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C_2-Symmetric Bisprolinamide as a Highly Efficient Catalyst for Direct Aldol Reaction

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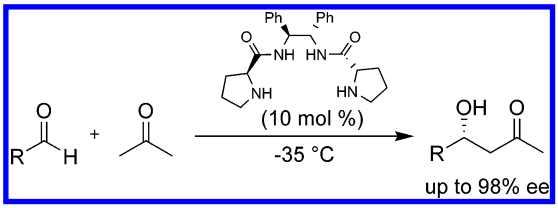
ABSTRACT



The catalytic activity of the prolinamide-type catalysts may be improved by introducing additional prolinamide moiety into the catalyst, while the enantioselectivity can still be maintained or further improved. A C_2-symmetric bisprolinamide with two prolinamide moieties has been found to be an excellent catalyst for direct aldol reaction with more than doubled reactivity and better asymmetric induction than its monoprolinamide counterpart.

The aldol reaction is an important tool in organic synthesis due to its usefulness in synthesizing β-hydroxy carbonyl compounds, which are subunits of many natural products.[1] Direct aldol reaction does not require preformed enolate, and therefore, it is more convenient to carry out and is highly atomically economic. Although highly enantioselective transition-metal catalysts have been developed,[2] there have been many efforts directed toward developing highly efficient organocatalysts for this reaction in recent years,[3] since environmentally benign methods are currently in vogue.[4] Since the early discovery of List and Barbas that L-proline may be used as the catalyst for the enantioselective direct aldol reaction,[5] several proline-derivatives have been synthesized and applied for highly enantioselective direct aldol

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reaction.[3,5,6] However, the catalytic activity of these catalysts is normally quite low; to achieve a good yield in reasonable time, large loading of the catalyst (20−30 mol %) is required. Most recently, Gong and co-workers reported a very promising prolinamide catalyst **1** (Figure 1), which yields very high

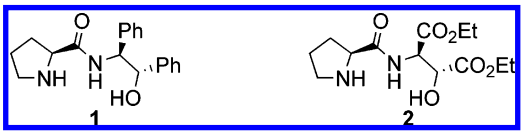


Figure 1. Gong's prolinamide catalysts**1** and **2**.

enantioselectivities for the aldol products when 20 mol % of **1** is used in the reactions.[6] While our work was still in progress, the same group reported a new catalyst **2** with much improved reactivity through finely tuning the electronic effects.[7]

Besides the electronic effects that can be utilized to improve the catalyst reactivity, we envisioned that the reactivity might be improved by incorporating more than one prolinamide moiety into the catalyst structure to generate a catalyst with multiple reaction centers, based on the hypothesis that the chance for the substrate to meet with the reaction center increases when the number of the reaction centers is increased. Herein, we wish to report a C_2-symmetric bisprolinamide catalyst that has retained the asymmetric induction power of its monoprolinamide counterpart but with more than doubled reactivity.[8]

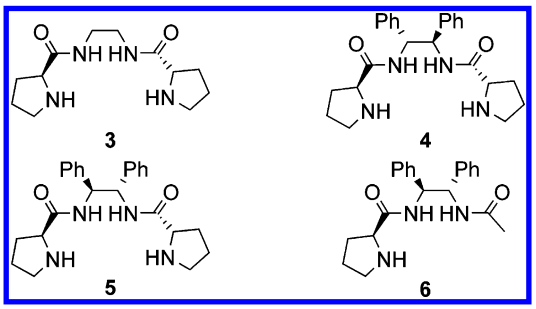
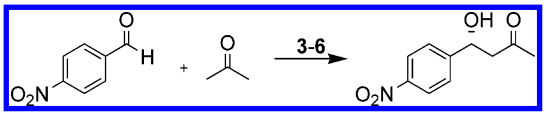


Figure 2. C_2-Symmetric bisprolinamide catalysts **3**−**5** and monoprolinamide catalyst **6**.

In our design of catalyst with two prolinamide moieties, to achieve uniformity of asymmetric induction of the two reaction centers, we introduced C_2-symmetry. Thus, we synthesized C_2-symmetric bisprolinamide catalysts **3**,[9] **4**, and **5** (Figure 2). In these catalysts, each reaction center has a remote amide hydrogen to promote the reactivity and enantioselectivity.[6,7] Catalysts **3**−**5** may be readily prepared from *N*-carbobenzyloxy-L-proline and corresponding diamine in just two steps. To verify our hypothesis, monoprolinamide catalyst **6** was also synthesized for comparison.

Table 1. Direct Aldol Reaction of 4-Nitrobenzaldehyde and Acetone Catalyzed by Catalysts **3**−**6**[a]



entry	catalyst	time (h)	T (°C)	yield[b] (%)	ee[c] (%)
1	**3**	1.5	rt	94	22
2	**4**	1.5	rt	93	45
3	**5**	1.5	rt	93	68
4	**5**	7	0	91	77
5	**5**	12	−25	90	89
6	**5**	12	−35	88	98
7	**5**	5	−35	75[d]	98
8	**6**	5	−35	35[d]	98
9[e]	**1**	24	−25	66	93

[a] All reactions were performed with 0.25 mmol of 4-nitrobenzaldehyde and anhydrous acetone (0.5 mL) using 10 mol % of the catalyst. [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess was determined by HPLC; absolute configuration of the major enantiomer was determined by comparing the measured optical rotation with the reported data.[6] [d] Conversions; determined by ^{1}H NMR spectroscopy. [e] Taken from ref 6c, with 20 mol % of catalyst **1**.

Indeed, these catalysts show very high reactivity (Table 1). For example, with 10 mol % of catalyst **3**, the reaction of 4-nitrobenzaldehyde and acetone finished within 1.5 h at room temperature with high yield (entry 1). The ee value was nonetheless very low (22%). After phenyl groups were introduced into the diamine moiety, the two diastereomeric catalysts **4** and **5** maintained high reactivity, yet the enantioselectivities were increased, with catalyst **5** better than **4** (entries 2 and 3). The reaction conditions were further optimized for catalyst **5** to increase the enantioselectivity, and it was found that the enantioselectivity was dependent on temperature: The ee value of the aldol product increases while the reaction temperature is lowered (entries 3−5), and the best ee value was obtained at −35 °C (98% ee, entry 6). Although monoprolinamide catalyst **6** also induces the same level of enantioselectivity, it is clear that it has only half of the reactivity of that of **5** (entries 7 and 8). Catalyst **5** is also more reactive than similar monoprolinamide catalyst **1**,[6] since only half the amount of the catalyst and half the reaction time is required to achieve an even better yield than **1** (entries 6 and 9).

To test the substrate generality of this new catalyst, the reaction of various aldehydes with acetone was studied under

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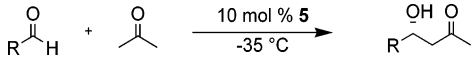
(8) While our paper was under revision, Xiao published a related work of bifunctional prolinamide catalyst, see: Chen, J.-R.; Lu, H.-H.; Li, X.-Y.; Chen, L.; Wan, J.; Xiao, W.-J. *Org. Lett.* **2005**, *7*, 4543.

(9) Catalyst **3** is a known compound; see: Alcón, M. J.; Iglesias, M.; Sánchez, F.; Viani, I. *J. Organomet. Chem.* **2000**, 284.

the optimized conditions. The results are summarized in Table 2. As shown in Table 2, aldehydes with nitro

Table 2. Direct Aldol Reaction of Vaious Aldehydes and Acetone Catalyzed by Catalyst 5



entry	R	yield[b] (%)	ee[c] (%)
1	4-$NO_2C_6H_4$	88	98
2	3-$NO_2C_6H_4$	86	89
3	2-$NO_2C_6H_4$	81	93
4	4-BrC_6H_4	79	93
5	4-ClC_6H_4	81	96
6	4-FC_6H_4	74	89
7	2,6-$Cl_2C_6H_3$	85	86
8	4-CNC_6H_4	71	82
9	Ph	69	90
10	4-MeC_6H_4	65	93
11	4-$MeOC_6H_4$	52	96
12	Me_3C	57	98
13	*c*-C_6H_{11}	78	97

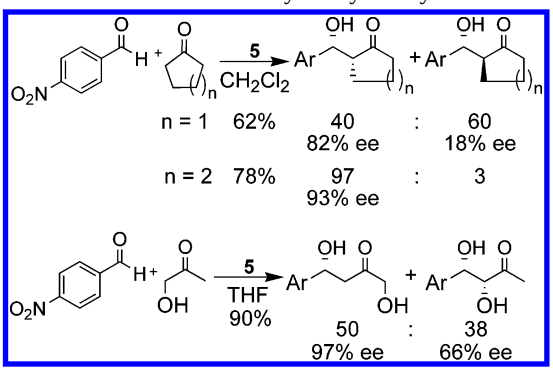
[a] All of the reactions were conducted with the aldehyde (0.25 mmol) and catalyst 5 (0.025 mmol) in anhydrous acetone (0.5 mL) at −35 °C for 12−24 h (48 h for entries 11−13). [b] Yield of isolated product after column chromatography. [c] Enantiomeric excess was determined by HPLC; absolute configuration of the major enantiomer was determined by comparing the measured optical rotation with the reported data.[6,7]

substitution all gave very good yields of the aldol products with excellent ee values (entries 1−3). Similarly, halogenated benzaldehydes all produced very good ee values and yields (entries 4−7). 4-Cyanobenzaldehyde gave the lowest ee value among all the aldehydes studied, yet the ee value was still good (entry 8). Aromatic aldehydes with electron-donating groups led to slightly inferior yields, but the enantioselectivities were excellent (entries 9−11). Aliphatic aldehydes are also good substrates for this reaction: Sterically demanding 2,2-dimethylpropanal (entry 12) led to a high enantioselectivity of 98%; similarly, cyclohexanecarbaldehyde also produced a high ee value of 97% (entry 13). It is worth noting that 4-methoxybenzaldehyde yielded the aldol products with 96% ee (entry 11), which is the highest ee value achieved so far for such a substrate.[10]

We also studied some other ketone substrates (Scheme 1). Cyclopentanone gave a dr of of 40:60 for the *anti*/*syn* products; with ee value of 82% and 18% ee, respectively.

(10) Previously the highest ee value achieved for this substrate was 82%; see: Ayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *Tetrahedron Lett.* **2004**, *45*, 4353.

Scheme 1. Direct Aldol Reaction of 4-Nitrobenzaldehyde and Some Ketones Catalyzed by Catalyst **5**



Cyclohexanone yielded a dr of 97:3 for the *anti*/*syn* products, with an ee of 93% for the major product (upper equation). It is interesting to note that catalysts **5** and **2**[6d] have the opposite preference for these two substrates in terms of enantioselectivity. Acetol gave a mixture of the two regioisomers, and the regioisomer of the less stable enamine has an ee value of 97% (lower equation).

Besides the fact that the catalyst loading may be reduced from 20 to 10 mol %, bisprolinamide catalyst **5** leads to higher enantioselectivities and yields than the corresponding monoprolinamide catalyst **1**[6] in most cases. The improved performance in enantioselectivity is probably due to the replacement of the hydroxy hydrogen in **1** by an amide hydrogen in catalyst **5**, since the hydrogen-bonding ability of this remote hydrogen atom is crucial to achieve high enantioselectivity.[6,7]

In summary, C_2-symmetric bisprolinamide **5** has been found to be an excellent catalyst for direct aldol reaction. The catalytic activity of the prolinamide-type catalysts may be improved by introducing additional reaction center(s) into the catalyst, while the enantioselectivity can still be maintained or further improved. Further tuning of the reactivity and enantioselectivity of catalyst **5** via electronic effects is currently underway.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds and HPLC analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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