Polymer-Supported Synthesis of Cyclic Ethers: Electrophilic Cyclization of Isoxazolines

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Polymer-supported synthesis of 2,5-disubstituted tetrahydrofurans via tandem 1,3-dipolar cycloaddition/electrophilic cyclization has been accomplished using a five-step reaction sequence to give 2-(cyanomethyl)-5-(iodomethyl)tetrahydrofuran (*cis:trans* ratio of 1:2) in 40% overall yield. The corresponding 2-(cyanomethyl)-6-(iodomethyl)tetrahydropyran was similarly formed in a 7% overall yield. The final electrophilic cyclization simultaneously releases the desired product and regenerates the initial polymer-bound functionality. In the process the desired cyclic ether is obtained exclusively; byproducts of the sequence are not cleaved from the polymer support. In addition the polymer support is sufficiently robust to be recovered and recycled through the reaction sequence.

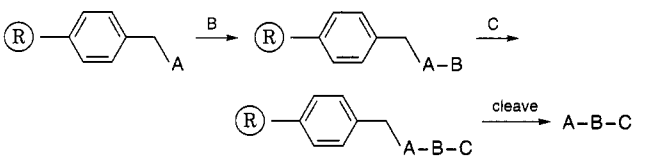
Introduction

Polymer-supported synthesis is an important tool for the development of new synthetic strategies in organic chemistry, and the literature associated with polymer supported reagents and catalysts is extensive. Merrifield's pioneering work[1] in the area of polypeptide synthesis delineated many of the benefits of polymer-supported strategies, with the most obvious being ease of workup and ease of product isolation. In addition, however, side product formation may often be minimized when a reactive species is covalently attached to a polymer support. Intrigued by these potential advantages, we set out to explore the application of polymer-supported reactions in relatively sophisticated multistep organic reaction schemes.[2]

The 2% cross-linked polystyrene/divinylbenzene used in our reactions is an insoluble solid in all solvents. Thus, the key benefit associated with polymer-supported synthesis is the ease of separation and purification. Polymer-supported multistep synthesis begins with a polymer-bound reactive moiety, which is exposed to a solution-phase reagent. Upon reaction, the product remains covalently bound to the polymer support, and purification consists simply of filtering and washing away the unreacted solution-phase reagents. The polymer support can thus be taken through a variety of reaction steps, the final one being cleavage of the desired target molecule from the polymer support. Depending upon the selectivity of the cleavage step, some side products may also be liberated, necessitating chromatography for final purification. Scheme 1 demonstrates this method where Ⓡ is the solid support and A is the reactive moiety. B and C are solution-phase reagents, which react with A and become bound to the polymer.

An important aspect of the benefits associated with polymer-supported synthesis is the relative site–site isolation envisioned when a reactive moiety is attached to a solid support. In a greatly simplified view, the polymer support can be seen as a relatively rigid backbone containing interspersed reactive sites. While this concept is an attractive one, the reality of the situation is not so clear-cut. Lightly cross-linked polymers, especially in the presence of a swelling solvent (vide infra),

Scheme 1



are quite flexible. Polymer-bound moieties, in fact, can and do react with one another. What is described as "site isolation" is really more of a kinetic phenomenon, i.e., it comes into play only when the rate of reaction between bound and unbound compounds is faster than the rate with which the polymer backbone deforms to allow the reactive sites to interact with one another.[3,4] The degree of cross-linking and reactive site loading are important features which determine the degree of site isolation observed. In particular, the rate of polymer deformation is faster for polystyrene with reduced or no cross-linking.[5]

A second important aspect of polymer use in synthesis is the ability of the polymer to swell in certain solvents. Ideally, the polymer will swell in the appropriate reaction solvent, thus allowing accessibility of solution-phase reagents to the reactive sites inside the resin beads. Such behavior also aids in the maintenance of the physical integrity of the beads under a variety of reaction conditions.[6] The accessibility of reactive sites is an obvious issue in solid-phase synthesis.[6,7] The swollen polymer support becomes more like a viscous liquid than a solid, allowing reagents to flow in and out of the matrix. While there may always be some inaccessible reaction sites, judicious choice of solvent should in principle lead to optimal utilization of the polymer-bound functionality.

The multistep organic synthesis that we have devised is unique to polymer-supported methodology. Polymer-supported methods have been extensively applied to the syntheses of polypeptides, polynucleotides, and oligosaccharides. These syntheses, however, generally utilize the repetition of one key reaction to give a large macromolecule. Thus, in the solid-phase synthesis of peptides,[1] formation of the amide bond is repeated with different

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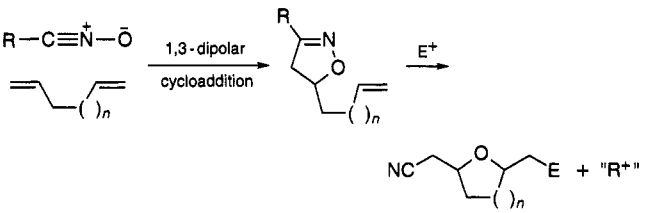
amino acids. The solid-phase synthesis of polynucleotides requires repeated 3′→5′ phosphodiester linkage construction.[8-11] Oligosaccharide synthesis employs repeated glycosylation.[12-14] Another area of solid-phase synthesis which has gained much attention recently is the utilization of immobilized catalysts and reagents for use in organic transformations. An excellent example is polymer-supported tributyltin hydride, an efficient and regeneratable reagent whose use simplifies product separation and purification as well as disposal of spent toxic reagent.[15-17] Others include polymer-bound transition metal hydroformylation catalysts to convert terminal olefins to aldehydes,[18,19] vanadium- and molybdenum-based epoxidation catalysts, polymer-bound through a hydroxypropylated (amino)methylpyridine ligand,[20] and mimics of biological redox systems such as NADH models used for the reduction of aldehydes to alcohols.[21]

Additional developments have included polymer-bound protecting groups,[22] such as vicinal diols to protect aldehydes or ketones;[23] such reagents permit the monoprotection of symmetrical diketones or aldehydes for reaction at the unprotected site.[24,25] Chiral auxiliaries have also been attached to solid supports; after use the (often expensive) auxiliary may be recovered and reused.[26] Examples include chiral amines for ketone alkylation,[27] chiral acrylates for asymmetric Diels-Alder reaction,[28] and chiral epoxides.[29] Our laboratory recently reported the attachment of a chiral pyrrolidine to a polymer support, followed by a three-step reaction sequence to form optically active 3,5-disubstituted γ-butyrolactones.[30] Multistep syntheses involving polymer-supported substrates are less common than examples employing polymer-supported catalysts or reagents. Elegant sequences based upon the attachment of one end of a bifunctional aldehyde to a polymer support have been

Scheme 2



used in the synthesis of insect sex attractants, helicenes, and benzodiazepinone tranquilizers.[31] Polymer-bound alkynes have been used in the synthesis of cylopentenones via the Pauson–Khand reaction.[32] More recently, polymer-supported multistep synthesis has been applied to the formation of libraries of compounds which can undergo biological testing.[33,34] In this and the following paper we report the multistep, polymer-supported syntheses of cyclic ethers of varying complexity and introduce a novel method of removal of the product from the solid support, which avoids the need of a separate cleavage step. A portion of this work has already been reported in preliminary form.[2]

Strategic Considerations

The focus of this work is the 1,3-dipolar cycloaddition/electrophilic cyclization sequence developed in these labs for the synthesis of 2,5-disubstituted tetrahydrofurans.[35,36] This process uses the addition of a nitrile oxide to an α,ω-diene to give an isoxazoline with a terminal olefin appendage, which can subsequently undergo an electrophilic cyclization to give a cyclic ether, as shown in Scheme 2.

In the final electrophilic cyclization step, electrophilic attack on the double bond is followed by addition of the isoxazoline oxygen; the R–C bond cleaves, leaving a nitrile. The process generates the cyclic ether and formally releases R^+. In applying this protocol to a polymer supported synthesis, we chose to design the system such that R^+ would remain attached to the solid support. We also envisioned the electrophilic cyclization as giving solely the desired cyclic ether target: any unwanted side products would remain attached to the polymer support.

The protocol as originally developed suffers one major drawback when carried out under normal homogeneous conditions.[37] Namely, its success requires selective monocycloaddition of the nitrile oxide to the α,ω-diene substrate. However, in solution a second nitrile oxide is free to react with the remaining double bond. Double addition is effectively suppressed by using the diene in 10-fold excess. However, this "solution" to the bis-addition problem becomes less attractive in the case of more complex or expensive dienes.

As an approach to solving this problem, we considered that covalent attachment of the nitrile oxide precursor to an insoluble polymer matrix would be potentially

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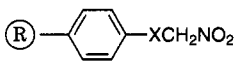


Figure 1.

Table 1. Iodocylization Results

R group	yield, %	*cis/trans*
tert-butyl	53	1/1
	70	1/1.4
	59	1/1.4
	55	1/1.6

beneficial due to the partial isolation of reactive groups bound to the support. The terminal double bond remaining after isoxazoline formation would be less accessible to another polymer-bound nitrile oxide, which would then have a higher probability of reacting instead with a second molecule of diene. The latter could then be used in smaller excess. An additional benefit of the polymer-supported method is that the iodocyclization reaction in principle could be designed to *liberate exclusively the target cyclic ether* and also regenerate a polymer-bound functional unit, which could be recycled through the synthetic scheme.

Achieving such a multistep reaction sequence on a polymer support represents a challenging synthetic goal. The targeted cyclic ethers are important structural elements in many polyether antibiotics[38-41] and, as a compound class, have proven to be important synthetic targets.[42] They are also of interest as unnatural furanosides for use in the synthesis of nucleosides.[43]

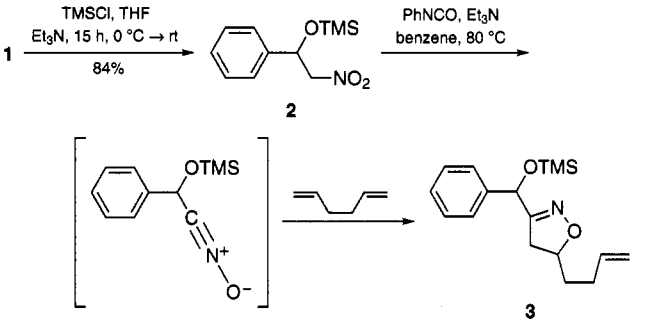
The planned synthesis had to meet two polymer-related prerequisites: (1) straightforward preparation of a polymer-bound nitrile oxide precursor and (2) incorporation of cation-stabilizing functionality in the polymer-bound group to facilitate the electrophilic cyclization. We felt it most convenient to meet these requirements in the context of the functionality accessible from Merrifield's polystyrene resin. Since commercially available resin[1,21] is chloromethylated polystyrene/divinylbenzene, the R group (cf. Scheme 2) of the target isoxazoline intermediate by necessity must contain a phenyl ring. Since the nitrile oxide is most easily formed from the phenyl isocyanate-mediated dehydration of a CH_2NO_2 moiety, the starting material is defined to contain phenyl and methylene groups proximal to a nitro function, i.e., Figure 1.

In order to identify suitable R groups for our purpose, we reviewed earlier work from these laboratories[35] and considered a variety of groups, for which the yields and *cis/trans* ratios of the 2,5-disubstituted tetrahydrofurans are given in Table 1. Clearly, the presence of an ether or acetal linkage is beneficial. We therefore envisioned a nitroaldol condensation between nitromethane and an aromatic aldehyde as a synthetic starting point.

Table 2. Base-Catalyzed Nitroaldol Condensation

base catalyst	% yield of 1
resin-supported base	76
sodium hydroxide	60
triethylamine	85

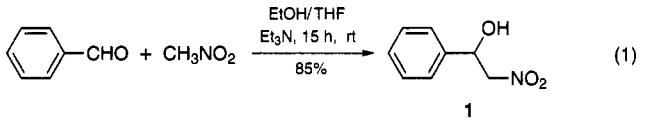
Scheme 3



Results and Discussion

Solution-Phase Synthesis. In order to develop a polymer-supported protocol, we felt it prudent to first investigate certain aspects of the synthetic scheme using conventional solution-phase synthesis. This work allowed us to identify and fully characterize each compound. The nitroaldol condensation[44-47] between benzaldehyde and nitromethane to give nitro alcohol **1** was carried out using different catalysts, as presented in Table 2.

We expected that the resin-supported base[48] would be impractical for use in the eventual polymer-supported synthetic scheme. Fortunately, triethylamine[49] yielded 85% of the nitro alcohol and was convenient to use as well (eq 1). Although ethanol is the usual solvent for such condensations, we used THF as a cosolvent in these experiments since ethanol alone swells the polymer support only relatively poorly.



(1)

We protected the alcohol as the trimethylsilyl ether **2** (Scheme 3). This reaction proceeded in an 84% yield; however, a small amount of β-nitrostyrene usually formed as well from dehydration of the nitro alcohol. This problem could be alleviated by using freshly silylated glassware.

We carried out the dehydration of the nitroalkane **2** to the nitrile oxide using 2 equiv of phenyl isocyanate with triethylamine as the base catalyst.[50,51] The use of benzene as the solvent facilitates the precipitation of diphenylurea. The nitrile oxide formed *in situ* reacts with excess 1,5-hexadiene to yield the desired isoxazoline

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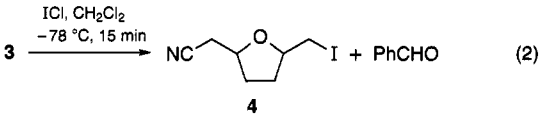
Table 3. Electrophilic Cyclization Results

electrophile	solvent	temp, °C	% yield	*cis:trans*
I_2	CH_2Cl_2	25	51	
ICl	CH_2Cl_2	−78	53	1:2.7
ICl	CH_2Cl_2	−94	48	1:2.8
ICl	*n*-pentane	−78	31	1:2.7
ICl	THF	−78	29	1:1.6

3. We carried out this reaction in a sealed tube with 10 equiv of diene, obtaining the isoxazoline in a 74% yield. When only 2 equiv of 1,5-hexadiene was used, the yield decreased to 62%.

We characterized isoxazoline **3** spectroscopically. The diastereomeric ratio of 1:1 was determined by ^{1}H NMR integration of the isoxazoline ring methylene protons. These protons are diastereotopic: in the ^{1}H NMR spectrum of one diastereomer, they appear as two doublets of doublets at 2.2 and 3.0 ppm and, for the other, as an apparent doublet at 2.65 ppm. The terminal double bond shows a multiplet at 5.8 ppm for the internal proton and two overlapping doublets of doublets at 5.0 ppm for the terminal protons. The IR spectrum revealed a weak C=N peak at 1640 cm^{-1} and a strong trimethylsilyl ether absorption at 1254 cm^{-1}.

We performed the electrophilic cyclization (eq 2) of isoxazoline **3** with different electrophiles, solvents, and at different temperatures. These data are presented in Table 3. Identification of the product, 2-(cyanomethyl)-5-(iodomethyl)tetrahydrofuran (**4**) was made by comparison with the literature data.[35] The *cis:trans* ratio was determined by capillary GLC analysis of the crude reaction mixture. The optimal reaction solvent was dichloromethane, which gave the highest yield and best *cis:trans* ratio. Lowering the temperature to −94 °C did not have a significant effect on the *cis:trans* ratio. Iodine monochloride was preferred over iodine because the reaction produced a much cleaner crude material which was less subject to decomposition upon handling. The electrophilic cyclization also regenerated benzaldehyde, the initial starting material, which was detected by ^{1}H NMR and recovered in the purification process. This outcome was especially encouraging in light of our desire to recycle polymer-bound aldehyde.

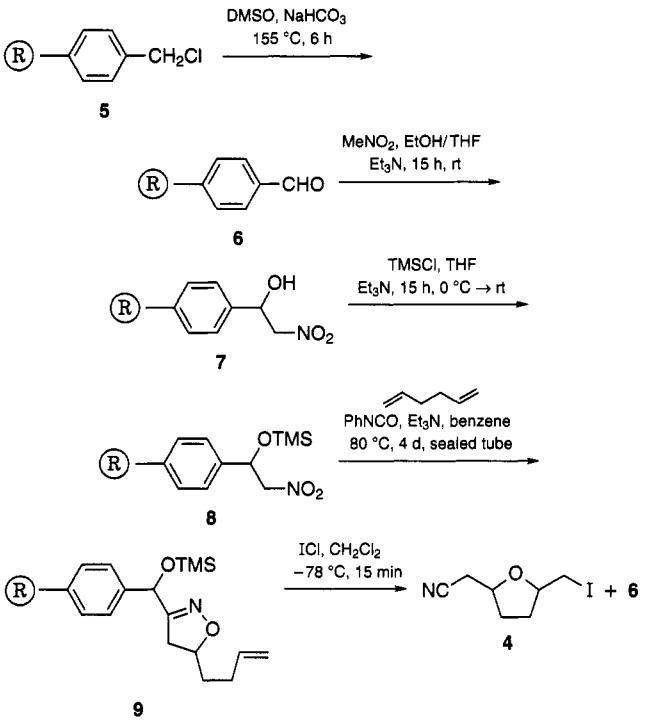


(2)

The relatively low yield of the electrophilic cyclization is due to the formation of a side product in which the electrophile simply adds across the double bond. This addition product coelutes with and is extremely difficult to separate from the tetrahydrofuran **4**; it is characterized by a ^{1}H NMR spectrum similar to that of the isoxazoline but without the terminal double-bond resonances. We expected that the problems encountered in purification would be alleviated by performing the synthetic sequence on the polymer because this side product should remain attached to the solid support during the formation and liberation of **4**.

The trimethylsilyl group appears to be sufficiently labile to allow the electrophilic cyclization to take place. To determine if modification of the silyl protecting group had any effect on the product yield and/or *cis/trans* ratio, we also synthesized the corresponding *tert*-butyldiphenylsilyl ether in 31% yield using imidazole in THF. The isoxazoline was subsequently formed in 46% yield (unoptimized). Upon electrophilic cyclization with iodine monochloride in dichloromethane, **4** was formed in 17% yield with a *cis:trans* ratio of 1:2.6. The reduced yield is most likely a reflection of the difference in lability of the protecting groups. The bulky silyl group had no effect on the diastereomeric ratio and thus was not seen as an improvement; we did not investigate any other protecting groups. Thus, in the sequence described above, we obtained the final product, 2-(cyanomethyl)-5-(iodomethyl)tetrahydrofuran, as a 1:2.7 mixture of *cis:trans* diastereomers in an 18% overall yield from benzaldehyde.

Scheme 4



Polymer-Supported Synthesis. With the synthesis of **4** worked out for the conventional solution-phase conditions, we focused our attention on the polymer-supported strategy. Commercially available 2% cross-linked Merrifield polymer **5** was oxidized directly to the aldehyde using dimethylsulfoxide and sodium bicarbonate at high temperature (Scheme 4).[52,53] We found that the simplest method of identifying the progress of this and all subsequent transformations was by recording FTIR spectra of a KBr pellet formed with crushed resin. Identification of polymer-supported compounds was made by comparison with the IR spectra previously obtained for the solution-phase analogs. The polymer-supported aldehyde **6** was thus identified by a strong carbonyl stretch at 1701 cm^{-1} and a weaker aldehyde C−H stretch at 2722 cm^{-1} in the IR spectrum (KBr pellet).

Nitroaldol condensation[49] proceeded using nitromethane and triethylamine in ethanol/THF to give polymer-supported nitro alcohol **7** (Scheme 4). The product exhibited strong nitro peaks in the IR spectrum at 1555 and 1375 cm^{-1}, a sharp free alcohol peak at 3559 cm^{-1}, and an H-bonded alcohol peak at 3423 cm^{-1}. In this reaction, it was crucial that the nitromethane be added first, followed by the base and then the solvents. Even so, we were unable to drive this condensation to comple-

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Table 4. Polymer-Supported Electrophilic Cyclization Results

mmol 4/g polymer support	% yield[a]	*cis*:*trans*[b]	equiv of 1,5-hexadiene[c]
0.24	35	1:2.1	3
0.19	28	1:1.8	2
0.13	20	1:2.0	
0.14	21		2
0.19	29		2
0.26	40	1:2.1	3
0.11	17[d]		2
0.07	11[d]		2

[a] Purified yields, mmol of 4/mequiv of aldehyde per gram of polymer support. [b] Ratio determined by capillary GLC analysis of the crude reaction mixture. [c] Equivalents calculated using 0.67 mequiv of aldehyde per gram of polymer support. [d] Polymer support recycled through synthetic scheme.

tion. A small aldehyde carbonyl peak at 1701 cm^{-1} was always present in the IR spectrum and did not decrease significantly in intensity after 14 h of reaction. This effect may be due to the inability of the highly polar nitromethane to readily diffuse into the less polar polymer matrix, even in the presence of swelling solvents.

The hydroxyl group of **7** was then protected as the trimethylsilyl ether; only minimal dehydration to the corresponding β-nitrostyrene occurred, as indicated by the appearance of a very weak conjugated nitro peak at 1350 cm^{-1} in the IR spectrum. The IR spectrum of the polymer-supported trimethylsilyl ether **8** lacked a free alcohol OH stretch and exhibited a new trimethylsilyl absorption at 1253 cm^{-1}.

Subsequent phenyl isocyanate-mediated dehydration of the nitroalkane moiety presumably generated the polymer-bound nitrile oxide,[50,51] which then underwent an intermolecular 1,3-dipolar cycloaddition with 1,5-hexadiene (2- to 3-fold excess) to give the polymer-bound isoxazoline **9**. Since the isoxazoline has no strong IR-active chromophores, we monitored this reaction by the disappearance of the nitro peaks at 1555 and 1375 cm^{-1} in the IR spectrum. The reaction was thus judged to have gone to completion after 4 days at 80 °C in a sealed tube.

Finally, electrophilic cyclization of the isoxazoline with iodine monochloride at −78 °C gave tetrahydrofuran **4** and regenerated the polymer-bound aldehyde **6**. The results are presented in Table 4. Using 3 equiv of 1,5-hexadiene, the overall yield was 0.26 mmol of **4** per gram of original Merrifield polymer. The overall yield using 2 equiv of 1,5-hexadiene was 0.19 mmol of **4** per gram of polymer. When the polymer-bound aldehyde was recycled through this reaction scheme a second time, **4** was obtained to the extent of 0.07 to 0.11 mmol per gram of polymer. In parallel with the solution-phase chemistry, the *cis*:*trans* ratio for **4** was 1:2.1. The percentage yields were determined from a quantification of the degree of functionalization of the polymer support at the aldehyde stage (vide infra). The increased percentage yields of the polymer-supported syntheses compared to solution phase suggest that some of the reaction steps may have proceeded with fewer side reactions than in the homogeneous system. The reaction most likely to benefit from the polymer-supported protocol is the 1,3-dipolar addition, in which isoxazoline production by mono-addition would be expected to predominate over bis-addition on the polymer, a consequence of some degree of effective site−site isolation.

A second significant benefit to derive from the polymer-supported synthesis is illustrated by the ^1H NMR spectrum of the crude material removed from the polymer support in the electrophilic cyclization, Figure 2. The reaction was quenched, the polymer support washed with dichloromethane, the aqueous layer extracted, and the solvent removed *in vacuo*. The ^1H NMR spectrum shows a mixture of both the *cis* and *trans* diastereomers of **4**, but absolutely none of the side product previously observed in the solution-phase version of the sequence.

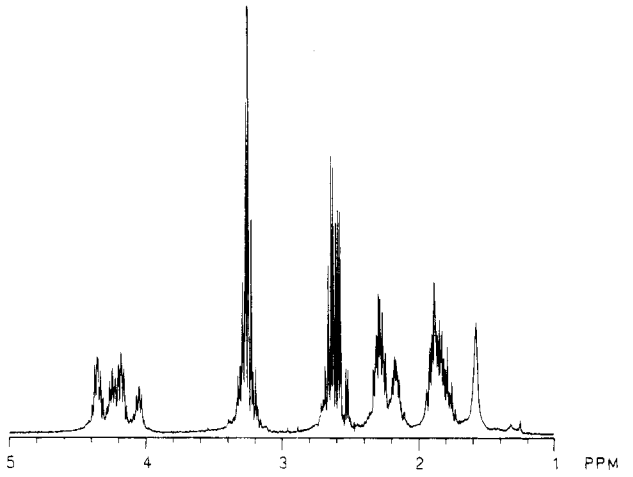


Figure 2. ^1H NMR of crude **4** cyclized from the polymer support.

As mentioned above, the polymer-supported aldehyde was regenerated in the final electrophilic cyclization. The lower yields from the recycled polymer-supported synthesis can be explained by comparing the IR spectrum of the initial polymer-supported aldehyde with that of the aldehyde after completion of the first synthetic sequence (Figure 3).

The aldehyde carbonyl stretch at 1700 cm^{-1} in the IR spectrum after the first electrophilic cyclization (Figure 3b) is approximately half as intense as the initial aldehyde carbonyl signal (Figure 3a), when compared to the intensities of polystyrene backbone stretches at 1600, 1492, and 1453 cm^{-1}. This observation is consistent with the 48−53% solution-phase yields for the final reaction.

Determination of the Degree of Polymer Functionality. A determination of the degree of functionalization of the polymer at the aldehyde stage was carried out in order to both accurately estimate the relative number of equivalents of α,ω-diene used and provide a meaningful percentage yield of **4**. We oxidized polymer-bound aldehyde **6** to the corresponding carboxylic acid **10** and neutralized with cesium hydroxide to give the polymer-supported salt **11**. Gravimetric determination of **11** proved a convenient quantification method (Scheme 5). The literature procedure[52] which recommended oxidation of the polymer-supported aldehyde **7** to the carboxylic acid using chromic acid was unsatisfactory because it did not go to completion, as evidenced by the incomplete disappearance of the C=O aldehyde stretch at 1700 cm^{-1} in the IR spectrum. The acetic acid reaction solvent failed to swell the polymer support significantly, and the chromic acid also turned the polymer support permanently green (presumably with complexed chromium). We therefore developed a superior polymer-supported carboxylic acid synthesis using *m*-chloroperbenzoic acid in 1,2-dimethoxyethane, a Baeyer−Villiger-type oxidation. This reaction was usually run at 55 °C overnight, but similar results were obtained after 6 h at 90 °C. The polymer-supported carboxylic acid from this

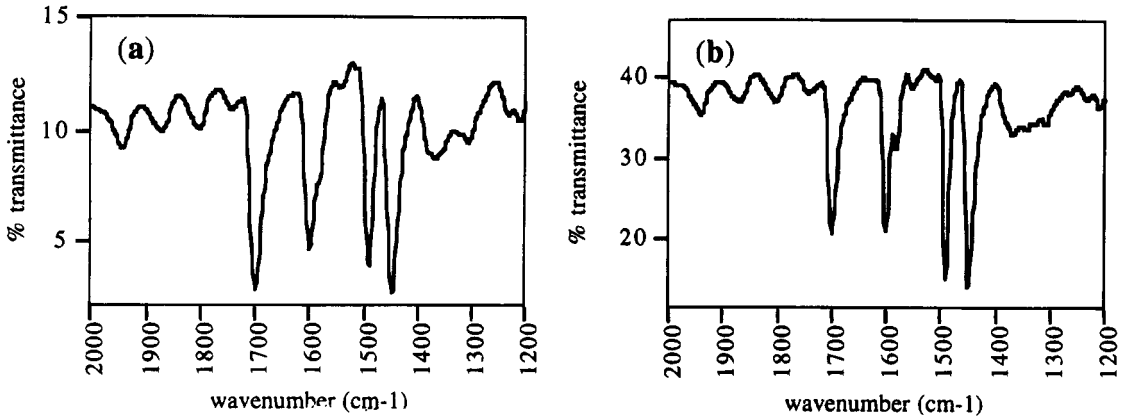
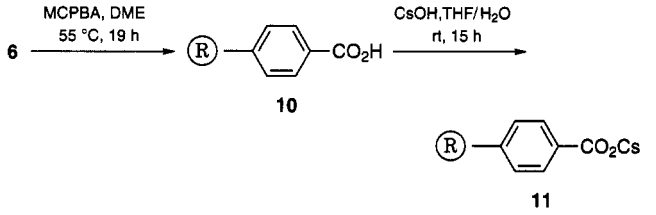
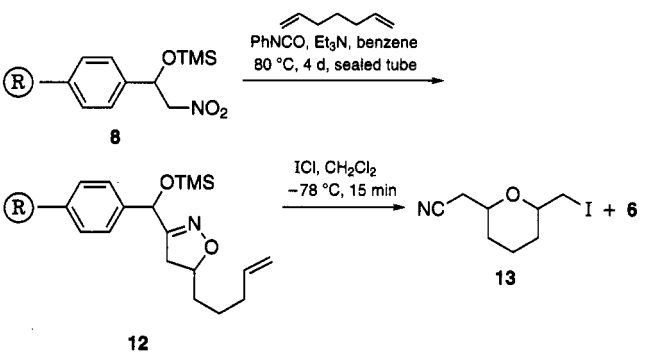


Figure 3. IR spectra of polymer-supported aldehyde **6** (a) and after one synthetic cycle (b). The aldehyde C=O stretch appears at 1700 cm^{-1}.

Scheme 5



Scheme 6



reaction was bright white and had carbonyl absorbances in the IR spectrum at 1731 (C=O free) and 1691 (C=O H-bonded) cm^{-1} as well as an OH stretch at 3457 cm^{-1}. The H-bonded carbonyl absorption is a clear indication of the lack of absolute site isolation associated with this type of polymer support. The neutralization with cesium hydroxide was carried out in a THF/H_2O (1:1) mixture which both swells the polymer support and solubilizes the base. The formation of the carboxylate salt is evident in the carbonyl region of the IR spectrum, which shows carboxylate absorbances at 1557 and 1384 cm^{-1}. Both the oxidation and neutralization reactions appear to go to completion by IR. Evidently, the extended reaction time allows for complete neutralization of all reactive sites.

The polymer-supported material was washed with the usual solvents and oven-dried to constant weight before and after neutralization to assure consistent measurements. This procedure reproducibly gave the degree of functionalization to be 0.65 ± 0.04 mequiv of aldehyde per gram of polymer. The percentage yields reported in Table 4 were obtained using this value.

This synthetic methodology was extended to the 1,3-dipolar cycloaddition using 1,6-heptadiene to form 2-(cyanomethyl)-6-(iodomethyl)tetrahydropyran (**13**) (Scheme 6). The isoxazoline was again characterized by the loss of the nitro peaks at 1555 and 1375 cm^{-1} in the IR spectrum. Using 3 equiv of the diene per mmol of polymer-bound aldehyde functionality, the reaction yielded 7.3% of tetrahydropyran **13** in a *cis*:*trans* ratio of 1:2.5. Identification of **13** was made by comparison with literature data.[37] This yield was considerably lower than that for tetrahydrofuran **4**, perhaps a consequence of the extended chain of the pentenyl group allowing formation of the bis-addition product in the 1,3-dipolar cycloaddition, but this possibility was not directly confirmed. The greater ease of five-membered ring formation over six-membered ring formation may also be a factor.

Conclusion

We have shown that polymer-supported, multistep synthetic sequences can deliver small molecule targets. The diversity of reactions, solvents, and conditions presented in this five-step sequence demonstrates the versatility of the polymer-supported methodology. Reaction conditions are only slightly, if at all, different from those used in conventional solution-phase synthesis. It is also significant that in our scheme the desired cyclic ether is obtained exclusively; no other products are cleaved from the polymer support. In addition, the polymer support is sufficiently robust to be recovered and recycled through the reaction sequence.

Experimental Section

All reactions were run under an inert atmosphere. Reagents and solvents were purified as follows: dichloromethane was distilled from P_2O_5; benzene and THF distilled from sodium/benzophenone; Et_3N and trimethylsilyl chloride were distilled from CaH_2; phenyl isocyanate was vacuum distilled from P_2O_5. 1,2-Dimethoxyethane was used as received. Infrared spectra were determined on a Galaxy 3000 series Mattson FTIR. NMR were run using a General Electric QE-300 spectrometer (^1H at 300 MHz and ^{13}C at 75 MHz). MPLC refers to column chromatography done at 10–15 psi through EM Lobar columns packed with LiChroprep Si60 (40–63 μm) with EtOAc/hexane as eluent and monitored by refractive index detection. Capillary gas chromatography (GLC) was performed on a Hewlett-Packard 5390A gas chromatograph using a J&W DB210 (0.25 mm × 30 m; film thickness 0.25 mm); gas pressures (psi) H_2 60, N_2 40, air 34, H_2 20.

For reactions involving a polymer support, the polymer was swollen in the reaction solvent for 30 min prior to adding other reagents. The reaction workup for the polymer substrate included suction filtration using a scintered glass funnel and washing with solvents of varying polarity, usually three times

each with water, DME, and ether. The polymer was then dried overnight under vacuum and an IR spectrum obtained of a KBr pellet. IR bands which are assigned to the polymer support are 3026, 2922, 1601, 1493, 1453, 759, and 698 cm^{-1}. All other bands reported are indicative of the new functionality attached to the polymer. Reactions were monitored by the appearance and/or disappearance of absorbances ascribed to functional group transformations occuring.

2-Nitro-1-phenylethan-1-ol (1).[49] To a solution of 0.24 mL (2.4 mmol) of benzaldehyde, 0.25 mL (4.7 mmol) of nitromethane, and 0.27 mL (4.7 mmol) of ethanol was added 3 drops of triethylamine. After the solution was stirred for 15 h at rt, the reaction was neutralized with 3 drops acetic acid, and 2 mL of ice water was added. The aqueous layer was extracted with ether (2 × 4 mL), dried ($MgSO_4$), and vacuum filtered. The solvent was removed by rotary evaporator to give a brown oil. The oil was purified by MPLC at 4 mL/min using 10/90 ethyl acetate/*n*-hexane to give 335 mg (85%) of **1** as a red oil: FTIR (neat) 3543, 1558, 1379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.86 (d, 1H), 4.45–4.60 (q, 2H), 5.45 (m, 1H), 7.40 (m, 5H).

1-Nitro-2-phenyl-2-[(trimethylsilyl)oxy]-1-ethane (2). In freshly silylated glassware, 882 mg (8.1 mmol) of trimethylsilyl chloride and 821 mg (8.1 mmol) of triethylamine were combined with 10 mL of THF; the mixture turned milky white. The solution was brought to 0 °C, and 709 mg (4.2 mmol) of **1** in 5 mL of THF was added dropwise using an addition funnel over 35 min. The mixture was stirred in an ice bath for 15 h (0 °C to rt), the reaction was quenched with 25 mL of ice water, and the mixture was extracted with ether (3 × 15 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed by rotary evaporator to give a light yellow oil. The material was purified by MPLC at 6 mL/min using 5/95 ethyl acetate/*n*-hexane to yield 858 mg (84%) of **2** as a clear liquid: FTIR (neat) 1559, 1381, 1113 cm^{-1}; ^1H NMR δ 0.03 (s, 9H), 4.40–4.52 (ddd, 2H), 5.41–5.45 (dd, 1H), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −0.32, 72.44, 82.68, 126.04, 128.57, 128.77. Anal. Calcd for $C_{11}H_{17}NO_3Si$: C, 55.20; H, 7.16; N, 5.85. Found: C, 54.99; H, 7.10; N, 6.00.

5-(3-Butenyl)-4,5-dihydro-3-(phenyl[(trimethylsilyl)-oxy]methyl)isoxazole (3). To a solution of 285 mg (1.2 mmol) of **2**, 991 mg (12.1 mmol) of 1,5 hexadiene, and 224 mg (2.3 mmol) phenyl isocyanate in a sealable tube was added 5 mL of benzene followed by 5 drops triethylamine. The tube was sealed, the solution was stirred at 89 °C for 50 h, and the reaction was cooled to room temperature, quenched with 25 drops of water, and stirred for 2 h. The mixture was filtered and dried (Na_2SO_4), and the solvent was removed by distillation. The desired product was purified by MPLC using 10/90 ethyl acetate/*n*-hexane to give 268 mg (74% yield) of **3** as a yellow oil as a 1:1 mixture of diastereomers: FTIR (neat) 1640, 1254, 1093, 1067, 879, 848 cm^{-1}; ^1H NMR δ 1.4 (m, 0.5H), 1.6 (m, 1H), 1.8 (m, 0.5 H), 2.0 (m, 1H), 2.15 (m, 1H), 2.2 (dd, 0.5H), 2.65 (d, 1H), 3.0 (dd, 0.5H), 4.5 (m, 1H), 5.0 (qq, 2H), 5.7 (s, 1H), 5.8 (m, 1H); ^{13}C NMR ($CDCl_3$) δ −0.2, 29, 34.2, 34.6, 37.4, 69.9, 80, 114, 125, 127, 128, 137, 142, 162. Anal. Calcd for $C_{17}H_{25}NO_2Si$: C, 67.28; H, 8.30; N, 4.62. Found: C, 67.09; H, 8.22; N, 4.67.

2-(Cyanomethyl)-5-(iodomethyl)tetrahydrofuran (4).[37] To a solution of 159 mg (0.52 mmol) of **3** in 3 mL of CH_2Cl_2 at −78 °C was added 0.63 mL of 1 M ICl in CH_2Cl_2, and the reaction mixture was stirred for 15 min. The reaction was quenched cold with 5 mL of aqueous sodium thiosulfate, the solution was brought to rt, and 20 mL of water was added. The organic layer was removed, the aqueous layer was extracted with dichloromethane (2 × 20 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed on a rotary evaporator to give 213 mg of a light yellow oil, which was purified by MPLC using 20/80 EtOAc/*n*-hexane at 4 mL/min to give 73 mg (55%) of **4** in a *cis*:*trans* ratio of 1:1.92 determined by capillary GC: initial temperature = 150 °C; initial time = 2 min; rate = 2 °C/min (*cis* 7.64 m/*trans* 7.81 min); R_f = 0.20, 20/80 EtOAc/hexane; FTIR (neat) 2251 (CN), 1061 (C—O) cm^{-1}; ^{1}NMR ($CDCl_3$) δ 1.87 (m, 2H), 2.16 (m, 0.67H), 2.28 (m, 1.33H), 2.62 (m, 2H), 3.24 (m, 2H), 4.04 (m, 0.33H), 4.17 (m, 0.67H), 4.23 (m, 0.33H), 4.36 (m, 0.67H); ^{13}C NMR ($CDCl_3$) δ *trans*10.20, 23.94, 31.31, 32.10, 74.60, 78.70, 117.04; *cis* 9.61, 24.22, 30.30, 31.07, 74.97, 79.21, 117.10.

Polymer-Supported Benzaldehyde 6. To a solution of 5.047 g of 2% cross-linked Merrifield polymer **5** (Aldrich, benzyl chloride form, ~1 mequiv/g) in 75 mL of DMSO was added 7.0764 g (84.2 mmol) of $NaHCO_3$. The reaction was refluxed at 155 °C for 6 h, cooled to rt, and worked up to give 4.9706 g of a light yellow solid: FTIR (KBr) 2722 (*CHO*), 1702 (C=O) cm^{-1}.

Polymer-Supported 2-Nitro-1-phenylethan-1-ol 7. To a solution of 2.087 g of **6** and 3.36 mL (62mmol) of nitromethane was added 3.62 mL (62 mmol) of ethanol, 10 mL of THF, and 0.86 mL (6.2 mmol) of triethylamine. After the solution was stirred overnight at room temperature, the reaction was worked up to give **7** as a light yellow solid: FTIR (KBr) 3559 (OH free), 3423 (OH), 1702 (w, C=O), 1555 (s, NO_2), 1375 cm^{-1} (m, NO_2).

Polymer-Supported 2-Phenyl-2-[(trimethylsilyl)oxy]-nitroethane 8. In freshly silylated glassware, 10.7 g of **7** was swollen in 60 mL of tetrahydrofuran. To this solution was added dropwise 2.7 mL (21.4 mmol) of trimethylsilyl chloride followed by the dropwise addition of 3.0 mL (21.4 mmol) of triethylamine. After the solution was stirred for 15 h at room temperature, the reaction was quenched with 15 mL of water. The polymer was then worked up to give **8** as a light yellow solid: FTIR (KBr) 1556 (NO_2), 1378 (NO_2), 1253 cm^{-1} (Si-$(CH_3)_3$).

Polymer-Supported 5-(3-Butenyl)-4,5-dihydro-3-(1-phenyl-1-[(trimethylsilyl)oxy]methyl)isoxazole 9. To a solution of 2.5 g of **8** in 10 mL of benzene in a pressure tube (Ace Glass) was added 0.6 mL (5 mmol) of phenyl isocyanate followed by 0.9 mL (7.8 mmol) of 1,5-hexadiene and 5 drops of triethylamine. The tube was sealed and heated at 80 °C for 4 d. The reaction was cooled, quenched with 10 mL of water, and allowed to stir overnight. The polymer was then worked up to give **9** as a light yellow solid: FTIR (KBr) 1253, 1071, 877, 844 cm^{-1}.

2-(Cyanomethyl)-5-(iodomethyl)tetrahydrofuran (4).[37] To a cooled (−78 °C) mixture of 2.23 g of **9** in 14 mL of CH_2Cl_2 was added 3.6 mL of 1 M ICl in CH_2Cl_2. After 30 min, the reaction mixture was removed from the cold bath, the reaction was quenched with 2.0 mL of aqueous sodium thiosulfate, and then the solution was stirred for 30 min until it reached rt and the polymer solution was light yellow in color. The polymer was then filtered and washed with 20 mL of hot water followed by 2 × 20 mL of CH_2Cl_2. The filtrate was poured into a separatory funnel and the organic layer removed. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried (Na_2SO_4). The solvent was removed on a rotary evaporator to give 222 mg of a brown oil. The oil was purified by MPLC using 20/80 ethyl acetate/*n*-hexane at 4 mL/min to give 146 mg (0.58 mmol) of **4** with a *cis*:*trans* ratio of 1:2.1 as judged by capillary GLC: initial temperature = 150 °C; initial time = 2 min; rate = 5 °C/min (*cis* 6.70 min/*trans* 6.88 min); R_f = 0.20, 20/80 EtOAc/hexane; IR (neat) 2251 (CN), 1061 (C—O) cm^{-1}; ^{1}NMR ($CDCl_3$) δ 1.87 (m, 2H), 2.16 (m, 0.67H), 2.28 (m, 1.33H), 2.62 (m, 2H), 3.24 (m, 2H), 4.04 (m, 0.33H), 4.17 (m, 0.67H), 4.23 (m, 0.33H), 4.36 (m, 0.67H); ^{13}C NMR ($CDCl_3$) δ *trans* 10.20, 23.94, 31.31, 32.10, 74.60, 78.70, 117.04; *cis* 9.61, 24.22, 30.30, 31.07, 74.97, 79.21, 117.10. The resulting polymer of this reaction was washed, filtered with 3 × 20 mL each of hot water, DME, ether, chloroform, and dichloromethane, and then dried under vacuum overnight: FTIR (KBr) 1701 cm^{-1} (C=O).

Polymer-Supported Benzoic Acid 10. To a mixture of 3.04 g of **6** in 25 mL of 1,2-dimethoxyethane was added 1.32 g (6.1–6.9 mmol) of *m*-chloroperbenzoic acid. The mixture was warmed to 55 °C and stirred for 19 h and then worked up and oven dried to give 3.07 g of **10** as a white solid: FTIR (KBr) 3457 (OH), 1731 (C=O free), 1691 (C=O H-bonded) cm^{-1}. The oxidation succeeds best with reagent-grade DME directly from the bottle; prior distillation of the solvent leads to much poorer results.

Polymer-Supported Cesium Carboxylate 11. To a solution of 1.0172 g of **10** in 6 mL of THF/H_2O (1/1) was added 2 mL of 25% cesium hydroxide (aq). The reaction was stirred

at room temperature for 15 h and then worked up and oven dried to give 1.1047 g (67% Cs gain) of **11**: FTIR (KBr Pellet) 1554, 1378 cm^{-1} (COOCs).

Polymer-Supported 5-(4-Pentenyl)-4,5-dihydro-3-(phenyl[(trimethylsilyl)oxy]methyl)isoxazole 12. To a solution of 2.50 g of **8** in 10 mL of benzene in a pressure tube (Ace Glass) was added 0.6 mL (5 mmol) of phenyl isocyanate followed by 0.7 mL (5.0 mmol) of 1,6-heptadiene and 6 drops of triethylamine. The tube was sealed and heated at 80 °C for 4 d. The reaction mixture was cooled, the reaction was quenched with 5 mL of water, and the solution was allowed to stir overnight. The polymer was then worked up to give 2.50 g of **12** as a light yellow solid: FTIR (KBr) 1253, 1071, 877, 844 cm^{-1}.

2-(Cyanomethyl)-6-(iodomethyl)tetrahydropyran (13).[37] To a cooled (−78 °C) mixture of 2.50 g of **12** was added 3.75 mL of 1 M ICl in CH_2Cl_2, and the reaction mixture was stirred for 30 min and then warmed to rt and the reaction was quenched wtih 2.5 mL of 1 M $Na_2S_2O_3$ (aq). The polymer was filtered and washed with CH_2Cl_2, the organic layer was removed from the aqueous layer, and the aqueous layer extracted with 2 × 20 mL of CH_2Cl_2. The combined organics were dried (Na_2SO_4), and the solvent was removed *in vacuo* to give 80.4 mg of crude product. The crude material was purified by MPLC using 25/75 ethyl acetate/*n*-hexane at 4 mL/min to give 32.4 mg (0.122 mmol) of **13** with a *cis:trans* ratio of 1:2.5 as judged by capillary GC of the crude reaction mixture: initial temperature = 150 °C; initial time = 2 min; rate = 5 °C/min (*cis* 10.03 min/*trans* 9.07 min); FTIR (neat) 2938, 2250, 1201, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (dq, 1H, J = 4.0, 12.0 Hz), 1.32 (dq, 1H, J = 4.0, 12.0 Hz), 1.43−1.96 (m, 4H), 2.55 (d, 1.43H, J = 6.0 Hz), 2.59 (d, 0.57H, J = 5.5 Hz), 3.17 (d, 1.43H, J = 6.0 Hz), 3.26 (dd, 0.57H, J = 6.5, 10.5 Hz), 3.32−3.44 (m, 0.71H), 3.65 (ddt, 0.71H, J = 5.5, 5.5, 6.0 Hz), 3.89 (q, 0.29 H, J = 6.0 Hz), 4.00 (ddt, 0.29H, J = 5.0, 6.5, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 8.7/6.8, 22.6/17.5, 24.7/23.0, 30.1/27.8, 30.5/28.8, 73.2/67.0, 77.4/72.1, 117.1.

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