Synthesis of Tertiary Amines Using a Polystyrene (REM) Resin

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Abstract: A range of tertiary amines was constructed using a "traceless" linker on a polystyrene resin (REM resin), starting from secondary amines, primary amines, and resin-bound "ammonia". The methodology is characterized by three essential steps conducted under ambient conditions: (1) coupling of the starting amine (Michael addition) to the resin, (2) activation (quaternization), and (3) cleavage of the product amine (Hofmann elimination). The linker is compatible with both acid and base sensitive protecting group strategies. The nature of the chemistry ensures that the tertiary amine products are obtained in consistently high purity (95% or greater). After cleavage of the product, REM resin is regenerated and can be reused for repeat syntheses. The yield and purity of repeat batches is maintained over 5 cycles, allowing the automated synthesis of >0.5 g quantities of pure tertiary amine.

In recent years, solid phase chemistry has evolved from being largely the preserve of peptide and oligonucleotide chemists to become a mainstream activity carried out by an ever-increasing number of organic chemists. The principal driving force for this change of emphasis has been the search within the pharmaceutical industry for libraries of small organic molecules to generate new leads and accelerate the process of drug discovery.[1] Solid phase synthesis is particularly suitable for combinatorial chemistry, and its advantages over traditional solution phase chemistry have been discussed many times before.[2] One limitation of early solid phase linker strategies was the presence of a resin-tethering substituent in the final product. Many strategies involved an ester or amide linkage to a polystyrene resin, which upon cleavage produced a carboxylic acid, amide, ester, or alcohol group in the product.[3] Such polar and metabolically labile substituents often compromise bioavailability and are best avoided unless they contribute significantly to binding to the target protein. Hence, much effort is now being directed toward the development of "traceless linkers" which leave no evidence of resin attachment in the final product. For the attachment of aromatic groups to resins, Ellman[4] and Veber[5] have described silicon-based traceless linkers and Sucholeiki has described a thioether linker.[6] Another approach which has proved useful for the synthesis of heterocycles, such as diketopiperazines,[7] quinazolinediones,[8] benzodiazepines, and hydantoins,[9] involves an intramolecular cyclization step to facilitate cleavage from the resin.

Tertiary amines are an extremely important class of compound from the drug discovery perspective. Indeed no less than a quarter of registered drugs contain tertiary amines.[10] They are particularly common in drugs which are active within the central nervous system. Our study was prompted by the conspicuous lack of a methodology whereby tertiary amines could be constructed on a resin from commercially available primary and secondary amines using a traceless linker.[11] Such a strategy would preferably require the nitrogen of the amine to be part of the bond which is broken during cleavage from the resin. We concluded that the classical Hofmann elimination reaction would serve our purposes well.[12,13] The reaction is usually considered to be a useful method for the synthesis of alkenes and indeed had previously been used by Bradley and co-workers to synthesize dehydroalanine derivatives on a resin.[14] It became apparent that we could achieve our objective of releasing a tertiary amine into solution while the alkene component remained resin-bound.

The sequence of reactions required to produce the tertiary amine is shown in Scheme 1.[15] In the first step, the acrylate-functionalized polystyrene resin **2**[16] is prepared from commercially available (hydroxymethyl)polystyrene resin **1** and acryloyl chloride. A primary or secondary amine then undergoes a Michael addition to **2** to give a secondary or tertiary

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1997.

(1) Terrett, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385.

(2) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.

(3) Frechet, J. M. J. In *Polymer-supported Reactions in Organic Synthesis*; Hodge, P., Sherrington, D. C., Eds.; John Wiley & Sons: New York, 1980; Chapter 6, p 294.

(4) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006.

(5) Chenera, B.; Finkelstein, J. A.; Veber, D. F. *J. Am. Chem. Soc.* **1995**, *117*, 11999.

(6) Sucholeiki, I. *Tetrahedron Lett.* **1994**, *35*, 7307.

(7) Gordon, D. W.; Steele, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 47.

(8) Smith, A. L.; Thomson, C. G.; Leeson, P. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1483.

(9) Hobbs DeWitt, S.; Kiely, J. S.; Stankovic, C. J.; Schroeder, M. C.; Reynolds Cody, D. M.; Pavia, M. R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909.

(10) This estimate was obtained by searching the World Drugs Index (Derwent Information Ltd.) for compounds with a tradename which also contain a tertiary amine group.

(11) The parallel synthesis of tertiary amines has been reported previously using (a) an ester or amide tether to polystyrene resin (Green, J. *J. Org. Chem.* **1995**, *60*, 4287) or (b) solution phase methods incorporating solid phase scavengers (Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193).

(12) β-Eliminations of carboxylic acids from a solid support have been reported previously: (a) Katti, S. B.; Misra, P. K.; Haq, W.; Mathur, K. B. *J. Chem. Soc., Chem. Commun.* **1992**, 843. (b) Eritja, R.; Robles, J.; Fernandez-Forner, D.; Albericio, F.; Giralt, E.; Pedroso, E. *Tetrahedron Lett.* **1991**, *32*, 1511.

(13) Hofmann, A. W. *Annalen* **1851**, *78*, 253.

(14) Blettner, C.; Bradley, M. *Tetrahedron Lett.* **1994**, *35*, 467.

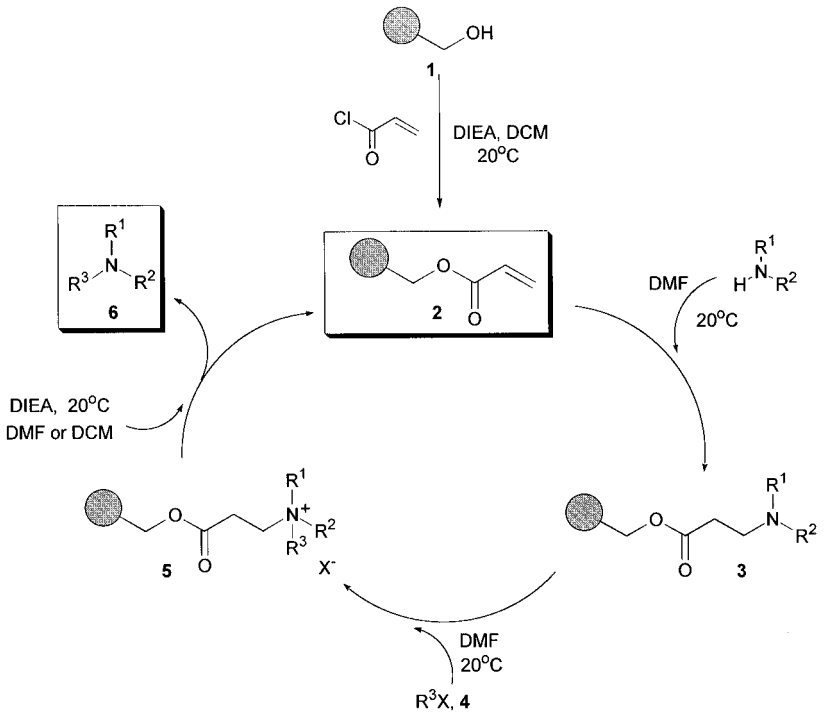
(15) Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209.

(16) The resin has also been prepared from Merrifield resin and cesium acrylate: Cody, D. R.; DeWitt, S. H. H.; Hodges, J. C.; Kiely, J. S.; Moos, W. H.; Pavia, M. R.; Roth, B. D.; Schroeder, M. C.; Stankovic, C. J. PCT Int. App. WO 9408711; *Chem. Abstr.* **1995**, *122*, 106536.

(17) Ramage, R.; Stewart, A. S. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1947.

S0002-7863(96)03829-2 CCC: $14.00

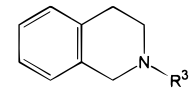
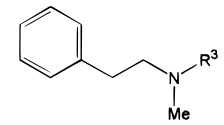
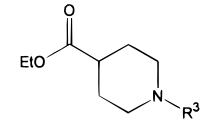
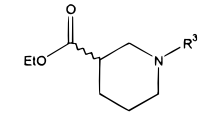
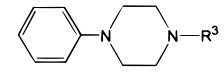
Scheme 1



amine **3**, respectively. In the former case, the secondary amine can be converted to a tertiary amine by adding a reductive alkylation step. Quaternization of the tertiary amine with an alkyl halide **4** sets the scene for a facile Hofmann elimination of the resulting quaternary ammonium salt **5**, releasing the tertiary amine **6** into solution. Since **2** is regenerated after cleavage of the product and is initially functionalised via a Michael reaction, we refer to the resin, in our laboratories, as REM resin.

Initially, we demonstrated the methodology with the synthesis of a small library of 10 tertiary amines (**6a**−**j**) derived from commercially available secondary amines (Table 1). 1,2,3,4-Tetrahydroisoquinoline, *N*-methylphenethylamine, ethyl isonipecotate, ethyl nipecotate, and *N*-phenylpiperazine were found to undergo addition to REM resin at room temperature in dimethylformamide (DMF) (18 h). The reactions were carried out in disposable polypropylene tubes using 10 equiv of the amine. The resulting tertiary amines were quaternized using allyl bromide or *p*-nitrobenzylbromide (5 equiv) in DMF at room temperature (18 h). Heating to 50 °C produced no benefit in terms of either the yield or purity of the final product. The Hofmann elimination was promoted using 2 equiv of diisopropylethylamine (Hunig's base, DIEA). Either DMF or dichloromethane (DCM) served as suitable solvents. Isolation of the product was easier when DCM was used, but in this case increased amounts of aliphatic impurities were also present, presumably dissolved from the polypropylene tubes and the polystyrene resin. Fortunately, these were easily removed, together with any DIEA·HBr salt, by running the DCM solution through a silica solid phase extraction (SPE) cartridge containing powdered potassium carbonate. A combination of 1 equiv of DIEA and 10 equiv of powdered potassium carbonate was also effective for promoting the Hofmann elimination. Upon evaporation of the cleavage solution, only the desired amine **6b** and a small amount of plasticizer were observed by NMR. The DIEA, having been deprotonated by the K_2CO_3, was volatile. For product **6b**, it was found that triethylamine (TEA) could be used in place of DIEA without compromising either yield or purity (Table 1).

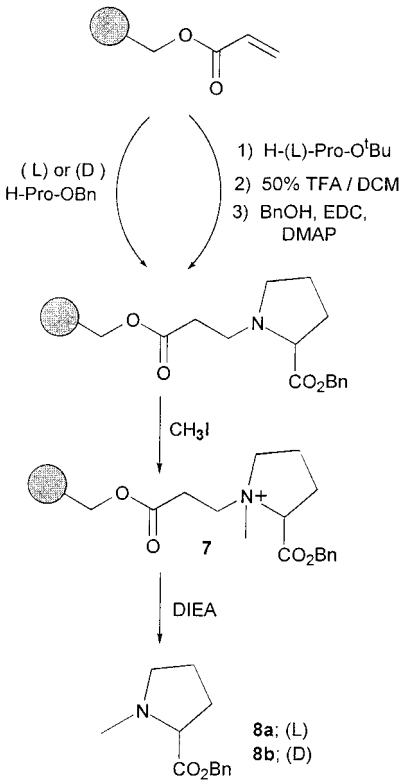
Table 1. A Library of Tertiary Amines Produced on REM Resin

Tertiary Amine	R^3= allyl % yield[a]	% purity[b]	R^3= *p*-nitrobenzyl % yield[a]	% purity[b]
	**6a;** 88 87[c]	99	**6b;** 72 66[d] 70[e]	98
	**6c;** 81	99	**6d;** 61	99
	**6e;** 78	98	**6f;** 64	98
	**6g;** 41	97	**6h;** 48	96
	**6i;** 75	99	**6j;** 47	97

[a] Percent yields for 3 steps based on the resin substitution level determined by the Fmoc quantitation method.[17] [b] Percent purity as determined by gas chromatography. [c] Yield obtained using the 3-bromopropionate ester of hydroxymethylpolystyrene resin in place of the acrylate ester. [d] Yield obtained using 2 equiv of TEA in place of DIEA for the elimination step. [e] Yield obtained using 1 equiv of DIEA and 10 equiv of K_2CO_3 for the elimination step.

The purity of the products after SPE was determined by gas chromatography to be greater than 95%. The high purity is presumably due to the nature of the chemistry involved. Each step in the sequence has to be successful in order for the final Hofmann elimination to occur. Pure product is even obtained

Scheme 2



in some cases where the quaternary ammonium intermediate contains more than one possible site for the Hofmann elimination to occur. For example, in the synthesis of the nipecotate esters **6g** and **6h**, the desired products are still obtained in reasonable yield (41 and 48%, respectively) and excellent purity (97 and 96%, respectively), presumably because any compound formed by elimination occurring within the piperidine ring remains resin-bound.

The synthesis of **6a** was repeated using the 3-bromopropionate ester of (hydroxymethyl)polystyrene resin as the solid phase starting material in place of the acrylate ester. The subsequent quaternization and elimination steps were performed as before. No significant difference in either the yield or purity of product **6a** was observed compared to the REM resin synthesis (Table 1). This may suggest that the mechanism of addition of the secondary amine to the resin is the same: the amine initially promoting elimination of the 3-bromopropionate ester to the acrylate, followed by a Michael addition.

Since the methodology is conceivably of value for constructing libraries of N-terminally alkylated α-amino acid derivatives, the effect of the reaction sequence on the chiral integrity of the α-carbon was examined. Either L- or D-proline benzyl ester (10 equiv) in DMF was added to REM resin (Scheme 2). After quaternization using methyl iodide (10 equiv) in DMF, the *N*-methylproline benzyl esters (**8a** and **8b**) were eliminated from the resin using DIEA (5 equiv) in DCM. We were concerned that treatment of the quaternized α-amino ester **7** with base may racemize the α-carbon, in addition to promoting the desired Hofmann elimination. The chiral purity of the two products was therefore determined using chiral HPLC (CHIRACEL OJ column). The L-enantiomer **8a** had an enantiomeric purity of 97.8% (61% overall yield). The D-enantiomer **8b** had an enantiomeric purity of 96.4% (69% overall yield).

We wanted to assess the acid stability of the linker by attempting to synthesize **8a** via a *tert*-butyl ester intermediate (Scheme 2). After adding proline *tert*-butyl ester to REM resin, the ester was cleaved using 50% TFA in DCM (6 h, 20 °C), and the resulting acid was converted to the benzyl ester using benzyl alcohol, 4-(dimethylamino)pyridine (DMAP), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide (EDC) in DCM (18 h, 20 °C). After quaternization with iodomethane and cleavage with DIEA, **8a** was obtained in 53% yield and 97% purity (92% enantiomeric purity).

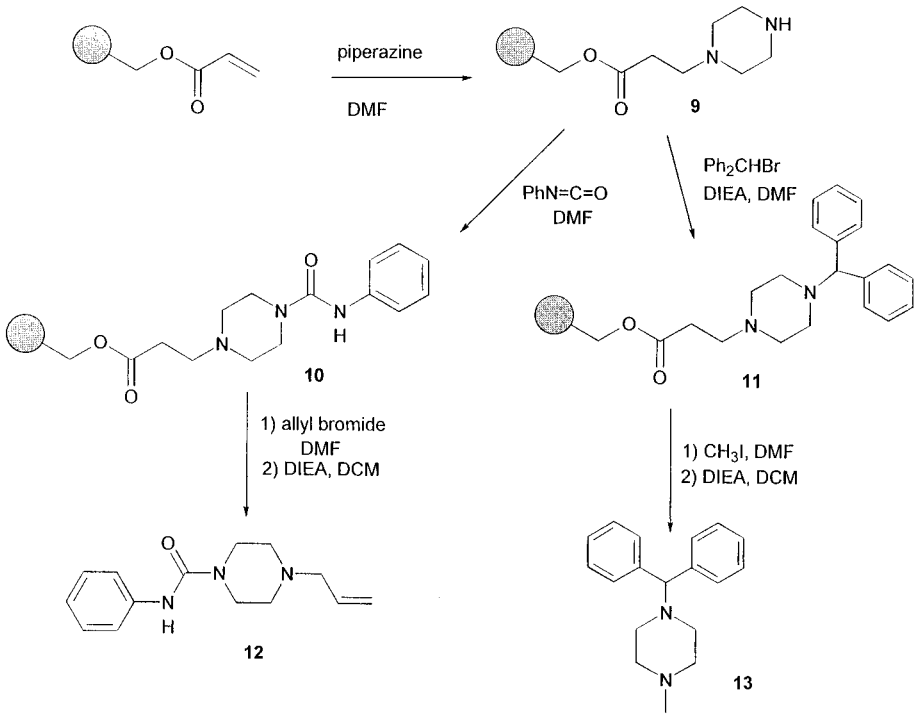
It is possible to use REM resin to perform syntheses requiring the monoalkylation of diamines, without the use of protecting groups. For example, piperazine can be added to REM resin to give the monoalkylated derivative **9**, which can then be acylated or alkylated cleanly at the second nitrogen (Scheme 3). Subsequent reaction with phenyl isocyanate or benzhydryl bromide generates **10** or **11**, respectively. Quaternization and elimination provides products **12** and **13** in 36 and 44% overall yields, respectively. The purity of **12** and **13** was >99% by gas chromatography. The high purity of **13** demonstrates that although quaternization at the "wrong" nitrogen in piperazines may occur, it does not reduce the purity of the final product. Again, only the correct product can cleave from the resin. The synthesis of **13,** the antiemetic drug, *marzine*, serves to demonstrate the utility of REM methodology for preparing pharmacologically interesting compounds.

We have found that the method works well when the quaternization step can be conducted at ambient temperature using reactive alkyl halides, e.g., allyl, benzyl, and methyl halides. However, if less-reactive alkylating agents are used, the quaternization step requires heat. For example, quaternization of a resin-bound tertiary amine with *n*-butyl iodide does not occur to any appreciable extent at 20 °C in DMF, but requires heating at 60 °C for 24 h. Unfortunately, the elevated temperature causes the Hofmann elimination to occur prematurely, releasing the *n*-butyl derivative into solution where it becomes susceptible to quaternization by a second equivalent of *n*-butyl iodide. Nonetheless, we were able to isolate 2-*n*-butyl-1,2,3,4-tetrahydroisoquinoline in 56% yield, after SPE purification to remove a small amount of 2,2-bis(*n*-butyl)-1,2,3,4-tetrahydroisoquinolinium iodide. We are currently working on a new linker which should be more thermally stable once quaternized and thereby prevent premature cleavage from the resin occurring when less-reactive alkyl halides are used. An attempt to quaternize resin-bound 1,2,3,4-tetrahydroisoquinoline using isopropyl iodide was unsuccessful at 60 °C, presumably due to steric hindrance.

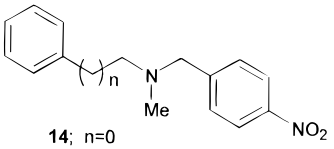
The primary amines, benzylamine and phenethylamine, underwent the Michael addition using the same conditions as the secondary amines. The resulting resin-bound secondary amines were then reductively alkylated with *p*-nitrobenzaldehyde in the presence of sodium triacetoxyborohydride. Both were quaternized using methyl iodide in DMF and eliminated using DIEA in dichloromethane. Although the synthesis starting from phenethylamine gave a good yield of product **6d** (75%), the benzylamine-derived product **14** was isolated in only 8% yield. This probably reflects the difficulty of quaternizing the poorly nucleophilic bisbenzylic intermediate. When **14** was synthesized by reversing the reductive alkylation and quaternization steps, using paraformaldehyde and *p*-nitrobenzyl bromide, respectively, a much improved yield (86%) was obtained.

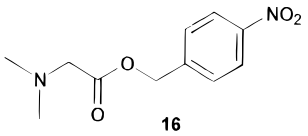
Tertiary amines can also be made from a resin-bound equivalent of ammonia, as shown in Scheme 4. The ammonia equivalent **15** is derived from the coupling of Fmoc-*β*-alanine to hydroxymethyl resin, followed by Fmoc deprotection using piperidine. Double reductive alkylation using paraformaldehyde, followed by quaternization using *p*-nitrobenzyl bromoacetate and Hofmann elimination, provided **16** in 38% yield (for four steps) and 97% purity. Sequential reductive alkylation

Scheme 3



using *p*-nitrobenzaldehyde and paraformaldehyde, followed by quaternization using benzyl bromide and Hofmann elimination, provided **14** in 31% yield (for five steps) and 98% purity.



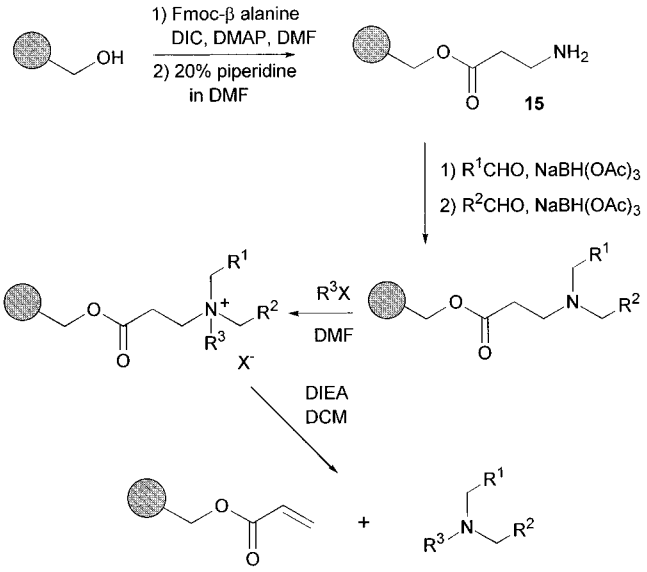


Reaction Monitoring. The current shortage of reliable and nondestructive analytical techniques for monitoring on-resin reactions is often rate limiting in the development of new solid phase chemistry. Two techniques which have been employed successfully are FT-IR, in which the resin sample is prepared as a KBr disk, and gel phase ^{13}C NMR,[18] in which the resin is swollen in a suitable solvent, often $CDCl_3$, DMF, or benzene. FT-IR is destructive since the resin must be prepared as a powder and the information content of a spectrum is often limited. Gel phase NMR produces very broad lines and often the use of ^{13}C-enriched material is required to improve the sensitivity of the technique. Fortunately, both FT-IR and ^{13}C gel phase NMR are reasonably effective for monitoring reactions carried out on REM resin.

The resin contains a conjugated carbonyl group whose IR absorption shifts to higher frequency as deconjugation occurs during the Michael addition. Of course, the technique is not quantitative, but we can reasonably assume the reaction to be complete when no further shift occurs. In addition, the band at 1403 cm^{-1}, due to in-plane bending of the alkene CH, disappears during the reaction. The carbonyl absorption

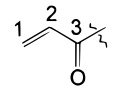
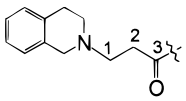
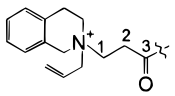
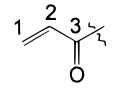
(18) Look, G. C.; Holmes, C. P.; Chinn, J. P.; Gallop, M. A. *J. Org. Chem.* **1994**, *59*, 7588.

Scheme 4



frequencies observed during the synthesis of 2-allyl-1,2,3,4-tetrahydroisoquinoline **6a** are shown in Table 2 (see also pp 24−27 of the Supporting Information). Not surprisingly, there is no significant shift in the position of the carbonyl band during quaternization; therefore, this reaction cannot be followed by IR. It is apparent that the carbonyl band returns to its original position after the Hofmann elimination as REM resin is regenerated. The presence of other functional groups can sometimes help reaction monitoring. For example, the reductive alkylations and quaternizations using nitro-containing compounds were followed by observing the intensity of the NO_2 absorption at 1523 cm^{-1}. The poor yield of **14** obtained initially (8%) was ascribed to the slowness of the quaternization of the bisbenzylic intermediate, on the basis of the intensity of the NO_2 peak being little changed after the attempted cleavage. This is supported by the fact that **14** was obtained in much better yield simply by reversing the reductive alkylation and quaternization steps. Since the quaternary ammonium compound is

Table 2. Reaction Monitoring Using FT-IR and ^{13}C NMR

	FT-IR (cm^{-1})	^{13}C NMR (ppm)		
	C^3=O	C^1	C^2	C^3
	1717	128	131	166
	1728	53	32	172
	1729	53	28	169
	1718	128	131	166

common to both routes, the final cleavage step cannot be causing the problem.

To facilitate the use of gel phase ^{13}C NMR to monitor the reactions in a more quantitative way, ^{13}C-enriched REM resin was prepared. Acrylic acid, in which each of the three carbons was 99% ^{13}C, was diluted to 20% enrichment using natural abundance acrylic acid and then coupled to (hydroxymethyl)-polystyrene resin using the carbodiimide method (DIC, DMAP, DCM, 20 °C, 18 h). The positions of the three labeled acrylate resonances, after the resin was swollen in $CDCl_3$, are given in Table 2. The carbonyl carbon in REM resin is clearly visible at 166 ppm, but the vinyl resonances (128 and 131 ppm) overlap with the aromatic resonances due to the polystyrene resin (Figure 1). After treatment with a 20% solution of 1,2,3,4-tetrahydroisoquinoline in DMF for 18 h at 20 °C, the carbonyl resonance is shifted downfield due to deconjugation. Two new resonances at 53 and 32 ppm are due to the methylenes next to the nitrogen and carbonyl, respectively. The resonances in the labeled resin show multiplicity, theoretically 2 doublets and 1 triplet, due to coupling between neighboring ^{13}C nuclei. The absence of a carbonyl resonance at 166 ppm was suggestive of the Michael reaction having proceeded to completion. To demonstrate the value of using 20% ^{13}C enriched resin, the ^{13}C spectrum of natural abundance resin is also shown in Figure 1.

After treatment with allyl bromide in DMF (5 equiv, 18 h, 20 °C), the carbonyl resonance was shifted slightly upfield (169 ppm). Somewhat unexpectedly, the the position of the CH_2 adjacent to nitrogen was unchanged, but the CH_2 next to the carbonyl was shifted upfield (28 ppm). In solution, the position of a carbon resonance adjacent to nitrogen is shifted downfield, by 3−8 ppm, upon quaternization. In this case, where the compound is resin-bound, the shift does not occur, conceivably due to shielding effects from the many aromatic groups found in polystyrene resin. The lack of resonance at 32 ppm is suggestive of the reaction having gone to completion.

The Hofmann elimination was promoted using 2 equiv of DIEA in DMF (18 h, 20 °C). The carbonyl resonance shifted back to its original position at 166 ppm, and the two allyl resonances were visible despite the overlying aromatic resonances of the resin. The resonance at 28 ppm had completely disappeared, suggesting the elimination was complete.

Resin Recycling. Both FT-IR and gel phase ^{13}C NMR showed that the resin regenerated after the cleavage of **6a** to be identical to the starting resin. We were therefore curious to discover whether the regenerated resin was reusable and in particular whether yield and purity would be maintained for a second batch of **6a**.

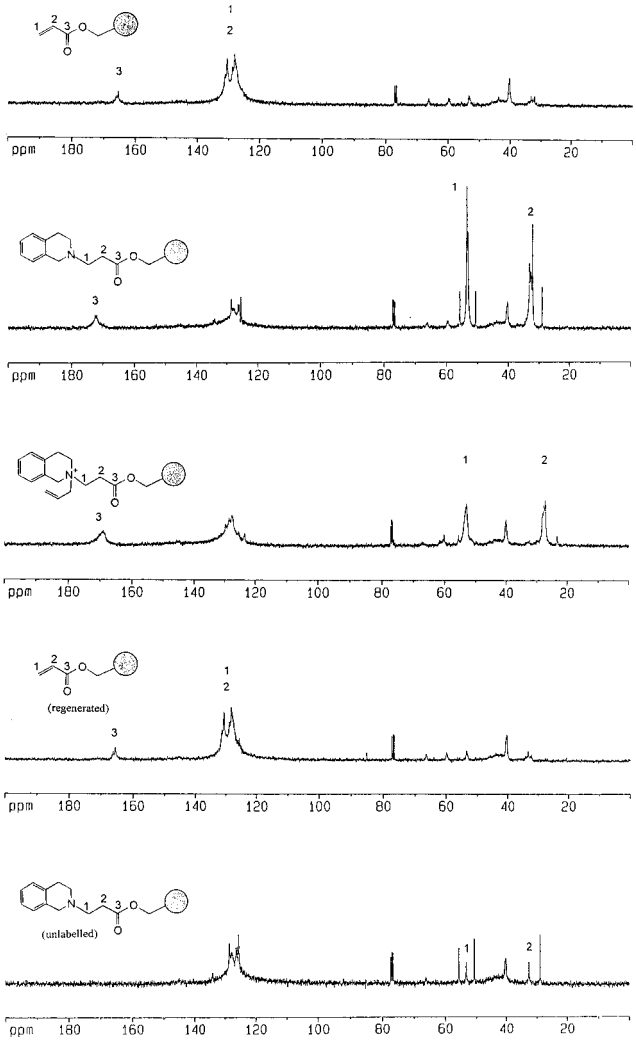
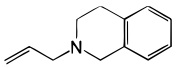


Figure 1. Gel phase ^{13}C spectra of resin-bound intermediates in the synthesis of **6a**.

A single batch of unlabeled REM resin (300 mg) in a single polypropylene tube was used for the repeat synthesis of four batches of **6a**, using the reaction conditions described earlier (18 h per reaction at 20 °C). The yields for the four batches after purification by SPE were as follows: (1) 33 mg (86%); (2) 36.5 mg (95%); (3) 31.5 mg (82%); (4) 33.8 mg (88%). Thus, the yield showed no sign of deteriorating over four cycles. The purity of the products was also maintained, since the 400 MHz ^1H NMR spectra of **6a** for each of the four cycles were virtually identical (see pp 19−22 of the Supporting Information). Although the above sequence of reactions demonstrated the reusability of REM resin, a total of 216 h was required to produce 135 mg of product from 300 mg of REM resin (2.1 mg of product per 1 g of resin per hour). We were eager to discover whether each cycle could be condensed into a single working day.

The four cycles were thus repeated over 4 days, allowing 2.5 h for each of the three reactions within a cycle. The yields and purities for the four batches of **6a** are given in Table 3. Again, the yield and purity shows no sign of deteriorating over 4 cycles. The lower yields, compared to the first recycling experiment, indicate that one or more of the reactions are not going to completion. Nonetheless, this protocol is more efficient

Table 3. Manual REM Resin Recycling

 **6a**	Yield (mg)	% Yield[a]	% Purity[b]
CYCLE 1	60.3	47	98.9
CYCLE 2	62.1	48	99.3
CYCLE 3	59.6	46	98.8
CYCLE 4	64.0	50	99.0

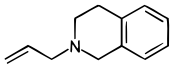
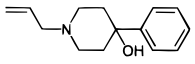
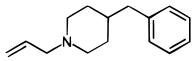
[a] Percent yields for 3 steps based on the resin substitution level determined by the Fmoc quantitation method.[17] [b] Percent purity as determined by gas chromatography.

in terms of the amount of compound generated in a given time (246 mg in 30 h = 8.2 mg of product per 1 g of resin per hour). These results also suggest that the high purity of the final products is not dependent upon individual reactions within the sequence going to completion, since only the correct product cleaves from the resin.

In order to attempt to discover which of the three steps was rate and yield limiting, we performed an experiment in which REM resin was reacted with two amines in sequence: 1,2,3,4-tetrahydroisoquinoline (10 equiv) in DMF for 2.5 h at 20 °C, followed after washing the resin by 4-benzylpiperidine (30 equiv) in DMF for 18 h at 20 °C. The Michael adduct was then treated with allyl bromide (5 equiv) in DMF for 2.5 h at 20 °C, followed after washing the resin by methyl iodide (25 equiv) in DMF for 18 h at 20 °C. Cleavage was then performed using DIEA (2 equiv) in DCM for 2.5 h at 20 °C, followed after washing the resin by more DIEA (10 equiv) in DCM, for a further 42 h at 20 °C. This experiment could potentially produce up to four products, 2-allyl-1,2,3,4-tetrahydroisoquinoline, 2-methyl-1,2,3,4-tetrahydroisoquinoline, 1-allyl-4-benzylpiperidine and 1-methyl-4-benzylpiperidine, if both the Michael addition and quaternization steps are incomplete after 2.5 h. The crude product from the 2.5 h cleavage step was analyzed by GC-MS (see p 32 of the Supporting Information). Two products, 2-allyl-1,2,3,4-tetrahydroisoquinoline and 2-methyl-1,2,3,4-tetrahydroisoquinoline, are apparent in a ratio of 4.8:1, respectively. The lack of any 4-benzylpiperidine-containing products suggests that the Michael addition is progressing to completion. However, the presence of 2-methyl-1,2,3,4-tetrahydroisoquinoline indicates that the quaternization using allyl bromide is only about 80% complete after 2.5 h. The cleavage step appeared to be complete after 2.5 h, since no further product was evident after prolonged treatment of the resin with a large excess of DIEA. Thus, the yield-limiting step in the manual-recycling synthesis appears to be the quaternization.

The full potential of this recycling strategy would be realized if the above protocol could be automated using a continuous flow system capable of running 24 h a day until the desired amount of product has been synthesized (see Scheme 1). Toward this goal, we used a MultiSyntech SyRo II robot to synthesize three tertiary amines, **6a**, **17,** and **18** (Table 4). The reaction block comprises 60 individual 5 mL glass vessels. To each vessel was added 100 mg of REM resin. The resin samples were then treated, in three groups of 20, with one of the starting amines: 2-allyl-1,2,3,4-tetrahydroisoquinoline, 4-hydroxy-4-phenylpiperidine, or 4-benzylpiperidine (5 equiv, DMF, 50 °C, 2 h). All samples were then quaternized with allyl bromide (10 equiv, DMF, 50 °C, 2 h) and eliminated using DIEA (5 equiv, 1,4-dioxane, 50 °C, 2 h). The dried resin was reused

Table 4. Automated REM Resin Recycling

	Tertiary Amine	Yield (mg)	% Yield[a]	% Purity[b]
6a		340	28	98
17		680	45	98
18		625	41	99

[a] Percent yields for 3 steps based on the resin substitution level determined by the Fmoc quantitation method.[17] [b] Percent purity as determined by reverse phase HPLC (see also the Supporting Information).

through five cycles of addition, quaternization, and elimination. The crude products from the five cycles were pooled, partitioned between ethyl acetate and 5% aqueous Na_2CO_3, separated, and evaporated to give **6a**, **17,** and **18**. Purity and yields are given in Table 4. Although a considerable amount of pure **6a** was obtained (340 mg), the percentage yield is somewhat lower than expected based on the manual synthesis result. It would appear that heating the reactions to 50 °C may have had a detrimental effect on the yield of **6a**, rather than the desired effect of driving the reactions further toward completion. On the other hand, it is conceivable that the lower yield of **6a** was due to a technical fault with the robotic system since the percentage yields of **17** and **18** are similar to that obtained for **6a** in the manual synthesis. Further optimization of the robotic synthesis is clearly required to reproduce the yields obtained manually. Nonetheless, hundreds of milligrams of pure tertiary amine were produced by a method which required little human intervention.

Conclusions. We have designed the first traceless linker which allows the assembly of tertiary amines on a polystyrene resin (REM resin) from either ammonia or primary or secondary amines. The Hofmann elimination is an effective cleavage mechanism for releasing tertiary amines into solution under mildly basic conditions. The purity of the products obtained using REM resin is consistently high, presumably due to the nature of the chemistry involved. The mild conditions involved in this new methodology are well suited to multiple parallel synthesis and the production of combinatorial libraries by manual or automated methods. Starting from a secondary amine, two sites of diversity can be introduced during a synthesis. From a primary amine, three sites of diversity are introduced. We have found that any racemization occurring during the synthesis of N-alkylated α-amino ester derivatives on REM resin is likely to be minimal. The REM linker is stable to both mildly acidic and basic conditions, making possible Fmoc protection of amines and *tert*-butyl ester protection of carboxylic acids. Boc protection of amines is also likely to be compatible with the resin, since the cleavage conditions are likely to be similar to those used for deprotecting *tert*-butyl esters. Diamines can be immobilized on REM resin and cleanly monoalkylated or monoacylated.

A combination of FT-IR and ^{13}C NMR enabled efficient tracking of the reactions involved in REM resin methodology. Using 20% ^{13}C-enriched resin enabled useful spectra to be obtained after just 10 min of acquisition time. In the case of the synthesis of **6a**, the three steps were shown to proceed to completion under ambient conditions, explaining the high yield and purity of the product.

REM methodology would appear to offer good scope for an effective automated resin recycling strategy, capable of producing multigram amounts of pure tertiary amine for use in biological assays where a larger amount of material is required, e.g., in *in vivo* experiments. The purity of the final product was found to be similar whether or not the individual reactions were driven to completion. Recycling could also be useful for producing large amounts of feedstock compounds for daughter library synthesis. We have also been able to reuse the 20% ^{13}C-enriched resin for reaction monitoring. This is very desirable in view of the high cost of synthesis. The recycling of resins for solid phase synthesis is not a new concept, having previously been reported by Wang and co-workers[19] for the synthesis of peptide hydrazides on (Hydroxymethyl)polystyrene resin and by McManus and co-workers[20] for the synthesis of carboxylic acids and esters using polymer-bound oxazolines. Nonetheless, surprisingly little practical reuse of resins is evident from the literature. Since resin handling is perhaps the most technically difficult and time-consuming operation within a automated system, the reuse of a single batch of resin within an individual reaction vessel becomes an attractive proposition, even when the resin is not a particularly expensive starting material.

Experimental Section

REM Resin Synthesis. (Hydroxymethyl)polystyrene resin (1 g, 0.58 mmol) [Bachem California, 0.58 mmol/g] was added to a 10 mL Biorad polypropylene tube. Anhydrous dichloromethane (7 mL) and diisopropylethylamine (866 μL, 5 mmol) were added, followed by acryloyl chloride (404 μL, 5 mmol). The vessel was then placed on a Stuart Scientific SB1 tube rotator and agitated for 4 h at 20 °C. The tube was placed on a VacMaster sample processing station, and the resin was washed with DCM (3 × 3 mL) and methanol (2 × 3 mL) and then dried in vacuo.

Synthesis of 2-Bromopropionate-Functionalized Polystyrene Resin. (Hydroxymethyl)polystyrene resin (0.5 g, 0.29 mmol) [Bachem California, 0.58 mmol/g] was suspended in a solution of 2-bromopropionoyl chloride (252 μL, 2.5 mmol) and DIEA (95 μL, 0.55 mmol) in anhydrous DCM (5 mL). After agitating on the rotator for 1.25 h at 20 °C, the resin was washed using the VacMaster station with DCM (3 × 3 mL) and methanol (2 × 3 mL) and dried in vacuo.

General Procedure for the Michael Addition. REM resin (500 mg, 0.29 mmol) was swollen with a solution of the amine (2.9 mmol, 10 equiv) in DMF (5 mL) in a polypropylene tube. After agitating on the rotator for 18 h at 20 °C, the resin was washed using the VacMaster station with DMF (3 × 2 mL), DCM (3 × 2 mL) and methanol (2 × 2 mL) and dried in vacuo.

General Procedure for the Reductive Alkylation. The resin (0.29 mmol) was swollen with a solution of the aldehyde (1.45 mmol) and acetic acid (50μl) in DMF (5 mL). Sodium triacetoxyborohydride (1.45 mmol) was added as a solid, and the suspension was agitated on the rotator for 18 h at 20 °C. The resin was washed using the VacMaster station with DMF (3 × 2 mL), 5% DIEA in DMF (3 × 2 mL), DMF (3 × 2 mL), DCM (3 × 2 mL), and methanol (2 × 2 mL) then dried in vacuo.

General Procedure for the Quaternization. The resin (0.29 mmol) was swollen with a solution of allyl bromide or *p*-nitrobenzyl bromide (1.45 mmol, 5 equiv) in DMF (5 mL) and was agitated on the rotator for 18 h at 20 °C. The resin was washed using the VacMaster station with DMF (3 × 2 mL), DCM (3 × 2 mL), and methanol (2 × 2 mL) and then dried in vacuo.

General Procedure for the Hofmann Elimination. A suspension of the resin in DCM (5 mL) containing DIEA (0.58 mmol) was agitated on the rotator for 5 h at 20 °C. The resin was drained and washed using the VacMaster station with DCM (3 × 3 mL). The filtrate was collected and evaporated.

(19) Chang, J. K.; Shimizu, M.; Wang, S. *J. Org. Chem.* **1976**, *41*, 3255.
(20) Colwell, A. R.; Duckwall, L. R.; Brooks, R.; McManus, S. P. *J. Org. Chem.* **1981**, *46*, 3097.

SPE Purification. The hydrobromide salt of DIEA and a trace amount of plasticizer was removed using an ISOLUTE-XL solid phase extraction column, containing 500 mg of silica and 50 mg of dried, powdered K_2CO_3. The crude material was loaded in DCM (0.7 mL), eluted with heptane (3 mL, plasticizer elutes) and then ethyl acetate (3 mL, elutes amine). Evaporation of the EtOAc provided the product as a colorless gum.

Procedure for On-Resin Cleavage of *tert*-Butyl Esters. The resin obtained from the coupling of L-proline *tert*-butyl ester to REM resin (1.113 g, 0.75 mmol) was suspended in 50% trifluoroacetic acid in DCM (10 mL) in a polypropylene tube. After agitating on the rotator for 6 h at 20 °C, the resin was drained and washed using the VacMaster station with DCM (3 × 10 mL), 25% DIEA in DCM (3 × 10 mL), DCM (3 × 5 mL), and methanol (2 × 10 mL) and dried in vacuo.

Procedure for Urea Formation from Resin-Bound Piperazine. Resin **9** (0.50 g, 0.38 mmol) was suspended in a solution of phenyl isocyanate (410μl; 3.8 mmol) in DMF (7 mL) in a polypropylene tube. After agitating on the rotator for 20 h at 20 °C, the resin was drained and washed using the VacMaster station with DMF (3 × 5 mL), DCM (3 × 5 mL) and methanol (2 × 5 mL) and dried in vacuo.

Procedure for Alkylation of Resin-Bound Piperazine. Resin **9** (0.661 g, 0.486 mmol) was suspended in a solution of DIEA (846 μL, 4.86 mmol) and benzhydryl bromide (1.20 g, 4.86 mmol) in *N*-methyl-2-pyrrolidinone (7 mL) in a 15 mL glass test tube. After 18 h of stirring at 80 °C, the resin was filtered using a sintered glass funnel and washed with DMF (3 × 5 mL), DCM (3 × 5 mL), and methanol (2 × 5 mL) and dried in vacuo.

^{13}C-Enriched REM Resin. To a solution of acrylic acid (6.9 μL 99% [1,2,3-^{13}C$_3$]acrylic acid [Cambridge Isotope Laboratories] and 27.4 μL normal acrylic acid, total 0.5 mmol) and 4-(dimethylamino)pyridine (15 mg, 0.125 mmol) in DCM (2.5 mL) was added diisopropylcarbodiimide (78.5 μL, 0.5 mmol). After 30 min of agitation of the rotator, (Hydroxymethyl)polystyrene resin (250 mg, 0.15 mmol) was added, and the suspension was agitated on the rotator for 18 h at 20 °C. The resin was drained, washed (3 × 2 mL DCM, 3 × 2 mL DMF, 3 × 2 mL DCM, 2 × 2 mL CH_3OH), and dried in vacuo.

General Procedure for Manual Recycling Synthesis of Tertiary Amine 6a and for the Reaction-Monitoring Experiment. REM resin (1.0 g, 0.74 mmol) was suspended in a solution of 1,2,3,4-tetrahydroisoquinoline (927μl; 7.4 mmol) in DMF (7 mL) in a 15 mL polypropylene tube [Crawford Scientific] and agitated on a rotator for 2.5 h. The resin was drained and washed using the VacMaster station with DMF (4 × 2.5 mL) and then briefly dried under reduced pressure. The resin was resuspended in a solution of allyl bromide (326 μL, 3.7 mmol) in DMF (7 mL) and agitated on the rotator for 2.5 h. The resin was drained and washed using the VacMaster station with DMF (4 × 2.5 mL) and DCM (4 × 2.5 mL), then briefly dried under reduced pressure. The resin was resuspended in a solution of DIEA (266 μL, 1.48 mmol) in DCM (7 mL) and agitated on the rotator for 2.5 h. The resin was drained and washed using the VacMaster station with DCM (3 × 3 mL). The filtrate was collected and evaporated. The residue was partitioned between diethyl ether (3 mL) and aqueous sodium carbonate (2 mL, 5% w/v). The organic layer was separated, and the aqueous layer was reextracted with ether (2 × 2 mL). The combined organic extracts were dried (potassium carbonate) and evaporated to dryness. 2-Allyl-1,2,3,4-tetrahydroisoquinoline was obtained as a colorless oil. [Note: an aqueous extraction was used in this case for purification, since too much material was obtained for purification using a 500 mg silica SPE cartridge.]

General Procedure for Automated Recycling Synthesis of Tertiary Amines 6a, 17, and 18. REM resin (100 mg, 0.07 mmol) was added to the 60 glass vessels (5 mL) of a MultiSynTech SyRo II synthesis robot as an isopycnic slurry in DCM/DMF (1:1, 5 × 1 mL transfers per 100 mg of resin). The vessels were then drained, and the resin was washed with DMF (3 × 2 mL). Michael addition was carried out at 50 °C for 2 h by treating the swollen REM resin (20 vessels per amine, i.e., 2 g of resin per cycle) with 5 equiv of the secondary amines in DMF (2 mL). The vessels were then drained, and the functionalized resins were washed thoroughly with DMF (5 × 2 mL). Quaternization was accomplished by treating each resin portion with allyl bromide (10 equiv in DMF, 2 mL) for 2 h at 50 °C, before the vessels were again drained and washed with DMF (5 × 2 mL). Cleavage of the

crude products from the resin was carried out by treating each individual resin sample with diisopropylethylamine (5 equiv) in 1,4-dioxane (2 mL) at 50 °C for 2 h. The resin was then drained and washed with methanol (5 mL), and the combined filtrates were evaporated using a vacuum centrifuge (Savant SpeedVac). The individual products from each of the three starting amines were then pooled. This process was then repeated by returning the reaction vessels to the synthesis robot and repeating this sequence of Michael addition, quaternization, and Hofmann elimination a further 4 times (each resin portion was reacted with the same amine in all five cycles). Each total pooled product **6a**, **17**, or **18** was then partitioned between ethyl acetate (50 mL) and aqueous potassium carbonate (50 mL, 2 M). The organic phase was separated, and the aqueous phase was washed a further 2 times with ethyl acetate (50 mL). The organics were then combined, dried (K_2CO_3), and evaporated. [Note: An aqueous extraction was used in this case for purification, since too much material was obtained for purification using a 500 mg silica SPE cartridge.]

Determination of Resin Loading. The loading of (Hydroxymethyl)polystyrene resin was determined by the Fmoc quantitation method,[17] i.e., coupling of Fmoc-glycine, followed by deprotection using piperidine. The absorbance due to the liberated fulvene adduct was measured at 300 nm.

Gas Chromatography Procedure. The compounds were dissolved in methanol and loaded onto a Shimadzu 14A GC, fitted with a RTX-1 column (100% dimethylpolysiloxane; 30 m × 0.25 mm). Film thickness: 0.25 μm. Carrier gas: helium. Pressure: 2 kg/cm^2. Flame ionization detector. External standard: *n*-hexadecane.

Chiral HPLC Procedure. After purification by SPE, the compound (**8a** or **8b**) was dissolved in hexane/ethanol (3:1) and injected onto a Perkin Elmer HPLC system, comprising a CHIRALCEL OJ column (25 cm × 0.46 cm), Series 200 LC pump, ISS200 advanced LC sample processor, Diode array 235C detector, Nelson link 600 interface, and LC1010 oven. Eluent: hexane/isopropyl alcohol/diethylamine (99:1:0.1). Flow rate: 1 mL/min. UV detection at 220 nm. Temperature: 30 °C. Compound **8a** eluted at 21.86 min; **8b** eluted at 18.24 min. See also p 29 of the Supporting Information.

FT-IR Procedure. The resin sample was prepared as a 13 mm diameter 2% w/w KBr disk, and the spectrum was recorded on a Perkin Elmer 16PC Fourier transform infrared spectrometer. Resolution: 2 cm^{-1}. Apodization: weak. Number of scans: 5. Range: 4000−400 cm^{-1}. Smooth: 6.

Gel Phase ^{13}C NMR Procedure. The resin (100 mg) was added to a 5 mm NMR tube and swollen with $CDCl_3$. A PTFE vortex plug was inserted into the tube, and the resin was compressed at the bottom of the tube. The ^{13}C spectrum was recorded on a Bruker DRX400 spectrometer using a 5 mm inverse probe at 100.6 MHz ^{13}C frequency (non-spinning). Data size: 32K. Sweep width: 30 303 Hz. Acquisition time: 0.52 s. Relaxation delay: 1.0 s; 30° pulse with Waltz decoupling. Number of scans: 526 (10 min).

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Supporting Information Available: Characterization data for all compounds, including 400 MHz ^{1}H NMR data and spectra and HR-MS data; elemental analysis, gas chromatograph trace, and a ^{13}C NMR spectrum for **6a**; 400 MHz ^{1}H NMR spectra for the four batches of **6a** obtained during the manual recycling experiment; FT-IR spectra for the resin-bound intermediates in the synthesis of **6a**; Chiral HPLC data for compounds **8a** and **8b**; HPLC data for the compounds **6a**, **17**, and **18** obtained by automated resin recycling; and GC-MS data for the reaction monitoring of the manual recycling experiment (36 pages). See any current masthead page for ordering and Internet access instructions.

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