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A Highly Enantioselective Amino Acid-Catalyzed Route to Functionalized α-Amino Acids

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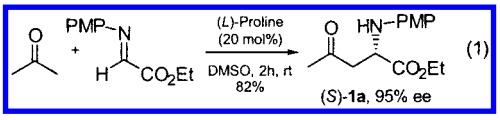
The development of syntheses providing enantiomerically pure α-amino acids has intrigued generations of chemists and been the subject of intense research. This effort has provided a diversity of methodologies,[1] which not only allow for the stereoselective construction of naturally occurring amino acids but also permit the rational design of optically active nonproteinogenic amino acids. These amino acids in particular have enjoyed increased popularity mainly due to their implementation into nonscissile peptide mimics and peptide isosteres.[2]

Several strategically different approaches toward α-amino acids involving a carbon−carbon bond-forming event are conceivable (Scheme 1, paths a−c). A very attractive solution is provided through the addition of cyanide to an imine (Strecker reaction, path a), which affords, upon hydrolysis of the intermediate α-amino nitrile, the corresponding α-amino acid.

While the classical Strecker reaction yields racemic products, a variety of asymmetric versions of this landmark reaction have recently been developed utilizing both stoichiometric and catalytic amounts of chiral sources.[3] Two other very versatile approaches consist of the addition of electrophiles to glycine enolate derivatives (path b),[4] and conversely, of the addition of nucleophiles to electrophilic glycine templates (path c),[5] both of which have been used successfully as a methodology to access unnatural amino acids.

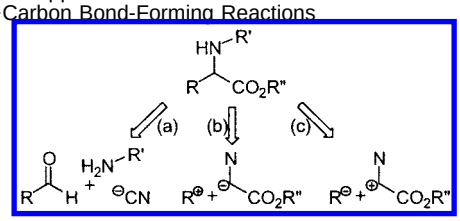
Following path c, we reasoned that, according to our previously established concept of amino acid-catalysis involving enamine intermediates,[6] such an enamine formed between a ketone and proline might serve as nucleophile and add stereoselectively to α-imino esters in a Mannich-type reaction.[7] Herein, we disclose an important extension of amino acid-catalyzed direct Mannich-type reactions using an α-imino glyoxylate as acceptor, which provides novel functionalized α-amino acids with excellent regio-, diastereo-, and enantioselectivities.

In an initial experiment, *N*-PMP-protected α-imino ethyl glyoxylate[8] (0.1 M) and L-proline (20 mol %) were subjected to our previously established standard conditions and stirred in acetone/DMSO (1:4) at room temperature. After 2 h, the imine was consumed and the corresponding α-amino acid **1a** was formed as the only detectable product and isolated in 82% yield and 95% ee (eq 1).



Encouraged by this result, we further explored the scope of this transformation by reaction of various ketones with *N*-PMP-protected α-imino ethyl glyoxylate under the same reaction conditions (Table 1). In all cases, we found that the reactions proceeded smoothly, typically affording only one single product in high yield. For example, the reaction with 2-butanone as donor (Table 1, entry 2) gave rise to α-amino acid **2** in 72% yield with an ee >99%. Significantly, the predominant diastereomer was formed from the regioselective nucleophilic attack of the more substituted α-carbon atom of the ketone. Very similar results were obtained with 3-pentanone, cyclohexanone, and 5-hexen-2-one as donors, affording the corresponding Mannich adducts **3**−**5** with excellent regio-, diastereo-, and enantioselectivities (Table 1, entries 3−5). Although the yield of **3** is lower due to a decreased reaction rate as compared to the other donors studied, it is noteworthy that, for the first time, 3-pentanone was employed successfully in these proline-catalyzed reactions.[9] We also investigated the donor properties of substituted acetone derivatives and found that the reactions of both fluoroacetone and hydroxyacetone furnished the corresponding Mannich products **6** and **7**, respectively, with very high regioselectivity (Table 1, entries 6 and 7). With hydroxyacetone as donor, a single diastereomer was formed with an ee of 99%.[10]

Scheme 1. Approaches to α-Amino Acids Based on Carbon−Carbon Bond-Forming Reactions



In light of these results and the operational simplicity of our reactions, we screened a number of solvents that are environmentally more friendly as well as more suitable for potential industrial applications and were pleased to find that in the reaction with acetone as donor (eq 1), **1a** could be obtained in comparable yields and enantioselectivities in all the solvents studied.[11] Moreover, reducing the amount of proline to 5 mol % or the amount of ketone donor[12] to 2 equiv did not result in any loss of yield and enantioselectivity. This constitutes a significant improvement as compared to the reaction conditions for related aldol and Mannich-type reactions reported previously.[13] The absolute stereochemistry at the newly formed α-stereocenter was determined to be (*S*) by synthesis and comparison to known isopropyl ester **1b** (Table 1, entry 1).[5d] Thus, L-proline catalyzes the synthesis of functionalized L-amino acids. This stereochemical outcome is in accord with our previously proposed transition states.[6e,7d] The Mannich products can be readily further modified (Scheme 2), which includes facile oxidative removal of the PMP group[14] and in situ derivatization as well as the diastereoselective reduction of the keto group yielding lactone **10**. NMR studies of **10** and **11** also confirmed the anticipated *syn*-stereochemistry.[15]

In summary, proline-catalyzed Mannich-type reactions of *N*-PMP-protected α-imino ethyl glyoxylate with a variety of unmodified ketones provide functionalized α-amino acids **1**−**7** in high

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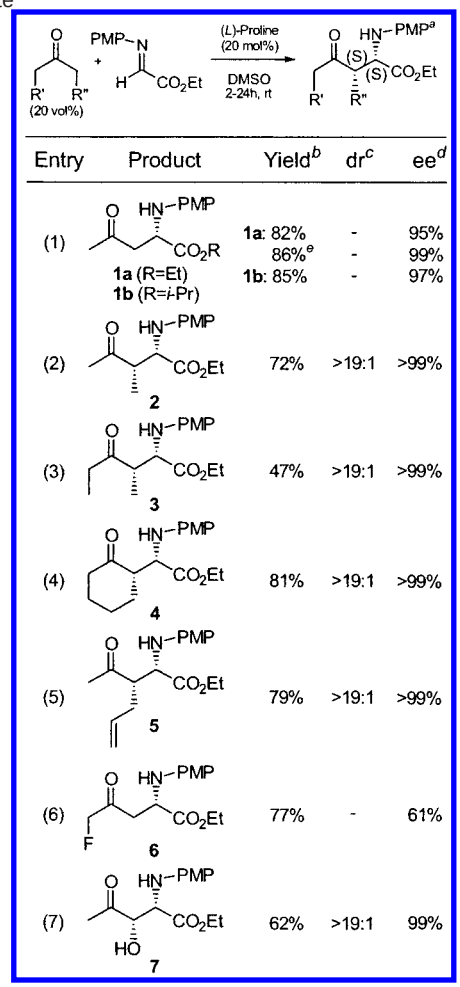
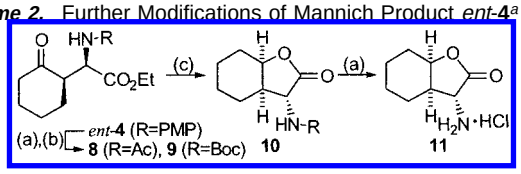
Table 1. Products from the Proline-Catalyzed Mannich-Reaction of Unmodified Ketones with *N*-PMP-Protected α-Imino Ethyl Glyoxylate



Entry	Product	Yield[b]	dr[c]	ee[d]
(1)	**1a** (R=Et) **1b** (R=*i*-Pr)	**1a**: 82% 86%[e] **1b**: 85%	- - -	95% 99% 97%
(2)	**2**	72%	>19:1	>99%
(3)	**3**	47%	>19:1	>99%
(4)	**4**	81%	>19:1	>99%
(5)	**5**	79%	>19:1	>99%
(6)	**6**	77%	-	61%
(7)	**7**	62%	>19:1	99%

[a] PMP = *p*-methoxyphenyl. [b] Isolated yields of pure product after column chromatography. In a typical experiment, *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol) was dissolved in anhydrous DMSO (4 mL), the corresponding ketone donor (1 mL) was added followed by L-proline (20 mol %), and the mixture was stirred for 2−24 h at room temperature. Following aqueous workup with half-saturated ammonium chloride solution and extraction with ethyl acetate, the organic layer was dried ($MgSO_4$), filtered, and concentrated and the residue purified by column chromatography (silica, hexanes/ethyl acetate mixtures) to afford the corresponding Mannich addition product. [c] dr = syn/anti as determined by NMR. [d] The ee values of products **1**−**7** were determined by chiral-phase HPLC analysis. [e] Acetone was used as solvent.

Scheme 2. Further Modifications of Mannich Product *ent*-**4**[a]



[a] Reagents and conditions: (a) $PhI(OAc)_2$, MeOH, 0 °C, 30 min, 1 h; 1 N HCl, 0 °C, 30 min; (b) aqueous Na_2CO_3, Ac_2O (64%), or Boc_2O (68%). (c) L-Selectride, THF, −78 °C, 89%.

yields with excellent regio-, diastereo-, and enantioselectivities. In the case of **2**−**5** and **7**, two adjacent stereogenic centers are created simultaneously upon carbon−carbon bond-formation with complete stereocontrol. Furthermore, the keto-functionality present in these products offers a particularly attractive site for versatile modifications. Our methodology utilizes achiral, readily available, and rather inexpensive starting materials, does not require any preactivation of substrates or metal ion assistance, and can be carried out in environmentally friendly solvents under operationally simple reaction conditions. In the laboratory, these reactions were readily performed on a gram scale. Further studies addressing the scope and applicability are currently under investigation and will be disclosed in a full paper.

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Supporting Information Available: Complete analytical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The imine was preformed and isolated prior to the reaction. For its preparation, see ref 5a. We have also investigated the one-pot three-component Mannich reaction. In this case, however, the reaction does not proceed to completeness and considerable amounts of the corresponding aldol product are formed. PMP = *p*-methoxyphenyl.

(9) This donor gave no products in related aldol reactions. See ref 6b.

(10) Hydroxyacetone also furnished excellent stereoselectivities in related aldol reactions. See ref 6b and the following: Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

(11) Acetone: 86% yield, 99% ee. $CHCl_3$: 84%, 98% ee. EtOAc: 65%, 98% ee. Toluene: 81%, 83% ee. THF: 79%, 97% ee. 1,4-Dioxane: 81%, 98% ee.

(12) For this purpose, the following donors were studied: acetone, hydroxyacetone, cyclohexanone, and 2-butanone.

(13) Only DMSO and $CHCl_3$ provided satisfactory results in related aldol and Mannich-type reactions. See refs 6b,e and 7d. In these cases, 20 mol % catalyst and 20 vol % ketone donor were typically employed.

(14) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410. The dr and ee were not affected by this protocol. Removal of the keto group and ester cleavage of **9** provides access to *(R)*-cyclohexylglycine, which was recently posted on www.InnoCentive.com.

(15) See Supporting Information. Similar *syn*-selectivities in Mannich-type reactions have been reported earlier. See refs 5a and 7b,d.

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