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Direct organocatalytic asymmetric Mannich-type reactions in aqueous media: one-pot Mannich-allylation reactions

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Abstract—The first direct organocatalytic asymmetric Mannich-type reactions in aqueous media are demonstrated herein. L-Proline-catalyzed reactions in aqueous media to provide β-formyl substituted α-amino acid derivatives with excellent diastereoselectivities (dr up to 19:1, *syn*/*anti*) and high enantioselectivities (ee between 72 and >99%). These conditions provided for the development of novel one-pot asymmetric syntheses of cyclic γ-allyl substituted α-amino acid derivatives (ee up to >99%). This was accomplished by combining the proline-catalyzed Mannich-type reactions with indium promoted allylations in aqueous media.

Mannich-type reactions are among the most important carbon–carbon bond-forming reactions in organic chemistry. They provide for the creation of structurally diverse nitrogen containing compounds from simple and readily available starting materials.[1] The increasing demand of today's pharmaceutical industry for optically active nitrogen containing molecules has driven the development of asymmetric versions of the Mannich reaction.[2] Recently, the first Lewis acid-catalyzed asymmetric Mannich-type reactions were reported that employed preformed enolate equivalents.[3] Thereafter, direct catalytic asymmetric Mannich-type reactions have been described that utilize unmodified carbonyl donors in organic solvents.[4]

Reactions that are performed in aqueous media have gained increased interest in synthetic chemistry over the past decade not only for the advantages accorded by avoiding extensive drying of reactants, catalysts and solvents, but also for the unique reactivity and selectivity that sometimes results.[5,6] In this context, the development of a Lewis acid-catalyzed asymmetric Mannich-type reaction in aqueous media was a significant achievement.[6] This method utilized preformed silyl enol ethers for the addition to a preformed imine. However, to the best of our knowledge there is no report of a catalytic asymmetric Mannich-type reaction with unmodified carbonyl compounds in aqueous media. Based on our research of applying small organic molecules as catalysts for asymmetric synthesis, we have developed novel routes for the synthesis of optically active compounds from simple starting materials.[7,8b,c] One important aim of this research is to develop organocatalytic asymmetric carbon–carbon bond-forming transformations in aqueous media as well.[8] Herein we disclose the first direct asymmetric L-proline-catalyzed Mannich-type reactions with unmodified aldehydes in aqueous media, providing functional amino acids with excellent diastereo- and enantioselectivities.

In an initial experiment, 4-decenal (0.2 M), *N*-PMP-protected α-imino ethyl glyoxylate (0.1 M) and L-proline (10 mol%) were stirred in 1/9 H_2O/THF at room temperature. After 17 h the imine was consumed and the only detectable product was the β-formyl-functionalized α-amino acid derivative **1** which could be isolated in 88% yield, with excellent dr>19:1 and >99% ee (Table 1, entry 1). Significantly, the high enantioselectivity provided by L-proline catalysis was maintained in different water containing solvents (entries 2–5).

Encouraged by these results we reacted the *N*-PMP-protected α-imino ethyl glyoxylate as described vide infra with a set of different aldehydes to afford optically active β-formyl functionalized amino acids **2**–**8** (Table 2).[9] In all cases, the reactions proceeded smoothly with high enantioselectivities. For aldehydes with R >Pentyl a predominant diastereomer (dr >19:1) was formed as determined by ^{1}H NMR.[10] For example,

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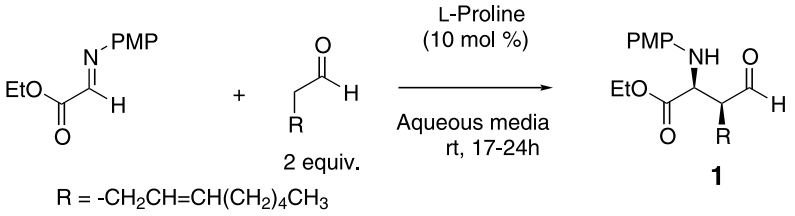
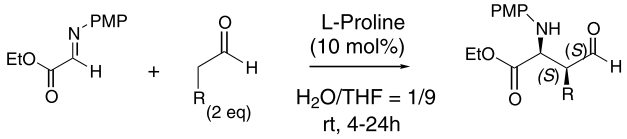
Table 1. Asymmetric synthesis of **1** in aqueous media



Entry	Conditions	Yield (%)[a]	dr[b]	ee (%)[c]
1	1/9 H_2O/THF	88	>19:1	>99
2	1/9 H_2O/dioxane	89	>19:1	>99
3	1/9 H_2O/CH_3CN	67	>19:1	>99
4	1/9 H_2O/EtOH	57	10:1	95
5	1/9 H_2O/DMF	40	>19:1	99

[a] Yields of isolated pure products after column chromatography.
[b] dr = *syn*/*anti* as determined by NMR after column chromatography.
[c] The ee's of products **1**–**8** were determined by chiral-phase HPLC analyses.

Table 2. Proline-catalyzed aqueous Mannich reactions of unmodified aldehydes with *N*-PMP-protected α-imino ethyl glyoxylate

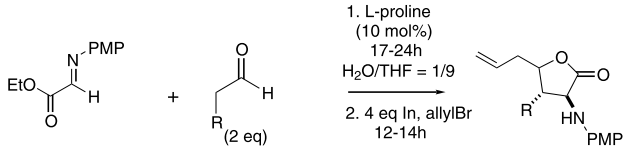


Entry	R	Yield (%)[a]	dr[b]	ee (%)[c]	Product
1	$CH_3(CH_2)_4CH{=}CHCH_2$-	88	>19:1 (>19:1)[d]	>99 (>99)[e]	**1**
2	*n*-Pentyl-	82	>19:1 (>19:1)[d]	95	**2**
3	*n*-Hexyl-	84	15:1 (>19:1)[d]	99 (96)[f]	**3**
4	*n*-Butyl-	79	7:1 (>19:1)[d]	95	**4**
5	$CH_2{=}CHCH_2$-	64	5:1 (>19:1)[d]	89	**5**
6	$PhCH_2$-	78	5:1 (>19:1)[d]	91	**6**
7	*i*-Pr-	75	10:1 (>19:1)[d]	72	**7**
8	Me-	67	2:1 (4:1)[d]	99	**8**

[a] Yields of isolated pure products after column chromatography.
[b] dr = *syn*/*anti* as determined by NMR after column chromatography.
[c] The ee's of products **1**–**8** were determined by chiral-phase HPLC analyses.
[d] dr = *syn*/*anti* as determined by NMR of the crude product after extraction.
[e] Reaction performed in 1/1 H_2O/THF.
[f] Reaction performed in 1/5 H_2O/THF.

the octanal adduct **2** was isolated in 84% yield with 99% ee. Noteworthy, yield and diastereoselectivity were not compromised when compared to reactions performed in THF. The ee was also not affected for most of the aldehydes tested. Slight decreases in ee, however, were noted in some cases (entries 5 and 7). The reactions could also be performed on gram-scale without loss of diasteromeric ratio or enantioselectivity. Remarkably, in one case (Table 1, entry 1), high ee is maintained in a 1/1 H_2O/THF solvent system. This result is considerably better compared to our previous studies concerning the proline-catalyzed intermolecular aldol reactions where the stereoselectivity of the aldol transformation drops off steeply with increasing water content.[7c,8c] In solvent systems containing greater than 30 vol% water, essentially racemic aldol products are obtained supporting the role of intermolecular hydrogen bonding in directing the stereochemical outcome of the reaction.

Table 3. One-pot asymmetric synthesis of γ-allyl substituted α-amino acid derivatives



Entry	R	Yield (%)[a]	dr[b]	ee (%)[c]	Product
1	*i*-Pr-	64 (63)[d] (61)[e]	2:1 (2:1)[d] (1:1)[e]	73 (93)[d] (93)[e]	**9**
2	$CH_3(CH_2)_4CH{=}CHCH_2$-	77 (78)[f]	1:1 (1:1)[f]	>99 (>99)[f]	**10**

[a] Yields of isolated pure product after column chromatography based on two steps.
[b] dr determined by NMR after column chromatography.
[c] The ee's of the major diastereomer as determined by chiral-phase HPLC analyses.
[d] Reactions performed in THF.
[e] Reaction performed stepwise in THF. The L-proline was removed by extractive work-up prior to allylation of the crude β-formyl amino acid derivative **7**.
[f] Reaction performed in 1/4 H_2O/THF.

N-PMP-protected α-imino-alkyl glyoxylates may therefore represent privileged electrophiles in that high stereoselectivities can be obtained with minimal or indirect interaction between the proline carboxylate and the imine nitrogen.

The stereochemistry of these reactions was the same as our previous results in organic solvents with L-proline forming a reactive enamine intermediate with the aldehyde, implicating an *si*-facial attack on the imine from its *si*-face.[4f] Hence, in aqueous media, L-proline provides functional L-amino acids with *syn*-diastereoselectivity.[11]

Direct asymmetric Mannich-type reactions are highly suitable as entries for tandem reactions in aqueous media. This was demonstrated by a novel one-pot Mannich/indium promoted allylation sequence that afforded the highly functionalized lactones **9** and **10** as a mixture of two diastereomers in 64 and 77% yield and with an ee of 73 and >99%, respectively (Table 3).[12] ^{1}H NMR studies revealed that there was no significant asymmetric induction for the allyl-indium reaction step. Furthermore, indium-promoted allylation of the isolated amino acid derivative **7** (dr >19:1) provided lactone **9** that was structurally identical to the product derived from the one-pot procedures.[13] Hence, the C-2 center of the β-formyl amino acid derivatives does not enolize upon γ-allylation (vide supra). Noteworthy, lactone **10** could also be obtained in high yield and excellent ee in 1/4 H_2O/THF (entry 2). Moreover, performing the one-pot Mannich/allylation sequence in THF improved the ee of **9** to 93%. This is in accordance with the results presented in Table 2 where a higher ee was obtained for proline-catalyzed reactions with long-chain aldehydes in aqueous media.

In conclusion, we have demonstrated for the first time direct organocatalytic asymmetric Mannich-type reactions with unmodified aldehydes in aqueous media. The methodology provides a simple route for the synthesis of both enantiomeric forms of highly optically active α- and β-amino acid derivatives from cheap and readily available starting materials. Moreover, the reactions can be performed on gram scale under operationally simple and safe conditions. Reactions in aqueous media also provide for the potential coupling of this chemistry with enzymes and other reactions known to work under these conditions. We have demonstrated this potential in the development of a novel one-pot asymmetric Mannich/allylation sequence that provided cyclic γ-allyl substituted α-amino acid derivatives in good yield and high ee. Further development of organocatalytic asymmetric Mannich-type reactions and other C–C bond-forming transformations in aqueous media are under investigation.

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9. In a typical experiment, *N*-PMP-protected α-imino ethyl glyoxylate (0.5 mmol), the corresponding aldehyde donor (1.0 mmol) and L-proline (10 mol%) was dissolved in 9/1 H_2O/THF. The total volume of the reaction mixture was 5 mL. After stirring for 2–24 h at room temperature, the mixture was worked-up by addition of half-saturated ammonium chloride solution and extraction with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, concentrated and the residue purified by column chromatography (silica, hexanes/ethyl acetate mixtures) to afford the corresponding Mannich addition product. The ee's of all products were determined by chiral HPLC analysis.
10. β-Formyl functionalized amino acids can epimerize upon column chromatography, decreasing the dr. However, the crude products are stable upon storage at 0°C in EtOAc for months.
11. NMR, optical rotation and chiral-phase HPLC analysis of Mannich products **1**–**4**, **7** and **8** were identical to those reported in Ref. 4f.
12. In a typical experiment, the *N*-PMP protected α-imino ethyl glyoxylate (0.5 mmol), the aldehyde (1 mmol) and L-proline (10 mol%) were stirred in 1/9 H_2O/THF for 17–24 h at room temperature. Then indium powder (2 mmol) and allyl bromide (2 mmol) was added to the reaction mixture that was stirred for an additional 12–14 h. The reactions were quenched by extraction with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, concentrated and the residue purified by column chromatography (silica, hexanes/ethyl acetate mixtures) to afford the corresponding lactone products. 4-Allyl-2-(*p*-methoxyphenylamino)-2-(2-methylethyl)-butyrolactone (**9**): ^{1}H NMR (250 MHz): ~2:1 mixture of diastereomers, * denotes minor diastereomer, δ 1.12 (m, 6H, 3H*, CHCH_3), 2.04 (m, 1H), 2.14 (m, 1H), 2.27 (m, 0.5H*), 2.45 (m, 0.5, 1H*), 2.47 (m, 1H), 2.49 (m, 0.5H*), 3.82 (bs, 3H, 1.5H*, ArOCH_3), 4.02 (d, J=5.4 Hz, 0.5H*), 4.09 (d, J=5.1 Hz, 1H), 4.38 (m, 1H), 4.74 (m, 05H*), 5.30 (m, 2H, H*), 5.94 (m, H, 0.5H*), 6.76 (d, J=8.2 Hz, 2H, H*), 6.85 (d, J=8.2 Hz, 2H, H*); ^{13}C NMR (125 MHz): (major diastereomer) δ 176.1, 132.6, 119.3, 116.2, 115.1, 79.6, 56.0, 52.1, 39.4, 35.1, 28.9; HPLC (Daicel Chiralpak AD, hexane/*i*-PrOH=99:1, flow rate 1.0 mL/min, λ=254 nm) was used to determine the ee of the major diastereomer, HPLC (Daicel Chiralpak AS, hexane/*i*-PrOH=90:10, flow rate 1.0 mL/min, λ=254 nm) was used to determine the ee of the minor diastereomer; HRMS calcd for $C_{17}H_{23}NO_3$ (M+): 289.1673; found: 289.1675.
13. This procedure afforded **9** with a dr of 1:1 and 93% ee.