J|A|C|S
COMMUNICATIONS

Published on Web 02/27/2007

A Simple Primary−Tertiary Diamine−Brønsted Acid Catalyst for Asymmetric Direct Aldol Reactions of Linear Aliphatic Ketones

Sanzhong Luo,*,† Hui Xu,† Jiuyuan Li,† Long Zhang,‡ and Jin-Pei Cheng*,†,‡

Beijing National Laboratory for Molecular Sciences (BNLMS), Center for Chemical Biology, Institute of Chemistry and Graduate School, Chinese Academy of Sciences, Beijing 100080, China, and Department of Chemistry and State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China

Received December 31, 2006; E-mail: luosz@iccas.ac.cn; chengjp@mail.most.gov.cn

Inspired by the exquisite stereocontrol in the enzymatic enamine processes, chemists have long been pursuing a simple chemical mimic for asymmetric enamine catalysis, and this aim has now been partially fulfilled with the renaissance of organocatalysis.[1] Since the pioneering work of List, Barbas, and co-workers in 2000,[2] there has been dramatic advance in developing enamine-based asymmetric organocatalysts.[1] However, unlike the natural enzymes such as type I aldolases and decarboxylases that normally employ primary amine of a lysine moiety to form the enamine intermediate,[3] most of the presently successful enamine organocatalysts utilize secondary amines instead (e.g., chiral pyrrolidine derivatives).[4] For example, in the enamine-based organocatalysis of asymmetric direct aldol reactions,[1,5] a large portion of the previous research efforts has been devoted to the modifications of chiral pyrrolidines, and many synthetically important ketone donors, such as linear aliphatic ketones, still remain as difficult substrates.[5] It is therefore of great demand to develop primary amine catalysts to expand the utility of the enamine-based organocatalysis. In this context, exploration of efficient and stereoselective primary amine catalysts has become a much-attempted research endeavor,[6] but unfortunately, it has turned out to be an elusive goal despite of the success of the current organocatalysts.[4] Recently, Jacobsen and Tsogoeva independently reported primary amine−thiourea conjugates as enantioselective organocatalysts for Michael addition to nitroolefins.[7] Simple primary amino acids were found to act as stereoselective catalysts for direct aldol reactions.[8] Upon the completion of this paper, Barbas reported that a primary amino acid, L-threonine, could catalyze the *syn*-selective aldol reaction of α-hydroxyketones.[8g] Those primary amino acids demonstrated low efficiency (20−30 mol % loading), however, and only worked for the few selected substrates. Therefore, new strategies regarding the design of primary amine catalysts with high efficiency, high stereoselectivity, as well as broad substrate scope become increasingly desirable.

Although chiral diamines have been frequently explored in organocatalysis,[9] primary−tertiary diamines were mostly overlooked in catalyst development, and in one earlier investigation, they exhibited very low catalytic activity.[9b,10] We report herein a simple chiral primary−tertiary diamine catalyst for asymmetric aldol reactions. We found that simple primary−tertiary diamines such as chiral *trans*-*N*,*N*-dialkylated diaminocyclohexanes **1** (Figure 1) would nicely address the challenges mentioned above. Direct aldol reaction of acetone was selected first as a benchmark for catalyst screening and evaluation. To our delight, catalyst **1d** allowed for high enantioselectivity, high diastereoselectivity, as well as high regioselectivity for a broad range of substrates including the once challenging linear aliphatic ketone donors under ambient temperature. Worthy of noting also is that we obtained herewith unprecedented *syn* diastereoselectivity for ethyl ketones.[5i]

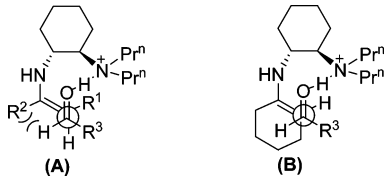


Figure 1. Proposed transition state for the reaction of acyclic ketone (A) and cyclohexanone (B).

Some screening results are listed in Table 1. As can be seen, strong acidic additive such as TfOH was shown to be essential for catalysis. The reaction became very sluggish, affording only trace product if TfOH was absent (Table 1, entry 3 vs 2). Both catalysts **1** and **2** jointly with TfOH could catalyze the reaction, where **1d** gave the optimal results (Table 1, entry 5). The poor catalytic performances observed for **1a**, **1g**, and **2** highlight the importance of the *N*,*N*-dialkylated diaminocyclohexane structure. The catalysis of **1d** could be further improved by adding another less acidic additive (entry 11). Under the latter conditions, the loading of catalyst could be reduced to as low as 2 mol % while still maintaining the same enantioselectivity and a quite significant activity (entry 12). The role of the second acidic additive is probably related to its possible function in facilitating the enamine catalytic cycle.[7]

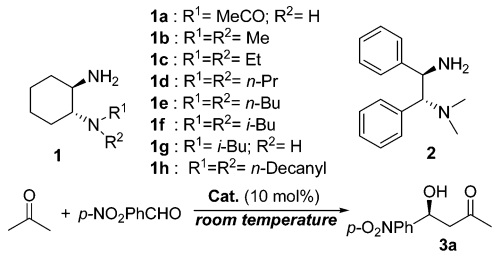
Application scope of the catalytic system was then examined, and the results are summarized in Table 2. It shows that **1d** worked very well with acetone. A range of aromatic aldehydes bearing either electron-rich or electron-deficient substitutes all underwent reaction with acetone in high yields and enantioselectivity at room temperature (Table 2, entries 1−7). Unfortunately, the reaction with aliphatic aldehydes gave poor yields probably due to the self-condensation of aliphatic aldehydes. With regard to other aldol donors, a range of small aliphatic ketones was also found to be applicable under the present conditions. Significantly, the reaction of ethyl ketones occurred preferentially at the methylene carbon with good regioselectivity (4 → 20:1 *b*:*l*), favoring the branched aldol products with high enantioselectivity (87−96% ee, Table 2, entries 8−13). More interestingly, the branched products were obtained with unexpected diastereoselectivity, favoring the *syn* isomers (up to 12:1).[11] To the best of our knowledge, no other publications have reported direct asymmetric aldol reactions of small aliphatic ketones with *syn* selectivity.[8g] In contrast, the reactions with secondary amine catalysts generated either linear or *anti*-selective products with small aliphatic ketones, such as 2-butanone.[5d−h]

The reactions of benzyloxyacetone and a variety of aromatic aldehydes also produced branched products with complete regioselectivity and good *syn* selectivity and enantioselectivity (Table, 2, entries 14−17). Further substrate exploration indicated that the

† Chinese Academy of Sciences.
‡ Nankai University.

10.1021/ja069372j CCC: $37.00

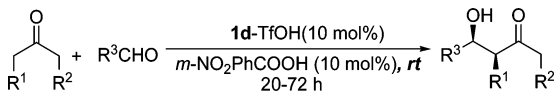
Table 1. Screening Results



entry[a]	catalyst	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**/TfOH	24	trace	
2	**1b**	24	trace	
3	**1b**/TfOH	24	86	70
4	**1c**/TfOH	19	86	82
5	**1d**/TfOH	**19**	**83**	**94**
6	**1e**/TfOH	19	46	93
7	**1f**/TfOH	24	12	53
8	**1g**/TfOH	24	33	39
9	**1h**/TfOH	24	70	94
10	**2**/TfOH	24	17	75
11[d]	**1d**/TfOH	**19**	**94**	**95**
12[e]	**1d**/TfOH	48	88	95

[a] Reaction in neat acetone (0.5 M). [b] Isolated yields. [c] Determined by chiral HPLC. [d] 10 mol % of *m*-nitrobenzoic acid was added. [e] 2 mol % of catalyst system **1d**/TfOH/*m*-NO_2PhCOOH (1:1:1).

Table 2. Asymmetric Direct Aldol Reactions of Ketones[a]



entry	R^1, R^2	R^3	yield (%)[b]	rr[c] *b:l*	dr[c] *syn:anti*	ee (%)[d]
1	H, H	3-NO_2Ph	**3b**/96	–	–	94
2	H, H	4-CNPh	**3c**/95	–	–	94
3	H, H	1-Napth	**3d**/93	–	–	97
4	H, H	2-ClPh	**3e**/97	–	–	95
5	H, H	3-BrPh	**3f**/92	–	–	92
6	H, H	Ph	**3g**/56	–	–	94
7	H, H	4-MeOPh	**3h**/21	–	–	93
8[e]	Me, H	4-NO_2Ph	**4a**/95	9:1	10:1	96
9[e]	Me, H	2-NO_2Ph	**4b**/97	8:1	9:1	96
10[e]	Me, H	2-ClPh	**4c**/85	>10:1	12:1	87
11	Me, H	1-Napth	**4d**/53	4:1	5:1	92
12[e]	Me, Me	4-NO_2Ph	**4e**/78	–	9:1	>95
13	Me, Et	4-NO_2Ph	**4f**/75	>20:1	4:1	96
14	BnO, H	4-NO_2Ph	**4g**/98	>20:1	9:1	97
15	BnO, H	4-ClPh	**4h**/91	>20:1	10:1	92
16	BnO, H	1-Napth	**4i**/99	>10:1	5:1	>99
17	BnO, H	Ph	**4j**/76	>20:1	5:1	86
18	H, Et	4-NO_2Ph	**4k**/92	1:5	–	88
19	H, ^{i}Pr	4-NO_2Ph	**4l**/56	1:>20	–	85
20	$-(CH_2)_3-$	4-NO_2Ph	**4m**/99	–	1:9	98[f]

[a] Reaction with 20 equiv of ketones under neat conditions. [b] Isolated yields. [c] Determined by ^{1}H NMR; rr = regioisomer ratio; *b:l* = the ratio of branched and linear products. [d] Determined by HPLC. [e] Reactions under 4 °C with 20 mol % of catalyst. [f] Enantiomeric excess of the *anti* isomer, reaction with 2.0 equiv of cyclohexanone in CH_2Cl_2 for 12 h.

reaction of longer ketones, such as methyl propyl ketone and methyl *iso*-butyl ketone, produced linear products instead of the branched ones with good regioselectivity (5 and >20:1 *l*:*b*) and enantioselectivity (Table 2, entries 18 and 19). Similar switch on linear and branched product distribution has also been observed previously on primary amine−thiourea catalysis of asymmetric Michael additions of small aliphatic ketones.[7a]

Following the line of the pioneering study of Hine[10] on primary−tertiary diamine-catalyzed α-hydrogen exchange of ketones as well as our own experimental observations, a bifunctional enamine catalysis may be assumed in our cases for the asymmetric direct aldol reaction catalyzed by chiral primary−tertiary diamine **1d**/TfOH. The *syn* diastereoselectivity could be explained by a *Z*-enamine transition state as proposed in Figure 1A.[7,8g] In this model, the protonated tertiary amine served as a directing hydrogen-bonding donor. Consistent with this model, the reaction of cyclohexanone, which is capable only of forming an *E*-enamine (Figure 1B), should render *anti* diastereoselectivity, and this was exactly what was observed (Table 2, entry 20).

To conclude, the simple chiral primary−tertiary diamine catalyst developed in this work for asymmetric direct aldol reactions not only demonstrated high enantioselectivity and unprecedented *syn* diastereoselectivity but also enlarged the applicable substrate scope to include the once challenging small aliphatic ketones. Detailed mechanism study and further exploration of this catalyst in other important reactions is under our intensive investigations.

Acknowledgment. This work is supported by NSFC and Institute of Chemistry. We thank Prof. M.-X. Wang, Prof. Q.-H. Fan, and Prof. D. Wang for helpful discussions.

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

References

(1) For reviews, see: (a) Dalko, P. L.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5176. (b) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*: Wiley-VCH: Weinheim, Germany, 2005.

(2) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395−2396. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260−5267.

(3) Heine, A.; DeSantis, G.; Luz, J. G.; Mitchell, M.; Wong, C.-H.; Wilson, I. A. *Science* **2001**, *294*, 369−374.

(4) (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548−557. (b) List, B. *Chem. Commun.* **2006**, 819−824. (c) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580−591.

(5) For recent examples, see: (a) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752−1755. (b) Kano, T.; Takai, J.; Tokuda, O.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3055−3057. (c) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210−1212. (d) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734−735. (e) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958−961. (f) Tang, Z.; Yang, Z.-H.; Chen, X.-H.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *J. Am. Chem. Soc.* **2005**, *127*, 9285−9289. (g) Torri, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983−1986. (h) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem.—Asian J.* **2006**, 210−215 and references therein. (i) Mitsumori, S.; Zhang, H.; Cheong, P. H.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1041−1042.

(6) For earlier examples, see: Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970−6979 and references therein.

(7) (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170−7171. (b) Lalonde, M. P.; Chen, Y. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366−6370. (c) Tsogoeva, S. B.; Wei, S. *Chem. Commun*. **2006**, 1451−1453.

(8) (a) Córdova, A.; Zou, W.; Dziedzic, P.; Ibrahem, I.; Reyes, E.; Xu, Y. *Chem.—Eur. J.* **2006**, *12*, 5383−5397 and references therein. (b) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. F., III. *Tetrahedron Lett.* **2004**, *45*, 325−328. (c) Amedjkouh, M. *Tetrahedron:Asymmetry* **2005**, *16*, 1411−1414. (d) Pizzarello, S.; Weber, A. L. *Science* **2004**, *303*, 1151−1151. (e) Davies, S. G.; Sheppard, R. L.; Smith, A. D.; Thomson, J. E. *Chem. Commun.* **2005**, 3802−3804. (f) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801−2803. (g) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288−289. (h) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308−2311.

(9) (a) Saito, S.; Yamamoto, H. *Acc. Chem. Res.* **2004**, *37*, 570−579. (b) Nakadai, M.; Saito, S.; Yamamoto, H. *Tetrahedron* **2002**, *58*, 8167−8177.

(10) Hine, J. *Acc. Chem. Res.* **1978**, *11*, 1−7.

(11) The absolute and relative configuration of the products **3** and **4** was assigned by comparison with literature; see refs 5f, 5g, 8g and: Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519−522.

JA069372J