ABSTRACT

SCOPE, MECHANISM, AND APPLICATION OF A RHODIUM CARBENOID-INITIATED CLAISEN REARRANGEMENT

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2001

During the course of a total synthesis effort, it was discovered that α-diazoketone-derived rhodium (II) carbenoids react with enantiomerically enriched allylic alcohols to furnish tertiary α-hydroxyketones with excellent chirality transfer. Described herein are investigations into the scope and mechanism of this novel process as well as its application to the total synthesis of the anti-tumor agent (±)-hydroxymethylacylfulvene (269).

Investigations into the scope and limitations of this reaction have revealed a high degree of generality with regard to both α-diazoketone and allylic alcohol, enabling the synthesis of a wide variety of enantiomerically enriched tertiary homoallylic α-hydroxy carbonyl compounds (e.g., 104a-g, 111a-f, 117a-f, 121a-f, 127a-f, and 131a-c).

Mechanistically, it has been demonstrated that α-diazoketones and allylic alcohols combine under rhodium (II) catalysis to initially furnish α-allyloxyenols (e.g., 143), which subsequently undergo thermal [3,3]-rearrangement at a rate highly influenced by enol substituents. If desired, α-allyloxyenols may also be intercepted prior to rearrangement and converted to several useful derivatives (e.g., 105c and 154).

Extending the reaction scope to propargylic alcohols revealed that the derived α-propargyloxy enols (e.g., 229) are also capable of undergoing a rhodium (II)-catalyzed [2,3]-rearrangement in competition with Claisen rearrangement. Proper catalyst selection enables control over which rearrangement pathway operates. In addition, [2,3]-rearrangement may be promoted by other Lewis acids including the asymmetric Lewis acid [Cu-(S,S)-Ph-pybox(H2O)2](OTf)2 (254), which furnishes allenic α-hydroxyketone 231 in 90% ee.
SCOPE, MECHANISM, AND APPLICATION OF A RHODIUM CARBENOID-INITIATED CLAISEN REARRANGEMENT

A Dissertation
Presented to the Faculty of the Graduate School
of
Yale University
in Candidacy for the Degree of
Doctor of Philosophy

by
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Dissertation Director: Professor John Louis Wood

December 2001
To My Family
ACKNOWLEDGMENTS

Finally, a chance to write in the active voice! I didn’t realize at the outset what a tremendous undertaking the writing of a Ph.D. dissertation would be. To summarize the last five years of one’s life in a single document in a clear and concise manner is certainly not easy. Then, just when you think you’re all done, you have to write this little section, which I think is nearly as difficult to write as the other 400 or so pages because you have to summarize the more personal aspects of the past five years, the people who’ve helped you, and their significance to you, in only a few pages. That’s a lot of information to squeeze into such a small section…so I used 1½-spaced instead of double-spaced type.

First of all, I would like to thank my advisor, Professor John L. Wood for giving me the opportunity to work in his group and for giving me my summer project. Isn’t there a book called “Endless Summer”? Seriously, I want to thank John for all of his support, both intellectual and financial, and for his guidance around the pitfalls that sometimes appear during long-term projects. Even in times of slow progress and confusing observations, John always trusted me and gave me license to work things out, and for that I am very grateful.

I would also like to thank the members of my dissertation committee, Professor Frederick E. Ziegler and Professor David J. Austin, for their time and suggestions and for their letters of support. Extra thanks are owed to Professor Ziegler for helping me choose Yale. It’s a decision I have never regretted.

There are three people to whom I owe more than I can possibly repay in a lifetime. Fortunately, though, I don’t think they’ve been keeping a tab. They are my parents, George and Evelyn, and my brother Daniel. They are my greatest advisors, confidants, and supporters. I can ask their advice and know that the action they recommend is the correct course of action without a shred of doubt. In times of uncertainty, their love and guidance always steered me in the right direction. To Dora, thank you for all of your love and support. Everything is much easier with you in my corner.

Thanks to my professors at UMass-Dartmouth for rigorously preparing me for the future, especially Professors Gerald B. Hammond, Michelle Mandrioli, Alan Bates, Donald Boerth, Ralph Tykodi, Timothy Su, Russell Bessette, and Joseph Deck. You
were tough, but I realize now that you had to be. I am especially grateful to Professor Gerald B. Hammond for introducing me to the world of independent research and for treating me like any other graduate student in his group. Your mentorship made the transition to graduate-level work much less turbulent for me. Thank you to Professor Chang-Ning Wu for encouraging me to be open-minded when it came to the idea of graduate school.

I must thank the members of the Wood group, past and present, for creating such a wonderful environment in which to learn and work. It has been a pleasure and a privilege to work alongside all of you. To Brian Stoltz and Derek Pflum, thank you for starting me off on the right foot at Yale. Derek, your efforts and observations gave birth to this project and laid a solid foundation on which to build. To Dejah Petsch, thank you for always encouraging me and for your remarkable hawk-like vision when it came to proofreading. To Alexandra Holubec, thank you for group T-shirts, group birthdays, group lunches, group custom music mix CD’s, and for somehow finding a way to make a party out of even the most mundane of tasks. To Stuart Chaffee, my friend and classmate, I never told you this, but I was glad that you picked a bench next to me in the new lab because I thought it would be cool to work next to you. It really has been a great time. Thanks for not letting up until I finally pulled my nose out of the books a bit. I’ll always remember the trip to Mohegan Sun (“You gotta win big or lose it all, buddy!”), Monday-night bowling with Doan, Lasagna Chaffee-style, and cruising in the mack daddy caddy. I’ll always treasure my souvenir from the Dresden Room. Thanks to Jon Njardarson for being a supercharged idea machine and for always putting strange results in a positive light and to Mauricio Navarro Villalobos for being a friend and adopted cousin. Thanks to Brian Thompson and Jens Graeber for being such entertaining lab partners, Brian for being my impersonation cohort and Jens for being so damn German. Special thanks go to Jens for enhancing my work ethic by making me afraid to take vacations. The amount of design and engineering that you put into your practical jokes is truly staggering. I can only aspire to your level. Thanks so much to Dave Spiegel (Mazeltov!) and Doug (D.T.P.) Fuerst for proofreading this thesis and providing numerous corrections and suggestions that have significantly improved its quality. Thanks also for all the brainstorming on HMAF. Thank you to Kazuhiko Tamaki and
Matt Weiss for all their assistance with reagents, conditions, and ideas. To the remainder of the crew: Ryan, Pete, Ivar, Munenori, Ioana, The Wayne, Brad, Roger, Gregg, and Andy: thanks for making the lab such a great place to spend time.

As for non-Wood group personnel, thank you to the Ziegler group (a.k.a. Martha Sarpong) for the occasional chemical and for always being so upbeat. Thanks to Bessie Wiggins for keeping the lab as healthy a place to work as possible and for always providing cheerful conversation. I’m going to miss that familiar “Hi, George” in the morning. Thanks to Dan Webster for his Herculean efforts to keep Sterling Chemistry Laboratory alive. He’s on the job every day and we’re all pretty happy about that. I would also like to acknowledge Dr. Ben Bangerter and Susan DeGala for their assistance in obtaining NMR’s and X-Ray crystal structures, respectively. Finally, to the rest of my friends at Yale, thanks so much for making these past five years so enjoyable and memorable. I wish all of you the best of everything in the future.

New Haven, Connecticut
July 2001

George A. Moniz
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\alpha]_D^{20}$</td>
<td>specific rotation at 20ºC and 589 nm</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl, acetate</td>
</tr>
<tr>
<td>aq.</td>
<td>aqueous</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>$n$-Bu</td>
<td>$n$-butyl</td>
</tr>
<tr>
<td>$t$-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>but</td>
<td>butanoate</td>
</tr>
<tr>
<td>BuLi</td>
<td>butyl lithium</td>
</tr>
<tr>
<td>calc’d</td>
<td>calculated</td>
</tr>
<tr>
<td>cap</td>
<td>caprolactamate</td>
</tr>
<tr>
<td>cat.</td>
<td>catalytic amount</td>
</tr>
<tr>
<td>c</td>
<td>concentration in g/100 mL</td>
</tr>
<tr>
<td>Cl</td>
<td>chemical ionization</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-benzoquinone</td>
</tr>
<tr>
<td>dec.</td>
<td>decomposition</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>$N,N$-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>$N,N$-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et$_2$O</td>
<td>diethyl ether</td>
</tr>
</tbody>
</table>
EtOAc  ethyl acetate
FAB  fast atom bombardment
h  hour
HPLC  high performance liquid chromatography
HRMS  high resolution mass spectrometry
hv  light
Hz  hertz
IR  infrared (spectrum)
J  coupling constant
k  rate constant
KHMDS  potassium hexamethyldisilazide
LDA  lithium diisopropylamide
m  multiplet or medium
M  mass or metal
m-CPBA  m-chloroperoxybenzoic acid
MDR  multiple drug resistance
min  minutes
mmHg  millimeters of mercury
mmol  millimole
mol  mole
mol%  mole percent
mp  melting point
NMR  nuclear magnetic resonance
OAc  acetate
OTFA  trifluoroacetate
oct  octanoate
p-ABSA  p-acetamidobenzenesulfonyl azide
pfb  perfluorobutyrate
pfm  perfluorobutyramide
Ph  phenyl
PhH  benzene
p-NBSA  p-nitrobenzenesulfonyl azide
PPh₃  triphenylphosphine
ppm  parts per million
p-TSA  p-toluenesulfonic acid
py  pyridine
rt  room temperature
s  singlet, strong, or second
sec  seconds
 t  triplet
t₁/₂  half life
T  temperature
TBS  tert-butyldimethylsilyl
tfa  trifluoroacetate
THF  tetrahydrofuran
TLC  thin layer chromatography
TMS  trimethylsilyl
tpa  triphenylacetate
TsOH  p-toluenesulfonic acid
w  weak
Δ  heat at reflux
ΔH‡  enthalpy of activation
ΔS‡  entropy of activation
1.1 Tertiary Alcohols: Significance

1.1.1 Tertiary Alcohols in Natural Products

The tertiary alcohol moiety is found in numerous biologically active and structurally intriguing natural products including trichodimerol (BMS-182123, 1, Figure 1.1),\(^1\) the farnesyl transferase-inhibitor zaragozic acid A (2, Figure 1),\(^2\) the protein-kinase C-inhibitor K252a (3),\(^3\) and anti-tumor compounds fostriecin (4),\(^4\) camptothecin (5),\(^5\) illudin M (6)\(^6\) and illudin S (7).\(^7\) In addition, numerous natural products contain ether moieties that can be accessed from a tertiary alcohol precursor. Such compounds include the antibiotic pentalenolactone (8)\(^8\) and the phospholipase-C inhibitor hispidospermidin (9).\(^9\)
1.2 Methods for the Asymmetric Preparation of Tertiary Alcohols

1.2.1 Overview of Established Methodologies

Despite the prevalence of tertiary alcohols in numerous medicinally relevant natural products, few methods exist for the enantioselective introduction of the tertiary
alcohol moiety into a molecular framework. Current methodologies can be broadly classified into two categories: (1) Ring-opening of enantiomerically enriched epoxides and, (2) Asymmetric nucleophilic addition to ketones. A more elaborate description of both categories follows.

1.2.2 Ring-Opening of Enantiomerically Enriched Epoxides.

While epoxide ring-opening is intuitively a very attractive approach to asymmetric tertiary alcohols, few general methodologies have been reported based on this disconnection. In 1993, Itoh et al. reported the development of phenyl glycidyl sulfide (R)-10 as a chiral building block for preparing a variety of substituted tertiary alcohols (Scheme 1.1).10 The ingenuity of this approach rested in the ability of this epoxy thioether to function as a bis-electrophile. Thus, either enantiomer of a given tertiary alcohol could, in principle, be synthesized without preparing the enantiomeric epoxide. For example, treatment of (R)-10 with the Grignard reagent derived from p-bromoanisole afforded the intermediate phenylthio-substituted tertiary alcohol 11 (Scheme 1.1). This intermediate then underwent ring-closure to generate a second epoxide (12), which was then opened with iso-propyl magnesium bromide to furnish tertiary alcohol (R)-13. Reversing the order of Grignard addition would presumably generate the enantiomeric species (S)-13. This was not attempted, however, nor were other investigations into reaction generality. An additional drawback to this approach was that (R)-10 could be prepared in a maximum of 86% ee.
Scheme 1.1

A related approach was reported by Stoodley et al. in 1997, wherein vinylogous esters such as 14 bearing a chiral auxiliary were first epoxidized using DMDO, then subjected to methanolysis conditions to furnish the ring-opened tertiary $\alpha$-hydroxyacetal 16 in high enantiomeric excess following recrystallization (Scheme 1.2).\textsuperscript{11}

Scheme 1.2

Also in 1997, Salazar et al. reported a ring-opening/elimination process to furnish tertiary allylic alcohols (Scheme 1.3).\textsuperscript{12} Epoxide 17, prepared via Sharpless asymmetric epoxidation of geraniol, was treated with iodine and triphenylphosphine in the presence of imidazole to furnish allylic alcohol 19 in 77% yield and 95% ee. However, with other epoxides, polyiodinated by-products were co-produced thus severely limiting the utility of this method. The reaction was postulated to proceed via intermediate 18.
1.2.3 Nucleophilic Addition to Ketones

1.2.3.1 Overview

The addition of nucleophiles to ketones represents another, more extensively investigated approach for the asymmetric synthesis of tertiary alcohols. Reports to date encompass both auxiliary-based methods wherein the ketone already contains resident chirality as well as additions to prochiral ketones in the presence of chiral Lewis acids and ligands.

1.2.3.2 Auxiliary-Based Approaches to Asymmetric Tertiary Alcohol Synthesis

In an early contribution, Soai and Ishizaki reported diastereoselective additions of allylsilanes to α-ketoamides (e.g., 20, Scheme 1.4) derived from (S)-proline methyl ester under Lewis-acid catalyzed conditions. Importantly, following chromatographic separation, the diastereomeric α-hydroxyamide addition products (e.g., 21) could be easily converted to the corresponding enantioenriched methyl ketones (e.g., 22).
This report was shortly followed by others describing related chiral auxiliaries, such as the (S)-indoline-derived α-ketoamides (e.g., 23, Scheme 1.5) developed by Kim and coworkers, which afforded slightly improved diastereoselectivities. Separation of the diastereomeric addition products (e.g., 24) was followed by acidic hydrolysis to furnish the corresponding α-hydroxyacids (e.g., (R)-(25)) in excellent enantiomeric excess.

Scheme 1.5

A further variation on this strategy was reported in 1991 by Fujisawa, who employed (S)-prolinol to prepare single diastereomeric α-ketoaminals (e.g., 26, Scheme 1.6), which exhibited excellent diastereofacial selectivity in the addition of Grignard reagents to furnish tertiary α-hydroxyaldehydes (e.g., (S)-28) upon hydrolysis of the intermediate hydroxyaminals (e.g., 27).15

Scheme 1.6

Several non-amino acid-derived chiral auxiliaries have also been reported. In 1994, Ozaki et al. reported highly diastereoselective Mukaiyama aldol additions to α-ketoesters such as 29 as part of an ongoing investigation of L-quebrachitol-derived chiral
auxiliaries (Scheme 1.7). Saponification of the intermediate \( \alpha \)-hydroxyester (e.g., 30) followed by methylation furnished enantioenriched citramalic acid derivatives (e.g., (R)-31).

**Scheme 1.7**

![Scheme 1.7](image)

Ley and Cox have reported diastereoselective additions to \( \pi \)-allyltricarbonyliron lactone complexes (e.g., 32), which generate tertiary dienols (e.g., (R)-34) following a two-step hydrolysis protocol (Scheme 1.8). Finally, in a highly interesting 1995 report, Tietze expanded the technology of auxiliary-based approaches, reporting very good diastereoselectivities in allylsilane additions to ketones in the presence of neopseudoephedrin ligand 36 (Scheme 1.9). This ligand precomplexes with the ketone (e.g., 35) forming oxazolidinium ion 37 which is subsequently attacked by the nucleophile in an \( S_N2 \) sense to furnish adduct 38. Cleavage of the pendant amide can be achieved under dissolving metal conditions to furnish tertiary homoallylic alcohols (e.g., 39).
Despite the excellent diastereoselectivities attainable, each of the above methodologies suffers from the same fundamental drawback of all auxiliary-based asymmetric methods, that is, the need to install and subsequently remove the chiral controller. The recognition of this shortcoming has led to the development of catalytic asymmetric methods for the synthesis of tertiary alcohols.

1.2.3.3 Catalytic Asymmetric Methodologies for Tertiary Alcohol Synthesis

The first milestone accomplishment in non-auxiliary-based asymmetric tertiary alcohol preparation was made by Seebach who, in 1992, reported high enantioselectivities in Grignard additions to prochiral ketones in the presence of TADDOL (α,α,α’,α’-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol, 41, Scheme 1.10). Unfortunately, while highly enantioselective with aromatic ketones (e.g., 40), this reaction afforded only modest levels of enantioselectivity with aliphatic ketones. An additional drawback was the requirement that a stoichiometric amount of the TADDOL ligand be employed. Nevertheless, this result marked the beginning of an evolution from auxiliaries to asymmetric ligands as the chiral control element in tertiary alcohol synthesis.
To date, the most significant advances in catalytic asymmetric tertiary alcohol synthesis have been those of Evans and coworkers, who have employed $C_2$-symmetric, bidentate bis(oxazolinyl) (box) and tridentate bis(oxazolinyl) pyridine (pybox) ligands to promote a variety of Lewis acid-catalyzed additions to pyruvate esters with excellent enantioselectivities.20 These transformations represent the state-of-the-art in asymmetric tertiary alcohol preparation, offering enantioselectivities equal or superior to those obtainable via chiral auxiliary-based approaches (See Schemes 1.4-1.9). Examples of these methodologies are presented in Scheme 1.11.

In 1997, Evans first reported an exceptionally general method for syn-aldol addition of silylketene acetals (e.g., 44) to methyl pyruvate (43), employing low catalyst loadings of the Lewis acid $[\text{Cu}((S,S)-t-$Bu-box])$(\text{OTf})_2$ (45, Scheme 1.11).21 This reaction generated ($S$)-tertiary $\alpha$-hydroxyesters (e.g., (S)-46) with remarkable diastereo- and enantioselectivity and in excellent yield via an exceedingly simple experimental procedure. Evans later expanded the scope of this methodology, demonstrating that the corresponding anti-aldol transformation could be accomplished by simply switching to the $[\text{Sn}((S,S)-\text{Ph-pybox})]$(OTf)$_2$ catalyst (47).22 With equivalent catalyst loadings, this Lewis acid complex affords the corresponding ($R$)-tertiary $\alpha$-hydroxyester (e.g., ($R$)-48) in equivalent yield and diastereomeric/enantiomeric excess.
In 2000, Evans moved beyond aldol addition chemistry, reporting the enantioselective copper-catalyzed carbonyl-ene reaction between methyl pyruvate (43) and olefins (e.g., 49). Amazingly, to achieve this remarkable transformation requires only that the experimentalist add the [Cu((S,S)-t-Bu-box)](SbF₆)₂ catalyst system (50) to a solution of olefin and methyl pyruvate in dichloromethane at 40°C. The (S)-α-hydroxyester (e.g., (S)-51) is isolated 48 hours later by chromatography in 98% ee.

Critical to the enantioselectivity of these reactions is the use of methyl pyruvate (43), since this substrate is capable of two-point chelation to the Cu(II)box/pybox or Sn(II)pybox catalyst. This results in a rigid catalyst-substrate complex that enables
excellent \( \pi \)-facial discrimination in the addition step. A combination of X-Ray crystallographic analysis and molecular mechanics calculations have revealed that these complexes assume a distorted square planar configuration in the case of the \([\text{Cu}(\text{S},\text{S}-t\text{-Bu-box})]\)-pyruvate species (52, Figure 1.2) and a square-pyramidyl configuration (53) when 43 is bound to \([\text{Cu}((\text{S},\text{S})-t\text{-Bu-pybox})]\).24 Nucleophilic attack in both complexes occurs from the more accessible ketone \( si \) face. No stereochemical model has yet been proposed for the \([\text{Sn}((\text{S},\text{S})-\text{Ph-pybox})](\text{OTf})_2\)-catalyzed aldol process.

**Figure 1.2** - Geometry of Pyruvate-[Cu(S,S)-t-Bu-box] and Pyruvate--[Cu(S,S)-t-Bu-pybox] Complexes.

1.3 A Novel Approach to Asymmetric Tertiary Alcohol Synthesis: The Rhodium Carbenoid-Initiated Claisen Rearrangement.

1.3.1 The Total Synthesis of the K252a Furanose: An Intriguing Observation

In 1995, a total synthesis of (+)-K252a (3) was accomplished in our laboratories wherein key intermediate 54 derives from acetoacetate derivative 55.25 In planning the synthesis of 55, several available methods for the asymmetric synthesis of \( \alpha \)-hydroxy carbonyl compounds were considered and eventually a sigmatropic rearrangement
approach was selected. This approach called for the preparation of \( \alpha \)-allyloxy-\( \beta \)-ketoester \( \textbf{58} \) (Scheme 1), a substrate believed to be accessible via rhodium-mediated O-H insertion chemistry employing \( \alpha \)-diazo-\( \beta \)-ketoester \( \textbf{59} \) and allylic alcohol \((S)\)-(+)\( \textbf{60}\).26 The primary concern in advancing \( \textbf{58} \) via [3,3]-rearrangement was the ability of either

**Scheme 1.12**

E-enol(ate) \[
\begin{array}{c}
\text{retro} \\
\text{[3,3]} \end{array}
\]

\[
\textbf{57}, \ X = \text{H or Metal}
\]

\[
\begin{array}{c}
\text{retro} \\
\text{[1,2]} \end{array}
\]

\[
\textbf{58}
\]

\[
\textbf{55}
\]

\[
\textbf{54}
\]

hydrogen bonding (if done thermally, \( X = \text{H, } \textbf{57}, \text{ Scheme 1.12} \)) or chelation (if promoted by base, \( X = \text{M} \)) to effect stereocontrol by stabilizing the \((E)\)-enol(ate) transition structure. Although base-promoted reactions would likely provide a greater degree of geometric control, either scenario was expected to convert an \((S)\)-allylic alcohol-derived OH-insertion product (e.g., \( \textbf{58} \)) to \((S)\)-\( \textbf{56}\). A [1,2]-migration of the allyl moiety would then furnish \( \textbf{55} \). In anticipation of isolating \( \alpha \)-allyloxy ester \( \textbf{58} \), methyl diazoacetoacetate \( \textbf{59} \) was subjected to rhodium (II) acetate-catalyzed decomposition in the presence of \((S)\)-(+) \( \textbf{3}-\text{buten-2-ol} \ (\textbf{60}, \ 98\% \text{ ee}) \) revealing that these substrates instead combined to
form (R)-56 (66% isolated yield, 95% ee) in what appeared to be an extraordinarily stereoselective tandem OH-insertion/[3,3] rearrangement process (Scheme 1.13).

**Scheme 1.13**

![Scheme 1.13 Diagram]

Having obtained neither of the anticipated products (58 or (S)-56), the initially accepted mechanism involving the intermediacy of a discrete OH-insertion product became questionable. In its place, an anion-accelerated mechanism, wherein an intermediate (Z)-rhodium enolate (i.e., 61) would account for both the observed reactivity and sense of chirality transfer, began to be considered.

### 1.3.2 Evidence Against an Initial OH-Insertion Step

With the hope of obtaining further evidence to either confirm or refute the intermediacy of α-allyoxy-β-ketoester 58, the independent synthesis of this species was undertaken and its reactivity investigated directly (Scheme 1.14). Exposure of 59 to
TBSOTf and Et₃N produced a diazo substrate 62 which combined with (S)-(+)−60 (98% ee) in the presence of Rh₂(OAc)₄ to cleanly generate a mixture of diastereomeric OH-insertion products 63. Deprotection furnished suspected intermediate 58. Interestingly, when exposed to reaction conditions that had previously furnished the Claisen product (R)-56 (benzene at reflux for 20 min, Scheme 1.13), 58 produced only a trace of 56. When the reaction time was increased to 18h, the Claisen product could be isolated in significant quantity, however, under these conditions chirality transfer was diminished and the opposite (previously expected) enantiomer [(S)-(−)-56] predominated (75% yield, 60% ee). These results clearly suggested that the rhodium-initiated reaction proceeded via a unique pathway that afforded greater stereocontrol than the corresponding thermal rearrangement. A more detailed investigation of this process was therefore warranted and efforts commenced with a thorough literature search both to confirm the novelty of this process and to gain knowledge about related transformations.

1.3.3. Claisen Rearrangement of 2-Heterosubstituted Allyl Enol Ethers

At the outset of these investigations, a survey of the pertinent literature revealed few examples of similar 1-heteroatom-substituted allyl enol ether [3,3]-rearrangements
(Scheme 1.15). The most relevant studies with regard to the newly discovered rhodium carbenoid-initiated process were those of Koreeda and co-workers, who demonstrated that the potassium enolate (65) of α-allyloxyketone 64 underwent very facile [3,3] rearrangement at -23°C to furnish the corresponding tertiary α-hydroxyketone 66.²⁸

Scheme 1.15

**Koreeda**

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\overset{\text{O}}{\text{O}} & \quad \overset{\text{Me}}{\text{O}} \\
\overset{\text{KH}}{\text{THF, -23°C}} & \quad \overset{\text{1) [3,3]} \text{H}^+}{\text{Me}} \\
\overset{\text{2)} \text{H}^+}{\text{Ph}} & \quad \overset{\text{O}}{\text{Me}} \\
\text{64} & \quad \text{65} & \quad \text{66}
\end{align*}
\]

**Salomon**

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\overset{\text{O}}{\text{O}} & \quad \overset{\text{Me}}{\text{O}} \\
\overset{\text{TMSCl, Et₃N}}{\text{DMF, ∆}} & \quad \overset{\text{[3,3]} \text{MeSiO}}{\text{Me}} \\
\overset{\text{Me}}{\text{Ph}} & \quad \overset{\text{O}}{\text{Me}} \\
\text{67} & \quad \text{68} & \quad \text{69} & \quad \text{70}
\end{align*}
\]

**Barluenga**

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\overset{\text{N}}{\text{O}} & \quad \overset{\text{Me}}{\text{Me}} \\
\overset{\text{Neat \ 40°C}}{\null} & \quad \overset{\text{Me}}{\text{N}} \\
\text{71} & \quad \text{72}
\end{align*}
\]

Eight years prior to Koreeda’s report, Kachinski and Salomon had reported a similar process wherein α-allyloxy acetophenones (e.g., 67, Scheme 1.15) were converted to the corresponding trimethylsilyl enol ethers (e.g., 68) which underwent in situ rearrangement to the protected α-hydroxyketones (e.g., 69).²⁹ However, unlike Koreeda’s studies, 69 was treated by Salomon only as a transient intermediate en route to allyl ketones (e.g., 70), which were prepared by oxidative cleavage of 69. Barluenga et al. reported rearrangements of 1-amino-substituted allyl enol ethers (e.g., 71), which also proceeded rapidly under very mild conditions to furnish tertiary α-aminoaldehydes (e.g.,
Importantly, the extremely facile conditions reported for these [3,3] rearrangements lent credence to the concept that the rhodium-initiated rearrangement proceeded via a similarly accelerated 1-substituted allyl enolate such as 61 (Scheme 1.13).

**1.3.4 [3,3]- Versus [2,3]-Rearrangement In Enolates of α-Allyloxy Carbonyl Compounds**

It is important to stress at this stage that enolates of α-allyloxy carbonyl compounds are not always straightforward in their reactivity. In many instances, the [2,3] mode of rearrangement is highly competitive with [3,3]-rearrangement or even the dominant pathway. This is especially true with enolates of α-allyloxyesters or acids, which undergo [2,3]-rearrangement exclusively. For example, Nakai and coworkers showed that treatment of acid 73 with two equivalents of LDA generates dianion 74, which undergoes exclusive [2,3]-rearrangement to furnish α-hydroxyacid 75 (Scheme 1.16).31

**Scheme 1.16**

![Scheme 1.16](image-url)

Similarly, treatment of α-trimethylsilyl methyl ester 79 with tetra-N-butylammonium fluoride (TBAF) gives rise to α-hydroxyester 81 via [2,3]-rearrangement of enolate 80 (Scheme 1.17).32 Importantly, the corresponding silylketeneacetal 77 undergoes exclusive [3,3]-rearrangement under thermal conditions, a result consistent with those of Salomon (See Scheme 1.15).
In connection with their studies on [3,3]-rearrangements of α-allyloxyketone enolates (See Scheme 1.15), Koreeda and Luengo noted that [2,3]-rearrangement product 83 could be co-produced when the corresponding [3,3]-rearrangement was slowed (Scheme 1.18).\textsuperscript{27} Specifically, they reported that with the lithium enolate (82), [2,3]-product 83 comprised up to 20% of the product mixture. This coincided with a tremendous drop in the rate of [3,3]-rearrangement, a result linked to reduction of the free alkoxide character of the enolate oxygen.

Thomas and Dubini also reported observing [2,3]-rearrangement of enolate 85, derived from KOtBu-deprotonation of related α-allyloxyketone 84 (Scheme 1.19).\textsuperscript{33}
However, the experimental procedure for 86 describes the production of “2.7 g of material which was mainly the title substance” suggesting that some [3,3]-rearrangement may have been observed. The conclusion drawn from the seemingly contradictory results presented above was that α-allyloxyketone enolates are variable in their reactivity and while one rearrangement pathway may be desired, it must be anticipated that the other may interfere.

**Scheme 1.19**

\[
\begin{array}{c}
\text{MeO} \\
\text{O} \\
\text{O} \\
\text{OKOKO} \\
\text{tBu} \\
\end{array}
\quad \text{MeO} \\
\text{O} \\
\quad \text{Me} \\
\quad \text{Me} \\
\quad \text{Me} \\
\text{[2,3]} \\
\text{OH} \\
\]

\[
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Me} \\
\end{array}
\quad \text{Me} \\
\quad \text{Me} \\
\quad \text{Me} \\
\quad \text{THF, 0ºC, 1.5 h} \\
\quad (65\% \text{ yield}) \\
\]

1.3.5 [2,3]-Rearrangements of Ylides Derived from α-Diazo carbonyl Compounds

With regard to the rhodium carbenoid aspect of the reaction, a comprehensive literature survey revealed that, while Claisen rearrangements of the type depicted in Scheme 1.13 had never been reported, it was well established that Rh(II) carbenoids could interact with allylic ethers or acetals to furnish oxonium ylides which subsequently undergo [2,3]-rearrangement. Doyle had shown that Rh(II)-catalyzed decomposition of ethyl diazo acetate (87) in the presence of allylic acetals (e.g. 88, Scheme 1.20) furnished allylic ethers (e.g., 90), presumably via [2,3]-rearrangement of ylide 89.\(^{34}\)

**Scheme 1.20**

\[
\begin{array}{c}
\text{EtO} \\
\text{O} \\
\text{N}_2 \\
\text{H} \\
\end{array}
\quad \text{EtO} \\
\text{O} \\
\quad \text{Me} \\
\quad \text{OMe} \\
\quad (10 \text{ equiv}) \\
\quad \text{Rh}_2(\text{OAc})_4 \\
\quad \text{neat, 25ºC} \\
\quad (57\% \text{ yield}) \\
\]

\[
\begin{array}{c}
\text{EtO} \\
\text{O} \\
\text{H} \\
\end{array}
\quad \text{EtO} \\
\text{O} \\
\quad \text{OMe} \\
\quad \text{OMe} \\
\quad \text{[2,3]} \\
\quad \text{OMe} \\
\]

18
Pirrung later demonstrated that similar transformations could be achieved using α-diazoketones as well as α-diazoesters (Scheme 1.21). For example, decomposition of α-diazoketone 91 with Rh$_2$(OAc)$_4$ in CH$_2$Cl$_2$ at room temperature furnished ether 93 via an analogous [2,3]-rearrangement of the intermediate ylide 92.$^{35}$

Scheme 1.21

Whether the newly discovered reaction under investigation bore any mechanistic resemblance to these processes remained to be determined.

1.3.6 Preliminary Investigations of Reaction Scope

With a firm grasp of the reactivity issues associated with α-allyloxyketone enolate rearrangements and with a knowledge of related rhodium carbenoid-initiated processes, an investigation into the scope of the rhodium carbenoid-initiated Claisen rearrangement was initiated.$^{27}$ These efforts commenced with a survey of allylic alcohols to determine their compatibilities with the rearrangement protocol employing methyl diazoacetoacetate (59, Table 1.1). It was during the course of these assays that a critical correlation was established between alcohol structure and reaction outcome.
Table 1.1 - Survey of Allylic Alcohol Compatibility With α-Diazoketone 59

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Alcohol (94) [ee]</th>
<th>[3,3] Product (95) (yield) [ee]</th>
<th>Insertion Product (96) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
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<td><img src="image" alt="Structure_b" /></td>
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</tr>
<tr>
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</tr>
<tr>
<td>c</td>
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</tr>
<tr>
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<td><img src="image" alt="Structure_k" /></td>
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</tr>
<tr>
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<td><img src="image" alt="Structure_t" /></td>
<td><img src="image" alt="Structure_u" /></td>
</tr>
</tbody>
</table>

Although the study outlined in Scheme 1.14 disproved the intermediacy of α-allyloxy-β-ketoester 58 en route to the Claisen product (56), formation of such “OH-insertion products” was found to be a competing side reaction of unknown mechanistic origin. Furthermore, the degree to which this process competed with [3,3]-rearrangement was highly dependent upon the substitution pattern of the allylic alcohol component. As can be surmised from Table 1.1, the reaction was most selective when performed with allylic alcohols possessing at least one substituent on the hydroxyl-bearing carbon (C1) and no substituent at C2. Deviation from this substitution pattern resulted in significant quantities of OH-insertion by-product. The origin of this substituent effect was unclear. It also remained uncertain at this stage whether both products arose from a common
intermediate or whether the OH-insertion product was the result of an independent process.

As with the prototype reaction (Scheme 1.13), chirality transfer from other enantiomerically enriched allylic alcohols was excellent in almost every case examined with the exception of 4-methyl-3-penten-2-ol (94e, Table 1.1, Entry E), which generated [3,3]-product (95e, Table 1.1) of substantially lowered enantiomeric excess. In all cases, (S)-allylic alcohols (94c-g, Table 1.1) furnished homoallylic (R)-β-hydroxy-α-ketoesters (95c-g, Table 1.1) in which the pendant olefin was of trans geometry, a stereochemical outcome consistent with a chair-like transition state possessing an equatorially disposed methyl group and a Z-enolate (e.g., 59, Scheme 1.13).27,36 No [2,3]-rearrangement products were ever observed. With regard to diastereoselectivity, use of 3-penten-2-ol (94g, Table 1.1) furnished a 7:1 mixture of diastereomeric rearrangement products. It was subsequently found that diastereoselectivity could be greatly improved by introducing an additional substituent at the pentenol C-3 position (i.e., 3-methyl-3-penten-2-ol (94f, Table 1.1)) to generate a single diastereomeric rearrangement product (95f). However, the reason for this substituent-based enhancement in diastereoselectivity was unclear.

Having demonstrated the generality of the rearrangement protocol with regard to allylic alcohol and having established critical structure-reactivity relationships with this component, it was next sought to explore the reactivity of other α-diazoketones under similar conditions. Two excellent substrates were found in regioisomeric diazotetralones 97 and 100. As can be surmised from Table 1.2, 97 and 100 exhibited superior selectivity, generating only very small quantities of OH-insertion by-product 102a when
allyl alcohol was employed with 100. Again, no [2,3]-rearrangement products were observed. While chirality transfer was not investigated with these two substrates, similar diastereoselectivities were observed for 97 and 100 with 3-penten-2-ol (94g, Table 1.2) and 3-methyl-3-penten-2-ol (94f) as were observed with methyl diazoacetoacetate (59).

Table 1.2 -Rh(II)-Initiated Reaction of α-Diazoketones 97 and 100 with Allylic Alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Alcohol (87)</th>
<th>[3,3] Product (98/101) (yield)</th>
<th>Insertion Product (99/102) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H H H OH</td>
<td>(72) (42)</td>
<td>(0) (7)</td>
</tr>
<tr>
<td>b</td>
<td>H Me Me H</td>
<td>(67) (60)</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>c</td>
<td>H H Me OH</td>
<td>(67) (73)</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>d</td>
<td>H Me OH</td>
<td>(72) (52)</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>e</td>
<td>Me H Me H</td>
<td>(74) (66)</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>f</td>
<td>Me Me H Me</td>
<td>(66) (52)</td>
<td>(0) (0)</td>
</tr>
<tr>
<td>g</td>
<td>Me Me Me H</td>
<td>(63) (66)</td>
<td>(0) (0)</td>
</tr>
</tbody>
</table>

1.3.7 Conclusion

The importance of these early investigations must not be understated. Through careful experimentation and contemplation of the observations made during those experiments, a single deviant result developed into the beginnings of a novel method for
the asymmetric synthesis of tertiary alcohols. Further careful experimentation began to define the scope and limitations of the reaction, uncovering important substituent effects that influenced both reaction outcome and diastereoselectivity. While the reasons for these substituent effects were not clear, knowledge of their existence would unquestionably assist future studies. The results presented in Tables 1.1 and 1.2 indicated that the developed reaction conditions could potentially be applied to a wide variety of α-diazoketones and allylic alcohols, thereby warranting further investigations into the scope and limitations of the reaction as well as reaction optimization. In addition, with evidence in hand refuting the intermediacy of α-allyloxy-β-ketoester 58 (Scheme 1.14), it remained to be determined what reactive intermediate, if not 58, was generated upon carbenoid capture and under what conditions it rearranged to the observed Claisen product. These endeavors will form the basis of the discussion presented in the following chapters.

1.4 Notes and References


Chapter 2

Further Investigations into the Scope and Limitations of the Rhodium Carbenoid-Initiated Claisen Rearrangement

2.1 Efforts to Optimize [3,3]-Rearrangement

2.1.1 Overview

In considering the substrate combinations investigated thus far, it was clear that the worst selectivity for [3,3]-rearrangement over OH-insertion was that observed with methyl diazoacetoacetate (59) and allyl alcohol (94a). Since no investigation of reaction conditions had yet been attempted in an effort to optimize the ratio of [3,3]-rearrangement product 95 to OH-insertion product 96, several reaction parameters were systematically varied in an effort to reduce the prevalence of OH-insertion by-product 96a derived from diazo substrate 59 and allyl alcohol (94a).

2.1.2 Effect of Catalyst Ligand

Examples of ligand-dependent reactivity are nearly ubiquitous in the literature of Rh(II) carbenoids. So commonly does the ligand on the Rh(II) center influence reaction outcome that a review devoted entirely to this subject has recently appeared in the literature. Therefore it seemed reasonable to assume that variations in catalyst structure would have an observable effect on the outcome of the Rh(II)-catalyzed reaction of 59 with allyl alcohol (94a). With this in mind, several rhodium (II) catalysts were examined for their effects on the ratio of [3,3]-product 95a to OH-insertion product 96a (Table 2.1). The catalysts utilized in this investigation included the parent dirhodium (II) tetraacetate...
(Rh\textsubscript{2}(OAc)\textsubscript{4}), the electronically similar but more soluble dirhodium (II) tetraoctanoate (Rh\textsubscript{2}(oct)\textsubscript{4}), the electron-deficient dirhodium (II) tetraperfluorobutyrate (Rh\textsubscript{2}(pfb)\textsubscript{4}),\textsuperscript{2} and the electron-rich dirhodium (II) tetracaprolactamate (Rh\textsubscript{2}(cap)\textsubscript{4}).\textsuperscript{3} Experimentally, 0.1 mol\% of each catalyst was added to a solution of 59 (1.0 equiv) and allyl alcohol (94\textsubscript{a}, 1.2 equiv) in benzene-\textit{d}\textsubscript{6}. The reaction mixture was then heated at reflux for 20 minutes. Deuterated solvent was employed to enable direct NMR measurement of product ratios, thereby ensuring that product mixtures would not be enriched by differential evaporation. All reactions were performed using 100 mg of diazo substrate at 0.1 M concentration.

**Table 2.1 - Effect of Catalyst Ligand on [3,3]/OH-Insertion Ratio with 59 and 94\textsubscript{a}**

<table>
<thead>
<tr>
<th>Rh\textsubscript{2}L\textsubscript{4} (0.1 mol%)</th>
<th>95\textsubscript{a} : 96\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}</td>
<td>56 : 44</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(oct)\textsubscript{4}</td>
<td>53 : 47</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(pfb)\textsubscript{4}</td>
<td>60 : 40</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(cap)\textsubscript{4}</td>
<td>45 : 55\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}A 40 min reaction time was required for complete consumption of 59

Disappointingly, little change in product ratio was observed upon varying the catalyst ligand. This appeared to indicate that both [3,3]-rearrangement and OH-insertion processes responded similarly to changes in catalyst electronics. However, it was recognized that this behavior could also be consistent with a scenario wherein both products derive from a common intermediate via individual, catalyst-independent processes.
2.1.3 Effect of Catalyst Loading

Although invariant with regard to ligand, it was deemed possible that product distribution could be altered by changing the catalyst loading (Table 2.2). In particular, such a dependence would be manifest if the rate laws for both the [3,3]-rearrangement and OH-insertion processes contained a rhodium (II) term to different orders. However, equivalent product ratios were observed at 0.1 mol%, 1.0 mol% and 5.0 mol% catalyst loadings of Rh₂(OAc)₄.

**Table 2.2 - Effect of Catalyst Loading on [3,3]/OH-Insertion Ratio with 59 and 94a**

<table>
<thead>
<tr>
<th>Catalyst Loading</th>
<th>95a:96a</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 mol%</td>
<td>56:44</td>
</tr>
<tr>
<td>1.0 mol%</td>
<td>54:46</td>
</tr>
<tr>
<td>5.0 mol%</td>
<td>56:44</td>
</tr>
</tbody>
</table>

2.1.4 Effect of Reaction Stoichiometry

In light of unsuccessful efforts to exploit the Rh(II) catalyst as an avenue to reaction optimization, attention was turned to modification of more classical reaction parameters. Efforts in this area commenced with a variation of reagent stoichiometry which did significantly alter reaction outcome. Unfortunately, as can been seen from Table 2.3, the quantity of OH-insertion by-product 96a increased steadily with increasing alcohol equivalency, becoming the predominant product when six equivalents of allyl alcohol (94a) were employed. The reason for this result was unclear, however, this study revealed that reaction environment rather than catalyst had the greatest influence over the ratio of 95a to 96a. This was not expected at the outset of these investigations.
Table 2.3 - Effect of Stoichiometry on [3,3]/OH-Insertion Ratio with 59 and 94a

<table>
<thead>
<tr>
<th># Equivalents</th>
<th>94a</th>
<th>95a:96a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>56:44</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>39:61</td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td>16:84</td>
<td></td>
</tr>
</tbody>
</table>

2.1.5 Effect of Solvent and Temperature

As with other conditions, variations of solvent and temperature were largely unsuccessful at favoring production of 95a over 96a. With regard to the former, use of benzene proved to be optimal. Efforts to employ either 1,2-dichloroethane or dichloromethane afforded no improvements in selectivity and generated crude product mixtures containing significant quantities of unidentifiable polar side-products. Also problematic with dichloromethane was that Rh$_2$(OAc)$_4$-catalyzed decomposition of 59 was slowed significantly at lower temperatures. Coordinating solvents such as THF completely inhibited Rh(II)-catalyzed decomposition of 59. Explorations of reaction temperature were impeded by slow decomposition of 59 at lower temperatures and revealed no selectivity improvement at higher temperatures (i.e., toluene, reflux).

Taken together, all efforts to optimize the reaction of 59 and 94a led to the conclusion that the initially employed reaction conditions were also the optimal conditions for this process. Therefore, these conditions (1.2 equivalents of allylic alcohol, Rh$_2$(OAc)$_4$, benzene, reflux) were adopted as standard and an investigation of reaction scope was launched.
2.2 Investigation of Additional Diazo Substrates

2.2.1 Overview

The success of diazotetralone substrates 97 and 100 (Table 1.2) in furnishing the desired Claisen rearrangement products to the virtual exclusion of OH-insertion by-products inspired optimism regarding the generality of the newly discovered method. Furthermore, the apparent insensitivity of these substrates to variations in alcohol structure when compared to methyl diazoacetoacetate 59 offered further encouragement. Studies thus commenced with a survey of several α-diazo ketones in an effort to expand the pool of functional diazo substrates. In addition, it was hoped to establish that the excellent chirality transfer observed with substrate 59 could be achieved with other α-diazo ketones, an issue that had not yet been addressed. No efforts were made at this stage to elucidate the mechanism of the reaction, however, alcohol substitution effects would continue to be scrutinized for their influence on reaction outcome, enantioselectivity, and diastereoselectivity.

2.2.2 α-Diazo Phenylacetone

The excellent selectivity observed with α-diazo-β-tetralone (97) led to the selection of its acyclic analog, α-diazo phenylacetone (103) as the first substrate to be investigated.4,5 As can be discerned from Table 2.4, 103 proved at least as efficient a substrate as its cyclic counterpart, generating exclusively the desired Claisen products (104a-g) in good yields under standard conditions with all allylic alcohols examined. The corresponding OH-insertion by-products 105a-g were not observed, nor were [2,3]-rearrangement products. As with methyl diazoacetoacetate (59), transfer of chirality from enantiomerically enriched (S)-allylic alcohols 94a-g was excellent with the exception of 4-methyl-3-
penten-2-ol (94e), which again afforded [3,3]-product 104e in reduced enantiomeric excess. Use of 3-penten-2-ol (94g) afforded a 7:1 mixture of diastereomeric [3,3]-rearrangement products, the major isomer possessing the relative stereochemistry indicated for 104g in Table 2.4. However, in accord with earlier studies, use of 3-methyl-3-penten-2-ol (94f) afforded a single diastereomer of [3,3]-rearrangement product 104f. As with 59, (S)-allylic alcohols 94a-g afforded

**Table 2.4 - Rh(II)-Initiated Reaction of α-Diazoketone 103 with Allylic Alcohols 94a-g**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Alcohol (94)(ee)</th>
<th>[3,3] Product (104) (yield)</th>
<th>Insertion Product (105) (yield)</th>
</tr>
</thead>
<tbody>
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<td>a</td>
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<td><img src="structure_a" alt="Structure" /></td>
<td><img src="structure_a" alt="Structure" /></td>
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<td>c</td>
<td><img src="structure_c" alt="Structure" /></td>
<td><img src="structure_c" alt="Structure" /></td>
<td><img src="structure_c" alt="Structure" /></td>
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<tr>
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<td><img src="structure_g" alt="Structure" /></td>
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</tr>
</tbody>
</table>

*Enantiomeric excess determined by Mosher ester analysis of the derived diols

(R)-α-hydroxyketones 104a-e with a pendant (E)-olefin, a result consistent with an analogous chair-like transition state (e.g., 106, Scheme 2.1) possessing a (Z)-enolate and an equatorially disposed methyl substituent.
Importantly, these studies demonstrated that the excellent stereochemical control observed with α-diazo-β-ketoester 59 was not unique to this substrate, but a fundamental characteristic of this reaction that could manifest itself with other α-diazoketones. In addition, substituent effects on reaction enantioselectivity and diastereoselectivity observed with 59 also appeared to extend to α-diazoketone 103. Encouraged by these results, further investigations into α-diazoketone compatibility were conducted.

2.2.3 α-Diazoacetylacetone (3-Diazo-2,4-Pentanedione)

The next substrate chosen for investigation was α-diazoacetylacetone (107), a variation on methyl diazoacetoacetate (59). Unfortunately, unlike its β-ketoester counterpart, β-diketone 107 gave rise almost exclusively to known allylic ester 108, the product of Wolff rearrangement followed by alcohol trapping (Scheme 2.2), when treated with 94c under the standard reaction conditions. Only trace amounts of the desired [3,3]-rearrangement product 109 were observed with this substrate.
Presumably, the selective formation of 108 was due to an existing predisposition of 107 for Wolff rearrangement, magnified by the presence of two equally migration-prone methyl ketones. No further investigations were conducted with this substrate.

2.2.4 3-Diazo-2-Butanone

It was next sought to pursue analogs of β-diazo-α-tetralone (100) since such substrates would represent a different class of α-diazoketone than 97, 59, and 103, possessing only a single ketocarbonyl group as a stabilizer for the diazo moiety. It was hoped that the rhodium (II) carbenoids derived from such monostabilized α-diazoketones, by virtue of being more reactive than those of the doubly stabilized species, would interact with the allylic alcohol before deleterious rearrangement processes (e.g., Wolff rearrangement) could take place.

To this end, 3-diazo-2-butanone (110) was selected as the first member of this class of α-diazoketone to be investigated. The results of studies employing this diazo substrate are compiled into Table 2.5. As can be surmised from the data presented, 110 proved to be an excellent substrate for the rearrangement protocol, generating exclusively the product of [3,3]-rearrangement (111a-f) in good yield with allylic alcohols 94a-f.
Table 2.5 - Rh(II)-Initiated Reaction of $\alpha$-Diazoketone 110 with Allylic Alcohols 94a-f

![Chemical Structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Alcohol (94) [ee]</th>
<th>[3,3] Product (111) (yield)</th>
<th>Insertion Product (112) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
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<td>(0)</td>
</tr>
<tr>
<td>b</td>
<td><img src="imageb" alt="Structure" /></td>
<td>(59)</td>
<td>(0)</td>
</tr>
<tr>
<td>c</td>
<td><img src="imagec" alt="Structure" /></td>
<td>(64) [93]</td>
<td>(0)</td>
</tr>
<tr>
<td>d</td>
<td><img src="imaged" alt="Structure" /></td>
<td>(59) [79]</td>
<td>(0)</td>
</tr>
<tr>
<td>e</td>
<td><img src="imagee" alt="Structure" /></td>
<td>(60) [41]</td>
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</tr>
<tr>
<td>f</td>
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<td>(60) [91]</td>
<td>(0)</td>
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</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>[3,3] Product (111) (yield)</th>
<th>Insertion Product (112) (yield)</th>
</tr>
</thead>
<tbody>
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<td>(0)</td>
</tr>
<tr>
<td>b</td>
<td><img src="imageb" alt="Structure" /></td>
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<td>(0)</td>
</tr>
<tr>
<td>c</td>
<td><img src="imagec" alt="Structure" /></td>
<td>(64) [93]</td>
<td>(0)</td>
</tr>
<tr>
<td>d</td>
<td><img src="imaged" alt="Structure" /></td>
<td>(59) [79]</td>
<td>(0)</td>
</tr>
<tr>
<td>e</td>
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<td>(60) [41]</td>
<td>(0)</td>
</tr>
<tr>
<td>f</td>
<td><img src="imagef" alt="Structure" /></td>
<td>(60) [91]</td>
<td>(0)</td>
</tr>
</tbody>
</table>

$a$ Enantiomeric excess determined by Mosher ester analysis of the derived diols

Initially, use of refluxing benzene afforded low yields of 111a-f (ca. 30%) due to evaporation of the relatively volatile [3,3]-products during solvent removal. This problem was remedied by changing the reaction solvent to pentane, from which $\alpha$-hydroxyketones 111a-f could be isolated in good yields. Importantly, the reduction in reaction temperature accompanying this change in solvent did not decelerate the reaction of 110 with Rh$_2$(OAc)$_4$, a result in sharp contrast to that observed with the doubly stabilized 59 (See Section 2.1.5) that illustrated the enhanced reactivity of monostabilized $\alpha$-diazoketones towards Rh(II)-catalyzed decomposition.

As with 59 and 103, enantiomerically enriched (S)-allylic alcohols (94c-f) furnished homoallylic (R)-$\alpha$-hydroxyketones (111c-f) possessing (E)-olefins. Again, chirality transfer was excellent except when alcohol 94e was employed. Given the poor
diastereoselectivity consistently observed with 3-penten-2-ol (94g), only 3-methyl-3-penten-2-ol (94f) was employed with this substrate, furnishing a single diastereomer of [3,3]-rearrangement product 111f.

2.2.5 Determination of Relative and Absolute Stereochemistry in the α-Diazoophenylacetone and 3-Diazo-2-Butanone Series

The absolute and relative configurations of α-hydroxyketones 104c-g and 111c-g derived from α-diazoophenylacetone (103) and 3-diazo-2-butanone (110), respectively, were established by chemical correlation with the corresponding rearrangement products derived from 59 (i.e., 95c-g, Table 1.1, Section 1.3.6). An example is shown in Scheme 2.3.

Scheme 2.3

Tandem saponification/oxidative decarboxylation of β-hydroxy-α-ketoester 95f was accomplished by treatment with 1N NaOH followed by 30% H2O2 to furnish the corresponding α-hydroxyacid 113. Treatment of 113 with phenyllithium in THF provided α-hydroxyketone 104f, the product of the rhodium carbenoid-initiated Claisen rearrangement with 103 and 3-methyl-3-penten-2-ol (94f). Similarly, treatment of 113 with phenyllithium in THF provided α-hydroxyketone 111f, the product of the rhodium carbenoid-initiated Claisen rearrangement with 110 and 3-methyl-3-penten-2-ol (94f).
with methyllithium provided access to the corresponding α-hydroxyketone 111f derived from 3-diazo-2-butanone (110). Comparison of NMR spectra confirmed that the rearrangement protocol employing 103 and 110 provided entry into the same diastereomeric series observed with 59. Comparison of optical rotation data unambiguously confirmed that 103, 110, and 59 also gave rise to the same enantiomeric series, that is, α-hydroxyketones 104f and 111f were of the (R) absolute configuration.

2.3 Monostabilized α-Diazoketones: Competitive Reactivity

2.3.1 Overview

It was felt that the synthetic utility of the rhodium carbenoid-initiated Claisen rearrangement likely resided with the large variety of accessible monostabilized α-diazoketones more than with doubly stabilized α-diazoketones, which were more limited in type and number. This belief, coupled with the excellent reactivity of the prototype substrate, 3-diazo-2-butanone (110), led to an expansion of the investigation with monostabilized α-diazoketones. However, it was also recognized that the heightened reactivity of monostabilized rhodium (II) carbenoids might offer entry into diverse reaction pathways in more complex substrates. Thus, besides demonstrating generality, it was hoped to evaluate the ability of the rhodium carbenoid-initiated Claisen rearrangement to compete with other established Rh(II) carbenoid reactions.

2.3.2 Ethyl 4-Diazo-5-Oxohexanoate: A Functionalized, Monostabilized α-diazoketone

Efforts commenced with functionalized α-diazoketone 116, selected to assess the effect of pendant functionalities on the reactivity of the monostabilized rhodium carbenoid. Specifically, this substrate was designed such that the ester carbonyl group
would be poised to interact with the rhodium carbenoid, forming a 5-membered cyclic carbonyl ylide species that could potentially inhibit the rhodium carbenoid-initiated Claisen process.\textsuperscript{14}

The synthesis of \textbf{116} is outlined in Scheme 2.4. Alkylation of 1-benzoylacetaone (\textbf{114}) with ethyl bromopropionate was accomplished using potassium tert-butoxide in tert-butanol to furnish known ketoester \textbf{115} in 75\% yield.\textsuperscript{15} This compound was then subjected to the debenzoylating diazo transfer protocol developed by Taber with DBU and \textit{p}-nitrobenzenesulfonyl azide (\textit{p}-NBSA) to furnish the desired \textit{\alpha}-diazo ketone \textbf{116} in 47\% yield.\textsuperscript{16}

\textit{Scheme 2.4}

With ample quantities of \textbf{116} in hand, the reactivity of this diazo substrate was investigated with allylic alcohols \textbf{94a-f}. As can be seen from Table 2.6, \textit{\alpha}-diazo ketone \textbf{116} proved to be an effective substrate, affording good yields of [3,3]-rearrangement products \textbf{117a-f} to the exclusion of the corresponding OH-insertion products \textbf{118a-f}. No products derived from carbonyl ylide addition were observed, indicating either a preference of the rhodium carbenoid for interaction with the allylic alcohol or breakdown of the intermediate carbonyl ylide in the presence of allylic alcohols.\textsuperscript{17}
Table 2.6 - Rh(II)-Initiated Reaction of α-Diazoketone 116 with Allylic Alcohols 94a-f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Alcohol (94)</th>
<th>[3,3] Product (117) (yield)</th>
<th>Insertion Product (118) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td></td>
<td>(58)</td>
<td>(0)</td>
</tr>
<tr>
<td>b</td>
<td></td>
<td>(49)</td>
<td>(0)</td>
</tr>
<tr>
<td>c</td>
<td></td>
<td>(51)</td>
<td>(0)</td>
</tr>
<tr>
<td>d</td>
<td></td>
<td>(51)</td>
<td>(0)</td>
</tr>
<tr>
<td>e</td>
<td></td>
<td>(49)</td>
<td>(0)</td>
</tr>
<tr>
<td>f</td>
<td></td>
<td>(53)</td>
<td>(0)</td>
</tr>
</tbody>
</table>

2.3.3 [3,3]-Rearrangement Versus C-H-Insertion: 3-Diazo-2-Heptanone and 7-Methyl-3-Diazo-2-octanone

An additional process that was anticipated to compete with the Claisen rearrangement in monostabilized systems was intramolecular C-H-insertion, a well-precedented reaction of both monostabilized and doubly stabilized rhodium (II) carbenoids that typically furnishes 5-membered carbocycles.18,19 To assess the extent to which this process would compete with the Claisen rearrangement, the synthesis of α-diazoketone 120 was undertaken. This substrate possessed a pendant alkyl chain of sufficient length to enable 5-membered intramolecular C-H-insertion to take place.

The synthesis of α-diazoketone 120 is described in Scheme 2.5. Deprotonation of 1-benzoylacetonate (114) with K₂CO₃ in refluxing toluene was followed by treatment with
n-butyl bromide to furnish β-diketone 119 in 40% yield.\textsuperscript{20} Debenzoylating diazo transfer then proceeded in 43% yield to furnish α-diazoketone 120.

\textit{Scheme 2.5}

```
\begin{center}
\begin{tikzpicture}
\node[align=center] (1) at (0,0) {114};
\node[align=center] (2) at (2,0) {119};
\node[align=center] (3) at (4,0) {120};

\draw[->] (1) -- (2) node[pos=0.5,above] {1) K$_2$CO$_3$, n-Bu$_4$NBr Toluene, Λ, 6 h (40\% yield)};
\draw[->] (2) -- (3) node[pos=0.5,above] {2) n-butyl bromide Toluene, 60ºC, 12 h (43\% yield)};
\end{tikzpicture}
\end{center}
```

Table 2.7 shows the results of the reaction of α-diazoketone 120 with allylic alcohols 94a-f. In all instances, the [3,3]-rearrangement products 121a-f were isolated in good yield and in the absence of corresponding OH-insertion products 122a-f. In addition, no product derived from the anticipated C-H-insertion process was observed.

\textbf{Table 2.7 - Rh(II)-Initiated Reaction of α-Diazoketone 120 with Allylic Alcohols 94a-f}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Alcohol (94)</th>
<th>[3,3] Product (121) (yield)</th>
<th>Insertion Product (122) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H H H Me Me OH</td>
<td>(64)</td>
<td>(0)</td>
</tr>
<tr>
<td>b</td>
<td>H H Me Me Me Me OH</td>
<td>(51)</td>
<td>(0)</td>
</tr>
<tr>
<td>c</td>
<td>H H Me Me Me Me OH</td>
<td>(65)</td>
<td>(0)</td>
</tr>
<tr>
<td>d</td>
<td>H H Me Me Me Me Me</td>
<td>(61)</td>
<td>(0)</td>
</tr>
<tr>
<td>e</td>
<td>Me Me Me Me Me OH</td>
<td>(60)</td>
<td>(0)</td>
</tr>
<tr>
<td>f</td>
<td>Me Me Me Me Me Me OH</td>
<td>(59)</td>
<td>(0)</td>
</tr>
</tbody>
</table>

Importantly, to evaluate the propensity of this substrate to undergo intramolecular
C-H-insertion, 120 was treated with Rh$_2$(OAc)$_4$ under the rearrangement conditions in the absence of allylic alcohol. Interestingly, under these conditions, 120 did not furnish the expected C-H-insertion product 123. Rather, only enone 124 was isolated in 24% yield (Scheme 2.6) via β-hydride elimination of the intermediate carbenoid.$^{21,22}$

Scheme 2.6

![Scheme 2.6](image)

Taking advantage of the knowledge that C-H-insertion into methine C-H bonds is significantly more facile than insertion into methyl C-H bonds,$^{23}$ a more reactive C-H insertion substrate, α-diazoketone 126, was prepared as shown in Scheme 2.7. Alkylation of 114 under the previously employed conditions with 4-methyl-1-bromopentane furnished β-diketone 125 which was subjected to debenzoylating diazo transfer to furnish branched α-diazoketone 126. The results of Claisen reactions employing this diazo substrate are summarized in Table 2.8.
As with 120, reaction of 126 with allylic alcohols 94a-f furnished only the desired [3,3]-rearrangement products 127a-f to the exclusion of OH-insertion products 128a-f and both β-elimination and C-H-insertion products. When exposed to the identical reaction conditions in the absence of allylic alcohol, 126 gave rise again exclusively to elimination product 129 (23% yield)24 (Scheme 2.8). Thus, it was evident that the competing β-elimination process may be completely suppressed in the presence of an allylic alcohol, while C-H insertion is not at all competitive.

Scheme 2.8
2.3.4 Terminal Monostabilized \(\alpha\)-Diazoketones: \(\alpha\)-Diazoacetophenone

Thus far, terminal monostabilized \(\alpha\)-diazoketones were the only class of \(\alpha\)-diazoketone not explored for compatibility with the rhodium carbenoid-initiated Claisen rearrangement. To investigate this class of \(\alpha\)-diazoketone, \(\alpha\)-diazoacetophenone (130) was selected as a representative substrate.\(^{25}\) Unfortunately, investigations of 130 were curtailed by disappointing early results.

Table 2.9 - Rh(II)-Initiated Reaction of \(\alpha\)-Diazoketone 130 with Allylic Alcohols\(^{26}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Alcohol [%ee]</th>
<th>[3,3] Product (131) (yield) [%ee](^a)</th>
<th>Insertion Product (132) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>94a [98]</td>
<td>(46)</td>
<td>(6)</td>
</tr>
<tr>
<td>b</td>
<td>94c [98]</td>
<td>(45) [80]</td>
<td>(0)</td>
</tr>
<tr>
<td>c</td>
<td>94f [92]</td>
<td>(40)(^b) [90](^c)</td>
<td>(0)</td>
</tr>
</tbody>
</table>

\(^a\) Enantiomeric excess determined by Mosher ester analysis of the derived diols
\(^b\) Isolated as a 4:1 mixture of diastereomers
\(^c\) Enantiomeric excess of major diastereomer

As can be seen from Table 2.9, only moderate yields of [3,3]-rearrangement products 131\(a-c\) were observed with allylic alcohols 94a, 94c, and 94f. Some OH-insertion by-product (132a) was isolated with allyl alcohol (94a). However, more disappointing was the poor level of chirality transfer observed with enantiomerically enriched allylic alcohol 94c. Furthermore, the [3,3]-rearrangement product (131c) derived from alcohol 94f was isolated as a 4:1 mixture of diastereomers. This was the worst diastereoselectivity observed with this transformation to date, a particularly
disappointing result given that allylic alcohol 94f afforded single diastereomeric [3,3]-products with all other diazo substrates investigated. It was thus concluded that terminal, monostabilized α-diazoketones such as 130 were poor substrates for the rhodium carbenoid-initiated Claisen rearrangement.

2.4 Summary and Conclusions

Further examples of the novel rhodium-initiated reaction introduced in Chapter 1 were presented. These studies demonstrated both the generality of the reaction with regard to diazo substrate and, more importantly, that the excellent level of chirality transfer observed with diazo substrate 59 was attainable with other α-diazoketones. Furthermore, the sense of chirality transfer observed with other diazo substrates, whereby (S)-allylic alcohols furnish (R)-α-hydroxyketones, was the same as that observed with 59. Both doubly stabilized α-diazoketones (e.g., 103) and monostabilized α-diazoketones (e.g., 110) were shown to be excellent substrates for the reaction protocol, combining with a number of allylic alcohols (94a-g) to furnish tertiary homoallylic α-hydroxyketones in good yields.

During the course of these studies, several limitations of the reaction were also uncovered. Claisen rearrangement could not successfully compete with Wolff rearrangement in substrates susceptible to this process. However, a competing β-elimination process was shown to be subordinate to Claisen rearrangement in the presence of allylic alcohols. Substituent effects were once again shown to influence product distribution, enantioselectivity, and diastereoselectivity in a manner analogous to that observed with diazo substrate 59. However, the origin of these substituent effects remained elusive. All efforts to eliminate the OH-insertion by-product (96a) derived
from 59 and allyl alcohol (94a) by catalyst alteration failed. Variation of reaction conditions either amplified the OH-insertion process or had no effect. Finally, use of terminal, monosubstituted α-diazoketones (e.g., 131) afforded much poorer chirality transfer and diastereoselectivity than all other substrates.

2.5 Experimental Section

2.6.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using freshly distilled solvents. All commercially obtained reagents were used as received. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. High-performance liquid chromatography (HPLC) was performed with either a Rainin Microsorb 80-199-C5 or 80-120-C5 column. Infrared spectra were acquired using a MIDAC M-1200 FTIR. 1H and 13C NMR spectra were recorded using Bruker AM500 or Bruker Avance 400/500 MHz spectrometers. Chemical shifts are reported as δ values relative to internal chloroform (1H δ 7.27 ppm, 13C δ 77.0 ppm) or benzene-d6 (1H δ 7.15 ppm). Where inseparable mixtures of diastereomers are isolated, 1H NMR spectral integration reflects a 1:1 mixture. Melting points are uncorrected. High-resolution mass spectra were acquired at the University of Illinois Mass Spectrometry Center.

The determination of enantiomeric excess by Mosher ester derivatization involved esterification of the appropriate substrate with the acid chloride prepared from (S)-MTPA (Et3N, DMAP, CH2Cl2). Enantiomeric excess was measured from the crude reaction
mixtures via 500 MHz $^1$H NMR in either CDCl$_3$ or benzene-$d_6$. In each case, an identical analysis was performed on racemic substrate.

2.6.2 Preparative Procedures

Preparation of $\alpha$-Diazophenylacetone (103)

![Diagram of the preparation of $\alpha$-Diazophenylacetone (103)]

$\alpha$-Diazophenylacetone (103). To a stirred solution of phenylacetone (133, 4.32 g, 32.2 mmol, 1.0 equiv) and $p$-ABSA (8.72 g, 36.3 mmol, 1.1 equiv) in CH$_3$CN (250 mL) at 0°C was added dropwise DBU (7.2 mL, 48.1 mmol, 1.5 equiv). The mixture was allowed to stir for 45 minutes with warming to room temperature. The dark orange mixture was concentrated under reduced pressure with concomitant adsorption onto silica gel. Flash chromatography (6:1 hexanes:ethyl acetate eluent) afforded $\alpha$-diazophenylacetone (103, 3.35 g, 65% yield) as bright orange crystals. Spectral data corresponded exactly with literature values.$^5$

Representative Procedure for the Preparation of $\alpha$-Hydroxyketones in Table 2.4 ($\alpha$-Hydroxyketone (R)-(+)104c).

![Diagram of the representative procedure for the preparation of $\alpha$-Hydroxyketones]
**α-Hydroxyketone (R)-(+)−104c.** A stirred mixture of α-diazoketone 103 (102 mg, 0.637 mmol, 1.0 equiv), (S)-(+)−3-buten-2-ol (94c, 55 mg, 0.763 mmol, 1.2 equiv) and Rh2(OAc)4 (1.0 mg, 0.0023 mmol, 0.003 equiv) in benzene (7 mL) was immersed in a 100°C (preheated) oil bath and heated under reflux for 5 min. The mixture was cooled and concentrated and the residue purified by flash chromatography (10:1 hexanes:EtOAc eluent) affording α-hydroxyketone (R)-(+)−104c (120 mg, 77% yield) as a clear yellow oil: 1H NMR (500 MHz, CDCl3) δ 8.01 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 5.33−5.48 (comp m, 2H), 3.91 (s, 1H), 2.75 (dd, J=6.8, 14.1 Hz, 1H), 2.54 (dd, J=7.3, 14.1 Hz, 1H), 1.61 (m, 6H); 13C NMR (125 MHz, CDCl3) δ 204.4, 134.5, 132.8, 130.2, 129.5, 128.4, 124.5, 79.0, 44.3, 26.7, 18.0; IR (thin film/NaCl) 3466 (br m), 3061 (w), 3027 (w), 2976 (m), 2935 (m), 2917 (m), 2856 (w), 1672 (s), 1597 (m), 1578 (w), 1449 (m), 1374 (m), 1263 (m), 1160 (m), 973 (s), 946 (m), 716 (s), 697 (m) cm−1; HRMS (EI) m/z found: 205.1227, [calc'd for C13H17O2 (M+H): 205.1229]; [α]D20 +5.5° (c 1.20, CHCl3).

**α-Hydroxyketone (±)-104a**

---

**α-Hydroxyketone (±)-104a.** 1H NMR (500 MHz, CDCl3) δ 8.00 (m, 2H), 7.55 (m, 1H), 7.44 (m, 2H), 5.74 (m, 1H), 5.02 (m, 2H), 4.04 (s, 1H), 2.78 (dd, J=7.1, 14.1 Hz, 1H),
2.62 (dd, $J=7.3, 14.1$ Hz, 1H), 1.61 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) 204.1, 134.2, 132.9, 132.2, 129.5, 128.3, 119.2, 78.7, 45.4, 26.7; IR (thin film/NaCl) 3458 (br m), 3075 (m), 2979 (m), 2933 (w), 1673 (s), 1597 (m), 1577 (w), 1448 (m), 1371 (m), 1268 (m), 1236 (m), 1222 (m), 1165 (m), 921 (m), 715 (m), 699 (m) cm$^{-1}$; HRMS (EI) m/z found: 191.1070, [calc'd for C$_{12}$H$_{15}$O$_2$ (M+H): 191.1072].

$\alpha$-Hydroxyketone (±)-104b.

$\alpha$-Hydroxyketone (±)-104b. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.00 (m, 2H), 7.54 (m, 1H), 7.44 (t, $J=7.4$ Hz, 2H), 5.07 (tq, $J=1.3$, 6.0 Hz, 1H), 3.95 (s, 1H), 2.73 (dd, $J=7.4$, 14.7 Hz, 1H), 2.59 (dd, $J=7.4$, 14.8 Hz, 1H), 1.63 (s, 3H), 1.61 (s, 3H), 1.48 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 204.7, 135.9, 134.5, 132.7, 129.4, 128.3, 117.6, 79.3, 39.7, 26.8, 25.8, 17.9; IR (thin film/NaCl) 3470 (br m), 3059 (w), 2975 (m), 2930 (m), 2859 (w), 1672 (s), 1597 (m), 1577 (w), 1449 (m), 1375 (m), 1269 (m), 1231 (m), 1156 (m), 1088 (m), 971 (m), 945 (m), 718 (s), 697.0 (m) cm$^{-1}$; HRMS (EI) m/z found: 219.1383, [calc'd for C$_{14}$H$_{19}$O$_2$ (M+H): 219.1385].
**α-Hydroxyketone (R)-(+)\-104d.**

![Reaction Scheme](attachment:reaction_scheme.png)

**α-Hydroxyketone (R)-(+)\-104d.** ¹H NMR (500 MHz, CDCl₃) δ 8.03 (m, 2H), 7.56 (m, 1H), 7.46 (t, J=7.8 Hz, 2H), 5.21 (q, J=6.6 Hz, 1H), 3.83 (br s, 1H), 2.83 (d, J=13.9 Hz, 1H), 2.56 (d, J=13.9 Hz, 1H), 1.60 (s, 3H), 1.59 (s, 3H), 1.52 (d, J=6.7 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 205.0, 134.9, 132.6, 131.4, 129.7, 128.3, 128.3, 124.5, 79.3, 50.6, 27.6, 17.5, 13.5; IR (thin film/NaCl) 3469 (m), 3060 (w), 2977 (m), 2919 (m), 2861 (w), 1671 (s), 1597 (m), 1578 (w), 1449 (m), 1268 (m), 1228 (m), 1155 (m), 967 (m), 718 (m), 697 (m) cm⁻¹; HRMS (EI) m/z found: 218.1308, [calc'd for C₁₄H₁₈O₂ (M⁺): 218.1307]; [α]D²⁰ +5.6° (c 1.77, CHCl₃).

**α-Hydroxyketone (R)-(−)-104e.**

![Reaction Scheme](attachment:reaction_scheme.png)

**α-Hydroxyketone (R)-(−)-104e.** ¹H NMR (500 MHz, CDCl₃) δ 7.83 (m, 2H), 7.47 (m, 1H), 7.37 (m, 2H), 5.43 (dq, J=1.4, 15.6 Hz, 1H), 5.35 (dq, J=6.2, 15.6 Hz, 1H), 3.56 (s, 1H), 1.59 (s, 3H), 1.55 (dd, J=1.4, 6.1 Hz, 3H), 1.07 (s, 3H), 1.02 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 206.9, 138.5, 137.1, 131.7, 129.4, 127.8, 124.6, 83.9, 43.5, 23.1,
22.9, 22.3, 18.1; IR (thin film/NaCl) 3475 (br s), 3060 (w), 3026 (w), 2970 (s), 2938 (m), 2878 (w), 1666 (s), 1596 (m), 1447 (m), 1370 (m), 1255 (m), 1233 (m), 1133 (m), 977 (s), 714 (s), 695 (s) cm⁻¹; HRMS (EI) m/z found: 233.1549, [calc'd for C₁₅H₂₁O₂ (M+H): 233.1542]; [α]D²⁰ -9.1° (c 1.35, CHCl₃).

α-Hydroxyketone (R,R)-(+)–104f.

α-Hydroxyketone (R,R)-(+)–104f. ¹H NMR (500 MHz, CDCl₃) δ 7.98 (m, 2H), 7.53 (m, 1H), 7.43 (m, 2H), 4.94 (m, 1H), 4.15 (s, 1H), 2.86 (q, J=7.0 Hz, 1H), 1.58 (s, 3H), 1.49 (s, 3H), 1.33 (dd, J=0.8, 6.7 Hz, 3H), 1.23 (d, J=7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 204.8, 136.7, 134.9, 132.6, 129.6, 128.2, 122.3, 81.5, 50.1, 25.7, 14.0, 13.5, 13.0; IR (thin film/NaCl) 3457 (br m), 3060 (w), 2979 (m), 2933 (m), 2878 (s), 1667 (s), 1597 (m), 1577 (w), 1449 (m), 1376 (m), 1253 (m), 1164 (s), 961 (m), 712 (s), 690 (m) cm⁻¹; HRMS (EI) m/z found: 233.1546, [calc'd for C₁₅H₂₁O₂ (M+H): 233.1542]; [α]D²⁰ +11.2° (c 1.25, CHCl₃).
α-Hydroxyketones \((R,R)\)-(+)\-104g and 134.

**α-Hydroxyketone \((R,R)\)-(+)\-104g.**  
\(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.98 (m, 2H), 7.56 (m, 1H), 7.45 (m, 2H), 5.27 (ddq, \(J=1.5, 8.5, 15.3\) Hz, 1H), 5.14 (dq, \(J=6.3, 15.3\) Hz, 1H), 2.81 (m, 1H), 1.58 (s, 3H), 1.50 (dd, \(J=1.5, 6.3\) Hz, 3H), 1.15 (d, \(J=6.8\) Hz, 3H);  
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 204.8, 134.9, 132.6, 131.2, 129.5, 128.3, 127.0, 80.9, 44.9, 24.4, 17.9, 14.4; IR (thin film/NaCl) 3456 (br m), 3061 (w), 3026 (w), 2976 (m), 2936 (m), 2878 (w), 2855 (w), 1668 (s), 1597 (w), 1576 (w), 1448 (m), 1257 (m), 1240 (m), 1165 (m), 971 (m), 714 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 219.1381, [calc'd for C\(_{14}\)H\(_{19}\)O\(_2\) (M+H): 219.1385]; \([\alpha]_{D}^20\) +3.2° (c 1.20, CHCl\(_3\)).

**α-Hydroxyketone 134.**  
\(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.01 (m, 2H), 7.59 (m, 1H) 7.48 (m, 2H), 5.51-5.63 (comp m, 2H), 2.78 (m, 1H), 1.74 (d, \(J=4.9\) Hz, 3H), 1.55 (s, 3H), 0.83 (d, \(J=6.7\) Hz, 3H);  
\(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 205.2, 134.4, 132.9, 131.6, 129.4, 128.5, 127.3, 80.8, 45.7, 26.1, 18.0, 15.5; IR (thin film/NaCl) 3462 (br m), 3027 (w), 2975 (m), 2933 (m), 2856 (w), 1666 (s), 1597 (m), 1577 (w), 1448 (m), 1374 (m), 1258 (s), 1237 (m), 1166 (s), 970 (s), 715 (s), 690 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 219.1391, [calc'd for C\(_{14}\)H\(_{19}\)O\(_2\) (M+H): 219.1385].
Representative Procedure for Determination of Relative and Absolute Stereochemistry of $\alpha$-Hydroxyketones (R)-104c-g.

Preparation of $\alpha$-hydroxyketone (+)-104f from $\alpha$-hydroxyacid (+)-113.

To a stirred solution of $\alpha$-hydroxyacid (+)-113 (394 mg, 2.29 mmol, 1.0 equiv) in THF (20 mL) at 0°C was added dropwise a solution of phenyllithium (1.8 M, 4.2 mL, 7.56 mmol, 3.3 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 12 h after which it was recooled to 0°C, quenched with H$_2$O (10 mL), and acidified with 4N HCl (2 mL). The heterogeneous mixture was extracted with CH$_2$Cl$_2$ (3 x 25 mL) and the combined organic layers dried over MgSO$_4$, filtered, and concentrated under reduced pressure. Flash chromatography (10:1 hexanes:EtOAc eluent) afforded $\alpha$-hydroxyketone (+)-104f (77 mg, 14% yield) that was identical spectroscopically to that obtained by reaction of $\alpha$-diazoketone 103 with alcohol (S)-(−)-94f under Rh(II)-catalyzed conditions. Absolute stereochemistry was assigned by optical rotation: $[\alpha]_D^{20} +11.0^\circ$ ($c$ 3.4, CHCl$_3$).
**Preparation of β-Ketoester (±)-108**

![Reaction Scheme](image)

β-Ketoester (±)-108. To a stirred solution of 3-diazo-2,4-pentanedione (107, 141 mg, 1.12 mmol, 1.0 equiv) and (±)-3-buten-2-ol (94c, 0.12 mL, 1.38 mmol, 1.2 equiv) in PhH (10 mL) was added Rh$_2$(OAc)$_4$ (1.0 mg, 0.002 mmol, 0.002 equiv). The mixture was immersed in a pre-heated oil bath and heated under reflux for 10 min after which it was cooled to room temperature and concentrated under reduced pressure. Flash chromatography of the residue (8:1 hexanes:ethyl acetate eluent) furnished β-ketoester (±)-108 (149 mg, 78% yield, 1:1 mixture of diastereomers) as a colorless oil whose spectral data corresponded exactly with reported values.7

**Representative Procedure for Preparation of α-Hydroxyketones in Table 2.5 (α-Hydroxyketone (R)-(−)-111c).**

![Reaction Scheme](image)

(α-Hydroxyketone (R)-(−)-111c. To a stirred solution of 3-diazo-2-butanone (110, 78 mg, 0.795 mmol, 1.0 equiv) and (S)-(+)−3-buten-2-ol (94c, 83 µL, 0.958 mmol, 1.2 equiv) in pentane (8 mL) was added Rh$_2$(OAc)$_4$ (1.7 mg, 0.004 mmol, 0.005 equiv). The mixture was immersed in a preheated oil bath and heated under reflux for 15 min, after
which it was cooled and concentrated under reduced pressure (0°C). Flash chromatography of the resulting residue (8:1 pentane:Et2O eluent) afforded \(\alpha\)-hydroxyketone \((R)-(\cdot)-111c\) (72 mg, 64% yield) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.52 (m, 1H), 5.32 (m, 1H), 3.71 (s, 1H), 2.37 (m, 2H), 2.19 (s, 3H), 1.64 (d, \(J=6.5\) Hz, 3H), 1.34 (s, 3H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 211.9, 129.6, 124.4, 78.8, 42.6, 24.9, 24.0, 18.0; IR (thin film/NaCl) 3477 (br m), 3027 (w), 2976 (m), 2935 (m), 2921 (m), 2858 (w), 1711 (s), 1451 (w), 1357 (m), 1161 (m), 972 (s) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 143.1075, [calc'd for C\(_8\)H\(_{15}\)O\(_2\) (M+H): 143.1072]; \([\alpha]\)\(\text{D}_{20}\) -35.8° (c 3.6, CHCl\(_3\)).

\(\alpha\)-Hydroxyketone \((\pm)-111b\).

\(\alpha\)-Hydroxyketone \((\pm)-111b\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.01 (t, \(J=7.2\) Hz, 1H), 3.70 (br s, 1H), 2.39 (m, 2H), 2.17 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.34 (s, 3H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 212.2, 135.5, 117.4, 78.9, 38.0, 25.8, 24.8, 23.8, 18.0; IR (thin film/NaCl) 3480 (br s), 2975 (s), 2928 (s), 2861 (m), 1710 (s), 1451 (m), 1375 (s), 1355 (s), 1164 (s), 1118 (s), 1098 (s), 940 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 157.1234, [calc'd for C\(_9\)H\(_{17}\)O\(_2\) (M+H): 157.1229].
α-Hydroxyketone (R)(-)-111d.

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{Me} & \quad \text{O} \quad \text{Me}
\end{align*}
\]

\[110 \quad \xrightarrow{\text{Rh}_2(\text{OAc})_4 \text{pentane, } \Delta \text{ 10 min}} \quad \text{Me} \quad \text{O} \quad \text{Me} \]

\[\text{(S)(-)-94d} \quad \xrightarrow{\text{Me} \quad \text{N}_2 \quad 110 + \quad \text{Me}} \quad \text{(R)(-)-111d}
\]

α-Hydroxyketone (R)(-)-111d. \(1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.25 (q, \(J=6.7\) Hz, 1H), 3.41 (br s, 1H), 2.43 (d, \(J=13.9\) Hz, 1H), 2.36 (d, \(J=13.9\) Hz, 1H), 2.21 (s, 3H), 1.60 (s, 3H), 1.56 (d, \(J=6.7\) Hz, 3H), 1.33 (s, 3H); \(1^C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 212.4, 131.4, 123.8, 79.3, 48.9, 25.5, 24.3, 17.1, 13.5; IR (thin film/NaCl) 3479 (br m), 2978 (m), 2924 (m), 2863 (w), 1709 (s), 1451 (m), 1357 (m), 1157 (m), 1116 (m), 967 (w) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 157.1231, [calc'd for C\(_9\)H\(_{17}\)O\(_2\) (M+H): 157.1229]; \([\alpha]_D^{20}\) -23.7° (c 1.9, CHCl\(_3\)).

α-Hydroxyketone (R)(-)-111e.

\[
\begin{align*}
\text{Me} & \quad \text{N} \quad \text{Me} \\
\text{Me} & \quad \text{O} \quad \text{Me}
\end{align*}
\]

\[110 \quad \xrightarrow{\text{Rh}_2(\text{OAc})_4 \text{pentane, } \Delta \text{ 10 min}} \quad \text{Me} \quad \text{O} \quad \text{Me}
\]

\[\text{(S)(-)-94e} \quad \xrightarrow{\text{Me} \quad \text{N}_2 \quad 110 + \quad \text{Me}} \quad \text{(R)(-)-111e}
\]

α-Hydroxyketone (R)(-)-111e. \(1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.57 (dq, \(J=1.4, 15.7\) Hz, 1H), 5.45 (dq, \(J=6.3, 15.6\) Hz, 1H), 2.16 (s, 3H), 1.69 (dd, \(J=1.4, 6.3\) Hz, 3H), 1.31 (s, 3H), 1.05 (s, 3H), 0.95 (s, 3H); \(1^C\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 213.1, 137.1, 124.2, 82.7, 42.5, 27.1, 23.3, 21.9, 20.4, 18.2; IR (thin film/NaCl) 3471 (br s), 3027 (w), 2971 (s), 2939 (s), 2880 (m), 1701 (s), 1449 (m), 1358 (s), 1127 (s), 1065 (w), 982 (s) cm\(^{-1}\).
HRMS (EI) m/z found: 171.1384, [calc'd for C_{10}H_{19}O_{2} (M+H): 171.1385]; [\alpha]D^{20} - 40.7° (c 2.8, CHCl_{3}).

\(\alpha\)-Hydroxyketone \((R,R)-(-)-111f\).

\(\alpha\)-Hydroxyketone \((R,R)-(-)-111f\). \(1H\) NMR (500 MHz, CDCl_{3}) \(\delta\) 5.26 (m, 1H), 3.47 (br s, 1H), 2.50 (q, \(J=7.0\) Hz, 1H), 2.17 (s, 3H), 1.51 (m, 6H), 1.32 (s, 3H), 1.17 (d, \(J=7.0\) Hz, 3H); \(13C\) NMR (125 MHz, CDCl_{3}) \(\delta\) 212.2, 137.5, 121.5, 81.6, 49.1, 24.2, 24.0, 13.1, 13.0; IR (thin film/NaCl) 3472 (br m), 2975 (m), 2936 (m), 1708 (s), 1451 (m), 1356 (m), 1160 (m), 969 (w) cm\(^{-1}\); HRMS (EI) m/z found: 171.1390, [calc'd for C_{10}H_{19}O_{2} (M+H): 171.1385]; [\alpha]D^{20} -32.6° (c 10.7, CHCl_{3}).

Representative Procedure for Determination of Relative and Absolute Stereochemistry of \(\alpha\)-Hydroxyketones \((R)-111c-g\).

\(\alpha\)-Hydroxyketone \((R,R)-(-)-111f\).
Preparation of $\alpha$-Hydroxyketone $\alpha$-(R)-(−)-111f from $\alpha$-Hydroxyacid (+)-113.

To a stirred solution of $\alpha$-hydroxyacid (+)-113 (342 mg, 2.37 mmol, 1.0 equiv) in THF (25 mL) at 0°C was added dropwise a solution of methyllithium (1.4 M, 6.0 mL, 8.40 mmol, 3.5 equiv). The resulting mixture was allowed to warm to room temperature and stirred for 12 h after which it was recooled to 0°C, quenched with H2O (10 mL), and acidified with 1N HCl (5 mL). The heterogeneous mixture was extracted with Et2O (4 x 50 mL) and the combined organic layers dried over MgSO4, filtered, and concentrated under reduced pressure. Flash chromatography (10:1 pentane:Et2O eluent) afforded $\alpha$-hydroxyketone (-)-(−)-111f (77 mg, 23% yield) that was identical spectroscopically to that obtained by by reaction of $\alpha$-diazoketone 110 with alcohol (S)-(−)-94f under Rh(II)-catalyzed conditions. Absolute stereochemistry was assigned by optical rotation: $[\alpha]_{D}^{20} -31.0^\circ$ (c 2.1, CHCl3).

Preparation of $\alpha$-Diazoketone 116.

\[ \text{115} \xrightarrow{p\text{-NBSA, DBU, CH}_2\text{Cl}_2, 0^\circ\text{C}} \text{116} \]

$\alpha$-Diazoketone 116. To a stirred solution of diketone 115 (2.10 g, 8.46 mmol, 1.0 equiv) and $p$-NBSA (3.61 g, 15.8 mmol, 1.9 equiv) in CH2Cl2 (50 mL) at 0°C was added dropwise DBU (2.5 mL, 16.7 mmol, 2.0 equiv). The resulting mixture was stirred for 20 min at 0°C and then concentrated. Flash chromatography (3:2 hexanes:EtOAc eluent)
afforded 116 (688 mg, 44% yield) as an orange oil. ¹H NMR (500 MHz, CDCl₃) δ 4.15 (q, J=7.1 Hz, 2H), 2.59 (m, 4H), 2.23 (s, 3H), 1.27 (t, J=7.1 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 191.0, 172.6, 60.7, 31.9, 25.2, 19.0, 14.1; IR (thin film/NaCl) 2983 (m), 2935 (m), 2080 (s), 1733 (s), 1636 (s), 1374 (s), 1327 (s), 1196 (s), 1018 (m), 977 (w), 847 (w) cm⁻¹. Due the unstable nature of this compound, satisfactory HRMS results could not be obtained.

Representative Procedure for Preparation of α-Hydroxyketones in Table 2.6 (α-Hydroxyketone (±)-117c).

α-Hydroxyketone (±)-117c. To a stirred solution of α-diazoketone 116 (82 mg, 0.446 mmol, 1.0 equiv) and (±)-3-buten-2-ol (94c, 46 µL, 0.531 mmol, 1.2 equiv) in benzene (5 mL) was added Rh₂(OAc)₄ (1.0 mg, 0.023 mmol, 0.005 equiv). The resulting mixture was immersed in a preheated oil bath and heated under reflux for 15 min. The mixture was cooled and concentrated and the residue purified by flash chromatography (4:1 pentane:Et₂O eluent) to provide α-hydroxyketone (±)-117c (52 mg, 51% yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.55 (m, 1H), 5.34 (m, 1H), 4.14 (q, J=7.2 Hz, 2H), 2.88 (ddd, J=6.2, 7.4, 18.4 Hz, 1H), 2.80 (ddd, J=5.9, 6.7, 18.5 Hz, 1H), 2.64 (ddd, J=5.8, 7.4, 17.2 Hz, 1H), 2.57 (ddd, J=6.5, 6.6, 17.3 Hz, 1H), 2.33-2.45 (m, 2H),
α-Hydroxyketone (±)-117a.

α-Hydroxyketone (±)-117a. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.74 (m, 1H), 5.10-5.15 (comp m, 2H), 4.13 (q, $J=$7.1 Hz, 2H), 2.89 (ddd, $J=$6.0, 7.4, 18.5 Hz, 1H), 2.81 (ddd, $J=$5.8, 6.9, 18.5 Hz, 1H), 2.65 (ddd, $J=$5.8, 7.4, 17.3 Hz, 1H), 2.58 (ddd, $J=$6.2, 6.8, 17.3 Hz, 1H), 2.50 (ddt, $J=$0.9, 7.4, 14.1 Hz, 1H), 2.45 (ddt, $J=$1.2, 7.2, 14.1 Hz, 1H), 1.40 (s, 3H), 1.25 (t, $J=$7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.3, 172.5, 132.3, 119.1, 78.5, 60.7, 44.0, 31.4, 28.0, 25.1, 14.1; IR (thin film/NaCl) 3492 (br m), 2981 (m), 2934 (m), 1735 (s), 1713 (s), 1451 (w), 1375 (m), 1349 (m), 1208 (s), 1177 (s), 1033 (m), 923 (w), 857 (w) cm$^{-1}$; HRMS (EI) $m/z$ found: 215.1282, [calc'd for C$_{11}$H$_{19}$O$_4$ (M+H): 215.1283].

α-Hydroxyketone (±)-117b.
α-Hydroxyketone (±)-117b.  $^1$H NMR (500 MHz, CDCl$_3$) δ 5.05 (m, 1H), 4.15 (q, J=7.1 Hz, 1H), 3.49 (s, 1H), 2.90 (dt, J=6.9, 18.3 Hz, 1H), 2.80 (dt, J=6.3, 18.5 Hz, 1H), 2.66 (ddd, J=6.1, 7.4, 17.3 Hz, 1H), 2.58 (dt, J=6.4, 17.2 Hz, 1H), 2.43 (m, 2H), 1.72 (s, 3H), 1.64 (s, 3H), 1.40 (s, 3H), 1.27 (t, J=7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 212.9, 172.5, 136.1, 117.5, 79.0, 60.7, 38.2, 31.3, 28.1, 25.9, 25.1, 18.1, 14.2; IR (thin film/NaCl) 3488 (br m), 2981 (m), 2917 (m), 1735 (s), 1714 (s), 1449 (w), 1376 (m), 1205 (s), 1179 (s), 1092 (m), 1035 (m), 1007 (w) cm$^{-1}$; HRMS (EI) m/z found: 243.1589, [calc'd for C$_{13}$H$_{23}$O$_4$ (M+H): 243.1596].

α-Hydroxyketone (±)-117d.

α-Hydroxyketone (±)-117d. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.28 (m, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.40 (s, 1H), 2.92 (dt, J=6.7, 18.7 Hz, 1H), 2.87 (dt, J=6.7, 18.7 Hz, 1H), 2.63 (dt, J=6.8, 17.2 Hz, 1H), 2.55 (dt, J=6.6, 17.2 Hz, 1H), 2.48 (d, J=13.9 Hz, 1H), 2.35 (d, J=13.9 Hz, 1H), 1.59 (m, 6H), 1.36 (s, 3H), 1.26 (t, J=7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 213.2, 172.6, 131.5, 124.3, 79.0, 60.7, 49.0, 31.7, 28.1, 25.8, 17.3,
14.1, 13.5; IR (thin film/NaCl) 3493 (br m), 2981 (m), 2930 (m), 2863 (w), 1736 (s), 1712 (s), 1449 (m), 1376 (m), 1206 (s), 1166 (s), 1034 (m), 1007 (m) cm⁻¹; HRMS (EI) m/z found: 243.1590, [calc'd for C₁₃H₂₃O₄ (M+H): 243.1596].

α-Hydroxyketone (±)-117e.

α-Hydroxyketone (±)-117e. ¹H NMR (500 MHz, CDCl₃) δ 5.62 (dq, J=1.4, 15.6 Hz, 1H), 5.51 (dq, J=6.3, 15.6 Hz, 1H), 4.14 (q, J=7.2 Hz, 2H), 2.93 (ddd, J=6.1, 7.1, 18.7 Hz, 1H), 2.77 (dt, J=6.4, 18.8 Hz, 1H), 2.56 (m, 2H), 1.73 (dd, J=1.4, 6.3 Hz, 3H), 1.35 (s, 3H), 1.26 (t, J=7.2 Hz, 3H), 1.08 (s, 3H), 1.00 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 213.7, 172.8, 136.9, 124.7, 82.7, 60.6, 42.8, 34.2, 28.4, 23.2, 22.1, 20.9, 18.3, 14.2; IR (thin film/NaCl) 3510 (br m), 1976 (s), 2937 (m), 2880 (w), 1736 (s), 1711 (s), 1449 (w), 1375 (s), 1349 (m), 1208 (s), 1178 (s), 981 (w) cm⁻¹; HRMS (EI) m/z found: 257.1759, [calc'd for C₁₄H₂₅O₄ (M+H): 257.1753].

α-Hydroxyketone (±)-117f.
**α-Hydroxyketone (±)-117f.**  
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.27 (m, 1H), 4.15 (q, $J$=7.1 Hz, 2H), 2.86 (m, 2H), 2.65 (td, $J$=7.3, 17.1 Hz, 1H), 2.52 (q, $J$=7.0 Hz, 1H), 2.43 (dt, $J$=6.5, 17.1 Hz, 1H), 1.52 (m, 6H), 1.36 (s, 3H), 1.27 (t, $J$=7.2 Hz, 3H), 1.17 (d, $J$=7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 212.9, 172.6, 137.6, 121.8, 81.4, 60.7, 49.4, 31.7, 28.2, 24.2, 14.2, 13.3, 13.2, 13.1; IR (thin film/NaCl) 3479 (br s), 2979 (s), 2933 (s), 2933 (s), 1737 (s), 1709 (s), 1449 (m), 1375 (s), 1207 (s), 1164 (s), 1033 (m), 1002 (m) cm$^{-1}$; HRMS (EI) $m/z$ found: 257.1745, [calc'd for C$_{14}$H$_{25}$O$_4$ (M+H): 257.1753].

**Preparation of α-Diazoketone 120.**

![Diagram of the preparation reaction](image)

**Preparation of α-Diazoketone 120.** To a stirred solution of β-diketone 119 (5.94 g, 27.2 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (200mL) at 0°C was added DBU (8.0 mL, 53.5 mmol, 2.0 equiv). This mixture was allowed to stir for 5 min, before $p$-NBSA (12.6 g, 55.3 mmol, 2.0 equiv) was added portionwise over 10 min. The resulting dark orange mixture was allowed to stir for 10 min, after which it was concentrated with concomitant adsorption onto silica gel. Flash chromatography (5:1 hexanes:ethyl acetate eluent) furnished a yellow oil which was triturated with hexanes. Filtration afforded α-diazoketone 120 (1.63g, 43% yield) as a bright yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.33 (t, $J$=7.2 Hz, 2H), 2.24 (s, 3H), 1.42 (m, 4H), 0.93 (t, $J$=7.2 Hz, 3H); $^{13}$C NMR
(100 MHz, CDCl₃) δ 191.2, 29.1, 25.4, 21.9, 13.8, 13.7; IR (thin film/NaCl) 2959 (m), 2931 (m), 2873 (w), 2067 (s), 1642 (s), 1465 (w), 1368 (m), 1331 (m), 954 (w) cm⁻¹. Due to the unstable nature of this compound, satisfactory HRMS results could not be obtained.

**Representative Procedure for Preparation of α-Hydroxyketones in Table 2.7 (α-Hydroxyketone (±)-121c).**

\[ \text{α-Hydroxyketone (±)-121c.} \]

To a stirred solution of α-diazoketone 120 (75 mg, 0.538 mmol, 1.0 equiv) and (±)-3-buten-2-ol (94c, 58 µL, 0.669 mmol, 1.2 equiv) in benzene (5 mL) was added Rh₂(OAc)₄ (1.2 mg, 0.003 mmol, 0.006 equiv). The mixture was immersed in a pre-heated oil bath and heated under reflux for 10 min, after which it was cooled and the solvent removed under reduced pressure. Flash chromatography of the residue (6:1 hexanes:ethyl acetate eluent) furnished α-hydroxyketone (±)-121c (64 mg, 65% yield) as a clear, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 5.51 (m, 1H), 5.32 (m, 1H), 3.76 (s, 1H), 2.52 (ddd, \( J=6.8, 8.2, 17.7 \) Hz, 1H), 2.47 (ddd, \( J=6.5, 8.0, 17.5 \) Hz, 1H), 2.37 (m, 1H), 1.64 (dd, \( J=1.3, 6.3 \) Hz, 3H), 1.58 (m, 2H), 1.33 (s, 3H), 1.31 (m, 2H), 0.91 (t, \( J=7.5 \) Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 214.2, 129.6, 124.6, 78.7, 42.9, 35.8, 25.6, 25.0, 22.4, 18.0, 13.8; IR (thin film/NaCl) 3480 (br m), 3027 (w), 2960 (s), 2934 (s), 2874 (s), 1707 (s), 1453 (m), 1369 (m), 1149 (m), 1036 (m), 973 (m) cm⁻¹; HRMS (EI) m/z found: 184.1461 [calc'd for C₁₂H₂₂O₂ (M+H): 184.1463].
**α-Hydroxyketone (±)-121a.**

![Reaction Scheme]

1H NMR (500 MHz, CDCl$_3$) δ 5.76-5.68 (comp. m, 1H), 5.12-5.08 (comp. m, 2H), 3.83 (s, 1H), 2.58-2.45 (comp. m, 4H), 1.60 (m, 2H), 1.32 (m, 2H), 0.92 (t, $J$=7.5 Hz, 3H); 13C NMR (125 MHz, CDCl$_3$) δ 213.8, 132.3, 118.8, 78.5, 44.0, 35.8, 25.6, 25.1, 22.4, 13.8; IR (thin film/NaCl) 3479 (br. m), 3079 (w), 2960 (m), 2934 (m), 2874 (m), 1707 (s), 1454 (m), 1368 (m), 1152 (m), 1036 (m), 919 (m) cm$^{-1}$; HRMS (EI) m/z found: 171.1376 [calc'd for C$_{10}$H$_{19}$O$_2$ (M+H): 171.1372].

**α-Hydroxyketone (±)-121b.**

![Reaction Scheme]

1H NMR (500 MHz, CDCl$_3$) δ 5.02 (m, 1H), 3.76 (s, 1H), 2.52 (ddd, $J$=6.5, 8.9, 17.1 Hz, 1H), 2.45 (ddd, $J$=6.4, 8.4, 17.6 Hz, 1H), 2.40 (m, 2H), 1.69 (s, 3H), 1.62 (s, 3H), 1.60-1.52 (comp. m, 2H), 1.35 (s, 3H), 1.31 (m, 2H), 0.91 (t, $J$=7.5 Hz, 3H); 13C NMR (125 MHz, CDCl$_3$) δ 214.4, 135.4, 117.6, 78.8, 38.2, 35.7, 25.8, 25.6, 25.0, 22.3, 18.0, 13.8; IR (thin film/NaCl) 3480 (br. m), 2961 (s), 2932 (s), 2916 (s), 2874 (s), 1707 (s), 1454 (m), 1368 (m), 1152 (m), 1036 (m), 919 (m) cm$^{-1}$. HRMS (EI) m/z found: 239.1376 [calc'd for C$_{10}$H$_{19}$N$_2$O$_2$ (M+H): 239.1378].
2874 (m), 1706 (s), 1453 (m), 1377 (m), 1119 (s), 1040 (s) cm⁻¹; HRMS (EI) m/z found: 199.1694 [calc'd for C₁₂H₂₃O₂ (M+H): 199.1698].

α-Hydroxyketone (±)-121d.

α-Hydroxyketone (±)-121d. ¹H NMR (500 MHz, CDCl₃) δ 5.25 (m, 1H), 3.65 (s, 1H), 2.57 (ddd, J=6.5, 8.4, 17.6 Hz, 1H), 2.51 (ddd, J=6.5, 8.3, 17.6 Hz, 1H), 2.44 (d, J=13.8 Hz, 1H), 2.36 (d, J=14.0 Hz, 1H), 1.63-1.50 (comp. m, 2H), 1.60 (s, 3H), 1.57 (d, J=6.5 Hz, 3H), 1.37-1.29 (m, 2H), 1.33 (s, 3H), 0.92 (t, J=7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 214.7, 131.6, 123.8, 79.2, 49.2, 36.2, 25.7, 25.7, 22.4, 17.2, 13.9, 13.5; IR (thin film/NaCl) 3479 (br. m), 2959 (s), 2933 (s), 2873 (m), 1705 (s), 1454 (m), 1379 (m), 1142 (m), 1119 (m), 1041 (w) cm⁻¹; HRMS (EI) m/z found: 198.1621 [calc'd for C₁₂H₂₂O₂ (M+H): 198.1620].

α-Hydroxyketone (±)-121e.
**α-Hydroxyketone (±)-121e.** ¹H NMR (500 MHz, CDCl₃) δ 5.60 (m, 1H), 5.48 (dq, J=6.3, 15.8 Hz, 1H), 3.72 (s, 1H), 2.56 (ddd, J=6.3, 8.8, 17.5 Hz, 1H), 2.46 (ddd, J=6.5, 8.5, 17.5 Hz, 1H), 1.73 (dd, J=1.5, 6.0 Hz, 3H), 1.60-1.49 (comp. m, 2H), 1.34 (s, 3H), 1.32 (m, 2H), 1.08 (s, 3H), 0.98 (s, 3H), 0.92 (t, J=7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 215.3, 137.2, 124.0, 82.5, 42.7, 38.7, 25.9, 23.4, 22.4, 22.0, 20.4, 18.2, 13.9; IR (thin film/NaCl) 3467 (br. m), 3027 (s), 2961 (s), 2934 (s), 2874 (m), 1697 (s), 1451 (m), 1368 (m), 1125 (s), 1067 (s), 982 (m) cm⁻¹; HRMS (CI) m/z found: 213.1857 [calc'd for C₁₃H₂₅O₂ (M+H): 213.1855].

**α-Hydroxyketone (±)-121f.**

![Reaction Scheme]

**α-Hydroxyketone (±)-121f.** ¹H NMR (500 MHz, CDCl₃) δ 5.24 (m, 1H), 3.76 (s, 1H), 2.54 (ddd, J=5.6, 9.4, 17.4 Hz, 1H), 2.51 (q, J=6.8 Hz, 1H), 2.44 (ddd, J=6.2, 8.9, 17.1 Hz, 1H), 1.66-1.55 (comp. m, 2H), 1.50 (s, 3H), 1.49 (s, 3H), 1.31 (s, 3H), 1.31 (m, 2H), 1.17 (d, J=6.5 Hz, 3H), 0.91 (t, J=7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 214.5, 137.7, 121.5, 81.4, 49.5, 36.1, 25.8, 24.3, 22.4, 13.9, 13.2, 13.1, 13.0; IR (thin film/NaCl) 3468 (br. m), 2961 (s), 2935 (s), 2874 (m), 1704 (s), 1453 (m), 1375 (m), 1362 (m), 1148 (m), 1034 (m) cm⁻¹; HRMS (CI) m/z found: 211.1692 [calc'd for C₁₃H₂₃O₂ (M-H): 211.1698].

68
Preparation of (Z)-Enone 124

(Z)-Enone 124. To a stirred solution of α-diazoketone 120 (97 mg, 0.692 mmol, 1.0 equiv) in benzene (7 mL) was added Rh\(_2\)(OAc)\(_4\) (3.0 mg, 0.007 mmol, 0.01 equiv). The resulting mixture was immersed in a pre-heated oil bath, heated at reflux for 10 min, and then cooled to room temperature. Partial concentration under reduced pressure followed by flash chromatography (100% CH\(_2\)Cl\(_2\) eluent) furnished (Z)-enone 124 (20 mg, 26% yield) as a pale yellow oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 6.15 (d, \(J=11.5\) Hz, 1H), 6.07 (dt, \(J=7.0, 11.5\) Hz, 1H), 2.59 (qd, \(J=1.5, 7.5\) Hz, 2H), 2.21 (s, 3H), 1.46 (sextet, \(J=7.5\) Hz, 2H), 0.94 (t, \(J=7.5\) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) δ 199.3, 148.4, 127.2, 31.6, 31.3, 22.4, 13.7; IR (thin film/NaCl) 2961 (s), 2933 (s), 2873 (s), 1694 (s), 1614 (s), 1458 (m), 1415 (s), 1355 (s), 1178 (s), 969 (m), 738 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 112.0889 [calc'd for C\(_7\)H\(_{12}\)O (M+): 112.0888].

Preparation of β-Diketone 125.

β-Diketone 125. To a stirred solution of 1-benzoylacetonone (114, 4.5 g, 27.5 mmol, 1.0 equiv) in toluene (45 mL) was added n-Bu\(_4\)NBr (468 mg, 1.45 mmol, 0.05 equiv) and
K$_2$CO$_3$ (14.9 g, 108 mmol, 3.9 equiv). The resulting suspension was immersed in a pre-heated oil bath and heated at reflux for 3 h. The dark yellow mixture was then cooled to 45°C and a solution of 4-methyl-1-bromopentane (5.0 g, 30.2 mmol, 1.1 equiv) in toluene (4 mL) was added dropwise over 20 min. The mixture was allowed to stir for 12 h, after which it was filtered and the filtrate concentrated under reduced pressure. The resulting dark brown residue was purified by flash chromatography (6:1 cyclohexane: ethyl acetate eluent) to furnish β-diketone 125 (1.61 g, 24% yield) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.99 (m, 2H), 7.61-7.46 (comp. m, 3H), 4.43 (t, $J=7.0$ Hz, 1H), 2.14 (s, 3H), 2.04-1.88 (comp. m, 2H), 1.51 (m, 1H), 1.33-1.16 (comp. m, 4H), 0.84 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 204.5, 196.4, 136.4, 133.6, 128.8, 128.6, 63.5, 38.6, 29.2, 27.7, 27.6, 25.4, 22.4; IR (thin film/NaCl) 2954 (s), 2868 (m), 1722 (s), 1676 (s), 1596 (m), 1580 (m), 1448 (m), 1357 (m), 1278 (m), 1216 (m), 694 (m) cm$^{-1}$; HRMS (EI) $m/z$ found: 247.1696 [calc'd for C$_{16}$H$_{23}$O$_2$ (M+H): 247.1698].

**Preparation of α-Diazoketone 126.**

![Reaction Scheme](image)

**Preparation of α-Diazoketone 126.** To a stirred solution of β-diketone 125 (3.44 g, 13.6 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (100 mL) at 0°C was added DBU (4.0 mL, 26.7 mmol, 2.0 equiv). This mixture was allowed to stir for 5 min, before $p$-NBSA (6.36 g, 27.6 mmol, 2.0 equiv) was added portionwise over 10 min. The resulting dark orange mixture was allowed to stir for 10 min, after which it was concentrated with concomitant
adsorption onto silica gel. Flash chromatography (8:1 hexanes:ethyl acetate eluent) furnished a yellow oil, which was trituated with hexanes. Filtration and concentration under reduced pressure afforded α-diazoketone 126 (678 mg, 30% yield) as a bright yellow oil. 1H NMR (400 MHz, CDCl3) δ 2.30 (t, J=7.6 Hz, 2H), 2.22 (s, 3H), 1.60-1.42 (comp. m, 3H), 1.22 (m, 2H), 0.87 (d, J=6.8 Hz, 6H); 13C NMR (100 MHz, CDCl3) δ 191.1, 27.7, 37.9, 25.4, 24.8, 22.5; IR (thin film/NaCl) 2955 (s), 2928 (s), 2870 (m), 2067 (s), 1642 (s), 1468 (m), 1367 (s), 1322 (s), 1127 (w), 958 (w) cm⁻¹. Due the unstable nature of this compound, satisfactory HRMS results could not be obtained.

Representative Procedure for Preparation of α-Hydroxyketones in Table 2.8 (α-Hydroxyketone (±)-127c).

α-Hydroxyketone (±)-127c. To a stirred solution of α-diazoketone 126 (58 mg, 0.345 mmol, 1.0 equiv) and (±)-3-buten-2-ol (94c, 36 μL, 0.415 mmol, 1.2 equiv) in benzene (4 mL) was added Rh₂(OAc)₄ (1.0 mg, 0.002 mmol, 0.006 equiv). The mixture was immersed in a pre-heated oil bath and heated under reflux for 10 mins, after which it was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash chromatography (8:1 hexanes:ethyl acetate eluent) afforded α-hydroxyketone (±)-127c (43 mg, 59% yield) as a clear, colorless oil. 1H NMR (500 MHz, CDCl3) δ 5.52 (m, 1H), 5.33 (m, 1H), 2.48 (m, 1H), 2.38 (m, 1H), 1.65 (dd, J=1.3,
6.3 Hz, 3H), 1.63-1.51 (comp. m, 3H), 1.34 (s, 3H), 1.16 (m, 2H), 0.89 (d, \( J=6.5 \) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 214.2, 129.6, 124.6, 78.6, 42.9, 38.5, 36.3, 27.9, 25.0, 22.5, 22.5, 21.3, 18.0; IR (thin film/NaCl) 3479 (br m), 2956 (s), 2936 (s), 2903 (s), 2871 (s), 1707 (s), 1455 (m), 1367 (m), 973 (m) cm\(^{-1}\); HRMS (EI) \( m/z \) found: 212.1777 [calc'd for C\(_{13}\)H\(_{24}\)O\(_2\) (M\(^+\)): 212.1776].

\( \alpha \)-Hydroxyketone (±)-127a.

\( \alpha \)-Hydroxyketone (±)-127a. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.71 (m, 1H), 5.11-5.07 (comp. m, 2H), 3.82 (s, 1H), 2.55-2.42 (comp. m, 2H), 1.67-1.48 (comp. m, 3H), 1.35 (s, 3H), 1.17 (m, 2H), 0.88 (d, \( J=6.5 \) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 213.8, 132.3, 118.7, 78.4, 44.0, 38.5, 36.3, 27.8, 25.0, 22.4, 21.3; IR (thin film/NaCl) 3478 (br. m), 3078 (w), 2955 (s), 2903 (m), 2871 (m), 1707 (s), 1456 (w), 1367 (m), 949 (w) cm\(^{-1}\); HRMS (EI) \( m/z \) found: 199.1701 [calc'd for C\(_{12}\)H\(_{23}\)O\(_2\) (M\(^+\)): 199.1698].

\( \alpha \)-Hydroxyketone (±)-127b.
**α-Hydroxyketone (±)-127b.** 1H NMR (400 MHz, CDCl$_3$) $\delta$ 5.02 (m, 1H), 2.55-2.35 (comp. m, 2H), 1.70 (d, $J$=1.2 Hz, 3H), 1.66-1.52 (comp. m, 3H), 1.63 (s, 3H), 1.36 (s, 3H), 1.16 (m, 2H), 0.89 (d, $J$=6.8 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 214.9, 135.8, 118.0, 79.2, 38.9, 38.6, 36.6, 28.3, 26.3, 25.5, 22.9, 21.8, 18.5; IR (thin film/NaCl) 3482 (br. m), 2955 (s), 2931 (s), 2871 (s), 1706 (s), 1453 (m), 1453 (m), 1366 (m), 1087 (w) cm$^{-1}$; HRMS (CI) m/z found: 227.2011 [calc'd for C$_{14}$H$_{27}$O$_2$ (M+H): 227.2011].

**α-Hydroxyketone (±)-127d.**

![Diagram](image)

**α-Hydroxyketone (±)-127d.** 1H NMR (500 MHz, CDCl$_3$) $\delta$ 5.25 (m, 1H), 3.66 (s, 1H), 2.55 (ddd, $J$=6.5, 8.5, 17.6 Hz, 1H), 2.49 (ddd, $J$=6.3, 8.5, 18.0 Hz, 1H), 2.44 (d, $J$=14.3 Hz, 1H), 2.36 (d, $J$=14.3 Hz, 1H), 1.63-1.53 (comp. m, 3H), 1.60 (s, 3H), 1.57 (d, $J$=6.5 Hz, 3H), 1.33 (s, 3H), 1.18 (m, 2H), 0.89 (d, $J$=6.0 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 214.7, 131.6, 123.8, 79.2, 49.2, 38.5, 36.7, 27.9, 25.7, 22.5, 22.5, 21.4, 17.2, 13.5; IR (thin film/NaCl) 3478 (br m), 2955 (s), 2870 (m), 1706 (s), 1454 (m), 1384 (m), 1366 (m), 1165 (w) cm$^{-1}$; HRMS (CI) m/z found: 227.2010 [calc'd for C$_{14}$H$_{27}$O$_2$ (M+H): 227.2011].
\( \text{\(\alpha\)-Hydroxyketone (\(\pm\))-127e.} \)

\[
\begin{align*}
\text{126} + \text{\(\pm\)-94e} & \xrightarrow{\text{Rh}_2(\text{OAc})_4, \text{benzene}, \Delta, 10 \text{ min}} \\
\text{\(\pm\)-127e}
\end{align*}
\]

\( \text{\(\alpha\)-Hydroxyketone (\(\pm\))-127e.} \) \(1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.58 (dq, \(J=1.5, 15.8\) Hz, 1H), 5.46 (dq, \(J=6.5, 15.8\) Hz, 1H), 3.70 (s, 1H), 2.51 (ddd, \(J=6.5, 8.8, 17.5\) Hz, 1H), 2.43 (ddd, \(J=6.5, 8.6, 17.6\) Hz, 1H), 1.72 (dd, \(J=1.3, 6.0\) Hz, 3H), 1.62-1.51 (comp. m, 3H), 1.33 (s, 3H), 1.14 (m, 2H), 1.06 (s, 3H), 0.96 (s, 3H), 0.88 (d, \(J=6.5\) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 215.3; 137.2, 124.1, 82.5, 42.7, 39.2, 38.5, 27.9, 23.5, 22.5, 22.0, 21.7, 20.4, 18.3; IR (thin film/NaCl) 3468 (br m), 2957 (s), 2872 (s), 1698 (m), 1468 (m), 1384 (m), 1367 (m), 1131 (m), 981 (w) cm\(^{-1}\); HRMS (Cl) \(m/z\) found: 231.2160 [calc'd for C\(_{15}\)H\(_{29}\)O\(_2\) (M+H): 241.2168].

\( \text{\(\alpha\)-Hydroxyketone (\(\pm\))-127f.} \)

\[
\begin{align*}
\text{126} + \text{\(\pm\)-94f} & \xrightarrow{\text{Rh}_2(\text{OAc})_4, \text{benzene}, \Delta, 10 \text{ min}} \\
\text{\(\pm\)-127f}
\end{align*}
\]

\( \text{\(\alpha\)-Hydroxyketone (\(\pm\))-127f.} \) \(1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.24 (m, 1H), 3.76 (br. s, 1H), 2.55-2.49 (comp. m, 2H), 2.43 (m, 1H), 1.65-1.45 (comp. m, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.31 (s, 3H), 1.23-1.13 (comp. m, 2H), 1.18 (d, \(J=7.2\) Hz, 3H), 0.89 (d, \(J=6.5\) Hz, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 214.6, 137.7, 121.5, 49.5, 38.6, 36.7, 27.9, 24.3,
22.5, 21.5, 13.2, 13.1, 13.0; IR (thin film/NaCl) 3467 (br m), 2955 (s), 2871 (s), 1704 (s), 1457 (m), 1384 (w), 1336 (m), 1350 (w), 1148 (w) cm⁻¹; HRMS (Cl) m/z found: 241.2165 [calc'd for C₁₅H₂₉O₂ (M+H): 241.2168].

**Preparation of (Z)-Enone 129**

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{N}_2 & \quad \text{Me} \\
126 & \quad \text{Rh}_2(\text{OAc})_4 \\
\text{PhH, } \Delta, \text{ 10 min} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
124 & 
\end{align*}
\]

(Z)-**Enone 129.** To a stirred solution of \(\alpha\)-diazoketone 126 (59 mg, 0.353 mmol, 1.0 equiv) in benzene (4 mL) was added Rh\(_2\)(OAc)\(_4\) (1.6 mg, 0.004 mmol, 0.01 equiv). The resulting mixture was immersed in a pre-heated oil bath and heated under reflux for 10 min. After cooling to room temperature, the mixture was partially concentrated under reduced pressure and subjected to flash chromatography (100% CH\(_2\)Cl\(_2\) eluent) to furnish (Z)-enone 126 (12 mg, 23% yield) whose spectral data corresponded with literature values.\(^{23}\)

**Representative Procedure for Preparation of \(\alpha\)-Hydroxyketones in Table 2.9 (\(\alpha\)-Hydroxyketone (+)-131b).**

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{N}_2 & \quad \text{Me} \\
130 & \quad \text{Rh}_2(\text{OAc})_4 \\
\text{C}_2\text{H}_4\text{Cl}_2, \Delta, \text{ 10 min} & \quad \text{Me} \\
\text{HO} & \quad \text{Me} \\
(+)-131b & 
\end{align*}
\]
**α-Hydroxyketone (+)-131b.** To a stirred solution of α-diazoketone 130 (44 mg, 0.298 mmol, 1.0 equiv) and (S)-(+-)94c (31 µL, 0.358 mmol, 1.2 equiv) in 1,2-dichloroethane (3mL) was added Rh$_2$(OAc)$_4$ (1.3 mg, 0.003 mmol, 0.01 equiv). The mixture was immersed in a pre-heated oil bath and heated under reflux for 10 min, after which it was cooled and concentrated under reduced pressure. Flash chromatography of the residue (6:1 hexanes:ethyl acetate eluent) afforded α-hydroxyketone (+)-131b (26 mg, 45% yield) as a clear yellow oil. $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.59 (s, 1H), 7.54-7.31 (comp. m, 5H), 5.64 (m, 1H), 5.34 (m, 1H), 3.66 (s, 1H), 2.85 (m, 1H), 2.74 (m, 1H), 1.67 (m, 3H); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 200.2, 138.2, 131.3, 128.8, 128.0, 125.8, 123.3, 81.2, 40.5, 18.1; IR (thin film/NaCl) 3485 (br. m), 3028 (w), 2917 (w), 1726 (s), 1448, 1343 (w), 1072 (w), 970 (m), 755 (m), 699 (m) cm$^{-1}$; HRMS (EI) $m/z$ found: 190.0992 [calc'd for C$_{12}$H$_{14}$O$_2$ (M+): 190.0994]; $[^{\alpha}]$D$^{20}$ +75.8º (c 1.1, CHCl$_3$).

**α-Hydroxyketone (±)-131a**

$\xrightarrow{\text{C}_2\text{H}_4\text{Cl}_2, \Delta 10 \text{ min}}$ 

**α-Hydroxyketone (±)-131a.** $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.61 (s, 1H), 7.45-7.32 (comp. m, 3H), 7.51 (m, 2H), 5.72 (m, 1H), 5.20 (m, 2H), 3.71 (s, 1H), 2.86 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.2, 138.4, 131.5, 129.3, 128.5, 126.2, 120.7, 81.5, 42.0; IR (thin film/NaCl) 3492 (br. m), 3075 (w), 3027 (w), 2616 (w), 2836 (w), 1725 (s), 1448
(m), 1260 (w), 923 (w), 758 (m), 699 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 177.0916 \[calc'd for \(\text{C}_{11}\text{H}_{13}\text{O}_{2}\) (M+H): 177.0916].

\(\alpha\)-Hydroxyketone (+)-131c (4:1 mixture of diastereomers)

\[\text{Rh}_2(\text{OAc})_4\]

\[\text{C}_2\text{H}_4\text{Cl}_2, \Delta 10 \text{ min}\]

\[\text{α}-\text{Hydroxyketone (+)-131c}. \quad \text{1H NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 9.65 \ (d, J=1.6 \text{ Hz, 1H}), 9.64 \ (d, J=1.6 \text{ Hz, 1H}), 7.56 \ (m, 4H), 7.48-7.26 \ (\text{comp. m, 6H}), 5.52 \ (m, 1H), 5.22 \ (m, 1H), 3.78 \ (d, J=1.2 \text{ Hz, 1H}), 3.71 \ (d, J=1.6 \text{ Hz, 1H}), 3.15 \ (q, J=7.1 \text{ Hz, 1H}), 3.05 \ (q, J=7.1 \text{ Hz, 1H}), 1.65 \ (m, 3H), 1.59 \ (m, 3H), 1.42 \ (m, 3H), 1.38 \ (m, 3H), 1.07 \ (d, J=6.8 \text{ Hz, 3H}), 0.94 \ (d, J=7.2 \text{ Hz, 3H}); \text{13C NMR} \ (100 \text{ MHz, CDCl}_3) \ \delta \ 200.7, 200.0, 138.6, 136.3, 128.8, 128.7, 128.2, 127.7, 127.3, 126.2, 125.8, 123.0, 122.9, 84.0, 49.4, 47.4, 14.1, 14.0, 13.3, 12.2; \text{IR (thin film/NaCl)} \ 3443 \ (m), 3421 \ (m), 2981 \ (m), 2930 \ (m), 2859 \ (m), 1721 \ (s), 1711 \ (s), 1446 \ (m), 1319 \ (m), 1194 \ (m), 962 \ (m), 799 \ (m), 747 \ (m), 701 \ (s) \text{ cm}^{-1}; \text{HRMS (EI) } m/z \text{ found: } 218.1302 \ \ [\text{calc'd for } \text{C}_{14}\text{H}_{18}\text{O}_{2} \text{ (M+): } 218.1307] \ \ [\alpha]D^{20} +96.4^\circ \text{ (c=1.3, CHCl}_3). \]

2.6 Notes and References


(11) For preparative procedure, spectral data, and optical rotation data, see refs 10a and 10b.


(19) For a comprehensive review, see ref 8.


(22) Enone 124 was the sole product by NMR analysis of the crude reaction mixture. Presumably, the low isolated yield is due to the volatility of 124.

(23) See ref. 16c.


(26) Use of 1,2-dichloroethane as solvent was necessary since the intermediate Rh(II) carbenoid reacted with benzene to furnish cycloheptatriene i, see: Ritter, K.; Hanack, M. Tetrahedron Lett. 1985, 26, 1285.
APPENDIX ONE: SPECTRA RELEVANT TO CHAPTER TWO
Figure A.1.1 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 104b.
Figure A.1.3 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 104b.

Figure A.1.2 FTIR Spectrum (thin film/NaCl) of Compound 104b.
Figure A.1.4 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 104c.
Figure A.1.6 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 104c.

Figure A.1.5 FTIR Spectrum (thin film/NaCl) of Compound 104c.
Figure A.1.7 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 104d.
Figure A.1.9: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 104d.

Figure A.1.8: FTIR Spectrum (thin film/NaCl) of Compound 104d.
Figure A.1.10 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 104e.
Figure A.1.12: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 104e.

Figure A.1.11: FTIR Spectrum (thin film/NaCl) of Compound 104e.

(Images of NMR and FTIR spectra are present.)
Figure A.1.13 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 104f.
Figure A.1.15 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 104f.

Figure A.1.14 FTIR Spectrum (thin film/NaCl) of Compound 104f.
Figure A.1.16 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 104g.
Figure A.1.18 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 1014.

Figure A.1.17 FTIR Spectrum (thin film/NaCl) of Compound 1048.
Figure A.1.19 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 134.
Figure A.1.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 134.

Figure A.1.20 FTIR Spectrum (thin film/NaCl) of Compound 134.
Figure A.1.22 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 111b.
Figure A.1.23 FTIR Spectrum (thin film/NaCl) of Compound 111b.

Figure A.1.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 111b.
Figure A.1.25 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 111c.
Figure A.1.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 111c.

Figure A.1.26 FTIR Spectrum (thin film/NaCl) of Compound 111c.
Figure A.1.28 $^1$H NMR (500 MHz, CDCl$_3$) of Compound $111d$. 
Figure A.1.30: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 111d.

Figure A.1.29: FTIR Spectrum (thin film/NaCl) of Compound 111d.
Figure A.1.31 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 111e.
Figure A.1.33 13C NMR (125 MHz, CDCl₃) of Compound 111e.

Figure A.1.32 FTIR Spectrum (thin film/NaCl) of Compound 111e.
Figure A.1.34 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 111f.
Figure A.1.3.6: $^1$H NMR (125 MHz, CDCl$_3$) of Compound III.

Figure A.1.3.5: FTIR Spectrum (thin film/NaCl) of Compound III.
Figure A.1.37 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 116.
Figure A.1.39 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 116.

Figure A.1.38 FTIR Spectrum (thin film/NaCl) of Compound 116.
Figure A.1.40 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 117a.
Figure A.1.42 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound $^{117a}$.

Figure A.1.41 FTIR Spectrum (thin film/NaCl) of Compound $^{117a}$. 

[Graph of $^{13}$C NMR spectrum]

[Graph of FTIR spectrum]
Figure A.1.43 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 117b.
Figure A.1.45: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 117b.

Figure A.1.44: FTIR Spectrum (thin film/NaCl) of Compound 117b.
Figure A.1.46 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 117c.
Figure A.1.48: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 117c.

Figure A.1.47: FTIR Spectrum (thin film/NaCl) of Compound 117c.
Figure A.1.49 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 117d.
Figure A.1.50 FTIR Spectrum (thin film/NaCl) of Compound 117d.

Figure A.1.51 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 117d.
Figure A.1.52 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 117e.
Figure A.1.54 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 117e.

Figure A.1.55 FTIR Spectrum (thin film/NaCl) of Compound 117e.
Figure A.1.55 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 117f.
Figure A.1.57: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 117.

Figure A.1.56: FTIR Spectrum (thin film/NaCl) of Compound 117.
Figure A.1.58 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 120.
Figure A.1.60 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 120.

Figure A.1.59 FTIR Spectrum (thin film/NaCl) of Compound 120.
Figure A.1.61 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 121a.
Figure A.1.63 \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) of Compound 121a.

Figure A.1.62 FTIR Spectrum (thin film/NaCl) of Compound 121a.
Figure A.1.64 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 121b.
Figure A.1.65 FTIR Spectrum (thin film/NaCl) of Compound 121b.

Figure A.1.66 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 121b.
Figure A.1.67 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 121c.
Figure A.1.69  $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 121c.

Figure A.1.68 FTIR Spectrum (thin film/NaCl) of Compound 121c.
Figure A.1.70 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 121d.
Figure A.1.72: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 121d.

Figure A.1.71: FTIR Spectrum (thin film/NaCl) of Compound 121d.
Figure A.1.73 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 121e.
Figure A.1.75: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 121e.

Figure A.1.74: FTIR Spectrum (thin film/NaCl) of Compound 121e.
Figure A.1.76 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 121f.
Figure A.1.77 FTIR Spectrum (thin film/NaCl) of Compound 121f.

Figure A.1.78 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 121f.
Figure A.1.79 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 124.
Figure A.1.81 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 124.

Figure A.1.80 FTIR Spectrum (thin film/NaCl) of Compound 124.
Figure A.1.82 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 125.
Figure A.1.84 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 125.

Figure A.1.83 FTIR Spectrum (thin film/NaCl) of Compound 125.
Figure A.1.85 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 126.
Figure A.1.86 FTIR Spectrum (thin film/NaCl) of Compound 126.

Figure A.1.87 \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) of Compound 126.
Figure A.1.88 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 127a.
Figure A.1.90 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 127a.

Figure A.1.89 FTIR Spectrum (thin film/NaCl) of Compound 127a.
Figure A.1.91 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 127b.
Figure A.1.92 FTIR Spectrum (thin film/NaCl) of Compound 127b.

Figure A.1.93 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 127b.
Figure A.1.94 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 127c.
Figure A.1.96 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 127c.

Figure A.1.95 FTIR Spectrum (thin film/NaCl) of Compound 127c.
Figure A.1.97 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 127d.
Figure A.1.99: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 127d.

Figure A.1.98: FTIR Spectrum (thin film/NaCl) of Compound 127d.
Figure A.1.100 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 127e.
Figure A.1.102 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 127e.

Figure A.1.101 FTIR Spectrum (thin film/NaCl) of Compound 127e.
Figure A.1.103 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 127f.
Figure A.1.105 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 127f.

Figure A.1.104 FTIR Spectrum (thin film/NaCl) of Compound 127f.
Figure A.1.106 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 131a.
Figure A.1.107 FTIR Spectrum (thin film/NaCl) of Compound 131a.

Figure A.1.108 13C NMR (100 MHz, CDCl3) of Compound 131a.
**Figure A.1.109** $^1$H NMR (400 MHz, CDCl$_3$) of Compound 131b.
Figure A.1.111 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 131b.

Figure A.1.110 FTIR Spectrum (thin film/NaCl) of Compound 131b.
Figure A.1.112 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 131c.
Figure A.1.114 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 131c.

Figure A.1.113 FTIR Spectrum (thin film/NaCl) of Compound 131c.
Chapter 3

The Discovery of α-Alkoxy Enols: New Reactive Intermediates in Organic Synthesis

3.1 Probing Mechanism: Early Endeavors and Unsettling Observations

3.1.1 Overview

The efforts described in the previous chapter established the rhodium carbenoid-initiated Claisen rearrangement as a general method for asymmetric tertiary alcohol synthesis. However, a mechanistic understanding of this novel transformation was far from being realized. Several features of the reaction were empirically understood, such as the effects of substituents on enantio- and diastereoselectivity. However, other observations awaited explanation, such as the catalyst-invariant, yet stoichiometrically dependent competition between [3,3]-rearrangement and OH-insertion (See Section 2.1). Therefore, concomitant with investigations into reaction scope, probe experiments such as those described in Section 2.1 were continually being conducted in an effort to gain mechanistic insight by observing responses to specific perturbations. These studies were greatly facilitated by the discovery of the α-diazoephynlacetone (103) substrate.

3.1.2 Temperature-Dependent Reactivity of α-Diazoacetone 103

As mentioned in Section 2.1.5, investigations of temperature dependence were hampered by slow decomposition of α-diazo-β-ketoester 59 at room temperature by Rh$_2$(OAc)$_4$. The dichotomous behavior of the α-diazoephynlacetone substrate (103) (thermally stable, yet readily decomposed by Rh(II) at low temperatures) rendered this
substrate much more useful than 59 for temperature-based reactivity studies. In conducting these studies with 103 and allyl alcohol (94a), a startling temperature dependence was noted. As can be seen from Table 3.1, reaction of 103 with 94a at reflux temperatures afforded exclusively (>99:1) $\alpha$-hydroxyketone 104a via [3,3]-rearrangement. However, the identical reaction at room temperature afforded an almost completely inverted product ratio, generating the as yet unseen OH-insertion product 105a in a 92:8 ratio with 104a.

![Chemical Reaction Diagram]

**Table 3.1 - Effect of Temperature on Product Distribution with 103 and 94a.**

<table>
<thead>
<tr>
<th>Temperature</th>
<th>104a:105a</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux (80ºC)</td>
<td>&gt;99:1</td>
<td>77%</td>
</tr>
<tr>
<td>25ºC</td>
<td>8:92</td>
<td>75%</td>
</tr>
</tbody>
</table>

Thus, while [3,3]-rearrangement could be carried out free of OH-insertion at elevated temperatures, formation of OH-insertion product 105a became tremendously competitive as reaction temperature decreased.

Such a result was considered to be in accord with three possible mechanistic scenarios. First, both products could arise from two independent processes that are always in competition (Mechanism A, Scheme 3.1). In this scenario, Rh(II)-catalyzed decomposition of 103 at lower temperatures favors production of an intermediate (136) from which 105a derives. At elevated temperatures, this intermediate is either converted into a second species (135) that gives rise to 104a, or else 135 is formed directly at elevated temperatures. A second imagined scenario was one where both 104a and 105a
derive from a common intermediate and the [3,3]-rearrangement process is significantly slower than OH-insertion at room temperature (Mechanism B). Finally, it was expected that such temperature dependence would be observed if $104a$ derived directly from $105a$ (Mechanism C), however, earlier studies refuting the intermediacy of $\alpha$-allyloxyketones en route to [3,3]-rearrangement products with substrate 59 cast doubt on this last scenario (See Section 1.3.2).

**Scheme 3.1**

**A. Thermal Discrimination of Intermediates**

\[
\begin{align*}
103 + 94a & \xrightarrow{\text{PhH, } \Delta} \text{137} \\
103 + 94a & \xrightarrow{\text{Rh}_2(\text{OAc})_4} \text{137} \\
\end{align*}
\]

\[
\begin{align*}
\text{135} & \xrightarrow{\Delta} \text{136} \\
\text{136} & \xrightarrow{\text{OH-Ins.}} \text{105a} \\
\end{align*}
\]

\[
\begin{align*}
\text{135} & \xrightarrow{[3,3]} \text{135} \\
\text{135} & \xrightarrow{\text{OH-Ins.}} \text{136} \\
\end{align*}
\]

**B. Thermal Discrimination of Products from a Common Intermediate**

\[
\begin{align*}
\text{137} & \xrightarrow{\text{PhH, } \Delta} \text{104a} \\
\text{137} & \xrightarrow{\text{PhH, } 25ºC} \text{105a} \\
\end{align*}
\]

**C. Direct Thermal Interconversion of Products**

\[
\begin{align*}
\text{105a} & \xrightarrow{\text{PhH, } \Delta} \text{104a} \\
\end{align*}
\]
3.1.3 Effect of Alcohol Substitution on the [3,3]/OH-Insertion Competition with 103

Having never observed OH-insertion products (e.g., 105a) with substrate 103 under the standard reaction conditions (benzene, reflux), the effect of alcohol substituents on the [3,3]-rearrangement/OH-insertion competition with this substrate was never examined. The determination that OH-insertion was the dominant process at room temperature now rendered such investigations possible. To this end, 103 was decomposed with Rh\(_2\)(OAc)\(_4\) in the presence of 3-buten-2-ol (94c) at room temperature (Scheme 3.2). While significantly slower than at reflux temperatures (ca. 4 h at room temperature), [3,3]-rearrangement did proceed, furnishing \(\alpha\)-hydroxyketone 104c to the exclusion of the corresponding OH-insertion product 105c. Thus, the presence of an alkyl substituent on the hydroxyl-bearing carbon of the allylic alcohol continued to exert a profound influence on reaction selectivity even at reduced temperatures.

**Scheme 3.2**

![Diagram](image)

3.1.4 Re-examination \(\alpha\)-Allyloxyketones as Potential Intermediates

During the course of the above investigation, it was observed that treatment of 103 and 94c with Rh\(_2\)(OAc)\(_4\) at room temperature resulted in a rapid dediazotization event. Nitrogen evolution was observed to be complete in less than 2 minutes and was accompanied by a loss of the characteristic yellow solution color imparted by the \(\alpha\)-diazoketone. Complete production of 104c, however, required four hours. Analysis of
the reaction mixture by thin-layer chromatography during this four-hour interval revealed an intermediate species that was slowly consumed as \(104c\) was formed. This marked the first time that an intermediate had ever been observed with this rhodium-initiated reaction. Furthermore, it was recognized that complete conversion of \(103\) to a single species immediately discredited the concept of a rhodium enolate intermediate (e.g., \(106\), Scheme 3.3) since only 1 mol\% of \(\text{Rh}_2(\text{OAc})_4\) was employed. An effort was thus made to isolate this transient species via chromatography. Surprisingly, the compound isolated was \(\alpha\)-allyloxyketone \(105c\), a disheartening result that called into question early experiments refuting the intermediacy of such species in a related system (See Section 1.3.2). Suspecting the worst, the independent synthesis of this compound was undertaken in an effort to establish its competency as an intermediate.

Treatment of commercially available \((S,S)-1\text{-phenylpropylene oxide (138)}\) with catalytic sulfuric acid in the presence of racemic \(94a\) furnished \(\beta\)-allyloxyalcohol \(139\) as 

\[
\begin{align*}
\text{PhH, rt, 2 min} \quad (-\text{N}_2(\text{g}))
\end{align*}
\]
a 1:1 mixture of diastereomers in 30% yield via epoxide ring-opening (Scheme 3.4).\(^1\)

Swern oxidation then furnished \(\alpha\)-allyloxyketone \(105c\). Interestingly, \(105c\) could not be made to undergo Claisen rearrangement with or without added \(\text{Rh}_2(\text{OAc})_4\) even upon prolonged heating, a result consistent with those obtained earlier with \(\alpha\)-allyoxy-\(\beta\)-ketoester \(58\) derived from methyl diazoacetoacetate (\(59\), Scheme 1.13). However, it was not possible to avoid the realization that the reaction conditions employed both in this earlier study and in the current experiment did not adequately reflect those of the actual carbenoid-initiated process. Thus, it was entirely possible that an \textit{in situ}-generated catalyst was promoting [3,3]-rearrangement of \(\alpha\)-allyloxyketones \(58\) and \(105c\) to their respective \(\alpha\)-hydroxyketones. Since an \textit{in situ} marker would be the only means of testing against this eventuality, the isotope labeling study presented in Scheme 3.5 was devised.
Decomposition of 103 with Rh$_2$(OAc)$_4$ in the presence of deuterium-labeled 3-buten-2-ol (140) and 105c under standard conditions gave rise to exclusively deuterated [3,3]-rearrangement product 141 and unaltered 105c. The absence of protic [3,3]-rearrangement product 104c unquestionably established that α-allyloxyketone 105c was an idle species under the reaction conditions, not a reactive intermediate en route to 104c. The identical experiment with α-allyloxy-β-ketoester 58 supported the same conclusion (Scheme 3.6). Treatment of a mixture of 59, 140, and suspected intermediate 58 with Rh$_2$(OAc)$_4$ under standard conditions furnished deuterated α-hydroxyketone 142 and unaltered 58.

Scheme 3.6
3.2 Identification of the Actual Reaction Intermediate

3.2.1 Observation of an \( \alpha \)-Allyloxy Enol

Reassured by the isotope labeling experiments depicted in Scheme 3.5 and 3.6, efforts were concentrated towards identifying the unknown intermediate by non-invasive methods. Since it was clear that isolation efforts resulted in the conversion of the intermediate species to OH-insertion product \( 105c \), \textit{in situ} observation by NMR spectroscopy was attempted. In the event, a solution of \( 103 \) and \( 94c \) in benzene-\( d_6 \) was treated with \( \text{Rh}_2(\text{OAc})_4 \) again resulting in complete decomposition of \( 103 \) as evidenced by rapid loss of nitrogen and solution decolorization. Analysis of the reaction mixture by \(^1\)H NMR spectroscopy revealed a species that was similar but not identical to OH-insertion product \( 105c \). Rather, the NMR spectrum observed was consistent with enol \( 143 \). In accord with observations made using thin-layer chromatography, continued monitoring by \(^1\)H NMR revealed that the disappearance of this intermediate and the appearance of \( \alpha \)-hydroxyketone \( 104c \) occurred concurrently (Scheme 3.7).

\textit{Scheme 3.7}

\[ \begin{array}{c}
\text{103} \quad \text{Rh}_2(\text{OAc})_4 \\
\text{benzene-}d_6 \\
\text{rt, 2 min} \\
\text{(-N}_2(\text{g})) \\
\end{array} \quad \begin{array}{c}
\text{143} \\
\text{4 h, rt} \\
[3,3] \\
\text{[67% yield]} \\
\end{array} \quad \begin{array}{c}
\text{(S)-(+)94c} \\
\end{array} \]

Importantly, \( 143 \) appeared by \(^1\)H NMR as a single isomer in benzene-\( d_6 \). As a precaution, the identical experiment was performed in \( \text{CD}_2\text{Cl}_2 \), again revealing a single compound by \textit{in situ} NMR analysis. This isomer was tentatively assigned the (Z)-
geometry based on the stereochemical outcome of the Claisen rearrangement, which at room temperature just as under the standard reflux conditions, furnished \((R)-(+)\)-104c.

### 3.2.2 Confirmation of α-Allyoxy Enols as Reaction Intermediates

Having tentatively assigned structure 143 to the observed intermediate, some precedent was sought both for the existence of such stable enol species and their preparation from α-diazoketones. A thorough literature search uncovered a 1986 report by McGarrity describing the acid-catalyzed decomposition of related α-diazoketone 144, which, in the presence of methanol, furnished \((Z)-\alpha\)-methoxyenol 145.\(^3\) The structure of 145 was established by single crystal X-Ray analysis. Seeking to verify similar reactivity under Rh(II)-catalyzed conditions, a solution of 144 and methanol (1.2 equiv) in dichloromethane was treated with Rh\(_2\)(OAc)\(_4\) resulting, as with 103, in loss of nitrogen and solution decolorization. The colorless mixture was cooled to -30°C and the solvent removed under reduced pressure leaving a white solid that was spectroscopically identical to 145 (Scheme 3.8). Tautomerization of enol 145 to α-methoxyketone 146 could be monitored by \(^1\)H NMR, complete conversion requiring ca. 4.5 h.\(^4\)

**Scheme 3.8**

Alternatively, using conditions reported by McGarrity, 145 could be trapped as the corresponding \((Z)\)-enol acetate 147 whose structure was confirmed by single crystal X-
ray analysis. Thus, it was established for the first time that rhodium (II)-catalyzed decomposition of an α-diazoketone in the presence of an aliphatic alcohol furnishes a (Z)-alkoxy enol.

To demonstrate that this reactivity extended to allylic alcohols, the Rh$_2$(OAc)$_4$-catalyzed decomposition of 144 was carried out in the presence of allylic alcohols 94a, 94c, and 150 (1.2 equiv), furnishing single isomers of the corresponding α-allyloxy enols 148, 149, and 151, respectively (Scheme 3.9). As shown in Figure 3.1, subsequent [3,3]-rearrangement of enol 149 could be monitored by $^1$H NMR in CD$_2$Cl$_2$ and was found to proceed with equal facility to that observed with enol 143. Complete conversion to α-hydroxyketone 152 was observed in ca. 3.5 hours. The spectrum of 3-buten-2-ol (94c) in
CD$_2$Cl$_2$ is provided in Figure 3.1 as a reference since excess allylic alcohol (1.2 equiv) was employed.

**Figure 3.1** - [3,3]-Rearrangement of $\alpha$-Allyloxy Enol 149 as Monitored by $^1$H NMR

Returning to the possible mechanistic pathways presented in Scheme 3.1, it was now clear that Mechanism B, wherein both OH-insertion and [3,3]-rearrangement products derive from a single intermediate, was operative. Moreover, the nature of the unknown intermediate (137, Scheme 3.1) and the means by which it affords these two products were now understood.

### 3.2.3 $\alpha$-Alloxy Enols as Versatile Synthetic Intermediates

While [3,3]-rearrangement of enols 143 and 149 was extremely rapid relative to the corresponding reaction of allyl vinyl ether,$^5$ it was felt that rearrangement was still
rather slow when compared to other possible reaction pathways. Thus, efforts were made to divert the reactivity of $\alpha$-allyoxy enol 143 before rearrangement could occur. As can be seen from Scheme 3.10, enol 143 was readily intercepted prior to rearrangement, enabling its conversion to the corresponding trifluoroacetate (153) or the more synthetically useful triflate (154) by treatment with the appropriate anhydride and triethylamine. Both reactions furnished a single isomeric enol derivative in good yields. Tautomerization to the formal OH-insertion product (105c) could also be accomplished simply by addition of triethylamine in the absence of anhydride. To ensure that the excellent geometric control observed with 153 and 154 was derived from direct trapping of the enol and not a stereoselective enolization of 105c, the isotope labeling study depicted in Scheme 3.11 was performed. Treatment of a solution of $\alpha$-diazoketone 103,
deuterium-labeled 3-buten-2-ol (140), and 105c with Rh$_2$(OAc)$_4$ effected decomposition of 103 and enol formation. The mixture was then subjected to the trifluoroacetate trapping conditions employed in Scheme 3.10 to furnish exclusively deuterated enol trifluoroacetate 155 (44% yield) and unaltered OH-insertion product 105c (91% recovery). Thus, enol trapping proceeded more rapidly than tautomerization under these conditions resulting in retention of enol geometry.

Scheme 3.11

![Scheme 3.11](image)

3.2.4 Confirmation of (Z)-Geometry in Enols Derived from 103 and 144

It had been established that Rh(II)-catalyzed decomposition of 144 in the presence of methanol furnished known (Z)-enol 145. It was not known whether the same (Z)-selectivity was exhibited with allylic alcohols, although this was very likely. The stereochemical outcome of the Claisen rearrangement of enol 143 certainly suggested a (Z)-enol geometry. Nevertheless, given that enol trapping was more rapid than tautomerization (See Scheme 3.11), it was recognized that the geometry of enols 143 and 145 could be inferred from the geometry of derivatives. With this in mind, decomposition of α-diazoketone 103 with Rh$_2$(OAc)$_4$ in the presence of allylic alcohol (1.2 equiv) was followed by treatment with trifluoroacetic anhydride and triethylamine affording enol trifluoroacetate 156 in 73% yield (Scheme 3.12). Exhaustive hydrogenation with PtO$_2$ furnished a single diastereomer of propyloxy trifluoroacetate.
To confirm that \textbf{157} possessed the indicated relative stereochemistry, an independent synthesis of this diastereomer was carried out. Acid-catalyzed ring-opening of (\textit{S},\textit{S})-1-phenylpropylene oxide (138) with \textit{n}-propanol was followed by treatment with trifluoroacetic anhydride and triethylamine to furnish propyloxy trifluoroacetate that was identical in all respects to \textbf{157}. Since this diastereomer would arise via hydrogen addition across the double bond of a (\textit{Z})-enol trifluoroacetate, structure \textbf{156} was deemed correct. Confirmation of (\textit{Z})-geometry in enols derived from \textit{\alpha}-diazoketone 144 was more straightforward since these enols furnished crystalline derivatives. Treatment of enol 148 with triflic anhydride and triethylamine furnished enol triflate \textbf{159}, whose structure was established by single crystal X-ray analysis (Scheme 3.13).

\textit{Scheme 3.12}
3.2.5 Proposed Mechanism of Enol Formation

It is widely accepted that rhodium (II) carbenoids possess significant electrophilic character at the carbenoid carbon. Indeed, most reactions of rhodium carbenoids are believed to begin by attack of a nucleophile on this carbon. In considering the reaction with allylic alcohols to form enols, it is expected that the first step of this process bears some resemblance to the reactions of rhodium carbenoids with allylic acetals and ethers discussed in Section 1.3.5. The relevant mechanistic aspects of these reactions are reiterated here using allylic acetal 88 as an example (Scheme 3.14). Reaction of 88 with ethyl diazoacetate in the presence of Rh\(_2\)(OAc)_4 furnishes homoallylic ether 90. This reaction is believed to proceed via nucleophilic attack of the acetal oxygen lone pairs on the rhodium carbenoid (160) to furnish rhodium-bound ylide 161. Detachment of the rhodium complex leaves ylide 89, which undergoes [2,3]-rearrangement to furnish 90.

Scheme 3.14

In the rhodium (II)-catalyzed reaction of allylic alcohols (e.g., 94c) with 103, an analogous nucleophilic attack of oxygen on the derived rhodium carbenoid 162 is believed to take place to furnish the analogous rhodium-bound ylide 163 (Scheme 3.15).
However, unlike with 161, rhodium detachment is followed by intramolecular proton transfer to furnish \((Z)\)-enol 143\(^{10}\). Presumably, this [1,5]-shift occurs much more rapidly than [2,3]-rearrangement when an acidic proton is the migrating group.

**Scheme 3.15**

3.2.6 Stability of Rhodium Carbenoid-Derived Allyloxy Enols

Once generated, rhodium carbenoid-derived enols are remarkably stable, undergoing tautomerization only very slowly to furnish the formal OH-insertion products. This property is critical since enol stability enables Claisen rearrangement to compete successfully with tautomerization. This property is also remarkable considering that the most commonly invoked images of enols are those of seldom observed, short-lived tautomers of aldehydes and ketones. However, even a cursory survey of the relevant literature reveals that simple enols, if generated under neutral conditions, have significant lifetimes due to a high kinetic barrier to tautomerization in the absence of acid or base. For example, Bosnich has reported the preparation of the enol form of methyl
ethyl ketone (164) via Rh(I)-catalyzed isomerization of 3-buten-2-ol (94c, Scheme 3.16).\textsuperscript{11} Remarkably, once isolated from the catalyst, 164 requires 14 days to tautomerize completely. This impressive result represents only one of many observations of enol stability under neutral conditions. Indeed, review articles devoted to the subject of stable simple enols appeared as early as 1979.\textsuperscript{12}

**Scheme 3.16**

\[
\begin{align*}
\text{94c} & \quad \xrightarrow{\text{[Rh(diphos)]}_2\text{(ClO}_4)_2, \text{acetone, 25°C, 9 min}} \quad \text{164} & \quad \xrightarrow{14 \text{ days, 25°C}} \quad \text{165}
\end{align*}
\]

With an understanding of the reactive intermediate at work in the rhodium carbenoid-initiated Claisen rearrangement, two observations merit further discussion. First, it was shown in Table 2.3 that increasing the number of equivalents of allyl alcohol (94a) employed in reaction with α-diazo-β-ketoester 59 resulted in increased quantities of OH-insertion by-product 96a (Scheme 3.17). While not obvious at the time of its discovery, this effect is now readily explained in terms of enol tautomerization, which should be more rapid in the presence of increasing quantities of a proton source such as 94a. Second, it was found that treatment of allyloxy enol 143 with triethylamine resulted in rapid conversion to the formal OH-insertion product 105c at 0°C (See Scheme 3.10). Presumably, the presence of triethylamine activates a base-catalyzed tautomerization pathway that is significantly accelerated relative to the non-catalyzed process.
3.2.7 Use of Deuterium Substitution to Inhibit Tautomerization

In researching the literature of simple enols, a report by Hoffman was found wherein deuterium substitution was employed to prolong enol lifetime (Scheme 3.18). \(^{13}\)

**Scheme 3.18**

![Scheme 3.18](image)

Protic enol 166 underwent complete tautomerization to \(\alpha\)-methoxyketone 168 in approximately 15 minutes. However, the corresponding deuterio-enol 167 required 20 days to achieve the same result. It was immediately recognized that deuterium substitution might be used to improve the ratio of 95a to 96a observed with \(\alpha\)-diazo-\(\beta\)-ketoester 59 by slowing the tautomerization event that furnished 96a. Thus, 59 was decomposed with Rh\(_2\)(OAc)_4 in the presence of allyl alcohol-OD (170, 1.2 equiv) in benzene-\(d_6\) to furnish a 84:16 mixture of 171 and 172 (Scheme 3.19). \(^{14}\) This represented a dramatic improvement over the 56:44 ratio observed with an equivalent quantity of protic allyl alcohol (94a) under the identical conditions.

**Scheme 3.19**

![Scheme 3.19](image)
3.3 Acyclic Diastereoselection and Chirality Transfer in the Rhodium Carbenoid-Initiated Claisen Rearrangement

3.3.1 Origin of Diastereomeric Claisen Rearrangement Products with 3-Penten-2-ol

It was shown in Chapter 2 that use of 3-penten-2-ol 94g in the carbenoid-initiated Claisen rearrangement with α-diazoketone 103 afforded only modest diastereoselectivity (i.e., \((R,R)\)-104g : 134 7:1) while use of 3-methyl-3-penten-2-ol (94f) afforded a single diastereomeric Claisen product ((\(R,R\))-104f, Scheme 3.20). At the time of these discoveries, explanations of chirality transfer and diastereoselectivity were severely impeded by a lack of understanding of reaction mechanism. Thus, the origin of the minor
diastereomer (134) observed with 94g was not clear, nor was it clear why introduction of an additional C-3 methyl substituent on the allylic alcohol framework should have such a dramatic effect on reaction diastereoselection. Such issues were now approachable in
light of the new understanding that \( \alpha \)-diazoketones and allylic alcohols combine to furnish (Z)-allyloxy enols, which are the species that undergo [3,3]-rearrangement.

The mechanistic issues that are considered to govern preparation of the major diastereomer (104g) derived from \( \alpha \)-diazoketone 103 and 3-penten-2-ol (94g) are described in Scheme 3.21. Initially, these two substrates combine in the presence of Rh(II) to furnish (Z)-enol 173, which is observed as a single isomer by \(^1\)H NMR. With the (Z)-enol geometry secured, the stereochemical outcome of the Claisen rearrangement is consistent with a chair-like transition state, wherein the equatorially disposed methyl substituent gives rise to the product (E)-olefin and where \( \sigma \)-bond formation occurs at the Re-faces of both the enol and the pendant olefin generating the (R,R) configuration at the two newly formed stereocenters. The minor diastereomer 134 must therefore arise from Scheme 3.21

![Scheme 3.21](image)

an erosion of this arrangement that exposes the opposite diastereoface of either the enol or the pendant olefin. Modifications to substrate and transition state structure that would be expected to cause such a condition are outlined in Scheme 3.22. With regard to substrate integrity, geometric inversion of (Z)-enol 173 to the corresponding (E)-enol 174 would expose the opposite, \textit{si} diastereoface, giving rise to (S,R)-134. However, this was considered highly unlikely since no evidence of (E)-enol production had ever been observed with any allylic alcohol. Furthermore, such a thermal interconversion would
necessarily have to pass through the tautomized \( \alpha \)-allyoxyketone (e.g., 105g), which was shown not to enolize under the rearrangement conditions (See Scheme 3.5). Similarly, isomerization of the pendant pentenyl group would also expose the opposite diastereoface to furnish \((R,S)-134\). However, such isomerization was also highly unlikely under the reaction conditions. Attention was thus turned to transition state structure. The Claisen rearrangement is known to proceed selectively via a chair-like transition state, however, fidelity to this transition state is not always absolute and rearrangement via a boat-like transition state is sometimes observed.\(^{15}\) Therefore, it was considered that chair-like transition state 176, while clearly favored, experience competition from one of two boat-like transition states 177 and 179, derived from inversion of the lower half or upper half, respectively, of chair 176. While either 177 or 179 would furnish the relative stereochemistry present in 134, boat-like transition state 177 was immediately discredited since Claisen rearrangement via this transition state would also generate a \((Z)\)-olefin (i.e., 178, Scheme 3.22) not found in 134. Thus, it was concluded that minor diastereomer 134 must be arising from a competition between chair-like transition state 176 and boat-like transition state 179.
Scheme 3.22

Enol Isomerization

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Ph} \\
\text{(Z)-enol} & \quad \text{(E)-enol} \\
\text{173} & \quad \text{174} \\
\end{align*}
\]

Enol Isomerization

Pendant Olefin Isomerization

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Ph} \\
\text{(S)} & \quad \text{(S)} \\
\text{173} & \quad \text{175} \\
\end{align*}
\]

Olefin Isomerization

Lower Chair-Boat Inversion

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Ph} \\
\text{(S)} & \quad \text{(S)} \\
\text{176} & \quad \text{177} \\
\end{align*}
\]

[3,3] 

Upper Chair-Boat Inversion

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Ph} \\
\text{(S)} & \quad \text{(S)} \\
\text{176} & \quad \text{179} \\
\end{align*}
\]

[3,3] 

3.3.2 Origin of Chair/Boat Interconversion

In instances where chair/boat interconversion would not furnish diastereomers, reductions in enantioselectivity would be expected since boat-like transition states such as 179 would expose the opposite enol enantioface. In examining chirality transfer from
enantioenriched allylic alcohols with diazo substrate \textit{103} (See Table 2.4), the only significant reduction in product chirality relative to that of the starting allylic alcohol was that observed with alcohol \textit{94e}. The poor chirality transfer observed with this alcohol is similarly explained by a competition between chair-like transition state \textit{180} which generates \((R)-\textit{104e}\) and boat-like transition state \textit{181} which erodes enantiomeric excess by generating the enantiomeric species \((S)-\textit{104e}\) (Scheme 3.23).

\textit{Scheme 3.23}

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {\textit{103}};
\node (2) at (2,0) {\textit{94e}};
\node (3) at (2,-2) {\textit{94c}};
\node (4) at (4,0) {\textit{180}};
\node (5) at (4,-2) {\textit{181}};
\node (6) at (6,0) {\textit{182}};
\node (7) at (8,0) {\textit{104e}};
\node (8) at (8,-2) {\textit{104c}};
\draw[->] (1) -- (2);
\draw[->] (2) -- (3);
\draw[->] (2) -- (4);
\draw[->] (2) -- (5);
\draw[->] (2) -- (6);
\draw[->] (3) -- (4);
\draw[->] (3) -- (5);
\draw[->] (3) -- (6);
\end{tikzpicture}
\end{center}

Such competition was not observed with allylic alcohol \textit{94c}, which afforded near quantitative chirality transfer via transition state \textit{182}. Inspecting allylic alcohols \textit{94e} and \textit{94g} for some commonality that could correlate the deviant results observed with these two alcohols reveals that both \textit{94e} and \textit{94g} furnish enols that are substituted at C6 of the enol framework (Figure 3.2). This observation, coupled with the excellent chair fidelity
observed with all other non-C6-substituted allyoxy enols, forced the conclusion that substitution of C6 on the enol framework induces an interconversion of chair and boat transition states.

**Figure 3.2 - C6-Substituted Allyloxy Enols**

Chair/boat inversion in the case of enol 183 likely occurs due to a well-precedented undesirable pseudo-1,3-diaxial interaction in chair-like transition state 180, which is alleviated in boat-like transition state 181 (Scheme 3.24). The reason for chair/boat interconversion with enol 173 is less clear. One possible explanation for this phenomenon may be found in the work of Daub, who proposed that, in the chair-like Claisen rearrangement transition state, the substituents about the newly forming carbon-carbon bond are not staggered, but rather approach a semi-eclipsed conformation. In this model, significant gauche-gauche interactions exist in the chair-like transition state for enol 173 (See Scheme 3.25), significantly elevating its free energy. This narrows the free energy gap between 176 and the corresponding boat-like transition state 179, in which, through a similar contortion, this interaction may be somewhat relieved.
3.3.3 Improved Diastereoselectivity with 3-Methyl-3-penten-2-ol (94f)

Given that enol 173 undergoes [3,3]-rearrangement through both chair-like transition state 176 and boat-like transition state 179, the effect of an additional enol C5 substituent in improving diastereoselectivity is easily rationalized. As can be seen in Scheme 3.26, this additional substituent causes significant transannular strain in boat-like transition state 185, elevating its free energy relative to chair-like transition state 184. Thus, rearrangement via 185 is efficiently suppressed. An analogous observation was made by Metz in the rearrangement of geometrically pure (Z)-N-silyl ketene N,O-acetals (Scheme 3.27).\textsuperscript{18} Rearrangement of the C5-unsubstituted species 186 furnished a 91:9 mixture of \textit{anti}-amide 190 and \textit{syn}-amide 191 via chair-like
and boat-like transitions states 188 and 189, respectively. Introduction of a C5 trimethylsilyl group (i.e., 187) improved diastereoselectivity to 99.2:0.8 192:193.

**Scheme 3.27**

The poor diastereoselectivity observed with α-diazoketone 130 may also be explained in terms of this beneficial transannular interaction. As depicted in Scheme 3.28, the enol (194) derived from reaction of 130 with alcohol 94f, while possessing the C5 substituent, lacks the complementary C2 substituent, resulting in more facile interconversion between chair and boat-like transition states and, consequently, poor diastereoselectivity ((S,R)-131c: (R,R)-131c 4:1, See Table 2.9).
3.4 Summary and Conclusions

Critical discoveries regarding the mechanism of the rhodium carbenoid-initiated Claisen rearrangement were presented. These findings evolved from investigations of temperature-dependent reactivity during which a discrete intermediate species was detected. Naïve attempts to isolate this intermediate resulted in the isolation of OH-insertion product 105c, however, isotope labeling studies irrefutably established that this species did not undergo conversion to 104c under the reaction conditions. While not isolable, observation of the intermediate could be achieved by NMR, resulting in the discovery that α-keto rhodium (II) carbenoids react with allylic alcohols to furnish (Z)-α-allyloxy enols (e.g., 143). This finding was confirmed by preparation of known α-methoxy enol 145 and by conversion of α-allyloxy enols to a number of derivatives. Importantly, these studies establish that rhodium (II)-mediated OH-insertions of α-diazoketones proceed via initial proton transfer to oxygen followed by tautomerization.
With the (Z)-enol geometry established, both the sense of chirality transfer and the diastereoselectivity of the Claisen rearrangement are predicted by a chair-like transition state such as 176. The minor diastereomer (134) observed with α-diazoketone 103 and 3-penten-2-ol (94g) is believed to arise via boat-like transition state 179, which competes with chair-like transition state 176. The improved diastereoselectivity offered by allylic alcohol 94f is attributed to the additional C3 substituent on the allylic alcohol framework. This substituent is believed to bias the transition state competition towards chair-like transition state 184 by causing significant non-bonded interactions in the corresponding boat-like transition state (185). Similar transition state competitions are presumed responsible for both the poor chirality transfer observed with allylic alcohol 94e and the poor diastereoselectivity/chirality transfer afforded by α-diazoketone 130.

3.5 Experimental Section

3.5.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using freshly distilled solvents. All commercially obtained reagents were used as received. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. High-performance liquid chromatography (HPLC) was performed with either a Rainin Microsorb 80-199-C5 or 80-120-C5 column. Infrared spectra were acquired using a MIDAC M-1200 FTIR. 1H and 13C NMR spectra were recorded using Bruker AM500 or Bruker Avance 400/500 MHz spectrometers. Chemical shifts are reported as δ values relative to internal
chloroform ($^1H\ \delta\ 7.27\ ppm,\ ^{13}C\ \delta\ 77.0\ ppm$) or benzene-d$_6$ ($^1H\ \delta\ 7.15\ ppm$). Where inseparable mixtures of diastereomers are isolated, $^1H$ NMR spectral integration reflects a 1:1 mixture. Melting points are uncorrected. High-resolution mass spectra were acquired at the University of Illinois Mass Spectrometry Center.

### 3.5.2 Preparative Procedures

**Preparation of $\alpha$-Allyloxyketone 105a**

To a stirred solution of a-diazoketone 103 (30 mg, 0.188 mmol, 1.0 equiv) and allyl alcohol (94a, 15 µL, 0.221 mmol, 1.2 equiv) in C$_6$D$_6$ (2 mL) was added Rh$_2$(OAc)$_4$ (1.0 mg, 0.002 mmol, 0.01 equiv). The resulting mixture was stirred overnight at room temperature. Analysis of an aliquot by $^1H$ NMR revealed the presence of both 104a and 105a in a 92:8 ratio. The mixture was concentrated and the residue purified by flash chromatography (8:1 hexanes: ethyl acetate eluent) to furnish 105a (27 mg, 75% yield) as a clear yellow oil. $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.21-7.32 (comp m, 5H), 5.84 (m, 1H), 5.20 (m, 1H), 5.13 (m, 1H), 4.71 (s, 1H), 3.96 (m, 1H), 3.88 (m, 1H), 2.04 (s, 3H); $^{13}C$ NMR (125 MHz, CDCl$_3$) $\delta$ 207.0, 136.0, 133.8, 128.8, 128.5, 126.9, 117.7, 86.7, 70.1, 25.1; IR (thin film/NaCl) 3064 (w), 3031 (w), 2863 (w), 1719 (s), 1493 (w), 1452 (w), 1354 (m), 1098 (m), 1071 (m), 927 (w), 744 (m), 701 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 191.1069, [calc'd for C$_{12}$H$_{15}$O$_2$ (M+H): 191.1072].
Preparation of α-Allyoxy Ketone 105c.

α-Allyoxy Ketone 105c. To a mixture of (S,S)-1-phenylpropylene oxide (138, 102 mg, 0.760 mmol, 1.0 equiv) and (±)-3-buten-2-ol (94c, 0.13 mL, 1.50 mmol, 2.0 equiv) in CH₂Cl₂ (0.8 mL) at 0°C was added concentrated H₂SO₄ (8 µL). The yellow mixture was stirred for 30 min at 0°C, warmed to room temperature, diluted with CH₂Cl₂ (5 mL), and washed with saturated NaHCO₃ solution (3 x 5 mL). The organic phase was dried over MgSO₄, filtered, and concentrated to provide 64 mg of a crude mixture of the desired ring-opened product (139, 1:1 mixture of diastereomers) and phenylacetone (133). A solution of this oil in CH₂Cl₂ (1 mL) was added to a mixture of oxalyl chloride (19 µL, 0.221 mmol 1.0 equiv) and DMSO (31 µL, 0.434 mmol, 2.0 equiv) in CH₂Cl₂ (1 mL) at -78°C. After stirring for 30 min at -78°C, triethylamine (0.11 mL, 0.791 mmol, 3.6 equiv) was added and the mixture warmed to room temperature. After a further 30 min at room temperature, 1N HCl solution (1 mL) was added and the organic phase separated, dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography (8:1 hexanes:EtOAc eluent) afforded 105c (1:1 mixture of diastereomers, 24 mg, 16% yield) as a colorless oil. Separation of diastereomers could be achieved by careful flash chromatography (1:3 pentane:CH₂Cl₂ eluent). First diastereomer to elute: ¹H NMR (500
MHz, CDCl₃) δ 7.29-7.45 (comp m, 5H), 5.73 (ddd, J=7.1, 10.2, 17.3 Hz, 1H), 5.17 (m, 2H), 4.88 (s, 1H), 3.96 (quint, J=6.4 Hz, 1H), 2.12 (s, 3H), 1.37 (d, J=6.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 208.4, 139.2, 136.5, 128.6, 128.2, 126.6, 116.6, 84.6, 76.2, 24.9, 21.1; IR (thin film/NaCl) 3065 (w), 3031 (w), 2978 (m), 2930 (w), 2868 (w), 1717 (s), 1494 (m), 1421 (m), 1354 (m), 1210 (m), 1094 (s), 1072 (s), 925 (m), 742 (m), 700 (s) cm⁻¹; HRMS (EI) m/z found: 205.1226, [calc'd for C₁₃H₁₇O₂ (M+H): 205.1229].

Second diastereomer to elute: ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.41 (comp m, 5H), 5.75 (ddd, J=7.7, 10.0, 17.6 Hz, 1H), 5.20 (d, J=10.1 Hz, 1H), 5.13 (d, J=17.3 Hz, 1H), 4.86 (s, 1H), 3.83 (6.7, 1H), 2.14 (s, 3H), 1.31 (d, J=6.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 207.0, 139.1, 136.7, 128.7, 128.4, 127.1, 117.3, 84.7, 75.2, 25.5, 21.5; IR (thin film/NaCl) 3065 (w), 3030 (w), 2978 (m), 2929 (w), 1720 (s), 1493 (w), 1451 (m), 1421 (m), 1374 (w), 1353 (m), 1221 (w), 1187 (w), 1091 (s), 1071 (s), 994 (m), 745 (m), 701 (s) cm⁻¹; HRMS (EI) m/z found: 205.1227, [calc'd for C₁₃H₁₇O₂ (M+H): 205.1229].

Disproving the Intermediacy of 105c via Isotope Labelling

To a stirred solution of α-diazoketone 103 (54mg, 0.336 mmol, 1.0 equiv), allylic alcohol 140 (30 mg, 0.405 mmol, 1.2 equiv), and 105c (69 mg, 0.339, 1.0 equiv) in benzene (4
mL) was added Rh$_2$(OAc)$_4$ (0.4 mg, 0.0007 mmol, 0.002 equiv). The resulting mixture was immersed in a preheated oil bath, heated under reflux for 20 min, then cooled and concentrated under reduced pressure. Flash chromatography of the residue (3:1 CH$_2$Cl$_2$:pentane eluent) furnished deuterated α-hydroxyketone 141 (56 mg, 81% yield) and unaltered 105c (57 mg, 83% recovery). α-hydroxyketone 141: $^1$H NMR (500 MHz, CDCl$_3$) δ 8.01 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 5.36 (s, 1H), 3.92 (s, 1H), 2.75 (ddd, $J$=1.0, 7.1, 14.1 Hz, 1H), 2.54 (ddd, $J$=1.0, 7.5, 14.1 Hz, 1H), 1.60 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 204.4, 134.5, 132.8, 129.9 (t, $J$=22.7 Hz), 129.5, 128.3, 124.4, 78.9, 44.2, 26.7, 17.6; IR (thin film/NaCl) 3496 (br. s), 1064 (w), 2927 (m), 1673 (s), 1588 (m), 1445 (s), 1370 (s), 1230 (s), 1159 (s), 963 (m), 711 (m) cm$^{-1}$; HRMS (EI) m/z found: 206.1288 [calc'd for C$_{13}$H$_{16}$O$_2$D (M+H): 206.1291].

**Disproving the Intermediacy of 58 via Isotope Labelling**

![Disproving the Intermediacy of 58 via Isotope Labelling](image)

To a stirred solution of α-diazo-β-ketoester 59 (48 mg, 0.341 mmol, 1.0 equiv), allylic alcohol 140 (30 mg, 0.414 mmol, 1.2 equiv), and α-allyloxy-β-ketoester 58 (62 mg, 0.335 mmol, 1.0 equiv) in benzene (4 mL) was added Rh$_2$(OAc)$_4$ (0.2 mg, 0.0004 mmol, 0.001 equiv). The mixture was immersed in a preheated oil bath and heated under reflux for 20 min, after which it was cooled to room temperature and concentrated under
reduced pressure. The residue was purified by flash chromatography (6:1 pentane:diethyl ether eluent) to furnish deuterated β-hydroxy-α-ketoester 142 (31.0 mg, 50% yield) and unaltered 58 (52 mg, 84% recovery). β-hydroxy-α-ketoester 142: 1H NMR (500 MHz, CDCl3) δ 5.33 (m, 1H), 3.87 (s, 3H), 3.14 (s, 1H), 2.68 (ddd, J = 1.0, 7.1, 14.0 Hz, 1H), 2.40 (ddd, J = 1.0, 7.7, 14.0 Hz, 1H), 1.65 (s, 3H), 1.46 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 198.6, 162.7, 131.0 (t, J = 23.0 Hz), 123.5, 78.5, 52.7, 42.4, 24.4, 17.9; IR (thin film/NaCl) 3523 (br m), 2959 (m), 2939 (m), 2919 (m), 2857 (w), 2227 (w), 1743 (s), 1729 (s), 1451 (m), 1437 (m), 1295 (s), 1040 (s) cm⁻¹; HRMS (EI) m/z found: 188.1034, [calc'd for C₉H₁₄O₄D (M+H): 188.1033].

Rhodium (II)-Catalyzed Preparation of Known Enol 145

Enol 145. To a stirred solution of α-diazoketone 144 (61 mg, 0.272 mmol, 1.0 equiv) and methanol (13 μL, 0.321 mmol, 1.2 equiv) in CD₂Cl₂ (3 mL) was added Rh₂(OAc)₄ (1.8 mg, 0.003 mmol, 0.01 equiv). The mixture was allowed to stir at room temperature until nitrogen evolution was observed to have ceased (ca. 2 min). The colorless mixture was then cooled to -30°C and the solvent removed in vacuo, leaving behind a white solid that was redissolved in CDCl₃ (1.5 mL). The solution was transferred by syringe to a septum-covered NMR tube that had previously been purged with nitrogen for 20 min.¹⁹
Analysis by NMR afforded spectral data identical with those reported previously for 145.³

**Preparation of Enol Acetate 147.**

![Diagram of enol acetate preparation](image)

Enol Acetate 147. To a stirred solution of α-diazoketone 144 (733 mg, 3.30 mmol, 1.0 equiv) and methanol (0.15 mL, 3.70 mmol, 1.1 equiv) in CH₂Cl₂ (30 mL) was added Rh₂(OAc)₄ (15.0 mg, 0.033 mmol, 0.01 equiv) resulting in loss of N₂(g). The resulting colorless solution was added dropwise with careful air exclusion to a mixture of acetic anhydride (19 mL, 0.20 mol, 61 equiv) and BF₃•OEt₂ (63 mL, 0.50 mmol, 0.15 equiv) at -78°C. After stirring for 30 min at -78°C, the mixture was warmed to room temperature and concentrated under reduced pressure. The residue was redissolved in Et₂O (50 mL) and washed with sat. NaHCO₃ solution (careful-much CO₂(g) pressure!) until washings were basic as indicated by pH paper. The organic phase was dried over MgSO₄, filtered, and concentrated. Flash chromatography (1:1 hexanes:CH₂Cl₂ eluent) afforded enol acetate 147 (780 mg, 88% yield) as a colorless viscous oil which solidified upon cooling (0°C) overnight. Material prepared in this manner was spectroscopically identical to that prepared under reported conditions.³ Recrystallization from heptane afforded crystals suitable for X-Ray analysis.
Preparation and $^1$H NMR Observation of $\alpha$-Allyoxy Enol 148.

![Reaction Scheme](image)

$\alpha$-Allyoxy Enol 148. To a stirred solution of $\alpha$-diazoketone 144 (50 mg, 0.225 mmol, 1.0 equiv) and allyl alcohol ($94a$, 16 µL, 0.235 mmol, 1.0 equiv) in C$_6$D$_6$ (3 mL) was added Rh$_2$(OAc)$_4$ (1.0 mg, 0.0023 mmol, 0.01 equiv) resulting in rapid N$_2$(g) loss and decolorization of the reaction mixture. $^1$H NMR of an aliquot (1 mL) revealed complete conversion of 144 to 148. $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 7.51 (m, 2H), 7.25 (m, 2H), 6.90-7.00 (comp m, 6H), 6.10 (br s, 1H), 5.66 (ddt, $J$=5.8, 10.4, 17.1 Hz, 1H), 5.00 (dq, $J$=1.6, 17.2 Hz, 1H), 4.94 (dq, $J$=1.2, 10.2 Hz, 1H), 3.84 (dt, $J$=1.3, 5.8 Hz, 2H).

Preparation and $^1$H NMR Observation of $\alpha$-Allyoxy Enol 149.

![Reaction Scheme](image)

$\alpha$-Allyoxy Enol 149. To a stirred solution of $\alpha$-diazoketone 144 (45 mg, 0.202 mmol, 1.0 equiv) and 3-buten-2-ol ($94c$, 18 µL, 0.208 mmol, 1.0 equiv) in C$_6$D$_6$ (2 mL) at room temperature was added Rh$_2$(OAc)$_4$ (1.2 mg, 0.0027 mmol, 0.01 equiv) resulting in rapid conversion of 144 to enol 149 with concomitant loss of N$_2$(g). $^1$H NMR (500 MHz,
$\text{C}_6\text{D}_6 \delta 7.51$ (m, 2H), 7.26 (m, 2H), 6.91-7.00 (com p m, 6H), 6.12 (br s, 1H), 5.64 (ddd, $J=6.6, 8.1, 10.5$ Hz, 1H), 4.90 (m, 2H), 4.07 (m, 1H), 1.07 (d, $J=6.4$ Hz, 3H).

**Preparation and $^1\text{H}$ NMR Observation of $\alpha$-Allyoxy Enol 151.**

![Diagram](attachment:image_url)

**$\alpha$-Allyoxy Enol 151.** To a stirred solution of $\alpha$-diazoketone 144 (51 mg, 0.229 mmol, 1.0 equiv) and 2-methyl-2-propen-1-ol (150, 20 µL, 0.238, 1.0 equiv) in $\text{C}_6\text{D}_6$ (2.5 mL) at room temperature was added Rh$_2$(OAc)$_4$ (1.0 mg, 0.0024 mmol, 0.01 equiv) resulting in rapid N$_2$(g) loss and decolorization of the reaction mixture. $^1\text{H}$ NMR analysis of an aliquot showed complete conversion of 144 to enol 151. $^1\text{H}$ NMR (500 MHz, $\text{C}_6\text{D}_6$) $\delta$ 7.52 (m, 2H), 7.26 (m, 2H), 6.92-7.00 (comp m, 6H), 6.16 (br s, 1H), 4.94 (s, 1H), 4.78 (s, 1H), 3.81 (s, 2H), 1.51 (s, 3H).

**Preparation and $^1\text{H}$ NMR Observation of $\alpha$-Allyloxy Enol 143.**

![Diagram](attachment:image_url)
**α-Allyloxy Enol 143.** To a stirred solution of α-diazoketone 103 (57 mg, 0.356 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 31 mL, 0.358 mmol, 1.0 equiv) in C₆D₆ (4 mL) was added in one portion Rh₂(OAc)₄ (1.6 mg, 0.0036 mmol, 0.01 equiv) resulting in rapid conversion of 103 to 143 with concomitant loss of N₂(g) and solution decolorization. ¹H NMR (500 MHz, C₆D₆) δ 7.29 (m, 2H), 7.00-7.15 (comp m, 3H), 5.90 (br s, 1H), 5.62 (m, 1H), 4.91 (d, J=1.0 Hz, 1H), 4.88 (m, 1H), 3.99 (m, 1H), 1.88 (s, 3H), 1.05 (d, J=6.4 Hz, 3H).

**Preparation and ¹H NMR Observation of α-Allyloxy Enol 147.**

![Reaction Scheme](image)

**α-Allyloxy Enol 173.** To a stirred solution of α-diazoketone 103 (27 mg, 0.169 mmol, 1.0 equiv) and 3-penten-2-ol (94g, 17 µL, 0.166 mmol, 1.0 equiv) in C₆D₆ (2 mL) was added in one portion Rh₂(OAc)₄ (1.0 mg, 0.002 mmol, 0.01 equiv) resulting in rapid conversion of 103 to 173 with concomitant loss of N₂(g). ¹H NMR (400 MHz, C₆D₆) δ 7.33 (m, 2H), 7.00-7.17 (comp m, 3H), 5.98 (br s, 1H), 5.28 (m, 2H), 4.01 (m, 1H), 1.90 (s, 3H), 1.44 (d, J=4.8 Hz, 3H), 1.11 (d, J=6.4 Hz, 3H).
α-Hydroxyketone 152. To a stirred solution of α-diazoketone 144 (85 mg, 0.382 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 40 µL, 0.462, 1.2 equiv) in CD₂Cl₂ (4 mL) was added Rh₂(OAc)₄. Once nitrogen evolution was complete (ca. 2 min), an aliquot (ca. 0.5 mL) of this mixture was transferred via syringe to a septum-capped NMR tube that had previously been purged with nitrogen for 20 min. The N₂(g) inlet was removed and ¹H NMR spectra (500 MHz) were acquired every 20 min for 4 h. When conversion of 149 to 152 was complete as judged by ¹H NMR, the NMR sample was returned to the reaction flask and the combined solution concentrated under reduced pressure. Flash chromatography (10:1 hexanes: ethyl acetate eluent) furnished α-hydroxyketone 152 (61 mg, 59% yield) as a clear, pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (m, 2H), 7.53-7.27 (comp. m, 8H), 5.51-5.31 (comp. m, 2H), 4.08 (s, 1H), 3.12 (ddt, J=1.1, 6.9, 13.4 Hz, 1H), 2.84 (ddt, J=1.1, 6.8, 13.6 Hz, 1H), 1.63 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 200.9, 142.0, 134.7, 131.6, 132.6, 130.1, 128.8, 128.0, 127.9, 125.5, 124.5, 81.5, 43.1, 18.1; IR (thin film/NaCl) 3503 (br. m), 3059 (w), 3027 (w), 2916 (w), 1677 (s), 1579 (m), 1447 (s), 1254 (s), 1216 (m), 971 (m), 711 (s), 700 (s) cm⁻¹; HRMS (EI) m/z found: 266.1316 [calc'd for C₁₈H₁₈O₂ (M+): 266.1307].
Preparation of Enol Trifluoroacetate 153.

Enol Trifluoroacetate 153. To a stirred solution of α-diazoketone 103 (87 mg, 0.546 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 57 µL, 0.658 mmol, 1.2 equiv) in CH₂Cl₂ (6 mL) was added Rh₂(OAc)₄ (2.4 mg, 0.0054 mmol, 0.01 equiv). Once nitrogen evolution was complete (ca. 2 min), the mixture was cooled to -78°C before trifluoroacetic anhydride (116 µL, 0.821 mmol, 1.5 equiv) and triethylamine (0.19 mL, 1.37 mmol, 2.5 equiv) were added in rapid succession. The pale red solution was allowed to stir at -78°C for 10 mins before it was warmed to room temperature and concentrated under reduced pressure. Flash chromatography (4:1 pentane: CH₂Cl₂ eluent) furnished enol trifluoroacetate 153 (103 mg, 63% yield) as a clear, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.40 (m, 5H), 5.71 (ddd, J=6.9, 10.3, 17.3 Hz, 1H), 5.05 (ddd, J=1.0, 1.6, 10.2 Hz, 1H), 4.95 (dt, J=1.2, 17.2 Hz, 1H), 4.04 (m, 1H), 1.98 (s, 3H), 1.21 (d, J=6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.3 (q, J=42.3 Hz), 143.4, 138.6, 132.4, 132.3, 129.4, 129.0, 128.4, 116.2, 114.7 (q, J=285.5 Hz), 75.7, 20.6, 15.5; IR (thin film/NaCl) 3084 (w), 2982 (m), 2932 (w), 1796 (s), 1445 (m), 1362 (s), 1296 (s), 1224 (s), 1177 (s), 1149 (s), 778 (s), 707 (s) cm⁻¹; HRMS (EI) m/z found: 300.0974 [calc'd for C₁₅H₁₅O₃F₃ (M+): 300.0973].
Preparation of Enol Triflate 154

![Chemical structure](image)

**Enol Triflate 154.** To a stirred solution of α-diazoketone 103 (70 mg, 0.435 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 45 µL, 0.519 mmol, 1.2 equiv) in CH₂Cl₂ (5 mL) was added Rh₂(OAc)₄ (2.0 mg, 0.0045 mmol, 0.01 equiv). Once nitrogen evolution was complete (ca. 2 min), the mixture was cooled to -78°C before trifluoromethanesulfonic anhydride (110 µL, 0.654 mmol, 1.5 equiv) and triethylamine (0.15 mL, 1.09 mmol, 2.5 equiv) were added in rapid succession. The mixture was allowed to stir for 15 min at -78°C before being warmed to room temperature. Concentration under reduced pressure afforded a residue that was purified by flash chromatography (4:1 pentane: CH₂Cl₂ eluent) to furnish enol triflate 154 (111 mg, 76% yield) as a clear, colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.36 (comp. m, 5H), 5.83 (ddd, J₁=7.0, 10.2, 17.6 Hz, 1H), 5.08 (ddd, J₂=1.2, 1.5, 10.5 Hz, 1H), 4.12 (m, 1H), 2.95 (dt, J₃=1.2, 17.2 Hz, 1H), 2.00 (s, 3H), 1.31 (d, J₄=6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 146.4, 138.5, 133.1, 131.6, 129.5, 128.5, 118.5 (q, J₅=319.7 Hz), 116.5, 76.7, 20.7, 16.0; IR (thin film/NaCl) 2983 (w), 1931 (w), 1416 (s), 1300 (m), 1247 (s), 1209 (s), 1148 (s), 1050 (m), 939 (s), 797 (s), 701 (s) cm⁻¹; HRMS (EI) m/z found: 336.0639 [calc'd for C₁₄H₁₅O₄F₃S (M⁺): 336.0643].
Preparation of α-Allyloxy Ketone 105c via Enol Tautomerization

A solution of α-diazoketone 103 (65 mg, 0.408 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 42 µL, 0.485, 1.2 equiv) in CH₂Cl₂ (4 mL) was treated with Rh₂(OAc)₄ (2.0 mg, 0.0045 mmol, 0.01 equiv) resulting in rapid N₂(g) loss. Once gas evolution was complete, the mixture was cooled to 0°C and treated with triethylamine (85 µL, 0.611 mmol, 1.5 equiv). This mixture was stirred at 0°C for 15 min, before being warmed to room temperature and concentrated under reduced pressure. Flash chromatography of the residue furnished 105c (51 mg, 61% yield) as a clear, colorless oil.

Evidence of Direct Enol Trapping via Isotope Labelling

To a stirred solution of α-diazoketone 103 (60 mg, 0.376 mmol, 1.0 equiv), allylic alcohol 140 (33.1 mg, 0.453 mmol, 1.2 equiv), and α-allyloxy ketone 105c (76.1 mg, 0.373 mmol, 1.0 equiv) in CH₂Cl₂ (4 mL) was added Rh₂(OAc)₄ (1.7 mg, 0.004 mmol, 0.01 equiv). Once nitrogen evolution was judged to be complete (ca. 2 min), the mixture
was cooled to -78°C and treated sequentially with trifluoroacetic anhydride (0.6 mL, 4.25 mmol, 11 equiv) and triethylamine (0.10 mL, 0.719 mmol, 2.0 equiv). The pale red mixture was stirred for 15 min at -78°C before being warmed to room temperature and concentrated under reduced pressure. Careful flash chromatography of the residue furnished deuterated enol trifluoroacetate 155 (50 mg, 44% yield) and unaltered 105c (69 mg, 91% recovery). Enol trifluoroacetate 155: 1H NMR (400 MHz, CDCl3) δ 7.40 (m, 5H), 5.70 (dd, J=8.4, 14.0 Hz, 1H), 5.06 (dd, J=1.2, 8.4 Hz, 1H), 2.95 (dd, J=1.0, 13.8 Hz, 1H), 1.98 (s, 3H), 1.20 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 155.4 (q, J=42.8 Hz), 143.3, 138.6, 132.4, 132.3, 129.4, 129.0, 128.4, 116.3, 114.7 (q, J=286 Hz), 75.6 (t, J=22.3 Hz), 20.5, 15.5; IR (thin film/NaCl) 3085 (w), 2979 (w), 2932 (w), 1796 (s), 1362 (m), 1300 (m), 1117 (s), 1150 (s), 1135 (s), 776 (m), 701 (m) cm⁻¹; HRMS (EI) m/z found: 301.1031 [calc'd for C15H14O3F3D (M+): 301.1036].

Preparation of Enol Trifluoroacetate 156.

Enol Trifluoroacetate 156. To a stirred solution of α-diazoketone 103 (160 mg, 1.00 mmol, 1.0 equiv) and allyl alcohol (94a, 81 µL, 1.20 mmol, 1.2 equiv) in CH₂Cl₂ (10 mL) was added Rh₂(OAc)₄ (4.4 mg, 0.011 mmol, 0.01 equiv) resulting in rapid loss of N₂(g). The reaction mixture was then cooled to -78°C and treated successively with
trifluoroacetic anhydride (0.21 mL, 1.49 mmol, 1.5 equiv) and triethylamine (0.28 mL, 2.01 mmol, 2.0 equiv). The resulting pale red solution was allowed to stir for 5 min at -78°C before being warmed to room temperature and washed with saturated NaHCO₃ solution (2 x 10 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. Flash chromatography (6:1 pentane:CH₂Cl₂ eluent) afforded 156 (210 mg, 73% yield) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.42 (m, 5H), 5.83 (m, 1H), 5.15-5.20 (comp m, 2H), 4.00 (dt, J=1.4, 5.7 Hz, 2H), 1.98 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 155.4 (q, J=42.5 Hz), 144.2, 133.2, 131.7, 131.5, 129.4, 129.2, 128.5, 117.7, 114.7 (q, J=285.5 Hz), 70.3, 15.4; IR (thin film/NaCl) 3085 (w), 2924 (w), 2874 (w), 1796 (s), 1445 (w), 1360 (m), 1299 (m), 1224 (s), 1178 (s), 1147 (s), 1127 (s), 1013 (w), 988 (w), 776 (m), 701 (m) cm⁻¹; HRMS (EI) m/z found: 287.0901, [calc'd for C₁₄H₁₄O₃F₃ (M+H): 287.0895].

Preparation of α-Propyloxy Trifluoroacetate 157 via Hydrogenation of 156

α-Propyloxy Trifluoroacetate 157. To a solution of enol trifluoroacetate 156 (116 mg, 0.405 mmol, 1.0 equiv) in EtOAc (4 mL) was added PtO₂ (21 mg, 0.092 mmol, 0.23 equiv). The heterogeneous mixture was rapidly stirred under 1 atm H₂(g) pressure for 16 h at room temperature and then filtered. Concentration under reduced pressure provided
an oil that was purified by flash chromatography (4:1 pentane:CH₂Cl₂ eluent) affording
the single diastereomeric trifluoroacetate 157 (55 mg, 47% yield) as a colorless oil. ¹H
NMR (500 MHz, CDCl₃) δ 7.35 (m, 5H), 5.24 (m, 1H), 4.37 (d, J=5.2 Hz, 1H), 3.41 (dt,
J=6.6, 9.2 Hz, 1H), 3.31 (dt, J=6.4, 9.1 Hz, 1H), 1.61 (m, 2H), 1.37 (d, J=6.4 Hz, 3H),
0.94 (t, J=7.4 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 156.7 (q, J=41.7 Hz), 137.6,
128.4, 128.2, 127.3, 114.5 (q, J=285.6 Hz), 82.6, 77.8, 71.3, 22.9, 14.9, 10.5; IR (thin
film/NaCl) 3033 (w), 2967 (m), 2940 (w), 2879 (w), 1787 (s), 1454 (w), 1380 (m),
1223 (s), 1166 (s), 1110 (m), 1077 (m), 1053 (m), 757 (w), 732 (m), 702 (m) cm⁻¹; HRMS (EI)
m/z found: 291.1209, [calc'd for C₁₄H₁₈O₃F₃ (M+H): 291.1208].

**Preparation of α-Propyloxy Trifluoroacetate 157 via Epoxide Ring-Opening**

Concentrated H₂SO₄ (10 µL) was added to a stirred mixture of (S,S)-1-phenylpropylene
oxide (138, 251 mg, 1.87 mmol, 1.0 equiv) and n-propanol (0.42 mL, 5.62 mmol, 3.0
equiv) in CH₂Cl₂ (1.5 mL) at 0°C. After stirring for 40 min at 0°C, the mixture was
washed with saturated NaHCO₃ solution (2 x 5 mL). The organic phase was separated,
dried over MgSO₄, filtered, and concentrated under reduced pressure to provide 379 mg
of an oil that was used without further purification. To a solution of 272 mg of this oil in
CH₂Cl₂ (14 mL) at 0°C was added trifluoroacetic anhydride (0.30 mL, 2.12 mmol, 1.0
equiv), triethylamine (0.40 mL, 2.88 mmol, 1.4 equiv) and DMAP (26 mg, 0.213 mmol, 0.10 equiv). The resulting mixture was stirred for 20 min at 0°C before being washed with saturated NaHCO₃ solution (2 x 5 mL), the organic phase dried over MgSO₄, filtered, and concentrated under reduced pressure. Flash chromatography (6:1 pentane:CH₂Cl₂ eluent) afforded 157 (288 mg, 71% yield) as a colorless oil that was spectroscopically identical to that prepared by hydrogenation of 156.

**Preparation of \(\alpha\)-Allyoxy Enol Triflate 159**

\[
\begin{align*}
\begin{array}{ccc}
\text{144} & \xrightarrow{1) \text{Rh}_2(O\text{Ac})_4 (1.0 \text{ mol\%})} & \text{94a} \\
\text{2) (CF}_3\text{SO}_2\text{O}, \text{Et}_3\text{N}} & \text{CH}_2\text{Cl}_2, -78^\circ\text{C} & \text{159}
\end{array}
\end{align*}
\]

\(\alpha\)-Allyoxy Enol Triflate 159. To a stirred solution of \(\alpha\)-diazoketone 144 (101 mg, 0.454 mmol, 1.0 equiv) and allyl alcohol (37 µL, 0.544 mmol, 1.2 equiv) in CH₂Cl₂ (5 mL) was added Rh₂(OAc)₄ (2.7 mg, 0.006 mmol, 0.01 equiv) resulting in rapid N₂(g) loss. Once complete, the solution was cooled to -78°C and treated with trifluoromethanesulfonic anhydride (0.11 mL, 0.654 mmol, 1.4 equiv) and Et₃N (0.25 mL, 1.80 mmol, 4.0 equiv) in rapid succession. The mixture was allowed to stir for 15 min at -78°C before being warmed to room temperature, diluted with CH₂Cl₂ (5 mL), and washed with sat. NaHCO₃ solution (3 x 10 mL). Combined aqueous phases were backwashed with CH₂Cl₂ (2 x 10 mL). Combined organic phases were dried over MgSO₄, filtered and rotavapped. The resulting residue was purified by flash
chromatography (4:1 pentane:CH₂Cl₂ eluent) affording enol triflate 159 (121 mg, 69% yield) as a white solid. Recrystallization from pentane afforded crystals suitable for X-Ray analysis. ¹H NMR (500 MHz, CDCl₃) δ 7.16-7.36 (comp m, 10H), 5.98 (m, 1H), 5.26 (m, 2H), 4.22 (dt, J=1.3, 5.8 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 148.8, 134.5, 132.8, 131.7, 130.7, 130.0, 129.7, 129.2, 128.7, 128.6, 128.2, 118.4, 118.4 (q, J=318 Hz), 70.7; IR (thin film/NaCl) 3072 (m), 2938 (m), 2880 (w), 1967 (w), 1894 (w), 1654 (m), 1414 (s), 1214 (s), 1134 (s), 997 (s), 963 (s), 824 (s), 766 (m), 697 (s) cm⁻¹; m.p. 53-55°C (pentane).

3.6 Notes and References

(1) An 10% yield of phenylacetone 133 was also isolated.

(2) Prepared via sodium borodeuteride reduction of methyl vinyl ketone, see:


(5) The half-life for Claisen rearrangement of allyl vinyl ether has been reported to be 297 h at 80°C in benzene-\textit{d}_6, see: Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. \textit{J. Am. Chem. Soc.} \textbf{1987}, \textit{109}, 1160 and references therein.

(6) Hydrogenation was periodically halted and the mixture analyzed by $^1$H NMR. No olefin isomerization was ever observed.


(10) Although the transient species \textbf{163} can be envisioned with or without rhodium, the known influence of asymmetric rhodium catalysts on other sigmatropic rearrangements suggests its inclusion, see: Pierson, N.; Fernádez-García; C.; McKervey, M. A. \textit{Tetrahedron Lett.} \textbf{1997}, \textit{38}, 4705.


(14) Allyl alcohol-OD (170) was prepared according to the method of Bosnich, see Ref 10.


(18) Metz, P.; Mues, C. Synlett 1990, 97.

(19) The rigorous exclusion of air was critical to the observation of enol 145 since facile oxidative cleavage of the enol double bond takes place in air to furnish benzoic acid and methyl benzoate, see Ref. 3.
APPENDIX TWO: SPECTRA RELEVANT TO CHAPTER THREE
Figure A.2.1 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 105a.
Figure A.2.2 13C NMR (125 MHz, CDCl3) of Compound 105a.

Figure A.2.3 FTIR Spectrum (thin film/NaCl) of Compound 105a.
Figure A.2.4 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 105c First Diastereomer.
Figure A.2.6. $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 105c First Diastereomer.

Figure A.2.5. FTIR Spectrum (thin film/NaCl) of Compound 105c First Diastereomer.
Figure A.2.7 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 105c Second Diastereomer.
Figure A.2.9 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 105c Second Diastereomer.

Figure A.2.8 FTIR Spectrum (thin film/NaCl) of Compound 105c Second Diastereomer.
Figure A.2.10 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 141.
Figure A.2.12: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 141.

Figure A.2.11: FTIR Spectrum (thin film/NaCl) of Compound 141.
Figure A.2.13 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 142.
Figure A.2.15  $^{13}$C NMR (125MHz, CDCl$_3$) of Compound 142.

Figure A.2.14  FTIR Spectrum (thin film/NaCl) of Compound 142.
Figure A.2.16 $^1$H NMR (500 MHz, C$_6$D$_6$) of Compound 143.
Figure A.2.17 $^1$H NMR (500 MHz, C$_6$D$_6$) of Compound 148.
Figure A.2.18 $^{1}$H NMR (500 MHz, C$_6$D$_6$) of Compound 149.
Figure A.2.19 $^1$H NMR (500 MHz, C$_6$D$_6$) of Compound 151.
Figure A.2.20 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 152.
Figure A.2.21 FTIR Spectrum (thin film/NaCl) of Compound 152.

Figure A.2.22 13C NMR (100 MHz, CDCl₃) of Compound 152.
Figure A.2.23 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 153.
Figure A.2.25 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 153.

Figure A.2.24 FTIR Spectrum (thin film/NaCl) of Compound 153.
Figure A.2.26 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 154.
Figure A.2.26 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 154.

Figure A.2.27 FTIR Spectrum (thin film/NaCl) of Compound 154.
Figure A.2.29 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 155.
Figure A.2.31 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 155.

Figure A.2.30 FTIR Spectrum (thin film/NaCl) of Compound 155.
Figure A.2.32 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 156.
Figure A.2.34: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 156.

Figure A.2.33: FTIR Spectrum (thin film/NaCl) of Compound 156.
Figure A.2.35 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 157.
Figure A.2.37. 13C NMR (125 MHz, CDCl3) of Compound 157.

Figure A.2.36. FTIR Spectrum (thin film/NaCl) of Compound 157.
Figure A.2.38 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 159.
Figure A.2.39 FTIR Spectrum (thin film/NaCl) of Compound 159.

Figure A.2.40 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 159.
Figure A.2.16 $^1$H NMR (400 MHz, C$_6$D$_6$) of Compound 173.
APPENDIX THREE: X-RAY CRYSTALLOGRAPHY REPORTS RELEVANT TO CHAPTER THREE
A. Crystal Data
Empirical Formula  
C_{17}H_{16}O_{3}

Formula Weight  
268.31

Crystal Color, Habit  
colorless, cutblock

Crystal Dimensions  
0.24 X 0.28 X 0.30mm

Crystal System  
monoclinic

Lattice Type  
Primitive

Lattice Parameters  
a = 7.8065(2) Å
b = 11.3336(5) Å
c = 16.5721(6) Å
β = 94.158(2)°
V = 1462.37(8) Å³
Space Group  
P2₁/n(#14)

Z value  
4

Dcalc  
1.219 g/cm³

F000  
568.00

μ(MoKα)  
0.83 cm⁻¹

B. Intensity Measurements
Diffractometer  
Nonius Kappa CCD

Radiation  
MoKα (λ=0.71069 Å)

Graphite monochromated

Take-off Angle  
2.8°

Crystal to Detector Distance  
35 mm

Temperature  
23.0°C

Scan Rate  
60 s/frame

Scan Width  
1°/frame

2θmax  
61.0°

No.of Reflections Measured  
Total:4330

Corrections  
Lorentz-polarization

C. Structure Solution and Refinement
Structure Solution  
Direct Methods (SIR92)
Refinement Full-matrix least-squares

Function Minimized \[ \sum w(|Fo|-|Fc|)^2 \]
Leas tSquares Weights \[ 1/\sigma^2(Fo) \]
p-factor 0.0100
Anomalous Dispersion All non-hydrogen atoms
No. Observations (I>3.00\(\sigma(I)\)) 2631
No. Variables 245
Reflection/Parameter Ratio 10.74
Residuals:R;Rw 0.050; 0.054
Goodness of Fit Indicator 2.77
Max Shift/Error in Fina lCycle 0.00
Maximum peak in Final Diff. Map 0.18e-/Å³
Minimum peak in Final Diff. Map -0.17e-/Å³

Atomic coordinates and Biso/Beq for Enol Acetate 147

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X-RAY CRYSTALLOGRAPHY REPORT FOR ENOL TRIFLATE 159

A. Crystal Data
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Formula Weight: 384.37
crystal color, habit: colorless, plate
Crystal Dimensions: 0.08 X 0.22 X 0.26 mm
Crystal System: orthorhombic
Lattice Type: Primitive
Lattice Parameters: a = 10.0680(2) Å, b = 17.4948(5) Å, c = 20.1991(5) Å, V = 3557.8(1) Å³
Space Group: Pbca (#61)
Z value: 8
Dcalc: 1.435 g/cm³
F₀₀₀: 1584.00
µ(MoKα): 2.32 cm⁻¹

B. Intensity Measurements
Diffractometer: Nonius KappaCCD
Radiation: MoKα (λ = 0.71069 Å)
graphite monochromated
Take-off Angle: 2.8°
Crystal to Detector Distance: 35mm
Temperature: -90.0°C
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Scan Width: 1°/frame
2θ max: 61.0°
No. of Reflections Measured: Total: 5928
Corrections: Lorentz-polarization, Secondary Extinction (coefficient: 6.74585e-07)

C. Structure Solution and Refinement
Structure Solution: Direct Methods (SIR92)
Refinement: Full-matrix least-squares
Function Minimized: \( \Sigma w (|F_o| - |F_c|)^2 \)
Least Squares Weights: \( 1/\sigma^2F_o \)
p-factor: 0.0100
Anomalous Dispersion: All non-hydrogen atoms
No. Observations (I>5.00\(\sigma(I)\)): 2899
No. Variables: 235
Reflection/Parameter Ratio: 12.34
Residuals: R; Rw: 0.041; 0.047
Goodness of Fit Indicator: 2.76
Max Shift/Error in Final Cycle: 0.00
Maximum peak in Final Diff. Map: 0.68 e-/Å³
Minimum peak in Final Diff. Map: -0.31 e-/Å³

Atomic coordinates and Biso/Beq for Enol Triflate 159

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Chapter 4

Kinetic Analysis Of the Rhodium Carbenoid-Initiated Claisen Rearrangement

4.1 Overview

Of the numerous mechanistic questions raised at the outset of these investigations, only two matters remained unresolved. First, the exceedingly mild conditions required for Claisen rearrangement of α-allyloxy enols raised questions regarding the nature of the rearrangement process. Specifically, it was uncertain whether rearrangement was promoted by the rhodium (II) carboxylate catalyst or simply a thermal process. If the latter, the factors that enabled such facile rearrangement would need to be identified. Second, the enhanced selectivity for [3,3]-rearrangement over OH-insertion afforded by secondary allylic alcohols relative to primary allylic alcohols remained unexplained. Having established that “OH-insertion” products actually arise from tautomerization of intermediate allyloxy enols, this selectivity difference presumably reflected differences in the relative rates of Claisen rearrangement and tautomerization with allylic alcohol substitution. It was recognized that the answers to these questions resided at a level of mechanistic detail not accessible by the experimental techniques employed in the previous chapters. Rather, kinetic measurements appeared necessary for resolving these issues.
4.2 Effect of Catalyst on Rearrangement Rate

4.2.1. Selection of Catalyst System and Representative Enol

To facilitate these investigations, an α-allyloxy enol was sought that would undergo rearrangement at room temperature at an easily monitored rate. Two additional requirements were imposed to facilitate reaction monitoring by $^1$H NMR spectroscopy. These were: (1) the enol selected should furnish uncomplicated spectra with well-separated resonances, and (2) the $^1$H NMR resonances of the resulting [3,3]-rearrangement product could not overlap with those of the enol. After an initial survey of enols derived from α-diazo ketones 103, 144, and 110, it was found that α-allyloxy enol 149 derived from α-diazo ketone 144 and 3-buten-2-ol (94c) was optimal for these studies, displaying well-resolved signals in both CD$_2$Cl$_2$ and benzene-$d_6$, and undergoing complete rearrangement within a reasonable time interval at 25°C (See Figure 3.1).

With regard to catalyst, dirhodium (II) tetraacetate (Rh$_2$(OAc)$_4$), the catalyst employed both preparatively and in previous mechanistic studies, was considered unsuitable for investigations of catalyst-dependent kinetics owing to its poor solubility in available deuterated solvents. A more soluble rhodium (II) catalyst was necessary to ensure accurate and consistent solution concentrations of Rh(II). In addition, more rapid dediazotization/enol formation was desired to ensure complete conversion of α-diazo ketone to allyloxy enol before any rearrangement would take place. The catalyst found to best satisfy these two criteria was the electron-deficient Rh$_2$(tfa)$_4$ catalyst which was freely soluble in the required reaction media (CD$_2$Cl$_2$ and benzene-$d_6$) and afforded more rapid dediazotization than Rh$_2$(OAc)$_4$ (i.e., 10 seconds vs. 2 minutes with Rh$_2$(OAc)$_4$). Importantly, to make certain that reaction outcome would not be altered
under the planned conditions with the Rh$_2$(tfa)$_4$ catalyst, $\alpha$-diazoketone 103 was treated with Rh$_2$(tfa)$_4$ in the presence of (S)-(+) 94c (98% ee) at room temperature (Scheme 4.1), rapidly generating enol 143. Claisen rearrangement then proceeded at room temperature at approximately the same rate observed with Rh$_2$(OAc)$_4$ (See Scheme 3.2), furnishing (R)-104c in 96% ee. Thus, reaction outcome and chirality transfer were identical employing both the Rh$_2$(OAc)$_4$ and Rh$_2$(tfa)$_4$ catalysts.

**Scheme 4.1**

4.2.2 Influence of Catalyst on Rearrangement Rate of Enol 149.

Having established the invariance of reaction outcome with regard to catalyst, kinetic investigations were initiated. Treatment of a mixture of $\alpha$-diazoketone 144 and 3-buten-2-ol (94c, 1.2 equiv) in CD$_2$Cl$_2$ with 1 mol% Rh$_2$(tfa)$_4$ resulted in rapid conversion to enol 149. A sample of the reaction mixture was then transferred to an NMR tube and Claisen rearrangement of 149 to $\alpha$-hydroxyketone 152 monitored at 25ºC. The integration of the enol C4 methyl doublet was measured every 10 minutes versus the corresponding doublet of residual 94c, which was employed in excess to serve as an internal standard of constant concentration. To assess the effect of catalyst concentration on rearrangement rate, this process was repeated employing 5 mol% Rh$_2$(tfa)$_4$. The influence of catalyst ligand on rearrangement rate was explored by utilizing 1 mol% Rh$_2$(OAc)$_4$ as the decomposition catalyst. Finally, to investigate the possibility of
Bronsted acid-catalysis, an additional experiment was performed wherein 144 was decomposed with 1 mol % Rh$_2$(tfa)$_4$ and the resulting solution of enol 149 treated with proton sponge (1.0 equiv). Rearrangement was then monitored in an identical fashion. All reactions exhibited first-order kinetic behavior (See Experimental Section), enabling facile determination of rate constants. The results of these analyses are summarized in Table 4.1. As can be surmised from the data presented, a five-fold increase in catalyst concentration had no significant effect on the rate of rearrangement of enol 149, nor did changes in catalyst ligand or the inclusion of an acid scavenger. Thus, it was concluded that the ease of [3,3]-rearrangement of α-allyloxy enol 149 was not due to Rh(II)- or Bronsted acid-catalysis.

**Table 4.1** - Effect of Catalyst on Rate of Claisen Rearrangement of Enol 149 at 25°C
4.3 Substituent Effects on the Rate of Claisen Rearrangement of α- Allyloxy Enols

4.3.1 Influence of Substituents on the Rate of the Aliphatic Claisen Rearrangement

Having demonstrated that the rapid rate of rearrangement of enol 149 was not due to catalysis by Rh(II) or adventitious protic acid, it was considered that the ease of rearrangement exhibited by enol 149 and other α-allyloxy enols might be intrinsic and not the result of conditions present during their formation. It is well known that the rate of the aliphatic Claisen rearrangement is dramatically influenced by the substituents present on the allyl vinyl ether skeleton. Numerous experimental rate measurements and theoretical studies have demonstrated that electron-donating substituents (EDS, Figure 4.1) at C1, C2, C4, and C6 of allyl vinyl ether (197) increase the rate of rearrangement, while electron donors at C5 cause deceleration.2,3 Rearrangement of 197 has been shown to proceed with a half-life of 297 h at 80°C in benzene-d6.4 Introduction of a C2 siloxy substituent was shown by Ireland to significantly increase the rate of rearrangement, conversion of 199 to 200 proceeding with a half-life of 210 min at 32°C (Scheme 4.2).5 Furthermore, introduction of additional substituents onto the silylketene acetal (i.e., 199) skeleton could induce further dramatic alterations in rate. For example, introduction of a
C4 pentyl group caused a 35-fold rate acceleration, rearrangement of 201 to 202 proceeding with a half-life of only 6 minutes at 32°C. Introduction of a C6 methyl group (i.e., 203) resulted in only a slight acceleration in rate, however, placement of an additional methyl group at C1 (i.e., 205) again resulted in significant acceleration. Similar substituent effects were noted by Curran who demonstrated that

**Scheme 4.2**

Introduction of methoxy substituents into the allyl vinyl ether framework could be used to induce significant variations in [3,3]-rearrangement rate (Scheme 4.3). For example, introduction of a C6 methoxy substituent afforded a 9-fold increase in rearrangement rate relative to the parent (197) while introduction of the same substituent at C4 afforded a 96-fold increase in rate. Amazingly, simply relocating the methoxy substituent to the adjacent C5 position caused a 40-fold deceleration in the rate of [3,3]-rearrangement.
Barluenga reported half-lives for the Claisen rearrangements of several 1-amino-substituted allyl vinyl ethers which also demonstrated the accelerating effects of electron-donating substituents at C1 (i.e., 71, Scheme 4.4), C4 (i.e., 213) and C6 (i.e., 215) as well as the decelerating effect of such substituents at C5 (i.e., 217).7

Scheme 4.3

Scheme 4.4
Undoubtedly, the most significant studies with regard to Claisen rearrangement of \( \alpha \)-allyloxy enols such as \( 149 \) were those of Koreeda, who thoroughly investigated the anionic variant of this process and found that [3,3]-rearrangements of \( \alpha \)-allyloxy enolates were dramatically accelerated by the alkoxy substituent at C1 (Scheme 4.5).\(^8\) Furthermore, this rate-enhancing effect was attenuated as the free alkoxide character of the C1 substituent decreased. For example, Claisen rearrangement of potassium enolate \( 65 \) proceeded with a half-life of 3.3 h at \(-23^\circ C\). The corresponding sodium enolate (219) required slightly increased temperature (0\(^\circ\)C) to achieve a similar half-life while lithium enolate 82 required near-reflux temperatures. Koreeda also studied the Claisen rearrangement of silyl enol ether 220, reporting a half-life of 0.5 h at 71\(^\circ\)C for this process. This rate appeared on the order of that observed for enol 149 leading to the hypothesis that Claisen rearrangements of \( \alpha \)-allyloxy enols such as 149 were facilitated by the electron-donating character of the C1 hydroxyl group.

**Scheme 4.5**

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</table>
4.3.2 Effect of Substituents on the Rearrangement Rate of α-Allyloxy Enols

To assess the influence that electron-donating groups would exert on the rate of Claisen rearrangement of α-allyloxy enols, enols 148, 149, and 150 were prepared and their in situ Claisen rearrangements to the corresponding α-hydroxyketones monitored by $^1$H NMR spectroscopy with regular integration of appropriate resonances (See Experimental Section). All integrations were measured versus residual allylic alcohol which was again employed in slight excess to serve as a standard of constant concentration. Experiments were performed in benzene-$d_6$ at 40ºC since all three enols underwent [3,3]-rearrangement at reasonable rates at this temperature. Dirhodium (II) tetratrifluoroacetate (Rh$_2$(tfa)$_4$) was again employed as the decomposition catalyst at 1.0 mol% catalyst loading in each case. As may be surmised from Scheme 4.6, similar rate effects were observed in the rearrangement of α-allyloxy enols as were observed by Ireland (See Scheme 4.2), Curran, (See Scheme 4.3), and Barluenga (See Scheme 4.4), that is, electron-donating substituents at C4 caused significant acceleration of the Claisen rearrangement, while analogous substitution at the adjacent C5 position caused a tremendous reduction in rearrangement rate. In addition to establishing a mechanistic commonality between the rearrangement of α-allyloxy enols and other Claisen variants, these results also explain the enhanced selectivity for [3,3]-rearrangement over tautomerization afforded by secondary allylic alcohols relative to primary allylic alcohols. Assuming that enol tautomerization occurs at a steady rate regardless of enol substitution, it follows that the enhanced rate of Claisen rearrangement afforded by an enol C4-alkyl substituent enables rearrangement to compete much more efficiently with
tautomerization in C4-substituted enols (e.g., 149) than in enols lacking this beneficial substituent (e.g., 148).

**Scheme 4.6**

To assess the effect of the electron-donating C1-hydroxyl group on the rate of Claisen rearrangement of α-allyloxy enols, 149 was converted to its trifluoroacetate derivative 223. Claisen rearrangement of 223 to 224 was then monitored by 1H NMR at 40°C in benzene-\(d_6\), measuring the integration of the C4 methyl resonance versus the methyl singlet of toluene which was added as an internal standard of constant concentration (Scheme 4.7). Under these conditions, 223 exhibited a tremendously
reduced rate of Claisen rearrangement ($t_{1/2}=14$ h) relative to its enol precursor (149, $t_{1/2}=8.8$ min). In accord with Koreeda’s studies (See Scheme 4.5), this deceleration was attributed to a sequestration of electron donation from the C1-enol hydroxyl group. In merging these results with those of Koreeda, a more complete trend of Claisen rate versus the electron donating ability of the C1-oxy substituent may be presented (Figure 4.2).

Figure 4.2 - Rate of Claisen Rearrangement Versus C1-Oxy Substituent

4.3.3 Arrhenius Analysis of Claisen Rearrangement of Enol 149

To quantify the rate acceleration observed with enol 149 relative to the parent allyl vinyl ether (197), the rate of Claisen rearrangement of enol 149 was measured at several temperatures in benzene-$d_6$. In each experiment, 1.0 mol% Rh$_2$(tfa)$_4$ was used as the decomposition catalyst and the C4-methyl resonance was integrated at regular intervals versus the corresponding methyl doublet of 3-buten-2-ol (94c), employed in excess to serve as an internal standard. The rate constants and half-lives measured at
each temperature are presented in Table 4.2. This data was incorporated into an

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>k (s⁻¹) x 10⁴</th>
<th>t₁/₂ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>0.64</td>
<td>180</td>
</tr>
<tr>
<td>20</td>
<td>1.3</td>
<td>89</td>
</tr>
<tr>
<td>25</td>
<td>2.0</td>
<td>58</td>
</tr>
<tr>
<td>30</td>
<td>3.8</td>
<td>30</td>
</tr>
<tr>
<td>35</td>
<td>6.7</td>
<td>17</td>
</tr>
<tr>
<td>37</td>
<td>8.5</td>
<td>14</td>
</tr>
<tr>
<td>40</td>
<td>13</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Arrhenius plot (Figure 4.3) from which standard linear regression furnished a slope of –10694 K corresponding to an energy of activation (Eₐ) of 21.2 kcal/mol and a ΔH‡ of 20.6 kcal/mol at 25°C (298 K). This represents a ΔΔH‡ of −4.8 kcal/mol between enol 149 and the parent allyl vinyl ether 197. The intercept of 27.45 (ln A) obtained from linear regression was subjected to Eyring analysis (where A = (κkT/h)exp(ΔS‡/R)), revealing a ΔS‡ of −6.0 e.u. (cal/K mol) at 25°C (298 K),¹¹,¹² a value similar to the −7.0 e.u. measured for the 5-methoxy-substituted allyl vinyl ether 211.¹³
4.4 Summary and Conclusions

The kinetics of the rhodium carbenoid-initiated Claisen rearrangement were investigated in detail. These studies commenced with an investigation of catalyst influence on reaction rate which revealed that Claisen rearrangement of $\alpha$-allyloxy enols proceeds at a rate independent of both rhodium (II) catalyst concentration and ligand. An additional experiment performed in the presence of an acid scavenger ruled out the possibility of Bronsted acid-catalysis of Claisen rearrangement. Subsequent kinetic studies revealed that the rate of Claisen rearrangement of $\alpha$-allyloxy enols was dramatically influenced by substituents on the enol skeleton. Specifically, electron-donating substituents at C4 caused dramatic rate accelerations while identical substituents at C5 caused significant deceleration. These observations were in accord with reports of substituent effects on the rate of other Claisen variants. These findings also clarified the
origin of the superior selectivity for [3,3]-rearrangement over OH-insertion afforded by secondary allylic alcohols relative to primary allylic alcohols. This enhanced selectivity derives from the accelerating effect of the C4-alkyl substituent which enables Claisen rearrangement to compete much more efficiently with tautomerization in C4-alkyl-substituted enols (i.e., enols derived from secondary allylic alcohols) than in enols lacking this substituent. Conversion of the enol hydroxyl group in 149 to the corresponding trifluoroacetate (223) resulted in a tremendous reduction in [3,3]-rearrangement rate leading to the conclusion that Claisen rearrangement of α-allyloxy enols is greatly facilitated by the electron-donating character of the enol hydroxyl group, a result in accord with studies of the anionic variant of this process. Finally, variable temperature kinetic experiments established a $\Delta H^\ddagger$ of 20.6 kcal/mol for Claisen rearrangement of 149, corresponding to a $\Delta\Delta H^\ddagger$ of -4.8 kcal/mol between enol 149 and the parent allyl vinyl ether 197 and demonstrating a substantial enthalpic contribution to rate acceleration. The entropy of activation ($\Delta S^\ddagger$) for rearrangement of 149 was measured at −6.0 e.u., a value in accord with those measured for other Claisen variants, confirming that [3,3]-rearrangements of α-allyloxy enols proceed via a similarly ordered transition state.

4.5 Experimental Section

4.5.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using freshly distilled solvents. All commercially obtained reagents were used as received. Analytical thin-layer chromatography (TLC) was
performed using silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. High-performance liquid chromatography (HPLC) was performed with either a Rainin Microsorb 80-199-C5 or 80-120-C5 column. Infrared spectra were acquired using a MIDAC M-1200 FTIR. $^1$H and $^{13}$C NMR spectra were recorded using Bruker AM500 or Bruker Avance 400/500 MHz spectrometers. All kinetic measurements were performed using a Bruker AM500 spectrometer. Chemical shifts are reported as $\delta$ values relative to internal chloroform ($^1$H $\delta$ 7.27 ppm, $^{13}$C $\delta$ 77.0 ppm) or benzene-d$_6$ ($^1$H $\delta$ 7.15 ppm). Melting points are uncorrected. High-resolution mass spectra were acquired at the University of Illinois Mass Spectrometry Center.

4.5.2 Experimental and Preparative Procedures

Preparation of $\alpha$-Hydroxyketone 104c via Rh$_2$(tfa)$_4$-Catalyzed Decomposition of $\alpha$-Diazoketone 103.

![Chemical reaction diagram]

To a stirred solution of $\alpha$-diazoketone 103 (35 mg, 0.219 mmol, 1.0 equiv) and (S)-(+)−3-buten-2-ol (94c, 23 µL, 0.265 mmol, 1.2 equiv) in CH$_2$Cl$_2$ (2.5 mL) was added Rh$_2$(tfa)$_4$ (1.7 mg, 0.0026 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. The resulting green mixture was stirred for overnight at room temperature, then concentrated under
reduced pressure. Purification of the residue by flash chromatography (10:1 hexanes: ethyl acetate eluent) afforded \((R)-\text{104c}\) (38 mg, 84% yield, 96% ee) as a clear yellow oil.\(^{14}\)

\(^1\)H NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol% \(\text{Rh}_2(\text{tfa})_4\) in \(\text{CD}_2\text{Cl}_2\) at 25°C

To a stirred solution of \(\alpha\)-diazoketone 144 (98 mg, 0.441 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 40 µL, 0.462 mmol, 1.05 equiv) in \(\text{CD}_2\text{Cl}_2\) (4.5 mL) was added \(\text{Rh}_2(\text{tfa})_4\) (3.0 mg, 0.0046 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. Once complete (ca. 10 s), an aliquot (0.75 mL) of the reaction mixture was transferred via syringe to a septum-covered NMR tube which had previously been purged with \(\text{N}_2(\text{g})\) for 20 min. Conversion of 149 to 152 was monitored by \(^1\)H NMR at 25°C, spectra being collected every 10 minutes (8 scans per collection). The integration of the allylic methyl doublet of enol 149 was measured at each collection period along with the corresponding signal of residual 3-buten-2-ol (94c), which remained constant. The ratio of these two values was calculated at each interval and the natural log of this value plotted versus elapsed reaction time. The data collected in this fashion and the derived rate constant/half life are presented below.
<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>ln (enol/std)</th>
</tr>
</thead>
<tbody>
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<td>1200</td>
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<td>1800</td>
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<tr>
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<td>3000</td>
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<tr>
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<tr>
<td>4200</td>
<td>-0.579</td>
</tr>
<tr>
<td>4800</td>
<td>-0.73</td>
</tr>
</tbody>
</table>

\[ k = 2.5 \times 10^{-4} \text{ s}^{-1} \]
\[ t_{1/2} = 46 \text{ min} \]

---

**In(enol/std) vs. Time for [3,3]-Rearrangement of Enol 149**

1 mol% Rh₂(tfa)₄, CD₂Cl₂, 25°C

\[ y = -2.45E-04x + 4.33E-01 \]
\[ R^2 = 9.89E-01 \]
H NMR-Monitored Claisen Rearrangement of Enol 149 with 5 mol% Rh\(_2\)(tfa)\(_4\) in CD\(_2\)Cl\(_2\) at 25ºC

To a stirred solution of α-diazoketone 144 (98 mg, 0.441 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 40 µL, 0.462 mmol, 1.05 equiv) in CD\(_2\)Cl\(_2\) (4.5 mL) was added Rh\(_2\)(tfa)\(_4\) (14.2 mg, 0.022 mmol, 0.05 equiv) resulting in rapid loss of nitrogen gas. NMR sample preparation and kinetic measurements proceeded in the manner described above. The data collected and the derived rate constant/half life are presented below.

<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>ln (enol/std)</th>
</tr>
</thead>
<tbody>
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<td>1800</td>
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<td>4200</td>
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<td>4800</td>
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</tr>
<tr>
<td>5400</td>
<td>-0.578</td>
</tr>
</tbody>
</table>

\(k = 2.4 \times 10^{-4} \text{ s}^{-1}\) \(t\(_{1/2}\) = 48 \text{ min}\)
To a stirred solution of α-diazoketone 144 (47 mg, 0.211 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 19 µL, 0.219 mmol, 1.04 equiv) in CD₂Cl₂ (2.0 mL) was added Rh₂(OAc)₄ (1.0 mg, 0.002 mmol, 0.01 equiv) resulting in loss of nitrogen gas. NMR sample preparation
and kinetic measurements proceeded in the manner described above. The data collected and the derived rate constant/half life are presented below.

<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>ln (enol/std)</th>
</tr>
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<td>1200</td>
<td>1.221</td>
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<td>1800</td>
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<td>2400</td>
<td>0.943</td>
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<td>3000</td>
<td>0.803</td>
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<td>3600</td>
<td>0.67</td>
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<td>4200</td>
<td>0.543</td>
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<tr>
<td>4800</td>
<td>0.415</td>
</tr>
<tr>
<td>5400</td>
<td>0.25</td>
</tr>
</tbody>
</table>

\[ k = 2.3 \times 10^{-4} \text{ s}^{-1} \]
\[ t_{1/2} = 50 \text{ min} \]

\[ y = -2.28 \times 10^{-4} x + 1.50 \times 10^{0} \]
\[ R^2 = 9.99 \times 10^{-1} \]
1H NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol% Rh$_2$(tfa)$_4$ and Proton Sponge in CD$_2$Cl$_2$ at 25ºC

To a stirred solution of $\alpha$-diazoketone 144 (50 mg, 0.224 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 20 µL, 0.231 mmol, 1.03 equiv) in CD$_2$Cl$_2$ (2.2 mL) was added Rh$_2$(tfa)$_4$ (1.5 mg, 0.002 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. Once complete (ca. 10 s), proton sponge (47 mg, 0.219 mmol, 1.0 equiv) was added. NMR sample preparation and kinetic measurements proceeded in the manner described above. The data collected and the derived rate constant/half life are presented below.

<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>ln (enol/std)</th>
</tr>
</thead>
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<tr>
<td>1200</td>
<td>-0.3</td>
</tr>
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<td>1800</td>
<td>-0.449</td>
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<td>2400</td>
<td>-0.598</td>
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<tr>
<td>3000</td>
<td>-0.74</td>
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<tr>
<td>3600</td>
<td>-0.875</td>
</tr>
<tr>
<td>4200</td>
<td>-1.016</td>
</tr>
<tr>
<td>4800</td>
<td>-1.174</td>
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<tr>
<td>5400</td>
<td>-1.321</td>
</tr>
<tr>
<td>6000</td>
<td>-1.461</td>
</tr>
<tr>
<td>6600</td>
<td>-1.599</td>
</tr>
</tbody>
</table>

$k = 2.4 \times 10^{-4}$ s$^{-1}$ \hspace{1cm} $t_{1/2} = 48$ min
In (enol/std) vs. Time for [3,3]-Rearrangement of Enol 149
1 mol% Rh₂(tfa)₄ and 1.0 equiv Proton Sponge, CD₂Cl₂, 25°C

\[ y = -2.41E-04x - 1.44E-02 \]
\[ R^2 = 1.00E+00 \]

1H NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol% Rh₂(tfa)₄ in Benzene-\textit{d}₆ at 40°C

To a stirred solution of \( \alpha \)-diazoketone 144 (84 mg, 0.379 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 34 µL, 0.392 mmol, 1.04 equiv) in benzene-\textit{d}₆ (4 mL) was added Rh₂(tfa)₄ (2.5 mg, 0.004 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. Once complete (ca.
10 s), an aliquot (0.75 mL) was transferred via syringe to a septum-covered NMR tube which had previously been purged with \( N_2(g) \) for 20 min. The NMR tube was inserted into a magnet and heated to 40ºC. Once this temperature was reached, the sample was allowed to equilibrate for 10 min before data collection was initiated. Conversion of \( 149 \) to \( 152 \) was monitored by \(^1\)H NMR at 40ºC, spectra being collected every 2 minutes (8 scans per collection). The integration of the allylic methyl doublet of enol \( 149 \) was measured at each collection period along with the corresponding signal of residual 3-butene-2-ol (94c), which remained constant. The ratio of these two values was calculated at each interval and the natural log of this value plotted versus elapsed reaction time. The data collected and the derived rate constant/half life are presented below.

<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>ln (enol/std)</th>
</tr>
</thead>
<tbody>
<tr>
<td>510</td>
<td>0.027</td>
</tr>
<tr>
<td>630</td>
<td>-0.15</td>
</tr>
<tr>
<td>750</td>
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<td>-0.633</td>
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<td>1110</td>
<td>-0.796</td>
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<tr>
<td>1230</td>
<td>-0.952</td>
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<tr>
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<td>-1.103</td>
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</tr>
<tr>
<td>1590</td>
<td>-1.415</td>
</tr>
<tr>
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<td>-1.546</td>
</tr>
<tr>
<td>1830</td>
<td>-1.715</td>
</tr>
<tr>
<td>1950</td>
<td>-1.917</td>
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</tbody>
</table>

\( k = 1.3 \times 10^{-3} \text{ s}^{-1} \) \hspace{1cm} \( t_{1/2} = 8.8 \text{ min} \)
\[ y = -1.32E-03x + 6.81E-01 \]

\[ R^2 = 9.99E-01 \]

\[ \text{In}(\text{enol/std}) \text{ vs. Time for [3,3]-Rearrangement of Enol 149} \]

1 mol% Rh\(_2\)(tfa)\(_4\), benzene-\(d_6\), 40°C

\[ \text{1H NMR-Monitored Claisen Rearrangement of Enol 148 with 1 mol\% Rh}_2(tfa)_4 \text{ in Benzene-}d_6 \text{ at 40°C} \]

To a stirred solution of \(\alpha\)-diazoketone 144 (79 mg, 0.357 mmol, 1.0 equiv) and allyl alcohol (94a, 25 \(\mu\)L, 0.369 mmol, 1.03 equiv) in benzene-\(d_6\) (3.5 mL) was added Rh\(_2\)(tfa)\(_4\) (2.3 mg, 0.003 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. NMR sample preparation and temperature equilibration were performed in a manner identical
to that reported above. Conversion of 148 to 221 was monitored by $^1$H NMR at 40°C, spectra being collected every 10 minutes (8 scans per collection). Due to competing tautomerization, reduction in enol concentration due to Claisen rearrangement was measured indirectly via integration of the allylic multiplet of $\alpha$-hydroxyketone 221 and subtraction of this value from the initial integration of the allylic multiplet of enol 148. These integral values were measured relative to that of the allylic multiplet of residual allyl alcohol (94a), which remained constant. The data collected and the derived rate constant/half life are presented below.

<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>ln (enol$_{p}$-[3,3]/std)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1200</td>
<td>0.312</td>
</tr>
<tr>
<td>1800</td>
<td>0.245</td>
</tr>
<tr>
<td>2400</td>
<td>0.181</td>
</tr>
<tr>
<td>3000</td>
<td>0.096</td>
</tr>
<tr>
<td>3600</td>
<td>0.038</td>
</tr>
<tr>
<td>4200</td>
<td>-0.007</td>
</tr>
<tr>
<td>4800</td>
<td>-0.062</td>
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<tr>
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<td>-0.12</td>
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<tr>
<td>6000</td>
<td>-0.163</td>
</tr>
<tr>
<td>6600</td>
<td>-0.224</td>
</tr>
</tbody>
</table>

$k = 9.8 \times 10^{-5} \text{ s}^{-1}$ \hspace{1cm} $t_{1/2} = 118 \text{ min}$
**In(enol/std) vs. Time for [3,3]-Rearrangement of Enol 148**

1 mol% Rh\(_2\)(tfa)\(_4\), benzene-\(d^6\), 40ºC

\[ y = -9.80 \times 10^{-5}x + 4.12 \times 10^{-1} \]

\[ R^2 = 9.94 \times 10^{-1} \]

---

\(^1\)H NMR-Monitored Claisen Rearrangement of Enol 151 with 1 mol% Rh\(_2\)(tfa)\(_4\) in Benzene-\(d^6\) at 40ºC

![Chemical Structures](image)

To a stirred solution of α-diazoketone 144 (56 mg, 0.251 mmol, 1.0 equiv) and 2-methyl-2-propen-1-ol (150, 22 µL, 0.261 mmol, 1.04 equiv) in benzene-\(d^6\) (2.5 mL) was added Rh\(_2\)(tfa)\(_4\) (1.7 mg, 0.003 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. NMR sample preparation and temperature equilibration were performed in a manner identical

---

![Graph](image)
to that reported above. Conversion of 148 to 222 was monitored by $^1$H NMR at 40°C, spectra being collected every 10 minutes (8 scans per collection). Due to competing tautomerization, reduction in enol concentration due to Clasien rearrangement was measured indirectly via integration of the allylic multiplet of $\alpha$-hydroxyketone 222 and subtraction of this value from the initial integration of the allylic multiplet of enol 151. These integral values were measured relative to that of the allylic multiplet of residual 2-methyl-2-propen-1-ol (150), which remained constant. The data collected and the derived rate constant/half life are presented below.

<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>$\ln$ (enol$_{0}$-[3,3]/std)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1.639</td>
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<tr>
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<tr>
<td>3000</td>
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<tr>
<td>3600</td>
<td>1.611</td>
</tr>
<tr>
<td>4200</td>
<td>1.605</td>
</tr>
</tbody>
</table>

$k = 1.1 \times 10^{-5} \text{ s}^{-1}$  \  \  $t_{1/2} = 18 \text{ h}$
Preparation of α-Hydroxyketone 221 and α-Allyloxy Ketone 225

To a stirred solution of α-diazoketone 144 (99 mg, 0.446 mmol, 1.0 equiv) and allyl alcohol (94a, 36 µl, 0.529 mmol, 1.2 equiv) in benzene (5 mL) was added Rh₂(OAc)₄ (2.0 mg, 0.005 mmol, 0.01 equiv). The resulting mixture was immersed in a pre-heated oil bath and heated at reflux for 15 min, after which it was cooled and concentrated under reduced pressure. Flash chromatography of the residue (8:1 hexanes: ethyl acetate...
eluent) furnished α-hydroxyketone 221 (47 mg, 42% yield) and α-allyoxy ketone 225 (37 mg, 33% yield) both as a clear, yellow oils. α-Hydroxyketone 221: 1H NMR (400 MHz, CDCl3) δ 7.74 (m, 2H), 7.53-7.28 (comp. m, 8H), 5.75 (m, 1H), 5.13 (m, 1H), 5.03 (m, 1H), 4.19 (s, 1H), 3.15 (m, 1H), 2.99 (ddt, J=1.2, 7.0, 13.4 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ 200.8, 141.7, 132.7, 132.3, 130.1, 128.9, 128.1, 128.0, 125.6, 120.4, 81.4, 43.9; IR (thin film/NaCl) 3447 (br. m), 3062 (w), 3027 (w), 2917 (w), 1676 (s), 1447 (m), 1229 (m), 925 (m), 699 (s) cm⁻¹; HRMS (EI) m/z found: 252.1148  [calc'd for C17H16O2 (M+): 252.1150].

α-Allyoxy ketone 225: 1H NMR (400 MHz, CDCl3) δ 8.01 (m, 2H), 7.53-7.27 (comp. m, 8H), 5.97 (ddt, J=5.8, 10.0, 17.2 Hz, 1H), 5.68 (s, 1H), 5.32 (dq, J=1.6, 17.4 Hz, 1H), 5.24 (dq, J=1.2, 10.2 Hz, 1H), 4.13 (dt, J=1.2, 6.0 Hz, 2H); 13C NMR (100 MHz, CDCl3) δ 197.3, 136.2, 135.0, 134.0, 133.2, 129.1, 128.8, 128.4, 127.5, 118.1, 83.9, 70.5; IR (thin film/NaCl) 3063 (w), 3028 (w), 2861 (w), 1693 (s), 1597 (m), 1448 (m), 1220 (m), 1099 (m), 1071 (m), 697 (s) cm⁻¹; HRMS (CI) m/z found: 253.1232  [calc'd for C17H17O2 (M+H): 253.1229].
Preparation of α-Hydroxyketone 222 and α-Allyloxy Ketone 226

To a stirred solution of α-diazoketone 144 (103 mg, 0.463 mmol, 1.0 equiv) and 2-methyl-2-propen-1-ol (150, 47 µl, 0.559 mmol, 1.2 equiv) in toluene (5 mL) was added Rh$_2$(OAc)$_4$ (2.1 mg, 0.005 mmol, 0.01 equiv). The resulting mixture was immersed in a pre-heated oil bath and heated at reflux for 15 min, after which it was cooled and concentrated under reduced pressure. Flash chromatography of the residue (8:1 hexanes: ethyl acetate eluent) furnished α-hydroxyketone 222 (23 mg, 19% yield) and α-allyloxy ketone 226 (74 mg, 60% yield) both as a clear, yellow oils. α-Hydroxyketone 222: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.56 (m, 2H), 7.47-7.28 (comp. m, 8H), 4.91 (m, 1H), 4.64 (m, 1H), 4.05 (s, 1H), 3.26 (dd, J=0.8, 13.6 Hz, 1H), 2.97 (dd, J=0.4, 13.6 Hz, 1H), 1.55 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.9, 142.3, 141.5, 134.9, 132.6, 130.3, 128.8, 128.0, 127.9, 125.4, 116.6, 81.2, 47.4, 24.1; IR (thin film/NaCl) 3505 (br. m), 3069 (w), 2969 (w), 2919 (w), 1675 (s), 1597 (m), 1447 (m), 1235 (m), 1214 (m), 669 (s) cm$^{-1}$; HRMS (EI) m/z found: 266.1300 [calc'd for C$_{18}$H$_{18}$O$_2$ (M$^+$): 266.1307].

α-allyloxy ketone 226: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.50 (m, 2H), 7.41-7.28 (comp. m, 8H), 5.63 (s, 1H), 5.01 (m, 1H), 4.96 (m, 1H), 4.04 (d, J=12.5 Hz, 1H), 4.00 (d, J=12.5 Hz, 1H), 1.76 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 197.4, 141.4, 136.4, 135.0, 133.2, 129.2, 128.8, 128.4, 128.3, 127.4, 113.3, 83.8, 73.5, 19.6; IR (thin film/NaCl) 2859 (w),
1693 (s), 1597 (m), 1449 (s), 1240 (m), 1220 (m), 1112 (s), 758 (m), 697 (s) cm⁻¹; HRMS (El) m/z found: 265.1225 [calc'd for C₁₈H₁₇O₂ (M-H): 265.1229].

¹H NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol% Rh₂(tfa)₄ in Benzene-d₆ at 15°C

To a stirred solution of α-diazoketone 144 (66 mg, 0.296 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 27 µL, 0.311 mmol, 1.05 equiv) in benzene-d₆ (3 mL) was added Rh₂(tfa)₄ (2.0 mg, 0.003 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. Once complete (ca. 10 s), an aliquot (0.75 mL) was transferred via syringe to a septum-covered NMR tube which had previously been purged with N₂(g) for 20 min. The NMR tube was inserted into the magnet and cooled to 15°C. Once this temperature was reached, the sample was allowed to equilibrate for 30 min before data collection was initiated. Conversion of 149 to 152 was monitored by ¹H NMR at 15°C, spectra being collected every 30 minutes (8 scans per collection). The integration of the allylic methyl doublet of enol 149 was measured at each collection period along with the corresponding signal of residual 3-buten-2-ol (94c), which remained constant. The data collected and the derived rate constant/half life are presented below.
### Table

<table>
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<tr>
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<td>14400</td>
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<td>16200</td>
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<td>18000</td>
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```
k = 6.4 \times 10^{-5} \text{ s}^{-1}
t_{1/2} = 180 \text{ min}
```
$^1$H NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol% Rh$_2$(tfa)$_4$ in Benzene-$d_6$ at 20°C

To a stirred solution of α-diazoketone 144 (72 mg, 0.329 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 30 µL, 0.346 mmol, 1.05 equiv) in benzene-$d_6$ (3.3 mL) was added Rh$_2$(tfa)$_4$ (2.0 mg, 0.003 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. NMR sample preparation proceeded as described above. The NMR tube was inserted into the magnet and cooled to 20°C. Once this temperature was reached, the sample was allowed to equilibrate for 20 min before data collection was initiated. Conversion of 149 to 152 was monitored by $^1$H NMR at 20°C, spectra being collected every 10 minutes (8 scans per collection). Kinetic measurements proceeded in the manner described above. The data collected and the derived rate constant/half life are presented below.

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<td>6000</td>
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$k = 1.3 \times 10^{-4} \text{ s}^{-1}$  \hspace{1cm} $t_{1/2} = 89 \text{ min}$
In(enol/std) vs. Time for [3,3]-Rearrangement of Enol 149
1 mol% Rh2(tfa)4, benzene-d6, 20°C

$y = -1.30E-04x + 1.07E+00$
$R^2 = 9.96E-01$

$0 \quad 800 \quad 1600 \quad 2400 \quad 3200 \quad 4000 \quad 4800 \quad 5600 \quad 6400$

Time (s)

$\ln(\text{enol/std})$

$0 \quad 0.2 \quad 0.4 \quad 0.6 \quad 0.8 \quad 1$

$1H$ NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol% Rh$_2$(tfa)$_4$ in Benzene-$d_6$ at 25°C

To a stirred solution of $\alpha$-diazoketone 144 (79 mg, 0.354 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 32 µL, 0.369 mmol, 1.04 equiv) in benzene-$d_6$ (3.5 mL) was added Rh$_2$(tfa)$_4$ (2.3 mg, 0.003 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. NMR sample
preparation proceeded as described above. The NMR tube was inserted into the magnet and warmed to 25°C. Once this temperature was reached, the sample was allowed to equilibrate for 20 min before data collection was initiated. Conversion of 149 to 152 was monitored by $^1$H NMR at 25°C, spectra being collected every 10 minutes (8 scans per collection). Kinetic measurements proceeded in the manner described above. The data collected and the derived rate constant/half life are presented below.

<table>
<thead>
<tr>
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$k = 2.0 \times 10^{-4} \text{ s}^{-1}$  $t_{1/2} = 58 \text{ min}$
1H NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol% Rh$_2$(tfa)$_4$ in Benzene-$d_6$ at 30ºC

\[ \text{O} \]
\[ \text{N}_2 \]
\[ \text{144} \]
\[ \text{HO} \]
\[ \text{O} \]
\[ \text{Me} \]
\[ \text{149} \]
\[ + \]
\[ \text{OH} \]
\[ \text{Me} \]
\[ \text{94c} \]
\[ \text{Rh}_2$(tfa)$_4$ (1.0 mol %) ]
\[ \text{benzene}-d_6 \text{ rt } (-\text{N}_2(g)) ]
\[ \text{30ºC} \]
\[ \text{benzene}-d_6 \ [3,3] \text{ Ph} \]
\[ \text{HO} \]
\[ \text{O} \]
\[ \text{Me} \]
\[ \text{152} \]

To a stirred solution of $\alpha$-diazoketone 144 (84 mg, 0.376 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 39 µL, 0.450 mmol, 1.2 equiv) in benzene-$d_6$ (4 mL) was added Rh$_2$(tfa)$_4$ (2.8 mg, 0.004 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. NMR sample preparation proceeded as described above. The NMR tube was inserted into the magnet and warmed to 30ºC. Once this temperature was reached, the sample was allowed to equilibrate for 20 min before data collection was initiated. Conversion of 149 to 152 was monitored by 1H NMR at 30ºC, spectra being collected every 10 minutes (8 scans per collection). Kinetic measurements proceeded in the manner described above. The data collected and the derived rate constant/half life are presented below.

<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>ln(enol/std)</th>
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\[ k = 3.8 \times 10^{-4} \text{ s}^{-1} \]
\[ t_{1/2} = 30 \text{ min} \]
\[
\text{In(enol/\text{std}) vs. Time for [3,3]-Rearrangement of Enol 149}
\]

\[
1 \text{ mol}\% \text{ Rh}_2(\text{tfa})_4, \text{ benzene-}d_6, 30^\circ\text{C}
\]

\[
y = -3.78E-04x + 6.05E-01
\]

\[
R^2 = 9.99E-01
\]

\[
\begin{array}{c}
\text{1H NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol\% Rh}_2(\text{tfa})_4 \text{ in Benzene-}d_6 \text{ at 35°C}
\end{array}
\]

To a stirred solution of \(\alpha\)-diazoketone 144 (80 mg, 0.361 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 38 µL, 0.438 mmol, 1.2 equiv) in benzene-\(d_6\) (4 mL) was added \(\text{Rh}_2(\text{tfa})_4\) (2.4 mg, 0.004 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. NMR sample
preparation proceeded as described above. The NMR tube was inserted into the magnet and warmed to 35ºC. Once this temperature was reached, the sample was allowed to equilibrate for 10 min before data collection was initiated. Conversion of 149 to 152 was monitored by ¹H NMR at 30ºC, spectra being collected every 10 minutes (8 scans per collection). Kinetic measurements proceeded in the manner described above. The data collected and the derived rate constant/half life are presented below.

<table>
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<td>-2.797</td>
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k = $6.7 \times 10^{-4}$ s⁻¹  
$t_{1/2} = 17$ min

In(enol/std) vs. Time for [3,3]-
Rearrangement of Enol 149
1 mol% Rh₂(tfa)₄, benzene-d₆, 35ºC

\[ y = -6.66E-04x + 3.86E-01 \]
\[ R² = 1.00E+00 \]
\(^{1}\)H NMR-Monitored Claisen Rearrangement of Enol 149 with 1 mol \% Rh\(_2\)(tfa), in Benzene-\(d_6\) at 37°C

To a stirred solution of \(\alpha\)-diazoketone 144 (80 mg, 0.361 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 38 \(\mu\)L, 0.438 mmol, 1.2 equiv) in benzene-\(d_6\) (4 mL) was added Rh\(_2\)(tfa), (2.4 mg, 0.004 mmol, 0.01 equiv) resulting in rapid loss of nitrogen gas. NMR sample preparation proceeded as described above. The NMR tube was inserted into the magnet and warmed to 37°C. Once this temperature was reached, the sample was allowed to equilibrate for 10 min before data collection was initiated. Conversion of 149 to 152 was monitored by \(^{1}\)H NMR at 30°C, spectra being collected every 10 minutes (8 scans per collection). Kinetic measurements proceeded in the manner described above. The data collected and the derived rate constant/half life are presented below.

<table>
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\[ k = 8.5 \times 10^{-4} \text{ s}^{-1} \]

\[ t_{1/2} = 14 \text{ min} \]
Preparation of Enol Trifluoroacetate 223

To a stirred solution of α-diazoketone 144 (85 mg, 0.382 mmol, 1.0 equiv) and 3-buten-2-ol (94c, 40 µL, 0.462 mmol, 1.2 equiv) in CH\(_2\)Cl\(_2\) (4 mL) was added Rh\(_2\)(OAc)\(_4\) (1.7 mg, 0.0038 mmol, 0.01 equiv) resulting in decolorization of the reaction mixture and rapid N\(_2\)(g) loss. Once complete, the mixture was cooled to -78°C and treated with
trifluoroacetic anhydride (80 µL, 0.566 mmol, 1.5 equiv) followed by Et\textsubscript{3}N (0.12 mL, 0.863 mmol, 2.3 equiv). After 10 min the mixture was warmed to room temperature and concentrated and the residue purified by flash chromatography (4:1 pentane:CH\textsubscript{2}Cl\textsubscript{2} eluent) to provide enol trifluoroacetate 223 (78 mg, 56% yield) as white needles. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 7.29-7.37 (comp m, 5H), 7.13-7.20 (comp m, 5H), 5.81 (ddd, J=7.0, 10.3, 17.3 Hz, 1H), 5.11 (dt, J=1.1, 10.3 Hz, 1H), 4.99 (dt, J=1.1, 17.2 Hz, 1H), 4.22 (m, 1H), 1.30 (d, J=6.3 Hz, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) δ 155.3 (q, J=42.6 Hz), 145.4, 138.5, 133.7, 132.4, 131.9, 130.1, 129.3, 128.5, 128.3, 128.2, 128.1, 116.3, 114.8 (q, J=283.7 Hz), 76.0, 20.7; IR (thin film/NaCl) 3085 (w), 3061 (w), 2982 (w), 2932 (w), 2932 (w), 1801 (s), 1446 (m), 1358 (m), 1258 (s), 1222 (s), 1171 (s), 1135 (s), 1050 (m), 921 (m), 776 (s), 697 (s) cm\textsuperscript{-1}; HRMS (EI) m/z found: 362.1127, [calc'd for C\textsubscript{20}H\textsubscript{17}F\textsubscript{3}O\textsubscript{3} (M\textsuperscript{+}): 362.1130]; m.p. 57-59°C (pentane).

\textsuperscript{1}H NMR-Monitored Claisen Rearrangement of Enol Trifluoroacetate 223 in Benzene-\textit{d}6 at 40°C

To a stirred solution of enol trifluoroacetate 223 (78 mg, 0.215 mmol, 1.0 equiv) in benzene-\textit{d}6 (3 mL) was added toluene (17 mL, 0.160 mmol, 0.75 equiv). An aliquot (0.75 mL) of this mixture was transferred via syringe to a septum-covered NMR tube which
had previously been purged with N$_2$(g) for 20 min. The NMR tube was inserted into the magnet and heated to 40°C. Once this temperature was reached, the sample was allowed to equilibrate for 20 min before data collection was initiated. Conversion of 223 to 224 was monitored by $^1$H NMR at 40°C, spectra being collected every 60 minutes (8 scans per collection). The integration of the allylic methyl doublet of 223 was measured at each collection period along with the methyl singlet of toluene, which remained constant.

The data collected and the derived rate constant/half life are presented below.

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$k = 1.3 \times 10^{-5}$ s$^{-1}$  \hspace{2cm} $t_{1/2} = 14$ h
Confirmation of Structure of Trifluoroacetate 224

To a stirred solution of α-hydroxyketone 152 (30 mg, 0.113 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (2 mL) at 0°C was added in rapid succession trifluoroacetic anhydride (19 µL, 0.135 mmol, 1.2 equiv), triethylamine (23 µL, 0.165 mmol, 1.5 equiv) and 4-$N$-$N$-diethylaminopyridine (DMAP, 2.3 mg, 0.019 mmol, 0.17 equiv). This mixture was allowed to stir overnight with warming to room temperature, after which it was
concentrated under reduced pressure. The residue was purified by flash chromatography (10:1 hexanes: ethyl acetate eluent) to furnish trifluoroacetate 224 (22 mg, 55% yield) as a clear, colorless oil whose spectral data matched exactly that of material derived from Claisen rearrangement of 223. 1H NMR (500 MHz, CDCl₃) δ 7.68-7.27 (comp. m, 10H), 5.44 (m, 1H), 5.08 (m, 1H), 3.45 (dd, J=9.5, 15.0 Hz, 1H), 3.09 (m, 1H), 1.60 (dt, J=1.5, 6.0 Hz, 3H); 13C NMR (125 MHz, CDCl₃) δ 155.1 (q, J=43.0 Hz), 136.2, 134.0, 133.0, 131.3, 129.1, 129.1, 128.6, 128.3, 124.5, 114.2 (q, J=286.2 Hz), 112.0, 91.9, 40.3, 17.9; IR (thin film/NaCl) 3031 (w), 2920 (w), 1788 (s), 1691 (s), 1448 (m), 1368 (m), 1254 (m), 1224 (s), 1173 (s), 1150 (s), 669 (m) cm⁻¹; HRMS (EI) m/z found: 362.1133 [calc’d for C₂₀H₁₇O₃F₃ (M⁺): 362.1130].

4.6 Notes and References


(6) See Ref. 4b


(9) For $^1$H NMR spectra of α-allyloxy enols 148, 149, and 151, see Appendix Two.


(12) For an example of the application of this theory to the Claisen rearrangement, see: Schuler, F. W.; Murphy, G. W. J. Am. Chem. Soc. 1950, 72, 3155.

(13) See Ref. 4b.

(14) Enantiomeric excess determined by Mosher ester analysis of the derived diol.
Figure A.4.1 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 221.
Figure A.2.3: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 221.

Figure A.4.2: FTIR Spectrum (thin film/NaCl) of Compound 221.
Figure A.4.4 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 225.
Figure A.4.6 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 225.

Figure A.4.5 FTIR Spectrum (thin film/NaCl) of Compound 225.
Figure A.4.7 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 222.
Figure A.4.9 ¹³C NMR (125 MHz, CDCl₃) of Compound 222.

Figure A.4.8 FTIR Spectrum (thin film/NaCl) of Compound 222.
Figure A.4.10 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 226.
Figure A.4.11 FTIR Spectrum (thin film/NaCl) of Compound 226.

Figure A.4.12 13C NMR (125 MHz, CDCl3) of Compound 226.
Figure A.4.13 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 223.
Figure A.4.14 FTIR Spectrum (thin film/NaCl) of Compound 223.

Figure A.4.15 $^{13}$C NMR (125MHz, CDCl$_3$) of Compound 223.
Figure A.4.16 $^1$H NMR (500 MHz, C$_6$D$_6$) of Compound 224.
Figure A.4.18 $^{13}$C NMR (125MHz, CDCl$_3$) of Compound 224.

Figure A.4.17 FTIR Spectrum (thin film/NaCl) of Compound 224.
Chapter 5
Catalyst-Based Control of [2,3]- and [3,3]-Rearrangement in $\alpha$-Diazoketone-Derived Propargyloxy Enols

5.1 Efforts to Extend the Rhodium Carbenoid-Initiated Claisen Rearrangement to Propargylic Alcohols

5.1.1 Initial Efforts

The investigations into the scope and limitations of the rhodium carbenoid-initiated Claisen rearrangement presented in Chapter 2 encompassed a variety of $\alpha$-diazoketones and allylic alcohols and revealed the generality of the reaction with regard to both components. However, mechanistic insight gained in subsequent studies suggested that the utility of this novel process might not be limited solely to allylic alcohols. Rather, it was expected that the scope of the reaction could be extended to include propargylic alcohols as well. This was desirable since Claisen rearrangement of the intermediate propargyloxy enols (e.g., 229) would generate tertiary $\alpha$-hydroxyketones possessing a pendant allene (e.g., 230), a synthetic handle of significant versatility (Scheme 5.1).
To explore the reactivity of propargylic alcohols under the standard Claisen conditions, α-diazoketone 103 was treated with 1 mol % Rh$_2$(OAc)$_4$ in the presence of 3-butyn-2-ol (228) in refluxing benzene for 10 minutes (Scheme 5.2). Curiously, the expected [3,3]-rearrangement product (230) was isolated as a 2.3:1 mixture with the regioisomeric α-hydroxyketone 231, the product of apparent [2,3]-rearrangement of enol 229. In light of new mechanistic knowledge regarding the reaction of α-diazoketones with alcohols, this result was considered to be consistent with three possible mechanistic scenarios shown in Scheme 5.3. First, since propargyloxy enol 229 is believed to arise via
**Scheme 5.3**

A. [2,3]-Rearrangement via Enol Precursor Ylide 232

![Scheme 5.3 A.](image)

B. Competitive [2,3] and [3,3]-Rearrangement of α-Allyloxy Enol 229

![Scheme 5.3 B.](image)

C. Product Interconversion via [1,2]-α-Ketol Rearrangement

![Scheme 5.3 C.](image)

Proton transfer from an ylide such as 232 (with or without Rh(II) coordination), it was deemed possible that this ylide species could undergo [2,3]-rearrangement (path b, Mechanism A in Scheme 5.3) in competition with proton transfer (path a). Although not observed with allylic alcohols, the propensity of related ylides derived from allylic ethers
to undergo facile [2,3]-rearrangement lent credence to this concept (See Section 1.3.5). Alternatively, it was conceivable that both [2,3]-rearrangement product 231 and [3,3]-rearrangement product 230 could derive from a common intermediate enol (229) since enolates of α-allyloxy carbonyl compounds are known to vacillate between these two rearrangement pathways (See Section 1.3.4). Finally, it was recognized that [2,3]-rearrangement product 231 could also arise via [1,2]-α-ketol shift of the pendant allene of [3,3]-product 230. The outcome of such a tandem [3,3]/[1,2] process would be indistinguishable from that of direct [2,3]-rearrangement of enol 229. Furthermore, a retro-[1,2]-shift could convert 231 to 230 and thus these two species might be in dynamic equilibrium. Identification of the origin of 231 thus represented a significant mechanistic problem.

5.1.2 Efforts to Influence Product Distribution

Uncertain of the mechanistic origin of [2,3]-product 231, investigations analogous to those described in Chapter 2 (Section 2.1) were initiated in an effort to establish some correlation between reaction conditions and reaction outcome. These studies again commenced with variations of catalyst ligand and loading and revealed a dramatic dependence of reaction outcome on the nature of the Rh(II) catalyst employed. As shown in Table 5.1, increased quantities of the apparent [2,3]-rearrangement product (231) were observed with increased catalyst loadings of Rh₂(OAc)₄ (Entries 1-3). Production of 231 could be further augmented by employing the more electron-deficient Rh₂(tfa)₄ catalyst which, in 10 min at room temperature, resulted in rapid and exclusive production of 231 at 0.25 mol% catalyst loading (Entry 4). Efforts employing an equivalent catalyst
loading of Rh₂(OAc)₄ at room temperature required 12 hours for complete conversion and offered no selectivity (Entry 5). Importantly, use of the highly soluble Rh₂(oct)₄ catalyst (0.25 mol%) required reflux temperatures and furnished a 3.5:1 mixture of 230 and 231 (Entry 6), demonstrating that the enhanced reactivity and selectivity exhibited by Rh₂(tfa)₄ was not due exclusively to the enhanced solubility of this catalyst in the reaction medium.⁵ Suspecting that catalyst electronics were responsible for the observed effects, an electron-rich rhodium (II) catalyst, Rh₂(cap)₄, was employed, resulting in essentially exclusive production of [3,3]-rearrangement product 230 (Entry 7).⁶

Table 5.1 - Effect of Catalyst on Ratio of α-Hydroxyketones 230 and 231

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Conditions</th>
<th>Catalyst Loading (mol%)</th>
<th>230:231</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh₂(OAc)₄, Δ, 10 min</td>
<td>0.25</td>
<td>10.5:1</td>
</tr>
<tr>
<td>2</td>
<td>Rh₂(OAc)₄, Δ, 10 min</td>
<td>1.0</td>
<td>2.3:1</td>
</tr>
<tr>
<td>3</td>
<td>Rh₂(OAc)₄, Δ, 10 min</td>
<td>5.0</td>
<td>1:1.6</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(tfa)₄, rt, 10 min</td>
<td>0.25</td>
<td>1:57</td>
</tr>
<tr>
<td>5</td>
<td>Rh₂(OAc)₄, rt, 12 h</td>
<td>0.25</td>
<td>1.3:1</td>
</tr>
<tr>
<td>6</td>
<td>Rh₂(oct)₄, Δ, 10 min</td>
<td>0.25</td>
<td>3.5:1</td>
</tr>
<tr>
<td>7</td>
<td>Rh₂(cap)₄, Δ, 10 min</td>
<td>0.25</td>
<td>30:1</td>
</tr>
</tbody>
</table>

*Ratios determined by ¹H NMR analysis of crude reaction mixtures

Such catalyst influence was considered to be in accord with all three possible mechanistic scenarios presented in Scheme 3.5. In the first scenario, wherein [2,3]-rearrangement product 231 arises via ylide 232 (Mechanism A, Scheme 3.5), modulation of reaction outcome by Rh(II) was reasonable in light of recent studies demonstrating the influence of asymmetric Rh(II) catalysts on [2,3]-rearrangement of related ylides.⁷ For mechanisms B and C, the Lewis acidity of the rhodium (II) catalyst was expected to be
the prevailing factor, promoting an S_NI’ displacement to furnish 231 in mechanism B and [1,2]-α-ketol rearrangement of 230 to 231 in mechanism C (Scheme 5.4). In both situations, increased production of 231 would be expected in the presence of a more Lewis acidic Rh(II) catalyst such as Rh_2(tfa)_4, an assumption borne out experimentally.⁸

**Scheme 5.4**

5.1.3 Mechanistic Studies

Since all three mechanistic hypotheses presented in Scheme 5.3 could potentially exhibit catalyst-dependent reactivity, further studies were necessary to delineate which mechanism was operative. Initial efforts focused on differentiating mechanism A from mechanisms B and C by NMR monitoring. Thus, treatment of a solution of 103 and 228 in benzene-"d6 with 1 mol% Rh_2(OAc)_4 resulted, as before, in loss of nitrogen gas and decolorization of the reaction mixture. Analysis of the reaction mixture by ^1^H NMR initially revealed only enol 229, which, over time, gave rise to both [3,3]-rearrangement
product 230 and [2,3]-rearrangement product 231 simultaneously (Scheme 5.5). These observations discredited mechanism A since, were [2,3]-rearrangement

Scheme 5.5

competitive with enol formation, both 231 and 229 would be expected to appear as the initial products, 229 eventually giving rise only to [3,3]-rearrangement product 230.

To address the possibility that 230 and 231 were rapidly equilibrating species under the reaction conditions (Mechanism C, Scheme 5.3), isotope-labeling studies were again employed, exploiting the effect of catalyst on reaction outcome. Treatment of α-diazoketone 103 with 0.25 mol% Rh\textsubscript{2}(cap)\textsubscript{4} in the presence of 3-butyn-2-ol (2-D) (233)\textsuperscript{9} in refluxing benzene furnished deuterium-labeled α-hydroxyketone 234 (Scheme 5.6). The identical reaction employing 0.25 mol% Rh\textsubscript{2}(tfa)\textsubscript{4} at room temperature furnished the deuterium-labeled regioisomer (235, Scheme 5.6). With labeled
α-hydroxyketones 234 and 235 in hand, the isotope-labeling study described in Scheme 5.7 was carried out. A benzene solution of α-diazoketone 103, 3-butyn-2-ol (228), and deuterated α-hydroxyketone 234 was treated with 1.0 mol% Rh\(_2\)(tfa)\(_4\) at room temperature. This furnished [2,3]-rearrangement product 231 free of deuterium incorporation and recovered 234, demonstrating that [1,2]-α-ketol rearrangement of 234 to 235 was not occurring under the reaction conditions. Similarly, treatment of 103, 228, and 235 in benzene with 0.25 mol% Rh\(_2\)(cap)\(_4\) under reflux conditions furnished exclusively protic α-hydroxyketone 230 indicating that the reverse [1,2]-shift was also not operative.
It was thus evident that α-hydroxyketones 230 and 231 must arise from enol 229 via independent pathways. However, the role of the rhodium (II) catalyst in discriminating between these two pathways was unclear. The remarkably mild conditions required to generate 231 employing the electron-deficient Rh$_2$(tfa)$_4$ catalyst indicated a significant rate acceleration in the presence of this species. To quantify this rate enhancement, kinetic measurements similar to those described in Chapter 4 were employed. In the event, α-diazoketone 103 was decomposed in the presence of 3- butyn-2-ol (228) with both 1.0 mol% Rh$_2$(OAc)$_4$ and 0.1 mol% Rh$_2$(tfa)$_4$, furnishing exclusively enol 229 in both instances. Conversion of 229 to 231 was then monitored by $^1$H NMR spectroscopy, measuring the integration of enol resonances at regular intervals (See...
Experimental Section). As may be seen from Table 5.2, these measurements revealed a startling difference in the rate of conversion of 229 to 231 in the presence of the two Rh(II) catalysts. Conversion of 229 to 231 proceeded with a half-life of 3.5 h at 40°C in the presence of 1.0 mol% Rh$_2$(OAc)$_4$, but with a half-life of only 5.4 min at 25°C in the presence of 0.1 mol% Rh$_2$(tfa)$_4$. This represented a 39-fold increase in rate with a 10-fold lower catalyst loading at a significantly reduced temperature. Furthermore, using 1.0 mol% Rh$_2$(tfa)$_4$ at 25°C, conversion of 229 to 231 was complete before a single $^1$H NMR spectrum could be acquired (ca. 1 min). Thus, formation of 231 could be accelerated to a staggering degree simply by switching the dediazotizataton catalyst. To demonstrate that this rate enhancement derived from interaction of enol 229 with Rh$_2$(tfa)$_4$, two equimolar solutions of $\alpha$-diazoketone 103 and 3-butyn-2-ol (228) in benzene-$d_6$ were treated with 1.0 mol% Rh$_2$(OAc)$_4$ to effect dediazotization and formation of 229. Once complete, 0.5 mol% Rh$_2$(tfa)$_4$ was added to one mixture. Analysis of aliquots after 5 min revealed

**Table 5.2** - Variation in Half-Life for Conversion of 229 to 231 with Rhodium Catalyst

<table>
<thead>
<tr>
<th>Catalyst and Loading</th>
<th>t$_{1/2}$, Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mol% Rh$_2$(OAc)$_4$</td>
<td>3.5 h, 40°C</td>
</tr>
<tr>
<td>0.1 mol% Rh$_2$(tfa)$_4$</td>
<td>5.4 min, 25°C</td>
</tr>
<tr>
<td>1.0 mol% Rh$_2$(tfa)$_4$</td>
<td>&lt;1 min, 25°C</td>
</tr>
</tbody>
</table>
complete conversion of 229 to 231 in the Rh₂(tfa)₄-treated mixture and less than 5% conversion in the presence of 1.0 mol% Rh₂(OAc)₄ alone (Scheme 5.8). The role of Rh(II) as a catalyst for [2,3]-rearrangement of enol 229 was thus made evident.\textsuperscript{10}

**Scheme 5.8**

It was demonstrated in Chapter 4 that [3,3]-rearrangement of \( \alpha \)-allyloxy enols proceeds at a rate independent of both Rh(II) catalyst loading and the ligand on the Rh(II) center (See Table 4.1). It thus seemed reasonable that the analogous [3,3]-rearrangement of propargyloxy enols would demonstrate similar catalyst invariance. This hypothesis was supported by the data in Table 5.1, which showed that [2,3]-rearrangement is scarcely observable in the presence of an electron-rich rhodium catalyst but becomes more competitive at higher loadings of Rh(II) and the dominant reaction in the presence of more Lewis acidic Rh(II) catalysts. These data, along with the results depicted in Scheme 5.8, pointed to a mechanism wherein enol 229 bifurcates between rearrangement pathways and [2,3]-rearrangement is dramatically facilitated by Rh(II). If true, it was expected that addition of a catalyst inhibitor subsequent to enol formation might reduce the prevalence of the competing [2,3]-rearrangement pathway.
5.1.4 Suppression of [2,3]-Rearrangement via Competitive Inhibition of Rh(II)

Rhodium (II) carboxylate catalysts are dimeric compounds possessing four bridging carboxylate ligands and one vacant axial coordination site per metal atom (e.g., 236, Scheme 5.9). This coordination site is readily susceptible to attack by Lewis bases and numerous complexes of rhodium (II) carboxylates with axial ligands have been studied crystallographically.\textsuperscript{11} Furthermore, such complexation is presumably the basis for the reduced reactivity exhibited by Rh(II) catalysts towards diazo decomposition in coordinating solvents.\textsuperscript{12} Both 1:1 (e.g., 237) and 2:1 (e.g., 238) ligand-Rh(II) complexes are known, however, thermodynamic studies of Rh(II)-Lewis base binding have demonstrated that coordination of a single Lewis basic ligand to one metal center results in a dramatic reduction in the Lewis acidity of the remaining vacant metal center.\textsuperscript{13}

Having demonstrated the Rh(II)-catalyzed nature of [2,3]-rearrangement of enol 229, it was hoped that addition of a Lewis-basic additive subsequent to $\alpha$-diazoketone decomposition but prior to [2,3]-rearrangement might suppress this competing pathway by sequestering the Lewis acidity of the Rh(II) metal center.

Table 5.3 shows the results of additives on the ratio of 230:231 generated in the presence of 5 mol\% Rh$_2$(OAc)$_4$ under standard reflux conditions. In each experiment, $\alpha$-
diazoketone 103 was treated with 5 mol% Rh$_2$(OAc)$_4$ in the presence of 3-butyn-2-ol (228, 1.2 equiv). Once dediazotization was complete as evidenced by cessation of N$_2$(g) release, the indicated quantity of inhibitor was added and the mixture was heated to reflux for 10 min. In the absence of inhibitor, a 1:1.6 ratio of 230:231 was observed as before (See Table 5.1). Addition of acetonitrile (2 equiv) resulted in an inverted product ratio that could be increased to 4:1 230:231 in the presence of greater quantities (i.e., 10 equiv) of this inhibitor. A study by Drago was subsequently discovered that reported equilibrium constants for 1:1 binding of several Lewis bases to Rh$_2$(butanoate)$_4$. In that study, amines were found to be the strongest coordinating ligands (e.g., piperidine, K$_{eq}$ = 1.0x10$^5$ M$^{-1}$), however, the tendency of amines to effect enol tautomerization (See Scheme 3.10) prohibited their use as inhibitors. Fortunately, binding of

Table 5.3 - Effect of Lewis Basic Additives on Production of α-Hydroxyketone 231

<table>
<thead>
<tr>
<th>Additive</th>
<th>Quantity (equiv)</th>
<th>230:231$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>no additive</td>
<td>-</td>
<td>1 : 1.6</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>2.0</td>
<td>2.0 : 1</td>
</tr>
<tr>
<td>CH$_3$CN</td>
<td>10.0</td>
<td>4.4 : 1</td>
</tr>
<tr>
<td>Me$_2$S</td>
<td>2.0</td>
<td>53 : 1</td>
</tr>
</tbody>
</table>

$^a$Ratios determined by $^1$H NMR analysis of crude reaction mixtures
tetrahydrothiophene was reported to be nearly as thermodynamically favorable ($K_{eq} = 1.7 \times 10^7 \text{ M}^{-1}$), proceeding with a binding constant 1.5x10$^4$-times greater than that of acetonitrile ($K_{eq} = 1.15 \times 10^3 \text{ M}^{-1}$). The desire to use a more volatile analog of tetrahydrothiophene led to the selection of dimethyl sulfide which, when employed as an inhibitor (2.0 equiv), resulted in essentially complete elimination of [2,3]-rearrangement product 231 (Table 5.3). To assess whether this catalyst-inhibitory activity would be manifest under more Lewis-acidic conditions, $\alpha$-diazoketone 103 was treated with 1.0 mol% Rh$_2$(OAc)$_4$ in the presence of 3-butyn-2-ol (228, 1.2 equiv) giving rise to enol 229 which was then treated with dimethyl sulfide (2.0 equiv). In sharp contrast to results obtained in the absence of this inhibitor (See Scheme 5.8), addition of 1.0 mol% Rh$_2$(tfa)$_4$ did not promote conversion of 229 to 231. Rather, only [3,3]-rearrangement product 230 was isolated upon heating the reaction mixture to reflux (Scheme 5.10). It was thus concluded that [3,3]-rearrangement of $\alpha$-propargyloxy enol 229 was analogous to the corresponding transformation of $\alpha$-allyloxy enols (e.g., 143), that is, a non-catalytic process that proceeds at a rate independent of rhodium (II). Furthermore, the rate of [3,3]-rearrangement could be readily surpassed by that of rhodium (II)-catalyzed [2,3]-rearrangement in the presence of a sufficiently Lewis-acidic rhodium (II) species.$^6$

Scheme 5.10
5.2 Scope and Limitations of [3,3]- and [2,3]-Rearrangement of Propargyloxy Enols

5.2.1 Doubly Stabilized α-Diazoketones

Having established the basis for the divergent reactivity of enol 229, an investigation into the scope of both rearrangement processes was launched. These efforts commenced with a survey of several propargylic alcohols to assess their compatibility with both rearrangement processes using α-diazoketone 103. As may be surmised from the data presented in Table 5.4, [2,3]-rearrangement was readily effected using the Rh$_2$(tfa)$_4$ catalyst at 0.25 mol% catalyst loading at room temperature and the desired [2,3]-rearrangement products 243a-d were isolated in good to modest yields. No competition from either [3,3]-rearrangement or OH-insertion was observed. A substantially reduced yield was observed with 2-methyl-3-butyn-2-ol (241), presumably due to inefficient carbenoid capture by the more sterically hindered tertiary hydroxyl group. The corresponding [3,3]-rearrangement process was effected using 0.5 mol% Rh$_2$(cap)$_4$, and revealed substituent effects analogous to those observed with allylic alcohols. Specifically, use of primary propargylic alcohols such as 239 and 240 furnished substantial amounts of OH-insertion by-products, OH-insertion being the exclusive outcome in the case of alcohol 240. With secondary and tertiary propargylic alcohols, however, [3,3]-rearrangement proceeded smoothly under the standard reflux conditions, furnishing allenyl α-hydroxyketones 242c,d in good yields and to the exclusion of the corresponding [2,3]-rearrangement products.
Table 5.4 - [3,3]- and [2,3]-Rearrangement of Propargyloxy Enols Derived From α-Diazoketone 103

\[
\begin{array}{c}
\text{Entry} & \text{Alcohol} & \text{Conditions} & \text{Yield} 242 & \text{Yield} 243 \\
\hline
a & \text{239} & \text{A}^a & 22\%^c & 87\% \\
b & \text{240} & \text{A}^d & - & 68\% \\
c & \text{228} & \text{B} & 81\% & 82\% \\
d & \text{241} & \text{B} & 52\% & 50\% \\
\end{array}
\]

*Conditions A: 0.5 mol% Rh\(_2\)(cap)\(_4\), PhH, reflux, 10 min.  
**Conditions B: 0.25 mol% Rh\(_2\)(tfa)\(_4\), PhH, rt, 10 min.  
\(^a\) A 44% yield of tautomerized product was also isolated. \(^d\) An 83% yield of tautomerized product was isolated exclusively.

Efforts to achieve [3,3]-rearrangement with α-diazo-β-ketoester 59 were less successful. Use of 0.5 mol% Rh\(_2\)(cap)\(_4\) in refluxing benzene resulted in only very slow decomposition of this diazo substrate ultimately furnishing OH-insertion products. The corresponding [2,3]-rearrangement process, however, was readily performed using 0.25 mol% Rh\(_2\)(tfa)\(_4\) under reflux conditions to furnish allenyl α-hydroxyketones 244a-d in good yields (Table 5.5).
Table 5.5 - [2,3]-Rearrangement of Propargyloxy Enols
Derived From α-Diazo-β-Ketoester 59

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Yield 244</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>239</td>
<td>62%</td>
</tr>
<tr>
<td>b</td>
<td>240</td>
<td>61%</td>
</tr>
<tr>
<td>c</td>
<td>228</td>
<td>60%</td>
</tr>
<tr>
<td>d</td>
<td>241</td>
<td>43%</td>
</tr>
</tbody>
</table>

5.2.2 Monostabilized α-Diazoketones

While both [3,3]- and [2,3]-rearrangement could be achieved selectively using a variety of propargylic alcohols with diazo substrate 103, the former process was plagued by competing enol tautomerization with primary propargylic alcohols. Furthermore, [3,3]-rearrangement was entirely impracticable with α-diazo-β-ketoester 59 due to the inability of the electron-rich Rh₂(tfa)₄ catalyst to efficiently dediazotize this substrate. It was hoped that such limitations would not extend to monostabilized α-diazoketones since these substrates had previously demonstrated excellent [3,3]-rearrangement/tautomerization selectivity even with primary allylic alcohols. In addition, the more reactive monostabilized diazo functionality was expected to be readily decomposed by electron-rich rhodium (II) catalysts. With this in mind, α-diazoketone 116 was investigated for compatibility with the established [3,3]- and [2,3]-
rearrangement conditions. As may be surmised from Table 5.6, existing conditions for [3,3]-rearrangement were easily extended to this diazo substrate, use of 0.25 mol% Rh2(cap)4 furnishing α-hydroxyketones 245a-d without competition from [2,3]-rearrangement. Efforts to effect [2,3]-rearrangement using the Rh2(tfa)4 catalyst, however, resulted only in intractable mixtures of products. It was recognized from Table 5.1 that milder rhodium (II) catalysts could selectively promote [2,3]-rearrangement if employed at high enough catalyst loadings. After significant experimentation, it was discovered that use of 5 mol% Rh2(oct)4 furnished [2,3]-rearrangement products 246a-c with complete selectivity and in good yields thereby obviating use of the harsher Rh2(tfa)4 catalyst. An exception was propargylic alcohol 241, which required 20 mol% Rh2(oct)4 to eliminate completely the presence of [3,3]-rearrangement product 245d. Presumably, the rate of [3,3]-rearrangement was more competitive with this substrate combination due to acceleration by the geminal methyl substituents in the derived propargyloxy enol in a manner analogous to that observed with allyloxy enols (See
Table 5.6 - [3,3]- and [2,3]-Rearrangement of Propargyloxy Enols Derived From α-Diazoketone 116

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Conditions</th>
<th>Yield 245</th>
<th>Yield 246</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td><img src="#" alt="Alcohol" /></td>
<td>A&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60%</td>
<td>-</td>
</tr>
<tr>
<td>b</td>
<td><img src="#" alt="Alcohol" /></td>
<td>A</td>
<td>66%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>68%</td>
<td>-</td>
</tr>
<tr>
<td>c</td>
<td><img src="#" alt="Alcohol" /></td>
<td>A</td>
<td>60%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>65%</td>
<td>-</td>
</tr>
<tr>
<td>d</td>
<td><img src="#" alt="Alcohol" /></td>
<td>A&lt;sub&gt;c,d&lt;/sub&gt;</td>
<td>41%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>40%</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions A: 0.25 mol% Rh₂(cap)₄, PhH, reflux, 10 min.  
<sup>b</sup> Conditions B: 5 mol% Rh₂(oct)₄, PhH, reflux, 10 min.  
<sup>c</sup> 20 mol% Rh₂(oct)₄ was employed.  
<sup>d</sup> An 11% yield of enone 247 was also isolated.

Chapter 4, Section 4.3.2). Inefficient carbenoid capture was also observed with tertiary propargylic alcohol 241, furnishing an 11% yield of known enone 247 via β-elimination of the uncaptured Rh(II) carbenoid (Scheme 5.11).<sup>15</sup>

Scheme 5.11

![Scheme 5.11]

Similar results were obtained with monostabilized α-diazoketone 120 (Table 5.7). Use of 0.25 mol% Rh₂(cap)₄ in refluxing benzene selectively furnished [3,3]-
rearrangement products 248a-d, while use of 5 mol% Rh₂(oct)₄ selectively generated the corresponding [2,3]-rearrangement products 249a-c under the same conditions. Poor carbenoid capture was observed with propargylic alcohol 241 for both processes, furnishing enone 124 (See Scheme 2.6) as a by-product in 5% yield under Rh₂(cap)₄ conditions and as the exclusive product in 25% yield under Rh₂(oct)₄ conditions.

**Table 5.7 - [3,3]- and [2,3]-Rearrangement of Propargyloxy Enols Derived From α-Diazoketone 120**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Conditions</th>
<th>Yield [3,3]</th>
<th>Yield [2,3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>239</td>
<td>A&lt;sup&gt;a&lt;/sup&gt; B&lt;sup&gt;b&lt;/sup&gt;</td>
<td>68%</td>
<td>62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>240</td>
<td>A&lt;sup&gt;c&lt;/sup&gt; B&lt;sup&gt;d&lt;/sup&gt;</td>
<td>67%</td>
<td>66%</td>
</tr>
<tr>
<td>c</td>
<td>228</td>
<td>A&lt;sup&gt;e&lt;/sup&gt; B&lt;sup&gt;f&lt;/sup&gt;</td>
<td>69%</td>
<td>60%</td>
</tr>
<tr>
<td>d</td>
<td>241</td>
<td>A&lt;sup&gt;c&lt;/sup&gt; B&lt;sup&gt;d&lt;/sup&gt;</td>
<td>38%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions A: 0.25 mol% Rh₂(cap)₄, PhH, reflux, 10 min.  
<sup>b</sup> Conditions B: 5 mol% Rh₂(oct)₄, PhH, reflux, 10 min.  
<sup>c</sup>A 5% yield of enone 124 was also isolated  
<sup>d</sup> Only enone 124 was isolated in 25% yield
5.3 Catalysis of [2,3]-Rearrangement by Other Lewis Acids

5.3.1 Exploration of Non-Rh(II) Lewis Acids

The determination that Rh\(_2\)(tfa)\(_4\) was functioning as a Lewis acid catalyst to promote [2,3]-rearrangement of propargyloxy enols led to an investigation of other Lewis acidic additives for similar activity. Numerous Lewis acids were screened as shown in Scheme 5.12. In each experiment, enol 229 was generated initially via treatment of 103 and 228 (1.2 equiv) with Rh\(_2\)(OAc)\(_4\). Additives were introduced once enol formation was complete as evidenced by cessation of N\(_2\)(g) release. In general, more powerful catalysts such as MgBr\(_2\) and TiCl\(_4\) as well as those possessing triflate, trifluoroacetate, fluoride, and some with acetate ligands were rendered useless by associated adventitious acid, which catalyzed enol tautomerization. Those highlighted afforded an improvement in [2,3]-selectivity over that observed in the presence of 1.0 mol% Rh\(_2\)(OAc)\(_4\) alone.

Conditions employed and selectivities observed with these additives are summarized in Table 5.8. As may be surmised from the data presented, most of these Lewis acids...
afforded only very modest catalysis of [2,3]-rearrangement when employed at stoichiometric loadings under refluxing benzene conditions. Two exceptions were the highly electrophilic silver(I) species AgBF$_4$ and AgSbF$_6$, which were highly efficient [2,3]-rearrangement catalysts at 5 mol\% catalyst loading at room temperature.$^{16}$

Table 5.8 - Influence of Non-Rh(II) Lewis Acids on Rearrangement of Enol 229

If employed in stoichiometric quantities at elevated temperature, AgBF$_4$ could also be used to promote cyclization of 231 to dihydrofuran 250 in very good yield (Scheme 5.13).$^{17}$ Further studies demonstrated that this transformation could be accomplished in situ following [2,3]-rearrangement in the presence of stoichiometric loadings of AgBF$_4$. 

\[
\begin{array}{|c|c|c|}
\hline
\text{Lewis Acid Additive} & \text{Conditions} & 230:231^a \\
\hline
\text{no additive} & \text{PhH, } \Delta, \text{ 10 min} & 2.3 : 1 \\
\text{AgNO}_3 (1.0 \text{ equiv}) & \text{PhH, } \Delta, \text{ 10 min} & 1 : 1.3 \\
\text{AgNO}_3 (5.0 \text{ equiv}) & \text{PhH, } \Delta, \text{ 10 min} & 1 : 1.6 \\
\text{AgNO}_3 (10.0 \text{ equiv}) & \text{PhH, } \Delta, \text{ 10 min} & 1 : 1.6 \\
\text{CuSO}_4 (1.0 \text{ equiv}) & \text{PhH, } \Delta, \text{ 10 min} & 1 : 2.5 \\
\text{SnCl}_2 (1.0 \text{ equiv}) & \text{PhH, } \Delta, \text{ 10 min} & 1 : 1.3 \\
\text{SnCl}_2 (3.0 \text{ equiv}) & \text{PhH, } \Delta, \text{ 10 min} & 1 : 1.3 \\
\text{AgBF}_4 (5 \text{ mol\%}) & \text{PhH, rt, 2 min} & 1 : 60 \\
\text{AgSbF}_6 (5 \text{ mol\%}) & \text{PhH, rt, 2 min} & 1 : 48 \\
\hline
\end{array}
\]

$^a$Ratios determined by $^1$H NMR analysis of crude reaction mixtures
It was felt that the poor catalytic activity observed with the remaining catalysts in Table 5.8 was attributable, in part, to poor solubility in the non-polar organic reaction medium as evidenced by the invariance in product ratio with increased loadings of both AgNO₃ and SnCl₂. It was thus deemed worthwhile to explore more organic-soluble forms of these catalysts. Consideration of ligand availability and ease of preparation led to the selection of bis(oxazolinyl)pyridine (pybox) Lewis acids [Cu-(S,S)-Ph-pybox](OTf)₂ (251) and [Sn-(S,S)-Ph-pybox](OTf)₂ (252) for investigation.¹⁸ As may be seen from Scheme 5.14, both complexes displayed excellent catalytic activity, promoting [2,3]-rearrangement of enol 229 at room temperature and at low catalyst loadings. Curiously, use of the Cu(II) catalyst (251) also resulted in the isolation of dihydrofuran 250 in 19% yield. This species was not generated by Sn(II) catalysis. Suspecting that cyclization of 231 was occurring in the presence of Cu(II) in a manner analogous to that observed with Ag(I) (See Scheme 5.13), 231 was treated with both catalyst 251 and Rh₂(OAc)₄ only to find that these conditions did not lead to formation of 250.
Seeking further certainty that 250 was not derived from 231 under Cu(II)-catalyzed reaction conditions, the isotope labeling study depicted in Scheme 5.15 was performed. Diazoketone 103 was treated with Rh$_2$(OAc)$_4$ (1 mol%) in the presence of both 3-butyn-2-ol (228) and deuterium labeled $\alpha$-hydroxyketone 235. Once enol formation was complete, catalyst 251 (5 mol%) was added resulting in a mixture of protic and deuterated [2,3]-rearrangement products 231 and 235 but exclusively protic 250. Thus, cyclization of 235 did not take place under the reaction conditions leading to the conclusion that dihydrofuran 250 must arise via a competing side-reaction in the presence of Cu(II) catalyst 251.
5.4 Asymmetric Catalysis of [2,3]-Rearrangement

5.4.1 The First Catalytic Asymmetric [2,3]-Rearrangement of Propargyloxy Enols

It was theorized that the (Z)-geometry of diazoketone-derived alkoxy enols would enable these species to participate in bidentate chelation with the Cu(II) pybox catalyst, resulting in a rigid chiral environment that could lead to substantial asymmetric induction in the [2,3]-rearrangement (e.g., 255, Scheme 5.16). Such chelation has been shown by Evans to be necessary for achieving high levels of asymmetric induction in carbonyl addition processes (See Figure 1.2). To investigate this possibility, α-diazoketone 103 was decomposed with Rh$_2$(OAc)$_4$ (1 mol%) in the presence of propargyl alcohol (239) resulting in the formation of enol 253, which was observable by $^1$H NMR spectroscopy. Treatment of the benzene enol solution with 2.5 mol% of the hydrated complex, [Cu-(S,S)-Ph-pybox(H$_2$O)$_2$](OTf)$_2$ (254) furnished, in 5 min at room temperature, allenic α-hydroxyketone (S)-(+)243a in 61% yield and 90% ee accompanied by dihydrofuran (S)-(−)256 in 30% yield and 30% ee. Thus, it was demonstrated that [2,3]-rearrangement
could be promoted with a high degree of asymmetric induction via an experimentally simple three-step, two-metal-catalyzed process.

Scheme 5.16

5.4.2 Determination of Absolute Stereochemistry of (+)-243a and (-)-256

The absolute stereochemistry of α-hydroxyketone 243a was determined by chemical correlation as shown in Scheme 5.17. Exhaustive hydrogenation of 243a was followed by treatment with bromine and sodium hydroxide to furnish known α-hydroxyacid 257. Comparison of optical rotation data established that 257 prepared from allenic α-hydroxyketone 243a was of the (S)-configuration, thus 243a was also of the (S)-configuration. The structure of dihydrofuran 256 was first confirmed by
conversion into known tetrahydrofuran 258 as shown in Scheme 5.18. Wittig homologation of 256 furnished the olefinated dihydrofuran, which was exhaustively hydrogenated to furnish 258. Spectral data for material prepared from 256 corresponded exactly with that reported for 258. The absolute stereochemistry of 256 was determined by Ag(I)-catalyzed cyclization of (S)-243a to (S)-256 which was of the same optical rotation as material derived from enol 253.

5.4.3 Origin of Asymmetric Induction

The high degree of asymmetric induction afforded by catalyst 254 presumably arises due to bidentate chelation of the (Z)-propargyloxy enol to the copper (II) center in a manner analogous to that discussed in Chapter 1, Section 1.2.3.3 (See Figure 1.2). In an effort to define a model for the sense of asymmetric induction afforded by such a complex (e.g., 255, Scheme 5.16), Monte Carlo calculations were performed using the parameters contained in the Merck Molecular Force Field (MMFF). The model developed by Evans for binding of pyruvate esters to Cu(II) pybox complexes was
followed in performing these calculations, wherein, to simulate the square-pyramidal geometry of known [Cu(pybox)(substrate)]\(^{2+}\) complexes, the \(N_\text{pyridine-Cu-Opropargyloxy}\) bond angle was constrained to \(160^\circ\).\(^{24,25}\) In addition, to prevent flexing of the alkyne, the angle of the propargyl moiety was constrained to \(180^\circ\).

These calculations resulted in three low-energy structures (259-261). In the global minimum structure (259), the propargyl side-chain was situated in close proximity to the enol olefin and appeared poised to participate in an \(S_N1'\) process. This structure was separated by 9.4 kcal/mol from the next lowest-energy structure (260), in which the alkyne was oriented away from the copper-bound enol. The propargyl side-chain was equally inaccessible in 261. Further optimization of complex 259 was carried out using semi-empirical parameters contained in the PM3 (tm) force field using the identical angle constraints employed in the Monte Carlo calculations. Minimization afforded complex

**Figure 5.1** - Calculated Minimum Energy Complexes of Enol 253 with Catalyst 254 via Monte Carlo Simulation

![Diagram of complexes](image)

- **259**
  - \(E = 35.2\) kcal/mol
- **260**
  - \(E = 44.6\) kcal/mol
- **261**
  - \(E = 44.8\) kcal/mol
262, which successfully predicts the sense of asymmetric induction observed experimentally (Figure 5.2).

Figure 5.2 - Minimized Computational Structure of Reactive Catalyst-Enol Complex 262

5.4.4 Efforts to Optimize the Asymmetric [2,3] Rearrangement

Having demonstrated that [2,3]-rearrangement of enol 253 could be catalyzed in high enantiomeric excess, a survey of other commercially available ligands was conducted in an effort to optimize the ratio of [2,3]-rearrangement product 243a to dihydrofuran 256. Unfortunately, as may be seen from Table 5.9, bis-aquo copper (II) complexes derived from isopropyl(pybox) ligand (263) and phenyl-methyl(pybox) ligand (264) afforded increased quantities of byproduct 256. With regard to metal center, the less catalytically active [Sn-(S,S)-Ph-pybox)](OTf)2 complex (252) displayed enhanced selectivity for [2,3]-rearrangement over the corresponding Cu(II) systems. However, [2,3]-rearrangement product 243a prepared with this catalyst was optically inactive. Although reaction selectivity remains an unresolved problem, it is hoped that further efforts to optimize and generalize the catalytic asymmetric [2,3]-rearrangement process will ultimately yield a highly enantioselective method for tertiary alcohol synthesis.
Furthermore, the competing production of 256, if optimized, may provide a valuable entry to functionalized, enantioenriched dihydrofurans.

Table 5.9 - Variation in Production of Dihydrofuran 256 with Catalyst

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Catalyst Loading</th>
<th>Solvent and Conditions</th>
<th>Time</th>
<th>243a:256</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Catalyst 254" /></td>
<td>2.5 mol%</td>
<td>Benzene, rt</td>
<td>5 min</td>
<td>2.0 : 1</td>
</tr>
<tr>
<td><img src="image" alt="Catalyst 263" /></td>
<td>5 mol%</td>
<td>Benzene, rt</td>
<td>5 min</td>
<td>1 : 6.7</td>
</tr>
<tr>
<td><img src="image" alt="Catalyst 264" /></td>
<td>5 mol%</td>
<td>Benzene, rt</td>
<td>5 min</td>
<td>1 : 6.7</td>
</tr>
<tr>
<td><img src="image" alt="Catalyst 252" /></td>
<td>30 mol%</td>
<td>CH₂Cl₂, reflux</td>
<td>30 min</td>
<td>&gt;25 : 1</td>
</tr>
</tbody>
</table>

5.5 Summary and Conclusions

Efforts to extend the scope of the Rhodium carbenoid-initiated Claisen rearrangement to propargylic alcohols revealed unprecedented reactivity. Specifically, reaction of α-diazoketone 103 with 3-butyn-2-ol (228) in the presence of Rh₂(OAc)₄ was
found to furnish both [3,3]-rearrangement product 230 and the regioisomeric $\alpha$-hydroxyketone 231, the product of apparent [2,3]-rearrangement of enol 249. It was subsequently discovered that the relative quantities of the two products formed was highly dependent upon the rhodium (II) catalyst employed. Use of the electron-deficient Rh$_2$(tfa)$_4$ catalyst resulted in rapid formation of 231 at room temperature, while use of the electron-rich Rh$_2$(cap)$_4$ catalyst required reflux conditions and resulted in essentially exclusive production of [3,3]-rearrangement product 230. Extensive mechanistic studies revealed that both 230 and 231 were derived from enol 249, the former via thermal [3,3]-rearrangement and the latter via a Rh(II)-promoted [2,3]-rearrangement wherein the Rh(II) catalyst functions in a Lewis acidic capacity.

Investigations into substrate generality revealed that the control exerted by the Rh(II) ligand over the reactivity of enol 249 could be extended to other $\alpha$-diazoketone-derived propargyloxy enols. With doubly stabilized $\alpha$-diazoketones 103 and 59, use of Rh$_2$(tfa)$_4$ afforded exclusively [2,3]-rearrangement products in good yields. Use of Rh$_2$(cap)$_4$ afforded [3,3]-rearrangement products with 103, however this catalyst could not efficiently dediazotize 59. Importantly, in accord with studies of $\alpha$-allyloxy enols, tautomerization was observed to compete with [3,3]-rearrangement in $\alpha$-propargyloxy enols derived from 103 and primary propargylic alcohols. With monostabilized $\alpha$-diazoketones 116 and 120, the Rh$_2$(cap)$_4$ catalyst was again employed to furnish [3,3]-rearrangement products in good yields, however, efforts to effect [2,3]-rearrangement with Rh$_2$(tfa)$_4$ resulted in intractable mixtures of products. This problem was circumvented by use of 5 mol% of the milder, yet highly soluble Rh$_2$(oct)$_4$ catalyst, which furnished [2,3]-rearrangement products in good yields.
A survey of other Lewis acids revealed that [2,3]-rearrangement could be successfully catalyzed by Ag(I), Cu(II) and Sn(II) catalysts, Ag(I) also being capable of catalyzing a subsequent cyclization to functionalized dihydrofurans. Finally, treatment of enol 253 derived from α-diazoketone 103 and propargyl alcohol (239) with the asymmetric Lewis acid [Cu-(S,S)-Ph-pybox(H2O)2](OTf)2 (254) resulted in rapid [2,3]-rearrangement at room temperature to furnish α-hydroxyketone (S)-(+)243a in 90% ee. Thus, through detailed understanding of reaction mechanism, initially undesired reactivity was fashioned into a novel catalytic asymmetric process. It is hoped that these initial studies will eventually form the basis of a general two-metal-catalyzed asymmetric method for the preparation of tertiary alcohols.

5.6 Experimental Section

5.6.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using freshly distilled solvents. All commercially obtained reagents were used as received. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. High-performance liquid chromatography (HPLC) was performed with either a Rainin Microsorb 80-199-C5 or 80-120-C5 column. Infrared spectra were acquired using a MIDAC M-1200 FTIR. 1H and 13C NMR spectra were recorded using Bruker AM500 or Bruker Avance 400/500 MHz spectrometers. Chemical shifts are reported as δ values relative to internal chloroform (1H δ 7.27 ppm, 13C δ 77.0 ppm) or benzene-d6 (1H δ 7.15 ppm). Where
inseparable mixtures of diastereomers are isolated, $^1$H NMR spectral integration reflects a 1:1 mixture. All kinetic measurements were performed using a Bruker AM500 spectrometer. Melting points are uncorrected. High-resolution mass spectra were acquired at the University of Illinois Mass Spectrometry Center.

The determination of enantiomeric excess by Mosher ester derivatization involved esterification of the appropriate substrate with the acid chloride prepared from (S)-MTPA (Et$_3$N, DMAP, CH$_2$Cl$_2$). Enantiomeric excess was measured from the crude reaction mixtures via 500 MHz $^1$H NMR in either CDCl$_3$ or benzene-$d_6$. In each case, an identical analysis was performed on racemic substrate.

5.6.2 Experimental and Preparative Procedures

Representative Procedure for Effecting [3,3]-Rearrangement with $\alpha$-Diazoketone 103 ($\alpha$-Hydroxyketone (±)-230, Table 5.4, Entry c)

$\alpha$-Hydroxyketone (±)-230. To a stirred solution of $\alpha$-diazoketone 103 (95 mg, 0.593 mmol, 1.0 equiv) and 3-butyn-2-ol (228, 56 µL, 0.714 mmol, 1.2 equiv) in benzene (6 mL) was added Rh$_2$(cap)$_4$ (1.9 mg, 0.003 mmol, 0.005 equiv). The mixture was immersed in a preheated oil bath and heated at reflux for 10 min, then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography (8:1 hexane:EtOAc eluent) to furnish allenyl $\alpha$-hydroxyketone (±)-230.
(97 mg, 81% yield, 2.5 :1 mixture of diastereomers) as a pale yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.11 (m, 2H), 8.09 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 5.34-5.48 (comp m, 2H), 4.54 (s, 1H), 4.52 (s, 1H), 1.74 (dd, $J$=3.2, 7.1 Hz, 3H), 1.67 (s, 3H), 1.66 (s, 3H), 1.65 (dd, $J$=3.4, 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 204.2, 202.2, 133.2, 130.2, 130.1, 128.3, 128.2, 97.0, 90.6, 90.4, 76.8, 26.3, 26.1, 13.4, 13.3; IR (thin film/NaCl) 3446 (br m), 3061 (w), 2983 (w), 2927 (w), 2858 (w), 1964 (w), 1674 (s), 1597 (m), 1448 (m), 1370 (m), 1239 (s), 1133 (m), 1095 (m), 946 (m), 697 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 202.0997, [calc'd for C$_{13}$H$_{14}$O$_2$ (M+): 202.0994].

$\alpha$-Hydroxyketone (±)-242a and $\alpha$-Propargyloxy Ketone 263

\begin{center}
\begin{tikzpicture}
    \node[align=center] (a) at (0,0) {\textbf{N$_2$} \hspace{1cm} Me \hspace{1cm} $\text{\textbf{+}}$ \hspace{1cm} $\text{\textbf{0.5 mol\%}}$ \hspace{1cm} $\text{\textbf{Rh}_2(\text{cap})_4}$ \hspace{1cm} \textbf{benzene, $\Delta$} \hspace{1cm} 10 min

\textbf{\textit{103}} \hspace{1cm} \textbf{\hspace{3cm} 239} \hspace{1cm} \textbf{\hspace{3cm} \textit{(-)\textbf{-242a}} \hspace{1cm} (22% yield) \hspace{1cm} \textit{263} \hspace{1cm} (44% yield)}

\end{tikzpicture}
\end{center}

$\alpha$-Hydroxyketone (±)-242a. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.08 (m, 2H), 7.45-7.60 (comp m, 3H), 5.53 (t, $J$=6.6 Hz, 1H), 5.06 (dd, $J$=6.7, 11.6 Hz, 1H), 4.99 (dd, $J$=6.6, 11.6 Hz, 1H), 4.58 (s, 1H), 1.68 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 207.9, 201.8, 133.3, 130.1, 128.4, 96.6, 79.3, 76.3, 26.1; IR (thin film/NaCl) 3445 (br m), 3064 (w), 2989 (w), 2933 (w), 2933 (w), 1955 (m), 1676 (s), 1448 (m), 1368 (m), 1247 (s), 1131 (m), 1100 (m), 941 (m), 856 (m), 717 (s), 696 (m) cm$^{-1}$; HRMS (EI) $m/z$ found: 188.0841, [calc'd for C$_{12}$H$_{12}$O$_2$ (M+): 188.0837].
**α-Propargyloxy Ketone 263.** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.36-7.41 (comp m, 5H), 5.09 (s, 1H), 4.32 (dd, $J$=2.5, 15.9 Hz, 1H), 4.07 (dd, $J$=2.4, 16.0 Hz, 1H), 2.49 (t, $J$=2.4 Hz, 1H), 5.09 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 205.6, 135.0, 128.9, 127.5, 85.6, 78.7, 75.5, 56.2, 25.7; IR (thin film/NaCl) 3286 (br s), 3063 (w), 3032 (w), 2905 (w), 2860 (w), 2117 (w), 1722 (s), 1418 (m), 1453 (m), 1355 (s), 1098 (s), 1073 (s), 1028 (m), 748 (m), 701 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 187.0757, [calc'd for C$_{12}$H$_{11}$O$_2$ (M-H): 187.0759].

**α-Propargyloxy Ketone 264**

![Chemical Reaction Diagram]

**α-Propargyloxy Ketone 264.** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42-7.31 (comp. m, 5H), 5.04 (s, 1H), 4.26 (dq, $J$=2.4, 15.6 Hz, 1H), 4.04 (dq, $J$=2.4, 16.0 Hz, 1H), 2.16 (s, 3H), 1.86 (t, $J$=2.4 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 206.2, 135.4, 128.8, 128.7, 127.3, 85.6, 83.6, 74.2, 56.9, 25.6, 3.6; IR (thin film/NaCl) 3062 (w), 3030 (w), 2920 (w), 2858 (w), 2226 (w), 2225 (w), 1721 (s), 1452 (m), 1354 (m), 1094 (m), 1071 (m), 745 (m), 701 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 201.0911 [calc'd for C$_{13}$H$_{14}$O$_2$ (M-H): 201.0916].
α-Hydroxyketone (±)-242d.

![Chemical Structure](image)

α-Hydroxyketone (±)-242d.  $^1$H NMR (500 MHz, CDCl$_3$) δ 8.09 (m, 2H), 7.41-7.56 (comp m, 3H), 5.32 (septet, $J=2.8$ Hz, 1H), 4.49 (s, 1H), 1.74 (d, $J=2.8$ Hz, 3H), 1.67 (d, $J=2.8$ Hz, 3H), 1.64 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 202.4, 201.2, 133.4, 133.1, 130.2, 128.1, 100.4, 95.7, 77.3, 26.2, 19.9, 19.5; IR (thin film/NaCl) 3449 (br m), 2982 (m), 2934 (w), 1967 (w), 1675 (s), 1596 (m), 1448 (m), 1255 (s), 1127 (m), 942 (m), 705 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 216.1157, [calc'd for C$_{14}$H$_{16}$O$_2$ (M$^+$): 216.1150].

Representative Procedure for Effecting [2,3]-Rearrangement with α-Diazoketone 103 (α-Hydroxyketone (±)-243b, Table 5.4, Entry b)

![Chemical Structure](image)

α-Hydroxyketone (±)-243b. To a stirred solution of α-diazoketone 103 (113 mg, 0.705 mmol, 1.0 equiv) and 2-butyn-1-ol (240, 63 µL, 0.842 mmol, 1.2 equiv) in benzene (7 mL) was added Rh$_2$(tfa)$_4$ (1.2 mg, 0.0018 mmol, 0.0025 equiv) resulting in rapid loss of N$_2$(g). The resulting pale green solution was stirred for 10 min at room temperature, then
concentrated under reduced pressure. Flash chromatography of the residue (15:1 hexane:acetone eluent) afforded allenyl α-hydroxyketone (±)-243b (97 mg, 68% yield) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.54 (m, 2H), 7.37 (m, 3H), 4.87 (dq, $J$=3.0, 10.8 Hz, 1H), 4.80 (dq, $J$=3.0, 10.3 Hz, 1H), 4.72 (s, 1H), 2.10 (s, 3H), 1.76 (t, $J$=3.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.5, 205.9, 138.7, 128.5, 128.2, 127.5, 100.0, 85.5, 77.1, 26.0, 14.8; IR (thin film/NaCl) 3448 (br. m), 3060 (w), 2984 (w), 2926 (w), 1957 (m), 1710 (s), 1448 (m), 1356 (m), 1062 (m), 756 (m), 703 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 201.0915 [calc'd for C$_{13}$H$_{14}$O$_2$ (M-H): 201.0916].

α-Hydroxyketone (±)-243a

α-Hydroxyketone (±)-243a. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.52 (m, 2H), 7.32-7.53 (comp m, 3H), 5.81 (t, $J$=6.7 Hz, 1H), 5.03 (dd, $J$=6.7, 11.5 Hz, 1H), 5.00 (dd, $J$=6.6, 11.5 Hz, 1H), 4.61 (s, 1H), 2.12 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.4, 206.6, 140.2, 128.6, 128.4, 126.6, 93.7, 81.7, 79.3, 24.8; IR (thin film/NaCl) 3453 (br m), 3061 (w), 3028 (w), 1956 (m), 1714 (s), 1492 (m), 1356 (s), 1173 (m), 1063 (m), 855 (m), 765 (m), 701 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 188.0842, [calc'd for C$_{12}$H$_{12}$O$_2$ (M+): 188.0837].
α-Hydroxyketone (±)-231

α-Hydroxyketone (±)-231 (2.4:1 mixture of diastereomers). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.54 (m, 2H), 7.53 (m, 2H), 7.32–7.41 (comp m, 3H), 5.72 (m, 1H), 5.36–5.45 (comp m, 1H), 4.57 (s, 1H), 4.52 (s, 1H), 2.11 (s, 3H), 2.10 (s, 3H), 1.76 (dd, $J$=3.3, 7.3 Hz, 3H), 1.71 (dd, $J$=3.3, 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.2, 203.9, 140.4, 128.6, 128.3, 128.3, 126.8, 94.0, 93.9, 90.6, 90.3, 82.0, 24.8, 24.7, 13.9; IR (thin film/NaCl) 3454 (br s), 3061 (w), 3029 (w), 2988 (w), 2925 (w), 1965 (m), 1713 (s), 1491 (m), 1447 (m), 1355 (s), 1175 (m), 1065 (m), 765 (m), 701 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 202.0997, [calc'd for C$_{13}$H$_{14}$O$_2$ (M+) : 202.0994].

α-Hydroxyketone (±)-243d

α-Hydroxyketone (±)-243d. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.54 (m, 2H), 7.36 (m, 3H), 5.59 (septet, $J$=3.5 Hz, 1H), 4.53 (s, 1H), 2.08 (s, 3H), 1.79 (d, $J$=3.5 Hz, 3H), 1.73 (d, $J$=3.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 207.6, 201.2, 140.7, 128.5, 128.2, 126.8,
100.3, 92.8, 82.2, 24.7, 20.2, 20.1; IR (thin film/NaCl) 3460 (br. m), 2979 (w), 2920 (w), 1713 (s), 1447 (m), 1353 (m), 1118 (m), 764 (m), 700 (s) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 217.1220 [calc'd for C\(_{14}\)H\(_{17}\)O\(_2\) (M+H): 217.1229].

**Representative Procedure for Effecting [2,3]-Rearrangement with \(\alpha\)-Diazoketone 59**

\((\alpha\)-Hydroxy-\(\beta\)-Ketoester (±)-244a, Table 5.5, Entry a\)

\[\begin{array}{c}
\text{MeO}_2\text{C} \quad \text{N}_2 \quad \text{O} \\
\text{Me} \\
59 \\
\hline
\text{MeO}_2\text{C} \quad \text{O} \\
\text{Me} \\
239 \\
\hline
\end{array}\]

\[\begin{array}{c}
\text{MeO}_2\text{C} \quad \text{O} \\
\text{Me} \\
(±)-244a \\
\end{array}\]

\(\alpha\)-Hydroxy-\(\beta\)-Ketoester (±)-244a. To a stirred solution of \(\alpha\)-diazoo-\(\beta\)-ketoester 59 (129 mg, 0.905 mmol, 1.0 equiv) and propargyl alcohol (239, 63 \(\mu\)L, 1.08 mmol, 1.2 equiv) in benzene (9 mL) was added Rh\(_2\)(tfa)\(_4\) (1.5 mg, 0.0023 mmol, 0.0025 equiv). The mixture was immersed in a preheated oil bath and heated under reflux for 10 min, after which it was cooled and concentrated under reduced pressure. Flash chromatography of the residue (6:1 hexane:EtOAc eluent) afforded allenyl \(\alpha\)-hydroxy-\(\beta\)-ketoester (±)-244a (95 mg, 62% yield) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.70 (t, \(J=6.5\) Hz, 1H), 5.05 (dd, \(J=6.5, 11.8\) Hz, 1H), 5.02 (dd, \(J=6.5, 12.0\) Hz, 1H), 4.31 (s, 1H), 3.83 (s, 3H), 2.33 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 207.6, 202.2, 169.8, 90.8, 81.4, 80.0, 58.5, 24.7; IR (thin film/NaCl) 3457 (br. m), 3069 (w), 3009 (w), 2957 (w), 1958 (m), 1725 (s), 1436 (m), 1357 (m), 1260 (s), 1193 (m), 1154 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 171.0660 [calc'd for C\(_8\)H\(_{11}\)O\(_4\) (M+H): 171.0657].
\(\alpha\)-Hydroxy-\(\beta\)-Ketoester (±)-244b

\[
\begin{align*}
\text{MeO}_2C\overset{\text{N}_2}{\text{Ketoester}} + \overset{\text{Me}}{\text{OH}} & \xrightarrow{0.25 \text{ mol\% Rh}_2(tfa)_4\text{ benzene, } \Delta 10 \text{ min}} \overset{\text{MeO}_2C}{\text{MeO}_2C} \\
\end{align*}
\]

\(\alpha\)-Hydroxy-\(\beta\)-Ketoester (±)-244b. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.91 (dq, \(J=3.0, 10.8\) Hz, 1H), 4.88 (dq, \(J=3.0, 10.8\) Hz, 1H), 4.34 (s, 1H), 3.82 (s, 3H), 2.40 (s, 3H), 1.70 (t, \(J=3.0\) Hz, 3H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 206.7, 203.9, 169.7, 98.1, 85.2, 78.0, 53.2, 25.5, 13.9; IR (thin film/NaCl) 3456 (br. m), 2988 (w), 2956 (w), 2928 (w), 1960 (m), 1725 (s), 1436 (m), 1356 (m), 1253 (s), 1106 (s) cm\(^{-1}\); HRMS (EI) \(m/\text{z}\) found: 184.0735 [calc'd for C\(_9\)H\(_{12}\)O\(_4\) (M\(^+\)): 184.0736].

\(\alpha\)-Hydroxy-\(\beta\)-Ketoester (±)-244c

\[
\begin{align*}
\text{MeO}_2C\overset{\text{N}_2}{\text{Ketoester}} + \overset{\text{Me}}{\text{OH}} & \xrightarrow{0.25 \text{ mol\% Rh}_2(tfa)_4\text{ benzene, } \Delta 10 \text{ min}} \overset{\text{MeO}_2C}{\text{MeO}_2C} \\
\end{align*}
\]

\(\alpha\)-Hydroxy-\(\beta\)-Ketoester (±)-244c (2.4:1 mixture of diastereomers). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.59 (m, 2H), 5.45 (m, 2H), 4.25 (s, 2H), 3.82 (s, 6H), 2.34 (s, 3H), 2.33 (s, 3H), 1.71 (dd, \(J=3.0, 7.0\) Hz, 3H), 1.70 (dd, \(J=3.0, 7.0\) Hz, 3H); \(^1\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 204.3, 204.3, 202.7, 202.6, 170.0, 170.0, 91.5, 90.8, 81.9, 81.8, 53.4, 24.7, 24.6, 13.6, 13.6; IR (thin film/NaCl) (3459, br. m), 2956 (w), 2928 (w), 1968 (w), 1725 (s),
α-Hydroxy-β-Ketoester (±)-244d

α-Hydroxy-β-Ketoester (±)-244d. 1H NMR (500 MHz, CDCl3) δ 5.45 (septet, J=2.8 Hz, 1H), 4.19 (s, 1H), 3.82 (s, 3H), 2.34 (s, 3H), 1.74 (t, J=2.5 Hz, 6H); 13C NMR (125 MHz, CDCl3) δ 203.1, 201.7, 170.1, 101.7, 89.5, 82.1, 53.3, 24.7, 19.9, 19.9; IR (thin film/NaCl) 3462 (br. m), 2984 (w), 2954 (w), 2911 (w), 1972 (w), 1726 (s), 1437 (m), 1356 (m), 1265 (s), 1143 (m) cm⁻¹; HRMS (EI) m/z found: 197.0816 [calc'd for C₁₀H₁₃O₄ (M-H): 197.0814].

Representative Procedure for Effecting [3,3]-Rearrangement with α-Diazoketone 116 (α-Hydroxyketone (±)-245a, Table 5.6, Entry a)

α-Hydroxyketone (±)-245a. To a stirred solution of α-diazoketone 116 (100 mg, 0.543 mmol, 1.0 equiv) and propargyl alcohol (239, 38 µL, 0.652 mmol, 1.2 equiv) in benzene
(3 mL) was added Rh$_2$(cap)$_4$ (1.0 mg, 0.0015 mmol, 0.0027 equiv). This mixture was heated at reflux for 10 min, then cooled and concentrated under reduced pressure. Purification of the residue by flash chromatography (4:1 hexane:EtOAc eluent) afforded allenyl α-hydroxyketone (±)-245a (74 mg, 64% yield) as a yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.27 (t, $J=6.5$ Hz, 1H), 5.03 (dd, $J=6.5$, 11.3 Hz, 1H), 5.00 (dd, $J=6.5$, 11.5 Hz, 1H), 4.14 (q, $J=7.0$ Hz, 2H), 3.87 (s, 1H), 2.97 (dt, $J=6.5$, 19.0 Hz, 1H), 2.87 (dt, $J=6.5$, 18.5 Hz, 1H), 2.67 (dt, $J=6.5$, 17.0 Hz, 1H), 2.61 (dt, $J=6.5$, 17.5 Hz, 1H), 1.52 (s, 3H), 1.26 (t, $J=7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 210.3, 207.4, 172.4, 95.6, 79.2, 76.9, 60.7, 30.9, 28.2, 24.4, 14.2; IR (thin film/NaCl) 3466 (br. m), 2983 (m), 2934 (w), 1955 (m), 1716 (s), 1374 (m), 1208 (m), 1100 (m), 1077 (m) cm$^{-1}$; HRMS (EI) $m/z$ found: 213.1128 [calc'd for C$_{11}$H$_{17}$O$_4$ (M+H): 213.1127].

α-Hydroxyketone (±)-245b

α-Hydroxyketone (±)-245b. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.90 (q, $J=3.0$ Hz, 1H), 4.14 (q, $J=7.0$ Hz, 2H), 4.01 (br. s, 1H), 2.92 (ddd, $J=6.5$, 7.2, 18.9 Hz, 1H), 2.86 (ddd, $J=6.5$, 7.0, 18.5 Hz, 1H), 2.65 (dt, $J=6.5$, 17.5 Hz, 1H), 2.59 (ddd, $J=6.5$, 7.0, 17.0 Hz, 1H), 1.59 (t, $J=3.0$ Hz, 3H), 1.51 (s, 3H), 1.26 (t, $J=7.0$ Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 211.1, 206.5, 172.3, 101.8, 78.6, 77.5, 60.7, 30.4, 28.0, 24.0, 14.2, 13.8; IR (thin film/NaCl) 3476 (br. m), 2983 (m), 2932 (m), 1957 (m), 1735 (s), 1715 (s), 1374 cm$^{-1}$. 

345
(m), 1349 (m), 1193 (s), 1104 (s) cm⁻¹; HRMS (EI) m/z found: 227.1276 [calc'd for C₁₂H₁₈O₄ (M+H): 227.1283].

α-Hydroxyketone (±)-245c

α-Hydroxyketone (±)-245c (2.2:1 mixture of diastereomers). ¹H NMR (500 MHz, CDCl₃) δ 5.41 (m, 2H), 5.19 (m, 2H), 4.14 (q, J=7.5 Hz, 4H), 3.86 (s, 1H), 3.83 (s, 1H), 2.99 (dt, J=6.5, 18.5 Hz, 1H), 2.96 (dt, J=6.5, 18.5 Hz, 1H), 2.86 (dt, J=6.5, 18.5 Hz, 2H), 2.66 (dt, J=6.5, 17.0 Hz, 2H), 2.60 (dt, J=6.5, 17.0 Hz, 2H), 1.74 (dd, J=3.0, 7.0 Hz, 3H), 1.73 (dd, J=3.0, 7.3 Hz, 3H), 1.49 (s, 6H), 1.26 (t, J=7.5 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 211.1, 204.2, 204.1, 172.7, 96.3, 96.3, 90.9, 90.9, 77.7, 61.1, 31.2, 28.6, 28.6, 24.8, 14.5, 14.3, 14.2; IR (thin film/NaCl) 3479 (br. m), 2984 (m), 2931 (m), 1963 (w), 1733 (s), 1715 (s), 1447 (m), 1374 (m), 1349 (m), 1208 (s) cm⁻¹; HRMS (EI) m/z found: 225.1133 [calc'd for C₁₂H₁₇O₄ (M-H): 225.1127].

α-Hydroxyketone (±)-245d
α-Hydroxyketone (±)-245d. 1H NMR (500 MHz, CDCl₃) δ 5.08 (septet, J=3.0 Hz, 1H), 4.15 (q, J=7.0 Hz, 2H), 2.00 (dt, J=6.5, 19.0 Hz, 1H), 2.86 (dt, J=6.5, 18.5 Hz, 1H), 2.66 (dt, J=6.5, 16.5 Hz, 1H), 2.58 (dt, J=6.5, 17.0 Hz, 1H), 1.77 (d, J=3.0 Hz, 6H), 1.48 (s, 3H), 1.27 (t, J=7.0 Hz, 3H); 13C NMR (125 MHz, CDCl₃) δ 211.0, 200.9, 172.4, 100.7, 94.6, 77.7, 60.7, 30.7, 28.2, 24.3, 20.3, 20.1, 14.2; IR (thin film/NaCl) 3479 (br. m), 2982 (m), 2934 (m), 2911 (m), 1968 (w), 1736 (s), 1716 (s), 1374 (m), 1348 (m), 1189 (s) cm⁻¹; HRMS (EI) m/z found: 239.1286 [calc'd for C₁₃H₁₉O₄ (M-H): 239.1283].

Representative Procedure for Effecting [2,3]-Rearrangement with α-Diazoketone

116 (α-Hydroxyketone (±)-246a, Table 5.6, Entry a)

α-Hydroxyketone (±)-246a. To a stirred solution of α-diazoketone 116 (51 mg, 0.274 mmol, 1.0 equiv) and propargyl alcohol (239, 19 µL, 0.326 mmol, 1.2 equiv) in benzene (3 mL) was added Rh₂(oct)₄ (11.4 mg, 0.015 mmol, 0.05 equiv) resulting in rapid loss of N₂(g). Once complete, the reaction mixture was immersed in a preheated oil bath and heated at reflux for 10 min, after which it was cooled and concentrated under reduced pressure. Flash chromatography of the residue (3:2 pentane:Et₂O eluent) afforded allenyl α-hydroxyketone (±)-246a (34.9 mg, 60% yield) as a clear yellow oil. 1H NMR (400 MHz, CDCl₃) δ 5.20 (t, J=6.8 Hz, 1H), 5.04 (dd, J=6.9, 11.4 Hz, 1H), 5.00 (dd, J=6.4, 11.6 Hz, 1H), 4.13 (q, J=7.2 Hz, 2H), 4.09 (s, 1H), 2.48 (ddd, J=5.3, 9.6, 16.0 Hz, 1H),
2.28 (s, 3H), 2.33-2.08 (comp. m, 3H), 1.26 (t, J=7.2 Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 208.9, 207.4, 173.4, 94.2, 79.3, 78.8, 60.6, 31.8, 28.5, 23.9, 14.2; IR (thin film/NaCl) 3465 (br. m), 2982 (m), 2932 (m), 1954 (m), 1731 (s), 1713 (s), 1374 (m), 1356 (m), 1184 (s), 1100 (s) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 213.1119 [calc'd for C\(_{11}\)H\(_{17}\)O\(_4\) (M+H): 213.1127].

\(\alpha\)-Hydroxyketone (\(\pm\))-246b

\[\text{EtO}_2\text{C}\begin{array}{c}\text{N}_2 \\
\text{Me}
\end{array} + \text{Me} \begin{array}{c}\text{OH} \\
\end{array} \xrightarrow{\text{5 mol\% Rh}_2\text{oct}_4 \text{ benzene, } \Delta \text{10 min}} \text{Me} \begin{array}{c}\text{HO} \\
\end{array} \begin{array}{c}\text{EtO}_2\text{C} \\
\text{Me}
\end{array}
\]

\(\alpha\)-Hydroxyketone (\(\pm\))-246b. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.92 (m, 2H), 4.11 (q, J=7.2 Hz, 2H), 4.05 (s, 1H), 2.42 (m, 1H), 2.23 (s, 3H), 2.30-2.10 (comp. m, 3H), 1.56 (t, J=3.0 Hz, 3H), 1.24 (t, J=7.3 Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 209.7, 206.3, 173.3, 100.6, 80.6, 77.8, 60.5, 31.0, 28.6, 23.2, 14.2, 13.9; IR (thin film/NaCl) 3459 (br. m), 2983 (m), 2932 (w), 1956 (m), 1734 (s), 1712 (s), 1443 (m), 1374 (m), 1186 (m), 1114 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 227.1286 [calc'd for C\(_{12}\)H\(_{18}\)O\(_4\) (M+H): 227.1283].

\(\alpha\)-Hydroxyketone (\(\pm\))-246c
α-Hydroxyketone (±)-246c (2.3:1 mixture of diastereomers). $^1$H NMR (500 MHz, CDCl$_3$) δ 5.42 (m, 2H), 5.11 (m, 2H), 4.13 (q, $J$=7.5 Hz, 4H), 4.00 (s, 1H), 3.98 (s, 1H), 2.46 (ddd, $J$=5.5, 10.0, 16.4 Hz, 1H), 2.46 (ddd, $J$=5.5, 9.5, 16.3 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 2.22-2.07 (comp. m, 4H), 1.73 (dd, $J$=3.5, 7.0 Hz, 6H), 1.25 (t, $J$=7.5 Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 209.1, 204.0, 204.0, 173.4, 94.6, 94.5, 90.7, 90.5, 79.3, 79.2, 60.5, 28.6, 28.6, 23.7, 23.7, 14.1, 13.8, 13.7; IR (thin film/NaCl) 3464 (br m), 2982 (m), 2930 (m), 1964 (w), 1733 (s), 1714 (s), 1444 (m), 1373 (m), 1356 (m), 1185 (s), 1106 (s) cm$^{-1}$; HRMS (EI) $m/z$ found: 225.1137 [calc'd for C$_{12}$H$_{17}$O$_{4}$ (M-H): 225.1127].

α-Hydroxyketone (±)-246d

α-Hydroxyketone (±)-246d. $^1$H NMR (500 MHz, CDCl$_3$) δ 4.99 (septet, $J$=3.0 Hz, 1H), 4.13 (q, $J$=7.2 Hz, 2H), 3.93 (s, 1H), 2.46 (ddd, $J$=6.0, 9.9, 16.0 Hz, 1H), 2.29 (m, 1H), 2.26 (s, 3H), 2.16 (ddd, $J$=6.0, 9.8, 14.5 Hz, 1H), 2.09 (ddd, $J$=6.5, 9.8, 14.5 Hz, 1H), 1.76 (d, $J$=3.0 Hz, 6H), 1.26 (t, $J$=7.0 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 209.5, 201.2, 173.5, 100.8, 93.2, 79.6, 60.5, 31.9, 28.7, 23.6, 20.2, 20.0, 14.2; IR (thin film/NaCl) 3466 (br. m), 2980 (m), 2933 (m), 2858 (w), 1374 (s), 1713 (s), 1588 (w), 1354 (m), 1188 (s), 1098 (m) cm$^{-1}$; HRMS (EI) $m/z$ found: 241.1437 [calc'd for C$_{13}$H$_{21}$O$_{4}$ (M+H): 241.1440].
Ethyl 4,5-Dioxohexanoate (265)

![Molecular structure of Ethyl 4,5-Dioxohexanoate (265)](image)

**Ethyl 4,5-dioxohexanoate (265)**. Inefficient carbenoid capture (e.g., by 2-methyl-3-butyn-2-ol (241)) in the presence of significant moisture and oxygen can give rise to this species in varying amounts.\(^{26}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.14 (q, \(J=7.0\) Hz, 2H), 3.03 (t, \(J=6.5\) Hz, 2H), 2.66 (t, \(J=6.5\) Hz, 2H), 2.36 (s, 3H), 1.26 (t, \(J=7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 197.6, 197.0, 172.3, 60.9, 30.8, 28.0, 23.6, 14.1; IR (thin film/NaCl) 2984 (w), 2936 (w), 1733 (s), 1717 (s), 1395 (m), 1376 (m), 1351 (m), 1202 (s), 1076 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 173.0810 [calc'd for C\(_8\)H\(_{13}\)O\(_4\) (M+H): 173.0814].

**Representative Procedure for Effecting [3,3]-Rearrangement with \(\alpha\)-Diazoketone**

120 (\(\alpha\)-Hydroxyketone (±)-248a, Table 5.7, Entry a)

![Chemical reaction for [3,3]-Rearrangement](image)

**\(\alpha\)-Hydroxyketone (±)-248a**. To a stirred solution of \(\alpha\)-diazoketone 120 (139 mg, 0.992 mmol, 1.0 equiv) and propargyl alcohol (239, 69 \(\mu\)L, 1.19 mmol, 1.2 equiv) in benzene (10 mL) was added Rh\(_2\)(cap)\(_4\) (1.6 mg, 0.0024 mmol, 0.0025 equiv). The resulting mixture was heated at reflux for 10 min, then cooled to room temperature. Concentration
under reduced pressure provided a residue that was purified by flash chromatography (6:1 hexane:EtOAc eluent), affording allenyl \(\alpha\)-hydroxyketone \((\pm)-248\) (113 mg, 68% yield) as a colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.20 (t, \(J=7.0\) Hz, 1H), 5.00 (dd, \(J=7.0, 15.0\) Hz, 1H), 4.98 (dd, \(J=6.5, 15.0\) Hz, 1H), 4.10 (br. s, 1H), 2.64 (dt, \(J=7.5, 17.5\) Hz, 1H), 2.51 (dt, \(J=7.5, 17.5\) Hz, 1H), 1.61 (m, 2H), 1.48 (s, 3H), 1.33 (sextet, \(J=7.5\) Hz, 2H), 0.92 (t, \(J=7.5\) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 211.9, 207.6, 95.5, 78.9, 35.4, 25.9, 24.0, 22.3, 13.8; IR (thin film/NaCl) 3467 (br. s), 2958 (s), 2934 (s), 2873 (s), 1955 (m), 1710 (s), 1455 (m), 1360 (m), 1125 (m), 853 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 168.1153 [calc'd for C\(_{10}\)H\(_{16}\)O\(_2\) (M\(^{+}\)): 168.1150].

\(\alpha\)-Hydroxyketone \((\pm)-248b\)

\(\alpha\)-Hydroxyketone \((\pm)-248b\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.88 (m, 1H), 4.20 (s, 1H), 2.58 (ddd, \(J=6.5, 8.3, 17.5\) Hz, 1H), 2.50 (ddd, \(J=6.5, 8.5, 17.4\) Hz, 1H), 1.59 (m, 2H), 1.56 (t, \(J=3.5\) Hz, 3H), 1.47 (s, 3H), 1.32 (m, 2H), 0.92 (t, \(J=7.3\) Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 212.9, 206.7, 101.6, 78.6, 77.2, 34.8, 26.0, 23.7, 22.3, 13.8, 13.8; IR (thin film/NaCl) 3466 (br. m), 2959 (s), 2933 (s), 2873 (m), 1957 (m), 1708 (s), 1456 (m), 1354 (m), 1125 (m), 1092 (m), 851 (m) cm\(^{-1}\); HRMS (EI) \(m/z\) found: 182.1303 [calc'd for C\(_{11}\)H\(_{18}\)O\(_2\) (M\(^{+}\)): 182.1307].
α-Hydroxyketone (±)-248c

\[
\text{Me}_{-\text{Me}}\text{Me}_{-\text{Me}}\text{N}_{2} + \text{Me}_{-\text{Me}}\text{Me}_{-\text{Me}}\text{OH} \xrightarrow{0.25 \text{ mol}\% \text{Rh}_{2}(\text{cap})_{4} \text{ benzene, } \Delta \text{ 10 min}} \text{Me}_{-\text{Me}}\text{OH} \cdot \text{MeMe Me} \text{MeMe Me}
\]

α-Hydroxyketone (±)-248c (2.2:1 mixture of diastereomers). \( ^1\text{H NMR (500 MHz, CDCl}_3 \) δ 5.40 (m, 2H), 5.15 (dq, \( J=3.0, 6.0 \text{ Hz, 2H} \)), 4.09 (s, 1H), 4.08 (s, 1H), 2.68 (dt, \( J=7.5, 17.0 \text{ Hz, 1H} \)), 2.65 (dt, \( J=7.5, 16.5 \text{ Hz, 1H} \)), 2.51 (ddd, \( J=7.0, 8.0, 17.2 \text{ Hz, 1H} \)), 2.51 (ddd, \( J=7.0, 8.0, 16.0 \text{ Hz, 1H} \)), 1.75 (dd, \( J=3.5, 7.0 \text{ Hz, 3H} \)), 1.74 (dd, \( J=3.5, 7.0 \text{ Hz, 3H} \)), 1.62 (m, 4H), 1.47 (s, 6H), 1.34 (sextet, \( J=7.5 \text{ Hz, 2H} \)), 1.34 (sextet, \( J=7.5 \text{ Hz, 2H} \)), 0.94 (t, \( J=7.5 \text{ Hz, 3H} \)), 0.93 (t, \( J=7.5 \text{ Hz, 3H} \)); \( ^{13}\text{C NMR (125 MHz, CDCl}_3 \) δ 212.2, 204.0, 95.8, 95.8, 90.1, 90.1, 35.3, 35.3, 26.0, 26.0, 24.1, 24.0, 22.3, 22.3, 14.0, 13.9, 13.8; IR (thin film/NaCl) 3466 (br. m), 2959 (s), 2933 (s), 2873 (m), 1964 (w), 1711 (s), 1456 (m), 1370 (m), 1125 (m), 1037 (m) cm\(^{-1}\); HRMS (EI) \( m/z \) found: 181.1227 [calc'd for \( \text{C}_{11}\text{H}_{17}\text{O}_{2} \text{ (M-H)} \): 181.1229].

α-Hydroxyketone (±)-248d

\[
\text{Me}_{-\text{Me}}\text{Me}_{-\text{Me}}\text{N}_{2} + \text{Me}_{-\text{Me}}\text{Me}_{-\text{Me}}\text{OH} \xrightarrow{0.25 \text{ mol}\% \text{Rh}_{2}(\text{cap})_{4} \text{ benzene, } \Delta \text{ 10 min}} \text{Me}_{-\text{Me}}\text{OH} \cdot \text{MeMe Me} \text{MeMe Me}
\]

α-Hydroxyketone (±)-248d. \( ^1\text{H NMR (500 MHz, CDCl}_3 \) δ 5.01 (m, 1H), 4.05 (s, 1H), 2.65 (ddd, \( J=6.5, 8.5, 17.5 \text{ Hz, 1H} \)), 2.48 (ddd, \( J=6.5, 8.5, 17.2 \text{ Hz, 1H} \)), 1.77 (d, \( J=2.0 \text{ Hz, 3H} \)), 1.76 (d, \( J=2.0 \text{ Hz, 3H} \)), 1.60 (m, 1H), 1.43 (s, 3H), 1.33 (sextet, \( J=7.5 \text{ Hz, 2H} \)),
0.92 (t, \( J=7.5\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 212.5, 201.2, 100.0, 94.5, 77.7, 35.3, 26.0, 24.0, 22.3, 20.3, 20.1, 13.8; IR (thin film/NaCl) 3469 (br. m), 2959 (s), 2934 (s), 2872 (m), 1968 (w), 1708 (s), 1449 (m), 1364 (m), 1348 (m), 1123 (m) cm\(^{-1}\); HRMS (EI) \( m/z \) found: 195.1376 [calc’d for C\(_{12}\)H\(_{19}\)O\(_2\) (M-H): 195.1385].

Representative Procedure for Effecting [2,3]-Rearrangement with \( \alpha \)-Diazoketone

120 (\( \alpha \)-Hydroxyketone (\( \pm \))-249a, Table 5.7, Entry b)

\( \alpha \)-Hydroxyketone (\( \pm \))-249a. To a stirred solution of \( \alpha \)-diazoketone 120 (106 mg, 0.752 mmol, 1.0 equiv) and propargyl alcohol (239, 53 \( \mu \)L, 0.910 mmol, 1.2 equiv) in benzene (8 mL) was added Rh\(_2\)(oct)\(_4\) (29.3 mg, 0.038 mmol, 0.05 equiv) resulting in rapid N\(_2\)(g) loss. Once complete, the reaction mixture was immersed in a preheated oil bath and heated at reflux. After 10 min, the mixture was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (6:1 hexane:EtOAc eluent), affording allenyl \( \alpha \)-hydroxyketone (\( \pm \))-249a (77.2 mg, 62% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 5.23 (t, \( J=6.5\) Hz, 1H), 5.01 (dd, \( J=6.5, 11.0\) Hz, 1H), 4.97 (dd, \( J=6.5, 11.5\) Hz, 1H), 4.02 (s, 1H), 2.25 (s, 3H), 1.83 (m, 2H), 1.46 (m, 1H), 1.34 (sextet, \( J=7.5\) Hz, 2H), 1.07 (m, 1H), 0.91 (t, \( J=7.0\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 209.4, 207.4, 94.9, 79.6, 78.8, 37.0, 25.3, 23.8, 22.8, 13.9; IR (thin film/NaCl) 3467 (br. s), 2957 (s), 2872 (s), 1954 (s), 1711 (s), 1588 (m), 1357 (s),
1193 (s), 1136 (s), 852 (s) cm⁻¹; HRMS (EI) m/z found: 169.1225 [calc'd for C₁₀H₁₇O₂ (M+H): 169.1229].

**α-Hydroxyketone (±)-249b**

![Diagram of α-Hydroxyketone (±)-249b]

**α-Hydroxyketone (±)-249b.** ¹H NMR (500 MHz, CDCl₃) δ 4.87 (m, 2H), 4.05 (s, 1H), 2.19 (s, 3H), 1.86 (dd, J=7.3, 9.8 Hz, 2H), 1.56 (t, J=3.0 Hz, 3H), 1.42 (m, 1H), 1.31 (sextet, J=7.4 Hz, 2H), 0.96 (m, 1H), 0.89 (t, J=7.3 Hz, 3H); ¹³C NMR (500 MHz, CDCl₃) δ 210.4, 206.5, 101.1, 81.4, 77.2, 35.9, 25.4, 23.3, 22.9, 14.0, 13.9; IR (thin film/NaCl) 3467 (br. m), 2957 (s), 2929 (m), 2862 (m), 1956 (m), 1709 (s), 1429 (m), 1356 (m), 852 (m) cm⁻¹; HRMS (EI) m/z found: 182.1307 [calc'd for C₁₁H₁₈O₂ (M+): 182.1307].

**α-Hydroxyketone (±)-249c**

![Diagram of α-Hydroxyketone (±)-249c]

**α-Hydroxyketone (±)-249c (2.3:1 mixture of diastereomers).** ¹H NMR (500 MHz, CDCl₃) δ 5.38 (m, 1H), 5.15 (m, 1H), 5.13 (m, 1H), 2.25 (s, 3H), 2.23 (s, 3H), 1.81 (dd,
\( J = 7.5, 9.5 \text{ Hz, } 2\text{H} \), 1.80 (dd, \( J = 7.5, 9.5 \text{ Hz, } 2\text{H} \)), 1.74 (dd, \( J = 3.5, 7.3 \text{ Hz, } 3\text{H} \)), 1.73 (dd, \( J = 3.5, 7.3 \text{ Hz, } 3\text{H} \)), 1.50-1.42 (comp. m, 2H), 1.33 (sextet, \( J = 7.0 \text{ Hz, } 4\text{H} \)), 1.13-1.03 (comp. m, 2H), 0.91 (t, 6H); \(^{13}\text{C NMR (125 MHz, CDCl}_3\)) \( \delta \) 209.8, 209.8, 204.0, 204.0, 95.2, 95.1, 90.1, 89.9, 80.2, 80.1, 36.9, 36.9, 25.4, 23.7, 23.7, 22.9, 22.9, 13.9, 13.8, 13.7; IR (thin film/NaCl) 3468 (br. m), 2957 (s), 2930 (s), 2863 (m), 1964 (m), 1711 (s), 1461 (m), 1355 (s), 1135 (m), 868 (m) cm\(^{-1}\); HRMS (EI) \( m/z \) found: 183.1381 [calc'd for \( \text{C}_{11}\text{H}_{19}\text{O}_2 \text{ (M+H)} \): 183.1385].

**Preparation of Deuterium-Labeled \( \alpha \)-Hydroxyketone (\( \pm \))-234**

\( \alpha \)-Hydroxyketone (\( \pm \))-234. To a stirred solution of \( \alpha \)-diazoketone 103 (73 mg, 0.456 mmol, 1.2 equiv) and alcohol (\( \pm \))-233 (30 \( \mu \)L, 0.377 mmol, 1.0 equiv) in benzene (5 mL) was added \( \text{Rh}_2\text{(cap)}_4 \) (3.1 mg, 0.005 mmol, 0.01 equiv). The mixture was immersed in a preheated oil bath and heated at reflux for 10 min, after which it was cooled and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (CH\(_2\)Cl\(_2\) eluent) to afford \( \alpha \)-Hydroxyketone (\( \pm \))-234 (2.5:1 mixture of diastereomers, 35 mg, 38% yield) as a yellow oil. \(^1\text{H NMR (500 MHz, CDCl}_3\)) \( \delta \) 8.12 (m, 2H), 8.09 (m, 2H), 7.58 (m, 2H), 7.46 (m, 4H), 5.45 (m, 2H), 4.54 (s, 1H), 4.52 (s, 1H), 1.67 (s, 3H), 1.67 (s, 3H), 1.67 (s, 3H), 1.74 (d, \( J = 3.0 \text{ Hz, } 3\text{H} \)), 1.64 (s, \( J = 3.5 \text{ Hz, } 3\text{H} \)); \(^{13}\text{C NMR (125 MHz, CDCl}_3\)) \( \delta \) 204.3, 204.2, 202.2, 202.1, 133.4, 133.2, 130.2, 130.1, 128.3, 128.2,
97.0, 96.9, 90.4 (t, J = 25.3 Hz), 26.3, 26.1, 13.3, 13.2; IR (thin film/NaCl) 3448 (br. m),
2980 (w), 2924 (w), 1955 (m), 1675 (s), 1597 (m), 1449 (m), 1371 (m), 1351 (w), 1254
(s), 1128 (s), 1096 (s) cm⁻¹; HRMS (EI) m/z found: 204.1130 [calc’d for C₁₃H₁₄O₂D
(M+H): 204.1135].

**Preparation of Deuterium-Labeled α-Hydroxyketone (±)-235**

![Chemical structure](image)

**α-Hydroxyketone (±)-235.** A mixture of α-diazoketone 103 (84 mg, 0.524 mmol, 1.0
equiv) and alcohol (±)-233 (68 µL, 0.899 mmol, 1.6 equiv) in benzene (5 mL) was treated
with Rh₂(tfa)₄ (3.4 mg, 0.005 mmol, 0.01 equiv). After 10 min at room temperature, the
mixture was concentrated under reduced pressure and the residue purified by flash
chromatography (CH₂Cl₂ eluent) to afford D-5 (2.4:1 mixture of diastereomers, 27 mg,
25% yield) as a clear yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.55-7.51 (comp. m,
4H), 7.42-7.31 (comp. m, 6H), 5.72 (m, 2H), 4.58 (s, 1H), 4.53 (s, 1H), 2.11 (s, 3H), 2.10
(s, 3H), 1.75 (d, J=3.2 Hz, 3H), 1.71 (d, J=3.6 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ
207.2, 207.1, 140.3, 128.6, 128.5, 128.3, 128.2, 126.7, 94.0, 94.0, 90.3 (t, J=28.0 Hz),
82.0, 24.8, 24.7, 13.8, 13.7; IR (thin film/NaCl) 3452 (br. m), 3028 (w), 2979 (w), 2922
(w), 1955 (w), 1713 (s), 1448 (m), 1354 (m), 1171 (m), 763 (m), 700 (s) cm⁻¹; HRMS
(EI) m/z found: 204.1130 [calc’d for C₁₃H₁₄O₂D (M+H): 204.1135].
Evidence Against [1,2]-α-Ketol Shift Under the Conditions of [3,3]-Rearrangement via Isotope Labelling

\[
\begin{align*}
\text{N}_2\text{Me} & \quad + \quad \text{Me} \quad \text{Me} \\
103 & \quad \quad \quad \quad \quad (\pm)-228 \\
\text{Rh}_2(\text{cap})_4^{235} & \quad \quad \text{benzene, } \Delta \\
10 \text{ min} & \quad \quad (\pm)-230 \\
\end{align*}
\]

To a stirred solution of α-diazoketone 103 (19 mg, 0.119 mmol, 1.0 equiv), 3-butyln-2-ol (228, 11 µL, 0.140 mmol, 1.2 equiv) and deuterated α-hydroxyketone (±)-235 (24 mg, 0.119 mmol, 1.0 equiv) was added Rh₂(cap)₄ (0.8 mg, 0.0012 mmol, 0.01 equiv). The mixture was immersed in a preheated oil bath, heated at reflux for 10 min, then cooled and concentrated under reduced pressure. Purification of the residue was accomplished via careful column chromatography (CH₂Cl₂ eluent) to furnish α-hydroxyketone (±)-230 (17 mg, 72% yield) and recovered deuterated α-hydroxyketone (±)-235 (23 mg, 96% recovery).

Disproving [1,2]-α-Ketol Shift Under the Conditions of [2,3]-Rearrangement via Isotope Labelling

\[
\begin{align*}
\text{N}_2\text{Me} & \quad + \quad \text{Me} \quad \text{Me} \\
103 & \quad (\pm)-228 \\
\text{Rh}_2(\text{tfa})_4^{234} & \quad \quad \text{benzene, } \text{rt} \\
5 \text{ min} & \quad (\pm)-231 \\
\end{align*}
\]
To a stirred solution of α-diazoketone 103 (12 mg, 0.075 mmol, 1.0 equiv), 3-butyn-2-ol (228, 7 µL, 0.089 mmol, 1.2 equiv) and deuterated α-hydroxyketone (±)-234 (16 mg, 0.076 mmol, 1.0 equiv) was added Rh₂(tfa)₄ (0.5 mg, 0.0008 mmol, 0.01 equiv) resulting in rapid loss of nitrogen. The resulting pale green mixture was allowed to stir for 5 min, after which it was concentrated under reduced pressure. The residue was purified by column chromatography (CH₂Cl₂ eluent) to furnish α-hydroxyketone (±)-231 (11 mg, 74% yield) and unaltered deuterated α-hydroxyketone (±)-234 (15 mg, 98% recovery).

**Generation and Observation of Enol 229**

![Chemical Reaction Diagram](attachment://enol_diagram.png)

To a stirred solution of α-diazoketone 103 (36 mg, 0.225 mmol, 1.0 equiv) and 3-butyn-2-ol (228, 21 µL, 0.268 mmol, 1.2 equiv) in C₆D₆ (2.5 mL) was added Rh₂(OAc)₄ (1.0 mg, 0.0023 mmol, 0.01 equiv) resulting in rapid loss of N₂(g) and decolorization of the reaction mixture. Analysis by ¹H NMR revealed complete conversion of 103 to enol 229. ¹H NMR (500 MHz, C₆D₆) δ 7.29 (m, 2H), 7.00-7.13 (comp m, 3H), 6.13 (br s, 1H), 4.15 (qd, J=2.2, 6.6 Hz, 1H), 1.96 (d, J=2.2 Hz, 1H), 1.88 (s, 3H), 1.20 (d, J=6.6 Hz, 3H).
Generation and Observation of Enol 253

\[
\begin{align*}
103 \quad &+ \quad \text{Rh}_{2} \text{(OAc)}_{4} (1 \text{ mol%}) \\
\text{benzene-}d_{6}, \text{ rt, 2 min} \quad &\rightarrow \\
239 \quad &\rightarrow \\
253
\end{align*}
\]

To a stirred solution of \(\alpha\)-diazoketone 103 (53 mg, 0.311 mmol, 1.0 equiv) and propargyl alcohol (239, 18 \(\mu\)L, 0.309 mmol, 0.99 equiv) in C\(_{6}\)D\(_{6}\) (3 mL) was added Rh\(_{2}\)(OAc)\(_{4}\) (1.4 mg, 0.003 mmol, 0.01 equiv) resulting in N\(_{2}\)(g) loss with concomitant conversion to enol 253. \(^{1}\)H NMR (400 MHz, C\(_{6}\)D\(_{6}\)) \(\delta\) 7.22 (m, 2H), 7.10-7.00 (comp. m, 3H), 5.97 (s, 1H), 3.85 (d, \(J\)=2.8 Hz, 2H), 1.93 (t, \(J\)=2.4 Hz, 1H), 1.83 (s, 3H).

Procedure for Measurement of Half-Lives for Conversion of 229 to 231 via \(^{1}\)H NMR Spectroscopy (Table 5.2)

A solution of enol 229 in benzene-\(d6\) was generated at previously described using the appropriate Rh(II) catalyst, noting the time of catalyst addition. An aliquot (0.25 mL) of this solution was transferred via syringe into a septum-covered NMR tube that was previously purged with N\(_{2}\)(g) for 20 min. This sample was inserted into the cryomagnet at the appropriate temperature. \(^{1}\)H NMR spectra were recorded every 10 min for rearrangement of 229 in the presence of 1 mol\% Rh\(_{2}\)(OAc)\(_{4}\) at 40\(^{\circ}\)C and every minute for rearrangement in the presence of 0.1 mol\% Rh\(_{2}\)(tfa)\(_{4}\). The time at which the methyl ketone singlet of 231 and the vinyl methyl singlet of 229 were of equivalent integration was taken as the reaction half-life.
Nitrogen gas was bubbled through a solution of α-diazoketone 103 (23 mg, 0.145 mmol, 1.0 equiv) in benzene (2 mL) for 15 min. To this degassed solution was added 3-butyn-2-ol (228, 14 µL, 0.179 mmol, 1.2 equiv) followed by Rh$_2$(OAc)$_4$ (1.0 mg, 0.002 mmol, 0.01 equiv). Once dediazotization/enol formation was complete as evidenced by cessation of N$_2$(g) release, dimethyl sulfide (21 µL, 0.286 mmol, 2.0 equiv) was added resulting in a rapid change in solution color from green to red. A solution of Rh$_2$(tfa)$_4$ (1.3 mg, 0.0016 mmol, 0.01 equiv) in CH$_2$Cl$_2$ (0.5 mL) was added, turning the solution a darker red color. This mixture was allowed to stir for 6 min after which it was immersed in a preheated oil bath and heated at reflux for 15 min. The mixture was cooled to room temperature and concentrated under reduced pressure. Flash chromatography of the residue (8:1 hexanes:ethyl acetate eluent) furnished α-hydroxyketone (±)-230 (19 mg, 65% yield, 2.5:1 mixture of diastereomers) as a clear yellow oil.
Catalysis of [2,3]-Rearrangement with AgBF₄

To a stirred solution of α-diazoketone 103 (51 mg, 0.317 mmol, 1.0 equiv) and 3-butyne-2-ol (228, 30 µL, 0.383 mmol, 1.2 equiv) in benzene (3 mL) was added Rh₂(OAc)₄ (1.4 mg, 0.003 mmol, 0.01 equiv). Once nitrogen gas evolution was complete (ca. 2 min), AgBF₄ (3.1 mg, 0.015 mmol, 0.05 equiv) was added. The resulting cloudy mixture was allowed to stir for 2 min after which it was immediately quenched with triethylamine (0.5 mL) and concentrated. Flash chromatography (8:1 hexanes:ethyl acetate eluent) furnished α-hydroxyketone (±)-231 (51 mg, 80% yield, 2.4:1 mixture of diastereomers) as a clear, colorless oil.

Cyclization of α-Hydroxyketone (±)-231 with AgBF₄
To a stirred solution of α-hydroxyketone (±)-231 (42 mg, 0.209 mmol, 1.0 equiv) in benzene (2 mL) was added AgBF$_4$ (52 mg, 0.267 mmol, 1.2 equiv). The resulting mixture was immersed in a pre-heated oil bath and heated at reflux for 5 min, after which it was cooled and concentrated. Purification of the residue by flash chromatography (8:1 hexanes:ethyl acetate eluent) furnished dihydrofuran (±)-250 (31 mg, 72% yield, 2.4:1 mixture of diastereomers) as a clear yellow oil. Separation of diastereomers was accomplished by careful column chromatography (pentane:diethyl ether eluent). The first diastereomer to elute was 250a: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.47 (m, 2H), 7.32 (m, 3H), 6.22 (dd, $J$=2.0, 6.5 Hz, 1H), 5.89 (d, $J$=6.5 Hz, 1H), 5.14 (m, 1H), 2.22 (s, 3H), 1.41 (d, $J$=6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.3, 140.5, 132.0, 129.3, 128.5, 127.8, 125.0, 98.5, 82.9, 25.1, 21.8; IR (thin film/NaCl) 3061 (w), 2972 (w), 2926 (w), 2866 (w), 1715 (s), 1447 (w), 1350 (m), 1102 (m), 754 (m), 699 (m) cm$^{-1}$; HRMS (EI) $m/z$ found: 203.0709 [calc'd for C$_{13}$H$_{15}$O$_2$ (M+H): 203.0708]. The second diastereomer to elute was 250b: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.50 (m, 2H), 7.38-7.28 (comp. m, 3H), 6.17 (dd, $J$=2.5, 6.0 Hz, 1H), 5.92 (dd, $J$=1.5, 6.0 Hz, 1H), 5.19 (m, 1H), 2.20 (s, 3H), 1.37 (d, $J$=6.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 209.4, 140.8, 132.3, 129.1, 128.5, 127.7, 125.1, 98.8, 83.1, 25.6, 22.0; IR (thin film/NaCl) 2974 (w), 1714 (s), 1489 (w), 1447 (w), 1350 (m), 1102 (m), 1085 (m), 1052 (w), 753 (m), 699 (m) cm$^{-1}$; HRMS (EI) $m/z$ found: 203.0700 [calc'd for C$_{13}$H$_{15}$O$_2$ (M+H): 203.0782].
One-Pot, Tandem [2,3]-Rearrangement/Cyclization with AgBF₄

To a stirred solution of α-diazoketone 103 (92 mg, 0.572 mmol, 1.0 equiv) and 3-butyn-2-ol (228, 54 µL, 0.689 mmol, 1.2 equiv) in benzene (6 mL) was added Rh₂(OAc)₄ (2.5 mg, 0.006 mmol, 0.01 equiv) resulting in rapid N₂(g) loss. Once complete (ca. 2 min), AgBF₄ (119 mg, 0.609 mmol, 1.1 equiv) was added and the mixture heated at reflux for 10 min. The cooled mixture was concentrated under reduced pressure and the residue purified by flash chromatography (pentane:diethyl ether 8:1) to furnish dihydrofuran 250 (84 mg, 73% yield, 2.4:1 mixture of diastereomers) as a clear yellow oil.

Catalysis of [2,3]-Rearrangement with [Cu-(S,S)-Ph-pybox])[(OTf)₂ (251)

To a stirred solution of α-diazoketone 103 (161 mg, 1.00 mmol, 1.0 equiv) and 3-butyn-2-ol (228, 94 µL, 1.20 mmol, 1.2 equiv) in benzene (10 mL) was added Rh₂(OAc)₄ (4.7
mg, 0.01 mmol, 0.01 equiv) resulting in rapid N₂(g) loss. Once complete (ca. 2 min), [Cu-(S,S)-Ph-pybox])(OTf)₂ (251, 0.03 M solution in CH₂Cl₂, 1.7 mL, 0.051 mmol, 0.05 equiv) was added. The mixture was allowed to stir for 5 min, after which it was quenched with triethylamine (0.25 mL) and concentrated under reduced pressure. Flash chromatography of the residue (10:1 hexanes:ethyl acetate eluent) furnished α-hydroxyketone 231 (135 mg, 67% yield, 2.3:1 mixture of diastereomers) as a clear, colorless oil and dihydrofuran 250 (40 mg, 19% yield, 1:1 mixture of diastereomers) as a clear, yellow oil.

Investigation of Interconversion Between α-Hydroxyketone 231 and Dihydrofuran 250.

To a stirred solution of α-diazoketone 103 (19 mg, 0.119 mmol, 1.0 equiv), 3-butyn-2-ol (228, 11 µL, 0.140 mmol, 1.2 equiv), and deuterated α-hydroxyketone 235 (13 mg, 0.063 mmol, 0.5 equiv) in benzene (1 mL) was added Rh₂(OAc)₄ (0.5 mg, 0.001 mmol, 0.01 equiv) resulting in N₂(g) loss. Once gas evolution had ceased, [Cu(S,S)-Ph-
pybox][OTf₂ (251, 0.03 M solution in CH₂Cl₂, 97 uL, 0.003 mmol, 0.025 equiv) was added. The mixture was allowed to stir for 25 min, after which, Et₃N (0.5 mL) was added. The red solution was concentrated under reduced pressure and the residue purified by flash chromatography (8:1 hexane:EtOAc eluent) to afford a mixture of 231 and 235 (0.0284 g, 100% recovery 235 + 64% yield 231) and exclusively protic 250 (1:1 mixture of diastereomers, 4 mg, 16% yield).

**Catalysis of [2,3]-Rearrangement with [Sn-(S,S)-Ph-pybox]](OTf₂ (252)**

![Chemical Reaction Diagram]

To a stirred solution of α-diazoketone 103 (33 mg, 0.209 mmol, 1.0 equiv) and 3-butyn-2-ol (228, 20 μL, 0.255 mmol, 1.2 equiv) in CH₂Cl₂ (2 mL) was added Rh₂(OAc)₄ (1.0 mg, 0.002 mmol, 0.01 equiv). Once nitrogen evolution was complete, [Sn-(S,S)-Ph-pybox]](OTf₂ (252, 0.03M solution in CH₂Cl₂, 1.0 mL, 0.031 mmol, 0.15 equiv) was added and the mixture allowed to stir for 35 min at room temperature. Concentration of the reaction mixture under reduced pressure provided a residue that was purified by flash chromatography (8:1 hexanes:ethyl acetate eluent) to furnish α-hydroxyketone 231 (32 mg, 76% yield, 2.2:1 mixture of diastereomers) as a clear, colorless oil.
Asymmetric [2,3]-Rearrangement using \([\text{Cu}(\text{S},\text{S})\text{-Ph-pybox(H}_2\text{O})_2] \text{(OTf)}_2\) (254)

\[
\begin{array}{c}
\text{PhH, rt, 5 min} \\
\end{array}
\]

A stirred solution of \(\alpha\)-diazoketone 103 (353 mg, 2.20 mmol, 1.0 equiv) and propargyl alcohol (239, 0.15 mL, 2.6 mmol, 1.2 equiv) in benzene (22 mL) was treated with \(\text{Rh}_2(\text{OAc})_4\) (9 mg, 0.02 mmol, 0.01 equiv) at room temperature resulting in vigorous \(\text{N}_2(\text{g})\) loss. Once gas evolution had ceased (ca. 3 min), \([\text{Cu}(\text{S},\text{S})\text{-Ph-pybox(H}_2\text{O})_2] \text{(OTf)}_2\) (254, 42 mg, 0.055 mmol, 0.025 equiv) in \(\text{CH}_2\text{Cl}_2\) (1 mL) was added. The mixture was allowed to stir for 5 min, after which triethylamine (0.5 mL) was added as a quench. The mixture was concentrated under reduced pressure and the residue purified by flash chromatography (8:1 hexanes:EtOAc eluent) to furnish (\(\text{S})\text{-(+)-243a}\) (251 mg, 61% yield, 90% ee) as a colorless oil and (\(\text{S})\text{--(-)-256}\) (125 mg, 30% yield, 30% ee) as a clear yellow oil. (\(\text{S})\text{--(+)-243a}\): \([\alpha]^{20}_{\text{D}} +179.5^\circ\) (c 1.3, CHCl₃).

(S)-(−)-256: \(^1\text{H NMR}\) (400 MHz, CDCl₃) \(\delta\) 7.48-7.27 (comp. m, 5H), 6.23 (m, 1H), 6.04 (m, 1H), 4.88 (m, 1H), 2.22 (s, 3H); \(^{13}\text{C NMR}\) (100 MHz, CDCl₃) \(\delta\) 209.0, 140.2, 129.3, 128.6, 127.9, 127.6, 125.1, 98.7, 75.8, 25.6; \(\text{IR}\) (thin film/NaCl) 3059 (w), 2856 (m), 1715 (s), 1490 (w), 1447 (w), 1416 (w), 1351 (m), 1229 (w), 1200 (w), 1068 (s) cm\(^{-1}\); \(\text{HRMS (EI)}\) \text{m/z} found: 186.0677 [calc'd for C\(_{12}\)H\(_{10}\)O\(_2\) (M-2H): 186.0681]; \([\alpha]^{20}_{\text{D}}\) -13.4° (c 1.3, CHCl₃).
Confirmation of Structure of Dihydrofuran 256

To a solution of methyl triphenylphosphonium iodide (278 mg, 0.687 mmol, 2.0 equiv) in THF (4 mL) was added dropwise, sec-butyl lithium (1.3 M solution in THF, 0.58 mL, 0.754 mmol, 2.2 equiv) at room temperature. The orange mixture was stirred for 2 h, after which a solution of (±)-256 (64 mg, 0.340 mmol, 0.5 equiv) in THF (1 mL) was added dropwise, the resulting mixture allowed to stir overnight at room temperature. The mixture was concentrated under reduced pressure with concomitant adsorption onto silica gel. Flash chromatography (12:1 hexane:EtOAc eluent) furnished a pale yellow oil (35 mg), a fraction (27 mg) of which was dissolved in methanol (1 mL) and added to a suspension of Rh/Al₂O₃ in MeOH under H₂(g) (1 atm). This mixture was allowed to stir for 18 h after which the Rh/Al₂O₃ was removed by filtration and the filtrate concentrated under reduced pressure. Flash chromatography of the residue (12:1 hexane: EtOAc eluent) afforded tetrahydrofuran 258 (14 mg, 38% yield) as a yellow oil. ¹H NMR spectral data for this material matched reported values.²² ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.21 (comp. m, 5H), 3.95 (td, J=6.5, 7.7 Hz, 1H), 3.79 (td, J=6.0, 8.2 Hz, 1H), 2.25 (ddd, J=4.5, 8.1, 12.5 Hz, 1H), 2.09 (m, 1H), 2.01 (m, 1H), 1.91 (m, 1H), 1.71 (m, 1H), 0.87 (d, J=6.5 Hz, 3H), 0.82 (d, J=6.5 Hz, 3H).
Determination of Absolute Stereochemistry of (+)-243a

A solution of α-hydroxyketone (+)-243a (144 mg, 0.762 mmol, 1.0 equiv) in methanol (2 mL) was added to a suspension of Pd/C (17.1 mg) in methanol (6 mL) under H2(g) (1 atm). The mixture was stirred at room temperature for 1h, then filtered to remove Pd/C. Concentration of the filtrate under reduced pressure afforded a pale yellow oil (143 mg) that was used without further purification. To a solution of the oil (133 mg, 0.690 mmol, 1.0 equiv) in dioxane (3 mL) was added 4N NaOH (20 mL). The resulting suspension was stirred rapidly at room temperature as bromine (106 µL, 2.07 mmol, 3.0 equiv) was added slowly dropwise, allowing the faint yellow color that developed during each addition to dissipate before the next addition (ca. 3 min delay). Once addition was complete, the mixture was washed with Et2O (2 x 10 mL). The organic washes were discarded and the aqueous layer was acidified with 1N HCl and extracted with CH2Cl2 (3 x 20 mL). The combined organic phases were dried (MgSO4), filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (6:1 EtOAc:hexane/1% HOAc eluent) to afford α-hydroxyacid (S)-(+)257 (72 mg, 54%) as a white solid whose spectral and physical data matched those reported in the literature.21 The optical rotation of material derived from (+)-243a was measured at [α]D20 + 23.2° (c 1.5, EtOH).
Determination of Absolute Stereochemistry of (-)-256

To a solution of (S)-(+)\textsuperscript{243a} (65 mg, 0.347 mmol, 1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (4 mL) at room temperature was added H\textsubscript{2}O (50 µL) and AgBF\textsubscript{4} (72 mg, 0.370 mmol, 1.1 equiv). The mixture was allowed to stir for 5 h, after which it was concentrated under reduced pressure with concomitant adsorption onto silica gel. Flash chromatography (6:1 hexane:EtOAc eluent) afforded (S)-(−)\textsuperscript{256} (30 mg, 46% yield) as a pale yellow oil. [\alpha]\textsubscript{D}\textsuperscript{20} -14.4\textdegree (c 1.4, CHCl\textsubscript{3}).

5.7 Notes and References


(5) Both Rh$_2$(tfa)$_4$ and Rh$_2$(oct)$_4$ are freely soluble in benzene at room temperature.


(10) Subsequent to these studies, a report has appeared describing the use of rhodium (II) carboxamidates as Lewis acid catalysts for inverse electron-demand Diels-Alder reactions, thus providing proof of concept that rhodium (II) species can function as effective Lewis acids, see: Doyle, M. P.; Phillips, I. M.; Hu, Wenhao. *J. Am. Chem. Soc.* **2001**, *123*, 5366.


(14) (a) Drago, R. S.; Bilgrien, C. J. *Polyhedron*, **1988**, *7*, 1453. (b) Ref 10a

(16) A control experiment performed with HBF$_4$ resulted only in enol tautomerization indicating that HBF$_4$ was not the active catalyst.


(20) The enantiomeric excess of (+)-255 was determined by Mosher ester analysis of the derived diol and that of (-)-256 was determined by Mosher ester analysis of the derived alcohol.


(23) All calculations were performed using: Spartan version 5.0, Wavefunction, Inc. 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612 U.S.A.

(24) Use of this angle constraint is preceded in the work of Evans et al., see Ref 15a.

(25) This orientation, wherein the propargyloxy oxygen is bound in the ligand plane was selected based on two criteria: (1) The equivalent model with pyruvate esters (i.e., ketone bound in ligand plane) successfully predicts the stereochemical outcome of Mukaiyama aldol reactions (See ref. 15a), and (2) The equatorial site (ligand plane) is more strongly coordinating than the axial site, making this orientation consistent with the notion that electron conduction must proceed from the enol hydroxyl to the propargyloxy arm to effect an SNI’ displacement.

(26) Such oxidative by-products are preceded and are believed to be derived from molecular oxygen, see: Elzinga, J.; Hogveen, H.; Schudde, E. P. J. Org. Chem. 1980, 45, 4337.
APPENDIX FIVE: SPECTRA RELEVANT TO CHAPTER FIVE
Figure A.5.1 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 230
Figure A.5.3 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 230.

Figure A.5.2 FTIR Spectrum (thin film/NaCl) of Compound 230.
Figure A.5.4 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 231.
Figure A.5.6  $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 231.

Figure A.5.5 FTIR Spectrum (thin film/NaCl) of Compound 231.
Figure A.5.7 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 234.
Figure A.5.9 13C NMR (125 MHz, CDCl₃) of Compound 234.

Figure A.5.8 FTIR Spectrum (thin film/NaCl) of Compound 234.
Figure A.5.10 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 235.
Figure A.5.11 FTIR Spectrum (thin film/NaCl) of Compound 235.

Figure A.5.12 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 235.
Figure A.5.13 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 242a.
Figure A.5.15: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 242a.

Figure A.5.14: FTIR Spectrum (thin film/NaCl) of Compound 242a.
Figure A.5.16 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 263.
Figure A.5.17 FTIR Spectrum (thin film/NaCl) of Compound 263.

Figure A.5.18 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 263.
Figure A.5.19 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 243a.
Figure A.5.20 FTIR Spectrum (thin film/NaCl) of Compound 243a.

Figure A.5.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 243a.
Figure A.5.22 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 264.
Figure A.5.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 264.

Figure A.5.23 FTIR Spectrum (thin film/NaCl) of Compound 264.
Figure A.5.25 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 243b.
Figure A.5.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 243b.

Figure A.5.26 FTIR Spectrum (thin film/NaCl) of Compound 243b.
Figure A.5.28 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 242d.
Figure A.5.30  $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 242d.

Figure A.5.29 FTIR Spectrum (thin film/NaCl) of Compound 242d.
Figure A.5.31 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 243d.
Figure A.5.33 \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) of Compound 243d.

Figure A.5.32 FTIR Spectrum (thin film/NaCl) of Compound 243d.
Figure A.5.34 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 244a.
Figure A.5.35 13C NMR (125 MHz, CDCl3) of Compound 244a.

Figure A.5.36 FTIR Spectrum (thin film/NaCl) of Compound 244a.
Figure A.5.37 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 244b.
Figure A.5.39 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 244b.

Figure A.5.38 FTIR Spectrum (thin film/NaCl) of Compound 244b.
Figure A.5.40 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 244c.
Figure A.5.41 FTIR Spectrum (thin film/NaCl) of Compound 244c.

Figure A.5.42 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 244c.
Figure A.5.43 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 244d.
Figure A.5.45 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 244d.

Figure A.5.44 FTIR Spectrum (thin film/NaCl) of Compound 244d.
Figure A.5.46 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 245a.
Figure A.5.47 FTIR Spectrum (thin film/NaCl) of Compound 245a.

Figure A.5.48 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 245a.
Figure A.5.49 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 245b.
Figure A.5.50  FTIR Spectrum (thin film/NaCl) of Compound 245b.

Figure A.5.51  $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 245b.
Figure A.5.52 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 245c.
Figure A.5.53 FTIR Spectrum (thin film/NaCl) of Compound 245c.

Figure A.5.54 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 245c.
Figure A.5.55 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 245d.
Figure A.5.57: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 245d.

Figure A.5.56: FTIR Spectrum (thin film/NaCl) of Compound 245d.
Figure A.5.58 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 246a.
Figure A.5.60  $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 246a.

Figure A.5.59 FTIR Spectrum (thin film/NaCl) of Compound 246a.
Figure A.5.61 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 246b.
Figure A.5.63 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 246b.

Figure A.5.62 FTIR Spectrum (thin film/NaCl) of Compound 246b.
Figure A.5.64 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 246c.
Figure A.5.65 FTIR Spectrum (thin film/NaCl) of Compound 246c.

Figure A.5.66 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 246c.
Figure A.5.67 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 246d.
Figure A.5.69 13C NMR (125 MHz, CDCl3) of Compound 246d.

Figure A.5.68 FTIR Spectrum (thin film/NaCl) of Compound 246d.
Figure A.5.70 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 265.
Figure A.5.72 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 265.

Figure A.5.71 FTIR Spectrum (thin film/NaCl) of Compound 265.
Figure A.5.73 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 248a.
Figure A.5.75: $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 248a.

Figure A.5.74: FTIR Spectrum (thin film/NaCl) of Compound 248a.
Figure A.5.76 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 248b.
Figure A.5.78 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 248b.

Figure A.5.77 FTIR Spectrum (thin film/NaCl) of Compound 248b.
Figure A.5.79 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 248c.
Figure A.5.80 FTIR Spectrum (thin film/NaCl) of Compound 248c.

Figure A.5.81 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 248c.
Figure A.5.82 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 248d.
Figure A.5.84 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 248d.

Figure A.5.83 FTIR Spectrum (thin film/NaCl) of Compound 248d.
Figure A.5.85 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 249a.
Figure A.5.87. $^1$H NMR (300 MHz, CDCl$_3$) of Compound 249a.

Figure A.5.86. FTIR Spectrum (thin film/NaCl) of Compound 249a.
Figure A.5.88 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 249b.
Figure A.5.89 13C NMR (100 MHz, CDCl3) of Compound 249b.

Figure A.5.90 FTIR Spectrum (thin film/NaCl) of Compound 249b.
Figure A.5.91 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 249c.
Figure A.5.93  $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 249c.

Figure A.5.92 FTIR Spectrum (thin film/NaCl) of Compound 249c.
Figure A.5.94 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 250a.
Figure A.5.96 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 250a.

Figure A.5.95 FTIR Spectrum (thin film/NaCl) of Compound 250a.
Figure A.5.97 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 250b.
Figure A.5.99 \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) of Compound 250b.

Figure A.5.98 FTIR Spectrum (thin film/NaCl) of Compound 250b.
Figure A.5.100 $^1$H NMR (500 MHz, C$_6$D$_6$) of Compound 229.
Figure A.5.101 $^1$H NMR (500 MHz, C$_6$D$_6$) of Compound 253.
Figure A.5.102 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 256.
Figure A.5.103 FTIR Spectrum (thin film/NaCl) of Compound 256.

Figure A.5.104 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 256.
Chapter 6

Efforts Toward the Total Synthesis of

(±)-Hydroxymethylacylfulvene

6.1 Background

6.1.1 The Illudin Sesquiterpenes: From Poison to Phase II

Illudins M (6) and S (7) are sesquiterpene natural products isolated from toxic mushrooms of the genus Omphalotus (O. illudens) and the closely related Lampteronymes (L. japonicus).\(^1\)\(^2\) The toxicity of these mushrooms is well established\(^3\) and isolation efforts were driven initially by the desire to identify the factor responsible for their toxic nature. However, subsequent investigations by the National Cancer Institute Developmental Therapeutics Program revealed that 6 and 7 possessed potent anti-proliferative activity against a variety of rodent solid tumors and leukemias.\(^4\) Unfortunately, the utility of these compounds was limited by poor therapeutic indices \textit{in vivo}, particularly in solid tumor systems. In 1999, two new illudin congeners, neoilludins A (265) and B (266) were isolated from the same mushroom and found to possess poor anti-tumor activity.\(^5\)
The promising biological activity exhibited by 6 and 7 has resulted in a substantial effort to develop less toxic analogs of these compounds that retain the desirable anti-tumor properties. The most significant contributions in this area have been those of McMorris et al., who, through extensive manipulation of the illudin core, established key structure-activity relationships for both anti-tumor activity and toxicity, enabling the development of illudin analogs possessing greatly enhanced therapeutic indices. First-generation analog dehydroilludin M (267) demonstrated antitumor activity against human metastatic MV 522 lung carcinoma xenografts similar to mitomycin C and superior to nine known anticancer agents including cisplatin, cytoxan, and paclitaxel. The efficacy of second-generation analog acylfulvene (268) exceeded that of mitomycin C, demonstrating similar anti-tumor activity but markedly prolonged life span when compared to mitomycin C. These studies culminated with the development of third-generation analog hydroxymethylacylfulvene (HMAF, 269), which caused complete tumor regression in all animals at the maximum tolerated dose of 10 mg/Kg three times per week for three weeks. Furthermore, this potent in vivo anti-tumor activity was
accompanied by an increase in life span of more than 150%. In subsequent studies, 269 has also demonstrated excellent activity against breast, colon, and skin cancer cell lines derived from human tumors and has been found to be effective against the MDR phenotype.\textsuperscript{9,10} Currently, hydroxymethylacylfulvene (269) is in Phase II clinical trials including studies in breast, colon, prostate, renal, pancreatic, ovarian, non-small-cell lung, and cervical cancers. The National Cancer Institute is also conducting a Phase I study in pediatric cancer patients with solid tumors.\textsuperscript{11,12}

**Figure 6.2 - Illudin Analogs Offering Enhanced Therapeutic Indices**

\[
\begin{align*}
\text{Dehydroilludin M (267)} & \quad \text{Acylfulvene (268)} \\
\text{Hydroxymethylacylfulvene (HMAF) (269)}
\end{align*}
\]

### 6.1.2 Prior Synthetic Efforts Toward Hydroxymethylacylfulvene (269).

At the outset of these investigations, only a single racemic total synthesis of hydroxymethylacylfulvene had been accomplished by McMorris in 13 steps.\textsuperscript{13} Material employed in clinical trials is semi-synthetic, prepared from natural illudin S (7) isolated from cultures of *Omphalaotus (O. illudens)*. Conversion of 7 to 269 is accomplished via a tandem retro-prins reaction/formylation in the presence of formaldehyde and 1N H\textsubscript{2}SO\textsubscript{4}.
During the course of our investigations, Brummond reported a second, 11-step synthesis of 269 relying on an allenic Pauson-Khand cyclization to furnish key intermediate 272, which is then advanced to 269 (Scheme 6.2). This report was shortly followed by a formal non-racemic synthesis of (R)-269 wherein the initial racemic route was intersected by enantiomerically enriched intermediate (R,R)-270. Although, in principle, the asymmetric dihydroxylation conditions could be modified to furnish (S,S)-274 which would ultimately lead to (S)-269, such modifications were not attempted.
6.2 Synthetic Studies Toward Hydroxymethylacylfulvene

6.2.1 Retrosynthetic Analysis

The selection of HMAF (269) as a synthetic target was prompted by a desire to apply the rhodium carbenoid-initiated Claisen methodology developed in the preceding chapters to a biologically relevant total synthesis. It was felt that 269 was an ideal target for synthesis within this context, possessing challenging structural features for which the Rh(II) methodology appeared well-suited. The proposed approach to 269 employing the rhodium carbenoid-initiated Claisen rearrangement is outlined in Scheme 6.3. Late-stage incorporation of the hydroxymethyl substituent would be achieved by formylation of fulvene 268 (See Scheme 6.1) which should be readily formed upon reduction of diketone 275 following methylation.

In contemplating the synthesis of 275, it was recognized that opening of the 6-membered carbocycle employing a retro-aldol disconnection would furnish triketone 276, preparable via ozonolysis of olefin 277. This compound was expected to be preparable via rhodium carbenoid-initiated Claisen rearrangement employing cyclopropylidene allylic alcohol 278 and α-diazoketone 279, installing the tertiary alcohol and spirocyclopropane moieties in a single convergent step. Importantly, it was felt that the chirality transfer afforded by the rhodium carbenoid-initiated Claisen rearrangement would offer entry to either enantiomer of 269 by employing the appropriate enantiomer of alcohol 278. With this in mind, synthesis of the allylic alcohol component (278) was expected to proceed via Wittig olefination of protected α-hydroxyketone 280 which would be prepared from trans-2,3-butanediol (281), a compound available commercially
in optically pure \((R,R)\) and \((S,S)\) forms. Synthesis of the \(\alpha\)-diazoketone component was envisioned to proceed via diazo transfer to diketone 282, which would be prepared from \(\alpha\)-phenylthioacetone (283) and cyclopentenone (284).

\textit{Scheme 6.3}

6.2.2 Synthesis of the \(\alpha\)-Diazoketone Component: A Catalytic Michael Reaction

In implementing the synthesis of diketone 282, numerous conditions were unsuccessfully employed in an effort to achieve Michael addition of \(\alpha\)-phenylthioacetone (283) to cyclopentenone (284). In each case, only starting materials were recovered. A report by Yamamoto was subsequently discovered wherein Michael additions were accomplished in the presence of catalytic potassium \(\text{tert-butoxide}\) and 18-crown-6. Application of these conditions with slight modification to the system under investigation afforded very interesting results (Scheme 6.4). Treatment of a toluene solution of 283 with 7.5 mol\% \(t\)BuOK and 10 mol\% 18-crown-6 followed by addition of 284 afforded, in
1 hour at 0°C, the desired Michael adduct 285, in 55% yield. However, this transformation could not be achieved in the presence of stoichiometric \( \text{tBuOK} \). Furthermore, treatment of 285 with stoichiometric \( \text{tBuOK} \) promoted retro-Michael addition. These observations pointed to the mechanism indicated in Scheme 6.5, wherein the enolate derived from the additional Michael addition serves as the base for the next equivalent of 283. The retro-addition observed in the presence of stoichiometric \( \text{tBuOK} \) is reasonable if the adduct enolate (287) is in unfavorable equilibrium with enolate 286 and cyclopentenone (284). In the presence of 7.5 mol% \( \text{tBuOK} \), the maximum amount of equilibrating enolate that can be present is also 7.5 mol%. However, in the presence of stoichiometric base, all adduct 285 can be converted to 287, resulting in complete retro-addition.
With adduct 285 in hand, oxidation of the sulfide was accomplished using 1.0 equiv of \textit{m}CPBA to furnish the corresponding sulfoxide (288), which was not purified before being treated with CaCO$_3$ in refluxing toluene to afford the diketone 282 in 85\% yield.\textsuperscript{18} It was subsequently found that Michael addition and sulfide oxidation could be performed in one pot and the resulting sulfoxide filtered only through a silica gel plug prior to elimination to afford a greatly enhanced yield of 282 over the three steps. Diazo transfer to 282 was accomplished using \textit{p}-acetamidobenzenesulfonyl azide (\textit{p}-ABSA)\textsuperscript{19} and DBU, providing \textit{\alpha}-diazoketone 279 in 71\% yield (Scheme 6.6).
6.2.3 Synthesis of the Allylic Alcohol Component

Efforts were next focused on the synthesis of allylic alcohol substrate 278. This early-stage intermediate was expected to be the vehicle for introducing asymmetry in the proposed synthesis of HMAF (269) and therefore a scalable synthetic route was required that could be readily extended to asymmetric intermediates. The synthesis of 278 had previously been reported by Huet et al., however, the route employed was neither practical for large-scale synthesis nor amenable to an asymmetric synthesis. An independent route to 278 was thus devised as shown in Scheme 6.7.
Commercially available 2,3-butanediol (281) was converted to the corresponding p-methoxybenzyl acetal 289 by treatment with anisaldehyde and catalytic TsOH under Dean-Stark conditions. DIBAL-promoted acetal migration/reduction followed by Swern oxidation furnished known p-methoxybenzyl-protected α-hydroxyketone 290. Importantly, since diol 281 is commercially available in both enantiomeric (S,S) and (R,R) forms, it was expected that this route could be readily extended to the synthesis of either enantiomer of ketone 290. Wittig homologation of 290 with cyclopropyl ylide 291 initially afforded only a very poor yield (ca. 15%) of olefinated product (292). However, a 1988 report by McMurry was subsequently discovered that reported enhanced yields for related Wittig reactions in the presence of tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1, 293). Use of this additive (10 mol%) resulted in a greatly enhanced yield of protected allylic alcohol 292, which, upon treatment with DDQ, furnished cyclopropyldiene allylic alcohol 278.

6.2.4 Implementation of the Rhodium Carbenoid-Initiated Claisen Rearrangement and Advancement to Triketone 276.

With both α-diazoketone (279) and allylic alcohol (278) components in hand, the key rhodium carbenoid-initiated Claisen rearrangement step could now be attempted. After significant experimentation, it was found that formation of [3,3]-product 277 proceeded optimally using the Rh2(tpa)4 catalyst (1 mol%) in refluxing toluene (Scheme 6.8). Thus, the vicinal tertiary alcohol and spirocyclopropane moieties were installed in a single, convergent step. Use of other catalysts resulted either in significant quantities of Wolff Rearrangement, or else in intractable mixtures of products. Although the
maximum attainable yield of 277 was a modest 35%, this was deemed acceptable temporarily in light of the rapid and scalable syntheses of the two reaction components. Ozonolysis of 277 furnished triketo 276, thus setting the stage for 6-membered ring-closure.

Scheme 6.8

6.2.5 Efforts to Effect Cyclization of Triketo 276

Cyclization of triketo 276 to ring-closed intermediate 275 was initially attempted via homoenoalte aldol condensation. Unfortunately, subjecting 276 to a number of standard equilibrating base conditions (KO-tBu/t-BuOH, NaOEt/EtOH, Triton B/MeOH) resulted only in decomposition of 276, as did treatment with strong bases such as LDA and KHMDS (Scheme 6.9). Efforts thus turned towards alternative cyclization methods. A report was found describing a diethylaluminum iodide-catalyzed tandem Michael addition/aldol/elimination process that furnishes Baylis-Hillman-type adducts. Unfortunately, efforts to effect this sequence with triketo 276 afforded no reaction under the reported low-temperature reaction conditions and furnished only decomposition products at room temperature.
It was next considered that ring-closure might be accomplished via 6-endo-trig ketyl radical cyclization employing samarium (II) iodide. It is well established that intramolecular additions of SmI₂-derived ketyl radical anions to α,β-unsaturated ketones and esters proceed selectively via the 5-exo-trig mode of addition.\(^\text{25}\) However, a recent report describing selective and high-yielding 6-endo-trig cyclizations into cyclopentenones inspired optimism regarding this approach.\(^\text{26}\) An additional concern was the possibility that the initially generated ketyl radical might promote ring-opening of the vicinal spirocyclopropane ring.\(^\text{27}\) To investigate the reactivity of \(276\) towards radical cyclization, a THF solution of the triketone at \(-78^\circ\text{C}\) was titrated with a solution of SmI₂, resulting in complete conversion to single diastereomeric spirocycle \(296\) (Scheme 6.10). The relative stereochemistry present in \(296\) was established via X-Ray crystallography and presumably arises via a transition state such as \(295\), wherein tridentate Sm(III) chelation controls ketyl radical orientation\(^\text{28}\) and enone diastereofacial selectivity is dictated by interaction with the spirocyclopropane moiety.
While structurally intriguing, tricycle 296 was not a synthetically viable intermediate en route to 269 and thus an effort was made to inhibit the 5-exo-trig cyclization pathway. After significant experimentation, it was found that selective reduction of diketone 277 could be achieved using K-Selectride®, however, conversion of ketone 297 to diketone 298 via selective ozonolytic cleavage of the pendant tri-substituted alkene proved difficult and has not yet been achieved in reasonable yield (Scheme 6.11).

**Scheme 6.11**

**6.2.6 Proposed Future Work**

Although selective ozonolysis of 297 has thus far proven unsuccessful, preliminary results suggest that diketone 298 may be preparable via K-Selectride® reduction of triketone 276, which, in early experiments, appeared to proceed with similar carbonyl chemoselectivity to diketone 277. It is expected that diketone 298, if attainable,
will be predisposed towards 6-endo-trig ketyl radical cyclization under SmI$_2$ conditions, furnishing tricycle 299 (Scheme 6.12).\(^{26}\)

**Scheme 6.12**

Should SmI$_2$-based approaches fail, an alternative strategy is envisioned wherein irradiation of 276 or 298 will furnish oxtanes 300 or 301, respectively, via intramolecular Paterno-Buchi reaction (Scheme 6.13).\(^ {29,30}\) Treatment with base will then rupture the oxetane ring to provide tricyclic intermediates 302 and 303, which will ultimately be advanced to (±)-hydroxymethylacylfulvene (269). Finally, with a synthetic route established, use of enantioenriched allylic alcohol (S)-278 will furnish natural (R)-269, which has been shown to exhibit two-fold greater potency than the unnatural (S)-enantiomer.
6.3 Summary and Conclusions

Efforts toward the total synthesis of (±)-hydroxymethylacylfulvene (269), a potent anti-tumor agent, were described. The synthetic route devised employed as a key step the rhodium carbenoid-initiated Claisen rearrangement between α-diazoketone 279 and allylic alcohol 278, installing the vicinal spirocyclopropane and tertiary alcohol moieties in a single, convergent step. Efforts to effect 6-membered ring closure of triketone 276 under basic and Lewis acid-catalyzed aldol conditions were uniformly unsuccessful. Efforts to effect 6-endo-trig cyclization of a SmI₂-derived ketyl radical furnished only spiro tricycle 296 via the 5-exo-trig mode of addition. Future efforts will focus on biasing substrate electronics to disfavor 5-exo-trig cyclization or employing a [2+2] cycloaddition/ring-opening strategy to prepare the illudane carbocyclic core. It is hoped that these endeavors will culminate in the total synthesis of enantioenriched (R)-269.

6.4. Experimental Section

6.4.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under a nitrogen atmosphere using freshly distilled solvents. All commercially obtained reagents were used as received. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 pre-coated plates (0.25 mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. High-performance liquid chromatography (HPLC) was performed with either a Rainin Microsorb 80-199-C5 or 80-120-C5 column. Infrared spectra were acquired using a MIDAC M-1200 FTIR. ¹H and ¹³C NMR spectra were recorded using Bruker AM500 or Bruker Avance 400/500.
MHz spectrometers. Chemical shifts are reported as $\delta$ values relative to internal chloroform ($^1$H $\delta$ 7.27 ppm, $^{13}$C $\delta$ 77.0 ppm) or benzene-$d_6$ ($^1$H $\delta$ 7.15 ppm). Where inseparable mixtures of diastereomers are isolated, $^1$H NMR spectral integration reflects a 1:1 mixture. Melting points are uncorrected. High-resolution mass spectra were acquired at the University of Illinois Mass Spectrometry Center.

6.4.2 Preparative Procedures

**Preparation of $\alpha$-Phenylthioketone 285**

$\alpha$-Phenylthioketone 285. A mixture of potassium tert-butoxide (27 mg, 0.240 mmol, 0.075 equiv) and 18-crown-6 (38 mg, 0.327 mmol, 0.010 equiv) in toluene (30 mL) was stirred for 1 hour at room temperature after which it was cooled to 0°C. $\alpha$-phenylthioacetone (283, 543 mg, 3.26 mmol, 1.0 equiv) was added dropwise over 15 min and the resulting mixture allowed to stir an additional 15 min. Cyclopentenone (284, 0.29 mL, 3.46 mmol, 1.1 equiv) was then added dropwise over 30 min. After 1 h, the reaction mixture was poured into brine (100 mL) and the biphasic mixture extracted with Et$_2$O (2 x 200 mL). The combined organic phases were dried over MgSO$_4$, filtered and concentrated. Purification of the residue was accomplished by flash chromatography (4:1 hexanes: ethyl acetate eluent) to furnish diketone 285 (445 mg, 55% yield, 1:1 mixture of diastereomers) as a clear, yellow oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.41-7.30 (comp. m,
10H), 3.53 (d, J=9.5 Hz, 1H), 3.50 (d, J=10.5 Hz, 1H), 2.70-2.50 (comp. m, 4H), 2.44-2.33 (comp. m, 3H), 2.32 (s, 3H), 2.28 (s, 3H), 2.24-2.11 (comp. m, 4H), 1.87 (m, 1H), 1.79 (m, 1H), 1.58 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 217.0, 216.9, 203.6, 27.5, 203.6, 133.0, 132.9, 132.1, 131.8, 129.3, 129.2, 128.5, 128.4, 62.9, 62.7, 43.5, 43.3, 38.4, 38.1, 36.9, 36.7, 28.0, 27.6, 27.5; IR (thin film/NaCl) 2969 (w), 2928 (w), 1742 (s), 1705 (s), 1481 (w), 1439 (w), 1356 (m), 1160 (m), 747 (m), 693 (m) cm$^{-1}$; HRMS (EI) m/z found: 248.0867 [calc'd for C$_{14}$H$_{16}$O$_2$S (M+): 248.0871].

Three-Step, Two-Pot Preparation of Diketone 282

Diketone 282. To a stirred mixture of potassium tert-butoxide (23 mg, 0.203 mmol, 0.073 equiv) and 18-crown-6 (25 mg, 0.0214 mmol, 0.078 equiv) in toluene (25 mL) at 0°C was added α-phenylthioacetone (283, 463 mg, 2.78 mmol, 1.0 equiv). The resulting mixture was allowed to stir for 15 min before cyclopentenone (284, 0.28 mL, 3.39 mmol, 1.2 equiv) was added dropwise over 30 min. The reaction mixture was allowed to stir for 2 h after which $m$-CPBA (576 mg, 3.34 mmol, 1.2 equiv) was added. After 5 min, the reaction mixture was decanted into a saturated solution of NaHCO$_3$ (150 mL) and the resulting two-phase mixture extracted with CH$_2$Cl$_2$ (3 x 100 mL). The combined organic
phases were dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure to furnish an orange residue that was purified by high-pressure elution through a plug (ca. 10 g) of silica gel (100% ethyl acetate eluent) to provide 610 mg of a yellow oil that was redissolved in toluene (6 mL). CaCO\textsubscript{3} (460 mg) was added and the mixture heated at reflux for 1 h. Once cooled to room temperature, the mixture was loaded directly onto a column of silica gel (20 g). Flash chromatography (hexanes: acetone 3:2 eluent) furnished diketone \textbf{282} (271 mg, 71% yield) as a clear, yellow oil. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 6.01 (m, 1H), 3.56 (s, 2H), 2.60 (m, 2H), 2.38 (m, 2H), 2.20 (s, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 209.2, 202.8, 173.0, 132.6, 47.3, 35.3, 31.6, 30.2; IR (thin film/NaCl) 3001 (w), 2922 (w), 1707 (s), 1676 (s), 1618 (m), 1435 (m), 1409 (m), 1359 (m), 1159 (m), 841 (w) cm\textsuperscript{-1}; HRMS (EI) \textit{m/z} found: 138.0675 [calc'd for C\textsubscript{8}H\textsubscript{10}O\textsubscript{2} (M\textsuperscript{+}): 138.0681].

\textbf{Preparation of \(\alpha\)-Diazoketone 279}

![Diagram of the reaction](image)

\(\alpha\)-Diazoketone 279. To a stirred solution of diketone \textbf{282} (132 mg, 0.96 mmol, 1.0 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (9 mL) at 0\textdegree C was added \(p\)-ABSA (265 mg, 1.16 mmol, 1.2 equiv). The resulting mixture was allowed to stir for 10 min at 0\textdegree C after which DBU (0.19 mL, 1.27 mmol, 1.3 equiv) was added dropwise, turning the solution deep red. After 10 min, the mixture was partially concentrated under reduced pressure, then loaded onto a column
of silica gel (10 g). Flash chromatography (100% ethyl acetate eluent) furnished α-diazoketone 279 (112 mg, 71% yield) as a yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.54 (s, 1H), 2.80 (m, 2H), 2.47 (m, 2H), 2.40 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 206.5, 187.7, 159.7, 125.8, 33.6, 28.9, 27.4; IR (thin film/NaCl) 2111 (s), 1701 (m), 1659 (s), 1558 (s), 1437 (w), 1385 (w), 1294 (w), 1219 (s), 1009 (w), 850 (m) cm$^{-1}$. Due to the unstable nature of this compound, satisfactory HRMS results could not be obtained.

**Preparation of α-Aryloxyketone (±)-290**

![Diagram](image)

α-Aryloxyketone (±)-290. To a stirred solution of acetal 289 (10.1 g, 48.3 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (350 mL) at 0°C was added slowly dropwise diisobutylaluminum hydride (11 mL, 63 mmol, 1.3 equiv). The resulting mixture was allowed to stir for 5 min, after which it was quenched by dropwise addition of a 20%(w/w) solution of potassium sodium tartrate (600 mL). Once addition was complete, the mixture was allowed to stir for 1 h with warming to room temperature. The organic layer of the biphasic mixture was separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2 x 100 mL). The combined organic phases were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to furnish a clear oil (10.2 g) that was used without further purification.
Dimethyl sulfoxide (7.3 mL, 102 mmol, 1.8 equiv) was added dropwise to a solution of oxalyl chloride (5.0 mL, 58.3 mmol, 1.0 equiv) in CH₂Cl₂ (280 mL) at -78°C. This mixture was allowed to stir for 15 min, before a solution of the above-prepared oil (10.2 g) in CH₂Cl₂ (20 mL) was added dropwise. Once addition was complete, the mixture was allowed to stir for 30 min after which triethylamine (27 mL, 194 mmol, 3.3 equiv) was added. The mixture was stirred for 30 min with warming to room temperature and then washed successively with 1N HCl (3 x 100 mL), water (1 x 200 mL), and saturated NaHCO₃ solution (2 x 100 mL). The organic phase was dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was distilled under vacuum (bp 150°C, 5 mmHg) to furnish known α-aryloxyketone (±)-290 (9.28 g, 92% yield) as a clear, colorless oil.²²

**Preparation of Allylic Ether (±)-292**

![Diagram](image-url)

**Allylic Ether (±)-292.** To a suspension of hexane-rinsed sodium hydride (60% dispersion in mineral oil, 853 mg, 21.3 mmol, 1.4 equiv) in THF was added cyclopropyl triphenylphosphonium bromide and the resulting mixture was heated at reflux for 2 h. The orange mixture was cooled to 50°C and a solution of ketone (±)-290 (3.16 g, 15.2 mmol, 1.0 equiv) and TDA-1 (293, 0.5 mL, 1.56 mmol, 0.10 equiv) in THF (5 mL) was added dropwise resulting in a gradual dulling of the bright orange solution color. The mixture was allowed to stir at 50°C for 1 h, after which it was cooled to room
temperature, filtered, and the filtrate concentrated under reduced pressure. Purification of
the residue by flash chromatography (10:1 hexanes: ethyl acetate eluent) furnished allylic
ether (±)-292 (2.22 g, 63% yield) as a clear, colorless oil. 1H NMR (400 MHz, CDCl3) δ
7.26 (m, 2H), 6.89 (m, 2H), 4.39 (d, J=11.6 Hz, 1H), 4.24 (q, J=6.4 Hz, 1H), 4.21 (d,
J=11.6 Hz, 1H), 3.81 (s, 3H), 1.84 (m, 3H), 1.32 (d, J=6.4 Hz, 3H), 1.10-1.01 (comp. m,
4H); 13C NMR (100 MHz, CDCl3) δ 158.9, 131.1, 129.2, 124.8, 119.1, 113.6, 77.5, 69.3,
55.2, 19.5, 14.6, 2.6, 1.3; IR (thin film/NaCl) 3045 (w), 2975 (m), 2934 (m), 2860 (m),
2836 (m), 1612 (m), 1513 (s), 1443 (m), 1369 (m), 1247 (s), 1083 (s), 1038 (s), 822 (m)
cm⁻¹; HRMS (EI) m/z found: 232.1462 [calc'd for C15H20O2 (M+): 232.1463].

Preparation of Allylic Alcohol (±)-278

Allylic Alcohol (±)-278. To a solution of allylic ether (±)-292 (353 mg, 1.52 mmol, 1.0
equiv) in CH₂Cl₂ (15 mL) was added H₂O (0.1 mL) followed by DDQ (375 mg, 1.65
mmol, 1.1 equiv). The mixture was allowed to stir for 12 min, after which it was filtered.
The filtrate was partially concentrated under reduced pressure at 0°C, then applied to a
short column of silica gel (4g). Flash chromatography (100% CH₂Cl₂ eluent, pooled
fractions concentrated under reduced pressure at 0°C) furnished allylic alcohol (±)-278
(106 mg, 62% yield) as a clear, colorless oil. 1H NMR (400 MHz, CDCl3) δ 4.48 (q,
J=6.5 Hz, 1H), 1.84 (m, 3H), 1.81 (br. s, 1H), 1.33 (d, J=6.4 Hz, 3H), 1.15 (m, 2H), 0.95
α-Hydroxyketone (±)-277. To a stirred solution of allylic alcohol (±)-278 (37 mg, 0.326 mmol, 1.0 equiv) and α-diazoketone 279 (78 mg, 0.476 mmol, 1.5 equiv) in toluene (5 mL) was added Rh₂(tpa)₄ (6.5 mg, 0.005 mmol, 0.0015 equiv). The mixture was immediately immersed in a preheated oil bath and heated under reflux for 5 min, after which it was cooled to room temperature and concentrated under reduced pressure. Flash chromatography of the residue (3:2 hexanes: ethyl acetate eluent) furnished α-hydroxyketone (±)-277 (28 mg, 35% yield) as a clear, yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 6.79 (t, J=2.0 Hz, 1H), 5.37 (m, 1H), 3.42 (s, 1H), 2.84 (m, 2H), 2.48 (t, J=5.0 Hz, 2H), 1.60 (m, 3H), 1.48 (m, 3H), 1.29 (s, 3H), 1.00 (ddd, J=4.2, 5.8, 9.8 Hz, 1H), 0.90 (ddd, J=4.6, 6.0, 9.9 Hz, 1H), 0.78 (ddd, J=4.5, 6.0, 9.5 Hz, 1H), 0.54 (ddd, J=4.2, 6.0, 9.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 210.4, 203.8, 166.7, 137.0, 136.2, 127.0, 81.5, 35.3, 34.4, 28.4, 23.4, 17.0, 13.6, 12.3, 9.6; IR (thin film/NaCl) 3477 (br. m),
Preparation of Triketone (±)-276

Triketone (±)-276. A solution of α-hydroxyketone (±)-277 (97 mg, 0.392 mmol, 1.0 equiv) in methanol (6 mL) was cooled to -78°C. The surface of the reaction mixture was exposed to a stream of ozone for 6 min, after which the mixture was purged by bubbling N₂(g) through the solution for 20 min. Dimethylsulfide (0.75 mL) was added and the mixture warmed to 0°C. After 30 min at this temperature, the mixture was concentrated under reduced pressure and the residue purified by flash chromatography (3:7 hexane: ethyl acetate eluent) to furnish triketone (±)-276 (66 mg, 71% yield) as a clear, colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 6.78 (t, J=2.0 Hz, 1H), 4.12 (s, 1H), 4.00-2.85 (comp. m, 2H), 2.48 (m, 2H), 1.87 (s, 3H), 1.55 (m, 1H), 1.41-1.23 (comp. m, 3H), 1.10 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 210.7, 210.2, 204.2, 204.2, 167.1, 135.5, 79.4, 41.6, 34.4, 28.4, 23.2, 21.3, 14.8, 10.7; IR (thin film/NaCl) 3457 (br. w), 2983 (w), 2932 (w), 1711 (s), 1677 (s), 1367 (m), 1120 (w), 1102 (m), 940 (w) cm⁻¹; HRMS (FAB) m/z found: 237.1128 [calc'd for C₁₃H₁₇O₄ (M+H): 237.1127].
**Preparation of Spirocycle (±)-296**

![Reaction Scheme](image)

**Spirocycle (±)-296.** To a stirred solution of triketone (±)-276 (5 mg, 0.021 mmol, 1.0 equiv) in THF (0.5 mL) at -78°C was added dropwise a solution of samarium (II) iodide (ca. 0.1 M, 315 μL). The mixture was allowed to stir for 10 min, after which it was quenched cold with a saturated solution of NH₄Cl (1 mL) and allowed to warm to room temperature. The biphasic mixture was extracted with ethyl acetate (3 x 2 mL) and the combined organic phases dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography furnished spirocycle (±)-296 (3.8 mg, 76% yield) as a white solid. Crystals suitable for X-Ray analysis were obtained by slow evaporation of a solution of 296 in ethyl acetate. 

$^1$H NMR (400 MHz, CDCl₃) δ 2.81 (br. s, 1H), 2.68-2.60 (comp. m, 1H), 2.56 (br. s, 1H), 2.48-2.35 (comp. m, 2H), 2.29 (m, 1H), 2.27 (m, 1H), 2.15 (m, 1H), 1.04 (s, 3H), 0.98 (s, 3H), 0.88-0.75 (comp. m, 4H); $^{13}$C NMR (125 MHz, CDCl₃) δ 218.5, 215.4, 80.4, 61.7, 45.6, 37.1, 34.9, 24.3, 20.6, 16.5, 10.7, 2.2; IR (thin film/NaCl) 3440 (br. m), 2976 (w), 2932 (w), 1744 (s), 1458 (w), 1401 (w), 1380 (w), 1133 (m), 902 (m) cm⁻¹; HRMS (FAB) m/z found: 238.1205 [calc'd for C₁₃H₁₈O₄ (M⁺): 238.1205].
Preparation of Ketone (±)-297

Ketone (±)-297. To a stirred solution of diketone (±)-277 (33 mg, 0.132 mmol, 1.0 equiv) in THF (2 mL) at 0°C was added, very slowly dropwise, K-Selectride® (1.0 M solution in THF, 130 µL, 0.130 mmol, 1.0 equiv) over a 5 min interval. The mixture was allowed to stir for 5 min, after which it was quenched with a saturated solution of NH₄Cl (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the residue was accomplished by flash chromatography (1:1 hexanes: ethyl acetate eluent) to furnish ketone (±)-297 (12 mg, 37% yield, 1.5:1 mixture of diastereomers) as a clear, yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 6.79 (q, J=2.5 Hz, 1H), 6.76 (q, J=2.5 Hz, 1H), 5.41 (m, 2H), 5.32 (m, 2H), 5.07 (m, 2H), 4.02 (s, 1H), 3.97 (s, 1H), 2.84-2.67 (comp. m, 2H), 2.59-2.31 (comp. m, 4H), 1.71 (m, 2H), 1.60 (t, J=1.5 Hz, 3H), 1.58 (t, J=1.5 Hz, 3H), 1.49 (m, 3H), 1.47 (m, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.02-0.89 (comp. m, 4H), 0.79 (m, 2H), 0.51 (ddd, J=5.2, 7.0, 12.1 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 202.8, 143.9, 143.5, 142.5, 136.4, 126.3, 126.1, 80.4, 80.9, 78.5, 78.2, 35.5, 35.5, 32.7, 32.7, 31.1, 31.0, 23.4, 16.9, 16.8, 13.5, 12.8, 12.8, 9.7, 9.6; IR (thin film/NaCl) 3433 (br. s), 2972 (m), 2935 (m), 2860 (m), 1710 (m), 1653 (s), 1448 (m), 1377 (m), 1125 (s), 1056
(s), 917 (w) cm$^{-1}$; HRMS (FAB) $m/z$ found: 233.1541 [calc'd for C$_{15}$H$_{21}$O$_2$ (M-H$_2$O): 233.1542].

6.5 Notes and References


(28) Such tridentate ligation has been employed previously to direct the stereochemical outcome of SmI$_2$-derived ketyl radical cyclization processes, see: Molander, G. A.; McWilliams, J. C.; Noll, B. C. J. Am. Chem. Soc. 1997, 119, 1265.


APPENDIX SIX: SPECTRA RELEVANT TO CHAPTER SIX
Figure A.6.1 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 285
Figure A.6.3 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 285.

Figure A.6.2 FTIR Spectrum (thin film/NaCl) of Compound 285.
Figure A.6.4 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 282.
Figure A.6.6: $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 282.

Figure A.6.5: FTIR Spectrum (thin film/NaCl) of Compound 282.
Figure A.6.7 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 279.
Figure A.6.9 $^{13}$C NMR (100 MHz, CDCl₃) of Compound 279.

Figure A.6.8 FTIR Spectrum (thin film/NaCl) of Compound 279.
Figure A.6.10 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 292.
Figure A.6.12 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 292.

Figure A.6.11 FTIR Spectrum (thin film/NaCl) of Compound 292.
Figure A.6.13 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 278.
Figure A.6.14 FTIR Spectrum (thin film/NaCl) of Compound 278.

Figure A.6.15 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 278.
Figure A.6.16 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 277.
Figure A.6.18 $^{13}$C NMR (100 MHz, CDCl$_3$) of Compound 277.

Figure A.6.17 FTIR Spectrum (thin film/NaCl) of Compound 277.
Figure A.6.19 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 276.
Figure A.6.21 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 276.

Figure A.6.20 FTIR Spectrum (thin film/NaCl) of Compound 276.
Figure A.6.22 $^1$H NMR (400 MHz, CDCl$_3$) of Compound 296.
Figure A.6.23 FTIR Spectrum (thin film/NaCl) of Compound 296.

Figure A.6.24 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 296.
Figure A.6.25 $^1$H NMR (500 MHz, CDCl$_3$) of Compound 297.
Figure A.6.26 FTIR Spectrum (thin film/NaCl) of Compound 297.

Figure A.6.27 $^{13}$C NMR (125 MHz, CDCl$_3$) of Compound 297.
APPENDIX SEVEN: X-RAY CRYSTALLOGRAPHY REPORTS
RELEVANT TO CHAPTER SIX
X-RAY CRYSTALLOGRAPHY REPORT FOR SPIROCYCLE 296

A. Crystal Data
Empirical Formula
C_{13}H_{18}O_{4}
238.28
Formula Weight
colorless, plate
Crystal Color, Habit
0.05 X 0.10 X 0.25 mm
Crystal Dimensions
monoclinic
Crystal System
Primitive
Lattice Type
a = 9.745(1) Å
b = 7.680(1) Å
c = 17.163(1) Å
Lattice Parameters
β = 104.086(4)°
V = 1245.9(2) Å^3
Space Group
P2_{1}/c (#14)
Z value
4
Dcalc
1.270 g/cm^3
F000
512.00
µ(MoKα)
0.93 cm^(-1)

B. Intensity Measurements
Diffractometer
Nonius Kappa CCD
Radiation
MoKα (λ = 0.71069 Å)
graphite monochromated
Take-off Angle
2.8°
Crystal to Detector Distance
33 mm
Temperature
-90.0°C
Scan Rate
80s/frame
Scan Width
2.0°
20max
52.1°
No. of Reflections Measured
Total: 2645
Corrections
Lorentz-polarization
C. Structure Solution and Refinement

Structure Solution Direct Methods (SIR92)
Refinement Full-matrix least-squares
Function Minimized \[ \Sigma w \left( |F_o| - |F_c| \right)^2 \]
Least Squares Weights \( 1/\sigma^2(F_o) \)
p-factor 0.0100
Anomalous Dispersion All non-hydrogen atoms
No. Observations (I>3.00\(\sigma(I)\)) 1376
No. Variables 226
Reflection/Parameter Ratio 6.09
Residuals: R, Rw 0.040 ; 0.040
Goodness of Fit Indicator 1.60
Max Shift/Error in Final Cycle 0.00
Maximum peak in Final Diff. Map 0.22 e\(^-/\text{Å}^3\)
Minimum peak in Final Diff. Map -0.20 e\(^-/\text{Å}^3\)

<table>
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<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Beq</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(1)</td>
<td>0.5677(2)</td>
<td>0.4493(2)</td>
<td>0.41698(10)</td>
<td>4.66(5)</td>
</tr>
<tr>
<td>O(2)</td>
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APPENDIX EIGHT: NOTEBOOK CROSS-REFERENCE
NOTEBOOK CROSS-REFERENCE

The following notebook cross-reference table has been included to facilitate access to the original spectroscopic data acquired for the compounds presented in this dissertation. Each compound is assigned a folder name (e.g., GAM14-179-3) that corresponds to an archived characterization folder containing hard copies of all spectroscopic data. The folder name also serves as a notebook citation. For example, GAM14-179-3 corresponds to notebook GAM 14, page 179, compound 3. The spectral filenames provided for each compound are organized by type (i.e., $^1$H NMR, $^{13}$C NMR, IR), and correspond to files stored on CD-ROM. All notebooks, characterization folders, and spectral data are stored in the Wood Group archives.

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ABOUT THE AUTHOR

George A. Moniz was born October 16, 1974, the second son of Evelyn S. and George E. Moniz, Jr. George was raised along with his brother Daniel in Swansea, Massachusetts, a coastal town roughly 50 minutes south of Boston situated between the cities of Fall River, Massachusetts and Providence, Rhode Island. He attended the E. S. Brown Elementary School in Swansea for two years before moving to St. Michael’s School in Fall River for the remainder of his elementary education. He then attended Bishop Connolly High School also in Fall River where he was a member of the National Honor Society and a varsity letter recipient, graduating summa cum laude in 1992.

George selected chemistry as his major when he began his undergraduate studies at the University of Massachusetts Dartmouth and began to develop a fondness for the field, enjoying both laboratory manipulations and the theoretical aspects of the science. He became interested in organic chemistry after taking classes in the subject in his sophomore year, attracted by the idea that a person could construct complex molecules by stringing along a series of established reactions.

During his freshman and sophomore years, George helped pay for college by working part-time at a local pharmacy where he saw the pharmaceutical applications of organic chemistry. Deciding to pursue a career in the pharmaceutical industry and seeking research experience, George approached Professor Gerald B. Hammond, his instructor for first-semester organic chemistry, for a position in his research group. George spent two enjoyable years in the Hammond group working on a number of projects and co-authoring several scientific papers. He financed the remainder of his undergraduate education by winning monetary awards and fellowships and graduated summa cum laude in 1996. The following fall, George began graduate studies at Yale University. He received his Master’s Degree in 1998 and his Doctorate in 2001 under the direction of Professor John L. Wood. George will be returning to Massachusetts where he has accepted a post-doctoral position with Professor David A. Evans at Harvard University. He has been awarded a National Institutes of Health post-doctoral fellowship.