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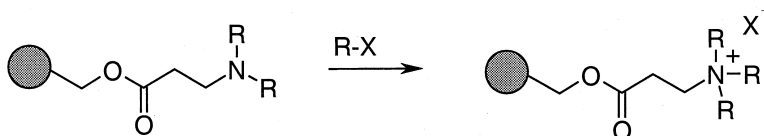
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Optimization of Reaction Conditions for REM Resin-Bound Quaternization Reactions

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Received August 17, 2001

A study into the effect of reaction variables on the quaternization of REM resin-bound tertiary amines was undertaken. The influence of resin matrix, solvent, reaction time, temperature, and amount of quaternization agent on the outcome of reaction was evaluated by reaction monitoring using ^{19}F NMR. The highest yields of tertiary amine products were seen when DMSO was used as reaction solvent in conjunction with a reaction time of 18 h at room temperature. The use of heating for extended reaction times tended to depress yields, indicating product cleavage during quaternization. Quaternization on PS-DVB resin was found to be more robust than reaction on PS−PEG matrices where yields were generally considerably lower than the observed conversions. DMSO was the most efficient reaction solvent for both resins despite poor swelling of the quaternization starting material.

Tertiary amines are an extremely important class of compounds from a drug discovery perspective, a fact reflected in the presence of this moiety in more than a quarter of registered drugs.[1] REM resin methodology is an efficient solid-phase protocol for the synthesis of 3° amines.[2] As shown in Scheme 1, in its simplest form the REM resin **1** undergoes Michael addition with a 2° amine to give a polymer bound 3° amine, **2**. Quaternization of **2** with an alkyl halide then gives a quaternary ammonium salt, **3**, which on exposure to base gives the 3° amine product, **4**, by a facile Hofmann elimination while regenerating acrylate ester **1**.

We have previously identified the quaternization process as both the slowest and the yield-limiting step.[2b] The quaternization is typically performed at 20−60 °C (depending on quaternization reagent) for 18 h in DMF. To explore the scope for further optimization of the REM resin method, a systematic study of the effect of key reaction variables on the quaternization process was undertaken. Many such optimization processes have been reported including studies on the effect of resin matrix,[3] resin loading,[4] resin cross-linking,[5] reaction solvent,[6] and even agitation method[7] on the outcome of solid-supported reactions. The initial variables studied were solvent (21 solvents and mixtures) and resin matrix (3 resins). This was followed by a more detailed study

Scheme 1
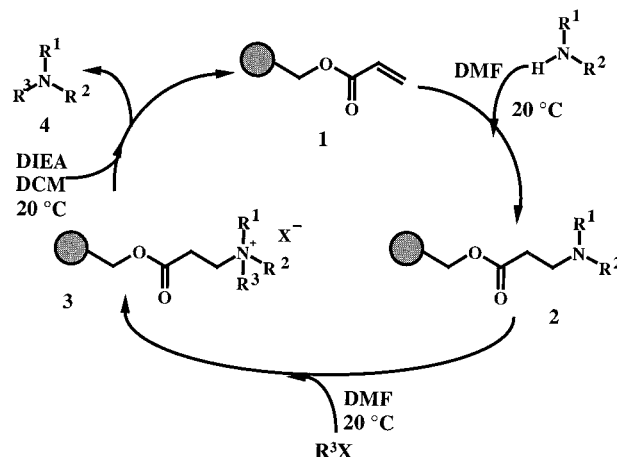
into the effect of reaction temperature, reaction time, amount of quaternization reagent, and solvent on quaternization. For this purpose three reaction times (0.5, 3, and 18 h), three reaction temperatures (20, 50, and 80 °C), the three best solvents identified from the initial study, and three amounts of quaternization reagent (5, 10, and 20 equiv) were used to monitor the quaternization of two amines (**6** and **7**) with two quaternization reagents (**8** and **9**) on the two best resins from the initial study. This gave a total of 648 experiments, which required reaction monitoring in order to acquire meaningful data from the study.

Difficulties in monitoring quaternization by either IR or ^{13}C gel-phase NMR have been previously reported.[2b] However, we found that the use of ^{19}F NMR allows rapid monitoring of quaternization by the incorporation of a fluorine atom into both the 2° amine and alkyl halide components of the reaction.[8] Thus, by comparison of integrals of the signals arising from the amine and the alkyl halide, the extent of quaternization could be determined. A further advantage of ^{19}F gel-phase NMR is its wide spectral range,
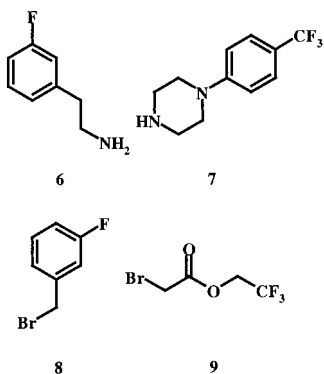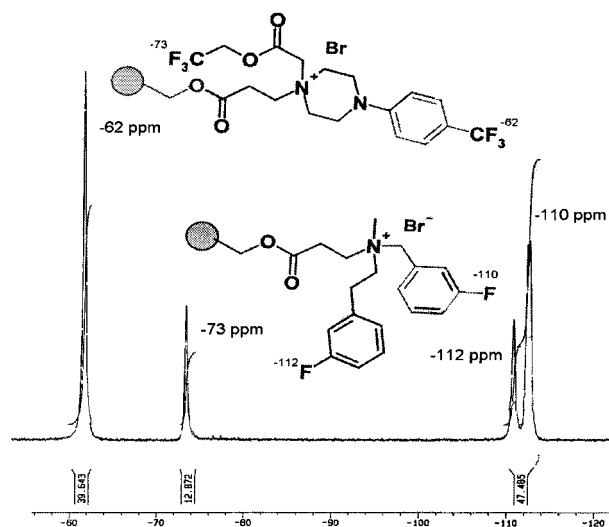
Figure 1. Simultaneous analysis of two reaction samples by ^{19}F NMR.

allowing the combination of different quaternization samples (Figure 1) and effectively doubling sample throughput. Prior to analysis by ^{19}F NMR, samples were shaken with a dilute 10-fold excess of ethereal hydrochloric acid in order to prevent any cleavage of product initiated by unquaternized Michael adduct **2**.

The initial variables considered for the study were resin matrix and solvent. With this in mind, REM resins based on polystyrene cross-linked with 1% divinyl benzene (PS-DVB), macroporous polystyrene, and a polystyrene−poly(ethylene glycol) graft copolymer (PS−PEG) were prepared and Michael reaction was performed to give **5** (PS-DVB = 1.20 mmol/g, PS−PEG = 0.26 mmol/g, macro-PS = 0.77 mmol/g). The quaternization was then performed using a number of different solvents and mixtures (Figure 2), according to the reaction in Scheme 2. Reactions were monitored by ^{19}F NMR for PS-DVB and PS−PEG resins. Because of the poor swelling of the macroporous polystyrene resin, monitoring of these reactions by NMR was not possible, and so they were evaluated by product cleavage.
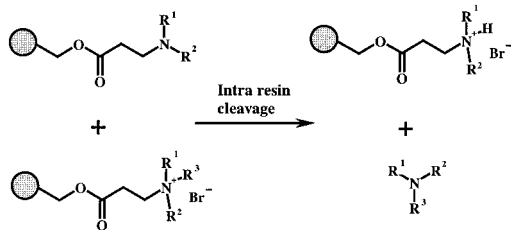
Scheme 2
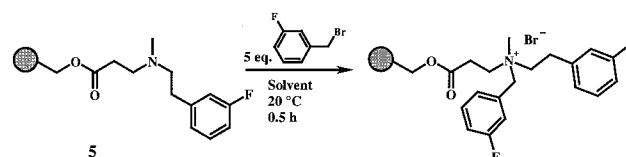
Interestingly this initial study identified a number of solvents giving significantly higher conversions with the PS-DVB-based resin than DMF, the most commonly used solvent for quaternization. Macroporous polystyrene generally gave poor yields of product, although water was a good solvent for this resin. Water also appeared to be a solvent of choice for PS−PEG-based quaternizations. The higher yields (macroporous PS) and conversions (PS−PEG) seen here may be due to the insolubility of the benzyl bromide quaternization agent in water. This would provide a high concentration of reagent within the polymer and so would increase rates. A similar observation has been made in a report on the epoxidation of olefins by polymeric acids.[9] The failure of quaternization on PS-DVB resins with water as a solvent is presumably a result of the poor swelling of these resins in aqueous media, thus preventing access of reagents. Because of the generally poor results observed with macroporous polystyrene, this resin was not utilized for further studies. The reason for the poorer performance of macroporous PS is not clear, although difficulties in accessing all reactive sites on macroporous resins have been reported.[10]

Next, the effect of reaction temperature, reaction time, amount of quaternization reagent, and solvent on quaternization was further evaluated. In addition to reaction monitoring by ^{19}F NMR, final products were cleaved from resin to assess yield and compare this with the conversion observed by NMR. This allowed the evaluation of any loss of material during quaternization, which was particularly thought to be a problem at high reaction temperatures where a thermal retro Michael reaction may occur.[11] Additionally, unquaternized **2** may act as a base for intraresin Hofmann elimination during quaternization (Scheme 3). Once col-

^{a} Conversion by NMR ^{b} Isolated yield   **Solvent**
^{c} Reaction not attempted with Macro-PS
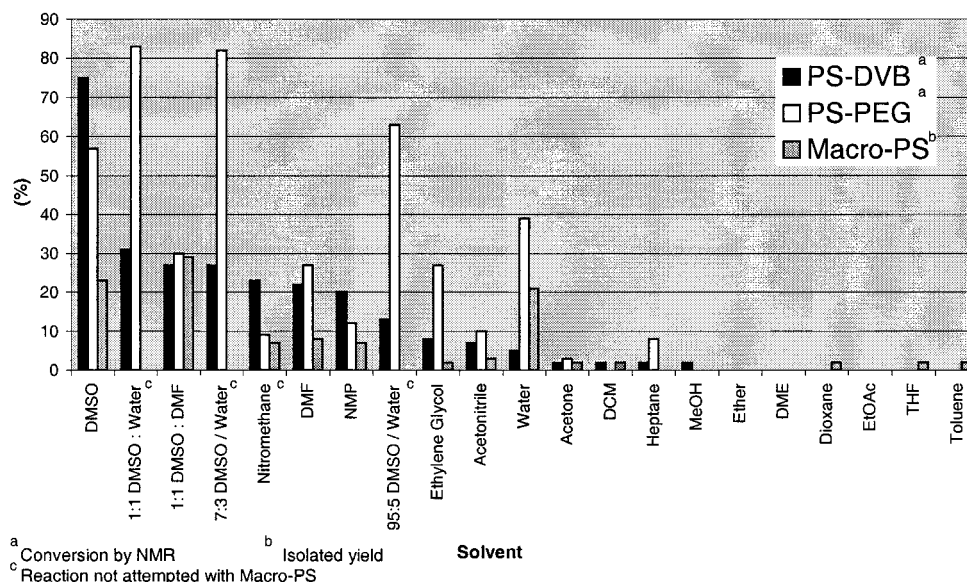
Figure 2. Results of quaternization reaction (Scheme 2).

Scheme 3

lected, the data were analyzed using the Minitab statistical software, and the initial results are presented in Figures 3 and 4.[12]

As shown in Figures 3 and 4, the conversion is consistently higher for quaternization on PS−PEG. This would be expected because the long, flexible PEG spacers of such matrixes provide separation from the hydrophobic PS backbone, thus providing an environment more conducive to charged species.[3a] The isolated yields, however, are consistently lower than those seen with PS-DVB, suggesting appreciable premature cleavage of product or retro Michael reaction during quaternization. This was attributed to the increased flexibility of the PS−PEG side chains favoring site-to-site interactions between polymer-bound species and therefore possible intraresin Hofmann eliminations. Not surprisingly, when the amount of quaternization reagent used was increased from 5−10 to 20 equiv, the isolated yield and conversion with both resins increase, albeit by typically less than 10%. The effects of temperature, time, and solvent on quaternization are investigated more thoroughly in Figures 5−7 for PS-DVB resins.

For both resins DMSO clearly provided the highest yields regardless of reaction time or temperature, supporting the earlier evidence (Figure 2) for the use of DMSO as the solvent of choice for polymer-bound quaternization. At room temperature all solvents displayed a gradual increase in yield as reaction time increased. With heating at 50 °C, however, only quaternization on PS-DVB in DMF showed increases in yield with longer reaction times, all other solvents giving the highest yields after 3 h. Heating at 80 °C resulted in generally poorer yields, especially with 18 h reaction times.
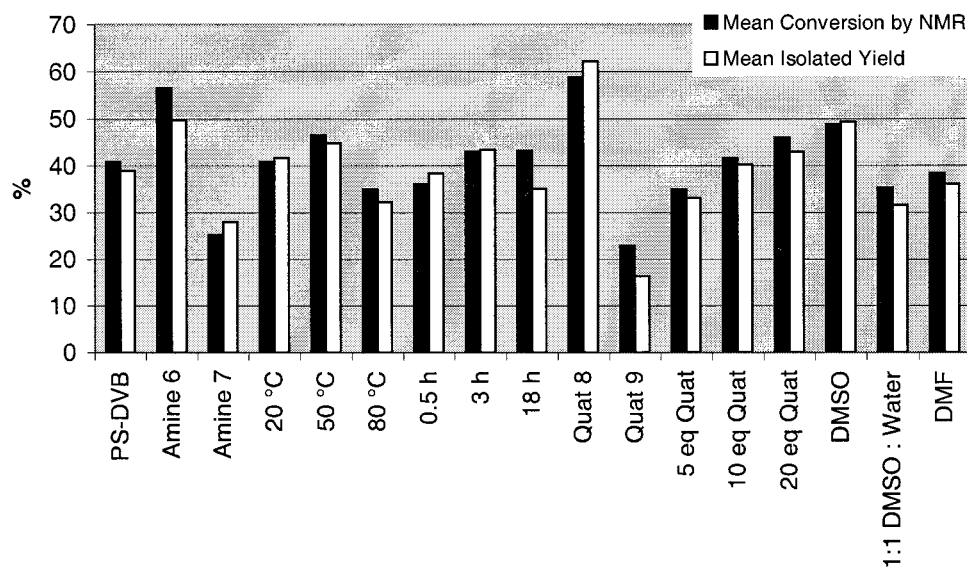

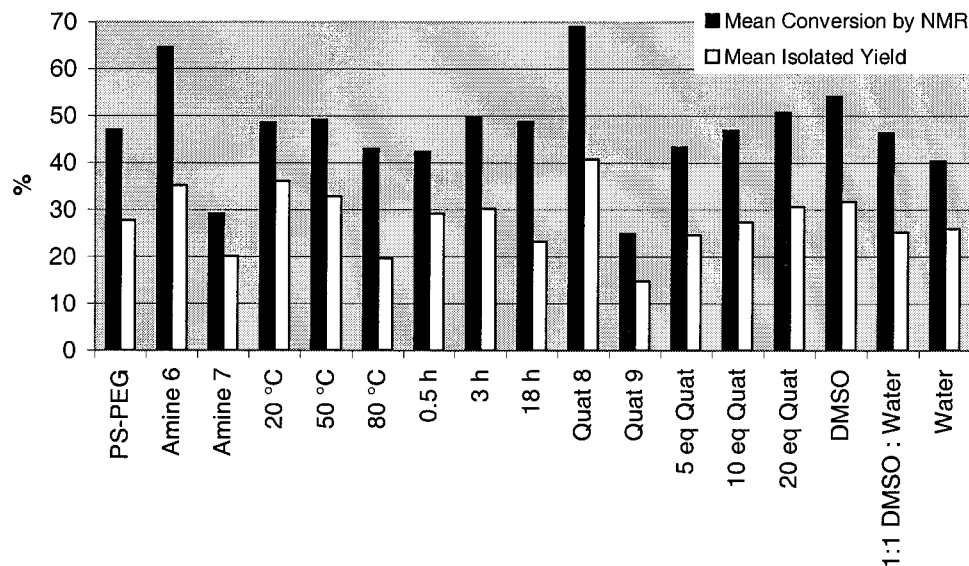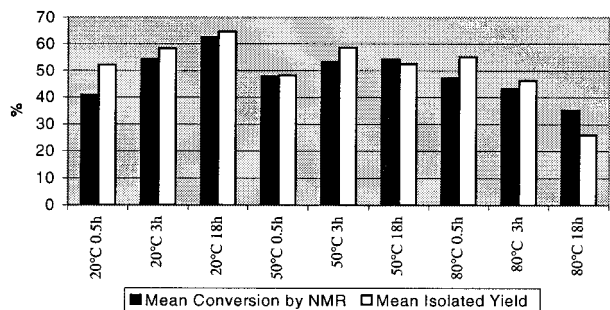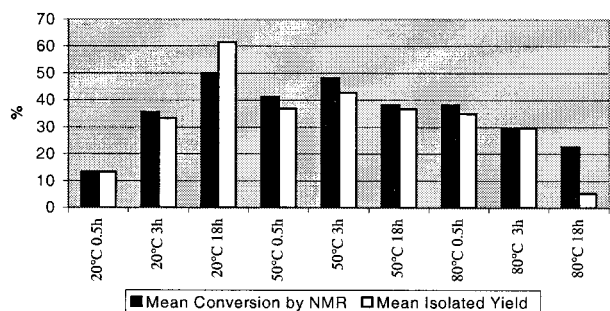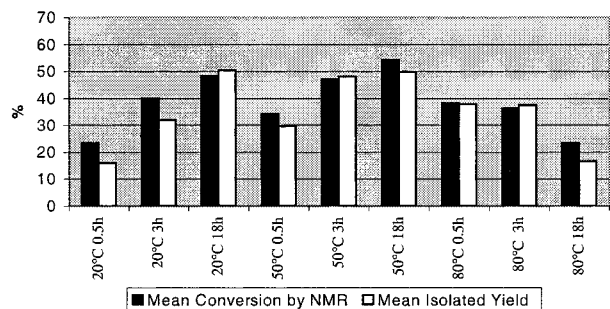**Figure 3.** Results for quaternization on PS-DVB resin.

Figure 4. Results for quaternization on PS−PEG resin.

**Figure 5.** Results for quaternization in DMSO on PS-DVB resin.

Figure 6. Results for quaternization in 1:1 DMSO/water on PS-DVB resin.

Figure 7. Results for quaternization in DMF on PS-DVB resin.

Overall the highest yields for all solvents were seen after quaternization at room temperature for 18 h.

The fact that DMSO provided the highest yields may be simply a result of the solvent's high polarity. In solution, such quaternization processes would occur via an S_N2 mechanism, which would be favored by polar aprotic solvents such as DMSO.[13] Indeed, a study on the synthesis of quaternary ammonium salts in solution showed that polar aprotic solvents gave the highest rates.[14] Another possibility that may have a contribution is a reaction between DMSO and the alkyl halide quaternization reagent to form an activated sulfonium salt.[15] This does not, however, explain the high yields observed in aqueous DMSO where such an intermediate would be hydrolyzed. The high rates seen are particularly intriguing in light of the fact that, for PS-DVB-based resins at least, little swelling in DMSO is seen with starting material **2** (2 vs 5.3 mL/g in DMF).[16] However, on evaluation of the swelling of the final quaternization product **3**, DMSO was seen to give a high degree of swelling (8.2 vs 6.8 mL/g in DMF). In light of these data, we expected a slow initial rate of quaternization in DMSO due to poor swelling of the starting material and restricted access of reagents to the polymer interior. To observe the rate of product formation, quaternization of **5** (PS-DVB) was
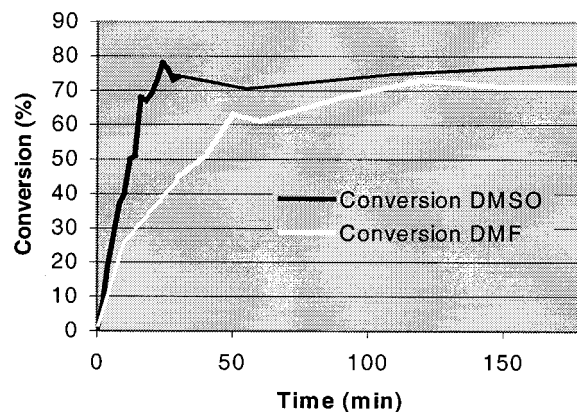
Figure 8. Rate of conversion for quaternization of PS-DVB-bound **6** with **8** in DMSO and DMF.

performed with 10 equiv of bromide **8** at room temperature in both DMSO and DMF. Reactions were monitored by ^{19}F NMR at regular intervals over 180 min. Both solvents displayed a relatively rapid initial rise in conversion to around 70% before leveling off to a much slower rate of increase (Figure 8). The initial rate of increase in DMSO, however, was much more rapid than that seen in DMF. One possible explanation for the high performance of DMSO as a quaternization solvent involves the interplay of several effects. First is a reagent concentration effect. If the resin is considered as a second solvent phase, then the largely nonpolar quaternization reagents would prefer the polymer interior to the highly polar bulk solvent (DMSO). This would result in a high concentration of quaternization reagent within the polymer and consequent increases in reaction rate.[9] Once initiated, quaternization would be favored by DMSO, which would stabilize the charged transition state and final products.[13] As reaction proceeds and the polymer interior becomes more polar, the preference of the quaternization reagent for the polymer interior would become less marked, resulting in a lower concentration of reagent within the polymer. This would lead to a slowing of rate similar to that seen in Figure 8. This may be expected to be offset somewhat by the high degree of swelling displayed by the quaternized product in DMSO, resulting in easier access to the polymer interior by reagents.

In summary, a study into the effects of reaction variables on REM resin-bound quaternization reactions has been performed. This has highlighted DMSO as a more effective solvent than the traditionally used DMF for these reactions. The high yields seen with DMSO may be a consequence of a combination of the solvent's ability to stabilize reactions involving charged transition states/products, an initial concentration of the quaternization reagent into the polymer interior, and the high swelling seen by the quaternization product in DMSO. Highest yields of products were seen after quaternization at room temperature for 18 h, in agreement with the conditions previously reported.[2] The use of heating for extended reaction times tended to depress yields, indicating product cleavage during quaternization. Quaternization on PS-DVB resin was found to be more robust than those reactions on PS−PEG matrixes where yields were generally considerably lower than the observed conversions. In addition, reaction on macroporous polystyrene was found to give

poor initial rates of quaternization. Perhaps surprisingly water was found to be an effective solvent for quaternization on PS−PEG and macroporous resins, an observation attributed to a reagent concentration effect. The success of quaternization in water may eventually lead to a reduction of organic waste solvent from the process.

Experimental Section

General. All resins were purchased from Argonaut Technologies. REM resin synthesis and Michael reaction were performed according to published procedures.[2b] Loading levels of amine prior to quaternization were confirmed by microanalysis (N and F determination was performed on a Perkin-Elmer 2400 elemental analyzer). Gel-phase ^{19}F NMR spectra were obtained on CDCl$_3$ suspensions of resin and were recorded on a Bruker DRX-400 NMR instrument with a 5 mm dual probe with the ^{1}H channel tuned to ^{19}F at 376.50 MHz. A 1D spin−echo with a gradients pulse program was used with a ^{19}F 90° pulse width of 19.5 μs and two 1 ms gradients of 15% of the maximum gradient strength of 60 G cm^{-1}. The data were collected in 64 scans with a sweep width of 56 500 Hz. The pulse program was implemented in automation, and shimming was not found to be necessary, thus allowing a turnaround time of <5 min per sample.

Quaternization. A suspension of Michael product **2** (0.05 mmol) in the appropriate solvent (1 mL) was treated with quaternization reagent **8** or **9** (0.25−1 mmol) and agitated for the correct time at the correct temperature. Once reaction time was complete, the suspension was filtered, washed (3 × 1 mL DMF, DCM, MeOH), and air-dried. Samples for analysis by ^{19}F NMR were resuspended in DMF (1 mL) and treated with HCl in diethyl ether (2 M, 0.25 mL, 0.5 mmol). The resin was then agitated at room temperature for 0.5 h, filtered, washed as above, and air-dried.

Hofmann Elimination. A suspension of REM resin-bound quaternary ammonium salt (0.05 mmol) in DCM (1 mL) was treated with diisopropylethylamine (0.017 mL, 0.1 mmol) and agitated at room temperature for 6 h. The mixture was then filtered through potassium carbonate (∼50 mg), the resin was washed with DCM (3 × 1 mL), and the combined organic layers were concentrated in vacuo. Yield was determined by ^{1}H NMR with an *N*-methyl maleimide internal standard (CDCl$_3$ solution, 3 mg/mL, 0.0276 mmol/mL).

Supporting Information Available. The complete data set for the investigation, gel-phase ^{19}F NMR spectra of intermediates, and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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