GOLD-CATALYZED CYCLIZATIONS OF MONO-ALLYLIC DIOLS AND ETHERS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

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To my family
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</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>TES</td>
<td>Triethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethane sulfonyl</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>Tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>t&lt;sub&gt;R&lt;/sub&gt;</td>
<td>Retention time</td>
</tr>
<tr>
<td>Tr</td>
<td>Trityl</td>
</tr>
<tr>
<td>Ts</td>
<td>Tosyl</td>
</tr>
<tr>
<td>TsDPEN</td>
<td>N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine</td>
</tr>
<tr>
<td>vs</td>
<td>Versus</td>
</tr>
<tr>
<td>X</td>
<td>Halogens</td>
</tr>
<tr>
<td>Xylyl</td>
<td>Dimethylphenyl</td>
</tr>
</tbody>
</table>
GOLD-CATALYZED CYCLIZATIONS OF MONO-ALLYLIC DIOLS AND ETHERS

By

Berenger Biannic

December 2011

Chair: Aaron Aponick
Major: Chemistry

Over the past decade, gold catalysis has emerged as an important methodology for the construction of complex organic structures. Its capability to form C-C and C-X bonds by activation of π-systems under mild conditions makes it a valuable asset for the synthetic community. The work presented in this thesis is aimed at expanding the π-activation to allylic alcohols in order to synthesize oxygen heterocycles from readily accessible mono-allylic diols. Saturated oxygen heterocycles are found in numerous biologically active natural products, and my thesis work has focused on developing a mild and general method for the preparation of substituted chiral 2-vinyltetrahydropyrans. The method was expanded to the cyclization of allylic ethers and the relative rate of reaction was studied for different protecting groups on the allylic moiety.

This thesis also documents the synthesis of substituted 2H-chromenes via gold-catalyzed cyclization of o-(1-hydroxyallyl)-phenols obtained from inexpensive and readily available salicylaldehydes. The products are obtained in good to excellent yields and the substrate scope of this reaction is quite broad. As such, a diverse range of products with varied substitution patterns and differing electronics in the aromatic ring is
readily available. This method gives direct access to substituted $2H$-chromenes which should be useful for further modification toward the preparation of biologically active molecules.
CHAPTER 1
INTRODUCTION

1.1 General Considerations in Homogeneous Gold-Catalysis

Throughout history, gold has served many roles. First used in art, due to its color and its outstanding durability, gold grew to be the basis of the universal currency in civilizations until the last hundred years.¹ For thousands of years, gold has kept its status as a precious rare metal, indicator of wealth for antique civilizations, and striking material used to decorate ancient items and palaces. Although European chemists during the Renaissance tried to investigate the transmutation of common metals (lead, mercury, iron…) into gold, the scientific community did not show a strong interest in studying the features of this element. The neglect of gold in modern science was mostly due to the common belief that materials made out of gold would be extremely expensive.

The development of homogeneous organometallic catalysis applied to synthesis, opened an innovative area of investigation in organic chemistry giving access to more complex structures in shorter reaction times. One the most famous example was reported in the mid 1970’s by Richard F. Heck²a and Tsunomu Mizoroki²b with the discovery of palladium-catalyzed coupling reactions.

Although catalysts based on expensive metals such as palladium, ruthenium, rhodium or platinum have been intensively investigated for synthetic purposes, the study of gold catalysis begun relatively late on the organometallic time scale. Even if few applications of gold catalysis were described in the 1990s,³ the “boom” happened in the early 2000’s with the development of new phosphine- or carbene-ligated gold salts as catalysts.⁴ In comparison with other precious metal catalysts used in organic
chemistry, gold salts are relatively affordable even though gold metal is one of the most expensive (Table 1-1),\textsuperscript{5,6} many factors influence the price of the catalysts including the nature of the ligand, sensitivity and demand.\textsuperscript{7}

Table 1-1. Precious metals price/gram as of August 2011.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Price/gram in US $</th>
<th>Catalyst</th>
<th>Price/gram in US $</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold</td>
<td>64.22</td>
<td>AuCl/AuCl(_3)</td>
<td>171.50/143.00</td>
</tr>
<tr>
<td>Iridium</td>
<td>37.10</td>
<td>IrCl(_3)</td>
<td>174.20</td>
</tr>
<tr>
<td>Osmium</td>
<td>14.13</td>
<td>OsCl(_3)</td>
<td>537.00</td>
</tr>
<tr>
<td>Palladium</td>
<td>26.80</td>
<td>PdCl(_2)</td>
<td>46.50</td>
</tr>
<tr>
<td>Platinum</td>
<td>65.12</td>
<td>PtCl(_2)/PtCl(_4)</td>
<td>137.00/117.00</td>
</tr>
<tr>
<td>Rhenium</td>
<td>10.58</td>
<td>ReCl(_3)</td>
<td>291.00</td>
</tr>
<tr>
<td>Rhodium</td>
<td>65.37</td>
<td>RhCl(_3)</td>
<td>295.00</td>
</tr>
<tr>
<td>Ruthenium</td>
<td>5.83</td>
<td>RuCl(_3)</td>
<td>44.00</td>
</tr>
<tr>
<td>Silver</td>
<td>1.43</td>
<td>AgCl</td>
<td>5.40</td>
</tr>
</tbody>
</table>

The three most prevalent oxidation states of gold are Au(0), Au(I) and Au(III).

Without stabilizing ligands, Au(I) salts disproportionate into Au(0) and Au(III) in aqueous media.\textsuperscript{1} New robust water and air stable gold complexes (Figure 1-1) have been designed by synthetic chemists to counter those limitations in the course of a chemical reaction.\textsuperscript{4}

![Figure 1-1. Gold(I) salts commonly used in homogeneous catalysis.](image)

The unusual and surprising chemical and physical properties of gold complexes have been proposed to be closely related to relativistic effects (Figure 1-2). Among the elements, gold is the element that exhibits the largest relativistic effect.\textsuperscript{8} Gold metal is more resistant to oxidation than silver or mercury but gold element also accounts for
reaching a higher oxidation state (Au$^{3+}$ vs Ag$^+$ or Hg$^{2+}$). This relativistic effect is described as gold having a contracted s orbital and expanded 5d orbital. As a result, the size of the atom of gold is comparable to that of silver. The tighter binding of the s electrons coupled to a greater energy cohesion of gold metal makes this metal harder to oxidize and gold cationic species excellent Lewis acids.

Both gold(I) and gold(III) species are considered soft carbophilic Lewis acids that can easily activate soft electrophiles such as double and triple C-C bonds (Figure 1-2). The high Lewis acidity of gold is explained by a relatively low-lying lowest unoccupied molecular orbital. Also, since it is a soft Lewis acid, coordination to soft Lewis bases such as phosphine ligands, or thioethers are highly favored (Figure 1-1). Finally, the trapping of an electrophile by a gold cation is facilitated by the strong back-bonding character of this atom. The relativistic expansion of the gold’s 5d orbitals increases the back-bonding effect and therefore facilitates the electron delocalization (Figure 1-2).

![Gold electronic configuration: [Xe] 5d$^{10}$ 6s$^1$](image)

Figure 1-2. Gold and relativistic effect.

The robustness of gold catalysts combined with their exceptional chemoselectivity$^9$ to bind π-systems makes Au-catalysis a major area of investigation for synthetic chemists and has become a significant tool in total synthesis.$^{10}$ In fact, the requirement
for low catalyst loadings, minimal use of additives, mild reaction conditions and tolerance of oxygen functional groups are the key arguments for the use of gold catalysis and those properties can be applied to a diverse set of reactions.

1.2 Gold-Catalyzed Addition on π-Systems

Gold-catalyzed activation of alkynes has been one the first and most investigated reaction since the development of robust ligated gold complexes. Gold cationic species behave as π-acids by taking electron density from multiple bonds to induce electrophilic character (Figure 1-3). This π-complex can be further attacked by a nucleophile.

![Figure 1-3. π-system activation by gold(I).](image)

Alkynes can be activated very easily by cationic gold complexes under mild conditions. Arcadi and co-workers reported in 2004 an efficient synthesis of indole 1-7 starting from 2-ethynylaniline 1-6 in high yield at room temperature (Figure 1-4). Addition on the alkyne can also be performed intermolecularly. Hydration of 1-8 using only 0.01 mol% of catalyst was investigated by Nolan and co-workers (Figure 1-4). The reaction proceeded in high yield using water as a co-solvent.

In 2000, Hashmi developed the synthesis of substituted phenols catalyzed by gold(III) chloride starting from furan 1-10 (Figure 1-4). They are notoriously unreactive
dienes in Diels-Alder reactions, even in intramolecular transformations. However, in the presence of AuCl₃, 1-10 underwent a Diels-Alder reaction to form 1-11 through activation of the alkyne moiety, and after breaking the oxygen bridge, mediated by the catalyst, 1-12 was obtained in 97% yield.

Figure 1-4. Selected examples of gold-catalyzed activation of alkynes.

Figure 1-5. Au-catalyzed alkoxylation of alkyne applied to the total synthesis of Bryostatin 16.

Trost and co-workers applied the gold-catalyzed alkoxylation of alkynes to the total synthesis of a complex natural molecule: Bryostain 16 (Figure 1-5). They reported the
intramolecular alkoxylation of 1-13 catalyzed by 20 mol % of gold(I) species in 73% yield. It is worth noting that the reaction proceeds smoothly in the presence of an acetal, conjugated systems and an unprotected free alcohol.

Nucleophilic addition to allenes is also carried out under mild conditions. In 2006, Widenhoefer and co-workers reported the gold-catalyzed cyclization of 1-15 to form 1-16 in high yield and moderate dr (Figure 1-6). In 2008, the same group also published the intermolecular hydroamination of 1-17 with 1-18 at room temperature. C-C bond forming reactions have also been reported by Ohno and co-workers in 2007 to synthesize dihydroquinoline 1-21 from allenic aniline 1-20. This hydroarylation of allenes proceeds at room temperature and gave high yields.

![Chemical Structures](image)

Figure 1-6. Selected examples of gold-catalyzed activation of allenes.

Formation of a chiral center is one of the advantages of using allenes as electrophiles. The development of chiral bisphosphines ligands or phosphate counter anions for stereoselective activation of allenes or alkenes by cationic gold complexes
has been successfully investigated by several synthetic groups and has proven to be highly efficient.\textsuperscript{21} For example, Toste and co-workers reported the enantioselective intramolecular hydroamination of allenes using a chiral phosphine ligand based gold catalyst 1-24 (Figure 1-7).\textsuperscript{22} Pyrrolidine 1-23 was synthesized in excellent yield and 99% ee from allene 1-22 under mild conditions. In 2007, the same group reported the hydroalkoxylation of allene promoted by a Au(I) using a chiral counter anion silver salt 1-27.\textsuperscript{23} Excellent enantioselectivity is obtained for 1-26 as well.

In gold catalysis, low enantioselectivity is often found, mostly due to the distance between the chiral ligand and the substrate.\textsuperscript{20} This problem could be overcome by using chiral counter-anions which are much closer to the metal and consequently to the substrate. These two different approaches should give access to a larger library of chiral species to screen in a process optimization.

\textbf{Figure 1-7. Selected examples of enantioselective addition on allenes.}

Despite the success of gold-catalyzed activation of alkynes or allenes, addition of nucleophiles to olefins remains limited. Several examples have been reported in the
literature; however higher temperatures are needed in order to fully activate the olefin. For example, He and co-workers published the gold-catalyzed addition of a phenol derivative 1-29 to the alkene 1-28 in 84% yield in toluene at 85 °C (Figure 1-8).²⁴ For the intramolecular reaction, Windenhoefer and co-workers reported the cyclization of the carbamate protected amine 1-31 to form the substituted pyrrolidine 1-32 in 91% yield at the same temperature.²⁵

\[
\begin{align*}
\text{MeO} & \quad \text{OH} \\
1-28 & \quad \rightarrow \\
& \quad \text{MeO} \quad \text{O} \\
& \quad \text{OMe} \\
1-29 & \quad \text{O} \\
& \quad \text{OMe}
\end{align*}
\]

Figure 1-8. Selected examples of gold-catalyzed activation of alkenes.

**1.3 Metal Catalyzed Activation of Unsaturated Alcohols**

Unsaturated alcohols are readily available intermediates in organic chemistry. Transformations of unsaturated alcohols under protic or Lewis acidic conditions have been extensively studied and reviewed.²⁶⁻³¹ A selection of revelant, modern metal-catalyzed reactions of allylic, propargylic and benzylic alcohols will be presented in this dissertation.

Allylic alcohols can be easily prepared from inexpensive compounds (usually by reduction of a propargylic alcohols or reduction of unsaturated carbonyl compounds). Their reactivity in the presence of Lewis acids (Pd,²⁶ Ru,²⁷ Rh,²⁸ Fe²⁹, Pt³⁰ and Bi³¹) is
well documented but still needs further advancements since the catalyst loadings necessary remain relatively high (usually more than 5 mol %).

Select examples of this activation are shown Figure 1-9. Although the method developed by Uenishi\textsuperscript{26g} is efficient and highly diastereoselective, a relatively high loading of palladium catalyst is required for full conversion (Figure 1-9). Intermolecular Friedel-Crafts reactions can also be performed using ruthenium-based catalysts.\textsuperscript{27a} 1-35 was readily converted into 1-37 at room temperature using camphorsulfonic acid as a co-catalyst. Platinum(II) salts have been used by Mashima and co-workers to activate allylic alcohol 1-36.\textsuperscript{32} Only 1 mol % of catalyst is necessary but the reaction required heating to reflux for 6 hours to afford 1-39.

![Chemical equations and figures]

Figure 1-9. Selected examples of Pd, Ru and Pt-catalyzed activation of allylic alcohols.

Activation of allylic alcohols by gold-catalysts has been extensively investigated by our group;\textsuperscript{33} these developments will be discussed in detail in the chapters 2 and 3 of this dissertation.
Propargyl alcohols are extremely versatile intermediates in complex synthesis. They can be transformed into a myriad of different functional groups depending on the reaction conditions. Activated by a transition metal salt, they are commonly used in the synthesis of 5-membered heterocycles.

Our group reported in 2009 the synthesis of furans, pyrroles and thiophenes by gold-catalyzed activation of propargyl alcohols. The selected example (Figure 1-10) shows that the starting material 1-40 can easily be converted into 1-41 with a 92% yield using only 0.05 mol % of catalyst. In 2010, Castanet and co-workers developed a method to synthesize furans from a propargylic alcohol 1-42, a boronic acid 1-43, and carbon monoxide with a low loading of rhodium catalyst (Figure 1-10). The yield is moderate but the reaction proceeds from commercially available starting materials.

Ru-catalyzed propargyl nucleophilic substitutions have also been reported. Uemura and co-workers showed in 2005 that 1-45 can be easily transformed into 1-46 using 5 mol % of catalyst with the nucleophile as the solvent (Figure 1-10). The reaction proceeded at 60°C in only 15 minutes.

Ionization under mild acidic conditions of benzylic alcohols has been also throughly investigated by the synthetic community. Any type of C-X bond can be formed in the benzylic position through an S_N1 mechanism (Figure 1-11). Cation 1-48 is formed after treatment of 1-47 under Lewis acidic conditions and 1-49 is obtained after addition of the nucleophile and loss of water.

Campagne et al. reported in 2006 the direct activation of benzyl alcohols in presence of 5 mol % of Lewis acid and tosylamine (Figure 1-12). Among the different Lewis acids tested, Au^{3+} species proved to be the best catalyst for this transformation.
Use of organic acids or TiCl$_4$ gave poor yields and side products. $\beta$-ketoesters can also be used as nucleophiles for this type of transformation (Figure 1-12). Despite the fact that this reaction needs a high catalyst loading, a broad range of metals can be used.

Better yields are given by treating 1-52 with 10 mol % of inexpensive FeCl$_3$•6H$_2$O.

![Chemical Reaction Diagram](image1)

Figure 1-10. Selected recent examples of metal-catalyzed activation of propargyl alcohols.

![Chemical Reaction Diagram](image2)

Figure 1-11. Mechanism of metal-catalyzed nucleophilic substitutions on benzylic alcohols.
Figure 1-12. Selected examples of metal-catalyzed activation of benzylic alcohols.

Friedel-Crafts reactions can also be achieved through the same methodology using electron-rich aromatic nucleophiles (Figure 1-13). Bismuth triflate was successfully used by Rueping and co-workers to do an intramolecular arylation (Figure 1-13). The reaction conditions are very mild and give an easy access to fluorene derivatives. Using 10 mol % of HAuCl₃ (Figure 1-13), Beller et al. developed a method to arylate benzylic alcohol 1-56 with o-xylene. This method can also be extended to the ionization of benzylic acetates and carboxylates.

Figure 1-13. Selected examples of metal-catalyzed arylation of benzyl alcohols.
Over the past decade, metal-catalyzed activation of unsaturated alcohols has been extensively studied. The substrates are easily accessible through synthesis and relatively stable but they are also very reactive under the correct conditions and give access to complex structures. However, allylic alcohols are much more difficult to activate under mild conditions. Therefore, innovative new methodologies warrant investigation to expand this area.

1.4 Gold-Catalyzed [3,3]-Sigmatropic Rearrangement

Unsaturated alcohols and ethers are important intermediates used in sigmatropic rearrangement. Transition metal catalysts can easily activate unsaturations and therefore favor the formation of carbon-carbon or carbon-heteroatom sigma-bonds via addition to the \( \pi \)-bond. Gold catalysts were described as excellent \( \pi \)-acids.\(^1\) Consequently they became an efficient tool to catalyze sigmatropic rearrangements.

A [3,3]-sigmatropic rearrangement is a pericyclic reaction where three pairs of electrons are shifted in a suprafacial manner and where a \( \sigma \)-bond migrates to another position on the same molecule. [3,3]-sigmatropic rearrangements typically proceed at high temperature but can be catalyzed by Lewis acids in order to use milder reaction conditions (Figure 1-14).\(^43\) The best known [3,3]-sigmatropic rearrangements are the Cope rearrangement (Figure 1-15),\(^44\) Claisen rearrangement,\(^45\) Carroll rearrangement\(^46\) and the Fischer indole synthesis.\(^47\)

![Figure 1-14. [3,3]-sigmatropic rearrangement.](image-url)
In recent years, gold catalysts have been successfully applied to a series of [3,3]-sigmatropic rearrangements, such as the Claisen rearrangement (Chapter 2), rearrangement of allylic/propargyl esters, and the Overmann rearrangement as well. In 2007, Nolan and co-workers reported the Au-catalyzed rearrangement of allylic acetates using a N-heterocyclic ligand into a linear allylic acetate (Figure 1-16). The scope of the reaction proved to be broad and high yielding. More recently, Yang and co-workers developed a highly efficient gold(I)-catalyzed Overman rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides in water (Figure 1-16). This reaction is very clean, did not need further purification, and can be conducted on a multi-gram scale.

The reactivity of more reactive propargylic acetates in the presence of gold catalysts has also been investigated. In 2007, Toste and co-workers gave evidence for
a cationic intermediate during the gold-catalyzed sigmatropic rearrangement of 1-63 to form 1-65 (Figure 1-16). The ring expansion of 1-64 to form 1-65, catalyzed by gold, showed the strong cationic nature of the allene formed in the first step.

Figure 1-16. Selected examples of Au-catalyzed [3,3]-sigmatropic rearrangements.

Among [3,3]-sigmatropic rearrangements, Claisen-type reactions have been the most popular transformations catalyzed by gold cationic species. However, most reports showed the activation of propargylic or allenic derivatives. We aimed at exploring further this type of rearrangement catalyzed by gold using allyl vinyl ethers to synthesize hex-5-enones in a one-pot process.
CHAPTER 2
GOLD-CATALYZED SYNTHESIS OF SUBSTITUTED HEX-5-EN-ONES BY CLAISEN REARRANGEMENT

2.1 Gold-Catalyzed Claisen Rearrangements

2.1.1 Generalities

The [3,3] sigmatropic rearrangement of allyl vinyl ethers is one of the oldest and most versatile ways to make carbon-carbon bonds in organic synthesis.\(^{51}\) Discovered by Rainer Ludwig Claisen in 1912, the Claisen rearrangement usually requires high temperatures (Figure 2-1), but more convenient methods have been developed by the synthetic community over the past 50 years to catalyze this reaction.\(^{51}\) Two different classes of catalysts can be defined; hard Lewis acids such as protic acids (Figure 2-1) catalyze the reaction by coordination to the oxygen atom and soft Lewis acids such as Pd\(^{2+}\) or Hg\(^{2+}\) catalyze the reaction by coordination to the \(\pi\)-bonds.\(^{51}\)

![Figure 2-1. Different types of Claisen rearrangement.](image)

Gold complexes have proven to be efficient soft Lewis acids that activate unsaturated C-C bonds. Therefore, they could be employed to catalyze Claisen rearrangements. Gold catalysts are usually more chemoselective than other metals used to catalyze Claisen rearrangement such as Pd(II) or Ir(III)\(^{52}\) species. They are also described as mild Lewis acids that are moisture and oxygen stable.\(^1\),\(^{52}\) The mild Lewis
acidity is usually not suitable to activate olefins but performs extremely well with alkynes or allenes. Consequently, gold-catalyzed rearrangements of allyl vinyl ethers have not been explored. This Chapter will describe the different types of gold-catalyzed Claisen rearrangements of propargylic and allenic ethers and our attempts to expand this reactivity to the rearrangement of allyl vinyl ethers.

2.1.2 Gold-Catalyzed Propargylic and Allenic Claisen Rearrangement

In the Claisen rearrangement reactions catalyzed by soft Lewis acids, the electrophilic metals bind to the enol ether and thus cannot activate the olefin. This limitation is also true for gold complexes. Using a more electron-rich π-olefin could counter this limitation. Gold complexes are carbophilic and easily form π-complexes with alkynes or allenes. With this method of activation, propargylic or allenic Claisen rearrangements catalyzed by gold salts have become possible.

In 2004, Toste and co-workers reported the first gold-catalyzed acetylenic Claisen rearrangement (Figure 2-2). This method provided easy access to homo-allenic alcohols under mild conditions and low catalyst loadings. The reaction was also highly stereoselective; enantioenriched propargyl vinyl ether 2-1 was converted to 2-2 in 91% yield with high transfer of chirality. The reaction worked through a 6-exo-dig addition of the enol ether to the gold-alkyne complex 2-6 followed by rearrangement of 2-7 to form allene 2-8 (Figure 2-3).

More recently, Krafft and co-workers reported the Au(I)-catalyzed Claisen rearrangement of allenyl vinyl ether 2-3 to form substituted 1,3-dienes 2-4. The reaction proceeded under mild conditions with low catalyst loadings as well (Figure 2-2).
Figure 2-2. Gold-catalyzed propargylic and allenic Claisen rearrangement.

Figure 2-3. Detailed mechanism of Au-catalyzed propargyl Claisen rearrangement.

Figure 2-4. Au-catalyzed Claisen rearrangement applied to the total synthesis of Azadirachtin.
This methodology has been applied to the total synthesis of Azadirchtin in 2007 by Ley and co-workers (Figure 2-4). The key Claisen rearrangement step catalyzed by a gold(I) complex gave access to allene 2-11 from vinyl-propargyl ether 2-10 in 80% yield. The reaction proceeded with 5 mol % of catalyst (15 mol % of gold(I) species) which is a relatively high catalyst loading in gold catalysis.

2.1.3 Gold-Catalyzed Heterocycle Synthesis through Claisen Rearrangement

Cationic gold-complexes are excellent catalysts for cascade reactions; they have proven to be very stable under various sets of conditions and can promote unusual processes. As described above, they are very efficient at catalyzing propargylic and allenic Claisen rearrangement which led to either the allene or the diene that can be further activated using the same catalyst.

Figure 2-5. Au-catalyzed cascade synthesis of 5-membered heterocycles.

In 2005, Kirsch and co-workers investigated the Au-catalyzed cascade propargyl-Claisen rearrangement/heterocyclization of propargyl vinyl ether 2-12 to form substituted pyran 2-14 (Figure 2-5). This method is very high yielding and can give access to tri- or tetra-substituted furans. The same methodology was applied to the
synthesis of pyrrole by Saito and co-workers in 2010 using vinyl-propargyl tosylamide 2-15.\textsuperscript{57}

2.1.4 Gold-Catalyzed Aromatic Claisen Rearrangement

The aromatic Claisen rearrangement catalyzed by gold salts was reported in 2006 by He and co-workers.\textsuperscript{58} Rearrangement of aryl allyl ether 2-18 catalyzed by generated \textit{in situ} Ph\textsubscript{3}PAuOTf gave \textit{o}-allyl phenol 2-19 which was further transformed into the dihydrobenzofuran by addition of the phenol to the olefin (Figure 2-6).

To show that the first step was a Claisen rearrangement, the authors synthesized the 2,6-disubstituted aryl allyl ether 2-21 (Figure 2-6). This compound was treated under the same conditions as 2-18 and 2-22 was afforded. The first step was presumably a Claisen rearrangement to give 2-23. Since this compound could not be re-aromatized, the allyl group must undergo a Cope rearrangement\textsuperscript{59} to give phenol 2-22.

Figure 2-6. Au-catalyzed aromatic Claisen rearrangement.
These reports demonstrate that gold-complexes can catalyze the Claisen rearrangement, but surprisingly, gold-catalyzed rearrangement of allyl vinyl ethers has not been explored.

2.2 Gold-Catalyzed Synthesis of Substituted Hex-5-en-2-ones, an Initial Study

2.2.1 Initial Considerations

At the beginning of my PhD study, we were interested in developing new methodologies using cationic gold catalysts to form complex structures by cascade reactions. The absence of reports describing activation of allyl vinyl ethers by gold led us to investigate this area. We also proposed that the carbophilicity of Au(I) species could be used to form allyl vinyl ethers through addition of an allyl alcohol to an alkyne. This process would afford hex-5-ene-2-ones derivatives 2-28 (Figure 2-7) by cascade reactions both catalyzed by the same gold(I) species from inexpensive, commercially available allylic alcohols and alkynes.

Many different reliable methods have been developed over the past 100 years to synthesize vinyl allyl ethers. However, a simple methodology using environmentally benign activators remains unexplored. Also, allyl vinyl ethers are not easy to process and purify by flash chromatography, they are sensitive to moisture, and unstable under protic conditions.

Figure 2-7. Au-catalyzed cascade activation of alkyne/Claisen rearrangement.
The alkyne 2-26 could be activated with a gold(I) salt which would catalyze addition of the allylic alcohol 2-25 to obtain intermediate 2-27. The latter could then perform a thermal or Au-catalyzed Claisen rearrangement to form 2-28 (Figure 2-7).

The proposed mechanism of this sequential transformation can be detailed as followed (Figure 2-8). A Au(I)-complex activates alkyne 2-30 and the allylic alcohol attacks it to form the allyl vinyl ether 2-31. The latter would then rearrange to form 2-32 and, after protodeauration, give the expected product 2-33. An alternative pathway could be envisioned. Protodeauration could occur earlier in the sequence and allyl vinyl ether 2-34 could be obtained from 2-31. Rearrangement would then form 2-35 which, after decomplexation of the gold species, would afford 2-33.

![Detailed proposed mechanism](image)

**Figure 2-8.** Detailed proposed mechanism.

### 2.2.2 Results

To test this hypothesis, we initiated a study of the gold-catalyzed cascade addition of allylic alcohol to alkynes followed by Claisen rearrangement to form hex-5-en-2-ones 2-33 (Figure 2-8). This reaction was tried using many different conditions and different types of substrates. However, the expected reaction did not occur and other transformations took place instead (Figure 2-9). Instead of the desired transformation,
the activation of the allylic alcohol by the gold complex was observed and the product 2-36 of the condensation between two allylic alcohols 2-34 was isolated. Interestingly, the formation of acetophenone 2-37 was also observed. It is likely that the molecule of water released during the formation of 2-36 hydrates the alkyne in presence of a gold complex.\textsuperscript{12} This problem was overcome by screening different types of drying agents (Entries 3 and 4, Table 2-1). It was found that 4Å molecular sieves were the most efficient water scavenger since no acetophenone 2-37 was detected by \textsuperscript{1}H-NMR of the crude material (Entries 4-7, Table 2-1). Product 2-36 was obtained when CH\textsubscript{2}Cl\textsubscript{2} and benzene were used as solvent (Entries 1 and 6, Table 2-1).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2-9}
\caption{Gold-catalyzed reactions with crotyl alcohol and phenylacetylene.}
\end{figure}

Table 2-1. Attempts of cascade Au-catalyzed addition of allylic alcohols on alkyynes/Claisen rearrangements.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst (mol %)</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>PPh\textsubscript{3}AuCl/AgOTf (5)</td>
<td>rt</td>
<td>2-36+2-37</td>
</tr>
<tr>
<td>2</td>
<td>Toluene</td>
<td>PPh\textsubscript{3}AuCl/AgOTf (5)</td>
<td>rt and reflux</td>
<td>2-38+2-39+2-37</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>PPh\textsubscript{3}AuCl/AgOTf (5)</td>
<td>CaCl\textsubscript{2}, rt</td>
<td>2-38+2-39+2-37</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>PPh\textsubscript{3}AuCl/AgOTf (5)</td>
<td>MS 4Å, rt</td>
<td>2-38+2-39 (3:1)</td>
</tr>
<tr>
<td>5\textsuperscript{a}</td>
<td>Toluene</td>
<td>PPh\textsubscript{3}AuCl/AgOTf (5)</td>
<td>MS 4Å, rt</td>
<td>2-38+2-39 (3:1)</td>
</tr>
<tr>
<td>6</td>
<td>Benzene</td>
<td>PPh\textsubscript{3}AuCl/AgOTf (5)</td>
<td>MS 4Å, rt</td>
<td>2-36</td>
</tr>
<tr>
<td>7</td>
<td>PhNMe\textsubscript{2}</td>
<td>AuCl\textsubscript{3}/AgOTf (2)</td>
<td>MS 4Å, rt</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

\textsuperscript{a} No phenylacetylene used.

Surprisingly, when toluene was used as solvent for this transformation (Figure 2-9), the allylic alcohol 2-34 was activated by the gold complex to act as an electrophile.
The reaction proceeded as a Friedel-Crafts reaction where toluene was alkylated in both the ortho and para positions. Both products 2-38 and 2-39 (ratio 3:1) were obtained but were too volatile to be isolated. No Friedel-Crafts product was formed when benzene was used as solvent (Entry 6, Table 2-1) but the reaction gave ether 2-36 as a single product. The reaction using dimethylphenylamine as an electron-rich solvent was also tried, but no conversion was observed (Entry 7, Table 2-1).

_These observations form the basis for studying the Au-catalyzed dehydrative transformations that form the majority of this thesis._

Several years later, after working on the Au-catalyzed activation of allylic alcohols, we decided to drastically change the reaction conditions and substrates of this cascade reaction. A more activated alkyne and a more hindered allylic alcohol were chosen as substrates. Steric hindrance on the olefin moiety of 2-40 should disfavor the condensation of two molecules of allylic alcohol (Figure 2-10) and therefore should favor the addition to alkyne 2-41. Also, diphenyl acetylene 2-41 is an electron rich alkyne and thus a better soft Lewis base for complexation with gold(I) (Figure 2-10).

In this event, 2-42 was observed in 30% yield using 3-methyl-2-buten-1-ol 2-40 and diphenylacetylene 2-42 in a 1:1 ratio. A more coordinating solvent (THF) and a more stable catalyst 1-3 seemed to favor the formation of the hex-5-en-2-one 2-42 (Figure 2-10). When three equivalents of alkyne 2-41 were used, the yield was increased from 30% to 65%. When less sterically hindered allylic alcohol 2-43 was used, 2-44 was obtained in 89% yield in a 10:1 diastereomeric mixture.
Despite these encouraging results, further experiments carried out in our laboratory showed that this method is limited to a narrow substrate scope. However, we believe that this methodology is still of interest and can become an efficient tool for the formation of chiral hex-5-en-2-ones 2-28. Further optimization reactions are being conducted in our laboratory.

2.3 Outcome

The set of experiments described in the previous section showed that the Au-catalyzed intermolecular addition of allylic alcohols to alkynes followed by Claisen rearrangement worked only for a specific type of substrate and can hardly be extended to a broader scope of reactants (Figure 2-11). However, it was also demonstrated that, in the presence of cationic gold species, allylic alcohols can be activated and act as
electrophiles (Figure 2-11). As shown above, alkylation of toluene (solvent) in the ortho and para positions took place (Figure 2-9) in lieu of the hydroalkoxylation of the alkyne (Figure 2-11).

As shown above, alkylation of toluene (solvent) in the ortho and para positions took place (Figure 2-9) in lieu of the hydroalkoxylation of the alkyne (Figure 2-11).

Figure 2-11. Au-catalyzed activation of allylic alcohols.

This conclusion led us to investigate a different set of nucleophiles and allylic alcohol electrophiles for activation by a cationic gold species (Figure 2-12). The major work presented in this thesis is the formation of saturated oxygen-containing heterocycles by intramolecular alkoxylation of allylic alcohols catalyzed by gold-complexes.

Figure 2-12. Au-catalyzed alkoxylation of allylic alcohols.

This work, described herein, represents a new and exciting mode of reactivity in Au-catalysis.
CHAPTER 3
GOLD-CATALYZED CYCLIZATION OF MONO-ALLYLIC DIOLS TO FORM 2-VINYL TETRAHYDROPYRANS

3.1 Background and Significance

3.1.1 Tetrahydropyrans in Nature

Saturated oxygen heterocycles are commonly found in biologically active natural molecules and consequently, they have been extensively studied by the scientific community. Among these, tetrahydropyrans are found very frequently in synthetic targets due to their potent biological activities (Figure 3-1).

![Saturated oxygen heterocycles](image)

Figure 3-1. Selected examples of natural molecules containing tetrahydrofuran motifs.

For example, Spirastrellolide A 3-1, extracted from the marine sponge Spirastrella coccine,\(^62\) shows a potent inhibition of the protein phosphatase 2. This molecule has three different saturated oxygen heterocycles types: a tetrahydrofuran, a spiroketal and a bis-spiroketal. (+)-SCH 351448 3-2, isolated from a microbial metabolite by Hedge
and co-workers at the Schering-Plough Research Institute, selectively activates low-density lipoprotein receptors (LDL-R). This molecule is a macrolactone containing two different tetrahydropyran motifs. Brevetoxin 1 is a cyclic polyether produced by Karenia brevis, a marine dinoflagellate found in the Gulf of Mexico, known to be the organism responsible for the Florida red tide. For human beings, 3-3 is a neurotoxin that binds to voltage-gated sodium channels in nerve cells. This complex structure is very challenging to synthesize due to the ten fused oxygen heterocycles, and thus, is still an important synthetic target for chemists.

Classical methods of tetrahydropyran synthesis are efficient but still remain limited when applied to the preparation of complex chiral structures. Organometallic chemistry proved to be a unique tool to create diversity in high yield and high stereoselectivity.

### 3.1.2 Transition Metal-Catalyzed Synthesis of Tetrahydropyrans

Due to the exceptional abundance of tetrahydropyrans in nature, the synthetic community continues to expand the scope of new methodologies to synthesize THPs. Even though a variety of classical methods to synthesize these structures have proven to be very efficient, this section will only focus on modern metal-catalyzed cyclization reactions forming the THP ring system.

Most recent methods using cationic metals as catalysts involve the intramolecular hydroalkoxylation of unactivated alkenes (Figure 3-2). In this general reaction, the metal coordinates to the double bond in 3-4 to form π-complex 3-5 activating it towards nucleophilic addition. Proton transfer then gives 3-7. Even though this method usually requires high temperatures and long reaction times, the substrates are extremely easy to synthesize.
Widenhoefer and co-workers reported the platinum-catalyzed cyclization of alkenol 3-8 to form 3-9 in moderate yield and very high diastereoselectivity (Figure 3-3). This transformation tolerated a large number of functional groups including pivaloate and acetate esters, amides, silyl and benzyl ethers. The same reaction has been investigated by He and co-workers using silver triflate as catalyst. 3-11 was obtained in high yield from 3-10 using 5 mol % of catalyst and triphenylphosphine. This reaction stands as one of the simplest modern methods to construct cyclic ethers. Lanthanides have also been studied for the activation of non-activated olefins. Marks and co-workers developed the hydroalkylation of 3-12 by ytterbium(III) triflate to form 3-13 in ionic liquid. Ln(OTf)₃-catalyzed processes usually require toxic, highly polar, moderately
coordinating solvents, therefore the authors used a non volatile, environmentally benign imidazolium-based ionic liquid. Even though activation of non-activated olefins by a cationic metal is very practical, reaction conditions remain vigorous, with long reaction times, and high temperatures. Therefore, substitution on allylic alcohols appears to be a good alternative for the preparation of unsaturated oxygen heterocycles.

Inter- and intramolecular substitution reactions of allylic alcohols have been reported using various metal-based catalyst systems. Different mechanistic scenarios were suggested: a syn S$_{N}$2 process with Pd(II) (Figure 3-4), a π-allyl metal complex formation with Pd(0), Pt(0), Rh(I) or Ru(II), and a stabilized allyl cation with Fe(III) or Bi(III).

![Figure 3-4. Metal-catalyzed activation of allylic alcohols.](image)

Selected examples of preparation of tetrahydropyrans from mono-allylic diols are presented in Figure 3-5. Cossy and co-workers investigated the cyclization of 3-14 to form 3-15 catalyzed by 5 mol % of iron trichloride (Figure 3-5). The reaction proceeded through formation of an allyl cation intermediate and gave access to 2,6-disubstituted tetrahydropyrans in high dr. Uenishi and co-workers used palladium(II) as catalyst to perform the same transformation. Although the catalyst loading was
relatively high, the reaction proceeded under mild conditions and gave 3-17 in high yield as a single diastereomer. The enantioselective formation of 3-20 through cyclization of 3-18 has been developed by Kitamura and co-workers. They designed a new ligand 3-19 which they combined with a Trost-type ruthenium(II) catalyst \([\text{CpRu(CH}_3\text{CN)}_3]\)PF₆ to perform the extremely efficient formation of 3-20 in high yield and high ee.

![Chemical structures](image)

Figure 3-5. Selected examples of metal-catalyzed cyclization of mono-allylic diols.

Among all the metal-catalyzed strategies reported to synthesize unsaturated oxygen heterocycles, gold catalyzed hydroalkylation of allenes has proven to be highly efficient. Exo-hydrofunctionalization of allenes with oxygen nucleophiles had been reported by Widenhoefer and co-workers in 2006 (Figure 3-6). Allenes were activated under mild conditions and 3-22 was obtained in high yield with a moderate cis:trans ratio. Inspired by Echavarren and co-workers recent report, the same group developed the enantioselective cyclization of 3-23 to form 3-25 in 96% yield and 88% ee (Figure 3-6). 3-24 was identified to be the most efficient ligand for this hydroalkoxylation.
Even though allenes are very reactive unsaturated C-C bonds, they are not as practical to synthesize as unsaturated alcohols. Therefore, allylic alcohols could be used as potential surrogates giving similar outcomes.

3.1.3 Gold-Catalyzed Activation of Allylic Alcohols

Surprisingly, gold-catalyzed activation of allylic alcohol was poorly investigated before 2006. Only few reports have been published and they usually involved the formation of an allyl cation intermediate generated by gold(III) species (Figure 3-7). Subsequent nucleophilic attack formed the regioisomeric substitution products 3-27 and 3-28.

Figure 3-7. Gold(III)-catalyzed activation of allylic alcohols.
Chan and co-workers reported the Au(III)-catalyzed nucleophilic substitution of allylic alcohols with carbon nucleophiles.\textsuperscript{81} Under mildly Lewis acidic conditions, 1,3-diketones 3-29 could be added to phenyl-substituted allylic alcohols such as cinnamyl alcohol 3-30 (Figure 3-8). The same group also reported the allylic alkylation of arenes and heteroaromatics with allylic alcohols under similar conditions.\textsuperscript{82} For formation of C-N bonds, Liu and co-workers reported the Au(III)-catalyzed direct aminations of allylic alcohol 3-35 with tosylamine.\textsuperscript{83} It is noteworthy that this report contained several examples of non-aromatic allylic alcohol substrates.

More development of gold-catalyzed activation of allylic alcohols reported by our group will be discussed in detail below and in chapters 4 and 5 of this dissertation.

3.2 Au-Catalyzed Synthesis of 2-Vinyltetrahydropyrans

3.2.1 Initial Study, Optimization and Control Experiments

To prove the hypothesis that allylic alcohols could be activated under mild conditions with a gold(I) species to form 2-vinyltetrahydropyran from mono-allylic diols,
the synthesis of 3-40 was designed (Figure 3-9). Diol 3-40 was synthesized in three synthetic steps from the commercially available δ-valerolactone 3-37. The cyclization of 3-40 to synthesize 3-41 proceeded in 10 minutes at room temperature using 5 mol % of the catalyst system Ph\textsubscript{3}PAuCl/AgOTf. Unfortunately, the product is volatile, and was not fully isolated. The reaction was very fast and a full conversion was observed. Following this encouraging result, the synthesis of diols with a higher molecular weight was carried out. The preparation of 3-45 had been attempted but oxidation of 3-43 failed under various conditions (Figure 3-10).

![Diagram](image.png)

Figure 3-9. Synthesis of 3-41.

Figure 3-10. Synthesis of 3-45.

An alternate method for substrate synthesis was attempted and two different diols 3-49 and 3-51 were synthesized from 3-48 (Figure 3-11). The latter was the product of the cross metathesis of 3-47 and crotonaldehyde catalyzed by Grubbs 2\textsuperscript{nd} generation catalyst\textsuperscript{87} 3-49 and 3-51 were synthesized using one equivalent of Grignard reagent followed by deprotection of the terminal alcohol with potassium carbonate in methanol.
The hydrolysis of the ester and the addition to the aldehyde 3-48 using an excess of Grignard reagent in a one-pot process was attempted but did not give satisfactory yields.

Cyclization of 3-51 proceeded smoothly in 15 minutes using 5 mol % of catalyst and 3-52 was obtained in 91% yield. The transformation proceeded for 3-49 as well but, 3-50 was too volatile to easily be isolated and the yield quantified. Nevertheless, 3-50 has been clearly identified by $^1$H-NMR.

![Chemical reaction diagram]

Figure 3-11. Synthesis of 2-vinylTHPs 3-50 and 3-52.

A larger amount of diol 3-51 was synthesized for catalyst screening using different conditions (Figure 3-12, Table 3-1). High yields were obtained using only 1 mol % of PPh$_3$AuCl/AgOTf or 2 mol % AuCl$_3$ (Entry 1 and 4, Table 3-1). The table also shows that the cationic gold(I) complex was the active species because no conversion was observed using PPh$_3$AuCl or AgOTf separately. When 3-51 was treated in presence of a protic acid (Entry 9, Table 3-1), only 9% yield of 3-52 was isolated.
Figure 3-12. Au-catalyzed cyclization of 3-51.

Table 3-1. Optimization and control experiment.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading (mol %)</th>
<th>Time</th>
<th>Yield of 3-52 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AuCl₃</td>
<td>2</td>
<td>30 min</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>AuCl₃</td>
<td>1</td>
<td>100 min</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>PPh₃AuCl, AgOTf</td>
<td>5</td>
<td>20 min</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>PPh₃AuCl, AgOTf</td>
<td>1</td>
<td>40 min</td>
<td>96</td>
</tr>
<tr>
<td>5a</td>
<td>AuCl</td>
<td>1</td>
<td>16 h</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>PPh₃AuCl</td>
<td>5</td>
<td>16 h</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>AgOTf</td>
<td>5</td>
<td>16 h</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>AgCl</td>
<td>5</td>
<td>48 h</td>
<td>0</td>
</tr>
<tr>
<td>9b</td>
<td>TfOH</td>
<td>1</td>
<td>40 min</td>
<td>9</td>
</tr>
</tbody>
</table>

a 49% diol 3-51 recovered. b 46% diol 3-51 recovered.

3.2.2 Substrate Scope

The scope of this transformation has been investigated using the optimized conditions showed above (Entry 4, Table 3-1). Prior to exploring the functional group and substituent tolerance, 3-57 was synthesized in order to test the reaction with a different olefin geometry (Figure 3-13). 3-55 was synthesized by addition of 3-54 to cyclohexane carboxaldehyde using n-BuLi followed by hydrogenation of the propargylic alcohol and deprotection of the terminal silyl ether with hydrogen fluoride. When diol 3-57 was subjected to the standard conditions, trans product 3-52 was isolated in similar yield and similar reaction time as 3-51.
Figure 3-13. Synthesis of 3-52 from cis monoallylic diol 3-57.

Further substitution on the olefin moiety has also been investigated. Trans diol 3-60 was prepared in two steps by addition of vinyl magnesiumchloride to 3-59\(^90\) followed by cross metathesis with hex-5-en-1-ol (Figure 3-14).\(^87\) When 3-60 was treated under the standard conditions, 3-61 was obtained in 91% yield after 2.5 hours. The same substrate was used to test the lower limit of catalyst loading. Gratifyingly, 3-61 was obtained in 82% yield by treating 3-60 with only 0.1 mol % of catalyst system for 48 hours.

Figure 3-14. Synthesis of 3-61.

The influence of substituents on the 2- and 6-positions of the THP ring was then investigated. Oxidation of geraniol 3-62 to form geranial 3-63\(^91\) using standard Swern conditions gave 92% yield without isomerization of the double bond (oxidation with PCC gave 3-62 as a mixture E:Z 70:30). Addition of cyclohexylmagnesium chloride to 3-63 gave...
followed by quenching of the reaction with acetyl chloride then provided 3-64. The non-allylic double bond was selectively epoxidized with \( m \text{CPBA} \) and diol 3-66 was afforded after reduction and epoxide ring opening using an excess of \( \text{LiAlH}_4 \) at reflux in ether. Au-catalyzed cyclization of 3-66 under standard conditions provided 3-67 in 89% yield.

![Chemical reactions](image_url)

Figure 3-15. Synthesis of 3-67.

To further test the functional group compatibility of this transformation, the synthesis of a set of molecules with various groups suited for further synthetic transformations was designed. Substrates were prepared by addition of an excess of Grignard or organolithium reagents to 3-68 at -78°C (synthesis of 3-68 will be described in detail section 3.2.4.).

Cyclization reactions of 3-69 were conducted using the optimized conditions and the functional group tolerance proved to be broad with the transformations proceeding smoothly at room temperature. To our delight, 3-73 was successfully synthesized but required 5 mol % of catalyst at reflux. Interestingly, cyclization reactions to form 3-76 and 3-77 both failed. The starting materials were recovered after treating them under standard conditions or with 5 mol % of catalyst at reflux. This is probably due to the
deactivation of the \( \beta \)-hydroxyl group by hydrogen bonding to form 3-76. On the other hand, strong affinity of sulfur for gold cationic species inhibits the cyclization to obtain 3-77.

Figure 3-16. Functional group scope.

### 3.2.3 Diastereoselective Synthesis of 2,6-Disubstituted-THPs.

Dr. Chuan-Ying Li investigated the diastereoselective synthesis of 2,6-disubstituted THPs and 2,5-disubstituted THF (Figure 3-17). Compounds 3-80 to 3-84 were successfully synthesized in high yield with moderate to high diastereomeric ratio by reducing the reaction temperature to \(-50^\circ\text{C}\) or \(-78^\circ\text{C}\).
3.2.4 Scalable Preparation of 2-Vinyltetrahydropyrans

In the course of this study, a scalable preparation of 2-vinyltetrahydropyrans \textbf{3-89} through Au-catalyzed cyclization of \textbf{3-88} (Figure 3-18) was required. \textbf{3-68} was prepared by cross metathesis of \textbf{3-85} and \textbf{3-86} using only 1 mol % of Grubbs 2\textsuperscript{nd} generation catalyst.\textsuperscript{87} The reaction was first attempted using 3 mol % of catalyst and a TBDMS protected hex-5-en-1-ol \textbf{3-87}. Unfortunately, the product proved to be difficult to purify by flash chromatography due to the formation of various byproducts. This issue was overcome by reducing the catalyst loading to 1 mol % and by using free alcohol \textbf{3-85}.\textsuperscript{92} Since Grignard reagents are not particularly expensive, the unsaturated aldehyde \textbf{3-68} was treated with an excess of \textit{n}-hexyl magnesium bromide at 0°C to form \textbf{3-88} in high yield. The Au-catalyzed cyclization of \textbf{3-88} smoothly provided \textbf{3-89} in 91% yield on a 10 mmol scale with a 0.5 mol % catalyst loading. Only 25 mg of gold catalyst was used to cyclize 2.14 grams of diol \textbf{3-88}. We have never encountered any difficulty when performing this reaction; and predict that this transformation can tolerate larger scale and much lower catalyst loading.
Figure 3-18. Scalable preparation of 3-89.

3.3 Stereoselective Au-Catalyzed Synthesis of 2-VinylTHPs

3.3.1 Olefin Dependant Transfer of Chirality

_Cis_ and _trans_ allylic diols gave access to the _trans_ vinyl-THP in similar reaction times and similar yields (Figures 3-12 and 3-13). Formation of a cationic intermediate has also been ruled out (Figure 3-19) by treating 3-40 and 3-90 under the same conditions. 3-90, 3-91 and 3-92 failed to cyclize even using higher temperatures, higher catalyst loading or even using more Lewis acidic gold catalysts such as AuCl₃.

Figure 3-19. Evidence for a non-cationic mechanism.
In the previous section, we used racemic substrates and therefore, we obtained same *trans* racemic products. Since the mechanism proved to be non-cationic, we hypothesized that using enantioenriched allylic alcohols would provide non-racemic tetrahydropyrans under optimized conditions. The synthesis of chiral substrates with different olefin geometries was designed in order to understand the mechanism of this transformation and also to demonstrate that this methodology can give access to enantiorich 2-vinyltetrahydropyrans.

Aldehyde 3-97 was synthesized using the osmium-catalyzed dihydroxylation of terminal olefin 3-95 followed by cleavage of the diol using lead(IV) acetate. Enantioenriched propargyl alcohol 3-98 was prepared by enantioselective addition of the TBDMS protected hex-5-yn-1-ol to 3-97 using the method developed by Carreira and co-workers (Figure 3-20).93 Reduction of the alkyne by either hydrogen in presence of Lindlar catalyst or hydrosilylation catalyzed by ruthenium(II) catalyst,94 both followed by fluoride anion mediated deprotection, gave 3-99 and 3-101 in good yield and high ee. Enantiomers 3-100 and 3-102 were synthesized from *cis* 3-99 and *trans* 3-101 in high yield and excellent transfer of chirality with both 90% ee. These structures were designed in order to determine the absolute configuration of 3-100 and 3-102 by X-ray crystallography (with a heavy atom on the phenyl ring). Unfortunately, growing crystals from products 3-100 and 3-102 was not successful. However, HPLC analysis and optical rotation measurements showed that 3-100 and 3-102 were enantiomers.
A scalable and more practical synthesis of substrates 3-109 and 3-110 was developed (Figure 3-21). Ynone 3-107 was first synthesized by addition of 3-54 to 3-105 followed by Swern oxidation of the propargyl alcohol. Even though this method was very efficient, this process provided a small amount of impurities with 3-107, not separable by flash chromatography, and did not give acceptable yields when treated with the Noyori catalyst. Addition of the acetylide of 3-54 to Weinreb amide 3-104 gave ynone 3-107 in slightly lower yield but excellent purity suitable for the next step. Using a modified protocol of the asymmetric transfer hydrogenation with 1 mol % of Noyori catalyst (R,R-TsDPEN-Ru) 3-108 was obtained in good yield and high ee. Conventional
reductions of the triple bond to form cis and trans diols followed by deprotection of the terminal alcohols gave 3-109 and 3-110 in excellent yields and 96% ee.

Figure 3-21. Synthesis of 3-109 and 3-110.

Substrates 3-109 and 3-110 were subjected to the standard conditions (Table 3-2). They both transferred the chirality to 3-111 and 3-112 in presence of gold(I) species (Entries 1 and 2, Table 3-2) also giving enantiomers. Interestingly, reducing or increasing the temperature of the reaction led to significantly lower yields and a small loss of chirality (Entries 3 and 4, Table 3-2). A control experiment was conducted showing that the product did not epimerize in presence of a cationic gold complex (Entry 5, Table 3-2).
Table 3-2. Au-catalyzed transfer of chirality.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>ee (%)</th>
<th>Cond$^a$</th>
<th>Product</th>
<th>ee (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-109</td>
<td>96</td>
<td>40 min rt</td>
<td>3-111</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>3-110</td>
<td>96</td>
<td>35 min rt</td>
<td>3-112</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>3-109</td>
<td>96</td>
<td>100 min 0°C</td>
<td>3-111</td>
<td>87</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>3-109</td>
<td>96</td>
<td>10 min reflux</td>
<td>3-111</td>
<td>87</td>
<td>60</td>
</tr>
<tr>
<td>5$^a$</td>
<td>3-111</td>
<td>93</td>
<td>60 min rt</td>
<td>3-111</td>
<td>93</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$ 1 mol % Ph$_3$PAuC/AgOTf, CH$_2$Cl$_2$, MS 4Å.

The absolute configuration of 3-111 and 3-112 were determined by comparing optical rotations of known derivatives (Figure 3-22). 3-111 and 3-112 both were treated with ozone and the reaction was quenched with NaBH$_4$ to reduce the ozonides to form alcohols 3-113 and 3-114.

![Chemical structure](image)

Figure 3-22. Absolute configuration of 3-111 and 3-112.

The scope of the reaction was expanded to more complex chiral structures sharing similar skeletons with naturally occurring molecules. Following the same synthetic
strategies described above in this section (3-115 was synthesized in three synthetic step from aminoethanol),\textsuperscript{98} enantioenriched morpholines 3-120 and 3-121 were synthesized in high yield from 3-118 and 3-119 (Figure 3-23). The Au-catalyzed cyclization proceeded smoothly even in presence of a tosyl-protected nitrogen in the allylic position.

Figure 3-23. Synthesis of morpholines 3-120 and 3-121.

The absolute configuration of 3-120 was determined by comparing optical rotation of the known derivative 3-122, obtained after reductive ozonolysis, mesylation and reduction with LiAlH₄, to the literature value (Figure 3-24).\textsuperscript{99}

Figure 3-24. Absolute configuration of 3-120.

Phenols have also been investigated as nucleophiles (Figure 3-25). Alkyne 3-126\textsuperscript{100} was synthesized by protection of 3-123 followed by hydroboration of the olefin,
oxidation of the alcohol followed by Corey-Fuchs alkylation of the aldehyde 3-125.

Following the same strategy as described above, 3-128 and 3-130 were obtained in high yields and 97% ee. When these substrates were exposed to the reaction conditions, chirality transfer was observed but with a substantial loss of ee. The absolute configuration of the products was also consistent with the previously shown examples (Figure 3-26).\textsuperscript{101}

Figure 3-25. Synthesis of 3-129 and 3-131.
Figure 3-26. Absolute configuration of **3-129** and **3-133**.

Enantioenriched methylene tetrahydropyrans have been successfully synthesized (Figure 3-27). Starting from inexpensive starting materials, propargylic alcohol **3-142** was synthesized by a copper-catalyzed coupling reaction between **3-136** and **3-141** in 96% yield. **3-136** is the product of the allylic chlorination of TBDMS-protected alcohol **3-134**. Propargyl alcohol **3-141** has been prepared by elimination of **3-140** using an excess of LDA.

**3-143** and **3-145** were obtained following standard procedures described above in this section in high yield and high ee (Figure 3-28). The Au-catalyzed cyclization of these two substrates proceeded smoothly and gave **3-144** and **3-146** in high yields and excellent ee via chirality transfer.
Figure 3-27. Synthesis of propargyl alcohol 3-142.

Figure 3-28. Synthesis of 3-144 and 3-146.
3.3.2 Additional Stereocenters Influence

The influence of additional stereocenters on positions 4 and 6 of the tetrahydropryan ring has also been studied. In theory, our method should give access to two different diastereomers depending on the olefin geometry, but having another stereocenter on the substrate might also alter the transfer of chirality. To study this influence, the synthesis of 3-154 and 3-156 was first investigated (Figure 3-28). Ring opening of the chiral epoxide 3-149 followed by removal of the TMS group and benzylation of the homopropargylic alcohol gave 3-150 in 40% yield. The ynone formed by addition of 3-150 to Weinreb amide 3-151 was subjected to the modified protocol of Noyori transfer hydrogenation to give 3-152 in 71% yield. Reduction of the alkynes and deprotection of the terminal alcohols gave 3-153 and 3-155 (dr was determined by Mosher ester analysis) which were treated under the optimized conditions to afford the two diastereomers 3-154 and 3-156 in high yields and diastereoselectivity with excellent chirality transfer. The dr of the products 3-154 and 3-156 was determined by $^1$H-NMR.

2,6-Disubstituted morpholines with a stereocenter in 6-position (Figure 3-29) were also synthesized. 3-159 was prepared by ring opening of epoxide 3-158, protection of the resulting alcohol and propargylation of the N-tosylamide. 3-160 was obtained in only 20% yield, due to the presence of the sulfonamide in the propargylic position. The asymmetric Noyori transfer hydrogenation of an ynone containing a N-sulfonamide in propargylic position has never been reported to date. 3-162 and 3-164 (dr was determined by Mosher ester analysis) were then synthesized following standard procedures in 93:7 dr and both cyclized to form 3-163 and 3-165 with high transfer of
chirality and good yields. The dr of the products 3-163 and 3-165 was determined by $^1$H-NMR.

Figure 3-28. Synthesis of 3-154 and 3-156.
Figure 3-29. Synthesis of 3-163 and 3-165.

Gratifyingly, in presence of additional stereocenters, this method proved to be highly efficient and gave access to two diastereomers starting from a common propargylic alcohol.

3.3.3 Failed Attempts

Several substrates did not give satisfactory results under the optimized conditions (Figure 3-30). Those substrates have been synthesized following similar procedures developed in this chapter. 3-166 fully reacted after 2 h but did not give the expected product. Unfortunately, no material was recovered after work-up. Dioxolane 3-168 and benzodioxolane 3-170 failed to react even using a higher catalyst loading and longer reaction time. This can be explained by hydrogen-bonding between the two hydroxyl
groups. It appears likely that the terminal alcohol hydrogen bonds with the central ethereal oxygen and not with the allylic alcohol.

Figure 3-30. Failed attempts.

In the course of the initial study of chirality transfer, the synthesis of \(3-173\) was undertaken (Figure 3-31). Surprisingly, while \(3-172\) easily converted to \(3-173\) in high yield and 95% ee, \(3-174\) failed to cyclize and a trityl-shift to the primary alcohol was observed. It seems that a substrate containing a tertiary carbon next to the \(trans\) allylic alcohol will fail to cyclize under the optimized conditions. Experiments shown Figure 3-31 also suggested that \(cis\) allylic alcohols are more reactive substrates than \(trans\) allylic alcohols in presence of gold(I) species. To support these statements, \(3-177\) and \(3-179\) were synthesized and also both failed to provide the desired products (Figure 3-32).
3.3.4 Predictive Stereochemical Mnemonic

Analysis of the stereochemical outcome of the reaction should help to gain an understanding of how the allylic alcohol influences the $\pi$-facial discrimination. From these data, it was shown that the nucleophile added to the olefin in a syn manner to the hydroxyl group. This mnemonic shown in Figure 3-30 has proven to be a reliable stereochemical predictor for this transformation that provided both enantiomeric and diastereomeric products.
3.3.5 Proposed Catalytic Cycle

With these studies, it has demonstrated that gold-catalyzed cyclization reactions of mono-allylic diols exhibit a large functional group tolerance and a high degree of π-facial selectivity. The desired tetrahydropyran enantiomer and diastereomer can be easily synthesized from chiral allylic alcohols based on olefin geometry.

A mechanistic study has also been undertaken to understand the high reactivity and selectivity observed with allylic alcohol substrates. This dehydrative transformation
gave products resulting from a formal syn S_{\text{N}2}' mechanism (Figure 3-32). It is proposed that the Au-complex first activates the π-bond of 3-185 to form π-complex 3-186, followed by anti addition of the pendant nucleophilic alcohol. This attack could be facilitated by hydrogen bonding with the alcohol (3-187). Loss of water by anti-elimination then forms 3-189 and regenerates the active catalyst.

Our group is currently exploring the mechanism of this reaction with more details. We are studying especially the position of the gold towards the π-bond as well as the importance of the hydrogen-bonding between the two alcohols.

3.4 Au-Catalyzed Cyclization of Mono-Allylic Ethers to Form 2-Vinyltetrahydropyrans, a Comparative Study

3.4.1 Initial Approach

We strongly believed that the method shown above would be highly suitable for the preparation of chiral natural molecules containing tetrahydropyran motifs. In the course of the application of this methodology to the synthesis of the Spirastrellolide A,\textsuperscript{109} the synthesis of 2,6-disubstituted THP 3-191 was designed. Unfortunately, difficulties were encountered due to the protecting group scheme.

Partial retrosynthesis of 3-190 (Figure 3-35) shows that a scalable and enantioselective synthesis of 3-191 was required to further attach this THP to the other fragments of the molecule. The first approach was to prepare 3-191 from an aldol reaction\textsuperscript{110} mediated by titanium chloride with 3-195\textsuperscript{111} using the Evan’s auxiliary 3-194 as the source of chirality, followed by removal of the TBDMS group (figure 3-36). However, cleavage of the silyl ether 3-196 using TBAF or acidic conditions lead to the elimination of the β-hydroxy acetylazolidinone 3-197. Various temperatures and reaction conditions were examined but did not give satisfactory results.
One potential solution to this problem is to use a different leaving group. The same transformation was attempted but a methyl ether instead of the free allylic hydroxyl group. Aldol reaction gave the enantiopure alcohol 3-199 in moderate yield, which was treated with 5 mol % catalyst at 0°C. To our delight, the expected product 3-200 was obtained as a single diastereomer in 89% yield. It appears that other groups can eliminate during this transformation and also that the reaction was perfectly
diastereoselective. In comparison, Dr. Chuan-Yang Li showed that low temperatures (-50 or -78°C) were required in order to obtain a dr up to 12:1 starting from mono-allylic diols.\textsuperscript{33a}

![Chemical structure](image.png)

Figure 3-37. Efficient synthesis of 3-200.

### 3.4.2 Synthetic Aspect

Although the features of Au-catalyzed cyclization of mono-allylic diol are attractive from a synthetic point of view, the disadvantage is that both the nucleophile and the electrophile are alcohols (Figure 3-38). Having two unprotected non-eqivalent alcohols on the same molecule might involve a complex protection/deprotection scheme. The problem would be partially solved if the electrophilic alcohol was protected with a group that would tolerate a large panel of reaction conditions and that would not need to be removed before the Au-catalyzed cyclization. This lead us to expand the method to the elimination of other leaving groups, which can be used as protecting group if needed.

Since alcohols are considered very poor leaving groups, but perform extremely well in this system, it seemed likely that a fairly robust group could perform satisfactorily here. As part of a shared project with Thomas Ghebreghiorgis, the relative speed of reaction using different types of leaving groups on the allylic moiety was studied. First, we faced several challenging practical aspects. Since the reaction proved to be very
fast, a continuous analytical method was necessary. The monitoring of the reaction by GC analysis using \( n \)-decane as an internal standard was explored. Also, it was observed that reproducible results could not be obtained when using the catalyst system \( \text{Ph}_3\text{PAuCl/AgOTf} \). Therefore, the use of the “Echavarren catalyst”: \((\text{MeCN})\text{Au}[\text{P(t-Bu)}_2(\text{o-biphenyl})]\text{SbF}_6 \) emerged as a better alternative. This catalyst has the advantages of higher molecular weight and the catalyst is already activated.

![Chemical structure](image)

**Figure 3-38. Allylic alcohol purpose.**

The reaction proved to be very fast and our initial studies showed that the reaction proceeded even after high dilution of the reaction mixture for GC analysis. In a typical experiment, the reaction is generally filtered through a short plug of silica, but for small aliquots (25 \( \mu \)L), it was not practical. To address this problem, the use of a metal scavenging reagent was explored to stop the reaction. To the best of our knowledge, the use of resin bound scavenging agents in homogeneous gold catalysis has never been reported in the literature and needed to be validated.

### 3.4.3 Validation of Au-Catalyst Quenching Method Using QuadraPure™

To determine if this method would be reliable, a validation experiment was performed. 3-40 was treated with 5 mol % of 1-5 and the reaction quenched with QuadraPure™ MPA beads 3-201 after 1, 3 and 5 minutes (Figure 3-39 and 3-40). As a control experiment, a 25 \( \mu \)L sample taken after 3 minutes was diluted in 400 \( \mu \)L of
CH$_2$Cl$_2$ but was not exposed to the resin. After 16 hours, this aliquot showed a 95% conversion showing that 3-201 is necessary to stop the reaction.

![Reaction Scheme](image)

Figure 3-39. QuadraPure™ MPA 3-201.

![Conversion Graph](image)

Figure 3-40. Quenching experiment using 3-201.

The reproducibility of the analysis needs to be mentioned. At several points in the experiment showed above (Figure 3-40), the analysis has been done five times with the same sample. For each set of data, an error of 2% in average was obtained with a standard deviation of 0.92%.

This experiment validated the method to study the relative speed of reaction between different substrates and showed that the analytic method is reliable (Figure 3-41).
Figure 3-41. Illustrated protocol for monitoring the conversion of 3-40.

3.4.4 Comparison of Different Leaving/Protecting Groups

Several commonly used protecting groups have been screened under the optimized conditions. The synthesis of compounds 3-204 - 3-208 was performed by reduction of propargyl alcohol 3-202 to form trans allylic alcohol 3-203\textsuperscript{112} (Figure 3-42). The latter was protected on the allylic moiety followed by the deprotection of the terminal non-allylic alcohol with PPTS in methanol or TBAF.

Figure 3-42. Synthesis of 3-204-3-208.

Cyclizations of protected allylic alcohols have been achieved using 5 mol % catalyst at rt. The reactions were monitored by GC analysis and the conversions of each substrates are reported Figure 3-43. From the graph, it was shown that Me, Bn, TBDPS
and THP groups could be suitable for this transformation (Figure 3-43). However, the allyl ester 3-208 cyclized very slowly. This method could provide a good alternative synthetic strategy to the Pd(0) activation of allyl esters to form π-allylpalladium complexes\textsuperscript{113} since this transformation is chemoselective for acetals (3-207) and ethers.

3-208 failed to cyclize due to the hydrogen bonding involved between the hydroxyl group and the ester moiety. The proposed mechanism (Figure 3-34) shows that the addition on the π-bond is facilitated by the hydrogen bonding. When 3-208 is used as substrate, the oxygen from the ester doing the hydrogen bonding is less rich in electrons than an ethereal oxygen. Therefore, Au-catalyzed addition of the alcohol to the olefin is slower (Figure 3-43)

![Figure 3-43. Screening of commonly used protecting groups.](image-url)
After studying the different leaving groups, it was also important to investigate the tunability of the olefin. Depending on the synthetic strategy, two different types of olefins could be obtained; it was then important to compare their behavior under the same reaction conditions.

### 3.4.5 Influence of Olefin Geometry and Substituent on the Allyl Moiety

The rate of the reaction with different olefin geometries of substrates **3-40** and **3-209** were compared. Both molecules cyclized very rapidly in similar times and percent conversions (Figure 3-44). **3-209** proceeded slightly faster but **3-40** gave a higher conversion.

![Chemical structures](image)

Conditions: 5 mol % Au[P(t-Bu)_2(o-biphenyl)]SbF_6, CH_2Cl_2, MS 4 Å.

![Graph](image)

Figure 3-44. Reaction progress in cis- and trans-diols.

The conversions of cis- and trans-methyl ethers **3-204** and **3-210** to form **3-41** under standard conditions has also been explored. This experiment showed that the
cyclization proceeded extremely well with methyl ethers with almost no noticeable difference between both substrates 3-204 (89% conversion) and 3-210 (93% conversion). Methyl ethers proved to be suitable for this transformation and could be used in a complex synthetic scheme. They have the advantage of being resistant to a large variety of reaction conditions.

![Diagram](image)

Conditions: 5 mol % 1-5, CH₂Cl₂, MS 4Å.

Figure 3-45. Reaction progress in cis- and trans-methyl ethers.

Finally, the effect of a substituent on the allylic alcohol has been explored. Primary ethers 3-204 and 3-210, and secondary ethers 3-211 and 3-212 were compared under the standard conditions (Figure 3-46). This set of experiments showed that secondary allyl ethers 3-211 and 3-212 slowly converted to 3-52. However, acceptable yields were
obtained if the reaction is run for 48 hours. Also, it appeared that cis-ethers 3-210 and 3-212 reacted slightly faster than the trans-ethers 3-204 and 3-211.

\[
\begin{align*}
\text{OH} & \quad \text{OMe} \\
\text{R} = \text{H} & \quad \text{3-204} \\
\text{R} = \text{Cy} & \quad \text{3-211} \\
\text{vs} & \\
\text{OH} & \quad \text{OMe} \\
\text{R} = \text{H} & \quad \text{3-210} \\
\text{R} = \text{Cy} & \quad \text{3-212} \\
\text{Std.} & \\
\text{Cond.:} & \\
& \quad \text{3-41} \\
& \quad \text{3-52}
\end{align*}
\]

Conditions: 5 mol % 1-5, CH₂Cl₂, MS 4 Å.

Figure 3-46. Comparison of 1° and 2° allylic ethers.

3.5 Outcome and Current Work

Gold-catalyzed dehydrative transformations is a growing field of investigation with many new avenues to be explored. The initial studies demonstrated that the gold-catalyzed exo-cyclization of monoallylic diols to form 2-vinyltetrahydropyrans occurs in high yield; has a large functional group tolerance; and exhibits a high degree of π-facial selectivity. The reaction scope has been extended to a large variety of leaving groups on the allylic moiety. We believe that having the choice of different
protecting groups on the allylic alcohols for the Au-cyclization is a very useful tool that warrants further exploration in a synthetic project.

Even though the chirality transfer study provided several evidence about the mechanism of the reaction; further investigation needs to be conducted to rule out any other type of potential mechanism such as a syn addition/syn elimination. To explore the reaction mechanism, Thomas Ghebreghiorgis and I are studying the relative position of the gold species on the olefin.

Compounds 3-213, 3-214 and 3-215 were designed to show that the activation of the olefin proceeds in an anti manner and rule out a potential syn-addition of the hydroxyl group to the metal (Figure 3-47). Thomas Ghebreghiorgis first showed that the reaction did not proceed when both allylic and non allylic alcohols were on opposite side and that no hydrogen-bonding was possible between them (Figure 3-47). It shows that the reaction was an anti-addition, indeed the concave structure of 3-214 does not give much room to the gold species to complex on the opposite side of the pendant non-allylic alcohol and therefore drastically slowed the reaction down. On the other hand, if the reaction was proceeding as a syn-addition, the transformation should be favored and proceeded more rapidly. 3-216 was isolated in 83% yield after 24 hours using 5 mol % of catalyst. The last experiment performed was to treat 3-215 under the standard conditions (Figure 3-47). With this substrate, the nucleophilic attack comes from inside the concavity of 3-215 allowing for H-bonding. In theory, complexation of gold should favor the reaction and syn-addition would be unfavored due to the difficult access to the internal position. The reaction proceeded extremely fast with only 1 mol % of catalyst and 3-217 was isolated in 96% yield. This set of experiments, shown Figure
3-47, is consistent with an anti-addition of the pendant non allylic alcohol to the gold-olefin complex. Moreover, Thomas Ghebreghiorgis demonstrated that hydrogen-bonding is necessary for the reaction to proceed.

![Diagrams showing the reaction process with structural formulas and expected results.](image)

Figure 3-47. Evidence for a Au-catalyzed anti-addition.

Further studies are on-going in our laboratory in collaboration with Professor Daniel H. Ess, a computational chemist at Brigham Young University.
CHAPTER 4
AU-CATALYZED CYCLIZATION OF O-(1-HYDROXYALLYL)-PHENOLS TO FORM
2H-CHROMENES

4.1 Background and Significance

4.1.1 2H-Chromenes in Biological Active Pharmaceuticals

The 2H-chromene structural motif is an important core structure found in many different biologically active molecules (Figure 4-1).\textsuperscript{114} Examples include numerous types of pharmaceutical, fungicidal, and insecticidal agents.

![Figure 4-1. 2H- and 4H-chromenes.](image)

Selected examples of biologically active 2H-chromenes are shown Figure 4-2. They include anti-HIV agent 4-3,\textsuperscript{115} anti-tumor drug Acronycine 4-4,\textsuperscript{116} anti-oxidant vitamin K$_1$ 4-5,\textsuperscript{117} and antibiotic Iclaprim 4-6.\textsuperscript{118} The latter is currently on phase II of clinical trials for treatment of nosocomial infections. Antifungal and insecticidal activity was also reported for 2H-chromenes. Selected examples are shown Figure 4-2 for 4-7\textsuperscript{119} and 4-8.\textsuperscript{120}

Although 2H-chromenes are important in a variety of fields, their preparation remains a challenge and synthetic methods are often limited to specific substrates. For these reasons, more general methods need to be developed to have fast and efficient access to a wide variety of these highly useful compounds.
4.1.2 Classical Methods of $2\text{H}$-Chromenes Synthesis, Scope and Limitations

Efficient classical methods have been reported for the synthesis of $2\text{H}$-chromenes. They have proven to be highly reliable for the preparation of simple molecules (Figure 4-3). A brief description of each of these types of reactions follows.

Figure 4-2. Selected examples of $2\text{H}$-chromenes in pharmaceuticals.

Figure 4-3. Summary of $2\text{H}$-chromenes synthesis classical methods.
2H-chromenes can be easily synthesized by addition of α,β-unsaturated carbonyl 4-14 to salicylaldehyde 4-13. Kay and co-workers reported the synthesis of 3-ketochromenes 4-16 by an intermolecular Baylis-Hillman reaction followed by Michael addition and subsequent elimination (Figure 4-4).\textsuperscript{121,122} This method is extremely practical and easy to scale up, however, reaction times are long and this transformation is limited to a narrow substrate scope. A Petasis condensation has been reported by Finn and co-workers to synthesize substituted 2H-chromenes (Figure 4-4).\textsuperscript{123} This reaction gave 4-20 in high yield through coordination of the phenolate to the boronic acid 4-17 and addition to the iminium ion followed by S\textsubscript{N}2' cyclization. This reaction appears to be limited to benzaldehydes as no examples has been reported with ketone substrates.

![Figure 4-4](image)

Figure 4-4. Synthesis of 2H-chromenes by addition to the benzaldehyde.

Electrophilic aromatic substitution is a very efficient way to synthesize chromenes. Larock and co-workers reported the alkyne activation by iodide to synthesize 4-aryl chromenes (Figure 4-5).\textsuperscript{124} Compound 4-23 was obtained in 77% yield from 4-21 using 2 equivalents of iodine at room temperature. This method is also very reliable but all the
reported examples contain an aryl group on the alkyne moiety and gave low yields with electron withdrawing groups on the phenol ring. A more conventional protocol has been reported by Nichols and co-workers (Figure 4-5). They synthesized 4-27 from 4-24 in three synthetic steps. Triflate 4-25 was obtained by treating carboxylic acid 4-24 with thionyl chloride under Friedel-Crafts conditions followed by formation of the enolate with NaHMDS and trapping with (TfO)_2NPh. Pd(0)-catalyzed coupling of 4-26 and 4-25 gave 4-27 in 77% yield. This method required three synthetic steps but could give access to a large variety of 2H-chromenes.

![Chemical structure 1](image1)

![Chemical structure 2](image2)

**Figure 4-5.** Synthesis of 2H-chromenes through aromatic nucleophilic substitutions.

One of the most common ways to synthesize 2,2-dimethylchromenes is by oxidative pyranocyclization. Use of this method has been well documented and an example is shown Figure 4-6. As can be seen, 4-30 was readily prepared from 4-28 in 81% yield using one equivalent of DDQ in benzene at reflux. This method is limited to the synthesis of 2,2-disubstituted chromenes.
Figure 4-6. Oxidative pyranocyclization.

4.1.3 Modern Metal-Catalyzed Synthesis of 2H-Chromenes

More recent developments have been reported over the past 10 years using transition metal catalysts. These transformations usually occur under mild conditions and exhibit a larger substrate scope with a high chemoselectivity. Transition metal-catalyzed hydroarylation reactions have been extensively employed to synthesize 2H-chromenes (Figure 4-7).

Figure 4-7. Metal-catalyzed electrophilic aromatic substitutions.

Youn and co-workers reported the Pd(II)-catalyzed oxidative cyclization of ether 4-33 to form 2H-chromene 4-34 (Figure 4-8).\(^{128}\) The reaction proceeded in good yield at room temperature in dioxane using one equivalent of oxidizing agent (benzoquinone). Ohno and co-workers successfully activated allenes with a gold(I) species to form benzopyrans (Figure 4-8).\(^{129}\) Compound 4-35 was obtained from 4-36 using 1 mol % of catalyst in dioxane at 60°C for 1 hour. In 2003, Echavarren and co-workers investigated the reaction of alkynes with electron rich arenes catalyzed by Pt(II) (Figure 4-8).\(^{130}\) Product 4-38 can be easily prepared from 4-37 using only 1 mol % of catalyst.
The reactions presented above all required electron rich arenes in order to facilitate the electrophilic aromatic substitution. Low or moderate yields were obtained with neutral or electron-poor aromatic rings. However, reaction conditions were mild and allowed for low catalyst loadings.

Figure 4-8. Selected examples of metal-catalyzed hydroarylation.

Other modern methods have been investigated. Among these, the Ru-catalyzed ring closing metathesis of dienes to form 2H-chromenes is a practical and versatile transformation (Figure 4-9). Compound 4-39 was treated with 2 mol % of Grubbs 2nd generation catalyst at room temperature and gave 4-40 in 97% yield. This method tolerates a large variety of functional groups on the phenyl moiety but an additional substitution on the diene requires much higher catalyst loadings and temperatures. Additionally, styrenes are not always the most stable substituents. Jana and co-workers recently reported the FeCl₃-catalyzed intramolecular alkyne/carbonyl metathesis of 4-41 to form 4-43 (Figure 4-9). The reaction proceeded using 15 mol % of catalyst in good yield. The substrates are easily synthesized from salicylaldehyde derivatives and the
catalyst used is inexpensive. However, this transformation does not tolerate any substitution at the 2- and 4-positions of the 2H-chromene.

![Chemical reaction diagram]

Figure 4-9. Other selected modern examples of 2H-chromenes synthesis.

### 4.2 Rationale

A large panel of interesting methodologies has been reported for the synthesis of 2H-chromenes but a more general and reliable methodology has remained elusive. In an ideal synthesis, the new method should tolerate a large variety of functional groups and substitution while also allowing for substrates originating from easily accessible and inexpensive starting materials. In the course of the study of Au-catalyzed conversion of mono-allylic diols to form tetrahydropyrans,\(^ {33}\) the endo-cyclization was investigated (Figure 4-10). Unsuccessful results were obtained with aliphatic alcohols 4-44a and 4-44b but we were interested in the behavior of a benzylic allylic alcohol under the same optimized conditions. Additionally, we hypothesized that the conformational constraint of 4-46 may favor the cyclization to form 4-1.
4.3 Optimization of Reaction Conditions

To test this hypothesis, 4-47 was prepared from the corresponding benzealdehydes and treated with Au-complexes. A variety of conditions were screened for the dehydrative cyllization of 2-(1-hydroxyallyl)phenol 4-47 to form 2H-chromene 4-48 (Figure 4-11 and Table 4-1). For reactions using dichloromethane as solvent, only decomposition products were observed (Entries 1-4, Table 4-1). More coordinating solvents such as THF, Dioxane or MeCN proved to be better alternatives for this reaction. Gratifyingly, the highest yield was obtained using 5 mol % of catalyst 1-3 and AgOTf in THF at reflux (Entry 9, Table 4-1). Surprisingly, the reaction required heating and no conversion was observed at room temperature. A control experiment was conducted with 5 mol % of AgOTf but no conversion was observed, demonstrating that both the Au- and Ag-complex are required for the reaction (Entry 15, Table 4-1).
Figure 4-11. Au-catalyzed cyclization of 3-52.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Cat (mol %)</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph3PAuCl/AgOTf (5)</td>
<td>CH2Cl2</td>
<td>30 min</td>
<td>rt</td>
<td>Decomp</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>AuCl3 (2)</td>
<td>CH2Cl2</td>
<td>10 min</td>
<td>rt</td>
<td>Decomp</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>AuCl/AgOTf (2)</td>
<td>CH2Cl2</td>
<td>30 min</td>
<td>rt</td>
<td>Decomp</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>1-3/AgOTf</td>
<td>CH2Cl2</td>
<td>20 min</td>
<td>rt</td>
<td>Decomp</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Ph3PAuCl/AgOTf</td>
<td>THF</td>
<td>16 h</td>
<td>rt</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>Ph3PAuCl/AgOTf</td>
<td>THF</td>
<td>16 h</td>
<td>66°C</td>
<td>21</td>
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<tr>
<td>7</td>
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<td>1-3/AgOTf (5)</td>
<td>THF</td>
<td>16 h</td>
<td>rt</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>1-3/AgOTf (5)</td>
<td>MeCN</td>
<td>16 h</td>
<td>82°C</td>
<td>42</td>
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<tr>
<td>9</td>
<td>H</td>
<td>1-3/AgOTf (5)</td>
<td>THF</td>
<td>5 h</td>
<td>66°C</td>
<td>82</td>
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<tr>
<td>10</td>
<td>H</td>
<td>1-3/AgOTf (5)</td>
<td>Dioxane</td>
<td>1 h</td>
<td>101°C</td>
<td>55</td>
</tr>
<tr>
<td>11</td>
<td>H</td>
<td>4-49 (5)</td>
<td>THF</td>
<td>4 h</td>
<td>66°C</td>
<td>Decomp</td>
</tr>
<tr>
<td>12</td>
<td>Cl</td>
<td>1-3/AgOTf (5)</td>
<td>Toluene</td>
<td>1 h</td>
<td>0°C</td>
<td>NR</td>
</tr>
<tr>
<td>13</td>
<td>Cl</td>
<td>1-3/AgOTf (5)</td>
<td>Toluene</td>
<td>20 min</td>
<td>rt</td>
<td>Decomp</td>
</tr>
<tr>
<td>14</td>
<td>Cl</td>
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<td>Toluene</td>
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<td>111°C</td>
<td>Decomp</td>
</tr>
<tr>
<td>15</td>
<td>Cl</td>
<td>AgOTf (5)</td>
<td>THF</td>
<td>16 h</td>
<td>66°C</td>
<td>NR</td>
</tr>
</tbody>
</table>

a The reactions were carried out on a 0.5 mmol scale at 0.2 M in substrate with the indicated solvent, temperature, and time. b Isolated yields.

Several additional Lewis acids such as BF3·OEt2, Zn(OTf)2, InBr3, Yb(OTf)3, FeCl3, and Pd(OAc)2 were also screened, but in all cases only trace amount of product were observed accompanied by extensive decomposition.

### 4.4 Substrate Scope

Using the optimized conditions, the substrate scope of this transformation was explored, with emphasis on the electronic nature of the benzene ring. All substrates contain a phenolic hydroxyl group ortho to the allylic alcohol. Substrates 4-51 were synthesized by addition of an excess of Grignard reagent to salicylaldehyde derivatives 4-50 (Figure 4-12). These substrates proved to be fairly reactive and the best results
were obtained when they are quickly purified by flash chromatography and immediately subjected to the Au-catalyzed cyclization conditions.

![Scheme](image)

Figure 4-12. Preparation of substrates.

The electronics of the group para to the nucleophilic hydroxyl group was first varied. The reaction proceeded in a similar fashion when the \( p \)-hydrogen was replaced with a methoxy group (Entry 1, Table 4-2). Addition of an activating group on the phenyl moiety might facilitate the formation of a carbocation and does not alter the yields or reaction times. Inclusion of the dioxolane moiety, however, failed to cyclize and gave a fast decomposition of 4-62 after one hour (Entry 7, Table 4-2). These results imply that the formation of a stabilized carbocation is not suitable for this transformation. The yield was higher and the reaction time shortened with a \( p \)-nitro substituent (Entry 2, Table 4-2). This reaction was observed to be smoother and can be conducted at room temperature giving 79% yield after 48 hours (Entry 3, Table 4-2). In this case, having a deactivating group on the benzene ring makes the substrate more stable under Lewis acidic conditions and the cyclization proceeds more easily. When 4-56 was treated under the optimized conditions, the reaction time was shortened and gave 75% yield. Deactivating substituents on the benzene ring increase the acidity of the phenol and therefore facilitate the addition to the olefin. The same trend was observed with other benzenoid substrates and substituted naphthol also reacted cleanly (Entries 4-6 and 8, Table 4-2).
Table 4-2. Reaction scope.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="#" alt="Structure 4-52" /></td>
<td><img src="#" alt="Structure 4-53" /></td>
<td>20</td>
<td>74</td>
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<tr>
<td>2</td>
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<td><img src="#" alt="Structure 4-55" /></td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td><img src="#" alt="Structure 4-56" /></td>
<td><img src="#" alt="Structure 4-57" /></td>
<td>48(^b)</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td><img src="#" alt="Structure 4-58" /></td>
<td><img src="#" alt="Structure 4-59" /></td>
<td>0.3</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td><img src="#" alt="Structure 4-60" /></td>
<td><img src="#" alt="Structure 4-61" /></td>
<td>20</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td><img src="#" alt="Structure 4-62" /></td>
<td><img src="#" alt="Structure 4-63" /></td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>7</td>
<td><img src="#" alt="Structure 4-64" /></td>
<td><img src="#" alt="Structure 4-65" /></td>
<td>1</td>
<td>Decomp</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields. \(^b\) Reaction performed at room temperature.

4.5 Substituent Effects on the Allyl Moiety

As can be seen in Table 4-2, the functional group tolerance on the aryl moiety seemed to be quite broad in this transformation. The next step of the investigation was
to study the substitution on the allyl moiety. To this end, substrates 4-68 were prepared by addition of an excess of the corresponding Grignard reagent to 5-chlorosalicylaldehyde 4-66 or 5-chloro-2-hydroxyacetophene 4-67 (Figure 4-13).

Figure 4-13. Synthesis of substrates 4-68.

Using this method, a methyl group was systematically included on each position in the substrates and the effect on the Au-catalyzed cyclization was studied. Methyl substitution in position 2 of the 2H-chromene does not affect the yield or reaction time (Figure 4-14). An increased in the reaction rate was observed when tertiary allylic alcohol 4-73 was treated under the standard conditions and gave similar yield (Figure
This rate acceleration can be due to the Thorpe-Ingold effect having geminal substituents in allylic position. Also, the elimination step could proceed faster because a tertiary alcohol should be easier to eliminate than a secondary or primary alcohol.

Surprisingly, **4-76** was obtained only in trace amounts, even after 48 hours, with the majority of the starting diol **4-75** recovered. It is likely that substitution at this position is difficult because alkoxymetalation would form a 3° alkyl-gold intermediate (Figure 4-14).

Geminal dimethyl groups in position of 2 of 2H-chromenes are commonly found in natural products.\(^ {114}\) The formation of **4-80** through cyclization of **4-78** using the optimized conditions (Figure 4-15) was explored. Unfortunately, purification by flash chromatography of **4-78** produced the allylic alcohol **4-79** which failed to cyclize under the standard conditions.\(^ {133}\) To solve this isomerization problem, it was decided to use the crude material of **4-78** for the Au-catalyzed endo cyclization. Gratifyingly, **4-80** was obtained in 73% yield over two steps.

The nature of the different substituents on the allylic region appeared to have a large impact on the reactivity of this transformation. The type of substituent on the benzylic alcohol is also important because it may control the elimination step. Therefore, a broader substituent scope on the allylic moiety was investigated.
4.6 A Convenient Synthesis of Neoflavenes

4.6.1 Neoflavenes

Neoflavenes, also called 4-phenyl-2H-chromenes were originally isolated from a natural source. It is one of the five main structural types found in the neoflavonoid derivatives (Figure 4-16).\textsuperscript{134} Attention to their biological action appeared relatively late and their activity remains limited. However, neoflavenes are extremely important intermediates for the synthesis of more complex structures (Figure 4-17) such as Haematoxylin 4-83\textsuperscript{135} (stain used in microbiology) or Procyanidin B\textsubscript{2} 4-84\textsuperscript{136} (promotes hair growth).\textsuperscript{137}
Figure 4-17. Selected examples of natural products from the neoflavonoid family.

Several synthetic methods have been developed to prepare neoflavenes. Suzuki cross coupling (Figure 4-18)\textsuperscript{138} and ring closing metathesis (Figure 4-18)\textsuperscript{139} gave good yields but the scope of the reaction is limited to electron-rich arenes. In addition, the synthesis of 4-87 required five synthetic steps. An alternative method relies on electrophilic aromatic substitution by metal activation of an alkyne (Figure 4-18),\textsuperscript{140,141} however, selectivity between 4-90 and 4-91 is moderate.

M = Hg(II), Pt(IV)

Figure 4-18. Metal-catalyzed synthesis of Neoflavenes.
4.6.2 Au-Catalyzed Synthesis of Neoflavenes

Using the same methodology described in Chapter 4 of this dissertation; a convenient synthesis of neoflavenes starting from inexpensive starting materials was developed. Substrates were synthesized in two steps from salicylaldehyde 4-13 by palladium-catalyzed coupling with iodobenzene derivatives\textsuperscript{142} followed by addition of vinyl magnesium bromide to ketone 4-93 at low temperature (Figure 4-19).

Substrates 4-94 were treated under the previously optimized conditions (Figure 4-20), and 4-95 was obtained in excellent yield after a brief reaction time. Elimination step is facilitated by having an electron donating group on the top phenyl moiety. Compounds 4-96 and 4-97 proceeded smoothly in 3 and 24 hours respectively, in good yields. Inclusion of a nitro group in para position reduced the reactivity significantly and only 33\% of 4-98 was obtained after 24 hours at reflux. The elimination of water after addition to the π-bond can be drastically slowed down with the presence of a nitro group in para position of the top phenyl ring. It appears very clearly from these results that electron-donating groups in para position to the allylic alcohol accelerate the reaction and electron withdrawing groups slow down the elimination step. To further probe this hypothesis, 4-99 was treated under the same standard conditions and gave 4-100 in
good yield after 4 hours. As expected, adding an electron donating group in para position of the other benzene ring gave shorter reaction time.

Figure 4-20. Au-catalyzed synthesis of Neoflavene.

4.7 Mechanistic Considerations and Control Experiments

Mechanistically, formation of a cationic intermediate was first suggested where gold would behave as a typical Lewis Acid and ionize the benzylic position. However, a set of experiments conducted using transposed allylic alcohols showed that gold(I) was not Lewis acidic enough to form a carbocation and therefore 4-101 and 4-102 failed to cyclize. Nevertheless, we cannot rule out the formation of a cationic intermediate for substrates such as 4-94 which may be more ionizable (Figure 4-21). Alternatively, the mechanism may proceed via a fully formed cation, but instead may have partial positive charge on this cation and thus be accelerated by electron donating groups. It is also possible that more than one mechanism exists. These results are congruent with the data discussed Table 4-2. Formation of a cationic intermediate is highly unlikely since
activating groups on the benzene moiety did not give satisfactory yields and since having withdrawing groups give smoother conversion.

Figure 4-21. Control experiments.

In further control experiments, cyclization of substrates 4-103 and 4-104 using triflic acid (Figure 4-22) did not proceed and gave extensive decomposition. This set of experiments also demonstrates that formation of a cationic intermediate was not suitable for this transformation.

Figure 4-22. Control experiments using triflic acid.

The other mechanistic explanation is that gold(I) acts as a π-acid and activates the olefin, which is the generally accepted role in Au-catalyzed processes.\(^1\) Allyl alcohol 4-105 would be activated by the gold(I) species followed by nucleophilic addition to form 4-106 which, after protodeauration and elimination, would give 4-107 (Figure 4-23).
In the course of a related project, the synthesis of Daedalin A 4-108\textsuperscript{144} (prevents hyperpigmentation and exhibits anti-inflammatory activity)\textsuperscript{145} has been investigated. Daedalin A was an interesting target as known syntheses of this molecule are relatively long (over 10 steps)\textsuperscript{146} and the utility of this method for the transfer of chirality from the allylic alcohol to the 2-position of the 2H-chromene could be proven (Figure 4-24). However, the model substrate 4-111 failed to give the expected result (Figure 4-24). Surprisingly, 4-112 was obtained as major product resulting from the \textit{exo}-cyclization. Only traces of \textit{endo} product 4-113 were detected by \textsuperscript{1}H-NMR and a longer investigation was not pursued. This experiment confirmed the \(\pi\)-complex formation between the olefin and the gold catalyst and again giving further evidence to rule out the cationic nature of this transformation with these types of substrates.

![Figure 4-23. \(\pi\)-activation of the olefin.](image)

![Figure 4-24. Model Study Daedalin A.](image)
4.8 Outcome

In conclusion, a convenient and a highly adabtable catalyst/substrate system for the gold(I)-catalyzed *endo*-cyclization of *o*-(1-hydroxyallyl)-phenols to form 2H-chromenes has been reported. The sustrbstrate scope proved to be broad including electron rich and electron deficient groups on the benzene moiety. This method was extended to the synthesis of neoflavenes.

Control experiments shown in this section suggest that the mechanism may be substrate dependant. However, for a majority of substrates, it appears that the olefin is activated by the cationic gold(I) species followed by dehydrative elimination. For more electron rich substrates, formation of a cationic intermediate could not be ruled out.
CHAPTER 5
CONCLUSION AND OUTLOOK

Over the past five years, the activation of unsaturated alcohols by gold complexes has been intensively investigated and these studies have led to the discovery of efficient methodologies that utilize readily available substrates to increase molecular complexity. These transformations are typically simple to perform, the reactions conditions are mild and the yields are high.

The work described in this thesis work focused on the development of new methodologies for the construction of oxygen heterocycles using gold salts as catalysts. Gold-catalyzed dehydrative cyclization is a growing field of investigation with many new avenues to be explored. Our initial studies demonstrated that the gold-catalyzed exo-cyclization of monoallylic diols to form 2-vinyltetrahydropyrans occurs in high yields (Figure 5-1); it has a large functional group tolerance and exhibits a high degree of π-facial selectivity with traceless transfer of chirality. Further investigations showed that allylic ethers can be used as electrophiles and perform in high yield and high diastereoselectivity. From a synthetic prospective, the tuning of the allylic moiety could become an efficient tool in the synthesis of complex natural molecules and could save multiple protection/deprotection steps.

The methodology was also extended to endo-cyclization reactions which appear to be a much more challenging transformation (Figure 5-1), but the synthesis of substituted 2H-chromenes was readily accomplished. This methodology has a broad scope and the substrates are extremely easy to synthesize from inexpensive starting materials.
Despite the progress made in this field, challenging aspects such as enantioselective intermolecular reactions remain unsolved. However, intermolecular additions of allylic alcohols to alkynes are being investigated by our group and will provide a more thorough mechanistic understanding of the reactivity of unsaturated alcohols in the presence of cationic gold species. Application of these methodologies to the total synthesis of complex natural products has started to emerge and reports are expected to multiply as new reactions are developed.

Figure 5-1. Dehydrative gold-cyclization of allylic alcohols and ethers.
CHAPTER 6
EXPERIMENTAL SECTION

6.1 General Remarks

All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Anhydrous solvents were transferred via syringe to flame-dried glassware, which had been cooled under a stream of dry nitrogen. Anhydrous tetrahydrofuran (THF), acetonitrile, ether, dichloromethane, and pentane were dried using a mBraun solvent purification system. Analytical thin layer chromatography (TLC) was performed using 250 μm Silica Gel 60 F254 pre-coated plates (EMD Chemicals Inc.). Flash column chromatography was performed using 230-400 Mesh 60Å Silica Gel (Whatman Inc.). The eluents employed are reported as volume/volume percentages. Melting points were recorded on a MEL-TEMP® capillary melting point apparatus and are uncorrected. High performance liquid chromatography (HPLC) was performed on Shimadzu. Gas Chromatography analyses were obtained using a Hewlett Packard HP 5890 Series II - FID Detector. Proton nuclear magnetic resonance (¹H NMR) spectra were recorded using Varian Unity Inova 500 MHz and Varian Mercury 300 MHz spectrometers. Chemical shift (δ) is reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS, 0.0 ppm) or CDCl₃ (7.26 ppm). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded using a Varian Unity Inova 500 MHz and Varian Unity Mercury 300 spectrometer at 75 MHz. Chemical shift is reported in ppm relative to the carbon resonance of CDCl₃ (77.00 ppm). Specific Optical rotations were obtained on a JASCD P-2000 Series Polarimeter (wavelength = 589 nm). Infrared
spectra were obtained on a Perkin Elmer Spectrum RX-1 at 0.5 cm\(^{-1}\) resolution and are reported in wave numbers. High resolution mass spectra (HRMS) were obtained by The Mass Spectrometry Core Laboratory of University of Florida, and are reported as m/e (relative ratio). Accurate masses are reported for the molecular ion (M+) or a suitable fragment ion.

### 6.2 Chemical Procedures

#### 6.2.1 Synthesis of Substituted 2-Vinyltetrahydropyrans

![2-vinyltetrahydro-2H-pyranyl](image)

**2-vinyltetrahydro-2H-pyran (3-41).**

Dry CH\(_2\)Cl\(_2\) (1.0 mL) was added to an aluminum foil covered test tube containing PPh\(_3\)AuCl (12.0 mg, 0.025 mmol), AgOTf (6.1 mg, 0.025 mmol) and activated MS 4Å (25 mg). After stirring for 10 minutes, a solution of (\(E\))-hex-1-ene-1,6-diol 3-40 (75.2 mg, 0.50 mmol) in dry CH\(_2\)Cl\(_2\) (1.0 mL) was added. After TLC analysis showed the reaction to be complete (15 min), it was diluted with CH\(_2\)Cl\(_2\) and filtered through a short plug of silica. The solution of crude product was concentrated, and then purified by flash chromatography (5% EtOAc/hexanes) to give the product as a colorless oil that satisfactorily matched all reported data above.

![mixed](image)

**(E)-7-oxohept-5-enyl acetate (3-48).**

A solution of hex-5-enyl acetate 3-47 (170.1 mg, 1 mmol) and crotonaldehyde (350.1 mg, 5 mmol) in dry CH\(_2\)Cl\(_2\) (2 mL) was added to a solution of Grubbs 2\(^{\text{nd}}\) generation catalyst (25.5 mg, 0.03 mmol, 3 mol \%) in dry CH\(_2\)Cl\(_2\) (3 mL). The mixture
was stirred at reflux for 2 hours and then cooled to rt. Silica gel (200 mg) was added and the reaction mixture was stirred open to air for 30 min. The solvent was removed and the crude product was purified by flash chromatography (50% EtOAc/hexanes) to give the product as a yellow oil (116.8 mg, 92%) that satisfactorily matched all previously reported data.

(E)-1-cyclohexylhept-2-ene-1,7-diol (3-51).

A solution of cyclohexylmagnesium bromide (2 M in Et₂O, 1.120 mL, 3.3 eq.) was added dropwise to a solution of 3-48 (100 mg, 0.78 mmol) in dry THF (6 mL) at -78°C. The mixture was stirred 2 hours and then quenched with NH₄Cl (6 mL of a saturated aqueous solution), diluted with water (30 mL) and extracted with CH₂Cl₂ (3x20 mL). The combined organic layers were dried over MgSO₄, concentrated, and purified by flash chromatography (30% EtOAc/hexanes) to give the product as a colorless oil (146.9 mg, 71%). Rᵣ = 0.12 (20% EtOAc/hexanes); IR (neat) 3356, 2924, 2852, 1449, 1003, 433 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.59 (dt, J = 6.3, 15.3 Hz, 1H), 5.45 (dd, J = 6.9, 15.3 Hz, 1H), 3.75 (t, J = 7.2 Hz, 1H), 3.63 (t, J = 6 Hz, 2H), 2.06 (q, J = 6.9 Hz, 2H), 1.86-0.88 (m, 18H); ¹³C NMR (75 MHz, CDCl₃): δ 132.7, 132.1, 77.84, 62.93, 43.88, 32.40, 32.18, 29.0, 28.9, 26.7, 26.3, 26.2, 25.6; HRMS (ESI) Calcd for C₁₃H₂₃O₂ (M-H)⁺ 211.1693, found 211.1704.

(E)-2-(2-cyclohexylvinyl)-tetrahydropyran (3-52).
Dry CH₂Cl₂ (0.7 mL) was added to an aluminum foil covered test tube containing PPh₃AuCl (1.3 mg, 0.003 mmol), AgOTf (0.7 mg, 0.003 mmol) and activated MS 4Å (25 mg). After stirring for 10 minutes, a solution of diol 3-51 (56.1 mg, 0.26 mmol) in dry CH₂Cl₂ (0.7 mL) was added. After TLC analysis showed the reaction to be complete (40 min), it was diluted with CH₂Cl₂ and filtered through a short plug of silica. The solution of crude product was concentrated, and then purified by flash chromatography (5% EtOAc/hexanes) to give the product as a colorless oil (48.6 mg, 96%). Rᵣ = 0.81 (5% EtOAc/hexanes); IR (neat) 2925, 2851, 1448, 1085, 968, 412 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.59 (dd, J = 6.3, 15.3 Hz, 1H), 5.39 (dd, 6.3, 15.3 Hz, 1H), 3.98 (dt, J = 2.7, 10.8 Hz, 1H), 3.70 (dd, J = 6.0, 10.5 Hz, 1H), 3.45 (dt, J = 2.4, 11.7 Hz, 1H), 1.95-0.97 (m, 17H); ¹³C NMR (75 MHz, CDCl₃): δ 137.8, 128.9, 78.7, 68.6, 40.5, 32.9, 33.0, 32.5, 26.4, 26.3, 26.1, 23.7; HRMS (ESI) Calcd for C₁₃H₂₃O (M+H)⁺ 195.1754, found 195.1749.

7-(tert-butyldimethylsilyloxy)-1-cyclohexylhept-2-yn-1-ol (3-55).

A solution of nBuLi in hexane 2.5M (1.04 mL, 2.6 mmol) was added dropwise over 10 minutes at -78°C to a solution of tert-butyl(hex-5-ynyloxy)dimethylsilane 3-54 (500.8 mg, 2.36 mmol) in dry THF (35 mL). The reaction was then stirred at the same temperature for 45 minutes and a solution of cyclohexane carboxaldehyde (344.2 mg, 3.07 mmol) in dry THF (3 mL) was added. The mixture was allowed to warm to -30°C and stirred for 30 minutes, quenched with NH₄Cl (20 mL of a saturated aqueous solution), diluted with water (20 mL) and extracted with CH₂Cl₂ (2x30 mL). The organic
layers were dried over MgSO₄ and then purified by flash chromatography (20% EtOAc/Hexanes) to give the product as a colorless oil (697.2 mg, 91%). Rᵋ = 0.42 (10% EtOAc/hexanes); IR (neat) 3333, 3011, 2852, 1446 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.01 (d, J = 7.2 Hz, 1H), 3.61 (t, J = 7.2 Hz, 2H), 2.21 (q, J = 7.1 Hz, 2H), 1.99-0.95 (m, 15H), 0.86 (s, 9H), 2.20-0.91 (m, 19H), 0.86 (s, 9H), 0.08 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 86.2, 80.5, 67.6, 62.9, 44.5, 32.1, 28.8, 28.3, 26.6, 26.1, 25.4, 19.7, 18.7, 18.5, -5.1; HRMS (ESI) Calcd for C₁₉H₃₅O₂Si (M-H)⁺ 323.2401, found 323.2398.

(Z)-1-cyclohexylhept-2-ene-1,7-diol (3-56).

Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 30 mg) was added to a solution of 3-55 (150.2 mg, 0.46 mmol) in a mixture of EtOAc/pyridine/1-hexene (10:1:1, 250 μL). The reaction mixture was stirred 16h under H₂ (1 atm). After filtration over celite and removal of the solvent, crude product was recovered as colorless oil which was used for the next step without further purification.

A solution of HF pyridine (550 μL) was added dropwise at 0°C to a solution of the silane obtained above (116.1 mg, 0.35 mmol) in dry THF (4 mL). The reaction was stirred for 2 hours at the same temperature and NaHCO₃ saturated (30 mL of a saturated aqueous solution) was added dropwise. After dilution in water (20 mL), the crude product was extracted with CH₂Cl₂ (2x30 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by vacuum. Flash chromatography (30% EtOAc/Hexanes) afforded the product as a colorless oil (58.4 mg, 78%). Rᵋ = 0.12 (20% EtOAc/hexanes); IR (neat) 3330, 2924, 2852, 1449 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ
5.42 (dt, $J = 7.2, 11.1$ Hz, 1H), 5.36 (dd, $J = 9, 10.5$ Hz, 1H), 4.09 (t, $J = 7.2$ Hz, 1H),
3.61 (t, $J = 6.3$ Hz, 2H), 2.06 (q, $J = 6.9$ Hz, 2H), 2.20-0.81 (m, 19H); $^{13}$C NMR (75 MHz,
CDCl$_3$): $\delta$ 132.7, 131.6, 72.1, 62.9, 44.2, 32.4, 29.0, 28.8, 27.7, 26.7, 26.3, 26.2, 26.1;
HRMS (ESI) Calcd for C$_{13}$H$_{23}$O$_2$ (M-H)$^+$ 211.1693, found 211.1704.

\[
\text{(E)-2-(2-cyclohexylvinyl)tetrahydro-2H-pyran (3-52).}
\]

Dry CH$_2$Cl$_2$ (0.3 mL) was added to an aluminum foil covered test tube containing
PPh$_3$AuCl (0.7 mg, 0.001 mmol), AgOTf (0.4 mg, 0.001 mmol) and activated MS 4Å (25 mg).
After stirring for 10 minutes, a solution of diol 3-57 (21.1 mg, 0.10 mmol) in dry
CH$_2$Cl$_2$ (0.3 mL) was added. After TLC analysis showed the reaction to be complete (40
min), it was diluted with CH$_2$Cl$_2$ and filtered through a short plug of silica. The solution of
crude product was concentrated, and then purified by flash chromatography (5%
EtOAc/hexanes) to give the product as a colorless oil (17.9 mg, 92%) that satisfactorily
matched all reported data above.

\[
\text{(E)-1-(6-hydroxyhex-1-enyl)-cyclohexanol (3-60).}
\]

A solution of hex-5-en-1-ol (100.2 mg, 1 mmol) and 1-vinylcyclohexanol 3-59
(252.4 mg, 2 mmol) in dry CH$_2$Cl$_2$ (2 mL) was added to a solution of Grubb’s $2^{\text{nd}}$
generation catalyst (42.5 mg, 0.05 mmol, 5 mol %) in dry CH$_2$Cl$_2$ (3 mL). The mixture
was stirred at reflux for 1 hour and then cooled to rt. Silica gel (200 mg) was added and
the reaction mixture was stirred open to air for 1 hour. The solvent was removed and
the crude product was purified by flash chromatography (20% EtOAc/hexanes) to give the product as a yellow oil (116.8 mg, 93%). \( R_f = 0.18 \) (20% EtOAc/hexanes); IR (neat) 3417, 2976, 2932, 2860, 1382, 1120, 423 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 5.63 (m, 2H), 3.63 (t, \( J = 6.6 \) Hz, 2H), 2.06 (q, \( J = 6.9 \) Hz, 1H), 1.74-1.26 (m, 16H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 138.2, 127.8, 89.1, 81.9, 71.5, 62.9, 38.3, 32.3, 32.2, 25.7, 25.6, 22.4, 22.3; HRMS (ESI) Calcd for C\(_{12}\)H\(_{19}\)O (M-H)\(^+\) 179.1427, found 179.1436.

2-(cyclohexylidenemethyl)tetrahydropyran (3-61).

Dry CH\(_2\)Cl\(_2\) (0.7 mL) was added to an aluminum foil covered test tube containing PPh\(_3\)AuCl (1.3 mg, 0.003 mmol), AgOTf (0.7 mg, 0.003 mmol) and activated MS 4Å (25 mg). After stirring for 10 minutes, a solution of diol 3-60 (51.5 mg, 0.26 mmol) in dry CH\(_2\)Cl\(_2\) (0.7 mL) was added. After TLC analysis showed the reaction to be complete (2.5 hours), it was diluted with CH\(_2\)Cl\(_2\) and filtered through a short plug of silica. The solution of crude product was concentrated, and then purified by flash chromatography (5% EtOAc/hexanes) to give the product as a colorless oil (42.1 mg, 91%). \( R_f = 0.85 \) (5% EtOAc/hexanes); IR (neat) 2929, 2852, 1086, 1033 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 5.08 (dd, \( J = 8.1, 0.9 \) Hz, 1H), 4.04-3.92 (m, 2H), 3.44 (dt, \( J = 11.7, 2.7 \) Hz, 1H), 2.14-2.03 (m, 4H), 1.82-1.22 (m, 12H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 142.9, 123.4, 74.4, 68.4, 37.1, 32.8, 29.7, 28.6, 28.0, 26.9, 26.0, 23.7; HRMS (ESI) Calcd for C\(_{12}\)H\(_{19}\)O (M-H)\(^+\) 179.1427, found 179.1436.
(E)-1-cyclohexyl-3,7-dimethyl octa-2,6-dienyl acetate (3-64).

A solution of cyclohexylmagnesium bromide (2 M in Et₂O, 1.083 mL, 1.1 eq.) was added dropwise at 0°C to a solution of geranial 3-63 (300 mg, 1.97 mmol) in dry THF (10 mL). The mixture was stirred 20 minutes and then acetyl chloride (309 μL, 3.94 mmol) was added dropwise. The reaction mixture was warmed to rt and stirred for 2h, then quenched with water (20 mL) and extracted with Et₂O (3x20 mL). The organic layers were dried over MgSO₄, concentrated, and the crude product was purified by flash chromatography (10% EtOAc/Hexanes) to give the product as a colorless oil (477.2 mg, 87%). Rᵣ = 0.57 (20% EtOAc/hexanes); IR (neat) 2928, 2854, 1727, 1264, 1247, 740 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.24 (dd, J = 7.5, 9.6 Hz, 1H), 5.00 (m, 2H), 2.07-1.98 (m, 7H), 1.75-0.85 (m, 20H); ¹³C NMR (75 MHz, CDCl₃): δ 170.7, 140.8, 131.8, 124.2, 122.6, 75.5, 42.4, 39.9, 29.0, 28.5, 26.6, 26.4, 26.2, 26.0, 25.9, 21.5, 17.9, 17.0; HRMS (ESI) Calcd for C₁₈H₂₉O₂ (M-H)⁺ 277.2185, found 277.2168.

(E)-1-cyclohexyl-3,7-dimethyloct-2-ene-1,7-diol (3-66).

A solution of meta-chloroperoxybenzoic acid (77% max., 244.7 mg, 1.09 mmol) in CH₂Cl₂ (2 mL) was added dropwise at 0°C to a solution of 3-64 (276.4 mg, 0.99 mmol) in CH₂Cl₂ (8 mL). After for 3 hours, the reaction mixture was quenched with NaOH (10 mL of a 1M aqueous solution), diluted with water (20 mL) and extracted with CH₂Cl₂ (2x40 mL). The combined organic layers were dried over MgSO₄ and the solvent removed to give the product as a crude colorless oil which was used for the next step without further purification.
A solution of the epoxide 3-65 obtained above (292.0 mg, 0.99 mmol) in Et$_2$O (5 mL) was added dropwise over 10 min at 0°C to a vigorously stirred suspension of lithium aluminum hydride 95% (119 mg, 2.98 mmol) in dry Et$_2$O (10 mL). The reaction mixture was allowed to warm to rt and was then stirred at reflux for 45 minutes. The reaction was cooled to 0°C and was added successively water (120 μL), NaOH (120 μL of a 15% aqueous solution) and then water (360 μL). After filtration, the solution was dried over MgSO$_4$ and purified by flash chromatography (15% to 30% EtOAc/hexanes) to give the product as a colorless oil (110.2 mg, 40% over 2 steps). IR (neat) 3373, 2923, 2851, 1001, 423 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.15 (d, $J = 9.0$ Hz, 1H), 4.04 (t, $J = 8.7$ Hz, 1H), 1.99 (t, $J = 6.6$ Hz, 2H) 1.91-0.86 (m, 24H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 139.05, 126.84, 73.08, 71.11, 44.52, 44.39, 43.67, 40.27, 29.49, 29.17, 28.79, 26.79, 26.35, 26.23, 22.63, 16.89. HRMS (ESI) Calcd for C$_{16}$H$_{29}$O$_2$ (M-H)$^+$ 253.2162, found 253.2175.

(E)-2-(2-cyclohexylvinyl)-2,6,6-trimethyltetrahydropyran (3-67).

Dry CH$_2$Cl$_2$ (0.5 mL) was added to an aluminum foil covered test tube containing PPh$_3$AuCl (0.9 mg, 0.002 mmol), AgOTf (0.5 mg, 0.002 mmol) and activated MS 4Å (25 mg). After stirring for 10 minutes, a solution of diol 3-66 (45.0 mg, 0.18 mmol) in dry CH$_2$Cl$_2$ (0.4 mL) was added. After TLC analysis showed the reaction to be complete (6 hours), it was diluted with CH$_2$Cl$_2$ and filtered through a short plug of silica. The solution of crude product was concentrated, and then purified by flash chromatography (5% EtOAc/hexanes) to give the product as a colorless oil (37.2 mg, 89%). $R_f = 0.81$ (5%
EtOAc/hexanes); IR (neat) 2970, 2925, 2852, 1093, 430, 409 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.45 (d, \(J = 16.2\) Hz, 1H), 5.27 (dd, \(J = 15.9, 6.3\) Hz, 1H), 1.92-0.81 (m, 26H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 136.1, 132.0, 73.3, 72.3, 40.7, 37.0, 33.9, 33.1, 32.9, 32.8, 32.5, 27.7, 26.5, 26.3, 17.2.; HRMS (ESI) Calcd for C\(_{16}\)H\(_{27}\)O (M-H\(^+\)) 235.2049, found 235.2062.

6.2.2 Gram-Scale Preparation of 3-89

\(\text{(E)-7-Hydroxyhept-2-enal (3-68).}\)

A solution of Grubbs 2\(^{\text{nd}}\) generation catalyst (169.6 mg, 0.2 mmol, 1 mol %) in anhyd CH\(_2\)Cl\(_2\) (50 mL, degassed by bubbling with argon for 30 min) was prepared in a flame-dried 250 mL flask equipped with a reflux condenser. To the reaction vessel, a solution of 5-hexen-1-ol 3-85 (2.0032 g, 20 mmol) and crotonaldehyde 3-86 (7.0050 g, 100 mmol) in anhyd CH\(_2\)Cl\(_2\) (50 mL, degassed by bubbling with argon for 30 min) was added and the mixture was immediately heated to reflux for 2 h by immersing into an oil bath that had been preheated to 50\(^{\circ}\)C, at which point TLC analysis indicated a complete reaction. The crude mixture was then cooled to rt, silica gel (8 g) was added to the flask, and the resulting slurry was vigorously stirred open to air for 30 min. The mixture was then adsorbed onto the silica gel under reduced pressure and purified by flash chromatography (50% EtOAc-hexanes) to give 2.4601 g (96%) of the title compound as a brown oil; \(R_I = 0.25\) (50% EtOAc-hexanes); IR (neat): 3418, 2937, 2863, 2741, 1683, 1635, 1134, 1060, 977 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) = 9.49 (d, \(J = 7.8\) Hz, 1 H), 6.87 (dt, \(J = 15.6, 6.6\) Hz, 1 H), 6.13 (ddt, \(J = 15.6, 7.8, 1.8\) Hz, 1 H), 3.68 (t, \(J = 6.2\) Hz, 2H).
2 H), 2.43-2.35 (m, 2 H), 2.01 (br, 1 H), 1.67-1.59 (m, 4 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 194.4, 159.1, 133.0, 62.1, 32.4, 32.0, 24.1; HRMS (ESI) Calcd for C$_7$H$_{16}$NO$_2$ (M+NH$_4$)$^+$ 146.1176, found 146.1165.

(E)-Tridec-5-ene-1,7-diol (3-88)

A solution of n-hexylmagnesium bromide (0.97 M in Et$_2$O, 34.02 mL, 2.2 equiv) was added in a dropwise fashion to a solution of 3-68 (1.9225 g, 15.0 mmol) in THF (75 mL) at 0˚C. The mixture was stirred 30 min at the same temperature and then quenched with aq sat. NH$_4$Cl (50 mL), diluted with H$_2$O (100 mL), and extracted with EtOAc (3x80 mL). The combined organic layers were dried (MgSO$_4$), concentrated, and the residue was purified by flash chromatography (40% EtOAc-hexanes) to give 2.8244 g (88%) of the title compound as a yellow oil: $R_f$ = 0.33 (50% EtOAc-hexanes); IR (neat): 3346, 2929, 2857, 1457, 1058, 968 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.62 (dt, $J$ = 15.6, 6.3 Hz, 1 H), 5.45 (dd, $J$ = 15.6, 6.9 Hz, 1 H), 4.02 (q, $J$ = 6.3 Hz, 1 H), 3.63 (t, $J$ = 6.0 Hz, 2 H), 2.06 (q, $J$ = 6.9 Hz, 2 H), 1.94 (br, 1 H), 1.60-1.23 (m, 14 H), 0.88 (t, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 133.7, 131.6, 73.3, 62.8, 37.5, 32.3, 32.0, 29.4, 25.6, 25.5, 22.8, 14.2; HRMS (ESI) Calcd for C$_{13}$H$_{23}$ (M+H-2H$_2$O)$^+$ 179.1794, found 179.1790.

(E)-2-(Oct-1-enyl)tetrahydro-2H-pyran (3-89)
Anhyd CH$_2$Cl$_2$ (25 mL, degassed by bubbling with argon for 30 min) was added to an aluminum foil covered, flame dried, 100 mL flask containing Ph$_3$PAuCl (24.8 mg, 0.05 mmol, 0.5 mol %), AgOTf (12.8 mg, 0.05 mmol, 0.5 mol %), and activated 4 Å MS (950 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the diol 3-88 (2.1432 g, 10.0 mmol) in anhyd CH$_2$Cl$_2$ (25 mL, degassed by bubbling with argon for 30 min) was then added. After 5 hours, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (30 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (5% EtOAc/hexanes) to give 1.7944 g (91%) of the title compound as a colorless oil; R$_f$ = 0.95 (5% EtOAc/hexanes); IR (neat): 2927, 2854, 2728, 1463, 1086, 967 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 5.65$ (ddt, $J = 15.6, 6.6, 0.9$ Hz, 1 H), 5.44 (ddt, $J = 15.6, 6.6, 1.5$ Hz, 1 H), 4.01-3.95 (m, 1 H), 3.75-3.70 (m, 1 H), 3.46 (dt, $J = 11.4, 1.5$ Hz, 1 H), 2.00 (q, $J = 6.3$ Hz, 2 H), 1.85-1.22 (m, 14 H), 0.86 (t, $J = 6.3$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 132.1, 131.3, 78.5, 68.5, 32.5, 32.4, 31.9, 29.3, 29.1, 26.1, 23.6, 22.8, 14.2$; HRMS (ESI) calcd for C$_{13}$H$_{25}$O (M+H)$^+$ 197.1891, found 197.1900.

6.2.3 Representative Procedures for the Preparations of 3-71 - 3-75

(E)-Trimethyl[3-(tetrahydro-2H-pyran-2-yl)allyl]silane (3-74)

Anhyd CH$_2$Cl$_2$ (1.6 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (2.3 mg, 0.0046 mmol, 1.0 mol %), AgOTf (1.2 mg, 0.0046 mmol, 1.0 mol %), and activated 4 Å MS (30 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol (100.2 mg, 0.46
mmol) in anhyd CH₂Cl₂ (1.6 mL) was then added. After 40 min, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH₂Cl₂ (4 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (5% EtOAc/hexanes) to give 83.8 mg (92%) of the title compound 3-74 as a colorless oil; Rᵢ = 0.95 (50% EtOAc/hexanes); IR (neat): 3418, 2937, 2863, 2741, 1683, 1635, 1134, 1060, 977 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 5.61 (dt, J = 15.3, 7.8 Hz, 1 H), 5.30 (dd, J = 15.3, 6.3 Hz, 1 H), 4.95 (d, J = 11.4 Hz, 1 H), 3.69 (t, J = 8.4 Hz, 1 H), 3.43 (t, J = 11.1 Hz, 1 H), 1.81-1.34 (m, 8 H), -0.03 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃): δ = 130.2, 128.5, 78.9, 69.46, 32.8, 26.1, 23.7, 22.9, -1.8; HRMS (ESI) calcd for C₁₁H₂₂OSi (M+H)⁺ 199.1513, found 199.1525.

![Chemical structure](image)

(E)-2-[4-(1,3-Dioxolan-2-yl)but-1-enyl]tetrahydro-2H-pyran (3-71)

Colorless oil; Rᵢ = 0.92 (50% EtOAc/hexanes); IR (neat): 2935, 2850, 1808, 1083, 1048 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 5.61 (ddt, J = 15.3, 7.4, 1.5 Hz, 1 H), 5.43 (ddt, J = 15.3, 6.0, 0.9 Hz, 1 H), 4.80 (t, J = 4.8 Hz, 1 H), 3.95-3.64 (m, 5 H), 3.40 (dt, J = 11.7, 3.3 Hz, 2 H), 2.10 (q, J = 7.4 Hz, 2 H), 1.79-1.18 (m, 8 H); ¹³C NMR (75 MHz, CDCl₃): δ = 132.0, 130.8, 104.3, 78.3, 68.5, 65.1, 33.5, 32.4, 27.0, 26.1, 23.6; HRMS (ESI) calcd for C₁₂H₂₁O₃ (M+H)⁺ 213.1485, found 213.1482.

![Chemical structure](image)

(E)-2-[2-(Furan-2-yl)vinyl]tetrahydro-2H-pyran (3-72)
Yellow oil; R$_f$ = 0.95 (50% EtOAc/hexanes); IR (neat): 2937, 2848, 1726, 1083, 1013 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.32 (d, $J$ = 1.8 Hz, 1 H), 6.41 (dd, $J$ = 16.2, 1.5 Hz, 1 H), 6.34 (dd, $J$ = 3.9, 1.8 Hz, 1 H), 6.21 (d, $J$ = 3.3 Hz, 1 H), 6.15 (dd, $J$ = 16.2, 5.4 Hz, 1 H), 3.46 (dt, $J$ = 11.7, 2.7 Hz, 1 H), 4.08-4.03 (m, 1 H), 3.94 (ddt, $J$ = 10.8, 5.4, 1.8 Hz, 1 H), 3.52 (dt, $J$ = 11.4, 3.0 Hz, 1 H), 1.90-1.41 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 152.9, 141.9, 129.7, 118.1, 111.4, 107.9, 77.6, 68.6, 32.4, 26.1, 23.7; HRMS (ESI) calcd for C$_{11}$H$_{14}$O$_2$ (M)$^+$ 178.0984, found 178.0994.

(E)-2-[2-(Cyanomethyl)vinyl]tetrahydro-2H-pyran (3-73)

Pale yellow oil; R$_f$ = 0.78 (5% EtOAc/hexanes); IR (neat): 2920, 2849, 2732, 2251, 1723, 1119, 1083 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.88 (ddt, $J$ = 15.6, 5.1, 1.5 Hz, 1 H), 5.61 (ddt, $J$ = 15.6, 5.4, 1.5 Hz, 1 H), 4.04-3.99 (m, 1 H), 3.85-3.79 (m, 1 H), 3.48 (dt, $J$ = 5.4, 2.7 Hz, 1 H), 3.11 (dt, $J$ = 11.4, 1.5 Hz, 2 H), 1.89-1.25 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 136.7, 117.9, 117.5, 76.9, 68.6, 32.0, 25.9, 23.5, 20.5; HRMS (ESI) calcd for C$_9$H$_{14}$NO (M+H)$^+$ 152.1075, found 152.1072.

(E)-2-(3-Phenylprop-1-enyl)tetrahydro-2H-pyran (3-75)

Colorless oil; R$_f$ = 0.95 (50% EtOAc/hexanes); IR (neat): 3026, 2934, 2843, 1495, 1452, 1085, 698 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.30-7.16 (m, 5 H), 5.82 (dt, $J$ = 15.3, 6.9 Hz, 1 H), 5.53 (dd, $J$ = 15.3 6.3 Hz, 1 H), 3.99 (dt, $J$ = 11.4, 2.1 Hz, 1 H), 3.81-3.75 (m, 1 H), 3.46 (dt, $J$ = 11.4, 2.7 Hz, 1 H), 3.36 (d, $J$ = 6.9 Hz, 2 H), 1.66-1.26 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 140.3, 132.9, 130.3, 128.8, 128.6, 128.6, 78.2,
68.5, 38.9, 32.3, 26.0, 23.6; HRMS (ESI) calcd for C\textsubscript{14}H\textsubscript{17}O (M-H\textsuperscript{+}) 209.1302, found 201.1279.

![Image](image.png)

**1-bromo-4-(pent-4-enyloxy)benzene (3-95).**

To a solution of 4-bromophenol 3-93 (346.2 mg, 2 mmol) in dry DMF (10 mL), was added successively 5-bromopentene 3-94 (327.8 mg, 2.2 mmol) and K\textsubscript{2}CO\textsubscript{3} (552.0 mg, 4 mmol). The reaction mixture was stirred at 70°C overnight and then quenched with water (20 mL) and extracted with Et\textsubscript{2}O (3x20 mL). The organic layers were dried over MgSO\textsubscript{4}, concentrated, and the crude product was purified by flash chromatography (100% hexanes) to give the product as a colorless oil. (444.3 mg, 92%). \( R_f = 0.77 \) (100% hexanes); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta = 7.37 \) (d, \( J = 9 \) Hz, 2H), 6.80 (d, \( J = 9 \) Hz, 2H), 5.95-5.82 (m, 1 H), 5.14-5.03 (m, 2 H), 3.94 (t, \( J = 6.6 \) Hz, 2H), 3.94 (t, \( J = 6.6 \) Hz, 2H), 2.26 (q, \( J = 6.6 \) Hz, 2 H); \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta = 158.3, 137.8, 132.3, 116.4, 115.5, 112.8, 67.5, 30.2, 28.5. \)

![Image](image.png)

**5-(4-bromophenoxy)pentane1,2-diol (3-96).**

A solution of osmium tetroxyde 4% in water (83 \( \mu \)L, 0.0124 mmol) was added at rt to a mixture of 3-95 (300.0 mg, 1.24 mmol) in acetone/water 5/1 (15 mL) and NMO 5% in water (283 \( \mu \)L, 1.34 mmol). The reaction mixture was stirred at rt overnight and
quenched with Na$_2$SO$_4$ (75 mL). Diluted with water (20 mL) and extracted with ethyl acetate (3x20 mL). The organic layers were dried over MgSO$_4$, concentrated and the crude product was purified by recrystallization in hexanes to give the product as a white solid (293.4 mg, 86%); $^1$H NMR (300 MHz, CDCl$_3$): δ = 7.38 (d, J = 9 Hz, 2H), 6.81 (d, J = 9 Hz, 2H), 5.96-5.83 (m, 1 H), 3.98 (t, J = 6.6 Hz, 2H), 3.74-3.46(m, 2H), 2.81 (s, 1H), 2.52 (s, 1 H), 1.95 (m, 2H), 1.68 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 158.2, 132.5, 116.5, 113.1, 72.1, 68.3, 67.0, 29.9, 25.6; HRMS (ESI) calcd for C$_{11}$H$_{15}$BrO$_3$Na (M+Na)$^+$ 297.0097, found 297.0083.

4-(4-bromophenoxy)butanal (3-97).

Pb(OAc)$_4$ (266.9 mg, 0.59 mmol) was added portionwise over 20 minutes at 0°C to a solution of 3-96 (150.0 mg, 0.54 mmol) in dry benzene (2 mL). The reaction mixture was stirred at rt 3 hours and then filtered through a short plug of celite. The solvent was removed and the crude was then diluted in CH$_2$Cl$_2$ (5 mL) to be applied to a short plug of silica to give the product as a white solid (96.5 mg, 74%). $R_f$ = 0.82 (100% CH$_2$Cl$_2$); $^1$H NMR (300 MHz, CDCl$_3$): δ = 9.84 (t, J = 1.5 Hz, 1H), 7.35 (d, J= 9 Hz, 2H), 6.75 (d, J = 9 Hz, 2H), 5.96-5.83 (m, 1 H), 3.98 (t, J = 6.6 Hz, 2H), 3.96 (t, J = 6.6 Hz, 2H), 2.66 (t, J = 6.9 Hz, 2H), 2.12 (q, J = 6.6 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ = 201.8, 157.9, 132.5, 116.4, 113.2, 67.1, 40.7, 22.1; HRMS (ESI) Calcd for C$_{10}$H$_{11}$BrO$_2$Br (M)$^+$ 241.9918, found 241.9942.
(R)-1-(4-bromophenoxy)-10-(tert-butyldimethylsilyloxy)dec-5-yn-4-ol (3-98).

A 10 mL flask was charged with Zn(OTf)$_2$ (1.4540 g, 4.0 mmol) and (+)-N-methylephedrine (717.0 mg, 4.0 mmol) was added. To the flask was added toluene (0.5 mL) and triethylamine (627 μL, 4.5 mmol). The resulting mixture was stirred for 2 h at r.t. before tert-butyl(hex-5-ynyloxy)dimethylsilane 3-54 (807.1 mg, 3.8 mmol) was added in one portion. After stirring for 0.25 h at rt aldehyde 3-97 (243.1 mg, 1 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 5 hours. The reaction was quenched by addition of NH$_4$Cl (sat.) (3 mL). The reaction mixture was poured into a separatory funnel containing diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined ethereal portion was washed with NaCl (sat.) (10 mL), dried over anhydrous MgSO$_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (30% Hexanes/CH$_2$Cl$_2$) to give the product as a colorless oil (364.4 mg, 80%) and 90% ee as determined by HPLC analysis (Chiralcel OD-H, 10% iPrOH in hexanes, 1.0 mL/min, 254 nm), t, 4.8 (minor), 5.5 (major); $R_l = 0.11$ (30% hexanes/CH$_2$Cl$_2$); $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.36$ (d, $J = 9$ Hz, 2H), 6.77 (d, $J = 9$ Hz, 2H), 4.44 (q, $J = 6$Hz, 1 H), 3.98 (t, $J = 6.6$ Hz, 2H), 3.63(t, $J = 6.9$ Hz, 2H), 2.26 (t, $J = 6.6$ Hz, 2H), 1.98-1.52 (m, 10H), 0.90 (s, 9H), 0.05 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 158.2$, 132.4, 116.5, 113.0, 85.9, 81.3, 68.0, 62.8, 62.5, 34.8, 32.1, 26.2, 25.3, 25.2,
18.7, 18.5, -5.1; HRMS (ESI) Calcd for C_{22}H_{34}BrO_{2}Si (M+Na)^+ 477.1486, found 477.1431.

(R)-(Z)-10 (4-bromophenoxy)dec-5-ene-1,7-diol (3-99).

Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 30 mg) was added to a solution of 3-98 (228.5 mg, 0.50 mmol) in a mixture of EtOAc/pyridine/1-hexene (10:1:1, 250 μL). The reaction mixture was stirred 2 days under H_2 (1 atm). After filtration over celite and removal of the solvent, crude product was recovered as a colorless oil which was used for the next step without further purification. A solution of TBAF (1.0M in THF, 2.0 mL) was added dropwise at 0°C to a solution of the silane obtained above in dry THF (5 mL). The reaction was stirred 16h at the same temperature and NaHCO_3 saturated (30 mL of a saturated aqueous solution) was added dropwise. After dilution in water (20 mL), the crude product was extracted with EtOAc (2x30 mL), the combined organic layers were dried over MgSO_4 and the solvent removed by vacuum. Flash chromatography (40% EtOAc/Hexanes) afforded the product as a colorless oil (156.4 mg, 91%) and 90% ee as determined by HPLC analysis (Chiralcel OD-H, 10% iPrOH in hexanes, 1.0 mL/min, 254 nm), t, 3.3 (minor), 11.7 (major); R_f = 0.16 (50% EtOAc/hexanes); \(^1\)H NMR (300 MHz, CDCl_3): \(\delta = 7.36 \ (d, \ J = 9 \ Hz, 2H), 6.77 \ (d, \ J = 9 \ Hz, 2H), 5.59-5.39 \ (m, 2H), 4.48 \ (q, \ J = 6 \ Hz, 2H), 3.95(t, \ J = 6.6 \ Hz, 2H), 3.64 \ (t, \ J = 6.9 \ Hz, 2H), 2.24-1.39 \ (m, 12H); \(^{13}\)C NMR (75 MHz, CDCl_3): \(\delta = \)
HRMS (ESI) Calcd for C₁₆H₂₃BrO₃Na (M+Na)⁺ 365.0723, found 365.0715.

\(\text{(R)-(E)-10 (4-bromophenoxy)dec-5-ene-1,7-diol (3-101).}\)

\([\text{Cp}^*\text{Ru(MeCN)}₃]\text{PF}_6\) catalyst (3 mol %, 7.6 mg, 0.015 mmol) was added to a solution of 3-98 (228.5 mg, 0.50 mmol) and ethoxydimethylsilane (78 μL, 0.75 mmol) in CH₂Cl₂ (3 mL) at 0°C. The ice-bath was removed and the reaction mixture stirred for 15 minutes at rt. After filtration over a short plug of florisil and removal of the solvent, crude product was recovered as a yellow oil which was used for the next step without further purification. A solution of TBAF (1.0M in THF, 2.0 mL) was added dropwise at 0°C to a solution of the silane obtained above and CuI (19.0 mg, 0.1 mmol) in dry THF (5 mL). The reaction was stirred 16 h at the same temperature and NH₄Cl (sat.) (5 mL) was added dropwise. After dilution in water (20 mL), the crude product was extracted with EtOAc (2x30 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by vacuum. Flash chromatography (40% EtOAc/hexanes) afforded the product as a colorless oil (123.5 mg, 72%) and 90% ee as determined by HPLC analysis (Chiralcel OD-H, 10% iPrOH in hexanes, 1.0 mL/min, 254 nm), t₁, 12.3 (major), 13.6 (major); \(R_l = 0.18\) (50% EtOAc/hexanes); \(^1\)H NMR (300 MHz, CDCl₃): 7.35 (d, \(J = 9\) Hz, 2H), 6.77 (d, \(J = 9\) Hz, 2H), 5.67 (dt, \(J = 15.0, 6.6\) Hz, 1H), 5.51 (dd, \(J = 15.0, 6.6\) Hz, 1H), 4.12 (q, \(J = 6.3\) Hz, 1H), 3.95 (t, \(J = 5.7\) Hz, 2H), 3.64 (t, \(J = 6.3\) Hz, 2H), 2.07 (q, \(J = 7.2\) Hz, 2H), 1.90-1.26 (m, 8H); \(^1^3\)C NMR (75 MHz, CDCl₃): \(\delta = 158.2, 133.3, 132.4, \ldots\)
132.1, 116.5, 112.9, 72.8, 68.3, 62.9, 33.9, 32.3, 32.0, 25.5, 25.5; HRMS (ESI) Calcd for C_{16}H_{23}BrO_{3}Na (M+Na)^{+} 365.0728, found 365.0707.

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

(+)-(E)-2-(5-(4-bromophenoxy)pent-1-enyl)tetrahydro-2H-pyran (3-100).

Anhyd CH$_2$Cl$_2$ (1.0 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (1.6 mg, 0.0029 mmol, 1.0 mol%), AgOTf (0.8 mg, 0.0029 mmol, 1.0 mol%), and activated 4 Å MS (30 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol $R$-42 (100.0 mg, 0.29 mmol) in anhyd CH$_2$Cl$_2$ (0.5 mL) was then added. After 40 min, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (4 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (5% EtOAc/hexanes) to give 74.5 mg (79%) of the title compound (-)-3-100 as a colorless oil; $R_f = 0.90$ (5% EtOAc/hexanes) and 90% ee as determined by HPLC analysis (Chiralcel OD-H, 1% iPrOH in hexanes, 1.0 mL/min, 254 nm), $t_r$ 5.5 (major), 6.0 (minor) that satisfactorily matched previously reported data.

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\text{Br} & \quad \text{Br}
\end{align*}
\]

(-)-(E)-2-(5-(4-bromophenoxy)pent-1-enyl)tetrahydro-2H-pyran (3-102).

Anhyd CH$_2$Cl$_2$ (1.0 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (1.6 mg, 0.0029 mmol, 1.0 mol%), AgOTf (0.8 mg, 0.0029 mmol, 1.0 mol%), and activated 4 Å MS (30 mg). The heterogeneous mixture was vigorously stirred for 10 minutes and a solution of the corresponding diol 3-101 (100.0
mg, 0.29 mmol) in anhyd CH₂Cl₂ (0.5 mL) was then added. After 40 min, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH₂Cl₂ (4 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (5% EtOAc/hexanes) to give 80.1 mg (85%) of the title compound (-)-3-102 as a colorless oil; Rₚ = 0.90 (5% EtOAc/hexanes); and 90% ee as determined by HPLC analysis (Chiralcel OD-H, 1% iPrOH in hexanes, 1.0 mL/min, 254 nm), t, 5.5 (minor), 6.0 (major); [α]₀ = -5.8 (c 1.0, CHCl₃); IR (neat): 3058, 2945, 2866, 1734, 1690, 1242, 737 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.36 (d, J = 9 Hz, 2H), 6.77 (d, J = 9 Hz, 2H), 5.65-5.48 (m, 2H), 4.00 (d, J = 13.5 Hz, 1H), 3.94(t, J = 6.6 Hz, 2H), 3.75 (t, J = 10.8 Hz, 1H), 3.47 (t, J = 11.1Hz, 1H), 2.24 (q, J = 7.5 Hz, 2H), 1.91-1.31 (m, 10H); ¹³C NMR (75 MHz, CDCl₃): δ = 158.2, 132.8, 132.4, 132.4, 119.1, 103.6, 68.6, 67.7, 62.8, 34.2, 32.5, 27.3, 26.0, 25.3; HRMS (ESI) Calcd for C₁₆H₂₀BrO₂ (M-H)+ 323.0667, found 323.0647.

6.2.4 Synthesis of 3-111 and 3-112

Compounds 3-54 and 3-104⁹⁵ have been described in the literature and when prepared here satisfactorily matched all previously reported data.

9-(tert-butyldimethylsilyloxy)-1-phenylnon-4-yn-3-one (3-107).

A solution of nBuLi in hexane 1.6M (2.41 mL, 3.85 mmol) was added dropwise over 10 minutes at -78°C to a solution of 3-54 (742.0 mg, 3.5 mmol) in dry THF (12 mL). The reaction was then stirred at the same temperature for 45 minutes and a solution of 3-104 (773.2 mg, 4 mmol) in dry THF (5 mL) was added. The mixture was allowed to
warm to room temperature and stirred for 2 hours, quenched with NH₄Cl (10 mL of a saturated aqueous solution), diluted with water (20 mL) and extracted with CH₂Cl₂ (2x30 mL). The organic layers were dried over MgSO₄ and then purified by flash chromatography (gradient; 1-5% EtOAc/hexanes) to give the product as a colorless oil (759.8.2 mg, 63%). Rᵣ = 0.75 (10% EtOAc/hexanes); IR (neat) 3028, 2942, 2871, 17.29, 1673, 1603, 1496, 1454 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.30-7.17 (m, 5H), 3.62 (t, J = 5.1 Hz, 2H), 2.97 (t, J = 6.9 Hz, 2H), 2.86 (t, J = 7.8 Hz, 2H), 2.39 (t, J = 6.5 Hz, 2H), 1.66-1.61 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 187.2, 140.5, 128.7, 128.5, 126.4, 94.8, 81.1, 62.5, 47.1, 32.0, 30.1, 26.1, 24.5, 18.9, 18.5, -5.2; HRMS (ESI) Calcd for C₂₁H₃₃O₂Si (M+H)⁺ 344.2213, found 344.2217.

(R)-9-(tert-butyldimethylsilyloxy)-1-phenylnon-4-yn-3-ol (3-108)

Noyori catalyst [(R,R)-TsDPEN-Ru(p-cymene)Cl] (13.8 mg, 0.022 mmol, 0.01 eq) was added to a mixture of ynone 3-107 (747.3 mg, 2.17 mmol), sodium formate (1.4758 g, 21.7 mmol, 10 eq), TBAC (180.9 mg, 0.65 mmol, 0.3 eq) in CH₂Cl₂ (5 mL) and deionized H₂O (5 mL). The biphasic mixture was strongly stirred for 20 hours at room temperature, diluted with water (10 mL) and extracted with CH₂Cl₂ (2 x 10 mL). The organic layers were dried over MgSO₄ and then purified by flash chromatography (gradient; 2-10% EtOAc/Hexanes) to give the product as a colorless oil (550.8 mg, 73%) and matched all the previously reported data. Rᵣ = 0.25 (10% EtOAc/hexanes); [α]₀ = -7.7 (c 1.00, CH₂Cl₂); IR (neat) 3372, 2930, 2858, 1712, 1673, 1496, 1454 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.46-7.31 (m, 5H), 4.50 (q, J = 5.7 Hz, 1H), 3.78 (t, J = 6.3
Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.40 (t, J = 5.1 Hz, 2H), 2.14 (m, 2H), 1.94 (bs, 1H),
1.80-1.71 (m, 4H), 1.04 (s, 9H), 0.20 (s, 6H): $^{13}$C NMR (75 MHz, CDCl$_3$): δ 141.7, 128.7,
128.6, 126.1, 86.0, 81.4, 62.8, 62.2, 39.9, 32.1, 31.7, 26.2, 25.3, 18.7, 18.5, -5.1.

The enantiomeric excess (96%) was determined by HPLC analysis (Chiralcel
OD-H, 3% iPrOH in hexanes, 0.5 mL/min, 254 nm), t, 15.9 (minor), 20.3 (major).

(R,Z)-9-phenylnon-5-ene-1,7-diol (3-109).

Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 100 mg)
was added to a solution of 3-108 (508.1 mg, 1.44 mmol) in a mixture of Pentane/EtOAc
(10:1, 14.5 mL, 0.1M). The reaction mixture was stirred 1 hours under H$_2$ (1 atm). After
filtration over celite and removal of the solvent, crude product was recovered as a
colorless oil which was used for the next step without further purification.

A solution of TBAF 1M in THF (5.76 mL, 5.76 mmol, 4 eq) was added dropwise at
0°C to a solution of the silane obtained above (511.3 mg, 1.44 mmol) in dry THF (14
mL, 0.1M). The reaction was stirred for 3 hours at the same temperature and water (10
mL) was added dropwise. After dilution in brine (4 mL), the crude product was extracted
with EtOAc (3 x 30 mL), the combined organic layers were dried over MgSO$_4$ and the
solvent removed by vacuum. Flash chromatography (gradient; 30-40% EtOAc/hexanes)
afforded the product as a colorless oil (275.8 mg, 82% over two steps). $R_f$ = 0.29 (50%
EtOAc/hexanes); [α]$_D$ = +33.9 (c 1.00, CH$_2$Cl$_2$); IR (neat) 3328, 2931, 1452, 1153, 1044,
913, 699 cm$^{-1}$, $^1$H NMR (300 MHz, CDCl$_3$): δ 7.30-7.15 (m,5H), 5.50-5.41 (m, 2H), 4.43
(q, J = 7.0 Hz, 1H), 3.62 (t, J = 6.3 Hz, 2H), 2.71-2.65 (m, 2H), 2.16-1.37 (m, 10H); $^{13}$C
NMR (75 MHz, CDCl$_3$): δ 142.1, 132.9, 132.4, 128.6, 128.6, 128.6, 126.0, 67.2.5, 62.8, 39.2,
32.2, 31.9, 27.6, 26.0; HRMS (ESI) Calcd for C_{15}H_{26}NO_2 (M+NH_4)^+ 252.1958, found 252.1958.

The enantiomeric excess (96%) was determined by HPLC analysis (Chiralcel OD-H, 5% iPrOH in hexanes, 0.8 mL/min, 254 nm), t_r 22.8 (minor), 27.5 (major).

(R,E)-9-phenylnon-5-ene-1,7-diol (3-110)

Red-Al® (65%wt in Toluene, 3.3 mL, 6.5 mmol, 10 eq) was added dropwise at 0°C to a solution of 3-108 (224.8 mg, 0.65 mmol) in dry THF (7 mL, 0.1M). The reaction mixture was stirred 20h under N_2, quenched with sodium potassium tartrate (7 mL of a saturated aqueous solution), diluted with brine (3 mL) and extracted with EtOAc (3x30 mL). The organic layers were dried over MgSO_4 and the crude product was recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF 1M in THF (1.95 mL, 1.95 mmol, 3 eq) was added dropwise at 0°C to a solution of the silane obtained above (226.2 mg, 0.65 mmol) in dry THF (7 mL, 0.1M). The reaction was stirred for 3 hours at the same temperature and water (5 mL) was added dropwise. After dilution in brine (2 mL), the crude product was extracted with EtOAc (3x15 mL), the combined organic layers were dried over MgSO4 and the solvent removed by vacuum. Flash chromatography (gradient; 30-40% EtOAc/hexanes) afforded the product as a colorless oil (141.1 mg, 93% over two steps); R_f = 0.16 (40% EtOAc/hexanes; [α]_D = -8.7 (c 1.00, CH_2Cl_2); IR (neat) 3340, 2932, 2860, 1054, 970, 699 cm^{-1}; ^1H NMR (300 MHz, CDCl_3): δ 7.30-7.15 (m, 5H), 5.70-5.60 (dt, J = 6.3, 15.3 Hz, 1H), 5.54-5.46 (ddt, J = 1.5, 6.6, 15.3 Hz, 1H), 4.07 (q, J = 6.5 Hz, 1H), 3.63 (t, J =
6.5 Hz, 2H), 2.72-2.65 (m, 2H), 2.07 (q, \( J = 134 \) Hz, 2H), 1.91-1.42 (m, 8H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 142.2, 133.4, 132.1, 128.6, 128.6, 126.0, 72.5, 62.9, 39.0, 32.3, 32.1, 32.0, 25.5; HRMS (ESI) Calcd for C\(_{15}\)H\(_{26}\)NO\(_2\) (M+NH\(_4\))\(^{\cdot}\) 252.1958, found 252.1960.

The enantiomeric excess (96%) was determined by HPLC analysis (Chiralcel OD-H, 5% iPrOH in hexanes, 0.8 mL/min, 254 nm), \( t_r \) 29.7 (minor), 32.3 (major).

\((R,E)-2-(4-phenylbut-1-enyl)tetrahydro-2H-pyran (3-111)\)

Dry CH\(_2\)Cl\(_2\) (1.1 mL) was added to an aluminum foil covered test tube containing PPh\(_3\)AuCl (2.1 mg, 0.0042 mmol, 1 mol %), AgOTf (1.1 mg, 0.0042 mmol, 1 mol %) and activated MS 4Å (80 mg). After stirring for 10 minutes, a solution of diol \( 3\text{-}109 \) (100.3 mg, 0.42 mmol) in dry CH\(_2\)Cl\(_2\) (1.1 mL) was added. After TLC analysis showed the reaction to be complete (40 min), it was diluted with CH\(_2\)Cl\(_2\) and filtered through a short plug of silica. The solution of crude product was concentrated, and then purified by flash chromatography (5% EtOAc/hexanes) to give the product as a colorless oil (86.5 mg, 94%); \([\alpha]_D = -14.1 \) (c 1.00, CH\(_2\)Cl\(_2\)).

The enantiomeric excess (93%) was determined by HPLC analysis (Regis Pirkle Covalent , 1% iPrOH in hexanes, 0.5 mL/min, 254 nm), \( t_r \) 13.3 (minor), 19.8 (major);

The absolute configurations of \( 3\text{-}111 \) and \( 3\text{-}112 \) have been determined by comparison of optical rotations with known derivatives \((R)-3\text{-}113 \) and \((S)-3\text{-}114\).

\((S,E)-2-(4-phenylbut-1-enyl)tetrahydro-2H-pyran (3-112)\).
Dry CH$_2$Cl$_2$ (1.4 mL) was added to an aluminum foil covered test tube containing PPh$_3$AuCl (2.8 mg, 0.0056 mmol, 1 mol %), AgOTf (1.4 mg, 0.0056 mmol, 1 mol %) and activated MS 4Å (80 mg). After stirring for 10 minutes, a solution of diol 3-110 (131.2 mg, 0.56 mmol) in dry CH$_2$Cl$_2$ (1.4 mL) was added. After TLC analysis showed the reaction to be complete (35 min), it was diluted with CH$_2$Cl$_2$ and filtered through a short plug of silica. The solution of crude product was concentrated, and then purified by flash chromatography (5% EtOAc/hexanes) to give the product as a colorless oil (109.8 mg, 91%) and matched all the previously reported data; 18 R$_f$ = 0.80 (5% EtOAc/hexanes); [α]$_D$ = +13.6 (c 1.00, CH$_2$Cl$_2$); IR (neat) 2931,1158, 1083, 1035 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): δ 7.30-7.15 (m, 5H), 5.72 (dt, J = 15.6, 6.6 Hz,1H), 5.51 (dd, J = 15.6 ,6.3 Hz, 1H), 3.99 (m, 1H), 3.74 (m, 1H), 2.46 (dt, J = 2.7, 11.4 Hz, 1H), 2.70 (t, J = 7.2, 2H), 2.34 (q, J = 7.5 Hz, 2H), 1.85-1.26 (m, 6H); 13C NMR (75 MHz, CDCl$_3$): δ 142.2, 132.1, 131.0, 128.6, 128.5, 126.0, 78.4, 68.5, 35.8, 34.4, 32.3, 26.1 23.6; HRMS (ESI) Calcd for C$_{15}$H$_{21}$O (M+H)$^+$ 217.1587, found 217.1593.

The enantiomeric excess (93%) was determined by HPLC analysis (Regis Pirkle Covalent , 1% iPrOH in hexanes, 0.5 mL/min, 254 nm), t$_r$ 13.3 (major), 19.8 (minor).

(R)-(tetrahydro-2H-pyran-2-yl)methanol (3-113).

3-111 (74.6 mg, 0.35 mmol) was dissolved in dry CH$_2$Cl$_2$/MeOH (1/1, 8 mL), and the solution was cooled to -78°C. Ozone was passed into the solution using a gas dispersion tube. At the end of the reaction, after approximately 30 min, the solution becomes blue, was purged 5 min with O$_2$, warmed up to 0°C, NaBH$_4$ (131.5 mg, 3.46 mmol, 10 eq) was added portionwise at the same temperature and stirred 2 hours at
room temperature. H₂O (5 mL) was added and the crude was extracted with CH₂Cl₂ (3x10mL) and dried over MgSO₄. The solution of crude product was concentrated, and then purified by flash chromatography (gradient; 5, 10, 20% EtOAc/hexanes) to give the product as a colorless oil (37.5 mg, 93%), [α]D = -16.3 (c 1.00, CHCl₃) that satisfactorily matched all previously reported data.¹⁷

(S)-(tetrahydro-2H-pyran-2-yl)methanol (3-114).

3-112 (60.8 mg, 0.28 mmol) was dissolved in dry CH₂Cl₂/MeOH (1/1, 6mL), and the solution was cooled to -78°C. Ozone was passed into the solution using a gas dispersion tube. At the end of the reaction, after approximately 30 min, the solution becomes blue, was purged 5 min with O₂, warmed up to 0°C, NaBH₄ (106.7 mg, 2.82 mmol, 10 eq) was added portionwise at the same temperature and stirred 2 hours at room temperature. H₂O (5 mL) was added and the crude was extracted with CH₂Cl₂ (3x10mL) and dried over MgSO₄. The solution of crude product was concentrated, and then purified by flash chromatography (gradient; 5, 10, 20% EtOAc/hexanes) to give the product as a colorless oil (15.6 mg, 48%), [α]D = +15.7 (c 1.00, CHCl₃) that satisfactorily matched all previously reported data.

6.2.5 Synthesis of 3-120 and 3-121

Compound 3-115 has been described in the literature and when prepared here satisfactorily matched all previously reported data.
(R)-N-(2-(tert-butyldimethylsilyloxy)ethyl)-N-(4-hydroxy-5-methylhex-2-ynyl)-4-methylbenzenesulfonamide (3-117).

A 100 mL flask was charged with Zn(OTf)₂ (3.9996 g, 11.0 mmol) and (+)-N-methylephedrine (1.9723 g, 10.0 mmol) was added. To the flask was added toluene (29 mL) and triethylamine (1.1110 g, 11 mmol). The resulting mixture was stirred for 2 h at rt before 3-115 (3.6758 g, 10.0 mmol) in toluene (1 mL) was added in one portion. After stirring for 0.25 h at rt isobutylaldehyde 3-116 (721.1 mg, 10 mmol) was added in one portion. The reaction mixture was stirred at r.t. for 24 hours. The reaction was quenched by addition of NH₄Cl (sat.) (10 mL). The reaction mixture was poured into a separatory funnel containing CH₂Cl₂ (10 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2x20 mL). The combined organic portion was washed with NaCl (sat.) (10 mL), dried over anhydrous MgSO₄, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (gradient; 10, 20% EtOAc/hexanes) to give the product as a colorless oil (4.0432 g, 92%) which decomposed rapidly and was used for the next steps the same day; Rᵣ = 0.78 (50% EtOAc/hexanes); ¹H NMR (300 MHz, CDCl₃): δ = 7.74 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.30 (s, 2H), 3.91 (br, 1 H), 3.82 (t, J = 6.0 Hz, 2H), 3.32 (dt, J = 1.5, 5.5 Hz, 2H), 2.42 (s, 1H), 1.64 (m, J = 6.5 Hz, 1H), 1.29 (d, J = 5.5 Hz, 1H), 0.88 (s, 9H), 0.81 (dd, J = 6.5, 1.5 Hz, 6H), 0.06 (s, 6H); HRMS (ESI) Calcd for C₂₂H₃₄NNaO₄SSi (M+Na)⁺: 462.2105, found 462.2093.
(R,Z)-N-(4-hydroxy-5-methylhex-2-enyl)-N-(2-hydroxyethyl)-4-methylbenzene sulfonamide (3-118).

Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 141.6 mg) and quinoline (141.6 mg) were added to a solution of 3-117 (708.4 mg, 0.68 mmol) in dry MeOH (8.1 mL). The reaction mixture was stirred 2 days under H₂ (1 atm). After filtration over celite and removal of the solvent, crude product was recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF (1.0M in THF, 4.83 mL) was added dropwise at 0°C to a solution of the silyl ether obtained above in dry THF (5 mL). The reaction was stirred 16h at the same temperature and NaHCO₃ saturated (30 mL of a saturated aqueous solution) was added dropwise. After dilution in water (3 mL), the crude product was extracted with CH₂Cl₂ (2x20 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by vacuum. Flash chromatography (Gradient 20%, 50%, 70% EtOAc/hexanes) afforded the product as a colorless oil (489.0 mg, 93%); Rᵣ = 0.15 (60% EtOAc/hexanes); [α]D = +23.3 (c 1.00, CH₂Cl₂); IR (neat) 3333, 2959, 2873, 1593, 1503, 1456, 1384, 1368 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.65 (d, J = 8.5 Hz, 2H), 7.27 (d, 8.5 Hz, 2H), 5.53 (t, J = 10.0 Hz, 1H), 5.37-5.32 (m, 1H), 4.02-3.85 (m, 3H), 3.93 (t, J = 11.0 Hz, 2H), 3.26-3.16 (m, 2H), 3.08 (br, 1H), 2.87 (br, 1H), 2.43 (s, 3H), 1.65-1.58 (m, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.77 (d, J = 6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 143.8, 136.6, 135.5, 130.0, 127.3, 127.0, 72.0, 61.8, 49.9, 46.4, 34.1, 21.7, 18.4, 18.1; HRMS (ESI) Calcd for C₁₆H₂₅NNaO₄S (M+Na)⁺: 350.1397; found 350.1387.

Enantiomeric excess (97%) was determined by HPLC analysis (Chiralpack IA, 10% iPrOH in hexanes, 1.0 mL/min, 254 nm), tᵣ 14.1 (minor), 15.3 (major).

A solution of 3-117 (794.0 mg, 1.80 mmol) in THF (2 mL) was added dropwise at 0°C to a suspension of LiAlH₄ (205.2 mg, 5.40 mmol) in THF (2.5 mL). The reaction was stirred at the same temperature for 3h and quenched by addition of H₂O (200 μL). The crude mixture was treated with a NaOH solution (15% in H₂O, 200 μL), H₂O (600 μL) and stirred at r.t. for 1h. After filtration, the crude mixture was dried over MgSO₄, recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF (1.0M in THF, 5.4 mL) was added dropwise at 0°C to a solution of the silyl ether obtained above in dry THF (9 mL). The reaction was stirred 16h at the same temperature and NaHCO₃ saturated (30 mL of a saturated aqueous solution) was added dropwise. After dilution in water (20 mL), the crude product was extracted with CH₂Cl₂ (3x20 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by vacuum. Flash chromatography (Gradient 30, 40, 50, 60, 70% EtOAc/hexanes) afforded the product as a colorless oil (394.7 mg, 67%); Rᵣ = 0.18 (60% EtOAc/hexanes); [α]D = +14.7 (c 0.60, CH₂Cl₂); IR (neat) 3408, 2959, 2929, 2874, 1598, 1469, 1446, 1335 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.70 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz), 5.63 (dd, J = 15.5, 6.5 Hz, 1H), 5.54 (dt, J = 15.5, 6.0 Hz, 1H), 3.88 (dd, J = 15.0, 5.5 Hz, 1H), 3.80-3.72 (m, 4H), 3.28-3.17 (m, 2H), 3.04 (br, 1H), 2.52 (br, 1H), 2.43 (s, 3H), 1.70-1.64 (m, 1H), 0.86 (dd, J = 21.0, 6.5 Hz, 6H); ¹³C NMR (75 MHz,
CDCl₃): δ = 143.8, 136.5, 136.3, 130.0, 127.5, 126.6, 77.2, 61.2, 51.4, 50.0, 33.8, 21.7, 18.3, 18.1; HRMS (ESI) Calcd for C₁₆H₂₅NNaO₄S (M+Na)⁺ 350.1397, found 350.1389.

Enantiomeric excess (94%) was determined by HPLC analysis (Chiralpack IA, 20% iPrOH in hexanes, 1.0 mL/min, 254 nm), tₘ 9.4 (major), 15.8 (minor).

(S,E)-2-(3-methylbut-1-enyl)-4-tosylmorpholine (3-120).

Anhyd CH₂Cl₂ (1.3 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph₃PAuCl (5.0 mg, 0.010 mmol, 2.0 mol%), AgOTf (2.5 mg, 0.010 mmol, 2.0 mol%), and activated 4 Å MS (100 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-118 (163.0 mg, 0.50 mmol) in anhyd CH₂Cl₂ (1.3 mL) was then added. After 3 h, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH₂Cl₂ (10 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 50%, 90% CH₂Cl₂/hexanes) to give 143.2 mg (93%) of the title compound as a white solid; [α]D = +119.1 (c 1.00, CH₂Cl₂).

Enantiomeric excess (96%) was determined by HPLC analysis (Regis Pirckel Covalent, 10% iPrOH in hexanes, 1.5 mL/min, 254 nm), tₚ 22.0. (minor), 31.5 (major).

(R,E)-2-(3-methylbut-1-enyl)-4-tosylmorpholine (3-121).
Anhyd CH₂Cl₂ (0.7 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph₃PAuCl (3.2 mg, 0.006 mmol, 2.0 mol%), AgOTf (1.6 mg, 0.006 mmol, 2.0 mol%), and activated 4 Å MS (50 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-119 (105.6 mg, 0.32 mmol) in anhyd CH₂Cl₂ (0.8 mL) was then added. After 3 h, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH₂Cl₂ (10 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 50%, 90% CH₂Cl₂/hexanes) to give 90.1 mg (91%) of the title compound as a white solid; mp 93-95 °C; R_f = 0.16 (50% CH₂Cl₂/hexanes); [α]D = -121.0 (c 1.00, CH₂Cl₂); IR (neat) 2960, 2867, 1725, 1597, 1449, 1349 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.64 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 5.76 (ddd, J = 15.5, 6.5, 1.0 Hz, 1H), 5.26 (ddd, J = 15.5, 6.5, 1.0 Hz, 1H), 3.99 (dt, J = 7.0, 2.5 Hz, 1H), 3.92 (dd, J = 12.0, 2.0 Hz, 1H), 3.70 (dt, J = 12.0, 2.5 Hz, 1H), 3.55 (ddd, J = 23.5, 11.0, 2.0 Hz, 1H), 2.44 (s, 3H), 2.39 (dt, J = 11.0, 3.0 Hz, 1H), 2.28-2.50 (m, 1H), 2.11 (t, J = 10.8 Hz, 1H), 0.97 (d, J = 6.6 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 144.1, 142.4, 130.0, 129.8, 128.0, 123.6, 76.1, 65.9, 50.5, 45.5, 31.0, 22.1, 21.7; HRMS (ESI) Calcd for C₁₆H₂₄NO₅S (M+H)+ 310.1471, found 310.1476.

Enantiomeric excess (93%) was determined by HPLC analysis (Regis Pirckel Covalent, 10% iPrOH in hexanes, 1.5 mL/min, 254 nm), t_r 22.0. (major), 31.5 (minor).

The absolute configurations of 3-120 and 3-121 have been determined by comparison of optical rotation with known derivative 3-122.
(S)-2-methyl-4-tosylmorpholine (3-122).

3-120 (80.3 mg, 0.25 mmol) was dissolved in dry CH₂Cl₂/MeOH (1/1, 10mL), and the solution was cooled to -78°C. Ozone was passed into the solution using a gas dispersion tube. At the end of the reaction, after approximately 10 min, the solution becomes blue, was purged 5 min with O₂, warmed up to 0°C, NaBH₄ (47.3.3 mg, 1.25 mmol, 3 eq) was added portionwise at the same temperature and stirred 2 hours at room temperature. H₂O (2 mL) was added and the crude was extracted with CH₂Cl₂ (3x10mL) and dried over MgSO₄. The crude product was concentrated and recovered as a colorless oil which was used for the next step without further purification.

Et₃N (37.8 mg, 0.38 mmol) and MsCl (43.0 mg, 0.38 mmol) were added to a solution of the alcohol obtained above in dry CH₂Cl₂ (2 mL) at 0°C. The reaction mixture was stirred at r.t. for 18h and applied to a short plug of silica. The crude was concentrated and recovered as a yellow oil which was used for the next step without further purification.

A solution of the mesylate obtained above in dry THF (1 mL) was added dropwise at 0°C to a suspension of LiAlH₄ (47.7 mg, 1.17 mmol) in dry THF (1 mL). After 40 min at reflux, TLC analysis indicated a complete reaction and the mixture was quenched by addition of H₂O (50 μL). The crude mixture was treated with a NaOH solution (15% in H₂O, 50 μL), H₂O (150 μL) and stirred at r.t. for 1h. After filtration, the crude mixture was dried over MgSO₄, and purified by flash chromatography (100% CH₂Cl₂) to give 33.3 mg (64%) of the title compound as a colorless oil that satisfactorily matched all previously reported data. [α]D = +29.8 (c = 0.8, CH₂Cl₂); lit. [α]D = +31.7 (c = 0.8, CH₂Cl₂).99
6.2.6 Synthesis of 3-129 and 3-131

Compound 3-126 has been described in the literature and when prepared here satisfactorily matched all previously reported data.

A 50 mL flask was charged with Zn(OTf)$_2$ (1.6750 g, 4.61 mmol) and (+)-N-methylephedrine (827.5 mg, 4.61 mmol) was added. To the flask was added toluene (9 mL) and triethylamine (641 μL, 4.61 mmol). The resulting mixture was stirred for 2 h at rt before 3-126 (1.00 g, 3.85 mmol) in toluene (1 mL) was added in one portion. After stirring for 0.25 h at rt iso-butylaldehyde (415.8 mg, 5.77 mmol) was added in one portion. The reaction mixture was stirred at rt for 20 hours. The reaction was quenched by addition of NH$_4$Cl (sat.) (3 mL). The reaction mixture was poured into a separatory funnel containing diethyl ether (10 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined ethereal portion was washed with NaCl (sat.) (10 mL), dried over anhydrous MgSO$_4$, filtered and concentrated invacuo. The crude material was purified by flash chromatography (gradient: 5,10% EtOAc/hexanes) to give the product as a colorless oil (1.0987 g, 87%); $R_l = 0.15$ (10% EtOAc/hexanes); $[\alpha]_D = +4.5$ (c 1.00, CH$_2$Cl$_2$); IR (neat) 3399, 2958, 2931, 2859, 1491, 1254, 925, 838, 780 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 7.17-7.06 (m, 2H), 6.87 (t, $J = 7.4$ Hz, 1H), 6.77 (d, $J = 7.8$ Hz, 1H), 4.13 (t, $J = 5.4$ Hz, 1H), 2.81 (t, $J = 7.8$ Hz, 2H), 2.50 (dt, $J = 7.5$, 1.5 Hz, 2H), 1.87-1.76 (m,1H), 1.64 (d, $J = 5.7$ Hz, 1H), 1.02 (s, 9H), 0.95 (dd, $J = 6.9$, 4.5 Hz, 6H) 0.24 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$):
δ = 153.8, 131.4, 130.6, 127.6, 121.2, 118.6, 86.1, 80.5, 68.4, 34.8, 30.6, 26.0, 19.5, 18.4, 18.3, 17.6, -3.9; HRMS (ESI) Calcd for C_{20}H_{33}O_{2}Si (M+H)^+: 333.2244, found 333.2257.

Enantiomeric excess (98%) was determined by HPLC analysis (Regis Pirckel Covalent, 2% iPrOH in hexanes, 0.3 mL/min, 254 nm), t_r 19.1 (minor), 20.3 (major);

(R,E)-2-(5-hydroxy-6-methylhept-3-enyl)phenol (3-128).

[Cp*Ru(MeCN)_{3}]PF_{6} catalyst (3 mol%, 23.0 mg, 0.045 mmol) was added to a solution of 3-127 (500.0 mg, 1.51 mmol) and ethoxydimethylsilane (236.0 mg, 2.26 mmol) in CH_{2}Cl_{2} (5 mL) at 0° C. The ice-bath was removed and the reaction mixture stirred for 15 minutes at rt. After filtration over a short plug of florisil and removal of the solvent, crude product was recovered as a yellow oil which was used for the next step without further purification. A solution of TBAF (1.0M in THF, 6.04 mL) was added dropwise at 0°C to a solution of the silane obtained above and CuI (28.7 mg, 0.15 mmol) in dry THF (7.5 mL). The reaction was stirred 16h at the same temperature and NH_{4}Cl (sat.) (5 mL) was added dropwise. After dilution in water (20 mL), the crude product was extracted with EtOAc (2x30 mL), the combined organic layers were dried over MgSO_{4} and the solvent removed by vacuum. Flash chromatography (20% EtOAc/Hexanes) afforded the product as a colorless oil (265.4 mg, 80%); R_f = 0.18 (50% EtOAc/Hexanes); [α]_{D} = -8.0 (c 1.00, CH_{2}Cl_{2}); IR (neat) 3347, 2960, 2930, 2874, 1457, 1368, 1240, 1000, 973, 752 cm^{-1}; ^{1}H NMR (300 MHz, CDCl_{3}): δ = 7.12 (m, 2H), 6.85 (t, J = 7.4 Hz, 2H), 6.57 (d, J = 7.8 Hz, 1H), 5.70 (dt, J = 15.3, 6.6 Hz, 1H), 5.49
(ddt, $J = 15.3, 7.5, 1.2$ Hz, 1H), 5.29 (bs, 1H), 3.77 (t, $J = 6.9$ Hz, 1H), 2.71 (t, $J = 6.9$ Hz, 2H), 2.38 (q, $J = 7.5$ Hz, 2H), 1.66 (m, 2H), 0.87 (dd, $J = 18.3, 6.3$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 153.8, 132.6, 131.9, 130.5, 128.0, 127.4, 120.9, 115.6, 78.6, 33.9, 32.7, 30.1, 18.4, 18.3$; HRMS (ESI) Calcd for C$_{14}$H$_{24}$NO$_2$ (M+NH$_4$)$^+$: 238.1802, found 238.1803.

Enantiomeric excess (98%) was determined by HPLC analysis (Chiralcel OD-H, 10% iPrOH in hexanes, 1.0 mL/min, 254 nm), $t_r$ 12.3 (major), 13.6 (major).

(S,E)-2-(3-methylbut-1-enyl)chroman (3-129).

Anhyd CH$_2$Cl$_2$ (1.4 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (16.9 mg, 0.034 mmol, 5.0 mol %), AgOTf (8.7 mg, 0.034 mmol, 5.0 mol%), and activated 4 Å MS (90 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-128 (150.0 mg, 0.68 mmol) in anhyd CH$_2$Cl$_2$ (1 mL) was then added. After 2.5 hours, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (10 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 0, 5% EtOAc/hexanes) to give 122.1 mg (89%) of the title compound 3-129 as a colorless oil; $R_f = 1.0$ (5% EtOAc/hexanes); $[\alpha]_D = +69.4$ (c 1.04, CH$_2$Cl$_2$); IR (neat) 2958, 2928, 2869, 2583, 1488, 1230, 971, 752 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.11$-$7.02$ (m, 2H), 6.85-6.80 (m, 2H), 5.79 (ddt, $J = 15.6, 6.3, 1.2$ Hz, 1H), 5.56 (ddt, $J = 15.6, 6.6, 0.9$ Hz, 1H), 4.50-4.43 (m, 1H), 2.92-2.71 (m, 2H), 2.40-2.28 (m, 1H), 2.05-1.99 (m, 1H), 1.88-1.77 (m, 1H), 1.02 (dd, $J = 6.6, 0.9$ Hz, 6H);
$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 154.9, 140.6, 129.7, 127.4, 126.7, 122.0, 120.2, 117.0, 76.8, 30.9, 28.3, 24.7, 22.4, 22.3$; HRMS (ESI) Calcd for C$_{14}$H$_{19}$O (M+H)$^+$: 203.1430, found 203.1433.

(R,Z)-2-(5-hydroxy-6-methylhept-3-enyl)phenol (3-130).

Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 30 mg) was added to a solution of 3-127 (335.6 mg, 1.01 mmol) in dry MeOH (5 mL). The reaction mixture was stirred 1.5 hour under H$_2$ (1 atm). After filtration over celite and removal of the solvent, crude product was recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF (1.0M in THF, 4.0 mL) was added dropwise at 0°C to a solution of the silane obtained above in dry THF (5 mL). The reaction was stirred 16h at the same temperature and NaHCO$_3$ saturated (30 mL of a saturated aqueous solution) was added dropwise. After dilution in water (20 mL), the crude product was extracted with EtOAc (2 x 30 mL), the combined organic layers were dried over MgSO$_4$ and the solvent removed by vacuum. Flash chromatography (Gradient 15, 20% EtOAc/hexanes) afforded the product as a colorless oil (192.7 mg, 87%); $R_f = 0.35$ (30% EtOAc/hexanes); $[\alpha]_D = +1.2$ (c 1.00, CH$_2$Cl$_2$); IR (neat) 3337, 2959, 2930, 1491, 1457, 1259, 1015, 924, 838, 753 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.12$ (m, 2H), 6.85 ($J = 7.4$ Hz, 2H), 6.57 (d, $J = 7.8$ Hz, 1H), 6.47 (br, 1H), 5.70-5.60 (m, 1H), 5.41 (t, $J = 9.0$ Hz, 1H), 4.08 (t, $J = 8.0$ Hz, 1H), 2.82-2.25 (m, 4H), 1.71-1.60 (m, 2H), 1.80 (br, 1H); 0.87 (dd, $J = 27.0$, 6.9 Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 154.2, 132.9, 131.3,$
130.8, 128.0, 127.6, 120.5, 115.7, 72.9, 33.8, 30.6, 28.2, 18.5, 18.1; HRMS (ESI) Calcd for C$_{14}$H$_{24}$NO$_{2}$ (M+NH$_4$)$^+$: 238.1802, found 238.1800.

Enantiomeric excess (97%) was determined by HPLC analysis (Chiralcel OD-H, 3% iPrOH in hexanes, 1.0 mL/min, 254 nm), t$_r$ 12.8 (minor), 13.4 (major).

![Structure](image)

$(R,E)$-2-(3-methylbut-1-enyl)chroman (3-131).

Anhyd CH$_2$Cl$_2$ (1.2 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (10.8 mg, 0.022 mmol, 5.0 mol%), AgOTf (5.6 mg, 0.022 mmol, 5.0 mol%), and activated 4 Å MS (80 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-130 (96.4 mg, 0.43 mmol) in anhyd CH$_2$Cl$_2$ (1 mL) was then added. After 2 h, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (10 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 0, 5% Et$_2$O/hexanes) to give 80.8 mg (92%) of the title compound $(R)$-42 as a colorless oil; $R_f$ = 1.0 (5% EtOAc/hexanes); $[\alpha]_D = -67.4$ (c 1.00, CH$_2$Cl$_2$).

The absolute configurations and ee of 3-130 and 3-131 have been determined by HPLC analysis and comparison of optical rotations with known derivatives 3-132 and 3-133.

![Structure](image)

$(S)$-chroman-2-ylmethanol (3-132).
3-129 (64.3 mg, 0.32 mmol) was dissolved in dry CH$_2$Cl$_2$/MeOH (1/1, 10mL), and the solution was cooled to -78ºC. Ozone was passed into the solution using a gas dispersion tube. At the end of the reaction, after approximately 10 min, the solution becomes blue, was purged 5 min with O$_2$, warmed up to 0ºC, NaBH$_4$ (35.3 mg, 0.95 mmol, 3 eq) was added portionwise at the same temperature and stirred 2 hours at room temperature. H$_2$O (5 mL) was added and the crude was extracted with CH$_2$Cl$_2$ (3x10mL) and dried over MgSO$_4$. The solution of crude product was concentrated, and then purified by flash chromatography (20% EtOAc/hexanes) to give the product as a colorless oil (45.9 mg, 88%); [α]$_D$ = +87.6 (c = 1.01, MeOH) that satisfactorily matched all previously reported data.$^{101}$

Enantiomeric excess (70%) was determined by HPLC analysis (Chiralcel AD, 3% iPrOH in hexanes, 0.6 mL/min, 254 nm), t, 25.4 (major), 30.7 (minor).

![Chemical Structure](image)

(R)-chroman-2-ylmethanol (3-133).

3-131 (31.4 mg, 0.15 mmol) was dissolved in dry CH$_2$Cl$_2$/MeOH (1/1, 8mL), and the solution was cooled to -78ºC. Ozone was passed into the solution using a gas dispersion tube. At the end of the reaction, after approximately 10 min, the solution becomes blue, was purged 5 min with O$_2$, warmed up to 0ºC, NaBH$_4$ (28.6 mg, 0.77 mmol, 5 eq) was added portionwise at the same temperature and stirred 1 hours at room temperature. H$_2$O (5 mL) was added and the crude was extracted with CH$_2$Cl$_2$ (3x10 mL) and dried over MgSO$_4$. The solution of crude product was concentrated, and then purified by flash chromatography (20% EtOAc/hexanes) to give the product as a colorless oil (19.6 mg, 77%) that satisfactorily matched all previously reported data.
Enantiomeric excess (70%) was determined by HPLC analysis (Chiralcel AD, 3% iPrOH in hexanes, 0.6 mL/min, 254 nm), t<sub>r</sub> 25.4 (minor), 30.7 (major).

6.2.7 Synthesis of 3-144 and 3-146

Compounds 3-136<sup>103</sup> and 3-141 (>98% ee)<sup>104</sup> have been described in the literature and when prepared here satisfactorily matched all previously reported data.

\[
\text{(R)-1-((benzyloxy)-8-(tert-butyldimethylsilyloxy)-6-methyleneoct-3-yn-2-ol (3-142).}
\]

To a solution of 3-141 (573.5 mg, 3.25 mmol) and in dry DMF (3.25 mL) was added at rt, potassium carbonate (583.8 mg, 4.22 mmol), tetrabutylammonium bromide (157.0 mg, 0.49 mmol, 10 mol %) and copper iodide (61.9 mg, 0.33 mmol, 10 mol%). The mixture was stirred at the same temperature for 10 minutes and 3-136 (1.5210 g, 6.5 mmol, 2 eq) was added in one portion. After 48 hours, TLC analysis showed disappearance of the alcohol, water (3 mL) was added, the crude extracted with CH<sub>2</sub>Cl<sub>2</sub> (3x10 mL), dried over MgSO<sub>4</sub> purified by flash chromatography (Gradient 5, 10% EtOAc/hexanes) to give the product as a colorless oil (669.6 mg, 55%); <i>R<sub>f</sub></i> = 0.26 (10% EtOAc/ hexanes); [α]<sub>D</sub> = -0.8 (c 1.00, CH<sub>2</sub>Cl<sub>2</sub>); IR (neat) 3421, 2954, 2929, 2858, 1255, 1102, 835, 776 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.36-7.25 (m, 5H), 5.09 (q, <i>J</i> = 1.5Hz, 1H), 4.87 (q, <i>J</i> = 1.5 Hz, 1H), 4.60 (d, <i>J</i>=2.1 Hz, 2H), 3.73-3.52 (m, 5H), 2.98 (d, <i>J</i> = 1.5 Hz, 2H), 2.40-2.28 (m,1H), 2.05-1.99 (m, 1H), 1.88-1.77 (m, 1H), 1.02 (dd, <i>J</i> = 0.9, 6.6 Hz, 6H), 2.48 (d, <i>J</i> = 4.5 Hz, 1H), 2.29 (t, <i>J</i> = 6.8 Hz, 2H), 0.88 (s, 9H), 0.04 (s, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 141.5, 137.9, 128.7, 128.1, 128.0, 112.8, 83.6,
80.4, 74.1, 73.6, 62.4, 62.1, 39.1, 26.7, 26.1, 18.5, -5.1; HRMS (ESI) Calcd for C_{22}H_{35}O_3Si (M+H)^+: 375.2350, found 375.2346.

(R,E)-8-(benzyloxy)-3-methyleneoct-5-ene-1,7-diol (3-143).

[Cp*Ru(MeCN)_3]PF_6 catalyst (15.4 mg, 0.03 mmol, 3 mol%) was added to a solution of 3-142 (372.1 mg, 0.99 mmol) and ethoxydimethylsilane (207.0 mg, 1.98 mmol) in CH_2Cl_2 (3 mL) at 0°C. The ice-bath was removed and the reaction mixture stirred for 15 minutes at rt. After filtration over a short plug of florisil and removal of the solvent, crude product was recovered as a yellow oil which was used for the next step without further purification. A solution of TBAF (1.0M in THF, 2.97 mL) was added dropwise at 0°C to a solution of the silane obtained above and CuI (38.0 mg, 0.20 mmol, 20 mol %) in dry THF (5 mL). The reaction was stirred 16 h at the same temperature and NH_4Cl (sat.) (5 mL) was added dropwise. After dilution in water (20 mL), the crude product was extracted with EtOAc (2 x 30 mL), the combined organic layers were dried over MgSO_4 and the solvent removed by vacuum. Flash chromatography (40% EtOAc/Hexanes) afforded the product as a colorless oil (183.4 mg, 70%); R_f = 0.23 (50% EtOAc/hexanes); [α]_D = +5.8 (c 1.00, CH_2Cl_2); IR (neat) 3416, 2954, 2929, 2858, 1471, 1454, 1389, 1361 cm^{-1}; ^1H NMR (300 MHz, CDCl_3): δ = 7.38-7.26 (m, 5H), 5.77 (dt, J = 15.9, 6.6 Hz, 1H), 5.50 (ddd, J = 15.6, 6.6, 1.5 Hz, 1H), 4.87 (d, J = 8.1 Hz, 2H), 4.56 (s, 2H), 4.33 (m,1H), 3.68 (t, J = 6.3 Hz, 2H), 3.51 (dd, J = 9.6, 3.3 Hz, 1H), 3.37 (dd, J = 9.6, 8.4 Hz, 1H), 2.77 (d, J = 6.6 Hz, 1H), 2.62 (br, 1H), 2.28 (t, J = 6.3 Hz, 1H), 1.71 (br, 1H); ^13C NMR (75 MHz, CDCl_3): δ = 144.5, 138.0,
130.8, 130.6, 128.7, 128.0, 128.0, 113.1, 74.4, 73.5, 71.3, 60.5, 39.2, 39.1; HRMS (ESI) Calcd for C₁₆H₂₆NO₃ (M+NH₄)⁺: 280.1907; found 280.1916.

\[
\begin{align*}
\text{(R,E)-2-(3-(benzyloxy)prop-1-enyl)-4-methylenetetrahydro-2H-pyran (3-144).}
\end{align*}
\]

Anhyd CH₂Cl₂ (0.6 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph₃PAuCl (3.4 mg, 0.007 mmol, 3.0 mol%), AgOTf (1.7 mg, 0.007 mmol, 3.0 mol%), and activated 4 Å MS (50 mg). The heterogeneous mixture was vigorously stirred for 10 minutes and a solution of the corresponding diol 3-143 (61.4 mg, 0.22 mmol) in anhyd CH₂Cl₂ (0.6 mL) was then added. After 3 hours, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH₂Cl₂ (10 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 0%, 10% Et₂O/hexanes) to give 46.2 mg (85%) of the title compound as a colorless oil; Rᶠ = 0.25 (10% Et₂O/hexanes); [α]D = -13.3 (c 1.00, CH₂Cl₂); IR (neat) 2945, 1721, 1658, 1452, 1366 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.34-7.24 (m, 5H), 5.88-5.75 (m, 2H), 4.75 (d, J = 1.8 Hz, 2H), 4.52 (s, 2H), 4.11  (ddd, J = 10.8, 5.4, 1.8 Hz, 1H), 4.03 (d, J = 3.9 Hz, 2H), 3.84-3.78 (m, 1H), 3.43 (dt, J = 11.7, 2.7 Hz, 1H), 2.36-2.07 (m, 4H); ¹³C NMR (75 MHz, CDCl₃): δ = 144.2, 138.5, 133.41, 128.6, 128.0, 127.9, 127.8, 109.1, 78.6, 72.4, 70.3, 68.8, 41.3, 35.2; HRMS (ESI) Calcd for C₁₆H₂₁O₂ (M+H)⁺: 245.1536, found 245.1529.

The enantiomeric excess (98%) was determined by HPLC analysis (Regis Pirckel Covalent, 1% iPrOH in hexanes, 0.8 mL/min, 254 nm), t, 14.9 (minor), 19.6 (major).
(R,Z)-8-(benzyloxy)-3-methyleneoct-5-ene-1,7-diol (3-145)

Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 25 mg) and quinoline (25 mg) were added to a solution of 3-142 (254.3 mg, 0.68 mmol) in dry MeOH (5 mL). The reaction mixture was stirred 3 days under H₂ (1 atm). After filtration over celite and removal of the solvent, crude product was recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF (1.0M in THF, 2.04 mL) was added dropwise at 0°C to a solution of the silane obtained above in dry THF (5 mL). The reaction was stirred 16h at the same temperature and NaHCO₃ saturated (30 mL of a saturated aqueous solution) was added dropwise. After dilution in water (20 mL), the crude product was extracted with EtOAc (2x30 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by vacuum. Flash chromatography (Gradient 20, 40% EtOAc/hexanes) afforded the product as a colorless oil (192.7 mg, 87%); Rᵢ = 0.30 (50% EtOAc/hexanes); [α]D = +4.0 (c 1.00, CH₂Cl₂); IR (neat) 3398, 2924, 1722, 1453, 1381, 1275 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ = 7.38-7.26 (m, 5H), 5.65-5.45 (m, 2H), 4.85 (d, J = 10.2 Hz, 2H), 4.64 (dt, J = 7.8, 3.6 Hz, 1H), 4.56 (s, 2H), 3.68 (t, J = 7.8 Hz, 2H), 3.48-3.36 (m, 2H), 2.97-2.71 (m, 3H), 2.27 (t, J = 6.0 Hz, 2H), 1.91 (br, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 144.7, 138.0, 131.2, 129.8, 128.7, 128.1, 128.0, 112.8, 74.1, 73.6, 66.9, 60.8, 38.3, 34.7; HRMS (ESI) Calcd for C₁₆H₂₃O₃ (M+H)⁺: 263.1642, found 263.1651.
Anhyd CH$_2$Cl$_2$ (0.8 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (4.4 mg, 0.009 mmol, 3.0 mol%), AgOTf (2.2 mg, 0.009 mmol, 3.0 mol%), and activated 4 Å MS (60 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-145 (80.1 mg, 0.29 mmol) in anhyd CH$_2$Cl$_2$ (0.8 mL) was then added. After 2.5 hours, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (10 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 0, 10% Et$_2$O/hexanes) to give 65.2 mg (92%) of the title compound as a colorless oil; [α]$_D$ = +12.9 (c 1.00, CH$_2$Cl$_2$).

The enantiomeric excess (97%) was determined by HPLC analysis (Regis Pirckel Covalent, 1% iPrOH in hexanes, 0.8 mL/min, 254 nm), $t_r$ 14.9 (major), 19.3 (minor).

6.2.8 Synthesis of 3-154 and 3-156

Compound 3-150 has been synthesized by benzylation of the known (S)-1-(tert-butyl(dimethyl)silyloxy)hex-5-yn-3-ol (99% ee).$^{105}$ Compound 3-151 has been described in the literature and when prepared here satisfactorily matched all previously reported data.$^{106}$

(S)-(3-(benzyloxy)hex-5-ynyl)oxy)(tert-butyl)dimethylsilane (3-150).
(S)-1-(tert-butyldimethylsilyloxy)hex-5-yn-3-ol (191.4 mg, 0.83 mmol) in THF (1mL) was added dropwise at 0°C to a suspension of sodium hydride (39.8 mg, 1.67 mmol) in THF (2 mL). The mixture was stirred at rt for 1 hour and benzyl bromide (198.9 μL, 1.67 mmol) was added in one portion. The reaction was stirred 16h at the same temperature and H2O (5 mL) was added dropwise. The crude product was extracted with CH2Cl2 (2x20 mL), the combined organic layers were dried over MgSO4 and the solvent removed by vacuum. Flash chromatography (Gradient 0, 5% EtOAc/Hexanes) afforded the product as a colorless oil (223.8 mg, 85%); Rf = 0.71 (10% EtOAc/hexanes); [α]D = -18.6 (c = 1.00, CH2Cl2); IR (neat) 2956, 2859, 1472, 1259, 1113, 838, 774, 666 cm⁻¹; 1H NMR (500 MHz, CDCl3): δ 7.37-7.25 (m,5H), 4.58 (ABq, J = 11.4 Hz, ΔυAB = 43.2 Hz, 2H), 3.80-3.69 (m, 3H), 2.48 (dd, J = 5.7, 2.7 Hz, 2H), 2.00 (t, J = 2.7 Hz, 1H), 1.90-1.82 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); 13C NMR (75 MHz, CDCl3): δ = 138.8, 128.6, 128.0, 127.8, 81.4, 74.4, 71.9, 70.3, 59.6, 37.5, 26.2, 24.3, 18.5, -5.1; HRMS (ESI) Calcd for C19H31O2Si (M+H)+: 319.2088, found 319.2078.

(S)-3-(benzyloxy)-1-(tert-butyldimethylsilyloxy)tridec-5-yn-7-one (3-151a).

A solution of nBuLi in hexane 1.6M (2.41 mL, 3.85 mmol) was added dropwise over 10 minutes at -78°C to a solution of 3-150 (451.3 mg, 1.42 mmol) in dry THF (6 mL). The reaction was then stirred at the same temperature for 45 minutes and a solution of 3-151 (367.4 mg, 2.12 mmol) in dry THF (1 mL) was added. The mixture was allowed to warm to room temperature and stirred for 2 hours, quenched with NH4Cl (10 mL of a saturated aqueous solution), diluted with water (20 mL) and extracted with
CH₂Cl₂ (2x30 mL). The organic layers were dried over MgSO₄ and then purified by flash chromatography (gradient; 0, 5% EtOAc/Hexanes) to give the product as a colorless oil (476.6 mg, 78%). Rᵣ = 0.43 (5% EtOAc/hexanes); [α]D = +22.4 (c 1.00, CH₂Cl₂); IR (neat) 2956, 2930, 2860, 1720, 1672, 1273, 1168, 1099, 1071, 699 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.35-7.28 (m, 5H), 4.62 (ABq, J = 11.5 Hz, ΔυAB = 53.8 Hz, 2H), 3.87-3.80 (m, J = 6.0 Hz, 1H), 3.76 (m, 2H), 2.68 (dd, J = 5.5, 2.5 Hz, 2H), 2.54 (t, J = 7.5 Hz, 2H), 1.87 (q, J = 6.0Hz., 2H), 1.67 (m, J = 7.3 Hz, 2H), 1.35-1.30 (m, 6H), 0.92-0.88 (m, 12H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ 188.5 138.4, 128.6, 128.0, 127.9, 90.9, 82.4, 74.2, 72.1, 59.4, 45.8, 37.7, 31.7, 28.9, 26.2, 26.0, 25.0, 24.3, 22.7, 18.5, 14.3, -5.1, -5.1; HRMS (ESI) Calcd for C₂₆H₄₃O₃Si (M+H)^+: 431.3122; found 431.31125.

(3S,7R)-3-(benzyloxy)-1-(tert-butyldimethylsilyloxy)tridec-5-yn-7-ol (3-152).

Noyori catalyst [(R,R)-TsDPEN-Ru(p-cymene)Cl] (11.6 mg, 0.018 mmol, 0.02 eq) was added to a mixture of ynone 3-151a (396.3 mg, 0.92 mmol), sodium formate (635.6 mg, 9.20 mmol, 10 eq), TBAC (85.4 mg, 0.28 mmol, 0.3 eq) in CH₂Cl₂ (4 mL) and deionized H₂O (4 mL). The biphasic mixture was strongly stirred for 20 hours at room temperature, diluted with water (10 mL) and extracted with CH₂Cl₂ (2x10 mL). The organic layers were dried over MgSO₄ and then purified by flash chromatography (gradient; 5, 10% EtOAc/hexanes) to give the product as a colorless oil (274.1 mg, 71%); Rᵣ = 0.23 (10% EtOAc/hexanes); [α]D = +11.9 (c 1.00, CH₂Cl₂); IR (neat) 3428, 2924, 2857, 1470, 1256, 1097, 836, 776, 734, 607 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ...
7.45-7.28 (m, 5H), 4.62 (ABq, J = 11.5 Hz, ΔυAB = 67.5 Hz, 2H), 4.35 (q, J = 6.0 Hz, 1H), 3.80-3.71 (m, 3H), 2.57-2.48 (m, 2H), 1.92-1.41 (m, 13H), 1.36-1.26 (m, 12H), 0.08 (s, 6H); 13C NMR (75 MHz, CDCl3): δ 138.7, 128.6, 127.9, 127.8, 83.4, 82.1, 74.7, 71.8, 62.9, 59.6, 38.3, 37.6, 32.0, 29.2, 26.1, 25.4, 24.5, 22.8, 18.5, 14.3, -5.1, -5.1; HRMS (ESI) Calcd for C26H45O3Si (M+H)+: 433.3133, found 433.3146.

Diasteromeric ratio (97:3) was determined by Mosher’s Ester analysis.

\[
\text{Diasteromeric ratio (97:3)}
\]

(3S,7R,Z)-3-(benzyloxy)tridec-5-ene-1,7-diol (3-153).

Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 14.0 mg) and quinoline (14.0 mg) were added to a solution of 3-152 (69.3 mg, 0.16 mmol) in dry MeOH (1 mL). The reaction mixture was stirred 1.5 h under H2 (1 atm). After filtration over celite and removal of the solvent, crude product was recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF (1.0M in THF, 320 μL) was added dropwise at 0°C to a solution of the silyl ether obtained above in dry THF (1 mL). The reaction was stirred 16h and the mixture applied directly to flash chromatography (Gradient 30, 40, 50% EtOAc/hexanes) to afford the product as a colorless oil (41.3 mg, 81%); \( R_f = 0.24 \) (50% EtOAc/hexanes); [α]D = +20.3 (c 1.00, CH2Cl2); IR (neat) 3368, 2928, 2857, 1454, 1063, 736, 697 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl3): δ = 7.36-7.26 (m, 5H), 5.54 (m, 2H), 4.56 (ABq, J = 11.5 Hz, ΔυAB = 43.5 Hz, 2H), 4.36 (q, J = 6.8 Hz, 1H), 3.78-3.66 (m, 3H), 2.58-2.54 (m, 2H), 2.32-2.27 (m, 2H), 2.12 (bs, 1H), 1.85-1.71 (m, 2H), 1.2-1.27 (m, 9H), 0.88 (t, J = 6.8 Hz, 3H); 13C NMR (75 MHz, CDCl3): δ 138.1, 135.7, 128.7, 128.1,
Anhyd CH$_2$Cl$_2$ (200 μL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (0.4 mg, 0.001 mmol, 1.0 mol %), AgOTf (0.2 mg, 0.001 mmol, 1.0 mol%), and activated 4 Å MS (20 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-153 (24.1 mg, 0.08 mmol) in anhyd CH$_2$Cl$_2$ (150 μL) was then added. After 20 min, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (5 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 50, 70% CH$_2$Cl$_2$/hexanes) to give 19.0 mg (84%) of the pure diastereomer 3-154 as a colorless oil; R$_f$ = 0.65 (80% CH$_2$Cl$_2$/hexanes); [α]$_D$ = -9.2 (c 0.50, CH$_2$Cl$_2$); IR (neat) 2925, 2857, 1459, 1257, 1069, 735, 707 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ = 7.38-7.26 (m, 5H), 5.68 (ddt, $J$ = 15.5, 6.5, 1.0 Hz, 1H), 5.44 (ddt, $J$ = 15.5, 7.5, 1.0 Hz, 1H), 4.55 (d, $J$ = 2.0 Hz, 2H), 4.23-4.20 (m, 1H), 3.95-3.78 (m, 3H), 2.01 (q, $J$ = 7.5 Hz, 2H), 1.90-1.21 (m, 14H), 0.88 (t, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 139.1, 132.7, 130.9, 128.6, 127.7, 127.6, 72.9, 71.0, 70.2, 63.0, 36.5, 32.6, 31.9, 30.1, 29.3, 29.1, 22.8, 14.3; HRMS (ESI) Calcd for C$_{20}$H$_{31}$O$_2$ (M+H)$^+$: 303.2319, found 303.2321.

Diastereomeric ratio (4:96) was determined by $^1$H NMR of the crude material.
(3S,7R,E)-3-(benzyloxy)tridec-5-ene-1,7-diol (3-155).

A solution of 3-152 (184.0 mg, 0.43 mmol) in THF (1 mL) was added dropwise at 0°C to a suspension of LiAlH₄ (49.0 mg, 1.29 mmol) in THF (1 mL). The reaction was stirred at the same temperature for 48h, diluted with Et₂O (3 mL) and quenched by addition of H₂O (500 μL). The crude mixture was treated with a NaOH solution (15% in H₂O, 50 μL), H₂O (150 μL) and stirred at rt for 1h. After filtration, the crude mixture was dried over MgSO₄, recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF (1.0M in THF, 1 mL) was added dropwise at 0°C to a solution of the silyl ether obtained above in dry THF (3 mL). The reaction was stirred 16h and the mixture applied directly to flash chromatography (Gradient 30%, 40%, 50% EtOAc/Hexanes) to afford the product as a colorless oil (120.6 mg, 88%); Rᵣ = 0.22 (50% EtOAc/hexanes); [α]D = +14.1 (c 1.00, CH₂Cl₂); IR (neat) 3364, 2928, 2851, 1061, 1071, 739, 690 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.63-7.26 (m, 5H), 5.63 (dt, J = 15.0, 7.5 Hz, 1H), 5.56 (dd, J = 15.0, 6.3 Hz, 1H); 4.56 (ABq, J = 11.5 Hz, ΔυAB = 72.1 Hz, 2H), 4.03 (q, J = 6.5 Hz, 1H), 3.76-3.67 (m, 3H), 2.43-2.30 (m, 3H), 1.79-1.75 (m, 3H), 1.52-1.27 (m, 10H), 0.87 (t, J = 7.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 138.4, 136.5, 128.7, 128.1, 128.0, 127.0, 78.0, 73.1, 71.3, 60.8, 37.5, 36.5, 36.3, 32.0, 29.4, 25.6, 22.8, 14.3; HRMS (ESI) Calcd for C₂₀H₃₃O₃ (M+H)⁺: 321.2424, found 321.2431.
((2S,4R)-4-(benzyloxy)-2-((E)-oct-1-enyl)tetrahydro-2H-pyran (3-156).

Anhyd CH$_2$Cl$_2$ (250 μL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (0.6 mg, 0.001 mmol, 1.0 mol%), AgOTf (0.3 mg, 0.001 mmol, 1.0 mol%), and activated 4 Å MS (20 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-155 (37.3 mg, 0.12 mmol) in anhyd CH$_2$Cl$_2$ (250 μL) was then added. After 35 min, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (5 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 50, 70% CH$_2$Cl$_2$/hexanes) to give 30.5 mg (87%) of the pure diastereomer 3-156 as a colorless oil; R$_f$ = 0.60 (80% CH$_2$Cl$_2$/hexanes); [α]$_D$ = +2.3 (c 0.50, CH$_2$Cl$_2$); IR (neat) 2925, 1466, 1150, 1080 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ = 7.37-7.24 (m, 5H), 5.71 (ddt, J = 15.5, 6.5, 1.0 Hz, 1H), 5.51 (ddt, J = 15.5, 6.0, 1.5 Hz, 1H), 4.60 (s, 2H), 4.08 (ddd, J = 11.5, 5.0, 2.0 Hz, 1H), 3.75 (dd, J = 11.0, 6.5 Hz, 1H), 3.62-3.56 (m, 1H), 3.44 (dt, J = 13.0, 2.5 Hz, 1H), 2.13-1.97 (m, 4H), 1.64-1.25 (m, 10H), 0.90 (t, J = 7.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 138.9, 132.0, 130.3, 128.6, 127.8, 127.8, 74.8, 69.7, 66.2, 38.9, 32.8, 32.5, 31.9, 29.3, 29.1, 22.8, 14.3; HRMS (ESI) Calcd for C$_{20}$H$_{31}$O$_2$ (M+H)$^+$: 303.2319, found 303.2322.

6.2.9 Synthesis of 3-163 and 3-165

Compound 3-159 has been synthesized in two steps from the known (S)-N-(3-(benzyloxy)-2-hydroxypropyl)-4-methylbenzenesulfonyl amide 3-159a (99%
Compound 3-151 has been described in the literature and when prepared here satisfactorily matched all previously reported data.  

\[
\begin{align*}
\text{(S)-N-(3-(benzoxyl)-2-(tert-butylidimethylsilyloxy)propyl)-4-methyl-N-(prop-2-ynyl)benzenesulfonamide (3-159).} \\
\end{align*}
\]

To a solution of (S)-N-(3-(benzyloxy)-2-hydroxypropyl)-4-methylbenzenesulfonamide 3-159a (2.1503 g, 6.42 mmol) and imidazole (1.3110 g, 19.3 mmol) in DMF (32.1 mL) was added portionwise at r.t. TBDMSCl (1.9352 g, 12.8 mmol). The reaction mixture was stirred at 80°C for 2 hours, cooled to rt and quenched with H₂O (50 mL). The crude product was extracted with Et₂O (2x100 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by vacuum. The recovered colorless oil was used for the next step without further purification.

To a solution of the silyl ether obtained above and CsCO₃ (8.3200 g, 25.7 mmol) in dry acetone (40 mL) was added propargyl bromide (80% wt in toluene, 3.8199 g, 25.7 mmol) in one portion. The reaction mixture was stirred at rt for 2h, cooled to rt and quenched with H₂O (40 mL). The crude product was extracted with CH₂Cl₂ (2x50 mL), the combined organic layers were dried over MgSO₄ and the solvent removed by vacuum. Purification by flash column chromatography (10% EtOAc/hexanes) gave 1.6431 g (53%) of 3-159 as a pale yellow oil; Rᵣ = 0.44 (10% EtOAc/hexanes); [α]D = -2.5 (c 1.00, CH₂Cl₂); IR (neat) 2955, 2928, 2857, 1453, 1349, 1256, 1161, 837 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.73 (d, J = 8.0 Hz, 2H), 7.35-7.27 (m, 7H), 4.55 (ABq, J =
12.0 Hz, \( \Delta \nu_{AB} = 17.2 \) Hz, 2H), (dABq, \( J = 18.0, 2.0 \) Hz, \( \Delta \nu_{AB} = 42.9 \) Hz, 2H), 4.15-4.11 (m, 1H), 3.57-3.50 (m, 2H), 3.33 (dd, \( J = 14.5, 5.0 \) Hz, 1H), 3.23 (dd, \( J = 14.5, 5.0 \) Hz, 1H), 2.42 (s, 3H), 1.97 (t, \( J = 2.0 \) Hz, 1H), 0.89 (s, 9H), 0.09 (d, \( J = 10.5 \) Hz, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 143.7, 138.5, 136.1, 129.6, 128.5, 128.2, 127.9, 127.8, 73.3, 74.0, 73.6, 72.6, 71.5, 49.6, 39.2, 26.0, 21.7, 18.2, -4.5, -4.6; HRMS (ESI) Calcd for C\(_{26}\)H\(_{38}\)NO\(_4\)SSi (M+H)\(^+\): 488.2285, found 488.2292.

![Chemical Structure](image)

N-((S)-3-(benzyloxy)-2-(tert-butyldimethylsilyloxy)propyl)-N-((R)-4-hydroxydeca-2-ynyl)-4-methylbenzenesulfonamide (3-160).

A solution of nBuLi in hexane 1.6M (1.20 mL, 3.0 mmol) was added dropwise over 10 minutes at -78°C to a solution of 3-159 (976.1 mg, 2.0 mmol) in dry THF (9 mL). The reaction was then stirred at the same temperature for 45 minutes and a solution of 3-151 (519.9 mg, 3.0 mmol) in dry THF (1 mL) was added. The mixture was allowed to warm to room temperature and stirred for 2 hours, quenched with NH\(_4\)Cl (10 mL of a saturated aqueous solution), diluted with water (20 mL) and extracted with CH\(_2\)Cl\(_2\) (3x20 mL). The organic layers were dried over MgSO\(_4\) and then purified by flash chromatography (gradient; 5, 10% EtOAc/hexanes) to give an inseparable mixture of product and unreacted 3-159 which was used for the next step; \( R_f = 0.44 \) (10% EtOAc/hexanes); [\( \alpha \)]\(_D\) = -0.8 (c 1.00, CH\(_2\)Cl\(_2\)); IR (neat) 2955, 2929, 2858, 1678, 1352, 1163, 1092, 837, 778, 663 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.73 (d, \( J = 8.0 \) Hz, 2H), 7.36-7.29 (m, 7H), 7.35-7.28 (m, 5H), 4.55 (ABq, \( J = 12.0 \) Hz, \( \Delta \nu_{AB} = 21.9 \) Hz, 2H), 4.45 (ABq, \( J = 19.0 \) Hz, \( \Delta \nu_{AB} = 47.9 \) Hz, 2H), 4.15-4.10 (m, 1H), 3.57-3.50 (m, 2H),
3.35-`3.27 (m, 2H), 2.42 (s, 3H), 2.23 (t, \( J = 7.0 \) Hz, 2H), 1.49-1.43 (m, 2H), 1.30-1.22 (m, 5H), 0.91-0.86 (m, 12H), 0.09 (d, \( J = 10 \) Hz, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 186.9, 144.1, 138.3, 135.8, 129.8, 128.6, 128.1, 128.0, 127.9, 85.3, 84.6, 73.7, 72.3, 71.8, 50.1, 45.4, 39.4, 31.7, 28.8, 26.0, 23.9, 22.7, 21.7, 18.2, 14.2, -4.5, -4.6.

Noyori catalyst [(R,R)-TsDPEN-Ru(p-cymene)Cl] (19.3 mg, 0.030 mmol, 0.02 eq) was added to a mixture of above product and 3-159 (891.3 mg, 1.48 mmol), sodium formate (1.006 mg, 14.8 mmol, 10eq), TBAC (123.4 mg, 0.44 mmol, 0.3 eq) in CH\(_2\)Cl\(_2\) (8 mL) and deionized H\(_2\)O (8 mL). The biphasic mixture was strongly stirred for 20 hours at rt, diluted with water (10 mL) and extracted with CH\(_2\)Cl\(_2\) (2x10 mL). The organic layers were dried over MgSO\(_4\) and then purified by flash chromatography (Gradient; 5, 10, 20% EtOAc/hexanes) to give the product as a colorless oil (177.9 mg, 20%); \( R_f = 0.15 \) (10% EtOAc/hexanes); \([\alpha]_D = +6.9 \) (c 1.00, CH\(_2\)Cl\(_2\)); IR (neat) 3513, 2954, 2928, 2857, 1349, 1162, 1092, 837, 778, 660 cm\(^{-1}\); \(^{1}\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 7.76 (d, \( J = 8.5 \) Hz, 2H), 7.37-7.30 (m, 7H), 4.57 (ABq, \( J = 12.0 \) Hz, \( \Delta \nu_{AB} = 18.4 \) Hz, 2H), 4.57 (dABq, \( J = 18.5 \), 3.0 Hz, \( \Delta \nu_{AB} = 37.7 \) Hz, 2H), 4.17-4.13 (m, 1H), 4.04 (br, 1H), 3.60-3.52 (m, 2H), 3.35 (dt, \( J = 15.0 \), 5.0 Hz, 1H), 3.23 (dt, \( J = 14.5 \), 6.0 Hz, 1H), 2.43 (s, 3H), 1.45-1.24 (m, 11H), 0.92-0.88 (m, 12H), 0.11 (d, \( J = 11.0 \) Hz, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 143.6, 138.4, 136.4, 129.6, 128.5, 128.3, 127.9, 127.8, 87.0, 78.2, 73.6, 72.6, 71.5, 71.5, 62.3, 49.8, 39.4, 37.6, 37.6, 31.9, 29.1, 26.0, 25.1, 22.8, 21.7, 18.2, 14.3, -4.5, -4.6; HRMS (ESI) Calcd for C\(_{33}\)H\(_{52}\)NO\(_5\)SSi (M+H): 602.3330, found 600.3354.

Diastereomeric ratio (93:7) was determined by Mosher’s Ester analysis.
**N-((S)-3-(benzyloxy)-2-hydroxypropyl)-N-((R,Z)-4-hydroxydec-2-enyl)-4-methylbenzenesulfonamide (3-162)**

Lindlar catalyst (5% palladium on calcium carbonate, poisoned with lead, 30.0 mg) and quinoline (30.0 mg) were added to a solution of 3-160 (60.3 mg, 0.16 mmol) in dry MeOH (1 mL). The reaction mixture was stirred 2 hours under H₂ (1 atm). After filtration over cotton and removal of the solvent, crude product was recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF (1.0M in THF, 300 μL) was added dropwise at 0°C to a solution of the silyl ether obtained above in dry THF (1 mL). The reaction was stirred 16h and the mixture applied directly to flash chromatography (Gradient 40, 50% EtOAc/hexanes) to afford the product as a colorless oil (34.8 mg, 71%); Rᵣ = 0.17 (50% EtOAc/hexanes); [α]₀ = +14.7 (c 1.00, CH₂Cl₂); IR (neat) 3410, 2918, 2851, 1451, 1333, 1158, 1018, 814, 658 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ = 7.67 (d, J = 8.0 Hz, 2H), 7.35-7.27 (m, 7H), 5.51 (dd, J = 11.0, 9.0 Hz, 1H), 5.22-5.17 (m, 1H), 4.52 (s, 2H), 4.30 (q, J = 8.5 Hz, 1H), 4.05-3.95 (m, 3H), 3.53 (d, J = 5.5 Hz, 2H), 3.29 (dd, J = 15.0, 3.5 Hz, 1H), 3.20 (dd, J = 15.0, 6.5 Hz, 1H), 2.91 (br, 1H), 2.55 (br, 1H), 2.41 (s, 3H), 1.54-1.23 (m, 11H), 0.85 (t, J = 6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 143.8, 138.0, 137.8, 136.9, 130.0, 128.7, 128.2, 128.1, 127.4, 125.4, 73.8, 71.8, 69.8, 66.7, 50.3, 46.4, 37.1, 32.0, 29.4, 25.5, 22.8, 21.7, 14.3; HRMS (ESI) Calcd for C₂₇H₃₉NNaO₅S (M+Na)⁺: 512.2441, found 512.2435.
(2S,6S)-2-(benzyloxymethyl)-6-((E)-oct-1-enyl)-4-tosylmorpholine (3-163).

Anhyd CH$_2$Cl$_2$ (160 μL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (1.0 mg, 0.001 mmol, 3.0 mol%), AgOTf (0.5 mg, 0.001 mmol, 3.0 mol%), and activated 4 Å MS (20 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-162 (31.3 mg, 0.06 mmol) in anhyd CH$_2$Cl$_2$ (200 μL) was then added. After 2.5 hours, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (5 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 0, 5% EtOAc/hexanes) to give 23.8 mg (79%) of the pure diastereomer 3-163 as a colorless oil; R$_f$ = 0.44 (10% EtOAc/hexanes); [α]$_D$ = +2.6 (c 1.00, CH$_2$Cl$_2$); IR (neat) 2918, 2850, 1347, 1168, 981, 815, 663 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): δ = 7.60 (d, $J$ = 8.0 Hz, 2H), 7.34-7.26 (m, 7H), 5.77 (ddt, $J$ = 15.0, 6.5, 1.0 Hz, 1H), 5.30 (ddt. $J$ = 15.0, 6.5, 1.0 Hz, 1H), 4.50 (s, 2H), 4.05-4.02 (m, 1H), 3.83-3.78 (m, 1H), 3.64 (dt, $J$ = 11.5, 2.0 Hz, 1H), 3.55 (dd, $J$ = 11.5, 2.0 Hz, 1H), 3.50 (dd, $J$ = 10.5, 5.0 Hz, 1H), 3.40 (dd, $J$ = 10.5, 5.5 Hz, 1H), 2.42 (s, 3H), 2.11 (t, $J$ = 11.5 Hz, 1H), 2.02 (t, $J$ = 11.5 Hz, 1H), 1.99 (q, $J$ = 7.0 Hz, 2H), 1.33-1.20 (m, 8H), 0.86 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 144.1, 138.0, 135.8, 132.5, 130.0, 128.7, 128.1, 128.0, 128.0, 126.4, 76.4, 74.4, 73.7, 70.7, 50.2, 47.6, 32.6, 31.9, 29.1, 29.0, 22.8, 21.8, 14.3; HRMS (ESI) Calcd for C$_{27}$H$_{38}$NO$_4$S (M+H)$^+$: 472.2516; found 472.2534.
Diastereomeric ratio (93:7) was determined by $^1$H NMR of the crude material. The relative configuration of the major diastereomer was determined by NOE DIFF experiments as follows:

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A solution of 3-161 (70.4 mg, 0.12 mmol) in THF (250 μL) was added dropwise at 0°C to a suspension of LiAlH$_4$ (13.3 mg, 0.35 mmol) in THF (0.5 mL). The reaction was stirred at the same temperature for 1 h, diluted with Et$_2$O (1 mL) and quenched by addition of H$_2$O (15 μL). The crude mixture was treated with a NaOH solution (15% in H$_2$O, 15 μL), H$_2$O (45 μL) and stirred at rt for 1 h. After filtration, the crude mixture was dried over MgSO$_4$, recovered as a colorless oil which was used for the next step without further purification.

A solution of TBAF (1.0M in THF, 350 μL) was added dropwise at 0°C to a solution of the silyl ether obtained above in dry THF (1 mL). The reaction was stirred 16 h and the mixture applied directly to flash chromatography (Gradient 40, 50% EtOAc/hexanes) to afford the product as a colorless oil (120.6 mg, 88%); R$_f$ = 0.21 (50% EtOAc/hexanes); $[\alpha]_D = +5.5$ (c 1.00, CH$_2$Cl$_2$); IR (neat) 3429, 2926, 2858, 1335, 1159,
1091, 1020, 922, 815, 751, 657 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.65$ (d, $J = 8.0$ Hz, 2H), 7.31-7.23 (m, 7H), 5.54 (dd, $J = 15.5$, 6.5 Hz, 1H), 5.43 (dt, $J = 15.5$, 6.5 Hz, 1H), 4.50 (s, 2H), 3.95 (br, 2H), 3.80 (dABq, $J = 15.5$, 6.5 Hz, $\Delta\nu_{AB} = 58.6$ Hz, 2H), 3.19 (dd, $J = 14.5$, 4.0 Hz, 1H), 3.14 (dd, $J = 15.0$, 7.0 Hz, 1H), 2.86 (d, $J = 3.5$ Hz, 1H), 2.39 (s, 3H), 1.42-1.22 (13H), 0.84 (t, $J = 6.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 143.8, 138.7, 137.9, 136.5, 130.0, 128.7, 128.1, 128.0, 127.6, 125.1, 73.7, 72.2, 71.8, 69.6, 51.6, 50.7, 37.1, 32.0, 29.4, 25.5, 22.8, 21.7, 14.3; HRMS (ESI) Calcd for C$_{27}$H$_{43}$N$_2$O$_5$S (M+NH$_4$)$^+$: 507.2887, found 507.2908.

(2S,6R)-2-(benzyloxymethyl)-6-((E)-oct-1-enyl)-4-tosylmorpholine (3-165).

Anhyd CH$_2$Cl$_2$ (150 μL) was added to an aluminum foil covered, flame dried, test tube containing Ph$_3$PAuCl (0.9 mg, 0.001 mmol, 3.0 mol %), AgOTf (0.5 mg, 0.001 mmol, 3.0 mol%), and activated 4 Å MS (20 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding diol 3-164 (29.3 mg, 0.06 mmol) in anhyd CH$_2$Cl$_2$ (150 μL) was then added. After 2 hours, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH$_2$Cl$_2$ (5 mL). The solution of crude product was concentrated in vacuo, and purified by flash chromatography (Gradient 0, 5% EtOAc/hexanes) to give 23.5 mg (83%) of the pure diastereomer 3-165 as a colorless oil; $R_f = 0.55$ (10% EtOAc/hexanes); [$\alpha$]$_D = -18.3$ (c 1.00, CH$_2$Cl$_2$); IR (neat) 2922, 1347, 1168, 815, 668, 649 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.59$ (d, $J = 8.0$ Hz, 2H), 7.32-7.26 (m, 7H), 5.77 (ddt, $J = 15.5$, 7.0, 1.5 Hz, 1H), 5.48 (ddt, $J = 15.5$, 6.0, 1.5 Hz, 1H), 4.51 (ABq, $J = 12.0$ Hz, $\Delta\nu_{AB} = 19.0$ Hz, 2H),
4.22 (q, J = 5.0 Hz, 1H), 4.06-4.02 (m, 1H), 3.60-3.55 (m, 2H), 3.00 (dd, J = 11.5 Hz, 2H), 2.90 (dd, J = 11.0, 5.5 Hz, 1H), 2.81 (dd, J = 11.5, 6.0 Hz, 1H), 2.42 (s, 3H), 2.00 (q, J = 7.0 Hz, 2H), 1.35-1.17 (m, 8H), 0.85 (t, J = 7.0 Hz, 3H); \(^{13}\text{C}\) NMR (75 MHz, CDCl\textsubscript{3}): δ 144.0, 138.1, 136.4, 132.3, 129.9, 128.6, 128.0, 127.9, 126.2, 73.6, 71.2, 69.3, 69.1, 49.2, 46.9, 32.6, 31.8, 29.0, 22.8, 21.7, 14.3; HRMS (ESI) Calcd for \(\text{C}_{27}\text{H}_{37}\text{NNaO}_{4}\text{S} (\text{M+Na})^+: 494.2336\), found 494.2332.

Diastereomeric ratio (8:92) was determined by \(^1\text{H}\) NMR of the crude material.

### 6.2.10 Synthesis of 3-199 and 3-200

(S)-3-((R,Z)-3-hydroxy-9-methoxynon-7-enoyl)-4-isopropylazolidin-2-one (3-199).

A solution of TiCl\textsubscript{4} in toluene 1.0M (5.0 mL, 5.0 mmol) was added dropwise over 5 minutes at -78°C to a solution of Evans auxiliary 3-194 (428.0 mg, 2.5 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (5 mL). The reaction was then stirred at the same temperature for 10 minutes and a solution of iPr\textsubscript{2}NEt (869.3 μL, 5.0 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was added. The dark red mixture was stirred at the same temperature for 1 hour. Aldehyde 3-198 (711.0 mg, 5 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (1 mL) was added dropwise over 5 minutes and stirred at the same temperature for 2 hours. The reaction mixture was quenched with NH\textsubscript{4}Cl (3 mL of a saturated aqueous solution), diluted with water (20 mL) and extracted with CH\textsubscript{2}Cl\textsubscript{2} (3×20 mL). The organic layers were dried over MgSO\textsubscript{4} and then purified by flash chromatography (Gradient; 30, 35, 40% EtOAc/hexanes) to give 297.7 mg (38%) of product as a yellow oil; \(R_f = 0.22\) (50% EtOAc/hexanes); IR (neat) 3444, 2921, 1771,
1698, 1386, 1203, 1091, 1020 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 5.59-5.49\) (m, 2H), 4.44-4.41 (m, 1H), 4.35-3.92 (m, 6H), 3.31 (s, 3H), 3.07-3.04 (m, 2H), 2.39-2.35 (m, 1H), 2.10 (q, \(J = 4.5\) Hz, 1H), 1.58-1.43 (m, 4H), 0.91 (d, \(J = 7\) Hz, 3H), 0.87 (d, \(J = 7\) Hz, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)): \(\delta 172.9, 154.3, 133.4, 126.5, 68.2, 68.0, 63.7, 58.6, 58.1, 42.7, 36.3, 28.6, 27.5, 25.5, 18.1, 14.8\).

\[(S)-4\text{-isopropyl-3-(2-((2R,6S)-6-vinyltetrahydro-2H-pyran-2-yl)acetyl)oxazolidin-2-one (3-200).}\]

Anhyd CH\(_2\)Cl\(_2\) (0.4 mL) was added to an aluminum foil covered, flame dried, test tube containing Ph\(_3\)PAuCl (4.2 mg, 0.007 mmol, 5.0 mol %), AgOTf (2.1 mg, 0.007 mmol, 5.0 mol %), and activated 4 Å MS (30 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding alcohol 3-199 (43.4 mg, 0.14 mmol) in anhyd CH\(_2\)Cl\(_2\) (0.4 mL) was then added at -5°C. After 2 hours at 0°C, TLC analysis indicated a complete reaction and the mixture filtered through a short plug of silica with CH\(_2\)Cl\(_2\) (5 mL). The solution of crude product was concentrated \textit{in vacuo}, and purified by flash chromatography (100% CH\(_2\)Cl\(_2\)) to give 34.6 mg (89%) of the pure diastereomer 3-200 as a colorless oil; \(R_t = 0.30\) (10% EtOAc/hexanes); \([\alpha]_D = +35.5\) (c 1.00, CH\(_2\)Cl\(_2\)); IR (neat) 2937, 2862, 1782, 1702, 1388, 1304, 1205, 1121, 1074, 1021, 920 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 5.84-5.78\) (m, 1H), 5.17 (dt, \(J = 1.5, 17.5\) Hz, 1H), 5.03 (dt, \(J = 1.5, 10.5\) Hz, 1H), 4.44 (dt, \(J = 8.5, 3.5\) Hz, 1H), 4.25 (t, \(J = 9\) Hz, 1H), 4.18 (dd, \(J = 9, 3.5\) Hz, 1H), 3.95-3.83 (m, 2H), 3.41 (dd, \(J = 16, 7.5\) Hz, 1H), 2.91 (dd, \(J = 16, 5\) Hz, 1H), 2.40-2.33 (m, 1H), 1.89-1.84 (m, 1H), 1.67-1.54 (m, 3H), 1.35-1.25 (m,
2H), 0.91 (d, J = 7 Hz, 3H), 0.86 (d, J = 7 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 171.2, 154, 139.5, 114.3, 78.3, 74.3, 63.5, 58.6, 42.2, 31.3, 31.2, 28.5, 23.5, 18.1, 14.9; HRMS (ESI) Calcd for C$_{15}$H$_{24}$NO$_4$ (M+H)$^+$: 282.1700, found 282.1701.

6.2.11 Synthesis of 3-206 and 3-208

Compounds 3-40,$^{147}$ 3-41,$^{147}$ 3-52,$^a$ 3-204,$^{148}$ 3-205,$^{149}$ 3-207,$^{150}$ 3-209,$^{148}$ and 3-210 $^{148}$ have been described in the literature and when prepared here satisfactorily matched all previously reported data (Figure 6-1).

![Figure 6-1. Chemical structures of known compounds.](image)

3-206 and 3-208 were prepared in two steps from (E)-7-(tetrahydro-2H-pyran-2-yloxy)hept-2-en-1-ol 3-207; protection of the allyl alcohol with 3 equivalents of TBDPSCI or BzCl in presence of 3 equivalents of Et$_3$N in CH$_2$Cl$_2$ at room temperature followed by deprotection of the terminal non allylic alcohol using 10 mol % of PPTS in MeOH at room temperature.

![image](image)

(E)-7-(tert-butyldiphenylsilyloxy)hept-5-en-1-ol (3-206).
Colorless oil; $R_f = 0.30$ (30% EtOAc/hexanes); IR (neat) 3343, 2932, 2857, 1471, 1462, 1427, 1112, 1055, 969 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.69-7.66 (m, 4H), 7.42-7.36 (m, 6H), 5.65 (dt, $J = 15.0$, 6.5 Hz, 1H), 5.55 (dt, $J = 15.0$, 5.5 Hz, 1H) 4.16 (d, $J = 5.5$ Hz, 1H), 3.64 (t, $J = 6.5$ Hz, 2H), 2.05 (q, $J = 7.0$ Hz, 2H), 1.59-1.41 (m, 4H), 1.29 (bs, 1H), 1.05 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 135.8, 134.2, 131.1, 129.8, 129.4, 127.8, 64.9, 63.1, 32.5, 32.2, 27.1, 25.6, 19; HRMS (ESI) Calcd for C$_{23}$H$_{32}$NaO$_2$Si (M+Na)$^+$: 391.2064, found 391.2082.

(E)-7-hydroxyhept-2-enyl benzoate (3-208).

Colorless oil; $R_f = 0.18$ (30% EtOAc/hexanes); IR (neat) 3390, 2936, 2862, 1418, 1452, 1273, 113, 1070, 1026, 973, 712 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.01 (d, $J = 6.3$ Hz, 2H), 7.53-7.36 (m, 3H), 5.82 (dt, $J = 15.6$, 6.3 Hz, 1H), 5.65 (dt, $J = 15.3$, 6.9 Hz, 1H), 4.72 (d, $J = 6.0$ Hz, 2H), 3.60 (t, $J = 6.3$ Hz, 2H), 2.08 (q, $J = 6.9$ Hz, 2H), 1.71 (bs, 1H), 1.60-1.41 (m, 4H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 166.6, 136.2, 133.1, 130.5, 129.8, 128.5, 124.4, 65.8, 62.8, 32.3, 32.1, 25.2; HRMS (ESI) Calcd for C$_{14}$H$_{18}$NaO$_3$ (M+Na)$^+$: 257.1148, found 257.1152.

6.2.12 Synthesis of 3-207

3-207 was prepared in two steps from (E)-7-(tert-butyldimethylsilyloxy)hept-2-en-1-ol,$^{151}$ protection of the allyl alcohol using 3 equivalents of 3,4-dihydro-2H-pyran and 10 mol % of PPTS in CH$_2$Cl$_2$ at room
temperature followed by deprotection of the terminal non allylic alcohol using 2 equivalents of TBAF in THF at room temperature.


Colorless oil; \( R_f = 0.35 \) (30% EtOAc/hexanes); IR (neat) 3410, 2938, 2864, 1177, 1075, 1023, 970 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta 5.73 \) (dt, \( J = 15.5, 7.0 \) Hz, 1H), 5.59 (dt, \( J = 15.5, 7.0 \) Hz, 1H), 4.63 (dd, \( J = 4.0, 3.0 \) Hz, 1H), 4.19 (ddq, \( J = 12.0, 5.5, 1.0 \) Hz, 1H), 3.92 (dd, \( J = 12.0, 7.0 \) Hz, 1H), 3.87 (dd, \( J = 8.5, 5.0 \) Hz, 1H), 3.64 (t, \( J = 6.5 \) Hz, 2H), 3.52-3.48 (m, 1H), 2.09 (q, \( J = 7.0 \) Hz, 2H) 1.86-1.36 (m, 11H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta 134.3, 126.7, 98.0, 68.0, 63.0, 62.4, 32.4, 32.2, 30.9, 25.7, 25.4, 19.8 \); HRMS (ESI) Calcd for C\(_{11}\)H\(_{22}\)NaO\(_3\) (M+Na\(^+\)): 237.1467; found 237.1463.

6.2.13 Synthesis of 3-211 and 3-212

3-211 and 3-212 were prepared in three steps from 2-(hex-5-ynyloxy)tetrahydro-2H-pyran 5-1 (Figure 5.2).\(^ {152} \)

![Diagram of synthesis](image)

Figure 6-2. Synthesis of 3-211 and 3-212.
(E)-7-cyclohexyl-7-methoxyhept-5-en-1-ol (3-211).

Colorless oil; R_f = 0.28 (30% EtOAc/hexanes); IR (neat) 3402, 2928, 2853, 1450, 1095, 972 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.55 (dt, \(J = 15.3, 7.0\) Hz, 1H), 5.25 (dd, \(J = 15.3, 8.1\) Hz, 1H), 3.64 (t, \(J = 6.0\) Hz, 2H), 3.22 (s, 3H), 3.17 (t, \(J = 7.7\) Hz, 1H), 2.10 (q, \(J = 7.0\) Hz, 2H), 1.94-1.83 (m, 2H), 1.73-0.89 (m, 14H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 134.7, 129.4, 87.6, 62.8, 56.2, 42.6, 32.4, 32.2, 29.5, 29.0, 26.8, 26.3, 26.3, 25.7; HRMS (ESI) Calcd for C\(_{14}\)H\(_{26}\)NaO\(_2\) (M+Na): 249.1825; found 249.1832.

(Z)-7-cyclohexyl-7-methoxyhept-5-en-1-ol (3-212).

Colorless oil; R_f = 0.30 (30% EtOAc/hexanes); IR (neat) 3375, 2924, 2852, 1450, 1085, 970 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 5.64 (dt, \(J = 11.1, 7.5\) Hz, 1H), 5.20 (dd, \(J = 11.1, 9.6\) Hz, 1H), 3.68-3.59 (m, 3H), 3.21 (s, 3H), 2.17-2.02 (m, 2H), 1.91-0.88 (m, 16H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 134.0, 129.7, 81.1, 63.0, 56.2, 43.0, 32.6, 29.5, 28.8, 27.8, 26.9, 26.4, 26.1; HRMS (ESI) Calcd for C\(_{14}\)H\(_{26}\)NaO\(_2\) (M+Na): 249.1825; found 249.1835.

**General procedure for the Au-catalyzed cyclization.**

A solution of hexane (0.15 mmol) and the substrate (0.3 mmol) in dry CH\(_2\)Cl\(_2\) (1 mL) was added in one portion at room temperature to an aluminum foiled covered 5 mL vial containing a solution of (Acetonitrile)(2-biphenyl)di-tert-butylphosphine]gold(I)
hexafluoroantimonate (11.6 mg, 0.015 mmole, 5 mol%) in dry CH₂Cl₂ (0.5 mL) and activated MS 4Å (70 mg) under N₂. The reaction was monitored by taking 25 μL aliquots which were immediately diluted in 400 μL of dry CH₂Cl₂ containing 15-20 mg of beads Quadrapure™ MPA. 1 μL of this solution was subjected to gas chromatography analysis.

6.2.14 Determination of Conversion of 3-41.

The conversion was determined by Gas Chromatography analysis of 2-vinyltetrahydro-2H-pyran 3-41 and n-decane. A calibration plot had been made using known quantities of 3-41 and n-decane (Figure 5-3).

Column: RESTEK Rtx®-5 (Crossbond 5% diphenyl – 95% dimethyl polysiloxane), 30 meters, 0.25 mm ID, 0.5 μm df.

Temperature: 60 °C for 3 min, 10 °C increase → 110 °C, 40 °C increase → 275 °C, 275 °C for 2 min.

Time: tᵣ (3-41): 5.1 min; tᵣ (n-decane): 7.4 min.

![Calibration plot of 3-41 vs n-decane.](image)

Figure 6-3. Calibration plot of 3-41 vs n-decane.
6.2.15 Determination of Conversion of 3-52.

The conversion was determined by Gas Chromatography analysis of (E)-2-(2-cyclohexylvinyl)tetrahydro-2H-pyran 3-52 and n-decane. A calibration plot had been made using known quantities of 3-52 and n-decane (Figure 5-4).

Column: RESTEK Rtx®-5 (Crossbond 5% diphenyl – 95% dimethyl polysiloxane), 30 meters, 0.25 mm ID, 0.5 μm df.

Temperature: 60 °C for 3 min, 10 °C increase → 110 °C, 20 °C increase → 275 °C, 275 °C for 8 min.

Time: $t_R$ (n-decane): 7.4 min; $t_R$ (3-52): 13.4 min.

\[
y = 1.0782x + 0.013 \\
R^2 = 0.9976
\]

Figure 6-4. Calibration plot of 3-52 vs n-decane.
6.2.16 General Procedures for the Preparation of 2H-Chromenes

Compounds 4-1, 4-53, 4-55, 4-61, 4-80, 4-48, 4-76, 4-74, 4-95, 4-96 and 4-100 have been described in the literature and when prepared here satisfactorily matched all previously reported data.

Representative procedure for the preparation of substrates:

To a solution of salicylaldehyde derivative (1 mmol) in anhydrous THF (5 mL) was added dropwise vinyl magnesium bromide (1.0 M solution in THF, 2.5 mL, 2.5 eq) at -78°C. After TLC analysis indicated a complete conversion, the reaction was quenched with a saturated aqueous solution of NH₄Cl (5 mL) and warmed to room temperature. The crude mixture was extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extract was dried over MgSO₄, purified by flash chromatography and immediately taken on to the next step.

Representative procedure for the Au-catalyzed preparation of 2H-chromenes:

Anhydrous THF (2.5 mL) was added to an aluminum foil covered, flame dried, flask containing 12 (26.5 mg, 0.05 mmol, 5.0 mol%), 10 (12.3 mg, 0.05 mL, 5.0 mol%), and activated 4 Å MS (80 mg). The heterogeneous mixture was vigorously stirred for 10 min and a solution of the corresponding o-(1-hydroxyallyl)phenol (1 mmol) in THF (2.5 mL) was added. The mixture was then immediately heated to reflux by immersing into an oil bath that has been preheated to 70°C. After TLC analysis indicated a complete reaction, the mixture was filtered through a short plug of silica with CH₂Cl₂ (4 mL). The solution of the crude product was concentrated in vacuo, and purified by flash chromatography (5% EtOAc/hexanes or 100% hexanes).
6.2.17 Characterization of New 2H-Chromenes.

8-bromo-6-nitro-2H-chromene (4-57).

Pale yellow solid; mp 130-133 °C; Rf = 0.75 (20% EtOAc/hexanes); IR (neat) 3090, 2919, 1507, 1347, 1265, 1097, 902, 741, 694 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.25 (d, J = 2.5 Hz, 1H), 7.78 (d, J = 2.5 Hz, 1H), 6.42 (dt, J = 10.0, 2.0 Hz, 1H), 5.91 (dt, J = 10.0, 3.3 Hz, 1H), 5.14 (dd, J = 3.3, 2.0 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 156.3, 141.9, 128.8, 124.3, 122.9, 122.6, 121.1, 109.9, 67.9; HRMS (ESI) Calcd for C₉H₇BrNO₃ (M+H)⁺: 255.9609, found 255.9599.

6-bromo-8-methoxy-2H-chromene (4-59).

Colorless oil; Rf = 0.64 (10% EtOAc/hexanes); IR (neat) 2917, 2849, 1567, 1480, 1271, 1215, 1033, 845 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 6.87 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.33 (dt, J = 10.0, 2.0 Hz, 1H), 5.82 (dt, J = 10.0, 3.5 Hz, 1H), 4.88 (dd, J = 3.5, 2.0 Hz, 2H), 3.85 (s, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 148.7, 142.1, 124.4, 123.8, 123.3, 121.7, 115.4, 113.0, 66.0, 56.5; HRMS (ESI) Calcd for C₁₀H₈BrO₂ (M-H)⁺: 238.9708; found 238.9713.
2-(2-bromophenyl)-2H-chromene (4-65).

Colorless oil; R\textsubscript{f} = 0.15 (hexanes); IR (neat) 1684, 1653, 1560, 1507, 1457, 1227, 1203, 1112, 1020, 748 cm
\(^{-1}\); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.61 (dd, \(J = 8.0, 1.5\) Hz, 1H), 7.57 (dd, \(J = 8.0, 1.0\) Hz, 1H), 7.30 (ddt, \(J = 7.8, 0.5\) Hz, 1H), 7.15 (m, 2H), 7.00 (dd, \(J = 7.5, 1.5\) Hz, 1H), 6.87 (dt, \(J = 7.5, 1.0\) Hz, 1H), 6.82 (dd, \(J = 8.0, 0.5\) Hz, 1H), 6.51 (ddd, \(J = 10.0, 2.0, 0.5\) Hz, 1H), 6.33 (dd, \(J = 3.5, 2.5, 1H\), 5.79 (dd, \(J = 10.0, 3.5, 1H\)\); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 153.5, 140.2, 133.1, 129.8, 129.8, 128.9, 128.1, 126.9, 124.3, 124.0, 121.7, 121.6, 121.2, 116.0, 76.4; HRMS (ESI) Calcd for C\textsubscript{15}H\textsubscript{12}BrO (M+H\textsuperscript{+}): 287.0072, found 287.0078.

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\begin{align*}
\text{Br} & \\
\text{C} & \\
\text{H} & \\
\text{O} & 
\end{align*}
\]

4-(4-bromophenyl)-2H-chromene (4-97).

Colorless oil; R\textsubscript{f} = 0.55 (5% EtOAc/hexanes); IR (neat) 3047, 2964, 2832, 1481, 1447, 1222, 1114, 1066, 1011, 805, 757 cm
\(^{-1}\); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.52 (d, \(J = 8.5\) Hz, 2H), 7.21 (d, \(J = 8.5\) Hz, 2H), 7.16 (dt, \(J = 7.8, 2.0\) Hz, 1H), 6.89 (m, 3H), 5.78 (t, \(J = 4.0\) Hz, 1H), 4.83 (d, \(J = 4.0\) Hz, 2H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \(\delta\) 154.9, 137.4, 136.4, 131.8, 130.5, 129.7, 125.8, 123.5, 122.0, 121.5, 120.5, 116.5, 65.3; HRMS (ESI) Calcd for C\textsubscript{15}H\textsubscript{11}BrO (M\textsuperscript{+}): 285.9993, found 285.9999.
4-(4-nitrophenyl)-2H-chromene (4-98).

Yellow solid; mp 88-92 °C; \( R_f = 0.35 \) (10% EtOAc/hexanes); IR (neat) 2849, 1597, 1516, 1484, 1346, 1224, 853, 761, 697 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) 8.27 (d, \( J = 7.0 \) Hz, 2H), 7.52 (d, \( J = 7.0 \) Hz, 2H), 7.20 (dt, \( J = 7.0, 2.0 \) Hz, 1H), 6.90 (m, 3H), 5.91 (t, \( J = 4.0 \) Hz, 1H), 4.88 (d, \( J = 4.0 \) Hz, 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 154.9, 145.2, 135.9, 130.2, 129.7, 125.6, 124.0, 122.8, 122.2, 121.7, 116.8, 100.0, 65.2; HRMS (ESI) Calcd for C\(_{15}\)H\(_{12}\)NO\(_3\) (M+H): 254.0817; found 254.0814.
LIST OF REFERENCES


(5) http://www.metalprices.com/

(6) http://www.sigmaaldrich.com/


(64) a) For recent reviews, see: (a) Nakata, T. Chem. Rev. 2005, 105, 4314. (b) Inoue, M. Chem. Rev. 2005, 105, 4379.


(91) Although geranial is commercially available and non-expensive, it comes as a mixture E/Z isomers also called citral.


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BIOGRAPHICAL SKETCH

Berenger Biannic was born in 1982 in Toulouse (France) where he was raised and graduated from Lycée Marcellin Berthelot in 2000. He attended the University of Paul Sabatier in the same city and moved to the Université d’Orléans where he received his bachelor’s degree in chemistry as well as his master’s degree in synthesis of bioactive molecules under the supervision of Prof. Jean-Yves Merour and Dr. Sylvain Routier. His research focused on the synthesis of a new class of potent indolic topoisomerase inhibitors. In 2006 he started his doctoral research at the University of Florida under the guidance of Dr. Aaron Aponick where he works on the development of gold-catalyzed transformations of allylic alcohols and its applications towards the synthesis of natural molecules.