Chemical Library Purification Strategies Based on Principles of Complementary Molecular Reactivity and Molecular Recognition

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Abstract: A new methodology for solution-phase chemical library synthesis and purification is described. This approach applies fundamental properties of complementary molecular reactivity and recognition (CMR/R) as the basis for a general purification strategy. Specifically, parallel solution-phase reactions are purified by resins containing molecular recognition or molecular reactivity functionalities complementary to those of solution-phase reactants, reagents, and byproducts. When used in sequential or simultaneous combinations, various CMR/R resins remove excess reactants, reagents, and byproducts from solution-phase reaction products, which are isolated in purified form by filtration. Where reactions involve the need to remove byproducts or reagents that do not inherently contain sequestrable functionality, sequestration can be effected by the design and use of tagged reactants or reagents containing artificially-imparted molecular recognition functionality. An extension of this methodology utilizes CMR/R resins as the "quench phase" instead of a liquid-phase workup commonly used in other library purification strategies. Hence, the essential features of complementary molecular reactivity or molecular recognition required for reaction workup are expressed on resins. The CMR/R library purification strategy is general and highly amenable to automation. Examples are illustrated with amine acylations, the Moffatt oxidation, and the reaction of organometallics with carbonyl compounds.

Introduction

During the last few years, the exploration and utilization of combinatorial chemistry as a pharmaceutical drug discovery technology has rapidly evolved.[1] Whereas initial demonstrations of its use focused on the solid-phase synthesis of oligomers of amino acids[2] or nucleotides,[3] or on unnatural oligomers of other chemical building blocks (e.g. peptoids),[4] more recently the library synthesis of nonoligomeric small molecules has become an area of intense research activity.[5−8] Inherent in any approach to produce chemical libraries is the need to rapidly purify, isolate, and manipulate chemical library members during their intermediate and final synthetic steps of preparation. As the domain of chemical libraries expands into the diverse arena of organic small molecules, the demand is increasing for general methodologies to accomplish high-throughput product purification and isolation.

The initial solution to this conceptual challenge came by applying the technology of substrate-linked polymer-supported synthesis, wherein covalent tethering of library members to polymer supports is the molecular basis for product purification and isolation. This approach had previously been proven as a valuable strategy for the solid-phase synthesis peptides, peptoids, and other oligomers. Thus in 1992−93, the Ellman group[5a] and the Parke-Davis group[5b] independently reported on the solid-phase synthesis of the small organic chemical class of benzodiazepines. These seminal papers ushered in the era of small molecule solid-phase organic chemistry (SPOC). More recently, the use of liquid-phase extractive protocols (LPEP) has been reported as a second conceptual strategy for chemical library product purification. In this approach, whole molecule partitioning properties provide the molecular basis for product purification and isolation. Curran *et al.* have recently reported

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on the use of fluorous-containing stannane reagents which are easily separated from products by the separation of the reaction mixtures into three phases: aqueous, organic, and fluorous.[7] Cheng *et al.* have reported on the utilization of pH-adjusted liquid-phase extraction protocols for the purification and isolation of products away from reactants and reagents.[8] In both of these liquid-phase extractive approaches, the chemical library members were synthesized in solution phase rather than on a polymer support. Reactants and reagents were either chosen or designed to be separated easily from library products based on their selective partitioning into aqueous acidic, basic, fluorous, or organic phases. Herein we report on a third general strategy for small molecule chemical library synthesis which relies on inherent or artificially-imparted molecular recognition and/or molecular reactivity functionality as the basis for product purification and isolation.

Results and Discussion

With few exceptions, the synthesis of small molecule organic compounds relies on a serial number of reactions that can be categorized into one or more of the following classes: (1) bimolecular reactions (two reactants); (2) multicomponent reactions (more than two reactants); (3) reactions requiring catalysts to effect transformation; (4) reactions requiring reagents to effect transformation.

Regarding the first two classes, there are inherent reactive functionalities present in reactants that are not present in the resulting products; hence separation of products from excess reactant(s) on the basis of these inherent differences in *molecular reactivity* could form a basis for high-throughput purification of chemical library products. Additionally, in these reaction classes there are frequently byproducts formed which differ from products in their chemical functionality. While these byproduct forms are not usually reactive, they could be separated from products on the basis of *selective molecular recognition*.

Regarding the third and fourth reaction classes (as well as exceptions to reaction classes one and two listed above), there may not be the routine opportunity to separate products from catalysts, reagents, and byproducts based on inherent differences in molecular reactivity and/or molecular recognition. In these cases, *artifical-tagging* of catalysts, reagents, or reactants with desired functionality would allow for a quite general (and highly controllable) strategy for their separation from chemical library products based on *artificially-imparted molecular recognition* functionality. Incumbent on the tagging process is the requirement that the tag not interfere with the performance of the coded catalyst, reagent, or reactant class.

Fundamental to the success of such a library purification approach is the identification of a process for removing the above-mentioned reactants, byproducts, catalysts, and reagents (inherently functionalized or artificially tagged) by an "affinity phase" containing complementary molecular-recognition and/ or molecular-reactivity functionality. Implementation of this approach has led us to develop a general complementary molecular recognition/reactivity (CMR/R) library purification strategy with the following attributes: (1) library members are synthesized in solution phase; (2) reactants, catalysts, and reagents possess inherent or artificially-imparted recognition functionality to enable their post-reaction sequestration;[9] (3) the removal of solution-phase excess reactants, reagents, byproducts, and/or catalysts is accomplished by incubation and filtration of

the reaction mixture through resins containing complementary molecular-reactivity or -recognition functionality (CMR/R resins). Use of this strategy to sequester nonproduct species also allows the advantageous employment of multiple resins simultaneously, even if the functionalities present on the various resins are mutually incompatible.[10] The polymer-bound CMR/R functionalities, because of site isolation, react with or bind their solution-phase reaction counterparts faster than cross-quenching with an incompatible CMR/R resin; (4) purified products are obtained by simple filtration away from the selectively sequestered nonproduct species.[11] This process is highly adaptable to either benchtop (manual) library synthesis or to roboticized (automated) library synthesis.

This fundamental molecular recognition approach for chemical library product purification and isolation offers complementarity to the previously reported polymer-linked SPOC and solution-phase LPEP approaches. Reactions can be run in solution phase, obviating the need for linking initial reactant functionality to polymer supports.[12] Validation studies for reactions (performed to-date) require less time than SPOC reactions, where validation of reactions involves polymer-linked substrates in a heterogeneous medium. The CMR/R approach allows for the rapid purification of products by incubation with multiple CMR/R resins simultaneously, avoiding serial and more time-consuming liquid−liquid phase extractions for product isolation and purification. An extension of this purification methodology utilizes CMR/R resins as the "workup phase" instead of a liquid−phase workup commonly used in the other two approaches. Hence, the essential features of complementary molecular reactivity or molecular recognition functionality needed for reaction workup (proton transfer, metal exchange, protecting group transfer) are expressed on resins. When used in conjunction with the above sited reactant-, catalyst-, reagent-, and/or byproduct-CMR/R resins, reaction *purification and quenching* can be rapidly accomplished with minimal handling. While possessing these general advantages, the present methodology is not universally applicable, nor need it be used exclusive of SPOC and LPEP chemical library purification protocols. In practice, we have frequently utilized both SPOC and CMR/R, or LPEP and CMR/R, product purification strategies within a multistep chemical library synthesis.

Scheme 1 illustrates the CMR/R approach for a chemical library step which relies on the inherent molecular reactivity properties of reactants[13] and/or the inherent molecular recognition properties of byproducts as the basis for product purification and isolation. In parallel reaction chambers, excess reactants **B** are utilized to drive the solution-phase reactions of **A** to completion (formation of products **C**). Thus, as in the more common substrate-linked solid-phase organic chemistry (SPOC)

(9) After this manuscript was submitted, a report was published which disclosed the use of scavenging resins to remove excess amines or electrophiles from parallel solution-phase reactions: Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron. Lett.* **1996**, *37*, 7193−7196.
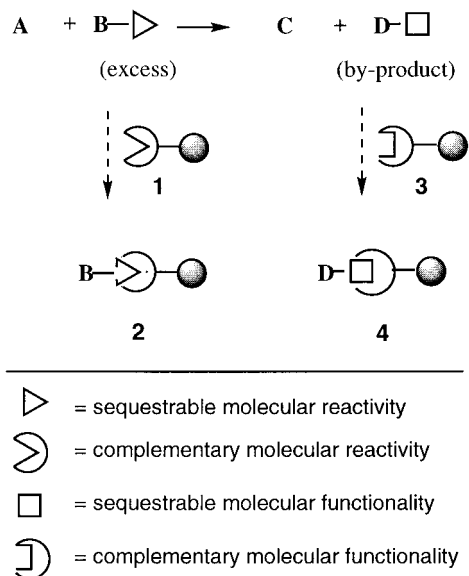
(10) The simultaneous use of multiple polymers in organic synthesis has been reported. In fact, multiple polymers containing mutually-incompatible functionality have been shown to be effective because of their spatial separation from each other. See: (a) Cohen, B. J.; Kraus, M. A.; Patchornik, A. *J. Am. Chem. Soc.* **1981**, *103*, 7620−7629. (b) Parlow, J. J. *Tetrahedron. Lett.* **1995**, *36,* 1395−1396.

(11) The alternative sequestration strategy where product is trapped by polymer away from solution-phase reagents has recently been described: Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574−2583.

(12) While the present sequestration purification strategy for solution-phase chemical libraries does rely on CMR/R resins to remove reactants and reagents, there is not the same concern about resin-loading capacity as in the substrate-linked solid-phase synthesis method. High-density functionalized resins can be used for CMR/R purification as there is not the concern about site-isolation that plagues substrate-linked solid-phase synthesis.

(13) The terms reactant and reagent have explicit meanings in the context of this strategy. A reactant is a starting material which becomes chemically incorporated into the product. A reagent is a chemical which mediates a transformation but does not become incorporated into the product.

Scheme 1. Illustration of the Use of Complementary Molecular Reactivity/Recognition (CMR/R) Resins for the Removal of Excess Reactants and/or Byproducts from Solution-Phase Reactions

Scheme 2. Application of CMR/R Technology for the Rapid Purification of Parallel Amine Acylation Reactions

approach, excesses of one or more reactants are utilized to completely consume a limiting reactant (**A**). After solution-phase reactions are complete, the excess reactants **B** are selectively removed from each reaction medium by CMR/R resin **1**. Resin **1** contains functionality complementary to the reactive functionality of **B**.[14] Reaction with, and sequestration of, excess **B** forms the polymer-bound adducts **2**. Simple incubation of the parallel reaction mixtures with resin **1**, followed by filtration and concentration, affords purified products **C**. If sequestrable byproducts **D** (containing inherently accessible molecular recognition functionality) are also formed, the concomitant use of a second CMR/R resin **3** is also used to chemoselectively sequester **D** as the polymer-bound adducts **4**. Resin **3** contains molecular recognition functionality complementary to **D**.

Scheme 2 illustrates the solution-phase parallel reactions of excess acylating agents **6**−**9** with amines **5** as a specific application. A complementary molecular reactivity resin **14** was used to effect removal of excess reactants (acylating agents **6**−**9**), and a complementary molecular recognition resin **19** or **20** was used to effect sequestration of the byproduct (HCl). The reaction of 2.5−5.0 fold excess acylating agents (isocyanates **6**, acid chlorides **7**, alkyl chloroformates **8**, and sulfonyl chlorides **9**) with primary or secondary amines **5** afforded ureas **10**, amides **11**, carbamates **12**, and sulfonamides **13** with excellent conversion and purity. Commercially available aminomethyl polystyrene resin **14** was utilized to chemoselectively react with excess isocyanate, acid chloride, sulfonyl chloride, or alkyl chloroformate after complete *solution-phase* conversion of amines **5**. Except for those cases employing isocyanates as the acylating agent, amberlyst A-21 resin **19** or polyvinylpyridine **20** was also used during the course of reaction to sequester the byproduct HCl.

Table 1 illustrates the results obtained by the parallel reactions of aniline, benzylamine, and dibenzylamine with the indicated acylating agents **6**−**9**. In all cases, good to excellent mass
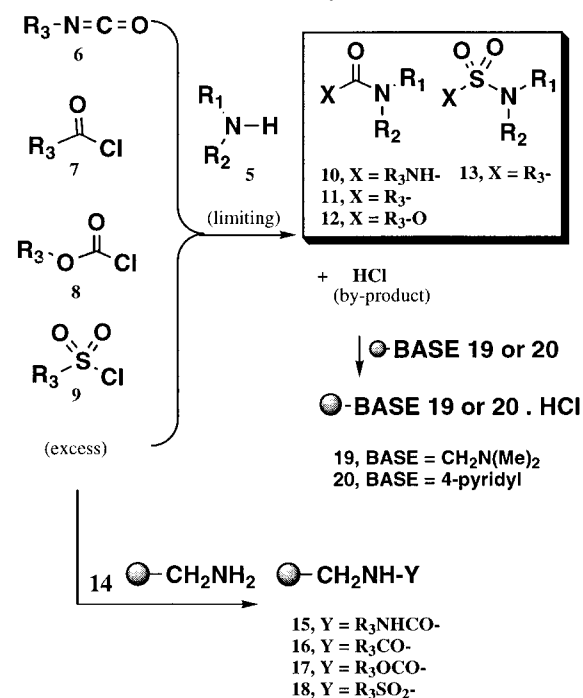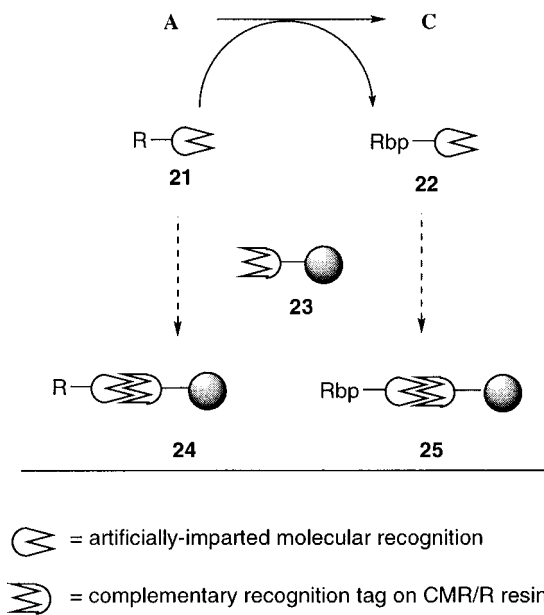
Table 1. Mass Yields and Purities of Solution-Phase Amides, Ureas, Carbamates, and Sulfonamides Purified by CMR/R Sequestration of Excess Acylating Agents

entry	amine **5**	acylating agent **6**−**9**	products **10**−**13**	% mass yield/ HPLC purity
a	PhNH₂	PhCOCl	PhCONHPh	99.5/97.8
b	PhNH₂	CH₃COCl	CH3CONHPh	57.8/97.9
c	PhNH₂	Bn-N=C=O	BnNHONHPh	100/97.8
d	PhNH₂	i-Pr-N=C=O	i-Pr-NHCONHPh	50.0/98.6
e	PhNH₂	p-Me-PhSO₂Cl	p-Me-PhSO2NHPh	100/98.3
f	PhNH₂	EtOCOCl	EtOCONHPh	95.8/99.7
g	BnNH₂	PhCOCl	PhCONHBn	100/98.1
h	BnNH₂	i-Pr-N=C=O	i-Pr-NHCONHBn	100/94.8
i	BnNH₂	p-Me-PhSO₂Cl	p-Me-PHSO₂NHBn	93.9/97.7
j	(Bn)₂NH	PhCOCl	PhCON(Bn)₂	100/97.7
k	(Bn)₂NH	i-Pr-N=C=O	i-Pr-NHCON(Bn)₂	100/98.6
l	(Bn)₂NH	p-Me-PhSO₂Cl	p-Me-PhSO₂N(Bn)₂	88.6/99.1

recovery was obtained (50−100%). With only two exceptions, mass recovery > 88% was realized. ESI or APCI mass spectral analysis of products gave the expected M + H peak in all cases. HPLC, mass spectral, and NMR analyses of all products demonstrated that the aminomethyl polystyrene CMR/R resin **14** had removed (within the limits of detection) all of the excess isocyanate, acid chloride, alkyl chloroformate, or sulfonyl chloride from each reaction medium. HPLC analyses indicated purities > 95%. The tandem use of the reactant CMR/R resin **14** and the byproduct CMR/R resin **19** or **20** allowed the solution-phase reactions to be performed with excesses of acylating agent and then products **10**−**13** isolated in purified form by direct filtration.

Scheme 3 illustrates the conceptual employment of artificially-tagged reagents or reactants, which greatly amplifies the general utility of the CMR/R library purification strategy. Purification of products **C** away from excess artificially-tagged reactants/ reagents **21** and the artificially-tagged byproducts **22** is effected. In this reaction design, reactants **A** are completely converted to products **C** through the agency of excess tagged reactants/ reagents **21**. During the course of the parallel solution-phase reactions, each **21** is converted into its artificially-tagged

(14) In contrast to substrate-linked solid-phase synthesis where every permutation of substrate diversity ultimately is attached to the polymer support, the present purification strategy requires the attachment of only a single representative functionality that finds general utility for all reactions being sequestered for that particular reaction type.

Scheme 3. Illustration of the Use of Artificially-Imparted Molecular Recognition in CMR/R Technology: Artificially-Encoded Reagents


= artificially-imparted molecular recognition

= complementary recognition tag on CMR/R resin

Scheme 4. Application of Artificially-Encoded Reagents in CMR/R Strategies: The Parallel Moffatt Oxidation of Hydroxyethylamines Using the Amine-Encoded Diimide **28**

byproduct **22**. Both **21** and **22** contain a common functional group *tag* which enables them to be sequestered by CMR/R resin **23** as polymer-bound adducts **24** and **25**. Resin **23** contains a recognition *tag* specific and complementary to the *tag* linked to the reagents and byproducts. Using this model of artificially-imparted complementary molecular recognition, simple incubation of the final solution-phase reaction mixtures with CMR/R resin **23**, followed by filtration, affords purified products **C** isolated away from polymer-bound reagent/reactant adducts **24** and byproduct adducts **25**. Several considerations of the choice of molecular recognition tag merit further comment. The tag functionality must be inert (in reactivity) to other reactant and reagent species. The tag also must not interfere with the performance of the encoded reactant/reagent. Its site of attachment to the reagent/reactant should ideally be in a robust location, such that multiple byproduct forms (known and perhaps unidentifiable) which are formed are likely to retain the artificial tag. This precaution maximizes the opportunity to obtain pure products after post-reaction sequestration by the CMR/R resins, even if the identities of all solution-phase byproducts are not known.

The parallel Moffatt oxidations of secondary alcohols to ketones illustrate the employment of artificially-imparted molecular recognition in a CMR/R library purification strategy. As shown in Scheme 4, the parallel oxidation of the hydroxy-ethylamines **26a–f** to their corresponding ketones **27a–f** was effected by the tertiary amine-tagged carbodiimide **28** (EDC) in combination with DMSO and catalytic dichloroacetic acid. During the course of reaction, the tagged-diimide **28** was converted to the tagged byproduct urea **29** in each reaction chamber. After alcohols were consumed, both **28** and **29** were sequestered from solution by incubation with a combination of two CMR/R resins (sulfonic acid-substituted resin **30** and tertiary amine-substituted resin **31**).[15] It is noted that the simultaneous use of CMR/R resins containing mutually incompatible functionality (sulfonic acid and tertiary amine) is allowed due to mutual site-isolation. Resin **31** removed the HCl from the tagged solution-phase species **28** and **29** (proton transfer), and
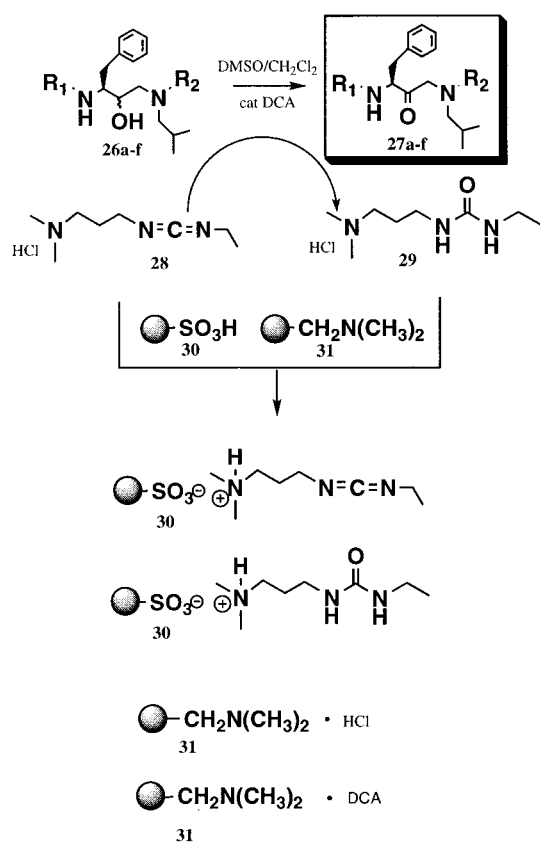
CMR/R sulfonic acid resin **30** then sequestered the free base forms of **28** and **29** based on complementary molecular recognition. Simple filtration afforded the ketone products **27a–f**.

Table 2 lists those alcohols oxidized according to the above protocol. Mass spectral analysis of crude products gave the expected parent ion in each case, with no detection of starting alcohols, tagged diimide **28**, or the tagged urea byproduct **29**. Both proton and ^{13}C NMR also indicated that, within the limits of detection, no alcohol remained and the tagged diimide and tagged urea byproduct had been totally sequestered from each reaction mixture by the combination of CMR/R resins **30** and **31**. Figure 1 illustrates a typical proton NMR and HPLC tracing observed in this study. This example of the use of artificially-tagged reagents bodes well for future applications wherein traditionally-used solution-phase reagents or reactants are tagged to enable their post-reaction sequestration by complementary-tagged resins.

Finally, Scheme 5 illustrates the general use of CMR/R resins to quench (workup) *in situ* formed products, termed pre-**C**. Pre-**C** are defined as unstable, unprotected, or otherwise nonisolable forms of products which require conversion into more isolable product forms **C**. Upon completion of reactions, the *in situ* generated pre-**C** (e.g. unprotonated, metal-chelated, or unprotected) are converted into isolable forms **C** (protonated, metal-free, or protected) by use of a CMR/R resin **32**. The function of **32** is either to quench pre-**C** or to protect pre-**C** as a stable form **C**. During the course of quenching, resin **32** (containing quenching molecular functionality Q) is converted to its spent form **33** (containing quenched functionality q). This workup strategy obviates the need for subsequent solution-phase extractive quenching and/or protecting group transformations.

The addition of organometallic reactants to aldehydes was chosen to demonstrate the multiple utilities of CMR/R workup
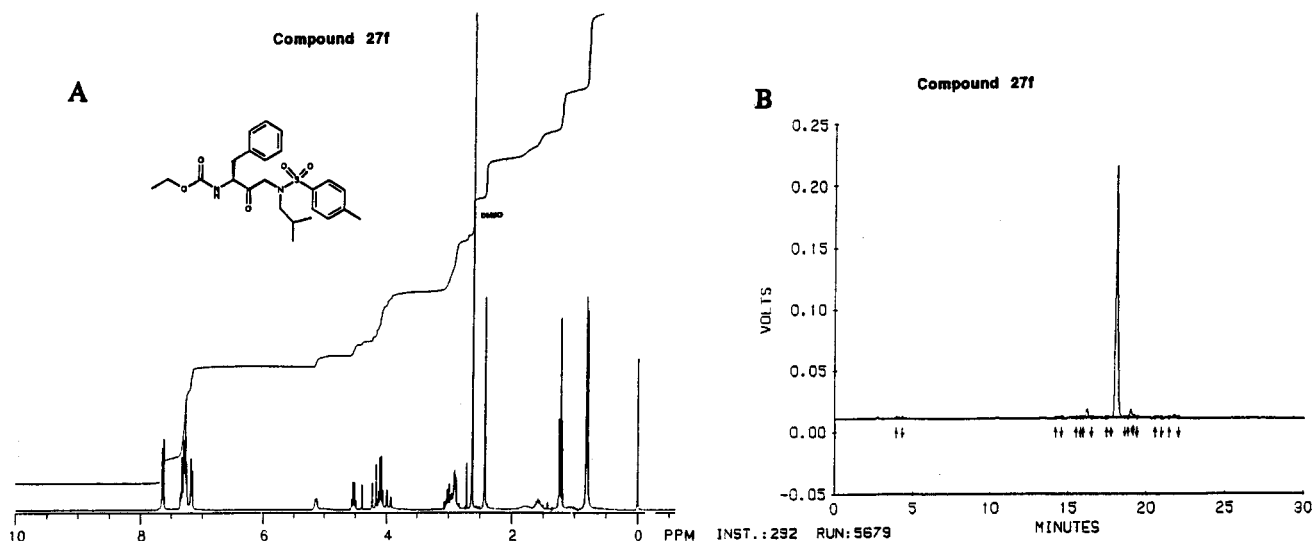
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(15) Alternative use of polystyrene sulfonate sodium salt to directly sequester the EDC amine hydrochloride and byproduct urea hydrochloride gave inferior results.

Figure 1. Purity of compound **27f** after direct isolation away from CMR/R resins **30** and **31**: (A) proton NMR spectrum; (B) HPLC tracing.

Table 2. Artificially-Encoded Reagents as a CMR/R Strategy for Purification of Parallel Solution-Phase Reactions: Mass Yields and Purities of Moffatt Oxidation Products

| Entry	R1	R2	% mass yield of **27** / HPLC purity[a]
a			48 / 92%
b			80 / 87%
c			92 / 71%
d			61 / 93%
e			79 / 82%
f			58 / 91%

[a] HPLC purities as determined by UV detection at 245 nm. Impurities are not due to starting alcohol, encoded diimide **28**, or the encoded urea byproduct **29**. CMR/R resin breakdown is believed to be the source of the minor contaminants.

resins in solution-phase chemical library synthesis. As illustrated in Scheme 6, aldehydes **34** were reacted with an excess of of either *n*-butyllithium or allylmagnesium chloride **35**, giving rise to *in situ*-generated metal alkoxides Pre-**36**. After solution-phase reactions, CMR/R resin **37** (amberlite IRC-50S, carboxylic acid functionalized) was added to the reaction mixture to quench the metal alkoxides Pre-**36**. Proton transfer from the CMR/R resin converted the metal alkoxides to their isolable forms **36**, while generating the spent CMR/R resin **38**. Resin **37** also served a dual role in quenching any excess butyllithium or allylmagnesium chloride **35** as volatile butane or propene gas **39**, respectively. Employment of this CMR/R resin-workup technique obviates the need to pace all reactions through various

Scheme 5. General Illustration of CMR/R Technology for Rapid, Automatable Reaction Workup
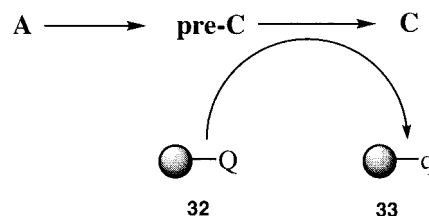
Scheme 6. Utilization of CMR/R Technology for the Simultaneous Workup of Metalated Alkoxides, Quenching of Excess Organometallic Reactants, and Sequestration of Excess Carbonyl Reactants
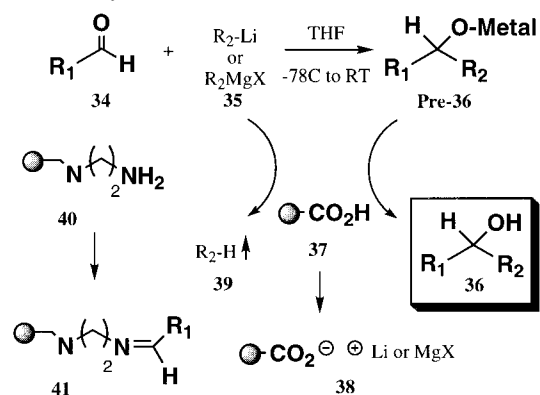
liquid-phase extractive protocols. Filtration directly afforded the desired carbinols **36** in 75−97% isolated yields, and >95% purity. See Table 3.

Regarding entry *e*, the reaction of 6-methylpyridine-2-carboxaldehyde with allyl Grignard did not proceed to completion despite the use of excess Grignard reactant. Figure 2A shows the GC/MS total ion chromatogram of the product isolated after exposure to the quenching CMR/R resin **37**. The peak at 3.60 min retention time is due to unreacted aldehyde **34e**, while the peak at 5.57 min is due to the desired carbinol product **36e**. In this case, simple employment of the additional CMR/R resin **40** (containing primary amine functionality) led to sequestration of any unreacted aldehyde, removing these reactant contaminants as resin-bound imine adducts **41**.

Figure 2B shows the total ion chromatogram of the product isolated subsequent to exposure to both resins **37** (quench/workup) and **40** (reactant removal), indicating complete se-
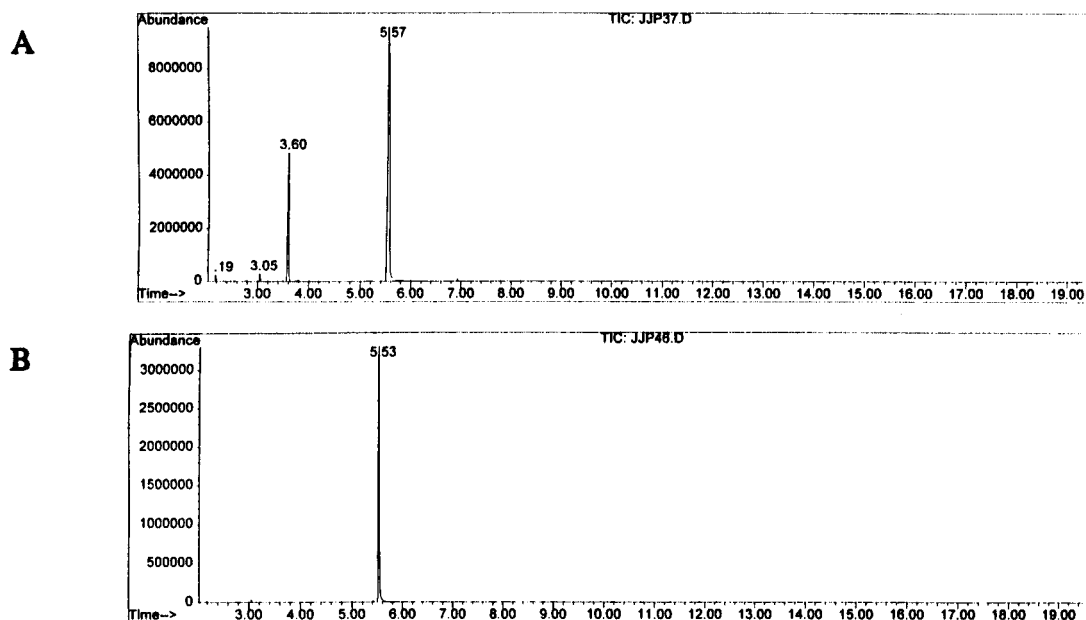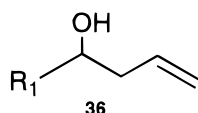
Figure 2. (A) GC/MS total ion chromatogram of compound **36e** before treatment with CMR/R resin **40**. (B) GC/MS total ion chromatogram of compound **36e** after treatment with CMR/R resin **40**.

Table 3. CMR/R strategies for reaction workup: Mass yields and purities of isolated alcohols

entry	R1	% mass yield of 36	GC purity,[a] %
a	phenyl	90	>99
b	1-naphthyl	99	96.6
c	3-methoxyphenyl	96	95.6
d	phenethyl	94	95.3
e	6-methylpyridinyl-2-yl	99	>99[b]
f	5-methylfuran-2-yl	88	>99

[a] Purities as determined from integration of the GC/MS total ion chromatogram. [b] This purity reflects the utilization of both CMR/R resins **37** and **40** for purification. Without the concomitant use of CMR/R resin **40**, the GC purity was 77.9%, with starting aldehyde **34e** as the major (20.5%) impurity. See Figure 2.

questration of the contaminating aldehyde by the amine-containing resin **40**. This example again demonstrates that various combinations of CMR/R resins can be used either sequentially or simultaneously, depending on the specific requirements of the reaction system; moreover, the simultaneous use of the mutually incompatible resins **37** (carboxylic acid) and **40** (primary amine) are allowed because of their mutual site-isolation. We have used this CMR/R resin workup method to run many organometallic addition reactions in parallel. The Experimental Section details the results obtained for the reaction of a variety of aldehydes with *n*-butyllithium or allylmagnesium chloride.

Conclusion

In summary, we have demonstrated that parallel reactions can be purified and isolated in a high throughput format by employing a purification and quenching paradigm based on principles of complementary molecular recognition and molecular reactivity (CMR/R). Notable attributes of this approach compared to existing methods of SPOC (substrate-linked synthesis) and/or LPEP (liquid-phase extraction protocols) purification paradigms include: (1) use of excess reactants or reagents to drive solution phase reactions to completion, (2) avoidance of the need for substrate linkage to a polymer support, (3) minimization of prelibrary validation times, (4) employment of tagging procedures to enable purification of solution-phase reactions based on artificially-imparted molecular recognition, (5) avoidance of liquid-phase extraction protocols for reaction quench and/or workup, (6) minimization or avoidance of chromatography for purification of products, and (7) straightforward applicability to automation.

Experimental Section

General. GC/MS was performed using a 6890 Hewlett Packard gas chromatograph utilizing a capillary column (crosslinked 5% PH ME siloxane, 30 M × 0.25 mm × 0.25 um film thickness) and a Hewlett Packard 6890 Series mass selective detector. A temperature program from 60 °C or 100 °C to 250 °C at 20 °C/min was employed. HPLC purities were determined with a Spectra Physics pump (SP8800) and a 20 λbax Rx C8 column, eluting with a gradient system of 40/60 to 100/0 MeCN/H_2O (for compounds **10**−**13**) or 50/50 to 100/0 MeCN/H_2O (for compounds **27**) over 30 min at 1 mL/min, and detected by UV at 245 nm using a Spectra Physics detector (Spectra 100). Amberlyst 15, Amberlyst A-21, and poly(4-vinylpyridine) were obtained from Aldrich Chemical Co., and aminomethylpolystyrene was obtained from BACHEM Bio-science Inc.. Amberlyst A-21, poly(4-vinylpyridine), and aminomethylpolystyrene resins were washed thoroughly with CH_2Cl_2 (6 × 15 mL/g × 15 min) and dried in a vacuum oven overnight before use. Amberlyst 15 was prewashed in DMSO prior to use. Amberlite IRC-50S (methacrylic acid−DVB, ∼10 mmol/g) was purchased from Aldrich Chemical Co. and washed with THF, followed by diethyl ether prior to use. Aniline, benzylamine, dibenzylamine, benzoyl chloride, acetyl chloride, benzyl isocyanate, isopropyl isocyanate, *p*-toluenesulfonyl chloride, ethyl chloroformate, and EDC HCl were purchased from Aldrich Chemical Co. DMSO was dried over molecular sieves, and CH_2Cl_2 was freshly distilled prior to use.

General Procedure I (for compounds 10 and 11).[16] This procedure was conducted in a parallel reaction format. To each 7 mL scintillation vial containing 1.0 mL dry CH_2Cl_2 and dry Amberlyst A-21 (CMR/R resin **19**: 0.25 g, 1.175 mmol, 4.7 mequiv/g), amine **5** (0.1 mmol) was added (aniline, 9.2 μL; benzylamine, 11.0 μL; or dibenzylamine, 19.8 μL), followed by addition of acylating reactant **6** or **7** (0.25 mmol) (benzoyl chloride, 29.9 μL; acetyl chloride, 17.8 μL; benzyl isocyanate, 31.2 μL; or isopropyl isocyanate, 25.1 μL). When acylating reactants were isocyanates, Amberlyst A-21 was not used. Each vial was closed tightly, and the mixture was agitated at rt with an orbital shaker for

16 h. The mixture was transferred to a fritted plastic cartridge containing aminomethylpolystyrene (CMR/R resin **14**: 0.577 g, 0.45 mmol, 0.78 mequiv/g) and diluted with 6.0 mL of dry CH_2Cl_2. The resulting mixture was agitated at rt for 3 h and then filtered. The resin was washed with CH_2Cl_2 (4 × 6 mL × 15 min). The combined filtrate and washings were concentrated and transferred to a vial, and the solvent was blown off by a stream of N_2. The resulting product was dried in a vacuum oven overnight. Each product was weighed and analyzed by NMR (^{1}H, ^{13}C, APT), mass spectrometry, and HPLC.

Benzanilide (11a): 19.6 mg, 99.5%; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.90 (m, 3H), 7.65 (d, J = 7.6 Hz, 2H), 7.55 (m, 1H), 7.48 (t, J = 7.4 Hz, 2H), 7.37 (t, J = 8.0 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H);[16] HPLC purity (retention time): 97.8% (12.1 min).

General Procedure II (for compounds 12 and 13).[16] This procedure was conducted in a parallel reaction format. To each 7 mL scintillation vial containing 1.0 mL of dry CH_2Cl_2 and dry poly 4-vinylpyridine (CMR/R resin **20**: 0.25 g), amine **5** (0.1 mmol) was added (aniline, 9.2 μL; benzylamine, 11.0 μL; or dibenzylamine, 19.8 μL), followed by acylating reactant **8** or **9** (0.50 mmol). Each vial was closed tightly, and the mixture was agitated at rt with an orbital shaker for 16 h. The mixture was transferred to a fritted plastic cartridge containing aminomethylpolystyrene (CMR/R resin **14**: 1.125 g, 0.90 mmol, 0.80 mequiv/g) and diluted with 10.0 mL of dry CH_2Cl_2. The resulting mixture was agitated at rt for 3 h and then filtered. The resin was washed with CH_2Cl_2 (4 × 10 mL × 15 min). The combined filtrate and washings were concentrated and transferred to a vial, and the solvent was blown off by a stream of N_2. The resulting product was dried in a vacuum oven overnight to afford the desired sulfonamides or carbamates. Each product was weighed and analyzed by NMR (^{1}H, ^{13}C, APT), mass spectrometry, and HPLC.

N-Phenyl p-toluenesulfonamide (13e): 24.9 mg, 100%. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.68 (d, J = 8.3 Hz, 2H), 7.22 (m, 4H), 7.09 (m, 3H), 6.97 (s, 1H), 2.37 (s, 3H);[16] HPLC purity (retention time): 98.3% (13.5 min).

Moffatt Oxidation. The oxidations of alcohols **26a−f** to carbonyls **27a−f** were performed in parallel. An example of the EDC−Moffatt oxidation and the demonstration of tagged-reagent sequestration by CMR/R polymers **30** and **31** is exemplified with the formation and purification of **27d** (Table 2, entry d). To N-[2-hydroxy-3-[[(4-methylphenyl)sulfonyl](2-methylpropyl)amino]-1-(S)-(phenylmethyl)propyl]benzenepropanamide (**26d**) (28.7 mg, 0.055 mmol) and EDC HCl **28** (53 mg, 0.275 mmol) in a 1:1 mixture of DMSO and CH_2Cl_2 (0.5 mL) in a 7 mL scintillation vial was added dichloroacetic acid (0.3 M in DMSO, 0.9 mL). The mixture was agitated on an orbital shaker for 24 h. The mixture was transferred to a fritted plastic cartridge containing Amberlyst 15 (585 mg, 2.75 mmol) and Amberlyst A-21 (59 mg, 0.275 mmol) and agitated for 20 h. The mixture was filtered, and the resins were washed once with CH_2Cl_2. The combined filtrates were concentrated under a stream of N_2. The residue was retreated with EDC HCl **28** (53 mg, 0.275 mmol) and dichloroacetic acid (0.3 M in DMSO, 0.9 mL) in 1:1 DMSO/CH_2Cl_2 (0.5 mL). After 24 h the reaction was quenched into Amberlyst 15 (CMR/R resin **30**: 585 mg, 2.75 mmol) and Amberlyst A-21 (CMR/R resin **31**: 59 mg, 0.275 mmol) and agitated for 20 h. Filtration and concentration as before yielded **27d** as a yellow oil.

N-[3-[[(4-Methylphenyl)sulfonyl](2-methylpropyl)amino]-2-oxo-1-(S)-(phenylmethyl)propyl]benzenepropanamide (27d): 61% mass yield; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 7.63 (d, J = 8.0 Hz, 2H), 7.33−7.13 (cb, 10H), 7.09 (dd, J = 8,2 Hz, 2H), 5.96 (d, J = 7 Hz, 1H), 4.75 (q, J = 7, 1H), 4.11 (d, J = 19 Hz, 1H), 3.91 (d, J = 19 Hz, 1H),

3.00 (dd, J = 14,7 Hz, 1H), 2.95−2.80 (cb, 5H), 2.48 (dt, J = 15,7 Hz, 1H), 2.45 (dt, J = 15,7 Hz, 1H), 2.42 (s, 3H), 1.57 (m, 1H), 0.79 (d, J = 7 Hz, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 204.1, 172.5, 143.8, 140.9, 137.2, 136.21, 129.9, 129.7, 129.4, 129.1, 128.8, 128.0, 127.8, 126.8, 57.1, 56.5, 55.8, 38.4, 37.6, 31.8, 27.2, 22.1, 20.4; HRMS m/z 521.2456 (C$_{30}$H$_{37}$N$_2$O$_4$S$_1$ requires 521.2474); HPLC Purity (retention time): 92.7% (20.2 min).

Utilization of Workup and Reactant Sequestering CMR/R Resins: Reaction of Grignard Reactants with Carbonyl Compounds. Under conditions of parallel reaction synthesis, a solution of allylmagnesium chloride **35** (2.0 M solution in a tetrahydrofuran, 0.30 mL, 0.60 mmol) was added to each vial containing a solution of aldehyde **34** (0.50 mmol) in tetrahydrofuran (freshly distilled) at −78 °C (acetone/CO$_2$) and the resulting solution stirred at room temperature for 2.5 h. Amberlite IRC-50S (CMR/R resin **37**: 0.80−1.0 g, 8−10 mmol, ~10.0 mequiv/g) was added to each vial, and the mixture was stirred for an additional 4 h. The mixture was filtered, and the polymer was rinsed with tetrahydrofuran until no more UV activity was seen in the eluant. The solvent was removed to afford essentially pure carbinol products **36** (R$_2$ = allyl). Isolated yields were in the range of 88−99% with purity in the range of 95−99%. Products were characterized by GC/MS, TLC, and proton NMR.

Upon observation of the GC/MS of product **36e**, remaining starting aldehyde, 6-methyl-2-pyridinecarboxaldehyde, was detected. To purify this reaction mixture the following procedure was performed:

The residue was dissolved into dichloromethane, and the polyamine CMR/R resin **40** (0.50 g, 1.49 mmol) was added. The slurry was stirred at rt for 5 h. The mixture was filtered, and the polymer was rinsed with dichloromethane until no more UV activity was seen in the eluant. The solvent was removed to afford the carbinol **36e**, demonstrated to be >99% pure by GC/MS analysis.

1-Phenyl-3-buten-1-ol (36a):[16] 90% mass yield; ^{1}H NMR (CDCl$_3$): δ 2.06 (d,1H), 2.56 (m,2H), 4.78 (m,1H), 5.20 (m,2H), 5.85 (m,1H), 7.33 (m,5H); HRMS m/z 148.0866 (C$_{10}$H$_{12}$O$_1$ requires 148.0888); GC/MS purity (retention time): >99% (3.30 min).

1-(6-Methyl-2-pyridyl)-3-buten-1-ol (36e): 99% mass yield; ^{1}H NMR (CDCl$_3$): δ 2.55 (m,2H), 2.63 (s,3H), 4.85 (m,1H), 5.10 (m,-2H), 5.88 (m,1H), 7.14 (m,2H), 7.66 (t,1H); HRMS m/z 163.0984 (C$_{10}$H$_{13}$N$_1$O$_1$ requires 163.0970); GC/MS purity (retention time): 99% (5.53 min).

Utilization of Workup and Reactant Sequestering CMR/R Resins: Reaction of n-Butyllithium Reactions with Carbonyl Compounds. Under conditions of parallel reaction synthesis, a solution of n-butyllithium (1.6 M solution in hexanes, 0.36 mL, 0.57 mmol) was added to a solution of aldehyde **34** (0.50 mmol) in tetrahydrofuran (freshly distilled) at −78 °C (acetone/CO$_2$) and the resulting solution stirred at rt for 2.5 h. Amberlite IRC-50S (CMR/R resin **37**: 0.80−1.0 g, 8−10 mmol, ~10.0 mequiv/g) was added and stirred for 4 h. The mixture was filtered, and the polymer was rinsed with tetrahydrofuran until no more UV activity was seen in the eluant. The solvent was removed to afford the essentially pure carbinol products **36** (R$_2$ = n-butyl). Yields were in the range 75−94% with purity in the range of 72−99%. Products were characterized by GC/MS, TLC, and proton NMR.

Upon observation of the GC/MS of examples **36i** and **36k**, remaining starting material carboxaldehyde was detected. To purify this reaction mixture the following procedure was performed:

The residue was dissolved into dichloromethane and the polyamine CMR/R resin **40** (0.50 g, 1.49 mmol) was added. The slurry was stirred at rt for 5 h. The mixture was filtered, and the polymer was rinsed with dichloromethane until no more UV activity was seen in the eluant. The solvent was removed to afford the pure carbinols **36i** and **36k**.

1-(1-Naphthyl)-1-pentanol (36i):[16] 94% mass yield; ^{1}H NMR (CDCl$_3$): δ 0.96 (t,3H), 1.43 (m,4H), 1.97 (m,2H), 2.18 (bs,1H), 5.48 (t,1H), 7.56 (m,3H), 766 (d,1H), 7.70 (d,1H), 7.93 (d,1H), 8.15 (d,-1H); HRMS m/z 214.1363 (C$_{15}$H$_{18}$O$_1$ requires 214.1357); GC/MS purity (retention time): 97% (7.09 min).

Preparation of the Polyamine CMR/R Resin (40). Merrifield's resin (2% cross-linked, 325 g, 0.549 mol, 1.69 mmol/g) was added to diethylenetriamine (955 g, 9.25 mol) and the mixture heated at 100 °C for 4 h. The polymer was filtered and successively rinsed two times

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(16) Compounds **11a**, **13e**, and **36a** are known compounds whose spectral characterizations have been previously reported. The proton and/or carbon NMR data obtained by us for these compounds agree with those reported. Compound 11a: Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177−6180. Compound **13e**: Chang, Y. H.; Chia, F-T.; Zon, G. *J. Org. Chem.* **1981**, *46*, 342−354. Compound 36a: Smith, G. G.; Voorhees, K. J. *J. Org. Chem.* **1970**, *35*, 2182−2185. Compounds **36h** and **36i** have been previously reported but not fully characterized. For these two compounds complete analytical data are reported herein. Compound 36h: Roblin, R. O., Jr.; Davidson, D.; Bogert, M. T. *J. Am. Chem. Soc.* **1935**, *57*, 151−159. Compound 36i: Condon, F. E.; Mitchell, G. *J. Org. Chem.* **1980**, *45*, 2009−2010.

with 10% triethylamine in dimethylformamide, once with dimethyl-formamide, four times with 10% triethylamine in tetrahydrofuran, three times with tetrahydrofuran, and three times with methanol. The polymer was then vacuum-dried to a constant weight. Anal. Calcd: N, 6.41 (4.57 mequiv/g), Cl, 0. Found: N, 4.18 (2.98 mmol/g), Cl, 0.

Supporting Information Available: Complete spectral data (^{1}H NMR, ^{13}CMR, ESI-MS, APCI-MS, and HRMS) and chromatograms (HPLC and GC/MS) of reaction products **10−13a−l**, **27a−f**, and **36a−m** are provided (92 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered online from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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