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Direct catalytic asymmetric three-component Mannich reactions with dihydroxyacetone: enantioselective synthesis of amino sugar derivatives

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Abstract

Highly enantioselective, amino acid-catalyzed, one-pot three-component asymmetric Mannich reactions between dihydroxyacetone, *p*-anisidine, and aldehydes are presented. The reactions proceeded with high chemo- and stereoselectivity and furnished the corresponding α,α′-dihydroxy-β-aminoketones in high yields with 82–95% ee.
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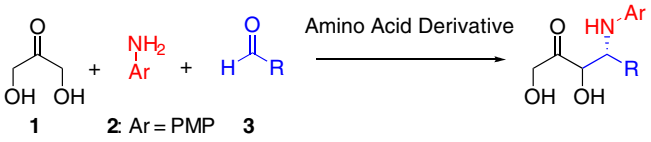
The classical Mannich reaction,[1] in which an aminomethyl group is introduced at the α-position to a carbonyl compound, is an important reaction in organic chemistry.[2] The resulting Mannich bases are of particular interest due to their biological activity, and use as synthetic building blocks and precursors of pharmaceutically valuable γ-amino alcohols.[2] The development of catalytic asymmetric Mannich-type reactions has received increased attention in recent years.[3] They are used for the synthesis of valuable chiral nitrogen-containing compounds such as amino acid derivatives, β-lactams, and amino alcohols.[4–12] Direct catalytic Mannich-type reactions between ketones and preformed imines are catalyzed by organometallic complexes[4] with high enantioselectivity. Moreover, organocatalytic direct asymmetric Mannich-type reactions have been developed that are catalyzed by Brønsted acids,[5] cinchona alkaloids,[6] proline derivatives,[7,8] and linear amino acid derivatives.[9] In this context, one notable transformation is the proline-catalyzed, one-pot three-component Mannich reaction using ketones as nucleophiles reported by List and co-workers.[7a] Other important recent Mannich transformations, which were independently developed by Enders,[10] Westermann,[11] and our group,[12] for the synthesis of amino sugars and polyhydroxylated amino acids employ protected dihydroxyacetone derivatives, such as 2,2-dimethyl-1,3-dioxane-5-one, as donors. To make this $C_3 + C_n$ strategy more economic, it would be highly desirable if unmodified dihydroxyacetone (DHA, **1**),[13] which costs >230 times less than 2,2-dimethyl-1,3-dioxane-5-one, could be used directly as the biomimetic donor (Eq. 1):[14] natural aldolase enzymes use dihydroxyacetone phosphate as the donor.[15] However, despite intense research on the catalytic enantioselective Mannich reaction, there is no example of a direct catalytic highly enantioselective Mannich reaction with DHA **1** as the donor.



(1)

Based on our results that a primary amino acid or a small peptide can catalyze enantioselective aldol reactions and

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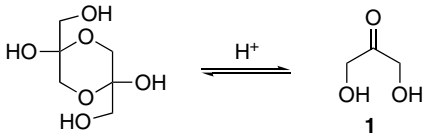
Mannich reactions using DHA **1** as the donor,[9a,14a] we decided to investigate the possibility of developing a catalytic asymmetric one-pot three-component Mannich reaction between **1**, anilines, and aldehydes (Eq. 1). Herein, we present the first examples of highly catalytic, enantioselective, one-pot three-component Mannich reactions with DHA as the donor which give the corresponding dihydroxy-β-aminoketones in high yields and up to 95% ee.

In an initial catalyst screen, the dimer of DHA **1** (0.25 mmol, Eq. 2), *p*-anisidine (0.23 mmol) **2**, 4-nitrobenzaldehyde (0.25 mmol), and acetic acid (0.023 mmol) were mixed in the presence of a catalytic amount of an amino acid derivative or peptide (20 mol %) in DMF (0.5 mL) (Table 1). We found that all the amino acids and peptides **5**–**12** tested catalyzed the formation of the corresponding PMP (*para*-methoxyphenyl)[16] protected β-amino ketone **4a** (Table 1). Proline **6** and threonine derivative **8**,[9b,d,e] mediated the Mannich reaction with the highest enantioselectivity. Moreover, the amino acids or peptides with a primary amine functionality were *anti*-selective whereas proline was *syn*-selective, which is in accordance with the literature.[9]

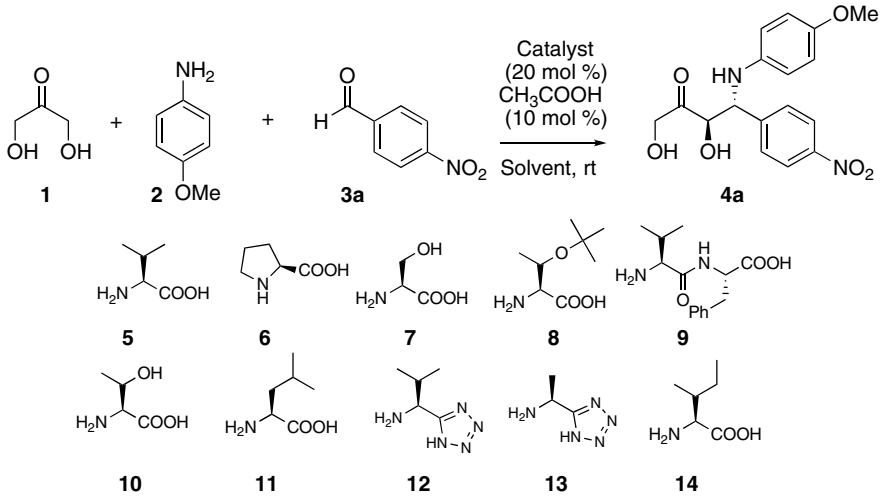
The role of the acetic acid is to catalyze the conversion of DHA dimer into monomer. Attempts to further improve the enantioselectivity of the reaction by changing acetic acid to benzoic acid derivatives were not successful.



(2)

Moreover, a solvent screen revealed that *N*-methylpyrrolidinone (NMP) gave the highest asymmetric induction when amino acid **8** was used as the catalyst. Under these conditions the dihydroxyacetone derived product **4a** was assembled in an asymmetric fashion with 4:1 dr (*anti*:*syn*) and 94% ee (Table 1, entry 11). Thus, we decided to use O-protected amino acid **8** as the catalyst and NMP

Table 1
Catalyst screen for the enantioselective Mannich reaction between **1**, **2** and **3a**[a]

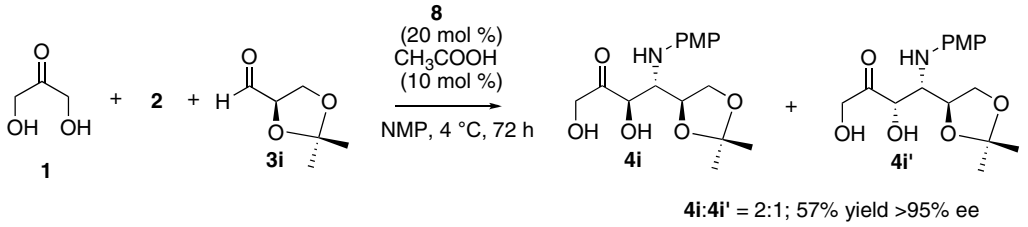


Entry	Catalyst	Solvent	Time (h)	Conv.[b] (%)	dr[c]	ee[d] (%)
1	**5**	DMF	48	46	3:1	14
2	**6**	DMF	48[e]	50[e]	1:3[e]	77[e]
3	**7**	DMF	48	51	2:1	23
4	**8**	DMF	18	100	3:1	87
5	**9**	DMF	18[f]	90[f]	2:1[f]	11[f]
6	**10**	DMF	72	40	2:1	38
7	**11**	DMF	48	85	2:1	20
8	**12**	DMF	17	50	1:1	7
9	**13**	DMF	18	80	1:1	6
10	**14**	DMF	48	47	2:1	8
11	**8**	NMP	18	81	4:1	94
12	**8**	DMSO	18	83	2:1	83

[a] Experimental conditions: A mixture of the dimer of DHA **1** (0.25 mmol), *p*-anisidine **2** (0.23 mmol), aldehyde **3a** (0.25 mmol), acetic acid (0.023 mmol) and catalyst (20 mol %) in 0.5 mL solvent was stirred at room temperature under the conditions shown in Table.
[b] Conversion as determined by NMR analysis.
[c] *Anti*/*syn* ratio as determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Determined by chiral-phase HPLC analysis.
[e] The data is given for the major *syn*-**4a**′ diastereoisomer.
[f] 5 equiv of water were added.

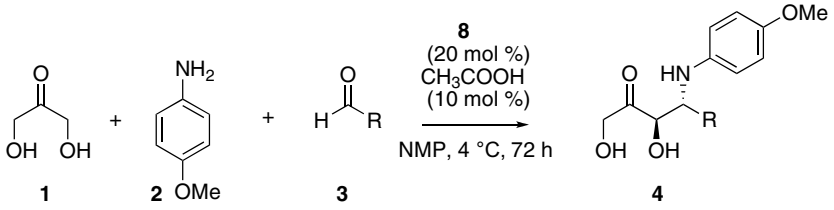
as the solvent (Table 2).[17] Decreasing the temperature to 4 °C slightly improved the enantioselectivity of the reaction (entry 1).

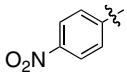
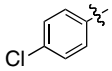
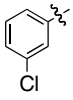
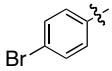
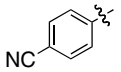
The organocatalytic Mannich-type reactions between DHA **1**, *p*-anisidine **2**, and acceptor aldehydes **3a**–**h** proceeded smoothly with moderate to high *anti*-selectivity (2:1–10:1 dr) and gave the corresponding α,α′-dihydroxy-β-amino ketones **4a**–**h** in high yields and ee's (82–95% ee). The reaction was effective for aliphatic and aromatic acceptor aldehydes. Moreover, the protected amino acid **8**-catalyzed one-pot three-component reaction between **1**, **2** and α-glyoxylate **2b** furnished the corresponding polyhydroxylated amino acid derivative **4b** in 80% yield with 10:1 dr and 87% ee. The use of protected D-glyceraldehyde **3i** as the acceptor allowed for the stereoselective assembly of 3-amino-D-psicose **4i** and 3-amino-D-fructose derivatives **4i′**, respectively, in a 2:1 ratio and 57% yield (>95% ee based on the starting D-glyceraldehyde derivative **3i**; Eq. 3).



(3)

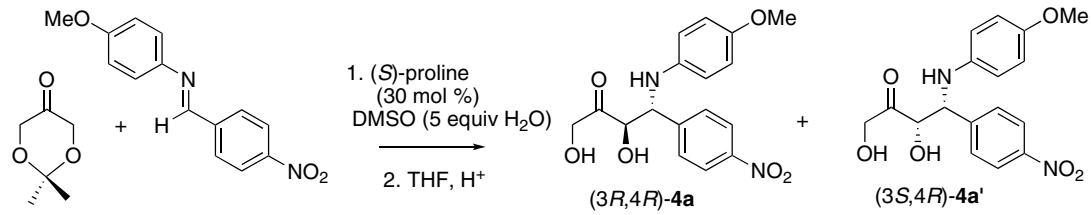
Table 2
Amino acid **8**-catalyzed enantioselective Mannich-type reactions between DHA **1**, **2** and aldehydes **3**[a]



Entry	R	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1		**4a**	72	3:1	95
2	CO_2Et	**4b**	80	10:1	87
3		**4c**	84	3:1	93
4		**4d**	64	3:1	94
5		**4e**	74	3:1	93
6	Ph	**4f**	58	3:1	87
7		**4g**	80	2:1	82
8		**4h**	60[e]	2:1	86[e]

[a] Experimental conditions: A mixture of the dimer of DHA **1** (0.25 mmol), *p*-anisidine **2** (0.23 mmol), aldehyde **3** (0.25 mmol), acetic acid (0.023 mmol) and catalyst **8** (20 mol %) in 0.5 mL NMP was stirred under the conditions displayed in Table.
[b] Isolated yield of pure compound **4**.
[c] *Anti*/*syn* ratio as determined by ^{1}H NMR of the crude reaction mixture.
[d] Determined by chiral-phase HPLC analysis.
[e] Results after 96 h.

The stereochemical outcome of the reaction was determined by synthesizing **4a** and **4a′** with the known absolute configuration in a 1:3 (*anti*:*syn*) ratio by the (*S*)-proline catalyzed Mannich-type reaction with 2,2-dimethyl-1,3-dioxane-5-one as the donor followed by acid catalyzed deprotection (Eq. 4).[12]



(4)

Comparison of the retention times of these products by chiral-phase HPLC analysis with the products **4a** and **4a′** derived using the catalyst screened in Table 1 confirmed that the same major enantiomers were formed. On the basis of the absolute configuration, we propose transition-state model **I** to account for the diastereo- and enantioselectivity of the linear (*S*)-amino acid catalyzed formation of DHA derived ketones **4** and transition state **II** to account for the (*S*)-proline catalyzed Mannich reaction (Fig. 1). Hence, the linear (*S*)-amino acids form a *cis*-enamine with DHA, possibly due to hydrogen-bonding, that is attacked by the *N*-PMP protected imine from its *Re*-face providing the dihydroxy-β-amino ketones with an *anti*-configuration. In contrast, (*S*)-proline forms the *trans*-enamine which is attacked from its *Si*-face providing the products with *syn*-configuration. This is in accordance with the literature.[7–12]

In summary, we have reported amino acid-catalyzed, one-pot three-component Mannich reactions between dihydroxyacetone, *p*-anisidine, and aldehydes. The reaction is an inexpensive direct entry to α,α′-dihydroxy-β-amino ketones in high yields and 82–95% ee. The biomimetic one-pot reaction can also be used for the synthesis of amino sugars. Further investigations of DHA in asymmetric reactions, catalyst design, and mechanistic and molecular modeling studies are ongoing.

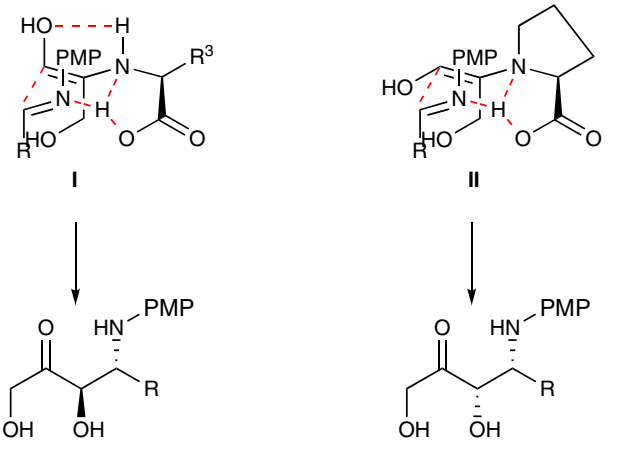


Fig. 1. (a) Proposed transition state models **I** and **II** for the direct primary (*S*)-amino acid- and proline-catalyzed three-component asymmetric Mannich reactions with DHA, respectively.

Acknowledgement

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17. Typical experimental procedure for the Mannich reactions with DHA. To a stirred solution of aldehyde **3** (0.25 mmol), acetic acid (0.023 mmol) and *p*-methoxyanisidine **2** (0.225 mmol) in NMP (0.5 mL) were added catalyst **8** (20 mol %) and the dimer of DHA **1** (0.25 mmol). The reaction mixture was stirred at +4 °C for 72 h. The crude reaction mixture was purified by column chromatography (pentane–EtOAc mixtures) to afford the corresponding dihydroxy-β-amino ketones **4**. *anti*-**4a**: Yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.16$ (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 6.72 (d, $J = 8.4$ Hz, 2H), 6.57 (d, $J = 8.4$ Hz, 2H), 4.89 (d, $J = 4.4$ Hz, 1H), 4.81 (d, $J = 4.0$ Hz, 1H), 4.45 (d, $J = 20$ Hz, 1H), 4.15 (d, $J = 20$ Hz, 1H), 3.70 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 210.1$, 153.6, 148.0, 145.2, 139.2, 128.9, 124.1, 116.3, 115.2, 77.3, 67.4, 61.0, 55.9; HRMS (ESI): calcd for [M+Na] ($C_{17}H_{18}N_2O_6$) requires *m*/*z* 369.1057; found, 369.1049, $[\alpha]_D^{23}$ −25.0 ($c = 1$, $CHCl_3$). The enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane–*i*-PrOH = 88:12, $\lambda = 254$ nm), 1.0 mL/min; *anti*-diastereomer:major enantiomer $t_r = 63.9$ min, minor enantiomer = 83.7 min. *syn*-**4a**′: Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.16$ (d, $J = 8.70$ Hz, 2H), 7.52 (d, $J = 8.70$ Hz, 2H), 6.47 (d, $J = 8.80$ Hz, 2H), 5.00 (d, $J = 2.04$ Hz, 1H), 4.60 (d, $J = 2.34$ Hz, 1H), 4.55 (s, 2H), 4.43 (d, $J = 19.91$ Hz, 1H), 4.11 (d, $J = 19.98$, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 209.4, 153.7, 141.7, 139.2, 129.4, 128.2, 126.1, 115.6, 114.9, 78.3, 66.2, 60.0, 55.7; $[\alpha]_D$ −4.5 ($c = 0.5$, $CHCl_3$). HRMS (ESI): calcd for $[M+H]^+$ ($C_{17}H_{18}N_2NaO_6$) requires *m*/*z* 369.1057; found, 369.1049. The enantiomeric excess was determined by HPLC with an OD-H column (*n*-hexane–*i*-PrOH = 88:12, $\lambda =$ 254 nm), 1.0 mL/min; *syn*-diastereomer:major enantiomer $t_r =$ 47.5 min, minor enantiomer = 55.7 min.