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New N-terminal prolyl-dipeptide derivatives as organocatalysts for direct asymmetric aldol reaction

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Abstract—A series of new N-terminal prolyl-dipeptide derivatives have been synthesized and evaluated as organocatalysts for the direct asymmetric aldol reaction of acetone with electron-deficient aromatic aldehydes. At room temperature, the presence of 10 mol % of catalysts **2** and **5** efficiently catalyzes the direct asymmetric aldol reaction to give the aldol adducts with modest to excellent enantiomeric excesses (ee) values, which are up to 96%.

The aldol reaction is one of the most powerful carbon–carbon bond formation methods in organic synthesis.[1] Since List et al. demonstrated that L-proline itself could catalyze the intermolecular direct asymmetric aldol reaction,[2] the concept of small organic molecules as catalysts has received considerable attention and asymmetric organocatalysis has become a new and intriguing field in synthetic chemistry.[3] Proline and several proline-derived catalysts have been developed for the direct asymmetric aldol reaction,[4–13] such as pyrrolidinyltetrazole,[6] benzoimidazole–pyrrolidine,[7] and L-prolinamide derivatives.[8–10] Though the pyrrolidinyltetrazole and benzoimidazole–pyrrolidine increase the reactivity and expand the solvent scope of the direct asymmetric aldol reaction, no obvious improvement in enantioselectivity has been achieved as compared to that of L-proline. At low temperatures, most of the L-prolinamide derivatives are often able to catalyze intermolecular ketone aldolization with high enantioselectivity. Small peptides can be ideal asymmetric organocatalysts because of their diversified structures and functionality. But only a few successful examples catalyzed by the small peptides for direct aldol reactions have been reported.[11] Based on N-terminal prolyl dipeptides, we replaced C-terminal carboxylic acid by tetrazole and benzoimidazole, which can lead to higher acidity and solubility of the catalysts to improve the reactivity and selectivity of the reaction. Herein, we wish to report the applications of five new N-terminal prolyl-dipeptide derivatives **1**–**5** in the direct aldol reaction between acetone and electron-deficient aromatic aldehydes at room temperature.

Catalysts **1**–**5** (shown in Fig. 1) were readily prepared from *N*-carbobenzyloxy-L-proline and the corresponding α-amino acid tetrazole and α-aminobenzoimidazole by the known reaction sequences in just two steps (see the Supplementary data),[14–16] and to afford the product (for example, **2**) in 52% total yield based on *N*-carbobenzyloxy-L-proline. The structure of **1** was confirmed by single X-ray crystallographic analysis (see the Supplementary data).

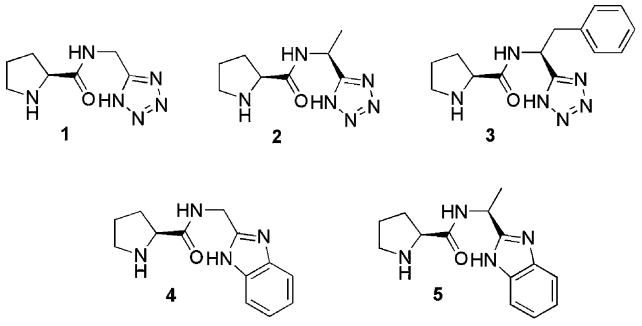

Figure 1. The chiral organocatalysts **1**–**5**.

Keywords: Organocatalyst; N-terminal prolyl-dipeptide derivatives; Direct aldol reaction; Asymmetric catalysis.
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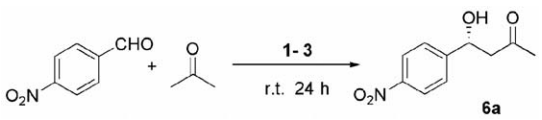
Table 1. Direct aldol reaction of acetone and 4-nitrobenzaldehyde catalyzed by catalysts **1**–**3**



Entry	Catalyst	Solvent	Catalyst (mol %)	Yield[a] (%)	ee[b] (%)
1	**1**	DMF	20	51	86
2	**2**	DMF	20	68	96
3	**3**	DMF	20	43	88
4	**2**	DMF	10	60	92
5	**2**	DMF	10	20	74[c]
6	**2**	DMSO	10	64	82
7	**2**	1,4-Dioxane	10	40	90
8	**2**	THF	10	75	59
9	**1**	DMF/H_2O[d]	10	67	42
10	**2**	DMF/H_2O[d]	10	61	46
11	**3**	DMF/H_2O[d]	10	63	67
12	**2**	DMF	10	64	96[e]
13	**2**	DMF	10	64	86[f]

[a] Isolated yield after silica gel column chromatography.
[b] The ee values were determined by HPLC analyses (Daicel Chiralpack AS-H) with hexane/2-propanol as the eluent.
[c] The reaction was performed at −25 °C.
[d] The mixture of (9:1) (DMF/water) was employed as a solvent, the reaction time was 18 h.
[e] The reaction was performed in the presence of 10 mol % Et_3N.
[f] The reaction was performed in the presence of 20 mol % Et_3N.

First, at room temperature, we evaluated the catalytic properties of catalysts **1**–**3** in *N*,*N*-dimethylformamide (DMF). As an initial test run, the aldol reaction between acetone and 4-nitrobenzaldehyde was examined, and the results are summarized in Table 1. Compared to catalyst **1**, catalysts **2** and **3** led to aldol adduct with high enantioselectivity (Table 1, entry 1 vs 2 and 3) which could be attributed to the introduction of the other chiral center in catalysts **2** and **3**. Catalyst **2** gave aldol adduct with excellent enantioselectivity and ee value up to 96% (Table 1, entry 2) in comparison to that of catalyst **3**. This result is presumably due to the steric bulk of their substituted groups, which plays an important role in the stereo-control. Moreover, it is noteworthy that even loading of catalyst **2** was reduced from 20 to 10 mol %, there is no significant change in yield or selectivity (Table 1, entry 2 vs 4).

It is well known that temperature exerts a significant effect on the enantioselectivity of the direct asymmetric aldol reaction. In most cases, the enantioselectivities of catalysts ascend with decreasing temperature. However, as seen in Table 1, entries 4 and 5, ee value of the aldol adduct was decreased at lower temperature. Therefore, the room temperature condition was appropriate for the direct aldol reaction of 4-nitrobenzaldehyde and acetone and the best ee value was up to 96% ee (Table 1, entry 2).

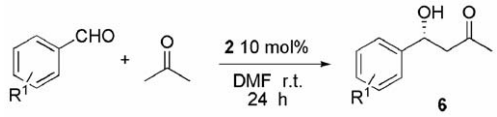
We also examined the solvent effect in this reaction. It was found that dimethylsulfoxide (DMSO), 1,4-dioxane and tetrahydrofuran (THF) were also suitable solvents for the direct asymmetric aldol reaction besides DMF (Table 1, entries 6–8). Our experimental results also indicated that catalyst **3** (Table 1, entry 11) could tolerate the presence of 10% of water with the ee values of the products remaining at moderate level.

Interestingly, the addition of triethylamine (Et_3N) with an equal molar amount of catalyst slightly improved the reaction yield and the enantioselectivity as compared to that with the catalysts in the absence of additives (Table 1, entry 4, 60% yield with 92% ee vs entry 12, 64% yield with 96% ee). However, while the loading of Et_3N was increased to 200% molar amount of catalyst, the ee value of aldol adduct was decreased (Table 1, entry 13).

To investigate the scope of the substrate of catalyst **2**, the reactions of various aromatic aldehydes with acetone were studied under the optimized conditions (using 10 mol % of **2** as catalyst, in the presence of 10 mol % Et_3N). As shown in Table 2, the reactions of various aromatic aldehydes, which bear an electron-withdrawing group on the benzene ring, proceeded smoothly in excellent enantioselectivities (up to 96%) to furnish the aldol adducts (Table 2, entry 2). In addition, halogenated benzaldehydes led to decreased yields. Interestingly, the ee values of the products remained at good levels (Table 2, entries 7–9). On the other hand, this catalytic system was proven to be completely ineffective for the aromatic aldehydes with an electron-donating group or without any substitution (Table 2, entries 10 and 11).

Next, in order to increase the solubility of the catalysts, we replaced the C-terminal carboxylic acid with benzimidazole to gain two new dipeptide derivatives **4** and **5**. Using **4** and **5** as catalysts, we examined the reaction of 4-nitrobenzaldehyde with neat acetone under various conditions and the experimental results are listed in

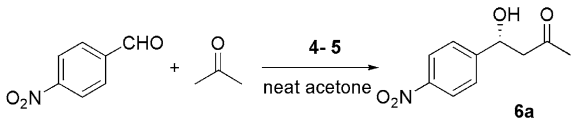
Table 2. Direct aldol reaction of acetone and various aromatic aldehydes catalyzed by catalyst **2**



Entry	R^1	Product	Et_3N (mol %)	Yield[a] (%)	ee[b] (%)
1	4-NO_2	**6a**	None	60	92
2	4-NO_2	**6a**	10	64	96
3	2-NO_2	**6b**	None	62	76
4	2-NO_2	**6b**	10	69	82
5	4-CN	**6c**	None	51	74
6	4-CN	**6c**	10	62	86
7	4-Cl	**6d**	10	46	83[c]
8	2-Cl	**6e**	10	45	76[c]
9	4-Br	**6f**	10	49	84[c]
10	4-H	**6g**	10	Traces	n.d.[c,d]
11	4-CH_3	**6h**	10	Traces	n.d.[c,d]

[a] Isolated yield after flash column chromatography on silica gel.
[b] The ee values were determined by HPLC analyses (Daicel Chiralpack AS-H) with hexane/2-propanol as the eluent.
[c] Reaction time was 48 h.
[d] Not determined.

Table 3. Direct aldol reaction of acetone and 4-nitrobenzaldehyde catalyzed by catalysts **4** and **5**



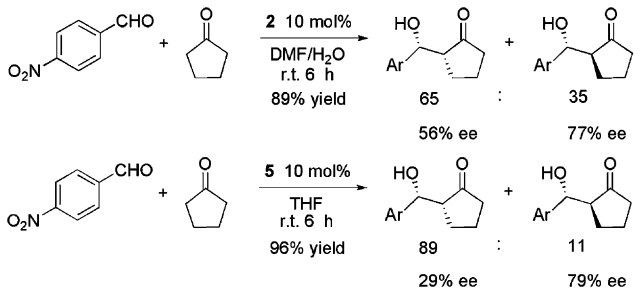
Entry	Catalyst	Catalyst (mol %)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**4**	10	48	32	59
2	**5**	10	24	73	96
3	**5**	5	24	60	90
4	**5**	10	24	26	57[c]

[a] Isolated yield after flash column chromatography on silica gel.
[b] The ee values were determined by HPLC analyses (Daicel Chiralpack AS-H) with hexane/2-propanol as the eluent.
[c] The reaction was performed at −25 °C.

Table 3. It was found that catalyst **5** showed significant catalytic activity to produce the aldol adduct with good yield and enantioselectivity, while catalyst **4** led to poor yield and enantioselectivity (Table 3, entry 2, 73% yield with 96% ee vs entry 1, 32% yield with 59% ee). Moreover, when the reaction was carried out under the same condition with only 5 mol % catalyst loading of **5**, the aldol product was also obtained in high enantioselectivity (Table 3, entry 3). Similar to catalyst **2**, the reaction catalyzed by **5** also resulted in poor yield and low enantioselectivity at low temperature (Table 3, entry 4, 26% yield with 57% ee).

Finally, we studied the direct aldol reaction of 4-nitrobenzaldehyde and cyclopentanone catalyzed by catalysts **2** and **5** (Scheme 1). In the case of catalyst **2**, the reaction was carried out for 6 h to afford the desired products in good yield and dr for the syn/anti products was 65:35 with ee value of 56% and 77%, respectively. The reaction catalyzed by **5** gave higher yield than that catalyzed by **2** up to 96%. The dr for the syn/anti products was 89:11 with ee value of 29% and 79%, respectively.

Our studies show that the enantioselectivities of catalysts **1**–**5** were remarkably improved for introducing the nitrogen-containing heterocyclic groups, compared to dipeptide catalysts H-Pro-Gly-OH,[11c] H-Pro-Ala-OH,[11d] and H-Pro-Phe-OH.[11e] Moreover, the catalyst loading of our dipeptide derivatives may be reduced to 10 mol %, while the catalyst loadings of other dipeptide catalysts were usually from 20 to 40 mol %.



Scheme 1. Direct aldol reaction of 4-nitrobenzaldehyde and cyclopentanone catalyzed by catalysts **2** and **5**.

In summary, five new N-terminal prolyl-dipeptide derivatives **1**–**5** have been first synthesized and applied as catalysts for the direct asymmetric intermolecular aldol reaction. The experimental results showed the reaction with moderate to excellent enantioselectivity at room temperature. Among these new catalysts, catalyst **2** is the most efficient one for the direct aldol reaction between acetone and electron-deficient aromatic aldehydes, which produces aldol products with 76–96% ee values under the optimized conditions. Catalyst **5** also shows a significant catalytic activity for the aldol reaction of 4-nitrobenzaldehyde with neat acetone in good yields and high enantioselectivities (up to 96% ee). Further investigation of catalyst **5** is in progress.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.08.084.

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