Preparation and Characterization of Reactive Macroporous Polymers Bearing Highly Accessible Functional Groups Obtained via Protective Group Chemistry†

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Polymerization of the protected functional monomers (4-vinylphenyl)diethoxymethane (1), *N*-[(4-vinylphenyl) methylene]-4-methoxy aniline (2), 4-((trifluoroacetamido)methyl)styrene (3), and 4-[[(*tert*-butoxycarbonyl)amino]methyl]styrene (4) with divinylbenzene as cross-linker in the presence of toluene as porogen led to macroporous functional polymeric supports. The polymers obtained have high surface area and pore volume as is evident from BET and electron microscopic study. Facile and near-quantitative elimination of the protecting groups of these polymer-bound functional groups reveals the permeability of these sites to the chemical reagents. This approach to reactive polymers is a novel methodology to obtain insolubilized functional polymer matrices with defined structures without interference of the functional groups during polymerization. Such materials are anticipated to find applications in newer types of polymer-aided chemistry.

Introduction

The motivation for developing cross-linked reactive polymers is attributed to the multitude of technological applications of these materials in separation science, organic synthesis biotechnology, etc.[1-3] Accessibility of the functional groups in these solid supports toward different chemical and biological agents is critical to their effectiveness for these applications. Thus, developing synthetic methodologies for easy incorporation of functional groups in the insoluble matrices as well as their location in the accessible regions of the matrices is of great significance. Fundamentally, two different approaches have been adopted for the preparation of functionalized polymer matrices: (a) chemical modification of a preformed polymer and (b) polymerization/copolymerization of appropriate functional monomers.[4,5] Both of the approaches present specific advantages and shortcomings. But the most important factor that governs their utilities is the structural homogeneity of the functional matrices and accessibility of the functional groups incorporated in these matrices.

Highly cross-linked polymeric networks, due to their rigid structures, offer superior thermomechanical properties and hence can often withstand severe experimental conditions such as high pressure and temperature.[6] But their poor solvation (swelling) in different solvents would render the functional groups less accessible to chemical manipulations. Therefore, the fundamental challenge in designing such types of functional polymers is to tailor structures with functional groups located in the accessible regions of the polymer surfaces. Our long interest in functional polymer chemistry[7] led us to pursue a systematic investigation on the synthesis and characterization of macroporous reactive polymers obtained through copolymerization of functional monomers. To eliminate the interference of naked functional groups (viz. aldehyde, amine, etc.[8]) with polymerization reactions, we have masked the functional groups of the monomers using well-known protecting group chemistry.[9] Accessibility of the functional groups in these polymers can be evaluated from the efficiency of deprotection of the masked functional groups in these macroporous matrices. Thus, extent of removal of protecting groups would manifest the nature of microenvironments and functional group locations in the matrices. This would provide the guidelines for the subsequent usefulness of these polymers for specific applications.

Toward this end, we have prepared macroporous polymer matrices of functional monomers bearing amino and aldehyde functional groups in protected form. Different types of protecting groups were used to evaluate their usefulness in insoluble polymeric systems. The Fourier transform infrared (FTIR) spectroscopy has been utilized to analyze the reaction sequences occurring during the

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deprotection process as well as reactivity of these functional groups toward different chemical reagents. The results obtained in this investigation are presented in this paper.

Results and Discussion

Synthesis of Monomers. Reactivity of aldehyde and amino groups toward a number of functional groups under mild conditions makes the reactive polymers bearing such functionalities particularly interesting.[10,11] However, such reactive groups also interfere with the polymerization reaction yielding ill-defined structures due to secondary reactions involving chain transfer, cross-linking, etc.[12] This necessiates protection of these functional groups to obtain well-defined polymer structures. *Protective group* approach has been utilized in the past to synthesize a number of linear, soluble functional polymers.[13] As protecting groups, we have chosen azomethine and acetal groups for masking aldehyde functionalities. For amino groups, trifluoroacetyl (TFA) and *tert*-butyloxycarbonyl (*t*-BOC) protecting groups were choosen. Four different monomers with masked functional groups thus obtained are (4-vinylphenyl)diethoxymethane (1), *N*-[(4-vinylphenyl)-methylene]-4-methoxyaniline (2), 4-((trifluoroacetamido)-methyl)styrene (3), and 4-[[(*tert*-butoxycarbonyl)-amino]methyl]styrene (4). The monomers 1 and 2 contain masked aldehyde groups and monomers 3 and 4 contain masked amino groups.

Earlier reported synthesis of the acetal protected vinyl benzaldehyde involves a multistep procedure.[14] A one-step Wittig reaction to obtain this monomer 1 directly in the protected form from a readily available starting material has been reported recently.[15] Standard Schiff base formation reaction involving 4-vinylbenzaldehyde and 4-methoxyaniline offered the monomer 2. For the synthesis of 3 and 4, 4-vinylbenzylamine was subjected to appropriate protective group chemistry. Methods for the synthesis of 4-vinylbenzylamine (in isomerically pure form) reported in the literature are tedious multistep processes.[16] We developed a relatively simpler method to synthesize this compound. Reduction of 4-cyanostyrene (conveniently prepared by Wittig reaction)[17] with lithium aluminum hydride offered the desired amino derivative in satisfactory yield. Treatment of this 4-vinylbenzylamine with trifluoroacetic anhydride and di-*tert*-butyl dicarbonate offered 3 and 4, respectively. All the four monomers except 1 are crystalline solids and satisfactory analytical data testify to their purity.

Preparation of Macroporous Polymers Containing Protected Functional Monomers. Objective of this research effort is to prepare rigid functional polymer networks exhibiting efficient accessibility of the functional groups toward different chemical operations. The key to obtaining such polymeric matrices is the preparation of macroporous polymeric networks possessing appropriate surface area and porosity. This type of surface property would result in locating the functional groups on the porous surfaces and hence can be available for chemical manipulations in the solid phase. Extensive efforts have been undertaken in recent years to monitor the surface morphologies of the macroporous polymers and several variables have been identified to obtain such materials with tailored surface properties.[18] There are several factors which can determine the pore size, pore volume, surface area, and accessibility of the sites in a macroporous polymer matrix. But the most important determinants are the initial concentration of monomers in the polymerization mixture and solvating property of the porogenic agent. On the basis of the documented experimental parameters to prepare macroporous polymers with larger pores and high surface areas, we have evolved optimal conditions for the synthesis of our macroporous functional polymer networks. Toluene was selected as the porogenic agent for this study and the concentration of the monomer mixture in toluene was 50% (v/v) in each case. The monomer mixture consisted of ~10 mol % functional monomer and 25 mol % styrene and the remaining being commercially available divinylbenzene. After polymerization followed by working up to remove the soluble contaminants, the polymers were ground and sieved to appropriate particle sizes. Morphological properties of the polymers were studied by different surface analytical techniques. The surface area and pore volumes of the polymer particles were determined by nitrogen adsorption technique (BET analysis). The results thus obtained along with polymer composition data are summarized in Table I. These polymers possess high surface area and larger pore volumes, thus indicating the formation of macroporous structures. The current results parallel the earlier observations that use of a porogen (above a critical concentration) which is a good solvent for the polymer chain results in macroporous networks with large pores and adequate surface area.[16b,18a] Scanning electron microscopy (SEM) provides a further line of evidence to the presence

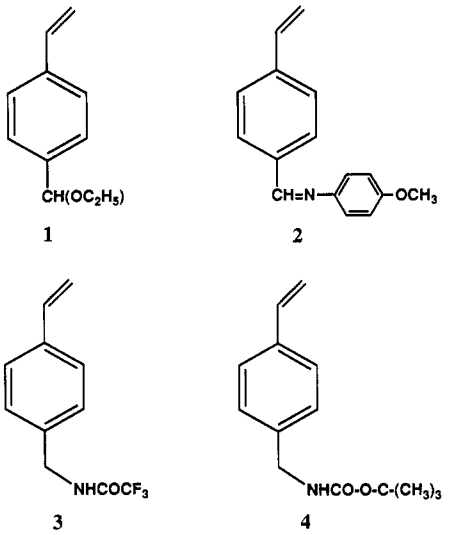

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Table I. Preparation and Characterization of the Macroporous Reactive Polymer Networks Bearing Protected Functional Groups

polymer code	type of functional monomer	mol % of the functional monomer[a]	specific surface area (m^2/g)	pore vol (cm^3/g)
P-1	1	10	252	1.32
P-2	2	9.5	255	1.25
P-3	3	10.5	245	1.35
P-4	4	9.0	248	1.28

[a] All the copolymers contain 25 mol % styrene and remaining constituents of the copolymers are commercially available divinylbenzene in addition to the appropriate amounts of the respective functional monomers.

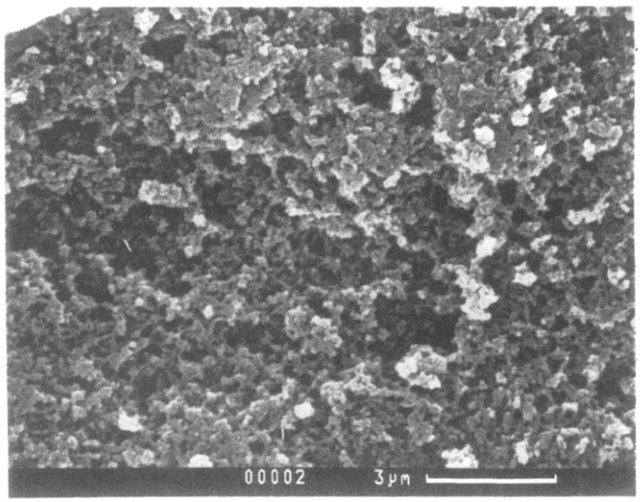

Figure 1. SEM photomicrograph of the macroporous copolymer matrix containing 1 as the functional monomer.

of macroporous morphology in these matrices. A typical micrograph of the copolymer **P-1** prepared using **1** as the functional monomer is shown in Figure 1 which illustrates the presence of macroporous texture. The state of the masked functional groups in the polymer matrices was investigated by FTIR spectroscopy, which reveals their stability during polymerization and subsequent workup operation (vide infra).

Deprotection of Polymer-Bound Masked Functional Groups. Although macroporous polymeric supports possess superior materials properties, rigid structures resulting from high cross-linking density present limitations for diffusion of chemical agents toward the functional groups embedded in the matrix. While surface analytical techniques provide information on structure and porous morphologies of such polymers, evaluation of the nature of the microenvironment and the reactivity of functional groups (and hence their accessibility) needs chemical probes. Thus, the extent of reactivity of these polymer-bound functional groups would be dependent on their location in the accessible regions of the polymer surfaces. The type of protective groups used in the present study are known to be removed quantitatively in low molecular weight organic compounds as well as linear soluble polymers.[13] Hence, the ease with which these protective groups can be removed from these macroporous polymeric matrices would reflect their availability for subsequent chemical manipulations.

The acetal and azomethine protecting groups are usually removed by acid-catalyzed hydrolysis. We deprotected the acetal groups in the copolymer **P-1** in the solid phase by treating the polymer particles in dioxane containing

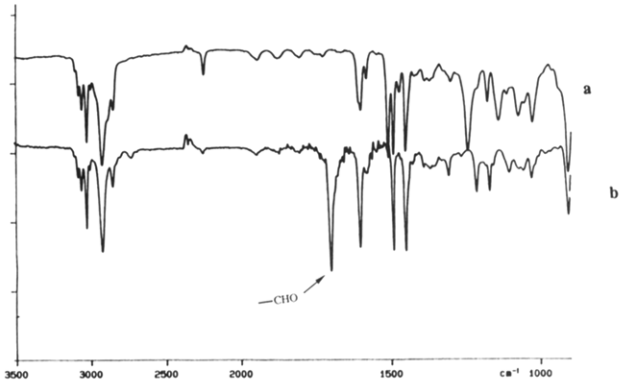

Figure 2. Infrared spectra of the macroporous copolymer of **1** and DVB: (a) before hydrolysis and (b) after hydrolysis.

aqueous trifluoroacetic acid. The reaction mixture was heated to 80 °C with constant stirring under nitrogen and was kept at this temperature for 12 h. After filtration, the polymer particles were thoroughly washed with methanol and dried to constant weight. Under this condition, it is possible to cleave the acetal group quantitatively to obtain aldehyde-functionalized copolymers. Generation of the aldehyde group and disappearance of acetal group was monitored by FTIR spectroscopy. The spectra of the pre- and posthydrolyzed copolymers are shown in Figure 2. The spectrum (Figure 2a) of the unhydrolyzed copolymer **P-1** shows the vibration band at 1150 cm^{-1} due to ethereal C–O–C stretching and no peak is evident due to carbonyl functionality. In case of the hydrolyzed copolymer (**P-1h**), as can be seen from Figure 2b, the stretching band at 1150 cm^{-1} disappeared and is replaced by a new peak at 1695 cm^{-1} corresponding to the vibrational stretching of the aldehyde carbonyl group. Copolymer **P-2** containing an azomethine-protected aldehyde functional group was hydrolyzed in a similar manner. But the only variation was the use of dilute HCl instead of trifluoroacetic acid. The infrared analysis of the polymer **P-2** and its hydrolyzed product (Figure 3) attests to the complete deprotection. A characteristic C=N stretching band at 1640 cm^{-1} due to the azomethine group in the polymer **P-2** (Figure 3a) is absent in the spectrum of the hydrolyzed polymer (**P-2h**). In the latter case, instead a new peak at 1695 cm^{-1} is evident in the FTIR spectrum (Figure 3b) indicating the generation of the aldehyde functional group. In both cases the deprotection reactions are evidently quantitative. These findings demonstrate the versatility of such types of protecting groups in solid-phase chemical manipulations. Furthermore, quantitative deprotection also attests to highly macroporous textures of these copolymer networks where the functional groups are located in the accessible microenvironments, facilitating the diffusion and reaction of reagents at these sites.

Functional polymer networks with protected amino functionality were prepared by polymerizing TFA and *t*-BOC protected vinyl benzyl amine (**3** and **4**) monomers. These types of protecting groups have been found to be easily cleaved as is reported in peptide synthesis literature.[19] A recent report describes complete removal of *t*-BOC groups used to protect phenol moieties in macroporous polymers.[20] But removal of such protecting groups used for masking amines in macroporous polymers re-

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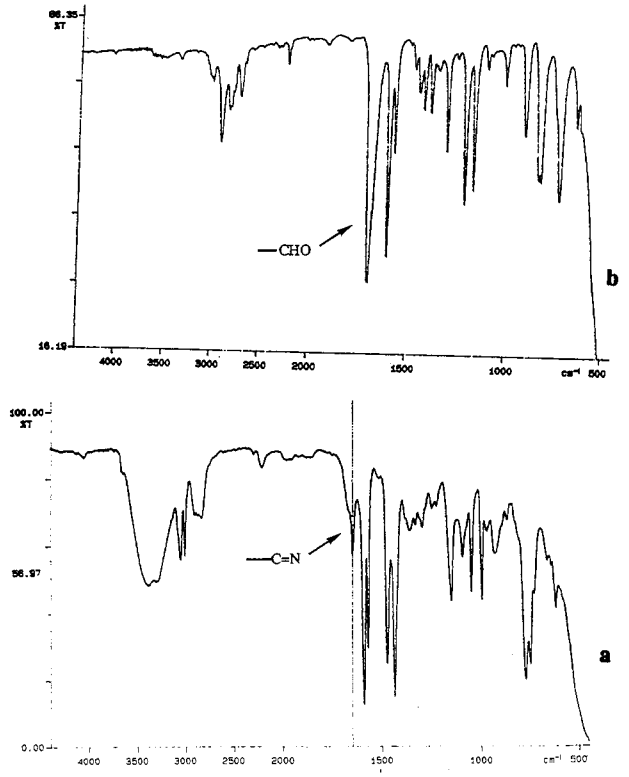

Figure 3. Infrared spectra of the macroporous copolymer of **2** and DVB: (a) before hydrolysis and (b) after hydrolysis.

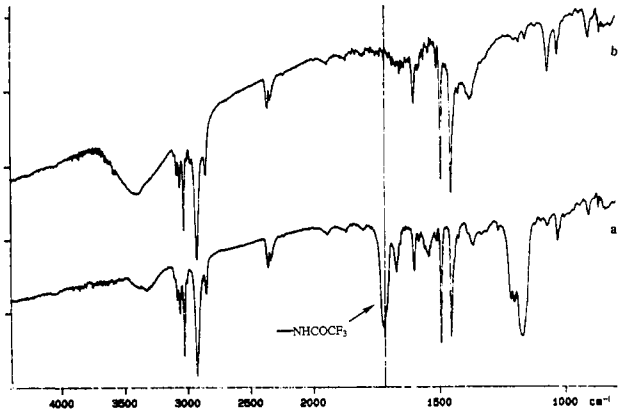

Figure 4. Infrared spectra of the macroporous copolymer of **3** and DVB: (a) before hydrolysis and (b) after hydrolysis.

mained unexplored. To remove the TFA protecting group from the masked aminated copolymer **P-3**, the polymer was treated with 5% NaOH solution in dioxane:methanol (5:5 v/v) mixture and kept at 70 °C for 24 h with stirring. Extent of deprotection to generate polymer bound free amines was studied by the analysis of the IR spectra of the copolymers. The FTIR spectra of the TFA protected copolymer (**P-3**) and its hydrolyzed product **P-3h** are shown in Figure 4. The presence of the 1718-cm^{-1} peak due to the amide carbonyl group in the spectrum of the polymer **P-3** (Figure 4a) and its complete disappearance in the spectrum of the polymer **P-3h** (Figure 4b) testify to quantitative conversion of the amide to free amine groups in the matrix. We attempted to remove *t*-BOC protecting groups by heating the corresponding polymer **P-4** at 80 °C in 10% trifluoroacetic acid in dry dioxane for 24 h. The FTIR spectra of the *t*-BOC protected amine copolymer (**P-4**) and its hydrolyzed product **P-4h** are shown in Figure 5. The spectrum of the unhydrolyzed

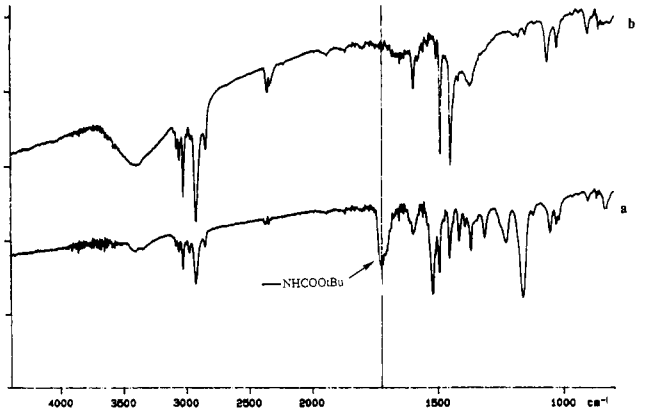

Figure 5. Infrared spectra of the macroporous copolymer of **4** and DVB: (a) before hydrolysis and (b) after hydrolysis.

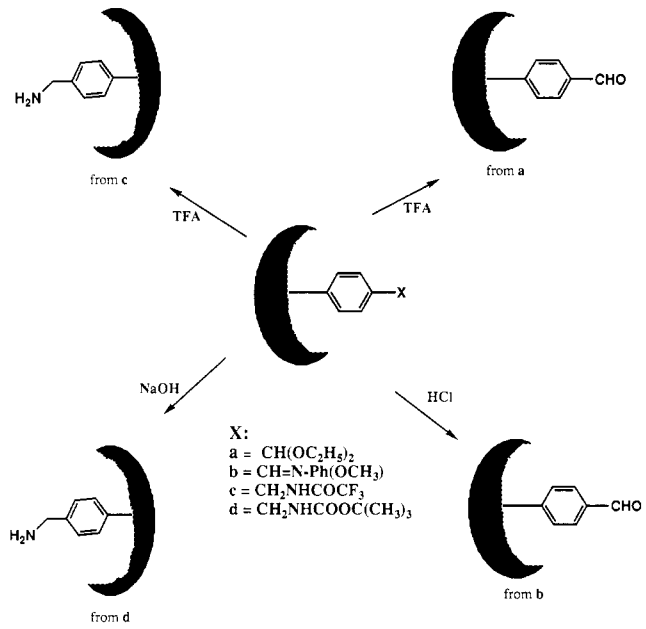

Figure 6. Schematic illustration of the reaction pathways to generate different free functional groups through deprotection.

polymer **P-4** (Figure 5a) shows the characteristic carbamate carbonyl stretching at 1725 cm^{-1} and in the spectrum of its hydrolyzed product (Figure 4b) this peak has completely disappeared confirming complete cleavage of the *t*-BOC protecting group to yield copolymer bearing free amino groups. Thus, under optimized reaction conditions, it became possible to deprotect different types of masked functional groups in macroporous polymer matrices. The deprotection processes leading to generation of the free functional groups in these networks are illustrated schematically in Figure 6.

The functional macroporous polymeric supports carrying free aldehyde and amino functionalities thus obtained can be used as reactive solid-phase agents. As a preliminary study, aldehyde containing polymers were allowed to react with an amine and a diol to give a polymer-bound Schiff base and an acetal, respectively. Thus, the polymer **P-1h** was treated with ethylene glycol in toluene and allowed to reflux with stirring in the presence *p*-toluenesulfonic acid. After refluxing for 24 h with azeotropic removal of the water, the aldehyde functional groups in the polymers were converted to the acetal derivatives. The formation of the acetal group was evident from the infrared spectral analysis of the polymer, which

showed the diminishing intensity of the 1695-cm^{-1} stretching band (due to carbonyl group) and appearance of a new band at 1155 cm^{-1} due to the acetal linkage. Similarly, refluxing this polymer with aniline in a toluene medium for 24 h with azeotropic distillation of water led to the formation of the corresponding azomethine polymer. In addition to the characteristic infrared spectral changes, the polymer shows a light coloration, which is visual indication of the Schiff base formation. These preliminary results demonstrate accessibility and reactivity of these functional groups bound to a rigid matrix toward solution-phase agents. Detail results of this study utilizing these polymers as insolubilized protecting groups will be published separately.

Conclusions

A new approach has been illustrated to prepare rigid reactive polymeric matrices with functional groups located in the accessible regions of the polymer surfaces. Translation of the classical protecting group chemistry to solid phase has a great potential for the preparation of new generation functional polymeric materials. The quantitative chemistry of protecting group removal from macroporous polymers reveals the importance of materials engineering of these polymers where the choice of appropriate porogen and polymerization procedure contribute to locating the functional groups on the accessible regions of the polymer matrices for the diffusion of reagents to these sites. Thus, with critical consideration of the functional and protecting groups, polymeric matrices with well-defined structure and morphology would lead to material design of polymeric solid supports to carry out interesting polymer-assisted organic chemistry.

Experimental Section

Materials. All chemicals were of reagent grade and were obtained from Aldrich unless stated otherwise. Whenever required, reagents were purified by either recrystallization or distillation prior to use. The solvents were purified following standard purification procedures.

Instrumentation and Analyses. Elemental analyses were carried out at Galbraith Laboratories, TN. Melting points were determined on a Buchi melting point apparatus. ^1H and ^{13}C NMR spectra were recorded on General Electric QE 300 spectrometer operating at 300 and 75 MHz for ^1H and ^{13}C nuclei, respectively. Unless stated otherwise, the spectra were recorded in $CDCl_3$ as solvent and chemical shift values reported are relative to tetramethylsilane (TMS) as the internal reference. Infrared spectra were recorded using a Perkin-Elmer 1600 FTIR spectrophotometer. Specific surface areas of the polymers were determined from N_2 adsorption measurements using an Ominsorp 100 analyzer. Electron micrographs were obtained with a Cam Scan Series 2 scanning electron microscope after vacuum coating of the samples with gold.

Monomer Synthesis. *(4-Vinylphenyl)diethoxymethane (1).* Procedure for the synthesis of this monomer has been reported recently.[15]

N-[(4-Vinylphenyl)methylene]-4-methoxyaniline (2). 4-Vinylbenzaldehyde[14] (5 g, 37.8 mmol) and 4-methoxyaniline (4.7 g, 37.8 mmol) were dissolved in 100 mL of absolute ethanol and the reaction mixture was allowed to reflux for 2 h in the presence of 10 mg of 4-*tert*-butylcatechol. After this was cooled to room temperature, yellow crystals appeared. After filtration and concentration of the filtrate, another crop of crystals was obtained. Recrystallization of the combined solid from ethanol offered pure **2** in 62% yield, mp 51 °C; ^1H NMR 3.85 (s, 3H, CH_3O–Ph), 5.23, 5.71 (two dd, 2H, vinyl CH_2), 6.83 (dd, 1H, vinyl CH), 7.25–7.86 (m, 8H, ArH), 8.43 (s, 1H, –N=CH). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; N, 5.90; H, 6.37. Found: C, 80.75; N, 5.82; H, 6.54.

4-Vinylbenzylamine. Under nitrogen atmosphere, to a stirred suspension of 2.3 g (60 mmol) of lithium aluminum hydride in 40 mL of dry diethyl ether, 6.5 g (50 nmol) of 4-cyanostyrene[17] dissolved in 25 mL of dry diethyl ether was added in a dropwise manner. After stirring at room temperature for 1 h, it was heated to reflux for 0.5 h. The reaction mixture was subsequently cooled to 0 °C and quenched with 10 mL of 10% aqueous sodium hydroxide followed by 10 mL of water. After suspension was stirred for 0.5 h, it was filtered off and the solid was washed with 15 mL of diethyl ether. The combined filtrate was extracted with 300 mL of diethyl ether (3 × 100 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to yield the amine as a clear yellowish viscous oil (5 g, 75.0%). ^1H NMR δ 1.63 (br s, 2H, $-NH_2$), 3.94 (s, 2H, $-CH_2N$), 5.23, 5.71 (two dd, 2H, vinyl CH_2), 6.72 (dd, 1H, vinyl CH), 7.33 (d, 2H, ArH), 7.53 (d, 2H, ArH).

4-((Trifluoroacetamido)methyl)styrene (3). This monomer was synthesized in a manner similar to a reported procedure[13a] by reacting 4-vinylbenzylamine with trifluoroacetic anhydride. The spectral properties and melting point of this compound match with the reported data.

4-[[(tert-Butoxycarbonyl)amino]methyl]styrene (4). Under nitrogen atmosphere, to a stirred solution of 2.66 g (20 mmol) of vinylbenzylamine in 20 mL of dry dioxane (cooled to 10 °C), 4.6 g (21 mmol) of di-*tert*-butyl dicarbonate in 15 mL of dry dioxane was added slowly. The reaction mixture was allowed to stir over night at room temperature and was quenched by treating with 5 mL of water. After the solvent was removed under vacuum, the solid residue was recrystallized from ethanol to give 3.3 g (70% yield) of **4** as a light yellow solid, mp 108 °C; ^1H NMR δ 1.53 (s, 9H, *tert*-butyl CH_3), 3.12 (br, s, 1H, NH–COO), 4.24 (d, 2H, $-CH_2N$), 5.24, 5.75 (two dd, 2H, vinyl CH_2), 6.72 (dd, 1H, vinyl CH), 7.33 (d, 2H, ArH), 7.52 (d, 2H, ArH). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; N, 6.00; H, 8.21. Found: C, 71.92; N, 5.95; H, 8.25.

General Procedure for the Synthesis Macroporous Polymers. Typical polymerization recipe consists of a toluene solution of technical divinylbenzene, styrene, and the protected functional monomer at a molar ratio of 50:43:7. Concentration of the monomer in toluene is 50% (v/v). In a 100-mL round-bottom flask the monomer and free-radical initiator, AIBN (1%, w/w with respect to total monomer) were dissolved in toluene and the polymerization mixture was bubbled with argon for 2 h. After the argon was disconnected, the flask was stoppered and was heated to 70 °C for 8 h. Subsequently, the temperature was raised to 90 °C and maintained for 3 h. After cooling, the polymer was washed with methanol, filtered, and ground. The particles were sieved to 60–125-mm size and refluxed with methanol for 10 h to remove any unreacted monomer and soluble components. The polymer was filtered off and was dried under vacuum at 60 °C for 12 h.

Deprotection Procedures for Masked Functional Groups. *Hydrolysis of Acetal Protecting Groups in Polymer P-1.* Polymer **P-1** (0.5 g) taken in a 100-mL round-bottom flask was treated with 30 mL of dioxane containing 5 mL of 20% aqueous trifluoroacetic acid. With continuous stirring, the mixture was warmed to 80 °C and kept at that temperature for 12 h under nitrogen. After cooling down to room temperature, the polymer suspension was filtered through a sintered glass funnel and was washed thoroughly with methanol. The washed polymer was dried under vacuum at 60 °C for 8 h. The dry polymer was analyzed by FTIR.

Hydrolysis of Azomethine Protecting Groups in Polymer P-2. In a 100-mL round-bottom flask 0.5 g of polymer **P-2** was suspended in 40 mL of dioxane, and to this 5 mL of 2 N HCl was added slowly. With continuous stirring, the mixture was warmed to 80 °C and kept at that temperature for 15 h under nitrogen. After the heating source was removed, the reaction mixture was allowed to cool to room temperature. The polymer suspension was filtered through a sintered glass funnel and was washed thoroughly with methanol. After the polymer was dried at 60 °C for 8 h, the hydrolyzed polymer was analyzed for its structure by FTIR.

Hydrolysis of TFA Protecting Groups in Polymer P-3. Polymer **P-3** (0.5 g) taken in a 100-mL round-bottom flask was treated with 40 mL of dioxane:methanol (1:1 v/v) containing 5

mL of 10% aqueous NaOH. With continuous stirring, the mixture was warmed to 80 °C and kept at that temperature for 15 h under nitrogen. Subsequently the reaction mixture was allowed to cool to room temperature. After the polymer suspension was filtered through a sintered glass funnel and washed thoroughly with methanol, the polymer was dried at 60 °C under vacuum for 8 h. The extent of hydrolysis in this dried polymer was analyzed by FTIR.

Hydrolysis of t-BOC Protecting Groups in Polymer P-4. In a 100-mL round-bottom flask, 0.5 g of polymer **P-4** was suspended in 40 mL of 10% trifluoroacetic acid in dioxane. With continuous stirring, the mixture was heated to reflux for 24 h under nitrogen. After the reaction mixture was cooled to room temperature, the polymer suspension was filtered through a sintered glass funnel and was washed thoroughly with 0.2 N methanolic NaOH followed by pure methanol. After the polymer was dried at 60 °C for 8 h, the hydrolyzed polymer was analyzed for its structure by FTIR.

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