Title
Synthesis of Functionalyzed $\alpha,\alpha$-Dibromo Esters through Claisen Rearrangements of Dibromoketene Acetals and the Investigation of the Phosphine-Catalyzed [4 + 2] Annulation of Imines and Allenoates

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Synthesis of Functionalized α,α-Dibromo Esters through Claisen Rearrangements of Dibromoketene Acetals and the Investigation of the Phosphine-Catalyzed [4 + 2] Annulation of Imines and Allenoates

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

Nathan John Dupper

2017
ABSTRACT OF THE DISSERTATION

Synthesis of Functionalized α,α-Dibromo Esters through Claisen Rearrangements of Dibromoketene Acetals and the Investigation of the Phosphine-Catalyzed [4 + 2] Annulation of Imines and Allenoates

by

Nathan John Dupper

Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2017

Professor Ohyun Kwon, Chair

Allylic alcohols can be transformed into γ,δ-unsaturated α,α-dibromo esters through a two-step process: formation of a bromal-derived mixed acetal, followed by tandem dehydrobromination/Claisen rearrangement. The scope and chemoselectivity of this tandem process is broad and it tolerates many functional groups and classes of allylic alcohol starting material. The diastereoselectivity of the Claisen rearrangement was investigated with moderate to excellent diastereomeric selectivity for the formation of the γ,δ-unsaturated α,α-dibromo esters. The product α,α-dibromo esters are also shown to be valuable chemical building blocks. They were used in the synthesis of the ynolate reaction intermediate, as well as other carbon–carbon bond-forming reactions. Highly functionalized lactones were also shown to be simply prepared from the γ,δ-unsaturated α,α-dibromo ester starting materials formed via the Claisen rearrangement.
A phosphine-catalyzed [4 + 2] annulation of imines and allenoates is also investigated herein. A synthesis of the core structure of the ergot alkaloid lysergic acid was attempted using an annulation of the alkyl imine derived from tert-butyl 4-bromo-3-(2-oxoethyl)-1H-indole-1-carboxylate and ethyl 2-methylbuta-2,3-dienoate to form the key tetrahydropyridine ring. The imine investigated was shown to have rapid tautomeration to the more stable enamine moiety, which was not conducive for the annulation process. Other routes for the synthesis of the ergot alkaloid core structure were also investigated.

Chiral bicyclic phosphines were applied to the annulation between ethyl 2-methylbuta-2,3-dienoate and various imines, which produces 6-substituted guvacine analogues in good yield with excellent enantiomeric excess. The bridged bicyclic chiral phosphines can be accessed quickly from trans-4-hydroxyproline. A new chiral phosphine (1S,4S,5R)-5-(4-anisyl)-2-tosyl-2-aza-5-phosphabicyclo[2.2.1]heptane was identified as an efficacious catalyst for the [4 + 2] annulation between ethyl 2-methylbuta-2,3-dienoate and aryl imines. A variety of aryl and heteroaryl imines were tested under this annulation process, affording 6-substituted guvacine esters. Utilizing this method, both \((R)\) and \((S)\)-aplexone were synthesized and tested to reveal that \((R)\)-aplexone is the eutomer responsible for the reduction of cellular levels of cholesterol in the zebrafish model.
The dissertation of Nathan John Dupper is approved.

Michael E. Jung

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2016
I would like to dedicate this to my wife, Brianna, who has always supported and helped me through this journey. From my first application, until now, you have been by my side. You have always believed in me and pushed me to do my best academically and as a balanced human being. Thank you for all the kindness and love that you have shown me. This literally could not have happened without you. You were the best partner that I could have possibly had. Next, I would like to thank my family. Mom, Dad, Matt, Maegen, Kristi, Kyle, Amy, Joe, and all of my nieces and nephews. Their love and support was such a huge help during these years. Thank you for being so involved and understanding. I am so thankful that I was gifted such an incredible family.

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Relative cellular levels of cholesterol in zebrafish embryos treated with aplexone (AP) or atorvastatin (AT), both at 40 µM, DMSO used as a control.
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Chapter 1

Functionalized $\alpha,\alpha$-Dibromo Esters through the Claisen Rearrangement of Dibromoketene Acetals
1.1 Claisen Rearrangements of Halogenated Allyl Vinyl Ethers

*The Claisen Rearrangement*

Since its discovery, the Claisen rearrangement has been a powerful tool for chemical synthesis (Scheme 1.1.1). The [3.3]-sigmatropic rearrangement was first applied to allyl vinyl ethers, or allyl benzyl ethers, but has since come to include the aza-Claisen (X = N) and the thio-Claisen (X = S) rearrangements. Unlike the Cope rearrangement of 1,5-hexadiene, the formation of the Claisen rearrangement product is thermodynamically favorable due to the formation of the strong C=O double bond. Many reviews have been published on this subject, and it continues to provide an inspiration to numerous synthetic methodologies.

![Claisen Rearrangement](image)

**Scheme 1.1.1 Claisen Rearrangement**

An added benefit of the Claisen rearrangement is that it typically follows a highly ordered six-membered transition state. In practical terms, this means that wise choice of olefin geometry can provide a specific rearranged product (Figure 1.1.1). The ability to control the stereochemical outcome of the methodologies that rely upon the Claisen rearrangement or its variants make the rearrangement of allyl vinyl ethers a valuable tool for synthetic organic chemists. Much of the expansion of the Claisen rearrangement focuses on novel methods to form the allyl vinyl ether.

![Claisen Rearrangement Stereochemistry](image)

**Figure 1.1.1 Claisen Rearrangement Stereochemistry**

![Johnson–Claisen Rearrangement](image)

**Scheme 1.1.2 Johnson–Claisen Rearrangement**
Johnson and coworkers developed a method in which allylic alcohols can be transformed into the corresponding ketene acetal by reacting them with orthoesters, usually triethyl orthoacetate, under acidic conditions (Scheme 1.1.2). The ketene acetal formed by the net loss of two equivalents of alcohol and the addition of the allylic alcohol into the orthoester is rarely isolated. Typically, the ketene acetal is allowed to undergo the Claisen rearrangement in situ. While this method is general, it does typically require harsh heating conditions in order to realize the [3.3]-sigmatropic rearrangement. The Eschenmoser–Claisen rearrangement is similar to the Johnson–Claisen in that allyl alcohols are transformed into the γ,δ-unsaturated amides (Scheme 1.1.3). The Eschenmoser–Claisen reacts N,N-dimethylacetamide dimethyl acetal with the allylic alcohol under acidic conditions. The ketene acetal is not normally isolated, the amide product is formed after rearrangement in situ.

The ketene acetal precursor to the Claisen rearrangement has also been synthesized via a Tebbe olefination of allyl esters. This provides a quick method for the synthesis of allyl vinyl ether intermediate at low temperatures, however the highly reactive nature of the Tebbe reagent will limit the number of applicable substrates. Heating the resulting ketene acetal is often required to form the desired ester products (Scheme 1.1.4).

**Scheme 1.1.3 Eschenmoser–Claisen Rearrangement**

**Scheme 1.1.4 Ketene Acetal Formation by Tebbe Reagent**

**Claisen Rearrangements of Halogenated Allyl Vinyl Ethers**
Although limited varieties of halogenated allyl vinyl ethers have been employed for Claisen rearrangements, to the best of our knowledge none have utilized the dibromoketene acetal intermediate prior to our report. Many of the original publications that discuss the [3.3]-sigmatropic rearrangement of halogenated allyl vinyl ethers note that the halogen substituent of the vinyl group promotes the reaction to occur at lower temperatures. This type of rate enhancement has been described and studied by Carpenter. The use of halogenated allyl vinyl ethers to produce halogenated γ,δ-unsaturated carboxylates is an attractive transformation. Recently, there has been a great deal of attention given to the stereoselective and enantioselective introduction of halogens. The use of the highly selective nature of the [3.3]-sigmatropic rearrangement offers a unique means of selective halogen introduction.

Burkhart and coworkers studied a halogenated Claisen rearrangement, in which cinnamyl alcohol derived allyl difluorovinyl ethers were able to undergo a [3.3]-sigmatropic rearrangement at rather low temperatures (refluxing CCl₄). This method was able to generate γ,δ-unsaturated α,α-difluoroaldehydes (Scheme 1.1.5).

In a similar manner, Samartino and coworkers developed an anionic oxy-Claisen [3.3]-sigmatropic rearrangement. In this variation, allyl α-fluoroacetates are able to quickly undergo rearrangements at cryogenic temperatures to afford predominantly the cis products. Due to the use of excess lithium diisopropylamide (LDA) the rearranged products were observed to epimerize at the α-position. Although lowering the equivalents of LDA gave better cis:trans ratio, it lowered the yield significantly (Figure 1.1.6).
In 1987 Gelb and coworkers synthesized and studied fluorinated phospholipid analogs. They used a clever rendition of the Claisen rearrangement to access a variety of analogs. Allyl trifluorovinyl ethers were synthesized at –60 °C and underwent the rearrangement at unusually low temperatures. The authors note that they could not determine if the rearrangement occurred at –60 °C, or if it occurred upon warming to room temperature. After the rearrangement, the acid fluorides were directly hydrolyzed into carboxylic acids (Figure 1.1.7).

Sauvêtre and coworkers reported a transformation of potassium allyl alkoxides into α-bromo acids. The halogenated vinyl species was introduced by the regioselective and stereoselective addition of the potassium alkoxide into 1,1-difluoro-2-bromoethylene. The allyl vinyl ether was not isolated due to its quick rearrangement into the acid fluoride. These products were directly hydrolyzed into the carboxylic acid. The yields and trans:cis ratio of this rearrangement were modest to good. This method provides a general way to transform allyl alcohols into γ,δ-unsaturated α-bromocarboxylic acid (Scheme 1.1.8).
**Scheme 1.1.8** Stereoselective Formation of $\alpha$-Bromo Acids via Halogenated Claisen

**Background of the Dibromoketene Acetal Claisen Rearrangement**

During our synthetic endeavor towards the indole alkaloid reserpine, a robust method to form a $\gamma,\delta$-unsaturated $\alpha,\alpha$-dibromo ester was required.\(^\text{11}\) A 6π electrocyclization was the key step in this synthetic study and the desired triene was accessed from the corresponding vinyl bromide, which could be prepared by an E2 elimination of the $\gamma,\delta$-unsaturated $\alpha,\alpha$-dibromo ester. This $\alpha,\alpha$-dibromo ester was accessed by the dibromoketene acetal derived from the mixed acetal. The authors realized this through a reaction sequence that is shown in Scheme 1.1.9. The sequence begins with the addition of an allylic alcohol into the chlorinated ether facilitated by halophilic silver(I) salts. The resulting mixed acetal can then undergo a dehydrobromination to form the dibromoketene acetal. This reactive intermediate readily undergoes a Claisen rearrangement at $-78^\circ C$ to generate the $\gamma,\delta$-unsaturated $\alpha,\alpha$-dibromo ester.
While working on reserpine, our group were intrigued by the high efficiency of this unprecedented dibromoketene acetal rearrangement (Scheme 1.1.10). We also noted that this reaction sequence was robust, suitable for gram-scale syntheses in a complex total synthesis setting, and utilized simple starting materials. There are numerous methods for the preparation of allylic alcohols and the chlorinated tribromoethyl ether is operationally simple to synthesize on a large scale. Consequently, we wished to investigate the generality of this new method and explore potential synthetic applications of the α,α-dibromo esters.
Introduction to α,α-Dibromo Esters

α,α-Dibromo esters are a class of halogenated esters that have not been extensively studied in the field of synthetic organic chemistry. With the exception of the works of Shindo, which use α,α-dibromo esters as precursors to the formation of the reactive ynolate species, not many studies exist about their preparation and application. A survey of the literature revealed that there are limited routes to α,α-dibromo esters. Work by Shindo has shown that they can be formed in either a two-step process from the corresponding acid halide, or a two-step process from the corresponding ester (Scheme 1.1.11). The first of these processes involves the use of the reactive acid halide as the starting material, as well as the harsh conditions of the Hell–Volhard–Zelinsky reaction to install the first α-bromide (method A). The second method involves a two-step process that requires the use of two equivalents of the brominating reagent 1,2-dibromotetrachloroethane (method B). Neither method is suitable for the preparation of more complex α,α-dibromo esters, especially ones with acidic protons.

Method A

\[
\begin{align*}
\text{Method A} & \quad \text{Br}_2 \quad \text{high temp.} \quad \text{then R'OH} \\
\text{R-O-X} & \quad \text{R-Br} \quad \text{LDA} \quad \text{(CCIBr}_2)_2 \\
\text{R-Br} & \quad \text{R-Br} \quad \text{LDA} \quad \text{(CCIBr}_2)_2 \\
\text{R-Br} & \quad \text{R-Br} \quad \text{LDA} \quad \text{(CCIBr}_2)_2 
\end{align*}
\]

Method B

\[
\begin{align*}
\text{Method B} & \quad \text{LDA} \quad \text{(CCIBr}_2)_2 \\
\text{R-Br} & \quad \text{R-Br} \quad \text{LDA} \quad \text{(CCIBr}_2)_2 \\
\text{R-Br} & \quad \text{R-Br} \quad \text{LDA} \quad \text{(CCIBr}_2)_2 
\end{align*}
\]

Scheme 1.1.11 Preparation of α,α-Dibromo Esters

To date, the most common use for α,α-dibromo esters was to transform them into the reactive intermediate ynolate. This little used intermediate has been championed by Shindo and coworkers. They discovered a quick and reliable way to transform α,α-dibromo esters to ynolate,
by treating with 4 equivalents of tert-butyllithium. After two rounds of lithium halogen exchange and the ejection of an alkoxide, the ynolate is formed.

Over the past two decades, Shindo has showed the use of this intermediate in a variety of transformations (Scheme 1.1.12). For example, the ynolates can undergo 1,3-dipolar cycloadditions to various isoxazolidinones\textsuperscript{14}, cycloaddition–Dieckmann condensation\textsuperscript{15} to give cyclic unsaturated ketones, and olefinations of ketones and aldehydes to generated highly substituted unsaturated acids.\textsuperscript{16} Despite this intriguing work, the α,α-dibromo esters has not been studied to a great extent. We hoped that developing a new, operationally simple method for the development of α,α-dibromo esters could help encourage further investigation of this functional handle.

**Scheme 1.1.12** Common Uses of Ynolates

1.2 Results and Discussion – Dibromoketene Acetal Rearrangement

*Mixed Acetal Formation*

We first needed to find a general way to convert allylic alcohols into the mixed acetals. This began by screening reaction conditions with the transformation of the simple allylic alcohol, 2-methylprop-2-enol (1a) into the mixed acetal 3b (Table 1.2.1). The use of toluene at −15 °C was optimal for acetal formation (entries 1–4). We next screened a number of silver(I) salts, and found
that silver(I) triflate (AgOTf) was necessary to facilitate the transformation in useful yields (entries 4–7). Next, our attention was turned to the choice of base. In order to investigate a mild method to generate the mixed acetals, entries 1–7 utilize 4Å molecular sieves as the basic medium; however this reaction proved to be problematic. While the mixed acetals could be formed, it was found that the reaction conditions were less suitable for larger scale reactions and led to decomposition to bromal. This decomposition is likely due to the acid-catalyzed hydrolysis of the desired mixed acetal. To circumvent this problem, we screened a variety of bases and found that silver(I) carbonate (Ag$_2$CO$_3$) was optimal to afford the desired mixed acetal (entries 8–10). The use of more dissociative counterions such as hexafluoroantimonate (SbF$_6^-$) led to complete decomposition of the starting material (entries 11–12).

Table 1.2.1 Optimization of the Mixed Acetal Formation

<table>
<thead>
<tr>
<th>entry</th>
<th>silver salt</th>
<th>temp.</th>
<th>base</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOTf</td>
<td>rt</td>
<td>MS$^a$</td>
<td>DCM</td>
<td>50%</td>
</tr>
<tr>
<td>2</td>
<td>AgOTf</td>
<td>–40 °C</td>
<td>MS$^a$</td>
<td>DCM</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>AgOTf</td>
<td>–78 °C</td>
<td>MS$^a$</td>
<td>DCM</td>
<td>NR$^b$</td>
</tr>
<tr>
<td>4</td>
<td>AgOTf</td>
<td>–15 °C</td>
<td>MS$^a$</td>
<td>tol.</td>
<td>0–84%</td>
</tr>
<tr>
<td>5</td>
<td>Ag$_2$O</td>
<td>–15 °C</td>
<td>MS$^a$</td>
<td>tol.</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>AgNO$_3$$^c$</td>
<td>–15 °C</td>
<td>MS$^a$</td>
<td>tol.</td>
<td>31%</td>
</tr>
<tr>
<td>7</td>
<td>AgCOCF$_3$</td>
<td>–15 °C</td>
<td>MS$^a$</td>
<td>tol.</td>
<td>12%</td>
</tr>
<tr>
<td>8</td>
<td>AgOTf</td>
<td>–15 °C</td>
<td>K$_2$CO$_3$</td>
<td>tol.</td>
<td>0%</td>
</tr>
<tr>
<td>9</td>
<td>AgOTf</td>
<td>–15 °C</td>
<td>NaHCO$_2$</td>
<td>tol.</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>AgOTf</td>
<td>–15 °C</td>
<td>Ag$_2$CO$_3$</td>
<td>tol.</td>
<td>71%</td>
</tr>
<tr>
<td>11</td>
<td>AgSbF$_6$</td>
<td>–15 °C</td>
<td>Ag$_2$CO$_3$</td>
<td>tol.</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>AgSbF$_6$</td>
<td>–78 °C</td>
<td>Ag$_2$CO$_3$</td>
<td>tol.</td>
<td>0%</td>
</tr>
</tbody>
</table>
4Å molecular sieves used at 4 wt. equiv. Starting material recovered. 2 equiv of silver salt used.

With the suitable conditions for the conversion of allylic alcohols 1 to mixed acetals 3, we then investigated the reaction’s generality (Table 1.2.2). Compounds 3a-f show that acyclic allylic alcohols can undergo the formation of the mixed acetals in good to excellent yields. Varying the olefin substitution, as in compounds 3b, 3e, and 3f, does not have an effect on the yield of the mixed acetals formation.

Table 1.2.2 Mixed Acetal Formation

<table>
<thead>
<tr>
<th>R'</th>
<th>R''</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>62%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>83%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>90%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>62%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>76%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>77%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>65%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>91%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>65%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>88%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>71%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>75%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>80%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>72%</td>
</tr>
<tr>
<td>CH₂CH(=O)OH</td>
<td>CH₂CH(=O)OH</td>
<td>94%</td>
</tr>
</tbody>
</table>

*a* Secondary alcohols were run at 0 °C. *b* Compounds were isolated as a mixture of diastereomers.
Cyclic allylic alcohols 1g–p also form the mixed acetal in good to excellent yields. Even more complex tetrahydropyridine \(^{18}\) 1p could generate the desired acetal in high yield. It was found that cyclohexyl and cycolhexenyl alcohols 1g, 1n and 1o could efficiently form the desired compounds in good yields. The reaction showed a tolerance to a silyl ether (3d) and a sulfonamide (3p), as well as a variety of nonparticipating olefins.

**Other Attempted Acetal Formations**

Some allylic alcohols failed to give the desired mixed acetals (Table 1.2.3). For instance 2-Methyl-3-butanol (1q) was unable to proceed to the acetal. Despite this, secondary cyclic alcohols (1o and 1p) could readily produce the desired acetal products. The methyl group in 1q may be available for deprotonation, to afford methanol and bromal as the decomposition products, which were both seen in the crude \(^1\)H-NMR. Trisubstituted cyclic olefins 1r–1t also were not able to be transformed into the corresponding acetals. Potentially, an explanation to this observation is that the loss of bromal and methanol, as in the case with 2-methy-3-butanol, would reveal a very stable tertiary allyl carbocation, which can would lead to further decomposition (Scheme 1.2.1). Basic work-up and the use of neutralized silica gel for chromatography did not lead to the isolation of the mixed acetal.

**Table 1.2.3 Notable Failed Mixed Acetal Formation**

<table>
<thead>
<tr>
<th>R' (\rightarrow) OH</th>
<th>R' (\rightarrow) OMe</th>
<th>R' (\rightarrow) OMe</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>

12
During the course of our investigation we also wished to determine if allyl amines 4 could be used for the dibromoketene acetal aza-Claisen rearrangement through intermediate 5 (Scheme 1.2.2). The products that would be formed would contain the highly reactive imidate species 6 that have been used as nucleophilic species in numerous reactions as well as in the formation of various heterocycles.\(^\text{19}\)

<chemistry>
\begin{equation}
\text{Scheme 1.2.2 Aza-Dibromoketene Acetal}
\end{equation}
\end{chemistry>

Under our optimized conditions the hemiaminal ether 6 was not formed. Thinking that the tolenesulfonyl protected amine 4a\(^\text{20}\) group may make the allyl amine too electron poor to undergo addition into the oxonium ion, we next attempted to use the more nucleophilic benzyl protected allyl imine 4b.\(^\text{21}\) The changed protecting group did not lead to the formation of the desired product (Scheme 1.2.3). While the conditions tested failed to yield desired results, further optimization of the reaction conditions may result in the formation of hemiaminal ether.

<chemistry>
\begin{equation}
\text{Scheme 1.2.3 Attempted Formation of Hemiaminal Ether}
\end{equation}
\end{chemistry>

We attempted to realize an indolyl vinyl ether rearrangement to furnish substituted indole products (Scheme 1.2.4). When tert-butyl 3-(hydroxymethyl)-1H-indole-1-carboxylate (7)\(^\text{22}\) was
submitted to the acetal formations conditions, decomposition was observed. Bromal and methanol were seen in the crude $^1$H-NMR. The decomposition can be reasoned to occur due to the displacement of a molecule of bromal and methanol via the mechanism shown in Scheme 1.2.4.

![Scheme 1.2.4 Attempted Indolyl alcohol acetal formation](image)

**Dibromoketene Acetal Claisen Rearrangement**

With a variety of mixed acetals available to us, the Claisen rearrangement was then investigated. It was determined that potassium tert-butoxide (t-BuOK) in the presence of 18-crown-6 was optimal for the dehydrohalogenation to form the ketene acetal. (2,2,6,6-Tetramethylpiperidin-1-yl)oxy radical (TEMPO) was used in this reaction as a radical scavenger to avoid radical debromination of the starting material. The use of these conditions proved to be effective for the desired dehydrohalogenation/rearrangement. With these conditions a wide array of γ,δ-unsaturated α,α-dibromo esters could be formed as shown in Table 1.2.4.

Compounds 9a–c and 9f demonstrate that increasing steric demand of the olefin substituent on acetals 3a–c and 3e does not have a great impact on the yield of the Claisen rearrangement. For less hindered acetals 3a and 3c it was found that the rearrangement was able to be performed at –90 °C in order to increase the yield of the resulting α,α-dibromo esters 9b and 9c. While the yield of the formation of the isopropyl-substituted dibromo ester 9e is lower, it still is converted rapidly
at low temperature in moderate yield. Hindered quaternary centers can also be formed in high yields (9b, 9f and 9l–m). The bond forming event is able to occur efficiently despite the crowded steric environment of the dibromomethylene and the newly formed quaternary carbon.

Ring bearing acetics 3g–p can be rearranged to form γ,δ-unsaturated α,α-dibromo esters with several different substitution patterns. Exocyclic methylenes 9g and 9h can be formed in good to excellent yields. Vinyl substituted carbocycles 9l and 9m can be formed in high yields. Endocyclic olefin containing carbocycles 9n and 9o can also be formed in excellent yields. Both the silyl ether 3d and sulfonamide 3p are smoothly transformed from the acetal to the γ,δ-unsaturated α,α-dibromo ester 9d and 9p in high yields.

The formation of α,α-dibromo esters in this fashion avoids regioselectivity issues that would have plagued traditional methods that are based on enolate chemistry. Scheme 1.2.5 illustrates the formation of the γ,δ-unsaturated α,α-dibromo ester 9u. The acidic α-, γ- and α’-positions of the enone 1w would have prevented the clean formation of the α,α-dibromo ester via the established double bromination sequence. However, if (R)-10-hydroxy-carvone 1u is converted to the mixed acetal 3u via the chemoselective methods described herein, the α,α-dibromo ester 9u can be formed cleanly upon rearrangement without complication
### Table 1.2.4 Rearrangement of Mixed Acetals

Rearrangements performed at $-90 \, ^\circ C$.

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$9a$</td>
<td>$9b$</td>
<td>$9c$</td>
<td>$9d$</td>
<td></td>
</tr>
<tr>
<td>$76%^a$</td>
<td>$79%$</td>
<td>$83%^a$</td>
<td>$75%$</td>
<td></td>
</tr>
<tr>
<td>$9e$</td>
<td>$9f$</td>
<td>$9g$</td>
<td>$9h$</td>
<td></td>
</tr>
<tr>
<td>$68%$</td>
<td>$98%$</td>
<td>$98%$</td>
<td>$68%$</td>
<td></td>
</tr>
<tr>
<td>$9i$</td>
<td>$9m$</td>
<td>$9n$</td>
<td>$9o$</td>
<td></td>
</tr>
<tr>
<td>$75%$</td>
<td>$70%$</td>
<td>$85%$</td>
<td>$97%$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Rearrangements were performed at $-90 \, ^\circ C$. 
We next turned our attention to the diastereoselectivity of the rearrangement. Most studies on the diastereoselectivity of the Claisen rearrangement focus upon how the E/Z isomers of the allyl or vinyl portion of the ether affect the stereochemistry in the product. While the dibromoketene will never be able to take advantage of the highly ordered six-membered transition state provided by the [3,3]-sigmatropic rearrangement, it would be of good value to compare how the diastereoselectivity of the dibromoketene acetal rearrangement of cyclohexenyl methanol derived alcohols compare to other Claisen rearrangements.

The diastereoselectivity of this reaction was shown to have varied results (Table 1.2.5). Dibromo ester 9i was not formed in a highly diastereoselective manner. The Johnson–Claisen rearrangement of the alcohol 1i has shown to have higher selectivity favoring the trans-10 product.
This appears to show that the reactivity of the dibromoketene acetal impedes the selectivity of the [3.3]-sigmatropic for this particular substrate.

**Table 1.2.5 Diastereoselectivity of Rearrangement**

<table>
<thead>
<tr>
<th>R'</th>
<th>3</th>
<th>t-BuOK (2 equiv)</th>
<th>18-crown-6 (2.1 equiv)</th>
<th>TEMPO (30 mol%)</th>
<th>THF, –78 °C</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>3j</td>
<td>60% (1:2 dr)</td>
<td>9j²</td>
<td>98% (1:2 dr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(5S)-9j⁰</td>
<td>30% (Single Diastereomer)</td>
<td>9j²</td>
<td>62% (10:1 dr)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ₐ All diastereomeric ratios determined by ¹H-NMR. ² The relative stereochemistry of 5k and 5p was determined by NOE experiments.

**Scheme 1.2.6** Reported Johnson–Claisen rearrangement of the alcohol 1i

In order to further investigate the diastereoselectivity, acetal 3j was subjected to the rearrangement conditions. Despite the tert-butyl group locking the cyclohexene in the half-chair conformation, the diastereoselectivity was not improved. Even decreasing the temperature to –90 °C did not greatly affect the diastereoselectivity. The potential causes of this poor selectivity are twofold. First, there may be some steric congestion of the typically favored equatorial attack in the
Claisen transition state due to the bromo-substituents on the terminal vinyl carbon. A similar selectivity issue was observed by Ireland in an analogous rearrangement of alcohol 1j via ethanoate when large substituents were introduced at the terminal carbon (Scheme 1.2.7). In this example Ireland and coworkers observed that with a methyl substituted E-silyl enol ether (E)-12, the selectivity was eroded by 16% when compared to the rearrangement of (Z)-12 to form products cis/trans-13. Secondly, the high reactivity of the dibromoketene acetal causes poor differentiation of axial and equatorial attack.

**Scheme 1.2.7** Reported Ireland–Claisen rearrangement of the alcohol 1j

Carvone derived α,α-dibromo esters 9k was formed as a single diastereomer albeit in a modest yield. Another promising result was observed with the tetrahydropyridine dibromo ester 9p. The rearranged product 9p was obtained with 10:1 dr. Interestingly, the product formed arrived preferably from the equatorial attack resulting in the syn-product. This result can be rationalized by the blocking of the axial pathway of the tetrahydropyridine ring by the bulky toluenesulfonamido group. This orientation of the tosyl group can be seen in the X-ray crystal structure of the ethyl ester derivative of the allyl alcohol (Figure 1.2.1).
Other Attempted Rearrangements

The acetal of cinnamyl alcohol 1v could be synthesized in a 62% yield; however, when it was submitted to the rearrangement conditions, no rearranged product was observed (Scheme 1.2.8). This could be due to the energetic cost of breaking conjugation of the cinnamyl group. Although the corresponding Johnson–Claisen rearrangement is known, the reaction times are typically long, suggesting that either steric congestion due to the aromatic ring, or the energetic cost of breaking the conjugation could be the cause of this failed rearrangement to form 9v.

We attempted to also use benzyl vinyl ethers in this rearrangement (Scheme 1.2.9). Similar rearrangements have been reported26 but are very rare and typically require very harsh heating. We wished to investigate if the rate enhancement seen in the dibromoketene acetal Claisen rearrangement of allyl vinyl ethers would also be observed in the more rare rearrangements of benzyl vinyl ethers. While acetals 14 could be synthesized in good yields, once treated with base the acetals quickly decomposed and failed to give any rearrangement products 15.

Scheme 1.2.8 Attempted Cinnamyl Vinyl Ether Rearrangement
1.3 Results and Discussion - Application of α,α-Dibromo Esters

With the large assortment of α,α-dibromo esters available, our attention then turned to exploring the utility of these versatile compounds. As stated previously α,α-dibromo esters have been used in the formation of ynolates by Shindo. This methodology is useful for the formation of vinyl ethers,\textsuperscript{10} various heterocycles,\textsuperscript{11} and tetrasubstituted double bonds.\textsuperscript{12} Treating the dibromo ester 9g with 4 equivalents of tert-butyllithium (t-BuLi) generates ynolate intermediate 16. The olefination product 17 is formed upon the addition of acetophenone at ambient temperatures. We were able to form the tetrasubstituted unsaturated acid 17 in good yield and high \(E/Z\)-selectivity. It is notable that this is the first example of ynolate formation in the presence of an alkene.

Since vinyl bromides have numerous applications in cross coupling chemistry, we also desired to synthesize vinyl bromides from the α,α-dibromo ester 9g. Standard E2 elimination conditions were first attempted (Table 1.3.1). Both t-BuOK and DBU failed to generate any of the desired vinyl bromide 18 (entries 1 and 3–4). Trace amounts of the elimination product were
produced. Thankfully, treatment of 9g with potassium hexafluoroisopropoxide, generated by the use of t-BuOK in the presence of hexafluoroisopropanol (HFIP) and 18-crown-6, smoothly produces vinyl bromide 18 (entry 5).11 Interestingly, when HFIP is not included as a co-solvent this elimination does not take place (entry 6).

### Table 1.3.1. Screening of Elimination Conditions to Form 42

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>Equiv</th>
<th>temp.</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOK</td>
<td>1.2</td>
<td>0 °C</td>
<td>THF</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Li₂CO₃</td>
<td>5</td>
<td>0 °C</td>
<td>DMF</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>DBU</td>
<td>1.1</td>
<td>0 °C</td>
<td>THF</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>1.1</td>
<td>rt</td>
<td>THF</td>
<td>Decomp.</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOK, 18-crown-6</td>
<td>5</td>
<td>0 °C</td>
<td>THF:HFIP</td>
<td>80%</td>
</tr>
<tr>
<td>6</td>
<td>t-BuOK, 18-crown-6</td>
<td>5</td>
<td>0 °C</td>
<td>THF</td>
<td>NR</td>
</tr>
</tbody>
</table>

We hoped that vinyl bromide 18 could then be used to form the functionalized decalin system through the triene via a tandem Suzuki/6π-electrocyclization. We knew that this would require isomerization of the vinyl bromide to give the (2E,3E)-triene. This isomerization was something that was previously observed in the reserpine synthetic studies.

We surveyed a variety of cross-coupling partners 19a–19d to accomplish the triene formation. Electron rich boronic ester 19b failed to give any triene or electrocyclization product 21. This boronic ester did undergo the cross coupling in the analogous reserpine studies. The alkyl substituted boronic acids 19d and 19e also failed to undergo the desired Suzuki cross-coupling under a number of conditions to give the triene 20. We were able to obtained conversion 18 when we used styrenyl substituted boronic acids 19a and 19c. This lead to the conditions in entry 6 that
provided the desired substituted decalin 21a. This example, taken together with the synthetic studies of reserpine, show that this rearrangement provide a quick and efficient way to access triene products. The triene functionality can be difficult to produce under known conditions, and this method could help provide a powerful means to access trienes to the synthetic community interested in studying the little-used 6π electrocylization

**Table 1.3.2 Elaborating Vinyl Bromide 18 into Decalin Ring System**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd0 (10 mol%)</th>
<th>Base (xs)</th>
<th>19</th>
<th>Temp.</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh3)₄</td>
<td>Cs₂CO₃</td>
<td>19e</td>
<td>110 °C</td>
<td>Tol.</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh3)₄</td>
<td>K₂CO₃</td>
<td>19a</td>
<td>100 °C</td>
<td>THF:H₂O (3:1)</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PPh3)₄</td>
<td>K₂CO₃</td>
<td>19b</td>
<td>80 °C</td>
<td>PhH:EtOH (7:1)</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PPh3)₄</td>
<td>K₂CO₃</td>
<td>19c</td>
<td>80 °C</td>
<td>PhH:EtOH (7:1)</td>
<td>Complex Mix</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PPh3)₄</td>
<td>K₂CO₃</td>
<td>19d</td>
<td>100 °C</td>
<td>THF:H₂O (3:1)</td>
<td>Decomp</td>
</tr>
<tr>
<td>6</td>
<td>Pd(PPh3)₄</td>
<td>Cs₂CO₃</td>
<td>19a</td>
<td>110 °C</td>
<td>Tol.</td>
<td>54%</td>
</tr>
</tbody>
</table>

Tebbe olefination of the diene 18 was also investigated as a means of generating the triene 22 precursor to the decalin ring system. This means of generating the triene would have the added benefit of generating the (2E,3E)-triene directly without the isomerization required for the cross-coupling reaction. Unfortunately, this proved to be too harsh a condition for the relatively labile vinyl bromide. No decalin ring formation was observed.
We also attempted to utilize this diene 18 to simultaneously functionalize both the δ and α positions. We wished to realize a δ-addition of a Michael donor followed by the trapping of the resulting α-bromo enolate 23. If an aldehyde is used as the electrophile this would lead to a tandem Michael/Darzens reaction, which would generate highly functionalized α,β-epoxy ester 24 (Scheme 1.3.6). When we treated the dienes with the Michael donor dimethyl malonate there was no reaction. We also attempted the Michael addition using organocopper nucleophiles. Both Gilman reagents and cuprates generated from the Grignard reagent failed to generate any of the desired δ- or β-additions.

Both functional handles of the products of the dibromoketene acetal Claisen rearrangement can be used as synthetic leverage to afford unique and synthetically important building blocks.
Treatment of the Claisen product 9a with dimethyldioxirane (DMDO) produces the corresponding epoxide 25 which can be further functionalized. The more traditional m-CPBA epoxidation proved to be too unreactive to from the epoxide under all conditions tested.

Scheme 1.3.5 Oxidation of γ,δ-Unsaturated α,α-Dibromo Ester

We hoped to further show the use of the Claisen products via the two-step reduction/iodoetherification sequence. The DIBAL reduction smoothly transformed the Claisen product 9b to the alcohol 26 in a high yield. Interestingly, under these basic conditions, we did not observe any of the halohydrin convert to the epoxide 27. Even under harsher conditions, this transformation could not be realized (Scheme 1.3.10). Treatment of alcohol 26 with sodium hydride lead to decomposition.

Scheme 1.3.6 Reduction of the α,α-Dibromo Ester

Scheme 1.3.7 Attempted Bromoepoxide Formation

We next investigated if we could synthesize the tetrahydrofuran from the dibromo alcohol 26. However, when treated under a variety of etherification conditions, the alcohol was unable to form tetrahydrofuran product 28 (Scheme 1.3.9). Typically, these bromoepoxides are formed via an oxidation of a vinyl bromide. Perhaps the dibromomethylene is too sterically encumbered in
this alcohol due to both the nearby geminal dimethyl as well as the bromide not used in the $S_{N}2$ displacement.

Scheme 1.3.8 Haloetherification Attempt

The alkene and ester can also work in concert to form functionalized $\alpha,\alpha$-dibromobutyrolactones. Halogenated butyrolactones have gained attention for their potential as both biologically active compounds, and as unique synthetic building blocks.

Subjecting $\alpha,\alpha$-dibromoester $9b$ to a catalytic dihydroxylation produces dibromolactone $29$ in one step. $9b$ can also be converted to acid $30$, which can then undergo an iodolactonization to form the functionalized lactone $31$. Due to the unique conditions required for the E2 elimination to form the vinyl bromide, we presume that this elimination would extend to other $\alpha,\alpha$-dibromo ester with open $\beta$-hydrogens without any of the undesired E2 elimination.

Scheme 1.3.9 Formation of $\alpha,\alpha$-Dibromo-$\gamma$-Butyrolactone by Dihydroxylation

Scheme 1.3.10 Formation of $\alpha,\alpha$-Dibromo-$\gamma$-Butyrolactone by Iodoesterification

When a pendant protected alcohol is located on the rearranged product, a deprotection can be performed to unveil the unique vinyl substituted lactone. For example, we found that mild
deprotection of α,α-dibromoester 9d can lead to a vinyl substituted lactone 32 in one step. These studies, taken together, show that the rearranged products provide a unique and diversifiable platform to access these highly halogenated γ-butyrolactones.

**Scheme 1.3.11** Formation of α,α-Dibromo-γ-Butyrolactone by Deprotection

**Conclusion**

In summary, the dibromoketene acetal Claisen rearrangement has been investigated. Both cyclic and acyclic allylic alcohols can be transformed into α,α-dibromo esters in a two-step process. The sequence is compatible with a variety of functionalities, and can produce previously inaccessible dibromo esters. This method avoids the use of the traditional bromination of metal enolates and could have potential in the synthesis of other, more difficultly elaborated α,α-dibromo esters as long as the corresponding allylic alcohol could be prepared.

**Scheme 1.3.12** Dibromoketene Acetal Claisen Rearrangement
The α,α-dibromo esters produced are useful synthetic building blocks, and can be used in the context of complex synthesis. For example, the esters can be used for the established ynolate chemistry that has been pioneered by Shindo and coworkers. Vinyl bromides, which have numerous uses in carbon-carbon bond forming events, can also be easily accessed. Finally, we showed the use of this method by elaborating the α,α-dibromo esters into a number of unique α,α-dibromo-γ-butyrolactones.

In the future this methodology could be extended to other halo acetals, and may also be capable of being used in the aza- and thio-Claisen rearrangements. Future research could also focus on the formation of the unique dihaloketene acetal in new, mild conditions. This method also shows the incredible opportunity that total synthesis provides in the development of unique reactions.
Experimental:

General Procedures. All reactions were carried out in flamed-dried or oven-dried round bottomed flasks and Schlenk flasks. Glass water condenser was fitted over the flasks with rubber septa fitted over the condenser. All reactions were performed under positive pressure of argon. Stainless steel needles were used to inject acetylenes into refluxing reactions via syringe pump. Reactions were monitored through thin-layer chromatography (TLC) on 0.25-mm SiliCycle silica gel plates. Plates were visualized under UV light or with p-anisaldehyde or with potassium permanganate stain followed by heating (<1 min) with heat gun. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60 Å pore size, 40-63 µm). Organic solutions were concentrated through rotary evaporators.

Instrumentation. IR spectra were obtained on a Thermo Nicolet Avatar 370 FT-IR. NMR spectra were obtained from Bruker AV-300 and AV-500 instruments calibrated using residual undeuterated chloroform as an internal reference (7.26 and 77.00 ppm for $^1$H and $^{13}$C NMR Spectra, respectively). Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for $^{13}$C NMR spectra are reported in terms of chemical shift. The following abbreviations are used to denote the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Samples were analyzed on a Waters LCT Premier XE Time of Flight Instrument controlled by MassLynx 4.1 software. Samples were infused using direct loop injection from a Waters Acquity UPLC into the Multi Mode Ionization source. The lock mass standard for accurate mass determination was Leucine Enkephalin (Sigma
LCMS data was collected on an Agilent Technologies 6120 Quadrupole LC/MS using a C18 column.

**Materials** Reagents were used as received from commercial sources. Acetonitrile and dichloromethane were distilled from calcium hydride under positive pressure of argon. Tetrahydrofuran and diethylether were distilled from sodium and benzophenone under positive pressure of argon. Allylic alcohols 1a-c,f,o were purchased from Sigma-Aldrich. Tribromoacetaldehyde (bromal) was purchased from TCI-America. Reagents were used as received from commercial sources. Allylic alcohols 1r-t were made with established procedures.

Amines 4 were synthesized through established allyl amine protection procedures.

Alcohol 7 and compounds 19a-e was synthesized by know literature procedures or were purchased from commercial vendors Sigma-Aldrich or TCI-America.

**Preparation of novel compounds**

Ethyl esters S2 and S3 were synthesized through the method described by Chang and coworkers¹. S2 (5.1 g, 90%) was isolated as a liquid. Spectral data matched those reported in the literature ².

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The Reduction of S1 and S2 was carried out as described below.

**Cyclohex-1-en-1-ylmethanol (1g)** (3.2 g, 75%) was isolated as a liquid. Spectral data matched those reported in the literature.3

**Cyclopent-1-en-1-ylmethanol (1h)** (0.5 g, 78%) was isolated as a liquid. Spectral data matched those reported in the literature.4

**Synthesis of allylic Alcohols:**

(6-Phenyl-1-tosyl-1,2,5,6-tetrahydropyridin-3-yl)methanol (1p): Ester S35 (5.78 g, 10 mmol) was dissolved in CH₂Cl₂ (50 ml). The solution was placed in a dry ice/acetone bath. Once cooled, 1.0 M DIBAL in hexane (25 mL, 25 mmol, 2.5 equiv) was added dropwise. The reaction was stirred for 2 h. A saturated solution of sodium/potassium tartrate (25 mL) was added and then the mixture was warmed to ambient temperature. EtOAc (100 mL) was added and the solution was stirred vigorously overnight. The mixture was extracted with EtOAc (2 x 50 mL). The solution was dried (Na₂SO₄). The solvent was evaporated and the residue chromatographed through silica gel (EtOAc/hexanes, 40% EtOAc Rf = 0.3) to give the allylic alcohol 1p as a solid (2.77 g, 80%). M.p.: 102 °C; IR (CH₂Cl₂) νmax 3511, 2961, 1587, 1332, 1151 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, J = 8.0 Hz, 2H), 7.37–7.24 (m, 7H), 5.79 (b, 1H), 5.38–5.33 (m, 1H), 4.22 (d, J = 18.1

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Hz, 1H), 4.05–3.91 (m, 2H), 3.37 (d, J = 18.1 Hz, 1H), 2.52–2.40 (m, 2H) 2.41 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 143.3, 139.0, 137.5, 134.6, 129.5, 128.4, 127.5, 127.3, 127.1, 120.1, 64.7, 52.8, 41.0, 26.2, 21.5; HRMS (ESI) calcd for C$_{19}$H$_{22}$NO$_3$S [M + H]$^+$ m/z 344.1320, found 344.1337.

**Mixed Acetal Formation:**

![Diagram of acetal formation](image)

2-Methyl-3-(2,2,2-tribromo-1-methoxyethoxy)prop-1-ene (1b): Alcohol 1b (1 mmol), AgOTf (330 mg, 1.3 mmol), and Ag$_2$CO$_3$ (550 mg, 2 mmol) were placed in a round bottom flask, covered in aluminum foil, containing a magnetic stir bar. Toluene (5 mL) was added and the reaction was cooled with an ice/salt bath. Ether 2 (500 mg, 1.5 mmol) was added slowly to the vigorously stirred solution. The reaction was allowed to continue for 1 h. A saturated Na$_2$S$_2$O$_3$ was added (0.3 ml) and the reaction was taken out of the cooling bath and stirred for 30 min. The suspension was filtered through a silica plug and washed with EtOAc (25 mL). The solvent was evaporated and the residue chromatographed through silica gel (5% EtOAc in hexanes, $R_f = 0.5$) to give 3b as an oil (261 mg, 71%). IR (CH$_2$Cl$_2$) $v_{\text{max}}$ 1652, 1480, 1117, 1091 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.01 (s, 1H), 5.00 (s, 1H), 4.52 (s, 1H), 4.29 (s, 2H), 3.74 (s, 3H), 1.81 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.8, 114.1, 107.7, 74.3, 59.3, 46.5, 19.7; GCMS (EI+) calcd for C$_6$H$_8$Br$_3$O [M – CH$_3$O]$^+$ m/z 332.8, found 332.8.
3-Methyl-1-(2,2,2-tribromo-1-methoxyethoxy)but-2-ene (3b): Alcohol 1b was submitted to the above conditions to yield mixed acetal 3b (4.72 g, 62%) as an oil after being chromatographed through silica gel (5% EtOAc in hexanes, RF = 0.45). IR (CH₂Cl₂) νₘₐₓ 2366, 1452, 1100 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.52–5.47 (m, 1H), 4.56 (s, 1H) 4.48 (d, J = 6.9 Hz, 2H), 3.74 (s, 3H), 1.83 (s, 3H), 1.77 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.8, 119.6, 107.5, 67.7, 58.5, 46.9, 25.9, 18.3; GCMS (EI+) calcd for [C₈H₁₄Br₃O₂]+ m/z 377.8, found 377.8.

(E)-1-(2,2,2-Tribromo-1-methoxyethoxy)pent-2-ene (3c): Alcohol 1c was submitted to the above conditions to yield mixed acetal 3c (316 mg, 83 %) as an oil after being chromatographed through silica gel (5% EtOAc in hexanes, Rf = 0.5). IR (CH₂Cl₂) νₘₐₓ 2832, 2954, 1670, 1109 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.89–5.82 (m, 1H), 5.68–5.60 (m, 1H), 4.53 (s, 1H), 4.37 (dd, J = 6.4, 1.0, 2H), 3.69 (s, 3H), 2.15–2.07 (m, 2H), 1.02 (t, J = 7.46 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.2, 123.8, 107.4, 72.1, 58.6, 46.8, 25.3, 13.2; GCMS (EI+) calcd for [C₈H₁₃Br₃O₂]+ m/z 377.8, found 377.8.

(Z)-10,10,11,11-Tetramethyl-3-(tribromomethyl)-2,4,9-trioxa-10-siladodec-6-ene (3d): Alcohol 1d⁶ was submitted to the above conditions to yield mixed acetal 3d (447 mg, 90%) as an oil after being chromatographed through silica gel (0–5% EtOAc in hexanes, RF = 0.2). IR (CH₂Cl₂)

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$v_{\text{max}}$ 2935, 2889, 1453, 1067 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.82–5.75 (m, 2H), 4.58–4.55 (m, 3H), 4.34–4.31 (m, 2H), 3.76 (s, 3H), 0.94 (s, 9H), 0.12 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 133.6, 125.4, 107.9, 66.8, 59.6, 58.8, 46.4, 25.9, 18.3, −5.16, −5.17; GCMS (EI+) calcd for [C$_{13}$H$_{25}$Br$_3$O$_3$Si]$^+$ m/z 497.9, found 480.0.

$\text{(E)}$-4-Methyl-1-(2,2,2-tribromo-1-methoxyethoxy)pent-2-ene (3e): Alcohol 1e$^7$ was submitted to the above conditions to yield mixed acetal 3e (225 mg, 62%) as an oil after being chromatographed through silica gel (5% EtOAc in hexanes, $R_f = 0.55$). IR (CH$_2$Cl$_2$) $v_{\text{max}}$ 2960, 2927, 1455, 1137 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.77 (dd, $J = 15.5$ Hz, 6.4 Hz, 1H), 5.63–5.57 (m, 1H), 4.52 (s, 1H), 4.37 (d, $J = 6.3$ Hz, 2H), 3.69 (s, 3H), 2.35 (octet, $J = 6.8$ Hz, 1H), 1.02 (d, $J = 6.8$ Hz 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 143.5, 121.9, 107.4, 72.3, 58.5, 46.8, 30.2, 22.1, 22.0; GCMS (EI+) calcd for C$_9$H$_{15}$Br$_2$O$_2$ [M −Br]$^+$ m/z 314.9, found 314.9.

$\text{(E)}$-3,7-Dimethyl-1-(2,2,2-tribromo-1-methoxyethoxy)octa-2,6-diene (3f): Alcohol 1f was submitted to the above conditions to yield mixed acetal 3f (341 mg, 76%) as an oil after being chromatographed through silica gel (5% EtOAc in hexanes, $R_f = 0.6$). IR (CH$_2$Cl$_2$) $v_{\text{max}}$ 2972, 2733, 1671, 1436, 14071 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.49 (dt, $J = 7.0$ Hz, 1.2 Hz, 1H),

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5.15–5.10 (m, 1H), 4.57, (s, 1H), 4.50, (d, J = 6.9 Hz, 2H), 3.75 (s, 1H), 2.20–2.11 (m, 4H), 1.76 (s, 3H), 1.72 (s, 3H), 1.64 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 142.1, 131.9, 123.7, 119.4, 107.4, 67.5, 58.6, 47.0, 39.6, 26.2, 25.7, 17.7, 16.7; GCMS (EI+) calcd for C$_{12}$H$_{21}$Br$_2$O$_2$ [M – Br]$^+$ m/z 354.9, found 354.9.

1-((2,2,2-Tribromo-1-methoxyethoxy)methyl)cyclohex-1-ene (3g): Alcohol 1g was submitted to the above conditions to yield mixed acetal 3g (3.09 g, 76%) as an oil after being chromatographed through silica gel (10% EtOAc in hexanes, R$_f$ = 0.5). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2887, 2834, 1454, 1260 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.80 (app. s 1H), 4.50 (s, 1H), 4.24 (app. s, 2H), 3.73 (s, 3H), 2.13–2.07 (m, 4H), 1.67–1.59 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 133.8, 127.2, 107.3, 75.5, 59.2, 46.9, 26.1, 25.1, 22.4, 22.2; GCMS (EI+) calcd for C$_{10}$H$_{15}$Br$_2$O$_2$ [M – Br]$^+$ m/z 326.9, found 327.0.

1-((2,2,2-Tribromo-1-methoxyethoxy)methyl)cyclopent-1-ene (3h): Alcohol 3h was submitted to the above conditions to yield mixed acetal 3h (255 mg, 65%) as an oil after being chromatographed through silica gel (10% EtOAc in hexanes, R$_f$ = 0.48). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2919, 2843, 1457, 1099 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 5.78–5.76 (m, 1H), 4.52 (s, 1H), 4.44 (s, 2H), 3.73 (s, 3H), 2.41–2.36 (m, 4H), (qt, J = 7.5 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 139.8,
129.8, 107.5, 69.3, 59.1, 46.7, 33.1, 32.4, 23.4; GCMS (EI+) calcd for [C₉H₁₃Br₃O₂]⁺ m/z 391.8, found 391.8.

(4S)-4-(Prop-1-en-2-yl)-1-((2,2,2-tribromo-1-methoxyethoxy)methyl)cyclohex-1-ene (3i): Alcohol 1i⁸ was submitted to the above conditions to yield mixed acetal 3i (434 mg, 91 %) as an oil after being chromatographed through silica gel (5% EtOAc in hexanes, Rf = 0.5). Acetal 3i was isolated as a 1:1 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers. IR(CH₂Cl₂) νmax 2962, 2883, 1641, 1451, 1088 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.84–5.79 (m, 1+1H) 4.78–4.73 (m, 2+2H), 4.52–4.50 (s, 1+1H), 4.31–4.22 (m, 2+ 2H), 3.75 (s, 3H), 3.73 (s, 3H), 2.30–2.14 (m, 4+4H), 2.08–1.99 (m, 1+1H), 1.91–1.84 (m, 1+1H), 1.75 (s, 3+3H), 1.53–1.42 (m, 1+1H); ¹³C NMR (125 MHz, CDCl₃) δ 149.6, 149.5, 133.5, 133.4, 126.7, 126.5, 108.84, 108.82, 107.5, 107.2, 75.2, 74.6, 59.3, 59.1, 46.8, 46.7, 40.9, 40.8, 30.6, 30.5, 27.4, 27.3, 26.6, 26.5, 20.8, 20.7; GCMS (EI+) calcd for [C₁₃H₁₉Br₃O₂]⁺ m/z 445.9, found 445.9.

5-(Tert-butyl)-1-((2,2,2-tribromo-1-methoxyethoxy)methyl)cyclohex-1-ene (3j): Alcohol 1j⁹ was submitted to the above conditions to yield mixed acetal 3j (301 mg, 65%) as an oil after being chromatographed through silica gel (0–5% EtOAc in hexanes, Rf = 0.5). Acetal 3j was isolated as

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a 1:1 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers.

IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2947, 2857, 1529, 1066 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.82–5.76 (app. br. s, 1+1H), 4.51 (s, 1H), 4.49 (s, 1H), 4.33–4.18 (m, 2+2H), 3.76 (s, 3H), 3.72 (s, 3H), 2.33–2.00 (m, 3+3H), 1.97–1.77 (2+2H), 1.38–1.26 (m, 1+1H), 1.20–1.05 (m, 1+1H), 0.88 (s, 9H), 0.87 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 134.0, 133.9, 127.4, 127.1, 107.2, 106.9, 75.5, 74.7, 74.5, 59.1, 59.1, 59.1, 59.1, 46.9, 46.8, 44.1, 44.0, 32.32, 32.30 27.9, 27.7, 27.3, 27.2, 26.5, 26.4, 23.6, 23.5; GCMS (EI+) calcd for C$_{14}$H$_{25}$Br$_3$O$_2^+$ m/z 461.9, found 461.9.

(4S, 6S)-1-Methyl-4-(prop-1-en-2-yl)-6-(2,2,2-tribromo-1-methoxyethoxy)cyclohex-1-ene (3k): Alcohol 1k$^{10}$ was submitted to the above conditions to yield mixed acetal 3k (393 mg, 88%) as an oil after being chromatographed through silica gel (10% EtOAc in hexanes, $R_f$ = 0.6). Acetal 3k was isolated as a 1:1 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers. IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2361, 2336, 1444, 1314, 1092 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.65–5.57 (app. br. s, 1+1H), 4.82–4.77 (m, 2+2H), 4.75 (s, 1H), 4.69 (s, 1H), 4.59–4.40 (m, 1+1H), 3.90 (s, 3H), 3.80 (s, 3H), 2.37–2.67 (m, 2+2H) 2.17–2.00 (m, 2+2H) 1.92–1.90 (m, 3H), 1.87–1.86 (m, 3H), 1.79 (s, 3+3H) 1.75–1.68 (m, 1+1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 148.7, 148.6, 134.4, 134.3, 125.4, 125.2, 109.4, 107.3, 106.2, 80.3, 76.4, 60.8, 58.6, 47.9, 47.3, 40.6, 40.5, 35.9, 33.5, 30.8, 20.4, 20.1, 19.5; GCMS (EI+) calcd for C$_{13}$H$_{19}$Br$_2$O$_2$ [M–Br]$^+$ m/z 366.9, found 366.9.

(2-(2,2,2-Tribromo-1-methoxyethoxy)ethyldene)cyclopentane (3l): Alcohol 1l\textsuperscript{11} was submitted to the above conditions to yield mixed acetal 3l (289 mg, 71\%) as an oil after being chromatographed through silica gel (5\% EtOAc in hexanes, R\textsubscript{f} = 0.5). IR (CH\textsubscript{2}Cl\textsubscript{2}) \nu\textsubscript{max} 2955, 2866, 1508, 1128 cm\textsuperscript{−1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 5.39 (tt, J = 7.2, 1.0 Hz, 1H), 4.58 (s, 1H), 4.45 (d, J = 7.2 Hz, 2H), 3.69 (s, 3H), 2.23–2.15 (m, 4H), 1.59–1.53 (m, 4H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 150.3, 115.1, 107.6, 69.5, 58.4, 47.0, 33.8, 29.1, 26.3, 26.0; GCMS (EI+) calcd for [C\textsubscript{10}H\textsubscript{15}Br\textsubscript{3}O\textsubscript{2}]\textsuperscript{+} m/z 405.9, found 405.9.

(2-(2,2,2-Tribromo-1-methoxyethoxy)ethyldene)cyclohexane (3m): Alcohol 1m\textsuperscript{11} was submitted to the above conditions to yield mixed acetal 3m (316 mg, 75\%) as an oil after being chromatographed through silica gel (10\% EtOAc in hexanes, R\textsubscript{f} = 0.5). IR (CH\textsubscript{2}Cl\textsubscript{2}) \nu\textsubscript{max} 2930, 2854, 2662, 1444, 1078 cm\textsuperscript{−1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 5.64–5.58 (m, 1H), 4.58 (s, 1H), 4.47 (dt, J = 7.1, 1.1 Hz, 2H), 3.76 (s, 1H), 2.36 (app. q, J = 7.3 Hz, 4H), 1.79–1.64 (m, 6H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 146.7, 116.3, 107.4, 66.9, 58.4, 47.0, 37.1, 29.2, 28.3, 27.8, 26.6; GCMS (EI+) calcd for [C\textsubscript{11}H\textsubscript{17}Br\textsubscript{3}O\textsubscript{2}]\textsuperscript{+} m/z 419.9, found 419.9.

1-Methylene-2-(2,2,2-tribromo-1-methoxyethoxy)cyclohexane (3n): Alcohol 1n\textsuperscript{12} was submitted to the above conditions to yield mixed acetal 3n (325 mg, 80\%) as an oil after being chromatographed through silica gel (5\% in hexanes, EtOAc \textit{R}_{f} = 0.5). Acetal 3n was isolated as a 1:1 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers. IR (\text{CH}_2\text{Cl}_2) \nu_{\text{max}} 2934, 2841, 1445, 1107 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 5.06–5.01 (m, 1+2H), 4.92 (app. br. s, 1H), 4.56 (s, 1H), 4.54 (s, 1H), 4.34 (t, \textit{J} = 3.8 Hz, 1H), 4.30 (t, \textit{J} = 3.8 Hz, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 2.60–244 (m, 1+1H) 2.24–2.13 (m, 1+1H), 2.11–1.98 (m, 1+1H) 1.96–1.67 (m, 3+3H), 1.58–1.38 (m, 2+2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \delta 148.4, 146.5, 112.1, 110.0, 107.5, 105.3, 82.0, 77.5, 60.1, 58.7, 48.3, 47.6, 33.8, 33.1, 31.9, 31.7, 27.7, 27.6, 21.6, 21.1; GCMS (EI+) calcd for C\textsubscript{10}H\textsubscript{15}Br\textsubscript{2}O\textsubscript{2} [M − Br]\textsuperscript{+} \textit{m/z} 326.9, found 326.9.

3-(2,2,2-Tribromo-1-methoxyethoxy)cyclohex-1-ene (3o): Alcohol 1o was submitted to the above conditions to yield mixed acetal 3p (282 mg, 72\%) as an oil after being chromatographed through silica gel (10\% EtOAc in hexanes, \textit{R}_{f} = 0.5). Acetal 3o was isolated as a 1:1 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers. IR (\text{CH}_2\text{Cl}_2) \nu_{\text{max}} 2930, 1440, 1313, 1125 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \delta 5.99–5.83 (m, 2H), 4.66 (s, 1H),

4.47–4.41 (m, 1H), 3.74 (s, 3H), 2.15–2.05 (m, 1H), 2.04–1.80 (m, 4H), 1.67–1.57 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 132.5, 132.3, 126.6, 126.2, 107.3, 106.8, 74.5, 73.5, 58.5, 58.2, 48.0, 47.7, 29.7, 28.2, 25.1, 25.0, 19.0, 18.8; GCMS (EI+) calcd for C$_{13}$H$_{19}$Br$_2$O$_2$ [M – Br]$^+$ m/z 312.9, found 312.9.

2-Phenyl-1-tosyl-5-((2,2,2-tribromo-1-methoxyethoxy)methyl)-1,2,3,6-tetrahydropyridine (3p): Alcohol 1p was submitted to the above conditions to yield mixed acetal 3p (1.8 g, 94%) as an oil after being chromatographed through silica gel (20% EtOAc in hexanes, $R_f = 0.6$). Acetal 3p was isolated as a 1:1 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers. M.p.: 124 °C; IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 1597, 1332, 1155, 1152 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.74–7.69 (m, 2+2H), 7.34–7.22 (m, 7+7H), 5.86 (d, $J = 3.3$ Hz, 1H), 5.83 (d, $J = 3.3$ Hz, 1H), 5.35 (s, 1H), 5.33 (s, 1H), 4.44–4.29 (m, 2+2H), 4.25–4.05 (m, 2+2H), 3.67 (s, 3H), 3.64 (s, 3H), 3.50–3.35 (m, 1+1H), 2.55–2.39 (m, 5+5H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 143.24, 143.21, 138.8, 138.7, 137.5, 137.4, 131.1, 130.9, 129.6, 128.54, 128.5, 127.7, 127.6, 127.3, 127.2, 127.1, 123.9, 123.6, 107.5, 107.3, 71.7, 71.2, 59.7, 59.6, 52.6, 46.1, 45.8, 41.5, 41.4, 28.4 26.1, 21.56, 21.55; HRMS (ESI) calcd for C$_{22}$H$_{24}$Br$_3$NNaO$_4$S [M + Na]$^+$ m/z 659.8854, found 659.8880.
(5R)-2-Methyl-5-(3-(2,2,2-tribromo-1-methoxyethoxy)prop-1-en-2-yl)cyclohex-2-enone

(3u): Alcohol 1u\(^{13}\) was submitted to the above conditions with the following modifications: (I) Alcohol 1u and chloroether 2 were added as a solution in toluene (1 mL) to the silver salts in toluene (5 mL), and (II) The reaction was conducted at room temperature. Mixed acetal 3u (332 mg, 72%) was isolated as a heavy oil after being chromatographed through silica gel (10% EtOAc in hexanes, \(R_f = 0.35\)). Acetal 3u was isolated as a 1:1 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers. IR (CH\(_2\)Cl\(_2\)) \(\nu_{\text{max}}\) 2976, 2919, 1745, 1418, 1248 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.77 (app. br. s., 1+1H), 5.28 (s, 1+1H), 5.11 (s, 1+1H), 4.56 (s, 1H), 4.55 (s, 1H), 4.47–4.34 (m, 2+2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.09–2.91 (m, 1+1H), 2.74–2.59 (m, 2+2H), 2.54–2.36 (m, 2+2H), 1.82–1.80 (m, 3+3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 147.1, 146.9, 132.7, 132.6, 127.3, 127.1, 108.9, 108.7, 102.2, 101.9, 98.4, 97.8, 67.8, 67.7, 59.2, 58.9, 48.3, 48.2, 37.9, 37.8, 37.6, 36.3, 32.4, 32.2, 17.3, 16.7; GCMS (EI+) calcd for C\(_{13}\)H\(_{17}\)Br\(_2\)O\(_3\) [M – Br]\(^+\) m/z 380.9, found 381.0.

((2,2,2-tribromo-1-methoxyethoxy)methyl)benzene (36): 36 was synthesized as above, and was isolated as a heavy oil after being chromatographed through silica gel (10% EtOAc in hexanes, \(R_f = 0.5\)). IR (CH\(_2\)Cl\(_2\)) \(\nu_{\text{max}}\) 2936, 2865, 1456, 1075 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.51–7.32

\(^{13}\) Xuan, M.; Paterson, I.; Dalby, S. M. *Org. Lett.* **2012**, *14*, 5492–5495.
(m, 5H), 5.00 (dd, $J = 5.6, 11.7$ Hz, 2H), 4.63 (s, 1H), 3.69 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 137.5, 128.5, 127.2, 127.0, 107.8, 69.0, 66.9, 58.2.; HRMS could not be determined.

(E)-(3-(2,2,2-tribromo-1-methoxyethoxy)prop-1-en-1-yl)benzene (3v): 3v was synthesized as above, and was isolated as an oil (132 mg, 62%) after being chromatographed through silica gel (10% EtOAc in hexanes, $R_f = 0.5$). IR (CH$_2$Cl$_2$) $v_{max}$ 1563, 1102, 1073 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ δ 7.44-7.27 (m, 5H), 6.74 (d, $J = 16$ Hz, 1H), 6.37 (dt, $J = 16, 6$ Hz, 1H), 4.6-4.59 (m, 3H), 3.74 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 136.2, 134.0, 128.7, 128.2, 126.7, 124.3, 107.8, 71.7, 58.9, 46.5; HRMS could not be calculated.

Rearrangement reaction:

Methyl 2,2-dibromo-3,3-dimethylpent-4-enoate (3b): Acetal 9b (3.81 g, 10 mmol), 18-crown-6 (280 mg, 1.05 mmol, 2.1 equiv), and TEMPO, (27 mg, 0.175 mmol, 35 mol %) were placed into a round bottom flask. THF (10 mL) was added and the reaction was cooled in a dry ice/acetone bath. Once cooled, 1M $t$-BuOK in THF (1 mL, 1 mmol, 2 equiv) was added slowly. The reaction was stirred for 2 h, upon which sat. NH$_4$Cl (1 mL) was added and then the mixture was warmed to room temperature and partitioned between EtOAc (10 mL) and water (10 mL). The aqueous phase was washed with EtOAc (5 mL x 3). The combined organic phases were washed with sat. NaCl (5
mL) and dried (Na$_2$SO$_4$). The volatiles were evaporated and the residue was chromatographed through silica (10% EtOAc in hexanes, $R_f = 0.5$) to yield $\alpha,\alpha$-dibromo ester $3b$ (2.37 g, 79%) as an oil. IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2991, 1749, 1178 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.24 (dd, $J = 17.1$, 11.0 Hz, 1H), 5.24 (dd, $J = 0.6$, 0.8 Hz, 1H), 5.19 (dd, $J = 7.5$, 0.6 Hz, 1H), 3.87 (s, 3H), 1.50 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.1, 141.4, 115.1, 73.5, 54.2, 48.3, 24.8; GCMS (EI+) calcd for [C$_8$H$_{12}$Br$_2$O$_2$]$^+$ m/z 297.9, found 297.9.

**Methyl 2,2-dibromo-4-methylpent-4-enoate (9a):** Mixed acetal $3a$ was submitted to the above conditions with the following modifications, (1) the reaction was run at −90 °C using a liquid nitrogen/hexanes cooling bath, and (2) the reaction was allowed to stir for 3 h before being quenched. $\alpha,\alpha$-dibromo ester $9a$ (106 mg, 76%) was isolated as an oil after being chromatographed through silica gel (0–5% EtOAc in hexanes, $R_f = 0.55$). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2915, 1717, 1564, 1143 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.02 (t, $J = 1.4$ Hz, 1H), 4.90 (s, 1H), 3.88 (s, 3H), 3.43 (s, 2H), 1.81 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.8, 140.1, 117.6, 57.4, 54.5, 54.1, 23.4; GCMS (EI+) calcd for [C$_7$H$_{10}$Br$_2$O$_2$]$^+$ m/z 258.9, found 258.9.

**Methyl 2,2-dibromo-3-ethylpent-4-enoate (9c):** Mixed acetal $3c$ was submitted to the above conditions with the following modifications, (1) the reaction was run at −90 °C using a liquid nitrogen/hexanes cooling bath, and (2) the reaction was allowed to stir for 3 h before being
quenched. α,α-dibromo ester 9c (125 mg, 83%) as an oil after being chromographed through silica gel (0% EtOAc in hexanes, Rf = 0.5). IR (CH2Cl2) v_max 2885, 1730, 1438, 1253 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.63 (ddd, J = 16.9, 10.4, 9.0 Hz, 1H), 5.31 (dd., J = 10.4, 1.7 Hz, 1H) 5.21 (dq, J = 16.9, 0.7 Hz, 1H), 3.86 (s, 3H), 2.82–2.76 (m, 1H), 1.89–1.76 (m, 1H), 1.55–1.47 (m, 1H), 0.94 (t, J = 7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 166.3, 135.4, 120.9, 66.9, 58.2, 54.4, 25.0, 11.7; GCMS (EI+) calcd for [C₈H₁₂Br₂O₂]⁻ m/z 297.9, found 297.9.

**Methyl 2,2-dibromo-3-(((tert-butyldimethylsilyl)oxy)methyl)pent-4-enoate (9d):** Mixed acetal 3d was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9d (156 mg, 75%) as an oil after being chromographed through silica gel (5% EtOAc in hexanes, Rf = 0.6). IR (CH2Cl2) v_max 2851, 1759, 1475, 1107 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.79 (ddd, J = 16.9, 10.2, 8.8 Hz, 1H), 5.39–5.31 (m, 2H), 3.93–3.88 (m, 4H), 3.76–3.70 (m, 1H), 3.37 (q, J = 7.0 Hz, 1H) 0.91 (s, 9H), 0.08 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 166.1, 134.1, 121.2, 65.2, 64.5, 57.2, 54.3, 25.9, 18.5, −5.5; GCMS (EI+) calcd for C₁₃H₂₄BrO₃S [M−Br]− m/z 335.1, found 335.1.

**Methyl 2,2-dibromo-3-isopropylpent-4-enoate (9e):** Mixed acetal 3e was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9e (107 mg, 68%) as an oil after being
chromatographed through silica gel (10% EtOAc in hexanes, R_f = 0.6). IR (CH_2Cl_2) \nu_{\text{max}} 2901, 1756, 1455, 1234 cm\(^{-1}\); \textsuperscript{1}H NMR (300 MHz, CDCl_3) \delta 5.75 (dt, J = 16.9, 8.5 Hz, 1H), 5.31 (dd, J = 10.2, 1.8 Hz, 1H), 5.17 (dd, 16.9, 1.4 Hz, 1H), 3.85 (s, 3H), 2.87 (dd, J = 9.5, 3.8 Hz, 1H), 2.06–1.96 (m, 1H) 1.00 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl_3) \delta 166.7, 134.3, 120.9, 66.5, 61.1, 54.4, 31.3, 22.7, 19.6; GCMS (EI+) calcd for C_9H_{13}BrO_2 [M – HBr]^+ m/z 232.0, found 232.1.

![Chemical structure](image)

**Methyl 2,2-dibromo-3,7-dimethyl-3-vinloct-6-enoate (9f):** Mixed acetal 3f was submitted to the above rearrangement conditions to yield a mixture of \alpha,\alpha-dibromo ester 9f (180 mg, 98%) as an oil after being chromatographed through silica gel (0–5% EtOA in hexanes, R_f = 0.6). IR (CH_2Cl_2) \nu_{\text{max}} 2897, 1730, 1515, 1443, 1272 cm\(^{-1}\); \textsuperscript{1}H NMR (300 MHz, CDCl_3) \delta 6.07 (dd, J = 17.4, 10.8, 1H), 5.35 (dd, J = 10.8, 0.9, 1H), 5.21–5.09 (m, 2H), 3.87 (s, 3H), 1.97–1.81 (m, 4H), 1.72 (s, 3H), 1.62 (s, 3H), 1.44 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl_3) \delta 166.1, 139.3, 132.0, 123.8, 117.2, 74.8, 54.2, 51.1, 36.5, 25.7, 23.9, 19.0, 17.7; GCMS (EI+) calcd for C_{13}H_{20}BrO_2 [M – Br]^+ m/z 287.1, found 286.9.
Methyl 2,2-dibromo-2-(2-methylene cyclohexyl)acetate (9g): Mixed acetal 3g was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9g (1.6 g, 98%) as an oil after being chromatographed through silica gel (0–5% EtOAc in hexanes, Rf = 0.5). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2947, 2847, 1749, 1447, 1245 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.89 (s, 1H), 4.69 (s, 1H), 3.90 (s, 3H), 3.06–3.00 (m, 1H), 2.49–2.29 (m, 2H), 2.13–1.96 (m, 2H), 1.90–1.60 (m, 3H), 1.55–1.39 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.9, 146.5, 138.2, 65.1, 55.3, 54.6, 37.8, 31.9, 28.3, 25.8; GCMS (EI+) calcd for C$_{10}$H$_{14}$BrO$_2$ [M – Br]$^+$ $m/z$ 245.0, found 245.0.

Methyl 2,2-dibromo-2-(2-methylene cyclopentyl)acetate (9h): Mixed acetal 3h was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9h (106 mg, 68%) as an oil after being chromatographed through silica gel (0–5% EtOAc in hexanes, Rf = 0.5). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2353, 1745, 1428, 1159 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.13 (s, 1H), 4.90 (s, 1H), 3.95 (s, 3H), 3.76–3.69 (m, 1H), 2.61–2.29 (m, 3H), 2.07–1.88 (m, 2H), 1.63–1.53 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.6, 150.9, 110.2, 66.9, 54.7, 54.5, 36.2, 32.7, 24.7; GCMS (EI+) calcd for C$_9$H$_{12}$BrO$_2$ [M – Br]$^+$ $m/z$ 231.0, found 231.0.
Methyl 2,2-dibromo-2-(1-vinylcyclopentyl)acetate (9i): Mixed acetal 3i was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9i (122 mg, 75%) as an oil after being chromatographed through silica gel (0–5% EtOAc in hexanes, Rf = 0.55). IR (CH2Cl2) νmax 2847, 1738, 1632, 1004 cm⁻¹; (300 MHz, CDCl3) δ 5.99 (dd, J = 17.3, 10.7 Hz, 1H), 5.28 (dd, J = 10.7 Hz, 1H), 5.22 (d, J = 17.3 Hz, 1H), 3.82 (s, 3H), 2.26–2.19 (m, 2H), 2.04–1.98 (m, 2H), 1.77–1.70 (m, 2H), 1.67–1.62 (m, 2H); ¹³C NMR (125 MHz, CDCl3) δ 166.2, 139.1, 116.9, 72.9, 60.1, 54.2, 35.9, 24.6; GCMS (EI+) calcd for C₁₀H₁₄BrO₂ [M – Br]⁺ m/z 245.1, found 245.0.

Methyl 2,2-dibromo-2-(1-vinylcyclohexyl)acetate (9m): Mixed acetal 3m was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9m (119 mg, 70%) as an oil after being chromatographed through silica gel (10% EtOAc in hexanes, Rf = 0.5). IR (CH2Cl2) νmax 2456, 1741, 1443, 1240, 999 cm⁻¹; ¹H NMR (75 MHz, CDCl3) δ 5.71 (dd, J = 17.6, 10.9 Hz, 1H), 5.53 (dd, J = 10.9, 1 Hz, 1H), 5.24 (dd, J = 17.6, 1 Hz, 1H), 3.85 (s, 3H), 2.23 (br d, J = 13.3 Hz, 2H), 1.88 (dt, J = 13.3, 3.3 Hz, 2H), 1.70–1.60 (m, 3H), 1.52–1.34 (m, 2H), 1.22–1.01 (m, 1H); ¹³C NMR (125 MHz, CDCl3) δ 165.9, 137.4, 120.4, 76.6, 54.2, 50.8, 32.0, 25.7, 22.7; GCMS (EI+) calcd for [C₁₁H₁₆Br₂O₂]⁺ m/z 339.9, found 339.9.
Methyl 2,2-dibromo-3-(cyclohex-1-en-1-yl)propanoate (9n): Mixed acetal 3n was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9n (139 mg, 85%) as an oil after being chromatographed through silica gel (0–5% EtOAc in hexanes, Rf = 0.55). IR (CH2Cl2) νmax 2840, 1749, 1432 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 5.63 (br s, 1H), 3.88 (s, 3H), 3.34 (s, 2H), 2.04–2.00 (m, 4H), 1.63–1.51 (m, 4H); 13C NMR (125 MHz, CDCl3) δ 167, 132.9, 129.4, 69.0, 66.0, 65.5, 29.2, 25.5, 22.8, 21.8; GCMS (EI+) calcd for [C10H14Br2O2]⁺ m/z 325.9, found 325.9.

Methyl 2,2-dibromo-2-(cyclohex-2-en-1-yl)acetate (9o): Mixed acetal 3o was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9o (151 mg, 97%) as an oil after being chromatographed through silica gel (10% EtOAc in hexanes, Rf = 0.55). IR (CH2Cl2) νmax 2924, 1738, 1436 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 5.97–5.92 (m, 1H), 5.63 (dq, J = 10.2, 2.0 Hz, 1H), 3.90 (s, 3H), 3.26–3.20 (m, 1H), 2.05–1.98 (m, 3H), 1.92–1.85 (m, 1H), 1.61–1.48 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 166.5, 131.3, 126.1, 67.6, 54.6, 48.8, 26.7, 24.8, 21.4; GCMS (EI+) calcd for [C9H12Br2O2]⁺ m/z 309.9, found 310.0.
Methyl 2,2-dibromo-2-((5S)-2-methylene-5-(prop-1-en-2-yl)cyclohexyl)acetate (9i): Mixed acetal 22j was submitted to the above rearrangement conditions to yield α,α-dibromo ester 3i (110 mg, 60%) as an oil after being chromatographed through silica gel (10% EtOAc in hexanes, R_f = 0.65). Dibromo ester 9i was isolated as a 1:2 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers. IR (CH_2Cl_2) ν_max 2940, 2853, 1752, 1744, 1450, 1440 cm^{-1}; ^1H NMR (300 MHz, CDCl_3) δ 4.96–4.71 (m, 4H_{minor}+4H_{major}), 3.91 (s, 3H_{minor}), 3.89 (s, 3H_{major}), 3.40 (t, J = 6.1 Hz, 1H_{major}), 3.13–3.08 (m, 1H_{minor}), 2.88–2.79 (m, 1H_{major}), 2.55–2.12 (m, 5H_{minor}+4H_{major}), 1.96–1.88 (m, 1H_{major}), 1.83 (s, 3H_{major}), 1.81 (s, 3H_{minor}), 1.73–1.61 (m, 1H_{minor}+1H_{major}), 1.48–1.32 (m, 1H_{minor}); ^13C NMR (125 MHz, CDCl_3) δ 166.8, 166.7, 148.7, 147.3, 146.0, 145.7, 111.8, 110.5, 109.5, 108.4, 65.9, 64.7, 54.6, 54.5, 51.5, 44.9, 38.8, 37.4, 36.6 34.0, 33.3 33.1, 30.9, 21.8, 20.8; GCMS (EI+) calcd for [C_{13}H_{17}BrO_2]^+ m/z 365.9, found 366.0.

Methyl 2,2-dibromo-2-(5-(tert-butyl)-2-methylene cyclohexyl)acetate (9j): Mixed acetal 3j was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9j (187 mg, 98%) as an oil after being chromatographed through silica gel (0–5% EtOAc in hexanes, R_f = 0.55). Dibromo ester 9j was isolated as a 1:2 mixture of inseparable diastereomers. NMR spectroscopic data is provided for both isomers. IR (CH_2Cl_2) ν_max 2936, 2853, 1720, 1446 cm^{-1}; ^1H NMR (300
MHz, CDCl$_3$) $\delta$ 5.07 (m, 1H$_{\text{major}}$), 4.90 (s, 1H$_{\text{minor}+1H_{\text{major}}}$), 4.67 (s, 1H$_{\text{minor}}$), 3.91 (s, 3H$_{\text{major}}$), 3.90 (s, 3H$_{\text{minor}}$), 3.49–3.44 (m, 1H$_{\text{major}}$), 2.99–2.92 (m, 1H$_{\text{minor}}$), 2.55–2.46 (m, 1H$_{\text{minor}+1H_{\text{major}}}$), 2.36–2.19 (m, 2H$_{\text{minor}+2H_{\text{major}}}$), 2.05–1.87 (m, 2H$_{\text{minor}+2H_{\text{major}}}$), 1.84–1.63 (m, 1H$_{\text{minor}+1H_{\text{major}}}$), 0.92 ((s, 9H$_{\text{minor}+9H_{\text{major}}}$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 166.9, 166.5, 146.5, 116.3, 108.1, 66.6, 55.2, 54.6, 54.4, 51.9, 50.0, 47.7, 39.1, 33.5, 33.0, 32.4, 31.5, 28.4, 27.4, 27.3, 27.5, 26.8, 22.0; GCMS (EI+) calcd for C$_{14}$H$_{23}$BrO$_2$ [M – HBr]$^+$ $m/z$ 302.1, found 302.1

Methyl 2,2-dibromo-2-((1R,5R)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-en-1-yl)acetate (9k):

Mixed acetal 3k was submitted to the above rearrangement conditions to yield $\alpha,\alpha$-dibromo ester 9k (55 mg, 30%) as an oil after being chromatographed through silica gel (0–5% EtOAc, $R_f$ = 0.65). IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 2969, 1750, 1642, 1438 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.75–5.68 (m, 1H), 4.83 (s, 2H), 3.95 (s, 3H), 3.52–3.43 (m, 1H), 2.53–2.44 (m, 1H), 2.36–2.25 (m, 1H), 2.19–2.09 (m, 1H), 2.05–1.93 (m, 1H), 1.82 (s, 3H), 1.75–1.69 (m, 1H), 1.62 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 167.8, 148.9, 131.8, 129.2, 109.4, 69.2, 54.6, 50.9, 41.2, 34.4, 31.2, 21.9, 20.7; GCMS (EI+) calcd for C$_{13}$H$_{18}$BrO$_2$ [M – Br]$^+$ $m/z$ 287.1, found 287.1.
Methyl 2,2-dibromo-2-(5-methylene-2-phenyl-1-tosylpiperidin-4-yl)acetate (9p): Mixed acetal 3p was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9p (346 mg, 62%) as a thick oil after being chromatographed through silica gel (15% EtOAc in hexanes, Rf = 0.4). Dibromo ester 9p was isolated as a 10:1 mixture of inseparable diastereomers. NMR spectroscopic data is reported only for the major isomer. IR (CH₂Cl₂) νmax 2953, 1758, 1594, 1160 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, J = 8.2 Hz, 2H), 7.54–7.33 (m, 7H), 5.37 (app. s, 1H), 5.15 (s, 1H), 4.76 (s, 1H), 4.26 (d, J = 14.4 Hz, 1H), 3.82 (s, 3H), 3.74 (d, J = 14.4 Hz, 1H), 3.21–3.12 (m, 1H), 2.85–2.78 (m, 1H), 2.45 (s, 3H), 1.88 (ddd, J = 13.7, 12.3, 5.1, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 166.0, 143.6, 138.2, 137.9, 136.8, 129.8, 129.7, 128.9, 127.6, 126.5, 114.8, 64.0, 55.1, 54.7, 49.7, 47.6, 30.9, 21.5; HRMS (ESI) calcd for C₂₂H₂₄Br₂NO₄S [M + H]⁺ m/z 557.9774, found 557.9791.
(5R)-Methyl 2,2-dibromo-4-(4-methyl-5-oxocyclohex-3-en-1-yl)pent-4-enoate (9u): Mixed acetal 3u was submitted to the above rearrangement conditions to yield α,α-dibromo ester 9u (144 mg, 76%) as a heavy oil after being chromatographed through silica gel (10% EtOAc in hexanes, $R_f = 0.4$). IR (CH$_2$Cl$_2$) $\nu_{max}$ 2955, 2888, 1738, 1669, 1440, 1235 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.79–5.76 (m, 1H), 4.82–4.78 (m, 2H), 4.33–4.22 (m, 2H), 3.77 (s, 3H), 2.97–2.91 (m, 1H), 2.48 (dh, $J = 18.3$, 2.7 Hz, 1H), 2.25 (ddd, $J = 11.5$, 3.9, 0.9 Hz, 1H), 2.07 (dd, $J = 11.5$, 0.9 Hz, 1H), 2.00–1.94 (m, 1H), 1.86–1.84 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 158.5, 146.4, 131.9, 126.6, 109.1, 102.4, 67.6, 65.9, 57.9, 37.4, 34.2, 32.5, 16.5; GCMS (EI+) calcd for [C$_{13}$H$_{16}$Br$_2$O$_3$]$^+$ m/z 379.9, found 379.9.

Functionalization of dibromo esters:

(E)-2-(2-Methylene cyclohexyl)-3-phenylbut-2-enoic acid (17): Dibromo ester 9g (mg, 0.5 mmol, 2 equiv) was dissolved in THF (3 mL) and cooled in a dry ice/acetone bath. t-BuLi (4.9 equiv) was added slowly. The reaction was allowed to stir for 3 h before being warmed to 0 °C and stirred at that temperature for 30 min. The reaction was then warmed to RT and allowed to stir for 30 min. before the addition of acetophenone (30 mg, 0.25 mmol, 1.2 equiv) as a solution in
THF (0.5 mL). The reaction was stirred for 30 min. The reaction mixture was then partitioned between 1N NaOH (2 mL) and EtOAc (5 mL). The reaction was then extracted with 1N NaOH (5 mL x 3). The basic extract was then acidified to pH 3 with concentrated HCl. The acidified layer was then extracted with EtOAc (5 x 3 mL). The organic solution was then washed with water (5 mL x 3) and brine (5 ml). The solution was then dried (Na$_2$SO$_4$). The volatiles were evaporated to give the pure acid 7 as a heavy oil (55.6 mg, 87%). Acid 17 was isolated as a 5.6:1 mixture of E/Z isomers. NMR spectroscopic data is reported only for the major isomer. IR (CH$_2$Cl$_2$) $\nu_{\text{max}}$ 3062, 2925, 1687, 1489, 1296 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.41–7.30 (m, 3H), 7.26–7.21 (m, 2H), 5.00–4.97 (m, 1H), 4.90–4.88 (m, 1H), 2.89 (bd, $J = 13.7$ Hz, 1H), 2.37 (bd, $J = 13.7$ Hz, 1H), 2.27 (s, 3H), 1.90–1.57 (m, 6H), 1.42–1.30 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 174.2, 150.2, 144.1, 142.3, 131.4, 127.3, 126.5, 125.0, 108.6, 46.1, 35.8, 31.9, 27.1, 26.1, 23.7; HRMS (ESI) calcd for C$_{17}$H$_{19}$O$_2$ [M–H] $m/z$ 255.1385, found 255.1373.

\[(E)-\text{Methyl 2-bromo-2-(2-methylene cyclohexylidene)acetate (18)}: ~1$ M $t$-BuOK in THF (15 mL, 15 mmol, 5 equiv) was added slowly to a solution of hexafluoroisopropanol (15 mmol, 5.5 equiv) and 18-crown-6 (4.22 g 16.5 mmol, 5.5 equiv) in THF (85 mL) at 0 °C under argon and then the solution was stirred at 0 °C for 20 min. A solution of the α,α-$\alpha$-dibromo ester 9g (0.978 g, 3 mmol) in THF (5 mL) was added slowly. The mixture was stirred for 30 min, at which point sat. NH$_4$Cl (50 mL) was added. The mixture was warmed to room temperature and partitioned between EtOAc (100 mL) and water (50 mL). The aqueous phase was extracted with EtOAc (2 x 50 mL) and then the combined organic phases were washed with sat. aqueous NaCl solution (100 mL) and
dried (Na₂SO₄). The solvent was evaporated and the residue chromatographed through silica gel (10% EtOAc in hexanes, \( R_f = 0.4 \)) to give vinyl bromide 18 as a liquid (0.59 g, 80%). Vinyl bromide 18 was isolated as a 10:1 mixture of E/Z isomers. NMR spectroscopic data is reported only for the major isomer. IR (CH₂Cl₂) \( \nu_{\max} \) 2947, 1778, 1436, 913 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 4.87 (s, 1H), 4.82 (s, 1H), 3.76 (s, 3H), 2.58–2.48 (m, 2H), 2.39–2.32 (m, 2H), 1.78–1.72 (m, 4H); \(^1^\)C NMR (125 MHz, CDCl₃) \( \delta \) 166.2, 148.8, 147.8, 111.5, 105.5, 52.7, 35.8, 34.9, 27.2, 26.3; GCMS (EI+) calcd for [C₁₀H₁₃BrO₃]⁺ \( m/z \) 244.0, found 244.0.

Methyl 3-phenyl-3,4,5,6,7,8-hexahydronaphthalene-1-carboxylate (21): Vinyl bromide 18 (23.7 mg, 0.097 mmol) Cs₂CO₃ (95 mg, 0.291 mmol, 3 equiv), and the boronic acid 19a (21 mg, 0.145 mmol, 1.5 equiv) was added to a dried 4 mL vial. Toluene (1 mL) was added and the reaction mixture was deoxygenated by bubbling Ar through the solution for 15 min. Pd(PPh₃)₄ (11 mg, 9.7 µmol, 10 mol%) was added. The headspace was purged with Ar and the vial was then sealed and warmed to 100 °C for 18 h. The mixture was then cooled and loaded directly onto a silica gel column and was chromatographed (0–5% EtOAc in hexanes, \( R_f = 0.6 \)) to give the hexahydronaphthalene product 21 as a film (14.2 mg, 54%). IR (CH₂Cl₂) \( \nu_{\max} \) 2894, 1734, 1544, 1491 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.51–7.30 (m, 5H), 6.14–6.11 (m, 1H), 3.85–3.78 (m, 1H), 3.74 (s, 3H), 3.21–3.08 (m, 1H), 2.98–2.86 (m, 1H), 2.15–1.66 (m, 8H); \(^1^\)C NMR (125 MHz, CDCl₃) \( \delta \) 173.4, 140.6, 136.9, 129.3, 128.4, 127.5, 125.3, 123.1, 119.4, 52.2, 49.8, 33.9, 30.1, 28.2, 23.1, 22.8; GCMS (EI+) calcd for [C₁₈H₂₀O₂] \( m/z \) 269.1, found 269.1.
Methyl 2,2-dibromo-3-(2-methyloxiran-2-yl)propanoate (25): Dibromo ester 9a (286 mg, 1 mmol) was dissolved in CH₂Cl₂ (10 ml). The reaction was cooled in a dry ice/acetone bath and freshly prepared ~60-65 mM DMDO in acetone (25 ml, ~1.5 mmol, ~1.5 equiv). The reaction was then allowed to slowly warm to room temperature overnight. The solvent was evaporated and the residue was chromatographed through silica gel (10% EtOAc in hexanes, Rf = 0.3) to give epoxide 25 as an oil (266 mg, 88%). IR (CH₂Cl₂) νmax 2986, 1736, 1282, 1254 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.93 (s, 3H), 3.33 (dd, J = 15, 0.9 Hz, 1H), 2.87 (dd, J = 9.8, 5.1 Hz, 2H), 2.66 (dd, J = 4.7, 0.8 Hz, 1H), 1.43 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 166.6, 55.6, 54.7, 54.6, 54.2, 52.6, 22.0; GCMS (EI+) calcd for [C₇H₁₀Br₂O₃]⁺ m/z 299.9, found 299.9.

2,2-dibromo-3,3-dimethylpent-4-en-1-ol (26): Reduction of 9b was carried out as described in the synthesis of 1q. Product was run through a plug of silica (EtOAc) to give 26 as a waxy solid. IR (CH₂Cl₂) νmax 3959, 2364, 2337, 1450, 1091 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.23 (dd, J = 16, 11 Hz 1H), 5.28–5.19 (m, 2H); 4.07 (d, J = 7.6 Hz, 2H); 1.47 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 142.12, 115.1, 91.5, 71.6, 48.2, 25.4; HRMS could not be obtained.

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3,3-Dibromo-5-(hydroxymethyl)-4,4-dimethylhidrofurane-2(3H)-one (29): Dibromo ester 9b (15 mg, 50 µmol) and NMO (12 mg, 100 µmol, 2 equiv) were dissolved in THF (0.5 mL), t-BuOH (0.1 mL). 2 wt% OsO₄ (0.3 mL, 25 µmol, 50 mol%) was carefully added slowly to the solution at RT. The reaction was stirred for 12 h at which point it was quenched with corn oil (0.6 mL) and allowed to stir for 30 min. sat. aqueous. KHSO₄ solution (2 mL) and EtOAc (5 mL) were added. The reaction was washed with EtOAc (5 mL x 2) and combined organic phase was dried (Na₂SO₄). The solvent was evaporated and the residue chromatographed through silica gel (40% EtOAc in Hexane, Rf=0.2) to give lactone 29 (13 mg, 86%) as a heavy oil. IR (CH₂Cl₂) νmax 3572, 2880, 1787, 1482, 1266 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.98 (dd, J = 7.5, 3.7 Hz, 1H), 3.98–3.83 (m, 2H), 2.08 (bs, 1H), 1.44 (s, 3H), 1.20 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 167.8, 85.5, 66.2, 60.9, 49.1, 21.1, 20.4; GCMS (EI+) calcd for [C₁₇H₁₀BrO₃]⁺ m/z 299.9, found 300.0.

2,2-Dibromo-3,3-dimethylpent-4-enoic acid (30): Dibromo ester 9b (300 mg, 1 mmol) was dissolved in THF (1.5 mL), MeOH (1 mL), and 2N LiOH (1.5 mL, 3 mmol, 3 equiv). The reaction was stirred for 12 h, at which point, the reaction mixture was partitioned between 1N NaOH (5 mL) and EtOAc (10 mL). The reaction was then extracted with 1N NaOH (5 mL x 3). The basic aqueous extract was acidified to pH 3 with concentrated HCl. The acidified aqueous layer was
then extracted with EtOAc (10 x 3 mL). The organic solution was washed with water (10 mL x 2) and brine (5 ml). The solution was dried (Na₂SO₄). The volatiles were evaporated to give the pure acid 30 (189 mg, 66%) as a solid. M.p.: 148 °C decomposition; IR (CH₂Cl₂) νₘₐₓ 3114, 2794, 1715, 1470, 1265 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.26 (dd, J = 17.4, 10.6 Hz, 1H), 5.29 (d, J = 3.0, 2H), 5.25 (d, J = 13.8, 1H) 1.53 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 171.2, 140.9, 115.6, 72.9, 48.1, 24.9; HRMS (ESI) calcd for C₇H₉Br₂O₂ [M – H]⁻ m/z 284.8954, found 284.9001

3,3-Dibromo-5-(iodomethyl)-4,4-dimethyldihydrofuran-2(3H)-one (31): Acid 30 (26 mg, 90 µmol) was dissolved in THF (0.5 mL) and water (0.5 mL). Then, I₂ (25 mg 0.1 mmol, 1.1 equiv), KI (16 mg, 0.1 mmol, 1.1 equiv), and NaHCO₃ (25 mg, 0.3 mmol, 3 equiv) were added. The reaction was allowed to stir for 12 h, at which point sat. Na₂S₂O₃ (1 mL) was added. The mixture was washed with EtOAc (5 mL x 3) and dried (Na₂SO₄). The reaction was concentrated and run on a plug of silica eluting with Et₂O (25 mL). The solvent was evaporated to give pure iodolactone 31 (34.4 mg, 92%) as a white solid. M.p.: 111 °C; IR (CH₂Cl₂) νₘₐₓ 2866, 1788, 1454, 1170 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.74 (t, J = 6.7 Hz, 1H), 3.32–3.3 (m, 2H), 1.60 (s, 3H), 1.2 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 167.9, 85.5, 66.1, 60.9, 49.1, 21.1, 20.4; GCMS (EI+) calcd for [C₇H₉Br₂IO₂]⁺ m/z 413.8, found 413.8.
3,3-Dibromo-4-vinylidihydrofuran-2(3H)-one (32): Dibromo ester 9d (41 mg, 0.1 mmol) was added to MeOH (1 mL). AcCl (3 µL) was then added and the reaction was allowed to stir for 12 hr at RT, at which point sat. NaHCO₃ (0.5 mL) was added. The reaction was partitioned between EtOAc (5 mL) and water (5 mL). The mixture was the extracted with EtOAc (5 mL x 3), and dried (Na₂SO₄). The reaction was concentrated and the residue chromatographed through silica gel (0–5% EtOAc in Hexane, R₆ = 0.5,) to give lactone 32 (20 mg, 75%) as an oil. IR (CH₂Cl₂) νmax 2836, 1791, 1638 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.97–5.85 (m, 1H), 5.50 (d, J = 10.0 Hz, 1H), 5.60 (d, J = 13.7, 1H), 4.41 (dd, J = 9.1, 7.2 Hz, 1H), 4.20 (t, J = 9.1 Hz, 1H), 3.55–3.47 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 168.5, 129.7, 123.0, 69.4, 57.1, 54.9; GCMS (EI+) calcd for C₆H₇BrO₃ [M – HBr]⁺ m/z 187.9, found 188.
Reference:


Chapter 2

Investigation and Application of the Asymmetric Phosphine-Catalyzed [4 + 2] Annulation of Imines with Allenoates
2.1 Introduction to Phosphine Catalysis

Nucleophilic Phosphine Catalysis

Tertiary phosphine has been utilized in organic synthesis for many years. Most cases involve the use of stoichiometric amounts such as the Wittig olefination, Mitsunobu reaction, and the Staudinger reaction. In more recent years there has been a huge increase in the number of publications that utilize trisubstituted phosphorus as a ligand in organometallic chemistry. While these reactions have become widely used in organic chemistry laboratories, phosphine’s nucleophilic behavior as a main part of the reaction manifold has not had as much exposure. An early and fundamental example of nucleophilic phosphine catalysis was by Rauhut and Currier.\textsuperscript{1} In this reaction unsaturated esters were dimerized by reacting them with tributylphosphine. This reaction occurs through the addition of phosphine to the $\beta$-position of the unsaturated ester to form the phosphonium enolate, which generates the dimer upon the addition of another molecule of starting material and the elimination of the phosphine.

![Scheme 2.1.1 Rauhut–Currier Reaction and Proposed Mechanism](image-url)
Krische and coworkers have more recently reported the first intramolecular variant of the Rauhut–Currier reaction to synthesize acyl cycloalkenes.\(^2\) Bis-enone substrates can be reacted with catalytic amounts of tributylphosphine in order to form the cyclized products in good yields and as a single isomeric product due to steric or electronic bias.

Scheme 2.1.2a shows that the phosphine preferentially adds to the enone to generate the phosphonium enolate. This causes a cyclization onto the \(\alpha,\beta\)-unsaturated ester with a \(>95:5\) selectivity. This highlights the incredible electronic differentiation that is possible utilizing tributylphosphine. Steric hindrance also plays a large role in determining the selectivity of the initial phosphine addition to the bis-dienone. When a dimethyl bis-dienone was subjected to the reaction conditions it was observed that the phosphine adds selectively to the least sterically encumbered enone. This allows for the selective formation of the cyclized product in \(>95:5\)
selectivity. It is noteworthy that this methodology tolerates chiral centers on the tether (Scheme 2.1.2c). The xylose-derived mono-enone mono-enoate reacts to give enantiomerically pure cyclized cyclohexanone product with only a small amount of the other regioisomer.

 Shortly after Rauhut and Currier’s original 1963 disclosure, Morita published on a transformation that intercepted the phosphonium enolate with an aldehyde. In this case tricyclohexylphosphine was utilized as the catalyst. This reaction generates the β-hydroxy ketone and greatly expanded upon the first reported phosphine-catalyzed dimerization. Baylis and Hillman later reported that this transformation could also be performed with tertiary amines such as DABCO. The Morita–Baylis–Hillman (MBH) reaction has since become a powerful means to synthesize allylic alcohols.³

![Scheme 2.1.3](image-url)

**Scheme 2.1.3 a)** Morita’s Phosphine-Catalyzed Formation of Allylic Alcohols  **b)** Baylis–Hillman’s Tertiary Amine-Catalyzed Variant

In 1992 Fráter and coworkers studied the first intramolecular MBH reaction. They studied both the use of tertiary phosphine and tertiary amines.⁴ In this report they subjected unsaturated-
E-keto esters to catalysis conditions to form cyclized alcohol products with good yields. Interestingly, the phosphines were the only catalyst class to be able to realize the intramolecular MBH reaction.

![Scheme 2.1.4 First Intramolecular MBH Reaction](image)

The first reports by Rauhut, Currier and Morita showed that a tertiary phosphine could be used as a unique catalyst to access important structural motifs. The products of these reactions were also obtained in an atom economic fashion from simple starting materials – hinting at the ease of use and generality of this branch of organocatalysis. Despite this, relatively few publications were produced in this field for some time. However, in the 21st century there has been a large number of methodologies developed that utilize nucleophilic phosphine catalysis. The increase in interest of this mode of catalysis also coincided with the growth of organocatalysis in general.

During this explosion in popularity, phosphine-catalyzed reactions have been utilized to perform numerous reaction transformations. Typically they require phosphine to act as a nucleophile by adding to an electron deficient alkene. This generates the phosphonium enolate zwitterion which can be subsequently used in further transformations. For example, this type of reactivity is seen in the phosphine catalyzed Michael addition. Researchers White and Baizer investigated the reaction of electron deficient alkenes and alcohols in the presence of a phosphine catalyst. This example shows a unique phosphine-triggered general base catalysis. The proposed mechanism can be seen in Scheme 2.1.5.
Tertiary phosphine has also been used to catalyze aldol reactions via a stabilized phosphonium enolate. In 2005 Roush and coworkers reported that subjecting the bis-enone with triphenylphosphine lead to the formation of the intramolecular aldol product (Scheme 2.1.6). After the first cyclization of the symmetric bis-enone by a Rauhut–Currier reaction, the intermediate will then undergo a β-addition to generate the zwitterion shown. The zwitterion will then undergo a proton transfer to generate the phosphine stabilized enolate species, which will then proceed to the final aldol product. Interestingly, the final aldol product is less thermodynamically stable than the alternative dienone product that could be formed. This Rauhut–Currier/Aldol reaction can be used to synthesize 5,6-fused and 6,6-fused ring system utilizing stoichiometric phosphine. The reaction shows generality and tolerance to steric bulk. A sample of the products can be seen in Table 2.1.1.
Marinetti and coworkers were also able to exploit the phosphine’s role in the MBH reaction to synthesize complex dihydropyrroles. In this process they were able to obtain the cyclized product through a tandem aza-MBH/Michael addition (Scheme 2.1.7). The treatment of 1,6-dicarbonyl-2,4-diene compounds and imines in the presence of a phosphine catalyst leads to the MBH product that will subsequently undergo an aza-Michael reaction. The final product is
obtained after a proton transfer and the elimination of the phosphine. This reaction shows generality for both aryl imines as well as alkyl aldimines. Most phosphine-catalyzed reactions rely upon the stability of aryl aldimines in order to obtain high reaction yields. However, this is a rare example where alkyl imines are tolerated under phosphine-catalyzed reaction conditions, even 2-methyl-1-(N-tosylimino)propane can be tolerated. The high stereoselectivity of this reaction also shows the usefulness of this method.

Scheme 2.1.7 Phosphine Catalyzed Synthesis of Dihydropyrroles via Tandem Aza-MBH/Michael Addition

One of the most common modes of reactivity seen in phosphine catalysis is γ-umpolung addition. The first known study of phosphine-enabled γ-umpolung addition was done by Cristau in 1982. This method utilized stoichiometric phosphine to facilitate the γ-umpolung addition, but helped lead the way for future catalyzed variants. They found that when the vinyl phosphonium iodide was treated with lithium methoxide it would undergo γ-umpolung addition to form the
relatively stable phosphonium ylide. The $\gamma$-umpolung addition product could then be obtained after protonation, ion exchange, deprotection of the acetal, and elimination of the tertiary phosphine (Scheme 2.1.8).

Scheme 2.1.8 First-Reported Phosphine Mediated $\gamma$-Umpolung Additions

The phosphonium dienolate has become a powerful reaction intermediate for chemists to obtain products derived from $\gamma$-umpolung additions. This intermediate can be accessed by two different methods (Scheme 2.1.9). First, the phosphonium dienolate can be directly formed by the addition of the phosphine catalyst to an electron deficient allene. The alternative route begins with the addition of phosphine to but-2-ynoate to form the phosphonium zwitterion. The phosphonium dienolate is then formed after a proton transfer. These two methods have been widely used by researchers to develop novel phosphine-catalyzed reaction manifolds.

Scheme 2.1.9 Methods for the Formation of the Phosphonium Dienolate
Scheme 2.1.10 Proposed Mechanism for the Phosphine-Catalyzed γ-Umpolung Addition

γ-Umpolung additions products can be accessed via the proposed mechanism shown in Scheme 2.1.10. The phosphonium dienolate generated from the allene or the butynoate is able to activate the pronucleophile via deprotonation. The nucleophile will then add to the γ-position of the phosphonium salt to generate the zwitterion. After a proton transfer, the phosphine is then eliminated to regenerate the active phosphine catalyst and produce the γ-umpolung addition product. Trost and coworkers reacted methyl but-2-ynoate with a verity of carbon nucleophiles utilizing catalytic triphenylphosphine and acetic acid/sodium acetate as an additive.9 A sample of these products can be seen in Table 2.1.2. β-Ketoesters, β-diesters, and α-cyanosulfones are all tolerated and form the Umpolung products in good yields.
Table 2.1.2 Substrate Scope for Trost’s Phosphine-Catalyzed γ-Umpolung Addition

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO₂Me</td>
<td>Nuc-CO₂Me</td>
<td>52%</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>MeO₂C-CO₂Me</td>
<td>52%</td>
</tr>
<tr>
<td>71%</td>
<td>NC-SO₂Ph-CO₂Me</td>
<td>65%</td>
</tr>
</tbody>
</table>

**Phosphine-Catalyzed Annulation Reactions of Allenes**

In recent years there have been numerous annulation reaction methodologies published by groups throughout the synthetic community. Tong and coworkers published a unique phosphine catalyzed γ-umpolung addition that is followed by a cyclization to generate heavily decorated cyclopentene products. In this reaction 2-(acetoxymethyl)buta-2,3-dienoate is reacted with catalytic phosphine, cesium carbonate, and a pronucleophle. The cyclopentene products formed are proposed to go through the novel phosphonium diene intermediate. The umpolung addition leads to the zwitterion intermediate. After a proton transfer, the phosphonium salt can then be displaced in an SN2’ like mechanism to generate the final annulation product. In this reaction it is of note that the pronucleophile is not activated by the zwitterion, but by external base. This mechanism can be seen in Scheme 2.1.11.
Lu reported the first phosphine-catalyzed [3 + 2] reaction of electron deficient alkenes and phosphonium enolates generated by either but-2-ynoate or allenes. In this reaction, carbocycles can be synthesized readily under catalytic conditions with good regioselectivity. The general reaction and proposed mechanism can be seen in Scheme 2.1.12. Lu’s pioneering work has since become one of the most fundamental phosphine-catalyzed reactions, and has laid the foundation for many more recent methodologies.

When \( p \)-toluenesulfonimines are used as the electrophiles under Lu’s reaction conditions, dihydropyrroles can be formed. This biologically important motif can be formed in excellent yields and regioselectivity. The proposed mechanism of this reaction is the one presented in Table 2.1.12.
Aryl imines are well-tolerated in this reaction, generating the annulation products in good yields. However, alkyl imines only produced trace amounts of the annulation products.

Scheme 2.1.12 First Reported Phosphine-Catalyzed [3 + 2] Annulation of Allenoates/But-2-ynoates with Alkenes

Table 2.1.3 Substrate Scope for Lu’s Annulation [3 +2] of Allenoates and Imines

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trace</td>
<td></td>
</tr>
<tr>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>88%</td>
<td></td>
</tr>
</tbody>
</table>
Through the work of Kwon and Xue it has been shown that \( \gamma \)-substituted allenes or but-2-ynoates can be used to synthesize tetrasubstituted 2,5-dihydro-1H-pyroles in excellent yield and \( cis \)-selectivity. These reactions can tolerate a wide variety of substituents and, under Kwon’s conditions, different nitrogen protecting groups can be utilized on the imine. A selection of the products that can be accessed from these reactions are shown in Table 2.1.4.

**Table 2.1.4** Phosphine-Catalyzed Synthesis of Tetrasubstituted 2,5-Dihydro-1H-pyroles

This reaction can generate a wide variety of dihydropyrrole annulation products, which is of great interest to many synthetic groups. This motif is seen in numerous natural products and has been utilized by many in total syntheses. Natural products containing the pyrrolidine motif are shown in Figure 2.1.1. The aspidospermine related natural product ibophlidine and actinophyllic acid both have the pyrrolidine embedded into their core structure. Both compounds have received much attention in the synthetic community due to their unique molecular architecture. Kwon and coworkers have published syntheses of some of the members of this natural product family in
recent years. Efsevin has also received attention as a VDAC2 agonist which has been shown to be able to restore rhythmic heartbeats in zebrafish that experience tachycardia.

Figure 2.1.1 Pyrrolidine Containing Natural Products and Biologically Important Compounds

Krische and coworkers published an intramolecular variant of Lu’s [3 + 2] in 2001. This reaction is realized by connecting the alkynoate and the electron deficient alkene with a carbon tether. Polar solvents and high temperatures were required to achieve good yields for this annulation reaction (Scheme 2.1.13). The diquinanes products are formed in good yields and excellent selectivity.

Scheme 2.1.13 Intramolecular Phosphine-Catalyzed [3 + 2] Annulation Reaction Utilizing Tethered Alkynes

The same researchers later used this method to synthesis the natural product Hirsutene. The first [3.3.0] bicyclic ring system of the tricyclic core can be accessed quickly from the alkynoate shown in Scheme 2.1.14. It is during this annulation that the bridgehead quaternary carbon is formed with good selectivity. This intermediate is transformed to the natural products in six more steps.
Scheme 2.1.14 Krische’s Total Synthesis of Hirsutene

Kwon and coworkers expanded on the intramolecular phosphine-catalyzed [3 + 2] annulation reaction by utilizing an allenoate tethered to an electron deficient alkene. When a substituted aromatic ring is used as the linker, highly functionalized 2H-1-benzopyran-2-one products can be formed. These products are easily formed by treating the allenoate starting materials with catalytic tributylphosphine at room temperature. The products are obtained as a single diastereomer, and both electron donating and withdrawing groups can be accommodated. A selection of products can be seen in Table 2.1.5.

Table 2.1.5 Intramolecular Phosphine-Catalyzed [3 + 2] Annulation Utilizing Tethered Allenoates

Shi and coworkers expanded upon Lu’s [3 + 2] by utilizing penta-2,3,4-trienolates as a synthon. When reacting this starting material with electron deficient alkenes or aldimines in the presence of catalytic (50 mol%) tributylphosphine, the annulated cyclopentenes or dihydropyrroles are obtained in good to excellent yields (Scheme 2.1.15). Due to the sluggish nature of the reaction, heating was required and decreasing the catalytic loading led to low yields of the annulated products.
Scheme 2.1.15 Phosphine-Catalyzed [3 + 2] Annulation of Penta-2,3,4-trienolates and Electron Deficient Alkenes/Aldimines

Lu’s [3 + 2] reaction has since been shown to be widely applicable to form cyclopentenes as well as dihydropyrroles. Many research groups have studied this reaction and expanded the scope and generality of the annulation. The ease of syntheses of the starting material, the wide variety of electrophiles that are tolerated, and the excellent atom economy are the hallmarks of this reaction. It has also been utilized in total synthesis of complex natural products and has since been developed into a catalytic asymmetric process utilizing unique chiral phosphines.

Kwon and coworkers furthered the use of tertiary phosphine in an annulation reaction of α-methyl substituted allenoates with aldmines. The proposed mechanism can be seen in Scheme 2.1.16.19 This reaction initiates similarly to Lu’s [3 + 2] reaction with the addition of the nucleophilic phosphine to the electron deficient allene. The phosphonium dienolate formed will then add to the electron deficient imine to generate the vinyl phosphonium salt. After a proton transfer, a Michael addition will eject the tertiary phosphine, regenerating the active catalyst, and produce the annulated product. This robust method is capable of forming the tetrahydropyridine annulated products in excellent yields. When (2-aryl methyl)buta-2,3-dienoates are used, 2,6-disubstituted tetrahydropyridine products can be formed in excellent yields and high cis-selectivity. A selection of these products can be seen in Table 2.1.6.
A wide array of aryl groups are tolerated under the reaction conditions. Both electron rich and electron deficient aryl groups can be incorporated into the annulated products. The only alkyl imine that was able to be transformed into the desired tetrahydropyridine was the bulky N-(2,2-dimethylpropylidene)-4-methylbenzenesulfonamide. Potassium carbonate was required to generate high yields for this specific example. Styrenyl imines were not well tolerated under the attempted conditions, generating only a trace amount of the desired product. Furan and other heteroaryl substituents were also able to be incorporated in the annulation products. The 2,6-disubstituted tetrahydropyridine products are all formed with excellent yields and stereoselectivity regardless of the electronic environments of the aryl substituents.
Table 2.1.6 Selected Examples of the Phosphine-Catalyzed [4+2] Annulation of Imines and α-Methyl Substituted Allenoates

It is important to note that the tetrahydropyridine motif formed in the [4 + 2] annulation of imines and α-methyl substituted allenoates can be seen throughout many biologically important natural products (Figure 2.1.2). For instance, yohimbine, ajmalicine and many of the akuammiline natural products, such as aspidophylline A, strictamine, picrinine, and 2-(S)-cathafoline contain tetrahydropyridine motif embedded in their core structures. The phosphine-catalyzed [4 + 2] annulation may be applicable to the synthesis of a number of important biologically important compounds. In fact, Kwon and coworkers have used this annulation methodology to accomplish formal syntheses of the natural products macroline and alsonerine.²⁰ More recently, the Kwon group has used the phosphine-catalyzed [4 + 2] annulation reaction for the total synthesis of
hirsutine\textsuperscript{21} and a synthetic study towards the synthesis of reserpine.\textsuperscript{22} These synthetic endeavors can be viewed as exceptional examples of the usefulness of this methodology.

Kwon and coworkers have also extended the phosphine-catalyzed [4 + 2] annulation reaction to form cyclohexene products. This was done by reacting \( \alpha \)-methyl substituted allenoates with arylidinenemalononitriles with a tertiary phosphine catalyst.\textsuperscript{23} Interestingly, for the all carbon variant of the [4 + 2] annulation, the choice of the phosphine catalyst is capable of determining what regioisomer of the annulated products is favored. This methodology is depicted in Scheme 2.1.17.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{natural_products}
\caption{Natural Products containing the Tetrahydropyridine Motif}
\end{figure}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{all_carbon_variant}
\caption{All carbon Variant of the Phosphine-Catalyzed [4 + 2] Annulation}
\end{scheme}
Overview of Chiral Phosphine Catalysts

In more recent years, researchers have begun to utilize chiral phosphine catalysts to enable the above transformations to be accomplished in an asymmetric fashion. One can either employ a chiral species connected to a tertiary phosphine, or utilize a $P$-chiral center as the active catalyst. C$_2$-symmetric chiral phosphine offer a large, chiral pocket that can have a significant influence on the chiral transition state of these asymmetric reactions. However, these catalysts can have long, tedious syntheses from their commercially available chiral sources and derivatization may be difficult due to the lack of functional handles on the catalyst itself. A number of phosphine catalyst classes can be seen in Figure 2.1.3.

Figure 2.1.3 Common Chiral Phosphine Catalysts
Amino acid derived chiral phosphines offer a unique alternative to the problems that are associated with $\text{C}_2$-symmetric chiral phosphines. With the advance of modern peptide coupling chemistry the ability to make small dipeptides has become an operationally simple task. Not only that, but Nature has also provided many amino acid building blocks that can be utilized to synthesize the chiral backbone of the catalyst. A simplified view of the typical synthesis of the amino acid derived chiral phosphines can be seen in Scheme 2.1.18. Often threonine is used as the starting point for the catalyst synthesized. From there, one can synthesis the phosphino alcohol which can be protected and coupled to another peptide using standard amino acid coupling chemistry.

Amino acids also offer a simple way of introducing hydrogen bonding donors and accepters into the backbone. The ability to place hydrogen bonding participants into the catalyst backbone at strategic locations has a large benefit for catalyst design. Hydrogen bonding has a large impact on the preorganization of the transition state of the nucleophilic phosphine-catalyzed reactions that these systems are employed in.

**Scheme 2.1.18 Synthesis of Chiral Phosphine Catalysts Derived from Amino Acids**

In 2014 Kwon and coworkers published a new class of rigid [2.2.1] bicyclic chiral phosphine catalyst derived from amino acids. This novel catalyst has a $P$-chiral center that is
used for nucleophilic phosphine-catalysis. These catalysts are derived from trans-L-4-hydroxyproline in a six-step sequence (Scheme 2.1.19). Typically these phosphines are stored as the phosphine oxide and reduced directly prior to use.

\[\text{Scheme 2.1.19 Synthesis of Kwon’s [2.2.1] Bicyclic Chiral Phosphine Catalysts}\]

**Asymmetric Phosphine-Catalyzed Annulation Reactions**

The development of asymmetric phosphine-catalyzed annulation reactions has been investigated by many researchers in recent years. Both Kwon’s and Lu’s annulation protocols benefit from using simple starting materials and have a high degree of diastereoselectivity. This facet of the reaction manifold coupled with the use of a chiral phosphine catalyst can lead to remarkably selective reaction leading to a highly decorated chiral annulation product.

Zhang and coworkers published the first enantioselective variant of Lu’s [3 + 2] annulation reaction. In this work allenoates are reacted with electron deficient alkenes with the novel [2.2.1] chiral phosphine. The yields and ee’s range from poor to good and the cyclopentene products formed are of high synthetic value (Scheme 2.1.20). While this work was a large advancement in the field of phosphine catalysis, the catalyst in this methodology takes many steps to synthesize and requires the protection/deprotection of the phosphine by BH₃.
Despite the potential of asymmetric phosphine-catalyzed annulation reactions shown in the work of Zhang, the field remained dormant until 2005 when Fu and coworkers published an asymmetric variant of Kwon’s [4 + 2] annulation reaction of imines and allenoates. When Fu and coworkers utilized the C$_2$-symmetric chiral phosphine shown, they were able to access the tetrahydropyridine products in good yields and high ee. However, activating groups, such as esters or ketones, located on the α-methyl position were required to obtain the highest ee. When α-methyl allenoate were subjected to the reaction conditions the ee ranged from 68-76%. Alternatively when an ethyl ester is installed at this position, ee’s typically range from 96 to 99% (Scheme 2.1.21)
Scheme 2.1.21 Fu’s Asymmetric [4 + 2] Annulation Reaction of Imines and Allenoates

The imine derived from 1H-indole-2-carbaldehyde can be taken forward in this annulation with diethyl 2-vinylidenesuccinate used as the pronucleophile to form the indole substituted tetrahydropyridine product. The heteroaromatic substituted product can be formed as nearly a single diastereomer utilizing the same C$_2$-symmetric chiral phosphine catalyst and is highly enantioenriched. The annulation product can be taken forward with a two-step process to the 9-azabicyclo[3.3.1]nonane core structure of several natural products such as alsonerine and macroline (scheme 2.1.22).

Scheme 2.1.22 Synthesis of the 9-azabicyclo[3.3.1]nonane Core Structure

Asymmetric Phosphine-Catalyzed [3 + 2] Annulation Reactions
Jacobsen and coworkers made a significant contribution to the field of asymmetric phosphine-catalyzed [3 + 2] annulation of imines and allenotes.\(^\text{29}\) For this methodology they used a multifunctional chiral phosphine to both activate the allenoate and the electrophile, as well as preorganize the enantioselectivity determining step. They were able to generate the annulated product in good yield and excellent ee. The multifunctional catalyst is proposed to activate the diphenylphosphinoyl (DPP) imine via hydrogen-bonding to the thiourea. The tertiary phosphine is reasoned to form the phosphonium dienolate adjacent to the activated imine (Scheme 2.1.23).

\[
\begin{align*}
\text{CO}_2\text{Et}^+ & \quad \text{Bn}_2\text{N}^+ \quad \text{S}^- \\
\text{NDPP}^- & \quad \text{N}^+ \quad \text{PPh}_2^- \\
\text{H}_2\text{O} & \quad \text{Ar}^- \quad \text{t-BuO}_2^- \\
& \quad \text{(2.5 to 20 mol%)} \\
& \quad \text{TEA (5 mol%)} \\
& \quad \text{(20 mol%)} \\
\end{align*}
\]

\text{Scheme 2.1.23} Jacobsen’s Asymmetric Phosphine-Catalyzed Annulation Reaction

In 2011 Lu published on a remarkable variant of the [3 + 2] annulation of allenoates and DPP imines.\(^\text{25}\) In this annulation a novel dipeptide is used to obtain high yields and excellent ee’s. This reaction is the first reported to tolerate alkyl imines for the asymmetric phosphine-catalyzed annulation. Aryl imines are also well tolerated and generate high yields and ee’s (Scheme 2.1.24).
Scheme 2.1.24 Lu’s Asymmetric Phosphine-Catalyzed Annulation Reaction

Lu also used this methodology to complete a formal synthesis of (+)-trachelanthamidine. The key annulation to form the functionalized pyrrolidine was accomplished in 82\% yield and 96\% ee. A two-step conversion of the DPP protecting group of the annulation product to the toluenesulfonamide leads the key intermediate in the synthesis of (+)-trachelanthamidine (Scheme 2.1.25).

Scheme 2.1.25 Formal Synthesis of (+)-Trachelanthamidine.

Lu proposed that a hydrogen-bonding interaction between amide/carbamate portions of the catalyst and P=O of the DPP imines. They believe that the organization of the phosphonium dienolate and the imine in this manner leads to the selectivity observed in the product, as well as the speed of this process. When a methyl group is installed on the carbamate to probe the role of
hydrogen bonding in the transition state the ee drops significantly – pointing to the importance of hydrogen-bonding involved in this catalytic system (Scheme 2.1.26).

**Scheme 2.1.26** Transition State of the Dipeptide Derived Phosphine Catalyst.

In 2014 Kwon and coworkers showed the use of a rigid [2.2.1] bicyclic chiral phosphine derived from *trans*-Hyp could be used to synthesize highly functionalized dihydropyrroles in excellent yield, dr, and ee through an annulation involving imines and γ-substituted allenoates. Interestingly, in this catalytic system the pseudoenantiomers of the exo- and endo-aryl *P*-chiral center could be used to generate both enantiomers of the annulated products. These catalysts provide a short and straightforward synthesis of the dihydropyrrole products (Scheme 2.1.27).26

**Scheme 2.1.27** Kwon’s Asymmetric [3 + 2] Annulation Using [2.2.1] Bicyclic Phosphine Catalysts.

**Asymmetric Phosphine-Catalyzed [4 + 2] Annulation Reactions**
In 2011 the Zhao group published the use of the bifunctional chiral phosphine derived from L-isoleucine to facilitate the [4 +2] annulations of activated allenoates with N-tosylaldimines. These reactions are reasoned to proceed via a hydrogen-bonding assisted transition state similar to the one invoked in Lu’s asymmetric phosphine-catalyzed [3 + 2] annulation. The tetrahydropyridine products can be formed in high yield and ee. However, these high ee values are only observed with an activating group is placed on the α-methyl substituent (Scheme 2.1.28).

**Scheme 2.1.28** Zhao’s Asymmetric [4 + 2] Annulation Using Amino Acid Derived Chiral Phosphines

Later, in 2012, the Zhao group used a similar peptide-derived phosphine catalyst derived from L-isoleucine to synthesize cyclohexene products in an asymmetric manner (Scheme 2.1.29). This [4 + 2] annulation of diethyl 2-vinylidenesuccinate and dual activated alkenes is suggested to go via a hydrogen-bonding assisted transition state similar to the Lu’s transition state. The yields of the cyclohexene products are variable (32-94%) and ee’s range from 73 to 93% ee.

**Scheme 2.1.29** Zhao’s Asymmetric Phosphine-Catalyzed [4 + 2] Annulation
Guo and Sasai have reported catalytic asymmetric [4 + 2] annulations with sulfamate-derived cyclic imines and allenoates; however, high ee is only obtained for 2,6-disubstituted or 6,6-disubstituted tetrahydropyridine derivatives, respectively. Sasai utilized a chiral C$_2$-symmetric phosphine to catalyze the annulation of the electron deficient imine and the α-methyl substituted allenoate. In this case Sasai was only able to synthesize 6,6-disubstituted annulation products (Scheme 2.1.30). Guo was able to facilitate a similar transformation with the use of an amino acid derived chiral phosphine. The main differences are that aldimines are tolerated in this transformation, and there must be an activating group located on the α-methyl substituents of the allenoate. This results in the formation of 2,6-disubstituted annulation products (2.1.31).

Scheme 2.1.30 Synthesis of 6,6-Disubstituted tetrahydropyridine via Phosphine Catalysis

Scheme 2.1.31 Synthesis of Disubstituted Benzo[e]pyrido[1,2-c][1,2,3]oxathiazine 6,6-dioxide

Closing Remarks

Figure 2.1.4 Common [4 + 2] Annulation products
While huge advancements in the area of nucleophilic phosphine catalysis have taken place in the last decade, there still is much exploration to be done. In particular, there is still a need to expand the number of electrophiles and pronucleophiles that can be used for phosphine-catalyzed reactions. For example, many of the phosphine-catalyzed annulation methodologies available to chemists today require the use of aryl substituents on the imine or activated alkene electrophiles in order to obtain high enatio- and diastereoselectivity. Also many of the [4 + 2] annulations require the use of activating groups at the α-methyl substituent of the allenoate (Figure 2.1.4). These two requirements greatly limit what product structures can be accessed via phosphine catalysis. In order to overcome these limitations, researchers should investigate the use of novel nucleophiles, electrophiles and phosphine catalysts in hopes to expand the boundaries of the field.

2.2 Study of Asymmetric Phosphine-Catalyzed [4+2] Anulation of Non-Aryl Imines with α-Methyl Allenoates

Background and Previous Synthetic Studies

We wished to extend the phosphine-catalyzed [4+2] annulation methodology to alkyl imines. We wished to accomplish this in the context of a synthesis of the ergot alkaloid scaffold. The ergot alkaloids 1–7 have been a proving ground for many synthetic methodologies, and have intrigued chemists since the 1950’s for their interesting biological activity. Related compounds, such as cabergoline (5) and ergometrine (6) have been used to treat many conditions like prolactinoma and to treat heavy vaginal bleeding after child birth respectively. Lysergic acid diethylamide (7), the most infamous derivative, has been used as a chemical probe to investigate consciousness as well as other medicinal uses (Figure 2.2.1). 34
Since Woodward’s first total synthesis of lysergic acid in 1956, many groups have investigated the synthesis of ergot alkaloids. Some of the most impressive syntheses of the core structure of the ergot alkaloids are highlighted below. Oppolzer accessed the core structure via a remarkable inverse electron demand intramolecular Diels–Alder reaction. The diene is revealed via a retro Diels–Alder reaction of indole derived intermediate. This reaction proceeds with high selectivity as well as in good yield via the inverse electron demand intramolecular Diels–Alder reaction of the diene tethered to the imine. Oppolzer and coworkers could take product forward to lysergic acid (1)

Vollhardt and coworkers were also able to access this class of compounds through the clever use of a cycloaddition. In this case, a cobalt catalyzed [2 + 2 + 2] of nitrile and N,N-
diethyl propiolamide lead to the tetracyclic compound 12. Intermediate 12 could be taken to lysergic acid diethylamide (7) in two steps (Scheme 2.2.2). This example is still the shortest synthesis of any ergot alkaloid. Despite the low yield of the key step (17%) it is an excellent example of the high complexity that can be accessed rapidly by the cobalt catalyzed [2 + 2 + 2] cycloaddition.

![Scheme 2.2.2 Vollhardt’s Key Step in Ergot Alkaloid Core Structure Preparation]

Padwa later established that the core structure of lysergic acid could arise from a 1,3-dipolar cycloaddition using diazo intermediate 13. Treating the diazo compound 13 with a rhodium catalyst generates a carbene that, upon addition of the pendant carbonyl electrons, becomes the 1,3-dipole. The pendant alkene then undergoes the cycloaddition to generate the 3-oxo-7-oxa-2-azabicyclo[2.2.1]heptane-4-carboxylate product. Compound 14 can then be taken forward to tetracycle 15. The key steps of this synthesis can be seen in Scheme 2.2.3. Unfortunately, this intermediate was not able to be carried forward to the natural product. However, it shows the unique disconnects that can be used for complex natural product synthesis that the carbene can access.
Scheme 2.2.3 Padwa’s Key Step in Ergot Alkaloid Core Structure Preparation Key Steps

Ohino published a Pd(0)-catalyzed domino cyclization of an allene bearing amino and bromoindolyl groups. The allene can be synthesized in an enantioselective fashion, via a rather lengthy process that relies upon a (R)-Alpine borane reduction to generate high selectivity. Treating allene 16 with 10 mol% of Pd(PPh₃)₄ in the presence of potassium carbonate in DMF leads to the high yielding formation of tetracyclic skeleton of the ergot alkaloids. This unique and robust approach is shown in Scheme 2.2.4. The axial chirality of the allene is able to be transformed into the point chirality of domino cyclization product in an efficient manner. Ohino later took intermediate 17 forward to complete the total synthesis of lysergic acid (1), lysergol (4), and isolysergol (3).

Scheme 2.2.4 Ohino’s Key Step in Ergot Alkaloid Core Structure Preparation
Our proposed synthetic approach can be seen in Scheme 2.2.5. Phosphine-catalyzed annulation of 4-bromoindole derived alkyl imine 18 and \( \alpha \)-methyl allenolate 19 would generate tetrahydropyridine product 20. Annulated intermediate 20 could then be taken through a two-step processes to the core structure of the ergot alkaloids. First, a well-established isomerization to the unconjugated enone 21 could be formed. The formation of the core structure 22 could next be accomplished by an intramolecular Heck reaction to form the key carbon–carbon bond between C4 of the indole and the tetrahydropyridine.

![Scheme 2.2.5 Proposed Synthesis of the Ergot Alkaloid Core Skeleton](image)

Both the isomerization and the Heck reaction proposed in this synthesis have much literature precedence. The isomerization has been used in both Jia\(^35\) and Fukuyama’s\(^35\) syntheses. LMTP can be used to deprotonate the acidic \( \gamma \)-position of the unsaturated ester 23. At low temperatures the protonation affords the less thermodynamically stable alkene 24. In these cases the protonation does not occur in a highly selective manner (2:1 \( \text{trans: cis} \)); however, the \( \alpha \)-position is easy to isomerize under the basic conditions required for the subsequent Heck reaction. This allows for the proper stereochemical requirement for the \( \beta \)-hydride elimination of the Heck reaction. This isomerization as demonstrated by Jia can be seen in Scheme 2.2.6.
The Heck reaction has also been established in previous synthetic work by Jia and Fukuyama. In an example provided in Jia’s synthesis, the Heck reaction of indolyl chloride 25 is able to be catalyzed by \( \text{Pd}_2(\text{dba})_3 \text{CHCl}_3 \) in the presence of a base in refluxing dioxane. While high catalyst loading and low yield plague this transformation, the core structure 26 can still be accessed quickly from the tetrahydropyridine intermediate. Interestingly, recovered starting chloride 25 has the same \( \text{cis}:\text{trans} \) ratio, implying that the starting material can epimerize under the reaction conditions. In Fukuyama’s 2013 synthesis the Heck reaction is shown to be more successful.\(^{35f}\) This higher yield may be caused the fact that the more reactive bromide 27 is utilized, as well as the fact that the proper stereochemical requirements for the Heck reaction are already met with intermediate 27. In this transformation, 10 mol% of \( \text{Pd} (\text{PPh}_3)_4 \) and silver carbonate are employed in refluxing toluene to facilitate the formation of product 28 in a high yield. The Heck reactions utilized by Jian and Fukuyama in the synthesis of the lysergic acid are depicted in Scheme 2.2.7.
Since there is established chemistry for the isomerization and the Heck reaction, the key step, and the one that we wished to explore, would be the phosphine-catalyzed annulation to form the key tetrahydropyridine. Alkyl imines, such as imine 18, have not been studied in the phosphine-catalyzed [4 + 2] annulation. We wished to synthesize imine 18 from the corresponding aldehyde 29, which could be accessed by oxidative cleavage of the allylated indole 30. Compound 30 could arise from the commercially available 4-bromoindole (31). The retrosynthetic plan can be seen in Scheme 2.2.8.

Rather than purchasing the relatively expensive 4-bromoindole (31), we began our synthesis by a Leimgruber–Batcho indole synthesis utilizing 1-bromo-2-methyl-3-nitrobenzene (32) as the starting material. This two-step process produced 4-bromoindole (31) on a multigram scale and in good yield. Next, 4-bromoindole (31) was allylated under mild Pd(0) catalyzed
conditions utilizing allyl alcohol and triethylborane to afford 3-allyl-4-bromo-1H-indole (30) in high yield. A nitrogen protecting group was installed utilizing (Boc)$_2$O and catalytic DMAP, generating protected indole 33 in a high yield. Aldehyde 29 could then be accessed in high yield through a two-step osmium tetroxide catalyzed dihydroxylation followed by an oxidative cleavage of the crude diol 34 using excess sodium periodate (Scheme 2.2.9). This six-step process provided us with multigram-scale access to the aldehyde required for the synthesis of imine 18.

Scheme 2.2.9 Synthesis of Aldehyde 29

With the ability to synthesize large quantities of aldehyde 29 established, we next directed our attention to the formation of imine 18. To this end, we began screening Lewis acids to facility the imine formation. These attempts are summarized in Scheme 2.2.10. While this is a typical process in the synthesis of aryl imines, we were unable to generate any of the desired alkyl imine 18a-c under the conditions explored. Varying both the Lewis acid (TiCl$_4$, BF$_3$OEt$_2$, AlCl$_3$, etc.) and the sulfonamide (toluenesulfonamide, 4-nitrobenzenesulfonamide, benzenesulfonamide) as well as DPP failed to aid in the formation of the desired imine. These trials typically resulted in either recovery of starting material or decomposition of aldehyde 29.
Recently, Cid and coworkers published on the use of organocatalysts for the mild preparation of aryl and alkyl aldimines. In this report it was determined that both pyrrolidine and anthranilic acid could be used in the synthesis of aryl and alkyl imines. The reaction is believed to go through iminium intermediate such as the one shown in Scheme 2.2.11. We attempted these conditions with aldehyde and found that the use of the pyrrolidine could not catalyze the formation of the desired imines. Varying the amide and catalyst loading and the sulfonamide also failed to produce the desired transformation. The failure to obtain the product is likely caused by the instability of the iminium.

In the original publication, Cid cited the imine/enamine tautomerization as the cause of poor reactivity in some alkyl aldehydes. For these cases it was found that utilizing a β-amino acid as the catalyst could prepare the alkyl imine. Cid found that anthranilic acid could be used in these cases on the basis that intramolecular protonation of the imine could facilitate the imine formation through an intermediate such as iminium. A depiction of the proposed intermediate that occurs when anthranilic acid catalyzes this transformation is seen in Scheme 2.2.11. Unfortunately, in our case anthranilic acid failed to provide imine. Only starting material was obtained despite varying the catalyst loading, amine partner, time, and drying agent.

Scheme 2.2.10 Lewis Acid Mediated Imine Formation
After searching the literature for examples of the synthesis of alkyl imines it was found that there was another mild way to form alkyl imines. This is accomplished by reacting an alkyl aldehyde with toluenesulfinic acid and a sulfonamide to form stable α-sulfamido sulfones. The treatment of α-sulfamido sulfones with a mild base, typically sodium bicarbonate or potassium carbonate, provide the elimination of the arylsulfonic acid salt which forms the imine. This reaction sequence was found to be effective for our needs as well. Reacting aldehyde 29 with freshly prepared toluenesulfinic acid and toluenesulfonamide generated the α-sulfamido sulfone 37 cleanly upon filtration of the reaction mixture. After screening numerous conditions it was found that a brief basic wash of compound 37 dissolved in DCM with a saturated aqueous solution of sodium bicarbonate provided the desired toluenesulfonamide protected imine 18a in a high yield. This reaction sequence is shown in Scheme 2.2.12.
With access to the desired imine we next attempted the phosphine-catalyzed [4 + 2] annulation of compound 18a with α-methyl allenoate 19. We screened a variety of phosphine catalysts as well as reaction conditions to afford the annulation. The conditions that were attempted can be seen in Table 2.2.1. Entries 1–6 show the screening of different phosphines. Unfortunately we were not able to form any of annulation product 20. The amino acid-derived chiral phosphine 38 has been shown to facilitate a [3 + 2] annulation reaction of alkyl imines with allenoates; however, our required imine failed to produce the annulation product using catalyst 38 (entry 6). The products identified was typically the formation of aldehyde 29 that arises from hydrolysis of the imine. To avoid this we screened a number of drying agents (entries 7–12), again no annulation product 20 was found. Even a large excess of allenoate in the reaction mixture could not force the annulation to occur (entries 13 and 14).

We hoped that we could slowly release the imine by adding α-sulfamido sulfone 37 to the phosphine-catalyzed annulation conditions in the presence of sodium bicarbonate. Sadly, the tandem imine formation/[4 + 2] annulation failed to produce the desired results. Varying the phosphine (PBu₃, PMe₃, PCy₃, etc.) employed in the reaction did not help in the formation of the annulation product 20.
Table 2.2.1 Screening of Phosphine-Catalyzed Annulation Reaction of Imine 18a

<table>
<thead>
<tr>
<th>entry</th>
<th>phosphine (30 mol%)</th>
<th>temp.</th>
<th>additive</th>
<th>solvent</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PBu₃</td>
<td>rt</td>
<td>-</td>
<td>DCM</td>
<td>nr</td>
</tr>
<tr>
<td>2</td>
<td>PMe₃</td>
<td>rt</td>
<td>-</td>
<td>DCM</td>
<td>decomp.</td>
</tr>
<tr>
<td>3</td>
<td>PMe₃</td>
<td>0 °C</td>
<td>-</td>
<td>DCM</td>
<td>nr</td>
</tr>
<tr>
<td>4</td>
<td>PCy₃</td>
<td>rt</td>
<td>-</td>
<td>DCM</td>
<td>decomp</td>
</tr>
<tr>
<td>5</td>
<td>PCy₃</td>
<td>0 °C</td>
<td>-</td>
<td>DCM</td>
<td>nr</td>
</tr>
<tr>
<td>6</td>
<td>38</td>
<td>0°C</td>
<td>-</td>
<td>DCM</td>
<td>Decompl.</td>
</tr>
<tr>
<td>7</td>
<td>PBu₃</td>
<td>rt</td>
<td>MgSO₄</td>
<td>DCM</td>
<td>Decompl</td>
</tr>
<tr>
<td>8</td>
<td>PMe₃</td>
<td>°C</td>
<td>4 Å MS</td>
<td>DCM</td>
<td>Decompl</td>
</tr>
<tr>
<td>9</td>
<td>PMe₃</td>
<td>rt</td>
<td>K₂CO₃</td>
<td>DCM</td>
<td>Decompl</td>
</tr>
<tr>
<td>10</td>
<td>PMe₃</td>
<td>rt</td>
<td>4 Å MS</td>
<td>DCM</td>
<td>Decompl</td>
</tr>
<tr>
<td>11</td>
<td>PBu₃</td>
<td>rt</td>
<td>K₂CO₃</td>
<td>DCM</td>
<td>Decompl</td>
</tr>
<tr>
<td>12</td>
<td>PBu₃</td>
<td>rt</td>
<td>4 Å MS</td>
<td>DCM</td>
<td>Decompl</td>
</tr>
<tr>
<td>13ᵃ</td>
<td>PBu₃</td>
<td>rt</td>
<td>K₂CO₃</td>
<td>DCM</td>
<td>Decompl</td>
</tr>
<tr>
<td>14ᵃ</td>
<td>PMe₃</td>
<td>rt</td>
<td>4 Å MS</td>
<td>DCM</td>
<td>Decompl</td>
</tr>
</tbody>
</table>

ᵃ Allenoates were used in excess (10 equiv)

Scheme 2.2.13 Attempted Tandem Imine Formation/[4 + 2] Annulation

We presumed that imine 18a was rapidly converting to the enamine, thus placing the unsaturation in conjugation with the indole. When imine 18a is treated with 20 mol% PBu₃ we
observed its rapid decomposition. We believed that this was due to the tautomerization to the enamine under the slightly basic tertiary phosphine conditions. The ease of tautomerization of imine 18a lead us to look into other approaches to the core structure of lysergic acid.

We wished to block the α-protons in the imine and envisioned that we could accomplish this by using the glyoxal derived 4-bromoindole to form the imine. Without the α-protons there would not be the potential for the tautomerization of the imine to the enamine. We investigated this pathway with a model system deficient of the bromide. Indole can be transformed into the desired glyoxal 39 in a two-step reaction sequence, first by a C3 oxalylolation of 31 followed by a Rosenmund reduction of the acid chloride to form the glyoxal 39. Sadly, we were not able to identify conditions to form the corresponding imine of 40. We screened numerous conditions to be able to form the glyoxal imine 40 via the loss of water, but decomposition of the starting material was always observed (Scheme 2.2.14).

![Scheme 2.2.14 Attempted Formation of 4-Bromoindole Derived Glyoxal imine 40](image)

Another retrosynthetic disconnection that we investigated was using ketone 41 as an intermediate in the synthesis of the lysergic acid skeleton. Fukuyama and coworkers utilized a similar intermediate in a ergot alkaloid synthetic study. We envisioned that we could access ketone 41 via the corresponding aldehyde 42 by a nucleophilic addition of magnesium 4-bromoindol-1-ide bromide. We hoped that we could access aldehyde 42 via an oxidative cleavage of tetrahydropyridine 43 - the annulation product of a cinnamaldehyde derived imine with α-methyl allenoate. The retrosynthesis can be seen in Scheme 2.2.15. While the annulation product
is reported in our initial racemic [4 + 2] report, only trace amounts were obtained. We had hoped that judicious choice of Brønsted acid or water sequestering additive would help improve the yield of the annulation of allene 19 with 4-methyl-N-((1E,2E)-3-phenylallylidene)benzenesulfonamide (44). Despite many attempts, the yield could not be improved. Due to the low yields of the formation of annulation product 43 we could not investigate the oxidative cleavage of the alkene (Scheme 2.2.16).

Scheme 2.2.15 Retrosynthesis of Lysergic Acid Core Structure via Cinnamaldehyde derived Imine

Scheme 2.2.16 Attempted Synthesis of Aldehyde 42

A literature search revealed that there have been some reports of the use of glyoxal imines as electrophiles. In most of these cases the reaction requires a Lewis acid to activate the imine; however, we presumed that inherent reactivity of the phosphonium dienolate would be sufficient for the nucleophilic addition. We proposed that we could access the ketone 41 via an indole acylation between 4-bromoindole and annulation product 45, which we proposed could arise from a phosphine-catalyzed [4 + 2] annulation of glyoxal imine 46 with α-methyl allenoate. Using known imines 46a and 46b we probed the tolerance of the phosphine-catalyzed [4 + 2] annulation. We first tested the toluenesulfonamide protected imine 46a, but we only observed decomposition of the starting material despite varying the tertiary phosphine catalyst (PBu₃, PMe₃, PCy₃, PPh₃,
etc.) employed in the reaction. Switching the protecting group to the less electron withdrawing Boc, as in imine 46b, did not improve the outcome of this transformation.

Scheme 2.2.17 Retrosynthesis of Lysergic Acid Core Structure via Ethyl Glyoxalate Derived Imine 46

Scheme 2.2.18 Attempted Synthesis of Carboxylic Ester 45

Closing Remarks:
While our main goal was to synthesize the core structure of the ergot alkaloids, it was prompted by the desire to explore the limitations of the phosphine-catalyzed [4 + 2] annulation of imines with α-methyl allenoates. We wished to gain understanding of tolerance of the phosphine-catalyzed [4 + 2] annulation to non-aryl imines. While we did not accomplish the formation of ergot alkaloid core structure, we did gain valuable information of the types of imines that can be tolerated under the reaction manifold of the phosphine-catalyzed [4 + 2] annulation imines with α-methyl allenoates. Future work could focus on the development of more reactive phosphine catalysts that could stabilize prudently designed alkyl imines via hydrogen-bonding to avoid both enamine tautomerization and hydrolysis.

2.3 Asymmetric Phosphine-Catalyzed [4+2] of Imines with α-Methyl Allenoates Utilizing Chiral [2.2.1] Bicyclic Tertiary Phosphines

As mentioned above, we recently developed a class of trans-hydroxyproline (Hyp)-derived [2.2.1] bicyclic phosphines 47 (Figure 2.3.1). These catalysts can be synthesized easily on a gram
scale, and are also commercially available through Sigma−Aldrich™. As mentioned previously, we drew on these unique \( P \)-chiral catalysts in an asymmetric version of Lu’s \([3 + 2]\) annulation. Building on those results, herein we disclose the asymmetric synthesis of 6-substituted guvacines \( 49 \) through the \([4 + 2]\) annulation of imines \( 48 \) with \( \alpha \)-methylallenoates \( 19 \) (Scheme 2.3.1).

**Figure 2.3.1** Hyp-Derived [2.2.1] Bicyclic Phosphines

**Scheme 2.3.1** Asymmetric Synthesis of 6-Substituted guvacines through the \([4 + 2]\) Annulation of Imines with \( \alpha \)-Methylallenoates.

**Reaction Screening**

We began our investigation by treating \( p \)-nitrobenzenesulfonyl \((p\text{-Ns})\) protected imine \( 48a \) with allenoate \( 19 \) in the presence of catalyst \( 47a \) (Table 2.3.1, entry 1). While we obtained 80% ee, the yield was low despite complete consumption of the imine. One of the byproducts from entry 1 was \( p \)-nitrobenzenesulfonamide, formed from the hydrolysis of the imine. We suspected that beneficial effects would arise through inhibition of imine hydrolysis using water/acid-sequestering additives. After testing many inorganic salts, drying agents, and other additives
(Table 2.3.1, entries 2–4), we obtained the best results after adding 100 mg/mmol of 4 Å molecular sieves (89% yield, 79% ee; entry 4).

**Table 2.3.1. Asymmetric Allenoate–Imine [4 + 2] Annulation**

<table>
<thead>
<tr>
<th>entry</th>
<th>48</th>
<th>47</th>
<th>additive</th>
<th>ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>48a</td>
<td>47a</td>
<td>none</td>
<td>1:0.03</td>
<td>36</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>48a</td>
<td>47a</td>
<td>MgSO&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>42</td>
<td>77</td>
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<td>47a</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>47a</td>
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<td>89&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>1:0.02</td>
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<td>77</td>
</tr>
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<td>47c</td>
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<td>&gt;1:0.01</td>
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<td>77</td>
</tr>
<tr>
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<td>47d</td>
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<td>79</td>
</tr>
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<td>47e</td>
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<td>81</td>
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<td>48a</td>
<td>47f</td>
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<td>−48</td>
</tr>
<tr>
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<td>48a</td>
<td>47c</td>
<td>4 Å MS</td>
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<td>70</td>
<td>95</td>
</tr>
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<td>47c</td>
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<td>97</td>
</tr>
<tr>
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<td>47c</td>
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</tr>
<tr>
<td>14&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>47c</td>
<td>4 Å MS</td>
<td>1:0.05</td>
<td>29</td>
<td>97</td>
</tr>
</tbody>
</table>

<sup>a</sup> Regiomeric ratio of the γ:β′ adduct, determined by <sup>1</sup>H NMR of the crude reaction product.  <sup>b</sup> Isolated yield after column chromatography.  <sup>c</sup> Determined by SFC using a AS or OJ-H column.  <sup>d</sup> Ee of major product.  <sup>e</sup> AcOH (10 mol%) was added.
After vetting several solvents, CH₂Cl₂, the solvent employed in the original 2003 report, was found to be the most amenable solvent for this annulation. While the \( p \)-nitrobenzenesulfonyl group on the imine nitrogen gave higher selectivity for the \( \gamma \)-adduct, it should be noted that under these conditions the \( p \)-toluenesulfonyl group was also tolerated with similar yields and higher ee (Table 2.3.1, entry 5). The modular synthesis of our chiral phosphine catalysts 47 allowed for straightforward variation of the exocyclic substituents on both phosphorus and nitrogen atoms (Table 2.3.1, entries 4 and 8–10). With the exception of 47d, we found that catalysts 47a–47e afforded good yield and enantioselectivity. When catalyst 47c was used, one isomer was obtained almost exclusively (entry 7). Again, catalyst 47f provided opposite enantioselectivity as it did in the allenoate–imine [3 + 2] annulation reaction, but the enantioselectivity was lower (Table 2.3.1, entry 10). Based on the combination of regioselectivity, yield and ee, catalyst 47c was chosen for the enantioselective production of 6-substituted guvacines.

Evidently, the enantioselectivity dropped slightly in the presence of additives, particularly base (entry 1 vs entry 3). We hypothesized that the higher enantioselectivity in the absence of additives may have been caused by the presence of acidic \( p \)-nitrobenzenesulfonamide, a byproduct of the hydrolysis of the imine. The bifunctional chiral phosphines containing hydrogen bond donors are ubiquitous in asymmetric phosphine organocatalysis. We have also documented that reaction rate and enantioselectivity can be enhanced in the presence of Brønsted acid in the allene–imine [3 + 2] annulation employed in our total synthesis of (−)-actinophyllic acid. More than a dozen Brønsted acid additives were examined and acetic acid (10 mol%) was found to produce the best enantioselectivity, with a slight decrease in the product yield (entry 11). Other protecting groups on the imine nitrogen were also considered (entries 12–16). Reasonable yields of the guvaccine products from imines 48b, 48c and 48d were obtained in the presence of both 4 Å
molecular sieves and acidic acid (entries 12–14). \(p\)-Bromobenzenesulfonyl imine 48e and \(o\)-nitrobenzenesulfonyl imine 48f proved to be too labile under these conditions, providing the annulation products in lower yields (entries 15 and 16). Based on the combination of regioselectivity, product yield and enantioselectivity, -Ns protecting group was chosen for further application.

**Substrate Scope**

**Table 2.3.2.** Substrate Scope for the Asymmetric [4 + 2] Annulation

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<thead>
<tr>
<th>entry</th>
<th>48 (Ar(^1))</th>
<th>product</th>
<th>ratio(^a)</th>
<th>yield (%)(^b)</th>
<th>ee (%)(^c)</th>
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</thead>
<tbody>
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<td>1</td>
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<td>70</td>
<td>95</td>
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<td>95</td>
</tr>
<tr>
<td>3</td>
<td>48h, (m)-MeOC(_6)H(_4)</td>
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<td>1:0.01</td>
<td>66</td>
<td>97</td>
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<td>96</td>
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<td>5</td>
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<td>1:0.01</td>
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<td>98</td>
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<td>49m</td>
<td>1:0.01</td>
<td>53</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>48n, (p)-BrC(_6)H(_4)</td>
<td>49n</td>
<td>1:0.01</td>
<td>51</td>
<td>97</td>
</tr>
<tr>
<td>10</td>
<td>48o, (p)-FC(_6)H(_4)</td>
<td>49o</td>
<td>1:0.02</td>
<td>64</td>
<td>96</td>
</tr>
<tr>
<td>11</td>
<td>48p, (p)-CNC(_6)H(_4)</td>
<td>49p</td>
<td>&gt;1:0.01</td>
<td>51</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>48q, (p)-NO(_2)C(_6)H(_4)</td>
<td>49q</td>
<td>&gt;1:0.01</td>
<td>52</td>
<td>96</td>
</tr>
<tr>
<td>13</td>
<td>48r, 2-furyl</td>
<td>49r</td>
<td>&gt;1:0.01</td>
<td>63</td>
<td>93</td>
</tr>
<tr>
<td>14</td>
<td>48s, 2-thiophenyl</td>
<td>49s</td>
<td>&gt;1:0.01</td>
<td>59</td>
<td>96</td>
</tr>
</tbody>
</table>

\(^a\) Regiomer ratio of the \(\gamma:\beta'\) adduct, determined by \(^1\)H NMR of the crude reaction product. \(^b\) Isolated yield after column chromatography. \(^c\) Determined by SFC using a AS or OJ-H column.
Under the optimized conditions, a range of imines could be employed as substrates in this catalytic synthesis of guvacine derivatives with excellent enantioselectivities (Table 2.3.2). Imines derived from benzaldehyde with electron-donating substituents reacted with higher yield and stereoselectivity (Table 2.3.2, entries 2−5), while benzaldimines with electron-withdrawing substituents produced slightly lower yield and enantioselectivity (Table 2.3.2, entries 6−12). Those trends became more prominent for ortho-substituted benzaldimines (e.g., Table 2.3.2, entry 2 vs entry 6). While 48g provided the guvacine product 49g in 81% yield and 95% ee, imine 48k, derived from o-chlorobenzaldehyde, produced the product 49k in 29% yield and 74% ee. The absolute configuration of 6-substituted guvacine esters has been unambiguously assigned as R-configuration on the basis of X-ray diffraction of 49n. The ORTEP drawing of 49n is shown in Figure 2.3.2. Strikingly, the C6 phenyl substituent adopts the axial position of the half-chair conformer of the guvacine ester ring, presumably to minimize the steric repulsion with the adjacent p-nitrobenzenesulfonyl group. Heteroaryl imines were also suitable substrates for this annulation process (Table 2.3.2, entries 13 and 14). 2-Furyl and 2-thiophenyl substituent produced the guvacines in 93% and 96% ee, respectively.

![Figure 2.2.2 X-Ray Crystal Structure of Compound 49n](image-url)
Based on the transition state modeling for the allene–imine [3 + 2] annulation, we propose the transition state model TS1 for the [4 + 2] reaction between allenoate 19 and imine 48a (Figure 2.3.3). Two key favorable interactions in the stereochemistry-determining transition state are a Coulombic interaction between the allenoate C=O oxygen atom and the phosphorus atom of the phosphonium enolate and a hydrogen bond between the imine N-sulfonyl oxygen atom and a hydrogen atom (H11) on the α-carbon to the phosphonium center. The former locks the phosphonium dienolate in place and the latter allows for a controlled re face attack of the imine to give the (R)-annulation product. The P=O distance was measured at 2.59 Å and the natural bond orbital (NBO) interaction energy (ENBO) was 6.04 kcal/mol in the [3 + 2] annulation. Measured distances and natural bond orbital NBO interaction energies (ENBO) of these contacts were O19⋯H11 = 2.33 Å (ENBO = 1.88 kcal/mol) and O18⋯H58 = 2.50 Å (ENBO = 1.46 kcal/mol) in the [3+2] annulation.

![Figure 2.2.3 Proposed Transition State](image)

**Attempted Application of the [4 + 2] Annulation of Imines with α-Methyl Allenoates to Synthesize GABA Uptake Inhibitors**

During the course of the investigation into the [4 + 2] annulation of imines and α-methyl allenoate, we wished to investigate whether our methodology could be extended to the synthesis of the γ-aminobutyric acid (GABA) uptake inhibitors shown in Figure 2.3.4. The guvacine (51) moiety has also been identified as the pharmacophore for GABA uptake inhibition.44 GABA (50)
is one of the major mammalian inhibitory neurotransmitters and a plethora of diseases, such as Parkinson's, Huntington's, epilepsy, and schizophrenia, have been linked to dysfunction of GABAergic synapses.\textsuperscript{45} Subsequent studies have shown that a modification at the C6 position of guvacine (as in compounds 52 and 53) provided good results in GABA uptake inhibition.\textsuperscript{44b, 46}

\begin{center}
\textbf{Figure 2.3.4} GABA, Guvacine, and GABA Uptake Inhibitors
\end{center}

We envisioned that these GABA uptake inhibitors, and related compounds, could be accessed in an enantiomERICly pure form via the previously discussed annulation method. These studies required the use of non-aryl imines and took place in the broader goal of extending the phosphine-catalyzed [4 + 2] annulation to be able to tolerate non-aryl imines (as discussed in Chapter 2.2). We wished to target GABA uptake inhibitors 52 and 53 via an annulation of the imines 54 with an allenolate 19 shown in Scheme 2.3.2

\begin{center}
\textbf{Scheme 2.3.2} Proposed Retrosynthesis of Copounds 52 and 53
\end{center}

We first began by synthesizing the desired aldehydes from previously reported methods.\textsuperscript{44b, 47} Their synthesis is shown in Scheme 2.3.3. Methyl cyclopropanecarboxylate (57) is transformed
into the tertiary alcohol 58 via the addition of phenylmagnesium bromide in the presence of copper (II) oxide. A hot water-promoted cyclopropylcarbinyl rearrangement leads to the primary alcohol. Alcohol 59 can then be oxidized under Swern condition to give aldehyde 55. The primary alcohol 59 can also be reduced with palladium on carbon and hydrogen to generate compound 60. Alcohol 60 can be oxidized under the same conditions as before to give aldehyde 56.

Scheme 2.3.3 Synthesis of Aldehydes 55 and 56

With access to aldehydes 55 and 56 established, we next attempted to form the required imines in order to target GABA uptake inhibitors 52 and 53. Numerous reaction conditions were attempted, but no imine formation was seen. We screened a number of Lewis/Brønsted acids to afford the formation of imines 61 and 62. We also screened a series of dehydrating agents (4 Å MS, MgSO₄, etc.) Even under the more mild, two-step process that has been shown to work with more labile alkyl imines failed to produce the desired α-sulfamido sulfones 63 and 64. We believe that the desired imine is quite prone to hydrolysis and rapidly undergoes decomposition to the starting material when being isolated. Other synthetic pathways were proposed for the synthesis of compounds 52 and 53, however they relied on multiple steps to form the aldehyde intermediate 42. At this point we redirected our attention to the use of aryl imines for the annulation reaction,
believing that we could still target biologically important compounds that had yet to be formed in an asymmetric fashion.

Scheme 2.3.4 Attempts at Synthesizing Imines 61 and 62

Synthesis of Enantiopure Aplexone

Recent collaboration between the Chen lab and ours has revealed that the 6-substituted tetrahydropyridine containing compound, aplexone (65), regulates arteriovenous angiogenesis in zebrafish by acting on the HMG-CoA reductase pathway. In the same zebrafish studies, it was found that aplexone (65) lowered the levels of embryonic cholesterol to a similar degree as atorvastatin (trade name: Lipitor). Intrigued by the interesting biological activity of aplexone (65) we wished to investigate its synthesis. We believed that we could utilize the annulation of aryl imines with $\alpha$-methylallenoate 19 to synthesize biologically important compounds in an asymmetric fashion. The asymmetric synthesis of active pharmaceutical ingredients has gained considerable attention in recent years. In this vein, we wished to identify the eutomer of aplexone (65) in hopes of utilizing it for future biological studies.

Our substrate screening table (Table 2.3.2) revealed to us that we could synthesize the precursor to aplexone (65) with a good yield and in high ee (56%, 98% ee). Using catalyst 47c the
product is formed as the (R)-enantiomer. The annulation product can then be accessed through a high yielding Tebbe olefination/hydrolysis sequence (Scheme 2.3.5). Selective crystallization produced (R)-aplexone (65) in >99% ee. While this provided a quick and efficient way to access (R)-aplexone (R)-(65) in high ee, at this point we still needed a reliable way to produce the other enantiomer.

**Scheme 2.3.5** The Synthesis of R-Aplexone

We envisioned that we could gain access to the pseudoenantiomer of catalyst 47c from the cheap, naturally occurring starting material (R)-carvone (Figure 2.3.6). Utilizing carvone-derived catalyst 66 as a pseudoenantiomeric catalyst to the L-Hyp derived catalyst provides a few unique advantages. Firstly, both enantiomers of carvone are readily available from Nature. *trans*-4-Hydroxy-D-proline is relatively expensive to purchase, or must be made from the naturally occurring *trans*-4-hydroxy-L-proline. The established route is shown in Scheme 2.3.6. Secondly, this provided an opportunity to explore the use of this carvone-derived catalyst system in the context of the asymmetric [4 + 2] annulation reaction.
The synthesis of pseudeonantiomeric carvone-derived catalyst can be seen in Scheme 2.3.7. Utilizing established literature procedures, we transformed (R)-carvone into the known diol 72. The synthesis began with a nucleophilic epoxidation of (R)-carvone to generate α,β-epoxy-carvone 67. Next, we opened the epoxide under acidic conditions to form the halohydrin 68. After the formation of the 2-tetrahydropyranyl (THP) ether, 69 was cleanly transformed into the ring contraction product 70 via a Favorskii rearrangement. Deprotection of the THP gave compound 71. Lithium aluminum hydride reduction provided the known diol 72. Mesylation of the diol provided 73, the required precursor to the [2.2.1] bicyclic phosphine catalyst 66. Utilizing the conditions established in the synthesis of the Hyp-derived chiral phosphines were we able to obtain...
the dialkylation product 74 as a single isomer, after hydrogen peroxide oxidation. Hydrogenation of the isopropenyl group with Wilkinson's catalyst afforded the phosphine oxide 75. Compound 66 can be quickly and efficiently transformed into the active phosphine catalyst by a silane reduction.

Scheme 2.3.7 Synthesis of Catalyst 66

With the pseudoenantiomeric carvone-derived catalyst 66 available to us, we tested its use in the [4 + 2] annulation of (E)-N-benzylidene-4-methylbenzenesulfonamide (48c) with α-methyl allenoate 19. Unfortunately, when carvone-derived catalyst 66 was tested under the optimized reaction conditions, the resulting annulation product with the desired (S)-stereochemistry, but was formed in only a 35% yield and 93% ee. When compared to the L-Hyp-derived chiral phosphine 47c, which generated the (R)-annulation product 49c in 56% yield and 98% ee. It shows the
inferiority of catalyst 66 under these particular conditions. Thinking that hydrolysis caused by the addition of the acetic acid may be responsible for the low product yield, a reaction was run in the absence of acid. Interestingly, while the yield was seen to increase under these conditions there was no effect on the ee of the product. Even without the addition of acidic additives, the yield of this reaction was variable, and undesired decomposition products made purification a cumbersome procedure. The results of this study can be seen in Scheme 2.3.8.

Scheme 2.3.8 Synthesis of ent-49c through the Use of Catalyst 66

We reason that the endo isopropyl group in catalyst 66 provides much more steric encumbrance than the toluenesulfonamide group does in L-Hyp-derived chiral phosphine 47c. This added steric bulk causes the longer reaction times required for reaction completion (5 vs. 3 days), as well as the decrease of the enantioselectivity of annulation product. While the desired annulation product could be synthesized with catalyst ent-47c, we wished to have a more efficient and reproducible annulation procedure for the synthesis of ent-49c. To this end, we chose to synthesize ent-47c from D-Hyp. We accomplished this in the same way as reported previously. The 3-step process of an installation of the toluenesulfonyl protecting group on the nitrogen atom, the
reduction of the acid, and the ditosylation of the alcohols lead to the ditosylate 76. Compound 76 could then be transformed into the exo- and endo-aryl chiral phosphines oxides 77a and 77b. Exo-aryl phosphine oxide 77a was then reduced to give ent-49c (Scheme 2.3.9).

![Scheme 2.3.9 Synthesis of Catalyst Ent-47c](image)

Applying catalyst ent-47c, we were able to synthesize the (S)-enantiomer of the annulation product ent-49c in the same yield and ee that we previously experienced. Annulation product (S)-ent-49c could then be carried forward under the same optimized reaction/recrystallization conditions to form (S)-aplexone (66) (Scheme 2.3.10). Now, with access to both enantiomers of 66 we turned our attention to their biological evaluation.

![Scheme 2.3.10 Synthesis of (S)-65 through the use of catalyst ent-47c](image)
Biological Evaluation of (R)- and (S)-Aplexone

As reported previously, we examined the development of the caudal vein plexus in zebrafish embryos. This initial phenotypic assays revealed that (R)-aplexone is the active enantiomer, while (S)-aplexone did not affect plexus development at the concentrations tested. Specifically, (±)-aplexone produced a "no plexus" phenotype at a 10 µM concentration, while (R)-aplexone was more potent and able to produce a "no plexus" phenotype at only 5 µM concentration. (S)-Aplexone, on the other hand, did not disrupt plexus formation even at a 20 µM concentration. The images of this phenotypic screening can be seen in Figure 2.3.7.

Figure 2.3.7 Caudal vein regions of two-day-old zebrafish embryos treated with various concentrations of aplexone (##). Formation of the caudal vein plexus is disrupted by treatment with 10 µM or higher of (±)-aplexone (65) and 5 µM or higher of (R)-aplexone (65), but the caudal vein plexus forms normally even after treatment with 20 µM (S)-aplexone (65)

We next tested the abilities of (R) or (S)-aplexone to reduce cellular levels of cholesterol in zebrafish embryos (Graph 2.3.1). (±)-Aplexon was shown to reduce cholesterol levels to a similar extent as atorvastatin (AT). (R)-aplexone is the active enantiomer since it was shown to
reduce cholesterol levels to a greater extent than AT, while (S)-aplexone again has shown to no such activity.

![Chart 2.3.1](chart.png)

**Chart 2.3.1** Relative cellular levels of cholesterol in zebrafish embryos treated with aplexone (AP) or atorvastatin (AT), both at 40 µM, DMSO used as a control

**Closing Remarks**

In summary, we have demonstrated, for the first time, highly enantioselective [4 + 2] annulation of α-methylallenoate and imines for the construction of chiral guvacine derivatives. Using a class of rigid chiral [2.2.1] bicyclic phosphines, the methodology disclosed in this thesis gives the best enantioselectivity to-date for synthesizing 6-substituted guvacine derivatives. We have also demonstrated that (R)-aplexone is the active pharmaceutical ingredient (API) responsible for the compound’s cholesterol lowering effects. This methodology provides an expedient and economical way of producing (R)-aplexone, which will allow future studies into its mode of action and its medicinal potential. Further exploration of the catalyst structure, improvements in reaction efficiency and applications of this methodology to other synthetic endeavors are underway.
Experimental:

General Procedures. All reactions were carried out in flamed-dried or oven-dried round bottomed flasks and Schlenk flasks. Glass water condenser was fitted over the flasks with rubber septa fitted over the condenser. All reactions were performed under positive pressure of argon. Stainless steel needles were used to inject acetylenes into refluxing reactions via syringe pump. Reactions were monitored through thin-layer chromatography (TLC) on 0.25-mm SiliCycle silica gel plates. Plates were visualized under UV light or with p-anisaldehyde or with potassium permanganate stain followed by heating (<1 min) with heat gun. Flash column chromatography (FCC) was performed using SiliCycle Silica-P Flash silica gel (60 Å pore size, 40-63 µm). Organic solutions were concentrated through rotary evaporators.

Materials. Reagents were used as received from commercial sources. Acetonitrile and dichloromethane were distilled from calcium hydride under positive pressure of argon. Tetrahydrofuran and diethylether were distilled from sodium and benzophenone under positive pressure of argon.

Instrumentation. IR spectra were obtained on a Thermo Nicolet Avatar 370 FT-IR. NMR spectra were obtained from Bruker AV-300 and AV-500 instruments calibrated using residual undeuterated chloroform as an internal reference (7.26 and 77.00 ppm for $^1$H and $^{13}$C NMR Spectra, respectively). Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for $^{13}$C NMR spectra are reported in terms of chemical shift. The following abbreviations are used to denote the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Samples were analyzed on a Waters
LCT Premier XE Time of Flight Instrument controlled by MassLynx 4.1 software. Samples were infused using direct loop injection from a Waters Acquity UPLC into the Multi Mode Ionization source. The lock mass standard for accurate mass determination was Leucine Enkephalin (Sigma L9133). Enantiomeric excess for the annulation products 49 were determined out on a Mettler Toledo supercritical fluid chromatography (SFC) using a Chiral AS column (10 % MeOH as a modifier; 2 mL/min). Enantiomeric excess for Aplexone (65) were determined using an OJ-H column (10 % MeOH as a modifier; 2 mL/min). LCMS data was collected on an Agilent Technologies 6120 Quadrupole LC/MS using a C18 column.

**Preparation of Starting Material For Chapter 2.2:** 4-Bromoindole (31)\(^1\), 3-allyl-4-bromo-1H-indole (30),\(^2\) Glyoxal 39\(^3\), cinnimaldehyde imine 44,\(^4\) Glyoxal imines 46a\(^5\) and 46b\(^6\) were synthesized as previously reported.

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Preparation of Starting Material For Chapter 2.3: The catalysts, 47a and 47f were made as we previously reported. Allenoate 19⁷ and imines 48⁸ were prepared according to established literature procedures. Aldehydes 55 and 56 were prepared as previously established.⁹

Synthesis of Aldehyde 29:

`tert-Butyl 3-allyl-4-bromo-1H-indole-1-carboxylate (33):` 3-Allyl-4-bromo-1H-indole (30) and DMAP (15 mol%) were dissolved in acetonitrile and cooled in an ice bath. While the mixture stirred Boc₂O (1.2 equiv) was added in 3 additions. The reaction was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was concentrated in vacuo. The crude indole was purified by FCC on silica gel (20% EtOAc in hexanes, Rf = 0.3). Compound 33 was isolated as an oil (98%).IR (CH₂Cl₂) $\nu_{\text{max}}$ 2980, 2949, 2363, 1733, 1183 cm⁻¹; ¹H NMR (300 MHz, CDCl₃)

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δ 8.2 (d, J = 8.4, 1H); 7.43–7.40 (m, 2H); 7.16 (t, J = 8.4 Hz, 1H); 6.24–6.11 (m, 1H); 5.20–5.11 (m, 2H); 3.79 (dd, J = 5.9, 1.4 Hz, 2H); 1.7 (s, 9H); 13C NMR (125 MHz, CDCl3) δ 149.7, 136.6, 127.1, 125.1, 124.7, 124.6, 119.8, 116.2, 114.5, 114.3, 92.7, 84.0, 30.9, 28.2; LRMS (LCMS, EI+) Calculated for [M+H]+ C16H19BrNO2: m/z 336.06, found 336.1.

tert-Butyl 4-bromo-3-(2-oxoethyl)-1H-indole-1-carboxylate (29): Compound 33 was transformed into aldehyde 29 following the procedure described by Jia10. Aldehyde 29 was isolated as an oil in 80% yield. IR (CH2Cl2) νmax 2979, 2936, 2718, 2360, 2340, 1725 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 9.91 (t, J = 1.4 Hz, 1H), 8.2 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.38 (dd, J = 8.4, 7.8 Hz, 2H), 7.15 (t, J = 8.1 Hz, 1H), 4.07 (dd, J = 1.2, 0.3 Hz, 2H), 1.65 (s, 9H); 13C NMR (125 MHz, CDCl3) δ 199.4, 148.9, 137.0, 127.9, 127.2, 126.9, 125.9, 114.7, 113.9, 111.9, 84.5, 40.9, 28.1; LRMS (LCMS, EI+) [m]+ : m/z C15H16BrNO3Na [M+Na] m/z 360.02, 362.02, Found: 360.0, 362.0.

Synthesis of Imine 18a:

 tert-Butyl 4-bromo-3-((4-methylphenyl)sulfonamido)-2-tosylethyl-1H-indole-1-carboxylate (37): Aldehyde 29 (1 mmol), toluenesulfinic acid (1.2 mol), and toluenesulfonamide, (1.05 mmol) were dissolved in Et2O (2 mL). The reaction was allowed to stir for 2 days and filtered. The solid was washed was washed with water (10 mL), then cold Et2O (5 mL). Compound 37 was isolated as a white solid (0.854 mmol). M. p.: Decomposed at 61 °C; IR (CH2Cl2) νmax

2976, 2364, 3241, 1734, 1157 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.06–8.00 (m, 3H); 7.49 (dd, J = 8.1, 1.4 Hz, 2H); 7.37–7.34 (m, 2H); 7.11 (t, J = 8.1 Hz, 1H); 7.04 (d, J = 8.1 Hz, 2H); 6.59 (d, J= 8.1 Hz, 2H) 6.07 (d, J = 10.0 Hz, 1H); 5.21–5.13 (m, 1H); 4.05 (dd, J = 15.1, 3.5 Hz, 1H); 3.2 (dd, J = 15.0, 12.7 Hz, 1H); 2.52 (s, 3H); 2.22 (s, 3H); 1.67 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 176.2, 148.3, 145.6, 142.8, 137.0, 136.9, 132.7, 130.3, 129.9, 128.5, 127.8, 127.5, 127.0, 125.4, 125.0, 114.5, 113.1, 112.7, 84.3, 74.0, 28.1, 23.5, 21.9, 21.6; LRMS (LCMS, EI+) [m-Ts]⁺ C₂₂H₂₄BrN₂O₄S: m/z 491.06, found 491.1

**tert-Butyl (E)-4-bromo-3-(2-(tosylimino)ethyl)-1H-indole-1-carboxylate (18a):** Compound 37 (100 mg, 0.15 mmol) was dissolved in DCM (5 mL) and poured into a separatory funnel. A saturated solution of sodium bicarbonate (7 mL) was then added to the separatory funnel and the biphasic mixture was vigorously shaken for 15 seconds. The organic layer was quickly dried with NaSO₄ and concentrated in vacuo to afford imine 18a with minor enamine impurities. The imine was used directly for further studies. IR (CH₂Cl₂) νmax 2980, 2934, 2359, 2367, 1732, 1627, 1420, 1149; ¹H NMR (300 MHz, CDCl₃) δ 8.82 (t, J = 4.2 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 2H), 7.54 (s, 1H), 7.38–7.32 (m, 3H), 7.18 (t, J = 8.0 Hz, 1H), 4.21 (dd, J = 4.0, 0.9 Hz, 2H), 2.48 (s, 3H), 1.70 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 148.8, 144.7, 137.0, 134.3, 129.9, 128.3, 127.6, 127.1, 126.8, 125.6, 114.7, 113.7, 112.7, 84.6, 33.0, 28.1, 21.7; LRMS (LCMS, EI+) [M+H]+ C₂₂H₂₄BrN₂O₄S: m/z 491.06, Found 491.1.

**Phosphine Catalyst Preparation**

*General Procedure for Nickel-Catalyzed Arbuzov Reaction*

\[
\text{Ar–X} + \text{P(OEt)}_3 \xrightarrow{\text{cat. NiCl}_2} \text{ArP(OEt)}_2 \xrightarrow{160 \, ^\circ \text{C}} \text{Ar} \text{O} _\text{P(OEt)}_2 \]

129
A round bottom flask equipped with water condenser under argon was charged with aryl iodide/bromide\(^\text{11}\) (128.2 mmol) and NiCl\(_2\) (0.83 g, 6.41 mmol, 5 mol%). The mixture was placed in sand bath and heated to 160 °C using a heating mantle. At 160 °C, triethylphosphite (22.0 mL, 128.2 mmol) was added into the reaction mixture dropwise via needle and syringe. (Caution: only few drops of the triethylphosphite were added to initiate the reaction since the reaction is exothermic and produces large amount of gas. Once the reaction was initiated, the addition of triethylphosphite ensued and a green reaction mixture was observed.) After the addition, the reaction was kept at 160 °C for two more hours before cooling to room temperature. The cooled mixture was subjected to purification by FCC on silica gel (70% EtOAc in hexanes) to yield the arylphosphonate.

**Diethyl (4-methoxyphenyl)phosphonate:** 75% yield. Spectral data matches the reported literature.\(^\text{12}\)

**Diethyl (4-fluorophenyl)phosphonate:** 88% yield. Spectral data matches the reported literature.\(^\text{2}\)

**Diethyl naphthalen-1-ylphosphonate:** 96% yield. Spectral data matches the reported literature.\(^\text{2}\)

\(^{11}\) 4-Iodoanisole, 4-fluoroiodobenzene, 1-bromonaphthalene, and 2-bromonaphthalene are employed.

Diethyl naphthalen-2-ylphosphonate: 98% yield. Spectral data matches the reported literature.\textsuperscript{13}

**General Procedure for Preparing Exo/Endo Kwon Bicyclic Phosphine Oxides**

Under argon atmosphere, a flamed dried round bottom flask was charged with lithium aluminum hydride (1.95 g, 102.5 mmol). To the reaction flask, Et\textsubscript{2}O (52 mL) was added and cooled to 0 °C using an ice bath. Arylphosphonate (41 mmol) was added dropwise into the reaction mixture via needle and syringe at 0 °C. After the addition, the reaction was allowed to warm to room temperature by removing the cooling bath and stirred for one hour at room temperature. Before quenching, the reaction was diluted with Et\textsubscript{2}O (52 mL) at 0 °C. The reaction mixture was then quenched using Fieser workup at 0 °C with dropwise addition of H\textsubscript{2}O (1.95 mL). Then, 20% aq. NaOH (1.95 mL) was added dropwise followed by addition of H\textsubscript{2}O (5.85 mL). The reaction was allowed to stir for another hour at room temperature, forming white granular aluminum salt. NaSO\textsubscript{4} (20 g) was added to the mixture prior to removal of the solid, drying the solution. Under positive pressure of argon, reaction solution was transferred to another flamed dried round bottom flask via cannula by piercing into a cotton ball, filtering out the formed solid. The remaining solid was rinsed with two portions of Et\textsubscript{2}O (10 mL) and combined with the organic layer via cannula. The flask containing the organic solution was equipped with a distillation setup to distill off any volatile

liquid in the mixture at 1 mmHg to afford the crude arylphosphine, which was used without further purification except \textit{p}-fluorophenylphosphine. \textit{P}-Fluorophenylphosphine was extremely hygroscopic and required purification by distillation before alkylation as will be shown below. The primary arylphosphines are known in the literature\textsuperscript{*} with the exception of \textit{p}-fluorophenylphosphine and \textit{p}-methoxyphenylphosphine, which are highly pyrophoric and therefore were not characterized.

\[ \text{Ar} \text{--PH}_2 \xrightarrow{\text{nBuLi, THF, } -78 \, ^\circ\text{C}} \left[ \begin{array}{c} \text{TsN} \text{P} \text{Ar} \\ \text{Tso} \\ \text{Ts} \end{array} \right] + \left[ \begin{array}{c} \text{TsN} \text{P} \text{Ar} \\ \text{Tso} \\ \text{Ts} \end{array} \right] \]

To the flask containing arylphosphine (41 mmol), THF (247 mL) was added and the reaction was cooled to \(-78 \, ^\circ\text{C}\) using an acetone–dry ice bath. To deprotonate the arylphosphine, \textit{n}-butyl lithium in hexanes (82 mmol) was added to the reaction mixture at \(-78 \, ^\circ\text{C}\). After the addition, the reaction mixture was warmed to room temperature for two hours by removing the cooling bath. Before adding the tritosylated prolinol 1 (7.9 g, 13.7 mmol) in THF (137 mL), the reaction mixture was cooled to \(-78 \, ^\circ\text{C}\). The tritosylated prolinol solution was also cooled to \(-78 \, ^\circ\text{C}\) and transferred dropwise to the flask containing arylphosphine dilithium via cannula. (Important: To favor the formation of \textit{endo} catalysts, both the reaction mixture and the tritosylated prolinol solution needed to be kept at \(-78 \, ^\circ\text{C}\). Reactions run at higher temperature produced more \textit{exo} catalyst.) After the addition, the reaction mixture was allowed to warm to room temperature overnight and stirred for two days. Upon completion, the reaction was quenched by dropwise addition of 50\% aq. \text{NH}_4\text{Cl} (137 mL) at 0 \, ^\circ\text{C}\) followed by 30\% aq. \text{H}_2\text{O}_2 (27 mL). The resulting mixture was extracted with
DCM (2 x 100 mL). The combined organic layer was dried with NaSO$_4$ and concentrated in vacuo. The crude oxides were purified by FCC on silica gel (5% MeOH in EtOAc) to yield the exo- and endo-bicyclic phosphine oxides separately.

**Endo-4-methoxyphenyl Kwon Bicyclic Phosphine Oxide Ent-77b:** 78% combined yield; exo/endo = 1:1.3; white solid; mp: 54–55°C; IR (neat) $\nu_{\text{max}}$ 3420, 3062, 2983, 1683, 1597, 1505, 1344, 1172 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.79 (dd, $J = 11.1$, 8.8 Hz, 2H), 7.70 (d, $J = 8.2$ Hz, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 7.03 (dd, $J = 8.7$, 2.2 Hz, 2H), 4.57 (d, $J = 28.2$ Hz, 1H), 3.87 (s, 3H), 3.07–3.00 (m, 1H), 2.65–2.60 (m, 2H), 2.45 (s, 3H), 2.35 (dd, $J = 11.6$, 4.4 Hz, 1H), 2.11 (ddd, $J = 18.8$, 15.3, 3.4 Hz, 1H), 1.85–1.75 (m, 1H), 1.54–1.46 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 163.2, 144.1, 134.6, 133.3 (d, J$_{\text{C-P}} = 11.0$ Hz), 130.1, 127.3, 118.4 (d, J$_{\text{C-P}} = 100.8$ Hz), 114.6 (d, J$_{\text{C-P}} = 13.2$ Hz), 59.1, 55.5, 48.0, 40.3 (d, J$_{\text{C-P}} = 67.2$ Hz), 39.6 (d, J$_{\text{C-P}} = 62.3$ Hz), 36.2 (d, J$_{\text{C-P}} = 6.1$ Hz), 21.6; $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ 50.6; HRMS (ESI+) calcd for [C$_{19}$H$_{23}$NO$_4$PS]$^+$: m/z 392.1085, found 392.1097.

**Endo-1-naphthyl Kwon Bicyclic Phosphine Oxide:** 32% combined yield; exo/endo = 1:2; white solid; mp: 56–57 °C; IR (neat) $\nu_{\text{max}}$ 3401, 3061, 2979, 1682, 1597, 1344, 1169, 1149 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.69 (d, $J = 8.2$ Hz, 1H), 8.07 (d, $J = 8.3$ Hz, 1H), 7.94 (d, $J = 7.9$ Hz, 1H), 7.81 (dd, $J = 14.8$, 6.9 Hz, 1H), 7.64–7.57 (m, 4H), 7.52–7.48 (m 1H), 7.28 (d, $J = 8.1$ Hz, 2H),
4.61 (d, $J = 28.4$ Hz, 1H), 3.09–2.97 (m, 3H), 2.57 (dd, $J = 15.6$, 9.8 Hz, 1H), 2.51 (dd, $J = 11.4$, 4.3 Hz, 1H), 2.42 (s, 3H), 2.19 (ddd, $J = 18.9$, 15.5, 3.7 Hz, 1H), 1.70–1.62 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 144.0, 135.0, 133.8 (d, $J_{(C-P)} = 1.9$ Hz), 133.8 (d, $J_{(C-P)} = 7.9$ Hz), 133.5 (d, $J_{(C-P)} = 8.3$ Hz), 131.2 (d, $J_{(C-P)} = 10.5$ Hz), 130.0, 129.3, 128.0, 127.2, 126.9, 126.0 (d, $J_{(C-P)} = 5.8$ Hz), 124.7 (d, $J_{(C-P)} = 14.0$ Hz), 124.5 (d, $J_{(C-P)} = 94.0$ Hz), 58.0, 47.8, 40.0 (d, $J_{(C-P)} = 66.2$ Hz), 37.9 (d, $J_{(C-P)} = 64.2$ Hz), 35.6 (d, $J_{(C-P)} = 5.7$ Hz), 21.6; $^{31}$P NMR (121 MHz, CDCl$_3$) δ 55.1; HRMS (ESI+) calcd for [C$_{22}$H$_{23}$NO$_3$PS]$^+$: m/z 412.1136, found 412.1131.

**Endo-2-naphthyl Kwon Bicyclic Phosphine Oxide:** 51% combined yield; exo/endo = 2.6:1; yellow solid; mp: 68–69 °C; IR (neat) $\nu_{\text{max}}$ 3385, 3057, 2981, 1596, 1343, 1169, 1150, 1089 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.50 (d, $J = 13.6$ Hz, 1H), 8.00–7.97 (m, 2H), 7.91 (d, $J = 8.1$ Hz, 1H), 7.85–7.81 (m, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.65–7.58 (m, 2H), 7.35 (d, $J = 8.1$ Hz, 2H), 4.65 (d, $J = 28.4$ Hz, 1H), 3.14–3.00 (m, 2H), 2.82 (dd, $J = 15.2$, 2.1 Hz, 1H), 2.70 (s, 1H), 2.45–2.42 (m, 4H), 2.22 (ddd, $J = 18.9$, 15.4, 3.4 Hz, 1H), 1.62–1.53 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 144.2, 135.1 (d, $J_{(C-P)} = 2.5$ Hz), 134.7, 133.9 (d, $J_{(C-P)} = 9.0$ Hz), 132.6 (d, $J_{(C-P)} = 13.3$ Hz), 130.1, 129.1, 128.9 (d, $J_{(C-P)} = 12.0$ Hz), 128.7, 127.9, 127.3, 127.2, 125.7 (d, $J_{(C-P)} = 10.5$ Hz), 124.8 (d, $J_{(C-P)} = 94.5$ Hz), 59.1, 48.0 (d, $J_{(C-P)} = 4.3$ Hz), 40.4 (d, $J_{(C-P)} = 66.6$ Hz), 39.7 (d, $J_{(C-P)} = 62.1$ Hz), 36.3 (d, $J_{(C-P)} = 6.0$ Hz), 21.6; $^{31}$P NMR (121 MHz, CDCl$_3$) δ 50.4; HRMS (ESI+) calcd for [C$_{22}$H$_{23}$NO$_3$PS]$^+$: m/z 412.1136, found 412.1107.
Exo-4-methoxyphenyl Kwon Bicyclic Phosphine Oxide ent-77a: 61% yield; white solid; IR (film) ν_{max} 2978.54, 2885.1, 2841.3, 2222.1, 1916.6, 1597.1, 1505.1, 1341.7 cm^{-1}; ^1H (500 MHz, CDCl₃) δ 7.79 (d, J = 8.4 Hz, 2H), 7.63 (dd, J = 10.0, 8.7 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.99 (dd, J = 10.0, 2.5 Hz, 2H), 4.58 (d, J = 25 Hz, 1H), 4.14 (dd, J = 15, 10 Hz, 1H), 3.84 (s, 3H), 3.52 (dq, J = 25, 10 Hz, 1H), 2.77 (bs, 1H), 2.42 (s, 3H), 2.17–2.08 (m, 2H), 1.72–1.61 (m, 2H); ^13C (125 MHz, CDCl₃) δ 162.7, 143.7, 135.8, 132.2 (2C), 132.1 (2C), 129.7 (2C), 127.3 (2C), 114.4 (d, J^{CP} = 12.5 Hz), 58.8, 55.3, 46.3 (d, J^{CP} = 12.5 Hz), 39.9, 39.4, 35.4 (d, J^{CP} = 10 Hz), 34.4 (d, J^{CP} = 65 Hz); ^31P (202 MHz, CDCl₃) δ 41.8; HRMS (ESI) calcd for C₁₉H₂₂NO₄PS [M + H]^+ 392.1080, found 392.1097.

Exo-1-naphthyl Kwon Bicyclic Phosphine Oxide: 23% yield; white solid; IR (film) ν_{max} 3060.1, 2978.4, 2953.9, 2880.4, 2223.1, 1595.7, 1505.8, 1343.2 cm^{-1}; ^1H (500 MHz, CDCl₃) δ 8.46 (d, J = 10 Hz, 1H), 8.01 (d, J = 8 Hz, 1H), 7.91 (d, J = 8 Hz, 1H), 7.80 (d, J = 8 Hz, 2H), 7.62 (m, 3H), 7.47 (m, 1H), 7.34 (d, J = 8 Hz, 2H), 4.53 (d, J = 27 Hz, 1H), 4.28 (q, J = 8 Hz, 1H), 3.64 (dq, J = 15, 25 Hz, 1H), 3.27 (app. s, 1H), 2.42 (s, 3H), 2.31 (dd, J = 10.5, 2.1 Hz, 2H), 1.64 (m, 2H); ^13C (125 MHz, CDCl₃) δ 143.7, 135.7, 133.9 (d, J^{CP} = 8.9 Hz), 133.3 (d, J^{CP} = 2.5 Hz), 132.5 (d, J^{CP} = 7.5 Hz), 129.8, 129.1, 128.7 (d, J^{C–P} = 11.0 Hz), 128.1, 127.9, 127.5, 127.3, 126.0 (d, J^{CP} = 6.2 Hz), 124.2 (d, J^{CP} = 13.7 Hz), 45.9 (d, J^{CP} = 6.3 Hz), 38.1 (d, J^{CP} = 67.5 Hz), 36.0 (d, J^{CP} = 56.3 Hz).
Hz), 35.5 (d, $J_{CP} = 10$ Hz), 21.5; $^{31}$P (202 MHz, CDCl$_3$) $\delta$ 51.4; HRMS (ESI) calcd for C$_{22}$H$_{22}$NO$_3$PS [M + H]$^+$ 412.1094, found 412.1105.

Exo-2-naphthyl Kwon Bicyclic Phosphine Oxide: 37% yield; white solid; IR (film) $\nu_{\text{max}}$ 3060, 2991, 1595, 1436, 1341, 1223 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.31 (d, $J = 13.5$ Hz, 1H), 7.94 (dd, $J = 8.3$, 2.3 Hz, 1H), 7.89 (dd, $J = 13.0$, 8.0 Hz, 2H), 7.81 (d, $J = 8.5$ Hz, 2H), 8.75 (t, $J = 8.8$ Hz, 1H), 7.59 (dt, $J = 18.0$, 7.0 Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 4.64 (app. d, $J = 27$ Hz, 1H), 4.21 (dd, $J = 14.0$, 9.5 Hz, 1H), 3.55 (ddd, $J = 25.3$, 9.7, 5.5 Hz, 1H), 2.91 (app. s, 1H), 2.43 (s, 3H), 2.37–2.16 (m, 2H), 1.83–1.40 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 143.9, 135.8, 134.7, 132.4 (d, $J_{(C-P)} = 13.7$ Hz), 132.3 (d, $J_{(C-P)} = 9.3$ Hz), 130.0, 129.8 (d, $J_{(C-P)} = 23.0$ Hz), 129.1 (d, $J_{(C-P)} = 12.3$ Hz), 128.8, 128.6, 128.0, 127.9, 127.4, 125.0 (d, $J_{(C-P)} = 9.3$ Hz), 69.1, 46.5 (d, $J_{(C-P)} = 6.5$ Hz), 39.8 (d, $J_{(C-P)} = 67.2$ Hz), 35.6 (d, $J_{(C-P)} = 12.0$ Hz), 34.8 (d, $J_{(C-P)} = 64$ Hz), 21.6; $^{31}$P NMR (202 MHz, CDCl$_3$) $\delta$ 50.9; HRMS (MALDI) calcd for C$_{22}$H$_{22}$NO$_3$PSNa [M + Na]$^+$ 434.0950, found 434.0954.

Synthesis of Exo/Endo-4-fluorophenyl Kwon Bicyclic Phosphine Oxides

Under argon atmosphere, a flamed dried round bottom flask was charged with lithium aluminum hydride (10.0 g, 265 mmol). To the reaction flask, Et$_2$O (268 mL) was added and cooled to 0 ºC using an ice bath. 4-fluorophenyl phosphonate (24.5 g, 106 mmol) was added dropwise into the
reaction mixture via needle and syringe at 0 ºC. After the addition, the reaction was allowed to warm to room temperature by removing the cooling bath and stirred for one hour at room temperature. Before quenching, the reaction was diluted with Et₂O (268 mL) at 0 ºC. The reaction mixture was then quenched using Fieser workup at 0 ºC with dropwise addition of H₂O (10 mL). Then, 20% aq. NaOH (10 mL) was added dropwise followed by addition of H₂O (30 mL). The reaction was allowed to stir for another hour at room temperature, forming white granular aluminum salt. NaSO₄ (100 g) was added to the mixture prior to removal of the solid. Under positive pressure of argon, reaction solution was transferred to another flamed dried round bottom flask via cannula by piercing into a cotton ball, filtering out the formed solid. The remaining solid was rinsed with two portions of Et₂O (50 mL) and combined with the organic layer via cannula. The flask containing the organic solution was equipped with a distillation setup to distill off any volatile liquid in the mixture at 1 mmHg to afford the crude phosphine. The mixture was purified by vacuum distillation at 1 mmHg with internal vapor temperature of 160 ºC to give 4-fluorophenyl phosphine (10.5 g, 77%) as colorless oil which was used immediately for the next step.

**Endo-4-fluorophenyl Kwon Bicyclic Phosphine Oxide:** 50% combined yield; exolendo = 1:2.2; white solid; mp: 134–135 ºC; IR (neat) νmax 3421, 3066, 2982, 1591, 1499, 1343, 1166, 1091 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.91–7.86 (m, 2H), 7.70 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.23 (td, J = 8.6, 2.1 Hz, 2H), 4.59 (d, J = 28.7 Hz, 1H), 3.09–3.01 (m, 2H), 2.67–2.64 (m, 2H), 2.45 (s, 3H), 2.37 (dd, J = 11.7, 4.2 Hz, 1H), 2.16 (ddd, J = 19.0, 15.5, 3.4 Hz, 1H), 1.58–1.49 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 165.7 (d, J(C–P) = 255.0 Hz), 144.3, 134.5, 134.1 (dd,
$J_{C-P} = 11.1 \text{ Hz, } J_{C-F} = 8.9 \text{ Hz}$, 130.1, 127.3, 123.5 (d, $J_{C-P} = 96.7 \text{ Hz}$), 116.5 (dd, $J_{C-P} = 21.5 \text{ Hz, } J_{C-F} = 13.2 \text{ Hz}$), 59.0, 48.0, 40.3 (d, $J_{C-P} = 41.9 \text{ Hz}$), 39.8 (d, $J_{C-P} = 37.4 \text{ Hz}$), 36.3 (d, $J_{C-P} = 6.1 \text{ Hz}$), 21.6; $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ 49.9; HRMS (ESI+) calcd for [C$_{18}$H$_{20}$FNO$_3$PS]$^+$: m/z 380.0886, found 380.0931.

Exo-4-fluorophenyl Kwon Bicyclic Phosphine Oxide: 45% yield; white solid; IR (film) $\nu_{max}$ 2985.4, 2883.1, 1928.2, 1593.5, 1503.5, 1347.1 cm$^{-1}$; $^1$H (500 MHz, CDCl$_3$) $\delta$ 7.74–7.70 (m, 4H), 7.31 (d, $J = 5 \text{ Hz}$, 2H), 7.15 (dt, $J = 8.5$, 2.0 Hz, 2H), 4.55 (d, $J = 25 \text{ Hz}$, 1H), 4.11 (q, $J = 8.3 \text{ Hz}$, 1H), 3.46 (dq, $J = 25$, 5 Hz, 1H), 2.77 (app. s, 1H), 2.38 (s, 3H), 2.18–2.09 (m, 2H), 1.80– (m, 2H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 167.7 (d, $J_{C-P} = 255.0 \text{ Hz}$), 145.3, 134.5, 132.8 (dd, $J_{C-P} = 11 \text{ Hz, } J_{C-F} = 9 \text{ Hz}$), 130.1, 129.5 (d, $J_{C-P} = 96.7 \text{ Hz}$), 127.3, 116.5 (dd, $J_{C-P} = 21.5 \text{ Hz, } J_{C-F} = 13.2 \text{ Hz}$), 59.0, 48.0, 40.3 (d, $J_{C-P} = 41.9 \text{ Hz}$), 39.8 (d, $J_{C-P} = 37.4 \text{ Hz}$), 36.3 (d, $J_{C-P} = 6.1 \text{ Hz}$), 21.6; $^{31}$P (202 MHz, CDCl$_3$) $\delta$ 41.8; HRMS (ESI) calcd for C$_{18}$H$_{19}$FNO$_3$PS [M + H]$^+$ 380.0880, found 380.0880.

**General Procedure for Reducing Kwon Bicyclic Phosphine Oxides**

To a flamed dried flask under argon atmosphere, bicyclic phosphine oxide (2.56 mmol) was added followed by addition of DCM/toluene (51 mL, 1:1 ratio). Trichlorosilane (1.3 mL, 12.8 mmol) was added to the reaction mixture slowly. The reaction was allowed to stir at room temperature for two hours followed by quenching with H$_2$O (2.1 mL). Then, solid NaCO$_3$ (1.35g) was added to the
reaction mixture and stirred for another hour. The reaction mixture was dried over Na$_2$SO$_4$ (4 g) under argon before transferring the solution to another flask. The transferring step was done via cannula with positive pressure of argon by piercing into a cotton ball, filtering out the formed solid. The solid was rinsed with DCM (2 x 10 mL) and combined with the reaction solution. The resulting solution was concentrated in vacuo followed by purging the system with argon, preventing undesired oxidation. The flask containing crude solid phosphine was equipped with a water condenser under argon atmosphere. The crude phosphine was then purified by recrystallizing in pentane and EtOAc to afford bicyclic phosphine.

**Phosphine 47b**: 98% yield; white solid; IR (film) $\nu_{\text{max}}$ 2961.4, 2930.0, 2872.8, 1723.2, 1595.3, 1499.4 cm$^{-1}$; $^1$H (500 MHz, CDCl$_3$) $\delta$ 7.71 (d, $J = 10$ Hz, 2H), 7.31 (d, $J = 5$ Hz, 2H), 7.50–7.20 (m, 2H), 7.00–6.90 (m, 2H), 4.46 (d, $J = 10$ Hz, 1H), 3.33 (m, 2H), 2.69 (d, $J = 9$ Hz, 1H), 2.43 (m, 1H), 2.41 (s, 3H), 1.87 (dt, $J = 15$, 5 Hz, 1H), 1.40–1.30 (m, 2H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 162.6 (d, $J_{(C-P)}$ = 247 Hz), 143.5, 135.6, 1.35.1 (dd, $J_{(C-P)} = 25.0$, $J_{(C-F)} = 3.4$ Hz), 131.7 (dd, $J_{(C-P)} = 7.1$, $J_{(C-F)} = 16.4$ Hz), 129.8, 127.3, 115.8 (dd, $J_{(C-P)} = 20.7$ Hz, $J_{(C-F)} = 5.0$ Hz), 59.22 (d, $J_{CP}$ = 2.5 Hz), 51.31 (d, $J_{CP}$ = 20 Hz), 38.11 (d, $J_{CP}$ = 13.7 Hz), 36.44 (d, $J_{CP}$ = 3.8 Hz), 34.2, 34.1; $^{31}$P (202 MHz, CDCl$_3$) $\delta$ –17.5; HRMS (ESI) calcd for C$_{18}$H$_{19}$FNO$_2$PS [M + H]$^+$ 364.0931, found 364.0917.
**Phosphine 47c:** 100% yield; white solid; IR (film) $\nu_{\text{max}}$ 2961.4, 2930.1, 2873.1, 2837.2, 1723.9, 1595.3, 1499.4, 1341.3 cm$^{-1}$; $^1$H (500 MHz, CDCl$_3$) $\delta$ 7.72 (d, $J = 5$ Hz, 2H), 7.31 (d, $J = 10$ Hz, 2H), 7.21 (app. s, 2H), 6.86 (d, $J = 10$ Hz, 2H), 4.48 (d, $J = 10$ Hz, 1H), 3.77 (s, 3H), 3.35–3.30 (m, 2H), 2.71–2.61 (m, 1H), 2.57–2.37 (m, 4H), 1.96–1.88 (m, 1H), 1.50–1.34 (m, 2H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 159.6, 143.4, 135.6, 131.7, 131.5, 129.7, 127.3, 114.3, 59.2, 55.2, 51.4 (d, $J_{\text{CP}} = 21.3$ Hz), 38.2 (d, $J_{\text{CP}} = 12.5$ Hz), 36.3, 33.7 (d, $J_{\text{CP}} = 18.8$ Hz), 21.4; $^{31}$P (202 MHz, CDCl$_3$) $\delta$ −15.6; HRMS (ESI) calcd for C$_{19}$H$_{22}$NO$_3$PS [M + H]$^+$ 376.1131, found 376.1129.

**Phosphine 47d:** 99% yield; white solid; IR (film) $\nu_{\text{max}}$ 3046.4, 2974.9, 2923.7, 1596.5, 1341.3 cm$^{-1}$; $^1$H (500 MHz, CDCl$_3$) $\delta$ 8.16 (m, 1H), 7.84 (d, $J = 6.5$ Hz, 1H), 7.75 (m, 3H), 7.52 (m, 2H), 7.37 (t, $J = 7.57$ Hz, 1H), 7.80–7.35 (m, 3H), 4.46 (d, $J = 10$ Hz, 1H), 3.52 (d, $J = 6.7$ Hz, 1H), 3.44 (dq, $J = 30$, 14 Hz, 1H), 2.97 (dd, $J = 10$, 5 Hz, 1H), 2.58 (dd, $J = 32.5$, 12.5 Hz, 1H), 2.43 (s, 3H), 1.98 (dt, $J = 15$, 10 Hz, 1H), 1.56 (d, $J = 10$ Hz, 1H), 1.39 (m, 1H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 143.4, 136.2, 135.6, 133.7, 133.5 (d, $J_{\text{CP}} = 2.5$ Hz), 129.7, 129.0, 128.6, 127.3, 126.5, 126.05 (d, $J_{\text{CP}} = 1.3$ Hz), 126.02, 126.0, 124.8, 59.5, 51.7 (d, $J_{\text{CP}} = 22.5$ Hz), 36.7 (d, $J_{\text{CP}} = 3.8$ Hz), 36.0 (d, $J_{\text{CP}} = 13.7$ Hz), 34.3 (d, $J_{\text{CP}} = 20$ Hz), 21.4; $^{31}$P (202 MHz, CDCl$_3$) $\delta$ −22.4; HRMS (ESI) calcd for C$_{22}$H$_{22}$NO$_2$PS [M + H]$^+$ 396.1145, found 396.1279.

**Phosphine 47e:** 98% yield; white solid; IR (film) $\nu_{\text{max}}$ 2967, 2865, 1435, 1342 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.84–7.77 (m, 5H), 7.7 (d, $J = 6.0$ Hz, 1H), 7.52–7.50 (m, 2H), 7.49–7.31 (m, 4H), 7.21 (app. s, 2H), 6.86 (d, $J = 10$ Hz, 2H), 4.48 (d, $J = 10$ Hz, 1H), 3.77 (s, 3H), 3.35–3.30 (m, 2H), 2.71–2.61 (m, 1H), 2.57–2.37 (m, 4H), 1.96–1.88 (m, 1H), 1.50–1.34 (m, 2H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 159.6, 143.4, 135.6, 131.7, 131.5, 129.7, 127.3, 114.3, 59.2, 55.2, 51.4 (d, $J_{\text{CP}} = 21.3$ Hz), 38.2 (d, $J_{\text{CP}} = 12.5$ Hz), 36.3, 33.7 (d, $J_{\text{CP}} = 18.8$ Hz), 21.4; $^{31}$P (202 MHz, CDCl$_3$) $\delta$ −15.6; HRMS (ESI) calcd for C$_{19}$H$_{22}$NO$_3$PS [M + H]$^+$ 376.1131, found 376.1129.
3H), 4.56 (d, $J = 10.0$ Hz, 1H), 3.49–3.42 (m, 2H), 2.92–2.90 (m, 1H), 2.57–2.46 (m, 4H), 2.11–
2.01 (m, 1H), 1.48–1.41 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 143.5, 137.5 (d, $J_{(C-P)} = 24.7$
Hz), 135.7, 133.1 (d, $J_{(C-P)} = 5.0$ Hz), 132.7, 129.7, 129.1 (d, $J_{(C-P)} = 13.0$ Hz), 128.1 (d, $J_{(C-P)} =$
6.0 Hz), 127.7, 127.5, 127.3, 127.0, 126.9 (d, $J_{(C-P)} = 17.6$ Hz), 126.4, 69.5, 51.5 (d, $J_{(C-P)} = 20.1$
Hz), 38.1 (d, $J_{(C-P)} = 14.4$ Hz), 36.8 (d, $J_{(C-P)} = 4.5$ Hz), 34.1(d, $J_{(C-P)} = 22.1$ Hz), 21.5; $^{31}$P NMR
(202 MHz, CDCl$_3$) $\delta$ –15.1; HRMS (MALDI) calcd for C$_{22}$H$_{22}$NO$_2$PSNa [M + Na]$^+$ 418.1001, found 418.1012.

**General [4 + 2] Procedure**

![Chemical reaction diagram]

The imine 48 (0.1 mmol), 4 Å molecular sieves (10 mg) and the phosphine 47 (0.3 equiv) were
weighed and added to the flask in glove box. Distilled DCM (1.5 mL) was added via syringe under
argon. Acetic acid (10 mol%) was added, and then allenaote 19 (1.5 equiv) was added dropwise to
the reaction mixture via syringe. The flask with cap was sealed by Teflon tape and parafilm. The
contents were stirred at room temperature for three days. The crude reaction mixture was loaded
directly onto a silica gel column and separated chromatographically (hexane/EtOAc, 3:1) to afford
annulated product 49.

**Analytical Data of Novel Compounds**
Compounds 49c and Aplexone (65) have been synthesized previously; their spectral data are provided in the pertinent references. Complete spectral data are provided for all new compounds:

**Ethyl (R)-1-((4-nitrophenyl)sulfonyl)-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (49a)**: Yield: 70%; 95% ee; [α]_D^{20} = –28.2° (CHCl₃, c = 1.0); IR (film) 2984, 1708, 1349 cm⁻¹; \(^1\)H (500 MHz, CDCl₃) δ 8.29 (d, \(J = 8.9\) Hz, 2H), 7.96 (d, \(J = 8.9\) Hz, 2H), 7.29–7.26 (m, 3H), 7.21–7.19 (m, 2H), 7.06–7.05 (m, 1H), 5.40 (d, \(J = 6.9\) Hz, 1H), 4.51 (d, \(J = 18.0\) Hz, 1H), 4.21 (q, \(J = 7.2\) Hz, 2H), 3.53–3.48 (m, 1H), 2.74–2.56 (m, 2H), 1.29 (t, \(J = 7.2\) Hz, 3H); \(^1\)C (125 MHz, CDCl₃) δ 164.3, 149.9, 145.9, 137.6, 135.9, 128.8, 128.3, 128.2, 127.3, 127.1, 124.3, 61.1, 52.8, 39.9, 27.8, 14.2; HRMS (ESI) Calculated for [M+H]^+, C_{20}H_{21}N₂O₆S, \(m/z\) 417.1120, found 417.1112.

**Ethyl (R)-6-phenyl-1-(phenylsulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49b)**: Yield: 50%; 97% ee; [α]_D^{20} = –43.6° (CHCl₃, c = 1.0); IR (film) 2982, 1710, 1350 cm⁻¹; \(^1\)H (500 MHz, CDCl₃) δ 8.29 (d, \(J = 8.9\) Hz, 2H), 7.96 (d, \(J = 8.9\) Hz, 2H), 7.29–7.26 (m, 3H), 7.21–7.19 (m, 2H), 7.06–7.05 (m, 1H), 5.40 (d, \(J = 6.9\) Hz, 1H), 4.51 (d, \(J = 18.0\) Hz, 1H), 4.21 (q, \(J = 7.2\) Hz, 2H), 3.53–3.48 (m, 1H), 2.74–2.56 (m, 2H), 1.29 (t, \(J = 7.2\) Hz, 3H); \(^1\)C (125 MHz, CDCl₃) δ 164.3, 149.9, 145.9, 137.6, 135.9, 128.8, 128.3, 128.2, 127.3, 127.1, 124.3, 61.1, 52.8, 39.9, 27.8, 14.2; HRMS (ESI) Calculated for [M+H]^+, C_{20}H_{21}N₂O₆S, \(m/z\) 417.1120, found 417.1112.

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MHz, CDCl$_3$) $\delta$ 7.81 (dd, $J = 8.1$, 1.2 Hz, 2H), 7.56 (t, $J = 7.5$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 2H), 7.29–7.22 (m, 5H), 7.02–7.01 (m, 1H), 5.36 (d, $J = 6.8$ Hz, 1H), 4.51 (d, $J = 18.6$ Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 3.49–3.43 (m, 1H), 2.69–2.49 (m, 2H), 1.28 (t, $J = 7.2$ Hz, 3H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 164.6, 140.3, 138.0, 136.1, 132.7, 129.1, 128.6, 127.9, 127.6, 127.2, 126.9, 60.9, 52.2, 39.6, 27.1, 14.2; HRMS (ESI) Calculated for [M+H]$^+$, C$_{20}$H$_{22}$NO$_4$S, $m/z$ 372.1270, found 372.1265.

![Chemical structure of compound 49c](image)

**Ethyl (R)-6-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (49c):** Yield: 56%; 98% ee; $[\alpha]_D^{20} = -49.0^\circ$ (CHCl$_3$, c = 1.0).

![Chemical structure of compound ent-49c](image)

**Ethyl (S)-6-phenyl-1-tosyl-1,2,5,6-tetrahydropyridine-3-carboxylate (ent-49c):** Yield: 56%; 98% ee; $[\alpha]_D^{20} = +49.0^\circ$ (CHCl$_3$, c = 1.0). This annulation product was synthesized as described in the general [4 + 2] procedure, however **ent-4c** was used as the catalyst.
Ethyl (R)-1-((4-chlorophenyl)sulfonyl)-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (49d): Yield: 67%; 91% ee; $\left[\alpha\right]_{D}^{20} = +1.0^{\circ}$ (CHCl$_3$, c = 1.0); IR (film) 2979, 1706, 1531, 1324 cm$^{-1}$; $^1$H (400 MHz, CDCl$_3$) $\delta$ 7.93 (d, $J = 8.7$ Hz, 2H), 7.63 (d, $J = 8.7$ Hz, 2H), 7.49–7.41 (m, 5H), 7.25–7.23 (m, 1H), 5.56 (d, $J = 6.7$ Hz, 1H), 4.68 (d, $J = 18.5$ Hz, 1H), 4.40 (q, $J = 7.2$ Hz, 2H), 3.70–3.63 (m, 1H), 2.92–2.72 (m, 2H), 1.49 (t, $J = 7.2$ Hz, 3H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 164.5, 139.1, 138.8, 137.9, 136.0, 129.4, 128.7, 128.4, 128.0, 127.4, 127.2, 60.9, 52.4, 39.7, 27.4, 14.2; HRMS (ESI) Calculated for [M+H]$^+$, C$_{20}$H$_{21}$ClNO$_4$S, $m/z$ 406.0880, found 406.0879.

Ethyl (R)-1-((4-bromophenyl)sulfonyl)-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (49e): Yield: 46%; 94% ee; $\left[\alpha\right]_{D}^{20} = +1.4^{\circ}$ (CHCl$_3$, c = 1.0); IR (film) 2978, 1707, 1326 cm$^{-1}$; $^1$H (500 MHz, CDCl$_3$) $\delta$ 8.07 (dd, $J = 8.2$, 1.2 Hz, 1H), 7.71–7.67 (m, 3H), 7.31–7.26 (m, 5H), 7.15–7.14 (m, 1H), 5.42 (d, $J = 6.5$ Hz, 1H), 4.38 (dd, $J = 18.3$, 0.9 Hz, 1H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.60–3.55 (m, 1H), 2.86–2.78 (m, 2H), 1.28 (t, $J = 7.2$ Hz, 3H); $^{13}$C (125 MHz, CDCl$_3$) $\delta$ 159.2, 134.0, 132.6, 130.7, 126.9, 123.4, 123.2, 122.7, 122.3, 122.1, 121.8, 55.6, 47.1, 34.4, 22.1, 8.8; HRMS (ESI) Calculated for [M–H]$^+$, C$_{20}$H$_{19}$BrNO$_4$S, $m/z$ 448.0218, found 448.0220. C$_{20}$H$_{19}$BrNO$_4$S
Ethyl (R)-1-((2-nitrophenyl)sulfonyl)-6-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (49f): Yield: 29%; 97% ee; [α]$_D^{20}$ = −24.4° (CHCl$_3$, c = 1.0); IR (film) 2977, 1709, 1530, 1164 cm$^{-1}$; $^1$H (500 MHz, CDCl$_3$) δ 7.65 and 7.59 (AB system, $J$ = 8.6 Hz, 2H for each), 7.29–7.27 (m, 3H), 7.23–7.22 (m, 2H), 7.05–7.04 (m, 1H), 5.35 (d, $J$ = 6.8 Hz, 1H), 4.47 (d, $J$ = 18.5 Hz, 1H), 4.19 (q, $J$ = 7.2 Hz, 2H), 3.49–3.43 (m, 1H), 2.87–2.52 (m, 2H), 1.29 (t, $J$ = 7.2 Hz, 3H); $^{13}$C (125 MHz, CDCl$_3$) δ 164.5, 137.7, 136.4, 133.7, 133.5, 131.9, 130.9, 128.7, 128.3, 128.1, 127.5, 127.2, 124.5, 60.9, 52.4, 39.7, 27.4, 14.2; HRMS (ESI) Calculated for [M+H]$^+$, C$_{20}$H$_{21}$N$_2$O$_6$S, m/z 417.1120, found 417.1129.

Ethyl (R)-6-(2-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49g): Yield: 81%; 95% ee; [α]$_D^{20}$ = +14.0° (CHCl$_3$, c = 1.0); IR (film) 2986, 1712, 1531, 1164 cm$^{-1}$; $^1$H (500 MHz, CDCl$_3$) δ 8.20 (d, $J$ = 8.8 Hz, 2H), 7.89 (d, $J$ = 8.8 Hz, 2H), 7.22–7.19 (m, 1H), 7.11 (d, $J$ = 2.7 Hz, 1H), 6.94 (dd, $J$ = 1.2, 7.6 Hz, 1H), 6.79 (d, $J$ = 8.2 Hz, 1H), 6.75 (t, $J$ = 7.5 Hz, 1H), 5.75 (d, $J$ = 7.1 Hz, 1H), 4.52 (d, $J$ = 18.0 Hz, 1H), 4.23 (q, $J$ = 7.1 Hz, 2H), 3.69 (s, 3H), 3.68–3.67 (m, 1H), 2.87–2.56 (m, 2H), 1.30 (t, $J$ = 7.1 Hz, 3H); $^{13}$C (125 MHz, CDCl$_3$) δ 164.6, 156.5, 149.7, 146.2, 137.0, 129.5, 128.2, 127.3, 127.0, 126.8, 123.8, 120.3, 110.6,
60.9, 55.2, 47.3, 40.7, 29.5, 14.2; HRMS (ESI) Calculated for [M+H]^+, C_{20}H_{23}N_{2}O_{6}S, m/z
447.1226, found 447.1215.

Ethyl (R)-6-(3-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49h): Yield: 66%; 97% ee; [α]_D^{20} = -18.4° (CHCl₃, c = 1.0); IR (film) 2984, 1708, 1528, 1165 cm⁻¹; ^1H (500 MHz, CDCl₃) δ 8.28 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 7.18 (t, J = 7.9 Hz, 1H), 7.04–7.03 (m, 1H), 6.79–6.75 (m, 2H), 6.71 (br s, 1H), 5.35 (d, J = 6.8 Hz, 1H), 4.51 (d, J = 18.3 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 3.74 (s, 3H), 3.57–3.52 (m, 1H), 2.72–2.56 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^13C (125 MHz, CDCl₃) δ 164.3, 159.8, 149.9, 145.9, 139.2 135.9, 129.8, 128.2, 127.2, 124.3, 119.2, 113.6, 112.9, 61.1, 55.2, 52.7, 40.0, 27.9, 14.2; HRMS (ESI) Calculated for [M+H]^+, C_{20}H_{23}N_{2}O_{6}S, m/z 447.1226, found 447.1233.

Ethyl (R)-6-(4-methoxyphenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49i): Yield: 63%; 96% ee; [α]_D^{20} = -18.4° (CHCl₃, c = 1.0); IR (film) 2984, 1709, 1531, 1349, 1253, 1164 cm⁻¹; ^1H (500 MHz, CDCl₃) δ 8.29 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.9 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.04–7.03 (m, 1H), 6.79 (d, J = 8.6 Hz, 2H), 5.35 (d, J = 6.7 Hz, 1H), 4.48 (d, J = 18.3 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.76 (s, 3H), 3.51–3.45 (m, 1H), 2.69–
2.53 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H); \(^{13}\text{C}\) (125 MHz, CDCl\(_3\)) \(\delta\) 164.4, 159.4, 149.9, 146.1, 136.0, 129.0, 128.4, 128.2, 127.3, 124.3, 114.1, 55.3, 52.3, 39.8, 27.9, 14.2; HRMS (ESI) Calculated for [M–H]\(^+\), C\(_{20}\)H\(_{23}\)N\(_2\)O\(_6\)S, \(m/z\) 445.1069, found 445.1098.

![Ethyl (R)-1-((4-nitrophenyl)sulfonyl)-6-(p-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49j)](image)

**Ethyl (R)-1-((4-nitrophenyl)sulfonyl)-6-(p-tolyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49j):** Yield: 64%; 98% ee; \([\alpha]\)\(_D\)\(^{20}\) = \(-21.2^\circ\) (CHCl\(_3\), c = 1.0); IR (film) 1708, 1530, 1349, 1164 cm\(^{-1}\); \(^1\text{H}\) (500 MHz, CDCl\(_3\)) \(\delta\) 8.29 (d, \(J = 8.9\) Hz, 2H), 7.96 (d, \(J = 8.9\) Hz, 2H), 7.07 (s, 4H), 7.05–7.04 (m, 1H), 5.36 (d, \(J = 6.8\) Hz, 1H), 4.49 (d, \(J = 18.3\) Hz, 1H), 4.20 (q, \(J = 7.2\) Hz, 2H), 3.52–3.47 (m, 1H), 2.71–2.55 (m, 2H), 2.30 (s, 3H), 1.28 (t, \(J = 7.2\) Hz, 3H); \(^{13}\text{C}\) (125 MHz, CDCl\(_3\)) \(\delta\) 164.4, 149.9, 146.1, 138.1, 136.1, 134.5, 129.4, 128.2, 127.3, 127.0, 124.3, 61.0, 52.6, 39.8, 27.8, 21.0, 14.2; HRMS (ESI) Calculated for [M+H]\(^+\), C\(_{21}\)H\(_{23}\)N\(_2\)O\(_6\)S, \(m/z\) 431.1277, found 431.1277.

![Ethyl (R)-6-(2-chlorophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49k)](image)

**Ethyl (R)-6-(2-chlorophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49k):** Yield: 29%; 74% ee; \([\alpha]\)\(_D\)\(^{20}\) = \(+26.8^\circ\) (CHCl\(_3\), c = 1.0); IR (film) 2979, 1710, 1530, 1350, 1262, 1168, 1095 cm\(^{-1}\); \(^1\text{H}\) (500 MHz, CDCl\(_3\)) \(\delta\) 8.20 (d, \(J = 8.8\) Hz, 2H), 7.91 (d, \(J = 8.8\) Hz, 2H), 7.34 (dd, \(J = 8.8, 1.1\)Hz, 1H), 7.19 (dt, \(J = 7.8, 1.5\) Hz, 1H), 7.10–7.07 (m, 1H), 7.06
(dt, J = 7.8, 1.1 Hz, 1H), 6.99 (dd, J = 7.8, 1.4 Hz, 1H), 5.76 (dd, J = 7.2, 1.6 Hz, 1H), 4.49 (d, J = 18.1 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.81 (dd, J = 18.1, 2.8 Hz, 1H), 2.93–2.89 (m, 1H), 2.66–2.61 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H); 13C (125 MHz, CDCl₃) δ 164.3, 149.9, 145.0, 136.5, 136.1, 133.5, 130.2, 129.5, 128.5, 127.6, 127.5, 126.9, 123.9, 61.1, 50.4, 41.2, 29.5, 14.2; HRMS (ESI) Calculated for [M–H]+, C₂₀H₁₈ClN₂O₆S, m/z 449.0574, found 449.0584.

![Ethyl (R)-6-(3-chlorophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49i)](image)

Ethyl (R)-6-(3-chlorophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49i): Yield: 50%; 94% ee; [α]D²⁰ = −30.8° (CHCl₃, c = 1.0); IR (film) 2981, 1712, 1530, 1349, 1165 cm⁻¹; ¹H (500 MHz, CDCl₃) δ 8.32 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.26–7.21 (m, 2H), 7.12–7.11 (m, 2H), 7.04–7.02 (m, 1H), 5.36 (d, J = 6.8 Hz, 1H), 4.53 (d, J = 18.4 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.54–3.49 (m, 1H), 2.72–2.54 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H); ¹³C (125 MHz, CDCl₃) δ 164.2, 150.1, 145.8, 139.5, 135.45 135.4, 134.8, 130.2, 128.5, 128.1, 127.4, 125.2, 124.4, 61.2, 52.3, 40.0, 27.5, 14.2; HRMS (ESI) Calculated for [M+H]+, C₂₀H₂₀ClN₂O₆S, m/z 451.0731, found 451.0721.

![Ethyl (R)-6-(4-chlorophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49m)](image)

Ethyl (R)-6-(4-chlorophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49m): Yield: 53%; 97% ee; [α]D²⁰ = −31.6° (CHCl₃, c = 1.0); IR (film) 2982, 1712, 1530, 1349, 1165 cm⁻¹; ¹H (500 MHz, CDCl₃) δ 8.32 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.26–7.21 (m, 2H), 7.12–7.11 (m, 2H), 7.04–7.02 (m, 1H), 5.36 (d, J = 6.8 Hz, 1H), 4.53 (d, J = 18.4 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.54–3.49 (m, 1H), 2.72–2.54 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H); ¹³C (125 MHz, CDCl₃) δ 164.2, 150.1, 145.8, 139.5, 135.45 135.4, 134.8, 130.2, 128.5, 128.1, 127.4, 125.2, 124.4, 61.2, 52.3, 40.0, 27.5, 14.2; HRMS (ESI) Calculated for [M+H]+, C₂₀H₂₀ClN₂O₆S, m/z 451.0731, found 451.0721.
1531, 1349, 1165, 1099 cm⁻¹; ¹H (500 MHz, CDCl₃) δ 8.32 (d, J = 8.9 Hz, 2H), 7.98 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 7.02–7.01 (m, 1H), 5.38 (d, J = 6.8 Hz, 1H), 4.48 (d, J = 18.6 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.50–3.44 (m, 1H), 2.71–2.65 (m, 1H), 2.56–2.49 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H); ¹³C (125 MHz, CDCl₃) δ 164.2, 150.0, 145.9, 136.0, 135.5, 134.2, 128.9, 128.6, 128.1, 127.4, 124.5, 61.1, 52.1, 39.8, 27.3, 14.1; HRMS (ESI) Calculated for [M–H]⁺, C₂₀H₁₈ClN₂O₆S, m/z 449.0574, found 449.0576.

![Chemical Structure](image)

**Ethyl (R)-6-(4-bromophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49n):** Yield: 51%; 97% ee; [α]D²⁰ = –16.0° (CHCl₃, c = 1.0); IR (film) 2979, 1710, 1531, 1350, 1266, 1165, 1100 cm⁻¹; ¹H (300 MHz, CDCl₃) δ 8.33 (d, J = 9.0 Hz, 2H), 7.99 (d, J = 9.0 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 7.03–7.00 (m, 1H), 5.36 (d, J = 6.5 Hz, 1H), 4.49 (d, J = 18.9 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.52–3.43 (m, 1H), 2.72–2.47 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H); ¹³C (125 MHz, CDCl₃) δ 164.2, 150.1, 145.9, 136.5, 135.4, 132.0, 128.9, 128.1, 127.4, 124.5, 122.4, 61.2, 52.2, 39.8, 27.3, 14.2; HRMS (ESI) Calculated for [M–H]⁺, C₂₀H₁₈BrN₂O₆S, m/z 493.0069, found 493.0069.

![Chemical Structure](image)
Ethyl (R)-6-(4-fluorophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49o): Yield: 64%; 96% ee; \([\alpha]_D^{20} = -42.0^o\) (CHCl₃, c = 1.0); IR (film) 2982, 1711, 1531, 1350, 1266, 1199 cm⁻¹; \(^1\)H (500 MHz, CDCl₃) δ 8.32 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.23 (dd, J = 5.3, 8.6 Hz, 2H), 7.04–7.02 (m, 1H), 7.00 (t, J = 8.6 Hz, 2H), 5.38 (d, J = 6.8 Hz, 1H), 4.48 (d, J = 18.4 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.50–3.46 (m, 1H), 2.70–2.52 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H); \(^{13}\)C (125 MHz, CDCl₃) δ 164.2, 162.4 (d, J_C–F = 246 Hz), 150.0, 146.0, 135.6, 133.3, 129.0, 128.1, 124.7, 115.7, 115.6, 61.2, 52.1, 39.7, 27.5, 14.1; HRMS (ESI) Calculated for [M–H]⁺, C₂₀H₁₈FN₂O₆S, m/z 433.0870, found 433.0862.

![Image of molecule 49o](image)

Ethyl (R)-6-(4-cyanophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49p): Yield: 51%; 90% ee; \([\alpha]_D^{20} = -20.8^o\) (CHCl₃, c = 1.0); IR (film) 2980, 1710, 1531, 1350, 1267, 1165, 1100; \(^1\)H (400 MHz, CDCl₃) δ 8.24 (d, J = 8.8 Hz, 2H), 7.91 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H), 6.91–6.89 (m, 1H), 5.34 (d, J = 6.6 Hz, 1H), 4.38 (d, J = 18.7 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.41–3.35 (m, 1H), 2.66–2.39 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H); \(^{13}\)C (100 MHz, CDCl₃) δ 164.0, 150.2, 145.7, 142.8, 135.0, 132.7, 128.1, 127.9, 127.5, 124.6, 118.2, 112.3, 61.2, 52.3, 39.9, 26.8, 14.1; HRMS (ESI) Calculated for [M–H]⁺, C₂₁H₁₈N₃O₆S, m/z 440.0916, found 440.0926.
**Ethyl (R)-6-(4-nitrophenyl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49q):** Yield: 52%; 96% ee; \([\alpha]_D^{20} = -10.8^\circ\) (CHCl₃, c = 1.0); IR (film) 2983, 1709, 1529, 1349, 1267, 1165, 1099; ¹H (500 MHz, CDCl₃) δ 8.36 (d, J = 8.9 Hz, 2H), 8.20 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.04–7.01 (m, 1H), 5.49 (d, J = 6.7 Hz, 1H), 4.49 (d, J = 18.8 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.52–3.47 (m, 1H), 2.78–2.52 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H); ¹³C (125 MHz, CDCl₃) δ 163.9, 150.2, 147.7, 145.7, 144.6, 134.8, 128.2, 128.1, 127.7, 124.6, 124.1, 61.3, 52.1, 40.0, 26.9, 14.1; HRMS (ESI) Calculated for [M–H]⁺, C₂₀H₁₈N₃O₈S, m/z 460.0815, found 460.0818.

**Ethyl (R)-6-(furan-2-yl)-1-((4-nitrophenyl)sulfonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49r):** Yield: 63%; 93% ee; \([\alpha]_D^{20} = +69.8^\circ\) (CHCl₃, c = 1.0); IR (film) 2984, 1709, 1531, 1350, 1267, 1167, 1101; ¹H (500 MHz, CDCl₃) δ 8.30 (d, J = 8.9 Hz, 2H), 7.99 (d, J = 8.9 Hz, 2H), 7.08 (br d, J = 1.2 Hz, 1H), 7.07–7.04 (m, 1H), 6.17 (dd, J = 1.8, 3.3 Hz, 1H), 6.02 (d, J = 3.3 Hz, 1H), 5.44 (d, J = 7.1 Hz, 1H), 4.49 (d, J = 17.2 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.47–3.42 (m, 1H), 2.88–2.82 (m, 1H), 2.68–2.63 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H); ¹³C (125 MHz, CDCl₃) δ 164.4, 150.9, 149.9, 145.0, 142.2, 135.3, 128.6, 126.8, 124.0, 110.4, 108.1, 61.1, 47.7,
40.5, 29.3, 14.2; HRMS (ESI) Calculated for [M+H]^+, C_{18}H_{19}N_{2}O_{7}S, m/z 407.0913, found 407.0923.

![Structure of compound 49s](image)

**Ethyl (R)-1-((4-nitrophenyl)sulfonyl)-6-(thiophen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (49s):** Yield: 59%; 96% ee; [α]_D^{20} = +13.6° (CHCl₃, c = 1.0); IR (film) 2979, 1709, 1531, 1350, 1267, 1167, 1100; ^1H (500 MHz, CDCl₃) δ 8.28 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H), 7.14 (dd, J = 1.2, 4.9 Hz, 1H), 7.07–7.05 (m, 1H), 6.86–6.83 (m, 2H), 5.65 (d, J = 6.7 Hz, 1H), 4.51 (d, J = 17.8 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.68–3.63 (m, 1H), 2.86–2.82 (m, 1H), 2.70–2.65 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^13C (125 MHz, CDCl₃) δ 164.3, 150.0, 145.2, 140.8, 135.3, 128.4, 127.0, 126.6, 126.3, 125.8, 124.2, 61.1, 49.4, 40.1, 30.9, 14.2; HRMS (ESI) Calculated for [M–H]^+, C_{18}H_{17}N_{2}O_{6}S_{2}, m/z 421.0528, found 421.0557.

**Synthesis of Carvone Derived Catalyst 66**

![Reaction scheme](image)

**(1R,2S,3R,4R)-2-methyl-3-(((methylsulfonyl)oxy)methyl)-4-(prop-1-en-2-yl)cyclopentyl methanesulfonate (73):** To a stirred solution of diol 72 (85 g, 500 mmol) and triethylamine (174 mL, 1250 mmol) in CH₂Cl₂ (1250 mL) at 0 °C was added dropwise a solution of methanesulfonyl
chloride (97 mL, 1250 mmol). After stirring at 0 °C for 30 minutes, the reaction mixture was warmed to room temperature and stirred for 24 hours. The reaction was quenched by the addition of saturated aqueous NaHCO$_3$ solution (400 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 400 mL) and the combined organic portions were washed with brine, dried over Na$_2$SO$_4$, and concentrated by rotary evaporation to provide dimesylate 23 as a viscous liquid (160 g, 98% yield); IR (film) $\nu_{\text{max}}$ 3355, 2930, 2360, 1646 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.07 (t, $J = 3.6$ Hz, 1H), 4.93 (s, 1H), 4.73 (s, 1H), 4.10 (dd, $J = 10.0, 5.2$ Hz, 1H) 3.94 (dd, $J = 10.0, 7.2$ Hz, 1H), 3.10–3.03 (m, 1H) 3.01 (s, 3H), 2.97 (s, 3H), 2.25–2.12 (m, 3H), 2.06–1.79 (m, 1H), 1.79 (s, 3H), 1.17 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 142.5, 112.2, 85.6, 70.4, 44.3, 44.2, 42.1, 38.2, 37.1, 23.4, 14.7, 8.63; LRMS (MALDI) C$_{12}$H$_{22}$O$_6$S$_2$ 326.09, found 326.10.

(15,2R,4R,5R,7S)-2-(4-Methoxyphenyl)-7-methyl-5-(prop-1-en-2-yl)-2-phosphabicyclo[2.2.1]heptane 2-oxide (74): This reaction was carried following the general procedure for the synthesis of phosphine oxides. Compound 74 was isolated as a solid after purification with silica gel (5 to 10% MeOH in EtOAc, $R_f = 0.2$). 58% yield; white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.69 (dd, $J = 8.9, 10.7$ Hz, 2H), 6.99 (dd, $J = 2.1, 8.8$ Hz, 2H), 5.27 (s, 1H), 5.10 (d, $J = 1.4$ Hz, 1H), 3.85 (s, 3H), 2.96–2.84 (m, 1H), 2.72–2.56 (m, 1H), 2.43 (dt, $J = 5.2, 29.6$ Hz, 1H), 2.22–1.96 (m, 4H), 1.83 (t, $J = 13.9$ Hz, 1H), 1.76 (s, 3H), 1.03 (d, $J = 6.9$ Hz); $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ 54.6; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.1 (d, $J_{(\text{C}-\text{P})} = 2.9$ Hz), 142.7,
132.2 1 (d, $J_{C-P} = 10.2$ Hz), 125.5 1 (d, $J_{C-P} = 95.7$ Hz), 114.2 1 (d, $J_{C-P} = 12.1$ Hz), 112.7, 55.3, 45.2, 44.2, 43.0, 42.4 1 (d, $J_{C-P} = 3.4$ Hz), 27.4 1 (d, $J_{C-P} = 61.8$ Hz), 23.9, 20.4 1 (d, $J_{C-P} = 6.8$ Hz), 13.8 1 (d, $J_{C-P} = 16.0$ Hz); LRMS (LCMS, EI+) [M+H]$^+$ $C_{17}H_{23}O_2P$ $m/z$ 291.1, found 291.1.

(1S,2R,4R,5S,7S)-5-Isopropyl-2-(4-methoxyphenyl)-7-methyl-2-phosphabicyclo[2.2.1]heptane 2-oxide (75): Compound 74 was placed in a Erlenmeyer flask and was dissolved in PhH (0.1 M). Next, RhCl(PPh$_3$)$_3$ (10 mol%) was in the dissolved in the PhH solution. The flask was placed in a hydrogen bomb and pressurized to 40 bar with hydrogen. After 2 days, the mixture was concentrated and isolated as a white solid (85%) after FCC using silica gel (5 to 10% MeOH in EtOAc) 

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.67 (tt, $J = 8.6, 2.1$ Hz, 2H), 6.97 (dq, $J = 2.1, 8.7$ Hz, 2H), 3.82 (s, 3H), 2.08–2.01 (m, 6H), 1.89–1.75 (m, 3H), 1.00 (dd, $J = 3.0, 6.4$ Hz, 6H), 0.67 (d, $J = 6.2$ Hz, 3H); $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ 54.3; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 162.1 (d, $J_{C-P} = 2.7$Hz), 132.2 (d, $J_{C-P} = 9.8$ Hz), 125.5 (d, $J_{C-P} = 94.2$ Hz), 114.2 (d, $J_{C-P} = 12.5$ Hz), 55.3, 45.0, 44.7, 43.2 (d, $J_{C-P} = 1.2$ Hz), 42.8 (d, $J_{C-P} = 55.9$ Hz), 27.8 (d, $J_{C-P} = 63.7$ Hz), 22.0 (d, $J_{C-P} = 102$ Hz), 13.6 (d, $J_{C-P} = 16$ Hz), LRMS (LCMS, EI+) [M+H]$^+$ $C_{17}H_{25}O_2P$ $m/z$ 293.1, found 293.1.
(1S,2S,4R,5S,7S)-5-Isopropyl-2-(4-methoxyphenyl)-7-methyl-2-
phosphabicyclo[2.2.1]heptane (66): Compound 66 was synthesized following the general
procedure for reducing Kwon bicyclic phosphine oxides as described above. Compound 66 was
isolated as an off white solid that oxidizes in air. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.25–7.19 (m, 2H),
6.87 (dd, $J = 8.8$, 0.9 Hz, 2H), 3.80 (s, 3H), 2.19–1.98 (m, 4H), 1.74–1.55 (m, 3H), 1.50–1.39 (m,
1H), 1.23–1.07 (m, 1H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.3$ Hz, 3H), 0.86 (d, $J = 6.4$ Hz,
3H); $^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$ –9.9; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 159.9, 131.2 (d, $J_{C-P} =$
15.4 Hz), 114.0, 113.99, 55.1, 445.3, 43.8, 41.2, 41.19, 30.3 (d, $J_{C-P} = 21.0$ Hz), 30.1, 25.0 (d,
$J_{C-P} = 17.0$ Hz), 22.4, 21.7, 13.3; LRMS (LCMS, EI+) [M+H]$^+$ C$_{17}$H$_{23}$OP m/z 277.1, found 277.1.

Synthesis of Aplexone (3)
**Aplexone (66):** The annulation product 49c was placed in a 10 mL round bottom flask. THF was added (0.2 M), and the reaction was stirred at –40 °C for 10 min. Tebbe reagent\(^\text{15}\) in Toluene (~0.7 M; 2 equiv) was added dropwise to the cooled solution. The reaction was allowed to stir for 30 min, then was removed from the cooling bath and stirred for 45 min. The reaction was again cooled to at –40 °C and aqueous NaOH (3 M, 0.5 mL) was added slowly. Upon cessation of gas evolution the reaction was warmed to room temperature and allowed to stir for 1 hr. the reaction was filtered through a plug of silica using EtOAc. The filtrate was concentrated and the residue was dissolved in a HCl solution in acetone (0.1 M) and allowed to stand for 12 hr. The solution was then concentrated and the residue was purified through FCC (SiO\(_2\); EtOAc/Hexane, 15:85) to afford compound 65 upon concentrated to give an oil. The compound can be further purified, with an increase in ee, by recrystallization (EtOAc:Hexane, 1:4).

![Image](image_url) 

(R)-Aplexone (R-65): Yield: 90%; 99% ee; \([\alpha]_D^{20} = -27.0^\circ\) (CHCl\(_3\), c = 0.1);

![Image](image_url) 

(S)-Aplexone (S-65): Yield: 91%; 99% ee; \([\alpha]_D^{20} = +27.0^\circ\) (CHCl\(_3\), c = 0.1)

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**Aplexone Zebrafish Studies**

**Aplexone Treatment:**

Transgenic Tg(kdrl:GFP)la116 zebrafish embryos were treated with aplexone compounds beginning at 10 hours post fertilization (hpf). After two days of development, treated embryos were anesthetized with 0.01% tricaine and imaged using a Zeiss Axioplan 2 microscope.

**Cholesterol Assay:**

Zebrafish embryos used in cholesterol assays were treated with aplexone or atorvastatin from 10 hpf to 30 hpf at a concentration of 40 µM. Yolks were removed by vortexing in calcium-free Ringer’s solution with 1 mM EDTA at 4°C. The embryos were then washed with calcium-free Ringer’s solution, resuspended in cholesterol assay reaction buffer, and lysed by sonication. Cholesterol levels in embryo lysates were measured with an Amplex Red Cholesterol Assay Kit (ThermoFisher Scientific) and FLUOstar Omega microplate reader (BMG Labtech). Protein concentrations of the embryo lysates were measured by DC protein assay (Bio-Rad Laboratories) using a FLUOstar Omega microplate reader.

**ORTEP Representation of Compound (2R)-49n:**

The absolute stereochemistry of tetrahydropyridine 49c was determined by the known compound 49c. The absolute stereochemistry of tetrahydropyridine 49n was determined through X-ray

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7 Crystallographic data for 49n have been deposited with the Cambridge Crystallographic Data Centre as supplementary number CCDC 903385. These data can be obtained online free of charge [or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk].
crystallographic analysis. The absolute stereochemistries of the other compounds produced were assigned by analogy to compound \textit{49c} and \textit{49n}. 
SFC Traces of Annulation Products 49 and Aplexone (65)

![Graph showing SFC traces with peaks and indices.]

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![Graph showing SFC traces with peaks and indices.]

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