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Friedel–Crafts-type alkylation in aqueous media using resin-supported peptide catalyst having polyleucine

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ABSTRACT

The asymmetric Friedel–Crafts-type alkylation in aqueous media was realized by the resin-supported N-terminal prolyl peptide catalyst having a polyleucine tether. The hydrophobic polyleucine chain in the peptide catalyst was essential for the reaction efficiency and enantioselectivity. The resin-bound peptide catalyst could be reused at least for five times.

Chiral indole derivatives constitute a class of important structural units for natural products and pharmaceuticals.[1] Because the Friedel–Crafts-type alkylation of indole rings is a powerful way of obtaining optically active indole compounds, many kinds of asymmetric catalysts for Friedel–Crafts reactions of indoles have been developed to date.[2] After MacMillan and Austin reported the Michael-type addition of indoles to α,β-unsaturated aldehydes using an imidazolidin-4-one catalyst,[3] considerable attention has been paid to organocatalytic Friedel–Crafts-type alkylations for synthesizing indole derivatives.[4,5] Among them, those catalyzed by chiral amines have been well studied. Substrate enals are condensed with the catalysts to form iminium ion intermediates, which control the facial selectivity of the addition. So far, several types of chiral amines such as imidazolidinones,[3,6] proline derivatives,[7] aziridinyl methanol,[8] and cinchona alkaloid derivatives[9] have been employed for the catalytic enantioselective Friedel–Crafts-type alkylation through the iminium activation. Although peptide catalysts are also promising candidates for enantioselective organocatalysis,[10] there is no report on a Friedel–Crafts reaction using a peptide-based catalyst. Compared with relatively simple organocatalysts, peptide catalysts are easy to be optimized through the tuning of the sequence/number of the amino-acid residues.

Recently, as a catalyst for an asymmetric transfer hydrogenation in aqueous media, we have developed the resin-supported N-terminal prolyl peptide **1** having a hydrophobic tether (Fig. 1).[11] Because development of catalytic reactions in aqueous media has received increasing attention, we have tried to extend this peptide catalyst to other reactions, especially to C–C bond formations. Herein, we report the Friedel–Crafts-type reaction of indoles with enals under aqueous conditions using the resin-supported N-terminal prolyl peptide catalyst.

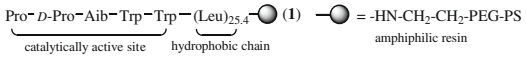
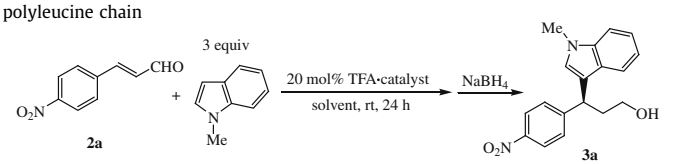


Figure 1. Resin-supported peptide catalyst.

In our previous study, it was revealed that (1) the polyleucine moiety in the peptide chain plays important roles both in the efficiency and in the stereoselectivity of catalysis in aqueous media, and (2) amphiphilic polyethyleneglycol-grafted cross-linked polystyrene (PEG-PS) resin support is essential for avoiding aggregation and sedimentation of a hydrophobic peptide catalyst. Accordingly, we first tried the reaction of 4-nitrocinnamaldehyde with *N*-methyl indole using trifluoroacetic acid (TFA) salt of the PEG-PS-

Table 1
Friedel–Crafts-type alkylation in aqueous media using prolyl catalyst having polyleucine chain



Entry	Catalyst	Solvent	Conversion[a] (%)	ee[b] (%)
1	Pro-(Leu)$_{25.4}$- (4)	THF	0	—
2	**4**	THF/H_2O = 2/1	11	24
3	**4**	THF/H_2O = 1/1	44	28
4	**4**	THF/H_2O = 1/2	59	22
5	Pro-	THF/H_2O = 1/2	8	<1
6	Proline	THF/H_2O = 1/2	5	<1

[a] Estimated by ^{1}H NMR of the crude mixture.
[b] Determined by chiral HPLC analysis using Chiralcel IA.

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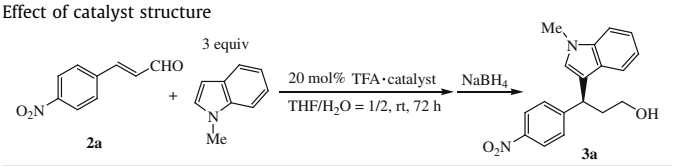
Table 2
Effect of catalyst structure



Entry	Catalyst	Yield[a] (%)	ee[b] (%)
1	Pro–*D*-Pro–Aib–Trp–Trp–$(Leu)_{25.4}$– (**1**)	85	88
2	Pro–*D*-Pro–Aib–Trp–Trp– (**5**)	19	30
3	Pro–*D*-Pro–Aib–*D*-Trp–Trp–$(Leu)_{24.4}$–	81	43
4	Pro–*D*-Pro–Aib–Trp–*D*-Trp–$(Leu)_{24.4}$–	87	41

[a] Isolated yield.
[b] Determined by chiral HPLC analysis using Chiralcel IA.

supported prolyl peptide having the polyleucine tether (**4**) as a catalyst (Table 1). When THF was used as a sole solvent, reaction did not proceed (entry 1). Upon addition of water to the solvent, the Friedel–Crafts reaction was promoted. Increasing the ratio of water in the solvent system enhanced the reaction rate (entries 2–4).[12] Similar solvent effect has been observed in our previous study on the transfer hydrogenation.[11] This acceleration effect is probably due to the intensified hydrophobic interaction between substrates and the catalyst. When the catalyst having no polyleucine chain was employed, the efficiency was very low (entry 5). Simple proline TFA salt also failed to catalyze the reaction (entry 6). These results indicate that the polyleucine moiety in peptide **4** provides a hydrophobic environment in aqueous media in which the reaction proceeded efficiently.

We then tried the peptide catalyst **1** having a β-turn inducing D-Pro-Aib unit (Table 2, entry 1). A high degree of asymmetric induction was realized at room temperature. This is in sharp contrast with the imidazolidinone catalyst which requires quite low temperature to obtain a product with high enantioselectivity.[3] With catalyst **5** having no polyleucine chain, the reaction rate and selectivity drastically decreased (entry 2). In the previous paper on the transfer hydrogenation, we had clarified that (1) the N-terminal five-residue part of peptide catalyst **1** takes β-turn conformation with the aid of the polyleucine chain under aqueous conditions, and (2) high enantioselectivity arose from the effective shielding of one stereotopic face of the iminium ion intermediate by the rigid peptide framework.[11] It might be reasonable to mention that the present alkylation underwent through the essentially same mechanism as above. The stereochemical outcome of this Friedel–Crafts-type reaction can be accounted for by the attack of the nucleophile from less shielded *Si* face of (*E*)-anti iminium ion (Fig. 2). Replacement of one of the two L-Trp residues with D-Trp brought about a dramatic decrease in enantioselectivity (entries 3 and 4). This might be because the inversion of the asymmetric carbon of the Trp residue significantly affected the three-dimensional structure of the whole peptide.

With peptide catalyst **1**, the substrate scope of the asymmetric Friedel–Crafts-type alkylation in aqueous media was investigated (Table 3).[13] The addition of *N*-methyl indole to 4- or 3-nitrocinnamaldehyde proceeded smoothly and afforded the product in good yield and enantioselectivity (entries 1 and 6). Although the addition to 4-chlorocinnamaldehyde was relatively slow (the conversion was 61% after 168 h), good selectivity was achieved (entry 2). The reaction between 2-nitrocinnamaldehyde and *N*-methyl indole was sluggish probably owing to steric hindrance (after 120 h, 21% yield with 61% ee in THF/H_2O = 1/2, 30% yield with 52% ee in H_2O). An aliphatic aldehyde could be used as an acceptor, though the yield and enantioselectivity were moderate (entry 3). Unsubstituted indole and *N*-methyl pyrrole could also be employed for the present alkylation with good enantioselectivity (entries 4 and 5). Since a solid-supported catalyst can be easily separated from the reaction mixture, the present resin-bound peptide might have an advantage for recycling.[14] The reusability of the catalyst, which was recovered after the reaction by filtration, was examined. Although the isolated yield decreased to some extent, the catalyst could be reused without losing enantioselectivity at least for five times (entries 7–11). It is also worth noting that the reaction

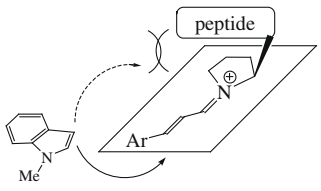
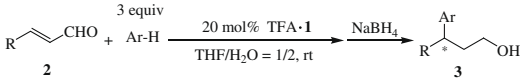
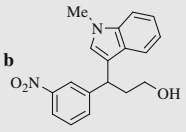
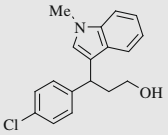
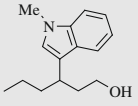
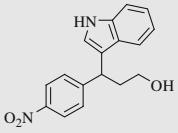
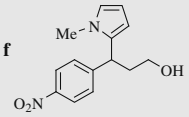
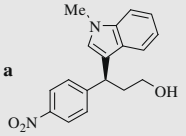


Figure 2. Schematic illustration of the enantiocontrol for the addition.

Table 3
Substrate scope and reusability of catalyst



Entry	3	Time (h)	Yield[a] (%)	ee[b] (%)
1	**b** 	72	73	87
2	**c** 	168	56	82
3	**d** 	72	44	52[c]
4	**e** 	48	84	87
5	**f** 	48	57	77
6	**a** 	72	85 (88)[d]	88 (94)[d]
7	(1st reuse of catalyst)	72	74	89
8	(2nd reuse of catalyst)	72	76	90
9	(3rd reuse of catalyst)	72	70	90
10	(4th reuse of catalyst)	72	70	90
11	(5th reuse of catalyst)	72	71	88

[a] Isolated yield.
[b] Determined by chiral HPLC analysis using Chiralcel IA unless otherwise noted.
[c] Determined by chiral HPLC analysis using Chiralcel OJ.
[d] Values in parentheses are the results of the reaction performed in H_2O.

proceeded even in the absence of THF, an organic co-solvent (entry 6 in parentheses).

In conclusion, the asymmetric Friedel–Crafts-type alkylation in aqueous media was realized by the N-terminal prolyl peptide catalyst having a polyleucine tether. The hydrophobic polyleucine chain in the peptide catalyst was essential for the reaction efficiency and enantioselectivity. Because the peptide catalyst used in this study was effective for the asymmetric transfer hydrogenation we had previously reported, this type of peptide is expected to have the extendibility to other reactions in aqueous media. A research from such a viewpoint is now underway in this laboratory.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.071.

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12. The reaction proceeded smoothly even in water (86% conversion and 21% ee under the same reaction conditions).
13. *Typical experimental procedure for Friedel–Crafts-type alkylations:* To a mixture of α,β-unsaturated aldehyde **2** (0.1 mmol) and trifluoroacetic acid salt of prolyl peptide catalyst **1** (150 mg, 0.02 mmol of prolyl group) in 0.67 mL of THF and 1.37 mL of distilled water, an indole compound or *N*-methyl pyrrole (0.3 mmol) was added. The mixture was stirred at room temperature for 48–168 h. Then the catalyst was filtered and washed with THF. After the removal of solvent under reduced pressure, the residue was dissolved in 1 mL of THF. Sodium borohydride (0.5 mmol) was added and the resulting solution was stirred for 30 min. The reaction mixture was treated with saturated aqueous ammonium chloride and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate. After the removal of solvent under reduced pressure, the crude product was purified using preparative TLC (hexane/EtOAc = 1/1). As for **3a** and **3c**, the product was contaminated with the corresponding alcohol of the starting aldehyde. In such a case, the contaminant was selectively re-oxidized to the aldehyde with 0.2 mmol MnO_2 in 1 mL of $CHCl_3$, and removed by means of preparative TLC (hexane/EtOAc = 1/1).
14. Examples for Friedel–Crafts alkylation using solid-supported catalysts: (a) Das, B.; Thirupathi, P.; Kumar, R. A.; Reddy, K. R. *Catal. Commun.* **2008**, *9*, 635; (b) Kantam, M. L.; Laha, S.; Yadav, J.; Sreedhar, B. *Tetrahedron Lett.* **2006**, *47*, 6213; (c) Corma, A.; Carcía, H.; Moussaif, A.; Sabater, M. J.; Zniber, R.; Redouane, A. *Chem. Commun.* **2002**, 1058; (d) Yu, P.; He, J.; Guo, C. *Chem. Commun.* **2008**, 2355.