RHODIUM(I)-CATALYZED CYCLOISOMERIZATION OF NITROGEN TETHERED ENE-ALLENES: FORMATION OF TETRAHYDROAZEPINES

by

Anthony David Casarez

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FACULTY OF ARTS AND SCIENCES

This Thesis was presented

by

Anthony David Casarez

It was defended on

11-24-04

and approved by

Kay M. Brummond, Ph.D., Associate Professor

Paul E. Floreancig, Ph.D., Associate Professor

Dennis P. Curran, Ph.D., Distinguished Service Professor

Thesis Director: Kay M. Brummond, Ph.D., Associate Professor
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Abstract: A novel cycloisomerization process involving nitrogen-tethered 1,6-ene-allenes has been realized. Subjecting ene-allene 9 to rhodium biscarbonyl chloride dimer produces tetrahydroazepine 10 in moderate to high yields. Substituting the allene moiety with the bulky tert-butyl-group (R4 = t-Bu), while employing a trans-alkene tether, afforded the corresponding azepines in the highest yields. This formal Alder-ene transformation tolerated not only a variety of alkyl-substituents on both the alkene and allene portions but also silyl-[R2 = SiMe3, SiMe2Bn; R4 = Si(i-Pr)3] and phenyl-(R2 = Ph, R4 = Ph) substituents. A deuterium labeling study aided in the postulation of two possible mechanisms for this cycloisomerization. During the course of this investigation, a novel carbon monoxide insertion reaction was observed. Our findings to date are reported and discussed herein.
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<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>AcOH</td>
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</tr>
<tr>
<td>MeCN</td>
<td>Acetonitrile</td>
</tr>
<tr>
<td>PhH</td>
<td>Benzene</td>
</tr>
<tr>
<td>BBEDA</td>
<td>bis(benzylidene)ethylenediamine</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Boc</td>
<td>t-butoxycarbonyl</td>
</tr>
<tr>
<td>TBS</td>
<td>t-butyldimethylsilyl</td>
</tr>
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<td>Carbobenzyloxy</td>
</tr>
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</tr>
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</tr>
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</tr>
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<td>1,2-Dimethoxyethane</td>
</tr>
<tr>
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</tr>
<tr>
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<td>Dimethylformamide</td>
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<tr>
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<tr>
<td>PPTS</td>
<td>Pyridinium-p-toluenesulfonate</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammoniumfluoride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydro-2H-pyran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
<tr>
<td>Ts</td>
<td>p-Toluenesulfonyl</td>
</tr>
<tr>
<td>Red-Al®</td>
<td>Sodium dihydro-\textit{bis}-(2-methoxyethoxy)-aluminate</td>
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1.0 INTRODUCTION

1.1 THE ALDER-ENE REACTION

The Alder-ene reaction is the substitution onto a π-bond of a molecule involving an olefin possessing an allylic hydrogen (Scheme 1). This “ene” reaction is one of such C-C bond forming transformations that may lead to a cyclic product if the “ene” and “enophile” are tethered to the same substrate (Scheme 1). Cycloisomerization reactions are important transformations in organic synthesis which find some of their highest utility in complex molecule development and natural product assemblage. This class of reactions displays absolute atom economy by dispensing with the need for added reagents and generation of stoichiometric by-products.

Scheme 1. The Alder-ene reaction

The Alder-ene reaction is a concerted six electron pericyclic reaction, analogous to the Diels-Alder cycloaddition. Historically, it has been promoted by high temperatures with varying degrees of success.
1.2 THE THERMAL ALDER-ENE REACTION OF DIENES

Under thermal conditions, a 1,6-diene cyclizes to provide a 5-membered ring. Using a mixture of the cis- and trans-diene, Huntsman has shown that only the cis-cyclopentane product is formed (Eq. 1). Furthermore, the cis-isomer is also obtained when employing a trisubstituted ene component (Eq. 2). Reacting a 1,7-diene can afford either the 6 or 8-membered ring closure. The conversion of 1,7-diene 1 to cyclohexane 2 (Eq. 3) occurs in low yield under elevated temperature. In thermal ene-reactions, formation of cyclohexane rings from 1,7-dienes versus cyclopentane rings from 1,6-dienes requires higher temperatures and provides the cycloisomerized products in lower yields. The scope of the thermal Alder-ene reaction was increased by using electron deficient enophiles. The reaction yields can be increased, and the temperature at which the cyclization is performed decreased, when implementing an unsaturated ester as the enophile (Eq. 4). More recently the employments of transition metal catalysts have facilitated the Alder-ene reaction at much lower temperatures. Owing to the advent of these mild
1.3 THE METALLO-ENE REACTION

Many researchers have implemented the use of allylic leaving groups on their substrates which, upon exposure to the proper metal catalyst, form a π-allyl-metal complex that facilitates cyclization. Better known as the metallo-ene reaction, this transformation has gained extensive use in organic synthesis and provides access to frameworks which were previously unattainable by thermal cycloisomerization methods of dienes. The first of these metallo-ene reactions utilized nickel\(^6\) and palladium\(^7,8\) to accomplish a carbon-carbon bond formation and could be shown to operate in a diastereo-selective manner when using chiral nonracemic substrates (Eq. 5, 6). A short time after initial report of the metallo-ene reaction with nickel and palladium, Oppolzer demonstrated that the cyclization could also be performed with a rhodium catalyst
Milder conditions that do not require a protic acid are also described using [Rh(COD)Cl]_2/Et_3N in MeCN solvent, but are reported to afford a lower yield (63%).

1.4 THE CATALYTIC ALDER-ENE REACTION OF ENYNES

1.4.1 Generality

Enynes have found widespread application as substrates in catalytic Alder-ene reactions within the realm of complex molecule synthesis. Transformations employing enynes result in predictable regiochemistry.\(^1,5\) The major product of a 1,6-enyne cycloisomerization reaction is a 1,4-diene as long as there is opportunity for β-hydride elimination at the allylic position.\(^5\) Substrate tolerance of this catalytic enyne cyclization has proven to be quite general for a range of molecules possessing electron donating or withdrawing groups on both the ene and enophile. A cyclic enamide cycloisomerizes with ease to give the 6,5-ring fused product in 90% yield (Eq. 8).\(^10\) Alkynone 4a also cyclizes to provide the \textit{exo}-cyclic pentenone 5a in a 63% yield.\(^11\)
1.4.2 Predictability

A cyclized 1,3-diene is commonly formed as the minor product in cycloisomerizations of 1,6-enynes. The 1,3-diene has been observed as the major product in cases when the substrate possesses less substitution around the participating points of unsaturation. This 1,3-regioisomer product (5, Eq. 10) can be formed exclusively if there is coordination to the metal complex by remote sites of appended unsaturation, positioned at a proper distance, that direct β-hydride elimination.\(^\text{12}\) For palladium, the highest degree of regioselectivity to form the 1,3-diene is achieved when there is a 3-carbon spacer between the reacting olefin and the tethered unsaturated moiety. Substitution patterns of the product can also be controlled by allylic heteroatom placement. An oxygen atom at the allylic position provides a 1,3-diene as product (Eq. 11).\(^\text{13}\) Relocating oxygen to the homoallylic position affords the expected 1,4-diene (Eq. 12).\(^\text{5}\)

\[
\begin{align*}
\text{Eq. 10} \\
\begin{array}{l}
\text{Pd(OAc)}_2 \ 4 \text{ mol\%} \\
\text{benzene, 60 }^\circ\text{C}
\end{array} \\
\begin{array}{c}
\text{4} \\
b, n = 1 \\
c, n = 2
\end{array} \\
\begin{array}{c}
\text{5} \\
\text{6}
\end{array} \\
\begin{array}{c}
76\%, \ 5b/6b \\
75\%, \ 5c/6c
\end{array} \\
\begin{array}{c}
21 \\
1.1
\end{array} \\
\begin{array}{c}
: \\
:
\end{array} \\
\begin{array}{c}
1 \\
1
\end{array}
\end{align*}
\]
1.5 THE ALDER-ENE REACTION OF ENE-ALLENES

Until recently, the use of allenes in Alder-ene chemistry had been relatively unexplored. Trost has reported a cycloisomerization of a 1,5-ene-allene using palladium (Eq. 13) to afford a 5-membered ring product.¹⁴ This product was an intermediate in the synthesis of petiodial. Due to the aprotic reaction conditions, the mechanistic pathway is likely to entail metallacycle formation (oxidative insertion) followed by β-hydride elimination and finally reductive elimination. The alternate pathway, under a protic environment, would involve hydrometallation followed by carbo-metallation, regenerating the metal-hydride species with a β-hydride elimination.

Weinreb has employed an imino-ene reaction with an alleny1-silane moiety to provide intermediates for enantioselective syntheses of (-)-montanine, (-)-coccinine, and (-)-pancracine.¹⁵ The reaction was executed thermally and exhibited excellent stereocontrol (Eq. 14).

1.6 DISCOVERY OF A NEW CYCLOISOMERIZATION REACTION

1.6.1 The motive behind discovery

Our laboratory has been actively investigating the scope of a catalytic Alder-ene reaction involving allenynes of various tether lengths and substitution patterns. For example, subjecting
allenylene 7 to rhodium bis-carbonyl chloride dimer produces cross-conjugated triene 8 in 93% yield in 3 hours at room temperature (Eq. 15). Malacria\textsuperscript{17} and Sato\textsuperscript{18} have reported on cross-conjugated triene formation using allenynes, however these transformations require stoichiometric amounts of transition metal complex. Livinghouse\textsuperscript{19} has also observed triene formation with allenyne substrates though they are produced as minor products under catalytic metal conditions. Our discovery of this rapid triene formation prompted us to employ ene-allenes as substrates to probe the possibility and/or selectivity of diene formation upon cyclization. Surprisingly, when ene-allene 9a was subjected to modified conditions (heating to reflux) used for triene formation, a cycloisomerization occurred to form the azepine 10a (Eq. 16)\textsuperscript{20} and not the expected 6-membered ring dienes 11a or 11b (Eq. 17).

1.6.2 Baldwin’s rules

A novel aspect of this cycloisomerization was the reversal from \textit{exo}-mode cyclization for allenyne substrates in triene formation (Eq. 15), to the exclusive \textit{endo}-mode cyclization for ene-
allene tethers regarding production of azepines (Eq. 16). Without catalyst, these Alder-ene transformations can mechanistically be represented by equations 18 and 19. Upon inspection of eq. 19, one realizes that trans-ring 10a’ should be the sole product due to the lack of orbital overlap between the allene and allylic hydrogen on the alkene tether to form the cis-ring 10a. Formation of a trans-double bond in a 7-membered ring is unfavored and results in a highly strained molecule. The trans-geometry outcome can be avoided by employing a stepwise mechanism, which would be accessed through the use of Lewis acids and/or transition metals vide infra.

According to Baldwin, 21 7-endo-dig ring closure is a stereoelectronically favored process; however in transition metal catalyzed Alder-ene reactions this mode of cyclization is not reported. An endo-dig-carbocyclization has been communicated by Yamamoto, though it is effected by allylsilane attack on an alkyne while using the catalyst as a Lewis acid (Eq. 20). 22
More often reported are 6-endo-trig cyclization of 1,6-enynes,\textsuperscript{23,1} though these examples are very substrate dependent. In Trost’s case, the substrates require a terminal alkyne and either a mono-substituted alkene or a 1,1-disubstituted alkene (Eq. 21).\textsuperscript{23} Conversely, macrocyclization demonstrates a more general substrate tolerance towards endo-trig cyclization.\textsuperscript{24} An oxaene endo-trig macro-cyclization using an allene has been reported by Trost under palladium catalyst conditions (Eq. 22).\textsuperscript{25}

1.7 OBSERVATION OF A CARBON MONOXIDE INSERTION PRODUCT

Subjecting ene-allene 9b to 9 mol% catalyst in DCE under a carbon monoxide environment produced the α-alkylidene cyclopentenone 12b in a low 13% yield (Eq. 23).
Insertion of carbon monoxide into an ene-allene system has been reported by Itoh,\textsuperscript{26} under similar conditions, providing a single example (Eq. 24). To date, no reports have been communicated for carbon monoxide insertion of nitrogen tethered ene-allenes to form 4-alkyldenehexahydro-cyclopenta[c]pyrrol-5-one systems like that represented by 12b (Eq. 23). Attempts at optimization of this insertion reaction will be discussed herein.

1.8 AZEPINE CONTAINING NATURAL PRODUCTS

1.8.1 Chalciporone

A number of natural products possess the azepine skeleton as part of their core structure (highlighted in blue, List 1). The first of these alkaloids, chalciporone, is shown to be an antisectiside and very pungent to the taste.\textsuperscript{27} It is a 2H-azepine and its biosynthesis is hypothesized to be the result of cyclization of a linear polyketide chain.\textsuperscript{28} Thus far, no total syntheses have been communicated for the fully functionalized natural product.
Steglich\textsuperscript{29} has observed that the 2$H$ azepine isomerizes, upon standing in organic solvent, to the more stable 3$H$ isomer (Eq. 25). This isomerization phenomenon may pose a formidable challenge during synthesis.

\begin{equation}
\text{solvent, rt}
\end{equation}

\textbf{1.8.2 Stenine and Stemonine}

Stemona alkaloids (stenine and stemonine, List 1) have been the topic of intensive pursuit among synthetic organic chemists since their discovery.\textsuperscript{30} Isolated from extracts of \textit{Stemona japonica} and \textit{Stemona tuberosa}, this class of alkaloids constitutes active components of the extracts which have been utilized as antitussives, antiparacitics, anthelmintics, and insecticides. The low quantities of pure stenine obtained from the extracts have compelled researchers\textsuperscript{31,32,33,34} to
engage in its synthesis, not only for further biological studies but also for determination of its absolute stereochemistry. The azepine core is often the last ring to be formed in these syntheses. Wipf (R = CO₂H, Eq. 26) and Hart (R = CO₂Et, Eq. 26) utilized lactamizations to install the azepine moiety while Morimoto employed N-alkylation with the corresponding iodide (R = CH₂I, Eq. 26).

![Chemical structure](image)

Stemonine has also been the target of synthetic effort for similar reasons. Williams used a reductive amination approach to install the azepine core as the first ring in the synthesis of Stemonine (Eq. 27).

![Chemical structure](image)

1.8.3 Balanol

Balanol is the most important of the five azepine natural products contained in list 1. Isolated from the fungi *Verticillium balanoides* and *Fusarium merismoides*, this alkaloid represents an exciting lead structure for inhibition of protein kinase C (PKC) which plays a critical role in regulating signal transduction pathways for many diseases like cancer, inflammation, cardiovascular dysfunctions, diabetic complications, asthma, central nervous system disorders, and HIV infection. Balanol possesses IC₅₀ values in the low nanomolar range but specificity
among PKC isoenzymes is poor.\textsuperscript{37} Its synthesis has been actively explored by a number of research groups,\textsuperscript{38,39,40,41} and derivation to analogs with higher specificity has also been examined.\textsuperscript{42,43} To access the azepine ring Lampe and Hughes\textsuperscript{39} begin from caprolactam which naturally provides this moiety. Nicolaou\textsuperscript{38} and Tanner\textsuperscript{41} both utilize similar $N$-alkylations (Eq. 28) while Naito\textsuperscript{40} employs a novel radical cyclization (Eq. 29).

\begin{equation}
\begin{array}{c}
\text{RN} \\
\text{LG}
\end{array}
\xrightarrow{\text{Eq. 28}}
\begin{array}{c}
\text{RN} \\
\text{LG}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{CHO} \\
\text{NOR}
\end{array}
\xrightarrow{\text{Sml}_2, \text{HMPA}}
\begin{array}{c}
\text{OH} \\
\text{NOR}
\end{array}
\text{Boc} \\
\text{Boc}
\text{OH}
\text{NOR}
\text{NOR}
\end{equation}

1.8.4 Austamide

Austamide (List 1) is a toxic metabolite produced from the fungus \textit{Aspergillus ustus} which was first identified by Steyn.\textsuperscript{44} It belongs to a class of alkaloids that is noted for their anthelmintic, paralytic, and insecticidal activities.\textsuperscript{45} Biosynthetically, it is thought to arise from tryptophan, proline, and one isoprene unit.\textsuperscript{46} Synthetically, its stereochemical elements pose a challenge, most notably the $\psi$-indoxyl spirocycle in conjunction with the azepine core. The first reported synthesis (racemic) was by Kishi\textsuperscript{47} in 1979, and the second (enantioselective) was by Corey\textsuperscript{48} twenty three years later. Kishi\textsuperscript{47} and Corey\textsuperscript{48} both formed the azepine ring through an oxidation-ring contraction process using the corresponding 8-membered ring (Eq. 30).
1. MCPBA, CH$_2$Cl$_2$
2. NaOMe, MeOH, 54%

Eq. 30
2.0 RESULTS AND DISCUSSION

2.1 REACTIVITY TRENDS OBSERVED FOR THE MITSUNOBU REACTION BETWEEN ALLEYLIC ALCOHOLS AND ALLYLIC TOSYLAMIDES

2.1.1 Coupling of allylic tosylamides with allylic-allenyl alcohols

Many cycloisomerization substrates in the current study were prepared via Mitsunobu reaction of the requisite alcohol with the corresponding $N$-allylic tosylamide (Tables 1 & 2). Performing the Mitsunobu reaction between an allylic tosylamide 13 and an allylic allenyl-alcohol 14 provided ene-allenes 9 in yields ranging from 55-86%; avg = 64% (Table 1).

![Chemical reaction diagram]

Table 1. Mitsunobu reaction of allylic allenyl-alcohols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tosylamide</th>
<th>Allylic alcohol</th>
<th>Yield (%)$^a$</th>
<th>Ene-allene</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>13a; $R^1 = Ph; R^2 = H$</td>
<td>14a; $R^3 = t$-Bu; $R^4 = H$</td>
<td>60</td>
<td>9c</td>
</tr>
<tr>
<td>2</td>
<td>13b; $R^1 = H; R^2 = Me$</td>
<td>14a; $R^3 = t$-Bu; $R^4 = H$</td>
<td>55</td>
<td>9d</td>
</tr>
<tr>
<td>3</td>
<td>13c; $R^1 = Me; R^2 = H$</td>
<td>14b; $R^3 = Ph; R^4 = H$</td>
<td>55</td>
<td>9e</td>
</tr>
<tr>
<td>4</td>
<td>13c; $R^1 = Me; R^2 = H$</td>
<td>14a; $R^3 = t$-Bu; $R^4 = H$</td>
<td>60</td>
<td>9f</td>
</tr>
<tr>
<td>5</td>
<td>13d; $R^1 = H; R^2 = H$</td>
<td>14c; $R^3 = R^4 = Me$</td>
<td>86$^b$</td>
<td>9b</td>
</tr>
</tbody>
</table>

$^a$Indicates isolated yield. $^b$Reaction was performed by Dr. Hongfeng Chen (ref. 20).

When the tert-butyl allylic allenyl-alcohol 14a was employed, yields of 55-60% were observed for the coupling with 13a, 13b, and 13c (entries 1, 2, 4). When employing the trisubstituted
allene 14c the highest yield was obtained for the series (86%, entry 5). Alcohol 14b reacted to give 9e in a 55% yield. A reason for the moderate yields for all but one entry (5) in table 1 is not exactly known but can be rationalized by considering the activated central carbon of the allene, which is electronically and sterically poised for S_N2' displacement of the leaving group. Displacing the leaving group in a S_N2' fashion would lead to an enamide by-product (Eq. 31) and reduce the overall yield of the desired ene-allene.

\[
\text{Eq. 31}
\]

2.1.2 Coupling of allylic-allenyl tosylamides with allylic alcohols

This allene reactivity hypothesis described above is further supported by the results observed for Mitsunobu reaction between allylic allenyl-tosylamides and allylic alcohols (Table 2) where the yields were consistently higher (67-90%; avg = 82%). Although substrates with allylic leaving

\[
\text{Table 2. Mitsunobu reaction of allylic alcohols.}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tosylamide</th>
<th>Allylic alcohol</th>
<th>Yield (%)^a</th>
<th>Ene-allene</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>15a; R^1 = t-Bu</td>
<td>16a; R^2 = Me, R^3 = R^4 = H</td>
<td>84</td>
<td>9g</td>
</tr>
<tr>
<td>7</td>
<td>15a; R^1 = t-Bu</td>
<td>16b; R^2 = H, R^3 = R^4 = Me</td>
<td>90</td>
<td>9h</td>
</tr>
<tr>
<td>8</td>
<td>15a; R^1 = t-Bu</td>
<td>16c; R^2 = H, R^3 = R^4 = -(CH_2)_4^-</td>
<td>86</td>
<td>9i</td>
</tr>
<tr>
<td>9</td>
<td>15a; R^1 = t-Bu</td>
<td>16d; R^2 = R^3 = H, R^4 = SiMe_3</td>
<td>67</td>
<td>9j</td>
</tr>
<tr>
<td>10</td>
<td>15a; R^1 = t-Bu</td>
<td>16e; R^2 = R^3 = H, R^4 = SiMe_2Bn</td>
<td>79</td>
<td>9k</td>
</tr>
<tr>
<td>11</td>
<td>15b; R^1 = C_6H_{13}</td>
<td>16f; R^2 = R^3 = H, R^4 = C_6H_{17}</td>
<td>83</td>
<td>9l</td>
</tr>
</tbody>
</table>

^aIndicates isolated yield.
groups can also undergo $S_N2'$ reactions, steric hindrance at the 2-position (terminus) of 16 along with its less activated $sp^2$ carbon (verses the $sp$ carbon of 14) appear to be the cause for the observed chemo-selectivity and lack of $S_N2'$ reactivity regarding the allylic alcohols submitted to Mitsunobu conditions. A secondary allylic alcohol also afforded the coupled amide in 75% yield as shown in eq. 32. On average, allylic allenyl-alcohols gave 18% lower yields when coupled to allylic tosylamides as opposed to using the alternate method of alkylating allylic allenyl-tosylamides with allylic alcohols. When possible, the latter method was employed over the former for substrate synthesis.

![Chemical Reaction](image.png)

**2.2 REACTIVITY OF ALKYL-SUBSTITUTED TRANS-ALKENE SUBSTRATES TOWARD CYCLOISOMERIZATION CONDITIONS**

An investigation into the scope and limitations of this newly discovered rhodium catalyzed azepine forming reaction was initiated. The results for the alkyl-substituted trans-alkene substrates are illustrated in table 3 and summarized below.
Placing methyl substitution on the alkene terminus fostered varying results, which were dependent on the substituent of the allene. Subjecting ene-allene 9n with hydrogen as the allene substituent and a methyl group on the alkene terminus (R₁ = Me, R₂ = H; entry 12) to 10 mol% catalyst in 1,4-dioxane under a carbon monoxide atmosphere gave a complex mixture by ¹H NMR upon inspection of the crude material. No individual compound could be isolated by column chromatography. Replacing hydrogen with a hexyl-group on the allene terminus (R₁ = Me, R₂ = C₆H₁₃; entry 13) afforded azepine 10a in 54% yield in 1,4-dioxane under an argon
atmosphere. The isolated yield for 10a had decreased by only 4% (compare entry 13 to 14) when performing the reaction in DCE versus 1,4-dioxane though the reaction rate had decreased by 11 fold. Substituting the hexyl group on 9a with a t-butyl moiety on the allene terminus (R^1 = Me, R^2 = t-Bu; entry 15) dramatically increased the yield by 45% under similar reaction conditions (compare entry 14 to 15). Exchanging DCE with 1,4-dioxane as solvent increased the reaction rate by 15 fold while decreasing the yield by 10% for conversion of 9f to 10f (compare entry 15 to 16). Performing the cycloisomerization of 9f with half the catalyst loading (2.5 mol% vs. 5 mol%) actually decreased the reaction rate by 2 fold and the yield by 10% (compare entry 16 to 17). Success with this bulky t-butyl substituent on 9f compelled our investigation to examine the tolerance of a phenyl ring on the allene terminus. In DCE solvent, no recognizable change of 9e was observed after 1.3 hours at reflux with 9 mol% catalyst in an argon atmosphere (R^1 = Me, R^2 = Ph; entry 18). Simply replacing DCE with 1,4-dioxane afforded azepine 10e in 45% yield (entry 19). Keeping 1,4-dioxane as solvent while exchanging argon with carbon monoxide increased the yield by 7% though decreased the reaction rate (compare entry 19 to 20). This same substrate 9e also cyclized in THF solvent after prolonged refluxing to afford 10e in 41% yield (entry 21).

Lengthening the methyl group on the alkene to a propyl-group while maintaining the hexyl substituent on the allene (R^1 = C_3H_7, R^2 = C_6H_{13}; entry 22) reduced the yield to 28% even after employing a 17 mol% catalyst loading. Fortunately, product formation of 10l could be increased to 53% by merely replacing DCE with 1,4-dioxane as solvent for the reaction (entry 23). Also noteworthy about this solvent change was the 5 fold increase on reaction rate and the 3-fold reduction of catalyst loading necessary for complete conversion (entry 23).
Generally, employing 1,4-dioxane as solvent versus DCE increased the reaction rates for all ene-allenes in table 3.

2.3 MECHANISM PROPOSALS FOR AZEPINE FORMATION

2.3.1 Evidence

Our discovery of this new azepine forming cycloisomerization reaction compelled us to investigate the mechanism by which transformation of ene-allenes to azepines was occurring. Ene-allene 9f was chosen as the ideal substrate for this inquiry due to the success that was achieved for its cyclization. Modification of 9f by substitution of the alkene tether with a tether that has been deuterated at the allylic position provided the necessary substrate 9o (Eq. 33). Subjecting 9o to 10 mol% catalyst in DCE under an argon atmosphere resulted in azepine 10o in 88% yield after 50 minutes at reflux (Eq. 33).\(^\text{20}\) Deuterium placement in the product azepine 10o suggests two probable mechanisms which are illustrated in scheme 2. In path A (Scheme 2)
Scheme 2. C-H insertion and metallocycle mechanisms from deuterium labeling study (the ligands on rhodium have been omitted for clarity).

activation of the alkene moiety occurs via allylic C-D insertion of rhodium at the position α to nitrogen providing intermediate I, a π-allyl-Rh species.49,50 This η-3 species (I) isomerizes to an η-1 species which then carbo-metallates onto the central carbon of the allene, effecting a 7-endo-dig cyclization resulting in intermediate III. The ensuing allylic-rhodium-hydride intermediate III then reductively eliminates to furnish the final product azepine 10o. In path B (Scheme 2), rhodium oxidatively adds to the system after precoordination of ene-allene 9o to furnish the bridged bicyclic intermediate II. The bicyclic complex II then undergoes β-deuteride elimination, resulting in intermediate III. Reductive elimination of III follows to arrive at the same deuterium labeled species 10o.

Not surprising, a substrate with the same tethers on nitrogen but employing a Boc protecting group instead of a tosyl-group (9p) also underwent cyclization to result in identical
placement of deuterium in the product \((10p)\), though in a lower 68% yield (Eq. 34). This lower yield may be attributed to a stronger complexation of the Boc group with the catalyst.

![Chemical Structure](image)

2.3.2 Precedence

In addition to C-H insertion of allylic amines reported by Tani and Otsuka, Trost has communicated an allylic C-H insertion to give 7-membered \(exo\)-alkylidenecycloheptenes from 1,6-enynes by employing a ruthenium catalyst (Scheme 3). In this mechanism (Scheme 3), which utilizes a deuterated substrate, Trost asserts that C-H activation must occur from the \(cis\)-alkenyl geometry \((a \rightarrow b)\) or isomerization from the \(trans\)- to the \(cis\)-geometry must happen after insertion (at intermediate \(b\)). The requirement for insertion into the \(cis\)-alkene moiety is rationalized by the strain that would ensue if \(trans\)-C-H insertion \((a' \rightarrow b', \text{ Scheme 4})\) occurred to provide, upon ring closure, a \(trans\)-double bond in a 7-membered ring \((c', \text{ Scheme 4})\).

![Scheme 3](image)
Itoh has reported a similar cyclization to that of our azepine formation which resulted in construction of an exo-alkylidene cycloheptene carbocycle from a 1,6-ene-allene, though no mechanism was proposed (Eq. 35).\textsuperscript{52} The second of Itoh’s communications\textsuperscript{26} regarding 7-membered ring formation from 1,6-ene-allenes illustrated an identical azepine product 10b (Eq. 36) as that described in our initial publication,\textsuperscript{20} using similar conditions (2.5 mol% vs. 5 mol% cat., CO vs. Ar atmosphere, and 1,4-dioxane vs. DCE), but disclosing a single azepine entry.

In this second publication by Itoh,\textsuperscript{26} two possible mechanisms for endo-mode cyclization of 1,6-ene-allenes were postulated. The first proposal is the C-H insertion model which we initially supported by a deuterium labeling study (path A, Scheme 2) as described in our publication of this azepine forming reaction.\textsuperscript{20} The second proposal from Itoh regarding 7-membered ring formation involves Lewis acid catalyzed attack of the olefin onto the allene center (Scheme 5). This Lewis acid catalyzed mechanism is criticized by Itoh to be unlikely due to the inability of
trapping the intermediate cationic species with D$_2$O or EtOD. Moreover, the reaction does not take place with Pt(II) which is an effective catalyst towards the cyclization of enynes involving a similar mechanism.$^{53,54,55}$

![Scheme 5. Lewis acid catalyzed cyclization of ene-allenes.](image)

### 2.4 Reactivity of Alkyl-Substituted *cis*-Alkene Substrates Toward Cycloisomerization Conditions.

![Table 4. Reactivity of alkyl-substituted *cis*-alkenyl substrates.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ene-allene</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>time (h)</th>
<th>Atmosphere</th>
<th>Yield (%)$^{\text{a}}$</th>
<th>Azepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>9q; R$^1$ = Me; R$^2$ = C$<em>6$H$</em>{13}$</td>
<td>10</td>
<td>DCE</td>
<td>2.5</td>
<td>Ar</td>
<td>0$^b$</td>
<td>10q</td>
</tr>
<tr>
<td>25</td>
<td>9d; R$^1$ = Me; R$^2$ = t-Bu</td>
<td>5</td>
<td>1,4-dioxane</td>
<td>2</td>
<td>Ar</td>
<td>43</td>
<td>10f</td>
</tr>
<tr>
<td>26</td>
<td>9d; R$^1$ = Me; R$^2$ = t-Bu</td>
<td>5</td>
<td>1,4-dioxane</td>
<td>0.17</td>
<td>Ar</td>
<td>36$^c$</td>
<td>10f</td>
</tr>
<tr>
<td>27</td>
<td>9d; R$^1$ = Me; R$^2$ = t-Bu</td>
<td>5</td>
<td>DME</td>
<td>5</td>
<td>Ar</td>
<td>30</td>
<td>10f</td>
</tr>
<tr>
<td>28</td>
<td>9d; R$^1$ = Me; R$^2$ = t-Bu</td>
<td>10</td>
<td>DCE</td>
<td>0.9</td>
<td>Ar</td>
<td>29</td>
<td>10f</td>
</tr>
</tbody>
</table>

$^a$Indicates isolated yield. $^b$Reaction was performed by Dr. Hongfeng Chen. $^c$Reaction was performed in the Personal Chemistry microwave oven at 140 °C in a sealed tube.

The *cis*-alkene substrate 9q (R$^1$ = Me, R$^2$ = C$_6$H$_{13}$; entry 24) was unreactive when subjected to 10 mol% catalyst in dichloroethane solvent under an argon atmosphere. However, the *cis*-isomer
**9d** underwent conversion in 43% yield in 1,4-dioxane, 30% in DME, and 29% in DCE. In an attempt to improve product formation, cyclization of **9d** was also carried out in the microwave (entry 26) though this alteration only diminished the yield by 7% when compared to the reaction performed in an oil bath (entry 25). It is relatively surprising that ene-allene **9d** reacts in DCE (entry 28) considering the unreactivity of **9q** which completely failed to cyclize in DCE (entry 24).

The poor yield observed for the **cis**-alkene substrate **9d** can be rationalized by considering the mechanistic pathways postulated in scheme 2. When employing pathway A (Scheme 2) for the cyclization of Z-olefins verses E-olefins there is allylic strain that must be overcome in order to effect and maintain C-H insertion when forming the π-allyl-Rh complex (Eq. 34).

Furthermore, in order to assume the reactive conformation I (Scheme 6) once C-H insertion has been achieved, the complex must progress from the η-3 coordination state **Id** to an η-1 state **Id′**. The carbon bearing rhodium in intermediate **Id′** must then rotate around the sp²-sp³ terminal C-C single bond and then isomerize back to an η-3 coordination state **Id″**. The π-allyl-rhodium intermediate **Id″** must then isomerizes to the η-1 intermediate **Id‴** in which another sp²-sp³ bond rotation must occur before the final isomerization back to an η-3 coordination state, resulting in intermediate I. The entire process illustrated in scheme 6 is an isomerization of the **cis**-alkene **9d** to its **trans**-alkene counterpart by way of π-allyl-rhodium intermediates **Id** and **Id″**, and η-1 alkyl intermediates **Id′** and **Id‴**.

---

**TsN**

**Scheme 2**

**Eq. 34**

---
Implementing path B from scheme 2 shows that the methyl group from the Z-alkene in the bicyclic intermediate IIId (Scheme 7) approaches a *syn*-pentane interaction with the lone pairs on nitrogen while the 6-membered ring is in the chair conformation. By adopting a boat configuration for the ring (IIId', Scheme 7), the *syn*-pentane interaction is relieved though the β-hydrogen is now orthogonal to the Rh-C bond, preventing the complex from undergoing β-
hydride elimination. When one considers the mechanistic factors presented in both Scheme 6 and Scheme 7 regarding cis-isomer reactivity, the low conversion becomes reconcilable.

### 2.5 Reactivity of Phenyl and Silyl-Substituted Trans-Ene-Allenes Toward Cycloisomerization Conditions

To further expand the scope of this azepine forming cycloisomerization reaction (9 → 10, table 5) our study employed the use of ene-allenes that have been substituted with either a phenyl or silyl-bearing substituent. The results of these substitutions regarding cyclization are depicted in table 5 and summarized below.

![Scheme 5: Reaction of phenyl and silyl-substituted trans-ene-allene substrates.](attachment:image)

**Table 5.** Reactivity of phenyl and silyl-substituted trans-ene-allene substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ene-allene</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>time (h)</th>
<th>Atmosphere</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Azepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>9c; R&lt;sup&gt;1&lt;/sup&gt; = Ph; R&lt;sup&gt;2&lt;/sup&gt; = t-Bu</td>
<td>9</td>
<td>1,4-dioxane</td>
<td>8.5</td>
<td>CO</td>
<td>95</td>
<td>10c</td>
</tr>
<tr>
<td>30</td>
<td>9c; R&lt;sup&gt;1&lt;/sup&gt; = Ph; R&lt;sup&gt;2&lt;/sup&gt; = t-Bu</td>
<td>10</td>
<td>1,4-dioxane</td>
<td>0.5</td>
<td>Ar</td>
<td>79</td>
<td>10c</td>
</tr>
<tr>
<td>31</td>
<td>9c; R&lt;sup&gt;1&lt;/sup&gt; = Ph; R&lt;sup&gt;2&lt;/sup&gt; = t-Bu</td>
<td>5</td>
<td>DME</td>
<td>2</td>
<td>Ar</td>
<td>90</td>
<td>10c</td>
</tr>
<tr>
<td>32</td>
<td>9c; R&lt;sup&gt;1&lt;/sup&gt; = Ph; R&lt;sup&gt;2&lt;/sup&gt; = t-Bu</td>
<td>11</td>
<td>DME</td>
<td>2.8</td>
<td>Ar</td>
<td>90</td>
<td>10c</td>
</tr>
<tr>
<td>33</td>
<td>9r; R&lt;sup&gt;1&lt;/sup&gt; = Ph; R&lt;sup&gt;2&lt;/sup&gt; = Si(i-pr)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>6</td>
<td>1,4-dioxane</td>
<td>14.3</td>
<td>Ar</td>
<td>48&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10r</td>
</tr>
<tr>
<td>34</td>
<td>9s; R&lt;sup&gt;1&lt;/sup&gt; = Me; R&lt;sup&gt;2&lt;/sup&gt; = Si(i-pr)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>6</td>
<td>1,4-dioxane</td>
<td>1.5</td>
<td>Ar</td>
<td>69</td>
<td>10s</td>
</tr>
<tr>
<td>35</td>
<td>9t; R&lt;sup&gt;1&lt;/sup&gt; = SiMe&lt;sub&gt;2&lt;/sub&gt;Bn; R&lt;sup&gt;2&lt;/sup&gt; = C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;</td>
<td>10</td>
<td>DCE</td>
<td>7</td>
<td>Ar</td>
<td>Trace</td>
<td>10t</td>
</tr>
<tr>
<td>36</td>
<td>9j; R&lt;sup&gt;1&lt;/sup&gt; = SiMe&lt;sub&gt;3&lt;/sub&gt;; R&lt;sup&gt;2&lt;/sup&gt; = t-Bu</td>
<td>10</td>
<td>DCE</td>
<td>1</td>
<td>Ar</td>
<td>82</td>
<td>10j</td>
</tr>
<tr>
<td>37</td>
<td>9k; R&lt;sup&gt;1&lt;/sup&gt; = SiMe&lt;sub&gt;3&lt;/sub&gt;Bn; R&lt;sup&gt;2&lt;/sup&gt; = t-Bu</td>
<td>10</td>
<td>DCE</td>
<td>1</td>
<td>Ar</td>
<td>97</td>
<td>10k</td>
</tr>
</tbody>
</table>

<sup>a</sup>Indicates isolated yield. <sup>b</sup>Gave a 40% yield but the starting material was contaminated with the cis-alkene isomer (~18%) which reacts slowly or not at all. The product was impure by <sup>1</sup>H NMR.
2.5.1 Phenyl-substituted alkene tethers

We first examined ene-allene 9c \((R^1 = \text{Ph}, R^2 = t\text{-Bu}; \text{entry 29})\) which afforded an excellent 95% yield though a prolonged reaction time in carbon monoxide. Exchanging the carbon monoxide atmosphere used for entry 29 to one of argon caused a reduction in conversion of 9c to 10c by 16% but concomitantly fostered a 17-fold increase in reaction rate (compare entry 29 to 30). Maintaining argon as the atmosphere but substituting 1,4-dioxane for DME caused an 11% increase in yield but a 4-fold reduction in reaction rate (compare entry 30 to 34). Replacing DME with DCE and increasing the catalyst loading by 6% resulted in a 17% decrease in yield of 10c (compare entry 31 to 32). Finally, in an effort to replace this esoteric tert-butyl group on the allene terminus with one that would be easier to remove after cyclization, we examined the affect of a triisopropylsilyl-substituted allenyl-tether on this phenyl-alkene series. Ene-allene 9r \((R^1 = \text{Ph}, R^2 = \text{Si}(i\text{-pr})_3; \text{entry 33})\) cyclized to give a 48% yield of azepine 10r after a lengthy 14.3 hours at reflux in 1,4-dioxane blanketed with an argon atmosphere. Unfortunately, azepine 10r was impure even after column chromatography.

2.5.2 Silyl substituted ene-allenes

The aim of employing silyl substituted ene-allenes 9r, 9s, 9t, 9j, and 9k as substrates was 2-fold. First, this moiety would provide a handle on the product azepines that allows for facile derivitization. Second, a silyl group would be easier to remove on the product than an alkyl-group of similar steric demand. With this rationale in mind, syntheses of both allenyl- and vinyl-silane substrates were undertaken. Cyclization of 9r \((R^1 = \text{Ph}, R^2 = \text{Si}(i\text{-pr})_3; \text{entry 33})\) was described as affording not only a low yield but also an impure product. By changing the styryl-tether of 9r to a crotyl-tether \((R^1 = \text{Me}, R^2 = \text{Si}(i\text{-pr})_3; \text{entry 34})\), the reaction yield was increased
to 69%. Implementing a hexyl substituted allene with a vinyl-silane moiety \((R^1 = \text{SiMe}_3, R^2 = \text{C}_6\text{H}_{13};\) entry 35) provided only a trace of the desired azepine product \(10t\) by \(^1\text{H}\) NMR. Replacing the hexyl substituent with the favored \(t\)-butyl group \((R^1 = \text{SiMe}_3, R^2 = \text{t-Bu};\) entry 36) had a drastic effect in that the cyclized product \(10j\) was isolated in 82% yield. Substituting the –\(\text{SiMe}_3\) group on \(9j\) with a –\(\text{SiMe}_2\text{Bn}\) group \((R^1 = \text{SiMe}_2\text{Bn}, R^2 = \text{t-Bu};\) entry 37) resulted in the highest yield of cycloisomerization observed to date (97%, \(10k\)) for nitrogen tethered ene-allenes.

2.6 REACTIVITY OF ALLYL-TETHERED ENE-ALLENES TOWARD CYCLOISOMERIZATION CONDITIONS

Allyl-tethered ene-allenes were the next class of substrates examined. The results for this facet of our cycloisomerization investigation are illustrated in table 6 and summarized below.

Employing an allyl-tether in conjunction with the hexyl-substituted allene moiety \((R^1 = \text{H}, R^2 = \text{C}_6\text{H}_{13};\) entry 38) provided azepines \(10u\) and \(10u'\) in a combined yield of 62%. Azepines \(10u\) and \(10u'\) are \(E/Z\) isomers about the exocyclic alkene, isolated as an inseparable mixture in a ratio of 1.3:1, respectively. Substituting the hexyl group on \(9u\) with a triisopropylsilyl-moiety caused an 11% increase in overall yield of \(10v\) and \(10v'\) while providing a marked escalation in
Table 6. Reactivity of allyl-tethered ene-allenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ene-allene</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>time (h)</th>
<th>Atmosphere</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Azepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>9u; R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;</td>
<td>10</td>
<td>DCE</td>
<td>4</td>
<td>Ar</td>
<td>62&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>10u; 10u'</td>
</tr>
<tr>
<td>39</td>
<td>9v; R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = Si(i-pr)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>5</td>
<td>1,4-dioxane</td>
<td>0.3</td>
<td>Ar</td>
<td>73&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10v; 10v'</td>
</tr>
<tr>
<td>40</td>
<td>9b; R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = Me</td>
<td>10</td>
<td>DCE</td>
<td>6</td>
<td>N&lt;sub&gt;2&lt;/sub&gt;</td>
<td>68&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10b</td>
</tr>
<tr>
<td>41</td>
<td>9b; R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = Me</td>
<td>5</td>
<td>1,4-dioxane</td>
<td>0.25</td>
<td>CO/Ar</td>
<td>85</td>
<td>10b</td>
</tr>
<tr>
<td>42</td>
<td>9w; R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = H</td>
<td>10</td>
<td>DCE</td>
<td>0.25</td>
<td>Ar</td>
<td>Trace</td>
<td>10w</td>
</tr>
</tbody>
</table>

<sup>a</sup>Indicates isolated yield. <sup>b</sup>Reaction was performed by Dr. Hongfeng Chen (ref. 20). <sup>c</sup>E/Z isomers were obtained in a ratio of 1.3:1. <sup>d</sup>E/Z isomers were obtained in a ratio of 5.8:1.

The E/Z ratio of 5.8:1 (compare entry 38 to 39). Replacing the hexyl chain on 9u with a methyl group and further substituting the allene terminus with an additional methyl group (R<sup>1</sup> = R<sup>2</sup> = Me; entry 40) marginally improved the yield of the corresponding azepine 10b by 6% (compare entries 38 and 40). Performing the cyclization of 9b in 1,4-dioxane in a partial carbon monoxide/argon environment afforded a substantial improvement in yield of 85% compared to 68% in DCE and a nitrogen atmosphere (compare entry 40 to 41). Removing all substitution from the allene (R<sup>1</sup> = R<sup>2</sup> = H; entry 42) gave a rapid reaction with substantial decomposition. The azepine 10w was only observed in trace amounts by crude <sup>1</sup>H NMR but was not isolable by silica gel chromatography.

2.6.1 Reasoning for observation of E/Z isomers

The prevalence of E/Z-isomers upon cyclization of 9u (entry 38) and 9v (entry 39) is postulated to originate from a lack of steric biasing in the transition state. When 1,2-distubstituted alkene tethers are used in substrates for cyclization, exclusive E-alkene products, with respect to the
exocyclic olefin, are observed (see tables 3, 4, & 5). This outcome can be rationalized while employing either path A or path B from scheme 2. The steric influence experienced in path A of scheme 2 is illustrated more clearly in scheme 8 below. Preferential formation of the \( E \)-isomer \( 10a \), indicated by the selective pathway (Scheme 8), is a result of the steric interaction between the alkene and allene termini (see \( Ia' \)). Exchange of the methyl group at the alkene terminus of \( 9a \) with a hydrogen atom (ene-allene \( 9u \)) reduces this steric biasing, denoted by the nonselective pathway (Scheme 8), which results in only a slight preference to form the \( E \)-isomer \( 10u \) over the \( Z \)-isomer \( 10u' \). The steric bulk of the triisopropylsilyl group in conversion of \( 9v \) to \( 10v \) and \( 10v' \) (table 6) increases this interaction, causing the product distribution to show a much higher concentration of the \( E \)-isomer over the \( Z \)-isomer. When employing path B from scheme 2 (illustrated clearly in Scheme 9) a recognizable \( A_{1,3} \) strain between the alkyl groups on the allene and alkene termini in intermediate \( IIa' \) is sufficient to drive the equilibrium towards formation of intermediate \( IIa \) which affords the \( E \)-alkene product \( 10a \) over the \( Z \)-isomer \( 10a' \) exclusively.

\[ \text{Scheme 8. Selective and nonselective cyclization employing C-H insertion mechanism} \]

\[ \text{(the ligands on rhodium have been omitted for clarity).} \]
When the alkene terminus is substituted with hydrogen and the allene terminus is substituted with a hexyl-group (9u), the similar A_{1,3} strain experienced in both intermediates II and II' only slightly biases the equilibrium to prefer the E-isomer over the Z-isomer (Scheme 10). However, in the case of 9v the steric encumberment is exacerbated by the bulkier triisopropylsilyl-group, conferring a substantial increase in E/Z ratio of 5.8:1 in the product isomers.

**Scheme 9.** Selective pathway of metallocycle mechanism (the ligands on rhodium have been omitted for clarity).

**Scheme 10.** Nonselective pathway of metallocycle mechanism (the ligands on rhodium have been omitted for clarity).
2.7 REACTIVITY OF 1,1-DISUBSTITUTED AND TRISUBSTITUTED OLEFIN SUBSTRATES TOWARD CYCLOISOMERIZATION CONDITIONS

2.7.1 1,1-Disubstituted ene-allenes

Success with the cyclization of both allyl- and 1,2-disubstituted alkenyl-tethers directed our attention to the examination of 1,1-disubstituted alkenyl-tethers. The ene-allene chosen to probe this variation on substitution was $9g$. The results for the conversion of $9g$ to $10g$ are compiled in table 7 and digested below.

![Chemical structure of 9g to 10g](image)

**Table 7.** Reactivity of ene-allene $9g$ to cycloisomerization conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. (mol%)</th>
<th>Solvent</th>
<th>time (h)</th>
<th>Atmosphere</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>5</td>
<td>1,4-dioxane</td>
<td>0.25</td>
<td>Ar</td>
<td>83</td>
</tr>
<tr>
<td>44</td>
<td>5</td>
<td>1,4-dioxane</td>
<td>0.33</td>
<td>Air$^b$</td>
<td>86</td>
</tr>
<tr>
<td>45</td>
<td>5</td>
<td>DCE</td>
<td>0.25</td>
<td>Ar$^c$</td>
<td>82</td>
</tr>
<tr>
<td>46</td>
<td>6</td>
<td>DCE</td>
<td>0.25</td>
<td>Ar$^b$</td>
<td>73</td>
</tr>
</tbody>
</table>

$^a$Indicates isolated yield. $^b$The soln was not degassed prior to or after addition of catalyst. $^c$The soln was degassed via freeze-pump-thaw method after the addition of catalyst.

Subjecting ene-allene $9g$ to 5 mol% catalyst in 1,4-dioxane under an argon atmosphere afforded azepine $10g$ in 83% yield (entry 43). We saw the reaction of $9g$ as an opportunity to assess the effect of residual gas molecules in the solution at the time of cyclization. As an extreme example, the normal argon environment was replaced with air from the outside atmosphere. Surprisingly, the yield of azepine $10g$ actually increased by 3% under air atmosphere conditions (compare entry 43 to 44). This finding suggests that the atmosphere in
which the reaction is run, when utilizing 1,4-dioxane as solvent, does not have a large impact on the product yield. Switching the atmosphere from air to argon and the solvent back to DCE from 1,4-dioxane, while carefully degassing the solution after addition of catalyst, resulted in an 82% yield of 10g (entry 45). Implementing these same conditions without degassing the solvent resulted in a 9% reduction in yield (compare entry 45 to 46). The data presented in entries 45 and 46 indicate that the residual gas concentration is a crucial factor when performing the cycloisomerization in DCE.

The encouraging results regarding transformation of 9g to 10g compelled our investigation to further examine the limits of substituent tolerance by replacing the alkenyl-methyl group on 9g with a bromine atom (9x). When ene-allene 9x was exposed to 5 mol% catalyst in an argon atmosphere and refluxed in 1,4-dioxane for 20 minutes the only observable phenomenon was substantial decomposition and no trace of the desired azepine 10x (Eq. 35).

\[
\begin{align*}
9x & \xrightarrow{\text{[Rh(CO)\textsubscript{2}Cl\textsubscript{2} 5 mol\%, Ar}}} 10x \\
& \quad \text{1,4-dioxane, reflux, 0.33 h}
\end{align*}
\]

Eq. 35

Eight percent of the original starting material was recovered as an impure fraction after column chromatography. Performing the reaction with 13 mol% catalyst (added in 2 portions) in 1,4-dioxane under an argon atmosphere at 50 °C instead of 110 °C also promoted decomposition with no sign of azepine 10x.
2.7.2 1,2,2-Trisubstituted ene-allenes

Our focus now shifted to substrates possessing trisubstituted alkenyl-tethers. The results for this series of ene-allenes towards cycloisomerization conditions are depicted in table 8 and synopsized in the proceeding paragraphs.

![Diagram](image)

**Table 8. Reactivity of Trisubstituted Alkene Substrates**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ene-allene</th>
<th>Cat (mol%)</th>
<th>Solvent</th>
<th>time (h)</th>
<th>Atmosphere</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Azepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>9&lt;sub&gt;i&lt;/sub&gt;, R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = -(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-; R&lt;sup&gt;3&lt;/sup&gt; = H; R&lt;sup&gt;4&lt;/sup&gt; = t-Bu</td>
<td>7</td>
<td>1,4-dioxane</td>
<td>13.3</td>
<td>Ar</td>
<td>78</td>
<td>10&lt;sub&gt;i&lt;/sub&gt;</td>
</tr>
<tr>
<td>48</td>
<td>9&lt;sub&gt;i&lt;/sub&gt;, R&lt;sup&gt;1&lt;/sup&gt; = R&lt;sup&gt;2&lt;/sup&gt; = -(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-; R&lt;sup&gt;3&lt;/sup&gt; = H; R&lt;sup&gt;4&lt;/sup&gt; = t-Bu</td>
<td>2.5</td>
<td>1,4-dioxane</td>
<td>1.6</td>
<td>Ar</td>
<td>66</td>
<td>10&lt;sub&gt;i&lt;/sub&gt;</td>
</tr>
<tr>
<td>49</td>
<td>9&lt;sub&gt;h&lt;/sub&gt;, R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = Me; R&lt;sup&gt;4&lt;/sup&gt; = t-Bu</td>
<td>10</td>
<td>DCE</td>
<td>1.5</td>
<td>Ar</td>
<td>0</td>
<td>10&lt;sub&gt;h&lt;/sub&gt;</td>
</tr>
<tr>
<td>50</td>
<td>9&lt;sub&gt;h&lt;/sub&gt;, R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = Me; R&lt;sup&gt;4&lt;/sup&gt; = t-Bu</td>
<td>11</td>
<td>1,4-dioxane</td>
<td>2.3</td>
<td>Ar</td>
<td>13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10&lt;sub&gt;h&lt;/sub&gt;</td>
</tr>
<tr>
<td>51</td>
<td>9&lt;sub&gt;h&lt;/sub&gt;, R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = Me; R&lt;sup&gt;4&lt;/sup&gt; = t-Bu</td>
<td>9</td>
<td>1,4-dioxane</td>
<td>6.7</td>
<td>CO</td>
<td>14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10&lt;sub&gt;h&lt;/sub&gt;</td>
</tr>
<tr>
<td>52</td>
<td>9&lt;sub&gt;y&lt;/sub&gt;, R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = Me</td>
<td>10</td>
<td>Toluene</td>
<td>3</td>
<td>Ar</td>
<td>0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10&lt;sub&gt;y&lt;/sub&gt;</td>
</tr>
<tr>
<td>53</td>
<td>9&lt;sub&gt;z&lt;/sub&gt;, R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = Me; R&lt;sup&gt;4&lt;/sup&gt; = C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;</td>
<td>10</td>
<td>Toluene</td>
<td>13</td>
<td>Ar</td>
<td>0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>10&lt;sub&gt;z&lt;/sub&gt;</td>
</tr>
<tr>
<td>54</td>
<td>9&lt;sub&gt;A&lt;/sub&gt;, R&lt;sup&gt;1&lt;/sup&gt; = H; R&lt;sup&gt;2&lt;/sup&gt; = R&lt;sup&gt;3&lt;/sup&gt; = -(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;4&lt;/sub&gt;-; R&lt;sup&gt;4&lt;/sup&gt; = t-Bu</td>
<td>10</td>
<td>1,4-dioxane</td>
<td>21.8</td>
<td>Ar</td>
<td>14&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10&lt;sub&gt;A&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Indicates isolated yield. <sup>b</sup>Determined by HPLC. <sup>c</sup>Determined by 1H NMR. <sup>d</sup>Reaction was performed by Dr. Hongfeng Chen.

In 1,4-dioxane with 7 mol% catalyst surrounded by an argon atmosphere, ene-allene 9<sub>i</sub> (R<sup>1</sup> = R<sup>2</sup> = -(CH<sub>2</sub>)<sub>4</sub>-; R<sup>3</sup> = H; R<sup>4</sup> = t-Bu; entry 47) which is a 1,1,2-trisubstituted alkene, reacted to provide azepine 10<sub>i</sub> in a 78% yield. Reducing the catalyst loading to 2.5 mol% as opposed to 7 mol% caused a decrease in product yield of 12% (compare entry 47 to 48).
Substitution in the form of the 1,2,2-trisubstituted alkenyl-tether embodied in \( 9h \) \( (R^1 = H, R^2 = R^3 = Me; R^4 = t\text{-Bu}; \text{entry 49}) \) was not tolerated under DCE/argon cycloisomerization conditions, as exemplified by this substrate’s lack of reactivity. Exchanging the solvent to 1,4-dioxane facilitates the transformation, albeit in a poor 13% yield (entry 50). Replacing argon with carbon monoxide marginally increased the yield by 1% though caused a 3-fold reduction in rate (entry 51). Substituting the \( t\text{-butyl} \) group on the allene terminus of \( 9h \) with a methyl group \( (R^1 = H, R^2 = R^3 = R^4 = Me; \text{entry 52}) \), while performing the reaction in toluene, was not a suitable alteration. Azepine \( 10y \) was not observed upon attempted cyclization of ene-allene \( 9y \). When the methyl group on \( 9y \) is replaced with a hexyl group \( (R^1 = H, R^2 = R^3 = Me, R^4 = C_6H_{13}; \text{entry 53}) \) and substrate \( 9z \) is heated to reflux in toluene for 13 hours with 10 mol\% catalyst under an argon atmosphere no azepine \( 10z \) is observed. Given the low yields for conversion of \( 9h \) to \( 10h \) in 1,4-dioxane, it is assumed that both \( 9y \) and \( 9z \) would not react to an appreciable extent in this solvent. In an attempt to improve conversion of the 1,2,2-tribstituted alkene series by reducing the steric bulk of the alkene terminus, a cyclopropylidene moiety \( (R^1 = H, R^2 = R^3 = -(CH_2)_2-, R^4 = t\text{-Bu}; \text{entry 54}) \) was used but it too also provided the corresponding azepine \( 10A \) in a low 14% yield.
2.8 REACTIVITY OF ENE-ALLENES SUBSTITUTED AT THE PROXIMAL ALLYLIC POSITION OF THE ALKENE

2.8.1 Monosubstitution at the proximal allylic position

When refluxing ene-allene $9m$, a substrate that is mono-substituted at the allylic position, in DCE with 10 mol% catalyst the two azepine products $10m$ and $10m'$ were isolated in a 1.4:1 ratio, respectively (Eq. 36). Nearly the same product ratio was also obtained when executing the reaction in 1,4-dioxane, meaning the product distribution is independent of solvent employed. Azepine $10m$ is the major product and possesses the expected olefin regiochemistry that has been consistently obtained throughout the course of investigation. However, azepine $10m'$ which was isolated as a single diastereomer has not been previously observed. The formation of $10m'$ raises interesting mechanistic curiosities which are examined by implementing both reaction manifolds illustrated in scheme 2.

In order for C-H insertion to occur at the allenyl position of $9m$ (adapted from Path A, Scheme 2) a rehybridization of both the allenic methylene carbon and the digonal central carbon...
of the allene must take place ($9m \rightarrow Im'$, Scheme 11). To the best of our knowledge, the π-allyl-Rh-alkylidene hydride species (or variants thereof) represented in $Im'$ has not been previously reported. Subsequently, intermediate $Im'$ must undergo carbometallation onto the less activated alkene tether, providing $IIIm'$. Depending on both the diastereomer undergoing reaction and the rate of reductive elimination, the alkyl-Rh-H species $IIIm'$ has the possibility of bearing substantial A1,2 strain. This A1,2 strain experienced in $IIIm'$ has the possibility of leading to one of the diastereomers ($10m'$) is obtained, for it is likely that only one set of diastereomers (the enantiomeric pair) participate in the reaction, or isomerization of the unpreferred diastereomers occurs at some point during the course of the mechanism.

Applying path B of scheme 2 to substrate $9m$ shows that the allenyl methylene hydrogens are more accessible for β-hydride elimination than the allylic methine hydrogen, regardless of the reacting diastereomer ($IIIm'$ and $IIIm''$, Scheme 12). The subsequent intermediates $IIIm'$ and $IIIm''$ are subject to the same A1,2 strain as described for path A (above). This strain causes biasing which leads one to assume a preference of $IIIm'$ over $IIIm''$ due to its reduced steric interaction. An experiment incorporating a diastereomically pure ene-allene would provide further insight towards the operative mechanism.
2.8.2 Disubstitution at the proximal allylic position

To probe the effect of additional substitution at the allylic position, substrate 9B was subjected to the reaction conditions listed in eq. 37. Azepine 10B was obtained as the only isolable product which is assumed to be the result of the same type of cycloisomerization that produced azepine 10m' from 9m (Schemes 11 and 12). However, the difference in olefin regiochemistry between azepines 10B and 10m' is thought to arise from an in situ Rh-catalyzed alkene isomerization on the initial product 10B' (Eq. 38).

The production of 10B was surprising in that cycloisomerization of all other ene-allenes in the current study never resulted in a conjugated dihydroazepine. The gem-dimethyl groups on the assumed intermediate 10B' may facilitate the isomerization from 10B' $\rightarrow$ 10B (Eq. 38) by
providing an ideal conformation for Rh-reinsertion, due to steric interactions. The fact that azepine 10m’ did not undergo the same type olefin isomerization suggests the difficulty of this reinsertion by rhodium when there is a substituent at the allylic position within the ring.

2.9 EFFECT OF SUBSTITUTION AT THE PROXIMAL POSITION OF THE ALLENE AND AT THE ALLYLIC SITE OF THE ALLENYL-TETHER ON CYCLOISOMERIZATION

During the course of investigation towards applying the allenic Pauson-Kand reaction to library development, the formation of allenes via Ireland-Claisen rearrangement had been extensively employed (Eq. 39). We envisioned ene-allene 9C (Scheme 13) as being an ideal substrate for exploring the effect of further substitution on both the allylic allenyl-position and on the allene itself. This substrate was easily accessed through an Ireland-Claisen rearrangement followed by methylation of the resulting carboxylic acid and an alkylation of nitrogen (Scheme 13).

Scheme 13. Synthesis of ene-allene 9C.
Upon refluxing ene-allene 9C in 1,4-dioxane with 5 mol% catalyst under a carbon monoxide atmosphere, a reaction was observed that afforded azepine 10C as a single diastereomer in a 24% yield (Eq. 40).\textsuperscript{1} A probable explanation for this poor yield can be rationalized by implementing either path A or B of scheme 2.

\[
\begin{align*}
\text{CbzN} & \text{• CO}_2\text{Me} \\
\text{[Rh(CO)₂Cl]₂, (5 mol%), CO} & \text{dioxane, reflux, 5.3 h, 24\%}
\end{align*}
\]

\text{Eq. 40}

The intermediates for path B of scheme 2 are clearly depicted in the reaction manifold presented in scheme 14. The energy value of the allylic strain that metallocycle IIC\textsuperscript{'} experiences (>4 kcal/mol) is substantially larger than that of IIC (~0.8 kcal/mol) which serves to bias path D over path C (Scheme 14). However, the overall strain in path D must also include the gauche interactions caused by the substituents both α and β to nitrogen.

\textbf{Scheme 14.} Metallocycle mechanism for ene-allene 9C.

\textsuperscript{1} Yield was determined by NMR. The absolute configuration and olefin geometry remain to be determined.
This high energy intermediate **IIIC** poses a formidable activation barrier for the reaction, which may have been the basis for its poor yield.

In path A of scheme 2, represented clearly in scheme 15, the steric interactions are dependent on the reacting conformation. The steric contribution is minimized for the conformation shown as **9C** in scheme 15. Ene-allene **9C** can then undergo C-H insertion, resulting in **IC'** which carbometallates onto the allenic portion of the molecule to provide

![Scheme 15. C-H insertion mechanism for ene-allene 9C.](image)

intermediate **IIIC'**. The allylic strain shown in **IIIC'** is an eclipsing interaction with an energy value >4 kcal/mol. This interaction can be avoided by carbometallating the opposite side of the allene. Rotating the sp^3^-sp^2 bond in intermediate **IC'** (as illustrated) generates a steric interaction in the reacting conformer of **IC** which must be overcome in order to proceed with the carbometallation that results in **IIIC**. The methyl groups responsible for the allylic strain illustrated in **IIIC** do not lie in a plain but possess a dihedral angle of ~60° which is approximately equivalent to a gauche interaction (~0.8 kcal/mol). Biasing for either path E or F (Scheme 15) relies in the energy value of the steric interaction depicted in intermediate **1D**.
If this value, in addition to the allylic strain in **IIIC**, is larger than the allylic strain in **IIIC′**, then path **E** would be favored. In either case, the steric demand for conversion of **9C** to **10C** or **10C′** in scheme 15 is high and provides a rationale for the low product yield.

**2.10 CARBON MONOXIDE INSERTION INTO AN ENE-ALLENE: FORMATION OF AN α-ALKYLIDENE CYCLOPENTENONE**

Upon performing the reaction for conversion of **9b** to **10b** (Table 6), an interesting result was observed. Insertion of carbon monoxide had taken place to afford an α-alkylidene cyclopentenone in a poor but isolable 13% yield (entry 55, Table 9). Attempts at optimization of this result by employing various reaction conditions are represented in table 9 and summarized below.

![Chemical structure](image)

**Table 9. Optimization Attempts for CO Insertion.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst Loading (mol%)</th>
<th>Atmosphere</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>DCE</td>
<td>9</td>
<td>CO</td>
<td>13</td>
</tr>
<tr>
<td>56</td>
<td>DCE</td>
<td>10</td>
<td>CO/Ar</td>
<td>18</td>
</tr>
<tr>
<td>57</td>
<td>1,4-dioxane</td>
<td>5</td>
<td>CO</td>
<td>14</td>
</tr>
<tr>
<td>58</td>
<td>1,4-dioxane</td>
<td>6</td>
<td>CO/Ar</td>
<td>17</td>
</tr>
</tbody>
</table>

<sup>a</sup>Indicates isolated yield.

Employing a partial carbon monoxide/argon atmosphere, while maintaining DCE as solvent, improved the yield by only 5% (compare entry 55 to 56). Utilizing a complete carbon monoxide atmosphere and exchanging DCE for 1,4-dioxane as solvent decreased the yield by 4% (compare entry 56 to 57). Keeping 1,4-dioxane and implementing a partial carbon monoxide/argon atmosphere improved the yield by 3% (compare entry 57 to 58).
Overall, the optimized conditions (entry 56) only improved the yield by 5% in comparison to the conditions employed (entry 55) upon original discovery of this carbon monoxide insertion product 12b.

Only a single report of carbon monoxide insertion using ene-allenes is present in the literature (Eq. 26). Wender has communicated a related transformation utilizing diene-enes with the identical catalyst (Eq. 41). He asserts that further substitution on the diene moiety causes formation of multiple products with isolation of only a moderate amount of the desired carbon monoxide insertion product.

![Reaction Diagram](image)

### 2.11 ELABORATION OF AZEPINES

#### 2.11.1 Hydroboration

Efforts to demonstrate the usefulness of these tetrahydroazepines for the construction of complex molecules are underway. Hydroboration of 10f with 9-BBN was slow and did not consume the majority of starting material. The only isolable compound 18f (6% yield) indicated hydroboration followed by elimination (Eq. 42).
2.11.2 Tamao-Fleming oxidation

Upon treatment with a fluoride source as the initial step in a Tamao-Fleming oxidation of azepine 10k, only protodesilation was witnessed to provide azepines 18k and 10D in 27% and 16% yields, respectively (Eq. 43).

\[
\begin{align*}
\text{TsN} & \quad \text{SiMe}_2\text{Bn} \\
\text{10k} & \quad \text{Fluoride source, THF:MeOH} \\
0^\circ \text{C to rt.} & \quad \text{TBAF: 27%, 18k} \\
& \quad \text{CF: identical TLC} \\
& \quad \text{16%, 10D} \\
& \quad \text{identical TLC}
\end{align*}
\]

Eq. 43

2.11.3 Reduction

Reduction of azepine 10k with Palladium on carbon under a hydrogen atmosphere (50 psi) selectively reduced the endocyclic enamide moiety, proceeding in 99% yield and leaving the exocyclic olefin intact (Eq. 44). Trials using 1 atm of hydrogen lead to decomposition along with the desired product.

\[
\begin{align*}
\text{TsN} & \quad \text{SiMe}_2\text{Bn} \\
\text{10k} & \quad \text{Pd on C, EtOH} \\
\text{H}_2 (50 \text{ psi}), \text{rt, 99\%} & \quad \text{TsN} \\
& \quad \text{SiMe}_2\text{Bn} \\
& \quad \text{19k}
\end{align*}
\]

Eq. 44

Reduction of azepine 10f under identical conditions as those utilized for 10k afforded the fully reduced hexahydroazepine 20f and a partially reduced tetrahydroazepine 21f in a 1.1:1 ratio, respectively (Eq. 45). Azepine 21f is a result of enamide reduction followed by isomerization of the exocyclic olefin into the ring. Reduction under 1 atm of hydrogen revealed similar results.
Selective reduction of the enamide functionality of 10f could be achieved with modified reductive amination conditions to furnish the desired hexahydroazepine 19f in 93% yield (Eq. 46). The procedure was tedious and required constant addition of reagents to achieve complete consumption of the starting material. An endeavor to simplify the method by using AcOH/NaBH$_3$CN displayed the same reaction trend and also did not improve the yield (57%).
3.0 CONCLUSIONS

Mitsunobu reactions provided key substrates in higher yields when employing allenyl-tosylamides as nucleophiles with allylic alcohols as pro-electrophiles. Yields were diminished when allylic tosylamides were utilized as nucleophiles with allenyl-allylic alcohols as pro-electrophiles.

A novel carbon-carbon bond forming cycloisomerization reaction resulting in tetrahydroazepines was discovered which proved to be tolerable to a host of various substrates. Long alkyl-chain ene-allene tethers reacted in lower yields compared to their branched alkyl-counterparts. Vinyl-silane and styryl-derived substrates reacted in high yield when employing a tert-butyl substituted allene. Phenyl substitution on the allene (ene-allene 9e) only provided azepine products in ethereal solvents. The substrate possessing an olefin with 1,1,2-trisubstitution, ene-allene 9i, provided the azepine in an acceptable 78% yield while 1,2,2-trisubstituted alkenyl-substrates, ene-allenes 9h and 9A, reacted with poor conversion (14% and 14%, respectively).

Three major factors contributed to the efficiency of this azepine forming cycloisomerization: steric bulk of the alkene and allene substituents, solvent, and atmosphere. The yield of cyclization is surprisingly higher when the substrate possesses bulkier substituents at the alkene and allene termini. This enhanced reactivity due to steric bulk is limited however to 1,2-disubstituted alkenyl- and 1,3-disubstituted allenyl-substrates. Implementing the use of
ethereal solvents, 1,4-dioxane particularly, facilitated the reaction by increasing both the rate and yield of cyclization. In the cases of substrates 9d and 9f, utilizing 1,4-dioxane allowed cyclization to occur when is was not previously observed or observed in trace amounts in DCE.

The lower boiling point solvents THF and DME were acceptable solvents for the cycloisomerization, but did prolong the reaction time when compared to 1,4-dioxane. Similarly, carbon monoxide retarded reaction progression and argon accelerated substrate conversion. A higher catalyst loading increases product formation and accelerates the reaction time.

A deuterium labeling study aided in the postulation of two working mechanisms (Scheme 2). The first activates the olefin moiety by allylic C-H insertion then closes down on the central carbon of the allene to result in 7-endo-dig cyclization followed by reductive elimination. The second mechanism effects transformation by way of a bridged metallocycle which undergoes β-hydride elimination followed by reductive elimination.

During the course of our examination of this cycloisomerization reaction, a novel carbon monoxide insertion was observed for ene-allene 9b to afford α-alkylidene cyclopentenone 12b in an 18% yield (Table 9). Efforts to improve the yield were not met with success. Selective reduction of the enamide moiety was achieved for azepines 10k and 10f, under differing conditions, to provide azepines 19k and 19f in 99% and 93% yield, respectively.

Further substrate exploration is necessary for application of this azepine forming methodology to library development or natural product synthesis. Ideally, additional investigation into this cycloisomerization reaction would lead to the development of milder conditions (room temperature verses reflux) and broader substrate tolerance.
APPENDIX A

EXPERIMENTAL

Unless otherwise noted, all reactions were carried out in flame dried glassware under a nitrogen atmosphere and commercially available compounds were used as received. Solvent column purification under a nitrogen atmosphere employing alumina and activated Q5 material was utilized to purify tetrahydrofuran (THF) and diethyl ether (ether). Dichloromethane (DCM) was purified with an alumina column under a nitrogen atmosphere. Toluene and dichloroethane (DCE) were freshly distilled from CaH2 prior to use. 1,4-Dioxane and 1,2-dimethoxyethane (DME) were freshly distilled from LiAlH4 prior to use. Methanol (MeOH), acetonitrile (MeCN), and dimethylformamide (DMF) were dried with and stored over 4Å molecular sieves. Purification of compounds by flash chromatography was performed using silica gel (32-63 µm particle size, 60 Å pore size). Analyses by TLC were performed on silica gel 60 F254 plates with a 250 µm thickness layer. Gas chromatography was performed on a gas chromatograph with a 15 ft RTX-5 column containing 5% diphenyl-crossbonds and a 95% dimethylpolysiloxane stationary phase with an internal diameter of 0.25 mm and film thickness of 0.25 µm. Purification by HPLC was performed using a silica gel column (5 µm packing, 250 mm x 10 mm). Nuclear magnetic resonance spectra (1H and 13C) were obtained on a 300 MHz instrument, reporting chemical shifts (δ) relative to their respective residual solvent peak. All NMR spectra were obtained at room temperature unless otherwise specified. Infrared spectra were obtained on
an FT-IR instrument. Mass spectrometry (EI) was performed on a high resolution mass spectrometer. Stereoisomers obtained are denoted with a superscript and a description at the bottom of the page. When possible, diastereomeric ratios are reported according to their relative integration in the $^1$H NMR spectrum or as a result of HPLC separation. Designation of $^1$H NMR splitting patterns are as follows: b = broad, d = doublet, h =heptet, m = multiplet, p = pentet, q = quartet, s = singlet, t = triplet. All melting points are uncorrected.

### A.1 SYNTHESIS OF ENE-ALLENES

The synthesis of each ene-allene is described sequentially, including an explanation of the synthesis(es) of the requisite precursor(s) for each substrate.

\[
\begin{array}{c}
\text{Cl} \\
\text{TsHN} \\
\end{array}
\xrightarrow{\text{13c}}
\begin{array}{c}
\text{TsHN} \\
\end{array}
\]

**$N$-[(E)-2-Butenyl]-4-methylbenzenesulfonamide (13c):**

To a solution of $p$-toluenesulfonamide (11.89 g, 69.44 mmol) in MeCN (180 mL) was added K$_2$CO$_3$ (36.89 g, 266.9 mmol) and the slurry heated to 50 °C whereupon (E)-1-chloro-2-butene (5.2 mL, 53 mmol) was added dropwise. After 27 h of heating at 50 °C, the solution was concd in vacuo and the crude solid partitioned between ethyl acetate/H$_2$O (200 mL/250 mL). The aqueous layer was separated and extracted with ethyl acetate (2 x 200 mL), acidified to pH 8 using HCl (3 M), and re-extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over MgSO$_4$, and concd in vacuo. The crude solid was purified via silica gel chromatography (ethyl acetate-hexanes 1:13-1:2) to afford 6.35 g of tosylamide 13c as an off-white solid in 53% yield (mp 57-60 °C). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.75 (1/2 AA'XX' d, $J = 8.3$ Hz, 2H), 7.32 (1/2 AA'XX' d, $J = 8.5$ Hz, 2H), 5.58 (dqt, $J = 15.2$, 6.5, 1.3 Hz, 1H), 5.34
(dtq, $J = 15.2, 6.4, 1.6$ Hz, 1H), 4.38-4.37 (bm, 1H), 3.51 (tdq, $J = 6.3, 1.2, 1.2$ Hz, 2H), 2.44 (s, 3H), 1.61 (ddt, $J = 6.4, 1.4, 1.3$ Hz, 3H).

2,3-Decadien-1-ol (14d): A solution of diisopropylamine (14 mL, 100 mmol) in 1,4-dioxane (305 mL) at rt was added CuBr (4.31 g, 30 mmol) and heptaldehyde (14 mL, 100 mmol). The solution was subsequently heated to 90 °C for 30 min to result in a light blue color. To this solution was added propargyl alcohol (15 mL, 250 mmol) and it was heated to 110 °C for 24 h whereupon substantial precipitate had formed. Upon cooling to rt, the mixture was vacuum filtered and the filtrate concd in vacuo. The resulting brown oil was dissolved in ethyl acetate (300 mL) and washed with HCl aq (4 M, 50 mL), H$_2$O (2 x 75 mL), and saturated NaHCO$_3$ (50 mL) whereupon a precipitate had formed. The solids were removed via vacuum filtration and the organic layer was washed with H$_2$O (50 mL), dried over Na$_2$SO$_4$, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:3) to afford 2.28 g of alcohol 14d as a light yellow oil in 15% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 5.36-5.27 (m, 2H), 4.12 (dd, $J = 5.4, 3.3$ Hz, 2H), 2.07-1.99 (m, 2H), 1.43-1.28 (m, 8H), 0.91-0.87 (m, 3H).

N-[(E)-2-butenyl]-N-(2,3-decadienyl)-4-methylbenzenesulfonamide (9a): Preparation of ene-allene 9a has previously been described.
2-(1,1-Dimethyl-2-propynyloxy)-tetrahydropyran (22):\textsuperscript{64} To a solution of 2-methyl-3-butyn-2-ol (11.5 mL, 119 mmol) in DCM (200 mL) was added 3,4-dihydro-2H-pyran (11.4 mL, 125 mmol) followed by PPTS (1.50 g, 5.97 mmol). After 31 h at rt excess 3,4-dihydro-2H-pyran (2.17 mL, 23.7 mmol) was added and after an additional 16 h the solution was washed with (½) saturated brine (3 x 30 mL), brine (40 mL), dried over Na$_2$SO$_4$, and carefully concd in vacuo (bath temp 0 °C). The residual DCM was removed by simple distillation and the THP-ether 22 was distd in vacuo (28 torr, 76 °C) to afford a 3.00 g fraction (91% pure by $^1$H NMR) and a 14.47 g fraction (88% pure by $^1$H NMR) to give a combined amount of 17.47 g in a calc'd 77% yield. $^1$H NMR (C$_6$D$_6$) $\delta$: 5.38-5.35 (m, 1H), 3.87 (ddd, $J = 11.2, 8.2, 3.4$ Hz, 1H), 3.42-3.35 (m, 1H), 2.07 (s, 1H), 1.79-1.61 (m, 4H), 1.62 (s, 3H), 1.51 (s, 3H), 1.37-1.20 (m, 2H).

2,3-Pentadien-1-ol (14c):\textsuperscript{65} To a solution of THP-ether 22 (89% purity, 17.47 g, 91.96 mmol) in THF (163 mL) at -78 °C was added $n$-butyllithium (1.6 M in hexanes, 92 mL, 147 mmol) dropwise. This solution was held at -78 °C for 30 min whereupon $p$-formaldehyde (undried, 5.88 g, 196 mmol) was added in portions. The mixture was slowly allowed to warm to rt and TLC analysis 24 h after $p$-formaldehyde addition indicated reaction completion. The solution was concd in vacuo and partitioned between ether/saturated NH$_4$Cl (300 mL/50 mL). The organic layer was washed with saturated NH$_4$Cl (2 x 40 mL), brine (2 x 50 mL), dried over Na$_2$SO$_4$, and concd in vacuo to afford 19.47 g of propargyl alcohol 23a in quantitative yield ($^1$H NMR was contaminated with minor impurities). $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$: 5.42-5.38 (m, 1H), 3.93 (d, $J = 6.1$ Hz, 1H), 3.46-3.86 (m, 1H), 3.37-3.30 (m, 1H), 1.83-1.50 (m, 3H), 1.64 (s, 3H), 1.53 (s, 3H), 1.40-1.15 (m, 3H). To a suspension of LiAlH$_4$ (670 mg, 17.7 mmol) in ether
(30 mL) at 0 °C was added a solution of the crude alcohol 23a (3.49 g, 17.6 mmol) in ether (8 mL) dropwise. The slurry was held at 0 °C until no further gas evolution whereupon it was heated at reflux for 4.3 h. The slurry was then cooled to 0 °C and carefully quenched with H₂O (Caution! Rapid gas evolution!). The solids were removed via vacuum filtration and the filtrate was dried over MgSO₄ and concd in vacuo to afford 1.24 g of allene 14c in a 72% yield (¹H NMR contained minor impurities).¹⁶¹H NMR (300 MHz, CDCl₃) δ: 5.19 (th, J = 2.8, 2.8 Hz, 1H), 4.07 (d, J = 5.6 Hz, 2H), 1.73 (s, 3H), 1.72 (s, 3H), 1.43 (bs, 1H).

\[ \text{TsN} - \text{Allyl} - \text{TsNH} \]
\[ \text{HO} \]
\[ \rightarrow \]
\[ \text{TsN} - \text{N} \]
\[ \text{9b} \]

*N-allyl-N-(4-methyl-2,3-pentadienyl)-4-methylbenzenesulfonamide (9b):* Preparation of ene-allene 9b has previously been described.²⁰

\[ \text{t-BuH} + \text{THPO} \rightarrow \text{OMe} \]
\[ \text{24a} \]

2-(5,5-Dimethyl-4-methoxy-2-hexynyloxy)-tetrahydropyran (24a): To a solution of n-butyllithium (1.6 M in hexanes, 20.0 mL, 32.0 mmol) in THF (81 mL) at -78 °C was added a solution of tetrahydro-2-(2-propynyloxy)-2H-pyran (4.0 mL, 28 mmol) in THF (15 mL). After 20 min at -78 °C trimethylacetaldehyde (3.1 mL, 28 mmol) was added as a solution in THF (8 mL). After 30 additional min at -78 °C neat methyliodide (7.0 mL, 0.11 mol) was added and the cold bath was removed. Upon reaching -20 °C HMPA (8.0 mL, 46 mmol) was added and TLC analysis indicated complete conversion after 45 min at rt. The solution was concd in vacuo and poured into brine (150 mL). The aqueous layer was extracted with ether (3x 100 mL) and the combined organic layer was washed with H₂O (3 x 100 mL), brine (100 mL), dried over K₂CO₃.
and concd in vacuo to afford 7.23 g of the crude THP-ether 24a as a yellow oil in quantitative yield.

5,5-Dimethyl-4-methoxy-2-hexyn-1-ol (23b). To a solution of crude 24a (6.8 g, 28 mmol) in MeOH (40 mL) was added p-toluenesulfonic acid mono-hydrate (713 mg, 3.45 mmol) in one portion. After 3.6 h at rt, another portion of p-toluenesulfonic acid mono-hydrate was added (71 mg, 0.37 mmol) and the solution was quenched with saturated NaHCO₃ (3.4 mL) after an additional 1.8 h. The mixture was concd in vacuo and poured into 100 mL of H₂O. The aqueous layer was extracted with ether (2 x 60 mL, then 25 mL) and the combined organic layers were dried over K₂CO₃, and concd in vacuo to afford 4.54 g of alcohol 23b in quantitative yield (¹H NMR possessed a slight amount of ether). ¹H NMR (300 MHz, CDCl₃) δ: 4.34 (d, J = 1.5 Hz, 2H), 3.54 (t, J = 1.6 Hz, 1H), 3.41 (s, 3H), 0.98 (s, 9H).

5,5-Dimethyl-2,3-hexadien-1-ol (14a). To a suspension of LiAlH₄ (989 mg, 26.1 mmol) in ether (250 mL) was added 5,5-dimethyl-4-methoxy-2-hexyn-1-ol 23b (1.00 g, 6.40 mmol) as a solution in ether (10 mL) dropwise. Ether (200 mL) was then added and the suspension was subsequently cooled to -78 °C whereupon I₂ (4.87 g, 19.2 mmol) was added in one portion. After an additional 3.5 h at -78 °C the suspension was quenched with saturated Rochelle’s salt aq (25 mL) and saturated Na₂S₂O₃ aq (25 mL) whereupon it was allowed to warm to 0 °C. After 45 min at 0 °C the organic layer was decanted off and the aqueous layer was extracted with ether (2 x 30 mL). The combined organic layers were dried over K₂CO₃ and concd in vacuo. The crude
oil was purified by silica gel chromatography (ether-pentane 1:3-1:2) to afford 500 mg of alcohol 14a as a clear oil in 62 % yield (\(^1\)H NMR possessed impurities). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 5.41 (q, \(J = 5.9\) Hz, 1H), 5.33 (dt, \(J = 6.1, 3.0\) Hz, 1H), 4.12 (ddd, \(J = 5.8, 5.8, 2.9\) Hz, 1H), 1.44 (t, \(J = 6.0\) Hz, 1H), 1.06 (s, 9H).

\[
\begin{array}{c}
\text{Ph} \equiv \text{(CHO)}_n \equiv \text{OH} \\
\text{Ph} \equiv \text{NH}_2
\end{array}
\]

3-Phenyl-2-propyn-1-ol (25a):\(^{11}\) A 250 mL round bottom flask was charged with phenyl acetylene (5.00 g, 49.0 mmol) and THF (100 mL). To the solution at -78 °C was added \(n\)-butyllithium (1.6 M in hexanes, 40 mL, 64 mmol) dropwise via syringe. To the solution after 40 min at -78 °C was added paraformaldehyde (2.94 g, 98.0 mmol) in one portion. TLC analysis indicated reaction completion after an additional 5.3 h whereupon it was quenched with saturated NH\(_4\)Cl (20 mL) and concd in vacuo. The crude residue was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (30 mL), dried over Na\(_2\)SO\(_4\), and concd in vacuo to afford 25a as a yellow oil.

\[
\begin{array}{c}
\text{Ph} \equiv \text{OH} \\
\text{Ph} \equiv \text{NH}_2
\end{array}
\]

\(N\)-(\(E\))-3-Phenyl-2-propenyl]amine (26a):\(^{11}\) To a solution of alcohol 25a (~49 mmol) and triethylamine (9.6 mL, 69 mmol) in DCM (200 mL) at 0 °C was added methanesulfonyl chloride (4.6 mL, 59 mmol) dropwise. Reaction completion was observed by TLC after 2.8 h whereupon it was quenched with saturated NH\(_4\)Cl (20 mL), washed with brine (30 mL), 1:1 brine/saturated NaHCO\(_3\) (2 x 30 mL), and again with brine (30 mL). The organic layer was dried over MgSO\(_4\) and concd in vacuo to provide a yellow oil. To this oil dissolved in DMF (50 mL) was added NaN\(_3\) (10.0 g, 154 mmol). The resulting solution was held at rt for 1 h followed by 40 °C

\(^{11}\) Reaction sequence was performed by Dr. Hongfeng Chen. References were not provided.
heating overnight. To the solution was added H₂O (200 mL) and the mixture was extracted with ether (5 x 100 mL). The combined organic layers were washed with H₂O (5 x 20 mL), brine (3 x 20 mL), dried over MgSO₄, and concd in vacuo to give the crude azide as a yellow oil. To this oil dissolved in ether (150 mL) at 0 °C was slowly added LiAlH₄ (10.0 g, 256 mmol) in portions. After 4 h, NaOH aq (1 N) was cautiously added followed by H₂O until the precipitate became white. The solids were removed by vacuum filtration and the filtrate was dried over Na₂SO₄ followed by concn in vacuo to afford 2.48 g of amine 26a in 38% yield (3 steps).

\[ \text{PhH}_2N \text{Ph} \rightarrow \text{TsHN Ph} \]

\[ \text{26a} \rightarrow \text{13a} \]

\( N\text{-[\((E)\text{-3-Phenyl-2-propenyl}\text{-4-methylbenzenesulfonamide (13a)\}:}} \)

To a solution of amine 26a (2.48 g, 18.6 mmol) and triethylamine (7.1 mL, 51 mmol) in DCM (50 mL) at 0 °C was added \( p \)-toluenesulfonfyl chloride (3.24 g, 17.0 mmol) in one portion. The temperature was then slowly raised to rt. Upon reaction completion (TLC), the solvent was removed in vacuo and the crude residue partitioned between ethyl acetate (200 mL) and saturated NH₄Cl/H₂O (1:12, 30 mL). The organic layer was washed with saturated NH₄Cl (30 mL), brine (2 x 30 mL), dried over Na₂SO₄, and concd in vacuo to afford 13a as a pale yellow solid (mp 80-94 °C, yield not determined). \(^1\)H NMR (300 MHz, CDCl₃) δ: 7.79 (d, \( J = 8.2 \) Hz, 2H), 7.37-7.22 (m, 7H), 6.44 (d, \( J = 15.8 \) Hz, 1H), 6.02 (dt, \( J = 15.9, 6.3 \) Hz, 1H), 4.75 (t, \( J = 6.1 \) Hz, 1H), 3.76 (ddd, \( J = 6.3, 6.3, 1.0 \) Hz, 2H), 2.42 (s, 3H).

\[ \text{TsHN} \text{Ph} + \text{HO} \text{-t-Bu} \rightarrow \text{TsHN} \text{-t-Bu} \]

\[ \text{13a} + \text{14a} \rightarrow \text{9c} \]

\( \text{General Procedure for the Mitsonobu Reaction: } N\text{-[\((E)\text{-3-phenyl-2-propenyl}\text{-4-methylbenzenesulfonamide (9c)\}:}} \)

To a solution of 5,5-dimethyl-2,3-
hexadien-1-ol 14a (98 mg, 0.773 mmol) in THF (2.28 mL) was added N-[(E)-3-phenyl-2-propenyl]-4-methylbenzenesulfonamide 13a (290 mg, 1.01 mmol) and PPh₃ (263 mg, 0.900 mmol). The flask was then cooled to 0 °C and DIAD (197 µL, 1.00 mmol) was added dropwise over a period of 15 min. At this rate the yellow color intensity dissipated after each drop. After 16 h, the solvent was removed under reduced pressure and the crude residue purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:6) to afford 182 mg of ene-allene 9c as a white solid (mp 90-99 °C) in 60% yield. The ¹H NMR showed 8% of the cis-alkene impurity. ¹H NMR (300 MHz, CDCl₃) δ: 7.74 (d, J = 8.2 Hz, 2H), 7.34-7.21 (m, 7H), 6.45 (d, J = 15.9 Hz, 1H), 5.96 (dt, J = 15.8, 6.7 Hz, 1H) 5.15 (dt, J = 6.2, 2.4 Hz, 1H), 4.99 (dt, J = 7.0, 6.5 Hz, 1H), 4.02 (d, J = 6.7 Hz, 2H), 3.91 (1/2 AB ddd, J = 15.2, 6.6, 2.4 Hz, 1H), 3.82 (1/2 AB ddd, J = 15.2, 7.2, 2.2 Hz, 1H), 2.42 (s, 3H), 1.00 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ: 202.6, 143.2, 137.7, 136.3, 133.9, 129.7, 128.5, 127.8, 127.2, 126.4, 123.8, 104.6, 88.3, 48.6, 46.6, 31.8, 30.1, 21.5; IR (KBr pellet) 3088, 3053, 3032, 3022, 2955, 2925, 2868, 1957, 1598, 1500, 1445, 1363, 1342 cm⁻¹; MS m/z (%) 91 (43), 117 (100), 212 (34), 286 (32), 338 (29), 380 (26), 395 (17); EI-HRMS calcd for C₂₄H₂₉NO₂S [M+] m/z: 395.1919, found: 395.1938.

N-(2-Butynyl)-4-methylbenzenesulfonamide (27): To a solution of 2-butyn-1-ol (5.34 mL, 71.4 mmol) and triethylamine (14.3 mL, 103 mmol) in DCM (150 mL) at 0 °C was added methanesulfonyl chloride (5.52 mL, 71.3 mmol) dropwise. To the slurry after 1 h at 0 °C was added saturated NH₄Cl (20 mL) and the organic layer was washed with saturated NaHCO₃:brine:H₂O (1:2:1, 3 x 100 mL), brine (2 x 50 mL), dried over MgSO₄ and concd in vacuo to afford a yellow oil. To this oil that was dissolved in DMF (100 mL) at 0 °C was added NaN₃ (9.27 g, 143 mmol) and the solution was allowed to warm to rt. After an additional 1 h the
solution was heated to 45 °C for 13.5 h whereupon it was diluted with H₂O (200 mL) and extracted with ether (5 x 100 mL). The combined organic layers were washed with H₂O (2 x 100 mL), dried over MgSO₄, and concd in vacuo to afford a crude oil. To this oil dissolved in ether (50 mL) at 0 °C was added LiAlH₄ (0.60 g, 16 mmol) in portions. After 2 h at 0 °C the slurry was quenched with minimal H₂O. The slurry was filtered and the filter cake was washed with ether (30 mL). The organic layer was carefully concd in vacuo to afford a yellow liquid. To this liquid dissolved in DCM (30 mL) at 0 °C was added triethylamine (3.7 mL, 27 mmol) and p-toluenesulfonylchloride (2.00 g, 10.5 mmol) whereupon it was allowed to warm to rt. After 4 h at rt the solvent was removed in vacuo and the crude residue was partitioned between ethyl acetate/H₂O (100 mL/20 mL), washed with brine (2 x 20 mL), dried over Na₂SO₄, and concd in vacuo. The resulting residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:4-1:1) to afford 1.34 g of tosylamide 27 in 8% yield (4 steps). ¹H NMR CDCl₃ δ: 7.78 (1/2 AA'XX' d, J = 8.3 Hz, 2H), 7.35-7.29 (m, 2H), 4.52-4.47 (bm, 1H), 3.77 (dq, J = 6.0, 2.4 Hz, 2H), 2.44 (s, 3H), 1.61 (t, J = 2.4 Hz, 3H).

\[
\text{TsHN} \quad \text{TsHN} \\
\begin{array}{c}
\text{27} \\
\text{13b}
\end{array}
\]

N-[(Z)-2-Butenyl]-4-methylbenzenesulfonamide (13b): A suspension of Lindler’s catalyst (5% Pd on CaCO₃ poisoned with Pb, 65 mg, 0.031 mmol) and N-(2-butynyl)-4-methylbenzenesulfonamide 27 (1.29 g, 5.78 mmol) in MeOH (20 mL) was evacuated and charged with H₂ (5x). To the suspension was added ethylenediamine (0.46 mL, 7.6 mmol) and the suspension was then evacuated and charged with H₂. After 25 h at rt the suspension was filtered and the filter cake was washed with MeOH. The solution was concd in vacuo and the crude residue was purified by silica gel chromatography to afford 1.26 g of tosylamide 13b in a
yield of 94%. 1H NMR CDCl₃ δ: 7.77 (1/2 AA’XX’ d, J = 8.3 Hz, 2H), 7.32 (1/2 AA’XX’ d, J = 8.0 Hz, 2H), 5.58 (dqt, J = 10.8, 6.9, 1.4 Hz, 1H), 5.30 (dtq, J = 10.8, 7.0, 1.7 Hz, 1H), 4.38-4.35 (bm, 1H), 3.62 (bt, J = 6.4 Hz, 2H), 2.44 (s, 3H), 1.57-1.53 (m, 3H).

N-[(Z)-2-Butenyl]-N-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9d): The general procedure for the Mitsunobu reaction (p. 56) was followed using N-[(Z)-2-butenyl]-4-methylbenzenesulfonamide 13b (154 mg, 0.683 mmol), PPh₃ (188 mg, 0.718 mmol), DIAD (140 µL, 0.711 mmol), and 5,5-dimethyl-2,3-hexadien-1-ol 14a (69 mg, 0.549 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 102 mg of ene-allene 9d as a clear oil in 55% yield. 1H NMR (300 MHz, CDCl₃) δ: 7.71 (1/2 AA’XX’ d, J = 8.3 Hz, 2H), 7.29 (1/2 AA’XX’ d, J = 8.1 Hz, 2H), 5.60 (dqt, J = 10.9, 6.9, 1.6 Hz, 1H), 5.27 (dtq, J = 10.8, 6.9, 1.7 Hz, 1H), 5.14 (dt, J = 6.2, 2.4 Hz, 1H), 5.00 (dt, J = 7.4, 6.2 Hz, 1H), 3.90 (d, J = 6.8 Hz, 2H), 3.89 (1/2 AB ddd, J = 15.0, 6.2, 2.5 Hz, 1H), 3.71 (1/2 AB ddd, J = 15.0, 7.5, 2.2 Hz, 1H), 2.42 (s, 3H), 1.62 (dd, J = 6.9, 0.8 Hz, 3H), 1.00 (s, 9H); 13C NMR (75 MHz, CDCl₃) δ: 202.4, 143.0, 137.9, 129.8, 128.3, 127.1, 124.9, 104.4, 88.8, 46.7, 43.1, 31.8, 30.0, 21.4, 12.9; IR (neat) 3027, 2960, 2925, 2863, 1969, 1611, 1455, 1342 cm⁻¹; MS m/z (%) 91 (100), 110 (49), 155 (85), 184 (95), 238 (53), 333 (11); EI-HRMS calcd for C₁₉H₂₇NO₂S [M+] m/z: 333.1763, found: 333.1748.

iii The sample possessed 3% ethyl acetate by 1H NMR.
4-Phenyl-2,3-butadien-1-ol (14b): Compound 24b was prepared as described for preparation of 24a (p. 53) using tetrahydro-2-(2-propynyloxy)-2H-pyran (3.00 mL, 21.3 mmol), benzaldehyde (2.15 mL, 21.2 mmol), n-butyllithium (1.6 M in hexanes, 14.7 mL, 23.5 mmol), iodomethane (5.3 mL, 85 mmol), HMPA (6.0 mL, 35 mmol), and THF (80 mL) to afford 5.87 g of the crude ether in quantitative conversion. Compound 23c was prepared as described for preparation of 23b (p. 54) using p-toluenesulfonic acid monohydrate (405 mg, 2.13 mmol) and MeOH (30 mL) to result in 4.04 g of the crude alcohol in quantitative conversion. Compound 14b was prepared as described for preparation of 14a (p. 54) using LiAlH4 (1.028 g, 27.1 mmol), alcohol 23c (1.34 g, 6.98 mmol), and ether (520 mL), which after purification by silica gel chromatography (ether-pentanes 1:3-1:2) afforded 296 mg of the alcohol in a calculated yield of 27%. IV 1H NMR (300 MHz, CDCl3) δ: 7.39-7.17 (m, 5H), 6.33 (dt, \( J = 6.2, 3.1 \) Hz, 1H), 5.80 (q, \( J = 6.0 \) Hz, 1H), 4.28-4.26 (m, 2H), 1.52 (bt, \( J = 5.8 \) Hz, 1H).

![Diagram](image-url)

N-[(E)-2-Butenyl]-N-(4-phenyl-2,3-butadienyl)-4-methylbenzenesulfonamide (9e): The general procedure for the Mitsunobu reaction (p. 56) was followed using N-[(E)-2-butenyl]-4-methyl-benzenesulfonamide 13c (635 mg, 2.82 mmol), PPh\(_3\) (665 mg, 2.53 mmol), DIAD (500 µL, 2.53 mmol), and 4-phenyl-2,3-butadien-1-ol 14b (275 mg, 1.88 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:6) to afford 366 mg of ene-allene 9e as a cloudy oil in 55% yield. 1H NMR (300 MHz, CDCl3) δ: 7.71 (1/2 AA’XX’ d, \( J = 8.3 \) Hz, 2H), 7.33-7.26 (m, 4H), 7.23-7.16 (m, 3H), 6.12 (dt, \( J = 6.4, 2.4 \) Hz, 1H), 5.55 (dqt, \( J = 15.2, 6.5, 1.2 \) Hz, 1H), 5.38 (q, \( J = 6.7 \) Hz, 1H), 5.28 (dtq, \( J = 15.2, 6.7, 1.6 \)

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IV The sample possessed 7% of ether by 1H NMR.
Hz, 1H), 3.96-3.90 (m, 2H), 3.81 (bd, \(J = 6.7\) Hz, 2H), 2.42 (s, 3H), 1.60 (ddt, \(J = 6.4, 1.5, 1.1\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \(\delta\): 206.1, 143.2, 137.6, 133.6, 130.8, 129.6, 128.6, 127.2, 127.2, 126.8, 125.1, 95.9, 90.7, 48.8, 45.3, 21.5, 17.6; IR (neat) 3086, 3063, 3032, 2925, 2858, 1947, 1729, 1602, 1496, 1450, 1342, 1158 cm\(^{-1}\); MS \(m/z\) (%): 55 (100), 91 (71), 115 (100), 128 (63), 130 (78), 155 (84), 184 (73), 238 (95), 353 (23); EI-HRMS calcd for C₂₁H₂₃NO₂S [M+] \(m/z\): 353.1450, found: 353.1436.

\(\text{TsN}t\)-Bu

\(\text{TsHN}t\)-Bu

13c

14a

9g

\(\text{N-}[(\text{E})-2\text{-Butenyl}]-\text{N-(5,5-dimethyl-2,3-hexadienyl)}\)-4-methylbenzenesulfonamide (9f): The general procedure for the Mitsunobu reaction (p. 56) was followed using \(\text{N-}[(\text{E})-2\text{-butenyl)}\)-4-methyl-benzenesulfonamide 13c (822 mg, 3.65 mmol), PPh₃ (958 mg, 3.65 mmol), DIAD (720 \(\mu\)L, 3.66 mmol), and 5,5-dimethyl-2,3-hexadien-1-ol 14a (354 mg, 2.81 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 561 mg of ene-allene 9f as a clear oil in 60% yield. \(^1\)H NMR matched that previously reported in the literature.\(^{20}\)

\(\text{t-Bu OH}\)

\(\text{t-Bu NH Ts}\)

14a

15a

\(\text{N-(5,5-Dimethyl-2,3-hexadienyl)}\)-4-methylbenzenesulfonamide (15a): To a soln. of 5,5-dimethyl-2,3-hexadien-1-ol 14a (364 mg, 2.89 mmol) and triethylamine (570 \(\mu\)L, 4.09 mmol) in DCM (14.5 mL) at -30 °C was added methansulfonyl chloride (270 \(\mu\)L, 3.49 mmol) dropwise. Precipitation was observed after 10 min and TLC analysis indicated reaction completion after 20 min. The crude solution was washed with H₂O (2 x 15 mL), brine (15 mL), dried over MgSO₄, and concd in vacuo to afford 531 mg of crude mesylate as a light yellow oil in 90% yield.\(^{69}\) This
crude oil was dissolved in MeCN (8.7 mL) and transferred via cannula to a flask charged with p-toluenesulfonamide (666 mg, 3.89 mmol) and K₂CO₃ (anhyd, 1.80 g, 13.0 mmol). The mixture was heated to 50 °C for 13 h, whereupon TLC analysis indicated complete consumption of starting material. The mixture was then concd in vacuo and partitioned between H₂O/ethyl acetate (50 mL/50 mL). The aqueous layer was extracted with ethyl acetate (2 x 25 mL) and the combined organic layers were washed with brine (20 mL), dried over MgSO₄, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:7) to afford 501 mg of allene 15a as a white solid (mp 47-50 °C) in 69% yield (1H NMR possessed a slight amount of impurities). ¹H NMR (300 MHz, CDCl₃) δ: 7.75 (1/2 AA’XX’ d, J = 8.2 Hz, 2H), 7.29 (1/2 AA’XX’ d, J = 8.5 Hz, 2H), 5.19 (dt, J = 6.2, 3.0 Hz, 1H), 5.10 (q, J = 6.0 Hz, 1H), 4.61 (bt, J = 5.6 Hz, 1H), 3.54 (ddd, J = 5.9, 5.9, 3.0 Hz, 2H), 2.41 (s, 3H), 0.98 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ: 200.8, 143.4, 137.1, 129.6, 127.1, 106.4, 89.4, 42.1, 31.8, 30.0, 21.4; IR (thin film) 3257, 2960, 2930, 2858, 1962, 1711, 1604, 1460, 1424, 1327, 1158 cm⁻¹; MS m/z (%) 91 (100), 155 (91), 184 (70), 264 (45), 279 (45); EI-HRMS calcd for C₁₅H₂₁NO₂S [M+] m/z: 279.1293, found: 279.1291.

\[ \text{TsHN} \quad 15a + \text{HO} \quad 16a \quad \rightarrow \quad \text{TsN} \quad 9g \]

\( N-(5,5\text{-dimethyl-2,3-hexadienyl})-N-(2\text{-methyl-2-propenyl})-4\text{-methylbenzenesulfonamide} \)

(9g): The general procedure for the Mitsunobu reaction (p. 56) was followed using \( N-(5,5\text{-dimethyl-2,3-hexadienyl})-4\text{-methylbenzenesulfonamide} \) 15a (99 mg, 0.35 mmol), PPh₃ (120 mg, 0.456 mmol), DIAD (90 µL, 0.46 mmol), and 2-methyl-2-propen-1-ol 16a (40 µL, 0.47 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-
hexanes 1:19-1:9) to afford 99 mg of ene-allene 9g as a colorless oil in 84% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.70 (1/2 AA'XX' d, $J = 8.3$ Hz, 2H), 7.27 (1/2 AA'XX' d, $J = 8.0$ Hz, 2H), 5.06 (dt, $J = 6.2$, 2.3 Hz, 1H), 4.90-4.83 (m, 3H), 3.84 (1/2 AB ddd, $J = 15.3$, 6.6, 2.3 Hz, 1H), 3.74 (s, 2H), 3.73 (1/2 AB ddd, $J = 15.2$, 7.4, 2.3 Hz, 1H), 2.40 (s, 3H), 1.69 (s, 3H), 0.97 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 202.4, 143.0, 140.0, 137.6, 129.6, 127.1, 114.2, 104.2, 87.7, 52.4, 46.4, 31.7, 30.0, 21.4, 19.8; IR (neat) 3078, 2960, 2930, 2904, 2963, 1962, 1655, 1593, 1445, 1342, 1163 cm$^{-1}$; MS m/z (%) 82 (69), 91 (100), 155 (56), 238 (68), 276 (31), 333 (22); EI-HRMS calcd for C$_{19}$H$_{27}$NO$_2$S [M+] m/z: 333.1763, found: 333.1759.

$N$-(5,5-Dimethyl-2,3-hexadienyl)-$N$-(3-methyl-2-butenyl)-4-methylbenzenesulfonamide (9h): The general procedure for the Mitsunobu reaction (p. 56) was followed using $N$-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide 15a (157 mg, 0.562 mmol), PPh$_3$ (192 mg, 0.734 mmol), DIAD (145 $\mu$L, 0.736 mmol), and 3-methyl-2-buten-1-ol 16b (74 $\mu$L, 0.73 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 176 mg of ene-allene 9h as a colorless oil in 90% yield. $^1$H NMR (300 MHz, CD$_2$Cl$_2$) $\delta$: 7.66 (1/2 AA'XX' d, $J = 8.3$ Hz, 2H), 7.31 (1/2 AA'XX' d, $J = 8.0$ Hz, 2H), 5.15 (dt, $J = 6.2$, 2.4 Hz, 1H), 5.05-4.93 (m, 2H), 3.84 (1/2 ddd, $J = 15.1$, 6.3, 2.6 Hz, 1H) 3.83-3.79 (m, 1H), 3.69 (1/2 AB ddd, $J = 15.0$, 7.5, 2.3 Hz, 1H), 2.42 (s, 3H), 1.66 (d, $J = 0.9$ Hz, 3H), 1.62 (bs, 3H), 1.00 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 202.2, 142.9, 137.8, 136.7, 129.5, 127.1, 118.9, 104.4, 88.7, 46.4, 44.3, 31.8, 30.0, 25.7, 21.4, 17.8; IR (neat) 2960, 2925, 2863, 1916, 1777, 1670, 1598, 1445, 1347 cm$^{-1}$; MS m/z (%) 69 (100), 91 (51), 110
EI-HRMS calcd for C_{20}H_{29}NO_{2}S [M+] m/z: 347.1919, found: 347.1905.

1-Cyclohexenylmethanol (16c):^{70} To a solution of 1-cyclohexenecarboxaldehyde (100 µL, 0.877 mmol) in DCM (9.0 mL) at -78 °C was added diisobutylaluminum hydride (1.0 M in hexanes, 970 µL, 0.970 mmol) dropwise. To the solution after 15 min at -78 °C was added MeOH (100 µL) dropwise and it was allowed to warm to rt. Upon reaching rt H_{2}O (2 mL) was added followed by HCl aq (1N, 20 mL) and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried over MgSO_{4} and concd in vacuo to afford 97 mg of crude alcohol 16c in 99% yield.

N-(5,5-Dimethyl-2,3-hexadienyl)-N-(methyl-1-cyclohexenyl)-4-methylbenzenesulfonamide (9i): The general procedure for the Mitsunobu reaction (p. 56) was followed using N-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide 15a (160 mg, 0.573 mmol), PPh_{3} (196 mg, 0.746 mmol), DIAD (147 µL, 0.746 mmol), and 1-cyclohexenylmethanol 16c (97 mg, 0.87 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 184 mg of ene-allene 9i as a colorless oil in 86% yield. \(^{1}\)H NMR (300 MHz, CDCl_{3}) \(\delta\): 7.68 (1/2 AA′XX′ d, \(J = 8.2\) Hz, 2H), 7.26 (1/2 AA′XX′ d, \(J = 8.0\) Hz, 2H), 5.57 (bs, 1H), 5.05 (dt, \(J = 6.2, 2.2\) Hz, 1H), 4.86 (dt, \(J = 7.3, 6.4\) Hz, 1H), 3.83 (1/2 AB ddd, \(J = 15.3, 6.4, 2.3\) Hz, 1H), 3.68 (1/2 AB ddd, \(J = 15.3, 7.6, 2.2\) Hz, 1H), 3.67 (bs, 2H), 2.39
(s, 3H), 1.98-1.86 (m, 4H), 1.61-1.46 (m, 4H), 0.97 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 202.3, 142.8, 137.8, 132.3, 129.4, 127.1, 126.4, 104.1, 88.0, 53.0, 46.1, 31.6, 30.0, 25.9, 25.1, 22.4, 22.2, 21.4; IR (neat) 3027, 2960, 2930, 2858, 2383, 1962, 1598, 1496, 1440, 1347 cm$^{-1}$; MS m/z (%): 91 (37), 95 (100), 155 (31), 184 (20), 278 (21), 316 (18), 373 (36); EI-HRMS calcd for C$_{22}$H$_{31}$NO$_2$S [M+] m/z: 373.2076, found: 373.2076.

(E)-3-(Trimethylsilyl)-2-propen-1-ol (16d): Compound 16d was prepared as described in the literature$^{71}$ using 3-trimethylsilyl-2-propyn-1-ol 25b (2.30 mL, 15.5 mmol), Red-Al$^{8}$ (65% wt in toluene, 7.2 mL, 25.2 mmol), and ether (19 mL) to afford 506 mg of the allylic alcohol that possessed 4% ether by $^1$H NMR to afford a calculated yield of 24%. The $^1$H NMR spectra matched that of the reported compound.

N-(5,5-Dimethyl-2,3-hexadienyl)-N-[(E)-3-(trimethylsilyl)-2-propenyl]-4-methylbenzene-sulfonamide (9j): Preparation of ene-allene 9j has previously been described.$^{20}$

3-(Benzhydryldimethylsilyl)-2-propyn-1-ol (25c): The procedure as described in the literature$^{72}$ was followed using tetrahydro-2-(2-propynyl-2H-pyran (340 $\mu$L, 2.42 mmol), benzylchlorodimethylsilane (500 $\mu$L, 2.66 mmol), $n$-butyllithium (1.51 mL, 2.42 mmol), and THF (4.8 mL) to provide THP-ether 29 in quantitative conversion after the first step. The second
step utilized crude ether 29 (2.42 mmol), p-toluenesulfonic acid monohydrate (13 mg, 0.050 mmol), and MeOH (4.8 mL) to provide alcohol 25c in quantitative conversion.

(E)-3-(Benzhydryldimethylsilyl)-2-propen-1-ol (16e): The procedure as described in the literature\textsuperscript{72} was followed using alcohol 25c (2.42 mmol), Red-Al® (65% wt in toluene, 1.53 mL, 4.91 mmol), and ether (7.4 mL) to provide, after purification by silica gel chromatography (ether-pentane 1:3-1:2), 399 mg of alcohol 16e as a slightly yellow oil in 80% yield. The \(^1\)H NMR spectra matched that of the reported compound.

\[ \text{TsHN} \quad \text{t-Bu} \quad \text{SiMe}_2\text{Bn} \quad \text{15a} \quad \text{+} \quad \text{HO} \quad \text{SiMe}_2\text{Bn} \quad \text{16e} \quad \rightarrow \quad \text{TsN} \quad \text{SiMe}_2\text{Bn} \quad \text{15b} \quad \text{N-[} (E)-3-(Benzyldimethylsilyl)-2-propenyl]-N-(5,5-Dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9k): Preparation for ene-allene 9k has previously been described.\textsuperscript{20}

\[ \text{C}_6\text{H}_{13} \quad \text{NHTs} \quad \text{14d} \quad \rightarrow \quad \text{C}_6\text{H}_{13} \quad \text{Br} \quad \text{28a} \quad \rightarrow \quad \text{C}_6\text{H}_{13} \quad \text{NHTs} \quad \text{15b} \quad \text{N-(2,3-Decadienyl)-4-methylbenzenesulfonamide (15b):} \textsuperscript{73} \text{ To a solution of alcohol 14d (2.28 g, 14.8 mmol) and CBr}_4 (5.40 g, 16.2 mmol) in DCM (50 mL) was added PPh}_3 (4.27 g, 16.3 mmol) in portions. Within 5 min a brown color change was noted and TLC inspection indicated reaction completion after 10 min whereupon it was quenched with H}_2\text{O (6 mL) and concd in vacuo. The crude oil was extracted with ether-hexanes (1:1, 2 x 100 mL) and the decanted organic phases were combined and concd in vacuo to give the crude allylic bromide 28a (yield not determined).} \textsuperscript{1}\text{H NMR (300 MHz, CDCl}_3) \delta: 5.44-5.31 (m, 2H), 3.94 (dd, } J = 7.9, 2.0 \text{ Hz,
2H), 2.03 (dt, \(J = 6.8, 6.8, 3.0\) Hz, 2H), 1.45-1.19 (m, 8H), 0.90 (t, \(J = 6.8\) Hz, 3H). The subsequent alkylation was carried out in the manner as that described for the formation of \(\text{13c}\) (p. 50) using bromide \(\text{28a}\) (1.24 g, 5.71 mmol), \(p\)-toluenesulfonamide (874 mg, 5.10 mmol), \(\text{K}_2\text{CO}_3\) (3.53 g, 25.5 mmol) and MeCN (18 mL). The crude residue was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:2) to afford 537 mg of pure allene \(\text{15b}\) as a slightly yellow oil in 34% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.76 (1/2 AA'XX' d, \(J = 8.3\) Hz, 2H), 7.31 (1/2 AA'XX' d, \(J = 8.5\) Hz, 2H), 5.25-5.15 (m, 1H), 5.08-4.99 (m, 1H), 4.48 (bs, 1H), 3.56 (ddd, \(J = 5.9, 5.9, 3.1\) Hz, 2H), 2.43 (s, 3H), 1.94 (dt, \(J = 7.0, 7.0, 3.0\) Hz, 2H), 1.40-1.25 (m, 8H), 0.91-0.85 (m, 3H).

**\(\text{N-(2,3-Decadienyl)-N-[(E)-2-hexenyl]-4-methylbenzenesulfonamide (9l)}\):** The general procedure for the Mitsunobu reaction (p. 56) was followed using \(\text{N-(2,3-decadienyl)-4-methylbenzenesulfonamide 15b}\) (160 mg, 0.519 mmol), PPh\(_3\) (217 mg, 0.828 mmol), DIAD (163 \(\mu\)L, 0.828 mmol), and 2-hexen-1-ol \(\text{16f}\) (92 \(\mu\)L, 0.78 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:6) to give 167 mg of ene-allene \(\text{9l}\) as a clear oil in 83% yield. \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\): 7.74 (1/2 AA'XX' d, \(J = 8.3\) Hz, 2H), 7.25 (1/2 AA'XX' d, \(J = 8.0\) Hz, 2H), 5.44 (bdt, \(J = 15.3, 6.6\) Hz, 1H), 5.29 (dt, \(J = 15.3, 6.5, 1.2\) Hz, 1H), 5.05-4.94 (m, 2H), 3.98-3.92 (m, 2H), 3.91-3.86 (m, 2H), 1.91-1.73 (m, 7H), 1.31-1.36 (m, 10H), 0.89-0.83 (m, 3H), 0.77 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 205.4, 143.1, 142.8, 136.0, 129.7, 127.3, 124.1, 92.6, 86.4, 48.4, 46.0, 34.4, 31.8, 29.3, 28.9, 28.8, 22.7, 22.3, 21.6, 14.2, 13.8; IR (neat) 2955, 2925, 2853, 1957, 1772, 1445, 1347,
N-(5,5-Dimethyl-2,3-hexadienyl)-N-[(E)-1-methyl-2-butenyl]-4-methylbenzenesulfonamide (9m): The general procedure for the Mitsunobu reaction (p. 56) was followed using N-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide 15a (184 mg, 0.659 mmol), PPh₃ (236 mg, 0.900 mmol), DIAD (175 µL, 0.842 mmol), and 1-methyl-2-buten-1-ol (100 µL, 0.979 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:7) to afford 171 mg of ene-allene 9m as a colorless oil in 75% yield. ¹H NMR (300 MHz, CDCl₃) δ: 7.71 (1/2 AA’XX’ d, J = 8.4 Hz, 4Hα), 7.27 (1/2 AA’XX’ d, J = 8.5 Hz, 4Hα), 5.47 (m, 2Hα), 5.32 (m, 1Hβ), 5.28 (m, 1Hβ), 5.19 (m, 4Hα), 4.47 (m, 2Hα), 3.76 (m, 4Hα), 2.41 (s, 6Hα), 1.61 (dd, J = 2.9, 1.5 Hz, 3Hβ), 1.59 (dd, J = 2.9, 1.5 Hz, 3Hβ), 1.23 (d, J = 1.7 Hz, 3Hβ), 1.21 (d, J = 1.7 Hz, 3Hβ), 1.03 (s, 9Hβ), 1.02 (s, 9Hβ); ¹³C NMR (75 MHz, CDCl₃) δ: 201.3, 143.0, 138.7, 131.0, 130.7, 129.6, 128.5, 127.9, 127.7, 127.3, 104.8, 104.6, 92.1, 54.8, 43.8, 32.3, 30.3, 21.6, 19.2, 18.8, 17.9; IR (neat) 3027, 2960, 2930, 2863, 1962, 1598, 1496, 1455, 1342 cm⁻¹; MS m/z (%) 69 (100), 184 (55), 91 (40), 155 (35), 252 (32), 347 (16), 332 (13), 348 (9); EI-HRMS calcd for C₂₀H₂₉NO₂S [M+] m/z: 347.1923, found: 347.1919.

aSpin set is a mixture of diastereomers. bSpin set results from resonance of one diastereomer. cSpectrum is reported as a mixture of diastereomers.
2,3-Butadiene-1-ol (14e):

To a solution of alcohol 25d (3.97 g, 37.9 mmol) in ether (95 mL) at -4 °C (NaCl ice bath) was added LiAlH4 (1.40 g, 37.0 mmol) in portions over a period of 15 min. The cold bath was then removed and the slurry was heated to reflux for 2.5 h once it had warmed to rt. The slurry was then cooled to 0 °C and a small amount of H2O was added to quench the remaining hydride. The solid was removed via vacuum filtration (washing with ether) and the filtrate was concd in vacuo to afford alcohol 14e as a brown liquid (yield not determined). 1H NMR (300 MHz, CDCl3) δ: 5.40-5.31 (m, 1H), 4.86 (ddd, \(J = 6.1, 3.1\) Hz, 2H), 4.15 (ddd, \(J = 6.3, 3.0, 3.0\) Hz, 2H).

TsHN\[13c\] + \[\text{14e}\] \rightarrow \text{TsN}\[9n\]

N-(2,3-Butadienyl)-N-[(\(E\))-2-butenyl]-4-methylbenzenesulfonamide (9n):

The general procedure for the Mitsunobu reaction (p. 56) was followed using \(N\)-[(\(E\))-2-butenyl]-4-methylbenzenesulfonamide 13c (320 mg, 1.42 mmol), PPh3 (520 mg, 1.98 mmol), 2,3-butadiene-1-ol 14e (160 mg, 2.28 mmol), and DIAD (390 µL, 1.98 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:9-1:6) to afford 268 mg of ene-allene 9n in 68% yield. 1H NMR (300 MHz, CDCl3) δ: 7.69 (1/2 AA’XX’ d, \(J = 8.3\) Hz, 2H), 7.29 (1/2 AA’XX’ d, \(J = 8.5\) Hz, 2H), 5.65-5.52 (m, 1H), 5.33-5.22 (m, 1H), 4.88 (dt, \(J = 6.8, 6.8\) Hz, 1H), 4.68 (dt, \(J = 6.5, 2.5\) Hz, 2H), 3.83 (dt, \(J = 7.0, 2.5\) Hz, 2H), 3.77 (bd, \(J = 6.7\) Hz, 2H), 2.42 (s, 3H), 1.65 (bd, \(J = 6.5\) Hz, 3H); 13C NMR (75 MHz, C6D6) δ: 209.4, 142.7, 138.5, 130.2, 129.5, 127.3, 125.6, 86.0, 75.7, 48.7, 45.4, 20.9, 17.4; IR (neat) 3063, 3027, 2966, 2919, 2859, 1952, 1716, 1670, 1598, 1491, 1440, 1342 cm\(^{-1}\); MS m/z (%) 55 (62), 91 (100), 155 (100), 184 (70), 238 (49), 255 (43), 262 (31), 277 (40); El-HRMS calcd for C15H19NO2S [M+] m/z: 277.1137, found: 277.1139.
(E)-2-Buten-1-ol-1,1-d₂ (16g): Compound 16g was prepared as described in the literature using ethyl crotonate (5.4 mL, 44 mmol), LiAlD₄ (1.83 g, 43.6 mmol), AlCl₃ (5.81 g, 43.6 mmol), and ether (220 mL) to afford 3.60 g of the crude alcohol in a calculated 86% yield.¹³¹H NMR (300 MHz, CDCl₃) δ: 5.79-5.67 (m, 2H), 1.72 (d, J = 4.9 Hz, 3H).

N-[(E)-2-Butenyl-1,1-d₂]-N-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9o): Preparation of ene-allene 9o has previously been described.²⁰

Di-t-butylinodicarbonate (29): Compound 29 was prepared as described in the literature using di-t-butyldicarbonate (24.8 g, 114 mmol), DMAP (630 mg, 5.16 mmol), formamide (2.05 mL, 51.6 mmol), N,N-diethylethylenediamine (8.85 mL, 61.8 mmol), and MeCN (26 mL) to afford 10.07 g of 29 as a white solid (mp 118-120 °C) in 90% yield (¹H NMR contained minor impurities).¹H NMR (300 MHz, CDCl₃) δ: 6.72 (s, 1H), 1.49 (s, 18H).

N-(5,5-Dimethyl-2,3-hexadienyl)-di-t-butylinodicarbonate (30): To a solution of imidazole (897 mg, 9.85 mmol) and triphenylphosphonium bromide (4.16 g, 9.85 mmol) in DCM (125 mL)

¹³¹ The sample was contaminated with ethanol and exhibited 77% purity by ¹H NMR.
at 0 °C was added a solution of alcohol 14a (832 mg, 6.59 mmol) in DCM (5 mL) dropwise. After 4.3 h at rt excess triphenylphosphonium bromide (835 mg, 1.98 mmol) was added and the reaction showed completion by TLC after an additional 1.5 h. To the crude solution was added silicon dioxide (1 g) whereupon the mixture became orange. The mixture was then concd in vacuo and the crude gel was triturated with pentane. The decanted organic solution was concd in vacuo to yield 741 mg of bromide 28b in 59% yield (1H NMR contained minor impurities). 1H NMR (300 MHz, CDCl₃) δ: 5.48 (td, J = 8.0, 6.1 Hz, 1H), 5.36 (dt, J = 6.1, 1.8 Hz, 1H), 3.96 (dt, J = 8.0, 1.7 Hz, 2H), 1.07 (s, 9H). To a solution of iminocarbonate 29 (29 mg, 0.13 mmol) in DMF (1.33 mL) at rt was added KH (35% wt in mineral oil, 20 mg, 0.17 mmol). After 30 min at rt neat bromide 28b (23 µL, 0.13 mmol) was added dropwise and precipitation was noted within 5 min of addition. The slurry was held at rt for 2.3 h then diluted with ethyl acetate and poured into H₂O (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with H₂O (4 x 15 mL), dried over MgSO₄, and concd in vacuo to furnish 39 mg of allenyliminocarbonate 30 as a slightly yellow oil in 90% yield (1H NMR contained mineral oil). 1H NMR (300 MHz, CDCl₃) δ: 5.29-5.18 (m, 2H), 4.21 (1/2 AB ddd, J = 15.4, 5.1, 3.3 Hz, 1H), 4.12 (1/2 AB ddd, J = 15.5, 5.5, 2.9 Hz, 1H), 1.50 (s, 18H), 1.03 (s, 9H).

N-[(E)-2-Butenyl-1,1-d₂]-N-(5,5-dimethyl-2,3-hexadienyl)-t-butoxycarbonylamine (9p): To a solution of 30 (60 mg, 0.19 mmol) in DCM (1.5 mL) at rt was added trifluoroacetic acid (27 µL, 0.35 mmol) dropwise. After 12 h at rt the solution was quenched with saturated NaHCO₃ (3 mL).
and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, and concd in vacuo afford 40 mg of carbamate 15c in 96% yield.¹⁷¹H NMR (300 MHz, CDCl₃) δ: 5.30-5.19 (m, 2H), 4.58 (bs, 1H), 3.80-3.65 (m, 2H), 1.44 (s, 9H), 1.04 (s, 9H). To a solution of alcohol 16g (51 µL, 0.58 mmol) and triethylamine (120 µL, 0.861 mmol) in DCM (2.9 mL) at -30 °C was added methansulfonyl chloride (54 µL, 0.70 mmol) dropwise. Precipitation was observed after 10 min and the slurry was held at -50 °C for 2 h. Upon warming to rt pentane (1 mL) was added and the precipitate filtered and washed with pentane (10 mL). The filtrate was washed with H₂O (5 mL), brine (5 mL), dried over MgSO₄, and concd in vacuo to afford 55 mg of crude mesylate 31 as a light yellow oil in 62% yield.⁶⁹ To a solution of carbamate 15c (104 mg, 0.460 mmol) in DMF (1.9 mL) at rt was added KH (35% wt in mineral oil, 54 mg, 0.47 mmol) and the resulting slurry held at rt for 1 h. To the slurry was added a solution of the crude mesylate 31 (55 mg, 0.36 mmol) in DMF (1.0 mL) dropwise. After 2 h the slurry was poured into H₂O (10 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic layers were washed with H₂O (4 x 10 mL), brine (10 mL), dried over MgSO₄, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 53 mg of ene-allene 9p as a clear oil in 41% yield.¹¹H NMR (300 MHz, CDCl₃) δ: 5.55 (dq, J = 15.2, 6.3 Hz, 1H), 5.39 (d, J = 15.4 Hz, 1H), 5.18 (dt, J = 6.2, 2.8 Hz, 1H), 5.11 (q, J = 6.2 Hz, 1H), 3.91-3.65 (m, 2H), 1.68 (dd, J = 6.2, 1.5 Hz, 3H), 1.45 (s, 9H), 1.03 (s, 9H).
N-[(Z)-2-Butenyl]-N-(2,3-decadienyl)-4-methylbenzenesulfonamide (9q):VI The general procedure for the Mitsunobu reaction (p. 56) was followed using N-[(Z)-2-butenyl]-4-methylbenzenesulfonamide 13b (304 mg, 1.35 mmol), PPh₃ (470 mg, 1.79 mmol), 2,3-decadien-1-ol 14d (267 mg, 1.73 mmol), and DIAD (350 µL, 1.78 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:9) to afford 339 mg of ene-allene 9q in 69% yield. ¹H NMR (300 MHz, CDCl₃) δ: 7.71 (1/2 AA'XX' d, J = 8.3 Hz, 2H), 7.29 (1/2 AA'XX' d, J = 8.0 Hz, 2H), 5.61 (dqt, J = 10.8, 7.0, 1.5 Hz, 1H), 5.28 (dtq, J = 10.8, 6.9, 1.7 Hz, 1H), 5.11 (tdt, J = 6.8, 6.4, 2.3 Hz, 1H), 4.90 (dtt, J = 6.9, 6.5, 2.8 Hz, 1H), 3.90 (d, J = 6.9 Hz, 2H), 3.85 (1/2 AB ddd, J = 15.1, 6.6, 2.4 Hz, 1H), 3.75 (1/2 AB ddd, J = 15.0, 7.2, 2.3 Hz, 1H), 2.42 (s, 3H), 1.95 (dt, J = 7.3, 6.9, 2.9 Hz, 2H), 1.65-1.61 (m, 3H), 1.41-1.23 (m, 8H), 0.91-0.85 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 205.1, 143.0, 129.6, 128.3, 127.2 (2C), 125.0, 92.6, 86.7, 46.5, 43.0, 31.6, 29.1, 28.7, 28.6, 22.6, 21.4, 14.0, 12.8.

**2-t-butyldimethylsiloxyethanal (32):** To a solution of t-butyldimethylsilylchloride (35.08 g, 232.7 mmol) and 4-(dimethylamino)pyridine (694 mg, 5.68 mmol) in DCM (380 mL) was added 2-buten-1,4-diol (9.30 mL, 113 mmol) dropwise. After 1 h at rt TLC analysis indicated complete consumption of starting material. The solution was diluted with DCM (100 mL), washed with H₂O (2 x 300 mL) and brine (300 mL), dried over MgSO₄, and concd in vacuo. The crude oil was dissolved in pentane whereupon the solids were filtered and the filtrate was concd in vacuo to afford 35.39 g of silyl ether 31 in 99% yield.⁷⁹ ¹H NMR (300 MHz, CDCl₃) δ: 5.55 (s, 2H), 4.23 (s, 4H), 0.90 (s, 18H), 0.067 (s, 12H). To a solution of silyl ether 31 (3.01 g, 9.49 mmol) in

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VI Reaction was performed by Dr. Hongfeng Chen.
DCM (19 mL) at -78 °C was bubbled a stream of O₃ for 15 min whereupon the solution turned blue. This solution was held at -78 °C and purged with N₂ until it became colorless. To the solution at -78 °C was added triphenylphosphine (2.49 g, 9.50 mmol) and it was then allowed to warm to rt. After 1 h at rt it was concd in vacuo and purified by silica gel chromatography (ether-pentane 1:9) to afford 2.27 g of aldehyde 32 in 63% yield.\textsuperscript{VII} \textsuperscript{1}H NMR (300 MHz, CDCl₃) δ: 9.70 (s, 1H), 4.21 (s, 2H), 0.93 (s, 9H), 0.10 (s, 6H).

\[
\begin{array}{c}
\text{H} & \text{O} & \text{OTBS} \\
\text{TBSO} & \text{OH} & \text{Si(Pr)}_3 \\
32 & 25e & 33
\end{array}
\]

\textbf{4-(Triisopropylsilyl)-2,3-buta dienyl-t-butyldimethylsilyl ether (33):} To a solution of triisopropylsilylacetylene (1.23 mL, 5.48 mmol) in THF (26 mL) at -78 °C was added n-butyllithium (1.6 M, 3.45 mL, 5.52 mmol) dropwise. To the solution, after 30 min at -78 °C, was added aldehyde 32 (1.00 g, 5.24 mmol) as a solution in THF (9 mL) dropwise. After an additional 40 min at -78 °C acetic acid (350 µL) was added and the mixture was allowed to warm to rt whereupon it was concd in vacuo and partitioned between H₂O/ether (100 mL/75 mL). The aqueous layer was washed with ether (75 mL) and the combined organic layers were washed with saturated NaHCO₃ (30 mL), dried over MgSO₄ and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:4) to afford propargyl alcohol 25e in 74% yield. \textsuperscript{1}H NMR (300 MHz, C₆D₆) δ: 4.42 (dd, J = 6.5, 3.9 Hz, 1H), 3.77 (dd, J = 9.9, 3.9 Hz, 1H), 3.65 (dd, J = 9.9, 6.5 Hz, 1H), 1.09 (s, 21H), 0.91 (s, 9H), 0.097 (s, 6H). To a solution of alcohol 25e (442 mg, 1.24 mmol) and PPh₃ (650 mg, 2.48 mmol) in THF (8.4 mL) at -15 °C was added DEAD (390 µL, 2.48 mmol) dropwise. Immediately following was addition of o-nitrobenzenesulfonyl hydrazide (540 mg, 2.48 mmol) as a solution in THF (4.0 mL) at a

\textsuperscript{VII} The yield discrepancy is due to the sample only being 91% pure by NMR.
rapid dropwise rate. This solution was allowed to slowly warm to rt and the reaction did not progress further after 17 h. The solution was then concd to a volume of ~5 mL where it was triturated with ice-cold hexanes, filtered, and concd in vacuo. The crude residue was purified by silica gel chromatography (hexanes) to afford 199 mg of allenyl ether 33 in 47% yield as a clear oil.\(^8^0\) \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\): 5.00 (q, \(J = 6.8\) Hz, 1H), 4.94 (dt, \(J = 6.9, 3.7\) Hz, 1H), 4.24 (dd, \(J = 6.6, 3.1\) Hz, 2H), 1.08 (s, 21H), 0.98 (s, 9H), 0.08 (s, 6H).

4-(Triisopropylsilyl)-2,3-butadien-1-ol (14f).\(^8^1\) To an emulsion of silylether 33 (221 mg, 0.648 mmol) in THF/H\(_2\)O (1:1, 3.6 mL) was slowly added AcOH (5.4 mL), at which point the emulsion became a solution. After 12 h at rt the solution was poured into H\(_2\)O (100 mL) and extracted with ethyl acetate (75 mL, 2 x 60 mL). The combined organic layers were washed with H\(_2\)O (30 mL), brine (40 mL), dried over MgSO\(_4\), and concd in vacuo. The residual AcOH was azeotroped with \(n\)-heptane (3 x 60 mL) to afford 147 mg of allenic alcohol 14f in quantitative yield. \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\): 4.92 (dt, \(J = 6.8, 3.3\) Hz, 1H), 4.86 (q, \(J = 6.7\) Hz, 1H), 3.96 (dd, \(J = 6.5, 3.3\) Hz, 2H), 1.05 (s, 21H).

\[\text{TsHN} \rightarrow \text{Ph} + \text{HO} \rightarrow \text{Si}(i-Pr)\_3 \rightarrow \text{TsN} \rightarrow \text{Ph} + \text{Si}(i-Pr)\_3 \rightarrow \text{9r}\]

\(N\)-(\((E)\)-3-Phenyl-2-propenyl\)-\(N\)-[4-(triisopropylsilyl)-2,3-butadienyl]-4-methylbenzene-sulfonamide (9r): The general procedure for the Mitsunobu reaction (p. 56) was followed using 4-(triisopropylsilyl)-2,3-butadien-1-ol 14f (86 mg, 0.38 mmol), THF (1.5 mL), \(N\)-(\((E)\)-3-phenyl-2-propenyl]-4-methylbenzenesulfonamide 13a (220 mg, 0.766 mmol), PPh\(_3\) (201 mg, 0.765 mmol), and DIAD (150 \(\mu\)L, 0.762 mmol). The solution was concd in vacuo and purified by
silica gel chromatography (ethyl acetate-hexanes 1:32-1:13) to afford 68 mg of ene-allene \(9r\) as a clear oil in 36% yield. \(^1\)H NMR (300 MHz, \(\text{C}_6\text{D}_6\)) \(\delta\): 7.76 (1/2 AA’XX’ d, \(J = 8.3\) Hz, 2H), 7.18-6.99 (m, 5H), 6.75 (1/2 AA’XX’ d, \(J = 8.0\) Hz, 2H), 6.34 (d, \(J = 15.8\) Hz, 1H), 6.00 (ddd, \(J = 15.8, 7.2, 6.1\) Hz, 1H), 4.81-4.66 (m, 2H), 4.24-4.00 (m, 2H), 4.01-3.79 (m, 2H), 1.86 (s, 3H), 0.97-0.93 (m, 21H); \(^{13}\)C NMR (75 MHz, \(\text{CD}_2\text{Cl}_2\)) \(\delta\): 211.5, 143.8, 138.0, 136.8, 134.0, 131.8, 130.1, 128.8, 127.5, 126.7, 124.3, 78.5, 77.9, 48.9, 46.6, 21.6, 18.5, 11.5; MS \(m/z\) (%) 91 (56), 117 (100), 183 (42), 294 (46), 452 (81), 495 (9); EI-HRMS calcd for \(\text{C}_{29}\text{H}_{41}\text{NO}_2\text{SiS} [\text{M}^+] \): 495.2627, found: 495.2639.

\[
\begin{align*}
\text{TsHN} & \quad + \quad \text{HO} & & \quad \text{Si(\text{t-Pr})}_3 \\
13c & & & 14f & & & 9s
\end{align*}
\]

**N-[(E)-2-butenyl]-N-[4-(triisopropylsilyl)-2,3-butadienyl]-4-methylbenzene-sulfonamide** (\(9s\)): The general procedure for the Mitsunobu reaction (p. 56) was followed using 4-(triisopropylsilyl)-2,3-butadien-1-ol \(14f\) (59 mg, 0.26 mmol), THF (1.1 mL), \(N\)-[(E)-2-butenyl]-4-methylbenzenesulfonamide \(13c\) (116 mg, 0.517 mmol), PPh\(_3\) (137 mg, 0.521 mmol), and DIAD (103 \(\mu\)L, 0.523 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 29 mg of ene-allene \(9s\) as a clear oil in 26% yield. \(^1\)H NMR (300 MHz, \(\text{C}_6\text{D}_6\)) \(\delta\): 7.75 (1/2 AA’XX’ d, \(J = 8.3\) Hz, 2H), 6.75 (1/2 AA’XX’ d, \(J = 8.0\) Hz, 2H), 5.51-5.37 (m, 1H), 5.35-5.24 (m, 1H), 4.80-4.75 (m, 1H), 4.71-4.63 (m, 1H), 4.22-4.12 (m, 1H), 4.03-3.95 (m, 1H), 3.88-3.74 (m, 2H), 1.85 (s, 3H), 1.42 (bd, \(J = 6.29\) Hz, 3H), 1.00 (s, 21 H); \(^{13}\)C NMR (75 MHz, \(\text{CDCl}_3\)) \(\delta\): 211.1, 143.0, 137.8, 130.5, 129.6, 127.2, 125.2, 78.1, 77.2, 48.1, 45.5, 21.5, 18.4, 17.7, 11.1; IR (neat) 2942, 2897, 2964, 1932, 1597, 1462, 1348, 1160 cm\(^{-1}\); MS \(m/z\) (%) 55 (63), 59 (73), 91 (81), 338 (31), 390 (100); EI-HRMS calcd for \(\text{C}_{29}\text{H}_{41}\text{NO}_2\text{SiS} [\text{M}^+] \): 390.1923, found: 390.1918.
N-(2,3-Decadienyl)-N-[(E)-3-(trimethylsilyl)-2-propenyl]-4-methylbenzenesulfonamide (9t):
The general procedure for the Mitsunobu reaction (p. 56) was followed using PPh₃ (79 mg, 0.30 mmol), N-(2,3-decadienyl)-4-methylbenzenesulfonamide 15b (67 mg, 0.22 mmol), (E)-3-(trimethylsilyl)-2-propen-1-ol 16d (44 µL, 0.29 mmol), and DIAD (58 µL, 0.30 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:6) to afford 63 mg of ene-allene 9t in 74% yield. ¹H NMR (300 MHz, C₆D₆) δ: 7.72 (1/2 AA'XX' d, J = 8.2 Hz, 2H), 6.77 (1/2 AA'XX' d, J = 8.1 Hz, 2H), 5.87 (dt, J = 18.6, 5.3 Hz, 2H), 5.74 (d, J = 18.7 Hz, 1H), 5.04-4.94 (m, 2H), 4.00-3.87 (m, 4H), 1.89 (s, 3H), 1.88-1.81 (m, 2H), 1.29-1.18 (m, 8H), 0.90-0.84 (m, 3H), -0.01 (s, 9H); ¹³C NMR (75 MHz, CD₂Cl₂) δ: 205.1, 143.4, 139.8, 137.9, 134.5, 129.6, 127.0, 92.4, 86.1, 46.5, 31.6, 29.6, 29.0, 28.7, 28.4, 22.5, 21.1, 13.7, -1.9; IR (thin film) 2955, 2926, 2855, 1963, 1618, 1599, 1458, 1350, 1305, 1305, 1248, 1161.

N-(2-Propenyl)-4-methylbenzenesulfonamide (13d):
To neat allylamine (8.1 mL, 0.11 mol) at 0 °C was cautiously added p-toluenesulfonylchloride (3.00 g, 0.0157 mol) in portions (Reaction exotherms upon each addition!). Analysis by TLC showed reaction completion after 1.25 h whereupon the allyl amine was removed in vacuo and the solid was partitioned between ethyl acetate/H₂O (1:1, 200 mL). The organic layer was washed with H₂O (100 mL), brine (100 mL), dried over MgSO₄, and concd in vacuo to afford 3.27 g pure allylic tosylamide 13d in 99% yield. ¹H NMR (300 MHz, CDCl₃) δ: 7.75 (1/2 AA'XX' d, J = 8.2 Hz, 2H), 7.31 (1/2 AA'XX' d, J =
8.2 Hz, 2H), 5.72 (ddt, J = 17.1, 10.4, 5.7 Hz, 1H), 5.17 (dd, J = 17.2, 1.2 Hz, 1H), 5.10 (dd, J = 10.0, 0.9 Hz, 1H), 4.38-4.36 (bm, 1H), 3.59 (dd, J = 6.0, 6.0 Hz, 2H), 2.43 (s, 3H).

\[ \text{TsHN} + \text{C}_6\text{H}_{13} \text{OH} \rightarrow \text{TsN} \]

\[ \text{9u} \]

\[ \text{N-(2,3-Decadienyl)-N-(2-propenyl)-4-methylbenzenesulfonamide (9u)}: \] Preparation for ene-allene 9u has previously been described.\textsuperscript{20}

\[ \text{TsHN} + \text{HO} + \text{Si(i-Pr)}_3 \rightarrow \text{TsN} \]

\[ \text{9v} \]

\[ \text{N-(2-Propenyl)-N-[4-(triisopropylsilyl)-2,3-butadienyl]-4-methylbenzenesulfonamide (9v):} \]

The general procedure for the Mitsunobu reaction (p. 56) was followed using 4-(triisopropylsilyl)-2,3-butadien-1-ol 14f (74 mg, 0.33 mmol), THF (1.3 mL), N-(2-propenyl)-4-methylbenzenesulfonamide 13d (136 mg, 0.645 mmol), PPh\textsubscript{3} (173 mg, 0.658 mmol), and DIAD (130 µL, 0.660 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:13) to afford 34 mg of ene-allene 9v as a clear oil in 25% yield. \textsuperscript{1}H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}) \( \delta \): 7.71 (1/2 AA'XX' d, J = 8.2 Hz, 2H), 6.76 (1/2 AA'XX' d, J = 8.5 Hz, 2H), 5.67-5.54 (m, 1H), 5.07-4.98 (m, 1H), 4.95-4.89 (m, 1H), 4.80-4.74 (m, 1H), 4.69-4.61 (m, 1H), 4.16-4.06 (m, 1H), 3.99-3.90 (m, 1H), 3.85-3.74 (m, 2H), 1.87 (s, 3H), 1.00 (s, 21 H); \textsuperscript{13}C NMR (75 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \( \delta \): 211.4, 143.7, 138.0, 133.2, 130.0, 127.4, 118.7, 78.4, 77.8, 49.3, 46.3, 21.6, 18.5, 11.5; IR (neat) 2942, 2889, 2864, 1933, 1594, 1462, 1348, 1166; MS \( m/z \) (%) 59 (28), 91 (55), 324 (34), 376 (100); EI-HRMS calcd for C\textsubscript{23}H\textsubscript{37}NO\textsubscript{2}SiS \[M+\] \( m/z \): 419.2314, found: 419.2325.
**N-(2-Propenyl)-N-(2,3-butadienyl)-4-methylbenzenesulfonamide (9w):** The general procedure for the Mitsunobu reaction (p. 56) was followed using \( N-(2\text{-propenyl})-4\text{-methylbenzenesulfonamide} \, 13d \) (102 mg, 0.484 mmol), \( \text{PPh}_3 \) (173 mg, 0.660 mmol), 2,3-butadiene-1-ol \( 14e \) (50 mg, 0.71 mmol), and DIAD (129 \( \mu \)L, 0.655 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 92 mg of ene-allene \( 9w \) in 72% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 7.70 (1/2 AA’XX’ d, \( J = 8.3 \) Hz, 2H), 7.28 (1/2 AA’XX’ d, \( J = 8.5 \) Hz, 2H), 5.66 (ddt, \( J = 17.4, 9.8, 6.4 \) Hz, 1H), 5.22-5.14 (m, 2H), 4.90 (dt, \( J = 6.8, 6.8 \) Hz, 1H), 4.70 (dt, \( J = 6.6, 2.5 \) Hz, 2H), 3.89-3.83 (m, 4H), 2.44 (s, 3H).

**N-(2-Bromo-2-propenyl)-N-(5,5-Dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9x):** \(^{62}\) To a flask charged with \( N-(5,5\text{-dimethyl-2,3-hexadienyl})-4\text{-methylbenzenesulfonamide} \, 15a \) (99 mg, 0.35 mmol) and \( \text{K}_2\text{CO}_3 \) (244 mg, 1.77 mmol) was added MeCN (1.2 mL) and 2,3-dibromo-1-propene (103 \( \mu \)L, 1.05 mmol). After 4 h of heating at reflux, TLC analysis indicated complete consumption of starting material. The slurry was concd in vacuo and partitioned between ethyl acetate/H\(_2\)O (1:1, 20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO\(_4\), and concd in vacuo. Purification by silica gel chromatography afforded 114 mg of pure ene-allene \( 9x \) as a slightly yellow oil in 81% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \): 7.73 (1/2 AA’XX’
d, \( J = 8.2 \text{ Hz}, 2\text{H} \), 7.30 (1/2 AA'XX' d, \( J = 8.4 \text{ Hz}, 2\text{H} \)), 5.87-5.85 (m, 1H), 5.61-5.59 (m, 1H), 5.13 (dt, \( J = 6.2, 2.3 \text{ Hz}, 1\text{H} \)), 4.96-4.88 (m, 1H), 4.08 (s, 2H), 3.89 (1/2 AB ddd, \( J = 15.2, 6.9, 2.1 \text{ Hz}, 1\text{H} \)), 3.82 (1/2 AB ddd, \( J = 15.2, 7.4, 2.3 \text{ Hz}, 1\text{H} \)), 2.43 (s, 3H), 1.00 (s, 9H).

\[
\begin{align*}
\text{TsHN} & \quad + \\
\text{14g} & \quad \text{14g} \\
\text{9y} & \quad \text{9y}
\end{align*}
\]

**N-(3-Methyl-2-butenyl)-N-(2,3-pentadienyl)-4-methylbenzene-sulfonamide (9y):** The general procedure for the Mitsunobu reaction (p. 56) was followed using 2,3-pentadien-1-ol 14g (145 mg, 1.68 mmol), THF (10 mL), N-(3-methyl-2-butenyl)-4-methylbenzenesulfonamide 13e (310 mg, 1.29 mmol), PPh\(_3\) (458 mg, 1.75 mmol), and DIAD (340 \( \mu \text{L}, 1.73 \text{ mmol} \)). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 220 mg of ene-allene 9y as a clear oil in 56% yield. \(^1\text{H NMR (300 MHz, CDCl}_3\) \( \delta \): 7.70 (1/2 AA'XX' d, \( J = 8.6 \text{ Hz}, 2\text{H} \)), 7.29 (1/2 AA'XX' d, \( J = 8.9 \text{ Hz}, 2\text{H} \)), 5.12-5.01 (m, 2H), 4.92-4.81 (m, 1H), 3.83 (bd, \( J = 7.2 \text{ Hz}, 2\text{H} \)), 3.79 (dd, \( J = 6.9, 2.2 \text{ Hz}, 2\text{H} \)), 2.43 (s, 3H), 1.68-1.62 (m, 6H), 1.61 (dd, \( J = 7.1, 3.1 \text{ Hz}, 3\text{H} \)).

\[
\begin{align*}
\text{TsHN} & \quad + \\
\text{14g} & \quad \text{14g} \\
\text{9z} & \quad \text{9z}
\end{align*}
\]

**N-(2,3-Decadienyl)-N-(3-methyl-2-butenyl)-4-methylbenzene-sulfonamide (9z):** The general procedure for the Mitsunobu reaction (p. 56) was followed using 2,3-decadien-1-ol 14d (578 mg, 3.75 mmol), THF (10 mL), N-(3-methyl-2-butenyl)-4-methylbenzenesulfonamide 13e (690 mg, 2.88 mmol), PPh\(_3\) (1.02 g, 3.89 mmol), and DIAD (766 \( \mu \text{L}, 3.89 \text{ mmol} \)). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 612 mg of ene-allene 9z as a clear oil in 70% yield. \(^1\text{H NMR (300 MHz, CDCl}_3\) \( \delta \): 7.70 (1/2
AA’XX’ d, J = 8.3 Hz, 2H), 7.28 (1/2 AA’XX’ d, J = 8.2 Hz, 2H), 5.10 (qt, J = 6.4, 2.4 Hz, 1H).
5.08-5.01 (m, 1H), 4.88 (ddt, J = 6.3, 6.3, 2.9 Hz, 1H), 3.84 (1/2 AB ddd, J = 15.4, 6.2, 2.4 Hz, 1H), 3.84 (bd, J = 7.7 Hz, 2H), 3.75 (1/2 AB ddd, J = 15.1, 7.2, 2.3 Hz, 1H), 2.42 (s, 3H), 1.95 (dd, J = 6.8, 6.8, 2.8 Hz, 2H), 1.67 (d, J = 0.9 Hz, 3H), 1.63 (d, J = 0.5 Hz, 3H), 1.41-1.24 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 205.0, 142.9, 136.6, 129.5, 127.3, 127.3, 119.2, 92.5, 86.9, 46.4, 44.3, 31.6, 29.2, 28.7, 28.6, 25.7, 22.6, 21.4, 17.8, 14.0.

**1-Ethoxycyclopropane-1-ol (34):**

To a flask charged with sodium (s, 1.51 g, 65.5 mg-atom), cut in small 5 mm cubes and washed with hexanes (2 x 10 mL), was added ether (28 mL) and the mixture was subsequently cooled to 0 °C before addition of chlorotrimethylsilane (3.65 mL, 28.8 mmol) and 3-chloropropionate (3.55 mL, 28.6 mmol). The flask was immersed in an ultrasonic cleaning bath$^{VIII}$ and held at 0 °C for 2.5 h then 2.2 h at rt whereupon a GC trace indicated complete conversion. The suspension was filtered over celite (30 mL) and concd in vacuo to give 2.82 g of the crude cyclopropane silylacetal 33 as an oil in 57% yield. To the crude silylacetal 33 dissolved in MeOH (7.2 mL) was added one drop of saturated HCl (in MeOH) and TLC indicated complete consumption of starting material after 2 h. The residual MeOH was carefully removed in vacuo (20 °C, 34 torr) and the crude residue was distilled (60 °C, 34 torr) to afford 178 mg of alcohol 34 as a colorless oil in 11% yield. $^1$H NMR (300 MHz, C$_6$D$_6$) δ: 3.61 (q, J = 7.1 Hz, 2H), 2.54 (bs, 1H), 1.09 (t, J = 7.1 Hz, 3H), 0.86-0.80 (m, 2H), 0.77-0.72 (m, 2H).

$^{VIII}$ Branson 2510 cleaning bath, 100 W, 42 KHz.
1-vinylcyclopropanol (16h):\textsuperscript{83} To a flask containing vinylmagnesium bromide (5.6 mmol) in THF (5.6 mL) at reflux was added 1-Ethoxycyclopropane-1-ol 34 (178 mg, 1.75 mmol) in THF (200 µL) via cannulae. After 40 min the solution was cooled to rt then rapidly poured into saturated NH₄Cl (10 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were dried over MgSO₄ and carefully concd in vacuo (bath temp 17 °C) to give 118 mg of crude cyclopropanol 16h in a calculated 24% yield.\textsuperscript{IX} \textsuperscript{1}H NMR (300 MHz, CDCl₃) δ: 5.61 (dd, \( J = 17.1, 10.6 \) Hz, 1H), 5.28 (dd, \( J = 17.1, 1.1 \) Hz, 1H), 5.07 (dd, \( J = 10.6, 1.0 \) Hz, 1H), 4.75 (s, 1H), 1.10-1.04 (m, 2H), 0.76-0.71 (m, 2H).

\[
\begin{align*}
\text{OMs} & \quad \text{t-Bu} \\
\text{TsHN} & \quad \text{35} \\
\end{align*}
\]

\[
\begin{align*}
\text{15a} & \quad \text{TsN} \quad \text{t-Bu} \\
\text{9A} & \quad \text{35} \\
\end{align*}
\]

\textsuperscript{N-(Ethyl-2-cyclopropylidene)-N-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9A):\textsuperscript{84} To a solution of alcohol 16h (118 mg, 1.40 mmol) and triethylamine (270 µL, 1.94 mmol) at -30 °C in DCM (7.0 mL) was added methansulfonyl chloride (130 µL, 1.68 mmol) dropwise. After 45 min at -30 °C the slurry was warmed to rt and was poured into a separatory funnel with ice/water (20 mL) and the organic layer was drawn off. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers dried over MgSO₄ and concd in vacuo to afford crude mesylate 35. To a solution of \textsuperscript{N-(5,5-Dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide 15a (112 mg, 0.401 mmol) in THF (1mL) at rt was}

\textsuperscript{IX} Sample possessed 70% ethanol by \textsuperscript{1}H NMR.
added NaH (60 wt., 17 mg, 0.43 mmol) and it was held at rt until no further gas evolution was observed. The solvent was evaporated via N₂ stream followed by addition of a solution of mesylate 35, Pd(PPh₃)₄ (19 mg, 0.016 mmol), and DMSO (570 µL) in THF (2.30 mL) via cannulae. After 18.5 h the mixture was concd in vacuo and partitioned between ethyl acetate/(½) saturated brine (20 mL/20 mL). The organic layer was washed with H₂O (20 mL), brine (20 mL), dried over MgSO₄, and concd in vacuo. Purification of the crude residue by silica gel chromatography afforded 35 mg of pure ene-allene 9A as a colorless oil in 25% overall yield (2 steps, ¹H NMR showed minor impurities). ¹H NMR (300 MHz, CDCl₃) δ: 7.70 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 7.27 (1/2 AA′XX′ d, J = 8.5 Hz, 2H), 5.68-5.60 (m, 1H), 5.10 (dt, J = 6.2, 2.4 Hz, 1H), 5.00 (dt, J = 7.2, 6.3 Hz, 1H), 3.98 (bd, J = 6.6 Hz, 2H), 3.87 (1/2 AB ddd, J = 15.0, 6.3, 2.5 Hz, 1H), 3.72 (1/2 AB ddd, J = 15.0, 7.4, 2.3 Hz, 1H), 2.41 (s, 3H), 1.07-1.01 (m, 4H), 0.99 (s, 9H); ¹³C NMR (75 MHz, CD₂Cl₂) δ: 202.7, 143.7, 138.5, 130.0, 127.5, 127.4, 113.3, 104.8, 89.2, 48.5, 47.1, 32.1, 30.2, 21.6, 2.7, 2.2; IR (neat) 3060, 2961, 2925, 2865, 1960, 1598, 1494, 1475, 1461, 1438, 1345, 1305, 1159; Ei-HRMS calcd for C₂₀H₂₇NO₂S [M+Na⁺] m/z: 368.1660, found: 368.1631.

3-Methyl-2-butenyl-2,2,2-trichloroethanimidate (35): A round bottom flask was charged with sodium hydride (60% wt in mineral oil, 28 mg, 0.12 mmol) and the emersion was washed with hexanes (3 mL). To the flask was added ether (33 mL) and 3-methyl-2-buten-1-ol (590 µL, 5.81 mmol) as a solution in ether (11 mL). Another portion of sodium hydride (60% wt in mineral oil, 27 mg, 0.12 mmol) was added and the slurry was cooled to -5 °C. Neat trichloroacetonitrile (580 µL, 5.78 mmol) was then added and after 4 h at -5 °C the suspension
was poured into pentanes (75 mL) containing MeOH (100 µL) and filtered. The filter cake was washed with pentanes (50 mL) and the filtrate concd in vacuo to give 1.066 g of crude imidate 35 in 80% yield (1H NMR showed an impurity). 1H NMR (300 MHz, CDCl3) δ: 8.25 (bs, 1H), 5.51-5.44 (m, 1H), 4.79 (d, J = 7.0 Hz, 2H), 1.79 (s, 3H), 1.74 (s, 3H).

N-(1,1-Dimethyl-2-propenyl)-2,2,2-trichloroacetamide (13f): To a solution of 3-methyl-2-butene-2,2,2-trichloroethanimidate 35 (212 mg, 0.921 mmol) in THF (4.6 mL) at -78 °C was added mercuric trifluoroacetate (87 mg, 0.19 mmol) in one portion under positive N2. The cold bath was removed after 10 min and the solution was allowed to warm to rt. After 1 h a solution of NaBH4 in DME (1 M, 200 µL) was added dropwise and the slurry was concd in vacuo. Purification by silica gel chromatography (ethyl acetate-hexanes 1:19-1:14; column was pretreated with 1% TEA/hexanes) afforded 134 mg of pure trichloroacetamide 13f in 63% yield. 1H NMR (300 MHz, CDCl3) δ: 6.58 (bs, 1H), 6.01 (dd, J = 17.4, 10.7 Hz, 1H), 5.21 (d, J = 17.4 Hz, 1H), 5.15 (d, J = 10.7 Hz, 1H), 1.52 (s, 6H).

N-(1,1-Dimethyl-2-propenyl)aminehydrochloride (26b): To a solution of N-(1,1-dimethyl-2-propenyl)-2,2,2-trichloroacetamide 13f (390 mg, 1.69 mmol) in EtOH (9.0 mL) was added a solution of NaOH aq (6 M, 8.5 mL, 51 mmol). After 18 h the solution was extracted with ether (3 x 30 mL) and the combined organic layers were washed with brine (20 mL), dried over Na2SO4 (a small amount of MgSO4 was added to clarify the solution) and filtered. The filter
cake was washed with ether (15 mL) and the filtrate was acidified by bubbling HCl (g) through the solution for 6 min. The resulting suspension was concd in vacuo and washed with benzene to afford 200 mg of pure aminehydrochloride salt 26b in 97% yield. $^1$H NMR (300 MHz, D$_2$O) $\delta$: 6.02 (dd, $J = 17.5$, 11.0 Hz, 1H), 5.34 (d, $J = 17.6$ Hz, 1H), 5.33 (d, $J = 10.8$ Hz, 1H), 1.48 (s, 6H).

\[
\text{Cl} \quad \text{H}_3\text{N} \quad \rightarrow \quad \text{TsH} \quad \text{N} \\
\text{26b} \quad \rightarrow \quad \text{13g}
\]

$N$-(1,1-Dimethyl-2-propenyl)-4-methylbenzenesulfonamide (13g): To a flask charged with $N$-(1,1-dimethyl-2-propenyl)aminehydrochloride 26b (170 mg, 1.40 mmol) was added DCM (7 mL) and $p$-toluenesulfonylchloride (323 mg, 1.70 mmol). To the suspension at 0 °C was added triethylamine (590 µL, 4.23 mmol) dropwise and it was then warmed to rt. After 18.7 h the mixture was concd in vacuo and the crude semisolid was partitioned between H$_2$O/ethyl acetate (20 mL/15 mL). The aqueous layer was extracted with ethyl acetate (2 x 15 mL) and the combined organic layers were washed with brine (15 mL), dried over MgSO$_4$, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:9-1:4) to afford 191 mg of tosylamide 13g as a slightly yellow oil in 57% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 7.75 (1/2 AA$^\prime$XX$^\prime$ d, $J = 8.3$ Hz, 2H), 7.27 (1/2 AA$^\prime$XX$^\prime$ d, $J = 8.3$ Hz, 2H), 6.73 (dd, $J = 17.3$, 10.6 Hz, 1H), 5.10 (d, $J = 17.3$ Hz, 1H), 4.96 (d, $J = 10.7$ Hz, 1H), 4.54 (bs, 1H), 2.42 (s, 3H), 1.30 (s, 6H).
\(N\)-(1,1-Dimethyl-2-propenyl)-\(N\)-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzene-sulfonamide (9B): The general procedure for the Mitsunobu reaction (p. 56) was followed using \(N\)-(1,1-Dimethyl-2-propenyl)-4-methylbenzenesulfonamide 13g (192 mg, 0.796 mmol), PPh\(_3\) (291 mg, 1.14 mmol), DIAD (277 \(\mu\)L, 1.41 mmol), and 5,5-Dimethyl-2,3-hexadien-1-ol 14a (133 mg, 1.05 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:6) to afford 47 mg of ene-allene 9B as a colorless oil in 17% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.74 (1/2 AA’XX’ d, \(J = 8.3\) Hz, 2H), 7.25 (1/2 AA’XX’ d, \(J = 8.0\) Hz, 2H), 5.93 (dd, \(J = 17.5, 10.7\) Hz, 1H), 5.40 (q, \(J = 6.6, 1\)H), 5.18 (dt, \(J = 6.3, 2.4\) Hz, 1H), 5.07 (d, \(J = 17.7\) Hz, 1H), 5.02 (dd, \(J = 10.8, 0.5\) Hz, 1H), 4.03 (1/2 AB ddd, \(J = 16.0, 6.4, 2.4\) Hz, 1H), 3.92 (1/2 AB ddd, \(J = 16.0, 7.0, 2.4\) Hz, 1H), 2.41 (s, 3H), 1.41 (s, 6H), 1.05 (s, 9H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 201.2, 144.3, 142.6, 141.1, 129.3, 127.0, 112.7, 104.4, 92.7, 62.6, 46.4, 32.1, 30.1, 26.9, 26.8, 21.5; IR (neat) 3083, 2960, 2930, 2863, 1962, 1598, 1455, 1327 cm\(^{-1}\); MS \(m/z\) (%) 69 (86), 91 (48), 155 (57), 184 (100), 252 (53), 347 (11); EI-HRMS calcd for C\(_{20}\)H\(_{29}\)NO\(_2\)S [M+] \(m/z\): 347.1919, found: 347.1928.

\[
\begin{align*}
\text{CbzHN} & \quad \text{OH} & \quad \text{CbzHN} & \quad \text{OH} \\
\text{CO}_2\text{H} & & \text{CO}_2\text{H} & & \text{CO}_2\text{H} & & \text{CO}_2\text{H}
\end{align*}
\]

2-Benzylxycarbonylamino-2,3-dimethyl-3,4-hexadienoic acid (17a):\(^{58}\) To a solution of 3-pentyn-1-ol (556 mg, 6.61 mmol) in DCM (10 mL) was added DCC (1.507 g, 7.30 mmol) and DMAP (810 mg, 6.63 mmol) followed by \(N\)-Cbz-alanine (1.56 g, 6.97 mmol) (an exothermic reaction was noted). After 1.5 h at rt the suspension was diluted with hexanes (7 mL) and filtered through a plug of silica (30 mL) which was washed with ethyl acetate-hexanes (1:1, 100 mL). The filtrate was concd in vacuo and purified by silica gel chromatography (ethyl-acetate-
hexanes 1:9-1:4) to afford 1.40 g of amino ester 36 in 73% yield. To a solution of diisopropylamine (580 µL, 4.15 mmol) in THF (4.2 mL) at -25 °C was added n-butyllithium (1.6 M in hexanes, 2.57 mL, 4.11 mmol) dropwise. The solution was then cooled to -78 °C whereupon amino ester 36 (475 mg, 1.64 mmol) was added as a solution in THF (4.0 mL). To the solution was added ZnCl₂ (0.5 M in THF, 4.0 mL, 2.0 mmol) and it was then allowed to warm to rt overnight whereupon it was diluted with ether (75 mL) and quenched with HCl aq (1 M, 20 mL). The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic layers were washed with HCl aq (1 M, 20 mL), brine (30 mL), dried over MgSO₄ and concd in vacuo to afford 403 mg of amino acid 17a in 85% yield.

2-[(E)-Benzyloxycarbonyl-2-butenylamino]-2,3-dimethyl-3,4-hexadienoic acid methyl ester (9C): To a solution of 17a (403 mg, 1.39 mmol) in DMF (3.5 mL) was added KHCO₃ (349 mg, 3.49 mmol) and iodomethane (175 µL, 2.81 mmol). After 2.3 h at rt the suspension was poured into H₂O (75 mL). The aqueous layer was extracted with ethyl acetate (3 x 80 mL) and the combined organic layers were washed with H₂O (75 mL), brine (75 mL), dried over MgSO₄ and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:7) to afford amino ester 17b in 38% yield. To a solution of amino ester 17b (99 mg, 0.33 mmol) in DMF (1.7 mL) at rt was added NaH (60% wt in mineral oil, 21 mg, 0.53 mmol) in one portion. After 20 min at rt crotylbromide (67 µL, 0.65 mmol) was added and TLC analysis indicated a complete reaction after 6 min. The slurry was poured into H₂O (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers
were washed with H₂O (3 x 15 mL), brine (15 mL), dried over MgSO₄, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:7) to afford 87 mg of ene-allene **9C** as a clear oil in 74% yield. **¹H NMR** (300 MHz, CDCl₃) δ: 7.36-7.28 (m, 5H), 5.62-5.44 (m, 2H), 5.24-5.14 (m, 1H), 5.11 (s, 2H), 4.16-3.99 (m, 1H), 3.85-3.51 (m, 4H), 1.77-1.72 (m, 3H), 1.65-1.61 (m, 5H), 1.59-1.55 (m, 4H).

### A.2 CYCLIZATION OF ENE-ALLENES TO FORM AZEPINES

The cycloisomerization of each ene-allene to form its corresponding azepine(s) is described sequentially.

**5-[(E)-Heptylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine** (10a; **entry 14, Table 3**): Cycloisomerization of ene-allene **9a** has previously been described.²⁰

**1-(4-Methylbenzenesulfonyl)-5-(1-methylethylidene]-4,5,6,7-tetrahydro-1H-azepine** (10b; **entry 40, Table 6**): Cycloisomerization of ene-allene **9b** has previously been described.²⁰

The **General Procedure for Azepine Formation**: **5-[(E)-2,2-Dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4-phenyl-4,5,6,7-tetrahydro-1H-azepine** (10c; **entry 31, Table 5**):
Ene-allene 9c (20 mg, 0.052 mmol) was dissolved in 1,2-dimethoxyethane (510 µL) and twice degassed via freeze-pump-thaw method followed by addition of [Rh(CO)2Cl]2 (2.0 mg, 0.0051 mmol) under an argon atmosphere. It was heated to reflux (95 °C) and reaction progress was monitored by TLC (benzene), reaching completion after 2 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 18 mg of azepine 10c as a colorless oil 90% yield. 1H NMR (300 MHz, C6D6) δ: 7.65 (1/2 AA′XX′ d, J = 8.1 Hz, 2H), 7.21-7.06 (m, 4H), 7.05-6.98 (m, 1H), 6.94 (d, J = 9.4 Hz, 1H), 6.73 (1/2 AA′XX′ d, J = 8.0 Hz, 2H), 5.35 (s, 1H), 4.91 (dd, J = 9.1, 7.9 Hz, 1H), 3.90 (d, J = 7.5 Hz, 1H), 3.45-3.28 (m, 2H), 2.81 (ddd, J = 20.7, 10.8, 5.0 Hz, 1H), 1.94 (bd, J = 16.9 Hz, 1H), 1.86 (s, 3H), 0.98 (s, 9H); 13C NMR (75 MHz, CD2Cl2) δ: 144.3, 143.9, 140.4, 137.1, 137.0, 130.2, 128.8, 128.6, 127.7, 127.1, 126.4, 112.7, 47.0, 32.7, 31.1, 29.2, 21.6; IR (thin film) 3058, 3022, 2955, 2899, 2863, 1649, 1598, 1491, 1450, 1352, 1332 cm⁻¹; MS m/z (%) 91 (100), 121 (84), 184 (49), 240 (43), 338 (60), 395 (30); El-HRMS calcd for C24H29NO2S [M+] m/z: 395.1919, found: 395.1921.

5-[(E)-2,2-Dimethylpropylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10f; entry 25, Table 4): The general procedure for azepine formation (p. 88) was followed using ene-allene 9e (29 mg, 0.086 mmol), [Rh(CO)2Cl]2 (2.0 mg, 0.0051 mmol), and 1,4-dioxane (860 µL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 2 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 12 mg of azepine 10f as a colorless oil 43% yield. The 1H NMR spectrum was identical to the product previously reported.20
4-Methyl-1-(4-methylbenzenesulfonyl)-5-[(E)-1-phenylmethylidine]-4,5,6,7-tetrahydro-1H-azepine (10e; entry 20, Table 3). The general procedure for azepine formation (p. 88) was followed using ene-allene 9e (23 mg, 0.065 mmol), [Rh(CO)₂Cl]₂ (1.4 mg, 0.0036 mmol), 1,4-dioxane (650 µL), under a carbon monoxide atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 15 min. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 11 mg of azepine 10e as a clear oil in 52% yield. ¹H NMR (300 MHz, CD₂Cl₂) δ: 7.57 (1/2 AA’XX’ d, J = 8.3 Hz, 2H), 7.32-7.26 (m, 2H), 7.23-7.19 (m, 1H), 7.16 (1/2 AA’XX’ d, J = 8.1 Hz, 2H), 7.07 (bd, J = 7.07 Hz, 1H), 6.40 (dd, J = 9.2, 1.6 Hz, 1H), 6.27 (s, 1H), 4.91 (dd, J = 9.2, 5.1 Hz, 1H), 3.72-3.66 (m, 2H), 3.33-3.22 (m, 1H), 2.69-2.65 (m, 2H), 2.35 (s, 3H), 1.24 (d, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CD₂Cl₂) δ: 144.1, 142.6, 138.0, 137.0, 130.0, 129.2, 128.4, 127.1, 126.9, 126.7, 125.4, 118.7, 47.9, 40.2, 30.8, 21.7, 20.9; IR (neat) 3053, 3022, 2960, 2925, 2879, 1721, 1644, 1598, 1491, 1455, 1347 cm⁻¹; MS m/z (%) 91 (100), 129 (38), 169 (36), 198 (72), 338 (17), 353 (16); EI-HRMS calcd for C₂₁H₂₃NO₂S [M⁺] m/z: 353.1450, found: 353.1454.

5-[(E)-2,2-Dimethylpropylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10f; entry 17, Table 3): The general procedure for azepine formation (p. 88) was followed using ene-allene 9f (118 mg, 0.355 mmol), [Rh(CO)₂Cl]₂ (3.4 mg, 0.0088 mmol), and
1,4-dioxane (2.60 mL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 6 min. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 89 mg of azepine 10f as a colorless oil 75% yield. The $^1$H NMR spectrum was identical to the product previously reported.20

5-[(E)-2,2-Dimethylpropylidene]-3-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10g; entry 43, Table 7): The general procedure for azepine formation (p. 88) was followed using ene-allene 9g (17 mg, 0.051 mmol), [Rh(CO)$_2$Cl]$_2$ (1.0 mg, 0.0026 mmol), and 1,4-dioxane (510 µL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 15 min. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 14 mg of azepine 10g as a colorless oil in 83% yield. $^1$H NMR (300 MHz, C$_6$D$_6$) δ: 7.74 (1/2 AA′XX′ d, $J = 8.3$ Hz, 2H), 6.76 (1/2 AA′XX′ d, $J = 8.4$ Hz, 2H), 6.39 (s, 1H), 5.18 (s, 1H), 3.49-3.43 (m, 2H), 2.46 (s, 2H), 2.45-2.39 (m, 2H), 1.87 (s, 3H), 1.45 (d, $J = 0.7$ Hz, 3H), 0.97 (s, 9H), $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$) δ: 143.9, 137.9, 137.2, 133.2, 130.1, 128.6, 127.1, 126.1, 122.6, 48.5, 43.7, 43.4, 32.4, 31.2, 32.1, 22.7, 21.6; IR (neat) 3027, 2955, 2925, 2963, 1665, 1593, 1434, 1342, 1158 cm$^{-1}$; MS m/z (%): 57 (72), 91 (100), 93 (71), 108 (77), 122 (70), 178 (65), 333 (68); EI-HRMS calcd for C$_{19}$H$_{27}$NO$_2$S [M+] m/z: 333.1763, found: 333.1769.
4,4-Dimethyl-5-[(E)-2,2-dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10h; entry 50, Table 8): The general procedure for azepine formation (p. 88) was followed using ene-allene 9h (70 mg, 0.20 mmol), [Rh(CO)\textsubscript{2}Cl\textsubscript{2}] (7.6 mg, 0.020 mmol), and 1,4-dioxane (2.0 mL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 2.3 h. The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 17 mg of impure azepine 10h as a slightly yellow oil. An HPLC purification of the impure sample provided 8 mg of pure product indicating a 13% overall yield. \textsuperscript{1}H NMR (300 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \(\delta\): 7.65 (1/2 AA’XX’ d, \(J\) = 8.4 Hz, 2H), 7.32 (1/2 AA’XX’ d, \(J\) = 8.3 Hz, 2H), 6.15 (d, \(J\) = 9.7 Hz, 1H), 5.30 (s, 1H), 4.70 (d, \(J\) = 9.8 Hz, 1H), 3.50-3.44 (m, 2H), 2.61-2.55 (m, 2H), 2.41 (s, 3H), 1.08 (s, 6H), 1.07 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \(\delta\): 144.1, 141.9, 136.1, 134.1, 130.0, 127.4, 125.9, 122.4, 50.1, 42.7, 32.4, 31.7, 30.7, 27.3, 21.6; IR (neat) 2960, 2868, 1650, 1598, 1465, 1347 cm\textsuperscript{-1}; MS m/z (%) 57 (56), 85 (59), 91 (92), 136 (51), 192 (49), 290 (83), 332 (100), 333 (32), 347 (34); El-HRMS calcd for C\textsubscript{20}H\textsubscript{29}NO\textsubscript{2}S \([\text{M+}] m/z\) 347.1919, found: 347.1925.

5-[(E)-2,2-Dimethylpropylidene]-2-(4-methylbenzenesulfonyl)-3,4,5,5a,6,7,8,9-octahydro-1H-benzo[c]azepine (10i; entry 47, Table 8): The general procedure for azepine formation (p. 88) was followed using ene-allene 9i (30 mg, 0.080 mmol), [Rh(CO)\textsubscript{2}Cl\textsubscript{2}] (2.2 mg, 0.0057 mmol), and 1,4-dioxane (780 \(\mu\)L) under an argon atmosphere. The crude solution was concd after 13.3 h and purified by silica gel chromatography (benzene), to afford 23 mg of azepine 10i as a colorless oil in 78% yield. \textsuperscript{1}H NMR (300 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \(\delta\): 7.67 (1/2 AA’XX’ d, \(J\) = 8.4 Hz,
2H), 7.32 (1/2 AA’XX’ d, J = 8.0 Hz, 2H), 6.09 (s, 1H), 5.32 (s, 1H), 3.68 (1/2 AB ddd, J = 13.0, 6.7, 4.8 Hz, 1H), 3.40 (1/2 AB ddd, J = 13.1, 9.2, 5.5 Hz, 1H), 2.98 (ddd, J = 14.6, 9.2, 6.8 Hz, 1H), 2.64-2.56 (m, 1H), 2.42 (s, 3H), 2.23-2.11 (m, 2H), 2.01-1.88 (m, 1H), 1.87-1.72 (m, 2H), 1.66-1.59 (m, 1H), 1.49-1.39 (m, 2H), 1.28-1.17 (m, 1H), 1.08 (s, 9H); 13C NMR (75 MHz, CD2Cl2) δ: 143.9, 138.5, 137.5, 136.9, 132.9, 130.0, 127.3, 119.9, 54.8, 50.6, 35.8, 35.6, 32.5, 31.5, 29.4, 28.0, 27.0, 21.6; IR (neat) 2930, 2858, 1660, 1598, 1445, 1347, 1168 cm⁻¹; MS m/z (%) 57 (78), 91 (100), 133 (43), 148 (54), 160 (70), 162 (80), 218 (98), 316 (26), 373 (26); EI-HRMS calcd for C22H31NO2S [M+] m/z: 373.2076, found: 373.2093.

5-(2,2-Dimethylpropylidene)-1-(4-methylbenzenesulfonyl)-4-(trimethylsilyl)-4,5,6,7-tetrahydro-1H-azepine (10j; entry 36, Table 5): Cycloisomerization of ene-allene 9j has previously been described.²⁰

4-(Benzhydryldimethylsilyl)-5-(2,2-dimethylpropylidene)-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10k; entry 37, Table 5): Cycloisomerization of ene-allene 9k has previously been described.²⁰
4-Propyl-5-[(E)-heptylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10l; entry 23, Table 3): The general procedure for azepine formation (p. 88) was followed using ene-allene 9l (27 mg, 0.068 mmol), [Rh(CO)₂Cl]₂ (1.6 mg, 0.0041 mmol), and 1,4-dioxane (680 µL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 33 min. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 14 mg of azepine 10l as a colorless oil 53% yield. ¹H NMR (300 MHz, CD₂Cl₂) δ: 7.66 (1/2 AA’XX’ d, J = 8.3 Hz, 2H), 7.31 (1/2 AA’XX’ d, J = 8.5 Hz, 2H), 6.35 (d, J = 9.3 Hz, 1H), 5.13 (bt, J = 7.1 Hz, 1H), 4.96 (dd, J = 9.3, 6.3 Hz, 1H), 3.64 (1/2 AB ddd, J = 13.8, 8.9, 4.0 Hz, 1H), 3.51 (1/2 AB ddd, J = 13.8, 6.6, 4.4 Hz, 1H), 2.78-2.71 (m, 1H), 2.62-2.50 (m, 1H), 2.41 (s, 3H), 2.24-2.15 (m, 1H), 1.82-1.72 (m, 2H), 1.43-1.17 (m, 12H), 0.90-0.85 (m, 3H), 0.84 (t, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CD₂Cl₂) δ: 144.0, 137.1, 137.0, 130.0, 127.7, 127.1, 126.5, 118.9, 48.7, 47.4, 37.4, 32.1, 30.0, 29.4, 28.4, 27.8, 23.0, 21.6, 21.1, 14.2, 14.1; IR (neat) 3042, 2955, 2920, 2853, 1726, 1650, 1593, 1455, 1343, 1163 cm⁻¹; MS m/z (%): 91 (65), 346 (100), 347 (28), 389 (19); EI-HRMS calcd for C₂₃H₃₅NO₂S [M+] m/z: 389.2389, found: 389.2373.

2,4-Dimethyl-5-[(E)-2,2-dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10m; Eq. 36); 5,7-Dimethyl-4-[(E)-2,2-dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10m;’ Eq. 36): The general procedure for azepine formation (p. 88) was followed using ene-allene 9m (84 mg, 0.242 mmol), [Rh(CO)₂Cl]₂ (9.3 mg, 0.0239 mmol), and DCE (1.20 mL) under an argon atmosphere.
progress was monitored by TLC (benzene), reaching completion after 2.3 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 33 mg of azepine 10m as a clear oil in 39% yield and azepine 10m′ as a white solid (mp 109-112 °C) in 27% yield.

1H NMR 10m (300 MHz, CD6) δ: 7.80 (1/2 AA’XX’ d, J = 8.3 Hz, 2H), 6.76 (1/2 AA’XX’ d, J = 7.9 Hz, 2H), 5.20 (bs, 1H), 4.96-4.91 (m, 1H), 3.74 (ddd, J = 13.7, 6.1, 4.5 Hz, 1H), 3.07 (ddd, J = 13.7, 8.3, 4.2 Hz), 2.66-2.55 (m, 1H), 2.54-2.43 (m, 2H), 1.95 (t, J = 1.25 Hz, 3H), 1.88 (s, 3H), 1.03 (s, 9H), 0.93 (d, J = 7.2 Hz, 3H); 13C NMR 10m (75 MHz, CD2Cl2) δ: 143.4, 138.7, 136.8, 135.5, 134.1, 131.2, 129.6, 127.0, 49.3, 31.8, 31.3, 31.0, 21.8, 21.3, 19.2; IR 10m (neat) 2950, 2919, 2853, 1731, 1660, 1593, 1455, 1347 cm−1; MS m/z (%) 57 (73), 68 (100), 91 (66), 122 (67), 192 (52), 332 (24), 347 (8); EI-HRMS calcd for 10m C20H29NO2S [M+] m/z: 347.1919, found: 347.1918. 1H NMR 10m′ (300 MHz, CD6) δ: 7.73 (1/2 AA’XX’ d, J = 8.3 Hz, 2H), 6.72 (1/2 AA’XX’ d, J = 8.2 Hz, 2H), 6.58 (d, J = 9.15 Hz, 1H), 5.87 (dd, J = 9.1, 1.1 Hz, 1H) 5.17 (d, J = 1.1 Hz, 1H), 4.53-4.39 (m, 1H), 2.40-2.27 (m, 1H), 2.12 (ddd, J = 13.2, 8.5, 5.8 Hz, 1H), 1.84 (s, 3H), 1.07 (s, 9H), 0.95 (d, J = 7.2 Hz, 3H), 0.90-0.80 (m, 1H), 0.75 (d, J = 6.8 Hz, 3H); 13C NMR 10m′ (75 MHz, CD2Cl2) δ: 144.2, 138.3, 137.4, 135.3, 130.1, 127.1, 123.0, 115.6, 45.8, 37.7, 32.6, 31.2, 21.6, 20.4, 19.7; IR 10m′ (thin film) 2955, 2919, 2853, 1737, 1639, 1598, 1455, 1347 cm−1; MS m/z (%) 57 (100), 71 (56), 85 (38), 91 (40), 177 (25), 347 (21); EI-HRMS calcd for 10m′ C20H29NO2S [M+] m/z: 347.1919, found: 347.1910.

**Attempted cycloisomerization of ene-allene 9n (entry 12, Table 3):** The general procedure for azepine formation (p. 88) was followed using ene-allene 9n (51 mg, 0.184 mmol), [Rh(CO)2Cl]2 (7.2 mg, 0.0185 mmol), and DCE (920 µL) under a carbon monoxide atmosphere.
Reaction progress was monitored by GC (Col. temp: 225 °C, inj. temp: 250 °C, det. temp: 250 °C), showing complete consumption of starting material after 3.3 h. After cooling to rt the solution was diluted with hexanes and purified by silica gel chromatography (ethyl acetate-hexanes 1:9; column was pretreated with 1% triethylamine/hexanes) to afford 3.4 mg of an impure, unidentifiable material.

\[
\begin{align*}
\text{TsN} & \quad \text{D} \quad \text{D} \\
\text{t-Bu} & \quad \quad \quad \quad \\
\text{9o} & \quad \quad \quad \quad \\
\rightarrow & \\
\text{D} & \quad \text{D} \\
\text{TsN} & \quad \text{t-Bu} \\
\quad & \quad \\
\text{10o} & 
\end{align*}
\]

5-[(E)-2,2-Dimethylpropylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine-2,6-d$_2$ (10o; Eq. 33): Cycloisomerization of ene-allene 9o has previously been described.$^{20}$

\[
\begin{align*}
\text{BocN} & \quad \text{D} \quad \text{D} \\
\text{t-Bu} & \quad \quad \quad \quad \\
\text{9p} & \quad \quad \quad \quad \\
\rightarrow & \\
\text{D} & \quad \text{D} \\
\text{BocN} & \quad \text{t-Bu} \\
\quad & \quad \\
\text{10p} & 
\end{align*}
\]

1-Carboxylic acid-t-butylester-5-[(E)-2,2-dimethylpropylidene]-4-methyl-4,5,6,7-tetrahydro-1H-azepine-2,6-d$_2$ (10p; Eq. 34). The general procedure for azepine formation (p. 88) was followed using ene-allene 9p (53 mg, 0.18 mmol), DCE (940 µL), and [Rh(CO)$_2$Cl]$_2$ (7.5 mg, 0.019 mmol) under an argon atmosphere. Reaction progress was monitored by GC (Col. temp: 225 °C, inj. temp: 250 °C, det. temp: 250 °C), reaching completion after 1.7 h. The solution was diluted with hexanes (1.5 mL) and purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 36 mg of azepine 10p as a colorless oil 68% yield. $^1$H NMR [300 MHz, (CD$_3$)$_2$SO, 60 °C] δ: 5.24 (bs, 1H), 4.74 (bd, J = 4.9 Hz, 1H), 3.70 (dd, J = 13.9, 5.2 Hz, 1H), 3.59 (dd, J = 13.9, 7.5 Hz, 1H), 3.08-2.97 (m, 1H), 2.66 (bt, J = 5.6 Hz, 1H), 1.40 (s, 9H), 1.11
(d, J = 7.2 Hz, 3H), 1.06 (s, 9H); $^{13}$C NMR [75 MHz, (CD$_3$)$_2$SO, 60 °C] δ: 152.0, 138.7, 134.7, 127.3 (t), 118.1, 79.4, 69.0, 31.0, 30.9, 30.8, 28.2 (t), 27.6; IR (thin film) 2959, 2925, 2869, 1705, 1634, 1458, 1391, 1366, 1347, 1252, 1206, 1171, 1140.

**Attempted cycloisomerization of ene-allene 9q (entry 24, Table 4):**

The general procedure for azepine formation was followed (p. 88) using ene-allene 9q (37 mg, 0.10 mmol), DCE (500 µL), and [Rh(CO)$_2$Cl]$_2$ (2.0 mg, 0.0051 mmol) under an argon atmosphere. Reaction progress was monitored by GC (Col. temp: 225 °C, inj. temp: 250 °C, det. temp: 250 °C), where the starting material was completely consuming after 23 h. A crude $^1$H NMR displayed no signs of the desired azepine 10q.

**1-(4-Methylbenzenesulfonyl)-5-[(E)-methylidene-1-(triisopropylsilyl)]-4-phenyl-4,5,6,7-tetrahydro-1H-azepine (10r; entry 33, Table 5):** The general procedure for azepine formation (p. 88) was followed using ene-allene 9r (23 mg, 0.046 mmol), 1,4-dioxane (460 µL), and [Rh(CO)$_2$Cl]$_2$ (1.1 mg, 0.0028 mmol) under an argon atmosphere. Monitoring the reaction by TLC (benzene) showed a halt in progress after 14.3 h of heating. The solution was concd in vacuo after 5 h of additional heating and purified by silica gel chromatography (benzene; column was pretreated with 1% triethylamine/hexanes) to afford 9.0 mg of azepine 10r as a slightly yellow oil in 40% yield ($^1$H NMR contained impurities). $^1$H NMR (300 MHz, C$_6$D$_6$) δ: 7.63 (1/2
AA’XX’ d, J = 8.3 Hz, 2H), 7.23-6.97 (m, 5H), 6.90 (d, J = 9.5 Hz, 1H), 6.72 (1/2 AA’XX’ d, J = 8.0 Hz, 2H), 5.41 (s, 1H), 4.90 (dd, J = 9.5, 7.2 Hz, 1H), 4.23 (d, J = 7.1 Hz, 1H), 3.44 (dt, J = 13.7, 4.6 Hz, 1H), 3.32 (ddd, J = 13.6, 10.3, 3.6 Hz, 1H), 2.70 (ddd, J = 15.3, 10.2, 4.9 Hz, 1H), 2.37-2.29 (m, 1H), 1.84 (s, 3H), 1.15-1.08 (m, 21H). 13C NMR (75 MHz, CD2Cl2) δ: 157.4, 144.3, 143.3, 136.4, 130.2, 129.1, 128.6, 127.9, 127.2, 126.5, 125.0, 112.0, 56.5, 47.0, 34.9, 21.6, 19.1, 12.6; IR (neat) 3060, 3023, 2942, 2886, 2864, 2357, 2332, 1655, 1594, 1488, 1465, 1401, 1349, 1164; EI-HRMS calcd for C29H41NO2SiS [M+Na+] m/z: 518.2525, found: 518.2535.

4-Methyl-1-(4-methylbenzenesulfonyl)-5-[(E)-methylidene-1-(triisopropylsilyl)]-4,5,6,7-tetrahydro-1H-azepine (10s; entry 34, Table 5): The general procedure for azepine formation (p. 88) was followed using ene-allene 9s (14 mg, 0.032 mmol), 1,4-dioxane (500 µL), and [Rh(CO)2Cl]2 (0.8 mg, 0.0021 mmol) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 1.3 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene; column was pretreated with 1% triethylamine/hexanes) to afford 33 mg of azepine 10s as a clear oil in 69% yield. 1H NMR (300 MHz, C6D6) δ: 7.67 (1/2 AA’XX’ d, J = 8.2 Hz, 2H), 6.73 (1/2 AA’XX’ d, J = 8.0 Hz, 2H), 6.57 (dd, J = 9.3, 1.2 Hz, 1H), 5.25 (s, 1H), 4.53 (dd, J = 9.3, 4.9 Hz, 1H), 3.60 (ddd, J = 13.3, 6.8, 3.7 Hz, 1H), 3.39 (ddd, J = 13.5, 9.0, 3.4 Hz, 1H), 3.02-2.94 (m, 1H), 2.64 (ddd, J = 15.4, 9.0, 3.4 Hz, 1H), 2.42 (ddd, J = 15.3, 6.9, 2.5 Hz, 1H), 1.84 (s, 3H), 1.08 (s, 21H), 0.97 (d, J = 7.1 Hz, 3H); 13C NMR (75 MHz, CD2Cl2) δ: 158.3, 143.6, 136.0, 129.8, 126.9, 126.0, 118.3, 118.1, 47.3, 41.4, 35.8, 21.5, 21.0, 18.9, 12.2; IR (neat) 2958, 2942, 2864, 2051, 1990, 1642, 1605, 1462,
1348, 1170; MS m/z (%) 59 (27), 91 (40), 163 (27), 390 (100), 391 (30); EI-HRMS calcd for C$_{24}$H$_{39}$NO$_2$SiS [M+(-i-Pr)] m/z: 390.1923, found: 390.1923.

5-[(E)-Heptylidene]-1-(4-methylbenzenesulfonyl)-4-(trimethylsilyl)-4,5,6,7-tetrahydro-1H-azepine (10t; entry 35, Table 5): The general procedure for azepine formation was followed (p. 88) using ene-allene 9t (28 mg, 0.068 mmol), [Rh(CO)$_2$Cl]$_2$ (1.1 mg, 0.0028 mmol), and DCE (400 µL) under an argon atmosphere. Reaction progress was monitored by GC (Col. temp: 225 °C, inj. temp: 250 °C, det. temp: 250 °C), where the starting material was completely consumed after 7 h. The solution was concd in vacuo and a crude $^1$H NMR showed a trace amount of azepine 10t. $^1$H NMR (300 MHz, C$_6$D$_6$) δ: 4.90 (t, $J$ = 7.2 Hz, 1H), 4.70 (dd, $J$ = 10.0, 6.6 Hz, 1H), 4.17-4.09 (m, 2H), 2.42 (d, $J$ = 6.5 Hz, 1H).

5-[(E)-Heptylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10u; entry 38, Table 6); 5-[(Z)-Heptylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1H-azepine (10u;’ entry 38, Table 6): Cycloisomerization of ene-allene 9u has previously been described.$^{20}$

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1-(4-Methylbenzenesulfonyl)-5-[(E)-1-(triisopropylsilyl)-methylidene]-4,5,6,7-tetrahydro-1H-azepine (10v; entry 39, Table 6); 1-(4-Methylbenzenesulfonyl)-5-[(E)-1-(triisopropylsilyl)-methylidene]-4,5,6,7-tetrahydro-1H-azepine (10v;′ entry 39, Table 6): The general procedure for azepine formation (p. 88) was followed using ene-allene 9v (17 mg, 0.040 mmol), 1,4-dioxane (400 µL), and [Rh(CO)₂Cl]₂ (0.8 mg, 0.0021 mmol) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 20 min. The solution was concd in vacuo and purified by silica gel chromatography to afford azepines 10v and 10v′ as an inseparable mixture in a combined yield of 73%. ¹H NMR indicated a ratio of 10w:10w′ of 5.8:1. ¹H NMR 10v (300 MHz, C₆D₆) δ: 7.65 (1/2 AA′XX′ d, J = 8.2 Hz, 2H), 6.74 (1/2 AA′XX′ d, J = 8.5 Hz, 2H), 6.58 (d, J = 9.4 Hz, 1H), 5.23 (s, 1H), 4.69 (dt, J = 9.2, 5.8 Hz, 1H), 3.45 (dd, J = 5.8, 5.8 Hz, 2H), 2.72 (d, J = 5.7 Hz, 2H), 2.50 (bddd, J = 5.7, 4.6 Hz, 2H), 1.86 (s, 3H), 1.09-1.07 (m, 21H); ¹³C NMR 10v (300 MHz, CD₂Cl₂) δ: 155.1, 144.2, 136.6, 130.6, 127.8, 127.1, 122.0, 103.6, 47.4, 39.4, 37.1, 21.6, 19.1, 12.5; IR (neat) X 3052, 2942, 2889, 2864, 2725, 1577, 1463, 1348, 1166 cm⁻¹; ¹H NMR 10v′ (300 MHz, C₆D₆) δ: 7.43 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 6.65 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 5.85 (d, J = 8.0 Hz, 1H), 5.23 (s, 1H), 4.81 (dd, J = 9.6, 8.0 Hz, 1H), 3.14 (bt, J = 4.4 Hz, 2H), 2.27-2.23 (m, 2H), 1.77 (s, 3H), 1.04-1.01 (m, 21H). EI-HRMS calcd for C₂₃H₃₇NO₂SiS [M+Na⁺] m/z: 442.2212, found: 442.2171.

Attempted cycloisomerization of ene-allene 9w (entry 42, Table 6): The general procedure for azepine formation (p. 88) was followed using ene-allene 9w (74 mg, 0.28 mmol), DCE (940 µL). The reaction was monitored by TLC (benzene), reaching completion after 30 min. The solution was concd in vacuo and purified by silica gel chromatography to afford azepines 10w and 10w′ as an inseparable mixture in a combined yield of 73%. ¹H NMR indicated a ratio of 10w:10w′ of 5.8:1. ¹H NMR 10w (300 MHz, C₆D₆) δ: 7.65 (1/2 AA′XX′ d, J = 8.2 Hz, 2H), 6.74 (1/2 AA′XX′ d, J = 8.5 Hz, 2H), 6.58 (d, J = 9.4 Hz, 1H), 5.23 (s, 1H), 4.69 (dt, J = 9.2, 5.8 Hz, 1H), 3.45 (dd, J = 5.8, 5.8 Hz, 2H), 2.72 (d, J = 5.7 Hz, 2H), 2.50 (bddd, J = 5.7, 4.6 Hz, 2H), 1.86 (s, 3H), 1.09-1.07 (m, 21H); ¹³C NMR 10w (300 MHz, CD₂Cl₂) δ: 155.1, 144.2, 136.6, 130.6, 127.8, 127.1, 122.0, 103.6, 47.4, 39.4, 37.1, 21.6, 19.1, 12.5; IR (neat) X 3052, 2942, 2889, 2864, 2725, 1577, 1463, 1348, 1166 cm⁻¹; ¹H NMR 10w′ (300 MHz, C₆D₆) δ: 7.43 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 6.65 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 5.85 (d, J = 8.0 Hz, 1H), 5.23 (s, 1H), 4.81 (dd, J = 9.6, 8.0 Hz, 1H), 3.14 (bt, J = 4.4 Hz, 2H), 2.27-2.23 (m, 2H), 1.77 (s, 3H), 1.04-1.01 (m, 21H). EI-HRMS calcd for C₂₃H₃₇NO₂SiS [M+Na⁺] m/z: 442.2212, found: 442.2171.

X Spectrum is of the E/Z mixture.
µL), and [Rh(CO)₂Cl]₂ (19 mg, 0.049 mmol) under an argon atmosphere. Reaction progress was monitored by TLC (ethyl acetate-hexanes), where the starting material was completely consumed after 2 h. The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:7; column was pretreated with 1% triethylamine/hexanes) to afford 7 mg of material that possessed a trace amount of the desired azepine 10w by ¹H NMR. ¹H NMR (300 MHz, CDCl₃) δ: 7.75 (1/2 AA'XX' d, J = 8.2 Hz, 2H), 7.30 (1/2 AA'XX' d, J = 8.1 Hz, 2H), 6.44 (d, J = 9.2 Hz, 1H), 5.03 (dt, J = 9.0, 5.4 Hz, 1H), 3.66 (dd, J = 5.9, 5.9 Hz, 2H), 2.84 (d, J = 5.4 Hz, 2H), 2.47 (dd, J = 6.0 Hz, 2H), 2.43 (s, 3H).

Attempted cycloisomerization of ene-allene 9x (Eq. 35): The general procedure for azepine formation was followed (p. 88) using ene-allene 9x (37 mg, 0.093 mmol), 1,4-dioxane (930 µL), and [Rh(CO)₂Cl]₂ (1.7 mg, 0.0044 mmol) under an argon atmosphere. The reaction was monitored by TLC (benzene), where substantial decomposition was observed after 20 min. The solution was concd in vacuo and purified by silica gel chromatography to afford two fractions of 1.9 mg and 2.9 mg of unidentifiable material.

Attempted cycloisomerization of ene-allene 9y (entry 52, Table 8):VI The general procedure for azepine formation was followed (p. 88) using ene-allene 9y (30 mg, 0.10 mmol), toluene (1.0 mL), and [Rh(CO)₂Cl]₂ (3.9 mg, 0.010 mmol) under an argon atmosphere. The solution was
heated to 90 °C for 3 h and was not refluxed. The solution was cooled to rt, diluted with hexanes, and filtered through a plug of silica gel, eluting with ethyl acetate/hexanes (1:4) to afford 16 mg of starting material (53% recovery) with no trace of the desired azepine 10y.

**Attempted cycloisomerization of ene-allene 9z (entry 53, Table 8):**

The general procedure for azepine formation (p. 88) was followed using ene-allene 9z (32 mg, 0.10 mmol), toluene (1.0 mL), and [Rh(CO)2Cl]2 (3.3 mg, 0.0085 mmol) under an argon atmosphere. The solution was heated to 90 °C for 13 h and was not refluxed. The solution was cooled to rt, diluted with hexanes, and filtered through a plug of silica gel, eluting with ethyl acetate/hexanes (1:4) to afford 22 mg of starting material (69% recovery) with no trace of the desired azepine 10z.

**9-[(E)-2,2-Dimethylpropylidene]-6-(4-methylbenzenesulfonyl)-6-azaspiro[2.6]non-4-ene (10A; entry 54, Table 8):** The general procedure for azepine formation (p. 88) was followed using ene-allene 9A (16 mg, 0.047 mmol), [Rh(CO)2Cl]2 (1.0 mg, 0.0026 mmol), and 1,4-dioxane (460 µL) under an argon atmosphere. To the solution was added [Rh(CO)2Cl]2 (0.8 mg, 0.002 mmol) after 20.3 h of heating and TLC analysis showed reaction completion after an additional 1.5 h at reflux. The crude solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 6.8 mg of azepine 10A as a clear oil in a calculated yield of
14%.\textsuperscript{XI} \textsuperscript{1}H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\): 7.70 (1/2 AA'XX' d, \(J = 8.3\) Hz, 2H), 6.81 (d, \(J = 9.0\) Hz, 1H), 6.73 (1/2 AA'XX' d, \(J = 8.0\) Hz, 2H), 5.57 (d, \(J = 8.9\) Hz, 1H), 5.38 (s, 1H), 3.62 (dd, \(J = 6.3, 6.3\) Hz, 2H), 1.83 (s, 3H), 1.47 (d, \(J = 5.9\) Hz, 1H), 1.45 (d, \(J = 6.5\) Hz, 1H), 1.04 (s, 9H), 0.51-0.46 (m, 2H), 0.060-0.035 (m, 2H); IR (neat) 2956, 2925, 2860, 1638, 1597, 1459, 1352, 1295, 1164; EI-HRMS calcd for C\textsubscript{20}H\textsubscript{27}NO\textsubscript{2}S [M+Na\textsuperscript{+}] \(m/z\): 368.1660, found: 368.1634.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\textbf{9B}};
\node at (1,0) {\textbf{10B}};
\draw[->] (0.5,0.5) -- (0.5,-0.5);
\end{tikzpicture}
\end{center}

4-(2,2-Dimethylpropyl)-7,7-dimethyl-1-(4-methylbenzenesulfonyl)-6,7-dihydro-1\textit{H}-azepine (10B; Eq. 37). The general procedure for azepine formation (p. 88) was followed using ene-allene 9B (22 mg, 0.064 mmol), [Rh(CO)\textsubscript{2}Cl\textsubscript{2}]\textsubscript{2} (2.3 mg, 0.0059 mmol), and dichloroethane (320 \(\mu\text{L}\)) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 1.5 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 7.5 mg of azepine 10B as a clear oil. A mixed fraction was purified by HPLC (silica column, ethyl acetate-hexanes 1:32) to afford an additional 2.6 mg of 10B for a combined yield of 45%. \textsuperscript{1}H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\): 7.69 (1/2 AA'XX' d, \(J = 8.3\) Hz, 2H), 6.97 (d, \(J = 9.4\) Hz, 1H), 6.70 (1/2 AA'XX' d, \(J = 8.6\) Hz, 2H), 5.39 (bt, \(J = 6.7\) Hz, 1H), 5.51 (d, \(J = 9.4\) Hz, 1H), 1.95 (d, \(J = 6.7\) Hz, 2H), 1.86 (s, 3H), 1.75 (s, 2H), 1.63 (s, 6H), 0.69 (s, 9H); \textsuperscript{13}C NMR (75 MHz, CD\textsubscript{2}Cl\textsubscript{2}) \(\delta\): 143.4, 138.5, 130.0, 129.7, 129.2, 128.9, 127.3, 120.2, 50.6, 44.3, 31.3, 29.9, 29.6, 29.2, 21.3; IR (neat) 3027, 2950, 2904, 2868, 1644, 1598, 1470, 1337 cm\textsuperscript{-1}.

\textsuperscript{XI} The sample possessed 34% of azepine 10B by \textsuperscript{1}H NMR.
MS m/z (%) 91 (33), 136 (32), 192 (100), 347 (27); EI-HRMS calcd for C_{20}H_{29}NO_{2}S [M+] m/z: 347.1919, found: 347.1916.

5-Ethylidene-3,5-dimethyl-2,3,4,5-tetrahydro-1H-azepine-1,2-carboxylic acid-2-methyl-1-benzyl ester (10C; Eq. 40): The general procedure for azepine formation (p. 88) was followed using ene-allene 9C (21 mg, 0.059 mmol), [Rh(CO)$_2$Cl]$_2$ (1.2 mg, 0.0031 mmol), and 1,4-dioxane (590 µL) under a carbon monoxide atmosphere. Reaction progress was monitored by TLC (ethyl acetate-hexanes), reaching completion after 17 h. The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 5.1 mg of azepine 10C as a colorless oil in a calculated yield of 24%.\textsuperscript{XiI} \textsuperscript{1}H NMR (300 MHz, CDCl$_3$) δ:

7.36-7.29 (m, 5H), 6.37 (bd, J = 9.3 Hz, 1H), 5.45 (qd, J = 6.9, 1.9 Hz, 1H), 5.13 (s, 2H), 4.82 (dd, J = 9.5, 4.1 Hz, 1H), 3.63 (bs, 3H), 3.22 (bq, J = 7.0 Hz, 1H), 3.17-3.06 (m, 1H), 1.64 (dd, J = 6.9, 1.8 Hz, 3H), 1.44 (s, 3H), 1.22 (d, J = 7.1 Hz, 3H), 1.18 (d, J = 7.1 Hz, 3H); IR (neat) 3032, 2945, 2879, 1742, 1716, 1670, 1450, 1378, 1312, 1276 cm$^{-1}$; MS m/z (%) 91 (100), 222 (61), 254 (41), 298 (28), 357 (17).

\textsuperscript{XiI} Composition of a 2.8 mg mixed fraction was determined by $^1$H NMR.
4-Isopropylidene-2-(4-methylbenzenesulfonyl)-hexahydrocyclopenta[c]pyrrol-5-one (12b; entry 56, Table 9): The general procedure for azepine formation (p. 88) was followed using ene-allene 9b (20 mg, 0.070 mmol), [Rh(CO)₂Cl]₂ (2.7 mg, 0.0070 mmol), and dichloroethane (350 µL) in a carbon monoxide/argon atmosphere (approximately 10%/90%). Reaction progress was monitored by TLC (ethyl acetate-hexanes), reaching completion after 45 min. The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:9-1:1.5) to afford 4 mg of 12b as a slightly yellow solid in 18% yield. ¹H NMR (300 MHz, C₆D₆) δ: 7.71 (1/2 AA’XX’ d, J = 8.2 Hz, 2H), 6.78 (1/2 AA’XX’ d, J = 8.0 Hz, 2H), 3.43 (dd, J = 9.3, 9.3 Hz, 1H), 3.04 (dd, J = 10.0, 6.6 Hz, 1H), 2.82 (dd, J = 9.7, 6.6 Hz, 1H), 2.76 (dd, J = 10.0, 3.3 Hz, 1H), 2.72-2.62 (m, 1H), 2.04 (s, 3H), 2.02 (dd, J = 17.4, 9.0, 1H), 1.94-1.81 (m, 1H), 1.87 (s, 3H), 1.70 (dd, J = 17.5, 7.5 Hz, 1H), 1.17 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ: 205.0, 151.0, 143.9, 133.1, 132.3, 129.7, 127.8, 54.0, 53.4, 44.4, 44.2, 35.2, 24.8, 21.6, 20.6; IR (neat) 2955, 2919, 2853, 1706, 1624, 1593, 1342, 1168 cm⁻¹; MS m/z (%) 65 (67), 79 (56), 91 (100), 135 (81), 164 (93), 319 (39); EI-HRMS calcd for C₁₇H₂₁NO₃S [M+] m/z: 319.1242, found: 319.1231.

5-[(E)-2,2-Dimethylpropylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-2,5,6,7-tetrahydro-1H-azepine (18f; Eq. 42): To a solution of azepine 10f (24 mg, 0.071 mmol) in THF (20 µL) at 0 °C was added 9-BBN (0.5 M in THF, 143 µL, 0.072 mmol) dropwise, whereupon the cold bath was removed. After 52 h at rt the solution was concd in vacuo and purified by silica gel chromatography (ethyl-acetate-hexanes 1:19-1:4; column was pre-treated with 1% triethylamine in hexanes) to afford 1.3 mg of azepine 18f in 6% yield (¹H NMR was contaminated with impurities). ¹H NMR C₆D₆ δ: 7.70 (1/2 AA’XX’ d, J = 8.2 Hz, 2H), 6.76 (1/2 AA’XX’ d, J = 8.2 Hz, 2H), 6.76 (1/2 AA’XX’ d, J = 8.2 Hz, 2H).
Hz, 2H), 5.28 (bs, 1H), 5.16 (bt, $J = 5.2$ Hz, 1H), 3.75 (bd, $J = 5.6$ Hz, 2H), 3.33 (t, $J = 6.3$ Hz, 2H), 2.23 (t, $J = 6.3$ Hz, 2H), 1.91 (s, 3H), 1.58 (d, $J = 0.9$ Hz, 3H), 0.95 (s, 9H).

$\text{TsN} \text{SiMe}_2\text{Bn} \quad \text{9k} \quad \rightarrow \quad \text{TsN} \text{SiMe}_2\text{Bn} + \quad \text{TsN} \text{SiMe}_2\text{Bn} \quad \text{18k} \quad + \quad \text{10D}$

5-[(E)-2,2-Dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-2,5,6,7-tetrahydro-1$H$-azepine (18k; Eq. 43); 5-[(E)-2,2-Dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1$H$-azepine (10D; Eq. 43): To a solution of the azepine 9k (18 mg, 0.038 mmol) in MeOH (150 $\mu$L) at 0 °C was added TBAF (1.0 M in THF, 150 $\mu$L, 0.150 mmol) dropwise and it was then warmed to rt. After 39 h at rt the solution was concd in vacuo and partitioned between ethyl acetate/H$_2$O (2 mL/2mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over MgSO$_4$ and concd in vacuo. The residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 3.3 mg of azepine 18k as a colorless oil in 27% yield and 1.9 mg of azepine 10D as a colorless oil in 16% yield ($^1$H NMR was contaminated with impurities). $^1$H NMR 18k (300 MHz, C$_6$D$_6$) $\delta$: 7.70 (1/2 AA’XX’ d, $J = 8.2$ Hz, 2H), 6.78 (1/2 AA’XX’ d, $J = 8.0$ Hz, 2H), 5.82-5.76 (m, 1H), 5.27 (bs, 1H), 5.10 (dt, $J = 11.5$, 5.0 Hz, 1H), 3.77 (dd, $J = 5.0$, 1.4 Hz, 2H), 3.25 (dd, $J = 6.0$, 6.0 Hz, 2H), 2.39 (dd, $J = 5.6$, 5.6 Hz, 2H), 1.90 (s, 3H), 0.91 (s, 9H). $^1$H NMR 10D (300 MHz, C$_6$D$_6$) $\delta$: 7.68 (1/2 AA’XX’ d, $J = 8.3$ Hz, 2H), 6.73 (1/2 AA’XX’ d, $J = 8.3$ Hz, 2H), 6.63 (d, $J = 9.1$ Hz, 1H), 5.12 (s, 1H), 4.70 (dt, $J = 9.1$, 5.6 Hz, 1H), 3.47 (dd, $J = 5.7$, 5.7 Hz, 2H), 2.51 (bd, $J = 5.7$ Hz, 2H), 2.41-2.35 (m, 2H), 1.86 (s, 3H), 0.93 (s, 9H).
5-(Benzhydryldimethylsilyl)-4-[(E)-2,2-dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-2,3,4,5,6,7-hexahydro-1H-azepine (19k; Eq. 44): To a solution of tetrahydroazepine 10k (48 mg, 0.102 mmol) in ethanol (2.5 mL) was added Palladium on carbon (10% wt, 9.5 mg, 0.0089 mmol). The system was pressurized and evacuated with H₂ (3 x 30 psi) before being fully pressurized to 50 psi on a Parr hydrogenator apparatus. It was shaken vigorously and indicated complete conversion after 4 h (TLC). The slurry was filtered over celite and concd in vacuo to give 48 mg of pure azepine 19k in 99% yield. ¹H NMR (300 MHz, CD₂Cl₂): 7.62 (1/2 AA′XX′d, J = 8.3 Hz, 2H), 7.32 (1/2 AA′XX′d, J = 8.0 Hz, 2H), 7.22-7.15 (m, 2H), 7.08-7.01 (m, 1H), 6.99-6.94 (m, 2H), 5.09 (s, 1H), 3.86-3.75 (m, 2H), 2.79 (ddd, J = 14.1, 6.3, 2.0 Hz, 1H), 2.71-2.56 (m, 2H), 2.41 (s, 3H), 2.13-1.99 (m, 3H), 1.96-1.86 (m, 1H), 1.78-1.61 (m, 2H), 1.06 (s, 9H), -0.12 (s, 6H); ¹³C NMR (75 MHz, CD₂Cl₂) δ: 143.7, 140.5, 137.6, 137.5, 136.8, 130.0, 128.6, 128.5, 127.4, 124.4, 51.4, 49.4, 37.2, 32.0, 31.0, 30.1, 28.8, 24.3, 21.6, 1342 cm⁻¹; MS m/z (%) 121 (38), 149 (68), 378 (100), 426 (74), 454 (74), 469 (15); EI-HRMS calcd for C₂₇H₃₉NO₂SSi [M+] m/z: 469.2471, found: 469.2467.

4-(2,2-Dimethylpropyl)-5-methyl-2,3,4,5,6,7-hexahydro-1H-azepine (20f; Eq. 45); 4-(2,2-Dimethylpropyl)-5-methyl-2,3,6,7-tetrahydro-1H-azepine (21f; Eq. 45): The procedure for reduction of 10k was followed using azepine 10f (23 mg, 0.069 mmol), Palladium on carbon (10% wt, 4.6 mg, 0.0043), and ethanol (1.72 mL) to afford 20 mg of product as a colorless oil. Separation via HPLC afforded azepines 20f and 21f in 1.1:1 ratio to result in 46% and 40% yields, respectively. ¹H NMR 20f (300 MHz, C₆D₆) δ: 7.72 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 8.3
Hz, 2H\(^a\)), 6.84 (d, \(J = 8.2\) Hz, 2H\(^a\)), 6.81 (d, \(J = 9.1\) Hz, 2H\(^a\)) 3.23-2.94 (m, 8H\(^b\)), 2.12-2.07 (m, 2H\(^a\)) 2.06-2.01 (m, 2H\(^a\)), 1.93 (s, 3H\(^a\)), 1.90 (s, 3H\(^a\)) 1.59-1.25 (m, 12H\(^b\)), 0.98 (d, \(J = 4.6\) Hz, 3H\(^a\)), 0.79 (s, 9H\(^a\)), 0.76-0.71 (m, 12H\(^b\)); MS \(m/z\) 20f (%): 57 (97), 91 (100), 182 (77), 277 (22), 280 (39); EI-HRMS calcld for 20f C\(_{19}\)H\(_{31}\)NO\(_2\)S [M+] m/z: 337.2076, found: 337.2073. \(^1\)H NMR 21f (300 MHz, CDCl\(_3\)) \(\delta\): 7.62 (1/2 AA'XX' d, \(J = 8.2\) Hz, 2H), 7.29 (1/2 AA'XX' d, \(J = 8.2\) Hz, 2H), 3.12-3.06 (m, 4H), 2.42 (s, 3H), 2.36-2.29 (m, 4H), 1.93 (s, 2H), 1.62 (s, 3H), 0.85 (s, 9H).

\(^{13}\)C NMR 21f (75 MHz, CDCl\(_3\)) \(\delta\): 143.1, 135.1, 134.2, 134.1, 129.6, 127.3, 48.5, 47.3, 46.6, 36.6, 36.2, 33.6, 30.2, 22.6, 21.5; IR 21f (neat) 2950, 2858, 1598, 1455, 1363, 1337 cm\(^{-1}\).

\(^a\)Spin set is absorption of a single diastereomer. \(^b\)Spin set is a mixture of diastereomers.

4-[(\(E\))-2,2-Dimethylpropyldiene]-5-methyl-1-(4-methylbenzenesulfonyl)-2,3,4,5,6,7-hexahydro-1\(^H\)-azepine (19f; Eq. 46):\(^89\) To a solution of tetrahydroazepine 10f (21 mg, 0.064 mmol) in dichloroethane (220 \(\mu\)L) was added acetic acid (3.7 \(\mu\)L, 0.065 mmol). To the solution after 5 min was added sodium triacetoxyborohydride (20 mg, 0.093 mmol). No change in starting material was observed after 1.3 h, whereupon acetic acid (6.4 \(\mu\)L, 0.109 mmol) and sodium triacetoxyborohydride (14 mg, 0.064 mmol) were added. No change in starting material was observed after and additional 1h, at which point acetic acid (7.4 \(\mu\)L, 0.13 mmol), sodium triacetoxyborohydride (27 mg, 0.13 mmol), and dichloroethane (100 \(\mu\)L) were again added. Analysis by TLC showed minimal change after 12 h (a faint lower spot). To the slurry was added trifluoroacetic acid (10.0 \(\mu\)L, 0.13 mmol) which resulted in a homogeneous solution. Within 1 h substantial conversion was observed (TLC) but the reaction did not progress after that point. During the course of the next 24 h, trifluoroacetic acid (15 \(\mu\)L, 0.19 mmol), and sodium
triacetoxyborohydride (41 mg, 0.19 mmol) were added in portions. Upon complete conversion
the mixture was quenched with NaOH aq (1N, 400 µL), diluted with water (5 mL), and extracted
with DCM (4 x 5 mL). The combined organic layers were washed with saturated NaHCO₃ (7
mL), brine (7 mL), dried over Na₂SO₄, and concd in vacuo. The crude residue was purified by
silica gel chromatography (ethylacetate-hexanes 1:19-1:9) to afford 20 mg of pure
hexahydroazepine 19f in 93% yield. ¹H NMR (300 MHz, C₆D₆) δ: 7.71 (1/2 AA'XX' d, J = 8.3
Hz, 2H), 6.82 (1/2 AA'XX' d, J = 8.5 Hz, 2H), 5.20 (s, 1H), 3.43 (ddd, J = 12.6, 7.2, 4.4 Hz,
1H), 3.35 (ddd, J = 13.8, 8.1, 3.2 Hz, 1H), 2.94 (ddd, J = 12.5, 7.6, 4.4 Hz, 1H), 2.77 (ddd, J =
13.8, 7.8, 3.3 Hz, 1H), 2.34 (1/2 AB ddd, J = 14.4, 7.5, 4.4 Hz, 1H), 2.25 (1/2 AB ddd, J = 14.4,
7.1, 4.5 Hz, 1H), 2.13-1.98 (m, 1H), 1.91 (s, 3H), 1.69 (ddd, J = 14.2, 8.1, 5.7, 3.3 Hz, 1H),
1.30-1.16 (m, 1H), 1.00, (s, 9H), 0.87 (d, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CD₂Cl₂) δ: 143.5,
140.4, 136.9, 136.8, 130.0, 127.4, 49.7, 47.5, 41.5, 36.9, 32.7, 31.7, 29.8, 21.7, 21.6; IR (neat)
2955, 2863, 1598, 1460, 1332, 1158 cm⁻¹; MS m/z (%) 91 (82), 124 (89), 180 (100), 320 (29),
335 (36); EI-HRMS calcd for C₁₉H₂₉NO₂S [M+] m/z: 335.1919, found: 335.1917.
APPENDIX B

NMR SPECTRA

B.1 ENE-ALLENES

The $^1$H and $^{13}$C NMR spectra for each ene-allene are reported sequentially.
B.2 AZEPINES

The $^1$H NMR and $^{13}$C spectra for each azepine are reported sequentially.
adc-III-138 60 deg. (301) DMSO-d$_6$
29. Hamprecht, D.; Josten, J.; Steglich, W. *Tetrahedron* 1996, 52, 10883. The researchers claimed that a total synthesis would soon be described but attempts at location in the literature proved unfruitful.
82. The procedure followed was adapted from a combination of the following two references: Fadel, A.; Canet, J. L.; Salaün, J. *Synlett* **1990**, 89. Salaün, J.; Marguerite, J. *Organic Synthesis* ; Wiley: New York, **1987**, 7, 131.