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3-Pyrrolidinecarboxylic Acid for Direct Catalytic Asymmetric *anti*-Mannich-Type Reactions of Unmodified Ketones

Haile Zhang, Maria Mifsud, 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 April 27, 2006; E-mail: ftanaka@scripps.edu; carlos@scripps.edu

Asymmetric Mannich and Mannich-type reactions are important carbon−carbon bond-forming reactions that provide access to enantiomerically enriched β-amino carbonyl derivatives.[1−8] The most desired versions are direct catalytic reactions that afford the *syn*- or *anti*-products with high diastereo- and enantioselectivities.[1] Methods that use unmodified aldehydes and ketones are more atom-economical than those that require preactivation of carbonyl compounds, such as preformation of silyl enol ethers. For Mannich or Mannich-type reactions involving unmodified aldehydes, both *syn*-[2] and *anti*-selective[3] methods that afford products with high enantioselectivity have been reported; for example, pyrrolidine derivatives and related amines have been used as catalysts.[2,3] For the reactions involving unmodified ketones, methods affording *syn*-Mannich products have been reported,[2b,4] but routes to the *anti*-products with high levels of diastereo- and enantioselectivities are limited to the reactions of α-hydroxyketones using Zn catalysts[1b,5] and the reactions of β-ketoesters using cinchona alkaloids.[6] Other examples of highly enantioselective *anti*-selective Mannich reactions of ketones use silyl enol ethers rather than unmodified ketones.[7] Here we report Mannich-type reactions between unmodified ketones and *N*-*p*-methoxyphenyl (PMP)-protected α-imino esters that afford *anti*-products with high diastereo- and enantioselectivities, using β-proline or 3-pyrrolidinecarboxylic acid (**1**) as catalyst.

We recently designed an *anti*-Mannich catalyst, (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid (**2**), and demonstrated the highly diastereo- and enantioselective *anti*-Mannich-type reactions of aldehydes using this catalyst (Scheme 1a).[3a] We suggested that key for the formation of *anti*-Mannich products is the use of enamine conformation **A** over **B** in the C−C bond-forming transition state.[3a] Catalyst **2**, however, was ineffective in the Mannich-type reactions of ketones. The **2**-catalyzed Mannich-type reaction between 3-pentanone and *N*-PMP-α-imino ethyl glyoxylate was very slow (Table 1, entry 1). Upon consideration of the transition states of the ketone reaction, we reasoned that the low efficiency of catalyst **2** in the ketone reaction originated from relatively slow formation of the enamine intermediates due to steric interaction with the methyl group of the catalyst (Scheme 1b). Note that proline does catalyze the *syn*-Mannich-type reactions of both aldehydes[2a] and ketones[4a−c] (Scheme 1c).

In the case of the Mannich-type reactions of isovaleraldehyde, although both the 3-carboxylic acid and 5-methyl groups of catalyst **2** were critical for excellent *anti*-selectivity and enantioselectivity, the 3-carboxylic acid group alone had a significant role in the stereoselection.[3a] We reasoned that unmethylated catalyst (*R*)-3-pyrrolidinecarboxylic acid ((*R*)-**1**) should afford *anti*-Mannich products in the ketone reactions; although enamine conformations **C** and **D** may have similar free energies, only **C** should advance to the C−C bond formation via transition state **E** (Scheme 1d). When proton transfer occurs from the acid at the 3-position of the catalyst to the imine nitrogen, the nucleophilic carbon of enamine **C** should be properly positioned to react with the imine, whereas the nucleophilic carbon of enamine **D** should be too far from the imine carbon to form a bond. Since **1** does not have an α-substituent on the pyrrolidine, neither enamine **C** nor **D** has a disfavored steric

Scheme 1

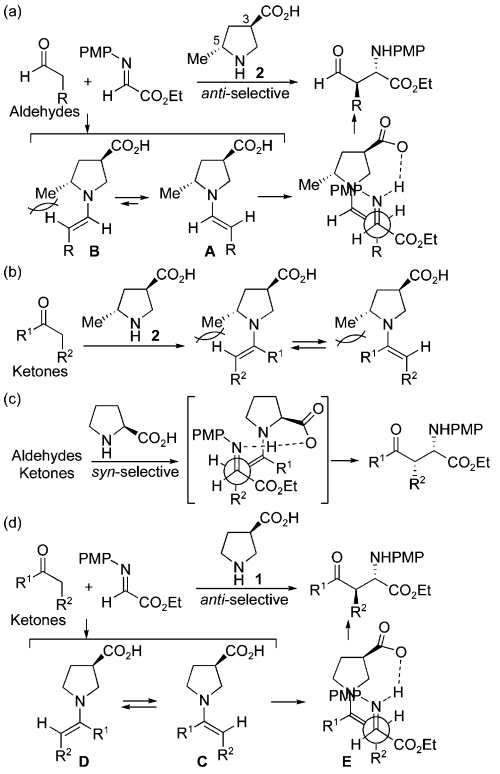
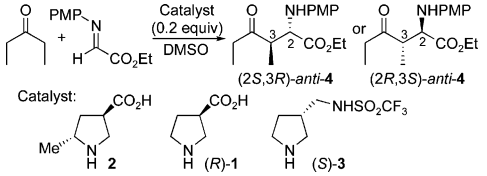


Table 1. Evaluation of Catalysts for the *anti*-Selective Mannich-Type Reaction of 3-Pentanone[a]



entry	catalyst	time	yield[b] (%)	dr[c] *anti*/*syn*	major *anti*-**4**	ee[d] (%)
1	**2**	3 d	<10			
2	(*R*)-**1**	29 h	75	94:6	(2*S*,3*R*)	97
3	(*S*)-**3**	3 d	83	94:6	(2*R*,3*S*)	85

[a] To a solution of *N*-PMP-protected α-imino ester (0.5 mmol, 1 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*-diastereomers). [c] Determined by HPLC before purification. [d] Determined by chiral-phase HPLC for *anti*-**4**.

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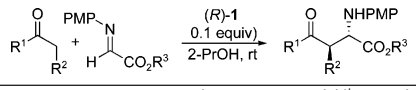
Table 2. (*R*)-**1**-Catalyzed *anti*-Mannich-Type Reactions of Ketones[a]



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

[a] Typical conditions: to a solution of imine (0.5 mmol, 1 equiv) and ketone (5.0 mmol, 10 equiv) in 2-PrOH (1.0 mL), (*R*)-**1** (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 NMR of isolated products. [d] Determined by chiral-phase HPLC for the *anti*-product. [e] Ketone (4 equiv) and (*R*)-**1** (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 (*S*)-**1** was used.

interaction like the one shown in Scheme 1b and enamine formation of ketones with **1** should be faster than that with **2**.

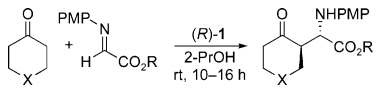
In fact, the (*R*)-**1**-catalyzed reaction was significantly faster than the **2**-catalyzed reaction and afforded the *anti*-Mannich product (2*S*,3*R*)-**4** in good yield with high diastereo- and enantioselectivities (Table 1, entry 2), supporting our design considerations. When the position of the carboxylic acid group on the pyrrolidine ring was changed from the 2- to the 3-position (that is, from proline to catalyst **1**), the stereochemistry of the product of the catalyzed reaction was altered from *syn* to *anti*. Catalyst (*S*)-**3**, which possesses a sulfonamide group, also catalyzed the reaction and afforded the *anti*-product, but the reaction catalyzed by **1** was faster and afforded higher enantioselectivity than the **3**-catalyzed reaction. These results indicate that the acid functionality at the 3-position on the pyrrolidine ring plays an important role in properly positioning the imine, as shown in Scheme 1d, for a faster reaction rate and for affording the *anti*-products with high diastereo- and enantioselectivities.

Evaluation of the (*R*)-**1**-catalyzed reaction to afford (2*S*,3*R*)-*anti*-**4** in various solvents at room temperature showed that the reaction in 2-PrOH provided the highest reaction rate, yield, *anti*-selectivity, and enantioselectivity of the solvents tested (Table 2, entry 1 and Supporting Information).

Amino acid (*R*)-**1** catalyzed Mannich-type reactions between a variety of ketones and α-imino esters and afforded the *anti*-products in good yields with high diastereo- and enantioselectivities in most cases (Tables 2 and 3). For the reactions of unsymmetrical methyl alkyl ketones, the reaction occurred predominantly at the more substituted α-position of the ketones (Table 2, entries 5−9). The regio-, diastereo-, and enantiomeric purities of the *anti*-products were readily improved by crystallization (Table 2, entries 5 and 6 and Table 3, entry 3). For the reactions of six-membered cyclic ketones, use of only 5 mol % of catalyst **1** and 2 equiv of ketone to the imine afforded the desired *anti*-products in good yields within approximately 12 h.

In summary, we have developed the (*R*)-**1**- and (*S*)-**1**-catalyzed *anti*-selective Mannich-type reactions of unmodified ketones that afford high diastereo- and enantioselectivities. We have demonstrated that the position of the acid group on the pyrrolidine ring directs the stereoselection of the catalyzed reaction, providing either *syn*- or *anti*-Mannich products.

Table 3. (*R*)-**1**-Catalyzed *anti*-Mannich-Type Reactions of Cyclic Ketones[a]



entry	X	R	catalyst (equiv)	product	yield[b] (%)	dr[c] *anti*/*syn*	ee[d] (%)
1[e]	CH_2	Et	0.1	**11**	96	>99:1	96
2	CH_2	*i*-Pr	0.05	**12**	94	>99:1	94
3	CH_2	*t*-Bu	0.05	**13**	92	>99:1	95
							(99)[f]
4	CH_2	$CH_2CH{=}CH_2$	0.05	**14**	95	>99:1	95
5	S	Et	0.1	**15**	78	>99:1	99
6	S	Et	0.05	**15**	71	>99:1	97
7	O	Et	0.1	**16**	82	>95:5	86
8	$C(OCH_2)_2$	Et	0.1	**17**	87	>99:1	97
9	$C(OCH_2)_2$	Et	0.05	**17**	80	>99:1	96

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

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Supporting Information Available: Experimental procedures, characterization data, spectral data, and X-ray crystal structures of **7** and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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