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A Highly Enantioselective Route to Either Enantiomer of Both α- and β-Amino Acid Derivatives

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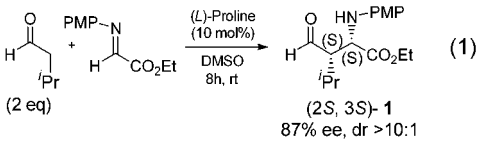
The Mannich reaction is a classic method for the preparation of β-amino ketones and aldehydes and therefore a very important carbon−carbon bond-forming reaction in organic synthesis. The versatility and potential to create both functional and structural diversity using this reaction have long stimulated the creativity of chemists. For example, it has been employed numerous times successfully as a key step in natural product synthesis as well as medicinal chemistry.[1]

The intense demand for stereoselective transformations encompassed in modern drug development has led to a number of asymmetric versions of this type of transformation. The first diastereoselective methods reported employed the addition of preformed enolates to preformed imines using stoichiometric amounts of chiral auxiliaries.[2] Only recently, the first examples of catalytic asymmetric additions of enolates to imines were reported.[3] One disadvantage of these reactions is the preparation and stability of the preformed enolates used. A significant advance was achieved when unmodified ketones were used in these catalytic asymmetric versions rather than preformed enolates to provide chiral β-amino ketones.[4] To date, however, no other unmodified donor has been used in a direct catalytic enantioselective Mannich-type reaction. In this context, the extension to aldehyde donors would be of particular interest,[5] since, in combination with amino acid catalysis, it would provide facile access to either enantiomer of β-amino acids, β-lactams, as well as β-amino alcohol derivatives (Scheme 1).[1b]

On the basis of our previous research,[4a,6] we became interested in whether enamine intermediates formed from aliphatic aldehydes might serve as nucleophiles in a stereoselective, amino acid-catalyzed Mannich-type addition to imines.[7] Herein, we disclose the successful, unprecedented use of unmodified aldehydes in direct catalytic asymmetric Mannich-type reactions with α-imino ethyl glyoxylate as an acceptor to form aldehyde-substituted α-amino acids with excellent diastereo- and enantioselectivities.

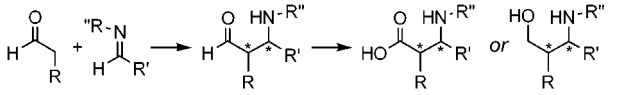
In an initial experiment, isovaleraldehyde (0.2 M), *N*-PMP-protected α-imino ethyl glyoxylate[8] (0.1 M), and L-proline (10 mol %) were stirred in DMSO at room temperature. After 8 h the imine was consumed and the only detectable product was the β-formyl functionalized leucine derivative **1**, which could be isolated in 80% yield, with dr > 10:1 and 87% ee (eq 1).



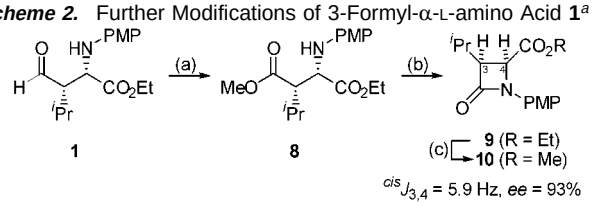
(1)

Next, we performed a solvent screen under the same reaction conditions and were pleased to find that the yields, diastereoselectivities, and enantioselectivities of **1** were comparable in all the solvents investigated, with dioxane providing the highest ee of **1** (ee = 93%).[9]

Scheme 1. Synthesis of β-Amino Carbonyl Compounds and Derivatives Based on Mannich Reactions of Aldehydes with Imines



Scheme 2. Further Modifications of 3-Formyl-α-L-amino Acid **1**[a]



[a] Reagents and Conditions: (a) i: $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O; ii: CH_2N_2, Et_2O, 89% two steps; (b) LHMDS, THF, −20 °C, 96%; (c) i: LiOH, Dioxane/H_2O; ii: CH_2N_2, Et_2O, 92% two steps.

To broaden the scope of this transformation, a number of aliphatic aldehydes were reacted with *N*-PMP-protected α-imino ethyl glyoxylate[10] under these reaction conditions to afford β-formyl functionalized amino acids **1**−**7** (Table 1). In all cases, the reaction proceeded smoothly with excellent enantioselectivities. Higher diastereoselectivities were achieved with increased bulkiness of the substituents on the aldehyde donor in the order of R = Me < Et < *i*-Pr < *n*-Pent. Significantly, in the case of aldehydes with a chain length longer than five carbon atoms (entries 4−7, Table 1), one diastereomer was formed predominantly (dr > 19:1) as determined by ^{1}H NMR.[11] This result constitutes an excellent entry into sterically demanding amino acid derivatives. For example, α-amino acid **6** was obtained as a single product with complete stereocontrol in 89% yield. It is noteworthy that these reactions proceed efficiently with only 1.5 equiv of aldehyde donor. For example, **1** could be obtained in gram quantities from a single reaction. Furthermore, the catalyst loading could be reduced to as low as 5% without diminishing the efficiency of the catalytic process. This is a significant improvement over our previous reports of ketones as donors in Mannich reactions[4a] and aldehydes as donors in Michael-type reactions.[7a]

These Mannich products are versatile synthons for other synthetically valuable building blocks. For example, the aldehyde group of the Mannich product **1** can be readily oxidized ($NaClO_2$) and subsequently esterified (CH_2N_2) to afford the aspartic acid derivative **8** without loss of the ee and dr (Scheme 2).

Base-promoted cyclization[12] of amino acid **8** by means of LHMDS provided the carbapenem antibiotic PS-6 precursor **9**[13] in excellent yield. ^{1}H NMR analysis of **9** and **10** revealed a cis relationship of the vicinal methine protons at C-3 and C-4 based on their vicinal coupling constant $^3J_{3,4} \approx 5.9$ Hz.[13] The absolute stereochemistry of **9** was determined to be (3*S*,4*S*) based on synthesis and comparison to the known α-alkyl-β-lactam **10**[14] via an efficient hydrolysis/esterification protocol. Thus, L-proline

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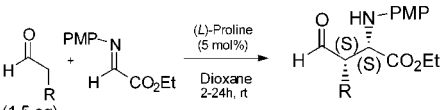
Table 1. Products from the Proline-Catalyzed Mannich Reaction of Unmodified Aldehydes with *N*-PMP-Protected α-Imino Ethyl Glyoxylate



Entry	R	Yield[b]	dr[c]	ee[d]	Product
(1)	*i*-Pr	81%	>10:1 (19:1)[e]	93%	**1**
(2)	Me	72%	1.1:1 (3:1)[e]	99%	**2**
(3)	Et	57%	1.5:1 (7:1)[e]	99%	**3**
(4)	*n*-Bu	81%	3:1 (>19:1)[e]	99%	**4**
(5)	*n*-Pent	81%	>19:1 (>19:1)[e]	>99%	**5**
(6)		89%	>19:1 (>19:1)[e]	99%	**6**
(7)		71%	>19:1 (>19:1)[e]	>99%	**7**

[a] PMP = *p*-methoxyphenyl. [b] Yields of isolated pure product after column chromatography. In a typical experiment, *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol) was dissolved in anhydrous dioxane (V_{tot} = 5 mL), the corresponding aldehyde donor (0.75 mmol) was added followed by L-proline (5 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 after column chromatography. [d] The ee values of products **1**−**7** were determined by chiral-phase HPLC analysis. [e] dr = syn/anti as determined by NMR of the crude product after extraction.

catalyzes a *si*-facial attack to the imine by an aldehyde enamine intermediate and provides L-amino acids with syn stereochemistry. This result is in accordance with the previously proposed transition states for proline-catalyzed Mannich reactions with ketones.[4a,d]

In conclusion, for the first time unmodified aldehydes were successfully used as donors in catalytic asymmetric Mannich-type reactions. We showed that the proline-catalyzed reaction of *N*-PMP-protected α-imino ethyl glyoxylate with aldehydes provides a highly enantioselective entry to functional amino acids, β-lactam antibiotics,[15] and serine protease inhibitors[16] and the corresponding products **1**−**7** were obtained in high yields and excellent diastereoselectivities. In addition, the number of different functionalities present in the products allows for a large variety of further chemical modifications. As demonstrated for derivatives **8**−**10**, our products can be efficiently converted into pharmaceutically valuable synthons. Moreover, our methodology is atom-economic, starts with achiral, readily available and inexpensive materials, and provides a facile route to either enantiomer of both α-amino acid and β-amino acid derivatives with high stereocontrol. Further research addressing the scope and applicability of this methodology is currently under investigation.

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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.

References

(1) For review, see: (a) Kleinmann, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Flemming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (c) Kobayashi, S.; Ishitani, H.; *Chem. Rev.* **1999**, *99*, 1069. (d) Denmark, S.; Nicaise, O. J.-C. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamomoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, 93. (d) For examples, see: *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Weinheim, 1997.

(2) See: (a) Palomo, C.; Oiarbide, M.; Gonzales-Rego, M. C.; Sharma, A. K.; Garcia, J. M.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1063. (b) Enders, D.; Ward, D.; Adam, J.; Raabe G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 981. (d) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *39*, 5287. (e) Seebach, D.; Betschart, C.; Schiess, M. *Helv. Chim. Acta* **1984**, *67*, 1593. Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (f) Arend, M.; Risch, N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2639. (g) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. *Tetrahedron* **1985**, *42*, 1693.

(3) (a) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180. (c) Ishihara, K.; Miyata, M.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 10520. (d) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 2060. (e) Ferraris, D.; Yong, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. (f) 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. (g) Kobayashi, S.; Matsubara, R.; Kitagawa, H. *Org. Lett.* **2002**, *4*, 143.

(4) (a) Notz, W.; Sakthivel, K.; Bui, T.; Zhong, G.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 199. (b) Juhl, K.; Gathergood, N.; Jorgensen, K. A. *Angew Chem., Int. Ed.* **2001**, *40*, 2995. (c) Yamasaki, S.; Iida, T.; Shibasaki, M. *Tetrahedron* **1999**, *55*, 8857. (d) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (e) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, ASAP.

(5) There have been reports of noncatalytic diastereoselective Mannich-type reactions of enamines derived from aldehydes with ternary iminium salts. See: (a) ref 1b. (b) Risch, N. Arend, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2422.

(6) (a) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III *J. Am. Chem. Soc.* **2001**, *123*, 5260. (c) Bui, T.; Barbas, C. F., III *Tetrahedron Lett.* **2000**, *41*, 6951. (d) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 4441.

(7) Such enamines were used successfully in Michael reactions and the self-aldolization of acetaldehyde. See: (a) Betancort, J. M.; Barbas, C. F., III *Org. Lett.* **2001**, *3*, 3737. (b) Córdova, A.; Notz, W.; Barbas, C. F., III *J. Org. Chem.* **2002**, *67*, 301.

(8) The imine was prepared according to Juhl et al. See ref 4b.

(9) EtOAc: 75% yield, *dr* > 10:1, 88% *ee*; Dioxane: 81% yield, *dr* > 10:1, 93% *ee*; $CHCl_3$: 62% yield, *dr* > 10:1, 74% *ee*; THF: 79% yield, *dr* > 10:1, 88% *ee*; Ether: 70% yield, *dr* > 10:1, 80% *ee*. The reactions were also performed at 4 °C in THF (75% yield, *dr* > 10:1 *dr*, 92% *ee*) and dioxane (82% yield, *dr* > 10:1, 96% *ee*).

(10) *n*-PMP aldimines preformed from benzaldehyde or *p*-nitrobenzaldehyde did not afford the Mannich products under these conditions.

(11) ^{1}H NMR of the crude reaction mixture showed a diastereomeric ratio of >19:1 and complete conversion of the imine. We observed that the Mannich products are unstable if stored at room temperature and prone to epimerization during silica gel column chromatography, which decreases the diastereomeric ratio and provides the other diastereoisomer in excellent *ee* (>98%). The Mannich products can be stored in solution (EtOAc) at −25 °C without decomposition, epimerization and loss of *ee*.

(12) (a) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331. (b) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227.

(13) (a) Manhas, M. S.; Ghosh, M.; Bose, A. K. *J. Org. Chem.* **1990**, *55*, 575. (b) Greff, Z.; Horvath, Z.; Nyitrai, J.; Kajtar-Peredy, M.; Brlik, J. *J. Chem. Research* **1990**, *S*, 170. (c) Greff, Z.; Horvath, Z.; Nyitrai, J.; Kajtar-Peredy, M.; Brlik, J. *J. Chem. Research* **1990**, *M*, 1201.

(14) Palomo, C.; Aizpurua, J. M.; Gracenea, J. J.; Garcia-Granada, S.; Pertierra, P. *Eur. J. Org. Chem.* **1998**, *2201*, 1. $[\alpha]_D = -95$ (c = 0.5, CH_2Cl_2); lit. $[\alpha]_D = -108.7$ (c = 1.0, CH_2Cl_2).

(15) (a) Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; Vol. 1, p 565. (b) Kant, J.; Walker, D. G. In *The Organic Chemistry of β-Lactams*; Page, M. I., Ed.; VCH: New York, 1993; p 121.

(16) (a) Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Dahlgren, M. E. *Tetrahedron* **1990**, *46*, 2255. (b) Magriotis, P. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4377. (c) Edwards, P. D.; Bernstein, P. R. *Med. Res. Rev.* **1994**, *14*, 127. (d) Mascaretti, O. A.; Boschetti, C. E.; Danelon, G. O.; Mata, E. G.; Roveri, O. A. *Current Med. Chem.* **1995**, *1*, 441.

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