

Organocatalytic Asymmetric Transfer Hydrogenation in Aqueous Media Using Resin-Supported Peptide Having a Polyileucine Tether

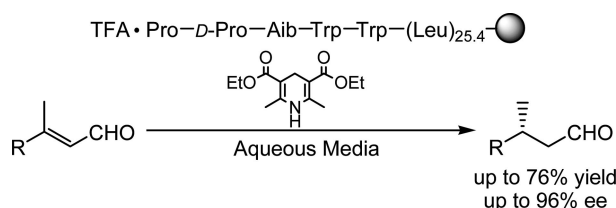
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ABSTRACT



A resin-supported N-terminal prolyl peptide having a β -turn motif and hydrophobic polyileucine chain effectively catalyzed the asymmetric transfer hydrogenation under aqueous conditions. The polyileucine tether provides a hydrophobic cavity in aqueous media that brought about a remarkable acceleration of the reaction. In addition, the polyileucine chain also turned out to be essential for high enantioselectivity.

In the body of living organisms, various reactions are catalyzed under aqueous conditions by naturally refined enzymes having inner hydrophobic catalytic active sites and outer hydrophilic peripheries. The hydrophobic cavities of enzymes play essential roles in accelerating reactions through the capture of organic substrates as well as in achieving highly stereoselective reactions.

On the other hand, an increasing attention has been paid to asymmetric organocatalysts in recent years.¹ Although the majority of the organocatalytic reactions have been performed in organic solvents, such reactions in water or aqueous media are of interest because of their relevance to reactions in living cells. In order to perform reactions in water or aqueous media, it would be effective to construct a hydrophobic space where organic substrates and reagents are concentrated near the

catalytic active site. So far, several well-designed asymmetric organocatalysts focusing on surfactant type,² dendrimer type,³ and solid support type⁴ catalysts have been reported mainly for aldol or Michael reactions.

Among a great many reports on organocatalytic reactions, asymmetric transfer hydrogenation of unsaturated aldehydes using NADH-like Hantzsch ester⁵ is of interest because this reaction seems to mimic biochemical reductions. The reaction is considered to proceed through the iminium ion formation between the secondary ammonium

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catalyst and the substrate aldehydes. Although a number of variants have appeared for the organocatalytic reduction with Hantzsch ester,^{5–7} a successful emulation of nature's efficiency and selectivity in an aqueous environment has not been realized yet.

We have developed an N-terminal prolyl peptide catalyst supported by polyethyleneglycol grafted on polystyrene (PEG-PS) resin⁸ for an aqueous aldol reaction.^{4a} PEG-PS-supported peptide catalysts can be easily prepared through conventional solid-phase peptide synthesis and can be readily removed from a reaction mixture by filtration. Such a supported peptide is an attractive candidate for an efficient asymmetric organocatalyst that works in aqueous media since it is easy to control hydrophobicity and stereostructure simply by changing peptide sequences. Herein we report on a novel PEG-PS-supported hydrophobic peptide catalyst for the asymmetric transfer hydrogenation in aqueous media.

Initially, we checked the efficiency of the proline-based catalysts for the reduction of (*E*)-3-phenylbut-2-enal with Hantzsch ester **1** in THF/H₂O = 2/1 (v/v) (Table 1). Both proline TFA salt (entry 1) and its PEG-PS-supported variant (entry 2) showed almost no activity under this aqueous condition. Since a simple proline salt is known to show some level of catalytic activity in toluene (47% conversion after 5 h),^{5c} the present result indicates water has an inhibitory effect for the proline-catalyzed reduction. For the purpose of generating a hydrophobic environment around the prolyl residue, a polyleucine chain was introduced between the proline and the solid support.⁹ The catalyst having 25.4 leucine residues on average considerably enhanced the reaction (entry 3). More interestingly, when the proportion

Table 1. Transfer Hydrogenation in Aqueous Media

entry	catalyst	solvent	conversion (%) ^a	ee (%) ^b
1	Proline	THF/H ₂ O = 2/1	3	n.d.
2	Pro-	THF/H ₂ O = 2/1	3	n.d.
3	Pro-(Leu) _{25.4} -	THF/H ₂ O = 2/1	21	27
4	Pro-(Leu) _{7.5} -	THF/H ₂ O = 1/2	21	7
5	Pro-(Leu) _{14.8} -	THF/H ₂ O = 1/2	40	19
6	Pro-(Leu) _{25.4} -	THF/H ₂ O = 1/2	63	24
7	Pro-(Leu) _{28.8} -NH- <i>n</i> -Butyl (= -HN-CH ₂ -CH ₂ -PEG-PS)	THF/H ₂ O = 1/2	70	21

^a Estimated by ¹H NMR of the crude mixture. ^b Determined by chiral HPLC analysis of the corresponding alcohol after NaBH₄ reduction in EtOH.

of water increased from THF/H₂O = 2/1 to 1/2, the reaction proceeded 3 times faster (entry 6), presumably because of the intensified hydrophobic interaction between the aldehyde, Hantzsch ester, and the catalyst. The length of polyleucine chain and the reaction rate were positively correlated up to about 25 leucine residues (entries 4–6). The reaction also proceeded smoothly in the presence of a nonsupported N-terminal prolyl polyleucine catalyst (entry 7). However, in this case, the 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. Therefore, in the following experiments, we used PEG-PS resin-supported hydrophobic peptides.^{10,11}

We optimized a terminal peptide sequence from the aspect of enantioselectivity (Table 2). Peptides including the D-Pro-Aib (Aib: 2-aminoisobutyric acid) sequence are known to form a β -turn structure in organic solvents through an intramolecular hydrogen bond.¹² Miller et al. showed that this β -turn motif can be successfully applied to the design of peptide-based asymmetric organocatalysts that work in nonpolar solvents.¹³ We anticipated that the D-Pro-Aib sequence combined with a hydrophobic polyleucine chain could also provide the rigid β -turn structure necessary to control facial selectivity even in aqueous media. Introducing the D-Pro-Aib sequence between the terminal L-prolyl group and the polyleucine tether turned out to be quite effective for enhancing selectivity despite the low reaction rate (entry 1). Furthermore, incorporation of one

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(6) Other examples for catalytic asymmetric reduction using Hantzsch esters: (a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781. (b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424. (c) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (d) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683. (e) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751. (f) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074. (g) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. (h) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562. (i) Kang, Q.; Zhao, Z.-A.; You, S.-L. *Adv. Synth. Catal.* **2007**, *349*, 1657. (j) Martin, N. J. A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976. (k) Guo, Q.-S.; Du, D.-M.; Xu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 759.

(7) Examples for reductions using Hantzsch esters incorporated in sequential reactions: (a) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (b) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (c) Zhao, G.-L.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 7417.

(8) PEG-PS resin is widely used in solid-phase peptide synthesis and is compatible with a variety of solvents, including water, by virtue of its amphiphilic nature. Bayer, E. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 113.

(9) The synthesis of the polyleucine tether was straightforward based on an established chemistry of the N-carboxyanhydride (NCA) polymerization. Leucine is suitable for this purpose because of its high hydrophobicity and high reactivity of its NCA. Simple polyleucine has been used as a catalyst for Juliá-Colonna epoxidation. For a review, see: Porter, M. J.; Roberts, S. M.; Skidmore, J. *Bioorg. Med. Chem.* **1999**, *7*, 2145.

(10) In the Juliá-Colonna epoxidation, resin-supported polyleucine was also used to facilitate efficient handling of the catalyst. Itsuno, S.; Sakakura, M. *J. Org. Chem.* **1990**, *55*, 6047.

(11) When (*R*)-2-(*tert*-butyl)-3-methyl-4-imidazolidinone salt (ref 5c) was used as a catalyst under aqueous conditions, the conversion and the enantioselectivity were modest (in THF/H₂O = 2/1, 42% conversion and 60% ee; in THF/H₂O = 1/2, 44% conversion and 59% ee).

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Table 2. Optimization of Terminal Peptide Sequence

entry	catalyst	solvent	conversion (%) ^a	ee (%) ^b
1	Pro-D-Pro-Aib-(Leu) _{25,4}	THF/H ₂ O = 2/1	4	77
2	Pro-D-Pro-Aib-Trp-(Leu) _{25,4}	THF/H ₂ O = 2/1	7	87
3	Pro-D-Pro-Aib-(Trp) ₂ -(Leu) _{25,4} (4)	THF/H ₂ O = 2/1	13	91
4	Pro-D-Pro-Aib-(Trp) ₃ -(Leu) _{25,4}	THF/H ₂ O = 2/1	12	89
5	4	THF/H ₂ O = 1/2	75	91
6	Pro-D-Pro-Aib-(Trp) ₂	THF/H ₂ O = 1/2	17	64

^a Estimated by ¹H NMR of the crude mixture. ^b Determined by chiral HPLC analysis of the corresponding alcohol after NaBH₄ reduction in EtOH.

or two Trp residue(s) into the peptide at the point next to Aib afforded even higher enantioselectivity (entries 2 and 3), while the insertion of three Trp brought about no additional improvement (entry 4). Concerning the reaction catalyzed by the peptide **4**, increasing the ratio of water from THF/H₂O = 2/1 to 1/2 brought about a remarkable acceleration of the reaction without loss of enantioselectivity (entry 5). Further increase in the ratio of water did not improve the reaction rate because of the limited solubility of Hantzsch ester **1** to water. A control experiment with the catalyst having no polyleucine tether resulted in only low reaction rate and a significant decrease in selectivity (entry 6). This indicates that the polyleucine chain provides an efficient hydrophobic cavity and allows the terminal peptide sequence to fold into a desirable secondary structure. This necessity of the hydrophobic moiety is in a sharp contrast to the results reported by Uozumi et al. in which the simple PEG-PS support behaved as an efficient hydrophobic sink for organic substrates in palladium-catalyzed reactions under aqueous conditions.¹⁴

Some typical unsaturated aldehydes were examined as hydride acceptors (Table 3). Reactions were performed in the presence of 20 mol % of catalyst **4** TFA salt with 1.2 equiv of Hantzsch ester **1** in THF/H₂O = 1/2. Aldehydes **2a–e** having aromatic groups of various sizes and electronic natures gave good yields and high levels of enantioselectivity (entries 1–5). The aldehyde **2f** possessing an *ortho* chloro group was hardly reduced to **3f** probably because of the steric hindrance (entry 6). Aliphatic aldehyde **2g** also showed excellent enantioselectivity even though the yield was moderate (entry 7).¹⁵ The absolute configurations of the major products **3a** and **3g** were determined in comparison with the authentic samples obtained by the reported method.^{5c,d} Considering the mechanistic similarity in all cases, which is based on the known mechanism through the

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(15) *E/Z* mixture (*E/Z* = 2/1) of **2g** was used as a starting material, whereas **2a–f** were only *E* isomers. Regardless, the high ee value of **3g** was obtained. This suggests that the enantioconvergence described by List et al. and MacMillan et al. occurred in this case as well (see refs 5b and 5c).

Table 3. Substrate Scope

entry		R	yield (%) ^a	ee (%) ^b
1	a		75	90
2	b		71	94
3	c		76	95 ^c
4	d		72	95 ^d
5	e		69	93 ^d
6	f		<1	n.d.
7 ^e	g		53	96 ^f

^a Isolated yields. ^b Unless otherwise noted, determined by chiral HPLC analysis of the corresponding alcohol after NaBH₄ reduction. ^c Determined by ¹H NMR in the presence of Eu(hfc)₃ as the chiral shift reagent after NaBH₄ reduction. ^d Determined by ¹H NMR after NaBH₄ reduction and derivatization of the corresponding alcohol to the Mosher ester with (–)-MTPA-Cl. ^e *E/Z* mixture of **2g** was used as a starting material (*E/Z* = 2/1). Reaction time was 10 h. ^f After NaBH₄ reduction, ee of the corresponding alcohol was determined according to the literature (see Supporting Information).

formation of the iminium ion,^{5c} all products were considered to have the same stereostructure.

In summary, we have developed a novel resin-supported peptide catalyst for the asymmetric transfer hydrogenation.¹⁶ With this catalyst, we attained the first highly enantioselective reaction in aqueous media. The hydrophobic leucine chain was essential for both reaction rate and selectivity, which imitates the performance of enzymes in the cell. Currently, the generality of the present catalyst design for the reactions in aqueous conditions is under investigation in our laboratory.

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Supporting Information Available: Synthesis of peptide catalysts and experimental details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) A full account of this survey including more detailed data and the structural insight into the peptide catalyst will be forthcoming.