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COMMUNICATION

Proline-based reduced dipeptides as recyclable and highly enantioselective organocatalysts for asymmetric Michael addition†

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A series of novel proline-based reduced dipeptides was developed and evaluated for a direct Michael addition of ketones and aldehydes to nitroalkenes. Excellent yields (up to 95%), diastereoselectivities (up to 98% dr) and enantioselectivities (up to 98% ee) were achieved in the presence of 5 mol% catalyst without any additional additives at room temperature.

Organocatalytic, asymmetric carbon–carbon and carbon–heteroatom bond-forming reactions have been extensively investigated in recent years.[1] The conjugate Michael addition reaction represents one of the most elegant and attractive ways to introduce chirality into Michael acceptors through asymmetric carbon–carbon bond formation.[2] Furthermore, the asymmetric conjugate addition of a carbon nucleophile to nitro alkenes is of fundamental importance, since it affords a useful synthetic method for chiral nitro alkanes that contain at least two vicinal stereogenic centers in a single step. Proline[3] and its pyrrolidine-based derivatives have been investigated and have been shown to be effective asymmetric catalysts for the Michael addition of aldehydes and ketones to nitroolefins.[4] However, these organocatalysts still have some drawbacks in that a high catalyst loading (10–30 mol%) is generally required and they are hard to recover. These problems limit the widespread application of the catalysts. A catalyst that overcomes these limitations would be advantageous.

In the organocatalyst field, peptides always have had an important status.[5,6] A series of proline-based dipeptides were evaluated for catalyzing the Michael addition by List in 2003[7] and Tsogoeva in 2009.[8] These peptides catalyzed reactions with high yields (65%–91%), but only showed moderate enantioselectivity (56–68% ee).[8] It is well known that even subtle changes in a catalyst's structure can often have a considerable influence on its performance. In this paper, a series of highly enantioselective and recoverable organocatalysts that were produced by subtle modifications of previously reported peptides is presented.

In our recent studies, a few proline amides[9–11] (Fig. 1, **1**–**3**) were investigated as organocatalysts for the model Michael addition reaction of cyclohexanone **12** to nitrostyrene **13**. They showed lower enantioselection (26%–31% ee, Table 1, entry 1–3) than

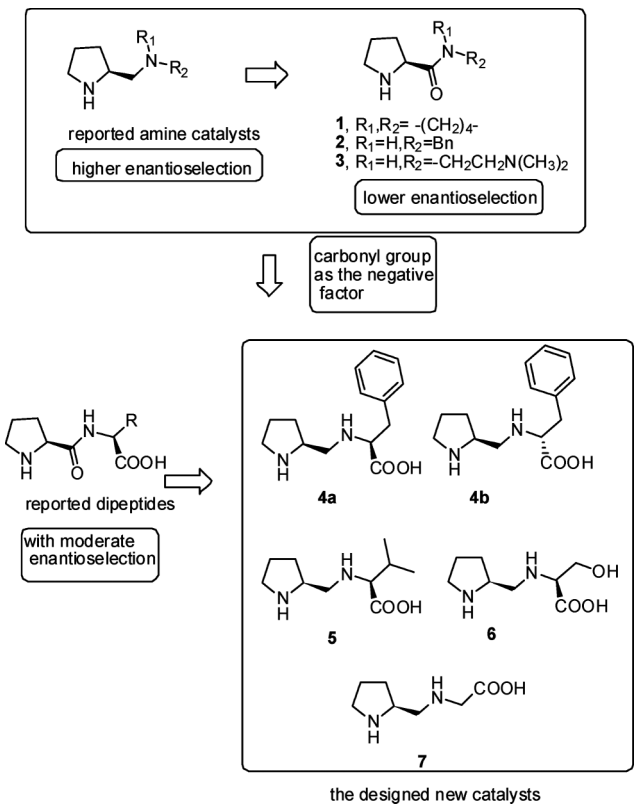

Fig. 1 The design of the new catalysts.

their amine analogue[11–13] (81%–99% ee). These results indicate that the carbonyl group has a negative impact on enantioselectivity. Inspired by this, we designed a series of proline-based reduced dipeptides by removing the carbonyl groups from previously reported dipeptides[7,8] (Fig. 1). From another point of view, the newly designed catalysts which contain a carboxyl group should be more water-soluble than the diamine catalyst. This thus provides an easy method to recover the catalysts by capitalizing on their solubility characteristics.[14]

As shown in Scheme 1, the proline-based reduced dipeptides were readily prepared from *N*-Boc-L-prolinol (**8**) in four steps. First **8** was oxidized to aldehyde **9** with pyridinium chlorochromate (PCC) and then the formyl group was transformed to the corresponding amine by reductive amination with an amino-acid methyl ester. After removal of the methyl ester and successively

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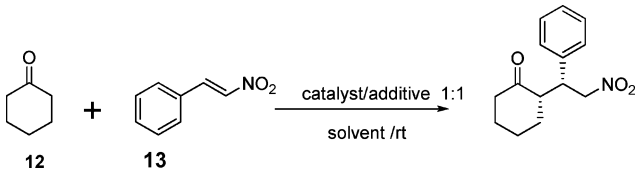
Table 1 Michael addition of cyclohexanone to *trans*-β-nitrostyrene



12 13

Entry[a]	Cat.	Mol (%)	Solvent	Additive	Time (h)	yield[b]	*syn*/*anti*[c]	ee(*syn*)[d]
1	**1**	20	DMSO	TFA	48	87%	95 : 5	26%
2	**2**	20	DMSO	TFA	48	86%	93 : 7	31%
3	**3**	20	DMSO	TFA	48	90%	98 : 2	33%
4	**4a**	15	MeOH		48	92%	99 : 1	98%
5	**4b**	15	MeOH		48	89%	99 : 1	98%
6	**5**	15	MeOH		48	91%	99 : 1	97%
7	**6**	15	MeOH		48	90%	99 : 1	96%
8	**4a**	5	MeOH		64	90%	99 : 1	98%
9	**4a**	1	MeOH		168	27%	98 : 2	93%
10	**5**	5	MeOH		72	trace	n.d.	n.d.
11	**6**	5	MeOH		72	trace	n.d.	n.d.
12	**7**	15	MeOH		48	85%	97 : 3	94%

[a] 5 eq ketone used. [b] Yields of isolated product after column chromatography. [c] Determined by ^{1}HNMR analysis of the crude product. [d] Enantioselectivities were determined for *syn*-product by chiral-phase HPLC analysis (Daicel Chiralpak AS-H).

deprotecting the *N*-Boc group, the target organocatalysts were obtained with 30–40% overall yield.

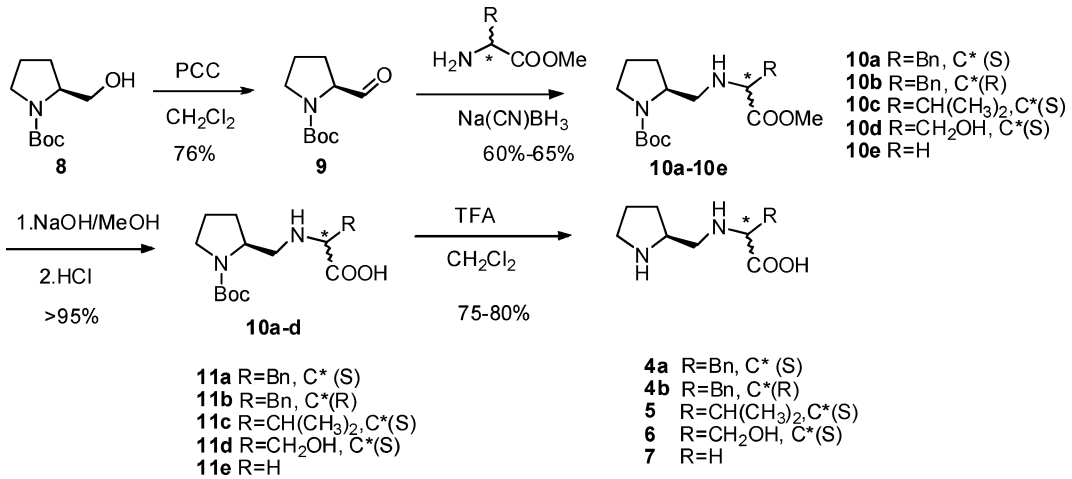
With the organocatalysts in hand, their catalytic performance was then examined for the model reaction of cyclohexanone **12** to nitrostyrene **13**. Representative results are summarized in Table 1.

As the results of Table 1 show, the modified organocatalysts require lower catalysts loadings (15 mol%, Table 1, entries 4, 6 and 7) than their peptide analogues (30 mol%)[7,8] to promote the reaction and they provide much better diastereo- and enantioselectivities (*syn* : *anti* 99 : 1, ee 96%–98%) than the corresponding peptides (*syn* : *anti* 95 : 5, ee 61%–68%).[7,8] These encouraging results indicate that the strategy for modification of the peptides is effective. The loading of catalyst **4a** can be reduced to 5 mol% with similar results but a longer reaction time is needed (Table 1, entry 8). When the loading was further reduced to 1 mol%, the yield and enantioselectivity were decreased even with a prolonged reaction time of 168 h (Table 1, entry 9). Unfortunately, when the loading of catalyst **5** and **6** were reduced to 5 mol%, only trace amounts of the product were observed after 72 h (Table 1, entries 10 and 11). Interestingly, the diastereoisomer **4b** and the catalyst **7** having no chiral center at δ-carbon atom also provided a high yield and similar enantioselectivity (Table 1, entry 5, 12). This means the most important stereoselector is the 2 position of the pyrrolidine ring. On the other hand, the reduced dipeptides which contain the carboxyl group can catalyze the reaction without any additive, so their reaction system is simpler than the diamine catalysts where an acidic additive is generally required to achieve good yield and enantioseleciton.[11,12,15] This advantage should make it more convenient to recover the catalyst.

Next, the addition of cyclohexanone to *trans*-β-nitrostyrene was used as a model reaction to examine the recyclability of catalyst **4a** (at 15 mol%). After the reaction was completed, the reaction mixture was concentrated and the residue was diluted with ethyl acetate to precipitate the catalyst, which was then easily recovered by filtration. The first time the catalyst was recovered, it was characterized by ^{1}HNMR to confirm that the structure did not change after the reaction. The catalyst was then used for the next run of the reaction. As Table 2 shows, catalyst **4a** could be reused for at least 6 times without a significant loss of stereoselectivity (ee > 96%) although the catalytic activity decreased gradually.

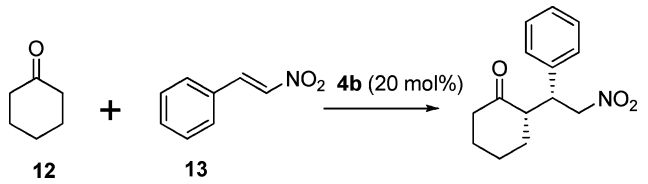
The scope of the Michael reactions using catalyst **4a** on MeOH was examined with a variety of carbonyl compounds and nitroolefins (Table 3).

As demonstrated in Table 3, catalyst **4a** can be applied to several different Michael reactions to produce a variety of carbonyl compounds and nitroolefins in MeOH. Cyclohexanone efficiently underwent Michael reactions with different aryl-substituted nitroolefins to give Michael adducts **14a–h** in high yields with excellent enantio- (94–98% ee) and diastereo-selectivities (*syn*/*anti* ratio up to 99/1). The results in Table 3 also show that the nature of the substituents on the aryl groups only slightly influences the yields and enantioselectivities. For nitroolefins with electron-rich groups (methyl and methoxy), the reaction proceeded smoothly to afford Michael adducts **14b–c** in excellent enantio- (98–99% ee) and diastereoselectivities (*syn*/*anti* 99/1) (Table 3, entries 2–3). For nitroolefins with electron-deficient groups, the Michael adducts **14d–h** were also obtained in high yields (87–96%) with excellent



Scheme 1 Synthesis of proline-based reduced dipeptides.

Table 2 Recycling studies of **4a** catalyzed Michael addition of cyclohexanone to *trans*-nitrostyrene[a]



Cycle[b]	Time (h)	Yield (%)[c]	ee (%)[d]	*syn* : *anti*[e]
1	12	93	98%	99 : 1
2	12	91	97%	99 : 1
3	16	88	96%	99 : 1
4	20	84	97%	98 : 2
5	24	80	97%	99 : 1
6	24	75	98%	97 : 3

[a] The reaction was conducted with 20 mmol of **12** and 100 mmol of **11** in 2 mL of solvent at room temperature. [b] The first recovered catalyst was characterized by ^{1}HNMR. [c] Yields of isolated products. [d] Determined by ^{1}H NMR. [e] Determined by Chiral HPLC.

enantio- (95–99% ee) and diastereoselectivities (*syn*/*anti* ratio up to 99/1) (Table 3, entries 4–8). The dihydro-2*H*-pyran-4(3*H*)-one and dihydro-2*H*-thiopyran-4(3*H*)-one also showed to be an efficient Michael donor with high yield(89–91%) and excellent enantioselectivities. (96–97% ee) (Table 3, entries 9,10). However, the cyclopentanone gave product **14k** with moderate diastereoselectivities (58% ee, Table 3, entry 11). The acyclic ketone donor, acetone has been tested under similar conditions. The reaction of acetone with *trans*-β-nitrostyrene **13** resulted in product **14m** with good yield (94%) but moderate enantioselectivity (51% ee) (Table 3, entry 12). With the increase of the length of side chain of the ketone, the enantioselectivity of the Michael addition process was improved (Table 3, entry 14, 15). The unsymmetrical ketone, 2-butanone took place at the more substituted sites and gave the thermodynamic controlled product **14n** with lower yield (67%) and better enantioselectivity (74%) (Table 3, entry 14) than **14m**. Furthermore, the 3-pentanone gave product **14l** with moderate yield (75%) and excellent enantioselectivity (94% ee) (Table 3, entry 12). Although the α,α′-disubstituted aldehyde iso-butyraldehyde gave product **14p** with moderate enantioselectivities (62% ee) (Table 3, entry 16), the linear aldehydes n-butyraldehyde and propanal are also suitable Michael donors with high diastereoselectivity as well as good enantioselectivity (87%–90% ee) (Table 3, entries 16,17). These results indicate that catalyst **4a** should be broadly applicable to the synthesis of γ-nitro carbonyl compounds.

To account for the stereochemical outcome of the Michael reaction, a plausible transition-state model is proposed in Fig. 2.

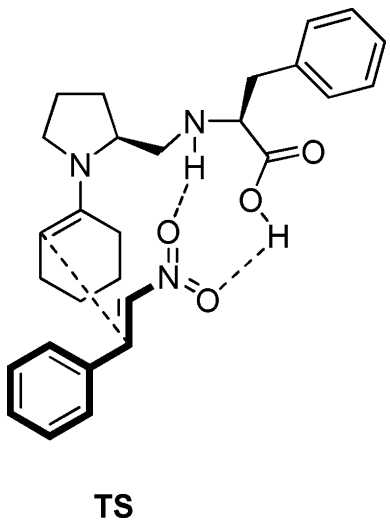
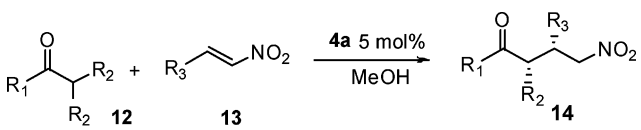


Fig. 2 A possible transition state.

Table 3 Michael reactions of ketones to nitroolefins[a]



Entry	R_1	R_2, R_3	R_4	Product	Yield (%)[b]	*syn* : *anti*[c]	ee (%)[d]
1	-$(CH_2)_4$-		Ph	**14a**	91%	99 : 1	98%
2	-$(CH_2)_4$-		4-Me-Ph	**14b**	90%	98 : 2	98%
3	-$(CH_2)_4$-		4-OMe-Ph	**14c**	80%	99 : 1	97%
4	-$(CH_2)_4$-		4-Cl-Ph	**14d**	91%	97 : 3	96%
5	-$(CH_2)_4$-		2-Cl-Ph	**14e**	87%	96 : 4	97%
6	-$(CH_2)_4$-		2,4-Cl-Ph	**14f**	92%	99 : 1	98%
7	-$(CH_2)_4$-		4-NO_2-Ph	**14g**	93%	99 : 1	95%
8	-$(CH_2)_4$-		2-NO_2-Ph	**14h**	90%	98 : 2	97%
9	-$(CH_2CH_2OCH_2)$-		Ph	**14i**	91%	99 : 1	97%
10	-$(CH_2CH_2SCH_2)$-		Ph	**14j**	89%	98 : 2	96%
11	-$(CH_2)_3$-		Ph	**14k**	78%	80 : 20	58%
12	Et	Me, H	Ph	**14l**	75%	98 : 2	94%
13	Me	H, H	Ph	**14m**	94%	—	51%
14	Me	Me, H	Ph	**14n**	67%	93 : 7	74%
15	H	Et, H	Ph	**14o**	90%	97 : 3	90%
16	H	Me, H	Ph	**14p**	87%	95 : 5	87%
17	H	Me, Me	Ph	**14q**	79%	—	62%

[a] Unless otherwise noted, the reaction was conducted with 5 mmol of **13** and 25 mmol of **12** in 1 mL of solvent at room temperature. [b] Yields of isolated products. [c] Determined by ^{1}HNMR, [d] Determined by Chiral HPLC.

As shown in **TS**, the secondary amine of the pyrrolidine ring activates the ketone through the formation of an enamine intermediate. The hydrogen bond donor, amine and carboxyl group, direct the nitrostyrene to attack the *re*-face of the enamine.

In summary, a new family of organocatalysts which can be used to promote highly efficient asymmetric Michael addition reactions of ketones and aldehydes to nitroolefins has been developed by modifying previously reported peptides. Among these, catalyst **4a** is the best. The main advantages of this catalyst are ease of synthesis and low loading (5 mol%) for high stereoselectivities (ee up to 98%, *syn*/*anti* up to 99/1) at room temperature. Moreover, the catalyst can be easily recovered and reused. These advantages make **4a** a potential catalyst for industrial applications.

Acknowledgements

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