91 (m, 1H), 2.17-2.06 (m, 3H), 1.96-1.88 (m, 1H), 1.72 (t, *J* = 6.8 Hz, 2H), 1.46 (d, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.04, 170.42, 143.44, 128.85, 128.56, 127.19, 126.17, 60.46, 58.35, 48.92, 47.27, 30.98, 30.96, 26.08, 22.01, 19.44, 18.15; HRMS(ESI$^+$) Calcd. for $C_{18}H_{28}N_3O_2$ $[M+H]^+$ = 318.2182, Found: 318.2187.

(*S*)-*N*-((*S*)-1-(benzylamino)-3-methyl-1-oxobutan-2-yl)pyrrolidine-2-carboxamide (14i)

Compound **14i** was prepared from Boc-L-Pro-OH, Boc-L-Val-OH and benzylamine. The same procedure as described above for the preparation of compound **14c** was used.
Yield 51%; white solid; mp 121-123 ^{o}C; $[\alpha]^{25}_D$ = -61.3^o (c = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.2 Hz, 1H), 7.35-7.32 (m, 5H), 6.75 (s, 1H), 4.49 (dd, *J* = 9.2, 5.6 Hz, 1H), 4.40 (dd, *J* = 9.2, 5.6 Hz, 1H), 4.19 (t, *J* = 8.4 Hz, 1H), 3.68 (dd, *J* = 4.2, 4.0 Hz, 1H), 3.06-3.00 (m, 1H), 2.96-2.91 (m, 1H), 2.28-2.19 (m, 1H), 2.15-2.07 (m, 1H), 1.93-1.86 (m, 2H), 1.75-1.68 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.25, 171.14, 138.12, 128.64, 127.74, 127.41, 60.33, 58.46, 47.21, 43.44, 30.88, 30.52, 28.27, 19.52, 18.45; HRMS(ESI$^+$) Calcd. For $C_{17}H_{26}N_3O_2$ $[M+H]^+$ = 304.2025, Found: 304.2029.

Typical procedure for direct aldol reactions by using dipeptide-like organocatalyst 14f in brine

To a mixed solvents of sat. aq. brine (0.5 mL) and ketone (0.5 mL) was added aldehyde (0.5 mmol), and the corresponding catalyst **14f** (1.6 mg, 0.005 mmol). The reaction mixture was stirred at 25 ^{o}C for 24 h. The mixture was then quenched with a solution of saturated NH_4Cl (0.5 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue which was purified through a flash column chromatography with *n*-hexane/ethyl acetate (1:1, V/V) to afford the pure aldol adduct. All these aldol products are known compounds[29,33,34] and the enantiomeric excess (*ee*) of the aldol adduct was determined by chiral HPLC analysis. For HPLC spectra of compounds **3a-j** and **15a-k**, please refer to Supplementary information.

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Notes and references

[a]Department of Medicinal Chemistry, School of Pharmacy, The Fourth Military Medical University, Changle West Road 169, Xi'an, 710032, P. R. China. Fax: +86-29-84776945; Tel: +86-29-84776807 ext. 605; *Corresponding author's E-mails: ping_an1718@outlook.com; syzhang@fmmu.edu.cn

† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: ^{1}H, ^{13}C NMR and HRMS of compounds **14a-i**, HPLC charts of aldol products **3a-j** and **15a-k** can be found in the Supplementary Information. See DOI: 10.1039/b000000x/

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