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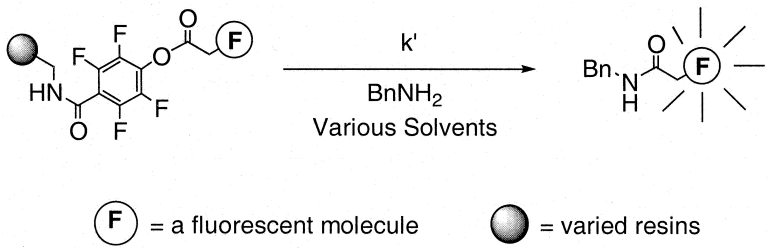

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Comparative Resin Kinetics Using in Situ Fluorescence Measurements

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The aminolysis of a novel activated ester resin was utilized for kinetic study via continuous in situ fluorescence measurements. A variety of resin compositions (polystyrene, JandaJel, ArgoPore, TentaGel, NovaGel, and PEGA) and solvents (dimethylformamide, acetonitrile, tetrahydrofuran, 1,2-dichlorethane, and toluene) were tested to compare their effects on the reaction rate. A linear relationship between the reaction rate and (solvent polarity × swelling of resin) was elucidated for the aminolysis reaction.

Introduction

Fluorescence techniques have been widely used in chemistry and biology for over a century.[1] With the advent of combinatorial chemistry, a variety of fluorescence techniques for resin beads have been developed and adopted for broad applications, which include encoding/decoding,[2] fluorescent molecule binding assays,[3] and catalytic activity detection.[4]

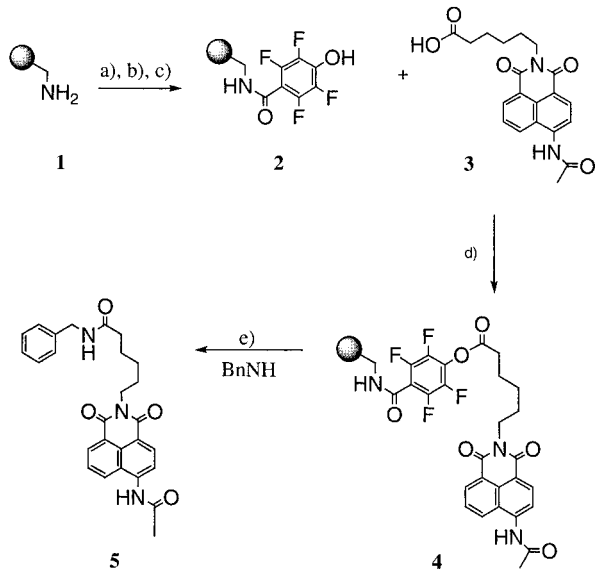
As the solid-phase synthesis field grows, understanding the factors affecting reaction kinetics on solid supports is imperative. The problem with studying the kinetics of solid-phase reactions is that it demands, in many cases (if not all), tedious sample preparation steps, which include cleaving the product from the solid support, filtering, washing, and transferring. Currently, there are few studies that can serve as a standard reference for solid-phase kinetics in various conditions.[5] While single resin bead FT-IR has been utilized successfully to quantify solid-phase reaction rates,[6] no comparable fluorescence kinetics has yet been demonstrated. Herein, we report a versatile method for determining resin bead kinetics using continuous fluorescence measurements of activated ester resins with a variety of resin compositions and solvent conditions.

Activated esters on solid supports were originally developed as convenient labeling reagents[7,8] and for library synthesis,[9] especially for amine nucleophiles. Most of the reported functionalities, such as nitrophenol, *N*-hydroxysuccinimide, HOBt (1-hydroxybenzotriazole), and Kaiser oxime, have been attached to a polystyrene resin solid support by a Friedel−Crafts reaction[10] or to a thiol resin by a maleimide linker,[7] thus limiting the selection of resin compositions. To overcome this limitation, we utilized a well-established amide bond formation method to couple the activated ester-forming linker with an aminomethyl resin (**1**), which is available in varied compositions.

Results and Discussion

Six representative aminomethyl resins, polystyrene (PS), JandaJel, Argopore, TentaGel (TG), NovaGel (NG), and PEGA, were coupled with tetrafluoro-4-hydroxybenzoic acid to give the respective tetrafluorophenol resins (**2**) (Scheme 1).[11] Resin **2** was then coupled to the environmentally insensitive, high quantum yield fluorescent molecule 4-acetamido-1,8-naphthalamide resin (**3**),[12] resulting in the activated ester resin (**4**). Upon reaction with a benzylamine solution, a highly fluorescent product (**5**) was cleaved from the solid phase and, from which the fluorescence intensity over time was measured. To determine solvent effects, the reaction was performed in five different solvent conditions: dimethylformamide (DMF), acetonitrile, tetrahydrofuran (THF), 1,2-dichloroethane (DCE), and toluene. The resins and solvents were chosen to be as general as possible for the cleavage reaction to give a fair representation of reaction rates in various conditions. Here, it must be said that the results and trends commented upon are for this particular cleavage reaction only and not representative of other systems. The general method, however, may be employed to study other reactions.

Scheme 1[a]



[a] Reagents and conditions: (a) tetrafluoro-4-hydroxybenzoic acid, DIC, HOBt, DMF; (b) piperidine, DMF; (c) HCl, DMF; (d) DIC, DMAP, DMF; (e) $BnNH_2$ (10 mM in various solvents).

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$$\frac{d[C]}{dt} = -\frac{d[A]}{dt} = k[A][B] \qquad \text{Eq. (1)}$$

When B is in excess, $k' = k[B]$

$$\frac{d[C]}{dt} = -\frac{d[A]}{dt} = k'[A] \qquad \text{Eq. (2)}$$

$$\int -\frac{d[A]}{[A]} = \int k'\,dt$$

$$-\ln[A] + \ln[A]_0 = k't$$

$$-\ln\left[\frac{A_0 - C}{A_0}\right] = k't \qquad \text{As } C = [A]_0 - [A]$$

$$\ln\left[\frac{1}{1 - \frac{C}{A_0}}\right] = k't \qquad \text{Eq. (3)}$$

$\frac{C}{A_0}$: Relative Conversion

Figure 1. Kinetics equations: A = activated ester resin (**4**), B = benzylamine, C = fluorescent product (**5**).

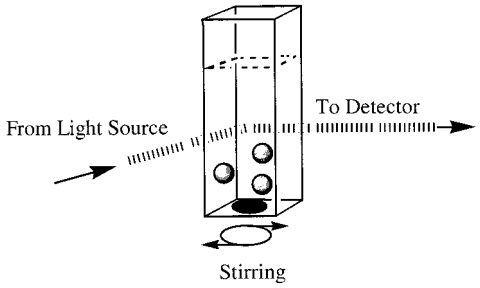

Figure 2. Cuvette schematic showing the light beam (from the source to the detector), resin beads, and stir bar.

Kinetically, the reaction is second order, but when pseudo-first-order kinetic conditions are imposed by placing benzylamine in excess, the experimental demands were simplified (Figure 1). This conversion has several significant advantages: (1) the kinetic reaction can be shortened from many hours (or even days) to less than 1 h; (2) the pseudo-first-order reaction rate constant (k') can be obtained from the slope of a linear equation (eq 3, Figure 1); (3) although the kinetic starting point was not exactly synchronized, resulting from experimental deviation, the calculation of k' was unaffected.

One of the great advantages of this in situ fluorescence measurement is the physical experiment design (Figure 2). Continuously stirring the reaction mixture in a large quantity of solvent minimizes the effect on the reaction rate of the diffusion of small molecules from/into the resin. In addition, the fluorescence observed is solely due to the fluorescent product released into solution, since the resin-bound molecules, for the most part, do not come in contact with the excitation light source.

Minor light-source−bead interactions do occur and are graphically evident through scattering seen as spikes or severe drops in intensity. Solvents of low density (DMF d = 0.944 g/mL, THF d = 0.889 g/mL, toluene d = 0.865 g/mL, acetonitrile d = 0.781 g/mL) showed little to no scattering. Presumably, this is because the beads remained primarily at the bottom of the cuvette and below the light source but were stirred enough so that **5** was evenly released into solution. Increased scattering was observed in solvents of higher density, such as DCE (d = 1.256 g/mL), where the beads primarily remained from the middle to the top of the cuvette solution and, therefore, more often in the beam's path. A key point to make here is that the scattering does not have a linear relationship with increasing density. As an example, dichloromethane (d = 1.325 g/mL) was tested, but its data were not included because of problems presumably arising from its density. Its high density did not cause the most scattering, as might be predicted from above, but instead gave poor results due to the beads, even with vigorous stirring, remaining clustered at the liquids surface. This prevented efficient mixing, thus making consistent measurements unobtainable.

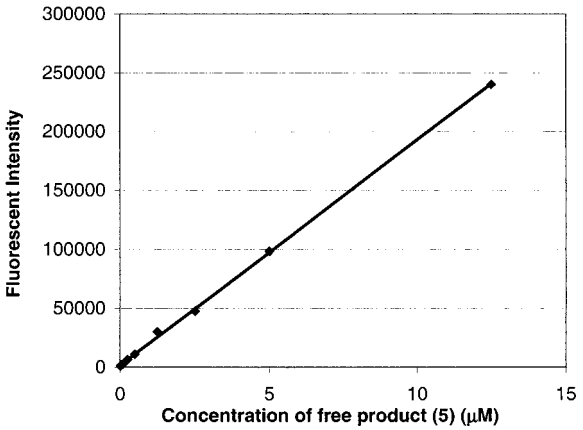

Figure 3. Instrument linearity: plot of fluorescent intensity vs free product concentration of **5** (μM) for a series of dilutions.

The greatest scattering was observed in DMSO, where, apparently, its density (d = 1.190 g/mL) was apparently nearly equal to the density of the resin beads. The near-equal densities resulted in an almost homogeneous distribution of resins about the suspension and, more consequently, in the beam's path. This excessive scattering led to unusable data.

In summary of the solvent density effect, the best data were obtained where beads remained out of the light path but were still efficiently mixed. Scattering appears to follow a bell curve trend, where initially scattering increases with increasing density, until a maximum is reached where the resin and solvent densities are approximately equal, and then decreases with further increasing density.

Here, it is important to note that while theoretically the amount of resin utilized in the reaction is insignificant, experimentally it must be controlled. It was found that linearity between fluorescence intensity and the concentration of free dye (**5**) could be achieved in the range of 10 nM to 10 μM. This correlates to concentrations low enough to allow for the use of a single bead, while at the same time it prohibits the use of excess beads (Figure 3).

To demonstrate that pseudo-first-order kinetics was operating, reaction rates were measured, using a PS resin, over a range of benzylamine concentrations representing a large excess of resin-bound dyes. As can be seen in Figure 4, a linear correlation exists between the increasing pseudo-first-order rate constant, k', and an increasing concentration of benzylamine in the range 1−13 mM.

Table 1. Second-Order Reaction Rate Constants (M^{-1} s^{-1}) of Six Resins Types in Five Solvents, Showing Solvent Polarity (Unitless), and Swelling Volume (mmol/g)[13a−f] (N/A = Solvent Swelling Volume Not Available

	DMF, PI = 6.4		acetonitrile, PI = 6.2		THF, PI = 4.2		DCE, PI = 3.7		toluene, PI = 2.3	
resin	*k*	swelling	*k*	swelling	*k*	swelling	*k*	swelling	*k*	swelling
polystyrene[a,b]	2.00	5.2	0.23	2.0	1.31	6.0	0.27	4.4	0.41	4.0
JandaJel[c]	2.65	6.0	0.22	N/A	1.90	7.4	0.20	N/A	0.22	N/A
ArgoPore[d]	1.31	5.6	1.43	5.3	1.17	5.4	0.28	N/A	0.16	5.7
TentaGel[e]	2.95	5	2.20	4	1.92	6	0.53	5	0.68	3.6
NovaGel[e]	2.57	7	1.51	5	1.62	7.5	0.72	N/A	0.29	N/A
PEGA[f]	2.95	8	1.83	6	1.95	4	0.26	5	0.21	3

[a] See published information of ref 13a. [b] See published information of ref 13b. [c] See published information of ref 13c. [d] Argonaught Technical Services. [e] White, P. Novabiochem Innovations, private communication March 1999. [f] See published information of ref 13f.

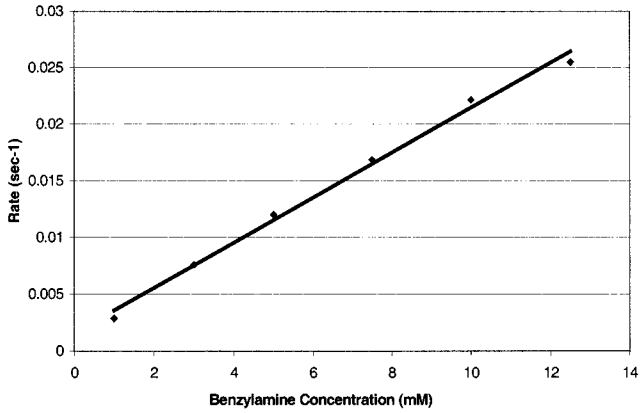

Figure 4. Pseudo-first-order kinetics: plot of rate vs benzylamine concentration.

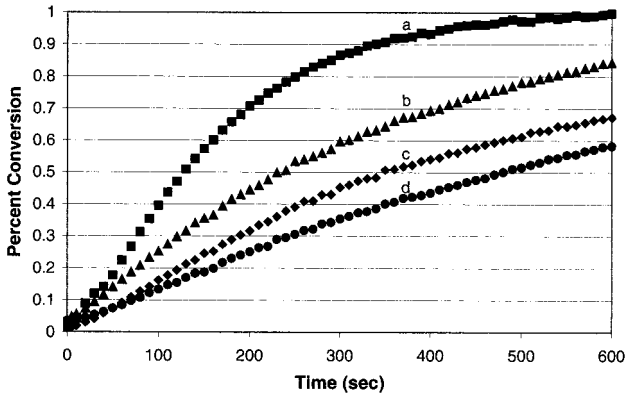

Figure 5. Plot of percent conversion (C/A_o) vs time for toluene series: (a) TG; (b) PS; (c) JandaJel; (d) Argopore. For graphical clarity, PEGA and NovaGel were omitted because of data overlap.

Upon addition of the benzylamine to the resin suspension in the cuvette, the fluorescence was recorded as a function of time (Figure 5). The raw data were then converted to Microsoft Excel and processed using eq 3. A linear plot of eq 3 gives a slope that is equal to the pseudo-first-order reaction rate constant (Figure 6). The data were converted to the second-order rate constants, and these are shown for six resin compositions in five different solvents. (Table 1).

One important factor that needed to be explored was the effect of various loading levels. For example, if two resins have different loading levels and it were found that the loading level affected the experimental rate constant, then a direct comparison of the two resin rates would be difficult and require some secondary mathematical treatment. To determine this effect, a series of experiments were conducted where the cleavage reaction was allowed to react to half-

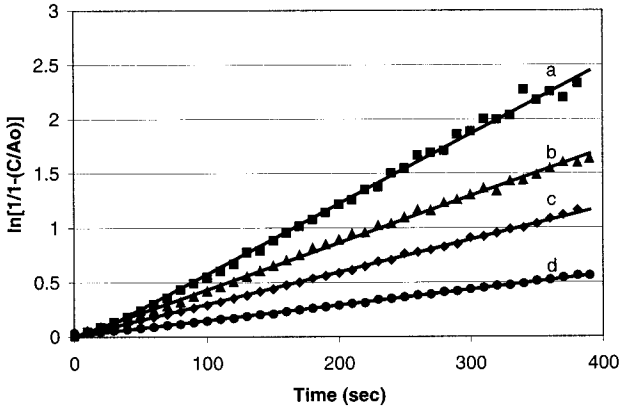

Figure 6. Example of toluene processed data series, showing plot of $\ln[1/(1 - C/A_o)]$ vs time: (a) TG; (b) PS; (c) JandaJel; (d) Argopore. For graphical clarity, PEGA and NovaGel were omitted because of data overlap.

completion. The reaction was stopped by washing the reaction with the a 1% acetic acid solution of the solvent being tested at a time correlated to half of the maximum fluorescent intensity. After the reaction was stopped, it was restarted by addition of benzylamine, and the fluorescence intensity vs time was measured. Comparison of the half-reacted resin rate with those reported in Table 1 indicated they were the same. This clearly demonstrates that the loading level of the resins was inconsequential to the reaction rate and eases the treatment of the data.

From the data in Table 1, two major factors governing resin performance were found: (1) resin swelling and (2) solvent polarity. In general, the rate tends to increase with higher polarity and greater resin swelling. Neither of these factors dominate; rather, it is a balance between the two factors that regulate the resin's performance. Although a resin may show excellent swelling in a low or moderately polar solvent, the rate may be faster in a high-polarity solvent where only moderate swelling is present. This is seen in the case of PS (Table 1) whose swelling increases in the order of CH_3CN (2.0 mL/g), toluene (4.0 mL/g), DCE (4.4 mL/g), DMF (5.2 mL/g), and THF (6.0 mL/g).[13a,b] Solvent polarity, in increasing polarity index, is as follows: toluene (2.3), DCE (3.7), THF (4.2), CH_3CN (6.2), DMF (6.4).

Argopore is a highly cross-linked, macroporous polymer that shows unique characteristics; its high degree of cross-linking prevents the resin from shrinking or swelling considerably. In solvents where other resins show good swelling characteristics, Argopore shows generally a slower rate, whereas in solvents where a resin's performance suffers

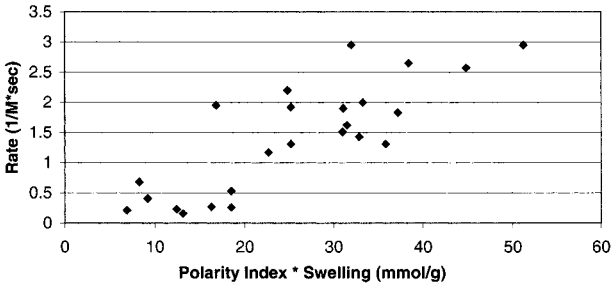

Figure 7. Linear relationship of rate (M^{-1} s^{-1}) vs (polarity index)-(swelling volume) (mmol/g). The outlying data point is for JandaJel in DMF.

from poor swelling properties in a particular solvent, for example, PS in CH_3CN (swelling, 2.0 mL/g), Argopore performs quite well, its high cross-linking preventing it from becoming adversely affected by any shrinkage factors, information that would be helpful in experimental design.

It is noteworthy that TG, NG, and PEGA are water-compatible, unlike PS resins, which were previously reported to be solid-phase labeling reagents for amines in organic solvents.[7,9] Thus, the activated esters based on these resins could be used directly to label physiologically active amines, including many neurotransmitters, without extraction procedures.

To visualize the trends graphically, the rate (M^{-1} s^{-1}) vs polarity index multiplied by the swelling volume (mmol/g) was plotted (Figure 7). This plotting effectively illustrates the linear relationship between the polarity and swelling cofactors and the reaction rate.

In conclusion, we have developed facile fluorescence labeling reagents using tetrafluorophenol-activated esters, and through continuous in situ fluorescence measurements, the effects of resin composition and solvents on solid-phase reaction kinetics could be determined. This comparative kinetic data will be useful as a reference for resin/solvent selection in solid-phase organic syntheses. However, it should be noted that the positive effects of increased solvent polarity and swelling toward the reaction rate were demonstrated only for the aminolysis reaction in this paper, and the application of this general trend to other types of reactions remains for further studies.

Experimental Section

General. All reagents were obtained from commercial sources and used as received but with the following exception: free trace amine was removed from DMF via the addition of *p*-toluenesulfonic acid resin (Argonaught Technologies, Inc., P/N 800287, lot. no. 00561) and allowed to stand for a minimum of 5 h. Solid-phase reagents were obtained from various sources: JandaJel (75−150 μm, 2% cross-linked, gift from Prof. Kim D. Janda and Dr. Patrick Toy),[13c] ArgoPore (0.99 mmol/g, 106−250 μm, Argonaut P/N 800048, lot no. 104-11), Argo PS (1.21 mmol/g, 75−150 μm, Argonaut P/N 800263, lot no. 00265), PEGA (0.06 mmol/g (wet), 150−300 μm, NovaBiochem catalog no. 01-64-0010), NovaSyn TG (0.45 mmol/g, 110 μm, NovaBiochem catalog no. 01-64-0094), and NovaGel (0.76 mmol/g, 75−150 μm, NovaBiochem catalog no. 01-64-0283). Spectra were collected using a Jobin-Yvon Horiba Spex Fluoromax-3 equipped with a stirring apparatus, and the temperature was regulated at 25.1 °C with a Fisher Scientific (model 9101) water circulator. Starna (3-Q-10) and Fisher Scientific (Supracil 3.0 mL) quartz fluorescence cuvettes were used in the fluorescence measurements. Data were obtained using Datamax (version 2.2) software and analyzed using Microsoft Excel. Time-based acquisition experiments were performed in which $\lambda_{ex} = 370$ nm and $\lambda_{em} = 455$ nm.

Representative Preparation of Tetrafluorophenol PS Resin (2). In a 20 mL glass vial, to an aminomethylated polystyrene resin (100 mg, 0.12 mmol) in DMF (10 mL) were added tetrafluoro-4-hydroxybenzoic acid (100 mg, 0.74 mmol), HOBt (100 mg, 0.74 mol), and DIC (diisopropylcarbodiimide, 100 μL, 0.060 mmol). After overnight shaking, the reaction mixture was transferred to a 35 mL polypropylene cartridge with a one-way Teflon stopcock and washed with DMF (20 mL, 5 times), methylene chloride, and methanol (20 mL, alternatively 5 times each), and DMF (20 mL, 5 times). To remove the undesirable ester side product, DMF (5 mL) and piperidine (0.17 mL, 1.8 mmol) were added to the cartridge and allowed to shake for 1.5 h. The resin was filtered and washed repeatedly with DMF. The resulting piperidine salt was removed via the addition of a 10% HCl solution (in DMF, 5 mL) to the resin, which was allowed to shake for 1.5 h. The mixture was then filtered, washed with DMF (50 mL), THF (100 mL), and methylene chloride (50 mL) and was dried by nitrogen gas flow. Negative staining with the ninhydrin test on the resin indicated the complete conversion of the amine functionality into fluorophenol (**2**).

Preparation of Activated Ester (4). Used directly from above, the tetrafluorophenol resin (0.12 mmol) (**2**) was suspended in DMF (10 mL), and 4-acetamido-1,8-naphthalimide-*N*-caproic acid (**3**) (100 mg, 0.22 mmol),[12] DIC (100 μL, 0.60 mmol), and DMAP (4-(dimethylamino)pyridine) (1 mg, 8.2×10^{-3} mmol) were subsequently added at room temperature. The resins were filtered and washed with DMF (10 mL, 5 times), THF (10 mL, 10 times), and methylene chloride (10 mL, 10 times) and were then dried by nitrogen gas flow. Experimental loading levels were determined by measuring the maximum fluorescent intensity after the reaction was allowed to proceed to completion and using the plot of Figure 3 to determine the concentration of **5**. By dilution of the sample to bring the fluorescent maximum within the range seen in Figure 3, the concentration of **5** was found, and a simple calculation gave the loading levels of **4** as follows: JandaJel (1.37 mmol/g), ArgoPore (0.82 mmol/g), Argo PS (0.96 mmol/g), PEGA (0.113 mmol/g), NovaSyn TG (0.41 mmol/g), and NovaGel (0.72 mmol/g).

Kinetics Measurement Procedure. Each activated ester resin (**4**) was initially suspended in a polypropylene frit-equipped syringe filter set with a 10% acetic acid solution (5×5 mL) of the solvent being tested. They were subsequently filtered and thoroughly rinsed (5×5 mL) with the solvent being tested (acid-free). A total of 5 mL of solvent was added to the filter syringe, after which 960 μL of the resin−solvent suspension was transferred to the cuvette with an emphasis on taking a minimum number of beads (<10 beads). A UV lamp allowed for enhanced detection of the individual resin beads in suspension. A total of 1 mL of the

given solvent was then added to the suspension in the cuvette. The cuvette was placed in the fluorometer, and 40 μL of a 500 mM solution of benzylamine in the solvent being tested was added to make the final benzylamine concentration 10 mM (total sample volume in the cuvette was 2.0 mL). The fluorometer was immediately triggered upon addition of benzylamine. **5** was characterized by LC−MS (*m*/*z* 458.1; see Supporting Information).

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Supporting Information Available. The standard deviations of rate constants in Table 1 and the LC−MS spectra (shown with UV and fluorescence detector plots) demonstrating the purity of compound **5** in the reaction mixture of resin **4** and benzylamine. This material is available free of charge via the Internet at http://pubs.acs.org.

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