Article

Catalysis of 3-Pyrrolidinecarboxylic Acid and Related Pyrrolidine Derivatives in Enantioselective *anti*-Mannich-Type Reactions: Importance of the 3-Acid Group on Pyrrolidine for Stereocontrol

Haile Zhang, Susumu Mitsumori, Naoto Utsumi, Masanori Imai, Noemi Garcia-Delgado, Maria Mifsud, Klaus Albertshofer, Paul Ha-Yeon Cheong, K. N. Houk, Fujie Tanaka, and Carlos F. Barbas

J. Am. Chem. Soc., **2008**, 130 (3), 875-886 • DOI: 10.1021/ja074907+

J|A|C|S
ARTICLES
Published on Web 12/29/2007

Catalysis of 3-Pyrrolidinecarboxylic Acid and Related Pyrrolidine Derivatives in Enantioselective *anti*-Mannich-Type Reactions: Importance of the 3-Acid Group on Pyrrolidine for Stereocontrol

Haile Zhang,[†] Susumu Mitsumori,[†] Naoto Utsumi,[†] Masanori Imai,[†] Noemi Garcia-Delgado,[†] Maria Mifsud,[†] Klaus Albertshofer,[†] Paul Ha-Yeon Cheong,[§] K. N. Houk,[§] 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, and Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

Received July 3, 2007; E-mail: ftanaka@scripps.edu; carlos@scripps.edu

Abstract: The development of enantioselective *anti*-selective Mannich-type reactions of aldehydes and ketones with imines catalyzed by 3-pyrrolidinecarboxylic acid and related pyrrolidine derivatives is reported in detail. Both (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid and (*R*)-3-pyrrolidinecarboxylic acid efficiently catalyzed the reactions of aldehydes with α-imino esters under mild conditions and afforded *anti*-Mannich products with high diastereo- and enantioselectivities (*anti*/*syn* up to 99:1, up to >99% ee). For the reactions of ketones with α-imino esters, (*R*)-3-pyrrolidinecarboxylic acid was an efficient catalyst (*anti*/*syn* up to >99:1, up to 99% ee). Evaluation of a series of pyrrolidine-based catalysts indicated that the acid group at the β-position of the pyrrolidine ring of the catalyst played an important role in forwarding the carbon−carbon bond formation and in directing *anti*-selectivity and enantioselectivity.

Introduction

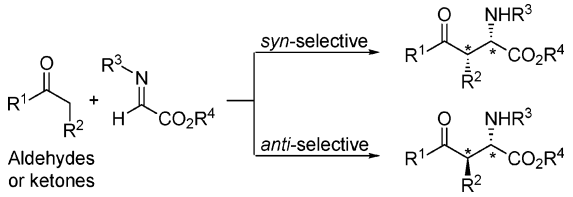
Mannich and Mannich-type reactions are important carbon−carbon bond-forming reactions for the synthesis of amino acids, amino alcohols, amino carbonyls, and their derivatives that contain two adjacent stereocenters; accordingly there is a demand for the direct catalytic reactions that afford *syn*- or *anti*-Mannich products with high diastereo- and enantioselectivities.[1−5] Because reactions that use unmodified carbonyl compounds as nucleophile sources are more atom economical than those that use preactivated carbonyl compounds, such as silyl enol ethers or preformed enamines, development of the reactions that use unmodified carbonyl compounds has been of interest. *syn*- or *anti*-Selective Mannich-type reactions of unmodified carbonyl compounds that afford products with high enantioselectivities have been performed using Zn-catalysts,[2a−e] Y-catalysts,[2f] Cu-catalysts,[2g,h] Pd-catalysts,[2i] cinchona alkaloids,[2j,k] and proline and related amine-based organocatalysts.[3] In Mannich-type reactions of α-hydroxyketones, Zn-catalysts selectively afforded *anti*- or *syn*-products depending on the protecting group on the reactant imine nitrogen.[2a−e] Cu-catalysts,[2g,h] Pd-catalysts,[2i] and cinchona alkaloids[2j,k] have been used for Mannich-type reactions of β-ketoesters. Proline and related amine-based enamine catalysis have been used for enantioselective Mannich-type reactions of aldehydes and ketones including simple alkylaldehydes and alkanones, in which in situ-formed enamine intermediates act as nucleophiles. When proline and related pyrrolidine derivatives that possess acidic groups at the α-position of pyrrolidine are used as catalysts for these Mannich-type reactions, typically *syn*-isomers are obtained as the major products.[3] Development of enamine-based Mannich-type reactions of aldehydes and of ketones that afford *anti*-products with high diastereo- and enantioselectivities is a current challenge.[4,5] Since Mannich-type reactions with α-imino esters are especially useful for syntheses of a variety of amino acid derivatives (Scheme 1),[1a−c,2g,3a−g,j−l,q,r−t] development of *anti*-Mannich-type reactions with α-imino esters is considerably important.[4,5a−c] We have recently reported in communications that pyrrolidine derivatives (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid and (*R*)-3-pyrrolidinecarboxylic acid catalyze *anti*-Mannich-type reactions of aldehydes[4a] and of ketones,[4b] respectively. To provide information for the further development of efficient,

[†] The Scripps Research Institute.
[§] University of California, Los Angeles.

(1) Enantioselective *syn*- or *anti*-selective Mannich-type reactions that use silyl enolates or glycine imines as nucleophiles: (a) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4584. (b) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090. (c) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (d) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (e) Kobayashi, S.; Hamada, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640. (f) Kobayashi, S.; Matsubara, R.; Nakamura, Y.; Kitagawa, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 2507. (g) Nakamura, Y.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 2481. (h) Hamada, T.; Manabe, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, 7768. (i) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (j) Ooi, T.; Kameda, M.; Fujii, J.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (k) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564. (l) Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 3533. (m) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230.

10.1021/ja074907+ CCC: $40.75

Scheme 1

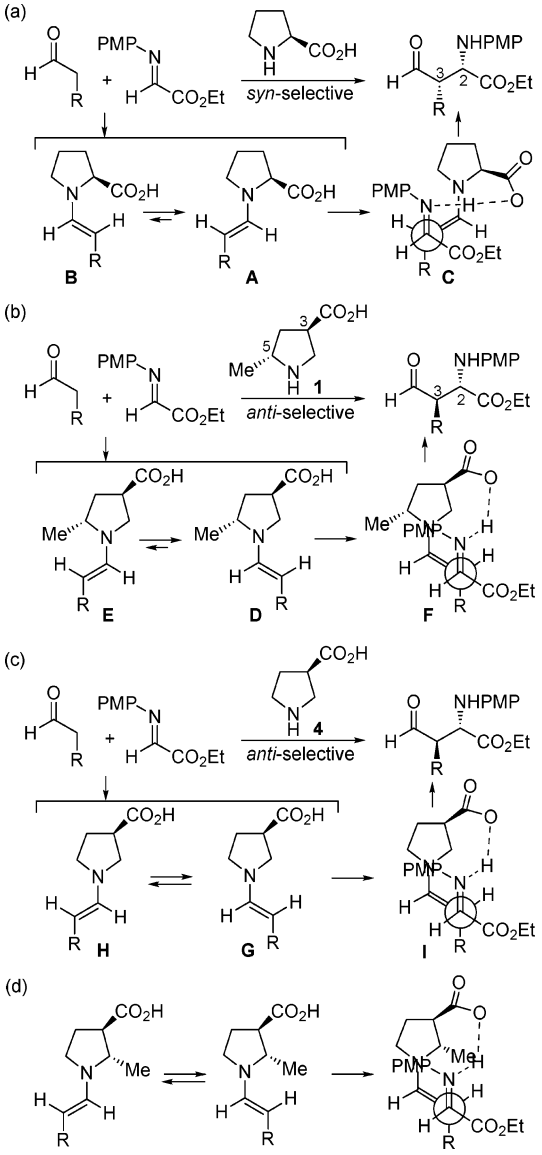


highly diastereo- and enantioselective organocatalytic methods of chemical transformations, here we report the details of the design of pyrrolidine-derived catalysts bearing acid groups at the 3-position of pyrrolidine for *anti*-Mannich-type reactions and the scope of the catalyzed *anti*-Mannich-type reactions, including reactions with α-imino esters.

Results and Discussion

Design and Evaluation of Catalysts for *anti*-Mannich-Type Reactions of Aldehydes. (*S*)-Proline catalyzes Mannich-type reactions between unmodified aldehydes and *N*-*p*-methoxyphenyl (PMP)-protected imine of ethyl glyoxylate and affords (2*S*,3*S*)-*syn*-products with high enantioselectivities.[3b,c] The stereochemical outcome of the proline-catalyzed reactions can been explained by the mechanism shown in Scheme 2a.[3c,6] With proline, (*E*)-enamines predominate. The s-*trans*-enamine conformation (**A**) of the (*E*)-enamine is used for the C−C bond-forming transition state (**C**); the *re* face of the enamine reacts with the *si* face of the imine. The C−C bond-forming transition state involving s-*cis*-enamine conformation **B** is disfavored compared to transition state **C**. There are two main possiblities for the predominant contribution of conformation **A** over **B** in the C−C bond-forming transition state. One is position matching between the nucleophilic carbon of the enamine and the electrophilic carbon of the imine in **A**: When the imine is protonated by the carboxylic acid, the enamine nucleophilic carbon of conformation **A** is positioned within a suitable reaction distance from the electrophilic carbon of the imine. The position of the enamine nucleophilic carbon of conformation **B**, however,

Scheme 2



(2) Enantioselective *syn*- or *anti*-selective Mannich-type reactions of hydroxyketones, β-ketoesters, a trichloromethyl ketone, or an imide that use other than enamine catalysis: (a) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712. (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (c) Yoshida, T.; Morimoto, H.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3470. (d) Trost, B.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (e) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (f) Sugita, M.; Yamaguchi, A.; Yamagawa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339. (g) Juhl, K.; Gathergood, N.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2995. (h) Foltz, C.; Stecker, B.; Marconi, G.; Bellemin-Laponnaz, S.; Wadepohl, H.; Gade, L. H. *Chem. Commun.* **2005**, 5115. (i) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1525. (j) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (k) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. (l) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (m) Morimoto, H.; Lu, G.; Aoyama, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 9588. (n) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Kohn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632.

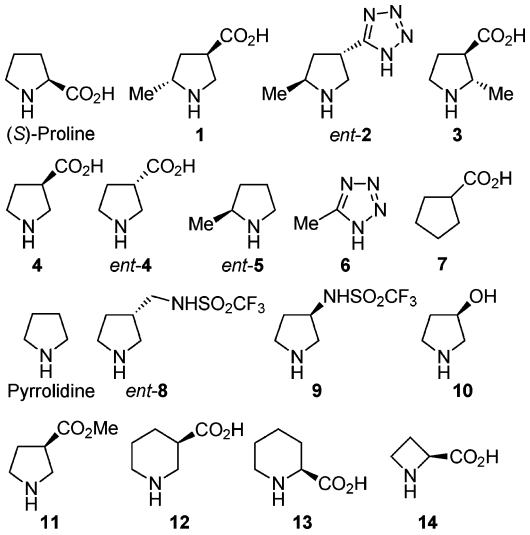
(3) Enamine-based enantioselective *syn*-selective Mannich or Mannich-type reactions that use aldehydes or ketones as nucleophiles: (a) Cordova, A.; Notz, W.; Zhong, G.; Betancort, J.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (b) Cordova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (c) Notz, W.; Tanaka, F.; Watanabe, S.; Chowdari, N. S.; Turner, J. M.; Thayumanuvan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624. (d) Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III. *Synlett* **2003**, 1906. (e) Notz, W.; Watanabe, S.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131. (f) Chowdari, N.; Suri, J.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 2507. (g) Chowdari, N.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 2839. (h) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (i) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (j) Zhuang, W.; Saaby, S.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476. (k) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077. (l) Enders, D.; Grondal, C.; Vrettou, M.; Raabe, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4079. (m) Enders, D.; Vrettou, M. *Synthesis* **2006**, 2155. (n) Enders, D.; Grondal, C.; Vrettou, M. *Synthesis* **2006**, 3597. (o) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 609. (p) Fustero, S.; Jimenez, D.; Sanz-Cervera, J. F.; Sanchez-Rosello, M.; Esteban, E.; Simon-Fuentes, A. *Org. Lett.* **2005**, *7*, 3433. (q) Janey, J. M.; Hsiao, Y.; Armstrong, J. D., III. *J. Org. Chem.* **2006**, *71*, 390. (r) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (s) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84. (t) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243.

(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. (c) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288. (d) Cheong, P. H.-Y.; Zhang, H.; Thayumanavan, R.; Tanaka, F.; Houk, K. N.; Barbas, C. F., III. *Org. Lett.* **2006**, *8*, 811. (e) Cordova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2002**, *43*, 7749.

(5) (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. (c) Kano, T.; Hato, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 8467. (d) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 3790. (e) Cheng, L.; Wu, X.; Lu, Y. *Org. Biomol. Chem.* **2007**, *5*, 1018.

(6) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249.

Chart 1



is not correctly positioned near the electrophilic carbon of the imine for bond formation under the proton transfer from the carboxylic acid to the imine. The other possibility is that conformation **B** has unfavorable steric interactions between the carboxylic acid and the enamine, and thus conformation **A**, which does not have such unfavorable interactions, predominates over conformation **B**. Although computational analysis of the transition state of the C−C bond-forming step suggests transition state **C**,[6] it has not been clearly explained why enamine conformation **A** is used more favorably than conformation **B** in the C−C bond-forming step. Therefore, in the design of catalysts of *anti*-selective Mannich-type reactions, we considered both possibilities.

To alter the selectivity from *syn* to *anti*, the reaction face of the enamine or imine must be reversed from that of the proline-catalyzed reactions. Since the 2-carboxylic acid of proline controls both enamine conformation and reaction faces of the enamine and the imine, we reasoned that separation of the steric and the acid roles of this group into two groups and placing of the groups at appropriate positions on a pyrrolidine ring should result *anti*-selectivity. We reasoned that a pyrrolidine derivative bearing substituents at 2- and 4-positions (or at 3- and 5-positions) should afford *anti*-products in the Mannich-type reactions: The acid group at the 3-position of pyrrolidine can be any acid functional group that engages the proton transfer to the imine in the transition state and the substituent at 5-position can be any functional group that cannot initiate proton transfer. Based on these considerations, we designed (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid (**1**) (Chart 1) as an *anti*-selective catalyst for the Mannich-type reactions of aldehydes (Scheme 2b). We hypothesized that the 5-methyl group of catalyst **1** controlled the enamine conformation to be present as s-*trans* conformation **D** rather than s-*cis* conformation **E** because of unfavorable steric interactions between the 5-methyl group and the enamine in conformation **E**. We reasoned that the 3-carboxylic acid of catalyst **1** should control the reaction faces of the enamine and the imine through the proton transfer from the carboxylic acid to the imine nitrogen. The proton transfer from the carboxylic acid to the imine nitrogen should also accelerate the reaction by increasing the imine electrophilicity. The 3-carboxylic acid and the 5-methyl group should be *trans* to avoid steric interactions between the 5-methyl group of catalyst **1** and the imine in the C−C bond-forming transition state. The *trans*-relationship between the 3-carboxylic acid and 5-methyl group should also block the approach of the imine to the enamine from the undesired reaction face. Thus, catalyst **1** should catalyze the Mannich-type reactions via transition state **F** that use s-*trans*-enamine conformation **D** of the (*E*)-enamine intermediate (Scheme 2b). In this transition state, *si*-face of the enamine reacts with the *si*-face of the imine. As we have preliminary reported[4a] and further describe below, amino acid **1** is an excellent catalyst for the *anti*-selective Mannich-type reactions of aldehydes and the product stereochemistry of the **1**-catalyzed reaction accords with the C−C bond formation through transition state **F**.

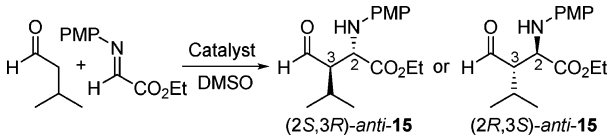
The acid group at the 3-position of **1** can be any functional group that engages the proton transfer to the imine in the transition state. The tetrazole derivative of (*S*)-proline, (*S*)-5-pyrrolidine-2-yl-1*H*-tetrazole, has been used as an efficient catalyst for Mannich reactions that can be catalyzed by proline, and the reactions catalyzed by this catalyst affords Mannich products with stereoselectivities similar to that obtained from proline catalysis;[3r] therefore, we reasoned that *ent*-**2** (Chart 1) should also be an excellent *anti*-Mannich catalyst.

The 5-methyl group of catalysts **1** and *ent*-**2** can be altered upon the degrees of its contribution to the stereoselectivities of the reactions. To determine the contribution of the carboxylic acid at the 3-position and of the methyl group at the 5-position of **1** to directing the stereochemical outcome of the reaction, we reasoned to evaluate (2*S*,3*R*)-2-methyl-3-pyrrolidinecarboxylic acid (**3**), which has a methyl group at the 2-position on the pyrrolidine, the unmethylated derivative (*R*)-3-pyrrolidinecarboxylic acid (**4**), and the pyrrolidine derivative without 3-carboxylic acid, (*R*)-2-methylpyrrolidine (**5**). If the acid group at the 3-position is the group that predominantly directs the stereochemical outcome, the use of unmethylated derivative **4** should also afford *anti*-products with high diastereo- and enantioselectivities. Because catalyst **4** is more readily accessed than catalyst **1**, this catalyst would be useful for *anti*-selective Mannich-type reactions if this catalyst provide reactivities and selectivities similar to catalyst **1**. As described below, reactions of many aldehyde nucleophiles catalyzed by **4** afforded *anti*-Mannich products with high diastereo- and enantioselectivities. With catalyst **4**, both enamine conformations **G** and **H** may be similarly present; that is, conformations **G** and **H** may have similar free energies (Scheme 2c). However, only conformation **G** should advance the C−C bond formation through transition state **I** (Scheme 2c). The nucleophilic carbon of enamine **G** should be properly positioned for the reaction with the electrophilic carbon of the imine, whereas the nucleophilic carbon of enamine **H** should be too far from the imine electrophilic carbon to form a bond.

Catalysts **1**−**14** were evaluated in the Mannich-type reaction of isovaleraldehyde and *N*-PMP-protected ethyl glyoxylate imine (Table 1). The reaction catalyzed by (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid (**1**) afforded (2*S*,3*R*)-*anti*-**15**[7] in a good yield with excellent diastereo- and enantioselectivities

(7) Determination of the absolute stereochemistry of **15** generated by the **1**-catalyzed reaction has been reported in our communication (ref 4a).

Table 1. Evaluation of Catalysts for the *anti*-Selective Mannich-Type Reaction of Isovaleraldehyde to Afford **15**[a]



entry	catalyst	catalyst load (equiv)	time (h)	yield[b] (%)	dr[c] *anti/syn*	major *anti*-enantiomer	ee[d] (%)
1	**1**	0.05	3	85	98:2	(2*S*,3*R*)	99
2	*ent*-**2**	0.05	3	87	98:2	(2*R*,3*S*)	99
3	**3**	0.05	6	75	97:3	(2*S*,3*R*)	91
4	**4**	0.05	4	81	99:1	(2*S*,3*R*)	94
5	*ent*-**4**	0.05	3	87	99:1	(2*R*,3*S*)	93
6[e]	*ent*-**5**	0.2	72	16	75:25	(2*R*,3*S*)	29 (19)
7[e]	*ent*-**5** + CF_3CO_2H	0.2	72	20	80:20	(2*R*,3*S*)	40 (18)
8[e]	*ent*-**5** + **6**	0.2	72	21	67:33	(2*R*,3*S*)	54 (40)
9[e]	*ent*-**5** + **7**	0.2	72	19	64:36	(2*R*,3*S*)	36 (46)
10[e]	**7**	0.2	72	9	63:37		
11[e]	pyrrolidine	0.2	72	20	89:11		
12	*ent*-**8**	0.05	2.5	83	94:6	(2*R*,3*S*)	85
13	**9**	0.05	4	93	87:13	(2*S*,3*R*)	94 (95)
14	**10**	0.3	24	35	93:7	(2*S*,3*R*)	20
15	**11**	0.3	14	<20	75:25		<5 (20)
16[e]	**12**	0.3	30	51	78:22	(2*S*,3*R*)	36 (12)
17[f]	**13**	0.3	14	82	1:1.4	(2*S*,3*R*)	98 (>99)
18	**14**	0.3	4	62	10:90	(2*S*,3*R*)	76 (80)

[a] Typical reaction conditions: To a solution of *N*-PMP-protected α-imino ester (0.25 mmol, 1.0 equiv) and aldehyde (0.5 mmol, 2.0 equiv) in anhydrous DMSO (2.5 mL), catalyst (0.0125 mmol, 0.05 equiv, 5 mol % to the imine) was added, and the mixture was stirred at room temperature (25 °C). [b] Isolated yield containing *anti*- and *syn*-**15**. [c] The diastereomeric ratio (dr) was determined by ^{1}H NMR or HPLC. [d] The ee of *anti*-**15** was determined by chiral-phase HPLC analysis. The ee of *syn*-**15** is indicated in parenthesis. [e] When catalyst 0.05 equiv was used, no product formation was detected on TLC after 3 h. [f] Taken from ref 4d.

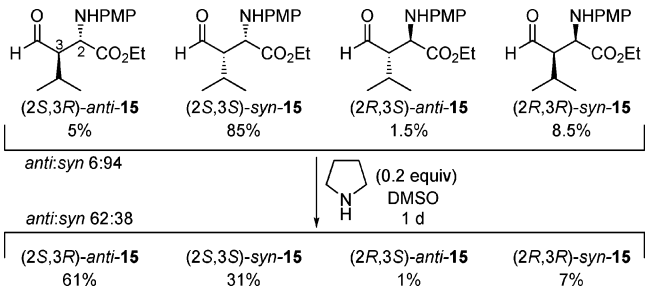
(*anti*/*syn* 98:2, 99% ee, entry 1).[8] The reaction using tetrazole derivative *ent*-**2** afforded the corresponding product enantiomer, (2*R*,3*S*)-*anti*-**15**, with the same degree of diastereo- and enantioselectivities as the reaction using catalyst **1**. Catalysts **1** and *ent*-**2** showed essentially the same level of catalytic efficiency. Reactions catalyzed by **1**- and by *ent*-**2** were approximately 2- to 3-fold faster than the corresponding proline-catalyzed reaction that afforded the *syn*-product. These results indicate that the tetrazole group at the 3-position of catalyst *ent*-**2** functions as efficiently as the carboxylic acid at the 3-position of catalyst **1**.

Although the reaction catalyzed by **3**, which has a methyl group at the 2-position on the pyrrolidine, was slightly slower than the reaction catalyzed by **1**, there was not a significant difference in rates of the reactions (entry 3 versus entry 1). The reaction catalyzed by **3** afforded the same *anti*-product (2*S*,3*R*)-**15** as that by catalyst **1** with the same degree of diastereoselectivity and slightly lower enantioselectivity (91% ee, entry 3) compared to the reaction catalyzed by **1** (99% ee, entry 1). These results suggest that both s-*trans* and s-*cis*-enamine conformations are present in the reaction catalyzed by **3** and that the C−C bond formation is controlled by proton transfer from the 3-carboxylic acid group to the imine (Scheme 2d). Regardless of the position of the methyl group of the catalysts, either at the 5-position or at the 2-position, the reaction faces of the enamine and the imine were the same in the formation of the major product. These results indicate that a methyl group at either the 5-position or the 2-position of the pyrrolidine ring of the catalyst does not significantly effect the enamine conformation. Although the 5-methyl group of catalyst **1** contributes to afford almost perfect *anti*-selectivity and enantioselectivity in the **1**-catalyzed reaction, no significant steric interaction is present between the enamine moiety and the methyl group at either the 5-position or the 2-position. On the other hand, the results indicate that the 3-acid group of the catalysts plays an important role in directing the stereochemical outcome. Significant contribution of the 3-acid group on the pyrrolidine ring of the catalysts in the stereocontrol of the reaction was also supported from results of the reaction catalyzed by unmethylated catalyst (*R*)-3-pyrrolidinecarboxylic acid (**4**). The reaction with catalyst **4** afforded the same *anti*-product (2*S*,3*R*)-**15** as did the reaction with **1**, and the enantiomeric excess of the *anti*-product (2*S*,3*R*)-**15** obtained using catalyst **4** was only slightly lower (94% ee, entry 4) than that with catalyst **1**. The major product obtained from the **4**-catalyzed reaction was in accord with a mechanism of C−C bond formation through transition state **I** (Scheme 2c).

The 3-acid group was essential not only for directing the product stereochemistry, but also for reaction progress: The reaction using (*S*)-2-methylpyrrolidine (*ent*-**5**), which lacked an acid group, did not afford the Mannich product after 3 h when 0.05 equiv (i.e., 5 mol %) of catalyst to the imine was used. Note that the reaction with 5 mol % of either **1** or *ent*-**2** afforded the *anti*-Mannich product in a good yield within a few hours. Reaction with a higher loading of *ent*-**5** (0.2 equiv) afforded the Mannich product, but the diastereo- and enantioselectivities were moderate (entry 6). The low yield of the reaction with *ent*-**5** was not improved by longer reaction time: A longer reaction time resulted in decomposition of the imine and Mannich product and formation of byproducts. Addition of acid (equivalent to the catalyst), such as CF_3CO_2H, methyltetrazole (**6**), or cyclopentanecarboxylic acid (**7**), to the *ent*-**5**-catalyzed

(8) To obtain the Mannich products generated from the reactions of aldehyde nucleophiles in an excellent dr, quick and careful workup and purification procedures were required. For example, the dr values of the products slightly (up to 4% variation) changed during silica gel flash column chromatography. Diastereomers of **15** were inseparable by typical silica gel flash column chromatography (see Supporting Information).

Scheme 3



reaction did not meaningfully enhance the reaction rate; the diastereo- and enantioselectivities of the reactions with these acids were also moderate (entries 7−9). Reaction catalyzed by cyclopentanecarboxylic acid (**7**) or by pyrrolidine also afforded the *anti*-product as the major isomer (entries 10 and 11, respectively). Since enantioselectivity was observed (although low) in the *ent*-**5**-catalyzed reactions, the 2-methyl group plays some role in the stereocontrol. The stereodirecting effect of the 2-methyl group of *ent*-**5** was in accord with that of the 3-acid group of catalyst **4**. A pyrrolidine derivative with a bulky 2-substituent has been demonstrated as an *anti*-selective catalyst in Mannich-type reactions of aldehydes,[5b] but catalyst *ent*-**5**, pyrrolidine with a 2-methyl group alone, did not provide high levels of stereocontrolling effects. These results indicate that the 3-acid group of **1** plays a significant role in directing the stereochemistry and in efficient reaction progress through proton transfer to the imine intramolecularly. The 5-methyl group of catalyst **1** cooperates with the stereodirecting effect of the 3-acid group to provide perfect *anti*-selectivity and enantioselectivity.

The *anti*-product can be generated by isomerization of the *syn*-product at the α-position of the aldehyde group (the 3-position of **15**). To test whether the isomerization of the product occurs under the Mannich-type reaction conditions, *syn*-rich **15** generated by the (*S*)-proline-catalyzed reaction was treated with catalysts. First, *syn*-rich **15** was treated with pyrrolidine under conditions similar to the catalyzed reactions in Table 1, entry 11, and the ratios of the diastereomers and enantiomers were analyzed. After 1 day, the *anti*-isomer became the major isomer (*anti*/*syn* = 1.6:1) as shown in Scheme 3; (2*S*,3*S*)-*syn*-**15** was converted to (2*S*,3*R*)-*anti*-**15** in the presence of pyrrolidine. Pyrrolidine isomerized the Mannich products either through enamine formation with the product and/or by acting as a base for enolization. This result indicates that the *anti*-isomer is more thermodynamically stable than the *syn*-isomer. The *anti*-isomer was also more thermodynamically favored in imidazole isomerization:[4a,9] In the presence of imidazole, the isomerization rate of **15** from *syn* to *anti* was faster than that from *anti* to *syn*. The ratio of the diastereomers obtained from the pyrrolidine-catalyzed reaction that afforded the *anti*-isomer as the major product may reflect the consequences of isomerization; the pyrrolidine-catalyzed reaction may not form the *anti*-product by kinetic control in the C−C bond-forming step.

Next, isomerization of *syn*-**15** to *anti*-**15** in the presence of pyrrolidine, *ent*-**5**, or **4** in $CDCl_3$ or in DMSO-d_6 was analyzed by ^{1}H NMR (Table 2). The isomerization rate with *ent*-**5**, which possesses 2-methyl group, was slower than that with pyrrolidine but the *anti*-isomer became the major isomer after 1 day.

(9) Ward, D. E.; Sales, M.; Sasmal, P. *J. Org. Chem.* **2004**, *69*, 4808.

Table 2. Isomerization of *syn*-**15** to *anti*-**15** Catalyzed by Pyrrolidines[a]

catalyst	catalyst load (equiv)	solvent	time	*syn*-**15**/*anti*-**15**[b]
pyrrolidine	0.2	$CDCl_3$	0 min	96:4[c]
			4 h	1:1
			24 h	1:2.5[d]
ent-**5**	0.2	$CDCl_3$	0 min	96:4[c]
			4 h	2:1
			24 h	1:2[d]
4	0.1	$CDCl_3$	0 min	96:4[c]
			3 h	95:5
			24 h	83:17[e]
4	0.1	DMSO-d_6	0 min	96:4[c]
			2 h	96:4
			7 h	95:5

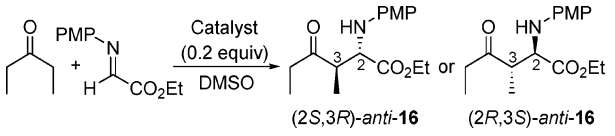
[a] Conditions: Mannich product **15** (0.1 M) and catalyst (0.2 or 0.1 equiv to **15** as indicated). [b] The ratio of *syn*-**15**/*anti*-**15** was determined by ^{1}H NMR. [c] Before addition of catalyst. [d] Includes decomposed products ∼20%. [e] Includes decomposed products ∼5%.

Diastereomeric ratio of **15** obtained from the *ent*-**5**-catalyzed reaction may also reflect the result of isomerization of the kinetically formed product. On the other hand, isomerization with **4**, which possesses 3-carboxylic acid, was significantly slower than that with pyrrolidine or with *ent*-**5**. Isomerization with **4** was negligible over the time range of the **4**-catalyzed Mannich-type reaction. The negligible isomerization of the Mannich product in the presence of **4** also supports that the *anti*-selectivity of the **1**- or **4**-catalyzed reaction is the result of the kinetic control at the C−C bond-forming step. In the isomerization with pyrrolidine or with *ent*-**5**, basic environs may contribute to acceleration of the isomerization rates.

To further understand the contribution of the 3-acid group of the catalysts, 3-substituted pyrrolidines, including *ent*-**8** and **9**, 3-hydroxypyrrolidine (**10**), and 3-pyrrolidinecarboxylic acid methyl ester (**11**), were also evaluated. The sulfonamide group that is present in catalysts *ent*-**8** and **9** has been used as an acid functionality in the enamine-based catalysts for Mannich reactions.[3t,5a,c] Catalysts *ent*-**8** and **9** (entries 12 and 13) had catalytic activity similar to **1**, **2**, **3**, and **4**, indicating that the sulfonamide group is also a good acid for catalysis in the *anti*-selective Mannich-type reaction. Since the *anti*-selectivity and enantioselectivity varied depending on the catalyst, the results also indicate that the distance and orientation between the 3-acid group of a catalyst, enamine nucleophilic carbon, and imine electrophilic carbon in the transition state affect to the *anti*-selectivity and enantioselectivity. 3-Hydroxypyrrolidine (**10**) was not a good catalyst (entry 14), indicating that hydroxyl group at the 3-position was not an efficient acid for this reaction. Reaction with methyl ester **11** was slow (entry 15), also supporting the importance of the acid group on pyrrolidine for catalysis.

Reaction catalyzed by 3-piperidinecarboxylic acid (**12**), a six-membered ring catalyst, was slow and afforded the product with moderate *anti*-selectivity and enantioselectivity (entry 16), indicating the importance of the five-membered pyrrolidine ring structure for efficient catalysis and high selectivity. We previously reported the (*S*)-pipecolic acid (**13**)-catalyzed reaction that afforded both *anti*- and *syn*-isomers (2*S*,3*R*)-**15** and (2*S*,3*S*)-**15** (*anti*/*syn* 1:1.4) with high enantioselectivities (entry 17).[4d] Computational analysis of the transition states of the C−C bond formation step of the **13**-catalyzed reaction suggested that the both s-*cis*- and s-*trans*-enamines were similarly used for the

Table 3. Evaluation of Catalysts for the *anti*-Selective Mannich-Type Reaction of 3-Pentanone[a]



entry	catalyst	time (h)	yield[b] (%)	dr[c] *anti*/*syn*	major *anti*–enantiomer	ee[d] (%)
1	**1**	72	<10			
2	**4**	29	75	94:6	(2*S*,3*R*)-**16**	97
3	*ent*-**8**	72	83	94:6	(2*R*,3*S*)-**16**	85
4	**9**	17	98	75:25	(2*S*,3*R*)-**16**	97 (*syn* 97)

[a] To a solution of *N*-PMP-protected α-imino ester (0.5 mmol, 1.0 equiv) and 3-pentanone (2.0 mL, 19 mmol, 38 equiv) in anhydrous DMSO (3.0 mL), catalyst (0.1 mmol, 0.2 equiv, 20 mol % to the imine) was added, and the mixture was stirred at room temperature (25 °C). [b] Isolated yield containing *anti*- and *syn*-**16**. [c] Determined by HPLC before purification. [d] Determined by chiral-phase HPLC for *anti*-**16**.

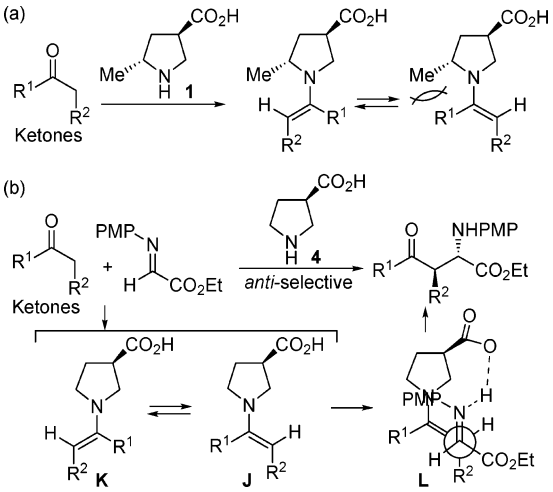
C−C bond formation in the **13**-catalyzed reaction and that thus both *syn* and *anti* products formed.[4d] Reaction catalyzed by 2-azetidinecarboxylic acid (**14**), a four-membered ring catalyst, afforded *syn*-products as the major product. Stereoselectivity of the product depended on the ring size of the amine catalyst and on the position of the acid.

The results of the catalyst evaluation indicate that the acid group at the 3-position of catalyst **1** plays a dominant role in forwarding reaction (efficient catalysis) and in directing stereochemistry through proton transfer to the imine. The 5-methyl group of catalyst **1** cooperatively contributes to the stereocontrolling effect of the 3-acid group to provide *anti*-products with excellent enantioselectivity as almost single enantiomer. The 5-methyl group of catalyst **1** has little effect on controlling the enamine conformation: There is no significant steric role of α-methyl group on pyrrolidine to control enamine conformation. The (*E*)-enamine of **1** (or **4**) is present as either s-*trans* **D** or s-*cis* **E** (or s-*trans* **G** or s-*cis* **H**), but only **D** (or **G**) advances to the C−C bond formation through **F** (or **I**). The preference of conformation **D** over **E** in the transition state of the C−C bond-forming step originates mainly from the proton transfer from the 3-acid group to the imine. Proper positioning of the enamine and the imine for efficient catalytic activity, high *anti*-selectivity, and high enantioselectivity is achieved by the proton transfer from the 3-carboxylic acid to the imine nitrogen.

Of the catalysts evaluated, catalysts **1** and *ent*-**2** were the most efficient catalysts for the *anti*-Mannich-type reactions of aldehydes with respect to the catalytic efficiency, *anti*-selectivity, and enantiostereoselectivity. When accessibility of catalysts was also considered, **4** had advantages. Therefore, catalysts **1** and **4** were further studied for the *anti*-Mannich-type reactions of aldehydes.

Design and Evaluation of Catalysts for *anti*-Mannich-Type Reactions of Ketones. Compared to the reactions of aldehydes, the reactions of ketones require additional consideration of steric interactions in formation of enamine intermediates. Although amino acid **1** was an excellent *anti*-selective catalyst for the Mannich-type reactions of aldehydes, the reaction of 3-pentanone in the presence of catalyst **1** was very slow (Table 3, entry 1). Whereas the α-methyl group on pyrrolidine did not hinder the formation of enamine intermediates with aldehydes, we reasoned that the low efficiency of catalyst **1** in the ketone reaction originated from relatively slow formation of the enamine intermediates due to steric interactions with the methyl group of the catalyst (Scheme 4a). We reasoned that unmethylated catalyst **4** should afford *anti*-Mannich products in the ketone reactions. Although enamine conformations **J** and **K** may have similar free energies, only **J** should advance to the C−C bond formation via transition state **L** (Scheme 4b). When proton transfer occurs from the acid at the 3-position of the catalyst to the imine nitrogen, the nucleophilic carbon of enamine **J** should be properly positioned to react with the imine, whereas the nucleophilic carbon of enamine **K** should be too far from the imine electrophilic carbon to form a bond. Since **4** does not have an α-substituent on the pyrrolidine, neither enamine **J** nor **K** has a disfavored steric interaction like the one shown in Scheme 4a and enamine formation of ketones with **4** should be faster than that with **1**.

Scheme 4

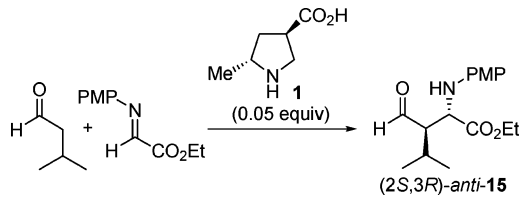


In fact, the reaction catalyzed by **4** was significantly faster than the **1**-catalyzed reaction and afforded *anti*-Mannich product (2*S*,3*R*)-**16**[10] in good yield with high diastereo- and enantioselectivities (entry 2, *anti*/*syn* 94:6, *anti* 97% ee). Catalyst *ent*-**8**, which possesses a sulfonamide group, also catalyzed the formation of the *anti*-product (entry 3), but the reaction catalyzed by **4** was faster and showed higher enantioselectivity than the *ent*-**8**-catalyzed reaction. Catalyst **9**, which also has a sulfonamide group, catalyzed the reaction more efficiently than *ent*-**8** did, and the ee of the product *anti*-**16** obtained from the **9**-catalyzed reaction was excellent (entry 4). These results indicate that the acid functionality at the 3-position on the pyrrolidine ring plays an important role in directing stereochemistry in the reactions of ketones as it did in the reactions of aldehydes. The acid group contributes to proper positioning of the imine for efficient catalytic activity and high *anti*-selectivity and enantioselectivity. Because catalyst **4** afforded the best results with respect to *anti*-selectivity and enantioselectivity, this catalyst was further investigated for the *anti*-Mannich-type reactions of ketones.

Mannich-Type Reactions of Aldehyde Donors Catalyzed by 1. Solvents were evaluated for the **1**-catalyzed Mannich reaction to afford (2*S*,3*R*)-*anti*-**15** in a good yield with high diastereo- and enantioselectivities in a short reaction time (Table

(10) Determination of the absolute stereochemistry of **16** generated by the **4**-catalyzed reaction has been reported in our communication (ref 4b).

Table 4. Solvent Effects on the *anti*-Mannich-Type Reaction of an Aldehyde Catalyzed by **1**[a]



entry	solvent	time (h)	yield[b] (%)	dr[c] *anti/syn*	ee[d] (%)
1	DMSO	3	85	98:2	99
2	DMF	3	78	97:3	98
3	CH_3CN	3	76	96:4	96
4	EtOAc	6	80	94:6	96
5	dioxane	5	77	97:3	95
6	CH_2Cl_2	3	85	91:9	93
7	THF	20	45	91:9	83
8	Et_2O	20	40	90:10	84
9	[bmim]BF_4	5	35	94:6	77

[a] Typical reaction conditions: To a solution of *N*-PMP-protected α-imino ester (0.125 mmol, 1.0 equiv) and aldehyde (0.5 mmol, 4.0 equiv) in anhydrous solvent (1.25 mL), catalyst (0.0063 mmol, 0.05 equiv, 5 mol % to the imine) was added, and the mixture was stirred at room temperature. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] The dr was determined by ^{1}H NMR. [d] The ee of (2*S*,3*R*)-*anti*-**15** was determined by chiral-phase HPLC analysis.

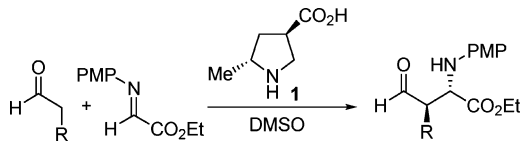
4). The reaction in DMSO provided the best *anti*-selectivity and enantioselectivity among those solvents tested (entry 1). Reactions in DMF, CH_3CN, EtOAc, and dioxane were as efficient with respect to reaction rate as that in DMSO and afforded high *anti*-selectivity and enantioselectivity (*anti*/*syn* 94:6−97:3, 95−97% ee, entries 2−5). Although ionic liquids were good solvents for the proline-catalyzed Mannich reaction affording *syn*-**15**,[3d] the **1**-catalyzed reaction in ionic liquid [bmim]BF_4 (bmim = 1-butyl-3-methylimidazolium) was slow (entry 9).

The scope of the **1**-catalyzed Mannich-type reaction with ethyl glyoxylate imine was examined using a series of aldehydes (Table 5). The reactions catalyzed by **1** afforded a series of *anti*-Mannich products (2*S*,3*R*)-**15** and (2*S*,3*R*)-**17**−**21** with excellent diastereo- and enantioselectivities (anti/*syn* 94:6−99:1, *anti* >97−>99% ee).[8] With 5 mol % catalyst loading, the reaction rates with catalyst **1** were approximately 2- to 3-fold faster than the corresponding proline-catalyzed reactions that afford the *syn*-products. Because of the high catalytic efficiency of **1**, the reactions catalyzed by only 1 or 2 mol % of **1** afforded the desired products in reasonable yields within a few hours (entries 5, 6, 8, and 9). For the reaction of a bulky aldehyde 3,3-dimethylbutanal, a higher loading of catalyst and a longer reaction time were required to afford the Mannich product *anti*-**22** (entry 10) than for the reactions of α-unbranched aldehydes.

These *anti*-Mannich products were generally more resistant to the isomerization at the α-position of the aldehyde carbonyl group than corresponding *syn*-Mannich products, which were often isomerized to *anti*-isomer[3b,c] or to α,*β*-unsaturated carbonyl compounds[11] (if applicable) during purification.[8] Thus, formation of highly enantiomerically enriched Mannich products in an *anti*-selective fashion was beneficial to access to amino acid derivatives in more pure forms than formation of corresponding *syn*-Mannich products.

(11) Utsumi, N.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2007**, *46*, 1878.

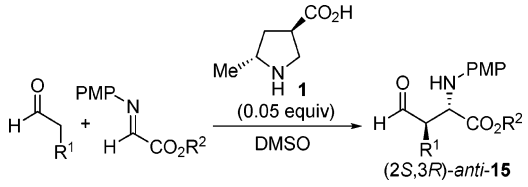
Table 5. *anti*-Mannich-Type Reactions of Aldehydes Catalyzed by **1**[a]



entry	R	catalyst load (equiv)	time (h)	product	yield[b] (%)	dr[c] *anti/syn*	ee[d] (%)
1	Me	0.05	1	(2*S*,3*R*)-**17**	70	94:6	>99[e]
2	*i*-Pr	0.05	3	(2*S*,3*R*)-**15**	85	98:2	99
3	*i*-Pr	0.3	1	(2*S*,3*R*)-**15**	86	93:7	>99
4	*n*-Bu	0.05	0.5	(2*S*,3*R*)-**18**	54	97:3	99
5[f]	*n*-Bu	0.02	1	(2*S*,3*R*)-**18**	71	97:3	99
6[f]	*n*-Bu	0.01	2	(2*S*,3*R*)-**18**	57	97:3	>99
7	*n*-Pent	0.05	3	(2*S*,3*R*)-**19**	80	97:3	>99
8[f]	$CH_2CH{=}CH_2$	0.02	3	(2*S*,3*R*)-**20**	72	96:4	>97
9	$CH_2CH(CH_2)_4CH_3$	0.02	3	(2*S*,3*R*)-**21**	84	99:1	>99
10	*t*-Bu	0.1	48	(2*S*,3*R*)-**22**	57	86:14	77

[a] Typical reaction conditions: To a solution of *N*-PMP-protected α-imino ester (0.25 mmol, 1.0 equiv) and aldehyde (0.5−1.0 mmol, 2−4 equiv) in anhydrous DMSO (2.5 mL), catalyst **1** (0.0125 mmol, 0.05 equiv, 5 mol % to the imine) was added, and the mixture was stirred at room temperature. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] The dr was determined by ^{1}H NMR or HPLC. [d] The ee of *anti*-product was determined by chiral-phase HPLC analysis. [e] The ee was determined by HPLC analysis of the corresponding oxime prepared with *O*-benzylhydroxylamine. [f] The reaction was performed in a doubled scale.

Table 6. *anti*-Mannich-Type Reactions of Aldehydes Catalyzed by **1**: Variation of α-Imino Glyoxylates[a]



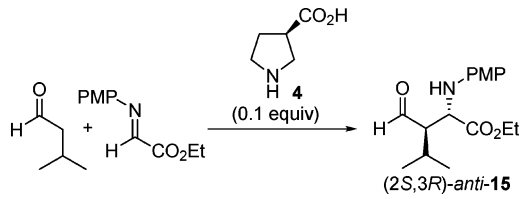
entry	R^1	R^2	time (h)	product	yield[b] (%)	dr[c] *anti/syn*	ee[d] (%)
1	*i*-Pr	*i*-Pr	1	(2*S*,3*R*)-**23**	92	97:3	98
2	*n*-Pent	*i*-Pr	1	(2*S*,3*R*)-**24**	85	96:4	>99
3	*i*-Pr	*t*-Bu	2.5	(2*S*,3*R*)-**25**	85	>99:1	98
4	*i*-Pr	$CH_2CH{=}CH_2$	3	(2*S*,3*R*)-**26**	87	98:2	97

[a] Reaction conditions: To a solution of *N*-PMP-protected α-imino ester (0.25 mmol, 1.0 equiv) and aldehyde (0.5−1.0 mmol, 2−4 equiv) in anhydrous DMSO (2.5 mL), catalyst **1** (0.0125 mmol, 0.05 equiv, 5 mol % to the imine) was added, and the mixture was stirred at room temperature. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] The dr was determined by ^{1}H NMR or HPLC. [d] The ee of *anti*-product was determined by chiral-phase HPLC analysis.

The use of catalyst **1** was also examined in *anti*-selective Mannich-type reactions of a series of *N*-PMP-protected glyoxylate imines to afford *anti*-products **23**−**26** (Table 6). The *anti*-products were obtained in good yields and excellent diastereo- and enantioselectivities. The reaction with a glyoxylate imine possessing a bulky group, *tert*-butyl, also proceeded smoothly and afforded the Mannich product with excellent *anti*-selectivity and enantioselectivity (entry 3).

Mannich-Type Reactions of Aldehyde Donors Using Catalysts 4 and *ent*-4. Evaluation of solvents for the **4**-catalyzed Mannich-type reaction that affords (2*S*,3*R*)-*anti*-**15** showed that DMSO was the best among solvents tested with respect to yield, *anti*-selectivity, and enantiomeric excess of the *anti*-Mannich product (Table 7). Whereas the reaction in aprotic solvents

Table 7. Solvent Effects on the *anti*-Mannich-Type Reaction of an Aldehyde Using Catalyst **4**[a]



entry	solvent	time (h)	yield[b] (%)	dr[c] *anti/syn*	ee[d] (%)
1	DMSO	2.5	87	95:5	93
2	DMF	3.5	84	95:5	91
3	CH_3CN	4.5	81	92:8	88
4	*N*-methylpyrrolidone (NMP)	8	65	93:7	87
5	EtOAc	8	72	91:9	82
6	dioxane	7	78	92:8	79
7	$CHCl_3$	6	68	88:12	78
8	toluene	8	68	93:7	83
9	2-PrOH	2	52	90:10	53
10	[bmim]BF_4	10	70	92:8	86

[a] Reaction conditions: To a solution of *N*-PMP-protected α-imino ester (0.125 mmol, 1.0 equiv) and aldehyde (0.25 mmol, 2.0 equiv) in anhydrous solvent (1.25 mL), catalyst **4** (0.0125 mmol, 0.1 equiv, 10 mol % to the imine) was added, and the mixture was stirred at room temperature. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] The dr was determined by HPLC. [d] The ee of (2*S*,3*R*)-*anti*-**15** was determined by chiral-phase HPLC analysis.

afforded the *anti*-Mannich product with good enantioselectivity, the reaction in 2-PrOH provided the *anti*-product with moderate ee. When the reactions in entry 1 (in DMSO) and in entry 9 (in 2-PrOH) were performed in the absence the catalyst, no formation of Mannich product **15** was detected after 2.5 h in either reaction. After 6.5 h, in 2-PrOH, formation of trace amounts of **15** (<5%, *anti*/*syn* = 4:1) was detected by ^{1}H NMR of the crude mixture. Formation of **15** in the absence of a catalyst was negligible for the time range of the catalyzed reaction shown in Table 7. When purified *syn*-**15** (*syn*/*anti* 96:4) in 2-PrOH (0.1 M) was treated with catalyst **4** (0.1 equiv to **15**), the *syn*/*anti* ratio of **15** was 95:5 at 3 h and 87:13 at 6 h. Although the isomerization rate in 2-PrOH was faster than that in $CDCl_3$ or in DMSO-d_6 (see Table 2), changes in the dr in 2-PrOH were negligible for the time range of the **4**-catalyzed Mannich reaction. These results suggested that background reaction (product formation without involving the catalyst) and isomerization of *syn*-**15** with low ee (if any) to *anti*-**15** were not main reasons for the moderate ee of *anti*-**15** obtained by the **4**-catalyzed reaction in 2-PrOH and that *anti*-**15** with moderate ee in 2-PrOH was formed at the C−C bond-forming step. The **4**-catalyzed reaction of isovaleraldehyde in 2-PrOH may partly proceed without desired stereocontrolling participation of the catalyst.

The scope of the Mannich-type reactions between aldehydes and glyoxylate imines catalyzed by **4** and *ent*-**4** was examined in reactions that afforded products **15** and **17**−**27** (Table 8). The *anti*-products were obtained with high diastereo- and enantioselectivities in most cases (*anti*/*syn* 93:7−99:1, *anti* 90−99% ee). In some cases, the enantioselectivity of the **4**-catalyzed reaction was slightly lower than that of the **1**-catalyzed reaction. However, reactions of aldehydes with a longer alkyl chain using catalyst **4** afforded *anti*-Mannich products with excellent enantioselectivities (entries 5−8). Reaction with a bulky aldehyde, 3,3-dimethylbutanal, proceeded efficiently in the presence of catalyst **4**, although the ee of the *anti*-product was moderate (entry 9). By using **4** or its enantiomer *ent*-**4**, both enantiomers of the *anti*-Mannich products were obtained in good yields with high enantioselectivities.

Mannich-type reactions of α,α-disubstituted aldehydes catalyzed by **4** afforded products **28** and **29** in good yields (Table 9), although the diastereo- and enantioselectivities were low to moderate and the *syn*-product was the major diastereomer in both cases. For the **4**-catalyzed Mannich reactions of α-branched aldehydes, use of 2-PrOH as the solvent provided good results with respect to reaction rate and yield. These **4**-catalyzed Mannich-type reactions of α,α-disubstituted aldehydes were significantly faster than the corresponding proline-catalyzed reactions.[3f]

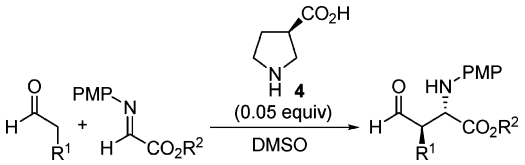
Enantioselective and asymmetric Mannich-type reactions constitute key steps for simple access to enantiomerically enriched β-lactams.[3b,c,12] Using Mannich product (2*R*,3*S*)-*anti*-**15** obtained by the *ent*-**4**-catalyzed reaction, *trans*-β-lactam (3*S*,4*R*)-**30** was synthesized via **31** (Scheme 5). We previously demonstrated that the corresponding *syn*-Mannich products generated from (*S*)-proline-catalyzed reactions were easily transformed to *cis*-β-lactams.[3b,c] With use of *anti*- or *syn*-Mannich-type reactions, highly enantiomerically enriched β-lactams with desired stereochemistries, either *trans* or *cis*, respectively, can be readily obtained.

Mannich-Type Reaction of Ketone Donors Using Catalysts 4 and *ent*-4. Evaluation of solvents for the **4**-catalyzed Mannich-type of reactions between 3-pentanone and *N*-PMP-protected ethyl glyoxylate imine showed that 2-PrOH was the best solvent tested to afford (2*S*,3*R*)-*anti*-**16** in good yield with high *anti*-selectivity and enantioselectivity within a short reaction time (Table 10, entry 9). The reactions in DMSO, DMF, and *N*-methylpyrrolidone (NMP) also proceeded well and afforded the *anti*-product with high selectivities. Whereas catalyst **4** was soluble in DMSO, DMF, and NMP, catalyst **4** was not completely soluble in $CHCl_3$, CH_3CN, dioxane, THF, and EtOAc in the presence of excess 3-pentanone under conditions of Table 10. Catalyst **4** was even less soluble in THF and EtOAc (or THF-3-pentanone or EtOAc-3-pentanone). The slow reaction rate and low yield in these solvents may originate from the low solubility of the catalyst. Catalyst **4** was also not completely soluble in alcohols, including 2-PrOH, but the reaction in alcohols proceeded well. The reaction rate in 2-PrOH was approximately 2-fold faster than that in DMSO and the reaction in 2-PrOH provided less byproducts than that in DMSO. The reaction in EtOH was also efficient, although the ee of the *anti*-Mannich product was slightly lower than that in 2-PrOH. When the reaction in MeOH (entry 11) was performed in the absence of catalyst **4**, no formation of the Mannich product was detected after 48 h, indicating that the catalyst is necessary for the reaction to proceed even in MeOH. Note that for the **4**-catalyzed reactions of aldehydes, 2-PrOH was not a good solvent; the ee of the *anti*-Mannich product of the aldehyde reaction was moderate in 2-PrOH (see Table 7).

The reactions of aldehydes in 2-PrOH may proceed without desired stereocontrolling participation of catalysts in the C−C bond-forming transition state. Enamine formation with ketones

(12) (a) Kobayashi, S.; Kobayashi, J.; Ishiani, H.; Ueno, M. *Chem. Eur. J.* **2002**, *8*, 4185. (b) Hata, S.; Iwasawa, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *Synthesis* **2004**, 1471. (c) Iza, A.; Vicario, J. L.; Carrillo, L.; Badia, D. *Synthesis* **2006**, 4065.

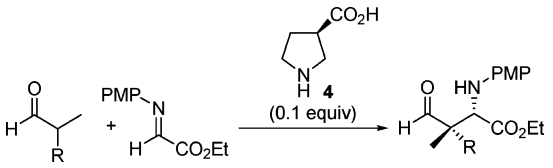
Table 8. *anti*-Mannich-Type Reactions of Aldehydes Catalyzed by **4** and *ent*-**4**[a]



entry	R^1	R^2	catalyst	time (h)	product	yield[b] (%)	dr[c] *anti*/*syn*	ee[d] (%)
1	Me	Et	**4**	4	(2*S*,3*R*)-**17**	75	93:7	96
2	*i*-Pr	Et	**4**	4	(2*S*,3*R*)-**15**	81	99:1	94
3	*i*-Pr	Et	*ent*-**4**	3	(2*R*,3*S*)-**15**	79	99:1	93
4	*n*-Bu	Et	**4**	2	(2*S*,3*R*)-**18**	60	99:1	95
5	*n*-Pent	Et	**4**	3	(2*S*,3*R*)-**19**	80	99:1	>97
6	$CH_2CH{=}CH_2$	Et	**4**	3	(2*S*,3*R*)-**20**	78	99:1	>97
7	$CH_2CH{=}CH(CH_2)_4CH_3$	Et	**4**	3	(2*S*,3*R*)-**21**	83	98:2	99
8	CH_2Ph	Et	**4**	1	(2*S*,3*R*)-**27**	87	96:4	99
9[e]	*t*-Bu	Et	**4**	16	(2*S*,3*R*)-**22**	88	95:5	63
10	*i*-Pr	*i*-Pr	**4**	3	(2*S*,3*R*)-**23**	82	98:2	91
11	*i*-Pr	*i*-Pr	*ent*-**4**	3	(2*R*,3*S*)-**23**	78	98:2	90
12	*i*-Pr	*t*-Bu	**4**	2.5	(2*S*,3*R*)-**25**	82	99:1	94
13	*i*-Pr	$CH_2CH{=}CH_2$	**4**	3	(2*S*,3*R*)-**26**	85	98:2	95

[a] Typical reaction conditions: To a solution of *N*-PMP-protected α-imino ester (0.25 mmol, 1.0 equiv) and aldehyde (0.5 mmol, 2.0 equiv) in anhydrous DMSO (2.5 mL), catalyst **4** or *ent*-**4** (0.0125 mmol, 0.05 equiv, 5 mol % to the imine) was added, and the mixture was stirred at room temperature. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] The dr was determined by ^{1}H NMR or HPLC. [d] The ee of *anti*-product was determined by chiral-phase HPLC analysis. [e] Catalyst **4** (0.1 equiv) and DMSO (0.5 mL) were used.

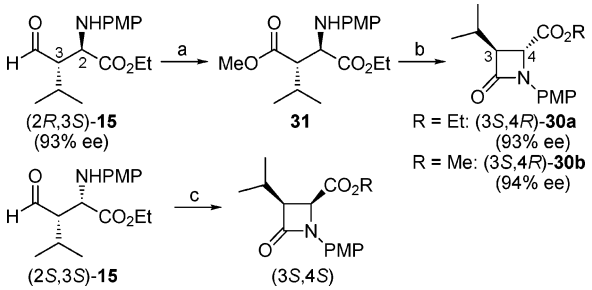
Table 9. Mannich-Type Reactions of α,α-Disubstituted Aldehydes Catalyzed by **4**[a]



entry	R	solvent	time (h)	product	yield[b] (%)	dr[c] *anti*/*syn*	*anti* ee[d] (%)	*syn* ee[d] (%)
1	Ph	2-PrOH	1	**28**	99	36:64	24	37
2	*n*-Pr	2-PrOH	28	**29**	95	37:63	34	9
3	*n*-Pr	DMSO	72	**29**	90	45:55	29	14

[a] To a solution of *N*-PMP-protected α-imino ester (0.25 mmol, 1.0 equiv) and aldehyde (0.5 mmol, 2.0 equiv) in solvent (2.5 mL), catalyst **4** (0.025 mmol, 0.1 equiv, 10 mol % to the imine) was added, and the mixture was stirred at room temperature. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] The dr was determined by ^{1}H NMR. [d] The ee was determined by chiral-phase HPLC analysis.

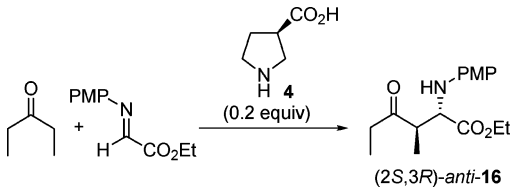
Scheme 5[a]



[a] Conditions: (a) (i) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O; (ii) $TMSCHN_2$; (b) LHMDS; (c) previously reported, see ref 3b,c.

is difficult compared to that with aldehydes and the reactions of ketones do not proceed without proper catalyst participation even in alcohol solvents. As a result, the reactions of ketones occur in 2-PrOH through the transition state that affords the *anti*-Mannich product in a highly stereocontrolled manner. That is, 2-PrOH does not interrupt the proton transfer from the

Table 10. Solvent Effects on the *anti*-Mannich-Type Reaction of 3-Pentanone Using Catalyst **4**[a]



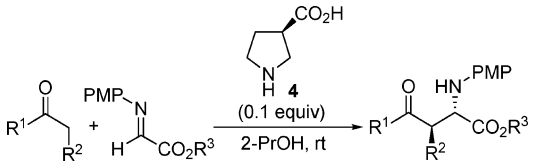
entry	solvent	time	yield[b] (%)	dr[c] anti/syn	ee[d] (%)
1	DMSO	29 h	75	94:6	97
2	DMF	38 h	74	87:13	97
3	NMP	40 h	65	93:7	96
4	$CHCl_3$	3 d	46	95:5	97
5	CH_3CN	3 d	51	97:3	95
6	dioxane	3 d	30	74:26	71
7	THF	3 d	<10	ND	ND
8	EtOAc	3 d	<10	ND	ND
9	2-PrOH	18 h	90	97:3	98
10	EtOH	18 h	91	95:5	92
11	MeOH	32 h	79	96:4	87

[a] Typical reaction conditions: To a solution of *N*-PMP-protected α-imino ester (0.1 mmol, 1.0 equiv) and 3-pentanone (0.4 mL, 3.8 mmol, 38 equiv) in anhydrous solvent (0.6 mL), catalyst **4** (0.02 mmol, 0.2 equiv, 20 mol % to the imine) was added, and the mixture was stirred at room temperature. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] The dr of the isolated product was determined by HPLC analysis. [d] The ee of (2*S*,3*R*)-*anti*-**16** was determined by chiral-phase HPLC analysis.

carboxylic acid of the catalysts to the imine in the C−C bond-forming transition state of the reactions of ketones. 2-PrOH may stabilize the charged transition states of enamine formation of ketones and the transition state of the C−C bond formation of the Mannich-type reactions of ketones, resulting in the faster reaction rate in this solvent than in other non-alcohol solvents tested.

The scope of **4**-catalyzed Mannich-type reactions between a variety of ketones and α-imino esters was examined in the formation of *anti*-products **16** and **32**−**55** (Tables 11−13). In most cases, *anti*-Mannich products were obtained in good yields

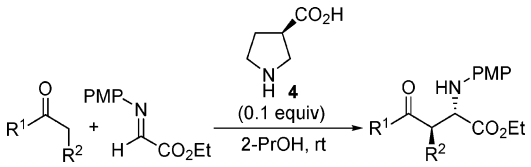
Table 11. *anti*-Mannich-Type Reactions of Acyclic Ketones Catalyzed by **4**[a]



entry	R^1	R^2	R^3	time (h)	product	yield[b] (%)	dr[c] *anti*/*syn*	ee[d] (%)
1	Et	Me	Et	20	**16**	91	97:3	97
2[e]	Et	Me	Et	48	**16**	77	97:3	98
3	Et	Me	*t*-Bu	20	**32**	93	>99:1	95
4	*n*-Pr	Et	Et	96	**33**	76	>99:1	82
5	Me	Me	Et	5	**34**	85[f]	~10:1 (>99:1)[g]	90 (>99)[g]
6[h]	Me	Me	Et	5	*ent*-**34**	81[f]	~10:1 (>99:1)[g]	88 (99)[g]
7	Me	Et	Et	10	**35**	81[f]	~10:1	92
8	Me	$CH_2CH{=}CH_2$	Et	14	**36**	85	>95:5	91
9	Me	$(CH_2)_3Cl$	Et	14	**37**	68	>95:5	84
10	Me	$(CH_2)_2CO_2Et$	Et	24	**38**	80	~9:1	93
11	Me	$(CH_2)_2CN$	Et	24	**39**	78	~9:1	90

[a] Typical conditions: To a solution of imine (0.5 mmol, 1.0 equiv) and ketone (5.0 mmol, 10 equiv) in 2-PrOH (1.0 mL), **4** (0.05 mmol, 0.1 equiv) was added, and the mixture was stirred at 25 °C. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] Determined by ^{1}H NMR of isolated products. [d] Determined by chiral-phase HPLC for the *anti*-product. [e] Ketone (4 equiv), **4** (0.05 equiv), at 4 °C. [f] Containing regioisomer (~5−10%). [g] Data after crystallization are shown in parentheses. The dr was determined by HPLC. [h] Catalyst *ent*-**4** was used.

Table 12. *anti*-Mannich-Type Reactions of α-Functionalized Acyclic Ketones Catalyzed by **4**[a]



entry	R^1	R^2	time (h)	product	yield[b] (%)	dr[c] *anti*/*syn*	ee[d] (%)
1	Me	OMe	3	**40**	78	~5:1	86
2[e,f]	Me	OBn	16	**41**	91	~4:1	90
3	Me	OH	1	**42**	71	~1:1	80 (10)
4[g]	Me	OH	1	**42**	62	~1:1	84 (8)
5[h]	Me	OH	1	**42**	53	~2:1	90 (12)
6[i]	Me	OH	6	**42**	60	~2:1	78 (55)
7[f]	Me	SMe	4	**43**	78	~1:1	48
8[h,j,k]	Et	N_3	24	**44**	58	1.3:1	69 (54)
9[f]	CH_2OBn	OBn	5	**45**	69	1.4:1	45 (9)
10[f,l]	CH_2OH	OH	24	**46**	41	~3:1	8

[a] Typical conditions: To a solution of imine (0.25 mmol, 1.0 equiv) and ketone (0.5 mmol, 2.0 equiv) in 2-PrOH (1.25 mL), **4** (0.025 mmol, 0.1 equiv) was added, and the mixture was stirred at 25 °C. [b] Isolated yield containing *anti*- and *syn*-diastereomers. [c] Determined by ^{1}H NMR of isolated products. [d] Determined by chiral-phase HPLC for the *anti*-product. The ee of *syn*-product is indicated in parenthesis. [e] Catalyst *ent*-**4** was used. [f] 2-PrOH (0.5 mL). [g] Ketone (10 equiv). [h] Reaction at 4 °C. [i] Catalyst **9** was used. [j] Catalyst **4** (0.2 equiv). [k] imine (0.2 mmol), ketone (0.4 mmol), **4** (0.02 mmol), and 2-PrOH (2.0 mL). [l] Ketone (1.0 equiv).

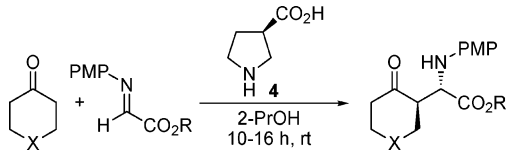
with high diastereo- and enantioselectivities. For the reactions of unsymmetrical methyl alkyl ketones, the reaction occurred predominantly at the more substituted α-position of the ketones (Table 11, entries 5−11). The regio-, diastereo-, and/or enantiomeric purities of the *anti*-products were readily improved by crystallization (Table 11, entries 5, 6; Table 13, entry 3). Catalyst **4** was also useful to catalyze the reactions of ketones bearing functional groups, such as halide, ester, and cyano groups, in their alkyl chains. The **4**-catalyzed reactions of these functionalized ketones afforded desired *anti*-Mannich products without special reaction conditions (Table 11, entries 9−11).

Reactions of α-heteroatom-bearing ketones were also catalyzed by **4** (Table 12). In all cases, C−C bond formation selectively occurred at the carbon bearing the heteroatom. The diastereo- and enantioselectivities of these products varied. Rates of the **4**-catalyzed reactions of these α-heteroatom-bearing ketones were generally faster than those of the **4**-catalyzed reactions of alkylketones and than those of the (*S*)-proline-catalyzed reactions of the same α-heteroatom-bearing ketones. The **4**-catalyzed reactions of methoxyacetone, benzyloxyacetone, and hydroxyactone afforded *anti*-Mannich products as the major products with high enantiomeric excess (entries 1, 2, and 5). The diastereoselectivity of the reaction of hydroxyacetone was poor compared to those of the reactions of alkylketones catalyzed by **4**. Use of DMSO as solvent for the reaction of hydroxyacetone did not improve the result: When the reaction was performed using the imine (1.0 mmol) and hydroxyacetone (10 mmol) in the presence of catalyst **4** (0.2 mmol) in DMSO (2.0 mL) at 25 °C, after 7 h product **42** was obtained in 67% yield (*anti*/*syn* = 1:2, *anti*-**42** 62% ee, *syn*-**42** <5% ee).

To analyze the product formation in the absence of the catalyst, the reactions of Table 12, entry 1 (the reaction of methoxyacetone) and entry 3 (the reaction of hydroxyacetone) were performed under the conditions of this table but in the absence of the catalyst. After 2.5 h, no formation of the Mannich product was detected for either reaction. When a mixture of the imine (0.1 mmol) and hydroxyacetone (0.45 mmol) in 2-PrOH (0.2 mL), which was more concentrated than the reaction in Table 12, entry 3, was stirred at room temperature for 6.5 h, formation of a small amount of Mannich product **42** (~10%, *anti*/*syn* = 1:4) was observed by ^{1}H NMR of the crude mixture. Although the Mannich-type reaction of hydroxyacetone proceeded in 2-PrOH without a catalyst, the reaction rate in the absence of the catalyst was much slower than the rate of the **4**-catalyzed reaction. These results indicate that the stereoselectivities of **40** and **42** obtained in the **4**-catalyzed reactions shown in Table 12 were not affected by the background reaction (product formation without involving the catalyst).

Isomerization of Mannich product **42** in the reaction mixture was not also the reason for the low dr of this product: When a mixture of purified product **42** (0.2 mmol; *anti*/*syn* = 1:2, *anti*-**42** 62% ee, *syn*-**42** <5% ee) and catalyst **4** (0.02 mmol) in 2-PrOH (0.4 mL) was stirred at 25 °C, the dr and ee values of

Table 13. *anti*-Mannich-Type Reactions of Cyclic Ketones Catalyzed by **4**[a]



entry	X	R	catalyst (equiv)	product	yield[b] (%)	dr[c] *anti/syn*	ee[d] (%)
1[e]	CH_2	Et	0.1	**47**	96	>99:1	96
2	CH_2	*i*-Pr	0.05	**48**	94	>99:1	94
3	CH_2	*t*-Bu	0.05	**49**	92	>99:1	95 (99)[f]
4	CH_2	$CH_2CH{=}CH_2$	0.05	**50**	95	>99:1	95
5	S	Et	0.1	**51**	78	>99:1	99
6	S	Et	0.05	**51**	71	>99:1	97
7	O	Et	0.1	**52**	82	>95:5	86
8	$C(OCH_2)_2$	Et	0.1	**53**	87	>99:1	97
9	$C(OCH_2)_2$	Et	0.05	**53**	80	>99:1	96
10	$(CH_2)_2$	Et	0.1	**54**	80	>95:5	84
11	$(CH_2)_3$	Et	0.1	**55**	65	>95:5	18

[a] Typical conditions: Imine (0.5 mmol, 1.0 equiv), ketone (1.0 mmol, 2.0 equiv), **4** (0.05 mmol, 0.1 equiv or 0.025 mmol, 0.05 equiv), 2-PrOH (1.0 mL), 25 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR of isolated products. [d] Determined by chiral-phase HPLC of the *anti*-product. [e] Ketone (5.0 mmol, 10 equiv). [f] Data after crystallization.

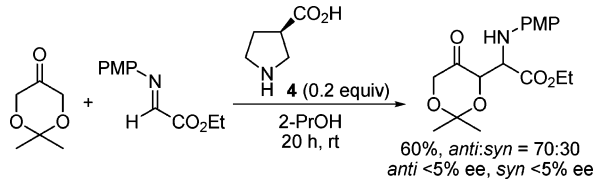
42 were unchanged at 1.5 and 4 h. Decomposition of **42** in this mixture was approximately <2% at 1 h and <5% at 4 h as estimated by ^{1}H NMR of the crude mixtures. The decomposition rate of **42** in the presence of catalyst **4** was similar to that in the absence of the catalyst, and these rates were faster than the decomposition rate of the Mannich product of 3-pentanone, **16**. However, the dr of **42** was not affected by the decomposition for the time range used for the catalyzed reaction. When a mixture of ethyl glyoxylate imine (0.1 mmol), hydroxyacetone (0.2 mmol), and Mannich product **42** (0.1 mmol; *anti*/*syn* = 1:2) in 2-PrOH (0.4 mL) was stirred at 25 °C for 4 h, the imine remained and the dr of **42** was not altered although some decomposed products formed (~10%). These results indicate that Mannich product **42** did not facilitate isomerization of **42** or equilibrium/exchange between **42** and the starting materials and did not act as a catalyst to form **42** for the time range of the **4**-catalyzed reaction.

In the **4**-catalyzed reaction of hydroxyacetone, formation of (*Z*)-enamine intermediate[4c] may be possible, because catalyst **4** does not have α-substituent on the pyrrolidine ring and because the hydroxy group is not a bulky group. Contributions of the (*Z*)-enamine and the (*E*)-enamine and/or contributions of enamine conformations **K** and **J** (Scheme 4) to the C−C bond-forming transition state may cause the low diastereoseoectivity of the **4**-catalyzed reaction of hydroxyacetone.

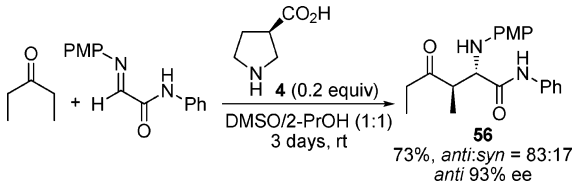
The **4**-catalyzed reactions of (methylthio)acetone, 1-azido-2-butanone, and α,α′-dibenzyloxyacetone also afforded Mannich products, although diastereo- and enantioselectivities were moderate (entries 7−9). For the reaction of dihydroxyacetone, although **4** catalyzed the reaction with much faster rate than proline did, the *anti*-product of the **4**-catalyzed reaction was almost racemic (entry 10). For highly enantioselective *anti*-Mannich-type reactions of α-azide ketones, α,α′-dibenzyloxyacetone, and dihydroxyacetone, we are developing other catalyst systems that will be reported separately.

For the reactions of six-membered cyclic ketones, use of only 5 mol % of catalyst **4** and 2 equiv of ketone to the imine afforded *anti*-Mannich products in good yields with high diastereo- and enantioselectivities within approximately 12 h (Table 13). The reaction of a seven-membered cyclic ketone was also efficiently

Scheme 6



Scheme 7



catalyzed by **4** and afforded *anti*-Mannich product with high diastereoselectivity and good enantioselectivity (entry 10). For the reaction between 2,2-dimethyl-1,3-dioxan-5-one[3k,l] and *N*-PMP-protected α-imino ethyl glyoxylate, however, use of catalyst **4** afforded the Mannich product with moderate diastereoselectivity as almost racemic form (Scheme 6).

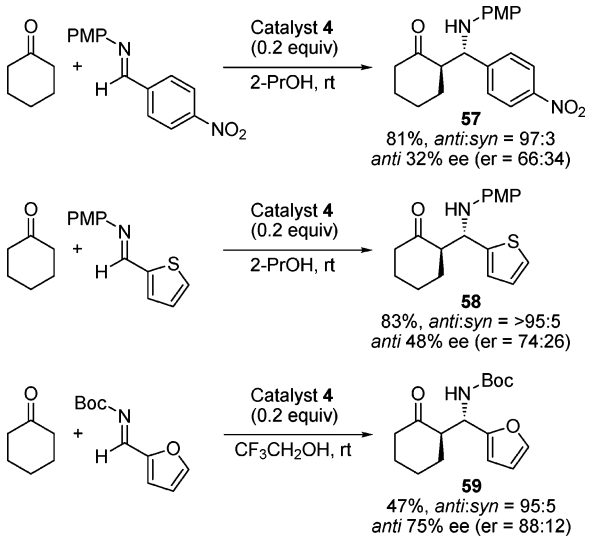
Structural differences in enamine intermediates with catalyst **4** may cause deviation of positioning of reacting carbons of enamine and imine from those of the most stable, desired transition state that affords *anti*-Mannich products as a single enantiomer, resulting in less differentiation of energies between transition states that afford different diastereomers and enantiomers.

Reactions with Imines Other Than α-Imino Esters Catalyzed by 4. As described above, pyrrolidine derivative **4** is useful for catalyzing enantioselective, *anti*-selective Mannich-type reactions between many of enolizable aldehydes or ketones and *N*-PMP-protected α-imino esters. To further explore the applicability of this catalyst, Mannich reactions with imines other than α-imino esters were performed.

As shown in Scheme 7, amino acid **4** efficiently catalyzed the reaction between 3-pentanone and an α-imino amide that was generated from glyoxyamide[13] and *p*-anisidine in situ; *anti*-

(13) Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett.* **2006**, *8*, 2071.

Scheme 8



Mannich product **56** was obtained in 93% ee. Note that when (*S*)-proline was used as catalyst for this reaction, the reaction rate was very slow (<10% after 4 days).

Whereas **4**-catalyzed reactions of α-imino esters generally afforded *anti*-Mannich products with high diastereo- and enantioselectivities, catalyst **4** was less optimal for reactions of imines of arylaldehydes with respect to enantioselectivities as shown in Scheme 8: The *anti*-Mannich products, **57**, **58**, and **59**, were obtained with high diastereoselectivities but ee values were moderate (reaction conditions were not optimized for these reactions). In the previously reported (*S*)-proline-catalyzed reaction, **57** was obtained with *anti*/*syn* = 1:2 (*syn* 84% ee).[3h] The absolute stereochemistry of the major enantiomer of *anti*-**57** generated by the **4**-catalyzed reaction was the same as that of the isomerized (at the carbonyl α-position)[9] product of major enantiomer of *syn*-**57** generated by (*S*)-proline-catalyzed reaction.[3h] This suggested that the configuration of the carbon bearing the amino group of the major enantiomer of *anti*-product **57** generated by the **4**-catalyzed reaction was *S* as shown in Scheme 8 (absolute configuration of *syn*-**57** generated by (*S*)-proline-catalyzed reaction was assumed by analogy). Formation of this major enantiomer is also in accord with transition state shown in Scheme 4b when the ester group is altered to *p*-nitrophenyl group. For imine that did not lead to high stereoselectivities, bond lengths and angles of the imines may differ from those of the glyoxylate imines, which lead to high *anti*-selectivity and enantioselectivity. As a result, transition states other than the most favored one may be involved in the C−C bond-forming step, leading to a mixture of enantiomers.

Conclusion

We have developed enantioselective *anti*-selective Mannich-type reactions of enolizable aldehydes and ketones with imines catalyzed by designed pyrrolidine derivatives bearing acid functional groups at the 3-position of the pyrrolidine.

For reactions between aldehydes and *N*-PMP-protected α-imino esters, catalysts **1** and **4** were efficient catalysts to afford Mannich products with high *anti*-selectivity and enantioselectivity. Catalyst **2** was also an efficient catalyst for the reaction as catalyst **1**. For the **1**- and **4**-catalyzed Mannich reactions of aldehydes, the 3-acid group on pyrrolidine was essential for efficient acceleration of the C−C bond formation and for stereocontrol as it engages proton transfer to the imine nitrogen at the C−C bond-forming step. In the reactions of aldehydes, the 5-methyl group of catalyst **1** cooperatively contributed to the stereodirecting effect of the 3-acid group to provide perfect *anti*-selectivity and enantioselectivity. Catalysis and stereocontrolling function provided by **1** and **4** originated in favored positioning of the nucleophilic carbon of the enamine and the electrophilic carbon of the imine under proton transfer from the 3-acid group of the catalyst to the imine nitrogen.

For reactions between ketones and *N*-PMP-protected α-imino esters or α-imino amide, catalyst **4** was useful to afford Mannich products with high *anti*-selectivity and enantioselectivity. Ketones applicable to the **4**-catalyzed reactions included acyclic and cyclic ketones and functionalized ketones, although *anti*-selectivity and enantioselectivity varied. Catalyst **4** also efficiently catalyzed the reactions of hindered ketones; these reactions are generally difficult with catalysis of pyrrolidine derivatives possessing α-substituents, such as proline.

In the **1**- or **4**-catalyzed reactions of reactants that did not provide products with high stereoselectivities, bond lengths and angles of the enamines and imines may vary from those of the best reactants; causing deviations from the perfect positioning of the reacting carbons. As a result, several transition states may be used in the bond formation, leading reduced selectivities. Importantly, our designed catalysts were useful for the reactions with α-imino esters and amide to provide highly diastereomerically and enantiomerically enriched amino acid derivatives containing two stereocenters.

Catalysts **1** and **4** are the smallest known catalysts for enantioselective *anti*-selective Mannich reactions of enolizable aldehydes and ketones. Compared to other larger catalysts containing binaphthyl groups[5a,d] or metal-coordinating groups,[2a−c,e] our catalyst designs are atom-economical. Our catalysts catalyze enantioselective *anti*-selective Mannich reactions under mild conditions using a low catalyst load. As we have shown here and in previous reports, *anti*- or *syn*-Mannich products can be enantioselectively generated by using catalysts that have an acid group at the 3-position or 2-position on a pyrrolidine ring. Further fine-tuning of the acid group at the 2- or 3-position of pyrrolidine and attachment of substituents at remaining positions of the acid-containing pyrrolidines should provide useful, highly diastereoselective and enantioselective catalysts for other Mannich and Mannich-type reactions and for reactions other than Mannich reactions, such as aldol and Michael reactions. Computational studies concerning Mannich-type reactions catalyzed by the series of pyrrolidine derivatives described here are currently under investigation by the Houk laboratory[4a] and will be reported in due course.

Acknowledgment. This study was supported in part by The Skaggs Institute for Chemical Biology.

Supporting Information Available: Detailed experimental procedures and product characterization, including synthesis of catalysts *ent*-**2**, **3**, and **9**, Mannich-type reactions, and synthesis of β-lactams. This material is available free of charge via the Internet at http://pubs.acs.org.

JA074907+