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Backbone Modification of β-Hairpin-Forming Tetrapeptides in Asymmetric Acyl Transfer Reactions

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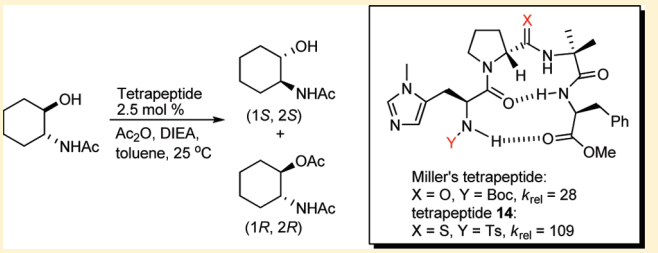
Supporting Information

ABSTRACT: Synthetic oligopeptides as mimics of enzymes have been increasingly exploited as catalysts for asymmetric reactions, but highly effective oligopeptide catalysts with relatively low molecular weight are still in great demand. In this paper, we showed the conformational engineering of the β-hairpin-forming tetrapeptide **4** which was first reported by Miller's group as the catalyst for the asymmetric acyl transfer reaction of *trans*-2-(*N*-acetylamino)cyclohexan-1-ol (k_{rel} = 28). Through our backbone modification strategy, thioamide and sulfonamide as the isosteres of amide were introduced in the β-hairpin secondary structure. The thioxo peptides also adopt β-hairpin conformations as the oxopeptide supported by the combined use of NMR, IR, and X-ray techniques. Thioxo tetrapeptide **14** formed a more constrained β-hairpin conformation and therefore delivered much higher enantioselectivity (k_{rel} = 109) in the same reaction. Moreover, the examination of the conformational changes of tetrapeptide **8** upon the protonation of the N^{π}-methylhistidine moiety provided evidence to explain the variation of its catalytic efficiency in the asymmetric acyl-transfer reaction.

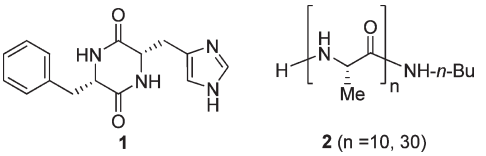


INTRODUCTION

Enzymes as the most powerful catalysts in nature exhibit extremely high specificity in the selection and the transformation of their substrates. Chemists have longed to imitate the active site of enzymes with synthetic oligopeptides which are much less complicated than enzymes. In recent years, more and more oligopeptide catalysts were successfully applied to various types of asymmetric syntheses.[1,2] The conformational rigidity is important for a chiral-inducing agent, and this is also true for oligopeptide catalysts. In this context, cyclic oligopeptides with reduced freedom of rotation present special rigidity. A typical example is the cyclic dipeptide catalyst **1** (Chart 1), documented by Inoue et al. in 1981, which can catalyze the asymmetric hydrocyanation of benzaldehyde with 90% ee.[3] Linear oligopeptides are much more flexible than cyclic oligopeptides, and a longer sequence is often needed to form a well-defined secondary conformation. It was reported that for poly-L-alanine **2**, the catalyst of the Juliá−Colonna epoxidation, only oligomers longer than 10-mer can form the stable α-helix structure crucial for the excellent asymmetric induction.[4]

The most applied tool for confining the conformation of a linear oligopeptide catalyst is the alternation of the α-amino acid side chains. In the side-chain modification strategy, α-amino acids with unnatural side chains are also utilized to lock an oligopeptide into the desired conformation.[5,2h] Compared to side-chain alternation, backbone modification provides more room in controlling the secondary structure of oligopeptides. Building blocks which have been found to have special folding characteristics such as β- or γ-amino acids (referred to as foldamers) can be incorporated in the peptide chain or even used to build the entire oligopeptide catalyst.[6,2e] Also, the amide moiety in the backbone of oligopeptides

Chart 1. Early Examples of Highly Enantioselective Oligopeptide Catalysts



1 **2** (n =10, 30)

can be replaced with its isosteres (Chart 2). As far as we know, this backbone modification strategy using amide isosteres was majorly employed to generate more protease-stable oligopeptides or oligopeptides with better bioactivities[7] but seldom utilized in the development of oligopeptide catalysts.[8]

A thioamide (Ψ[CSNH])[9] in which the oxygen of the amide is replaced by a sulfur atom is perhaps the closest structural mimic of amide (Chart 3, top). A thioamide NH is more acidic and therefore can form a much stronger hydrogen bond than an amide NH.[10] The larger radius of sulfur and the larger charge transfer from nitrogen to sulfur make thioamide have a higher barrier of the rotation about the C−N bond.[11] Thioamide replacement has been investigated in peptide design to determine whether it is a neutral, conformationally rigidifying, or conformationally destabilizing amide isostere. Computational studies predict that the conformational freedom of the residues preceding and following a thioamide is more restricted compared to an amide bond.[12] Miwa et al. inserted a thioamide linkage in peptides adopting α-helix or β-hairpin conformations and

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Chart 2. Commonly Employed Isosteres of Amide

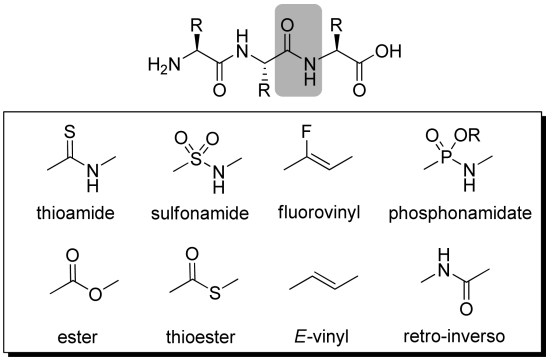
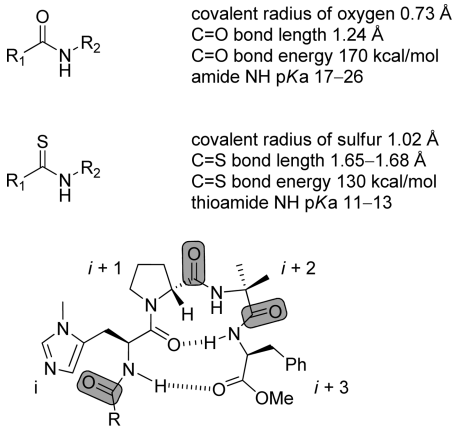


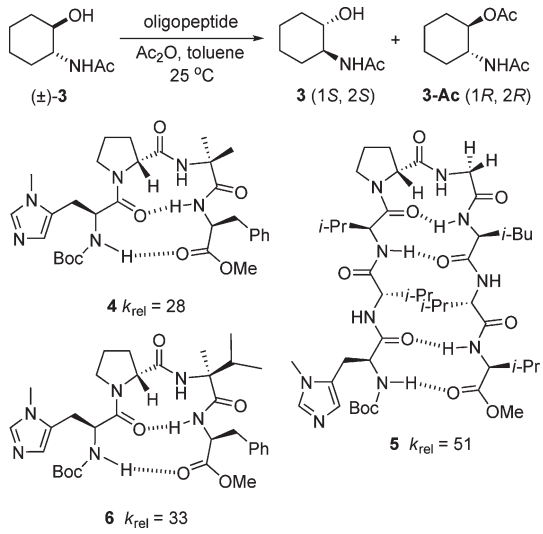
Chart 3. Backbone Modification through Thioamide Replacement



found that the thioxo peptides folded into conformations identical to the native peptides and even with increased thermal stability of an α-helix.[13] The reports from Seebach[14] and Helbing[15] also indicated that thioxo peptides adopted similar conformations as the corresponding oxopeptides together with some unknown conformers. But a more recent report from Kiefhaber's group demonstrated that introducing a thioamide linkage in an alanine-based α-helix caused strong destabilizing effect.[16] Our previous study found that the thioamide replacement in 1-methylhistidine methyl ester, a catalyst developed for asymmetric acylation reactions, strengthened the hydrogen bond between the catalyst and the substrate, but it also rotated the bond of the $C_\alpha-C_\beta$ of that amino acid derivative.[17]

Starting from 1998, Miller's research group designed a series of oligopeptides as the catalysts for asymmetric acyl transfer reactions and their work for the first time showed that short acyclic oligopeptides can serve as efficient asymmetric catalysts.[18,5e] Tetrapeptide **4** (Scheme 1) adopts a β-hairpin conformation induced by a D-Pro-Aib motif and it also bears a N^{π}-methylhistidine at the *N*-terminus as a nucleophilic catalyst. It afforded remarkable enantioselectivity (k_{rel} = 28) in the kinetic resolution of *trans*-2-(*N*-acetylamino)-cyclohexan-1-ol **3** (Scheme 1). Moreover, the D-Pro-Aib β-turn motif discovered in this study was afterward proved to be a versatile scaffold for attaining high enantioselectivities in many other reactions such as desymmetrized phosphorylation,[19] desymmetrized sulfonylation,[2c] asymmetric conjugate addition of azide,[20,5c] asymmetric

Scheme 1. β-Hairpin-Forming Tetrapeptides Designed for Asymmetric Acyl-Transfer Reactions



epoxidation,[21,8b] asymmetric aldol reaction,[2b] and atropisomer-selective aromatic bromination reaction,[2g] etc. Shortly after tetrapeptide **4** was reported, the same group showed that octapeptide **5** with a more rigid β-hairpin conformation by forming four interstrand hydrogen bonds gave a much higher enantioselectivity (k_{rel} = 51) in the same reaction.[18d] In 2004, Toniolo and co-workers showed that the side-chain modification of tetrapeptide **4** by replacing the Aib residue with a (α-Me)Val could afford slightly improved enantioselectivity (k_{rel} = 33) than tetrapeptide **4**.[5d] Alternatively, we envision that the improvement of the conformational rigidity of tetrapeptide **4** might be achieved by backbone modification rather than elongating the peptide sequence or the side-chain variation. Herein, we report on the backbone modification of tetrapeptide **4** through thioamide replacement in its β-hairpin structure. The conformation of the resulted thioxo peptides were investigated by combined NMR, IR, and X-ray analysis. One of these tetrapeptides with thioamide and sulfonamide replacement formed a more constrained β-hairpin conformation and therefore delivered much higher enantioselectivity (k_{rel} = 109) in the asymmetric acyl transfer reaction of **3**.

RESULTS AND DISCUSSION

Design and Synthesis of the Tetrapeptides. The mechanistic studies carried on the tetrapeptide **4** catalyzed asymmetric acyl-transfer reactions indicated that the substrate was first bound to the catalyst through an intermolecular hydrogen bond formed between the Aib amide NH and the acetamido carbonyl oxygen in the substrate and then the *N*-methylimidazole transferred acyl group to the alcohol embedded in a chiral auxiliary environment.[8a] We expected that the introduction of thioamide could possibly bring some degree of restriction rather than distortion of the β-hairpin conformation of tetrapeptide **4**. To test our hypothesis, we have designed modifications of tetrapeptide **4** at three amide sites (Chart 3, bottom). The incorporation of a thioamide at the protecting group of the *N*-terminus N^{π}-methylhistidine at the *i* position is expected to strengthen the second interstrand hydrogen bond of the β-hairpin structure. The insertion of a thioamide at the *i* + 1 position of the β-hairpin, the binding site of the catalyst, can reinforce the intermolecular

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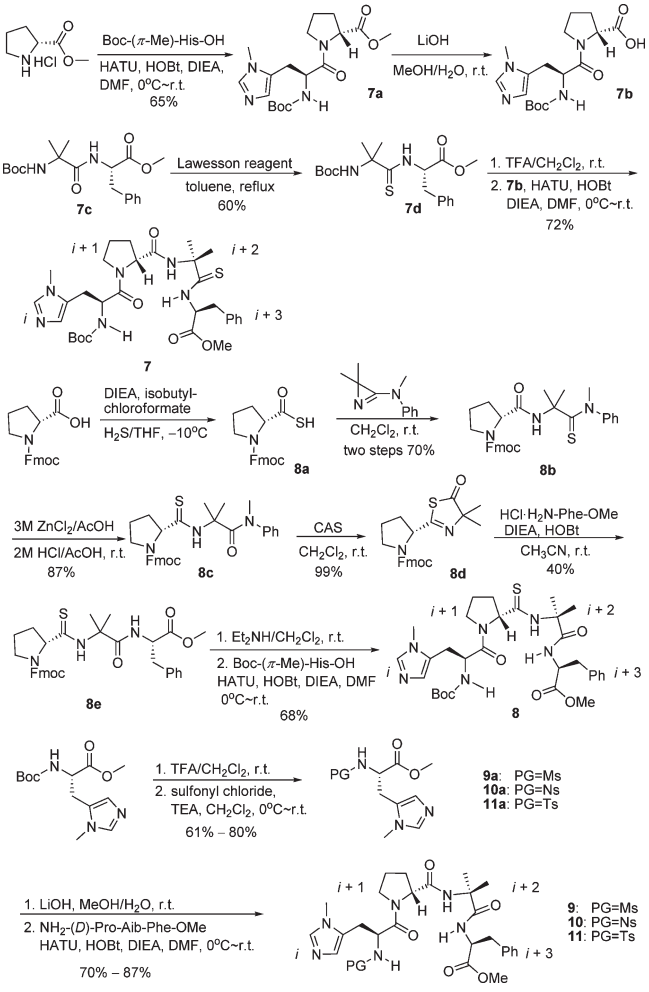
Scheme 2. Synthesis of Tetrapeptides 7−11



hydrogen bond with the substrate. The incorporation of a thioamide linkage at the $i + 2$ position of the β-hairpin is likely to make the first interstrand hydrogen bond stronger.

Among several methods developed to convert an oxygen atom to a sulfur atom in a molecule, Lawesson's reagent is the most frequently used one due to its facile procedure and racemization-free nature.[22] The reactivities of oxygen containing functional groups toward Lawesson's reagent is alcohol > amide > ketone > ester. We initially tried to synthesis the thioxo peptides by treating tetrapeptide **4** with an excessive amount of Lawesson's reagent.[23] But the direct thionation of tetrapeptide **4** led to a mixture of isomers and pure thionated tetrapeptides could not be obtained by column purification. Thus the thio-modified tetrapeptides were separately synthesized by fragment coupling of the thio-modified dipeptides (Scheme 2). Treatment of Boc-Aib-Phe-OMe **7c** with Lawesson's reagent in toluene for 5 h gave Boc-Aib-CSNH-Phe-OMe **7d** in 60% yield, which was then coupled with Boc-(π-Me)-His-D-Pro-OH **7b** to complete the synthesis of tetrapeptide **7** with a thioamide modification at the $i + 2$ position of the β-hairpin structure. But the same strategy did not work in the synthesis of tetrapeptide **8** with a thioamide modification at the $i + 1$ position of the β-hairpin structure. Because of the steric hindrance of 2-aminobutyric acid (Aib), the efficiency of the thionation of Boc-D-Pro-Aib-OMe using Lawesson's reagent was very low (in a control experiment, Lawesson's reagent worked well in the thionation reaction of Boc-D-Pro-Gly-OMe). Therefore, tetrapeptide **8** was synthesized

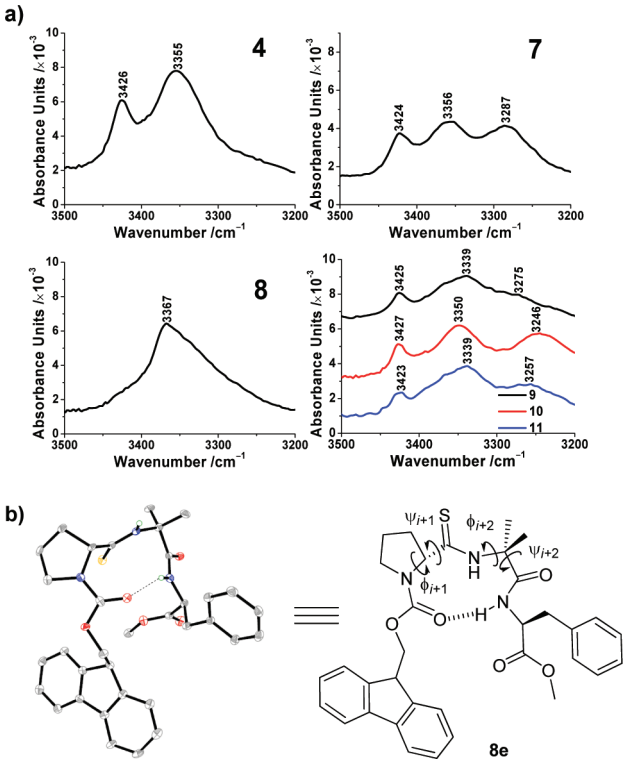


Figure 1. (a) Amide region of the FTIR absorption spectra of tetrapeptides **4** and **7**−**11** (2 mM in CH_2Cl_2). (b) X-ray crystal structure of tripeptide **8e**.

following the method developed by Heimgartner et al.[24] The Fmoc-protected D-Pro was first transformed to its thioacid **8a** with H_2S. Compound **8a** was treated with 2,2-*N*-trimethyl-*N*-phenyl-2*H*-azirin-3-amine to afford the thioamide **8b** in 70% yield. After the $ZnCl_2$/HCl-catalyzed isomerization, **8c** was obtained with a yield of 87% without any epimerization and was then further converted into **8d** under acidic condition with nearly quantitative yield. Treatment of **8d** with H_2N-Phe-OMe gave thioxo tripeptide **8e**, and finally the deprotected **8e** was coupled with Boc-(π-Me)-His-OH to give tetrapeptide **8**. The thio modification of the protecting group of the (π-Me)-histidine at the *i* position of the β-hairpin structure was not successful because the connection between Piv-CSNH-(π-Me)-His-OMe and Fmoc-D-Pro-Aib-Phe-OMe segments failed to gave the desired peptide coupling product. Alternatively, we noticed that a sulfonamide NH is also more acidic and has been previously applied in the modification of amino acid derived organocatalysts.[25] Therefore, catalysts **9**−**11** were constructed by introducing mesyl (Ms), nosyl (Ns), or tosyl (Ts) at the *i* position of the β-hairpin structure, respectively.

Conformational Analysis of Tetrapeptides 7−11. Tetrapeptides **7**−**11** were first subjected to conformational studies to determine their secondary structures. In the ^{1}H NMR titration experiments in which DMSO-d_6 was gradually added into the $CDCl_3$ solution (2 mM) of tetrapeptides **7**−**11**, the (π-Me)-His NHs and the Phe NHs constantly exhibited relatively small downfield shifts while the Aib NHs shifted downfield significantly.[26] This result implies that in each tetrapeptide, the (π-Me)-His NH and the Phe NH are intramolecularly hydrogen-bonded while the Aib NH is free amide NH. This pattern is same with tetrapeptide **4** and indicated that tetrapeptides **7**−**11** also have the β-hairpin structure as the oxo-tetrapeptide. Subsequently, we examined the amide region in the FT-IR absorption spectra of tetrapeptide **4** and tetrapeptides **7**−**11**

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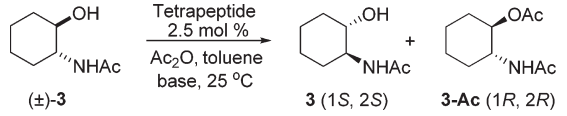
(Figure 1a). For tetrapeptide **4**, the absorption at 3426 cm^{-1} is caused by the regular stretching of the free Aib NH, and the intramolecular hydrogen-bonded (π-Me)-His NH and Phe NH both appear at a lower wavenumber of 3355 cm^{-1}.[18b] For tetrapeptide **7**, the band of the Aib NH at 3424 cm^{-1} is similar to the Aib NH of tetrapeptide **4**. The band of Phe thioamide NH at 3287 cm^{-1} corresponds to a typical thioamide NH absorption in a $1\leftarrow4_t$ C_{10} to β-turn of a 10-membered ring hydrogen bond.[27] The absorption of the (π-Me)-His NH at 3356 cm^{-1} is parallel with that of tetrapeptide **4**, implying that the second interstrand hydrogen bond in tetrapeptide **7** is not affected when a more acidic thioamide NH serves as the hydrogen bond donor in the first interstrand hydrogen bond. For tetrapeptide **8**, there is only one broad peak appeared at 3367 cm^{-1} which is assigned to be the overlap of the absorptions of the free Aib thioamide NH and the intramolecular hydrogen-bonded (π-Me)-His NH and Phe NH. Because of the overlap of these peaks, it is impossible to judge if the two interstrand hydrogen bonds are strengthened after the thioamide modification at the $i+1$ position of the β-hairpin structure. The crystal structure of tripeptide **8e** (Figure 1b) which is the synthetic precursor of tetrapeptide **8** clearly displays the type II′ β-turn conformation (the dihedral angles for tripeptide **8e** are $\phi_{i+1} = +58.6°$, $\psi_{i+1} = -133.2°$, $\phi_{i+2} = +57.7°$, and $\psi_{i+2} = +32.8°$). The thioamide plane is almost perpendicular to the plane of the β-turn. The length of the hydrogen bond between the (π-Me)-His C═O and the Phe amide NH is 2.21 Å, and the angle of 153.9°. For tetrapeptides **9**−**11**, the free Aib NHs fall in the region around 3423−3427 cm^{-1}. The (π-Me)-His sulfonamide NHs exhibit different levels of shifts to lower wavenumbers than free sulfonamide NHs (normally appearing at 3389 cm^{-1}), indicating that the (π-Me)-His sulfonamide NHs are all hydrogen-bonded.[28] The hydrogen-bonded Phe NHs falling in the region of 3339−3350 cm^{-1} shift to lower wavenumbers compared with tetrapeptide **4**. This shift implies that the first interstrand hydrogen bond of the β-hairpin structure is strengthened in tetrapeptides **9** and **11** when a more acidic sulfonamide NH serves as the hydrogen bond donor in the second interstrand hydrogen bond.

Kinetic Resolution Using Tetrapeptides 7−11. The catalytic efficiencies of tetrapeptides **7**−**11** were tested in the kinetic resolution reaction of *trans*-2-(*N*-acetylamino)cyclohexan-1-ol **3** (Table 1). To make sure that results from our laboratory are comparable with those reported by Miller's group, the kinetic resolution reaction of **3** was first run with tetrapeptide **4** prepared in our laboratory. The reaction reached 50% conversion in 65 min and the same selective factor ($k_{rel} = 28$) was obtained, which was in good agreement with Miller's report.[18b,d] Our initial attempts found that both thioxo tetrapeptides **7** and **8** showed lower enantioselectivities than tetrapeptide **4** in the kinetic resolution reactions of **3**. The selective factor for tetrapeptide **7** was 19 and tetrapeptide **8** also afforded a lower selective factor ($k_{rel} = 20$) at a considerably lowered rate with the half-reaction time up to 12 h. Among tetrapeptides **9**−**11**, we anticipated that tetrapeptide **10** would give the highest selective factor since it bears the most acidic sulfonamide NH. However, tetrapeptide **9** and **10** gave similar stereoselectivities as tetrapeptide **4**, but tetrapeptide **11** with Ts protected (π-Me)-histidine afforded a better result ($k_{rel} = 40$). To our surprise, when the reactions were conducted with 1 equiv of DIEA, the selective factor of tetrapeptide **8** was significantly enhanced to 63 and the reaction time for reaching 50% conversion of **3** was reduced to 45 min. Other modified tetrapeptides gave slightly higher selective factors in the presence of 1 equiv. of DIEA compared with the reaction condition without base. Several other bases were also tested in the kinetic resolution using tetrapeptide **8**. TEA in the reaction

Table 1. Asymmetric Acylation of 3 by Tetrapeptides 7−11[a]



(±)-**3** **3** (1*S*, 2*S*) **3-Ac** (1*R*, 2*R*)

cat.	time$_{1/2}$(min)	base	ee% (SM)[b]	ee % (prod)[b]	conv[c] (%)	k_{rel}[c]
7	120	none	78.8	77.6	50.4	19
8	720	none	79.5	78.6	50.3	20
9	90	none	81.3	82.1	49.8	25
10	150	none	82.7	84.0	49.6	30
11	120	none	84.7	87.4	49.2	40
7	100	DIEA	82.8	80.1	50.8	23
8	45	DIEA	90.2	90.6	49.9	63
9	90	DIEA	82.1	82.8	49.8	27
10	130	DIEA	83.8	84.9	49.7	32
11	120	DIEA	85.4	88.3	49.2	44
8	40	TEA	92.8	89.7	50.8	63
8	50	PMP	89.0	89.7	49.8	55
8	20	DABCO	84.2	82.3	50.6	27
8	540	pyridine	83.9	79.4	51.4	23

[a] Conditions: alcohol (0.032 mmol), catalyst (2.5 mol %), base (0.032 mmol), and Ac_2O (25 μL) in toluene (3.2 mL) were stirred at 25 °C. [b] Determined by GC analysis. [c] Calculated according to the method established by Kagan.[29]

afforded a same selective factor as DIEA. More hindered trialkylamine PMP (1,2,2,6,6-pentamethylpiperidine) gave a slightly lower selective factor ($k_{rel} = 55$) and a slower reaction rate. DABCO accelerated the reaction but reduced the enantioselectivity of the reaction ($k_{rel} = 27$), which might be due to the increased background reaction catalyzed by DABCO. Weak bases such as pyridine furnished a k_{rel} value of 23 with a much slower reaction rate.

Conformational Change of Tetrapeptide 8 Induced by Histidine Protonation. We proceeded to interpret the reason for the lower enantioselectivity when no base was present in the kinetic resolution reaction catalyzed by tetrapeptide **8**. In Toniolo's paper, they mentioned that the ^{1}H NMR spectrum of tetrapeptide **4** prepared in their laboratory was different from the one reported by Miller's laboratory, and this problem could be fixed by treating tetrapeptide **4** with 3 equiv of TEA. They concluded that such a difference in the ^{1}H NMR spectrum came from the protonation of the imidazole moiety in tetrapeptide **4** that they initially synthesized. We thought the less active tetrapeptide **8** we initially applied in the kinetic resolution reaction might also suffer from the same problem. Tetrapeptide **8** (spectrum A in Figure 2a) was hence treated with 3 equiv of TEA followed by evaporation, and the resulted tetrapeptide **8** was analyzed by ^{1}H NMR. Compared with spectrum A of the untreated tetrapeptide **8**, the chemical shifts of most of the protons changed in spectrum B (Figure 2a). The hydrogen ($\Delta\delta_H$ = 0.87 ppm) and the methyl ($\Delta\delta_{methyl} = 0.17$) on the N^{π}-methylimidazole ring significantly shifted upfield. The upfield shift was in agreement with the deprotonation process of a protonated histidine imidazole reported in the literature.[30] When a trace amount of solid $KHSO_4$ was added to the above NMR tube containing tetrapeptide **8**,[31] the signals of the protons (spectrum C) shifted toward the form in spectrum A, although the two spectra were not exactly the same. When a small amount of DIEA was further added to neutralize

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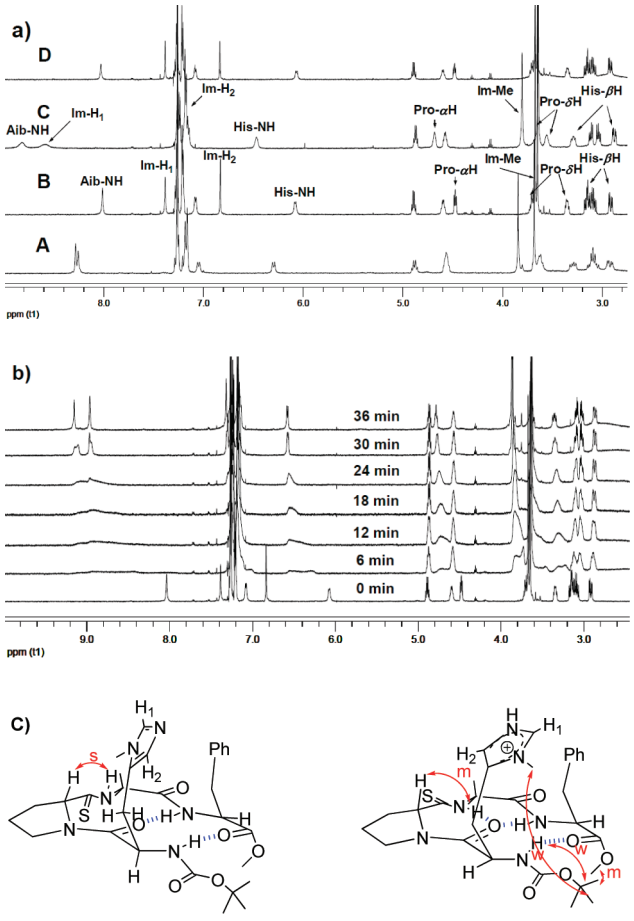


Figure 2. (a) ^{1}H NMR spectra of tetrapeptide **8** at different forms. (b) Time dependent ^{1}H NMR spectra of the protonation process of tetrapeptide **8**. (c) Conformations of tetrapeptide **8** at the free-base form and the protonated form.

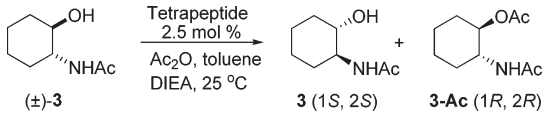
$KHSO_4$, the ^{1}H NMR signal (spectrum D) shifted back to be the same with spectrum B. This experiment showed that the *N*-methylimidazole moiety of tetrapeptide **8** we initially applied in the kinetic resolution reaction was partially protonated. The *N*-methylimidazole moiety can reversely bind proton, and the two conformations of the fully protonated form (spectrum C) and the free-base form (spectrum B and D) interconvert too quickly to be resolved by the NMR time scale (spectrum A).

The conformational transition of tetrapeptide **8** from the free-base form to the protonated form could be tracked by recording an ^{1}H NMR spectrum every 6 min ca. 0.5 h after the addition of solid $KHSO_4$ (Figure 2b). The proton signal of tetrapeptide **8** became broadened at first and then sharpened, a typical process of the conformational change in oligopeptides. It was also interesting to note that trace amount of H_2O in the $CDCl_3$ solution of the tetrapeptide **8** was necessary for the protonation of the *N*-methylimidazole moiety. If the $CDCl_3$ solution was thoroughly dried by 4 Å molecular sieves, tetrapeptide **8** did not undergo the conformation change upon the addition of solid $KHSO_4$, suggesting that a solid acid could not protonate tetrapeptide **8** directly.

From the comparison of the ^{1}H NMR spectra of tetrapeptide **8** at the free-base form and the fully protonated form (spectra B and C, respectively), the Aib thioamide NH ($\Delta\delta$ = 0.80 ppm), the Phe amide NH ($\Delta\delta$ = 0.08 ppm), the (π-Me)-His amide NH ($\Delta\delta$ = 0.39 ppm), the proline C_α-H ($\Delta\delta$ = 0.21 ppm), and C_δ-H ($\Delta\delta$ = 0.20 ppm) exhibited different extents of shift. This indicated that the conformation of tetrapeptide **8** has changed to some degree upon the protonation of the *N*-methylimidazole ring. The Aib thioamide NH ($\Delta\delta$ = 0.80 ppm) downfield-shifted considerably. But the Aib thioamide NHs in tripeptide **8e** did not shift downfield upon the addition of solid $KHSO_4$, suggesting that the downfield shift of the Aib thioamide NH in tetrapeptide **8** was not caused by the formation of an intermolecular hydrogen bond between the Aib thioamide NH and HSO_4^- anion. DMSO-d_6 titration experiments showed that the Aib thioamide NH, the (π-Me)-His NH, and the Phe NH are all intramolecularly hydrogen-bonded in the protonated form of tetrapeptide **8**.[32] ROESY spectra of tetrapeptides **8** at both forms were recorded, and the observed NOE differences are summarized in Figure 2c. The NOE between the C_α-H of proline and the Aib thioamide NH was strong in the free-base form of tetrapeptide **8**, which was in agreement with a typical type II′ β-turn conformation. Nevertheless, this signal was somewhat weaker in the protonated form of tetrapeptide **8**. The two strands of the β-hairpin structure were closer in the protonated form of tetrapeptide **8**, supported by the medium NOE between the Boc group and the methyl ester. The $1\leftarrow3_t$ C_7^{to} γ-turn is often observed in thioxo peptides (γ-turns are less frequently observed in normal oligopeptides) because the thioamide NH is a good hydrogen bond donor and has a strong preference to form a hydrogen bond.[33] We thus proposed the (π-Me)-His carbonyl was involved in a three-center (bifurcated) hydrogen bond[34] with the Aib thioamide NH and the Phe amide NH and tetrapeptide **8** at the protonated form adopted a β-turn conformation associated with a seven-membered $1\leftarrow3_t$ C_7^{to} γ-turn. This may explain the observation that the acyl-transfer reaction was extremely slow when using the partially protonated tetrapeptide **8**. That was because that the Aib thioamide NH formed an intramolecular hydrogen bond in the protonated from and was not available for anchoring the substrate. The two conformations of tetrapeptide **8** were in a fast equilibrium in the solution which was represented by spectrum A in Figure 2a. Due to the distortion of the β-hairpin conformation, the observed enantioselectivity of the partially protonated tetrapeptide **8** was relatively low. The phenomenon of the protonation of the *N*-methylimidazole in tetrapeptide **4** has been documented by Toniolo's group, but the catalytic efficiency of the protonated tetrapeptide **4** was not mentioned in their report.[5d] We found that the acyl transfer reaction with the protonated tetrapeptide **4** (by treatment of tetrapeptide **4** with solid $KHSO_4$) reached 50% conversion within 70 min, which was equally fast compared with tetrapeptide **4** in the free-base form, but gave a lowered selective factor of 17. This might suggest that in the protonated form of tetrapeptide **4**, the Aib NH is still a free amide NH and is capable of binding substrates. However, the β-hairpin conformation of tetrapeptide **4** may also be distorted and consequently gave a lower selective factor. It is still not clear to us why the conformations of these simple tetrapeptides change upon the protonation of the *N*-methylimidazole in histidine residue. The histidine protonation-induced conformational change is widely observed in pH-sensitive proteins. The activity of these proteins is thereby regulated by the protonation state of one or more histidine residues.[35]

Tetrapeptides with Two Backbone Modifications. The Ts modification at the protecting group of the (π-Me)-histidine residue (tetrapeptide **11**) strengthens the second interstrand hydrogen bond in the β-hairpin structure and also improves the stereoselectivity of the acyl transfer reaction. The thio modification at the $i+1$ position of the β-hairpin structure (tetrapeptide **8**) made the hydrogen bond

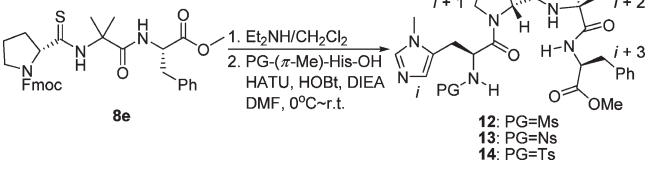
Table 2. Kinetic Resolution of 3 Catalyzed by Tetrapeptides 12−14[a]



cat.	time$_{1/2}$ (min)	DIEA (equiv)	ee (%) (starting material)[b]	ee (%) (prod)[b]	conv[c] (%)	k_{rel}[c]
12	75	1	88.9	88.1	50.2	47
13	75	1	92.5	87.2	51.5	49
14	40	1	92.8	93.9	49.7	108
14	40	0.2	92.6	94.0	49.6	109
14	60	0.1	94.4	91.4	50.8	80
14	55	none	92.4	91.6	50.2	76

[a] Conditions: alcohol (0.032 mmol), catalyst (2.5 mol %), DIEA, and Ac_2O (25 μL) in toluene (3.2 mL) were stirred at 25 °C. [b] Determined by GC analysis. [c] Calculated according to the method established by Kagan.[29]

Scheme 3. Synthesis of Tetrapeptides 12−14



between the catalyst and the substrate more favorable although at this stage we do not know if the thioamide modification could make the β-hairpin structure more constrained. It would be interesting to apply modifications simultaneous at both i and $i + 1$ position of the β-hairpin structure to generate even more effective tetrapeptide catalysts. Thus tetrapeptides **12**−**14** with two modifications were synthesized starting from **8e** (Scheme 3).

Tetrapeptides **12**−**14** were subsequently evaluated in the kinetic resolution reaction of **3** (Table 2). Tetrapeptides **12**−**14** all afforded better stereoselectivities than tetrapeptides **9**−**11**. To our delight, tetrapeptide **14** achieved a high selective factor of 108, and the time for reaching 50% conversion was only 40 min. Considering that tetrapeptide catalysts might also be sensitive to tiny amount of acid in the reaction system and this might significantly affect the stereoselectivity of the catalyst, the acyl-transfer reactions were conducted in the presence of 1 equiv of DIEA. The kinetic resolution reaction under no base conditions provided a substantially lower selective factor (k_{rel} = 76). The addition of 0.2 equiv of DIEA gave the same result as that with 1 equiv of DIEA.

The conformations of tetrapeptides **12**−**14** were investigated by FT-IR analysis. The non-hydrogen-bonded Aib thioamide NHs appears at about 3370 cm^{-1} (Figure 3). The absorptions of sulfonamide NHs in the range of 3248−3273 cm^{-1} are the same as those of tetrapeptides **9**−**11**. The absorption of the Phe NHs shift to lower wavenumbers after the thio modification ($\Delta\nu$ = 12−19 cm^{-1}), implying more tight first interstrand hydrogen bonds in tetrapeptides **12**−**14**. This suggested that the thio modification at the $i + 1$ position of the β-hairpin structure could make the β-hairpin conformation more constrained. It should still be noted that the thio modification does not always bring beneficial effects since the thio modification at the $i + 2$ position of the β-hairpin structure in tetrapeptide **7** did not lead to a more

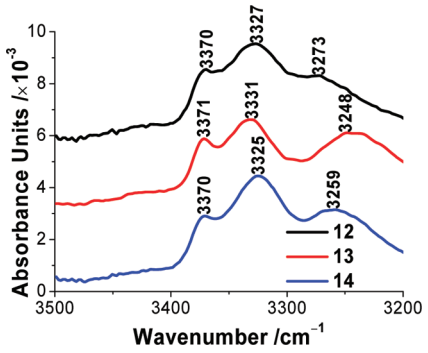


Figure 3. FT-IR absorption spectra for tetrapeptides **12**−**14**.

rigid β-hairpin structure. Tetrapeptides **10** and **14** bear the most acidic nosyl sulfonamide NH as the hydrogen bond donors and thus are capable of forming very strong interstrand hydrogen bonds, but they did not give the highest stereoselectivities in the asymmetric acyl transfer reactions. This observation was in agreement with Miller et al.'s conclusion that a very tight β-hairpin conformation does not necessarily lead to a higher stereoselectivity. They found that adding a covalent linkage between the two strands of the β-hairpin structure of octapeptide **5** resulted in a decreased stereoselectivity.[18d] This maybe in accord with the findings that a modicum of flexibility is necessary for the function of enzyme.

Finally, we examined the substrate scope of the asymmetric acyl-transfer reaction using tetrapeptide **14** (Table 3). Tetrapeptide **14** showed higher stereoselectivities for six- and seven-membered-ring *trans* cyclic acetamide-functionalized alcohols (entry 1 and 2, Table 3) than tetrapeptide **4** which gave k_{rel} values of 28 and 17, respectively.[18d] For substrate **16** with a double bond in the cyclohexane ring (entry 3), the value of k_{rel} was also high (k_{rel} = 77). However, the enantioselectivity for substrate **17** with a five-membered ring was low (entry 3), just like tetrapeptide **4** (k_{rel} = 6).[18d] Substrate **18** with an eight-membered ring also afforded reasonably high enantioselectivity (k_{rel} = 34) which had not been tested with tetrapeptide **4**. But substrate **19** with a double bond in the cyclooctane ring showed a diminished k_{rel} value of 4 (entry 6) under the same conditions. For the acyclic substrates **20** and **21**, both the activities and the

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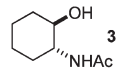
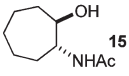
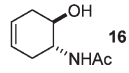
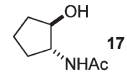
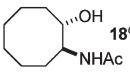
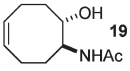
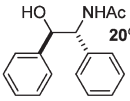
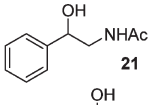
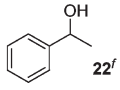
Table 3. Kinetic Resolutions with Tetrapeptide 14[a]

entry	substrates	time$_{1/2}$	ee %$_{S.M.}$[b]	ee %$_{prod.}$[b]	conv.%	k_{rel}
1	 **3**	40 min	92.6	94.0	49.6	109
2	 **15**	70 min	86.8	92.7	48.4	75
3	 **16**	50 min	–	90.6	51.3[c]	77
4	 **17**	120 min	53.1	68.4	43.7	9
5	 **18**[d]	40 min	67.8[e]	88.6[e]	43.4	34
6	 **19**	110 min	35.0	46.6	42.9	4
7	 **20**[d]	3 h	43.4[e]	25.3[e]	63.2	2
8	 **21**	4 h	13.5	13.4	50.2	1.5
9	 **22**[f]	24 h	–	–	1.5	–

[a] Conditions: alcohol (0.032 mmol), tetrapeptide **14** (2.5 mol %), DIEA (20 mol %), and Ac_2O (25 μL) in toluene (3.2 mL) were stirred at 25 °C. [b] Determined by GC analysis. [c] The enantiomers of the starting material can not be separated by chiral GC column; the conversion of the reaction was determined by achiral GC column. [d] The reaction was in a 4 × scale. [e] Determined by HPLC analysis. [f] The reaction was run under −60 °C.

enantioselectivities of tetrapeptide **14** declined. The reaction of 1-phenylethanol **22** (entry 9), which has no hydrogen-bonding site, was extremely slow. However, this substrate can be resolved (k_{rel} = 20) by an octapeptide which was identified through a fluorescence-based activity assay by Miller's group.[18f] This suggests that a longer oligopeptide with a more complicated conformation is needed to recognize unfunctionalized alcohols.

CONCLUSION

Much work is still needed toward designing an oligopeptide catalyst which can precisely fold into the three-dimensional conformation appropriate for a specific asymmetric transformation based on the knowledge we obtained from enzyme catalysis. The combinatorial screening technique is still the prominent method in the discovery of new oligopeptide catalysts. Nevertheless, conformational engineering of a known oligopeptide catalyst provides powerful tools in generating more effective catalysts. We found that tetrapeptide **14** generated by thioamide and sulfonamide replacement of tetrapeptide **4** adopted a more constrained β-hairpin conformation and thereby afforded much higher stereoselectivity in asymmetric acyl-transfer reactions. We believe the approaches we showed here, the backbone modification using amide isosteres, can be extended to other types of oligopeptide catalysts. Moreover, the conformational change of thioxo tetrapeptide **8** upon the protonation of its N^{π}-methylhistidine was examined. The distorted β-hairpin conformation with altered intramolecular hydrogen bond pattern caused the observed decreased activity and enantioselectivity in the acyl-transfer reaction. These studies provided useful information to understand the special characteristics of oligopeptide catalyst which resemble some features of enzymes, the changeable and regulable conformation of the catalyst.

EXPERIMENTAL SECTION

General Procedure for Peptide Coupling. Boc-L-(π-Me)-His-D-Pro-OMe (7a). To a solution of Boc-(π-Me)-L-His-OH (135 mg, 0.5 mmol) in DMF (10 mL) were added HOBt (88 mg, 0.65 mmol) and HATU (247 mg, 0.65 mmol). The mixture was stirred at 0 °C for 10 min, and then H_2N-D-Pro-OMe·HCl (108 mg, 0.65 mmol) and DIEA (165 μL, 1 mmol) were added. The solution was stirred at 0 °C for 1 h and overnight at room temperature. After removal of DMF under reduced pressure, the residue was diluted with CH_2Cl_2 and washed with 5% $NaHCO_3$, water, and brine, respectively. Dried over Na_2SO_4 and concentrated, the crude product was purified by chromatography on silica gel (eluent: 0−5% MeOH/CH_2Cl_2) to give **7a** in 65% yield: colorless oil; TLC R_f = 0.55 (8% MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ +35.7 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3427, 1746, 1710, 1650, 1422 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) (*trans*/*cis* = 0.8:0.2) δ 7.85 (s, 0.2H), 7.77 (s, 0.8H), 6.95 (s, 0.2H), 6.93 (s, 0.8H), 5.48 (d, *J* = 8.3 Hz, 0.8H), 5.35 (d, *J* = 9.2 Hz, 0.2H), 4.87 (t, *J* = 5.3 Hz, 0.2H), 4.63 (m, 0.8H), 4.47 (m, 0.2H), 4.41 (dd, *J* = 3.8, 8.4 Hz, 0.8H), 3.75−3.65 (overlapping s and m, 7H), 3.20−3.05 (m, 2H), 3.00−2.89 (m, 1H), 2.30−2.13 (m, 1H), 2.09−1.82 (m, 3H), 1.42 (s, 7.4H), 1.38 (s, 1.6H); ^{13}C NMR (100 MHz $CDCl_3$) δ 172.3, 169.0, 155.0, 137.1, 128.1, 124.6, 80.1, 59.1, 52.2, 51.5, 46.9, 32.0, 28.9, 28.2, 27.1, 24.5; HRMS (ESI) for $C_{18}H_{28}N_4O_5$ calcd for $[M + H]^+$ *m*/*z* 381.2132, found 381.2135.

Boc-Aib-CSNH-L-Phe-OMe (7d). To a solution of Boc-Aib-L-Phe-OMe (200 mg, 0.55 mmol) in toluene (10 mL) was added Lawesson's reagent (133 mg, 0.33 mmol). The mixture was stirred at 120 °C for 5 h. Then the reaction mixture was concentrated in vacuo and directly purified by chromatography on silica gel (eluent: 15% EtOAc/petroleum ether) to give the product as a yellow oil (125 mg, 60%): TLC R_f = 0.4 (20% EtOAc/petroleum ether); $[\alpha]^{20}_D$ +80.7 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3428, 3346, 1731, 1505, 808 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.73 (s, 1H), 7.31−7.21 (m, 3H), 7.16−7.06 (m, 2H), 5.34 (m, 1H), 5.06 (s, 1H), 3.72 (s, 3H), 3.44−3.34 (m, 1H), 3.28−3.18 (m, 1H), 1.64 (s, 3H), 1.57 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 207.3, 171.2, 154.3, 135.6, 129.2, 128.5, 127.1, 80.4, 62.0, 58.7, 52.3, 36.1, 28.8, 28.2; HRMS (ESI) for $C_{19}H_{28}N_2O_4S$ calcd for $[M + Na]^+$ *m*/*z* 403.1662, found 403.1655.

Boc-(π-Me)-L-His-D-Pro-Aib-CSNH-L-Phe-OMe (7). Compound **7** was synthesized by general peptide coupling between Boc-(π-Me)-L-His-D-Pro-OH (deprotection of **7a** with LiOH) and H_2N-Aib-CSNH-L-Phe-OMe·TFA (deprotection of **7d** with TFA): colorless oil, yield 72%; TLC R_f = 0.5 (8% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ +24.5 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3356, 1742, 1703, 1638, 1502 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.74 (d, *J* = 7.1 Hz, 1H), 7.42 (s, 1H), 7.30−7.18 (m, 5H), 6.83 (s, 1H), 6.77 (s, 1H), 5.83 (d, *J* = 7.1 Hz, 1H), 5.49 (dd, *J* = 7.6, 14.4 Hz, 1H), 4.55 (dd, *J* = 8.9, 14.7 Hz, 1H), 4.22 (dd, *J* = 3.5, 7.3 Hz, 1H), 3.73 (s, 1H), 3.66 (overlapping m and s, 4H), 3.41−3.23 (m, 2H), 3.16−3.02 (m, 2H), 2.95−2.85 (m, 1H), 2.16−1.77 (m, 4H), 1.70 (s, 3H), 1.42 (overlapping s and s, 12H); ^{13}C NMR (100 MHz $CDCl_3$) δ 207.4, 171.8, 170.5, 169.6, 155.4, 137.1, 136.0, 129.2, 128.4, 128.1, 126.9, 125.7, 80.1, 62.9, 61.1, 58.9, 52.4, 52.0, 47.4, 36.6, 31.9, 29.7, 28.4, 28.2, 27.5, 26.6, 24.9; HRMS (ESI) for $C_{31}H_{44}N_6O_6S$ calcd for $[M + H]^+$ *m*/*z* 629.3116, found 629.3115.

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Fmoc-D-Pro-1,3-thiazol-5(4*H*)-one (8d). Compound **8d** was synthesized according to the previous literature[24g] from D-Pro-OH: yellow oil; TLC R_f = 0.6 (50% EtOAc/petroleum ether); $[\alpha]^{20}_D$ +72.5 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz $CDCl_3$, two isomers) δ 7.82−7.70 (m, 2H), 7.68−7.51 (m, 2H), 7.45−7.26 (m, 4H), 4.75 (m, 1H), 4.59−4.44 (m, 1H), 4.42−4.31 (m, 1H), 4.30−4.23 (m, 0.5H), 4.19−4.11 (m, 0.5H), 3.55 (m, 2H), 2.41−2.11 (m, 2H), 2.09−1.90 (m, 2H), 1.43 (s, 1.5H), 1.39 (s, 1.5H), 1.33 (s, 1.5H), 1.32 (s, 1.5H); ^{13}C NMR (100 MHz $CDCl_3$, two isomers) δ 211.1, 210.8, 168.1, 167.8, 154.9, 154.7, 143.9, 143.67, 143.4, 141.3, 141.2, 127.7, 127.0, 125.2, 125.1, 124.9, 124.8, 119.9, 83.7, 67.6, 67.4, 61.2, 60.8, 47.4, 47.2, 46.8, 32.3, 31.0, 29.6, 24.5, 24.3, 23.3; HRMS (ESI) for $C_{24}H_{24}N_2O_3S$ calcd for $[M + H]^+$ *m*/*z* 421.1580, found 421.1572.

Fmoc-D-Pro-CSNH-Aib-L-Phe-OMe (8e). To a solution of **8d** (421 mg, 1 mmol) in CH_3CN (10 mL) were added DIEA (330 μL, 2 mmol), HOBt (276 mg, 2 mmol), and H_2N-L-Phe-OMe·HCl (238 mg, 1.1 mmol). The solution was stirred for 5 days at rt, diluted with CH_2Cl_2, and washed with 5% $NaHCO_3$, 5% $KHSO_4$, and brine, respectively. Dried over Na_2SO_4 and concentrated, the crude product was purified by chromatography on silica gel (eluent: 35% EtOAc/petroleum ether) to give pure product as a white solid (234 mg, 40%): mp 149−151 °C (from EtOAc−petroleum ether); TLC R_f = 0.4 (50% EtOAc/petroleum ether); IR (CH_2Cl_2) ν_{max} 3428, 3350, 3263, 1743, 1678, 1509, 1413 cm^{-1}; $[\alpha]^{15}_D$ +49.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz $CDCl_3$) (trans/cis =0.8:0.2) δ 8.48 (broad s, 1H), 7.76 (d, *J* = 7.1 Hz, 1H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.44−7.26 (m, 4H), 7.23−7.04 (m, 5H), 6.90 (s, 0.8H), 6.25 (s, 0.2H), 4.79 (m, 1H), 4.58−4.29 (m, 3H), 4.23 (broad s, 1H), 3.76−3.44 (m, 5H), 3.22−3.00 (m, 2H), 2.43−2.05 (m, 3H), 1.93−1.81 (m, 1H), 1.67 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 202.3, 172.3, 171.6, 156.2, 143.6, 141.1, 136.2, 129.2, 128.2, 127.7, 127.0, 126.7, 125.0, 119.9, 68.4, 67.8, 60.3, 53.4, 51.9, 47.0, 37.5, 32.2, 25.4, 24.3, 23.5; HRMS (ESI) for $C_{34}H_{37}N_3O_5S$ calcd for $[M + Na]^+$ *m*/*z* 622.2346, found 622.2346.

Boc-(π-Me)-L-His-D-Pro-CSNH-Aib-L-Phe-OMe (8). Compound **8** was synthesized by general peptide coupling between Boc-(π-Me)-L-His-OH and H_2N-D-Pro-CSNH-Aib-L-Phe-OMe (deprotection of **8e** with excess Et_2NH): yield 68%; white foam; TLC R_f = 0.5 (8% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ −55.9 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3367, 1636, 1508, 1099 cm^{-1}; ^{1}H NMR (600 MHz $CDCl_3$) δ 8.03 (s, 1H), 7.38 (s, 1H), 7.26−7.17 (m, 5H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.84 (s, 1H), 6.67 (d, *J* = 7.0 Hz, 1H), 4.89 (dd, *J* = 8.1, 14.9 Hz, 1H), 4.60 (dd, *J* = 7.7, 13.9 Hz, 1H), 4.48 (dd, *J* = 5.9, 7.9 Hz, 1H), 3.74−3.67 (overlapping m and s, 4H), 3.65 (s, 3H), 3.38−3.31 (m, 1H), 3.19−3.05 (m, 3H), 2.95−2.89 (m, 1H), 2.32−2.23 (m, 1H), 2.22−2.07 (m, 2H), 1.84−1.75 (m, 1H), 1.68 (s, 3H), 1.42 (overlapping s and s, 12H); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.9, 172.9, 172.4, 168.7, 155.5, 136.3, 135.0, 131.1, 129.2, 128.4, 126.8, 119.0, 80.2, 68.8, 60.7, 53.1, 52.2, 51.4, 48.2, 37.5, 33.3, 32.1, 28.1, 26.8, 25.6, 24.8, 22.5; HRMS (ESI) for $C_{31}H_{44}N_6O_6S$ calcd for $[M + H]^+$ *m*/*z* 629.3116, found 629.3115.

General Procedure for the Synthesis of N^{α}-Sulfonyl-(π-Me)-L-His-OMe. Mesyl-(π-Me)-L-His-OMe (9a). To a suspension of H_2N-(π-Me)-L-His-OMe (183 mg, 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added TEA (576 μL, 4 mmol) and the corresponding sulfonyl chloride (1.1 mmol in 5 mL of CH_2Cl_2) dropwisely. The solution was stirred at 0 °C for 30 min and at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2, washed by 5% $NaHCO_3$, water, and brine, respectively, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (eluent: 0−5% MeOH/CH_2Cl_2) to give the pure product: yield 61%; white solid; mp 136−137 °C (from CH_2Cl_2); TLC R_f = 0.5 (8% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ +3.5 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3340, 2962, 1745 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.34 (s, 1H), 6.67 (s, 1H), 4.43 (t, *J* = 5.5 Hz, 1H), 3.83 (s, 3H), 3.61 (s, 3H), 3.26−3.04 (m, 2H), 2.90 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 171.3, 137.9, 127.3, 126.4, 55.8, 52.8, 41.3, 31.7, 27.6; HRMS (ESI) for $C_9H_{15}N_3O_4S$ calcd for $[M + H]^+$ *m*/*z* 262.0856, found 262.0863.

Nosyl-(π-Me)-L-His-OMe (10a): yield 77%; light yellow solid; mp 100−102 °C (from CH_2Cl_2); TLC R_f = 0.55 (8% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ +3.2 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3332, 3054, 1748 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.27 (d, *J* = 8.7 Hz, 2H), 8.04 (d, *J* = 8.7 Hz, 2H), 7.29 (s, 1H), 6.46 (s, 1H), 4.37 (t, *J* = 4.8 Hz, 1H), 3.64 (s, 3H), 3.58 (s, 3H), 3.30−3.03 (m, 2H); ^{13}C NMR (100 MHz $CDCl_3$) δ 170.2, 149.5, 146.8, 137.4, 128.0, 127.2, 126.1, 123.8, 55.81, 52.1, 31.7, 27.5; HRMS (ESI) for $C_{14}H_{16}N_4O_6S$ calcd for $[M + H]^+$ *m*/*z* 369.0863, found 369.0858.

Tosyl-(π-Me)-L-His-OMe (11a): yield 80%; white solid; mp 176−178 °C (from CH_2Cl_2); TLC R_f = 0.55 (8% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ +11.7 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3326, 2963, 1745 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 2H), 7.32 (s, 1H), 7.27 (d, *J* = 7.7 Hz, 2H), 6.83 (broad s 1H), 6.65 (s, 1H), 4.16 (t, *J* = 5.0 Hz, 1H), 3.60 (s, 3H), 3.55 (s, 3H), 3.17−3.07 (m, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 170.6, 143.5, 138.3, 136.7, 129.6, 128.1, 127.0, 125.9, 55.6, 52.6, 31.7, 27.7, 21.5; HRMS (ESI) for $C_{15}H_{19}N_3O_4S$: Calcd for $[M + H]^+$ *m*/*z* 338.1169, found 338.1164.

Synthesis of Catalysts 9−11. Compounds **9**−**11** were synthesized by general peptide coupling between the corresponding N^{α}-sulfonyl-(π-Me)-L-His-OH (deprotection of **9a**−**11a** with LiOH) and H_2N-D-Pro-Aib-L-Phe-OMe.

Mesyl-(π-Me)-L-His-D-Pro-Aib-L-Phe-OMe (9): yield 70%; white foam; TLC R_f = 0.4 (8% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ + 47.0 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3339, 1738, 1678, 1641, 1504 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.42 (overlapping s and s, 2H), 7.30−7.17 (m, 5H), 6.87 (s, 1H), 6.56 (s, 1H), 6.27 (d, *J* = 5.1 Hz, 1H), 4.88 (dd, *J* = 7.9, 14.5 Hz, 1H), 4.40 (broad s, 1H), 4.17 (t, *J* = 5.6 Hz, 1H), 3.78−3.72 (m, 1H), 3.71 (s, 3H), 3.64 (s, 3H), 3.22−3.01 (m, 5H), 2.98 (s, 3H), 2.10−1.98 (m, 3H), 1.84−1.72 (m, 1H), 1.47 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 174.0, 173.3, 170.6, 170.0, 138.1, 136.4, 129.2, 128.3, 127.5, 126.7, 126.6, 61.3, 57.4, 54.0, 53.3, 52.3, 47.5, 41.1, 38.1, 31.6, 28.8, 27.9, 26.5, 24.9, 24.4; HRMS (ESI) for $C_{27}H_{38}N_6O_7S$: Calcd for $[M + H]^+$ *m*/*z* 591.2596, found 591.2588.

Nosyl-(π-Me)-L-His-D-Pro-Aib-L-Phe-OMe (10): yield 87%; white foam; TLC R_f = 0.5 (10% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ + 13.7 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3350, 1733, 1641, 1533 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 8.36 (d, *J* = 8.7 Hz, 2H), 8.10 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.45 (s, 1H), 7.26−7.13 (m, 5H), 6.90 (s, 1H), 6.79 (s, 1H), 4.94−4.84 (m, 1H), 4.21−4.09 (overlapping m, 2H), 3.68 (s, 3H), 3.63 (s, 3H), 3.30−3.15 (m, 2H), 3.13−2.94 (m, 3H), 2.88−2.78 (m, 1H), 2.03−1.76 (m, 3H), 1.68−1.57 (m, 1H), 1.53 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 174.0, 173.8, 170.3, 168.6, 149.9, 146.1, 137.9, 136.4, 129.2, 128.3, 128.2, 127.2, 126.8, 126.6, 124.6, 61.2, 57.3, 54.2, 53.2, 52.6, 47.4, 38.2, 31.6, 28.6, 28.3, 27.2, 24.8, 23.8; HRMS (ESI) for $C_{32}H_{39}N_7O_9S$ calcd for $[M + H]^+$ *m*/*z* 698.2603, found 698.2612.

Tosyl-(π-Me)-L-His-D-Pro-Aib-L-Phe-OMe (11): yield 77%; white foam; TLC R_f = 0.5 (8% MeOH/CH_2Cl_2); $[\alpha]^{25}_D$ +9.3 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3339, 1734, 1674, 1637, 1506 cm^{-1}; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.33−7.15 (m, 8H), 6.78−6.62 (overlapping s, s, d, 3H), 4.91 (dd, *J* = 7.9, 14.7 Hz, 1H), 4.20−4.15 (m, 1H), 4.06 (broad s, 1H), 3.67 (s, 3H), 3.51 (s, 1H), 3.40−3.32 (m, 1H), 3.23−3.03 (m, 3H), 2.94−2.85 (m, 2H), 2.43 (s, 3H), 2.15−1.86 (m, 3H), 1.78−1.65 (m, 1H), 1.49 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 173.9, 173.4, 170.2(2 Cs), 144.0, 138.1, 136.6, 136.5, 129.8, 129.3, 128.3, 127.9, 127.2, 126.7, 126.5, 61.5, 57.4, 54.0, 53.3, 52.3, 47.2, 31.3, 28.5, 27.3, 26.2, 24.9, 24.7, 21.5; HRMS (ESI) for $C_{33}H_{42}N_6O_7S$ calcd for $[M + H]^+$ *m*/*z* 667.2908, found 667.2914.

Synthesis of Tetrapeptides 12−14. Compound **12**−**14** was synthesized by general peptide coupling between corresponding N^{α}-sulfonyl-(π-Me)-L-His-OH and H_2N-D-Pro-CSNH-Aib-L-Phe- OMe.

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Mesyl-(π-Me)-L-His-D-Pro-CSNH-Aib-L-Phe-OMe (12): yield 57%; white foam; TLC R_f = 0.4 (8% MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ +19.3 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3327, 1738, 1678, 1641 1503 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 8.35 (s, 1H), 7.52 (s, 1H), 7.27−7.17 (m, 6H), 6.91 (s, 1H), 6.32 (broad s, 1H), 4.86 (m, 1H), 4.59 (t, *J* = 6.3 Hz, 1H), 4.40 (dd, *J* = 5.0, 9.2 Hz, 1H), 3.79−3.72 (m, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.25−3.11 (m, 3H), 3.10−3.03 (m, 2H), 3.02 (s, 3H), 2.23−2.08 (m, 3H), 1.80−1.71 (m, 1H), 1.68 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.6, 173.2, 172.3, 169.4, 137.7, 136.5, 129.3, 128.4, 127.2, 126.8, 126.5, 68.5, 61.0, 54.2, 53.2, 52.4, 48.2, 41.4, 38.1, 32.0, 28.5, 27.4, 24.8, 22.6; HRMS (ESI) for $C_{27}H_{38}N_6O_6S_2$ calcd for $[M + Na]^+$ *m*/*z* 629.2187, found 629.2180.

Nosyl-(π-Me)-L-His-D-Pro-CSNH-Aib-L-Phe-OMe (13): yield 75%; white foam; TLC R_f = 0.5 (8% MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ −5.5 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3331, 1736, 1676, 1639, 1533 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 8.72 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 8.8 Hz, 2H), 7.41 (s, 1H), 7.39 (s, 1H), 7.25−7.16 (m, 5H), 6.74 (s, 1H), 4.91 (td, *J* = 5.9, 9.2 Hz, 1H), 4.50 (t, *J* = 6.9 Hz, 1H), 4.10 (dd, *J* = 4.1, 10.6 Hz, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.38−3.28 (m, 1H), 3.23−2.95 (m, 4H), 2.84−2.76 (m, 1H), 2.08−1.93 (m, 3H), 1.72 (s, 3H), 1.59−1.49 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 204.2, 173.8, 172.5, 167.8, 149.9, 146.3, 138.1, 136.5, 129.2, 128.32, 128.26, 127.0, 126.9, 126.7, 124.4, 67.2, 61.0, 54.3, 53.0, 52.6, 48.0, 38.1, 31.7, 29.6, 29.1, 28.5, 24.8, 21.7; HRMS (ESI) for $C_{32}H_{39}N_7O_8S_2$ calcd for $[M + Na]^+$ *m*/*z* 736.2194, found 736.2198.

Tosyl-(π-Me)-L-His-D-Pro-CSNH-Aib-L-Phe-OMe (14): yield 79%; white foam; TLC R_f = 0.5 (8% MeOH/CH_2Cl_2); $[\alpha]^{20}_D$ −9.6 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) ν_{max} 3325, 1737, 1639, 1502 cm^{-1}; ^1H NMR (400 MHz $CDCl_3$) δ 9.14 (s, 1H), 7.83 (d, *J* = 7.9 Hz, 2H), 7.44 (s, 1H), 7.34−7.12 (m, 8H), 6.73 (s, 1H), 4.87 (dd, *J* = 8.2, 15.1 Hz, 1H), 4.64 (t, *J* = 5.8 Hz, 1H), 4.06 (dd, *J* = 4.0, 9.8 Hz, 1H), 3.66 (s, 3H), 3.60 (s, 3H), 3.27−3.00 (m, 5H), 2.90−2.81 (m, 1H), 2.42 (s, 3H), 2.10−1.94 (m, 3H), 1.70 (s, 3H), 1.63−1.52 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 203.6, 173.2, 172.4, 168.9, 143.6, 137. 8, 137.1, 136.6, 129.8, 129.3, 128.2, 127.14, 127.1, 126.8, 126.6, 67.8, 60.9, 54.0, 53.1, 52.4, 47.7, 38.0, 31.7, 31.6, 27.9, 27.4, 24. 6, 22.7, 21.5; HRMS (ESI) for $C_{33}H_{42}N_6O_6S_2$ calcd for $[M + Na]^+$ *m*/*z* 705.2499, found 705.2497.

Boc-(π-Me)-L-His-D-Pro-Aib-L-Phe-OMe (4). Compound **4** was synthesized according to the previous literature:[5d,18b] white foam; R_f = 0.4 (5% MeOH/CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.31−7.17 (m, 6H), 6.82 (s, 1H), 6.44 (s, 1H), 6.00 (d, *J* = 6.7 Hz, 1H), 4.88 (m, 1H), 4.56 (m, 1H), 4.16 (m, 1H), 3.70 (s, 3H), 3.65 (overlapping m and s, 4H), 3.21−3.06 (m, 4H), 2.94−2.87 (m, 1H), 2.15−2.03 (m, 2H), 2.00−1.91 (m, 1H), 1.84−1.76 (m, 1H), 1.50 (s, 3H), 1.41 (s, 9H), 1.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.0, 172.3, 170.7, 170.4, 155.2, 138.0, 136.5, 129.3, 128.2, 127.9, 126.9, 126.7, 80.1, 61.0, 57.3, 54.0, 52.1, 52.0, 47.2, 38.0, 31.4, 28.2, 28.1, 27.0, 26.1, 24.8, 24.7; $[\alpha]^{25}_D$ −27.6 (*c* 1.0, MeOH); IR (CH_2Cl_2) ν_{max} 3426, 3355, 1699, 1636, 1506, 1449 cm^{-1}.

General Procedure for the Kinetic Resolution of Racemic Alcohols. A stock solution of substrate was prepared by dissolving alcohols (0.16 mmol) in 16 mL of toluene (freshly distilled from Na). To an oven-dried reaction vessel was added 50 μL of catalyst solution (0.08 mmol catalyst in 5 mL of CH_2Cl_2, 0.0008 mmol) followed removal of CH_2Cl_2 by reduced pressure, and then 3.2 mL of the substrate solution was added. The mixture was stirred at 25 °C in a thermostatic bath for 25 min, then the base (0.0064 mmol) and 25 μL of acetic anhydride was introduced. During the reaction. Aliquots of 50 μL were removed per 5 min, quenched with 50 μL of methanol, and directly tested by chiral GC analysis. For substrate **18** and **20**, the reaction was conducted at 4 times scales, and quenched with 10 mL of methanol at the half conversion time. Then the solution was concentrated in vacuo, and purified by chromatography on silica gel to give products and recovered starting material for chiral GC or HPLC analysis. The k_{rel} value and conversion were calculated by the method of Kagan.[29]

Characterization of the Acylation Products. *trans-2-Acetamidocyclohexyl acetate (**3-Ac**):*[18a] TLC R_f = 0.5 (80% EtOAc/petroleum ether); ^1H NMR (400 MHz $CDCl_3$) δ 5.74 (d, *J* = 6.8 Hz, 1H), 4.65 (dt, *J* = 4.5, 10.6 Hz, 1H), 3.87 (m, 1H), 2.05 (overlapping m and s, 4H), 1.93 (overlapping m and s, 4H), 1.83−1.64 (m, 2H), 1.55−1.11 (m, 2H); ^{13}C NMR (100 MHz $CDCl_3$) δ 171.9, 169.6, 74.6, 52.8, 32.0, 31.0, 24.1, 24.0, 23.4, 21.1; GC analysis: Beta DEX 120 column (30 m × 0.25 mm × 0.25 μm film thickness), flow rate 20 cm/s, temperature 155 °C, t_R = 35.4 min (1*S*, 2*S*, minor), 36.3 min (1*R*, 2*R*, major). The absolute configuration of **3-Ac** was determined by the same GC stereoselective results compared with those of Miller's catalyst. GC analysis for starting material: Gamma DEX 225 column (30 m × 0.25 mm ×0.25 μm film thickness), flow rate 20 cm/s, temperature 180 °C, t_R = 17.4 min (1*R*, 2*R*, minor), 17.7 min (1*S*, 2*S*, major).

*trans-2-Acetamidocycloheptyl acetate (**15-Ac**):*[18a] TLC R_f = 0.45 (80% EtOAc/petroleum ether); ^1H NMR (400 MHz $CDCl_3$) δ 5.78 (d, *J* = 6.1 Hz, 1H), 4.81 (m, 1H), 4.02 (dq, *J* = 3.5, 8.8 Hz, 1H), 2.04 (s, 3H), 1.92 (s, 3H), 1.90−1.45 (m, 10H); ^{13}C NMR (100 MHz $CDCl_3$) δ 171.5, 169.3, 77.4, 55.1, 31.4, 31.3, 27.6, 24.0, 23.4, 22.5, 21.2; GC analysis: β DEX 120 column, flow rate 20 cm/s, temperature 135 °C for 80 min, 1 deg/min to 150 °C, keep 30 min, 2 deg/min to 220 °C, keep 10 min, t_R = 122.2 min (1*S*, 2*S*, minor), 124.1 min (1*R*, 2*R*, major). The absolute configuration of **15-Ac** was determined by the same GC stereoselective results compared with those of Miller's catalyst. GC analysis for starting material: Gamma DEX 225 column, flow rate 20 cm/s, temperature 180 °C, t_R = 24.5 min (1*R*, 2*R*, minor), 25.2 min (1*S*, 2*S*, major).

*trans-6-Acetamidocyclohex-3-enyl acetate (**16-Ac**):*[18a] TLC R_f = 0.45 (80% EtOAc/petroleum ether); ^1H NMR (400 MHz $CDCl_3$) δ 5.77 (d, *J* = 6.7 Hz, 1H), 5.60 (m, 2H), 4.98 (dd, *J* = 9.1, 15.1 Hz, 1H), 4.22 (m, 1H), 2.65−2.24 (m, 3H), 2.07 (s, 3H), 1.95 (overlapping m and s, 4H); ^{13}C NMR (100 MHz $CDCl_3$) δ 171.8, 169.8, 124.6, 123.9, 70.8, 48.7, 31.5, 30.5, 23.4, 21.1; GC analysis: γ DEX 225 column, flow rate 20 cm/s, temperature 160 °C, t_R = 28.6 min (1*S*, 2*S*, minor), 29.5 min (1*R*, 2*R*, major). The absolute configuration of **16-Ac** was determined by the same GC stereoselective results compared with those of Miller's catalyst. GC analysis for conversion: Rtx-5 column (30 m × 0.25 mm ×0.25 μm film thickness), flow rate 30 cm/s, temperature 220 °C, t_R = 3.2 min (starting material), 3.5 min (product), response factor = (mol starting material)(area product)/(mol product)(area starting material) = 1.296.

*trans-2-Acetamidocyclopentyl acetate (**17-Ac**):*[18d] TLC R_f = 0.45 (80% EtOAc/petroleum ether); ^1H NMR (400 MHz $CDCl_3$) δ 6.00 (s, 1H), 4.97 (q, *J* = 6.3 Hz, 1H), 4.14 (quintet, *J* = 7.4 Hz, 1H), 2.30−2.18 (m, 1H), 2.05 (overlapping m and s, 4H), 1.96 (s, 3H), 1.83−1.62 (m, 3H), 1.48−1.35 (m, 1H); ^{13}C NMR (100 MHz $CDCl_3$) δ 170.8, 170.1, 79.1, 55.5, 30.0, 29.7, 22.7, 20.8, 20.7; GC analysis: γ DEX 225 column, flow rate 25 cm/s, temperature 140 °C for 40 min, 1 deg/min to 220 °C, t_R = 45.5 min (1*R*, 2*R*, major), 49.3 min (1*S*, 2*S*, minor). The absolute configuration of **17-Ac** was determined by the same GC stereoselective results compared with those of Miller's catalyst. GC analysis for starting material: γ DEX 225 column, flow rate 25 cm/s, temperature 160 °C, t_R = 28.6 min (1*S*, 2*S*, major), 29.7 min (1*R*, 2*R*, minor).

*trans-2-Acetamidocyclooctyl acetate (**18-Ac**):* TLC R_f = 0.5 (80% EtOAc/petroleum ether); $[\alpha]^{20}_D$ +4.2 (*c* 1.0, EtOH) for 88.6% ee; ^1H NMR (400 MHz $CDCl_3$) δ 5.72 (d, *J* = 4.8 Hz, 1H), 4.90−4.99 (m, 1H), 4.44−4.11 (m, 1H), 2.04 (s, 1H), 1.92 (s, 1H), 1.88−1.40 (m, 12H); ^{13}C NMR (100 MHz $CDCl_3$) δ 171.8, 169.4, 76.2, 53.1, 30.6, 29.5, 25.7, 25.6, 24.8, 24.1, 23.4, 21.3; HRMS (ESI) for $C_{12}H_{21}NO_3$ calcd for $[M + Na]^+$ *m*/*z* 250.1414, found 250.1412. HPLC analysis: Chiralcel AD-H column, hexane/2-propanol = 90:10, flow rate 0.6 mL/min 210 nm, t_R = 9.2 min (1*R*, 2*R*, major), 11.1 min (1*S*, 2*S*, minor). The absolute configuration was determinded by comparing optical rotation value with reported 2-amino-cyclooctanol after removal of the acyl protection group, $[\alpha]^{20}_D$ −13.2

(*c* 1.0, EtOH) (lit.[36] $[\alpha]_D$ +19 (*c* 0.765, EtOH) for (1*S*, 2*S*) configuration) HPLC analysis for starting material: Chiralcel AD-H column, hexane/2-propanol = 90:10, flow rate 0.6 mL/min 210 nm, t_R = 10.7 min (1*R*, 2*R*, minor), 13.4 min (1*S*, 2*S*, major).

*trans-(Z)-8-Acetamidocyclooct-4-enyl acetate (**19-Ac**):* TLC R_f = 0.45 (80% EtOAc/petroleum ether); ^{1}H NMR (400 MHz $CDCl_3$) δ 5.86−5.59 (m, 3H), 4.84 (dt, *J* = 2.9, 8.4 Hz, 1H), 4.34−4.19 (m, 1H), 2.49−2.30 (m, 2H), 2.28−2.15 (m, 2H), 2.05 (s, 3H), 1.99−1.82 (overlapping m and s, 6H), 1.74−1.62 (m, 1H); ^{13}C NMR (100 MHz $CDCl_3$) δ 171.5, 169.0, 129.5, 128.8, 75.1, 51.1, 31.5, 31.1, 23.3, 23.0, 22.7, 21.0; HRMS (ESI) for $C_{12}H_{19}NO_3$ calcd for $[M + Na]^+$ *m*/*z* 248.1257, found 248.1260. GC analysis: γ DEX 225 column, flow rate 22 cm/s, temperature 170 °C for 40 min, 1 deg/min to 200 °C, keep 20 min. t_R = 38.5 min (1*S*, 2*S*, minor), 39.5 min (1*R*, 2*R*, major). The absolute configuration was determined by compared the stereoselective results with **18-Ac** after hydrogenation. GC analysis for starting material: β DEX 120 column, flow rate 20 cm/s, temperature 100 °C for 30 min, 1 deg/min to 120 °C, keep 40 min, t_R = 75.6 min (1*R*, 2*R*, minor), 76.4 min (1*S*, 2*S*, major).

*threo-2-Acetamido-1,2-diphenylethyl acetate (**20-Ac**):*[37] TLC R_f = 0.6 (80% EtOAc/petroleum ether); $[\alpha]^{20}_D$ −7.2 (*c* 1.0, EtOH) for 25.3% ee; ^{1}H NMR (400 MHz $CDCl_3$) δ 7.24−7.09 (m, 10H), 6.37 (d, *J* = 8.9 Hz, 1H), 6.07 (d, *J* = 7.4 Hz, 1H), 5.43 (dd, *J* = 7.4, 8.9 Hz, 1H), 2.09 (s, 3H), 1.96(s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 170.6, 169.3, 138.3, 136.8, 128.4, 128.3, 128.2, 127.7, 127.2, 127.0, 77.5, 57.7, 23.2, 21.0; HPLC analysis: Chiralcel AD-H column, hexane/2-propanol = 85:15, flow rate 0.6 mL/min 220 nm, t_R = 13.5 min (major), 18.0 min (minor). HPLC analysis for starting material: Chiralcel AD-H column, hexane/2-propanol = 85:15, flow rate 0.6 mL/min 220 nm, t_R = 23.1 min (minor), 26.5 min (major). The absolute configuration was not determined.

*2-Acetamido-1-phenylethyl acetate (**21-Ac**):*[38] TLC R_f = 0.45 (80% EtOAc/petroleum ether); ^{1}H NMR (400 MHz $CDCl_3$) δ 7.45−7.30 (m, 5H), 5.84 (dd, *J* = 4.3, 8.2 Hz, 1H), 5.79 (broad s, 1H), 3.73−3.53 (m, 2H), 2.11 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 170.4, 170.1, 137.6, 128.6, 128.4, 126.4, 74.5, 44.4, 23.2, 21.1; GC analysis: γ DEX 225 column, flow rate 20 cm/s, temperature 180 °C for 40 min, 1 deg/min to 220 °C, t_R = 34.6 min (major), 35.7 min (minor). GC analysis for starting material: the same conditions as the product, t_R = 46.1 min (minor), 47.4 min (major). The absolute configuration was not determined.

*1-Phenylethyl acetate (**22-Ac**):*[39] TLC R_f = 0.5 (5% EtOAc/petroleum ether); ^{1}H NMR (400 MHz $CDCl_3$) δ 7.41−7.24 (m, 5H), 5.88 (q, *J* = 6.6 Hz, 1H), 2.05 (s, 3H), 1.52 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 170.2, 141.6, 128.4, 127.8, 126.0, 72.2, 22.1, 21.3.

■ ASSOCIATED CONTENT

Supporting Information. Details of the ^{1}H NMR titration experiment, the ROESY spectra of tetrapeptide **8** in two forms, ^{1}H NMR, ^{13}C NMR, and HRMS spectra of catalysts **7**−**14**, and products in Table 3, HPLC and GC data, X-ray structural analysis data of **8e** (CIF). This material are available free of charge via the Internet at http://pubs.acs.org.

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