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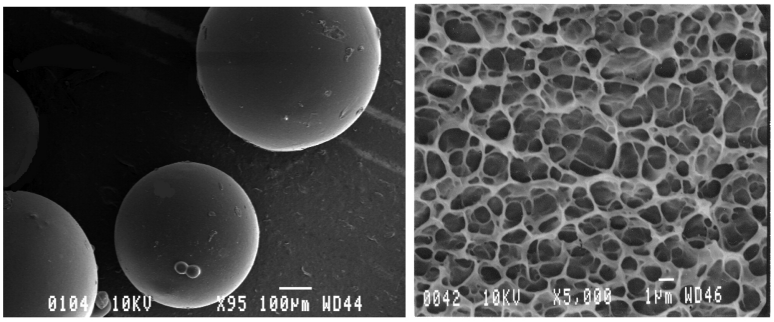

(A) **(B)**

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Functionalized Cross-Linked Poly(vinyl alcohol) Resins as Reaction Scavengers and as Supports for Solid-Phase Organic Synthesis

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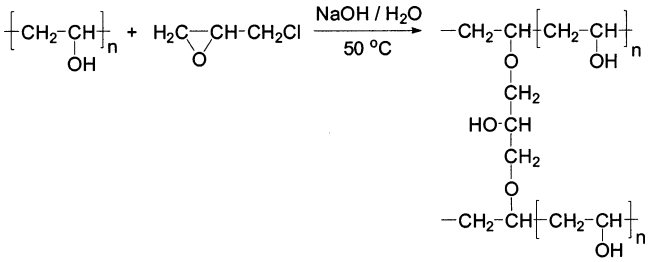
New hydrophilic poly(vinyl alcohol) (PVA-OH) resins were prepared by an inverse suspension polymerization using epichlorohydrin as a cross-linker. These novel resins swell in a variety of solvents commonly used in solid-phase organic synthesis, such as dicholomethane, dioxane, methanol, tetrahydrofuran, and dimethylformamide. In addition, PVA-OH shows excellent swelling in water. The cross-linked PVA-OH beads were functionalized with an aldehyde group and were tested as scavengers for primary amines in three different reactions: amide bond formation, reductive amination reaction, and urea formation. With 1−2 equiv of the PVA aldehyde resin, all the excess primary amines were successfully scavenged. The utility of PVA-OH resins as solid supports in mono- and dipeptide synthesis was also investigated using symmetrical anhydride and MSNT/MeIm (2,4,6-mesitylenesulfonyl-3-nitro-1,2,4-triazolide in the presence of 1-methylimidazol) methods.

Introduction

Combinatorial chemistry approaches commonly rely upon functionalized cross-linked polymers as solid supports for solid-phase organic synthesis (SPOS) and as scavengers to facilitate the purification of solution-phase chemistries.[1] In the arena of SPOS, there is continued interest in identifying more versatile solid supports. For example, resins that swell in a broad range of solvents should allow for the development of new solid-phase reactions.[2] The use of solid supports as scavengers to facilitate purification in solution-phase chemistry has also gained widespread acceptance.[3] For example, polymer resins bearing aldehyde groups have been used to selectively scavenge primary amines in the presents of secondary amines.[4] The main drawbacks of the scavenging approach are, however, the high cost of these supports coupled with the need to use them in large quantities due to low loading levels. There is a need to find practical polymeric scavengers for use in polymer-assisted solution-phase synthesis.

Poly(vinyl alcohol) (PVA-OH) is a common polymer readily available in different molecular weights and degrees of hydrolysis. A resin-based on PVA-OH, with one hydroxyl group per repeating unit, can in theory possess very high loading and thereby be an ideal support for SPOS in polar organic solvents, including water. Although PVA and cross-linked PVA hydrogels have been intensively investigated in many fields,[5−9] few efforts have been made to use this material as scavenger resins or as supports for solid-phase synthesis. In our recent work, cross-linked PVA-OH beads have been prepared by an inverse suspension polymerization using epichlorohydrin as a cross-linker.[10] Herein, we report the preparation of cross-linked PVA aldehyde resins and their use as scavenger resins for primary amines. The utility of PVA-OH resins as solid supports in mono- and dipeptide synthesis was also investigated using symmetrical anhydride[11] and MSNT/MeIm (2,4,6-mesitylenesulfonyl-3-nitro-1,2,4-triazolide in the presence of 1-methylimidazol) methods.[12]

Scheme 1. Preparation of the Cross-Linked PVA Beads



Results and Discussion

Preparation of Cross-Linked PVA-OH Beads. Cross-linked PVA-OH beads were prepared by inverse suspension polymerization, as illustrated in Scheme 1. The conditions were optimized in our previous work.[10] The cross-linking density and the mechanical properties are dependent on the amount of cross-linker and the duration of the precross-linking. The effect of the amount of the cross-linker on the loading, swelling, and macroporous nature of the cross-linked beads has been reported in our previous paper.[10] PVA-OH

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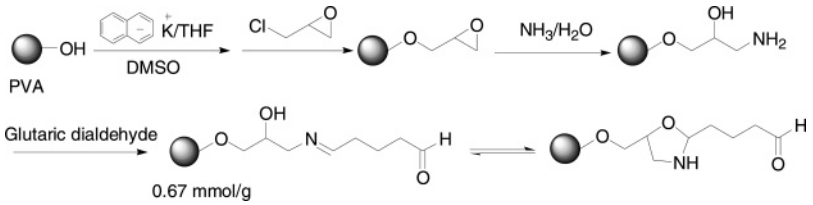
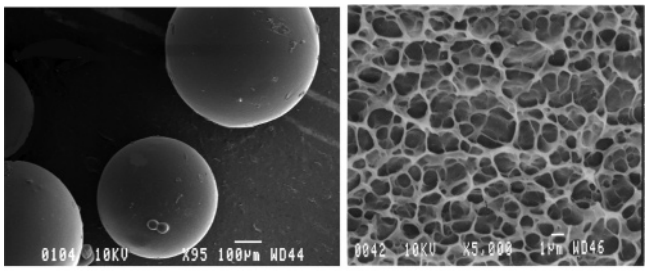
Scheme 2. Functionalization of the Cross-Linked PVA-OH Beads





(A) (B)

Figure 1. (A) Optical microscopic view of the cross-linked PVA beads and (B) scanning electron micrograph (SEM) of the porous structure of the cross-linked PVA beads.

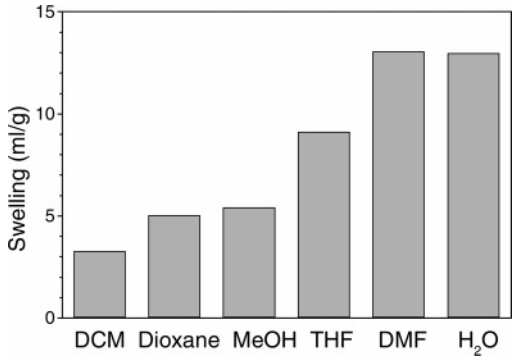


Figure 2. Swelling of the cross-linked PVA beads in various solvents.

beads with good particle shape and porous inner structure could be obtained when 7 mL of epichlorohydrin was used for the cross-linking as shown in Figure 1. It is clear from Figure 1B that the cross-linked PVA-OH beads are macroporous, which is expected to improve the accessibility of reagents to the resin. In this work, we used 7 mL epichlorohydrin during precross-linking and obtained beads with good swellability and fine macroporous structure.

Swelling Properties. An important physical property of a resin which determines its applicability to SPOS is its swelling properties. Swelling is usually measured by the volume change of beads before and after swelling[13,14] or by the weight increase of beads in the solvents.[15] We have measured the weight difference between the dry and the swollen beads and have expressed the swelling as volume per gram of beads. Figure 2 shows that the cross-linked PVA-OH beads swell in a range of solvents ranging in polarity from DCM to water. In DMF and water, the swelling of cross-linked PVA beads is 13 mL/g, whereas in a less polar solvent, such as DCM, the swelling is 3 mL/g. The excellent swelling properties in DMF and water make these PVA-OH resins ideal for use in SPOS, in which water may be the solvent or cosolvent.

Loading of Cross-Linked PVA-OH Beads. The loading of the solid support in combinatorial chemistry can influence the sensitivity of assays and on-bead analysis. Resins with low functional density are suitable for analytical purposes, such as sensitive on-bead screening of receptors (enzymes and antibodies), whereas resins with high loading find applicability in solid-phase synthesis and in scavenging reactants. PVA-OH has one functional group (OH) per repeating unit and can reach a theoretical high loading of 22.7 mmol/g. Cross-linking, however, reduces the number and the accessibility of the secondary alcohol groups and therefore decreases the loading of the cross-linked PVA-OH. In this study, the loading of the PVA-OH resin was measured by reaction of the PVA-OH resin with acetic anhydride in pyridine. The average loading of the cross-linked PVA-OH resin (with 7 mL of epichlorohydrin as a cross-linker) was 17.3 mmol/g.

Functionalization of PVA-OH Beads. A large variety of functional groups can be introduced into the PVA-OH beads by chemical modification of the hydroxyl groups. We chose a simple three-step procedure to convert the hydroxy to a terminal aldehyde group, as illustrated in Scheme 2. Elemental analysis of the nitrogen content of the PVA aldehyde resin showed the final loading to be 1.88 mmol/g. The amount of aldehyde groups was titrated to be 0.67 mmol/g by a rapid fluorescence determination.[16] The decrease of loading in comparison to the PVA resin may be due to the low reactivity of the secondary alcohol groups, and some of the OH groups may not be accessible in the cross-linked beads. The difference of the aldehyde loading determined by elemental analysis and fluorescence may be from two sources: one is the formation of a bicyclic product (reaction of the aldehyde group with the cyclic secondary amine in the five-membered ring shown in Scheme 2), and the other is the possible coupling of glutaric dialdehyde with two amine groups on both ends. However, the swelling profiles of the functionalized beads were practically the same as the original cross-linked PVA beads (error < 3%, data not shown), which is an indication that there was no significant further cross-linking during this step.

Reaction Scavenging. The PVA-aldehyde resins were tested as scavengers of excess primary amines in three different reactions: amide bond formation, reductive amination, and urea formation, as shown in Scheme 3. *p*-Anisidine and 4-methoxybenzylamine were chosen as representative primary amines, allowing for easy comparison of the ^{1}H NMR spectra between the products and starting amines. In each case, 2 molar equiv of the primary amines were reacted with 1 equiv of an electrophile. After reaction workup, the molar ratio of the product to the primary amine

Scheme 3. Evaluation of Functionalized PVA Aldehyde Beads as Scavengers of Primary Amines

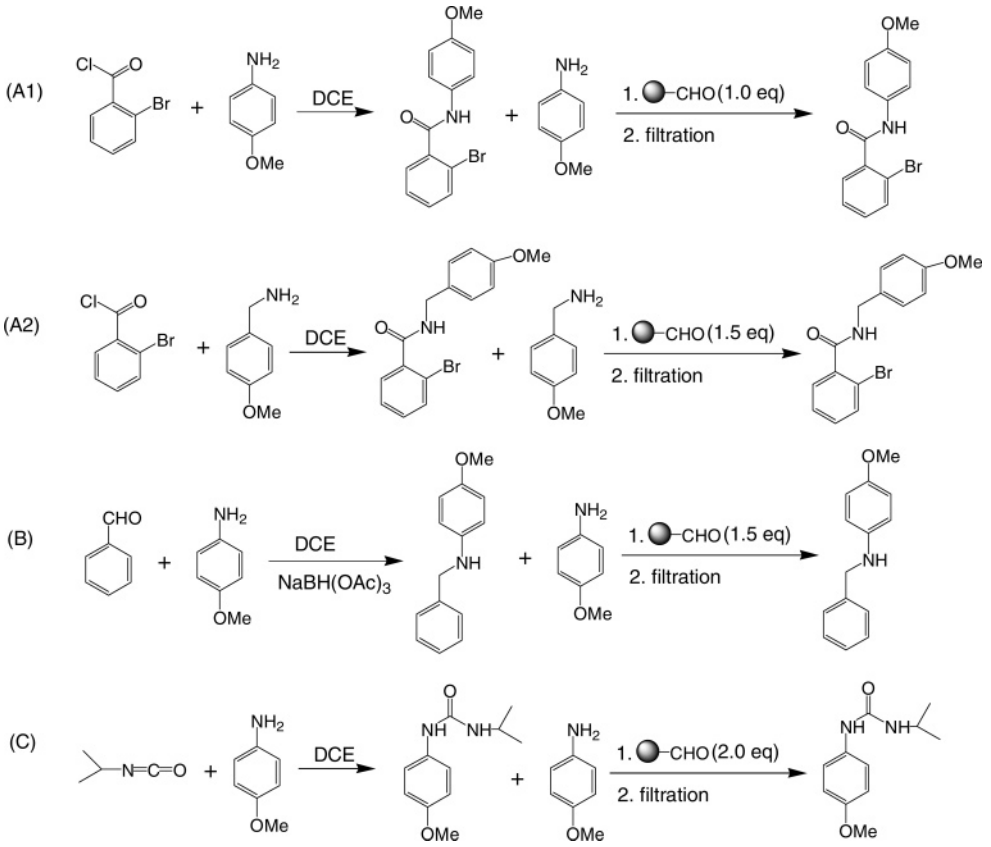


Table 1. Evaluation of the PVA-Aldehyde Resin as a Scavenger of Primary Amines

		product/amine ratio[b]			
reaction	resin amt (equiv)[a]	before adding resin	after adding resin	purity (%)[c]	yield (%)[d]
A1	2.0	2/1	1/0.06	>95	94.8
A2	2.0	2/1	1/0	>95	70.1
B	1.0	1/1	1/0.33	75	
	2.0	2/1	1/0	>95	90.4
C	1.0	1/1.5	1/0.36	67	
	1.5	1/1.5	1/0.075	93	
	2.0	2/1	1/0	>95	92.3

[a] Resin amount in equivalents. All reactions used 1 equiv of electrophile and 2 equiv of primary amine. [b] The product/amine ratios were determined by the integration of ^{1}H NMR signals. [c] Purity was determined by ^{1}H NMR analysis. [d] Yield measured by weight after scavenging with the resin.

was determined by ^{1}H NMR spectroscopy. The PVA-aldehyde resin was then added to scavenge leftover primary amine. Table 1 shows the results obtained on the basis of ^{1}H NMR analyses. In amide bond formation reaction A1, the molar ratio of product (the amide) to the primary amine before adding the PVA aldehyde resin was 2/1. After the addition of this scavenger resin, the excess primary amine was removed successfully, as shown in Figure 3. The ^{1}H NMR signals (Figure 3a) at 6.62−6.76 ppm are the aromatic protons of the *p*-anisidine, and the signals at 6.88−6.94 ppm and 7.51−7.55 ppm are attributed to the *p*-anisidine protons in the product. After the addition of the resin, as shown in Figure 3b, the ^{1}H NMR shows that the leftover *p*-anisidine has been successfully scavenged. Similarly, in amide formation A2, the molar ratio of the product to 4-methoxybenzylamine is 2/1, indicating a complete conversion of acid chloride to amide. After scavenging with PVA aldehyde resin, no trace of the primary amine was found in the mixture. For reductive amination B, the reaction proceeded to completion, as indicated by the molar ratio of secondary amine to the starting *p*-anisidine of 1/1. The leftover *p*-anisidine (1 equiv) was scavenged effectively with 2 equiv of aldehyde resins. In urea formation C, in which the reaction proceeded to only ∼50% conversion, all leftover *p*-anisidine could be scavenged with 2 equiv of PVA aldehyde resin. In all cases, the PVA aldehyde resin successfully scavenged all of the leftover primary amines, affording clean products.

It has been reported that scavenger resins can themselves become a source of impurities in reaction mixtures due to the leakage of linkers or the instability of the functional groups under the conditions used.[17] It is noteworthy to report that in our case, no such impurities were found during the scavenging reaction, which indicates that the functionalized PVA resins are clean and efficient in these reactions.

Mono- and Dipeptide Synthesis Using Cross-Linked PVA as a Solid Support. We have also briefly explored the use of the PVA-OH resin as a solid support for mono and dipeptide synthesis. Fmoc-Gly-OH was linked to the PVA-OH resin by the MSNT/MeIm and symmetric anhydride routes, as reported in Table 2. The MSNT/MeIm method gave a loading of 2.53 mmol/g, which was better than the 1.5 mmol/g from the symmetric anhydride method. The loading of the Fmoc-Gly-OH on the resin was determined by UV analysis of the liberated Fmoc group. The drop

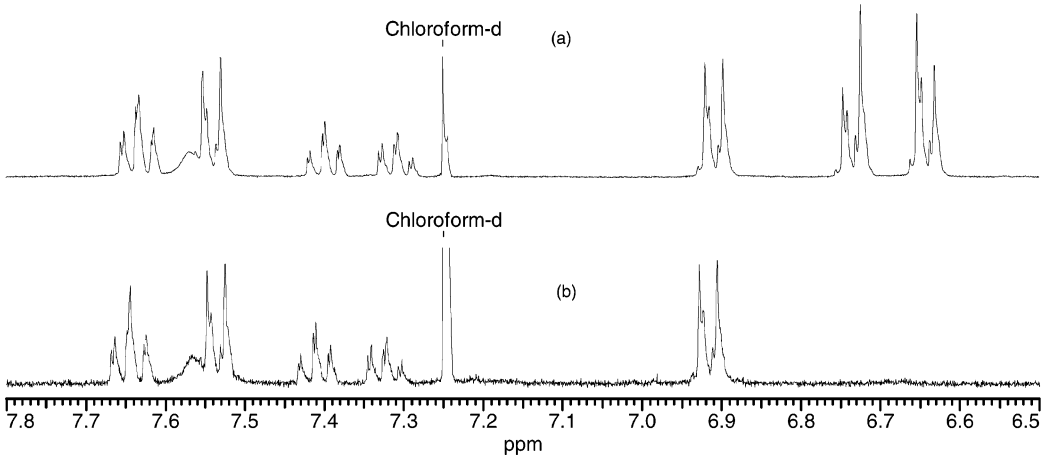


Figure 3. ^{1}H NMR spectra of the amide formation (reaction A) before (a) and after (b) the addition of PVA aldehyde resin.

Table 2. Attachment of Fmoc-Gly-OH to the Cross-Linked PVA-OH Resin[a] via Esterification

method	Fmoc-Gly-OH (equiv)	MSNT (equiv)	MeIm (equiv)	final loading[b] (mmol/g)	yield[c] (%)
MSNT/MeIm	5	5	3.75	2.53	58
		DICPDI	DMAP		
symmetric anhydride	5	2.5	0.1	1.51	26

[a] The original loading of the resins was 17.3 mmol/g determined by acetic anhydride method. [b] The final loading of the resins was determined by UV analysis at 290 nm. Measured the amount of FMOC group liberated upon treatment with 20% piperidine. [c] Yield was calculated by the ratio of final loading to original loading.

in loading from the PVA-OH beads (17.3 mmol/g) may be attributed to the low reactivity of the secondary alcohol group and potentially inaccessibile OH groups in the PVA resin. Although the yield of first attachment of the amino acid residue was relatively low, 58%, the final loading (2.53 mmol/g for MSNT/MeIm method) was higher than that of polymer supports currently available from commercial sources.[15]

The synthesis of a dipeptide was investigated. The coupling of Fmoc-Ala-OH and Fmoc-Phe-OH to the NH_2-Gly-O-PVA resin was performed after the free hydroxyl groups on PVA-OH beads were capped by reacting with acetyl chloride (Table 3). Good conversion to the dipeptide-O-PVA resin was achieved as determined by the final loading of the resin (95 and 92% yields by weight). Cleavage of the dipeptides from the resin was tried using 0.5 M NaOH in 2-propanol and resulted in the isolation of the dipeptide, NH_2-Phe-Gly-OH, in a low yield of ~40%. This was expected, since the secondary alcohol ester can be difficult to hydrolyze. More labile linkers would be beneficial, and work is in progress in our laboratories addressing this issue.

Conclusion

Hydrophilic PVA-OH can be cross-linked to make spherical macroporous resin beads with high loading of OH functional groups. The PVA-OH resins can be further functionalized to aldehydes. The PVA aldehyde resins, in turn, can serve as a scavenger to remove the excess primary amines. The reactivity of PVA-OH resins possessing free secondary hydroxyl groups was also tested as a support in solid-phase peptide synthesis. The high loading of the resins makes them ideal candidates for some applications, but conversion of the secondary OH groups to more reactive functional groups would render these resins more suitable as solid supports. The hydrophilic property, the high loading and the possibility to introduce different linkers and functional groups should make these resins promising for use in a variety of organic reactions, both as scavengers and as supports. Work is under way to explore the addition of special linkers to facilitate reactions in organic and aqueous media.

Experimental Section

Materials and Chemicals. Poly(vinyl alcohol) (98% hydrolyzed, with molecular weights of ~13 000 to 23 000) and epichlorohydrin (EP) (99%) were purchased from Aldrich; Fmoc-amino acid was purchased from Novabiochem; *N*-hydroxybenzotriazole hydrate (HOBt), 1-(mesitylene-2-sulfonyl)-3-nitro-1*H*-1,2,4-triazole (MSNT) and *N*-

Table 3. Coupling Yields of Fmoc-Amino Acids to NH_2-Gly-O-PVA Resin

amino acid derivatives	method	loading of starting material: FMOC-Gly-O-PVA[a] (mmol/g)	final loading[b] (mmol/g)	yield[c] (%)
Fmoc-Ala-OH	HATU/DIPEA	2.13	2.02	95
Fmoc-Phe-OH	HATU/DIPEA	2.13	1.97	92

[a] The free hydroxyl groups of the PVA resins were capped by acetyl chloride after the attachment of the first amino acid (Fmoc-Gly-OH), and the loading was checked again by UV at 290 nm. [b] The final loading of the resins was determined by UV analysis at 290 nm. Measured the amount of FMOC group liberated upon treatment with 20% piperidine. [c] Yield was calculated by the ratio of final loading to original loading.

methylimidazole (MeIm, redistilled, 99%) were purchased from Aldrich, [*o*-(7-azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU) was purchased from PE Biosystems. Potassium naphthalene solution in THF was prepared directly by the reaction of naphthalene with potassium in dry THF, and the concentration was titrated to be 0.45 M with the standard hydrochloric acid solution (0.1918 N). DMSO was dried with CaH_2 for 48 h and distilled. All other chemicals and solvents were purchased from Aldrich and were used without further purification.

Instruments. Scanning electron microscopy was performed on a JEOL, JSM-8400; ^{1}H NMR spectra were recorded on a Varian 400GX Fourier transform spectrometer; LC/MS measurements were performed on a Hewlett-Packard model 1100 instrument equipped with a PDA mass detector; UV spectra were recorded on Spectrophotometer 8453 (Agilent Hewlett-Packard) at 290 nm. Fluorescence spectra were recorded on an Edinburgh Instrument F-900 spectrometer. The wavelength of the excitation light was set at 345 nm, and the emission spectrum was recorded from 400 to 680 nm. The concentration of the unreacted dye was quantitated through the maximum emission at 540 nm.

Preparation of Cross-Linked PVA Beads. Cross-linked PVA beads were prepared as described previously.[10] After filtration, the beads were extracted using a Soxhlet extractor successively with water, ethanol, and acetone for 24 h to remove all the impurities. Then the beads were freeze-dried under vacuum.

Swelling of PVA beads in different solvents were investigated by monitoring the weight gain of the beads in the solvents. The preweighed dry PVA beads were placed into permeable bags, which were immersed into the selected solvents for 24 h at 21 °C. The excess solvents were removed by filtration, and the PVA beads were weighed in the bottles with cap so as to prevent the solvent from evaporation. The swelling volume (V_s) was calculated according to

$$V_s = \frac{M_2 - M_1}{M_1} \times \frac{1}{\rho}$$

where M_2 is the total weight of PVA beads with absorbed solvent, M_1 is the weight of the dry PVA beads, and ρ is the density of the solvent.

Determining the Loading of the Cross-Linked PVA-OH Beads. A 150-mg portion of PVA beads was placed in a 100-mL flask, followed by the addition of 1.0 mL of acetic anhydride and 5.0 mL of pyridine. The mixture was stirred at 60 °C for 12 h. At the end of the acetylation, 1.0 mL of water was added to the flask to convert the excess acetic anhydride into the corresponding acetic acid. The reaction mixture was titrated at room temperature with 0.501 N NaOH aqueous solution using a pH meter to record the titration curve. A blank control titration was made in the same way.

Functionalization of Cross-Linked PVA-OH Beads. A 1.0-g portion of PVA beads were placed into a 100-mL flask, and 25 mL of dry DMSO was added to swell the PVA resin. A known amount of potassium naphthalene solution in THF (0.45 M, 15 mL) was introduced into the flask via a double-tip syringe needle by high-pressure nitrigen, and the mixture was stirred for ~1 h. The dark green color of the mixture disappeared, and 3 mL of epichlorohydrine was introduced into the flask and agitated at 40 °C for 12 h. The epoxy resin was rinsed with large quantities of water, THF, and ethyl ether and dried in a vacuum oven overnight. The amination of the epoxy resin was accomplished by reacting 1 g of the dry beads with 15 mL of NH_3/H_2O for 4 h and then freeze-drying under vacuum. The dry beads were further reacted with 15 mL of 20% glutaric dialdehyde, agitated for 2 h, and washed thoroughly with water. The beads were freeze-dried again. The absolute amount of aldehyde group on the PVA resin was analyzed by fluorescence determination of the excess dansylhydrazine that was left after the reaction of PVA aldehyde resin with an approximately 2-fold excess of dansylhydrazine.[16]

Scavenging Amines Using Functionalized PVA Beads. Reaction A: Amide Formation (Reaction A1). To a small flask were added 0.1 mmol 2-bromobenzoyl chloride, 0.2 mmol *p*-anisidine (4-methoxyaniline), and 1 mL dichloroethane (DCE). After the mixture was stirred at room-temperature overnight, water was added to decompose the 2-bromobenzoyl chloride. The water phase was washed with DCE several times, and the oil phase was combined and dried over magnesium sulfate. After filtration, the solution was evaporated under vacuum. ^{1}H NMR spectrum of the dry product in chlorom-*d* ($CDCl_3$) was recorded. PVA-aldehyde resin (2 molar equiv) was added to the DCM solution of the crude products, and the mixture was shaken for 2 h. The product mixture was analyzed by ^{1}H NMR.

The amide formation reaction (reaction A2) was carried out in an identical manner, but *p*-anisidine (4-methoxyaniline) was replaced by 4-methoxyphenethylamine.

Reaction B: Reductive Amination. To a small flask, 0.1 mmol of benzaldehyde, 0.2 mmol of *p*-anisidine, 0.5 mmol of sodium hydroboroacetate, 3 drops of acetic acid, and 1 mL of DCE were added and stirred overnight. Workup was accomplished by washing the reaction mixture with 1 M NaOH solution. The solution was dried over magnesium sulfate and filtered. The solvent was evaporated under vacuum. The scavenging procedure was identical to that in reaction A.

Reaction C: Urea Formation. To a small flask were added 0.1 mmol isopropyl isocynate, 0.2 mmol *p*-anisidine (4-methoxyaniline), and 1 mL DCM. After the mixture was stirred overnight, the solution was concentrated in vacuo and analyzed by ^{1}H NMR. The scavenging procedure was the same as in reaction A.

Peptide Synthesis Using PVA Beads as Supports. Fmoc-Gly-OH was attached to the cross-linked PVA-OH beads by the use of symmetrical anhydride[11] and MSNT/MeIm[12] methods. After attachment of Fmoc-Gly-OH, any remaining hydroxyl groups on the resin were capped by reacting with acetyl choloride (2 equiv) in the presence of *N*,*N*-diisopropylethylamine (DIPEA, 2 equiv) at room temperature for 2 h. The coupling of Fmoc-Ala-OH and Fmoc-Phe-OH to the NH_2-Gly-O-PVA resin was carried out using HATU (5 equiv) and DIPEA (10 equiv) in DMF at room temperature. After the reaction (12 h), the resins were washed successively with DMF (5×); DCM (5×); MeOH (3×); and finally, with

diethyl ether (2×). Fmoc deprotection of the resins was accomplished with 20% piperidine in DMF (10 min) followed by washing with DMF (5×), DCM (5×), MeOH (3×), and diethyl ether (2×). The resins were dried under vacuum, and the loading of the Fmoc-amino acid was measured by UV analysis of the released Fmoc chromophore at 290 nm. Cleavage was performed using 0.5 N NaOH/2-propanol under refluxing conditions for 3 h.

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