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# New small $\gamma$ -turn type *N*-primary amino terminal tripeptide organocatalyst for solvent-free asymmetric aldol reaction of various ketones with aldehydes†

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New small  $\gamma$ -turn type *N*-primary amino terminal tripeptides were synthesized and their functionality as an organocatalyst was examined in the asymmetric aldol reaction of various ketones with different aromatic aldehydes under solvent-free neat conditions to afford the desired chiral *anti*-aldol products in good to excellent chemical yields, diastereoselectivities and enantioselectivities (up to 99%, up to *syn* : *anti* 13 : 87 dr, up to 99% ee).

## 1. Introduction

From the last decade, the process of developing chiral multifunctional organocatalysts and their application in asymmetric synthesis as an independent chiral source has been a new area of focus for scientists. Catalysts possessing either Lewis or Brønsted basic functionalities and a non-covalent hydrogen-bond donor group suitably positioned over a chiral scaffold have been synthesized in general for various asymmetric reactions.<sup>1</sup> However, it is always a difficult job to design and synthesize multifunctional organocatalysts with remarkable catalytic activity in diverse asymmetric reactions. In organocatalysis, peptide catalysis has been recognized as a powerful and useful tool in the synthetic organic chemistry field, because peptides are highly modular, structurally diverse and easily accessible from nature's chiral pool. Due to their broad synthetic applicability, the studies on the development of new peptide organocatalysts have been continuously explored and attained great progress over the years.<sup>2</sup> In the development of peptide organocatalysts, inspired by the efficient and stereospecific metal-free enzymatic processes, synthetic chemists

have devoted much effort in recent years towards the development of a broad range of short peptide-based asymmetric catalysts, which mimic various qualities of enzymes. The structural diversity available with short peptide sequences and the fact that peptides offer a more strictly defined asymmetric environment to the reactants, compared to single amino acids, makes this class of molecules particularly promising towards the development of a wide range of organocatalysts with fine-tuneable structural and electronic properties. As for the short peptide organocatalyst, Inoue and co-workers reported the first cyclic dipeptide as an organocatalyst for the asymmetric cyanation reaction of hydrogen cyanide with benzaldehyde.<sup>3</sup> Furthermore, Miller and co-workers introduced first linear peptide organocatalyst, wherein fixing by the hydrogen bonding, based on  $\beta$ -turn concept for asymmetric acylation reaction was reported.<sup>4</sup> Using these pioneering studies, a great number of short peptide organocatalysts based on  $\beta$ -turn concept were reported over various asymmetric reactions such as aldol reactions<sup>5</sup> and so on.<sup>6</sup> However, to the best of our knowledge, no research group has been reported the design and use of small peptide organocatalysts in an asymmetric reaction, fixing by the hydrogen bonding based on  $\gamma$ -turn concept. A  $\gamma$ -turn type peptide organocatalyst has different conformation with  $\beta$ -turn type and it is expected to show interesting catalytic activity in asymmetric reactions.

We designed a new small  $\gamma$ -turn type *N*-primary amino terminal tripeptide **X** containing the pyrrolidine ring as a backbone (Scheme 1). This peptide **X** has *N*-terminal side at nitrogen atom in pyrrolidine backbone and *C*-terminal exists at 2-position on the pyrrolidine ring. Amide carbonyl group at *N*-terminal side and amide amino group at *C*-terminal side are connected by  $\gamma$ -turn intramolecular hydrogen bonding. In

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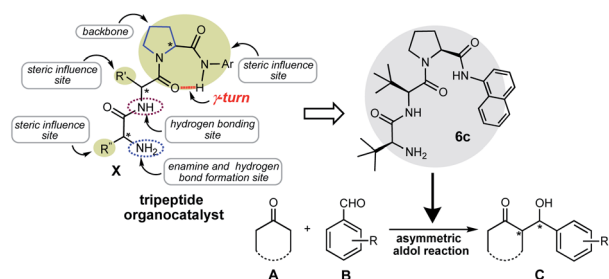
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Scheme 1 Concept of tripeptide organocatalyst design.

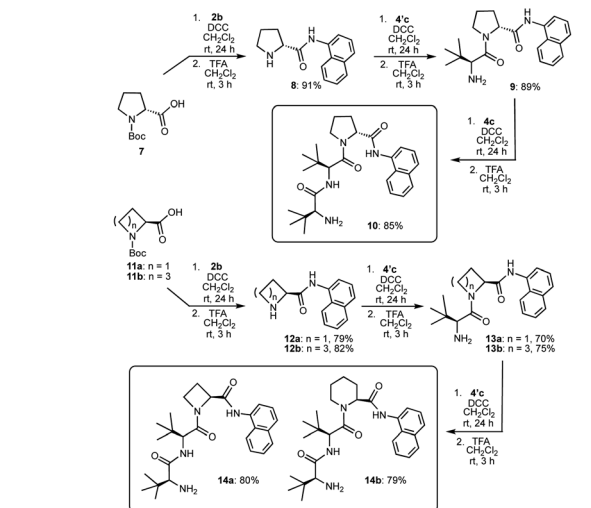
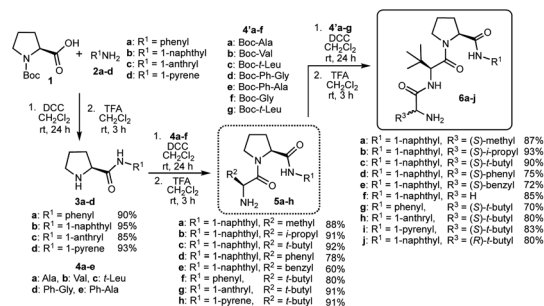
addition, **X** has both primary amino group for the formation of enamine with substrates and secondary amide group for the activation and fixing substrates on N-terminal side, and also the amide part at C-terminal side containing polycyclic aromatic substituent as steric influence site. Furthermore, alkyl or aryl substituents on the molecule act as steric and electric influence sites. The designed catalyst **X** was applied in the asymmetric aldol reaction, which is known as one of the practical reaction for creating  $\beta$ -hydroxyl carbonyl structural motif which is observed in numerous biologically active natural products and drug molecules.<sup>7</sup> There are several scientific reports that have proved the tremendous versatility of the chiral crossed aldol reaction using various organocatalysts, especially asymmetric crossed aldol reaction of ketones with aromatic aldehydes.<sup>8</sup> Therefore, we anticipated that our designed tripeptide **X** may act as an efficient organocatalyst for an enantioselective crossed aldol reaction over a wide range of aromatic aldehydes with ketones.

Herein, we describe the highly efficient catalytic activity displayed by our newly prepared tripeptide organocatalyst **6c** as **X** in the crossed aldol reaction of various ketones **A** with aromatic aldehydes **B** to afford the corresponding *anti*-aldol products **C** in good to excellent chemical yields and stereoselectivities (up to 99%, up to *syn* : *anti* = 13 : 87 dr, up to 99% ee) without the addition of any co-catalysts under eco-friendly solvent-free neat condition, which is still a challenging task in the asymmetric organocatalysis.

## 2. Results and discussion

### 2.1. Preparation and screening of catalysts

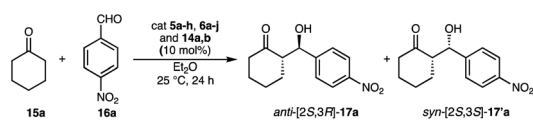
The tripeptide organocatalysts **6a–j** were prepared easily by the condensation reaction, starting from the reaction of *L*-*N*-Boc-proline **1** with amines **2a–d** as shown in Scheme 2. The first condensation of **1** with **2a–d** in the presence of DCC followed by the deprotection of Boc group of the crude *N*-protected proline amides afforded the corresponding proline amides **3a–d** at 85–95% yields. Next, the condensation of the obtained **3a–d** with *N*-Boc amino acids **4a–e** in the presence of DCC followed by the deprotection of the crude *N*-protected dipeptides gave the corresponding dipeptides **5a–h** at 60–92% yields. As amino acids,  $\gamma$ -substituted amino acids that are effective towards a conformation favorable to form  $\gamma$ -turn intramolecular hydrogen bonding were used. Furthermore, final condensation of the



Scheme 2 Preparation of di- and tripeptide organocatalysts.

dipeptides **5a–h** with *N*-protected **4'a–g**, respectively, in the presence of DCC followed by the deprotection afforded the corresponding tripeptides **6a–j** at 70–93% yields. Moreover, the diastereomer of **6c**, tripeptides **14a** and **14b** with azetidine and piperidine backbones, respectively, were also prepared using the same procedure used to prepare **6a–j**. Thus, the first condensation of *D*-*N*-Boc-**7**, *L*-*N*-Boc-**11a,b** with aromatic amine **2b** followed by the deprotection afforded the corresponding amides **8**, **12a**, **12b** at 79–91% yields. Next the condensations of **8**, **12a**, **12b** with *N*-Boc amino acid **4'c** followed by the deprotection gave the dipeptides **9**, **13a**, **13b** at 70–89% yields. Then, the final condensation of **9**, **13a**, **13b** with **4'c**, respectively, followed by the deprotection afforded the corresponding tripeptides **10**, **14a**, **14b** at 79–85% yields.

After the synthesis of the designed peptide organocatalysts, initially, we examined the crossed aldol reaction of cyclohexanone **15a** as an aldol donor and 4-nitrobenzaldehyde **16a** as an aldol acceptor using the precursor dipeptides **5a–h** of tripeptides **6a–h** as catalysts in Et<sub>2</sub>O at 25 °C (entries 1–8, Table 1). These dipeptide organocatalysts **5a–h** showed catalytic activity in this reaction, and the desired chiral aldol product **17** was obtained. However, only low to moderate chemical yields, moderate diastereoselectivities (**17a**: *anti* or **17'a**: *syn* forms), and low to moderate enantioselectivities were obtained in this reaction condition. The absolute configurations of **17a** and **17'a** were identified based on comparison with literature data.<sup>8</sup> We next tried this reaction using tripeptides **6a–j** as catalysts

Table 1 Aldol reaction of **15a** with **16a** using peptide catalysts


Entry	Catalyst	Yield <sup>a</sup> (%)	dr ( <i>syn</i> : <i>anti</i> ) <sup>b</sup>	ee <sup>c</sup> (%)	
				<i>syn</i> 17'a	<i>anti</i> 17'a
1	<b>5a</b>	18	33 : 67	18	34
2	<b>5b</b>	40	40 : 60	22	7
3	<b>5c</b>	52	67 : 33	63	10
4	<b>5d</b>	45	40 : 60	35	6
5	<b>5e</b>	33	47 : 53	35	8
6	<b>5f</b>	13	70 : 30	54	11
7	<b>5g</b>	20	72 : 28	54	13
8	<b>5h</b>	47	59 : 41	37	rac
9	<b>6a</b>	30	35 : 65	28	71
10	<b>6b</b>	19	40 : 60	28	74
11	<b>6c</b>	25	22 : 78	70	94
12	<b>6d</b>	16	23 : 77	25	50
13	<b>6e</b>	25	25 : 75	26	39
14	<b>6f</b>	58	25 : 75	1	30
15	<b>6g</b>	10	28 : 72	22	50
16	<b>6h</b>	26	25 : 75	30	80
17	<b>6i</b>	35	20 : 80	26	93
18	<b>6j</b>	20	35 : 65	7	-87
19	<b>10</b>	30	22 : 78	17	77
20	<b>14a</b>	20	30 : 70	44	86
21	<b>14b</b>	27	24 : 76	63	90

<sup>a</sup> Isolated yields. <sup>b</sup> Diastereoselectivity was determined by <sup>1</sup>H NMR using crude reaction mixture. <sup>c</sup> The ee value was determined by HPLC with a Daicel Chiralpak AD-H column.

(entries 9–18) under same reaction condition wherein catalysts **5a–h** were used. Encouraged by the result of dipeptide **5c**, possessing *t*-butyl group at N-terminal side which showed better catalytic activity, the substituent on the first amide part was fixed only to *t*-butyl group. Similar to **5a–h**, **6a–j** also showed catalytic activity in this reaction to afford the chiral aldol product *anti*-**17a**, but with low to moderate chemical yields. Interestingly, with the use of catalysts **6a–j** diastereoselectivity increased in the case of almost all catalysts and the main aldol product **17** was obtained in only *anti* form unlike the catalysts **5a–h**. Furthermore, enantioselectivity also quite increased with all the catalysts **6a–j**. Particularly, catalyst **6c** with *L*-*t*-Leu-*L*-*t*-Leu moiety at N-terminal side and 1-naphthyl group on amide amino moiety at C-terminal side afforded **17a** in fairly good enantioselectivity (94% ee) and with good diastereoselectivity (*syn* : *anti*/22 : 78), although chemical yield was low (25%) (entry 11). Also, the catalyst **6i** afforded **17a** in fairly good enantioselectivity (93% ee) and diastereoselectivity (*syn* : *anti*/20 : 80) (entry 17) similar to the catalyst **6c**, but owing to the toxicity and cost effectiveness of pyrenes, **6c** with 1-naphthyl group may be preferred. We have also examined the catalytic activity of catalysts **6j** with *D*-*t*-Leu-*L*-*t*-Leu chains at N-terminal side, **10** with *D*-

pyrrolidine ring, **14a** with four membered azetidine ring, and **14b** with six membered piperidine ring, respectively in this reaction. As a result, the catalysts **6j**, **10**, **14a** and **14b** did not show better catalytic activity than **6c** having *L*-*t*-Leu-*L*-*t*-Leu moiety at N-terminal side and five membered pyrrolidine ring. These results indicated that the chain length of N-terminal side, the size of backbone ring for forming  $\gamma$ -turn, the configuration and types of substituents at N-terminal side and the aromatic ring on amide amino group at C-terminal side are highly important for achieving satisfactory stereoselectivities, by shielding one enantiotopic face to attack from the aldol acceptor **16a** in this reaction condition using ether solvent.

With these results in hand, we tried to optimize the reaction conditions using tripeptide catalyst **6c**, that afforded the best enantioselectivity, to further improve the chemical yield and stereoselectivities (Table 2). An extensive screening of the reaction was further carried out by varying different parameters such as solvent, catalyst loading, and reaction temperature. First, the solvent screening was performed with different etheral (entries 2–4), non-polar aliphatic (entries 5 and 6), aromatic (entry 7), chlorinated (entries 8 and 9), protic and aprotic polar (entries 10–15) solvents and solvent free neat condition (entry 16). The reaction was carried out in the presence of 10 mol% of **6c** at 25 °C for 24 h. However, catalyst **6c** did not show enough catalytic activity to afford the aldol product **17a** in all solvents. On the other hand, both diastereoselectivity and the enantioselectivity were quite different according to characteristic solvents (entries 1–16). Interestingly, the chemical yield and stereoselectivities were greatly improved under neat condition to yield up to 52%, (*syn* : *anti*/22 : 78 dr) and 87% ee (*anti*) (entry 16). Although aldol reaction has been generally carried out under organic and water solvents system so far for obtaining satisfactory result, the successful examples of under neat condition have been reported by only a little group.<sup>9</sup> Next, we examined the effect of catalyst loading by varying from 30, 20, 5% and 1 mol% under superior neat reaction condition (entries 17–20). Good result (88%, *syn* : *anti*/22 : 78 dr, 96% ee) was obtained in the presence of 30 mol% of catalyst (entry 17). The use of 20 mol% also afforded good chemical yield and stereoselectivities. However, chemical yield and enantioselectivity were slightly decreased (79%, 22 : 78, 90% ee) (entry 18). When the reaction was carried out in the presence of 5 mol% of catalyst, diastereoselectivity and enantioselectivity was maintained to 22 : 78 (*syn* : *anti*) and 87% ee, but chemical yield was decreased to 20% (entries 19). Furthermore, the use of 1 mol% of **6c** brought about the large decrease of chemical yield and stereoselectivities (4%, *syn* : *anti*/22 : 78 dr, 65% ee) (entry 20). In addition, reaction temperature (0 and -25 °C) were also examined in the presence of superior 30 mol% of catalyst **6c** under neat condition (entries 21, 22). Best result was obtained at 0 °C for chemical yield and stereoselectivities (96%, *syn* : *anti*/20 : 80 dr, 98% ee) (entry 21). However, the reaction at -25 °C brought about the decrease of chemical yield (40%), although enough stereoselectivities were maintained (*syn* : *anti*/20 : 80 dr, 93% ee) (entry 22). Based on these results, it was revealed that the reaction in the presence of 30 mol% of catalyst at 0 °C for 24 h under solvent-free was the best reaction condition to

Table 2 Optimization of reaction conditions using catalyst **6c**

$15\mathbf{a} + 16\mathbf{a} \xrightarrow[\text{temp, solvent, 24 h}]{\text{cat. } 6\mathbf{c}} \text{anti-[2S,3R]-17a} + \text{syn-[2S,3S]-17'a}$							
Entry	Cat <b>6c</b> (mol%)	Temp. (°C)	Solvent	Yield <sup>a</sup> (%)	dr ( <i>syn</i> : <i>anti</i> ) <sup>b</sup>	ee <sup>c</sup> (%)	
						<i>syn</i> <b>17'a</b>	<i>anti</i> <b>17a</b>
1	10	25	Et <sub>2</sub> O	25	22 : 78	70	94
2	10	25	i-Pr <sub>2</sub> O	25	47 : 53	30	81
3	10	25	<sup>t</sup> BuOMe	18	45 : 55	47	83
4	10	25	THF	11	45 : 55	37	70
5	10	25	Pentane	20	40 : 60	53	79
6	10	25	Hexane	15	38 : 62	14	78
7	10	25	Toluene	15	38 : 62	70	80
8	10	25	CH <sub>2</sub> Cl <sub>2</sub>	13	28 : 72	40	67
9	10	25	CHCl <sub>3</sub>	10	38 : 62	45	93
10	10	25	CH <sub>3</sub> CN	18	35 : 65	23	51
11	10	25	DMSO	10	30 : 70	02	30
12	10	25	DMF	10	31 : 69	7	51
13	10	25	i-PrOH	10	41 : 59	8	55
14	10	25	MeOH	13	44 : 56	69	24
15	10	25	H <sub>2</sub> O	16	28 : 76	10	65
16	10	25	Neat	52	22 : 78	64	87
17	30	25	Neat	88	23 : 77	60	96
18	20	25	Neat	79	22 : 78	64	90
19	5	25	Neat	20	24 : 76	60	87
20	1	25	Neat	4	23 : 77	48	65
<b>21</b>	<b>30</b>	<b>0</b>	<b>Neat</b>	<b>94</b>	<b>20 : 80</b>	<b>64</b>	<b>98</b>
22	30	-25	Neat	40	21 : 79	43	93
23 <sup>d</sup>	30	0	Neat	98	24 : 76	55	93

<sup>a</sup> Isolated yields. <sup>b</sup> Diastereoselectivity was determined by <sup>1</sup>H NMR using crude reaction mixture. <sup>c</sup> The ee value was determined by HPLC with a Daicel Chiralpak AD-H column. <sup>d</sup> 1 g of substrate **15a** was used.

obtain the chiral aldol adduct **17a** in satisfactory chemical yield and stereoselectivities (entry 21). Furthermore, in order to demonstrate the practical utility of the catalyst **6c**, the reaction of **15a** with **16a** was conducted on gram scale (**15a**: 1 g) using the above optimized reaction conditions and the corresponding product **17a** was obtained in good chemical yield (98%), diastereoselectivity (*syn* : *anti*/24 : 76 dr), and enantioselectivity (93% ee). This result indicated that the catalyst **6c** can also be effective on practical scale (entry 23).

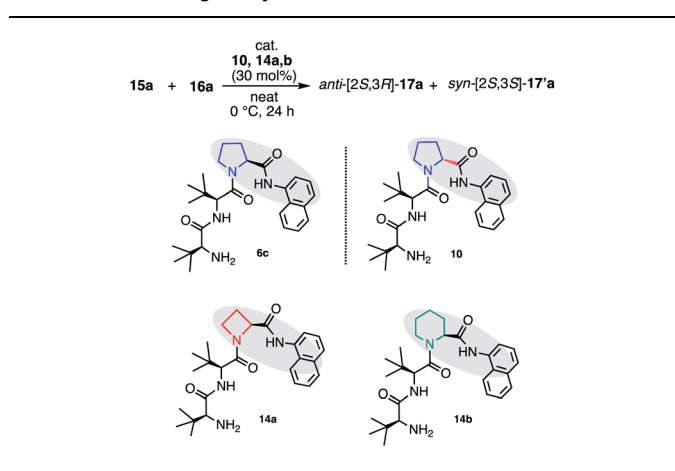
With best reaction conditions in hand, we tried to re-examine the catalytic activity of the prepared catalysts **10** (diastereomer of **6c**), and **14a**, **14b** having 4, 6 membered rings as back bone under the best solvent-free reaction condition (30 mol%, 0 °C, 24 h, neat), respectively (entries 2–4, Table 3). As a result, these catalysts showed satisfactory catalytic activities to afford **17a** in good chemical yields and stereoselectivities (72–90%, *syn* : *anti*/23 : 77–22 : 78 dr, 92–98% ee) in this reaction condition. Especially, the catalyst **14b** having 6 membered piperidine ring (entry 4) gave **17a** with excellent enantioselectivity in results similar to that of catalyst **6c** having 5 membered pyrrolidine ring (entry 1), although the decrease of chemical yield was observed. From the fact that all catalysts

showed satisfactory chemical yield and stereoselectivity, it is indicated that there is no restriction of ring size and the conformation to obtain the product with good chemical yield and stereoselectivity. Hence it might be possible to choose a suitable substrate in consideration of the distances between N-terminal side and C-terminal side of **6c**, **14a**, **14b**, respectively, for obtaining the corresponding product with satisfactory chemical yield and stereoselectivity (Scheme 3).

## 2.2. Substrate scope

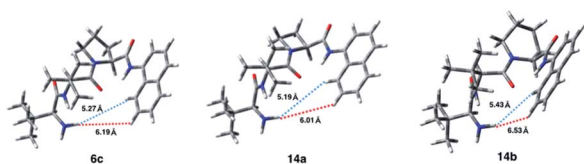
After the optimization of reaction conditions, we investigated the generality of the superior catalyst **6c** in the reactions of various ketones **15a–h** with aldehydes **16a–j** (Scheme 4). The reactions were carried out in the presence of catalyst **6c** (30 mol%) under best reaction conditions (0 °C, neat, 24 h). First, the reaction of cyclohexanone **15a** with nitro-substituted aromatic aldehydes **16b**, **16c** afforded the corresponding *anti*-aldol products **17b,c** in good to excellent chemical yields, diastereoselectivities and enantioselectivities (**17b**: 78%, *syn* : *anti*/22 : 78 dr, 99% ee, **17c**: 99%, up to *syn* : *anti*/20 : 80 dr, up to 99% ee). Furthermore, the reactions using the halogenated **16d–g** and *p*-cyano **16h** benzaldehydes, respectively, also

**Table 3** Catalytic activity of **10**, **14a**, **14b** under optimization of reaction conditions using catalyst **6c**



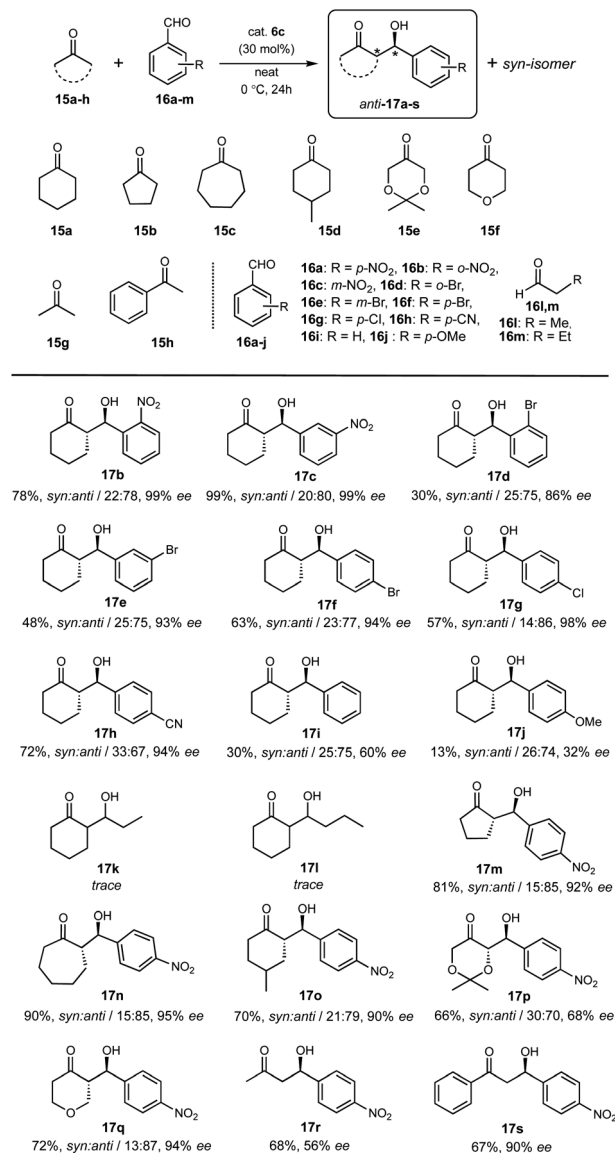
Entry	Catalyst	Yield <sup>a</sup> (%)	dr <sup>b</sup> ( <i>syn</i> : <i>anti</i> )	ee <sup>c</sup> (%)	
				<i>syn</i> <b>17'a</b>	<i>anti</i> <b>17a</b>
1	<b>6c</b>	96	20 : 80	60	98
2	<b>10</b>	90	22 : 78	44	96
3	<b>14a</b>	89	23 : 77	33	92
4	<b>14b</b>	72	20 : 80	38	98

<sup>a</sup> Isolated yields. <sup>b</sup> Diastereoselectivity was determined by <sup>1</sup>H NMR using crude reaction mixture. <sup>c</sup> The ee value was determined by HPLC with a Daicel Chiralpak AD-H column.



**Scheme 3** Structures of tripeptide organocatalysts.

afforded the corresponding *anti*-aldol adducts **17d–h** with satisfactory results (30–63%, *syn* : *anti*/25 : 75–14 : 86 dr, 93–98% ee). However, the use of simple benzaldehyde **16i** brought about the decrease of chemical yield and enantioselectivity (**17i**: 30%, *syn* : *anti*/25 : 75 dr, 60% ee). These results justified our finding that catalyst **6c** enhances the generality of application towards the aldol reaction using different substituted aromatic aldehydes. The aldol reactions of other various carbocyclic **15b–d**, heterocyclic **15e**, **15f**, and acyclic **15g,h** ketones with **16a** were also examined in the presence of **6c** (30 mol%) under best reaction condition (0 °C, neat, 24 h). The reaction of cyclopentanone **15b** with **16a** proceeded and afforded the corresponding *anti*-aldol product **17m** in fairly good chemical yield and stereoselectivity (81%, *syn* : *anti*/15 : 85 dr, 92% ee). The bulkier cycloheptanone **15c** also gave the *anti*-aldol product **17n** with good chemical yield, diastereoselectivity and excellent enantioselectivity (90%, *syn* : *anti*/15 : 85 dr, 95% ee). Moreover, the reaction using *p*-methyl cyclohexanone **15d** also afforded



**Scheme 4** Substrate scope for aldol reaction.

*anti*-aldol product **17o** in good chemical yield and stereoselectivity (70%, *syn* : *anti*/21 : 79, 90% ee). Although the use of heterocyclic 2,2-dimethyl-1,3-dioxan-5-one **15e** did not afford **17p** with satisfactory results (66%, *syn* : *anti*/30 : 70 dr, 68% ee), tetrahydropyran-4-one **15f** afforded the corresponding *anti*-aldol product **17q** in good chemical yield and diastereoselectivity with fairly good enantioselectivity (72%, *syn* : *anti*/13 : 87 dr, 94% ee). Finally, the reactions of acyclic acetone **15g** and acetophenone **15h** with **16a** also examined under same reaction condition. The use of **15g** gave the corresponding *anti*-aldol adduct **17r** in moderate results (60%, 59% ee), but **15h** afforded **17s** in moderate chemical yield and good enantioselectivity (67%, 90% ee). The *anti*-aldol products **17b–j,m–s** were characterized in accordance with full spectroscopic data originated from the previous report.<sup>8</sup> And also, absolute stereochemistry of **17b–j,m–s** were found to be equivalent to specific optical rotation values in literature.<sup>8</sup> These results justified our

finding that catalyst **6c** enhances the generality of application towards the aldol reaction using different substituted aromatic aldehydes. However, catalyst **6c** did not show catalytic activity with aliphatic aldehyde in the best reaction condition. Therefore, the reaction under different reaction conditions might need to be tried.

### 2.3. Reaction mechanism

Based on the excellent enantiopurity (98% ee) of the obtained optically active aldol product (*2S,3R*)-**17a** from the asymmetric aldol reaction of cyclohexanone **15a** with 4-nitrobenzaldehyde **16a** using catalyst **6c**, a model of the asymmetric reaction course is proposed as shown in Scheme 5.

First, the condensation of *N*-terminal primary amine peptide organocatalyst **6c** with aldol donor **15a** forms the enamine as intermediate **I**. The conformation of intermediate **I** is fixed by  $\gamma$ -turned intramolecular hydrogen bonding interactions between the amide carbonyl group at *N*-terminal side and the amide amino group at *C*-terminal side on pyrrolidine ring and also the amino hydrogen atom and the next amide amino group of organocatalyst species. Intermediate **I** might exist as **I-1** which is having less steric interaction between dipeptide chain on *N*-terminal side and the enamine part than that of intermediate **I-2**. This expectation was supported by the conformational analyses using scan of total energies and DFT calculations for the enamine intermediates **I-1** and **I-2** and the result indicated that the conformation of **I-1** is most stable (see the ESI† for details) (Fig. 1). Subsequently, more stable enamine intermediate **I-1** might attack 4-nitrobenzaldehyde **16a** through

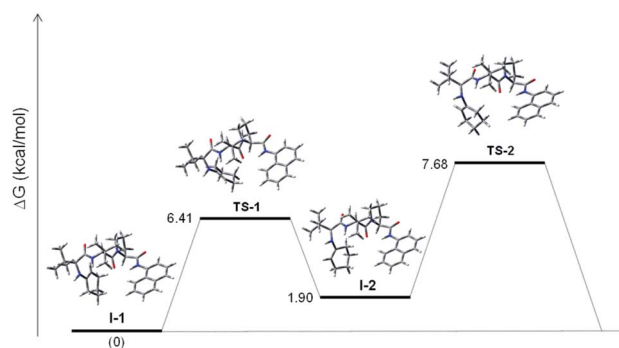


Fig. 1 Energy profile of the interconversion of **6c**.

possible transition states **TS-1** to **TS-4** as shown in afford [*2S,3R*]-**17a** as a major product than those of **TS-2**, **TS-3**, Scheme 5. In the **TS**, the reaction might proceed through **TS-1** to and **TS-4**, wherein the substrate **16a** has steric interactions from *N*-terminal side and *C*-terminal side fixed by  $\gamma$ -turn intramolecular hydrogen bonding. On the other hand, aldol acceptor **16a** might coordinate with amide hydrogen atom through hydrogen bonding at *N*-terminal side on **I-1** species in **TS-1**. Subsequently, the enamine moiety attacks the enantiotopic face of **16a** resulting **17a** as the major isomer.

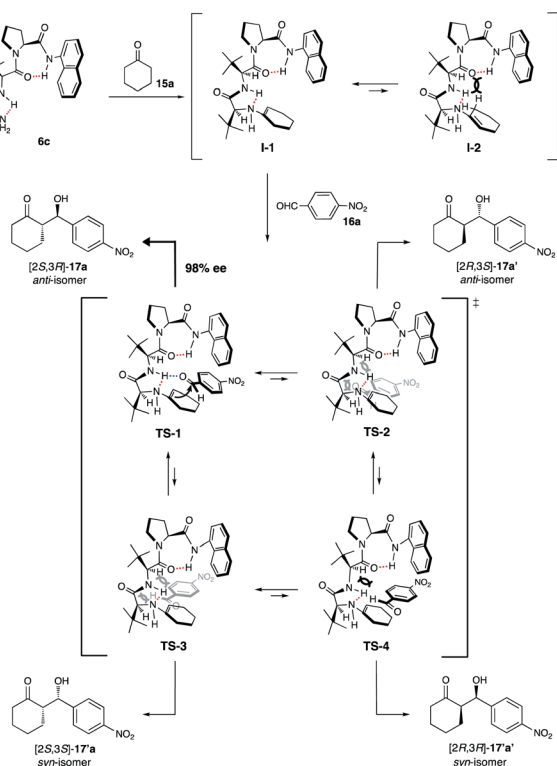
## 3. Conclusion

We have developed new small  $\gamma$ -turn type *N*-primary amino terminal tripeptides organocatalysts **6a–j** and their functionality as organocatalyst were examined in the asymmetric aldol reaction of various ketones **15a–h** with different aromatic aldehydes **16a–j** to afford the desired chiral aldol products **17a–s**. All the catalysts showed catalytic activity in this reaction. Particularly, catalyst **6c** showed good catalytic activity to afford the various chiral aldol products in satisfactory chemical yields and stereoselectivities (up to 99%, up to *syn* : *anti*/13 : 87 dr, up to 99% ee) under eco-friendly solvent-free condition.

## 4. Experimental

### 4.1 General information

Reagents and dry solvents were of the commercially available maximum grade and used without further purification. Reactions were performed under an inert atmosphere in flame dried and cooled glassware. The reaction progress was monitored by thin layer chromatography (TLC) using Merk silica plate gel 60 F254 aluminum sheet. The purification of products were carried out using column chromatography techniques in silica gel 60 N (40–50  $\mu$ m) purchased from Kanto Chemical Company. Visualization of the products was confirmed by ultraviolet light, iodine vapor and ninhydrin stain.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a JEOL JNM-ECA500 ( $^1\text{H}$  for 500 MHz and  $^{13}\text{C}$  for 125 MHz). All the spectra were recorded at 21  $^\circ\text{C}$ . Chemical shifts ( $\delta$ ) are reported in parts per million (ppm) relative to the signals of tetramethylsilane (TMS) using the residual solvents signals. Report data for  $^1\text{H}$  NMR spectroscopy was reported as:



Scheme 5 Plausible reaction course using catalyst **6c**.

chemical shift ( $\delta$  ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, dd = doublet of doublets, td = triplet of doublets, m = multiplet and br = broad), coupling constants ( $J$ ) and assimilation were measured in hertz (Hz). Optical rotation was measured by JASCO DIP-360 polarimeter. The melting point was measured using a Yanaco micro melting point apparatus. High resolution mass spectra (HRMS) data was collected by electron impact (EI) using Hitachi RMG-GMG and JEOL JNK-DX303 sector instruments. The enantiomeric excess (ee) was determined using high pressure liquid chromatography (HPLC) principle by DAICEL CHIRALPAK AD-H, OD-H column.

#### 4.2 General procedure for the synthesis of peptide organocatalysts 6a–j, 10 and 14a–b

To a solution of *N,N'*-dicyclohexylcarbodiimide (DCC) (1.29 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (10 mL) were added *N*-Boc-L-amino acids 4'a–f (0.86 mmol) at 0 °C and the reaction mixture was stirred for 1 hour. After 1 h, corresponding dipeptides 5a–h, 9 and 13a–b (0.95 mmol) were added, and the reaction was stirred for another 24 h at rt. The insoluble by-product DCU was filtered off and the filtrate evaporated to dryness. The obtained oily residue was dissolved in  $\text{CH}_2\text{Cl}_2$  and extracted sequentially with saturated aqueous  $\text{NaHCO}_3$  solution, aqueous HCl (1.0 M), and brine. The organic phase was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under a reduced pressure to afford the crude products that were used for next step without further purification. To the solution of the crude products in dry  $\text{CH}_2\text{Cl}_2$ , TFA was added in dropwise over a period of times (0.4 mL) at 0 °C and successively stirred at room temperature (r.t.) for 4 h. After the reaction completion, DCM and TFA were removed under a reduced pressure, the residue was basified by drop-wise addition of saturated  $\text{NaHCO}_3$  solution at 0 °C and stirred for 1 h at r.t. The crude products were extracted with  $\text{CHCl}_3$ , dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The residue was purified by flash column chromatography on  $\text{SiO}_2$  ( $\text{CHCl}_3$  : MeOH = 99 : 1 to 95 : 5) to obtain the corresponding tripeptide catalysts 6a–j, 10 and 14a, 14b.

#### 4.3 General procedure for the asymmetric aldol reaction of various ketones with aromatic aldehydes

The peptide catalyst 6c (30 mol%) was added to a solution of ketones 15a–h (0.4 mmol) and the aldehydes 16a–j (0.1 mmol) under the neat reaction condition. The reaction mixture was stirred at 0 °C for appropriate time until the reaction completion, monitored by thin layer chromatography (TLC). The reaction mixture was directly purified by flash column chromatography on  $\text{SiO}_2$  (*n*-hexane/ $\text{CH}_3\text{CO}_2\text{Et}$ ) to afford the corresponding aldol products 17a–s.

## Conflicts of interest

There are no conflicts to declare.

## Notes and references

- (a) A. Antenucci, S. Dughera and P. Renzi, *ChemSusChem*, 2021, **14**, 2785; (b) V. V. Kouznetsov and P. Galvis, *Tetrahedron*, 2018, **22**, 773; (c) Y. Nishikawa, *Tetrahedron Lett.*, 2018, **59**, 216; (d) C. Yalamanchili, G. Amar, A. G. Chittiboyina, S. C. Kumar Rotte, J. A. Katzenellenbogen, W. G. Helferich, A. Ikhlas and I. A. Khan, *Tetrahedron*, 2018, **74**, 2020; (e) G. M. Ziarani, R. Moradi and N. N. Lashgari, *Tetrahedron*, 2018, **74**, 1323; (f) C. E. Sleet, K. Uttam, U. K. Tambar and P. P. Maity, *Tetrahedron*, 2017, **73**, 4023; (g) M. M. Heravi, V. Zadsirjan, M. Dehghani and N. Hosseintash, *Tetrahedron: Asymmetry*, 2017, **28**, 587; (h) S. Ahmad, L. Shukla, J. Szawkalo, P. Roszkowski, K. Jan, J. K. Maurin and Z. Czarnocki, *Catal. Commun.*, 2017, **89**, 44; (i) F. E. Held and S. B. Tsogoeva, *Catal. Sci. Technol.*, 2016, **6**, 64.
- (a) E. A. C. Davie, S. M. Mennen, Y. Xu and S. J. Miller, *Chem. Rev.*, 2007, **107**, 5759; (b) S. J. Miller, *Acc. Chem. Res.*, 2004, **37**, 601; (c) J. D. Revell and H. Wennemers, *Curr. Opin. Chem. Biol.*, 2007, **11**, 269; (d) D. R. Kelly and S. M. Roberts, *Biopolymers*, 2006, **84**, 74; (e) A. Berkessel, *Curr. Opin. Chem. Biol.*, 2003, **7**, 409; (f) Y. Zhao, J. Rodrigo, A. H. Hoveyda and M. L. Snapper, *Nature*, 2006, **443**, 67; (g) C. A. Lewis and S. J. Miller, *Angew. Chem., Int. Ed.*, 2006, **45**, 5616; (h) C. A. Lewis, A. Chiu, M. Kubryk, J. Balsells, D. Pollard, C. K. Esser, J. Murry, R. A. Reamer, K. B. Hansen and S. J. Miller, *J. Am. Chem. Soc.*, 2006, **128**, 16454; (i) E. Delort, T. Darbre and J. L. Reymond, *J. Am. Chem. Soc.*, 2004, **126**, 15642; (j) A. Clouet, T. Darbre and J. L. Reymond, *Angew. Chem., Int. Ed.*, 2004, **43**, 4612; (k) F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2002, **124**, 3510; (l) P. Krattiger, C. McCarthy, A. Pfaltz and H. Wennemers, *Angew. Chem., Int. Ed.*, 2003, **42**, 1722; (m) M. Wiesner, J. D. Ravell, S. Tonazzi and H. Wennemers, *J. Am. Chem. Soc.*, 2008, **130**, 5610; (n) H. Wennemers, *Chem. Commun.*, 2011, **47**, 12036.
- (a) J. Oku and S. Inoue, *Makromol. Chem.*, 1979, **180**, 1089; (b) J. Oku and S. Inoue, *J. Chem. Soc., Chem. Commun.*, 1981, 229; (c) J. Oku, N. Ito and S. Inoue, *Makromol. Chem.*, 1982, **183**, 579.
- (a) S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann and E. M. Ruel, *J. Am. Chem. Soc.*, 1998, **120**, 1629; (b) E. R. Jarvomeissa, M. Vasbinder and S. J. Miller, *Tetrahedron*, 2000, **56**, 9773; (c) S. M. Mennen, J. T. Blank, M. B. Tran-Dube, J. E. Imbriglio and S. J. Miller, *Chem. Commun.*, 2005, 195.
- (a) O. Illa, O. Porcar-Tost, C. Robledillo, C. Elvira, P. Nolis, O. Reiser, V. Branchadell and R. M. Ortuno, *J. Org. Chem.*, 2018, **83**, 350; (b) S. B. Tsogoeva and S. B. Jagtap, *Synlett*, 2004, **14**, 2624; (c) S. B. Tsogoeva, S. B. Jagtap, Z. A. Ardemasova and V. N. Kalikhevich, *Eur. J. Org. Chem.*, 2004, **19**, 4014; (d) K. Yoshida, T. Shigeta, T. Furuta and T. Kawabata, *Chem. Commun.*, 2012, **48**, 6981.
- (a) Z. H. Du, B. X. Tao, M. Yuan, W. J. Qin, Y. L. XU, P. Wang and C. S. Da, *Org. Lett.*, 2020, **11**, 4444; (b) G. Coombs,

- M. H. Sak and S. J. Miller, *Angew. Chem., Int. Ed.*, 2019, **131**, 2; (c) C. E. Grunerfelder, J. K. Kisunzu and H. Wennemers, *Angew. Chem., Int. Ed.*, 2016, **55**, 1; (d) K. Akagawa, T. Hirata and K. Kudo, *Synlett*, 2016, **27**, 1217; (e) K. Akagawa, N. Sakai and K. Kudo, *Angew. Chem., Int. Ed.*, 2015, **127**, 1842; (f) X. Hu, D. Zhang, S. Zhang and P. Wang, *RSC Adv.*, 2015, **5**, 39557; (g) A. Bisticha, I. Triandafillidi and C. G. Kokotos, *Tetrahedron: Asymmetry*, 2015, **26**, 102; (h) Z. H. Du, W. Qin, B. Tao, M. Yuan and C. S. Da, *Org. Biomol. Chem.*, 2013, **11**, 1; (i) F. C. Wu, C. S. Da, Z. X. Du, Q. P. Guo, W. P. Li, L. Yi, Y. N. Jia and X. Ma, *J. Org. Chem.*, 2009, **74**, 4812; (j) V. Delia, H. Zwicknagl and O. Reiser, *J. Org. Chem.*, 2008, **73**, 3262; (k) J. D. Revell and H. Wennemers, *Curr. Opin. Chem. Biol.*, 2007, **11**, 269; (l) A. Cordova, W. Zou, P. Dziedzic, I. Ibrahim, E. Reyes and Y. Xu, *Chem.–Eur. J.*, 2006, **12**, 5383; (m) P. Dziedzic, W. Zou, J. Hafren and A. Cordova, *Org. Biomol. Chem.*, 2006, **4**, 38; (n) J. Kofoed, J. Nielsen and J. L. Reymond, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2445; (o) F. Tanaka and C. F. Barbas III, *Chem. Commun.*, 2001, 769.
- 7 (a) T. Ohashi and S. Hosokawa, *Org. Lett.*, 2018, **10**, 3021; (b) D. L. J. Clive and D. Liu, *J. Org. Chem.*, 2009, **74**, 4812; (c) B. Schetter and R. Mahrwald, *Angew. Chem., Int. Ed.*, 2006, **45**, 7506; (d) *Modern Aldol Reactions*, ed. R. Mahrwald, Wiley-VCH, Weinheim, Germany, 2004, vol. 1 and 2; (e) G. Casiraghi, F. Zanardi, G. Appendino and G. Rassu, *Chem. Rev.*, 2000, **100**, 1929.
- 8 (a) M. G. Emma, A. Tamburrini, A. Martinelli, M. Lombardo, A. Quintavalla and C. Trombini, *Catalysts*, 2020, **10**, 649; (b) I. A. Owolabi, U. V. Subba Reddy, M. Chennapuram, C. Seki, Y. Okuyama, E. Kwon, K. Uwai, M. Tokiwa, M. Takeshita and H. Nakano, *Tetrahedron*, 2018, **76**, 4705; (c) J. Dutta, N. Wakdikar and S. Tiwari, *Org. Biomol. Chem.*, 2017, **15**, 6746; (d) Z. Li, Y. Chen, C. Zheng, Y. Yin, L. Wang and X. Sun, *Tetrahedron*, 2017, **73**, 78; (e) V. Ashokkumar, C. Chithiraikumar and A. Siva, *Org. Biomol. Chem.*, 2016, **14**, 9021; (f) V. Ashokkumar, C. Chithiraikumar and A. Siva, *Org. Biomol. Chem.*, 2016, **14**, 9021; (g) C. L. Wu, X. K. Fu and S. Li, *Eur. J. Org. Chem.*, 2011, **7**, 1291; (h) C. L. Wu, X. K. Fu and S. Li, *Tetrahedron*, 2011, **67**, 4283; (i) C. L. Wu, X. K. Fu, X. B. Ma and S. Li, *Tetrahedron: Asymmetry*, 2010, **21**, 2465; (j) S. Guizzetti, M. Benaglia, L. Raimondi and G. Celentano, *Org. Lett.*, 2007, **9**, 1247; (k) K. Sakthivel, W. Notz, T. Bui and C. F. Barbas III, *J. Am. Chem. Soc.*, 2001, **123**, 5260.
- 9 (a) V. D. Juarez, C. E. Escobedo, M. P. Venegas, E. Juaristi, S. P. Estrada, S. R. Lima and H. L. Ruiz, *Tetrahedron*, 2021, **79**, 153; (b) C. G. A. Ortiz, M. P. Venegas, J. V. Caporali and E. Juaristi, *Tetrahedron*, 2019, **60**, 1749; (c) P. V. Milla, J. M. Sansano, C. Naajera, B. Fiser and E. G. Bengoa, *Eur. J. Org. Chem.*, 2015, **12**, 2514; (d) J. G. Hernandez, V. García-Lopez and E. Juaristi, *Tetrahedron*, 2012, **68**, 92; (e) J. G. Hernandez and E. Juaristi, *J. Org. Chem.*, 2011, **76**, 1464; (f) G. Ma, A. Bartoszewicz, I. Ibrahim and A. Cordova, *Adv. Synth. Catal.*, 2011, **353**, 3114; (g) J. G. Hernandez and E. Juaristi, *Tetrahedron*, 2011, **67**, 6953; (h) N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2006, **128**, 734; (i) P. Dziedzic, W. Zou, J. Hafren and A. Cordova, *Org. Biomol. Chem.*, 2006, **4**, 38.