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Asymmetric transfer hydrogenation in aqueous media catalyzed by resin-supported peptide having a polyleucine tether

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ABSTRACT

A resin-supported N-terminal prolyl peptide having a β-turn motif and a polyleucine tether has been developed for the organocatalytic asymmetric transfer hydrogenation under aqueous conditions. Polyleucine accelerated the reaction in a highly enantioselective manner by providing a hydrophobic microenvironment around the prolyl residue. The investigation of catalyst structures indicates that the L-form of polyleucine is essential for both reaction efficiency and enantioselectivity.

1. Introduction

Biochemical transformations are catalyzed by enzymes. The structural feature of most enzymes is that they have a hydrophobic cavity which enables a stereoselective reaction with high efficiency under aqueous conditions in living cells. Such an inner hydrophobic pocket is realized by an outer higher-order structure of an appropriately folded peptide chain.

Recently, increasing attention has been paid to the research area of organocatalysts.[1] Small peptides, which can be considered as simplified enzymes, have also been used for organocatalytic reactions. After the proline-catalyzed intermolecular asymmetric aldol reaction was reported by List,[2] both N-terminal prolyl-[3] and N-terminal primary amino[4] peptides have been explored to improve catalytic activity. Most of the reported peptide catalysts have relatively simple structures, typically consisting of a few residues, and there are only a limited number of examples of well-designed peptide catalysts incorporated with a secondary structure such as an α-helix for asymmetric organocatalytic reactions.[5]

On the other hand, organocatalytic reactions in water or aqueous media are of interest because such systems are relevant to enzymatic reactions under physiological conditions. As for the catalysts in aqueous reactions, those having a highly hydrophobic moiety seem promising. They are expected to construct a hydrophobic environment where organic substrates and reagents are concentrated near a catalytically active site in an aqueous environment. So far, surfactant type,[6] dendrimer type,[3h,7] and solid-supported type[3e,8] catalysts have been reported mainly for asymmetric aldol and Michael reactions under aqueous conditions. A peptide can be an attractive candidate for such a class of catalysts provided that a catalytically active site is supported appropriately by a hydrophobic peptide segment.

There are several reports on the organocatalytic asymmetric transfer hydrogenation of α,β-unsaturated aldehydes using NADH-like Hantzsch esters as a reductant.[9] The reaction proceeds through the formation of an iminium ion intermediate between a substrate enal and a secondary amine catalyst followed by hydride transfer from the Hantzsch ester. To date, all the reported reductions of this type have been performed in organic solvents.[9–11] Recently, we have demonstrated the first example of an asymmetric transfer hydrogenation in aqueous media by employing a resin-supported peptide catalyst.[12] The catalyst consists of a terminal five-residue peptide Pro-D-Pro-Aib-Trp-Trp, which is important for high asymmetric induction, and hydrophobic polyleucine chain, which accelerates the reaction by gathering substrates and supports the structure of the terminal sequence. Herein, we report a full account of that work.

2. Results and discussion

The efficiency of the reduction of (*E*)-3-phenylbut-2-enal with Hantzsch ester **1** in THF/H_2O = 2/1 (v/v) was examined using proline-based catalysts (Table 1). Although simple proline salt is reported to moderately promote the reaction in toluene (47% conversion after 5 h),[9c] the salt showed almost no catalytic activity under the present aqueous conditions (entry 1). This indicates that water has an inhibitory effect for the proline-catalyzed reduction. We thought that attaching a hydrophobic moiety to the catalyst would circumvent this problem. Polyethyleneglycol grafted on cross-linked polystyrene (PEG-PS) resin[13] has been claimed to be an effective solid-support for palladium-catalysts that work under aqueous conditions.[14] Therefore, PEG-PS-supported proline salt was tested, however, it did not provide any enhancement for the reaction (entry 2). In order to generate a hydrophobic microenvironment proximate to the prolyl residue, a polyleucine chain was introduced between the proline and the resin. Resin-bound polyleucine can be easily prepared through the ring-opening

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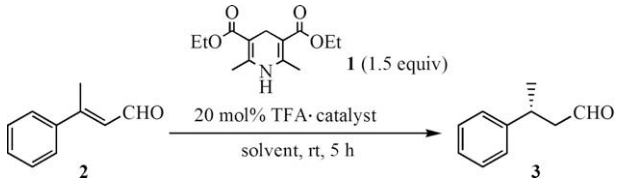
Table 1
Transfer hydrogenation in aqueous media

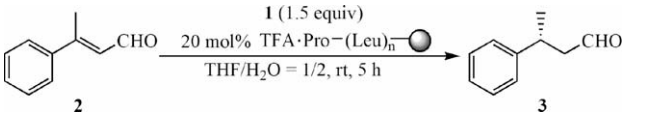


Entry	Catalyst[a]	Solvent	Conversion[b] (%)	ee[c] (%)
1	Proline	THF/H_2O = 2/1	3	n.d.
2	Pro–●	THF/H_2O = 2/1	3	n.d.
3	Pro–$(Leu)_2$–●	THF/H_2O = 2/1	3	n.d.
4	Pro–$(Leu)_{25.4}$–● (**4**)	THF/H_2O = 2/1	21	27
5	Pro–$(Phe)_{10}$–●	THF/H_2O = 2/1	1	n.d.
6	Pro–$(Leu)_{25.4}$–● (**4**)	THF/H_2O = 1/2	63	24
7	Pro-$(Leu)_{28.8}$–NH-*n*-Butyl	THF/H_2O = 1/2	70	21

[a] The symbol ● denotes PEG-PS resin.
[b] Estimated by ^{1}H NMR of the crude mixture.
[c] Determined by chiral HPLC analysis of the corresponding alcohol after $NaBH_4$ reduction in EtOH.

polymerization of leucine-*N*-carboxyanhydride (NCA) initiated by a terminal amino group on PEG-PS resin.[15] The catalyst having 25.4 leucine residues on average successfully promoted the reaction (entry 4), while the catalyst having only two leucine residues did not show any improvement (entry 3). Deca-phenylalanine was also tried as a hydrophobic segment for the prolyl catalyst. In this case, the reaction hardly proceeded in spite of its high hydrophobicity (entry 5). This indicates that the steric hinderance of the deca-phenylalanine moiety severely prevented the reaction and that a hydrophobic part is required so as not to hinder the terminal active site. It is noteworthy that the reaction was considerably accelerated when the ratio of water in the solvent system was increased from THF/H_2O = 2/1 to 1/2 (entry 6), presumably because of an intensified hydrophobic interaction among the aldehyde,

Table 2
Effect of the length of polyleucine chain



Entry	*n*	Conversion[a] (%)	ee[b] (%)
1	7.5	21	7
2	14.8	40	19
3	20.2	46	24
4	25.4	63	24
5	42.2	60	25

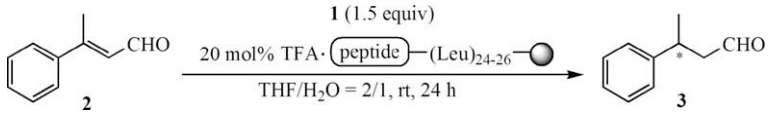
[a] Estimated by ^{1}H NMR of the crude mixture.
[b] Determined by chiral HPLC analysis of the corresponding alcohol after $NaBH_4$ reduction in EtOH.

Hantzsch ester, and the catalyst.[16] The reaction proceeded smoothly even in the absence of the solid support (entry 7). However, in this case, removal of the catalyst from the reaction mixture was laborious because the aggregating nature of the hydrophobic catalyst led to the formation of a gel. This observation demonstrates the superiority of the PEG-PS-immobilized catalyst.[17] Furthermore, there are additional merits for the resin-supported peptide catalyst: (1) a purification process in catalyst preparation can be omitted, (2) a catalyst can be readily removed from a reaction mixture by filtration, and (3) fine-tuning of a peptide catalyst could be accomplished through well-established solid-phase peptide synthesis.[18]

The effect of a polyleucine chain was investigated in relation with the reaction rate (Table 2). The length of the polyleucine tether and the reaction efficiency were positively correlated up to about 25 leucine residues (entries 1–4), but further extension of the chain did not improve the reaction rate any more (entry 5).

Next, terminal peptide sequences were surveyed from the aspect of stereoselectivity (Table 3). Enantioselectivity in this reaction is governed by the geometry of the iminium ion intermediate and by the facial selectivity of the nucleophilic attack by Hantzsch ester **1**. The latter factor should be controlled by the steric constraints of a peptide chain next to the prolyl group. Insertion of an amino acid having a bulky side chain such as Phe, Tyr, or

Table 3
Optimization of terminal peptide sequence



Entry	Peptide	Conversion[a] (%)	ee[b] (%)	Abs. config.[c]
1	Pro-Phe	68	33	*R*
2	Pro-Tyr	22	45	*R*
3	Pro-Trp	53	45	*R*
4	D-Pro-Trp	35	60	*S*
5	Pro-D-Trp	20	47	*R*
6	D-Pro-D-Trp	30	32	*S*
7	Pro-Trp-D-Leu	45	29	*R*
8	D-Pro-Trp-D-Leu	26	41	*S*
9	D-Pro-Trp-Trp	35	29	*S*
10	D-Pro-Trp-D-Trp	19	48	*S*
11	Pro-Pro	21	20	*R*
12	Pro-D-Pro-Trp	34	55	*R*
13	D-Pro-Pro-Trp	36	62	*S*
14	Pro-D-Pro-Aib	4	77	*R*
15	Pro-D-Pro-Aib-Trp	7	87	*R*
16	Pro-D-Pro-Aib-Trp-Trp (**6**)	13	91	*R*
17	Pro-D-Pro-Aib-Trp-Trp-Trp	12	89	*R*

[a] Estimated by ^{1}H NMR of the crude mixture.
[b] Determined by chiral HPLC analysis of the corresponding alcohol after $NaBH_4$ reduction in EtOH.
[c] Absolute configuration of the major product.

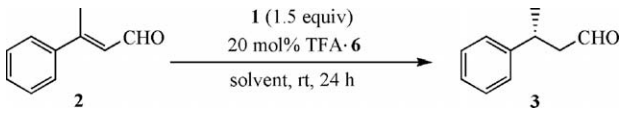
Trp between the proline and the polyleucine tether brought about somewhat enhanced selectivity (entries 1–3). Exchanging L-Pro with D-Pro in Pro-Trp sequence afforded improved enantioselectivity along with the reversal of the absolute configuration of the major product (entry 4). In contrast, the displacement of L-Trp by D-Trp in Pro-Trp sequence did not show a significant improvement (entry 5). Although D-Pro-Trp and Pro-D-Trp are antipodal to each other, the absolute values of ee's in entries 4 and 5 are quite different. Such a difference was also observed between the catalyst having Pro-Trp (entry 3) and D-Pro-D-Trp (entry 6) termini. These results mean that while enantioselectivity depends mainly on the structure of the terminal sequence, the polyleucine moiety participates in the stereochemical course of this catalytic reaction to some extent. To achieve higher enantioselectivity, various combinations of the L/D forms of Pro/Trp/Leu were examined. However, such an approach did not provide a significant enhancement in selectivity (entries 7–13).[19]

Then, D-Pro-Aib (Aib: 2-aminoisobutyric acid), a turn motif, was introduced into the N-terminal of the polyleucine moiety. A peptide including a D-Pro-Aib sequence is known to form a β-turn structure in organic solvents through an intramolecular hydrogen bond.[20] Miller et al. showed that this β-turn motif can be successfully applied to the design of peptide-based asymmetric catalysts working in nonpolar solvents.[21] We anticipated that a D-Pro-Aib sequence combined with hydrophobic polyleucine chain should also provide β-turn structure even in aqueous media. Inserting D-Pro-Aib between the terminal L-prolyl group and polyleucine tether turned out to be quite effective for enhancing the selectivity (entry 14). Furthermore, the incorporation of one or two Trp residue(s) into the peptide at the C-terminal site of Aib afforded even higher enantioselectivity (entries 15 and 16), while the insertion of three tryptophans did not bring about an additional improvement (entry 17).

By using highly enantioselective catalyst **6**, the effect of the content of water in the solvent system was examined (Table 4). By increasing the ratio of water up to THF/H_2O = 1/2, the reaction was accelerated without loss of enantioselectivity (entries 1–3). The reactions in even more water-rich solvents did not give a better result probably because of the limited solubility of Hantzsch ester **1** in water (entries 4 and 5).

Some typical unsaturated aldehydes were examined in this aqueous reaction system (Table 5). Reactions were performed in the presence of 20 mol % of catalyst **6** TFA salt with 1.2 equiv of Hantzsch ester **1** in THF/H_2O = 1/2. Aldehydes **2a**–**e** having aromatic groups of various sizes and electronic natures gave good yields and high levels of enantioselectivity (entries 1, 2, 4–6). Aldehyde **2f** possessing an *ortho* chloro group was hardly converted to **3f** probably because of steric hindrance (entry 7). Aliphatic aldehyde **2g** showed excellent enantioselectivity (entry 8) even though the substrate was used as a mixture of diastereomers (*E*/*Z* = 2/1).[22] Such an enantioconvergence has been also observed by other groups, and the reactions were considered to proceed through *E*/*Z* isomerization of enals prior to the face selective hydrogenation of the *E*-enals.[9b,c] This might be the case for the present result. The reuse of solid-supported catalyst **6** recovered by filtration after the reaction resulted in a somewhat decreased isolated yield, although the enantioselectivity was maintained (entry 3).[23]

Table 4
Effect of the ratio of water

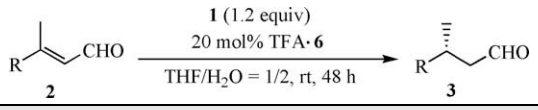


2 3

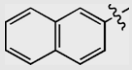
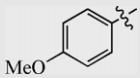
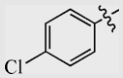
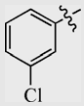
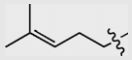
Entry	Solvent	Conversion[a] (%)	ee[b] (%)
1	THF/H_2O = 2/1	13	91
2	THF/H_2O = 1/1	48	91
3	THF/H_2O = 1/2	75[c]	91
4	THF/H_2O = 1/4	74	89
5	H_2O	29	82

[a] Estimated by ^{1}H NMR of the crude mixture.
[b] Determined by chiral HPLC analysis of the corresponding alcohol after $NaBH_4$ reduction in EtOH.
[c] Isolated yield of **3** was 50%.

Table 5
Substrate scope



2 3

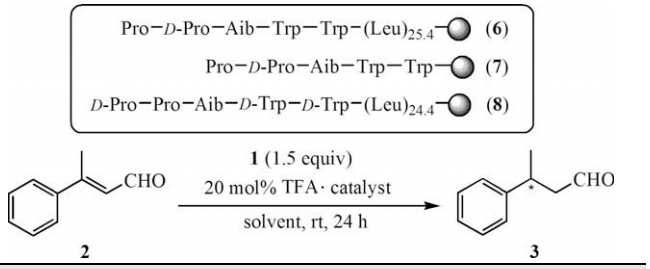
Entry	R		Yield[a] (%)	ee[b] (%)
1	**a**		75	90 (*R*)[c]
2	**b**		71	94
3	**b**	(reuse of catalyst)	65	95
4	**c**		76	95[d]
5	**d**		72	95[e]
6	**e**		69	93[e]
7	**f**		<1	n.d.
8[f]	**g**		53	96[g] (*S*)[e]

[a] Isolated yield.
[b] Unless otherwise noted, determined by chiral HPLC analysis of the corresponding alcohol after $NaBH_4$ reduction.
[c] Absolute configuration of the major product.
[d] Determined by ^{1}H NMR in the presence of Eu(hfc)$_3$ as the chiral shift reagent after $NaBH_4$ reduction.
[e] Determined by ^{1}H NMR after $NaBH_4$ reduction and derivatization of the corresponding alcohol to the Mosher ester with (−)-MTPA–Cl.
[f] *E*/*Z* mixture of **2g** was used as a starting material (*E*/*Z* = 2/1). Reaction time was 10 h.
[g] After $NaBH_4$ reduction, ee of the corresponding alcohol was determined according to the literature.

To clarify the roles of the polyleucine tether in the catalytic process under aqueous conditions, the optimized catalyst **6**, a catalyst without a polyleucine chain **7**, and a catalyst having an antipode peptide at the terminal active site **8** were tested for the reduction in THF and in THF/H_2O = 1/2, respectively (Table 6). Catalyst **6** showed high efficiency and selectivity both in THF and in aqueous media (entries 1 and 4). This indicates that the polyleucine tether works appropriately in aqueous media through providing a hydrophobic environment for the efficient reaction and keeping the stereostructure of the terminal peptide similar to that in THF.[24] Catalyst **7** showed the moderate reaction rate and high enantioselectivity in THF (entry 2). However, significant decreases in reactivity and selectivity were observed in THF/H_2O = 1/2 (entry 5).

Without a polyleucine tether, the inhibitory effect of water could not be suppressed, and the structure of the catalytically active site was considered to be disturbed in aqueous media because the intramolecular hydrogen bond to retain a rigid β-turn structure can be weakened by water molecules. With catalyst **8**, only low reactivity and selectivity were attained both in THF and in aqueous media (entries 3 and 6). Theoretically, to realize highly enantioselective and efficient reaction, one stereotopic face of the intermediate iminium ion should be shielded by peptide residues and the other face be open to the attack of Hantzsch ester **1**. In this case, the polyleucine chain might cover the stereotopic face needed to be accessible by the reducing agent, leading to the low conversion accompanied by decreased selectivity.

Table 6
Effect of catalyst structure and solvent



Entry	Catalyst	Solvent	Conversion[a] (%)	ee[b] (%)	Abs. config.[c]
1	**6**	THF	89	88	*R*
2	**7**	THF	51	86	*R*
3	**8**	THF	24	59	*S*
4	**6**	THF/H_2O = 1/2	75	91	*R*
5	**7**	THF/H_2O = 1/2	17	64	*R*
6	**8**	THF/H_2O = 1/2	20	52	*S*

[a] Estimated by ^{1}H NMR of the crude mixture.
[b] Determined by chiral HPLC analysis of the corresponding alcohol after $NaBH_4$ reduction in EtOH.
[c] Absolute configuration of the major product.

To obtain insights into the structures of the peptide catalysts, IR spectra of **4**, **6**, and **7** were measured. The N–H stretch region of resin-supported peptides swollen in CH_2Cl_2 and in CH_2Cl_2/DMSO = 9/1 is shown in Figures 1 and 2, respectively. Polyleucine-tethered prolyl catalyst **4** in CH_2Cl_2 showed a band at around 3300 cm^{-1} arising from an N–H stretch involved in typical amide-to-amide hydrogen bonds (Fig. 1a).[25] This is consistent with the fact that polyleucine forms a stable α-helix through strong intramolecular hydrogen bonds.[26] Catalyst **7** having the terminal peptide without polyleucine gave a slightly higher energy band which can be assigned to an N–H stretch involved in a β-turn hydrogen bond (Fig. 1b).[25] The spectrum of polyleucine-tethered peptide catalyst **6** also shifted to higher energy compared to that of **4** (Fig. 1c), implying that the terminal peptide of **6** formed a β-turn which is supported by an α-helix structure of polyleucine. Adding 10% DMSO, a strong hydrogen bond breaker, decreased the absorbance of **7** to the baseline level (Fig. 2b). In this solvent system, the structure of the independent β-turn peptide was considered to be disrupted, whereas the band around 3300 cm^{-1} of **4** attributed to a rigid α-helix was maintained (Fig. 2a). Interestingly, the shape of the band of **6** in CH_2Cl_2/DMSO = 9/1 was almost identical with the one in CH_2Cl_2 (Fig. 2c). These observations indicate that the terminal β-turn peptide combined with polyleucine chain has stronger structural rigidity than the one having no adjacent polyleucine tether. This coincides with the results in enantioselectivity of the reactions using catalysts **6** and **7** under aqueous and non-aqueous conditions (entries 1, 2, 4, and 5 in Table 6). The absolute configuration of the major product obtained with catalyst **6** can be accounted for by a stereochemical model of the iminium intermediate formed between a catalyst and an α,β-unsaturated aldehyde, which is considered to adopt an *E*-configuration.[9] Hantzsch ester **1** approaches to activated aldehyde **2a** from the less hindered *Si* face because the β-turn peptide residues effectively shields the *Re* face (Fig. 3). The IR spectra of catalyst **8** were almost identical with the ones of catalyst **6** both in CH_2Cl_2 and in CH_2Cl_2/DMSO = 9/1, suggesting that catalyst **8** also has a strong β-turn supported by an α-helix structure of polyleucine. However, the model of the intermediate formed with the catalyst having the terminal peptide and D-Leu residues shows that both the sides of the aldehyde are shielded by the peptide residues (Fig. 4). This explains the low reactivity and selectivity when catalyst **8** was used for the reaction (entries 3 and 6 in Table 6).

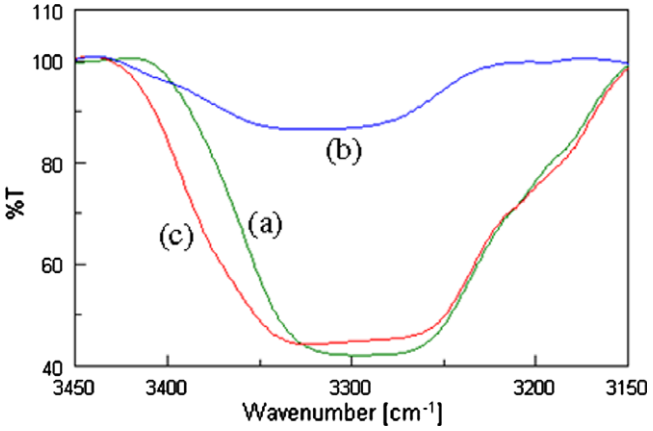


Figure 1. IR spectra of resin-supported peptide catalysts in CH_2Cl_2. (a) Pro-$(Leu)_{25.4}$-PEG-PS, (b) Pro-D-Pro-Aib-Trp-Trp-PEG-PS, and (c) Pro-D-Pro-Aib-Trp-Trp-$(Leu)_{25.4}$-PEG-PS.

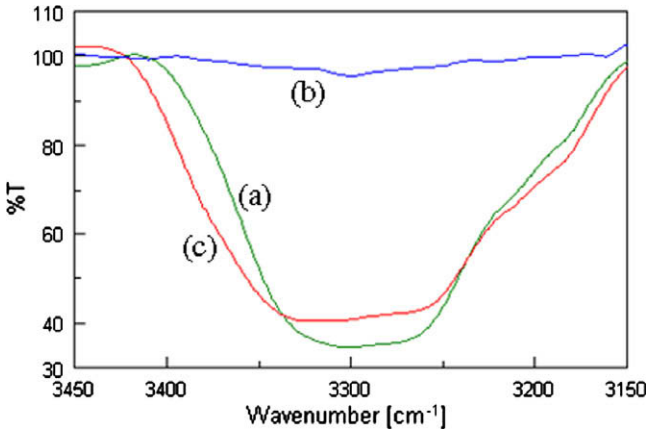


Figure 2. IR spectra of resin-supported peptide catalysts in CH_2Cl_2/DMSO = 9/1. (a) Pro-$(Leu)_{25.4}$-PEG-PS, (b) Pro-D-Pro-Aib-Trp-Trp-PEG-PS, and (c) Pro-D-Pro-Aib-Trp-Trp-$(Leu)_{25.4}$-PEG-PS.

3. Conclusion

In conclusion, the asymmetric transfer hydrogenation in aqueous media was attained using the resin-supported peptide catalyst having a polyleucine tether. Polyleucine played essential roles for both reaction efficiency and stereoselectivity by providing a hydrophobic microenvironment at the reaction center and maintaining the terminal peptide structure. This study demonstrates that sup-

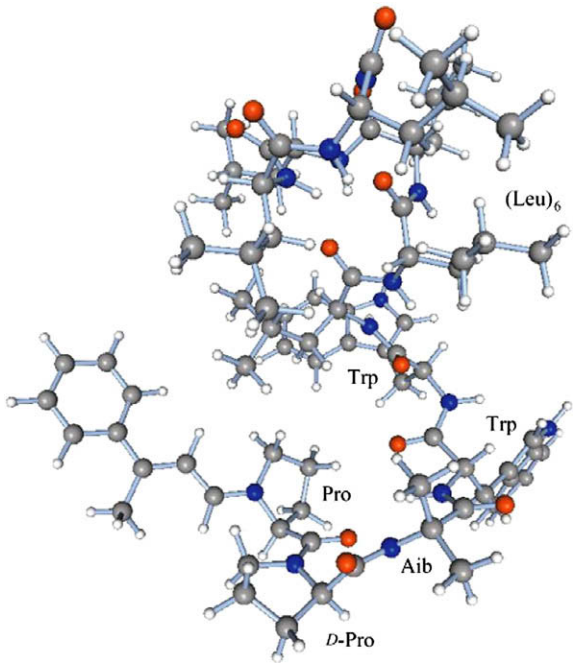


Figure 3. Plausible structure of the iminium intermediate formed between **2a** and Pro-D-Pro-Aib-$(Trp)_2$-$(Leu)_6$-NH_2.

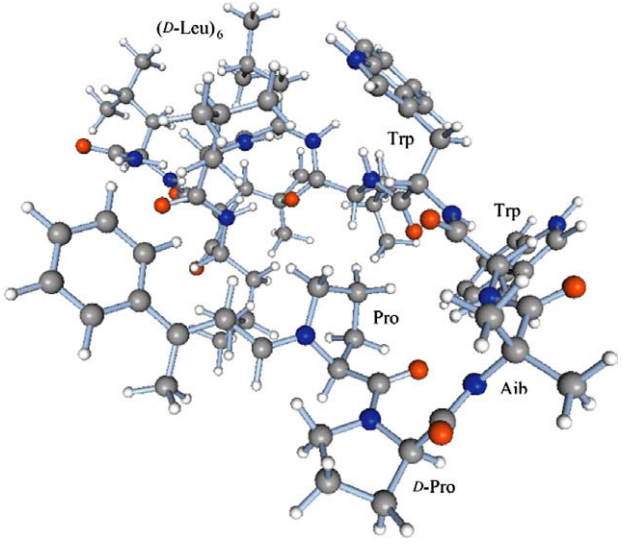


Figure 4. Plausible structure of the iminium intermediate formed between **2a** and Pro-D-Pro-Aib-$(Trp)_2$-$(D\text{-}Leu)_6$-NH_2.

porting a catalytically active peptide with a hydrophobic peptide segment can be a powerful strategy for developing a newly designed biomimetic catalyst. Currently, applications of the present catalyst for other organocatalytic reactions in aqueous media and an asymmetric reduction in complete water system[27] are under investigation in our laboratory.

4. Experimental

Preparation of peptide catalysts and general procedure for the asymmetric transfer hydrogenation were previously reported.[12] IR spectra of catalysts were recorded on a JASCO FT/IR-4100 spectrometer after resins were swollen in CH_2Cl_2 or in CH_2Cl_2/DMSO = 9/1 on NaCl plates. A plausible structure of the iminium intermediate formed between **2a** and Pro-D-Pro-Aib-$(Trp)_2$-(L- or D-$Leu)_6$-NH_2 was calculated by the MM2 method. As an initial structure, the oligoleucine part of this intermediate was assumed to have an α-helix structure according to the present IR data and the previous reports on oligoleucine derivatives.[26]

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