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Efficient Asymmetric α-Oxyamination of Aldehydes by Resin-Supported Peptide Catalyst in Aqueous Media

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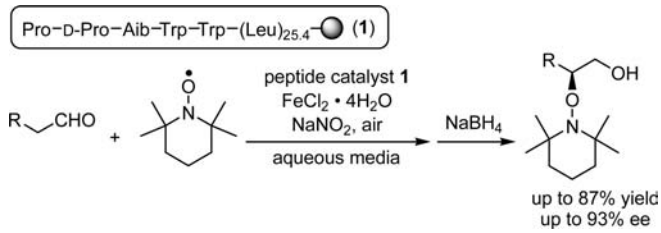
ABSTRACT



The resin-supported peptide catalyst having the terminal five-residue Pro-D-Pro-Aib-Trp-Trp combined with polyleucine successfully catalyzed the asymmetric α-oxyamination of aldehydes in aqueous media. The secondary structure and the chirality sense of the hydrophobic polyleucine chain significantly affected both reactivity and enantioselectivity.

Enzymes catalyze a variety of asymmetric reactions efficiently and selectively under aqueous conditions. Most of them possess a hydrophobic pocket to bind substrates and to let the reaction occur.[1] In the pocket, functional groups participating in a catalytic process are spatially arranged with the aid of the outer secondary structural framework of polypeptides, such as α-helix and β-sheet. To date, in the field of bioinspired catalysis, a number of attempts have been made to create an enzyme-pocket-like microenvironment in water by combining catalytically active groups with hydrophobic parts.[2−5] If a catalytically active group is surrounded by a hydrophobic periphery having an ideal three-dimensional structure, that system is expected to be a highly efficient asymmetric catalyst working under aqueous conditions. Most of the hydrophobic moieties employed for the reported catalysts are achiral, and there are few successful examples of enhancing reactivity and selectivity using a chiral hydrophobic segment with a specific structure.[6] So

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far, our group has developed poly(ethylene glycol)-polystyrene (PEG-PS) resin-supported peptide catalyst **1** (Figure 1)

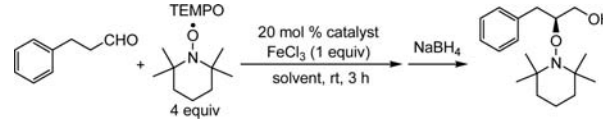
Figure 1. Resin-supported peptide catalyst.

possessing polyleucine as a chiral hydrophobe. The catalyst has a β-turn pentapeptide connected to the N-terminus of the α-helical polyleucine chain. With this catalyst, asymmetric hydrogenation[7] and Friedel−Crafts-type asymmetric alkylation[8] proceeded efficiently in aqueous media. Despite its simple primary structure, the polyleucine moiety was essential for both catalytic efficiency and enantioselectivity in these reactions.[9]

Recently, Sibi et al.,[10] MacMillan et al.,[11] and other groups[12] have reported a new class of chiral-amine-catalyzed asymmetric reactions which involve radical cation intermediates. For example, Sibi has developed enantioselective α-oxyamination of aldehydes using TEMPO in DMF or THF. In that reaction, the enamine intermediate formed between the amine catalyst and the aldehyde is oxidized through a single electron transfer (SET) mechanism, then the resulting planar radical cation undergoes enantioface-selective C−O bond formation with TEMPO. The reaction was achieved with chiral 4-imidazolidinone catalysts, while proline and diphenylprolinol were not suitable as catalysts because of quite low enantioselectivity.[10] In the reactions proceeding via iminium ion intermediates, we have shown that prolyl peptide **1** is the effective asymmetric catalyst even for the ones in which simple proline is a poor catalyst. Therefore, it is expected that prolyl catalyst **1** is also applicable to asymmetric reactions other than the conjugate additions to unsaturated iminium cations, provided that the reaction intermediate takes a planar structure.

We chose the α-oxyamination of aldehydes reported by Sibi as a target reaction because the enantioselectivity leaves room for improvement.[13] In the presence of peptide catalyst **1**, the oxyamination of 3-phenylpropanal with TEMPO using iron(III) chloride as an SET reagent was performed in THF/H_2O = 1/1 (v/v) at room temperature (Table 1, entry 1). The enantioselectivity was better than

Table 1. α-Oxyamination Using *N*-Proryl Peptide Catalyst



entry	catalyst	solvent	yield (%)	ee (%)[a]
1	Pro-D-Pro-Aib-Trp-Trp-(Leu)25.4- (1)	THF/H_2O = 1/1	26	86
2	**1**	THF/H_2O = 1/2	57	89
3	**1**	H_2O	47	89
4	proline	THF/H_2O = 1/1	trace	n.d.[b]
5	Pro-	THF/H_2O = 1/1	8	-16
6	Pro-(Leu)2-	THF/H_2O = 1/1	10	-11
7	Pro-(Leu)24.4-	THF/H_2O = 1/1	39	46
8	Pro-D-Pro-Aib-Trp-Trp- (2)	THF/H_2O = 1/2	8	39
9	Pro-D-Pro-Aib-Trp-Trp-(Ile)26.5- (3)	THF/H_2O = 1/2	20	13
10	Pro-D-Pro-Aib-Trp-Trp-(Val)26.3- (4)	THF/H_2O = 1/2	21	14
11	D-Pro-Pro-Aib-(D-Trp)2-(Leu)26.5- (5)	THF/H_2O = 1/2	14	-23

[a] Determined by chiral HPLC analysis using Chiralcel OD-H. [b] Not determined.

that reported for the same reaction by the imidazolidinone catalyst (82% ee) at lowered temperature.[10] The increase in the ratio of water in the solvent system to THF/H_2O = 1/2 brought about the acceleration of the reaction probably because of intensified hydrophobic interactions between the substrate and the catalyst (entry 2). It is noteworthy that the reaction proceeded smoothly even in the absence of the organic cosolvent (entry 3). The reaction was sluggish with proline (entry 4), PEG-PS resin-supported proline, or Pro-Leu-Leu (entries 5 and 6). On the contrary, introducing polyleucine between the terminal prolyl residue and the solid support effectively enhanced the reaction rate with a considerable change in enantioselectivity (entry 7).[14] This indicates that the polyleucine moiety not only provides a hydrophobic environment but also affects the stereochemical outcome of the reaction.

The importance of polyleucine was further endorsed by the fact that catalyst **2** lacking the polyleucine chain showed

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low catalytic performance (entry 8). When polyisoleucine or polyvaline was employed instead of polyleucine as a hydrophobic segment, poor reactivity and enantioselectivity were observed (entries 9 and 10). These results mean that the hydrophobic character of poly(amino acid) is not a sufficient condition for a good catalyst. Replacement of the terminal five residues of peptide **1** with their antipode also brought about the lowering of catalytic ability (entry 11). The same tendency was observed in our previous study on the asymmetric transfer hydrogenation.[7a] The sequence of the terminal peptide of **1** is an outcome of intensive optimization for our previous asymmetric hydrogenation. A brief screening of this position for the catalytic performance in the present reaction indicated that peptide **1** was most effective.

The structures of the resin-supported peptide catalysts were estimated by means of their IR spectra. In Figure 2, the

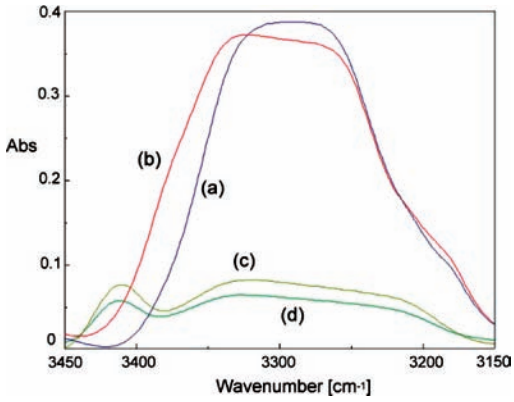

Figure 2. IR spectra of resin-supported peptide catalysts in CH_2Cl_2. (a) Pro-(Leu)$_{24.4}$-PEG-PS, (b) Pro-D-Pro-Aib-Trp-Trp-(Leu)$_{25.4}$-PEG-PS (**1**), (c) Pro-D-Pro-Aib-Trp-Trp-(Ile)$_{26.5}$-PEG-PS (**3**), (d) Pro-D-Pro-Aib-Trp-Trp-(Val)$_{26.3}$-PEG-PS (**4**).

region of intramolecularly hydrogen-bonded N−H stretching is shown.[15] Polyleucine with a prolyl residue gave the intense peak attributed to an α-helix, which is a common secondary structure of polyleucine.[16] Peptide catalyst **1** gave a similar band at slightly higher energy region. This suggests that the β-turn structure is present along with an α-helix.[17] Catalysts **3** and **4** showed only weak bands in this region, implying that the poly(amino acid) segment did not take a specific secondary structure.[18] These weak bands can be assigned either to the β-turn structure or to a weak intramolecular hydrogen bonding derived from a poly(amino acid) moiety, and we cannot discriminate them unambiguously. Catalyst **5** showed a similar spectrum with catalyst **1**, indicating that this catalyst also had both α-helix and β-turn structure (data not shown).

A schematic model of the radical cation intermediate, which is generated through the one-electron oxidation of the enamine formed between the peptide catalyst and the substrate aldehyde, is shown in Figure 3. In this model, one face of the radical

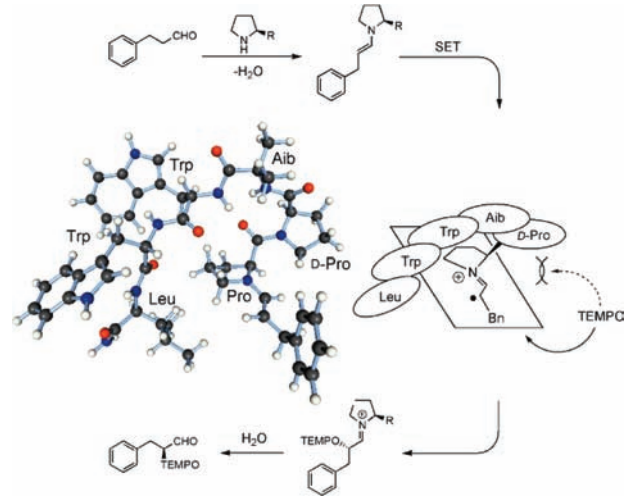

Figure 3. Plausible structure of the radical cation intermediate.

intermediate is covered with the peptide residues and the other face is accessible by TEMPO radical. In the cases of catalysts **3** and **4**, it is considered that the poly(amino acid) segment forms a random coil which could cover both faces of the intermediate regardless of the terminal structure, leading to low reactivity and selectivity. In our previous paper, we had indicated that the "mismatched" chirality of catalyst **5** between the terminal pentapeptide and the polyleucine chain could cause a shielding for the face of the planar intermediate, which should be open to the attack of the reagent.[7a] This might also be the case for the present α-oxyamination.

Then, the reaction conditions were optimized using peptide catalyst **1** (Table 2). As Sibi et al. demonstrated,[10] the use of iron(III) chloride could be decreased to a catalytic amount when dioxygen was used as the terminal oxidant (entry 1). Iron(II) chloride was also effective for this reaction and gave even a superior result (entry 2). It turned out that the condition under dioxygen atmosphere was not necessary, and the reaction

(14) Non-supported prolyl peptide having a polyleucine chain, Pro-(Leu)$_{28.8}$-NH-*n*-butyl, also catalyzed the reaction in THF/H_2O = 1/1 (29% yield and 44% ee). However, the preparation of the catalyst and the removal from the reaction mixture were laborious because of the gelating nature of the peptide solution. In Juliá−Colonna epoxidation, it has been reported that immobilization of polyleucine on resin beads can avoid the catalyst handling problem due to the gelation: Itsuno, S.; Sakakura, M. *J. Org. Chem.* **1990**, *55*, 6047.

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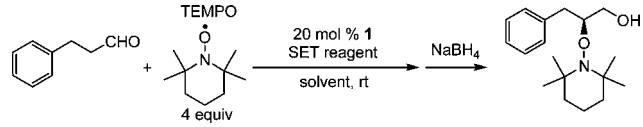
Table 2. α-Oxyamination with Catalytic Amount of Iron Salt



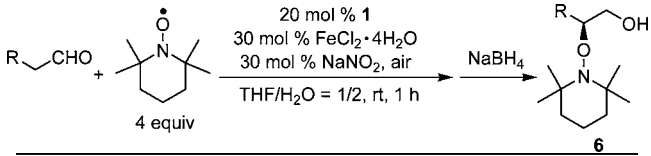
entry	SET reagent	solvent	time (h)	yield (%)	ee (%)[a]
1	$FeCl_3$ (0.3 equiv), $NaNO_2$ (0.3 equiv), O_2	$THF/H_2O = 1/2$	3	43	91
2	$FeCl_2{\cdot}4H_2O$ (0.3 equiv), $NaNO_2$ (0.3 equiv), O_2	$THF/H_2O = 1/2$	3	68	93
3	$FeCl_2{\cdot}4H_2O$ (0.3 equiv), $NaNO_2$ (0.3 equiv), air	$THF/H_2O = 1/2$	1	75	93
4[b]	$FeCl_2{\cdot}4H_2O$ (0.1 equiv), $NaNO_2$ (0.1 equiv), air	$THF/H_2O = 1/2$	24	79	91
5	$FeCl_2{\cdot}4H_2O$ (0.3 equiv), $NaNO_2$ (0.3 equiv), air	THF	1	6	70
6	$FeCl_2{\cdot}4H_2O$ (0.3 equiv), $NaNO_2$ (0.3 equiv), air	DMF	1	trace	n.d.[c]

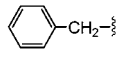
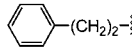
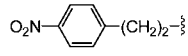
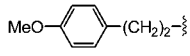
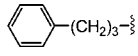
[a] Determined by chiral HPLC analysis using Chiralcel OD-H. [b] With 3 mol % of **1** used. [c] Not determined.

completed under air within 1 h (entry 3). This reaction system was so efficient that the amount of peptide catalyst **1** could be reduced to 3 mol % without significant loss in yield and selectivity, simply by the elongation of the reaction time (entry 4). The reactions in organic solvents resulted in poor yield (entries 5 and 6).

Finally, some aldehydes were tested in this aqueous reaction system, and oxyaminated products were obtained in good yield and enantioselectivity (Table 3). Compared with the results obtained with the imidazolidinone catalyst in organic solvent,[10] the peptide catalysis in aqueous media was proved to be more efficient.

Table 3. α-Oxyamination under Optimum Conditions



entry		R	yield (%)	ee (%)[a]
1	**a**		75	93
2	**b**		87	90
3	**c**		76	87
4	**d**		84	88[b]
5	**e**		73	87

[a] Determined by chiral HPLC analysis using Chiralcel OD-H, unless otherwise noted. [b] Determined by chiral HPLC analysis using Chiralcel IA.

In conclusion, the resin-supported peptide catalyst having polyleucine was effective for the asymmetric α-oxyamination of aldehydes particularly in aqueous media. The structure and chirality of the hydrophobic segment were important for the reaction rate and enantioselectivity. This observation would provide a new insight into the strategy for designing a biomimetic peptide catalyst. Because peptide catalyst **1** showed the generality for the reactions proceeding through the iminium ion and the radical cation intermediates under ambient conditions, wide applicability for various reactions can be expected. Research from such a viewpoint is now underway in this laboratory.

Acknowledgment. This work was supported in part by Global COE Program, Chemistry Innovation through Cooperation of Science and Engineering, MEXT, Japan.

Supporting Information Available: Experimental procedure and spectroscopic data for oxyaminated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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