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Asymmetric Synthesis of Quaternary α- and β-Amino Acids and β-Lactams via Proline-Catalyzed Mannich Reactions with Branched Aldehyde Donors

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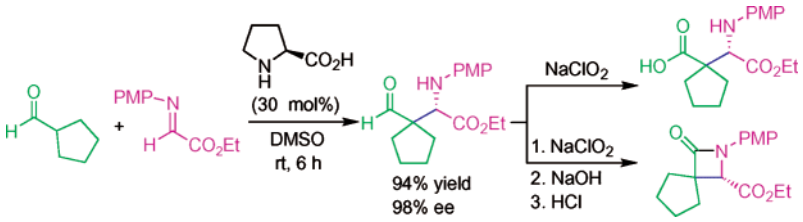
ABSTRACT



L-Proline-catalyzed direct asymmetric Mannich reactions of *N*-PMP protected α-imino ethyl glyoxylate with various α,α-disubstituted aldehydes affords quaternary β-formyl α-amino acid derivatives with excellent yields and enantioselectivities. The Mannich products are further converted to the corresponding quaternary α- and β-amino acids and β-lactams.

Optically active α- and β-amino acids are fundamental building blocks for the preparation of molecules important for the pharmaceutical and agrochemical industries such as peptides, proteins, and other natural products.[1] Furthermore, amino acids are extensively used as chiral auxiliaries and catalysts in modern organic synthesis. The asymmetric synthesis of quaternary amino acid derivatives is a difficult and challenging task.[2] Some of these unusual amino acids are components of enzyme inhibitors, and their incorporation into peptides is used to modulate secondary and tertiary structural conformations.[3] In particular, aspartic acid derivatives are structural components of virus inhibitors.[4]

Recently, proline- and proline derivative-catalyzed asymmetric aldol,[5] Mannich,[6] Michael,[7] Diels−Alder,[8] amination,[9] oxidation,[10] chlorination,[11] Robinson annulation,[12] and multicomponent or assembly reactions[13] have been developed. In

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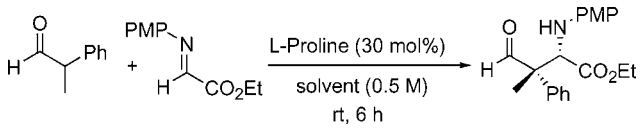
a continuation of our interest in organocatalysis, we report a two-step synthesis of aspartic acid derivatives that bear a quaternary carbon using an L-proline-catalyzed direct asymmetric Mannich reaction of *N*-PMP-protected α-imino ethyl glyoxylate (PMP = *p*-methoxyphenyl). For the first time, α,α-disubstituted aldehydes have been used as donors in the Mannich reaction to generate all-carbon quaternary stereogenic centers. The synthesis of all-carbon quaternary stereogenic centers is a challenging topic in asymmetric synthesis,[14] and one we have recently addressed using our organocatalytic aldol strategy.[5f]

We initially studied the Mannich reaction of *N*-PMP-protected α-imino ethyl glyoxylate with hydrotropaldehyde using a catalytic amount of L-proline (30 mol %) in DMSO at room temperature. The reaction was complete within 6 h and provided the Mannich product in 66% yield with very good enantioselectivity (86% ee) and diastereoselectivity (syn/anti = 85:15) (Table 1). We investigated a variety of

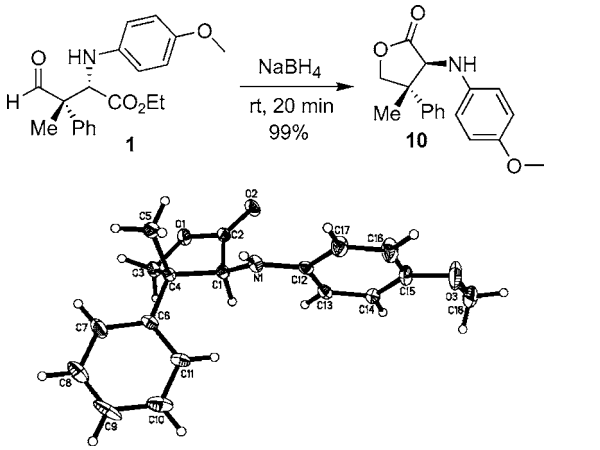
Table 1. Solvent Effect on the L-Proline-Catalyzed Quaternary Mannich Reaction



entry	solvent	yield (%)	syn/anti	ee (%) (syn)
1	DMSO	66	85:15	86
2	DMSO−H_2O (99:1)	21	87:13	83
3	DMSO−H_2O (95:5)	15	53:47	43
4	DMSO−H_2O (90:10)	15	43:57	41
5	DMF	24	88:12	81
6	NMP	25	61:39	57
7	CH_3CN	25	76:24	8
8	THF	6	78:22	18
9	dioxane	5	86:14	15
10	ether	10	86:14	8
11	EtOAc	14	78:22	18
12	CH_2Cl_2	36	80:20	2
13	MeOH	36	38:62	0
14	toluene	24	82:18	4
15	[bmim]BF_4	39	72:28	27

solvents for this Mannich reaction using an arbitrary reaction time of 6 h. As shown in Table 1, the yields and selectivities were very dependent on the solvent. The addition of 1% water decreased the product yield while the ee was maintained. The addition of 5% and 10% water gave diminishing yield as well as selectivities. Of the solvents screened, DMSO was the best. DMF also provided good diastereoselectivity and enantioselectivity, but the yield was low. The use of etherial solvents such as THF, dioxane, and ether gave poor yields and ee's. MeOH afforded the Mannich product in racemic form. Ionic liquid, [bmim]BF_4, also gave lower yield and poorer ee, in stark contrast to our previous results using ketones and unbranched aldehyde donors.[6d] Presumably, the coordination of solvent in the transition state influences the product formation in this Mannich reaction; solvent had little effect on Mannich reactions with linear aldehydes.[6e] We also evaluated the effects of catalyst loading (5, 15 mol %) and of different reactant concentrations (0.2, 0.1 M), but there was no improvement in stereoselectivities.

Scheme 1. Synthesis and X-ray Structure of γ-Lactone **10**



We next performed a catalyst screen for this quaternary Mannich reaction. Among the catalysts screened, proline, hydroxyproline, and *tert*-butyloxyproline provided the Mannich product in reasonable yield and with good stereoselectivities. 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. In contrast to the excellent results afforded by (*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/CF_3CO_2H, a bifunctional catalyst system, in the related aldol and Michael reactions of α,α-disubstituted aldehydes; this catalyst system was ineffective here.[5f,7e,15] Significantly, L-proline was shown to be a poor catalyst of this class of aldol reactions, exemplifying the distinct reaction specialization found among organocatalysts, a feature often associated with their enzymatic counterparts.

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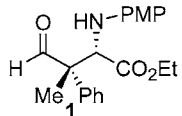
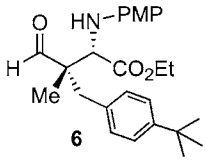
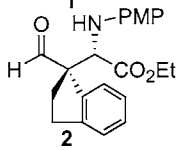
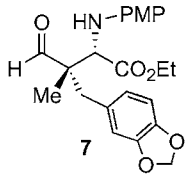
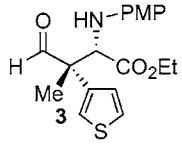
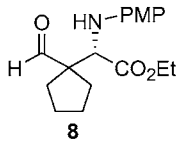
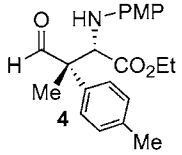
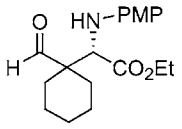
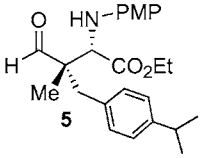
(15) Full details of the catalyst screen are provided in the Supporting Information.

Table 2. α,α-Disubstituted Aldehydes as Donors in the Synthesis of Quaternary β-Formyl-Substituted α-Amino Acid Derivatives

entry	product	time (h)	yield (%)	*syn*:*anti*	ee (*syn*/*anti*)	entry	product	time (h)	yield (%)	*syn*:*anti*	ee (*syn*/*anti*)
1	 **1**	6	66	85:15	86/25	6	 **6**	46	80	60:40	>99/10
2	 **2**	0.25	99	96:4	93/5	7	 **7**	45	91	70:30	88/52
3	 **3**	3.5	80	83:17	92/40	8	 **8**	6	94	–	98
4	 **4**	10	82	75:25	88/–	9	 **9**	48	85	–	55
5	 **5**	45	80	61:39	96/64						

[a] ee's were determined by chiral HPLC analysis of Mannich products or the corresponding oximes or lactones.

Encouraged by these results, we next studied the Mannich reaction using various α,α-disubstituted aldehydes as nucleophiles or donors in this reaction (Table 2). The quaternary β-formyl α-amino acid derivatives were obtained with excellent yields and ee's. In the case of indane aldehyde, the reaction was complete within 15 min and furnished the Mannich product in quantitative yield with 93% ee and a diastereomeric ratio of 96:4 (Table 2, entry 2). We also used alkyl, aryl, benzyl, and heteroaromatic substituted aldehydes to make highly functionalized amino acids. The reactions with aryl-substituted aldehydes are faster (0.25−10 h) than those of benzyl-substituted ones (45 h). The Mannich product **8** was also synthesized in DMF and NMP with good yield (77%, 72%) and good ee (94%, 84%, respectively). The Mannich products were formed with syn diastereoselectivity. In the case of α,α-disubstituted aldehydes, the corresponding *cis*- and *trans*-enamines are energetically less distinct relative to the enamine intermediates in the reactions of linear aldehydes,[6c−e] accounting for the reduced diastereoselectivity observed in this class of Mannich-type reactions.[16] The relative stereochemistry (syn/anti) of Mannich products was determined by X-ray analysis of lactone **10**, and the absolute stereochemistry was based on our previous Mannich reactions[6c] and X-ray analysis. Note that lactone **10** could be obtained in >99.9% ee after crystallization from methanol (Scheme 1).

The aldehyde functionality present in the α-amino acids derived from aldehyde donors can be further oxidized providing a straightforward route to functionalized aspartic acids (Table 3). As demonstrated, the aldehyde group was readily oxidized ($NaClO_2$) to afford the aspartic acid derivatives. For example, the cyclopentyl-L-aspartic acid **11**, an intermediate for a viral inhibitor, was made in two steps from inexpensive starting materials and catalyst in contrast to the reported multistep synthesis.[4] We also developed a highly efficient synthesis of spiro lactam **14** from Mannich product **8** in excellent yield for the first time using oxidation followed by simple base and acid treatment (Scheme 2). No racemization occurred under these conditions. The *N*-PMP group

Scheme 2. Synthesis of a Spiro Lactam **14**

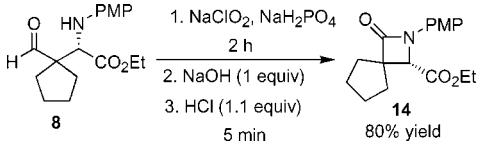
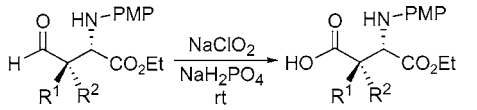
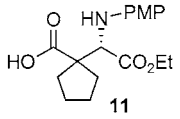
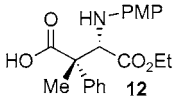
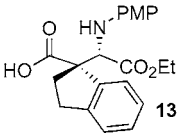


Table 3. Synthesis of Quaternary α- and β-Amino Acids

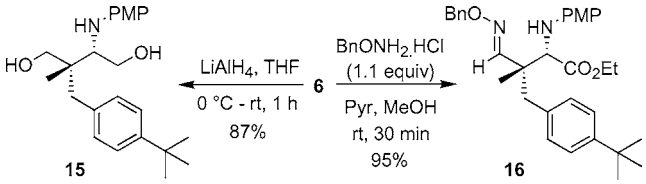


product	time (h)	yield (%)
 **11**	2	90
 **12**	4	73
 **13**	2	82

could be removed by oxidation with ceric ammonium nitrate. Thus, our methodology of proline-catalysis provides a mild, facile, and stereoselective route to functionalized quaternary α- and β-amino acids and β-lactams.

Alternatively, both the aldehyde and the ester functionality can be simultaneously reduced with $LiAlH_4$ to afford the amino diol. This was exemplified by the reaction shown in Scheme 3; **15** was obtained in 87% yield. Such 3-alkyl-

Scheme 3. Further Modifications of Mannich Product **6**



substituted 2-aminobutane-1,4-diols are ideal starting materials for the synthesis of chiral pyrrolidines, which have been employed as versatile and useful intermediates for the synthesis of antibacterial quinolinecarboxylic acids as medical bactericides.[17] Unnatural amino acids that contain carbonyl groups have been shown to be useful as reactive handles that provide for the facile modification of proteins and peptides.[18] 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 was readily converted to the corresponding oximes **16** under mild conditions without epimerization (Scheme 3). Oximes of this type were recently integrated into glycopeptide analogues containing unnatural sugar−peptide linkages.[19]

In conclusion, we have demonstrated for the first time that direct asymmetric Mannich reactions of *N*-PMP-protected α-imino ethyl glyoxylate with various α,α-disubstituted aldehydes afford quaternary β-formyl α-amino acid derivatives with excellent yields and enantioselectivities. These results provide an additional organocatalytic route to synthons containing chiral all-carbon quaternary centers. Highly efficient and two-step asymmetric syntheses of quaternary α- and β-amino acids and β-lactams were developed. These reactions can be performed under operationally simple and safe conditions without the requirement for an inert atmosphere or for dry solvents.

Acknowledgment. This study was supported in part by the NIH (CA27489) and the Skaggs Institute for Chemical Biology. We thank Dr. Raj K. Chadha for X-ray structural analysis.

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For example, the energy difference between *cis*- and *trans*-enamines of hydrotropaldehyde is 0.1608 kcal/mol, whereas propionaldehyde has a difference of 2.936 kcal/mol.

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(20) **General Experimental Procedure for Mannich Reaction.** To a glass vial charged with L-proline (17 mg) was added solvent (1 mL) followed by α-imino ethyl glyoxylate (104 mg, 0.5 mmol) and aldehyde (0.75 mmol), and the reaction was stirred at room temperature until completion as monitored by TLC. Then, half-saturated NH_4Cl solution and ethyl acetate were added with vigorous stirring, the layers were separated, and the organic phase was washed with water. 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 Mannich product.