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Direct asymmetric aldol reaction in aqueous media using polymer-supported peptide

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Abstract—PEG-PS resin-supported tripeptide/zinc chloride catalyst system has been developed for use in the direct asymmetric aldol reaction of acetone with aldehydes in aqueous media. The peptide catalyst could be separated from the reaction mixture by filtration, and was reusable at least five times without significant change in its activity and selectivity.

The direct asymmetric aldol reaction (DAAR) is one of the most powerful C–C bond forming reactions and has been intensively studied in recent years.[1] In 2000, List et al. reported that proline catalyzes the intermolecular DAAR under mild conditions, and proposed the reaction mechanism to be class I aldolase-like, that is, to involve the enamine intermediate.[2] Subsequently, a number of proline-related compounds have been prepared and applied as the catalyst for the DAAR, aiming at improving the catalytic performance.[3,4] In most cases, the reactions are carried out in organic solvents, and the addition of a small amount of water is known to bring about an acceleration of the reaction to some extent.[5] However, excess water sometimes causes a severe decrease in the enantioselectivity.[3] The DAAR catalyzed by prolines in aqueous media is of special interest because it is directly relevant to the class I aldolase-catalyzed reactions under physiological conditions, hence the reaction is potentially applicable in chemical biology. There are several studies on the direct aldol reaction under such conditions. Following earlier reports on proline-catalyzed non-enantioselective reactions,[6] there appeared a couple of papers on the DAAR catalyzed by proline-related compounds.[7,8] Among them, the reaction catalyzed by Pro-$(Phe)_n$–OMe ($n = 3$ or 4) showed marked enantioselectivity; the DAAR of hydroxyacetone and aldehydes proceeded with up to 96%ee in the presence of 10–20 mol % catalyst.[7] In this reaction, the weight-based amount of catalyst is sometimes comparable to that of the substrate aldehyde, because the catalyst has much higher molecular weight than the substrate. Particularly in such a case, it is highly desirable that the catalyst be recovered and reused. However, recyclability was not mentioned in that report. In this paper, we report a DAAR under aqueous conditions catalyzed by recyclable N-terminal prolyl peptides immobilized on a polymer solid.

For the solid support, we chose polyethyleneglycol grafted on cross-linked polystyrene (PEG-PS) resin. PEG-PS is widely used in solid-phase peptide synthesis (SPPS), and is known to be compatible with a variety of solvents, including water, by virtue of its amphiphilic nature.[9] Immobilized peptide catalysts were prepared on a terminally aminated PEG-PS (loading = 0.20 mmol/g) resin by the standard Fmoc SPPS procedure.[10,11] This resin-bound catalyst is advantageous particularly when the peptides are hydrophobic; the resin renders the peptides soluble in water due to the hydrophilic PEG chain and prevents the aggregation/sedimentation of the peptides. As a result, the resin-supported peptide can be used in a high concentration.

The reaction of *p*-nitrobenzaldehyde with acetone was performed as an initial test of the peptide catalyst (Table 1). Although a simple prolyl resin showed catalytic activity, enantioselectivity was low (entry 1). The selectivity was somewhat increased by incorporating one or two Phe residue(s) between the prolyl group and the resin (entries 2 and 3). Further insertion of Phe did not

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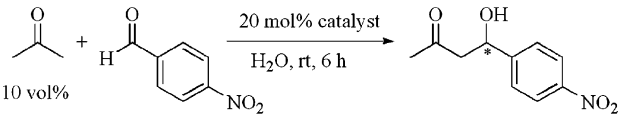
Table 1.



Entry	Catalyst[a]	Yield (%)[b]	ee (%)[c]	abs config[d]
1	Pro–●	85	12	*R*
2	Pro–Phe–●	78	27	*R*
3	Pro–Phe–Phe–●	100(100)[e]	34(64)[e]	*R*
4	*D*-Pro–Phe–Phe–●	81	26	*S*
5	*D*-Pro–Tyr–Phe–●	90(66)[e]	33(73)[e]	*S*

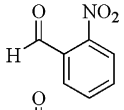
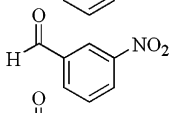
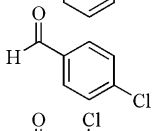
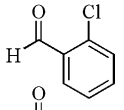
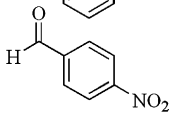
[a] The symbol ● denotes amino group terminated PEG-PS resin.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using Chiralcel OJ.
[d] Absolute configuration of the major product.
[e] Values in parentheses were those obtained under the following conditions: in acetone/H_2O/THF = 1/1/1 at 0 °C in the presence of 20 mol % $ZnCl_2$.

show any improvement. When the residues were substituted from Phe to other amino acids, such as Leu, Val, or Trp, only lower selectivity was observed. When D-Pro-Phe-Phe was used as a catalyst, a reversal of enantioselectivity was observed, but the degree of the selectivity was lower than that with the corresponding L-Prolyl catalyst (entry 4). This means that the residue next to the prolyl group has some influence on the selectivity. After screening with several amino acids at that position, D-Pro-Tyr-Phe was found to show a good result (entry 5). Then we optimized the reaction conditions for enantioselectivity. The best result was obtained when the reaction was performed in acetone/H_2O/THF = 1:1:1 (v/v/v) at 0 °C using 20 mol % of both the peptide catalyst and $ZnCl_2$ (entries 3, 5 in parentheses).[12] For the reaction in entry 5, the elongation of the reaction time from 6 to 20 h brought about the increase in the chemical yield from 66% to the quantitative yield without any significant loss of enantioselectivity (73%ee to 71%ee). It should be noted that Darbre's group has reported a DAAR under aqueous conditions catalyzed by zinc–proline complex.[8] They found that the catalyst prepared from L-proline preferentially gave the product aldol having (*S*)-configuration in the same reaction as the one we tested above. Such a mode of enantioselectivity is in disagreement with our results. This implies that the role of Zn(II) ion in our system is quite different from that of Darbre's group.

Next, the scope of the substrate was examined (Table 2).[13] The aromatic aldehydes having an electron-withdrawing substituent gave the corresponding adducts in high yield with modest to good enantioselectivity. In contrast, the resin-bound peptide did not catalyze the reaction of *p*-anisaldehyde, which has an electron-donating methoxy group.

A major drawback of the proline(-derivative)-catalyzed aldol reaction is its low efficiency, and as much as 10–40 mol %, typically 20 mol %, of catalyst is needed. In order to indirectly overcome this problem, multiple use of the catalyst has been investigated.[14,15] From the viewpoint of recycling, the solid-supported catalyst is advantageous because the products can be easily separated from the reaction mixture by simple filtration and washing. It was found that the immobilized peptide catalyst could be repeatedly used at least five times without large loss of yield or selectivity (Table 2, entries 5–9). The reaction using recycled catalyst proceeded even in the absence of $ZnCl_2$, but the efficiency and selectivity were slightly lower. Basically, adding $ZnCl_2$ to each cycle resulted in a better outcome.

Table 2. Aldol reactions between acetone and aldehydes with *D*-Pro–Tyr–Phe–● catalyst[a]

Entry	Aldehyde	Time (h)	Yield (%)[b]	ee (%)[c]
1		18	89	84[d]
2		24	83	76
3		30	50(91)[e]	72[d]
4		30	93	74[d]
5		20	100	71
6	(first reuse of cat.)	20	99	73
7	(second reuse of cat.)	20	92	75
8	(third reuse of cat.)	20	96	74
9	(fourth reuse of cat.)	20	96	71

[a] The reaction was carried out in acetone/H_2O/THF = 1/1//1 at 0 °C in the presence of 20 mol % $ZnCl_2$.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using Chiralcel OJ unless otherwise noted.
[d] Determined by chiral GC analysis using Chrompack Chirasil-Dex-CB.
[e] Yield based on the recovered starting aldehyde is shown in parentheses.

In conclusion, we have developed a reusable resin-immobilized tripeptide catalyst for the DAAR of acetone and aldehydes in aqueous media. Further studies on the peptide catalyst bound to the solid support are now under investigation in this laboratory.[16]

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11. The coupling reaction was performed in *N*,*N*-dimethylformamide (DMF) using each 3.0 equiv of *N*-α-9-fluorenylmethoxycarbonyl (Fmoc) amino acid, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluorophosphate, and 1-hydroxybenzotriazole (HOBT) along with 6.0 equiv of diisopropylethyl amine. Completion of the peptide bond formation was assured by the negative Kaiser test. Then, the Fmoc group was removed by treatment with 20% piperidine in DMF. After the removal of the Fmoc group on the terminal proline residue, the side chain protecting group was removed with 95:5 (v/v) trifluoroacetic acid/H_2O, if necessary. The whole resin was successively washed with dichloromethane and ethanol, and dried under reduced pressure.
12. The results for the supported Pro-Phe-Phe catalyzed reaction in the same conditions using other additives (20 mol %) are as follows: yield (%) [ee (%)] = 47[56] for $NiCl_2$, 7[68] for $InCl_3$, 98[63] for $CeCl_3$, and 79[53] for no additives.
13. *General experimental procedure*. To a mixture of the peptide catalyst and $ZnCl_2$ (20 mol % each) in acetone/H_2O/THF = 1:1:1 (v/v/v) was added aldehyde (ca. 0.1 mmol, 83 mM) and was stirred at 0 °C for the given time. Then the mixture was filtered and the resin was washed with EtOAc. Solvent was removed under reduced pressure. The crude mixture was purified by using preparative TLC (Wakogel B-5F®, hexane/EtOAc = 1/1). The ^1H NMR of the product was identical with that reported earlier.
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