**Peptide Catalysis**

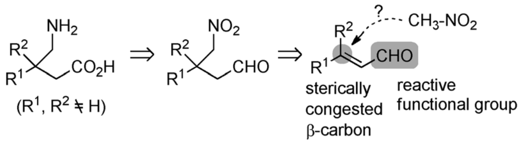
DOI: 10.1002/ange.201206916

# Construction of an All-Carbon Quaternary Stereocenter by the Peptide-Catalyzed Asymmetric Michael Addition of Nitromethane to β-Disubstituted α,β-Unsaturated Aldehydes**

*Kengo Akagawa and Kazuaki Kudo**

Recently, considerable attention has been devoted to the synthesis of chiral γ-amino acid derivatives[1–3] because of their biological activity in relation to γ-aminobutyric acid (GABA), a major inhibitory neurotransmitter in central nervous system.[4] γ-Amino acids are also of great value as non-proteinogenic amino acid components involved in biologically active short peptides such as pepstatin,[5] hapalosin,[6] and dolastatin 10.[7] Among the diverse structural variants of chiral γ-amino acids, those with a substituent at the β-position are an important class of pharmaceuticals, which includes baclofen,[8] pregabalin,[9] and phenibut.[10] Whereas a variety of methods have been developed for the synthesis of chiral β-monosubstituted γ-amino acids, there are only limited examples for the preparation of β-disubstituted derivatives.[11] Furthermore, the reported reaction scope is confined to those having two alkyl groups on the β-carbon of γ-amino acids, and catalytic enantioselective construction of an all-carbon-substituted quaternary stereocenter at the β-position has not yet been achieved.[12,13]

One plausible route to obtain a γ-amino acid with a quaternary chiral center at the β-position is an enantioselective Michael addition of nitromethane to a β-disubstituted α,β-unsaturated aldehyde followed by the transformation of functional groups (Scheme 1). However, although the Michael addition of nitromethane to β-monosubstituted substrates has been attained by chiral secondary amine catalysts through an iminium activation,[14] the application of such a catalytic system to a β-disubstituted α,β-unsaturated aldehyde has not been realized thus far.[15,16] Because the reaction center of the β-disubstituted substrate is sterically congested for C–C bond formation, it is supposed that side reactions such as the 1,2-addition of nitromethane and an aldol-type reaction of the products could accompany the reaction to a considerable extent, thus resulting in a decrease in the product yield. To suppress such side reactions and promote the desired conjugate addition, a catalyst with high potential for iminium activation is necessary.



*Scheme 1.* Proposal for the synthesis of γ-amino acids with an all-carbon quaternary center.

Meanwhile, our group has developed resin-supported peptide catalysts (Figure 1) for organocatalytic reactions.[17–19] The specific feature of these catalysts is that the presence of a helical segment, (AA)*n*, significantly enhances the reaction rate and the enantioselectivity under aqueous conditions. In some cases, this type of peptide catalyst was found to be superior to a conventional low-molecular-weight catalyst. We envisaged that, by employing the resin-supported peptide catalyst in aqueous media, the enantioselective Michael addition of nitromethane to β-disubstituted α,β-unsaturated aldehydes could be performed.

Pro-D-Pro-Aib-$(\mathrm{Trp})_2$–$(\mathrm{AA})_n$–●

$$(\mathrm{AA})_n = \begin{cases} (\mathrm{Leu})_{25.4} \\ (\mathrm{Leu\text{-}Leu\text{-}Aib})_2 \end{cases}$$

–● = amphiphilic resin

*Figure 1.* Resin-supported peptide catalyst.

Initially, the Michael addition of nitromethane to compound **6a**, which has methyl and phenyl groups at the β-position, was examined (Table 1). With resin-supported peptide **1**, which consists of a catalytically active N-terminal proline and polyleucine, the reaction proceeded smoothly in water to afford the product with moderate enantioselectivity (entry 1). The significant effect of the polyleucine portion of the catalyst was indicated by the result obtained when using D-prolyl polyleucine catalyst **2**. In this case, the mismatched chirality of the terminal prolyl group and the polyleucine chain sharply lowered the reaction rate and enantioselectivity (entry 2).[20] Catalyst **3**, which possesses five terminal residues and has been shown to be highly effective in asymmetric induction for other reactions,[17a,b] gave good enantioselectivity (entry 3).[21] In our recent study, it was found that replacement of the polyleucine unit with a $(\mathrm{Leu\text{-}Leu\text{-}Aib})_2$ sequence (Aib = 2-aminoisobutyric acid) improved the catalyst activity in an asymmetric Friedel–Crafts-type reaction in water.[17c] The use of catalyst **4** for the present reaction also

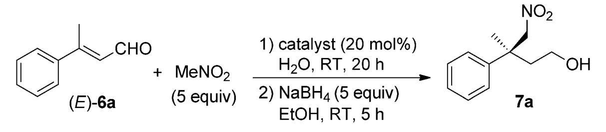
---

[*] Dr. K. Akagawa, Prof. Dr. K. Kudo
Institute of Industrial Science, University of Tokyo
4-6-1 Komaba, Meguro-ku, Tokyo 153-8505 (Japan)
E-mail: kkudo@iis.u-tokyo.ac.jp

[**] This work was supported by JSPS KAKENHI (23750171 to K.A. and 23550116 to K.K.), and by MEXT KAKENHI (24105506 to K.K.). The authors thank Mr. Atsushi Okumura for experimental assistance.

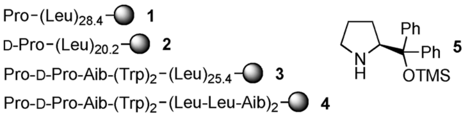
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206916.

***Table 1:*** Michael addition of nitromethane to β-disubstituted aldehyde.



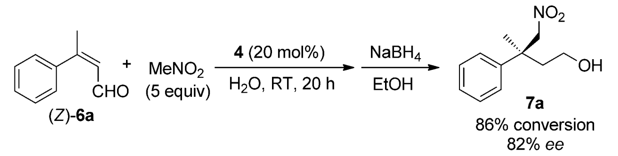
| Entry | Catalyst | Conversion [%] | *ee* [%] |
|---|---|---|---|
| 1 | **1** | 62 | −72[a] |
| 2 | **2** | 11 | 12 |
| 3 | **3** | 69 | 89 |
| 4 | **4** | 90 | 95 |
| 5 | **5** | 9 | 93 |
| 6[b] | **5** | 27 | 73 |
| 7[b,c] | **5** | 56 (12)[d] | 88 |
| 8[e] | **4** | 98 (70)[d] | 97 |
| 9[e,f] | **4** | 9 | 98 |

[a] A minus sign denotes the *R* isomer as the major product. [b] Reaction was performed in MeOH. [c] Benzoic acid (40 mol%) was added. [d] The value in parentheses is the yield of isolated product. [e] The amount of nitromethane was 10 molar equiv. [f] Reaction was performed in THF.

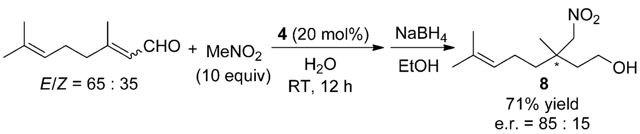


enhanced both the reaction rate and the enantioselectivity (entry 4). When diphenylprolinol silyl ether **5** was employed for the reaction as a control catalyst, the reaction gave low conversion in water (entry 5), whereas in methanol it gave the product with somewhat improved conversion, but with lowered enantioselectivity (entry 6). When the reaction was performed under the optimized conditions reported by Hayashi et al. for the Michael addition of nitromethane to β-monosubstituted substrates in the presence of benzoic acid,[14g] moderate conversion was attained (entry 7). However, many by-products were observed and the yield of the isolated desired product was only 12%. In the case of peptide catalyst **4**, the product could be isolated in 70% yield when an increased amount of nitromethane was employed (entry 8). The use of the peptide in water was important for catalyst effectiveness. This was demonstrated by the result of the reaction in an organic solvent, THF, which afforded the product with poor conversion (entry 9).

Concerning the stereochemical relationship of 3-methylcinnamaldehydes and the corresponding conjugate adducts, MacMillan et al. and List et al. independently reported the phenomenon of enantioconvergence in a hydride transfer reaction from a Hantzsch ester.[22] In the present reaction, such a phenomenon was also observed: the addition of nitromethane to (*Z*)-**6a** predominantly afforded the *S* adduct, which was the same configuration as the one obtained from (*E*)-**6a** (Scheme 2). Encouraged by this result, citral, a readily available mixture of the diastereomers geranial and neral, was used for the reaction. The 1,4-adduct with nitromethane was obtained in a higher enantiomeric ratio than the starting *E*/*Z* ratio of citral (Scheme 3). This is one of the few examples in which a good degree of enantioconvergence was obtained with citral.[23]



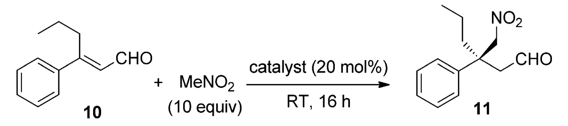
***Scheme 2.*** Stereoconvergence with the *Z* isomer as a starting material.



***Scheme 3.*** Michael addition of nitromethane to citral.

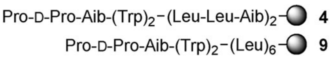
When 3-phenyl-2-hexanal (**10**), a more sterically demanding substrate than **6a**, was used, the yield of the desired product was quite low, despite the high level of enantioinduction (Table 2, entry 1). The low yield was due to side reactions. Accordingly, further optimization of reaction conditions was conducted with this substrate. It was found that reaction in 1:2 MeOH/H$_2$O gave the product in higher yield than the other solvent systems tested, along with a slight decrease in enantioselectivity (entry 5). A water-containing solvent system was essential for the efficient reaction, which is shown by the fact that use of MeOH alone as a solvent brought about a sharp decrease in the yield (entry 6). Additional optimization for conditions such as temperature, reaction time, and the amount of nitromethane somewhat improved the product yield (entry 7). Replacing the (Leu-Leu-Aib)$_2$ moiety of peptide catalyst **4** with a hexaleucine chain further increased the yield of the product and enhanced enantioselectivity (entry 8). Although the full effects of this helical part are not clear at present, the improvement of the

***Table 2:*** Optimization of reaction conditions.



| Entry | Catalyst | Solvent[a] | Yield[b] [%] | *ee* [%] |
|---|---|---|---|---|
| 1 | **4** | $H_2O$ | 13 | 96 |
| 2 | **4** | 1,4-dioxane/$H_2O$ | 22 | 92 |
| 3 | **4** | $CH_3CN/H_2O$ | 20 | 85 |
| 4 | **4** | DMF/$H_2O$ | 5 | 81 |
| 5 | **4** | MeOH/$H_2O$ | 40 | 90 |
| 6 | **4** | MeOH | <5 | 61 |
| 7[c] | **4** | MeOH/$H_2O$ | 47 | 91 |
| 8[c] | **9** | MeOH/$H_2O$ | 54 | 96 |

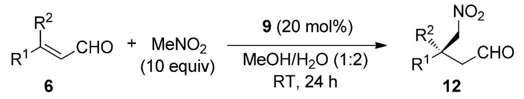
[a] All solvent mixtures shown are 1:2 cosolvent/water. [b] Estimated by $^1$H NMR spectroscopy. [c] Reaction was performed at 0°C for 24 h with 5 molar equiv of nitromethane.



reaction outcome by fine-tuning the peptide sequences demonstrates the potential of peptide catalysis.

The substrate scope was next investigated using 1:2 MeOH/H$_2$O with peptide catalyst **9**, (Table 3). The reaction using aldehyde **6a** gave the product in good yield and high enantioselectivity (entry 1).[24] Regardless of the electronic nature of the substituents on the phenyl ring, the products were obtained with high enantioselectivity (entries 2–7). The yield of isolated product was decreased to some extent in the case of a substrate with a strong electron-withdrawing group (entry 6). The introduction of an ethyl substituent in place of the methyl group at the β-position did not lower the enantioselectivity, and the products could be obtained in good to moderate yields with excellent *ee* values (entries 8–10).

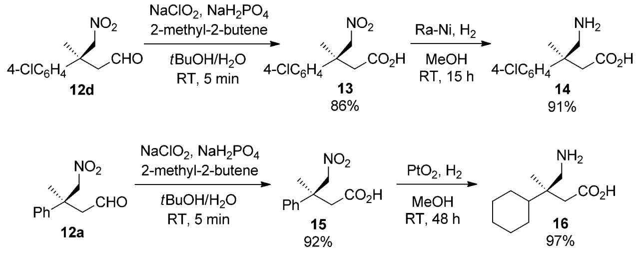
***Table 3:*** Substrate scope for the peptide-catalyzed asymmetric Michael addition of nitromethane to β-disubstituted aldehydes.



| Entry | R$^1$ | R$^2$ | **12** | Yield [%][a] | *ee* [%] |
|---|---|---|---|---|---|
| 1[b] | C$_6$H$_5$ | Me | **12a** | 82 | 98 |
| 2[c] | 4-MeC$_6$H$_4$ | Me | **12b** | 81 | 96 |
| 3 | 4-MeOC$_6$H$_4$ | Me | **12c** | 78 | 95 |
| 4[d] | 4-ClC$_6$H$_4$ | Me | **12d** | 70 | 95 |
| 5 | 3-ClC$_6$H$_4$ | Me | **12e** | 72 | 98 |
| 6 | 4-NO$_2$C$_6$H$_4$ | Me | **12f** | 64 | 97 |
| 7 | 2-naphthyl | Me | **12g** | 76 | 95 |
| 8[b,e] | C$_6$H$_5$ | Et | **12h** | 73 | 99 |
| 9[b] | 4-MeOC$_6$H$_4$ | Et | **12i** | 71 | 98 |
| 10[b] | 4-ClC$_6$H$_4$ | Et | **12j** | 65 | 99 |

[a] Yield of isolated product. [b] Reaction was performed at 0 °C. [c] Reaction time was 36 h. [d] Reaction time was 18 h. [e] The amount of nitromethane used was 5 molar equiv.

Finally, the 1,4-adducts of nitromethane were converted into β-disubstituted γ-amino acids (Scheme 4). Compound **12d** could be derivatized to the β-methylated analogue of baclofen by a simple procedure: Pinnick oxidation followed by reduction in the presence of Raney nickel. This is the first example of the asymmetric synthesis of a β-disubstituted γ-amino acid possessing a β-aryl group. When the reduction was performed with platinum(IV) oxide after the oxidation of **12a**, a new class of β-dialkylated γ-amino acids bearing a cyclohexyl group was obtained. These procedures offer the facile synthesis of highly congested β-disubstituted γ-amino acids.



***Scheme 4.*** Derivatization of products into β-disubstituted γ-amino acids.

In conclusion, the asymmetric Michael addition of nitromethane to β-disubstituted α,β-unsaturated aldehydes has been realized using a resin-supported peptide catalyst. The use of an aqueous solvent system was essential for effective reaction, and the hydrophobic helical part of the peptide significantly affected the reaction rate and enantioselectivity. With the optimized peptide catalyst, which has a hexaleucine chain, highly enantioenriched products with all-carbon-substituted quaternary centers were obtained. This reaction could provide a simple means of synthesizing sterically congested β-disubstituted γ-amino acids. The present study demonstrates the high potential of peptide catalysis for organocatalytic reactions in which a conventional low-molecular-weight catalyst is ineffective.

## Experimental Section

Water (334 μL) was slowly added to a round-bottom flask containing a β-disubstituted α,β-unsaturated aldehyde (0.05 mmol), resin-supported Pro-D-Pro-Aib-(Trp)$_2$-(Leu)$_6$ (52 mg, 0.01 mmol of the terminal prolyl group), and MeOH (167 μL). Nitromethane (0.5 mmol or 0.25 mmol) was added at room temperature or at 0 °C, and the resulting mixture was stirred with magnetic stirrer at ca. 500 rpm for the given time. The peptide catalyst was filtered off and washed with chloroform. After removal of the solvent, the residue was purified by preparative TLC (dichloromethane as eluent) to afford the product. In cases where isolation was not enough, further purification by preparative TLC with hexanes/ethyl acetate (2:1) was effective.

Received: August 27, 2012
Revised: October 5, 2012
Published online: November 9, 2012

**Keywords:** amino acids · asymmetric synthesis · heterogeneous catalysis · Michael addition · peptides

---

[1] For a review, see: M. Ordóñez, C. Cativiela, *Tetrahedron: Asymmetry* **2007**, *18*, 3–99.

[2] For recent selected examples of the synthesis of γ-amino acid derivatives with organocatalysts, see: a) D. Enders, C. Wang, J. W. Bats, *Angew. Chem.* **2008**, *120*, 7649–7653; *Angew. Chem. Int. Ed.* **2008**, *47*, 7539–7542; b) Y. Chi, L. Guo, N. A. Kopf, S. H. Gellman, *J. Am. Chem. Soc.* **2008**, *130*, 5608–5609; c) M. Wiesner, J. D. Revell, S. Tonazzi, H. Wennemers, *J. Am. Chem. Soc.* **2008**, *130*, 5610–5611; d) A. Baschieri, L. Bernardi, A. Ricci, S. Suresh, M. F. A. Adamo, *Angew. Chem.* **2009**, *121*, 9506–9509; *Angew. Chem. Int. Ed.* **2009**, *48*, 9342–9345; e) S. E. Park, E. H. Nam, H. B. Jang, J. S. Oh, S. Some, Y. S. Lee, C. E. Song, *Adv. Synth. Catal.* **2010**, *352*, 2211–2217; f) H. Y. Bae, S. Some, J. H. Lee, J.-Y. Kim, M. J. Song, S. Lee, Y. J. Zhang, C. E. Song, *Adv. Synth. Catal.* **2011**, *353*, 3196–3202; g) L.-T. Shen, L.-H. Sun, S. Ye, *J. Am. Chem. Soc.* **2011**, *133*, 15894–15897.

[3] For other selected recent examples for the synthesis of γ-amino acid derivatives, see: a) J. Deng, Z.-C. Duan, J.-D. Huang, X.-P. Hu, D.-Y. Wang, S.-B. Yu, X.-F. Xu, Z. Zheng, *Org. Lett.* **2007**, *9*, 4825–4828; b) M. Furutachi, S. Mouri, S. Matsunaga, M. Shibasaki, *Chem. Asian J.* **2010**, *5*, 2351–2354; c) Y. Zhu, S. Khumsubdee, A. Schaefer, K. Burgess, *J. Org. Chem.* **2011**, *76*, 7449–7457; d) C. Shao, H.-J. Yu, N.-Y. Wu, P. Tian, R. Wang, C.-G. Feng, G.-Q. Lin, *Org. Lett.* **2011**, *13*, 788–791.

[4] a) E. Roberts, *Biochem. Pharmacol.* **1974**, *23*, 2637–2649; b) I. A. Sytinsky, A. T. Soldatenkov, *Prog. Neurobiol.* **1978**, *10*, 89–133.

[5] a) H. Umezawa, T. Aoyagi, H. Morishima, M. Matsuzaki, M. Hamada, T. Takeuchi, *J. Antibiot.* **1970**, *23*, 259–262; b) D. H. Rich, *J. Med. Chem.* **1985**, *28*, 263–273.

[6] K. Stratmann, D. L. Burgoyne, R. E. Moore, G. M. L. Patterson, *J. Org. Chem.* **1994**, *59*, 7219–7226.

[7] a) G. R. Pettit, Y. Kamano, C. L. Herald, A. A. Tuinman, F. E. Boettner, H. Kizu, J. M. Schmidt, L. Baczynskyj, K. B. Tomer, R. J. Bontems, *J. Am. Chem. Soc.* **1987**, *109*, 6883–6885.

[8] a) B. A. Sachais, J. N. Logue, M. S. Carey, *Arch. Neurol.* **1977**, *34*, 422; b) G. H. Fromm, C. F. Terrence, A. S. Chattha, J. D. Glass, *Arch. Neurol.* **1980**, *37*, 768–771.

[9] a) P. Yuen, G. D. Kanter, C. P. Taylor, M. G. Vartanian, *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823–826; b) R. B. Silverman, *Angew. Chem.* **2008**, *120*, 3552–3556; *Angew. Chem. Int. Ed.* **2008**, *47*, 3500–3504.

[10] I. Lapin, *CNS Drug Rev.* **2001**, *7*, 471–481.

[11] For selected examples, see: a) S. Shuto, N. Shibuya, S. Yamada, T. Ohkura, R. Kimura, A. Matsuda, *Chem. Pharm. Bull.* **1999**, *47*, 1188–1192; b) D. Aguirre, C. Cativiela, M. D. Díaz-de-Villegas, J. A. Gálvez, *Tetrahedron* **2006**, *62*, 8142–8146; c) F. Felluga, F. Ghelfi, G. Pitacco, F. Roncaglia, E. Valentin, C. D. Venneri, *Tetrahedron: Asymmetry* **2010**, *21*, 2183–2191.

[12] For reviews on synthetic methods for constructing quaternary stereocenters, see: a) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; b) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; c) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614; d) J. P. Das, I. Marek, *Chem. Commun.* **2011**, *47*, 4593–4623.

[13] For selected examples of the construction of quaternary stereocenters with organocatalysts, see: a) T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem.* **2003**, *115*, 3926–3928; *Angew. Chem. Int. Ed.* **2003**, *42*, 3796–3798; b) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474–2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423; c) M. S. Kerr, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 8876–8877; d) N. S. Chowdari, J. T. Suri, C. F. Barbas III, *Org. Lett.* **2004**, *6*, 2507–2510; e) J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, D. W. C. MacMillan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5482–5487; f) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, *Angew. Chem.* **2005**, *117*, 107–110; *Angew. Chem. Int. Ed.* **2005**, *44*, 105–108; g) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119–125; h) K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka, T. Akiyama, *Angew. Chem.* **2009**, *121*, 9832–9834; *Angew. Chem. Int. Ed.* **2009**, *48*, 9652–9654; i) T. Kano, Y. Tanaka, K. Osawa, T. Yurino, K. Maruoka, *Chem. Commun.* **2009**, 1956–1958; j) E. Zhang, C.-A. Fan, Y.-Q. Tu, F.-M. Zhang, Y.-L. Song, *J. Am. Chem. Soc.* **2009**, *131*, 14626–14627; k) Q. Zhu, Y. Lu, *Angew. Chem.* **2010**, *122*, 7919–7922; *Angew. Chem. Int. Ed.* **2010**, *49*, 7753–7756; l) Y. Inokoishi, N. Sasakura, K. Nakano, Y. Ichikawa, H. Kotsuki, *Org. Lett.* **2010**, *12*, 1616–1619; m) Y.-H. Liao, X.-L. Liu, Z.-J. Wu, X.-L. Du, X.-M. Zhang, W.-C. Yuan, *Adv. Synth. Catal.* **2011**, *353*, 1720–1728.

[14] For selected examples, see: a) N. Halland, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 8331–8338; b) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897–3900; c) L. Hojabri, A. Hartikka, F. M. Moghaddam, P. I. Arvidsson, *Adv. Synth. Catal.* **2007**, *349*, 740–748; d) L. Zu, H. Xie, H. Li, J. Wang, W. Wang, *Adv. Synth. Catal.* **2007**, *349*, 2660–2664; e) H. Gotoh, H. Ishikawa, Y. Hayashi, *Org. Lett.* **2007**, *9*, 5307–5309; f) S. K. Ghosh, Z. Zheng, B. Ni, *Adv. Synth. Catal.* **2010**, *352*, 2378–2382; g) Y. Hayashi, T. Itoh, H. Ishikawa, *Angew. Chem.* **2011**, *123*, 4006–4010; *Angew. Chem. Int. Ed.* **2011**, *50*, 3920–3924; h) O. V. Maltsev, A. O. Chizhov, S. G. Zlotin, *Chem. Eur. J.* **2011**, *17*, 6109–6117; i) Y. Hayashi, D. Okamura, S. Umemiya, T. Uchimaru, *ChemCatChem* **2012**, *4*, 959–962.

[15] Another possible approach to obtaining a chiral β-disubstituted γ-amino acid is the Michael addition of an aldehyde to a β-disubstituted nitroolefin. Such a reaction has also not been achieved, although the asymmetric Michael addition to β-monosubstituted nitroolefins is well-established; see Ref. [2].

[16] The Michael addition of nitromethane to β-disubstituted α,β-unsaturated ketones has been reported, see: a) C. E. T. Mitchell, S. E. Brenner, S. V. Ley, *Chem. Commun.* **2005**, 5346–5348; b) P. Li, Y. Wang, X. Liang, J. Ye, *Chem. Commun.* **2008**, 3302–3304; c) P. Kwiatkowski, K. Dudziński, D. Łyżwa, *Org. Lett.* **2011**, *13*, 3624–3627.

[17] a) K. Akagawa, H. Akabane, S. Sakamoto, K. Kudo, *Org. Lett.* **2008**, *10*, 2035–2037; b) K. Akagawa, T. Fujiwara, S. Sakamoto, K. Kudo, *Org. Lett.* **2010**, *12*, 1804–1807; c) K. Akagawa, R. Suzuki, K. Kudo, *Adv. Synth. Catal.* **2012**, *354*, 1280–1286.

[18] For reviews on peptide catalysts, see: a) E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759–5812; b) H. Wennemers, *Chem. Commun.* **2011**, *47*, 12036–12041; c) M. Freund, S. B. Tsogoeva in *Catalytic Methods in Asymmetric Synthesis: Advanced Materials, Techniques, and Applications* (Eds.: M. Gruttadauria, F. Giacalone), Wiley, Hoboken, **2011**, pp. 529–578.

[19] For reviews on supported organocatalysts, see: a) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429; b) M. Gruttadauria, F. Giacalone, R. Noto, *Chem. Soc. Rev.* **2008**, *37*, 1666–1688.

[20] When simple resin-supported L-proline was used as a catalyst, the enantioselectivity was 25% *ee* (*R* selective). Dramatic changes in the *ee* values when combining L- or D-Pro with poly-L-Leu suggest the importance of the α-helical structure of polyleucine.

[21] The absolute configuration of the major product indicates *Si*-face attack of nitromethane on the substrate, which is consistent with the previously suggested model of the iminium intermediate in transfer hydrogenation; see: K. Akagawa, H. Akabane, S. Sakamoto, K. Kudo, *Tetrahedron: Asymmetry* **2009**, *20*, 461–466.

[22] a) S. G. Ouellet, J. B. Tuttle, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 32–33; b) J. W. Yang, M. T. H. Fonseca, N. Vignola, B. List, *Angew. Chem.* **2005**, *117*, 110–112; *Angew. Chem. Int. Ed.* **2005**, *44*, 108–110.

[23] a) X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 1135–1138; *Angew. Chem. Int. Ed.* **2008**, *47*, 1119–1122; b) H. Maeda, S. Yamada, H. Itoh, Y. Hori, *Chem. Commun.* **2012**, *48*, 1772–1774.

[24] When the catalyst recovered from the reaction was reused, the conversion decreased to 33% after 24 h. Zlotin et al. reported the mechanism for the deterioration of an amine catalyst by oxidation in the Michael addition of nitromethane to an α,β-unsaturated aldehyde (Ref. [14h]). In the present case, such oxidation is considered to be the cause of deactivation in the peptide catalyst.