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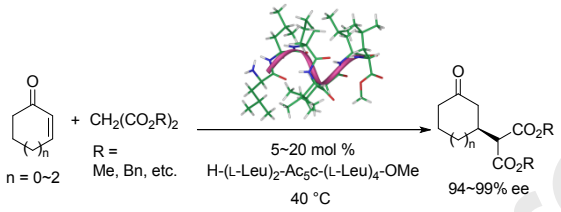

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Helical foldamer-catalyzed enantioselective 1,4-addition reaction of dialkyl malonates to cyclic enones

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ABSTRACT

The introduction of a five-membered ring α,α-disubstituted α-amino acid into L-Leu-based heptapeptides preferentially induced right-handed (*P*) helical structures. Using 5~20 mol % of a single helical foldamers-catalyst, enantioselective 1,4-addition reactions of dialkyl malonates to cycloalk-2-enones (5~7 rings) proceeded to give chiral 3-substituted cycloalkanones with 94~99% ee in moderate chemical yields, regardless of the ring size of substrates.

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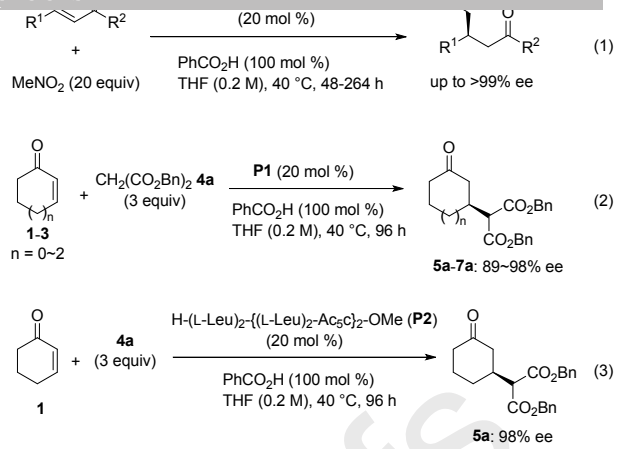
1.

Foldamers are "oligomers with specific compact three-dimensional structures".[1] Recently, foldamer- and peptide-catalyzed asymmetric reactions have been increasingly reported because foldamers are easily tailor-made for specific reactions, non-toxic, and inert toward oxygen and moisture. For example, helical urea oligomer-catalyzed 1,4-addition reactions,[2] *N*-terminal prolylproline-peptide-catalyzed C-C bond forming reactions,[3] turn-structure peptide-catalyzed asymmetric reactions,[4] β-peptide-catalyzed retro-aldol reactions,[5] and resin-bound helical peptide-catalyzed reactions[6] have been reported.

Previously, Toniolo group and then we reported that peptides with α,α-disubstituted α-amino acids (dAAs) preferentially formed helical secondary structures.[7] Their helical-screw directions and the α- or 3_{10}-helix of peptides were able to be controlled by the selections of dAAs. Furthermore, we demonstrated that helical L-Leu-based peptide-foldamers having dAAs can be applied to chiral catalyses for enantioselective epoxidation[8] and 1,4-addition reactions.[9] The helical octapeptide-foldamer H-(L-Trp)$_2$-(L-Leu-L-Leu-Ac$_5$c)$_2$-OMe (**P1**) (Ac$_5$c: 1-aminocyclopentane-1-carboxylic acid) catalyzed enantioselective 1,4-addition reactions of nitromethane (or dibenzyl malonate) to α,β-unsaturated ketones to give optically active 1,4-adducts with up to >99% ee (Scheme 1, eq. 1). Some chiral organocatalysts with an amino functional group catalyzed enantioselective 1,4-addition reactions of dialkyl malonates to cycloalk-2-enones, however; such a small organocatalyst was unable to be applied to different ring sizes of cycloalk-2-enones.[10] In particular, the enantiomeric excess of 3-substituted cyclopentanone by small organocatalysts was often unsatisfactory. On the other hand, helical octapeptide-foldamer **P1**-catalyzed 1,4-addition reaction of dibenzyl malonate to cyclic α,β-unsaturated ketones gave optically active 3-substituted cycloalkanones (cyclopentanone: 89% ee; cyclohexanone: 93% ee; cycloheptanone: 98% ee) (eq. 2). Furthermore, the octapeptide H-(L-Leu)$_4$-Ac$_5$c-(L-Leu)$_2$-Ac$_5$c-OMe (**P2**) without *N*-terminal L-Trp residues catalyzed the enantioselective 1,4-addition reaction of dibenzyl malonate to cyclohex-2-enone, giving 98% ee of the 1,4-adduct (eq. 3).[9] These results were better than those by small organocatalysts,[10] but the reaction required high catalyst loading (20 mol %) and catalysts needed two dAAs. Thus, there was room to improve the simplicity of the foldamer-catalyst, the enantiomeric excess, and conversions of 1,4-adducts. Here, we optimized the structure of peptide-foldamers and reaction conditions, enabling highly enantioselective 1,4-addition reactions of dialkyl malonates to varying cycloalk-2-enones.



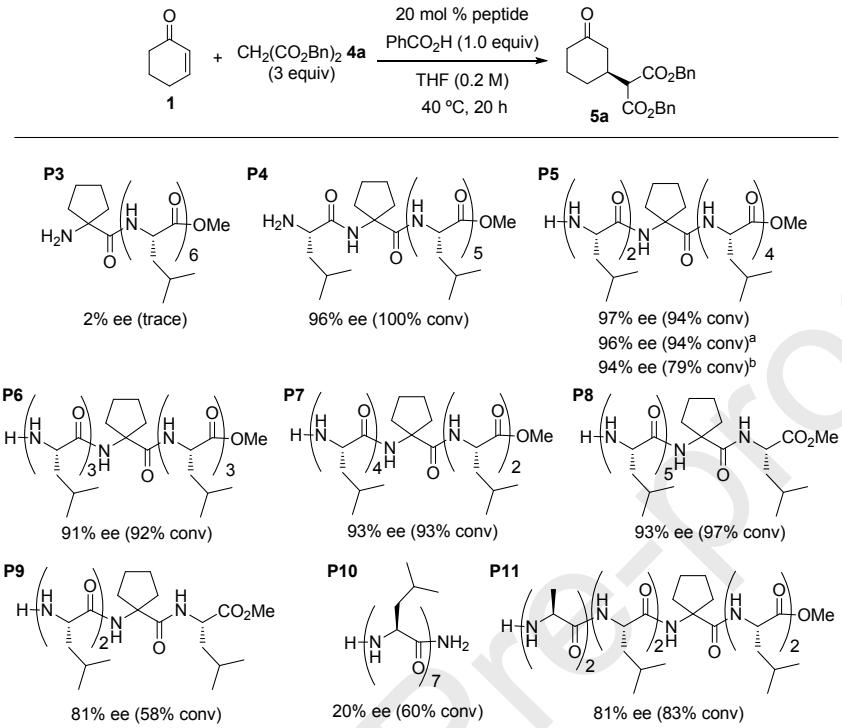
2. Results and Discussion

First, we examined the 1,4-addition reaction of dibenzyl malonate **4a** to cyclohex-2-enone **1** using 20 mol % L-Leu-based peptides (**P3**-**P9**) with an Ac$_5$c in the presence of benzoic acid in THF (Table 1). Although it has been reported that peptide-catalysts having two Ac$_5$c with the sequence -(L-Leu-L-Leu-Ac$_5$c)$_2$- formed helical structure, the peptides **P3**-**P9** have only one helicogenic α,α-disubstituted α-amino acid Ac$_5$c. The position of an Ac$_5$c in L-Leu-based heptapeptides only slightly influenced the enantiomeric excess of 1,4-adduct **5a**, except in the case of *N*-terminal Ac$_5$c. The *N*-terminal Ac$_5$c (**P3**) was detrimental to the 1,4-addition reaction because the amino group at the quaternary carbon may be sterically hindered. Among the heptapeptides (**P3**-**P8**) with an Ac$_5$c examined, the peptide **P5** with an Ac$_5$c at the third position from the *N*-terminus exhibited the greatest enantiomeric excess. Shortened tetrapeptide **P9** reduced the enantiomeric excess of the 1,4-adduct to 81% ee, whereas L-Leu heptapeptide **P10** without an Ac$_5$c gave 20% ee. These low enantiomeric excesses may be due to neither a peptide **P9** nor **P10** being able to form stable helical structures (*vide infra*). The tetrapeptide **P9** is too short to form a helical structure and L-Leu-homopeptide **P10** is too flexible to form a stable helical secondary conformation.[11] Replacement of the two *N*-terminal L-Leu with L-Ala (**P11**) slightly reduced the enantioselectivity (81% ee). The amount of peptide **P5** loading was reduced to 5 mol % without decreasing the enantiomeric excess (94% ee); however the use of 1 mol % catalyst **P5** reduced the enantiomeric excess to 75% ee. In the reaction of **1**, benzoic acid was not necessary, and without benzoic acid, the 1,4-addition reaction using **P5** proceeded well to give the 1,4-adduct **5a** with 97% ee in a good conversion.

The effects of solvents on the 1,4-addition reaction of cyclohex-2-enone **1** using 10 mol % of **P5** are shown in Table 2. The reaction slowly proceeded at a concentration of 0.1 M, and conversions were generally moderate. The use of MeOH was detrimental to the enantiomeric excess, but other solvents {THF, EtOAc, 1,4-dioxane, $CHCl_3$, MeCN, and cyclohexane (cHex)} were suitable for the enantioselective reaction. cHex improved the conversion, and the use of a mixture of THF and cHex (1 : 9) at the concentration of 0.4 M greatly improved both the conversion (>99%) and the enantiomeric excess (97% ee).

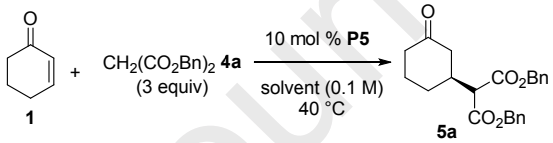
Scheme 1

Table 1. Peptide-foldamer-catalyzed enantioselective 1,4-addition reaction of dibenzyl malonate to cyclohex-2-enone.



[a]10 mol % catalyst and $PhCO_2H$ (0.50 equiv) were used (48 h).
[b] 5 mol % catalyst and $PhCO_2H$ (0.25 equiv) were used (48 h).

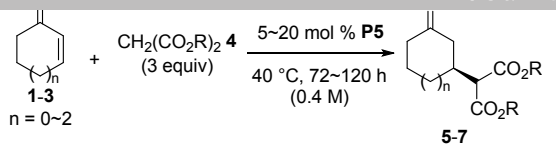
Table 2. Effects of solvents.



entry	solvent	time (h)	conv (%)	% ee
1	THF	89	52	97
2	MeOH	89	57	63
3	EtOAc	89	52	95
4	1,4-dioxane	89	57	94
5	$CHCl_3$	89	26	93
6	MeCN	89	30	90
7	cHex	89	>99	92
8	THF/cHex (3 : 1)	72	85	96
9	THF/cHex (1 : 1)	72	92	98
10	THF/cHex (1 : 3)	72	98	98
11	THF/cHex (1 : 9, 0.4 M)	23	>99	97

We examined different ring sizes of cycloalk-2-enones **1**~**3** as 1,4-addition acceptors and dialkyl malonates **4a**~**4d** as donors using peptide **P5**, as shown in Table 3. Cyclohex-2-enone **1** worked as an excellent 1,4-addition acceptor. Using 5 mol % peptide **P5**, 1,4-addition reactions with varying dialkyl malonates proceeded to give 1,4-adducts with excellent enantiomeric excesses in good isolated yields (entries 1-3). In the case of diisopropyl malonate **4d**, 5 mol % peptide **P5** gave a low chemical yield, and 10 mol % **P5** was needed for a good chemical yield (entry 4). This result may have been due to the bulkiness of the diisopropyl group because di-*tert*-butyl malonate did not react, although the electric properties of **4d** may also be concerned. Although the enantioselective 1,4-addition reaction of cyclopent-2-enone **2** using small chiral organocatalysts often gave a low enantiomeric excess of 1,4-adducts,[10] the reactions using 10 mol % peptide **P5** with different dialkyl malonates produced high enantiomeric excesses of 3-substituted cyclopentanones **6** in moderate chemical yields (entries 5-8). The 1,4-addition reaction of cyclohept-2-enone **3** using 10 mol % peptide **P5** with dibenzyl malonate also gave a 1,4-addition product with a high enantiomeric excess, but the chemical yield was low and the starting material was recovered. The isolated chemical yield was improved to 61% using 20 mol % peptide **P5** in THF. The 1,4-addition reactions of **3** with different dialkyl malonates using 20 mol % peptide **P5** gave excellent enantiomeric excesses of 1,4-adducts, but the reaction was very slow (5 days) and the isolated yields were unsatisfactory.

Table 3. Scope of substrates for enantioselective reactions.

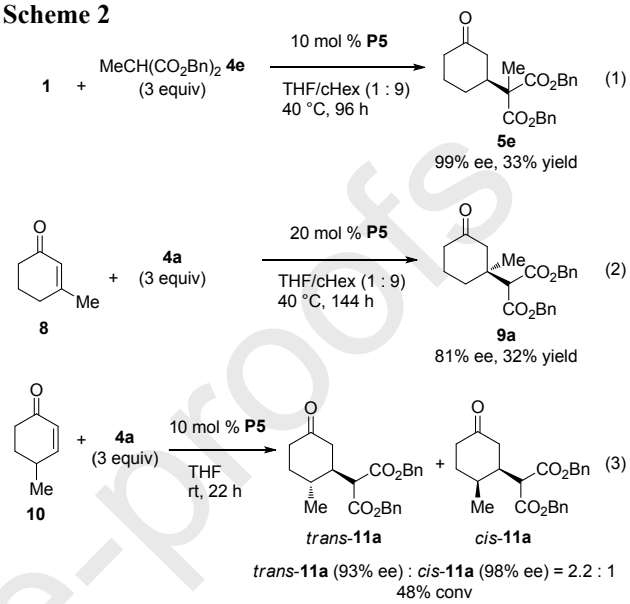


entry	substrate (n =)	R =	mol %	solvent	isolated yield (%)	% ee
1	**1**: (1)	Bn	5	THF/cHex (1 : 9)	**5a:** 86	97
2	**1**: (1)	Me	5	THF/cHex (1 : 9)	**5b:** 79	98
3	**1**: (1)	Et	5	THF/cHex (1 : 9)	**5c:** 74	99
4	**1**: (1)	^{i}Pr	10	THF/cHex (1 : 9)	**5d:** 78	99
5 [a]	**2**: (0)	Bn	10	THF/cHex (1 : 3)	**6a:** 78	97
6 [a]	**2**: (0)	Me	10	THF/cHex (1 : 3)	**6b:** 40	94
7 [a]	**2**: (0)	Et	10	THF/cHex (1 : 3)	**6c:** 50	96
8 [a]	**2**: (0)	^{i}Pr	10	THF/cHex (1 : 3)	**6d:** 41	98
9	**3**: (2)	Bn	10	THF/cHex (1 : 9)	**7a:** 24	99
10	**3**: (2)	Bn	10	THF	**7a:** 37	97
11	**3**: (2)	Bn	20	THF	**7a:** 61	98
12	**3**: (2)	Me	20	THF	**7b:** 74	99
13	**3**: (2)	Et	20	THF	**7c:** 51	99
14	**3**: (2)	^{i}Pr	20	THF	**7d:** 26	99

[a] The reaction was performed at 30ºC.

We examined 1,4-addition reactions for the construction of the quaternary center (Scheme 2). The 1,4-addition reaction of **1** with dibenzyl 2-methylmalonate **4e** using 10 mol % **P5** gave a highly enantiomeric excess 1,4-adduct (99% ee) with a quaternary carbon at a yield of 33%. On the other hand, the enantioselective 1,4-addition reaction of 3-methylcyclohex-2-enone **8** with dibenzyl malonate **4a** using 20 mol % **P5** slowly proceeded to give a 1,4-adduct (moderate 81% ee) with a quaternary stereogenic center at a yield of 32%. The reaction of racemic 4-methylcyclohex-2-enone **10** with **4a** using 10 mol % **P5** proceeded to give 3,4-*trans*-**11a** (93% ee) and 3,4-*cis*-**11a** (98% ee) in the ratio of 2.2 to 1, accompanied by the recovery of **10** (48% ee) in a conversion of 48%. The 1,4-addition reaction enantioselectively proceeded, but the kinetic resolution of racemate **10** was moderate, and a mixture of the diastereomers *trans*-**11a** and *cis*-**11a** was obtained.

Scheme 2



The preferred secondary structures of catalyst **P5** in solution and in the crystalline state were next examined. In the ^{1}H NMR spectra of **P5** in THF-d_8, NOE correlations between the N(*i*)-H and N(*i*+1)-H (*i* = 3~6) protons were observed. These NOE correlations suggested the formation of a helical conformation by these residues (3~7), although discrimination of a 3_{10}- or α-helix was not possible (Figure S1).[12] The FT-IR absorption spectra of Boc-protected **P5** and **P5** demonstrated weak absorption at 3430 cm^{-1} and strong absorption at 3330 cm^{-1} in Boc-protected **P5**, and strong absorption at 3330 cm^{-1} in **P5**, suggesting a helical conformation (Figure S2).[13] Although the CD spectra of **P6**, **P7**, and **P8** in 2,2,2-trifluoroethanol solution (50 μM) exhibited negative maxima at around 205 nm and 222 nm, characteristic for right-handed helical structures,[14] the CD spectrum of **P5** had a negative maximum at 200 nm and very weak negative maximum at around 230 nm, suggesting a helical structure together with other conformations. The CD spectra of **P9** and **P10** did not exhibit characteristic maxima for helical structure (Figure S3).

Recrystallization of catalyst **P5** from MeCN/H_2O gave crystals suitable for X-ray crystallographic analysis (Table S1). The structure was solved in a triclinic *P1* space group to visualize two crystallographically independent molecules, *A* and *B*, in the asymmetric unit.[15] The molecules *A* and *B* were right-handed (*P*) helical structures, and their peptide backbones were generally similar (Figure 1). The averaged ϕ and ψ torsion angles of residues 2-7 were -78.7° and -31.6° in molecule *A*, and -79.7° and -39.9° in molecule *B*, respectively. These values slightly differed from those of an ideal right-handed 3_{10}-helix (-60°; -30°) or α-helix (-57°; -47°) (Table S2).[16] The intramolecular hydrogen bonds of N(*i*+3)-H···O=C(*i*) (*i* = 1~3) type (3_{10}-helix), and those of N(*i*+4)-H···O=C(*i*) (*i* = 1~3) type (α-helix) were observed in both molecules *A* and *B*. Thus, N(5)-H was bound by bifurcated hydrogen bonds to O(1)=C(1) and O(2)=C(2), and N(6)-H was bound by bifurcated hydrogen bonds to O(2)=C(2)

and it was a weak hydrogen bond in both molecules *A* and *B* (Table S3).

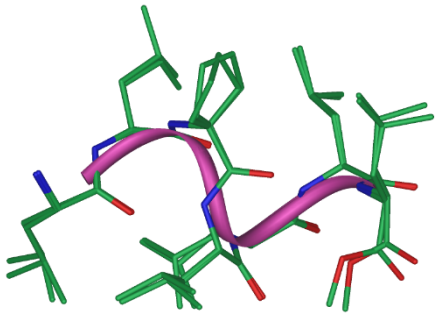


Figure 1. Superimposed structures of molecules *A* and *B* determined by the X-ray crystallographic analysis of **P5**.

3. Conclusion

In summary, we demonstrated that an L-Leu-based heptapeptide having only one cyclic α,α-disubstituted α-amino acid Ac_5c preferentially formed a right-handed (*P*) helical structure. The peptide-foldamer **P5** was able to catalyze the enantioselective 1,4-addition reaction of varying dialkyl malonates to cycloalk-2-enones with excellent enantiomeric excesses, regardless of the ring sizes of substrates.

Acknowledgments

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Supplementary Material

Supplementary data (Experimental section, spectroscopic data of new compounds, NOE ^{1}H NMR spectra of **P5**, FT-IR spectra of Boc-**P5** and **P5**, CD spectra of peptides, X-ray crystallographic parameters of **P5**, ^{1}H and ^{13}C NMR chart, and HPLC chart for determination of % ee (PDF)) associated with this article can be found in the online version, at http://xxxxxxxxxx.

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15. CCDC 1923343 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
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L-Leu-based helical structure was constructed using only one cyclic amino acid

Helical peptide catalyzed asymmetric 1,4-addition reactions to varying cyclic enones

High enantiomeric excesses of 3-substituted cycloalkanones (5~7 rings) were obtained

Reaction proceeded under mild reaction conditions (40ºC) and no additive was needed