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Vinyl Cations As Cyclopentenone Precursors Via C–h Insertion Or Alkene Addition Reactions

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University of Vermont

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VINYL CATIONS AS CYCLOPENTENONE PRECURSORS VIA C–H INSERTION
OR ALKENE ADDITION REACTIONS

A Dissertation Presented

by

Magenta Julliet Hensinger

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ABSTRACT

We report that Lewis acid mediated reactions of β-hydroxy-α-diazo carbonyls provide facile access to vinyl cation intermediates, which can form mono- and bicyclic cyclopentenone ring systems. Vinyl cations are *sp* hybridized cations that can be exploited as carbene surrogates or as electrophiles. The methodology reported in this dissertation is important because cyclopentenone rings are common motifs in natural products or can be used as synthetic intermediates.

The first portion of this dissertation will discuss vinyl cations we've used as carbene surrogates in metal free C–H insertion reactions. Treating β-hydroxy-α-diazo carbonyls with a Lewis acid provided vinyl cation intermediates after loss of hydroxide and nitrogen gas. A 1,2-methylene shift then provided a vinyl cation which can insert into an inert C–H bond to give mono- and bicyclic cyclopentenone rings. Modification at the point of insertion to a more substituted center provides a competitive elimination type reaction. This result sparked a deeper investigation into the concertedness of the C–H insertion. Further expansion of this work included migratory aptitude studies in the 1,2-shift step for non-symmetric aliphatic and tetralone systems.

The second portion of this dissertation forms vinyl cations in a similar fashion, but uses them as electrophiles that are susceptible to a nucleophilic attack by a pendant alkene. This reaction, which we hypothesize proceeds through a unique acylium intermediate, forms α-alkylidene cyclopentenones in good yields. The efficiency of this reaction was influenced by the group adjacent to the vinyl cation. Aryl groups which were electron rich or were sterically hindered formed α-alkylidene cyclopentenones in higher yields than electron poor aryl rings or alkyl groups. Other nucleophiles were investigated but were not productive compared the alkene nucleophile.

CITATIONS

Material from this dissertation has been published in the following forms:

†Authors contributed equally, *Primary Investigator

Hensinger, M. J., Dodge, N. J., Brewer, M..* (2020). Substituted α-alkylidene cyclopentenones via the intramolecular reaction of vinyl cations with alkenes. Organic Letters, 22, 497-500.

Cleary, S. E.†, **Hensinger, M. J**.†, Qin, Z.-X., Hong, X.*, Brewer, M..* (2019). Migratory aptitudes in rearrangements of destabilized vinyl cations. The Journal of Organic Chemistry, 84, 15154-15164.

DEDICATION

I dedicate this thesis to my loving family, Randy, Donna, & Jade Hensinger, and grandmother Helen Bauman for their constant support and encouragement of my curiosity.

ACKNOWLEDGMENTS

This thesis would not be possible without the support of the many wonderful people in my life. First, I would like to acknowledge my amazing advisor, Professor Matthias Brewer, for his unwavering support and kindness shown to me during my dissertation. Words cannot express how much I appreciate having him as a PI. He is a wonderful leader and mentor, who encouraged a healthy work-life balance and curiosity in my dissertation project. I would not be the chemist I am today without his guidance. Thank you so much.

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I would not be where I am today without the support of my research group past and present. Dr. Geoffrey Giampa, Dr. Ramya Srinivasan, Dr. Nicolas Dodge, and Dr. Jian Fang provided me with technical support and were key resources when I started my graduate career. I especially want to thank Dr. Sarah Cleary, my amazing mentor, who worked closely with me on the vinyl cation project. To my current group members, Evan

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Ac_2O	Acetic anhydride
ACN	Acetonitrile
AcOH	Acetic acid
$AgBF_4$	Silver tetrafluoroborate
AgOTf	Silver trifluoromethanesulfonate
BCF	Tris(pentafluorophenyl)borane
BF_3	Boron Trifluoride
$BF_3 \cdot Et_2O$	Boron trifluoride etherate
BF_2OH	Difluorohydroxyborane
Bn	Benzyl
Br_2	Bromine
Bu_4NPF_6	Tetrabutylammonium hexafluorophosphate
CD_3I	Iodomethane d3
$(C_6F_5)_3B$	Tris(pentafluorophenyl)borane
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
$C_2H_4Cl_2$	1,2-Dichloroethane
CH_3COOH	Acetic acid
CH_2N_2	Diazomethane
$CaCl_2$	Calcium chloride
CO	Carbon monoxide
$CoBr_2$	Cobalt (II) bromide
$(COCl)_2$	Oxalyl chloride
$Co_2(CO)_8$	Dicobalt carbonyl
CSA	Camphorsulfonic acid
CuCl	Copper (I) chloride
CuI	Copper (I) iodide
Cu(I)O	Copper (I) oxide
$Cu(hfacac)_2$	Copper(II) hexafluoroacetylacetonate hydrate
Cy	Cyclohexyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density-functional theory
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMPU	N,N'-Dimethylpropyleneurea
DMSO	Dimethyl sulfoxide
dr	distereotopic ratio
DTBP	Di-tert-butyl peroxide
$Dy(OTf)_3$	Dysprosium (III) trifluoromethanesulfonate
EDG	Electron donating group

Ee	Enantiomeric excess
$Et_3Al_2Cl_3$	Ethylaluminium sesquichloride
Et_3N	Triethylamine
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_3SiH	Triethyl silane
EWG	Electron withdrawing group
FDA	Food and drug administration
$FeCl_3$	Iron (III) chloride
H_2	Hydrogen
HCl	Hydrochloric acid
HFIP	Hexaluoro-2-propanol
HNO_2	Nitrous acid
H_2O	Water
H_2SO_4	Sulfuric acid
HWE	Horner-Wadsworth-Emmons
I_2	Iodine
$In(OTf)_3$	Indium (III) trifluoromethanesulfonate
JACS	Journal of the American Chemical Society
KCN	Potassium Cyanide
K_2CO_3	Potassium carbonate
KHMDS	Potassium bis(trimethulsilyl)amide
KIE	Kinetic isotope effect
KOAc	Potassium acetate
KOH	Potassium hydroxide
L.A.	Lewis acid
LDA	Lithium diisopropyl amide
LiCl	Lithium Chloride
$LiNTf_2$	Bis(trifluoromethane)sulfonimide
$LiPF_6$	Lithium hexafluorophosphate
*m*CPBA	*meta*-Chloroperoxybenzoic acid
MeCN	Acetonitrile
MeOAc	Methyl acetate
MeOD	Deuterated methanol
MeOH	Methanol
$(Me)_3SiCHN_2$	Trimethylsilyldiazomethane
MgO	Magnesium oxide
$MgSO_4$	Magnesium sulfate
MsCl	Methanesulfonyl chloride
MW	Microwave
*n*BuLi	*n*-Butyl lithium
$(nBu)_4NCl$	Tetra-*n*-butylammonium chloride
$NaBH_4$	Sodium borohydride

NaHCO$_3$	Sodium bicarbonate
NaH	Sodium hydride
NaI	Sodium iodide
NaOMe	Sodium methoxide
Na$_2$SO$_4$	Sodium sulfate
NMR	Nuclear magnetic resonance
O$_3$	Ozone
(OMe)$_3$CH	Trimethoxymethane
p-ABSA	4-Acetamidobenzenesulfonyl azide
Pd/C	Palladium on carbon
PdCl$_2$(MeCN)	Bis(acetonitrile)palladium dichloride
Ph	Phenyl
PhCH$_3$	Toluene
PhH	Benzene
PhI(OAc)$_2$	(Diacetoxyiodo)benzene
PKR	Pauson-Khand Reaction
PMP	*p*-Methoxyphenyl
P$_2$O$_5$	Phosphorus pentoxide
PtO	Platinum oxide
PPh$_3$	Triphenylphosphine
(PPh$_3$)AuCl	Chloro(triphenylphosphine)gold(I)
p-TsN$_3$	Tosyl azide
Rh$_2$(OAc)$_4$	Rhodium(II) acetate dimer
SnCl$_4$	Tin (IV) chloride
*t*BuOMe	*tert*-Butyl methoxide
TBS	*tert*-Butyldimethulsilyl ether
THF	Tetrahydrofuran
Tf	Triflate
TMS	Trimethylsilane
TMSCH$_2$N$_2$	Trimethulsilyldiazomethane
TMSCN	Trimethylsilyl cyanide
TS	Transition state
TsCl	Tosyl chloride
UV	Ultraviolet
WCA	Silylium-monocarba-*closo*-dodecaborate salts
ZnBr$_2$	Zinc bromide

CHAPTER 1: GENERAL BACKGROUND ON α-DIAZO CARBONYLS, C–H INSERTION, VINYL CATIONS, AND 5-MEMBERED RINGS

This dissertation describes experimental studies that elucidate the ability of vinyl cations to act as carbene surrogates and as electrophiles in reactions that generate cyclopentenone ring systems. These studies were made possible by the observation that vinyl cations can be accessed by the reaction of β-hydroxy-α-diazo carbonyls with a Lewis acid. The Brewer group has a long-standing interest in studying nitrogen containing molecules and has exploited them for use in bond fragmentation reactions, C–H insertions, dipolar cycloadditions, and now as vinyl cation precursors. In Chapter 1, I will introduce the topics that are central to my dissertation, including diazo carbonyl compounds, C–H insertions, and vinyl cations.

In Chapter 2, I will discuss the C–H insertion reaction I developed which uses vinyl cations as carbene surrogates to insert at a remote, unactivated C–H bond. Treating β-hydroxy-α-diazo carbonyls with a Lewis acid provided vinyl cation intermediates after loss of hydroxide and nitrogen gas. A 1,2-methylene shift then provided a vinyl cation which can insert into an inert C–H bond to give mono- and bicyclic cyclopentenone rings. The identity of the products formed from this reaction varies depending on the point of insertion, which allowed for further probing of the mechanism both experimentally and computationally. Furthermore, in Chapter 3, I describe my work to gain a more detailed understanding of how vinyl cations react. This work focused on understanding which groups are more likely to undergo a 1,2-shift across the alkene of a vinyl cation, i.e. the migration across the vinyl cation of nonequivalent groups.

Finally, in Chapter 4, I will discuss how these vinyl cations can be used as electrophiles that are susceptible to intramolecular attack by a pendant alkene. Using vinyl cations as carbene surrogates and as electrophiles generates cyclopentenone ring systems. These systems are prevalent themselves in natural products, and they can be modified to access alternative scaffolds or functional groups. Thus, this research should have beneficial use in natural product total syntheses that contain a 5-membered ring system.

1.1 The Diazo Functional Group

The diazo functional group is a versatile building block that has many synthetic applications, most notably as carbene precursors (Scheme 1.1). However, non-stabilized diazoalkanes are known to be hazardous reagents, due to toxicity and explosivity, with diazomethane (CH_2N_2) being the most dangerous.[1, 2]
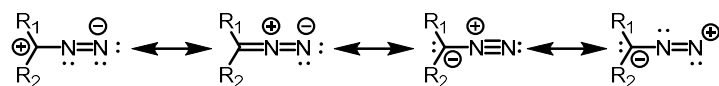
Scheme 1.1 Diazo functional group and its resonance structures

Fortunately, the diazo group can be stabilized by aryl rings or electron withdrawing groups such as ketones, esters, phosphoryl, and sulfonyl substituents (Figure 1.1). These types of diazo compounds are much safer to work with.[3]
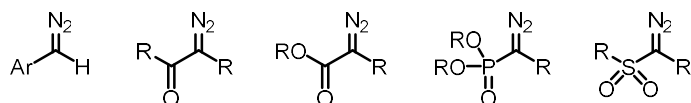
Figure 1.1 Stabilization of diazo functional group

1.1.1   Preparation of Diazo Carbonyls

Because diazo compounds have many uses in synthesis many methods have been devised prepare these compounds. These include: (1) acylation of diazoalkanes, (2) diazo-group transfer, (3) diazotization, (4) triazene fragmentation, (5) cleavage of *N*-alkyl-*N*-

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nitrosos, (6) oxidation of hydrazones, to name a few (Scheme 1.2).[2, 4, 5, 6, 7] Advanced safety

measures in the preparation of diazo carbonyls make them attractive and accessible

intermediates that can be taken advantage of.[8]
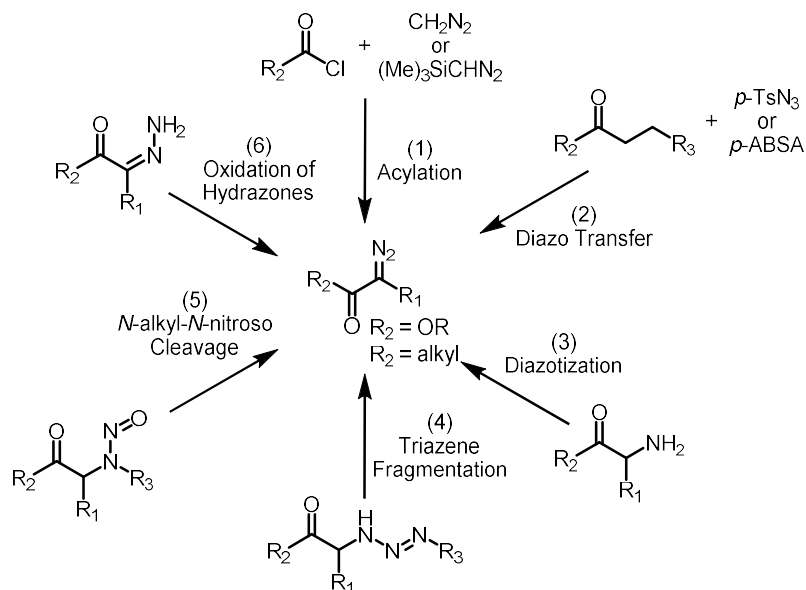
Scheme 1.2 Methods to form diazo carbonyl compounds

Formation of diazo carbonyls through acylation involves the use of acid chloride or

anhydride precursors that react with an excess of diazomethane (Scheme 1.2, (1)).[9]

Although this is a fine method to form diazocarbonyls, there are some drawbacks.

Diazomethane is prepared from rearrangement of nitrosoamide precursors, the most

common being Diazald, or *N*-methyl-*N*-nitroso-toluenesulfonamide. However,

diazomethane is a gas which is toxic and explosive. Diazomethane should be freshly

prepared as an ethereal solution using specialty glassware with flame-polished joints

behind a blast shield.[10] Trimethylsilyldiazomethane ($TMSCH_2N_2$) is often used as a non-

explosive substitute to diazomethane, although it is just as toxic.[11]

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This method forms terminal diazo groups, so formation of diazo carbonyls through acylation would not work with cyclic substrates and more substituted acyclic systems.[9] Diazo transfer reactions are an easy and convenient method to incorporate diazo functionality onto these systems, and is much safer than using diazomethane. A donor transfers a diazo group to the acceptor.[12] A representative example is shown in Scheme 1.2. The reaction proceeds by deprotonation of the α-keto ester **1.1** with a base to generate the enolate, which attacks the terminal nitrogen on the sulfonyl azide. Proton transfer, then loss of sulfonamide generates diazo carbonyl **1.4**.[13] Diazo transfer reactions are generally the preferred method to form diazo carbonyls today.
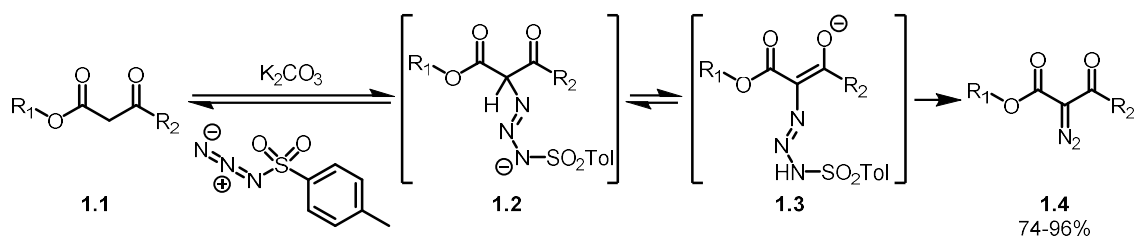
Scheme 1.3 Formation of diazo carbonyls by diazo transfer

Other, less common methods of forming diazo carbonyls include diazotization, triazene fragmentation, and *N*-alkyl-*N*-nitroso cleavage. Diazotization is the transformation of a primary or aryl amine to a diazo group using either nitrous acid or a nitrite. This method is commonly used to form diazo's from of α-animo carbonyl compounds as shown in Scheme 1.4,[14, 15] and it can be used to form fresh ethyl diazoacetate.[9]
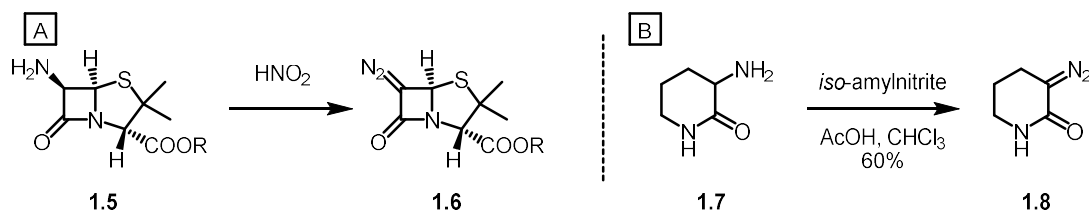
Scheme 1.4 Diazotization to form α-amino carbonyl compounds

The preparation of diazo carbonyls via triazene fragmentation is uncommon. The triazene starting material is traditionally prepared by either an addition of nitrogen nucleophiles to diazonium salts or by treatment of alkyl azides with the appropriate organometallic reagent (such as a Grignard or alkyl lithium). However, these methods are not suitable for compounds containing sensitive functional groups.[5, 16] The Raines group developed a mild method to access the triazene starting material, and thus diazo carbonyls, using phosphine reagent **A** (Scheme 1.5).[5]
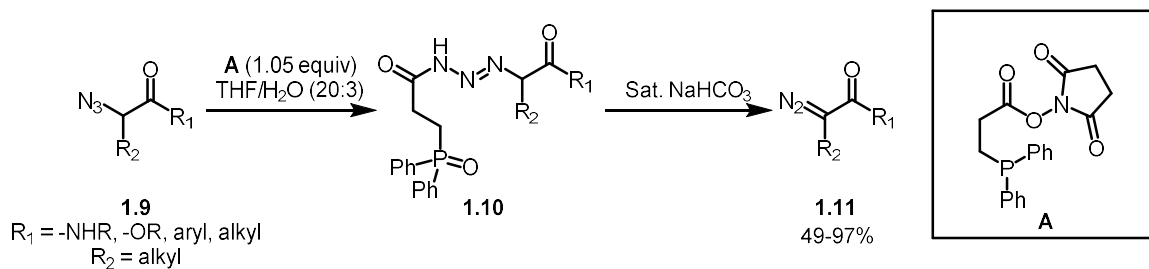
Scheme 1.5 Mild method to access triazene starting material leading to diazo carbonyls

1.1.2   Reactions of diazo carbonyls

Once prepared, there are many methods to take advantage of diazo carbonyl reactivity, and because of that, they are common intermediates or reagents in natural product syntheses. Diazo carbonyls can be used in reactions such as: (1), α,α-substitution reactions, (2) Wolff rearrangements, (3) cyclopropanation, (4) ylide formation, (5) C–H/X–H

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insertion, and (6) 1,3-dipolar cycloadditions (Scheme 1.6). I will highlight some of these methodologies in notable natural product total syntheses.
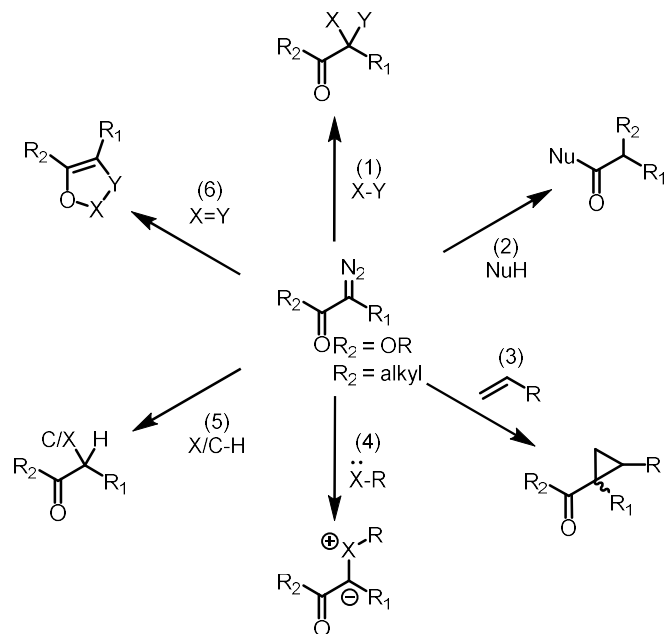
Scheme 1.6 Diazo carbonyls used in a wide variety of transformations

Diazo carbonyls are used in the Wolff rearrangement, which results in a 1,2-shift to gove a ketene intermediate that then can react with nucleophiles.[8, 17] Snyder and Corey took advantage of this rearrangement to access members of the dolabellane diterpenoid family. From diazo ketone **1.12** they formed the ring-contracted ester **1.15** via ketene **1.14** and carbene intermediate **1.13** in 68% yield (Scheme 1.7).[18]
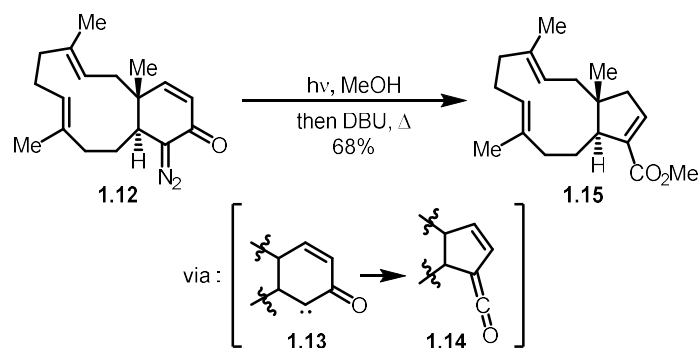
Scheme 1.7 Wolff rearrangement leading to precursor for dolabellane natural products

One of the most extensively studied uses of α-diazo carbonyls is their ability to act as carbene precursors that act in cyclopropanation reactions of alkenes or participate in C–H and X–H insertion reactions. The sheer bulk of research in these fields has provided numerous reviews outlining these methods.[8, 19, 20, 21, 22, 23, 24, 25] Typically, transition metal catalysts such as rhodium, ruthenium, cobalt, palladium, and copper are used to activate the carbene formed from diazo decomposition, which can then react with an olefin to generate the cyclopropane or react with a C–H/X–H bond.[8]

Reisman and coworkers utilized α-diazo carbonyls when installing a cyclopropane in their total synthesis of (+)-Salvileucalin B. Starting from diazo ketone **1.16**, they installed the cyclopropane **1.17** moiety in 65% yield (Scheme 1.8, A).[26] Cyclopropanes formed from α-diazo carbonyls are commonly used in the Buchner reaction, in which cycloheptatrienes **1.19** are formed from cyclopropane ring opening (Scheme 1.8, B). However, this was not the case in Reisman and coworkers synthesis, since the Buchner reaction product would contain an *anti*-Bredt olefin and thus be geometrically strained (Scheme 1.8, B).[8, 27]
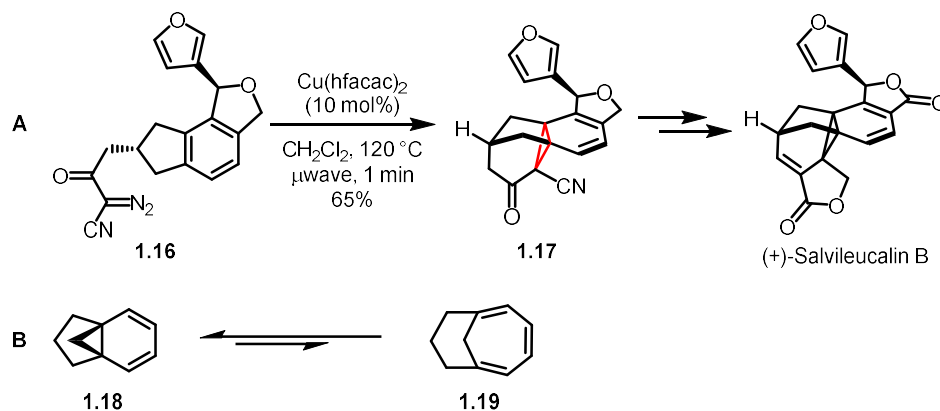
Scheme 1.8 a) Reisman and coworkers (+)-Salvileucalin B synthesis utilizing cyclopropanation strategy, b) Unlikely Buchner reaction due to geometric constraints

Other exploitations of diazo carbonyls involve the formation of ylides, which arise from carbenes and carbenoids reacting with a Lewis basic heteroatom species. These ylides can then be used in [2,3]-sigmatropic rearrangements, [1,2]-insertions, or dipolar cycloadditions (Scheme 1.9).[8]
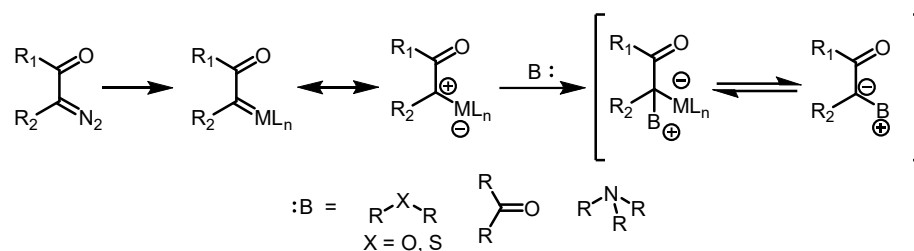
Scheme 1.9 Ylides formed from carbene/carbenoid reaction with Lewis base

This methodology has been applied in many natural product syntheses; one excellent example comes from the Wood group, who used ylide **1.21**, formed from diazo ketone **1.20**, in a 1,3-dipolar cycloaddition with a propiolate ester (Scheme 1.10). Impressively, they were able to form diastereomerically pure oxabicycle **1.22** in 75% yield.[28]
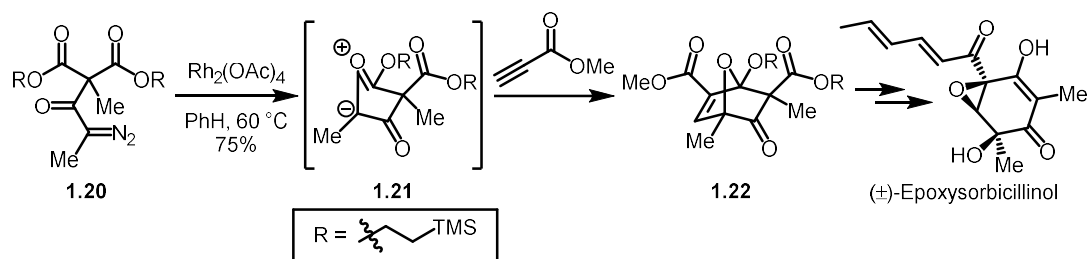
Scheme 1.10 Wood and coworkers Epoxysorbicillinol synthesis with key 1,3-cycloaddition

The Brewer group has taken advantage of diazo carbonyl compounds previously to access a library of tethered aldehyde ynoates through a fragmentation reaction (Scheme 1.11).[29, 30] Starting from γ-silyloxy-β-hydroxy-α-diazoester **1.23**, dihydroxylation via Lewis acid generates vinyl diazonium **1.24**. A Grob-like C–C bond fragmentation occurs from lone pair donation of the γ-oxygen atom and liberation of nitrogen gas to provide ynoate **1.25**. Loss of the *t*-butyldimethylsilyl group gives aldehyde ynoate products (**1.26**). The Brewer group was able to synthesize these fragmentation products in good to excellent yields through this methodology,[29] and later expand on this work to access tethered aldehyde ynones when the starting diazo carbonyl was a diazo ketone.[30] This methodology was applied in the total synthesis of demissidine, cycloclavnine, and the C,D,E core of the *aspidosperma* alkaloids.[31, 32]
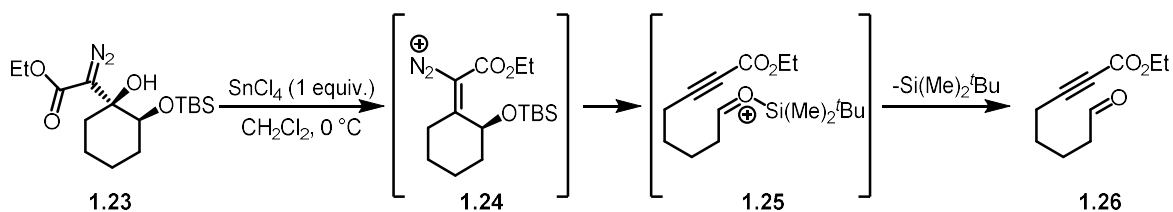
Scheme 1.11 Fragmentation reaction from diazo carbonyl precursors

1.2 C–H Insertion Reactions

The diazo functional group are often used as carbene precursors for C–H insertion reactions. A C–H insertion reaction results in the formation of a new carbon-carbon bond

via the insertion of a carbene into a carbon-hydrogen bond through a three membered transition state.[23] As formation of C–C bonds is a major challenge in organic synthesis, the C–H insertion method is attractive, since it allows direct bond formation at a typically inert center. In addition, carbon-hydrogen bonds are fundamental in organic compounds and natural products, so manipulation and activation of these bonds is of great interest.

1.2.1   C–H Insertion with Use of Transition Metal Catalysts

Carbenes and carbenoids often react in C–H insertions. A carbene is a divalent charge neutral carbon that has a nonbonding electron pair. Carbenes can adopt a singlet state, in which the electrons have opposite spins, or a triplet state, in which the electrons have parallel spins.[25, 33] A carbenoid is when a carbene is bound to an organometallic complex, this increases the stability of the carbene and allows for greater control over the reactivity and the chemo-, regio- and stereoselectivity (Figure 1.2).[24]

singlet carbene   triplet carbene   carbenoid
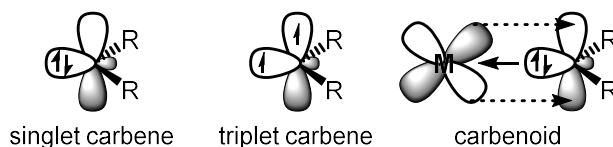
Figure 1.2 Carbenes and Carbenoids

The diazo group can be activated by a transition metal catalyst, such as copper, ruthenium, rhodium, cobalt, palladium, and others to form carbenoids. As described by Doyle and coworkers, the reaction initiates with the formation of metal carbenoid **1.27** from the transition metal catalyst and a diazo starting material. The carbenoid will react with a C–H bond, in which the C–C bond forming reaction occurs through a triangular transition state **TS1.1** as the metal dissociates (Scheme 1.12).[34]
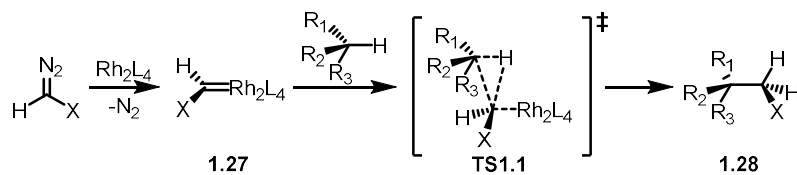
Scheme 1.12 C–H insertion leading to new C–C bond

Factors that change the reactivity and selectivity of the carbenoid depend largely on the electronic nature of groups adjacent to the carbenoid, the transition metal used, sterics, and the chemical properties of the ligands on the metal. Electron withdrawing groups (EWG) increase the electrophilicity while electron donating groups (EDG) decrease the electrophilicity but increase the stability/selectivity. This splits carbenoids into three different classes: acceptor, acceptor/acceptor, and donor/acceptor, with the latter being the common type used in C–H insertions (Figure 1.3).[24]
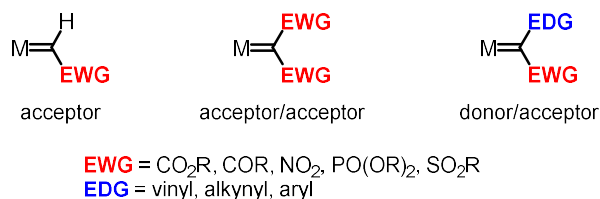
Figure 1.3 Classes of carbenoids

The most common metals used for C–H insertion reactions are copper and rhodium metals, as they offer the best balance for control of the carbenoid intermediates. The ligands on the catalyst provide a high level of stereo- and regiocontrol for the C–H insertion reaction. For example, Davies and coworkers reported in 2014 an insertion reaction to access silyl ethers of type **1.31**, which they later used as precursors to access dihydrobenzofurans. Impressively, an electron-deficient carbenoid was compatible with the electron-rich aryl rings, generating these products in high yields, distereotopic ratios,

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and enantioselectivity (Scheme 1.13).[35] C–H insertion using a transition metal catalyst is certainly a powerful tool to form new C–C bonds with great selectivity and stereocontrol.
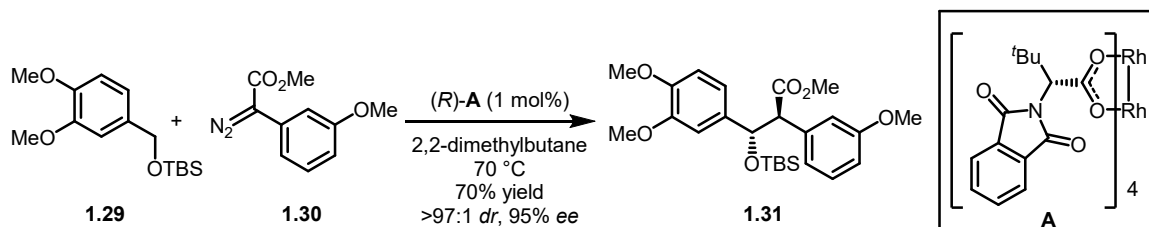
Scheme 1.13 Davies C–H insertion leading to new C–C bond using rhodium catalyst

1.2.2 C–H Insertion without the Use of Transition Metal Catalysts

Stated previously, diazo carbonyls are common precursors used in C–H insertion reactions and are activated by transition metal catalysts, typically rhodium- or copper-based catalysts. Chemo-, enantio-, stereo-, and regioselectivity are all tunable depending on the ligands used on the catalyst.[23, 24] However, due to the cost and increasing scarcity of rhodium and other transition metal catalysts, finding alternative methods for the decomposition of diazo compounds for use in C–H insertion is attractive.

Recently, there have been impressive reports of accessing these carbenes in atypical manners. For example, Arnold and coworkers report a biocatalytic pathway, in which cytochrome P411 enzymes provide a platform for C–H insertion by generating the carbene from activated diazo carbonyls and the iron-heme cofactor.[36, 37] Their latest report includes an impressive lactone-carbene insertion to 1° and 2° α-amino C–H bonds.[38]

Earth-abundant metals have been used for evoking C–H/C–X insertion reactions, however this requires forcing thermal decomposition in order to initiate the reaction.[39, 40] The Davies group discovered that a metal catalyst is not needed to achieve thermal

decomposition of the diazo, and in 2012 they reported a controlled thermal decomposition to yield free carbenes that inserted into a N–H bond.[41]
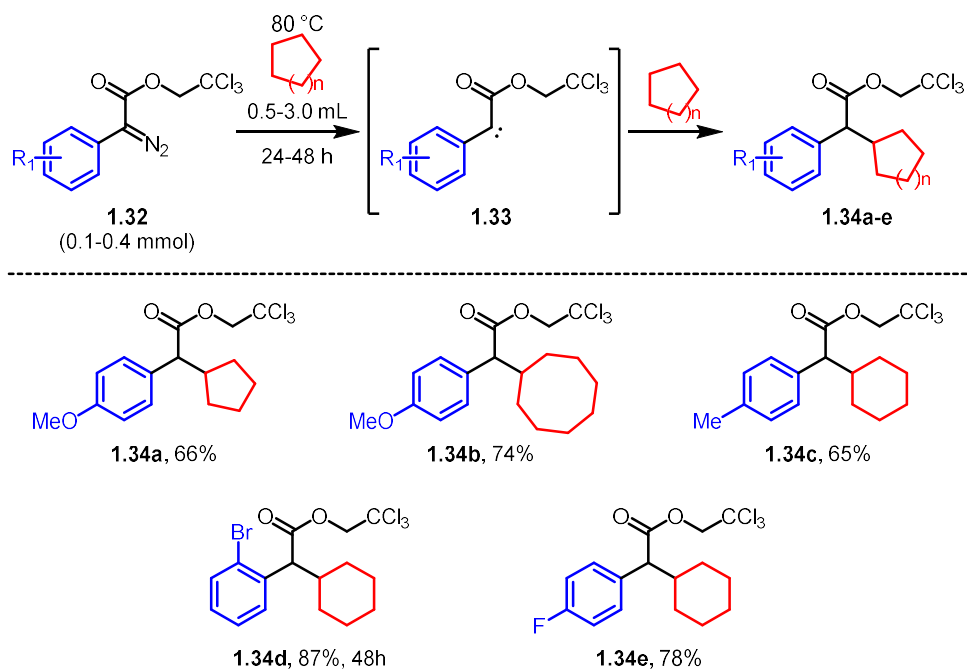
Scheme 1.14 Davies and coworkers diazo decomposition using heat to evoke a carbene

Using this knowledge, the Davies group later expanded on this work and used thermal decomposition to access free carbene **1.33** from diazo ester **1.32**. This carbene then reacted with the solvent to provide functionalized alkanes in moderate to good yields (Scheme 1.14).[42]

Utilization of a diazo functional group is not the only method to evoke a C–H insertion reaction. Another, less common, method includes a 1,5 C–H insertion of alkylidene carbenes from vinyl halides, in which the carbene forms from α-elimination of the vinyl halide.[43, 44, 45] The Borhan group used this type of C–H insertion to functionalize the C5 position in their total synthesis of (-)-Salinosporamide A. They originally attempted to directly functionalize the C5 position with a carbonyl moiety through anionic, radical, and cationic strategies, to no avail. However, C–H insertion strategy gave the fused lactam

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1.37, in which the newly formed C–C bond acts as a masked carbonyl, allowing them to access the lactone moiety in (-)-Salinosporamide A (Scheme 1.15).[44]
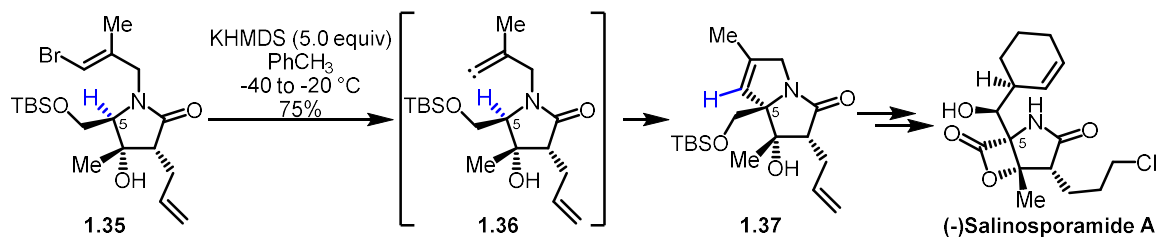
Scheme 1.15 Borhan and coworkers synthesis of (-)-Salinosporamide A

The methods stated above demonstrate that there are a variety of reactions available to form a carbene that can participate in a C–H insertion reaction. Some, like using the diazo functional group and a transition metal to form a carbene, have been extensively studied by multiple groups and act as a key reaction in many natural product syntheses. Others, like using an enzyme to evoke the carbenoid, show great promise and provide a potential alternative to traditional transition metals. Another intermediate that shows promise for use as a carbene surrogate for C–H insertion, and other bond forming reactions, are vinyl cations.

1.3 Vinyl Cations: A General Overview

Vinyl cations have been regarded as unpredictable reactive intermediates that are difficult to control and lead to undesirable side reactions.[46] Although first postulated in 1944, it wasn't until 20 years later, in 1964, that Grob and Cseh provided experimental evidence that vinyl cations could form from the solvolysis of vinyl halides.[47, 48, 49] From that point, the scientific community became interested in this supposedly "unattractive" intermediate.[46]

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Vinyl cations **1.38** are disubstituted carbenium ions with an empty *p*-orbital on the sp^2 hybridized carbon; originally they were thought to be similar to trisubstituted carbenium ions **1.39** (Figure 1.4). Due to their *sp* hybridized nature, vinyl cations are typically linear in conformation.[50] This preference for a linear geometry makes it difficult to form vinyl cations in small ring systems, especially though solvolysis.[51]

1.38   **1.39**
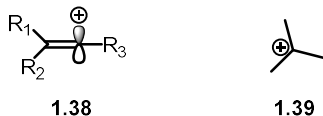
Figure 1.4 Carbocation intermediates

When first investigated in the 70's and 80's, vinyl cations were mainly generated through sovolysis reactions of alkenes via an S$_N$1 type mechanism. Solvolysis of vinyl halides to form α-arylvinyl cations was common, however, later examples demonstrated using a "super leaving" group, such as a trifluoromethane sulfonate anion (triflate) or nonafluorobutane sulfonate anion (nonaflate) provided easier access to vinyl cations. Good leaving groups are a necessity, since vinylic carbons have a strong bond to the leaving group due to the sp^2 hybridization and increased electronegativity.[50] In addition to solvolysis, vinyl cations were also formed by protonation of acetylenes, however this often required harsh conditions such as using strong acids.[52, 53] Aryl groups, alkenes, or even cyclopropanes all were used to stabilize the vinyl cation ntermediate.[46, 54]

The first rearrangement of vinyl cations was accomplished by Stang and coworkers in 1970, which is when a group migrates across the double bond of the vinyl cation to give a new structurally similar isomer of the molecule (i.e. **1.41** → **1.42**). They demonstrated that a phenyl migrated preferentially across the vinyl cation **1.41**, which gave the rearranged ketone **1.43** exclusively (Scheme 1.16).[49] Later studies also demonstrated that a β-anisyl

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rearrangement is 76x faster than a phenyl migration, which indicates that groups that can better stabilize the cationic intermediate migrate faster.[50] The interest in vinyl cations grew, and books and multiple reviews have come out detailing the early research done on these species.[46, 48, 55]
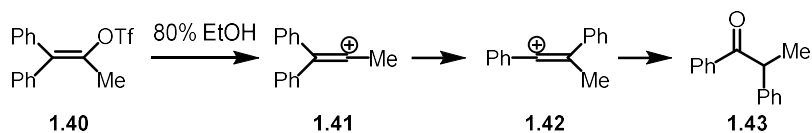
Scheme 1.16 Migration across the vinyl cation intermediate

1.3.1 Vinyl cations as Electrophiles

In the past decade, more research has emerged on vinyl cations, demonstrating their versatility and encouraging further detailed investigations of their reactivity. The brunt of the research has been focused on vinyl cations acting as electrophiles. The solvolysis to generate a vinyl cation was initially thought to behave in an S_N1 type fashion, and the reason they were slow to form was due to their low thermodynamic stability. This also makes them highly reactive and hard to control intermediates. Mayr and coworkers probed the electrophilicity of vinyl cations and in a recent publication argue that they are actually sluggish electrophiles.[56]
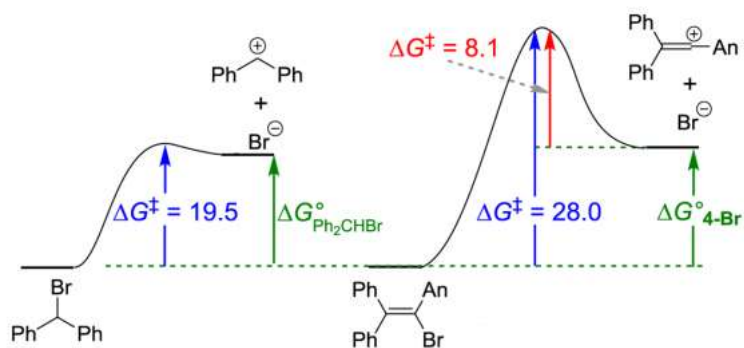
Figure 1.5 Gibbs energy profiles (kcal mol⁻¹) for ionization of benzhydryl bromide and vinyl bromide[56]

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They assert that vinyl cation formation is slow because there is a high intrinsic barrier to go from a sp^2 to sp hybridized carbon. They argue that the reverse is true as well, and the barrier to return to a sp^2 hybridized carbon is why vinyl cations are sluggish electrophiles (Figure 1.5). Importantly, they discovered that vinyl cations react faster with weak nucleophiles while the benzhydrylium ions react faster with strong nucleophiles. However, overall, the electrophilicity between vinyl cations and benzhydrylium ions are comparable. With this knowledge in mind, it may be important to consider the type of nucleophile when vinyl cations are used as electrophiles.[56]

The Niggemann group reported the generation of vinyl triflimides through vinyl cation intermediates. Taking advantage of Mayr's earlier study, they use bistriflimide anion (TFSI), which is a poor nucleophile, to accomplish this (Scheme 1.17).[56, 57, 58] Their design forms the vinyl cation in a supramolecular framework which has a dual purpose. First it gives selective protonation of the alkyne starting material to generate the vinyl cation, and second it allows the TFSI to add preferentially, even though other nucleophiles are present. They chose lithium as their templating metal, because the Li^+ complex aids the addition of the TFSI to the alkyne, and they can obtain the nucleophile readily from LiTFSI. Additives were necessary for successful transformation; $LiPF_6$ was used to form the supramolecular framework and Bu_4NPF_6 improved the solubility of $LiNTF_2$.[58]
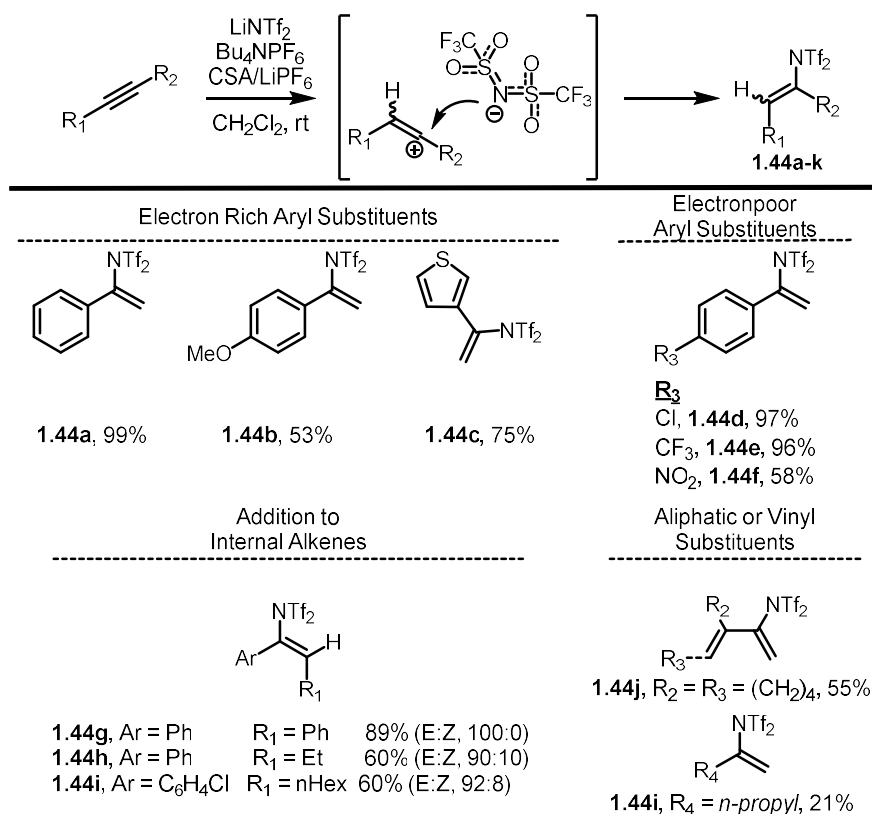
Scheme 1.17 Vinyl triflimide formation via vinyl cations

With optimized conditions in hand, they moved towards evaluating the substrate scope

(Scheme 1.17). When the vinyl cation is stabilized by an aryl ring, they received good to

excellent yields, with the best results coming from moderately electron-poor aryl rings

(**1.44a-1.44f**). Electron rich rings often suffered oxygen addition/hydrolysis of TFSI, to

provide a ketone side product, lowering the yield of the vinyl triflimide (**1.44b**). In addition,

when they tested aliphatic or vinylic substituents, they received a depressed yield of

product (**1.44j** & **1.44i**).[58] Other vinyl cation studies report similar findings, further

enforcing that aliphatic groups are poor at stabilizing vinyl cations.[59, 60] Nevertheless, it is

noteworthy they were able to form alkyl substituted vinyl triflimides even under these

circumstances.

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Gaunt and coworker took advantage of electrophilic vinyl cations to form an all carbon tetrasubstituted alkene (Scheme 1.18).[61] A common way to form vinyl cations is to protonate an alkyne with a strong acid or other proton sources.[62, 63] This group took advantage of this reactivity but used the alkyne starting material as a nucleophile to react with a carbon electrophile, which forms the vinyl cation intermediate. They proposed that activation of a diaryliodonium triflate with a Cu(I) salt released an electrophilic aromatic ring, which the alkyne added to as a nucleophile. This generated an electrophilic vinyl cation which is attacked by a tethered arene nucleophile in a Friedel-Crafts type reaction.[61]
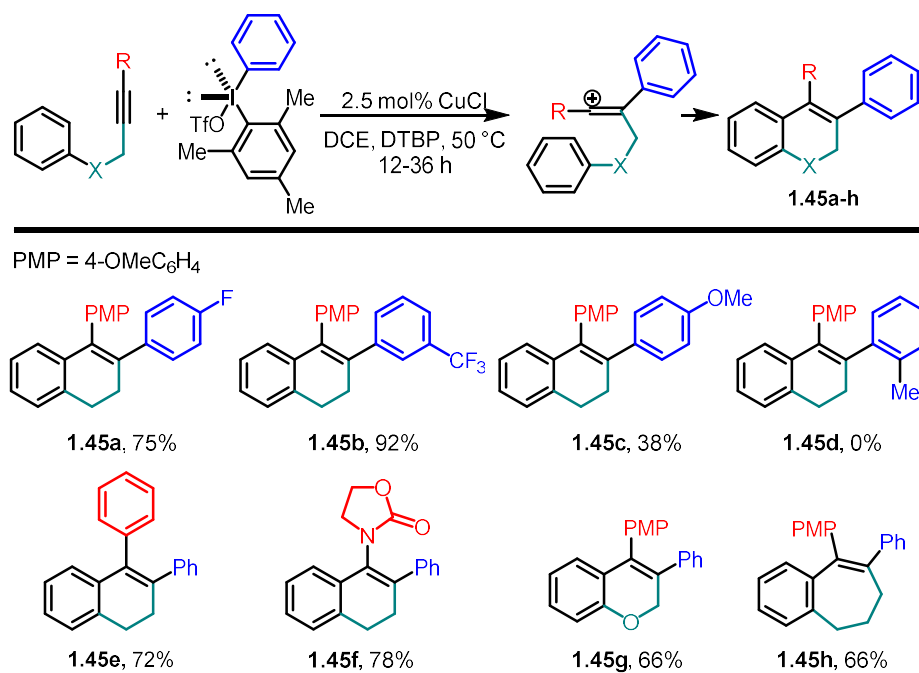
Scheme 1.18 Tetrasubstituted products from vinyl cations

This reaction works well with aryl groups displaying halogen and electron withdrawing substituents (**1.45a** and **1.45b**). However, low amounts of product formed when the aryl ring was 4-methoxyphenyl (**1.45c**), and no products were observed with ortho-substituted aryl groups (**1.45d**) indicating that the electrophile is important. Modification of the alkyne

(R) revealed that groups that could stabilize the vinyl cation performed well, as did heteroatom functional groups (**1.45e** & **1.45f**). In addition, oxygen and nitrogen linkages on the tether also performed well, further demonstrating the efficiency of this process (**1.45g**). Finally, a 7-membered ring could even be formed with a longer tether (**1.45h**). Finally, Modified arenes on the alkyne starting material were tested, and the resulting products were formed in good to excellent yields with both electron donating and electron withdrawing groups.[61]

In our group, Dr. Jian Fang took advantage of the electrophilicity of vinyl cations in an intramolecular electrophilic vinylation of aryl rings to prepare tricyclic 1-indenones (Scheme 1.19). This took advantage of prior work that showed that Lewis acids react with β-hydroxy-α-diazo ketones to release hydroxide and nitrogen gas to provide a linear vinyl cation **1.47**. This linear vinyl cation is destabilized by the adjacent carbonyl and a 1,2-methylene shift occurs to generate the cyclic vinyl cation **1.48**. Dr. Fang took advantage of this process by capturing vinyl cation **1.48** via an intramolecular electrophilic aromatic substitution to generate indanone products.[64]

1.46a, R$_1$, R$_2$, R$_3$ = H
1.46b, R$_1$ = OMe, R$_2$, R$_3$ = H
1.46c, R$_1$ = H, R$_2$, R$_3$ = Me

1.47   **1.48**

1.49a, 80%
1.49b, 68%
1.49c, 75%
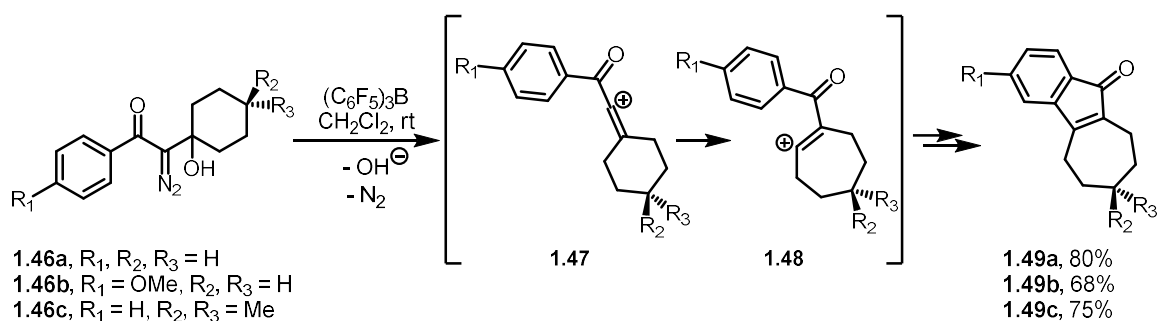
Scheme 1.19 Electrophilic vinylation onto vinyl cations yields indenone products

Through this process, he formed substituted indenones in moderate to good yields. Electron-rich aryl rings gave lower than expected yields (**1.49b**), presumably due to the increased stability of linear vinyl cation **1.47**, which would in turn slow the rearrangement to **1.48**. He demonstrated that the cyclohexane portion of the ring could be substituted at the γ-position with good yields of the resulting indenones (**1.49c**).[64]

1.3.2   Vinyl cations as carbene surrogates in C–H insertions

Described above, vinyl cations have been studied extensively as electrophiles, and multiple publications have emerged to provide valuable methods to exploit this intermediate. However, demonstrating the versatility of vinyl cations, there have also been numerous reports indicating that they can act as a carbene surrogate. One of the first examples of using vinyl cations in this fashion was disclosed by Schegolev and coworkers in 1974, where vinyl cation intermediate **1.51**, generated in a non-nucleophilic solvent (dichloromethane-dichloroethane mixture), provided cyclopentenones by the reaction of acyl chloride **1.50** with 2-butyne (Scheme 1.20). Importantly, they discovered that this led to an intramolecular insertion reaction yielding cyclopentenone **1.54**.[65]
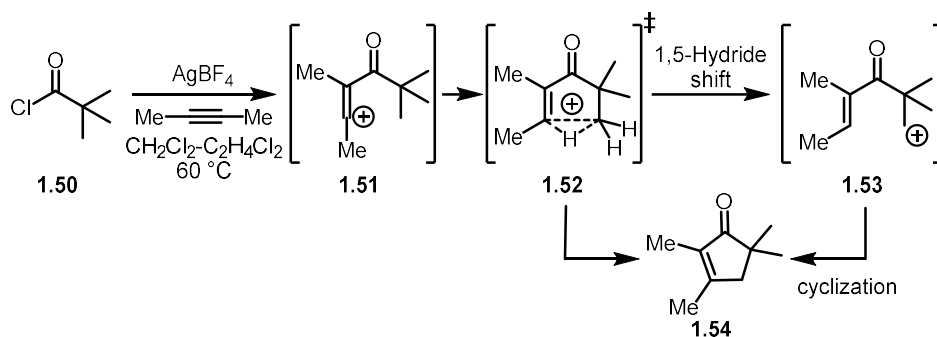
Scheme 1.20 Carbene-like vinyl cations leading to cyclopentenones

In 2006, Metzger and coworkers provided additional evidence in support of vinyl cations acting as carbenes to perform C–H insertion reactions. They reported reaction of

an alkyne and isopropyl chloroformate, in the presence of $Et_3Al_2Cl_3$ and Et_3SiH as a hydride donor, which generated cyclopentane **1.56** in 74% yield. They propose that after vinyl cation formation, there is a concerted 1,5-hydride shift to form the cyclopentane **1.55**. Computational studies also provided evidence of a concerted cyclization (Scheme 1.21).[66]
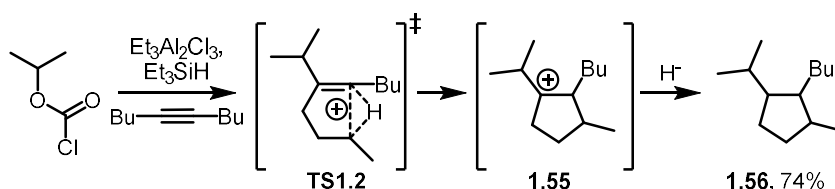
Scheme 1.21 Cyclopentanes from C–H insertion of vinyl cations

Along this vein, Gaunt and coworkers provide experimental proof that the 1,5-hydride shift and cyclization is a concerted process in their system as well. When testing an enantioenriched alkyne **1.57**, they received back an enantioenriched cyclopentene **1.60**. If the C–H insertion was stepwise, they would have a scrambled stereocenter and not have retention of stereochemistry (Scheme 1.22).[67]
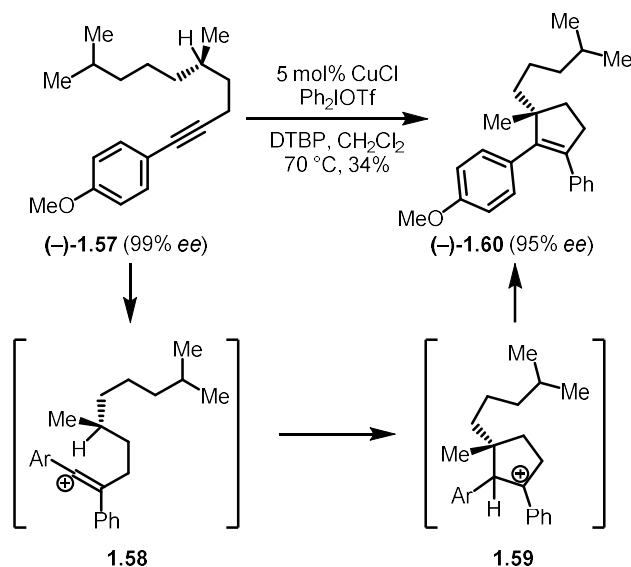
Scheme 1.22 Retention of stereochemistry indicates concerted C–H insertion

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Most recently, Nelson and coworkers demonstrated in their 2018 study that silylium-monocarba-*closo*-dodecaborate salts (WCA) generated vinyl cations from cyclohexenyl triflates, providing various hydrocarbon products in good yields. They describe the weakly coordinating anion as enhancing the Lewis acidity of the silicon, which allowed ionization of the vinyl triflate **1.61**, leading to the formation of the vinyl cation **1.62**. The vinyl cation **1.62** then inserted into the alkane solvent to provide hydrocarbon products (Scheme 1.23 and Table 1.1, entry 1 and 2).[68]
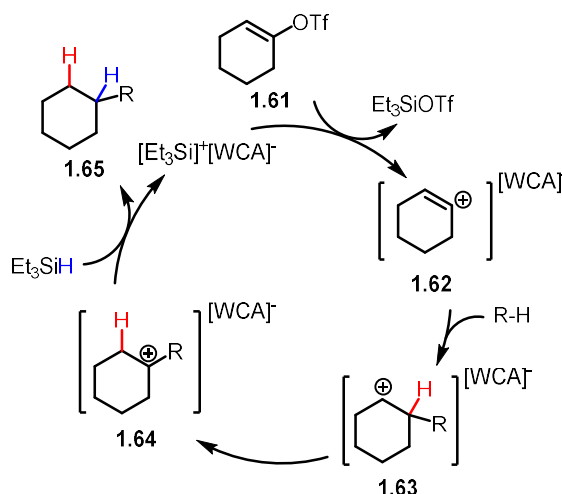
Scheme 1.23 Proposed catalytic cycle for Nelsons developed C–H insertion

Further demonstrating the practicality of this reaction they alkylated a steroid in good diastereomeric ratio (Table 1.1, entry 3). Expanded studies used the electrophilic nature of the vinyl cations to form sp^3-sp^2 bonds in arene solvents.[68] This was impressive, since vinyl cations have been shown to be difficult to form by ionization in arene solvents.[69] The group performed extensive mechanistic studies on their system to better understand the C–H insertion mechanism. These studies supported the formation of a persistent 3° carbocation, and a nonclassical mechanism.[69] They later expanded this work to demonstrate that they

could form vinyl cations in this manner under strongly basic conditions. This reaction was also compatible when heteroatoms were present.[70]

Table 1.1 Representative examples for C–H insertion into unactivated alkanes

Entry	Vinyl Triflate	Solvent	Product
1	1.66	C_6H_{12}	1.67, 87%
2	1.66	C_7H_{14}	1.68, 88%
3	1.69	C_6H_{12}	1.70, 88% (15:1 *d.r.*)

1.4   The Importance of 5-Membered Ring Carbocycles

The 5-membered ring is a ubiquitous scaffold in natural products and organic materials; for example, at least 12 of the top 200 drugs in 2019 contain a 5-membered carbocycle, and there is an even greater quantity of medicinal drugs that contain a 5-membered heterocycle.[71] Figure 1.6 shows several 5-membered ring-containing natural products that could potentially be prepared using the methodology we developed.
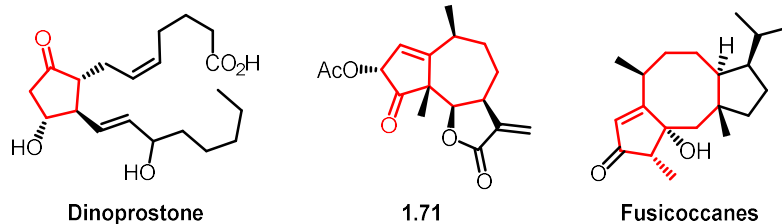
Figure 1.6 Biologically active natural products with 5-membered ring scaffold

The prostaglandin family, which has a monocyclic cyclopentanone or cyclopentenone ring, include multiple medicinally important compounds. For example, dinoprostone is a drug used for inducing labor (Figure 1.6).[72] Aside from monocylic compounds, a number of natural products contain fused 5-membered ring heterocycles. Acetylate pseudoguaianolide **1.71** contains a fused 5,7,5-ring system, and has been shown to have anti-inflammatory properties in addition to cytotoxic activity against Jurkat cells.[73, 74] Fusicoccanes are a family of compounds that share a 5,8,5-fused ring system and have also demonstrated biological activities. Brewer group member Evan Howard is currently targeting a member of this family utilizing our C–H insertion chemistry.[75, 76]

1.4.1 Methods to form 5-Membered Ring Carbocycles

Popular methods to form 5-membered carbocycles include ring contraction methodology, such as the Favorskii reaction or a radical ring contraction, and cyclizations.[77, 78]

The Favorskii rearrangement is a ring contraction that traditionally involves an α-halo ketone and a base, however epoxides in the presence of Lewis acids have also been used.[79, 80] In the classic example, deprotonation at the epsilon (ε) position generates an enolate which attacks the α-position leading to loss of the halide and formation of a cyclopropanone (**1.73**). The cyclopropenone **1.73** is attacked by an equivalent of nucleophile, leading to

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esters, carboxylic acids, or amides depending on the nucleophile used (Scheme 1.24).[81, 82, 83]
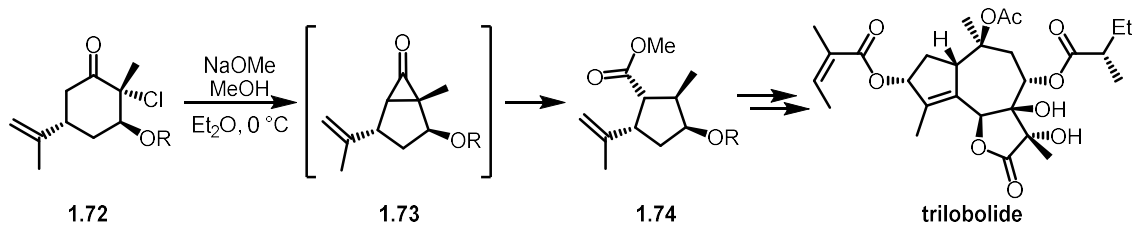
Scheme 1.24 Favorskii rearrangement used for synthesizing building blocks

Other ways to synthesize 5-membered hydrocarbon rings include ring forming reactions such as the Conia-ene reaction. The Conia-ene reaction uses thermal or Lewis-acid means to form a carbonyl enolate, which then reacts with a pendant alkene or alkyne to form new ring systems. The Toste group developed a gold(I)-catalyzed Conia-ene reaction to access functionalized cyclopentane products, in addition to bicyclic systems and cyclopentanone rings. Importantly, they received products in high yields and distereoselectivity using neutral conditions at room temperature (Scheme 1.25).[84]
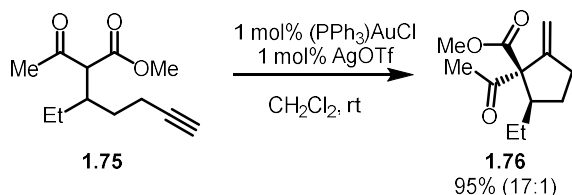
Scheme 1.25 Conia-ene reaction leading to functionalized cyclopentanes

1.4.2 Methods to form cyclopentenone ring systems

Cyclopentenone rings are not only a common motif in natural products, but they are useful building blocks that can be manipulated to access a wide range of products. There are various strategies to form cyclopentenones, including ring closing metathesis, oxidation of the corresponding cyclopentene, or C–H insertion reactions.

One of the most well-known methods to prepare cyclopentenones is the Nazarov cyclization, in which cyclopentenones are formed by the Lewis acid promoted 4π electrocyclization of cross conjugated dienones (Scheme 1.26).[85, 86] Importantly, an achiral starting material could be used to provide a chiral product. Although this method is an important way to form cyclopentenone rings, it has drawbacks that make it limited in scope. Issues include the necessity of multiple equivalents of a strong Lewis acid, regioselectivity during the elimination, loss of a stereocenter due to the elimination of a proton **(1.79 →** **1.80**), and non-selective enolate protonation.[87]

Scheme 1.26 Classical Nazarov cyclization

However, there have been improvements to the Nazarov cyclization which mitigated some of these issues. For example, Denmark and coworkers installed a silicon on the diene to take advantage of the β-silicon effect, which allowed them to have a level of regiocontrol in the elimination step.[88] More recent examples have greatly improved upon the Nazarov cyclization and provided alternative methods of accessing the pentadienyl cation (**1.78**). For example, protonation of alkoxytrienes using mild conditions or activation of allenes have both been used to access the pentadienyl cation.[85, 86, 87]

Cascade systems have also been developed to access the pentadienyl cation. Using a gold catalyst, alkyne activation followed by metathesis and electrocyclic ring opening leads to the pentadienyl cation, which can then participate in a Nazarov cyclization.[85] In addition, there have been advances on asymmetric Nazarov cyclizations using chiral

catalysts to achieve good stereocontrol. The Rueping group used chiral Brønsted acids to achieve good enantiocontrol, however, the reaction suffered from poor diastereoselectivity.[89] Using a transition metal catalyst with an appropriate ligand has overcome the stereoselectivity issues. The Tang group use a Cu(II) catalyst with a tris(oxazoline) ligand (A) to achieve good regio- and enantioselectivity. Importantly, this method gives only one diastereomer of the cyclopentenone product in good yields with high *ee* of up to 98% (Scheme 1.27).[90]
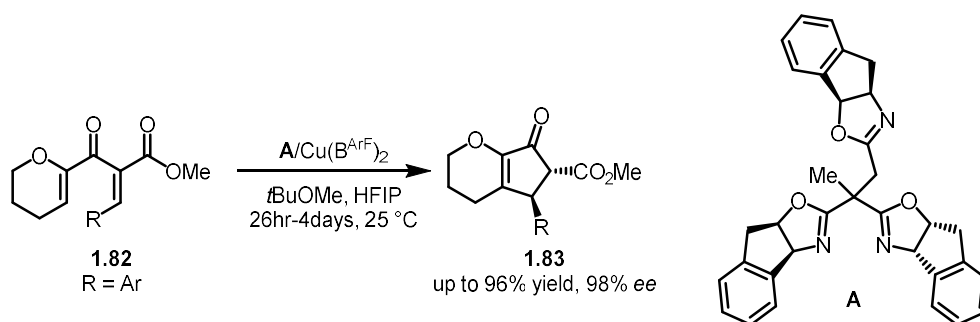
Scheme 1.27 Tang and coworkers modified Nazarov cyclization

The Pauson-Khand reaction (PKR) is another popular method to form cyclopentenone rings. This reaction is a cobalt catalyzed [2+2+1] cycloaddition between a triple bond, carbon monoxide, and an alkene (Scheme 1.28).[91] However, there were issues with the original reaction. To start, both the carbon monoxide and the $Co_2(CO)_8$ catalyst are toxic. In addition, regioselectivity was an issue when using asymmetric alkenes. This was improved upon in the intramolecular version of the PKR.[91, 92]
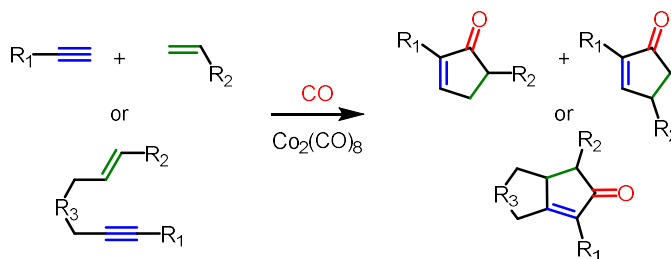
Scheme 1.28 [2+2+1] Pauson-Khand cycloaddition

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Numerous improvements have been made to overcome the issues regarding the toxicity of the PKR. CoBr$_2$, with the proper reductant and additive, has been demonstrated as a successful catalyst in the PKR reaction. Alternative metals such as rhodium have been developed as well. Other advances include using carbon monoxide surrogates, such as formic acid or aldehydes, to safely obtain a CO equivalent.[92]

As cyclopentenones represent ubiquitous scaffold in natural products, or can be used as a building block to access more highly functionalized systems, it is imperative there are multiple methods to access this ring system. Although the above methodologies represent nice ways to access cyclopentenone ring systems, some do have their drawbacks, such as being reliant on transition metal catalysts. In this dissertation, I will discuss how we can access cyclopentenone ring systems efficiently using vinyl cations as a carbene surrogate in a C–H insertion or as electrophiles in a nucleophilic addition reaction. These vinyl cations can be formed easily by the Lewis acid mediated reactions of β-hydroxy-α-diazo carbonyls.

CHAPTER 2: The C–H Insertion of Vinyl Cations Leading to Cyclopentenones

2.1   Inspiration and Precedence

The ability to exploit unconventional intermediates in new reactions is attractive. Furthermore, while C–H insertion reactions typically use transition metal catalysts, alternative methods that may lead to different reactivities and scopes should be investigated. In addition, transition metals, especially platinum group elements (platinum, palladium, ruthenium, rhodium, etc.), are high risk according to the 2015 British Geological Survey. This survey based their claim on a variety of factors, such as concentration, recycling rate, and global governance, to name a few.[93] This is important to alleviate some the necessity for use of transition metals. In the context of C–H insertions, transition metal catalysts are typically used to form a carbene from a diazo precursor. The carbene in turn can insert into a C–H bond. However, vinyl cations, unorthodox intermediates, have been demonstrated to be useful carbene surrogates.[65, 66, 68]

Schegolev and coworkers demonstrated that they could form vinyl cation **2.3** by electrophilic addition of alkyne **2.1** onto acyl cation **2.2**, derived from the reaction of the corresponding acid chloride with the Lewis acid AgBF$_4$ (Scheme 2.1). At this point, they report an unusual transformation occurring, that is, a cyclization to form cyclopentenone product **2.7** in 73% yield.[65]
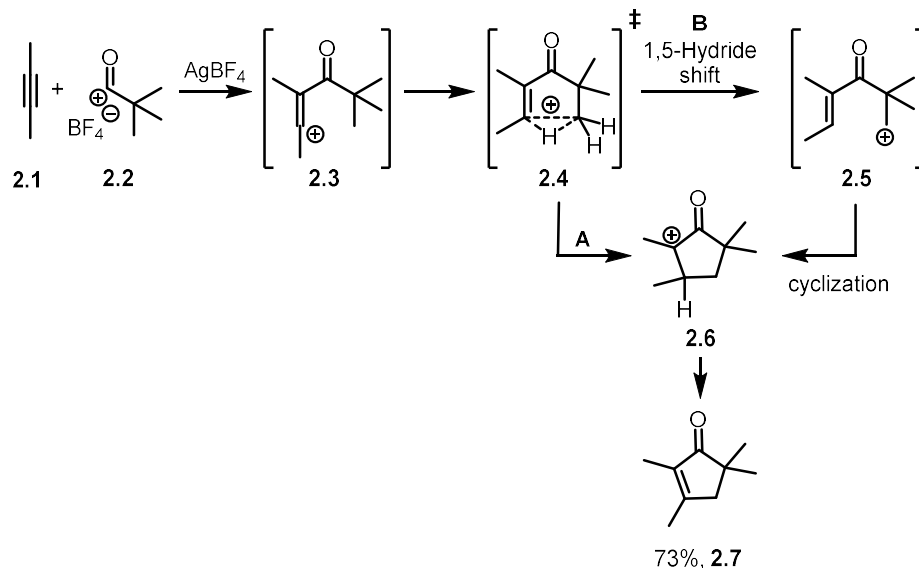
Scheme 2.1 Cyclopentenones through C–H insertion

This result can be rationalized by two different pathways (Scheme 2.1). Pathway A would occur through a concerted C–H insertion reaction to form a new C–C bond, while in pathway B a stepwise 1,5-hydride transfer would form a primary carbocation **2.5** followed by cyclization to provide the cyclopentenone product.[65] At the time of this discovery, the knowledge about the reactivity of vinyl cations was limited. As described in Chapter 1, Section 1.3.1, by this point it had been demonstrated that vinyl cations could be trapped inter- and intramolecularly by nucleophiles.[94] However, Schegolev and coworkers' result showed a different pathway by which a vinyl cation could be exploited.

The research group expanded on this work to investigate the reaction on different alkyl groups. Modification of the acyl cation to include a cyclohexane ring (i.e. **2.9**) provided vinyl cation **2.10** after nucleophilic attack of propyne. However, instead of forming the expected cyclopentenone ring, they isolated fluoroketone **2.12** in 35% yield. It appears as though an intramolecular 1,5-hydride shift gave 2° carbocation **2.11**, which was trapped by

a fluoride counterion from the tetrafluoroborate salt.[95] This indicates that the cyclohexyl substituent reacted by a stepwise pathway.
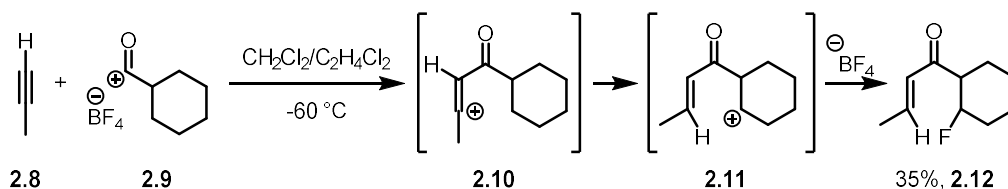
Scheme 2.2 Fluoride capture of 2° carbocation formed after stepwise hydride migration

Metzger and coworkers also demonstrated that vinyl cations can act as carbene surrogates in their synthesis of cyclopentane rings (Scheme 2.3). Initially, they were attempting to form alkylated alkene **2.15** by attack of a hydride on vinyl cation intermediate **2.14**. The vinyl cations themselves could be formed from the Lewis acid promoted reaction of alkyl chlorofomates and alkynes.[66]
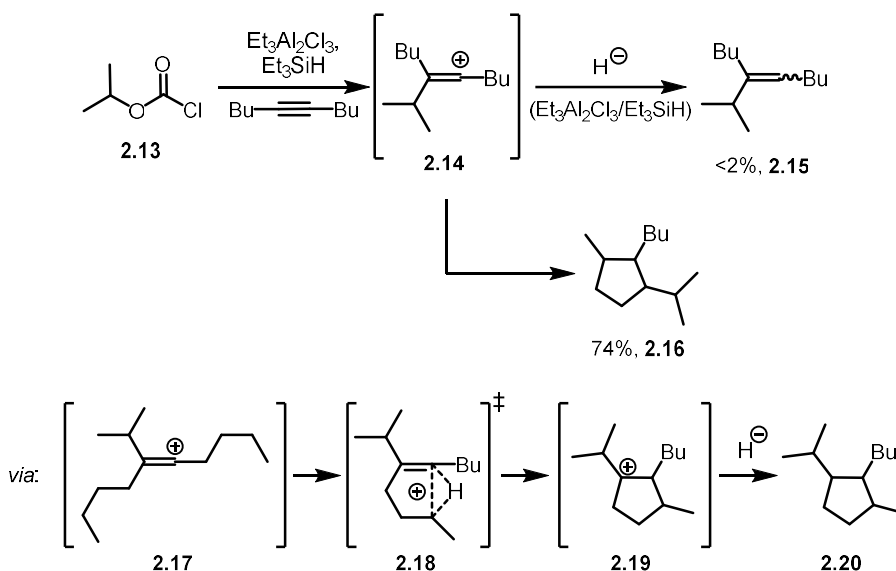
Scheme 2.3 C–H insertion on 2° position gives cyclopentane products

However, they unexpectedly isolated cyclopentane **2.16** in 74% yield as a mixture of four diastereomers. The expected alkene product was only formed in <2% yield. They

propose that after formation of the vinyl cation a concerted 1,5-H shift and cyclization occurs to form cyclopentyl carbocation **2.19** which is then attacked by a hydride derived from Et$_3$SiH (Scheme 2.3). They hypothesize the C–H insertion is concerted based on the absence of alternative side products observed in previous studies of 2° cations. Computational modeling indicated when the point of insertion is primary it was a concerted reaction. Although they did not model a system where the point of insertion is secondary, since they did not isolate side products that would be produced through a stepwise reaction, they believe this insertion at secondary cations is also concerted.[66]

Although both Schegolev and Metzger's independent publications set a precedence for vinyl cations to act as carbene surrogates in C–H insertion reactions, they were limited in their ability to form the vinyl cations themselves. A method to form vinyl cations is the loss of a leaving group on the alkene, however, as stated in the introduction, this often requires harsh conditions or a super-leaving group. The use of diazo carbonyls in mild reaction conditions allows facile access to vinyl cation intermediates. Wenkert reported that alkynes **2.24** can be formed from β-hydroxy-α-diazo ketones **2.21** derived from acyclic aldehydic starting materials. These alkynes are formed from the elimination of a hydrogen atom on vinyl diazonium **2.23**, which liberates molecular nitrogen to generate the acetylenes (Scheme 2.4).[96, 97, 98, 99]
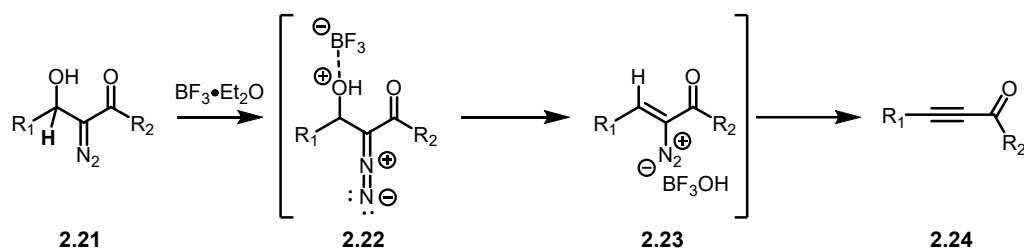
Scheme 2.4 Acetylenes through hydride elimination

Along this vein, Pellicciari and Padwa prepared β-hydroxy-α-diazo ketones **2.25**, by the reaction of cyclic ketones and lithiated diazo esters (Scheme 2.5). Treating these with BF$_3$•Et$_2$O caused loss of hydroxide and delivered vinyl diazonium **2.26**. In this case there is no adjacent hydrogen to abstract, and loss of nitrogen gas generated linear vinyl cation **2.27**. This vinyl cation is destabilized by the adjacent carbonyl, because, the empty *p*-orbital on the vinyl cation are perpendicular to the carbonyl π-orbitals. A migration across the vinyl cation ensues to generate a more stable, cyclic vinyl cation (**2.28**).[98]
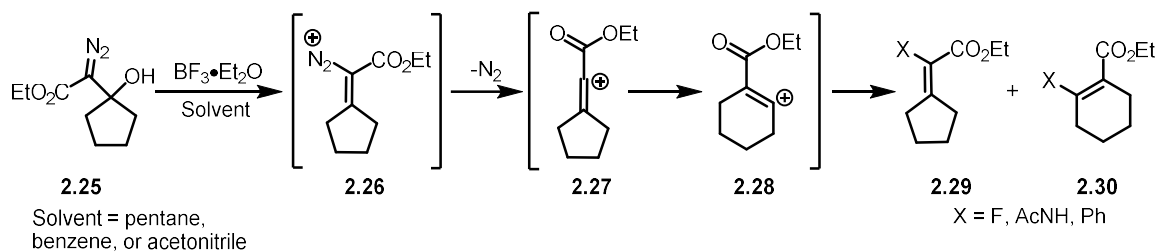
Scheme 2.5 β-Hydroxy-α-diazo esters provide a convenient method to access vinyl cations

When the starting β-hydroxy-α-diazo esters contained a cyclopentane ring, the researchers isolated products **2.29** and **2.30**, which would result from capture of the linear and cyclic vinyl cations by the solvent or Lewis acid counterions (Scheme 2.5). However, when the starting β-hydroxy-α-diazo esters contained a cyclohexane ring, unsaturated lactone **2.35** was formed in 75% yield. In this case, a ring contraction occurred after the

formation of the cyclic vinyl cation **2.33** to generate allylic carbocation **2.34**. This allylic

carbocation cyclizes with the adjacent ester to form the lactone ring (**2.35**, Scheme 2.6).[98]
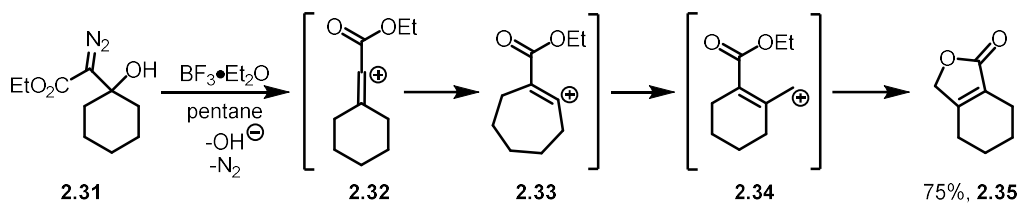
Scheme 2.6 Ring contraction provides lactone products

There are two key takeaways from these publications. First, vinyl cations have been

demonstrated to act as carbene surrogates that can undergo C–H insertion at an inert C–H

bond to form five membered rings.[65, 66] Second, vinyl cations can be formed easily from

diazo carbonyl containing compounds through extrusion of nitrogen. However, since a

product that would result from a C–H insertion on the methyl ester had not been identified

in Padwa and Pellicciari's work, diazo esters may be unlikely to participate in a C–H

insertion mechanism.[98] It was hypothesized that vinyl cations derived from β-hydroxy-α-

diazo ketones might participate in a C–H insertion reaction, as the C–H insertion may be a

faster reaction than ring contraction.

2.2   Preparation of β-Hydroxy-α-diazoketones and Initial Results

The initial studies were conducted in collaboration with Dr. Sarah Cleary. The

preparation of the β-hydroxy-α-diazo ketone starting material was straightforward. First,

commercially available acid chlorides were treated with diazomethane and triethyl amine

to generate diazo ketones (**2.37a-2.37c**, Scheme 2.7). Of note, acid chlorides with an acidic

α-proton (**2.37d-2.37f**) required the use of three equivalents of diazomethane in lieu of

triethyl amine, since triethyl amine deprotonated the α-proton of the acid chlorides providing a ketene.[100]
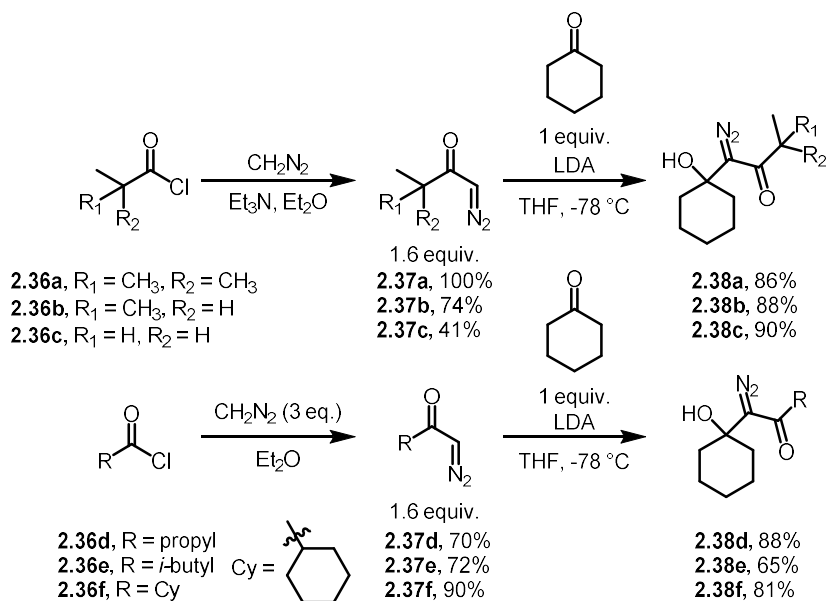
Scheme 2.7 Synthesis of β-hydroxy-α-diazoketones

The addition of the corresponding diazo ketone to cyclohexanone at first provided low yields or recovered starting material. This reaction is sensitive to temperature changes, therefore the LDA needed to be added down the side of the reaction flask slowly. Originally, we were using a 1:1 ratio of diazo ketone to cyclohexanone. However, the addition is reversible and seemed to favor starting material at equilibrium. Using the diazo ketone in excess allowed for the successful addition reaction and gave moderate to good yields of the β-hydroxy-α-diazo ketone products.[29] Other methods of deprotonating the diazo, such as using DBU, did not increase yields.

Dr. Cleary and I initiated our studies by screening various Lewis acids and solvent systems (Table 1). Basing our reaction conditions off prior Brewer group publications, we used $SnCl_4$ in CH_2Cl_2 to test the C–H insertion reaction on the *t*-butyl diazo ketone **2.38a**.[29,]

[30] Delightfully, this provided the C–H insertion product **2.39** in 83% yield. BF$_3$•Et$_2$O,

In(OTf)$_3$, Dy(OTf)$_3$, P$_2$O$_5$, and FeCl$_3$ all provided lower yields or no conversion of starting

material. In addition, we were limited as to solvent choice because the resulting

cyclopentenone product **2.39** is volatile. Initially, it was determined that SnCl$_4$ in CH$_2$Cl$_2$

gave the optimal yield for this transformation.[101] Products that would arise from ring

contraction after formation of the cyclic vinyl cation (e.g. **2.34**, Scheme 2.6),[98] were not

isolated.
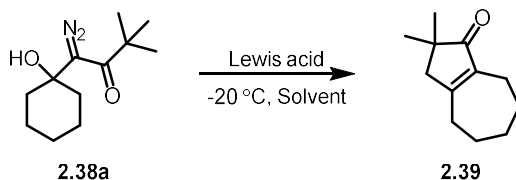
Table 2.1 Initial optimization studies for the C–H insertion reaction

Entry	Lewis acid	Solvent	Yield
1	SnCl$_4$	CH$_2$Cl$_2$	83%
2	SnCl$_4$	MeCN	24%
3	BF$_3$•Et$_2$O	CH$_2$Cl$_2$	58%
4[a]	BF$_3$•Et$_2$O	MeCN	-
5[a]	In(OTf)$_3$	CH$_2$Cl$_2$	-
6	Dy(OTf)$_3$	MeCN	60%
7[b]	P$_2$O$_5$	CH$_2$Cl$_2$	35%
8[a]	FeCl$_3$	MeCN	-

[a] Product was either a minor product or no starting material was consumed
[b] Product was isolated with impurities

We propose this reaction occurs by the mechanism shown in Scheme 2.8. The

Lewis acid will coordinate to the 3° alcohol to yield vinyl diazonium cation **2.40**. Then,

loss of molecular nitrogen provides linear vinyl cation **2.41**. We also observe this visually;

after the SnCl$_4$ is added to the β-hydroxy-α-diazo ketone there is gas evolution and the

color change from bright vibrant yellow to colorless indicating the extrusion of nitrogen.[101]
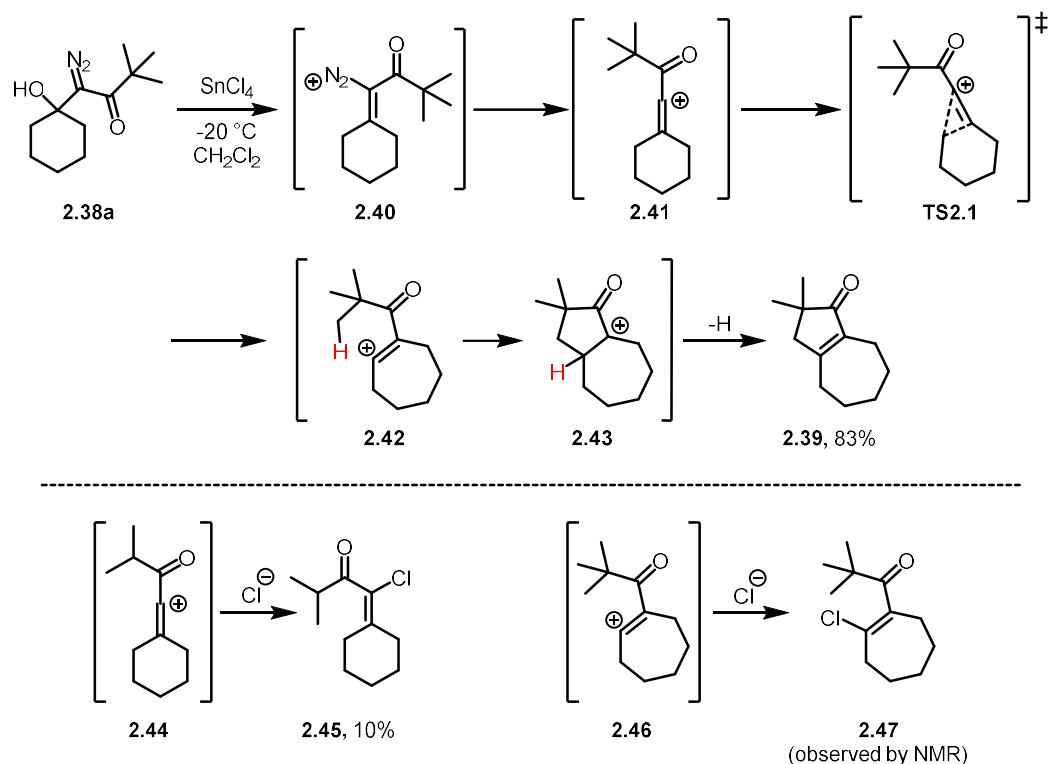
Scheme 2.8 Hypothesized mechanism of the C–H insertion reaction and counterion trapping

The vinyl cation **2.41** is destabilized by the adjacent carbonyl and undergoes a ring expansion via a 1,2-methylene shift via transition state **TS2.1** to form the more stable cyclic vinyl cation **2.42**, which can undergo a C–H insertion at an unactivated, remote C–H methyl bond. Subsequent elimination of a proton generates the cyclopentenone product **2.39**. The main side products we observed in this reaction come from intermolecular trapping of the respective vinyl cations by the chloride counter ion from the Lewis acid. Vinyl cations can act as electrophiles and we isolated the respective vinyl chloride side products (e.g. **2.45**) or observed them by NMR (**2.47**).[101, 102]

2.3 Modification of the α' and β' Portion of the Diazo Ketones

With the optimal reaction conditions in hand, we investigated the scope of the C–H insertion reaction leading to fused bicyclic cyclopentenones. Specifically, Dr. Cleary

worked on modification of the ring size and monocyclic variants of the C–H insertion reaction, while I modified the point of insertion.

I initiated this work by modifying the α' substitution of the diazo ketone. There is an apparent trend that with the decreasing number of possible insertion sites (*t*-butyl, isopropyl, methyl) there is a gradual decrease in the yield (Table 2.2, Entries 1-3). The side products detected in this reaction were the intermolecular attack of a counterion on the linear or cyclic vinyl cations.[101]
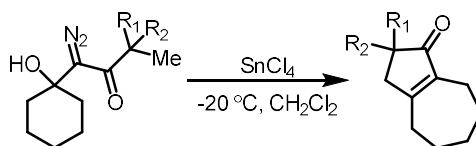
Table 2.2 Modification at point of insertion

Entry	R_1, R_2	Yield
1	CH_3, CH_3	83%
2	CH_3, H	70%
3	H, H	62%

The trend of decreasing yields with decreasing points of insertion can be explained in a few different ways. It could be that with a greater quantity of protons, such as the *t*-butyl group having nine protons (Table 2.2, entry 1) as opposed to the ethyl group with three protons (Table 2.2, entry 3), there is a greater probability of insertion to occur. Another possibility is that the Thorpe-Ingold effect is increasing the rate of cyclization for the sterically hindered substrates. In the Thorpe-Ingold effect, or the *gem*-dialkyl effect, the replacement of methylene hydrogens with more sterically demanding alkyl groups will decrease the internal bond angle and increase the rate of cyclization. As observed in Table 2.3, the rate of epoxide ring formation from chlorohydrins is increased with a more

substituted system.[103] If the rate of cyclization is higher for more sterically hindered substrates, then there is a lower probability for counterion trapping to occur on the vinyl cation after ring expansion (**2.42**, Scheme 2.8).
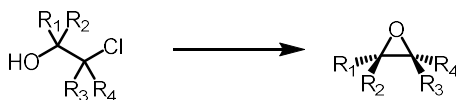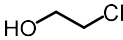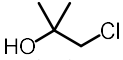
Table 2.3 Relative rates of ring closure of chlorohydrins

Compound	Relative Rate
	1
	252
	11,600

To determine if insertion can occur with more substitution present, methylene and methine substituents **2.38d** and **2.38e** were prepared and subjected to SnCl$_4$. These substrates provided interesting results in terms of reactivity. Using SnCl$_4$, substrate **2.38d** provided the desired cyclopentenone product (**2.48**) in low yield (32%). Methine substituent **2.38e** was prepared to test if an all carbon quaternary center could be formed; however, **2.38e** did not yield the desired cyclopentenone product **2.49**. The major product that did form in this reaction could not be separated from the chlorotrapped side products when using SnCl$_4$ as the Lewis acid (Scheme 2.9). To combat this, I used the Lewis acid tris(pentafluorophenyl)borane (BCF, $(C_5F_6)_3B$) that should not liberate a counterion to be trapped during the intermediate steps. With no chloride side products, I could determine the reaction product of the methine substituent **2.38e**, in which there was an elimination of hydrogen to generate alkene **2.50** (77% yield).[101]
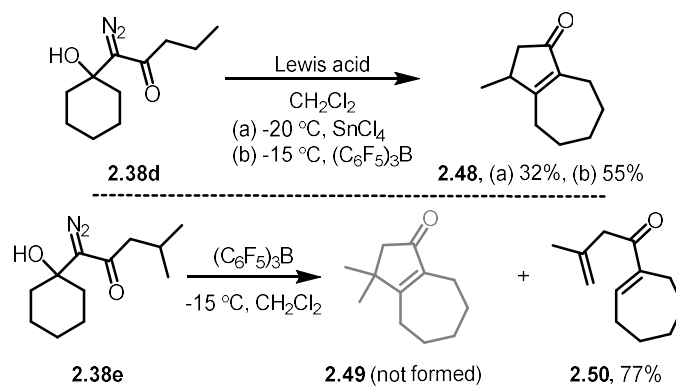
Scheme 2.9 Substitution at the β-position of diazo ketones

Subjecting the other substrates to BCF led to improved yields of the desired insertion. Of note, the cyclopentenone product yields derived from the *t*-butyl, isopropyl, and ethyl β-hydroxy-α-diazo ketone derivatives increased from 83, 70, 62% to 88, 82, 70% respectively when BCF was the Lewis acid (Table 2.4, entries 1-3). In addition, the initially low yielding (32%) propyl derivative (**2.38d**) provided cyclopentenone **2.48** in a more useful 55% yield when subjected to BCF (Scheme 2.9).[101]
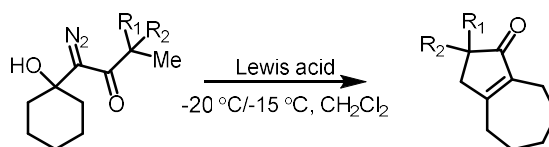
Table 2.4 Change in Lewis acid increases yield

Entry	R₁, R₂	Lewis acid SnCl₄ (-20 °C)	Lewis acid BCF (-15 °C)
1	CH₃, CH₃	83%	88%
2	CH₃, H	70%	82%
3	H, H	62%	70%

In all cases, there was a 1,2-methylene shift across the alkene to give the seven-membered ring. This shift results in formation of a new vinyl cation that can insert at a C–H bond or, in the case of the methine substituent **2.38e**, has the potential to accept a hydride.

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In the case of the methine substituent **2.38e**, there was no formation of the desired cyclopentenone product **2.49**, and instead the elimination product **2.50** was the major product. After further inspection of the crude NMR of the reaction with the methylene substituent **2.38d**, there was no indication of an elimination product.
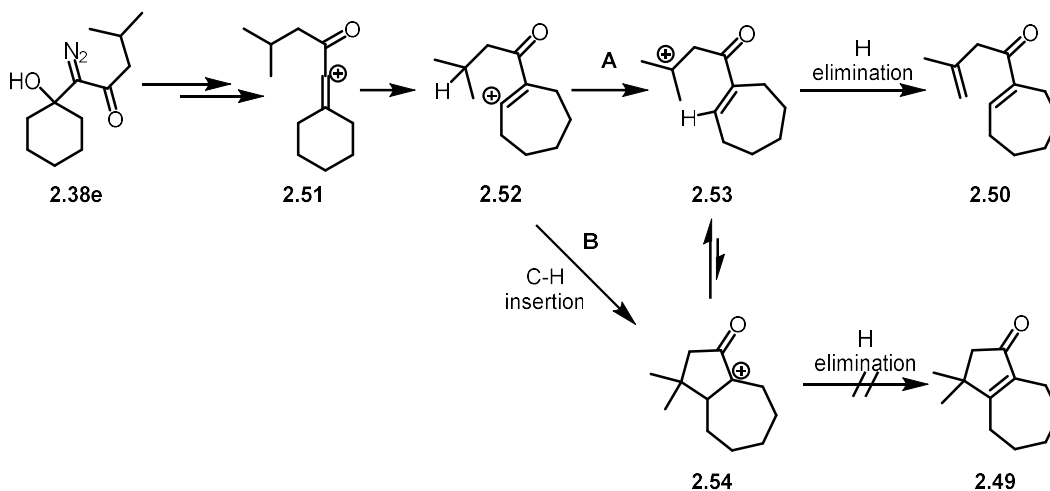
Scheme 2.10 Divergent pathways leading to elimination product

So, we hypothesize that this reaction may be stepwise when the site of insertion is a methine position. After loss of the hydroxide and nitrogen, there is a 1,2-methylene shift across the linear vinyl cation **2.51** to form the bent cyclic vinyl cation **2.52** (Scheme 2.10). If the reaction is stepwise, it will proceed through pathway A. In this pathway, the hydride is transferred to the vinyl cation to generate tertiary vinyl cation **2.53**. An elimination of a hydrogen will provide the diene **2.50**. If the C–H insertion reaction is concerted through pathway B, then there will be a formation of α-keto cation **2.54**. However, there is not an elimination of a hydrogen to give cyclopentenone **2.49**. It is possible that there was an insertion to form α-keto cation **2.54** but a ring opening leads to tertiary carbocation **2.53**,

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which gives diene **2.50** after elimination of hydrogen. Investigations into the concertedness of the C–H insertion reaction will be discussed in Section 2.9.

2.4   Substitution of the Cyclohexanone Ring System

Dr. Cleary and I then modified the cyclohexanone portion of the β-hydroxy-α-diazo ketone. These studies were important as natural products that could be synthesized utilizing this chemistry have varying degrees of substitution in the core ring system (Figure 1.6, Chapter 1, Section 1.4).   Substitution of the ring was tolerated, although yields were slightly diminished compared to the unsubstituted cyclohexanone. Dr. Cleary prepared the *t*-butyl substituted cyclohexanone which delivered cyclopentenone **2.56** in 66% yield. I prepared the dimethyl **2.57** variant, which provided cyclopentenone **2.58** in a good yield of 78%.[101]

However, the preparation of the tetramethyl substituted β-hydroxy-α-diazo ketone was particularly difficult. The tetramethyl cyclohexanone precursor is sterically hindered, so the bulky *t*-butyl diazo ketone **2.59** did not effectively react in the addition reaction. Changing it to the less sterically hindered isopropyl diazo ketone provided the desired β-hydroxy-α-diazo ketone **2.63**, albeit in a low yield of 48%. Cyclopentenone **2.64** was synthesized in 53% from the tetramethyl β-hydroxy-α-diazo ketone **2.63**. As previously demonstrated, the isopropyl derived β-hydroxy-α-diazo ketone (see Table 2.4) provides a depressed yield of the cyclopentenone product compared to the *t*-butyl derivative. In addition, yields observed for substituted cyclopentenones **2.56** and **2.58** are lower than unsubstituted variants. These points help explain the reduced yield for this substrate.
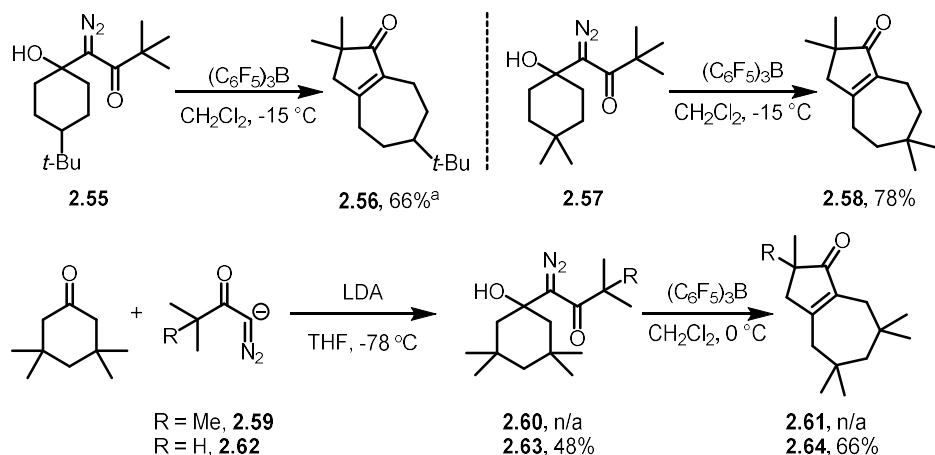
Scheme 2.11 Substitution of the cyclohexane portion of the β-hydroxy-α-diazo ketone
[a]1 equiv. of MgSO$_4$ was used in reaction

2.5 Modification of the β-Hydroxy-α-Diazo Ketone Ring Size

Dr. Cleary studied the C–H insertion reaction when the ring size of the β-hydroxy-α-diazo ketones was modified. Again, the steric bulk of the lithiated *t*-butyl diazo ketone **2.59** caused issues during the addition reaction, so the less substituted lithiated isopropyl diazo ketone **2.62** was used to prepare the insertion precursors, which were then reacted with both SnCl$_4$ and BCF (Table 2.5).[101]

When SnCl$_4$ was used as the Lewis acid, the major product for the cyclobutane β-hydroxy-α-diazo ketone **2.65** was chloride trapped product **2.67**, with the desired product **2.66** forming in trace amounts (Table 2.5, entry 1). The cyclopentenone and cycloheptanone β-hydroxy-α-diazo ketones (**2.68** and **2.71**) successfully formed the desired insertion product (**2.66** and **2.72**) albeit in low yields (Table 2.5, entries 2&3). Again, the major side product from these reactions is the formation of the chloride trapped products **2.70** and **2.73**.[101]
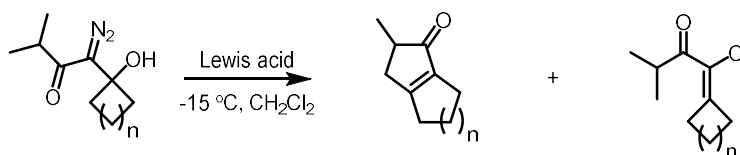
Table 2.5 Affect of β-hydroxy-α-diazo ketone ring size on reaction outcome

Entry	Compound	n	Lewis acid	Product	Yield	Product	Yield
1	**2.65**	1	SnCl$_4$	**2.66**	<5%	**2.67**	68%
2	**2.68**	2	SnCl$_4$	**2.69**	21%	**2.70**	30%
3	**2.71**	4	SnCl$_4$	**2.72**	42%	**2.73**	24%
4	**2.65**	1	(C$_6$F$_5$)$_3$B	**2.66**	0%	-	-
5	**2.68**	2	(C$_6$F$_5$)$_3$B	**2.69**	60%	-	-
6	**2.71**	4	(C$_6$F$_5$)$_3$B	**2.72**	66%	-	-

When the Lewis acid was switched to BCF, the yields of both cyclopentenone **2.69** and **2.72** improved greatly since this Lewis acid should not liberate a counterion to be trapped by the vinyl cation (Table 2.5, entries 5&6). However, the cyclopentenone **2.66** product derived from the cyclobutane β-hydroxy-α-diazo ketone **2.65** did not form.
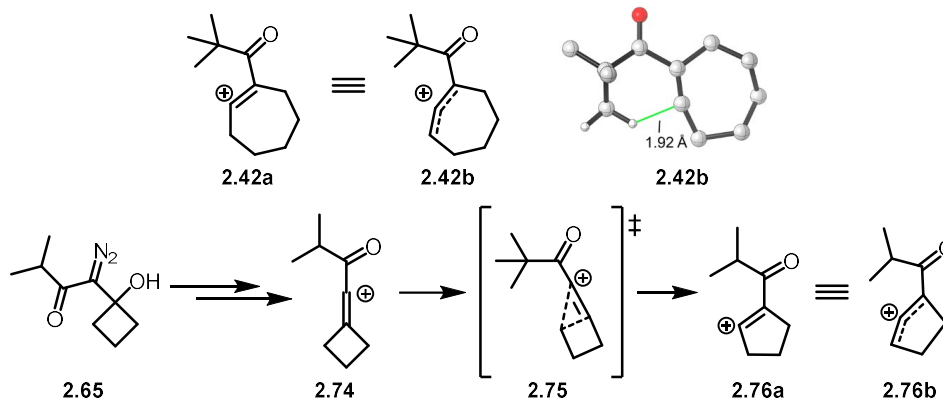
Scheme 2.12 Ring strain from vinyl cation formed after ring expansion

Our computational collaborator, Professor Xin Hong, optimized the geometry of the cyclic vinyl cation **2.42a** in the seven membered ring system (Scheme 2.12). Vinyl cation

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2.42a cannot be completely linear due to the ring strain in the seven-membered ring, although it does contort the internal bond angles as seen in **2.42b**.[102] If the vinyl cation formed from the cyclobutane to cyclopentene ring expansion of **2.74** is similar structurally to **2.42b**, then vinyl cation **2.76b** would exhibit a large amount of ring strain. This would make **2.76a** unlikely to form, overall decreasing the yield of the desired product.

2.6   Monocyclic Cyclopentenone Systems from Linear β-Hydroxy-α-diazo Ketones

Dr. Cleary further tested the C–H insertion reaction on acyclic variants **2.77** and **2.79** to provide monocyclic cyclopentenones. These variants are useful since they resemble the biologically active prostaglandin motif. The isopropyl β-hydroxy-α-diazo ketone **2.77** provided the monocyclic cyclopenteneone **2.78** in 33% yield, while the *t*-butyl β-hydroxy-α-diazo ketone provided **2.80** in 63% yield, again demonstrating the efficiency of the more substituted system.[101]

$$R = H, \textbf{2.77}$$
$$R = Me, \textbf{2.79}$$

$$\textbf{2.78}, 33\%$$
$$\textbf{2.80}, 63\%$$
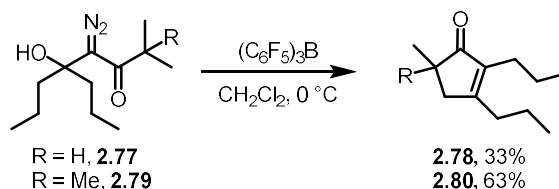
Scheme 2.13 Preparation of monocyclic cyclopentenone variants

It is hypothesized that the lower yields for the monocyclic cyclopentenones could be explained by decomposition of the vinyl cation to a volatile alkyne. Since Schegolev and coworkers had demonstrated that vinyl cations can be formed from the Friedel-Crafts type acylation of acyl cations and alkynes (Scheme 2.1, Section 2.1), it is not unreasonable that the reverse could occur.[104] After formation of linear vinyl cation **2.81**, the acyl-sp$_2$ carbon

bond could break to form acylium **2.83** and alkyne **2.84** (Scheme 2.14). These products were not isolated, however, potentially due to the volatility of acylium **2.83** and alkyne **2.84**. However, as will be described in Chapter 3, I was able to isolate an alkyne side product to provide experimental evidence for this pathway. The formation of alkyne side product **2.87** was not observed in the cyclic variants of our study. This is reasonable as the formation of alkynes in cyclic systems would be unfavorable sue to strain. In fact, alkyne **2.87** which would form from the reverse Friedel-Crafts of **2.85**, is so unstable that it has a half-life of an hour at -76 °C.[105]
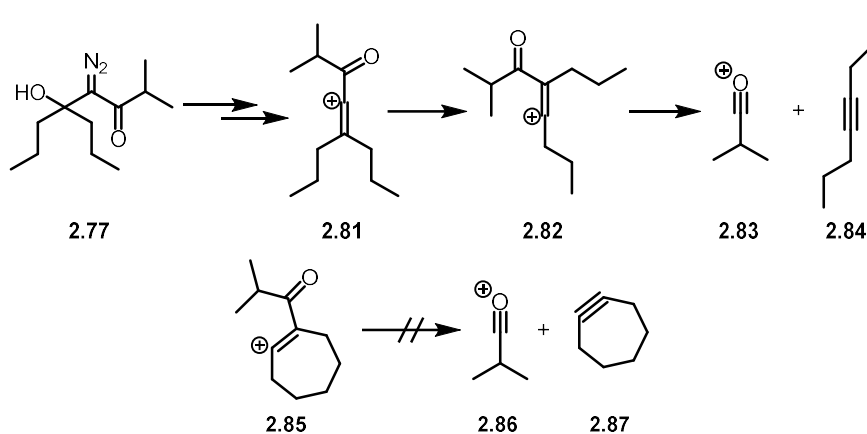
Scheme 2.14 Alkyne formed from reverse Friedel-Crafts type decomposition

2.7   Synthesis of Fused Ring Systems via the Developed C–H Insertion Methodology

To further expand the substrate scope, I planned to prepare the fused 6,6,5-cyclopentenone **2.89**. This substrate would be of interest because it would incorporate Dr. Cleary's ring expansion investigations and demonstrate that we can easily form fused ring systems with our methodology.

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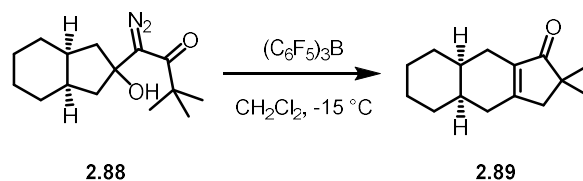
Scheme 2.15 Synthesis of 6,6,5-fused cyclopentenones

To start, I set out to prepare the β-hydroxy-α-diazo ketone **2.88** precursor. First, anhydride **2.90** was reduced to diol **2.91** using NaBH$_4$ and iodine.[106] Initially, I used TsCl to make the alcohols a better leaving group, but this gave poor, inconsistent yields. Mesylating both alcohols provided a consistent yield of 59%, which were susceptible to S$_N$2 attack to provide the dinitrile in 73% yield. The dinitrile was subsequently transformed into the diacid in 93% yield.[107] Finally, ketone **2.93** was accessed from diacid **2.92** in 56% yield by a one-pot cyclization and decarboxylation (Scheme 2.16).[108]
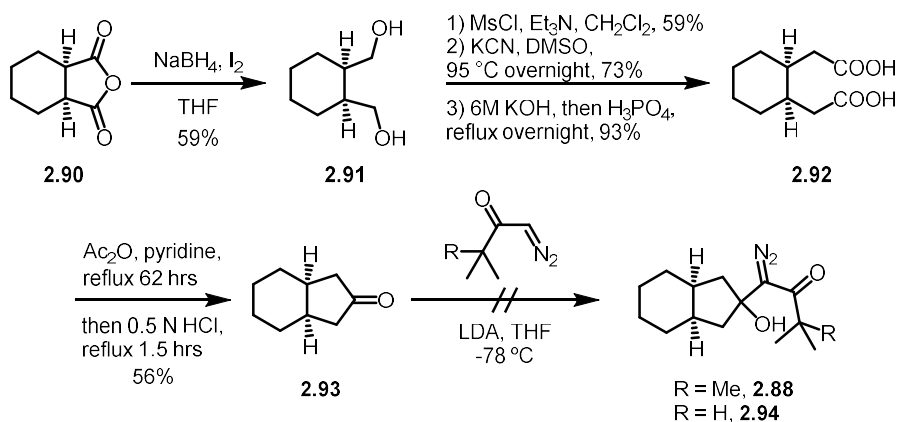
Scheme 2.16 Sequence to prepare β-hydroxy-α-diazo ketone 2.88 & 2.94

The final addition step to generate the starting β-hydroxy-α-diazo ketone **2.88** gave impure desired product and poor yields. I used the more substituted *t*-butyl diazo ketone, however, due to the smaller ring size the addition may not have been favorable. Dr. Cleary also had issues with the addition reaction when the ring was a cyclopentanone using the *t*-

butyl diazo ketone (R = Me). If this system is investigated further in the future, it might be easier to synthesize the isopropyl diazo ketone (R = H) which should be less sterically hindered and may add successfully into ketone **2.94**.

2.8 Failed Attempts at Incorporating Heteroatoms Near Point of Insertion

After investigating several symmetrical hydrocarbon substrates, I turned towards investigating the C–H insertion with heteroatoms present near the point of insertion. To this end I attempted to prepare multiple β-hydroxy-α-diazo ketones (**2.95**, **2.97**, **2.99**) which all incorporated a heteroatom near the point of insertion.
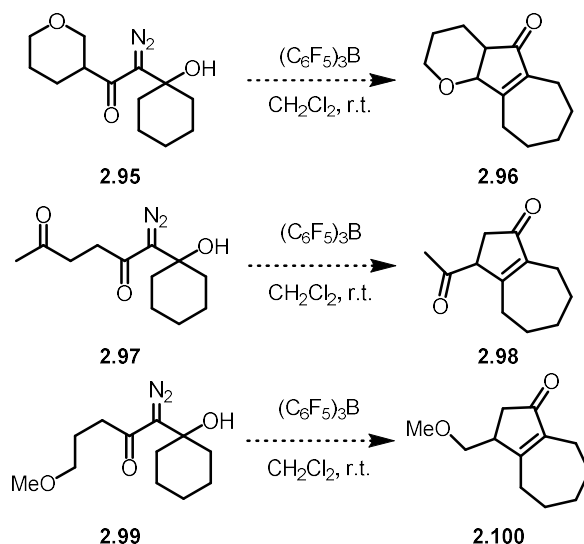
Scheme 2.17 Desired C–H insertion products when a heteroatom is near point of insertion

To synthesize diazo ketone **2.95**, I subjected dihydropyran to oxalyl chloride, which in turn formed an α-keto acid chloride. After decarbonylation using heat, nucleophilic attack provided the desired unsaturated carboxylic acid in 50% yield, which was then reduced using Pd/C and hydrogen gas to provide carboxylic acid **2.101** in 73% yield.[109, 110]

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To incorporate the diazo we would typically next form the acid chloride that would need to be purified with vacuum distillation. To avoid this, I tried an alternative method to form diazo ketone **2.102**. Using methyl chloroformate, I formed an anhydride from carboxylic acid **2.101**, which then reacted with diazomethane to form diazo ketone **2.102** in a low yield of 31%.[111] The addition reaction worked well, and the desired β-hydroxy-α-diazo ketone **2.95** was formed in quantitative yield.
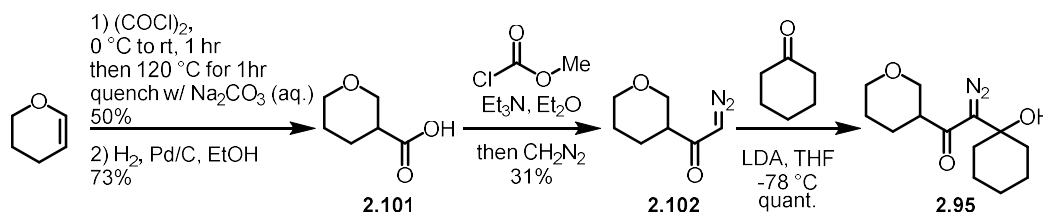
Scheme 2.19 Synthesis of pyran containing β-hydroxy-α-diazo ketone 2.95

However, when I subjected β-hydroxy-α-diazo ketone **2.95** to the C–H insertion conditions, I did not receive the desired product, but instead a complex mixture. I suspect that the Lewis acid coordinates to the pyran thus preventing the reaction. Switching to SnCl$_4$ did not yield desired products.
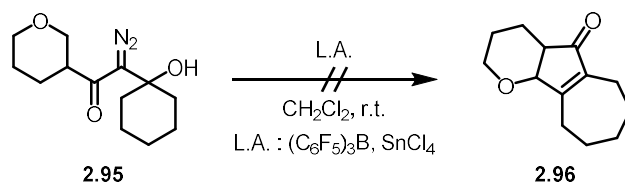
Scheme 2.20 Failed preparation of cyclopentenone 2.96 when point of insertion is adjacent to a heteroatom

There are a few possible products that could arise from this substrate. After loss of the hydroxide and the diazo group, it is possible there was counterion capture of the linear vinyl cation **2.103** to provide **2.104** and **2.105**. Discussed in Scheme 2.21, we have identified and isolated the chloride trapped linear vinyl cation when SnCl$_4$ is used as the

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Lewis acid. However, there have also been cases where we have observed the pentafluorobenzene trapped product using ^{19}F NMR, but we have not isolated it. Since BCF should not liberate a counterion, we suspect this is due to the boron Lewis acid coordinating to the carbonyl oxygen and delivering the pentafluorobenzene to the vinyl cation.

With this in mind, the cyclic vinyl cation **2.106** may have also been trapped by counterions to provide **2.107** and **2.108**. If the C–H insertion is stepwise when the point of insertion is 2°, then the methylene cation **2.109** formed after hydride transfer would be stabilized by the adjacent oxygen atom. This may lead to capture by the counterion to provide **2.110** and **2.11**. It is also possible that the hydride was transferred from the methylene carbon not adjacent to the oxygen atom to provide cation **2.112**, which may be prone to elimination before C–H insertion. However, none of these products were isolated.
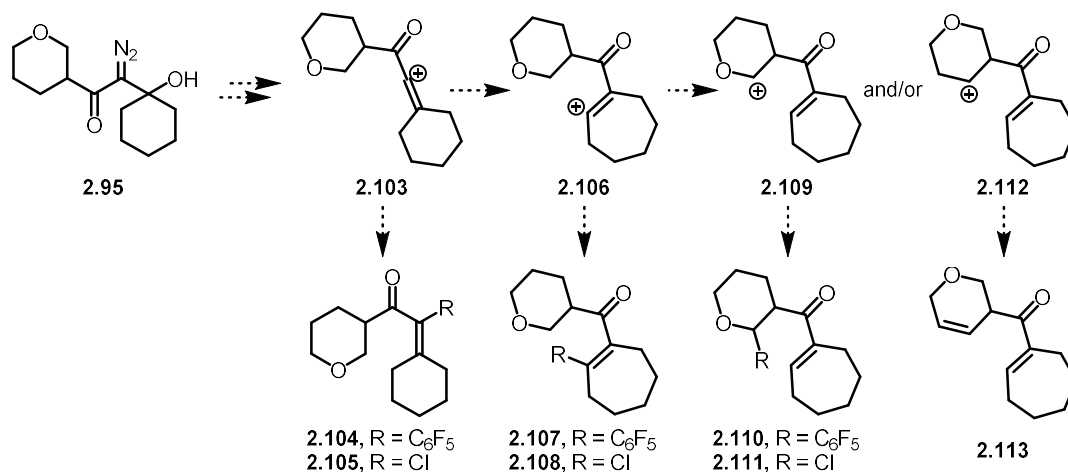
Scheme 2.21 Potential synthetic pathways with the pyran substituent

Moving forward, I turned my attention towards preparing cyclopentenone **2.97**, where there is a ketone adjacent to the point of insertion. Insertion adjacent to a ketone is

desirable, since this functional group would have been a useful synthetic handle for natural product syntheses.

I prepared diazo ketone **2.114** from the reaction of diazomethane with the anhydride prepared from the reaction of levulinic acid and methylchlorofomate.[111] However, the preparation of β-hydroxy-α-diazo ketone **2.97** was not trivial. This reaction posed similar sensitivity to workup and temperature changes that were observed in earlier substates and would often return starting material. The main complication arose from the diazo ketone **2.114** itself. There are two sites for deprotonation by LDA to occur, the proton adjacent to the diazo group and the α proton of the distal ketone. Although the diazo ketone proton should be more acidic, it is possible competitive deprotonation may occur. Furthermore, the diazo ketone may add into the ketone of another equivalent of diazo ketone **2.114**.
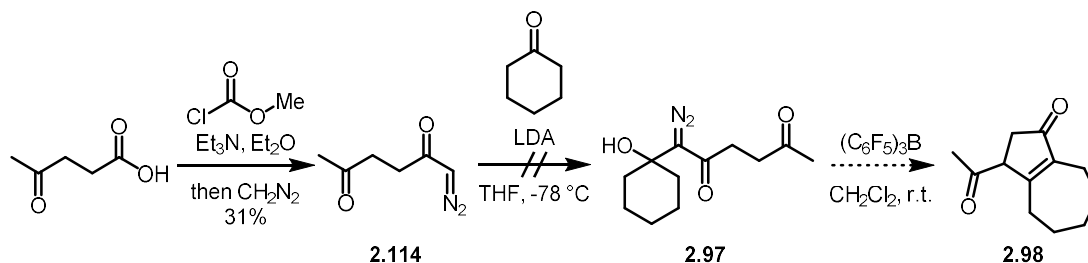
Scheme 2.22 Unproductive formation of β-hydroxy-α-diazo ketone 2.97

Since the ketone substate was unproductive, I moved to synthesize β-hydroxy-α-diazo ketone **2.99** which contained a pendant methoxy functional group. My high school ACS project SEED student, Zachary Taylor, assisted me in preparing this starting material. First, the acid catalyzed butyrolactone ring opening provided methyl ester **2.115** in 59% yield.[112] Next, saponification of this ester yielded the corresponding carboxylic acid, which could be converted to the mixed carboxylic–carbonic anhydride and reacted with diazomethane

to prepare diazo ketone **2.116**.[111] This diazo ketone **2.116** added into cyclohexanone to provide a good yield of β-hydroxy-α-diazo ketone **2.99**.
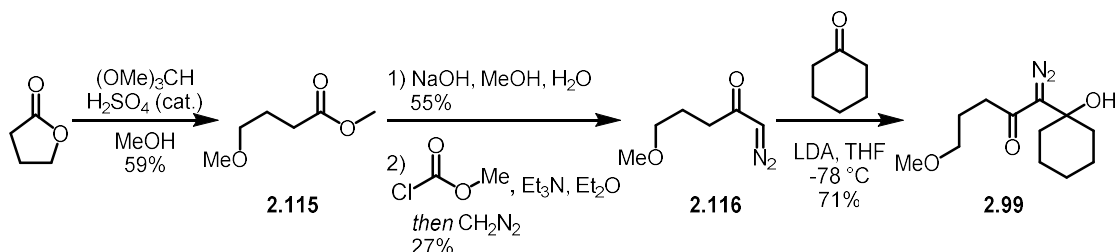
Scheme 2.23 Synthesis of β-hydroxy-α-diazo ketone 2.99

With β-hydroxy-α-diazo ketone **2.99** in hand, we investigated the C–H insertion. However, this reaction was unproductive, and we could not isolate or determine what products this reaction produced. Again, similar to **2.95** (Scheme 2.20), it's possible that the BCF coordinated to the oxygen on the ether ring, suppressing the reaction. There are a few different pathways this reaction can take, such as intermolecular capture of vinyl cations **2.117** and **2.118**. An alternative pathway that may be likely with this substrate is insertion at a more distant position to generate 6,7-fused system **2.120**, if the methoxy is promoting insertion at that site. However, we did not isolate any of these possible products, and purification attempts returned complex mixtures.
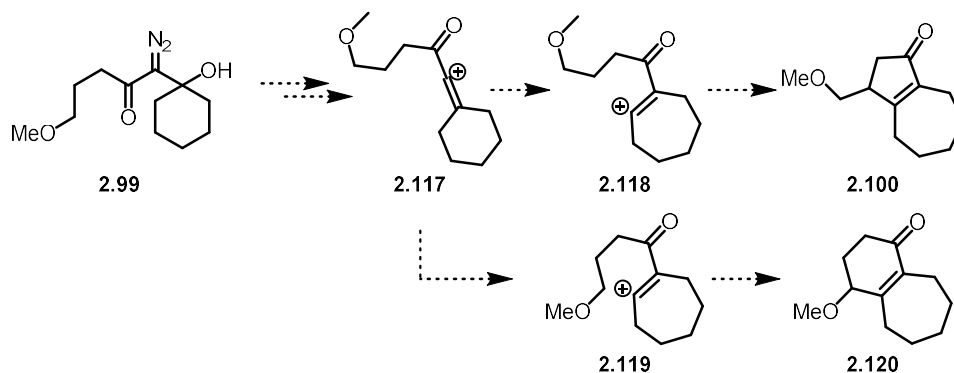
Scheme 2.24 Potential pathways with a methoxy ether substituent

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2.9 Investigations into the Mechanism of the C–H Insertion Reaction

With the initial substrate scope completed, I turned towards investigating the mechanism of the C–H insertion. Previously demonstrated, when the point of insertion was a methyl or a methylene on a linear carbon chain, the product formed by the desired C–H insertion (Scheme 2.25).
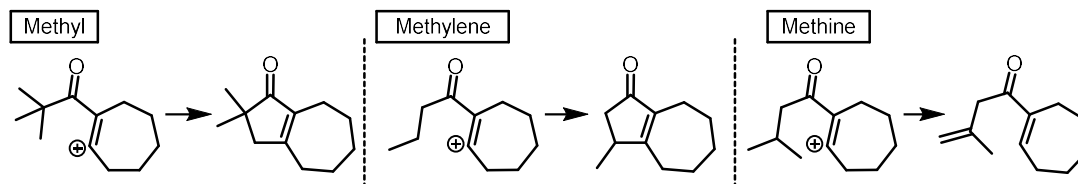
Scheme 2.25 Modification at point on insertion provides different results

However, when the point of insertion was a methine substituent, the resulting product was a diene (Scheme 2.25). In all cases, a 1,2-shift across the alkene generated the 7-membered ring, which results in a new vinyl cation that can insert at a C–H bond or accept a hydride. If the insertion step is a stepwise process, the hydride shift would result in a 1°, 2°, or 3° carbocation. However, it is possible that the mechanism is concerted or stepwise, depending on the substrate used.

2.9.1 When the Point of Insertion is Primary

To investigate the concertedness of the reaction, I turned towards preparing β-hydroxy-α-diazo ketone **2.124** that has a deuterium atom at the point of insertion (Scheme 2.26). First, I methylated propionic acid with deuterated methyl iodide. Over two equivalents of LDA was necessary to deprotonate the carboxylic acid and the α-proton on the carboxylate. Although this procedure was successful for larger branched carboxylic acids in the literature, the highest yield of deuterated carboxylic acid **2.122** formed was 16%.[113] It is possible this smaller carboxylic acid was more volatile and evaporated during workup, so

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I generated the deuterated isobutyric acid **2.122** on a 33 mmol scale, evaporated most of

the solvent off, and added oxalyl chloride and catalytic DMF to form the crude acid

chloride, which I immediately subjected to diazomethane. After 3 steps starting from

propionic acid, I synthesized the deuterated diazo ketone **2.123** in an abysmal 8% yield.

However, this was enough to move forward and successfully form deuterated β-hydroxy-

α-diazo ketone **1.124** in a manageable 78% yield.
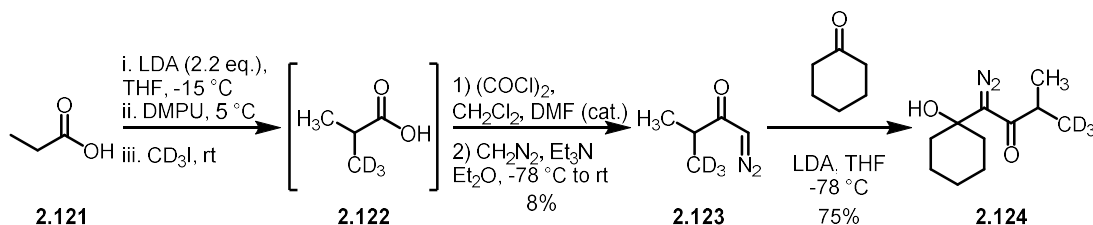
Scheme 2.26 Preparation of deuterated β-hydroxy-α-diazo ketone 2.124

The β-hydroxy-α-diazo ketone **2.124** was subjected to 1 eq. of BCF in CH_2Cl_2 to

determine the kinetic isotope effect on the C–H insertion. The ratio of insertion at hydrogen

vs. deuterium was 1.15, which indicates a low KIE (Scheme 2.27).
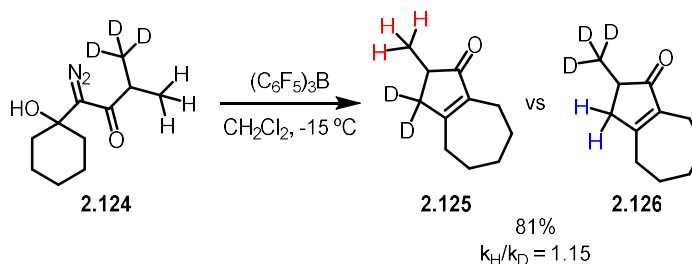
Scheme 2.27 KIE study of C–H insertion reaction when point of insertion is 1°

Based on literature data, this low KIE is indicative of a concerted reaction. The DuBois

group measured the kinetic isotope effect of their developed Rh-catalyzed amination

reaction (Scheme 2.28), in which a Rh-bound nitrene C–H inserts to form an oxathiazinane

heterocycle. They prepared mono-deuterated sulfamate **2.128** and subjected it to the

amination conditions to receive a 1.9(±0.2) ratio of heterocycles **2.128** and **2.129**.

Rhodium-catalyzed carbene insertion reactions are concerted if the KIE is between 1.2 and

2.1; the low KIE of 1.9(±0.2) obtained in my studies indicates a concerted C–H insertion

mechanism.[114, 115] Based on this publication and other literature results,[115] we can conclude

that the reaction is concerted when the point of insertion is 1°. The concertedness of this

reaction is corroborated with computational data, which is discussed in further detail in

Section 2.10.[102]
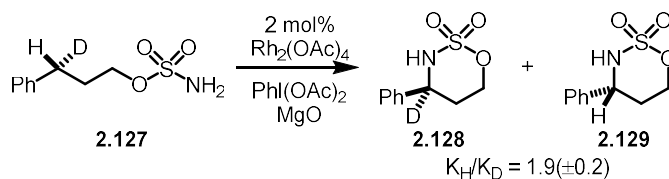
Scheme 2.28 KIE of Du Bois and coworkers Rh-catalyzed C–H amination

In addition, we also wanted to perform a kinetic isotope study in the 1° system where

the point of insertion is an isotopically labeled carbon. An alternate synthesis was used to

prepare the ^{13}C isotopically labeled β-hydroxy-α-diazo ketone **2.135**. This method was

more efficient than the method used to form β-hydroxy-α-diazo ketone **2.124**. First,

deprotonation of diester **2.130** using sodium hydride followed by subsequent alkylation

with ^{13}CH$_3$I afforded isotopically labeled diester **2.131** in 94% yield (Scheme 2.29).[116]

Decarboxylation of diester **2.131** to give acid **2.132** was optimized on an unlabeled model

substrate. Krapcho decarboxylation conditions using LiCl, followed by saponification,

failed to provide the carboxylic acid product. Furthermore, preparation of the diacid first

through saponification, and then decarboxylation using KOAc or Cu(I)O was

unproductive. However, subjecting the protonated diacid to MW conditions provided the desired unlabeled carboxylic acid product in a moderate yeild.[117]
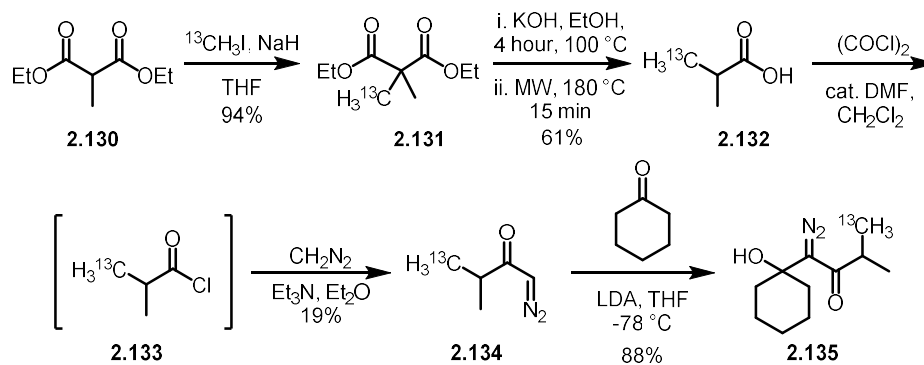
Scheme 2.29 Synthesis of isotopically labeled β-hydroxy-α-diazo ketone 2.135

Appling these optimized conditions to the labeled diester **2.131** successfully provided labeled carboxylic acid **2.132**. Saponification using KOH followed by acidic workup provided the diacid precursor, which is not very soluble in organic solvents. The crude material from the saponification was used immediately in the microwave reaction. Subjecting the dilute diacid to MW irradiation provided labeled carboxylic acid **2.132** in 61% yield.[117] This yield may be not be accurate because pressure built up from the production of CO_2 caused some of the reaction mixture to expel from the MW tube, resulting in a loss of material.

Carboxylic acid **2.132** was subjected to oxalyl chloride to form the acid chloride **2.133**, which was used without purification in the next reaction, gives diazo ketone **2.134** in 19% yield over two steps. Finally, the addition of lithiated diazo ketone **2.134** to cyclohexanone provided **2.135** in 88% yield.
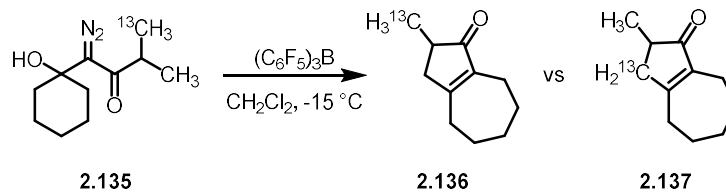
Scheme 2.30 ^{13}C labeled isotopic labeling study

β-Hydroxy-α-diazo ketone **2.135** was subjected to BCF to observe the ^{13}C kinetic isotope effect on the C–H insertion mechanism. This resulted in cyclopentenone products **2.136** and **2.137** in about a 1:1 ratio of ^{13}C insertion and ^{12}C insertion by quantitative NMR. At the moment, we are unsure of the exact ratio and the overall meaning of these results and are currently investigating this in further detail along with our computational collaborator.
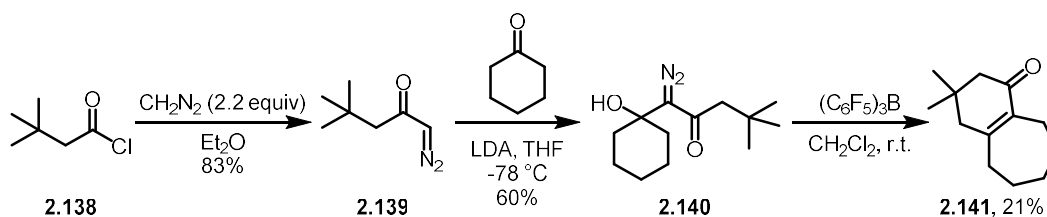
Scheme 2.31 C–H insertion at extended 1° center

To observe the potential of the C–H insertion occurring on an extended system I prepared β-hydroxy-α-diazo ketone **2.140**. Gratifyingly, when β-hydroxy-α-diazo ketone **2.140** was subjected to the C–H insertion conditions, it provided the 6,7-fused ring **2.141** in 21% yield (Scheme 2.31). This result demonstrates that the C–H insertion can occur when the point of insertion is extended by one carbon unit. This type of product was not observed for isovaleryl β-hydroxy-α-diazo ketone **2.38e**, which indicates that hydride transfer/elimination is faster than a C–H insertion at the distant methyl.

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2.9.2   When the Point of Insertion is Secondary

Based on the KIE studies performed in Section 2.9.1, we hypothesize that the C–H insertion is concerted when the point of insertion is primary. I next turned towards investigating the mechanism when the point of insertion is secondary to determine if it was a concerted or a stepwise process using similar KIE studies.

I attempted to form the β-hydroxy-α-diazo ketone **2.142** where the point of insertion contained a deuterium atom. First, I needed to form the respective diazo ketone from corresponding carboxylic acid. Initially, I planned to form the carboxylic acid through deuteration of crotonic acid using hydrogenation, and then exchange the deuterium at the α-position for hydrogen through enolate chemistry.
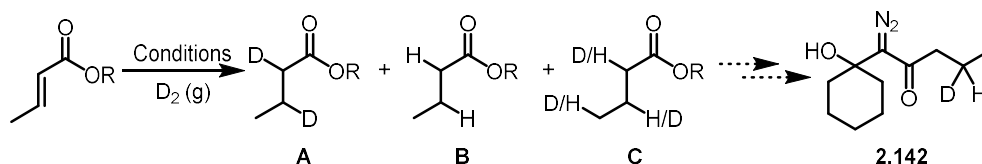
Table 2.6 Conditions tested for mono deuteration at β-position

Entry	Conditions	R
1	Pd/C, EtOH	H
2	PtO, MeOD	H
3	PtO, EtOAc	H
4	PtO, EtOAc	Et
5	PtO, MeOAc	Et
6	PtO, 1,4-dioxane	Et

However, this venture was unsuccessful (Table 2.6). In all cases I obtained hydrogenated product **B** in addition to deuterated product **A** as an inseparable mixture, or only hydrogenated product **B**. Initially, I hypothesized Pd/C was the issue since it has been shown that commercially available Pd/C can have a range of acidity and quality.[118] With

this in mind, I switched the catalyst to PtO and ran the reaction in deuterated methanol to remove any source of hydrogen (Table 2.6, entries 1 &2). However, this still provided undesirable hydrogenated product. Switching the solvent to ethyl acetate (entry 3) provided only hydrogenated product.

Suspecting that our D_2 gas may be impure, I ran the hydrogenation conditions on styrene to test the purity. Deuterated styrene was the only product, which indicated that the issue was the unsaturated carboxylic acid. Switching to the ethyl ester, the deuterated product was formed in higher ratios, although hydrogenated product was still prevalent (Table 2.6, entries 4-6). Frustratingly, there was also deuteration at the γ position of the ester (**C**). This is due to hydride migration through chain walking, and provides evidence as to why we were forming mixtures of deuterated and hydrogenated products when no source of hydrogen was avalible.[119]
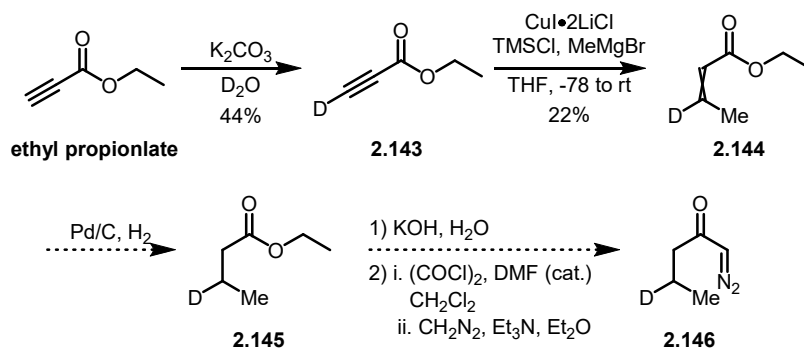
Scheme 2.32 Proposed scheme to access diazo ketone with deuteration at the β'-position

An alternative synthesis to diazo ketone **2.146** is outlined in Scheme 2.32. Starting from ethyl propionlate, the hydrogen on the alkyne is replaced with deuterium, returning deuterated ester **2.143** with 90% deuterium incorporation at the terminal alkyne.[120] Copper mediated addition of a methyl gave alkene **2.144** in a 22% yield. This yield may be

improved if MeMgCl is used instead of MeMgBr.[121] Future work includes reduction of the alkene with Pd/C and hydrogen gas to provide ester **2.145**. Diazo ketone **2.146** can be accessed by saponification, acid chloride formation, and acylation to install the diazo functional group.

Shifting gears, I decided to investigate alternative secondary systems as another means to study the C–H insertion when the point of insertion is a methylene. As previously demonstrated, there was no elimination product when the point of insertion was 2°, in the case of the linear carbon chain (Scheme 2.9). To this end, I prepared cyclohexyl β-hydroxy-α-diazo ketone **2.38f**, in which the point of insertion is in a ring system and is secondary. Surprisingly, the desired 6,5,7-fused cyclopentenone **2.147** was not formed, but rather alkene **2.148** was the only compound I could isolate cleanly (Scheme 2.33). Other products included the counterion trapping of the vinyl cation intermediates, which were inseparable from other minor products.
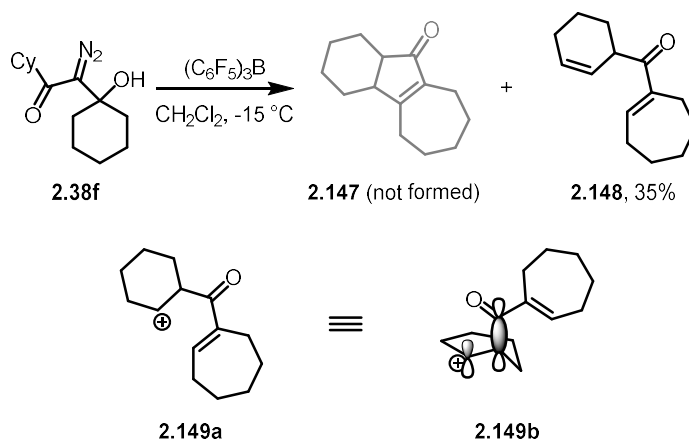
Scheme 2.33 Substrate where point of insertion is 2° and in a ring system

We currently do not know what factors promote the formation of alkene **2.148**. However, this substrate is interesting, because it could help to prove that insertion is stepwise in the case of the secondary substrate depending on stability of the resulting

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cation. The 2° cation formed by hydride transfer may be more stable than the α-keto cation that would result from ring closure. If it is not an equilibrium type process, it is likely the orbitals do not align appropriately for ring closure to occur. However, there was no elimination product for the propyl derivative, which indicates the cyclohexane ring structure may be playing a roll. If stepwise, the transfer of a hydride will generate a secondary carbocation in the cyclohexane ring. It is possible the acyl group adopts an orientation (**2.149b**) that will allow hyperconjugation between the vacant *p* orbitals of the carbenium ion with the carbon-carbon bond of the acyl group, stabilizing the carbocation.[122] This stabilization may direct the mechanism to a more stepwise manner, and the elimination product would be formed. Another possibility is that the cycloheptene ring should face away from the cyclohexane ring system to alleviate A-1,3 strain, and it would not be able to attack the empty orbital from the top face.

I was curious to determine if a cyclopentyl analog would undergo C–H insertion. I hypothesized that there would be more ring strain from the secondary cation **2.154a** formed after hydride transfer. This strain would prevent the acyl group to be axial in orientation (**2.154c**) and instead adopt a typically more stable equatorial position (**2.154b**). Therefore, ring closure would be the preferable pathway (Scheme 2.34). It is also possible there is fewer nonbonding interactions on the smaller cyclopentenone ring system and the cyclohepteneone ring system could be positioned over the carbocation, priming it for attack.
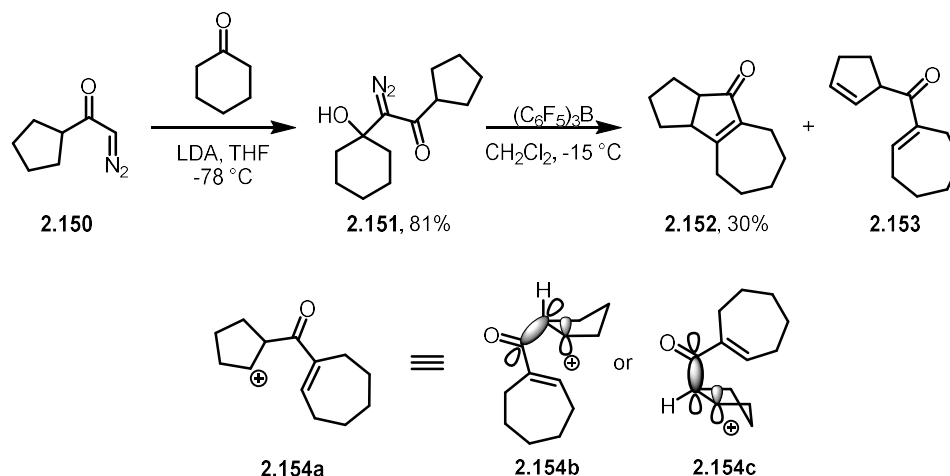
Scheme 2.34 Greater ring strain in intermediate cation provides fused bicyclic products

To test this, I prepared the cyclopentyl β-hydroxy-α-diazo ketone **2.151** and applied the

C–H insertion conditions. I obtained the desired fused bicyclic system **2.152** in 30% yield,

in addition to a small (~5%) amount of alkene **2.153**. However, the alkene from elimination

was inseparable from another unidentified side product, so the yield and characterization

of **2.153** is not definitive. If the C–H insertion is stepwise for substrates with a 2° and 3°

point of insertion, then the stability of the resulting cation may dictate the ratio of C–H

insertion vs. alkene product formed.
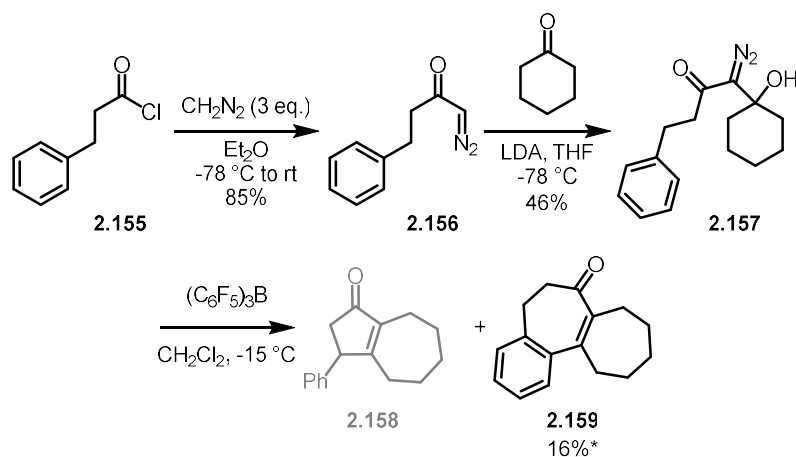
Scheme 2.35 Intramolecular electrophilic vinylation with extended system

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With this is mind, I prepared β-hydroxy-α-diazo ketone **2.157**, which has a phenyl ring adjacent to the point of insertion. However, if a 2° carbocation is formed, it would be stabilized by the adjacent aromatic ring, potentially giving rise to other undesirable side products. In fact, when testing this substrate, the cyclopentenone **2.158** that would arise from a C–H insertion was not detected. Instead the only isolable product I received is what I believe to be product **2.159**, which formed in approximately 16% yield. The actual yield is likely lower due to impurities in the product.

This result is not completely unsurprising. Dr. Jiang Fang studied systems that formed indanone products **2.164** from an intramolecular electrophilic aromatic substitution reaction onto the cyclic vinyl cation (Scheme 2.36). When the tether length was extended by one carbon, he received naphthol **2.163**, formed from tautomerization of the cyclohexenone product, and indene-2-one **2.164**. The latter formed from the reaction of the aromatic ring with the linear vinyl cation.[64] It is likely I received similar products, although they could not be identified as I received many complex mixtures.
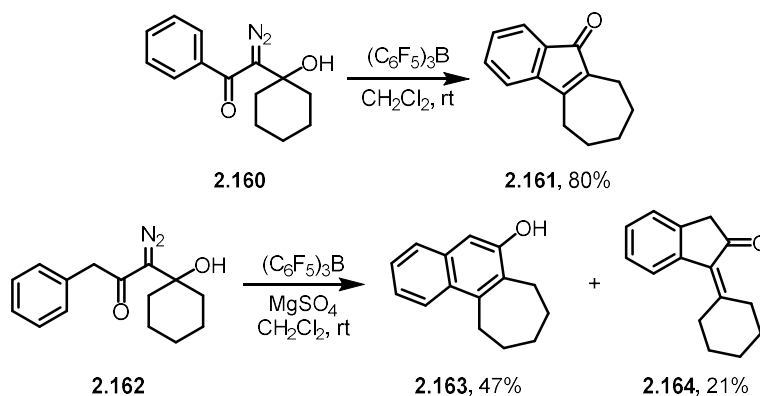
Scheme 2.36 Dr. Fangs investigations on intramolecular aromatic substitution reactions on vinyl cations

2.9.3   When the Point of Insertion is Tertiary

I next turned my attention to further investigate when the point of insertion is a methine position. As stated previously, the cyclopentenone resulting from C–H insertion is not formed when the point of insertion is tertiary. We hypothesize that this occurs via hydride transfer to the vinyl cation to give a 3° carbocation (e.g. **2.53**, Scheme 2.10). In this case cyclization would be energetically disfavorable, thus allowing competitive elimination to occur. However, I hypothesized that if the elimination would be a disfavored process, there would be a possibility for insertion at a methine center.
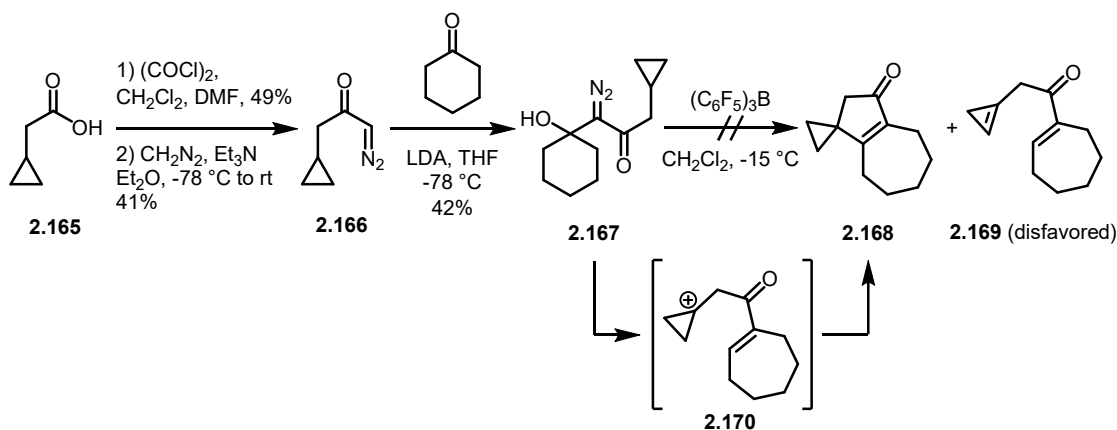
Scheme 2.37 Using a cyclopropane to form a quaternary center

To this end, I prepared cyclopropane derivative **2.167**. I postulated that the 3° carbocation **2.170** formed after a stepwise 1,5-hydride transfer would not yield elimination product cyclopropene **2.169**, but instead cyclopentenone **2.168**. I based this hypothesis on the stability of cyclopropenes, which have a ring strain of 228 kJ mol^{-1}. This strain would make the energetically favored product the cyclopentenone ring system.[123]

However, I was unable to isolate either the desired cyclopentenone product **2.168** or the cyclopropene product **2.169**, or determine the products formed from this reaction. It is

possible that the cyclopropene **2.168** was formed, but it's instability would cause quick decomposition, which is common for cyclopropenes without some sort of stabilization.[123] Furthermore, cyclopropenes need to be handled carefully to avoid contact with air. For example, in their synthesis of 3-arylcyclopropenes, Rubin and coworkers report that after removal of solvent *in vacuo* the air had to be displaced with inert gas and the products purified by vacuum distillation. In addition, samples exposed to air and then purged with N_2 gas decomposed completely within two weeks.[124]

2.9.4   Taking Advantage of the β-silyl Effect to Promote Ring Closure

When the point of insertion is a tertiary center, insertion does not occur. Shifting focus, I turned towards stabilizing the α-keto cation **2.54** formed after C–H insertion by taking advantage of the β-silicon effect. The β-silicon effect would stabilize the resulting empty π orbital of the α-keto cation through hyperconjugation with the C–Si σ orbital.[125] If the 3° carbocation **2.174** and α-keto cation **2.175** are in equilibrium, then the Si–C bond could stabilize the α-keto cation **2.175** and make it more stable, therefore allowing deprotonation at the β position, forming the cyclopentenone product. One issue would be the migratory preference of the carbon bearing the silyl group, but further studies into migratory aptitude indicated the more sterically hindered side migrates preferentially (migratory aptitude work is discussed further in Chapter 3).[60]
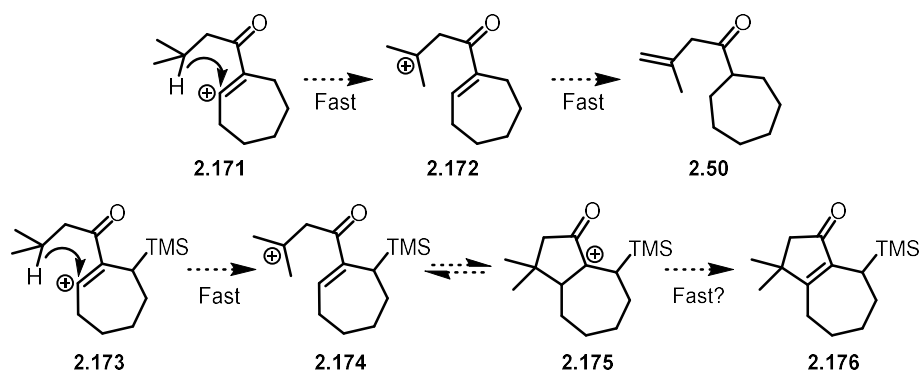
Scheme 2.38 Stabilization from Si–C bond yields fast ring closure?

Unfortunately, I was unable to form the silylated β-hydroxy-α-diazo ketone **2.182** starting material necessary to conduct this experiment (Scheme 2.39). To initiate the synthesis, cyclohexenone was brominated in the presence of triethyl amine to give 2-bromocyclohexenone **2.178**.[126] Enone **2.178** was protected with ethylene glycol to provide ketal **2.179**.[127] Metal-halogen exchange, silylation, and subsequent deprotection afforded α-(trimethylsilyl) cyclohexenone **2.180** in high yield.[128] Finally, the enone was reduced to the α-(trimethylsilyl) cyclohexanone **2.181** using L-selectride.[129] This reduction step was challenging. The product contained impurities, even after purification, and the yields ranged from 0-63%. In addition, the product decomposed to cyclohexanone over time. Other types of reduction reactions, such as hydrogenation, provided only cyclohexanone as the product. Due to the lability of the trimethyl silyl group, I switched to triethyl silane, which gave a consistent yield of 62%.
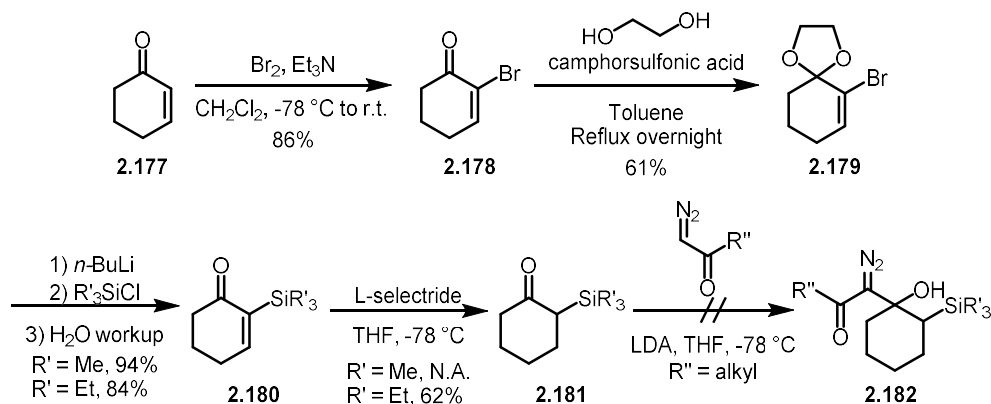
Scheme 2.39 Synthetic sequence to β-hydroxy-α-diazo ketone 2.182

Unfortunately, the addition step of a lithiated diazo ketone was unproductive, and the reaction failed under the normal addition conditions. However, aldol type addition reactions to α-silyl ketones have been done previously.[130] With this in mind, I modified the procedure to match known literature. Premixing the diazo ketone for 1 hour with LDA to deprotonate the diazo ketone and then quick addition of silane **2.181** should have facilitated the reaction. However, this procedure did not generate the desired product. Modification of the diazo ketone to a less substituted alkyl group also failed. The α-silyl ketone may be too sterically hindered for the addition to occur.

2.10 Computational Investigations of the C–H Insertion

Our computational collaborator, Dr. Xin Hong at Zhejiang University in China, modeled the C–H insertion for three classes of carbonyl compounds (ketone, ester, and amide) which all reacted in distinct ways when treated with Lewis acids.[102] This provided valuable insight and computational data into the mechanism of the C–H insertion. I will

discuss in detail the DFT-computed free energy profile of the C–H insertion, and briefly touch upon the ester and amide results.
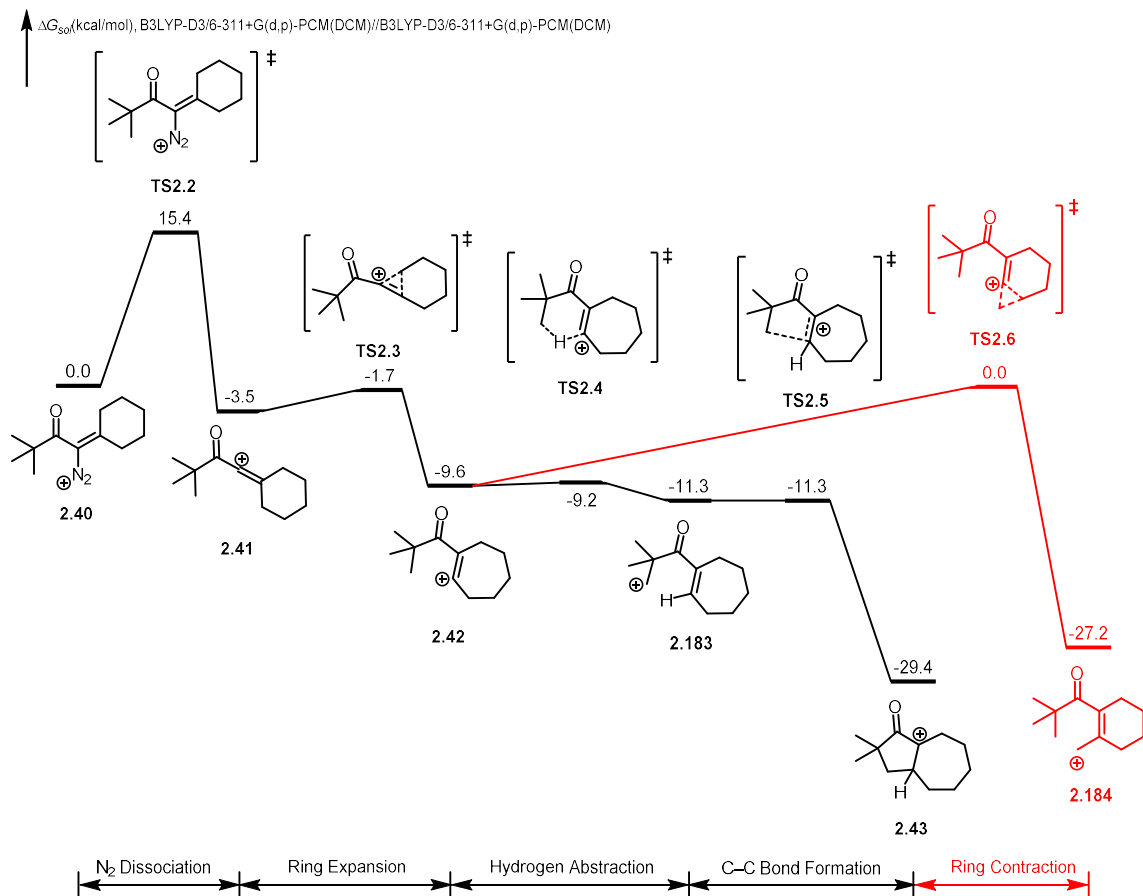
Figure 2.1 DFT energy profile of the C–H insertion with diazo ketones

When the diazo carbonyl is a diazo ketone the C–H insertion is the energetically favorable reaction pathway. From diazonium **2.40**, the nitrogen dissociates through **TS2.2** to provide linear vinyl cation **2.41** (Figure 2.1). The loss of nitrogen is the rate limiting step in this reaction. After this initial energy barrier, the subsequent transformations are rapid with low energy barriers. The ring expansion from the linear vinyl cation **2.41** to the cyclic vinyl cation **2.41** (via **TS2.3**) has an energy barrier of 1.8 kcal/mol. From cyclic vinyl cation

2.42 the C–H insertion occurs with no energy barrier through **TS2.4** and **TS2.5**, indicating a concerted reaction. [102]

In the case of the ketone substrate, the competing ring contraction from **2.42** to **2.184** (via **TS2.6**) is less favorable than the C–H insertion, with a barrier of 9.6 kcal/mol. Importantly, although 1° carbocation **2.183** was observed in the computations, there is no free energy barrier from **2.183** to **TS2.5**. Again, this suggests that the C–H insertion step to go from cyclic vinyl cation **2.42** to cyclopentanone **2.43** occurs through a dynamically concerted fashion. This is supported by my experimental KIE studies discussed in Section 2.9.1.

DFT calculations of diazo esters indicate that a loss of nitrogen and a 1,2-methylene shift to form a cyclic vinyl cation are favorable transformations. However, the ring contraction is 3.9 kcal/mol more favorable than the C–H insertion which ultimately gives way to a lactone product. This is corroborated with Dr. Cleary's experimental results and previous investigations by Pelliciari and Padwa.[98, 102]
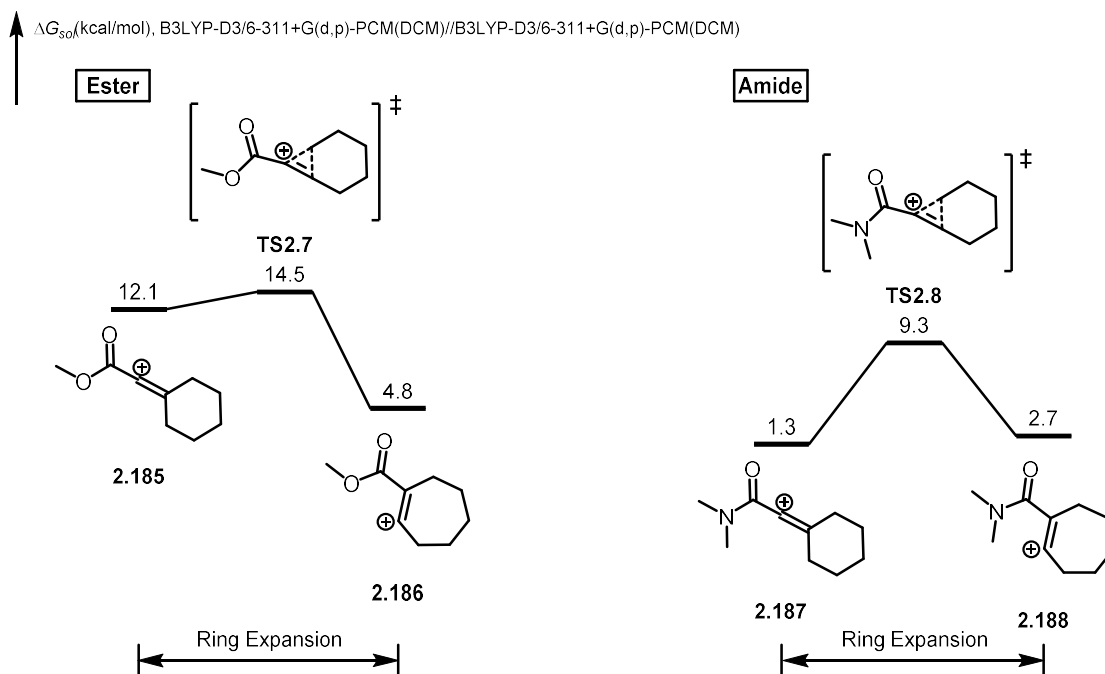
Figure 2.2 Energy diagrams of the ring expansion step of the diazo ester and diazo amide substrates

When the diazo carbonyl identity is a ketone or an ester, computational calculations indicate that linear vinyl cations formed after nitrogen dissociation are short lived and rapidly undergo ring expansion, which limits the amount of counterion trapping. Again, this is confirmed with experimental results from our 2017 Chemical Science paper[101] and Dr. Cleary's 2019 JACS paper.[102] However, the amide substrate has a higher energy barrier to ring expand (8 kcal/mol), providing a longer lifetime of linear vinyl cation **2.187** (Figure 2.2). Dr. Cleary got a substantial amount of vinyl triflates that would result from attack of the Lewis acid counterion onto the linear vinyl cation. There was no formation of the C–H insertion product.[102]

These studies indicate that the identity of the diazo carbonyl is important for the C–H insertion to occur. When the diazo carbonyl is a diazo ketone the ring expansion from linear to cyclic vinyl cation and C–H insertion have very low energy barriers. Thus, the

energetically favorable product is the C–H insertion step. With a diazo ester, the migration step to provide a cyclic vinyl cation is also energetically favorable. However, the C–H insertion is not favorable in this case, and a ring contraction occurs to provide lactone products. Finally, when a diazo amide is used, the ring expansion from a linear vinyl cation to the cyclic vinyl cation is slow, which provides a longer lifetime for intermolecular attack from a counterion to occur.

2.11   Summary of Chapter 2

This chapter described work that explored the C–H insertion reaction of systems that are symmetrical. The discoveries made raised interesting questions and gave way to exciting avenues for further exploration. Modification of the diazo ketone portion of the molecule provided multiple insights into the mechanism of this reaction.

First, when the point of insertion is a primary position, the yield of cyclopentenone products decrease by about 10% as the number of insertion positions decrease (*t*-butyl > *i*-propyl > ethyl). This could be due to the Thorpe-Ingold effect or simply that decreasing the potential sites of insertion decreases the probability of insertion occurring. The main side products from this reaction was intermolecular trapping of the linear or cyclic vinyl cations by a chloride or other counterions, so a slower insertion would provide more opportunities for this undesired reaction to occur. It was also demonstrated that the insertion can occur at a primary position on an extended system leading to the formation of a 6-membered ring. The insertion at a primary position is a concerted process, supported by both experimental and computational data.

Second, when the point of insertion is secondary, there is potential for a C–H insertion reaction and/or a competitive elimination reaction depending on the substrate. When the point of insertion was on a linear carbon chain, the cyclopentenone product arising from a C–H insertion was the preferred product. However, when the point of insertion was in a ring system, there is a potential for an alkene to form through elimination, depending on the ring size. When the ring was a cyclohexane ring, a diene product was isolated. When the ring was a cyclopentane ring, a cyclopentenone product was isolated as the major product with a minor amount of diene. If the reaction is stepwise when the point of insertion is secondary, stabilization of the resulting empty p orbital after hydride transfer would likely result in an elimination reaction. The concertedness of this reaction has yet to be determined but is currently being investigated.

Third, when the point of insertion is tertiary, the C–H insertion does not occur and there is a competitive elimination reaction. The formation of this alkene is indicative of a hydride transfer to the vinyl cation, which generates a stabilized tertiary carbocation. It is possible the C–H insertion occurred to provide a α-keto cation, but the tertiary carbocation is more stable and is formed from ring opening. I attempted to stabilize the α-keto cation to make it a more energetically favorable by taking advantage of β-silyl effect, however, preparation of the starting material to test this was unsuccessful. Making the elimination product highly unfavorable through use of a cyclopropane ring was also not productive.

Modification of the cyclohexane portion of the starting material was also investigated. Substitution of the cyclohexane ring was tolerated, providing various substituted 5,7-fused cyclopentenone ring systems in good yields. Modification of the ring system was also

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tolerated, however, the product yields and identity varied depending on the ring size. When the starting ketone was a four membered ring, there was not a 1,2-methylene shift across the vinyl cation alkene bond to form the five membered ring. This is likely due to the ring strain a cyclic vinyl cation would possess in a five membered system. The main products from this system were trapping of the linear vinyl cation with a counterion or return of starting material. However, ring expansion from a five to six membered ring and a seven to eight membered ring was possible and gave good yields of the resulting cyclopentane products.

Finally, linear systems of symmetrical carbon chains were investigated. These substrates were advantageous to study, since the products from these reactions would be structurally similar to prostaglandin type bioactive natural products. The monocyclic cyclopentenones were formed in poor to good yields depending on the identity of the diazo ketone.

CHAPTER 3: Migratory Aptitude of Rearrangement of Vinyl Cations

3.1   Inspiration

Up until this point, we had only investigated symmetrical cyclic and acyclic systems. Although this gave good insight into the C–H insertion reaction, many natural products are not symmetrical. In fact, the natural products (Figure 3.1) we could target using our developed chemistry have varying levels of substitution in their cores (indicated in blue).

Dinoprostone   3.1   Fusicoccanes
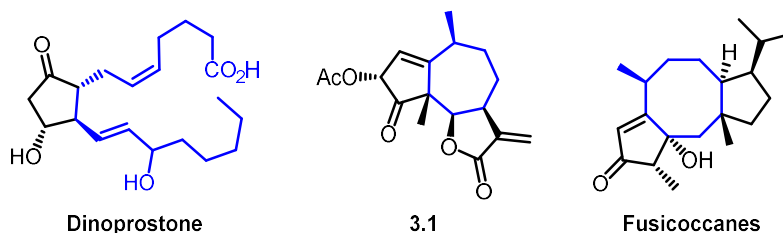
Figure 3.1 Natural products with varying levels of substitution

Therefore, it is imperative we investigate the migration of nonequivalent substituents during the 1,2-methylene shift from the linear vinyl cation to the cyclic vinyl cation (Scheme 3.1). For example, vinyl cation **3.3** can rearrange by two divergent pathways depending on whether the red (**3.4**) or blue (**3.7**) group migrates, leading to two different cyclopentenone products (**3.6** vs **3.9**). This migratory preference is known as the migratory aptitude, i.e. which group has the greater ability to migrate across the vinyl cation bond during this rearrangement reaction.
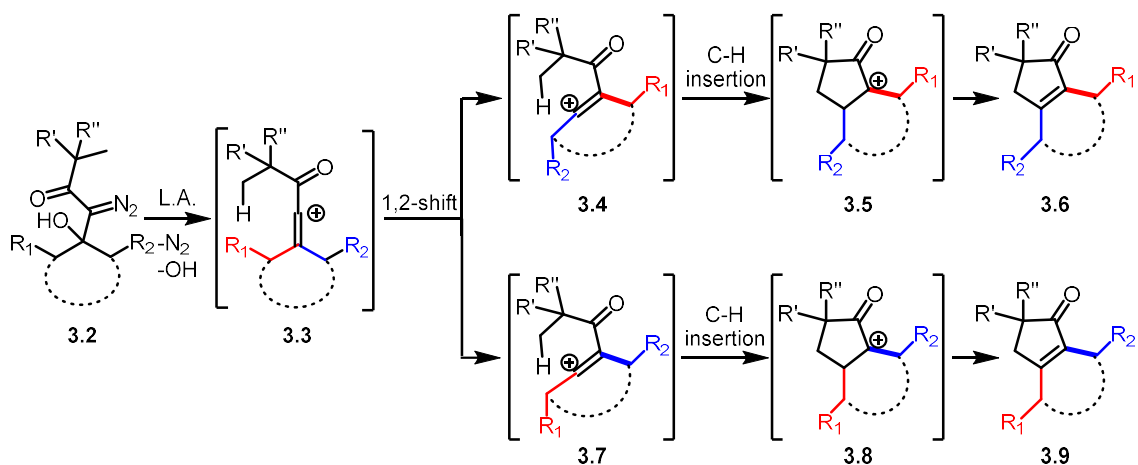
Scheme 3.1 Migratory aptitude of nonequivalent systems

3.2 Carbocations and Migratory Aptitude

Carbocations were first understood as intermediates that could form in reactions starting in the early 20th century, and since that point, represent one of the most important intermediates in organic chemistry. Carbocations are electrodeficient cationic species which act as an electrophile or can participate in rearrangement reactions. The rearrangement of carbocations was first formally outlined by Whitmore in 1932.[131, 132] When investigating the dehydration of butyl alcohol, three different alkenes were generated. He describes that the heterolytic cleavage of an atom generates the primary carbocation, and then either a 1,2-hydride or methyl shift generates a new secondary or primary carbocation (Scheme 3.2).[132]
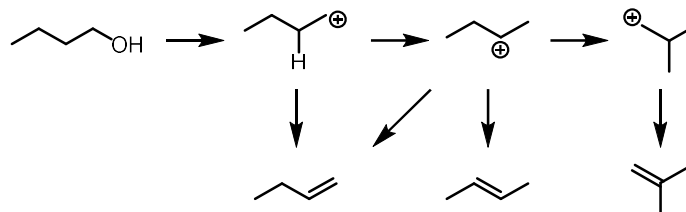
Scheme 3.2 Migration of hydride or methyl provides multiple new products

Migratory aptitude examines the migration of bonds in a reaction, that is, which bonds will be more likely to migrate in a system based on factors such as stability or electronics.

The migratory aptitude in cationic systems has been investigated extensively in cationic rearrangement reactions such as the Pinacol-Pinacolone rearrangement, the Wagner−Meerwein rearrangement, or the Baeyer−Villiger oxidation, but rather limitedly in rearrangements of vinyl cations.

The Pinacol−Pinacolone rearrangement is a classic rearrangement example. This rearrangement is the conversion of a diol to a ketone that proceeds through a carbocation intermediate after a loss of water. The Pinacol−Pinacolone rearrangement follow similar migration patterns present in other cationic systems, that is the group that better stabilizes the carbocation intermediate is more likely to migrate (Scheme 3.3). Ferguson and coworkers reported that an anisyl group, which has a methoxy substitution at the para position, is more likely to migrate than a *m*-tolyl group (99:1, Entry 1). When methoxy was present at the meta position of the aryl ring, the *m*-tolyl was more likely to migrate (39:61, Entry 2). Finally, the *m*-methoxyphenyl was less likely to migrate compared to the phenyl ring (38:62, Entry 3). These examples further demonstrate that the aryl ring which can better stabilize the carbocation through the bridged phenonium ion is more likely to migrate.[133]

Entry	R_1	R_2	Migration %	
			R_1	R_2
1	Anisyl	*m*-Tolyl	99	1
2	*m*-Methoxyphenyl	*m*-Tolyl	39	61
3	*m*-Methoxyphenyl	Phenyl	38	62
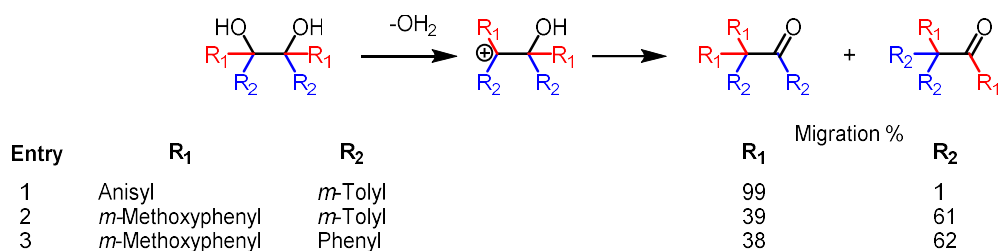
Scheme 3.3 Pinacol−Pinacolone rearrangement

Cationic systems proceeding through the Wagner−Meerwein rearrangement, such as the reaction of a pinacol to a pinacolone, exhibit similar migration patterns in which the

group that's more likely to stabilize a cationic intermediate is more likely to migrate.[134] Other migratory rearrangements like the Baeyer−Villiger oxidation also follows this trend, where the group that is most likely to stabilize a positive charge will migrate preferentially.[135, 136]

The Wagner−Meerwein rearrangement is a 1,2-migration across a carbocation that is not stabilized by a heteroatom.[137] If the migrating group is an aryl ring, it stabilizes the carbocation through a "phenonium ion" (**3.12 & 3.14**, Scheme 3.4), the formation of a bridged carbocation with an aryl ring.[134, 137] This is exemplified in recent work by Jacobson and coworkers. They investigated an aryl-iodide-catalyzed Wagner−Meerwein rearrangement to form 1,3-difluorinated products and studied the relative rates of migration with differing electronics on the aryl ring. They discovered that when X = aryl, electron rich arenes were consumed more rapidly and forming a bridged carbocation intermediate (**3.12** and **3.14**) before fluorination. This example demonstrates that aryl rings are more likely to migrate because of the ability to form this bridged phenonium ion.[137]
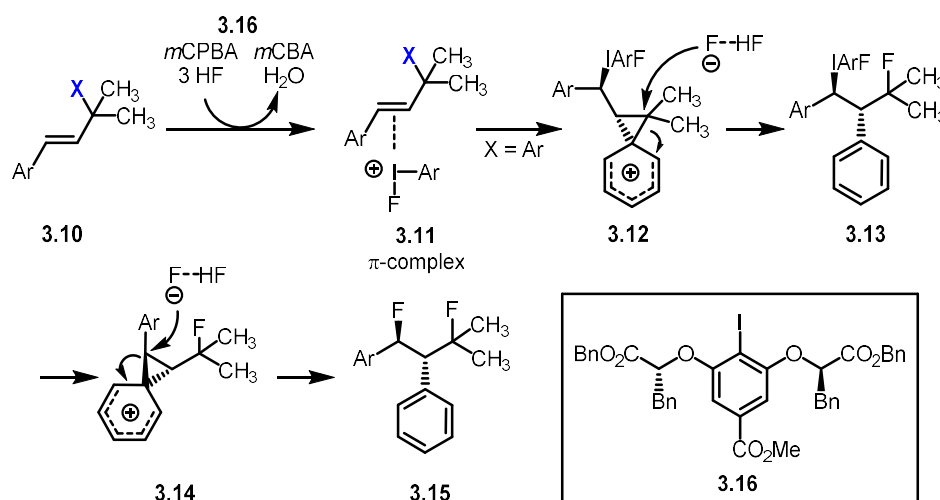
Scheme 3.4 Wagner−Meerwein rearrangement through phenonium bridged ion intermediate

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Other rearrangement reactions, such as the Baeyer−Villiger oxidation, in which a ketone is oxidized to an ester, the group that can best stabilize a positive charge migrates more readily. The migratory trend in the Baeyer−Villiger oxidation is as follows: *tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > methyl*.[135, 136] Additionally, it was determined that aryl groups that contain a para or ortho directing substituents, like methoxy or methyl, were much more likely to migrate than substitution groups that have the opposite effect, like nitro.[138]

To help explain the mechanism of the Baeyer−Villiger oxidation, Brinck and coworkers modeled the BF$_3$ catalyzed oxidation of acetone to methyl acetate computationally (Scheme 3.5). The reaction of acetone and BF$_3$•H$_2$O$_2$ generates complex **3.17**, at which point the BF$_3$ assisted proton transfer through **TS3.1** provided the Criegee intermediate **3.18** where BF$_3$ is bound to the inner oxygen. After transfer of the BF$_3$ to the outer oxygen *via* **TS3.2**, the migration step will occur. The methyl group forms a three-membered ring with the inner oxygen through **TS3.3** and migrates to the oxygen. This migration forms a new C−O bond, while releasing BF$_2$•OH and HF.[139]
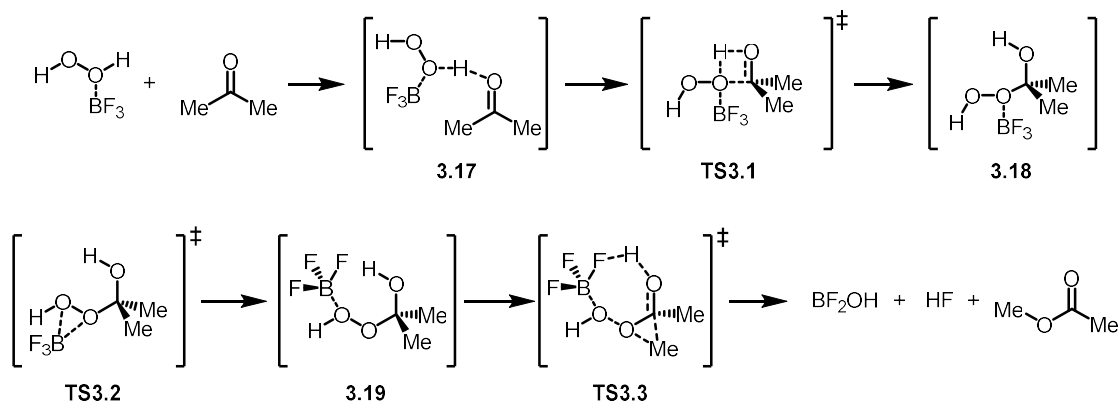
Scheme 3.5 Baeyer−Villiger oxidation of acetone to give methyl acetate

Although the migration across carbocations have been studied extensively, less work

has been dedicated to vinyl cations. Previously discussed in Chapter 1, Section 1.3, Stang

and coworkers have investigated the migratory aptitude of nonequivalent groups across

vinyl cations and showed the group that was more apt to stabilize the vinyl cation migrated

preferentially (eg. migration of a phenyl vs. methyl).[48, 49]

Pellicciari and coworkers also observed the migration of an aryl ring vs. a phenyl ring

across a vinyl cation. The $BF_3 \cdot Et_2O$ decomposition of 2-diazo-3-hydroxy-3,3-

diarylpropanoates **3.20** provided a vinyl cation that was captured by acetonitrile to give

two *N*-acyl *β*-enamino ester derivatives (Scheme 3.6). The migrating group depended

heavily on the electronic effects of the aryl groups.[140]
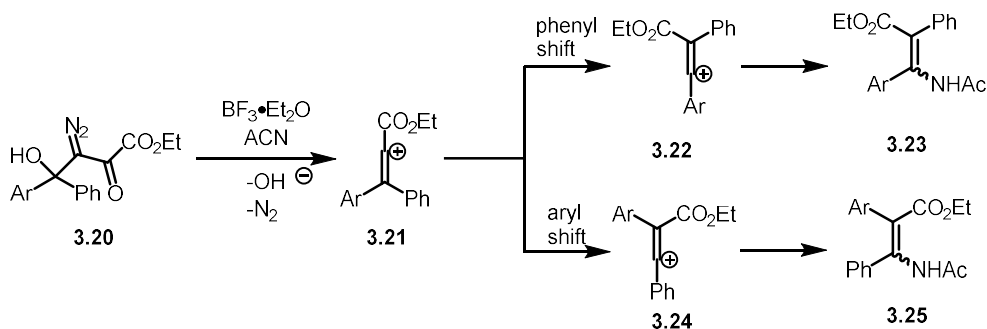
Scheme 3.6 Formation of diaryl enamino esters from benzophenones

They discovered that phenyl migration is preferred when in the aryl group contains an

electron withdrawing group (such as an *p*-NO$_2$) but aryl group migration is favored when

an electron donating group is present. The group analyzed the migratory aptitude in respect

to their parametrized resonance effects (R_{eff}), inductive effects, and Hammett σ values,

where **19** is the phenyl migration and **20** is the aryl migration (Figure 3.2). Their data fit

well to the resonance effects, an aryl ring with an electron donating group is more likely to

migrate to the electrophilic vinyl cation. However, resonance is not the only factor that effects the migration, as they did not see any correlation with inductive or Hammet σ values.[140]
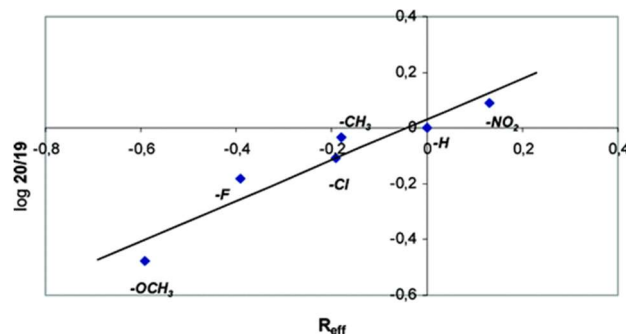
Figure 3.2 Aryl rings with an electron donating group is more likely to migrate

3.3 Migratory Aptitude Between Phenyl and Alkyl Groups

We started our investigation by comparing the migration of an alkyl chain and a phenyl ring (Scheme 3.7). To achieve this we prepared β-hydroxy-α-diazo ketones **3.26** and **3.30** which were surprisingly challenging to make. The addition of the sterically hindered lithiated diazo ketone to the respective ketones would often result in low yields of desired **3.26** and **3.30** that had to be purified multiple times to obtain pure sample. However, enough was obtained to move forward with our studies. Dr. Cleary investigated the methyl vs. phenyl migration (**3.26**) and I investigated the ethyl vs. phenyl migration (**3.30**). Treatment of the β-hydroxy-α-diazo ketones with 1 equiv. of BCF at 0 ºC provided the desired cyclopentenone products, albeit in low yields. Yields were determined by NMR using 1,3,5-trimethoxybenzene as the internal standard due to the volatility of the resulting cyclopentenones.[60]

3.26, R = Me
3.30, R = Et

3.27; 16%[a]
3.31; 30%[a]

3.28; 2%[a]
3.32; not observed

3.29; 7%[a]
3.33; 27%[a]

[a]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard. The group that migrated is colored red
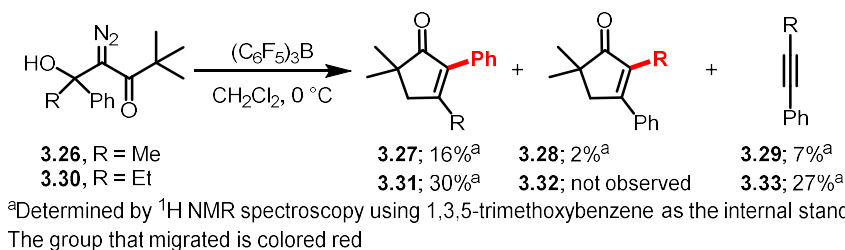
Scheme 3.7 Phenyl vs. alkyl migratory aptitude

In both cases the phenyl ring migrated preferentially compared to the alkyl group (**3.27** & **3.31**). While cyclopentenone **3.28** formed from the migration of the methyl group was identified in trace yields, the ethyl migration product (**3.32**) was not observed.[60] These results are consistent with other cationic rearrangements. Presumably, the aryl ring migrates preferentially due to the formation of a bridged phenonium ion intermediate, as described for the Wagner−Meerwein rearrangement.[134]

We received a low yield of isolated products, while the remainder of our material was undetermined. I isolated alkyne **3.33**, and after reviewing previous trials, discovered that this undesired side product was consistently forming in the linear systems. Although we hypothesized that this product was a potential side product previously, at the time we had not had experimental proof to back up the claim. Even though I had isolated the pure alkyne **3.33** in the phenyl vs. ethyl system **3.30**, it was difficult to isolate alkyne **3.29**. In the case of the phenyl vs. methyl system, this alkyne side product would be very volatile, and it was likely lost during the workup.[60]

We hypothesize this alkyne is formed from a reverse Friedel-Crafts acylation. In cyclic systems, an alkyne would be less likely to form due to the high ring strain that would be present in the cycloalkyne product. However, this strain would not be present in a linear

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system and linear vinyl cation **3.35** could undergo fragmentation of the vinyl acyl bond to provide alkyne **3.33** and acylium ion **3.36** (Scheme 3.8).

| 3.30 | | 3.34 | | 3.35 | | 3.33 | 3.36 |

Scheme 3.8 Formation of the alkyne through reverse Friedel-Crafts acylation

3.4   Migratory Competition Studies of Tetralone Systems

I next turned my attention towards investigating the migration between sp^3 and sp^2 bonds in tetralone based systems. Unlike the previous study, there should not be a formation of a phenonium ion, allowing us to compare the sp^3 vs sp^2 migration more directly. In this case, the empty *p*-orbital on the vinyl cation would be perpendicular to the tetralone aromatic π system. It is important to note that the Baeyer-Villiger oxidation has selective migration of the aryl ring in tetralone systems, however, these migrations are between adjacent sp^3 centers.[141]

The β-hydroxy-α-diazo ketones (**3.40a-3.40e**) in these tetralone systems were arduous to form and many required multiple purifications. Lithiated diazo ketones (**3.37** and **3.38**) did not add easily to the tetralone ketone under normal reaction conditions, but lithiated diazo esters did add with good yields of products. This indicated to me that the issue lies in the lithiated diazo ketone. I suspected the *t*-butyl diazo ketone was too sterically hindered to effectively add into the tetralone system, however, the isopropyl diazo ketone also failed to react under normal reaction conditions.

Since diazo esters added smoothly into tetralone, it's possible that the nucleophilicity of the lithiated diazo ketones may be less than that of the diazo esters, inhibiting their addition. To circumvent this issue, I optimized the solvent system of the addition reaction to make the diazo anion less stable, which made it more reactive, with a more non-polar solvent system. After extensive optimization, a solvent system composed of 3.5:1 hexanes:THF was determined to be optimal for tuning the reactivity, while still providing a system in which the tetralones were soluble. I was thus able to obtain the tetralone β-hydroxy-α-diazo ketones, albeit in low yields (Scheme 3.9).

3.37, R = Me
3.38, R = H

3.39a, R_1 = H; R_2 = H
3.39b, R_1 = H; R_2 = NO$_2$
3.39c, R_1 = NO$_2$; R_2 = H
3.39d, R_1 = H; R_2 = Br
3.39e, R_1 = H; R_2 = OMe

3.40a, 43%, R_1 = H; R_2 = H
3.40b, 39%, R_1 = H; R_2 = NO$_2$
3.40c, 25%, R_1 = NO$_2$; R_2 = H
3.40d, 50%, R_1 = H; R_2 = Br
3.40e, 24%, R_1 = H; R_2 = OMe
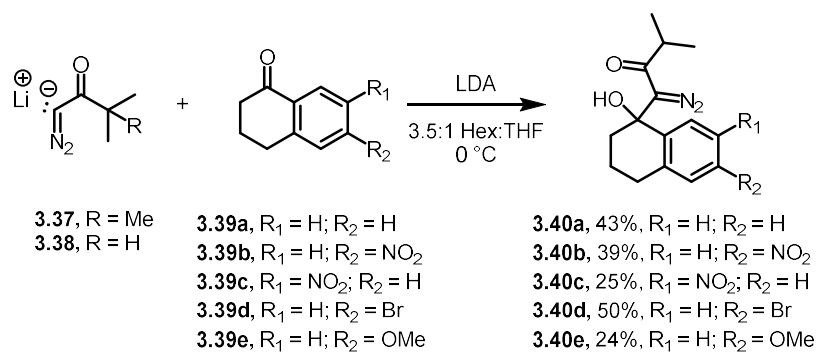
Scheme 3.9 Addition reaction into tetralone systems

Treating the tetralone β-hydroxy-α-diazo ketone (**3.40a**) with excess BCF gave cyclopentenone **3.41a**, in which the alkyl group migrated preferentially in 27% yield. The aryl group migration product was not observed. This trend continued for other tetralone systems electron withdrawing groups (**3.41b – 3.41d**). When an electron donating group was present on the aryl ring, aryl migration was preferred (**3.41e**, 37%) over alkyl migration (**3.42e**, 14%).[60]
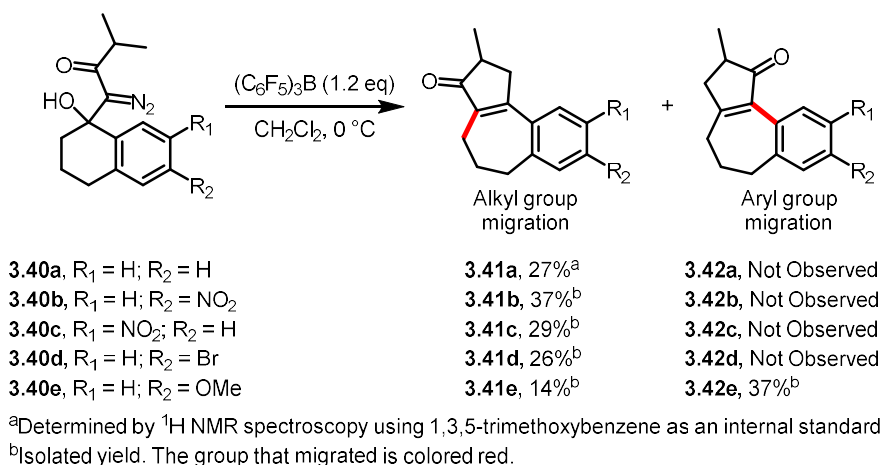
Scheme 3.10 Migratory aptitude of tetralone systems

3.40a, R_1 = H; R_2 = H	**3.41a**, 27%[a]	**3.42a**, Not Observed
3.40b, R_1 = H; R_2 = NO_2	**3.41b**, 37%[b]	**3.42b**, Not Observed
3.40c, R_1 = NO_2; R_2 = H	**3.41c**, 29%[b]	**3.42c**, Not Observed
3.40d, R_1 = H; R_2 = Br	**3.41d**, 26%[b]	**3.42d**, Not Observed
3.40e, R_1 = H; R_2 = OMe	**3.41e**, 14%[b]	**3.42e**, 37%[b]

[a]Determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.
[b]Isolated yield. The group that migrated is colored red.

We are not positive why the electron donating groups on the aryl ring promotes migration, but we believe it has to do with stabilization of the vinyl cation **3.43**. In the case of the electron withdrawing aryl rings, there would not be sufficient stabilization of the intermediate vinyl cation if the aryl group migrates, so the alkyl group migrates. However, the electron donating methoxy group (**3.40e**) increases the electron density of the sp^2 carbon, and thus migrates preferentially. We currently hypothesize this occurs through resonance form **3.44** (Scheme 3.11).[60]
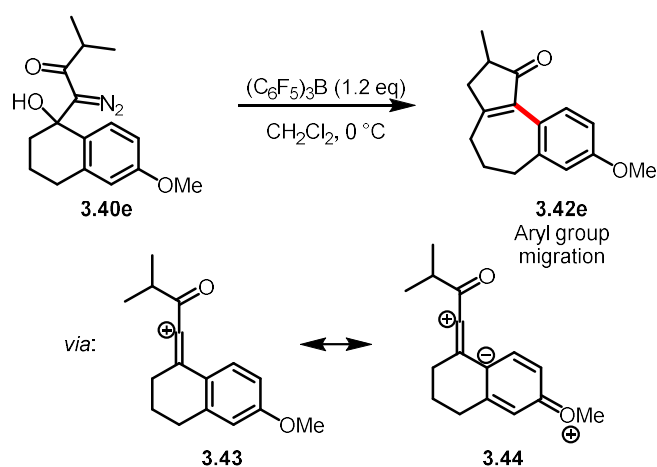
Scheme 3.11 Stabilization of vinyl cation through electron denisty

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3.5 Migratory Aptitude between Alkyl Groups

We then turned our attention towards investigating the migratory aptitude of alkyl groups to observe if the Baeyer−Villiger migration trends held true in our system (Table 3.1). Dr. Cleary was the main investigator on the migratory aptitude of nonequivalent alkyl groups, but I finalized some of the yields and collected characterization data (entry 2 & 3). In the competition experiment between a 1º alkyl chain and a methyl group (**3.45**) the regiomeric ratio was 1.7 to1, favoring alkyl chain migration (entry 1). The ratio of regio isomers was determined by integrating the crude ^{1}H NMR spectrum. Isolated yields gave skewed results because these cyclopentenones were difficult to purify and chromatography returned nearly equal quantities of **3.46** and **3.47**.[60]

Next, the competition between a 2º alkyl group (cyclohexane ring) and a methyl was evaluated (**3.48**, entry 2). The 2° alkyl group migrated preferentially with a regiomeric ratio of ~16 to 1. The isolated yields for both these cyclopentenones were low, with the major 2° migration product **3.49** recovered in 16% yield and the minor methyl product **3.50** recovered in trace (<5%) yields. The main product from this reaction was the alkyne that arises from the reverse Friedel-Crafts acylation.[60]
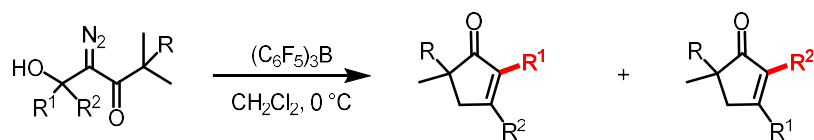
Table 3.1 Migratory aptitude between alkyl groups

Entry	α-diazo ketone	Product **a** isolated yield	Product **b** isolated yield	NMR ratio[a] a : b
1	3.45	3.46, 21%	3.47, 23%	1.7 : 1
2	3.48	3.49, 16%	3.50, 1%	~16 : 1
3	3.51	3.52, 50%	3.53, 6%	4.4 : 1

[a]Regiomeric ratio, determined from ^{1}H NMR integrations of crude reaction. The group that migrated is colored red.

Moving forward, the migratory competition between a 1° group and a 2° group was investigated (**3.51**, entry 3). The 2° group migrated preferentially, providing cyclopentenone **3.52** in 50% yield, with 1° alkyl migration product **3.53** forming in approximately 6% yield. The minor product **3.53** was isolated in an 1:1 mixture with the major product **3.52**, with a combined yield of 11%. Separation of the two cyclopentenone isomers from one another was unsuccessful, making the characterization of the minor isomer difficult. To overcome this, the insertion reaction was performed on a large scale, using SnCl$_4$ as the Lewis acid for cost efficiency. This reaction allowed isolation of enough clean minor isomer for full characterization. The crude ^{1}H NMR spectroscopy from the

reaction of BCF with **3.51** could be analyzed, providing a ratio of 4.4:1 of **3.52** to **3.53**.[60]

Entries 1-3 indicate that the migrating group is one which can best stabilize the vinyl cation

intermediate, which is again supported by other rearrangements such as the

Baeyer−Villiger oxidation.[135, 136]
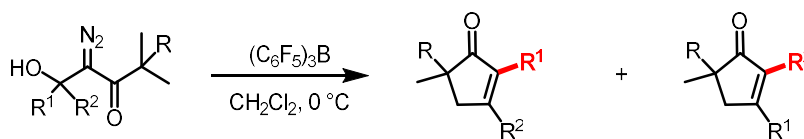
Table 3.2 Sterically hindered β-hydroxy-α-diazo ketones failed to react

Entry	α-diazo ketone	Product **a** isolated yield	Product **b** isolated yield	NMR ratio[a] **a : b**
4	**3.54**		no reaction	
5	**3.55**		no reaction	

[a]Regiomeric ratio, determined from ^{1}H NMR integrations of crude reaction. The group that migrated is colored red.

Therefore we expect that a 3º alkyl group will migrate preferentially when compared

to a 1º or methyl group (Table 3.2, Entry 4 & 5). However, the sterically hindered β-

hydroxy-α-diazo ketones (**3.54** and **3.55**) failed to react with BCF and only returned

starting material. Other Lewis acids such as SnCl$_4$ and BF$_3$•Et$_2$O failed to promote the

reaction. Modification of the diazoketone portion of the molecule to a less bulky isopropyl

group was unproductive. It appears that steric hindrance imparted by the 3° substrate may

suppress coordination with the Lewis acids and thus prevents vinyl cation formation.[60]

3.6   Mechanistic Considerations

To gain a better understanding of the mechanism, and what factors influence the migration, we studied diazo ketone **3.51** computationally with our collaborator, Prof. Xin Hong. The linear vinyl cation that forms after loss of hydroxide and nitrogen can exhibit two conformations (**3.56** and **3.57**, Figure 3.3, A) that have similar energies. Additionally, there is a beneficial electrostatic interaction between the vinyl cation and the carbonyl oxygen in both isomers, so the migration could occur from the group which is cis and/or trans from the carbonyl.[60]

3.56	3.57	TS3.4	TS3.5
$\varDelta\varDelta G^{\ddagger} \approx 0.0$ kcal/mol	$\varDelta\varDelta G^{\ddagger} \approx -0.4$ kcal/mol	$\varDelta\varDelta G^{\ddagger} \approx 0.0$ kcal/mol	$\varDelta\varDelta G^{\ddagger} \approx 6.9$ kcal/mol
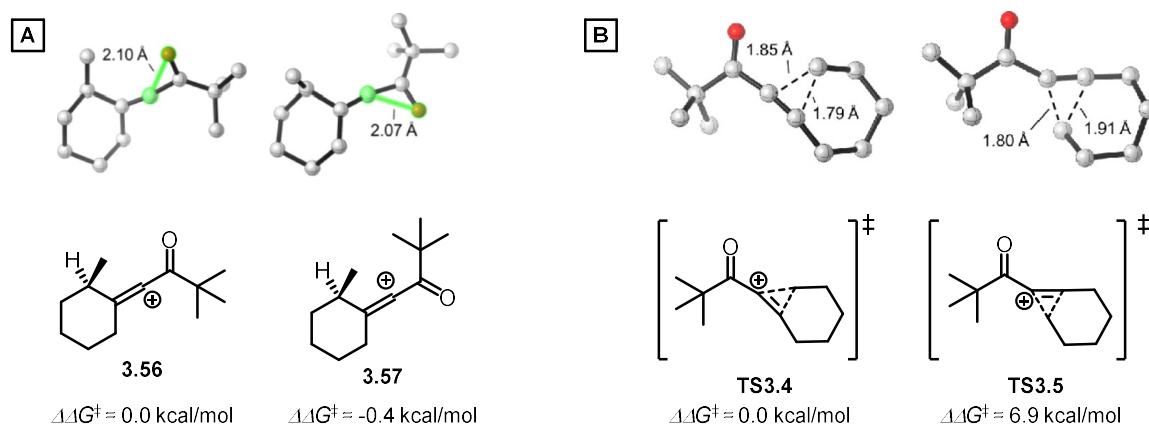
Figure 3.3 DFT calculations on the stability of the linear vinyl cations formed from loss of nitrogen

Modeling the unsubstituted cyclohexane-based system showed that the group that is cis to the carbonyl (**TS1**, Figure 3.3, B) migrates preferentially across the alkene, with the trans group (**TS2**) exhibiting an energy barrier 6.9 kcal/mol higher. With this in mind, it is expected that these two isomers would give different products, **3.56** would give isomer **3.58** and **3.57** would give **3.59** (Figure 3.4). Initially, we hypothesized that since **3.56** and **3.57** have similar energies, the reaction outcome would be controlled by the irreversible migration step. However, when this reaction was computationally modeled, migration of

the less substituted group had a lower energy barrier (**3.57** to **3.58**, 3.6 kcal/mol, Figure 3.4) compared to the more substituted group (**3.56** to **3.59**, 5.8 kcal/mol, Figure 3.4). The increase in energy for the more substituted group was presumed to be from a steric interaction between the bulky migrating group and the carbonyl oxygen (**TS3.7**). These energies predict that the major product would result from migration of the 1° group (**3.53**), and the 2° migration product (**3.52**) would be minor. However, experimental results were not in line with this prediction.[60]
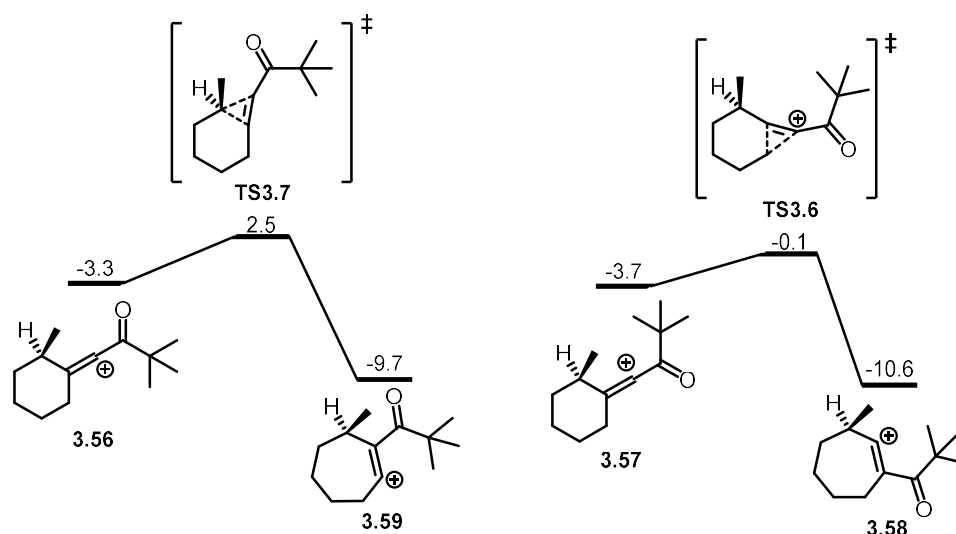
Figure 3.4 Energy diagram for the migration across the linear vinyl cation

A more comprehensive computational study was performed to understand the migration patterns leading to cyclopentenones **3.52** and **3.53**. The Lewis acid mediated loss of the β-hydroxy provides two diastereomeric vinyl diazoniums (**3.60** and **3.64**, Scheme 3.12 & 3.13). Although these cannot directly isomerize by rotation, the dehydroxylation step is reversible, so the (*E*)-isomer **3.60** and (*Z*)-isomer **3.64** are in equilibrium. The (*E*)-isomer **3.60** is 1.9 kcal/mol lower than the (*Z*)-isomer **3.64**, presumably due to allylic 1,3-strain between the diazo and methyl groups in **3.64**.[60]

Scheme 3.12 Energy diagram leading to the major cyclopentenone product
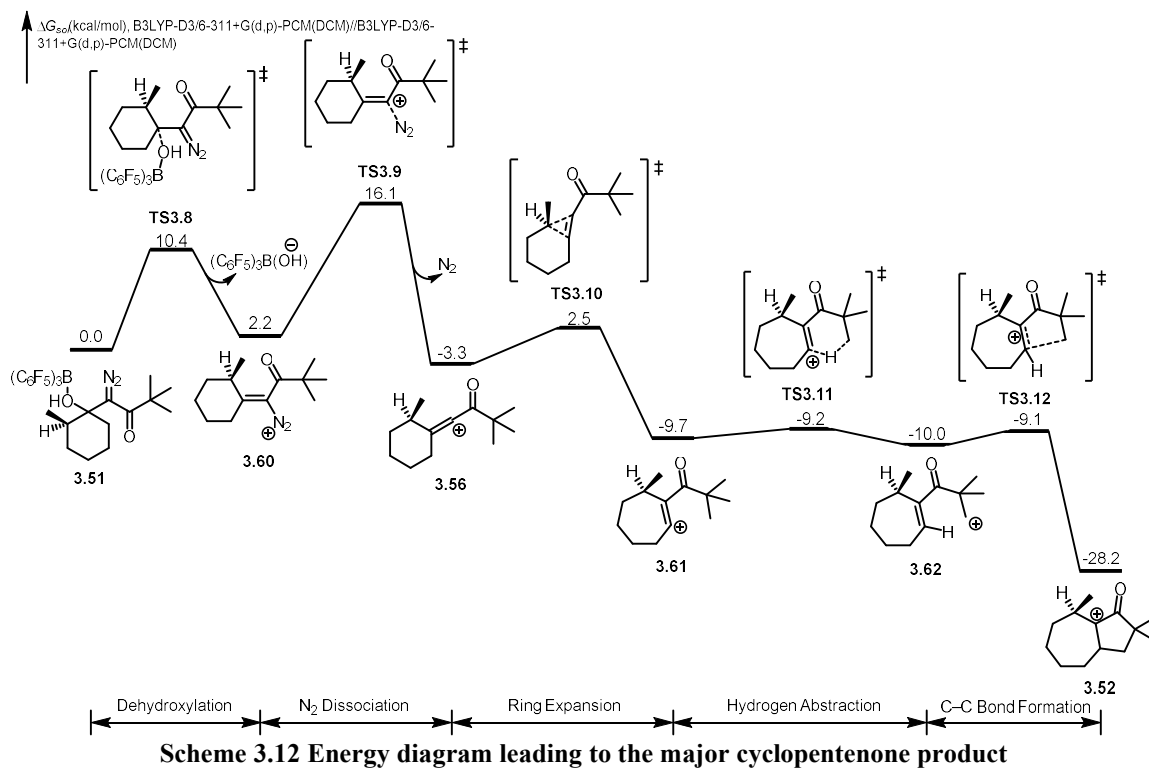
The loss of nitrogen is the rate limiting step in these reaction sequences, and the energy to lose molecular nitrogen for the (*E*)-isomer **3.60** is 3 kcal/mol lower than that of the (*Z*)-isomer **3.64**, likely due to lack of steric hinderance around the nitrogen (**TS3.9** vs. **TS3.15**). This leads to the preferential formation of the vinyl cation isomer **3.56**.[60]
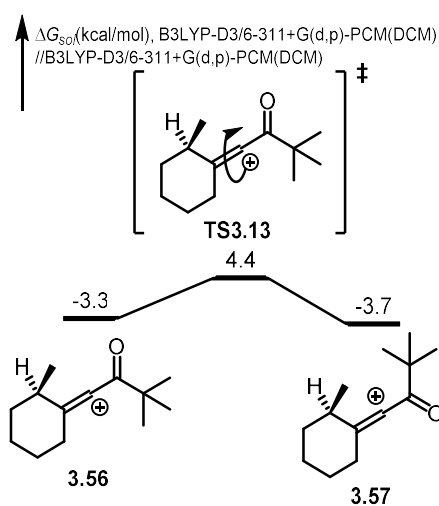
Computational experiments demonstrated that the energy it would take for the bond rotation to go from vinyl cation **3.56** to vinyl cation **3.67** is 7.7 kcal/mol via **TS3.13** (Figure 3,5), whereas the irreversible migration across the alkene to form **3.61** through **TS3.10** is 5.8 kcal/mol. As some of the minor product was isolated, a small amount of vinyl cation **3.56** rotated to provide linear vinyl cation **3.67**, in which the irreversible migration of the 1° group provided **3.64**. In both instances, there would be a rapid insertion after the migration step to form the major and minor cyclopentenones **3.52** and **3.53**.[60]
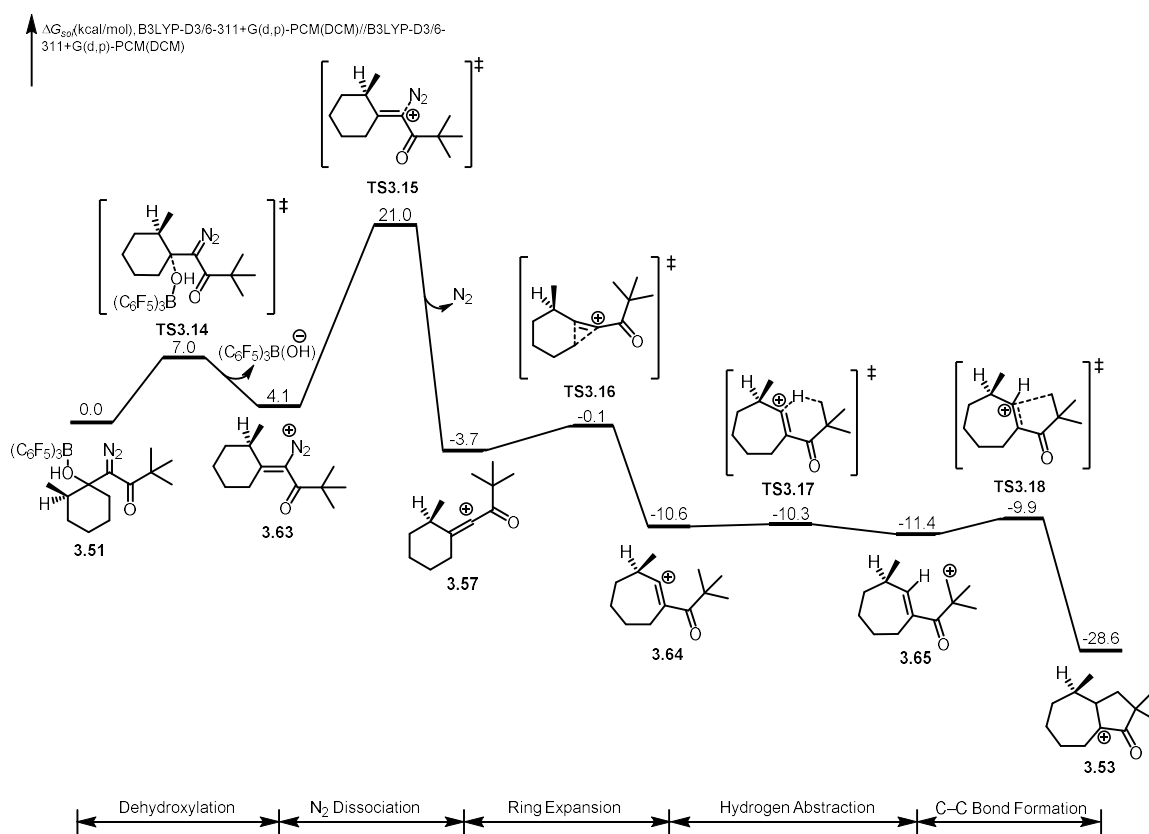
Scheme 3.13 Energy diagram leading to the minor cyclopentenone product

To summarize the calculations, although the energies between the two linear vinyl cations **3.56** and **3.57** are about equivalent, the dissociation of nitrogen to form the linear vinyl cation (**3.56**) leading to the major product has a smaller energy barrier. This is due to diazonium **3.60** not suffering from a unfavorable allylic 1,3-strain between the methyl and diazo group that diazonium **3.63** exhibits. Although it's possible linear vinyl cation **3.56** proceeds through a C–C bond rotation to form vinyl cation **3.57**, it is more energetically favorable to undergo an irreversible bond migration and rapid insertion to form the major product **3.52**.

3.7   Summary of Chapter 3

This chapter focused on understanding the migratory aptitude of nonequivalent substituents during the 1,2-methylene shift across the linear vinyl cation formed after nitrogen dissociation. When comparing a phenyl vs. an alkyl migration in a linear system, the phenyl ring migrates preferentially over a methyl or an ethyl substituent. This is consistent with other cationic rearrangements, as the phenyl ring can form a bridged phenonium intermediate. It was discovered that a competitive reverse Friedel-Crafts acylation could occur in the acyclic systems, which provides an alkyne side product.

The migratory competition studies of tetralone systems was also investigated. In these systems, the phenonium ion intermediate would not be able to form, so it would allow us to compare the sp^3 vs sp^2 migration more directly. It was discovered that the alkyl group migrated preferentially compared to an electron neutral or electron poor aryl ring. No aryl ring migration was observed in these systems. When the aryl ring was an electron rich system, the aryl ring migrated preferentially compared to the alkyl group.

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The migratory competition between alkyl groups was also observed. When comparing the migration between a methyl and a primary alkyl chain, the primary alkyl chain migrated preferentially in a 1.7:1 regiomeric ratio of cyclopentenone products. The competition between a secondary alkyl group and methyl was also evaluated, and the secondary alkyl group migrated preferentially in about a 16:1 ratio. Finally, the migratory competition between a primary and a secondary alkyl group was investigated. The secondary alkyl group migrated preferentially in a 4.4:1 ratio. These results are consistent with other cationic rearrangement reactions such as the Baeyer-Villiger oxidation, the more substituted system will migrate preferentially.

CHAPTER 4: VINYL CATIONS AS ELECTROPHILES IN AN ALKENE ADDITION REACTION

4.1 Inspiration and Precedence

As stated in my introduction, while vinyl cations have shown promise in C–H insertion reactions as carbene surrogates, they are more commonly used as electrophiles for addition reactions (see Chapter 1, Section 1.3.1 & Section 1.3.2). The question therefore is, what is more favorable: vinyl cations acting as carbene surrogates or vinyl cations acting as an electrophile? In order to fully understand the vinyl cation intermediates used in our methodology, we chose to analyze the competition between the multiple reaction pathways vinyl cations can participate in.

We had previously demonstrated that vinyl cations can act as a carbene surrogate for the insertion into a remote, inert C–H bond (Scheme 4.1, A). The specifics of this reaction have been extensively outlined in Chapters 2 and 3. When the diazo ketone portion of the molecule only has sp^3 hybridized bonds, there is a C–H insertion at an inert carbon-hydrogen bond (**4.2** → **4.3**). However, we wanted to examine what the reaction outcome would be when both sp^3 *and* sp^2 bonds are present on the diazo ketone portion of the molecule (Scheme 4.1, B). Would the vinyl cation act as an electrophile to provide alkene addition intermediate **4.7**, or would a C–H insertion be the preferred pathway to provide cyclopentenone **4.8**? If the latter is true, this would be a useful reaction as this alkene could be used as a synthetic handle to build functionality on these molecules.
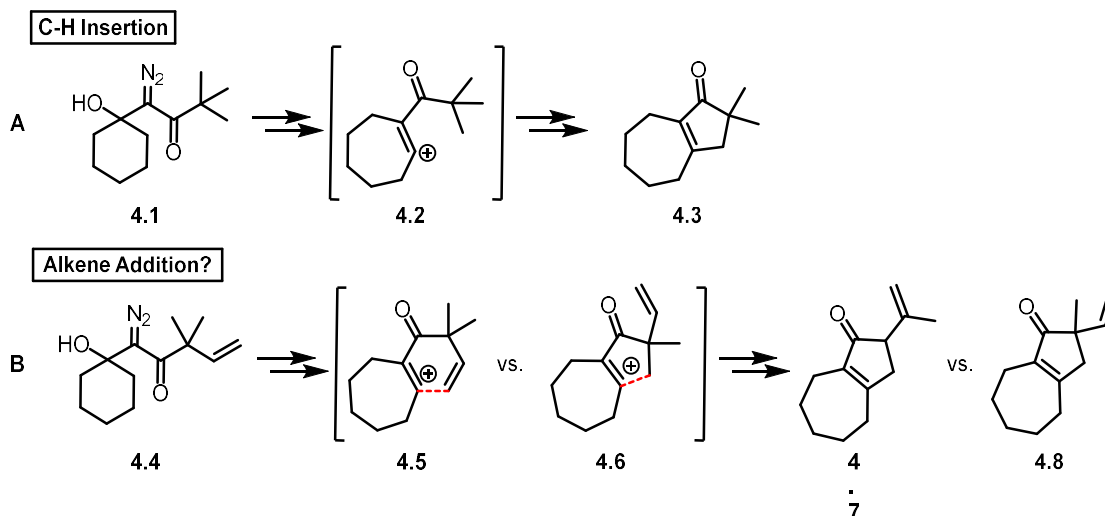
Scheme 4.1 C–H insertion vs. alkene addition

Precedence for the alkene addition pathway comes from a key result by Karpf in a 1984 publication (Scheme 4.2). In this work, he describes formation of linear vinyl cation **4.9** from the reaction of an acid chloride with an alkyne in the presence of a Lewis acid. The vinyl cation (**4.9**) acted as an electrophile, which was attacked by a pendant alkene to generate secondary carbocation **4.10**. A ring contraction provided tertiary carbocation **4.11**, which was either captured by the Lewis acid counterion (**4.12**) or forms an alkene by loss of a proton (**4.13** and **4.14**).[142]
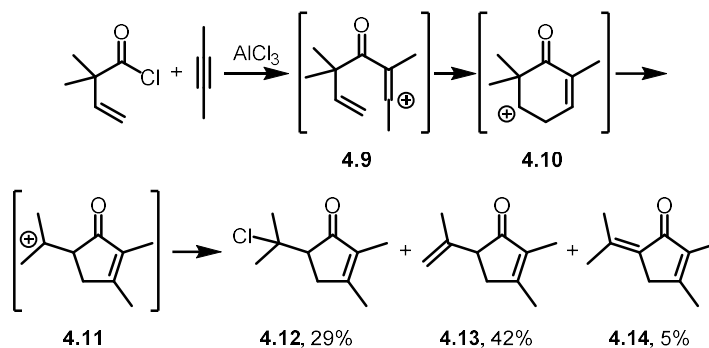
Scheme 4.2 Alkene addition onto vinyl cations lead to cyclopentenone rings

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Notably, when there is not a *gem* dimethyl group adjacent to the carbonyl on the acid chloride, the reaction does not proceed through the ring contraction (Scheme 4.3). Instead there will be loss of a proton and tautomerization to form substituted phenols **4.16** and **4.18**.[142]
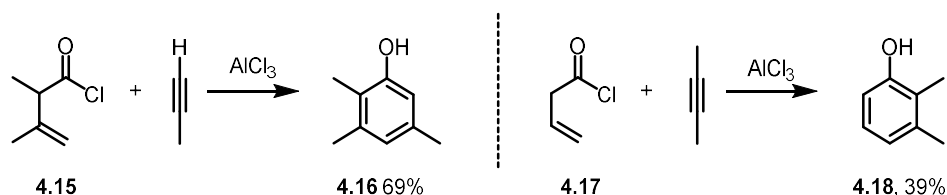
Scheme 4.3 Phenol ring formation when using less substituted acid chlorides

4.2   Preparation of the Starting Diazo Ketone

To start our studies, diazo ketone **4.23** was prepared using known procedures. First, treatment of alcohol **4.19** with concentrated HCl provided chlorides **4.20** and **4.21** in a combined yield of 69% via an S_N1 process. These were used without purification. The chlorides were diluted in THF and slowly added to magnesium turnings to form the corresponding Grignard reagent, which was quenched with finely crushed dry ice. After sublimation of the solid CO_2, acidic workup provided the carboxylic acid **4.22** in a 65% yield. Carboxylic acid **4.22** was treated with oxalyl chloride to provide an acid chloride, which was purified by distillation and then reacted with ethereal diazomethane to give diazo ketone **4.23** in a 73% yield over two steps.[143] β-Hydroxy-α-diazo ketone **4.4** was formed in 62% yield by the addition of diazo ketone **4.23** to cyclohexanone.[59]
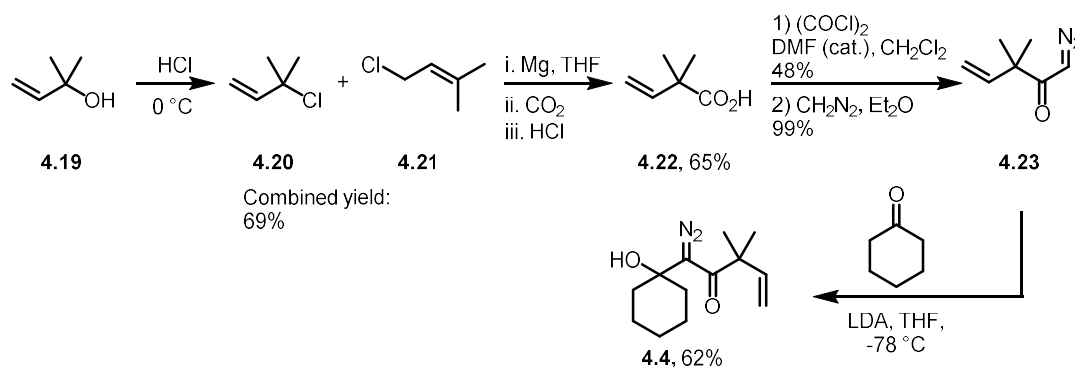
Scheme 4.4 Synthesis of diazo ketone starting material

4.3 Initial Results on a More Substituted Diazo Alcohol System

Dr. Nick Dodge performed the initial investigations on this reaction. Choosing conditions based off the optimized C–H insertion that was developed by Dr. Cleary and I, Dr. Dodge subjected diazo ketone **4.4** to BCF at -15 ℃. He observed three products by TLC and isolated three compounds after purification of the crude mixture by silica-gel chromatography. However, a majority of his reaction mass was missing. The expected compounds that would come from alkene addition **4.7** or C–H insertion **4.8**, were isolated in trace yield. The major product he did isolated was γ,δ-unsaturated carboxylic acid **4.24** (Scheme 4.5).[144]
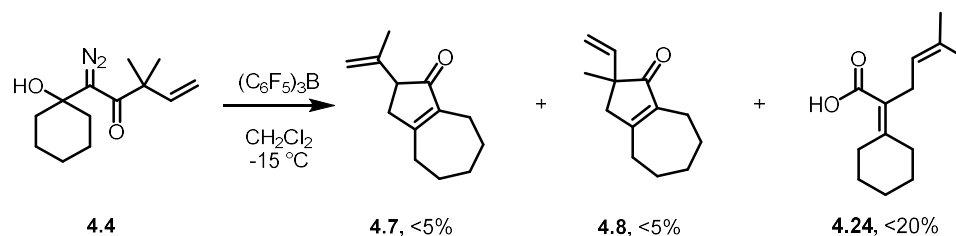
Scheme 4.5 Dr. Dodge's initial results using substituted β-hydroxy-α-diazo ketones

This reaction is quenched with saturated sodium bicarbonate to remove excess Lewis acid, but this would also deprotonate the carboxylic acid, so it is likely most of the product

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was in the disposed aqueous layer. The procedure was modified to remove the workup step

and with this modified procedure, Dr. Dodge isolated lactone **4.25** in 66% yield (Scheme

4.6). As this compound had not been reported in the literature before this point, he subjected

lactone **4.25** to ozonolysis to confirm the identity by cleavage of the alkene. He received

cyclohexanone and keto ester **4.26**, confirmed by crude NMR and GCMS, proving the

formation of the lactone.[144] The cyclization of carboxylic acid **4.24** to lactone **4.25** is not

surprising. Concentration of the carboxylic acid while in the presence of the Lewis acid

promotes the ring closure to lactone **4.25**. Further modification of this reaction to include

a dilute acidic workup also provided access to the lactone.
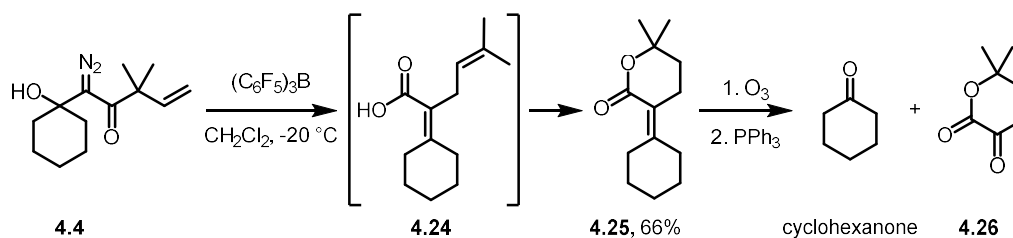
Scheme 4.6 Removal of workup provides evidence for lactone formation

When I took over the project, I was not able to replicate Dr. Dodge's yield of 66%. In

fact, the yields of the lactone **4.25** fluctuated with each trial. I hypothesized that the lactone

decomposes on the silica column, and quick elution during column chromatography

provided a consistent yield of 49% (Scheme 4.7).

I tested this reaction on a linear system with alkyl groups and received lactone **4.30** in

38% yield. In both substrates, I received trace amounts of alkene addition (**4.7** & **4.27**) and

C–H insertion products (**4.8** & **4.28**). This reaction did not improve using other Lewis acids

such as SnCl₄, BF₃•Et₂O, or In(OTf)₃, likely due to competitive capture of the vinyl cations with the Lewis acid counterions.[59]
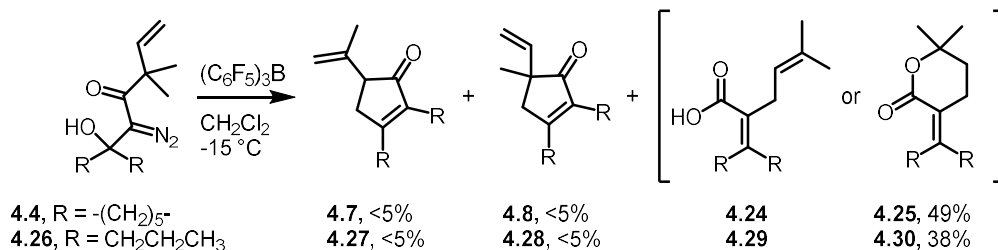
Scheme 4.7 Lactone ring formation from more substituted alcohols

We hypothesize the transformation from the β-hydroxy-α-diazo ketone **4.4** to the three unique products occurs through the pathways shown in Scheme 4.8. First, β-hydroxy-α-diazo ketone will react with BCF to lose hydroxide and molecular nitrogen and form common intermediate linear vinyl cation **4.31**. In pathways A and B, there will be a 1,2-shift across the linear vinyl cation to provide cyclic vinyl cation **4.5**. Path A proceeds by a nucleophilic intramolecular attack by the alkene side chain onto electrophilic vinyl cation. Deviating from Karpf's proposed mechanism,[142] we hypothesize that this will form acylium intermediate **4.32**, which could be attacked by the trisubstituted alkene to form **4.7** after loss of a hydrogen (Scheme 4.8, A).
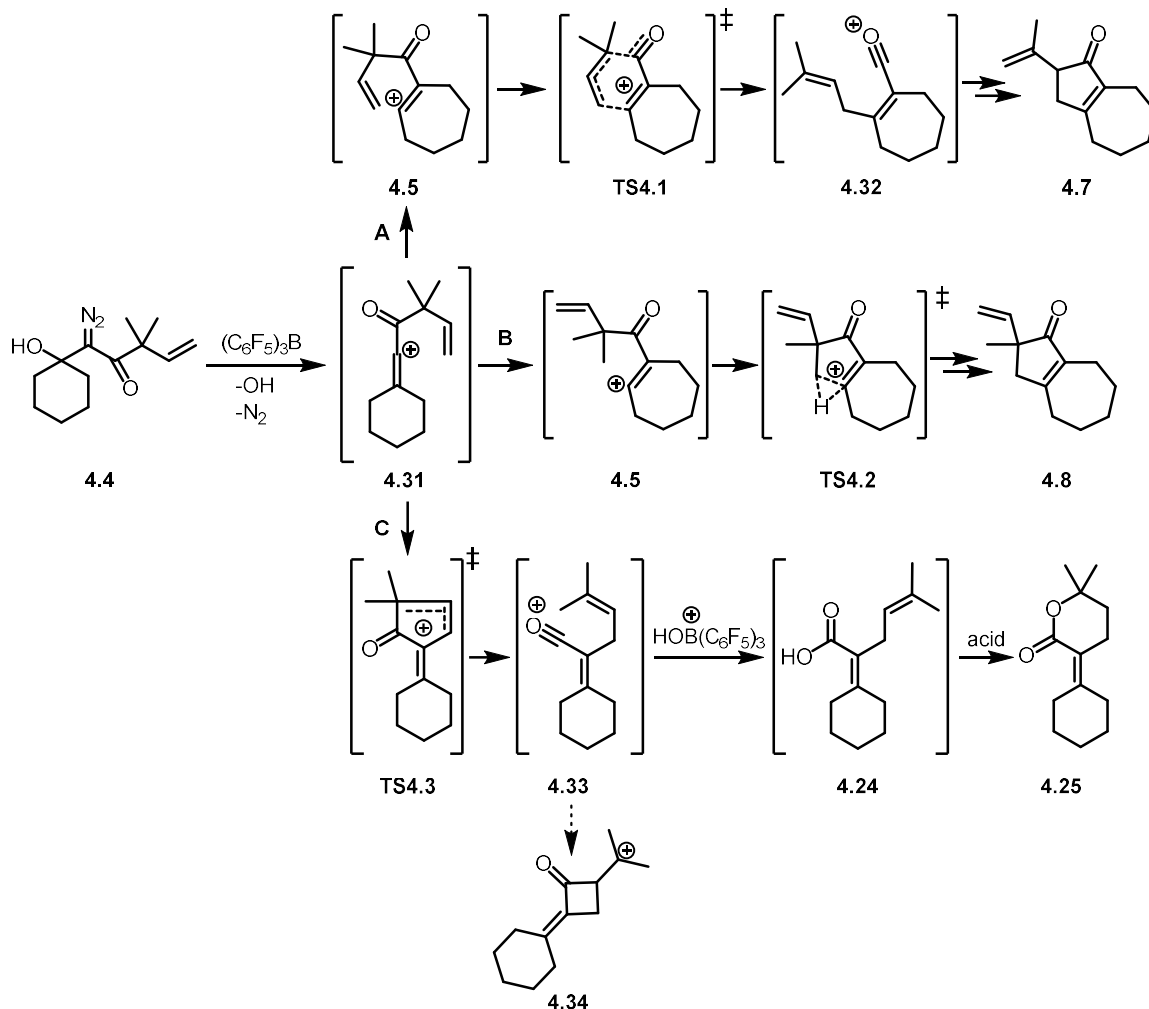
Scheme 4.8 Pathways to form the cyclopentenone and lactone products

In pathway B, we propose that the cyclic vinyl cation will act as a carbene surrogate and participate in a C–H insertion reaction to form cyclopentenone **4.8**. Since both cyclopentenones **4.7** and **4.8** were formed in trace yields, these pathways are less likely to occur, and pathway C is the most energetically favorable. In pathway C, migration across the linear vinyl cation **4.31** is slower than nucleophilic attack by the pendant alkene, which gives acylium **4.33**. Formation of cyclobutanone ring **4.34** could occur through nucleophilic attack of the alkene on the electrophilic acylium, however, this small ring

system would be unstable and thus this is an unlikely pathway. As these reactions are run

under dry conditions, we propose there is a delivery of a hydroxide from the Lewis acid to

form carboxylic acid **4.24**.[59]

4.4   Initial Results on a Less Substituted System

Dr. Dodge turned his attention to modifying the substitution at the β-position of the β-

hydroxy-α-diazo ketone and prepared a secondary alcohol from the addition of diazo

ketone **4.23** onto benzaldehyde. When **4.35a** was subjected to BCF, he received

cyclopentenone **4.36** in 90% yield (Scheme 4.9).[144] He graduated before he could explore

this reaction further, and I took over the project from here.
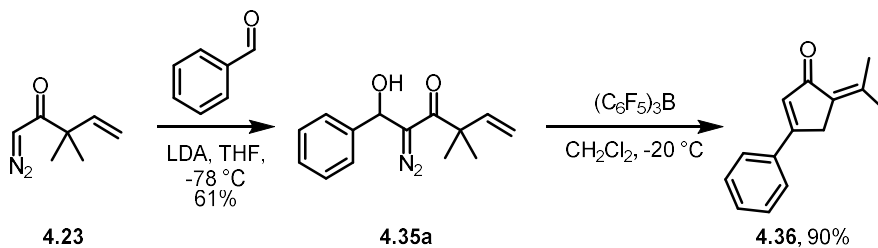
Scheme 4.9 Dr. Dodge's initial result on less substituted system

When I took over this project, I was not able to reproduce the 90% yield of

cyclopentenone **4.36** using Dr. Dodge's conditions. In fact, I thought that I was forming a

different compound completely as my ^{1}H NMR peaks did not match the experimental

spectra reported in his thesis. Taking a closer look revealed that Dr. Dodge's initial results

contained solvent impurities, which inflated his yield. Furthermore, I believe there was

BCF Lewis acid in his cyclopentenone **4.36** data, which shifted the peaks in the NMR. I

confirmed this by adding a small amount of BCF and to a pure sample of cyclopentenone

4.36; the peaks shifted to match those indicated in Dr. Dodge's thesis.

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So, I moved to optimize the reaction conditions. When BCF was used as the Lewis acid at -20 °C, cyclopentenone product **4.37a** was isolated in 63% yield (Table 4.1, entry 1). Diluting the reaction did not improve the yield, and I isolated a mixture of cyclopentenones **4.36a** and **4.37a** (entry 2). At first, I was isolating mixtures of these cyclopentenones in inconsistent ratios. I discovered that the acidity of the silica gel used in the purification affected the ratio between the two isomers. Using a small amount of triethyl amine in the eluent system isomerized external alkene **4.37a** to internal alkene **4.36a** cleanly with no loss of yield. Increasing the reaction temperature to room temperature improved the yield of **4.36a** to 69% (entry 3), but a temperature of 35 °C diminished the yield (entry 5). Lewis acids such as Sc(OTf)$_3$ and BF$_3$•Et$_2$O did not provide good yields of cyclopentenone products (entry 6 &7).
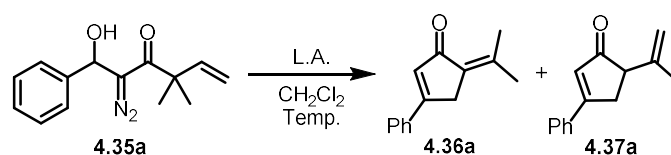
Table 4.1 Optimization for alkene addition reaction

Entry	Lewis acid	Conc. (M)	Temp. (°C)	Yield 4.36a	Yield 4.37a
1[a]	(C$_6$F$_5$)$_3$B	.2	-20	-	63%
2[a]	(C$_6$F$_5$)$_3$B	.4	-20	59%	
3[b]	(C$_6$F$_5$)$_3$B	.4	Rt	69%	-
4[b]	(C$_6$F$_5$)$_3$B	.2	Rt	67%	-
5[b]	(C$_6$F$_5$)$_3$B	.4	35	59%	-
6[b]	Sc(OTf)$_3$	.2	Rt	30%	-
7[b]	BF$_3$•Et$_2$O	.2	-20	40%	-

[a] Purified using untreated silica gel. [b] Purified using silica gel washed with 0.5% Et$_3$N.

We hypothesize the mechanism to form cyclopentenone **4.36a** initiates with a loss of hydroxide and nitrogen gas to provide linear vinyl cation **4.38** (Scheme 4.10). A hydride will migrate across the vinyl cation to form linear vinyl cation **4.39**. Vinyl cation **4.39** acts as an electrophile, and the nucleophilic alkene will attack this center through **TS4.4** to provide acylium intermediate **4.40**. Attack of the acylium at the carbon center by the pendant alkene, followed by hydride elimination, provides cyclopentenone **4.36a**.
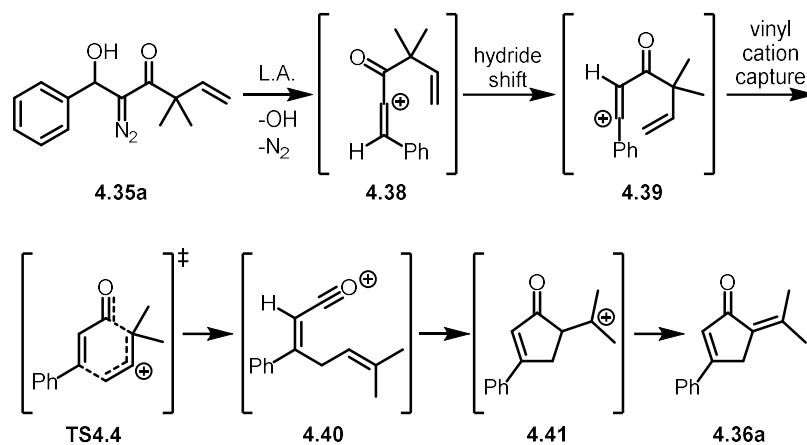
Scheme 4.10 Mechanism for the alkene addition reaction

It is important to note that this reaction subverts two possible side reactions that may be formed in a system with a 2° alcohol. First, this reaction does not suffer from the reverse Friedel-Crafts acylation observed in other linear systems which provide alkyne side products (Scheme 4.11, A).[60] Second, although Wenkart reported loss of hydrogen when using β-hydroxy-α-diazo ketones derived from aldehydic starting materials,[96] there were no elimination products of type **4.42** isolated. It can be concluded that nucleophilic attack on the linear vinyl cation **4.39** is a faster reaction than the reverse Friedel-Crafts acylation. Additionally, the removal of hydrogen to provide **4.45** is less likely to occur than loss of the diazo functional group.
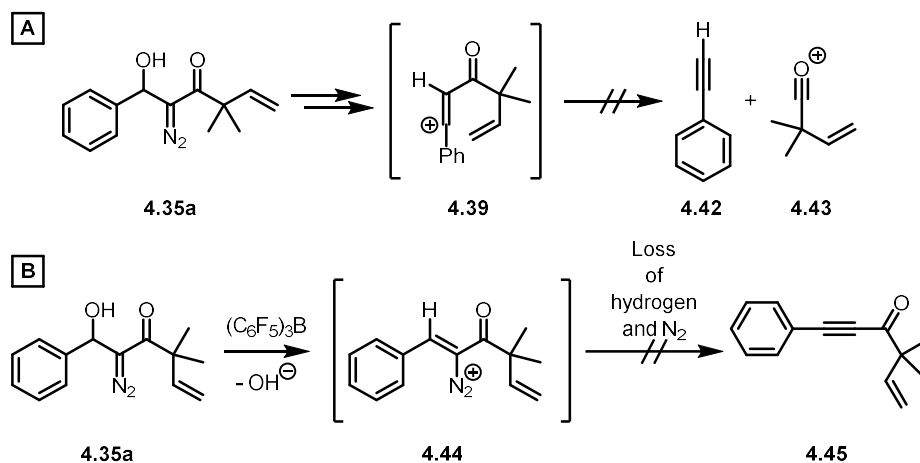
Scheme 4.11 Competitive side products not observed

4.5   Substrate Scope of the Alkene Addition Reaction

With optimized conditions in hand, I turned towards investigating the substrate scope of the alkene addition by varying the starting aldehyde (Table 4.2). The β-hydroxy-α-diazo ketones were formed in yields between 21-73% by adding lithiated diazo ketone **4.23** to aldehydes.

With the vinyl cation precursors in hand, we assessed the scope of the reaction. A methyl at the para position did not affect the reaction outcome and **4.35b** gave cyclopentenone **4.36b** in a comparable yield of 64% which is comparable to the yield obtained for **4.36a**. Curiously, increasing the steric bulk of the aryl ring increased the yield of the cyclopentenone dramatically. Cyclopentenones **4.36c** and **4.36d** were formed in 89% and 93% yield respectively. We also demonstrated that this reaction could be performed on a 1 mmol scale without loss of yield when preparing cyclopentenone **4.36d**. It is hypothesized that steric hinderance may be promoting the vinyl cation formation or it is protecting the linear vinyl cation from intermolecular attack by a Lewis acid counterion.

The yield was high for other sterically encumbered systems; when the R group was a napthyl group the yield of the cyclopentenone **4.36e** was 54% but the more sterically hindered anthracenyl provided cyclopentenone **4.36f** in 77% yield.[59]

Table 4.2 Substrate scope of alkene addition

| 4.36a, 69% | 4.36b, 64% | 4.36c, 89% | 4.36d, 93%
 [a]88% | 4.36e, 54% | 4.36f, 77% | 4.36g, 29% | 4.36h, 10% |

| 4.36i, 60% | 4.36j, 64% | 4.36k, 56% | 4.36l, 73% | 4.36m, 36% | 4.36n, 25% | 4.36o, 13% |
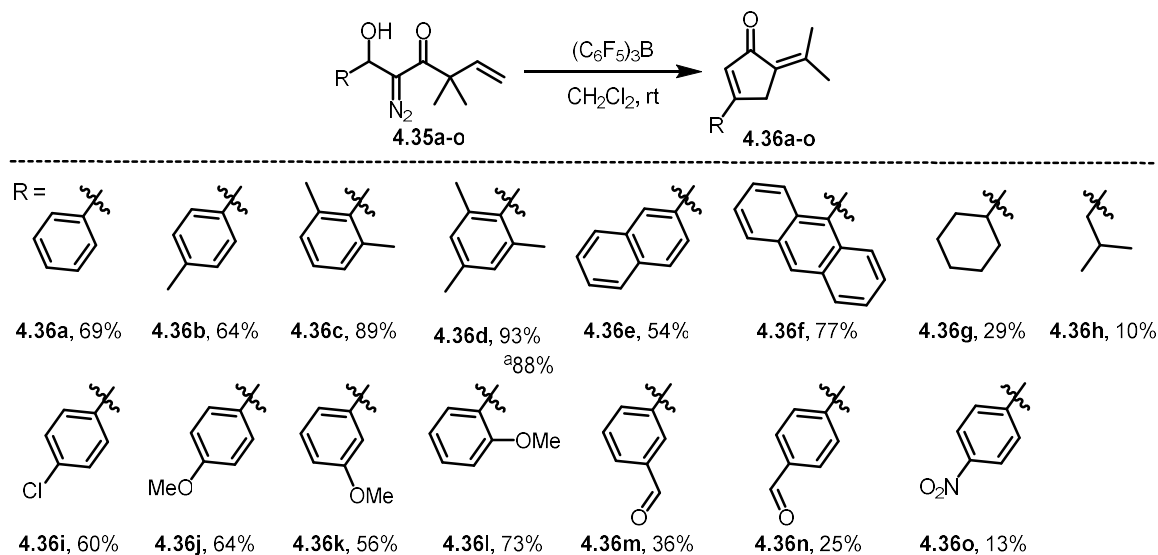
[a]Yield on a 1 mmol scale.

Modification of the starting material to aliphatic groups was not productive and provided cyclopentenones **4.36g** and **4.36h** in 29% and 10% yields respectively. The side products formed from these substrates were isolated as a complex mixture. This is not completely surprising since α-styrenyl cations are stabilized by the adjacent aryl ring, without that stabilization present the vinyl cation may be slow to rearrange or suffer from additional side reactions. Modification of the electronics of the aryl ring to include electron neutral or electron rich groups gave significantly higher yields than electron poor rings. Substitution at the para position of the ring with a chloro- or a methoxy group provided yields of cyclopentenones **4.36i** and **4.36j** in 60% and 61% yield. Substitution at the meta position of the ring with a methoxy group did not have much effect on the reaction outcome

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and provided cyclopentenone **4.36k** in 56% yield. Methoxy substitution at the ortho position provided cyclopentenone **4.36l** in 73% yield, again signifying that sterically hindered aryl rings increase the yield of cyclopentenone product.[59]

With electron poor groups on the aryl ring, the yield decreased dramatically. Substitution with an aldehyde at the meta (**4.36m**) or para (**4.36n**) position provided 36% and 25% yields respectively. Substitution with a nitro group at the para position provided a low yield of 13% (**4.36o**). The electron poor aryl ring, similar to the aliphatic group, may not be sufficient stabilization for the intermediate vinyl cation formed from this reaction.[59]
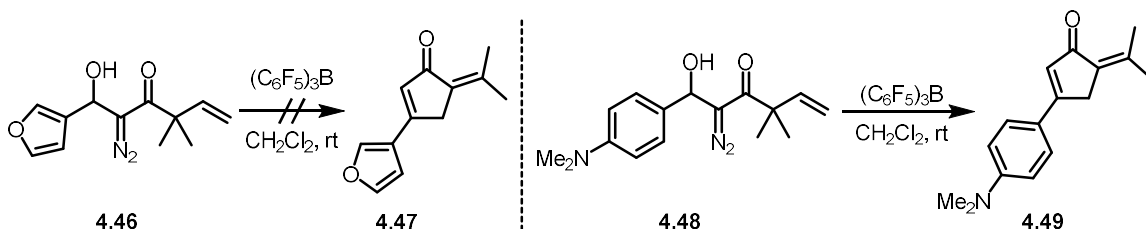
Scheme 4.12 Modification of aromatic system to heteroatom containing systems

Changing the aromatic system to a furan ring **4.46** was unsuccessful and returned a black sticky material that was observed as a complex mixture of products by NMR. It is likely that the BCF may be coordinating to the furan moiety and inhibiting the reaction that would lead to cyclopentenone **4.47**. Modification of the ring system to an aromatic ring which contained an amino group (**4.48**) gave peculiar results. The crude NMR was clean to an extent, and purification of the material provided a magenta colored solid with clean ^{1}H and ^{13}C NMRs that would match the expected NMR data for cyclopentenone **4.49**. This material has some interesting physical characteristics. It is a bright lime green when dissolved in hexanes:DCM (Figure 4.1, A) and when dissolved in CDCl₃, the solution is

orange against a white background and dark green against a black background (Figure 4.1, B).
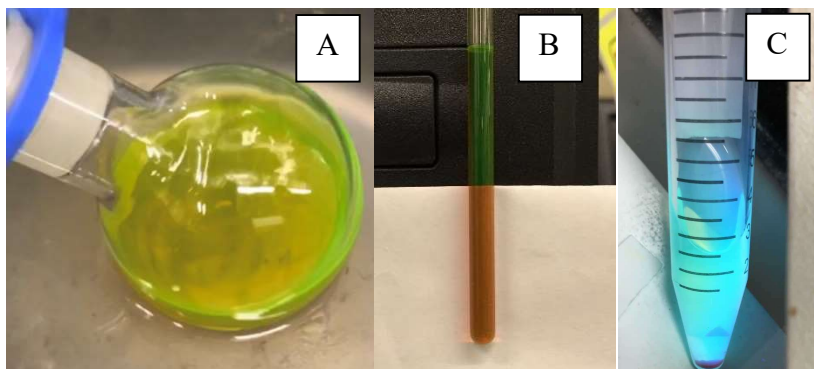
Figure 4.1 Interesting physical characteristics of aniline system

In all trials, a yield could not be determined because the product is impure. Although the ^{1}H and ^{13}C NMRs are clean, the ^{19}F NMR have three peaks which indicate that BCF is still present in the mixture. I believe that some BCF is coordinating to the nitrogen group on the aniline ring which inflates the yield of cyclopentenone **4.49**. Attempts to remove the BCF from the mixture was unsuccessful. Dissolving the material in DCM and then using a centrifuge gave a red solid and a green solution which fluoresced cyan under UV light (Figure 4.1, C). Doing this multiple times did not alter the presence of BCF peaks. Using an internal standard on the purified cyclopentenone was also futile as the cyclopentenone **4.49** was only somewhat soluble in CDCl$_3$. For the internal standard to be accurate, I would need to transfer the whole sample into the NMR tube.

Scheme 4.13 Pyridine ring leads to pentafluoro trapped products

I also modified the starting material to include a pyridine ring (Scheme 4.13). As pyridine rings are privileged scaffolds in FDA approved medicinal drugs and agrochemicals, it would be advantageous if we could incorporate this scaffold through our reaction.[145] However, diazo ketone **4.49** provided pentafluorophenyl trapped alkenes **4.50** and **4.51** in a combined yield of 92% instead of desired cyclopentenone **4.52**. Furthermore, this reaction required 2 equivalence of BCF; starting material was returned when only 1 equivalent was used. It is likely that the BCF is coordinating to the pyridine ring which is enabling the transfer of the pentafluorobenzene ring to the intermediate vinyl cations.

4.6   Investigations into the Mechanism of the Alkene Addition Reaction

We hypothesize that there is a formation of an acylium intermediate after the attack of the vinyl cation by the initial alkene. We propose this intermediate because of the results obtained on a more substituted β-hydroxy-α diazo ketone system (Scheme 4.7). We received carboxylic acid and lactone products in these systems, which could be formed from the attack of a hydroxide ion onto the electrophilic center of the acylium intermediate.[59] I wanted to test the validity of an acylium intermediate being formed in this reaction, so I set out to prepare acid chloride **4.53**. Friedel-Crafts reactions are known to occur through an acylium intermediate when an acid chloride is reacted with a Lewis acid.

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By applying Friedel-Craft acylation conditions to acid chloride **4.53**, the acylium intermediate **4.40** proposed in our mechanism will form. If cyclopentenone **4.36a** forms, it does not necessarily prove the reaction proceeds through an acylium intermediate (Scheme 4.14). However, if the cyclopentenone does not form it provides evidence that acylium **4.40** is not an intermediate as indicated in the proposed reaction mechanism (Scheme 4.10).
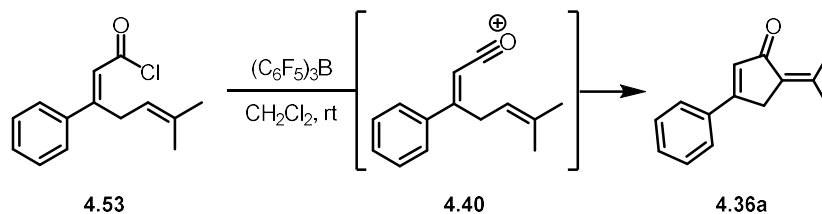
Scheme 4.14 Determining if an acylium is formed in our proposed mechanism

The synthesis of acid chloride **4.53** has been a challenging task. The first synthetic iteration involved forming ester **4.56**, which could then be converted to acid chloride **4.53** through saponification and acid chloride formation (Scheme 4.15). To start, I formed alkyne **4.55** in a 50% yield from the reaction of phenyl acetylide and ethyl chloroformate.[146] I attempted to directly from ester **4.56** through a copper mediated 1,4-conjugate addition reaction, however this was unproductive.[147] Switching gears, I prepared vinyl iodide **4.57** in a 80% yield from reaction of alkyne **4.55** and sodium iodide in concentrated acetic acid.[148] This vinyl iodide could then participate in a palladium catalyzed Negishi cross coupling reaction with allylic bromide to form ester **4.56**.[149] However, this also failed to form the desired ester.

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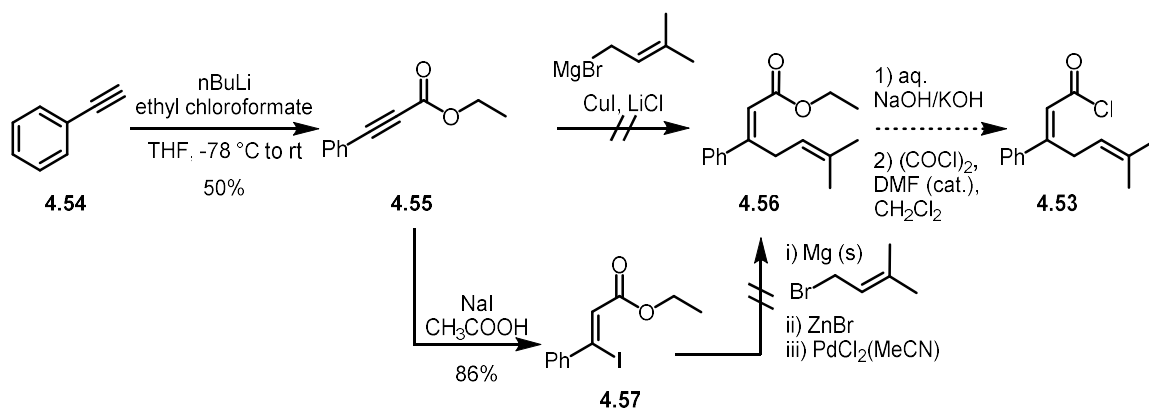
Scheme 4.15 Failed attempts to form ester via coupling reactions

The second iteration focused on forming ketone **4.59** and then performing a Horner-Wadsworth-Emmons (HWE) reaction to form ester **4.56** (Scheme 4.16). Preparation of this ketone was relatively straightforward. Starting with benzaldehyde, I formed the silyoxy acetonitrile **4.58** in 83% yield from trimethylsilyl cyanide and triethyl amine;[150] other bases such as DMAP were tested but gave low conversion of product.[151] Addition of the allylic chloride formed a vinyl silyl ether, which could be transformed to ketone **4.59** using potassium fluoride and catalytic tetrabutyl ammonium chloride in a 57% yield over two steps.[152, 153]
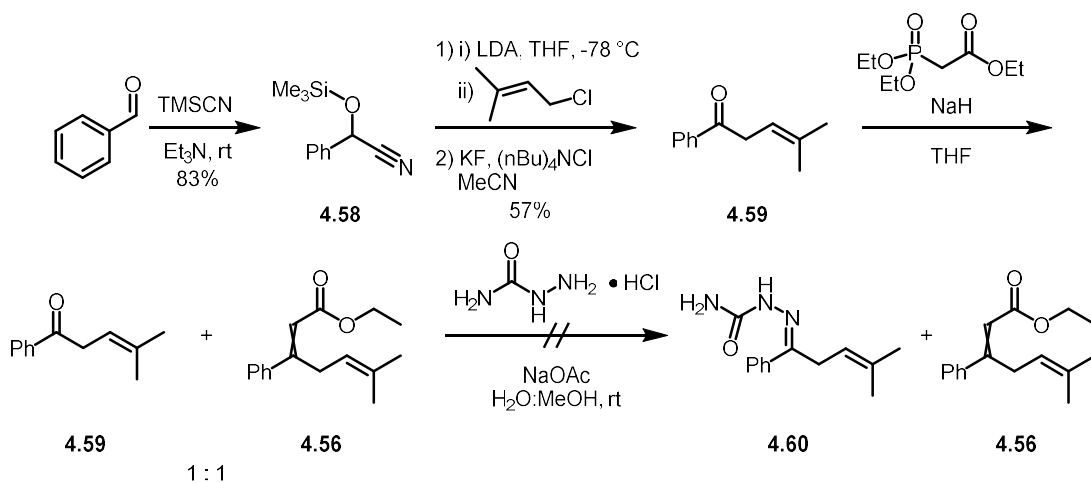
Scheme 4.16 Attempts at accessing ester through HWE reaction

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However, when I attempted to form vinyl ester **4.56** via a HWE reaction I received a 1:1 mixture of the starting ketone **4.59** and ester **4.56**. Whether the ester **4.56** was the desired *E* isomer or the undesired *Z* isomer is not known at this time. To separate the undesired starting ketone **4.59** from the product, I attempted to form semicarbizide **4.60**, which should be a solid that can be filtered away from the product.[154] This was unproductive.
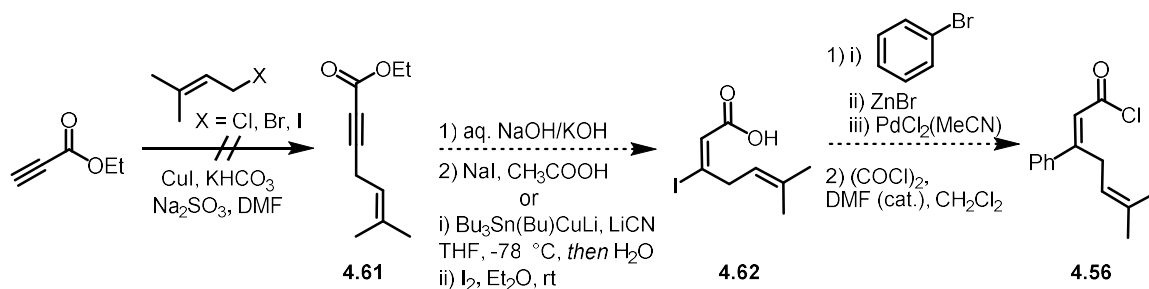
Scheme 4.17 Current synthetic sequence to acid chloride 4.56

With the help of an undergraduate student, Isabelle Petrucci, I am currently working on forming acid chloride **4.56** using a new sequence (Scheme 4.17). Starting with ethyl propiolate, Isabelle attempted a copper mediated coupling reaction onto the alkyne using prenyl chloride.[155] This was unsuccessful, although we believe if we modify the halide to a bromide or iodide it will increase the electrophilicity of the coupling partner to form alkyne **4.61**. Once alkyne **4.61** is formed, saponification of the ester will form a carboxylic acid. I hypothesize we could form vinyl iodide **4.62** using one of two methods. The first is using conditions described previously, that is, sodium iodide in acetic acid, to form vinyl iodide **4.62**.[148] However, this may provide the undesired isomer. If that is the case, we can prepare a vinylstannane using Bu$_3$Sn(Bu)CuLi followed by addition of iodine to form the

E-vinyl iodide **4.62**.[156] A Negishi coupling followed by acid chloride formation would form our desired product **4.56**.[149]

4.7   Evaluations of the Reverse Friedel-Crafts Acylation

In Chapter 3, I discussed our studies of the migration of non-equivalent groups across the vinyl cation. When one of the migrating groups was an aryl and the other was an alkyl chain a large amount of alkyne **4.66** (Scheme 4.18) was formed. This indicated that a reverse Friedel-Crafts acylation was competing with the C–H insertion in this acyclic system.[60]
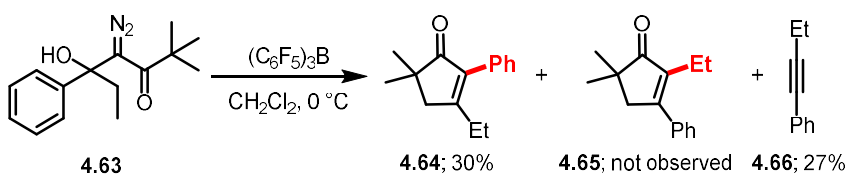
Scheme 4.18 Competitive reverse Friedel-Crafts acylation in C–H insertion study

It would be interesting to know if alkene addition is faster than the reverse Friedel-Crafts acylation. To test this, I prepared β-hydroxy-α diazo ketone **4.67** in 36% yield from propiophenone and diazo ketone **4.23** (Scheme 4.19). Of note, the purification of β-hydroxy-α diazo ketone **4.67** from the propiophenone starting material was not trivial and required multiple purifications.
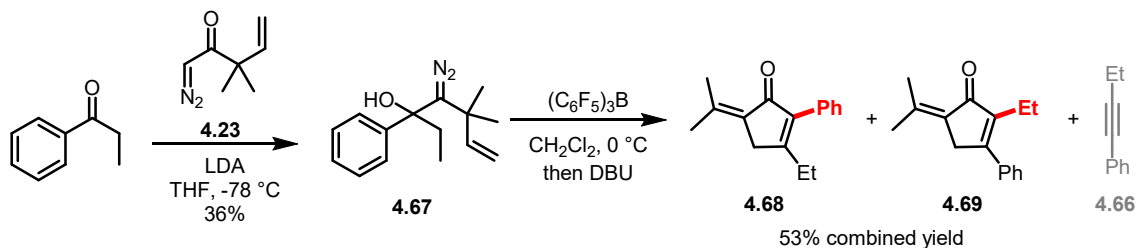
Scheme 4.19 Alkene addition is faster than reverse Friedel-Crafts acylation

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When **4.67** was subjected to BCF, the only products I could isolate were cyclopentenone **4.68** and **4.69** in a combined yield of 53%. I suspect that the phenyl ring migrates preferentially based on the data we received for our earlier migration investigations.[60] Importantly, alkyne **4.66** was not formed, indicating that nucleophilic attack onto the vinyl cation is faster than the reverse Friedel-Crafts acylation. No lactone or carboxylic acid products were formed. This is significant because when both potential migrating groups are alkyl chains, lactone and carboxylic acid products are favored, likely due to the slow migration of an alkyl group.

4.8   Efforts to Stabilize the Intermediate Vinyl Cations

The alkene addition reaction worked best with neutral and electron rich aryl groups. When the aryl group was electron deficient or the substituent was an alkyl group the reaction gave low yields of cyclopentenone products. We hypothesize that the vinyl cation formed after hydride transfer was not sufficiently stabilized by these substituents, which led to the decreased yield. This prompted me to investigate the stabilization of the intermediate vinyl cation through other means.
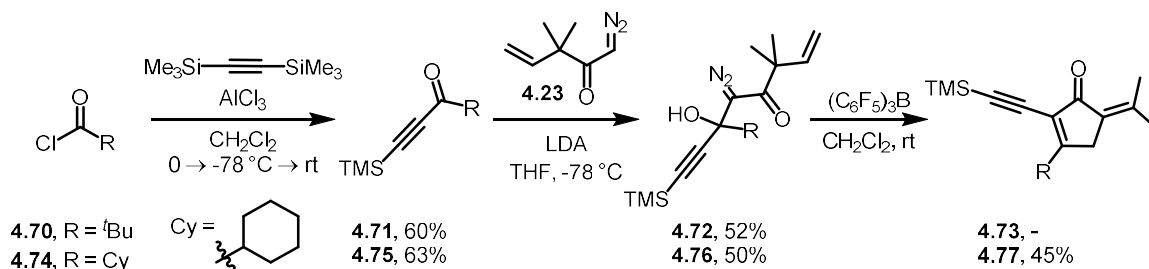
Scheme 4.20 Vinyl cation stabilization using alkynes

I set out to prepare β-hydroxy-α-diazo ketones **4.72** and **4.76** (Scheme 4.20). These incorporate an alkyne side chain, which should offer some stabilization to the intermediate

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vinyl cations. Vinyl cations can be stabilized using aryl rings, alkenes, and cyclopropanes; I hypothesized that an alkyne may also offer stabilization.[46, 54] The starting ketone was prepared by a Friedel-Crafts reaction of the appropriate acid chloride with bis[trimethylsilyl]acetylene.[157] Addition of diazo ketone **4.23** onto these ketones provided the *tert*-butyl (**4.72**) and cyclohexyl (**4.76**) vinyl cation precursors in 52% and 50% respectively.[59] When the substrate bearing the *tert*-butyl group (**4.72**) was subjected to BCF, no cyclopentenone product was identified, and the reaction provided a complex mixture. When the cyclohexane variant **4.76** was tested, the cyclopentenone product was generated in 45% yield, unoptimized. Other Lewis acids such as $SnCl_4$ and $Sc(OTf)_3$ provided low yields of cyclopentenone products. As this alkyne could be used as a synthetic handle, this may be an interesting methodology to investigate further if it was optimized.[59] This study also demonstrated that if the vinyl cation is stabilized, cyclopentenone rings that contain alkyl substituents can be formed in higher yields than those without some form of stabilization present.

4.9   Modification of the Diazo Ketone

I turned my attention towards investigating the types of nucleophiles that could be used to attack the vinyl cation. Along this vein, I prepared β-hydroxy-α diazo ketone **4.84**, which incorporates an alkyne to act as a nucleophile. Starting from alcohol **4.78**, I prepared chloride **4.79** in 57% yield.[158] When I subjected the unprotected alkyne **4.79** to Grignard conditions to form the carboxylic acid, I received only starting material, likely due to the Grignard reacting with the acidic acetylenic hydrogen atom. Switching to the TMS protected acetylene **4.81** allowed the carboxylic acid formation to occur and KOH was then

used to remove the TMS group. Diazo ketone **4.82** was formed in 24% yield by the addition

of diazomethane onto the corresponding acid chloride. Addition of lithiated diazoketone

4.83 onto benzaldehyde provided the β-hydroxy-α diazo ketone **4.84** in 35% yield (Scheme

4.21).
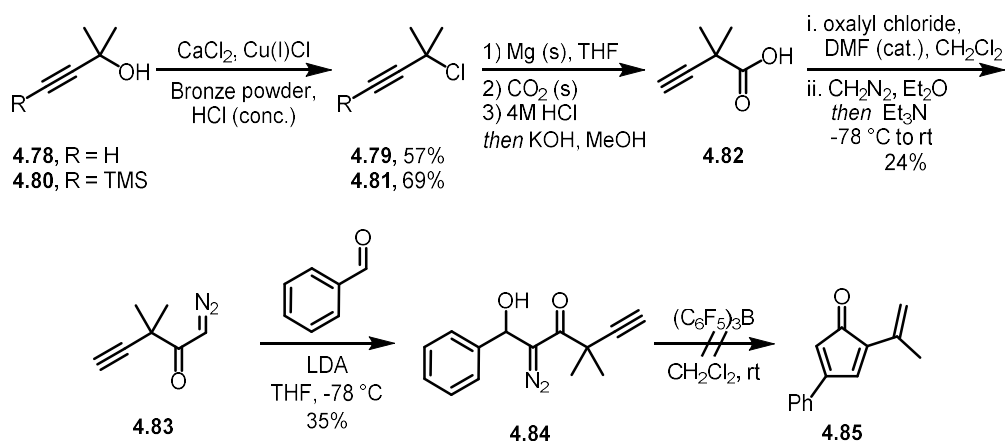
Scheme 4.21 Preparation of the diazo ketone bearing an alkyne

Subjecting β-hydroxy-α-diazo ketone **4.84** to BCF, did not form cyclopentadiene **4.85**

and instead returned a complex mixture. Considering the proposed mechanism (Scheme

4.22), there are a few alternative reactions paths that may have suppressed the formation

of the cyclopentadienone **4.85**. If the addition of the alkyne to the vinyl cation is stepwise

(pathway **A**), a new vinyl cation (**4.87**) will form. This vinyl cation may be captured by the

Lewis acid counterion or chloride from the solvent. However, this pathway is unlikely, as

the formation of the strained cyclic vinyl cation **4.87** is likely to be short lived.
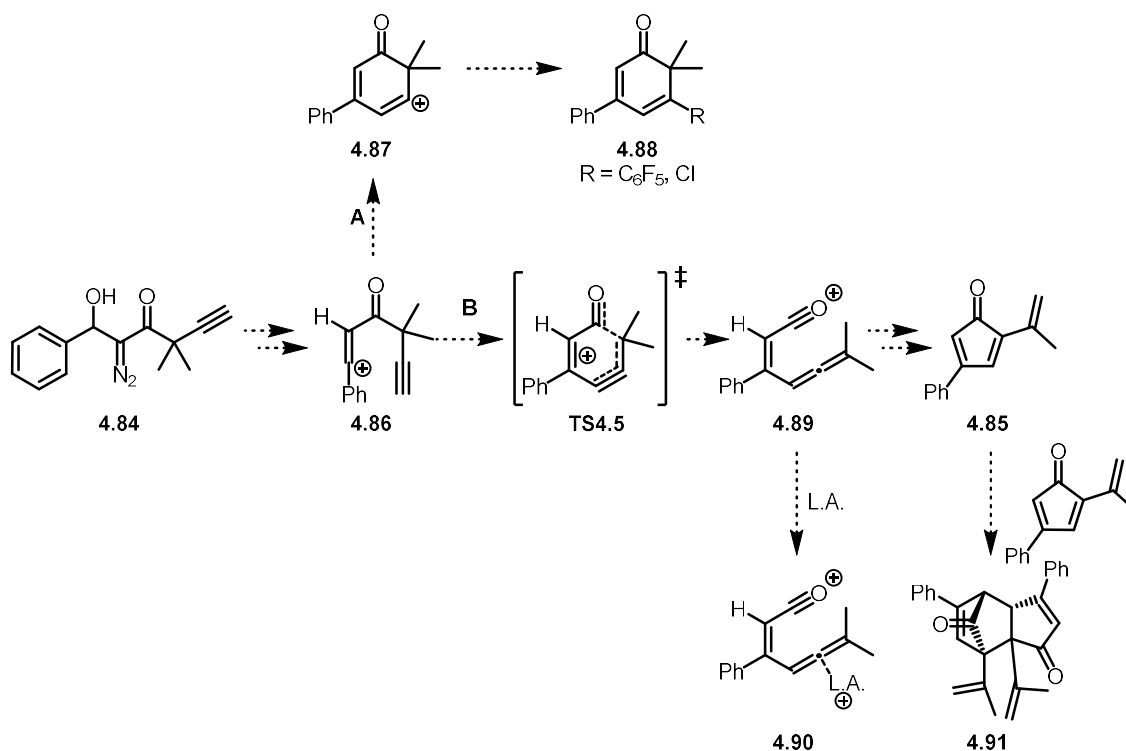
Scheme 4.22 Pathways that may be suppressing the cyclopentadiene formation

In pathway **B**, the reaction occurs through a concerted nucleophilic attack and fragmentation via **TS4.5**, to give allene **4.89**. However, the Lewis acid may be reacting with the alkyne starting material or the allene. BCF is a strongly Lewis acidic borane, and while this Lewis acid works well with our system, other side reactions may be possible. BCF is used in 1,1-carboboration reactions of alkynes, and has shown to form an equimolar mixture of E/Z alkenes from non-activated acetylenes in minutes at room temperature (Scheme 4.23).[159] It may be possible that products resulting from the carboboration of alkyne **4.84** and **4.86** were formed in the reaction. Additionally, the central carbon atoms of allenes are known to be activated by Lewis acids, which makes them more electrophilic.[160] If that is the case, allene **4.89** may be more susceptible to nucleophilic attack by a counterion. Even if cyclopentadienone **4.85** was formed, they are known to be

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unstable and prone to dimerization.[161] If that is the case, it is possible dimer **4.91** may have

been formed but not isolated.

R = Ph, ^{t}Bu, ^{n}Pr, -(CH$_4$)Cl, -(CH$_2$)$_3$Ph
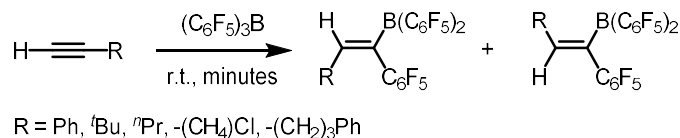
Scheme 4.23 BCF leading to carboboration of unactivated alkynes

I further modified the nucleophile to include a vinyl ester **4.92** which would lead to

lactone **4.94**. I hypothesized that the alkene would attack the vinyl cation **4.98** to generate

acylium **4.99**. The aldehyde would then attack the electrophilic acylium, leading to the

formation of lactone **4.94**. I suspected that if this was not a favorable process, then

carboxylic acid **4.95** would be formed. However, neither of these products were isolated.

As described by Cleary et. al. in the 2019 JACS publication, β-hydroxy-α diazo esters

don't adopt a conformation that favors C–H insertion.[102] If the ester in this example is also

oriented S-cis (away from the vinyl cation) it is likely that the alkene addition would not

occur.
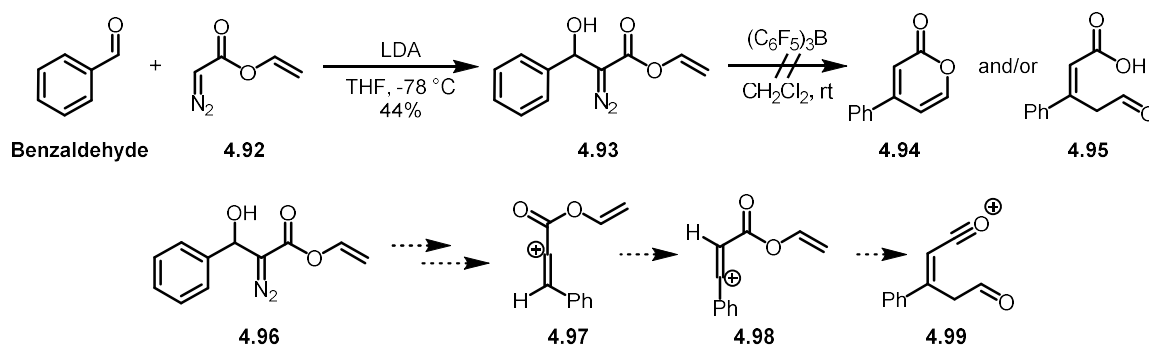
Scheme 4.24 Vinyl ester as nucleophile leading to lactone products

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I wanted to observe if it is necessary to have substitution on the diazo ketone portion of the molecule in order to successfully form cyclopentenone **4.102** (Scheme 4.25, A). This study would be useful, as this alkene could act as synthetic handle to build upon the cyclopentenone. Considering other side products that may be possible is phenol **4.103**, as described by Karpf using an unsubstituted alkyne in their system.[142] Currently, we assume the alkene addition and bond fragmentation is concerted as indicated in Scheme 4.10. In this case, we would not expect this product, but if we did return phenol it may indicate a stepwise process. However, we could not study this substrate as the formation of β-hydroxy-α-diazo ketone **4.101** was unsuccessful
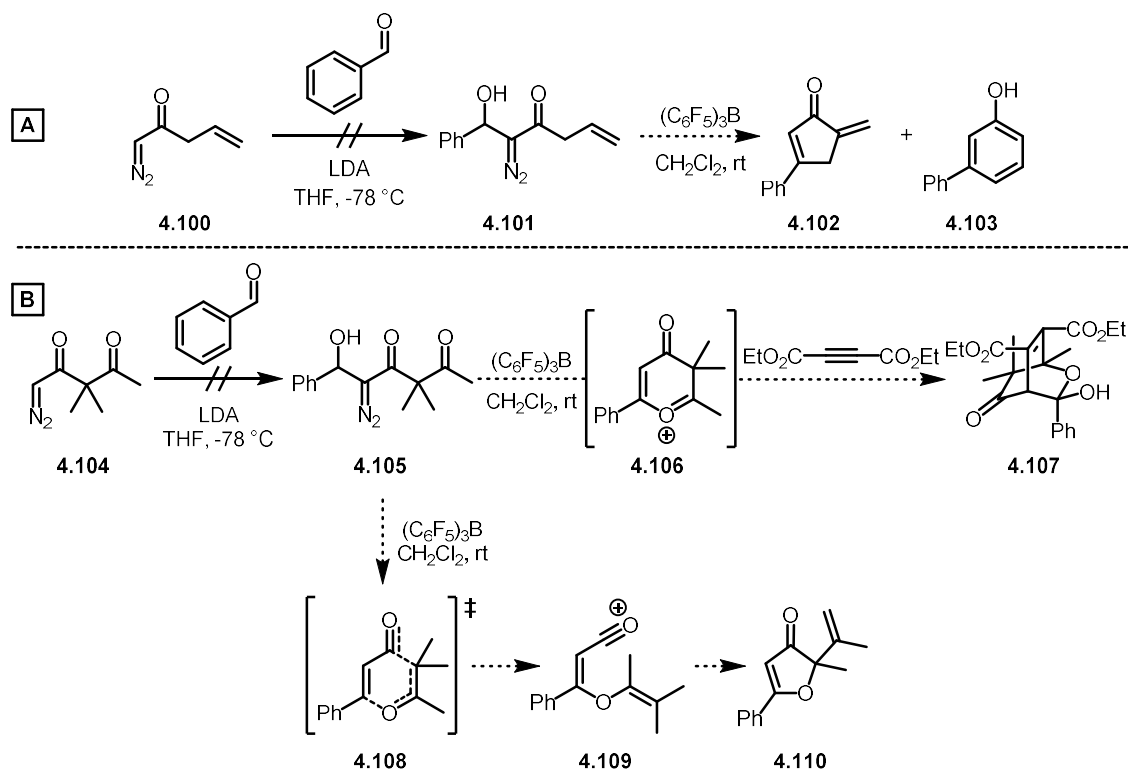
Scheme 4.25 Unsuccessful investigations into alternative nucleophiles

I planned to investigate if a ketone could capture the vinyl cation intermediate, however, the preparation of β-hydroxy-α diazo ketone **4.105** was unsuccessful. This may be due to competitive deprotonation of the hydrogen adjacent to the δ-ketone on the diazo ketone, or addition of the diazo ketone **4.104** onto itself. This would have been an interesting substrate to test. I hypothesize two pathways it could react by (Scheme 4.25). If the capture of the vinyl cation and then bond fragmentation is stepwise, intermediate **4.106** would be formed. This intermediate would be an attractive 1,3-dipole to be used in a cycloaddition reaction. To test this theory, I would have added dimethyl acetylenedicarboxylate to the reaction to observe the formation of bicyclo **4.107**. If the nucleophilic attack onto the vinyl cation and the fragmentation was a concerted process, it may have been likely that lactone **4.110** would be formed. Although these substrates could not be tested due to difficulties forming the starting material, it would be interesting to observe if other nucleophiles could be used to attack the vinyl cation for future work.

4.10   Concluding Remarks and Future Outlooks

In this chapter, I discussed using vinyl cations as an electrophile to access cyclopentenone ring systems. When the starting β-hydroxy-α diazo ketone contains a more substituted alcohol at the β-position and the migrating groups are an alkyl substituent, migration across the vinyl cation is slow. There is a competitive fragmentation reaction which generates an acylium intermediate that is captured by a hydroxyl group to provide carboxylic acid and lactone products. When the β-hydroxy-α diazo ketone contains a less substituted alcohol at the β-position, a hydride migrates across the vinyl cation to provide a linear vinyl cation that gets captured by a nucleophilic pendant alkene.

When the β-hydroxy-α diazo ketone contains an electron neutral or electron rich aryl ring, the reaction works well and gives cyclopentenone products in good yields. Surprisingly, when the aryl ring is a sterically bulky group, the yield increases dramatically. We hypothesize that the sterics help to promote the alkene addition or protect the vinyl cation from intermolecular attack. When the aryl ring is electron poor or when the group is an alkyl chain, the yield decreases dramatically, likely due to the instability of the resulting vinyl cation. Future work includes studying the mechanism further in hopes of confirming the intermediate the acylium ion. Additionally, I determined that nucleophilic attack onto the vinyl cation is a faster process than retro Friedel-Crafts acylation. Stabilization of the vinyl cation is also necessary for the alkene addition reaction. Electron neutral or electron rich aryl rings stabilize the vinyl cations the best, however, alkynes may also be suitable. Further investigation into stabilizing the intermediate vinyl cation will be necessary for this reaction to be practical.

While the addition reaction works well with an alkene nucleophile, other nucleophiles such as alkynes and vinyl esters were not suitable for this transformation. It is possible that these compounds are not suitable nucleophiles for vinyl cations, or they are slow to react which gives way to other undesirable reactions. Future work into the alkene addition reaction will be to probe the mechanism and determine a method for stabilizing the intermediate vinyl cation. Other work includes modifying the diazo ketone with groups other than a *gem* dimethyl to determine if more complex cyclopentenone ring systems can be formed.

Chapter 4: EXPERIMENTAL PROCEDURES

4.1 Methods and Materials

All reactions were performed under an inert atmosphere of nitrogen and in flamedried glassware or a microwave tube. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether (Et_2O), acetonitrile (CAN), and *N,N*-dimethylformamide (DMF) were all dried via the solvent-dispensing system. Diisopropyl amine (*i*Pr_2NH) and triethyl amine (Et_3N) were distilled fresh prior to use from CaH_2. Trimethylsilyl chloride (TMSCl), tetralone, and benzaldehyde were distilled before use. All other commercially available reagents were obtained from suppliers without further purification.

Reactions were monitored by TLC (thin-layer chromatography) on silica gel on glass plates and were visualized using UV light, ceric ammonium molybdate, iodine, or potassium permanganate. Flash column chromatography was performed on CombiFlash® Rf 150 system sing RediSep® Rf Gold silica columns or on silica gel (230-400 mesh). Centrifugal thin-layer chromatography was performed using a Harrison Research brand chromatotron and silica gel plates.

^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), ^{19}F NMR (471 MHz), COSY, and NOE spectra were recorded on a Bruker Asend 500 MHz spectrometer at room temperature. ^{1}H NMR is referenced to tetramethyl silane (TMS) at 0 ppm or $CDCl_3$ at 7.26 ppm. ^{1}H NMR chemical shifts are reported in ppm (δ units) downfield from TMS. ^{13}C NMR spectra are referenced to the $CDCl_3$ signal at 77.0 ppm. HMBC and HSQC data were collected on a 500 MHz Varian spectrometer. IR data was collected on a Shimadzu IR Affinity-1 FTIR

and the values are reported in wavenumbers. Exact mass data was acquired in ESI mode using Waters Xevo G2-XS LCMS-QTOF.

The following α-diazo ketones used are known compounds that were prepared by reacting diazomethane with the corresponding acid chlorides in accordance with standard literature procedures : [t-butyl][162], [i-propyl][163], [n-propyl][164], [i-butyl][164], and [ethyl][165]. 6-Bromo-3,4-dihydro-2H-naphthalen-1-one,[166] 1-diazo-3,3-dimethylpent-4-en-2-one,[143] 2,6-dimethylbenzaldehyde,[167] and 2,4,6-trimethylbenzaldehyde[168] were prepared following known procedures.

General Procedure A: Preparation of β-hydroxy-α-diazo ketones

A cold (–78 °C) solution of LDA (1.5 equiv) [prepared by addition of n-butyllithium in hexanes (1.5 equiv) to a solution of iPr$_2$NH (1.7 equiv) in THF (3 mL per mmol of n-butyllithium)] was added dropwise over 30 min via cannula down the side of a chilled flask containing a cold (–78 °C) stirred solution of ketone (1 equiv) and α-diazo ketone (1.6 equiv) in THF (3 mL per mmol of ketone). The mixture was maintained at –78 °C until complete conversion was achieved as monitored by TLC. Saturated aqueous NH$_4$Cl solution (5 mL) was added quickly to the reaction mixture at –78 °C, the reaction flask was removed from the cold bath and an additional portion of saturated NH$_4$Cl (15 mL) or 1 equiv. of AcOH in hexanes (16.4 mL per mmol AcOH) was added. The mixture was extracted three times with EtOAc (15 mL), the organic layers were combined, washed with saturated aqueous NaHCO$_3$ (50 mL), brine (50 mL), and dried over anhydrous CaCl$_2$. The solvent was removed in vacuo to provide an oily residue that was subjected to flash silica gel chromatography to afford the desired β-hydroxy-α-diazo ketone.

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General Procedure B: Preparation of β-hydroxy-α-diazo ketones of tetralone derivatives

A –78 °C solution of LDA (1.5 equiv) [prepared by adding n-butyllithium in hexanes (1.5 equiv) to a solution of iPr$_2$NH (1.7 equiv) in dry hexanes (3 mL per mmol of n-butyllithium)] was added dropwise over 10 min down the side of a chilled flask containing a cold (–78 °C) solution of ketone (1 equiv) and α-diazo ketone (1.6 equiv) in dry hexanes (3 mL per mmol of n-butyllithium) and dry THF (2.5 mL per mmol of ketone) under an atmosphere of nitrogen. The mixture was maintained at –78 °C for 45 minutes. One equiv. of AcOH in hexanes (16.4 mL per mmol AcOH) was added to the dark red reaction at -78 °C under nitrogen at which point the mixture became yellow. The reaction flask was removed from the cold bath and allowed to warm to room temperature. The reaction mixture was poured into a separatory funnel containing water (50 mL), the layers were separated, and the aqueous layer was extracted three times with EtOAc (15 mL). The organic layers were combined, washed with saturated aqueous NaHCO$_3$ (50 mL), brine (50 mL), and dried over anhydrous CaCl$_2$. The solvent was removed in vacuo to provide an oily residue that was subjected to flash silica gel chromatography to afford the desired β-hydroxy-α-diazo ketone.

General Procedure C: Tin(IV) chloride-promoted cyclopentenone formation

A 1M solution of SnCl$_4$ in CH$_2$Cl$_2$ (1 equiv) was added quickly as a stream to a stirred –20 °C solution of diazo ketone (1 equiv) in CH$_2$Cl$_2$ (20 mL/mmol of diazo ketone). The bright yellow reaction mixture was stirred at –20 °C for 10 min during which gas evolved and the solution's color diminished. Saturated aqueous NaHCO$_3$ (20 mL) was added and

the mixture was transferred to a separatory funnel with the aid of 10 mL CH_2Cl_2. The layers were separated, and the aqueous layer was extracted three times with Et_2O (10 mL). The organic layers were combined and washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum that did not exceed 125 mmHg. The residue was purified by silica gel flash column chromatography.

General Procedure D: Tris(pentafluorophenyl)borane-promoted cyclopentenone formation

A –15 °C solution of 0.1M diazo ketone (1 equiv) in CH_2Cl_2 was rapidly added to a stirred –15 °C solution of 0.1M tris(pentafluorophenyl)borane (1 equiv) in CH_2Cl_2. The reaction mixture was stirred at –15 °C for 10 min during which gas evolved and the solution's color diminished. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture was transferred to a separatory funnel with the aid of 10 mL CH_2Cl_2. The layers were separated, and the aqueous layer was extracted three times with Et_2O (10 mL). The organic layers were combined and washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum that did not exceed 125 mmHg. The residue was purified by silica gel flash column chromatography.

4.2 Experimental Procedures for THE C–H INSERTION OF VINYL CATIONS

LEADING TO CYCLOPENTENONES

Compound Characterization for Chapter 2

<u>Characterization data for diazo ketones</u>

1-cyclopentyl-2-diazoethanone (**2.150**): To a cold (–78 °C) solution of excess

diazomethane (3.8 equiv) [prepared by addition of Diazald® (3.8 equiv) in

Et$_2$O (2.5 ml per mmol of Diazald®) to a solution of KOH (4.0 equiv) and

water (2 mL per gram of KOH) in 2-(2-ethoxyethoxy)ethanol (5.8 mL per gram KOH).

Diazomethane was generated at 70°C and distilled into a separate round bottom flask.]

cyclopentanecarbonyl chloride (790 μL, 6.5 mmol) was added dropwise under an

atmosphere of N$_2$. The reaction was warmed slowly and left to stir for 66 hours. The

resulting oil was diluted with Et$_2$O (20 mL), washed with saturated aqueous NaHCO$_3$ (20

mL), brine (20 mL), and dried over anhydrous MgSO$_4$. The solvent was removed in vacuo

to provide 750 mg of the title compound as a bright yellow oil (84%): R_f = 0.42

(hexanes/EtOAc 3.7:1); 1H NMR (500 MHz, CDCl$_3$): δ 5.24 (s, 1H), 2.82-2.81 (m, 1H),

1.91-1.75 (m, 4H), 1.74-1.65 (m, 2H), 1.63-1.52 (m, 2H); 13C NMR (125 MHz, CDCl$_3$):

δ 197.9, 53.2, 49.6, 29.4, 25.6. MS (ESI): Calculated for [C$_7$H$_9$N$_2$O]$^-$: 137.0715. Found:

137.0705
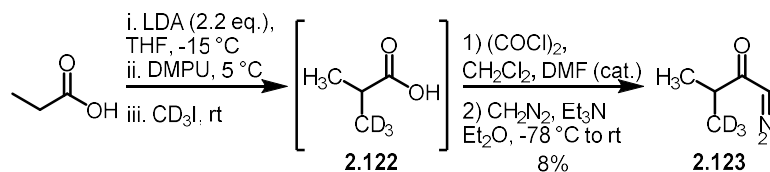
1-diazo-3-[²H₃]-methylbutan-2-one (**2.123**): Carboxylic acid **2.122** was prepared following a known procedure using propionic acid (2.5 mL, 33.4 mmol) and used immediately in the following reactions assuming quantitative yield.[169]

To a 0 °C mixture of carboxylic acid **2.122** and catalytic DMF in CH_2Cl_2 (0.57 mL/mmol) was added oxalyl chloride (3.4 mL, 39.6 mmol) dropwise. The mixture was maintained at 0 °C for one hour then allowed to warm to room temperature and maintained for 3 hours. The solvent was removed *in vacuo* and the acid chloride was used immediately without further purification. To a -78 °C solution of freshly prepared ethereal diazomethane (42.9 mmol) was added Et₃N (4.6 mL, 33.0 mmol), then acid chloride, and then slowly warmed to room temperature. The following day, the solution was diluted with pentane (15 mL), and the organic layer was washed with sodium bicarbonate (25 mL), brine (25 mL), and dried over MgSO₄. The crude orange oil was purified using silica gel flash chromatography (pentane/Et₂O, gradient elution 0 to 10% Et₂O) to give 321 mg (8% yield) of the title compound as a bright yellow oil: R_f = 0.55 (3.7:1 hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃): δ 5.27 (s, 1H), 4.28 (br. s, 1H), 1.13 (d, J = 7.0 Hz, 3H); ¹³C (125 MHz, CDCl₃): δ 199.3, 60.4, 39.2, 18.8, 18.1 (pent, J = 20.0 Hz). MS (ESI): Calculated for $[C_5H_6D_3N_2O]^+$: 116.0903. Found: 116.0895.

Diethyl-[2-¹³C₁]-2-dimethylpropanedioate (**2.131**): Prepared from diethyl methyl

malonate (2.4 mL, 13.8 mmol), iodomethane-¹³C (960 μL, 15.4 mmol), and sodium hydride (60% dispersion in mineral oil, 616 mg, 15.4 mmol) in THF

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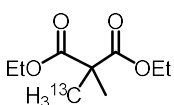
(1 mL/mmol iodomethane-^{13}C) following a known procedure.[116] **2.131** was isolated without purification to give 2.50 g (96% yield) as a yellow oil: ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.18 (q, J = 7.1 Hz, 4H), 1.43 (d, J = 130.1 Hz, 3H), 1.43 (d, J = 4.8 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); [13]C (125 MHz, CDCl$_3$): δ 173.1, 173.1, 61.3, 52.6, 59.9, 49.9 (d, J = 34.7 Hz), 22.9, 14.2. MS (ESI): Calculated for [C$_8$[13]CH$_{17}$O$_4$]$^+$: 190.1160. Found: 190.1156.

2-[[13]C$_1$]-Methylpropanoic acid (2.132): To a solution of KOH (2.70 g, 48.1 mmol) in ethanol (1 ml/mmol) and water (0.5 ml/mmol) was added **2.131** (1.28 g, 6.8 mmol). The mixture was warmed to 100 °C and was maintained at this temperature for 4 hours. The reaction was cooled to room temperature, the ethanol was evaporated, and 10 mL of water was added. Then, 4M HCl was added until the solution was acidic. The mixture was added to a microwave vessel with a stir bar and capped with a septum. The mixture was heated to 180 °C for 15 min. After, the aqueous solution was extracted with CH$_2$Cl$_2$ (4x20 mL) and the organic layers were combined and dried over MgSO$_4$. The solvent was removed in *vacuo* and **2.132** was isolated without purification to give 318 g (52% yield) as a colorless oil: ^{1}H NMR (500 MHz, CDCl$_3$): δ 11.99 (bs , 1H), 2.59 (dqq, J = 21.1, 14.0, 6.9, 4.6 Hz, 1H), 1.20 (dd, J = 128.1, 7.0 Hz, 3H), 1.21 (dd, J = 7.0, 5.2 Hz, 3H); [13]C (125 MHz, CDCl$_3$): δ 184.2, 34.0 (d, J = 34.0 Hz), 18.8. [C$_3$[13]CH$_7$O$_2$]$^-$: 88.0480. Found: 88.0482.
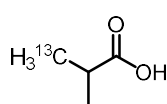
1-diazo-3-[[13]C$_1$]-methylbutan-2-one (2.134): To a 0 °C mixture of carboxylic acid **2.132** (968 mg, 10.9 mmol) and catalytic DMF in CH$_2$Cl$_2$ (0.57 mL/mmol) was added oxalyl chloride (950 μL, 10.9 mmol) dropwise. The mixture was
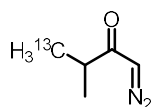
maintained at 0 °C for one hour then allowed to warm to room temperature and maintained overnight. The solvent was removed *in vacuo* and the acid chloride was used immediately without further purification. To a -78 °C solution of freshly prepared ethereal diazomethane (14.2 mmol) was added Et₃N (1.5 mL, 10.9 mmol), then the acid chloride, and then slowly warmed to room temperature. The following day, the solution was diluted with pentane (15 mL), and the organic layer was washed with sodium bicarbonate (25 mL), brine (25 mL), and dried over MgSO4. The crude orange oil was purified using silica gel flash chromatography (3:1 pentane/Et₂O) to give 229 mg (19% yield) of the title compound as a bright yellow oil: R_f = 0.22 (3:1 pentane:Et₂O); ^{1}H NMR (500 MHz, CDCl₃): δ 5.31 (s, 1H), 2.50 (s, 1H), 1.13 (dd, J = 127.6, 6.9 Hz, 3H), 1.13 (dd, J = 6.9, 5.3 Hz, 3H); ^{13}C (125 MHz, CDCl₃): δ 199.4, 53.1, 39.5 (d, J = 33.2 Hz), 18.9, 18.9. MS (ESI): Calculated for $[C_4{}^{13}CH_7N_2O]^-$: 112.0592. Found: 112.0595.

Characterization data for β-hydroxy-α-diazo ketones for Chapter 2

1-Diazo-1-(1-hydroxycyclohexyl)-3,3-dimethylbutan-2-one (**2.38a**):   Prepared from cyclohexanone (75 µL, 0.73 mmol) and 1-diazo-3,3-dimethyl-2-butanone (147 mg, 1.17 mmol) following General Procedure A with the modification that 1M acetic acid in THF (0.73 mL, 0.73 mmol) was used to quench the reaction in place of NH₄Cl. The oily yellow residue was purified by silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 140 mg (86% yield) of the title compound as a yellow oil: R_f = 0.65 (hexanes/EtOAc 4:1); 1H NMR (500 MHz, CDCl₃): δ 4.61 (s, 1H), 1.92 (dt, J = 12.8, 4.5 Hz, 2H), 1.76 (dtt, J = 14.2, 10.7, 3.7 Hz, 2H), 1.62-1.50 (m, 3H), 1.46 (ddt, J = 13.9, 9.1, 4.8 Hz, 2H), 1.37-1.24 (m, 1H), 1.22 (s, 9H); 13C
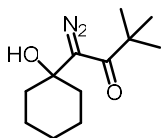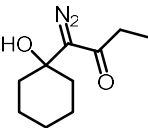
NMR (125 MHz, CDCl$_3$): δ 203.0, 72.0, 68.3, 44.8, 36.0, 26.5, 25.4, 21.9; IR (film) 3449 (br), 2932, 2862, 2068, 1605, 1304, 1196. MS (ESI): Calculated for [C$_{12}$H$_{20}$N$_2$O$_2$Na]$^+$: 247.1422. Found: 247.1422.

1-Diazo-1-(1-hydroxycyclohexyl)-3-methylbutan-2-one (**2.38b**): Prepared from cyclohexanone (130 μL, 1.3 mmol) and 1-diazo-3-methyl-2-butanone (248 mg, 2.21 m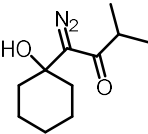mol) following General Procedure A. The crude yellow oil material was purified using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 242 mg (88% yield) of the title compound as a yellow oil which solidified upon standing in freezer: R_f = 0.50 (3.7:1 hexane/EtOAc); 1H NMR (500 MHz, CDCl$_3$) 4.36 (s, 1H), 2.81 (hept, J = 6.8 Hz, 1H), 1.96-1.88 (m, 2H), 1.81 – 1.71 (m, 2H), 1.63 – 1.56 (m, 3H), 1.49 – 1.40 (m, 2H), 1.35-1.24 (m, 1H), 1.13 (d, J = 6.8 Hz, 6H); 13C NMR (125 Mhz, CDCl$_3$) δ 201.0, 71.1, 71.0, 36.4, 36.2, 25.3, 21.8, 18.5; IR (film) 3397 (br), 2934, 2860, 2070, 1620, 1248. MS (ESI): Calculated for [C$_{11}$H$_{18}$N$_2$O$_2$Na]$^+$: 233.1266. Found: 233.1263.

1-Diazo-1-(1-hydroxycyclohexyl)butan-2-one (**2.38c**): Prepared from cyclohexanone (170 μL, 1.6 mmol) and 1-diazo-2-butanone (275 mg, 2.80 mmol) following General Procedure A. The crude yellow oil was purified using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 15% EtOAc) to give 284 mg (90% yield) of the title compound as a yellow oil: R_f = 0.26 (6:1 hexane/EtOAc); 1H NMR (500 MHz, CDCl$_3$) δ 4.28 (s, 1H), 2.50 (q, J = 7.4 Hz, 2H), 1.97 – 1.90 (m, 2H), 1.81 – 1.70 (m, 2H), 1.63 – 1.54 (m, 3H), 1.50 – 1.42 (m, 2H), 1.35-1.24 (m, 1H), 1.14 (t, J = 7.4 Hz, 3H); 13C NMR (125 Mhz, CDCl$_3$) δ 197.3, 72.2, 70.9, 36.2, 32.0, 25.3, 21.8, 8.3;

IR (film) 3441, 2931, 2854, 2067, 1626 cm-1. MS (ESI): Calculated for $[C_{10}H_{16}N_2O_2Na]^+$:

219.1109. Found: 219.1119.

1-Diazo-1-(1-hydroxycyclohexyl)pentan-2-one (**2.38d**): Prepared from cyclohexanone
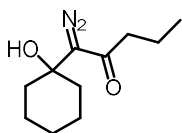
 (170 µL, 1.7 mmol) and 1-diazo-2-pentanone (307 mg, 2.74 mmol)

following General Procedure A. The crude yellow oil was purified using

silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 10%

EtOAc) to give 314 mg (88% yield) of the title compound as a yellow oil which solidified

upon standing in freezer: R_f = 0.29 (6:1 hexane/EtOAc); 1H NMR (500 MHz, CDCl₃) δ

4.33 (s, 1H), 2.44 (t, J = 7.4 Hz, 2H), 1.96-1.89 (m, 2H), 1.80 – 1.71 (m, 2H), 1.67 (h, J =

7.4 Hz, 2H), 1.62-1.55 (m, 3H), 1.49 – 1.41 (m, 2H), 1.34 – 1.24 (m, 1H), 0.95 (t, J = 7.4

Hz, 3H); 13C NMR (125 Mhz, CDCl₃) δ 196.9, 72.6, 71.9, 40.6, 36.2, 25.3, 21.8, 18.1,

13.6; IR (film) 3425, 2931, 2862, 2067, 1620 cm-1.   MS (ESI): Calculated for

$[C_{11}H_{18}N_2O_2Na]^+$: 233.1266. Found: 233.1262.
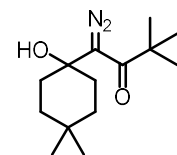
1-Diazo-1-(1-hydroxycyclohexyl)-4-methylpentan-2-one   (**2.38e**):   Prepared   from
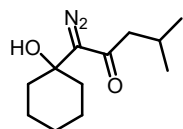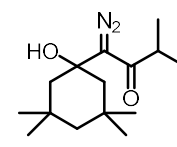
 cyclohexanone (0.10 mL, 0.10 mmol) and 1-diazo-4-methyl-2-pentanone

(189 mg, 1.50 mmol) following Genearl Procedure A. The crude yellow

oil was purified using silica gel flash column chromatography (hexanes/EtOAc, gradient

elution 0 to 10% EtOA) to give 145 mg (65% yield) of the title compound as a yellow oil

which solidified upon standing in freezer: R_f = 0.33 (6:1 hexane/EtOAc); 1H NMR (500

MHz, CDCl₃) δ 4.39 (s, 1H), 2.32 (d, J = 7.1 Hz, 2H), 2.19-2.09 (m, 1H), 1.97-1.89 (m,

2H), 1.81-1.70 (m, 2H), 1.63-1.53 (m, 3H), 1.50-1.41 (m, 2H), 1.35 – 1.23 (m, 1H), 0.96

(d, J = 6.6 Hz, 6H); 13C NMR (125 Mhz, CDCl₃) δ 196.8, 73.1, 71.0, 47.5, 36.2, 26.0,

25.3, 22.4, 21.8; IR (film) 3340, 2931, 2862, 2075, 1589 cm-1. MS (ESI): Calculated for $[C_{12}H_{20}N_2O_2Na]^+$: 247.1422. Found: 247.1418

1-Diazo-1-(1-hydroxy-4,4-dimethylcyclohexyl)-3,3-dimethylbutan-2-one (**2.58**):

Prepared from 4,4-dimethylcyclohexanone (125 mg, 0.99 mmol) and 1-diazo-3,3-dimethyl-2-butanone (204 mg, 1.62 mmol) following General Procedure A. The oily yellow residue was purified by silica gel flash column chromatography (12:1 hexanes/EtOAc) to give 217 mg (86% yield) of the title compound as a yellow oil which solidified upon standing in freezer: R_f = 0.64 (hexanes/EtOAc 3.7:1); 1H NMR (500 MHz, CDCl$_3$): δ 4.50 (s, 1H), 1.93-1.85 (m, 2H), 1.71-1.59 (m, 4H), 1.22 (s, 9H), 1.21-1.15 (m, 2H), 0.95 (s, 3H), 0.91 (s, 3H); 13C NMR (125 MHz, CDCl$_3$): δ 202.7, 71.4, 68.2, 44.6, 34.4, 31.9, 30.7, 29.2, 26.4, 25.2; IR (film) 3439, 2953, 2928, 2068, 1599, 1306, 1200. MS (ESI): Calculated for $[C_{14}H_{24}N_2O_2Na]^+$: 275.1735. Found: 275.1737.

1-diazo-1-(1-hydroxy-3,3,5,5-tetramethylcyclohexyl)-3-methylbutan-2-one (**2.64**):

Prepared from 3,3,5,5-tetramethylcyclohexanone (300 μL, 1.6 mmol) and 1-diazo-3-methylbutan-2-one (306 mg, 2.7 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 3% EtOAc) to give 207 mg (48% yield) of the title compound as a bright yellow oil: R_f = 0.70 (3.7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.56 (s, 1H), 2.79 (hept, J = 6.8 Hz, 1H), 1.98 (d, J = 13.6 Hz, 2H), 1.42 (d, J = 13.7 Hz, 1H), 1.26 (s, 6H), 1.19 (d, J = 13.7 Hz, 2H), 1.13 (d, J = 6.8 Hz, 6H), 0.91 (s, 6H);

^{13}C (125 MHz, CDCl$_3$): δ 201.6, 73.8, 72.4, 51.8, 47.1, 36.7, 36.3, 31.8, 28.4, 18.7. MS (ESI): Calculated for [C$_{15}$H$_{26}$N$_2$O$_2$K]$^+$: 305.1632. Found: 305.1635.

2-diazo-2-(1-hydroxycyclohexyl)-1-(oxan-3-yl)ethanone (**2.95**): Prepared from cyclohexanone (70 µL, 0.70 mmol) and 2-diazo-1-(oxan-3-yl)ethanone (174 mg, 1.1 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 70% EtOAc) to give 171 mg (97% yield) of the title compound as a bright yellow solid: R$_f$ = 0.30 (3.7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.19 (s, 1H), 4.00-3.88 (m, 2H), 3.48 (t, J = 11.0 Hz, 1H), 3.42-3.34 (m, 1H), 2.90-2.79 (m, 1H), 1.94-1.86 (m, 3H), 1.84-1.62 (m, 5H), 1.62-1.53 (m, 3H), 1.50-1.40 (m, 2H), 1.36-1.23 (m, 1H); ^{13}C (125 MHz, CDCl$_3$): δ 197.0, 71.2, 69.1, 68.1, 45.5, 36.4, 36.3, 26.2, 25.4, 25.1, 21.9. MS (ESI): Calculated for [C$_{13}$H$_{20}$N$_2$O$_3$Na]$^+$: 275.1371. Found: 275.1359.
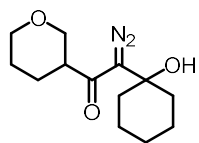
1-diazo-1-(1-hydroxycyclohexyl)-5-methoxypentan-2-one (**2.99**): Prepared from (60 µL, 0.58 mmol) and diazo (134 mg, 0.94 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 20% EtOAc) to give 101 mg (73% yield) of the title compound as a bright yellow solid: R$_f$ = 0.27 (3.7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.28 (s, 1H), 3.35 (t, J = 6.15 Hz, 2H), 3.27 (s, 3H), 2.52 (t, J = 7.23 Hz, 2H), 1.91-1.82 (m, 4H), 1.75-1.66 (m, 2H), 1.60-1.50 (m, 3H), 1.45-1.37 (m, 2H), 1.30-1.20 (m, 1); ^{13}C (125 MHz, CDCl$_3$): δ 196.3, 73.1, 71.4, 71.0, 58.6, 36.3, 35.2, 25.4, 24.4, 21.8. MS (ESI): Calculated for [C$_{12}$H$_{20}$N$_2$O$_3$Na]$^+$: 263.1371. Found: 263.1358.
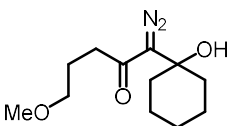
1-Diazo-1-(1-hydroxycyclohexyl)-3-[²H₃]-methylbutan-2-one (**2.124**): Prepared from cyclohexanone (160 μL, 1.6 mmol) and 1-diazo-3-[²H₃]-methylbutan-2-one (292 mg, 2.5 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 7% EtOAc) to give 256 mg (75% yield) of the title compound as a bright yellow solid: R_f = 0.55 (3.7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl₃): δ 4.37 (s, 1H), 2.80 (dt, J = 13.6, 6.7 Hz, 1H), 1.96-1.89 (m, 2H), 1.81-1.71 (m, 2H), 1.65-1.55 (m, 3H), 1.50-1.42 (m, 2H), 1.36-1.24 (m, 1H), 1.13 (d, J = 6.8 Hz, 3H); ^{13}C (125 MHz, CDCl₃): δ 201.3, 71.2, 71.1, 36.3, 36.3, 25.4, 21.9, 18.6, 17.8 (pent, J = 19.5 Hz). MS (ESI): Calculated for $[C_{11}H_{15}D_3N_2O_2Na]^+$: 236.1454. Found: 236.1457.
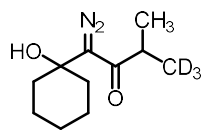
1-Diazo-1-(1-hydroxycyclohexyl)-3-[¹³C₁]-methylbutan-2-one (**2.135**): Prepared from cyclohexanone (100 μL, 1.0 mmol) and diazo **2.134** (186 mg, 1.6 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 185 mg (88% yield) of the title compound as a bright waxy yellow solid: R_f = 0.31 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl₃): δ 4.36 (s, 1H), 2.81 (dqq, J = 13.7, 6.7, 4.6, 1H), 1.97-1.89 (m, 2H), 1.81-1.70 (m, 2H), 1.64-1.55 (m, 3H), 1.50-1.42 (m, 2H), 1.35-1.27 (m, 1H), 1.13 (dd, J = 127.9, 6.8 Hz, 3H), 1.13 (dd, J = 6.8, 5.3 Hz, 3H); ^{13}C (125 MHz, CDCl₃): δ 201.3 (d, J = 1.6 Hz), 71.2, 71.2, 36.6 (d, J = 34.2 Hz), 36.3, 25.5, 22.0, 18.7. MS (ESI): Calculated for $[C_{10}{}^{13}CH_{18}N_2O_2Na]^+$: 234.1299. Found: 234.1291.

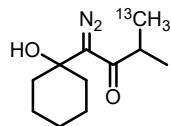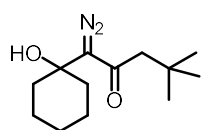**1-diazo-1-(1-hydroxycyclohexyl)-4,4-dimethylpentan-2-one** (**2.141**): Prepared from cyclohexanone (140 μL, 1.4 mmol) and 1-diazo-4,4-dimethylpentan-2-one (310 mg, 2.2 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 6% EtOAc) to give 199 mg (60% yield) of the title compound as a bright yellow oil: R_f = 0.39 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.53 (s, 1H), 2.33 (s, 2H), 1.98-1.90 (m, 2H), 1.82-1.71 (m, 2H), 1.63-1.53 (m, 4H), 1.51-1.42 (m, 2H), 1.34-1.24 (m, 1H), 1.04 (s, 9H); [13]C (125 MHz, CDCl$_3$): δ 196.7, 74.1, 71.2, 51.1, 36.3, 32.8, 29.7, 25.5, 21.9.

1-cyclohexyl-2-diazo-2-(1-hydroxycyclohexyl)ethanone (**2.38f**): Prepared from cyclohexanone (180 μL, 1.7 mmol) and 1-cyclohexyl-2-diazoethanone (301 mg, 2.0 mmol) following General Procedure A. The crude yellow oil was purified using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 11% EtOAc) to give 352 mg (82% yield) of the title compound as a yellow oil which solidified upon standing in freezer: R_f = 0.50 (5:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.40 (s, 1H), 2.50 (tt, J = 11.8, 3.4 Hz, 1H), 1.96-1.87 (m, 2H), 1.85-1.78 (m, 2H), 1.78-1.70 (m, 4H), 1.70-1.64 (m, 1H), 1.63-1.55 (m, 3H), 1.51-1.40 (m, 4H), 1.31-1.20 (m, 4H); ^{13}C NMR (125 Mhz, CDCl$_3$) δ 200.6, 71.3, 71.2, 46.7, 36.4, 28.8, 25.8, 25.7, 25.5, 22.0. MS (ESI): Calculated for [C$_{14}$H$_{22}$N$_2$O$_2$Na]$^+$: 273.1579. Found: 273.1569.
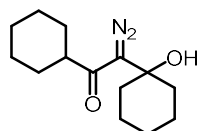
1-cyclopentyl-2-diazo-2-(1-hydroxycyclohexyl)ethanone (**2.151**): Prepared from cyclohexanone (120 μL, 1.2 mmol) and 1-cyclopentyl-2-diazoethanone (252 mg, 1.82 mmol) following General Procedure A. The crude yellow oil

was purified using silica gel flash column chromatography (hexanes/EtOAc, gradient elution 0 to 8% EtOAc) to give 215 mg (78% yield) of the title compound as a yellow oil: R_f = 0.61 (3.7:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.38 (s, 1H), 3.00 (quin, J = 7.8, 1H), 1.97-1.89 (m, 2H), 1.85-1.78 (m, 5H), 1.78-1.68 (m, 5H), 1.63-1.56 (m, 3H), 1.51-1.42 (m, 2H), 1.34-1.23 (m, 1H); ^{13}C NMR (125 Mhz, CDCl$_3$) δ 200.1, 71.8, 71.0, 47.2, 36.3, 29.3, 26.2, 25.4, 21.9. MS (ESI): Calculated for [C$_{13}$H$_{21}$N$_2$O$_2$]$^+$: 237.1603. Found: 237.1593.

1-diazo-1-(1-hydroxycyclohexyl)-4-phenylbutan-2-one (**2.157**): Prepared from
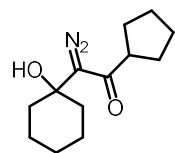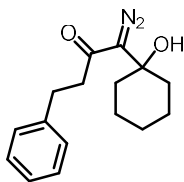

cyclohexanone (120 µL, 1.2 mmol) and 1-diazo-4-phenylbutan-2-one (328 mg, 1.9 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 11% EtOAc), isolated, and put under high vacuum at which point it started to decompose. The mixture of product and decomposition product was then repurified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 11% EtOAc), to give 149 mg (46% yield) of the title compound as a bright yellow solid: R_f = 0.42 (3.7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29 (t, J = 7.36 Hz, 2H), 7.23-7.16 (m, 3H), 4.26 (s, 1H), 2.96 (t, J = 7.39 Hz, 2H), 2.76 (t, J = 7.39 Hz, 2H), 1.94-1.86 (m, 2H), 1.79-1.68 (m, 2H), 1.62-1.50 (m, 4H), 1.48-1.39 (m, 2H), 1.33-1.22 (m, 1H); ^{13}C (125 MHz, CDCl$_3$): δ 195.8, 140.5, 128.7, 128.5, 126.5, 77.4, 71.1, 40.6, 36.3, 30.8, 25.5, 21.9. MS (ESI): Calculated for [C$_{16}$H$_{20}$N$_2$O$_2$Na]$^+$: 295.1422. Found: 295.1412.

3-cyclopropyl-1-diazo-1-(1-hydroxycyclohexyl)propan-2-one (**2.167**): Prepared from cyclohexanone (210 μL, 2.0 mmol) and 1-cyclopropyl-3-diazopropan-2-one (404 mg, 3.2 mmol) following General Procedure A. The crude orange oil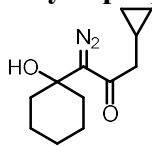 was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 187 mg (42% yield) of the title compound as a bright yellow oil: R_f = 0.55 (3.7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 4.32 (s, 1H), 2.39 (d, J = 6.9 Hz, 2H), 1.98-1.90 (m, 2H), 1.81-1.71 (m, 2H), 1.64-1.56 (m, 2H), 1.51-1.42 (m, 2H), 1.35-1.25 (m, 1H), 1.08-0.99 (m, 1H), 0.60-0.55 (m, 2H), 0.17 (dt, J = 5.56, 4.86 Hz, 2H); ^{13}C (125 MHz, CDCl$_3$): δ 196.7, 72.4, 71.2, 44.0, 36.4, 25.5, 21.9, 7.0, 4.0. MS (ESI): Calculated for [C$_{12}$H$_{17}$N$_2$O$_2$]$^-$: 221.1290. Found: 221.1273.

Characterization data for cyclopentenones and vinyl chlorides for Chapter 2

2,2-Dimethyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (**2.39**): Prepared by subjecting diazo ketone **2.39** (0.14 mmol) to General Procedure C or D. The colorless oily residue was subjected to silica gel flash column chromatography (100% CH$_2$Cl$_2$) which gave the title compound as a colorless oil in 21 mg (83% yield) from procedure B and 22 mg (88% yield) from procedure C: R_f = 0.27 (100% CH$_2$Cl$_2$); 1H NMR (500 MHz, CDCl$_3$): δ 2.42 (dd, J = 6.5, 5.8 Hz, 2H), 2.37 (s, 2H), 2.30, (t, J = 5.6, 2H), 1.76-1.81 (m, 2H), 1.67-1.62 (m, 2H), 1.51-1.55 (m, 2H), 1.08 (s, 6H); 13C NMR (125 MHz, CDCl$_3$): δ 213.2, 173.4, 139.4, 48.9, 43.1, 33.5, 31.3, 26.8, 26.4, 25.1, 23.8. MS (ESI): Calculated for [C$_{12}$H$_{19}$O]$^+$: 179.1436. Found: 179.1430.
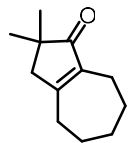
2-Methyl-2,3,5,6,7,8-hexahydroazulen-1(4*H*)-one (**SI1**), **1-Chloro-1-cyclohexylidene-3-methylbutan-2-one** (**2.45**): Prepared by subjecting diazo ketone **2.38b** to General Procedure C (67.6 mg, 0.32 mmol) or General Procedure D (69.8 mg, 0.33 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 10% Et$_2$O) to give 2-Methyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (**SI1**) as a faint yellow oil in 36.6 mg (70% yield) from General Procedure C and 44.8 mg (82% yield) from General Procedure D; (R_f = 0.15 in 10:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.74 (dd, J = 18.4, 6.6 Hz, 1H), 2.47 – 2.41 (m, 2H), 2.41-2.32 (m, 1H), 2.32-2.26 (m, 2H), 2.09 (d, J = 18.4 Hz, 1H), 1.82-1.75 (m, 2H), 1.65 (pent, J = 5.4 Hz, 2H), 1.53 (pent, J = 5.4 Hz, 2H), 1.15 (d, J = 7.7, 1.4 Hz, 3H); ^{13}C NMR (125 Mhz, CDCl$_3$) δ 211.5, 174.9, 140.9, 40.8, 39.9, 33.5, 31.2, 26.7, 26.3, 23.6, 16.6. MS (ESI): Calculated for [C$_{11}$H$_{16}$ONa]$^+$: 187.1099. Found: 187.1096.

In addition, General Procedure C gave 1-Chloro-1-cyclohexylidene-3-methylbutan-2-one (**9**) in 10% yield: R_f = 0.83 (100% CH$_2$Cl$_2$); ^{1}H and ^{13}C NMR data matched previously reported values.[170] MS (ESI): Calculated for [C$_{11}$H$_{18}$ClO]$^+$: 201.1046. Found 201.1046.

2,3,5,6,7,8-Hexahydroazulen-1(4H)-one (**SI2**): Prepared by subjecting diazo ketone **2.38c** to General Procedure C (100 mg, 0.50 mmol) or D (64.1 mg, 0.33 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 25% Et$_2$O) to give the title compound as a faint yellow oil in 46.8 mg (62% yield) from procedure C and 35.1 mg (70% yield) from procedure D: R_f = 0.34 (3.7:1 hexane/EtOAc); ^{1}H NMR and ^{13}C NMR values match previously reported data.[171]
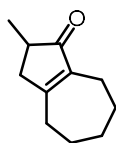
139

3-Methyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (2.48): Prepared by subjecting diazo
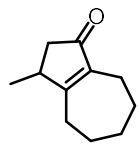
ketone **2.38d** to General Procedure C (119 mg, 0.56 mmol) or D (77.5 mg, 0.37 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 10% Et$_2$O) to give the title compound as a faint yellow oil in 30.0 mg (32% yield) from procedure C and 33.8 mg (55% yield) from procedure D: R_f = 0.15 (5:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.70 (dddd, J = 18.5, 7.0, 7.0 7.0, 1.6 Hz, 1H), 2.61 (dd, J = 18.6, 6.5 Hz, 1H), 2.48 (dt, J = 16.0, 6.0, 6.0 Hz, 1 H), 2.41 (dt, J = 16.0, 6.0, 6.0 Hz, 1 H), 2.35-2.24 (m, 2H), 1.99 (dd, J = 18.5, 1.6 Hz, 1H), 1.85-1.73 (m, 2H), 1.66-1.60 (m, 2H), 1.54-1.48 (m, 2H), 1.15 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 Mhz, CDCl$_3$) δ 208.0, 180.9, 141.8, 43.2, 37.1, 31.5, 31.2, 26.5, 26.4, 23.2, 19.1. MS (ESI): Calculated for [C$_{11}$H$_{16}$ONa]$^+$: 187.1099. Found: 187.1097.

1-(Cyclohept-1-en-1-yl)-3-methylbut-3-en-1-one (2.49): Prepared by subjecting diazo

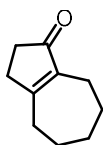ketone **2.38e** to General Procedure D (69.6 mg, 0.31 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 7% Et$_2$O) to give 43.4 mg (77% yield) of the title compound as a faint yellow oil: R_f = 0.74 (3.7:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.11 (t, J = 6.7 Hz, 1H), 4.90 (s, 1H), 4.74 (s, 1H), 3.38 (s, 2H), 2.52-2.47 (m, 2H), 2.37-2.31 (m, 2H), 1.81-1.76 (m, 2H), 1.75 (s, 3H), 1.57-1.52 (m, 2H), 1.48-1.42 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 199.2, 146.0, 145.2, 140.8, 113.9, 46.4, 32.3, 29.1, 26.1, 25.8, 25.6, 22.8. MS (ESI): Calculated for [C$_{12}$H$_{18}$ONa]$^+$: 201.1255. Found: 201.1251.

2,2,6,6-Tetramethyl-2,3,5,6,7,8-hexahydroazulen-1(4*H*)-one (**2.58**): Prepared by subjecting diazo ketone **2.57** to General Procedure D (85.6 mg, 0.34 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 10% Et$_2$O) to give 54.4 mg (78% yield) of the title compound as a faint yellow oil: R_f = 0.60 (3.7:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.4-2.34 (m, 2H), 2.33 (s, 2H), 2.26-2.20 (m, 2H), 1.55-1.50 (m, 2H), 1.45-1.40 (m, 2H), 1.07 (s, 6H), 0.98 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 213.8, 173.0, 139.3, 49.2, 43.4, 39.8, 39.0, 34.1, 29.3, 28.9, 25.6, 19.3. MS (ESI): Calculated for [C$_{14}$H$_{23}$O]$^+$: 207.1749. Found: 207.1757.

2,5,5,7,7-pentamethyl-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one (**2.64**): Prepared by subjecting diazo ketone **2.63** to General Procedure D (55.3 mg, 0.24 mmol). The crude brow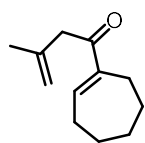n oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 9% Et$_2$O) to give 34.8 mg (66% yield) of the title compound as a white crystalline solid: R_f = 0.61 (3.7:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.75 (dd, J = 18.56, 6.44 Hz, 1H), 2.44-2.29 (m, 3H), 2.19 (dt, J = 14.60, 8.49 Hz, 2H), 2,10 (d, J = 18.84 Hz, 1H), 1.50 (s, 2H), 1.17 (d, J = 7.44 Hz, 3H), 0.97 (s, 6H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 211.3, 173.9, 139.2, 58.5, 44.7, 41.8, 40.1, 34.9, 34.4, 33.4, 31.8, 31.4, 31.0, 30.6, 17.2. MS (ESI): Calculated for [C$_{15}$H$_{25}$O]$^+$: 221.1905. Found: 221.1898.

2-Methyl-[2,2-²H₂]-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (**2.125**) and **2-[²H₃]Methyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one** (**2.126**): Prepared by subjecting diazo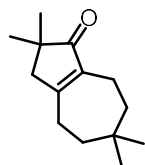 ketone **2.124** to General Procedure D (59.1 mg, 0.28 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et₂O, gradient elution 0 to 10% Et₂O) to give 38.0 mg (81% yield) of the title compound as a faint yellow oil: $R_f =$ 0.46 (3.7:1 hexane/EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 2.57 (dd, J = 18.34, 6.54 Hz, 0.50 H), 2.46 (dd, J = 5.48 Hz, 2H), 2.40-2.34 (m, 1H), 2.31 (dd, J = 5.22 Hz, 2H), 2.11 (d, J = 18.32 Hz, 0.53 H), 1.84-1.76 (m, 2H), 1.70-1.63 (m, 2H), 1.59-1.51 (m, 2H), 1.17 (d, J = 7.39 Hz, 1.15H).

2.125 MS (ESI): Calculated for $[C_{11}H_{15}D_2O]^+$: 167.1405. Found: 167.1406. **2.126** MS (ESI): Calculated for $[C_{11}H_{14}D_3O]^+$: 168.1467. Found: 168.1467.

2-[¹³C]Methyl-2,3,5,6,7,8-hexahydroazulen-1(4H)-one (**2.136**) and **2-Methyl-[3-¹³C]-2,3,5,6,7,8-hexahydroazulen-1(4H)-one** (**2.137**): Prepared by subjecting diazo ketone **2.135** to General Procedure D (54.6 mg, 0.26 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et₂O, gradient elution 0 to 10% Et₂O) to give 23.9 mg (56% yield) of the title compound as a colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 2.74 (dtd, J = 64.58, 18.20, 6.81, 1H), 2.44 (t, J = 5.19 Hz, 2H), 2.41-2.33 (m, 1H), 2.32-2.27 (m, 2H), 2.10 (td, J = 64.10, 18.44 Hz, 1H), 1.82-1.75 (m, 2H), 1.70-1.1 (m, 2H), 1.56-1.49 (m, 2H), 1.15 (ddd, J = 65.60, 60.51, 7.42 Hz, 3H); ¹³C NMR (125 Mhz, CDCl₃) δ 211.7 (q, J = 1.42 Hz), 175.0 (dd, J = 17.05, 15.58 Hz), 141.1, 41.0, 40.1

(d, J = 2.98 Hz), 39.9 (d, 3.36 Hz), 33.7, 31.4, 26.9, 26.47, 23.8 (t, J = 1.63 Hz), 16.8. MS (ESI): Calculated for $[C_{10}{}^{13}CH_{17}O]^+$: 166.1313. Found: 166.1320.

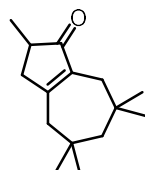**3,3-dimethyl-2,3,4,5,6,7,8,9-octahydro-1*H*-benzo[7]annulen-1-one** (**2.141**): Prepared by subjecting diazo ketone **2.140** to General Procedure D (63.2 mg, 0.27 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 7% Et$_2$O) to give 11.1 mg (21% yield) of the title compound as a colorless oil: R_f = 0.45 (4:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 2.52-2.47 (m, 2H), 2.33-2.28 (m, 2H), 2.27 (s, 2H), 2.21 (s, 2H), 1.80-1.73 (m, 2H), 1.56-1.50 (m, 2H), 1.44-1.36 (m, 2H), 1.01 (s, 6H); ^{13}C NMR (125 Mhz, CDCl$_3$) δ 198.8, 160.6, 137.1, 50.8, 47.8, 36.9, 32.9, 32.5, 28.4, 26.5, 25.1, 23.8.

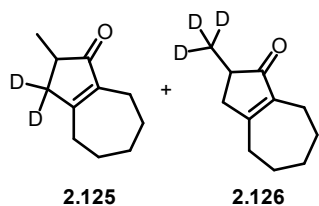**Cyclohept-1-en-1-yl(cyclohex-2-en-1-yl)methanone** (**2.148**): Prepared by subjecting diazo ketone **2.38f** to General Procedure D (79.7 mg, 0.32 mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 5% the 5% to 30% Et$_2$O) to give 23.1 mg (35% yield) of the title compound as a faint yellow oil: R_f = 0.36 (10:1 hexane/EtOAc); 1H NMR (500 MHz, CDCl$_3$) δ 7.05 (t, J = 6.80 Hz, 1H), 5.88-5.82 (m, 1H), 5.63-5.58 (m, 1H), 3.86-3.80 (m, 1H), 2.51-2.48 (m, 2H), 2.39-2.32 (m, 2H), 2.08-1.99 (m, 2H), 1.84-1.75 (m, 4H), 1.58-1.53 (m, 3H), 1.50-1.43 (m, 3H); 13C NMR (125 Mhz, CDCl$_3$) δ 203.2, 145.3, 144.0, 129.6, 126.0, 42.5, 32.5, 29.2, 26.6, 26.3, 26.3, 26.0, 24.9, 21.2. MS (ESI): Calculated for $[C_{14}H_{21}O]^+$: 205.1592. Found: 205.1583.
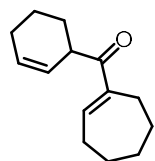
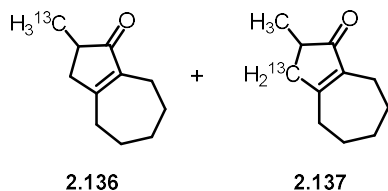**3,3a,4,5,6,7,8,9a-octahydro-1H-cyclopenta[a]azulen-9(2H)-one** (**2.152**): Prepared by subjecting diazo ketone **2.151** to General Procedure D (62.5 mg, 0.26 mmol). The crude
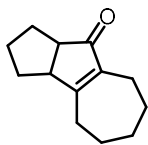
brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 16% Et$_2$O) to give 14.9 mg (30% yield) of the title compound as a faint yellow oil: R_f= 0.53 (3.7:1 hexane/EtOAc);

1H NMR and 13C NMR values match previously reported data.[172]

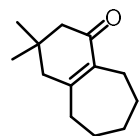**5,8,9,10,11,12-hexahydrobenzo[*a*]heptalen-7(6*H*)-one (2.159)**: Prepared by subjecting diazo ketone **2.157** to General Procedure D (X mg, X mmol). The crude brown oil was purified by flash silica gel column chromatography (hexanes/Et$_2$O, gradient elution 0 to 10% Et$_2$O) to give X mg (X% yield) of the title compound as white solid: R_f = X (X:X hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.32 (d, J = 7.57 Hz, 1H), 7.29-7.24 (m, 1H), 7.21-7.17 (m, 2H), 2.95-2.89 (m, 2H), 2.80-2.75 (m, 2H), 2.72 (dd, J = 6.99, 5.58 Hz, 2H), 2.63-2.59 (m, 2H), 1.91-1.84 (m, 2H), 1.78-1.72 (m, 2H), 1.68-1.62 (m, 2H); ^{13}C NMR (125 Mhz, CDCl$_3$) δ 207.6, 148.4, 141.9, 140.9, 139.6, 127.7, 127.7, 127.6, 126.9, 48.3, 37.3, 32.4, 31.2, 29.8, 27.1, 26.6. MS (ESI): Calculated for [C$_{16}$H$_{19}$O]$^+$: 227.1436. Found: 227.1432
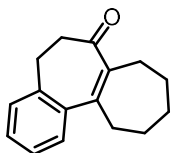
4.3 Experimental Procedures for MIGRATORY APTITUDE OF REARRANGEMENTS OF VINYL CATIONS

Characterization data for β-hydroxy-α-diazo ketones for Chapter 3

4-Diazo-5-hydroxy-2,2-dimethyl-5-phenylheptan-3-one (2.30): Prepared from propiophenone (240 μL, 1.80 mmol) and 1-diazo-3,3-dimethylbutan-2-one (363 mg, 2.88 mmol) following General Procedure A with the modification that the reaction was quenched with 1 equiv of AcOH in THF (16.4 mL per mmol AcOH). The crude yellow oil was purified using silica gel flash chromatography (hexanes/EtOAc,
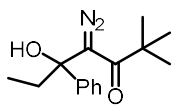
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gradient elution 0 to 15% EtOAc), the desired compound was isolated, then resubjected to

silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 30% CH_2Cl_2) to

give 158 mg (34% yield) of the title compound as a bright yellow oil which solidified upon

standing in freezer: R_f = 0.61 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41-

7.37 (m, 2H), 7.35-7.30 (m, 2H), 7.27-7.23 (m, 1H), 5.34 (s, 1H), 1.98 (dq, *J* = 7.4 Hz,

1H), 1.77 (dqd, *J* = 14.8, 7.4, 1.2 Hz, 1H), 1.20 (s, 9H), 0.86 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$): δ 202.6 145.6, 128.2, 127.3, 125.0, 77.2, 69.4, 44.7, 33.4, 26.3, 7.6.

MS (ESI): Calculated for $[C_{15}H_{20}N_2O_2K]^+$: 299.1162. Found: 299.1147.

1-Diazo-1-(1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylbutan-2-one
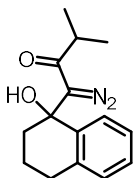
(3.40a): Prepared from tetralone (150 µL, 1.13 mmol) and 1-diazo-3-methyl-2-butanone (203 mg, 1.81 mmol) following General Procedure B. The crude orange solid was purified using silica gel flash chromatography

(hexanes/EtOAc, gradient elution 0 to 9% EtOAc), the desired compound was isolated,

then resubjected to silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to

100% CH_2Cl_2) to give 144 mg (43% yield) of the title compound as a bright yellow solid:

R_f = 0.50 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H),

7.27-7.18 (m, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 5.26 (s, 1H), 2.88-2.73 (m, 3H), 2.51-2.40 (m,

1H), 2.07 (td, *J* = 11.9, 2.8 Hz, 1H) 2.03-1.93 (m, 1H), 1.77-1.64 (m, 1H), 1.15 (d, *J* = 6.8

Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.6, 137.4, 136.4, 129.1, 128.5, 127.4, 126.8,

74.1, 72.9, 37.6, 36.7, 29.1, 20.4, 18.8, 18.4. MS (ESI): Calculated for $[C_{15}H_{18}N_2O_2K]^+$:

297.1005. Found: 297.0991.

6-nitrotetralone (3.39b): To a vigorously stirred biphasic solution (0 ºC) solution of 6-amino-1-tetralone (398 mg, 2.5 mmol) in CH_2Cl_2 (4.2 ml/mmol 6-amino-1-tetralone) and saturated sodium bicarbonate (3.4 mL/mmol oxone) was added oxone (4.5 g, 29.6 mmol) dissolved in DI water (2.4 mL/mmol oxone). Let reaction warm to room temperature and ran overnight. Organic phase was separated, the aqueous phase was washed three times with CH_2Cl_2 (50 mL) and dried over Na_2SO_4.[173] The crude orange solid was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 14% EtOAc) to give 216 mg (46% yield) of the title compound as a pale yellow powder: R_f = 0.35 (3.7:1 hexane/EtOAc); ^{1}H NMR values matched previously reported spectra for **3.39c**.
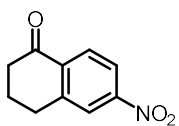
1-Diazo-1-(1-hydroxy-6-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylbutan-2-one (3.40b): Prepared from 6-nitro tetralone (262 mg, 1.37 mmol) and 1-diazo-3-methyl-2-butanone (246 mg, 2.19 mmol) following General Procedure B. The crude orange solid was purified using silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 100% CH_2Cl_2) to give 161 mg (39% yield) of the title compound as a bright yellow solid: R_f = 0.29 (3.7:1 hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (dd, J = 8.7, 2.3 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 5.32 (s, 1H), 2.95-2.89 (m, 2H), 2.83 (hept, J = 6.8 Hz, 1H), 2.51 (ddd, J = 13.2, 6.6, 2.3 Hz, 1H), 2.13-2.02 (m, 2H), 1.83-1.72 (m, 1H), 1.17 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.5, 147.7, 143.5, 139.4, 129.0, 124.2, 121.7, 73.5, 72.0, 36.9, 29.1, 19.9, 18.8, 18.4. MS (ESI): Calculated for $[C_{15}H_{17}N_3O_4Na]^+$: 326.1117. Found: 326.1119.

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1-Diazo-1-(1-hydroxy-7-nitro-1,2,3,4-tetrahydronaphthalen-1-yl)-3-methylbutan-2-
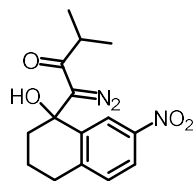
one (3.40c): Prepared from 7-nitro tetralone (229 mg, 1.20 mmol) and 1-diazo-3-methyl-2-butanone (216 mg, 1.93 mmol) following General Procedure B. The crude orange brown oil was purified using silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 90% CH_2Cl_2), the desired compound was isolated, then resubjected to silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 14% EtOAc) to give 90.5 mg (25% yield) of the title compound as a bright yellow solid: R_f = 0.28 (3.7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (d, J = 2.3 Hz, 1H), 8.07 (dd, J = 8.4, 2.3 Hz, 1H), 7.30 (d, J = 8.5 Hz, 1H), 5.34 (s, 1H), 2.94-2.89 (m, 2H), 2.84 (hept, J = 6.8 Hz, 1H), 2.51 (ddd, J = 13.1, 6.5, 2.5 Hz, 1H), 2.12-2.02 (m, 2H), 1.82-1.72 (m, 1H), 1.17 (app t, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.5, 147.1, 145.2, 138.5, 130.4, 123.2, 73.4, 72.1, 36.9, 36.9, 29.2, 19.8, 18.9, 18.4. MS (ESI): Calculated for $[C_{15}H_{17}N_3O_4Na]^+$: 326.1117. Found: 326.1111.

1-(6-Bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-1-diazo-3-methylbutan-
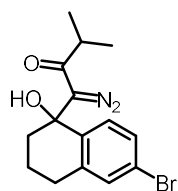
2-one (3.40d): Prepared from 6-bromo tetralone (90.9 mg, 0.40 mmol) and 1-diazo-3-methyl-2-butanone (75.8 mg, 0.68 mmol) following General Procedure B. The crude orange solid was purified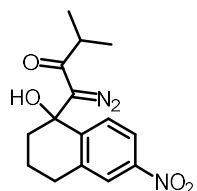 using silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 50 to 60% CH_2Cl_2) to give 67.8 mg (50% yield) of the title compound as a bright yellow solid: R_f = 0.53 (100% CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 8.5, 2.1 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 5.27 (s, 1H), 2.87-2.70 (m, 3H), 2.49-2.41 (m, 1H), 2.08-1.95 (m, 2H), 1.75-1.62 (m, 1H), 1.16 (d, J = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.7,

139.8, 135.7, 132.0, 130.2, 129.4, 122.7, 73.8, 37.4, 36.9, 28.9, 20.3, 18.9, 18.5. MS (ESI): Calculated for $[C_{15}H_{17}BrN_2O_2Na]^+$: 359.0371. Found: 359.0365.

**1-Diazo-1-(1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-3-**
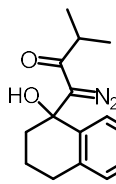
methylbutan-2-one (3.40e): Prepared from 6-methoxy tetralone (150 mg, 0.85 mmol) and 1-diazo-3-methyl-2-butanone (156 mg, 1.39 mmol) following General Procedure B. The crude orange brown oil was purified using silica gel flash chromatography (hexanes/CH$_2$Cl$_2$, gradient elution 0 to 75% CH$_2$Cl$_2$) to give 58.5 mg (24% yield) of the title compound as a bright yellow solid: R_f = 0.42 (3.7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.56 (d, *J* = 8.7 Hz, 1H), 6.81 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 5.22 (s, 1H), 3.79 (s, 3H), 2.86-2.70 (m, 3H), 2.44 (ddd, *J* = 13.1, 6.5, 2.5 Hz, 1H), 2.05 (td, *J* = 12.6, 2.8 Hz, 1H), 2.02-1.93 (m, 1H), 1.74-1.63 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 200.6, 159.4, 139.1, 128.9, 113.3, 113.2, 73.9, 73.1, 55.3, 37.9, 36.8, 29.5, 20.6, 18.9, 18.4. MS (ESI): Calculated for $[C_{16}H_{20}N_2O_3Na]^+$: 311.1372. Found: 311.1370.

Characterization data for cyclopentenones for Chapter 3

3,5,5-Trimethyl-2-phenylcyclopent-2-enone (3.27),[174] 2,5,5-trimethyl-3-phenylcyclopen-2-enone (3.28),[174] and prop-1-yn-1-ylbenzene (3.29):[175] Prepared by
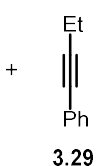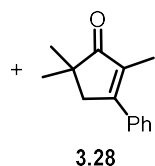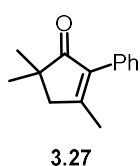
subjecting diazo ketone **3.26** to 1 equivalent of tris(pentafluorophenyl)borane following General Procedure D. Yields of the title compounds (16%, 2 %, and 7%, respectively) were determined using quantitative ^{1}H NMR with 1,3,5-

trimethoxybenzene as an internal standard. ^{1}H NMR values for **3.27**, **3.28** and **3.29** matched those previously reported.[174, 175]

3-Ethyl-5,5-dimethyl-2-phenylcyclopent-2-en-1-one (3.31) and but-1-yn-1-ylbenzene (3.33): Prepared by subjecting β-hydroxy-α-diazo ketone **3.30** (64.8 mg, 0.25 mmol) to General Procedure D with the modification that the aqueous layer was extracted 4 times with CH_2Cl_2 (10 mL) instead of Et_2O. The yield of the title compounds was determined using quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene (41.8 mg, 0.25 mmol) as an internal standard. Cyclopentenone **3.31** was formed in 30% yield and alkyne **3.33** was formed in 27% yield.
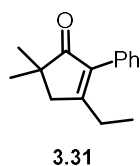
3-Ethyl-5,5-dimethyl-2-phenylcyclopent-2-en-1-one (3.31): R_f = 0.51 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.39 (t, J = 7.6 HZ, 2H), 7.31 (tt, J = 7.4, 1.3 Hz, 1H), 7.28-7.26 (m, 2H), 2.55 (q, J = 7.6 Hz, 2H), 2.54 (s, 2H), 1.19 (s, 6H), 1.16 (t, J = 7.6 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 212.1, 173.4, 137.1, 132.4, 129.3, 128.3, 127.6, 45.9, 43.3, 25.5, 24.8, 12.4. MS (ESI): Calculated for $[C_{15}H_{19}O]^+$: 215.1436. Found: 215.1431.

But-1-yn-1-ylbenzene (3.33): R_f = 0.76 (4:1 hexanes:EtOAc); ^{1}H NMR values matched those previously reported.[176]

2-Methyl-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (3.41a): Prepared by subjecting β-hydroxy-α-diazo ketone **3.40a** (66.5 mg, 0.27 mmol) to General Procedure D with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the aqueous layer was washed 4 times with
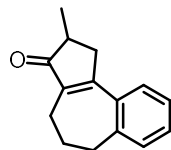
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CH$_2$Cl$_2$ (10 mL) instead of Et$_2$O during the workup. The yield of cyclopentenone **3.41a** was 27% as determined using quantitative ^{1}H NMR with 1,3,5-trimethoxybenzene (45.4 mg, 0.27 mmol) as an internal standard. In a separate experiment, **3.41a** was isolated by silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to provide a pale yellow solid: R$_f$ = 0.53 (4:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.56 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.34-7.27 (m, 2H), 7.21 (dd, *J* = 6.7, 2.3 Hz, 1H), 3.23 (ddt, *J* = 17.1, 6.9, 2.5 Hz, 1H), 2.87-2.76 (m, 2H), 2.59 (dq, *J* = 17.1, 2.6 Hz, 1H) 2.56-2.50 (m, 3H), 2.10-1.93 (m, 2H), 1.27 (d, *J* = 7.4, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 212.6, 162.5, 144.3, 140.0, 134.5, 130.0, 129.9, 127.7, 126.5, 39.1, 38.5, 36.0, 26.7, 26.4, 16.9. MS (ESI): Calculated for [C$_{15}$H$_{17}$O]$^+$: 213.1279. Found: 213.1272.

2-Methyl-8-nitro-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (3.41b): Prepared by
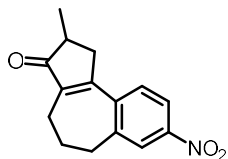
subjecting β-hydroxy-α-diazo ketone **3.40b** (65.8 mg, 0.22 mmol) to General Procedure D with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the reaction mixture was concentrated under vacuum without workup. The crude oil was subjected to silica gel flash chromatography (hexanes/CH$_2$Cl$_2$, gradient elution 0 to 100% CH$_2$Cl$_2$) to give 20.8 mg (37% yield) of the title compound as a pale brown solid: R$_f$ = 0.22 (3.7:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.13 (dd, *J* = 8.5, 2.3 Hz, 1H), 8.08 (d, *J* = 2.3 Hz, 1H), 7.69 (d *J* = 8.6 Hz, 1H), 3.29-3.20 (m, 1H), 2.98-2.85 (m, 2H), 2.66-2.55 (m, 4H), 2.15-1.97 (m, 2H), 1.30 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 211.8, 159.2, 147.9, 145.6, 143.2, 140.8, 128.4, 124.5, 121.5, 39.2, 38.5, 35.8, 26.7, 26.1, 16.7. MS (ESI): Calculated for [C$_{15}$H$_{16}$NO$_3$]$^+$: 258.1130. Found: 258.1125.

2-Methyl-9-nitro-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (3.41c): Prepared by subjecting β-hydroxy-α-diazo ketone **3.40c** (60.5 mg, 0.20 mmol) to General Procedure D with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the reaction mixture was concentrated under vacuum without workup. The crude oil was subjected to silica gel flash chromatography (hexanes/ CH_2Cl_2, gradient elution 0 to 94% CH_2Cl_2) to give 14.8 mg (29% yield) of the title compound as a pale brown solid: R_f = 0.24 (4:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.41 (d, J = 2.3 Hz, 1H), 8.14, (dd, J = 8.3, 2.3 Hz, 1H), 7.38 (d, J = 8.4, 1H), 3.28 (dt, J = 17.0, 7.0, 2.6 Hz, 1H), 3.01-2.86 (m, 2H), 2.67 (dq, J = 17.0, 2.8 Hz, 1H), 2.62-2.55 (m, 3H), 2.13-1.94 (m, 2H), 1.30 (d, J = 7.4, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 212.0, 159.2, 151.3, 146.9, 142.1, 135.8, 130.9, 124.3, 122.6, 39.1, 38.5, 36.0, 26.9, 25.5, 16.7. MS (ESI): Calculated for $[C_{15}H_{16}NO_3]^+$: 258.1130. Found: 258.1122.

8-Bromo-2-methyl-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (3.41d): Prepared by subjecting β-hydroxy-α-diazo ketone **3.40d** (71.7 mg, 0.21 mmol) to General Procedure D with the modification that 1.2 equiv of tris(pentafluorophenyl)borane was used and the reaction mixture was concentrated under vacuum without workup. The crude oil was subjected to silica gel flash chromatography (hexanes/CH_2Cl_2, gradient elution 0 to 75% CH_2Cl_2), the desired compound was isolated with impurities and was further purified by silica gel flash chromatography (8:1 hexanes/EtOAc) to give 15.9 mg (26% yield) of the title compound as a colorless solid: R_f = 0.50 (100% CH_2Cl_2); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.43-7.39

(m, 2H), 7.37 (s, 1H), 3.22-3.14 (m, 1H), 2.84-2.72 (m, 2H), 2.59-2.43 (m, 4H), 2.09-1.89 (m, 2H), 1.27 (d, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 212.1, 161.0, 146.1, 140.5, 133.4, 132.7, 129.5, 129.1, 124.2, 39.0, 38.4, 35.8, 26.8, 25.9, 16.8. MS (ESI): Calculated for [C$_{15}$H$_{16}$BrO]$^+$: 291.0385. Found: 291.0385.

8-Methoxy-2-methyl-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (3.41e) and 8-methoxy-2-methyl-3,4,5,6-tetrahydrobenzo[e]azulen-1(2H)-one (3.42e): Prepared by subjecting β-hydroxy-α-diazo ketone **3.40e** (57.5 mg, 0.20 mmol) to General Procedure D with the modification that 1.2 eq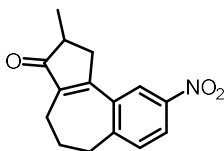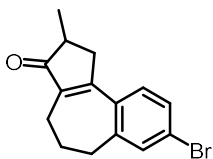uiv of tris(pentafluorophenyl)borane was used and the reaction mixture was concentrated under vacuum without workup. The crude oil was subjected to silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 11% EtOAc) to give 18.1 mg (37% yield) of **3.41e** and 6.7 mg (14% yield) of **3.42e** as pale orange solids:
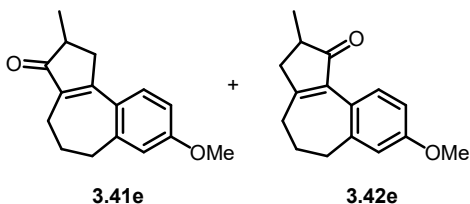
8-Methoxy-2-methyl-1,4,5,6-tetrahydrobenzo[e]azulen-3(2H)-one (3.41e): R$_f$ = 0.30 (3.7:1 hexane/EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.52 (d, J = 8.7 Hz, 1H), 6.80 (dd, J = 8.7, 2.7 Hz, 1H), 6.74 (d, J = 2.7 Hz, 1H), 3.85 (s, 3H), 3.23-2.16 (m, 1H), 2.86-2.78 (m, 2H), 2.59-2.47 (m, 4 H), 2.07-1.89 (m, 2H), 1.26 (d, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 212.5, 162.1, 160.9, 146.4, 138.0, 129.6, 127.2, 115.5, 111.4, 55.4, 38.9, 38.7, 36.6, 27.2, 25.6, 17.0. MS (ESI): Calculated for [C$_{16}$H$_{19}$O$_2$]$^+$: 243.1385. Found: 243.1384.

8-Methoxy-2-methyl-3,4,5,6-tetrahydrobenzo[e]azulen-1(2H)-one (3.42e): R$_f$ = 0.20 (8:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.84 (d, J = 8.7 Hz, 1H), 6.80 (dd, J

= 8.6, 2.7 Hz, 1H), 6.71 (d, J = 2.8 Hz, 1H), 3.81 (s, 3H), 2.88 (dd, J = 18.5, 7.0 Hz, 1H), 2.65 (t, J = 5.5 Hz, 2H), 2.61 (t, J = 7.0 Hz, 2H), 2.53 (app pd, J = 7.4, 2.8 Hz, 1H), 2.25 (dd, J = 18.5, 2.7 Hz, 1H), 2.16-2.05 (m, 2H) 1.25 (d, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 210.7, 172.4, 158.9, 144.2, 135.7, 130.3, 123.6, 114.9, 110.7, 55.3, 40.6, 40.5, 34.4, 33.6, 28.8, 16.9. MS (ESI): Calculated for [C$_{16}$H$_{19}$O$_2$]$^+$: 243.1385. Found: 243.1386.

4.4 Experimental Procedures for VINYL CATIONS AS ELECTROPHILES IN AN ALKENE ADDITION REACTION

Characterization data for β-hydroxy-α-diazo ketones for Chapter 4

1-diazo-1-(1-hydroxycyclohexyl)-3,3-dimethylpent-4-en-2-one (**4.4**): Prepared from
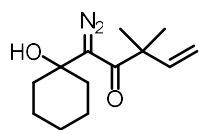
cyclohexanone (160 μL, 1.6 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (341 mg, 2.5 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 8% EtOAc) to give 235 mg (62% yield) of the title compound as a bright yellow solid: R$_f$ = 0.44 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.90 (dd, J = 17.5, 10.5 Hz, 1H), 5.21 (d, J = 10.5 Hz, 1H), 5.10 (d, J = 18.0 Hz, 1H), 4.49 (s, 1H), 1.94-1.87 (m, 2H), 1.80-1.70 (m, 2H), 1.60-1.50 (m, 3H), 1.47-1.4 (m, 2H), 1.3-1.27 (m, 1H), 1.28 (s, 6H); [13]C (125 MHz, CDCl$_3$): δ 199.2, 141.0, 115.1, 71.7, 50.5, 36.0, 25.4, 24.2, 21.9; IR (film) 2934 (br), 2070, 1605, 1346, 1288 cm^{-1}. MS (ESI): Calculated for [C$_{13}$H$_{20}$N$_2$O$_2$Na]$^+$: 259.1422. Found: 259.1430.

5-Diazo-6-hydroxy-3,3-dimethyl-6-propylnon-1-en-4-one (**4.26**): Prepared from 4-heptanone (170 μL, 1.2 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (258 mg, 1.9 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 20% EtOAc) to give 150 mg (50% yield) of the title compound as a bright yellow oil: R_f = 0.48 (4:1 hexanes:EtOAc); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.91 (dd, J = 17.5, 11.0 Hz, 1H), 5.23 (d, J = 11.0 Hz, 1H), 5.11 (d, J = 17.5 Hz, 1H), 4.90 (s, 1H), 1.70-1.58 (m, 4H), 1.45-1.30 (m, 4H), 1.28 (s, 6H), 0.92 (t, J = 7.0 Hz, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 199.4, 141.2, 115.3, 75.2, 69.3, 50.8, 41.4, 24.4, 17.2, 14.4. MS (ESI): Calculated for [C$_{14}$H$_{24}$N$_2$O$_2$Na]$^+$: 275.1735. Found: 275.1732.
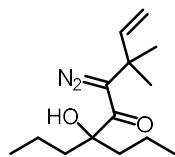
2-diazo-1-hydroxy-4,4-dimethyl-1-phenylhex-5-en-3-one (**4.35a**): Prepared from benzaldehyde (180 μL, 1.7 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (379 mg, 2.7 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 252 mg (61% yield) of the title compound as a bright yellow solid: R_f = 0.30 (3.7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.41-7.36 (m, 4H), 7.35-7.29 (m, 1H), 6.04 (d, J = 3.6 Hz, 1H), 5.92 (dd, J = 17.5, 10.6 Hz, 1H), 5.21 (d, J = 10.6 Hz, 1H), 5.12 (d, J = 17.5 Hz, 1H), 3.26 (d, J = 3.5 Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.7, 141.2, 138.5, 128.9, 128.5, 126.0, 115.5, 70.0, 50.3, 24.3; IR (film) 2974 (br), 2081, 1603, 1346, 1317 cm^{-1}. MS (ESI): Calculated for [C$_{14}$H$_{16}$N$_2$O$_2$Na]$^+$: 267.1109. Found: 267.1105.

2-diazo-1-hydroxy-4,4-dimethyl-1-(4-methylphenyl)hex-5-en-3-one (**4.35b**): Prepared

from *p*-tolualdehyde (150 μL, 1.3 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (289 mg, 2.1 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 14% EtOAc) to give 182 mg (54% yield) of the title compound as a bright yellow solid: R_f = 0.28 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.25 (d, J = 6.6 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H), 6.00 (s, 1H), 5.92 (dd, J = 17.5, 10.5 Hz, 1H), 5.21 (d, J = 10.7 Hz, 1H), 5.11 (d, J = 17.6 Hz, 1H), 3.26 (s, 1H), 2.34 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.6, 141.2, 138.1, 135.7, 129.5, 125.9, 115.4, 71.3, 69.7, 50.3, 24.3, 21.3. MS (ESI): Calculated for [C$_{15}$H$_{18}$N$_2$O$_2$Na]$^+$: 281.1266. Found: 281.1266.

2-diazo-1-(2,6-dimethylphenyl)-1-hydroxy-4,4-dimethylhex-5-en-3-one (**4.35c**):
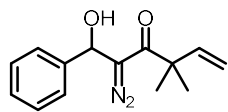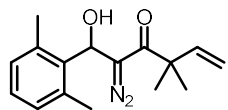
Prepared from 2,6-dimethylbenzaldehyde (221 mg, 1.6 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (355 mg, 2.6 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 6% EtOAc) to give 254 mg (58% yield) of the title compound as a bright yellow solid: R_f = 0.40 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.09 (t, J = 7.5 Hz, 1H), 7.01 (d, J = 7.6 Hz, 2H), 6.38 (d, J = 2.4 Hz, 1H), 5.93 (dd, J = 17.5, 10.7 Hz, 1H), 5.22 (d, J = 10.6 Hz, 1H), 5.13 (d, J = 17.6 Hz, 1H), 3.61 (d, J = 2.51 Hz, 1H), 2.39 (s, 6H), 1.34 (s, 3H), 1.31 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 198.2, 141.1, 137.0, 133.0, 129.5, 128.5, 115.5, 68.6, 67.7, 50.5, 24.4, 24.3, 20.8. MS (ESI): Calculated for [C$_{16}$H$_{20}$N$_2$O$_2$Na]$^+$: 295.1422. Found: 295.1425.

2-diazo-1-hydroxy-4,4-dimethyl-1-(2,4,6-trimethylphenyl)hex-5-en-3-one (**4.35d**):
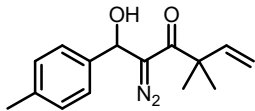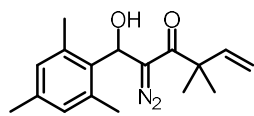
Prepared from 2,4,6-trimethylbenzaldehyde (210 μL, 1.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (309 mg, 2.2 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (CH$_2$Cl$_2$/Et$_2$O, gradient elution 0 to 1% Et$_2$O) to give 222 mg (55% yield) of the title compound as a bright yellow solid: R$_f$ = 0.52 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.82 (s, 2H), 6.34 (d, J = 2.5 Hz, 1H), 5.92 (dd, J = 17.4, 10.6 Hz, 1H), 5.21 (d, J = 10.7 Hz, 1H), 5.13 (d, J = 17.7 Hz, 1H), 3.56 (d, J = 2.5 Hz, 1H), 2.35 (s, 6H), 2.24 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 198.1, 141.1, 138.0, 136.9, 130.2, 130.1, 115.4, 68.8, 67.5, 50.4, 24.3, 24.3, 21.0, 20.6. MS (ESI): Calculated for [C$_{17}$H$_{22}$N$_2$O$_2$Na]$^+$: 309.1579. Found: 309.1587.

2-diazo-1-hydroxy-4,4-dimethyl-1-(naphthalen-2-yl)hex-5-en-3-one (**4.35e**): Prepared from 2-napthaldehyde (221 mg, 1.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (313 mg, 2.3 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 173 mg (42% yield) of the title compound as a bright yellow solid: R$_f$ = 0.35 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.92 (s, 1H), 7.88-7.81(m, 3H), 7.52-7.46 (m, 2H), 7.40 (dd, J = 8.6, 1.6 Hz, 1H), 6.21 (d, J = 3.6 Hz, 1H), 5.94 (dd, J = 17.5, 10.7 Hz, 1H), 5.21 (d, J = 10.6 Hz, 1H), 5.13 (d, J = 17.4 Hz, 1H), 3.32 (d, J = 3.3 Hz, 1H), 1.33 (s, 3H), 1.32 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.5, 141.2, 136.1, 133.3, 133.3, 128.8, 128.3, 127.8, 126.5, 126.4, 125.0,

123.7, 115.6, 71.4, 69.8, 50.3, 24.3. MS (ESI): Calculated for $[C_{18}H_{18}N_2O_2Na]^+$: 317.1266. Found: 317.1256.

1-(anthracen-9-yl)-2-diazo-1-hydroxy-4,4-dimethylhex-5-en-3-one (**4.35f**): Prepared from 9-anthracenecarboxaldehyde (269 mg, 1.3 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (289 mg, 2.1 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 14% EtOAc) to give 279 mg (62% yield) of the title compound as a bright yellow solid: $R_f = 0.25$ (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl$_3$): δ 8.51 (d, $J = 8.8$ Hz, 2H), 8.47 (s, 1H), 8.01 (d, $J = 8.4$ Hz, 2H), 7.53 (t, $J = 7.0$ Hz, 2H), 7.50-7.44 (m, 3H), 5.95 (dd, $J = 17.5$, 10.7 Hz, 1H), 5.17 (d, $J = 10.7$ Hz, 1H), 5.12 (d, $J = 17.5$ Hz, 1H), 4.15 (s, 1H), 1.40 (s, 3H), 1.33 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 198.0, 141.0, 131.7, 130.0, 129.7, 129.5, 127.2, 126.6, 125.1, 124.6, 115.6, 70.8, 67.3, 50.5, 24.5, 24.4. MS (ESI): Calculated for $[C_{22}H_{20}N_2O_2Na]^+$: 367.1422. Found: 367.1429.
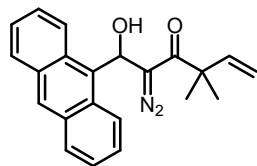
1-cyclohexyl-2-diazo-1-hydroxy-4,4-dimethylhex-5-en-3-one (**4.35g**): Prepared from cyclohexanecarboxaldehyde (160 μL, 1.3 mmol) and 1-diazo-3,3-dimethylpent-4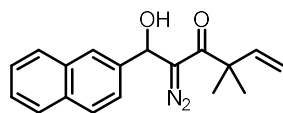-en-2-one (288 mg, 2.1 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 8% EtOAc) to give 158 mg (63% yield) of the title compound as a bright yellow solid: $R_f = 0.43$ (4:1 hexanes:EtOAc); ^1H NMR (500 MHz, CDCl$_3$): δ 5.93 (dd, $J = 17.3$, 10.5 Hz, 1H), 5.24 (d, $J = 10.7$ Hz, 1H), 5.13 (d, $J = 17.5$ Hz, 1H), 4.36 (dd, $J = 8.2$, 5.8 Hz, 1H), 2.71 (d, $J = 5.6$ Hz, 1H), 2.05-1.98 (m, 1H), 1.81-1.70
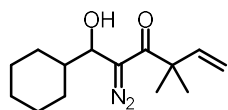
(m, 2H), 1.70-1.62 (m, 1H), 1.59-1.49 (m, 2H), 1.29 (s, 3H), 1.29 (s, 3H), 1.26-1.10 (m, 3H), 1.10-0.94 (m, 2H); ^{13}C (125 MHz, CDCl$_3$): δ 196.7, 141.3, 115.4, 72.5, 68.2, 50.3, 41.9, 29.3, 29.2, 26.4, 26.0, 25.8, 24.4, 24.3. MS (ESI): Calculated for [C$_{14}$H$_{22}$N$_2$O$_2$H]$^+$: 251.1760. Found: 251.1767.

5-diazo-6-hydroxy-3,3,8-trimethylnon-1-en-4-one (**4.35h**): Prepared from

isovaleraldehyde (370 μL, 3.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (288 mg, 2.1 mmol) following General Procedure A with the modification that the aldehyde was 1.6 equiv, the α-diazo ketone was 1 equiv, and the LDA was 1.1 equiv. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 12% EtOAc) to give 190 mg (40% yield) of the title compound as a bright yellow oil: R$_f$ = 0.40 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.92 (dd, J = 17.5 10.7 Hz, 1H), 5.23 (d, J = 10.6 Hz, 1H), 5.13 (d, J = 17.7 Hz, 1H), 4.89 (dd, J = 8.6, 5.6 Hz, 1H), 3.07 (s, 1H), 1.76 (hept, J = 6.7 Hz, 1H), 1.59 (ddd, J = 13.7, 8.6, 6.2 Hz, 1H), 1.30-1.25 (m, 7H), 0.94 (dd, J = 6.6, 2.5 Hz, 6H); ^{13}C (125 MHz, CDCl$_3$): δ 196.9, 141.2, 115.4, 69.5, 65.7, 50.3, 42.1, 24.7, 24.3, 24.2, 23.2, 22.1. MS (ESI): Calculated for [C$_{12}$H$_{20}$N$_2$O$_2$Na]$^+$: 247.1422. Found: 247.1419.

1-(4-chlorophenyl)-2-diazo-1-hydroxy-4,4-dimethylhex-5-en-3-one (**4.35i**): Prepared
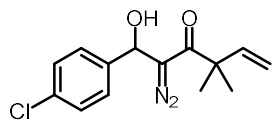
from 4-chlorobenzaldehyde (197 mg, 1.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (320 mg, 2.3 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 13% EtOAc) to give 164 mg (42% yield) of the title compound as a bright yellow solid: R$_f$ = 0.45 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz,

CDCl$_3$): δ 7.37-7.30 (m, 4H), 6.01 (d, J = 3.6 Hz, 1H), 5.91 (dd, J = 17.5, 10.6 Hz, 1H),

5.22 (d, J = 10.7 Hz, 1H), 5.12 (d, J = 17.5 Hz, 1H), 3.31 (d, J = 3.6 Hz, 1H), 1.31 (s, 3H),

1.29 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.4, 141.0, 137.4, 134.1, 129.0, 127.3, 115.6,

71.3, 69.3, 50.3, 24.3, 24.3. MS (ESI): Calculated for [C$_{14}$H$_{15}$ClN$_2$O$_2$Na]$^+$: 301.0720.

Found: 301.0713.

2-diazo-1-hydroxy-1-(4-methoxyphenyl)-4,4-dimethylhex-5-en-3-one   (**4.35j**):
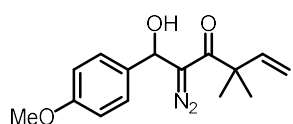
Prepared from *p*-anisaldehyde (0.17 mL, 1.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (313 mg, 2.3 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash

chromatography (hexanes/EtOAc, gradient elution 0 to 16% EtOAc) to give 282 mg (73%

yield) of the title compound as a bright yellow solid: R$_f$ = 0.22 (4:1 hexanes:EtOAc); ^{1}H

NMR (500 MHz, CDCl$_3$): δ 7.32-7.08 (m, 2H), 6.92-6.88 (m, 2H), 5.98 (d, J = 3.4 Hz,

1H), 5.92, (dd, J = 17.6, 10.7 Hz, 1H), 5.21 (d, J = 10.6 Hz, 1H), 5.12 (d, J = 17.5 Hz, 1H),

3.81 (s, 3H), 3.28 (d, J = 3.0 Hz, 1H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ

196.8, 159.7, 141.2, 130.5, 127.3, 115.5, 114.2, 71.2, 69.7, 55.4, 50.3, 24.3, 24.3. MS

(ESI): Calculated for [C$_{15}$H$_{18}$N$_2$O$_3$Na]$^+$: 297.1215. Found: 297.1223.

2-diazo-1-hydroxy-1-(3-methoxyphenyl)-4,4-dimethylhex-5-en-3-one   (**4.35k**):
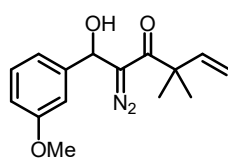
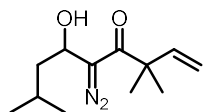Prepared from *m*-anisaldehyde (160 μL, 1.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (298 mg, 2.2 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash

chromatography (hexanes/EtOAc, gradient elution 0 to 25% EtOAc) to give 173 mg (45%

yield) of the title compound as a bright yellow solid: R$_f$ = 0.28 (4:1 hexanes:EtOAc); ^{1}H

NMR (500 MHz, CDCl$_3$): δ 7.29 (t, J = 7.9 Hz, 1H), 6.97-6.91 (m, 2H), 6.85 (ddd, J = 8.3, 2.5, 0.6 Hz, 1H), 6.01 (s, 1H), 5.92 (dd, J = 17.5, 10.6 Hz, 1H), 5.91 (d, J = 10.7 Hz, 1H), 5.12 (d, J = 17.4 Hz, 1H), 3.81 (s, 3H), 3.24 (s, 1H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.6, 160.1, 141.2, 140.1, 129.9, 118.2, 115.6, 114.1, 111.5, 69.9, 55.4, 50.3, 24.3, 24.3; IR (film) 3005 (br), 2081, 1711, 1360, 1221 cm^{-1}. MS (ESI): Calculated for [C$_{15}$H$_{18}$N$_2$O$_3$Na]$^+$: 297.1215. Found: 297.1219.

2-diazo-1-hydroxy-1-(2-methoxyphenyl)-4,4-dimethylhex-5-en-3-one (**4.35l**): Prepared
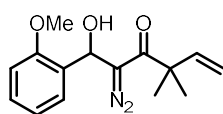
from *o*-anisaldehyde (180 μL, 1.5 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (318 mg, 2.4 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 20% EtOAc) to give 216 mg (52% yield) of the title compound as a bright yellow oil: R$_f$ = 0.22 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.50 (dd, J = 7.6, 1.1 Hz, 1H), 7.29 (dt, J = 7.9, 1.7 Hz, 1H), 7.00 (dt, J = 7.6, 0.9 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.05 (d, J = 5.3 Hz, 1H), 5.91 (dd, J = 17.6, 10.6 Hz, 1H), 5.18 (d, J = 10.7 Hz, 1H), 5.09 (d, J = 17.5 Hz, 1H), 3.82 (s, 3H), 3.79 (d, J = 5.3 Hz, 1H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 197.0, 156.0, 141.4, 129.4, 127.3, 126.9, 121.0, 115.1, 110.4, 70.1, 67.0, 55.5, 50.3, 24.4, 24.4. MS (ESI): Calculated for [C$_{15}$H$_{18}$N$_2$O$_3$Na]$^+$: 297.1215. Found: 297.1212.

3-(2-diazo-1-hydroxy-4,4-dimethyl-3-oxohex-5-en-1-yl)benzaldehyde (**4.35m**):
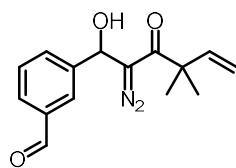
Prepared from isophthalaldehyde (187 mg, 1.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (310 mg, 2.2 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash

chromatography (hexanes/EtOAc, gradient elution 0 to 20% EtOAc) to give 82.0 mg (22% yield) of the title compound as a bright yellow solid: R_f = 0.21 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 10.02 (s, 1H), 7.93 (br.s, 1H), 7.84 (dt, J = 7.7, 1.3 Hz, 1H), 7.68-7.64 (m, 1H), 7.56 (t, J = 7.7 Hz, 1H), 6.12 (d, J = 3.6 Hz, 1H), 5.92 (dd, J = 17.5, 10.5 Hz, 1H), 5.23 (d, J = 10.7 Hz, 1H), 5.13 (d, J = 17.5 Hz, 1H), 3.83 (s, 1H), 1.32 (s, 3H), 1.30 (s, 3H); [13]C (125 MHz, CDCl$_3$): δ 196.3, 192.2, 141.0, 140.4, 136.8, 132.0, 129.6, 129.5, 127.2, 115.7, 71.1, 69.0, 50.3, 24.3, 24.3. MS (ESI): Calculated for [C$_{15}$H$_{16}$N$_2$O$_3$Na][+]: 295.1059. Found: 295.1066.

4-(2-diazo-1-hydroxy-4,4-dimethyl-3-oxohex-5-en-1-yl)benzaldehyde (**4.35n**):
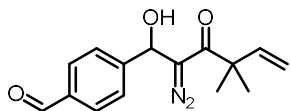
Prepared from terephthalaldehyde (188 mg, 1.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (305 mg, 2.2 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 14% EtOAc) to give 81.0 mg (21% yield) of the title compound as a bright yellow solid: R_f = 0.15 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 9.99 (s, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 6.10 (s, 1H), 5.90 (dd, J = 17.3, 10.6 Hz, 1H), 5.20 (d, J = 10.7 Hz, 1H), 5.10 (d, J = 17.3 Hz, 1H), 3.75-3.62 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H); [13]C (125 MHz, CDCl$_3$): δ 196.2, 191.9, 145.8, 141.0, 136.2, 130.3, 126.6, 115.7, 71.0, 69.2, 50.3, 24.3, 24.3. MS (ESI): Calculated for [C$_{15}$H$_{16}$N$_2$O$_3$Na][+]: 295.1059. Found: 295.1063.

2-diazo-1-hydroxy-4,4-dimethyl-1-(4-nitrophenyl)hex-5-en-3-one (**4.35o**): Prepared
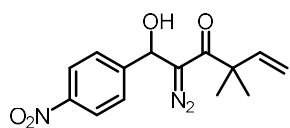
from 4-nitrobenzaldehyde (315 mg, 2.1 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (471 mg, 3.4 mmol) following General

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Procedure B. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 17% EtOAc) to give 128 mg (21% yield) of the title compound as a bright orange solid: $R_f = 0.17$ (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.25 (d, $J = 8.9$ Hz, 2H), 7.57 (d, $J = 8.8$ Hz, 2H), 6.11 (d, $J = 4.0$ Hz, 1H), 5.91 (dd, $J = 17.6, 10.6$ Hz, 1H), 5.24 (d, $J = 10.6$ Hz, 1H), 5.13 (d, $J = 17.4$ Hz, 1H), 3.26 (d, $J = 4.1$ Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.2, 147.9, 146.2, 140.9, 126.9, 124.1, 115.9, 70.7, 69.0, 50.4, 24.3, 24.3. MS (ESI): Calculated for [C$_{14}$H$_{15}$N$_3$O$_4$Na]$^+$: 312.0960. Found: 312.0971.

2-diazo-1-(furan-3-yl)-1-hydroxy-4,4-dimethylhex-5-en-3-one (**4.46**): Prepared from 3-
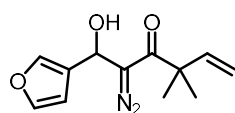
furaldehyde (120 µL, 1.4 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (309 mg, 2.2 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 14% EtOAc) to give 141 mg (43% yield) of the title compound as a bright yellow solid: $R_f = 0.32$ (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.49-7.47 (m, 1H), 7.41 (t, $J = 1.8$ Hz, 1H), 6.33 (dd, $J = 1.7, 0.7$ Hz, 1H), 5.89 (d, $J = 0.7$ Hz, 1H), 5.93 (dd, $J = 17.5, 10.7$ Hz, 1H), 5.23 (d, $J = 10.7$ Hz, 1H), 5.14 (d, $J = 17.5$ Hz, 1H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.4, 143.9, 141.1, 140.2, 123.9, 115.6, 108.3, 70.7, 64.3, 50.3, 24.3, 24.3.

2-diazo-1-(4-(dimethylamino)phenyl)-1-hydroxy-4,4-dimethylhex-5-en-3-one (**4.48**):
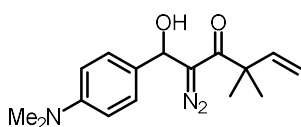
Prepared from 4-dimethylamino-benzaldehyde (310 mg, 2.0 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (180 mg, 1.3 mmol) following General Procedure A with the exception that 1.0 mL of nBuLi (1.4 mmol)

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and 240 µL of diisopropyl amine (1.7 mmol) was used. The crude orange oil was purified using silica gel flash chromatography (CH$_2$Cl$_2$/Et$_2$O, gradient elution 0 to 1% Et$_2$O) to give 144 mg (38% yield) of the title compound as a bright yellow solid: R$_f$ = 0.23 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.23 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 5.96-5.89 (m, 2H), 5.20 (d, J = 10.7 Hz, 1H), 5.12 (d, J = 17.6 Hz, 1H), 2.95 (s, 6H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.8, 150.6, 141.3, 127.0, 126.0, 115.4, 112.6, 69.9, 50.3, 40.6, 24.3, 24.3.

5-diazo-6-hydroxy-3,3-dimethyl-6-phenyloct-1-en-4-one (**4.67**): Prepared from
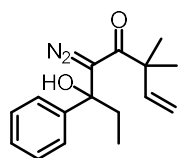
propiophenone (130 µL, 1.0 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (223 mg, 1.6 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 20% EtOAc), the desired compound was isolated, then resubjected to silica gel flash chromatography (hexanes/CH$_2$Cl$_2$, gradient elution 0 to 50% CH$_2$Cl$_2$) to give 98.4 mg (36% yield) of the title compound as a bright yellow solid: R$_f$ = 0.28 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.40-7.35 (m, 2H), 7.35-7.30 (m, 2H), 7.25 (tt, J = 7.2, 1.3 Hz, 1H), 5.89 (dd, J = 17.6, 10.6 Hz, 1H), 5.27 (s, 1H), 5.25 (d, J = 10.5 Hz, 1H), 5.10 (d, J = 17.6 Hz, 1H), 1.95 (dq, J = 7.2 Hz, 1H), 1.75 (dqd, J = 14.8, 7.4, 1.0 Hz, 1H), 1.25 (s, 3H), 1.22 (s, 3H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 199.1, 145.7, 141.0, 128.3, 127.5, 125.1, 115.6, 77.1, 71.9, 50.6, 33.5, 24.2, 24.1, 7.6. MS (ESI): Calculated for [C$_{16}$H$_{20}$N$_2$O$_2$Na]$^+$: 295.1422. Found: 295.1417.

6-cyclohexyl-5-diazo-6-hydroxy-3,3-dimethyloct-1-en-7-yn-4-one (**SI3**): Prepared from
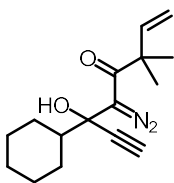
1-cyclohexylprop-2-yn-1-one (170 mg, 1.2 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (265 mg, 1.9 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 7% EtOAc), the desired compound was isolated, then resubjected to silica gel flash chromatography (hexanes/CH$_2$Cl$_2$, gradient elution 0 to 90% CH$_2$Cl$_2$) to give 61.1 mg (18% yield) of the title compound as a bright yellow oil: R$_f$ = 0.42 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.92 (dd, J = 12.0, 10.7, 1.4 Hz, 1H), 5.27 (dd, J = 10.7, 1.4 Hz, 1H), 5.17 (d, J = 1.5 Hz, 1H), 5.15 (dd, J = 17.5, 1.2 Hz, 1H), 2.62 (s, 1H), 2.03 (d, J = 11.8 Hz, 1H), 2.00-1.90 (m, 1H), 1.85-1.76 (m, 2H), 1.68 (d, J = 11.7 Hz, 1H), 1.63 (d, J = 10.5 Hz, 1H), 1.30 (d, J = 1.14 Hz, 3H), 1.29 (d, J = 1.14 Hz, 3H), 1.28-1.09 (m, 5H); ^{13}C (125 MHz, CDCl$_3$): δ 198.5, 140.8, 115.7, 80.0, 75.9, 75.8, 69.7, 50.8, 47.8, 28.5, 27.3, 26.3, 26.2, 26.0, 24.2, 24.1. MS (ESI): Calculated for [C$_{16}$H$_{22}$N$_2$O$_2$Na]$^+$: 297.1579. Found: 297.1566.

6-*tert*-butyl-5-diazo-6-hydroxy-3,3-dimethyl-8-(trimethylsilyl)oct-1-en-7-yn-4-one
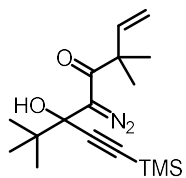
(**4.72**): Prepared from 4,4-dimethyl-1-(trimethylsilyl)pent-1-yn -3-one (204 mg, 1.1 mmol) and 1-diazo-3,3-dimethylpent-4-en-2-one (254 mg, 1.8 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 10% EtOAc) to give 184 mg (52% yield) of the title compound as a bright yellow solid: R$_f$ = 0.61 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.77 (s, 1H), 5.94 (dd, J = 17.5, 10.6 Hz, 1H), 5.28 (d, J = 10.6 Hz, 1H), 5.16 (d, J = 17.4 Hz, 1H), 1.31 (s, 3H), 1.29 (s,

3H), 1.02 (s, 9H), 0.18 (s, 9H); ^{13}C (125 MHz, CDCl$_3$): δ 199.5, 140.8, 115.7, 102.0, 92.3, 79.3, 67.9, 51.0, 44.9, 25.3, 24.4, 24.2, -.2. MS (ESI): Calculated for [C$_{17}$H$_{28}$N$_2$O$_2$SiNa]$^+$: 343.1817. Found: 343.1801.

6-cyclohexyl-5-diazo-6-hydroxy-3,3-dimethyl-8-(trimethylsilyl)oct-1-en-7-yn-4-one

(**4.76**): Prepared from 1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-one (248 mg, 1.2 mmol)
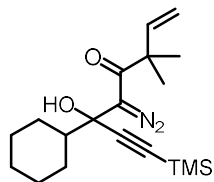
and 1-diazo-3,3-dimethylpent-4-en-2-one (262 mg, 1.9 mmol) following General Procedure A. The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 6% EtOAc)

to give 208 mg (50% yield) of the title compound as a bright yellow solid: R$_f$ = 0.58 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 5.92 (dd, J = 17.5, 10.7 Hz, 1H), 5.26 (d, J = 10.6 Hz, 1H), 5.14 (d, J = 17.3 Hz, 1H), 5.10 (s, 1H), 2.09-2.02 (m, 1H), 1.97 (tt, J = 11.4, 3.0 Hz, 1H), 1.83-1.73 (m, 2H), 1.71-1.64 (m, 1H), 1.60-1.55 (m, 1H), 1.54 (s, 1H), 1.29 (s, 3H), 1.29 (s, 3H), 1.26-1.08 (m, 5H), 0.18 (s, 9); ^{13}C (125 MHz, CDCl$_3$): δ 198.5, 140.9, 115.7, 100.6, 93.5, 69.8, 50.8, 48.0, 28.8, 27.6, 26.4, 26.2, 26.0, 24.2, 24.1, -.1. MS (ESI): Calculated for [C$_{19}$H$_{30}$N$_2$O$_2$SiNa]$^+$: 369.1974. Found: 369.1971.

ethenyl 2-diazo-3-hydroxy-3-phenylpropanoate (4.93): Prepared from benzaldehyde
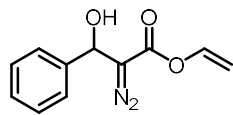
(130 µL, 1.2 mmol) and ethenyl diazoacetate (219 mg, 2.0 mmol) following General Procedure A. The crude orange oil was purified

using silica gel flash chromatography (hexanes/EtOAc, gradient elution 0 to 14% EtOAc) to give 127 mg (44% yield) of the title compound as a bright yellow oil: R$_f$ = 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.46-7.39 (m, 4H), 7.37-7.31 (m, 2H), 5.95 (d, J = 3.5 Hz, 1H), 4.89 (d, J = 14.1 Hz, 1H), 4.61 (dd, J = 6.2, 1.6 Hz, 1H), 2.77 (br.

s., 1H); ^{13}C (125 MHz, CDCl$_3$): δ 163.4, 140.8, 138.8, 128.9, 128.6, 128.5, 125.7, 97.5, 68.5, 63.1.

Characterization data for cyclopentenones for Chapter 3

General Procedure E: Tris(pentafluorophenyl)borane-promoted cyclopentenone formation

A room temperature solution of 0.2 M diazo ketone (1 equiv) in CH$_2$Cl$_2$ was rapidly added to a room temperature solution of 0.2 M tris(pentafluorophenyl)borane (1 equiv) in CH$_2$Cl$_2$. The reaction mixture was maintained at room temperature for 30 min as gas evolved and the solution changed color. The solvent was removed in vacuo to give an oily residue that was subjected to flash silica gel chromatography to afford the cyclopentenone product.

2-cyclohexylidene-5-methylhex-4-enoic acid (4.24): Prepared from β-hydroxy-α-diazo ketone **4.4** following General Procedure E with the exception that both flasks were cooled to -20 °C for the duration of the experiment and sodium bicarbonate was added at the completion of the reaction. The aqueous layer was acidified with 1M HCl, washed with Et$_2$O (three 10 mL portions), and combined organic layers were washed with brine and dried with MgSO$_4$. This afforded carboxylic acid **4.24** in varied yields as a colorless oil: R$_f$ = 0.25 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 10.93 (br.s, 1H), 5.05 (t, J = 6.5 Hz, 1H), 3.03 (d, J = 6.5 Hz, 2H), 2.56 (m, 2H), 2.27 (m, 2H), 1.69 (s, 3H), 1.66 (s, 3H), 1.64-1.57 (m, 6H); ^{13}C (125 MHz, CDCl$_3$): δ 152.1, 132.4, 123.3, 122.3, 100.1, 32.8, 32.1, 28.6, 28.5, 28.4, 26.6, 25.9, 18.0. MS (ESI): Calculated for [C$_{13}$H$_{21}$O$_2$]$^+$: 209.1542. Found: 209.1539.
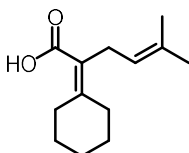
3-cyclohexylidene-6,6-dimethyloxan-2-one (**4.25**): Prepared from β-hydroxy-α-diazo ketone **4.4** (73.3 mg, 0.31 mmol) following General Procedure E with the exception that both flasks were cooled to -20 °C for the duration of the experiment. The crude orange oil was purified using silica gel flash chromatography (6:1 hexanes/Et$_2$O) to give 31.4 mg (49% yield) of the title compound as a pale yellow oil that solidified to an off-white solid upon standing in the freezer: R$_f$ = 0.29 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.82-2.77 (m, 2H), 2.56 (t, J = 7.2 Hz, 2H), 2.28-2.22 (m, 2H), 1.82 (t, J = 7.2 Hz, 2H), 1.67-1.57 (m, 6H), 1.37 (s, 6H); ^{13}C (125 MHz, CDCl$_3$): δ 167.1, 157.6, 116.5, 79.5, 33.8, 32.1, 32.1, 28.6, 27.9, 27.4, 26.4, 22.7. MS (ESI): Calculated for [C$_{13}$H$_{21}$O$_2$]$^+$: 209.1542. Found: 209.1541.
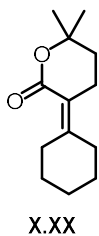
3-(heptan-4-ylidene)-6,6-dimethyloxan-2-one (**4.30**): Prepared from β-hydroxy-α-diazo ketone **4.26** (83.9 mg, 0.33 mmol) following General Procedure E with the exception that both flasks were cooled to -20 °C for the duration of the experiment. The crude orange oil was purified using silica gel flash chromatography (7:1 hexanes/Et$_2$O) to give 28.5 mg (38% yield) of the title compound as a colorless oil: R$_f$ = 0.50 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 2.58-2.50 (m, 4H), 2.15-2.10 (m, 2H), 1.80 (t, J = 7.0 Hz, 2H), 1.52-1.42 (m, 4H), 1.34 (s, 6H), 0.98 (t, J = 7.3 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 167.4, 160.3, 119.0, 79.9, 36.8, 36.5, 33.7, 27.4, 22.7, 22.3, 20.5, 14.7, 14.6. MS (ESI): Calculated for [C$_{14}$H$_{25}$O$_2$]$^+$: 225.1855. Found: 225.1860.
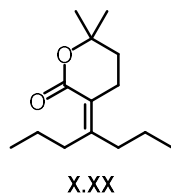
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3-phenyl-5-(propan-2-ylidene)cyclopent-2-en-1-one (**4.36a**): Prepared from β-hydroxy-

α-diazo ketone **4.35a** (67.8 mg, 0.28 mmol) following General Procedure
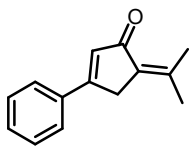
E. The crude orange oil was purified using silica gel flash

chromatography (9:1 hexanes/EtOAc with 0.5% Et_3N) to give 38.3 mg (69% yield) of

4.36a as a pale yellow foam: R_f = 0.39 (3.7:1 hexanes:EtOAc); ^{1}H NMR (500 MHz,

$CDCl_3$): δ 7.70-7.65 (m, 2H), 7.47-7.43 (m, 3H), 6.71 (t, J = 1.7 Hz, 1H), 3.55 (s, 2H), 2.36

(s, 3H), 1.98 (s, 3H); ^{13}C (125 MHz, $CDCl_3$): δ 196.8, 163.6, 146.1, 134.2, 131.1, 130.9,

129.7, 129.0, 126.7, 34.7, 24.3, 20.0. MS (ESI): Calculated for $[C_{14}H_{15}O]^+$: 199.1123.

Found: 199.1121.

3-phenyl-5-(prop-1-en-2-yl)cyclopent-2-en-1-one (**4.37a**): Prepared from β-hydroxy-α-

diazo ketone **4.35a** (74.6 mg, 0.30 mmol) following General Procedure

E with the exception that the reaction was run for 15 minutes at -15 °C.

The crude orange oil was purified using silica gel flash chromatography (hexanes/EtOAc,

gradient elution 0 to 10% EtOAc) to give 35.5 mg (60% yield) of **4.37a** as a pale yellow

foam: R_f = 0.33 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 7.6 Hz,

2H), 7.52-7.44 (m, 3H), 6.60 (s, 1H), 4.97 (s, 1H), 4.93 (s, 1H), 3.35-3.25 (m, 2H), 2.96

(d, J = 17.1 Hz, 1H), 1.71 (s, 3H); ^{13}C (125 MHz, $CDCl_3$): δ 208.7, 172.8, 142.5, 133.9,

131.6, 129.1, 127.1, 127.0, 114.4, 54.3, 35.0, 19.5. MS (ESI): Calculated for $[C_{14}H_{15}O]^+$:

199.1123. Found: 199.1128.

3-(4-methylphenyl)-5-(propan-2-ylidene)cyclopent-2-en-1-one (**4.36b**): Prepared from
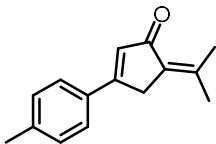
β-hydroxy-α-diazo ketone **4.35b** (72.8 mg, 0.28 mmol) following

General Procedure E. The crude orange oil was purified using silica gel

flash chromatography (6:1 hexanes/EtOAc with 1.0% Et$_3$N) to give 37.8 mg (64% yield) of the title compound as a pale yellow foam: R$_f$ = 0.30 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.57 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 7.9 Hz, 2H), 6.66 (s, 1H), 3.52 (s, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.96 (s, 3H); [13]C (125 MHz, CDCl$_3$): δ 196.9, 163.7, 145.6, 141.4, 131.4, 130.3, 129.8, 129.7, 126.7, 34.6, 24.2, 21.6, 20.0. MS (ESI): Calculated for [C$_{15}$H$_{17}$O]$^+$: 213.1279. Found: 213.1275.

3-(2,6-dimethylphenyl)-5-(propan-2-ylidene)cyclopent-2-en-1-one (**4.36c**): Prepared
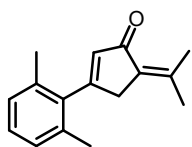
from β-hydroxy-α-diazo ketone **4.35c** (76.0 mg, 0.28 mmol) following General Procedure E. The crude orange oil was purified using silica gel

flash chromatography (12:1 hexanes/EtOAc with 0.5% Et$_3$N) to give 56.2 mg (89% yield) of the title compound as a pale yellow foam: R$_f$ = 0.48 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.15 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 2H), 6.20 (s, 1H), 3.32 (s, 2H), 2.37 (s, 3H), 2.20 (s, 6H), 1.91 (s, 3H); [13]C (125 MHz, CDCl$_3$): δ 197.0, 168.1, 146.6, 136.7, 136.3, 134.2, 129.3, 128.0, 127.6, 38.0, 24.4, 20.1, 19.9. MS (ESI): Calculated for [C$_{16}$H$_{19}$O]$^+$: 227.1436. Found: 227.1442.

5-(propan-2-ylidene)-3-(2,4,6-trimethylphenyl)cyclopent-2-en-1-one (**4.36d**): Prepared

from β-hydroxy-α-diazo ketone **4.35d** (77.4 mg, 0.27 mmol) following General Procedure E. The crude orange solid was purified using silica

gel flash chromatography (13:1 hexanes/EtOAc with 0.5% Et$_3$N, material loaded onto column with CH$_2$Cl$_2$ due to insolubility) to give 60.3 mg (93% yield) of the title compound as a pale yellow foam: R$_f$ = 0.57 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.91 (s, 2H), 6.18 (t, J = 1.8 Hz, 1H), 3.30 (s, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 2.17 (s, 6H), 1.90

(s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 197.1, 168.4, 146.4, 137.8, 136.5, 134.2, 133.8, 129.5, 128.4, 38.2, 24.4, 21.1, 20.0, 20.0. MS (ESI): Calculated for [C$_{17}$H$_{21}$O]$^+$: 241.1592. Found: 241.1587.

1 mmol scale: Prepared from β-hydroxy-α-diazo ketone **4.35d** (302 mg, 1.0 mmol) following General Procedure E. The crude orange solid was purified using silica gel flash chromatography (13:1 hexanes/EtOAc with 1% Et$_3$N, material loaded onto column with CH$_2$Cl$_2$) to give 193 mg (80% yield) of the title compound as a pale yellow foam. It was noted that earlier fractions contained impure product. The fractions were isolated, and the orange oily mixture was purified using silica gel flash chromatography (13:1 hexanes/EtOAc with 1% Et$_3$N), to yield an additional 18.5 mg of product, providing a total yield of 212 mg (88% yield).
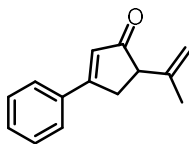
3-(naphthalen-2-yl)-5-(propan-2-ylidene)cyclopent-2-en-1-one (**4.36e**): Prepared from β-hydroxy-α-diazo ketone **4.35e** (88.4 mg, 0.30 mmol) following General Procedure E. The crude brown solid was purified using silica gel flash chromatography (9:1 hexanes/EtOAc with 0.5% Et$_3$N) to give 40.6 mg (54% yield) of the title compound as a pale yellow foam: R$_f$ = 0.34 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.11 (s, 1H), 7.94-7.82 (m, 3H), 7.78 (dd, J = 8.6, 1.8 Hz, 1H), 7.58-7.51 (m, 2H), 6.83 (t, J = 1.6 Hz, 1H), 3.69 (s, 2H), 2.39 (s, 3H), 2.02 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.8, 163.3, 146.0, 134.5, 133.2, 131.5, 131.5, 129.7, 128.9, 128.7, 127.9, 127.6, 126.9, 126.6, 123.9, 34.7, 24.3, 20.1. MS (ESI): Calculated for [C$_{18}$H$_{17}$O]$^+$: 249.1279. Found: 249.1284.

3-(anthracen-9-yl)-5-(propan-2-ylidene)cyclopent-2-en-1-one (**4.36f**): Prepared from β-hydroxy-α-diazo ketone **4.35f** (76.1 mg, 0.22 mmol) following General Procedure E. The crude brown solid was purified using silica gel flash chromatography (5:2 CH_2Cl_2/hexanes with 1.0% Et_3N) to give 50.5 mg (77% yield) of the title compound as a pale brown solid: R_f = 0.38 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.48 (s, 1H), 8.04 (d, J = 8.4 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.53-7.44 (m, 4H), 6.59 (s, 1H), 3.64 (s, 2H), 2.46 (s, 3H), 1.93 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.7, 166.2, 147.3, 139.3, 131.7, 131.3, 129.6, 128.9, 128.1, 127.6, 126.3, 125.6, 125.4, 40.2, 24.5, 20.1. MS (ESI): Calculated for [C$_{22}$H$_{19}$O]$^+$: 299.1436. Found: 299.1440.

**3-cyclohexyl-5-(propan-2-ylidene)cyclopent-2-en-1-one** (**4.36g**): Prepared from β-hydroxy-α-diazo ketone **4.35g** (67.0 mg, 0.27 mmol) following General Pro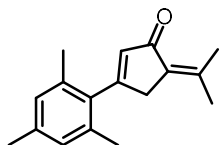cedure E. The crude orange oil was purified using silica gel flash chromatography (4:1 hexanes/Et_2O with 0.5% Et_3N), the desired compound was isolated, then subjected to silica gel flash chromatography (50:1 CH_2Cl_2/Et_2O with 0.5% Et_3N) to give 16.1 mg (29% yield) of the title compound as an off-white solid: R_f = 0.58 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.03 (s, 1H), 3.09 (s, 2H), 2.29 (s, 3H), 1.92-1.85 (m, 5H), 1.85-1.78 (m, 2H), 1.75-1.68 (m, 1H), 1.40-1.17 (m, 6H); ^{13}C (125 MHz, CDCl$_3$): δ 197.6, 176.4, 144.8, 131.2, 129.6, 41.3, 35.3, 31.5, 26.2, 26.2, 24.1, 19.8. MS (ESI): Calculated for [C$_{14}$H$_{21}$O]$^+$: 205.1592. Found: 205.1583.

3-(2-methylpropyl)-5-(propan-2-ylidene)cyclopent-2-en-1-one (**4.36h**): Prepared from β-hydroxy-α-diazo ketone **4.35h** (59.6 mg, 0.26 mmol) following General

Procedure E. The crude yellow oil was purified using silica gel flash chromatography (6:1 pentane/Et$_2$O with 0.5% Et$_3$N), the desired compound was isolated, then subjected to silica gel flash chromatography (8:1 CH$_2$Cl$_2$/pentane) to give 4.9 mg (10% yield) of the title compound as a colorless oil: R$_f$ = 0.40 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 6.06-6.04 (m, 1H), 3.06 (s, 2H), 2.29 (s, 4H), 2.27 (s, 1H), 1.94 (hept, J = 6.8 Hz, 1H), 1.86 (s, 3H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C (125 MHz, CDCl$_3$): δ 197.5, 170.9, 144.7, 134.0, 129.7, 42.3, 37.4, 27.1, 24.1, 22.8, 19.8. MS (ESI): Calculated for [C$_{12}$H$_{19}$O]$^+$: 179.1436. Found: 179.1430.

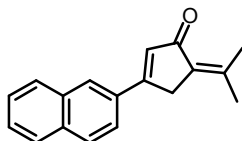**3-(4-chlorophenyl)-5-(propan-2-ylidene)cyclopent-2-en-1-one** (**4.36i**): Prepared from
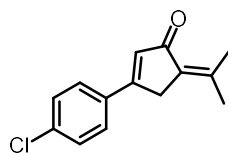
β-hydroxy-α-diazo ketone **4.35i** (75.2 mg, 0.27 mmol) following General Procedure E. The crude orange oil was purified using silica gel flash chromatography (6:1 hexanes/EtOAc with 0.5% Et$_3$N) to give 37.5 mg (60% yield) of the title compound as a pale yellow foam: R$_f$ = 0.42 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.60 (dt, J = 8.6, 2.6 Hz, 2H), 7.42, (dt, J = 8.6, 2.6 Hz, 2H), 6.68 (t, J = 1.7 Hz, 1H), 3.52 (s, 2H), 2.36 (s, 3H), 1.97 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.5, 162.1, 146.6, 136.9, 132.7, 131.4, 129.5, 129.3, 128.0, 34.6, 24.3, 20.1. MS (ESI): Calculated for [C$_{14}$H$_{14}$ClO]$^+$: 233.0733. Found: 233.0733.

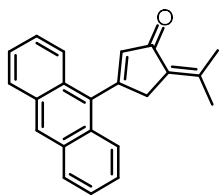**3-(4-methoxyphenyl)-5-(propan-2-ylidene)cyclopent-2-en-1-one** (**4.36j**): Prepared
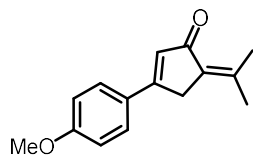
from β-hydroxy-α-diazo ketone **4.35j** (70.8 mg, 0.26 mmol) following General Procedure E. The crude orange oil was purified using silica gel flash chromatography (2:1 hexanes/EtOAc with 1.5% Et$_3$N) to give 36.2 mg (61% yield) of the title compound as a pale yellow foam: R$_f$ = 0.15 (4:1

hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.61 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.9 Hz, 2H), 6.60 (t, J = 1.5 Hz, 1H), 3.86 (s, 3H), 3.50 (s, 2H), 2.35 (s, 3H), 1.95 (s, 3H); [13]C (125 MHz, CDCl$_3$): δ 196.9, 163.4, 161.9, 145.2, 129.8, 129.2, 128.4, 126.7, 114.4, 55.6, 34.7, 24.2, 19.9. MS (ESI): Calculated for $[C_{15}H_{17}O_2]^+$: 229.1227. Found: 229.1220.

3-(3-methoxyphenyl)-5-(propan-2-ylidene)cyclopent-2-en-1-one (**4.36k**): Prepared
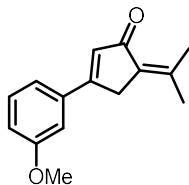
from β-hydroxy-α-diazo ketone **4.35k** (71.2 mg, 0.26 mmol) following General Procedure E. The crude orange oil was purified using silica gel flash chromatography (6:1 hexanes/EtOAc with 1.5% Et$_3$N) to give 33.1

mg (56% yield) of the title compound as a pale yellow foam: R_f = 0.20 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.36 (t, J = 7.9 Hz, 1H), 7.29-7.24 (m, 1H), 7.17 (t, J = 2.0 Hz, 1H), 6.98 (dd, J = 8.2, 2.5 Hz, 1H), 6.68 (t, J = 1.7 Hz, 1H), 3.86 (s, 3H), 3.52 (s, 2H), 2.35 (s, 3H), 1.97 (s, 3H); [13]C (125 MHz, CDCl$_3$): δ 196.6, 163.4, 159.9, 146.0, 135.5, 131.3, 129.9, 129.6, 119.1, 116.1, 112.2, 55.4, 34.6, 24.2, 19.9. MS (ESI): Calculated for $[C_{15}H_{17}O_2]^+$: 229.1227. Found: 229.1225.
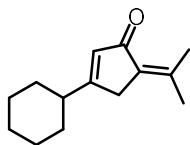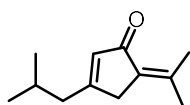
3-(2-methoxyphenyl)-5-(propan-2-ylidene)cyclopent-2-en-1-one (**4.36l**): Prepared from
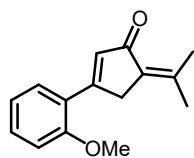
β-hydroxy-α-diazo ketone **4.35l** (61.2 mg, 0.22 mmol) following General Procedure E. The crude orange oil was purified using silica gel flash

chromatography (3:1 hexanes/EtOAc with 1.5% Et$_3$N) to give 36.6 mg (73% yield) of the title compound as a pale yellow foam: R_f = 0.22 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.56 (dd, J = 7.8, 1.6 Hz, 1H), 7.40 (ddd, J = 8.70, 7.40, 1.65 Hz, 1H), 7.05-7.00 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 3.92 (s, 3H), 3.58 (s, 2H), 2.36 (s, 3H), 1.96 (s, 3H); [13]C (125 MHz, CDCl$_3$): δ 198.1, 160.1, 159.2, 145.1, 135.4, 131.8, 129.2, 128.9, 123.4, 120.7,

111.5, 55.5, 36.5, 24.3, 20.1. MS (ESI): Calculated for $[C_{15}H_{17}O_2]^+$: 229.1227. Found: 229.1226.

3-(3-oxo-4-(propan-2-ylidene)cyclopent-1-en-1-yl)benzaldehyde (**4.36m**): Prepared from β-hydroxy-α-diazo ketone **4.35m** (71.5 mg, 0.26 mmol) following General Procedure E. The crude orange oil was purified using silica gel flash chromatography (3:1 hexanes/EtOAc with 0.5% Et$_3$N) to give 20.9 mg (36% yield) of the title compound as a pale yellow foam: R$_f$ = 0.19 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 10.09 (s, 1H), 8.14 (t, J = 1.70 Hz, 1H), 7.97-7.93 (m, 2H), 7.64 (t, J = 7.6 Hz, 1H), 6.78 (t, J = 1.7 Hz, 1H), 3.60 (s, 2H), 2.38 (s, 3H), 2.00 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.3, 191.8, 161.8, 147.2, 137.0, 135.3, 132.4, 132.3, 132.1, 129.8, 129.4, 127.1, 34.7, 24.4, 20.2. MS (ESI): Calculated for $[C_{15}H_{15}O_2]^+$: 227.1072. Found: 227.1067.
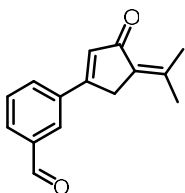
4-(3-oxo-4-(propan-2-ylidene)cyclopent-1-en-1-yl)benzaldehyde (**4.36n**): Prepared from β-hydroxy-α-diazo ketone **4.35n** (63.3 mg, 0.23 mmol) following General Procedure E. The crude orange oil was purified using silica gel flash chromatography (3:1 hexanes/EtOAc with 0.5% Et$_3$N) to give 13.0 mg (25% yield) of the title compound as a pale yellow foam: R$_f$ = 0.11 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 10.07 (s, 1H), 7.96 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 6.81 (t, J = 1.7 Hz, 1H), 3.58 (s, 2H), 2.37 (s, 3H), 2.00 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 196.2, 191.6, 161.6, 147.6, 139.8, 137.6, 133.5, 130.3, 129.4, 127.3, 34.7, 24.4, 20.2. MS (ESI): Calculated for $[C_{15}H_{15}O_2]^+$: 227.1072. Found: 227.1076.
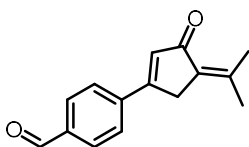
**3-(4-nitrophenyl)-5-(propan-2-ylidene)cyclopent-2-en-1-one (4.36o)**: Prepared from β-hydroxy-α-diazo ketone **4.35o** (66.9 mg, 0.23 mmol) following General Procedure E. The crude orange oil was purified using silica gel flash chromatography (4:1 hexanes/EtOAc with 0.5% Et$_3$N), the desired compound was isolated, then subjected to silica gel flash chromatography (8:1 CH$_2$Cl$_2$/hexanes with 0.5% Et$_3$N) to give 7.1 mg (13% yield) of the title compound as a light orange foam: R$_f$ = 0.15 (4:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.30 (dt, J = 8.9, 2.4 Hz, 2H), 7.81 (dt, J = 8.9, 2.4 Hz, 2H), 6.81 (t, J = 1.8 Hz, 1H), 3.58 (s, 2H), 2.38 (s, 3H), 2.01 (s, 3H); ^{13}C (125 MHz, CDCl$_3$): δ 195.9, 160.3, 148.9, 148.3, 140.3, 134.2, 129.3, 127.5, 124.3, 34.7, 24.5, 20.3. MS (ESI): Calculated for [C$_{14}$H$_{14}$NO$_3$]$^+$: 244.0974. Found: 244.0972.
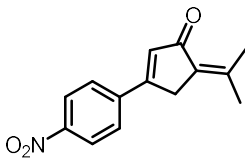
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