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Acyclic β-amino acid catalyzed asymmetric *anti*-selective Mannich-type reactions

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Abstract—The ability of a primary amine containing acyclic β^3-amino acids to catalyze direct asymmetric *anti*-selective Mannich-type reactions is presented. The reactions are generally highly diastereo- and enantioselective to give the corresponding Mannich products with up to >19:1 dr (*anti*/*syn*) and 88–99% ee.

1. Introduction

The direct asymmetric Mannich reaction is one of the most important C–C bond-forming reactions in the construction of optically active nitrogen containing compounds.[1–3] In particular, the development of catalytic stereoselective methods for the asymmetric directed Mannich-type reaction has recently been the subject of intense research.[4–6] One powerful way of catalyzing the direct asymmetric Mannich reaction is the use of proline and proline derivatives as catalysts.[7] More recently, acyclic amino acids and their derivatives have been successfully used as catalysts for the direct intermolecular asymmetric Mannich reaction.[8] There are several reports of organocatalytic direct *syn*-selective asymmetric Mannich-type reactions.[5,7,8] However, there are only a few reports of organocatalytic *anti*-selective Mannich-type reactions.[9] In this context, Maruoka[10] and Barbas have developed chiral cyclic amine and pyrrolidine derivatives, respectively, as catalysts for *anti*-selective Mannich-type reactions with ketones as nucleophiles.[11] Moreover, Barbas et al. most recently showed that linear α-amino acids can catalyze the highly *anti*-selective addition of hydroxyacetone to imines.[11b] Based on our original findings that acyclic amino acids can catalyze highly enantioselective, direct asymmetric Mannich reactions and the recent reports of β-amino acid catalyzed asymmetric aldol reactions,[8,12] we envisioned that linear β-amino acids could possibly be used as catalysts for the direct asymmetric Mannich-type reaction. In addition, we predicted that the use of a homologous β-amino acid as a catalyst would change the facial selectivity on the attack of the chiral (*E*)-enamine intermediate resulting in an *anti*-selective Mannich-type reaction via the possible transition state **I** as compared to transition state **II** and transition state **III** of the linear amino acid catalyzed *syn*-selective Mannich reaction (Scheme 1). Molecular modeling indicated that the proton transfer from the carboxyl group of the β-amino acid to the nitrogen of the imine would be more favored in transition state **I** as compared to transition state **II**.

Herein, we report for the first time that acyclic β^3-amino acids catalyze direct asymmetric *anti*-selective Mannich-type reactions with ketones as nucleophiles with high diastereo- and enantioselectivity (up to >19:1 dr, 88–99% ee).

2. Results and discussion

After an initial catalyst and solvent screen, we found that β^3-amino acids, such as **4**–**6**, catalyzed the asymmetric addition of cyclohexanone **1a** to *N*-*para*-methoxyphenyl (PMP) protected α-imino glyoxylate **2** in wet DMSO to form amino acid derivative **3a** (Table 1).[13]

To our delight, the reactions were highly chemo-, diastereo-, and enantioselective and gave amino acid derivative **3a** in 52–92% yield with >19:1 dr (*anti*/*syn*) and 90–94% ee, respectively (entries 1–3). Notably, the acyclic β-amino acid catalyzed reactions proceeded with excellent *anti*-selectivity. In comparison, α-amino acids such as alanine **7** catalyze the reaction with high *syn*-selectivity (entry 4).[8] Thus,

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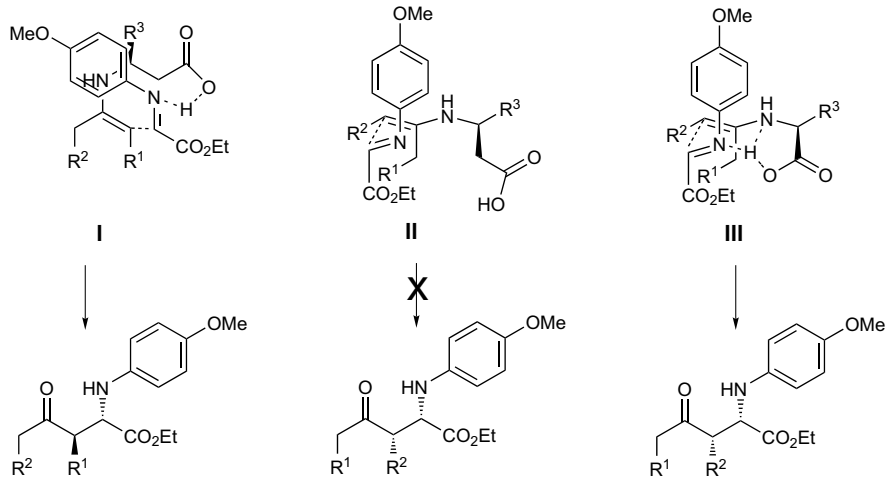
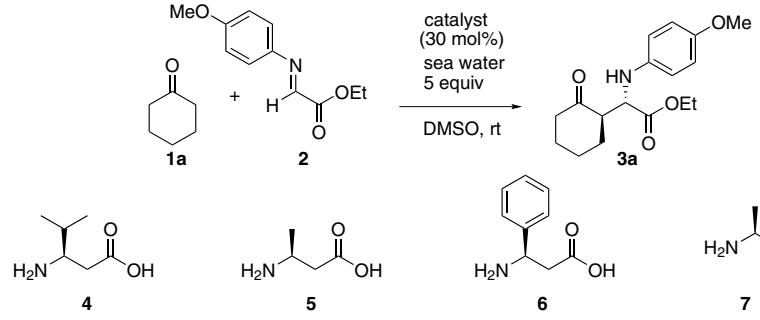


Scheme 1.

Table 1. Catalyst screen for the enantioselective Mannich-type reactions between **1a** and **2**[a]



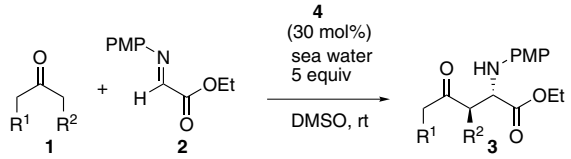
Entry	Cat.	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**4**	16	68	>19:1	94
2	**5**	16	52	>19:1	91
3	**6**	16	92	>19:1	90
4	**7**	14	60[e]	1:16[e]	98[e]
5	**5**	16	48	>19:1	90[f]

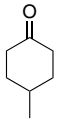
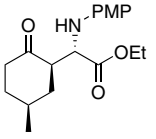
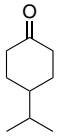
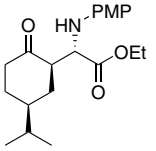
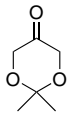
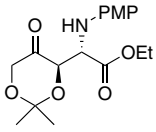
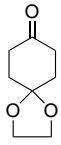
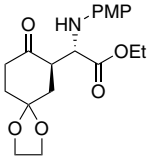
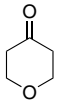
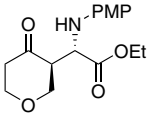
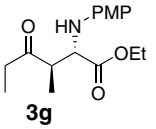
[a] Experimental conditions: A mixture of **1** (0.25 mmol), cyclohexanone **1a** (2.5 mmol), synthetic sea water (1.25 mmol, Aldrich ASTM D665), and catalyst (30 mol %) in 1.0 mL DMSO was stirred under the conditions displayed in the table.
[b] Isolated yield of pure compound **3a**.
[c] *anti*/*syn* ratio as determined by the ^{1}H NMR of the crude reaction mixture.
[d] Determined by chiral-phase HPLC analysis.
[e] Reaction conditions according to Ref. 8.
[f] 0.8 M NaCl solution (1.25 mmol) was used instead of synthetic seawater ASTM D665.

the strategy of employing the homologous acyclic β-amino acids as catalysts for *anti*-selective Mannich-type reactions was successful. Moreover, a small amount of synthetic sea-water ASTM D665 (purchased from Aldrich) improved the enantioselectivity and accelerated the β-amino acid catalyzed reactions.[14] The small amount of synthetic sea water can also be exchanged for a 0.8 M NaCl solution, which gave similar results (entry 5). Encouraged by these results, we decided to investigate the scope of the acyclic β-amino acid catalyzed Mannich-type reaction between different ketones **1** and imine **2** using amino acid **4** as the catalyst (Table 2).[15]

(*S*)-β-Homovaline **4** generally mediated the Mannich-type reactions with ketones **1a**–**1g** with excellent *anti*-selectivity and high enantioselectivity to give the corresponding amino acid derivatives **3a**–**3g** in up to >19:1 dr and 88–99% ee. The reactions with cyclohexanones as nucleophiles were the most efficient. For example, the Mannich-type reaction between ketone **1b** and imine **2** gave the corresponding diastereomers **3b** and **3b′** (**3b**:**3b′**—2:1) in 60% combined yield with 99% ee, respectively (entry 2). The β-homovaline **4**-catalyzed Mannich addition with linear aliphatic 3-pentanone **1g** as the donor was slow and low yielding but highly diastereo- and enantioselective (entries 6 and 7). Nevertheless, the results show that the plethora of primary amine containing β-amino acids should be considered as catalysts for direct asymmetric *anti*-selective Mannich-type reactions with ketones as nucleophiles.

Table 2. β[3]-Amino acid **4**-catalyzed enantioselective Mannich-type reactions between ketones **1** and **2**[a]



Entry	Ketone	Product	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	**3a**	16	68	>19:1	94
2	 **1b**	 **3b** **3b'**	16	60[e] (**3b**:**3b**′—2:1)[e]	>19:1	99
3	 **1c**	 **3c** **3c'**	16	51[f] (**3c**:**3c**′—1:1)[f]	>19:1	94
4	 **1d**	 **3d**	16	70	1:2	99
5	 **1e**	 **3e**	16	44	>19:1	93
6	 **1f**	 **3f**	16	20	>19:1	99
7	**1f**	**3f**	16	27[g]	>19:1[g]	99[g]
8	 **1g**	 **3g**	72	12	>19:1	88

[a] Experimental conditions: A mixture of **2** (0.25 mmol), ketone **1** (2.5 mmol), sea water (1.25 mmol), and catalyst (30 mol %) in 1.0 mL DMSO was stirred under the conditions displayed in the table.
[b] Isolated yield of pure compound **3**.
[c] *anti*/*syn* ratio as determined by ^{1}H NMR of the crude reaction mixture.
[d] Determined by chiral-phase HPLC analysis.
[e] Combined yield of **3b** and **3b**′ (**3b**:**3b**′—2:1 as determined by ^{1}H NMR of the crude reaction mixture).
[f] Combined yield of **3c** and **3c**′ (**3c**:**3c**′—1:1 as determined by ^{1}H NMR of the crude reaction mixture).
[g] Reaction performed with β[3]-amino acid **6** as the catalyst. PMP = *para*-methoxyphenyl.

The stereochemical outcome of the reaction was determined by epimerization of the (2*S*,3*S*)-*syn*-diastereomer of the Mannich product **3a** derived by (*S*)-proline catalysis and comparison with the literature.[11a,16] The experiment revealed that (2*S*,3*R*)-*anti*-**3a** was formed by (*S*)-β[3]-amino acid catalysis. On the basis of the absolute configuration,

we propose transition-state model **I** to account for the diastereo- and enantioselectivity of the (*S*)-β^3-amino acid catalyzed formation of (*S*)-amino acid derivatives **3** (Scheme 1). As a result, the (*S*)-β-amino acids form an enamine with the ketone, which is attacked by the N-PMP protected imine from its *Re*-face providing (2*S*,3*R*)-*anti*-β-amino acid derivatives.

3. Conclusion

In conclusion, we have reported for the first time that primary amine containing acyclic β^3-amino acids catalyze direct *anti*-selective Mannich-type reactions with ketones as nucleophiles. The reactions generally proceeded with high diastereo- and enantioselectivity and the corresponding amino acid derivatives are assembled in an asymmetric fashion with up to >19:1 dr and 88–99% ee. Thus, a great number of β^3-amino acids should be considered as catalysts for the direct asymmetric Mannich reaction. Further investigations of the use of acyclic β-amino acids as catalysts in asymmetric Mannich reactions, mechanistic and molecular modeling studies are ongoing.

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13. In a typical experiment, ketone **1a** (2.5 mmol) was dissolved in DMSO (1 mL) and the β-amino acid (0.07 mmol, 30 mol %) was added to the solution followed by the N-PMP-protected α-imino ester **2** (0.25 mmol) and sea water (1.25 mmol, 5 equiv). After stirring for 14 h, the reaction mixture was purified by flash column chromatography (toluene/EtOAc mixtures) to give the pure amino acid derivative **3a**. Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, $J = 8.75$ Hz, 2H), 6.63 (d, $J = 8.75$ Hz, 2H), 4.17 (m, 2H), 3.98 (d, $J = 3.90$ Hz, 1H), 3.74 (s, 3H), 3.14–3.08 (m, 1H), 2.50–2.41 (m, 1H), 2.38–2.28 (m, 1H), 2.18–2.10 (m, 2H), 1.98–1.88 (m, 2H), 1.76–1.66 (m, 2H), 1.21 (t, $J = 7.14$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.0, 173.1, 152.8, 142.2, 115.6, 114.8, 61.2, 59.1, 55.7, 53.6, 41.8, 30.5, 26.9, 24.6, 14.1. MS: calcd for $C_{17}H_{23}NO_4Na$ (MNa^+) 328.1525, found 328.1519. HPLC (AD, hexane/isopropanol 90:10, 0.5 mL/min, $\lambda = 254$ nm): t_R (*anti* minor enantiomer) = 33.4 min; t_R (*anti* major enantiomer) = 41.6 min. $[\alpha]_D^{25} = +18.0$ (c 1.0, 94% ee).
14. The addition of either synthetic seawater or 0.8 M NaCl solution had a better effect than the addition of pure water. Synthetic sea water ASTM D665 was purchased from Aldrich and contains 0.5–0.9 M NaCl. The addition of NaCl has also been succesfully used in a chiral pyrrolidine-catalyzed direct Michael reaction. See: Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966.
15. In a typical experiment, ketone **1** (2.5 mmol) was dissolved in DMSO (1 mL) and the β-amino acid (0.07 mmol, 30 mol %) was added to the solution followed by the N-PMP-protected α-imino ester **2** (0.25 mmol) and sea water (1.25 mmol, 5 equiv). After stirring for the time given in the table, the reaction mixture was purified by flash column chromatography (toluene/EtOAc mixtures) to give the pure amino acid derivative **3a**.
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