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Prolylprolinol-Catalyzed Asymmetric Michael Addition of Aliphatic Aldehydes to Nitroalkenes

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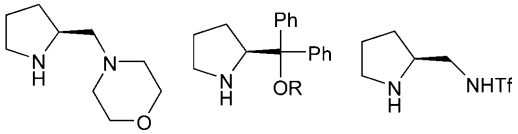
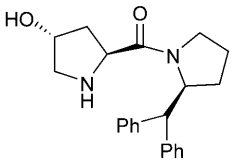
Abstract: Several novel prolylprolinol catalysts have been designed and synthesized. This type of compound showed high catalytic efficiency on promoting the direct addition of unmodified aldehydes to nitroalkenes. Among the catalysts surveyed, the least bulky member (**8d**) exhibited the best performance on both efficiency and stereoselectivity, providing the products with up to 97% *ee* value with 1.5–5 mol% catalyst loading. Additionally, computational studies of the transition state have been conducted to explain the high diastereo- and enantioselectivity.

Keywords: aldehydes; bifunctional catalysts; Michael addition; nitroalkenes; organocatalysis

As a highly efficient and atom-economic reaction, the Michael addition plays a prominent role in constructing carbon-carbon bonds in organic synthesis.[1] With the current interest in stereochemistry, the organocatalytic asymmetric Michael addition of various nucleophiles to electron-deficient olefins has attracted much attention in recent decades.[2] Since the addition of aliphatic aldehydes to nitroalkenes[3] could generate versatile synthetic building blocks, several L-proline-derived catalysts have been developed and successfully applied, which can be generally divided into two types: a bulky type[4] and a bifunctional type,[5] according to the activating modes (Figure 1). Pyrrolidine-morpholine **1** was the first catalyst reported by Barbas III's group for the Michael addition of unmodified aldehydes to nitroalkenes.[4s] As the most representative bulky type catalyst, diphenylprolinol trimethylsilyl ether **3**, described by Hayashi's group, also exhibited excellent diastereo- and enantioselectivity on this reaction.[4o]





Compared with type A, bifunctional catalysis[6] is deemed to be a more efficient mode for the conjugate addition of aldehydes to nitroalkenes since both the carbonyl and the nitro group could be activated simultaneously by enamine formation and hydrogen bonding.[7] The introduction of sulfonamide (catalyst **4**),[5o] amino alcohol,[5b] (thio)urea,[5c,j,l] camphor[5d] and sulfamide[5a] moieties into amine catalysts as H-bond donors has led to satisfactory results in the above re-

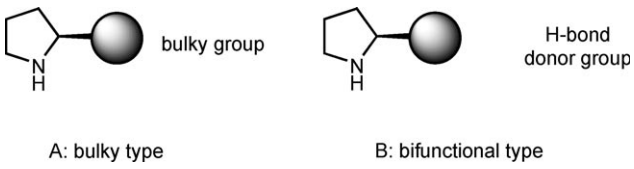


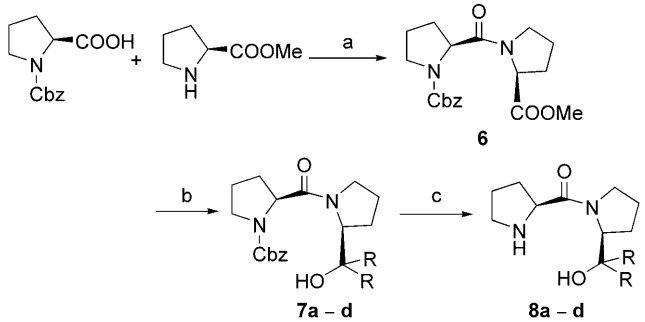
Figure 1. Catalyst types for the reaction of aliphatic aldehydes with nitroalkenes.

action. In addition, 4-hydroxyprolylamide **5** and tripeptide H-D-Pro-Pro-Asp-NH_2, reported by Palomo[5k] and Winnemers groups,[5f,g] respectively, showed excellent diastereo- and enantioselectivity on this reaction.

After the golden rush of organocatalysis, "low loading", "simple", "reusable" and "scalable" have become the new keywords in modern catalyst design.[8] Although several great catalysts have been documented, high catalyst loading (10–20 mol%) and a large excess of aldehyde (up to 10 equiv.) were generally required, hence it still remains a challenge to develop novel catalysts for the asymmetric addition of aldehydes to nitroalkenes with low catalyst loading.

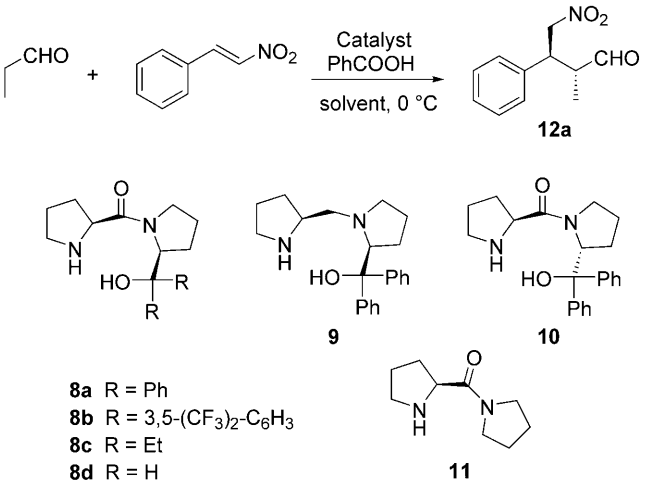
We noticed that diphenylprolinol **2**, one of the most typical bifunctional organocatalysts[9], showed quite low activity in the addition of aldehydes compared to its silyl ether **3**.[4n] As suggested by Jørgensen et al., its low catalyst turnover was ascribed to the formation of relatively stable and unreactive hemiaminal species between diphenylprolinol and aldehyde.[10] Based on this viewpoint, we envisioned that the formation of hemiaminal would be prevented when the amino and hydroxy groups are far enough from each other, thus we chose prolylprolinol as a backbone to develop a new class of catalysts. The novel prolylprolinol compounds were easily prepared in three steps as illustrated in Scheme 1. The key intermediate *N*-(*N*-Cbz-prolyl)proline methyl ester **6** formed by condensation of Cbz-L-proline and L-proline methyl ester can be easily converted into different alcohols **7a–d**, and the desired prolylprolinol compounds **8a–d** can be obtained after the deprotection of the Cbz group.

To get initial information on our hypothesis, the catalytic activity of the compound **8a** was firstly evaluated in the model reaction of propanal with nitrostyrene in comparison with diphenylprolinol **2**. The reaction was carried out in dichloromethane at 0 °C with 10 mol% of the catalyst together with benzoic acid as an additive, and the results are summarized in Table 1. To our delight, the reaction mediated by 10 mol% of **8a** was completed within 3 h, providing addition product **12a** in a yield of 93%, *syn*:*anti* ratio of 89:11, and 88% *ee* (Table 1, entry 2), while diphenylprolinol **2** showed very low catalytic activity (Table 1, entry 1). Fortunately, the catalyst loading can be reduced to 3 mol% without erosion of the diastereo- and enantioselectivity, although a prolonged time was required (Table 1, entries 3 and 4). In turn, several solvents were examined (Table 1, entries 5–8).



Scheme 1. Synthetic routes to prolylprolinols **8a–d**. *Reagents and conditions:* a) DCC, CH_2Cl_2, 0 °C, 2 h, 97%; b) for **7a–c**: RMgBr, THF, −15 °C, 4–6 h, 25–64%; for **7d**: $NaBH_4$/LiCl, THF, −5 °C, 2 h, 82%; c) 10% Pd/C, H_2, MeOH, 4 h, 85%.

Table 1. Optimization of catalytic asymmetric conjugation additions of propanal to nitrostyrene.[a]



Entry	Catalyst (mol%)	Solvent	Time [h]	Yield [%][b]	*dr*[c]	*ee*[d] [%]
1	**2** (20)	CH_2Cl_2	72	<5	nd	nd
2	**8a** (10)	CH_2Cl_2	2.5	93	89:11	88
3	**8a** (5)	CH_2Cl_2	8	92	84:16	87
4	**8a** (3)[e]	CH_2Cl_2	20	92	87:13	88
5	**8a** (3)[e]	$CHCl_3$	24	91	85:15	87
6	**8a** (3)[e]	hexane	36	80	88:12	86
7	**8a** (3)[e]	toluene	64	90	92:8	91
8	**8a** (3)[e]	THF	72	<20	nd	nd
9	**9** (10)	CH_2Cl_2	1.5	93	75:25	36
10	**10** (10)	CH_2Cl_2	2.5	94	88:12	57
11	**8b** (3)[e]	CH_2Cl_2	24	93	95:5	92
12	**8c** (3)[e]	CH_2Cl_2	24	92	85:15	89
13	**8d** (3)[e]	CH_2Cl_2	20	94	94:6	93
14	**11** (3)[e]	CH_2Cl_2	20	92	87:13	82

[a] Unless otherwise specified, all reactions were carried out using propaldehyde (0.6 mmol), nitrostyrene (0.20 mmol), x mol% catalyst and the equivalent amount of benzoic acid in 1 mL indicated solvent at 0 °C.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy of the crude products.
[d] Determined by chiral-phase HPLC on Chiralcel OD-H.
[e] 5 mol% benzoic acid were added.

Dichloromethane was still the most appropriate one in terms of both reactivity and stereoselectivity.

Encouraged by these preliminary results, further modification of the catalyst structure was carried out to improve the stereoselectivity. The effect of carbonyl group of **8a** was firstly taken into consideration. For this purpose, the corresponding reduced product **9** was prepared and tested. In this case, a rather low diastereo- and enantioselectivity (75:25 *dr* and 36% *ee*) were observed though the catalytic activity was comparable to **8a** (Table 1, entry 9). This might suggest that the rigidity of the Pro-Pro scaffold is vital to achieve high stereoselectivity. Next, the (*S*,*R*)-prolyl-prolinol **10**, a diastereomer of **8a**, was prepared and used for assessing the effect of the configuration of the prolinol moiety. As a consequence, a marked decrease in enantioselectivity was observed, indicating the obvious configuration mismatch (Table 1, entry 10). Further efforts were made to investigate the impact of R groups for catalysts **8a–d**. Unexpectedly, bulky groups were not necessary to improve the diastereo- and enantioselectivity. Among the four catalysts surveyed, the least bulky one **8d** provided the best results (94:6 *dr*, 93% *ee*, Table 1, entry 13). Catalyst **11**, which bears no hydroxy group, was also effective albeit providing inferior enantioselectivity (Table 1, entry 14). According to the above observations, we speculated that the formation of an H-bond between the hydroxy and the nitro group would be helpful to fix their location in the transition state, while playing a weak role in activating nitrostyrene. The less bulky R group favored the formation of an H-bond, thus leading to better enantioselectivity. Besides, a more acidic hydroxy group was also beneficial for the formation of an H-bond, so **8b** also showed an excellent performance (95:5 *dr*, 92% *ee*; Table 1, entry 11). Considering synthetic accessibility and atomic economy, **8d** was chosen for further investigations.

Next, various acid and base additives were examined and the results are listed in Table 2. The reaction were finished after 8 h with 75% *ee* when no additive was used. Apparently, acid additives with appropriate pK_a values enhanced both the reactivity and enantioselectivity (Table 2, entries 2–5). However, addition of a strong acid such as 3,5-dinitrobenzoic acid or TFA caused detrimental effects on the reaction (entries 6 and 8). Moreover, addition of L-(+)-tartaric acid did not lead to any obvious synergy or mismatch (Table 2, entry 9). The presence of an equivalent of water showed slight effects on the reaction rate and enantioselectivity (Table 2, entry 10). In contrast, base additives, like DABCO, DIPEA, DMAP and imidazole, caused a significant decline in conversions and stereoselectivities (Table 2, entries 11–14). When benzoic acid served as additive, the loading of **8d** could be further reduced to 1.5 mol% (Table 2, entry 15).

Table 2. Effect of additives on the reaction[a].

Entry	Additive[b]	Time [h]	Conversion [%][c]	*dr*[d]	*ee*[e] [%]
1	None	8	>99	91:9	75
2	PhCOOH	3	>99	93:7	88
3	4-MeO-C_6H_4COOH	4	>99	89:11	85
4	4-F-C_6H_4COOH	4	>99	90:10	87
5	4-NO_2-C_6H_4COOH	5	>99	89:11	84
6	3,5-di-NO_2-C_6H_3COOH	24	<50	n.d.[f]	n.d.
7	CH_3COOH	3	>99	92:8	76
8	CF_3COOH	24	<30	n.d.[f]	n.d.
9	tartaric acid	8	>99	96:4	80
10[g]	H_2O	8	>99	94:6	81
11	DABCO	5	>99	86:14	79
12	DIPEA	10	>99	76:24	59
13	DMAP	12	>99	63:37	64
14	imidazole	10	>99	82:18	72
15[h]	PhCOOH	36	90[i]	91:9	88

[a] Unless otherwise specified, all reactions were carried out using propanal (0.6 mmol), nitrostyrene (0.20 mmol) and 3 mol% **8d** at room temperature.
[b] 5 mol% additive were employed.
[c] Conversion estimated by TLC analysis.
[d] Determined by ^{1}H NMR spectroscopy of the crude products.
[e] Determined by chiral-phase HPLC on Chiralcel OD-H.
[f] Not determined.
[g] One equivalent of H_2O was added.
[h] With 1.5 mol% **8d**.
[i] Isolated yield.

Under the above optimized conditions, the Michael addition reactions of other aliphatic aldehydes with nitrostyrene were investigated in the presence of 1.5 mol% of **8d** at room temperature. As shown in Table 3, the corresponding adducts **12a–12f** were afforded in high yields (71–90%) with good stereoselectivities (77–88% *ee*) after 36–60 h (Table 3, entries 1–4). The reaction of isovaleraldehyde proceeded more slowly than that of unbranched aldehydes due to the hindrance of the isopropyl group, so 3 mol% of **8d** was employed (Table 3, entry 5). The less reactive isobutyraldehyde was also tolerated in the presence of

Table 3. Addition reaction between aldehydes and nitroalkenes catalyzed by **8d**.[a]

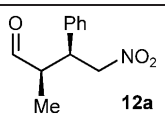
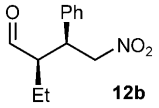
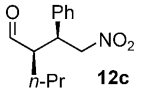
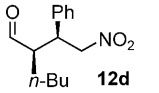
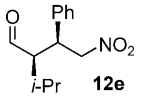
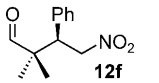
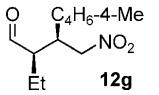
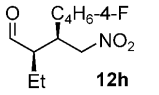
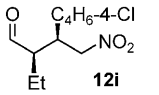
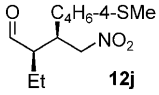
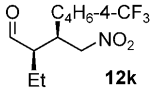
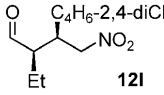
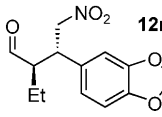
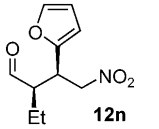
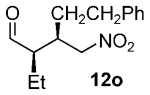
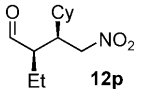
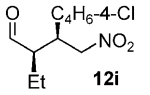
Entry	Product	**8d** [%]	Temperature [°C]	Time [h]	Yield [%][b]	*dr*[c]	*ee*[d] [%]
1	 **12a**	1.5	r.t.	36	90	91:9	88
		5	−20	36	88	96:4	96
2	 **12b**	1.5	r.t.	40	87	94:6	83
		5	−20	36	92	98:2	93
3	 **12c**	1.5	r.t.	48	85	92:8	78
		5	−20	48	83	99:1	93
4	 **12d**	1.5	r.t.	60	83	96:4	77
		5	−20	48	84	99:1	93
5	 **12e**	3	r.t.	60	82	97:3	82
		5	−20	60	78	99:1	93
6	 **12f**	10[e]	r.t.	60	71	–	80
7	 **12g**	5	−20	36	97	99:1	93
8	 **12h**	5	−20	24	98	98:2	93
9	 **12i**	5	−20	20	96	98:2	95
10	 **12j**	5	−20	35	94	99:1	92
11	 **12k**	5	−20	12	99	98:2	95
12	 **12l**	5	−20	28	94	99:1	95
13	 **12m**	5	−20	60	96	97:3	93
14	 **12n**	5	−20	40	96	98:2	81

Table 3. (Continued)

Entry	Product	**8d** [%]	Temperature [°C]	Time [h]	Yield [%][b]	*dr*[c]	*ee*[d] [%]
15	 **12o**	5	−20	36	93	95:5	92
16	 **12p**	5	−20	60	75	91:9	97
17[f]	 **12i**	5	−20	24	95	98:2	96

[a] Unless otherwise specified, all reactions were carried out on 0.2 mmol scale using x mol% **8d** and 5 mol% benzoic acid.
[b] Isolated yield.
[c] Determined by ^{1}H NMR spectroscopy of the crude products.
[d] Determined by chiral-phase HPLC.
[e] 10 mol% benzoic acid were added.
[f] Reaction carried out on a 10-mmol scale.

10 mol% of **8d**, furnishing a moderate yield of **12f** with good enantioselectivity (Table 3, entry 6). A significant improvement in the diastereo- and enantioselectivity was achieved when the reactions were carried out at lower temperature. The diastereoselectivity was raised up to more than 99:1 and enantioselectivity up to 96% *ee* at −20 °C. In these cases, 5 mol% of **8d** was added to shorten the reaction time. As in previous reports, the reaction selectively afforded the *syn* isomer with the (*R*,*S*) absolute configuration.[6n]

Then the reactions of a variety of β-arylnitroalkenes with butyraldehyde were further examined. Addition products **12g–n** were obtained in excellent yields with high diastereo- and enantioselectivities. Electron-withdrawing groups on the benzene ring accelerated the reaction significantly. For instance, the reaction of 4-trifluoromethylnitrostyrene with butyraldehyde was complete after 12 h, giving the adduct **12k** in almost quantitative yield (Table 3, entry 11), whereas the reaction of 3,4-methylenedioxynitrostyrene needed nearly 60 h (Table 3, entry 13). Further experiments demonstrated that β-alkylnitroalkenes are also excellent Michael acceptors (Table 3, entries 15 and 16).

Enlargement of the reaction scale was also tried. The addition of butyraldehyde to 4-chloronitrostyrene was carried out on a 10-mmol scale at −20 °C mediated by 5 mol% of **8d**, affording **12i** in 95% yield without any decline in diastereo- and enantioselectivity (Table 3, entry 17). Moreover, the catalyst was easily recovered by a simple aqueous acid/base work-up after the reaction was finished and can be reused.[11]

To better understand the high diastereo- and enantioselectivity, the model reaction between propanal and notrostyrene catalyzed by **8d** was studied by DFT calculations at the BHandH/6-311++G(d,p) level.[12] The reliability of the BHandH/6-311++G(d,p) method can be found elsewhere.[13] As shown in Figure 2, **TS1**, which leads to the formation of the major product observed experimentally, is found to be much more stable than **TS2**. Evidently, the O−

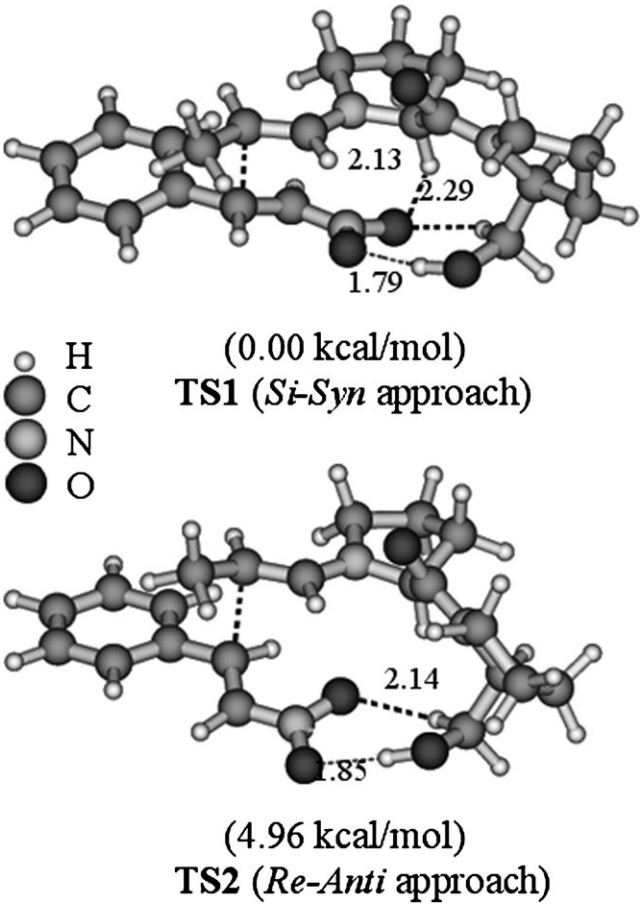


Figure 2. The calculated transition structures of the reaction between propanal and nitrostyrene catalyzed by **8d** along with the relative free energies. All distances are in Å.

H···O and the C–H···O hydrogen bonds help to discriminate between the two possible transition-state models **TS1** and **TS2** by 4.96 kcal mol^{-1} and the shorter O–H···O hydrogen bond indicates its dominant role. The involvement of the C–H group, even though it is a minor role, to fix the location of nitrostyrene in the transition states also explains why the simplest catalyst **8d** with no bulky group on the prolinol moiety exhibited the highest diastereo- and enantioselectivity.

In summary, we have developed a novel bifunctional prolylprolinol catalyst **8d** for the asymmetric conjugate addition of aliphatic aldehydes to nitroalkenes. This catalyst exhibited rather high catalytic efficiency and good to excellent levels of stereoselectivity. Due to its synthetic simplicity and recoverability, we believe **8d** is an ideal candidate for laboratory- or large-scale preparations. Further applications of the catalyst are being studied in our laboratory.

Experimental Section

General Procedure

To a solution of the corresponding nitroalkene (0.2 mmol, 1.0 equiv.) in 1 mL of dichloromethane, 5 mol% of catalyst and 5 mol% of benzoic acid were added, the mixture was stirred at the indicated temperature for 20 min, then freshly distilled aldehyde (0.6 mmol, 3.0 equiv.) was added. The resulting solution was stirred at the same temperature for 12–60 h. Then it was quenched with 1 M HCl (1 mL), and extracted with ethyl acetate (3×1 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and purified over silica gel by flash column chromatography to afford the corresponding Michael adducts **12a–p**.

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