The Application of Tandem O-H Insertion/Ring-Closing Metathesis to the Synthesis of
Unsaturated Cyclic Ethers: Approaches to Rogioloxepane and Isolaurepinnacin

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Jason H. Stengel
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This dissertation titled

The Application of Tandem O-H Insertion/Ring-Closing Metathesis to the Synthesis of

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by

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ABSTRACT
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The utilization of rhodium-mediated insertion reactions and ring-closing metathesis (RCM) in a tandem process has been examined as a synthetically useful route to the preparation of unsaturated cyclic ethers. The strategy employed involves the formation of a rhodium-mediated carbenoid through the catalytic decomposition of various $\alpha$-diazoesters in the presence of olefinic-substituted alcohols. The first transformation of the tandem process provides an $\alpha$-alkoxy ester possessing two tethered olefins (C=C) poised for a subsequent ring-closing metathesis reaction, affording an unsaturated cyclic ether.

The marine metabolites rogioloxepane and isolaurepinnacin were chosen as synthetic targets for the application of this methodology due in part to their structural core of an oxepene, a seven-membered unsaturated cyclic ether. The oxepene core can be constructed via the tandem process. The target molecules can be completed through elaboration of the alkyl side chains at C2 and C6 to differentiate and delineate the natural product syntheses. Variations in the structural composition of the $\alpha$-diazoester and the olefinic alcohol would also allow for the preparation and study of structural analogs of the natural product.
A similar methodology was applied to a synthesis of (+/-)-pironetin, a substituted dihydropyranone possessing six chiral centers, which is a potential immunosuppressant and antitumor agent. Alternatively, interesting bicyclic compounds resulted from a competing ylide reaction followed by a subsequent 1,3-dipolar cycloaddition with a tethered olefin.

Approved: _____________________________________________________________

Mark C. McMills

Associate Professor of Chemistry and Biochemistry
DEDICATION

To my loving wife, Dyani, and our amazing son, Pierson.
ACKNOWLEDGMENTS

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Finally, my greatest appreciation is for my family, who have been endlessly patient with me and supportive throughout my tenure as a graduate student.
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<tr>
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<td>dimethyl sulfoxide</td>
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<td>Full Form</td>
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<td>--------------</td>
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<td>dr</td>
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<td>EDA</td>
<td>ethyl diazoacetate</td>
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<td>ee</td>
<td>enantiomeric excess</td>
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<td>hexamethylphosphorous triamide</td>
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<tr>
<td>IMes</td>
<td>1,3-dimesitylimidazolin-2-ylidene (mesityl substituted NHC)</td>
</tr>
<tr>
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<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
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<tr>
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<td>methyl alcohol (methanol)</td>
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<tr>
<td>Mesityl</td>
<td>2,4,6-trimethylphenyl</td>
</tr>
<tr>
<td>MW</td>
<td>microwave (also μwave)</td>
</tr>
<tr>
<td>NHC</td>
<td>N-heterocyclic carbene</td>
</tr>
<tr>
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<td>sodium hydroxide</td>
</tr>
<tr>
<td>p-ABSA</td>
<td>para-acetamidobenzensulfonyl azide</td>
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<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
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<tr>
<td>p-DBSA</td>
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<td>quartet</td>
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</table>
quint  quintet
PhCH$_3$  toluene
PhH  benzene
PPh$_3$  triphenylphosphine
rac  racemic
RAR  rearrangement
RCM  ring-closing metathesis
R$_f$  retention factor
Rh$_2$(acam)$_4$  dirhodium(II) tetraacetamide
Rh$_2$(cap)$_4$  dirhodium(II) tetrakis(caprolactam)
Rh$_2$(hex)$_4$  dirhodium(II) tetrahexanoate
Rh$_2$(MEOX)$_4$  dirhodium(II) tetrakis(methyl 2-oxooxazolidine-4-carboxylate)
Rh$_2$(MEPY)$_4$  dirhodium(II) tetrakis(methyl 2-oxopyrrolidine-5-carboxylate)
Rh$_2$(MPPIM)$_4$  dirhodium(II) tetrakis(methyl 2-oxo-1-(3-phenylpropanoyl)imidizolidine-4-carboxylate)
Rh$_2$(OAc)$_4$  dirhodium(II) tetraacetate
Rh$_2$(oct)$_4$  dirhodium(II) tetraoctanoate
Rh$_2$(pfb)$_4$  dirhodium(II) tetrakis(perfluorobutyrate)
Rh$_2$(piv)$_4$  dirhodium(II) tetrapivalate
Rh$_2$(tfa)$_4$  dirhodium(II) tetrakis(trifluoroacetate)
Rh$_2$(tfacam)$_4$  dirhodium(II) tetrakis(trifluoroacetamide)
Rh$_2$(TPA)$_4$  dirhodium(II) tetrakis(triphenylacetate)
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ROMP</td>
<td>ring-opening metathesis polymerization</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>SIMes</td>
<td>saturated IMes (H₂IMes)</td>
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<td>silica gel</td>
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<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBSCI</td>
<td>tert-butyl(dimethyl)silyl chloride</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>Total Ion Chromatogram</td>
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<td>triisopropylsilyl</td>
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<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
<td>TME</td>
<td>2,3-dimethyl-2-butene</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tr</td>
<td>triphenylmethyl (trityl)</td>
</tr>
<tr>
<td>T.S.</td>
<td>transition state</td>
</tr>
<tr>
<td>TsN₃</td>
<td>p-toluenesulfonyl azide</td>
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CHAPTER 1: INTRODUCTION

Overview

The synthesis of naturally occurring compounds is a continually expanding and vital part of organic chemistry. A number of the currently used medicinal therapeutics come directly from or are derived from natural sources. Exploration of the chemical components and/or metabolites of plants, microbes, fungi, and other living organisms can provide target compounds or scaffolds for the synthesis or modification of therapeutically relevant components. Efficient and specific synthetic production of these compounds could ultimately decrease the environmental impact of the synthetic endeavor.

One major challenge the synthetic organic chemist will confront is the efficient synthesis of complex scaffolds which often contain complex ring systems and/or possess significant numbers of stereocenters. The development and implementation of efficient methodologies that can form several bonds with precise regio- and stereocontrol could be advantageous in addressing this issue.

There are a number of chemical transformations that exemplify elegant and innovative methodologies which have had a profound impact on organic chemistry in simplifying previously intricate or excessive step count transformations. Examples range from the Diels-Alder and Ugi (four-component) reactions, which utilize simple starting materials to converge to one very complex product, to asymmetric reactions such as the Sharpless dihydroxylation and epoxidation reactions along with the asymmetric aldol reactions, all of which enable the preparation of complex molecules from both simple and complex reagents.
As a practical progression in organic synthesis, addition of tandem and cascade reactions to the construction of complex molecules have developed systems beyond limited linear reaction sequences.\textsuperscript{1-4} These types of processes form several bonds in one operation often leading to the construction of functionalized polycyclic structures with some degree of regio- or stereochemical control, and more importantly, can be applied in asymmetric synthesis.\textsuperscript{5-11}

The two significant chemical transformations discussed herein, catalytic X-H activation/insertion\textsuperscript{12} (Scheme 1.1, Eq. 1) and ring-closing metathesis\textsuperscript{13,14} (Scheme 1.1, Eq. 2), found their practical beginnings in the early to mid 1960's, while in the mid 1980's to early 1990's, found applications to natural product synthesis. The application of stereoselective C-H/ O-H insertion,\textsuperscript{15-27} as well as the use of asymmetric catalysis in the metathesis reaction,\textsuperscript{28-33} soon followed and were applied to a number of elegant syntheses providing the requisite stereoisomers with excellent enantio- and diastereoselectivity.

\begin{equation}
\begin{array}{c}
\text{R} = \text{H, X} = \text{C, O} \\
\text{MLn} \quad \text{MLn} \\
\text{MLn-1} \quad \text{MLn-1}
\end{array}
\end{equation}

Scheme 1.1. X-H insertion and RCM transformations.

The application of tandem, domino, cascade, and/or one-pot reactions have been investigated extensively since the mid to late 1980's, and the number of reviews
published on these synthetic methods\textsuperscript{2-4,10,34-44} is a testament to the importance and utility of these reaction types.

The formation of carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds is at the core of synthetic organic chemistry. There are innumerable methods in which these transformations have been accomplished. The usual synthetic convention is through the reaction of two activated carbon species that couple to generate a new carbon-carbon bond.\textsuperscript{45} One efficient method to affect this transformation is through the use of carbenes or carbenoid substrates, most effectively completed utilizing transition metal-stabilized carbenes or carbenoids generated through metal-catalyzed decomposition. Carbenes have been of interest to chemists for decades, generally as a tool to research bonding and hybridization until the mid 1970’s. Much of their use was limited due to the highly reactive nature of the substrate. The discovery that various transition metals, such as copper, rhodium, molybdenum, and ruthenium could be used to mediate carbone reactivity made it possible to use the ‘carbene’ without a number of unwanted side reactions that can potentially occur. The large number of transition metal catalyzed carbone/carbenoid type transformations since the mid 1960’s is likely due to the improved reactivity of the continually developing pool of catalysts. Reactions utilizing metallocarbenoids such as cyclopropanation of olefins and X-H insertions have experienced an increase in utility, thanks in part to the work of a number of researchers in the field such as Teyssié,\textsuperscript{46-57} Kirmse,\textsuperscript{58-69} Padwa,\textsuperscript{70-95} Doyle,\textsuperscript{77,96-119} Hashimoto,\textsuperscript{120-131} McKervey,\textsuperscript{23,25,119,132-136} Davies,\textsuperscript{20,137-142} Taber,\textsuperscript{16,22,26,45,143-163} and Moody,\textsuperscript{18,75,80,104,164-179} as well as many others.\textsuperscript{180}
The olefin metathesis reaction began as a relatively unpredictable reaction, that required the use of a glove box, owing to the highly water and oxygen sensitive nature of the early RCM catalysts. Through the pioneering work of Schrock\textsuperscript{181-184} and Grubbs, \textsuperscript{185-187} as well as others in the field\textsuperscript{188-191} the ruthenium and molybdenum catalysts currently used are more robust, being especially tolerant to conditions that would have proven disastrous to earlier RCM catalysts. The RCM reactions that can be catalyzed are much broader in scope and applicability.

Background

Carbenes

The discovery and use of carbenes in organic synthesis has undergone a number of major developments since the early 1960’s, and thus this highly reactive species has become a very important mechanistic tool for the study of bonds and carbon structure and a synthetic tool in various C-C and C-X bond-forming reactions.

The term ‘carbene’ was conceived by Doering, Winstead, and Woodward.\textsuperscript{192} The study of carbenes has evolved along with the terminology used to describe them. Methylene, the parent carbene is described as a “free carbene” and this terminology is invoked when referring to simple divalent carbon species (1, Figure 1.1). Free carbenes can be generated by two general methods; 1) \textit{via} the photolysis or thermolysis of suitable carbene precursors such as ketenes or compounds containing a diazo-group or 2) \textit{via} the 1,1-elimination of HX from R\textsubscript{2}CHX compounds.\textsuperscript{65,66,193-199} The multiplicity of free carbenes is generally unpredictable\textsuperscript{200} with singlet and triplet states being observed experimentally through matrix isolation techniques.\textsuperscript{201-203} The synthetic utility of free
carbenes in organic chemistry is limited due to the high reactivity and low selectivity of these species.\textsuperscript{204,205}

\textit{History, Structure and Reactivity}

Carbenes are described as neutral bivalent carbon intermediates in which two substituents are covalently bound to carbon and the two remaining electrons are distributed between two non-bonding orbitals. A singlet carbene is formed if the two electrons are spin paired (1), while a triplet carbene (2) forms if the spins of the electrons are parallel (\textbf{Figure 1.1}). The ground-state of methylene (\text语{CH}_2) is considered to be a triplet state whereas a molecule such as fluorocarbene (\text语{HFC}_2) and difluorocarbene (\text语{F}_2\text{C}_2) are considered to be ground-state singlet in nature.\textsuperscript{206} These electronic structures have been predicted based on experimental evidence in which the carbene attacks an olefin as well as \textit{Ab Initio} calculations. An alternative structure to the excited singlet state and the triplet carbene is proposed to be an \textit{sp} triplet (3, \textbf{Figure 1.1}).\textsuperscript{198,207,208}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Electronic structure of carbene.}
\end{figure}

A singlet state carbene possesses a $p$-orbital containing two non-bonding spin-paired electrons and an empty orthogonal $sp^2$ orbital, where the fully occupied $p$-orbital has anionic character and the empty $sp^2$-orbital maintains cationic character. Singlet
(electrophilic) carbenes are generally associated with reactions such as cyclopropanation, insertion, and ylide generation. The electrophilic/nucleophilic character of the singlet carbene is strongly dependent on the electron withdrawing/donating ability of the groups attached adjacent to the carbene carbon. Substituents which are electron donating in nature (doubly bonded heteroatoms, such as oxygen and nitrogen) render the carbene carbon nucleophilic. Carbon monoxide (4) and isocyanides (5), for example, contain divalent carbon atoms which exhibit nucleophilic reactivity as stable divalent carbon compounds (Figure 1.2).

![Figure 1.2. Nucleophilic Carbenes.](image)

Reactive, unstable carbenes include those in which the divalent carbon is singly bound to a heteroatom or bonded to substituents which are less capable of maintaining resonance, such as alkyl groups. These “destabilizing” substituents render the divalent carbon more electrophilic in character and thus, reactive.66

The triplet state behaves as a biradical with unpaired electrons in each of the orthogonal $sp^2$ and $p$-orbitals. Carbenes of this type participate in hydrogen abstraction/recombination reactions.209 In order to control the outcome of the reaction it is necessary to be able to determine the multiplicity of the ground state of the carbene during generation.
Following the findings that transition metals are capable of catalyzing the decomposition of diazo-containing species, the term carbenoid was invoked to reflect the “carbene-like” structure of the reacting species, where a metal stabilizes the carbene carbon (Figure 1.3).

Carbenoids derived from early transition metals such as tungsten, molybdenum, chromium, and iron, are often stable, isolable compounds (7) that are relatively unreactive in various synthetic methods. Reactive carbenoids (8) exist mainly as transient species in catalytic processes and are usually derived from late transition metals such as rhodium, ruthenium, copper, and palladium. Reactive carbenoids have found greater utility in organic synthesis than their stable counterparts. Interaction of the metal with the carbene drastically lowers reactivity and increases selectivity of the carbene. Furthermore, generation of these species occurs almost exclusively in the singlet state and they react similar to dipolar intermediates.

Transition Metal Catalysts

The development of highly efficient transition metal catalysts for diazo-decomposition reactions has been one of the most significant advances for the synthetic
utility of carbenoid chemistry, with copper and rhodium being the most significant metal atoms utilized.\textsuperscript{219,220}

The preferential use of rhodium and copper catalysts is due in large part to their ability to substitute a wide variety of ligands, which has resulted in the development of a broad spectrum of catalysts. This arsenal of catalysts has allowed for the steric and electronic fine-tuning of the diazo-decomposition reaction. Chemo- and stereoselectivity in diazo-decomposition reactions may be controlled by modification of the diazo-compound (chiral auxiliaries), through metal-ligand differentiation,\textsuperscript{77} or both.\textsuperscript{221}

These reactions, generally considered catalytic in metal, involve attack of the nucleophilic diazo-containing carbon on a vacant electrophilic coordination site of the metal catalyst. The electron-rich diazo carbonyl compounds provide three potential sites for electrophilic addition to the metal catalyst (Figure 1.4).

![Figure 1.4](image_url)

*Figure 1.4. Alternative electrophilic adducts of diazo carbonyl compounds.*

Mechanistic details have been deduced from protonation studies of diazo-containing substrates (Scheme 1.2).\textsuperscript{222}

Simple diazoalkanes have two obvious sites for protonation, the diazo-carbon and the terminal nitrogen atom (9a $\leftrightarrow$ 9b). In the case of unsubstituted non-carbonyl
substrates, it was concluded that C-protonation is the thermodynamically favored position, while N-protonation appears to be the kinetically favored process. In the series containing diazocarbonyl substitution (10a ↔ 10b) O-protonation is also a likely protonation site, and at low temperature (-60°C to -80°C) superacids (e.g. HF-SbF₅-SO₂ or FSO₃H-SbF₅-SO₂) produce the O-protonated enoldiazonium ions 11a (cis) and 11b (trans). Neither the C- or N-protonated species were detected under these conditions. Under aqueous acidic conditions however, C-protonation does occur and H/D exchange studies indicate that the process is reversible. Applying hard/soft Lewis acid/base principles to the process, protonation should occur preferentially at the ‘harder’ Lewis basic site, whereas electrophilic addition of soft Lewis acids (e.g. Rh⁺², Cu⁺²/⁺¹, and Ru⁺², etc…) should occur preferentially at the ‘softer’ Lewis basic site. All things considered, only attack by an electrophilic metal catalyst on carbon is presumed to be productive in the formation of metallocarbenoid species.
Copper Catalysts

Heterogeneous copper catalysts such as copper-bronze and copper(II) sulfate were the first useful transition metal catalysts employed in diazo-decomposition reactions. Homogenous copper catalysts were developed in the 1960’s as alternatives to the heterogeneous catalysts due to uncertainties with the actual active catalytic species found in the catalytic reactions. The introduction of catalysts such as copper(II) trifluoromethanesulfonate (copper triflate, Cu(OTf)₂) and copper(II) chloride further advanced the basic understanding of copper catalysis in carbene transformations when, in both cases, diazo compounds were found to reduce Cu(II) to Cu(I). After this revelation it was determined that Cu(I) rather than Cu(II) was the active catalytic species.²¹⁶,²²⁴,²²⁵ Copper(II) complexes are favored in diazo-decomposition owing to the air-sensitive nature of Cu(I) catalysts. In the case of copper (II) pre-catalysts, most often two
bidentate ligands are bound to the metal. The catalytic sequence is presumed to follow a Cu(II) to Cu(I) reduction, followed by the dissociation of one of the two bidentate ligands during diazo-decomposition. The active copper(I) catalyst can be generated from the Cu(II) precatalyst by reduction with phenylhydrazine at room temperature, heating with a diazo substrate, or through reaction of the desired ligand with Cu(I) salts, such as Cu(I)-tert-butoxide (Scheme 1.3).

\[ \text{Scheme 1.3. Generation of catalytically active Cu(I) compounds.} \]

A number of copper catalysts found and developed have been useful for diazo-decomposition including several developed with chiral ligands for enantioselective reactions (Figure 1.5).
Copper(I) Catalysts

<table>
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<tr>
<th>Copper Complex</th>
<th>Formula</th>
<th>Reference</th>
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<tr>
<td>Cu(OSO₂CF₃)</td>
<td>(RO₃)PCuCl</td>
<td>Cu(BF₄)</td>
</tr>
<tr>
<td>(CuOTf)</td>
<td>homogeneous</td>
<td>Cu(PF₆)</td>
</tr>
<tr>
<td>12</td>
<td>trialkyl/aryl phosphite</td>
<td>14</td>
</tr>
<tr>
<td>13</td>
<td>Cu(I) chlorides</td>
<td>15</td>
</tr>
</tbody>
</table>

Copper(II) Catalyst Complexes

- bis-oxazolines
- semicorrins
- Cu(acac)₂ derivatives

**Figure 1.5.** Typical copper catalysts for diazo-decomposition.

The asymmetric Cu(I) bis-oxazolines²²⁶ (17) and semicorrins²²⁷ (18) have proven to be efficient in inter- and intramolecular cyclopropanation reactions, providing excellent enantiocontrol (Scheme 1.4).

![Scheme 1.4](Ph=Ph, EDA, 1 mol% 18 (R = CMe₂OH), DCE, 25°C, PhCO₂Et + PhCO₂Et, 73% (92% ee), 27% (80% ee))

Scheme 1.4. Cu(I) semicorrin catalyzed asymmetric cyclopropanation.

Recently Fu and co-workers have developed and investigated the use of a variety of copper(I) complexes in O-H insertions²²⁸ (vide infra, pp. 85, Scheme 1.45),
cyclopropanations\textsuperscript{229} (Scheme 1.5), [4 + 1] cycloadditions\textsuperscript{230} (Scheme 1.6), and other synthetically useful processes.\textsuperscript{231}

Fu’s work (Scheme 1.5) utilized a new class of bidentate, $C_2$-symmetric ligands based on planar—chiral heterocycles. The combination of bisazaferrocene ligand (20) and CuOTf invoke high levels of enantioselectivity in cyclopropanations. The ligand (20) resembles bis-oxazolines (17) and semicorrins (18) in that they are each bidentate ligands with ligating sites that are sp$^2$-hybridized nitrogen. Increasing the steric demand of the diazoester increases stereoselectivity in the use of this ligand, a similar finding to that of complexes 16-18. The use of the sterically demanding BHT ester of diazooacetic acid provided >93:7 trans-selectivity and >87% ee with a chemical yield of 64-90%.

![Scheme 1.5. Cyclopropanation with Fu’s catalyst.](image)

Fu further developed $C_2$-symmetric heterocyclic ligands, demonstrating that copper catalyzed [4+1] cycloaddition reactions of aryl diazoesters and enones afforded 2,3-dihydrofurans with yields up to 92% (dr >20:1), and enantioselectivities up to 93% ee using (-)-21 as ligand (Scheme 1.6). Similar to the substrate requirements for the previous cyclopropanation reaction (vide supra), the diazoester is necessarily bulky and
aryl-substituted enones provide the best selectivities, although good enantioselectivities are reported for both alkyl and aryl enones. Interestingly, this reaction was only efficient with the use of 21 as ligand, where the use of 20 and derivatives of bis-oxazolines and semicorrins (16-18) were unsuccessful.

![Scheme 1.6. Fu’s [4+1] cycloaddition.](image)

**Rhodium Catalysts**

Dirhodium(II) tetraacetate (Rh\(_2\)(OAc)\(_4\)), prepared and characterized in the 1960’s, was first introduced, as an effective catalyst for diazo-decomposition by Teyssie and co-workers in 1973.\(^{51}\) Rhodium(II) acetate has been the single most widely used catalyst for metal carbene transformations since its preparation. Rhodium(II) catalysts, in general, provide increased control over chemoselectivity than their copper based counterparts. The wide variety of ligands such as bridging carboxylate and carboxamidate ligands allows for electronic and steric fine-tuning and amplification of selectivity. These
catalysts are generally useful for most diazo-decomposition reactions with the exception of those with diazomethane.

The common oxidation states of rhodium are (+1, +2, and +3), with Rh\(^{+2}\) being the dominant oxidation state in rhodium carbenoid chemistry. Rh(II) tends to dimerize, and complexes of bridging carboxylates and carboxamidates form a paddle wheel structure around the Rh-Rh bond axis (Figure 1.6).

![Figure 1.6. Rhodium(II) carboxylate/carboxamidate.](image)
Typical catalyst systems are based upon this general structure (Figure 1.7). A crystal structure of the bis(phenyl isonitrile) complex of Rh(II) acetate is depicted in Figure 1.8.232

Rhodium(II) complexes with carboxylate ligands are a class of D_{4h} symmetric compounds with bridging ligands occupying four equatorial sites on each rhodium atom. The remaining two axial sites (one per rhodium atom) are coordinatively unsaturated, and this is where reaction with diazo-species occurs. Rhodium-rhodium bond lengths are typically longer than predicted values (2.37-2.44 Å) and by analogy can serve as a measure of reactivity of a particular complex. Rhodium(II) carboxamidates are a class of C_{2} symmetric compounds. The decrease in symmetry being due to the formation of the (cis-2,2)-isomer with near exclusion of the (trans-2,2)-, (3,1)-, and (4,0)-isomeric structures.
The stereoelectronic nature of the catalyst, and thus the carbenoid, can be modified by variation of the ligand. This variation can affect Rh-Rh bond length, increasing or decreasing reactivity. In general the paddle wheel structure of the Rh(II) carboxylate complex (Figure 1.6, top) presents an atomic array at each rhodium face which resembles a circular wall with an electron rich exterior and electron deficient center. Introduction of carboxamide ligands and the strongly electron-donating nitrogen atom has the effect of decreasing the Rh-Rh bond distance, thereby decreasing reactivity. The decrease in reactivity provides an enhancement in selectivity for the Rh(II) carboxamidate catalysts.\textsuperscript{219}

The variation in the Rh-Rh bond distances and thus the Rh-C bond length in Rh-carbenoids is said to result from $\pi$-back-bonding (IVb, Scheme 1.7).\textsuperscript{232} This phenomenon is possible through donation of electron density from one of two degenerate, filled metal-$\pi^*$ orbitals (which arises from the overlap of two antibonding Rh $d_{xz}$ or Rh $d_{yz}$). An increase in $\pi$-back-bonding results in shorter Rh-Rh and Rh-C bond lengths, where the degree of back-bonding can be influenced by the electronic nature of the
ligands (i.e. carboxylate vs. carboxamidate) as well as the $\pi$-acceptor/$\sigma$-donor capabilities of the carbenoid carbon.

The $\pi$-acceptor capacity of a substrate decreases with attached groups which are electron donating (from a resonance perspective) and the $\sigma$-donor capabilities of the substrate are affected by the inductive effects of attached substituents. The ability of the incoming carbene to accept electron density from the Rh-$\pi^*$ orbital as well as donate electron density into the Rh-$\sigma^*$ orbital is ultimately dependent on the competing inductive/resonance effects associated with carbenoid species.

Scheme 1.7. $\pi$-back-bonding in Rh-carbenoids.

Doyle$^{114}$ has proposed a model based on molecular modeling in which the Rh(II) carboxamidate-carbenoid intermediate possesses a formal Rh-C single bond (no $\pi$-back-bonding). The electrophilic carbon in this case resembles that found in a carbocation rather than an alkylidene carbon of a metal-carbene complex (IIIa vs IIIb)
The choice of catalyst (Figure 1.6) is highly dependent on the type of carbene transformation and conditions desired. Replacement of the acetate ligands with hexanoate or octanoate (24) increases the solubility of the Rh(II) complex in hydrocarbon solvents while displaying similar reactivity to the parent Rh(II) acetate (22). Pivalate (piv, 27) and triphenylacetate (TPA, 23) ligands are bulky ligands and could be utilized in situations where steric control is desired to promote selectivity. Increasing electron-withdrawing groups increases the reactivity (electrophilicity) of the carbenoid by placing a larger charge density on the carbene carbon. Ligands of this nature include perfluorobutyl (pfb, 25) and trifluoromethyl (-CF₃, 26).

Rhodium(II) triphenylacetate (23) has been shown to be a highly efficient catalyst for C-H insertion reactions of α-diazo-β-ketoesters,¹²⁴ whereas rhodium(II) caprolactam (29), a carboxamide catalyst, has proven to be efficient in cyclopropanation reactions.⁷⁷ Variation of the ligand surrounding rhodium can also modify the solubility of the complex, which could be advantageous for low temperature reactions. In general a screening of possible catalysts should be undertaken for catalytic diazo-decomposition reactions in order to optimize the pairing of catalyst with substrate.

Moody and co-workers demonstrated some variation in chemoselectivity of rhodium(II) carboxylates and carboxamidates in the decomposition of α-diazomalonic ester (31, Scheme 1.8). Remarkable levels of chemoselectivity were observed with the Rh(II) acetate catalyzed reaction providing the morpholine derivative (32) in high chemical yield via an intramolecular O-H insertion reaction, while the carboxamidate
catalyst (Rh(II) trifluoroacetamide) produced the 2-oxo-3-ester indole (33) via aromatic C-H insertion.\textsuperscript{219}

![Scheme 1.8: Probe of catalyst chemoselectivity: C-H vs. O-H insertion.](image)

The two reaction motifs utilized to form 32 and 33 also demonstrates the influence of the ligands on the reactivity of the rhodium carbenoid with the perfluoroacetamide providing product in shorter reaction times than the usually more reactive Rh(II) carboxylate.

From this study it was evident that Rh(II) perfluorocarboxamides promote aromatic C-H insertion in preference to alternative reactions such as aliphatic C-H insertion, addition to olefins and alkynes, O-H insertion, and carbonyl ylide formation, all of which are observed when Rh(II) carboxylates are used.

Catalyst design and development continues to be the central issue in transition metal-catalyzed reactions of $\alpha$-diazo compounds. The development of dirhodium carboxylate catalysts has been advanced owing to their superior catalytic reactivity. McKervey\textsuperscript{133-135,233-239} and Davies\textsuperscript{240-242} pioneered the prolinate type chiral Rh(II)
catalysts, with Davies’ Rh$_2$(S-DOSP) catalyst (34a, Figure 1.9) known to retain catalytic activity at -78°C, in non-polar, aprotic solvents.

A series of chiral rhodium(II) catalysts have been prepared by coordination of $C_1$ symmetric ligands from amino acid derivatives around the dirhodium core. Ikegami and Hashimoto’s phthalimide-protected tetracarboxylates (35a-d) have been successful in promoting enantioselective aromatic C-H insertion reactions in the formation of indanones.$^{129}$ These catalysts provide a highly efficient route to quaternary carbons with excellent enantioselectivity (up to 95% ee), but are limited in scope. Pirrung$^{243}$ and Zhang developed Rh(II) catalysts based on $C_2$ symmetric binaphthoyl phosphate ligands (36). The biaryl phosphonate catalysts effectively promote in carbonylcarbene dipolar cycloaddition reactions.$^{243,244}$

The dirhodium carboxamidate catalysts developed by Doyle$^{97-100,103-105,108,109,114}$ are more selective, but not as reactive in comparison to the carboxylate catalysts. In
general, chiral Rh(II) carboxamidates (Figure 1.10) are effective catalysts for promoting enantiocontrol in intramolecular cyclopropanation reactions with allylic and homoallylic substrates, but generally less successful in intermolecular reactions. Prior to the introduction of Davies’ prolinate catalysts Doyle245 had achieved enantioselectivities comparable to those of Cu(I) semicorrin227 and bis-oxazoline226 catalyzed intermolecular cyclopropanations with chiral Rh(II) azetidinone carboxamidates (Figure 1.10).

Other transition metals have also been utilized as catalysts for diazo-decomposition. Palladium(II) in the form of chloride (PdCl₂) or acetate (Pd(OAc)₂), has been shown to be the most effective transition metal catalysts for cyclopropanation reactions of olefins with diazomethane. However, the palladium catalysts have shown little synthetic value in cyclopropanation reactions with diazoester substrates. Although copper and rhodium complexes have proven to be most efficacious catalysts, there have been several recent reports of the use of alternative transition metal complexes such as ruthenium, gold, iron and cobalt in the synthetic transformation of α-diazo compounds.246
Diazo Substrates

α-Diazocarbonyl Compounds

In addition to the importance ascribed to the electronics and steric nature of the catalyst is the overall structure of the diazo-substrate. The reactivity of the diazo center toward the catalyst can be manipulated by the addition or deletion of electron withdrawing or donating ligands α to the diazo center (Figure 1.11). Electron withdrawing groups α to the diazo-center stabilize the diazo–substrate, which facilitates their preparation. Alternatively, the presence of an electron-donating substituent α to the diazo-center decreases thermal stability, increasing reactivity, which in turn hinders the preparation of these types of diazo-derivatives.

\[
\begin{align*}
\text{Increasing Stability} & \\
\begin{array}{c}
\text{Z} \bigg\rightarrow \text{O} \bigg\rightarrow \text{O} \\
\text{N}_2 \bigg\leftarrow \text{Z} \bigg\rightarrow \text{Y}
\end{array} & \\
\begin{array}{c}
\text{Z} \bigg\rightarrow \text{O} \bigg\rightarrow \text{R} \\
\text{N}_2 \bigg\leftarrow \text{Z} \bigg\rightarrow \text{R}
\end{array} & \\
\begin{array}{c}
\text{R} = \text{aryl, vinyl, alkyl, H} \\
\text{Z, Y = R, OR, NR}_2
\end{array}
\end{align*}
\]

Increasing Reactivity

Figure 1.11. General diazo compound stability and reactivity.

α-Diazocarbonyl compounds are the preferred structural motif for diazo-decomposition reactions, mainly for their ease of preparation and the ability to control reactivity through modification of Rh(II)L₄ ligands. Within this class of diazo compounds, those with two flanking electron-withdrawing groups are much more stable
than those with a single electron-withdrawing group. Stability of the diazo-moiety decreases with increasing electron withdrawing capacity of the attached group, where diazoesters are generally more stable than diazoketones and diazoamides are more stable than diazoesters. The thermal stability of substituted diazocarbonyl compounds follows the general profile depicted in Figure 1.12.

![Figure 1.12](image)

The preparation of α-diazocarbonyl compounds is usually facilitated either through diazo-transfer reaction (Scheme 1.9, Eq. 1) or by acylation of diazoalkanes (Scheme 1.9, Eq. 2). Alicyclic α-diazoketones have been synthesized most often through the acylation of activated carbonyl compounds such as acid chlorides and anhydrides (40). The most common method used for the preparation of α-diazoester compounds and cyclic diazoketones (38) is the transfer of a diazo-moiety from a diazo-transfer reagent (usually an arylsulfonyl azide) to a mono- or bisactivated methylene compound (37).
The diazo-transfer procedure works very well for cases in which the diazo-acceptor is doubly activated by two flanking carbonyl groups, however in cases where only one carbonyl group is present this method is often much less efficient or fails completely. Attempts to optimize the transfer reagent/base pairing can provide satisfactory results, but in some cases, better results can be obtained through a deformylating diazo-transfer reaction (Scheme 1.10). This method involves the Claisen condensation of the diazo-acceptor (42) with ethyl formate, introducing a strongly activating formyl group (43). In the course of the diazo-transfer reaction the formyl group is released as the sulfonamide (45).
The mechanism for the transfer of a diazo group onto activated methylene compounds (Scheme 1.11) proceeds in most cases through an intermediate triazine (48). The azide reacts with the carbanion of the enolate (47) forming the triazine which spontaneously decomposes with a concurrent proton shift producing the diazo moiety (49) and sulfonamide (39).

Scheme 1.11. Mechanism of diazo-transfer onto active methylene compound.

A recent report by Wurz describes the in situ preparation of ethyl diazoacetate from glycine ethyl ester hydrochloride (an extension of the classical preparation of EDA\textsuperscript{220}) and subsequent cyclopropanation in a one-pot protocol (Figure 1.13).\textsuperscript{254} Wurz had sought to overcome the explosive nature of EDA, and thus proposed the use of the classical conditions for preparation of the substrate in the presence of catalyst and olefinic substrate.

Figure 1.13. Wurz’s in situ preparation of EDA and subsequent cyclopropanation.
Ethyl diazoacetate was formed and simultaneously consumed upon the addition of a sodium nitrite solution to glycine ethyl ester hydrochloride in the presence of Rh(II) octanoate and at least three equivalents of olefin substrate. The reaction has been conducted on gram scale and provides chemical yields of >70%. Extension of this protocol to other types of diazo-substrates has yet to be investigated.

_Vinyl Diazocarbonyl Compounds_

Diazo compounds containing an olefin attached α to the diazo moiety have been classified electronically as a push-pull diazo-system by Davies,\textsuperscript{255} following the electron flow in the substrate (i.e. having one electron-donating group and one electron-withdrawing group present with the diazo-carbon, \textbf{50}). The vinyldiazo substrates (\textbf{50}) are relatively reactive and thermally unstable, quickly decomposing at room temperature via 6π-electrocyclization process (1,3-dipolar cycloaddition) to the thermally stable 3\textit{H}-pyrazole (\textbf{51}, Scheme 1.12).\textsuperscript{256} Substitution at the diazo-carbon has a marked effect on the rate of cyclization, where electron-withdrawing groups are stabilizing and electron-donating groups enhance the rate of cyclization.\textsuperscript{257} Furthermore, the addition of a second electron-withdrawing group at the vinyl terminus enhances the stability such that these compounds are indefinitely stable at room temperature.\textsuperscript{20}

\[ \textbf{50} \xrightarrow{\Delta} \textbf{51} \]

_Scheme 1.12. Electrocyclization of vinyldiazo esters._
Preparation of vinyldiazo compounds is slightly more cumbersome than their saturated and/or bis-activated counterparts due mainly to their thermal instability (Scheme 1.12). The most efficient method to obtain the vinyldiazo substrate is through a simple diazo-transfer method with the use of DBU as base and p-ABSA as the diazo-transfer reagent. The sulfonamide by-product of this reaction is a solid and can be quickly removed by filtration, facilitating workup and minimizing the occurrence of electrocyclization. Davies has reported alternative methods for the preparation of these types of diazo compounds, but the simple diazo-transfer methodology with p-ABSA has proven far superior in our hands.

The lack of thermal stability in the vinyldiazomethane series requires the use of a very active catalyst to induce rapid nitrogen extrusion in order to avoid the 6π-electrocyclization process. This prohibits the use of most copper and rhodium(II) carboxamide catalysts, which require longer reaction times and/or higher temperature to affect decomposition and metallocarbenoid formation.

Vinylcarbenoid species, resulting from the diazo-decomposition of vinyldiazo compounds, are susceptible to nucleophilic attack at both the carbenoid site and the terminal vinylogous position (Figure 1.14). Davies found that electron-withdrawing ligands bound to rhodium tend to increase electrophilicity at the vinylogous carbon and thus, reasoned that the use of highly electron-withdrawing molybdenum hexacarbonyl complexes would further enhance vinylogous reactivity.
He investigated diazo-decomposition of vinyl diazo ester (52) in the presence of MeOH and Rh$_2$(S-TBSP)$_4$ or Mo(CO)$_6$/S-TBSP, which provided a mixture of oxo-substituted butenoates (Scheme 1.13 and Table 1.1). The major compounds formed in reactions with Rh(II) catalyst were carbenoid insertion products 55 and 56.

The molybdenum catalyzed reactions generated products derived from attack at the vinyl terminus, with an apparent preference for the Z-isomer. In the cases of vinylogous insertion with Rh(II) catalyst the E-isomer was predominant.

Davies has also reported that highly electrophilic diruthenium(I, I) mixed carbonyl carboxylate complexes also caused significant enhancement of vinylogous vs. carbenoid reactivity in vinylicarbenoids. Under similar reaction conditions as shown in Scheme
the diRu(I,I) mixed carbonyl complexes generated product ratios of $75:11:14:0$ for structures 53-56, with chemical yields of 28-46%, thus demonstrating the enhanced selectivity for insertion at the electrophilic vinylogous position.

Table 1.1. Davies' vinylogous vs. carbenoid insertion (Scheme 1.13).

<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>total yield, %</th>
<th>53 : 54 : 55 : 56</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Ph</td>
<td>Mo(CO)&lt;sub&gt;6&lt;/sub&gt;/S--TBSP-H</td>
<td>93</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>Rh&lt;sub&gt;2&lt;/sub&gt;(S-TBSP)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mo(CO)&lt;sub&gt;6&lt;/sub&gt;</td>
<td>87</td>
</tr>
<tr>
<td>=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Mo(CO)&lt;sub&gt;6&lt;/sub&gt;/S--TBSP-H</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rh&lt;sub&gt;2&lt;/sub&gt;(S-TBSP)&lt;sub&gt;4&lt;/sub&gt;</td>
<td>55</td>
</tr>
</tbody>
</table>

The molybdenum catalyzed reactions generated products derived from attack at the vinyl terminus, with an apparent preference for the Z-isomer. In the cases of vinylogous insertion with Rh(II) catalyst the E-isomer was predominant.

Through further investigations, Davies and co-workers have reported high diastereoselectivities with vinyl- and aryl-substituted α-diazoesters (‘donor/acceptor’ systems) in cyclopropanation reactions. Through their studies they concluded that aryl- and vinyldiazo acetates were much more chemoselective than those derived from unsubstituted diazoacetates (traditional diazoacetates). Increased chemoselectivity has been obtained with the traditional diazoacetates with the use of
bulky ester substituents and/or the use of Rh(II) acetamides\textsuperscript{264} rather than Rh(II) acetate or with the use of iron porphyrin\textsuperscript{265} catalysts which have not been broadly studied in metal catalyzed diazo-decomposition reactions. Davies’ Rh\textsubscript{2}(S-DOSP)\textsubscript{4} catalyst was capable of affecting 98\% ee in cyclopropanations with vinyl- and phenyldiazoesters when the same system was ineffective for chiral induction in cyclopropanations with diazoacetates. The enhanced chemoselectivity of the vinyldiazoesters in this instance is attributed to the demands imposed by the trajectory of approach of the alkene to the donor/acceptor substituted carbenoids in comparison to that of the carbenoid derived from diazoacetate. A demanding approach by the alkene is consistent with a reaction that proceeds through a later transition state, in which bond formation occurs with closer proximity of the rhodium carbenoid and the incoming C-H/X-H. The donor/acceptor carbenoids are more stabilized electronically than the diazoacetates and are less reactive and more chemoselective.\textsuperscript{266}

Hammett studies of the electronics of a variety of substituted diazoesters in competitive cyclopropanation reactions with various electron-rich and electron-deficient alkenes concluded that increasing the electron-donating capability of the substituent attached to the diazo-carbon increased the chemoselectivity of the resulting carbenoid. These studies also showed that the reaction was virtually solvent independent (when this is usually not the case for vinyldiazoesters), and that the use of more electron-deficient catalysts such as Rh\textsubscript{2}(TFA)\textsubscript{4} and Rh\textsubscript{2}(S-DOSP)\textsubscript{4} greatly increased chemoselectivities in comparison to Rh\textsubscript{2}(OAc)\textsubscript{4}. 
Reactions of Metallocarbenes/carbenoids

There are several reaction pathways available to the metallocarbenoid intermediate. The particular pathway is determined in part by the catalyst employed for diazo-decomposition as well as the substrate(s) available to the resulting carbenoids. Yates\textsuperscript{211} suggested that transition metal catalysts react with diazo compounds to generate electrophilic carbene species (\ref{57}). The catalytic activity of the transition metals is dependent on the coordinative unsaturation at the metal center, allowing them to react as electrophiles with diazo compounds. Electrophilic addition of the metal to the diazo-carbon causes extrusion of dinitrogen producing the metal-stabilized carbene (\ref{57}). The carbenoid entity is transferred to an electron rich substrate, completing the catalytic cycle (Scheme 1.14).

![Scheme 1.14. Doyle's Proposed catalytic cycle for diazo-decomposition.](image)

The pioneering work of Teyssie and co-workers in the 1970’s expanded the utility of diazo compounds especially through Rh(II) catalysis (Scheme 1.15). Their work expounded on the extent of catalysis, resulting in a vast library of successful
transformations from O-H\textsuperscript{51} and X-H\textsuperscript{50} insertions to cyclopropanations of olefins\textsuperscript{267} and addition to aromatic compounds.\textsuperscript{56}

\begin{align*}
\text{O-H Insertion} & \\
\begin{array}{c}
\text{EtO} \\
\text{N}_2 \\
\text{EtO} \\
\text{EtOH}
\end{array}
& \xrightarrow{\text{Rh}_2(O\text{Ac})_4} \\
\text{EtO} & \text{O} \\
\text{O} & \text{EtOH} \\
\text{O} & \text{EtO} \\
\text{EtO} & \text{O} \\
\text{EtO} & \text{O}
\end{align*}

\begin{align*}
\text{Cyclopropanation} & \\
\begin{array}{c}
\text{MeO} \\
\text{N}_2 \\
\text{MeO} \\
\text{N}_2
\end{array}
& \xrightarrow{\text{Rh}_2(O\text{Ac})_4} \\
\text{MeO} & \text{C} \\
\text{C} & \text{MeO}_2C \\
\text{C} & \text{MeO}_2C
\end{align*}

\begin{align*}
\text{Buchner reaction} & \\
\begin{array}{c}
\text{MeO} \\
\text{N}_2 \\
\text{MeO} \\
\text{N}_2
\end{array}
& \xrightarrow{\text{Rh}_2(O\text{Ac})_4} \\
\text{MeO} & \text{O} \\
\text{O} & \text{MeO}_2C \\
\text{O} & \text{MeO}_2C \\
\text{O} & \text{MeO}_2C \\
\text{O} & \text{MeO}_2C \\
\text{O} & \text{MeO}_2C
\end{align*}

Scheme 1.15. Pioneering work of Teyssie and co-workers.

*Cyclopropanation*

Cyclopropanes are formed by the insertion of a carbene carbon into an olefin. The simplest of routes to these compounds employs dihalocarbene{s, most often dichlorocarbene, derived from base induced elimination of halocarbons (Scheme 1.16).}
Scheme 1.16. Formation of dihalocarbene.

The mechanism for this transformation first proposed by Doering and Hoffman$^{268}$ involves first the removal of a proton from haloform (58) forming trihalomethide ion (61). In the second step the loss of halide ion from 61 gives the neutral dihalocarbene (62). In the presence of excess olefin (63, Scheme 1.17) the carbene inserts into the C=C producing dihalocyclopropanes (64, 65).

Scheme 1.17. Mechanism of simple cyclopropanation.

Later Simmons and Smith$^{269}$ reported that the use methylene iodide and zinc-copper couple produces cyclopropanes with a stereospecific outcome (Scheme 1.18). The cyclopropanes isolated from reaction of methylene iodide (67) with pure trans-3-hexene (66) and pure cis-3-hexene (69) were the trans- (68) and cis-cyclopropane (70) adducts, respectively. This initial methodology was made more accessible and reproducible through the further development of organozinc reagents such as $\text{Et}_2\text{Zn}/\text{CH}_2\text{I}_2$ or $\text{ZnI}_2/\text{CH}_2\text{N}_2$.$^{270}$
Kochi and Salomon’s report on the role of copper catalysts in the cyclopropanation of olefins with diazo compounds further expanded the basic understanding of copper catalysis in general.\cite{271} Their findings that Cu(II) triflate was reduced by diazo compounds to the catalytically active Cu(I) triflate were consistent with prior observations and thus fortified this conclusion. These findings, however, did not unveil unique mechanistic insights. Palladium(II) acetate and rhodium(II) acetate were later introduced as alternatives to copper catalysts and their unique characteristics in carbenoid transformations were identified.\cite{48,57}

Anciaux and Teyssie\cite{267} first reported the use of rhodium(II) carboxylates and palladium(II) derivatives as catalysts in the cyclopropanation of olefins with diazoesters. Mechanistically it was concluded that the rhodium catalysts promote a carbenoid mechanism involving electrophilic attack on the olefin, whereas the palladium catalysts undergo an olefin coordination mechanism, not dissimilar to that of Cu(OTf)$_2$.

The significant difference in the mechanism of cyclopropanation lies in the number of vacant metal coordination sites in the catalyst. Palladium(II) acetate and Cu(I) triflate, for example possess more than one vacant coordination site, and display
complimentary selectivities in cyclopropanation reactions. These types of catalysts tend to form \( \pi \)-complexes with olefins (Figure 1.15), where stereoelectronic effects from the coordinated olefin can affect reactivity, and in certain cases, selectivity.

![Catalytic cycle for cyclopropanation: Pd(II) and Cu(I) catalysis.](image)

Figure 1.15. Catalytic cycle for cyclopropanation: Pd(II) and Cu(I) catalysis.

Apparent trends for catalysts that are capable of forming \( \pi \)-complexes (Cu(I) triflate) show that carbenoid addition tends to preferentially occur at the less substituted double bond whereas those which do not form \( \pi \)-complexes [Cu(acac)\(_2\)], favor addition at the more substituted olefin (Scheme 1.19).
Alternatively, catalysts that possess only one vacant coordination site per metal atom, such as Rh(II) carboxylates, do not display such a propensity for formation of olefin complexes in solution, however gas-solid phase measurements indicate the existence of such complexes. In general the mechanism of cyclopropanation with metallocarbenoids and alkenes, as proposed by Doyle\textsuperscript{272} (Figure 1.16), proceeds through the initial formation of a \( \pi \)-complex between the olefin and the electrophilic carbenoid complex (\textit{71a}, \textit{71s}). A \( \sigma \)-bond then forms between the electrophilic carbenoid center and either end of the olefin with backside displacement of the catalyst. This forms a second \( \sigma \)-bond, closing the cyclopropane ring, with regeneration of the catalyst.

Scheme 1.19. Chemoselectivity in cyclopropanation.
It is assumed that the sterically less demanding terminus of the olefin is positioned in closer proximity to the ligand “face”, which is established by the equatorial ligands (i.e. bridging acetate/amidate). The stereochemical outcome of the reaction is determined by the face of the olefin that approaches the carbenoid, providing two possible $\pi$-complexes $71a$ and $71s$. The favored transition state ($T_s$) occurs via $71s$, where the larger substituent ($R^1$) of the approaching olefin is positioned in a syn-relationship to the larger carbalkoxy substituent of the metallocarbenoid. Upon formation of the $\pi$-complex the original alkene structure moves down and rotates such that the larger substituent ($R^1$) eclipses the carbenoid hydrogen rather than the larger carbalkoxy substituent. Progression of the reaction through $T_s$ produces the trans-cyclopropane ring ($72t$), where the two largest substituents are positioned in an anti-relationship. Reaction progression through $71a$, approach of the larger substituent ($R^1$) in an anti-relationship to the carbalkoxy substituent, gives the less favorable $T_c$, resulting from upward movement.
of the less sterically demanding substituent ($R^3$) and rotation finally placing the two larger substituents ($R^1$ and carbalkoxy) in a syn-relationship, ultimately forming the cis-cyclopropane ($72c$). Previously proposed mechanisms for cyclopropanations involving alkylidenemetal complexes of tungsten and iron invoke the intermediacy of a metallocyclobutane which is ruled out in Doyle’s mechanism.

A recent example of the use of cyclopropanation in natural product synthesis was reported by Martin co-workers (Scheme 1.20). In their total synthesis of (+)-ambruticin S ($75$) the diazoester $73$ provided an 80% yield of cyclopropyl lactone $74$ in 92% ee with the use of Doyle’s Rh$_2$(MEPY)$_4$ catalyst (Figure 1.10, vide supra).

![Diagram](attachment:image.png)

Scheme 1.20. Cyclopropanation in the synthesis of (+)-ambruticin S.

There are alternative substrates that have shown reaction profiles similar to that of diazo compounds. $\alpha$-Nitroesters and ketones ($76$) undergo cyclopropanation reactions with olefins in the presence of a rhodium(II) catalyst and hypervalent iodine(III) (Scheme 1.21), where the reactive species, an iodonium ylide ($77$), is prepared in-situ under solvent free conditions. Interestingly these substrates show a preference for cyclopropanation over O-H insertion limiting there utility in these types of reactions.
Cyclopropanation reactions have also been carried out in aqueous solvent with the use of Rh(II) carboxylates, Nishiyama’s Ru(II) Py-box, and Katsuki’s Co(II) Salen complexes.\textsuperscript{254}

Asymmetric cyclopropanations of olefins with diazoacetates have been most successful with the use of copper catalysts such as \textbf{16-18} (\textit{Figure 1.5}) and rhodium(II) carboxamides with pyrrolidinone and oxazolidinone ligands (\textit{Figure 1.10}). Rhodium(II) carboxylates are relatively ineffective in asymmetric cyclopropanations with diazoacetates, however with vinyl- and phenyl diazoesters, Rh$_2$(OAc)$_4$ provides high yields and up to de > 50:1 in cyclopropanation reactions of styrene (\textbf{Scheme 1.22}). The use of chiral catalyst Rh$_2$(S-DOSP)$_4$ provided cyclopropanes (\textbf{81a-b}) with enantioselectivities greater than 98% for both vinyl- and phenyl diazoesters.
The difference in reactivity of the carbenoids derived from diazoacetates versus vinyl- and arylcarbenoids is due to the differences in the electronic nature of the resultant Rh(II)-carbenoids. Vinyl- and arylcarbenoids are less stable than those derived from diazoacetates and are thus more prone to reaction with olefins with varying electron density.\textsuperscript{275}

**Insertion Reactions**

**C-H Insertion Reactions.**

A number of the reported mechanistic aspects of the rhodium catalyzed C-H activation process have been widely accepted including; 1) the rate-determining step of the reaction is dinitrogen extrusion catalyzed by Rh\textsubscript{2}L\textsubscript{4}, 2) order of reactivity of C-H bonds proceeds from 1° being least reactive to 3° being most reactive, (with C-H bonds adjacent to heteroatoms displaying enhanced reactivity), 3) the electron-donating vs. electron-withdrawing character of the catalyst’s ligands affect the reactivity of the resulting rhodium-carbenoid, and 4) the configuration of the carbon of the activated C-H bond is retained.\textsuperscript{251} The generally accepted mechanism for rhodium catalyzed reactions of diazocarbonyl compounds, including C-H insertion, (Scheme 1.23) is assumed to involve a 3-centered transition state (Figure 1.17) in which the C-C bond and C-H bond are formed in a concerted non-synchronous fashion.\textsuperscript{251,276} The reactive catalyst, ML\textsubscript{n} (I) is available following solvent dissociation. Nucleophilic attack of the diazo compound on the metal center provides intermediate ylide II. Rhodium carbenoid III is generated upon extrusion of nitrogen, maintaining the core structure of the dirhodium tetraacetate with only slight elongation of the Rh-Rh bond. Transfer of the carbene moiety to the
appropriate functional group (i.e. olefin, C-H bond, X-H bond, carbonyl, or aromatic X-H bond) results in product formation.

Rhodium is not thought to have an immediate role in transfer of hydrogen from the insertion species to the carbenoid compound (Scheme 1.23, Scheme 1.31, and Figure 1.17). Only one of the rhodium atoms is bound to the carbenoid carbon throughout the reaction with the second rhodium atom assisting in the reaction. Chemoselectivity in the reaction is highly dependent on catalyst electrophilicity and substitution at both the carbenoid and substrate. The role of rhodium and details of the concerted non-synchronous process have been deduced through experimental and theoretical investigations.²⁵¹

Although alternative theories of the transition state and the mechanism of the insertion process have been proposed, the widely accepted concerted non-synchronous
mechanism involving a 3-centered transition state (Figure 1.17) has been supported with theoretical calculations and product development evidence.\textsuperscript{152,251,276}

![Figure 1.17. 3-Centered transition state proposed for C-H insertion.](image)

The first reported use of a C-H insertion reaction in organic synthesis was Wenkert’s preparation of the steroid skeleton 83 from diazoketone 82 with the use of rhodium(II) acetate as catalyst in 59\% yield (Scheme 1.24).\textsuperscript{277} The use of cupric sulfate catalyzed decomposition of 82 provided poor yields of 83.

![Scheme 1.24. Wenkert’s C-H insertion reaction.](image)

Doyle’s achiral catalysts (Figure 1.10) have provided higher yields of intramolecular C-H insertion products with excellent chiral induction. For example (Scheme 1.25), the conversion of diazoacetate 84 to lactone 85 was accomplished in
moderate to good yield with the use of either oxazolidinone or imidazolidinone catalysts with high enantioselectivities. The use Rh₂\((R\text{-MPIM})_4\), provided the opposite antipode of 85 \((1R, 5S)\).\(^{278}\) In this particular example, the use of Rh₂\((\text{OAc})_4\) failed to produce the desired racemic C-H insertion product and the use of azetidinone (Rh₂\((S\text{-MEAZ})_4\) and pyrrolidinone (Rh₂\((S\text{-MEPY})_4\) catalysts provided dimer 86 as the major product or low yield of the desired C-H insertion product.

\[
\begin{align*}
84 & \xrightarrow{\text{Rh}_2(\text{L}^*)_4} 85 + 86 \\
L^* = \text{S-MEAZ}: & 0\% \quad L^* = \text{S-MEAZ}: 53\% \\
L^* = \text{S-MPY}: & 8\%, 34\%\text{ee} \quad L^* = \text{S-MEPY}: 15\% \\
L^* = \text{S-MEOX}: & 35\%, 76\%\text{ee} \quad L^* = \text{S-MEOX}: ---- \\
L^* = \text{S-MPPIM}: & 73\%, 91\%\text{ee} \quad L^* = \text{S-MPPIM}: ---- \\
L^* = R\text{-MPIM}: & 59\%, 89\%\text{ee} \quad L^* = R\text{-MPIM}: ---- \\
\end{align*}
\]

Scheme 1.25. Stereoselective C-H insertion.

\textit{C-C Insertion Reactions.}

Carbene insertion into C-C bonds is a rare occurrence in comparison to C-H insertion and cyclopropanation reactions, most often demonstrated in intramolecular ring expansion reactions utilizing various carbene precursors such as 87. These types of reactions are more often thermal or photolytic in activation, rather than transition metal catalyzed. They have been argued to occur through two separate pathways, 1) \textit{via} photoexcited diazo compounds (carbene precursors) and 2) through real carbene chemistry.\(^{279}\) The early reports of C-C insertion were assumed to occur through carbene insertion into a
C-C bond (real carbene chemistry), however through reinvestigation the early mechanistic conclusions have been refuted.\textsuperscript{280-282} It is now believed that the majority of C-C insertion products were derived from rearrangement of carbene precursors, rather than actual carbene insertion into the C-C bonds and that even in the absence of nitrogenous carbene precursors a mixture of precursor and carbene chemistry is likely involved.

Huang and Platz\textsuperscript{281} and Thamattoor and co-workers\textsuperscript{280} reported on the rearrangement and intermolecular chemistry of cyclopropylmethylcarbene, reaffirming the postulation that alternative pathways are involved in the decomposition of nitrogenous carbene precursors (Scheme 1.26).

Decomposition of diazarine 87 in the presence of carbene traps (2,3-dimethyl-2-butene (TME) and propylamine) gave all possible products 88-91. They found that the concentration of TME depressed the yield of 88 at 25-100°C, but had no effect on the outcome at temperatures between 0°C and -25°C. The temperature dependence concluded that 88 and 90 were not derived from a common precursor. The formation of 89, which is only attainable through the intervention of a carbene intermediate (93), (90 could be derived from 92 → 95) supports this conclusion as well. Of the various intermediates in the reaction, the pure carbene (if substituted) could assume a trans-configuration which would also impede the C-C insertion/ring expansion process.
One of the few reports of transition metal catalyzed C-C bond insertion reactions of α-diazocarbonyl compounds was in 1962 by Lansbury and Colson (Scheme 1.27). They found that the copper catalyzed decomposition of 97 produced C-H insertion product 99 in 12% yield when conducted in nonpolar solvent, whereas the only isolable compounds found with the use of more polar solvents, resulted from C-C insertion (98, 1% yield). The remaining material from the reactions was an intractable tar. Prior to this report, carbenes derived from copper catalyzed decomposition of diazoacetic esters were not believed to undergo C-H insertion reactions.
Most reports of C-C insertion reactions to date occur via thermal or photochemical decomposition of carbene precursors.\textsuperscript{285-288} There have been a few reports of C-C insertion/ring expansion reactions through the use of Fischer-carbenes,\textsuperscript{289} Brønsted or Lewis acid-catalyzed\textsuperscript{290} C-C insertion reactions, and formal C-C insertion reactions of alkynes catalyzed by nickel complexes.\textsuperscript{291,292} Insertion into C-C bonds by transition metal stabilized carbenes/carbenoids has not been discussed at length in the literature.

**X-H Insertions Reactions.**

The most characteristic reactions of carbenoids (carbenes) are cyclopropanation of olefins and insertion into single bonds. Until the 1990’s C-H insertion reactions were utilized much more than polar X-H bond insertions in organic syntheses. One notable exception was the preparation of carbapenems such as (-)-thienamycin via Rh(II) acetate catalyzed intramolecular N-H insertion of β-lactams (Scheme 1.28).\textsuperscript{293} The alternative
photolytic pathway results in a 9:1 ratio of imide (101, via Wolff RAR) to lactam (100), whereas the Rh(II) catalyzed pathway provides >99:1 of bicyclic β-lactam 100.

![Scheme 1.28. N-H insertion in the preparation of carbapenem (-)-thienamycin.](image)

The first report of general X-H insertion reactions was by Teyssie\textsuperscript{50,51} in the 1970’s. He\textsuperscript{51} found that the reaction of diazoacetic esters with alcohols, water, or weak acids in the presence of Rh(II) acetate gave the corresponding α-alkoxy, α-hydroxyl, or α-carboxy compounds in near quantitative yields. The rhodium catalyzed process provided higher yields and better chemoselectivity than both the photochemical and CuCl catalyzed processes.

Teyssie\textsuperscript{50} later reported that phenol, thiophenol, and isomeric butyl mercaptans all provided good yields of X-H insertion product at room temperature (Scheme 1.29). The use of aniline as substrate required that the reaction be conducted at higher temperature. These reactions could be carried out either neat or in solution (benzene or ethylene glycol dimethyl ether).
Scheme 1.29. Teyssie’s X-H insertion reactions.

The accepted mechanism for rhodium catalyzed X-H insertion\textsuperscript{47,174} (X = N, O, S, Si, or halide) is thought to proceed via a stepwise process involving an ylide intermediate (IV, Scheme 1.30). Formation of the metallocarbenoid (II) results in theoretical breaking of the Rh-Rh bond and the development of electron density on the non-carbenoid rhodium atom (Scheme 1.31).\textsuperscript{251} The nucleophile (\textsuperscript{\textbf{)} XHR) attacks the carbenoid carbon producing ylide IV. The dirhodium bond is then reformed with dissociation of the new ylide V, which then rearranges through a 1,2-proton transfer from oxygen to the carbanion, providing the insertion product (VI) and regenerating the catalyst.
The difference between the mechanisms of C-H and X-H insertion is that the former is a concerted non-synchronous process, whereas the latter occurs in a stepwise manner (cf. Scheme 1.23 and Figure 1.17).

**O-H Insertion Reactions.**

There have been several recent investigations concerning the insertion of carbenoids into the O-H bond of an alcohol or other heteroatom-H bond utilizing transition metal catalysis. Thus far, only a limited number of reports have involved the use of vinyldiazo substrates. The most successful examples to date involve the
use of ethyl diazoacetate (EDA) derived rhodium carbenoids for the synthesis of α-alkoxy esters\textsuperscript{47}

EDA has also been used in an O-H insertion reaction utilizing a homoscorpionate substituted copper, providing the desired insertion products in >95\% yield\textsuperscript{295}. Alternatively, Sc(OTf)\textsubscript{3} has been used as a catalyst for decomposition of the diazo-moiety providing O-H, N-H, and S-H insertion products in moderate to good yields (40-70\%)\textsuperscript{296}. As the catalyst pool for diazo-decomposition grows the utility of the O-H insertion reaction has and will continue to expand as well. Fu’s work (\textit{vide infra}) with the ligands \textbf{124} and \textbf{125} (\textbf{Figure 1.22}) are a prime example of the advancement in utility of this transformation.

In the past it has been noted that insertion reactions involving hydroxylic bonds (O-H) have suffered from low yields and poor selectivities\textsuperscript{297}, particularly with the use of functionalized carbenes and alcohols\textsuperscript{224}. There have been several efforts invoked in part to overcome these problems. Noels and Teyssie\textsuperscript{47} reported that the use of dirhodium tetraacetate (Rh\textsubscript{2}(OAc)\textsubscript{4}) or Copper (II) catalysts with poorly coordinating counterions such as trifluoromethane sulfonate anion allowed for more efficient insertion reactions between EDA and saturated alcohols (\textbf{Scheme 1.32}).

![Scheme 1.32. Insertion reactions of EDA with saturated alcohols.](image-url)
The yields of these reactions were good, but still suffered from side reactions such as oligomerization and dimerization. Other intricacies in the reaction gleaned from this research were that even though O-H bonds are thermodynamically more stable than C-H bonds, there was no evidence of C-H insertion products. The relative reactivities of the alcohols in question were determined to be dependent on steric hindrance with EtOH > tPrOH > tBuOH. The reaction with EDA was also determined to be first order in rhodium and in the early stages of the reaction also first order in diazoester. A high preference for OH insertion over cyclopropanation was also observed with a variety of unsaturated alcohols, where yields of ether product increased with increasing steric bulk at the ester portion of the diazoester.

As previously stated, it has been determined that O-H insertion prevails over all modes of reactivity in α-diazocarbonyl compounds irrespective of the catalyst employed. Exemplary is the reaction of diazoester 102a-c provided, in varying yields, only the product of O-H insertion (103a-c) with no evidence (NMR) of alternative product formation (Scheme 1.33).75

![Scheme 1.33. Prevalence of O-H insertion over other modes of reactivity.](image-url)
An exhaustive search of the literature revealed several examples of intra- and intermolecular O-H insertion reactions \( \textit{via} \) transition metal-catalyzed diazo-decomposition,\(^{18,47,75,83,86,168,170-174,259,296,298-313} \) Lewis acid catalysis,\(^{250,303} \) and photochemically induced reactions,\(^{58,252,314,315} \) as well as ionic liquid promoted\(^{316,317} \) processes. These reports provide only moderate stereoselectivities, with a few exceptions, and vary in reaction scope, which is widely dependent on catalyst.\(^{175} \) Mechanisms for the various processes are generally agreed upon, however still under dispute.\(^{175,315,318} \)

An interesting synthesis of tetrahydrofuran and \( \gamma \)-butyrolactone derivatives reported by Wang and co-workers\(^{298} \) utilized Rh(II) catalyzed diazo-decomposition/O-H insertion reaction to access the former and photo-induced Wolff rearrangement/intramolecular nucleophilic addition to obtain the latter derivatives \( \text{(Scheme 1.34)} \). Their report exemplifies the utility and versatility of hydroxy-substituted diazo substrates.

![Scheme 1.34. Versatility of hydroxyl-diazo compounds.](image-url)
The diazo-decomposition of 104 under the specified conditions resulted in complete conversion of starting material in only ten minutes with the sole formation of O-H insertion product (105). The appropriately positioned hydroxyl function provides substituted tetrahydroyfurans upon O-H insertion reaction.

Alternatively, under photo-induced conditions the nucleophilic hydroxyl group attacks the intermediate ketene (106), formed via Wolff rearrangement, producing 107. The yield of lactone accessed via the photo-induced pathway suffered slightly due to extended reaction times (14-17 h), side reactions, and elimination of labile substituents in the position $R^3$ resulting in 108.

Inter- and intramolecular insertions of rhodium carbenoids into heteroatom-hydrogen (X-H) bonds are facile processes, resulting in the formation of ethers and heterocycles, respectively. The X-H insertion reaction is thought to occur via ylide intermediates. The effective generation of ylides and ylide intermediates in transition metal-catalyzed reactions of diazo compounds depends on the catalyst, diazo compound, and heteroatom. The steric environment of both substrates can effect ylide formation as well as the nucleophilicity of the heteroatom and competition with other transformations such as cyclopropanation. Intramolecular reactions can easily form 5-7 member ring ethers. Intramolecular reactions can easily form 5-7 member ring ethers.

$\beta$-Elimination

Transformations of diazocarbonyl compounds possessing $\beta$-hydrogen atoms may suffer from competition reactions such as 1,2-hydride or 1,2-alkyl shifts (Scheme 1.35).
Scheme 1.35. β-elimination in α-diazo-β-alkyl compounds.

The 1,2-hydride/alkyl shifts can be synthetically useful, but are limited in application to α-diazoketols. Deng and co-workers\textsuperscript{319} utilized this methodology in the preparation of β-alkynyl-β-ketoesters (110) from the corresponding β-hydroxy compounds (109, Scheme 1.36).

Scheme 1.36. β-hydride elimination: synthetic application.

Moody and co-workers\textsuperscript{172} studied in detail the competition between O-H insertion and β-elimination reactions. The decomposition of diazoester 111 with a variety of Rh(II) carboxylates, in the presence of water provided α-hydroxy compound (112) and α,β-unsaturated compound (113) in varying ratios (Scheme 1.37).
Scheme 1.37. Catalyst effect on O-H insertion/β-elimination.

It was determined from this work that increasing the electron-withdrawing capability of the ligands in the rhodium catalyst increased the amount of β-elimination product, where Z:E ratio also increases along the same trend. Bulky strongly electron-donating ligands gave product ratios for $112:113$ of $\geq10:1$ and strongly electron-withdrawing ligands provided ratios of 1:1-5. Taber$^{148}$ previously speculated that the intermediacy of rhodium carbenoids bearing electron-withdrawing groups favors the formation of the less entropically demanding (earlier T.S.) β-elimination product.

_Ylide Formation_

Another competing reaction which can compete with insertion reactions as well as cyclopropanation is the formation of ylides. Metal carbenes derived from α-diazocarbonyl compounds are sufficiently electrophilic to readily react with Lewis bases such as heteroatom organic bases (most often sulfur, nitrogen, and oxygen) (Scheme 1.38). The intermediate metal-stabilized ylides (114) of copper and rhodium catalysts generally form weaker metal carbon bonds than the adjacent $\text{R}_2\text{C}--\text{B}^+$ bond, which permits preferred cleavage at the metal—carbon bond.
Scheme 1.38. Ylide formation.

The ease of carbene transfer from the metal to the heteroatom is the basis for the synthetic utility of this diazo-decomposition methodology. The catalytically generated ylides (115) can undergo four possible types of reactions; 1) [2,3]-sigmatropic rearrangement reactions of allyl-substituted ylide intermediates, 2) [1,2]-insertion, or Stevens rearrangement, 3) β-hydride elimination (vide supra), and 4) dipolar cycloaddition reactions.$^{320}$

Oxonium ylide formation has only recently emerged as a synthetic tool due to past assumptions that oxonium ylides were not viable, due to the lack of reactivity of diazocarbonyl compounds towards ethers. Rhodium carboxylates and homogenous copper catalysts are efficient in the generation of metal-stabilized oxonium ylides. The most useful reactions of these types of ylides are [2,3]-sigmatropic rearrangements and [1,2]-insertion or Stevens rearrangements.

Selectivity in ylide formation and subsequent reactions is governed by the choice of catalyst, diazocarbonyl substrate, and solvent. C-H insertion reactions and cyclopropanation can compete with ylide formation. The formation and reactions of sulfonium, oxonium, and nitrogen ylides has been extensively studied and a number of
reviews have been written.\textsuperscript{2,218,320-323} Ylide formation can compete with insertion reactions when the substrates contain Lewis basic heteroatoms.

\textit{Green chemistry with Carbenoids}

In general, reactions of carbenoids are conducted under anhydrous conditions in non-nucleophilic solvents (DCM, DCE, PhH, or hydrocarbon) due to competing O-H insertion reaction with water. Interestingly however, there have been a few reports of O-H insertion reactions conducted in water (as solvent) with the use of hydrophobic catalysts and alcohols.\textsuperscript{254,324} The combination of hydrophobic catalyst (rhodium(II) pivalate, 27) and hydrophobic substrate (116) in the diazo-decomposition of EDA provided the \( \alpha \)-alkoxy ester (117) in 45\% yield (\textbf{Scheme 1.39}).\textsuperscript{254} Although, the yield of 117 was modest, the same reaction with hydrophilic substrates resulted in only trace amounts of O-H insertion product with predominant water insertion. The rationale for these reactions is that a hydrophobic pocket is created around the reactive carbenoid center.

\begin{center}
\begin{tikzpicture}
  \node [above] at (0,0) {EDA};
  \node [above] at (1.5,0) {116};
  \node [above] at (3,0) {45\%};
  \node [above] at (4.5,0) {117};
  \draw [-stealth] (0,0) -- (1.5,0);
  \draw [-stealth] (1.5,0) -- (3,0);
  \draw [-stealth] (3,0) -- (4.5,0);
  \node at (0.5,-0.5) {EtO_2C};
  \node at (1,-0.5) {N_2};
  \node at (1.5,-0.5) {H};
  \node at (2,0) {+};
  \node at (2.5,-0.5) {Ph};
  \node at (3,0) {\textasciitilde OH};
  \node at (3.5,-0.5) {H_2O};
  \node at (4,0) {EtO_2C};
  \node at (4.5,-0.5) {\textasciitilde OH};
  \node at (4,-0.5) {Ph};
  \node at (0,-1) {0.5 mol\% Rh_2(piv)_4};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.39.} O-H insertion reaction in water.

Yadav and co-workers\textsuperscript{316} have reported a green protocol for effective O-H insertion reactions of \( \alpha \)-diazoketones with the use of ionic liquids as solvent/catalyst/promoter. Although the mechanism and ‘catalytic-promoter’ nature of
the solvent is in question, the results are interesting, in that no side reactions occurred and the yield of O-H insertion product was 80-90% (Scheme 1.40).

\[ \text{R} = \text{alkyl, aryl} \]

\[ \text{R'} = \text{H, alkyl, benzyl, cyclopropyl, propargyl, allyl} \]

Scheme 1.40. Yadav’s ionic liquid ‘promoted’ O-H insertion.

**Stereoselective and Asymmetric Reaction Strategies in Organic Chemistry**

There are a number of methods which exact regio- and stereocontrol; heteroatom-directed organic reactions\(^{325}\) take advantage of the stereoelectronic interaction between a heteroatom substituent and an incoming catalyst or substrate (Scheme 1.41).

\[ \text{Scheme 1.41. Heteroatom directed epoxidation.} \]

Chiral Auxiliaries (\(X_C\)) are enantiomerically pure compounds which are linked to a substrate prior to a reaction in order to influence the stereochemical outcome. After the reaction the \(X_C\) can be cleaved providing enantio- and/or diastereomERICALLY enriched
products. There are a variety of compounds that could be used in this means, a few examples include sulfinamides, sulfoxides, camphor and carbohydrate derivatives (118 and 119, Figure 1.18), alcohols, amines, oxazolidinones, and oxazolines, and the list could go on. Auxiliaries 118 and 119 readily form chiral enamides or esters, respectively, through reaction with nucleophilic amines or acids. Sulfinamides (120) form chiral imines through condensation with aldehydes and ketones.

![Figure 1.18. Chiral Auxiliaries.](image_url)

The predeterminate factor in the type of $X_C$ to use is the functionality present in the substrate. The failings of this type of chiral induction are in the need to use stoichiometric amounts of enantiomerically pure auxiliary and the number of additional steps that are involved (introduction and removal of the $X_C$). The advantage of this method is that it has been extensively investigated and is well understood, allowing for a well planned reaction with a foreseeable outcome. Chiral auxiliaries also allow for the isolation of enantiomerically pure compounds (after removal of the auxiliary, 123 for example) with standard separation techniques (Scheme 1.42).
Organocatalysis has been described as a process in which the reagents and catalysts consist of small molecules containing only the atoms C, H, O, N, S, P, and halogens.\textsuperscript{327} Asymmetric synthesis through the use of organocatalysts predates the use of organometallic catalysts. The former has experienced disdain due to substrate dependency and lack of generality.\textsuperscript{328} However, a number of useful reactions have been developed relying on this type of catalysis; from Woodward’s synthesis of Erythromycin (Scheme 1.43, Eq. 1) to the Diels-Alder reaction catalyzed by MacMillan’s imidazolidinone organocatalysts (Scheme 1.43, Eq. 2).\textsuperscript{329}
Organocatalysis has been most notable in aldol-type transformations; however, over the past decade an expansive research effort has opened the door for organocatalytic cycloadditions, nucleophilic substitution, Michael additions, Mannich-type reactions, aza-Henry, and Baylis-Hillman reactions. For some time the only familiar and therefore the most successful organocatalysts were proline and cinchona alkaloid derivatives (Figure 1.19). The library of organocatalysts continues to grow with the addition of \(N\)-heterocyclic carbenes, imidazolidinone catalysts (MacMillan catalysts), chiral thioureas, and chiral BINOL derivatives (Figure 1.20).

Figure 1.19. Proline and cinchona alkaloid ‘parent’ organocatalysts.
The advantages of organocatalysts are that they are usually robust, inexpensive, readily available and non-toxic. Their use does not require demanding reaction conditions such as air/oxygen/moisture free atmosphere, low temperature, or absolute solvents. Organocatalytic processes are viewed as green approaches and will undoubtedly undergo further expansion beyond their current utility.

![Organocatalysts](image)

**Figure 1.20. Alternative classes of organocatalysts.**

**Asymmetric C-H Insertion and Cyclopropanation**

In studies directed toward the asymmetric synthesis of tropanes Davies found that the use of methyl ester-substituted vinylidazomethanes provided high levels of enantioselectivity in hydrocarbon solvents. The hydrocarbon solvent also suppressed the occurrence of vinylogous attack of the substrate on the vinylcarbenoid.

The use of chiral catalysts as well as chiral auxiliaries has been successful in carbenoid chemistry. Chiral Auxiliaries are most often chiral oxazolidin-2-ones or chiral secondary alcohols. The oxazolidinones are utilized most often as auxiliaries.
through their attachment to substrates at the nitrogen position and can also be used as chiral hydroxyl protecting groups. Enantipure alcohols are attached to prochiral substrates to form chiral esters. Following reaction with the substrate, diastereomers are formed and with cleavage of the auxiliary, enantio- (one prochiral center) and/or diastereomerically (two or more prochiral centers) pure products can be obtained.

Davies\textsuperscript{340} has been successful in conducting stereoselective tandem cyclopropanation/Cope rearrangement reactions with pantolactone-\text{X}_C derived vinyldiazoesters where chiral catalysts were unsuccessful. An adverse effect in the use of chiral auxiliaries is that they restrict one face of the carbenoid, which allows for competing intramolecular reactions to occur.\textsuperscript{221,341}. The results are often dependent on the choice of auxiliary. Davies\textsuperscript{221} was successful in affecting high levels of diastereoselectivity through chiral induction with the use of chiral lactate and pantolactone auxiliaries (\textbf{Scheme 1.44, Eq. 1}) whereas Doyle\textsuperscript{341} achieved only modest enantioselectivities with chiral oxazolidinones (\textbf{Scheme 1.44, Eq. 2}).
Scheme 1.44. Chiral auxiliary use in cyclopropanation.

The rigid structure which allows for facial selectivity develops from the association of the carbonyl of the auxiliary with the carbenoid carbon (Figure 1.21). Conformer B is disfavored due to the bulky R group pointing toward the metal complex.
Asymmetric O-H Insertion Reactions

Fu and co-workers (vide supra) have developed an asymmetric copper catalyzed version of O-H insertion with a Cu(OTf)₂/bisazaferrocene catalyst system (Figure 1.22, 124). Prior to Fu's work (Scheme 1.45), the greatest chiral induction achieved in an O-H insertion reaction via diazo-decomposition was with Doyle's chiral Rh₂(MEPY)₄ catalyst producing only 8% ee.²⁹⁴

\[
\text{RO-H} + \text{N}_2\text{O} \quad \rightarrow \quad \text{RO-H} + \text{Ar}\text{OR}^1
\]

1.05 eq.

\[
\begin{array}{c}
\text{N} \\
\text{FeMe} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{N} \\
\end{array}
\quad \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\end{array}
\]

Scheme 1.45. Fu’s asymmetric O-H insertion.

The stereoelectronic nature of the alcoholic substrate was probed and it was determined that strongly electron withdrawing groups and steric bulk hindered or prohibited the reaction. A decrease in the ligand to metal ratio or the use of other available ligands (cf. 16-18, Figure 1.5) resulted in decreased yields and stereoselectivity.

Figure 1.22. Fu’s chiral bisazaferrocene ligands.
**Tandem Reactions Utilizing Catalytic Diazo-decomposition**

There are several examples of tandem or cascade processes involving the use of metallocarbenoids. In these recent examples, only one reaction has been found in which ring-closing metathesis (RCM) has been utilized in tandem with Rh(II) catalyzed diazo-decomposition. Davies and co-workers invoked a two-step, one pot, three-component coupling strategy in the preparation of tetrasubstituted cycloheptadienes (126, Scheme 1.46). The two steps include 1) an enyne metathesis between an alkyne and vinyl ether and 2) Rh(II) catalyzed [4+3] cycloaddition to form cycloheptadiene (126).

![Scheme 1.46. Tandem/one-pot enyne metathesis/[4+3] cycloaddition.](image)

Davies also reported the effective kinetic resolution of a racemic mixture of substituted dienes through the use of Rh$_2$(DOSP)$_4$ catalysts (R/S-34a). Catalyst 34a was found to be highly discriminating, selecting diene topology and differentiating propargylic stereochemistry. In the reaction (Scheme 1.47) the catalyst reacts preferentially with E-127, formed from the enyne metathesis, producing 129 in 40-65% yield, 50-82% de, and 95-99% ee.
The cyclopropanation/Cope rearrangement sequence (a formal [4+3] cycloaddition) is one of the more notable reactions of vinylcarbenoids and one of the few tandem processes utilizing catalytic diazo-decomposition reactions. Davies and co-workers have thoroughly investigated this process and continue to apply it in synthetic applications.
Padwa and co-workers\textsuperscript{361} synthesized polyheterocyclic systems via a tandem process involving catalytic diazo-decomposition, 1,3-dipolar cycloaddition, and Mannich-cyclization (Scheme 1.49). Diazomide 130 cyclizes to the 1,3-oxazolium-4-oxide (isomünchnone) 131 in the presence of catalytic dirhodium perfluorobutyrate (25). A 1,3-dipolar cycloaddition ensues between the isomünchnone and the tethered olefin providing bicyclic adduct 132 (85-98%), which possesses a “masked” \(N\)-acyliminium ion. The polyheterocyclic product 133 (85-95%) is then obtained upon exposure of 132 to Lewis acid via Mannich-cyclization of the ‘unmasked’ \(N\)-acyliminium ion. The process described by Padwa provides access to complex products with high stereoselectivity and chemical yield.

Scheme 1.49. Tandem carbenoid cyclization-dipolar cycloaddition-Mannich cyclization.
Olefin Metathesis

Introduction

The 2005 Nobel Prize in Chemistry was awarded to Chauvin, Grubbs, and Schrock for their development of metathesis catalysts and synthetic methods utilizing those catalysts. Chauvin contributed to the mechanistic understanding of the metathesis reaction postulating the existence and role of a metallacyclobutane in the mechanism. Grubbs and Schrock have contributed both catalyst and synthetic methodology development of ruthenium and molybdenum based catalysts respectively. There have been a number of elegant syntheses reported utilizing the RCM methodology in the synthesis of simple carbocycles and heterocyclic rings alike. Metathesis is one of the most highly utilized reactions in both industrial and academic labs.

Mechanism for Olefin Metatheses

The mechanism for ring-closing and cross metathesis reactions (Scheme 1.50) is initiated through the loss of a ligand, usually a trisubstituted phosphine (PR₃) from the Ru-alkylidene precatalyst. This generates a free coordination site on ruthenium for complexation with the incoming olefin. A formal [2+2] cycloaddition reaction occurs to form the resulting metallacyclobutane. It is thought that the rate-limiting step for metathesis reactions involving the first generation catalyst developed by Grubbs is the formation of the metallacyclobutane and alternatively for Grubbs' second generation catalyst, loss of the phosphine ligand is assumed to be the slow step. The metallacyclobutane undergoes a cycloreversion reaction, with subsequent coordination to
the second incoming olefin followed by cycloaddition and another cycloreversion, resulting in product formation and regeneration of the active catalytic species.

The cross metathesis (CM) reaction often times suffers in chemical yield due to the lack of control of the olefin substrates. In the mechanism shown, six possible products could be formed including the (E)- and (Z)-isomers of the desired product. Ring-closing metathesis (RCM) is usually considered a more efficient process due to the steric constraints imposed upon the two reacting olefins. Conducting the reaction under relatively dilute conditions increases the probability of obtaining the desired ring closed product rather than a side product resulting from a possible cross metathesis reaction. Dilution of the reaction mixture provides an environment in which the probability of intermolecular collisions is decreased, thereby minimizing the amount of cross-metathesis product. In general, as with most reactions, the intermolecular versions of these reactions are favored under high substrate concentrations, whereas the intramolecular versions are more favorable with lower substrate concentration (0.01-0.002 M).

Scheme 1.50. Catalytic cycle for metathesis. Cross-metathesis shown.
In the case of metathesis reactions involving metal alkylidenes (CM, RCM, ROMP, etc…) the mechanism of the reactions involves the intermediacy of a metallacycle. In metathesis reactions with olefins the metal alkylidene adds to the olefin in a [2 + 2] cycloaddition producing a metallocyclobutane intermediate. Following a retrocycloaddition a new metal alkylidene is formed along with the metathesis product (in CM reactions). In RCM reactions (Scheme 1.51) the second metal alkylidene undergoes another [2 + 2] cycloaddition with the alternative olefin, thus forming the requisite metallocyclobutane intermediate once again, which provides a new metal alkylidene and the cyclized olefin. Each step in the reaction mechanism is reversible and under thermodynamic control.369

The RCM reaction allows for two competing reaction pathways for the intermediate metal alkylidene, 1) RCM occurs, providing cyclic olefin products, or 2) Intermolecular reaction occurs, forming oligomers and polymers (acyclic diene metathesis polymerization, ADMET). Also, when the cyclic olefin is formed it is then possible for yet another reaction to take place, ring-opening metathesis polymerization (ROMP). The outcome of the reaction is dependent on kinetic and thermodynamic parameters.
Carbonyl olefination is also possible using metal alkylidenes, however after formation of the oxametallocyclobutane intermediate and subsequent retrocycloaddition a metal oxo-species is formed. This species is stable and catalytically inactive, thus the need for stoichiometric amounts of expensive metal alkylidenes.

**Olefin Metathesis Reactions**

There are a number of potentially useful metathesis reactions available for mono- or diolefins (Scheme 1.52). The most interesting of these reactions is the ring-closing metathesis reaction. Formerly, RCM was a shot in the dark with classical recipes calling for unknown amounts, loosely identified, and variably stable catalysts. Recent advances in catalyst development have brought RCM to the forefront and it is now a top choice for consideration in reaction manifolds requiring the synthesis of cyclic olefins.
Olefin Metathesis Catalysts

Classical metal alkylidenes (Figure 1.23) such as those based on tungsten and titanium (Tebbe reagent) were moderately successful in the metathesis of unfunctionalized olefin coupling partners. The Tebbe reagent stands out due to its kinetic preference to react with olefins in the presence of esters.
toward synthetically useful catalysts were reported by Schrock \(^{371,372}\) and Bassett, \(^{373}\) who developed moderately robust, selective, and tolerable molybdenum and tungsten catalysts for ROMP, CM, and RCM reactions.

Early studies involving tantalum and niobium (Group V transition metals) \(^{181,374}\) based catalysts provided the groundwork for further development of tungsten and molybdenum (Group VI transition metals) based catalysts. The first metathesis catalysts of the general type M(CHR')(NAr)(OR)\(_2\) were based on tungsten. Molybdenum complexes are, however, preferred due to their ease of synthesis, cost, functional group tolerance (compared to tungsten), and molybdacyclobutane complexes are much less stable than tungstacyclobutane complexes.

**Molybdenum-based Metathesis Catalysts**

Schrock \(^{367}\) is credited with the preparation of the first well-defined highly active metathesis catalysts. Schrock’s catalysts are based on a four-coordinate molybdenum(VI) center with two alkoxide ligands, an arylimido ligand, and an alkylidene moiety. The Schrock catalysts are highly reactive toward oxygen, water, and moderate/weak Brønsted acids, therefore they must be handled in an inert atmosphere and reaction solvents and substrates must be thoroughly dried and purified.

The Schrock-type catalysts [Mo(CHR')(NAr)(OR)\(_2\), Figure 1.24 and Figure 1.25] are electron deficient 14-electron species (including the lone pair of the imido nitrogen) and are capable of bimolecular reactions with themselves, such as ligand redistribution. The bimolecular reactions are prohibited due to the bulky ligand architecture. All of the ligands are necessarily bulky in order to facilitate isolation of the
initiator compound (Figure 1.24), which can be utilized in the synthesis of a variety of Mo(CHR')(NAr)(OR)₂ complexes by treatment with the desired alkoxide. The imido group can be varied, however it must be stable enough to be carried through the three step synthesis required to prepare the precursor.⁴⁶⁷

![Figure 1.24. Schrock catalyst “universal precursor”](image)

The NAr and OR ligands are permanently bound to the Mo-metal center, whereas the nature of the alkylidene changes throughout the metathesis process. The latter affects the reactivity and stability of intermediates, where methylene complexes (Mo=CH₂) are the most reactive and thus, least stable. Increasing the substitution (Mo=CH₂ → Mo=CHR' → Mo=CR') of the metal alkylidene, increases the stability of this intermediate and decreases its reactivity, which is dependent on the stereoelectronics of the olefinic substrate as well as the conformation of the complex.

The d-orbital utilized for π-bonding with the imido group lies in the N-M-C plane, a consequence of this is that the alkylidene must also lie in the N-M-C plane. This restriction allows for the occurrence of rotamers (syn and anti, Scheme 1.53), which can be drastically different in their reactivities. In most cases the syn form is the most stable.
Interconversion is possible either through rotation about the Mo=C bond or by reaction with an olefin.

![Diagram of Mo-alkylidene rotamers](image_url)

**Scheme 1.53. Mo-alkylidene rotamers.**

One of the most important determinants of reactivity in a given alkylidene complex is the electron-withdrawing ability of the attached alkoxide. In general, the metal becomes more electrophilic with more electron-withdrawing alkoxide ligands. For example, when R = tBu ([Scheme 1.53](#)) the alkylidene complex is much less reactive than when R = C(Me)(CF₃)₂, with a reactivity difference on the order of ~10⁵ for most olefinic substrates. The increase in electron-withdrawing ability of the alkoxide ligand has also been shown to decrease the rate of *anti*-syn interconversion with the *syn* form being dominant, however the *anti*-rotamer is the more reactive. Minimizing rotamer interconversion is advantageous in predicting the stereochemical outcome of the reaction.

The formation of di-, tri- or tetrasubstituted olefins via RCM requires a highly reactive metathesis catalyst, where the Mo-alkylidenes serve well. These catalysts are also capable of forming ring sizes of 5-7 members. Reaction times for highly substituted olefins and larger rings are longer, however.
Ruthenium-based Metathesis Catalysts

Grubbs further expanded the scope of metathesis reactions with the development of active, air stable catalysts, which are tolerant to functional groups such as ketones, amides, esters, aldehydes, and protic functionalities such as alcohols, water, and acids. The Grubbs catalysts (Figure 1.26) are based on a ruthenium metal center surrounded by five ligands, two neutral electron-donating species (phosphines or NHCs), two mono-anionic groups (halides, usually chlorine), and an alkylidene unit (derivatives of methylidene). Grubbs catalysts possessing two phosphine ligands are referred to as first generation and those which possess NHCs are called second generation catalysts.

The first generation catalysts (138a/b/e/g and 139a) are versatile in their utility and extraordinarily robust in comparison to the Schrock catalysts, however they are inferior in terms of their reactivity. First generation catalysts are inefficient or incapable of enabling metatheses of highly substituted olefins, such as RCM for the formation of
tri- and tetrasubstituted cycloalkenes. Electronically deactivated substrates are also inactive in metatheses reactions with the first generation catalysts. These drawbacks have been addressed with the development of the second generation catalysts (138c/d/f, 139b, and 140) which are more reactive and still retain broad functional group tolerance.375

The metathesis catalysts developed by Grubbs and Schrock differ mainly in their functional group tolerance, selectivity (and rate of reaction), and air/oxygen stability. Grubbs' ruthenium based catalysts (Figure 1.26) are much more air/oxygen stable and thus, easier to handle, however speed is sacrificed. The molybdenum based catalysts are extremely air/oxygen sensitive (Figure 1.24 and Figure 1.25) and must be handled under air-free conditions (i.e. glove box). The Hoveyda group has also contributed to the development of metathesis catalysts, and there are currently 'hybrid' catalysts available containing both molybdenum (Schrock-Hoveyda, 137) and ruthenium metals (Hoveyda-Grubbs, 139)376 The hybrids bear the ligand/structural motif of the parent Grubbs and Schrock catalysts with modifications developed and introduced by Hoveyda (Figure 1.25 and Figure 1.26).

The metathesis catalyst (138a), a first generation bis-trialkylphosphine ruthenium benzylidene complex has been utilized in RCM reactions forming a number of ring sizes including 7- and 8-member carbocycles and cyclic ethers as well as bicyclic377 and macrocyclic molecules.

Initiation rates for the ruthenium based catalyst systems are governed by the size of the halide ligands, alkylidene moiety, and the nature and dissociability of the
phosphine ligand. Catalysts containing larger halide ligands initiate faster, whereas smaller alkylidene moieties cause slower initiation rates. A higher rate of dissociation for the phosphine ligand translates into increased initiation rates.

\[
\begin{align*}
138a: & \ R = \text{Ph}, \ L = \text{PCy}_3; \text{Ru gen-1} \\
138b: & \ R = \text{CH}=\text{CPh}_2, \ L = \text{PCy}_3 \\
138c: & \ R = \text{Ph}, \ L = \text{IMes} \\
138d: & \ R = \text{Ph}, \ L = \text{H}_2\text{IMes}; \text{Ru gen-2} \\
138e: & \ R = \text{CH}=\text{C(CH}_3)_2, \ L = \text{PCy}_3 \\
138f: & \ R = \text{CH}=\text{C(CH}_3)_2, \ L = \text{H}_2\text{IMes} \\
138g: & \text{Cp = cylopentyl} \\
139a: & \ L = \text{PCy}_3; \text{Hoveyda-Grubbs Catalyst 1st Generation} \\
139b: & \ L = \text{H}_2\text{IMes}; \text{Hoveyda-Grubbs Catalyst 2nd Generation} \\
\end{align*}
\]

**Figure 1.26.** Current Ru(II)-alkylidene metathesis catalysts.

The dissociation rates of the phosphine ligands in derivatives of the second generation Grubbs catalyst 138d have been determined experimentally and found to vary dramatically with the nature of the phosphine ligand (Figure 1.27).
A number of chiral Mo-based catalysts (Figure 1.25, 136/137) have been prepared and utilized in asymmetric RCM (ARCM) reactions. Grubbs and Fujimara\textsuperscript{369} prepared the chiral catalyst 136 through the use of Schrock’s universal precursor. The first example of asymmetric ring-closing metathesis (ARCM) was conducted using 136 and resulted in a 38% chemical yield with 48%ee. The catalyst 136 was also successfully used in kinetic resolution of dienes where the unreactive antipode of the diene was isolated in up to 84%ee. The activity of 136 resembles that of 135a/b. A polymer-supported recyclable molybdenum-based chiral catalyst for enantioselective olefin metathesis has been reported by Schrock and co-workers\textsuperscript{30} A number of asymmetric ruthenium alkylidene catalysts (141-144, Figure 1.28) have also been prepared and provide moderate to good yields with high levels of chiral induction (5-97% ee).
Piers and co-workers\textsuperscript{378-383} have developed 4-coordinate ruthenium catalysts (Figure 1.29), which obviate the presence of the labile phosphine or carbene ligands present in the Grubbs catalysts. The absence of the dissociable ligand circumvents the initiation step completely providing direct access to the active 14-electron species and eliminating the presence of free phosphine/NHC from interfering in the metathesis reaction. The Piers modified Grubbs catalysts are much more active, approaching the Schrock catalysts in activity, while still retaining the tolerance attributes ascribed to the original ruthenium alkylidenes.
For example, when comparing the activity of Grubbs 2nd generation catalyst (138d), Piers catalyst (145a and 146a), and the Schrock catalyst (135b), and Grubbs fast initiating catalyst (140) in the RCM reaction of diallyldiethylmalonate at 0°C in CD₂Cl₂ it was found that 146a outperformed the others quite dramatically (Scheme 1.54).

Scheme 1.54. RCM activity of Piers catalyst.

Problems encountered when conducting ring-closing metathesis reactions include polymerization (ADMET) of the acyclic diene, cross-metathesis (CM), ring-opening (ROMP) and polymerization of the resulting ring-closed product, and the possible inhibition of the metathesis catalyst. In addition to these problems, the metal alkylidene catalysts can activate the substrate (A, Figure 1.30) and in the case of allylic ethers substrates there is potential for β-elimination (B, Figure 1.30) to consume the propagating catalytic species. Likewise, inhibition can occur through the formation of stable chelated substrate-alkylidene adducts (C and D, Figure 1.30), particularly in the case of allylic and α,β-unsaturated esters/amides.³⁶⁹
Ghosh\textsuperscript{384} and Fürstner\textsuperscript{385} have reported the use of additives such as Ti(O\textit{i}Pr)\textsubscript{4} as an additive in RCM reactions in which there is potential for the formation of a stable chelate such as C or D (Figure 1.30) in the attempt to conduct a metathesis reaction. The additive’s function is to disrupt the formation of a stable metal complex between the catalyst and Lewis basic site.

The choice of metathesis catalyst (chiral or achiral) is usually based on precedent, the type of functional groups present in the reacting substrates, and the metathesis transformation of interest, however there is no ‘magic catalyst’ that will accomplish all of the desired transformations available and thus a thorough screening/optimization must take place as in the case of the rhodium carbenoid transformations.\textsuperscript{375}

\textit{Ring-closing Metathesis reactions: Formation of Unsaturated Ethers via RCM Reaction}

Heterocycles are a predominant structural motif in a number of natural product and other therapeutically important molecular scaffolds. There have been a number of methods developed for the formation of such structures (entire book and journal series...
have been devoted to the preparation and use of heterocycles\textsuperscript{386}, one of which is the RCM reaction\textsuperscript{387} of tethered dienes.

In a preparation of carbasugars, Ovaa et al. found that simply interchanging a protecting group (trichloroacetamide to tert-butyloxycarbamate, Scheme 1.55) turned a resistant substrate into a viable substrate for RCM reaction in the presence of Grubbs’ 1\textsuperscript{st} generation catalyst.\textsuperscript{388}

![Scheme 1.55. Subtle substrate change allows for RCM.](attachment:image)

Prior to this report, van Boom et al. demonstrated the strength of Grubbs’ first generation catalyst in the preparation of oxepines\textsuperscript{389} and pyranopyrans\textsuperscript{390} The pyranopyran syntheses involved the cyclization of a diene possessing a phenyl substituted \textit{cis}-olefin, an example of RCM with a non-terminal alkene (Scheme 1.56).
Scheme 1.56. RCM with disubstituted olefin.

Oxepene (152a) was isolated in 99% yield with the use of 5 mass% catalyst in DCM at 20°C for 24 hrs, whereas 152b was obtained in 79% yield at 80°C for 24 hrs with 5 mass% catalyst (Scheme 1.57). This demonstrated that the allylic substituent may be a significant factor in the outcome of the RCM reaction in these substrates.

Scheme 1.57. Oxepene formation.

The role of the allylic substituent was further investigated by Ovaa (Scheme 1.58) in similar reactions, with substrates possessing an acetonide protecting group with opposite orientation and implementation of a larger protecting group at the methanol substituent. Substrate 153a was ring closed in 85% yield and the more oxygenated substrates (153b and 153c) were isolated in 77% and 53% yield, respectively. The
increased oxygen content in the molecule provides the opportunity for the formation of a stable 6-member chelated substrate-alkylidene adduct. These findings are exemplary of the role of the stereoelectronic nature of the substrate in RCM reactions.

Scheme 1.58. Oxepene formation with variable allylic substituents.

Synthetic targets: New classes of drugs

Synthetic targets are often chosen out of necessity, usually due to the need for a new compound with a particular therapeutic use. Alternatively, a target may be chosen simply as a result of its complexity and the chemist’s interest in the imposed synthetic challenge. The rapid growth of resistant bacteria is one example in which synthetic targets have been chosen based on need.

There are a number of drug-resistant bacteria and deadly viruses with ineffective or no treatment. Once an antibiotic has been discovered and proven effective it is used in humans as a therapeutic. After widespread use the effectiveness of the antibiotic begins to decrease within months to years.\textsuperscript{391} For example, over the past fifty years \textit{Staphylococcus aureus} has become resistant to most antibiotics. \textit{S. aureus} was formerly treated with methicillin, a beta-lactamase-resistant beta-lactam antibiotic of the penicillin
class of antibiotics, which targets beta-lactamase producing gram-positive bacteria. Strains of *S. aureus* resistant to all penicillins are referred to as methicillin-resistant *S. aureus* (MRSA). Current treatments\textsuperscript{392,393} for MRSA are limited to approximately ten therapeutic agents including vancomycin\textsuperscript{392} (a glycopeptide therapy which disrupts bacterial cell wall construction), linezolid\textsuperscript{394-396} (the first commercially available oxazolidinone)\textsuperscript{***} antibiotic, first new class of antibiotics in three decades!), and daptomycin\textsuperscript{397,398} (a lipopeptide antibiotic). Vancomycin has been considered the antibiotic of last resort and has been used in the treatment of a number of infections, most notably *Enterococcus sp.* and after 29 years vancomycin-resistant enterococci have acquired five genes producing a bacterium variant with clinically important resistance.\textsuperscript{391}

The incidence of MRSA is reaching paramount levels and with the emergence of vancomycin-resistant Enterococcus (VRE) and the reports of vancomycin-resistant *S. aureus* (VRSA)\textsuperscript{399} it is all too evident that continued drug development is necessary to attempt to stay a step ahead of the infectious diseases we are treating.

Linezolid as well as the quinolones\textsuperscript{400} (Figure 1.31) are evidence that synthetic compounds can match the potency and efficacy/selectivity of natural product derived antibiotics. Investigation of natural compounds and continuing synthetic efforts will allow for further development and derivitization of drugs which are losing potency.
Research Objectives

Metalocarbenoid and metal alkylidene reactions have developed into attractive means of chemical transformations in natural product synthesis and organic chemistry as a whole. The versatility of the transition metal catalyzed diazo-decomposition reaction alone makes available a diverse array of potential synthons and highly functionalized molecules, and with the use of robust ruthenium alkylidene catalysts, metatheses reactions can be conducted with diversely functionalized olefins. Of the former type of transformation, stereoselective C-H and O-H insertion reactions are excellent candidates for the formation of C—C and C—O bonds in otherwise difficult to construct molecules. Combination of an X-H insertion reaction with the tolerant ring-closing metathesis reaction in sequence could provide a versatile route toward highly functionalized cyclic and bicyclic natural products.

The goals of the following research were to develop a concise stereoselective protocol for a sequential or one-pot X-H insertion/RCM methodology and demonstrate its feasibility in a synthetic scheme. The tandem process was to be utilized as a synthetic approach to three interesting natural products. The targets were chosen based on the
presence of medium-sized six- and seven-membered heterocyclic ring core structures, which can be difficult to form synthetically. Of the three compounds, isolaurepinnacin and rogioloxepane have known anti-fungal properties and pironetin has shown anti-tumor activity. The latter product was to be prepared through a tandem C-H insertion/RCM sequence, whereas the former two were to be obtained through the use of tandem O-H insertion/RCM reactions. These studies will help define the limits of the metallocarbenoid and metal alkylidene reactions and their applicability in tandem processes in the synthesis of natural products.
CHAPTER 2: FIRST GENERATION SYNTHESIS OF PIRONETIN: C-H INSERTION REACTIONS

Introduction

There are a growing number of natural products (155-158, Figure 2.1) which possess or can be accessed easily through bicyclic lactone synthons. Accessing the core scaffold of these types of molecules through simple/efficient processes would prove beneficial due to the molecular complexity inherent in forming the basic core structures.401

![Figure 2.1. Natural products containing lactone moieties.](image)

There are a number of examples of catalytic enantioselective intramolecular C-H insertion in which 4-, 5-, or 6-membered carbocyclic rings have been formed.402276,403 The direct formation of α,β-substituted-γ- and δ-lactones by a tandem methodology, however, has not been mentioned in the literature to date, with no examples placing ring-closing metathesis in tandem with an insertion methodology.

There has been one report of the synthesis of bicyclic γ-lactones via RCM reaction of a diene-tethered lactone (Scheme 2.1).404 The yields reported for 6- and 8-membered carbocycles (X = CH₂) were 40-85%, whereas the corresponding oxygen-
containing heterocycles (X = O) were formed in 15-20% yields. It was assumed that the decreased yields for the oxygenated series were due to issues associated with the formation of larger rings rather than a result of the presence of the oxygen.

\[
\begin{align*}
\text{SO}_2\text{Ph} & \quad \text{Mes} - \text{N} & \quad \text{N-Mes} \\
\text{Cl-Ru} & \quad \text{Cl} & \quad \text{PCy}_3 \\
\text{DCM, 40°C} & \\
\text{SO}_2\text{Ph} & \quad \text{Mes} \\
\end{align*}
\]

Scheme 2.1. Bicyclic γ-lactone synthesis via RCM.

We envisioned implementing a tandem C-H insertion/RCM methodology in a planned synthesis of (+/-)-pironetin (155), a potential plant growth regulator and immunosuppressant that shows remarkable antitumor activity. The retrosynthetic disconnections summarized in Scheme 2.2 describe an intramolecular route where two lactone rings are formed simultaneously via tandem C-H insertion/RCM reaction.
An intermolecular C-H insertion/RCM approach to the lactone moiety present in 155 could be implemented with use of substrates 165 and 166 shown in Scheme 2.3.

Scheme 2.3. Disconnection for an intermolecular approach to unsaturated lactones.
Intramolecular Approach to the Tandem Sequence

Vinyl-diazoesters (166a-c) and β-keto-α-diazoesters (167a-c and 168a-c) were investigated as coupling partners for the intramolecular construction of bicyclic-γ-lactone core scaffolds. As is shown in Scheme 2.4, the bicyclic lactones (169a-c and 172a-c) could be obtained via olefin metathesis between the diene generated from an intramolecular C-H insertion reaction. Some chemical limitation to this methodology is likely, especially through the kinetic and thermodynamic limitations known in the C-H insertion and RCM reactions. Intramolecular C-H insertion reactions are governed by a kinetic preference for the formation of a five-membered ring and a tendency to insert into C-H bonds adjacent to heteroatoms. In consideration of these limitations, it appeared that the formation of a bicyclo[4.4.0]lactone ring, as well as other ring sizes such as bicyclo[5.3.0], would be feasible through the tandem methodology provided.
My investigations were initiated with parallel experiments designed to study the reactivity and regiochemical insertion of an all carbon $\alpha$-vinyldiazoester (166a, Figure 2.2), compared to an oxygenated series of derivatives (166b-c). This series of reactions would help to determine the likelihood of an intramolecular C-H insertion reaction occurring in the absence/presence of an oxygen atom within the olefinic tether. The presence of an oxygen atom is a necessary structural requirement for the synthesis of (+/-)-pironetin.
Examination of the ratio of possible C-H insertion products (Scheme 2.5) formed via the insertion reaction of substrates 166a-c would provide information as to determine the feasibility of a model system providing the correct outcome.
While several insertion sites are possible, the likely outcome for the intramolecular reaction of vinyldiazo substrates 166 will be the formation of substituted $\gamma$-butyrolactone 175, while providing $\delta$-lactone 176a in the all carbon series due to the accessibility of a second C-H bond. In the series of compounds that include 166b-c, the generation of an oxonium ylide (176b and 176d) could be a potential reaction, leading to compounds 176c and 176e, respectively via subsequent sigmatropic rearrangement. A solution to the question of selectivity of these substrates will be accomplished through proper catalyst screening.

The $\alpha$-diazo-$\beta$-ketoesters 167a-c, devoid of the second olefinic bond, will be utilized as an alternative to the vinyldiazoester substrates (166a-c). This will provide a mono-olefinic substrate for demonstration of the C-H insertion reaction, without the additional reactivity questions associated with the additional olefinic site. Subsequently, an olefin could be introduced in these substrates through reduction of the ketone with sodium borohydride (NaBH$_4$) followed by dehydration of the alcohol with phosphorous oxychloride (POCl$_3$) to give a new diene substrate (178, Scheme 2.6). Davies has used this methodology to generate simple vinyl-diazo species.\textsuperscript{256} In this case however, the tethered olefin retained in the ester portion of the molecule would need to be longer (i.e. $n \geq 2$,) in order for the subsequent RCM reaction to be effective and provide substrates that have the structural features necessary for a pironetin-like scaffold.
Ultimately, substrates 168a-f possessing the $\gamma,\delta$-unsaturation required could be prepared via an aldol condensation of EDA derivatives with acrolein derivatives (Scheme 2.7).

Construction of the $\alpha$-vinyldiazoester precursors (179a-c) was accomplished by DCC coupling of unsaturated alcohol with $trans$-styryl acetic acid (Scheme 2.8, Eq. 1). The resulting ester (179a-c) is then diazotized (Scheme 2.8, Eq. 2) using a protocol developed by Davies\textsuperscript{425} with the diazo-transfer reagent $p$-acetamidobenzenesulfonyl azide ($p$ABSA) providing $\alpha$-vinyldiazoesters 166a-c. This diazo-transfer reagent ($p$ABSA) provides a number of advantages over alternative reagents such as methanesulfonyl azide ($MsN_3$) due in large part to its increased stability and decreased shock sensitivity. More
importantly from a functional standpoint, reagents such as pABSA provide solid sulfonamide by-products that can be removed by simple filtration through a celite pad. The use of p-dodecylbenzenesulfonyl (pDBSA) azide as the diazo-transfer reagent provided similar results for diazoester preparation.

![Chemical structure](image)

Scheme 2.8. Tethered Olefin-ester preparation (Eq. 1) and subsequent diazo transfer (Eq. 2).

The formation of various “push/pull” diazo-substrates, substrates that contain both electron donating (containing olefinic or alkynyl groups) as well as electron withdrawing groups adjacent to the diazo-containing carbon, provides functional difficulties not associated with the formation of simple diazo-moieties possessing two electron-withdrawing substituents such as the β-oxo-substituted α-diazoester 167. It has been found that the vinyldiazo compounds (166a-c) react in a $6\pi$ electrocyclization process to form the more stable 3H-pyrazole (166d, Scheme 2.9, Eq. 1).

In a majority of reactions run, the preparation of α-vinyldiazoesters resulted in 8-10% 3H-pyrazole contamination (166d, Scheme 2.9, Eq. 1). Attempts to prepare α-
vinylidiazoester substrates from alternative vinylacetates (R = H or Me) resulted in base-induced isomerization of the double bond into conjugation with the carbonyl and very low yields of diazo-substrate. In the specific case of vinyl acetate (R = H), no diazoester was isolated and near quantitative conversion to crotyl esters was observed (Scheme 2.9, Eq. 2).

\[119\]

- **166a**: \( X = CH_2, n = 1 \)
- **166b**: \( X = O, n = 1 \)
- **166c**: \( X = O, n = 0 \)
- **166d**: 3H-pyrazole
- **166e**: \( X = O \) or \( CH_2 \)

**Scheme 2.9. Issues associated with preparation of α-vinylidiazoesters**.

Discussion of the thermal instability of the vinyl-diazo compounds has been limited to date.\textsuperscript{256} Fortunately, the undesired electrocyclization reaction can be minimized if the substrate is stored in solution at temperatures less than 0°C. Generally, the most effective method found for obtaining reaction scale quantities of the vinyl-containing diazocarbonyl species is to prepare the substrate and use immediately, to further minimize any electrocyclization issues.

The α-diazo-β-ketoesters **167a-c** were synthesized by acetoacetylation of the corresponding alcohol with diketene followed by diazo-transfer with \( p \)ABSA (Scheme
The resulting diazo-compounds of this general type are thermally stable and can be kept indefinitely in the absence of light. The ultimate price paid for this additional stability, however, is a marked decrease in reactivity (diazo-decomposition) at ambient temperatures. The α-diazo-β-ketoester substrates (167a-c) introduce a versatile functional group which may be transformed into an olefin, either prior to insertion (vide supra, Scheme 2.6) or via modified Corey-Fuchs\textsuperscript{426} procedure or Wittig-type olefination following insertion, for the ensuing RCM reaction. One further complication is the ability of the resulting carbonyl moiety to participate in a carbonyl-olefination\textsuperscript{427,428} RCM reaction. It appears likely that substrates 168a-f will introduce greater versatility at both stages of the tandem insertion/RCM sequence.

![Scheme 2.10. Preparation of α-diazo-β-ketoesters.](image)

Studies conducted by Davies\textsuperscript{240,260,261} and Doyle\textsuperscript{262,264} concerning the selectivity/reactivity profile of various diazo-compounds (vide supra) prompted our use of the vinyldiazo substrates (166, donor/acceptor diazo-substrates), as well as the use of Rh(II) acetate and the chiral Rh\textsubscript{2}(S-DOSP)\textsubscript{4} catalyst (34a) as a logical starting point for screening the C-H insertion of the tandem protocol.
Difficulties arising from the synthesis and overall use of these compounds (*vide infra*) took time to overcome, but once the stability/reactivity of the compounds was secured, it then became indispensable to the success of the sequence. Several alternative diazo series (167a-c) were also investigated. The main functional difference between diazo-compounds 166 and 167 is their inherent chemical reactivity (directly related to stability). It is known that diazo compounds of type 167 are more robust than those of type 166 due to stereo-electronic effects. However, the vinyldiazo substrates appear to be more chemoselective (*vide supra*).266

One initial goal of this research project is to determine the feasibility of placing two disparate chemical methodologies in tandem, namely the efficient use of X-H insertion followed by metathesis of the resulting tethered dienes, while the overarching goal is to find functionally simple conditions that could be used to conduct these two powerful tandem reactions in a single pot. A one-pot reaction sequence would add to the efficiency of this sequence and provide a necessary advance for industrial labs. Our initial efforts were focused on understanding the basic reactivity of the two tandem reaction modes separately prior to investigating the one-pot methodology.

*Intramolecular C-H Insertion Reaction Results*

The intramolecular pathway proved to be precarious with the major products obtained from decomposition of vinyldiazo compounds being complicated by the presence of a 3H-pyrazole, resulting from the electrocyclization process, rather than diazo-decomposition. However, decomposition of 166b-c provided products resulting not from the expected C-H insertion reaction, but rather, from a competing formation of
an oxonium ylide, followed by a rearrangement of the pendant olefin (cf. Scheme 2.5, 176b → 176c).\textsuperscript{300,429}

A small portion of the results obtained through the use of substrates 166a-c and 167a-c are shown in Table 2.1 and Table 2.2, respectively. All of the crude reaction mixtures were analyzed by GC/MS and \textsuperscript{1}H-NMR prior to workup and/or purification. The most prevalent components discovered during an analysis of the crude mixture indicated the presence of the 3H-pyrazole and oxonium ylide/RAR products. There was little evidence of C-H insertion product in the crude reaction mixture and, upon workup of the reaction, the predominant compounds isolated were 3H-pyrazole, oxonium ylide/RAR products, and α-hydroxy compounds resulting from the insertion of adventitious water. Use of the Rh$_2$(S-DOSP)$_4$ does in fact provide the required insertion product albeit in 20% chemical yield and no discernable asymmetric induction (Table 2.1). Some catalyst screening was conducted for the reaction but in a limited set of catalysts, none provided greater chemical yield and more importantly a cleaner reaction. It appears that changing from the vinyl species to the b-ketoester does little to increase the chemical yield of the insertion reaction. The oxonium formation/rearrangement pathway becomes more prevalent with the stabilized diazo compound. Limited catalyst and condition screening again provided the insertion product in 20% chemical yield. Investigation of both pathways was not entirely exhaustive and thus a more thorough solvent/catalyst screening could prove to be beneficial for the elaboration of this set of substrates.
Intromolecular Approach to the Tandem Sequence

It is likely that an intramolecular C-H insertion pathway will provide more stereo- and regiocontrol based on structural constraints to the degrees of freedom available to the
system. It would also provide an avenue for the preparation of complex synthetic targets in only a few steps or possibly via a one-pot approach. However, we may be able to access a similar class of compounds or core structure utilizing an intermolecular pathway. Intermolecular C-H insertions have been reported in the literature, but the propensity for side reactions increases greatly, even at high concentration. Steric and entropic effects have a great influence on intramolecular reactions and with high dilution these reactions tend to proceed with much more predictable results than the former. However, the need for an alternative, yet similar, route to the desired scaffold was necessary due to the complexity of the reaction and the impending results of the intramolecular pathway.

The tandem intermolecular process was to be examined through the use of diazoesters 180 and 184 and olefinic substrates 181a-c (Scheme 2.11, Figure 2.3, Figure 2.4). This combination of substrates would provide an expeditious route to analogous pironetin core structures (vide supra, Scheme 2.3). The presence of the acetate group will provide insight into the feasibility of the proposed intermolecular route to the core structure of (+/-)-pironetin.

Preparation of the diazoester substrates was conducted in similar fashion to that of the diazoester substrates utilized in the intramolecular route. Diazoester 184 was to be
utilized prior to 187, under similar reaction conditions as described for the intramolecular sequence. Substrate 187 would be utilized after successful completion of the insertion reaction with substrate 184.

![Scheme 2.11. Proposed preparation of advanced intermediates.](image)

It is known that C-H activation preferentially occurs at sites adjacent to electron donating substituents that can stabilize the development of positive charge at the carbon undergoing C-H cleavage. Therefore, the substituent $R_1$ would prove to be vital in the role of substrate activation. The C-H insertion reaction could potentially occur at multiple sites with substrates 181. The protecting group ($R_1$) chosen would ultimately enhance or reduce the electronic influence of the neighboring oxygen as well as introduce a potential site for insertion or oxonium ylide formation. Consideration of side reactions such as ylide formation and cyclopropanation is also necessary due to the presence of the olefin and high oxygenation of the substrates.

In order to further investigate the preference for the desired reaction pathway (point of insertion) four substrates (Figure 2.4) were chosen as C-H (181a-c, 188-189)
and O-H (190) activation substrates to examine a number of potential variables. The primary factor to be determined was the preferred reaction pathway, C-H vs. O-H insertion. It is widely known that the O-H bond is much more reactive than the C-H bond, however if the proper catalyst and reaction parameters are chosen, one may affect an alternative transformation. Secondly, the three substrates that were chosen for C-H activation posses multiple sights for potential insertion to occur. Substrates 188 and 189 have a doubly activated acetal C-H bond as well as allylic sites. The 2-(allyloxy)ethyl acetate structure (181b) posses two activated C-H bonds and one deactivated C-H bond, with a fourth potential reaction site at the carbonyl oxygen via oxonium-ylide formation. Compound 190 contains an O-H bond which should be the preferred site of reaction, however all of the substrates posses an alkene, which provides yet another possible reaction, cyclopropanation.

![Figure 2.4. Intermolecular insertion substrates.](image)

It was assumed that insertion would occur at an activated position adjacent to oxygen. The acetate group could prove to be deactivating and in combination with the activating ethereal oxygen, insertion should occur at the preferred site (C-H). These
assumptions indicate that substrate 181b would provide direct access to an advanced intermediate (182 → 183 or 185 → 186, Scheme 2.11) for the preparation of (+/-)-pironetin. Variability in the chain length would enable examination of the subsequent RCM to different sized heterocycles, providing an avenue for derivation and preparation of pironetin analogues.

Several characteristics of the diazo-decomposition and intermolecular insertion reaction have been determined to be significant in affecting the desired transformation. For instance, if the vinyldiazo compounds have been prepared more than 24 hours in advance and stored in the freezer, it is necessary to increase the concentration of the diazo-species to at least two equivalents (relative to alcohol), owing to the loss of reactive diazo substrate to pyrazole formation. Alternatively, the use of freshly prepared vinyldiazo substrate minimizes the development of pyrazole, and increases the yield of insertion product.

It has also been noted that the diazo-decomposition reactions of α-diazo-β-ketoesters (184/187) proceed much more efficiently in the presence of excess substrate, minimizing the incidence of side reactions or intermolecular dimerization. The temperature of the reaction must be maintained at 0°C or below in the case of the vinyldiazo substrates, prohibiting electrocyclization. On the other hand, α-diazo-β-ketoesters need to be heated, even in the presence of catalyst (80-110°C). The most important variable of these reactions appears to be the choice of catalyst. The “electronically neutral” Rh(II) acetate dimer was chosen as the starting point for catalyst screening, as in the intramolecular reactions. Alternative rhodium(II) catalysts were
chosen on the basis of electron donating/withdrawing capacity of the ligands. Copper(II)
catalysts were also examined in the diazo-decomposition of α-homovinyl diazoesters and
α-diazo-β-ketoesters.

*Intermolecular C-H Insertion Reaction Results*

Screening of the intermolecular process was undertaken with the preceding
assumptions in mind. Diazoester substrates 180b and 184 were introduced to each of the
insertion substrates 181 and 188-190 using the conditions specified in Table 2.3. Davies’
DOSP catalyst was utilized at first due to the need for low temperature reaction
conditions (obviation of pyrazole) and then the catalyst and conditions were varied
according to the results obtained. The use of diazoesters 184 allowed for higher reaction
temperatures, but the screening process was conducted in a similar fashion starting with
Rh₂[(S)-DOSP]₄ and Rh₂(OAC)₄.

### Table 2.3. Intermolecular vinyldiazo C-H insertion results

<table>
<thead>
<tr>
<th>Entry</th>
<th>Diazooester</th>
<th>Substrate</th>
<th>Ligand</th>
<th>Solvent (°C)</th>
<th>Results(Product)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180b</td>
<td>181a</td>
<td>(S)-DOSP</td>
<td>Hex (0)</td>
<td>192a</td>
</tr>
<tr>
<td>2</td>
<td>180b</td>
<td>181b</td>
<td>(S)-DOSP</td>
<td>Hex (0)</td>
<td>192b</td>
</tr>
<tr>
<td>3</td>
<td>180b</td>
<td>181c</td>
<td>(S)-DOSP</td>
<td>Hex (0)</td>
<td>ylide</td>
</tr>
<tr>
<td>4</td>
<td>180b</td>
<td>181a</td>
<td>OAc</td>
<td>DCE (0-25)</td>
<td>192a</td>
</tr>
<tr>
<td>5</td>
<td>180b</td>
<td>181b</td>
<td>OAc</td>
<td>DCE (0-25)</td>
<td>192b</td>
</tr>
<tr>
<td>6</td>
<td>184</td>
<td>181a/b</td>
<td>OAc</td>
<td>DCE (83)</td>
<td>ylide</td>
</tr>
<tr>
<td>7</td>
<td>180a/b</td>
<td>190</td>
<td>OAc</td>
<td>DCE (25)</td>
<td>193a (60%)</td>
</tr>
<tr>
<td>8</td>
<td>184</td>
<td>190</td>
<td>OAc</td>
<td>DCE (83)</td>
<td>193b (20%)</td>
</tr>
</tbody>
</table>
Interestingly, in all cases using either of the diazoester substrates the resultant reaction mixtures were overwhelmingly complex. The only isolable compounds resulting from diazo-decomposition reactions with substrates 181 were derived from ylide formation followed by a 1,3-dipolar cycloaddition reaction (Scheme 2.12). The crude product mixture of each reaction was analyzed by GC/MS prior to any work-up or purification procedure and in each case the predominant entity appeared to be the result of ylide formation followed by subsequent RAR/reaction. The structures of compounds 192a and 193b are speculative, based on GC/MS and 1H-NMR/COSY analysis.

Scheme 2.12. Cycloadducts resulting from ylide formation.

Reactions of diazoesters 180 and 184 with activated substrates 188-189 unfortunately resulted in intractable product mixtures, even at moderate to high concentrations (0.2 - 1.0 M, with respect to diazoester substrate). On the other hand, the results of diazo-decomposition of 180 and 184 in the presence of substrate 190, resulted in relatively clean conversion to the O-H insertion product (Scheme 2.13). Yields of O-
H insertion product decreased with higher reaction temperatures, a result of pyrazole formation (Table 2.3, entries 7 and 8).

\[ \text{EtO}_2\text{C} \rightleftharpoons \text{N}_2 + \text{Rh}_2(\text{OAc})_4 \rightarrow \text{EtO}_2\text{C} \rightleftharpoons \text{N}_2 + \text{O} \text{Rh}_2(\text{OAc})_4 \]

180b 190 193a

184 190 193b

Scheme 2.13. Diazo-decomposition in the presence of alcohol.

A number of catalysts (cf. Figure 1.7, 23-30) were investigated in the diazo-decomposition reaction with substrates 181a-c, and 188-190. In all cases the results were similar to those presented in Table 2.3. The use of Doyle’s chiral catalysts (cf. Figure 1.10) provided intractable crude product mixtures as well.

Conclusions: Intra- and Intermolecular C-H Insertion Reaction Screening

While both the intra- and intermolecular pathways have provided some interesting results, the desired advanced intermediates for the synthesis of (+/-)-pironetin have not been obtained in appreciable/preparative yields. With the use of acetylated vinyl- and allyloxy ethanol in intermolecular reactions, we saw the result of β-alkoxy substituents deactivating the desired C-H bond. This then allowed for the formation of an ylide intermediate via nucleophilic attack of the more electron dense carbonyl oxygen on the electrophilic carbene. The oxonium ylide intermediate then undergoes a 1,3-dipolar
cycloaddition. The results are similar to that obtained with 166c and 167b-c via the intramolecular pathway in which the ethereal oxygen attacks the electrophilic carbene (Scheme 2.5, Table 2.1, and Table 2.2).

The lack of detection of C-H insertion products in the intermolecular reaction was in agreement with literature findings, and is suspected to be a result of using multifunctional substrates. On the other hand the use of the less reactive diazo-compound 166 and 180 provides evidence of C-H insertion product along with the interesting oxonium ylide products, respectively. Further investigation of alternative catalysts and conditions is necessary to demonstrate the viability of the C-H insertion/RCM route. The lack of success in C-H insertion did not allow for investigation of the RCM portion of the tandem process.

In light of the issues encountered with the C-H insertion reaction, I attempted to approach the core structure through a cross-metathesis/C-H insertion tandem process (Scheme 2.14). The CM reaction was attempted with a variety of metathesis catalysts, under a variety of conditions, with both diazo and non-diazo substrates, yet the olefin product was not realized. Lewis acids, BCl₃ derivatives, have recently been demonstrated to be beneficial in these types of process, but were not utilized in my attempts. Revisiting this protocol may also prove to be beneficial. The subsequent C-H (or O-H) insertion reaction may prove to be facile with high dilution and the use of an alternative protecting group.
It was determined that with the desired substrates ylide formation was a highly likely process in both the intra- and intermolecular diazo-decomposition reaction. These findings prompted us to investigate alternative substrates for further study and implementation of an alternative tandem process. The information gleaned from attempted C-H insertion with the desired oxygenated substrates (predominant ylide formation/RAR) and the propensity for insertion with adventitious water prompted the investigation of a tandem O-H insertion/RCM tandem sequence. An alternative synthetic target was also considered at this point.
CHAPTER 3: SYNTHETIC METHODS DEVELOPMENT: TANDEM O-H INSERTION/RCM METHODOLOGY

Introduction

The stereoselective preparation of highly substituted oxygen heterocycles has attracted considerable attention over the past few decades. Medium-sized cyclic ethers are common structural units in naturally occurring compounds, most notably within marine natural products such as ionophores and the brevetoxins. Although a variety of methods exist for dihydro- and tetrahydrofuran synthesis, there are few examples of single-step strategies. In light of the results obtained for the attempted C-H insertion reactions, we considered the application of the tandem methodology to other types of core structures that could be prepared utilizing an O-H insertion reaction. Rather than a C-H insertion, an O-H insertion would be coupled with RCM in the tandem methodology to construct unsaturated ethers.

Currently, there are a growing number of examples of intra- and intermolecular O-H insertion reactions via decomposition of diazo-compounds (vide supra). In the cases reported, most have found that poor stereo- and/or diastereoselectivities result from O-H insertion. It was thought that further investigation of the O-H insertion results previously found would provide a viable route to α-alkoxyesters possessing two olefin tethers. The tethered olefins could be utilized in a RCM reaction providing unsaturated cyclic ethers as advanced intermediates. Once each half of the tandem process was refined, efforts to induce asymmetry would be undertaken.
There are several examples of tandem-type reactions \( \textit{vide supra} \), due in part to increasing environmental demands and decreased costs resulting from efficiency. To my knowledge, there is only one reported example to date, in which a metathesis reaction has been utilized in tandem with a rhodium(II) catalyzed diazo-decomposition step\(^{342} \) \( \textit{vide supra} \), Scheme 1.46).

Retrosynthetic Analysis of the Tandem O-H Insertion/RCM Methodology

\textit{Intermolecular Tandem Sequence: C-H vs. O-H Insertion/RCM}

Accessing substituted unsaturated cyclic ethers (\textbf{Scheme 3.1, Eq. 1}) can be accomplished in similar fashion to my proposed approach to the bicyclic lactones/(+/-)-pironetin (\textbf{Scheme 3.1, Eq. 3}). The only difference in the construction of these molecules is that the insertion occurs between the carbenoid carbon and an O-H bond rather than a C-H bond. The application of a C-H insertion methodology could also be invoked (\textbf{Scheme 3.1, Eq. 2}), as was previously discussed. The cyclic ether is formed in the subsequent step via the RCM reaction of the two tethered olefins realized after the insertion. The change in insertion provides different set of potential advanced intermediates, which could be utilized in a practical synthesis of cyclic ether containing natural products.
Scheme 3.1. Retrosynthetic analysis of unsaturated cyclic ethers, example with vinyldiazoester.

The carbenoid precursors to be utilized in the reaction screening (Figure 3.1) represent two different classes of diazoester. Compound 180 is a vinyldiazoester which is less stable as a diazo-species and more reactive as a metallocarbenoid in comparison to \( \alpha \)-diazo-\( \beta \)-ketoesters 184 and 187, which are stable diazoesters, but less reactive as metallocarbenoids. The homovinyldiazoester 196, is presumed to behave in similar fashion to \( \alpha \)-alkyldiazoacetates. The differences in the relative stabilities/reactivities are due to the electronic nature of the substituent directly attached to the diazo/carbenoid carbon. Electron-donating groups increase the electron density at the diazo carbon thereby increasing its basicity and reactivity to the metal-centers open chelation sites. Electron-withdrawing groups have the opposite effect.
Figure 3.1. Diazoester substrates.

O-H Insertion reaction: Catalyst Screening and Reaction Optimization Results for α-vinyl diazo and α-diazo-β-ketoesters

The first goal of the O-H insertion/RCM methodology was to optimize the insertion process through catalyst/condition screening with diazoester substrates (180, 184, 187, and 194, Figure 3.1) in diazo-decomposition reactions with primary unsaturated alcohols. The next step was to optimize the RCM reaction with the insertion products, followed by an investigation of a one-pot methodology. The optimized conditions for the tandem process would then be applied to the synthesis of a natural product to further demonstrate utility.

After overcoming the problems associated with vinyl diazoester 180, the O-H insertion reaction proved to be facile providing moderate to good yields of α-alkoxyester (Table 3.1, Eq. 4).

The insertion reaction was conducted under a variety of conditions using two different methods. Method A utilized conventional heating, whereas method B utilized microwave irradiation to promote the reaction. The vinyl diazo substrates, being confined by their propensity to cyclize at elevated temperature, were introduced to olefinic alcohol substrate at room temperature. Each diazoester substrate was subjected to the conditions of Method B (170°C, 10 min.) in the presence of alcoholic substrate, but in the absence of
catalyst, to confirm the necessity of catalyst in the transformation (Table 3.1, entry 1). In each case the only compounds present in the product mixtures were determined to be the result of thermal decomposition, pyrazole formation. Diazoester 184 was recovered in near quantitative yield in the absence of catalyst.

The best catalysts for the reaction with vinyl diazo substrates were dirhodium carboxylates, with Rh₂(OAC)₄ and Rh₂(S-DOSP)₄ providing the best results. Doyle’s catalysts did not perform well in the reaction (Table 3.1, entry 6), however it is known that these catalysts perform well in C-H insertion and cyclopropanation reactions at elevated temperatures. The heightened reactivity of the vinyl diazo substrate is demonstrated by its ease of decomposition a room temperature (Table 3.1, entries 2-5), but more importantly the reaction can be conducted at low temperature (Table 3.1, entry 7), which may be beneficial to instill stereocontrol.

Optimum conditions for O-H insertion via diazo-decomposition of α-vinyl diazoesters were finally determined to be the use of 0.1 mol% Rh₂(OAc)₄ with respect to diazoester, in DCE solvent at 0°C overnight, using two equivalents of diazoester with respect to alcohol (Table 3.1, entries 8-11). In nearly every reaction the isomeric product 198 was formed. Under the optimum conditions the ratio of 194:198 was decreased in every case. The development of 198 is believed to occur via a thermal [1,3]-hydride shift. This isomer becomes more prevalent as the product is exposed to elevated temperatures (Table 3.1, entries 12 and 13). Decreased yields of O-H insertion product are seen with the use of method B, a consequence of the electrocyclization process.
Primary alcohols varying in chain length were investigated in the insertion reaction as a means to vary the ring size of the ensuing RCM product. The diazo-decomposition reactions that were conducted using a vinyldiazo substrate with secondary alcohols to form $\alpha$-alkoxyester provided significantly lower yields, likely attributable to

![Chemical structure](image)

Table 3.1. Vinyldiazo O-H insertion.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>n</th>
<th>$\text{N}_2$:ROH</th>
<th>L</th>
<th>Method$^a$</th>
<th>Isolated yield ($194:198$)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>0</td>
<td>2:1</td>
<td>N/A</td>
<td>B (170°C)</td>
<td>0%$^c$</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>0</td>
<td>2:1</td>
<td>OAc</td>
<td>A (25°C)</td>
<td>55% (3:1)</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>1</td>
<td>2:1</td>
<td>OAc</td>
<td>A (25°C)</td>
<td>44% (2:1)</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>2</td>
<td>2:1</td>
<td>(S)-DOSP</td>
<td>A (25°C)</td>
<td>66% (4:1) (racemic)</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>3</td>
<td>2:1</td>
<td>OAc</td>
<td>A (25°C)</td>
<td>86% (5:1)</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>3</td>
<td>2:1</td>
<td>(R)-MEPY</td>
<td>A (25°C)</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>3</td>
<td>2:1</td>
<td>(S)-DOSP</td>
<td>A (0°C)</td>
<td>74% (racemic)</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>0</td>
<td>2:1</td>
<td>OAc</td>
<td>A (0°C)</td>
<td>99% (3:1)</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>1</td>
<td>2:1</td>
<td>OAc</td>
<td>A (0°C)</td>
<td>91% (4:1)</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>2</td>
<td>2:1</td>
<td>OAc</td>
<td>A (0°C)</td>
<td>70% (&gt;99:1)</td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>3</td>
<td>2:1</td>
<td>OAc</td>
<td>A (0°C)</td>
<td>86% (8:1)</td>
</tr>
<tr>
<td>12</td>
<td>Me</td>
<td>3</td>
<td>2:1</td>
<td>OAc</td>
<td>B (170°C)</td>
<td>31% (3:2)</td>
</tr>
<tr>
<td>13</td>
<td>Et</td>
<td>2</td>
<td>2:1</td>
<td>OAc</td>
<td>B (170°C)</td>
<td>42% (1:1)</td>
</tr>
</tbody>
</table>

$^a$Reactions using microwave irradiation were run for 10 min. at 170°C in DCE solvent unless noted otherwise. $^b$Yields determined following purification and are not corrected for recovered starting material unless otherwise noted. $^c$Quantitative isolation of 3H-pyrazole.
steric factors of the carbenoid formed. I also considered that decreased yields might also result with the use chiral catalysts and racemic alcohol, due to the possibility that only one antipode of the racemic alcohol mixture could react with the chiral rhodium carbenoid. I noticed no significant decrease in yield with the use of Rh₂(S-DOSP)₄, indicating that the catalyst was not discriminating one antipode from another, which would also indicate that this catalyst may not induce chirality in this transformation (Table 3.1, entries 4 and 7).

The O-H insertion reaction results for diazoester substrate 184 (Table 3.2) were comparable to those of the vinyl diazo substrate 180. α-diazo-β-ketoester 184 required elevated reaction temperatures and in contrast to the vinyl diazoester an excess of alcohol was used to ensure substrate availability. Method B, microwave irradiation, provided excellent yields of insertion product and this method was chosen as the optimum route for diazo-decomposition of further α-diazo-β-ketoesters. This substrate (184) permitted the screening of a variety of dirhodium carboxamide catalysts (cf. Figure 1.7 and Figure 1.10). Alcohol substrate 5-hexen-1-ol provided the best yields of α-alkoxyester in reactions with the vinyl diazo compounds and thus was studied with substrate 184.

The dirhodium carboxylate catalysts (Table 3.2, entries 2, 6-8) out performed the carboxamidate catalysts (Table 3.2, entries 5, 9-13) once again in this reaction, with Rh₂(OAc)₄ being the catalyst of choice. In the instances where an asymmetric catalyst was used, there was little or no evidence of significant chiral induction (Table 3.2, entries 5, 6, and 13). This result is in accordance with previous findings reported in the literature for O-H insertion reactions utilizing dirhodium catalysts (vide supra).
Table 3.2. α-diazo-β-ketoester O-H insertion reaction optimization/screening.

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>N$_2$:ROH</th>
<th>L</th>
<th>Method$^a$</th>
<th>Isolated yield of 197$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>1:2.5</td>
<td>OAc</td>
<td>A (83°C)</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1:2.5</td>
<td>OAc</td>
<td>B (170°C)</td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>1:5</td>
<td>OAc</td>
<td>A (83°C)</td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>1:5</td>
<td>OAc</td>
<td>B (170°C)</td>
<td>83%</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>1:2.5</td>
<td>(R)-MEPY</td>
<td>B (170°C)</td>
<td>32% (racemic)</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>1:2.5</td>
<td>(S)-DOSP</td>
<td>B (170°C)</td>
<td>65% (racemic)</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>1:2.5</td>
<td>pfb</td>
<td>B (170°C)</td>
<td>27% (58%)$^c$</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>1:2.5</td>
<td>TPA</td>
<td>B (170°C)</td>
<td>46%</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>1:2.5</td>
<td>tfacam</td>
<td>B (170°C)</td>
<td>38%</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>1:2.5</td>
<td>acam</td>
<td>B (170°C)</td>
<td>40%</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>1:2.5</td>
<td>cap</td>
<td>B (170°C)</td>
<td>29%</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
<td>1:2.5</td>
<td>S-MPPIM</td>
<td>B (170°C)</td>
<td>0%</td>
</tr>
<tr>
<td>13</td>
<td>3</td>
<td>1:2.5</td>
<td>4S-MEOX</td>
<td>B (170°C)</td>
<td>13% (6%ee)</td>
</tr>
</tbody>
</table>

$^a$Reactions using microwave irradiation were run for 10 min. at 170°C in DCE solvent unless noted otherwise. $^b$Yields determined following purification and are not corrected for recovered starting material unless otherwise noted. $^c$Recovered starting material.

The isolated α-alkoxyester (197) did exhibit some keto-enol tautomerization, evidenced through proton NMR experiments. This phenomenon was thought to be insignificant, but may aid in facilitating a reduction/dehydration step in preparing the unsaturated α-alkoxyβ-ketoester (199, Scheme 3.2). However, conducting this reaction
after diazo-decomposition would allow for formation of the more highly substituted olefin 200.

![Scheme 3.2. Potential reduction/dehydration of α-alkoxyβ-ketoesters.](image)

**Diversification of the Diazoester Substrate**

The diazoester compounds studied to this point had provided very promising results in the O-H insertion reaction. However, with the understanding that alternative substrates may be necessary in applying the tandem process to a practical problem, I sought to diversify my arsenal of diazoesters. Potential problems with the vinyl diazo substrates may arise in attempts at ring-closure, due to steric issues associated with non-terminal olefins, and diazoester 184 requires a number of steps to install an alkene moiety. Therefore, I considered the preparation and use of compounds 196 and 187 to serve as analogues of 180 and 184, respectively.

An alternative set of natural products possessing unsaturated cyclic ether core structures were also considered for application of the proposed O-H insertion/RCM methodology (201/204, Scheme 3.3). Accessing core structures 201 could be accomplished through the use of diazoester substrates of type 187 and 196 (Scheme 3.3, Eq. 1), whereas core structure 204 would require the use of either 180 or 196 (Scheme 3.3, Eq. 2). If the chosen target were to contain a carbonyl moiety at C3 (201), then
derivatives of 187 would be optimal diazo substrates. On the other hand, if C3 (201) is a methylene, the use of 187 would require a deoxygenation step, therefore diazo substrate 196 would be preferred. Ultimately the use of 196 (m = 1, 2, 3…) and 203 (n = 0, 1, 2, 3…) would permit variation in ring size and alternative positioning of the double bond in the ensuing RCM reaction.

My initial efforts in the preparation of α-diazo-β-ketoesters 187a-b involved the condensation of ethyl diazoacetate (EDA) with unsaturated aldehydes in an aldol reaction. Excellent yields have been reported for both the butyllithium and DBU promoted reactions\textsuperscript{447,448} of EDA and saturated aldehydes. However, the reaction was unsuccessful (Scheme 3.4) with unsaturated aldehyde substrates, providing 0-5% yield of α-diazo-β-hydroxyester (206a-b). The low yields of 187a-b were assumed to be a result
of base induced elimination. Attempting to purify these compounds or directly oxidize the crude material resulted in complex mixtures.

Scheme 3.4. BuLi/DBU-promoted aldol reaction of EDA with unsaturated aldehydes.

Although the DBU and BuLi promoted EDA-aldol reaction was unsuccessful, it is known that ethyl acetate participates in simple aldol reactions with unsaturated esters using lithium diisopropylamide (LDA) as base. Preparation of 187a-b was accomplished via aldol condensation of EtOAc with either crotonaldehyde (R = Me) or trans-cinnamaldehyde (R = Ph). The resulting β-hydroxyester (206a-b) was oxidized to the β-ketoester which was diazotized via diazo-transfer reaction in good yield (Scheme 3.5).

Scheme 3.5. Preparation of α-diazo-β-ketoesters.
Attempted oxidation of the allylic alcohols 206a-b through the usual methods (Jones oxidation, PCC, PDC) resulted in poor yields and in some cases cleavage of the alkene, the latter was assumed to be due to the presence of air/water during distillation. Jones oxidation of the allylic alcohols resulted in low yields (<40%), whereas PCC and PDC did not provide any of the desired β-ketoester product. The use of freshly prepared manganese (IV) oxide, an efficient oxidant for allylic alcohols, has previously been used in the oxidation of similar compounds319 and provided excellent yields of 207a-b.

Initial attempts at the preparation of 196 from methyl pent-4-enoate (208a) failed with the use of the usual diazo-transfer protocol (Scheme 3.6, Eq. 1). Reactions with mercuric-EDA dimers (209b) or α-lithio-EDA with allylic bromides were also unsuccessful in providing the homovinyldiazoesters. The coupling of argento-EDA dimers (209b) and cinnamyl bromide did provide 196b, albeit in 26% yield, where reaction with allyl or prenyl bromide failed. All of these efforts were an attempt to expedite the preparation of diazo species. In the end, a benzoylation-debenzoylation/diazotransfer protocol450,451 was invoked which provided 196a and 196b in 19% and 56% overall yield, respectively, for the two step process (Scheme 3.7).

\[\text{Methyl pent-4-enoate was prepared from commercially available pent-4-enoic acid via DCC coupling reaction.}\]
Scheme 3.6. Unsuccessful preparation of homovinyldiazoesters.

Alternative chemical methods for the preparation of these compounds (196) were investigated, such as Wittig and Horner-Wadsworth-Emmons (HWE) olefination (Scheme 3.8). Wittig chemistry has been utilized by Davies for the preparation of vinyl diazoesters from 2-carboxylethyltriphenylphosphonium chloride and aryl aldehydes. It was assumed that a one carbon homologation of the phosphonium salt would increase the pKₐ of the substrate significantly; however, a variety of Wittig and HWE protocols were attempted.

Scheme 3.7. Benzoylation/diazo-transfer route to homovinyldiazoesters.
Horner-Wadsworth-Emmons chemistry was not successful due to the lack in acidity of adjacent hydrogen. The Wittig chemistry was successful to a degree, with isolation of the olefinic acid (212) in 5-33% yield. The subsequent esterification and diazotization reactions resulted in very poor yields for the 3-4 step process. This process may eventually be useful in preparing a diverse library of 5-arylpent-4-enoates once it is optimized for homovinyldiazo substrates; however the olefin terminus is lost during RCM so I focused on the benzoylation/diazo-transfer protocol for preparation of 196.

Scheme 3.8. Attempted Wittig reaction.

O-H Insertion Reaction Optimization/Screening Results for α-homovinyldiazo and α-diazo-β-keto-γ,δ-unsaturated esters

The homovinyldiazoesters (196) were initially studied under similar reaction conditions (Methods A and B) as the α-vinyldiazoesters (180). In addition to the previously described O-H insertion substrates (Table 3.1), secondary allylic alcohols were investigated bearing ester (213) and amide (214) functionalities (Figure 3.2). The
substrates 215-217 are derived from 213 and are more advanced in terms of their synthetic potential. Deprotection of the benzyl- or trityloxy groups would provide a hydroxy handle for a number of chemical transformations.

![Figure 3.2. Secondary allylic alcohol O-H insertion substrates.](image)

The results for the diazo-decomposition reactions of α-homovinyldiazoester (196) with various catalysts are summarized in Table 3.3. Each diazo-decomposition reaction was monitored by TLC until the diazoester was consumed or after 48 hours. In all cases the diazoester was consumed within 48 hours, with TLC analysis showing the development of a new compound with higher \( R_f \) value (with respect to starting materials) which was easily oxidized (KMnO₄ stain detection). The catalyst was removed from the crude reaction mixture, which was then analyzed by GC/MS and \(^1\)H-NMR experiments, purified by column chromatography and the data collected from the isolated entities was compared to that of the crude mixture.

The initial results obtained for the reaction of 196c with the primary olefinic alcohols showed that method B might be the best route for obtaining adducts 205 (entries 2 and 6, Table 3.3). However, the secondary substrate (213) provided insertion product (205) using Method A (entries 9 and 11), albeit in poor yield. Method B did not prove to be beneficial with this diazoester and secondary alcohols.
Table 3.3. Homovinyldiazoester O-H insertion results.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R/Substrate</th>
<th>n</th>
<th>N$_2$:ROH</th>
<th>ML$_n$</th>
<th>Method</th>
<th>Yield $205a$ $(a:b:c:d)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>0</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (25°C)</td>
<td>0% (0:30:0:0)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>0</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>B (170°C)</td>
<td>28% (1:2:0:0)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (25°C)</td>
<td>0% (0:30:0:0)</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>B (170°C)</td>
<td>0% (0:50:0:0)</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>2</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (25°C)</td>
<td>0% (0:30:0:0)</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>2</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>B (170°C)</td>
<td>11% (1:2:0:0)</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>3</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (25°C)</td>
<td>0% (0:30:0:0)</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>3</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>B (170°C)</td>
<td>0% (0:60:0:0)</td>
</tr>
<tr>
<td>9</td>
<td>$^{213}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (25°C)</td>
<td>11% (1:3:0:0)</td>
</tr>
<tr>
<td>10</td>
<td>$^{213}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>B (170°C)</td>
<td>0% (0:60:0:0)</td>
</tr>
<tr>
<td>11</td>
<td>$^{213}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (0°C)</td>
<td>11% (1:4:0:0)</td>
</tr>
<tr>
<td>12</td>
<td>$^{214a}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (25°C)</td>
<td>0% (0:30:0:0)</td>
</tr>
<tr>
<td>13</td>
<td>$^{214a}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (0°C)</td>
<td>5% (1:6:0:0)</td>
</tr>
<tr>
<td>14</td>
<td>$^{213}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(TPA)$_4$</td>
<td>A (83°C)</td>
<td>0% (0:2:0:8)</td>
</tr>
<tr>
<td>15</td>
<td>$^{213}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(S-DOSP)$_4$</td>
<td>A (0°C)</td>
<td>0% (0:60:0:0)</td>
</tr>
<tr>
<td>16</td>
<td>$^{217b}$</td>
<td>1</td>
<td>1:5</td>
<td>Cu(acac)$_2$</td>
<td>A (110°C)</td>
<td>0% (0:2:0:8)</td>
</tr>
<tr>
<td>17</td>
<td>$^{213}$</td>
<td>1</td>
<td>1:5</td>
<td>Cu(hfacac)$_2$</td>
<td>A (25°C)</td>
<td>0% (0:40:0:0)</td>
</tr>
<tr>
<td>18</td>
<td>$^{213}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(5$R$-MPPIM)$_4$</td>
<td>A (25°C)</td>
<td>intractable</td>
</tr>
<tr>
<td>19</td>
<td>$^{217a}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(tfacam)$_4$</td>
<td>B (170°C)</td>
<td>0% (0:60:0:0)</td>
</tr>
<tr>
<td>20</td>
<td>$^{213}$</td>
<td>1</td>
<td>1:5</td>
<td>Rh$_2$(tfacam)$_4$</td>
<td>A (25°C)</td>
<td>0% (0:40:0:0)</td>
</tr>
</tbody>
</table>
A major competing reaction of $\alpha$-alkyl-$\alpha$-diazoesters is $\beta$-hydride elimination to form dienes. Cyclopropanation of alkenes and dimerization of the diazoester can also be deleterious to the availability and production of rhodium carbenoid. The use of Rh$_2$(TPA)$_4$ (entry 14, Table 3.3) was to be beneficial in two ways; 1) it is a bulky ligand, which tends to suppress $\beta$-hydride elimination and 2) it is an electron donating ligand, which suppresses cyclopropanation in C-H insertion/cyclopropanation reactions. I did not expect rhodium(II) acetate to be the only catalyst to give product and was dismayed to find that none of the catalysts screened gave any discernable O-H insertion product. Although the data presented in Table 3.3 is only a small portion of the results obtained, it is representative of all substrates and catalysts that have been previously mentioned. In summary, the homovinyl diazoester was determined to be an unlikely candidate for practical synthetic purposes at this time, pending further catalyst screening.

Studies involving the diazo-decomposition of $\alpha$-diazo-$\beta$-keto-$\gamma,\delta$-unsaturated esters (187) were much more promising O-H insertion reactions. The data obtained form diazo-decomposition of this substrate is presented in Table 3.4. Again, method B was determined to be the most efficient with this type of substrate in the presence of excess olefinic alcohol substrate and rhodium(II) carboxylates bearing electron-withdrawing ligands (Table 3.4, entries 1, 5, and 6). Reactions at room temperature with this type of substrate were previously determined inefficient and thus the diazo-decomposition reaction was conducted at reflux temperature when method A was used.
\[
\begin{align*}
\text{EtO} & \quad \text{N}_2 \\
\text{O} & \quad \text{HO} \quad \text{R}_2 \quad \text{n} \\
\text{Rh}_2\text{L}_4 & \quad \text{EtO} \\
\text{O} & \quad \text{O} \quad \text{O} \quad \text{O} \\
\end{align*}
\]

\[187 \quad \rightarrow \quad 202\]

Table 3.4. O-H insertion reactions with $\alpha$-diazo-$\beta$-keto-$\gamma,\delta$-unsaturated esters.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>n</th>
<th>N$_2$:ROH</th>
<th>ML$_n$</th>
<th>Method$^a$</th>
<th>Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>213</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>B (170°C)</td>
<td>59%</td>
</tr>
<tr>
<td>2</td>
<td>213</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>A (83°C)</td>
<td>48%</td>
</tr>
<tr>
<td>3</td>
<td>213</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(tfacam)$_4$</td>
<td>A (25°C)</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>213</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>A (25°C)</td>
<td>55%</td>
</tr>
<tr>
<td>5</td>
<td>217b</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>B (170°C)</td>
<td>84%</td>
</tr>
<tr>
<td>6</td>
<td>217b</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(pfb)$_4$</td>
<td>B (170°C)</td>
<td>78%</td>
</tr>
<tr>
<td>7</td>
<td>217b</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(5R-MEPy)$_4$</td>
<td>B (170°C)</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>217b</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(S-DOSP)$_4$</td>
<td>B (170°C)</td>
<td>42%c</td>
</tr>
<tr>
<td>9</td>
<td>217b</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(TPA)$_4$</td>
<td>B (170°C)</td>
<td>39%</td>
</tr>
<tr>
<td>10</td>
<td>217b</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(tfacam)$_4$</td>
<td>B (170°C)</td>
<td>39%</td>
</tr>
<tr>
<td>11</td>
<td>216</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(OAc)$_4$</td>
<td>B (170°C)</td>
<td>78%</td>
</tr>
<tr>
<td>12</td>
<td>215</td>
<td>1</td>
<td>1:2.5</td>
<td>Rh$_2$(tfacam)$_4$</td>
<td>A(83°C)</td>
<td>18%</td>
</tr>
</tbody>
</table>

$^a$Reactions using microwave irradiation were run for 10 min. at 170°C in DCE solvent unless noted otherwise. $^b$Yields were determined following purification and are not corrected for recovered starting material unless otherwise noted. $^c$The isolated product was a racemate.

Initially, the decomposition of 187 was conducted in the presence of substrate 213 (Table 3.4, entries 1-4), where the yield of 202 was only moderate. This was determined to be the result of oxonium ylide formation/RAR, which was confirmed qualitatively through GC/MS experiments. The use of substrate 217 replaced the electron rich carbonyl with an ether function, which was intended to minimize the formation of oxonium ylide. This was the case and the yield of insertion product 202 was increased
The use of carboxamidate catalysts was not beneficial (Table 3.4, entries 5-6), nor was the use of rhodium(II) carboxylates bearing electron-donating ligands (Table 3.4, entry 9). The strongly electron-withdrawing ligands did not outperform Rh$_2$(OAc)$_4$ in reactions of 187 with any of the substrates 213-217 (Table 3.4, entries 4 and 6). Diazodecomposition with the Weinreb amide 214 provided similar results to those obtained with 213. The use of copper(II) catalysts did not provide the desired O-H insertion product.

Utilization of substrate 215 would provide access 8-membered-multifunctional heterocycles upon completion of a pending RCM reaction. Decomposition of 187 in the presence of Rh$_2$(OAc)$_4$ and 215 provided the insertion adduct in 18% yield as a mixture of diastereomers. The lower yields for reactions of diazoester 187 are partially a consequence of the keto-enol tautomerization, which complicated purification.

Early reactions of 187 with allylic alcohol substrates (namely allyl alcohol) provided products resulting from oxonium ylide. A [2,3]-rearrangement of the ylide resulted in the formation of $\alpha$-allyl-$\alpha$-hydroxy compounds (40-70% yield with the use of Rh$_2$(tfacam)$_4$ (Scheme 3.9). This result was quite notable with the use of rhodium(II) carboxamidates, but minimized or obviated with the use of rhodium(II) carboxylate catalysts.

Scheme 3.9. [2,3]-rearrangement of oxonium ylide adduct.
Intermolecular Tandem O-H Insertion/Ring-closing Metathesis: Sequential & One-Pot Reactions

Having an optimized procedure for O-H insertion in hand for both the α-vinyl diazo and α-diazo-β-ketoesters, I sought to determine the optimum reaction conditions for a subsequent and/or one-pot RCM reaction for the O-H insertion adducts. The RCM reaction optimization was conducted using three different methods under conventional thermal conditions (refluxing solvent) or via microwave (MW) irradiation. Methods A, B, and C are step-wise procedures that involve first an O-H insertion reaction, followed by removal of Rh₂(OAc)₄, and then introduction of the RCM catalyst. Method E is the same as methods A-C, with the exception that the Rh₂(OAc)₄ is not removed from the reaction prior to the addition of metathesis catalyst. Methods D and F are one-pot protocols where diazoester is added to a solution of olefinic alcohol substrate, Rh₂(OAc)₄, and metathesis catalyst.² The catalysts utilized in the optimization of the RCM reaction are shown in Figure 3.3.

² Details for each method are described in the experimental section.
The RCM reactions were originally conducted using the O-H insertion adducts derived from olefinic primary alcohol substrates \((R = H, n = 0-3, \text{Eq. 8})\). The results for the intermolecular stepwise tandem reactions of \(\alpha\)-vinylidiazooesters are presented in Table 3.5. Along with the potential issues normally associated with RCM reactions (cross-metathesis, polymerization, catalyst inhibition, etc…vide supra) is that of the isomerization of the \(\gamma,\delta\)-alkene. Migration of the olefin has been detected with insertion products (Table 3.1, 198), and as a consequence of heating in the RCM reaction it was assumed that the prevalence of 198 could become more pronounced. The uncertainty was whether this compound would actually undergo ring closure due to the increased steric demand. Alternatively, upon ring-closure of 194 the olefin would still be prone to isomerization, however this was not found to occur.
Table 3.5. RCM reactions with O-H insertion adducts 194.

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>RCM catalyst(^a)</th>
<th>Method(^b)</th>
<th>Yield (204:218)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>138d</td>
<td>A (40°C, 1 h)</td>
<td>53.5% (19:1)(^d)</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>138a</td>
<td>A (40°C, 1.5 h)</td>
<td>21% (20:1)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>138d</td>
<td>A (40°C, 4 h)</td>
<td>21% (3:2)</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>138a</td>
<td>A (40°C, 5 h)</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>138d</td>
<td>A (40°C, 45 min)</td>
<td>70% (99:1)</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>138a or d or 139a or b</td>
<td>A, B, C, D, E, or F</td>
<td>0%(^e,f)</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>139b</td>
<td>C (140°C, 5 min)</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>139a</td>
<td>A (40°C, 3 h)</td>
<td>14% (^f)</td>
</tr>
<tr>
<td>9</td>
<td>0</td>
<td>139b</td>
<td>A (40°C, 4 h)</td>
<td>49% (4:1)(^d)</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>138a</td>
<td>A (40°C, 1 h)</td>
<td>10% (^f)</td>
</tr>
</tbody>
</table>

\(^a\)10 mol% of catalyst. \(^b\)Method details are in the experimental section. \(^c\)Determined by GC analysis. \(^d\)Starting material \(\alpha,\beta\)-unsaturated compound isolated in addition to isomerized RCM adduct. \(^e\)The RCM product was detected by GC/MS analysis with the use of both 138d and 139b, but could not be isolated in either case. \(^f\)Ratio of 204:218 was not determined.

Method A, the stepwise process, where diene is added to a solution of metathesis catalyst in refluxing DCM provided the best results for RCM of the O-H insertion adducts 194 (Table 3.5). The 2\(^{nd}\) generation catalysts 138d and 139b performed better than the first generation catalysts, in particular with closing the 6-7 member rings (Table 3.5 entries 4 and 5). The use of method B did not provide any detectable desired RCM products, however isomerized compound 218 was detectable by GC/MS for all substrates, but was not isolated. This was most likely a result of heating the diene prior
to addition of the catalyst, allowing for the double bond migration to occur. The reactions using method B, however were permitted to reflux for the entire 48 hours due to continued presence of starting material. Evidence for ring-closure of the trisubstituted substrate 198 was found in GC/MS analysis of the crude mixture. A compound corresponding to the desired molecular weight, less one methylene unit, along with allylbenzene (Scheme 3.10) were prevalent in a majority of the RCM reactions, and particularly those subjected to method B.

Scheme 3.10. RCM reaction of trisubstituted olefin.

The one-pot reactions (methods D, E, and F) with insertion adducts 194 were carried out with the use of excess diazoester (2:1, with respect to olefinic substrate) and Rh₂(OAc)₄ as diazo-decomposition catalyst. In all instances of one-pot reactions, no RCM product was detected. Consideration of method E, the addition of metathesis catalyst to completed O-H insertion reaction pot, should still be considered as a viable route. Reactions using this protocol were only irradiated for short periods of time and with only 10 mol% catalyst. If the metathesis catalysts were permitted longer reaction
time and/or a larger amount of catalyst was employed (for example, three separate additions of 10 mol%) the outcome may be different.

Having successfully completed the tandem process with the vinyl diazoester adducts (194 → 204), I then examined the transformation of α-alkoxy-β-ketoesters (202 → 201). It was understood that catalyst inhibition could occur due to the presence of several Lewis basic sites. Thus, an additive (Ti(OiPr)4)384 that had previously been shown to obviate catalyst inhibition in RCM reactions of α,β-unsaturated enones was utilized in a number of RCM attempts.

The tandem O-H insertion/RCM reactions of α-diazo-β-ketoesters were not as successful as those of the α-vinyldiazoesters. The representative protocols described above and in the experimental section were invoked in a similar manner and the results are presented in Table 3.6. All four RCM catalysts were examined again, with stronger emphasis placed on the second generation set of catalysts, based on past performance. The compounds resulting from insertion of 187a/b and 217a/b were also preferred substrates, due to their synthetic advances. RCM products of these insertion adducts would require less steps to a potential target than insertion adducts obtained from the use of α-hydroxyester 213 and Weinreb amide 214.

Unfortunately, the substituted substrates 202 proved to be very resistant to ring-closure. Under no circumstances did this substrate provide any ring-closed material. Use of the Lewis acid Ti(OiPr)4, had no effect on the outcome either (Table 3.6, entries 1, 2, 4, 7, 9, and 10). Problems were assumed to be due to either catalyst inhibition from Lewis basic sites or the issue of electron deficient olefins (α,β-unsaturated esters). In an attempt to rule out any negative impact of the pendant R2 group I returned to an
unsubstituted insertion adduct. Interestingly, ring-closure did occur with an unsubstituted olefinic ether tether (Table 3.6, entries 11 and 12), with the use of either 2\textsuperscript{nd} generation catalysts (138d and 139b) and without the use of an additive. However, purification of these compounds was unsuccessful in the absence of any workup protocol, most likely due to residual ruthenium.

\[
\begin{align*}
\text{EtO} & \quad \text{O} \\
\text{O} & \quad \text{R}_2 \\
\text{EtO}_2\text{C} & \quad \text{EtO} \\
\text{O} & \quad \text{R}_1 \\
\text{n} & \quad \text{n} \\
\end{align*}
\]

(9)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{EtO} \\
\text{O} & \quad \text{R}_2 \\
\text{O} & \quad \text{R}_1 \\
\text{n} & \quad \text{n} \\
\end{align*}
\]

Table 3.6. RCM reactions with O-H insertion adduct 202.

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>Additive\textsuperscript{a}</th>
<th>RCM catalyst\textsuperscript{b}</th>
<th>Method\textsuperscript{c}</th>
<th>Yield\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Ph</td>
<td>CH\textsubscript{2}OTr</td>
<td>Ti(O\textsubscript{i}Pr\textsubscript{4})</td>
<td>138d</td>
<td>A (83°C, 48 h)</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Ph</td>
<td>CH\textsubscript{2}OTr</td>
<td>Ti(O\textsubscript{i}Pr\textsubscript{4})</td>
<td>139b</td>
<td>A (110°C, 4 h)</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Ph</td>
<td>CH\textsubscript{2}OTr</td>
<td>None</td>
<td>138d</td>
<td>C (170°C, 15 min)</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Ph</td>
<td>CH\textsubscript{2}OTr</td>
<td>Ti(O\textsubscript{i}Pr\textsubscript{4}),</td>
<td>139b</td>
<td>E</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Ph</td>
<td>CH\textsubscript{2}OBn</td>
<td>None</td>
<td>138d</td>
<td>D</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Ph</td>
<td>CH\textsubscript{2}OBn</td>
<td>None</td>
<td>139b</td>
<td>C (170°C, 5 min)</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>Ph</td>
<td>CH\textsubscript{2}OBn</td>
<td>Ti(O\textsubscript{i}Pr\textsubscript{4}),</td>
<td>138d</td>
<td>C (130°C, 15 min)</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>Ph</td>
<td>CH\textsubscript{2}OBn</td>
<td>None</td>
<td>139b</td>
<td>C</td>
<td>0%</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>Me</td>
<td>CH\textsubscript{2}OTr</td>
<td>Ti(O\textsubscript{i}Pr\textsubscript{4}),</td>
<td>139b\textsuperscript{e}</td>
<td>A (83°C, 48 h)</td>
<td>0%</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>Me</td>
<td>CH\textsubscript{2}OBn</td>
<td>Ti(O\textsubscript{i}Pr\textsubscript{4}),</td>
<td>139b\textsuperscript{e}</td>
<td>C</td>
<td>0%</td>
</tr>
<tr>
<td>11</td>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>none</td>
<td>139b</td>
<td>C</td>
<td>51.2%\textsuperscript{f,g}</td>
</tr>
<tr>
<td>12</td>
<td>0</td>
<td>Me</td>
<td>H</td>
<td>none</td>
<td>138d</td>
<td>E</td>
<td>20%\textsuperscript{f,g}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}30 mol\% of additive. \textsuperscript{b}10 mol\% of catalyst. \textsuperscript{c}Method details are in the experimental section. \textsuperscript{d}Determined by GC/MS analysis. \textsuperscript{e}30 mol\% of catalyst. \textsuperscript{f}Inseparable mixture. \textsuperscript{g}Crude mixture was quickly filtered through silica gel, without special catalyst removal workup.
These results did provide some insight into the reaction and further attempts to overcome the problems associated with the RCM of $\alpha,\beta$-unsaturated enones were to be worked out in a pending formal total synthesis (*vide infra*). At this time I had chosen to apply the tandem methodology to a formal total synthesis of (+/-)-rogioloxepane and (+/-)-isolaurepinnacin and ideally would have already optimized the RCM procedure, however, time constraints did not permit this. My synthetic efforts to overcome the problems associated with the desired substrates 202 are discussed in Chapter 4.

There were only two O-H insertion adducts isolated resulting from the diazo-decomposition of 196c. The RCM reaction of 205a in the presence of Grubbs’ 2nd generation catalyst (138d) resulted in an 55% yield of qualitatively pure material (220) (Scheme 3.11). Further purification resulted in dramatic loss of material. The ease of this reaction in comparison to other RCM results is due to the unhindered nature of the olefins.

![Scheme 3.11. RCM reaction of homovinyl diazo adducts (205a)](image)

Conclusions: Tandem O-H Insertion/RCM Screening

Difficulties in the tandem process appear to be substrate specific. Diazodecomposition/O-H insertion reactions of both $\alpha$-vinyl diazo (180) and $\alpha$-diazo-$\beta$-ketoesters (187) provide moderate to good yields of insertion adducts, whereas the homovinyl diazo substrate (196) suffer from more energetically favorable side reactions.
The vinyl- and homovinyl substrates were both found to ring close to unsaturated cyclic ethers in moderate yields with both 2nd generation Grubbs’ and Hoveyda-Grubbs catalysts. A tandem process with the vinyldiazoester is practicable, but at this time a one-pot procedure is not as efficient as a stepwise approach. A tandem process for diazoesters 187 and 196 will require further screening of both catalysts and conditions for the RCM and O-H insertion reactions, respectively. Unfortunately, these are the preferred substrates for the synthesis of rogioloxepane and isolaurepinnacin.

One-pot reactions conducted under conventional thermal diazo-decomposition conditions (oil bath heat source) appear to suffer at the metathesis stage. This may be due to decomposition of the catalyst on prolonged heating or arising from complications associated with the presence of the Rh(II) catalyst. The latter is less likely in light of the findings of Hodgson,455-457 who has reported a similar tandem one-pot cross-metathesis/oxonium ylide cyclization process.

Spectroscopic and chromatographic analysis of the crude tandem one-pot reactions shows greater than 90% conversion of the α-diazo-β-ketoesters (187) to the desired insertion product. The metathesis reaction however is ineffective in the presence of the rhodium(II) catalysts. In general, the desired substrates (202, R2 = CH2OTr, CH2OBn) appear to be non-functional in the RCM reaction at this stage, whereas unsubstituted substrates function moderately well (Table 3.6, entries 11 and 12). Further attempts at manipulating these substrates (202) as a means to completing the tandem process are detailed below.
The use of chiral catalyst \( \text{Rh}_2((S/R)\text{-DOSP})_4 \) developed by Davies\(^{458} \) resulted in relatively good yields of insertion product, however it appeared that no chiral induction occurred. Analysis through both chiral GC/MS and HPLC showed no more than 6% ee for this or any of the chiral catalyst used including Doyle’s chiral \( \text{Rh}_2(R/S\text{-MEPY})_4 \),\(^{459} \) \( \text{Rh}_2(R/S\text{-MEOX})_4 \),\(^{459} \) and \( \text{Rh}_2(R/S\text{-MPPIM})_4 \)^{110} catalysts. The Doyle catalysts were not effective in the O-H insertion reaction at all (Table 3.1, entry 6; Table 3.2, entries 5, 12, and 13, for example). It is assumed at this point that any asymmetric synthesis through O-H insertion would have to be conducted with the use of Fu’s catalyst system (\textit{vide supra}), due to the lack of chiral induction with the use of rhodium based chiral catalysts. Alternatively, there is precedence for the use of chiral auxiliaries in diazo-decomposition reactions, for example, Doyle has achieved good diastereocntrol with the use of \( \text{Rh}_2(R/S\text{-MEAZ})_4 \)^{308} in combination with a pantolactone chiral auxiliary in O-H insertion reactions.
CHAPTER 4: APPROACHES TO (+/-)-ROGIOLOXEPANE AND (+/-)-ISOLAUREPINNACIN

Introduction

The genus Laurencia one of many genera of red algae of the family Bonnemaisoniaceae provides a number of metabolites which are known to have antimicrobial and insecticidal properties.\textsuperscript{460-462,463-466} Two of these metabolites are rogioloxepane\textsuperscript{467-469} and isolaurepinnacin,\textsuperscript{470-472} which are the metabolites of Laurencia microladia and Laurencia pinnata, respectively.

There are few known examples of C\textsubscript{15} oxepenes in nature, included in this small population are (+)-rogioloxepane (221, Figure 4.1) and (-)-isolaurepinnacin (235, Figure 4.2) with the rogiolenynes being the more abundant. Other O-heterocyclic compounds, 5-, 6-, and 8-membered, are quite abundant and there are known examples of 9- and 12-membered along with a number of combinations of these in nature as well.\textsuperscript{467}

Both (+)-isolaurepinnacin and (+)-rogioloxepane have been previously synthesized and are quite innovative in their own right. One of the rogioloxepane syntheses utilized an RCM reaction in a similar fashion to that which I have proposed. The interesting aspects of my synthetic sequence lie in the simple starting materials and the ease with which a racemic synthesis can become chiral by changing the method of preparation of the starting material and then implementing the use of a chiral catalyst, such as Fu’s bisazaferrocene. Time constraints did not permit the pursuit of the chiral synthesis. The chiral synthons would be very similar to the 1,5-hexadien-3-ol that Crimmins utilized.\textsuperscript{469}
Synthetic Approaches: (+)-Rogioloxepane A

There are only a few examples of the total synthesis of rogioloxepane and of those some were achieved enantioselectively with the synthesis of (+)-rogioloxepane A (Figure 4.1).

Figure 4.1. Structure of (+)-rogioloxepane A.

The first total synthesis of (+)-rogioloxepane A, reported in 2001 by Matsumura et al., utilized an interesting \((\text{Bu}_3\text{Sn})_2\text{O}/\text{Zn(OTf)}_2\) promoted stereoselective cyclization of hydroxy-epoxide \((222)\) to form the \(\alpha,\omega\)-trans-disubstituted oxepene skeleton \((223)\) in 75% yield (Scheme 4.1).

Scheme 4.1. Matsumura’s oxepene formation.

This procedure demonstrated an efficient and highly stereoselective methodology for the preparation of highly functionalized medium sized oxygen heterocycles. The unsaturated epoxy alcohol was obtained in 15 steps and the target (+)-rogioloxepane A was realized following another 14 steps including a 4 step sequence employing a
modified Corey procedure to construct the *cis*-enyne moiety (Scheme 4.2, 225) in 56% yield.

Interestingly the olefination reaction was complete in one minute without isomerization of the double bond in conjugation with the aldehyde and the use of HMPT in place of PPh₃ was vital to the success of the reaction. Deprotection of the acetyl group and treatment with *n*-BuLi provided the enyne moiety (225). The final contribution from this work was that the previously proposed configurations of 6*R* and 13*R* were confirmed.

Two years later Crimmins and co-workers reported an alternative enantioselective total synthesis of (+)-rogioloxepane A in 21 steps from 1,5-hexadien-3-ol. The key steps in their synthesis were an asymmetric glycolate alkylation and ring-closing metathesis. The glycolate alkylation was employed for installation of the relative and absolute stereochemistry at both C7 and C12, whereas the RCM reaction provided the oxepene core.

The key glycolyloxazolidinone (228, Scheme 4.3) was formed from 1,5-hexadien-3-ol by, first a Sharpless kinetic resolution in which the unsaturated epoxy alcohol (226) was obtained in 98%ee, followed by a protection of the hydroxyl group,
alkylation of the epoxide, protection of the resulting hydroxyl group and deprotection of the former. The glycolic acid (227) was then converted to the mixed pivaloyl anhydride, which was subsequently added to the chiral oxazolidinone providing the glycolyloxazolidinone (228) in 70% overall yield.

![Scheme 4.3. Crimmins preparation of the key glycolyloxazolidinone.](image)

The N-acyl-oxazolidinone (229) was then obtained, following the introduction of the allyl moiety at C7, in 86% yield (dr ≥ 98:2). A ring-closing metathesis reaction was then attempted with the oxazolidinone in place, but attempts to reductively remove the chiral auxiliary were inefficient, providing both the desired oxepene and the saturated oxepane. It was assumed that trace amounts of ruthenium in the presence of hydrogen was facilitating the reduction of the double bond in the oxepene ring. Therefore, removal of the oxazolidinone followed by RCM provided the oxepene core (230, Scheme 4.4) in 96% yield.
The resulting ring-closed alcohol (230, Scheme 4.4) was subjected to Swern oxidation followed by an oxazolidinone-based asymmetric acetate aldol reaction which provided the alcohol (231) with inverted configuration. Following another sequence of protection, chiral auxiliary removal, and oxidation, the resulting aldehyde (232) was converted to the vinyl iodide (233) after exposure to the Stork ylide.

Sonogashira coupling furnished the final portion of the enyne moiety and following deprotection the free hydroxyl group at C6, the chloride (234) was obtained by reaction of the alcohol with CCl₄ and slow addition of trioctylphosphine to reduce the amount of the competing elimination reaction to form dienyne. The C13 bromide was introduced in
a similar fashion using Murai’s method after oxidative removal of the benzyl group with DDQ, thus providing (+)-rogioloxepane A (221).

**Synthetic Approaches: (+)-Isolaurepinnacin**

(+)-Isolaurepinnacin (235, Figure 4.2) was first isolated in 1981 by Fukuzawa and Masamune. They elucidated the structure and relative stereochemistry of the relevant carbon atoms (12S, 13S, 6R, 7R) by degradative reactions and mass spectral techniques and then by chemical correlation with Laurencin, a metabolite with crystallographically defined structure.462

![Figure 4.2. (+)-isolaurepinnacin.](image)

The first total synthesis of (+)-isolaurepinnacin (235) (as well as the first synthesis of a Laurencia acetogenin of the rare oxepane group) was completed by Berger and Overman in 12 synthetic steps and an overall yield of 15%. The key step in their synthesis was the Lewis acid promoted cyclization of the mixed acetal (236) to the oxepene (237, Scheme 4.5).
This particular reaction demonstrated the selective nature of acetal-alkene cyclization. The surprising integrity of the halide functionalities (no epimerization) shows potential for the use of other chiral α-halo-oxo-carbenium ions in the formation of other oxygen heterocyclic marine acetogenins.

The α-halo mixed acetal (236) was formed first by the Sharpless epoxidation of (Z)-2-penten-1-ol (238, Scheme 4.6) providing the epoxy alcohol (239) in 78% yield and 88% ee. This compound was then sulfonylated and the epoxide opened to give the bromohydrin in 94% yield, which in the presence of methyl lithium at -78°C provides the newly formed epoxide (240). Interestingly, this epoxide would not react cleanly with the desired organocuprates, but the allyltin reagent provided the desired (3S,4S)-vinylsilylbromohydrin (241) in relatively good yield at low temperature in the presence of ethylaluminumdichloride (EtAlCl₂).
Scheme 4.6. Preparation of (3S, 4S)-3-bromo-7-(trimethylsilyl)oct-7-ene-4-ol (421).

The (R)-α-chloroacetal (244) which constitutes the second half of the molecule necessary for the cyclization to occur was prepared through a series of oxidation/alkylation and oxidation/reduction steps in 39% yield over 5 steps. Conversion of the β-hydroxyl to the α-chloro compound was accomplished in 71% yield by reaction of the corresponding triflate with tetrabutylammonium chloride (TBAC) (240 → 241, Scheme 4.7).

Scheme 4.7. Preparation of (R)-α-Chloroacetal.
The mixed acetal (244) was first converted to a bromoether through reaction with bromodimethylborane (Me₂BBr), followed by reaction with (241) in the presence of AgOTf to provide the key intermediate mixed acetal (236, Scheme 4.8). The subsequent acetal-alkene cyclization (Scheme 4.5) occurred in the presence of BCl₃ in dichloromethane at -78°C in 90% yield, which was determined to proceed via the α-chloro ether intermediate (rather than the mixed acetal) which was isolable at short reaction times.

Finally the (E)-enyne portion of the molecule was introduced (Scheme 4.9) through first the mild Dess-Martin oxidation of the deprotected alcohol (237) and subsequent reaction with ethynylmagnesium bromide at -78°C to provide (245) in 74% yield. After investigation of a number of dehydration techniques, determined to be unselective, the authors found that stereoselective formation (>24:1) of the (E)-olefin was possible through the action of triflic anhydride on the hexacarbonyldicobalt complex of (245) in DCM at -78°C. The decomplexation of the hexacarbonyldicobalt from (+)-isolaurepinnacin (235) was accomplished with ceric ammonium nitrate.
The three major differences between the two oxepene molecules [(+)-rogioloxepane and (+)-isolaurepinnacin] are; 1) their relative configurations at the ring junctions and 2) the carbons bearing the halides, as well as 3) the cis vs. trans-enzyme moiety. (+)-Rogioloxepane has a trans-ring junction, where the two side chains are on opposite sides, whereas (+)-isolaurepinnacin has a cis-ring junction. With this in mind it was apparent that the racemic compounds are identical with the exception of the enyne moiety. This similarity in structure allows for a convergent synthesis of an oxepene core, which can then be elaborated to obtain the two different racemic compounds.

Synthetic Approaches: Tandem O-H Insertion/RCM Approach to (+/-)-Rogioloxepane and (+/-)-Isolaurepinnacin

The target molecules were chosen as part of an ongoing study directed at the development of strategies for the construction of medium-sized oxygen heterocycles. The core methodology was the construction of the oxepene core (246) through two key steps, both of which involve the use of transition metal catalysis. In the presence of a carefully chosen rhodium catalyst the diazo compounds (187a/b or 196) and olefinic
The olefinic alcohol and α-diazo substrates (vide supra) can be acquired in relatively few steps. The synthesis of the alcohols began with an ultrasound promoted Barbier-type reaction\textsuperscript{478} with allyl bromide and ethyl glyoxylate (Scheme 4.11, Eq. 1) to obtain Ethyl α-hydroxypent-4-enoate (213) in 45-66% yield. From this point two disparate routes were investigated in the preparation of insertion substrates 216 and 217. The first was the preparation of Weinreb amide (214a → 214b), which allows for easy
introduction of the ethyl portion (C14-C15 of both targets) of the side chain by Grignard reaction with ethylmagnesium bromide (Scheme 4.11, Eq. 2). Attempts to introduce the ethyl side chain without prior protection of the \( \alpha \)-hydroxy function resulted in low yield of 248 (28%), whereas the Grignard reaction with the TBS-protected \( \alpha \)-hydroxy Weinreb amide (214b) resulted in a quantitative yield of ketone (248).

\[
\text{CH}_3\text{Br} + \text{HCO}_2\text{H} \xrightarrow{\text{Sn}^0, 70\% \text{EtOH}, \text{sonication, 2 hr}} \text{CH}_3\text{CO}_2\text{H} \quad (1)
\]

Scheme 4.11. Preparation of 2-TBSyloxy-hept-6-en-3-one.

Reduction of the resulting ketone (248) with sodium borohydride or lithium aluminum hydride resulted in simultaneous desilylation and near quantitative yield of diol (Scheme 4.12). Attempts to selectively protect this substrate were unsuccessful, due to the lack of differentiation between the two secondary hydroxyl groups.

\[
\text{CH}_3\text{CO}_2\text{H} \xrightarrow{\text{Me(OOMe)NH-HCl, iPrMgBr, THF, -23°C}} \text{CH}_3\text{CO}_2\text{H} \quad (2)
\]

Alternatively, 215 is attainable by simply switching the protecting group of the Weinreb amide from tertbutyldimethylsilyl (TBS) to benzyl (Bn) (Scheme 4.13). The sequence 214a → 215 proceeds smoothly and in relatively high yield (> 65% over 3 steps). I had planned on a protection/deprotection strategy to obtain 216, but in light of the issues previously determined with substrates 217a/b (cf. Table 3.6) in the RCM reaction I chose to investigate 215 as a homologous substrate in the tandem process (Scheme 4.13). This congener could provide an 8-member ring on completion of the tandem process, however I was more interested in studying the relationship between the proximal placement of the protection group in relation to the hydroxyl group for O-H insertion as well as RCM reaction. It is known that proper placement of a bulky substituent can aid in the ring-closure of medium to large ring sizes.479

![Scheme 4.13. Preparation of 4-(benzyloxy)hept-6-en-3-ol.](image)

Insertion reactions with 215 were only attempted with the homovinyldiazoester 196, with the use of Rh₂(OAc)₄ using the previously successful conditions (Table 3.3, entry 11). The O-H insertion adduct was not obtained, with near quantitative conversion of the diazoester to diene. There was no evidence of cyclopropanation in this instance. I
did not have the opportunity to subject 215 to the tandem process with diazoesters 187 or 180.

In similar fashion to the preparation of 215, the analogous alcohols 217a/b were prepared starting from 213 (Scheme 4.14). The α-hydroxy ester 213 was reduced to the diol (251) with either lithium aluminum hydride (30-50% yield of diol) or sodium borohydride (68-75% yield of diol). Selective protection of the primary hydroxyl group of 251 as the trityl (triphenylmethyl) ether (217b) was accomplished in 70% chemical yield. The benzylether (217a) was also prepared, albeit in inferior yield (30-60%) due to less selectivity. Shorter reaction times for the latter were necessary to avoid protection of the secondary hydroxyl group. Preparation of the trityl ether proved to be quick, simple, and cheap, therefore this was the central insertion substrate utilized in what was thought to be the best route to a formal total synthesis.

\[
\begin{align*}
\text{OH} & \quad \overset{\text{LAH in Et}_2\text{O}}{\longrightarrow} \quad \text{LAH in Et}_2\text{O} \\
\text{O} & \quad \overset{\text{NaBH}_4 \text{ in (10:1) dioxane/95% EtOH}}{\longrightarrow} \quad \text{NaBH}_4 \text{ in (10:1) dioxane/95% EtOH} \\
\text{213} & \quad \overset{\text{Ph}_3\text{CCl, DMAP, NEt}_3, \text{rt > 12h}}{\longrightarrow} \quad \text{Ph}_3\text{CCl, DMAP, NEt}_3, \text{rt > 12h} \\
\text{OH} & \quad \overset{\text{217b}}{\longrightarrow} \quad \text{217b} \\
\text{O} & \quad \overset{\text{BnBr, Ag}_2\text{O, PhCH}_3, 0^\circ\text{C}}{\longrightarrow} \quad \text{BnBr, Ag}_2\text{O, PhCH}_3, 0^\circ\text{C} \\
\text{251} & \quad \overset{\text{217a}}{\longrightarrow} \quad \text{217a}
\end{align*}
\]


Diazo-decomposition/O-H insertion reactions utilizing α-diazo-β-ketoester 187a/b with the unsaturated mono-protected substrate (217b) provided yields of >70% of the desired insertion adduct (247, Scheme 4.15, Table 3.4, entries 5 and 6).
The best yields of insertion product (247) were obtained using microwave promoted (method B) reaction conditions (Table 3.4) however comparable yields (cf. Table 3.4, entry 1 vs. 2) were obtained with conventional (method A) reaction conditions. The methyl substituted olefin provided no advantage over the phenyl substituent in the insertion reaction and diazo compound 187c was not obtained in appreciable yield to be utilized.

One predominant side product (252 → 253) resulting from the diazo-decomposition of 187 in the presence of 217b was assumed (based on GC/MS and $^1$H-NMR analysis) to be derived from a formal ‘double-insertion’ reaction. This was possibly a result of decarboxylation of a hemiacetal intermediate (Scheme 4.16). Although interesting as a possible RCM candidate, this side product was not investigated further.
Attempts at the ring closure of 247 failed to provide isolable compound under a variety of conditions (Table 3.6, entries 1-10). The homovinylidiazosubstrate had also failed under a variety of conditions to undergo O-H insertion in preference to β-hydride elimination and cyclopropanation. Therefore, considering the high yield of the former and the resistance of the latter, the best path to take at the time seemed to be to devise a method to complete the RCM portion with substrate 247.

I had had some success in closing the oxepine-3-one structure with unsubstituted insertion adducts (Table 3.6, entries 11 and 12), and thus considered the removal of the trityl protection in favor of the smaller hydroxy group (Scheme 4.17, Eq. 1). Removal of the trityl protection proceeded smoothly, providing 254 in >80% yield.

\[
\text{TsOH, MeOH} \quad \begin{array}{c}
\text{DCM, 1 h} \\
\end{array}
\]

\[
\begin{array}{c}
\text{TrO} \quad \text{O} \quad \text{CO}_2\text{Et} \\
\text{R} \quad \text{O} \quad \text{CO}_2\text{Et}
\end{array}
\quad \begin{array}{c}
\text{HO} \quad \text{O} \quad \text{CO}_2\text{Et} \\
\text{R} \quad \text{O} \quad \text{CO}_2\text{Et}
\end{array}
\]

\[
\text{CeCl}_3/\text{NaBH}_4 \quad \begin{array}{c}
\text{MeOH} \\
\end{array}
\]

\[
\begin{array}{c}
\text{TrO} \quad \text{O} \quad \text{CO}_2\text{Et} \\
\text{R} \quad \text{O} \quad \text{CO}_2\text{Et}
\end{array}
\quad \begin{array}{c}
\text{HO} \quad \text{O} \quad \text{CO}_2\text{Et} \\
\text{R} \quad \text{O} \quad \text{CO}_2\text{Et}
\end{array}
\]

Scheme 4.17. Derivations of O-H insertion adduct 247

Alternatively, a second route at obtaining a viable RCM substrate was directed at the α,β-enone portion of 247. It was thought that this olefin may be too electron
deficient to participate in the RCM reaction, and if the ketone could be selectively reduced (1,2- vs. 1,4-reduction) a viable diene may be obtained. All attempts at the selective reduction failed using the usual protocol (Scheme 4.17, Eq. 2)

RCM reactions attempted with substrate 254 showed promise with detection of a potential ring-closed product in both GC/MS and $^1$H-NMR analyses of crude mixtures. There was evidence of a non-terminal olefin in the NMR spectrum of the crude material, along with the absence of terminal olefinic resonances, however, no product was isolated following a DMSO workup to remove the catalyst.

The final derivation of 247 was provided at the protection stage of the diol 251. An attempt at selective protection of the primary hydroxyl as the TBDMS ether proceeded in >64% yield (Scheme 4.18). Following the O-H insertion reaction (>60%, with 40% double insertion, cf. Scheme 4.16) 256 was subjected to various RCM reaction conditions.

The use 187b was utilized at this time as an added measure, based on the assumption that the phenyl ring may be causing further stereoelectronic inhibition, in conjunction with the $\alpha$,\$-unsaturated ketone moiety, of the RCM process. Using method A, and heating the reaction mixture in a sealed tube (Table 4.1, entry 1) a compound was
isolated which resembled 257 spectroscopically. A similar result was obtained on using Grubbs’ first generation catalyst (138a) under the usual conditions for method A (refluxing solvent). Compound 257 was isolated yet again, with the use of catalyst 138a. Finally, in the absence of additive, a mixture of a small amount of the desired compound along with starting material was isolated and confirmed by 1H-NMR analysis. In all of the final RCM reactions with analogues of 247, ring closure did occur, and after simply stirring the reaction open to air overnight, the ring-closed compounds (246 and 257) were sequestered.

![Diagram](image)

Table 4.1. RCM reactions with O-H insertion adduct 256

<table>
<thead>
<tr>
<th>Entry</th>
<th>RCM catalyst</th>
<th>Additive</th>
<th>Method (^b)</th>
<th>Yield (246/257)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>139b (2× 10 mol%)</td>
<td>3 eq. Ti(O(<em>{2}^{\text{Pr}}))(</em>{4})</td>
<td>G (55°C, 48 h, sealed tube)</td>
<td>&lt; 10% 257</td>
</tr>
<tr>
<td>2</td>
<td>138a (2× 10 mol%)</td>
<td>3 eq. Ti(O(<em>{2}^{\text{Pr}}))(</em>{4})</td>
<td>A (40°C, 48 h)</td>
<td>&lt; 10% 257</td>
</tr>
<tr>
<td>3</td>
<td>139b (10 mol%)</td>
<td>None</td>
<td>G (55°C, 48 h, sealed tube)</td>
<td>12% 246</td>
</tr>
<tr>
<td>4</td>
<td>138a (10 mol%)</td>
<td>TiCl(_{4})</td>
<td>G (55°C, 48 h, sealed tube)</td>
<td>&lt; 10% 257</td>
</tr>
<tr>
<td>5</td>
<td>138a (50 mol%)</td>
<td>TiCl(_{4})</td>
<td>A (40°C, 48 h)</td>
<td>20% 257</td>
</tr>
</tbody>
</table>

Decarboxylation of the product is assumed to be aided by the additive, which may contain small amounts of HCl.
Conclusions and Future Work

My retrosynthetic analysis shows the potential for not only a formal synthesis of the target compound, but also the possibility for preparation of a 2-oxo-analogue of rogioloxepane or isolaurepinnacin. The utility of the α-diazo-β-ketoesters are two-fold; 1) they could provide an alternate point of derivation for the construction of potentially potent analogues and more importantly, 2) this type of diazo compound is much more stable and chemoselective than the homovinyl diazo substrate and through the reaction mechanism of diazo-decomposition provides a later transition-state which is more conducive to insertion rather than diene formation. The latter is a drawback to the use of the homovinyldiazo substrate which, through the use of rhodium catalysts with moderate to strong electron-withdrawing groups, provides an early transition state in the diazo-decomposition and thus has a propensity to form the lower energy diene as the major product. 172

What remains to be concluded for the formal total synthesis is the formation of the oxepene core. The data collected was promising, however the yields for the RCM reaction were low and further analysis of the products is necessary to confirm the results. I have proposed a ring-closing metathesis strategy for the formal total synthesis of (+/-)-rogioloxepane A and (+/-)-isolaurepinnacin. Attempts at RCM with O-H insertion adduct 247 with trityl and benzyl protecting groups failed under a variety of conditions, however the RCM reaction with analogues 256 were successful, although the use of titanium based Lewis acids as additives resulted in concomitant decarboxylation. These results give merit to the proposed tandem methodology as it could be applied ot a formal
total synthesis. Further examination of potential natural product and/or synthetic targets would provide a possible avenue for the use of the vinyldiazo substrates in a total synthesis scheme, as well.

Since this work has been conducted, the use of BCl₃ derivatives have proven to be excellent additives in RCM reaction. With a more versatile set of RCM catalysts and further investigation of alternative additives, the formal total synthesis should be realized rather quickly.

Future Endeavors

The low yields for insertion reactions with homovinyl diazo esters are a result of competing side reactions such as β-elimination and hydrogen abstraction. Both of these competing reactions should be avoidable by the proper choice of catalyst, which has yet to be determined. Finding a way to convert homovinyl diazo compounds efficiently to O-H insertion products would be beneficial in the application of this methodology in light of the issues associated with the α,β-unsaturated dienes. The small amount of O-H insertion adduct that was isolated underwent RCM reaction relatively easily. A particularly important future avenue would be further screening of the homovinyl diazo substrates in order to obviate β-elimination and cyclopropanation as the major products.
EXPERIMENTAL

Materials and Methods.

Infrared (IR) Spectra were obtained using a Shimadzu Advantage FTIR-8400. Proton and carbon nuclear magnetic resonance (\(^1\)H and \(^{13}\)C NMR) spectra were recorded on a Bruker Avance 300 (\(^1\)H at 300 MHz; \(^{13}\)C at 75 MHz) running ICONNMR software. Chemical Shift data is reported in reference to CHCl\(_3\) resonance at 7.24 ppm and 77.0 ppm. Enantioenrichment was determined on a Hewlett Packard 6890 series GC using a Chirasil-Dextrose CB column (25 m × 0.25 mm × 0.28 μm). Mass spectra were determined using GC/MS on a Hewlett Packard 5890 series GC (w/opp column, 30 m) and 5971A series MS or a Shimadzu GC/MS-QP2010S using SRH5XLB column (0.25 μm ×30 m ×0.25 mm). Thin layer chromatography (TLC) was conducted on Merck aluminum backed silica gel 60 F\(_{254}\) TLC plates purchased from EMD Chemicals. Flash Chromatography was carried out using silica gel 40-63μm (60Å) purchased from SiliCycle. All solvents (1,2-dichloroethane, toluene, benzene, acetonitrile, and hexanes, dichloromethane (DCM)) were dried by refluxing over and then distillation from calcium hydride (CaH\(_2\)), under an inert atmosphere. All air and moisture sensitive reactions were performed in flame dried, argon flushed flasks and conducted under an inert atmosphere. All microwave reactions were run in a Biotage Initiator® microwave reactor using variable wattage, pressure, and temperature. In some cases flash chromatography was conducted on a Biotage SP1® flash chromatography system with12S, 25S, and 25M columns pre-packed with 40-63μm (60Å) silica gel.
General procedure for the esterification of trans-styrylacetic acid and pent-4-enoic acid.

Esterification: Method A.
Methyl 4-phenylbut-3-enoate and Ethyl 4-phenylbut-3-enoate: To a solution of alcohol (1.0 eq.), 10 mol% DMAP, and trans-styrylacetic acid (1.05 eq.) in DCM at 0°C was added a 1.0 M solution of DCC (1.5 eq.) in DCM dropwise via cannula over 1 hr. After stirring at 0°C for >24 hr (TLC determined alcohol consumed) the solution was quenched by the addition of Et₂O:NH₄Cl (1:1) and then filtered through a pad of Celite to remove the insoluble urea. The filtrate was then washed with water and the aqueous layer extracted twice with DCM, dried over Na₂SO₄, filtered and concentrated. The resulting yellow/brown oil can be triturated with cold hexanes to further remove solvated urea. Chromatography on silica gel (EtOAc/Hex) provides pure unsaturated ester in >90% yield.

Esterification: Method B.
Methyl pent-4-enoate and Ethyl pent-4-enoate: To a 200 ml round bottom flask equipped with a water cooled condenser and argon inlet/outlet was placed pent-4-enoic acid (49 mmol, 4.9 g), alcohol (1.4 mol, 46 g), and 5 mol% sulfuric acid (2.5 mmol, 0.24 g). The solution was heated to reflux for 24-48 hrs then cooled to room temperature and concentrated in vacuo. The resulting yellow-brown oil was diluted with EtOAc and washed with NaHCO₃, water, and then brine. The organic layer was then dried over Na₂SO₄, filtered, and concentrated to yield 3.5 g of light brown oil (56% at 24 hrs).
(E)-ethyl 4-phenylbut-3-enoate$^{346,350}$: $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.29 (m, 5H), 6.48 (d, $^3$J$_{HH}$ = 15.9 Hz, 1H), 6.29 (dt, $^3$J$_{HH}$ = 15.9 Hz, 7.0 Hz, 1H), 4.16 (q, $^3$J$_{HH}$ = 7.1 Hz, 2H), 3.23 (d, $^3$J$_{HH}$ = 7.0 Hz, 2H), 1.26 (t, $^3$J$_{HH}$ = 7.1 Hz, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 14.2, 38.5, 60.8, 121.8, 126.3, 127.5, 128.5, 133.3, 136.3, 163.5.

(E)-methyl 4-phenylbut-3-enoate$^{347,350}$: $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.28 (m, 5H), 6.48 (d, $^3$J$_{HH}$ = 15.9 Hz, 1H), 6.28 (dt, $^3$J$_{HH}$ = 15.9 Hz, $^4$J$_{HH}$(allylic) = 7.0 Hz, 1H), 3.70 (s, 3H), 3.24 (dd, $^3$J$_{HH}$ = 8.2 Hz, $^4$J$_{HH}$(allylic) = 7.0 Hz, 2H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 38.2, 51.8, 121.7, 126.3, 127.6, 128.5, 133.5.

Methyl 4-pentenoate: $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 5.78 (m, 1H), 5.01 (m, 2H), 3.65 (s, 3H), 2.38 (m, 4H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 28.8, 33.3, 51.5, 115.5, 136.7, 173.5.

Ethyl 4-pentenoate: $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 5.79 (m, 1H), 5.01 (m, 2H), 4.11 (q, $^3$J$_{HH}$ = 7.1 Hz, 2H), 2.36 (bs, 4H), 1.18 (t, $^3$J$_{HH}$ = 7.1 Hz, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 14.2, 28.8, 33.5, 60.2, 115.3, 136.7, 172.9.

General diazo-transfer procedure. Formation of vinyl diazoester and $\alpha$-diazo-$\beta$-ketoester

DBU (1.2-2.0 eq) was added dropwise to a solution of unsaturated ester and pABSA (1.2-2.0 eq) in CH$_3$CN at -20°C-0°C. The solution stirred for 30-120 min (TLC monitor) and was either quenched with saturated ammonium chloride solution and extracted with ether, or passed through a pad of silica gel followed by chromatography (if necessary) on silica
gel (Hex→50%EtOAc:Hex). Yields of α-diazoester vary from 60-80% for α-vinyl diazoesters and 80-96% for α-diazo-β-ketoesters.

![Diagram](image)

**E)-methyl 2-diazo-4-phenylbut-3-enoate**. From ester (0.65 mmol) and 1.2 eq. DBU and pABSA obtained 60-80% yield (not corrected for isolated pyrazole compound).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.31 (m, 5H), 6.48 (d, $^3$J$_{HH}$ = 15.9 Hz, 1H), 6.28 (d, $^3$J$_{HH}$ = 15.9 Hz, 1H), 3.7 (s, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 167, 135.9, 128.7, 126.9, 125.6, 123.1, 112.2, 106.1, 51.9.

![Diagram](image)

**E)-ethyl 2-diazo-4-phenylbut-3-enoate**. From ester (0.65 mmol) and 1.2 eq. DBU and pABSA obtained 60-80% yield (not corrected for isolated pyrazole compound).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.31 (m, 5H), 6.47 (d, $^3$J$_{HH}$ = 16.3 Hz, 1H), 6.17 (d, $^3$J$_{HH}$ = 16.3 Hz, 1H), 4.3 (q, 2H), 1.31 (t, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 165.2, 136.8, 128.7, 127.0, 125.8, 122.9, 111.5, 105.7, 61.4, 14.5.

**Representative procedures for the preparation of α-diazo-β-ketoester precursors.**

**E)-Ethyl 3-hydroxy-5-phenyl-4-pentenoate (206a).** A dry, 1-L, two-necked, round-bottomed flask, capped with septa and equipped with a magnetic stirring bar, a pressure equalizing dropping funnel, and an argon inlet was flushed with argon and charged with dry diethyl ether (200 mL) and diisopropylamine (15.4 mL, 110 mmol. The solution was cooled to 0°C and n-butyllithium (BuLi) (55.0 mL, 110 mmol, 2.0 M solution in
hexanes), was added. The reaction is stirred for 15 min and then cooled to −78°C. Dry EtOAc (9.7 mL, 100 mmol, was then added dropwise over 15 minutes and then stirred for 1 hr at −78°C. A solution of freshly distilled trans-cinnamaldehyde (12.9 mL, 100 mmol,) was then added rapidly via syringe in two portions. The reaction was stirred for 30 min. and quenched by the rapid addition of saturated aqueous ammonium chloride (NH₄Cl), (50 mL). The reaction mixture was poured into a 2-L separatory funnel containing 200 mL of diethyl ether. The reaction flask was rinsed with 100 mL of distilled water and 100 mL of diethyl ether. After thorough mixing, the layers were separated and the aqueous layer was extracted with diethyl ether (once, 100 ml). The combined organic layers were washed with brine (twice, 100 mL), dried over calcium chloride (CaCl₂), filtered, and evaporated under reduced pressure. **Crude ethyl 3-hydroxy-5-phenyl-4-pentenoate is used in the next step.** The product can be chromatographed on silica gel eluting with 20-50% EtOAc/hexanes [Rᵢ = 0.48 (50%EtOAc/Hex)].

![Chemical Structure (E)-Ethyl 3-oxo-5-phenyl-4-pentenoate](image)

¹H-NMR (300 MHz, CDCl₃): δ 7.23 (m, 5H), 6.58 (dd, ³JHH = 15.9 Hz, ⁴JHH = 1.02 Hz 1H), 6.15 (dd, ³JHH = 15.9 Hz, 6.1 Hz, 1H), 4.65 (m, 1H), 4.11 (q, 2H), 3.1 (d, ³JHH = 4.3 Hz, 1H), 2.56 (dd, ³JHH = 7.5 Hz, 4.92 Hz, 2H), 1.19 (t, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ 130, 129, 128, 127, 126, 68, 61, 41, 14. GC/MS, m/z, (rel. int.): RT 9.14 min, 55 (31), 77 (31), 91 (23), 104 (100), 115 (37), 131 (53), 133 (71), 202 (13), 220 M⁺(15).

**(E)-Ethyl 3-oxo-5-phenyl-4-pentenoate (207a):** A portion of the above aldol product (1.726 g, ~7.8 mmol) was dissolved in 15 ml DCE and added to 15 equivalents of activated MnO₂ with vigorous stirring, under nitrogen atmosphere at room temperature.
The reaction flask becomes warm due to the exothermic reaction. The addition of 10 ml DCE was necessary to facilitate stirring. The reaction stirred for 2.5 hr and was determined complete by TLC analysis (SM = 0.13 (DCM), Pdt = 0.34 (DCM). Crude product was chromatographed on Silica gel Eluting with DCE. Fractions containing the product as well as traces of cinnamaldehyde were combined for subsequent diazo-transfer reaction. Isolation of the subsequent diazoester confirms the preparation of the β-ketoester.

**(E)-Ethyl 2-diazo-3-oxo-5-phenyl-4-pentenoate (187a):** The above mixture (1.71 g, ~7.8 mmol, not accounting for cinnamaldehyde) was dissolved in 20 ml DCM under a nitrogen atmosphere and p-toluenesulfonyl azide (3.1 g, 15.6 mmol) was added and the solution was cooled to 0°C. DBU (2.37 g, 2.3 ml, 15.6 mmol) was then added dropwise over 10 min. The solution was monitored by TLC and the reaction was determined complete after 4 hrs (Rf 0.34, β-ketoester, was consumed). NH₄Cl (10 ml) was added and the solution stirred for 15 min, warming to room temperature. The resulting solution was extracted 3 times with 20 ml DCE dried over sodium sulfate and then filtered through 15 ml of dry silica gel (syringe barrel) eluting with 30%EtOAc/Hex. The solution was then concentrated providing a yellow oil containing a large amount of precipitate (~2.5g). The oily solid was then adsorbed onto silica gel (~5g) and chromatographed eluting with DCM. TsN₃ co-elutes with the diazo product and can be removed on trituration with PE, pentane, or hexanes to isolate 295.5 mg (15% yield, 14.7% over 3 steps).
(E)-Ethyl 2-diazo-3-oxo-5-phenyl-4-pentenoate (187a): $^1$H-NMR (300 MHz, CDCl$_3$): δ 7.85 (d, $^3$J$_{HH}$ = 15.8 Hz, 1H), 7.74 (d, $^3$J$_{HH}$ = 15.8 Hz, 1H), 7.59 (m, 2H), 7.36 (m, 3H), 4.32 (q, 2H), 1.34 (t, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 14.2, 61.3, 76.7, 121.6, 128.5, 128.7, 130.3, 134.5, 142.6, 161.2, 181.2. IR ($\lambda_{max}$, neat, cm$^{-1}$): 3060.82, 2979.82, 2144.7, 1701, 1697, 1639, 1589, 1340, 1209, 1139, 1045, 757, 703.

General procedure for the preparation of homovinyldiazoesters: Method A. Benzoylation-debenzoylation/diazo-transfer.

**Benzoylation procedure: Method A (part I).** TiCl$_4$ was added over 30 min. to a solution of benzoyl chloride (40.73 mmol, 5.72 g), Methyl 4-pentenoate (13.6 mmol, 1.55 g), and triethylamine (81.6 mmol, 11.3 ml) in 10 ml dry CH$_3$CN at 0°C. The mixture was then warmed to reflux for 15 min. and then cooled to room temperature and partitioned between water and EtOAc (3 × 30 ml). The combined organic layers were dried over MgSO$_4$, filtered, concentrated in vacuo, and the resulting oil was Kugelrhor distilled using aspirator vacuum (80-100°C) or chromatographed on silica gel (dichloromethane).

Methyl 2-benzoyl-4-penenoate (211a): $^1$H-NMR (300 MHz, CDCl$_3$): δ 7.96 (d, $^3$J$_{HH}$ = 7.95 Hz, 2H), 7.56 (t, $^3$J$_{HH}$ = 7.23, 1H), 7.45 (t, $^3$J$_{HH}$ = 7.92, 2H), 5.8 (m, 1H), 5.05 (dm, 2H), 4.4 (t, $^3$J$_{HH}$ = 7.2, 1H), 3.64 (s, 3H), 2.72 (tm, 2H). $^{13}$C-NMR (75 MHz, CDCl$_3$): δ 33.09, 52.52, 53.63, 117.5, 128.65, 128.81, 133.65, 134.41, 136.08, 169.87, 194.44.
**EtO**

**Ethyl 2-benzoyl-4-pentenoate (211b):** $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 14.0, 32.98, 53.96, 61.44, 117.39, 128.62, 128.72, 129.0, 133.5, 134.54, 176.41, 194.4. $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 14.0, 32.98, 53.96, 61.44, 117.39, 128.62, 128.72, 129.0, 133.5, 134.54, 176.41, 194.4. GC/MS (Shimadzu), m/z, (rel. int.): RT 12.08, 41 (2.36), 45 (0.66), 77 (45.92), 105 (100), 127 (6.99), 159 (1.05), 186 (1.03), 232 M$^+$ (0.84).

**Debenzoylation/diazo-transfer: Method A (part II).** Methyl 2-benzoyl-4-pentenoate (4.0 mmol, 873 mg, and p-toluenesulfonyl azide (1.18 g, 6 mmol) was dissolved in 10 ml CH$_3$CN in a dry 50 ml round bottom flask and cooled to 0°C with stirring. DBU (6 mmol, 913 mg) was added dropwise over 20 min. and the solution stirred at 0°C for another 1.5 hr then warmed to room temperature over night. The dark red solution was partitioned between water and hexanes. The organic layer was separated, washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated (crud mass = 450 mg, 89%). The resulting yellow oil was chromatographed on silica gel (20% EtOAc/Hex, $R_f$ = 0.42, 20%EtOAc/Hex) providing 151.2 mg (27%).

**Debenzoylation/diazo-transfer. Method A (part II-alternative).** DBU (803 mg, 5.28 mmol) was added dropwise over 15 minutes to a solution of benzyolated methyl ester (970 mg, 4.4 mmol) and TsN$_3$ (876 mg, 4.45 mmol) in DCM at 0°C. Monitored TLC 15 after DBU addition. The solution stirred for 3 hrs at which point the SM did not appear as a spot which quenched the fluorescence on the TLC plate (staining with p-anisaldehyde solution however did show a small amount of benzyolated ester.) The solution was poured into 50 ml of saturated aqueous NH$_4$Cl and then extracted with 50 ml of DCM. The organic layer was washed with water 3 x 50 ml and then with brine,
dried over Na₂SO₄, filtered, and stored in the freezer overnight. The orange oil was chromatographed on silica gel (5% EtOAc/Hex→20% EtOAc/Hex) isolating Rₜ = 0.45 (20% EtOAc/Hex) which stains blue with p-anisaldehyde solution. 1.423 g of yellow oil was obtained (~50%, 3.6:1, TsN₃:diazo). A second column was prepared with 60 g silica gel and the yellow oil was eluted with dichloromethane (TsN₃ = 0.63, diazo = 0.3 (aluminum)) to obtain 199.1 mg (32%) of golden yellow oil.

Methyl 2-diazo-4-pentenoate (196a): \(^1\)H-NMR (300 MHz, CDCl₃): \(\delta\) 5.75 (m, 1H), 5.10 (m, 2H), 3.72 (s, 3H), 3.00 (d, \(^3\)JHH = 6.45 Hz, 2H), \(^1\)C-NMR (75 MHz, CDCl₃): \(\delta\) 27.21, 51.84, 117.48, 132.35, 167.34. IR (\(\nu\) max, neat, cm⁻¹): 3083, 2983, 2954, 2908, 2848, 2082, 1699, 1641, 1438, 1344, 1207, 1191, 1134, 923, 744.

Ethyl 2-diazo-4-pentenoate (196b): \(^1\)H-NMR (300 MHz, CDCl₃): \(\delta\) 5.8 (m, 1H), 5.13 (m, 2H), 4.21 (q, \(^3\)JHH = 7.1 Hz, 2H), 3.02 (dt, \(^3\)JHH = 6.48 Hz, 2H), 1.25 (t, \(^3\)JHH = 7.1 Hz, 3H). \(^1\)C-NMR (75 MHz, CDCl₃): \(\delta\) 14.5, 27.3, 61.2, 117.6, 132.7, 168.8 (diazo carbon assumed to be at ~76 ppm). IR (\(\nu\) max, neat, cm⁻¹): 3083, 2981, 2933, 2908, 2084, 1689, 1465, 1371, 1205, 1130, 923, 742.

General procedure for the preparation of homovinyldiazoesters: Alkylation/deacylation-diazo transfer: Method B.

Alkylation of \(\beta\)-ketoester. Method B (part I).

Methyl acetoacetate (5 g, 43.05 mmol) and allyl bromide (5.2 g, 43.05 mmol) were placed in flame dried flask with 10 ml CH₃CN and the mixture was cooled to 0°C. DBU (7.864 g, 51.66 mmol) was added dropwise over 15 minutes and the resulting yellow
solution stirred for 1 hr at 0°C. The reaction was quenched with the addition of 20 ml of 1:1 (Et₂O:H₂O) and stirred for 30 min. The mixture was separated and the aqueous layer extracted with ether (2 × 50 ml) and dried over Na₂SO₄. After concentration a yellow oil was obtained (5.98 g) and was chromatographed on silica gel (Hexanes to 10%EtOAc/Hex) to obtain a clear oil (1.972 g, 30%) of pure product along with (2.263 g of >90% purity product (bis-alkylated: mono-alkylated ~1:10)).

Methyl 2-acetyl-4-pentenoate: ¹H-NMR (300 MHz, CDCl₃): δ 5.72 (m, 1H), 5.05 (m, 2H), 3.71 (s, 3H), 3.52 (t, J_HH = 7.4 Hz, 1H), 2.57 (t, J_HH = 7.4 Hz, 6.9 Hz, 2H), 2.2 (s, 3H). ¹³C-NMR (75 MHz, CDCl₃): δ 29.1, 32.2, 52.4, 59.1, 117.5, 134.1, 173.2, 202.0. GC/MS (Shimadzu), m/z, (rel. int.): RT 7.65 min.; 41 (11.05), 43 (100), 59 (9.75), 81 (14.34), 97 (4.28), 113 (16.66).

Deacylation-diazo transfer. Method B (part II). To a solution of Methyl 2-acetyl-4-pentenoate (3.95 g, 25.3 mmol) and TsN₃ (5.23 g, 26.55 mmol) in dry DCM (100 ml) under nitrogen atmosphere at 0°C was added DBU (4.04 g, 26.55 mmol) dropwise. The mixture stirred for 90 min (TLC monitor) at 0°C and then 100 ml of 15% NaOH solution was added and the mixture warmed to room temperature. The mixture was then extracted twice with DCM (50 ml) and the organic was washed with brine, dried over Na₂SO₄, filtered and concentrated to provide a viscous red oil. This can be triturated with cold hexanes to facilitate separation of the oily sulfonamide from the mixture. Chromatography on silica gel (10% EtOAc/Hex) provided 1.66 g (52%, losses due to volatility) of yellow fragrant oil.
Methyl 2-diazo-4-pentenoate (196a): $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 5.79 (m, 1H), 5.14 (m, 2H), 3.75 (s, 3H), 3.02 (d, $^3$J$_{HH}$ = 6.4 Hz, 2H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 27.3, 51.9, 117.6, 132.4, 179.1 (diazo carbon ~ 76 ppm). IR ($\nu_{max}$, neat, cm$^{-1}$): 3083, 2983, 2954, 2908, 2848, 2082 (C=N 2), 1699, 1438, 1344, 1207, 1191, 1134, 1089, 993, 923, 744.

Ethyl 2-diazopent-4-enoate (196b): $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$5.79 (m, 1H), 5.14 (m, 2H), 4.21 (q, $^3$J$_{HH}$ = 7.1 Hz, 2H), 3.02 (d, $^3$J$_{HH}$ = 6.5 Hz, 2H), 1.25 (t, $^3$J$_{HH}$ = 7.1 Hz, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$14.5, 27.3, 61.1, 117.5, 132.7, 168.8. IR ($\nu_{max}$, neat, cm$^{-1}$): 3083, 2981, 2933, 2908, 2848, 2084, 1689, 1479, 1371, 1334, 1299, 1205, 1130, 1020, 993, 923, 742.

General procedure for preparation of 2-alkyloxy-4-phenylbut-3-enyl esters and 2-alkoxy-3-oxohex-4-enyl esters.

Method A (conventional): To a flame dried argon flushed flask is placed 0.1-2.0 mol% Rh$_2$(OAc)$_4$, 1,2-dichloroethane (DCE) (5 ml), and olefinic alcohol (2 eq. relative to diazoester). The mixture is maintained at room temperature for reactions with vinyldiazoester or heated to reflux (83°C) in the case of $\alpha$-diazo-$\beta$-ketoesters. The solution is degassed by bubbling argon or nitrogen through for at least 10 min. The diazoester is added dropwise via cannula or syringe pump as a ~0.2 M solution in DCE. The reaction is monitored by TLC after complete addition of the diazo substrate (~30-60 min). Upon completion the reaction is concentrated and chromatographed on Silica Gel...
(5-20%EtOAc/Hexanes). Isolated yields of desired and isomerized insertion product vary from 40-80%, uncorrected for the amount of pyrazole present.

**Method B (microwave synthesis):** The Rh(II) catalyst (0.1 – 1.0 mol %) is placed in the flamed dried argon flushed 2-5 ml microwave reaction vessel followed by 2 ml of reaction solvent and 1-2 equivalents of olefinic alcohol (0.8 mmol). The solution is degassed by bubbling argon or nitrogen through for at least 10 min. A 0.2 M solution of diazo substrate (0.4 mmol) is added to the catalyst/substrate solution stirred for 10 seconds then irradiated for 5-10 min at 140-170°C. When the flask cools to room temperature the reaction mixture is concentrated and filtered through a short plug of silica gel eluting with DCM (for crude mixture analysis). The insertion product is then separated from excess alcohol by column chromatography on silica gel (EtOAc/Hex). Isolated yields of desired and isomerized insertion product vary from 60-80%, uncorrected for the amount of pyrazole present.

**Method A (Low-temperature reactions with vinyl diazoester substrates):** To a flame dried argon flushed flask equipped with magnetic stir bar and pressure equalizing cold-jacketed dropping funnel is placed 0.1-1mol% (relative to diazo substrate) Rh₂(S-DOSP)₄ followed by 10 ml anhydrous 1,2-dichloroethane. The solution is cooled to 0°C and stirred for 15 min. The alcohol is then introduced dropwise and stirred for another 15
min. An observable color change from green to blue occurs. The dropping funnel reservoir is then cooled to a maximum of 0°C and then charged with vinyl diazo substrate and added dropwise to the solution over a period of hours. When the reaction is complete as determined by TLC analysis the crude mixture is concentrated and filtered through a short plug of silica gel eluting with DCM (for crude mixture analysis). The insertion product is then isolated by column chromatography on silica gel (EtOAc/Hex). Isolated yields of desired and isomerized insertion product vary from 70-99%, uncorrected for the amount of pyrazole present.

(E)-methyl 2-(allyloxy)-4-phenyl-3-butenoate (194a): Prepared via the above general O-H insertion procedure (Method A) and was obtained in 99% yield. $R_f = 0.34$ (20% EtOAc/Hex). $^1$H-NMR (300 MHz, CDCl3): δ 7.3 (m, 5H), 6.74 (d, $^3J_{HH} = 15.9$ Hz, 1H), 6.2 (dd, $^3J_{HH} = 15.9$ Hz, $^2J_{HH} = 6.9$ Hz, 1H), 5.93 (m, 1H), 5.3 (dt, $^3J_{HH} = 17.2$ Hz, $^2J_{HH} = 1.4$ Hz, 1H), 5.2 (dt, $^3J_{HH} = 10.8$ Hz, 1H), 4.57 (d, $^3J_{HH} = 6.9$ Hz, 1H), 4.1 (m, 2H), 3.76 (s, 3H). $^{13}$C-NMR (75 MHz, CDCl3): δ 52.18, 70.36, 78.54, 118.02, 123.61, 126.61, 128.13, 128.49, 133.68, 134.14, 135.78, 170.98. IR ($v_{max}$, neat, cm$^{-1}$): 3082, 3060, 3026, 2952, 2864, 1747, 1647, 1577, 1573, 1496, 1450, 1334, 1259, 1120, 970, 777, 738, 692. GC/MS (HP), m/z (rel. int.): RT 12.32 min.; 39 (80.1), 41 (100), 59 (40.1), 77 (25.4), 91 (16.3), 103 (18.8), 115 (31.2), 131 (22.6), 173 (4.7), 232 M$^+$ (0.02); Anal. Calcd. For C$_{14}$H$_{16}$O$_3$: C, 72.38, H, 6.95, O, 20.67. Found: C, 71.88, H, 7.00, O, 21.23.

It was determined that the vinyl diazoester substrate could be introduced to the catalyst/alcohol mixture in one portion with little or no difference in yield of insertion adduct.
(E)-Methyl 2-(3-butenyloxy)-4-phenyl-3-butenoate (194b): Prepared via the above general O-H insertion procedure (Method A) and was obtained in 91% yield. R_f = 0.36 (20%EtOAc/Hex). 1H-NMR (300 MHz, CDCl_3): δ 7.3 (m, 5H), 6.74 (d, 3J_HH = 15.9, 1H), 6.2 (dd, 3J_HH = 15.9 Hz, 2J_HH = 6.78 Hz, 1H), 5.83 (m, 1H), 5.07 (m, 2H), 4.5 (dd, 3J_HH = 6.78 Hz, 1J_HH(allylic) = 1.14 Hz, 1H), 3.76 (s, 3H), 3.58 (m, 2H), 2.41 (q, 3J_HH = 6.84 Hz, 2H). 13C-NMR (75 MHz, CDCl_3): δ 33.95, 52.16, 69.16, 79.80, 116.62, 123.81, 126.63, 128.10, 128.49, 133.87, 134.57, 135.84, 171.08. IR (ν max, neat, cm⁻¹): 3082, 3060, 3026, 2979, 2906, 2867, 1747, 1643, 1577, 1496, 1434, 1330, 1259, 1199, 1118, 968, 918, 736, 692. GC/MS (HP), m/z (rel. int.): RT 12.66 min.; 39 (100), 41 (67.9), 55 (75.5), 59 (82.3), 77 (19.0), 103 (12.7), 115 (36.3), 131 (12.1), 187 (1.6), 246 M⁺ (0.04); Anal. Calcd. For C₁₅H₁₈O₃: C, 73.13, H, 7.37, O, 19.49. Found: C, 73.18, H, 7.47, O, 19.53.

(E)-Methyl 2-(3-methylbut-3-enyloxy)-4-phenyl-3-butenoate (194e): Prepared via the above general O-H insertion procedure (Method A, DCE:PhH (3:1)) and was obtained in 84% yield after chromatography on Biotage® with fraction collection at 254 nm. 1H-NMR (300 MHz, CDCl_3): δ 7.32 (m, 5H), 6.75 (d, 3J_HH = 15.9 Hz, 1H), 6.21 (dd, 3J_HH = 15.9 Hz, 4J_HH(allylic) = 6.7 Hz, 1H), 4.76 (d, 4J_HH(allylic) = 9.93 Hz, 2H), 4.52 (d, 3J_HH = 6.7 Hz, 1H), 3.76 (s, 3H), 3.62 (t, 3J_HH = 7.0 Hz, 2H), 2.38 (t, 3J_HH = 7 Hz, 2H), 1.75 (s, 3H).

(E)-Methyl 2-(4-pentenyloxy)-4-phenyl-3-butenoate (194c): Prepared via the above general O-H insertion procedure (Method A) and was obtained in 70% yield. R_f = 0.39 (20%EtOAc/Hex). 1H-NMR (300 MHz, CDCl_3): δ 7.3 (m, 5H), 6.74 (d, 3J_HH = 15.9 Hz, 1H), 6.2 (dd, 3J_HH = 6.78 Hz, 15.9 Hz, 1H), 5.73 (m, 1H), 4.92 (m, 2H), 4.49 (d, 3J_HH = 6.78 Hz, 1H), 3.75 (s, 3H), 3.53 (m, 2H), 2.08 (quart, 3J_HH = 7.1 Hz, 2H), 1.68 (quint, 3J_HH = 6.9, 2H). 13C-NMR (75 MHz, CDCl_3): δ 28.79, 30.18, 52.27, 69.34, 79.94, 114.95, 124.08, 126.75, 128.20, 128.62, 133.88, 136, 138.06, 171.32. IR (ν max, neat, cm⁻¹): 3064, 3028, 2997, 2950, 2873, 1716, 1643, 1494, 1434, 1330, 1286, 1257, 118, 1076, 993, 914, 775, 746, 700. GC/MS, m/z, (rel. int.): RT 13.12 min.; 39 (70), 41 (100), 55 (41.6), 59 (39.6), 69 (19.6), 77 (28.1), 91 (8.5), 103 (22.1), 115 (59.9), 131 (22.9), 133
(E)-Methyl 2-(5-hexenyloxy)-4-phenyl-3-butenoate (194d): Prepared via the above general O-H insertion procedure (Method A) and was obtained in 86% yield. \( R_f = 0.41 \) (20%EtOAc/Hex). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.3 (m, 5H), 6.67 (d, \( ^3J_{HH} = 15.9 \) Hz, 1H), 6.13 (dd, \( ^3J_{HH} = 6.75 \) Hz, 15.9 Hz, 1H), 5.7 (m, 1H), 4.9 (dm, 2H), 4.4 (dd, \( ^3J_{HH} = 6.75 \) Hz, \( ^4J_{HH(allylic)} = 1.26 \) Hz, 1H), 3.49 (s, 3H), 3.44 (m, 2H), 1.98 (quart, \( ^3J_{HH} = 7.05 \) Hz, 2H), 1.58 (quint, 2H), 1.41 (quint, 2H). \(^1^3\)C-NMR (75 MHz, CDCl\(_3\)): \( \delta \) 25.24, 29.08, 33.49, 52.23, 69.86, 79.91, 114.65, 124.13, 126.74, 128.19, 128.61, 133.85, 136.01, 138.61, 171.31. GC/MS, m/z, (rel. int.): RT 13.58 min.; 39 (72.7), 41 (100), 55 (87.5), 59 (40.7), 77 (28.4), 91 (9.6), 103 (24.3), 115 (60.4), 131 (30.6), 133 (35.3), 144 (1.4), 215 (3.8), 274 M\(^+\) (0.003); Anal. Calcd. For C\(_{17}\)H\(_{22}\)O\(_3\): C, 74.41, H, 8.09, O, 17.50. Found: C, 74.46, H, 8.07, O, 17.65.
Ring-closing Metathesis procedures

Method A (step-wise/conventional). To a flame dried argon flushed flask was placed 6-10 mol% metathesis catalyst and 1,2-dichloroethane to maintain a final substrate concentration of 0.05-0.005 M. Nitrogen was bubbled through the solution for 30 minutes and then heated to reflux with stirring for 15 minutes. After which time the diene substrate is added dropwise via cannula or syringe as a 0.2-0.05 M solution in reaction solvent (to give ~2-0.2 mM substrate concentration). The reaction is monitored by TLC (1-48hr). Formation of larger ring sizes requires longer reaction times. Yields vary from 70-92% as determined by GC/MS analysis (undecane/dodecane internal standard). GC analysis supports quantitative conversion of non-isomerized insertion product with the use of Grubbs 2nd generation (138d) and Hoveyda-Grubbs 2nd generation (139b) catalysts. Isolation of products resulting from RCM was conducted by first either a workup procedure which involved either stirring with DMSO ≥ 12 hr, addition of isocyanide, or simply stirring overnight open to air. Following workup/catalyst removal the concentrated material was chromatographed on silica gel (2.0 g SiO₂/0.01 mmol catalyst, EtOAc/Hex).

Method B (step-wise/conventional). Argon is bubbled through a solution of the diene substrate in solvent (5-30 ml DCM) in a 2-3 neck flask for 30-45 minutes. The mixture is heated to reflux then 10 mol% of metathesis catalyst is added in one portion through the side arm. The solution is refluxed for 4-12 hrs, cooled to room temperature and then
stirred open to air overnight (or other catalyst quenching protocol), followed by chromatographic separation of the mixture (2.0 g SiO$_2$/0.01mmol catalyst).

**Method C (step-wise/microwave synthesis).** Into a flame dried, argon flushed 2.5-5ml microwave reaction vessel is placed 4-10 mol% of metathesis catalyst and 2ml of reaction solvent (1,2-dichloroethane, toluene, or dichloromethane, or a mixture). The diene was then added as a 0.2-0.05 M (to give 0.2-0.5 mM substrate concentration) solution in the chosen reaction solvent and the vessel irradiated for 10-20 min (140-170°C). Reaction progress was checked by TLC and once diene is consumed, subjected to a work-up protocol (*vide supra*), followed by concentration and purification by column chromatography on silica gel (2.0 g SiO$_2$/0.01mmol catalyst).

**Method D (one-pot/conventional heating).** Both catalysts (0.1-1mol% Rh(II) catalyst and 4-10mol% metathesis catalyst) are added to a flame dried, argon flushed reaction flask and then diluted with 10 ml of 1,2-Dichloroethane. The solution is degassed for at least 10 min. The olefinic alcohol is added with stirring and maintained at the specified temperature (0°C for vinylidiao substrates and reflux temperature for the α-diazo-β-ketoesters) for a minimum of 15 min. The diazo substrate is then added dropwise as a 0.2 M solution in reaction solvent. Upon complete addition the reaction mixture is monitored by TLC (20%EtOAc/Hex). When complete the mixture is subjected to a workup protocol, concentrated, and purified (when possible) by column chromatography (2.0 g SiO$_2$/0.01mmol catalyst) after analysis of the crude reaction mixture by GC/MS and $^1$H-
NMR. Reactions w/vinyl diazo substrates were subsequently heated to reflux upon consumption of diazoester for the ensuing RCM reaction. The mixtures were not diluted to the preferred 0.005 M concentration (*vide supra*).

**Method E (sequential catalyst addition/conventional).** Same protocol as RCM method D, however the metathesis catalyst was added after the diazo compound was consumed and then the reaction was heated to reflux.

**Method F (one-pot/microwave synthesis).** Into a flame dried, argon flushed 2.5-5ml microwave reaction vessel was placed 4-10 mol% of metathesis catalyst, 0.1-1.0 mol% Rh(II) catalyst and 2ml of reaction solvent (1,2-dichloroethane, toluene, or dichloromethane, or a mixture). The substrates were then added (2:1, olefinic alcohol: diazoester) along with 2-3 ml of reaction solvent and the vessel is stirred at room temperature (in the case of vinyl diazoester substrate) until TLC analysis shows no SM diazo substrate and then irradiated for 10-20 min. (α-diazo-β-ketoester substrates were immediately irradiated). Reaction progress is checked by TLC and once diene substrate is consumed the mixture is subjected to a workup protocol, concentrated, analyzed by GC/MS and $^1$H-NMR, and then purified by column chromatography (2.0 g SiO$_2$/0.01mmol catalyst).

**Method G (step-wise/conventional, sealed tube reactions) (246/257).** The same general procedure as method A was followed, however the metathesis reaction was conducted in a sealed tube. When an additive was used, it was added to the α-alkoxy ester and stirred for 10 min. prior to the addition of catalyst.
Methyl 2,5-dihydrofuran-2-carboxylate (204a): Prepared via the above general RCM procedure (Method A, isocyanide quench) and was obtained in 53.5% yield. $R_f = 0.15$ (20%EtOAc/Hex). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 5.49 (m, 1H), 5.35 (m, 1H), 5.17 (m, 1H), 4.61 (m, 1H), 4.35 (m, 1H), 3.25 (s, 3H). GC/MS, m/z, (rel. int.): RT 7.06 min.; 39 (100), 41 (74.7), 59 (9.3), 69 (53.8), 128 M$^+$ (0.07). Satisfactory elemental analysis could not be obtained for this compound.

Methyl 2,5-dihydropyran-2-carboxylate (204b): Prepared via the above general RCM procedure (Method A, air quench) and was obtained in 86% yield as the dominant entity in an inseparable 2:1 mixture with stilbene. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 6.13 (m, 1H), 5.99 (dq, $^3$J$_{HH} = 10.23$ Hz, 2.76 Hz, 1.98 Hz, 1H), 4.85 (q, $^3$J$_{HH} = 2.7$ Hz, 2.6 Hz, 1H), 4.16 (m, 1H) 3.98 (m, 1H), 3.89 (s, 3H), 2.25 (m, 2H). Satisfactory elemental analysis could not be obtained for this compound.

Ethyl 2,5-dihydropyran-2-carboxylate (204b): Prepared via the above general RCM procedure (Method A, isocyanide quench) and was obtained in 21% yield. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 5.98 (m, 1H), 5.85 (dq, $^3$J$_{HH} = 10.3$), 4.68 (quintet, $^3$J$_{HH} = 5.4$ Hz, $^4$J$_{HH(allylic)} = 2.7$ Hz, 1H), 4.21 (q, $^3$J$_{HH} = 7.1$ Hz, 2H), 4.02 (m, 1H), 3.83 (m, 1H), 2.14 (bs, 2H), 1.28 (t, $^3$J$_{HH} = 7.1$ Hz, 3H). Satisfactory elemental analysis could not be obtained for this compound. Satisfactory elemental analysis could not be obtained for this compound.

Methyl 2,5,6,7-tetrahydrooxepine-2-carboxylate (204c): Prepared via the above general RCM procedure (Method A, isocyanide quench) and was obtained in 70.4% yield. $R_f = 0.20$ (20%EtOAc/Hex). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 5.91 (m, 1H), 5.77 (d, $^3$J$_{HH} = 11.3$ Hz, 1H), 4.74 (bs, 1H), 4.13 (m, 1H), 3.76 (s, 3H), 3.76 (m, 1H), 2.31 (m, 2H), 1.84 (quint, $^3$J$_{HH} = 5.89$ Hz, 2H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 14.16, 22.70,
(Z)-methyl 5,6,7,8-tetrahydro-2H-oxocine-2-carboxylate (204d): Attempted preparation via the above general RCM procedure (Method A, air quench) and the crude mixture analyzed. This compound was not isolated but was detected with GC/MS analysis and the designated peak in the TIC displayed a similar fragmentation pattern to that of similar compounds. $^1$H-NMR analysis of the crude mixture also displayed resonances indicative of non-terminal olefinic C-H. GC/MS, m/z, (rel. int.): RT 9.43 min.; 39 (73.5), 41 (54.6), 55 (42.6), 59 (100), 81 (18.3), 111 (12.1), 170 M$^+$ (0.04). Satisfactory elemental analysis could not be obtained for this compound.

Representative oxonium ylide/[2,3]-rearrangement.

(E)-methyl 2-allyl-2-hydroxy-3-oxohex-4-enoate: (Attempted preparation of (E)-methyl 2-(allyloxy)-3-oxohex-4-enoate with the use of Rh(II) carboxamidate catalysts): To a flame dried, argon flushed flask equipped with a reflux condenser topped with an argon inlet was placed 1.0 mol% Rh$_2$(cap)$_4$ (2.6 mg, 0.00396 mmol) and 3 ml PhCH$_3$. The solution was heated to reflux and allyl alcohol (33 μl, 0.475 mmol, 1.2 eq.) was added in one portion. Then 0.2 M solution of methyl 2-diazo-3-oxo-4-hexenoate (66.58 mg, 0.396 mmol) in PhCH$_3$ was then added dropwise over 10 min by syringe pump. The solution was stirred for 1 hr at reflux, at which point TLC analysis showed no diazoester substrate, then concentrated and chromatographed (silica gel, EtOAc/Hex, 0-20%) to provide 53.8 mg (68.5%) of a clear yellow oil. In almost every case, with the use of Rh(II) carboxamidates, the predominant product is the $\alpha$-hydroxy-$\alpha$-alkylated compound resulting from ylide RAR (vide supra).
(E)-methyl 2-allyl-2-hydroxy-3-oxohex-4-enoate: $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.1 (d, $^3\text{J}_{\text{HH}}$ = 12.3 Hz, 1H), 7.01 (m, 1H), 5.85 (m, 1H), 5.68 (d, $^4\text{J}_{\text{HH}}$ = 5.3 Hz), 5.25 (m, 2H), 4.6 (dt, $^3\text{J}_{\text{HH}}$ = 5.64 Hz, 2H), 3.8 (s, 3H), 1.90 (dd, $^3\text{J}_{\text{HH}}$ = 6.6 Hz, 3H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 18.3, 52.1, 55.6, 66.0, 118.5, 126.5, 131.5, 143.4, 161.8, 181.4.

(E)-ethyl 2-(3-methyl-2-butenyloxy)-3-oxo-4-hexenoate: Attempted preparation via general O-H insertion procedure Method B, however GC/MS analysis showed only product resulting from oxonium ylide/[2,3]-RAR reaction. Satisfactory elemental analysis could not be obtained for this compound.
(E)-ethyl 2-(3-butenyloxy)-3-oxo-4-hexenoate (202b): Prepared via general O-H insertion procedure (Method B, 1% rhodium acetate, 1:2 (diazo substrate: alcohol substrate). No pure compound was isolated the chromatographed material was a mixture of isomers and was used in subsequent RCM reaction (vide infra).

![Ethyl 3-oxo-3,6-dihydro-2H-pyran-2-carboxylate (201a)](image)

Ethyl 3-oxo-3,6-dihydro-2H-pyran-2-carboxylate (201a): Prepared via One-pot procedure (method B, 1% Rh$_2$(esp)$_2$ catalyst, and 8% Grubbs’ 2nd generation). Again the isolation of this compound seemed futile with no particular work-up procedure used. Analysis of the inseparable mixture indicates product is present albeit in low yield. Evidence for product is only the identification of M+1 peak in GC/MS at 7.9 min. Satisfactory elemental analysis could not be obtained for this compound.

![Z)-ethyl 3-oxo-2,3,6,7-terahydrooxepine-2-carboxylate (201b)](image)

(Z)-ethyl 3-oxo-2,3,6,7-terahydrooxepine-2-carboxylate (201b): Prepared via RCM procedure (Method C, 10% Hoveyda-Grubbs 2nd generation). Following quick filtration through silica gel eluting with PhCH$_3$/EtOAc (difficult purification) obtained 113.1 mg (51.2 %), of an inseparable mixture. GC/MS analysis detects the molecular ion (M+1), in addition the proton NMR indicates the presence of the cis-olefin resonances at 6.2 and 5.9 ppm with $^3$$J_{HH} = 12.3$ Hz and $^4$$J_{HH(allylic)} = 1.62$ Hz. $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ $^4$$J_{HH(allylic)} = 1.14$ Hz, 1H $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ GC/MS, m/z, (rel. int.): RT 11.09 min.; 29 (100), 43 (12), 54 (33), 82 (41), 138 (4.0), 184 M$^+$ (2.6).
(Z)-ethyl 3-oxo-2,3,6,7-tetrahydrooxepine-2-carboxylate (inseparable mixture)

(Z)-ethyl 7-((tert-butyldimethylsilyloxy)methyl)-3-oxo-2,3,6,7-tetrahydrooxepine-2-carboxylate (246): Prepared via the above general RCM procedure (Method G, isocyanide quench) and was obtained in 12% yield (corrected for starting material present). Rf = 0.67 (DCM). \(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta\) 6.39 (m, 1H), 5.74 (m, 1H), 5.1 (m, 1H), 4.2 (m, 3H), 3.67 (m, 2H), 2.4 (m, 1H) 1.8 (m, 1H), 0.8 (s, 9H), 0.0 (s, 6H). Satisfactory elemental analysis could not be obtained for this compound.
(Z)-7-((tert-butyldimethylsilyloxy)methyl)-6,7-dihydrooxepin-3(2H)-one (257): Prepared via the above general RCM procedure (Method G, isocyanide quench) and was obtained in 20% yield (corrected for starting material present). Rf = 0.28 (DCM). 1H-NMR (300 MHz, CDCl3): δ 5.66 (m, 1H), 5.4 (m, 1H), 5.1 (m, 1H), 3.7 (m, 4H), 2.5 (m, 1H), 2.1 (m, 1H), 0.8 (s, 9H), 0.0 (s, H). Satisfactory elemental analysis could not be obtained for this compound.
Procedures for the preparation of O-H insertion substrates.

Ethyl 2-hydroxypent-4-enoate (213): A 500 ml round bottom flask was charged with allyl bromide (89 mmol, 7.7 ml), ethyl glyoxylate as a 50% solution in toluene (44.5 mmol, 8.7 ml), two equivalents of powdered tin (89 mmol, 10.6 g), and 125 ml 70% ethanol. The mixture was placed in a sonicator for 2 hr at ambient temperature under a nitrogen atmosphere. The resulting solution was then diluted with chloroform (100 ml) and carefully neutralized with triethylamine to ~pH 6-7, filtered, separated and the organic layer was washed with brine and dried over MgSO₄. After filtration and concentration the yellow oil is distilled by Kugelrhth distillation, yielding a clear colorless oil 4.26g (66.5%).

![Ethyl 2-hydroxypent-4-enoate (213)](image)

Ethyl 2-hydroxypent-4-enoate (213): 

\[ \delta \text{H-NMR (300 MHz, CDCl}_3\text{):} \delta 5.78 \text{ (m, 1H),} \]
\[ 5.12 \text{ (dd, } ^3J_{HH} = 11.2 \text{ Hz, } 17.1 \text{ Hz,} ^2J_{HH} = 1.08 \text{ Hz, 2H),} \]
\[ 4.22 \text{ (m, 3H, -OCH}_2\text{, } \alpha\text{-CH-OH),} \]
\[ 2.79 \text{ (d, } ^3J_{HH} = 5.91 \text{ Hz, 1H, -OH),} \]
\[ 2.5 \text{ (m, 2H),} \]
\[ 1.27 \text{ (t, } ^3J_{HH} = 7.14 \text{ Hz, 3H).} \]

\[ ^{13}\text{C-NMR (75 MHz, CDCl}_3\text{):} \delta 14.24, 38.71, 61.72, 69.96, 118.69, 132.51, 174.44. \]

GC/MS(Shimadzu), m/z, (rel. int.): RT 6.75 min, 41 (57.2), 43 (100), 45 (9.6), 71 (58.37), 75 (33.8), 103 (21.3), 126 (2.92). IR \( \nu_{\text{max}} \text{, neat, cm}^{-1}\): 3470, 3080, 2983, 2939, 2910, 1735, 1643, 1465, 1444, 1436, 1369, 1301, 1271, 1213, 1137, 1080, 1027, 919, 862.

N,O-dimethyl 2-hydroxypent-4-enamide (214): A 250 ml three neck flask fitted with a water-cooled condenser, argon inlet/outlet, and a pressure equalizing dropping funnel was charged with Mg⁰ turnings (62 mmol, 1.5 g) one crystal of I₂, 100 ml dry THF, and isopropyl bromide (62 mmol, 7.6 g) in 50 ml THF. The mixture was heated to reflux on
an oil bath under an argon atmosphere until complete consumption of \( \text{Mg}^0 \). The resulting solution was transferred via cannula into a Schlenk flask and stored under argon. Titration of the resulting solution with 0.5 M isopropanol/benzene with 1,10-phenanthroline gave \( \sim 3.0 \) M solution of \( \text{iPrMgBr} \) in THF. A suspension of \( \alpha \)-hydroxy ester (27.7 mmol, 4.0 g) and N,O-dimethylhydroxylamine hydrochloride (110 mmol, 10.8 g) in 200 ml THF was cooled to -42°C under an argon atmosphere in a 500 ml round bottom flask. A solution of 3.0 M isopropylmagnesium bromide (166.5 mmol, 55.5 ml) was added dropwise over 2 hr. The solution was stirred for 2 hr at -30°C and then allowed to warm to 0°C and stirred for another 2 hr. 100 ml of 1:1 saturated ammonium chloride/EtOAc was added and the solution was warmed to room temperature and stirred vigorously for 1 hr. The solution was further diluted with 100 ml EtOAc and separated. The aqueous layer was extracted 3 times with 100 ml EtOAc. The organic layers were combined and washed with brine then dried over Na\(_2\)SO\(_4\), filtered and concentrated yielding a light yellow oil 1.92 g (43.7 % yield). When the reaction was run using only 1.55 eq. of hydroxylamine and 3.0 eq. of isopropylmagnesium bromide the yield was 54% at twice the scale.

\[
\begin{align*}
\text{N,O-dimethyl 2-hydroxypent-4-enamide (214a):} & \quad ^1\text{H-NMR (300 MHz, CDCl}_3): \quad \delta \enspace 5.82 \\
& \quad (m, 1\text{H}), 5.1 \ (dt, \delta_{JHH} = 17.5 \text{ Hz, 11.19 Hz, 2H}), 4.45 \ (\text{sextet, } \delta_{JHH} = 7.44 \text{ Hz, 1H}), 3.69 \\
& \quad (s, 3\text{H}), 3.28 \ (d, \delta_{JHH} = 8.04 \text{ Hz, 1H}), 3.22 \ (s, 3\text{H}), 2.4 \ (\text{dm, 2H}). \quad ^{13}\text{C-NMR (75 MHz, CDCl}_3): \quad \delta \enspace 32.45, 38.99, 61.39, 68.33, 118.05, 133.26, 174.15.
\end{align*}
\]
2-(tert-butyldimethylsilyloxy)-N-methoxy-N-methylpent-4-enamide (214b): Weinreb amide (1.31 g, 8.22 mmol) and TBSCl (1.5 g, 9.87 mmol) were dissolved in 20 ml CH₃CN and stirred under a nitrogen atmosphere at room temperature. Imidazole (1.4 g, 20.57 mmol) was added and the solution stirred under nitrogen at room temperature for 27 hrs, when TLC analysis showed no SM. The reaction was quenched with the addition of water (34 ml) and then extracted with ether (3 × 50 ml), dried over MgSO₄, and then concentrated to give 2.29 g (quantitative yield) of N,O-dimethyl 2-tertbutylsilyloxy-4-pentenamide which was used without further purification in the following Grignard reaction.

4-penten-1,2-diol (251): Sodium borohydride (NaBH₄) (4 eq., 3.4 g, 91 mmol) was added in one portion to a solution of ethyl 2-hydroxy-4-pentenoate (213) in 60 ml of 1,4-dioxane/EtOH (10:1) at room temperature with stirring. The solution stirred for 17 hrs at room temperature and was then concentrated. MeOH (70 ml) was added slowly with cooling and stirring and the mixture was co-evaporated twice from MeOH. A third portion of MeOH was added followed by ion-exchange resin (Dowex 50WX8, H⁺) until the solution became neutral. The solution was filtered and washed with MeOH (3 × 20 ml), concentrated, taken up in Et₂O/MeOH (1:1), dried over sodium sulfate (Na₂SO₄), filtered through a pad of celite, and concentrated. The resulting translucent light yellow
oil was adsorbed onto SiO₂ (~5 g) and chromatographed (EtOAc) providing 760 mg (32%) of clear slightly yellow oil.
4-penten-1,2-diol (251): $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 5.67 (m, 1H), 4.96 (m, 2H, appears as dddd), 4.36 (br, s, 2H, separates slightly depending on concentration), 3.58 (m, 1H), 3.46 (dd, $^2$J$_{HH}$ = 11.4 Hz (due to tetrahedral angle $\sim$109°), $^3$J$_{HH}$ = 2.76 Hz, 1H)3.28 (dd, $^3$J$_{HH}$ = 11.4 Hz, $^2$J$_{HH}$ = 7.56 Hz, 1H), 2.07 (t, $^3$J$_{HH}$ = 6.8 Hz, 2H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 37.4, 65.6, 71.3, 117.1, 133.9.

1-(trityloxy)pent-4-en-2-ol (217b): 4-penten-1,2-diol (363 mg, 3.5 mmol) and trityl chloride (0.975 mg, 3.5 mmol) in 2 ml DCM were placed in a 10 ml round bottom flask under nitrogen. N,N-dimethylamino pyridine (DMAP) (5mol%, 21 mg) was added followed by triethylamine (1.0 ml, 7.2 mmol). The solution stirred for 22 hrs at room temperature and was then diluted with 20 ml DCM and washed with water and brine (2 × 25 ml each) and dried over Na$_2$SO$_4$. The resulting oil was adsorbed onto 2.5 g SiO$_2$ and chromatographed on silica gel (Hex→20%EtOAc/Hex, 2CV, 5% grad) to afford 704.1 mg (58.7%) of a clear oil ($R_f$ = 0.19 (20%EtOAc/Hex).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 7.49 (d, $^3$J$_{HH}$= 7.98 Hz, 6H), 7.31 (m, 9H), 5.79 (m, 1H), 5.09 (dd, $^3$J$_{HH}$ = 17 Hz, 11 Hz, 3.5 Hz, 2H), 3.88 (bs, 1H), 3.19 (m, 2H), 2.41 (bs, 1H), 2.28 (m, 2H). $^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ 38, 66.9, 70.1, 86.6, 117.5, 126.9, 127.7, 128.6, 134.2, 143.8.
REFERENCES


(189) Baughman, T. W.; Wagener, K. B. In Metathesis Polymerization 2005, p 1-42.


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APPENDIX: SPECTRA

$^1$H, $^{13}$C, COSY, and HSQC Spectra of selected synthetic compounds

Representative $\alpha$-vinyl diazo compound precursors

(E)-methyl 4-phenylbut-3-enoate

![Diagram of (E)-methyl 4-phenylbut-3-enoate]
SpinWorks 2.5: (E)-methyl 4-phenylbut-3-enoate

transmitter freq.: 300.131284 MHz
time domain size: 2048 by 128 points
width: 2427.18 Hz = 8.087076 ppm = 1.185149 Hz/pt
number of scans: 4

F2: freq. of 0 ppm: 300.130048 MHz
processed size: 1024 complex points
window function: Sine
shift: 0.0 degrees

F1: freq. of 0 ppm: 300.130043 MHz
processed size: 1024 complex points
window function: Sine
shift: 0.0 degrees

SpinWorks 2.5: (E)-methyl 4-phenylbut-3-enoate

transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 3

F2: freq. of 0 ppm: 75.467758 MHz
processed size: 32768 complex points
LB: 0.000 GB: 0.0000

file: C:\Documents and Settings\Owner\Desktop\FID\January 2006\Jan24-2006-jason1\32\ser
expt: <cosygpmfqf>

file: C:\Documents and Settings\Owner\Desktop\FID\January 2006\Jan24-2006-jason1\11\fid
expt: <zgpg30>
SpinWorks 2.5: (E)-methyl 4-phenyl-3-butenate.

PPM

133.4998
128.5234
127.5533
126.2906
121.6608
51.8797
38.2097

file: C:\Documents and Settings\Owner\Desktop\FID\May22-2006-jason1\11\fid
expt: <dept135>
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 25

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
α-Vinyl diazo compounds

(E)-ethyl 2-diazo-4-phenylbut-3-enoate (196)
SpinWorks 2.5: (E)-methyl 2-diazo-4-phenylbut-3-enoate

file: C:\Documents and Settings\Owner\Desktop\FID\March 2006\Mar22-2006-jason1\11\fid
expt: zgpg30
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 1024
freq. of 0 ppm: 75.467750 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
Insertion Products: Vinlydiaoester/olefinic alcohol

(E)-methyl 2-(allyloxy)-4-phenylbut-3-enoate (194a)

SpinWorks 2.5:  (E)-methyl 2-(allyloxy)-4-phenylbut-3-enoate
SpinWorks 2.5: (E)-methyl 2-(allyloxy)-4-phenylbut-3-enoate

PPM

171.0463
135.8307
134.2138
133.7224
128.5434
128.1769
126.6653
123.6524
118.0975
78.5903
77.4238
77.0000
76.5761
70.4118
52.2411

file: C:\Documents and Settings\Owner\Desktop\FID\August 2008\Aug25-2008-jason1\11\fid
expt: <zgpg30>
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 12

freq. of 0 ppm: 75.467755 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
(E)-methyl 2-([but-3-enyloxy]-4-phenylbut-3-enoate (194b)

SpinWorks 2.5: (E)-methyl 2-(3-butenyloxy)-4-phenylbut-3-enoate

SpinWorks 2.5: (E)-methyl 2-(3-butenyloxy)-4-phenylbut-3-enoate

SpinWorks 2.5: (E)-methyl 2-(3-butenyloxy)-4-phenylbut-3-enoate

SpinWorks 2.5: (E)-methyl 2-(3-butenyloxy)-4-phenylbut-3-enoate
(E)-methyl 2-(4-pentyloxy)-4-phenylbut-3-enoate (194c)
(E)-methyl 2-(5-hexenyloxy)-4-phenylbut-3-enoate (194d)

\[
\text{MeO} \quad \text{O} \quad \text{O}
\]

SpinWorks 2.5: (E)-methyl 2-(5-hexenyloxy)-4-phenylbut-3-enoate

SpinWorks 2.5: (E)-methyl 2-(5-hexenyloxy)-4-phenylbut-3-enoate
SpinWorks 2.5: (E)-methyl 3-(5-hexenyloxy)-4-phenylbut-3-enoate

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<th>170.0</th>
<th>160.0</th>
<th>150.0</th>
<th>140.0</th>
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<th>50.0</th>
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<td>138.5284</td>
<td>135.8892</td>
<td>133.7958</td>
<td>128.5118</td>
<td>128.0952</td>
<td>126.6417</td>
<td>123.9859</td>
<td>114.5376</td>
<td>79.8141</td>
<td>77.4211</td>
<td>76.9974</td>
<td>76.5734</td>
<td>69.7733</td>
<td>52.1679</td>
<td>33.3849</td>
<td>28.9611</td>
<td>25.2314</td>
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Width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
Number of scans: 12

Freq. of 0 ppm: 75.467757 MHz
Processed size: 32768 complex points
LB: 1.000
GB: 0.0000
(E)-ethyl 2-(5-hexenyloxy)-4-phenylbut-3-enoate (194d)
(E)-methyl 2-(3-methylbut-3-enyloxy)-4-phenylbut-3-enoate (194e)

SpinWorks 2.5: (E)-methyl 2-(3-methylbut-3-enyloxy)-4-phenylbut-3-enoate.

SpinWorks 2.5: (E)-methyl 2-allyl-2-hydroxy-3-oxohex-4-enoate. (Attempted to prepare (E)-methyl...
Representative RCM products: $\alpha$-alkoxy-$\beta\gamma$-unsaturated ester derived unsaturated cyclic ethers

Methyl 2,5-dihydrofuran-2-carboxylate (204a)
Ethyl 5,6-dihydro-2H-pyran-2-carboxylate (204b)

SpinWorks 2.5: Ethyl 5,6-dihydro-2H-pyran-2-carboxylate
Methyl 2,5,6,7-tetrahydrooxepine-2-carboxylate (204c)

SpinWorks 2.5: Methyl 2,5,6,7-tetrahydrooxepine-2-carboxylate

PPM
7.6
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
1.039
1.032
1.000
1.402
4.212
2.146
2.105
7.2400
5.9725
5.9638
5.9543
5.9456
5.9353
5.9267
5.9166
5.9080
5.8990
5.8903
5.7830
5.7780
5.7727
5.7453
5.7403
5.7350
5.7309
4.7530
4.7452
4.7380
4.1838
4.1629
4.1436
4.1235
4.1044
4.0820
4.0583
3.8015
3.7832
3.7660
3.7425
3.7252
3.4869
3.4636
3.4402
3.4169
2.4337
2.4311
2.4285
2.4231
2.4171
2.4122
2.4016
2.3950
2.3761
2.3577
2.3396
2.2869
2.2812
2.2629
2.2436
2.2249
2.2065
2.1871
2.0180
1.8863
1.8665
1.8471
1.8272
1.8083
1.5859
1.2992
1.2772
1.2401
1.2317
1.2082
1.2063
1.1812
1.1578
0.8756
0.8553
0.8320
0.7881

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transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6188.12 Hz = 20.618001 ppm = 0.094423 Hz/pt
number of scans: 1

freq. of 0 ppm: 300.130024 MHz
processed size: 32768 complex points
LB: 0.000 GB: 0.0000
α-diazo-β-ketoesters.

(E)-ethyl 2-diazo-3-oxo-5-phenylpent-4-enoate (187a)
Representative insertion Products: $\alpha$-diazo-$\beta$-ketoester adducts.

(E)-ethyl 2-(but-3-enyloxy)-3-oxohex-4-enoate (202b)

![Chemical Structure](image)
(E)-ethyl 3-oxo-2-(pent-4-enyloxy)hex-4-enoate (202c)
The presence of two stereocenters allow for the formation of diastereomers. It was determined that the resonance for the $\alpha$-CH is buried under the olefinic methylene resonance at 5.1ppm (usual location for this resonance is 4.5-5 ppm). Integration and 2-D correlation spectroscopy corroborate this conclusion.
SpinWorks 2.5: IX-025_Crude reaction mixture (HSQC experiment)

SpinWorks 2.5: IX-025_Crude reaction mixture
Representative RCM products: $\alpha$-alkoxy-$\beta$-keto-$\omega$-unsaturated ester derived unsaturated cyclic ethers.

(Z)-ethyl 3-oxo-2,3,6,7-terahydrooxepine-2-carboxylate (201b)

![Chemical structure of (Z)-ethyl 3-oxo-2,3,6,7-terahydrooxepine-2-carboxylate](image)

SpinWorks 2.5: (Z)-ethyl 3-oxo-2,3,6,7-terahydrooxepine-2-carboxylate
Representative homovinyldiazo precursors.

Methyl pent-4-enoate
Methyl 2-benzoylpent-4-enoate (211a)

SpinWorks 2.5: Methyl 2-benzoylpent-4-enoate (BnCl contaminant)

SpinWorks 2.5: Methyl 2-benzoylpent-4-enoate (BnCl contaminant)
SpinWorks 2.5: VIII-103_F4.1-4.6 (77Reu.SM Methyl 2-benzoylpent-4-enoate)

PPM

194.4402
169.8655
136.0821
134.4146
133.6452
128.8073
128.6473
117.5032
77.5017
77.0780
76.6542
53.6270
52.5195
33.0891

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transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 12

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000
GB: 0.0000
Representative homovinyl diazo compounds.

Methyl 2-diazopent-4-enoate (196b)
(E)-methyl 2-diazo-5-phenylpent-4-enoate (196c)
SpinWorks 2.5: (E)-methyl 2-diazo-5-phenylpent-4-enoate

file: C:\Documents and Settings\Owner\Desktop\FID\May 2008\May28-2008-jason1\12\fid
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time domain size: 65536 points
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number of scans: 12
freq. of 0 ppm: 75.467751 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
Representative O-H insertion with homovinyldiazoester

diethyl 2,2'-oxydipent-4-enoate
Ethyl 2-(1-methoxy-1-oxopent-4-en-2-yl)oxy)pent-4-enoate (205e)

\[
\text{MeO}_2\text{C} \quad \text{O} \quad \text{CO}_2\text{Et}
\]
Methyl 2-(4-(benzyloxy)hept-6-en-3-yloxy)pent-4-enoate

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{OBn} \\
\end{align*}
\]

SpinWorks 2.5: VIII-147_F10-13Rf0.35 (DCM) 'Laurencin intermediate' use of homovinyldiazo

ppm

\[
\begin{array}{c}
\text{transmitter freq.: 300.131853 MHz} \\
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\text{width: 6188.12 Hz = 20.618001 ppm = 0.094423 Hz/pt} \\
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ppm

\[
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\text{LB: 0.000 GB: 0.0000} \\
\end{array}
\]
RCM product derived from homovinyldiazoester 196: α-alkoxy-γ,δ-unsaturated ester
derived unsaturated cyclic ethers

Ethyl 3,6-dihydro-2H-pyran-2-carboxylate (220)
SpinWorks 2.5: ethyl 3,6-dihydro-2H-pyran-2-carboxylate

file: C:\Documents and Settings\Owner\Desktop\FID\February 2008\Feb06-2008-jason1\30\fid
expt: zgpg30
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 25

freq. of 0 ppm: 75.467753 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
Insertion Reactions Efforts in the formal total synthesis of oxepene natural products.

(E)-ethyl 3-oxo-2-((1-(trityloxy)pent-4-en-2-yl)oxy)hex-4-enoate (247b)

\[
\text{EtO}_2\text{C} \quad \text{TrO} \\
\text{O} \\
\text{O} \\
\text{O}
\]

SpinWorks 2.5: (E)-ethyl 3-oxo-2-((1-(trityloxy)pent-4-en-2-yl)oxy)hex-4-enoate

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<th>5.6</th>
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<th>4.8</th>
<th>4.4</th>
<th>4.0</th>
<th>3.6</th>
<th>3.2</th>
<th>2.8</th>
<th>2.4</th>
<th>2.0</th>
<th>1.6</th>
<th>1.2</th>
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<th>0.4</th>
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time domain size: 65536 points
width:  6188.12 Hz = 20.618001 ppm = 0.094423 Hz/pt
number of scans: 1

freq. of 0 ppm: 300.130039 MHz
processed size: 32768 complex points
LB:    0.300    GB: 0.0000
(E)-1,1-bis(1-(trityloxy)pent-4-en-2-yloxy)pent-3-en-2-one (‘double-insertion product) (253)
SpinWorks 2.5: IX-136/146 Rb74(DCM)(E)-1.1-bis(1-ethylxoy)pent-4-en-2-yloxy)pent-3-en-2-one

PPM (F2)

6.8  6.4  6.0  5.6  5.2  4.8  4.4  4.0  3.6  3.2  2.8  2.4  2.0  1.6  1.2  0.8

PPM (F1)

130 120 110 100 90 80 70 60 50 40 30 20 10

file: C:\Documents and Settings\Owner\Desktop\Research items\papers_etc\FID\August 2008\Aug27-2008-jason1\31\ser
expt: <hsqcetgpsi2>

transmitter freq.: 300.131348 MHz
time domain size: 1024  by  256 points
width: 2551.02 Hz = 8.499680 ppm = 2.491231 Hz/pt
number of scans: 2

F2: freq. of 0 ppm: 300.130039 MHz
processed size: 1024 complex points
window function: Sine Squared
shift: 90.0 degrees

F1: freq. of 0 ppm: 75.467749 MHz
processed size: 1024 complex points
window function: Sine Squared
shift: 90.0 degrees
(E)-ethyl 3-oxo-2-(1-(trityloxy)pent4-en-2-yloxy)-5-phenylpent-4-enoate (247a)

SpinWorks 2.5: (E)-ethyl 3-oxo-2-(1-(trityloxy)pent4-en-2-yloxy)-5-phenylpent-4-enoate
(E)-ethyl 2-(5-(benzyloxy)hept-1-en-4-yloxy)-3-oxohex-4-enoate (247c)
(E)-ethyl 2-((tert-butyldimethylsilyloxy)pent-4-en-2-yloxy)-3-oxo-5-phenylpent-4-enoate (256b)
SpinWorks 2.5: IX-152_C1_F10-20_mon/bis insertion

PPM (F2)
-0.8
-0.4
0.0
0.4
0.8
1.2
1.6
2.0
2.4
2.8
3.2
3.6
4.0
4.4
4.8
5.2
5.6
6.0
6.4
6.8
7.2
7.6
8.0

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receiver freq.: 300.130018 MHz
width: 2873.56 Hz = 9.574360 ppm = 1.403107 Hz/pt
number of scans: 1
f1 freq. of 0 ppm: 300.130018 MHz
processed size: 1024 complex points
window function: Sine
shift: 0.0 degrees
F2 freq. of 0 ppm: 300.130018 MHz
processed size: 1024 complex points
window function: Sine
shift: 0.0 degrees
(E)-1,1-bis(1-\((\text{tert}-\text{butyldimethyl}silyloxy)\)pent-4-en-2-yloxy)pent-3-en-2-one ('double-insertion' adduct)
Representative Insertion substrates.

Ethyl α-hydroxypent-4-enoate (213)

![Chemical Structure](image)

SpinWorks 2.5: Ethyl 2-hydroxypent-4-enoate
SpinWorks 2.5: Ethyl 2-hydroxypent-4-enoate

PPM

180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0

174.4106
132.4749
118.6738
77.4287
77.0053
76.5815
69.9243
61.6974
38.6767
14.2096

file: C:\Documents and Settings\Owner\Desktop\FID\June 2008\Jun26-2008-jason1\51\fid
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 12

freq. of 0 ppm: 75.467750 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
Ethyl 2-(tert-butyldimethylsilyloxy)pent-4-enoate (248)

SpinWorks 2.5: Ethyl 2-(tert-butylsilyloxy)pent-4-enoate

PPM

file: C:\Documents and Settings\Owner\Desktop\FID\July 2008\Jul01-2008-jason1\50\fid

expt: zg30

transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6188.12 Hz = 0.094423 Hz/pt
number of scans: 1

freq. of 0 ppm: 300.130012 MHz
processed size: 32768 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: Ethyl 2-(tert-butyldimethylsilyloxy)pent-4-enoate

PPM

file: C:\Documents and Settings\Owner\Desktop\FID\July 2008\Jul01-2008-jason1\40\fid

expt: zg30

transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 0.275098 Hz/pt
number of scans: 12

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
SpinWorks 2.5. Ethyl 2-(tertbutylsilyloxy)pent-4-enoate

File: C:\Documents and Settings\Owner\Desktop\FID\July 2008\Jul01-2008\jason1\51\experiment: <hsqcetgpsi2>

transmitter freq.: 300.130864 MHz

time domain size: 1024 by 256 points

width: 2083.33 Hz = 6.941417 ppm = 2.034505 Hz/pt

number of scans: 2

F2: freq. of 0 ppm: 300.130023 MHz
processed size: 1024 complex points
window function: Sine Squared
shift: 90.0 degrees

F1: freq. of 0 ppm: 75.467749 MHz
processed size: 1024 complex points
window function: Sine Squared
shift: 90.0 degrees
4-penten-1,2-diol (251)

SpinWorks 2.5: pent-4-en-1,2-diol

file: C:\Documents and Settings\Owner\Desktop\FID\August 2008\Aug26-2008-jason1\10\fid
expt: <zg30>
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6188.12 Hz = 20.618001 ppm = 0.094423 Hz/pt
number of scans: 1

SpinWorks 2.5: pent-4-en-1,2-diol

file: C:\Documents and Settings\Owner\Desktop\FID\August 2008\Aug26-2008-jason1\11\ser
expt: <cosygpqf>
transmitter freq.: 300.131053 MHz
time domain size: 2048 by 128 points
width: 1683.50 Hz = 5.609222 ppm = 0.822022 Hz/pt
number of scans: 1

SpinWorks 2.5: pent-4-en-1,2-diol

file: C:\Documents and Settings\Date\Desktop\FID\August2008\Aug26-2008\jason111\ser expt: <cosygpqf>
transmitter freq.: 300.13153 MHz
time domain size: 2048 by 128 points
width: 1683.50 Hz = 5.609222 ppm = 0.822022 Hz/pt
number of scans: 1
1-(trityloxy)-4-penten-2-ol (217b)

![NMR Spectra of 1-(trityloxy)-4-penten-2-ol](image-url)

**SpinWorks 2.5: 1-(trityloxy)-4-penten-2-ol**

- **Transmitter freq.:** 300.131853 MHz
- **Time domain size:** 65536 points
- **Width:** 6188.12 Hz = 20.618001 ppm = 0.094423 Hz/pt
- **Number of scans:** 1
- **Freq. of 0 ppm:** 300.130024 MHz
- **Processed size:** 32768 complex points
- **LB:** 0.300
- **GB:** 0.0000

---

**SpinWorks 2.5: 1-(trityloxy)-4-penten-2-ol**

- **Transmitter freq.:** 75.475295 MHz
- **Time domain size:** 65536 points
- **Width:** 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
- **Number of scans:** 12
- **Freq. of 0 ppm:** 75.467750 MHz
- **Processed size:** 32768 complex points
- **LB:** 1.000
- **GB:** 0.0000
1-(tertbutylsilyloxy)pent-4-en-2-ol (217c)

SpinWorks 2.5: 1-(tertbutylsilyloxy)pent-4-en-2-ol

PPM

0.0  2.0  4.0  6.0  8.0  10.0  12.0  14.0

14.0 12.0 10.0 8.0 6.0 4.0 2.0 0.0

1.000 1.999 1.021 1.003 1.006 0.954 2.006 9.354

7.2400 5.8870 5.8634 5.8530 5.8398 5.8297

5.8063 5.7961 5.7828 5.7725 5.7489

5.1296 5.1246 5.1186 5.1136 5.0836

5.0802 5.0770 5.0732 5.0676 5.0614

5.0557 5.0497 5.0464

3.7304 3.7178 3.7083 3.6961 3.6847

3.6740 3.6615 3.6527 3.6401 3.6278

3.6154 3.5948 3.5825 3.4622 3.4391

3.4292 3.4061 2.3904 2.3775 2.2369

2.2146 2.1923 0.8906 0.8822 0.8731

0.8156 0.0734 0.0691 0.0612 0.0512

0.0419

file: C:\Documents and Settings\Owner\Desktop\FID\August 2008\Aug29-2008-jason1\41\fid
expt: zg30
transmitter freq.: 300.131853 MHz
time domain size: 65536 points
width: 6188.12 Hz = 20.618001 ppm = 0.094423 Hz/pt
number of scans: 1

freq. of 0 ppm: 300.130013 MHz
processed size: 32768 complex points
LB: 0.300 GB: 0.0000

file: C:\Documents and Settings\Owner\Desktop\FID\August 2008\Aug29-2008-jason1\40\fid
expt: zgpg30
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 12

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
2-hydroxy-N-methoxy-N-methylpent-4-enamide (214)

SpinWorks 2.5: VIII_101_Kugelrhordistillate_50-60C_2-hydroxy-N-methoxy-N-methylpent-4-enamide

SpinWorks 2.5: VIII-101_kugdistillate_2-hydroxy-N-methoxy-N-methylpent-4-enamide

SpinWorks 2.5: VIII-101_kugdistillate_2-hydroxy-N-methoxy-N-methylpent-4-enamide
SpinWorks 2.5: VIII-101_kugdist_2-hydroxy-N-methoxy-N-methylpent-4-enamide

PPM

200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0

133.2683
77.4737
77.0502
76.6276
68.3214
61.3832
38.9742

file: C:\Documents and Settings\Owner\Desktop\FID\January 2008\Jan18-2008-jason1\20\fid
expt: zgpg30
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 12

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000 GB: 0.0000
N-methoxy-N-methyl-2-(tetrahydro-2H-pyran-2-yloxy)pent-4-enamide (214d)
2-(benzyloxy)-N-methoxy-N-methylpent-4-enamide (214c)

SpinWorks 2.5: VIII-117_2-(benzyloxy)-N-methoxy-N-methylpent-4-enamide

File: C:\Documents and Settings\Owner\Desktop\FID\February 2008\Feb12-2008-jason1\40\fid
Experiment: <zg30>
Transmitter freq.: 300.131853 MHz
Time domain size: 65536 points
Width: 6188.12 Hz = 20.618001 ppm = 0.094423 Hz/pt
Number of scans: 16
Freq. of 0 ppm: 300.130003 MHz
Processed size: 32768 complex points
LB: 0.300 GB: 0.0000

SpinWorks 2.5: VIII-117_2-(benzyloxy)-N-methoxy-N-methylpent-4-enamide

File: C:\Documents and Settings\Owner\Desktop\FID\February 2008\Feb12-2008-jason1\41\ser
Experiment: <cosygpqf>
Transmitter freq.: 300.131291 MHz
Time domain size: 2048 by 128 points
Width: 2358.49 Hz = 7.858196 ppm = 1.151607 Hz/pt
Number of scans: 1
F2: Freq. of 0 ppm: 300.130000 MHz
Processed size: 1024 complex points
Window function: Sine
Shift: 0.0 degrees
F1: Freq. of 0 ppm: 300.130000 MHz
Processed size: 1024 complex points
Window function: Sine
Shift: 0.0 degrees
SpinWorks 2.5: V8-117_2-benzoyl-4-methoxy-4-methylpent-4-enamide

PPM

180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0

137.6788
133.7089
128.2689
127.8897
127.6742
117.5101
77.4207
76.9967
76.5730
71.3185
61.2458
36.6701

file: C:\Documents and Settings\Owner\Desktop\FID\February 2008\Feb13-2008-jason1\31\fid
expt: zgpg30
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 25

freq. of 0 ppm: 75.467754 MHz
processed size: 32768 complex points
LB: 1.000
GB: 0.0000
4-(benzyloxy)hept-6-en-3-one (248a)

SpinWorks 2.5: VIII-125_4-(benzyloxy)hept-6-en-3-one

SpinWorks 2.5: VIII-125_4-(benzyloxy)hept-6-en-3-one
SpinWorks 2.5: VIII-125, 4-benzoylhept-6-en-3-one

<table>
<thead>
<tr>
<th>PPM</th>
<th>200.0</th>
<th>180.0</th>
<th>160.0</th>
<th>140.0</th>
<th>120.0</th>
<th>100.0</th>
<th>80.0</th>
<th>60.0</th>
<th>40.0</th>
<th>20.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>212.8403</td>
<td>137.5118</td>
<td>133.1062</td>
<td>128.4837</td>
<td>127.9323</td>
<td>127.8081</td>
<td>117.9809</td>
<td>84.2680</td>
<td>77.4666</td>
<td>77.0433</td>
<td>76.6198</td>
</tr>
</tbody>
</table>

file: C:\Documents and Settings\Owner\Desktop\FID\February 2008\Feb14-2008-jason1\42\fid
expt: <zgpg30>
transmitter freq.: 75.475295 MHz
time domain size: 65536 points
width: 18028.85 Hz = 238.870826 ppm = 0.275098 Hz/pt
number of scans: 25

freq. of 0 ppm: 75.467749 MHz
processed size: 32768 complex points
LB: 1.000    GB: 0.0000
4-(benzyloxy)hept-6-en-1-ol (215)

SpinWorks 2.5: VIII-126_4-(benzyloxy)hept-6-en-3-ol (diast)

SpinWorks 2.5: VIII-126_4-(benzyloxy)hept-6-en-3-ol (diast)
3-(tetrahydro-2H-pyran-2-yloxy)hex-5-en-2-one (248c)
3-(tetrahydro-2H-pyran-2-yloxy)hex-5-en-2-ol (215c)
1-(benzyloxy)pent-4-en-2-ol (217a)
(+/-)-Rogioloxepane and (+/-)-Isolaurepinnacin formal synthesis targets.

(Z)-ethyl 7-((tert-butyldimethylsilyloxy)methyl)-3-oxo-2,3,6,7-tetrahydrooxepine-2-carboxylate (246)
(Z)-7-((tert-butyldimethylsilyloxy)methyl)-6,7-dihydrooxepin-3(2H)-one (257)