

Acyclic Chiral Amines and Amino Acids as Inexpensive and Readily Tunable Catalysts for the Direct Asymmetric Three-Component Mannich Reaction

Ismail Ibrahim, Weibiao Zou, Magnus Engqvist, Yongmei Xu, and Armando Córdoba*^[a]

Abstract: The direct three-component asymmetric Mannich reaction catalyzed by acyclic chiral amines or amino acids is presented. Simple acyclic chiral amines and amino acids—such as alanine–tetrazole (**9**), alanine, valine, and serine—catalyzed the three-component asymmetric Mannich reactions between

unmodified ketones, *p*-anisidine, and aldehydes with high chemo- and stereoselectivity, furnishing the corre-

Keywords: acyclic • amino acids • asymmetric catalysis • chiral amines • Mannich reaction

sponding Mannich bases with up to > 99% *ee*. This study demonstrates that the whole range of amino acids in nature, as well as nonproteogenic amino acid derivatives, can be considered in the design and tuning of novel, inexpensive organocatalysts for the direct asymmetric Mannich reaction.

Introduction

The Mannich reaction is one of the most important C–C bond-forming reactions for the production of nitrogenous molecules.^[1–2] It has been applied numerous times in the synthesis of pharmaceutically valuable compounds and natural products. Furthermore, it allows for the generation of structural diversity.

The initial stoichiometric and indirect stereoselective Mannich-type reactions utilized preformed chiral enol equivalents or imines.^[3] In this context, the development of catalytic asymmetric Mannich-type reactions has been an important achievement.^[4] The first examples of catalytic, asymmetric addition reactions of preformed enolates to imines by the groups of Kobayashi^[5] and Tomioka^[6] were followed by the work of Sodeoka and Lectka.^[7] In parallel to these excellent organometallic-complex-catalyzed indirect Mannich reactions, Shibasaki and co-workers reported direct enantioselective Mannich-type reactions that are catalyzed by heterodimetallic complexes.^[8] Recently, dinuclear zinc organometallic complexes and chiral copper(II)bisoxazoline (BOX) complexes have been utilized with much success by the groups of Shibasaki,^[9] Trost,^[10] and Jørgensen.^[11]

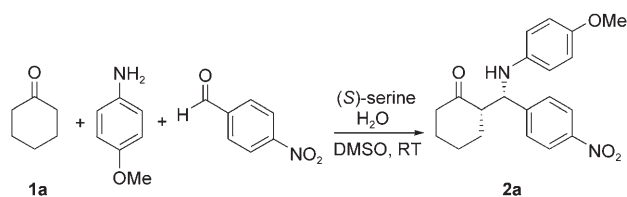
in direct catalytic Mannich-type reactions between ketones and preformed imines.

The renaissance in organocatalysis has also led to the development of several stereoselective Mannich reactions catalyzed by amino acids.^[12] The first example of a direct organocatalytic three-component Mannich reaction was reported by List^[13] and was followed by the excellent work of several groups.^[14] In all of these enamine-catalyzed Mannich-type reactions, proline and proline derivatives have been utilized as highly stereoselective catalysts. However, acyclic amino acids have not to our knowledge been investigated as catalysts for the direct asymmetric Mannich reaction.^[13–14] Our interest in investigating whether acyclic amino acids or amines would be able to catalyze the direct asymmetric Mannich reaction is based on the following: the dramatic expansion of catalyst structures that would arise, our interest in organocatalysis,^[15] the possible employment of a whole range of amino acids, and our finding that linear amino acids catalyze the direct asymmetric aldol reaction.^[16] Herein, we present the unprecedented ability of acyclic chiral amines and amino acids to catalyze the direct three-component Mannich reaction with high enantioselectivity.

Results and Discussion

We found that by stirring cyclohexanone **1a**, *p*-nitrobenzaldehyde, *p*-anisidine, H₂O,^[17] serine, and dimethylsulfoxide for 48 h, the corresponding Mannich product **2a** was formed in a 60% yield with 6:1 d.r. (*syn/anti*) and 94% *ee* (Scheme 1). The reaction proceeded with excellent chemo-

[a] I. Ibrahim, Dr. W. Zou, Dr. M. Engqvist, Dr. Y. Xu, Prof. Dr. A. Córdoba
Department of Organic Chemistry, Arrhenius Laboratory
Stockholm University, 106 91 Stockholm (Sweden)
Fax: (+46) 8-154-908
E-mail: acordova@organ.su.se
acordova1a@netscape.net



Scheme 1. The reaction of cyclohexanone **1a** (1.5 mmol), *p*-nitrobenzaldehyde (0.50 mmol), *p*-anisidine (0.45 mmol), H₂O (1 mmol, 18 μ L, 2 equiv),^[17] serine (30 mol %), and dimethylsulfoxide (DMSO; 2 mL) for 48 h produced the corresponding Mannich product **2a** in a 60% yield with 6:1 d.r. (*syn/anti*) and 94% *ee*.

selectivity and only trace amounts of aldol addition products were observed. Furthermore, the primary amino acid did not act as the amine component under our reaction conditions. In comparison, proline catalyzes the formation of **2a** in a 50% yield with 2:1 d.r. and 84% *ee*.^[13] Encouraged by our initial experiment, we screened several acyclic chiral amines and amino acids to be used as a catalyst for the direct one-pot three-component asymmetric Mannich reaction (Table 1).

All the amino acids tested catalyzed the reaction with excellent chemoselectivity and the simple aliphatic acyclic amino acids mediated the asymmetric assembly of **2a** with high enantioselectivity. For example, (S)-alanine (**4**) catalyzed the formation of **2a** in a 42% yield and 98% *ee* within 14 h (entry 7). The yield was increased to 68% by increasing the reaction time to 48 h, however, the *ee* was decreased to 86% (entry 5). Thus, loss of enantioselectivity occurred at prolonged reaction times. In order to increase the nucleophilicity of the amine and increase the yield of the Mannich product, we added one equivalent of dicyclohexyl amine to the reaction mixture. In fact, addition of dicyclohexyl amine to the reactions catalyzed by a linear amino acid (**4**) reduced the decrease of *ee* of **2a** (entry 8). Moreover, the aliphatic amino acids serine, valine, isoleucine, and leucine catalyzed the direct three-component asymmetric formation of **2a** with 2:1–6:1 d.r. and 91–94% *ee*. The addition of a small amount of water to the Mannich reactions catalyzed by a primary amino acid (1–5 equiv) slightly improved the yield of **2a**. The conversion of simple acyclic amino acids to tetrazole derivatives such as **9** improved the solubility as well as the catalytic efficiency of the organocatalysts in the asymmetric formation of **2a**.^[14f] For example, linear chiral amine **9** catalyzed the formation of **2a** in an 89% yield with 6:1 d.r. and 94% *ee* within 12 h (entry 14). In this case, the highest efficiency was obtained when no water was added to the reaction mixture. Moreover, linear dipeptides with an acyclic amino acid at the terminal residue were also catalysts for the direct three-component asymmetric Mannich reaction.^[18] Hence, there is the possibility to synthesize several new organocatalysts in a combinatorial fashion. We next investigated the three-component Mannich reactions catalyzed by an acyclic amino acid or a chiral amine for a set of different ketones and their application in the asymmetric synthesis of functional amino acid derivatives (Table 2).

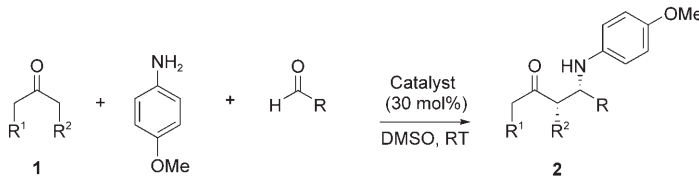
Table 1. Examples of screened catalysts for the direct catalytic asymmetric three-component Mannich reaction between **1a**, *p*-anisidine, and *p*-nitrobenzaldehyde.^[a]

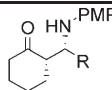
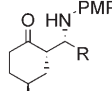
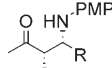
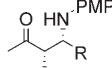
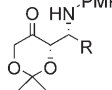
Entry	Catalyst	<i>t</i> [h]	Yield [%] ^[b]	d.r. ^[c]	Sel. [% <i>ee</i>] ^[d]
1	3	48	60	6:1	94
2	3	48 ^[e]	60 ^[e]	2:1 ^[e]	98 ^[e]
3	4	24	32	3:1	90
4	4	14	30	3:1	> 99
5	4	48 ^[f]	68 ^[f]	3:1 ^[f]	86 ^[f]
6	4	24 ^[g]	27 ^[g]	3:1 ^[g]	90 ^[g]
7	4	14 ^[h]	42 ^[h]	3:1 ^[h]	98 ^[h]
8	4	48 ^[e]	40 ^[e]	2:1 ^[e]	99 ^[e]
9	5	48	65	2:1	91
10	6	48	60	3:1	82
11	7	48	61	4:1	85
12	8	48	75	2:1	79
13	9	12	74	3:1	94
14	9	12 ^[g]	89 ^[g]	3:1 ^[g]	94 ^[g]
15	10	48	82	3:1	58
16	11	48	38	6:1	93
17	12	48	18	3:1	91

[a] In a typical experiment, the catalyst (30 mol %) was added to a mixture of ketone **1a** (1.5 mmol), *p*-anisidine (0.45 mmol), and *p*-nitrobenzaldehyde (0.5 mmol) and H₂O (1 mmol) in DMSO (2.0 mL). [b] Isolated yield of the pure aldol products after silica gel column chromatography based on the amine component. [c] *Syn/anti* ratio as determined by NMR analyses. [d] Determined by chiral-phase HPLC analyses. [e] 1 equiv of dicyclohexyl amine was added. [f] 5 equiv of water were added. [g] No water was added. [h] 10 equiv of the ketone were used.

The acyclic amino acids and chiral amine **9** catalyzed the three-component asymmetric Mannich reactions with high chemoselectivity, and the corresponding products and amino acid derivatives **2** were isolated in up to 90% yields and up to >99% *ee*. In particular, chiral amine **9** catalyzed the enantioselective Mannich reactions with excellent diastereo- and enantioselectivities when cyclic ketones were used as the donors. For example, the reaction between ketone **1a**, *p*-anisidine, and α -glyoxylate catalyzed by **9** furnished the corresponding amino acid derivative **2b** in a 71% yield with 16:1 d.r. and >99% *ee* (entry 1). Furthermore, the three-component enantioselective Mannich reactions with unsymmetrical ketones such as **1c** were highly regioselective when catalyzed by chiral amine **9** and linear amino acids, and C–C bond formation occurred at the methylene carbon. The *p*-methoxyphenyl (PMP) group of the Mannich products of

Table 2. Direct three-component asymmetric Mannich reactions catalyzed by an acyclic chiral amine or amino acid.^[a]



Entry	Cat.	Ketone	R	Product	<i>t</i> [h]	Yield [%] ^[b]	d.r. ^[c]	Sel. [% <i>ee</i>] ^[d]
1	9	1a	CO ₂ Et		12	71	16:1	> 99
2	4	1a	CO ₂ Et	2b	14	60 ^[e]	16:1 ^[e]	98 ^[e]
3	<i>ent</i> - 4	1a	CO ₂ Et	<i>ent</i> - 2b	14	61 ^[e]	16:1 ^[e]	97 ^[e]
4	9	1a	4-BrC ₆ H ₄	2c	13	90	1:1	88
5	9		4-NO ₂ C ₆ H ₄		13	87	4:1 ^[f]	96
6	4		CO ₂ Et		14	31 ^[e]	> 19:1 ^[e]	97 ^[e]
7	9	1c	CO ₂ Et	2e	16	73	> 19:1	88
8	9	1c	4-NO ₂ C ₆ H ₄		13	52	4:1	84
9	4		CO ₂ Et		14	47 ^[e]	16:1 ^[e]	98 ^[e]
10	9	1d	CO ₂ Et	2g	14	60	16:1	99

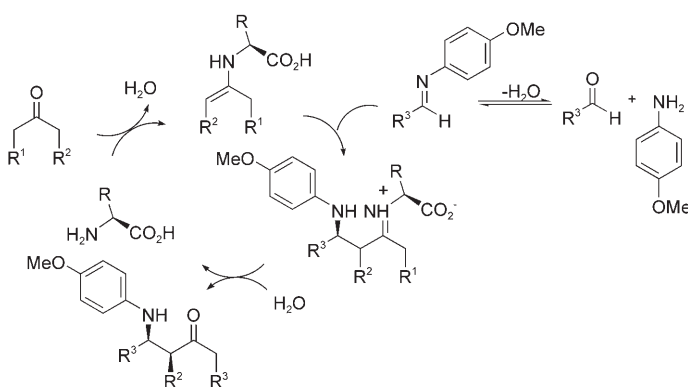
[a] In a typical experiment, the catalyst (30 mol%) was added to a mixture of ketone **1a** (1.5 mmol), *p*-anisidine (0.45 mmol), and aldehyde (0.5 mmol) in DMSO (2.0 mL). [b] Isolated yield of the pure aldol products after silica gel column chromatography based on the amine component. [c] *Syn/anti* ratio as determined by NMR analyses. [d] Determined by chiral-phase HPLC analyses. [e] 1 mmol H₂O was added. [f] The other diastereomer (**2d'**) with the methyl group pointing downwards was formed in a 1:1 (**2d'**/**2d**) ratio.

type **2** can be readily removed according to literature procedures.^[13–14] In addition, using the opposite enantiomer of the acyclic chiral amine or amino acid leads to the synthesis of the other enantiomer of the Mannich product (entry 3). Our investigation demonstrated that there is a large number of novel, simple organocatalysts that can be derived from acyclic natural and nonproteogenic amino acids, which could potentially be used and tuned as catalysts for the direct three-component asymmetric Mannich reaction.

Mechanism: The mechanism of the direct three-component Mannich reaction catalyzed by an acyclic amino acid is depicted in Scheme 2. The donor reacts with the primary amino acid, resulting in iminium formation. Next, the acceptor—in situ generated imine—reacts with the chiral enamine to give the desired enantiomerically enriched Mannich product after hydrolysis.

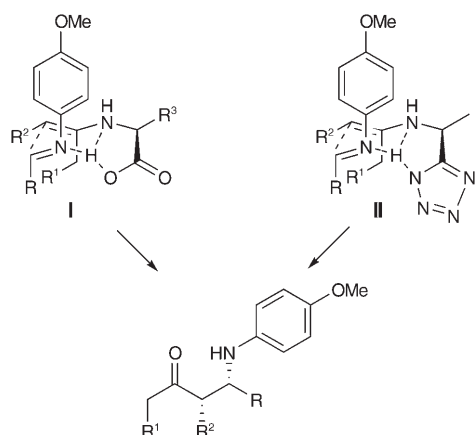
It was important to add 1–5 equivalents of water to the aldol reactions catalyzed by acyclic amino acid because it reduces the inhibition of intermediates of the catalytic cycle.^[14a]

Comparing the optical rotation values, NMR data, and retention times of chiral-phase HPLC analyses of Mannich product **2a** with the literature revealed that the *syn* diastereomer with a (2'*S*,1*S*)-**2a** absolute configuration was formed by acyclic and alanine–tetrazole catalysis.^[13] Furthermore, the spectral data and optical rotation values of amino acid derivatives of Mannich product **2b**, **2e**, and **2g** revealed that acyclic (*S*)-amino acids catalyze the formation of (*S*)-amino acid derivatives with *syn* relative stereochemistry.^[14] Based on the known absolute and relative configuration of Mannich product **2**,^[13–14] we propose that the direct acyclic asymmetric Mannich reactions catalyzed by (*S*)-amino acid and chiral amine **9** occurred via the plausible six-membered chair-like transition states **I** and **II**, respectively, for which the *Si* face of the catalytically generated chiral enamine is approached by the *Si* face of the in situ generated acceptor imine (Scheme 3). Thus, acyclic (*S*)-amino acids and amine **9** catalyzed the asymmetric synthesis



Scheme 2. Reaction mechanism of the direct asymmetric Mannich reaction catalyzed by a primary amino acid.

of functional linear (*S*)-amino acid derivatives with a *syn* relative configuration.



Scheme 3. Plausible transition states **I** and **II** for the direct three-component asymmetric Mannich reactions catalyzed by primary (*S*)-amino acid and amine **9**, respectively.

Conclusion

In summary, the first use of acyclic chiral amines and amino acids as catalysts for the direct asymmetric three-component Mannich reaction is presented. Simple linear amino acids and chiral amines such as alanine, valine, serine, isoleucine, and **9** catalyzed the direct three-component asymmetric Mannich reactions with excellent chemo-, regio-, and enantioselectivity, and the desired products were isolated in up to 90% yields and up to >99% *ee*. Hence, the study demonstrates that the full diversity of acyclic natural amino acids as well as nonproteogenic amino acid derivatives can be utilized in the design and tuning of novel, inexpensive organocatalysts for the direct asymmetric Mannich reaction. In addition, acyclic chiral amines and amino acids are environmentally benign and nontoxic. Development of novel catalyst libraries, mechanistic studies, and density functional theory calculations are ongoing.

Experimental Section

General methods: Chemicals and solvents were either purchased as puriss p.A. grade from commercial suppliers or purified by using standard techniques. For thin-layer chromatography (TLC), Merck 60 F254 silica gel plates were used and compounds were visualized by means of irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), Ce(SO₄)₂·H₂O (10 g), concentrated H₂SO₄ (60 mL), and H₂O (940 mL) followed by heating, or by treatment with a solution of *p*-anisaldehyde (23 mL), concentrated H₂SO₄ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed by using silica gel Merck 60 of particle size 0.040–0.063 mm. ¹H and ¹³C NMR spectra were recorded on a Varian AS 400 spectrometer: chemical shifts are given in δ relative to tetramethylsilane (TMS) and the coupling constants *J* are given in Hz. The spectra were recorded by using CDCl₃ as the solvent at room temperature, TMS served as the internal standard (δ =0 ppm) for ¹H NMR analyses, and CDCl₃ was used as the internal standard (δ =77.0 ppm) for ¹³C NMR analyses. GC analysis was carried out by using a Varian 3800 GC instrument with a CP-Chirasil-Dex CB chiral GC column (25 m×0.32 mm). HPLC analysis was carried out by using a Waters 2690 Millennium model with a pho-

todiode array detector. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter (δ =589 nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

Typical experimental procedure for the direct asymmetric Mannich reactions catalyzed by acyclic amino acid: A catalytic amount of acyclic (*S*)-amino acid or linear dipeptide (0.15 mmol, 30 mol %) was added to a vial containing the acceptor aldehyde (0.5 mmol), the donor ketone **2** (1.5 mmol), *p*-anisidine (0.45 mmol), and H₂O (1 mmol, 18 μ l) in DMSO (2 mL). After vigorously stirring the reaction mixture at room temperature for the times indicated in Tables 1 and 2, the reaction mixture was poured into an extraction funnel that contained brine (5.0 mL), which was then diluted with distilled H₂O (5.0 mL) and EtOAc (15 mL). The reaction vial was also washed with EtOAc (2 mL), which was poured into the extraction funnel. The aqueous phase was extracted with EtOAc (2×15.0 mL). The combined organic phases were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The reaction can also be quenched by directly putting the reaction mixture onto a silica gel column. The crude aldol product was purified by means of silica gel column chromatography (EtOAc/toluene mixtures) to furnish the desired Mannich product **2**. The *ee* values of the Mannich products **2** were determined by chiral-phase HPLC analysis.

Typical experimental procedure for the direct asymmetric Mannich reactions catalyzed by **9:** A catalytic amount of chiral amine **9** (0.15 mmol, 30 mol %) was added to a vial containing the acceptor aldehyde (0.5 mmol), the donor ketone **2** (1.5 mmol), and *p*-anisidine (0.45 mmol) in DMSO (2 mL). After vigorously stirring the reaction mixture at room temperature for the times indicated in Tables 1 and 2, the reaction mixture was poured into an extraction funnel that contained brine (5.0 mL), which was then diluted with distilled H₂O (5.0 mL) and EtOAc (15 mL). The reaction vial was also washed with EtOAc (2 mL), which was poured into the extraction funnel. The aqueous phase was extracted with EtOAc (2×15.0 mL). The combined organic phases were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The reaction can also be quenched by directly putting the reaction mixture onto a silica gel column. The crude aldol product was purified by silica gel column chromatography (EtOAc/toluene mixtures) to furnish the desired Mannich product **2**. The *ee* values of the Mannich products **2** were determined by chiral-phase HPLC analysis.

Compound 2a: HPLC (Daicel Chiralpak AD, *iso*-hexanes/*i*PrOH=85:15, flow rate 0.5 mL min⁻¹, λ =254 nm): major *anti* isomer: *t*_R=59.80 min; minor *anti* isomer: *t*_R=53.41 min; [α]_D=−7.0 (*c*=1.0, MeOH); ¹H NMR (CDCl₃, 400 MHz): δ =1.59–2.14 (m, 4H), 2.04 (m, 2H), 2.38 (m, 2H), 2.83 (m, 1H), 3.67 (s, 3H; OMe), 4.38 (brs, 1H), 4.79 (d, *J*=4.0 Hz, 1H), 6.45 (d, *J*=8.8 Hz, 2H), 6.66 (d, *J*=8.8 Hz, 2H), 7.54 (d, *J*=8.7 Hz, 2H), 8.12 ppm (d, *J*=8.7 Hz, 2H); ¹³C NMR (100 MHz): δ =24.9, 27.0, 28.8, 42.4, 55.5, 56.3, 58.0, 114.6, 115.5, 123.5, 128.5, 140.7, 146.9, 149.8, 152.6, 210.7 ppm; MALDI-TOF MS: *m/z* calcd for C₂₀H₂₂N₂O₄: 377.1477 [*M*+Na⁺]; found: 377.1481.

Compound 2b: HPLC (Daicel Chiralpak AS, *iso*-hexanes/*i*PrOH=94:6, flow rate 0.5 mL min⁻¹, λ =254 nm): major isomer: *t*_R=33.87 min; minor isomer: *t*_R=40.49 min; [α]_D=−40.1 (*c*=1.1, CHCl₃); ¹H NMR (CDCl₃, 400 MHz): δ =1.22 (t, *J*=7.0, 3H), 1.65–2.50 (m, 9H), 2.81 (m, 1H), 3.74 (s, 3H; OMe), 4.15 (m, 2H), 4.23 (d, *J*=5.3 Hz, 1H), 6.71–6.78 ppm (m, 4H); ¹³C NMR (100 MHz): δ =14.1, 24.7, 26.8, 29.5, 41.8, 53.5, 55.6, 58.0, 61.1, 114.6, 116.0, 141.0, 152.9, 173.4, 210.1 ppm.

Compound 2c: HPLC (Daicel Chiralpak AS, *iso*-hexanes/*i*PrOH=80:20, flow rate 0.5 mL min⁻¹, λ =254 nm): major *syn* isomer: *t*_R=26.61 min; minor *syn* isomer: *t*_R=25.10 min; [α]_D²⁵=−8.9 (*c*=1.8, CHCl₃); ¹H NMR (CDCl₃, 400 MHz; *syn/anti*=1:1): δ =1.59–1.73 (m, 6H), 1.82–1.93 (6H), 2.29–2.38 (m, 4H), 2.66–2.76 (m, 2H), 3.67 (s, 3H; OMe), 3.68 (s, 3H; OMe), 4.49 (d, *J*=6.8 Hz, 1H), 4.64 (d, *J*=4.42 Hz, 1H), 6.45 (d, *J*=5.0 Hz, 2H), 6.48 (d, *J*=5.0 Hz, 2H), 6.65 (d, *J*=3.5 Hz, 2H), 6.67 (d, *J*=3.5 Hz, 2H), 7.22 (d, *J*=5.9 Hz, 2H), 7.24 (d, *J*=5.9 Hz, 2H), 7.39 (d, *J*=3.4 Hz, 2H), 7.41 ppm (d, *J*=3.4 Hz, 2H); ¹³C NMR (100 MHz): δ =25.1, 25.2, 27.2, 27.3, 28.1, 28.8, 42.2 (2C), 55.8 (2C), 56.7, 57.4, 58.0, 58.6, 114.7, 114.9, 115.3, 115.8, 121.0, 121.2, 129.4, 129.6, 131.6, 131.7, 140.9, 141.2 (2C), 141.4, 152.5 (2C), 211.6, 212.8 ppm.

Compounds 2d and 2d': HPLC (Daicel Chiralpak AD, *iso*-hexanes/*i*PrOH=90:10, flow rate 0.5 mL min⁻¹, λ =254 nm): **2d** major isomer: t_R =84.18 min; minor isomer: t_R =71.50 min; **2d'** major isomer: t_R =54.90 min; minor isomer: t_R =51.60 min; $[\alpha]_D^{25}$ =-32.0 (c =1.4, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ =1.07 (dd, J =6.8 Hz, 6H), 1.62–1.74 (m, 2H), 1.87–1.93 (m, 4H), 1.96–2.03 (m, 4H), 2.39–2.44 (m, 2H), 2.92–2.97 (m, 2H), 3.65 (s, 3H; OMe), 3.66 (s, 3H; OMe), 4.78 (d, J =4.1 Hz, 2H), 6.45 (d, J =9.0 Hz, 4H), 6.66 (d, J =8.9 Hz, 4H), 7.53 (d, J =8.8 Hz, 4H), 8.13 ppm (d, J =8.8 Hz, 4H); ¹³C NMR (100 MHz, CDCl₃) δ =26.9, 32.9, 34.9, 35.2, 38.9, 41.1, 52.8, 55.8, 58.8, 114.9, 115.8, 123.8, 128.7, 140.9, 147.2, 150.1, 152.8, 210.9 ppm.

Compound 2e: HPLC (Daicel Chiralpak AS, *iso*-hexanes/*i*PrOH=94:6, flow rate 0.5 mL min⁻¹, λ =254 nm): major isomer: t_R =31.10 min; minor isomer: t_R =42.80 min; $[\alpha]_D^{25}$ =-71.0 (c =1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ =1.19–1.26 (m, 6H), 2.23 (s, 3H; CH₃) 3.04 (m, 1H), 3.67 (s, 3H; OMe), 4.10–4.20 (m, 2H), 4.32 (m, 1H), 6.65 (d, J =8.9 Hz, 2H), 6.76 ppm (d, J =8.9 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ =12.1, 14.1, 28.4, 49.1, 55.5, 59.4, 114.7, 115.7, 140.5, 140.7, 153.0, 172.7, 209.2 ppm.

Compound 2f: HPLC (Daicel Chiralpak AS, *iso*-hexanes/*i*PrOH=97:3, flow rate 0.5 mL min⁻¹, λ =254 nm): major isomer: t_R =33.20 min; minor isomer: t_R =29.39 min; $[\alpha]_D^{25}$ =-2.3 (c =1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ =1.10 (d, J =7.0 Hz, 3H; CH₃), 2.16 (s, 3H; CH₃) 2.99–3.06 (m, 1H), 3.67 (s, 3H; OMe), 4.77 (d, J =5.1 Hz, 1H), 6.41 (d, J =8.8 Hz, 1H), 6.67 (d, J =8.8 Hz, 2H), 7.52 (d, J =8.8, 2H), 8.18 ppm (d, J =8.7, 2H); ¹³C NMR (100 MHz, CDCl₃) δ =11.2, 29.5, 52.7, 55.8, 59.4, 115.0, 115.2, 124.1, 128.2, 140.4, 147.4, 128.2, 140.4, 147.4, 149.6, 153.0, 209.9 ppm.

Compound 2g: HPLC (Daicel Chiralpak AD, *iso*-hexanes/*i*PrOH=97:3, flow rate 0.5 mL min⁻¹, λ =254 nm): major isomer: t_R =32.95 min; minor isomer: t_R =37.41 min; $[\alpha]_D^{25}$ =-15.8 (c =1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ =1.23 (t, J =7.1 Hz, 3H), 1.44 (s, 3H; CH₃), 1.44 (s, 3H; CH₃), 1.49 (s, 3H; CH₃), 3.72 (s, 3H; OMe), 4.01 (d, J =16.6 Hz, 1H), 4.14 (m, 2H), 4.29 (dd, J =16.4, 1.5 Hz, 1H), 4.58 (d, J =2.0 Hz, 1H), 4.73 (m, 1H), 6.72–6.77 ppm (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ =14.4, 23.5, 24.5, 55.8, 59.1, 61.7, 67.0, 67.3, 101.1, 114.9, 117.2, 141.1, 153.8, 171.5, 206.5 ppm.

Synthesis of alanine-tetrazole (9): NH₄HCO₃ (0.89 g, 1.26 equiv) was added to a solution of Boc₂O (2.5 g, 1.3 equiv; Boc=1,1-dimethylethoxy-carbonyl) and Cbz-Ala (2.0 g; Cbz=phenylmethoxycarbonyl) in MeCN (14 mL) and pyridine (Py, 2.2 mL, 3 equiv), and the reaction mixture was stirred overnight at RT. The solvents were removed by evaporation and the residue was dissolved in EtOAc and washed with water (2×15 mL). The water was re-extracted with EtOAc and the combined volume of EtOAc was dried over MgSO₄, filtered, and concentrated. The crude product was weakly UV active and had an R_f value of 0.42 (MeOH/DCM 1:9). ¹H NMR (400 MHz, CDCl₃) of the crude Cbz-alanine-amide: δ =1.41 (d, J =7.1 Hz, 3H), 4.29 (m, 1H), 5.17 (m, 2H), 5.39 (brs, 1H), 6.11 (brs, 1H), 7.27 ppm (m, 5H).

Next, POCl₃ (0.55 mL, 1.2 equiv in DCM (5 mL)) was added dropwise to a solution of Cbz-alanine-amide (1.1 g) in Py (10 mL) at -10°C, and the resulting mixture was stirred for 3 h. When the starting material was observed as "depleted" by TLC analysis (MeOH/DCM 1:9), the mixture was poured onto ice (ca. 30 g). The organic phase was separated and the pyridine was removed by repeated washing with a hot, concentrated CuSO₄ solution. The organic phase was then predried with brine and later dried over MgSO₄. Filtration and concentration afforded the crude product as an oil. R_f =0.51 (MeOH/DCM 1:9); ¹H NMR (400 MHz, CDCl₃) of the crude Cbz-alanine-nitrile: δ =1.41 (d, J =6.8 Hz, 3H), 4.65 (m, 1H), 5.17 (m, 2H), 5.39 (brs, 1H), 7.28 ppm (m, 5H).

NaN₃ (300 mg, 1.1 equiv) and NH₄Cl (256 mg, 1.15 equiv) were simultaneously added to a solution of crude Cbz-alanine-nitrile (850 mg) in DMF (13 mL). The reaction mixture was heated to 90–95°C and kept at this temperature (3 h) until the TLC (HOAc/EtOAc 1:99) spot at R_f =0.63 did not increase in strength. The reaction mixture was poured onto ice (30 g), acidified to a pH close to 2 with 2 M HCl, and then extracted with CHCl₃ (3×20 mL). The organic phase was washed with water (20 mL), then predried with brine (20 mL), and finally dried over MgSO₄ before filtration and removal of the solvent by evaporation. Traces of

DMF were removed under reduced pressure. The crude product was obtained as a yellowish solid. ¹H NMR (400 MHz, CDCl₃) of the crude Cbz-alanine-tetrazole: δ =1.59 (d, J =6.9 Hz, 3H), 5.07 (m, 2H), 5.22 (m, 1H), 6.19 (brs, 1H), 7.28 ppm (m, 5H). The Cbz-alanine-tetrazole (825 mg) was dissolved in MeOH (10 mL) and a catalytic amount of Pd/C was added. After 17 h, the catalyst was filtered off by using celite and the solvent was removed under reduced pressure to quantitatively give alanine-tetrazole **9** as a white solid. ¹H NMR (400 MHz, [D₆]DMSO): δ =1.41 (d, J =6.8 Hz, 3H), 4.51 ppm (m, 1H); ¹³C NMR (100 MHz, [D₆]DMSO): δ =20.2, 44.4, 161.0 ppm.

Acknowledgements

We gratefully acknowledge the Swedish National Research Council, the Lars Hierta Foundation, the Carl Trygger Foundation, and the Wenner-Gren Foundation for financial support.

- [1] C. Mannich, W. Krösche, *Arch. Pharm.* **1912**, 250, 647.
- [2] For excellent reviews, see: a) E. F. Kleinmann in *Comprehensive Organic Synthesis*, Vol. 2 (Eds.: B. M. Trost, I. Fleming), Pergamon Press, New York, **1991**, Chapter 4.1; b) M. Arend, N. Westerman, N. Risch, *Angew. Chem.* **1998**, *110*, 1096; *Angew. Chem. Int. Ed.* **1998**, *37*, 1044; c) S. Denmark, O. J.-C. Nicaise in *Comprehensive Asymmetric Catalysis*, Vol. 2 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 93; d) M. Tramontini, L. Angiolini, *Tetrahedron* **1990**, *46*, 1791; e) H. Hellmann, G. Optiz, *α -Aminoalkylierung*, VCH, Weinheim, **1960**, p. 1; f) For examples, see: *Enantioselective Synthesis of β -Amino Acids* (Ed.: E. Juaristi), Wiley-VCH, Weinheim, **1997**; for a review of multicomponent reactions, see: D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.
- [3] a) R. Kober, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, H. Reuter, H. Puff, *Tetrahedron* **1985**, *41*, 1693; b) D. Enders, S. Oberbörsh, J. Adam, *Synlett* **2000**, 644; c) D. Seebach, M. Hoffmann, *Eur. J. Org. Chem.* **1998**, 1337; d) Y. Aoyagi, R. P. Jain, R. M. Williams, *J. Am. Chem. Soc.* **2001**, *123*, 3472, and references therein; e) U. Schöllkopf in *Topics in Current Chemistry*, Vol. 109 (Ed.: F. L. Boschke), Springer, Berlin, **1983**, pp. 45–85; f) D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark, M. T. Bilodeau, *J. Am. Chem. Soc.* **1990**, *112*, 8215; g) C. Palomo, M. Oiarbide, A. Landa, M. C. Gonzales-Rego, J. M. Garcia, A. Gonzales, J. M. Odriozola, M. Martin-Pastor, A. Linden, *J. Am. Chem. Soc.* **2002**, *124*, 8637, and references therein.
- [4] a) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069; b) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102.
- [5] a) H. Ishitani, M. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **1997**, *119*, 7153; b) S. Kobayashi, T. Hamada, K. Manabe, *J. Am. Chem. Soc.* **2002**, *124*, 5640; c) H. Ishitani, M. Ueno, S. Kobayashi, *Org. Lett.* **2002**, *4*, 143; d) H. Ishitani, S. Ueno, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8180.
- [6] H. Fujieda, M. Kanai, T. Kambara, A. Iida, K. Tomioka, *J. Am. Chem. Soc.* **1997**, *119*, 7153.
- [7] a) E. Hagiwara, A. Fujii, M. Sodeoka, *J. Am. Chem. Soc.* **1998**, *120*, 2474; b) A. Fujii, E. Hagiwara, M. Sodeoka, *J. Am. Chem. Soc.* **1999**, *121*, 545; c) Y. Hamashima, K. Yagi, H. Tamas, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 14530; d) Y. Hamashima, M. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240; e) D. Ferraris, B. Young, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **1998**, *120*, 4548; f) D. Ferraris, B. Young, C. Cox, W. J. Drury III, T. Dudding, T. Lectka, *J. Org. Chem.* **1998**, *63*, 6090; g) D. Ferraris, B. Young, C. Cox, T. Dudding, W. J. Drury III, L. Ryzhkov, T. Taggi, T. Lectka, *J. Am. Chem. Soc.* **2002**, *124*, 67; See also this excellent report: h) W. S. Josephsohn, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2004**, *126*, 3734.
- [8] S. Yamasaki, T. Iida, M. Shibasaki, *Tetrahedron Lett.* **1999**, *40*, 307.

- [9] a) S. Matsunaga, N. Kumagai, N. Harada, S. Harada, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 4712; b) T. Yoshida, H. Morimoto, N. Kumagai, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 3536; *Angew. Chem. Int. Ed.* **2005**, *44*, 3470; see also the excellent work: c) S. Harada, S. Handa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4439; *Angew. Chem. Int. Ed.* **2005**, *44*, 4365.
- [10] B. M. Trost, L. M. Terrell, *J. Am. Chem. Soc.* **2003**, *125*, 338.
- [11] a) K. Juhl, N. Gathergood, K. A. Jørgensen, *Angew. Chem.* **2001**, *113*, 3083; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995; b) M. Marigo, A. Kjaersgaard, K. Juhl, N. Gathergood, K. A. Jørgensen, *Chem. Eur. J.* **2003**, *9*, 2395; c) L. Bernardi, A. S. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2003**, *68*, 2583.
- [12] For excellent reviews, see: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; b) B. List, *Tetrahedron* **2002**, *58*, 5573; c) R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005; *Angew. Chem. Int. Ed.* **2003**, *42*, 975; d) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.
- [13] a) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; b) B. List, P. Porjaliev, W. T. Biller, H. J. Martin, *J. Am. Chem. Soc.* **2002**, *124*, 827.
- [14] a) W. Notz, K. Sakthivel, T. Bui, G. Zhong, C. F. Barbas III, *Tetrahedron Lett.* **2001**, *42*, 199; b) A. Córdova, W. Notz, G. Zhong, J. M. Betancourt, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1842; c) A. Córdova, S.-i. Watanabe, F. Tanaka, W. Notz, C. F. Barbas III, *J. Am. Chem. Soc.* **2002**, *124*, 1866; d) A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 7749; e) N. S. Chowdari, J. T. Suri, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2507; f) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* **2004**, 558; g) T. Itoh, M. Yokoya, K. Miyauchi, K. K. Nagata, Ohsawa, *Org. Lett.* **2003**, *5*, 4301; h) A. Münch, B. Wendt, M. Christmann, *Synlett* **2004**, 2751; i) W. Zhuang, S. Saaby, K. A. Jørgensen, *Angew. Chem.* **2004**, *116*, 1576; *Angew. Chem. Int. Ed.* **2004**, *43*, 4476; j) I. Ibrahim, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 2839; k) A. Córdova, *Synlett* **2003**, 1651; l) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987; m) W. Notz, S.-i. Watanabe, N. S. Chowdari, G. Ahong, J. M. Betancourt, F. Tanaka, C. F. Barbas III, *Adv. Synth. Catal.* **2004**, *346*, 1131; n) Y. Hayashi, W. Tsuboi, I. Ashimine, T. Urushima, M. Shoji, K. Sakai, *Angew. Chem.* **2003**, *115*, 3805; *Angew. Chem. Int. Ed.* **2003**, *42*, 3677; o) I. Ibrahim, A. Córdova, *Tetrahedron Lett.* **2005**, *46*, 3363; p) B. Westermann, C. Neuhäus, *Angew. Chem.* **2005**, *117*, 4145; *Angew. Chem. Int. Ed.* **2005**, *44*, 4077; q) D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem.* **2005**, *117*, 4147; *Angew. Chem. Int. Ed.* **2005**, *44*, 4079-; for other organocatalytic Mannich-type reactions, see: r) A. G. Wenzel, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 12964; s) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356; t) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem.* **2004**, *116*, 1592; *Angew. Chem. Int. Ed.* **2004**, *43*, 1566; u) T. B. Poulsen, C. Alemparte, S. Saaby, M. Bella, K. A. Jørgensen, *Angew. Chem.* **2005**, *117*, 2956; *Angew. Chem. Int. Ed.* **2005**, *44*, 2896.
- [15] a) I. Ibrahim, J. Casas, A. Córdova, *Angew. Chem.* **2004**, *116*, 6690; *Angew. Chem. Int. Ed.* **2004**, *43*, 6528; b) J. Casas, M. Engqvist, I. Ibrahim, B. Kaynak, A. Córdova, *Angew. Chem.* **2005**, *117*, 1367; *Angew. Chem. Int. Ed.* **2005**, *44*, 1343; c) A. Córdova, I. Ibrahim, J. Casas, H. Sundén, M. Engqvist, E. Reyes, *Chem. Eur. J.* **2005**, *11*, 4772; d) A. Córdova, M. Engqvist, I. Ibrahim, J. Casas, H. Sundén, *Chem. Commun.* **2005**, 2047; e) A. Córdova, H. Sundén, M. Engqvist, I. Ibrahim, J. Casas, *J. Am. Chem. Soc.* **2004**, *126*, 8914; f) H. Sundén, M. Engqvist, J. Casas, I. Ibrahim, A. Córdova, *Angew. Chem.* **2004**, *117*, 1367; *Angew. Chem. Int. Ed.* **2004**, *43*, 6532; g) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109; h) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673, and references therein.
- [16] A. Córdova, W. Zou, I. Ibrahim, E. Reyes, M. Engqvist, W.-W. Liao, *Chem. Commun.* **2005**, 3586.
- [17] Water was added because we have observed rate acceleration in proline-catalyzed Mannich reactions: see ref. [14o] and references therein.
- [18] The dipeptide ala-ala catalyzed the asymmetric three-component formation of **2a** after 48 h in 35% yield with 1:1 d.r. and 56% ee.

Received: June 29, 2005
Published online: September 28, 2005