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Synthesis of Cyclic Ethers Utilizing a Cyclization–Fragmentation Strategy

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Abstract—A variety of cyclic ethers have been prepared via both solution phase and polymer-supported sequences of 3+2 cycloaddition of nitrile oxides to alkenes and dienes to give isoxazolines, followed by electrophile-induced cyclization. Library generation by alkylative elaboration of isoxazolines was unsuccessful, but both simple and substituted dienes were found suitable for polymer-supported formation of cyclic ethers of ring sizes five through seven.

Introduction

Solid Phase Organic Synthesis (SPOS) has in principle many advantages over more traditional synthetic methods. Excess reagents and soluble side products can be washed away from the polymer thus making purification easier; resin bound toxic substances can be handled more easily and more safely; reactions that exhibit poor chemoselectivity can often be made more efficient by attachment of one of the components to the solid support. Reaction substrates may be linked to the polymer via any number of cleavable functional groups. Common modifications of the basic Merrifield-type resins for substrate attachment have included hydroxymethyl polystyrene, mercaptomethyl polystyrene, or oxidized (e.g. aldehyde or carboxylic acid) derivatives. With these types of linking strategies, part of the linkage function normally remains present in the product after cleavage from the solid support. Consequently, there has been considerable effort devoted to developing the so-called "traceless linkers" in order to circumvent this problem. One of the earliest, which utilizes a silicon–carbon bond that can later be cleaved from the final product, was described by Ellman in his synthesis of a library of 1,4-benzodiazepines, in which the final products were obtained by HF cleavage of the carbon–silicon bond.[1]

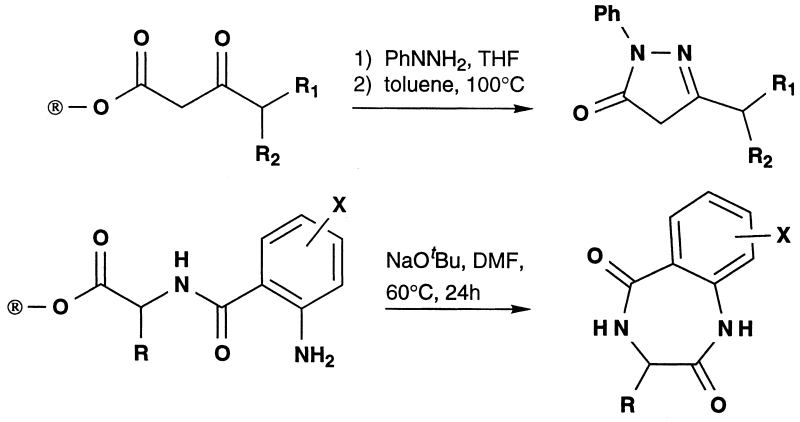

Figure 1. Literature examples of polymer-supported cyclization reactions.

Another tactic for traceless cleavage is via cyclization. This method has the advantage that usually only the desired compounds and not side products are cleaved from the polymer, thus making purification of the products much

Keywords: cyclization; ethers; isoxazolines; nitrile oxides; polymer support.

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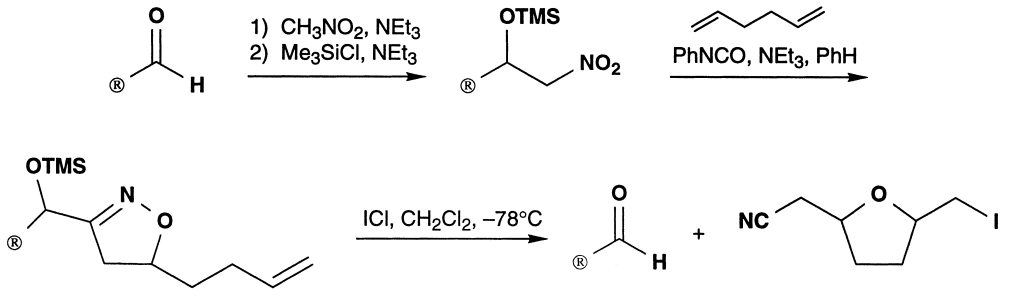


Scheme 1.

simpler. Fig. 1 shows two examples of this type that have been reported.[2]

The conversion of isoxazolines into cyclic ethers first reported by Kurth has been of particular recent interest to us. Cyclic ethers of various sizes can be synthesized by electrophilic cyclization between the oxygen of the isoxazoline and an activated olefin. While four- and eight-membered cyclic ethers are not accessible in this way, five-, six-, and seven-membered rings may be obtained in reasonable yields.[3]

In our laboratory Beebe showed that the Kurth methodology for the synthesis of 2,5-disubstituted tetrahydrofurans (THFs) could be adapted to the solid phase and incorporate a cyclization-based traceless linker strategy. In this study ICl was employed to initiate an electrophile-promoted cyclative cleavage process from a polymer-bound isoxazoline bearing a pendant alkene moiety as shown in Scheme 1.[4]

There are several advantages to using SPOS techniques rather than conventional solution-phase methodology in synthesizing cyclic ethers via isoxazolines, the most notable being ease in separation of byproducts at several stages. During isoxazoline synthesis the diphenylurea formed can easily be washed away from the polymer using excess solvent. Furthermore, only the desired cyclic ethers are cleaved from the polymer in the final step. Side products derived from addition to the alkene without concomitant cyclization remain polymer-bound under SPOS conditions. These side products are very difficult to separate from the desired cyclic ethers when the reaction is carried out in homogeneous solution. As a bonus, a "site-isolation" effect is observed under solid-phase conditions, obviating the need to employ a very large excess of diene in the dipolar cycloaddition step that forms the isoxazoline ring.

The cyclization reaction is thought to proceed via the cyclic isoxazolinium intermediates shown in Fig. 2.[5] A preference for the formation of the *trans* product is usually observed, a consequence of a nonbonding interaction between the electrophile and the isoxazoline ring: the *exo*-intermediate should be the more stable. Diastereoselectivity is solvent-dependent, presumably because of *endo*/*exo* equilibration between the isoxazolinium intermediates. Subsequent irreversible loss of "R^+" and N–O bond cleavage gives the cyclic ether.[6]

The goal of this project was to expand the range of cyclic ethers that could be synthesized in homogeneous solution as well as by SPOS, utilizing the electrophile-promoted cyclization strategy on a variety of specifically designed isoxazolines. Herein we describe the results of these efforts.

Results and Discussion

Our initial efforts were aimed at designing routes by which tetrahydrofurans of varying substitution patterns could be synthesized via an appropriate precursor isoxazoline **1**, shown retrosynthetically in Scheme 2.

We sought first to prepare a library of isoxazolines via alkylation α to the activating group 'G'. For this purpose

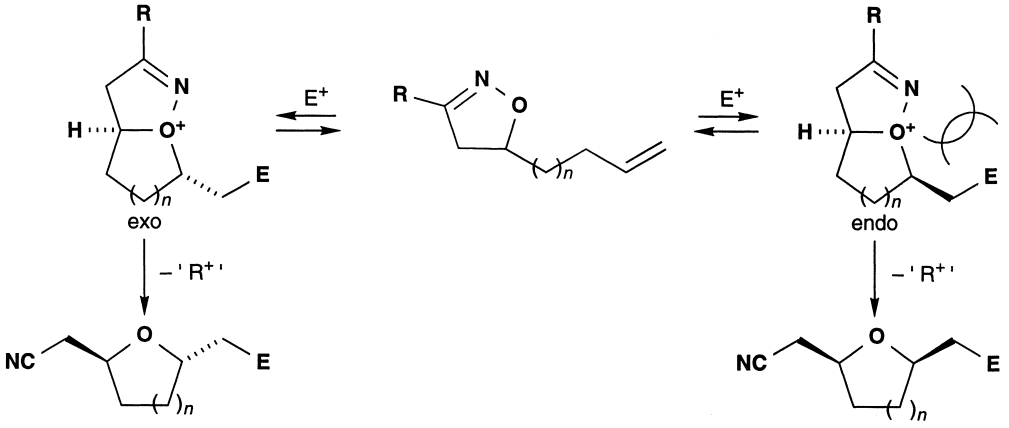
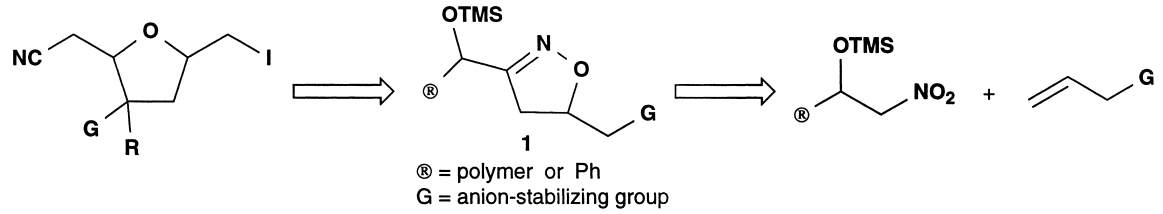


Figure 2. Proposed mechanism for the electrophilic cyclization.



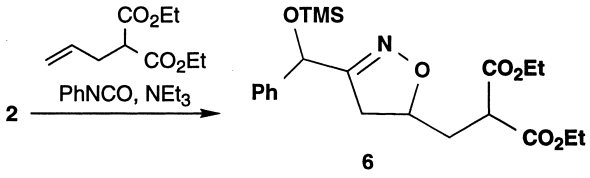
Scheme 2.

we chose allyl phenyl sulfone as the dipolarophile for the isoxazoline-forming cycloaddition. Prior to attempting the chemistry on the polymer, the solution equivalent was carried out.

The sulfone-substituted isoxazoline was prepared via the nitrile oxide by treatment of nitrosilyl ether **2** with phenyl-isocyanide, triethylamine, and allyl phenyl sulfone to give **3** in 84% yield as an inseparable mixture of diastereomers (Scheme 3). Separation of the diphenylurea byproduct from the desired isoxazoline was problematic, requiring tedious chromatography.

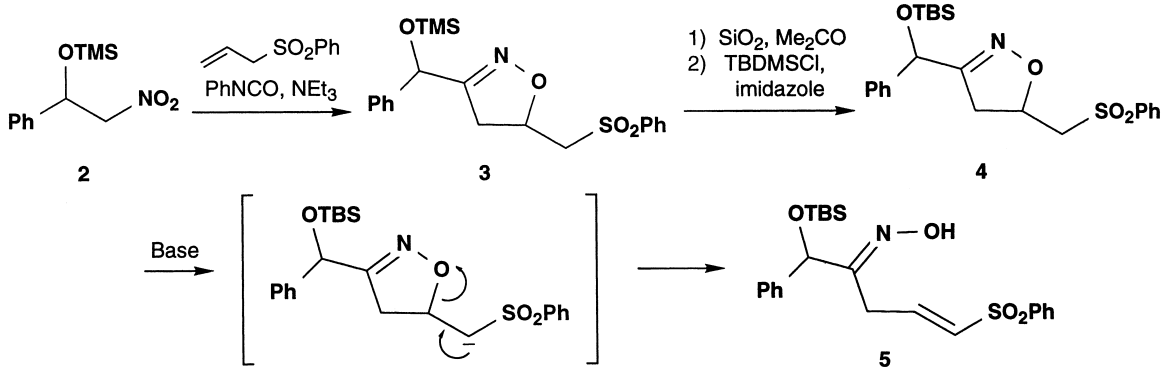
Alkylation was first attempted in the usual way[7] by treatment with *n*-BuLi in THF at −78°C followed by addition of allyl bromide in THF. Alkylation was not observed; instead, only the deprotected starting material was isolated. We therefore changed the protecting group to the TBDMS ether to improve stability, converting **3** into **4** in 92% yield, as shown.[8] However, alkylation of sulfone **4** with allyl bromide still failed: some starting material was isolated, along with a second substance. The same result was obtained using methyl iodide. Interestingly, treatment with *n*-BuLi followed by quenching with D_2O gave no deuterium incorporation in the recovered starting material. Using *sec*-BuLi under the original alkylating conditions, we found by TLC that all of the starting material was consumed. Allyl bromide was added, but again no alkylated product was obtained. In this case, the new compound observed in the previous alkylation attempts was obtained as a single product in virtually quantitative yield. Analysis by ^{1}H NMR revealed that the isoxazoline ring was no longer present; instead, there appeared a doublet at δ 6.13, a ddd pattern at δ 6.44, consistent with a *trans* disubstituted double bond, and two signals at δ 3.56 and δ 3.72 for diastereotopic methylene protons coupled to the hydrogen at δ 6.44. Evidently, formation of the anion α to the sulfone gave rise to ring-opening of the isoxazoline leading to the *trans*-α,β-unsaturated sulfone oxime **5**. In the ^{13}C NMR, resonances corresponding both to the carbon of the oxime functional group and to those of the α,β-unsaturated sulfone appeared. When formed in the presence of D_2O, deuterium was incorporated at the methylene α to the oxime group. This material underwent isomerization to at least two other substances upon storage for several hours.

It having become clear that the generation of an anion α to the isoxazoline opens the ring, we turned instead to a scheme designed to synthesize substituted tetrahydropyrans via introduction of a malonate-derived diester moiety that could be alkylated with suitable unsaturated species. We began by using diethyl allylmalonate as a dipolarophile. Under solution-phase conditions, 1,3-dipolar cycloaddition between **2** and diethyl allylmalonate with phenyl isocyanate as the dehydrating agent gave compound **6** in 44% yield, Eq. (1).

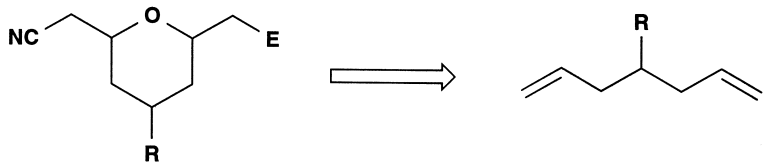


(1)

In initial alkylation attempts we chose LDA rather than the more commonly used NaH,[9] reasoning that the soluble base would be more suitable for the polymer-based system. Malonate-substituted isoxazoline **6** was treated with LDA in THF at 0°C and then allyl bromide. After stirring overnight, TLC showed only the starting material. Further



Scheme 3.

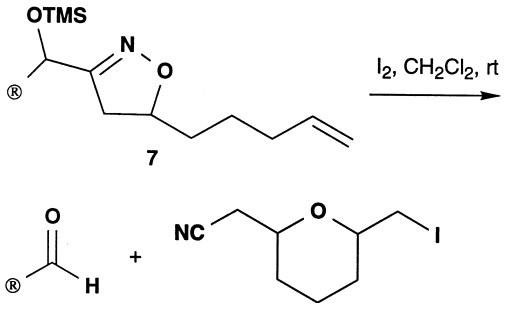


Scheme 4.

attempts with a variety of bases under several different sets of conditions also returned only the unreacted starting material. Treatment of compound **6** with the dimsyl anion followed by quenching with D_2O did not result in any deuterium incorporation, indicating, again, a system oddly resistant to deprotonation.

Failing to develop alkylation-based approaches, we returned to diene-based methodology. Following the published procedure,[4] polymer-bound 2-nitro-1-phenylethan-1-ol was prepared by reaction of polymer-bound benzaldehyde with CH_3NO_2 in THF and protected as the TMS ether to give the cycloaddition precursor. We repeated the published preparation of the simplest system, 2-(cyanomethyl)-6-(iodomethyl)tetrahydropyran. The required polymer-bound isoxazoline was synthesized by a 1,3-dipolar cycloaddition with 1,6-heptadiene.

Although ICl can be used successfully in the polymer-supported electrophile-induced cyclization, competing addition to the terminal double bond is a persistent problem.[4] In this study and in a related work we explored the use of several electrophile sources, including IBr, *N*-iodosuccinimide, PhSeCl, and PhSe(phthalimide), finding that the various sources of "I^+" showed only minimal differences in yields and stereoselectivities for cyclic ether products, while the Se-based reagents did not induce cyclization at all. As a result, we chose to use I_2, which is an effective cyclization promoter under homogeneous conditions and gives clean products provided that light is excluded and unconsumed I_2 is removed completely.[6] The polymer-bound isoxazoline was swollen in CH_2Cl_2, and 5 equiv. of I_2 were added in one portion. After the appropriate reaction time and workup, a 2.7% yield of 2,6-disubstituted THP was obtained (Eq. (2)), an average per step yield of 40%, somewhat poorer than earlier results with ICl. A *cis*/*trans* ratio of 1:2.6 was determined by GC analysis, identical to that found with ICl. Several optimization attempts were made, but the yields did not vary appreciably.

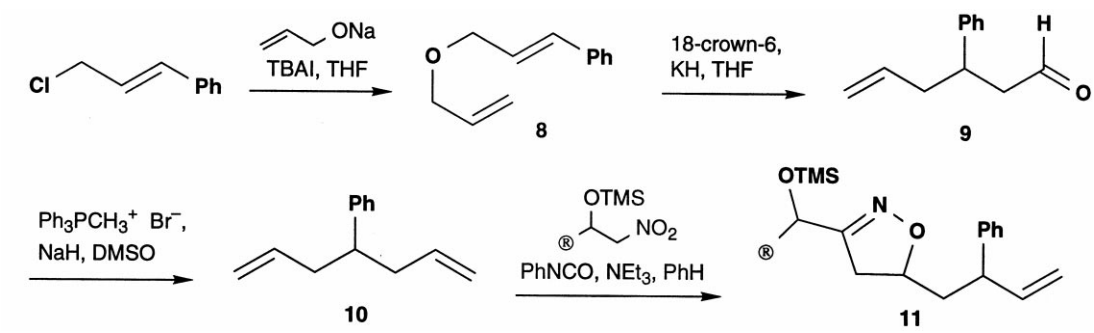


(2)

We then turned to the synthesis of 4-substituted 1,6-dienes, to provide access to 4-substituted THP derivatives (Scheme 4), hoping in addition that substitution in the diene would be beneficial in promoting the desired cyclization process.

Diene preparation was based on work of Greeves and Lee, who prepared δ,ϵ-unsaturated aldehydes from bis-allyl ethers by tandem 2,3-Wittig–anionic oxy-Cope rearrangements.[10] We prepared bis-allyl ether **8** by Williamson synthesis using cinnamyl bromide and allyl alcohol in 84% yield. Next, ether **8** was dissolved in THF, cooled to 0°C, and treated with 2.5 equiv. KH and 1.5 equiv. 18-crown-6, Scheme 5. After warming to rt, quenching, and work-up, aldehyde **9** was isolated in 96% yield. Finally, diene **10** was prepared in a 75% yield by Wittig olefination using standard conditions.

We proceeded directly with the polymer-supported 1,3-dipolar cycloaddition. Polymer bound 2-nitro-1-phenylethan-1-ol was treated with phenyl isocyanate, triethylamine, and 4-phenyl-1,6-heptadiene **10** in refluxing benzene, giving isoxazoline-containing polymer **11**, which was then swollen in dry CH_2Cl_2 and treated with 5 equiv. I_2. The mixture was stirred in the dark overnight, and the excess I_2 quenched with aqueous $Na_2S_2O_3$. After filtration



Scheme 5.

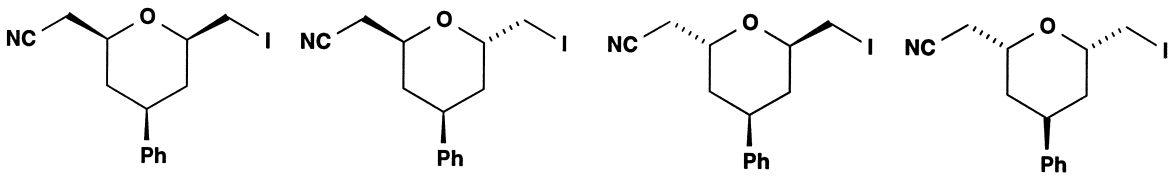


Figure 3. Diastereomers of substituted tetrahydropyrans **12**.

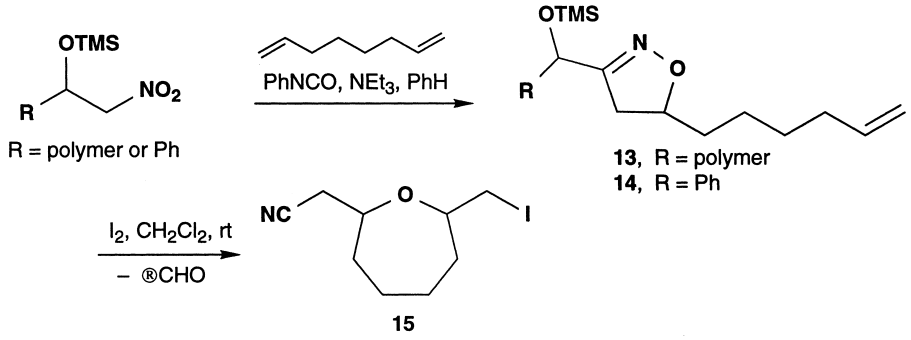
and removal of solvent an oil remained which was found by GC to consist of a 1:1:1:1 mixture of the four possible diastereomers **12**, Fig. 3. The most characteristic absorbances in the ^{1}H NMR were the pairs of doublets of doublets that corresponded to the hydrogens α to the iodide and nitrile groups. The four-step yield was a respectable 7.8%, an average per step yield of 53%. This particular system therefore provides proof of the concept for an approach to libraries of 4-substituted tetrahydropyrans beginning with appropriately substituted allylic halides.

We next attempted to synthesize a seven-membered ring ether utilizing both solution-phase and polymer-supported conditions. The 1,3-dipolar cycloadditions were successfully carried out between 1,7-octadiene and both solution-phase and polymer-bound nitrile oxides. Following electrophilic cyclization on the products **13** and **14**, respectively, oxepane **15** was isolated from **14** in solution in 52% yield (final step yield only), and in 8.1% overall yield from the polymer, corresponding to 53% per step (Scheme 6). GC analysis revealed that both products consisted of a 1:1 mixture of *cis* and *trans* diastereomers.

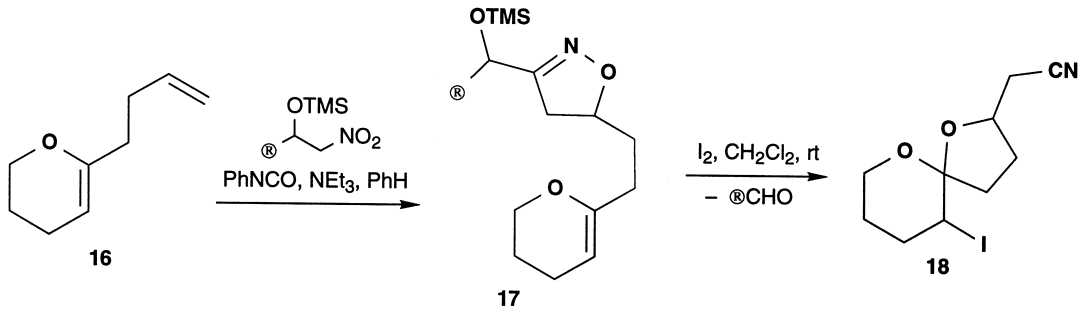
Finally, we investigated formation of a spiroketal using this methodology. Spiroketals have been synthesized in solution previously in this way. The starting diene, **16**, was prepared in one step from dihydropyran utilizing the reported procedure.[11] Following 1,3-dipolar cycloaddition and subsequent electrophilic cyclization, **18** was obtained in a 7.4% overall yield, 52% per step (Scheme 7). The diastereomer ratio was determined by GC analysis again to be 1:1.

Conclusion

We have expanded the scope of the polymer-supported multistep preparation of cyclic ethers to include both seven-membered rings and spirocyclic derivatives, and to demonstrate that libraries of substituted tetrahydropyrans are in principle accessible given the relative ease of preparation of the precursors. Diene-based approaches analogous to those previously reported were successful, although the benefits of reducing the need for large excesses of diene and eliminating multiple tedious purification steps were partly tempered by the modest overall yields for the four-step sequence on the polymer. Alternative approaches based on alkylations of two different isoxazoline-based systems were unsuccessful; a novel ring opening process was found to arise from deprotonation α to the 5-position of the isoxazoline ring.



Scheme 6.



Scheme 7.

Experimental

General procedures

See Ref. 4b for general information regarding purification of solvents and reagents, carrying out of reactions, polymer handling, and analytical procedures. Fourier Transform IR spectra were obtained on a Matson Genesis II with the Golden Gate Attenuated Total Reflectance (ATR) attachment. Radial chromatography was done on a Chromatotron using radial plates of either 1-, 2-, or 4-mm thickness of silica gel 60 PF; bands were visualized by UV. Capillary GC was done on a Shimadzu 14A using a DB-101 column. Conditions: Initial temp 150°C, hold time 2.0 min, ramp 5°/min, final temp 240°C, hold time 5.0 min.

4,5-Dihydro-5-{[(phenyl)sulfonyl]methyl}-3-{phenyl[(trimethylsilyl)oxy]methyl}isoxazole (3). To a solution of 3.0 g (12.5 mmol) **2** in 50 mL Et_2O was added 3.4 g (18 mmol) allyl phenyl sulfone and 0.1 mL triethylamine. Over a period of three days a total of 3.5 g (36 mmol) phenyl isocyanate was added in portions. The reaction mixture was quenched with 10 mL water, filtered, and the filtrates dried ($MgSO_4$), and evaporated to give a yellow oil. Chromatography (3:2 Et_2O/hexane) gave 4.05 g of a light yellow oil estimated by NMR to contain 3.5 g (72% yield) of a ca. 1:1 mixture of diastereomers of **3**, the remainder being residual allyl phenyl sulfone: ^{1}H NMR δ 0.12 (s, 9H), 2.56 (dd, 0.5H, J=7.4, 17.2 Hz), 2.87 (dd, 0.5H, J=10.5, 17.7 Hz), 3.04 (m, 1H), 3.25 (dd, 0.5H, J=10.3, 16.9 Hz *and* dd, 0.5H, J=7.6, 14.2 Hz), 3.39 (dd, 0.5H, J=4.8, 14.1 Hz), 3.52 (dd, 0.5H, J=5.1, 14.4 Hz), 4.79 (m, 0.5H), 4.89 (m, 0.5H), 5.66 (s, 1H), 7.25–7.95 (m, 10H). Loss of the trimethylsilyl group accompanied all preparative scale purification attempts of **3**, necessitating the use of the crude material in subsequent experiments.

4,5-Dihydro-5-{[(phenyl)sulfonyl]methyl}-3-{phenyl[(*tert*-butyldimethylsilyl)oxy]methyl}isoxazole (4). Crude **3** (5.67 g total, ca. 4.0 g **3**, remainder allyl phenyl sulfone) was deprotected by being dissolved in 10 mL MeOH containing 1.25 g citric acid. After 1 h at rt the solvent was removed, the residue taken up in 1:1 Et_2O/hexane, filtered, and run down a short silica column. Allyl phenyl sulfone was eluted, the solvent was changed to MeOH, and the product was removed. Evaporation of solvent gave an oil which was taken up in Et_2O, dried ($MgSO_4$), and evaporated to give 2.47 g (ca. 72% yield) of the alcohol, which was used without further purification: ^{1}H NMR δ 2.62 (dd, 0.5H, J=7.5, 17.7 Hz), 2.95–3.20 (m, 3H), 3.25 (dd, 0.5H, J=7.5, 14.4 Hz), 3.43 (dd, 0.5H, J=4.8, 14.1 Hz), 3.49 (dd, 0.5H, J=5.1, 14.1 Hz), 4.82 (m, 1H), 5.53 (s, 0.5H), 5.56 (s, 0.5H), 7.25–7.95 (m, 10H). A mixture of 5.63 g of this alcohol, 2.90 g (42.7 mmol) imidazole, and 3.14 g (20.8 mmol) *tert*-butyldimethylchlorosilane in 30 mL CH_2Cl_2 was stirred at rt for 18 h. The solvent was removed, and the residue was taken up in 1:1 Et_2O/hexane and filtered through a short silica plug. Removal of solvent gave 6.75 g (92% yield) essentially pure **4**: FTIR (neat) 1321, 1251, 1151, 1070, 877, 844 cm^{-1}; ^{1}H NMR δ 0.05 (s, 3H), 0.08 (s, 3H), 0.92 (s, 4.5H), 0.93 (s, 4.5H), 2.57 (dd, 0.5H, J=7.4, 17.6 Hz), 2.86 (dd, 0.5H, J=10.2, 17.7 Hz), 3.00 (dd, 0.5H, J=8.1, 14.4 Hz), 3.06 (dd, 0.5H, J=6.3, 17.7 Hz), 3.22 (dd, 0.5H, J=8.1, 14.4 Hz), 3.25 (dd, 0.5H, J=9.9, 17.7 Hz), 3.38 (dd, 0.5H, J=4.9, 14.4 Hz), 3.51 (dd, 0.5H, J=4.8, 14.4 Hz), 4.81 (m, 0.5H), 4.89 (m, 0.5H), 5.67 (s, 1H), 7.25–7.90 (m, 10H); ^{13}C NMR: δ −5.0, −3.5/−3.0, 25.0, 37.2/37.3, 59.3/59.5, 72.5, 122.7, 125.3, 125.8, 126.4, 131.6, 137.0/137.3, 157.8/158.0; HRMS: calcd for $C_{22}H_{28}NO_4SSi$ $(M-CH_3)^+$ 430.1501, found 430.1508.

***E*-1-Phenyl-5-[(phenyl)sulfonyl]-1-[(*tert*-butyldimethylsilyl)oxy]-4-penten-2-one oxime (5).** A solution of 460 mg (1.07 mmol) of **4** in 3 mL of THF was cooled to −78°C, treated with 1.8 mL of *sec*-BuLi (1 M in THF), and stirred at −78°C for 10 min. TLC (4:1 hexane/ethyl acetate) showed complete loss of the starting material. The mixture was quenched with water, the layers separated, the aqueous layer extracted with Et_2O, and the combined Et_2O layers dried (Na_2SO_4). The solvent was removed to give a viscous red oil, a quantitative yield of a 1:1 mixture of (presumably) *syn* and *anti* oximes, one of which could by obtained in relatively pure form by a sequence of column chromatography using hexane followed by radial chromatography using 1:1 Et_2O/hexane: FTIR (neat) 3408 (br), 3060, 3030, 2950, 2935, 2891, 2856, 1636, 1593, 1458, 1446, 1398, 1313, 1255, 1147, 1097, 974, 862, 845, 777, 739, 700 cm^{-1}; ^{1}H NMR δ −0.02 (s, 3H), 0.02 (s, 3H), 0.85 (s, 9H), 3.56 (dd, 1H, J=8.7, 14.1 Hz), 3.72 (dd, 1H, J=6.5, 14.1 Hz), 5.38 (s, 1H), 6.13 (d, 1H, J=15.9 Hz), 6.44 (ddd, 1H, J=6.5, 8.7, 15.9 Hz), 7.15–7.85 (m, 10H), 8.1 (br s, 1H); partial ^{13}C NMR for the isomer mixture δ 133.5, 137.6, 140.5, 141.1, 155.2, 158.7; HRMS calcd for $C_{19}H_{22}NO_4SSi$ $(M-C_4H_9)^+$ 388.1039, found 388.1022.

5-[2,2-Bis(ethoxycarbonyl)]ethyl-4,5-dihydro-3-{phenyl-[(trimethylsilyl)oxy]methyl}isoxazole (6). To a solution of 5.76 g (24.0 mmol) of **2** and 9.64 g of diethyl allylmalonate (48.0 mmol) in 50 mL of benzene was added 17.86 g phenyl isocyanate (99.6 mmol) and 50 drops of triethylamine. The solution was refluxed for two days, cooled, water was added, and the solution was stirred for 18 h at rt. The mixture was filtered, and the solvent evaporated. The product was purified by column chromatography (10% EtOAc/hexane) to yield **6** as a viscous yellow oil (4.41 g, 41%) as a 1:1 mixture of diastereomers, which proved to be inseparable: FTIR (neat) 1749, 1733, 1252, 1071, 877, 844 cm^{-1}; ^{1}H NMR δ 0.04 (s, 4.5H), 0.06 (s, 4.5H), 1.14 (m, 6H), 1.88 (m, 1H), 2.05 (t, 1H J=7.1 Hz), 2.15 (dd, 0.5H, J=7.8, 17.1 Hz), 2.60 (m, 1H), 3.01 (dd, 0.5H, J=10.5, 17.1 Hz), 3.43 (dd, 0.5H, J=5.7, 9.0 Hz), 3.50 (t, 0.5H, J=7.2 Hz), 4.07 (m, 4H), 4.35 (m, 0.5H), 4.43 (m, 0.5H), 5.60 (s, 1H), 7.12–7.25 (m, 5H); ^{13}C NMR: δ −0.33/−0.30, 13.8, 33.3/33.6, 37.1, 47.8/47.9, 60.8, 68.7/68.8, 76.0/76.4, 124.6, 124.7, 126.9, 127.4, 139.3, 159.9, 168.0; HRMS: calcd for $C_{20}H_{28}NO_6Si$ $(M-CH_3)^+$ 406.1686, found 406.1687.

Polymer-supported 5-(4-pentenyl)-4,5-dihydro-3-{phenyl-[(trimethylsilyl)oxy]methyl}isoxazole (7). To 1.1 g of polymer-bound nitrosilyl ether[4] and 10 mL of benzene was added 1 mL phenyl isocyanate (9.2 mmol), 1.0 g 1,6-heptadiene (10.4 mmol), and 0.5 mL triethylamine (3.6 mmol). The solution was refluxed for four days, cooled, treated with water, and stirred for 18 h at rt. The usual

workup gave polymer **7** as a yellow solid: FTIR (powder) 1253, 1071, 877, 842 cm^{-1}.

Polymer-supported 5-(2-phenyl-4-pentenyl)-4,5-dihydro-3-{phenyl[(trimethylsilyl)oxy]methyl}isoxazole (11). To 1.1 g of polymer-bound nitrosilyl ether and 10 mL of benzene was added 1 mL phenyl isocyanate (9.2 mmol), **9** (1 g, 5.81 mmol), and 1.0 mL triethylamine (7.2 mmol). The solution was refluxed for four days, cooled, treated with water, and stirred for 18 h at rt. The usual workup gave polymer **11** as a yellow solid: FTIR (powder) 1635, 1253, 1066, 915, 868, 841 cm^{-1}.

5-(5-Hexenyl)-4,5-dihydro-3-{phenyl[(trimethylsilyl)oxy]-methyl}isoxazole (13). A solution of 1.11 g of 2-nitro-1-phenyl-1-[(trimethylsilyl)oxy]ethane (4.6 mmol), 3.71 g of phenylene diisocyanate (23.0 mmol), 2.04 g of 1,7-octadiene (8.5 mmol), and 0.5 mL of triethylamine in 50 mL benzene was refluxed for three days, cooled, treated with water, and stirred for 18 h at rt. The mixture was filtered, and the volatiles evaporated. The product was purified by column chromatography (10% EtOAc/hexane) to yield 0.61 g (40% yield) of a clear liquid, which proved to be a 1:1 mixture of diastereomers of **13**: ^{1}H NMR δ 0.05 (s, 9H), 1.40–1.90 (m, 6H), 2.10–2.25 (m, 2H), 2.41 (dd, 1H, J=8.7, 17.0 Hz), 2.82 (d, 1H, J=9.3 Hz), 3.22 (dd, 1H, J=10.2, 16.0 Hz), 4.65 (m, 1H), 5.13 (m, 2H), 5.90 (m, 1H), 7.40–7.65 (m, 5H); ^{13}C NMR δ −0.34, 24.4, 24.6, 28.3, 33.3, 34.9, 36.9, 69.4, 80.4, 114.3, 120.5, 128.0, 128.9, 136.9, 140.0, 160.0; HRMS: calcd for $C_{19}H_{29}NO_2Si$ 331.1968, found 331.1956.

Polymer-supported 5-(5-hexenyl)-4,5-dihydro-3-{phenyl-[(trimethylsilyl)oxy]methyl}isoxazole (14). To 1.1 g of polymer-bound nitrosilyl ether and 10 mL of benzene was added 1 mL phenyl isocyanate (9.2 mmol), 1.1 g 1,7-octadiene (10.0 mmol), and 0.5 mL triethylamine (3.6 mmol). The solution was refluxed for four days, cooled, treated with water, and stirred for 18 h at rt. The usual workup gave polymer **14** as a yellow solid: FTIR (powder) 1645, 1254, 1069, 876, 840 cm^{-1}.

Polymer-supported 4,5-dihydro-5-[2-(4,5-dihydro-2*H*-pyranyl)ethyl]-3-{phenyl[(trimethylsilyl)oxy]methyl}isoxazole (17). To 1.5 g of polymer-bound nitrosilyl ether and 10 mL of benzene was added 1 mL phenyl isocyanate (9.2 mmol), 0.9 g 6-(3-butenyl)-3,4-dihydro-2*H*-pyran (6.5 mmol), and 1.0 mL triethylamine (7.2 mmol). The solution was refluxed for four days, cooled, treated with water, and stirred for 18 h at rt. Workup gave polymer **17** as a yellow solid: FTIR (powder) 1268, 1067, 876, 841 cm^{-1}.

General procedure for polymer-supported cyclic ether formation

The appropriate polymer was swollen in dry CH_2Cl_2 and treated with 5 equiv. of I_2. The reaction was then stirred for 18 h at rt. The formation of cyclic ethers was monitored by TLC (9:1 hexane/EtOAc). Sat. aq. $Na_2S_2O_3$ was added, and the mixture stirred overnight. The polymer was filtered, and the organic layer was washed with sat. aq. $Na_2S_2O_3$, dried ($MgSO_4$), and evaporated to yield an oily residue.

2-(Cyanomethyl)-6-(iodomethyl)-4-phenyltetrahydropyran (12). In 7.1% yield via polymer **11**; FTIR (neat) 2251 cm^{-1}; ^{1}H NMR δ 0.78–2.00 (m, 5H), 2.52 (dd, 1H, J=6.0, 10.5 Hz), 2.58 (dd, 1H, J=1.5, 6.3 Hz), 3.17 (m, 2H), 3.50–3.80 (m, 2H), 4.00–4.50 (m, 2H), 6.99–7.68 (m, 5H); ^{13}C NMR δ 8.2, 24.6, 29.7, 37.5, 38.0, 38.4, 40.8, 120.6/121.3, 124.4, 126.3/128.0, 129.0/129.3, 130.5; HRMS: calcd for $C_{14}H_{16}INO$ 341.0277, found 341.0265.

(2*R,7*R**)- and (2*R**,7*S**)-2-(Cyanomethyl)-7-(iodomethyl)-oxepane (15).** Yield in solution from **13**, 52%; yield via polymer **14**, 8.1%; FTIR (neat) 2251 cm^{-1}; ^{1}H NMR δ 0.75–1.61 (m, 8H), 2.47–2.55 (m, 1H), 2.97–3.06 (m, 2H), 3.11–3.17 (m, 1H), 3.60–4.00 (m, 2H); ^{13}C NMR: δ 11.2, 11.3, 25.1, 25.2, 26.1, 36.3, 72.7, 81.4, 119.0; HRMS: calcd for $C_9H_{14}INO$ 279.0129; found 279.0120; Anal. calcd for $C_9H_{14}INO$: C, 38.73; H, 5.06; N, 5.02; found: C, 38.47; H, 5.09; N, 4.97.

(5*R,6*S**,8*S**)- and (5*R**,6*S**,8*R**)-8-(Cyanomethyl)-5-iodo-1,7-dioxaspiro[5.4]decane (18).**[6] Yield via polymer **17**, 7.4%; FTIR (neat) 2251 cm^{-1}; ^{1}H NMR δ 1.32–2.06 (m, 8H), 2.51 (dd, 1H, J=5.7, 10.5 Hz), 2.60 (dd, 1H, J=1.5, 6.0 Hz), 2.72–2.82 (m, 1H), 3.15–3.19 (m, 2H), 3.49–3.76 (m, 2H), 4.40 (m, 1H); ^{13}C NMR δ 21.0/25.3, 26.0/26.8, 29.9/30.7, 34.4/34.5, 38.2/39.4, 62.8, 72.8, 75.3, 106.7, 117.6/117.7; HRMS: calcd for $C_{10}H_{14}NO_2$ $(M-I)^+$ 180.1024, found 180.1024.

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References

1. Ellman, J. A.; Plunkett, M. J. *J. Org. Chem.* **1995**, *60*, 6006.
2. (a) Mayer, J. P.; Zhang, J.; Bjergarde, K.; Lenz, D.; Gaudino, J. *Tetrahedron Lett.* **1996**, *37*, 8081. (b) Tietze, L. F.; Steinmetz, A. *Synlett* **1996**, 667.
3. (a) Kurth, M. J.; Rodriguez, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 7577. (b) Kurth, M. J.; Rodriguez, M. J. *Tetrahedron* **1989**, *45*, 6963. (c) Kurth, M. J.; Rodriguez, M. J.; Olmstead, M. M. *J. Org. Chem.* **1990**, *55*, 283. (d) Kurth, M. J.; Kantorowski, E. *J. Mol. Diversity* **1996**, *2*, 207.
4. (a) Beebe, X.; Kurth, M. J.; Schore, N. E. *J. Am. Chem. Soc.* **1992**, *114*, 10 061. (b) Beebe, X.; Schore, N. E.; Kurth, M. J. *J. Org. Chem.* **1995**, *60*, 4196.
5. (a) Evans, D. E.; Sacks, W. A.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. (b) Hughes, D. L. *Tetrahedron Lett.* **1978**, *19*, 3959. (c) Cresp, T. M.; Probery, C. L.; Sondheimer, F. *Tetrahedron Lett.* **1978**, *19*, 3955. (d) Evans, D. E.; Sacks, W. A.; Whitney, R. A.; Mandel, N. G. *Tetrahedron Lett.* **1978**, *19*, 727.
6. Rodriguez, M. J. Ph.D. Thesis, University of California, Davis, 1988.
7. Julia, M.; Ward, D. *Bull. Soc. Chim. Fr.* **1973**, 3065.
8. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
9. Corey, E. J.; Chaykovsky, M.; Greenwald, R. *J. Org. Chem.* **1963**, *28*, 1128.
10. Greeves, N.; Lee, W. *Tetrahedron Lett.* **1997**, *38*, 6449.
11. Boeckman, R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997.