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Amino acid-catalyzed direct enantioselective synthesis of β-amino-α-oxyaldehydes

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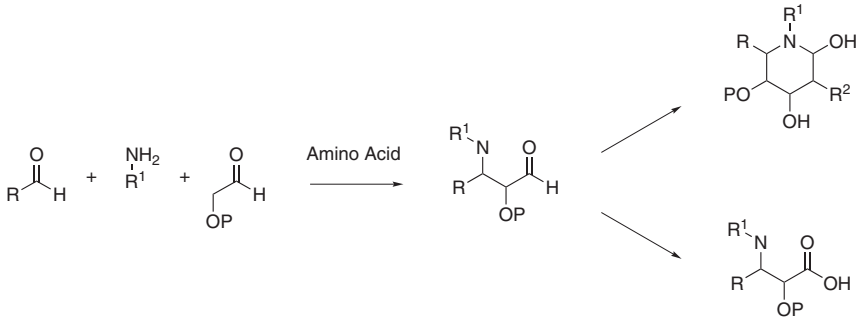
Abstract—The first direct amino acid-catalyzed asymmetric syntheses of α-oxy-β-aminoaldehydes are presented. The organocatalytic Mannich reactions between unmodified α-oxyaldehydes and anilines proceeded with excellent enantioselectivities. In most cases, the corresponding α-oxy-β-aminoaldehyde adducts were isolated in high yield with excellent chemo- and enantioselectivity. For example, orthogonally protected 3-amino-tetroses and α-amino acid derivatives were isolated in up to >99% ee.

The Mannich reaction has found a multitude of applications in organic chemistry. The resulting Mannich bases are of particular interest due to their utilization as synthetic building blocks and precursors of pharmaceutically valuable compounds.[1,2] Chemists have developed several stoichiometric indirect stereoselective Mannich transformations that utilize preformed enol equivalents or imines.[3,4] The first successful examples of catalytic asymmetric additions of enolates to imines led to an intense study of catalytic indirect Mannich reactions.[5] Recently, heterodimetallic complexes and di-nuclear zinc organo-metallic complexes were reported as catalysts for highly enantioselective direct Mannich-type reactions.[6,7] Moreover, chiral copper(II) bisoxazoline (BOX) complexes are also catalysts for direct asymmetric Mannich-type reactions.[8] Most recently, organocatalysis has been added to the synthetic repertoire for this important transformation.[9,10] In particular, amino acid derivatives,[11] chiral Brønsted acids[12] and peptide derivatives[13] are successful in catalyzing asymmetric Mannich reactions.

Despite this research on the catalytic enantioselective Mannich reaction, there is, to our knowledge, no example of a direct catalytic enantioselective Mannich reaction involving glycoaldehyde derivatives as donors. This potential catalytic Mannich reaction would constitute an effective and economic new entry to the asymmetric synthesis of C-4 amino sugars and β-amino-α-hydroxy-aldehydes, which are important chiral building blocks for the synthesis of pharmaceutically valuable C-6 aza-sugars[14] and β-amino-α-hydroxy-acid derivatives (Eq. 1).[2f] Based on retrosynthetic analysis and our previous research on the development of organocatalytic



(1)

Keywords: Asymmetric catalysis; Proline derivatives; α-Oxyaldehydes; Mannich reaction; Amino sugars.
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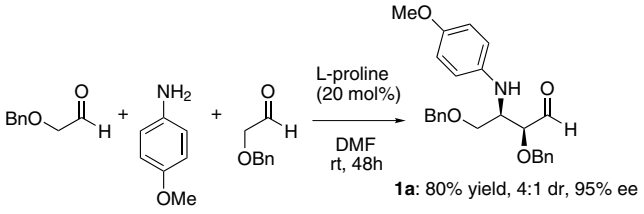
reactions,[14e,15] we became interested as to whether amino acids would catalyze the synthesis of protected β-amino-α-oxyaldehyde derivatives.

In an initial experiment, we reacted α-benzyloxyacetaldehyde (3 mmol) with *p*-anisidine (1 mmol) in the presence of a catalytic amount of L-proline (20 mol %) in DMF (4 mL) at room temperature (Eq. 2).[16] The reaction was quenched after 48 h, and to our delight, 3-(amino-*p*-methoxyphenyl (PMP))-threose **1a** was isolated using silica-gel chromatography in 80% yield with 95% ee. The Mannich reactions were also readily performed in *N*-methylpyrrolidinone (NMP) without decreasing the enantioselectivity.



1a: 80% yield, 4:1 dr, 95% ee

(2)

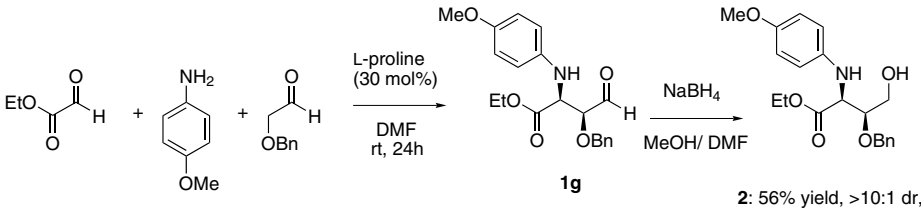
We also found that hydroxyproline and proline derived dipeptides catalyzed the formation of 3-amino-threose **1a**. For example, *trans*-4-hydroxyproline catalyzed the reaction between benzyloxyacetaldehyde and anisidine furnishing **1a** in 54% yield with >99% ee.

Next, we performed the corresponding proline- and hydroxyproline-catalyzed self-Mannich reactions with a set of different protected glycolaldehydes (Table 1). The reactions were effective and the corresponding protected 3-amino-tetrose derivatives **1a**–**f** were isolated in good yields with up to >99% ee. The reactions proceeded with excellent chemoselectivity and only trace amounts of self-aldol adducts could be detected. We found that ether-functionalized α-oxyaldehydes (entries 1–2 and 7–8) and bulky silyloxy substituents were required to obtain sufficient reaction efficiency (entries 3–6).[17] For example, when the TBS protected α-oxyaldehyde was used the corresponding 3-amino-tetrose **1b** was isolated in 90% yield with 99% ee (entry 3). Hydroxy-L-proline also catalyzed the formation of **1b** with excellent enantioselectivity (entry 4). The amino-tetroses **1** obtained had orthogonal protective groups and are very useful and versatile synthetic chiral building blocks for the asymmetric synthesis of polyhydroxylated amines.[14] The aromatic amine component was also varied with success and furnished the corresponding protected 3-amino-aryltetroses.

The reactions were operationally simple and were performed by a mix and stir procedure. Furthermore, they were readily performed at 2 g scale in the presence of air without decreasing the yield and the ee of the product. We also examined the proline-catalyzed addition of protected glycol aldehydes to *N*-PMP-protected imines. Hence, protected glycol aldehydes were reacted with *N*-PMP-protected α-imino-glyoxylate esters and aromatic imines in the presence of a catalytic amount of L-proline (Table 2). The reactions proceeded with excellent chemoselectivity furnishing exclusively the corresponding β-amino-α-oxyaldehydes and amino acid derivatives **1g**–**l** in good yield with up to >99% ee. For example, protected α-amino acid derivative **1g** was isolated in 89% yield with a dr of 19:1 and 98% ee. The different protected β-amino-α-oxyaldehydes were readily converted to the corresponding amino alcohols and β-amino-α-hydroxy-acids.[10] Thus, the amino acid-catalyzed asymmetric Mannich reactions with glycoaldehydes as donors provide a complementary novel metal-free route to Shibasaki's[7a] and Trost's[7b] β-amino-α-hydroxy-acid syntheses.[7,18]

The amino acid-catalyzed Mannich reactions can also be performed as one-pot three-component reactions between acceptor aldehydes, *p*-anisidine and α-oxyaldehydes. This was exemplified by the one-step asymmetric synthesis of orthogonally protected 4-hydroxythreonine. Thus, the reaction between ethyl glyoxylate, *p*-anisidine and α-benzyloxyacetaldehyde in the presence of a catalytic amount of proline exclusively furnished the corresponding α-amino acid derivative **1g**, which was selectively reduced in situ to the desired 4-hydroxythreonine derivative **2** in 56% yield with $a > 10{:}1$ dr (*syn*/*anti*) and in 98% ee (Eq. 3). Hence, the reaction proceeded with excellent chemo- and enantioselectivity and no self-Mannich adduct **1a** was formed.

The absolute configuration of the 3-amino-3-deoxythreoses **1a** was (3*R*,2*S*).[19] On the basis of the absolute configuration, we propose transition-state model **I** to account for the diastereo- and enantioselectivity of the amino acid catalyzed formation of β-amino-α-oxyaldehydes (Fig. 1). Hence, the L-proline derivative forms an enamine with the α-oxyaldehyde that is attacked by the in situ generated imine from its *si*-face providing 3-amino-D-threose derivatives. This is in accordance



1g

2: 56% yield, >10:1 dr, 98% ee

(3)

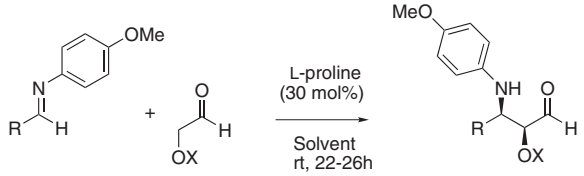
Table 1. Organocatalytic one-step asymmetric synthesis of protected amino-tetroses

1

Entry	Amino acid	X	Ar	Prod.	Yield (%)[a]	dr[b]	ee (%)[c]
1	L-Proline	Bn	PMP	**1a**	80	4:1	95
2	L-Hydroxyproline	Bn	PMP	**1a**	54	3:1	>99[d]
3	L-Proline	TBS	PMP	**1b**	90	1:1	99
4	L-Hydroxyproline	TBS	PMP	**1b**	51	4:1	>99[d]
5	L-Proline	TIBS	PMP	**1c**	50	1:1	95
6	L-Proline	TBDPS	PMP	**1d**	58	1:1	91
7	L-Proline	Bn	Ph	**1e**	65[e]	10:1[e]	88[e]
8	L-Proline	Bn	*p*-BrC_6H_4	**1f**	63[e]	4:1[e]	76[e]

[a] Isolated yield of the pure products after silica-gel chromatography.
[b] dr = *syn*/*anti* ratio of the isolated product as determined by NMR.
[c] Determined by chiral-phase HPLC analyses.
[d] Using 30 mol % catalyst. Bn = benzyl, TBS = *tert*-butyldimethylsilyl, TIBS = triisobutylsilyl, TBDPS = *tert*-butyldiphenylsilyl.
[e] The result of the corresponding 2-aminothreitol obtained by in situ reduction of the 3-aminothreitol with $NaBH_4$.

Table 2. Direct catalytic cross-Mannich-type reactions with protected glycol aldehydes



1

Entry	Solvent	R	X	Prod.	Yield (%)[a]	dr[b]	ee (%)[c]
1	DMF	CO_2Et	Bn	**1g**	89	19:1	98
2	NMP	CO_2Et	TBS	**1h**	95	2:1	99
3	NMP	4-BrC_6H_4	TBS	**1i**	80	3:1	82
4	DMF		Bn	**1j**	60	3:1	95
5	DMF	Ph	Bn	**1k**	96[d]	7:1	n.d.[e]
6	DMF	4-FC_6H_4	Bn	**1l**	74[d]	7:1	n.d.[e]

[a] Isolated yield of the pure products after silica-gel chromatography.
[b] dr = *syn*/*anti* ratio of the isolated product as determined by NMR.
[c] Determined by chiral-phase HPLC analyses. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.
[d] Reaction performed at −20 °C.
[e] We were not able to determine the ee of the product either by chiral-HPLC analyses (chiral columns tried: AD, OJ, AS, OD-H, OB, AK) or with NMR shift reagents.

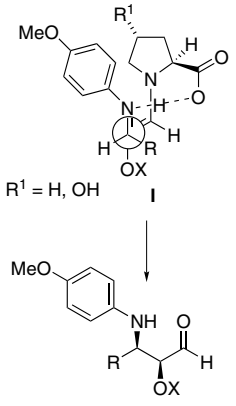


Figure 1. Transition-state models evoked to account for the enantioselectivity of the L-proline and hydroxyproline catalyzed reactions.

with the transition states of previously reported proline-catalyzed Mannich reactions, in which *si*-facial attack occurs.[10,11,20]

In conclusion, we have developed the first direct catalytic enantioselective Mannich reaction that provides β-amino-α-oxyaldehydes and 3-amino-tetroses in high yield with up to >99% ee. A screen revealed that proline and its derivatives catalyze the reaction with excellent enantioselectivity. The method allows direct and stereoselective access to orthogonally protected amino polyols and 1,2-amino alcohols. Further elaboration of this transformation and its synthetic application to de novo formation of aza-sugars and β-amino-α-hydroxy-acids is ongoing in our laboratory.

Acknowledgements

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16. Typical experimental procedure (Table 1, entry 1): to a vial containing α-benzyloxyacetaldehyde (3 mmol) and *p*-anisidine (1 mmol) in DMF (4 mL) was added a catalytic amount of L-proline (30 mol %). After 48 h of vigorous stirring, the reaction was quenched by addition of aqueous

NH_4Cl and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure following purification of the crude product mixture by silica-gel column chromatography (EtOAc:toluene, 1:10) to afford 3-amino-erythrose **1a** in 80% yield (*syn*:*anti* = 4:1) as a slightly yellow oil. The ee of **1a** was 98% as determined by chiral-phase HPLC analysis. (2*S*,3*R*)-2-Benzyloxy-3-(-methoxyphenylamino)-threose **1a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 (m, 1H), 3.74 (s, 3H), 4.18 (m, 1H), 4.22 (m, 1H), 4.49–4.57 (m, 4H), 4.82 (d, J = 11.8 Hz, 1H), 6.54 (d, J = 9.0 Hz, 2H), 6.75 (d, J = 9.0 Hz, 2H), 7.20–7.38 (m, 10H), 9.73 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 65.0, 68.0, 73.6, 74.0, 82.0, 115.1, 115.3, 125.5, 128.0, 128.2, 128.4,128.5, 128.7, 128.9, 137.4, 138.0, 140.4, 152.8, 203.2; $[\alpha]_D^{24}$ −21 (c = 9.1, $CHCl_3$); MALDI-TOF MS: 428.1842; $C_{25}H_{27}NO_4$ ($M + Na^+$: calcd 428.1838). In order to determine the enantioselectivity of **1a**, we reduced it in situ with excess $NaBH_4$ to the corresponding protected threitol: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56 (m, 1H), 3.63 (m, 1H) 3.75 (s, 3H), 3.81 (m, 2H), 3.88 (m, 2H), 4.43 (m, 1H), 4.50–4.58 (m, 3H), 4.77 (d, J = 11.6 Hz, 1H), 6.60 (d, J = 8.9 Hz, 2H), 6.77 (d, J = 8.9 Hz, 2H), 7.29–7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.9, 56.1, 62.8, 68.6, 72.8, 73.5, 78.3, 115.1, 116.0, 128.0,1 28.1, 128.6, 129.0, 138.0, 138.4, 141.0, 152.8; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 96:4, flow rate 0.5 mL/min, λ = 254 nm): major isomer: t_R = 83.51 min; minor isomer: t_R = 114.0 min; MALDI-TOF MS: 430.1999; $C_{25}H_{29}NO_4$ ($M+Na^+$: calcd 430.1994).

17. The compounds are sensitive and they epimerize and racemize upon silica-gel column chromatography. The β-amino-α-oxyaldehyde products should be stored at −35 °C.
18. Amino acid-catalyzed Mannich reactions with hydroxyacetone as the donor furnished products that failed to be converted to β-amino-α-hydroxy acids. See Refs. 11a,b.
19. Protected amino alcohol **1a** was converted to the known peracetylated (2*R*,3*S*)-2-aminothreitol with $[\alpha]_D^{24}$ +40 (c = 0.1, MeOH). The reported optical rotation for peracetylated (2*R*,3*S*)-aminothreitol is $[\alpha]_D^{25}$ +40.3 (c = 1.12, MeOH) Wade, P. A.; D'Ambrosio, S. G. *J. Carbohydr. Chem.* **1995**, *14*, 1329.
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