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FULL PAPER

Asymmetric 1,4-addition Reactions Catalyzed by N-terminal Thiourea-modified Helical L-Leu-peptide with Cyclic Amino Acids

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Abstract: N-terminal thiourea-modified L-Leu-based peptide {(3,5-diCF_3Ph)NHC(=S)-(L-Leu-L-Leu-Ac_5c)$_2$-OMe} with five-membered ring α,α-disubstituted α-amino acids (Ac_5c) catalyzed a highly enantioselective 1,4-addition reaction between β-nitrostyrene and dimethyl malonate. The enantioselective reaction required only 0.5 mol % chiral peptide-catalyst in the presence of ^{i}Pr$_2$EtN (2.5 equiv), and gave a 1,4-adduct with 93% ee of an 85% yield. As Michael acceptors, various β-nitrostyrene derivatives such as methyl, *p*-fluoro, *p*-bromo, and *p*-methoxy substituents on the phenyl group, 2-furyl, 2-thiophenyl, and naphthyl β-nitroethylenes could be applied. Furthermore, various alkyl malonates and cyclic β-keto-esters could be used as Michael donors. It became clear that the length of the peptide chain, a right-handed helical structure, amide N-Hs, and the N-terminal thiourea moiety play crucial roles in asymmetric induction.

Introduction

Incorporation of α,α-disubstituted α-amino acids (dAAs) into L-amino acid-based peptides induces stable secondary structures such as β-turn, 3_{10}-helix, α-helix, and planar conformation. α-Aminoisobutyric acid (Aib), α-methylated amino acids, and cyclic dAAs are known to induce helical structures in their peptides.[1] We previously reported that α-helical L-Leu-based peptides with cyclic dAAs could be used as chiral catalysts for the epoxidation of chalcone derivatives (Juliá-Colonna epoxidation) (Figure 1-1).[2] Furthermore, we reported that α-helical L-Leu-based peptides with cyclic dAAs could catalyze the enantioselective 1,4-addition reaction of α,β-unsaturated ketones (Figure 1-2).[3] These results demonstrate that cyclic dAA-containing helical peptides could be applied to chiral catalysis using the N-terminal amino group of peptides. The N-terminal amino group would form an iminium with the carbonyl function of a substrate, and accelerate the reaction. The two aforementioned reactions generated products with excellent enantiomeric excesses. However, the helical peptides can only be applied to catalysis for limited kinds of asymmetric reactions, and not for the variety of reactions (Figure 1).[4]

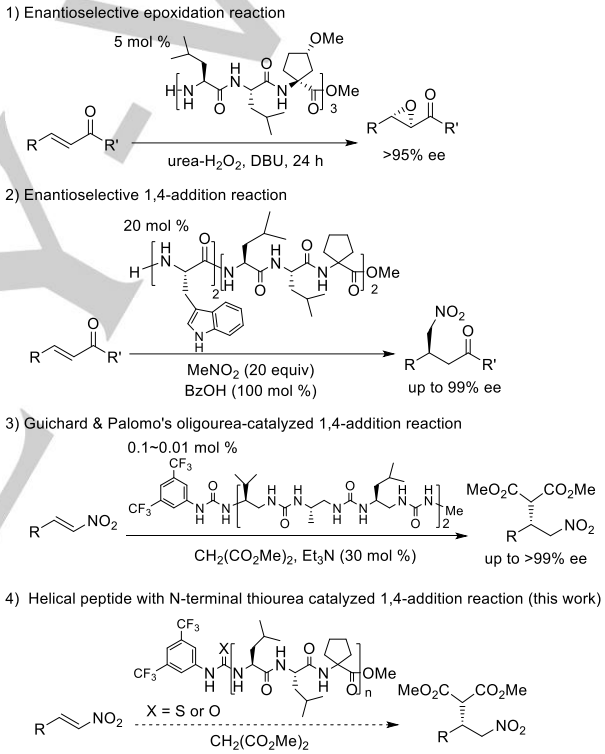


Figure 1. Helical foldamer-catalyzed asymmetric reactions

We hypothesized that N-terminal modification of peptide-catalysts may change the reaction type, and broaden the acceptable range of substrates for helical peptide catalysts. Recently, Guichard, Palomo, and coauthors reported that helical oligo(thio)urea foldamer at low loadings catalyzed the Michael addition reaction between nitroolefins and dialkyl malonates to give 1,4-adducts with excellent enantioselectivities (Figure 1-3).[5] These results led us to examine the reaction using helical L-Leu-based peptides with N-terminal (thio)urea modification because the N-terminal (thio)urea moiety may activate nitroolefins and the amide N(2)-H, N(3)-H, and N(4)-H of peptides, which might trap dialkyl malonates by hydrogen bonds. Furthermore, helical L-α-

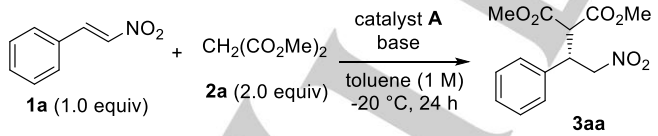
amino acid-based peptides were considered to be easily prepared. Thus, we hypothesized that cyclic dAA-containing the L-Leu-based peptide with N-terminal (thio)urea may catalyze the enantioselective 1,4-addition reaction between nitroolefins and dialkyl malonates, like the helical oligo(thio)urea foldamer does (Figure 1-4).

Results and Discussion

We constructed a helical structure using L-Leu-based peptides with 1-aminocyclopentanecarboxylic acid (Ac_5c).[6] The peptide sequence –(L-Leu-L-Leu-Ac_5c)$_n$– was selected because the sequence forming α-helix was used as a helical peptide-catalyst for epoxidation and 1,4-addition reactions of α,β-unsaturated ketones in our group. We introduced the thiourea or the urea moiety with the 3,5-bis(trifluoromethyl)phenyl group at the N-terminal of helical L-Leu-based peptides. Also, we prepared peptides having an additional (thio)urea moiety at the N-terminal urea of L-Leu peptide.[7]

First, we checked the 1,4-addition reaction between β-nitrostyrene **1a** (1.0 equiv) and dimethyl malonate **2a** (2.0 equiv) in toluene (1 M) at -20°C using Et_3N (0.10 equiv) and 1.0 mol % peptide-catalyst **A** {(3,5-diCF_3Ph)NHC(=S)-(L-Leu-L-Leu-Ac_5c)$_2$-OMe}, which is a hexapeptide with N-terminal thiourea. Under these conditions, the reaction was incomplete after 24 h (61% conv) and the ee of product **3aa** was a moderate 75% (entry 1 in Table 1).[8] Usage of 1.0 equiv Et_3N improved the conversion (>99%), but the ee of the product was still a moderate 73%, and increase of Et_3N (5.0 equiv) improved the ee of **3aa** to 90% (entries 2, 3). The use of ^{i}Pr$_2$EtN instead of Et_3N further improved the ee of product **3aa** to 93% (entry 4). The catalytic amount of **A** could be reduced to up to 0.5 mol % without decreasing ee, but the use of a 0.1 mol % catalyst was detrimental to the high ee, and ee was decreased to 83% (entries 5, 6). The use of a reduced amount of ^{i}Pr$_2$EtN (0.30 equiv) decreased the conversion %, although ee of **3aa** was mostly retained (entry 8). Finally, the use of 0.5 mol % peptide **A** and ^{i}Pr$_2$EtN (2.5 equiv) was found to be suitable for the reaction (entry 7).

Table 1. Optimization of 1,4-addition reaction using helical peptide with N-terminal thiourea.

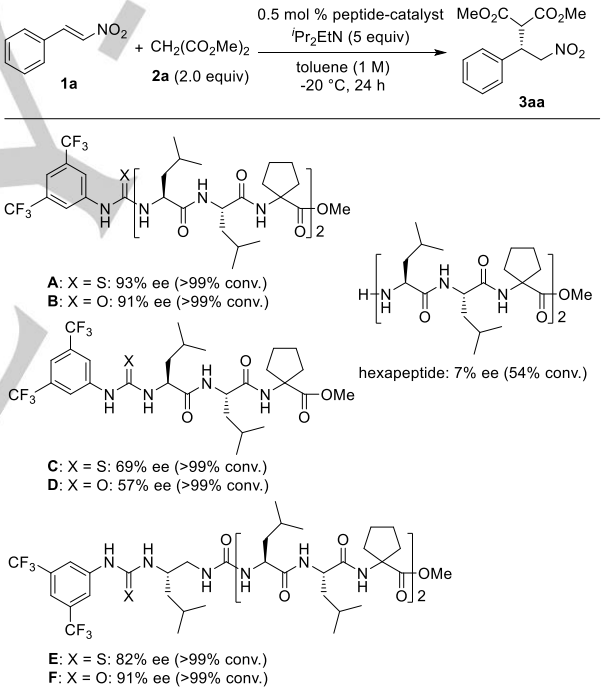


Entry	Catalyst **A** mol %	Base (equiv)	Conv. (%)[a]	Ee (%)[b]
1	1.0	Et_3N (0.10)	61	75
2	1.0	Et_3N (1.0)	>99	73
3	1.0	Et_3N (5.0)	>99	90
4	1.0	^{i}Pr$_2$EtN (5.0)	>99	93
5	0.5	^{i}Pr$_2$EtN (5.0)	>99	93
6	0.1	^{i}Pr$_2$EtN (5.0)	>99	83
7	0.5	^{i}Pr$_2$EtN (2.5)	>99	93
8	0.5	^{i}Pr$_2$EtN (0.30)	76	89

[a] Conversion % was determined by ^{1}H NMR spectrum. [b] The enantiomeric excess (ee) was determined by chiral HPLC analysis.

Next, we examined various peptide catalysts, as shown in Scheme 1. The reaction using catalyst **B** with the N-terminal urea also afforded the 1,4-addition product **3aa** with an excellent 91% ee. Contrary to catalysts **A** and **B**, catalysts **C** and **D**, which are tripeptides, gave product **3aa** with a moderate 57-69% ee. The length of catalysts **C** and **D** may be too short to form helical structures, and ee of **3aa** was unsatisfactory. Catalyst **E** with thiourea and urea moieties showed 82% ee, and catalyst **F** with two ureas gave a product with 91% ee, which was mostly the same as catalyst **B**. The hexapeptide without an N-terminal (thio)urea gave the product **3aa** with a low 7% ee. Thus, the peptide-catalyst **A** gave the best result.

Scheme 1. Screening of peptide-catalysts.



We studied the generality of Michael acceptors, as shown in Scheme 2. The 1,4-addition reactions between nitroalkenes **1a-n** (1.0 equiv) and dimethyl malonate **2a** (2.0 equiv) were performed using 0.5 mol % peptide-catalyst **A** in the presence of ^{i}Pr$_2$EtN (2.5 equiv) in toluene (1 M) at -20°C. Nitroethylenes **1a-l** with β-aryl groups such as *o*-tolyl, *m*-tolyl, and *p*-tolyl groups smoothly reacted with **2a** to give chiral 1,4-adducts **3aa**-**da** with 92-95% ee. *p*-Fluoro, *p*-chloro, *p*-bromo, and *p*-methoxy substituents on the β-phenyl group weakly affected the isolated yields of 1,4-adducts, but the ee of **3ea**-**ha** remained excellent (90-92% ee). The reaction of heteroaromatic 2-furyl, and 2-thiophenyl β-nitroethylenes, and 2-naphthyl and 1-naphthyl β-nitroethylenes also proceeded to give 1,4-adducts **3ia**-**la** with an excellent 90-95% ee. However, nitroethylenes **1m**,**n** with an

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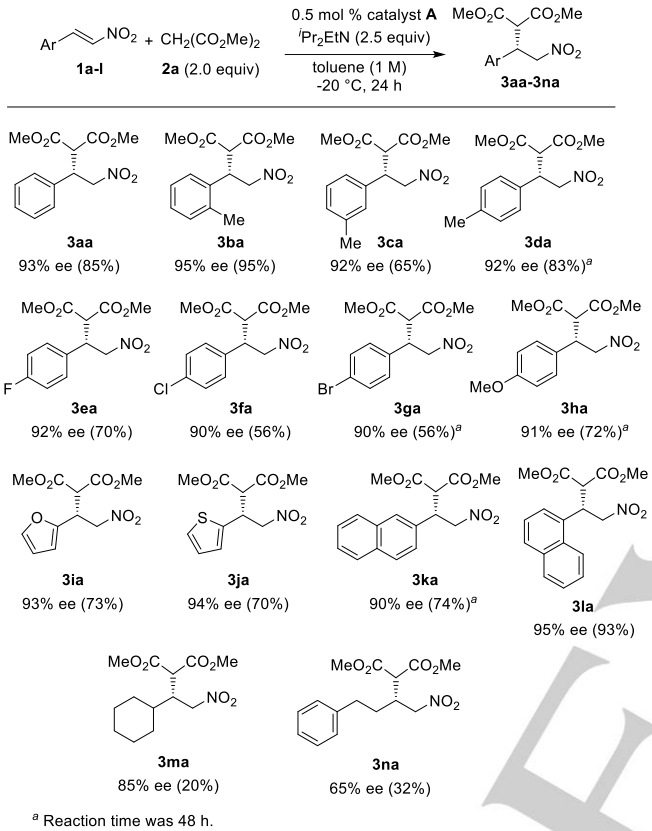
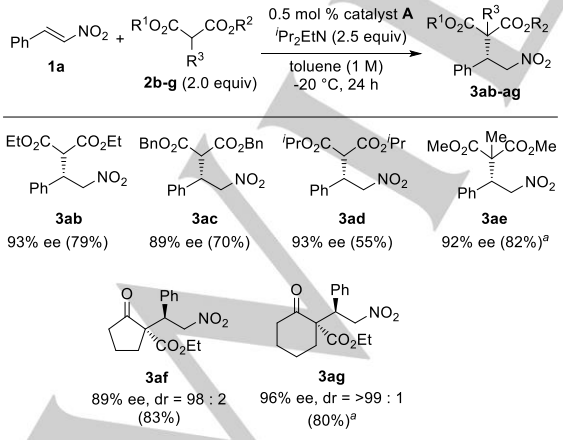
aliphatic β-substituent gave chiral 1,4-adducts **3ma**,**na** with a moderate 65-85% ee in low chemical yields. The 1,4-addition reaction using a gram scale **1a** proceeded without problems to give **3aa** with 93% ee.

Scheme 2. Scope of Michael acceptors.



[a] Reaction time was 48 h.

Scheme 3. Generality of Michael donors.



[a] Reaction time was 96 h.

Scheme 3 shows the generality of Michael donors. The reaction of **1a** with diethyl, dibenzyl, and diisopropyl malonates **2b**-**d** gave chiral 1,4-adducts **3ab**-**ad** with an excellent 91-93% ee. However, the reaction with di-*tert*-butyl malonate did not proceed because the bulky *tert*-butyl ester may hinder the approach of N-H of the helical peptide. The 1,4-addition reaction of **1a** with dimethyl 2-methylmalonate **2e** gave the 1,4-adduct **3ae** (92% ee) with a quaternary carbon. It should be noted that the reaction of **1a** with cyclic β-ketoesters **2f** and **2g** proceeded diastereo- and enantio-selectively to give 1,4-adducts **3af** (88% ee) and **3ag** (96% ee) with a stereogenic quaternary center, respectively.

The catalyst **A** became crystals suitable for X-ray crystallographic analysis by recrystallization from DMF/H_2O. The structure was solved in an orthorhombic $P2_12_12_1$ space group to show two crystallographically independent right-handed (*P*) helical molecules, ***a*** and ***b***, in the asymmetric unit (Figure 2). The structures of the two molecules ***a*** and ***b*** are very similar at the peptide-backbone, but some differences are observed at the C-terminal ester, the isobutyl side chain of L-Leu, and the N-terminal (3,5-diCF_3Ph) moiety, as shown by superimposition of the structures.

In both molecules ***a*** and ***b***, three intramolecular hydrogen bonds of the N(*i*+3)-H···O=C(*i*) (*i* = 1, 2, and 3) *i* ← *i*+3 type, which correspond to the 3_{10}-helix, were observed. The N-terminal thiourea N(0)-H and N(1)-H were intermolecularly hydrogen-bonded to the carbonyl O(4')=C(4') of the neighboring (–1+*x*,*y*,*z*) molecule, and also an intermolecular hydrogen-bond N(2)-H···O(5')=C(5') (–1+*x*,*y*,*z*) was observed. The mean values of ϕ and ψ torsion angles for amino acid residues (1-5) were –64.8° and –30.2° in molecule ***a***, and –63.7° and –32.6° in molecule ***b***, respectively. These values are in good accordance with those of the right-handed (*P*) 3_{10}-helical conformation (–60° and –30°).[9] The ϕ and ψ torsion angles of the C-terminal residue (6) in molecule ***b*** were +50° and +31.9°, respectively, which are opposite signs to those of the preceding residues. Those of the C-terminal residue (6) in molecule ***a*** were distorted (+59.8° and –144.7°, respectively).

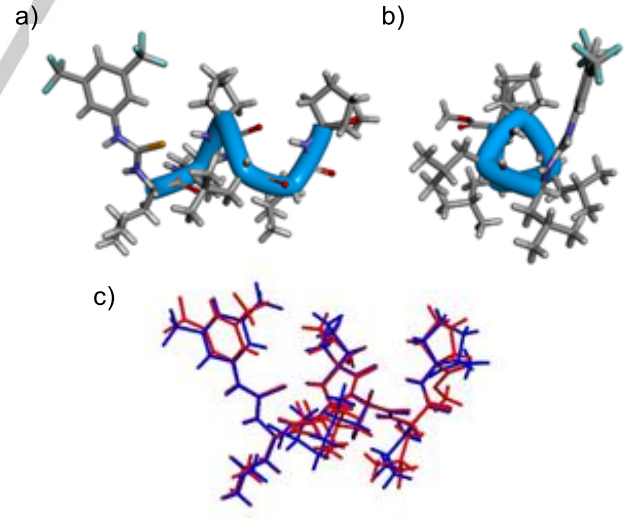


Figure 2. X-ray crystallographic analysis of peptide catalyst **A**. a) molecule ***a*** (side view); b) molecule ***a*** (top view); c) superimposition of molecules ***a*** and ***b***.

The circular dichroism (CD) spectra of peptide-catalysts **A**-**D** were measured in 2,2,2-trifluoroethanol solution (0.05 mM). The CD spectra of **A** and **B** showed a positive maximum at 195 nm and negative maxima at 208 and 222 nm, suggesting the formation of right-handed (*P*) helices.[10] On the other hand, the

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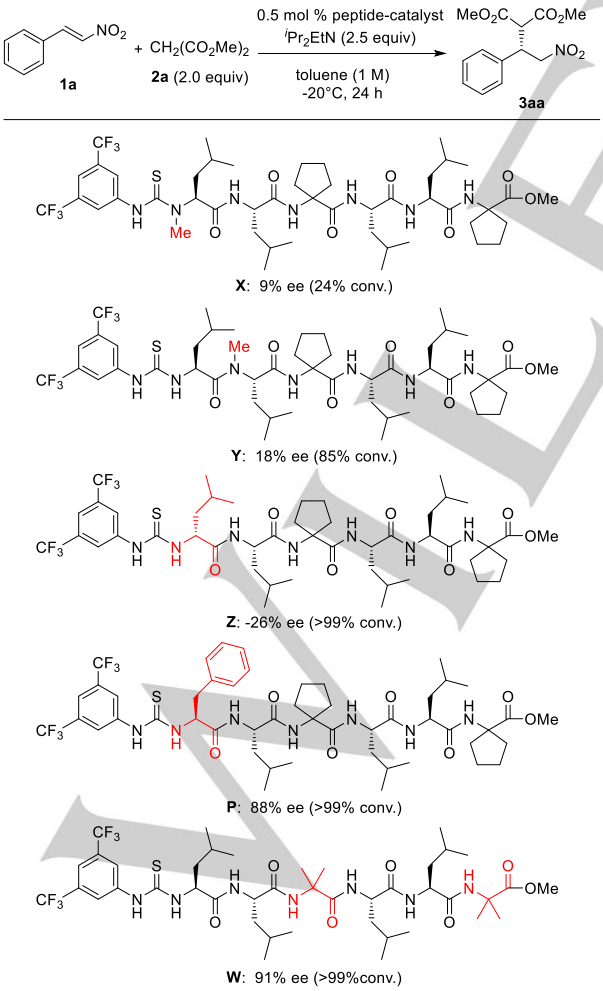
CD spectra of peptide-catalysts **C** and **D** did not show characteristic maxima for the helical structure because the length of **C** and **D** may be too short for the formation of the helical structure.(Figure S1).

To examine which N-Hs of the peptide-catalyst plays a crucial role in the asymmetric 1,4-addition reaction, we examined the reaction using N-methylated peptides (Scheme 4). Without a peptide-catalyst, the reaction proceeded to give racemate **3aa** at a 25% conversion. The reaction using 0.5 mol % N(1)-methylated peptide **X** gave the 1,4-adduct with 9% ee at a 24% conversion, and that using N(2)-methylated peptide **Y** produced the 1,4-adduct with 18% ee at an 85% conversion. These results suggest that the N-terminal thiourea N(1)-H is important for the catalytic reaction because the two N(0)-H and N(1)-H may be used for activation of β-nitrostyrene. On the other hand, N(2)-H may be used to form a hydrogen bond to dialkyl malonate for asymmetric induction, and without N(2)-H the reaction itself proceeded to give the 1,4-adduct with low enantioselectivity. The reaction using peptide catalyst **Z** with D-Leu at the N-terminal residue instead of L-Leu proceeded to give the enantiomeric 1,4-adduct with -26% ee at >99% conversion, and that using catalyst **P** with N-terminal L-Phe afforded the 1,4-adduct with 88% ee at >99% conversion. Thus, the direction of the side-chain substituent at the N-terminus as well as helix is important for this asymmetric induction.

Scheme 4. Effect of amide N-H, D-Leu, L-Phe, and dAA on enantioselective reaction.



To evaluate the effect of cyclopentyl ring on the reaction, Ac_5c in catalyst **A** was replaced with Aib to produce catalyst **W**. The reaction using catalyst **W** with Aib gave the 1,4-adduct with 91% ee at >99% conversion. Thus, the side chain structures of dAAs are of secondary importance, but the induction of helix by dAA is important.

Effects of temperature were studied using peptide catalyst **A** under the same reaction conditions (Table S4). The reaction at room temperature gave product **3aa** with 84% ee and that at 60 °C afforded **3aa** with 77% ee, both in quantitative conversion. These results mean that the Ac_5c-containing helical peptide secondary structure might be stable at these elevated temperatures.

We considered the plausible mechanisms of the enantioselective 1,4-addition reaction, as follows. The helical peptide N-terminal thiourea N(0)-H and N(1)-H, which were intermolecularly hydrogen-bonded to the peptide O(4')=C(4') by the X-ray crystallographic structure, may capture the nitroalkene by hydrogen bonds of type N(0)-H···O=N (nitro) and N(1)-H···O=N (nitro). Dialkyl malonate may be trapped by hydrogen bonds with N(2)-H and N(3)-H of the peptide, and be directed to the enantio-face of nitroalkene.

In conclusion, we demonstrated that N-terminal thiourea-modified L-Leu-based peptide catalyzed highly enantioselective 1,4-addition reactions between nitroolefins and dialkyl malonates. The peptide catalyst **A** formed a right-handed helical structure because Ac_5c induced a helical structure and L-Leu controlled the helical-screw sense to right-handedness. In comparison with a Guichard urea-oligomer catalyst, the reaction using peptide **A** required a large amount (0.5 mol %) of catalyst loading, but the chemical yields and enantiomeric excesses of 1,4-products were very good. Helical structures of peptides composed of L-amino acids and dAAs have been well-studied, and can be precisely designed and easily prepared. The N-terminal modification of helical peptide catalysts would change the applicable reaction type and broaden the acceptable substrates. Such modification of peptide catalysts is currently underway in our group.

Experimental Section

General procedure for Michael addition reaction: A solution of β-nitrostyrene (0.50 mmol), dialkyl malonate (1.0 mmol), peptide catalyst **A** (2.44 mg, 0.5 mol %), and $^{i}Pr_2EtN$ (0.21 mL,1.25 mmol) in toluene (0.5 mL) was stirred at –20°C for 24 h under an Ar atmosphere. Then, the reaction was quenched with 1 N aqueous HCl, extracted with $CHCl_3$, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the crude product was purified by flash chromatography on silica gel to give a 1,4-adduct.

Reaction on gram scale: A solution of **1a** (1.00 g, 6.70 mmol) and peptide catalyst **A** (32.5 mg, 0.5 mol %) in dried toluene (6.70 mL, 0.1 M) was cooled to –20°C, and then dimethyl malonate **2a** (1.53 mL, 13.4 mmol) and $^{i}Pr_2EtN$ (2.85 mL,16.7 mmol) were added at –20°C under an Ar atmosphere. After being stirred for 24 h, the reaction mixture was diluted with 1 N aqueous HCl, extracted with $CHCl_3$, and dried over Na_2SO_4. Removal of the solvent afforded a crude 1,4-adduct, which was purified by column chromatography on silica gel (20% EtOAc in *n*-hexane) to give **3aa** (1.24 g, 66% yield, 93% ee).

Determination of % ee: The enantiomeric excess (% ee) of products was determined by HPLC using the chiral column DAICEL CHIRALPAK AD-H, AS-H, IB N-5, or YMC-SC.

X-ray crystallography: CCDC-2069500 (for peptide-catalyst **A**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe.

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Keywords: helix • peptide • conformation • organocatalyst • α,α-disubstituted α-amino acid

[1] a) C. Toniolo, M. Crisma, F. Formaggio, C. Valle, G. Cavicchioni, G. Precigoux, A. Aubry, J. Kamphuis, *Biopolymers* **1993**, *33*, 1061-1072; b) E. Benedetti, *Biopolymers (Pept. Sci.)*, **1996**, *40*, 3-44; c) C. Toniolo, M. Crisma, F. Formaggio, C. Peggion, *Biopolymers* **2001**, *60*, 396-419; d) M. Tanaka, *Chem. Pharm. Bull.* **2007**, *55*, 349-358; e) M. Crisma, C. Toniolo, *Biopolymers* **2015**, *104*, 46-64; f) M. Crisma, M. De Zotti, F. Formaggio, C. Peggion, A. Moretto, C. Toniolo, *J. Pept. Sci.* **2015**, *21*, 148-177.

[2] a) M. Nagano, M. Doi, M. Kurihara, H. Suemune, M. Tanaka *Org. Lett.*, **2010**, *12*, 3564-3566; b) Y. Demizu, N. Yamagata, S. Nagoya, Y. Sato, M. Doi, M. Tanaka, K. Nagasawa, H. Okuda, M. Kurihara, *Tetrahedron* **2011**, *67,* 6155-6165; c) S. Juliá, J. Masana, J. C. Vega, *Angew. Chem., Int. Ed.* **1980**, *19*, 929-931; *Angew. Chem.* **1980**, *92*, 968-969; d) S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc. Perkin Trans. 1* **1982**, 1317-1324.

[3] a) A. Ueda, T. Umeno, M. Doi, K. Akagawa, K. Kudo, M. Tanaka, *J. Org. Chem.* **2016**, *81*, 6343-6356; b) A. Ueda, M. Higuchi, T. Umeno, M. Tanaka, *Heterocycles*, **2019**, 99, 989-1002; c) T. Umeno, A. Ueda, M. Doi, T. Kato, M. Oba, M. Tanaka, *Tetrahedron Lett.* **2019**, *60*, 151301.

[4] a) G. Licini, M. Bonchio, Q. B. Broxterman, B. Kaptein, A. Moretto, C. Toniolo, P. Scrimin, *Biopolymers (Pept. Sci.)* **2006**, *84,* 97-104; b) H. Wennemers, *Chem. Commun.*, **2011**, *47*, 12036-12041; c) B. A. F. Le Bailly, L. Byrne, J. Clayden, *Angew. Chem. Int. Ed.*, **2016**, *55*, 2132-2136; *Angew. Chem.* **2016**, *128*, 2172-2176; d) K. Akagawa, K. Kudo, *Acc. Chem. Res.* **2017**, *50*, 2429-2439; e) A. J. Metrano, S. J. Miller, *Acc. Chem. Res.* **2019**, *52*, 199-215; f) Z. C. Girvin, M. K. Andrews, X. Liu, S. H. Gellman, *Science* **2019**, *366*, 1528-1531; g) P. Čmelová, D. Vargová, R. Šebesta, *J. Org. Chem.* **2021**, *86*, 581-592.

[5] D. Bécart, V. Diemer, A. Salaün, M. Oiarbide, Y. R. Nelli, B. Kauffmann, L. Fischer, C. Palomo, G. Guichard, *J. Am. Chem. Soc*. **2017**, *139*, 12524-12532.

[6] a) Y. Demizu, M. Tanaka, M. Nagano, M. Kurihara, M. Doi, T. Maruyama, H. Suemune, *Chem. Pharm. Bull.* **2007**, *55*, 840-842; b) Y. Demizu, M. Doi, M. Kurihara, H. Okuda, M. Nagano, H. Suemune, M. Tanaka, *Org. Biomol. Chem.* **2011**, *9*, 3303-3312.

[7] J. Fremaux, L. Mauran, K. Pulka-Ziach, B. Kauffmann, B. Odaert, G. Guichard, *Angew. Chem. Int. Ed.* **2015**, *54*, 9816-9820; *Angew. Chem.* **2015**, *127*, 9954-9958.

[8] Representative references of small-molecule catalysts for enantioselective reactions between dialkyl malonates and nitroalkenes: a) D. R. Niguez, G. Guillena, D. A. Alonso, *ACS Sustainable Chem. Eng.* **2017**, *5*, 10649-10656; b) M. Isik, M. Y. Unver, C. Tanyeli, *J. Org. Chem.* **2015**, *80*, 828-835; c) R. Baran, E. Veverkova, A. Skvorcova, R. Sebesta, *Org. Biomol. Chem.* **2013**, *11*, 7705-7711; d) B. V. S. Reddy, M. Swain, S. M. Reddy, J. S. Yadav, *RSC Advances* **2013**, *3*, 8756-8765; e) M. Terada, H. Ube, Y. Yaguchi, *J. Am. Chem. Soc.* **2006**, *128*, 1454-1455; f) J. Wang, H. Li, W. Duan, L. Zu, W. Wang, *Org. Lett.* **2005**, *7*, 4713-4716; g) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672-12673; h) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119-125.

[9] a) C. Toniolo, E. Benedetti, *Trends Biochem. Sci.* **1991**, *16*, 350-353; b) R. M. J. Liskamp, *Recl. Trav. Chim. Pays-Bas.* **1994**, *113*, 1-19; c) L. Pal, G. Basu, P. Chakrabarti, *Proteins: Struct. Funct. Genet.* **2002**, *48*, 571-579; d) C. Toniolo, M. Crisma, F. Formaggio, C. Peggion, Q. B. Broxterman, B. Kaptein, *Biopolymers (Pept. Sci.)* **2004**, *76*, 162-176.

[10] a) C. Toniolo, A. Polese, F. Formaggio, M. Crisma, J. Kamphuis, *J. Am. Chem. Soc.* **1996**, *118*, 2744-2745. b) G. Yoder, A. Polese, R. A. G. D. Silva, F. Formaggio, M. Crisma, Q. B. Broxterman, J. Kamphuis, C. Toniolo, T. A. Keiderling, *J. Am. Chem. Soc.* **1997**, *119*, 10278-10285.

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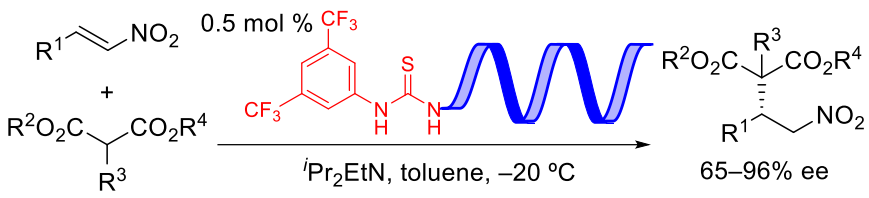

N-terminal thiourea-modified helical L-Leu-based peptide (0.5 mol %) catalyzed a highly enantioselective 1,4-addition reaction between various β-nitrostyrenes and dialkyl malonates to give 1,4-adducts with a 65-96% ee. The length of the peptide chain, right-handed helical structure, amide N-Hs, and the N-terminal thiourea moiety played crucial roles in the asymmetric induction.