Expanding the structural diversity of discrete polymers accessible through iterative exponential growth

by

Khrystofor Khokhlov

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Signature of

Authored by……
Khrystofor Khokhlov
Department of Chemistry
08/02/2023

Certified by……
Jeremiah A. Johnson
Full Professor
Thesis Supervisor

Accepted by……...
Adam Willard
Associate Professor
Department of Chemistry Graduate Officer

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ABSTRACT

Iterative exponential growth is a powerful method for the synthesis of atomically defined macromolecules. However, preparation of enantiopure IEG-ready monomers can be challenging, which may limit the attractiveness of IEG as a tool for the study of structure-relationship properties in discrete macromolecules, both in materials and in biological systems. Here, we present a new strategy for the synthesis of orthogonally protected monomers, suitable for IEG through cycles of azidation, alkyne deprotection, and CuAAC, in fewer steps and from readily available and affordable building blocks. This monomer synthesis wqas achieved through the development of a novel allylation methodology.

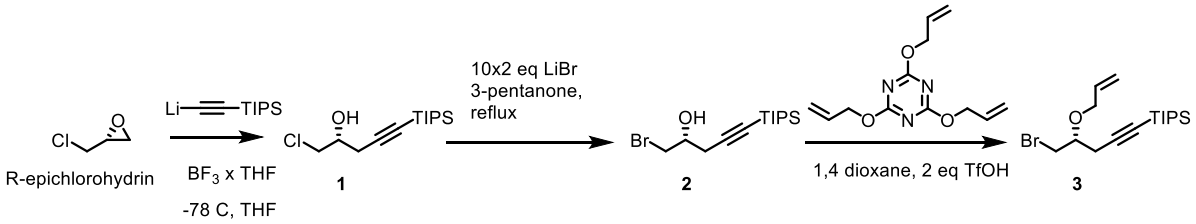


Figure 1. Optimized route to IEG-ready monomer from commercial epichlorohydrin.

Using alkynylation of epichlorohydrin, LiBr Finkelstein, and TfOH-promoted allylation, we have been able to prepare a monomer for 3A (number of carbons in each polymer repeat unit, excluding alkyne) IEG in just three steps. Furthermore, the same reactions can be integrated in the synthesis of other IEG architectures (2A/4A/5A), thus expanding the structural diversity and readily accessible substrate scope for atomically defined macromolecules. The configurations of stereogenic centers in IEG-mer backbones are defined by the starting material (R or S epichlorohydrin) and can be further controlled by combining different stereoisomers in desired fashion. This work outlines a conceptual strategy to diversify and expand the chemical space of discrete macromolecules and enable efficient and quick access to a variety of IEG-mer scaffolds.

Thesis Supervisor: Jeremiah A. Johnson
Title: Full Professor

TABLE OF CONTENTS

Chapter I. Synthesis of 3A IEG monomer through novel allylation methodology

Chapter II. References

Khrystofor Khokhlov – Johnson Lab

September 2023

Introduction

Perfect control over macromolecular structure remains a holy grail of polymer chemistry.[1] Currently available methods of synthetic organic chemistry allow precise preparation of nearly any possible structure; however, there is often a tradeoff between scalability of synthesis and intricacy of target molecule. Methods of precision synthesis, such as solid-phase[2] and flow[3] methodologies, allow nearly perfect control of macromolecular sequence, at the expense of scalability, while stochastic polymerization is almost infinitely scalable, but yields a mixture of molecules with varying structures.[4]

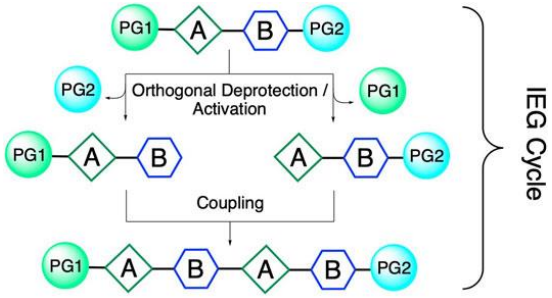


Figure 2. General IEG scheme [adapted[5]]. PG = "protecting group."

Iterative exponential growth[6] (IEG) enables a compromise between these two extremes, making it possible to prepare atomically defined macromolecules with regular sequences on multigram scale. IEG relies on the presence of orthogonal chemical reactivities in a starting molecule, which can be used for selective coupling, yielding doubled asymmetric telechelic macromolecules with the same orthogonal moieties[5]. IEG was pioneered by Whiting in the synthesis of atomically defined polyethylene,[7] with the Wittig reaction serving as a coupling step for molecular doubling. Uniform IEG-mers (IEG-derived macromolecules) enabled fundamental studies of structure-property relationships of polymers, affording higher levels of insight and clarity than were previously possible with disperse polymer mixtures. Whiting's report was followed by significant expansion of IEG methodology, with Pd-catalyzed cross coupling for synthesis of discrete conjugated polymers being a major example,[8–13] in addition to amidation[14–18] and esterification.[19–23] However, many of these syntheses encountered issues with higher oligomers, such as byproduct formation, decreasing yields and purification challenges. The application of additional extremely efficient reactions such as CuAAC (Cu(I)-catalyzed azide–alkyne cycloaddition),[24] thiol-ene[25,26] and SuFEX (Sulfur(VI) fluoride exchange)[27] coupling has tremendously advanced the field. The Johnson group made significant contributions to the field by developing IEG schemes based on CuAAC-coupling of epichlorohydrin-derived building blocks, including a scalable flow-IEG setup[28] (in collaboration with the Jamison group).

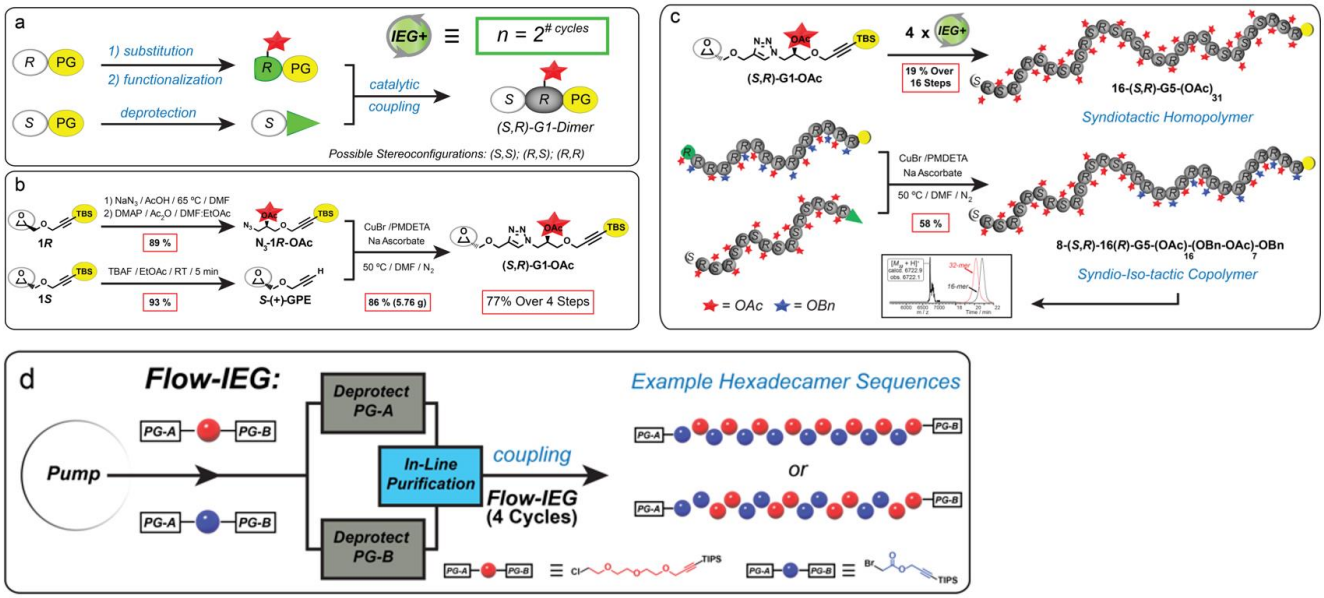


Figure 3. Summary of Johnson group IEG+ and flow IEG research.

One of the major achievements of the Johnson group approach was the development[29] of IEG+ methodology, which allows the introduction of sequence variability in the IEG-mer backbone without compromising scalability. The Johnson group has also pioneered[30,31] synthesis of IEG-mers with thiol-ene-functionalizable side chains to study phase segregation and self-assembly of uniform diblock copolymers. Introduction of allyl pendants to the IEG-mer backbone allowed late-stage functionalization through thiol-ene radical click coupling, which significantly simplifies access to diverse discrete polymer structures. However, the synthetic route to these IEG-ready monomers required 6 steps to generate 1-alkyne monomer from epichlorohydrin with overall 33% yield, and 5 steps to 1-N_3 monomer with 41% yield.

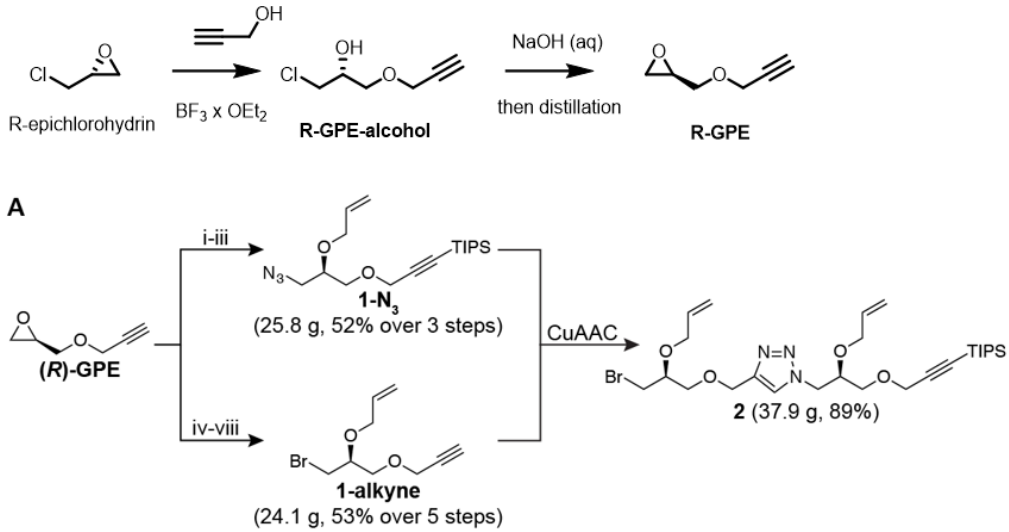


Figure 4. Preparation of "allyl-IEG" polymers from epichlorohydrin.[31] A: Synthesis of allyl-IEG dimer 2 from (R)-GPE. (i) *n*BuLi, TIPSCl, THF, –78 °C to r.t.; (ii) NaN_3, AcOH, DMF,

65 °C; (iii) Allyl bromide, NaH, DMF, r.t.; (iv) *t*-BuOH, $Mg(ClO_4)_2$, r.t.; (v) Allyl bromide, NaH, DMF, r.t.; (vi) H_3PO_4, r.t.; (vii) TsCl, 4-DMAP, TEA, DCM, r.t.; (viii) 5 eq LiBr, DMF, 45 °C. [partially adapted from IEG NIH grant].

In addition to conformationally flexible 5A architecture, the Johnson group has also developed a 2A IEG scaffold, which allows for the preparation of macromolecules with a more rigid backbone.[32] Out of the possible range of epichlorohydrin-derived scaffolds from 2A to 5A, this leaves only 1A, 3A, and 4A as previously unsynthesized structures.

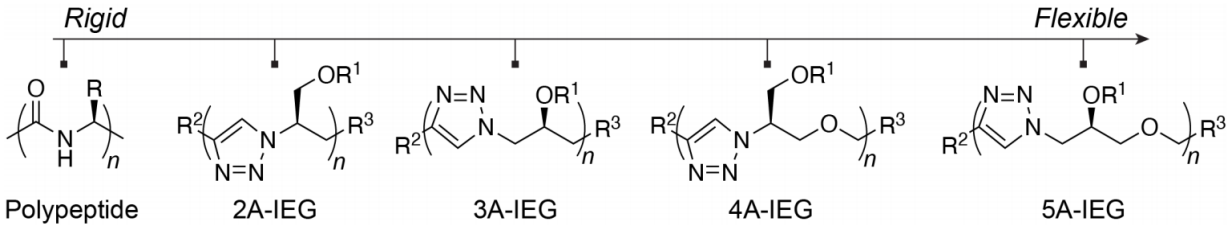


Figure 5. Potential range of structures of IEG-derived triazolamers [adapted[32]].

Most of the existing IEG precedents cover only simple macromolecular architectures with little sequence complexity and functionality, often with no stereogenic centers.[5] Triazolamers developed by the Johnson group bypass these limitations, but syntheses of IEG-ready monomers from epichlorohydrin can be complex. We hypothesized that optimization of existing synthetic routes from epichlorohydrin to IEG monomers would allow us to make syntheses of IEG-mers more accessible to facilitate their applications and expand the accessible chemical space of IEG-derived macromolecules. Doing so would provide us with a reliable, scalable and convenient platform for the study of discrete macromolecules in any medium of interest, thus allowing us to fully investigate how macromolecular structure determines polymer properties, which is a central question of polymer science.

Results and discussion

One goal was to develop strategies that would minimize the use of protecting groups. Our first idea was to obviate the introduction of allylic side chains through deprotonation/allylation (which makes tBuO protection necessary) by introducing an allyl functionality through allyl alcohol. This reaction has already been used for addition of tBuOH to GPE epoxide in the synthesis of a 5A IEG monomer, so we used analogous conditions; allyl alcohol turned out to be a slightly weaker nucleophile, but heating at 45 °C overnight in neat allyl alcohol (5 equivalents, with 0.1 equivalent of $Mg(ClO_4)_2$ catalyst) allowed quantitative epoxide opening. Unfortunately, upon transformation to the corresponding tosylate it turned out that the typical 35 °C conditions employed for S_N2 azidation are insufficient; we did not observe reaction completion even after 5 days, and an increase in temperature risks [3+2] cycloaddition of the azide to the allyl moiety (observed in the 5A-IEG system[31]). For these reasons we chose to pursue alternative routes toward the allylated scaffold (even though it should be viable for unreactive side chains like iPr).

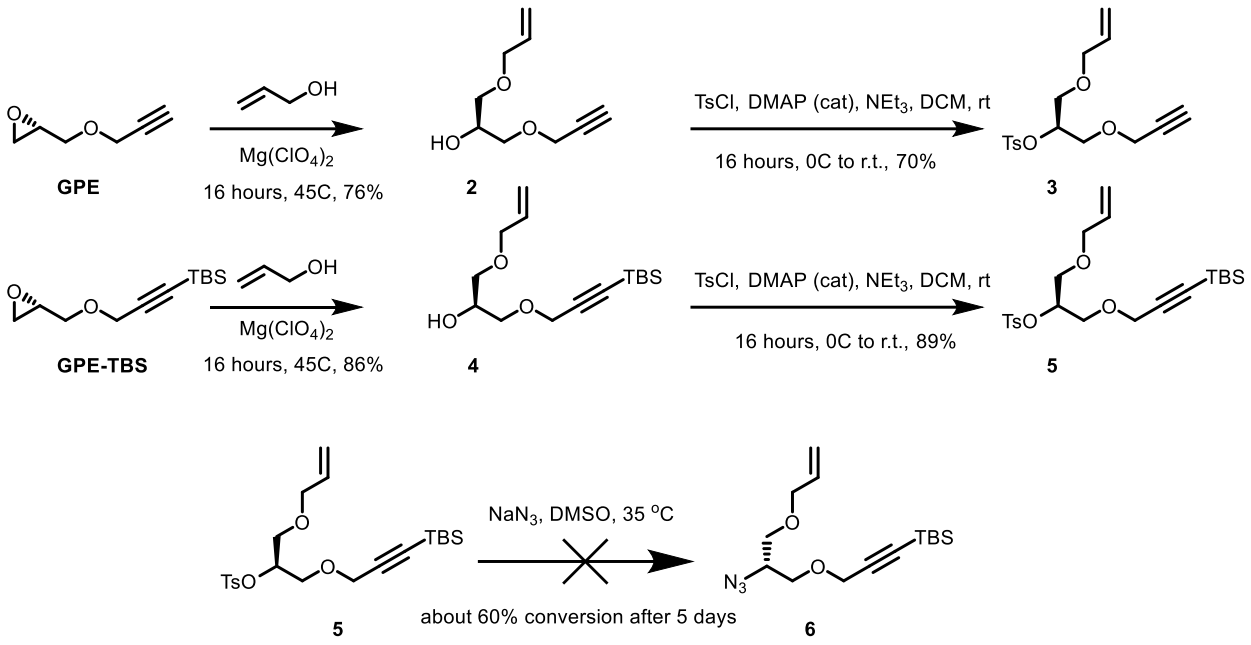


Figure 7. Attempt to develop 4A-IEG scheme with allyl side chain. While technically sound, overall the 4A scheme turned out to be incompatible with allyl functionality since at least 45 °C is necessary[32] for azidation of tosylate at acceptable rate (~overnight).

After the analysis of the current 5A and 2A synthetic schemes, it became evident that there were two major obstacles to overcome: the introduction of an alkyne protecting group, and the necessity of using tBuO as placeholder for Br to introduce allylic functionality, thus making it necessary to remove tBu with strong acid, prepare tosylate and then carry out the Finkelstein reaction with excess LiBr. If it was possible to introduce an already protected alkyne functionality and functionalize the hydroxyl moiety without needing to replace a halogen with a protecting group, the synthesis would be more efficient. Fortunately, it is possible to introduce an alkyne to the epichlorohydrin scaffold as silylated acetylene. A previous Johnson group member had experimented[33] with this reaction and it was included in one of the Johnson group patents; however, it was never explored further, most likely due to the difficulty of efficient hydroxyl functionalization without replacing chloride. Traditional allylation procedures utilizing allyl bromide/alcohol in basic conditions would likely be inapplicable for this scaffold due to the adjacent halogen, necessitating the development of an efficient and convenient allylation protocol taking place in acidic or neutral media, in order to prevent epoxide formation.

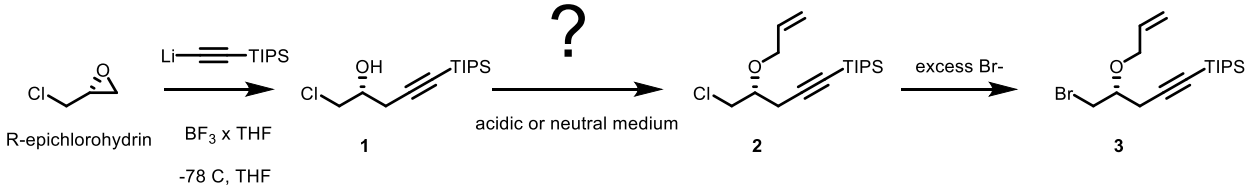


Figure 8. Proposed optimization of 3A-IEG monomer synthesis.

Thus, we sought a synthon for an allyl cation. Initial attempts to implement Pd-catalyzed allylation with allyl methyl carbonate[34] afforded a complex mixture of products. Since we

had concerns about halide reactivity with the Pd catalyst, this route was abandoned in favor of Lewis acidic conditions. We considered O-Allyl 2,2,2-trichloroacetimidate, a standard reactant for this type of transformation promoted by triflic acid;[35,36] however, multiple screening attempts afforded suboptimal yields (typically in the 30–40% range; an outlier with ~60% was achieved when 0.5 equivalents of TfOH were used). Furthermore, this reagent is not available at affordable prices and its preparation[32] can be dangerous on required scale (relies on NaH). We found that triallyl cyanurate[37] can also generate allylic cations under Lewis acidic conditions. Since this reagent is commercially available at a relatively low cost, we attempted to optimize this reaction with 0.1–1 eq of triflic acid, but only observed suboptimal yields (around 60%).

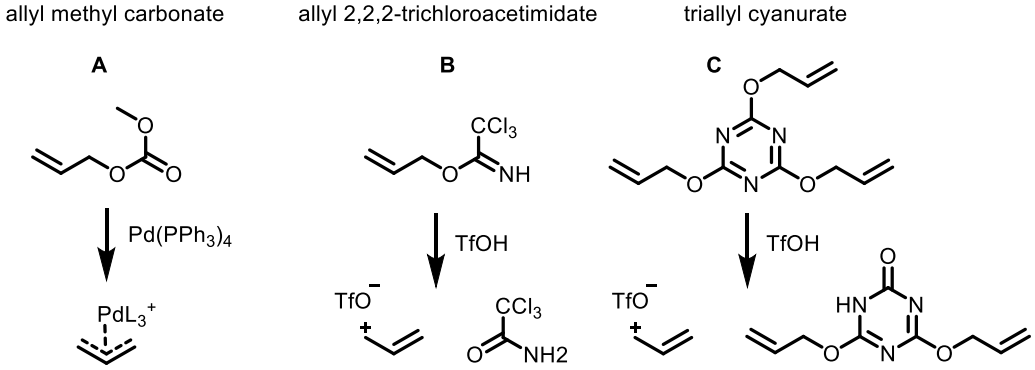


Figure 9. Potential allylating reagents.

There was a literature precedent covering studies of allylation kinetics,[38] where the authors reported nearly instantaneous allylation when 2 equivalents of TfOH are used, due to the synergy of positive charge repulsion and thermodynamic favorability of carbonyl formation. These prior studies used dimethoxy triazine with a single allyl group, but more allyl groups only make allyl cation generation faster since the leaving allyl group is between two protonated nitrogen atoms, while with dimethoxy triazine, an alternative, less-reactive doubly protonated form is possible. When applied to chlorohydrin **1**, we found that the reaction was nearly quantitative and fast (15–20 minutes on 1 mmol scale without cooling, about 30–40 minutes with temperature control). With this method in hand, we proceeded to prepare ~11 g of allylated chlorohydrin (~85% yield after column chromatography). Nevertheless, there remained difficulty with poor chloride reactivity in the azidation reaction. Existing literature precedents implement this reaction through iodide catalysis at high temperatures (70–120 °C), but this option was not feasible for our scaffold due to the possibility of unwanted [3+2] cycloaddition of the azide with the allyl group.[31]

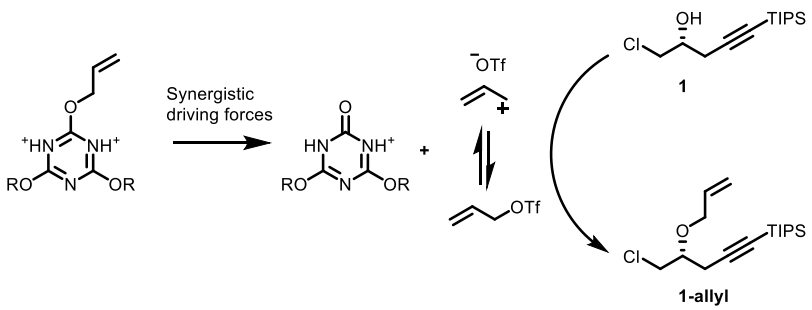


Figure 10. Allyl cation generation scheme.[38] R = allyl in our case, but Me in referenced study.

Therefore, we sought to develop Finkelstein reaction conditions to replace the chloride with a more reactive bromide. Due to the stronger nature of the C-Cl bond as compared to the C-Br bond, such reactions usually require large bromide excess or large amounts of chloride scavenger,[39,40] such as CH_2Br_2 or dibromoethane, which can be toxic and dangerous. Therefore, we decided to attempt optimization of Finkelstein conditions with just LiBr. Fortunately, there is literature precedent[41] reporting a convenient procedure utilizing 3-pentanone as a solvent. LiBr turned out to be surprisingly soluble in refluxing 3-pentanone (120 °C), such that the reaction was well-suited to scale-up; however, we observed unfavorable reaction kinetics: substitution was extremely slow for the allylated chloride; even after two iterations of overnight exposure to 10 eq of LiBr, only about 60% of the starting material was converted to bromide. Addition of potassium iodide as a catalyst negligibly improved the yield, but this reaction still required two overnight iterations. We also explored conducting the Finkelstein reaction on chlorohydrin **1** under the following conditions: two iterations (2 hours, then 3 hours, with 10 eq of LiBr each). These conditions resulted in quantitative chloride replacement, yielding exclusively brominated product. Allylation of the brominated species also went smoothly with nearly quantitative yield.

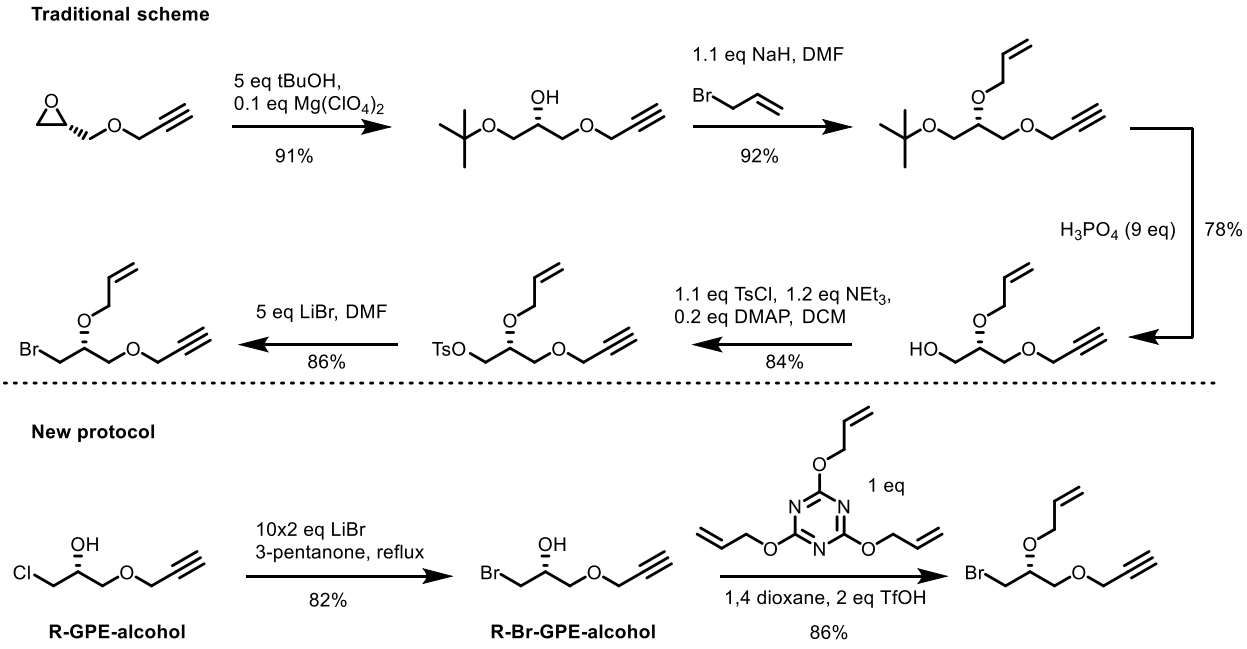


Figure 11. Comparison of previous method[31] and new protocol in 5A system.

Extending these conditions to GPE-alcohol was successful, allowing preparation of 5A-alkyne monomer in just two steps (1 g scale, 70% yield) as opposed to the previously required five steps with 43% yield. We are yet to implement the resulting monomer in IEG synthesis; however, we believe that this method could considerably expand the chemical space of readily accessible IEG-mer structures. Overall, we have developed an extremely efficient synthetic pathway from commercially available enantiopure epichlorohydrin to ready-to-go IEG monomer, which was conducted in ~3–4 days on ~25 g scale. This advance should make access to large amounts of discrete macromolecules significantly easier, which would greatly facilitate the research of their properties in materials and biological systems.

Experimental methods:

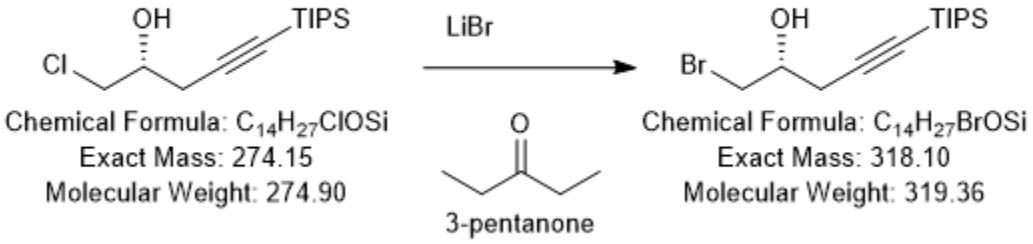
All reagents and solvents were purchased from Aldrich or VWR unless otherwise indicated. 1H and 13C nuclear magnetic resonance (1H NMR) spectra were obtained from Bruker AVANCE-400 NMR spectrometers at MIT. NMR spectra were analyzed using MestReNova NMR 14.3.3 software and referenced to the residual chloroform peak at 7.26 ppm.

Epichlorohydrin alkynylation with TIPS-acetylene[42]

Source: *Org. Lett.* **2003**, *5*, 25, 4815–4818

TIPS-acetylene

Halogen exchange: 3A Finkelstein reaction in 3-propanone[41]

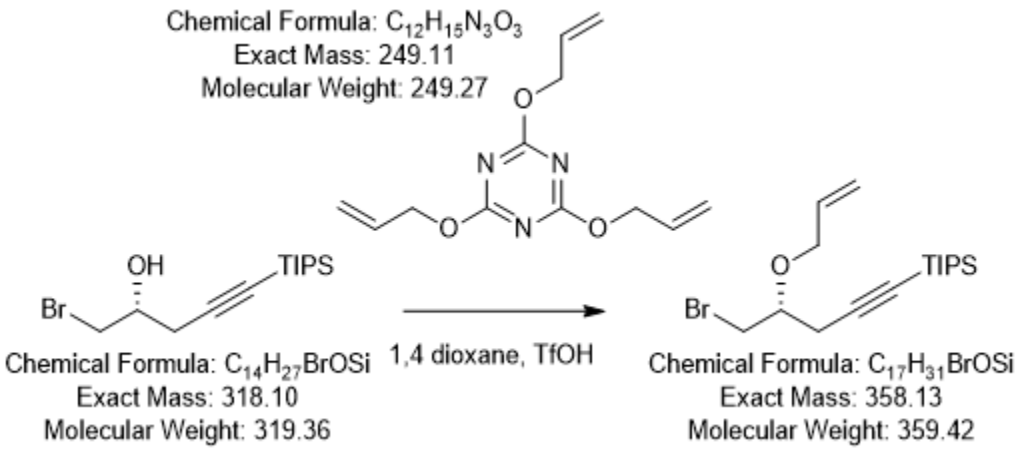


Source: SYNTHETIC COMMUNICATIONS, 24(5), 733-743 (1994)

Lithium bromide (LiBr, 31.6 g, 364 mmol) was slowly added to refluxing 3-pentanone (110 mL) until almost all LiBr was dissolved except a few solid particles. Then chlorohydrin (10 g, 36.4 mmol) was added dropwise over 5 minutes. After 24 hours solution was washed with 100 mL of cold water and resubjected to 10 eq LiBr. After another 24 hours reaction solution was once more washed with 2x100 mL water, dried with Na_2SO_4, filtered and concentrated to obtain bromohydrin as orange oil (8.74 g,

75.2% crude yield). ^{1}H NMR (400 MHz, CDCl3) δ 3.97 (m, 1H), 3.59 (dd, J = 18.9, 5.3 Hz, 2H), 2.65 (dd, J = 16.9, 6.1 Hz, 2H), 2.35 (broad s, 1H), 1.07 (m, 21H).

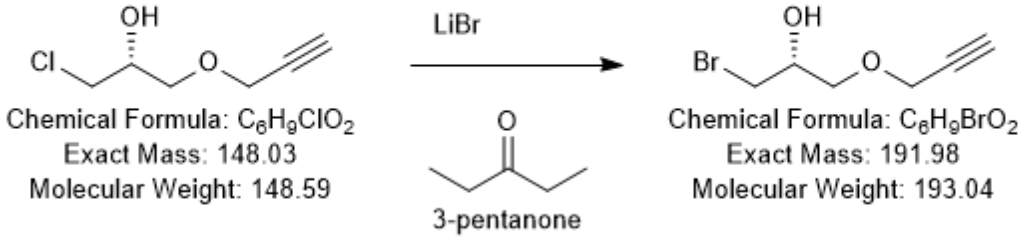
Allylation of 3A alcohol with cyanurate[38]



Source: J. Org. Chem. 2018, 83, 4568−4580

Bromohydrin (4.4 g, 13.8 mmol) and 2,4,6-Triallyloxy-1,3,5-triazine (3.79 g, 15.18 mmol) were dissolved with 25 mL dioxane in a 40 mL vial. Vial was put in a room temp aluminum heating block for heat dissipation, triflic acid (TfOH, 2.5 mL, 27.6 mmol) was added dropwise through teflon cap over 2 minutes. Slight browning and warming of reaction were observed, solution became dark after a few minutes. Reaction was quenched after 30 minutes by dropwise pyridine (1.25 mL, 15.2 mmol) addition. Reaction solution was poured into 100 mL ether, extracted with 3x70 mL 1M HCl and 1x100 mL water. Organic phase was dried with Na_2SO_4, filtered, concentrated, and purified through silica gel plug chromatography on 30 g silica (in 500 mL column, eluted with 300 mL of 5% ethyl acetate/hexanes, collected with test tubes), yielding about 3.6 g of allylated product as yellow oil (81.68% yield). ^{1}H NMR (400 MHz, CDCl3) δ 5.93 (ddt, J = 17.3, 10.4, 5.7 Hz, 1H), 5.35 – 5.16 (m, 2H), 4.13-4.11 (m, 2H), 3.73 – 3.67 (m, 1H), 3.64 – 3.54 (m, 2H), 2.63 (d, J = 6.2 Hz, 2H), 1.06 (m, 21H).

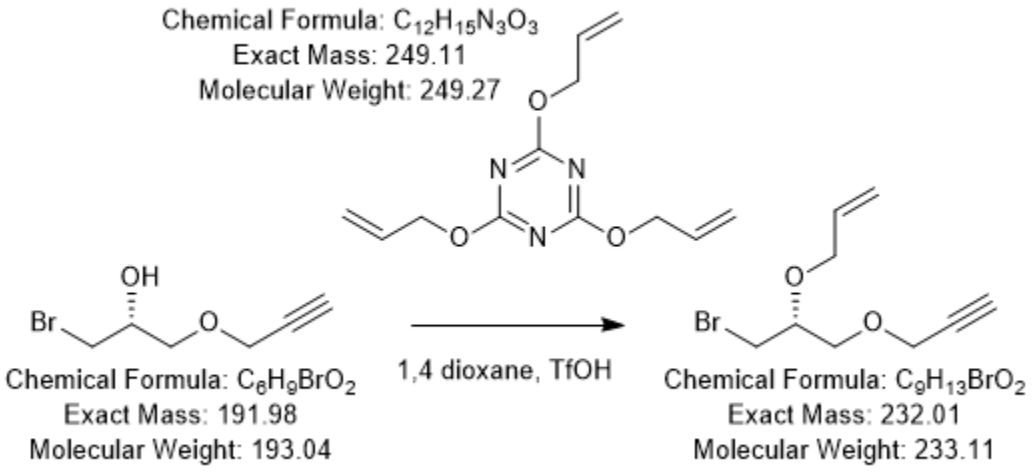
Halogen exchange: 5A Finkelstein in 3-propanone



Source: SYNTHETIC COMMUNICATIONS, 24(5), 733-743 (1994)

Lithium Bromide (LiBr, 29.17 g, 336 mmol) was added to solution of chlorohydrin (5 g, 33.6 mmol) in 80 mL of 3-pentanone at rt and then heated up while stirring. The reaction was heated at 120°C for 2 hours, then concentrated, redissolved with 100 mL water and extracted with 100 mL ethyl acetate. Organic fraction was concentrated to obtain orange oil. Next day it was redissolved in 80 mL pentanone and subject to another LiBr portion for 3 hours at 120°C. Then reaction solution was concentrated, redissolved with 100 mL water and extracted with 100 mL ethyl acetate. Organic fraction was dried with Na_2SO_4, filtered and concentrated to obtain bromohydrin as orange oil (5.32 g, 82% crude yield). ^{1}H NMR (400 MHz, CDCl3) δ 4.21 (d, J = 2.4 Hz, 2H), 4.00 (dt, J = 10.8, 5.4 Hz, 1H), 3.67 (d, J = 5.1 Hz, 2H), 3.57 – 3.44 (m, 2H), 2.49 – 2.41 (m, 2H).

Allylation of 5A alcohol with cyanurate

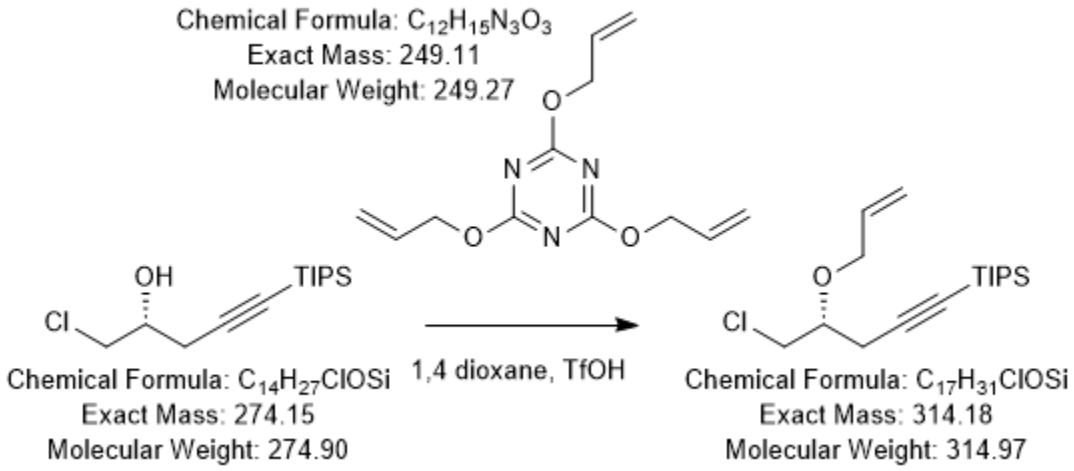


Source: J. Org. Chem. 2018, 83, 4568−4580

Bromohydrin (965 mg, 5 mmol) and 2,4,6-Triallyloxy-1,3,5-triazine (0.685 g, 2.75 mmol) were dissolved with 5 mL dioxane in a 20 mL vial. Vial was put in a room temp aluminum heating block for heat dissipation, triflic acid (TfOH, 0.44 mL, 5 mmol) was

added dropwise through teflon cap. Slight browning and warming of reaction were observed, solution became dark after a few minutes. Reaction was quenched after 30 minutes by dropwise pyridine (0.3 mL, 4.25 mmol) addition. Reaction solution was poured into 60 mL water and extracted with 60 mL ethyl acetate. Organic phase was washed with 80 mL of water and 60 mL of aqueous saturated $NaHCO_3$ solution. Resulting solution was dried with Na_2SO_4, filtered, concentrated and purified through silica gel plug chromatography (with 5% ethyl acetate/hexanes eluent), yielding about 1 g of allylated alcohol as yellow oil (85.8% yield). ^{1}H NMR (400 MHz, CDCl3) δ 5.93 (ddt, J = 17.3, 10.4, 5.8 Hz, 1H), 5.36 – 5.17 (m, 2H), 4.21 – 4.19 (m, 2H), 4.14 (m, 2H), 3.74 – 3.67 (m, 3H), 3.52 (ddd, J = 18.4, 10.2, 5.0 Hz, 2H), 2.45 (t, J = 2.3 Hz, 1H).

Allylation of 3A Cl alcohol with cyanurate



Source: J. Org. Chem. 2018, 83, 4568−4580

Alcohol (10.65 g, 38.7 mmol) and 2,4,6-Triallyloxy-1,3,5-triazine (10.6 g, 42.57 mmol) were dissolved in 70 mL dioxane in 150 mL roundbottom flask, which was placed on room temperature water bath. Triflic acid (TfOH, 7 mL, 77.4 mmol) was added dropwise over 5 minutes. After 30 minutes reaction was quenched with pyridine (6.8 mL, 85 mmol) dropwise, solution was poured in 250 mL 1M HCl and extracted with 3x200 mL ether. Organic phase was washed with 2 x 200 mL water and 250 mL brine, dried with Na_2SO_4, filtered and concentrated. Crude product was purified through silica gel plug chromatography (5% ethyl acetate/hexanes eluent) to yield about 7.6 g of allylated chlorohydrin as yellow oil (62.34% yield). ^{1}H NMR (400 MHz, CDCl3) δ 5.95 (ddt, J = 17.3, 10.4, 5.7 Hz, 1H), 5.39 – 5.17 (m, 2H), 4.15 (m, 2H), 3.79 – 3.66 (m, 3H), 2.64 (d, J = 5.7 Hz, 2H), 1.09 (m, 21H).

Addendum: side projects

1. Atomically defined Fujita cages

My first project in Johnson lab was an attempt to prepare atomically precise nanostructures: coordination star polymers based on $Pd_{12}L_{24}$ Fujita cages with IEG-mers as branches.

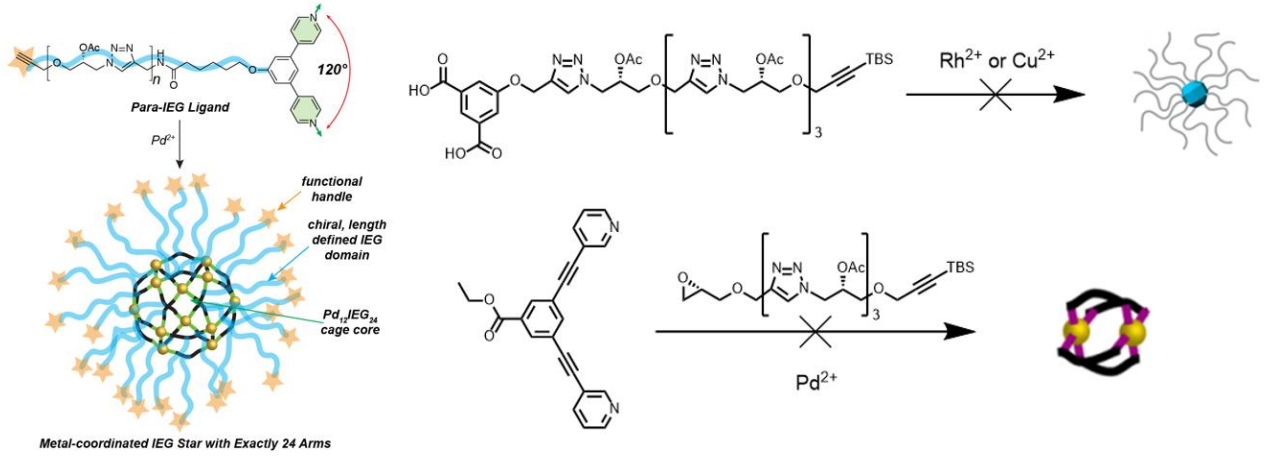


Figure A1. Fujita and Rh/Cu cages idea[43,44] [partially adapted from IEG NIH grant].

We have used the 5A IEG system as the most readily accessible, but all attempts to prepare a coordination star polymer were unsuccessful due to triazole competition with pyridine-based ligands. NMR experiment revealed that the presence of IEG tetramers prevents the formation of even the simplest Pd_2L_4 Fujita cages.

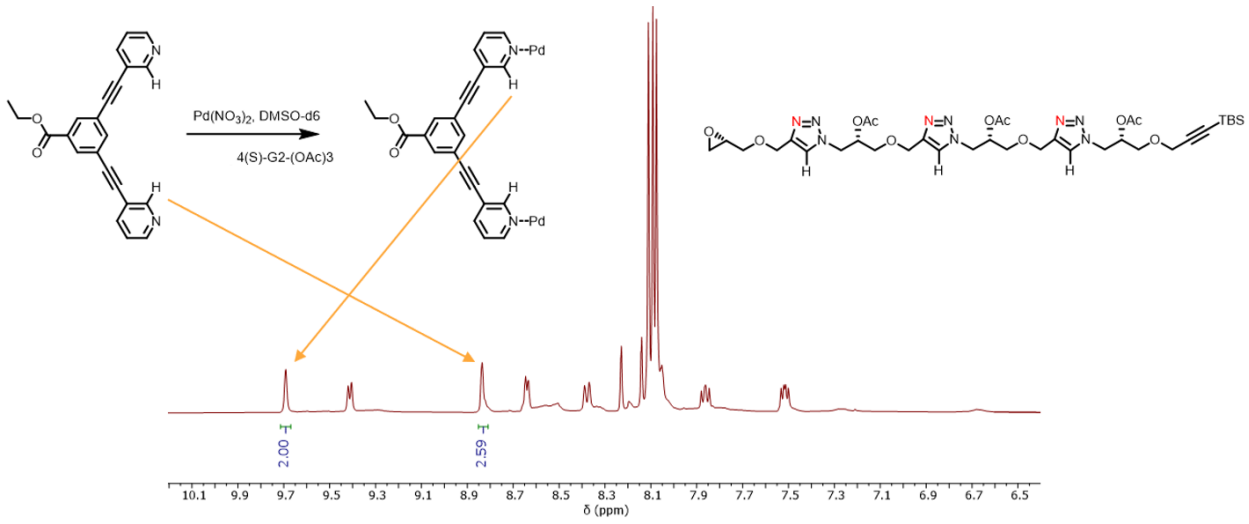


Figure A2. NMR experiment shows evidence of cage disruption in presence of IEG-mer

Attempts were made to prepare alternative coordination cages based on Rh^{2+} or Cu^{2+} coordination; unfortunately, these experiments yielded only insoluble amorphous solids (not soluble in water, DMF, NMP, THF, DCM, chloroform, DMSO). Despite these directives ultimately proving unsuccessful, the time spent on this work shone light on just how time-consuming our current synthetic strategies are for these particular monomers, which provided motivation for 3A IEG process development.

2. Spirocyclic linking agent for ROMP synthesis of chemically cleavable polymers.

In collaboration with Dr. Peyton Shieh, we have attempted to prepare a spirocyclic linking agent to reduce the content of silicon-based linking nodes in resulting polymer:

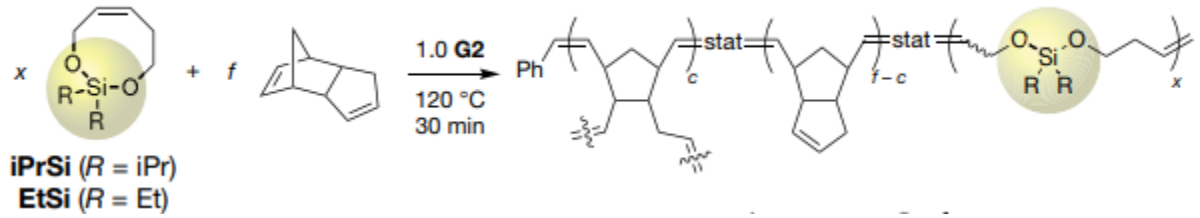
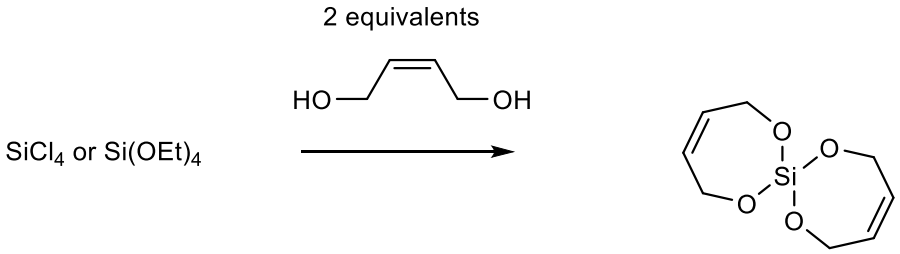


Figure A3: Current crosslinker approach [figure adapted[45]]

We have decided to base our synthesis on condensation of cis-1,4-Butenediol with active silicone agent (either $SiCl_4$ or $Si(OEt)_4$).



$SiCl_4$ displayed excessive reactivity, yielding insoluble polymerized products even under extreme dilution conditions. Therefore, we concentrated our efforts on extending the diol condensation approach from germanium[46] to silicone. In the literature precedent the spirocycle is prepared through distillation conditions; combination of $Ge(OEt)_4$ and diol in chlorobenzene is heated until the solvent is distilled off; then heat is increased until ethanol is distilled off reaction medium, yielding the spirocyclic product.

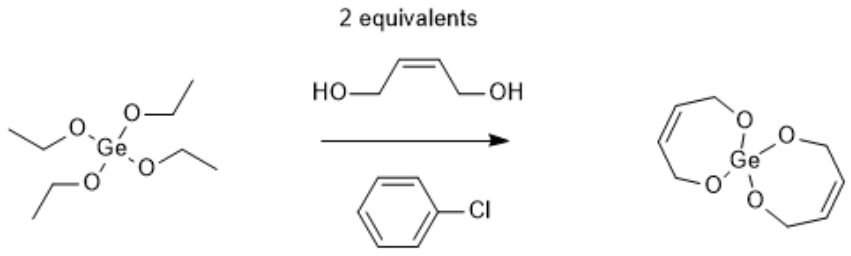
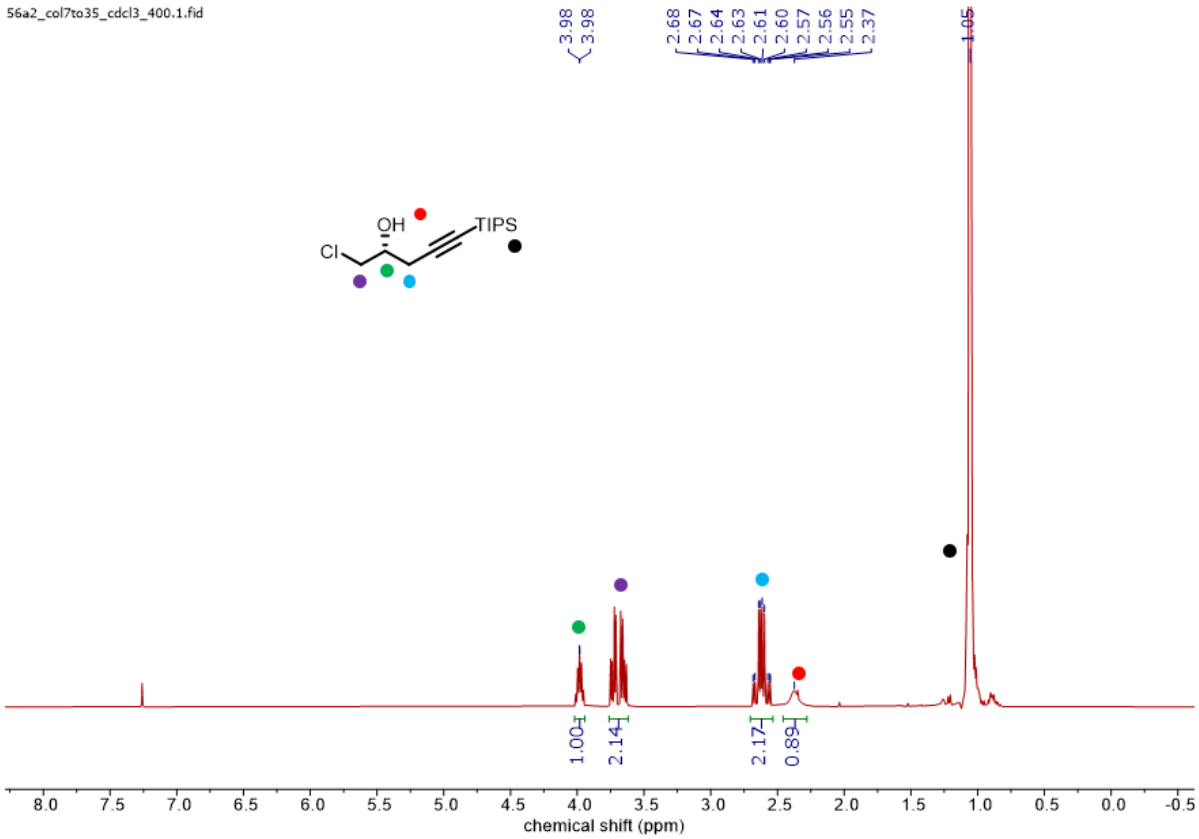
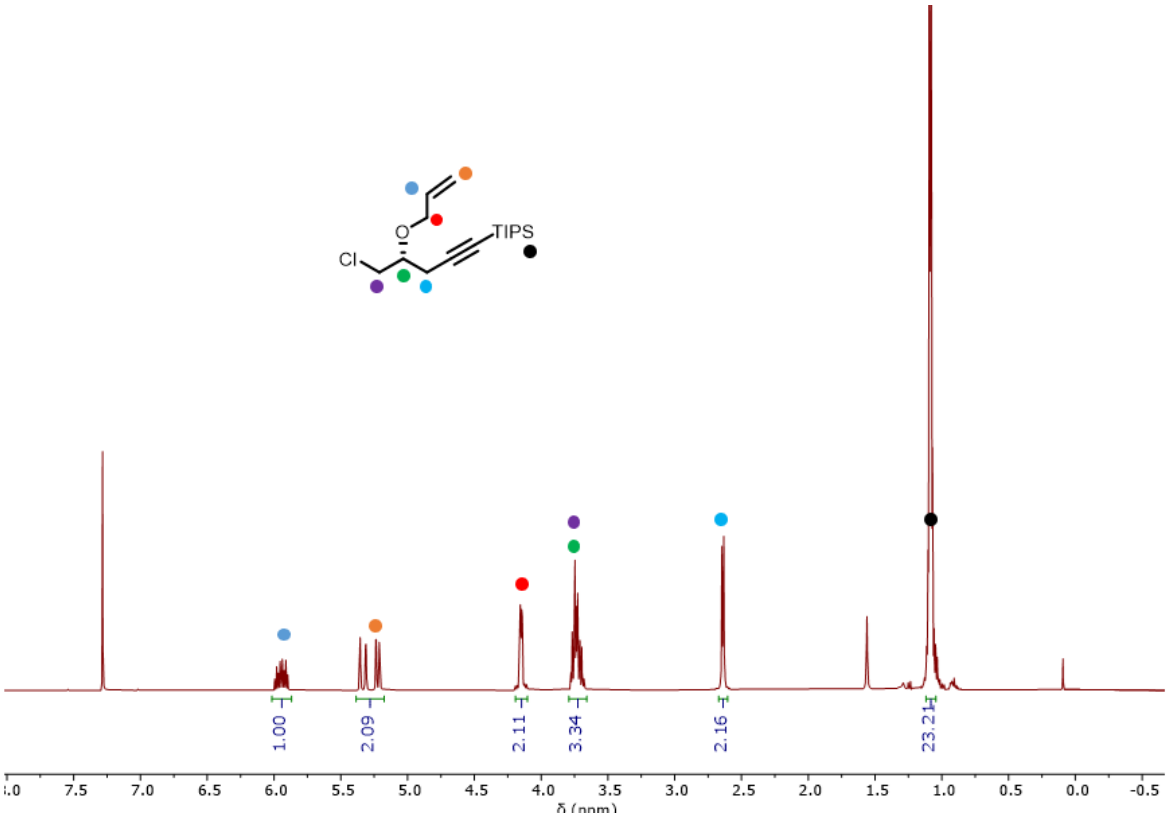


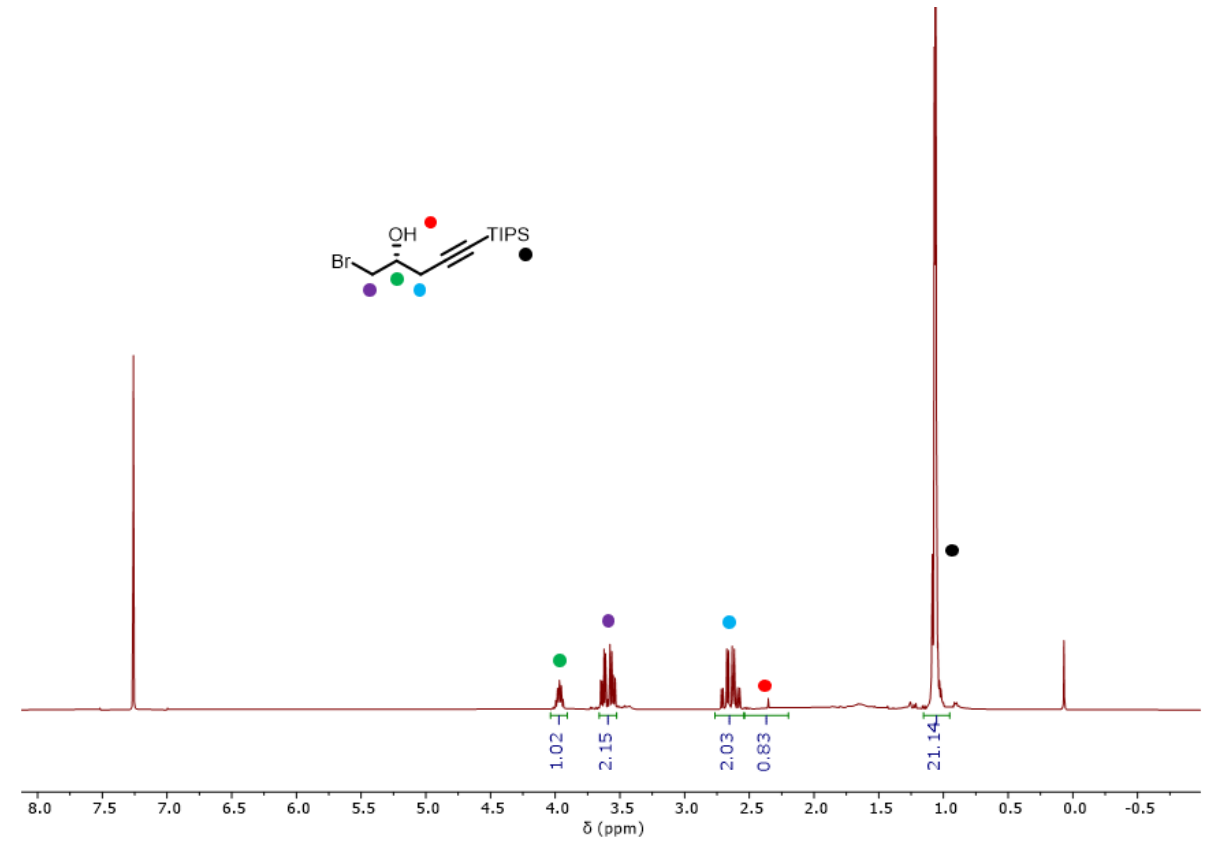
Figure A4: Spirocycle synthesis precedent with germanium.

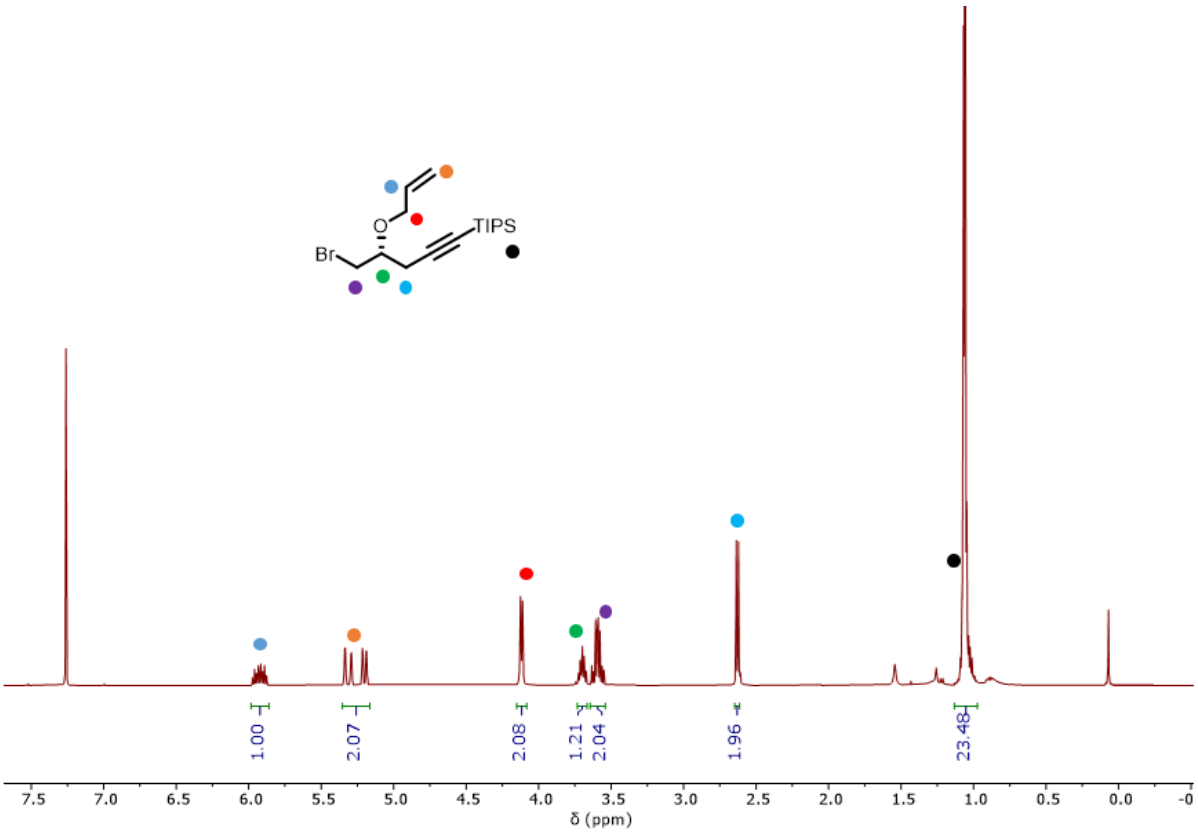
However, any attempts to replicate this reaction with silicon yielded only insoluble polymer solids. Attempts at further heating to distill off the spirocyclic orthosilicate resulted only in thermal decomposition (even distillation under vacuum). However, attempts to replicate the condensation with germanium have also yielded solids; therefore, it is possible that rather than reaction not being possible, our conditions were simply flawed.

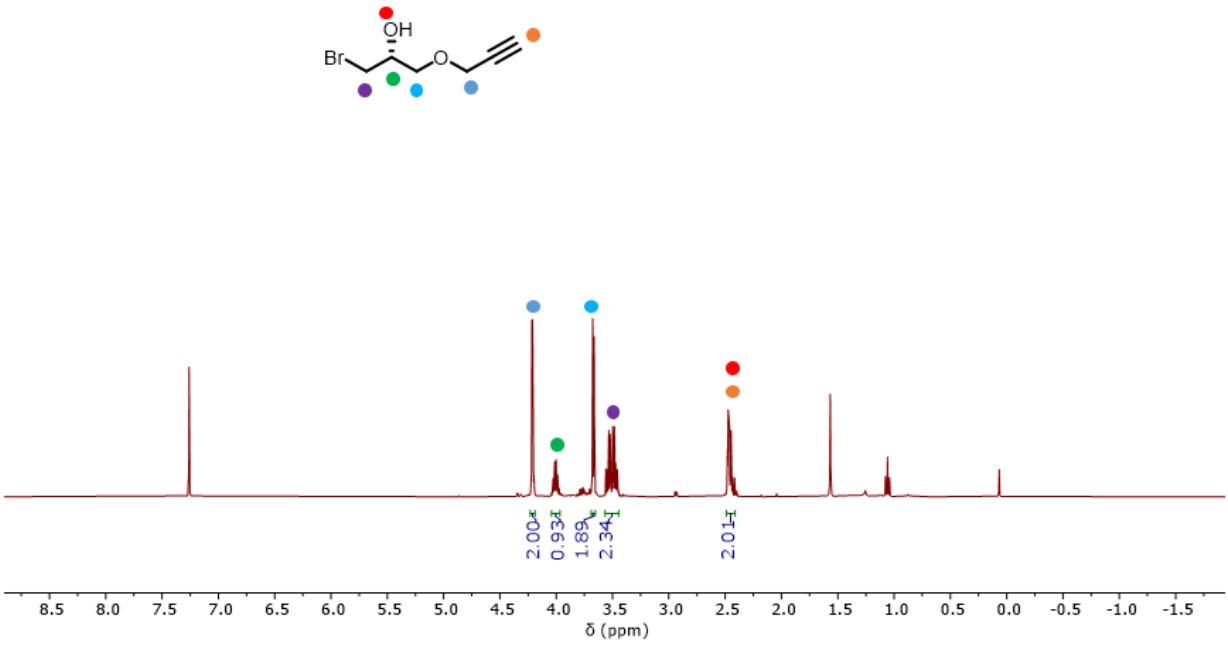
1H NMR spectra:

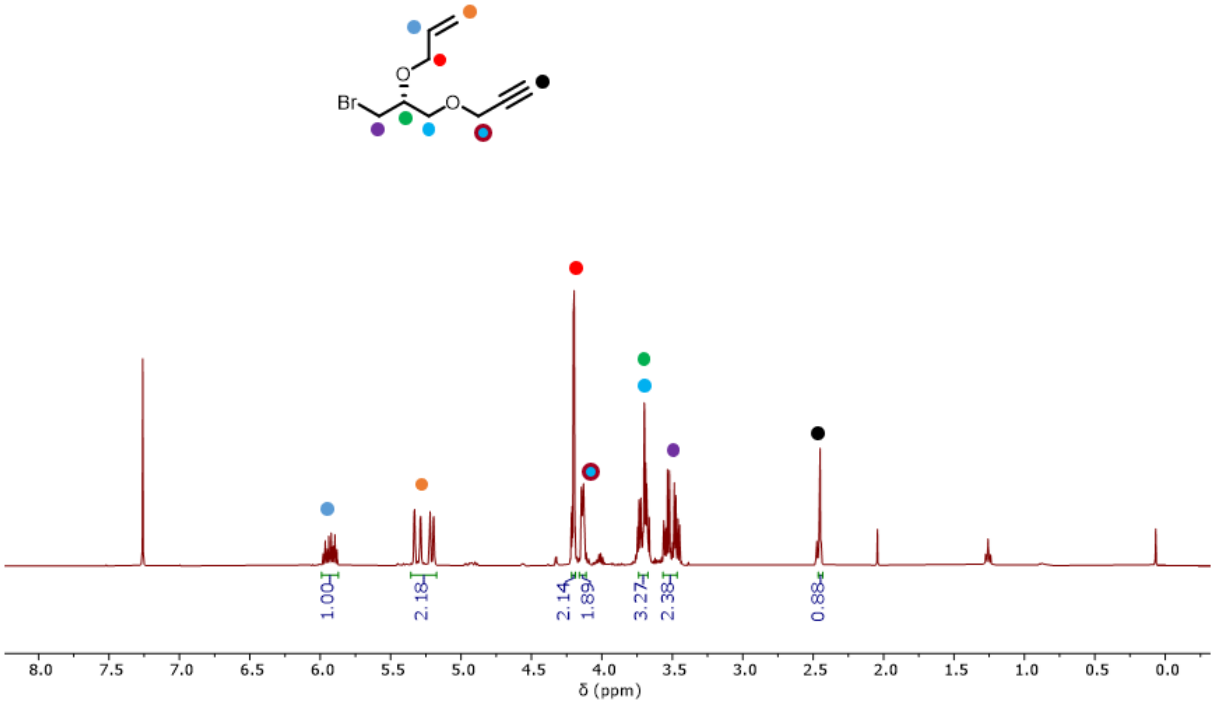





OH
TIPS
Br
1.02
2.15
2.03
0.83
21.14
δ (ppm)


O
TIPS
Br
1.00
2.07
2.08
1.21
2.04
1.96
23.48
δ (ppm)


OH
Br
O
2.00
0.93
1.89
2.34
2.01
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
δ (ppm)


Br
O
O
1.00
2.18
2.14
1.89
3.27
2.38
0.88
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
δ (ppm)

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