Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 989–992

4-*trans*-Amino-proline based di- and tetrapeptides as organic catalysts for asymmetric C–C bond formation reactions

Svetlana B. Tsogoeva,[a,*] Sunil B. Jagtap[a] and Zoya A. Ardemasova[b]

[a]*Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany*
[b]*St.-Petersburg State University, Department of Chemistry, Natural products chemistry chair, Universitetsky pr. 26, Petrodvorez, 198504 St.-Petersburg, Russia*

Received 22 February 2006; accepted 15 March 2006
Available online 12 April 2006

Abstract—4-*trans*-Amino-proline based di- and tetrapeptides have been successfully applied as chiral organocatalysts in the enantioselective conjugate addition of nitroalkanes to cyclic enones and the direct aldol reaction. Two 4-*trans*-amino-proline residues were shown to be sufficient enough to catalyze the conjugate addition reactions with up to 88% ee and up to 100% yield. It has been demonstrated that 4-*trans*-amino-proline based di- and tetrapeptides are significantly more active than L-proline (at 30 mol %) and can catalyze the direct aldol reaction with good yield and enantioselectivity within 3 h and at lower catalyst loading (5 mol %).

1. Introduction

Short peptides and peptide-like molecules have recently been found to be excellent asymmetric catalysts for a number of enantioselective organic transformations[1–3] including the acylation reactions,[4–6] conjugate additions,[7–10] hydrocyanation of aldehydes[11] and imines,[12–14] phosphorylation,[15] Baylis–Hillman,[16] and direct aldol reactions.[17–23]

In our work directed toward enantioselective C–C bond forming reactions, we have recently investigated, for the first time, some L-histidine based dipeptides as chiral organocatalysts for asymmetric Michael additions[9] and aldol reactions.[22]

Recently, Hanessian et al.[24,25] reported the catalytic asymmetric conjugate addition of nitroalkanes to cyclic enones in the presence of L-proline as a catalyst and *trans*-2,5-dimethylpiperazine as excess additive. Subsequently, we demonstrated the potential of a 4-*trans*-amino-proline based tripeptide as a chiral catalyst, in combination with *trans*-2,5-dimethylpiperazine for asymmetric conjugate addition of nitroalkanes to prochiral acceptors.[10]

However, 4-*trans*-amino-proline based di- and tetrapeptides have never been examined for these reactions. This prompted our present study. We were interested in exploring whether there was a correlation between the amount of catalytic centers (secondary amine functionalities) and the catalytic activity of the oligo-α-amino acid.

Herein, we report an investigation of the potential of peptides **1** and **2** (Fig. 1) as organic catalysts for the Michael and aldol reactions, which are regarded to be among the more synthetically important carbon–carbon bond forming reactions.

2. Results and discussion

Chiral peptide catalysts **1** and **2** were successfully prepared by classical methods already described in our previous report.[10] The catalytic efficiency of **1** and **2** was initially examined on the enantioselective addition of nitroalkanes to cyclic enones and the results are summarized in Table 1.

Using **1** (2 mol %) as a catalyst in the presence of *trans*-2,5-dimethylpiperazine as an additive resulted in the formation of Michael adducts **3**–**9** in 40–100% yields and 57–88% ee. We found that the bulkiness of R_1 and R_2 in the nitroalkanes did effect the reactivities and enantioselectivities. The

* Corresponding author. Tel.: +49 0 551 393285; fax: +49 0 551 399660; e-mail: stsogoe@gwdg.de

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.03.012

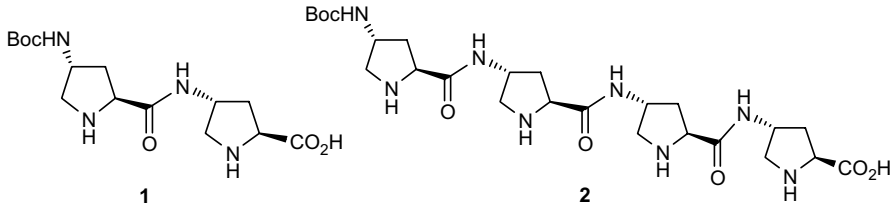
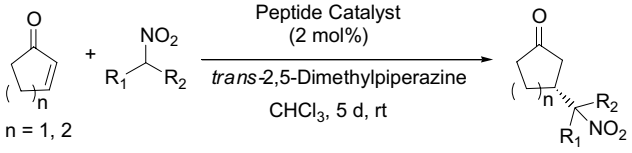
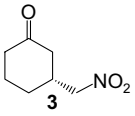
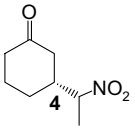
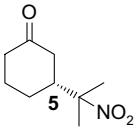
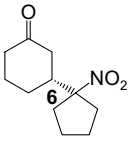
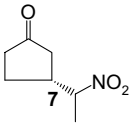
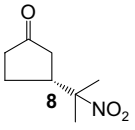
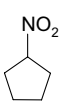
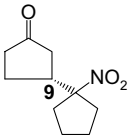


Figure 1.

Table 1. Conjugate addition of nitroalkanes to cyclohex-2-en-1-one and cyclopent-2-en-1-one catalyzed by peptides **1** and **2** (2 mol %) in the presence of *trans*-2,5-dimethylpiperazine (100 mol %)



Nitroalkane	Product	Peptide **1**		Peptide **2**	
		Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
CH_3NO_2	 **3**	75	57	75	55
$CH_3CH_2NO_2$	 **4**	100	LP: 66[c] MP: 67[d]	100	LP: 58[c] MP: 59[d]
	 **5**	46	77	80	81
	 **6**	100	88	57	82
$CH_3CH_2NO_2$	 **7**	65	LP: 61[c] MP: 54[d]	71	LP: 47[c] MP: 48[d]
$(CH_3)_2CHNO_2$	 **8**	40	76	50	64
	 **9**	64	77	41	60

[a] Isolated yields after column chromatography.
[b] % ee measured by ^{13}C NMR of corresponding ketal with (2*R*,3*R*)-2,3-butane diol.
[c] % ee of less polar (LP) isomer.
[d] % ee of more polar (MP) isomer.

larger the R_1 and R_2 (Me → Et → *i*-Pr → Cp), the higher the enantioselectivity (Table 1, **3**–**6**). These results can be rationalized by the fact that during nucleophilic attack, the enone forms an iminium ion intermediate[26,27] with

the peptide catalyst, thus impairing the approach of bulky nucleophiles. The large nucleophile does react slowly, but is more selective with the activated enone. The highest enantioselectivity (88% ee, product **6**) was therefore observed for nitrocyclopentane, while the lowest ones for nitromethane (57% ee, product **3**). Additionally, the ring size of the enones also affected the enantioselectivity. Higher levels of asymmetric induction were observed with cyclohexenone (66–88% ee, products **4**–**6**) compared to cyclopentenone (54–77% ee, products **7**–**9**).

Similar trends were observed for tetrapeptide catalyst **2** with respect to the enantioselectivities and yields when varying the size of the cyclic enones and nitroalkanes (Table 1).

With both peptide catalysts **1** and **2**, approximately equimolar amounts of diastereomers for products **4** and **7** were formed from nitroethane, respectively (Table 1).

Whereas similar results in terms of reaction rates were observed with peptide catalysts **1** and **2**, slightly higher enantioselectivities were obtained in the presence of dipeptide **1**, with respect to tetrapeptide **2**. Maximum enantioselectivity (88%) was achieved with as little as two 4-*trans*-amino-proline residues (catalyst **1**). These results demonstrate that in the case of conjugate additions of nitroalkanes to cyclic enones, there is no increase in catalytic activity or selectivity with increasing chain length of the peptide catalyst.

Chiral catalysts **1** and **2** were also applied to the enantioselective aldol reaction of acetone and 4-nitrobenzaldehyde with the results are shown in Table 2. Initial screening studies with dipeptide **1** identified DMSO as the optimal solvent and +10 °C as the most suitable temperature for the reaction (entries 1 and 2 vs entry 3).

Interestingly, peptides **1** and **2** in 15 and 5 mol % loading, respectively, showed higher or similar yields (83% and 62%, entries 3 and 4) and approximately the same enantioselectivities (Table 2, 73% ee and 75% ee, entries 3 and 4) as L-proline (68%, 76% ee)[28] at 30 mol %. This represents a 15% increase in yield compared to the L-proline-catalyzed reaction.

In these studies, the catalyst loading for the aldol reaction was reduced from 30 mol %, as reported in the literature,[28] to 5 mol %. The observed reaction times decreased from 24–48 h (for L-proline) to 3–4 h (for peptide catalysts **1** and **2**).

3. Conclusion

In conclusion, 4-*trans*-amino-proline based di- and tetrapeptides have been successfully applied as chiral catalysts in the enantioselective conjugate addition of nitroalkanes to cyclic enones. Two 4-*trans*-amino-proline residues were shown to be sufficient enough to catalyze the conjugate addition of nitroalkanes to cyclic enones with up to 88% ee and up to 100% yield.

Although direct aldol reactions are well documented, we have demonstrated for the first time that 4-*trans*-amino-proline based di- and tetrapeptides can catalyze the aldol reaction with good yields and enantioselectivities at +10 °C within 3–4 h. These studies revealed that peptide catalysts **1** and **2** are significantly more active than L-proline and allow us to reduce the catalyst loading from 30 to 5 mol %. In this respect, the use of oligo- and poly-α-amino acids seems to be a research area with a great deal of potential.

4. Experimental

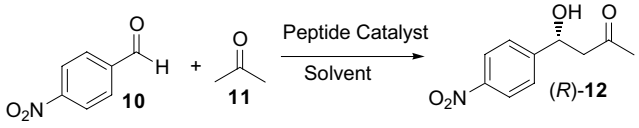
4.1. General

All solvents were purified by standard procedures and distilled prior to use. Reagents obtained from commercial sources were used without further purification. TLC chromatography was performed on precoated aluminum silica gel SIL G/UV_{254} plates (Marcherey, Nagel Co.) or silica gel 60-F_{254} precoated glass plates (Merck). ^{1}H NMR spectra were recorded with Varian Unity 300. ESI mass spectra were measured with a LCQ Finnigan spectrometer. High-resolution mass spectra were recorded with a Bruker APEX IV 7T FT-ICR instrument. A Perkin–Elmer 241 polarimeter was used for optical rotation measurements.

4.2. Dipeptide 1

^{1}H NMR (300 MHz, CD_3OD) δ 1.43 (s, 9H, $C(CH_3)_3$), 1.96–2.12 (m, 2H), 2.29–2.34 (m, 2H), 2.83 (dd, $J = 4.5$,

Table 2. Asymmetric aldol reaction of acetone with 4-nitrobenzaldehyde catalyzed by peptides **1** and **2**



Entry	Peptide (mol %)	Solvent	T (°C)	Reaction time (h)	Yield (%)	ee[a] (%)
1	**1** (15)	DMF	−10	20	59	79
2	**1** (15)	DMF	+10	6	83	68
3	**1** (15)	DMSO	+10	4	83	73
4	**2** (5)	DMSO	+10	3	62	75

[a] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak AS) in comparison with authentic racemic material.

11.4 Hz, 1H), 3.09–3.23 (m, 2H), 3.49–3.55 (m, 1H), 3.82 (t, $J = 7.8$ Hz, 1H), 4.00 (quin, $J = 5.4$ Hz, 1H), 4.14 (t, $J = 8.1$ Hz, 1H), 4.36 (quin, $J = 5.4$ Hz, 1H). ESI-MS (positive ion): $m/z = 343.1$ $[M+H]^+$, 684.9 $[2M+H]^+$. HRMS (ESI): calcd for $C_{15}H_{26}N_4O_5$ $[M+H]^+$ 343.19760; found 343.19760.

4.3. Tetrapeptide 2

^{1}H NMR (300 MHz, CD_3OD) δ 1.42 (s, 9H, $C(CH_3)_3$), 1.99–2.13 (m, 4H), 2.27–2.35 (m, 4H), 2.85–2.93 (m, 2H), 3.16–3.21 (m, 4H), 3.57–3.61 (m, 2H), 3.88–4.05 (m, 4H), 4.17–4.44 (m, 4H). ESI-MS (positive ion): $m/z = 567.7$ $[M+H]^+$. HRMS (ESI): calcd for $C_{25}H_{42}N_8O_7$ $[M+H]^+$ 567.32492; found 567.32477.

4.4. General procedure for the *Michael* reaction

4.4.1. (*R*)-(+)-3-(2-Nitropropane-2-yl) cyclohexanone 5. 2-Nitropropane (0.63 mmol) was added to a stirred solution of 2-cyclohexen-1-one (0.5 mmol), *trans*-2,5-dimethylpiperazine (0.5 mmol), and peptide catalyst (2 mol %) in predried solvent ($CHCl_3$, 4 mL), and the reaction mixture stirred at room temperature for 5 days. The reaction mixture was worked up as described in the literature.[24] The residues were purified by chromatography on SiO_2-column (hexane/ethyl acetate) to afford the desired product **5**. The enantiomeric excess of the product was measured by ^{13}C NMR of corresponding ketal with (2*R*,3*R*)-2,3-butane diol.[24] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48–2.34 (m, 3H), 2.31–2.21 (m, 1H), 2.19–2.08 (m, 2H), 1.85–1.76 (m, 1H), 1.71–1.53 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 1.48–1.34 (m, 1H). ^{13}C NMR (150.8 MHz, $CDCl_3$) δ 208.9 (C=O), 90.6 ($C_{quat.}$), 46.5 (CH), 42.6 (CH_2), 40.7 (CH_2), 25.9 (CH_2), 24.3 (CH_2), 23.3 (CH_3), 22.5 (CH_3). ESI-MS (positive ion): m/z 208.1 $[M+Na]^+$.

4.5. General procedure for the aldol reaction

4.5.1. (4*R*)-(4-Nitrophenyl)-4-hydroxy-2-butanone 12. Peptide catalyst (5–15 mol %) was added to a dry acetone/DMSO (or DMF) (1:4) mixture and stirred for 20 min. 4-Nitrobenzaldehyde (0.05 M) was added and the resulting mixture stirred at room temperature under nitrogen. After completion of the reaction, the mixture was worked up as described in the literature.[28] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.84 (m, 2H), 3.58 (br s, 1H), 5.24 (m, 1H), 7.53 (d, 2H), 8.20 (d, 2H). HPLC (Daicel Chiralpak AS): *n*-hexane/2-propanol = 75:25, flow rate 1 mL/min, $\lambda = 254$ nm: t_R (major) = 18.84 min, t_R (minor) = 26.58 min.

Acknowledgment

The authors gratefully acknowledge the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for generous financial support.

References

1. Review: Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481–2495.
2. Review: Groeger, H; Wilken, J.; Berkessel, A. In *Simple Amino Acids and Short-chain Peptides as Efficient Metal-free Catalysts in Asymmetric Synthesis*. Schmalz, H.-G., Wirth, T., Eds.; Organic Synthesis Highlights V; WILEY-VCH: Weinheim, 2003; pp 178–186.
3. Review: Tsogoeva, S. B. *Lett. Org. Chem.* **2005**, *2*, 208–213.
4. Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784–6785.
5. Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *Chem. Commun.* **2003**, 1781–1785.
6. Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638–11643.
7. Horstmann, T. E.; Guerin, D. J.; Miller, S. J. *Angew. Chem.* **2000**, *112*, 3781–3784; *Angew. Chem., Int. Ed.* **2000**, *39*, 3635–3638.
8. Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134–2136.
9. Tsogoeva, S. B.; Jagtap, S. B. *Synlett* **2004**, 2624–2626.
10. Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A.; Kalikhevich, V. N. *Eur. J. Org. Chem.* **2004**, 4014–4019.
11. Tanaka, K.; Mori, A.; Inoue, S. *J. Org. Chem.* **1990**, *55*, 181–185.
12. Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911.
13. Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem.* **2000**, *112*, 1336–1338; *Angew. Chem., Int. Ed.* **2000**, *39*, 1279–1281.
14. Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014.
15. Sculimbrene, B. R.; Miller, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10125–10126.
16. Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741–3743.
17. (a) Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262–5263; (b) Tang, Z.; Jiang, F.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *PNAS* **2004**, *101*, 5755–5760; (c) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285–2287.
18. Martin, H. J.; List, B. *Synlett* **2003**, 1901–1902.
19. Kofoed, J.; Nielsen, J.; Reymond, J.-L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2445–2447.
20. Szöllősi, G.; London, G.; Baláspiri, L.; Somlai, C.; Bartók, M. *Chirality* **2003**, *15*, S90–S96.
21. Shi, L.-X.; Sun, Q.; Ge, Z.-M.; Zhu, Y.-Q.; Cheng, T.-M.; Li, R.-T. *Synlett* **2004**, 2215–2217.
22. Tsogoeva, S. B.; Wei, S.-W. *Tetrahedron: Asymmetry* **2005**, *16*, 1947–1951.
23. Zou, W.; Ibrahem, I.; Dziedzic, P.; Sundén, H.; Córdova, E. A. *Chem. Commun.* **2005**, 4946–4948.
24. Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975–2978.
25. Hanessian, S.; Govindan, S.; Warrier, J. S. *Chirality* **2005**, *17*, 540–543.
26. Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147–1168.
27. For iminium and enamine catalysis, see: List, B. *Chem. Commun.* **2006**, 819–824.
28. Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.