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Readily Tunable and Bifunctional L-Prolinamide Derivatives: Design and Application in the Direct Enantioselective Aldol Reactions

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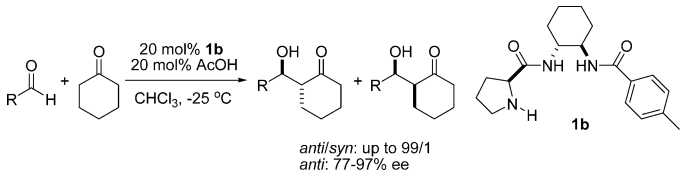
ABSTRACT



Readily tunable and bifunctional L-prolinamides as novel organocatalysts have been developed, and their catalytic activities were evaluated in the direct asymmetric Aldol reactions of various aromatic aldehydes and cyclohexanone. High isolated yields (up to 94%), enantioselectivities (up to 99% ee), and *anti*-diastereoselectivities (up to 99:1) were obtained under the optimal conditions.

Enantioselective organocatalysis has recently provided a research avenue in which to explore the fundamental chemical parameters such as reactivity, selectivity, and mechanism and in doing so has led to the discovery of many valuable reactions and catalysts.[1] In this endeavor, the design and the development of multifunctional chiral organocatalysts are of great importance: one catalyst molecule possesses two or more reaction-promoting functionalities such that activity and selectivity can be tuned by a simple modification of the structural motif of the catalyst. Thus, an elegant alignment of the steric and electronic properties of the catalyst would determine the reaction efficiency.

The aldol reaction ranks among the most important carbon−carbon bond-forming reactions in organic synthesis.[2] Several efficient asymmetric methodologies for this reaction using organocatalysts have been developed, of which the most remarkable advances in the domain of proline and its derivative catalysts were made by List and Barbas,[3] MacMillan,[4] Jørgensen,[5] Gong,[6] and Yamamoto.[7] According to the Houk−List model,[8] the catalysts are believed to stabilize the transition state through hydrogen bonding in proline and

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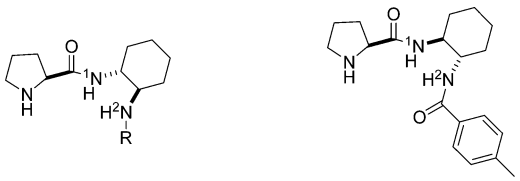
its derivative-catalyzed Aldol reactions. Therefore, a subtle change in catalyst structure may change the pK_a value of the catalyst to affect the strength of hydrogen bondings, such that a dramatic enhancement of the catalytic activity and selectivity may be anticipated.[9] However it is a significant challenge to realize this goal. Herein, we describe a new series of tunable and bifunctional organocatalysts in attaining the direct asymmetric aldol reaction with high efficiency.

Scheme 1. Tunable and Bifunctional Organocatalysts



1a:R=4-Me$C_6H_4SO_2$; pK_{a1}:36.8, pK_{a2}:25.9

1b:R=4-MeC_6H_4CO; pK_{a1}:36.8, pK_{a2}:35.7

1c:R=4-ClC_6H_4CO; pK_{a1}:36.0, pK_{a2}:33.9

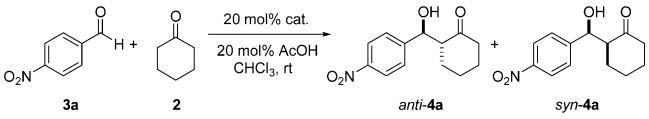
1d:R=CF_3CO; pK_{a1}:36.0, pK_{a2}:27.9

1e:R=FCH_2CO; pK_{a1}:35.5, pK_{a2}:34.8

1f: pK_{a1}:35.7 pK_{a2}:34.3

A variety of bifunctional L-prolinamide derivatives **1**, as shown in Scheme 1, were prepared from commercially available L-proline and enantiopure (*R*,*R*)- or (*S*,*S*)-1,2-diaminocyclo-hexane. The structures of **1** were confirmed by X-ray crystallographic analysis (see the Supporting Information). The pK_a of the diamide can be readily tuned by varying the R group (Scheme 1).[10] The catalytic activity of these new catalysts were then evaluated in a direct asymmetric aldol reaction of 4-nitrobenzaldehyde **3a** with cyclohexanone **2**.

Table 1. Enantioselective Direct Aldol Reaction of 4-Nitrobenzaldehyde (**3a**) and Cyclohexanone (**2**) under Various Conditions



3a **2** *anti*-**4a** *syn*-**4a**

entry	catalyst	time (h)	yield[b] (%)	dr (*anti*/*syn*)[c]	ee[d] (%)
1	**1a**	2	73	84/16	54
2	**1b**	5	**81**	75/25	**86**
3	**1c**	8	89	76/24	80
4	**1d**	12	63	77/23	73
5	**1e**	7	79	73/27	73
6	**1f**	24	89	79/21	69
7	**1b**	**24**	**89**	**96/4**	**92**[e]
8	**1b**	120	74	79/21	65[f]
9	**1b**	5	83	91/9	57[g]
10	**1b**	5	90	85/15	55[h]

[a]The reactions were conducted with **1** (20 mol %), AcOH (20 mol %), **3a** (0.5 mmol), and **2**/$CHCl_3$ (1:1) (2 mL) for 6−24 h. [b] Isolated yield of mixture of *anti*/*syn*. [c] Determined by chiral HPLC analysis of the mixture of *anti*/*syn* product. [d] Determined by chiral HPLC. [e] At −25 °C. [f] Without AcOH, 120 h. [g] In the presence of 20 mol % of **1b** and 10 mol % of AcOH. [h] In the presence of 20 mol % of **1b** and 40 mol % of AcOH.

As can be seen from the results summarized in Table 1, the catalytic activities and the steroselectivities of **1a**−**f** were significantly influenced by the tuning of the amide moiety. Among the catalytic systems examined, **1b** with 20 mol % of acetic acid (AcOH) exhibited excellent catalytic efficiency, affording **4a** in 81% yield and good stereoselectivity (*anti*/*syn* 75:25; 86% ee) (Table 1, entry 2).[11] Note that **1b** showed a superior level of enantiocontrol to its diastereomer **1f** (Table 1, entry 2 vs entry 6). This indicates that (1*R*,2*R*)-diaminocyclohexanes can be superior to L-prolines in enhancing stereochemical control. As solubility is not an issue for our tunable bifunctional catalysts of L-prolinamide derivatives, as compared to that of the proline catalyst, excellent selectivity (*anti*/*syn* 96:4; 92% ee) was achieved by decreasing the reaction temperature to −25 °C (Table 1, entry 7).

Significantly, we found that the concentration of AcOH has a remarkable effect on the catalytic activity and selectivity. Without adding AcOH, the reaction proceeded slowly in low selectivity (Table 1, entry 8 vs entry 2). A ratio of AcOH to **1b** of 1:2 enhanced the activity by 24 times with an improved yield and increased diastereoselectivity, but decreased enantioselectivity (Table 1, entry 9 vs entry 8), whereas use of a ratio of AcOH to **1b** of 2:1 led to similar

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(10) The pK_a values of **1a**−**f** were estimated by evaluating the free energy change ΔGa (pK_a = ΔGa/2.303*RT*). The geometries of **1a**−**f** optimized at the HF/6-31G* level were employed to perform self-consistent reaction field (SCRF) calculations at the B3LYP/6-31+G* level, for calculating free energies of solvation in the chloroform. All calculations were performed by using the Gaussian 03 program. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. Gaussian, Inc., Wallingford CT, 2004.

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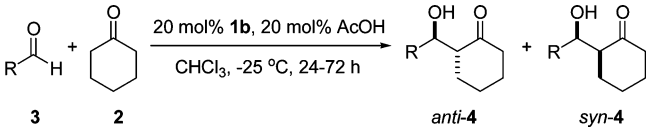
results in better yield but poorer selectivity (Table 1, entry 10 vs entry 9). We concluded that the 1:1 ratio of AcOH to **1b** gave the optimal performance, where the ee value was the most satisfactory (Table 1, entry 2 vs entries 8−10).

A representative selection of aldehydes was evaluated under the optimized conditions and the results obtained are summarized in Table 2. The reactions of various substituted

Table 2. Scope of the Aldehydes **3** for the Direct Aldol Reaction with Cyclohexanone **2** under Optimal Conditions[a]

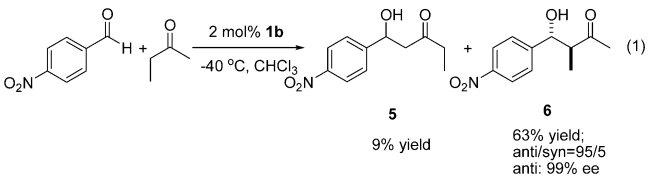


entry	R	product	yield[b] (%)	dr (*anti*/*syn*)[c]	ee (%, *anti*)[d]
1	4-$NO_2C_6H_4$	**4a**	89	96/4	92
2	4-$NO_2C_6H_4$	**4a**[e]	83	97/3	87
3	4-$NO_2C_6H_4$	**4a**[f]	81	98/2	97
4	2-$NO_2C_6H_4$	**4b**	94	99/1	96
5	3-$NO_2C_6H_4$	**4c**	78	96/4	94
6	4-CNC_6H_4	**4d**	89	97/3	92
7	4-CLC_6H_4	**4e**	88	96/4	94
8	2-CLC_6H_4	**4f**	83	97/3	92
9	4-BrC_6H_4	**4g**	76	98/2	97
10	Ph	**4h**	73	83/17	87
11	1-naphthyl	**4l**	41	97/3	90
12	2-furfuryl	**4j**[f]	53	87/13	93
13	4-MeC_6H_4	**4k**	53	80/20	77

[a] The reactions were conducted with **1b** (20 mol %), AcOH (20 mol %), **3** (0.5 mmol), and **2**/$CHCl_3$ (1:1) (2 mL) for 24−72 h (see the Supporting Information) at −25 °C. [b] Isolated yield of the mixture of *anti*/*syn*. [c] Determined by analysis of the mixture of *anti*/*syn* product. [d] Determined by HPLC. [e] In the presence of 2 mol % of **1b** and 2 mol % of AcOH. [f] In the presence of 20 mol % of **1d** and 20 mol % of AcOH at −40 °C.

benzaldehydes, which bear an electron-withdrawing group on the benzene ring, proceeded smoothly in excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to 97%) to furnish the Aldol adducts **4a**−**g** (Table 2, entries 1 and 3−9), while the stereoselectivities of the reactions with benzaldehyde and *p*-tolualdehyde were somewhat lower possibly due to their electron-rich character (Table 2, entries 10 and 13). Similarly, other aromatic aldehydes, such as 1-naphthaldehyde and 2-furaldehyde, underwent clean reactions as well, and gave the corresponding adducts in 90 and 93% ee, respectively (Table 2, entries 11 and 12). Furthermore, it is noteworthy that even with as little as 2 mol % catalyst loading of **1b** and 2 mol % AcOH, the reaction took place in high diastereoselectivity, although there was a slight decrease in enantioselectivity (Table 2, entry 1 vs entry 2). Very recently, Gong et al. reported a highly efficient organocatalyst for the same reaction as entries 1 and 2. They achieved a 83% yield with a diasteomeric ratio of anti/syn = 95:5 and an ee (anti) of 79%.[6]

The reaction of 4-nitrobenzaldehyde with butanone was also investigated (eq 1) to examine the scope of the Aldol donors. Significantly, the reaction preferentially occurred at the C-3 position to afford the Aldol product **6** as the major product in remarkably high diastereoselectivity (95:5) and enantioselectivity (99% ee). Interestingly, we noticed that with Gong's catalyst yields of 56% for **5** and 42% for **6** were obtained.[6]



(1)

Based on the L-proline catalysis model,[8] we believe that the two N−H groups of the diamide group play a key role in stabilizing the transition state, where these two tunable functionalities not only activate the aldol acceptor but also locate the *re*-face of the acceptor proximate to the attack by the enamine. AcOH also plays an important role, as it may provide a proton to accelerate the formation of enamine; whereas the excessive AcOH may have a negative effect on the hydrogen bonding of diamide, which in turn depresses the catalytic efficacy.

In conclusion, we have developed a series of novel L-prolinamide organocatalysts with readily tunable bifunctionalities. Their catalytic activities were evaluated for the direct asymmetric Aldol reactions of various aromatic aldehydes and cyclohexanone. High isolated yields (up to 94%), enantioselectivities (up to 99% ee), and anti-diastereoselectivities (up to 99:1) were obtained using our catalytic system. Studies directed to the extension of this tunable hydrogen bonding−Lewis base dual-activation strategy to other reactions as well as the mechanistic aspects are currently underway.

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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