J|A|C|S
COMMUNICATIONS

Published on Web 12/20/2006

Direct Catalytic Asymmetric Synthesis of *anti*-1,2-Amino Alcohols and *syn*-1,2-Diols through Organocatalytic *anti*-Mannich and *syn*-Aldol Reactions

S. S. V. Ramasastry, Haile Zhang, Fujie Tanaka, and Carlos F. Barbas, III*

The Skaggs Institute for Chemical Biology and the Departments of Chemistry and Molecular Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received October 27, 2006; E-mail: carlos@scripps.edu

Chiral 1,2-amino alcohols and 1,2-diols are common structural motifs found in a vast array of natural and biologically active molecules.[1] Recently, significant efforts have been applied toward the development of direct catalytic asymmetric approaches to the construction of these units based on the addition of unmodified α-hydroxyketones to imines or aldehydes in Mannich-type and aldol reactions, respectively.[2,3] Although the elegant studies of Shibasaki and Trost have provided routes to both *syn*- and *anti*-1,2-amino alcohols and diols using metal-based catalysis,[2] highly enantioselective organocatalytic approaches have been limited to *syn*-1,2-amino alcohols and *anti*-1,2-diols.[3] Here we describe simple and efficient routes to highly enantiomerically enriched *anti*-1,2-amino alcohols and *syn*-1,2-diols through direct asymmetric Mannich, Mannich-type, and aldol reactions catalyzed by primary amine-containing amino acids.

To generate *anti*-1,2-amino alcohols and *syn*-1,2-diols, we sought to design novel catalysts. In the reactions of α-hydroxyketones with (*S*)-proline, products form via a reaction involving an (*E*)-enamine **A** for both Mannich-type and aldol reactions[3] (Scheme 1). With pyrrolidine-derived catalysts or secondary amines, (*E*)-enamine intermediates predominate because of steric interactions in (*Z*)-enamine **B**. The stereochemistry of the product can be explained by transition state **C** or **D** because the *si* face of the (*E*)-enamine reacts (Scheme 1a). To selectively form *anti*-Mannich products in reactions involving alkylaldehydes and alkanone-derived nucleophiles, we previously designed catalysts (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid and (*R*)-3-pyrrolidinecarboxylic acid ((*R*)-*β*-proline), respectively.[4,5] With the latter catalyst, reactions proceed through transition state **E**, and the reaction face of the (*E*)-enamine is reversed from that of the (*S*)-proline-catalyzed reaction (Scheme 1b). These catalysts were, however, less than optimal for reactions of α-hydroxyketones.[6]

For reactions of α-hydroxyketones, we reasoned that the use of a (*Z*)-enamine in the C−C bond-forming transition state should generate *anti*-Mannich and *syn*-aldol products. In our early studies of aldol reactions involving unmodified hydroxyacetone mediated by antibody catalysis, we noted preferential reaction of a (*Z*)-enamine of hydroxyacetone formed with the primary amine of the lysine side chain, the key catalytic residue of the aldolase, rather than reaction through an (*E*)-enamine as we had observed with cyclic ketones.[7] We reasoned that, with primary amines, (Z)-enamines of α-hydroxyketones **F** should predominate over (*E*)-enamines **G**.[8] When (*Z*)-enamine **F** reacts in the C−C bond-forming transition state (**H** or **I**), *anti*-Mannich or *syn*-aldol products should form predominately (Scheme 1c). Studies of direct asymmetric aldol and Mannich-type reactions catalyzed by primary amine-containing amino acids have been reported.[9] However, within these studies, reactions of α-hydroxyketones were either not tested or, when tested, enantioselectivities of the products were moderate.

On the basis of our design considerations, we first evaluated a variety of natural acyclic amino acids and their derivatives, including amino acids **1**−**3**, for the Mannich-type and aldol reactions of hydroxyacetone that afforded **4** and **5**, respectively (Figure 1 and Table 1). In accord with our hypothesis, primary amine-containing amino acids predominantly provided *anti*-Mannich product **4** or *syn*-aldol product **5**, but the *anti*/*syn* ratios and ee's were varied. For the Mannich-type reaction, reactions catalyzed by L-Trp (**1**) and O-*t*Bu-L-Thr (**3**) afforded *anti*-**4** with high dr and ee (entries 1 and 4). *N*-Methyl-L-Trp catalysis provided only trace amounts of product. For the aldol reaction, the reaction catalyzed by **3** afforded *syn*-**5** with the best dr and ee (entry 9). The L-Thr (**2**)-catalyzed aldol reaction provided the next best *syn*-selectivity and enantioselectivity (entry 8). Other natural amino acids did not provide significant *syn*-selectivity or enantioselectivity (data not shown). With all catalysts tested, C−C bond formation with hydroxyacetone selectively occurred at the carbon bearing the hydroxyl group.

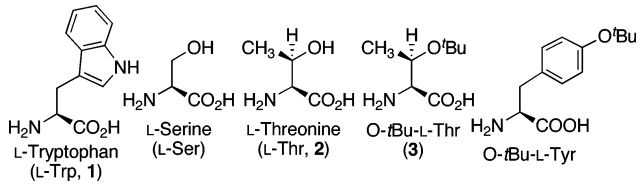
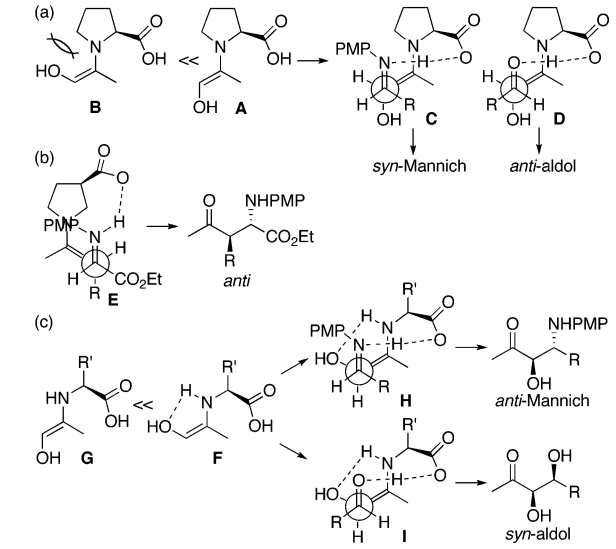


Figure 1. Structures of catalysts studied.

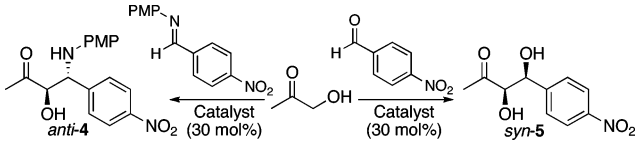
Scheme 1



Conditions were optimized for the **1**- and **3**-catalyzed Mannich-type reactions. Using the optimized conditions, Mannich and Mannich-type reactions of hydroxyacetone with a variety of imines were performed in DMF for catalyst **1** or *N*-methylpyrrolidone (NMP) for catalyst **3** at 4 °C (Table 2). The reaction with catalyst **1** was faster than that of catalyst **3**. Reaction time was 16−20 h with **1** and 48 h with **3**. The desired *anti*-amino alcohols **4**, **6**−**8** were obtained in good yields with excellent diastereoselectivities (up to >15:1) and enantioselectivities (90−98% ee) in most cases. Significantly, reaction of unmodified 1-hydroxy-2-butanone provided the *anti*-product regioselectively with excellent dr and ee

10.1021/ja0677012 CCC: $37.00

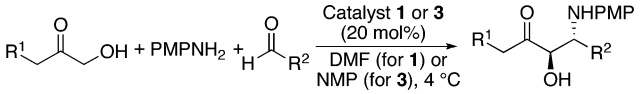
Table 1. Evaluation of Catalysts for the *anti*-Mannich-type and *syn*-Aldol Reactions[a]



entry	product	catalyst	time (h)	yield[b] (%)	dr[c] *anti:syn*	ee[d] *anti*/*syn*
1	**4**	L-Trp (**1**)	4	75	5:1	87/68
2	**4**	L-Ser	28	77	3:1	75/33
3	**4**	L-Thr (**2**)	48	74	2:1	66/14
4	**4**	**3**	22	85	8:1	94/56
5	**4**	O-*t*Bu-L-Tyr	22	50	3:1	75/45
6	**5**	L-Trp (**1**)	18	80	1:2.5	5/40
7	**5**	L-Ser	22	75	1:2	10/50
8	**5**	L-Thr (**2**)	16	88	1:3	0/62
9[e]	**5**	**3**	48	>95	1:18	58/98
10[e]	**5**	O-*t*Bu-L-Tyr	24	71	1:3	14/50

[a] Reaction was performed in DMSO at 25 °C except as indicated. See Supporting Information. [b] Isolated yield. [c] Determined by NMR of unpurified product. [d] Determined by chiral-phase HPLC. [e] Reaction performed in NMP at 4 °C.

Table 2. Mannich and Mannich-type Reactions Catalyzed by **1** or **3**[a]



entry	R^1	R^2	product	catalyst	yield[b] (%)	dr[c] *anti:syn*	ee[d] (%)
1[e]	H	*p*-$NO_2C_6H_4$	**4**	**1**	95	12:1	95
2				**3**	85	>15:1	98
3	H	*p*-CNC_6H_4	**6**	**1**	83	>10:1	90
4				**3**	78	9:1	90
5	H	*p*-BrC_6H_4	**7**	**1**	89	>10:1	93
6				**3**	71	>10:1	94
7	H	*p*-ClC_6H_4	**8**	**1**	85	>10:1	92
8				**3**	76	>10:1	91
9	H	C_6H_4	**9**	**1**	75	4:1	77
10	H	*p*-$MeOC_6H_4$	**10**	**1**	72	1.3:1	53
11[e,f]	H	CO_2Et	**11**	**1**	67	2:1	91
12[e]	Me	*p*-$NO_2C_6H_4$	**12**	**1**	70	>19:1	96

[a] See Supporting Information for conditions. [b] Isolated yield. [c] Determined by ^{1}H NMR of isolated products. [d] Determined by chiral-phase HPLC for *anti*-product. [e] Preformed imine was used. [f] Reaction was performed at 25 °C.

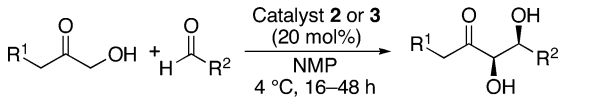
(entry 12). To the best of our knowledge, there are no other reports concerning direct asymmetric reactions with 1-hydroxy-2-butanone.

Aldol reactions catalyzed by **2** and **3** were also optimized, and the reactions were performed in NMP and NMP−water (9:1) at 4 °C (Table 3). Desired *syn*-diols were obtained with high dr (up to 18:1) and ee (up to 98% ee). Both dr and ee increased with the addition of water in many cases (entries 5, 8, and 11 vs 6, 9, and 12). The aldol reaction of 1-hydroxy-2-butanone catalyzed by **3** also afforded excellent results (entry 16).

The absolute configuration of *anti*-**4** obtained from the **1**-catalyzed reaction and of *syn*-**5** obtained from the **3**-catalyzed reaction was determined to be (3*R*,4*R*)-**4** and (3*R*,4*S*)-**5**, respectively (see Supporting Information); these results are in accord with our predicted transition states **H** and **I** (Scheme 1).

In summary, we have developed simple and efficient routes to highly enantiomerically enriched *anti*-1,2-amino alcohols and *syn*-1,2-diols through direct asymmetric Mannich, Mannich-type, and aldol reactions involving unmodified α-hydroxyketones catalyzed by primary amine-containing amino acids. These results provide additional support for our original hypothesis suggesting that amino acid catalysis played a key role in prebiotic chemistry facilitating the asymmetric synthesis of the molecules of life.[10] Further studies on the full scope of these reactions will be reported in the near future.

Table 3. Aldol Reactions Catalyzed by **2** or **3**[a]



entry	R^1	R^2	product	catalyst	yield[b] (%)	dr[c] *syn:anti*	ee[d] (%)
1	H	*p*-$NO_2C_6H_4$	**5**	**2**	75	15:1	90
2				**3**	>95	18:1	98
3[e]				**3**	83	18:1	97
4	H	*p*-ClC_6H_4	**13**	**2**	65	7:1	92
5				**3**	81	7:1	92
6[e]				**3**	78	14:1	94
7	H	*p*-BrC_6H_4	**14**	**2**	67	7:1	84
8				**3**	89	3:1	82
9[e]				**3**	80	12:1	92
10[f]	H	*p*-CNC_6H_4	**15**	**2**	60	5:1	86
11				**3**	78	5:1	80
12[e]				**3**	69	7:1	93
13	H	1-naphthyl	**16**	**2**	70	8:1	86
14				**3**	87	10:1	80
15[e]				**3**	78	6:1	86
16	Me	*p*-$NO_2C_6H_4$	**17**	**3**	78	12:1	94

[a] See Supporting Information for conditions. [b] Isolated yield. [c] Determined by ^{1}H NMR of isolated products. [d] Determined by chiral-phase HPLC for *syn*-product. [e] Reaction in NMP−water (9:1). [f] Reaction time 96 h.

Acknowledgment. This research was supported by The Skaggs Institute for Chemical Biology.

Note Added after ASAP Publication. Ref 10 was corrected on December 21, 2006.

Supporting Information Available: Experimental details, product characterization, and X-ray structure of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis II*; Wiley-VCH: Weinheim, Germany, 2003, and references therein.

(2) (a) Yoshikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (b) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169. (c) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (d) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (e) Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339. (f) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (g) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (h) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778.

(3) (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (d) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131.

(4) (a) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040. (b) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630.

(5) For other *anti*-Mannich reactions involving organocatalysis, see: (a) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (b) Franzen, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

(6) The β-proline-catalyzed reaction afforded **4** in good yield (91%) but with moderate dr (∼1:1) and ee (50% ee for the *anti*-isomer).

(7) Hoffmann, T.; Zhong, G.; List, B.; Shabat, D.; Anderson, J.; Gramatikova, S.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **1998**, *120*, 2768.

(8) For (*Z*)-enamine intermediates between primary amines and alkanones, see: (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (b) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451. For computational studies of a hydroxyacetone enamine, see: (c) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273.

(9) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Tanaka, F.; Thayumanavan, R.; Mase, N.; Barbas, C. F., III. *Tetrahedron Lett.* **2004**, *45*, 325. (c) Cordova, A.; Zou, W.; Ibrahem, I.; Reyes, E.; Engqvist, M.; Liao, W.-W. *Chem. Commun.* **2005**, 3586. (d) Bassan, A.; Zou, W.; Reyes, E.; Himo, F.; Cordova, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7028. (e) Jiang, Z.; Liang, Z.; Wu, X.; Lu, Y. *Chem. Commun.* **2006**, 2801.

(10) Chowdari, N. S.; Ramachary, D. B.; Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 9591.

JA0677012