ORGANIC SYNTHESIS AND METHODOLOGY RELATED TO THE MALARIA DRUG ARTEMISININ

By

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This manuscript is dedicated to my family and friends who have supported me through out my life.
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ABSTRACT

Malaria is a global epidemic, resulting in the deaths of nearly one million people every year. Part 1 of this dissertation will focus on the history of Malaria and ways to combat this devastating disease. Artemisinin has emerged as the drug of choice for treatment of malaria due to its effectiveness against all strains of the malaria parasite. Access to artemisinin through isolation, bio-engineering, and chemical synthesis will be described. Our attempts to access the artemisinin family of anti-malarials through the total synthesis of dihydro-epi-deoxyarteannuin B and dihydroartemisinic acid will be discussed fully. Key features of the syntheses will include alkylation of menthone derivatives using Noyori’s zincate enolate method and nucleophilic addition to a hindered ketone using either organocerium or acetylide nucleophiles. In addition, two alternative olefin metathesis approaches are described for the final cyclization.

Problems associated with the olefination of a key intermediate in our efforts toward dihydroartemisinic acid led us to develop a two-step olefination of ketones and aldehydes. Part II will discuss this olefination strategy which consists of acetylide addition to generate a propargyl alcohol followed by a Meyer–Schuster rearrangement to the corresponding α,β-enone. A complete history of the Meyer–Schuster rearrangement will be presented, highlighting the short comings of the method prior to our work. A complete overview of our research pertaining to the Meyer–Schuster reaction will be given. Key topics will include development of a Au(III)-catalyzed rearrangement of propargyl ethynyl ethers into α,β-unsaturated esters and its use in the olefination of hindered ketones, efforts to control the (E/Z)-selectivity of the Meyer–Schuster rearrangement, and the search for more affordable catalysts.
Malaria is the most devastating tropical parasitic disease in the world and is ranked in the top three of communicable diseases it terms of deaths.\textsuperscript{1} The size and the scope of the malaria pandemic are astounding with the World Health Organization (WHO) reporting an estimated 247 million cases in 2006. Of those cases, nearly 1 million resulted in death, mostly in children under the age of 5.\textsuperscript{2} It is estimated that a child dies from malaria every 40 seconds, resulting in the loss of thousands of adolescents every day.\textsuperscript{1} Malaria is so deadly that many experts contend it has contributed significantly to the proliferation of the sickle-cell trait. When inherited from both parents the sickle-cell mutation is fatal, yet when inherited from only one parent the trait is protective against malaria. Natural selection would tend to remove the sickle cell trait from the gene pool, but the risk of death from malaria is so severe that the sickle cell trait remains a prominent and needed mutation.\textsuperscript{3,4}

With the staggering number of malaria cases every year, malaria may be perceived as a global problem. In reality, malaria is centered in tropical regions and extends into subtropical regions across five continents putting 3.3 billion people at risk. Currently, 109 countries are considered to have malaria epidemics with nearly half of those countries being located in Africa.\textsuperscript{2} (Figure 1).

Unlike tropical areas, temperate regions possess distinct seasons, and their cold winters are a key element in the fight against malaria. The life cycle of the malaria parasite is highly temperature dependant. In order to become infectious to other individuals, the parasite inside the mosquito must undergo a highly specific life cycle change. The amount of time necessary for this transformation is inversely proportional to the ambient temperature. As
average temperatures decline, the time necessary for the life cycle change approaches the life span of the mosquito, leaving a much smaller window for transmission. At temperatures of 16 °C and below malaria parasite development ceases completely. Seasonal temperatures have the most pronounced affect on malaria, but other climate factors such as humidity and rainfall must also be considered when assessing transmission rates.

The correlation between malaria and poverty may also be responsible for the malaria epidemic in the tropical regions. Areas of the world where malaria is prevalent have lower per-capita gross domestic products (GDP) than areas that are unaffected (Figure 2). From 1965 to 1990, countries with major segments of their populations living in regions at high risk for malarial transmittance had an average growth of per-capita GDP of 1.9 % less than that of countries with little malaria risk.
The correlation between poverty and malaria is undisputable; however, there is debate as to whether malaria causes poverty or poverty results in the proliferation of malaria. Most likely it is a combination of both.\textsuperscript{1,2} Wealthier nations possess the resources to initiate government control programs such as the draining of swamplands and other breeding grounds, along with large scale spraying of pesticides. General urban development including improved housing significantly reduces individuals’ exposure to mosquitoes and the malaria parasite. These factors combined with personal expenditures on bednets and household insecticides led to the elimination of malaria in wealthier nations with temperate climates by the 1950’s. Although economic development and wealth are important factors in controlling malaria, they are not enough by themselves. Wealthy countries with high year-round temperatures still suffer from malaria and are unable to eliminate the disease.\textsuperscript{1} 

Malaria has much broader social and economic impacts than simply causing a lower average growth in GDP in affected countries. Malaria infected regions not only have slower growing economies, but they are also forced to spend a significant amount of their GDP on combating the disease. These costs include personal and private medical costs as well as loss
of income due to illness and death. This financial burden is most severe for people in the lowest income brackets. With most of their disposable income going towards prevention and treatment of malaria there is little money for schooling, migration, or savings resulting in serious social costs. The lack of proper education is a major obstacle in combating not only malaria but also sexually transmitted diseases like HIV. Limited female education and low availability of birth control, combined with high infant mortality rates, have led to high fertility rates. In order to assure a certain number of surviving heirs, couples are forced to have large numbers of children. The net result is large population growth in poor malaria stricken countries, causing a magnification of the problem.8-11

Despite the obstacles facing those areas impacted by malaria, modern medicine has afforded ways to combat this disease. Currently, there are three major classes of anti-malarial drugs—the quinoline family, the artemisinin family, and all other antimalarials12 (Figure 3). The need for so many classes of antimalarial drugs originates from the ability of the malaria parasite to develop drug resistance. The two most widely used antimalarial drugs are chloroquine and the antifolate sulphadoxine/pyrimethamine.

Chloroquine is a member of the quinoline family of antimalaria drugs. The quinoline family of compounds draws their origin from quinine, a centuries old malaria treatment isolated from the bark of Cinchona.13 While quinine has excellent antimalarial activity, it requires multiple doses per day over 7 days. This long treatment schedule has led to problems associated with toxicity. Structural elucidation of quinine and medicinal chemistry studies led to derivatives including chloroquine and amodiaquine, which only have to be administered over 3 days, reducing the chances of a toxic build-up in the body.13 This short treatment period, combined with the malaria parasite’s low propensity to develop resistance to it, have made chloroquine the drug of choice for many years.14
While there are four different species of the malaria parasite, \( \textit{Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, and Plasmodium falciparum} \) \( \textit{Plasmodium falciparum} \) is the strain that is responsible for severe malaria that results in death.\(^{15}\) \( \textit{Plasmodium falciparum} \)'s life cycle within the human body consists of several distinct phases. Initially, the parasite takes up residence in hepatocytes, where it quickly develops and causes the release of merozoites. The newly released merozoites then invade erythrocytes. Once inside the erythrocytes the malaria parasite goes through a series of evolutions resulting in the eventual release of more merozoites, which then infect more cells (Figure 4).\(^{15}\)

Malaria symptoms manifest during the phase of the \( \textit{Plasmodium} \)'s life cycle in which it inhabits the erythrocyte. The parasites' survival at this stage is dependent on modifications to the cells metabolic processes. These modifications, while ensuring the parasites' survival, also allow for drugs to differentiate between infected cells and healthy cells. This makes them
susceptible to chemotherapeutic attack. While *Plasmodium* is present in the host erythrocyte, it degrades up to 80% of the hemoglobin present.\textsuperscript{16} As a result, large amounts of Fe(II) heme are released and are subsequently oxidized to Fe(III) hematin. The hematin then aggregates to form a pigment called hemozoin.\textsuperscript{16} Chloroquine’s activity is believed to lie in its ability to prevent hemozoin formation by binding with heme through $\pi-\pi$ stacking of their planar aromatic structures.\textsuperscript{17} These chloroquine-heme complexes are toxic to the parasite, though the exact source of their toxicity is under debate (Figure 5).\textsuperscript{18-19}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{\textit{Plasmodium falciparum} Cycle Within Humans
Heptaocytes: a cell of the main tissue of the liver
Erythrocytes: red blood cells
Merozoites: a daughter cell of a protozoan parasite}
\end{figure}
While the ability of the malaria parasite to develop resistance to chloroquine is quite low, widespread usage over a long time period has resulted in increased resistance in many areas of the world. The recent globalization of chloroquine resistant malaria parasites has brought to the forefront the need for alternative treatments (Figure 6). Other drugs from the quinoline family can be substituted for chloroquine in many cases, but due to their similar structure and biological activity, resistance to these drugs tends to develop rapidly.\(^{14}\)

Since their isolation in the early 1970’s, the artemisinin family of antimalarials have seen unprecedented growth in their frequency of use.\(^{2,20,21}\) This rapid switch from the commonly used quinolines to the artemisins is due to the aretemisinins’ remarkable ability to combat quinoline resistant strains of the malaria parasite. To date, there have been no examples of any strain of the malaria parasite showing resistance to the artemisinin family of drugs.\(^{2,22}\)
Their high level of activity against all strains of the malaria parasite is attributed to their mode of action. Like the quinoline family of drugs, the artemisinin family of drugs are believed to derive their activity through interaction with Fe(II) heme, but by a drastically different pathway, related to the unique endoperoxide bridge of the artemisinins (Figure 7).

Figure 7: The Structure of Artemisinin and its Derivatives

9a R = H, Dihydroartemisinin
9b R = Me, Artemether
9c R = Et, Arteether
10 R = CO(CH2)2COONa, Artesunate
It is generally accepted that the endoperoxide bridge is the source of artemisinin’s activity. Derivatives lacking the peroxide bridge (deoxyartemisinin) have shown no activity against the malaria parasite.\textsuperscript{23} There is believed to be an interaction between the peroxidic bond in artemisinin and the Fe(II) heme generated from the parasites degradation of hemoglobin within the erythrocyte. The result is cleavage of the peroxide bridge yielding carbon-centered free radicals\textsuperscript{15} (Figure 8).

Figure 8\textsuperscript{15}. General Reactivity of Artemisinin After Reductive Activation of the Endoperoxide Function
The free radicals rapidly react, causing destruction of anything in the immediate proximity. The artemisinins can also target the malaria parasite in stages of its life cycle outside of the erythrocyte through other mechanisms.\textsuperscript{15} In addition, the artemisinins pose little threat to uninfected cells. Micromolar concentrations are necessary to induce toxicity to mammalian cells, while only nanomolar concentrations are required to kill the malaria parasite. These low dosage requirements have resulted in very few instances of negative side-effects from treatment.\textsuperscript{24} The only shortcoming of the artemisinin family of drugs is their relatively short half-lives in the body, on the order of 2-3 hours.\textsuperscript{25} For this reason, they are usually administered in combination with other antimalarial drugs that have longer half-lifes. The World Health Organization (WHO) now suggests artemisinin combinational therapy as the first-choice to treat malaria.\textsuperscript{2}

In summary, malaria is a global epidemic resulting in nearly 1 million deaths every year.\textsuperscript{2} Efforts to combat this devastating disease such as government control programs and distribution of bednets have done little to stop its spread. With advances in modern medicine, treatment of malaria through drug therapy is now a reality. The malaria parasite shows resistance to many of the original quinoline family of antimalarial drugs, but it has yet to show resistance to artemisinin and its derivatives. The outstanding biological properties of artemisinin have made it an important target for both isolation and synthetic chemists.
Artemisinin 1, a unique sesquiterpene lactone endoperoxide, is an efficient and universal antimalarial drug. It is also the precursor to a larger family of more potent antimalarials that are derivatized at C(10), which includes artemether 9, artesunate 10, artemisone, and many others (Figure 9). This class of drugs has received considerable attention due to their effectiveness against all strains of the malaria parasite. Amazingly, despite the fact that artemisinin-based combinational and monotherapies have been in use for over a decade, there have been no reported cases of the malaria parasite showing resistance in humans. As a result, the demand for artemisinin has increased significantly.

Figure 9: Artemisinin and Related Compounds
Artemisinin is isolated from the leaves of *Artemisia annua*, a leafy plant native to China and Vietnam commonly referred to as sweet wormwood (Figure 10). The Chinese have used cold teas made from the leaves of *A. annua* to treat malaria and other ailments since as early as the 2nd century B.C.\(^2^9\) In spite of its widespread use, it was not until 1972 during a comprehensive investigation into Chinese herbal medicine ordered by Chairman Mao Tse-Tsung that artemisinin was isolated and identified as the active ingredient.\(^2^3\) It took another seven years before the structure was finally elucidated.\(^3^0\) Today, the three main sources of artemisinin are direct isolation from the leaves of *Artemisia annua*, bioengineering, and chemical synthesis.

![Figure 10: Artemisinin is a Natural Product Extracted from Artemisia annua or Sweet Wormwood (Qinghao). cmbi.bjmu.edu.cn/.../200382031.jpg](http://cmbi.bjmu.edu.cn/.../200382031.jpg)

Direct isolation from the plant is the main source of artemisinin. Artemisinin content in the plant ranges from 0.01 to 1.4 wt % based on dry leaf mass, depending on which species of *A. annua* is being examined.\(^3^1\) An estimated 120 million courses of artemisinin-based combinational therapies are needed every year to combat the malaria epidemic.\(^2\) An average
course of treatment comprises 20 tablets, each contain 20 mg of artemether, which is obtained from artemisinin in a 60\% chemical yield.\textsuperscript{28} This information, combined with the average amount of leaf harvested per acre in a given season, predicts that 35,000 acres of \textit{A. annua} plantations are needed to meet the global need.\textsuperscript{31} On a global scale this is a relatively small portion of land. However, these calculations assume an isolation efficiency of 100\%, which is far from the actual isolation efficiency of 60\%.

The largest processing centers for the extraction of artemisinin from \textit{Artemisia annua} are located in China and Vietnam. A mixture of hexanes and petroleum ether is used to extract artemisinin from the leaves of the plant. The advantages are the simplicity of the process and the low capital cost necessary for start up and maintenance. The disadvantage is that this technique is very hazardous to both the workers and the environment. These highly flammable solvents have low vapor pressure, and the generation of explosive hydrocarbon/oxygen mixtures is problematic. Emission of greenhouse gases, smog generation, and the entrapment of hexanes in the resulting biomass, which is commonly used as animal feed, also detract from this method. In an attempt to make the extraction process more efficient and environmentally friendly, other extraction techniques have been developed. These techniques have not yet been fully investigated and have not made it beyond laboratory scale. Even with the advances in isolation techniques, the viability of using only cultured \textit{A. annua} as the source for artemisinin remains cost prohibitive.\textsuperscript{35}

An alternative to agricultural drug production, which has long production cycles and is highly dependent on weather and climate, is biosynthesis. Biosynthesis is the process in which chemical compounds are created from simpler starting materials with-in a living organism. Biosynthesis has the advantages of being easier to scale, requiring less space, and being more efficient in terms of product produced per kg of starting material.\textsuperscript{36} All of these factors point to the possibility of using biosynthesis to create an affordable source of artemisinin. Unfortunately, the direct bioconversion of simple starting materials to artemisinin has yet to be achieved.\textsuperscript{37} Most efforts aim at the bioconversion of simple chemicals into artemisinic acid, another constituent of \textit{A. annua}, which can then be transformed chemically to artemisinin.\textsuperscript{38} The biosynthesis of artemisinic acid can be achieved by the use of engineered yeast\textsuperscript{36,39} or through enzyme manipulation of other heterologous hosts.\textsuperscript{40,41}
The most efficient yeast developed for the production of artemisinic acid is *Saccharomyces cerevisiae*. The yeast was engineered by Keasling and co-workers to perform three key transformations. The first was the conversion of simple sugars into farnesyl pyrophosphate (FPP) using a modified biosynthetic pathway. This new pathway produced higher yields of the desired FPP as compared to the naturally occurring, unmodified pathway. The second step was the conversion of farnesyl pyrophosphate into amorphadiene. To achieve this transformation the amorphadiene synthase gene (ADS) from *A. annua* was isolated and then expressed into the high FPP producer. The third step involved cloning of a new cytochrome P450 which could carry out a three-step oxidation of amorphadiene into artemisinic acid (Figure 11).

The transgenic yeast produced artemisinic acid at an efficiency of 100 mg/L. To help gauge that number, one needs to look at the natural source of artemisinic acid. Artemisinic acid can be isolated in 1.9 % relative to the biomass of *A. annua* compared with 4.5 % from the yeast. The yeast is therefore capable of a productivity that is over two times greater than the plant. In addition, the yeast can produce artemisinic acid in 4–5 days compared to several months for *A. annua*. The efficiency of the process can be greatly improved by moving from laboratory to industrial scale. The use of bioreactors with the same yeast resulted in a 25-fold improvement from 100 mg/L to 2.5 g/L isolated yield.

There has also been interest in the bioconversion of arteannuin B (refer to Figure 9) to artemisinin. Arteannuin B can also be isolated from *Artemisia annua*. It occurs at a relative abundance of three times that of artemisinin. In addition, there are several synthetic routes to arteannuin B. Unfortunately, all attempts to convert arteannuin B to artemisinin through enzymatic or microbial transformations have failed. An enzyme involved in the bioconversion of arteannuin B to artemisinin in *A. annua* has been isolated and purified, but all attempts to express it into a heterologous host have been unsuccessful. The only success has been the in vitro bioconversion of arteannuin B to artemisinin by incubation with an extract from *A. annua* L.
Figure 11: Schematic Representation of the Engineered Artemisinic Acid Biosynthetic Pathway in *S. cerevisiae*
In addition to extraction and bioengineering efforts, access to artemisinin through total synthesis is being explored. The reported syntheses all use similar end game strategies, either employing a singlet oxygen/acid rearrangement of ketone 12 or an ozone/acid rearrangement of vinyl silane 13 to install the endoperoxide functionality (Figure 12).

Figure 12: Early Approaches Toward Artemisinin, Path A was Explored by Hofheinz and Later Modified by Yadav, Path B was Explored by Avery

Where the syntheses differ is in their construction of precursors 12 and 13. The first reported total synthesis was completed by Schmid and Hofheinz. The synthesis begins with commercially available (−)-isopulegol 14, which is converted into ketone 15 through a protection/hydroboration/oxidation sequence in 58 % yield over 5 steps. Ketone 15 was then alkylated with the Stork–Jung vinylsilane giving intermediate 17 as a 6:1 mixture of diastereomers in 62 % yield (Figure 13). For a full discussion on the Stork–Jung vinylsilane refer to chapter 3.
A large excess of lithium methoxy(trimethylsilyl)methylide was added to 17, giving alcohol 18 as a 8:1 mixture of diastereomers. Lactonization followed by unmasking of the ketone from the vinylsilane gave bicyclic intermediate 19. Subsequent desilylation triggered enol ether formation and ring opening to give artemisinin precursor 20. Treatment of 20 with molecular oxygen, methylene blue and hv followed by addition of formic acid gave artemisinin 1 in 30% yield (Figure 14).

Figure 13: Construction of the Schmid and Hofheinz Singlet Oxygen Precursor 17

Figure 14: Schmid and Hofheinz End Game Strategy
The next three total syntheses of artemisinin completed by the Avery, Zhou, and Yadav labs all used similar alkylation strategies to obtain their singlet oxygen or ozone rearrangement precursors. The only exception was a formal synthesis completed by Ravindranathan and co-workers, in which an intra-molecular Diels–Alder reaction was employed to give access to the singlet oxygen precursor.

The discovery by Roth and Action in 1989 that dihydroartemisinic acid could be converted directly to artemisinin through exposure to singlet oxygen instantly made dihydroartemisinic acid an important synthetic target (Figure 15). The first group to take advantage of this new access point to artemisinin was the Liu lab, though other groups soon followed. Immediately recognizing the great potential for accessing artemisinin through dihydroartemisinic acid, we also began developing a short and efficient route to dihydroartemisinic acid. Our first proposed pathway to dihydroartemisinic acid will be discussed in chapter 3.

Figure 15: First Example of Dihydroartemisinic Acid Being Converted into Artemisinin

In addition to accessing artemisinin through artemisinic acid, we also hypothesized that it may be possible to convert (+)-dihydro-epi-deoxyarteannuin B into artemisinin through a dyotropic ozonide rearrangement (Figure 16). Generation of the ozonide followed by treatment with a Lewis acid should cause the lactone to open giving intermediate. A 1,2-shift of the ozonide bridge followed by ring closure would generate artemisinin.
With our end game strategies in place, we turned our attention to the synthesis of both artemisinic acid 21 and (+)-dihydro-epi-deoxyarteannuin B 22. Chemical synthesis of these two molecules would allow us to test our proposed ozonide rearrangement and would also provide general contributions to artemisinin research as a whole.
CHAPTER 3
SYNTHESIS OF (+)-DIHYDRO-EPI-DEOXYARTEANNUIN B AND
(-)-DIHYDROARTEMISINIC ACID

(+)-Dihydro-epi-deoxyarteannuin B 22, which also occurs naturally in Artemisia annua, is a key intermediate in our long term efforts to develop an efficient synthetic route to artemisinin 1. Both artemisinin and 22 derive their origins from dihydroartemisinic acid 21, another extract from A. annua, through a nonenzymatic autooxidation process (Figure 17). Both 21 and 22 have also been converted chemically into semisynthetic 1.

The common feature in both 21 and 22 is the decalin ring system. An efficient way to establish the decalin ring system is therefore paramount in developing an economical approach to artemisinin 1. Several groups have approached the decalin ring system through the Diels–Alder reaction. The Ravindranathan and Meinwald labs both used intramolecular Diels–Alder reactions to establish the decalin system (Figure 18).
Ravindranathan and co-workers further elaborated 27 to complete a formal synthesis of artemisinin 1. However, due to the low yield and poor selectivity in their key Diels–Alder step the overall efficiency of the synthesis was quite low.\(^{50}\)

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![Chemical Reaction Diagram](image)

Figure 18: Eq (1) Ravindranathan Intramolecular Diels-Alder,\(^{50}\) Eq (2) Meinwald Intramolecular Diels-Alder\(^{65}\)

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Avery and co-workers chose to use an aldol cyclization of ketone 30 to generate bicyclic enone 31 in their pursuit of artemisinin derivatives.\(^{67}\) The aldol condensation proved to be much more difficult than the authors had envisioned. Under normal aldol conditions they saw significant epimerization of the propanol side chain. They were able to combat the epimerization by incorporation of \(L\)-proline into the reaction mixture, but yields were still quite low (Figure 19).\(^{67}\)

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![Chemical Reaction Diagram](image)

Figure 19: Avery and Co-Workers’ Strategy to Avoid Epimerization
In the course of their investigation into electroreductive cyclizations,\textsuperscript{68} Schwaebe and Little investigated the electroreductive cyclization of epoxy ketone \textit{32} to give bicycle \textit{33}.\textsuperscript{69} The reaction proceeded in high yield, but there was no control of stereochemistry (Eq 4, Figure 20). Dreiding and co-workers experienced a similar problem in their Zn-Cu cyclization of ketone \textit{36}. Dreiding was able to access the tricyclic core of artemisinic acid in a single operation. Unfortunately, none of the stereoisomers obtained were consistent with naturally occurring artemisinic acid (Eq 6, Figure 20).\textsuperscript{70} Schwaebe and Little were later able to overcome the selectivity problem by using samarium iodide (Eq 5, Figure 20).\textsuperscript{69}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure20.png}
\caption{Electrocyclic Strategies to the Decalin Ring System}
\end{figure}

Other methods employed to access the arteannuin ring system include an anodic coupling reaction developed by Wu and Moeller\textsuperscript{71} (Eq 7, Figure 21) and a tandem oxy-Cope/ene reaction developed by Barriault and Deon\textsuperscript{72} (Eq 8, Figure 21). While the anodic coupling reaction has the advantage of providing direct access to the tricyclic core of the arteannuins in a single step, preparation of \textit{38}, the coupling precursor, is cumbersome.\textsuperscript{71} The
tandem oxy-Cope/ene reaction, on the other hand, proceeds with excellent diastereoselectivity and builds complexity quickly. With this as their key step, Barriault and Deon were able to complete the total synthesis of (+)-arteannuin M 42 in ten steps with an overall yield of 14.1%.  

![Figure 21: Other Approaches Towards the Decalin Rings System](image)

In our retro synthetic analysis of dihydro-\textit{epi}-deoxyarteannuin B 22, we planned on constructing the decalin ring system through a ring closing metathesis of diene 45. Diene 45 would be constructed from ketone 44 by olefination followed by oxidation of the primary alcohol to trigger lactonization. Ketone 44 was envisioned to be prepared from silyloxy menthone 43 by alkylation with a methyl vinyl ketone equivalent followed by vinyl Grignard addition. The starting material for our synthesis was isopulegol 14 (Figure 22).
For the conversion of isopulegol 14 to ketone 43, we planned to modify a known literature procedure and expected few problems.\(^\text{67}\) Our first anticipated challenge was the alkylation of ketone 43. We needed to prepare a Michael adduct between methyl vinyl ketone (MVK) and an unstabilized cyclohexanone enolate. Unfortunately, methyl vinyl ketone is a poor electrophile for this transformation due to competing polymerization. To circumvent the competing polymerization, a number of MVK equivalents\(^\text{73,74}\) have been developed for carrying out this transformation. The Stork–Jung vinylsilane\(^\text{54}\) 16 was identified as the MVK equivalent that best met our needs (Figure 23). The weakness of the Stork–Jung vinylsilane 16 is its lengthy preparation.\(^\text{75-80}\) Therefore, we needed to develop a short and efficient route to prepare 16 on large scale.

Figure 22: Our Retro-Synthetic Analysis

Figure 23: The Stork–Jung Vinylsilane
The original synthesis of 16 by Stork and Jung can be seen in Figure 24.\textsuperscript{75} The synthesis begins with propargyl alcohol \textbf{46}, which is converted to the trimethylsilyl acetylene \textbf{47} before regioselective reduction of the triple bond using lithium aluminum hydride. Subsequent iodination gave the (Z)-iodo silane \textbf{48} exclusively. Organocuprate addition followed by a two-step conversion of the primary alcohol to the iodide finished the synthesis. While several slightly modified procedures have been developed,\textsuperscript{76-80} the Stork–Jung method remains the most commonly used procedure.

There are a couple notable modifications of the original Stork–Jung procedure.\textsuperscript{75} The first is a method developed by Zweifel and Lewis that allowed for the preparation of the (E)-iodo silane \textbf{52} by use of iso-butylaluminum hydride instead of lithium aluminum hydride as the reducing agent.\textsuperscript{80} Second, Sato and co-workers showed that (E)-iodo-alcohols \textbf{54} could be prepared through a titanium-catalyzed hydromagnesiation of propargyl alcohol \textbf{53} followed by trapping with iodine (Figure 25).\textsuperscript{76,77}

\begin{center}
\includegraphics[width=\textwidth]{synthesis.png}
\end{center}

\textbf{Figure 24: The Original Synthesis of the Stork–Jung Vinylsilane}\textsuperscript{75} 16
Our lab envisioned constructing the Stork–Jung vinyl silane 16 by the use of a titanium-catalyzed hydromagnesiation of 2-butynol 55 followed by trapping with trimethylsilyl chloride, based on Sato’s protocol. The optimized conditions can be seen in Figure 26. It was found that 2.3 equivalents of i-BuMgCl and 5 mol% of Cp₂TiCl₂ in diethyl ether at 60 °C gave the cleanest reaction and the highest yield. Trapping with trimethylsilyl chloride could be done with or without the toxic hexamethylphosphoramide (HMPA) additive, however yields decrease by 10-15% without it. Subsequent conversion of the vinyl alcohol to the vinyl iodide by triphenylphosphine and N-iodosuccinimide gave us a convenient two-step protocol for the generation of the Stork–Jung vinylsilane 16.

Figure 26: Dudley Lab Succint Method for Preparation of Stork–Jung Vinilsilane 16
With a short and efficient way to prepare the Stork–Jung vinylsilane 16, we turned our attention to the preparation of the second alkylation partner, ketone 43. The synthesis begins with the hydroboration of isopulegol 14. The first concern was the large price difference between crude ($55 for 1 L, Aldrich) and pure isopulegol ($32 for 1 mL, Aldrich). The diastereoselective hydroboration of refined isopulegol was known to provide a crystalline diol 56. This led us to develop a recrystallization procedure which allowed us to start from bulk isopulegol which is over 500 times cheaper than the pure form (Figure 27).

Monoprotection of the primary alcohol of 56 with triisopropylsilyl chloride (TIPSCI) followed by Swern oxidation gave us silyloxymenthone 43 (Figure 28).

Figure 27: Hydroboration of Bulk Isopulegol vs. Pure Isopulegol

Figure 28: Conversion of Diol 56 to Ketone 43
Coupling of silyloxymenthone 43 with the Stork–Jung vinylsilane 16 proved to be more difficult than we had anticipated (Table 1). Initial attempts at alkylation of 43 (Z = OTIPS) under standard conditions yielded 59 in a modest 45% yield (Table 1, Entry 6). Similar alkylations of menthone (58, Z = H) also proved problematic (Table 1, Entries 1 and 3).84-86

Table 1. Allylation of Menthone and Silyloxymenthone 43

<table>
<thead>
<tr>
<th>Entry</th>
<th>Z</th>
<th>Substrate</th>
<th>R–X</th>
<th>Additive(s)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>58</td>
<td>allyl bromide</td>
<td>none</td>
<td>60</td>
<td>1742</td>
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<tr>
<td>2</td>
<td>OBn</td>
<td>15 16</td>
<td>none</td>
<td></td>
<td>61</td>
<td>5346</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>58</td>
<td>allyl iodide</td>
<td>HMPA</td>
<td>60</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>58</td>
<td>allyl iodide</td>
<td>HMPA, Et2Zn</td>
<td>60</td>
<td>~80a</td>
</tr>
<tr>
<td>5</td>
<td>OTIPS</td>
<td>43</td>
<td>allyl iodide</td>
<td>HMPA, Et2Zn</td>
<td>62</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>OTIPS</td>
<td>43</td>
<td>16</td>
<td>HMPA</td>
<td>59</td>
<td>45</td>
</tr>
<tr>
<td>7</td>
<td>OTIPS</td>
<td>43</td>
<td>16</td>
<td>HMPA, Et2Zn</td>
<td>59</td>
<td>89</td>
</tr>
</tbody>
</table>

a Estimated by 1H NMR spectroscopy.
We believe the problem lies in the conformation of enolate C. A_1,2 strain forces the enolate C to adopt a conformation in which the adjoining alkyl substituents must adopt a pseudoaxial orientation, blocking both the top and bottom faces (Table 1). The use of diethylzinc as an additive according to Noyori’s protocol provided for substantial improvements (Table 1, cf. Entries 3 and 4; 6 and 7). Optimal conditions were determined to be 1.0 equivalents of ketone 43 plus 1.1 equivalents lithium diisopropylamide, 1.0 equivalents of hexamethyldiphosphoramide (HMPA), 1.0 equivalents of diethylzinc, and 1.5 equivalents of the Stork–Jung vinylsilane 16 from −78 °C to room temperature for eight hours giving ketone 59 in 89% yield.

Addition of vinyl Grignard to the sterically congested ketone 59 failed to give the desired tertiary alcohol. Fortunately, the use of the organocerium reagent made from freshly prepared vinylmagnesium bromide and freshly activated CeCl_3 cleanly added to give the desired alcohol 63 in up to 91% yield. An additional three-step procedure beginning with the addition of lithium trimethylsilylacetylide, followed by deprotection and reduction also afforded 63 in a 85% percent overall yield. The three step process avoids the need for the careful preparation of the organocerium reagent and can be performed in a shorter amount of time with less technical difficulty (Figure 29).

![Figure 29: Vinyl Addition to Silyloxymenthone 59](image)

Removal of the silyl ether under acidic conditions followed by oxidation of the resulting diol yielded lactone 64 in excellent yield. The vinylsilane was then selectively epoxidized over
the terminal olefin with m-CPBA, presumably due to the shielding effect of the lactone. Subsequent treatment of epoxide 65 with trifluoroacetic acid resulted in formation of ketone 66. Waiting until this point in the synthesis to unmask the ketone allowed us to avoid the need for lengthy protecting group strategies. Wittig methylenation\(^9\) of ketone 66 proceeded with moderate yield; however, the most disappointing development was that all attempts at effecting a ring-closing metathesis (RCM)\(^9\) reaction on the resulting diene 45 failed (Figure 30).

![Figure 30: Elaboration to First Metathesis Precursor 63-22](image)

The failed ring-closing metathesis may be attributed to steric congestion around the vinyl substituent. In addition to steric congestion, the spiro-tricyclic product 22 may be significantly more strained than the diene precursor 45 prohibiting cyclization. Reductive opening of the lactone with lithium aluminum hydride did allow for the ring-closing metathesis to proceed in low yield. Subsequent tetrapropylammonium perruthenate (TPAP) oxidation successfully yielded (+)-dihydro-epi-deoxyarteannuin B 22 (Figure 31). The lower yield associated with the final lactonization step compared with the earlier lactonization step (63 to 64) lends credence to our hypothesis that the failed RCM is partially due to mild strain associated with the spiro-lactonization step. Cross metathesis by-products resulting from the
ruthenium catalyst reacting with the mono-substituted alkene but then failing to cyclize led us to consider the possibility of using Hoye’s relay ring closing metathesis (RRCM) strategy to force the catalyst onto the disubstituted olefin. Olefination of ketone 66 with phosphonium salt 68 (prepared from 5-hexen-1-ol in two steps) provided the desired RRCM substrate 69, albeit in modest yield. Despite the moderate yield in the olefination step, vast improvements were seen in the subsequent relay ring closing metathesis step (Figure 31).

In summary, we have successfully completed the total synthesis of (+)-dihydro-epideoxyarteannuin B 22 from bulk isopulegol 14. We were able to develop an efficient alkylation strategy based on Noyori’s protocol that allowed us to alkylate menthone derivatives in high yield. These alkylated derivatives can serve as valuable building blocks in the synthesis of a variety of artemisinin related compounds. Two solutions were developed to overcome the initial failure of the late stage ring closing metathesis. These studies will provide
valuable information for our future research into the chemical synthesis of members of the artemisinin family of antimalarial compounds.

Upon successful completion of (+)-dihydro-epi-deoxyarteannuin B, our next course of action was to approach artemisinin through the known oxidation of dihydroartemisinic acid 21. Prior approaches to the decalin ring system of dihydroartemisinic acid 21 were discussed previously in our discussion of (+)-dihydro-epi-deoxyarteannuin B 22.

Our proposed synthesis of dihydroartemisinic acid 21 can be seen in Figure 32. We planned to begin with the same silyloxymenthone derivative 43 that we had prepared previously for our synthesis of (+)-dihydro-epi-deoxyarteannuin B 22. Alkylation with allyl iodide followed by olefination would give us α,β-unsaturated ester 70. We then wanted to complete a one pot methylation and ring-closing metathesis based on Rainier’s work with the Takai reagent. Hydrolysis of the silyl ether followed by an acidic oxidation was intended to give a mixture of carboxylic acids 72 and 21. Carboxylic acid 21 can then be oxidized to artemisinin using singlet oxygen.

Figure 32: Proposed Synthesis of Dihydroartemisinic Acid 21

With the alkylation conditions for the conversion of 43 to 62 having been worked out previously we immediately began investigations into the olefination of ketone 62. We first
looked at the olefination of a model system 60, which lacked the triisopropylsilyl moiety. Ketone 60 could be made from (−)-menthone 58 by alkylation with allyl iodide (Figure 33). To our surprise, the Horner–Wadsworth–Emmons (HWE) olefination failed to give any of the desired product. Believing that the steric hindrance of the ketone may be to blame for the lack of reactivity, we next examined the HWE olefination of (−)-menthone 58. Again the HWE olefination provided no reaction (Figure 33). A search of the literature yielded no examples of menthone or similar derivatives being olefinated by the use of stabilized Wittig or HWE reagents.

![Figure 33: Olefination Attempts on Menthone and Menthone Derivatives](image)

The neighboring alkyl groups of these ketones (58 and 60) screen against nucleophilic attack. Thus, we found ourselves in need of an efficient way to olefinate hindered ketones. This led us to develop an alternative olefination strategy sequence, which began with acetylide addition followed by Meyer–Schuster rearrangement—a formal 1,3 hydroxy shift of a propargyl alcohol to the corresponding enone (Figure 34).116-117

Acetylide additions are relatively insensitive to steric congestion, and it was believed that acetylide addition to ketone 60 should proceed smoothly (Figure 34). Rearrangement of
the resulting propargyl alcohol to the α,β-unsaturated enone via the Meyer–Schuster rearrangement would complete our desired olefination. Unfortunately, the traditional Meyer–Schuster reaction is limited in scope and often requires harsh reaction conditions. We therefore need to develop mild and general reaction conditions to effect this transformation.

Figure 34: Proposed Olefination Strategy

In summary, we designed a concise route to dihydroartemisinic acid 21. In order to test the feasibility of this route, we first have to develop a method for the olefination of hindered ketones. We proposed a two-step olefination consisting of acetylide addition followed by Meyer–Schuster rearrangement. The scope of the original Meyer–Schuster rearrangement is limited due to harsh reaction conditions. Our efforts into developing mild reaction conditions for this powerful transformation will be discussed fully in Part II.

Addendum:

We have successfully implemented the two-step olefination strategy outlined above. Ethoxyacetylene cleanly added to ketone 60 with the use of n-BuLi in THF to give propargyl alcohol 73. Treatment of propargyl alcohol 73 with 5 mol % AuCl₃ and 5.0 equivalents of ethanol in methylenechloride at room temperature gave what appears to be the desired α,β-
unsaturated ester 74 (Figure 35). These are preliminary results and are based on analysis of only the $^1$H NMR (spectra immediately follow). However, these initial findings support the feasibility of the approach.

![Chemical Diagram](image)

**Figure 35: Implementation of Our Olefination Strategy Towards Dihydroartemisinic Acid 21**
GENERAL EXPERIMENTAL PROCEDURES:

$^1$H NMR and $^{13}$C NMR spectra were recorded on a 300 MHz spectrometer using CDCl$_3$ as the deuterated solvent. The chemical shifts ($\delta$) are reported in parts per million (ppm) relative to the residual CHCl$_3$ peak (7.26 ppm for $^1$H NMR and 77.0 ppm for $^{13}$C NMR for all compounds except for 22, which was referenced to 7.27 ppm for $^1$H NMR and 77.2 ppm for $^{13}$C NMR). The coupling constants ($J$) are reported in Hertz (Hz). IR spectra were recorded on an FTIR spectrometer on NaCl discs. Mass spectra were recorded using chemical ionization (CI), electron ionization (EI), fast atom bombardment (FAB), or electrospray ionization (ESI). Yields refer to isolated material judged to be $\geq 95\%$ pure by $^1$H NMR spectroscopy following silica gel chromatography. All chemical were used as received unless otherwise stated. Tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were purified by passing through a column of activated alumina. The $n$-BuLi solutions were titrated against a known amount menthol dissolved in tetrahydrofuran using 1,10-phenanthroline as the indicator. The purifications were performed by flash chromatography using silica gel F-254 (230-499 mesh particle size). HMPA was distilled under reduced pressure over CaH$_2$, and stored under an inert atmosphere. Diisopropylamine was distilled over CaH$_2$, under an inert atmosphere, and used fresh.
(E)-3-Trimethylsilylbut-2-en-1-ol [49]

To an oven-dried, three-necked, round-bottom flask equipped with a pressure-equalizing dropping funnel, reflux condenser, and septum was added isobutylmagnesium chloride in diethyl ether (46.0 mL, 92.0 mmol) under argon. To the Grignard solution was added bis(cyclopentadienyl)titanium dichloride (0.50 g, 2.0 mmol) at 0 °C. The reaction was held at 0 °C for 30 min then 2-butyn-1-ol (3.0 mL, 40.0 mmol) was added dropwise as a solution in diethyl ether (100 mL). The reaction was then heated to reflux and held for 16 hr. The reaction was then allowed to cool to room temperature and hexamethylphosphoramide (19.0 mL, 109 mmol) was added dropwise as a solution of THF (125 mL) followed by chlorotrimethylsilane (14.0 mL, 109 mmol). The reaction was heated to reflux and held for 16 hr, then allowed to cool to room temperature. Saturated aqueous NH₄Cl solution was added to quench the reaction and the mixture was extracted three times with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄ and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 20/1-5/1) to give 49 as a pale yellow oil (4.38 g, 76%):

^1^H NMR (300 MHz, CDCl₃) δ 0.07 (s, 9H), 1.71 (dt, J = 1.7, 0.8 Hz, 3H), 4.27 (dd, J = 6.0, 0.8 Hz, 2H), 5.88 (tq, J = 5.8, 1.7 Hz, 1H). ^1^C NMR (75 MHz, CDCl₃) δ -2.4, 14.6, 59.5, 137.5, 139.2. IR (neat) 3324, 2954, 1621, 1440, 1359, 1247 cm⁻¹; MS m/z 143.1 [65, M – H]⁺. CH: Calcd for C₇H₁₆OSi: C, 58.27; H, 11.18. Found: C, 58.04; H, 10.88.
(E)-3-Iodo-1-methylpropenyl)trimethylsilane [16]

(E)-3-Trimethylsilanylbuto-2-en-1-ol (49, 0.20 g, 1.4 mmol, 1.0 equiv) and triphenylphosphine (0.40 g, 1.5 mmol, 1.1 equiv) were weighed into an oven-dried, two-necked, round-bottomed flask equipped with an argon inlet and septum. Methylenechloride (3.5 mL) was added via syringe followed by the addition of N-iodosuccinimide (0.34 g, 1.5 mmol, 1.1 equiv, freshly recrystallized from dioxane/carbontetrachloride). The flask was wrapped in aluminum foil and the reaction mixture was stirred for 1 h in an ice bath and then 3 h at room temperature. When the reaction was complete (as determined by TLC), 5 mL of hexanes were added and the mixture was immediately filtered through 4 g of silica gel with the aid of 200 mL of hexanes. The filtrate was concentrated in vacuo give a thick yellow oil. (Note: Material at this stage was judged to be >95% pure by \(^1\)H NMR and was suitable for use.) Subsequent filtration through 2 g of neutral alumina with 100-150 mL of hexanes and concentration in vacuo afforded 0.29 g (82%) of 1 as a pale yellow liquid:

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.06 (s, 9H), 1.71 (d, \(J = 1.8\) Hz, 3H), 3.93 (d, \(J = 8.4\) Hz, 2H), 6.02 (tq, \(J = 8.4, 1.8\) Hz, 1H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) -2.5, 1.2, 13.7, 134.2, 143.2; IR (neat) 2954, 1604, 1437, 1247, 1143, 835 cm\(^{-1}\). MS \(m/z\) 254.2 [12, M\(^+\)].
(2S,5R)-5-Methyl-2-((R)-1-methyl-2-triisopropylsilyloxy-ethyl)-cyclohexanone [43]


$^1$H NMR: $\delta$ 3.68 (dd, $J = 5.1$, 9.6 Hz, 1H), 3.61 (dd, $J = 5.6$, 9.6 Hz, 1H), 2.33 (m, 1H), 2.30 (m, 1H), 2.12 (ddd, $J = 3.0$, 6.0, 9.0 Hz, 1H), 1.95-2.04 (m, 2H), 1.75-1.92 (m, 2H), 1.29-1.51 (m, 2H), 1.04 (m, 21H), 0.99 (d, $J = 6.4$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 3H).

$^1$H NMR spectra for intermediates are given.
(2S, 3R, 6S)-3-Methyl-6-(1-methyl-2-triisopropylsilylanyloxy-ethyl)-2-((E)-3-trimethylsilylbut-2-enyl)-cyclohexanone [59]

To a THF solution (6 mL) of n-BuLi (1.44 mL, 3.38 mmol, 2.35 M) was added diisopropylamine (0.52 mL, 3.68 mmol) at −78 °C under an argon atmosphere. The reaction mixture was held at −78 °C for 15 min. then allowed to warm to room temperature and keep there for 30 min before being recooled to −78 °C. Next, 43 (1.00 g, 3.07 mmol) was added dropwise as a solution in THF (2.0 mL). The reaction was held at −78 °C for 40 min. before being allowed to warm to 0 °C and held for 30 min., after which the reaction was recooled to −78 °C. Hexamethylphosphoramide (0.53 mL, 3.07 mmol) was added, the reaction mixture was stirred for 5 min, and then diethyl zinc (0.31 mL, 3.07 mmol) was added. A solution of 16 (1.19 g, 4.6 mmol) in 2 mL of THF was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous NH₄Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 50/1) to give 59 as a clear colorless oil (1.24 g, 89%).

$^1$H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 0.95 (d, $J$ = 6.7 Hz, 3H), 1.03-1.06 (m, 21H), 1.33-1.49 (m, 2H), 1.55 (s, 3H), 1.64-1.68 (m, 3H), 1.82-1.99 (m, 3H), 2.05-2.26 (m, 3H), 2.34-2.48 (m, 2H), 3.65 (d, $J$ = 4.8 Hz, 2H), 5.64 (tq, $J$ = 6.5, 1.7 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl₃) δ -2.1, 12.0, 14.4, 15.7, 18.0, 20.7, 25.4, 31.1, 35.1, 41.3, 53.3, 58.4, 65.7, 136.0, 137.9, 213.0; IR (neat) 2953, 2866, 1712, 1617, 1463, 1246, 1098, 836 cm⁻¹; HRMS (ESI) Calcd for C₂₆H₅₂O₂Si₂ (M + Na⁺) 475.3404. Found 475.3388.
(2S, 3R, 6R)-2-Allyl-6-isopropyl-3-methyl-cyclohexanone [60]
To a THF solution (4 mL) of n-BuLi (2.31 mL, 4.27 mmol, 1.85 M) was added diisopropylamine (0.65 mL, 4.66 mmol) at −78 °C under an argon atmosphere. The reaction mixture was held at −78 °C for 15 min. then allowed to warm to room temperature and keep there for 30 min before being recooled to −78 °C. Next, (−)-menthone (0.67 mL, 3.88 mmol) was added dropwise as a solution in THF (2.0 mL). The reaction was held at −78 °C for 40 min. before being allowed to warm to 0 °C and held for 30 min., after which the reaction was recooled to −78 °C. Hexamethylphosphoramidate (0.68 mL, 3.88 mmol) was added, the reaction mixture was stirred for 5 min, and then diethyl zinc (5.62 mL, 3.88 mmol, 0.69 M) was added. A solution of allyl iodide (1.07 mL, 11.67 mmol) in 2 mL of THF was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous NH₄Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 50/1) to give 60 as a clear colorless oil (0.64 g, 85%).

^1^H NMR (300 MHz, CDCl₃) δ 0.87 (dd, J = 13.3, 6.5 Hz, 6H), 1.05 (d, J = 6.2 Hz, 2H), 1.21-1.67 (m, 4H), 1.87 (dq, J = 8.7, 2.7 Hz, 1H), 1.99-2.16 (m, 4H), 2.27-2.38 (m, 2H), 4.91-5.05 (m, 2H), 5.84 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H).

(2S,3R,6R)-2-Allyl-3-methyl-6-(R-1-methyl-2-triisopropylsilyoxyethyl)-cyclohexanone [62]

To a THF solution (6 mL) of n-BuLi (1.54 mL, 3.23 mmol, 2.1 M) was added diisopropylamine (0.49 mL, 3.52 mmol) at −78 °C under an argon atmosphere. The reaction mixture was held at −78 °C for 15 min. then allowed to warm to room temperature and keep there for 30 min before being recooled to −78 °C. Next, 43 (0.96 g, 2.94 mmol) was added dropwise as a solution in THF (2.0 mL). The reaction was held at −78 °C for 40 min. before being allowed to warm to 0 °C and held for 30 min., after which the reaction was recooled to −78 °C. Hexamethylphosphoramide (0.61 mL, 3.52 mmol) was added, the reaction mixture was stirred for 5 min, and then diethyl zinc (0.36 mL, 3.52 mmol) was added. A solution of allyl iodide (1.0 mL, 10.95 mmol) in 2 mL of THF was added dropwise and the reaction mixture was allowed to warm to room temperature and stirred overnight. Saturated aqueous NH₄Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 50/1) to give 62 as a clear colorless oil (0.86 g, 80%).

^1^H NMR (300 MHz, CDCl₃) δ 0.91-1.14 (m, 21H), 1.20-1.68 (m, 7H), 1.80-2.02 (m, 4H), 2.20-2.49 (m, 5H), 3.66 (dd, J = 4.9, 1.8 Hz, 2H), 4.89-5.06 (m, 2H), 5.84 (ddt, J = 17.1, 10.1, 6.8 Hz, 1H) ^1^3^C^ NMR (75 MHz, CDCl₃) δ 5.3, 11.5, 15.6, 18.0, 20.5, 29.7, 30.5, 35.0, 40.4, 53.1, 57.7, 62.5, 65.6, 115.3, 137.3, 212.9.
Procedure 1: A flask containing CeCl$_3$ (0.066 g, 0.27 mmol) was heated to 140 °C under vacuum for 3 hr then cooled to 0 °C and placed under an argon atmosphere. THF (0.9 mL) was added and the mixture was allowed to stir for 2 hr. The resulting slurry was then cooled to −78 °C and vinylmagnesium bromide (2.5 mL, 0.94 mmol, 0.37 M) in THF was added. After 30 min, a solution of 59 (0.06 g, 0.13 mmol) in 0.5 mL of THF was added dropwise by syringe. The reaction mixture was held at −78 °C for 1 h and then allowed to warm to −15 °C and held for 1 h. Cold saturated aqueous NH$_4$Cl solution was added to quench the reaction and the mixture was extracted with diethyl ether. The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 50/1) to give 63 as clear colorless oil (0.56 g, 87%).

Procedure 2: To a THF solution (6 mL) of trimethylsilylacetylene (0.20 mL, 1.4 mmol) was added n-BuLi (0.51 mL, 1.1 mmol, 2.1 M) dropwise at −78 °C under an argon atmosphere. The excess dry ice was removed and the reaction was allowed to slowly warm to 0 °C over 1.5 hr, then recooled to −78 °C. Next, 59 (0.324 g, 0.72 mmol) was added dropwise as a solution in THF (2.0 mL) and the reaction was allowed to slowly warm to room temperature. Saturated aqueous NH$_4$Cl solution was added to quench the reaction and the mixture was extracted with diethyl ether. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO$_4$, filtered, and concentrated. The crude mixture was then added to a methanol solution saturated with potassium carbonate (7.0 mL) and left overnight. The reaction mixture was diluted with water and extracted with diethyl ether. The organic layer was washed with saturated aqueous sodium bicarbonate and brine. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate
= 20/1) to give a clear colorless oil (0.316 g), tentatively assigned as the propargyl alcohol corresponding to acetylide addition of ketone 59; 93%. A 15-mL round-bottomed flask was then charged with 5% Pd on BaSO₄ (31 mg, 0.014 mmol) under an atmosphere of hydrogen. The palladium turned a dark black color. Methanol (4.0 mL) and pyridine (0.07 mL, 0.87 mmol) were then added and the solution was allowed to mix for 15 min. The propargyl alcohol (0.295 g, 0.62 mmol) obtained earlier was then added as a solution in methanol (2.0 mL). After 18 hr the reaction mixture was filtered through a plug of Celite (hexanes/ethyl acetate = 20/1) and was then purified using silica gel column chromatography (hexanes/ethyl acetate = 100/1) to give 63 as clear colorless oil (0.274 g, 93%).

¹H NMR (300 MHz, CDCl₃) δ 0.00 (s, 9H), 0.77 (d, J = 7.2 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H), 1.03-1.13 (m, 21H), 1.32 (dd, J = 13.0, 3.3 Hz, 1H), 1.44 (dq, J = 12.5, 3.3 Hz, 1H), 1.55-1.79 (m, 8H), 1.96-2.05 (m, 1H), 2.16-2.23 (m, 1H), 2.32-2.40 (m, 1H), 3.35 (dd, J = 10.1, 4.0 Hz, 1H), 3.46 (dd, J = 10.3, 10.3 Hz, 1H), 4.37 (d, J = 1.3 Hz, 1H), 5.18 (dd, J = 10.5, 2.4 Hz, 1H), 5.32 (dd, J = 17.2, 10.5 Hz, 1H), 5.62 (dd, J = 17.2, 10.5 Hz, 1H), 5.73 (tq, J = 6.4, 1.6 Hz, 1H);

¹³C NMR (75 MHz, CDCl₃) δ -2.1, 11.9, 14.5, 18.0, 18.6, 20.6, 20.8, 28.6, 33.3, 34.5, 36.3, 51.5, 52.5, 65.6, 77.6, 114.1, 132.8, 142.3, 145.7; IR (neat) 3390, 2950, 2868, 1614, 1462, 1246, 1056, 835 cm⁻¹; HRMS (FAB) Calcd for C₂₈H₅₆O₂Si₂ (M + Na⁺) 503.3717. Found 503.3711. [α]₅₄₆ = −7.92° (c 0.001, CHCl₃).
(3R, 3aS, 6R, 7S, 7aS)-3,6-Dimethyl-7-((E)-3-trimethylsilanyl-but-2-enyl)-7a-vinyl-hexahydro-benzofuran-2-one [64]

To a methanol solution (8.5 mL) of 63 (0.113 g, 0.234 mmol) was added conc. HCl (88 μL, 2.87 mmol) at 0 °C under an argon atmosphere. After 2 hr the reaction was quenched with aqueous sodium bicarbonate and extracted with diethyl ether. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 10/1-5/1) to give a diol intermediate as a white crystalline solid (0.076 g, 0.234 mmol). ¹H NMR (300 MHz, CDCl₃) δ 0.03 (s, 9H), 0.78 (d, J = 7.3 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 1.04-1.14 (m, 1H), 1.18-1.30 (m, 3H), 1.48-1.60 (m, 3H), 1.64 (t, J = 1.5 Hz, 3H), 1.82-1.88 (m, 2H), 2.15-2.24 (m, 2H), 2.33-2.42 (m, 1H), 3.26 (dd, J = 11.0, 3.5 Hz, 1H), 3.39 (dd, J = 10.6, 10.6 Hz, 1H), 5.25 (ddd, J = 18.8, 14.1, 1.5 Hz, 2H), 5.66 (dd, J = 17.3, 10.8 Hz, 1H), 5.82-5.86 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ -2.2, 14.9, 18.6, 20.3, 20.5, 27.4, 31.5, 34.4, 36.0, 50.9, 52.2, 64.0, 79.3, 114.4, 137.4, 138.4, 144.3; IR (neat) 3306, 2953, 1614, 1456, 1246, 835 cm⁻¹. HRMS (EI) Calcd for C₁₉H₃₆O₂Si (M⁺) 324.2485. Found 324.2484. [α]₅₄⁶ = −9.80° (0.0012, CHCl₃); mp 65–67 °C.

To a mixture of the diol (0.076 g, 0.234 mmol), 4 Å molecular sieves (0.10 g), and N-methylmorpholine oxide (0.082 g, 0.7 mmol) in CH₂Cl₂ (2.0 mL) was added tetra-n-propylammonium perruthenate (0.008 g, 0.023 mmol) under an argon atmosphere. After 2.5 hr the reaction mixture was flushed through a plug of SiO₂ (hexanes/ethyl acetate = 10/1) to give lactone 64 as a white crystalline solid (0.075 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ 0.01 (s, 9H), 0.92 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H), 1.20-1.26 (m, 2H), 1.39-1.43 (m, 1H), 1.55-1.74 (m, 6H), 2.08-2.18 (m, 2H), 2.40-2.48 (m, 1H), 2.94 (apparent quint., J = 6.9 Hz, 1H), 5.22-5.32 (m, 2H), 5.63-5.72 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ -2.2, 9.1, 14.5, 20.7, 24.1, 28.1, 32.9, 33.7, 39.1, 43.4, 49.3, 87.5, 115.4, 134.7, 140.3, 140.4, 179.8; IR (neat) 2952, 1778, 1615, 1455, 1246, 1178, 835 cm⁻¹; HRMS (EI) Calcd for C₁₉H₃₂O₂Si (M⁺) 320.2172. Found 320.2168. [α]₅₄⁶ = −14.58° (c 0.0024, CHCl₃); mp 74–76°C.
$^1$H NMR

Intermediate Between 63 and 64°
Intermediate Between 63 and 64
(3R, 3aS, 6R, 7S, 7aS)-3,6-Dimethyl-7-(3-oxo-butyl)-7a-vinyl-hexahydro-benzofuran-2-one [66]

To a CH$_2$Cl$_2$ solution (5.0 mL) of 64 (0.075 g, 0.234 mmol) was added *m*-CPBA (0.064 g, 0.281 mmol) at 0 °C under an argon atmosphere. After 2 hr the reaction was quenched with aqueous sodium bicarbonate and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, filtered, and concentrated. The resulting residue was dissolved in CH$_2$Cl$_2$ (3.0 mL) and trifluoroacetic acid (60 μL, 0.8 mmol) was added. After 1 h the reaction was quenched with aqueous sodium bicarbonate and extracted with CH$_2$Cl$_2$. The organic layer was dried over MgSO$_4$, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 8/1) to give 66 as a white crystalline solid (0.062 g, 100%).

$^1$H NMR (300 MHz, CDCl$_3$) δ 0.94 (d, $J$ = 6.5 Hz, 3H), 1.08 (d, $J$ = 7.2 Hz, 3H), 1.19-1.25 (m, 2H), 1.39-1.51 (m, 1H), 1.59-1.94 (m, 6H), 2.11 (s, 3H), 2.30-2.41 (m, 1H), 2.63-2.74 (m, 1H), 2.90 (apparent quint., $J$ = 6.9 Hz, 1H), 5.29 (m, 1H), 5.66 (dd, $J$ = 17.3, 10.7 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 9.0, 20.1, 21.1, 24.0, 29.9, 30.5, 32.7, 38.7, 41.1, 43.5, 46.9, 87.6, 115.5, 140.1, 179.7, 209.1; IR (neat) 2929, 2359, 1771, 1714, 1448, 1177, 947 cm$^{-1}$; HRMS (CI) Calcd for C$_{16}$H$_{24}$O$_3$ (M + H$^+$) 265.1804. Found 265.1791. [α]$_{546}^0$ = –11.90° (c 0.0016, CHCl$_3$); mp 64–66 °C.
(3R, 3aS, 6R, 7S, 7aS)-3,6-Dimethyl-7-(3-methyl-but-3-enyl)-7a-vinyl-hexahydrop benzofuran-2-one [45]

To a THF solution (1.0 mL) of methyltriphenylphosphonium bromide (0.073 g, 0.2 mmol) was added n-BuLi (0.13 mL, 0.18 mmol, 1.4 M) at –40 °C under an argon atmosphere. The solution turned a bright yellow. The mixture was allowed to warm to 0 °C over 1 h then 66 (0.027 g, 0.10 mmol) was added as a solution in THF (1.0 mL). The mixture was then allowed to warm to room temperature and left overnight. The reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 20/1) to give 45 (0.008 g, 31%) as a clear colorless oil.

\[
\begin{align*}
\text{H} \text{NMR (300 MHz, CDCl}_3\text{)} & \delta 0.98 (d, J = 6.5 \text{ Hz, 3H}), 1.08 (d, J = 7.2 \text{ Hz, 3H}), 1.01-1.13 \text{ (m, 3H), 1.16-1.31 (m, 1H), 1.40-1.50 (m, 2H), 1.67-1.80 (m, 6H), 1.87-1.97 (m, 1H), 2.05-2.16 (m, 2H), 2.93 (apparent quint., } J = 6.9 \text{ Hz, 1H), 4.63 (d, } J = 7.1 \text{ Hz, 1H), 5.29 (ddd, } J = 18.8, 14.1, 1.5 \text{ Hz, 2H), 5.66 (dd, } J = 17.3, 10.8 \text{ Hz, 1H}); \\
\text{C} \text{NMR (75 MHz, CDCl}_3\text{)} & \delta 9.1, 20.4, 22.4, 24.1, 26.5, 32.4, 32.9, 37.6, 39.2, 43.4, 48.0, 87.7, 109.5, 115.3, 140.2, 146.3, 179.8; \\
\text{IR } (\text{neat}) & 3072, 2933, 1778, 1646, 1179, 945 \text{ cm}^{-1}; \\
\text{HRMS (Cl) } & \text{Calcd for C}_{16}\text{H}_{26}\text{O}_2 \text{ (M + H})^{+} = 263.2011. \text{ Found 263.2005.}
\end{align*}
\]
Hex-5-enyl-triphenyl-phosphonium iodide [68]

To a nitromethane solution (35 mL) of 6-iodo-1-hexene (3.1 g, 14.75 mmol) was added triphenylphosphine (3.9 g, 14.75 mmol). The mixture was heated to 50 °C for 18 hr then cooled to room temperature. The mixture was then diluted with diethyl ether (50 mL) and a white solid crashed out. The precipitate was gravity filtered and rinsed with diethyl ether (30 mL) to give 68 (4.7 g, 67 %) as a white crystalline solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ 1.52-1.80 (m, 4H), 2.02 (apparent q, $J = 6.9$ Hz), 3.52-3.62 (m, 2H), 4.81-4.91 (m, 2H), 5.62 (ddt, $J = 16.9$, 10.1, 6.7 Hz, 1H), 7.63-7.79 (m, 15H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 21.5, 21.6, 22.4, 23.1, 28.9, 29.1, 32.7, 115.2, 117.3, 118.4, 130.3, 130.5, 133.4, 133.5, 135.0, 137.4; mp 166–168 °C.
(3R, 3aS, 6R, 7S, 7aS)-3,6-dimethyl-7-((Z)-3-methyl-nona-3,8-dienyl)-7a-vinyl-hexahydrobenzofuran-2-one [69]

To a diethyl ether solution (2.0 mL) of hex-5-enyl-triphenyl-phosphonium iodide 68 (0.137 g, 0.29 mmol) was added n-BuLi (0.124 mL, 0.248 mmol, 2.0 M) at −78 °C under an argon atmosphere. The mixture was then allowed to warm to room temperature and then recooled to −78 °C. Next, 66 (7.6 mg, 0.029 mmol) was added as a solution in diethyl ether (1.0 mL) and allowed to warm to room temperature. After 4 hr the reaction was quenched with water and extracted with diethyl ether. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 20/1) to give 69 (3.5 mg, 37%) as a white crystalline solid.

$^1$H NMR (300 MHz, CDCl₃, Diagnostic Peaks) δ 0.98 (d, $J = 6.5$ Hz, 3H), 1.08 (d, $J = 7.0$ Hz, 3H), 2.93 (apparent quint., $J = 6.9$ Hz, 1H), 4.92-5.09 (m, 3H), 5.24-5.36 (m, 2H), 5.60-5.69 (m, 1H), 5.71-5.88 (m, 1H); HRMS (ESI) Calcd for C$_{22}$H$_{34}$O$_2$ (M + Na$^+$) 353.2457. Found 353.2460.
(+)-Dihydro-epi-deoxyarteannuin B [22]

To a CH$_2$Cl$_2$ (1.5 mL) solution of 69 (8.0 mg, 0.024 mmol) under an argon atmosphere in a 1-dram vial was added Grubbs 2$^\text{nd}$ generation catalyst (2.0 mg, 0.0024 mmol). The sealed vial was heated to 40 °C for 4 hr then cooled to room temperature and flushed through a plug of SiO$_2$. The resulting eluent was concentrated and purified using silica gel column chromatography (hexanes/ethyl acetate = 10/1) to give 22 (4.4 mg, 77%) as a white crystalline solid.

$^1$H NMR (300 MHz, CDCl$_3$) δ 0.95 (d, $J = 6.5$ Hz, 3H), 0.97-1.09 (m, 1H), 1.16 (d, $J = 7.1$ Hz, 3H), 1.17-1.25 (m, 2H), 1.37-1.48 (m, 1H), 1.62-1.76 (m, 6H), 1.85-1.93 (m, 1H), 2.02-2.13 (m, 3H), 3.15 (apparent quint., $J = 6.9$ Hz, 1H), 5.65 (q, $J = 1.5$ Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 9.5, 19.9, 23.7, 24.0, 29.9, 31.1, 32.7, 39.9, 43.0, 46.9, 83.4, 122.0, 142.5, 179.5; IR (neat) 2929, 1764, 1449, 1162, 909 cm$^{-1}$; HRMS (ESI) Calcd for C$_{15}$H$_{22}$O$_2$ (M + Na$^+$) 257.1518. Found 257.1518. [α]$^{546}_\text{o}$ = 14.2° (c 0.00056, CHCl$_3$); mp 68–70 °C. Copies of NMR spectra that support our structural and stereochemical assignments are provided on pages 78–93.
Pulse Sequence: dQ(pq)
In the course of our investigation into the total synthesis of dihydroartemisinic acid 21, we encountered the need to convert ketone 60 into α,β-unsaturated enone 74 (Figure 36). Initial attempts at olefination of 60 by the Horner–Wadsworth–Emmons reaction proved unsuccessful, with starting material being recovered in all cases. The lack of reactivity was attributed to the steric hinderance around the ketone. Therefore, an alternative method to access α,β-unsaturated carbonyl 74 was needed.

α,β-Unsaturated carbonyl compounds are common building blocks in organic synthesis. Their construction is most commonly achieved by the homologation of aldehydes and ketones through aldol condensations, Wittig olefinations, Horner–Wadsworth–Emmons (HWE) olefinations, or other olefination methods. The aldol condensation is the most atom economical of these approaches, producing only water as a by-product. While the aldol
condensation avoids the need for the use of toxic stoichiometric phosphines, phosphine oxides, and phosphonates associated with the Wittig and HWE reactions, it often provides inferior yields. In addition, all of the aforementioned olefination methods are sensitive to steric congestion around the carbonyl. As a consequence, they often fail to olefinate hindered carbonyl compounds, as illustrated in our failed olefination attempts of 60.

Therefore, alternative and atom-economical means of converting carbonyls into their homologated α,β-unsaturated carbonyl analogs was desirable. One potential method would be an addition/rearrangement sequence between a carbonyl and an acetylenic π-bond (Figure 37).

(a) stepwise annulation / electrocyclic ring-opening

(b) nucleophilic 1,2-addition / rearrangement

Figure 37: Atom-Economical Carbonyl Olefination Strategies

The nature of the alkyne utilized dictates which reaction pathway will be followed. Highly electron-rich alkynes (i.e., ynolates, ynamine, or ynamides, Figure 37a) undergo a formal [2+2] cycloaddition with the carbonyl to produce an oxatene intermediate, which then
undergoes electrocyclic ring opening to provide the homologated enoate/enamide H. The use of terminal alkynes opens the door to an alternative pathway. The acetylide can add to ketone G via a 1,2-nucleophilic addition to give propargyl alcohol E. The resulting propargyl alcohol E is capable of undergoing a variety of reactions, including the desired Meyer–Schuster rearrangement to give α,β-unsaturated carbonyl compound F (Figure 37b). To a certain extent, control over which pathway the propargyl alcohol follows can be achieved by careful selection of the reaction conditions. However, development of precise reaction conditions allowing for only the desired Meyer–Schuster reaction to take place is paramount to the success of the proposed two-stage olefination method. A full understanding of the Meyer–Schuster reaction is a prerequisite to the development of new reaction conditions.

The Meyer–Schuster reaction is a powerful rearrangement that converts propargyl alcohols into α,β-enones. The process formally involves a 1,3-shift of the hydroxyl moiety followed by tautomerization of the presumed allenol intermediate L (Figure 38).113-115

The reaction was first reported by Meyer and Schuster in 1922, and it was conducted in acidic media at elevated temperatures.116 The requirements of strong acid and high temperatures severely limited the scope of the Meyer–Schuster reaction.117 Substrates were confined to propargyl alcohols that lacked β-hydrogens. The presence of β-protons allowed for the Rupe rearrangement105 (Figure 39), which generally took precedence over the Meyer–Schuster reaction.117
Initial attempts to increase the efficiency and the scope of the Meyer–Schuster reaction focused on activation of the hydroxyl moiety by transition metal catalysts. Vanadium was the first transition metal to show promise. Chabardes and co-workers demonstrated that trialkyl orthovanadates could be used to prepare aliphatic α,β-unsaturated aldehydes from propargyl alcohols with a terminal alkyne. While avoiding the need for strong acid, temperatures in excess of 140 °C were still necessary to promote rearrangement. At these high temperatures catalyst degradation was problematic.

Catalyst decomposition was partially addressed by Pauling and co-workers, who developed more stable tris[triaryl]silyl] vanadates. The tris[triaryl]silyl] vanadate catalysts were also limited to the preparation of α,β-unsaturated aldehydes. Catalyst stability was advanced further by the Vol’pin lab with the development of a polymeric silyl vanadate catalyst. The polymeric catalyst showed much greater stability than its monomeric counterpart. The new catalyst allowed for lower catalyst loadings, but it did nothing to address the high temperature requirements. Despite its shortcomings, this novel vanadate chemistry was used by Hoffmann-La Roche in a variety of terpenoid syntheses (Figure 40).

Figure 39: Competing Rupe Rearrangement

Figure 40: Hoffmann-La Roche Inc. Application of Vanadate Catalyst
The orthovanadate-catalyzed rearrangement is thought to proceed by formation of an intermediate vanadate ester Q, which can then undergo a [3,3]-sigmatropic rearrangement to give allene ester R. Allene R then undergoes trans-esterification or hydrolysis to give allenol L, which tautomerizes to the α,β-enone F (Figure 41).

![Figure 41: Proposed Orthovanadate Mechanism](image)

Attempting to expand the scope of this potentially useful reaction, Chabardes and co-workers performed a comprehensive study on the use of a variety of oxo-derivatives of vanadium, molybdenum, rhenium, and tungsten to catalyze the rearrangement. Ultimately, low transformation rates, even under high dilution, and harsh reaction conditions limited the utility of the reaction.

The early oxovanadium work saw little use outside of industrial application, until it was resurrected by Chung and Trost in 2006. They found that in the presence of suitable electrophiles (initial work focused on imines), the vanadium allene intermediate R could be trapped to yield aldol-type products T, instead of undergoing hydrolysis to the Meyer–Schuster products (Figure 42).
Other early catalyst systems that were explored to activate the propargyl alcohol included a Ti/Cu system\(^{128}\) (which activated both the propargyl alcohol and the alkyne) and a vanadium-pillared montmorillonite system.\(^{129}\) Both catalyst systems improved the yield and lowered the reaction time of the rearrangement, but neither addressed the high temperature requirements. It was not until the development of a tetrabutylammonium perrhenate(VII)/\(\rho\)-toluenesulfonic acid catalyst system, in the early 1990’s by the Narasaka Lab, that the rearrangement could be carried out at room temperature without sacrificing yield.\(^{130}\) An attractive feature of this catalyst system is its ability to generate \(\alpha,\beta\)-unsaturated acylsilanes (Figure 43) in addition to \(\alpha,\beta\)-enones.

Recently, there has been a reemergence in the use of high oxidation-state metal-oxo complexes to catalyze the Meyer–Schuster rearrangement. In their investigation into the
rhenium(V)-catalyzed nucleophilic substitution of propargyl alcohols, the Toste Lab noticed the formation of Meyer–Schuster by-products. Using this as a starting point, Vidari and co-workers developed an efficient rhenium(V)-oxo catalyst to effect the Meyer–Schuster rearrangement of both alkyl and aryl substituted alkynols (Figure 44).

The rhenium-catalyzed reactions proceeded with high (E)-selectivity, which can be attributed to the isomerization of the (Z)-isomer to the more stable (E)-isomer under the reaction conditions. Terminal alkynes leading to the corresponding α,β-unsaturated enals were also supported by this catalyst system. Due to the high oxo-philicity of the rhenium catalyst, these reactions were performed under strictly anhydrous conditions. The ability of the rhenium catalyst to be recycled multiple times, without loss of catalytic efficiency, added to the appeal of the method.

Primary propargyl alcohols have proven to be very difficult substrates for the Meyer–Schuster reaction. To address this shortcoming in Meyer–Schuster methodology, Akai and co-workers developed a multi-catalyst system consisting of MoO₂(acac)₂, AuCl(PPh₃) and AgOTf, which allowed for the Meyer–Schuster rearrangement to proceed smoothly under mild conditions. Selected examples can be seen in Table 2.
Table 2: Mo-Au Combo Catalysis for Rearrangement of E into α,β-unsaturated Ketones F

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Time (h)</th>
<th>Substrate E</th>
<th>Product F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>E1</td>
<td>H</td>
<td>H</td>
<td>(CH₂)₂Ph</td>
<td>0.5</td>
<td>F1</td>
</tr>
<tr>
<td>2</td>
<td>E2</td>
<td>H</td>
<td>H</td>
<td>n-C₇H₁₅</td>
<td>0.5</td>
<td>F2</td>
</tr>
<tr>
<td>3</td>
<td>E3</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>1</td>
<td>F3</td>
</tr>
<tr>
<td>4</td>
<td>E4</td>
<td>H</td>
<td>Me</td>
<td>n-C₆H₁₃</td>
<td>0.25</td>
<td>F4</td>
</tr>
<tr>
<td>5</td>
<td>E5</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>2.5</td>
<td>F5</td>
</tr>
<tr>
<td>6</td>
<td>E6</td>
<td>Me</td>
<td>Ph(CH₂)₂</td>
<td>n-C₄H₉</td>
<td>2</td>
<td>F6</td>
</tr>
</tbody>
</table>

Primary (entries 1-3), secondary (entry 4), and tertiary (entries 5-6) propargyl alcohols all rearrange smoothly and in high yield. The low reaction times, typically less than an hour, and the ability of the rearrangement to proceed at room temperature can be attributed to the double activation of the propargyl alcohol. The Au and Ag catalysts activate the alkyne π-system, while the Mo catalyst activates the alcohol.¹²⁵,¹²⁶,¹³⁵-¹³⁷

The catalytic activity of all the transition metal catalysts discussed thus far originates from formation of a propargyl metal ester, which then undergoes rearrangement and trans-esterification to give the formal Meyer–Schuster rearrangement product (refer back to Figure 41). The transition metal oxo-catalysts are acting as “hard” Lewis acids, preferring to coordinate to the more Lewis basic lone pair of the oxygen than the “soft” π-system of the alkyne (Figure 45).
The drawback to these “hard” Lewis acid catalysts is they generally require harsh reaction conditions to carry out the catalytic cycle. An alternative approach would be first to functionalize the propargyl alcohol as an ether or ester. Ideally, this pre-functionalization would allow for the rearrangement to proceed under mild reaction conditions, through activation of the alkyne $\pi$-system by a “soft” Lewis acid (Figure 46).

There are several examples of propargyl ethers being successfully converted into $\alpha,\beta$-unsaturated carbonyl compounds. These processes typically involve hydration of the alkyne, followed by $\beta$-elimination of the ether alkoxide to generate the $\alpha,\beta$-unsaturated carbonyl. Although the end result is the same, the reactions are not strictly Meyer–Schuster rearrangements, and they involve distinct synthetic challenges.

In contrast, propargyl acetates can undergo a 1,3-migration of the acetate, yielding formal Meyer–Schuster products after hydrolysis (Figure 47, Eq. 16), or a 1,2-migration leading to metal carbenes, which have their own unique chemistry.
The Yamada lab has shown that covalent activation of the propargyl alcohol as a carbonate and the rearrangement/hydrolysis sequence can be merged into a single operation using high-pressure carbon dioxide, base, and a silver catalyst (Figure 47, Eq 17). However, functionalization of the propargyl alcohol in a separate step is much more common.

Cationic gold catalysts have received attention for their exceptional ability to activate carbon-carbon triple bonds. Zhang and co-workers exploited the affinity of gold salts towards acetylenic $\pi$-bonds to efficiently convert propargylic esters to $\alpha,\beta$-unsaturated carbonyl derivatives at room temperature. In the initial examination of the reaction, Zhang et al. focused on optimization of the rearrangement of propargyl esters derived from aldehydes, because they were less likely to undergo elimination to form enynes than propargyl esters derived from ketones. A variety of Au(I) and Au(III) catalysts were screened. $\text{Au(PPPh}_3\text{)NTf}_2$ provided the best results, and all further studies were conducted with this catalyst. Optimization allowed for catalyst loading to be lowered to 2 mol %, without sacrificing yield or selectivity; in almost all cases complete (E)-selectivity was achieved (Figure 48).
Simple extension of these optimized reaction conditions to substrates derived from ketones was not practical, with elimination to form enynes and other side reactions being substantial. Diligent optimization was required before the method was extended to the preparation of \( \beta,\beta \)-disubstituted \( \alpha,\beta \)-unsaturated ketones. Catalyst loading had to be increased to 5 mol % and solvent conditions had to be carefully controlled (Figure 49). The limitation in Zhang’s methodology is that it does not work for terminal alkynes, which readily undergo Markovnikov hydration under the reaction conditions.

The reaction is believed to proceed through a Au-catalyzed [3,3]-rearrangement\(^{140-146} \) of the propargylic ester \( \text{U} \), followed by Au activation of the intermediate allene \( \text{V} \) giving rise to intermediate \( \text{Z} \). Intermediate \( \text{Z} \) can then undergo hydrolysis/protiodeauration to give Meyer–Schuster products \( \text{F} \). With a suitable electrophile present, intermediate \( \text{Z} \) could be trapped to yield a wide range of products including alkenyl enol esters/carbonates,\(^{154} \) \( \alpha \)-ylidene-\( \beta \)-diketones,\(^{155} \) cyclopentenones,\(^{156} \) indoline-fused cyclobutanes,\(^{157} \) \( \alpha \)-ylidene-\( \beta \)-keto and –malonate esters,\(^{158} \) indenes,\(^{159} \) aromatic ketones,\(^{160} \) and \( \alpha \)-haloenones\(^{161,162} \) (Figure 50).
At the same time as Zhang’s work, another gold-based catalyst system was being developed in the lab of Nolan. During their investigation of a Au(I)/Ag(I) catalyst system designed to achieve a tandem [3,3]-sigmatropic rearrangement/intramolecular hydroarylation of phenylpropargyl acetates yielding indenes, Nolan and co-workers noticed Meyer–Schuster by-products when water was present in the reaction. Wishing to capitalize on this observation, the Nolan and Maseras labs modified the original Au(I)/Ag(I) catalyst system to convert a variety of propargyl acetates to their α,β-unsaturated carbonyl counterparts. The optimal conditions were determined to be 2 mol % of both (tBu)AuCl and AgSbF₆, in a 10:1 THF/H₂O solvent system at 60 °C for 8 hr (Table 3).

Nolan et al. found that these long reaction times could be avoided by the use of a microwave. Microwave irradiation at 80 °C allowed for the reaction to proceed in 12 minutes, without any negative effect on yield or selectivity (entry 2). A variety of substituents at the propargylic position were tolerated, including electron-rich (entry 3) and electron-deficient (entry 1) aryl groups, as well as simple alkyl groups (entry 7). Alkyl and aryl substituents on the alkyne were also tolerated. Terminal alkynes (entry 4), which have proved to be poor substrates for other methods, could also be used. However, the use of sterically bulky substituents, such as trimethylsilyl (TMS) and tert-butyl (entries 5 and 6), resulted in no reaction. In most cases, excellent (E)-selectivity was observed (e.g. entry 7).
Table 3: Selected Examples of [(I\textsubscript{t}Bu)AuCl]/AgSbF\textsubscript{6} Catalyzed Rearrangement\textsuperscript{[a]}

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Propargyl Acetate</th>
<th>Enone</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OAc</td>
<td>F</td>
<td>91</td>
</tr>
<tr>
<td>2\textsuperscript{[b]}</td>
<td>OAc</td>
<td>F</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>OAc</td>
<td>F</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>OAc</td>
<td>F</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>OAc</td>
<td>F</td>
<td>nr</td>
</tr>
<tr>
<td>6</td>
<td>OAc</td>
<td>F</td>
<td>nr</td>
</tr>
<tr>
<td>7</td>
<td>OAc</td>
<td>F</td>
<td>82</td>
</tr>
<tr>
<td>8</td>
<td>OAc</td>
<td>F</td>
<td>94</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: alkyne \textbf{U} (1 mmol), [(I\textsubscript{t}Bu)AuCl]/AgSbF\textsubscript{6} (2 mol\%), THF (10 mL), H\textsubscript{2}O (1 mL). \textsuperscript{[b]} performed in a microwave at 80 °C, reaction time 12 min.

While Nolan and co-workers’ method proved to be fairly general, perhaps the most interesting aspect of their study was their proposed mechanism. In an attempt to understand
better the reaction mechanism, Nolan and Maseras investigated the reaction both experimentally and computationally. Based on their findings, they suggested a $S_N2'$ type mechanism, instead of the more commonly accepted 1,3 shift of the propargyl acetate. The gold-catalyst was believed to activate water, instead of the $\pi$-system of the alkyne, to generate [(NHC)AuOH]. The AuOH complex acted as the the active catalyst (Figure 51).

![Figure 51: $S_N2'$ Type Addition of Au Catalyst](image)

Nolan and co-workers later extended this method to the preparation of $\alpha,\beta$-unsaturated carbonyls from propargyl alcohols, eliminating the functionalization step, using a similar catalyst system. High conversions were achieved for a variety of substrates; however, rearrangement of primary alcohols and terminal alkynes proved unsuccessful.

The Chung lab also found success in converting propargyl alcohols into $\alpha,\beta$-unsaturated ketones using a Au(I) catalyst system. Chung et al. screened a variety of Lewis acids including FeCl₃, InCl₃, GaCl₃, PtCl₂, Ag(OTf) and AuCl₃ before selecting [Au(PPh₃)](OTf). The only catalyst that gave complete conversion was [Au(PPh₃)](OTf), generated from AuCl(PPh₃) and Ag(OTf). Yields were generally moderate, and side reactions such as the Rupe rearrangement and enyne formation were problematic. Chung suggested a new mechanism for his Au(I) catalyst system featuring a cumulene intermediate, although it was purely speculative (Figure 52).
Although cationic gold is the most commonly used “soft” Lewis acid catalyst to achieve the Meyer–Schuster rearrangement, many other “soft” Lewis acids are also capable of catalyzing the rearrangement of propargyl acetates. During their investigation into the regioselective hydration of internal alkynes using a Hg(OTf)$_2$ catalyst, Nishizawa and co-workers attempted to influence the reaction site by using neighboring group participation. They hypothesized that by placing an acetate group in the propargylic position, directed hydration could be achieved through a coordination between the mercury catalyst and the acetate functionality. To test this hypothesis, they examined the reaction of propargyl acetate 89, in water with a catalytic amount of Hg(OTf)$_2$. Instead of obtaining the expected hydration products 91 and 92, the major product was vinyl ketone 90. Trace amounts of the dialkylated mercuric product 93 were also present (Figure 53).
Based on the initial findings, the Nishizawa lab chose to optimize the reaction for the formation of α,β-enones. A screening process revealed the optimal conditions to be 5 mol % Hg(OTf)$_2$ with 1.5 equivalents of water in acetonitrile, at room temperature for 4 hours. Despite optimization, yields were generally moderate and side reactions could not be avoided$^{166}$ (Figure 54).

![Figure 54: Optimized Hg(OTf)$_2$ Rearrangement$^{166}$](image)

In 2007, Nishizawa and co-workers further extended the method to include the formation of α,β-unsaturated esters from secondary-ethoxyalkynyl acetates.$^{167}$ The switch from aliphatic alkynes to the more electron rich ethoxy alkyne allowed for the reaction to proceed with only 1 mol % catalyst loading, compared with the 5 mol % required for aliphatic alkynes. Yields were generally high, and excellent (E)-selectivity was achieved for substrates containing alkyl substituents in the propargyl position (Eq 18, Figure 55). However, a mixture of (E/Z)-isomers were obtained when aryl substituents were introduced at the propargyl position (Eq 19, Figure 55).$^{167}$

While oxygen activated alkynes, which result in α,β-unsaturated esters after rearrangement, are the most common, other heteroatoms$^{168}$ have been utilized. α,β-unsaturated thioesters have been synthesized by the lab of Kataoka and Yoshimatsu.$^{169}$ They were able to convert γ-sulfur substituted propargyl alcohols to the Meyer–Schuster products using polyphosphoric acid trimethylsilyl ester, albeit in low yield with significant elimination to form enynes.
Very recently, the first example of a Meyer–Schuster rearrangement to form an α,β-unsaturated amide was realized by the Akai lab, using their aforementioned Mo/Au/Ag catalyst system (Figure 56). To the best of our knowledge, these two reports are the only examples of non-oxygen heteroatom activation of alkynes towards the Meyer–Schuster rearrangement.

In addition to strong acid, oxo-philic transition metals, and Lewis acid catalysis, the Meyer–Schuster reaction can also be catalyzed by ruthenium complexes. The ruthenium catalysts are limited to the conversion of propargyl alcohols with a terminal acetylene. The requirement for terminal alkynes can be explained by the proposed mechanism. The reaction is a two-step process. In the first step, a carboxylic acid is added to the alkyne, presumably through a Ru-allenylidene intermediate DD, which can only be formed from a terminal alkyne.
The resulting enol esters FF can be isolated or cleaved with strong acid to give Meyer–Schuster products GG (Figure 57).

Figure 57: Proposed Mechanism for the Ru-Catalyzed Isomerization of Propargyl Alcohols into α,β-Unsaturated Aldehydes

With the variety of methods now available for the mild execution of the Meyer–Schuster rearrangement, it has begun to be applied to the total synthesis of complex molecules. A representative example can be found in the Weinreb lab’s efforts towards the total synthesis of the marine alkaloid chartelline A. They needed to olefine a γ-lactam chemoselectively...
in the presence of a β-lactam. They found that they could chemoselectively add lithio tert-butylacetylhyde to the γ-lactam, which set the stage for the rearrangement. Standard Meyer–Schuster conditions (i.e. acid) gave the α,β-unsaturated ketone 106; however, the acidic conditions resulted in removal of the Boc protecting group. Gratifyingly, use of the milder tetrabutyl-ammonium perrhenate/p-toluenesulfonic acid catalyst system developed by the Narasaka130 lab allowed for the rearrangement to take place in quantitative yield without loss of the Boc group (Figure 58).178 Undoubtedly, the application of the Meyer–Schuster reaction to other total synthesis will be soon to follow.

Figure 58: Application of the Meyer–Schuster Reaction in Total Synthesis

In conclusion, the Meyer–Schuster reaction has evolved, from a simple acid-catalyzed rearrangement of tertiary propargyl alcohols to α,β-enals, into an elegant reaction whose reactivity can be precisely controlled by activation of the alcohol and alkynyl moieties independently or in tandem. Once limited only to the formation of α,β-unsaturated ketones and aldehydes, recent advances have made access to α,β-unsaturated esters,167,179 amides,134 thioesters,169 and acylsilanes130 a reality. A vast array of metals have been used to achieve
this transformation, including Au, Ag, Cu, Ti, Re, V, Mo, W, and Ru. The use of the Meyer–Schuster reaction has not been confined to method development; it has also found use in a variety of total synthesis.\textsuperscript{175-178} The variety of methods now available to execute the Meyer–Schuster rearrangement will undoubtedly lead to an increase in the use of this powerful reaction.

In the next chapter, our contributions to Meyer–Schuster methodology will be discussed. Key topics will include development of a Au(III)-catalyzed rearrangement of propargyl ethynyl ethers into α,β-unsaturated esters and its use in the olefination of hindered ketones,\textsuperscript{179} efforts to control the (E/Z)-selectivity of the Meyer–Schuster rearrangement,\textsuperscript{180} and the search for more affordable catalysts.\textsuperscript{181} It is important to note that our work pre-dates (and may have played a role in stimulating) much of the chemistry discussed above in Chapter 5.
Our interest in the Meyer–Schuster reaction stemmed from the desire to develop an efficient, atom-economical means to olefinate hindered ketones. As discussed in the previous chapter, classic olefination techniques such as the Wittig olefination, the Horner–Wadsworth–Emmons (HWE) olefination, and the aldol condensation are sensitive to steric congestion around ketones. The phosphorus-based reagents used in the Horner–Wadsworth–Emmons and Horner–Wittig olefinations are particularly sensitive to steric congestion and often fail to work on hindered substrates. An alternative approach would be to use a two-step olefination process, consisting of acetylide addition followed by rearrangement to the α,β-unsaturated carbonyl (Figure 59). Acetylide addition is relatively insensitive to steric congestion and is expected to proceed smoothly. Therefore, the limiting factor in the two-step olefination is the rearrangement.

Figure 59: Two-Step Olefination Strategy

An obvious choice for this rearrangement is the Meyer–Schuster reaction. The original Meyer–Schuster reaction was conducted in acidic media at elevated temperatures. Metal oxide
and transition metal catalysts have also been employed to carry out the Meyer–Schuster reaction, but limited scope, harsh reaction conditions, and a prevalence of side reactions have detracted from the usefulness of these methods. For a more detailed explanation of our proposed olefination strategy and a complete history of the Meyer–Schuster reaction, refer to Chapter 5. Note that our initial studies and publication pre-date much of the work described in Chapter 5. In order for the two-step olefination strategy to succeed, we needed to develop mild conditions for promoting the Meyer–Schuster rearrangement.

Our initial approach towards the Meyer–Schuster reaction derived its origins from a combination of (1) early oxo-vanadium chemistry, which showed the feasibility of using oxophilic reagents to effect the Meyer–Schuster rearrangement (refer to chapter 5), and (2) the observation that Cr(VI) salts can oxidize tertiary allylic alcohols through a 1,3 rearrangement\(^\text{182}\) (Eq 20, Figure 60). We hypothesized that these same Cr(VI) salts would be able to undergo a similar rearrangement with propargyl alcohols, to give chromate ester-allene II. Subsequent hydrolysis would yield the Meyer–Schuster product F (Eq 21, Figure 60).

\[
\begin{align*}
\text{OH} & \xrightarrow{\text{CrO}_3} \begin{array}{c}
\text{O} \quad \text{O} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{O} \\
\text{O} \quad \text{O}
\end{array} \\
\text{108} & \xrightarrow{\text{CrO}_3} \begin{array}{c}
\text{O} \quad \text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{109} & \xrightarrow{\text{CrO}_3} \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{110} & \xrightarrow{\text{CrO}_3} \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{111} & + \begin{array}{c}
\text{O} \quad \text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{112}
\end{align*}
\]

Eq (20): Cr(VI) Oxidation of Tertiary Allylic Alcohols

\[
\begin{align*}
\text{HO} & \xrightarrow{\text{CrO}_3} \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{E} & \xrightarrow{\text{CrO}_3} \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{HH} & \xrightarrow{\text{CrO}_3} \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{II} & \xrightarrow{\text{CrO}_3} \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
\text{F}
\end{align*}
\]

Eq (21): Our Proposed Cr(VI) Rearrangement of Propargyl Alcohols

Figure 60: Cr(VI) Rearrangements
Our ultimate goal was to develop an efficient means to olefinate hindered ketones, so we decided to use the propargyl alcohol 113, derived from 1-hexyne addition to (−)-menthone 58, as our model substrate (Eq 22, Figure 61). The first chromium reagent screened was pyridinium chlorochromate (PCC) (Eq 23, Figure 61). The starting propargyl alcohol 113 was completely consumed within 24 hours, but there was no evidence of the desired product. Other catalyst systems that were capable of undergoing 1,3-rearrangements were also tested, including MnO₂ and 1,1'-thiocarbonyl diimidazole (Eqs 23 and 24, Figure 61); even with elevated temperatures and extended reaction times, no reaction was observed.

On-n-Bu
n-BuLi, THF
−78 oC to rt
      96 %
OH
n-Bu
Eq (22)

Figure 61: Initial Oxo-philic Approaches to the Meyer-Schuster Rearrangement

In an attempt to limit the potential side reactions and to make ¹H NMR interpretation more facile, propargyl alcohol 113 was replaced with 117 in further studies. Propargyl alcohol 117 was readily prepared from phenylacetylene addition to diphenyl ketone 115 (Eq 26, Figure 62). Disappointingly, treatment of 117 with PCC again resulted in a complex mixture of products (Eq 27, Figure 62).
A concurrent report in the literature led us to consider an alternative approach. Campagne and co-workers observed Meyer–Schuster by-products when attempting a gold(III)-catalyzed nucleophilic substitution of propargyl alcohol 118 with ethanol (Eq 28, Figure 63). Based on these findings, similar conditions were applied to triphenyl propargyl alcohol 117. Propargyl alcohol 117 was treated with 10 mol % AuCl₃ and 2.5 equivalents of ethanol in dichloromethane at room temperature. After 24 hrs, a 2:3 mixture of ethyl ether 121 and the desired α,β-unsaturated ketone 122 was obtained (Eq 29, Figure 63).
Based on this initial hit, a series of experiments was conducted to determine the optimal conditions for this transformation. A quick screening of common organic solvents with 5 mol % of gold(III) chloride was performed (Table 4).

![Chemical structure](image)

Table 4: Solvent Screening With AuCl₃ Catalyst

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Mol % AuCl₃</th>
<th>Solvent</th>
<th>Equiv. H₂O</th>
<th>Temperature °C</th>
<th>Time h</th>
<th>% Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>117</td>
<td>5</td>
<td>CH₂Cl₂</td>
<td>6.0</td>
<td>25</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>117</td>
<td>5</td>
<td>H₂O</td>
<td>N.A.</td>
<td>25</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>5</td>
<td>H₂O</td>
<td>N.A.</td>
<td>Reflux</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>117</td>
<td>5</td>
<td>DMF</td>
<td>4.0</td>
<td>25</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>117</td>
<td>5</td>
<td>DMF</td>
<td>4.0</td>
<td>100</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>117</td>
<td>8</td>
<td>Et₂O</td>
<td>4.0</td>
<td>25</td>
<td>24</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>7</td>
<td>117</td>
<td>15</td>
<td>Ethanol</td>
<td>0</td>
<td>25</td>
<td>24</td>
<td>100ᵇ</td>
</tr>
<tr>
<td>8</td>
<td>117</td>
<td>3</td>
<td>THF</td>
<td>4.0</td>
<td>25</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>117</td>
<td>3</td>
<td>1,4-dioxane</td>
<td>4.0</td>
<td>25</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>117</td>
<td>3</td>
<td>1,4-dioxane</td>
<td>4.0</td>
<td>60</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>117</td>
<td>5</td>
<td>CH₃CN</td>
<td>0</td>
<td>25</td>
<td>24</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>12</td>
<td>117</td>
<td>5</td>
<td>CH₃CN</td>
<td>4.0</td>
<td>25</td>
<td>24</td>
<td>10%</td>
</tr>
<tr>
<td>13</td>
<td>117</td>
<td>5</td>
<td>CH₃CN</td>
<td>4.0</td>
<td>60</td>
<td>24</td>
<td>100%</td>
</tr>
</tbody>
</table>

ᵃ % conversion based on ¹H NMR. ᵇ gave exclusively the ethyl ether 121
Surprisingly, the only two solvents that provided any conversion to the desired α,β-unsaturated ketone 122 were diethyl ether (entry 6) and acetonitrile (entry 11). The lack of reactivity in dichloromethane with 6 equivalents of water and 5 mol% of AuCl₃ (entry 1) was most likely due to the lower catalyst loading; however, the switch from ethanol to water cannot be ruled out as the problem. Not wishing to increase the catalyst loading, we chose to optimize the reaction with acetonitrile as the solvent. The addition of water as an additive increased the conversion to 10%, and complete conversion could be achieved by heating the mixture to 60 °C for 24 hours (entries 12 and 13).

Although complete conversion of propargyl alcohol 117 could be achieved with 5 mol % of AuCl₃ in acetonitrile at 60 °C in 24 h, the reaction was not clean. There was a significant amount of an unidentified by-product present. The number of equivalents of water present in the reaction mixture was found to influence by-product formation (Table 5).

![Chemical Structure](image)

**Table 5: Screening of Water Equivalents**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Equivalents of H₂O</th>
<th>Ratio of 122 to 123&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>117</td>
<td>1.0</td>
<td>1 : 0.66</td>
</tr>
<tr>
<td>2</td>
<td>117</td>
<td>2.0</td>
<td>1 : 0.62</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>3.0</td>
<td>1 : 0.29</td>
</tr>
<tr>
<td>4</td>
<td>117</td>
<td>4.0</td>
<td>1 : 0.40</td>
</tr>
<tr>
<td>5</td>
<td>117</td>
<td>5.0</td>
<td>1 : 0.46</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ratios based on integration of ¹H NMR spectra for comparative purposes. Numbers do not necessarily reflect the mole fraction of the unknown product.

Three equivalents of water were found to be optimal for suppression of by-product formation. Unfortunately, the by-product could not be suppressed completely. It was thought
that perhaps the long reaction times (24 h) were contributing to by-product formation by allowing AuCl$_3$ to react with the solvent.

The reactions were limited to 2 hours and catalyst loading was increased to achieve complete conversion (Table 6). A 10 mol % catalyst loading resulted in complete conversion, but there was still significant by-product formation (entry 3). Decreasing the temperature resulted in incomplete conversion and appeared to have little effect on by-product formation (entry 4). A catalyst loading of 20 mol % was found to allow the reaction to go to completion with little by-product formation (entry 5). Based on these results, reaction time seemed to be less important than catalyst loading in prevention of by-product formation.

![Diagram](image.png)

**Table 6: Catalyst Loading**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Mol % AuCl$_3$</th>
<th>Temperature °C</th>
<th>% Conversion$^a$</th>
<th>Amount of 123$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>117</td>
<td>1</td>
<td>60</td>
<td>&lt; 10</td>
<td>N.D.</td>
</tr>
<tr>
<td>2</td>
<td>117</td>
<td>5</td>
<td>60</td>
<td>50</td>
<td>High</td>
</tr>
<tr>
<td>3</td>
<td>117</td>
<td>10</td>
<td>60</td>
<td>100</td>
<td>High</td>
</tr>
<tr>
<td>4</td>
<td>117</td>
<td>10</td>
<td>25</td>
<td>50</td>
<td>High</td>
</tr>
<tr>
<td>5</td>
<td>117</td>
<td>20</td>
<td>60</td>
<td>100</td>
<td>Low</td>
</tr>
<tr>
<td>6</td>
<td>117</td>
<td>50</td>
<td>60</td>
<td>100</td>
<td>Low</td>
</tr>
</tbody>
</table>

$^a$% Conversion determined by $^1$H NMR  
$^b$Amount of 123 present determined qualitatively by $^1$H NMR

We next examined the scope of the reaction using 20 mol % AuCl$_3$, 3.0 equivalents of water in CH$_3$CN at 60 °C as our standard conditions. The triphenyl tertiary propargyl alcohol 117 rearranged cleanly to afford $\alpha,\beta$-unsaturated ketone 122 in 90 % yield (Eq 30, Figure 64). Switching to the secondary propargyl alcohol 122 proved to be detrimental. The expected $\alpha,\beta$-unsaturated ketone 125 was obtained in only a 16 % yield. The other 84 % comprised of a complex mixture of unidentified by-products (Eq 31, Figure 64). The tertiary propargyl alcohol
126 also proved to be a poor substrate, giving only the elimination product 127 in a 79 % yield (Eq 32, Figure 64). Even at room temperature, only the elimination product 127 was observed.

\[
\text{Ph} \text{OH} \xrightarrow{20 \text{ mol} \% \text{ AuCl}_3, 3.0 \text{ equiv. H}_2\text{O}} \xrightarrow{\text{MeCN}, 60 ^\circ\text{C}, 18 \text{ hr}} \text{Ph} \text{O} \\
\text{OH} \xrightarrow{20 \text{ mol} \% \text{ AuCl}_3, 3.0 \text{ equiv. H}_2\text{O}} \xrightarrow{\text{MeCN}, 60 ^\circ\text{C}, 18 \text{ hr}} \text{O} \\
\text{OH} \xrightarrow{20 \text{ mol} \% \text{ AuCl}_3, 3.0 \text{ equiv. H}_2\text{O}} \xrightarrow{\text{MeCN}, 60 ^\circ\text{C}, 18 \text{ hr}} \text{Ph} \\
\]

\( 117 \) \rightarrow \( 122 \) 90%  \\
\( 124^a \) \rightarrow \( 125^b \) 16%  \\
\( 126^c \) \rightarrow \( 127 \) 79%

\( ^a \) 124 was prepared from 1-hexyne addition to benzaldehyde in an 84% yield  \\
\( ^b \) only the \((E)\)-isomer was observed based on \(^1\)H NMR  \\
\( ^c \) 126 was prepared from phenyl acetylene addition to 3-pentanone in an 98% yield

Figure 64: Initial Substrate Screening with MeCN

These initial results suggested that the conditions were unsuitable for substrates other than tertiary propargyl alcohols, which are incapable of undergoing elimination. In addition, the unidentified by-product was still present in all cases. Previously, we avoided the use of CH₂Cl₂ as a solvent, due to the lack of reactivity exhibited when 5 mol % gold catalyst loading was employed. Now using 20 mol % of AuCl₃ in our reactions, CH₂Cl₂ was re-examined (Figure 65). Gratifyingly, the use of 20 mol % of AuCl₃, in CH₂Cl₂, allowed for the conversion of propargyl alcohol 117 into 122 in an 87 % yield. The use of methylenechloride also increased the conversion of 124 to 125 from 16 % (in CH₃CN) to 44 %. Under the new conditions, formation of 128 from 126 was also possible, although elimination to 127 was still the major
product. Other advantages of the CH₂Cl₂ system were the reaction could be carried out at room temperature, and there was no sign of any by-product formation.

Although the switch from acetonitrile to methylenechloride eliminated by-product formation and led to higher yields, the overall efficiency of the reactions was still quite low. The gold(III) salt is presumed to catalyze the reaction through an initial activation of the π-system of the alkyne. Increasing the electron density of the π-system may aid the transformation by increasing gold’s affinity towards the π-system. To test this theory, the ethynyl ether versions of 117 and 124 were prepared from lithium ethoxyacetylide addition to the necessary ketone. These analogs were then subjected to the reaction conditions (Figure 6). The tertiary propargyl alcohol 129 rearranged cleanly to give the α,β-unsaturated ester 130 in a 99 % yield in less than 5 minutes (Eq 36, Figure 66). Rearrangement of secondary ethoxy propargyl alcohol 132 also proceeded smoothly; however, the increased yield and lower reaction time came at the sacrifice of selectivity (Eq 37, Figure 66).
The use of oxygen-activated alkynes expanded the scope of the reaction to a wider range of substitution patterns (Table 7). Preparation of both di- and tri-substituted olefins is supported (entries 3 and 4-7), and yields are generally excellent. Entries 1-3 highlight the evolution of the conditions. An attractive feature of these AuCl$_3$-catalyzed rearrangements is that they can be performed open to air with wet solvents, without sacrificing yield.

The use of oxygen-activated alkynes allowed for lowering of the catalyst loading. Table 8 recounts our efforts to determine the minimum catalyst loading needed to achieve the Meyer–Schuster rearrangement of ethoxyalkynyl carbinol 136. Below 5 mol % (entries 4 and 5), complete conversion is not achieved. Based on qualitative thin-layer chromatography (TLC) monitoring of the experiments, the reactions appear to proceed rapidly and then stall at a certain point. Why the reactions stall is not yet understood. Thus, 5 mol % catalyst loading was the minimum that allowed for complete conversion. The 5 mol % catalyst loading could be extended to a variety of substrates including aliphatic, aromatic, hindered, and unhindered propargyl alcohols (entries 6-8).
Table 7: Initial Screening of Substrates Using Oxygen Activated Alkynes

\[
\begin{array}{cccccc}
\text{Entry} & \text{R}^1 & \text{R}^2 & \text{R}^3 & \text{Substrate} & \text{Time} & \text{Product} & \text{Yield (%)}^b \\
1^a & \text{Ph} & \text{H} & \text{Bu} & 124 & 18 \text{ h} & 125 & 16 \\
2 & \text{Ph} & \text{H} & \text{Bu} & 124 & 18 \text{ h} & 125 & 44 \\
3 & \text{Ph} & \text{H} & \text{OEt} & 132 & < 5 \text{ min} & 133 & 86 \\
4 & \text{Ph} & \text{Ph} & \text{OEt} & 129 & < 5 \text{ min} & 130 & > 95 \\
5 & 4-\text{t-Bu}-\text{cyclohexyl} & \text{OEt} & 134 & < 5 \text{ min} & 135 & 82 \\
6 & \text{adamantyl} & \text{OEt} & 136 & < 5 \text{ min} & 137 & > 95 \\
7 & \text{t-Bu} & \text{Me} & \text{OEt} & 138 & < 5 \text{ min} & 139 & 86 \\
\end{array}
\]

^a CH\textsubscript{3}CN was used as the solvent and the reaction was heated to 60 °C. ^b Isolated yield of pure product, unless otherwise indicated.

Table 8: Catalyst Loading and Optimization^a

\[
\begin{array}{cccccc}
\text{Entry} & \text{R}^1 & \text{R}^2 & \text{Substrate} & \text{AuCl}^3 & \text{Product} & \text{Conversion (%)} \\
1 & \text{adamantyl} & 136 & 20 \text{ mol %} & 137 & > 95 \\
2 & \text{adamantyl} & 136 & 10 \text{ mol %} & 137 & > 95 \\
3 & \text{adamantyl} & 136 & 5 \text{ mol %} & 137 & > 95 \\
4 & \text{adamantyl} & 136 & 1 \text{ mol %} & 137 & \text{ca. 50}^b \\
5 & \text{adamantyl} & 136 & 0.1 \text{ mol %} & 137 & < 5^b \\
6 & \text{Ph} & \text{Ph} & 129 & 5 \text{ mol %} & 130 & > 95 \\
7 & \text{t-Bu} & \text{Me} & 138 & 5 \text{ mol %} & 139 & > 95 \\
8 & \text{n-Bu} & \text{n-Bu} & 140 & 5 \text{ mol %} & 141 & > 95 \\
\end{array}
\]

^a Typical procedure: Gold(III)chloride added to a solution of propargyl alcohol (1 equiv), EtOH (5 equiv), and CH\textsubscript{2}Cl\textsubscript{2} in an open flask at room temperature. See Chapter 7 for details. ^b After 24 h.
With the rearrangement under control, attention was switched to streamlining the two-step addition/rearrangement process. It was found that the two-stage olefination could proceed without purification of the intermediate propargyl alcohol. The advantages of carrying out the rearrangement on the crude alcohol were three-fold. The time necessary to complete the overall olefination of the carbonyl was significantly reduced, the high costs associated with silica gel and solvents were reduced, and the risk of losing material in the intermediate purification process was eliminated.

The new streamlined two-stage olefination process was applied to a diverse group of hindered ketones (Table 9). Benzophenone 115, adamantane 142, and pinacolone 143 produced alkenes 130, 137, and 139 in excellent yields (entries 1-3). Dienonate 145 was obtained from verbenone 144 in nearly quantitative yield (entry 4). The ethoxyacetylelde addition to camphor 146 and 3,3,5,5-tetramethylcyclohexanone 147 failed to go to completion resulting in slightly lower yields for alkenoates 148 and 149. However, the yields were still quite reasonable (entries 5 and 6).

As illustrated in Table 9, we developed an atom-economical olefination strategy. The limitation in the method is the (E/Z)-selectivity (entries 3-6). The effects of the reaction temperature on the (E/Z)-selectivity of the rearrangement of ethoxyacetylene 138 can be seen in Table 10. The selectivity shifted from favoring the (Z)-isomer to favoring the (E)-isomer by lowering the reaction temperature to −78 °C (entries 4 and 5). The effect of the temperature was found to be independent of reaction time (entries 3 and 5). While temperature could be used to influence the formation of the major isomer, all attempts to obtain a single isomer by varying the temperature were unsuccessful. Exposure of the purified (E/Z)-mixture of α,β-unsaturated ester 139 to the normal reaction conditions resulted in no observable change in the (E/Z)-ratio. This suggests that isomerization under the reaction conditions is not a contributing factor to the (E/Z)-selectivity. Ultimately, temperature control alone was insufficient to control selectivity.
Table 9: Olefination of Hindered Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhO</td>
<td>PhCO₂Et</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>142</td>
<td>137</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>143</td>
<td>139</td>
<td>99ᵇ</td>
</tr>
<tr>
<td>4</td>
<td>144</td>
<td>145</td>
<td>96ᶜ</td>
</tr>
<tr>
<td>5</td>
<td>146</td>
<td>147</td>
<td>68% (84%)ᵈ</td>
</tr>
<tr>
<td>6</td>
<td>148</td>
<td>149</td>
<td>73 (85)ᵈ</td>
</tr>
</tbody>
</table>

ᵃ See Chapter 7 for details. ᵇ Ca. 4:3 ratio of olefin isomers. ᶜ Ca. 2:1 ratio of olefin isomers. ᵈ 10 mol % of AuCl₃ employed. Value in parentheses is the calculated yield based on recovered ketone.
Table 10: Temperature Effect on (E/Z)-Selectivity$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Temperature $^a$°C</th>
<th>E/Z Ratio$^b$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 min</td>
<td>25</td>
<td>3:4</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>5 min</td>
<td>0</td>
<td>2:3</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>24 h</td>
<td>25</td>
<td>2:3</td>
<td>99</td>
</tr>
<tr>
<td>4$^c$</td>
<td>20 min</td>
<td>-78 to -30</td>
<td>2:1</td>
<td>99</td>
</tr>
</tbody>
</table>

$^a$Typical procedure: Gold(III) chloride added to a solution of propargyl alcohol 138 (1 equiv), EtOH (5 equiv), and CH$_2$Cl$_2$ at the indicated temperature. $^b$ Determined by $^1$H NMR. $^c$ 20 mol % of AuCl$_3$ was used.

To identify conditions that afford the enoate products stereoselectively, we examined the rearrangement of secondary propargyl alcohols (prepared by addition of lithium ethoxyacetylide to the corresponding aldehydes). The dampened reactivity of secondary propargyl alcohols, compared to that of the tertiary alcohols which ionize more easily, along with the greater steric distinction between the aliphatic substituent and the hydrogen were hoped to make stereocontrol more facile. A qualitative screening of gold catalysts, additives, and solvents was conducted, and the results can be seen in Figure 67.

Figure 67: Qualitative Screening for Optimal Conditions

catalyst: AuCl⋅AgSbF$_6$ > AuCl$_3$, AuCl, Ph$_3$P⋅AuCl >> AgSbF$_6$
additive: EtOH >> CF$_3$CH$_2$OH, AcOH, PhOH, morpholine, none
solvent: THF−CH$_2$Cl$_2$ > THF, CH$_2$Cl$_2$, EtOH, H$_2$O
Of the protic additives screened, which were believed to assist in the formal 1,3-hydroxy migration, ethanol was the most effective. A mixed solvent system of 1:1 THF and CH$_2$Cl$_2$ proved superior to the use of either solvent independently. Although all of the gold catalysts screened performed well, a mixed AuCl/AgSbF$_6$ system provided the best results. Similar to previous results, a 5 mol% catalyst loading was found to be optimal. The new rearrangement conditions were then tested on a series of representative secondary alcohols (Table 11). Neopentyl alcohol 150 yielded the non-enolizable enoate 151 with almost complete selectivity (entry 1a). Alkyl-substituted alcohols 152, 154, and 156 gave enoates 153, 155, and 157 (entries 2a-4a) without any elimination to the enynes. Addition of camphorsulfonic acid (CSA) to the reaction mixture improved the selectivity of most reactions (entries 1b-6b).

Table 11: Meyer-Schuster Reaction of Ethoxyalkynyl Carbinols$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%), $E$/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a$^a$</td>
<td>[Structure of 150]</td>
<td>[Structure of 151]</td>
<td>91 (97:3)</td>
</tr>
<tr>
<td>1b$^b$</td>
<td>[Structure of 150]</td>
<td>[Structure of 151]</td>
<td>93 ($E$ only)</td>
</tr>
<tr>
<td>2a$^a$</td>
<td>[Structure of 152]</td>
<td>[Structure of 153]</td>
<td>80 (94:6)</td>
</tr>
<tr>
<td>2b$^b$</td>
<td>[Structure of 152]</td>
<td>[Structure of 153]</td>
<td>82 (99:1)</td>
</tr>
<tr>
<td>3a$^a$</td>
<td>[Structure of 154]</td>
<td>[Structure of 155]</td>
<td>91 (63:37)</td>
</tr>
<tr>
<td>3b$^b$</td>
<td>[Structure of 154]</td>
<td>[Structure of 155]</td>
<td>90 (86:14)</td>
</tr>
<tr>
<td>4a$^a$</td>
<td>[Structure of 156]</td>
<td>[Structure of 157]</td>
<td>75 (57:43)</td>
</tr>
<tr>
<td>4b$^b$</td>
<td>[Structure of 156]</td>
<td>[Structure of 157]</td>
<td>78 (70:30)</td>
</tr>
</tbody>
</table>
Table 11: Continued

\[
\begin{array}{c|c|c}
\text{Entry} & \text{Substrate} & \text{Product} \\
5a^a & \text{158} & 72 (40:60) \\
5b^b & \text{159} & 70 (40:60) \\
6a^a & \text{132} & 90 (47:53) \\
6b^b & \text{133} & 92 (91:9) \\
\end{array}
\]

\textsuperscript{a}Solutions of AgSbF\textsubscript{6} (5 mol%) and AuCl (5 mol%) in 1:1 THF–CH\textsubscript{2}Cl\textsubscript{2} added sequentially to ethoxyalkynl carbinol (1.0 equiv) and EtOH (10 equiv) in 1:1 THF–CH\textsubscript{2}Cl\textsubscript{2}. No camphorsulfonic acid (CSA) was included unless otherwise indicated. \textsuperscript{b} 1.0 Equiv CSA.

The addition of camphorsulfonic acid (CSA) not only improved the selectivity of the reaction but also accelerated the reaction, while addition of 2,6-di-tert-butyl-4-methylpyridine (DTBMP, an acid scavenger) inhibited the reaction. These results suggest that exchangeable protons play a significant role in the gold-catalyzed rearrangement. To test whether the gold catalyst has an active role in the reaction mechanism, or if the reaction is simply catalyzed by acid generated under the reaction conditions, a series of control experiments were conducted. Propargyl alcohol 138 was exposed to a variety of acidic conditions (Figure 68).

Use of 20 mol % of TsOH·H\textsubscript{2}O in place of the gold catalyst resulted in a 70:15 mole ratio of 138 and 139, along with unidentified product, after 18 hours (Eq 38). Aqueous acidic conditions were also tested. The use of 1 equivalent of AcOH in a 1:1 THF–H\textsubscript{2}O mixture resulted in no reaction, while the use of 50 mol % HCl resulted in incomplete conversion after 1 hour. The use of strong acids like HCl is much more likely to promote undesired side reactions and can only be used with acid-stable compounds. Therefore, although acid may be generated under the reaction conditions, there seems to be an important role for the gold catalyst.
The exact role of the gold catalyst in the reaction mechanism is still unknown. One possible mechanistic sequence for the Meyer–Schuster rearrangement of 150 to 151 can be seen in Figure 69. Coordination between the cationic gold catalyst and the electron-rich $\pi$-system of the alkyne allows for $\gamma$-addition of ethanol to generate 1,1-diethoxyallene 161, after immediate expulsion of water. The formation of allene 161 is consistent with the lack of $\beta$-hydroxy ester byproducts in any of the reactions, which is in sharp contrast to the acidic hydrolysis of ethoxyalkynyl carbinols.\(^{176,177}\) The gold catalyst may or may not promote subsequent reincorporation of water to produce 162. The stereoselectivity of the reaction is presumably set in this step. Control experiments have shown that there is no isomerization of the (Z)-enoates to the (E)-enoates under the reaction conditions. Therefore, we believe that the non-thermodynamic product distribution is the result of kinetic control. Collapse of 162 yields $\alpha,\beta$-unsaturated ester 151.
Figure 69: Hypothesis on the Meyer–Schuster Reaction Pathway

The mechanism depicted in Figure 69 suggests that there is incorporation of an external alcohol into the α,β-unsaturated ester, based on competitive collapse of tetrahedral intermediate 162. Alcohol 150 was subjected to the standard reaction conditions with replacement of ethanol with n-propanol, following the assumption that ethanol and n-propanol would be ejected from the tetrahedral intermediate at a similar rate. α,β-Unsaturated ethyl (151) and n-propyl (163) esters were obtained in an approximately 1:1 ratio (Figure 70). Exposure of enoate ester 151 to the same reaction conditions yielded no evidence of trans-esterification. Therefore, n-propanol incorporation must occur before product formation, which is consistent with our mechanistic hypothesis.

Figure 70: Incorporation of External Alcohol Additive
Our research to this point has mainly focused on the use of cationic gold catalysts to achieve the Meyer–Schuster reaction. The use of cationic gold and other precious metal catalysts offer many advantages in synthesis. The ability of these catalyst to engage in redox chemistry, through facile interconversion between oxidation states, has contributed to their use in a variety of applications. However, when selectively using these catalysts for their \( \pi \)-Lewis acidity, their ability to engage in redox chemistry is unnecessary and often makes interpretation of the reaction mechanism difficult. Another limitation of the precious metal catalysts, which is often ignored or confined to a footnote, is their high cost. This makes low catalyst loading and high turnover essential for developing a cost effective method.

Working under the hypothesis that the Meyer–Schuster rearrangement of ethoxyalkynyl carbinols by late transition metal-catalysts stems from simple Lewis acid/base interactions, we became interested in identifying other Lewis acids that could provide similar or superior activity. Table 12 provides a summary of our catalyst screenings, which focused primarily (though not exclusively) on soft transition metal salts. In an open reaction vessel, ethoxyacetylene was dissolved in methylenechloride and treated with reagent-grade ethanol (ca. 5–10 equiv) and 1 mol % of various Lewis acid catalysts (and one protic acid, camphorsulfonic acid, entry 1) at room temperature. Reactions were allowed to proceed for up to 24 hours or until TLC analysis showed consumption of starting material. The lone protic acid (CSA) is listed first; the rest of the table is arranged by the typical cost of the catalysts (per mole), from lowest to highest.

From this general screening emerged three top choices: copper(II) triflate, indium(III) chloride, and scandium(III) triflate, and all further studies were conducted with these catalysts. Of these, indium(III) chloride was the least reactive; the copper and scandium triflates were comparable in reactivity. All three are air-stable powders and are convenient to handle and use.

It should be noted that many of the catalysts (most notably HfCl\(_4\) and PtCl\(_4\)) that provided trace conversion with 1 mol % catalyst loading could achieve complete conversion with increased catalyst loading. Even with the higher catalyst loading, HfCl\(_4\) was competitive with the aforementioned catalysts in terms of cost.
In an attempt to gain more insight on these Lewis acid-catalyzed Meyer–Schuster reactions, the effects of various additives were explored. Two acidic and two basic additives were chosen: 1 mol % CSA, 1.0 equivalent acetic acid (AcOH), 1 mol % 2,6-di-tert-butyl-4-methylpyridine (DTBMP), and 1.0 equivalent magnesium oxide (MgO). The effect of the...
additives on the reaction rate (qualitatively) and the stereoselectivity (quantitatively) of the reaction are summarized in Table 13.

![Reaction Scheme]

Table 13: Effect of Additives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Amount</th>
<th>Time (h)</th>
<th>E/Z Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>InCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>None</td>
<td>_</td>
<td>24</td>
<td>84:16</td>
</tr>
<tr>
<td>2</td>
<td>InCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CSA</td>
<td>1 mol %</td>
<td>6</td>
<td>67:33</td>
</tr>
<tr>
<td>3</td>
<td>InCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>DTBMP</td>
<td>1 mol %</td>
<td>24</td>
<td>75:25</td>
</tr>
<tr>
<td>4</td>
<td>InCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>AcOH</td>
<td>1.0 equiv</td>
<td>24</td>
<td>91:9</td>
</tr>
<tr>
<td>5</td>
<td>InCl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MgO</td>
<td>1.0 equiv</td>
<td>24</td>
<td>78:22</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>None</td>
<td>_</td>
<td>1.5</td>
<td>89:11</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>CSA</td>
<td>1 mol %</td>
<td>1.5</td>
<td>86:14</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DTBMP</td>
<td>1 mol %</td>
<td>24</td>
<td>76:24</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>AcOH</td>
<td>1.0 equiv</td>
<td>&lt; 1</td>
<td>89:11</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>MgO</td>
<td>1.0 equiv</td>
<td>24&lt;sup&gt;b&lt;/sup&gt;</td>
<td>76:24</td>
</tr>
<tr>
<td>11</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>None</td>
<td>_</td>
<td>1.2</td>
<td>90:10</td>
</tr>
<tr>
<td>12</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>CSA</td>
<td>1 mol %</td>
<td>&lt; 1</td>
<td>92:8</td>
</tr>
<tr>
<td>13</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>DTBMP</td>
<td>1 mol %</td>
<td>4</td>
<td>91:9</td>
</tr>
<tr>
<td>14</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>AcOH</td>
<td>1.0 equiv</td>
<td>&lt; 1</td>
<td>92:8</td>
</tr>
<tr>
<td>15</td>
<td>Sc(OTf)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MgO</td>
<td>1.0 equiv</td>
<td>24&lt;sup&gt;c&lt;/sup&gt;</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

<sup>a</sup> As observed by <sup>1</sup>H NMR  <sup>b</sup> Conversion (60%)  <sup>c</sup> Conversion (30%)
Lewis acid and protic acids catalyze the Meyer–Schuster reaction, so one would expect acidic additives to accelerate the reaction and basic additives to quench or retard the reaction. This hypothesis is supported by the results presented in Table 13. However, the fact that basic additives retard but do not quench the reaction suggests that protic acid, though helpful, is not required for catalytic activity. Therefore, one can choose between a short reaction time (e.g., entries 9 or 14) and reaction conditions that are presumably free of protic acid (e.g., entry 5).

Since the Sc(OTf)₃ and Cu(OTf)₂ were more reactive and gave better (E)-selectivity than the InCl₃ catalyst in the absence of additives, they were used in the two-step olefination of aldehydes and ketones. As expected, ethoxyacetylene addition to both ketones and aldehydes proceeded smoothly and with high isolated yields (Table 14).

The resulting secondary and tertiary propargyl alcohols were treated with either 1 mol % of Cu(OTf)₂ or Sc(OTf)₃ to complete the two-step olefination (Table 15). Use of EtOH as a co-solvent instead of an additive provided superior selectivity (entries 1-4). Aliphatic substitution at the propargyl position was universally tolerated. In the case of aliphatic di-substituted alkenes, (E)-selectivity increased as branching increased (entries 1-8). Stereoselection eroded when tri-
substituted alkenes were formed, or an aromatic group was introduced at the propargyl position (entries 9-12). The two catalyst systems gave similar results; however, scandium (III) triflate performed slightly better. Scandium(III) triflate also has the advantage of being recoverable and reusable after aqueous work up without loss of activity.\textsuperscript{185}

\begin{table}[h]
\centering
\caption{Scandium and Copper Rearrangements}
\begin{tabular}{cccccc}
\hline
Entry & Substrate & Catalyst & $R^1$ & $R^2$ & Product & Yield (\%)$^b$ & $E/Z$ Ratio$^c$
\hline
1$^a$ & Cu(OTf)$_2$ & & & & & 53 & 91:9
2$^a$ & Sc(OTf)$_2$ & $n$-Heptyl & H & 155 & 63 & $E$ only
3 & Cu(OTf)$_2$ & & & & 64 & 97:3
4 & Sc(OTf)$_2$ & & & & 70 & $E$ only
5 & Cu(OTf)$_2$ & Cyclohexyl & H & 157 & 71 & $E$ only
6 & Sc(OTf)$_2$ & & & & 75 & $E$ only
7 & Cu(OTf)$_2$ & tert-Butyl & H & 151 & 94 & $E$ only
8 & Sc(OTf)$_2$ & & & & 97 & $E$ only
9 & Cu(OTf)$_2$ & tert-Butyl & Me & 139 & 86 & 57:43
10 & Sc(OTf)$_2$ & & & & 89 & 58:42
11 & Cu(OTf)$_2$ & Phenyl & H & 133 & 90 & 76:24
12 & Sc(OTf)$_2$ & & & & 93 & 77:23
\hline
\end{tabular}
\end{table}

$^a$ EtOH (5.0 equiv) in CH$_2$Cl$_2$  $^b$ Isolated yield  $^c$ As observed by $^1$H NMR

Up until this point, our substrates had been limited to those containing aliphatic and aryl substituents. To test the functional group compatibility of this method, $N$-Boc-serine methyl ester 167 was converted to into the tert-butylidimethylsilyl (TBS) ether 168. It was then included
in the reaction mixture during the conversion of 156 to 157 (Figure 71). Ester 157 was isolated in 75 % yield, and the TBS protected N-Boc-serine methyl ester was recovered in near quantitative yield. The high recovery of 168 indicates that our current Meyer–Schuster conditions are compatible with typical alkyl esters, amine carbamates, and silyl ethers.

In our earlier gold(III) chloride catalyst work, we developed a two-stage olefination method that avoided the need to purify the propargyl alcohol intermediate. The use of the crude propargyl alcohol allowed for higher yields over the two steps and greatly reduced the time needed to complete the overall olefination. The use of 1 mol % scandium(III) triflate in place of 5 mol % of the more expensive gold(III) chloride had no negative effect and yields were generally excellent (Table 16).

A series of trisubstituted olefins were prepared (entries 1-7) in good to excellent yield, although control of stereochemistry was limited (entries 1-2, 7). Entries 1-4 illustrate the ability of this method to olefinate hindered ketones in excellent yields. Preparation of 169 is of particular interest since we were unable to prepare it through the use of the Horner–Wadsworth–Emmons reaction (refer to Chapter 3).
Table 16: Two-Stage Olefination of Ketones and Aldehydes

\[
\begin{array}{cccc}
\text{Entry} & \text{Substrate} & \text{Product} & \text{Yield (\%)}^b & \text{E/Z Ratio}^c \\
1 & (-)-menthone 58 & \text{169} & 98 & \text{n.d.}^6 \\
2 & verbenone 144 & \text{145} & 97 & 58:42 \\
3 & benzophenone 115 & \text{130} & 99 & - \\
4 & adamantanone 142 & \text{137} & 96 & - \\
5 & 4-\text{tert}-\text{butyl cyclohexanone} 170 & \text{171} & 60 & - \\
6 & cycloheptanone 172 & \text{173} & 78 & - \\
7 & acetophenone 174 & \text{175} & 93 & 39:61 \\
8 & pivaldehyde 166 & \text{151} & 80 & E \text{ only} \\
\end{array}
\]
Table 16: Continued

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)(^b)</th>
<th>E/Z Ratio(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>(-)-perillaldehyde 176</td>
<td><img src="image" alt="Product Structure" /> 177</td>
<td>94</td>
<td>89:11</td>
</tr>
<tr>
<td>10</td>
<td>4-methoxybenzaldehyde 178</td>
<td><img src="image" alt="Product Structure" /> 179</td>
<td>94</td>
<td>89:11</td>
</tr>
<tr>
<td>11</td>
<td>2-furaldehyde 180</td>
<td><img src="image" alt="Product Structure" /> 181</td>
<td>97</td>
<td>36:61(^d)</td>
</tr>
<tr>
<td>12</td>
<td>pentafluorobenzaldehyde 182</td>
<td><img src="image" alt="Product Structure" /> 183</td>
<td>80</td>
<td>(E) only</td>
</tr>
</tbody>
</table>

\(^a\) 1 mol % Sc(OTf)\(_3\), CH\(_2\)Cl\(_2\)/EtOH (4:1)  \(^b\) Isolated yield  \(^c\) Determined by \(^1\)H NMR unless otherwise stated  \(^d\) \(E\) and \(Z\) isomers were isolated separately  \(^e\) Unable to determine the \(E/Z\) ratio by \(^1\)H NMR

The method also proved efficient for the preparation of disubstituted olefins (entries 8-12). Excellent (\(E\))-selectivity was achieved for aliphatic substituents (entry 8); however, selectivity diminished when aryl (entries 10-12) or vinyl (entry 9) substituents were introduced (exception is entry 12). Both electron-rich (entries 10 and 11) and electron-deficient (entry 12) aryl substituents at the propargyl position were tolerated.

In our earlier studies using gold and silver salts to catalyze the Meyer–Schuster reaction, we suggested a mechanism in which the alcoholic additive becomes incorporated into 50 % of the product via an intermediate 1,1-diethoxy-allene 161 (refer to Figure 69). This hypothesis was supported by the observation that the ethyl and propyl esters were obtained in a roughly 1:1 ratio when \(n\)-propanol was used as the additive. This experiment was repeated...
with the use of the scandium(III) triflate catalyst. Instead of obtaining the expected 1:1 ratio of ethyl and propyl esters, we obtained a ratio of 25:75 (as estimated by $^1$H NMR, Eq 38 Figure 72). In other words, there was only a 25 % retention of the original ethoxy group. Based on our previous mechanism, the ethoxy group should be retained in at least 50 % of the product, even in the presence of excess n-propanol. The possibility of trans-esterification was eliminated by a control experiment in which pure ethyl ester 151 was subjected to the reaction conditions. There was no evidence of the propyl ester product, even after extended reaction times (Eq 39, Figure 72).

These observations led us to suggest a slightly modified mechanism for the scandium(III) triflate catalyst (Figure 73). Based on the consistent lack of β-hydroxy ester by-products, the scandium(III) triflate-catalyzed Meyer–Schuster reaction most likely also proceeds via intermediate 1,1-diethoxy-allene NN. Subsequent addition of a second equivalent of ethanol would give rise to tetrahedral intermediate OO, which can hydrolyze via intermediate PP to reach the α,β-unsaturated ester MM. Invoking ortho-ester intermediate OO can account for up to a 67 % incorporation of the alcohol additive; however, we observed a 75 % incorporation. One possible explanation would be dynamic alcohol exchange reactions of ortho-ester OO.
A series of experiments were conducted with varying amounts of \( n \)-PrOH. In every case, there was \textit{almost} complete statistical incorporation of the \( n \)-propanol additive (Table 17). These results provide support for a hemi-labile intermediate \( \text{OO} \), that can undergo partial equilibrium before proceeding irreversibly to the \( \alpha,\beta \)-unsaturated ester \( \text{MM} \). The equilibrium can also account for the high \( (E) \)-selectivity observed in the case of disubstituted olefins with the scandium catalyst, by allowing for the thermodynamic establishment of the olefin geometry at the stage of the \textit{ortho}-ester.

We have developed an efficient, two-step, atom-economical method for the olefination of aldehydes and ketones. The first step was acetylide addition to a carbonyl substrate. Acetylide addition is relatively insensitive to steric congestion, which allowed for the use of hindered ketones as substrates. The second step was the conversion of the resulting propargyl alcohol to the desired \( \alpha,\beta \)-enone by the use of Meyer–Schuster reaction. The Meyer–Schuster reaction was found to proceed more readily and with lower catalyst loading when the propargyl alcohol contained an oxygen-activated alkyne.
Gold(III) chloride was the first catalyst to provide consistent results. The relatively expensive gold catalyst required a 5 mol % catalyst loading and showed little stereochemical control. The lack of stereochemical control was partially addressed by the use of a Au(I)/Ag(I) catalyst system. Inclusion of 1.0 equivalent of CSA allowed for the preparation of a variety of disubstituted olefins with high \( (E) \)-selectivity. A screening of various Lewis acids revealed that the less expensive Sc(OTf)_3 could be substituted for the precious metal catalysts without sacrificing yield. Not only did the use of Sc(OTf)_3 allow for the catalyst loading to be lowered to 1 mol %, it also proved significantly more adept in controlling the stereochemistry of the rearrangement.

Future plans are to test scandium(III) triflate’s ability to catalyze the Meyer–Schuster rearrangement of propargyl alcohols derived from aliphatic alkynes, which have proven to be poor substrates for the gold catalysts. We would also like to determine whether the electronic nature of the alkyne affects the \( (E/Z) \)-selectivity of the reaction, for both the gold and scandium-based catalysts. Finally, further mechanistic experiments will be conducted to identify the exact role of gold and scandium salts in the reaction mechanism.

---

**Table 17: Incorporation of External Alcohol Additive**

<table>
<thead>
<tr>
<th>Entry</th>
<th>PrOH (equiv)</th>
<th>150:PrOH</th>
<th>151:163 (^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>50:50</td>
<td>55:45</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>33:67</td>
<td>42:58</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>25:75</td>
<td>38:62</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>17:83</td>
<td>25:75</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>9:91</td>
<td>22:78</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>1:99</td>
<td>16:84</td>
</tr>
</tbody>
</table>

\(^a\) As observed by \(^1\)H NMR
In conclusion, we outlined and discussed a strategy for the olefination of aldehydes and ketones using the Meyer–Schuster rearrangement of ethoxyalkynyl carbinols. The method appears to be limited only by the ability to access the requisite propargyl alcohols via ethoxyacetylide addition to carbonyls. This method is likely to find widespread application in organic synthesis, particularly for its unique ability to complete the olefination of hindered ketones in excellent yield.
GENERAL EXPERIMENTAL PROCEDURES:

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on 300 MHz spectrometer using CDCl$_3$ as the deuterated solvent. The chemical shifts ($\delta$) are reported in parts per million (ppm) relative to the residual CHCl$_3$ peak (7.26 ppm for $^1$H NMR, 77.0 ppm for $^{13}$C NMR). The coupling constants ($J$) were reported in Hertz (Hz). IR spectra were recorded on an FTIR spectrometer on NaCl discs. Mass spectra were recorded using chemical ionization (CI) or electron ionization (EI) techniques. Yields refer to isolated material judged to be $\geq$95% pure by $^1$H NMR spectroscopy following silica gel chromatography. All chemicals were used as received unless otherwise stated. Tetrahydrofuran (THF) was purified by passing through a column of activated alumina. The $n$-BuLi solutions were titrated with menthol dissolved in tetrahydrofuran using 1,10-phenanthroline as the indicator. The purifications were performed by flash chromatography using silica gel F-254 (230-499 mesh particle size).
(2S, 5R)-1-Hex-1-ynyl-2-isopropyl-5-methyl-cyclohexanol [113]

To a THF solution (5 mL) of 1-hexyne (0.44 mL, 3.94 mmol) was added n-BuLi (1.29 mL, 2.96 mmol, 2.29 M) dropwise over 5 min at −78 °C under argon atmosphere. The solution was allowed to warm to 0 °C over 1 h and held at 0 °C for an additional 30 min. The solution was then recooled to −78 °C and (−)-menthone (0.34 mL, 1.97 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 h and held at room temperature for an additional 3 h. Saturated aqueous NH₄Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 20/1 – 10/1) to give (2S, 5R-1-hex-1-ynyl-2-isopropyl-5-methyl-cyclohexanol (113) in 96 % yield (0.45 g) as a clear colorless oil.

¹H NMR (300 MHz, CDCl₃): δ 0.83-0.96 (m, 12H), 1.23-1.57 (m, 10H), 1.65-1.78 (m, 2H), 1.92 (dt, J = 13.6, 3.7 Hz, 1H), 2.20 (t, J = 7.2 Hz, 2H), 2.35-2.45 (m, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 13.5, 18.3, 18.6, 20.5, 21.8, 21.9, 23.9, 27.3, 28.2, 30.9, 34.9, 50.5, 50.9, 71.8, 83.7, 85.0 For full characterization refer to Spino, C.; Beaulieu, C. J. Am. Chem. Soc. 1998, 120(45), 11832–11833.
1,1,3-Triphenyl-2-propyne-1-ol [117]

To a THF solution (6 mL) of phenylacetylene (0.85 mL, 7.69 mmol) was added n-BuLi (3.3 mL, 6.59 mmol, 2.0 M) dropwise over 5 min at −78 °C under argon atmosphere. The solution was allowed to warm to 0 °C over 1 hr and held at 0 °C for an additional 30 min. The solution was then recooled to −78 °C and benzophenone (1.0 g, 5.52 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 h and held at room temperature for an additional 3 hr. Saturated aqueous NH₄Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 20/1 – 10/1) to give 1,1,3-triphenyl-2-propyne-1-ol (117) in 100 % yield (1.57 g) as a white crystalline solid.

¹H NMR (300 MHz, CDCl₃): δ 2.85 (s, 1H), 7.28-7.42 (m, 9H), 7.48-7.53 (m, 2H), 7.64-7.73 (m, 3H); For full characterization refer to Sanz, R.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Eur. J. Org. Chem.* **2006**, *6*, 1383–1386.
1-Phenyl-hept-2-yn-1-ol [118]

To a THF solution (6 mL) of 1-hexyne (0.76 mL, 6.59 mmol) was added n-BuLi (2.47 mL, 5.65 mmol, 2.29 M) dropwise over 5 min at –78 °C under argon atmosphere. The solution was allowed to warm to 0 °C over 1 h and held at 0 °C for an additional 30 min. The solution was then recooled to –78 °C and benzaldehyde (0.48 mL, 4.71 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 hr and held at room temperature for an additional 3 hr. Saturated aqueous NH₄Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 20/1 – 10/1) to give 1-phenyl-hept-2-yn-1-ol (118) in 84 % yield (0.75 g) as a clear yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 0.92 (t, J = 7.2 Hz, 3H), 1.32-1.61 (m, 4H), 2.08 (dd, J = 6.1, 3.1 Hz, 1H), 2.28 (td, J = 6.9, 1.9 Hz, 2H), 5.46 (d, J = 6.0 Hz, 1H), 7.29-7.46 (m, 3H), 7.55 (d, J = 7.2 Hz, 2H); For full characterization refer to Fuerstner, A.; Shi, N. J. Am. Chem. Soc. 1996, 118(49), 12349–12357.
3-Ethyl-1-phenyl-1-pentyn-3-ol [126]
To a THF solution (6 mL) of phenylacetylene (1.55 mL, 14.1 mmol) was added $n$-BuLi (4.6 mL, 10.6 mmol, 2.29 M) dropwise over 5 min at $-78 \, ^\circ\text{C}$ under argon atmosphere. The solution was allowed to warm to 0 °C over 1 hr and held at 0 °C for an additional 30 min. The solution was then recooled to $-78 \, ^\circ\text{C}$ and 3-pentanone (0.75 mL, 7.1 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 hr and held at room temperature for an additional 3 hr. Saturated aqueous NH$_4$Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO$_4$, filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 20/1 – 10/1) to give 3-ethyl-1-phenyl-1-pentyn-3-ol (126) in 100 % yield (1.33 g).

light yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.11 (t, $J = 7.4 \, \text{Hz}$, 6H), 1.77 (q d, $J = 7.4$, 4.5 Hz, 4H), 1.94 (br s, 1H), 7.28-7.33 (m, 3H), 7.40-7.44 (m, 2H). For full characterization refer to Galli, C. et al. J. Org. Chem. 1994, 59, 6786–6795.
Typical procedure for solvent screening with AuCl₃, Table 4

To a MeCN solution (1 mL) of 1,1,3-triphenyl-2-propyne-1-ol 117 (23.3 mg, 0.82 mmol) in a 1 dram vial under Ar was added AuCl₃ (1.2 mg, 0.004 mmol) at room temperature. After 24 hr, the reaction mixture was filtered through a plug of SiO₂ with the aid of an ethyl acetate/hexane mixture (1/7). The filtrate was concentrated and resulting residue was subjected to ¹H NMR. Conversion to 122 was 5 %.

Typical procedure for screening of water equivalence, Table 5

To a MeCN solution (1 mL) of 1,1,3-triphenyl-2-propyne-1-ol 117 (23.3 mg, 0.82 mmol) in a 1 dram vial under Ar was added water (44 μL, 2.46 mmol) followed by AuCl₃ (1.2 mg, 0.004 mmol). Reaction mixture was heated to 60 °C in an oil bath for 24 hr, then allowed to cool to room temperature. Reaction mixture was concentrated and the resulting residue was subjected to ¹H NMR. Qualitative ratio of 122 to the unidentified by-product was determined.

Typical procedure for AuCl₃ catalyst loading in CH₃CN, Table 6

To a MeCN solution (1 mL) of of 1,1,3-triphenyl-2-propyne-1-ol 117 (23.3 mg, 0.82 mmol) in a 1 dram vial under Ar was added water (44 μL, 2.46 mmol) followed by AuCl₃ (2.4 mg, 0.008 mmol). Reaction mixture was heated to 60 °C in an oil bath for 2 hr, then allowed to cool to room temperature. Reaction mixture was concentrated and the resulting residue was subjected to ¹H NMR. Qualitative ratio of 122 to the unidentified by-product was determined.

Typical procedure for preparation of α,β-unsaturated ketones 122 and 125 and enyne 127 in MeCN, Figure 63

To a MeCN solution (8 mL) of 1,1,3-triphenyl-2-propyne-1-ol 117 (102 mg, 0.36 mmol) in a 2-neck, 25 mL round bottom flask was added water (19 μL, 1.08 mmol) followed by AuCl₃ (22 mg, 0.073 mmol). Reaction was heated to 60 °C for 18 hr, then allowed to cool to room temperature. Reaction mixture was concentrated and the resulting residue was purified by flash chromatography (hexanes/ethyl acetate = 100/1) to give 122 in 90 % yield (92 mg).
1,3,3-triphenyl-propenone [122]: yellow oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.12 (s, 1H), 7.16-7.21 (m, 2H), 7.25-7.28 (m, 3H), 7.35-7.4 (m, 7H), 7.46-7.51 (m, 1H), 7.91 (d, J = 7.1 Hz, 2H); For full characterization refer to Gurdeep et al. *J. Chem. Soc. Perkin Trans. I.* 1985, 1289–1294.

(E)-1-Phenyl-hept-1-en-3-one [125]

$^1$H NMR (300 MHz, CDCl$_3$) δ 0.77-1.02 (m, 3H), 1.20-1.47 (m, 2H), 1.57-1.78 (m, 2H), 2.67 (t, J = 7.4 Hz, 2H), 6.75 (d, J = 16.2 Hz, 1H), 7.35-7.47 (m, 3H), 7.49-7.66 (m, 3H); For full characterization refer to Concellon, J.; Rodriguez-Solla, H.; Mejica, C. *Tetrahedron* 2006, 62(14), 3292–3300.

3-Ethyl-pent-3-en-1-ynyl benzene [127]

$^1$H NMR (300 MHz, CDCl$_3$) δ 1.14 (t, J = 7.5 Hz, 3H), 1.91 (dt, J = 6.8, 1.1 Hz, 3H), 2.18-2.27 (m, 2H), 5.81 (qt, J = 6.8, 1.2 Hz, 1H), 7.27-7.39 (m, 3H), 7.40-7.50 (m, 2H); For full characterization refer to Mayr, H.; Halberstadt-Kausch, I. *Chem. Ber.* 1982, 115(11), 3479–3515.
Typical procedure for the preparation of \(\alpha,\beta\)-unsaturated ketones 122, 125, and 128 in \(\text{CH}_2\text{Cl}_2\), Figure 64

To a \(\text{CH}_2\text{Cl}_2\) solution (8 mL) of 3-ethyl-1-phenyl-1-pentyn-3-ol 126 (0.10 g, 0.54 mmol) in an open flask was added 95 % ethanol (0.15 mL, 2.7 mmol) followed by \(\text{AuCl}_3\) (33 mg, 0.11 mmol). After 18 hr the reaction mixture was diluted with diethyl ether (10 mL) and concentrated. The resulting residue was purified by flash chromatography (hexanes/ethyl acetate = 100/1) to give 3-ethyl-1-phenyl-pent-2-en-1-one 128 in 31 % yield (31.8 mg).

Typical procedure for the preparation of ethoxy propargylic alcohols 129, 132, 134, 136, 138, 150, 152, 154, 156, 158

To a THF solution (7 mL) of ethyl ethynyl ether (0.7 g, ca. 40% by weight in hexanes, ca. 9 mmol was added \(n\)-BuLi (1.5 mL, 3.4 mmol, 2.3 M) dropwise over 5 min at –78 °C under argon atmosphere. The solution was allowed to warm to 0 °C over 1 hr and held at 0 °C for an additional 30 min. The solution was then recooled to –78 °C and pinacolone (0.30 mL, 2.4 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 hr and held at room temperature for an additional 3 hr. Saturated aqueous \(\text{NH}_4\text{Cl}\) solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over \(\text{MgSO}_4\), filtered, and concentrated. The residue was purified using silica gel column chromatography (hexanes/ethyl acetate = 20/1 – 7/1) to give 1-ethoxy-3-methyl-3-\textit{tert}-butyl-1-propyn-3-ol (138) in 83 % yield (0.34g).

\[
\text{Ph} \quad \text{Ph} \quad \text{OH} \quad = \quad \text{OEt}
\]

129

\textit{3-ethoxy-1,1-diphenyl-prop-2-yn-1-ol} (129): yellow oil; \(^1\text{H} \text{NMR} \) (300 MHz, \(\text{CDCl}_3\)) \(\delta\) 1.41 (t, \(J = 7.1 \text{ Hz}, 3\text{H}\)), 2.64 (s, 1H), 4.18 (q, \(J = 7.1 \text{ Hz}, 2\text{H}\)), 7.21-7.34 (m, 6H), 7.60-7.63 (m, 4H); \(^{13}\text{C} \text{NMR} \) (75 MHz, \(\text{CDCl}_3\)) \(\delta\) 14.4, 42.2, 74.4, 74.8, 95.9, 125.9, 127.2, 128.0, 146.1; \text{IR} \) (neat) 3543, 3444, 3060, 2982, 2263, 1450, 1170, 1004, 640 cm\(^{-1}\); \text{HRMS} \) (El) Calcd for \(\text{C}_{17}\text{H}_{16}\text{O}_2\) (M\(^+\)) 252.1150. Found 252.1153.
3-Ethoxy-1-phenyl-prop-2-yn-1-ol [132]

$^1$H NMR (300 MHz, CDCl$_3$) δ 1.39 (t, $J = 7.1$ Hz, 3H), 2.04 (d, $J = 5.9$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 5.51 (d, $J = 6.0$ Hz, 1H), 7.31-7.40 (m, 3H), 7.48-7.59 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 14.4, 38.8, 64.6, 74.8, 95.4, 126.5, 128.0, 128.5, 129.2; IR (neat) 3401, 2981, 2226, 1718, 1450 cm$^{-1}$; HRMS (El) calcd for C$_{11}$H$_{12}$O$_2$ (M$^+$) 176.0834. Found 176.0837.


4-tert-butyl-1-ethoxyethynyl-cyclohexanol [134]: white solid; $^1$H NMR (300 MHz, CDCl$_3$) δ 0.87 (s, 9H), 0.98 (t, $J = 11.9$, 3.5 Hz, 1H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.26-1.55 (m, 4H), 1.71 (br d, $J = 12.8$ Hz, 2H), 1.89 (s, 1H), 1.94 (br d, $J = 10.6$ Hz, 2H), 4.09 (q, $J = 7.1$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 14.3, 25.0, 27.6, 32.2, 41.1, 41.3, 47.1, 69.6, 74.4, 94.0; IR (neat) 3390, 2944, 2865, 2257, 1479, 1444, 1393, 1365, 1178, 1059, 900, 834 cm$^{-1}$; HRMS (Cl) Calcd for C$_{14}$H$_{24}$O$_2$ (M+H$^+$) 225.1855. Found 225.1856.

2-ethoxyethynyl-adamantan-2-ol [136]: clear, colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) δ 1.37 (t, $J = 7.1$ Hz, 3H), 1.53 (br s, 1H), 1.57 (br s, 1H), 1.68-1.80 (m, 7H), 1.88 (br s, 2H), 2.14 (br t, $J = 12.6$ Hz, 4H), 4.09 (q, $J = 7.1$ Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 14.6, 27.1, 27.3, 32.0, 35.9, 38.0, 39.8, 43.2, 72.7, 74.6, 93.9; IR (neat) 3426, 2902, 2854, 2666, 2259, 1712, 1450, 1247, 1010, 916, 866 cm$^{-1}$; HRMS (Cl) Calcd for C$_{14}$H$_{20}$O$_2$ (M+H$^+$) 221.1542. Found 221.1538.
1-ethoxy-3-methyl-3-tert-butyl-1-propyn-3-ol [138]: clear, colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.03 (s, 9H), 1.37 (t, $J$ = 7.1 Hz, 3H), 1.41 (s, 3H), 1.71 (s, 1H), 4.08 (q, $J$ = 7.1 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.3, 25.2, 25.6, 38.4, 41.9, 73.9, 74.2, 92.8; IR (neat) 3479, 2971, 2873, 2261, 1481, 1392, 1369, 1219, 1094, 1007, 908, 878 cm$^{-1}$; HRMS (Cl) Calcd for C$_{10}$H$_{19}$O$_2$ ([M+H]$^+$) 171.1385. Found 171.1390.

1-Ethoxy-4,4-dimethyl-pent-1-yn-3-ol [150]: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.97 (s, 9H), 1.38 (t, $J$ = 7.1 Hz, 3H), 4.03 (d, $J$ = 6.0 Hz, 1H), 4.10 (q, $J$ = 7.1 Hz, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.2, 25.2, 35.8, 38.0, 71.0, 74.3, 94.0; IR (neat) 3431, 2956, 2714, 2264, 1629 cm$^{-1}$; HRMS (El) calcd for C$_9$H$_{16}$O$_2$ (M$^+$) 156.1150. Found 156.1103.

1-Ethoxy-5-phenyl-pent-1-yn-3-ol [152]: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.38 (t, $J$ = 7.1 Hz, 3H), 1.66 (d, $J$ = 5.3 Hz, 1H), 1.97-2.03 (m, 2H), 2.78 (t, $J$ = 7.9 Hz, 2H), 4.11 (q, $J$ = 7.1 Hz, 2H), 4.41 (ap. q, $J$ = 5.3 Hz, 1H), 7.16-7.31 (m, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.3, 31.6, 38.8, 40.1, 61.7, 74.6, 94.0, 125.8, 128.3, 128.4, 141.6; IR (neat) 3400, 3084, 3061, 2931, 2862, 2262, 1722, 1603, 1496 cm$^{-1}$; HRMS (El) calcd for C$_{13}$H$_{16}$O$_2$ (M$^+$) 204.1145. Found 204.1150.
1-Ethoxy-dec-1-yn-3-ol [154]: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.86-0.90 (m, 3H), 1.21-1.46 (m, 10H), 1.37 (t, $J = 7.1$ Hz, 3H), 1.56-1.70 (m, 3H), 4.09 (q, $J = 7.1$ Hz, 2H), 4.39 (q, $J = 6.3$ Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.0, 14.2, 22.5, 25.3, 29.2, 29.2, 31.7, 38.6, 39.6, 62.3, 74.4, 93.5; IR (neat) 3381, 2927, 2263, 1722, 1467 cm$^{-1}$; HRMS (CI) calcd for C$_{12}$H$_{22}$O$_2$ (M+H$^+$) 199.1698. Found 199.1692.

1-Cyclohexyl-3-ethoxy-prop-2-yn-1-ol [156]: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.83-1.3 (m, 6H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.57-1.84 (m, 6H), 4.10 (q, $J = 7.1$ Hz, 2H), 4.18 (t, $J = 5.7$ Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.3, 25.9, 25.9, 26.4, 28.1, 28.6, 38.3, 44.6, 67.0, 74.5, 94.3; IR (neat) 3411, 2980, 2460, 1719, 1450 cm$^{-1}$; HRMS (Cl) calcd for C$_{11}$H$_{18}$O$_2$ (M+H$^+$) 183.1385. Found 183.1390.

1-Cyclohex-1-enyl-3-ethoxy-prop-2-yn-1-ol [158]: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.38 (t, $J = 7.1$ Hz, 3H), 1.55-1.65 (m, 8H), 2.07 (br s, 1H), 4.12 (q, $J =$7.1 Hz, 2H), 4.77 (d, $J = 5.5$ Hz, 1H), 5.85 (s, 1H); $^{13}$C NMR $\delta$ 14.3, 22.3, 22.5, 24.0, 24.9, 38.0, 66.7, 74.6, 94.6, 123.8, 138.0, 143.8; IR (neat) 3392, 2980, 2929, 2858, 2837, 2658, 2837, 2659, 2455, 2263, 1716 cm$^{-1}$; HRMS (El) calcd for C$_{11}$H$_{16}$O$_2$ (M$^+$) 180.1151. Found 180.1150.
$^1$H NMR

136
\[ ^1H \text{NMR} \]

![NMR Spectrum](image)

**Chemical Structure:**

```
OEt
\HHH
\HHH
```

**Peak at 138 ppm:**

- **Chemical Shifts:**
  - 8.0 - 7.5 ppm
  - 6.5 - 6.0 ppm
  - 5.5 - 5.0 ppm
  - 4.5 - 4.0 ppm
  - 3.5 - 3.0 ppm
  - 2.5 - 2.0 ppm
  - 1.5 - 1.0 ppm
  - 0.5 - 0.0 ppm
$^{1}H$ NMR
$^{13}$C NMR
Typical procedure for preparation of \(\alpha,\beta\)-unsaturated esters 130, 133, 135, 137, 139, 141 using AuCl\(_3\) (Table 7 and Table 8)

To a CH\(_2\)Cl\(_2\) solution (8 mL) of 1-ethoxy-3-methyl-3-\emph{tert}-butyl-1-propyn-3-ol (138) in an open flask was added 95\% ethanol (0.16 mL, 2.9 mmol) followed by AuCl\(_3\) (35 mg, 0.12 mmol, fine powder). After 5 min, the reaction mixture was filtered through a plug of SiO\(_2\) with the aid of an ethyl acetate/hexane mixture (1/7). The filtrate was concentrated and purified using silica gel column chromatography (hexanes/ethyl acetate = 50/1) to give 3,4,4-trimethyl-pent-2-enoic acid ethyl ester (139) in 86\% yield (85 mg).

\[
\text{Ph} \quad \text{O} \quad \text{Et} \\
\text{130}
\]

**Ethyl 3,3-diphenylpropenoate [130]:** yellow oil; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.01 (t, \(J = 7.1\) Hz, 3H), 4.95 (q, \(J = 7.1\) Hz, 2H), 8.09-8.12 (m, 2H), 8.18-8.30 (m, 8H); For full characterization refer to Le Tadic-Biadatti et al. *J. Org. Chem.* 1997, \textit{62}, 559–563 and Rathke, M. et al. *Synth. Commun.* 1990, \textit{20}, 869–875.

\[
\text{Ph} \quad \text{O} \quad \text{Et} \\
\text{133}
\]

**Ethyl cinnamate [133]:** yellow oil; \(^1\)H NMR (300 MHz, CDCl\(_3\), E-Isomer) \(\delta\) 1.33 (t, \(J = 7.1\) Hz, 3H), 4.26 (q, \(J = 7.1\) Hz, 2H), 6.44 (d, \(J = 16.0\) Hz, 1H), 7.35-7.53 (m, 5H), 7.69 (d, \(J = 16.0\) Hz, 1H); Z-Isomer \(\delta\) 1.24 (t, \(J = 7.1\) Hz, 3H), 4.18 (q, \(J = 7.1\) Hz, 2H), 5.95 (d, \(J = 12.6\) Hz, 1H), 6.95 (d, \(J = 12.6\) Hz, 1H), 7.33-7.38 (m, 3H), 7.57-7.59 (m, 2H); For full characterization refer to Wadsworth, E. *J. Am. Chem. Soc.* 1961, \textit{83}, 1733.
4-tert-butylcyclohexylidene-acetic acid ethyl ester [135]: clear, colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.84 (s, 9H), 1.04-1.28 (m, 3H), 1.26 (t, $J$ = 7.1 Hz, 3H), 1.76-1.95 (m, 3H), 2.14 (t d, $J$ = 13.5, 3.9 Hz, 1H), 2.27-2.32 (m, 1H), 3.86 (d q, $J$ = 13.7, 2.7, 1H), 4.12 (q, $J$ = 7.1 Hz, 2H), 5.58 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 14.3, 27.5, 28.4, 29.2, 29.5, 32.4, 37.9, 47.8, 59.4, 112.7, 163.5, 166.9; IR (neat) 3412, 2948, 2867, 1716, 1648, 1478, 1365, 1247, 1143, 1041, 862 cm$^{-1}$; HRMS (CI) Calcd for C$_{14}$H$_{24}$O$_2$ (M+H$^+$) 225.1855. Found 225.1849.

adamantan-2-ylidene-acetic acid ethyl ester [137]: clear, colorless oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.27 (t, $J$ = 7.1 Hz, 3H), 1.86 (br s, 6H), 1.93-1.96 (m, 6H), 2.43 (br s, 1H), 4.07 (br s, 1H), 4.13 (q, $J$ = 7.1 Hz, 2H), 5.58 (s, 1H); For full characterization refer to L. Griaud et al. Tetrahedron, 1998, 54, 11899–11906.

(E/Z)-3,4,4-trimethyl-pent-2-enoic acid ethyl ester [139]: clear, colorless oil; $^1$H NMR (300 MHz, CDCl$_3$, E-isomer) $\delta$ 1.10 (s, 9H), 1.28 (t, $J$ = 7.1 Hz, 3H), 2.16 (br d, $J$ = 1.1 Hz, 3H), 4.14 (q, $J$ = 7.1 Hz, 2H), 5.74 (q, $J$ = 1.1 Hz, 1H); $^1$H NMR (300 MHz, CDCl$_3$, Z-isomer) $\delta$ 1.20 (s, 9H), 1.28 (t, $J$ = 7.1 Hz, 3H), 1.84 (br d, $J$ = 1.3 Hz, 3H), 4.14 (q, $J$ = 7.1 Hz, 2H), 5.63 (q, $J$ = 1.3 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$, (E/Z)-mixture) $\delta$ 14.1, 14.3, 15.1, 23.9, 28.5, 29.0, 36.4, 37.9, 59.4, 60.0, 112.9, 116.6, 158.5, 167.2, 167.5, 167.9; IR (neat, (E/Z)-mixture) 2970, 2873, 1719, 1634, 1466, 1372, 1262, 1182, 1123, 1054, 868 cm$^{-1}$; HRMS (EI) Calcd for C$_{10}$H$_{18}$O$_2$ (M$^+$) 170.1307. Found 170.1306.
3-butyl-hept-2-enoic acid ethyl ester [141]: clear, colorless oil: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.89-0.94 (m, 6H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.28-1.47 (m, 8H), 2.13 (br t, $J = 7.6$ Hz, 2H), 2.59 (br t, $J = 7.6$ Hz, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 5.61 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 13.88, 13.92, 14.3, 22.4, 23.0, 29.8, 30.8, 31.9, 38.1, 59.3, 115.0, 164.8, 166.6; IR (neat) 2958, 2931, 2872, 1716, 1642, 1466, 1378, 1190, 1147, 1039, 862 cm$^{-1}$; HRMS (CI) Calcd for C$_{13}$H$_{24}$O$_2$ (M+H$^+$) 213.1855. Found 213.1857.
$^1$H NMR

![NMR Spectrum](image-url)

130
Typical two-step procedure for preparation of \(\alpha,\beta\)-unsaturated esters 130, 137, 139, 145, 147, 149 using AuCl\(_3\) (Table 9)

To a THF solution (2.6 mL) of ethyl ethynyl ether (0.13g, ca. 40 % by weight in hexanes, ca. 2 mmol) was added \(n\)-BuLi (0.40 mL, 0.75 mmol, 2.0 M) dropwise over 5 min at \(-78\) °C under argon atmosphere. The solution was allowed to warm to 0 °C over 1 hr and held at 0 °C for an additional 30 min. The solution was then recooled to \(-78\) °C and 2-adamantanone (75 mg, 0.5 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 hr and held at room temperature for an additional 3 hr. Saturated aqueous NH\(_4\)Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO\(_4\), filtered, and concentrated. To the concentrated mixture in an open flask was added 6 mL of CH\(_2\)Cl\(_2\), followed by 95 % ethanol (0.14 mL, 2.5 mmol) and AuCl\(_3\) (7.6 mg, .025 mmol, fine powder). [NOTE: 15.2 mg, 0.05 mmol of AuCl\(_3\) was used for the preparation of 147 and 149.] After 30 min, the reaction mixture was filtered through a plug of SiO\(_2\) with the aid of an ethyl acetate/hexane mixture (1/7). The filtrate was concentrated and purified using silica gel column chromatography (hexanes/ethyl acetate = 50/1) to give adamantan-2-ylidene-acetic acid ethyl ester (137) in 99 % yield (109 mg) over two steps.

\[
\begin{align*}
\text{145} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

\((4,6,6\text{-trimethyl-bicyclo[3.1.1]hept-3-en-}(2\text{E/Z})\text{-ylidene})\text{-acetic acid ester [145]}:)\quad \text{clear oil; } ^1\text{H NMR (300 MHz, CDCl}_3\text{, }E\text{-isomer) } \delta 0.86 \text{ (s, 3H), 1.28 (t, } J = 7.1 \text{ Hz, 3H), 1.40 (s, 3H), 1.68 (d, } J = 7.9 \text{ Hz, 1H), 1.90 (d, } J = 1.5 \text{ Hz, 3H), 2.20-2.45 (m, 1H), 2.53-2.63 (m, 2H), 4.08-4.20 (m, 2H), 5.32 (s, 1H), 7.13 (s, 1H);} \quad ^1\text{H NMR (300 MHz, CDCl}_3\text{, }Z\text{-isomer) } \delta 0.84 \text{ (s, 3H), 1.26 (t, } J = 7.1 \text{ Hz, 3H), 1.44 (s, 3H), 1.58 (d, } J = 8.8 \text{ Hz, 1H), 1.86 (d, } J = 1.4 \text{, 3H), 2.20-2.45 (m, 1H), 2.53-2.63 (m, 2H), 4.08-4.20 (m, 2H), 5.46 (s, 1H), 5.77 (s, 1H);} \quad ^13\text{C NMR (75 MHz, CDCl}_3\text{, E/Z mixture) } \delta 14.3, 14.4, 21.7, 21.8, 23.2, 23.6, 26.4, 26.5, 37.5, 38.1, 45.3, 47.8, 48.2, 49.0, 49.1, 53.1, 59.2, 59.3, 107.6, 110.0, 117.6, 121.6, 156.9, 158.0, 159.6, 161.2, 166.8, 167.4; \text{IR (neat)}
2979, 2930, 2870, 1708, 1622, 1466, 1443, 1380, 1370, 1226, 1164, 1040, 874, 705 cm⁻¹; HRMS (El) Calcd for C₁₄H₂₀O₂ (M⁺) 220.1463. Found 220.1462.

(1,7,7-trimethyl-bicyclo[2.2.1]hept-(2E/Z)-ylidene)-acetic acid ethyl ester [147]: clear, colorless oil; ¹H NMR (300 MHz, CDCl₃) diagnostic resonance signals for E and Z isomers appeared at δ 5.58 (br t, J = 2.3 Hz, 1H), 5.64 (br t, J = 2.0 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃, E/Z mixture) δ 12.7, 13.2, 14.5, 14.6, 19.0, 19.1, 19.8, 20.2, 27.5, 27.8, 34.0, 34.4, 38.6, 40.6, 44.0, 44.6, 48.2, 50.0, 53.9, 54.0, 59.6, 60.0, 108.2, 112.2, 166.9, 167.6, 175.6; IR (neat, E/Z mixture) 2955, 2874, 1714, 1652, 1450, 1368, 1306, 1288, 1200, 1177, 1097, 1048, 873, 850 cm⁻¹; HRMS (Cl) Calcd for C₁₄H₂₂O₂ (M+H⁺) 223.1698. Found 223.1695.

(3,3,5,5-tetramethyl-cyclohexylidene)-acetic acid ethyl ester [149]: clear, colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 0.95 (s, 6H), 0.97 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H), 1.33 (s, 2H), 1.95 (s, 2H), 2.61 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 5.69 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 14.3, 30.8, 30.9, 34.8, 34.9, 42.2, 51.1, 52.5, 59.4, 115.8, 160.4, 166.6; IR (neat) 2953, 2896, 1716, 1646, 1461, 1376, 1229, 1154, 1043, 862 cm⁻¹; HRMS (El) Calcd for C₁₄H₂₄O₂ (M⁺) 224.1776. Found 224.1771.
$^{13}$C NMR

$147$
Typical Procedure for the Gold-Catalyzed Meyer–Schuster Rearrangement of Ethoxyalkynyl Carbinols, 133, 151, 153, 155, 157, 159 (Table 11). A mixture of AuCl (7.4 mg, 0.032 mmol) in 1:1 CH$_2$Cl$_2$–THF (5 mL) was prepared and allowed to stir for 20 min to give a homogeneous solution with an insoluble residue. A separate 25 mL roundbottomed flask under argon was charged with 150 (100 mg, 0.64 mmol), EtOH (95 %, 0.36 mL, 6.4 mmol) and a solution of AgSbF$_6$ (11 mg, 0.032 mmol) in 1:1 CH$_2$Cl$_2$–THF (5 mL). The mixture of AuCl in 1:1 CH$_2$Cl$_2$–THF (5 mL) was then added dropwise. After 40 min, the reaction mixture was filtered through a plug of SiO$_2$ with the aid of 1:7 Et$_2$O–hexane. The filtrate was concentrated and purified using silica gel column chromatography (Et$_2$O–hexane, 1:50) to give ethyl 4,4-dimethylpent-2-enoate (151); yield 0.091 g (91 %, 97:3 E/Z ratio).

Typical Procedure for the Gold-Catalyzed Meyer–Schuster Rearrangement of Ethoxyalkynyl Carbinols in the Presence of Camphorsulfonic Acid (CSA) (Table 11) A mixture of AuCl (7.4 mg, 0.032 mmol) in 1:1 CH$_2$Cl$_2$–THF (5 mL) was prepared and allowed to stir for 20 min to give a homogeneous solution with an insoluble residue. A separate 25 mL roundbottomed flask under argon was charged with 150 (100 mg, 0.64 mmol), EtOH (95 %, 0.36 mL, 6.4 mmol), CSA (0.15 g, 0.64 mmol) and a solution of AgSbF$_6$ (11 mg, 0.032 mmol) in 1:1 CH$_2$Cl$_2$–THF (5 mL). The mixture of AuCl in 1:1 CH$_2$Cl$_2$–THF (5 mL) was then added dropwise. After 40 min, the reaction mixture was filtered through a plug of SiO$_2$ with the aid of 1:7 Et$_2$O–hexane. The filtrate was concentrated and purified using silica gel column chromatography (Et$_2$O–hexane, 1:50) to give ethyl (E)-4,4-dimethylpent-2-enoate (151); yield 0.093 g (93 %).

![Ethyl (E)-4,4-dimethyl-pent-2-enoate](image)

**Ethyl (E)-4,4-dimethyl-pent-2-enoate [151]**

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.08 (s, 9H), 1.29 (t, $J = 7.1$ Hz, 3H), 4.19 (q, $J = 7.1$ Hz, 2H), 5.73 (d, $J = 15.9$ Hz, 1H), 6.97 (d, $J = 15.9$ Hz, 1H); For full characterization refer to Comasseto, J. et. al. *Tetrahedron* 2005, 61, 2319–2326.
Ethyl 5-phenyl-pent-2-enoate [153]

$^1$H NMR (300 MHz, CDCl$_3$) E-isomer $\delta$ 1.21 (t, $J = 7.1$ Hz, 3H), 2.38-2.50 (m, 2H), 2.70 (t, $J = 7.1$ Hz, 2H), 4.11 (q, $J = 7.1$ Hz, 2H), 5.77 (d, $J = 15.6$ Hz, 1H), 6.93 (dt, $J = 15.6$, 6.8 Hz, 1H), 7.06-7.27 (m, 5H); Z isomer $\delta$ 1.28 (t, $J = 7.1$ Hz, 3H), 2.77 (t, $J = 7.1$ Hz, 2H), 2.94-3.03 (m, 2H), 4.16 (q, $J = 7.1$ Hz, 2H), 5.78 (d, $J = 11.2$, 7.3 Hz, 1H), 7.15-7.33 (m, 5H); For full characterization refer to Yamada, T. et. al. *J. Am. Chem. Soc.* **129**, **129**(43), 12902–12903.

(E)-Dec-2-enoic acid ethyl ester [155];

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.86-0.90 (m, 3H), 1.26-1.31 (m, 8H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.42-1.47 (m, 2H), 2.19 (ddd, $J = 14.6$, 7.1, 1.2 Hz, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 5.80 (br d, $J = 15.6$ Hz, 1H), 6.96 (dt, $J = 15.6$, 7.0 Hz, 1H); For full characterization refer to Concellón, J. M.; Concellón, C.; Méjica, C. *J. Org. Chem.* **2005**, **70**, 6111–6113.

(E/Z)-3-Cyclohexyl-acrylic acid ethyl ester [157]:

$^1$H NMR (300 MHz, CDCl$_3$) E-isomer $\delta$ 1.12-1.31 (m, 5H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.64-1.77 (m, 5H), 2.04-2.17 (m, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 5.76 (dd, $J = 15.8$, 1.4 Hz, 1H), 6.91 (dd, $J = 15.8$, 6.8 Hz); Z-isomer $\delta$ 1.12-1.31 (m, 5H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.64-1.77 (m, 5H), 3.23-3.34 (m, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 5.65 (dd, $J = 11.5$, 1.0 Hz, 1H), 6.02 (dd, $J = 11.5$, 9.8 Hz, 1H). For full characterization refer to Concellón, J. M.; Concellón, C.; Méjica, C. *J. Org. Chem.* **2005**, **70**, 6111–6113.
(E/Z)-3-(1-Cyclohexen-1-yl)-2-propenoic acid ethyl ester [159]:

$^1$H NMR (300 MHz, CDCl$_3$) E-Isomer δ 1.29 (t, $J = 7.1$ Hz, 3H), 1.65-1.73 (m, 4H), 2.11-2.16 (m, 2H), 2.20-2.25 (m, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 5.76 (d, $J = 16.4$ Hz, 1H), 6.16 (t, $J = 4.1$ Hz, 1H), 7.28 (d, $J = 15.7$ Hz, 1H); Z-Isomer δ 1.28 (t, $J = 7.1$ Hz, 3H), 1.57-1.63 (m, 4H), 2.17-2.2 (m, 2H), 2.24-2.26 (m, 2H), 4.16 (q, $J = 7.1$ Hz, 2H), 5.58 (d, $J = 12.7$ Hz, 1H), 6.00 (t, $J = 3.8$ Hz, 1H), 6.31 (dd, $J = 12.7$, 0.9 Hz, 1H); For full characterization refer to Stille, J. K. et. al. J. Am. Chem. Soc. 1987, 109, 813–817.
Typical procedure for the preparation of \( \alpha,\beta \)-unsaturated esters 133, 139, 151, 155, 157 using Sc(OTf)\(_3\), Table 15.
To a 4:1 v/v CH\(_2\)Cl\(_2\)/ethanol solution (10 mL) of 1-ethoxydec-1-yn-3-ol (154, 0.10 g, 0.51 mmol) in an open flask was added Sc(OTf)\(_3\) (2.5 mg, 0.005 mmol). Progress of the reaction was monitored by TLC analysis. After 1 hr, the reaction mixture was concentrated under reduced pressure and purified using silica gel column chromatography (hexanes/ethyl acetate, 50:1) to give ethyl \((E)\)-dec-2-enolate (155) in 70 % yield (70 mg).

Typical two-step procedure for the preparation of \( \alpha,\beta \)-unsaturated esters 130, 137, 145, 151, 169, 171, 173, 175, 177, 179, 181, 183 using Sc(OTf)\(_3\), Table 16.
To a THF solution (2.6 mL) of ethyl ethynyl ether (0.13 g, ca. 40 % by weight in hexanes, ca. 2 mmol) was added \( n \)-BuLi (0.40 mL, 0.75 mmol, 2.0 M) dropwise over 5 min at \(-78^\circ C\) under argon atmosphere. The solution was allowed to warm to 0 \(^\circ\)C over 1 hr and held at 0 \(^\circ\)C for an additional 30 min. The solution was then recooled to \(-78^\circ C\) and 2-adamanotane (142, 75 mg, 0.50 mmol) was added in one portion. The solution was allowed to warm to room temperature over 1 hr and held at room temperature for an additional 3 hr. Saturated aqueous NH\(_4\)Cl solution was added to quench the reaction and the mixture was extracted with ethyl acetate. The organic layer was washed sequentially with water, saturated aqueous sodium bicarbonate, and brine. The organic layer was dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. To the concentrated mixture in an open flask were added CH\(_2\)Cl\(_2\) (8 mL), absolute ethanol (2 mL), and Sc(OTf)\(_3\) (2.5 mg, 0.005 mmol). After 6 hr, the reaction mixture was concentrated under reduced pressure and purified using silica gel column chromatography (hexanes/ethyl acetate, 50:1) to give adamantant-2-yldene-acetic acid ethyl ester (137) in 96 % yield over two steps (106 mg).
(2-Isopropyl-5-methyl-cyclohexyldiene)-acetic acid ethyl ester [169]:

$^1$H NMR (300 MHz, CDCl$_3$, E/Z-mixture, diagnostic peaks) $\delta$ 2.55 (ddd, $J = 12.9$, 5.5, 1.5 Hz), 3.14 (dd, $J = 12.9$, 4.3 Hz), 3.48-3.52 (m), 4.13 (q, $J = 7.1$ Hz), 4.14 (q, $J = 7.1$ Hz), 5.63 (br s);

$^{13}$C NMR (75 MHz, CDCl$_3$, E/Z-mixture) $\delta$ 14.3, 18.1, 19.5, 20.5, 20.8, 21.8, 23.4, 26.1, 26.8, 27.0, 27.6, 30.4, 31.6, 33.6, 33.9, 35.4, 36.1, 40.0, 43.5, 50.8, 52.6, 55.9, 59.3, 59.4, 113.3, 116.3, 164.8, 167.1.

Cycloheptyldien-acetic acid ethyl ester [173]:

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.27 (t, $J = 7.1$ Hz, 3H), 1.51-1.56 (m, 4H), 1.60-1.69 (m, 4H), 2.37 (dt, $J = 1.3$ Hz, 2H), 2.87 (dt, $J = 1.3$ Hz, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 5.66 (quint, $J = 1.2$ Hz, 1H); For full characterization refer to Friese, A. et al. J. Med. Chem. 2002, 45, 1535–1542.

(E/Z)-Ethyl-β-methyl cinnamate [175]:

$^1$H NMR (300 MHz, CDCl$_3$) $E$-Isomer $\delta$ 1.32 (t, $J = 7.1$ Hz, 3H), 2.58 (d, $J = 1.2$ Hz, 3H), 4.22 (q, $J = 7.1$ Hz, 2H), 6.14 (q, $J = 1.3$ Hz, 1H), 7.1-7.5 (m, 5H); $Z$-Isomer $\delta$ 1.08 (t, $J = 7.1$ Hz, 3H), 2.18 (d, $J = 1.4$ Hz, 3H), 4.00 (q, $J = 7.1$ Hz, 2H), 5.91 (q, $J = 1.4$ Hz, 1H), 7.1-7.5 (m, 5H); For full characterization refer to Tsuda, T. et. al. J. Org. Chem. 1988, 53, 607–610.
(E/Z)-3-(4-Isopropenyl-cyclohex-1-enyl)-acrylic acid ethyl ester [177]:
Diagnostic peaks $^1$H NMR (300 MHz, CDCl$_3$) E-Isomer $\delta$ 5.77 (d, $J$ = 15.8 Hz, 1H), 6.18 (br s, 1H), 7.30 (d, $J$ = 15.8 Hz, 1H); Z-Isomer $\delta$ 5.61 (d, $J$ = 12.6 Hz, 1H), 6.02 (br s, 1H), 6.33 (d, $J$ = 12.6 Hz, 1H).

(E/Z)-Ethyl-3-(4-methoxyphenyl)-2-propenoate [179]:
$^1$H NMR (300 MHz, CDCl$_3$) E-Isomer $\delta$ 1.33 (t, $J$ =7.1 Hz, 3H), 3.84 (s, 3H), 4.25 (q, $J$ = 7.1 Hz, 2H), 6.31 (d, $J$ = 16.0 Hz, 1H), 6.90 (d, $J$=8.6 Hz, 2H), 7.48 (d, $J$ = 8.6 Hz, 2H), 7.64 (d, $J$ = 16.0 Hz, 1H); For full characterization refer to Aggarwal, V. et. al. J. Am. Chem. Soc. 2003, 125, 6034–6035. Z-Isomer $\delta$ 1.28 (t, $J$ = 7.1 Hz, 3H), 3.82 (s, 3H), 4.19 (q, $J$ = 7.1 Hz, 2H), 5.83 (d, $J$=12.7, 1H), 6.84 (d, $J$=12.7, 1H), 6.88 (d, $J$ = 8.5 Hz, 2H), 7.69 (d, $J$ = 8.7 Hz, 2H); For full characterization refer to Mueller, A. et. al. Org. Lett. 2007, 9, 5327–5329.

(E/Z)-Ethyl-3-(2-furyl)-propenoate [181]:
$^1$H NMR (300 MHz, CDCl$_3$) E-Isomer $\delta$ 1.32 (t, $J$ =7.1 Hz, 3H), 4.24 (t, $J$ = 7.1 Hz, 2H), 6.31 (d, $J$ = 15.8 Hz, 1H), 6.46 (dd, $J$ = 3.4, 1.8 Hz, 1H), 6.60 (d, $J$ = 3.4 Hz, 1H), 7.44 (d, $J$ = 15.8 Hz, 1H), 7.46 (d, $J$=6.5 Hz, 1H); For full characterization refer to Cristau, H. J. et. al. Tetrahedron 1998, 54, 1507–1522. Z-Isomer $\delta$ 1.32 (t, $J$ = 7.1 Hz, 3H), 4.22 (q, $J$ = 7.1 Hz, 2H), 5.74 (d, $J$ = 12.9 Hz, 1H), 6.50 (dd, $J$ = 3.5, 1.7 Hz, 1H), 6.79 (d, $J$=12.9 Hz, 1H), 7.47 (d, $J$ =1.6 Hz, 1H), 7.67 (d, $J$ = 3.5 Hz, 1H); For full characterization refer to Reetz, M. T. et. al. Eur. J. Org. Chem. 2003, 3485–3496.
(E)-3-Pentafluorophenyl-acrylic acid ethyl ester [183]:

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.35 (t, $J = 7.1$ Hz, 3H), 4.29 (q, $J = 7.1$ Hz, 2H), 6.74 (d, $J = 16.5$ Hz, 1H), 7.64 (d, $J = 16.5$ Hz, 1H); For full characterization refer to Shen, Y. et. al. Syn. Comm. 1991, 21, 1403–1408.
$^1H$ NMR

![NMR Spectrum](image)
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trimethylsilyl-2-propen-1-ol, a single synthon for the (E)-β-formylvinyl anion and cation.


133. Vidari performed control experiments in which pure (Z)-isomer was fully converted to the (E)-isomer under the standard reaction conditions.


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153. When 2-butane was used as a solvent there was always competitive elimination. The use of acetonitrile as the solvent was believed to lessen the reactivity of Au(PPh₃)NTf₂ through solvent coordination with the catalyst.


BIOGRAPHICAL SKETCH

Birth Place

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Educational Background

Florida State University, Tallahassee, FL
• August 2004 to August 2009
• Ph.D. in Organic Chemistry (anticipated completion in August 2009)
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• August 2000 to May 2004
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• Research Advisor: Professor James M. LoBue

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• August 1996 to June 2000
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Professional Experience

Florida Custom Synthesis, Inc., Tallahassee, FL
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Honors and Awards

• MDS Fellowship, 2004–present
• Florida State University Fellowship, 2005-2006, 2007-2008
• American Institute of Chemists Foundation Outstanding Senior Award, 2004
• Georgia Southern Physical Chemistry Award, 2003
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