Gold(III)-Catalyzed Cyclizations to Form Saturated Oxygen Heterocycles

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Gold(III)-Catalyzed Cyclizations to Form Saturated Oxygen Heterocycles

By

Ryan D. Lyski

Accepted in Partial Completion
of the Requirements for the Degree
Master of Science

A Thesis
Presented to
The Faculty of
Western Washington University

Kathleen L. Kitto, Dean of the Graduate School

ADVISORY COMMITTEE

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MASTER’S THESIS

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Ryan Lyski
May 29, 2015
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May 2015
Abstract

Gold catalysis has emerged over the past decade as an important methodology in the construction of organic molecules. Cationic gold complexes are robust, versatile, selective and efficient catalysts that can be used to enhance the electrophilicity of C-C unsaturated bonds. A current area of investigation is the use of gold to activate allylic alcohol/ether moieties for intramolecular $S_N2'$ nucleophilic attack to form oxygen heterocycles. We have discovered that sterically bulky, electron-withdrawing oxygen leaving groups drastically improved reaction efficiency, and bulky leaving groups in combination with substrate substituents enhanced diastereomeric ratios in the oxygen heterocycle products. These reactions proceeded smoothly in the presence of many functional groups to consistently afford high diastereoselectivity. This methodology was attempted in the synthesis complex spirocyclic ether structures, and used in progress towards total synthesis of the natural product ($\pm$)-centrolobine.
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Western Washington University Department of Chemistry
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<table>
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<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATR</td>
<td>Attenuated total reflectance</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Cat.</td>
<td>Catalyst</td>
</tr>
<tr>
<td>CDCl$_3$</td>
<td>Deuterated chloroform</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
</tr>
<tr>
<td>DI</td>
<td>Deionized</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropylazodicarboxylate</td>
</tr>
<tr>
<td>dppf</td>
<td>Bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>Ether</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>FTIR</td>
<td>Fourier-Transform Infrared Spectroscopy</td>
</tr>
<tr>
<td>g</td>
<td>Gram(s)</td>
</tr>
<tr>
<td>GC</td>
<td>Gas-Chromatography</td>
</tr>
<tr>
<td>GC/MS</td>
<td>Gas-Chromatography-Mass Spectrometry</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>Hex</td>
<td>Hexane</td>
</tr>
<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared Spectroscopy</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter(s)</td>
</tr>
<tr>
<td>mm</td>
<td>Millimeter(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole(s)</td>
</tr>
<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
</tr>
<tr>
<td>m. p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PPh₃</td>
<td>Triphenylphosphine</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>iPr</td>
<td>Isopropyl</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetra n-butylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td><em>Tert</em>-butyldimethylsilyl</td>
</tr>
<tr>
<td>t-BuOH</td>
<td><em>Tert</em>-butyl alcohol</td>
</tr>
<tr>
<td>TfOH</td>
<td>Trifluoromethylsulfonic acid</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyran</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
</tr>
</tbody>
</table>
1. Introduction

1.1. General Considerations in Gold-Catalysis

The development of homogeneous organometallic catalysis in organic synthesis has allowed access to more complex structures under mild and efficient reaction conditions. A famous example was the discovery of palladium-catalyzed coupling reactions in the mid 1970’s by Richard F. Heck and Tsunomu Mizoroki. Precious metal catalysts like palladium, ruthenium, rhodium and platinum have been extensively investigated in synthetic methodology, however the study of gold catalysis began relatively late in comparison.

A few applications of gold catalysis were described in the 1990’s, however the organometallic “gold rush” occurred in the first decade of the 21st century with the development of phosphine and carbene ligands to form stable gold catalyst salts. The introduction of these gold catalysts instigated a marked increase in the number of publications on the topic of gold catalysis with the greatest number of publications occurring in the most recent year of 2014 with 1,060 publications (Figure 1-1).

In comparison to other precious metals catalysts used in organic chemistry, gold salts are relatively affordable in cost per mole even though elemental gold metal is one of the most expensive metals (Table 1-1). There are several factors that influence the price of catalyst including the complexity of the ligand, the sensitivity, and the demand. Additionally, the impressive reactivity and robustness of gold catalysts allow for potentially lower catalytic loadings with higher turn-over numbers without loss of catalytic activity due to oxidation or poisoning.
Figure 1-1. Number of publications on the topic of gold catalysis from 1980-2015.

Table 1-1. Elemental and cationic salt price/mmol of precious metals as of September 2014.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Price/mmol in US $</th>
<th>Catalyst Form</th>
<th>Price/mmol in US $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold</td>
<td>7.74</td>
<td>AuCl / AuCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>52.88/57.63</td>
</tr>
<tr>
<td>Iridium</td>
<td>3.77</td>
<td>IrCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>72.55</td>
</tr>
<tr>
<td>Osmium</td>
<td>2.32</td>
<td>OsCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>195.24</td>
</tr>
<tr>
<td>Palladium</td>
<td>2.80</td>
<td>PdCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>9.40</td>
</tr>
<tr>
<td>Platinum</td>
<td>8.37</td>
<td>PtCl&lt;sub&gt;2&lt;/sub&gt; / PtCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>66.23/63.50</td>
</tr>
<tr>
<td>Rhenium</td>
<td>4.52</td>
<td>ReCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>96.26</td>
</tr>
<tr>
<td>Rhodium</td>
<td>4.47</td>
<td>RhCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>65.71</td>
</tr>
<tr>
<td>Ruthenium</td>
<td>0.21</td>
<td>RuCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10.25</td>
</tr>
<tr>
<td>Silver</td>
<td>0.06</td>
<td>AgCl</td>
<td>4.46</td>
</tr>
</tbody>
</table>
Gold exists in several oxidation states, the most prevalent of which are Au(0), Au(I), and Au(III). Au(I) has been intensively studied in catalysis due to its low oxidation state and linear coordination geometry.\textsuperscript{9,10} Au(I) catalysts are stable in the presence of a large number of functional groups, and have a simple geometry in ligand design. However, in the absence of stabilizing ligands, Au(I) undergoes a rapid disproportionation reaction into Au(0) and Au(III).\textsuperscript{11} Many commercially available water- and air-stable gold complexes have been synthesized to overcome the limitations associated with this reactivity as shown in Figure 1-2.\textsuperscript{4}

![Figure 1-2](image)

**Figure 1-2.** Commercially available Au(I) catalysts.

Though these ligands significantly reduce the disproportionation reaction of Au(I), this side reaction has been observed despite the presence of stabilizing ligands. Vyvyan and co-workers observed the disproportionation of 1-2 in a Claisen rearrangement of allyl aryl ethers.\textsuperscript{12} The synthetic community has assumed this disproportionation leads to decreased catalytic activity and increased side reactions as Au(0) precipitates out of solution, and Au(III) is considered less stable
Contrary to this belief, Au(III) was the catalytically active species in the reported Claisen rearrangement.

Gold(III) cationic complexes have been poorly investigated, largely because the scientific community has been focused on reaction methodologies involving Au(I) cationic complexes due to the simplicity of ligand design for these linear bicoordinate complexes, and the mild reaction conditions of this low oxidation state Lewis acid. However, there are some potential advantages to Au(III) complexes. First, the higher oxidation state of this gold complex makes it more electrophilic and oxophilic, which could indicate increased reactivity in the activation of $\pi$-systems by increasing the delocalization of electrons. Second, the tetracoordinate, square planar coordination geometry of Au(III) complexes allows for greater ability to tune cationic complexes through bi- or tri-dentate ligand design, and increased steric bulk near the reaction center may influence diastereoselective and enantioselective reactions. The work to be presented in this thesis focuses on the increased reactivity of Au(III), and commercially available ligands that allow for stereoselective transformations.

Gold was not considered for investigation in the early days of organometallic catalysis due to its lack of reactivity in its elemental form. The resistance of metallic gold to oxidation was believed to correspond to a diminished or absent reactivity as a cationic catalyst. The conditions needed to oxidize gold support this hypothesis; an extremely caustic mixture of hydrochloric acid and nitric acid, known as aqua regia (Latin for “regal water”), is required to form cationic gold salts. The unusual lack of reactivity of gold metal is orthogonal to the surprisingly
powerful reactivity of cationic gold in a broad range of organic transformations. These interesting effects of gold are closely related to relativistic effects. In computational analysis of the relativistic and non-relativistic 6s orbital radii it was observed gold exhibits the largest relativistic effects among the elements (Figure 1-3).\textsuperscript{16}

![Diagram showing relativistic and non-relativistic 6s orbital radii for different elements.](image)

**Figure 1-3.** The relativistic and non-relativistic 6s orbital radii. (Reprinted from ref. 12)

The relativistic effects observed in gold provide a theoretical framework for rationalizing observed reactivity as well as proposing potential hypothetical reactivity. The experimentally observed characteristics of cationic gold complexes may be theoretically described by the contraction of the 6s orbital and expansion of the 5d orbitals. This relativistic orbital interaction explains the observed yellow hue of gold metal. The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) are sufficiently close in energy due to
relativistic effects that the highest energy of visible light (blue) will be absorbed to allow an excitation of an electron from the HOMO to the LUMO, and thereby reflect all remaining light from the spectrum to give a yellow hue.

Additionally, the atomic radius of gold (144 pm) is significantly decreased and is comparable to the size of silver (144 pm) (Figure 1-3).\textsuperscript{17} This relativistic contraction results in tighter binding energy of the s electrons. This makes the cohesive metallic bonds much more difficult to oxidize, and gold cationic species exceptional Lewis acids.

\textbf{Figure 1-3.} Relativistic effects in gold.

\subsection*{1.2. Gold-Catalyzed Addition to $\pi$-Systems}

Gold(I) and gold(III) species are both Lewis acids with an affinity for $\pi$-bonds, and have the ability to activate soft electrophiles such as C-C double and triple bonds. The strong Lewis acidity of gold is due to the relative low energy of the lowest unoccupied molecular orbital (LUMO). This makes cationic gold species
ideal catalysts for the mild activation of π-systems. Additionally, since they are Lewis acids, these catalysts have access to a large selection of commercial available ligands through coordination of Lewis bases observed in phosphorous and nitrogen ligands which may be used to tune the electronic and steric environment of the coordination sphere. Finally, cationic gold delocalizes electrons, and stabilizes electrophiles through the strong back-bonding character of this atom. The relativistic expansion of the 5d orbitals in gold increases the back bonding effect and therefore facilitates electron delocalization.\(^5\)

1.3. Gold-Catalyzed Activation of Alkynes

The first and most widely investigated methodology concerning gold catalysis has been the activation of alkynes. Gold cationic complexes behave as chemoselective π-acids to remove electron density and promote electrophilic character, which can then be attacked by a nucleophile.

This synthetic methodology has been utilized in many examples for the mild activation of alkynes with cationic gold species. In 2004, Arcadi and co-workers used a cationic gold complex to activate an alkyne for intramolecular nucleophile attack on aniline 1-5 to form indole 1-6 in high yield and efficient reaction time (Scheme 1-1).\(^18\) An excellent example of the robustness and reactivity of gold catalyst was the intermolecular addition to an alkyne reported by Nolan and co-workers in which they were able to use 0.01 mol% of catalyst in the hydration of alkyne 1-7 to obtain ketone 1-8 in high yield using water as a co-solvent and nucleophile.\(^19\) Additionally, cationic gold complexes may be utilized in mild
activation of otherwise unreactive π-systems. Hashmi investigated the synthesis of hydroxyl-substituted isoindolines from a furan catalyzed by Au(III) chloride in a Diels-Alder reaction. In this reaction the cationic gold species first activates the terminal alkyne of 1-9 for intramolecular Diels-Alder reaction with the relatively unreactive furan diene. The oxophilic Au(III) chloride mediates scission of the oxygen bridge, and the restoration of aromaticity to afford isoindoline 1-12 in 97% yield.

Scheme 1-1. Selected examples of gold-catalyzed activation of alkynes.
Trost and co-workers utilized an intramolecular gold-catalyzed alkoxylation of an alkyne to form a tetrahydropyran in a late stage in the total synthesis of the complex natural product, Bryostatin 16 (Equation 1-1). This is an excellent use of Au(I) in the activation of an alkyne to afford the corresponding tetrahydropyran in 73% yield without side reactions or decreased reactivity in the presence of many other functional groups including acetal, conjugated systems and an unprotected alcohol.\textsuperscript{22}

\begin{equation}
\text{MeO}_2C-\text{C}-\text{MeO}-\text{C}=\text{C} \hspace{1cm} \text{MeO}_2C-\text{C}-\text{MeO}-\text{C}=\text{C} \\
\text{Ph}_3\text{OAuCl}/\text{AgSbF}_5 (20 \text{ mol}) \hspace{1cm} \text{NaHCO}_3, \text{CH}_2\text{Cl}_2/\text{MeCN} \hspace{1cm} 0^\circ\text{C to rt} \\
1-13 \hspace{5cm} 1-14
\end{equation}

(1-1)

1.4. Gold-Catalyzed Activation of Allenes

The ability to activate alkynes with cationic gold species has attracted the interest of many other groups towards the activation of other reactive $\pi$-bonds like allenes. In 2006, Widenhoefer and co-workers investigated the gold catalyzed cyclization of allene 1-15 to form tetrahydropyran 1-16 in high yield and moderate diastereomeric ratios (Scheme 1-2).\textsuperscript{23} Shortly after, in 2008, Widenhoefer observed the intermolecular hydroamination of allene 1-18 in good yield at room
temperature. In 2007, an electrophilic aromatic substitution was used by Ohno and co-workers to synthesize dihydroquinoline 1-21 from allenic aniline 1-20 in 92% yield in 5 minutes at room temperature.

**Scheme 1-2.** Selected examples of gold catalyzed activation of allenes.

The advantage of utilizing allenes as electrophiles in synthesis is the ability to form a stereogenic center by stereoselective activation. Chiral bisphosphine ligands and phosphate counterions have attracted significant interest for their ability to be synthesized from readily available sterically bulky, axially chiral binaphthalen derivatives. These privileged chiral resolving agents have been investigated thoroughly by several groups in enantioselective gold catalyzed reactions, and have proven to be efficient stereoselective ligands in synthesis.
Toste has published many examples of enantioselective gold-catalyzed reactions. In 2007, his group used a chiral phosphine ligand-based gold catalyst in the enantioselective intramolecular hydroamination of allenes in which they were able to obtain pyrrolidine 1-23 in quantitative yield and 99% enantiomeric excess (Scheme 1-3). Due to the linear bi-coordinate geometry of Au(I), low enantioselectivity is often observed because the steric bulk of the ligand is located relatively far from the reaction center.

Toste and co-workers hypothesized that chiral information may be moved closer to the reaction center by utilizing a chiral anion to associate near the electrophilic cation formed when the gold complex activates the substrate for nucleophilic attack. This group observed exceptional enantioselectivity in the Au(I) catalyzed hydroalkoxylation of allene 1-25 when they used chiral counter ion silver salt 1-27 in a non-polar solvent.

Though gold-catalyzed reactions have seen significant success in the activation of alkynes and allenes, this methodology is limited in the activation of alkenes. Several examples have been reported in literature, but unlike other palladium and platinum activation of alkenes, gold has required increased temperatures to promote electrophilic activation. He and co-workers found 85 °C was required to perform the gold-catalyzed addition of phenol to an alkene in 84% yield in 15 hours (Equation 1-2).
Scheme 1-3. Selected examples of enantioselective addition on allenes.

1.4. Metal-Catalyzed Activation of Unsaturated Alcohols

Unsaturated alcohols are ubiquitous, readily synthesized intermediates in organic chemistry. Transformations involving these functional groups under Brønsted or Lewis acidic conditions have been extensively investigated. Metal catalyzed activation of allylic, propargylic and benzylic alcohols have broad utility in organic synthesis and many reports have general applicability towards the use in gold catalysis.^{32-42}

Allylic alcohols or ethers can be synthesized by reduction of propargylic alcohols, reduction of α,β-unsaturated carbonyls, or olefin metathesis with allylic
alcohols or ethers. These allylic alcohol moieties can act as surrogates for allenes with similar reactivity, greater stability and simple preparation. Metal activation of allylic alcohols has been investigated, but the catalytic loadings remain relatively high in comparison to alkynes and allenes, and require higher temperatures or longer reaction times.

Several examples in the literature suggest the potential for these functional groups to allow for electrophilic activation with Lewis acid catalysis. Uenishi and co-workers demonstrated a highly efficient Pd(II)-catalyzed intramolecular cyclization for the formation – from chiral allylic alcohols – to afford tetrahydrofurans like 1-32 containing tetrasubstituted stereocenters. This reaction proceeded stereospecifically by 1,3-chirality transfer through a syn-S_N2 process to afford 2,2,6-trisubstituted tetrahydrofurans and spirofurans in high yields (Scheme 1-4). However, excessively high catalytic loading (30 mol %) was required for this reaction. Ruthenium(I)-catalyzed intermolecular Friedel-Crafts reactions have been reported by Wörle and co-workers which afforded 3-substituted indoles 1-35 in quantitative yields. This reaction required the use of camphorsulfonic acid as a co-catalyst. Mashima and co-workers used 1 mol % of a platinum(II) catalyst in the activation of allylic alcohol 1-37 for addition of aniline 1-36. Though the catalyst loading was low (1 mol%), the reaction required high temperatures in order to achieve good yield (86%) of 1-38.
Propargyl alcohols are versatile and useful intermediates in organic synthesis. Activation of these electrophiles with an alcohol leaving group allows for powerful transformations allowing access to numerous types of functional groups by altering reaction conditions. Due to their increased electron density these functional groups have been utilized in complex cascade reactions, and multi-step, one-pot procedures. Propargylic alcohols activated by metal salts are often used to form 5-membered heterocycles. In 2009, Aponick and co-workers developed a synthesis of furans, pyrroles and thiophenes by gold-catalyzed activation of propargyl alcohols. An excellent example from this work demonstrated the use of as little as 0.05 mol% of catalyst to convert a propargyl alcohol 1-39 into furan 1-40 in 92% yield in only 15 minutes (Scheme 1-5). An interesting intermolecular reaction to form furan 1-43 in modest yield from readily available aryl boronic acid
1-41, propargyl alcohol 1-42 and carbon monoxide under low rhodium(I) catalyst loading was reported in 2010 by Castanet and co-workers.\textsuperscript{38}

**Scheme 1-5.** Selected examples of metal catalyzed activation of propargylic alcohols.

Aponick and co-workers have recently reported on gold-catalyzed reactions of propargyl alcohols to form complex heterocyclic structures. This group developed a novel approach to unsaturated spiroketal structures that addresses the regioselectivity issues commonly reported in metal-catalyzed spiroketalization of alkynes.\textsuperscript{39} The reaction sequence is regulated by the use of an acetonide protecting group in 1-44, which in the process of the reaction undergoes extrusion of acetone to deliver a broad range of spiroketals like 1-44 in good yields and diastereoselectivities (**Scheme 1-6**). Aponick’s group has also described the synthesis of cyclic 2-oxodienes from propargyl alcohols, which can be used in a subsequent Diels-Alder reaction.\textsuperscript{40} The dehydrative cyclization reaction proceeds smoothly with 5 mol % catalyst in 5 minutes. The subsequent diene readily
underwent a cycloaddition in-situ with a variety of dienophiles. This method allowed for a new strategy to synthesize indolocarbazole alkaloids.

**Scheme 1-6.** Complex structures formed by Au(I) catalyzed activation of propargyl alcohols.

Ionization of benzylic alcohols under mild acidic conditions has also been extensively investigated. The resonance-stabilized cation formed after the loss of water may be reacted with any nucleophile, usually through an S<sub>N</sub>1 mechanism. This allows access to many carbon-carbon and carbon-heteroatom bonds. In 2006, Campagne and co-workers utilized this reactivity by activation of benzylic alcohols with 5 mol % of various Lewis acids in the nucleophilic substitution with tosylamine (Scheme 1-7). Of all the Lewis acids tested, Au(III) cationic salt proved to be the
best catalyst, and the use of organic acids gave poor yields and side products. This type of transformation has also been used in Michael style addition with β-ketoesters. This reaction worked well in the presence of various Lewis acids though the catalyst loading was high.

**Scheme 1-7.** Selected examples of Lewis acid activation of benzylic alcohols.

The facile synthesis, and Lewis acid activation under mild conditions of unsaturated alcohols makes these intermediates attractive substrates for investigation. Allylic alcohols, however, are less reactive and more difficult to activate under mild conditions but are much more accessible and versatile intermediates in organic synthesis. Cationic gold complexes have shown promising reactivity in this field, and activation of these systems for intramolecular cyclization is an attractive area for investigation of new methodology.
2. Metal-Catalyzed Cyclizations to Form Saturated Oxygen Heterocycles

2.1. Saturated Oxygen Heterocycles in Natural Products

Saturated oxygen heterocycles are ubiquitous structural motifs in biologically active natural products. The prevalence of these functional groups in synthetic targets with potent biological activities make them important structural components that have attracted the interest of the synthetic community.\(^{43}\)

![Figure 2-1](image)

**Figure 2-1.** Selected examples of natural products containing saturated oxygen heterocycles.

There are several natural products with complex saturated oxygen heterocycle structural motifs with excellent biological activity. Spirastrellolide A 2-
1, extracted from marine sponge *Spirastrella coccine*, is potent inhibitor of protein phosphatase 2. \(^4\)

This compound has spiroketal and bis-spiroketal structural features which are difficult functional groups to synthesize, but are essential for the activity of the molecule. Bryostatins are a group of macrolactones isolated from *Bugula neritina*, a species of bryozoan. \(^4\)

These architecturally complex organic structures are potent modulators of protein kinase C, and have demonstrated promising activities against cancer, HIV and Alzheimers. \(^4\)

An important feature of this molecule is the joined tetrahydropyran rings which form the structural manifold of this compound. Sorangicin A contains a characteristic dioxabicyclo[3.2.1]octane skeleton functionality. \(^4\)

This macrolide was isolated from myxobacteria *Sorangium cellulosum* and has demonstrated remarkable antibiotic activity against a broad spectrum of gram-positive and gram-negative bacteria, as well in the treatment of solid tumors resistant to alternative treatments (i.e., Taxol). \(^4\)

Brevetoxins are a class of marine ladder toxins produced by *Karenia brevis*, a marine dinoflagellate found in the Gulf of Mexico, known to be responsible for oceanic red tide. \(^4\)

These compounds bind to the voltage-gated sodium channels in nerve cells and disrupt the central nervous system. The complex cyclic polyether structure is exceedingly difficult to synthesize due to the ten fused oxygen heterocycles. Traditional approaches to the synthesis of cyclic ethers are efficient, but are limited in the application to complex chiral structures. \(^5\)

Metal based catalysis has proven to be a powerful synthetic tool to achieve high yield and stereoselectivity through the use of stable ligated complexes.
2.2. Transition Metal-Catalyzed Activation of Alkenes

The synthetic community has long recognized the power of metal-catalyzed intramolecular reactions and continues to expand the scope of these methodologies towards the synthesis of saturated oxygen heterocycles. Contemporary approaches utilize cationic metals as catalysts in the intramolecular hydroalkoxylation of unactivated alkenes. Alkenols are readily available, stable synthetic intermediates. Coordination of a metal activates the double bond by formation of $\pi$-complex for nucleophilic addition by an alcohol followed by protodemetalation (Scheme 2-1).

**Scheme 2-1.** General reaction mechanism of metal-catalyzed cyclization of alkenol.

In 2004, Widenhoefer and co-workers utilized only 0.5 mol % of platinum catalyst in the cyclization of alkenol 2-9 to form a tetrahydropyran 2-10 with excellent diastereoselectivity (Scheme 2-2). Though this transformation tolerates a large variety of functional groups like pivaloate and acetate esters, amides, silyl and benzyl ethers, only moderate yields were reported and high temperatures were required. This reaction was also investigated by He and co-workers using triphenylphosphine silver(I) triflate as a catalyst to obtain the tetrahydropyran 2-12 in 15 minutes at reflux in dichlorehane.
Lanthanides have promising activity that has been investigated in this methodology, but lanthanide salt-catalyzed processes usually requires toxic, highly polar, moderately coordinating solvents. Marks and co-workers were able to utilize an non-volatile environmentally benign imidazolium-based ionic liquid in the hydroalkoxylation using ytterbium(III) triflate to form a benzofuran 2-14. Cationic metal activation of olefins is a practical and efficient methodology in the synthesis of cyclic ethers, however harsh conditions including high temperatures and long reaction times are often required.

**Scheme 2-2.** Metal-catalyzed hydroalkoxylation/cyclization of unactivated alkenes.

2.3. Transition Metal-Catalyzed Activation of Allylic Alcohols

Activation of allylic alcohols for inter- and intramolecular substitution reactions has been investigated with many different metal-based catalysts. Several mechanisms
have been suggested for this type of reaction, which differ based on the metal employed in the activation of the allylic alcohol. A syn SN2’ process has been reported with Pd(II)\textsuperscript{56} (Scheme 2-3, A), a π-allyl metal complex formation with Pd(0),\textsuperscript{57} Pt(0),\textsuperscript{58} Rh(I)\textsuperscript{59} or Ru(II)\textsuperscript{60} (Scheme 2-3, B), and stabilized allyl cation with Fe(III)\textsuperscript{61} or Bi(III)\textsuperscript{62} (Scheme 2-3, C).

**Scheme 2-3.** Mechanistic pathways in the metal-catalyzed activation of allylic alcohols: A) syn SN2’, B) π-allyl metal complex, C) stabilized allyl cation.

In 2010, Cossy and co-workers investigated the iron(III) catalyzed activation of a mono-allylic diol 2-15 to form an allyl cation intermediate which intramolecular nucleophilic addition allow access to 2,6-disubstituted tetrahydropyrans 2-16 in good yield and moderate diastereostereomeric ratios (Scheme 2-4).\textsuperscript{61} Uenishi and co-workers used a palladium(II) catalyst to perform a syn SN2’ cyclization upon the allylic alcohol to form a tetrahydropyran 2-18 in 93% yield as a single diastereomer.\textsuperscript{56} Kitamura and co-workers reported the ruthenium(II) catalyzed
enantioselective cyclization of mono-allylic diol 2-19 to form tetrahydropyran 2-20 in 90% yield and 93% ee by utilizing a new chiral ligand 2-21 they developed.\textsuperscript{60}

Scheme 2-4. Selected examples of metal-catalyzed cyclization of allylic alcohols.

2.4. Gold-Catalyzed Activation of Allylic Alcohols

Prior to 2006, gold was poorly investigated in the activation of allylic alcohols, however there are several reports which suggest Au(I) or Au(III) could be exceptionally active catalysts in this methodology.\textsuperscript{1,63} When Au(III) is used to activate the allylic alcohol, evidence suggests a allyl stabilized cation is formed which may undergo regioisomerization. In 2009, Chan and co-workers investigated the Au(III)-catalyzed activation of cinnamyl alcohol 2-22 in an $S_N1$ nucleophilic substitution with 1,3-diketone 2-21 to afford 2-23 in good yield.
This same group also described the Au(III)-catalyzed activation of phenyl substituted allylic alcohols for electrophilic aromatic substitution with arenes and heteroaromatics like 2-26 in good yields. Liu and co-workers have reported work involving the formation in carbon-heteratom bonds in which they described the Au(III)-catalyzed amination of allylic alcohols like 2-28 in good yield.

**Scheme 2-5.** Selected examples of Au(III) catalyzed activation of allylic alcohols.

These examples represent the reactivity of cationic gold to activate allylic alcohols for intermolecular substitution. This methodology has also been applied in intramolecular reactions. Previous work completed in the Vyvyan group involved the investigation of Au(I)-catalyzed Claisen rearrangement of allyl aryl ethers. In this investigation they reported cationic Au(I) and Au(III) catalyzed the
reaction of several aryl allyl ethers. However, due to a competing cationic pathway Au(I) complexes catalyzed [3,3] and [1,3]-rearrangement products in substrates like 2-29 through an ionic mechanism rather than a concerted pathway to afford products 2-30, 2-31, and 2-32.67

Contrary to previously reported information this group discovered homogenous Au(III) was an exceptionally active catalyst that preferentially favored the intended product 2-30 by progressing through the hypothesized concerted [3,3]-rearrangement mechanism (Scheme 2-6). Encouraged by these results previous group members sought to investigate this reaction further with napthol derivatives. Utilizing 10 mol % of Au(OTf)₃ formed in situ, they were able to produce the single intended rearrangement product in 89% at 0°C in 6.25 hours.68 Though the catalyst loading was relatively high, this experiment illustrates the potential for homogenous Au(III) complexes to allow for increased reactivity while maintaining selectivity in the activation of allylic alcohols. Furthermore, researchers were also able to selectively form a cyclized product 2-34 in 66 % yield when using 10 mol % PPh₃PAuOTf.68 Additionally, a researcher in this group, Dimmit, found that the same gold catalyst could facilitate the formation of a lactone 2-36 from the cyclization of a carboxylic acid-containing allylic ether substrate 2-35.12

These experiments stimulated our interest to utilize the activation of allylic alcohols towards the formation of cyclic ethers and lactones. Our initial hypothesis was as follows: homogenous Au(III) may allow for increased and ligand-diversified reactivity over other metal based methodologies involving the
catalytic activation of allylic alcohols towards the intramolecular formation of saturated oxygen heterocycles and lactones.

**Scheme 2-6.** Selected examples Au(I) and Au(III) catalyzed activation of allylic alcohols for Claisen rearrangement.
3. Synthesis of Lactones

3.1. Lactones in Natural Products

Lactones are abundant structural motifs observed in natural products. The flowering plant genus *Goniothalamus* has been a resource for several cytoxic acetogenins and styryl-lactones such as cardioptalolactone 3-1, goniofufurone 3-2, and annonacin 3-3; all of which incorporate lactones in their molecular architectures (Figure 3-1). Therefore, facile methodologies to give access to these structural features would have broad utility in medicinal chemistry and natural product synthesis.

![3-1 Cardioptalolactone](image1)

![3-2 (+-)Goniofufurone](image2)

![3-3 Annonacin](image3)

**Figure 3-1.** Selected examples of lactone containing natural products.

Cationic gold complexes have been utilized in the catalytic cyclization to synthesize lactones by activation of unsaturated carbon systems. In 2006, Pale and co-workers utilized the strong Lewis acidity of Au(I) to activate alkyne 3-4 for intramolecular alkoxylation with a carboxylic acid. This reaction allowed access to
a myriad of substituted enol lactones like 3-5 in high yield (Scheme 3-1).\textsuperscript{71} This reactivity has also been employed with allylic alcohols. Bandini and co-workers utilized Au(I) complexes in the synthesis of functionalized \( \gamma \)-vinylbutyrolactones like 3-7 by intramolecular oxaallylic alkylation with primary alcohols like 3-6. This group reported good yields obtained for a range of malonyl and acetate derivatives.\textsuperscript{72}

\textbf{Scheme 3-1.} Selected examples of Au(I) catalyzed cyclization to form lactones.

In both examples, lactone formation was achieved efficiently with inexpensive readily available synthetic intermediates, and mild reaction conditions. However, like most gold-catalyzed reactive methodologies, lactone formation has primarily focused on Au(I) catalyst systems. Furthermore, electrophilic activation of carbon atoms has focused on Au(I) complexation directly with \( \pi \) bonds. As previously reported Au(III) is an exceptional catalyst to activate allylic ethers and alcohols by complexation with the allylic oxygen and the \( \pi \) bonds to delocalize
electrons for nucleophilic attack, and has been relatively unexplored in this application.

3.2. Gold(III)-Catalyzed Cyclization to Form γ-Butyrolactones

To test the hypothesis that allylic alcohols and ethers may be activated under mild conditions with Au(III) species to form γ-butyrolactones we synthesized a substrate for investigation by olefin-metathesis with ethyl pent-4-enoate 3-8 and diol 3-9 using Grubbs 2nd generation catalyst (Equation 3-1).

![Chemical反应](image)

(3-1)

Early in our work we had difficulty obtaining the desired cross-metathesis product in good yield and purity due to an unintended olefin isomerization to produce a complex mixture containing aldehyde 3-11. This undesirable olefin isomerization is a known problem in cross-metathesis. Although the mechanism is not completely understood it is believed to proceed through a β-hydride elimination (Scheme 3-1).
Scheme 3-1. Suggested mechanism of undesired ruthenium catalyzed isomerization.

\[
\begin{align*}
\text{Scheme 3-1} & \quad \text{Suggested mechanism of undesired ruthenium catalyzed isomerization.} \\
\end{align*}
\]

Grubbs and co-workers have reported the phenomenon of undesirable isomerization during olefin metathesis, and have also investigated the effect of additives on the prevention of this side reaction. Of the additives they tested, \( p \)-benzoquinone was found to prevent olefin isomerization of a number of allylic ethers and long-chain aliphatic alkenes during olefin metathesis reactions with a ruthenium-based catalysts.\(^7\) We utilized this mild, inexpensive, and effective additive to inhibit the formation of the aldehyde and improve product yield and purity in olefin-metathesis.

We attempted the cyclization of 3-10 with 10 mol % of catalyst systems \( \text{AuCl}_3 / \text{3AgOTf} \) and \( \text{Ph}_3\text{PAuCl} / \text{AgOTf} \). Deuterated chloroform was used as a solvent to enable observation of reaction progress by \( ^1\text{H} \) NMR. After 24 hours, the reaction had not progressed in either catalyst systems at room temperature (Equation 3-2). This result did not improve even with longer reaction times. In an effort to keep the reaction conditions mild, we first sought to optimize the substrate rather than increase the temperature or investigate the effects of additives in the reaction.
Toward improving the reactivity of our substrate, we hypothesized a mechanism for the reaction based on previously reports of homogenous cationic gold catalysis. Due to the oxophilicity of Au(III), we believed it would coordinate to the allylic alcohol oxygen and polarize the electrons of the π-bond activating the system for nucleophilic attack (Scheme 3-2). Therefore, if we were to install an electron withdrawing allylic ether it would increase the reactivity of the allylic ether system toward nucleophilic attack in the presence of Au(III). Additionally, we hypothesized that installation of an electron donating substituent for the ester could increase electron density on the carbonyl oxygen, which would increase the nucleophilicity of this atom in the reaction. To test this hypothesis we envisioned several electron withdrawing substituents we could install to form an allylic ether, and several electron donating substituents to install to form the ester.

**Scheme 3-2.** Purported mechanism Au(III) catalyzed activation of allylic ethers to form γ-butyrolactones.

We synthesized a t-butyl ester substrate by reaction of t-butyl alcohol 3-14 with acid chloride 3-13 to form ester 3-15 (Scheme 3-3). The poor yield observed
in this esterification was a result of water in the t-butyl alcohol and the elimination reaction to form isobutene. Olefin metathesis with diol 3-2 afforded substrate 3-16, which upon reaction with the gold catalyst systems again afforded less than 10% of product as determined by $^1$H NMR analysis. The isolated yields were not able to be determined due to the high volatility of the product. Therefore, all reported yields are relative conversion determined by $^1$H NMR analysis. Though this yield is low, we were encouraged that some product was formed.

We then hypothesized that the electron donating benzyl ester group with the ability to from a stable tropylium cation would be an exceptional electron donating substituent in this methodology. In order to synthesize intermediate 3-11 we utilized a Dean-Stark apparatus to shift the equilibrium to form the esterified products by extracting water from the reaction. This improved the esterification yield from the previously used procedure in the synthesis of the t-butyl ester 3-7. Cross metathesis with diol 3-2 afforded substrate 3-12 for gold cyclization. Unfortunately, this substrate also performed poorly in the cyclization to form lactone 3-8, again forming less than 10% products after 24 hours for both gold catalyst systems (Scheme 3-4).
Undeterred, we sought to optimize the allylic oxygen leaving group hypothesizing that the reaction efficiency would improve with an electron withdrawing leaving group. In order to optimize the allylic oxygen leaving group we choose an acetate group which could be easily and selectively installed on a primary alcohol. The facile installation of this functional group on substrates 3-10,
3-16, and 3-20 afforded the intended products in high yield and purity (Scheme 3-5).

Scheme 3-5. Synthesis of substrates 3-21, 3-22, and 3-24.

To our delight when these substrates were subjected to a Au(III) catalyst substrates 3-22 and 3-23 afforded the lactone product in good yield in 48 hours at room temperature (Scheme 3-6). Au(I) was not reactive in this transformation supporting our hypothesis regarding the increased Lewis acidity of Au(III) in combination with the substrate optimization was essential for promoting the reactivity. Based on this result we sought to further investigate Au(III) as an active catalyst and to further optimize our substrate with more powerful electron withdrawing groups.
Scheme 3-6. Gold-catalyzed cyclizations of substrates 3-21, 3-22, and 3-23.

Aryl allyl ethers have previously been reported by our group to promote the gold-catalyzed lactonization with carboxylic acids. Therefore, phenol based compounds offered an interesting opportunity to tune the reactivity of our allylic ether leaving group by utilizing the electronic effect of substituents on the aromatic ring. These phenolic structures may be installed by an efficient and simple method known as the Mitsunobu etherification. Furthermore, investigation of these sterically bulky leaving groups could provide useful insight for the investigation into diastereoselective and enantioselective synthesis of saturated oxygen heterocycles.

There were two important considerations in the design of these substituted phenol based leaving groups. Substituents that perturbed the electronics through resonance would have the greatest effect on the allylic ether oxygen, therefore electron withdrawing substituents were installed in the ortho and para positions. As previously reported aryl allyl ethers are reactive at the ortho position in Claisen
rearrangement reactions.\textsuperscript{12,67} Therefore, these aryl leaving groups must always be substituted at the \textit{ortho} positions to prevent this side reaction. We envisioned leaving groups to test as seen in 3-24, and 3-25 (Figure 3-1).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3-1.png}
\caption{Selected phenol leaving groups for allyl etherification.}
\end{figure}

These leaving groups were installed on the most effective ester substrate 3-20 with the benzyl ester in good yields by Mitsunobu etherification using diisopropyl azodicarboxylate (DIAD) and triphenylphosphine (Scheme 3-7), and then tested in Au(III)-catalyzed cyclization (Scheme 3-8).

\begin{scheme}[h]
\centering
\includegraphics[width=0.7\textwidth]{scheme3-7.png}
\caption{Mitsunobu etherification to synthesize substrates 3-26, and 3-27.}
\end{scheme}

As predicted, the reactivity in Au(III)-catalyzed cyclization increased as the electron withdrawing nature of the allylic ether leaving group increased, with the
best yield of the substrate with the 3-26 leaving group. This leaving group introduces the facility to install an electron withdrawing allylic ether leaving group for less reactive \( \pi \)-systems in gold catalysis. Additionally it was hypothesized that the steric bulk of this leaving group could be used in the stereoselective cyclizations to from cyclic ethers.

**Scheme 3-8.** Gold(III)-catalyzed lactonization of allyl aryl ethers.

Reactions conducted 0.25M in CDCl\(_3\) utilizing 10 mol% AuCl\(_3\) / 3 AgOTf as a catalyst with basic alumina added as desiccant. Yield determined by NMR. **Error! Bookmark not defined.**
4. Synthesis of Saturated Oxygen Heterocycles

4.1. Diastereoselective Synthesis of Saturated Oxygen Heterocycles

4.1.1. Gold-Catalyzed Cyclizations of Mono-Allylic Diols

In 2008, Aponick and co-workers reported the Au(I)-catalyzed cyclizations of mono-allylic diols to form the 6-membered oxygen heterocycles known as tetrahydropyrans. Several sources of cationic gold were investigated as shown in Scheme 4-1.\textsuperscript{74} AuCl\textsubscript{3} and Ph\textsubscript{3}PAuCl / AgOTf worked the best in this transformation giving tetrahydropyran 4-2 in excellent yields and short reaction times. This group chose not to investigate the Au(III) catalyst due to the assumption that oxophilicity of this species could hinder this catalyst in the presence of functional groups. They were also able to show that the homogenous Au(I) species is the active catalyst as Ph\textsubscript{3}PAuCl, AgOTf and triflic acid were poor Lewis acids for the transformation. An initial mechanistic investigation demonstrated that the reaction likely undergoes a S\textsubscript{N}2' mechanism rather than an allyl cation intermediate as demonstrated by the complete conversion of mono-allylic diol 4-3 to tetrahydropyran 4-4 in just 15 minutes, whereas substrate 4-5 failed to react in extended reaction times and higher temperatures.

According to the authors, AuCl\textsubscript{3} did not proceed through the allyl cation mechanism in this experiment either. To confirm this result was also true for homogenous Au(III), a simple experiment was devised with allylic alcohol 4-6 in which 5 mol \% of Au(OTf)\textsubscript{3} formed in situ was monitored by \textsuperscript{1}H NMR analysis at room temperature for 24 hours then in refluxed CDCl\textsubscript{3} for 24 h (Equation 4-1).
Dihydrofuran product 4-7 was not observed, supporting the hypothesis that Au(III) does not promote through an allyl cation intermediate.

Scheme 4-1. Investigation of Au(I) and Au(III) in catalytic cyclization of mono-allylic diols.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Loading (mol%)</th>
<th>time</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AuCl₃</td>
<td>2</td>
<td>100 min</td>
<td>96</td>
</tr>
<tr>
<td>Ph₃PAuCl/AgOTf</td>
<td>1</td>
<td>40 min</td>
<td>96</td>
</tr>
<tr>
<td>Ph₃PAuCl/AgOTf</td>
<td>5</td>
<td>16 h</td>
<td>0</td>
</tr>
<tr>
<td>AgOTf</td>
<td>5</td>
<td>16 h</td>
<td>0</td>
</tr>
<tr>
<td>TfOH</td>
<td>1</td>
<td>40 min</td>
<td>9</td>
</tr>
</tbody>
</table>

4.1.2. Gold(I)-Catalyzed Diastereoselective Synthesis of 2,6-disubstituted THPs and 2,5-disubstituted THF

Aponick and co-workers investigated the diastereoselective synthesis of 2,6-disubstituted tetrahydropyrans and 2,5-disubstituted tetrahydrofurans
Compounds 4-10 to 4-14 were successfully synthesized in high yield with moderate to high diastereomeric ratios by reducing the reaction temperature to -50°C or -78°C.

**Scheme 4-2.** Diastereoselective synthesis of 2,6-disubstituted THPs and THF.

We hypothesized that the allylic ether leaving group 3-26 introduced in chapter 3 would improve the diastereoselectivity in the Au(III)-catalyzed cyclization of cyclic ethers across a broad scope of substrates at room temperature.

This is because the electron withdrawing, sterically bulky leaving group would activate the reaction by promoting electron delocalization in the presence of Au(III) as previously reported, while the steric bulk would create a large energy difference between the transition state of the cis-equatorial diastereomer and trans-diastereomer. This is due to the concerted SN2' mechanism which means the sterically bulky allylic oxygen leaving group is still present in the transition state. In the tetrahydropyran transition state the substituents may occupy the axial or
equatorial position. If both substituents occupy the equatorial position they avoid the steric bulk of the 1,3-diaxial interactions in the ring, and the 6-membered cyclic ether will assume a relatively low energy chair-conformation 4-16. However, if a substituent occupies the axial position it encounters the 1,3 diaxial interactions of the tetrahydropyran ring, and assembles into the higher energy twist-boat conformation 4-17. The difference in energy between a substituent occupying the equatorial position over the axial position is referred to as the A-value. The relative energy difference between the transition states governs the diastereoselectivity of the reaction, therefore using substituents with relatively large A-values in combination with sterically bulky allylic oxygen leaving groups should create a greater energy difference between the transition states to preferentially form the cis-diastereomer.

Scheme 4-3. Representation of transition states in the substrate dictated diastereoselective formation of tetrahydropyrans.
4.2. Synthesis of Substrates for Gold(III)-Catalyzed Cycloetherfication

Substrates for Au(III)-catalyzed cyclization to form saturated oxygen heterocycles were prepared by nucleophilic addition to aldehydes with various Grignard reagents, followed by olefin cross-metathesis, and Mitsunobu etherification (Scheme 4-4).

Scheme 4-4. General synthesis of substrates for gold-catalyzed formation of cyclic ethers.
Table 4-1. Isolated yields from preparation of functionalized mono-allylic diols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>4-18</th>
<th>R</th>
<th>4-19 n</th>
<th>Yield 4-20a-h (%)</th>
<th>Yield 4-21a-h (%)</th>
<th>Yield 4-22a-h (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>a</td>
<td>Ph</td>
<td>1</td>
<td>87</td>
<td>71</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>Cy</td>
<td>1</td>
<td>91</td>
<td>57</td>
<td>_</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>t-Bu</td>
<td>1</td>
<td>50</td>
<td>73</td>
<td>58</td>
</tr>
<tr>
<td>4a</td>
<td>d</td>
<td>n-Hex</td>
<td>1</td>
<td>46</td>
<td>66</td>
<td>40</td>
</tr>
<tr>
<td>5a</td>
<td>e</td>
<td>Ph</td>
<td>1</td>
<td>58</td>
<td>80</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>Cy</td>
<td>0</td>
<td>84</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>t-Bu</td>
<td>0</td>
<td>48</td>
<td>--.c</td>
<td>--</td>
</tr>
<tr>
<td>8a</td>
<td>g</td>
<td>n-Hex</td>
<td>0</td>
<td>24</td>
<td>66</td>
<td>25</td>
</tr>
<tr>
<td>9a</td>
<td>h</td>
<td>Cy</td>
<td>2</td>
<td>49</td>
<td>53</td>
<td>42</td>
</tr>
</tbody>
</table>

*a*Yields reported in reference **Error! Bookmark not defined.**  
b/Product lost due to equipment malfunction.  
c Reaction formed a complex mixture, no product was isolated.

The olefin-metathesis step to form **4-21a-j** sometimes gave poor yields and low product purity due to the previously reported undesirable olefin isomerization.\textsuperscript{73} Additionally, in order to obtain higher yields it was necessary to use greater than 6 equivalents of the diol **3-2** because both alkenes of the reaction are considered type I, fast homodimerization species in the presence of Grubbs 2\textsuperscript{nd} generation catalyst.\textsuperscript{77} In order to obtain high yields with two fast homodimerization species, one of the species must be used in excess in order to achieve the statistical
outcome of equilibrium. Additionally, the intended products were often difficult to separate from the excess reagent.

Instead, we sought to improve upon reaction by using a protected allylic alcohol which would be a type II, slow homodimerization species.\(^7\) This would only require two equivalents of the reagent for good yields, and prevent the isomerization of the allylic alcohol to the aldehyde. We used cis-1,4-diacetoxo,2-butene (4-23), which allowed access to the protected diol, and an additional substrate 4-24 for gold-catalyzed cyclization with a leaving group previously shown to be sufficiently electron withdrawing to activate the allylic oxygen moiety. Furthermore, this acetate protecting group was easily removed in an hour in near quantitative yield to afford 4-21a (Scheme 4-5).

Scheme 4-5. Synthesis of intermediates 4-24 and 4-21a.

In order for the Mitsunobu etherification step to be chemoselective for the primary alcohol, the reaction was cooled to -20 °C. The secondary alcohol is more...
sterically hindered and therefore requires a higher activation energy than the primary alcohol. Chemoselectivity was generally good in this reaction with sufficient yields of the intended product, and was considered more efficient than using of a protecting group on the secondary alcohol.

A symmetrical substrate was also synthesized with intention to not only investigate diastereoselectivity, but the utility for Au(III) to be used in enantioselective reactions. To prepare this substrate a nucleophilic addition was performed on ethyl formate with a Grignard reagent prepared from 5-bromopentene. This intermediate was reacted in olefin metathesis with 4-23 to afford substrate 4-28 (Scheme 4-6). The acetate was removed to afford 4-29, and 3-26 was installed by Mitsunobu etherification to yield 4-28.

**Scheme 4-6. Synthesis of substrates 4-26, 4-27 and 4-28.**
4.3. Substrate Scope of the Diastereoselective Formation of Cyclic Ethers

A broad range of substrates were synthesized using the described methods to investigate the reaction scope of the Au(III)-catalyzed formation of cyclic ethers (Table 4-2). The experimental set-up for these reactions was designed with the intent to remove as much experimental variability as possible from analysis of the scope of this diastereoselective transformation. The reactions were performed under argon, at room temperature, in a dry culture tube with basic alumina as a desiccant. Basic alumina was used not only to adsorb any water that could potentially hinder the reaction, but also to neutralize any acidic protons which could deprotect the allylic ether leaving group, thereby decreasing diastereoselectivity. CDCl₃ was used as a solvent so the reaction could be monitored by ¹H NMR.

To our excitement, these reactions progressed to full conversion within 24 hours with 10 mol % of the Au(III) catalyst system. In support of our hypothesis the optimized allylic ether leaving group 3-25 increased the diastereoselectivity in this reaction at room temperature for all substrates, and in the case of forming tetrahydropyran rings we are not able to observe the minor diastereomer in determination of the diastereomeric ratio by ¹H NMR analysis in entries 3-6 and 10 of Table 4-2. Therefore, we assigned a diastereomeric ratio of 99:1 based on the sensitivity of the NMR. In comparison, substrates which used an allylic alcohol leaving group in the formation of tetrahydropyrans (entries 2, 3 and 12 of Table 4-2) exhibited consistently lower diastereomeric ratios of 4:1.
Table 4-2. Gold(III)-catalyzed cyclizations to form saturated oxygen heterocycles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="4-21f" alt="Image" /></td>
<td><img src="4-31" alt="Image" /></td>
<td>51</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="4-21c" alt="Image" /></td>
<td><img src="4-32" alt="Image" /></td>
<td>93</td>
<td>4:1</td>
</tr>
<tr>
<td>3</td>
<td><img src="4-21a" alt="Image" /></td>
<td><img src="4-33" alt="Image" /></td>
<td>96</td>
<td>4:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="4-22f" alt="Image" /></td>
<td><img src="4-31" alt="Image" /></td>
<td>93</td>
<td>7:1</td>
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<tr>
<td>5</td>
<td><img src="4-22c" alt="Image" /></td>
<td><img src="4-32" alt="Image" /></td>
<td>88</td>
<td>99:1</td>
</tr>
<tr>
<td>6&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="4-22d" alt="Image" /></td>
<td><img src="4-34" alt="Image" /></td>
<td>28</td>
<td>99:1</td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="4-22a" alt="Image" /></td>
<td><img src="4-33" alt="Image" /></td>
<td>53</td>
<td>99:1</td>
</tr>
<tr>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="4-22e" alt="Image" /></td>
<td><img src="4-35" alt="Image" /></td>
<td>74</td>
<td>3:1</td>
</tr>
<tr>
<td>9&lt;sup&gt;d&lt;/sup&gt;</td>
<td><img src="4-22j" alt="Image" /></td>
<td><img src="4-36" alt="Image" /></td>
<td>20, (46)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8:1</td>
</tr>
</tbody>
</table>
Reactions conducted at room temperature for 24 hours, 0.25M in CDCl$_3$ utilizing 10 mol% AuCl$_3$/3 AgOTf as a catalyst with basic alumina added as desiccant.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)$^a$</th>
<th>dr$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td><img src="image" alt="4-30" /></td>
<td><img src="image" alt="4-37" /></td>
<td>77</td>
<td>99:1</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="4-28" /></td>
<td><img src="image" alt="4-38" /></td>
<td>81</td>
<td>6:1</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="4-29" /></td>
<td><img src="image" alt="4-39" /></td>
<td>94</td>
<td>4:1</td>
</tr>
</tbody>
</table>

Reactions conducted at room temperature for 24 hours, 0.25M in CDCl$_3$ utilizing 10 mol% AuCl$_3$/3 AgOTf as a catalyst with basic alumina added as desiccant.

$^a$Isolated yield. $^b$Diastereomeric ratio determined by NMR. $^c$Relative conversion determined by NMR. $^d$Isolated yields reported in reference Error! Bookmark not defined.

In order to assign the configuration of the major diastereomers in the cyclization experiments, $^1$H NMR nuclear Overhauser effect spectroscopy (NOESY) was performed. This type of spectroscopy established correlations between nuclei which are physically close in proximity to each other in the molecule regardless of the bonds between them.$^{78}$ This spectroscopic experiment takes advantage of the nuclear Overhauser effect (NOE) by which nearby atoms (within approximately 5 Å) proceed through a cross-relaxation mechanism related to spin-lattice relaxation. The NOESY experiment was
performed in a one-dimensional fashion by pre-selecting the individual resonances of the protons located at the 2 and 6 positions on the tetrahydrofuran ring. Irradiation of the frequency of one resonance results in a strong negative signal, while neighboring nuclei are identified by weaker positive signal as a result of the NOE. In all of the experiments the major diastereomer of the Au(III)-catalyzed cyclization was the thermodynamically favored syn product (Figure 4-1).

Figure 4-1. $^1$H NMR Nuclear Overhauser effect spectra (NOESY) in the determination of the major and minor diastereomer of 4-28.
It is important to note that the diastereomeric ratio of the 5 and 7 membered heterocycles which utilized the optimized allylic ether leaving group were decreased in comparison to the tetrahydropyran substrates. This is largely due to the energy difference of the conformations of these cyclic structures. Tetrahydropyran molecules are very similar to cyclohexane adopting a stable chair conformation with bond angles as close to 109.5° as possible, and positioning sterically bulky substituents in the equatorial positions. The relative energy difference between the most stable conformations “chair” and “twist-boat” is 5.5 kcal/mol (Figure 4-1). However, in tetrahydrofuran the 5-membered ring has some torsional and ring strain. The energy difference between the axial and equatorial positions of the envelope conformation is significantly diminished and the ring rapidly interconverts between the two. In an oxepane the relative energy difference is also lower than in tetrahydropyran, and the ring may adopt many different lower energy conformations the analysis of which is actually quite complex. The “twist-chair” is the lowest energy conformation, while the “boat” forms are only few kilocalories per mole higher in energy.79

Therefore, the allylic ether leaving group we have introduced aids in the diastereoselective formation of these cyclic ethers. However, in order to improve the diastereomeric ratios observed in the tetrahydrofuran and oxepane reactions we would have to decrease the temperature of our reaction to shift the Boltzmann distribution to the most thermodynamically stable conformer.
In the oxepane example we observed a 20 % isolated yield of the intended product, however in this example we obtain only 46 % conversion of the starting material by $^1$H NMR analysis at 24 hours. We isolated a secondary product and determined the structure to be alkenone 4-50. We hypothesized alkenone formation occurred after the formation of the oxepane product by the original proposed S$_{N}2'$ mechanism. The Au(III) likely coordinates to the allylic ether present in the product, which acts to delocalize the $\pi$-electrons to promote an elimination to form an enol ether. Protodeauration of the complex followed by tautomerization, and elimination yields the observed alkenone product 4-50.
Analysis of the scope of the Au(III)-catalyzed reaction to form saturated oxygen heterocycles indicated this methodology is efficient for a broad range of substrates. As predicted the optimized allylic ether leaving group dramatically improved the diastereoselectivity of this reaction at room temperature for all substrates, however tetrahydropyrans and oxepanes had a lower diastereomeric ratio. Good isolated yields were reported though the catalyst loading was high. In order to determine the efficiency of this reaction an investigation was performed to optimize the conditions and analyze the reaction rate.
4.4. Optimization of Conditions and Control Experiments

To determine the optimal catalyst loading, and to confirm if homogenous Au(III) was the active catalyst a study was performed with mono-allylic diol substrate 4-21a to form tetrahydropyran 4-33 (Equation 4-2, Table 4-2). Quantitative GC yields were obtained in less than 10 minutes using only 1 mol % of AuCl₃ / 3 AgOTf (entry 2, Table 4-2). In comparison 1 mol % of PPh₃AuCl/AgOTf required 40 minutes to achieve a 94 % GC yield (entry 4, Table 4-2). This table also shows cationic gold(III) complex was the active species because no or very minimal conversion was observed using AuCl₃ and AgOTf separately. Additionally, transformation was not reactive with AgCl, basic alumina or MS 4 Å.

To test the robustness of the developed catalyst system a variety of solvents were tested in open air using substrate 4-24 to form tetrahydropyran 4-33 (Equation 4-3, Table 4-3). The majority of solvents tested gave quantitative yield of the product in less than 10 minutes with just 1 mol % of AuCl₃ / 3 AgOTf. Polar coordinating solvents like acetone, methanol and water (entries 7-9) were not suitable solvents for the reaction. This is likely because the solvent strongly coordinates to the Au(III) preventing the catalyst from interacting with the substrate.
Table 4-3. Catalyst loading and control experiments.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading (mol %)</th>
<th>Time</th>
<th>Yield of 4-38 (%)</th>
<th>dr</th>
<th>Additive</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AuCl₃ / 3 AgOTf</td>
<td>5</td>
<td>&lt;10 min</td>
<td>100</td>
<td>4:1</td>
<td>MS 4 Å</td>
</tr>
<tr>
<td>2</td>
<td>AuCl₃ / 3 AgOTf</td>
<td>1</td>
<td>&lt;10 min</td>
<td>100</td>
<td>4:1</td>
<td>MS 4 Å</td>
</tr>
<tr>
<td>3</td>
<td>AuCl₃ / 3 AgOTf</td>
<td>1</td>
<td>&lt;10 min</td>
<td>30</td>
<td>4:1</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>PPh₃AuCl / AgOTf</td>
<td>1</td>
<td>40 min</td>
<td>94</td>
<td>4:1</td>
<td>MS 4 Å</td>
</tr>
<tr>
<td>5</td>
<td>AuCl₃</td>
<td>1</td>
<td>24 h</td>
<td>26</td>
<td>4:1</td>
<td>MS 4 Å</td>
</tr>
<tr>
<td>6</td>
<td>AgOTf</td>
<td>15</td>
<td>24 h</td>
<td>0</td>
<td>--</td>
<td>MS 4 Å</td>
</tr>
<tr>
<td>7</td>
<td>AgCl</td>
<td>15</td>
<td>24 h</td>
<td>0</td>
<td>--</td>
<td>MS 4 Å</td>
</tr>
<tr>
<td>8</td>
<td>Basic Alumina</td>
<td>20</td>
<td>24 h</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>9</td>
<td>MS 4 Å</td>
<td>20</td>
<td>24 h</td>
<td>0</td>
<td>--</td>
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</table>
Table 4-4. Solvent considerations.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Dichloromethane</td>
<td>&lt;10 min</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Chloroform</td>
<td>&lt;10 min</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexane</td>
<td>&lt;10 min</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>&lt;10 min</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>Tetrahydrofuran</td>
<td>&lt;10 min</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>Ether</td>
<td>&lt;10 min</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>Acetone</td>
<td>24 h</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Methanol</td>
<td>24 h</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Water</td>
<td>24 h</td>
<td>0</td>
</tr>
</tbody>
</table>
5. Gold(III)-Catalized Cyclization to Form Spiroketals

5.1. Spiroketals in Nature

Spiroketals are a unique structural feature in which cyclic ethers are connected by single carbon called the spiro carbon. Each of the ketal oxygens joined by the spiro-carbon belongs to one of the rings. The spiroketal ring system is an important structural feature observed in a myriad of natural products with promising and diverse biological activity such as insect pheromones, polyether ionophores, macrolide antibiotics, and steroidal saponins. Some examples of this natural product which possess this spiroketal structural motif are tautomycin 5-1, okadaic acid 5-2, and spongistatin 5-3 which are all protein phosphatase inhibitors (Figure 5-1).

These rigid, structurally complex features often serve as pharmacophores in biological systems due to the conformational constraint of these moieties making them attractive targets in reaction methodology. The synthesis of spiroketals still remains a significant challenge in synthesis and few examples of metal catalyzed reactions to form these features have been reported.
5.2. Conformational Aspects of Spiroketal Structures

The stereochemistry of spiroketals is thermodynamically influenced by the anomeric effect. However, intramolecular hydrogen bonding, steric interactions and chelation may also contribute to the conformation of these spirocyclic systems. The anomeric effect is described as the propensity of an electronegative atom like oxygen at the anomeric carbon of a pyranose ring to occupy the axial position of the ring. This orientation allows the lone pair of the oxygen to interact with the $\sigma^*$ antibonding orbital of the C-O bond (Figure 5-2). If
the substituent is in the equatorial position of the ring this orbital interaction is not possible making this a conformation much higher in energy. Each anomeric interaction increases the stability by decreasing the total energy of the molecule by approximately 1.4 – 2.4 kcal/mol.87

![Anomeric Hydroxyl Structures](image)

**Figure 5-2.** Possible positions of an electronegative hydroxyl substituent at the tetrahydropyran anomeric carbon.

The 6,6-spiroketal core may exist in four different conformations which can be interconverted by ring flipping (**Figure 5-3**).88 The most thermodynamically stable conformation (A) has two anomeric interactions. Two possible conformations exhibit one anomeric effect (B and C). The most thermodynamically unfavorable isomer is the conformation with no anomeric effect (D).

The traditional method to synthesize spiroketals is the acid-catalyzed cyclization of a dihydroxyketone (**Equation 5-1**).89 This method is effective at synthesizing the thermodynamically favorable spiroketals stereoisomers which benefit from conformational anomeric effects.85 Since most synthetic targets have this conformation this method is often effective for synthesis.
Figure 5-3. Possible conformations of a spiroketal.

However, substrates with acid-labile functional groups limits the reaction scope. Additionally, synthesis of nonanomeric or thermodynamically unfavorable spiroketals are very challenging using this method.

\[
\begin{align*}
R_1 & \quad O \\
& \quad O \\
& \quad \text{no anomeric effect} \\
\end{align*}
\]

\[
\begin{align*}
R_1 & \quad O \\
& \quad O \\
A & \quad \text{2 anomeric effects} \\
\end{align*}
\]

\[
\begin{align*}
R_1 & \quad O \\
B & \quad \text{1 anomeric effect} \\
\end{align*}
\]

\[
\begin{align*}
C & \quad \text{1 anomeric effect} \\
R_1 & \quad O \\
& \quad O \\
\end{align*}
\]

\[
\begin{align*}
D & \quad \text{no anomeric effect} \\
R_1 & \quad O \\
& \quad O \\
\end{align*}
\]

\[ \text{Figure 5-3. Possible conformations of a spiroketal.} \]

\[ \text{However, substrates with acid-labile functional groups limits the reaction scope. Additionally, synthesis of nonanomeric or thermodynamically unfavorable spiroketals are very challenging using this method.} \]

\[ \text{(5-1)} \]

5.3. Metal-Catalyzed Spiroketalization

Cationic metal complexes have been found to be effective for the Lewis acid-catalyzed cyclization to form spiroketals. Floreancig and co-workers described the application of the thermodynamic stereocontrolled process to synthesize spiroketals by transposition/oxa-Michael addition. They reported high stereocontrol in the synthesis of spiroketals from allylic alcohols using rhenium (VII) oxide (Scheme 5-1). In 2010, Cossy described a Fe(III)-catalyzed
diastereoselective formation of spiroketals from allylic alcohols in good yield.\(^\text{91}\) This cyclization was proposed to proceed through a carbocation intermediate which allowed for the thermodynamically favorable diastereomer but excluded this reaction from stereo-retention towards enantioselective products. Aponick and co-workers have reported on the Au(I)-catalyzed spiroketalization of protected monoallylic propargyl alcohols.\(^\text{39}\) This approach to synthesize unsaturated spiroketal structures addressed the regioselectivity issues commonly reported in metal-catalyzed spiroketalization of alkynes.

**Scheme 5-1.** Selected examples of metal-catalyzed spiroketalizations.

The selected examples are powerful synthetic methods to yield spiroketals, but these synthetic methodologies are limited to the formation of the specific
substrates, and there are very few reports of the formation of reaction cascade to form bis-spiroketalts.

### 5.4. Gold(III)-Catalyzed Spiroketalization of Monoallylic Ketodiols

The recent work of a graduate student from Aponick's group sought to synthesize spiroketals from monoallylic ketodiols using cationic metals. Palmes discovered Pd(II) was the best catalyst in this reaction (Scheme 5-2), however homogenous Au(III) was not tested in this reaction. Au(I) was ruled out early in the investigation as being less efficient though it successfully catalyzed the reaction although in poor yield. Based on the results presented in this thesis we hypothesized homogenous Au(III) complexes may be able to activate the carbonyl and allylic alcohol moiety towards the formation of spiroketals, and the more synthetically difficult bis-spiroketalts utilizing a similar reaction cascade.

#### Scheme 5-2. Selected examples metal-catalyzed spiroketalization of monoallylic ketodiols.
To test our hypothesis, an unsubstituted monoallylic ketodiol was synthesized from commercially available $\delta$-valerolactone by formation of the corresponding Weinreb amide 5-15 and protection of the primary alcohol to afford the $t$-butyldimethylsilyl ether 5-16 (Scheme 5-3). Nucleophilic addition of a Grignard reagent prepared from 5-bromopentene to the substrate yielded 5-17. Which was then used in olefin cross-metathesis with Z-2-butene-1,4-diol to afford the mono-allylic ketodiol 5-18. The optimized allylic ether leaving group 2,6-dimethyl-4-nitrophenol was installed using Mitsunobu etherification, and the protecting group was removed to obtain the desired substrate 5-20.

Substrate 5-20 was then treated with 2 mol % of the catalyst AuCl₃/3 AgOTf in CDCl₃ with basic alumina added as a dessicant. TLC showed complete consumption of the starting material after just 5 minutes. However, due to the polarity of the compounds detected it was believed that this was the hemiketal that had been formed by the Lewis acid activation of the carbonyl, and the reaction was allowed to react overnight in order to form the spiroketal. The reaction was checked by ¹H NMR after 15 hours to show only the hemiketal had formed (Scheme 5-4). After heating the reaction at reflux for an additional 24 hours no spiroketal was formed. The hemiketal was isolated in 62% yield with good diastereoselectivity, however this yield is the result of the equilibrium formed between the hemiketal and the starting material in the presence of a Lewis acid.

**Scheme 5-4.** Au(III)-catalyzed spiroketallization of 5-20.

We believed it was unlikely the oxophilicity of Au(III) was preventing the reaction from progressing, and hypothesized that the sterically bulky allylic ether leaving group was preventing nucleophilic attack with the sterically bulky thermodynamically favored, axial, anomeric alcohol. Therefore, a smaller allylic ether leaving group could decrease the steric bulk and allow the reaction to
progress to completion. Substrate 5-22 was synthesized by olefin metathesis of 5-17 with Z-1,4-diacetoxy-2-butene and deprotection of the TBS ether. The acetoxy leaving group could enhance the reactivity of the allylic oxygen, while decreasing the steric bulk of this functional group.

**Scheme 5-5.** Synthesis of substrate 5-22.
6. Centrolobine

6.1. Introduction and Background of Centrolobine

The Au(III) catalyst methodology developed in this thesis was utilized toward the total synthesis of centrolobine. In 1959, a group of scientists discovered extracts from the heartwood of *Centrolobium robustum* exhibited bacteriostatic activity. It was not until 1964 that one of the active ingredients was extracted, isolated, and characterized as 2[β(p-hydroxyphenyl)ethyl-2-(p-methoxyphenyl)]tetrahydropyran, referred to as (+)-centrolobine ((+)-6-1, Figure 6-1).[^93]

![Figure 6-1. (+)-Centrolobine.](image)

Centrolobine has since been found in numerous plants in the Brazilian Amazon and the compound has acute antibiotic and antifungal activity, therefore making it a promising drug candidate or lead for antibiotics.[^93][^94][^95] Both enantiomers, (+)- and (−)-centrolobine, are active antibiotic agents and have been isolated from many different trees, primarily *Centrolobium robustum* and *Centrolobium tomentosum*.[^93][^94][^95] Additionally, (−)-centrolobine has recently been isolated from the stems of a completely different genus, *Brosimum potabile*.[^96]

The scientific community has developed an interest in the synthesis of this compound, and several total syntheses have been achieved.[^97] In the multiple synthetic pathways devised there have been many different methods by which the
central tetrahydropyran ring of centrolobine has been formed.\textsuperscript{97, 98, 99} We hypothesized that we would be able to incorporate our diastereoselective Au(III)-catalyzed etherification in a new stereoselective route towards centrolobine.

The absolute configuration of centrolobine was first determined in 2002 by the first enantioselective total synthesis of (−)-centrolobine (Scheme 6-1).\textsuperscript{98} The optically pure keto sulfoxide (\textit{R})-6-4 was prepared by condensation of glutaric anhydride (6-2) and (\textit{R})-6-3. This intermediate was then esterified with dimethylsulfate and potassium carbonate to obtain (\textit{R})-6-5. The 1,3 diketone was then stereoselectively reduced with DIBAL-H and ZnBr\textsubscript{2} to obtain 6-6 in high diastereomeric excess. From the proposed mechanism,\textsuperscript{100} and the characteristic $^1$H NMR spectrum for each diastereomer,\textsuperscript{101} the absolute configuration of the hydroxylic carbon on 6-6 was assigned as \textit{R} stereoisomer. In order to form the tetrahydropyran ring, this group followed the work of Olah\textsuperscript{102} and Nicolaou.\textsuperscript{103} By treating the hydroxyl ketone with excess Et\textsubscript{3}SiH and TMSOTf they were able to prepare the respective unsymmetrical cyclic ether by reductive condensation of carbonyl compounds. The stereospecificity of the etherification was directed by the \textit{R} hydroxyl group of 6-7, and the syn stereochemistry was assigned by $^1$H NMR Nuclear Overhauser enhancement experiments. This stereochemistry was conserved through the rest of the 9 step synthesis to obtain (−)-centrolobine in 26\% overall yield.
Scheme 6-1. First enantioselective total synthesis of (−)-centrolobine.

6.2. Total Synthesis of (±)-Centrolobine

Heidi Dimmitt, a prior Vyvyan group member, had developed a concise synthesis of centrolobine involving Au(I)-catalyzed tetrahydropyran formation (Scheme 6-2). The synthetic approach began with a nucleophilic addition of a Grignard reagent prepared from 5-bromo-1-pentene with p-anisaldehyde to form 6-12. Olefin-metathesis of the terminal alkene (Z)-2-butene-1,4-diol using Grubbs’ 2nd generation catalyst formed 6-13. The primary alcohol was reacted in a Mitsunobu etherification with 6-14 to form allyl aryl ether 6-15. Au(I) catalyzed
cyclization of this intermediate yield the central tetrahydropyran of centrolobine as a single diastereomer due to the sterically bulky leaving group 6-14. The terminal alkene was coupled to the THP protected 4-iodophenol using an alkyl Suzuki coupling to yield 6-17. Deprotection of the THP-protecting group completed the 6-step synthesis of (±)-centrolobine with an overall yield of 2%.

Scheme 6-2. Synthesis of (±)-centrolobine utilizing gold(I)-catalyzed ring formation.
Due to the low overall yield in the total synthesis of (±)-centrolobine we believed we could improve the synthetic pathway by utilizing fewer steps that promoted higher yields of reaction intermediates. First, we designed the synthesis around a the Au(III)-catalyzed cyclization step. In this design we hypothesized the sterically bulky allylic aryl group in centrolobine would enhance the diastereoselectivity of the reaction without installation of a sterically bulky leaving group. Second we hypothesize coupling the east and west fragments of centrolobine could be easily accomplished by an olefin metathesis reaction as the terminal alkene of the west fragment would be a type I fast homodimerization species, while the east fragment would be a type II slow homodimerization species. Lastly, these fragments could be assembled in high yield using a simple nucleophilic addition with the corresponding Grignard reagent (Scheme 6-3). Furthermore, we hypothesized that we may be able to obtain an enantiopure centrolobine by utilizing an enantioselective Corey-Bakshi-Shibata reduction to form the corresponding enantiopure western fragment.
Scheme 6-3. Retrosynthetic analysis of centrolobine towards a more efficient total synthesis with Au(III).

The synthesis began with the nucleophilic addition of prepared Grignard reagent. The western fragment was synthesized by a method similar to the pathway devised by Dimmit; by addition of 6-11 to p-anisaldehyde 6-10, however with an improved yield (85%, Scheme 6-4). The eastern fragment was synthesized by addition of vinyl magnesium bromide 6-18 to 6-17 in high yield.
Scheme 6-4. Nucleophilic addition with Grignard reagents in the preparation of intermediates 6-12 and 6-18.

Unfortunately, when these substrates were subjected to olefin metathesis with Grubbs 2\textsuperscript{nd} generation catalyst 6-18 proceeded through a rapid homodimerization/isomerization pathway to form the oxidized and conjugated species 6-19 (Equation 6-1). This side reaction occurred even in the presence of additives like \textit{p}-benzoquinone and acetic acid, which have been reported to suppress undesirable olefin isomerization.\textsuperscript{73} The formation of this species was likely also driven by Le Châtelier’s principle as the compound exhibited poor solubility in DCM and chloroform, and readily precipitated out of solution.

In order to prevent this undesirable product and make the reaction more robust and efficient, a protecting group was installed. In the course of this thesis work it was discovered that allylic acetoxy groups are exceptionally resistant to
olefin isomerization and may be used in stoichiometric equivalents for high yields. Therefore, we installed an acetoxy protecting group on to 6-18 by reaction of acetic anhydride and dimethylaminopyridine to synthesize 6-19 (Scheme 6-5).

When 6-12 and 6-19 were subjected to olefin metathesis conditions the reaction proceeded to the product 6-20 without the formation of any observable side products. Though the yield for this reaction was low, unreacted starting materials were recovered indicating the reaction had not gone to complete conversion. This can easily be improved by using a higher catalyst loading, a higher temperature and a longer reaction time.

The substrate 6-20 was then cyclized in one minute with just 1 mol % AuCl₃ / 3 AgOTf as a single diastereomer 6-21. Hydrogenation to reduce the olefin and remove the benzyl ether protecting group in single step was attempted on 6-21 using palladium on carbon and hydrogen gas. After 24 hours a nearly complete conversion of the starting material was observed by TLC, however a mixture of products was formed, none of which was the intended product (±)-controlobine.
Future work will attempt to improve the synthetic pathway of this reaction towards the total synthesis of (±)-centrolobine. First, the acetate protection may be performed with the in situ generated oxygen anion from the nucleophilic addition reaction. This would reduce the number of total steps and should increase the total yield across the two reactions. Though the yield of the olefin metathesis reaction was only 12% there was good recovery of the starting materials (81% recovered 6-19, and 41% recovered 6-12). Therefore, adjusting the reaction conditions to allow for increased catalyst loading, increased reaction temperature and longer reaction time should improve the observed yield in this reaction. The Au(III)-catalyzed cycloetherification to form 6-21 had a low isolated yield though complete conversion was observed by TLC after 1 minute. This is due to the complex mixture.
of minor products that formed in the approximately 15 minutes during the analysis of the reaction mixture by TLC. These undesirable side reactions may be prevented by reducing the reaction temperature, however a more detailed analysis of these minor products is required to determine the mechanism of side product formation. Lastly, though the hydrogenation was ineffective in this case the hypothesis is that excess hydrogenation may have cause undesirable side reactions to occur. Therefore, performing the hydrogenation under more mild conditions may allow access to the desired natural product (±)-centrolobine.
7. Conclusions and Future Work

The work presented in this thesis has demonstrated the synthesis of \( \gamma \)-butyrolactones and saturated oxygen heterocycles utilizing homogenous Au(III) complexes. We were able to synthesize the substrates by utilizing readily available starting materials, and efficient synthetic pathways. In the synthesis of \( \gamma \)-butyrolactones we observed electron donating, cation accepting ester substituents enhanced the reactivity in Au(III) catalysis. We were able to demonstrate the use of an electron withdrawing, sterically bulky allylic ether leaving groups allowed for increased reactivity in Au(III) catalyzed cyclizations to form \( \gamma \)-butyrolactones. The steric bulk of these allylic ether leaving groups allowed for stabilization of the transition state to increase diastereoselectivity in the synthesis of saturated oxygen heterocycles. This reaction performed smoothly in the presence of many different functional groups. We then sought to use the optimized conditions in more difficult saturated oxygen heterocycles structural moieties observed in complex synthetic targets.

In the attempt to synthesize spiroketal structural features we observed that Au(III) was an exceptional Lewis acid for activation of the ketone for nucleophilic addition, however the electron withdrawing allylic ether leaving group may have prevented the final spiroketalization due to steric bulk. The reactivity of Au(III) catalyst system was effectively used to synthesize the central tetrahydropyran structural feature in (\( \pm \))-centrolobine.

Based on these results we have hypothesized new routes in which this Au(III) catalyst system may be employed. We believe the oxophilicity of Au(III) is
potential advantageous in the catalytic activation of certain oxygen functional
groups like carbonyls, epoxides, and $\alpha,\beta$ – unsaturated carbonyls, which could introduce new reaction methodologies. Activation of these structural features could enable access to synthetically difficult molecular structures.
8. General Experimental Procedures

All procedures involving air- or moisture-sensitive reagents were performed in oven dried glassware under an argon atmosphere. Ether, THF, CH₂Cl₂ and toluene were dried by passing through a column of activated alumina using an Innovative Technology Pure Solv™ 400 Solvent Purification System. In all procedures, unless otherwise noted, concentration was performed using rotary evaporation. Dessicants like MgSO₄ and NaSO₄ were removed using gravity filtration and fluted filter paper (VWR Qualitative Filter Paper 415).

For purifications, column diameters, and solvent mixtures were given (for example “40 mm column, 6:1 Hex: EtOAc”). Flash chromatography was performed with hand packed columns of silica gel (Silicycle, Chemical Division, 230-400 mesh). Thin Layer Chromatography was done using Sorbent Technologies 200 μm silica layer fluorescence UV254 TLC plates.

¹H and ¹³C NMR spectra were acquired on either Varian Mercury (300 MHz) or UNITY INOVA (500 MHz) spectrometers. All chemical shifts were reported in ppm, and all coupling constants are reported in Hertz. ¹H chemical shifts were referenced to tetramethylsilane (TMS) at 0.00 ppm. ¹H NMR data are reported in the following format: chemical shift [integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) J, proton assignment]. ¹³C NMR spectra are referenced to CDCl₃ at 77.1 ppm.

Infrared spectra were obtained on a Thermo Scientific Nicolet iS10 FT-IR spectrometer with Smart iTR attachment. All absorptions are reported in cm⁻¹.
Absorbances in the IR spectrum are referenced to as: w = weak, m = medium, s = strong, and br = broad.

High resolution mass spectrometry was performed by the Mass Spectrometry Facility at the University of California, Irvine.
Preparation of 2,6-dimethyl-4-nitrophenol

Notebook Entry: RDLB037

2,6-dimethylphenol (20.0.34 g, 164 mmol), concentrated sulfuric acid (18M, 30 mL) were added to a 500 mL Erlenmeyer flask and stirred until the solid was dissolved forming a pink solution. After 5 minutes, the solution solidified to a pink solid. Glacial acetic acid (17.4 M, 100 mL) was added to dissolve the pink solid. The reaction mixture was stirred until solution was homogenous and then submerged in an ice bath. A mixture of nitric acid (15 mL, 16M) and sulfuric acid (15 mL, 18M) was added drop wise over a period of 1 hour. Reaction vessel was taken out of ice bath and allowed to slowly warm to room temperature. Na₂CO₃ was added slowly until pH was around 3. The reaction mix was vacuum filtered over filter paper and rinsed with cold water to provide 4-nitro-2,6-dimethylphenol (15.8941 g, green solid 58 %).

**FTIR**: 3030 (sp² C-H stretch), 2920 (sp³ C-H stretch), 1588/1517 (N-O stretch) cm⁻¹.

**¹H NMR** (CDCl₃, 500 MHz): δ 7.93 (s, 2H), 2.32 (s, 6H) ppm.

**¹³C NMR** (CDCl₃, 125 MHz): δ 157.9, 124.5, 123.7, 77.3, 77.0, 76.8, 15.9 ppm.
**Preparation of 1-cyclohexylhex-5-en-1-ol**

![Chemical Structure](image)

Notebook Reference: RDLA202

An oven dried 100 mL 2-neck round bottom flask with stir bar was charged with magnesium turnings (546.9 mg, 22.50 mmol) and fitted with a reflux condenser and placed under argon. THF (15 mL) was added via syringe followed by dibromoethane (4 drops) and allowed to stir for 10 mins in order to activate the magnesium. 5-bromo-1-pentene (1.78 mL, 15.0 mmol) was diluted in 10 mL and added drop wise over 15 minutes. The reaction was then heated at reflux for 1 hour. The reaction was cooled to room temperature and cyclohexyanecarboxaldehyde (1.91 mL, 15.8 mmol) was added via syringe and the reaction was heated at reflux for 2 hours. The reaction was cooled to room temperature, poured over 10% HCl (50 mL), extracted with ether (3 × 30 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resultant crude oil was purified via flash chromatography (6:1 Hex:EtOAc, *R*<sub>f</sub> = 0.18) to afford a clear, colorless oil (2.4761 g, 13.583 mmol, 91%).

**FTIR (ATR):** 3350 (br, OH stretch), 3076 (w, vinyl CH stretch), 2922, 2852 (m, alkyl CH stretch), 1640, 1449 (m, vinyl C-C stretch), 1316, 1261 (w, alkyl C-C stretch), 1086 (w, CO stretch), 991, 996, 908 (m) cm<sup>-1</sup>.

**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):** δ 5.83 (ddt, *J* = 17.0, 10.3, and 3.5, 2H), 5.04 (dd, *J* = 17.2, 1.6 1H), 4.95 (dd, *J* = 8.9, 1.1,1H), 3.60 (1H, sept., *J* 3.6), 2.07 (4H, q, *J* 5.1), 1.52-1.43 (8H, m) ppm.

**<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):** δ 138.9, 114.7, 75.7, 43.8, 33.3, 30.4, 29.3, 27.8, 26.6, 26.5, 26.4, 26.2 ppm.
Preparation of \((E)\)-7-cyclohexylhept-2-ene-1,7-diol

Notebook Reference: RDLA206

An oven dried 100 mL round bottom flask with a stir bar was charged with \(p\)-benzoquinone (88.1 mg, 0.815 mmol) and Grubbs 2nd Generation Catalyst (230.6 mg, 0.2716 mmol) and placed under argon. DCM (25 mL) was added via syringe followed by \((Z)\)-but-2-ene-1,4-diol (6.70 mL, 81.49 mmol) and 1-cyclohexylhex-5-en-1-ol (2.4761 g, 13.58 mmol). The reaction was stirred at room temperature for 2 days. An additional 4 equivalents of \((Z)\)-but-2-ene-1,4-diol was added every 24 h, and the reaction was monitored by TLC for consumption of starting material. The reaction mixture was concentrated \textit{in vacuo}, and purified via flash chromatography (2:1 Hex:EtOAc, \(R_f = 0.41\)) to afford a colorless oil (1.309 g, 7.725 mmol, 57 \%). \(E:Z\) ratio determined to be 6:1 by comparison of \(^1\)H NMR chemical shifts at 4.07 and 4.11 ppm.

\textbf{FTIR} (ATR): 3383 (br), 2924 (w), 1670 (m), 1449 (m), 969 (m) cm\(^{-1}\).

\textbf{\(^1\)H NMR} (500 MHz, CDCl\(_3\)): \(\delta\) 5.74-5.58 (m, 2H), 4.07 (d, \(J = 4.5\) Hz, 2H), 3.36-3.32 (m, 1H), 2.10-2.03 (m, 2H), 1.80-0.95 (m, 17H) ppm.

\textbf{\(^{13}\)C NMR} (125 MHz, CDCl\(_3\)): \(\delta\) 132.5, 129.2, 75.8, 63.2, 43.5, 33.3, 32.1, 29.1, 27.7, 26.4, 26.2, 26.1, 25.3 ppm.
Preparation of 1-cyclohexylpent-4-en-1-ol

Notebook Reference: RDLA203

An oven dried 100 mL 2-neck round bottom flask with stir bar was charged with magnesium turnings (546.9 mg, 22.50 mmol) and fitted with a reflux condenser and placed under argon. THF (15 mL) was added via syringe followed by dibromoethane (4 drops) and allowed to stir for 10 mins in order to activate the magnesium. 4-bromo-1-butene (1.53 mL, 15.0 mmol) was diluted in 10 mL and added drop wise over 15 minutes. The reaction was heated at reflux for 1 hour. The reaction was cooled to room temperature and cyclohexanecarboxaldehyde (1.91 mL, 15.8 mmol) was added via syringe and the reaction was heated at reflux for 2 hours. The reaction was cooled to room temperature, poured over 10% HCl (50 mL), extracted with ether (3 × 30 mL), dried over magnesium sulfate, and concentrated in vacuo. The resultant crude oil was purified via flash chromatography (6:1 Hex:EtOAc, Rf = 0.18) to afford a clear, colorless oil (2.107 g, 12.52 mmol, 83%).

FTIR (ATR): 3350 (br, OH stretch), 3076 (w, vinyl CH stretch), 2922, 2852 (m, alkyl CH stretch), 1640, 1449 (m, vinyl C-C stretch), 1316, 1261 (w, alkyl C-C stretch), 1086 (w, CO stretch), 991 (m), 996 (m), 908 (m) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 5.83 (ddt, J = 17.0, 10.3, 3.5, 1H), 5.04 (dd, J = 17.2, 1.6, 1H), 4.95 (dd, J = 8.9, 1.1, 1H), 3.60 (septet, J = 3.6, 1H), 2.07 (q, J = 5.1, 4H), 1.52-1.43 (m, 8H) ppm.

¹³C NMR (125 MHz, CDCl₃): δ 138.9, 114.7, 75.7, 43.8, 33.3, 30.4, 29.3, 27.8, 26.6, 26.5, 26.4, 26.2 ppm ppm.
Preparation of (E)-6-cyclohexylhex-2-ene-1,6-diol

An oven dried 50 mL round bottom flask with a stir bar was charged with p-benzoquinone (74.4 mg, 0.688 mmol) and Grubbs 2nd Generation Catalyst (194.7 mg, 0.2293 mmol) and placed under argon. DCM (25 mL) was added via syringe followed by (Z)-but-2-ene-1,4-diol (5.66 mL, 68.8 mmol) and 1-cyclohexylpent-4-en-1-ol (1.9298 g, 11.47 mmol). The reaction was stirred at room temperature for 2 days. An additional 4 equivalents of (Z)-but-2-ene-1,4-diol was added every 24 h, and the reaction was monitored by TLC for consumption of starting material. The reaction mixture was concentrated in vacuo, and purified via flash chromatography (1:1 Hex:EtOAc, Rf =0.41 ) to afford a colorless oil (368.6 mg, 1.859 mmol, 16%). E:Z ratio determined to be 6:1 by comparison of $^1$H NMR chemical shifts at 4.07 and 4.11 ppm.

**FTIR (ATR):** 3330(br, OH stretch), 2922 (s, vinyl CH stretch), 2851 (s, alkyl CH stretch), 1448 (m, vinyl C-C stretch), 1087, 1000 (s, CO stretch), 968 (s, vinyl CH oop bend) cm$^{-1}$.

**$^1$H NMR (500 MHz, CDCl$_3$):** $\delta$ 5.65 (m, 2H), 4.07 (d, $J = 4.5$ Hz, 2H, OCH), 3.34 (m, 1H), 2.06 (m, 2H), 1.75-0.94 (m, 13H) ppm.

**$^{13}$C NMR (125 MHz, CDCl$_3$):** $\delta$ 133.0, 129.3, 76.1, 63.7, 43.6, 33.6, 29.3, 27.7, 26.5, 26.4, 26.2, 25.5 ppm.
Preparation of (E)-1-cyclohexyl-6-(2,6-dimethyl-4-nitrophenoxy)hex-4-en-1-ol

An oven dried 50 mL flask with a stir bar was charged with triphenylphosphine (550.8 mg, 2.100 mmol) and 2,6-dimethyl-4-nitrophenol (367.8 mg, 2.200 mmol), and placed under argon. Dry THF (10 mL) was added to the flask via syringe followed by (E)-7-cyclohexylhept-2-ene-1,7-diol (368.6 1.859 mmol). The reaction flask was cooled to -78° C (dry ice/acetone bath). DIAD (0.41 mL, 2.1 mmol) was diluted with dry THF (10 mL) and added dropwise over 15 minutes. The reaction was stirred for 48 h. The reaction mixture was diluted with ether, washed with 10% NaOH solution (3 × 30 mL) and dried over anhydrous magnesium sulfate. The mixture was gravity filtered, concentrated in vacuo. The crude product was purified via column chromatography (2:1 Hex:EtOAc) to give (E)-1-(hex-2-en-1-yloxy)-2,4-dimethylbenzene (102 mg, 0.294 mmol,16%).

**FTIR (ATR):** 3402 (br), 2948 (m), 2934 (m) 2867 (m), 1588, 1508, 1472 (m), 1344, 1211 (s), 1100, 1078 (s) 963, 902 (s) cm\(^{-1}\).

**\(^1\)H NMR (500 MHz, CDCl\(_3\)):** δ 7.95 (s, 2H), 5.71 (ddddd, \(J = 13.4, 7.9, 6.7, 1.3, 1.3, 1H\)), 5.58 (ddddd, \(J = 12.6, 8.4, 5.9, 1.5, 1.5,1H\)), 5.19 (dd, \(J = 4.6, 2.0, 2H\)), 4.14 (ddd, \(J = 11.8, 5.7, 1.0, 1H\)), 3.92 (m, 2H), 2.33 (s, 6H), 2.15-0.96 (m, 12H) ppm.

**\(^13\)C NMR (125 MHz, CDCl\(_3\)):** δ 158.0, 134.5, 126.5, 124.5, 125.7, 103.1, 67.8 67.0, 43.5, 33.6, 32.3, 29.3, 27.6, 26.4, 25.2, 23.6, 15.9 ppm.
Preparation of 2,2-dimethyloct-7-en-3-ol

Notebook Reference: RDLA222

An oven dried 100 mL 2-neck round bottom flask with stir bar was charged with magnesium turnings (1.0338 g, 42.534 mmol) and fitted with a reflux condenser and placed under argon. THF (15 mL) was added via syringe followed by dibromoethane (4 drops) and allowed to stir for 10 mins in order to activate the magnesium. 5-bromo-1-butene (2.73 mL, 23.0 mmol) was diluted in 10 mL and added drop wise over 15 minutes. The reaction was then heated at reflux for 1 hour. The reaction was cooled to room temperature and pivaldehyde (2.00 mL, 18.41 mmol) was added via syringe and the reaction was heated at reflux for 2 hours. The reaction was poured over 10% HCl (50 mL), extracted with ether (3 × 30 mL), dried over magnesium sulfate, and concentrated in vacuo. The resultant crude oil was purified via flash chromatography (6:1 Hex:EtOAc, Rf = 0.46) to afford a clear, colorless oil (1.4026 g, 8.98 mmol, 50%).

**FTIR** (ATR): 3355 (br), 2953 (w), 2869 (m), 1640 (s), 1479, 1364 (s), 1076, 908 (s) cm\(^{-1}\).

**\(^1\)H NMR** (500 MHz, CDCl\(_3\)): \(\delta \) 5.92 – 5.78 (m, 1H), 5.06 (dq, \(J = 17.1, 1.7 \text{ Hz}, 1H\)), 4.97 (ddt, \(J = 10.2, 2.3, 1.2 \text{ Hz}, 1H\)), 3.21 (dd, \(J = 10.6, 1.9 \text{ Hz}, 1H\)), 2.38 – 2.27 (m, 1H), 2.11 (ddtt, \(J = 14.5, 8.7, 7.2, 1.4 \text{ Hz}, 1H\)), 1.61 (dddd, \(J = 13.8, 9.0, 7.1, 1.9 \text{ Hz}, 1H\)), 1.36 (dddd, \(J = 13.9, 10.6, 8.7, 5.3 \text{ Hz}, 1H\)), 1.03 – 0.77 (m, 10H), 0.75 (s, 1H) ppm.

**\(^{13}\)C NMR** (125 MHz, CDCl\(_3\)): \(\delta \) 138.9, 114.5, 79.8, 345.0, 33.8, 30.9, 26.4, 25.7 ppm.
Preparation of (E)-8,8-dimethylnon-2-ene-1,7-diol

\[
\begin{align*}
\text{HO} & \quad \text{Grubbs II Gen. Cat. (2 mol %)} & \quad \text{OH} \\
\text{4-20c} & \quad \text{p-benzoquinone (6 mol %)} & \quad \text{CH}_2\text{Cl}_2, \text{rt} & \quad \text{4-21c}
\end{align*}
\]

Notebook Reference: RDLA230

An oven dried 100 mL round bottom flask with a stir bar was charged with p-benzoquinone (53.9 mg, 0.500 mmol) and Grubbs 2\textsuperscript{nd} Generation Catalyst (141.3 mg, 0.1665 mmol) and placed under argon. DCM (25 mL) was added via syringe followed by (Z)-but-2-ene-1,4-diol (2.74 mL, 33.30 mmol) and 2,2-dimethyloct-7-en-3-ol (1.301 g, 8.324 mmol). The reaction was stirred at room temperature for 2 days. An additional 4 equivalents of (Z)-but-2-ene-1,4-diol was added every 24 h, and the reaction was monitored by TLC for consumption of starting material. The reaction mixture was concentrated \textit{in vacuo}, and purified via flash chromatography (3:1 Hex:EtOAc, \(R_f = 0.29\)) to afford a colorless oil (1.131 g, 6.071 mmol, 73\%). \(E:Z\) ratio determined to be 6:1 by comparison of \(^1\)H NMR chemical shifts at 4.11 and 4.14 ppm.

\textbf{FTIR (ATR)}: 3340 (br), 2948, 2867 (m), 1460, 1393, 1363, 1316 (w), 1080, 1001 (s), 969, 908 (s) cm\(^{-1}\).

\textbf{\(^1\)H NMR (500 MHz, CDCl\(_3\))}: \(\delta 5.77 - 5.63\) (m, 1H), 4.11 (d, \(J = 5.3\) Hz, 2H), 3.21 (d, \(J = 10.3\) Hz, 1H), 2.20 - 2.03 (m, 2H), 1.73 - 1.63 (m, 1H), 1.61 - 1.51 (m, 1H), 1.44 (dddd, \(J = 18.6, 12.2, 9.9, 5.7\) Hz, 2H), 1.34 - 1.22 (m, 1H), 0.91 (t, \(J = 2.0\) Hz, 9H).

\textbf{\(^{13}\)C NMR (125 MHz, CDCl\(_3\))}: \(\delta 133.3, 129.3, 79.8, 63.9, 34.9, 32.4, 31.2, 26.6, 25.0\) ppm.
Mitsunobu Etherification: Preparation of \((E)-9-(2,6\text{-dimethyl-4-nitrophenoxy})\text{-2,2-dimethylnon-7-en-3-ol}\)

\[ \begin{align*}
\text{4-21c} & \quad \text{OH} & \quad \text{3-25} & \quad \text{NO}_2 \\
\text{4-22c} & \quad \text{OH} & \quad \text{3-25} & \quad \text{NO}_2 \\
\end{align*} \]

Notebook Reference: RDLA244

An oven dried 50 mL flask with a stir bar was charged with triphenylphosphine (550.6 mg, 2.100 mmol) and 2,6-dimethyl-4-nitrophenol (367.8 mg, 2.200 mmol), and placed under argon. Dry THF (10 mL) was added to the flask via syringe followed by \((E)-8,8\text{-dimethylnon-2-ene-1,7-diol}\) (372.6 mg, 2.0 mmol). The reaction flask was cooled to -78° C (dry ice/acetone bath). DIAD (0.41 mL, 2.1 mmol) was diluted with dry THF (10 mL) and added dropwise over 15 minutes. The reaction was stirred for 48 h. The reaction mixture was diluted with ether, washed with 10% NaOH solution (3 x 30 mL) and dried over anhydrous magnesium sulfate. The mixture was gravity filtered, concentrated in vacuo. The crude product was purified via column chromatography (1 ½ in width, 18 in long column, 2:1 Hex:EtOAc) to give \((E)-9-(2,6\text{-dimethyl-4-nitrophenoxy})\text{-2,2-dimethylnon-7-en-3-ol}\) as a yellow oil (337.4 g, 1.006 mmol, 50 %).

**FTIR** (ATR): 3413 (br), 3119 (w), 2949 (m), 2867 (m), 1588, 1507, 1473 (m), 1345, 1308 (s), 1277, 1211, 1100, 1078 (s), 964, 903,767, 746 (m) cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): \( \delta \) 7.92 – 7.87 (m, 1H), 5.87 – 5.68 (m, 1H), 4.35 – 4.30 (m, 1H), 3.22 – 3.12 (m, 1H), 2.34 (t, \( J = 0.8 \text{ Hz} \), 3H), 2.22 – 2.05 (m, 1H), 1.76 – 1.64 (m, 0H), 1.58 – 1.35 (m, 1H), 1.32 – 1.19 (m, 1H), 0.89 (s, 4H) ppm.

**¹³C NMR** (125 MHz, CDCl₃): \( \delta \) 161.5, 143.4, 136.2, 132.6, 125.0, 124.2, 124.1, 79.7, 73.5, 35.0, 32.3, 30.9, 26.4, 25.7, 25.7, 16.8 ppm.
Preparation of 2,2-dimethylhept-6-en-3-ol

\[
\text{Mg} \rightarrow \text{BrMg} \rightarrow \text{THF, rt - reflux, 2h} \rightarrow \text{OH}
\]

Notebook Reference: RDLA223

An oven dried 100 mL 2-neck round bottom flask with stir bar was charged with magnesium turnings (1.0338 g, 42.534 mmol) and fitted with a reflux condenser and placed under argon. THF (15 mL) was added via syringe followed by dibromoethane (4 drops) and allowed to stir for 10 mins in order to activate the magnesium. 4-bromo-1-butene (2.58 mL, 23.0 mmol) was diluted in 10 mL and added drop wise over 15 minutes. The reaction was then heated at reflux for 1 hour. The reaction was cooled to room temperature and pivaldehyde (2.00 mL, 18.4 mmol) was added via syringe and the reaction was heated at reflux for 2 hours. The reaction was cooled to room temperature, poured over 10% HCl (50 mL), extracted with ether (3 x 30 mL), dried over magnesium sulfate, and concentrated in vacuo. The resultant crude oil was purified via flash chromatography (6:1 Hex:EtOAc, Rf = 0.40) to afford a clear, colorless oil (1.2454 g, 8.76 mmol, 48%).

**FTIR** (ATR): 3382 (br), 3078 (w), 2952, 2869 (m), 1449 (s), 1393, 1364 (s), 1075, 1005 (s), 909 (s) cm\(^{-1}\).

**\(^{1}\)H NMR** (500 MHz, CDCl\(_3\)): \(\delta\) 5.83 (ddt, \(J = 17.0, 10.2, 6.7\) Hz, \(1H\)), 5.02 (dq, \(J = 17.1, 1.7\) Hz, \(1H\)), 4.96 (ddt, \(J = 10.2, 2.3, 1.3\) Hz, \(1H\)), 3.19 (dq, \(J = 10.6, 1.9\) Hz, \(1H\)), 2.18 – 2.01 (m, \(2H\)), 1.75 – 1.63 (m, \(1H\)), 1.54 (dddd, \(J = 13.5, 10.1, 6.0, 1.9\) Hz, \(2H\)), 1.50 – 1.34 (m, \(1H\)), 1.33 – 1.19 (m, \(1H\)), 0.90 (d, \(J = 0.7\) Hz, \(9H\)) ppm.

**\(^{13}\)C NMR** (125 MHz, CDCl\(_3\)): \(\delta\) 138.9, 114.7, 79.3, 34.9, 31.3, 30.7, 25.7 ppm.
Preparation of 2,2-dimethylhept-6-en-3-ol

An oven dried 50 mL tube with stir bar was charged with magnesium turnings (729.2 mg, 30.00 mmol) and placed under argon. THF (15 mL) was added via syringe and 5-bromo-1-butene (1.74 mL, 15.0 mmol) was diluted in 10 mL and added drop wise over 15 minutes. The reaction was then heated at reflux for 1 hour. The reaction was cooled to 0 °C and benzenaldehyde (1.02 mL, 10.00 mmol) was added dropwise via syringe and allowed to warm to room temperature over 2 hours. The reaction was quenched with 10% HCl (50 mL), extracted with ether (3 × 30 mL), dried over magnesium sulfate, and concentrated in vacuo. The resultant crude oil was purified via flash chromatography (9:1 Hex:EtOAc, R\textsubscript{f} = 0.3 in 9:1 Hex:EtOAc) to afford a clear, colorless oil (1.5251 g, 8.65 mmol, 87%).

**FTIR**: 3345 (br), 3063, 3028 (w), 2934, 2860 (w), 1449 (s), 1393, 1364 (s), 1075, 1005 (s), 909 (s cm\(^{-1}\)).

**\(^1\)H NMR** (CDCl\(_3\), 500 MHz): \(\delta\) 7.37 (s, 2H), 7.44 – 7.26 (m, 2H), 5.81 (ddt, \(J = 16.9, 10.2, 6.7\) Hz, 1H), 5.06 – 4.94 (m, 2H), 4.71 (ddd, \(J = 8.1, 5.7, 2.6\) Hz, 1H), 2.15 – 2.05 (m, 2H), 1.92 – 1.66 (m, 3H), 1.62 – 1.50 (m, 1H), 1.42 (ddtd, \(J = 13.1, 10.5, 7.4, 5.6\) Hz, 1H) ppm.

**\(^{13}\)C NMR** (CDCl\(_3\), 500 MHz): \(\delta\) 144.8, 138.6, 128.5, 125.9, 114.7, 74.6, 38.5, 33.6, 25.1 ppm.
Preparation of (E)-7-hydroxy-7-phenylhept-2-en-1-yl acetate

Notebook Reference: RDLB174

Grubbs 2\textsuperscript{nd} generation catalyst (90.3 mg, 0.106 mmol) and \( p \)-benzoquinone (57.5 mg, 0.532 mmol) were charged in a flame dried 25 mL flask with stir bar and placed under argon. Anhydrous DCM (10 mL) was added via syringe, followed by a mixture of 4-20\textsuperscript{a} and Z-1,4-diacetoxy-2-butene. The syringe was rinsed twice with DCM into the flask. A reflux condenser was fitted to the flask and the reaction was heated at reflux overnight. The reaction was cooled to room temperature, filtered through a plug of silica, rinsed with EtOAc, and concentrated \textit{in vacuo}. The crude oil was purified by flash chromatography (6:3:1 Hex:EtOAc, \( R_f = 0.16 \) in 3:1 Hex:EtOAc). \( E:Z \) ratio determined to be 5:1 by comparison of \( ^1 \text{H} \) NMR chemical shifts at 4.49 and 4.59 ppm.

\textbf{FTIR:} 3345 (br), 3063, 3028 (w), 2934, 2860 (w), 1736 (s), 1453, 1381, 1386 (w), 1228, 1023 (s), 968, 700 (m) cm\textsuperscript{-1}.

\textbf{\( ^1 \text{H} \) NMR (CDCl\textsubscript{3}, 300 MHz):} \( \delta \) 7.33 (s, 2H), 7.42 – 7.19 (m, 2H), 5.82 – 5.63 (m, 1H), 5.67 – 5.46 (m, 1H), 4.67 (s, 1H), 4.73 – 4.55 (m, 1H), 4.49 (dt, \( J = 6.4, 1.0 \) Hz, 2H), 2.21 – 2.00 (m, 3H), 2.04 (s, 2H), 1.85 (s, 1H), 2.00 – 1.22 (m, 4H) ppm.

\textbf{\( ^{13} \text{C} \) NMR (CDCl\textsubscript{3}, 75 MHz):} \( \delta \) 170.85, 144.69, 135.95, 134.92, 128.46, 127.57, 125.84, 124.18, 123.66, 74.45, 74.38, 65.17, 60.27, 38.44, 32.05, 27.26, 25.53, 25.01, 21.01, 5.79 ppm.
Preparation of undeca-1,10-dien-6-ol

An oven dried 100 mL 2-neck round bottom flask with stir bar was charged with magnesium turnings (1.5191 g, 62.50 mmol) and fitted with a reflux condenser and placed under argon. THF (20 mL) was added via syringe followed by dibromoethane (4 drops) and allowed to stir for 10 mins in order to activate the magnesium. 5-bromo-1-pentene (6.51 mL, 55.0 mmol) was diluted in 10 mL and added drop wise over 15 minutes. The reaction was then heated at reflux for 1 hour. The reaction was cooled to room temperature and ethyl formate (2.02 mL, 25 mmol) was added via syringe and the reaction was heated at reflux for 2 hours. The reaction was cooled to room temperature, poured over 10% HCl (100 mL), extracted with ether (3 × 50 mL), dried over magnesium sulfate, and concentrated in vacuo. The resultant crude oil was purified via flash chromatography (6:1 Hex:EtOAc, Rf = 0.34) to afford a clear, colorless oil (3.5806 g, 21.278 mmol, 85%).

FTIR (ATR): 3330 (br), 3076, 2977 (w), 2930, 2859 (m), 1641, 1458, 1440, 1415 (m), 1324 (w), 933, 907, 826 (s) cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ 5.84 (ddt, J = 17.0, 10.2, 6.7 Hz, 2H), 5.08 – 4.95 (m, 4H), 3.64 (q, J = 6.5, 5.1 Hz, 1H), 2.18 – 2.03 (m, 4H), 1.71 – 1.38 (m, 9H), 1.35 – 1.25 (m, 1H) ppm.

¹³C NMR (125 MHz, CDCl₃): δ 138.7, 114.6, 71.6, 36.9, 33.7, 24.9 ppm.
Preparation of \((2E,11E)-7\text{-hydroxytrideca-2,11-diene-1,13-diyl diacetate}\)

Notebook Reference: RDLA198

An oven dried 100 mL round bottom flask with a stir bar was charged with \(p\)-benzoquinone (104.3 mg, 0.9652 mmol) and Grubbs 2\textsuperscript{nd} Generation Catalyst (273.1 mg, 0.3217 mmol) and placed under argon. DCM (30 mL) was added via syringe followed by \((Z)\)-but-2-ene-1,4-diacetoxy (20.52 mL, 128.7 mmol) and undeca-1,10-dien-6-ol (2.707 g, 16.09 mmol). The reaction was stirred at room temperature for 3 days. The reaction mixture was concentrated \textit{in vacuo}, and purified via flash chromatography (2:1 Hex:EtOAc, \(R_f = 0.21\)) to afford a colorless oil (2.328 g, 13.834 mmol, 86\%). \(E:Z\) ratio determined to be 6:1 by comparison of \(^1\text{H}\) NMR chemical shifts at 4.49 and 4.59 ppm.

\textbf{FTIR} (ATR): 3459 (br), 2933 (w), 1736 (s), 1442, 1363 (w), 1226, 1023 (s), 965 (m) cm\(^{-1}\).

\textbf{\(^1\text{H NMR}\)} (500 MHz, CDCl\(_3\)): \(\delta\) 5.78 (dtt, \(J = 15.7, 6.7, 1.2\) Hz, 2H), 5.69 – 5.52 (m, 2H), 4.56 – 4.49 (m, 4H), 3.61 (s, 1H), 2.23 – 2.03 (m, 10H), 1.63 – 1.47 (m, 4H), 1.50 – 1.37 (m, 4H) ppm.

\textbf{\(^{13}\text{C NMR}\)} (125 MHz, CDCl\(_3\)): \(\delta\) 170.8, 136.1, 124.1, 71.4, 65.1, 36.9, 32.2, 24.9 ppm.
Preparation of \((2E,11E)\)-trideca-2,11-diene-1,7,13-triol

![Chemical Structure](image)

Notebook Reference: RDLA255

Potassium hydroxide (392.8, 7.000 mmol) was charged in a 25 mL round bottom flask with a stir bar and absolute ethanol was added. Deionized water (2 mL) was added until the potassium hydroxide became soluble. \((2E,11E)-7\)-hydroxytrideca-2,11-diene-1,13-diyl diacetate (624.8 mg, 2.000 mmol) was diluted in 1 mL ethanol and added to the solution. The solution was allowed to stir for 1h and monitored for consumption of starting material by TLC. After 1h, when all the starting material had been consumed the reaction mixture was poured over a saturated sodium chloride solution (50 mL), extracted with ethyl acetate (3 × 30 mL), dried over MgSO\(_4\), and concentrated \textit{in vacuo}. The crude product was purified via column chromatography (0-5% EtOH/EtOAc) to afford a white solid (450.4 mg, 1.972 mmol, 99%)

\textbf{FTIR} (ATR): 3301 (br), 2927 (m), 2856 (m), 1437 (w), 1175, 1084 (m`), 966, 910 cm\(^{-1}\).

\textbf{\textsuperscript{1}HNMR} (500 MHz, CDCl\(_3\)): \(\delta\) 5.74 – 5.63 (m, 4H), 4.09 (dd, \(J = 5.1, 2.7\) Hz, 4H), 3.60 (s, 1H), 2.20 – 2.01 (m, 4H), 1.79-1.12 (m, 8H).

\textbf{\textsuperscript{13}CNMR} (125 MHz, CDCl\(_3\)): \(\delta\) 132.9, 129.4, 71.6, 63.7, 36.8, 32.1, 25.1 ppm.
Preparation of \((2E,11E)-1,13\text{-bis}(2,6\text{-dimethyl}-4\text{-nitrophenoxy})\text{trideca}-2,11\text{-dien}-7\text{-ol}\)

Notebook Reference: RDLA258

An oven dried 50 mL flask with a stir bar was charged with triphenylphosphine (725.1 mg, 2.765 mmol) and 2,6-dimethyl-4-nitrophenol (483.3 mg, 2.891 mmol), and placed under argon. Dry THF (10 mL) was added to the flask via syringe followed by 4-29 (287 mg, 1.25 mmol). The reaction flask was cooled to \(-78^\circ\text{C}\) (dry ice/acetone bath). DIAD (0.57 mL, 2.9 mmol) was diluted with dry THF (10 mL) and added dropwise over 15 minutes. The reaction was stirred for 48 h. The reaction mixture was diluted with ether, washed with 10% NaOH solution (3 × 30 mL) and dried over anhydrous magnesium sulfate. The mixture was gravity filtered, and concentrated \textit{in vacuo}. The crude product was purified via column chromatography (2:1 Hex:EtOAc) to give a pale, yellow solid (402.3 mg, 1.159 mmol, 67%).

\textbf{FTIR (ATR):}

\textbf{\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\))}: \(\delta 7.91 \ (\text{dh}, J = 1.3, 0.6 \text{ Hz}, 2\text{H}), 5.90 – 5.66 \ (\text{m}, 2\text{H}), 5.08 – 4.88 \ (\text{m}, 6\text{H}), 4.32 \ (\text{d}, J = 5.3 \text{ Hz}, 2\text{H}), 3.60 \ (\text{s}, 1\text{H}), 2.43 – 2.26 \ (\text{m}, 7\text{H}), 2.21 – 2.02 \ (\text{m}, 3\text{H}), 1.53 – 1.10 \ (\text{m}, 4\text{H}), 1.26 \ (\text{s}, 2\text{H}) \text{ ppm}\)

\textbf{\(^{13}\text{C NMR}\) (125 MHz, CDCl\(_3\))}: \(\delta\)
Gold-Catalyzed Cyclization of \((E)-6\text{-cyclohexylhex-2-ene-1,6-diol}\)

\[
\begin{align*}
\text{OH} & \quad \text{AuCl}_3 / 3 \text{AgOTf} \\
\text{CH}_2=CH-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH} & \quad \text{CDCl}_3, \text{rt} \\
\text{4-21f} & \quad \text{4-31} \\
\text{dr 4:1}
\end{align*}
\]

Notebook Reference: RDLA241

A flame dried 10 mL culture tube with stir bar was charged with AgOTf (31.6 mg, 0.150 mmol). AuCl\(_3\) (12.4 mg, 0.0500 mmol) was added by scoring the tip of a 50 \(\mu\)L micropipette loading the solid in the tip and breaking the tip into the reaction tube. Basic alumina (10 mg) was added to reaction tube to adsorb water and any HCL in solution. Deuterochloroform (2 mL) was added via syringe. The mixture was allowed to stir for 1 h, after which \((E)-1\text{-cyclohexyl-6-(2,6-dimethyl-4-nitrophenoxy)hex-4-en-1-ol}\) (142 mg, 0.500 mmol) was diluted in deuterochloroform (1 mL) and added via syringe. The reaction progress was monitored by NMR, after 24 h presence of products and absence of starting material indicated the reaction had ended with nearly complete conversion. The reaction mixture was filtered through a short plug of silica gel, and concentrated in \textit{vacuo}. The crude product was purified via column chromatography (30:1 Hex:EtOAc, \(R_f = 0.29\)). Fractions containing the major product were collected and concentrated in \textit{vacuo} to afford a clear, colorless oil (36.2 mg, 0.047 mmol, 40%). Fractions containing the minor product were collected and concentrated in \textit{vacuo} to yield a clear, colorless oil (10.1 mg, 11 %).
Transient 1D-NOESY was performed with selective excitations of the protons at 3.78 ppm and 3.06 ppm. Diaxial interactions were observed indicating the constituent of the major product is the *cis*-isomer.

Based on the yields of the diastereomers the diastereotopic ratio was determined to be 4:1.

**FTIR** (ATR): 2922 (s), 2851 (s), 1646, 1450, 1409, 1360 (w), 1203, 1075, 1013 (s), 987, 917, 888 (s) cm\(^{-1}\).

**\(^1\)HNMR** (500 MHz, CDCl\(_3\), Major Product): \(\delta\) 5.87 (ddd, \(J = 17.4, 10.7, 5.2, 1\)H), 5.23 (ddd, \(J = 17.3, 1.7, 1.7, 1\)H), 5.06 (ddd, \(J = 10.7, 1.7, 1.7, 1\)H), 3.78 (dddd, \(J = 11.2, 5.2, 1.6, 1.6, 1.6, 1\)H), 3.06 (ddd, \(J = 11.2, 6.8, 2.1, 1\)H), 1.96 (m, 1H), 1.87 (dddd, \(J = 13.4, 6.7, 3.9, 2.6, 1\)H), 1.75-0.81 (m, 13H) ppm.

**\(^{13}\)CNMR** (125MHz, CDCl\(_3\), Major Product): \(\delta\) 139.9, 113.9, 82.1, 43.2, 31.7, 29.3, 28.7, 27.1 ppm.

**\(^1\)HNMR** (500 MHz, CDCl\(_3\), Minor Product): \(\delta\) 5.88 (ddddd, \(J = 17.5, 10.9, 4.3, 0.8, 1\)H), 5.18 (m, 1H), 4.33 (ddddd, \(J = 6.2, 4.1, 4.9, 1.9, 1\)H), 3.35 (ddd, \(J = 11.0, 8.3, 3.1, 1\)H), 1.92 (m, 1H), 1.73 (m, 3H), 1.66-1.53 (m, 7H), 1.44 (ddddd, \(J = 18.4, 11.5, 3.9, 1\)H), 1.36 (dddd, \(J = 13.4, 9.9, 9.9, 4.2, 1\)H), 1.29-1.07 (m, 6H), 0.98-0.82 (m, 4H) ppm.

**\(^{13}\)CNMR** (125MHz, CDCl\(_3\), Minor Product): \(\delta\) 139.1, 115.6, 75.4, 72.3, 41.0, 29.1, 29.7, 28.9, 27.6, 26.7, 26.2, 26.1, 18.9 ppm.
Gold-Catalyzed Cyclization of (E)-8,8-dimethylnon-2-ene-1,7-diol

Notebook Reference: RDLA251

A flame dried 10 mL culture tube with stir bar was charged with AgOTf (38.5 mg, 0.150 mmol). AuCl₃ (15.2, 0.0500 mmol) was added by scoring the tip of a 50 μL micropipette loading the solid in the tip and breaking the tip into the reaction tube. Basic alumina (10 mg) was added to reaction tube to adsorb water and any HCL in solution. Deuterochloroform (2 mL) was added via syringe. The mixture was allowed to stir for 1 h, after which (E)-8,8-dimethylnon-2-ene-1,7-diol (0.500 mmol) was diluted in deuterochloroform (1 mL) and added via syringe. The reaction progress was monitored by NMR, after 24 h presence of products and absence of starting material indicated the reaction had ended with nearly complete conversion. The reaction mixture was filtered through a short plug of silica gel, and concentrated in vacuo. The crude product was purified via column chromatography (19:1 Hex:EtOAc, Rᵢ = 0.41). Fractions containing the pure product were collected and concentrated in vacuo to afford a clear, colorless oil (78.6 mg, 0.4671 mmol, 93 %).

Transient 1D-NOESY was performed with selective excitations of the protons at 3.78 ppm and 2.95 ppm. Diaxial interactions were observed indicating the constituent of the major product is the cis-isomer.
FTIR (ATR): 2956, 2920 (s), 2870 (m), 1521, 1458, 1341 (m), 1263, 1208, 1150, 1097 (s), 1026, 969 (s) cm$^{-1}$.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 5.86 (ddd, $J = 17.3$, 10.7, 4.6 Hz, 1H), 5.24 (dt, $J = 17.3$, 1.9 Hz, 1H), 5.03 (ddd, $J = 10.7$, 2.0, 1.6 Hz, 1H), 3.78 (dtd, $J = 11.4$, 4.0, 1.9 Hz, 1H), 2.95 (dd, $J = 11.3$, 1.9 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.65 – 1.42 (m, 4H), 1.29 – 1.13 (m, 2H), 0.90 (s, 9H) ppm.

$^{13}$C NMR (125MHz, CDCl$_3$): $\delta$ 140.2, 113.1, 85.3, 77.9, 34.2, 31.7, 26.1, 25.1, 24.0 ppm.
Gold-Catalyzed Cyclization of (E)-8,8-dimethylnon-2-ene-1,7-diol

Notebook Reference: RDLB172

A flame dried 10 mL culture tube with stir bar was charged with AgOTf (1.9 mg, 0.0075 mmol). AuCl₃ (0.8 mg, 0.00025 mmol) was added by scoring the tip of a 50 μL micropipette loading the solid in the tip and breaking the tip into the reaction tube. MS 4 Å (6 mg). DCM (1 mL) was added via syringe. The mixture was allowed to mix for 1 h, after which 4-21a (51.6 mg, 0.250 mmol) added via syringe. Reaction progress monitored by GC. The reaction mixture was filtered through a short plug of silica gel, and concentrated \textit{in vacuo}. The crude product was purified via column chromatography (19:1 Hex:EtOAc, Rₚ = 0.41). Fractions containing the pure product were collected and concentrated \textit{in vacuo} to afford a clear, colorless oil. Diastereomeric ratio determined to be 4:1 by GC using biphenyl as an internal reference.

\textbf{FTIR (ATR):} 3024, 2956, 2920 (w) cm⁻¹.

\textbf{¹H NMR (CDCl₃, 300 MHz):} δ 7.37 (tdd, J = 7.3, 6.6, 2.8, 1.4 Hz, 2H), 7.37 – 7.18 (m, 2H), 6.07 – 5.86 (m, 1H), 5.38 – 5.20 (m, 1H), 5.11 (dt, J = 10.6, 1.5 Hz, 1H), 4.44 (dd, J = 11.2, 2.2 Hz, 1H), 4.10 – 3.97 (m, 1H), 2.21 – 2.14 (m, 1H), 1.97 (dtd, J = 12.9, 4.7, 4.1, 2.3 Hz, 1H), 1.91 – 1.78 (m, 1H), 1.84 – 1.63 (m, 2H), 1.62 – 1.36 (m, 2H), 1.27 (d, J = 3.6 Hz, 1H), 1.02 – 0.80 (m, 1H) ppm.

\textbf{¹³C NMR (CDCl₃, 300 MHz):} δ 143.3, 139.4, 128.2, 127.2, 125.8, 114.4, 79.7, 78.6, 33.6, 31.3, 24.5, 22.6 ppm.
Gold-Catalyzed Cyclization of \((E)-1\text{-cyclohexyl-7-(2,6-dimethyl-4-nitrophenoxy)hept-5-en-1-ol}\)

A flame dried 10 mL culture tube with stir bar was charged with AgOTf (31.6 mg, 0.123 mmol). AuCl$_3$ (12.4 mg, 0.041 mmol) was added by scoring the tip of a 50 μL micropipette loading the solid in the tip and breaking the tip into the reaction tube. Basic alumina (10 mg) was added to reaction tube to adsorb water and any HCL in solution. Deuterochloroform (2 mL) was added via syringe. The mixture was allowed to stir for 1 h, after which \((E)-1\text{-cyclohexyl-6-(2,6-dimethyl-4-nitrophenoxy)hex-4-en-1-ol}\) (142 mg, 0.410 mmol) was diluted in deuterochloroform (1 mL) and added via syringe. The reaction progress was monitored by NMR, and after 24 h presence of products and absence of starting material indicated the reaction had proceeded with nearly complete conversion. The reaction mixture was filtered through a short plug of silica gel, and concentrated \textit{in vacuo}. The crude product was purified via column chromatography (19:1 Hex:EtOAc, R$_f$ = 0.39). Fractions containing the pure product were collected and concentrated \textit{in vacuo} to afford a clear, colorless oil (9.1 mg, 0.050 mmol, 12%). Fractions containing the major product and inseparable minor product were collected and concentrated \textit{in vacuo} to yield a clear, colorless oil mixture of two diastereomers (60.2 mg, 0.334 mmol, 81%, dr 6:1). Fraction 1 was determined to
be the cis diastereomer by dipolar interactions present in 1D-NOESY with selective excitations at 3.78 ppm and 3.06 ppm. GC-MS analysis in combination with isolated yields determined the total diastereomeric ratio to be 7:1. (Calculated yield of products from collection of data is 69.3 g, 0.357 mmol, 93 %)

**FTIR** (ATR): 2922 (s), 2851 (s), 1646, 1450, 1409, 1360 (w), 1203, 1075, 1013 (s), 987, 917, 888 (s) cm$^{-1}$.

**$^1$H NMR** (500 MHz, CDCl$_3$, Major Product): $\delta$ 5.87 (ddd, $J = 17.3, 10.6, 5.1$ Hz, 0H), 5.23 (dt, $J = 17.3, 1.7$ Hz, 0H), 5.06 (dt, $J = 10.6, 1.6$ Hz, 0H), 3.78 (ddt, $J = 13.1, 5.3, 1.8$ Hz, 1H), 3.06 (ddd, $J = 11.2, 6.7, 2.0$ Hz, 1H), 1.96 (dtq, $J = 11.9, 3.6, 1.8$ Hz, 1H), 1.95 – 1.82 (m, 1H), 1.76 – 1.68 (m, 1H), 1.72 – 1.61 (m, 1H), 1.62 (ddd, $J = 5.0, 3.8, 2.2$ Hz, 1H), 1.61 – 1.44 (m, 1H), 1.47 – 1.33 (m, 1H), 1.34 – 1.15 (m, 3H), 1.19 – 1.09 (m, 1H), 1.05 – 0.91 (m, 1H), 0.94 – 0.79 (m, 1H) ppm.

**$^{13}$C NMR** (125MHz, CDCl$_3$, Major Product): $\delta$ 139.9, 113.9, 82.1, 43.2, 31.7, 29.3, 28.7, 27 ppm.
Gold-Catalyzed Cyclization of \((E)-9-(2,6\text{-dimethyl-4-nitrophenox})-2,2\text{-dimethylnon}7\text{-en-3-ol}\)

![Chemical structure](image)

Notebook Reference: RDLA250

A flame dried 10 mL culture tube with stir bar was charged with AgOTf (0.150 mmol). AuCl₃ (0.0500 mmol) was added by scoring the tip of a 50 μL micropipette loading the solid in the tip and breaking the tip into the reaction tube. Basic alumina (0.150 mmol) was added to reaction tube to adsorb water and any HCL in solution. Deuterochloroform (2 mL) was added via syringe. The mixture was allowed to stir for 1 h, after which \((E)-9-(2,6\text{-dimethyl-4-nitrophenox})-2,2\text{-dimethylnon}7\text{-en-3-ol}\) (0.500 mmol) was diluted in deuterochloroform (1 mL) and added via syringe. The reaction progress was monitored by NMR, after 24 h presence of diastereotopic products and absence of starting material indicated the reaction had ended with nearly complete conversion. The reaction mixture was filtered through a short plug of silica gel, and concentrated \textit{in vacuo}. The crude product was purified via column chromatography (19:1 Hex:EtOAc, \(R_f = 0.40\)). Fractions containing the pure product were collected and concentrated \textit{in vacuo} to afford a clear, colorless oil (19.3 mg, 0.1147 mmol, 23%). Fractions containing the major product and inseparable minor product were collected and concentrated \textit{in vacuo} to yield a clear, colorless oil mixture of two compounds (53.7 mg). Fraction 1 was determined to be the \textit{cis} diastereomer by diaxial interactions present in 1D-
NOESY with selective excitations at 3.78 ppm and 2.95 ppm. GC-MS analysis in combination with isolated yields determined the total diastereomeric ratio to be 99:1. (Calculated yield of products from collection of data is 73.0 g, 0.434 mmol, 87 %).

**FTIR** (ATR): 2956, 2920 (s, C\textsubscript{vinyl}H stretch), 2870 (m, C\textsubscript{alkyl}H stretch), 1521, 1458, 1341 (m, C\textsubscript{alkyl}H bend), 1263, 1208, 11250, 1097 (s, CO stretch), 1026, 969 (s, C\textsubscript{vinyl}H oop bend) cm\textsuperscript{-1}.

\textsuperscript{1}HNMR (500 MHz, CDCl\textsubscript{3}): \delta 5.86 (ddd, J = 17.3, 10.7, 4.6 Hz, 1H), 5.24 (dt, J = 17.3, 1.9 Hz, 1H), 5.03 (ddd, J = 10.7, 2.0, 1.6 Hz, 1H), 3.78 (dt, J = 11.4, 4.0, 1.9 Hz, 1H), 2.95 (dd, J = 11.3, 1.9 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.65 – 1.42 (m, 4H), 1.29 – 1.13 (m, 2H), 0.90 (s, 9H) ppm.

\textsuperscript{13}CNMR (125MHz, CDCl\textsubscript{3}): \delta 140.2, 113.1, 85.3, 77.9, 34.2, 31.7, 26.1, 25.1, 24.0 ppm.
Gold-Catalyzed Cyclization of (2E,11E)-7-hydroxytrideca-2,11-diene-1,13-diyl diacetate

A flame dried 10 mL culture tube with stir bar was charged with AuCl₃ (11.6 mg, 0.250 mmol) and AgOTf (19.3 mg, 0.0750 mmol) and placed under argon. Deuterochloroform (2 mL) was added via syringe. The mixture was allowed to stir for 1 h, after which (2E,11E)-7-hydroxytrideca-2,11-diene-1,13-diyl diacetate (156.1 mg, 0.500 mmol) was diluted in deuterochloroform (1 mL) and added via syringe. The reaction progress was monitored by NMR, and after 24 h presence of products and absence of starting material indicated the reaction had completed with nearly complete conversion. The reaction mixture was filtered through a short plug of silica gel, and concentrated in vacuo. The crude product was purified via column chromatography (12:1 Hex:EtOAc, Rᵢ = 0.70) to afford a clear, colorless oil (0.0966 g, 0.406 mmol, 81%). The diastereomeric ratio was determined by NMR using the ratio of 2 and 6 proton chemical shifts of the major (3.32 and 3.80 ppm) and minor diastereomers (3.67 and 4.33 ppm) to determine a diastereomeric ratio of 7:1. The confirmation of these diastereomers was determined by 1D-NOESY with selective excitation of the chemical shifts 3.82 and 3.80 ppm.

FTIR (ATR): 2934 (m), 2859 (m), 1739 (s), 1440 (w), 1363 (w), 1127 (s), 1076 (s), 1023 (s), 966, 917 cm⁻¹.
$^1$HNMR (500 MHz, CDCl$_3$): δ 5.93 – 5.81 (m, 1H), 5.77 (dt, $J = 15.7$, 6.7, 1.2 Hz, 1H), 5.56 (dtt, $J = 15.4$, 6.5, 1.5 Hz, 1H), 5.27 – 5.16 (m, 1H), 5.07 (dt, $J = 10.6$, 1.6 Hz, 1H), 4.50 (dp, $J = 6.5$, 1.1 Hz, 2H), 3.85 – 3.76 (m, 1H), 3.32 (dddt, $J = 11.0$, 7.0, 5.0, 1.9 Hz, 1H), 2.16 – 2.02 (m, 2H), 2.06 (s, 3H), 1.85 (dtt, $J = 13.4$, 5.4, 2.0 Hz, 1H), 1.71 – 1.36 (m, 6H), 1.37 – 1.12 (m, 2H) ppm.

$^{13}$CNMR (125MHz, CDCl$_3$): δ 170.9, 139.7, 136.4, 123.9, 114.3, 78.2, 76.8, 65.3, 36.0, 32.3, 31.5, 31.3, 24.9, 23.6 ppm.
Gold-Catalyzed Cyclization of \((2E,11E)\)-trideca-2,11-diene-1,7,13-triol

Notebook Reference: RDLA256

A flame dried 10 mL culture tube with stir bar was charged with AgOTf (38.5 mg, 0.150 mmol). \(\text{AuCl}_3\) (15.2 mg, 0.0500 mmol) was added by scoring the tip of a 50 μL micropipette loading the solid in the tip and breaking the tip into the reaction tube. Basic alumina (10 mg) was added to reaction tube to adsorb water and any HCL in solution. Deuterochloroform (2 mL) was added via syringe. The mixture was allowed to stir for 1 h, after which \((2E,11E)\)-trideca-2,11-diene-1,7,13-triol (0.500 mmol) was diluted in deuterochloroform (1 mL) and added via syringe. The reaction progress was monitored by NMR, and after 24 h presence of products and absence of starting material indicated the reaction had completed with nearly complete conversion. The reaction mixture was filtered through a short plug of silica gel, and concentrated \textit{in vacuo}. The crude product was purified via column chromatography (15:1 Hex:EtOAc, \(R_f=0.32\)) to afford a clear, colorless oil (99 mg, 94%). The diastereomeric ratio was determined by NMR using the ratio of 2 and 6 proton chemical shifts of the major (3.32 and 3.80 ppm) and minor diastereomers (3.67 and 4.33 ppm) to determine a diastereomeric ratio of 4:1. The relative confirmation of these diastereomers was determined by 1D-NOESY with selective excitation of the chemical shifts 3.82 and 3.80 ppm.
**FTIR** (ATR): 2934 (m, C\textsuperscript{vinyl}H stretch), 2859 (m, C\textsuperscript{alkyl}H stretch), 1739 (s, ester carbonyl CO stretch), 1440 (w, C\textsuperscript{vinyl}H oop bend), 1363 (w, C\textsuperscript{vinyl}H stretch), 1127 (s, CO stretch), 1076 (s, CO stretch), 1023 (s, CO stretch), 966, 917 cm\textsuperscript{-1}.

**\textsuperscript{1}HNMR** (500 MHz, CDCl\textsubscript{3}): δ 5.98 – 5.78 (m, 0H), 5.32 – 5.15 (m, 1H), 5.14 – 5.00 (m, 1H), 3.77 (ddq, J = 11.1, 5.4, 2.0 Hz, 1H), 3.06 (ddd, J = 11.2, 6.7, 2.0 Hz, 1H), 2.01 – 1.79 (m, 2H), 1.71 (s, 3H), 1.70 – 1.49 (m, 5H), 1.54 – 1.33 (m, 1H), 1.39 – 1.20 (m, 1H), 1.25 (s, 1H), 1.25 – 1.11 (m, 2H), 0.98 (dtdd, J = 31.2, 15.8, 11.4, 7.1 Hz, 3H) ppm.

**\textsuperscript{13}CNMR** (125MHz, CDCl\textsubscript{3}): δ 170.9, 139.7, 136.4, 123.9, 114.3, 78.2, 76.8, 65.3, 36.0, 32.3, 31.5, 31.3, 24.9, 23.6 ppm.
Gold-Catalyzed Cyclization of (2E,11E)-1,13-bis(2,6-dimethyl-4-nitrophenoxo)trideca-2,11-dien-7-ol

Notebook Reference: RDLA264

A flame dried 10 mL culture tube with stir bar was charged with AgOTf (38.5 mg, 0.1500 mmol) and basic alumina (10 mg). AuCl₃ (15.2 mg, 0.0500 mmol) was massed into the tip of a scored micropipette, broken off into the tube and placed under argon. Deuterochloroform (1 mL) was added via syringe. The mixture was allowed to stir for 1 h, after which (2E,11E)-1,13-bis(2,6-dimethyl-4-nitrophenoxo)trideca-2,11-dien-7-ol (263.3 mg, 0.500 mmol) was diluted in deuterochloroform (1 mL) and added via syringe. The reaction progress was monitored by NMR, and after 24 h presence of products and absence of starting material indicated the reaction had completed with nearly complete conversion. The reaction mixture was filtered through a short plug of silica gel, and concentrated in vacuo. The crude product was purified via column chromatography (15:1 Hex:EtOAc, Rₖ = 0.28) to afford a clear, slight yellow oil (21.6 mg, 12%) as a single diastereomer.

**FTIR** (ATR): 2956, 2920 (s), 2870 (m), 1521, 1458, 1341 (m), 1263, 1208, 11250, 1097 (s), 1026, 969 (s) cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 7.91 (s, 1H), 5.95 – 5.64 (m, 1H), 5.29 – 5.14 (m, 0H), 5.13 – 5.00 (m, 0H), 4.31 (t, J = 4.9 Hz, 1H), 3.86 – 3.74 (m, 1H), 3.39 – 3.25
(m, 1H), 2.41 – 2.27 (m, 3H), 2.10 (q, J = 6.5 Hz, 1H), 1.84 (dq, J = 9.9, 3.9, 3.0 Hz, 1H), 1.57 (s, 3H), 1.51 (s, 1H), 1.76 – 1.12 (m, 2H), 0.85 (s, 3H) ppm.

$^{13}$CNMR (125MHz, CDCl$_3$): $\delta$ 139.6, 136.4, 132.6, 124.8, 124.1, 114.3, 78.2, 77.5, 73.5, 36.0, 34.0, 32.3, 31.4, 31.3, 29.7, 27.7, 24.9, 23.5, 16.8 ppm.
Catalyst Loading and Control Experiments in the Gold-Catalyzed Cyclization to Form 2-phenyl-6-vinyltetrahydro-2H-pyran

Notebook Reference: RDLB172

To a 2 mL vial was charged catalyst at the specified loading, internal reference biphenyl (19.3 mg, 0.125 mmol) and additive MS 4 Å (if specified, 20 % w/w). Anhydrous DCM (1 mL) was added via syringe and the catalyst was allowed to form over 30 minutes at room temperature. Substrate 4-21a (51.6 mg, 0.250 mmol) was massed into a syringe and added to the reaction vessel by mixing solution four times by mixing within the syringe. Every 10 minutes for 40 minutes an aliquot (25 μL) was removed from the reaction solution and passed through a short plug of silica and rinsed with DCM directly into a GC sample vial. Using the same procedure aliquots were taken at 4 hours and 24 hours. Samples were analyzed by GC-MS against known sample retention factors. See Table 4-2 for results.

**FTIR** (ATR): 3024, 2956, 2920 (w) cm\(^{-1}\).

**\(^1\)H NMR** (CDCl\(_3\), 300 MHz): δ 7.37 (tdd, J = 7.3, 6.6, 2.8, 1.4 Hz, 2H), 7.37 – 7.18 (m, 2H), 6.07 – 5.86 (m, 1H), 5.38 – 5.20 (m, 1H), 5.11 (dt, J = 10.6, 1.5 Hz, 1H), 4.44 (dd, J = 11.2, 2.2 Hz, 1H), 4.10 – 3.97 (m, 1H), 2.21 – 2.14 (m, 1H), 1.97 (dttd, J = 12.9, 4.7, 4.1, 2.3 Hz, 1H), 1.91 – 1.78 (m, 1H), 1.84 – 1.63 (m, 2H), 1.62 – 1.36 (m, 2H), 1.27 (d, J = 3.6 Hz, 1H), 1.02 – 0.80 (m, 1H) ppm.

**\(^13\)C NMR** (CDCl\(_3\), 300 MHz): δ143.3, 139.4, 128.2, 127.2, 125.8, 114.4, 79.7, 78.6, 33.6, 31.3, 24.5, 22.6 ppm.
Analysis of Solvent Effects in the Gold-Catalyzed Cyclization to Form 2-phenyl-6-vinyltetrahydro-2H-pyran

Notebook Reference: RDLB178

To a 2 mL vial were charged biphenyl (19.3 mg, 0.125 mmol), AuCl$_3$ (0.4 mg, 0.00125 mmol), and AgOTf (1.0 mg, 0.00375 mmol). Solvent (0.5 mL) was added via syringe and catalyst was allowed to form over 30 minutes at room temperature. Substrate 4-24 (31.0 mg, 0.125 mmol) was massed into a syringe and added to the reaction by mixing the syringe 4 times. Every 10 minutes for 40 minutes an aliquot (20 μL) was removed, filtered through a plug of silica and rinsed with DCM directly into a GC sample vial. A final aliquot was obtained using the same method after 12 hours. Samples were analyzed by GC-MS against known sample retention factors. See Table 4-3 for results.

**FTIR (ATR):** 3024, 2956, 2920 (w) cm$^{-1}$.

**$^1$H NMR (CDCl$_3$, 300 MHz):** δ 7.37 (tdd, $J = 7.3, 6.6, 2.8, 1.4$ Hz, 2H), 7.37 – 7.18 (m, 2H), 6.07 – 5.86 (m, 1H), 5.38 – 5.20 (m, 1H), 5.11 (dt, $J = 10.6, 1.5$ Hz, 1H), 4.44 (dd, $J = 11.2, 2.2$ Hz, 1H), 4.10 – 3.97 (m, 1H), 2.21 – 2.14 (m, 1H), 1.97 (dtd, $J = 12.9, 4.7, 4.1, 2.3$ Hz, 1H), 1.91 – 1.78 (m, 1H), 1.84 – 1.63 (m, 2H), 1.62 – 1.36 (m, 2H), 1.27 (d, $J = 3.6$ Hz, 1H), 1.02 – 0.80 (m, 1H) ppm.

**$^{13}$C NMR (CDCl$_3$, 300 MHz):** δ 143.3, 139.4, 128.2, 127.2, 125.8, 114.4, 79.7, 78.6, 33.6, 31.3, 24.5, 22.6 ppm.
Preparation of 5-hydroxy-N-methoxy-N-methylpentanamide

Notebook Reference: RDLB068

To a suspension of δ-valerolactone (0.65 mL, 6.955 mmol) and N,O-dimethylhydroxyamine hydrochloride (1.695g, 17.38 mmol) in 50 mL THF at -20 °C was added dropwise over a period of 30 minutes a solution of iPrMgCl (25 mL, 38.25 mmol). The mixture was stirred at -20 °C for 2 hours, then quenched with 25 mL of saturated NH₄Cl solution. The layers were separated and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried with anhydrous MgSO₄ and concentrated in vacuo. The crude product was purified by filtration through plug of silica with EtOAc to yield the 5-hydroxy-N-methoxy-N-methylpentanamide as colorless oil (472.9 mg, 42%, Rf = 0.3 in EtOAc) that satisfactorily matched previously reported data.

**FTIR** (ATR): 3405 (br), 2938, 2870 (m), 1637 (s), 1417 (m), 1386, 1324 (m), 1179 (s) cm⁻¹

**¹H NMR** (500 MHz, CDCl₃) δ 3.7 – 3.6 (m, 3H), 3.2 (s, 2H), 2.5 (t, J = 7.2 Hz, 1H), 1.7 (dtd, J = 8.2, 7.4, 6.6 Hz, 1H), 1.7 – 1.6 (m, 2H) ppm.

**¹³C NMR** (125 MHz, CDCl₃) δ 183.3, 62.1, 61.2, 32.1, 30.9, 19.9 ppm.
Preparation of 5-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methylpentanamide

![Chemical Structure](image)

Notebook Reference: RDLB070

To a solution of the alcohol (459.9 mg, 2.853 mmol) in 30 mL of DCM at 0 °C was added imidazole (427.3 mg, 6.277 mmol) followed by TBSCI (473.0 mg, 3.138 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 10 mL H2O. The layers were separated and the aqueous layer was extracted three times with DCM. The combined organic layers were washed with 1N HCl (15mL), saturated NaHCO3 (15 mL) and finally with brine (15 mL), dried with anhydrous MgSO4 and concentrated in vacuo. The crude product was purified by flash chromatography (hexanes to 15% EtOAc in hexanes) to yield 2.07g of (93%) of colorless oil that satisfactory matched all previously reported data.

**FTIR (ATR):** 3035, 2923, 2854 (w), 1586 (w), 1576, 1485, 1466, 1456 (s) cm⁻¹.

**¹H NMR (300 MHz, CDCl₃)** 3.70 – 3.52 (m, 5H), 3.13 (s, 3H), 3.12 (s, 2H), 2.40 (t, J = 7.4, 2H), 1.73 – 1.43 (m, 4H), 0.90 (s, 9H), 0.00 (s, 6H) ppm.

**¹³C NMR (75 MHz, CDCl₃)** 62.8, 61.1, 32.4, 25.9, 21.1, 18.3, -5.4 ppm
Preparation of 1-((tert-butyldimethylsilyl)oxy)dec-9-en-5-one

Notebook Reference: RDLB080

To an oven dried 50 mL reaction tube with stir bar was charged magnesium shavings (160.4 mg, 6.600 mmol), and heated with a heat gun under vacuum (10 Torr) for 10 minutes, then cooled under argon. Anhydrous THF (2 mL) was added via syringe. At room temperature 5-bromopentene (0.39 mL, 3.3 mmol) in THF (2 mL) was added over the period of 10 minutes. The reaction began to reflux indicating Grignard reagent formation, and was stirred for 30 mins after refluxing had subsided. The reaction was added dropwise to a solution of 5-((tert-butyldimethylsilyl)oxy)-N-methoxy-N-methylpentanamide (0.6000 2.200 mmol) in THF (4 mL) at -78 °C and stirred for 10 mins, then gradually warmed to 0 °C and stirred for 1h. Reaction quenched with water 10 mL, extracted with EtOAc (3×30 mL), washed with brine (3×30 mL), dried with MgSO₄, and concentrated in vacuo. Purified by column chromatography (9:1 Hex:EtOAc) to yield a colorless oil (0.2166 g, 35%) . Rᵣ = 0.47 in 9:1 Hex:EtOAc.

¹H NMR (300 MHz, CDCl₃): δ 5.74 (ddt, J = 17.0, 10.2, 6.7 Hz, 1H), 5.06 – 4.85 (m, 2H), 3.59 (t, J = 6.2 Hz, 2H), 2.39 (td, J = 7.3, 4.2 Hz, 4H), 2.11 – 1.95 (m, 2H), 1.74 – 1.40 (m, 6H), 0.87 (s, 9H), 0.02 (s, 6H) ppm

¹³C NMR (75 MHz, CDCl₃): δ 211.0, 138.0, 115.2, 62.8, 42.6, 41.8, 33.1, 32.27, 25.9, 22.8, 20.3, 18.3, -5.3 ppm
Preparation of (E)-1-((tert-butyldimethylsilyl)oxy)-11-hydroxyundec-9-en-5-one

Notebook Reference: RDLB086

To an oven dried 10 mL tube with stir bar was charged with Grubbs 2nd generation catalyst (64.4 mg, 0.0759 mmol) and p-benzoquinone (8.2 mg, 0.0759 mmol), and placed under argon. DCM (1 mL) added via syringe. Z-2-butene-1,4-diol (0.37 mL, 4.5 mmol) and alkenone (0.216 g, 0.759 mmol) were mixed and diluted into DCM (0.5 mL), then added to the reaction vessel. Reaction stirred overnight at rt. Crude mixture purified through short plug of silica, rinsed with DCM and concentrated in vacuo. Purified by column chromatography with 2:1 Hex:EtOAc to yield slightly red oil (145 mg, 60%).

**FTIR** (ATR): 3357 (br), 2928(m), 2856 (m), 1711 (s), 1462 (w), 1361, 1253 (w, CO stretch), 1095 (m) cm⁻¹.

**1H NMR** (300 MHz, CDCl₃) δ 5.65 – 5.57 (m, 2H), 4.07 – 4.01 (m, 2H), 3.57 (t, J = 6.2 Hz, 2H), 2.43 – 2.33 (m, 4H), 2.06 – 1.94 (m, 2H), 1.76 (s, 1H), 1.69 – 1.53 (m, 4H), 1.51 – 1.42 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H) ppm.

**13C NMR** (75 MHz, CDCl₃) δ 211.0, 132.0, 129.8, 63.5, 62.8, 42.6, 41.8, 32.2, 31.5, 25.9, 23.0, 20.3, 18.3, -5.4 ppm.
Preparation of (E)-1-((tert-butyldimethylsilyl)oxy)-11-(2,6-dimethyl-4-nitrophenoxy)undec-9-en-5-one

To a flame dried 10 mL tube was charged 2,6-dimethyl-4-nitrophenol (91.9 mg, 0.550 mmol) and triphenylphosphine (133.7 mg, 0.5100 mmol), and placed under argon. 5-18 (145 mg, 0.460 mmol) in THF (1 mL) added via syringe. DIAD (0.51 mmol) diluted in THF (1 mL) and added dropwise. Stirred room temperature for 48 hours. Reaction mixture diluted with EtOAc, washed with 10% NaOH, washed with brine, dried MgSO₄, and concentrated in vacuo. Purified by column chromatography with 9:1 Hex:EtOAc to yield yellow oil (83.9 mg, 40%). Rₓ = 0.27 in 9:1 Hex:EtOAc.

¹H NMR (300 MHz, CDCl₃): δ 7.90 (s, 2H), 5.75 (m, 2H), 4.31 (d, J = 4.7, 2H), 3.60 (t, J = 6.2 Hz, 2H), 2.40 (m, 2H), 2.33 (s, 6H), 2.08 (m, 2H), 1.74-1.44 (m 6H), 0.88 (s, 9H), 0.03 (s, 6H) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 210.7, 161.3, 135.4, 132.6, 125.6, 124.2, 73.73, 62.8, 42.8, 41.9, 32.4, 31.6, 26.0, 22.9, 20.4, 18.2, 16.8, -5.2
Preparation of (E)-11-(2,6-dimethyl-4-nitrophenoxy)-1-hydroxyundec-9-en-5-one

Notebook Reference: RDLB096

To a 10 mL tube was added alkenone (83.9 mg, 0.181 mmol) in THF (1 mL). TBAF (236.5 mg, 0.905 mmol) added and mixture stirred at room temperature overnight. Water (2 mL) added to the reaction vessel, extracted with EtOAc, dried over MgSO₄ and concentrated in vacuo. Purified by column chromatography with 1:1 Hex:EtOAc to yield a yellow oil (16.5 mg, 26%).

**¹H NMR** (300 MHz, CDCl₃): δ 7.90 (s, 2H), 5.87 – 5.61 (m, 2H), 4.32 (d, J = 4.0 Hz, 2H), 3.58 (m, 2H), 2.16 – 1.95 (m, 4H), 2.09 (s, 3H), 1.80 – 1.58 (m, 2H), 1.50 – 1.28 (m, 1H), 1.25 (s, 1H), 0.97 – 0.78 (m, 1H) ppm.

**¹³C NMR** (75 MHz, CDCl₃): δ 210.51, 161.30, 143.40, 135.86, 135.22, 132.50, 126.90, 125.54, 125.19, 124.13, 113.29, 98.67, 73.38, 73.27, 61.37, 58.95, 42.71, 41.90, 36.53, 32.96, 32.38, 31.62, 29.57, 25.85, 25.31, 24.94, 22.82, 22.64, 20.92, 18.65, 16.81 ppm.
Au(III)-Catalyzed Cyclization of (E)-11-(2,6-dimethyl-4-nitrophenoxy)-1-hydroxyundec-9-en-5-one

Notebook Reference: RDLB110

To a flame dried 5 mL scintillation vial with stir bar was charged AuCl₃ (0.001 mmol), AgOTf (0.003 mmol), and basic alumina (10 mg). The reaction vessel was placed under argon and 0.2 mL CDCl₃ was added via syringe. The mixture was heated at 60 °C for 1 hour to ensure catalyst formation, then cooled to room temperature. Substrate 5-20 was diluted in 0.3 mL CDCl₃ and added via syringe. Reaction checked by NMR after 24 hours to indicate ~60% conversion of substrate to hemiketal 5-21. The reaction was then heated at reflux overnight. No observable formation of spiroketal was observed. Reaction was passed through a plug of silica, and concentrated in vacuo. The crude mixture was purified by MPLC (25 mm Column, 5 mL/min, 1:1 Hex EtOAc) to afford hemiketal substrate (5.4 mg, 60 %). Diastereomeric ratio estimated from MPLC chromatogram approximately (10:1).

¹HNMR (500 MHz, CDCl₃): δ 7.92 (s, 2H), 5.75 (m, 2H), 4.33 (d, J = 4.6 Hz, 2H), 3.63 (m, 2H), 2.42 (m, 2H), 2.36 (s, 6H), 2.09 (m, 2H), 1.74-1.49 (m, 6H), 1.26 (s, 1H)
Preparation of 1-(4-methoxyphenyl)hex-5-en-1-ol

![Chemical Reaction Diagram]

Notebook Reference: RDLB078

To an oven dried 50 mL tube with stir bar was charged magnesium shavings (1.823 mg, 75.00 mmol) and place under argon. Anhydrous THF (15 mL) was added via syringe. 5-bromopentene (4.44 mL, 37.5 mmol) was added dropwise via syringe over 15 minutes. Solution generated enough heat to reflux. This was allowed to stir for 30 minutes. On the side an oven dried 250 mL round bottom flask with addition funnel and stir bar was assembled hot and placed under argon to cool. THF (40 mL) was added by syringe followed by p-anisaldehyde (3.04 mL, 25.00 mmol). The reaction vessel was cooled to -78 °C (dry ice/isopropanol bath). The prepared Grignard reagent 6-11 was added via cannula to the addition funnel and added dropwise to the solution over 10 minutes. The reaction vessel was warmed to 0 °C and stirred for 1 hour, then room temperature for 1 hour. The reaction was quenched with NH₄Cl (40 mL) added dropwise over 10 minutes. Organics were extracted with EtOAc, washed with brine, dried over MgSO₄, and concentrated in vacuo to afforded the desired compound with slight aldehyde impurity as determined by NMR. The crude product was purified by column chromatography (70 mm, 6:1 Hex:EtOAc) to yield
desired product 6-12 as a clear, colorless oil (4.4081, 21.368 mmol, 85%). Rf = 0.25 in 6:1 Hex:EtOAc.

**FTIR (ATR):** 3370 (br), 3085 (w), 2934, 2836 (w), 1640, 1611 (w), 1586, 1511, 1459, 1441 (w), 1302, 1243, 1173 (s), 994, 909 (s), 830 (m) cm⁻¹.

**¹H NMR (300 MHz, CDCl₃):** δ 7.27 (d, J = 8.9 Hz, 2H), 6.93 – 6.84 (d, J = 8.5 Hz, 2H), 5.78 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.04 – 4.90 (m, 2H), 4.67 – 4.59 (m, 1H), 3.81 (s, 3H), 2.07 (d, J = 6.7 Hz, 1H), 1.89 – 1.62 (m, 3H), 1.50 (dddd, J = 12.6, 10.4, 7.5, 5.2 Hz, 1H), 1.37 (dddd, J = 13.2, 10.8, 7.8, 5.6 Hz, 1H) ppm.

**¹³C NMR (75 MHz, CDCl₃):** δ 159.1, 138.6, 136.9, 127.1, 114.6, 113.8, 74.1, 55.3, 38.4, 33.6, 25.1, 16.2 ppm.
Preparation of 4-(benzyloxy)benzaldehyde

Notebook Reference: RDLB162

To a 100 mL round bottom flask with stir bar was charged with K₂CO₃ (6.190 g, 50.00 mmol). Acetone (50 mL) was added followed by p-hydroxybenzaldehyde (3.053 g, 25.00 mmol) and benzyl bromide (3.00 mL, 27.5 mmol). The reaction was fitted with a condenser, refluxed overnight, and TLC showed complete consumption of starting material. Reaction concentrated in vacuo. The crude mixture was diluted with EtOAc, washed with saturated K₂CO₃, washed with brine, dried MgSO₄ and concentrated in vacuo to yield the product 6-17 as a white solid (4.56 g, 21.5 mmol, 86 %) with no further purification necessary.

**FTIR** (ATR): 3057 (w), 2829 (w), 2745 (w), 1686 (s), 1598, 1574, 1509, 1462, 1452 (m), 1321, 1301, 1252, 1213 (m) cm⁻¹.

**¹H NMR** (500 MHz, CDCl₃): δ 9.89 (s, 1H), 7.88 – 7.81 (m, 2H), 7.47 – 7.30 (m, 5H), 7.26 (s, 1H), 7.12 – 7.05 (m, 2H), 5.16 (s, 2H) ppm.

**¹³C NMR** (75 MHz, CDCl₃): δ 215.2, 190.8, 163.7, 135.9, 132.0, 130.1, 128.7, 128.3, 127.5, 115.1, 70.3, 16.2 ppm.
Preparation of 1-(4-(benzyloxy)phenyl)prop-2-en-1-ol

\[
\begin{align*}
\text{H} & \text{O} \quad \text{6-17} \\
\text{4-\text{Bn}} & \quad \text{\underline{\text{MgBr}}} \\
\text{THF} & \quad -78 \text{ to rt, 2 h} \\
\text{\rightarrow} & \quad \text{OH} \\
\text{4-\text{Bn}} & \quad \text{6-18} \\
\end{align*}
\]

Notebook Reference: RDLB176, RDLB104

To oven dried 100 mL 2-neck round bottom flask with stir bar and addition funnel was charged substrate 6-17 (4.132 g, 19.46 mmol), and placed under argon. THF (40 mL) was added via syringe, and the reaction vessel was cooled to -78 °C. Vinyl magnesium bromide (1M in THF, 23.35 mL) was added drop wise over 10 minutes. The reaction was warmed to 0 °C and stirred for 1 hour after which TLC indicated complete conversion of starting material. NH₄Cl (40 mL) was added dropwise, extracted with EtOAc, washed with brine, dried with MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (75 mm, 6:1-3:1 Hex:EtOAc) to yield the desired product 6-18 as a white solid (4.0511 g, 16.86 mmol, 87 - 91 %). Rᵣ = 0.17 in 6:1 Hex:EtOAc.

**FTIR** (ATR): 3320 (br), 3068, 3031 (w), 2910 (w), 2867 (w), 1611, 1585, 1509, 1470, 1454, 1421, 1376 (m), 1318, 1302, 1244, 1194 (m), 987, 916 (s) cm⁻¹.

**¹H NMR** (300 MHz, CDCl₃): δ 7.50 – 7.32 (m, 4H), 7.40 – 7.14 (m, 3H), 7.07 – 6.86 (m, 2H), 6.15 – 5.95 (m, 1H), 5.34 (dtd, J = 17.1, 1.4, 0.5 Hz, 1H), 5.28 – 4.94 (m, 2H), 5.07 (s, 2H) ppm.

**¹³C NMR** (75 MHz, CDCl₃): δ 158.42, 140.32, 136.94, 135.09, 128.58, 127.95, 127.69, 127.43, 114.90, 114.79, 74.87, 70.04 ppm.
Preparation of 1-(4-(benzyloxy)phenyl)allyl acetate

Notebook Reference: RDLB184

To a flame dried 50 mL tube with stir bar was charge substrate 6-18 (1.201 g, 5.00 mmol) and placed under argon. DCM (20 ml) was added via syringe, and DMAP (1.466 g, 12.00 mmol) was added, followed by acetic anhydride (0.57 mL, 6.0 mmol). The reaction was refluxed for 1 hour upon which complete consumption of the starting material was observed. The organics were washed with 10 % HCl, then NaHCO₃, dried MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (40 mm, 12: Hex:EtOAc) to yield the intended product as a colorless amorphous solid (678.2 mg, 2.402 mmol, 48 %). Rf = 0.32 in 6:1 Hex:EtOAc.

**FTIR** (ATR): 3035 (w), 2934 (w), 1735 (s), 1645, 1610, 1586, 1513, 1466, 1454, 1418 (m), 1386, 1367, 1300, 1227, 1176 (m), 992, 908 (s) cm⁻¹.

**¹H NMR** (300 MHz, CDCl₃): δ 7.49 – 7.23 (m, 6H), 7.32 – 7.20 (m, 1H), 7.06 – 6.89 (m, 2H), 6.23 (d, J = 5.7 Hz, 1H), 6.00 (dddd, J = 17.0, 10.4, 5.7, 0.7 Hz, 1H), 5.36 – 5.17 (m, 2H), 5.06 (s, 2H), 2.09 (s, 3H) ppm.

**¹³C NMR** (75 MHz, CDCl₃): δ 170.01, 136.84, 136.33, 131.26, 128.70, 128.58, 127.98, 127.43, 116.49, 114.82, 75.78, 70.02, 21.28 ppm.
Preparation of \((E)-1-(4-(benzyloxy)phenyl)-7-(4-methoxyphenyl)hept-2-ene-1,7-diol\)

Notebook Reference: RDLB186

To an oven dried 2-neck 25 mL round bottom flask with stir bar was charged Grubbs 2\textsuperscript{nd} generation catalyst (20.4 mg, 0.02402 mmol) and \(p\)-benzoquinone (13.0 mg, 0.1201 mmol), and placed under argon. DCM (8 mL) was added to a mixture of substrate \(6\text{-}12\) (247.8 mg, 1.201 mmol) and \(6\text{-}19\) (678.2 mg, 2.402 mmol) and added to the flask via syringe. The flask was fitted with a reflux condenser and the reaction was heated with an oil bath at 40 °C overnight. TLC indicated presence of products. The reaction mixture was pass through a plug of silica and rinsed with EtOAc, and concentrated in \textit{vacuo}. The crude product was purified by column chromatography (40 mm, 6:1-3:1 Hex:EtOAc). Two fractions were collected. Starting material \(6\text{-}12\) was collected in fraction 1 (348.6 mg, 1.945 mmol, 81 % recovery). Starting material \(6\text{-}19\) was collected in fraction 2 (100.7 mg, 0.4881 mmol, 41 % recovery). Acetone was rinsed through the column, and concentrated in \textit{vacuo}. This was crude product was purified by column chromatography (40 mm, 3:1-2:1 Hex:EtOAc) to yield the
intended product **6-20** as a viscous oil (65.9 mg, 0.1431 mmol, 62 % reacted yield, 12 % overall yield).

**FTIR** (ATR): 3435 (br), 3050 (w), 2855 (w), 1729 (s), 1606, 1509, 1454, 1371, 1301 (w), 1238, 1174, 1018, 967 (s) cm⁻¹.

**¹H NMR** (300 MHz, CDCl₃): δ 7.46 – 7.19 (m, 9H), 7.01 – 6.83 (m, 4H), 6.56 – 6.48 (m, 1H), 5.95 (ddd, J = 15.9, 7.6, 2.9 Hz, 1H), 5.36 (tt, J = 9.7, 4.8 Hz, 1H), 5.07 (s, 2H), 4.65 – 4.58 (m, 1H), 3.80 (t, J = 2.6 Hz, 3H), 2.04 (s, 3H), 1.84 – 1.71 (m, 1H), 1.34 (dtt, J = 19.3, 9.8, 5.1 Hz, 1H), 1.26 (s, 1H) ppm.

**¹³C NMR** (75 MHz, CDCl₃): δ 170.38, 159.07, 159.00, 158.63, 136.84, 136.79, 136.77, 132.28, 132.19, 130.29, 129.30, 128.57, 127.97, 127.80, 127.41, 127.12, 127.07, 125.47, 125.42, 114.92, 113.85, 113.80, 77.20, 74.85, 74.81, 74.15, 74.02, 74.00, 70.01, 55.27, 38.55, 38.38, 34.42, 32.32, 29.69, 25.73, 21.63, 21.60, 21.36 ppm.
Au(III)-Catalyzed Cyclization of (E)-1-(4-(benzyl oxy)phenyl)-7-(4-methoxyphenyl)hept-2-ene-1,7-diol

Notebook Reference: RDLB192

To 5 mL scintillation vial AuCl$_3$ (0.4 mg, 0.001 mmol), AgOTf (1.0 mg, 0.00375 mmol), and MS 4 Å (3.3 mg, 20% w/w). The reaction was placed under argon and Anhydrous DCM (0.2 mL) was added via syringe. The catalyst was allowed to form over 30 minutes. Substrate 6-20 (57.4 mg, 0.125 mmol) was diluted in DCM (0.3 mL) and added via syringe. Reaction changed to purple color in less than 1 minute, and TLC taken indicated complete consumption of starting material. Reaction was passed through a plug of silica, rinsed DCM, and concentrated in vacuo. The crude product was purified by column chromatography (15:1-9:1 Hex:EtOAc) to yield the desired product 6-21 as a colorless solid (41.3 mg, 0.103 mmol, 82%).

$^{1}$HNMR (500 MHz, CDCl$_3$): $\delta$ 7.72 (dq, $J = 4.5, 2.4$ Hz, 2H), 7.53 (dd, $J = 5.9, 3.3$ Hz, 2H), 7.46 – 7.37 (m, 2H), 7.42 – 7.28 (m, 3H), 6.96 – 6.84 (m, 4H), 6.57 (dd, $J = 16.0, 1.2$ Hz, 1H), 6.17 (dd, $J = 16.0, 6.0$ Hz, 1H), 5.06 (s, 2H), 4.43 (dd, $J = 11.3, 2.1$ Hz, 1H), 4.31 (dq, $J = 10.6, 7.3$ Hz, 2H), 4.22 – 4.13 (m, 1H), 3.80 (s, 2H), 2.00 (dt, $J = 10.1, 3.8$ Hz, 1H), 1.86 – 1.66 (m, 4H), 1.66 – 1.44 (m, 2H), 1.26 (s, 10H), 1.03 – 0.74 (m, 8H) ppm.

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.67, 158.84, 158.25, 136.96, 135.58, 130.88, 130.14, 129.21, 129.00, 128.80, 128.54, 127.92, 127.60, 127.44, 127.27, 114.82,
113.64, 79.59, 78.83, 70.00, 55.27, 33.37, 31.74, 29.72, 29.69, 24.06, 22.68, 14.11 ppm.
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