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The Direct Organocatalytic Asymmetric Mannich Reaction: Unmodified Aldehydes as Nucleophiles

Wolfgang Notz, Fujie Tanaka, Shin-ichi Watanabe, Naidu S. Chowdari, James M. Turner, Rajeswari Thayumanavan, 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

carlos@scripps.edu

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The unprecedented application of unmodified aldehydes as nucleophilic donors in direct catalytic asymmetric Mannich-type reactions is disclosed in a full account. Our efforts in broadening the applicability of chiral pyrrolidine-based catalysts in direct asymmetric Mannich-type reactions led to the highly diastereo- and enantioselective and concise synthesis of functionalized α- and β-amino acids, β-lactams, and amino alcohols.

Introduction

In 1912, Carl Mannich disclosed his systematic studies of the three-component reaction between an enolizable CH-acidic substrate, an amine component, and an aldehyde to form a β-amino carbonyl compound.[1] It is generally assumed that, in a preequilibrium, the aldehyde and the amine form an imine (or an iminium salt thereof), which is subsequently attacked by the nucleophilic enol tautomer of the CH-acidic component. In this reaction, the proper choice of reaction conditions as well as reaction partners is key to successfully effect an aminoalkylation in a selective manner. Not only are the aldehyde and CH-acidic substrate both capable of forming the reactive iminium ion and serving as nucleophiles at the same time, but subsequent eliminations or competitive aldol reactions might diminish the efficiency of the reaction. To overcome these intricate problems of selectivity that could impose severe limitations on an otherwise powerful transformation, enormous efforts have been directed toward the development of new methodologies and variants, which today allow for the deliberate steering of this reaction toward a uniform product formation. These approaches include the use of preformed electrophiles (imines, hydrazones, iminium salts), nucleophiles (enolates, enol ethers, enamines), or both, and in many cases a catalyst is involved.[2] Hence, it became possible to assign a defined role to each reactant in the reaction mixture and the formation of byproducts can consequently be minimized.

Two key features render the Mannich-reaction and its products very attractive: (a) the reaction tolerates a large diversity of reactants[3] and (b) the β-amino carbonyl products are valuable synthons for natural product synthesis[4] and can be readily converted to derivatives that possess useful applications in paint and polymer chemistry, plant protection, and particularly medicine and the pharmaceutical industry. In light of this wide applicability, it is surprising that, unlike the parent aldol reaction, modern asymmetric Mannich-type reactions have emerged only in the past few years. These variants typically involve the addition of preformed enolate equivalents to preformed imines, and both stoichiometric[5] and catalytic[6] amounts of chiral controller have been employed.

Originally founded in the area of catalytic antibodies designed to operate with imine and enamine reaction mechanisms,[7] research in our laboratories has recently focused on translating these concepts to small molecule catalysis. These efforts have led to the development of amine-catalyzed direct asymmetric aldol,[8] Michael,[9] Diels−Alder,[10] and Mannich-type reactions.[11,12] The common feature of these reactions is the use of unmodified nucleophilic donors,[13] which, upon activation by intermediate enamine formation, add stereoselectively to the corresponding acceptors under very mild conditions.

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(3) Ammonia and primary and secondary aliphatic as well as aromatic amines can be used, and the active hydrogen component may be a ketone, ester, nitrile, nitro compound, an α-alkyl pyridine, hydrogen cyanide, or a thiol, as well as an electron-rich heterocyclic or aromatic systems.

(4) Mannich reactions have been involved in the key steps of natural product syntheses. Illustrative examples include the following: (a) Robinson's landmark synthesis of tropinone; see: Robinson, R. *J. Chem. Soc.* **1917**, *111*, 762. (b) Corey's synthesis of porantherine; see: Corey, E. J.; Balanson, R. D. *J. Am. Chem. Soc.* **1974**, *96*, 6516. (c) Overman's synthesis of strychnine; see: Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293.

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Herein, we disclose a full account of our efforts in the synthesis of functionalized α- and *β*-amino acids, *β*-lactams, and amino alcohols using unmodified aldehydes as nucleophilic donors and chiral pyrrolidine-based catalysts in the direct asymmetric catalytic Mannich-type reaction.

Results and Discussion

In recent years, optically active nonproteinogenic amino acids have gained increased importance mainly due to their implementation into peptide mimics and isosteres, their utility as versatile chiral synthetic intermediates, and due to the interest of pharmaceutical, agrochemical, and food industries in these compounds.[14] We deemed our proline-catalyzed Mannich-type reactions a suitable strategy to accomplish a stereoselective entry

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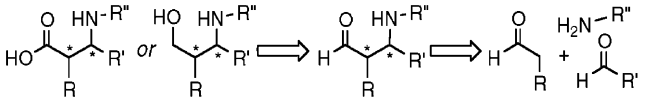
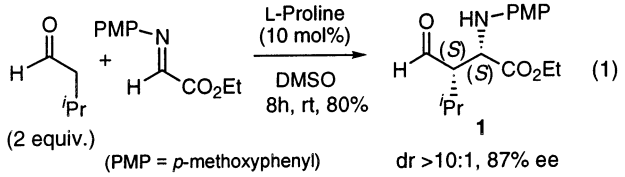
SCHEME 1. Retrosynthetic Analysis of β-Amino Carbonyl Compounds Based on Mannich Reactions of Unmodified Aldehydes with Imines



to both functionalized α- and β-amino acids and their derivatives.[15,16] As outlined in Scheme 1, the use of aldehydes as nucleophilic donors[17,18] offers a particularly attractive entry to functionalized β-amino acids and their derivatives including β-lactams and amino alcohols. Moreover, not only does this strategy involve the creation of two contiguous stereocenters upon carbon−carbon bond formation but it also provides for ready structural and functional diversity.

On the basis of our previous research results concerning the addition of ketones to α-imino ethyl glyoxylate[11b] affording functionalized α-amino acids with excellent diastereo- and enantioselectivities, the extension of this approach to aldehyde donors presented itself as a significant objective. 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. To evaluate this possibility, a mixture of isovaleraldehyde (2 equiv), L-proline (10 mol %), and *N*-PMP-protected α-imino ethyl glyoxylate (0.1 M) was stirred in DMSO at room temperature. We observed the formation of a single product, which could be isolated in 80% yield after 8 h and characterized as the β-formyl-substituted leucine derivative **1**. *This constitutes the first example of an unmodified aldehyde being successfully used in a catalytic asymmetric Mannich-type reaction*. Most significantly, **1** was isolated as the predominant diastereomer (dr > 10:1) with an ee of 87% (eq 1).[19]



(1)

We then performed an extensive screen of structurally diverse amine catalysts (Table 1). Although some of them have proven very useful in our earlier studies,[9,10a] in the reaction of heptanal with *N*-PMP-protected α-imino ethyl glyoxylate, only proline, hydroxyproline, and its *tert*-butyl ether derivative exhibited catalytic activity that affords the desired Mannich product in acceptable yield and very high stereoselectivities (entries 1−5). These results suggest that hydroxyproline should be suitable for immobilization through the hydroxy functionality for studies aimed at the construction of continuous-flow reaction systems or to aid in catalyst recovery and recycling. Compared to proline, amine catalysts with other substitution patterns of the ring system, catalysts containing additional heteroatoms in the ring system, and catalysts lacking the carboxylate functionality all compromised the chemical yield or stereoselectivity of the reaction, in many cases both.

A solvent survey, using isovaleraldehyde as donor, revealed the suitability of many commonly used solvents (Table 2) with 1,4-dioxane providing the best results in terms of yield (81%) and stereoselectivities (dr > 10:1, 93% ee). Interestingly, the ionic liquid [bmim]BF_4 is also a suitable solvent for this reaction, providing the desired Mannich product, albeit with diminished diastereoselectivity, with excellent enantiomeric excess at a significantly accelerated reaction rate. Moreover, using 1,4-dioxane as solvent, we established that the use of 1.5 equiv of isovaleraldehyde and 5 mol % of proline is sufficient to afford the desired Mannich product **1** in a very clean reaction, which almost completely suppressed the competing self-aldolization of the aldehyde donor.

Given the significance of aqueous reaction conditions in process chemistry, we next investigated the influence of water on the Mannich reaction of preformed α-imino ethyl glyoxylate with linear aldehydes. To our surprise,

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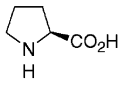
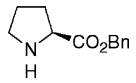
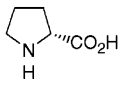
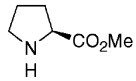
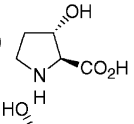
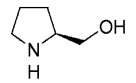
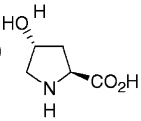
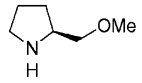
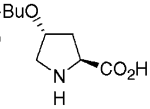
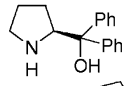
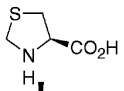
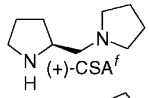
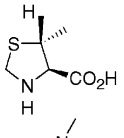
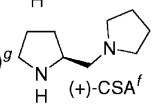
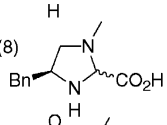
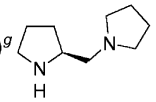
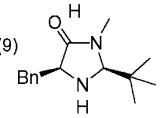
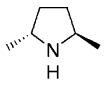
(16) For α-amino acids, several strategically different approaches are conceivable. Asymmetric Strecker reaction: (a) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (b) Davis, F. A.; Kee, S.; Zhang, H.; Fanelli, D. L. *J. Org. Chem.* **2000**, *65*, 8704. (c) Kunz, H. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Houben-Weyl: Stuttgart, Germany; 1995; Vol. E21b, p 1931. For an account comprising the important work on catalytic versions by Corey, Hoveyda, Jacobsen, Kobayashi, Lipton, and Shibasaki, see: (d) Yet, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 875. (e) Nogami, H.; Kanai, M.; Shibasaki, M *Tetrahedron Lett.* **2001**, *42*, 279. Addition of electrophiles to glycine enolate derivatives: (f) Seebach, D.; Hoffmann, M. *Eur. J. Org. Chem.* **1998**, *1337*, 7. (g) Aoyagi, Y.; Jain, R. P.; Williams, R. M. *J. Am. Chem. Soc.* **2001**, *123*, 3472 and references therein. (h) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085. (i) Schöllkopf, U. In *Topics in Current Chemistry*; Boschke, F. L., Ed.; Springer-Verlag: Berlin, Germany, 1983; Vol. 109, pp 45−85. Addition of nucleophiles to electrophilic glycine templates: (j) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5943. (k) O'Donnell, M. J.; Delgado, F.; Drew, M. D.; Pottorf, R. S.; Zhou, C.; Scott, W. L. *Tetrahedron Lett.* **1999**, *40*, 5831 and references cited therein. (l) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (m) Thompson, K. A.; Hall, D. G. *Chem. Commun.* **2000**, *23*, 2379. (n) Kobayashi, S.; Kitagawa, H.; Matsubara, R. *J. Comb. Chem.* **2001**, *3*, 401. See also refs 6m and 13a,b,d. For the use of imino glyoxylates in catalytic *aza*-Diels−Alder reactions, see: (o) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. For β-amino acid synthesis, see ref 5k and the following examples of alternative catalytic asymmetric synthesis of β-amino acid derivatives: (p) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperese, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615. (q) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (r) Nelson, S.; Spencer, K. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 1323. (s) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197. (t) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578.

(17) Noncatalytic diastereoselective Mannich-type reactions of enamines derived from aldehydes have been reported earlier. See: Risch, N.; Arend, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2422.

(18) Originally, only ketones were used successfully as donors in our proline-catalyzed aldol and Mannich-type reactions. See ref 8d. Recently, for the first time, we also used aldehydes successfully as donors in amine-catalyzed asymmetric Michael-type, aldol, and here Mannich-type reactions. See refs 9b, 8d, and 11c. Following these reports, several other groups described the successful use of unmodified aldehydes as nucleophiles. See: (a) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620. (b) Bøgevig, A.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790. (c) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (d) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798.

(19) For a preliminary account of these results, see ref 11c.

TABLE 1. Catalyst Screen for the Mannich-Type Reaction of Heptanal with α-Imino Ethyl Glyoxylate[a]

Entry	Catalyst	Time	Yield[b]	dr[c] syn:anti	ee (%)[c] syn(anti)	Entry	Catalyst	Time	Yield[b]	dr[c] syn:anti	ee (%)[c] syn(anti)
(1)		3h	88%	32:1	>99(31)	(10)		4h	<5%	1:1	53(35)
(2)		4h	73%	19:1	>99[d](6)	(11)		4h	<5%	1.4:1	47(1)
(3)		4h	69%	32:1	99(98)	(12)		18h	<5%	1:1.5	60(41)
(4)		26h	85%	32:1	99(20)	(13)[e]		22h	40%	<1:10	-- (76)
(5)		4h	91%	32:1	>99(76)	(14)		32h	<5%	1:3.3	2(21)
(6)		24h	12%	3.5:1	73(42)	(15)		2h	14%	2.8:1	57(32)
(7)		18h	78%	19:1	62(18)	(16)[g]		3h	17%	1:1.2	35(15)
(8)		22h	56%	1.7:1	64[d](4)	(17)[g]		6h	<5%	--	--
(9)		4h	<5%	1.3:1	11(27)	(18)		32h	<5%	2:1	35(21)

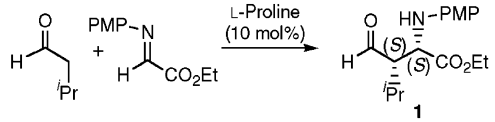
[a] PMP = *p*-methoxyphenyl. A mixture of heptanal (0.375 mmol), imine (0.25 mmol), and catalyst (0.05 mmol, 20 mol %) was stirred in DMSO (2.5 mL) at room temperature unless noted otherwise. [b] Isolated yield. [c] For entries 1−5, the dr and ee values were determined by chiral-phase HPLC of the extracted reaction mixture. For entries 6−18, these values were determined by chiral-phase HPLC of purified products. The major enantiomer for the syn product possessed (*S*,*S*)-configuration unless noted otherwise. [d] The major enantiomer for the syn product possessed (*R*,*R*)-configuration. [e] See ref 24. [f] (+)-CSA = (1*S*)-(+)-10-camphorsulfonic acid. [g] Reaction performed in THF.

and in sharp contrast to the related aldol reaction,[8a] we found that the reaction with *n*-heptanal as donor tolerated substantial amounts of water in the reaction mixture without eroding the enantioselectivity (Table 3). Whereas the presence of water did, however, affect the chemical yield of this reaction, the syn diastereoselectivity was not compromised and remained very high for all entries, typically being >19:1.[20]

Thus, anhydrous dioxane was selected as solvent of choice, and using these conditions a set of aldehydes was reacted with *N*-PMP-protected α-imino ethyl glyoxylate (Table 4). In all cases, the desired Mannich products were formed with excellent enantioselectivities. The diastereoselectivities obtained are dependent on the chain length as well as the bulkiness of the substituents of the aldehyde donors. Typically, aldehydes with a chain length longer than five carbon atoms afforded products, e.g. **5**−**9**, with excellent diastereoselectivities of dr > 19:1 (Table 4, entries 5−9), and higher diastereoselectivities were achieved with increased chain length in the order of R = Me < Et < *i*-Pr < *n*-Pent. Under these conditions, the sterically more demanding 3,3-dimethylbutyraldehyde did not undergo reaction to form the corresponding Mannich product. Similar observations were made, if acceptors other than preformed α-imino glyoxylates were employed under these conditions. For example, *N*-PMP aldimines preformed from benzaldehyde or *p*-nitrobenzaldehyde did not afford Mannich products in reactions with unmodified aldehydes as donors. However, we

(20) The application of aqueous reaction media allowed for the development of a novel one-pot Mannich/indium-promoted allylation tandem reaction affording γ-lactones, thus providing novel α-amino-γ-lactones with three contiguous stereocenters. See: Córdova, A.; Barbas, C. F., III *Tetrahedron Lett.* **2003**, *44*, 1923. For a complete study of the organocatalytic Mannich reaction in ionic liquids see: Chowdari, N. S.; Ramachary, D. B.; Barbas, C. F., III *Synlett* **2003**, 1906.

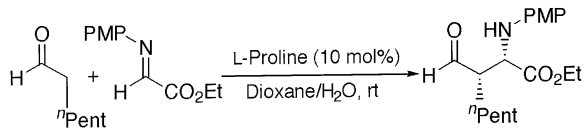
TABLE 2. Solvent Screen for the Mannich-Type Reaction of Isovaleraldehyde with α-Imino Ethyl Glyoxylate



solvent	yield (%) of **1**	ee (%) of **1**[a]
DMSO	81	87
Et_2O	70	80
$CHCl_3$	62	74
EtOAc	75	88
THF	79	88
	75	92[b]
dioxane	81	93
	82	96[b]
[bmim]BF_4	90	93

[a] dr >10:1 for all solvents, except for [bmim]BF_4 (dr = 5:1). [b] Reaction performed at 4 °C.

TABLE 3. Effect of Water on the Mannich-Type Reaction of *n*-Heptanal with α-Imino Ethyl Glyoxylate[a]



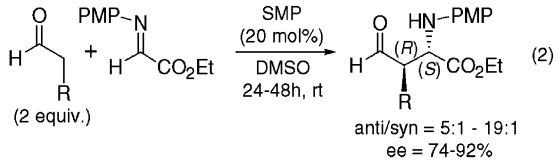
entry	dioxane:H_2O	yield[b] (%)	ee[c] (%)
1	100:0	>82	>99
2	99:1	>70	>99
3	98:2	>75	>99
4	95:5	>59	>99
5	90:10	>60	>99
6	85:15	>52	>99
7	80:20	44	>99

[a] PMP = *p*-methoxyphenyl. A mixture of *n*-heptanal (0.75 mmol), α-imino ethyl glyoxylate (0.5 mmol), and l-proline (0.05 mmol) was stirred in the indicated dioxane−H_2O mixture (5 mL) at room temperature for 16−24 h. [b] Isolated yield after column chromatography. [c] The ee of *syn*-**5** was determined by chiral-phase HPLC.

established different reaction conditions that allowed for this reaction to succeed (vide infra). An interesting example is provided by (*S*)-citronellal adduct **7** (Table 4, entry 7), which was formed with complete stereocontrol. When the (*R*)-enantiomer of citronellal was used, again only a single diastereomer was obtained. Thus, the absolute stereochemistry of the two newly formed stereogenic centers seems to be controlled by the catalyst proline to a very high degree independent of another chiral center present in the donor.

Whereas the reaction of propionaldehyde and butyraldehyde provided almost equal amounts of diastereomers (Table 4, entries 2 and 3) after their chromatographic isolation, we found that, in the cases of **1**−**4** (Table 4, entries 1−4), the diastereomeric ratio is significantly higher if determined directly after aqueous workup rather than after column chromatography. This indicates that compounds **1**−**4** are prone to epimerization during workup and purification on silica gel, which in turn provided the anti diastereomer in excellent ee values as observed for **1** (ee > 98%).[21,22]

The development of methodologies that provide for the direct and deliberate synthesis of all possible stereoisomers is an important task in asymmetric catalysis and is still required for direct Mannich-type reactions. For example, our proline-catalyzed asymmetric Mannich-type reactions with unmodified ketones and aldehydes have been limited in that, upon carbon−carbon bond formation, two new stereocenters could only be created with high syn diastereoselectivity without the option of providing for the corresponding β-amino carbonyl compounds with similarly high anti diastereoselectivity in a direct manner.[11,12] To address this issue, we reinvestigated a number of chiral pyrrolidine derivatives that have proven superior to proline in our earlier studies concerning organocatalysis with amines.[8a,b,e,9] In particular, we focused on pyrrolidine derivatives lacking the stereodirecting carboxylate functionality of proline and recently found that the commercially available (*S*)-2-methoxymethylpyrrolidine (SMP)[23] effected the desired transformation best.[24,25] When using DMSO as a solvent and 2 equiv of linear or branched aliphatic aldehyde, SMP catalysis afforded the corresponding β-formyl-functionalized amino acid derivatives with high anti diastereoselectivities (typically dr > 10:1, in many cases dr >19:1) and the enantiomeric excesses ranging from ee 74% to 92% (eq 2).



The absolute and relative configuration of the products obtained by SMP catalysis was established by careful imidazole-promoted anti → syn isomerization[26] of the anti products produced by SMP and its enantiomer RMP, respectively. Thus, SMP catalysis provides functionalized α-L-amino acid derivatives with anti stereochemistry.[24]

To date, only preformed α-imino ethyl glyoxylate was used as acceptor in our direct Mannich-type reactions employing unmodified aliphatic aldehydes as donors, which constituted a significant limitation of the generality of the reaction. It would be desirable to extend the scope of this reaction to other preformed imines as electrophiles and, as depicted in Scheme 1, eventually apply them under a more general and efficient one-pot three-component protocol. However, these transformations are very difficult to control, mainly due to the challenge of assigning a specific role to each reaction

(21) Whereas these products and the Mannich products described herein in general epimerize and racemize, respectively, when stored neatly at room temperature, they can be stored at −25 °C in solution (EtOAc) without decomposition, epimerization, and loss of ee.

(22) Typically, the syn/anti isomers are an inseparable mixture by preparative column chromatography. However, both the syn and anti isomers could be resolved by analytical HPLC.

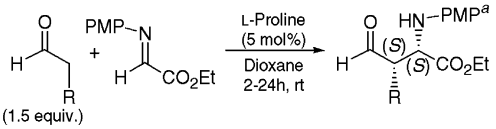
(23) This proline-derived amine was developed by Enders et al. as a chiral auxiliary and is commercially available in both enantiomeric forms. For an excellent review of its use in asymmetric synthesis, see: Enders, D.; Klatt, E. *Synthesis* **2001**, 1403.

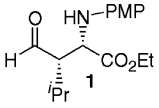
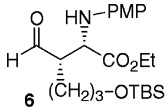
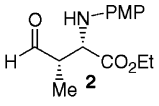
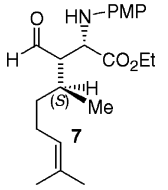
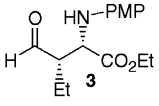
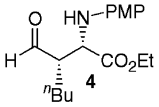
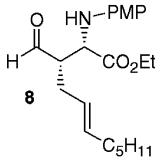
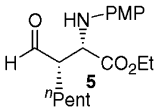
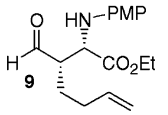
(24) Córdova, A.; Barbas, C. F., III *Tetrahedron Lett.* **2002**, *43*, 7749.

(25) SMP has been reported earlier to be an effective chiral auxiliary in Mannich-type reactions involving preformed SMP-enamines derived from ketones. See ref 5v. In these studies, SMP also directed the predominant formation of the anti diastereomer.

(26) Ward, D. E.; Sales, M.; Sasmal, P. K. *Org. Lett.* **2001**, *3*, 3671.

TABLE 4. Unmodified Aldehydes as Donors in the Synthesis of β-Formyl-Substituted α-Amino Acid Derivatives

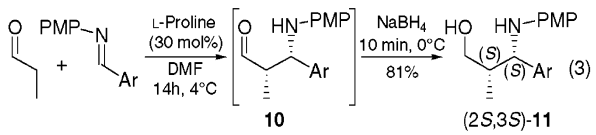


Entry	Product	Yield[b]	dr[c]	ee[d]	Entry	Product	Yield[b]	dr[c]	ee[d]
(1)	 **1**	81%	10:1 (19:1)[e]	93%	(6)	 **6**	81%	1.5:1	91%[f]
(2)	 **2**	72%	1.1:1 (3:1)[e]	99%	(7)	 **7**	42% 45%[g]	>19:1 >19:1[g]	- -
(3)	 **3**	57%	1.5:1 (7:1)[e]	99%					
(4)	 **4**	81%	3:1 (>19:1)[e]	99%	(8)	 **8**	89%	>19:1 (>19:1)[e]	99%
(5)	 **5**	81%	>19:1 (>19:1)[e]	>99%	(9)	 **9**	71%	>19:1 (>19:1)[e]	>99%

[a] PMP = *p*-methoxyphenyl. [b] Yields of isolated pure product after column chromatography. [c] dr = syn/anti as determined by NMR after column chromatography. [d] The ee values were determined by chiral-phase HPLC analysis. [e] dr = syn/anti as determined by NMR of the crude product after extractive workup. [f] Enantiomers could not be resolved completely by HPLC. [g] Results for (*R*)-citronellal as donor.

partner to avoid the formation of undesired side products, particularly those arising from aldol-type side reactions. Moreover, there is no report of a catalytic asymmetric three-component Mannich reaction with unmodified aldehydes as donors.[27] We therefore embarked on the search for a catalytic asymmetric one-pot three-component Mannich process that would involve aldehydes for both nucleophile and electrophile generation. Unlike traditional mixed Mannich-type reactions involving ketone nucleophiles and aldehyde-derived electrophiles, the exclusive use of aldehydes as both nucleophiles and electrophilic constituents in this reaction poses additional and significant obstacles.

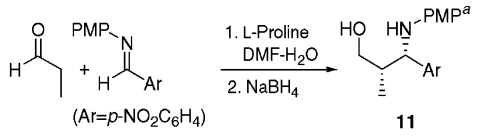
To minimize potential side reactions, we initially focused on Mannich-type reactions with preformed imines. In this context, aromatic imines are especially attractive since they are readily accessible and furthermore provide for a novel route for the synthesis of β-amino alcohol and acid derivatives that are used as chiral synthons for enzyme inhibitors and cancer drugs.[5k] We chose propionaldehyde as an aldehyde donor, *N*-(*p*-nitrobenzylidene)-*p*-anisidine as the preformed imine component, and L-proline (30 mol %) as the catalyst. In initial experiments, we varied the concentration of the imine (0.1−0.5 M) as well as the amount of propionaldehyde used (2−10 equiv) and found that lower concentration and fewer equivalents of propionaldehyde provided better yields of the desired Mannich product and less self-aldol product of propionaldehyde. We found that, to obtain the corresponding Mannich adduct **10** in a clean reaction, it was crucial that the propionaldehyde be added very slowly to the reaction mixture. Similar observations were made by others in related aldol reactions.[18d] The best results were obtained when performing the reaction in DMF at 4 °C[28] and adding the propionaldehyde (2 equiv) as a cold (4 °C) 1 M solution in DMF over 14 h via syringe pump addition. These conditions afforded the highest conversion and, upon in situ $NaBH_4$ reduction[29] of Mannich product **10**, provided β-amino alcohol **11** predominantly as one diastereomer in 81% yield and 99% ee (eq 3).



As in the case of the reaction of *n*-heptanal with *N*-PMP-protected α-imino ethyl glyoxylate (Table 3), we again assessed the impact of the presence of water on the reaction profile of the Mannich-type reaction of

(27) Following submission of this paper concerning one-pot three-component Mannich reactions involving aldehydes, Hayashi et al. reported similar results also obtained with proline catalysis: Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677.

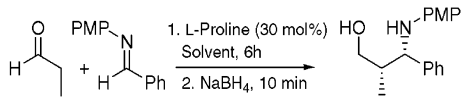
TABLE 5. Effect of Water on the Mannich-Type Reaction of Propionaldehyde with Preformed Aromatic Aldimines



entry	DMF:H_2O	yield[b] (%)	ee[c] (%)
1	100:0	>92	>97
2[d]	100:0	>85	>99
3	99:1	>92	>99
4	98:2	>88	>97
5	95:5	>96	>99
6	90:10	>90	>99
7	85:15	73	>97
8	80:20	75	97

[a] PMP = *p*-methoxyphenyl. For this reaction, a solution of propionaldehyde (2.5 mmol) in the indicated DMF−H_2O mixture (2 mL) was slowly added to a mixture of imine (0.5 mmol) and L-proline (0.15 mmol) in the indicated DMF−H_2O mixture (3 mL) over 5 h at 0 °C and the mixture was stirred for 1 h at the same temperature. [b] Isolated yield after column chromatography. [c] The ee of *syn*-**11** was determined by chiral-phase HPLC. [d] The reaction mixture was stirred at 4 °C for 18 h after slow addition of propionaldehyde.

TABLE 6. Temperature Effect on the Mannich-Type Reaction with Preformed Aldimines

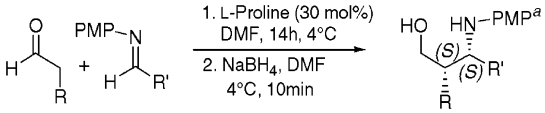


entry	solvent	temp (°C)	yield (%)	dr	ee (%)
1	DMF	4	65	4:1	93
2	DMF	−15	58	4:1	94
3	DMF/MeOH (95:5)	4	72	3:1	51
4	DMF/H_2O(95:5)	4	75	12:1	84
5	DMF/H_2O(95:5)	−15	94	>19:1	87

aldehydes with preformed aromatic aldimines (Table 5) and found that also this reaction tolerates significant amounts of water present in the reaction mixture without compromising the excellent enantiomeric excess obtained for Mannich product **11**. Furthermore, under all conditions the formation of the corresponding syn diastereomer was favored, with dr typically being >8:1. As can be inferred from entries 7 and 8, the presence of higher amounts of water does, however, have a detrimental effect on the chemical yield presumably due to partial hydrolysis of the imine.

We then probed the effect of the reaction temperature in an attempt to further optimize this reaction (Table 6). Thus, we performed the Mannich reaction of propionaldehyde with benzaldehyde-derived aldimine at lower temperatures in DMF as well as in the presence of a cosolvent. Whereas in DMF as solvent lowering the temperature to −15 °C exhibited no marked improvement compared to 4 °C (Table 6, entries 1 and 2), in the presence of water at −15 °C (entry 5), both the yield and diastereoselectivity of the reaction were increased significantly, while the ee was slightly diminished. The addition of methanol as cosolvent proved unsuccessful in improving the reaction results, affording the corresponding Mannich product in both diminished diastereoselectivity and enantiomeric excess (entry 3).

TABLE 7. Direct Asymmetric Proline-Catalyzed Mannich-Type Reactions of Unmodified Aldehydes with Preformed Aromatic Imines



entry	R	R′	product	yield[b] (%)	dr[c]	ee[d] (%)
1	Me	*p*-$NO_2C_6H_4$	**11**	81	>10:1	99
2	Me	*p*-CNC_6H_4	**12**	72	7:1	98
3	Me	*p*-BrC_6H_4	**13**	57	6:1	95
4	Me	*p*-ClC_6H_4	**14**	81	>10:1	93
5	Me	Ph	**15**	65	4:1	93
6	Me	*m*-BrC_6H_4	**16**	89	3:1	96
7	Pent	*p*-$NO_2C_6H_4$	**17**	60	>19:1	90

[a] PMP = *p*-methoxyphenyl. [b] Isolated yields of pure product after column chromatography. [c] dr = syn/anti as determined by NMR after column chromatography. [d] The ee values of products **11**−**17** were determined by chiral-phase HPLC analysis.

To broaden the scope of this transformation, a set of different *p*-anisidine-derived aromatic imines were reacted with propionaldehyde to afford aromatic β-amino alcohol derivatives **11**−**17** (Table 7). In all cases, the reaction proceeded in a clean manner affording amino alcohols **11**−**17** with very high enantioselectivities (ee 93−99%).[30] As in the cases of α-imino ethyl glyoxylate as acceptor, an increase of the diastereoselectivity was again observed with increasing chain length of the aliphatic aldehyde. For example, *n*-heptanal as a donor reacted smoothly with *N*-(*p*-nitrobenzylidene)-*p*-anisidine providing the corresponding amino alcohol **17** (Table 7, entry 7) in 60% yield with excellent diastereoselectivity of dr > 19:1 and enantioselectivity of 90% ee.

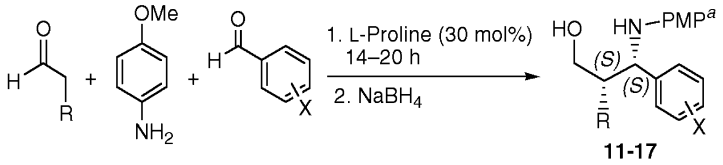
At this point, we were confident of succeeding in the development of a one-pot three-component protocol for the challenging task of directing the role of the aldehyde components. We were delighted to find that, as in the case of preformed imines, slow addition of propionaldehyde as 1 M solution in DMF to a mixture of *p*-anisidine (0.1 M), *p*-nitrobenzaldehyde (0.1 M), and L-proline (30 mol %) in DMF at 4 °C afforded, after in situ $NaBH_4$ reduction, β-amino alcohol **11** in 85% yield, >99% ee, and in a diastereomeric ratio of dr > 10:1 (Table 8, entry 1). Similar results were obtained when applying this protocol to other substituted aromatic aldehydes, which led to the formation of β-amino alcohol derivatives **12**−**17** with excellent enantioselectivities of 93−98% ee (Table 8, entries 2−6). In the case of the more reactive *p*-nitrobenzaldehyde, reduced amounts of propionaldehyde (2

(28) The reaction also proceeded well in other solvents. Dioxane (at 23 °C): 65% yield; dr > 10:1; 99% ee. THF (at 23 °C): 51% yield; dr > 10:1; 99% ee. Ether (at 23 °C): 40% yield; dr > 10:1; 99% ee. THF (at 4 °C): 36% yield; dr > 10:1; >99% ee. Dioxane (at 4 °C): 62% yield; dr > 10:1; 99% ee.

(29) We observed that Mannich product **15** was configurationally unstable if stored at room temperature or subjected to silica gel column chromatography. We therefore decided to reduce the aldehyde functionality of **15** with excess $NaBH_4$ prior to isolation and determination of ee.

(30) These reactions can be readily performed on a 10 mmol scale with no detrimental effect on yield or enantioselectivity as demonstrated for amino alcohol **16**.

TABLE 8. Direct One-Pot Three-Component Asymmetric Proline-Catalyzed Mannich-Type Reactions



11-17

				4 °C in DMF			-20 °C in DMF			-20 °C in DMF−H_2O (95:5)		
entry	R	X	product	yield[b] (%)	dr[c]	ee[c] (%)	yield[b] (%)	dr[c]	ee[c] (%)	yield[b] (%)	dr[c]	ee[c] (%)
1	Me	*p*-NO_2	**11**	85	>10:1	>99	87	65:1	98	90	25:1	99
2	Me	*p*-CN	**12**	65	5:1	93	83	65:1	99	79	21:1	97
3	Me	*p*-Br	**13**	81	10:1	91	77	16:1	89	80	29:1	93
4	Me	*p*-Cl	**14**	65	6:1	93	92	12:1	84	88	6:1	76
5	Me	H	**15**	65	4:1	93	82	4:1	94	89	24:1	88
6	Me	*m*-Br	**16**	77	4:1	97	86	11:1	90[d]	83	17:1	87
7	*n*-Pent	*p*-NO_2	**17**	73[e]	4:1[e]	75[d,e]	87	138:1	>99	85	11:1	>99

[a] PMP = *p*-methoxyphenyl. [b] Isolated yields of pure product after column chromatography. [c] The dr and ee values were determined by chiral-phase HPLC of the extracted mixture unless noted otherwise; dr = syn/anti. [d] The ee value was determined by chiral-phase HPLC after column chromatography. [e] The reaction was performed at 4 °C for 7 h.

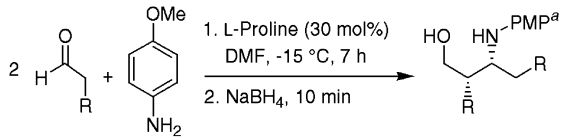
equiv) and L-proline (10 mol %) were sufficient to afford **11** in similar yield and stereoselectivities (80%, dr 12:1, 99% ee). When performed at lower temperatures and with water as a cosolvent, respectively, in the cases of electron-deficient aromatic systems an increase in diastereoselectivity and enantiomeric excess can be observed (Table 8, entries 1, 2, and 7), whereas in the cases of halogen-substituted aromatic systems the results are inconclusive.[31] We sought to extend these reactions to the SMP-catalyzed Mannich-type reaction. Application of conditions at Table 7, entry 1 to the same reaction except with the use of SMP as the catalyst produced a slow reaction and the yield of product **11** was very low after 24 h (<5%). When the same reaction was performed in DMF/H_2O (95:5) for 24 h, the yield was significantly improved (68%); however, the dr was 1:1 and the ee of the products was low (syn and anti were 11% and 39% ee, respectively).

It is important to note that these reactions typically proceeded with minimal formation of cross-aldol products or self-Mannich adducts being observed. However, when adding a DMF solution of propionaldehyde (5 equiv) to a solution of *p*-anisidine (1 equiv) and proline (20 mol %) in DMF in the absence of any other aldehyde, proline did catalyze the direct asymmetric self-Mannich reaction with propionaldehyde both as donor and acceptor component, which furnished self-Mannich adduct **18** in 85% yield with dr 4:1 and 82% ee (Table 9, entry 1). In a similar fashion, self-Mannich products **19**−**22** were obtained when hexanal, decanal, 4-pentenal, and isovaleraldehyde were used as the only aldehyde component present in the reaction mixture (Table 9, entries 2−5).

On the other hand, the addition of propionaldehyde to a solution of *p*-anisidine (1 equiv), proline (20 mol %),

(31) It is noteworthy that in some cases the ee as well as the syn/anti ratios are to some extent dependent on the workup procedure applied and workup times. For example, we found that, prior to the $NaBH_4$ reduction, in some cases extraction and drying of the organic phase ($MgSO_4$) resulted in improved syn/anti ratios and enantiomeric excesses compared to a direct one-pot reduction protocol. Furthermore, we showed that the Mannich products bearing an aldehyde functionality are slightly prone to epimerization, thus diminishing the syn/anti ratio. This might explain some of the lower selectivities observed (e.g. Table 8, entries 4 and 6).

TABLE 9. Formation of Self-Mannich Products



entry	R	product	yield[b]	syn:anti[c]	ee[d] (%)
1	Me	**18**	85	4:1	82
2	*n*-Bu	**19**	51	5:1	85
3	*n*-Octyl	**20**	90	4:1	81
4	allyl	**21**	92	5:1	87
5	*i*-Pr	**22**	64	2:1	18

[a] PMP = *p*-methoxyphenyl. [b] Isolated yields of pure product after column chromatography. [c] Determined by NMR after column chromatography. [d] Determined by chiral-phase HPLC analysis.

and isovaleraldehyde in DMF resulted in a complex reaction mixture consisting of cross-aldol and self-aldol products together with a number of unidentified side-products. If the sterically more hindered cyclohexanecarboxaldehyde is chosen as a potential aldimine component instead of isovaleraldehyde, again only self-Mannich adduct **18** is formed. These results clearly demonstrate that, using aliphatic aldehydes as nucleophiles, the careful choice of reaction partners as well as reaction conditions is key to a successful one-pot three-component Mannich reaction. Although the yields were slightly decreased in this three-component protocol as compared to the reactions with preformed imines, the diastereo- and enantioselectivities were not significantly affected. Regardless of the protocol applied, the absolute stereochemical outcome of the reaction was identical. The absolute stereochemistry of the products **11**−**22** was assigned to be (2*S*,3*S*) on the basis of NMR analysis and chiral-phase HPLC analysis of *β*-amino alcohol **15**. This product obtained by L-proline catalysis had the same retention time as known (2*S*,3*S*)-**15** synthesized independently earlier via known procedures.[32a,b] Furthermore, the NMR data of the major diastereomer of PMP-deprotected **15** were identical with those of the previously reported syn diastereomer.[32c] This stereochemical outcome is in full accord with the preceding results originating from L-proline catalysis and is explained best

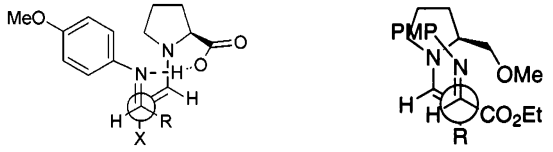
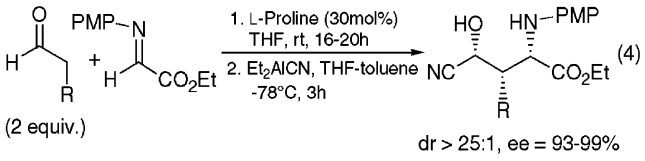


FIGURE 1. (Left) Chairlike Transition State for the proline-catalyzed direct asymmetric Mannich reaction. (Right) Possible transition state for the SMP-catalyzed direct asymmetric Mannich reaction.

invoking previously reported chairlike six-membered transition states (Figure 1, left) with L-proline directing a nucleophilic *si*-facial attack of the imine by the *si*-face of an assumed aldehyde derived enamine intermediate.[11a,33]

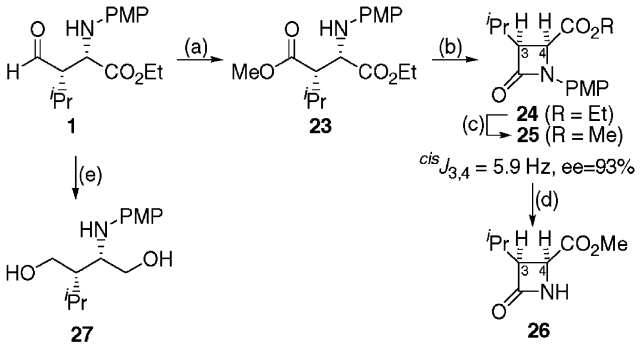
Lacking the stereodirecting carboxylate of proline, the topicity of the transition state for the SMP-catalyzed reaction is altered (Figure 1, right). The *si*-face of the imine is selectively attacked by the *re*-face of the enamine drawing the ethereal oxygen closer to the imine nitrogen, which if protonated, may provide for a favorable Coulombic interaction.[34] This attractive force could compensate for potential steric interactions between the pyrrolidine group of SMP and the PMP protecting group of the imine.

Common to all the Mannich products described above is the aldehyde functionality, which offers an attractive and versatile reaction site for further transformations. For example, we have recently demonstrated that Mannich products **1**−**9** (Table 4) from the reaction of unmodified linear and branched aliphatic aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate can be further transformed by subsequent treatment with Et_2AlCN in toluene/THF mixtures at low temperatures. This provided *β*-cyanohydroxymethyl α-amino acid derivatives with three contiguous stereogenic centers in a one-pot fashion and in a highly diastereo- and enantioselective manner (eq 4).[35]



The aldehyde functionality present in the α-amino acids derived from aldehyde donors (Table 4) can be further oxidized providing a straightforward entry to functionalized aspartic acids. As demonstrated for **1**, the aldehyde group was readily oxidized ($NaClO_2$) and subsequently esterified (CH_2N_2) to afford the aspartic acid derivative **23** without loss of the ee and dr (Scheme 2).

SCHEME 2. Synthesis of Aspartic Acid Derivatives and *β*-Lactams[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% (2 steps). (b) LHMDS, THF, −20 °C, 96%. (c) (i) LiOH, dioxane/H_2O; (ii) CH_2N_2, Et_2O, 92% (2 steps). (d) CAN, MeCN/H_2O, 0 °C, 87%. (e) $LiAlH_4$, THF, 0 °C, 88%.

Most importantly, however, base-promoted cyclization[36] of **23** by means of LHMDS furnished the known carbapenem antibiotic PS-6 precursor **24**[37] in excellent yield. ^{1}H NMR analysis of **24** and **25** confirmed the 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.[37] As shown for Mannich product **1**, the absolute stereochemistry was determined to be (3*S*,4*S*) on the basis of correlation by synthesis of known α-alkyl-*β*-lactam **25**[38] via oxidation and an efficient hydrolysis/esterification protocol and comparison to the data reported (Scheme 2). The absolute stereochemistry of products **2**−**9** was assigned accordingly based on the unique stereodirection during this reaction. Thus, our methodology of proline catalysis provides an alternative mild, facile, and stereoselective route to functionalized *β*-lactams with syn stereochemistry with L-proline catalyzing the formation of L-amino acids.

As in the cases reported previously, the *N*-PMP group in *β*-lactam **25** could be removed oxidatively. This was easily accomplished by treatment of **25** with CAN in MeCN/H_2O at 0 °C, which afforded **26**[39] in 87% yield. Alternatively, as exemplified for **1**, both the aldehyde and the ester functionality can be simultaneously reduced. Treatment of **1** with $LiAlH_4$ afforded diol **27** in 88% yield (Scheme 2). Such 3-alkyl-substituted-2-aminobutane-1,4-diols are ideal starting materials for the synthesis of chiral pyrrolidines, which, for example, have been employed as versatile and useful intermediates for the synthesis of antibacterial quinolinecarboxylic acids as medical bactericides.[40]

Unnatural amino acids that contain carbonyl groups have been shown to be useful as distinctively reactive

(32) (a) Vicario, J. L.; Badía, D.; Carrillo, L. *J. Org. Chem.* **2001**, *66*, 9030. (b)Vicario, J. L.; Badía, D.; Carrillo, L. *Org. Lett.* **2001**, *3*, 773. (c) Jaeger, V.; Buss, V.; Schwab, W. *Liebigs Ann. Chem.* **1980**, 122. HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 99:1, flow rate 1.0 mL/min, λ = 254 nm): t_R = 14.02 min.

(33) Very recently, calculations confirmed this stereochemical outcome. See: Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249.

(34) Electrostatic interactions have been observed in noncatalytic asymmetric Mannich-type reactions with preformed SMP enamines. See ref 2a and: Vinkovic, V.; Sunjic, V. *Tetrahedron* **1997**, *53*, 689.

(35) Watanabe, S.; Córdova, A.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2002**, *4*, 4519.

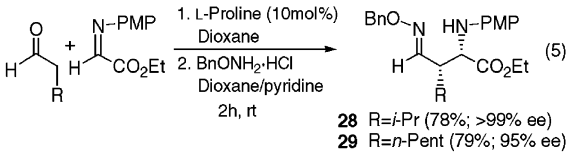
(36) (a) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331. (b) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227.

(37) (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. Res.* **1990**, *S*, 170. (c) Greff, Z.; Horvath, Z.; Nyitrai, J.; Kajtar-Peredy, M.; Brlik, J. *J. Chem. Res.* **1990**, *M*, 1201.

(38) 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)}.

(39) Palomo, C.; Aizpurua, J. M.; Ontoria, J. M.; Iturburu, M. *Tetrahedron Lett.* **1992**, *33*, 4823.

handles that provide for the facile modification of proteins and peptides.[41] As such they are key synthons in their own right and provide for facile diversification. For example, we found that the carbonyl group of these aldehyde donor derived amino acids is readily converted to the corresponding oxime under mild conditions without epimerization. Thus, in the reaction with isovaleraldehyde or heptanal as donor, *O*-benzylhydroxylamine hydrochloride and pyridine were added directly to the reaction mixture after complete consumption of the imino glyoxylate. Within 2 h, the formation of oxime **28** and **29**, respectively, as the only stereoisomer was complete (eq 5).



Oximes of this type were recently integrated into glycopeptide analogues containing unnatural sugar−peptide linkages.[42] Thus, reaction of these aldehyde-containing amino acids with a variety of hydroxylamines can provide for the synthesis of a diverse family of D- or L-amino acids with oxime-containing side chains. These oxime-containing amino acids can now be considered as building blocks in combinatorial syntheses.

Conclusion

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, and serine protease inhibitors.[43] The corresponding products were obtained in high yields and excellent syn diastereoselectivities. Notably, by switching to (*S*)-2-methoxymethylpyrrolidine (SMP) as catalyst, we accomplished the highly diastereoselective synthesis of the corresponding anti diastereomers in a direct manner. Thus, all four possible stereoisomers of functionalized α- and β-amino acids are now accessible with very high stereocontrol from achiral, readily available, and inexpensive starting materials and catalysts. Moreover, our methodology does not require separate preactivation of substrates nor Lewis-acidic heavy metals and can be performed on a multigram scale under operationally simple conditions. Most significantly, however, we developed a one-pot three-component protocol, which applies aliphatic aldehydes as nucleophilic donors and affords the corresponding Mannich products in a highly enantioselective manner with good syn diastereoselectivity and exceptional chemoselectivity. We demonstrated that an individual fine-tuning of the reaction parameters for a given combination of reactants allows for the optimization of yield and stereoselectivities. The number of different functionalities present in these Mannich products allows for a large variety of further chemical modifications. In particular, we exploited the presence of the aldehyde functionality and developed two novel asymmetric one-pot tandem reactions. The Mannich hydrocyanation reaction afforded β-cyanohydroxymethyl α-amino acid derivatives with three contiguous stereocenters as single diastereomers. Additionally, simple reaction of β-formyl-substituted-α-amino acid esters with substituted hydroxylamines can provide for the rapid generation of large families of oxime-containing amino acids, a testament to the versatility of the aldehyde functionality common to our Mannich products.

Considering the number of consecutive mechanistic events required for the one-pot, three-component Mannich reaction to occur without preactivation of components, the small amino acid proline possesses the remarkable ability to catalyze an in situ enamine formation, to form and activate the aldimine, which in the cases of enolizable aldehydes occurred without isomerization, to enhance the nucleophilicity of the donors by enamine formation, and finally to transfer its inherent chiral information to the products in a highly efficient manner. Proline is not unique with respect to its potential to mediate catalytic asymmetric reactions involving aldehyde donors. Indeed, the first account of an efficient reaction of this type involved the use of chiral diamines such as (*S*)-2-(morpholinomethyl)-pyrrolidine as catalysts[9b] of asymmetric Michael reactions where proline itself proved to be a poor catalyst of aldehyde addition. Proline, however, has proven to be the most versatile of organocatalysts in asymmetric aldehyde addition reactions working effectively in aldol, Mannich, and more recently amination reaction manifolds. Our account reported here reflects the advancement in the field of direct proline-catalyzed enantioselective carbon−carbon bond formation, and the results further underscore the value of proline catalysis in particular and organocatalysis in general. The unveiling potential of these strategies should continue to be an intriguing and rewarding endeavor for some time to come.

Experimental Section

Typical Procedure for the Catalytic Asymmetric Mannich-Type Reaction with Propionaldehyde and Preformed Aldimines: Formation of 11−17. Anhydrous DMF (3 mL) was added to a vial containing the corresponding aldimine (0.5 mmol) and proline (30 mol %) and placed in a 4 °C cold room. The reaction was initiated by slow addition (0.2 μL/min) of a precooled mixture of propionaldehyde (5.0 mmol) in anhydrous DMF (2 mL) with a syringe pump at 4 °C. After 14−15 h of total reaction time the reaction mixture was diluted with anhydrous Et_2O (2 mL) and the temperature decreased to 0 °C followed by reduction with $NaBH_4$ (400 mg) for 10 min.

(40) (a) Yoshida, T.; Takeshita, M.; Orita, H.; Kado, N.; Yasuda, S.; Kato, H.; Itoh, Y. *Chem. Pharm. Bull.* **1996**, *44*, 1128. (b) Ito, Y.; Kato, H.; Yasuda, S.; Kato, N.; Yoshida, T.; Takeshita, M. JP Patent 09059228, Mar 4, 1997. (c) Ito, Y.; Kato, H.; Yasuda, S.; Kado, N.; Yoshida, T.; Yamamoto, Y. Int. Patent WO 9622988, Aug 1, 1996. (d) Hirabayashi, S.; Ike, K.; Zanka, A.; Kawakami, T.; Ichihara, M. Int. Patent WO 9220652, Nov 26, 1992.

(41) For example, see: Cornish, V. W.; Hahn, K. M.; Schultz, P. G. *J. Am. Chem. Soc.* **1996**, *118*, 8150.

(42) Carbohydrate-based oximes derived from γ-keto amino acids were recently applied to the synthesis of glycopeptides with clustered oxime-linked glycans. See: Marcaurelle, L. A.; Shin, Y.; Goon, S.; Bertozzi, C. R. *Org. Lett.* **2001**, *3*, 3691 and references therein.

(43) Although the *p*-methoxyphenyl group (PMP) was used as the nitrogen protective group throughout our studies, other nitrogen protective groups are also conceivable, particularly in the case of glyoxylate imines. For an example, see: Nakamura, Y.; Matsubara, R.; Kiyohara, H.; Kobayashi, S. *Org. Lett.* **2003**, *5*; 2481. Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208.

Next, the reaction mixture was poured into a vigorously stirred biphasic solution of Et_2O and saturated aqueous NH_4Cl solution (or alternatively sodium phosphate buffer pH 7.2). The organic layer was separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino alcohols. The enantiomeric excesses of the products were determined by HPLC analysis with use of chiral stationary phases.

Typical Three-Component, One-Pot Procedure for the Catalytic Asymmetric Mannich-Type Reaction of Aldehydes and *p*-Anisidine: Formation of 11−17. To a vial containing the acceptor aldehyde (0.5 mmol), *p*-anisidine (0.5 mmol), proline (30 mol %), and anhydrous DMF (3 mL) was added the corresponding donor aldehyde (5.0 mmol) in anhydrous DMF (2 mL) at 4 °C with a syringe pump. After 15−16 h of total reaction time the temperature was decreased to 0 °C followed by dilution with anhydrous Et_2O (2 mL) and reduction with $NaBH_4$ (400 mg) for 10 min. Next, the reaction mixture was poured into a vigorously stirred biphasic solution of Et_2O and saturated aqueous NH_4Cl solution (or alternatively sodium phosphate buffer pH 7.2). The organic layer was separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic phases were dried ($MgSO_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired β-amino alcohols. The enantiomeric excesses of the products were determined by HPLC analysis with use of chiral stationary phases.

Typical Procedure for the Formation of Self-Mannich Products 18−22. To a vial containing *p*-anisidine (0.5 mmol) and L-proline (30 mol %) in DMF (5 mL) was added aldehyde (4 mmol) at − 15 °C and the solution was stirred for 7 h. After completion of the reaction the mixture was diluted with ether (2 mL) and treated with $NaBH_4$ (400 mg) at 0 °C for 10 min. The reaction mixture was poured into a half- saturated NH_4Cl solution and ether under vigorous stirring, the layers were separated, and the aqueous phase was extracted thoroughly with ether. The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/ethyl acetate) to afford the desired amino alcohols.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-nitrophenyl)propan-1-ol (11): ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3H, J = 7.0 Hz), 2.21 (m, 1H), 3.64 (m, 2H), 3.67 (s, 3H, OMe), 4.65 (d, 1H, J = 4.0 Hz), 6.42 (d, 2H, J = 8.8 Hz), 6.68 (d, 2H, J = 8.8 Hz), 7.51 (d, 2H, J = 8.8 Hz), 8.17 (d, 2H, J = 8.8 Hz); ^{13}C NMR (CD_3OD) δ 11.9, 41.6, 56.0, 60.8, 66.0; 115.0, 115.1, 123.9, 128.3, 141.0, 147.3, 150.6, 152.6; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 99:1, flow rate 1.0 mL/min, λ = 254 nm): major isomer t_R = 36.10 min, minor isomer t_R = 21.49 min; $[\alpha]_D$ −65.2 (*c* 0.2, MeOH); HR-MS 317.1496; $C_{17}H_{20}NO_2$ ($M + H^+$) calcd 317.1496.

***anti*/*syn*-11 (from SMP reaction):** HPLC (Daicel Chiralpak OD-H, hexane/*i*-PrOH 90:10, flow rate 1.0 mL/min, 254 nm) 28.0 min ((*S*,*S*)-**11**), 31.4 min ((*R*,*R*)-**11**), 35.6 min (anti), 50.0 min (anti); ^{1}H NMR (400 MHz, $CDCl_3$) (syn:anti = 1:1, * donates the anti diastereomer) δ 0.89 (d, J = 7.0 Hz, 3H* × $^1/_2$), 0.90 (d, J = 7.0 Hz, 3H × $^1/_2$), 2.12 (m, 1H* × $^1/_2$), 2.21 (m, 1H × $^1/_2$), 3.67 (s, 3H), 3.63−3.74 (m, 2H), 4.38 (d, J = 7.0 Hz, 1H* × $^1/_2$), 4.65 (d, J = 3.8 Hz, 1H × $^1/_2$), 6.43 (d, J = 8.8 Hz, 2H × $^1/_2$), 6.44 (d, J = 8.8 Hz, 2H* × $^1/_2$), 6.67 (d, J = 8.8 Hz, 2H* × $^1/_2$), 6.68 (d, J = 8.8 Hz, 2H × $^1/_2$), 7.48 (d, J = 8.8 Hz, 2H* × $^1/_2$), 7.51 (d, J = 8.8 Hz, 2H × $^1/_2$), 8.16 (d, J = 8.8 Hz, 2H* × $^1/_2$), 8.17 (d, J = 8.8 Hz, 2H × $^1/_2$); ^{13}C (100 MHz, $CDCl_3$) (syn:anti = 1:1) 11.6, 14.4, 41.0, 55.6, 60.4, 65.6, 66.2, 114.6, 114.7, 115.3, 123.6, 123.7, 128.0, 140.5, 140.7, 146.9, 147.0, 150.4, 152.2, 152.5.

(2*S*,3*S*)-2-Methyl-3-(4-methoxyphenylamino)-3-(4-bromophenyl)-propan-1-ol (18): ^{1}H NMR (CD_3OD) δ 0.94 (d, 3H, J = 7.3 Hz), 2.03 (m, 1H), 3.37 (dd, 1H), 3.55 (dd, 1H), 3.62 (s, 3H, OMe), 4.43 (d, 1H, J = 5.1 Hz), 6.47 (d, 2H, J = 9.2 Hz), 6.61 (d, 2H, J = 8.8 Hz), 7.25 (d, 2H, J = 8.4 Hz), 7.40 (d, 2H, J = 8.4 Hz); ^{13}C NMR (CD_3OD) δ 12.7, 43.6, 56.3, 60.8, 65.8; 115.7, 115.9, 130.6, 132.3, 143.7, 144.1, 153.2; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH 99:1, flow rate 1.0 mL/min, λ = 254 nm) major isomer t_R = 14.00 min, minor isomer t_R = 10.14 min; $[\alpha]_D$ −38.9 (*c* 0.6, $CHCl_3$); HR-MS 350.0753, $C_{17}H_{20}BrNO_2$ ($M + H^+$) calcd 350.0753, $C_{17}H_{20}BrNO_2$ 349.067732.

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Note Added after ASAP Posting. There was an error in the product structure in Table 3 in the version posted ASAP November 13, 2003; the corrected version was posted November 18, 2003.

Supporting Information Available: For new compounds, a complete set of analytical data is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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