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Resin-supported acid- and base-catalyzed one-pot sequential reaction including an enantioselective step

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Abstract—One-pot sequential acidic deacetalization and basic enantioselective aldol reaction were realized using Amberlite IR-120 (H^+-form) and a resin-supported peptide catalyst, and the reusability of the catalysts was demonstrated.

Biosynthesis in the cells of living organisms goes through multistep enzymatic reactions to convert a starting material into the final product, without separation of intermediates. The reactions in biosynthesis are highly specific and selective. One of the current trends in organic synthesis is an emulation of nature, that is, the development of sequential reactions using multiple catalysts in a single reaction vessel.[1] In such a reaction system, it is very important that any two catalysts should not be reactive with each other. Otherwise, catalytic activity might be lost due to mutual deactivation. For example, acid catalysts are usually incompatible with base catalysts because these two catalysts form a salt. In this regard, several one-pot sequential reactions using both acid and base catalysts, suitably designed to avoid neutralization, have appeared. A pioneering example in this field is a one-pot deacetalization/intramolecular aldol condensation using a mixture of cation- and anion-exchange resins, reported by Stowell and Hauck, Jr. in 1981.[2] It took almost two decades before other examples emerged in succession. These were either sol–gel matrix encapsulated acid/base reagents,[3] acidic/basic layered clays,[4] star-shaped polymers having acidic/basic core sites,[5] or mesoporous silica concomitantly bifunctionalized by acids and bases.[6] However, all of these precedents gave either achiral or racemic products and none of them has succeeded in emulating nature's stereoselectivity in reactions.

On the other hand, we have previously reported on the polymer supported peptide catalyzed direct asymmetric aldol reaction in aqueous media.[7] In this reaction, the catalytic cycle is supposed to proceed under basic conditions through the formation of a chiral enamine, just like class I aldolase. As the peptide catalyst is supported on polymer resin, it is expected that the combination of this resin with solid-supported strong acids such as cation-exchange resins[8] would promote successive transformation from the acetal to the aldol product in a stereoselective manner via the intermediacy of the aldehyde.

In this Letter, we report the first enantioselective successive acid- and base-catalyzed reactions on solid supports in a single reaction vessel.

The hydrolysis of 4-nitrobenzaldehyde dimethyl acetal followed by aldol reaction with acetone was attempted (Table 1). Commercially available Amberlite IR-120 (H^+-form) was used as an acid catalyst. This resin is a divinylbenzene-crosslinked partially sulfonated gel-type polystyrene. As a base catalyst, PEG–PS resin-supported proline was employed. The reaction was performed in H_2O/acetone/THF = 1:1:1 (v/v/v) at room temperature in the presence of 20 mol % of resin-supported proline and Amberlite (entry 1). After 20 h, the reaction mixture was analyzed by ^1H NMR and shown to contain the starting acetal, 4-nitrobenzaldehyde, and the corresponding aldol product with acetone in a ratio of 4:9:87. This means that both the hydrolysis of the acetal and the subsequent aldol reaction proceeded smoothly. The degree of dehydration of the aldol product was almost negligible. This is in stark contrast to the results previously reported for a one-pot sequential deacetalization/aldol condensation.[1b,2,4,6] This might be due to the milder reaction conditions used in the

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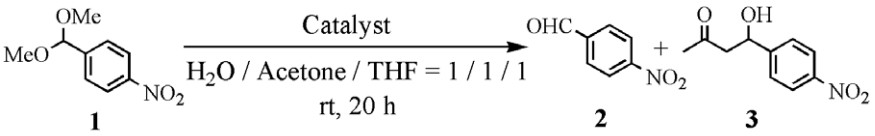
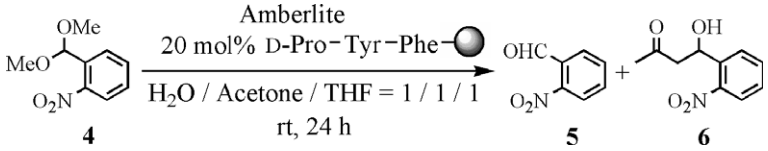
Table 1. One-pot tandem reaction using solid-supported acid and base catalysts



Entry	Catalyst	1:2:3[a]
1	20 mol % Pro–  + Amberlite	4:9:87[b]
2	20 mol % Pro– 	100:0:0
3	Amberlite	1:99:0
4	20 mol % Pro–  + 100 mol % *p*TsOH	0:100:0
5	20 mol % TFA·Pro– 	0:100:0

[a] Determined by crude ^{1}H NMR.
[b] Isolated yield of **3** was 70% and ee was 36% (*R* isomer was dominant).

Table 2. Reusability of catalysts



Entry	Reuse of catalyst	4:5:6[a]	ee of 6[b] (%)
1	First use	10:1:89[c]	73
2	Second use	9:3:88	77
3	Third use	8:3:89	77
4	Fourth use	9:4:87	77
5	Fifth use	10:6:84	79
6	Sixth use	7:7:86	76

[a] Determined by crude ^{1}H NMR.
[b] Determined by chiral HPLC analysis using Chiralcel OD-H.
[c] Isolated yield of **6** was 74%.

present study. As control experiments, reactions were performed in the absence of either of the two catalysts. Without Amberlite, the starting material was not consumed at all (entry 2). In the absence of the prolyl catalyst, 4-nitrobenzaldehyde became the only product (entry 3). When *p*-toluenesulfonic acid was used instead of Amberlite, a similar result was obtained, presumably due to neutralization of the weakly basic prolyl moiety (entry 4). A preformed salt of the prolyl catalyst also showed no catalytic activity for the aldol reaction (entry 5).

Next, an enantioselective version of this aldol reaction was attempted using a peptide having a sequence of D-Pro-Tyr-Phe supported on PEG–PS resin as a catalyst and 2-nitrobenzaldehyde dimethyl acetal as a starting material (Table 2). The reaction occurred at a similar rate and the corresponding aldol product was obtained (entry 1).[9,10] The enantioselectivity was of the same level as we have reported in a previous paper.[7] The reusability of the resin-supported catalysts was then examined (entries 2–6). The resins were easily separated from the reaction mixture by simple decantation and were thoroughly dried (N_2 flow and vacuum drying) before the next use. Although the rate of the aldol reaction somewhat decreased, almost the same level of catalytic activity was shown, even after the sixth use.

In conclusion, a one-pot cascade reaction including an enantioselective aldol reaction was realized using resin-supported acid and base catalysts, and catalyst reusability was demonstrated. This new usage of resin-supported acid and base catalysts can be expected to be applicable to a wide range of reaction sequences. Further study, including consecutive enantioselective reactions, is currently underway in this laboratory.

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9. Preparation of catalysts.
   Peptide catalyst (D-Pro-Tyr-Phe-PEG–PS): The resin-supported peptide catalyst was prepared by the standard Fmoc solid-phase peptide synthesis using terminally aminoethylated PEG–PS resin (amine loading = 0.20 mmol/g). The coupling reaction was performed in *N*,*N*-dimethylformamide (DMF) using 3.0 equiv each of *N*-α-9-fluorenylmethoxycarbonyl (Fmoc) amino acid, *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), and 1-hydroxybenzotriazole (HOBt) along with 6.0 equiv of diisopropylethylamine. The completion of peptide bond formation was assured by the negative Kaiser test. Then, the Fmoc group was removed by treatment with 20% piperidine in DMF. In this way, phenylalanine, *O*-*t*-butyl protected tyrosine, and D-proline residues were coupled in this order. After the Fmoc group on the terminal proline residue was removed and the resin was dried under reduced pressure, the protection group of the tyrosine was removed with 95:5 (v/v) trifluoroacetic acid/H_2O. The resin was successively washed with dichloromethane, DMF, triethylamine, DMF, dichloromethane, and ethanol, and dried completely under reduced pressure.
   Amberlite: Amberlite IR-120 (Na^+-form) was soaked with 1 N aqueous HCl and then collected by filtration. Soaking and filtration was repeated one more time. It was then thoroughly washed with water and dried under reduced pressure.
10. *General experimental procedure*: To a solution of 2-nitrobenzaldehyde dimethyl acetal (46.7 mg, 0.237 mmol) in 0.8 mL each of H_2O, acetone, and THF was added the peptide catalyst D-Pro-Tyr-Phe-PEG–PS (259 mg, 0.0479 mmol of prolyl group) and Amberlite (127 mg). The mixture was stirred at room temperature for 24 h. Then EtOAc was added to the reaction mixture and the supernatant solution was gathered by decantation. This extraction was repeated two more times. The crude mixture was obtained by removing the combined solvent under reduced pressure, and was analyzed by ^1H NMR to determine the conversion. Purification using preparative TLC (hexane/EtOAc = 1/1) afforded 36.9 mg (0.176 mmol, 74% yield) of aldol product **6**. The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column (hexane/2-propanol = 97/3, 1.0 mL min^{-1}; major isomer $t_R = 35.6$ min, minor isomer $t_R = 42.0$ min).