# ABSTRACT

Title of Dissertation:        Rhodium(II)-Stabilized Vinylcarbenes: Synthetic Applications in Ylide, Cyclopropanation, and C-H Insertion Reactions

Darren Bykowski, Doctor of Philosophy, 2006

Dissertation directed by:        Dr. Michael P. Doyle
Professor
Department of Chemistry and Biochemistry

A previously unknown cascade reaction in which two units of a rhodium(II)-stabilized vinylcarbene obtained from methyl *trans*-styryldiazoacetate react with benzylideneaniline is described; the products of the cascade reaction are complex bicyclic pyrrolidines.  An evaluation of reaction conditions for the formation of bicyclic pyrrolidine determined that slow addition of two equivalents of methyl *trans*-styryldiazoacetate to a refluxing dichloromethane solution of benzylideneaniline and 1 mol% $Rh_2(OAc)_4$ provided optimal yields of bicyclic pyrrolidine products.  A study was initiated to determine the scope of this cascade process, it was found that the only metal vinylcarbene which amendable to the cascade reaction was *trans*-styryldiazoacetate.

A series of endocyclic vinyldiazocarbonyl compounds were synthesized using one of two synthetic protocols, direct diazo transfer reaction with an unsaturated cyclic carbonyl compound or a reduction-dehydration of a diazo $\beta$-dicarbonyl compound.  The direct diazo transfer reaction with an unsaturated cyclic carbonyl was the most general and

commonly applied route to endocyclic vinyldiazocarbonyl compounds. Five endocyclic vinyldiazocarbonyl compounds were prepared using both strategies, including vinyldiazolactones of varying ring size and substitution, a cyclic vinyldiazoketone, and a vinyldiazolactam.

The endocyclic vinyldiazocarbonyl compounds which were prepared were evaluated as metal vinylcarbene precursors in asymmetric cyclopropanation and intermolecular C-H insertion reactions. The vinyldiazolactone derived from 5,6-dihydro-2$H$-pyran-2-one provided good enantioselectivities (>80% ee) in an intermolecular C-H insertion reaction with 1,4-cyclohexadiene and cyclopropanation reactions with styrene and terminal diene olefins using the catalyst Rh$_2$($S$,$R$-MenthAZ)$_4$. The azetidinate ligated dirhodium catalysts were the only dirhodium catalysts surveyed which provided enantioselectivities >40% ee in either intermolecular C-H insertion or cyclopropanation reactions.

RHODIUM(II)-STABILIZED VINYLCARBENES:

SYNTHETIC APPLICATIONS IN YLIDE, CYCLOPROPANATION

AND C-H INSERTION REACTIONS


BY

DARREN BYKOWSKI



Dissertation submitted to the Faculty of the Graduate School of the
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Doctor of Philosophy
2006




Advisory Committee:

| | |
|---|---|
| Professor | Michael P. Doyle, Chairman/Advisor |
| Professor | Jeffery Davia |
| Assoc. Professor | Andrei Vedernikov |
| Assoc. Professor | Lyle Isaacs |
| Professor | Marco Colombini |

**DEDICATION**


TO MY WIFE

Alex Hatch

"Organic chemistry just now is enough to drive one mad.  It gives me the impression of a primeval tropical forest...a monstrous and boundless thicket with no way of escape, and into which one may well dread to enter."

Friedrich Wohler (1800 – 1882)

# ACKNOWLEDGEMENTS

The acknowledgements section may be the most important part of this thesis. It is overwhelming to think of all the people who have guided, supported, and inspired me over the course of my studies in chemistry. Too many, in fact, for me to thank them all. However, to Jason's dismay I'll take a stab at it.

Of course, I would like to thank my graduate advisor, Professor Michael Doyle. When I was selecting a university and research group in which to pursue my PhD, my most important criteria was that I find an advisor who would allow me the independence to pursue ideas of my own. I don't think I realized at the time just how difficult that could be, both for the graduate student and their advisor, who must patiently watch the student struggle down avenues they do not always agree with. Looking back, I am truly gratefully for Mike's support and patience over my graduate career. I have been provided with a great deal of freedom over my time in this group, and leave having gained valuable confidence in my ability to effectively develop my own research interests. This would not have been possible without Professor Doyle's mentorship and support.

I would certainly not be in graduate school today if it were not for the exceptional experiences I had in chemistry as an undergraduate. Heading the list of my undergraduate mentors is Professor Rik Tykwinski of the University of Alberta. While still taking my first year organic courses, Rik gave me a position in his research group, which was just starting at that time. As an indication of how much I benefited from Rik's teachings, years later in my graduate studies I found that I was able to easily pass many of my cumes in

my first year of graduate school simply by remembering the group meeting questions and cume advice I picked up as a second year undergraduate. I am forever indebted to Rik for advice in chemistry, my career, and letters of recommendation.

One letter of recommendation from Rik is of particular importance to me, in my third year he managed to pawn me off to Boehringer-Ingelheim for a one year internship. My year at BI and the guidance I received from my supervisors there continues to influence my career path. I had the excellent fortune to work with a number of excellent chemists, my direct supervisors as I moved through different groups were Eric Malenfant, Dr. Pierre Beaulieu, and Jim Gillard. I would particularly like to thank Pierre, who has provided me with excellent advice and letters of recommendation and support. And after Boehringer-Ingelheim, there was MethylGene. Over two summers, I had the pleasure to work with Dr. Oscar Moradei and Dr. Dave Llewellelyn. In particular Oscar's impressive knowledge of synthetic organic chemistry, enthusiasm for his research, and displeasure with any meeting or paperwork that distracted him from the bench made him a joy to work for.

Moving back to the present day, I would like to thank Professor Jeff Davis, Professor Lyle Isaacs, Professor Andrei Vedernikov, and Professor Larry Sita, and Professor Marco Colombini for serving on my defense committee. Professor Isaacs taught the only course I have taken at Maryland, and I still find myself referring back to a few pages of notes from that class on occasion. I would like to thank Professor Davis for his valuable mentorship during my independent proposal.

My fellow graduate students Art Catino, Jason Nichols, and Kousik Kundu have been around for most of my time in this group. When my

reactions have failed to yield anything but inseparable mixtures of tar (which was most of the time), and I was reconsidering my career choice, it was Art, Jason, and Kousik who provided me with encouragement to come in the next day and keep trying. Along with Dr. J. P. Morgan, whose humor and intelligence were valuable additions to our group. Success comes much easier when you're surrounded by people who are as bright and motivated as they are; it has been my great fortune to be able to go through graduate school with them. I would like to add a special thanks to Art, whose apartment was always open and whose fridge was always stocked with beer. And Jason, my whitewater paddling partner and fellow hockey fan. Speaking of which, thanks to Jason and his wife, Rachel, for allowing me to watch the 2006 NHL playoffs in their home. Even though Oilers were playing 2-3 time zones behind us.

Much of my research has been conducted in collaboration with others, and I am very grateful to their contributions. In particular, I would like to thank Kou-Hui Wu for his considerable contributions to the vinyldiazolactone chemistry. I also had the good fortune to work with Dr. Ngozi Onyia, Sara Saba, Alicia Hajjar, and Benjamin von Hohenstaufen. Their contributions to my research, while not the subject of this thesis, are greatly appreciated by me. Dr. Neil Jacobsen, Dr. Wehao Hu, Dr. Ming Yan, Luisa Gronenberg, and John Colyer are gratefully acknowledged for their roles in the bicyclic pyrrolidine project discussed in Chapter 1. Dr. Chris Welch and his coworkers from the Merck analytical division are thanked for their participation in a dirhodium catalyst speciation study which shed new light upon the mechanism of catalyst formation.

Finally, I would like to thank my wife, Alex Hatch.  Alex has put up with more than she ever should have had to deal with, and I don't know how to thank her.  If it was not for her encouragement and constant support, I don't know if I could have made it through.  As difficult as graduate studies can be, I don't think being the spouse of a graduate student is easier.  Alex has always unselfishly provided the support I have needed, and deserves more thanks than anyone.

Again, to everyone I have listed above, and to those whom I am sure I have neglected to include, thank-you for your support and assistance over the years.

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| | |
|---|---|
| *p*-ABSA | *para*-Acetamidobenzenesulfonyl azide |
| Boc | *tertiary*-Butylcarbamate |
| *n*-Bu | *normal*-Butyl |
| *t*-Bu | *tertiary*-Butyl |
| *n*-BuLi | *normal*-Butyllithium |
| *m*-CPBA | *meta*-Chloroperoxybenzoic acid |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCE | 1,2-Dichloroethane |
| DDQ | 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone |
| DMAP | Dimethylaminopyridine |
| DMSO | Dimethyl sulfoxide |
| 2,2-DMB | 2,2-Dimethylbutane |
| DMF | *N*,*N*-Dimethylformamide |
| EDA | Ethyldiazoacetate |
| Et$_3$N | Triethylamine |
| EtOAc | Ethyl acetate |
| equiv | Equivalent |
| h | Hour |
| LDA | Lithium *N*,*N*-diisopropylamine |
| LHMDS | Lithium hexamethyldisilazide |
| Me | Methyl |
| MeCN | Acetonitrile |
| MeOH | Methanol |
| MsCl | Methanesulfonyl chloride |

| | |
|---|---|
| MsN$_3$ | Methanesulfonyl azide |
| OAc | Acetate |
| OPiv | Pivalate |
| Ph | Phenyl |
| rt | Room temperature |
| TBS | *tertiary*-Butyldimethylsilyl |
| THF | Tetrahydrofuran |
| TIPS | Triisopropylsilyl |

# SYNTHETIC APPLICATIONS OF

# VINYLDIAZOACETATES

## I.     BACKGROUND

Transition metal-stabilized carbenes have found widespread application in modern synthetic organic chemistry.[1-6]  Metal carbene intermediates are capable of performing a diverse array of reactions; the three most common reactions of carbenes include the [2+1] cycloaddition of olefins and alkynes,[7,8] formation of ylides upon reaction with heteroatoms,[9,10] and the insertion of metal carbenes into unactivated C—H bonds.[11-14]  Metal carbenes have gained widespread acceptance by the synthetic organic community, and are recognized as valuable tools in the construction of complex molecular architectures.[15-18]  In large part, this is due to the development of highly selective transition metal catalysts to mediate metal carbene reactions.[19]

**Scheme 1.1**

(1) [2+1] Cycloaddition

$$Z-CH=CH_2 \ + \ M=CR_2 \ \longrightarrow \ $$

(2) Insertion

$$\underset{Z}{\overset{Z}{Z-C-H}} \ + \ M=CR_2 \ \longrightarrow \ \underset{Z}{\overset{Z}{Z-C-CR_2}}\overset{H}{}$$

(2) Ylide formation

$$\underset{Z}{\overset{Z}{O:}} \ + \ M=CR_2 \ \longrightarrow \ \underset{Z}{\overset{Z}{\overset{\oplus}{O}-\overset{\ominus}{C}R_2}}$$
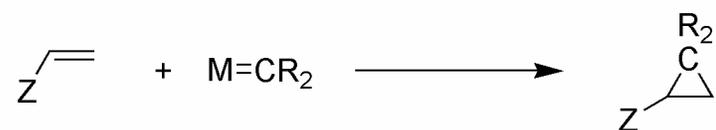
The catalytic cycle of transition metal-stabilized carbene reactions is generally well accepted and is believed to be applicable to a wide range of processes involving transition metal catalyzed reactions of diazoacetates, including C-H insertion, cyclopropanation, and ylide formation.[1,20] Scheme 1.2 illustrates the catalytic cycle in the context of a C—H insertion reaction.

**Scheme 1.2**

$$-\overset{\backslash}{\underset{/}{C}}-H \qquad -\overset{\backslash}{\underset{/}{C}}-\overset{H}{\underset{}{CR_2}}$$

$$L_nM=CR_2 \qquad\qquad N_2=CR_2$$

$$N_2 \qquad\qquad ML_n$$
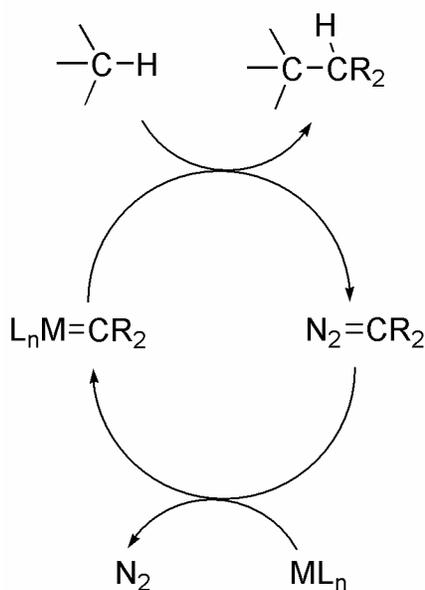
$ML_n$ = transition metal catalyst

Upon attack of the nucleophilic diazo carbon upon a metal catalyst, backbonding from the metal to carbon leads to extrusion of dinitrogen and formation of the metal carbene.[1,20] The metal carbene may be represented by either a double bond to the metal catalyst (**1a**), or as a charge separated structure (**1b**). Although depiction of the metal carbene as a charge separated

structure deemphasizes the stabilizing backbonding from the metal atom onto the metal carbene, it does highlight the electrophilic character of the metal-carbene carbon. Reaction of the metal carbene carbon with a nucleophilic substrate results in the concomitant release of the transition metal catalyst.

**Figure 1.1** Metal carbene resonance structures.

$$M=CR_2 \quad \longleftrightarrow \quad \overset{\ominus}{M}-\overset{\oplus}{C}R_2$$

$$\textbf{1a} \qquad\qquad \textbf{1b}$$
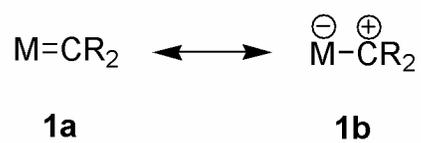
Metal carbenes readily react with adventitious water; and, therefore, care is taken to exclude water from the reaction by the use of flame-dried reaction apparatuses and anhydrous solvents. Deoxygenation of the system prior to addition of the diazo compound has been reported to increase isolated yields of metal carbene products, though this may be limited to specific reactions or processes.[21] Consequently, the reaction apparatus is often degassed with a steady flow of nitrogen prior to addition of the reagents, and subsequent reactions are performed under a nitrogen atmosphere. The ability of metal carbenes to react with numerous functionalities does limit the solvents which may be used in metal carbene reactions. Polar protic solvents are used in rare instances.[22,23] Ethereal solvents are rarely used in metal carbene reactions due to concerns of oxonium ylide formation upon reaction of the ethereal oxygen with the metal carbene.[9] Early metal carbene reactions were often performed in refluxing benzene using copper catalysts such as $CuSO_4$;[1] however, the

development of more active transition metal catalysts has allowed the formation and reaction of metal carbenes at lower temperatures.  Simple hydrocarbons such as 2,2-dimethylbutane (2,2-DMB), cyclohexane, and the halogenated solvent dichloromethane are now commonly used as solvents at temperatures ranging from -78 to 40 $^{\circ}$C.

## Catalysts

Asymmetric variants of all three previously described metal carbene reactions have been reported using asymmetric transition metal catalysts. Numerous transition metal catalysts are capable of forming metal carbenes *via* reaction of a metal carbene precursor (typically a diazo compound); however, dirhodium complexes have proven to be the most broadly applicable catalysts.[1,24] Asymmetric dirhodium catalysts have provided excellent enantioselectivities (>90% ee) in [2+1] cycloaddition, C—H insertion and select ylide reactions of diazoacetates.[5]  The most commonly used asymmetric dirhodium catalysts are comprised of four carboxylate or carboxamidate ligands bridging two dirhodium atoms.  Asymmetric aryl phosphine and phosphonates ligated dirhodium catalysts have also been reported;[25,26] however their synthetic applications have been quite limited and they will not be further described.

**Carboxylate Ligated Dirhodium Catalysts.**  Dirhodium tetracarboxylates are comprised of several catalyst families.  The most successful designs have been the *N*-sulfonylprolinates (**2a,b**)[27-29] and the *N*-pthalamido *tert*-leucine,

phenylalanine based catalysts (**3a**,**b**).[30,31] The conformational flexibility of these carboxylate ligands has led to some uncertainty in the mode of asymmetric induction in metal carbene reactions; reactions models constructed of them assume $D_2$ symmetry.[28,32] The carboxylate ligands are more electron withdrawing than the carboxamidate ligands, resulting in an electron deficient dirhodium core.[28,33] Carboxylate ligated dirhodium catalysts are capable of forming metal carbenes with diazoacetates which are unreactive towards most other common transition metal catalysts (i.e., dirhodium tetracarboxamidate and some copper catalysts).[34]

**Figure 1.2** Asymmetric carboxylate ligated dirhodium catalysts.



R = $p$-$^t$BuC$_6$H$_4$        Rh$_2$($S$-TBSP)$_4$    (**2a**)
R = $p$-(C$_{12}$H$_{25}$)C$_6$H$_4$    Rh$_2$($S$-DOSP)$_4$    (**2b**)



R = Bn      Rh$_2$($S$-PTPA)$_4$    (**3a**)
R = $t$-Bu    Rh$_2$($S$-PTTL)$_4$    (**3b**)
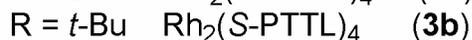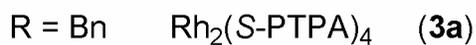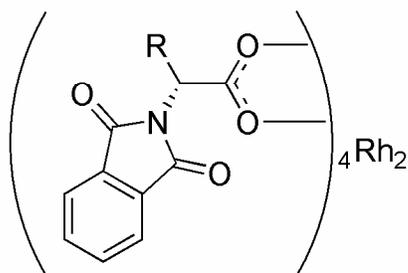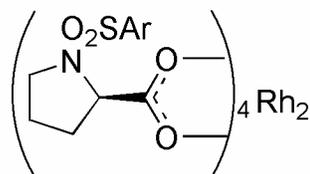
**Carboxamidate Ligated Dirhodium Catalysts.** Carboxamidate ligated dirhodium catalysts have provided excellent enantioselectivities in [2+1] cycloaddition reactions, C-H insertion reactions, and ylide processes. The carboxamidate ligands are comprised of a bridging lactam with an adjacent ester as the stereodirecting group. Modifications of the lactam ring have given rise to four classes of carboxamidate ligands: pyrrolidinate (**4**),[35] oxazolidinate (**5**),[36] immidazolidinate (**6a,b**),[37] and azetidinate (**7a-e**).[38] Early studies in

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carboxamidate ligand design established the use of esters as the optimal stereodirecting attachment; the use of aryl or alkyl groups led to significant losses in enantioselectivity.[35,39]

**Figure 1.3.** Carboxamidate ligated dirhodium catalysts.



Rh$_2$(*S*-MEPY)$_4$ (**4**)        Rh$_2$(*S*-MEOX)$_4$ (**5**)

R=CH$_2$CH$_2$Ph  Rh$_2$(*S*-MPPIM)$_4$  (**6a**)
R=C$_6$H$_4$-*t*Bu   Rh$_2$(*S*-TBOIM)$_4$  (**6b**)

| R=Me | Rh$_2$(*S*-MEAZ)$_4$ | (**7a**) |
| R=*i*-Bu | Rh$_2$(*S*-IBAZ)$_4$ | (**7b**) |
| R=*l*-menthyl | Rh$_2$(*S*,*S*-MenthAZ)$_4$ | (**7c**) |
| R=*d*-menthyl | Rh$_2$(*S*,*R*-MenthAZ)$_4$ | (**7d**) |

The azetidinate ligated catalysts (**7a-d**)[40-42] provide a more reactive dirhodium catalyst than other carboxamidate ligand structures.[33,41] The azetidinone based catalysts are the most reactive carboxamidate ligated dirhodium catalysts toward diazo compounds and are capable of reacting with

diazoacetates that are stable toward pyrrolidinate, oxazolidinate, and immidazolidinate ligated catalysts.[41]

## Diazo Compounds

**Physical Properties of Diazo Compounds.** Metal stabilized carbenes are most frequently generated by the reaction of transition metal catalysts with diazocarbonyl compounds.[1] The diazo functionality is often regarded with trepidation by chemists due to perceptions of the risk of explosion upon thermal or shock induced decomposition of the diazo moiety. Many of these concerns arise from accumulated data for the instability of diazoalkanes; however the presence of an electron withdrawing functionality adjacent to the diazo moiety often provides considerable stabilization to the diazo functionality. Diazo compounds utilized in modern catalytic processes are often substituted with at least one electron withdrawing group. Carbonyl, phosphonic ester, and silyl compounds have all been used to stabilize the diazo functionality.

The physical properties of ethyl diazoacetate (**8**) illustrate the stability of diazo compounds possessing an electron withdrawing group adjacent to the diazo functionality.[1] Ethyl diazoacetate (**8**) is stable to protonic decomposition in glacial acetic acid, can pass through a GC column at temperatures below 120 °C, and may be purified by distillation at atmospheric pressure (bp 140-141 °C).[1] In mesitylene at 100 °C, the half life of **8** is 109 h.[1] In contrast, the thermal decomposition of 2-diazopropane (**9**) has a half-life of approximately 3 h in diethyl ether at 0 °C.[1] As evidenced by the extensive use of $\alpha$-diazocarbonyl

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compounds in synthesis, simple precautions such as the use of well ventilated fume hoods and avoidance of high temperatures are sufficient to ensure the safe handling and use of diazo compounds substituted by electron withdrawing groups. All diazo compounds described throughout the research that is the subject of this dissertation will be α-diazocarbonyl compounds.

**Figure 1.4**. Stability of diazoacetates versus diazoalkanes.

$$H \quad CO_2Et \qquad Me \quad Me$$
$$N_2 \qquad \qquad N_2$$

**8**             **9**

$t_{1/2} = 109$ h, $100\ ^{o}C$       $t_{1/2} = 3$ h, $0\ ^{o}C$
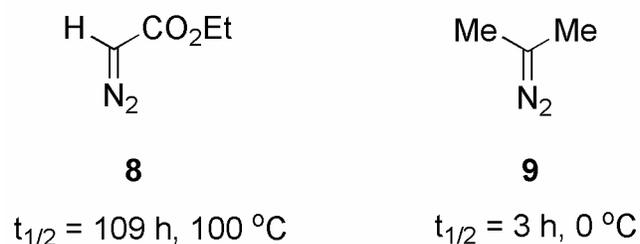
Most diazocarbonyl compounds (and the metal carbenes formed from them) may be classified according to the electron donating/accepting characteristics of their substituents: acceptor substituted, acceptor/acceptor substituted, and donor/acceptor substituted.[11] This classification scheme encompasses diazocarbonyl compounds used in catalytic processes and has been found to be useful in describing the reactivity of the diazo compound and metal carbene (*vide infra*).[4,11]

**Figure 1.5.** Classification of diazo compounds.



acceptor

**8**

acceptor/acceptor

**9**

donor/acceptor

**10**

**11**
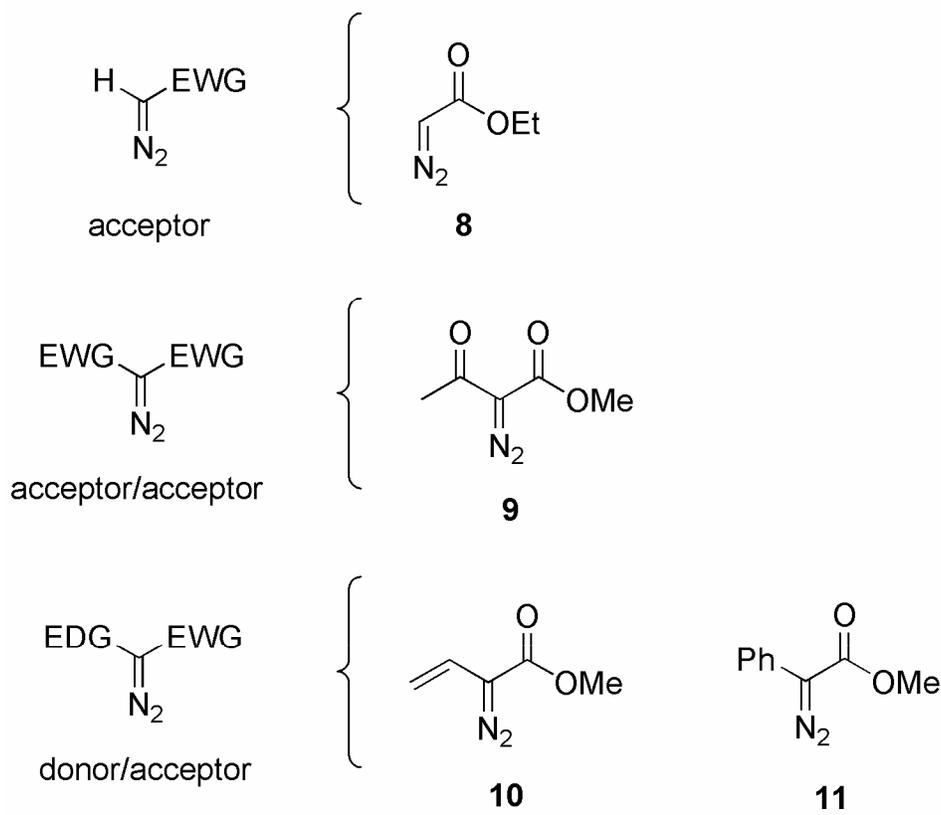
EWG = electron withdrawing group
EDG = electron donating group

**Preparation of Diazo Compounds.** Diazocarbonyl compounds are commonly used as precursors to metal carbenes in large part to their ease of preparation. One of the most frequently used methods of preparing diazocarbonyl compounds is the diazo transfer reaction.[1,43] Under standard conditions a carbonyl compound is treated with an amine base to form the corresponding enolate. This reacts with a diazo transfer agent (in almost all cases a sulfonyl azide) to provide the corresponding diazocarbonyl compound. Formation of the enolate almost always occurs with an amine base such as

triethylamine; stronger bases typically lead to substantially lowered yields of the diazocarbonyl product.[1]  This limits the diazo transfer methodology to substrates in which protons $\alpha$ to the carbonyl group are sufficiently acidic to undergo deprotonation by an amine base.

**Scheme 1.3**.
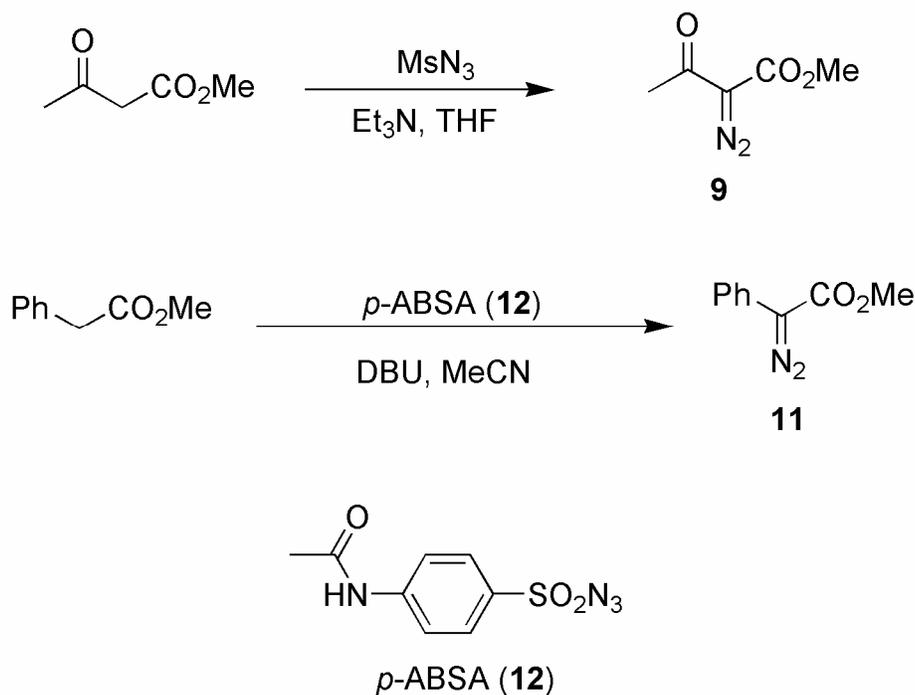


## Reactions of Donor/Acceptor Diazoacetates.

The study of the reactivity of metal carbenes generated from donor/acceptor diazoacetates has been a significant area of research in catalytic metal carbene chemistry over the past several years.[4,12-14]  Donor/acceptor substituted diazo compounds are largely comprised of vinyldiazoacetates and aryldiazoacetates (i.e., **10**, **11**).  In a number of cases, the reactivity observed

with metal carbenes generated from vinyl and aryldiazoacetates has differed substantially from that observed with the more traditionally utilized acceptor and acceptor/acceptor substituted diazo compounds. As will be described, the unique reactivities and selectivities observed with metal carbenes generated from donor/acceptor substituted diazo compounds have facilitated the efficient construction of complex molecular architectures.

Donor/acceptor substituted diazo compounds are more stable than acceptor substituted diazo compounds toward reaction with transition metal catalysts.[28,34] Consequently, donor/acceptor substituted diazo compounds are typically used in conjunction with the most reactive dirhodium catalysts, such as the previously described carboxylate or azetidinate ligated dirhodium catalysts (**2**, **3**, **7**).[28,41] The kinetic activity of the catalyst takes on particular importance with the use of vinyldiazoacetates. Although vinyldiazoacetates do not extrude dinitrogen as readily as acceptor substituted diazo compounds, they are in fact less stable than other diazoacetates. Vinyldiazoacetates readily undergo a [1,5]-cyclization to yield pyrazoles, as is illustrated by the cyclization of **13** to **14**.[34,44] This cyclization is often competitive with catalyst promoted extrusion of dinitrogen and metal-carbene formation.[34]

**Scheme 1.4**.



13

14

quantitative
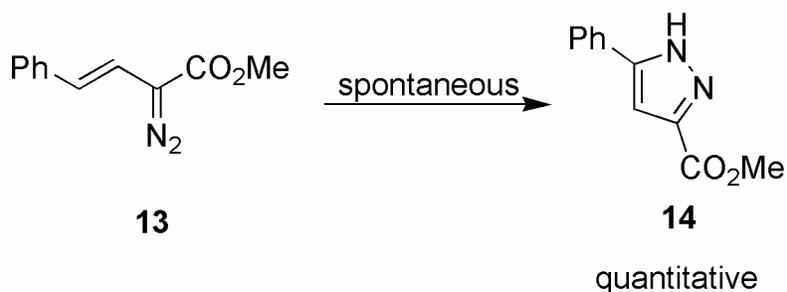
Vinyldiazoacetates used throughout the course of our studies[45] begin to cyclize to pyrazoles within several hours at room temperature. In my experience, chromatographic purification of vinyldiazoacetates is required immediately prior to use. Although the association constants of pyrazoles to dirhodium catalysts have not been determined, pyrazoles possesses a basic nitrogen which is expected to coordinate to dirhodium catalysts, substantially reducing catalyst efficiency. Typically, reactions of vinyldiazoacetates are performed with the reactive dirhodium tetracarboxylate catalysts (in particular **2a,b**), though the azetidinate ligated dirhodium catalysts (**7a-d**) are also sufficiently active to react with vinyldiazoacetates.

**Intermolecular cyclopropanation reactions of carbenes.** Cyclopropanes are frequently found as components of biologically active compounds; consequently, the development of stereoselective routes to functionalized cyclopropanes remains an active area of research.[7,8,46] Several methodologies may be used to construct a wide range of cyclopropanes, one of the more popular being the cyclopropanation of olefins by metal stabilized

carbenes.[7,8]  Asymmetric cyclopropanation reactions comprise some of the earliest examples of asymmetric catalysis; initial homogenous asymmetric catalysts for cyclopropanation reactions were copper based.[47-49]  More recently, dirhodium complexes have also been reported to catalyze the cyclopropanation of olefins with high stereoselectivities.[5,28]  Cyclopropanation reactions are arguably the best studied metal carbene transformations, and a wide range of asymmetric catalysts have enjoyed success in this area, including copper, dirhodium, ruthenium, and cobalt based catalysts.[1]

The cyclopropanation of donor/acceptor substituted diazo compounds have been reported to proceed with high stereoselectivities using dirhodium catalysts (Scheme 1.5).[4,28]  A study of the cyclopropanation of styrene with **11** demonstrates the applicability of different dirhodium catalyst systems to donor/acceptor metal-carbene cyclopropanations.[50]  Common dirhodium carboxamidate catalysts such as $Rh_2(MEPY)_4$ (**4**) and $Rh_2(MEOX)_4$ (**5**) provide poor enantioselectivities.  An increase in enantiomeric excess of **15** was observed upon the use of the carboxamidate ligated catalyst $Rh_2(S\text{-TBOIM})_4$ (**6b**), providing **15** with 77% ee when the reaction was conducted in dichlormethane.  The use of pentanes as the reaction solvent did not affect the enantioselectivitivity to an appreciable degree.  A pronounced solvent effect is observed with the prolinate derived dirhodium catalyst $Rh_2(S\text{-TBSP})_4$ (**2a**), pentanes proves to be the optimal solvent for the enantioselective cyclopropanation, providing 85% ee of **15**.  The asymmetric induction provided by *N*-sulfonylprolinate ligated dirhodium catalysts has been demonstrated on

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several occasions to have a substantial dependence on solvent, providing optimal levels of enantioselectivity in nonpolar hydrocarbons.[28]

**Scheme 1.5**.
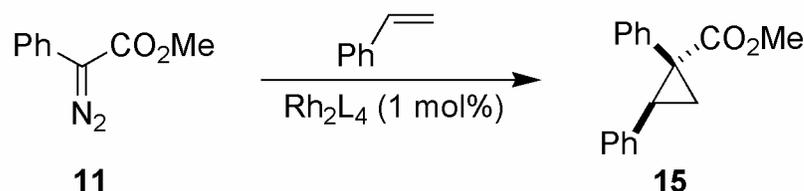
| Rh$_2$L$_4$ | solvent | yield | %ee |
|---|---|---|---|
| **4** Rh$_2$(S-MEPY)$_4$ | CH$_2$Cl$_2$ | 27 | 49 |
| **5** Rh$_2$(S-MEOX)$_4$ | CH$_2$Cl$_2$ | 57 | 41 |
| **6b** Rh$_2$(S-TBOIM)$_4$ | CH$_2$Cl$_2$ | 63 | 77 |
| **6b** Rh$_2$(S-TBOIM)$_4$ | pentanes | 69 | 75 |
| **3a** Rh$_2$(S-PTPA)$_4$ | CH$_2$Cl$_2$ | 95 | 34 |
| **2a** Rh$_2$(S-TBSP)$_4$ | CH$_2$Cl$_2$ | 77 | 61 |
| **2a** Rh$_2$(S-TBSP)$_4$ | pentanes | 73 | 85 |

The observation that nonpolar hydrocarbons such as pentanes were optimal solvents for asymmetric metal carbene reactions catalyzed by **2a** led to further development of the N-sulfonylprolinate ligand to provide prolinate based catalysts which were readily soluble in nonpolar solvents.[27,28] Incorporation of a dodecyl chain upon the N-sulfonylaryl ligand [Rh$_2$(S-DOSP)$_4$ (**2b**)] increases the catalyst solubility in nonpolar solvents. As will be demonstrated, Rh$_2$(S-DOSP)$_4$ (**2b**) has proven to be a highly effective catalyst for reactions of donor/acceptor substituted diazo compounds; it is the most commonly utilized catalyst in asymmetric reactions of donor/acceptor diazo compounds, providing excellent levels of stereoselectivity over a range of processes.[4]

Davies has applied the cyclopropanation of vinyldiazoacetates toward the synthesis of cyclopropane analogs of phenylalanine (**18a,b**).[27] Cyclopropane amino acids have seen extensive use in peptidomimetics, however their uses are often limited by complex asymmetric syntheses.[51] The cyclopropanation of styrene by vinyldiazoacetate **13** provides cyclopropane **16** in excellent yield and stereoselectivity. Oxidative cleavage of the olefin provides the carboxylic acid **17**, which has been used as a common intermediate in the synthesis of both diastereomers of the cyclopropane phenylalanine analog **18a,b**.

**Scheme 1.6**.



**13**       $Ph$    $CO_2Me$   $N_2$

$\xrightarrow[\text{pentanes}]{Rh_2(S\text{-}DOSP)_4 \text{ (2b)}}$

**16** (82%), 92% ee

$\xrightarrow[\text{2) NaIO}_4]{\text{1) RuCl}_3}$

**17** (72%)

**17** $\xrightarrow{\text{3 steps}}$ **18a** (43%)

**17** $\xrightarrow{\text{5 steps}}$ **18b** (48%)
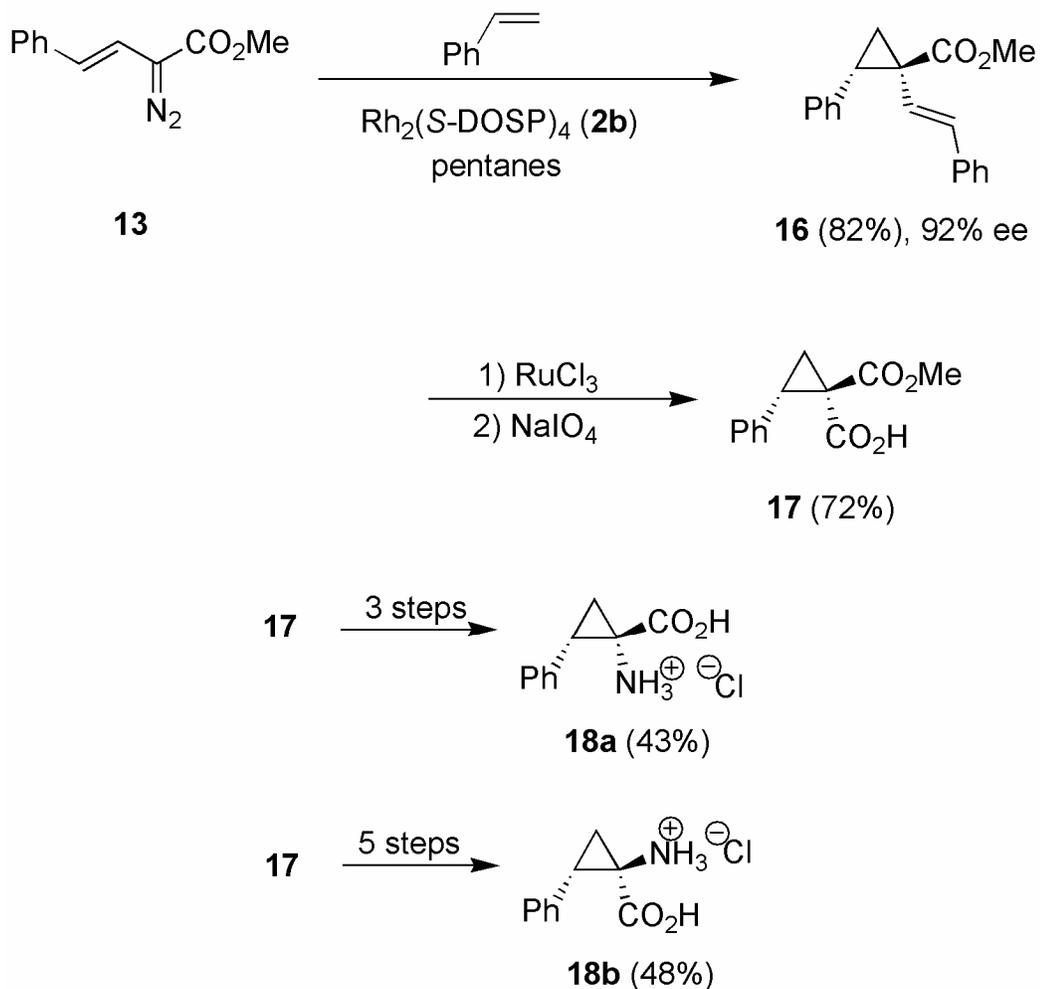
Corey has also utilized the previously described cyclopropanation in an elegant and concise stereoselective formal synthesis of sertraline (**22**), the active component of the antidepressant Zoloft®.[52]  Oxidative cleavage of the olefin and esterification of the resulting carboxylic acid provide the malonic ester **20**, which upon treatment with an arylcuprate, decarboxylation and acid promoted cyclization, yields **21**.  A stereoselective reductive amination of **21** provides sertraline (**22**).[52]

**Scheme 1.7.**
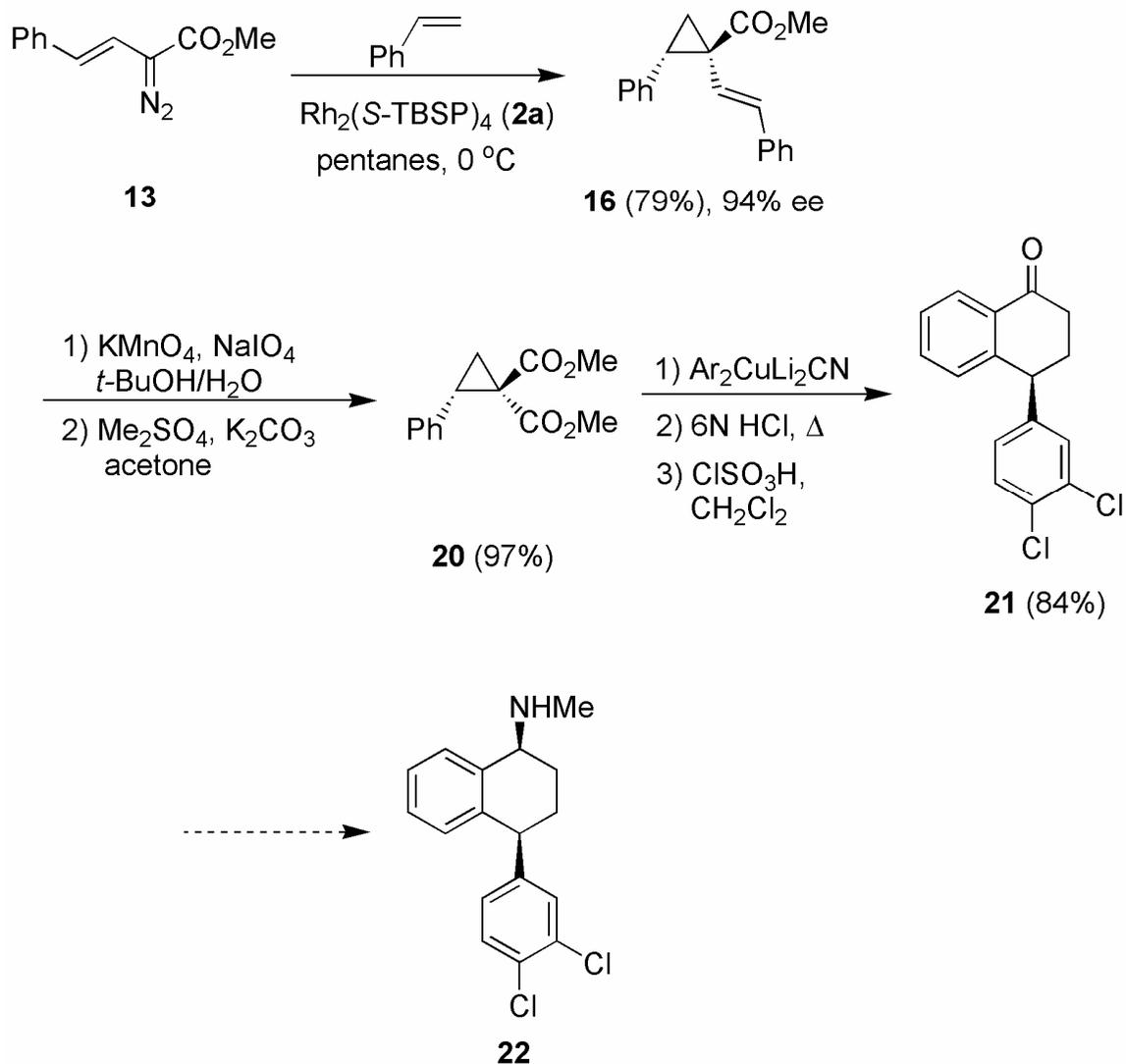


**Intermolecular C—H insertion reactions of carbenes.** The selective functionalization of unactivated carbon-hydrogen (C-H) bonds is a significant challenge to synthetic organic chemists.[53] The development of effective means of doing so possesses obvious advantages, providing rapid access to complex materials from simple hydrocarbons. The insertion of dirhodium-stabilized

carbenes into C—H bonds generally occurs with high regio- and stereoselectivity.[11] For many years, synthetically practical examples of C—H insertion reactions were limited to intramolecular variants.[11] Optically active dirhodium catalysts have provided high enantioselectivities in intramolecular C—H insertion reactions of diazoacetates (i.e., **23**).[11] Previous research within this group has described the asymmetric synthesis of several lignan lactones using this methodology.[16,54]

**Scheme 1.8**.
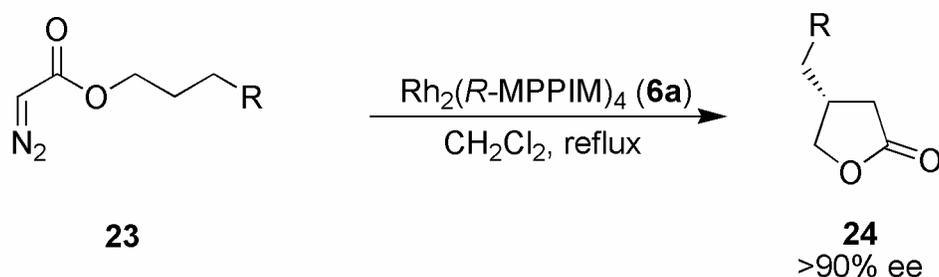


Initial research in C—H insertion reactions focused upon the intramolecular C—H insertion reactions of acceptor and acceptor/acceptor substituted diazo compounds. The dimerization of acceptor substituted diazo compounds (as previously described) has been implicated as a competitive reaction pathway to intermolecular C—H insertion reactions of acceptor substituted diazo compounds.[11] In some cases, slow addition of the diazo compound to a stirred solution of catalyst and C—H insertion substrate sufficiently supresses dimerization of the diazo compound to allow intermolecular C—H insertion to occur. However, in these instances poor selectivities have

been obtained for the insertion of acceptor substituted metal carbenes into C—H bonds (as exhibited by the reaction of **25**, **28**).[11,55]

**Scheme 1.9**.
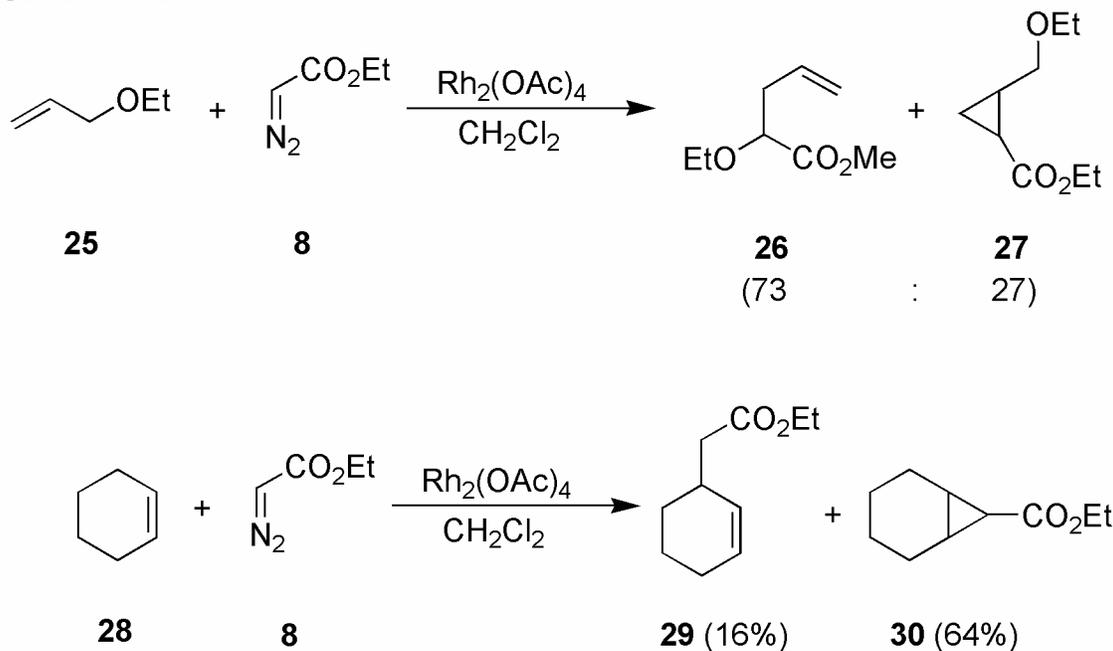


Carbon-hydrogen bonds are activated toward insertion by adjacent functionalities which stabilize the developing positive charge during insertion of the metal carbene.[56-58] Early studies of the regioselectivity of C—H insertion noted a general trend of reactivity toward metal carbene insertion to be methine>methylene>methyl C—H bonds.[57,59] Allylic and benzylic C—H bonds are highly activated toward insertion by metal-carbenes,[21,60-62] as are C—H bonds adjacent to heteroatoms.[21,63] However, acceptor substituted metal-carbenes *do not* readily undergo intermolecular insertion into C—H bonds activated by olefins or heteroatoms, but preferentially react with these functionalities in cyclopropanation or ylide forming reactions.[55] Acceptor

substituted metal-carbenes are often highly reactive toward the activating functionalities, rather than toward the adjacent C—H bonds. No C—H insertion products were observed in the reaction of allyl ether **25** with **8** (Scheme 1.9); the dominant reaction pathway was ylide formation and a rearrangement leading to **26**.[55] Likewise, cyclohexene provides cyclopropane **30** as the dominant product, the C—H insertion product **29** is obtained in 16% yield.[61,64] In the examples described, intermolecular C—H insertion of the acceptor substituted diazocompound **8** shows greater reactivity towards olefins and ethereal oxygen than the C—H bonds adjacent to these functionalities.

In the limited examples reported to date, acceptor/acceptor substituted metal carbenes provide intermolecular C—H insertion reactions with superior yields than acceptor substituted metal carbenes. The metal carbene generated from **9** undergoes insertion into cyclohexane C—H bonds using the $Rh_2(S\text{-}DOSP)_4$ (**2b**) catalyst, however the enantiomeric excess of **31** is negligible.[64] In the studies that have been reported, superior chemoselectivities for C—H insertion are observed with acceptor/acceptor substituted metal carbenes as compared to acceptor substituted metal carbenes. The reaction of **32** with **28** favors the formal[20] C—H insertion product **33** over cyclopropane **34**, though significant amounts of **34** are observed.[61] The limited reports of intramolecular C—H insertion of acceptor/acceptor substituted metal carbenes have indicated that these metal carbene species have appreciably superior efficiencies in intermolecular C—H insertion than acceptor substituted metal carbenes. However, chemoselectivity does remain an issue, and the only reported attempt

to perform an asymmetric intermolecular C—H insertion reaction resulted in a negligible degree of enantioselectivity for C—H insertion product **31**.[64] These issues have discouraged further investigations of acceptor/acceptor substituted metal carbenes in intermolecular C—H insertion reactions.

**Scheme 1.10**.



**9**

**31** (51%) 3% ee

**32**

**33**

**34**

(63%, 66 : 34 )
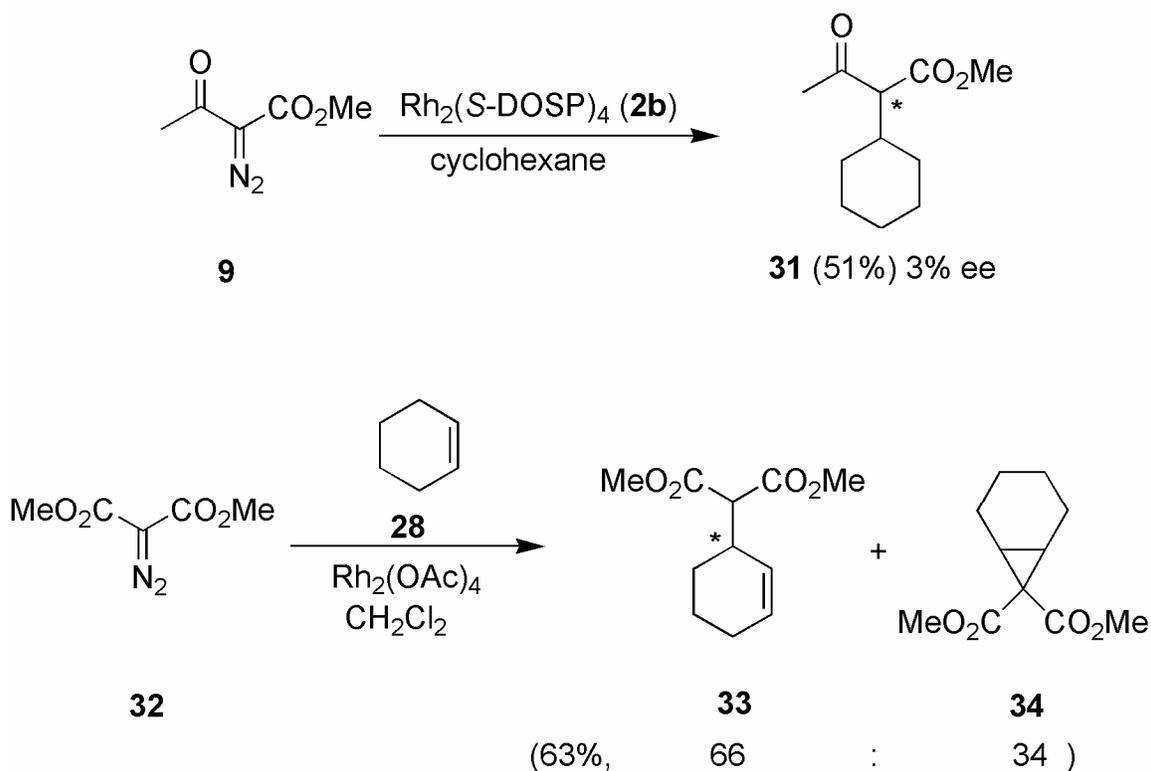
Donor/acceptor substituted metal carbenes, in contrast to acceptor substituted and acceptor/acceptor substituted metal carbenes, have been demonstrated to be highly effective reagents in asymmetric intermolecular C—H insertion reactions.[12-14,65] Over the last several years, numerous reports have described the intermolecular C—H insertion reactions of aryl- and vinyldiazoacetates.[21,64,66-69] Unlike the acceptor substituted diazo compounds,

metal carbenes derived from aryl- and vinyldiazoacetates are capable of undergoing high yielding insertion reactions into C—H bonds of substrates possessing other functionalities which may be reactive toward metal carbenes (olefins and heteroatoms). As will be described, examples of donor/acceptor substituted metal carbene insertions into C—H bonds have been reported with a wide variety of substrates and have found applications in the stereoselective syntheses of natural products and pharmaceutical agents.[15,67,69,70]

Donor/acceptor substituted metal carbenes undergo insertion into unactivated alkyl C—H bonds to provide C-H insertion products in good yield. Addition of vinyldiazoacetate **13** to a solution of Rh$_2$(DOSP)$_4$ (**2b**) in cyclohexane provides the C—H insertion product **35** in 50% isolated yield and with 83% ee.[64]

**Scheme 1.11**.



**13**                                        **35** (50%) 83% ee
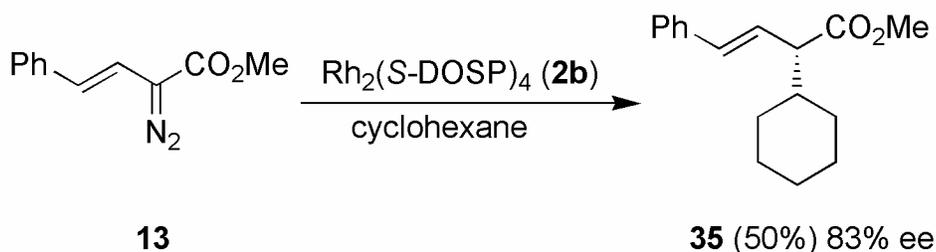
Benzylic C—H bonds are activated for metal carbene insertion, the reaction of **36** with vinyldiazoacetate **37** provides **38** with excellent enantiomeric excesses using Rh$_2$(R-DOSP)$_4$ (**2b**) catalyst.[70] In two further steps, **38** provides the naturally occurring phenol (+)-imperanene (**39**). The same insertion reaction,

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however using Rh$_2$(*S*-DOSP)$_4$ (**2b**), provides *ent*-**38**, which may be used to prepare (−)-conidendrin (**39**) in only three further steps.

**Scheme 1.12**.



**37**

**36**
Rh$_2$(*R*-DOSP)$_4$ (**2b**)
2,2-DMB, 50°C

**38** (43%) 91% ee

2 steps

**39** (+)-imperanene

**Scheme 1.13**.



**37**

**36**

Rh$_2$(S-DOSP)$_4$ (**2b**)
2,2-DMB, 50°C

*ent*-**38** (44%) 92% ee

3 steps

**39** (-)-conidendrin
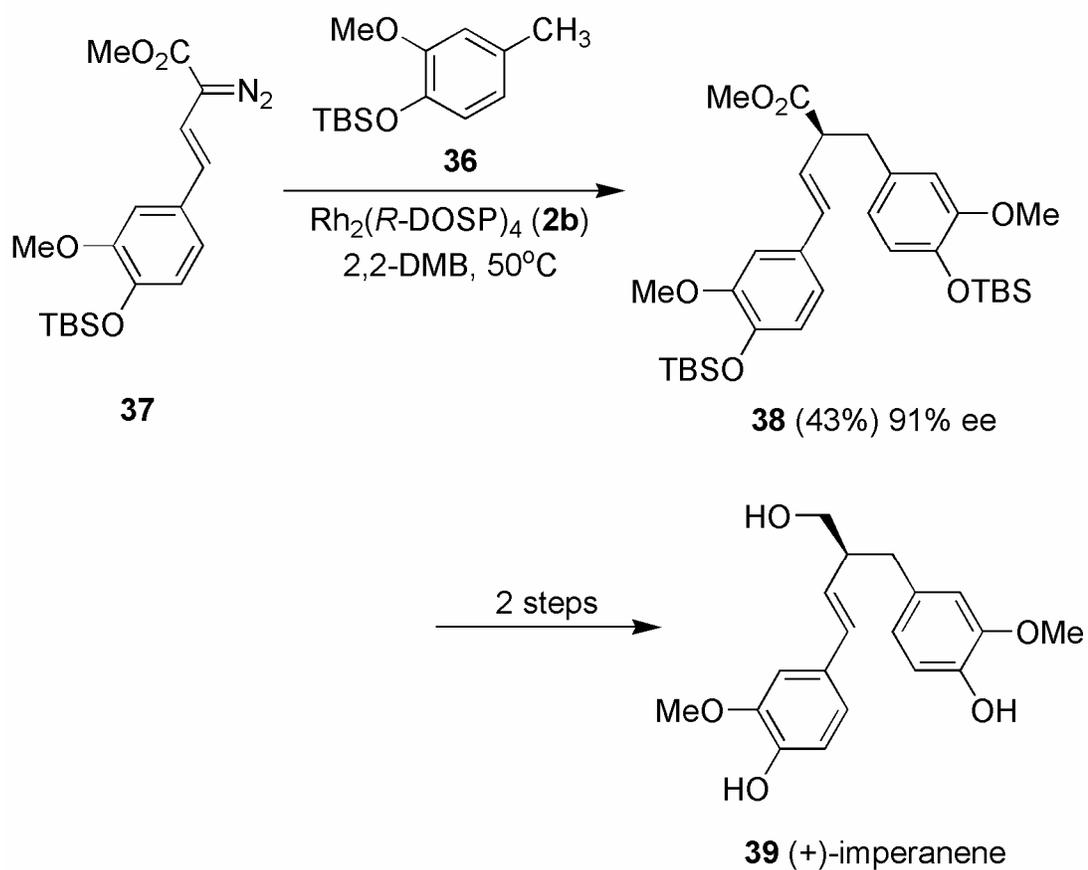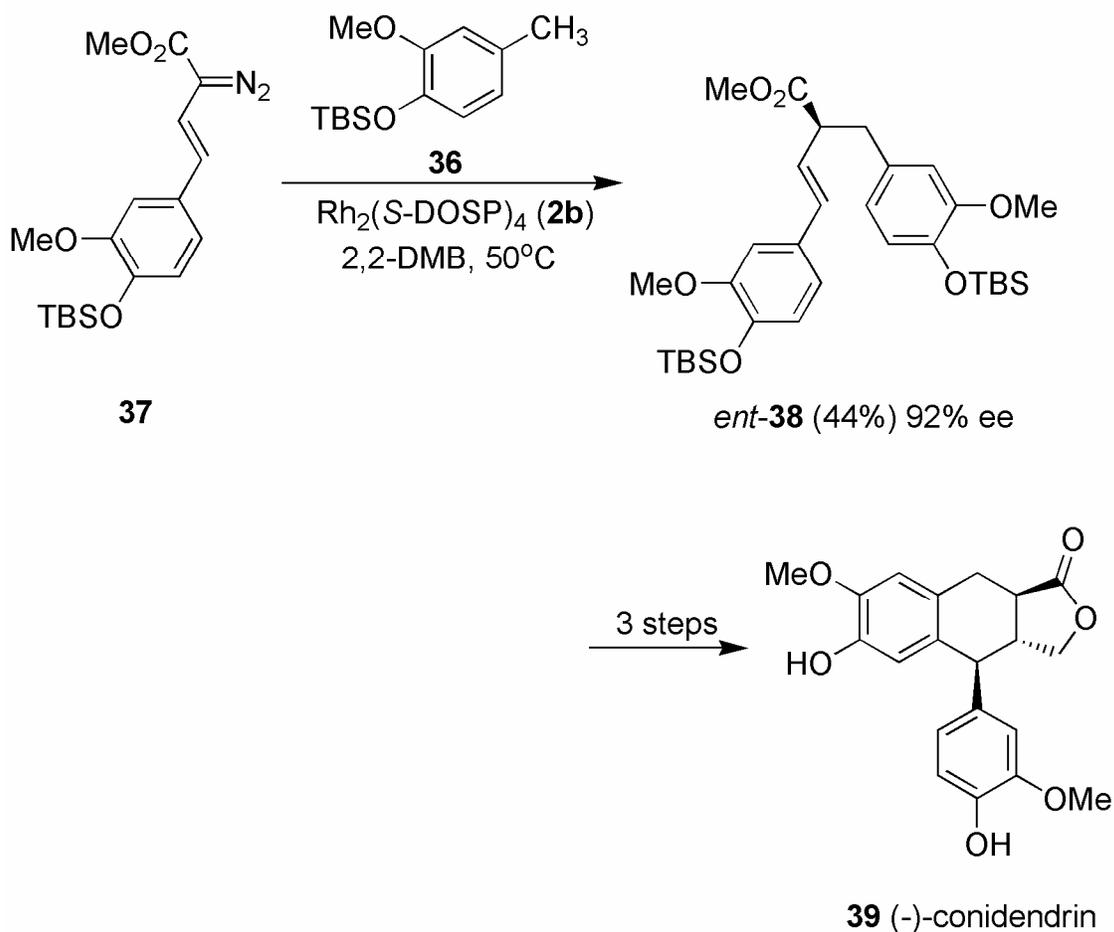
Aryldiazoacetates and vinyldiazoacetates have been shown to readily undergo insertion reactions $\alpha$ to heteroatoms. The Rh$_2$(S-DOSP)$_4$ (**2b**) catalyzed reaction of **11** with piperidine **40** provides a concise preparation of **41a**, the active component of Ritalin®.[68] An enhancement in the stereoselectivity of this reaction was reported by Winkler using the catalyst Rh$_2$(S-MEPY)$_4$ (**4**);[69] this is a rare example of a dirhodium carboxamidate catalyst providing higher levels of enantioselectivity than Rh$_2$(S-DOSP)$_4$ (**2b**) in the reaction of a donor/acceptor substituted diazo compound.

**Scheme 1.14.**
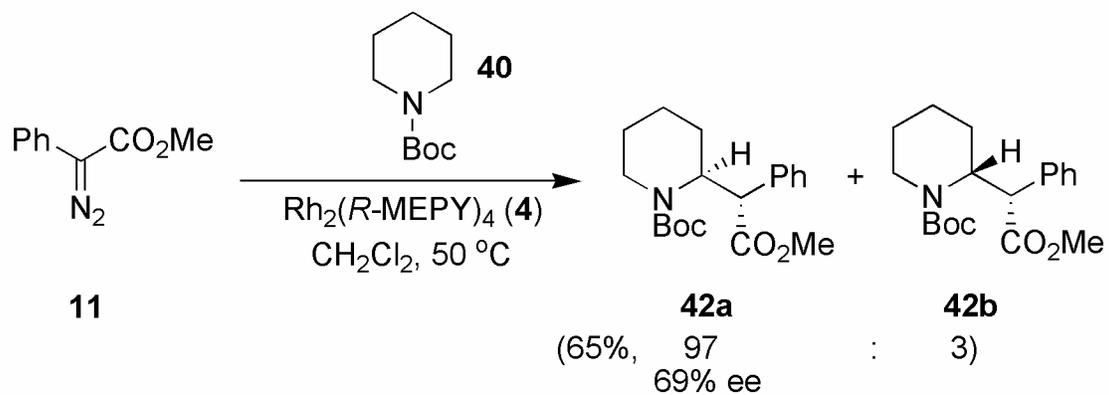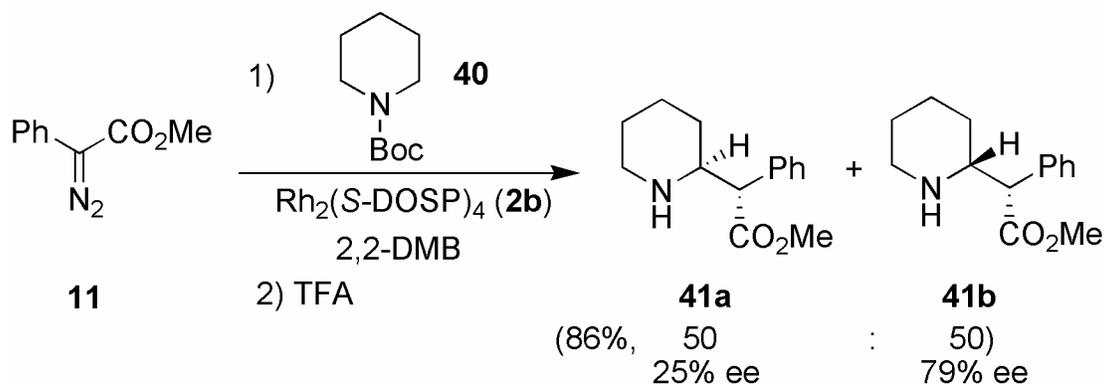


The $Rh_2(DOSP)_4$ (**2b**) catalyzed insertion reaction of vinyldiazoacetate **13** with tetraethoxysilane provides the *syn*-aldol type product **43** with good stereoselectivity.[71]

**Scheme 1.15.**



**13**

Si(OEt)$_4$

Rh$_2$(*R*-DOSP)$_4$ (**2b**)

2,2-DMB

**43** (32%)
80% de, 97% ee
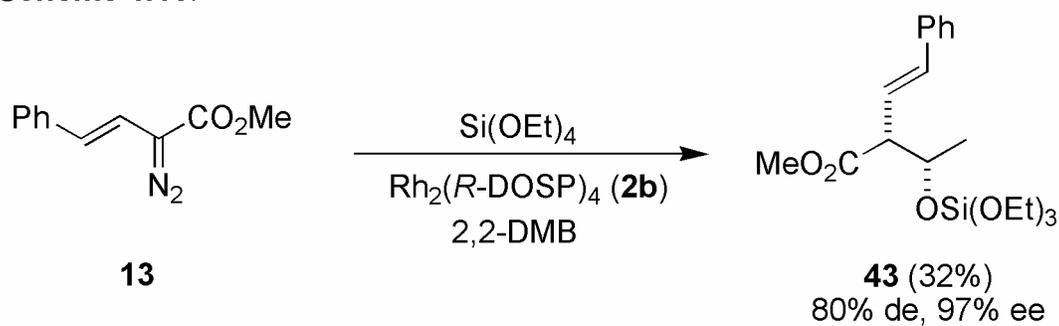
Insertion into allylic position often occurs readily with vinyldiazoacetates, however the products that are observed do not correspond to those expected from direct C—H insertion.[15,67,72]  The reaction of vinyldiazoacetate **13** with 1,3-cyclohexadiene (**44**) provides not the expected product **44**, but instead **46**.[67]

**Scheme 1.16.**



**13**

**44**

Rh$_2$(*S*-DOSP)$_4$ (**2b**)

hexanes

**45** (0%)        **46** (63%) 98% ee
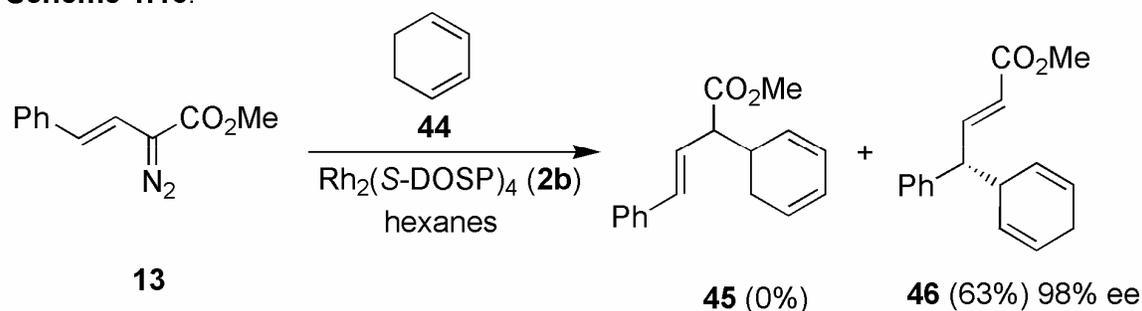
The most readily apparent mechanism for the formation of **46** would appear to be the expected C—H insertion to yield **45**, followed by a Cope rearrangement to **46**, with **46** being the thermodynamically favoured product.[67,72] This hypothesis was shown not to be valid, however, as heating **46** in refluxing hexane promoted the Cope rearrangement to yield **45**.[67]  As **45** is, in fact, the thermodynamic product of the Cope rearrangement, **45** would have been

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recovered under the C—H insertion reaction conditions. This led to the proposal that the reaction of diene **44** with the metal carbene of **13** proceeds through an concomitant C—H insertion/Cope rearrangement, as indicated by the proposed transition state **47**.[72]

**Figure 1.6**. Proposed C-H insertion/Cope rearrangement.



**47**
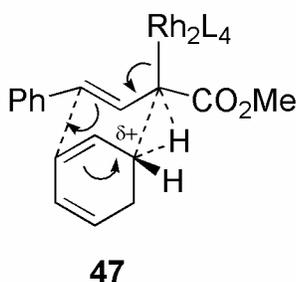
**Formation and Reactivity of Azomethine Ylides.** Our own work with donor/acceptor metal-carbene species came about during investigations in the formation of azomethine ylides *via* reaction of imines with metal carbenes.[45,73-75] Azomethine ylides are commonly used as intermediates in the synthesis of nitrogen containing heterocycles. Azomethine ylides are capable of undergoing intramolecular cyclization to form nitrogen heterocycles or acting as a 1,3-dipole in [3+2] cycloadditions (Scheme 1.17).[9,76] The reaction of metal carbenes with imines is a highly convergent means of generating azomethine ylides, imines and diazoacetates are easily prepared and a wide variety of ylides may be generated by the transition metal catalyzed reaction of diazoacetates to easily prepared imines.

**Scheme 1.17**.
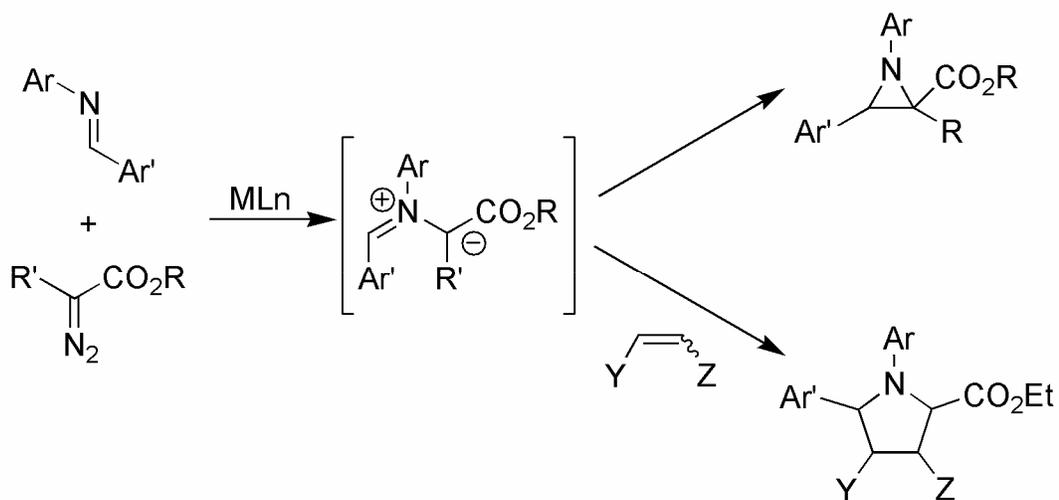


MLn = transition metal catalyst

Azomethine ylides generated from acceptor substituted versus donor/acceptor substituted metal carbenes have been shown to react along different reaction pathways.[45,73,77,78] As is demonstrated in the following examples, the azomethine ylides generated from the reaction of imines with acceptor substituted metal carbenes are prone to undergo [3+2] cycloaddition reactions,[77,78] while azomethine ylides generated from donor/acceptor substituted metal-carbenes instead proceed along intramolecular cyclization pathways.[45,73]

Recent reports from the laboratories of Che[78,79] and Scheidt[77] have described the efficient construction of pyrrolidine ring systems upon 1,3-dipolar cycloadditions of azomethine ylides. Using copper(I) triflate as a catalyst, Scheidt trapped azomethine ylides generated by the reaction of ethyl diazoacetate (**8**) (an acceptor substituted diazo compound) and benzylideneanilines with a series of dipolarophiles. As is demonstrated by the

formation of pyrrolidine **49**, the cycloaddition proceeded in good diastereoselectivity to provide 2,5-*trans* diastereomers exclusively. This stereoisomer is believed to arise from reaction of *trans*-azomethine ylide **48**. Studies by Che examined the use of a ruthenium-porphyrin catalyst under similar conditions, the reported stereoselectivities and yields of pyrrolidine products were not significantly different than those reported by Scheidt.[78,79] The catalyst used to form the metal carbene does not have a significant bearing on the reactivity of the resulting azomethine ylide, implying dissociation of the metal catalyst from the azomethine ylide prior to reaction of the ylide. No aziridine products resulting from intramolecular cyclization of the azomethine ylide prior to cycloadditon were reported by either Scheidt or Che.

**Scheme 1.18**.
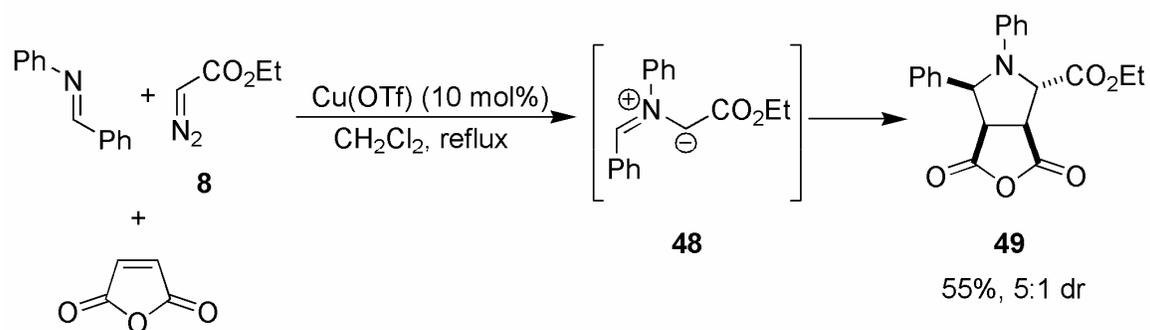


Jacobsen has reported the formation of aziridines **49a**,**b** arising from the reaction of the acceptor substituted diazo compound ethyl diazoacetate (**8**) and benzylideneanilines catalyzed by an asymmetric copper catalyst.[80] Yields were reported to be low, however, with typical isolated yields below 30%. Modest enantioselectivities were observed for the aziridine products, implying that the

reacting azomethine ylide species was associated with the catalyst. Aziridine formation by Lewis acid catalyzed reaction of imines and diazo compounds is well known (aza-Darzens reaction);[81-83] however, this process does not involve the formation of azomethine ylides. To date, the formation of aziridines from cyclization of azomethine ylides generated with acceptor substituted metal carbenes has not been demonstrated to provide synthetically useful yields.

**Scheme 1.19**.
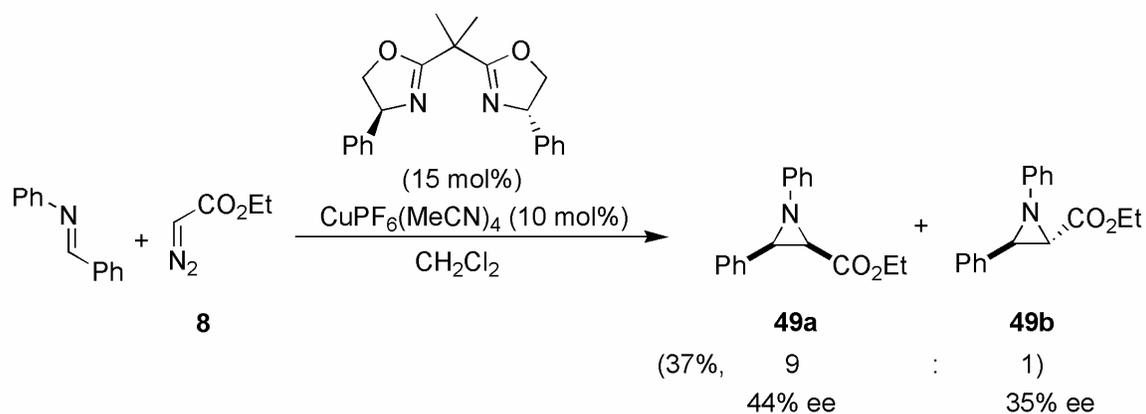


In recent years, our research group has become interested in the reactivity of donor/acceptor substituted diazo compounds with imines and the resulting azomethine ylides.[73-75] Using one molar equivalent of methyl phenyldiazoacetate (**11**) relative to the imine **50**, the aziridine **51** was obtained in 81% isolated yield, with *E*-**51** observed as the exclusive diastereomer. Presumably, the high level of diastereoselectivity arises from the preference for ylide structure **52b** *versus* **52a**, with steric interactions of the aryl rings disfavouring **52a**. Ring-closure of azomethine ylides is controlled by frontier molecular orbital interactions, the cyclization of **52b** occurs in a conrotatory fashion to yield *E*-**51**.[86-88]

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**Scheme 1.20**.



**50** Ar = *p*-NO$_2$C$_6$H$_4$     **11**     **51** (81%)



**52a**     **52b**
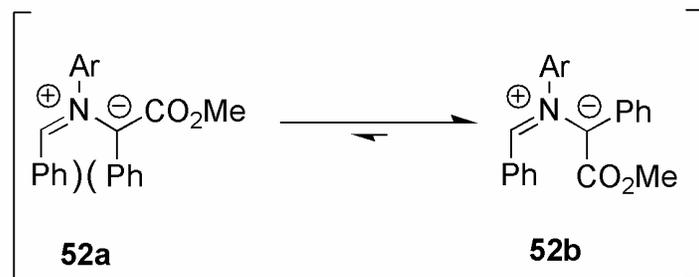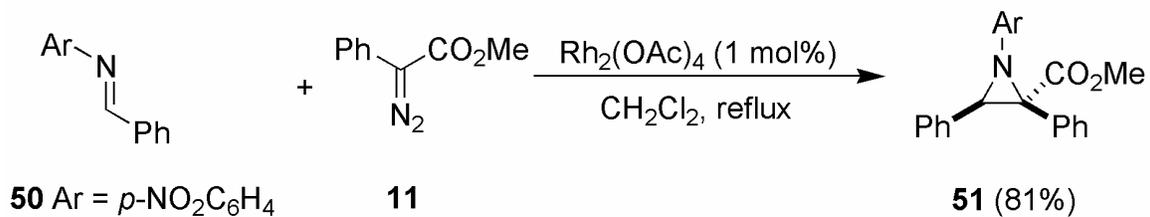
Further study of the reaction of imines with donor/acceptor diazoacetates led to the reaction of imines with vinyldiazoacetes.  Reaction of the metal carbene derived from vinyldiazoacetate **13** with imine **50** provides the azomethine ylide **53**, which undergoes [1,5] cyclization to provide dihydropyrrole **54**.[85]  Cyclization of the azomethine ylide  **53** results in formation of **54** with excellent diastereoselectivity (>95%).

**Scheme 1.21**.



(1 equiv)        (1 equiv)

**50**              **13**

Ar = p-NO$_2$C$_6$H$_4$

**53**

**54** (66%)    +   **55a,b**
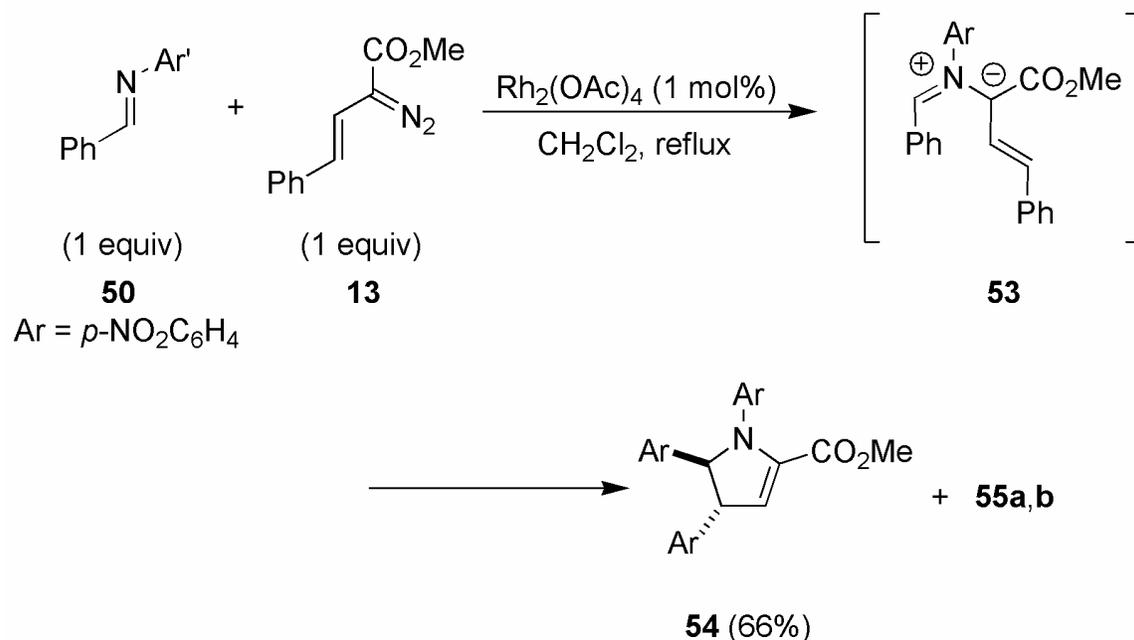
While studying the formation of **54**, an unexpected byproduct was isolated. Mass and NMR spectroscopies demonstrated that this byproduct was in fact two isomeric compounds comprised of the benzylidineaniline and two units of the metal-carbene derived from **13**. Previous literature describing the reactivity of azomethine ylide and metal carbene chemistry did not indicate what such a product might be; and the structure of this byproduct was not determined until an X-ray crystal structure was obtained of one of the byproducts, which identified it as the bicyclic pyrrolidine **55a**.[45] NMR spectroscopy determined that the second compound was the diastereomer **55b**.

Excited by the unprecedented reaction of two carbene units with an imine to form the stereochemically complex heterocycles **55a** and **55b**, attempts were undertaken to optimize this reaction pathway, the mechanism of which was unknown at the time. The molar ratio of vinyldiazoacetate **13** to imine was

increased from 1:1 to 2:1, and a variety of benzylideneanilines was used. The reaction of vinyldiazoacetate **13** with benzylideneanilines which did not posses an electron deficient *N*-aryl group provided bicyclic pyrrolidines **56-58** to the exclusion of dihydropyrrole.

**Scheme 1.22**.
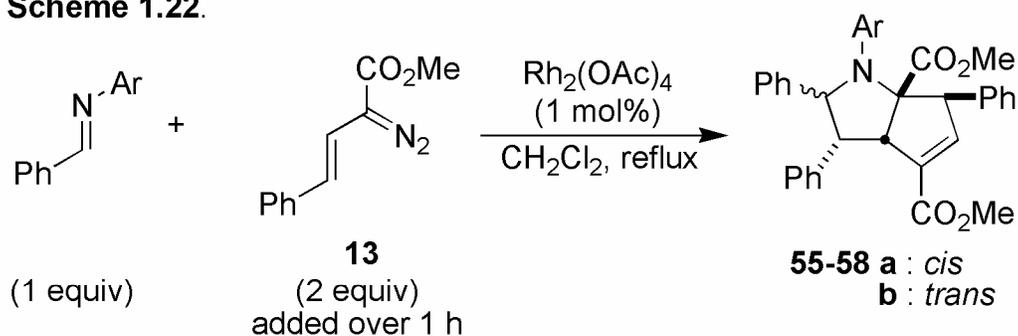


| Ar | Product | a:b | Yield (%) |
|---|---|---|---|
| *p*-NO$_2$C$_6$H$_4$ | **58** | 54:56 | 18 |
| Ph | **59** | 54:46 | 70 |
| *p*-MeOC$_6$H$_4$ | **60** | 61:39 | 38 |

## II.    RESULTS AND DISCUSSION


The development of methods for constructing complex products by a reaction between multiple components to form several carbon-carbon bonds in a single operation has been the subject of considerable research.[10,89-97]  The reactions of ylides have been a fruitful area of investigation in this regard.  The previously discussed dipolar cycloaddition reactions are a well studied and effective methods of rapidly preparing stereochemically complex heterocycles.[10,77-79,98-102]  The previously described study of the reaction of benzylideneanilines and vinyldiazoacetate **13** resulted in the discovery of an three component reaction which forms stereochemically complex bicyclic pyrrolidines.  An understanding of the mechanism for the formation of bicyclic pyrrolidines may allow the further development of novel strategies utilizing azomethine ylides in the concise preparation of complex heterocycles, as such this became the focus of our study.

The mechanism by which bicyclic pyrrolidines form was a subject of considerable interest to us upon elucidation of the structure **55a**.[45]  An early hypothesis was that dihydropyrrole was formed as the initial product: reaction of the dihydropyrrole with a second vinylcarbene provided bicyclic pyrrolidine **55b**.  However, the hypothesis failed to explain the reduced stereoselectivity observed for bicyclic pyrrolidine formation relative to dihydropyrrole.

**Scheme 1.23**.



**54** Ar = *p*-NO$_2$C$_6$H$_4$
**59** Ar = Ph
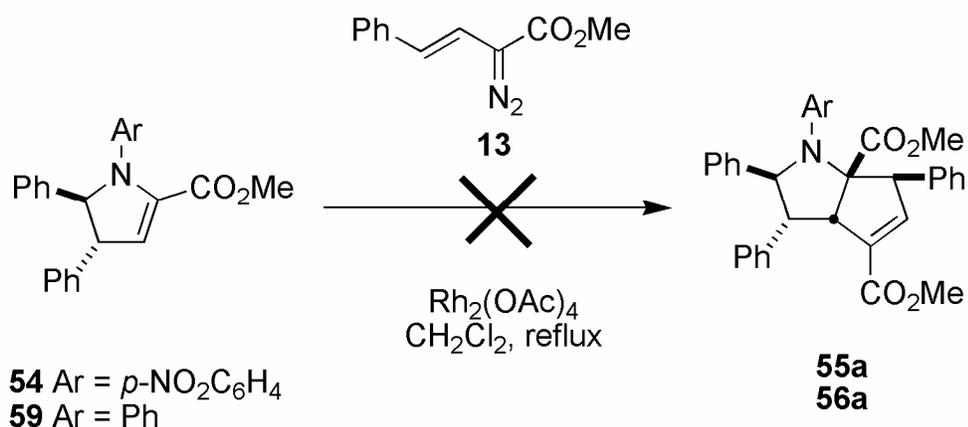
Despite these misgivings, the mechanistic hypothesis in which dihydropyrrole was an intermediate in the formation of bicyclic pyrrolidines was tested by subjecting dihydropyrroles **54**, and **59** to the standard reaction conditions used for the preparation of **55a**, **56a** (Scheme 1.23). Solutions of **54** or **59** and Rh$_2$(OAc)$_4$ were refluxed in dichloromethane, vinyldiazoacetate **13** was added in a solution of dichloromethane over 1 hour. Analysis of the reaction mixture by $^1$H NMR showed none of the corresponding bicyclic pyrrolidines to be present, demonstrating that dihydropyrroles are not intermediates in the formation of bicyclic pyrrolidines.

With our initial hypothesis refuted, we considered the possibility that the azomethine ylide **53** possessed a sufficient lifetime to react with the metal-carbene generated from **13**. According to this mechanism, the azomethine ylide **53** reacts with metal vinylcarbene **60** in a vinylogous fashion to provide **61**, a charge separated intermediate. Cyclization generates the bicyclic pyrrolidines **55a,b**.

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**Scheme 1.24.**
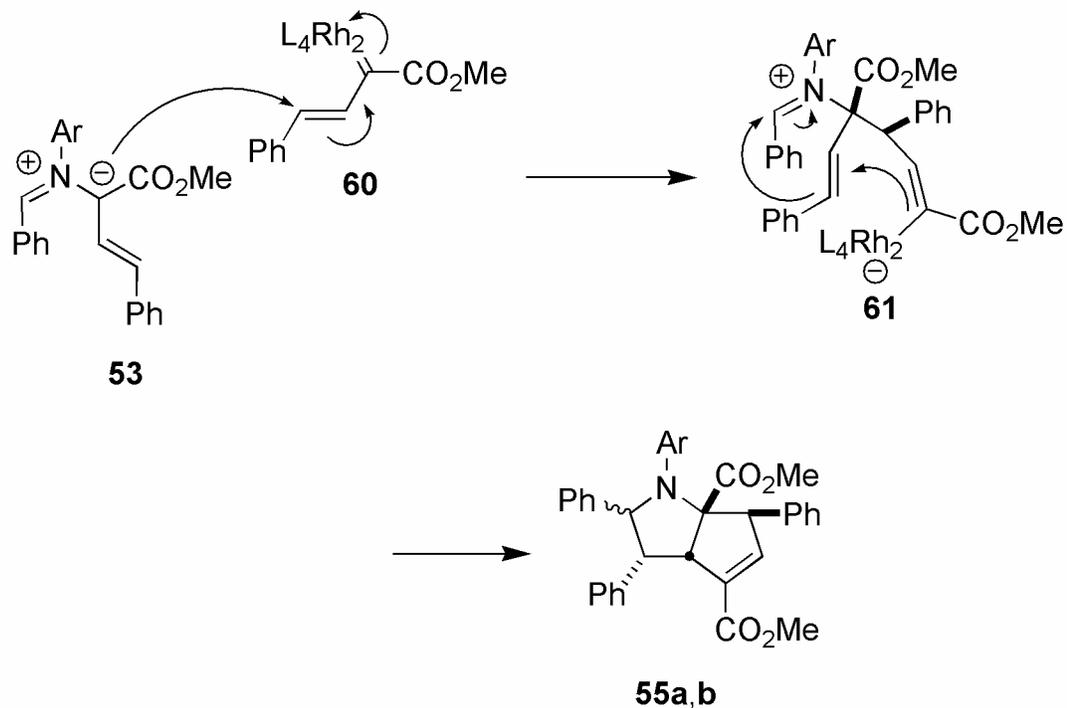


Searching the available literature on the reactivity of metal vinylcarbenes, we were struck by a series of accounts discussing the reactivity of enol ethers with rhodium-stabilized carbenes generated from vinyldiazoacetates.[103-105] As proposed by Davies, enol ethers may react with vinylcarbenes in a direct fashion, providing the cyclopropane **62**, or in a vinylogous manner, to provide cyclopentene **63** *via* the putative intermediate **64**.[104] The vinylogous reactivity of metal vinylcarbenes toward enol ethers is consistent with the reaction described in our proposed mechanism of azomethine ylide **53** and metal vinylcarbene **60**.

**Scheme 1.25.**



**63** via:



**64**
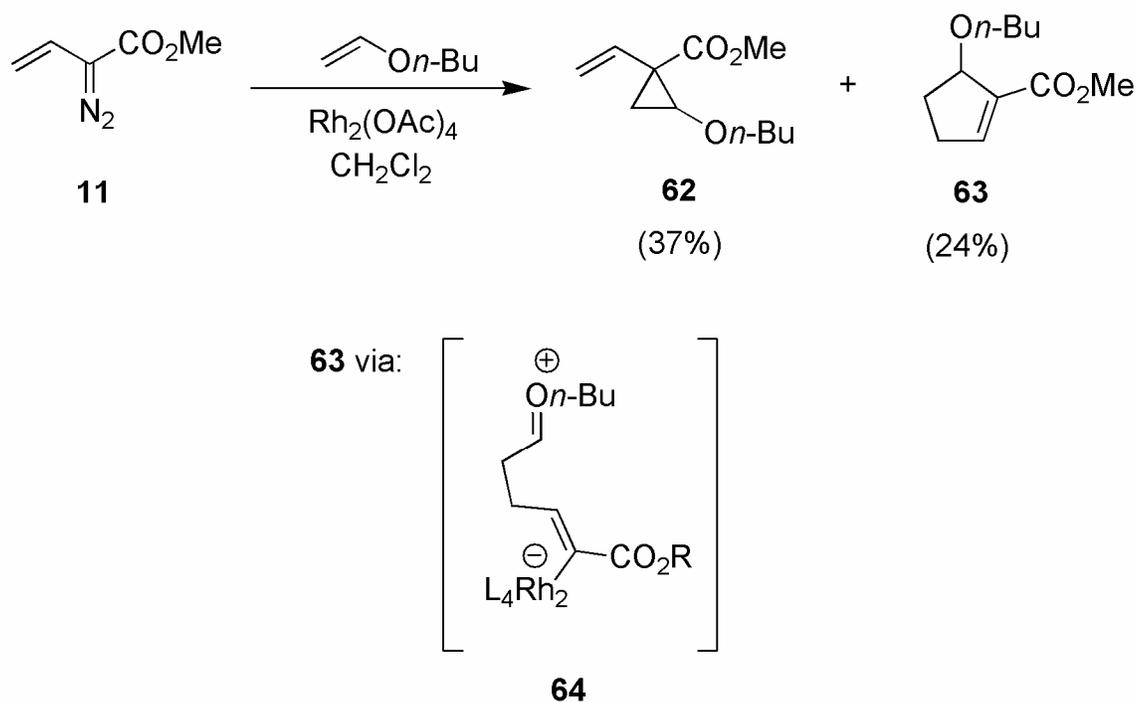
**Asymmetric catalyst study.** The catalyst $Rh_2(S\text{-}DOSP)_4$ (**2b**) provides an enantiomeric excess of 25% of the bicyclic pyrrolidine **56b**, enantiomeric excess of the diastereomer **56a** could not be determined by HPLC. Surprisingly, a very small amount of the dihydropyrrole **59** was also isolated. Dihydropyrrole **59** proved to be an unstable species; substantial decomposition was observed over several hours at room temperature. This was the only instance dihydropyrrole **59** was isolated from a reaction of vinyldiazoacetate **13** with benzylideneaniline. The enantiomeric excess of **59** could not be determined (attempted to measure by HPLC), however previous research with azomethine ylides leads us to expect that the precursor ylide **53** will not be catalyst associated[73] and, therefore, no asymmetric induction is expected to occur.

39

Scheme 1.26.
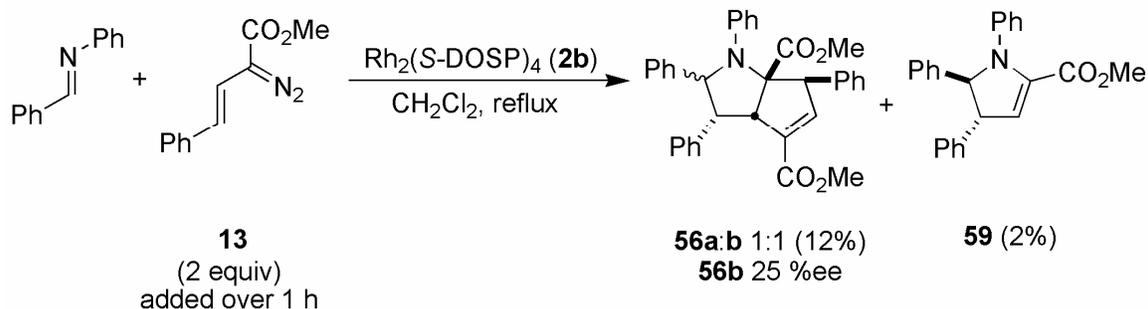


**Attempted trapping of azomethine ylide intermediate.** As was previously discussed, azomethine ylides derived from acceptor substituted metalcarbenes are commonly utilized as 1,3-dipoles in [3+2] cycloaddition reactions.[10,76,106] Trapping azomethine ylides with dipolarophiles results in the formation of substituted pyrrolidines. As numerous nitrogen containing heterocycles posses pharmaceutically valuable properties, the development of convergent routes to nitrogen containing heterocycles using azomethine ylides in cycloaddition reactions is of considerable interest. Trapping the azomethine ylide **53**, proposed to be a key intermediate in the formation of bicyclic pyrrolidines,[45] would provide access to an expanded range of functionalized pyrrolidines (**65**). Additionally, trapping the ylide in a dipolar cycloaddition reaction would confirm that azomethine ylide **53** is an intermediate in the formation of bicyclic pyrrolidines.

Trapping experiments were conducted by stirring the benzylideneaniline and $Rh_2(OAc)_4$ in a solution of dichloromethane with 10 equivalents of a

dipolarophile. Vinyldiazoacetate **13** (1 equivalent) was added over 1 hour. Upon completion of addition of **13**, the reaction mixture was refluxed for an additional hour, then the solvent was removed under reduced pressure. The reaction mixtures were analyzed by $^1$H NMR spectroscopy, the region from 5-7 ppm was searched for the existence of doublets exhibiting a coupling constant greater than 12 Hz that would be diagnostic of the *trans*-styryl vinyl hydrogens of **65**. To our surprise, no pyrrolidine **65** was observed in any reaction, the only identifiable components were bicyclic pyrrolidines **56a,b** and unreacted benzylidineaniline and dipolarophile.

**Scheme 1.27**.
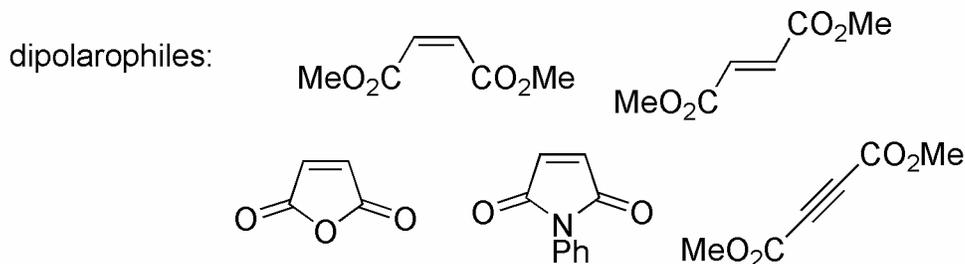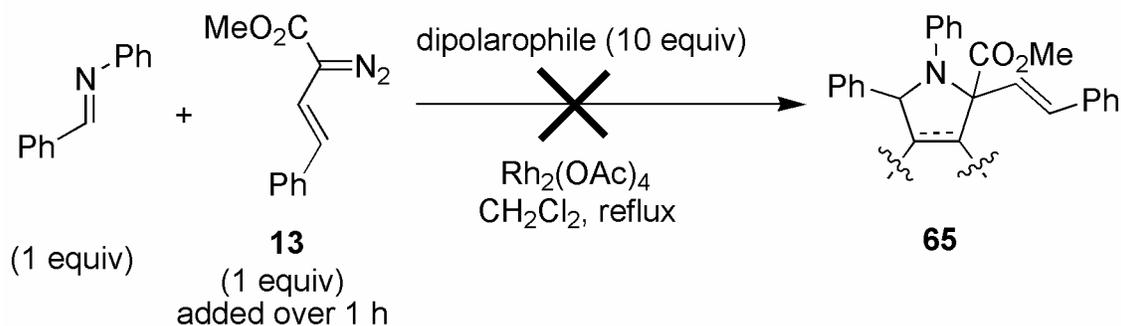


The failure of azomethine ylide **53** to react with dipolarophiles may be due to a decreased reactivity of the ylide **53** with dipolarophiles relative to the

41

azomethine ylide **48** (Scheme 1.18), due to steric or electronic effects. Alternatively, the carbene **60** (Scheme 1.24) may react with **53** at a much faster rate than the dipolarophiles evaluated (Scheme 1.27).

**Scope of vinyldiazoacetates in formation of bicyclic pyrrolidines.** In our attempts to exlore the scope of the formation of bicyclic pyrrolidines, a variety of vinyldiazoacetates other than **13** were examined. The vinyldiazoacetates **66-70** were prepared according to literature procedures and subjected to the reaction conditions used in the preparation of bicyclic pyrrolidines **56a**,**b** (Scheme 1.22). To our considerable surprise, neither the corresponding bicyclic pyrrolidine or, indeed, any imine reaction product, was observed. Vinyldiazoacetates **66-70** failed to react in any appreciable degree with benzylidineaniline. Upon completion of the reaction, ^{1}H NMR spectroscopic analysis showed no substantial component of the reaction mixture other than the unreacted imine.

**Scheme 1.28**.
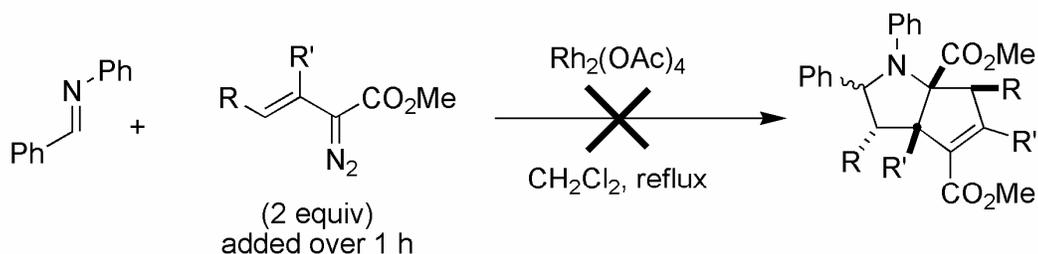


vinyldiazoacetates:
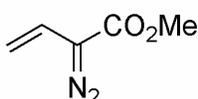


**66**
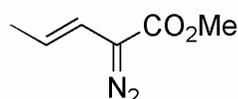


**67**
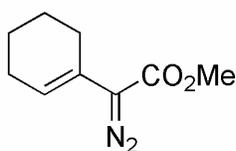


**68**
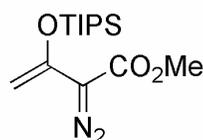


**69**
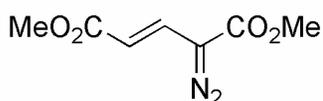


**70**

The surprising failure of metal vinylcarbenes other than that derived from **13** to react with benzylideneaniline to any appreciable extent provided the possibility of performing a selective three-component coupling of three distinct species to provide **71**, rather than the three-component coupling of two species that provide bicyclic pyrrolidines **55-58**. Although the metal vinylcarbenes resulting from **66-70** do not undergo addition to beznylideneaniline, as occurs with the metal vinylcarbene **13**, they may still be susceptible to vinylogous reaction with azomethine ylide **53**. This would allow a diverse array of substituted bicyclic pyrrolidines to be accessed. Unfortunately, upon addition of

a 1:1 solution of vinyldiazoacetate **13** and **66-70** to benzylideneaniline and Rh$_2$(OAc)$_4$ in refluxing dichloromethane, bicyclic pyrrolidines **56a,b** were the only observed reaction products (isolated yields were not determined).

**Scheme 1.29**.
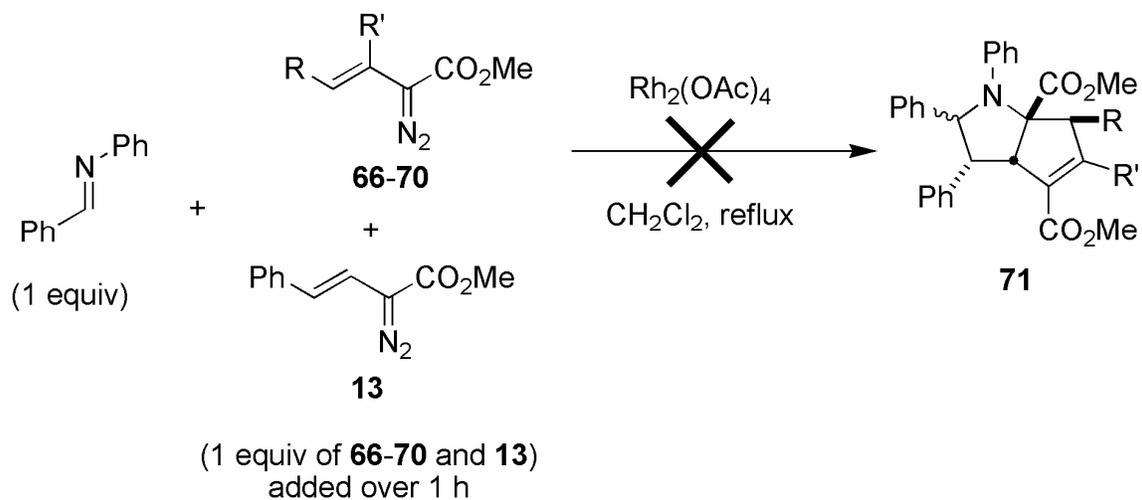
## III. CONCLUSION

Studies of the reaction of benzylideneanilines and vinyldiazoacetate **13** resulted in the discovery of a novel three-component reaction between one molecule of benzylideneaniline and two equivalents of **13**. The reaction of benzylideneaniline and two equivalents of **13** provides complex bicyclic pyrrolidines. The preparation of complex heterocycles in a stereoselective manner from easily prepared starting materials is of great value to synthetic organic chemists. Our study of the mechanism and optimization of conditions of bicyclic pyrrolidine formation was prompted by the desire to further expand scope three-component reaction to provide a wider variety of complex heterocycles. Ultimately, however, this reaction appears limited to methyl *trans*-styryldiazoacetate, **13**. All other vinyldiazoacetates failed to react with benzylideneaniline or the ylide formed by the reaction of **13** and benzylideneaniline.

## IV.  EXPERIMENTAL

**General Information:** NMR spectra were recorded on a Bruker DRX-400 MHz instrument and obtained as solutions in deuterochloroform unless otherwise noted. Chemical shifts of $^1$H NMR are quoted relative to internal $Me_4Si$ (0.00 ppm), those of $^{13}$C NMR are quoted relative to residual solvent (77.0 ppm).  High-resolution mass spectra were obtained on a JEOL SX102a spectrometer.  IR spectra obtained on a JASCO FT/IR-4100.  Thin layer chromatography was performed on Merck Silica Gel 40 $F_{254}$ glass backed plates, visualization was achieved with UV or $KMnO_4$ stain. Column chromatography was performed on 40-63 $\mu$m, 230-400 mesh, 60 A silica gel. Benzylidineaniline was prepared by condensation of aniline and benzaldehyde.[107]  Vinyldiazoacetate **69** was provided by Kousik Kundu.[108]  All other reagents were purchased from Aldrich unless otherwise specified. Anhydrous dichloromethane and tetrahydrofuran were obtained by dried by nitrogen forced-flow over activated alumina as described by Grubbs.[109]

**Synthesis of vinyldiazoacetates 13, 67, 70 via direct diazo transfer.**

**Representative procedure, 13:** To a solution of methyl *trans*-styrylacetate (0.22 g, 1.3 mmol) in acetonitrile (8 mL), *p*-ABSA (**12**) (0.37 g, 1.5 mmol) and DBU (0.23 mL, 1.5 mmol) are added.  After 3 h, the solvent is evaporated under reduced pressure and the resulting brown oil is purified by silica gel column chromatography on silica gel (4:1 hexanes/ethyl acetate) to provide **13** as an

orange oil (0.18 g, 71%); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.34-7.13 (comp, 5H), 6.44 (d, $J$ = 16.2 Hz, 1H), 6.13 (d, $J$ = 16.2 Hz, 1H), 3.79 (s, 3H); IR (neat) 2950, 2081, 1704 cm$^{-1}$.  $^1$H NMR and IR match reported spectra.[75]

**67:** Orange oil, 18%; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.74 (dd, $J$ = 16.0, 1.9 Hz, 1H), 5.31 (d, $J$ = 16.0 Hz, 1H), 3.81 (s, 3H), 1.81 (dd, $J$ = 6.6 Hz, 1.9 Hz, 3H); IR (neat) 2088, 1702 cm$^{-1}$.  $^1$H NMR and IR match reported spectra.[75]

**70:** Orange oil, 65%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.34 (d, $J$ = 16.0 Hz, 1H), 5.74 (d, $J$ = 16.0 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H); IR (neat) 2950, 2084 cm$^{-1}$.  $^1$H NMR and IR match reported spectra.[75]

**Synthesis of vinyldiazoacetates 66, 68.**

**66:** To a stirring solution of diazoacetoacetate **9** (0.70 g, 4.9 mmol) in methanol (30 mL) at 0 $^o$C was added NaBH$_4$ (0.45 g, 12 mmol) portionwise over 10 minutes, after which the solution was stirred for an additional hour.  This solution was added to saturated NaHCO$_{3(aq)}$ (30 mL) at 0 $^o$C and extracted three times with diethyl ether (80 mL each).  The combined organic extract was washed with ice-water and dried over anhydrous Na$_2$SO$_4$.  Upon filtration, the solvent was removed under reduced pressure and the crude alcohol was used without further purification.  The resulting yellow oil was stirred in anhydrous dichloromethane (15 mL) at 0 $^o$C and triethylamine (0.77 mL, 5.5 mmol) was added.  A solution of POCl$_3$ (0.20 mL, 2.1 mmol) in dichloromethane (2 mL) was added over 30

minutes by syringe pump and the reaction mixture was allowed to warm to room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (5:1 hexanes/diethyl ether) to provide **66** as a yellow oil (0.16g, 1.3 mmol, 10% yield); ^{1}H NMR (400 MHz, CDCl$_3$) $\delta$ 6.17 (dd, *J* = 17.3, 10.9 Hz, 1H), 5.12 (d, *J* = 10.9 Hz, 1H), 4.87 (d, *J* = 17.3 Hz, 1H), 3.82 (s, 3H); IR (neat) 2082, 1700 cm$^{-1}$. ^{1}H NMR and IR match reported spectra.[110]

**Ethyl 2-diazo-2-(1-cyclohexenyl)ethanoate (68)**: A solution of ethyl diazoacetate (**8**) (1.0 mL, 10 mmol) and cyclohexanone (1.0 mL, 10 mmol) in anhydrous THF (10 mL) was cooled to -78 $^o$C, a THF solution of LDA (10 mL, 10 mmol, 1.0 M) was added dropwise, and the resulting solution was stirred for one hour. Warming to 0 $^o$C, the reaction mixture was quenched with water and extracted three times with diethyl ether (60 mL each). The organic extract was washed with ice-water, then dried over anhydrous Na$_2$SO$_4$. Upon filtration of the mixture, the solvent was removed under reduced pressure, and the resulting brown oil was filtered through a silica gel plug (4:1 hexanes/ethyl acetate) to yield the crude alcohol as a yellow oil (0.28 g). The crude alcohol was stirred in anhydrous dichloromethane (15 mL) with triethylamine (0.74 mL, 5.4 mmol) at 0 $^o$C. A solution of POCl$_3$ (0.20 mL, 2.2 mmol) in dichloromethane (2 mL) was added over 30 minutes by syringe pump and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched by pouring the mixture over ice-water, and was extracted three times with

dichloromethane (30 mL each). The combined organic layer was washed with brine (20 mL) and dried over anhydrous $MgSO_4$. Upon filtration, the solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (5:1 hexanes/diethyl ether) to provide **68** as a yellow oil (0.08 g, 0.4 mmol, 6% yield); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta$ 6.13-5.93 (m, 1H), 4.21 (q, $J$ = 6.9, 2H), 2.50-1.41 (m, 8H), 1.25 (t, $J$ = 6.9 Hz, 3H); IR (neat) 2956, 2091, 1711 cm^{-1}. ^{1}H NMR and IR match reported spectra.[111]

## Scheme 1.22. Representative procedure of $Rh_2(OAc)_4$ catalyzed addition of 13 to benzylidineaniline.

A solution of **13** (0.40 g, 2.0 mmol) in $CH_2Cl_2$ (2 mL) was added via a syringe pump over one hour to a solution of $Rh_2(OAc)_4$ (4 mg, 0.01 mmol) and benzylideneaniline (0.20 g, 1.0 mmol) in refluxing $CH_2Cl_2$ (8 mL). After complete addition, the solution was allowed to reflux for an additional hour. The reaction mixture was filtered through a short silica gel plug and then washed with $CH_2Cl_2$ (50 mL). The solvent was removed under reduced pressure to leave a residue that was analyzed by ^{1}H NMR spectroscopy to determine the ratio of product diastereomers, comparing the integration of signals at 5.48 ppm (**56a**) and 5.00 ppm (**56b**). Column chromatography (5:1 hexanes/ethyl acetate) on silica gel afforded bicyclic product.

**56a**: ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta$ 7.79 (d, $J$ = 8.7 Hz, 2H), 7.50-6.81 (comp, 18H), 5.48 (d, $J$ = 7.2 Hz, 1H), 4.70 (t, J = 2.5 Hz, 1H), 4.45 (t, $J$ = 2.8 Hz, 1H), 3.94 (d, $J$ = 7.1 Hz, 1H), 3.88 (s, 3H), 3.00 (s, 3H), full characterization has been reported.[45]

**56b**: ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.24-6.76 (comp, 20H), 6.57 (t, $J$ = 7.2 Hz, 1H), 6.19 (br s, 1H), 5.34 (d, $J$ = 3.2 Hz, 1H), 5.00 (d, $J$ = 10.2 Hz, 1H), 4.30 (t, $J$ = 10.4 Hz, 1H), 4.16 (d, $J$ = 10.8 Hz, 1H), 4.00 (s, 3H), 3.32 (s, 3H); full characterization has been reported.[45]

**Scheme 1.26.  Rh$_2$(*S*-DOSP)$_4$ catalyzed addition of 13 to benzylidineaniline.**

A solution of **13** (0.49 g, 2.4 mmol) in CH$_2$Cl$_2$ (2 mL) was added via a syringe pump over one hour to a solution of Rh$_2$(*S*-DOSP)$_4$ (42 mg, 0.02 mmol) and benzylideneaniline (0.22 g, 1.2 mmol) in refluxing CH$_2$Cl$_2$ (8 mL).  After complete addition, the solution was allowed to reflux for an additional hour.  The reaction mixture was filtered through a short silica gel plug and then washed with CH$_2$Cl$_2$ (50 mL).  The solvent was removed under reduced pressure to leave a residue that was analyzed by ^{1}H NMR spectroscopy to determine the ratio of product diastereomers, comparing the integration of signals at 5.48 ppm (**56a**) and 5.00 ppm (**56b**).  Column chromatography (5:1 hexanes/ethyl acetate) on silica gel afforded bicyclic product **56b** and **59**.  Upon isolation, the enantiomeric excess of **56b** was measured by HPLC as described below.

**56b**: White crystalline solid (38 mg, 0.07 mmol, 6% yield).  HPLC: (Chiralpak-OD, hexanes/isopropyl alcohol 90:10, 1.0 mL/min, 220 nm, retention times of 3.2 min (major) and 4.3 min (minor), 25% ee; $[\alpha]_D^{27}$ +62.9° ($c$ = 0.20,  CH$_2$Cl$_2$).

**59**: Yellow oil (9 mg, 0.02 mmol, 2% yield).  ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.42-7.15 (m, 12H), 6.95 (t, J = 7.2 Hz, 1H), 6.76 (d, J = 7.6 Hz, 2H), 6.04 (d, J = 3.2 Hz, 1H), 4.66 (d, J = 5.2 Hz, 1H), 3.85 (dd, J = 5.2 Hz, 3.6 Hz), 3.80 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 Hz): δ 162.9, 147.5, 144.6, 142.6, 140.2, 129.1, 129.06, 129.0,

127.7, 127.6, 127.3, 126.1, 122.7, 119.9, 119.7, 79.9, 58.8, 52.2.  HRMS (FAB$^+$) calcd. for $C_{24}H_{21}NO_2$ (M$^+$ + 1): calcd 356.1651, found: 356.1651.

**Scheme 1.27.  Representative example of attempted reaction of azomethine ylide with dipolarophile dimethyl maleate.**

A solution of **13** (0.08 g, 0.4 mmol) in $CH_2Cl_2$ (1 mL) was added via a syringe pump over one hour to a refluxing solution of $Rh_2(OAc)_4$ (1 mg, 2E-3 mmol), benzylideneaniline (0.04 g, 0.2 mmol), and dimethyl maleate (0.25 mL, 2.0 mmol) in heated at reflux for one hour.  The reaction mixture was filtered through a short silica gel plug, washed with $CH_2Cl_2$ (50 mL).  The solvent was removed under reduced pressure and a $^1$H NMR was taken to determine if the cycloadduct **65** had formed.  The region of the $^1$H NMR from 5-7 ppm was searched for the existence of doublets exhibiting a coupling constant greater than 12 Hz, which would be diagnostic of the *trans*-styryl vinyl hydrogens of **65**.  No signals indicative of the cycloadduct **65** were observed, consequently no further workup was performed upon the reaction solution, which was discarded.

**Scheme 1.28.  Representative example of attempted reaction of benzylideneaniline with vinyldiazoacetate 66.**

A solution of **66** (0.14 g, 1.1 mmol) in $CH_2Cl_2$ (2 mL) was added via a syringe pump over one hour to a refluxing solution of $Rh_2(OAc)_4$ (2 mg, 0.01 mmol) and benzylideneaniline (0.10 g, 0.6 mmol).  After heating at reflux for one hour upon completion of addition of **66**, the reaction mixture was filtered through a short silica gel plug and washed with $CH_2Cl_2$ (50 mL).  The solvent was removed under

reduced pressure and a $^1$H NMR was taken, the only observable material by $^1$H NMR is unreacted benzylideneaniline.  No evidence is observed for products of any reaction of **66**.  As no evidence is observed for the products of any reaction of **66**, or unreacted **66**, the reaction was not worked up further and was discarded.

**Scheme 1.29.    Representative example of attempted reaction of benzylideneaniline with vinyldiazoacetate 13 and 66.**

A solution of **66** (0.07 g, 0.6 mmol) and **13** (0.10 g, 0.6 mmol) in $CH_2Cl_2$ (2 mL) was added via a syringe pump over one hour to a refluxing solution of $Rh_2(OAc)_4$ (2 mg, 0.01 mmol) and benzylideneaniline (0.10 g, 0.6 mmol).  After heating at reflux for one hour upon completion of addition of the solution of **66** and **13**, the reaction mixture was filtered through a short silica gel plug and washed with $CH_2Cl_2$ (50 mL).  The solvent was removed under reduced pressure and a $^1$H NMR was taken, bicyclic pyrrolidine product **56a,b** is observed as the major product.  Minor byproducts were not isolated and identified, the reaction solution was discarded.

3.84
3.85
3.85
3.86
3.81

4.66
4.67

6.04
6.04
6.95
6.97
6.75
6.77
7.16
7.17
7.17
7.26
7.28
7.30
7.40
7.42

CO$_2$Me

Ph—N

Ph

Ph

**59**

4.92

1.37

1.00

2.12
1.13

14.55

5.0

0.0

ppm (f1)

53

52.2
58.8
79.9
119.7
119.9
122.7
126.1
127.3
127.6
127.7
129.0
129.1
129.1
140.2
142.6
144.6
147.5
162.9

**59**

ppm (f1)
250   200   150   100   50   0

54
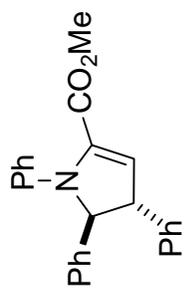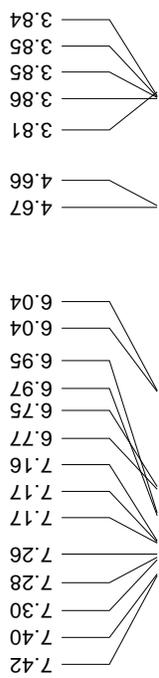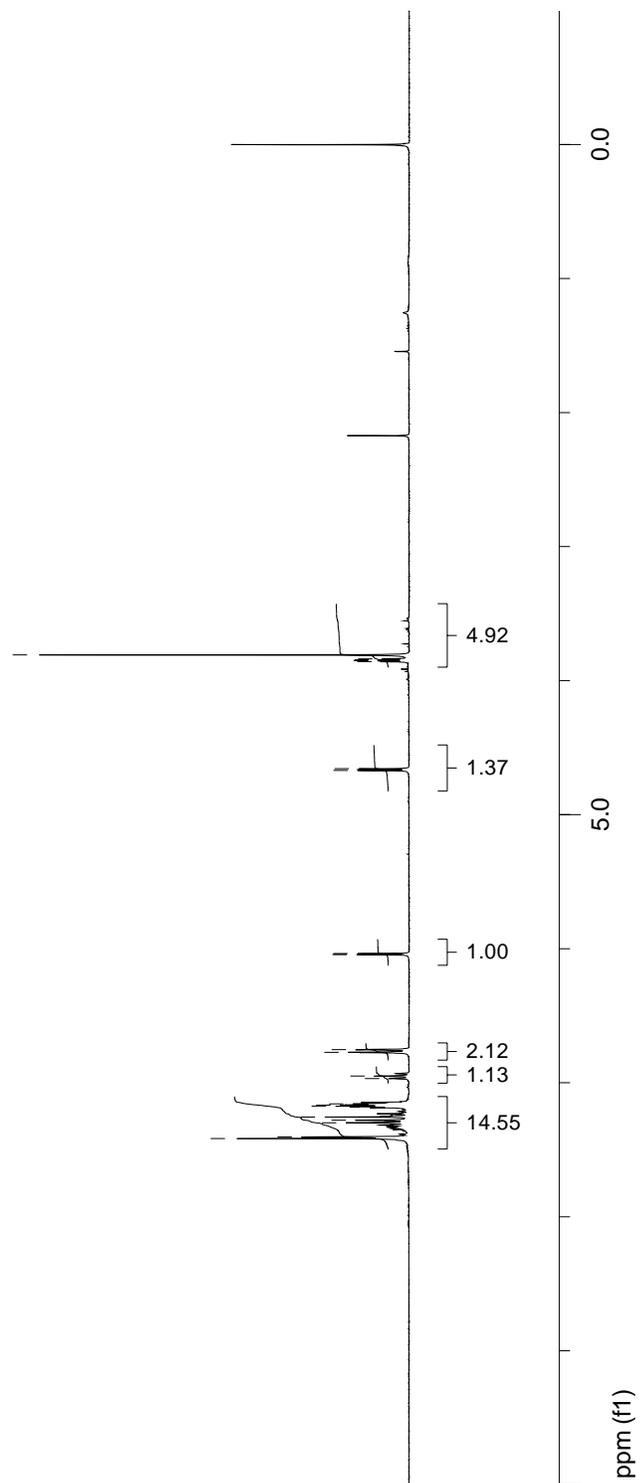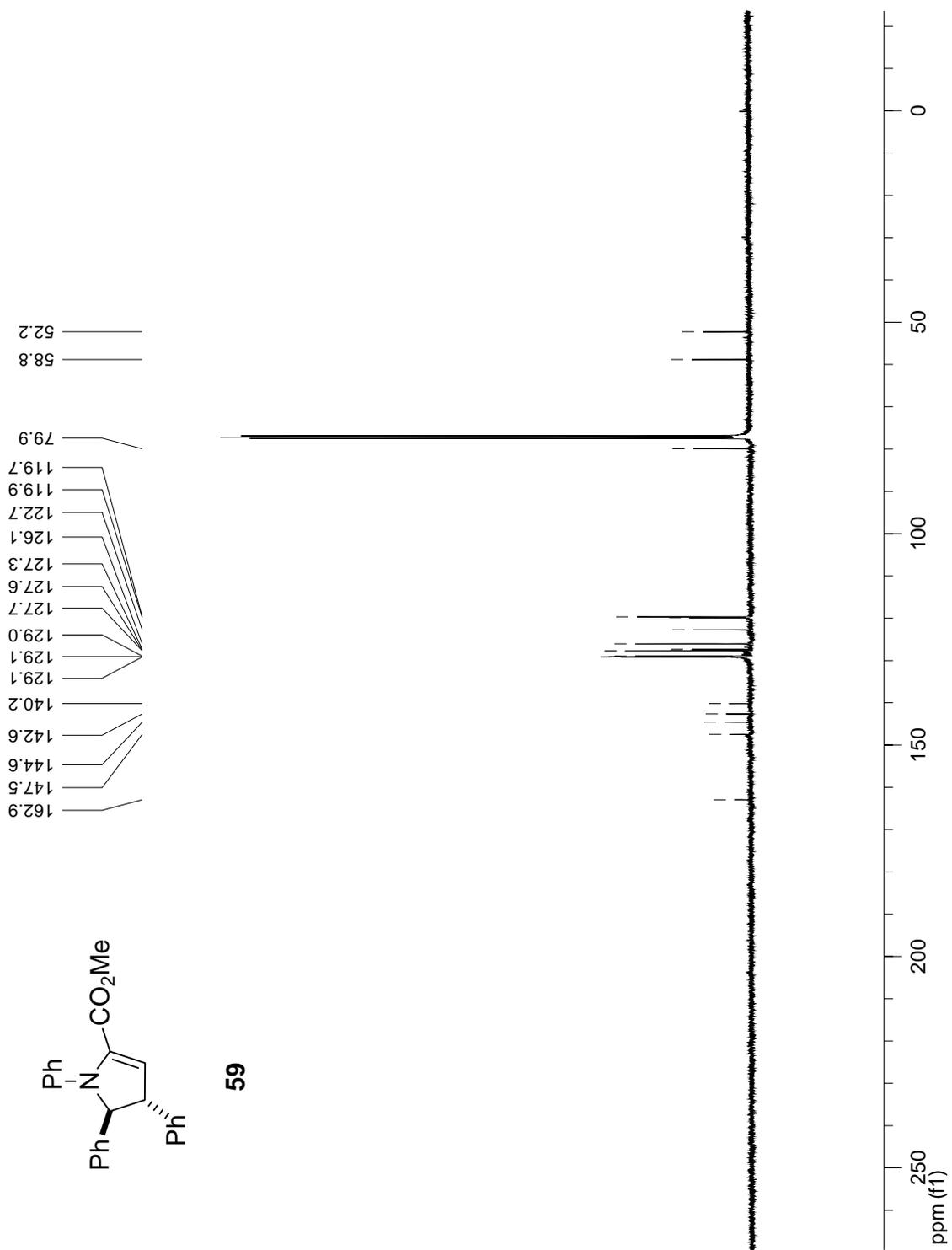
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# DESIGN AND SYNTHESIS OF ENDOCYCLIC

# VINYLDIAZOCARBONYL COMPOUNDS

## I.    BACKGROUND

As was described in the preceding chapter, vinyldiazoacetates are versatile synthetic reagents.  Metal carbenes formed from donor/acceptor diazo compounds, such as vinyldiazoacetates, posses unique reactivities in relation to other metal carbenes generated from acceptor and acceptor/acceptor substituted diazo compounds.[1,2]  The ability of vinyldiazoacetate and aryldiazoacetate derived metal carbenes to undergo intermolecular C—H insertion[3-6] and highly stereoselective cyclopropanation reactions[7,8] has provided efficient routes to complex molecules which posses biologically interesting properties.   The propensity of azomethine ylides generated from metal vinylcarbenes and aryl analogues to undergo intramolecular cyclization allows for the stereoselective construction of nitrogen containing heterocycles.[9-12]   As our investigations with metal vinylcarbenes have proceeded, however, it became apparent that limitations exist with this technology.

In the examples of ylide formation, cyclopropanation, and C—H insertion reactions of vinyldiazoacetates which were previously shown (Chapter 1), all vinyldiazoacetates possessed *trans*-vinyl substitution. In Davies' studies of cyclopropanation and C—H insertion reactions of vinyldiazoacetates using asymmetric dirhodium catalysts, *trans*-disubstitutedvinyldiazoacetates (**1**) are used to the exclusion of other substitution patterns.[1,3] The substituents *trans* to the diazoacetate includes aryl, alkyl, and vinyl groups.

**Figure 2.1**. *T*rans-vinyldiazoacetates.
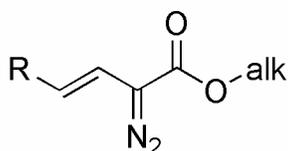


R = alkyl, aryl, vinyl
**1**

Few examples of reactions of vinyldiazoacetates possessing substitution patterns exist other than those with **1**. The vinyl group of vinyldiazoacetate **2** is itself susceptible to cyclopropanation; in reported attempts to perform intermolecular C—H insertion reactions with vinyldiazoacetate **2**, only oligomerization was observed.[13] The putative initial cyclopropanation product **3** is not isolated, but is consumed in a series of reactions involving carbonyl ylide rearrangement, cyclopropanation and a Cope rearrangement to provide **4**, which comprised of three units of **2**. Due to the propensity for oligomerization, mono-

substituted **2** is not used as frequently as *trans*-vinyldiazoacetates (**1**), and then only in cycloaddition reactions with highly reactive olefins.[14,15]

**Scheme 2.1**.
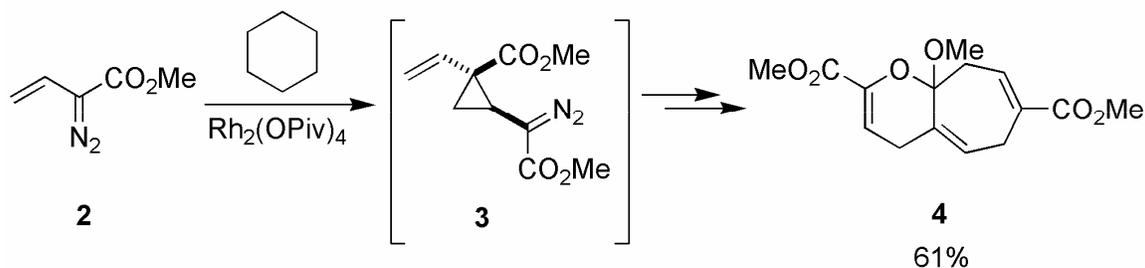


Examples of transition metal catalyzed reactions of disubstituted *cis*-vinyldiazoacetates are virtually nonexistent, and there are no examples of such vinyldiazoacetates being used in intermolecular C—H insertion or cyclopropanation reactions.[3] An explanation for the paucity of reactions utilizing *cis*-vinyldiazoacetates has been provided by Davies' report of the effects of carbene structure upon metal carbene reactivity.[13] In this study, several vinyldiazoacetates were added to a solution of the catalyst $Rh_2(OPiv)_4$ in cyclohexane. The metal carbene generated from *trans*-styryldiazoacetate **5a** undergoes C—H insertion into a cyclohexane C—H bond providing the intermolecular insertion product **6**. No intermolecular C—H insertion product was obtained with the analogous *cis*-styryldiazoacetate **5b**, however. Instead, the corresponding metal carbene undergoes intramolecular electrophilic aromatic substitution into the phenyl ring, resulting in the isolated indene **7**. Although other *cis*-vinyldiazoacetates were not reported in this study, it is reasonable to

infer that other intramolecular reactions could be observed when the metal carbene is located cis to functionalities other than a phenyl ring.

**Scheme 2.2**.



5a         6

33%



5b         7

86%
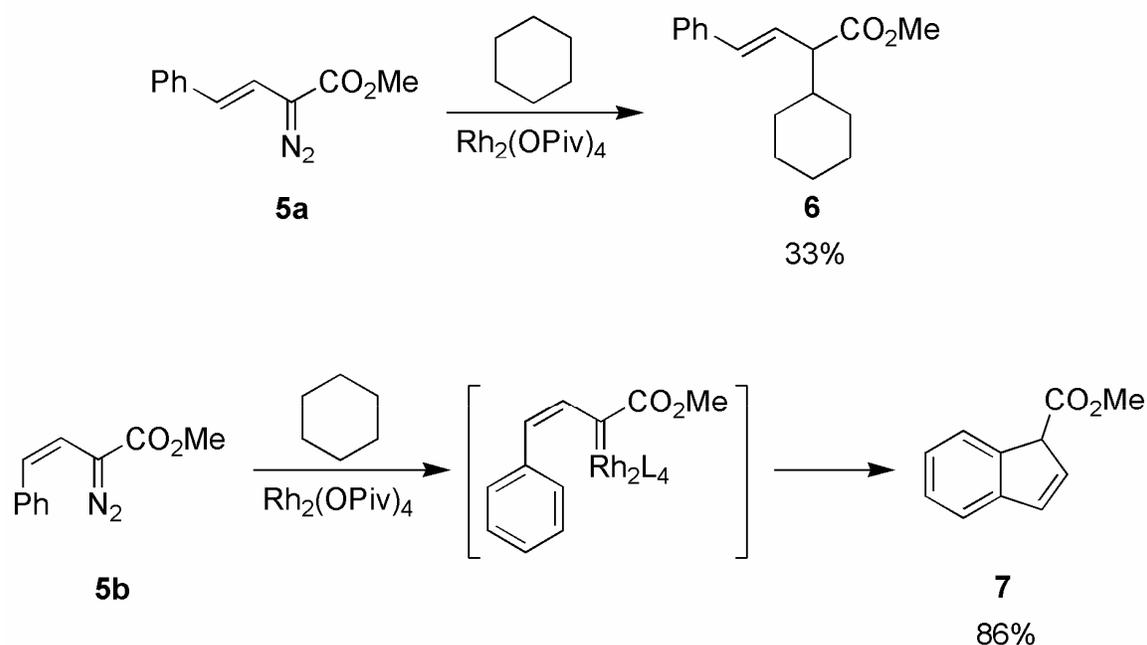
Examples of intermolecular metal carbene reactions using vinyldiazoacetates possessing substitution cis to the metal carbene are limited. The most noteworthy of these are intermolecular Si—H reactions of the *cis*-vinyldiazoacetates **8a**,**b** by Landais.[16,17] In these examples, an intermolecular metal carbene reaction is made favourable by selecting a highly reactive Si—H substrate for insertion.

**Scheme 2.3.**



**8a** R = $C_2H_3$
**8b** R = $C_5H_{11}$

**9a** 72%
**9b** 68%
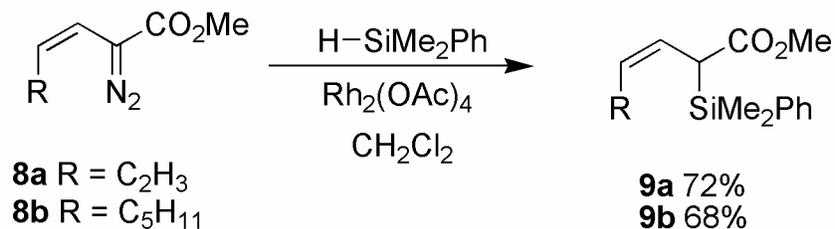
The relative reactivity of donor/acceptor substituted metal carbenes toward alkyl C—H and Si—H bonds is known from a series of competition experiments performed by Davies for reactions of methyl phenyldiazoacetate (**11**) and Rh$_2$(S-DOSP)$_4$ (**11**) with C—H and Si—H insertion substrates.[18] The Si—H insertion substrate Ph$_2^t$BuSi—H was measured to be 24,000 times more reactive with the metal carbene formed from **11** than the simple alkyl C—H bonds in cyclohexane.

**Figure 2.2**. Relative reactivity of C-H vs. Si-H.
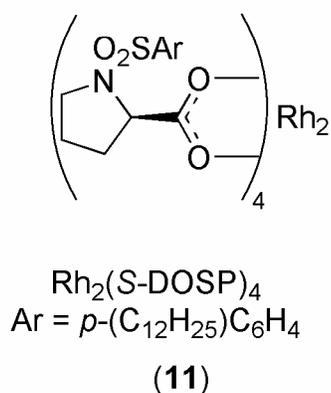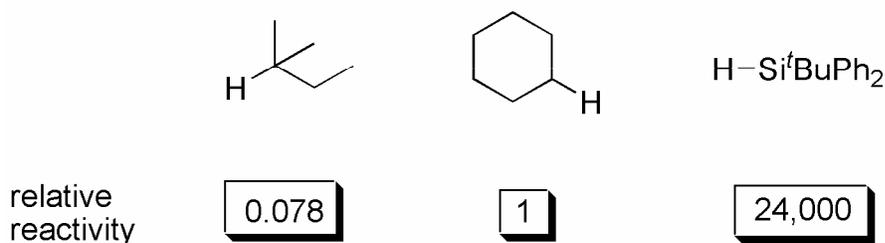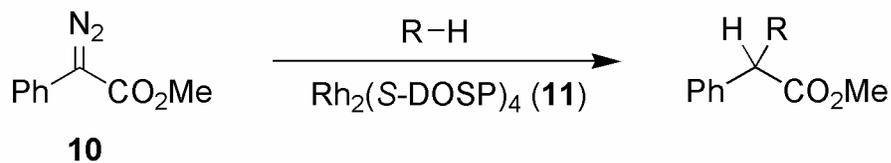
Rainier has used vinyldiazoacetates possessing substitution cis to the metal carbene in thio-Claisen rearrangements to provide access to complex indole alkaloids. The metal carbene generated from trisubstituted vinyldiazoacetate **13** reacts with **12** to provide, upon thio-Claisen rearrangement, **14**.[19] Intramolecular cyclization of the metal carbene generated from **13** is disfavoured due to high ring strain of the resulting cyclobutene product.

**Scheme 2.4.**



**14** (63%)
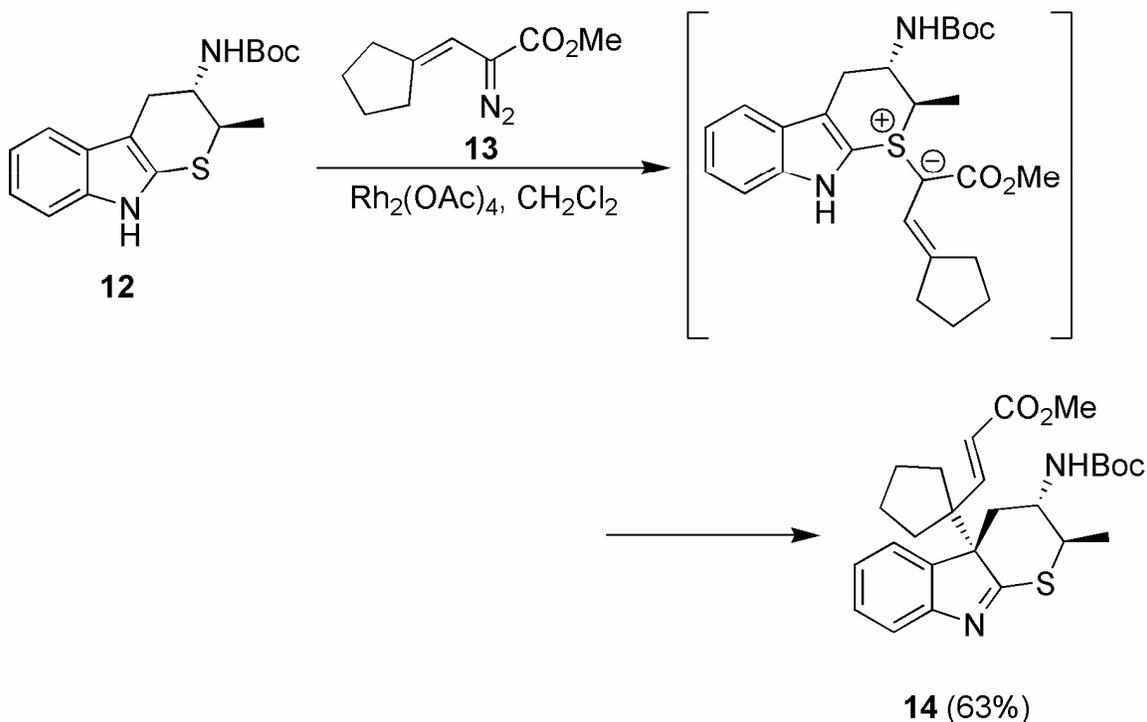
Further limiting the utilization of vinyldiazoacetates in synthetic applications, vinyldiazo compounds are unstable and readily undergo [1,5]-cyclizations to yield pyrazoles (i.e. **15**).[2,20] When vinyldiazoacetates are used in catalytic processes, pyrazole formation is particularly problematic as the basic nitrogen of pyrazoles may coordinate to transition metal catalysts. This would be expected to reduce catalyst efficiency, requiring increased catalyst loadings or preventing catalytic activity altogether. In our experience, it was critical to purify vinyldiazoacetates by column chromatography immediately prior to use; within hours of purifying **5a**, pyrazole formation was observed with **15** crystallizing as a white solid. Storing vinyldiazoacetates in a freezer at 4 °C does extend the lifetime of styryldiazoacetate **5a**, which could be kept overnight under these

conditions. Chromatographic purification, however, is still required to remove pyrazole **15** prior to subjecting **5a** to catalytic reactions.

**Scheme 2.5**.



**5a**

**15**

quantitative
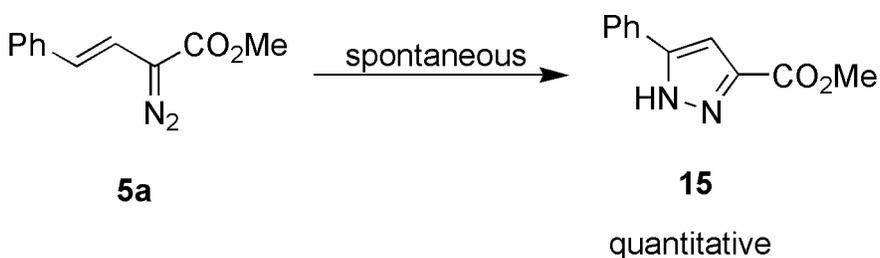
Pyrazole formation by vinyldiazoacetates is competitive with metal carbene formation from reactions with many transition metal catalysts. This was effectively shown in early attempts to perform asymmetric cyclopropanation reactions upon vinyldiazoacetates; **5a** failed to undergo extrusion of dinitrogen and metal carbene formation with the catalysts $Rh_2(MEPY)_4$ (**16**)[21] and the Masamune copper catalyst **17**[22], but instead cyclized to pyrazole **15**.[23] Their failure to react with vinyldiazoacetates led Davies to develop the more reactive carboxylate ligated dirhodium catalyst $Rh_2(S\text{-}DOSP)_4$ (**11**).[8] The instability of vinyldiazoacetates sharply limits the range of transition metal catalysts which may be used in conjunction with them.

**Scheme 2.6**.
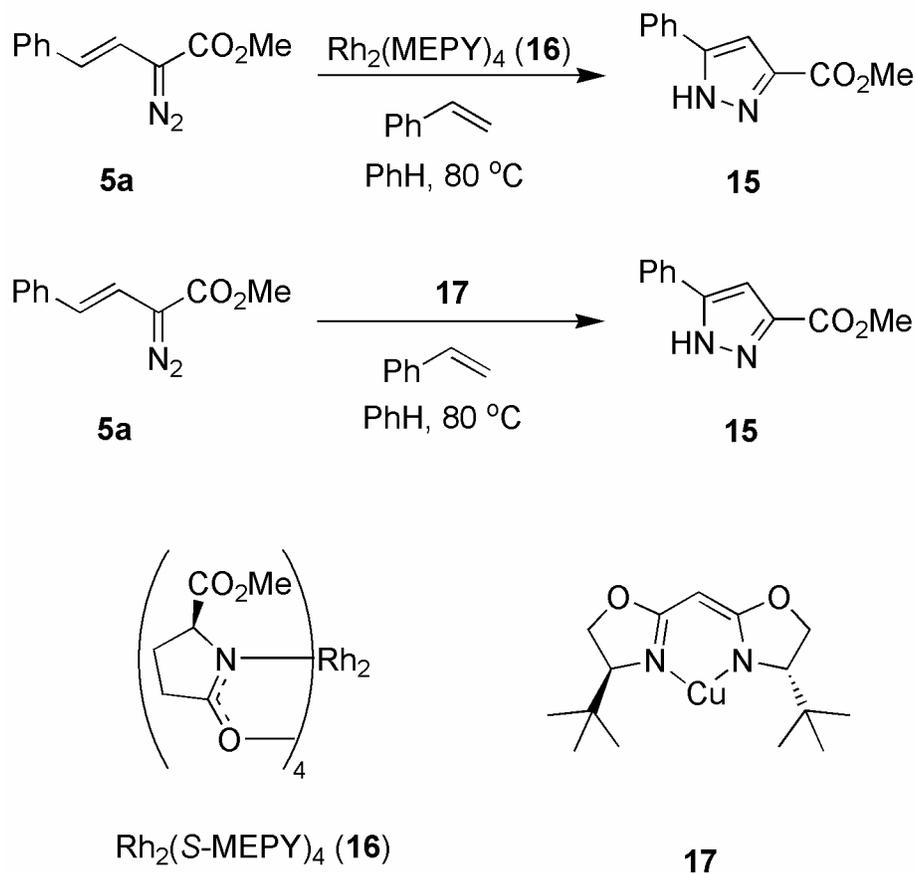


The previously described intramolecular cyclizations of vinyldiazoacetates (Scheme 2.5, 2.6) and the metal carbenes formed from *cis*-vinyldiazoacetates (Scheme 2.2) occur due to the ability of the vinyldiazoacetate or corresponding metal vinylcarbene to attain the correct conformation for cyclization. Endocyclic vinyldiazocarbonyl compounds (**22**) and their resulting metal carbenes, however, would not be susceptible to these intramolecular cyclization reactions. Pyrazole formation is impossible with such structures, requiring formation of an anti-Bredt olefin. Likewise, intramolecular C—H insertion reactions would be unlikely. The

two intramolecular cyclization pathways which are problematic in vinyldiazoacetates (Scheme 2.5) and metal *cis*-vinylcarbenes (Scheme 2.2) are unavailable to endocyclic vinyldiazocarbonyl compounds. It was envisioned that endocyclic vinyldiazocarbonyl compounds of the general structure **22** would act as donor/acceptor substituted diazo compounds, similar to vinyldiazoacetates and aryldiazoacetates. Intrigued by the possibility for expanding applicable substitution pattern available to metal vinylcarbenes, and providing a more operationally convenient vinyldiazocarbonyl compound, we turned to the challenge of synthesizing endocyclic vinyldiazocarbonyl species.

**Figure 3**. Endocyclic vinyldiazocarbonyl compound.



**22**
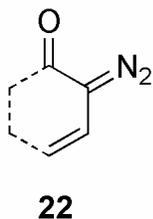
## II.   RESULTS AND DISCUSSION

Two synthetic strategies have been used in the construction of acyclic vinyldiazocarbonyl compounds, a reduction-dehydration of diazo $\beta$-dicarbonyl compounds[24] or, in a more direct route, diazo transfer to vinylcarbonyl

compounds.[25]  Each of these proved to be viable means of accessing endocyclic vinyldiazocarbonyl compounds.

Diazo β-dicarbonyl compounds such as **23** are readily prepared from the corresponding β-dicarbonyl precursor.[24]  Relatively weak amine bases (typically triethylamine) may be used, and mesyl azide acts as an efficient diazo transfer agent.  The ketone of **23** is selectively reduced to an alcohol with NaBH$_4$; treatment of the alcohol with a dehydrating agent such as POCl$_3$ forms the desired vinyldiazoacetate **2**.[24]  This reduction-dehydration protocol, and variations of it, are frequently employed in the synthesis of vinyldiazoacetates,[24] and may provide a suitable means of accessing endocyclic vinyldiazo compounds.

**Scheme 2.7**



**23**                                            **2**
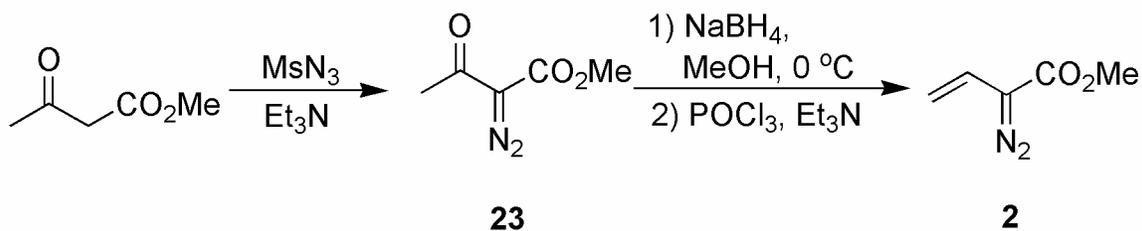
An alternative, and more concise, means of synthesizing vinyldiazoacetates is to perform a diazo transfer reaction on the vinylacetate substrate.[25]  The direct formation of vinyldiazoacetates and aryldiazoacetates from their vinyl- and arylacetate precursors has been reported to be a convenient means of accessing these diazo species when p-ABSA (**19**) is used as the

nitrogen transfer agent.  Sulfonyl azides other than **19**, such as mesyl azide, are not as effective in the synthesis of vinyl- and aryldiazoacetates.[25]

**Scheme 2.8**.

$$Ph\diagup\diagdown CO_2Me \xrightarrow[\text{MeCN}]{\text{DBU, }p\text{-ABSA (\textbf{19})}} Ph\diagup\diagdown \underset{N_2}{CO_2Me}$$

**5a** (89%)
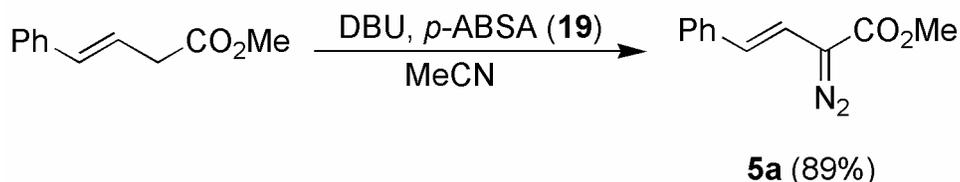
The direct formation of vinyldiazoacetates from corresponding vinylacetates offers the obvious advantage of requiring a single step as opposed to the three steps used by the previously described reduction-dehydration protocol.  However, in our experience,[26] the formation of vinyldiazoacetates and aryldiazoacetates by direct diazo transfer is highly substrate dependant.  In a number of instances, the workup and purification of vinyldiazoacetates is straightforward, accomplished by filtration through a short column of silica gel.  This approach, however, not infrequently suffers from low or negligible yields of the vinyldiazoacetate and the formation of byproducts whose separation from the diazoacetate is laborious.

To evaluate the scope of endocyclic vinyldiazocarbonyl compounds in asymmetric carbene transformations, several endocyclic vinyldiazocarbonyl compounds were synthesized  using both the reduction-dehydration and direct diazo transfer protocols.  To evaluate the use of a variety of endocyclic vinyldiazocarbonyl    structures,    a    diverse    selection    of    endocyclic

vinyldiazocarbonyl compounds which varied in the electronics of the carbonyl (lactones, ketone, lactam) and the size and substitution of the ring system were prepared. Described herein is the synthesis of several endocyclic vinyldiazocarbonyl compounds, and the construction of their dione (**24**) or unsaturated carbonyl (**25**) precursors.

**Scheme 2.9**.
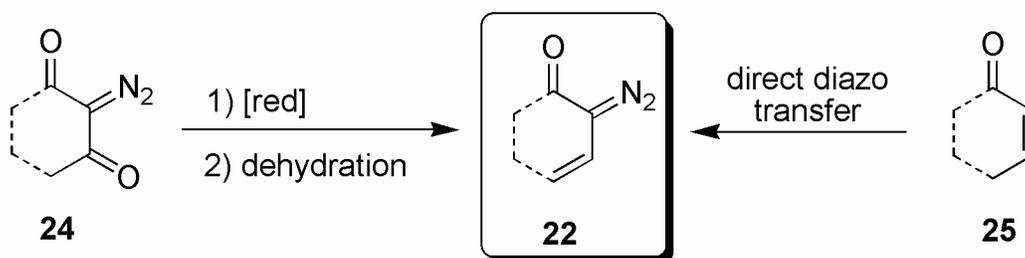


**3-Diazo-3,6-dihydro-2*H*-pyran-2-one (31)**. The β-ketolactone **28** was conveniently prepared according to the procedure reported by Weiler and coworkers from the carboxylic acid **26**.[27] The diazo compound **29** was easily prepared under mild diazo transfer conditions. Initial attempts to reduce the ketone of **29** using the hydride reducing agents sodium borohydride, sodium cyanoborohydride, and L-Selectride provided none of the desired alcohol **30**. Byproducts of these reductions were polar materials which were not readily isolable and were not identified. The reducing agent LiHAl(O-*t*Bu)$_3$ was found to provide alcohol **30**, albeit in low and somewhat capricious yield. Little consistency was observed in this reduction, yields of the crude mixture of **30** were consistently less than 20%, and in some instances none of the desired

71

alcohol was recovered. Dehydration of alcohol **30** proceeded smoothly to provide **31** (12% yield from **28**). Although the reduction-dehydration protocol is a viable route to vinyldiazolactone **31**, the unpredictable and low-yielding reduction step makes this an unreliable method of accessing **31**.

**Scheme 2.10**.
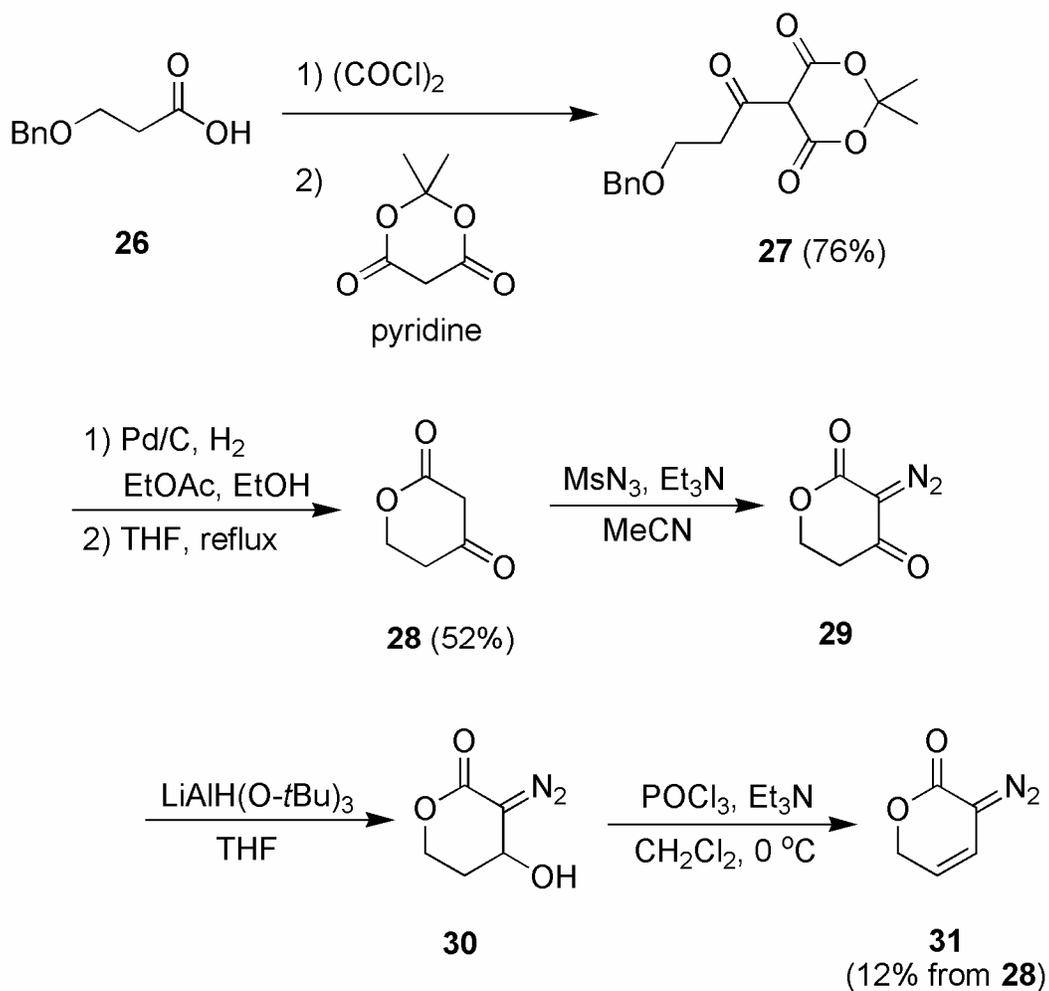


Requiring a more reliable and convenient means of preparing **31**, we turned our attention to direct diazo transfer of lactone **32** (Scheme 2.11). We were delighted to observe that using diazo transfer conditions for the preparation

of vinyldiazoacetates, vinyldiazolactone **31** was obtained in 47% yield from **32** (available from commercial sources).  Vinyldiazolactone **31** is conveniently isolated from the reaction mixture by flash chromatography, eluting as a bright yellow band.  Vinyldiazolactone **31** is conveniently accessed by the direct diazo transfer reaction of **32**, and as such was used extensively in our subsequent study of the reactions of endocyclic vinyldiazocarbonyl compounds.

**Scheme 2.11**.



**32**                    **31** (47%)
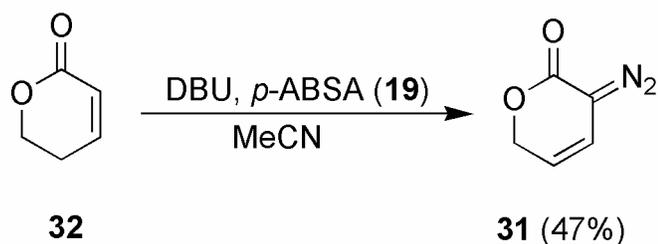
As was previously described, we expected the endocyclic vinyldiazocarbonyl compounds to be considerably more stable than acyclic vinyldiazocarbonyl compounds such as vinyldiazoacetates.  Vinyldiazolactone **31**, unable to undergo [1,5] cyclization of the vinyldiazo functional group, was stored in a freezer at 4 $^{\circ}$C for weeks without substantial decomposition as measured by ^{1}H NMR.  Slow decomposition of vinyldiazolactone **31** is observed when exposed to light and kept at room temperature over several days.  In later studies of the reactivity of endocyclic vinyldiazocarbonyl compounds (described in Chapter 3),  observed selectivities and yields of reactions for **31** which had been stored for up to one week at 4 $^{\circ}$C and material purified before use showed

no significant difference.  All endocyclic vinyldiazocarbonyl compounds described herein posses similar stabilities.

**3-Diazo-6,7-dihydrooxepin-2(3*H*)-one (35)**.  Lactone **34** was prepared from **33** using a known selenation/oxidation protocol, albeit in low yield.[28]  Diazo transfer was accomplished using the conditions described with **32** and provided **35** with similar yield to that obtained with **31**.

**Scheme 2.12**.
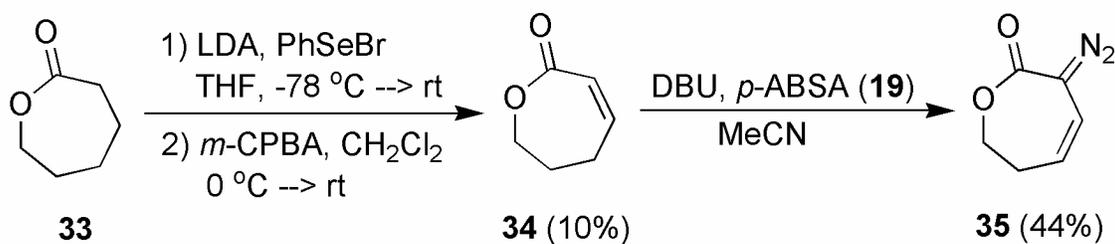
**3-Diazo-2-oxo-2,3-dihydrofuran-3-ide (38), and 3-Diazo-5-methyl-2-oxo-2,3-dihydrofuran-3-ide (39)**. Lactone **36**, and the related lactone **37**, provided none of the desired diazo lactones **38** or **39** upon treatment under diazo transfer conditions. A large number of products were observed, none of which could be isolated and characterized.

**Scheme 2.13**.



**36** R = H
**37** R = Me

**38** R = H
**39** R = Me
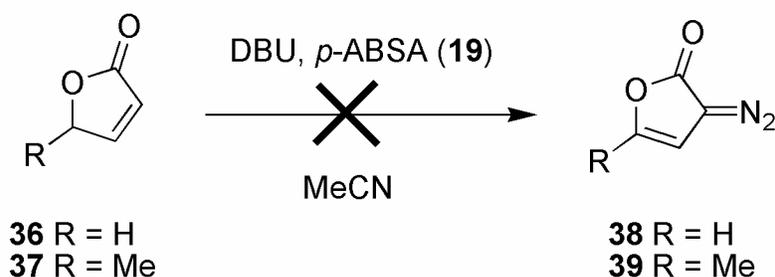
**3-Diazo-5-phenyl-3,6-dihydro-2*H*-pyran-2-one (44).** To prepare vinyldiazolactone **44**, the lactone precursor **43** was synthesized by ring closing metathesis of diene **41**, obtained by esterification of the homoallylic alcohol **40** with acrylic acid. Ring closing metathesis with Grubb's catalyst **42**[29] provided lactone **43** in excellent yield. Treatment of the lactone **43** with the diazo transfer agent *p*-ABSA (**19**) and DBU provided the vinyldiazolactone **44** in 39% yield.

**Scheme 2.14.**
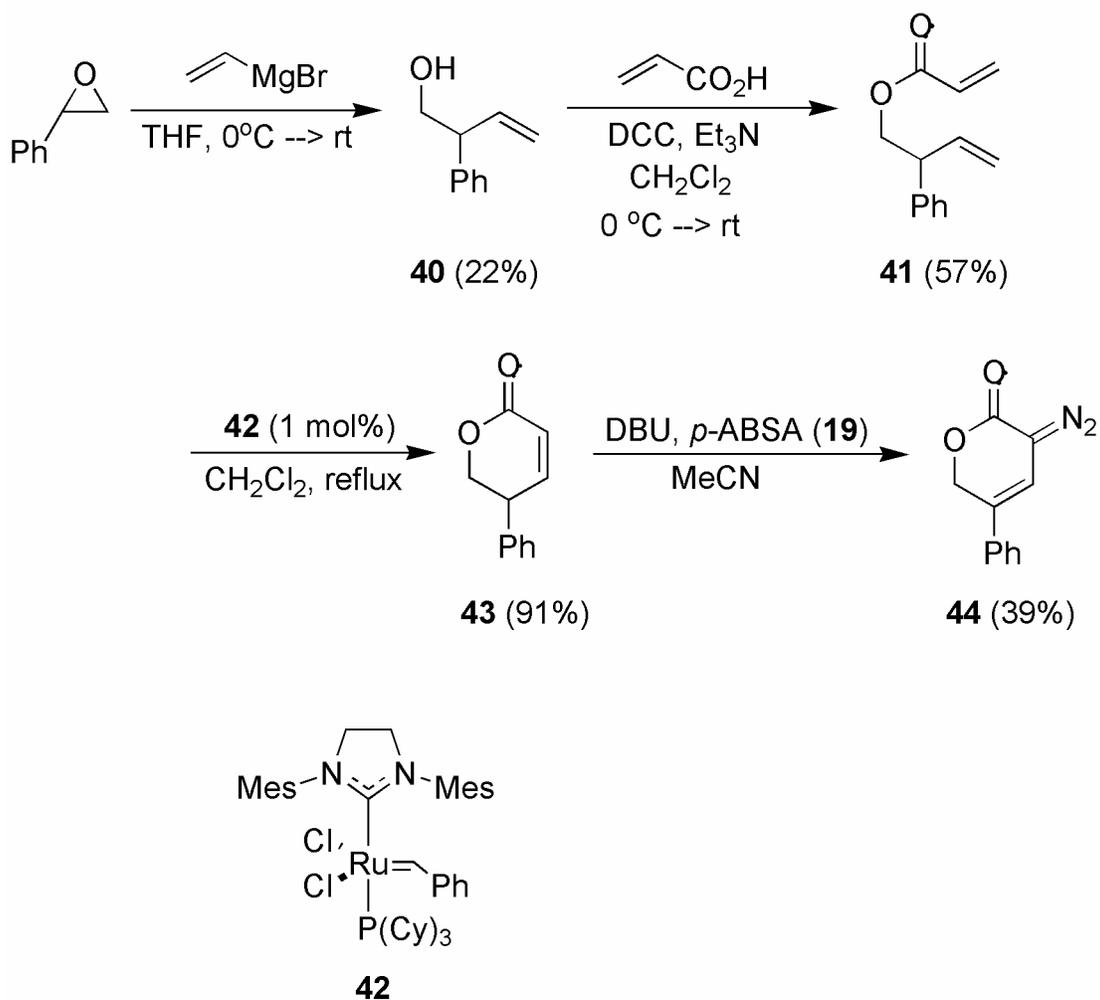


**6,6-Dimethyl-2-oxo-3,6-dihydro-2*H*-pyran-3-diazo (45)**. We anticipated that vinyldiazolactone **45** could be prepared from the β-lactone **47** using the reduction-dehydration protocol. As was demonstrated with the synthesis of vinyldiazolactone **31** from **28**, a diazo transfer to **47** followed by reduction of the ketone and dehydration would be expected to provide **35**. However, as the previously described reduction-dehydration protocol proceeded in poor yield and was unreliable in the preparation of **31**, this was not attempted. Instead, the

synthesis of unsaturated lactone **46** from **47** was pursued, with the aim of subsequently synthesizing vinyldiazolactone **45** by direct diazo transfer to **46**.

**Scheme 2.15**.



**45**                    **46**                    **47**
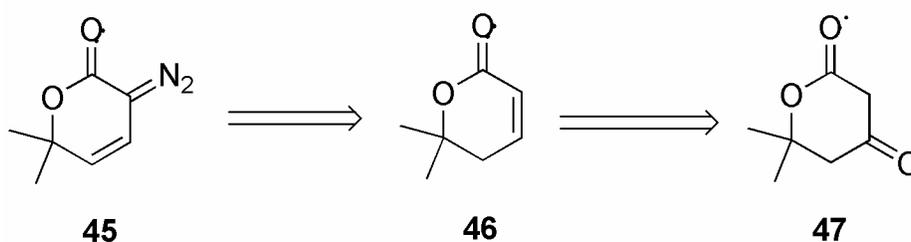
β-Ketolactone **47** was easily prepared in one pot by sequential enolization of methyl acetoacetate with NaH and LDA, followed by the addition of acetone.[30] Upon treatment of the reaction mixture with NaOH(aq), **47** was isolated by recrystallization in 37% yield.

**Scheme 2.16**.



1) NaH, THF, 0 °C
2) LDA
3) acetone
4) NaOHaq

**47** (37%)
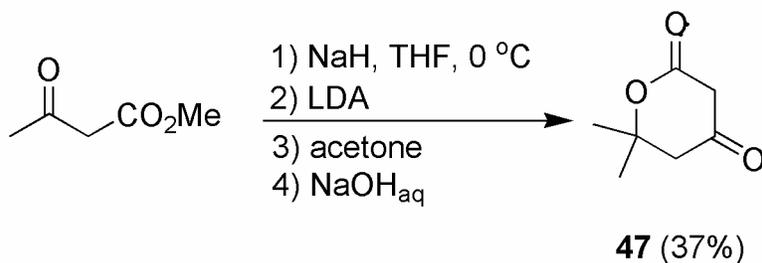
Initial attempts to prepare the unsaturated lactone **46** from the β-ketolactone **47** involved the reduction of the ketone using hydride reducing agents, followed by dehydration of the alcohol. However, standard hydride reducing agents NaBH₄, L-Selectride, and LiHAl(O-*t*Bu)₃ were unsuccessful in

the selective reduction of the ketone functionality of **46**, providing unreacted lactone and numerous byproducts. This is consistent with previous reports of attempts to reduce the ketone functional group of β-ketolactones using borohydride and aluminum hydride reducing agents, from which enolization of the dicarbonyl is believed to complicate the use of hydride reducing agents.[31,32] Amino-borane reducing agents have been reported to effectively reduce the ketone of β-ketolactones to the corresponding alcohols; treatment of ketone **47** with BH$_3$-$t$BuNH$_2$ using conditions described by Knight[31] did result in consumption of **47** and formation of the desired alcohol. Dehydration of the unpurified mixture using POCl$_3$ provided the desired lactone **46**. Unfortunately, **46** could not be readily separated from byproducts of the reaction, and the mass of the unpurified reaction mixture was <10% of the theoretical yield of **46**. Consequently, it was decided that the reduction-dehydration of **47** was not a promising route to the lactone **46**.

**Scheme 2.17**.
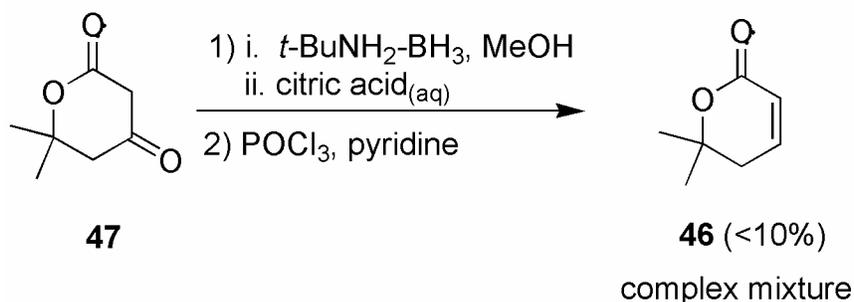


With the decision not to continue developing a reduction-dehydration conditions for the conversion of **46** to **47**, we considered conversion of the ketone

to a vinyl halide **48**. Subsequent reduction of **48** would provide the desired lactone **46**.

**Scheme 2.18**.



47                48                46
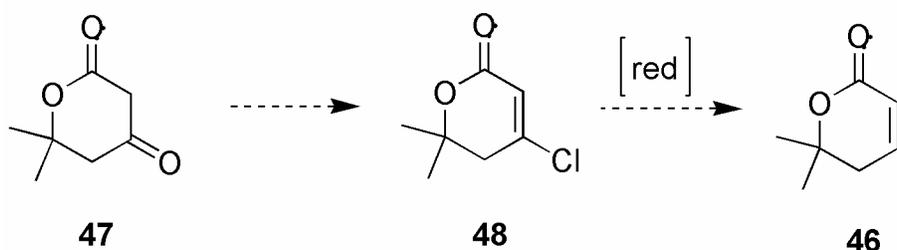
The conversion of ketones to vinyl chlorides is accomplished by the treatment of the ketone substrate with $PCl_5$ in refluxing dichloromethane.[33] Although **47** reacted cleanly and with complete conversion under these conditions, the reaction product was not lactone **48**. Analysis of the $^1H$ and $^{13}C$ NMR spectra of the reaction product indicated that the lactone likely opens under the reaction conditions to provide carboxylic acid **49** as the major product.

**Scheme 2.19**.



47                48a (0%)        49 (93%)
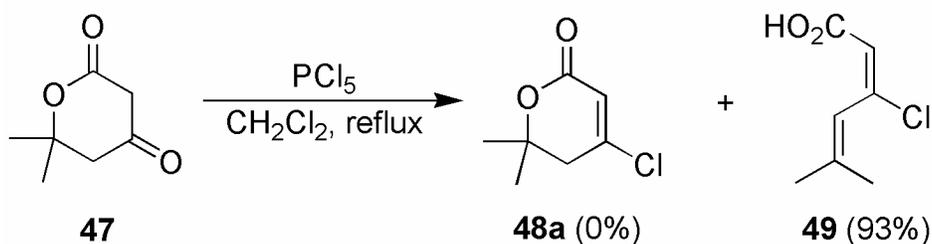
***tert*-Butyl 3-diazo-2-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (52)**. The *N*-Boc lactam **51** was prepared in good yields by selenylation of the

saturated lactam **50**, followed by oxidation with *m*-CPBA. Diazo transfer under using DBU and *p*-ABSA provided the desired vinyldiazolactam **52**.

**Scheme 2.20**.



**50**

1) LHMDS, PhSeBr
THF, -78 °C --> rt

2) *m*-CPBA, CH$_2$Cl$_2$
0 °C --> rt

**51** (56%)

DBU, *p*-ABSA (**19**)
MeCN

**52** (52%)
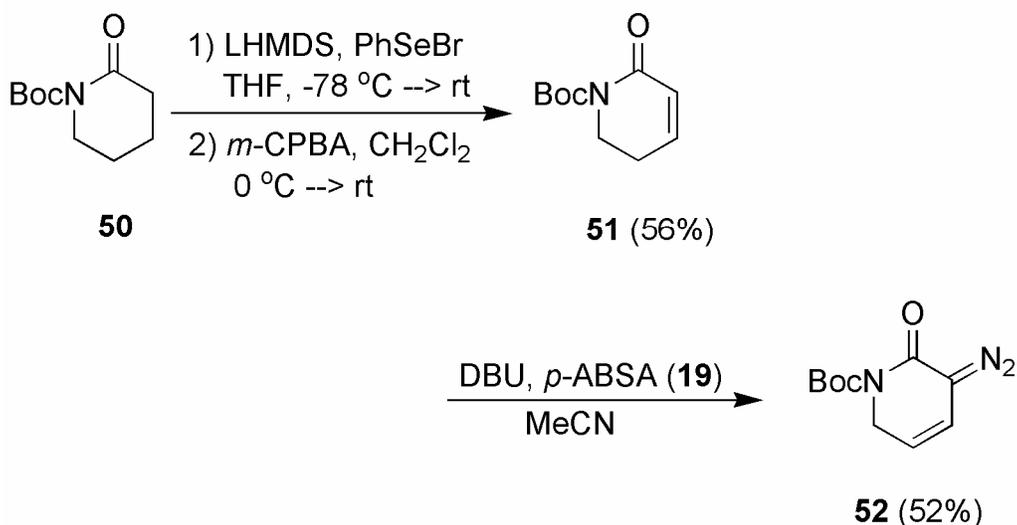
**1-Methyl-3-diazo-2-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (56)**.
The synthesis of the *N*-methylvinyldiazolactam **56** proved to be more challenging than the preparation of **51**. After several unsuccessful attempts to prepare the selenylated lactam **54**, it was determined that two equivalents of the base LHMDS were essential, in contrast to the one equivalent of base used in selenylation of **33** and **50**. Previous studies of the analogous sulfonylation of **53** have noted that one equivalent of base leads to recovery of unreacted **53** and a bis-sulfonylated lactam, whereas two equivalents of base provide mono-sulfonylated lactam.[34] Oxidation of the selenylated lactam **54** with *m*-CPBA provided the unsaturated lactam **55**.

**Scheme 2.21.**



**53**  **54** (90%)  **55** (89%)
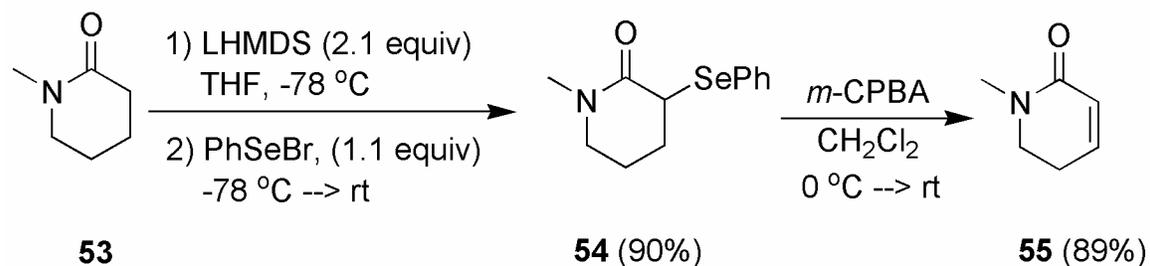
Unfortunately, attempts to affect diazo transfer to **55** using the reagents DBU and *p*-ABSA (**19**) failed to provide the vinyldiazolactam **56**. No reaction was observed with **55**, even after 24 h. This was not surprising, the *N*-methyllactam **55** is expected to posses a much less electrophilic carbonyl, and consequently less acidic vinylogous protons, than that of the previously described lactone systems or lactam **51**. It became necessary, therefore, to explore conditions in which stronger bases were utilized.

**Scheme 2.24**



**55**  **56**
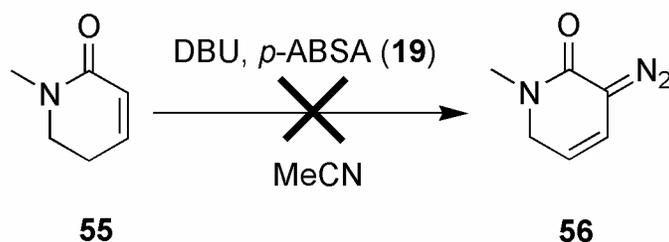
The guanidine amine base **57** was explored as an alternative to DBU; reactions were run in deuterated DMSO or acetonitrile and monitored by $^{1}$H NMR spectroscopy. The unsaturated lactam **55** was observed to react in each solvent,

albeit slowly.  After 24 hours, ^{1}H NMR shows **55** to be largely unreacted; however, uncharacterized reaction products are also observed.

**Scheme 2.23**.
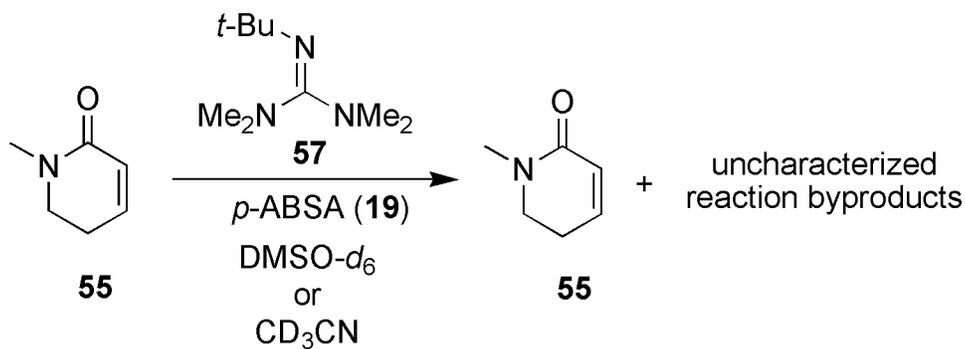


Early reports of diazo transfer preparations of vinyldiazoacetates had in some cases used strong bases such as LDA in conjunction with an HMPA additive and the diazo transfer species tosyl azide.[15,24]  Unfortunately, these conditions were not successful in providing significant amounts of **56**.  Analysis of the reaction mixture by ^{1}H NMR spectroscopy indicated that the desired vinyldiazolactam **56** was formed, but only as a very minor product.  Additional reactions without the use of the additive HMPA were also unsuccessful, resulting in the formation of numerous byproducts and no observable vinyldiazolactam **56**.

The use of diazo transfer agent *p*-ABSA (**19**) with LDA appeared to provide vinyldiazolactam **56** by ^{1}H NMR spectroscopic analysis of the reaction upon work up.  However, significant amounts of an unknown reaction byproduct always contaminated **56**.  Despite a significant effort to develop chromatography

conditions using several solvent systems, in all cases the uncharacterized byproduct co-eluted with **56**.

**Scheme 2.24**.
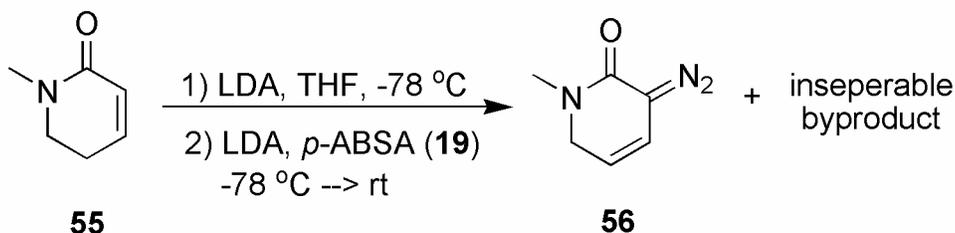


**2-Diazocyclohex-3-en-1-one (59)**.  Synthesis of vinyldiazoketone **59** was not viable under the direct diazo transfer conditions applied to the preceding lactones and lactams.  Standard diazo transfer conditions applied to the enone **58** did provide **59**; however numerous byproducts were also observed.  Due to several unidentified byproducts which co-eluted with **59** using column chromatography on silica gel, purification of **59** from the reaction mixture could not be achieved and an alternative preparation of the vinyldiazoketone **59** was pursued.

**Scheme 2.25**.
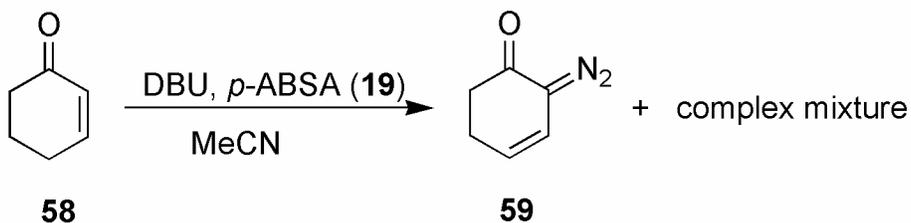
Following the protocol of Mueller and coworkers, the vinyldiazoketone **61** was formed in good yield from β-diketone **60**. Selective monoreduction of a ketone was performed using NaBH$_4$, as described by Korobitsyna and coworkers.[35] Dehydration of the resulting alcohol using POCl$_3$ provided the desired vinyldiazoketone **59**, albeit in poor yield. The low overall yield of **59** from **61** is attributable to the hydride reduction step, upon aqueous workup a very low yield of the crude alcohol is obtained.

**Scheme 2.26**.
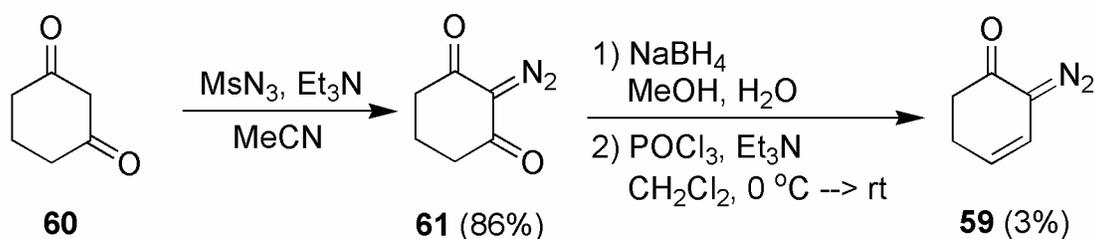


## III. CONCLUSION

Rhodium(II)-stabilized vinylcarbenes are valuable synthetic intermediates capable of undergoing a wide range of metal carbene reactions; their synthetic versatility has been described by us and other research groups in applications directed to the construction of complex molecular architectures.[1,9,10,19,36-38] Despite the recognized utility of metal vinylcarbenes, however, limitations with the acyclic vinyldiazoacetates which are most commonly used as vinylcarbene

precursors have limited the application of vinylcarbenes. Vinyldiazoacetates that are typically used as metal vinylcarbene precursors undergo a spontaneous [1,5]-cyclization reaction to form pyrazoles. This limits the operational convenience of vinyldiazoacetates and the scope of dirhodium catalysts with which they may be used in conjunction with to the most reactive catalysts. The substitution pattern of the majority of vinyldiazoacetates used in synthesis is limited to disubstituted *trans*-vinyldiazoacetates (**1**). The metal vinylcarbenes generated from *cis*-vinyldiazoacetates are vulnerable to intramolecular carbene reactions. It was our expectation that the endocyclic vinydiazocarbonyl compounds whose syntheses have been described in this chapter would not be susceptible to intramolecular cyclization of the diazo functionality or metal carbene. The increased stability of each the diazo functionality and metal carben of endocyclic vinyldiazocarbonyl compounds will enhance the operational convenience of the vinyldiazocarbonyl compound and range of intermolecular reactions which the metal vinylcarbene is capable of, relative to corresponding acyclic species.

**Figure 2.4**. Endocyclic vinyldiazocarbonyl compounds synthesized.
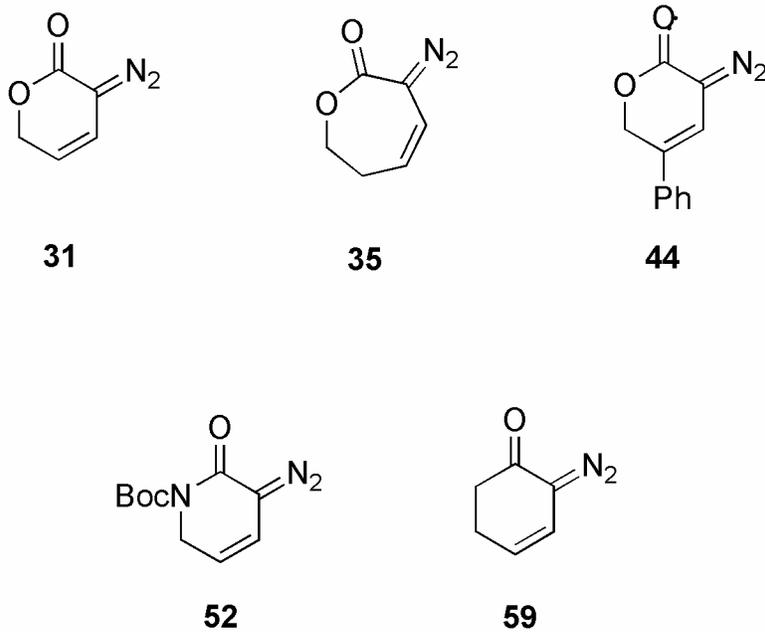


Five endocyclic vinyldiazocarbonyl compounds (**31**, **35**, **44**, **52**, **59**) were prepared. To evaluate the scope of endocyclic vinyldiazocarbonyl compounds in asymmetric metal carbene reactions, the structures were varied so that the reactivity of electronically and structurally variable endocyclic vinyldiazocarbonyls could be compared. To vary the carbonyl electronics, the analogous six-membered rings lactone **31**, lactam **52**, and ketone **59** were prepared. The seven-membered ring lactone **35** and substituted lactone **44** were also readily obtained for comparison to **31**.

The preparation of **31** was used to evaluate the efficiency of two common methods of vinyldiazoacetate synthesis toward the synthesis of endocyclic vinyldiazocarbonyl compounds, a reduction-dehydration protocol and the direct diazo transfer reaction. The results of this study indicated that a direct diazo

transfer reaction performed upon an unsaturated carbonyl compound was the most efficient means of generating the corresponding endocyclic vinyldiazocarbonyl compounds. Using this strategy, **31**, **35**, **44**, and **52** were obtained from corresponding unsaturated lactones and lactam. However, direct diazo transfer was unsuccessful in the preparation of **59**. The synthesis of **59** could be achieved using the reduction-dehydration protocol, albeit in poor yield. As we anticipated, the endocyclic vinyldiazocarbonyls **31**, **35**, **44**, **52** and **59** possesed a greater stability than acyclic vinyldiazo compounds. The endocyclic vinyldiazocarbonyl compounds could be kept in a freezer at 4 $^{\circ}$C for a period of weeks with only minor decomposition. In the study of dirhodium catalyzed reactions of these vinyldiazocarbonyl compounds (described in Chapter 3), we found no appreciable difference in yields and selectivities for **31** in reactions run with freshly purified **31** and **31** that had been stored for up to a week at 4 $^{\circ}$C.

## IV.    EXPERIMENTAL


**General Information:**  NMR spectra were recorded on a Bruker DRX-400 MHz instrument and obtained as solutions in deuterochloroform unless otherwise noted. Chemical shifts of ^{1}H NMR spectra are quoted relative to internal $Me_4Si$ (0.00 ppm); those of ^{13}C NMR spectra are quoted relative to solvent (77.0 ppm). NMR spectra of **31**, **35**, **52** and **59** were obtained using deuterated acetonitrile; chemical shifts of the ^{1}H NMR spectra are quoted relative to residual solvent (1.94 ppm), chemical shifts of the ^{13}C NMR spectra are quoted relative to solvent (1.2 ppm). NMR spectra of **44** were obtained in deuterated acetone; chemical shifts of the ^{1}H NMR spectrum are quoted relative to residual solvent (2.05 ppm), and chemical shifts of the ^{13}C NMR spectrum are quoted relative to solvent (30.8 ppm).   High-resolution mass spectra were obtained on a JEOL SX102a spectrometer. IR spectra obtained on a JASCO FT/IR-4100.   Thin layer chromatography was performed on Merck Silica Gel 40 $F_{254}$ glass backed plates, visualization was achieved with UV or $KMnO_4$ stain. Column chromatography was performed on 40-63 $\mu$m, 230-400 mesh, 60 A silica gel.  Mesyl azide was prepared by a previously published procedure.[39]  All reagents were purchased from Aldrich unless otherwise specified.   Anhydrous dichloromethane and tetrahydrofuran were obtained by dried by nitrogen forced-flow over activated alumina as described by Grubbs.[40]  This work was performed in collaboration with Kuo-Hui Wu, who is gratefully acknowledged for the preparation of **27**-**31**.

**5-[3-(Benzyloxy)propanoyl]-2,2-dimethyl-1,3-dioxane-4,6-dione        (27):**

Carboxylic acid **26** (7.5 g, 42 mmol) was dissolved in oxalyl chloride (7.5 mL, 86 mmol) in a round bottom flask and stirred for 4 hours, at which point excess oxalyl chloride was removed under reduced pressure.  The crude oil was then dissolved in anhydrous dichloromethane and the solution was added slowly to a solution of Meldrum's acid (5.0 g, 35 mmol) and pyridine (8.5 mL, 110 mmol) in anhydrous dichloromethane (40 mL).  The reaction solution was allowed to stir overnight, then washed with 1M $HCl_{(aq)}$ (40 mL), water (40 mL), and brine (40 mL).  The organic phase was dried over anhydrous $MgSO_4$, then filtered and concentrated under reduced pressure to a dark red oil.  Purification of the oil by column chromatography on silica gel (4:1 hexanes/ethyl acetate) provided **27** as a yellow oil (8.0 g, 32 mmol, 76% yield).  The ^{1}H NMR spectrum [(400 MHz, $CDCl_3$) $\delta$ 7.35-7.26 (comp, 5H), 4.54 (s, 2H), 3.86 (t, *J* = 4.0 Hz, 2H), 3.43 (t, *J* = 4.0 Hz, 2H), 1.70 (s, 6H)] matched the previously reported ^{1}H NMR spectrum.[27]

**Dihydro-2*H*-pyran-2,4(3*H*)-dione (28):**  The Meldrum's acid adduct **27** (8.0 g, 26 mmol) was stirred in a solution of ethyl acetate (25 mL) and ethanol (25 mL). 10% Pd/C (0.8 g) was added, the flask was placed under a hydrogen filled balloon, and the mixture was stirred overnight.  The black suspension was then filtered through a Celite plug, the filtered solution was washed with ethyl acetate, and the solution was evaporated under reduced pressure to provide a light yellow oil.  The oil was then dissolved in anhydrous THF (50 mL) and this solution was added to a refluxing solution of anhydrous THF (500 mL) over ten hours to effect

intramolecular cyclization. Upon completion of addition, the reaction was refluxed for an additional two hours, then allowed to cool to room temperature and concentrated to a yellow oil. Column chromatography on silica gel (1:1 hexanes/ethyl acetate) afforded **28** as a colourless oil (1.57 g, 16.1 mmol, 62%). The ^{1}H NMR spectrum [(400 MHz, CDCl$_3$): $\delta$ 4.59 (t, $J$ = 6.0 Hz, 2H), 3.57 (s, 2H), 2.73 (t, $J$ = 6.0 Hz, 2H)] matched the previously reported ^{1}H NMR spectrum.[27]

**3-Diazo-3,6-dihydro-2*H*-pyran-2-one (31) [Scheme 2.10]**: A solution of **28** (0.23 g, 2.0 mmol) and mesyl azide (0.24 g, 2.0 mmol) in acetonitrile (20 mL) was cooled to 0 $^o$C, after which triethylamine (0.28 mL, 2.0 mmol) was added, causing the reaction mixture to turn dark red. Twenty minutes after addition of triethylamine, the reaction mixture was concentrated under reduced pressure and filtered through a plug of silica gel (1:1 hexanes/ethyl acetate) to afford **29** as a yellow oil (0.19 g, 1.8 mmol, 90%). ^{1}H NMR (400 MHz, CDCl$_3$): $\delta$ 4.49 (t, $J$ = 6.0 Hz, 2H), 2.73 (t, $J$ = 6.0 Hz, 2H); IR cm$^{-1}$. A solution of **29** (0.19 g, 1.8 mmol) in anhydrous THF (10 mL) was stirred at 0 $^o$C, and a THF solution of LiAlH($^t$BuO)$_3$ (1.8 mL, 1 M, 1.8 mmol) was slowly added. The resulting solution was warmed to room temperature and stirred overnight, after which it was cooled to 0 $^o$C and quenched by the addition of water (10 mL). The reaction mixture was extracted three times with dichloromethane, the combined organic layer was dried over anhydrous MgSO$_4$ and filtered, then the organic solution was concentrated under reduced pressure to afford the alcohol **30** (40 mg) as a crude yellow oil. The unpurified alcohol was dissolved in anhydrous dichloromethane (5 mL),

triethylamine (1.2 mL, 8.0 mmol) was added, and the solution was cooled to 0 $^{\circ}$C. A solution of POCl$_3$ (0.28 mL, 3.0 mmol) in anhydrous dichloromethane (2 mL) was added to the solution over 30 min, after which the solution was allowed to warm to room temperature overnight.  The reaction was poured onto ice-water and the aqueous phase was extracted three times with dichloromethane.  The combined organic extract was washed with brine and dried over anhydrous MgSO$_4$.  Column chromatography on silica gel (1:1 ethyl acetate/hexanes) afforded **31** as an orange solid (27 mg, 0.22 mmol, 14% yield from **29**): mp 60 $^{\circ}$C; $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ 6.30 (dt, $J$ = 9.8, 1.8 Hz, 1H), 5.41 (td, $J$ = 9.8, 3.5 Hz, 1H), 4.96 (dd, $J$ = 3.5, 1.8 Hz, 2H); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$) $\delta$ 165.2, 115.0, 113.8, 70.8 (C=N$_2$ missing); IR (neat) 3073, 2882, 2098, 1668 cm$^{-1}$; HRMS (EI) calcd for C$_5$H$_4$N$_2$O$_2$ 124.0273, found 124.0275 (M+).


**3-Diazo-3,6-dihydro-2*H*-pyran-2-one (31) [Scheme 2.11]:** A solution of 3,5-dihydro-pyran-2-one (0.38 mL, 4.1 mmol) in acetonitrile (25 mL) was stirred in a round bottom flask at 0 $^{\circ}$C.  *p*-ABSA (**19**) (1.23 g, 5.1 mmol) and DBU (0.77 mL, 5.1 mmol) were added to the stirred solution. After three hours, the resulting brown solution was evaporated to a thick oil, which was purified *via* flash chromatography on silica gel (2:1 hexanes/ethyl acetate), eluting **31** as a bright yellow band.  Fractions were evaporated and dried under vacuum to yield **31** as an orange solid (0.24 g, 1.9 mmol, 47%).  Characterization data for **31** described in experimental of Scheme 2.10.

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**6,7-Dihydrooxepin-2(5*H*)-one** (**34**): *N*,*N*-Diisopropylamine (4.8 mL, 34 mmol) was stirred in anhydrous THF (100 mL) at -78 °C under a nitrogen atmosphere in a flame dried round bottom flask, a hexane solution of *n*BuLi (12 mL, 31 mmol, 2.5 M) was slowly added, and the solution was stirred for 15 minutes. ε-Caprolactone **33** (3.0 mL, 28 mmol) in a solution of THF (10 mL) was slowly added. Upon completion of addition the resulting yellow solution was stirred for 30 minutes. A solution of phenylselenyl bromide (6.67 g, 28 mmol) in THF (10 mL) was then quickly added, and the yellow solution was stirred for 15 minutes, at which time it was removed from the bath, allowed to warm to room temperature, and quenched by the addition of water (10 mL). Approximately two thirds of the solvent was removed under reduced pressure, and diluted with water (100 mL). The reaction mixture was extracted three times with diethyl ether (60 mL), then the combined organic extract was washed with brine (30 mL) and dried over anhydrous $MgSO_4$. The solution was concentrated to a red oil and purified by column chromatography on silica gel (2:1 hexanes/ethyl acetate) to provide the selenide as a clear oil (2.57 g, 9.5 mmol, 34% yield). The ^{1}H NMR spectrum [(400 MHz, $CDCl_3$) δ 7.63-7.58 (comp, 2H), 7.34-7.28 (comp, 3H), 4.60-4.54 (m 1H), 4.32-4.21 (comp, 2H), 2.20-1.60 (comp, 6H)] matched that previously reported. The selenide (2.57 g, 9.6 mmol) was then stirred in dichloromethane (25 mL) at 0 °C, and *m*-CPBA (3.28 g, 14.3 mmol) in a solution of dichloromethane (10 mL) was added. The reaction mixture was allowed to warm to room temperature and stir for 3 h, over which time a white solid precipitated. Saturated $NaHCO_{3(aq)}$ (30 mL) was added, the phases were

separated, and the aqueous phase was extracted two times with dichloromethane (30 mL each). The combined organic extract was washed with water (40 mL) and brine (30 mL), then dried over anhydrous $MgSO_4$. The mixture was filtered and evaporated under reduced pressure to a yellow oil which was purified *via* column chromatography on silica gel (1:1 hexanes/ethyl acetate) to provide **34** as a clear oil (0.30 g, 2.7 mmol, 28% yield from selenide). The $^1H$ NMR spectrum [(400 MHz, $CDCl_3$) $\delta$ 6.42 (dt, $J$ = 12.5, 4.7 Hz, 1H), 6.00 (td, $J$ = 12.5, 1.6 Hz, 1H), 4.31-4.27 (comp, 2H), 2.55-2.49 (comp, 2H), 2.16-2.10 (comp, 2H)] matched that previously reported.[28]

**3-Diazo-6,7-dihydrooxepin-2(3*H*)-one** (**35**): Prepared following the general procedure in experimental of Scheme 2.11: orange oil (0.13 g, 0.93 mmol, 44%); mp 63-65 $^oC$; $^1H$ NMR (400 MHz, $CD_3CN$) $\delta$ 5.79 (dt, $J$ = 11.5, 1.8 Hz, 1H), 5.50 (dt, $J$ = 11.5, 4.8 Hz, 1H), 4.45-4.33 (comp, 2H), 2.53-2.47 (comp, 2H); $^{13}C$ NMR (100 MHz, $CD_3CN$) $\delta$ 170.7, 123.4, 113.3, 68.2, 31.0 ($C=N_2$ missing); IR (neat) 2900, 2089, 1658 $cm^{-1}$. HRMS-EI $[M]^+$ calcd for $C_6H_6N_2O_2$ 138.0429, found 138.0436.

**2-Phenylbut-3-en-1-ol (40)**: Styrene oxide (3.0 mL, 26 mmol) was stirred in anhydrous THF (80 mL) in a flame dried round bottom flask under a nitrogen atmosphere at 0 $^oC$. A THF solution of vinylmagnesium bromide (30 mL, 27 mmol, 0.87 M) was added over 30 minutes, and the resulting brown solution was

allowed to warm to room temperature. Four hours after addition of vinylmagnesium bromide was complete, the reaction mixture was cooled to 0 $^{\circ}$C and quenched with 1M $HCl_{(aq)}$ (10 mL). Approximately two-thirds of the solvent was removed under reduced pressure, then the solution was diluted with water (80 mL) and extracted three times with diethyl ether (50 mL). The combined organic extract was washed with water (40 mL), brine (40 mL), and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated to a brown oil under reduced pressure, column chromatography on silica gel (5:1 hexanes/ethyl acetate) provided the alcohol **40** as a clear oil (0.86 g, 5.7 mmol, 22%). The $^1$H NMR spectrum [(400 MHz, $CDCl_3$) $\delta$ 7.35-7.15 (comp, 5H), 5.99 (ddd, $J$ = 17.9, 10.3, 7.6 Hz, 1H), 5.21-5.10 (comp, 2H), ), 3.79 (dd, $J$ = 7.2, 1.2 Hz, 2H), 3.50 (q, $J$ = 7.6 Hz, 1H) 1.76 (br s, 1H)] matched that previously reported.[41]

**2-Phenylbut-3-en-1-yl acrylate (41)**: Alcohol **40** (0.86 g, 5.8 mmol), acrylic acid (0.62 mL, 8.9 mmol), and several crystals of DMAP were stirred in anhydrous dichloromethane (60 mL) under a nitrogen atmosphere in a flame-dried round bottom flask at 0 $^{\circ}$C. A solution of DCC (1.68 g, 7.1 mmol) in dichloromethane (10 mL) was added over 30 minutes, and the reaction was allowed to warm the room temperature overnight. The white suspension which had formed was filtered through a Celite filter pad, washing three times with dichloromethane (20 mL). The filtrate was washed with saturated $NaHCO_{3(aq)}$ (40 mL), water (40 mL), brine (30 mL) and dried over anhydrous $MgSO_4$. The combined organic extract

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was concentrated to a clear oil under reduced pressure and purified by column chromatography on silica gel (6:1 hexanes/ethyl acetate), providing **41** as a clear oil (0.52 g, 2.6 mmol, 57%).  $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33-7.20 (comp, 5H), 6.34 (dd, $J$ = 17.2, 1.4 Hz, 1H), 6.06 (dd, $J$ = 17.4, 10.5 Hz, 1H); 6.00 (ddd, $J$ = 17.2, 10.4, 7.3 Hz, 1H), 5.76 (dd, $J$ = 10.4, 1.5, 1H), 5.18-5.10 (comp, 2H), 4.43 (dd, $J$ = 10.9, 7.7 Hz, 1H), 4.37 (dd, $J$ = 10.9, 6.9 Hz, 1H), 3.72 (fortuitous q, $J$ = 7.3 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.0, 140.3, 137.8, 130.9, 128.7, 128.4, 128.0, 127.0, 116.8, 67.0, 48.7; IR (neat) 3030, 2983, 1722 cm$^{-1}$; HRMS (EI) calcd for C$_{13}$H$_{14}$O$_2$ 202.0994, found 202.0990 (M+).


**5-Phenyl-5,6-dihydro-2*H*-pyran-2-one (43)**: A solution of **41** (0.30 g, 2.9 mmol) in anhydrous dichloromethane (100 mL) was stirred under a nitrogen atmosphere.  Grubbs' catalyst **42** (24 mg, 0.04 mmol) was added, and the reaction mixture was heated to reflux.  After 6h, the light brown solution was concentrated under reduced pressure and purified by column chromatography on silica gel (4:1 hexanes/ethyl acetate), providing **43** as a clear oil (0.23 g, 2.6 mmol, 91%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.39-7.22 (comp, 5H), 6.98 (ddd, $J$ = 9.9, 3.4, 1.3 Hz, 1H), 6.16 (dd, $J$ = 9.9, 2.3 Hz, 1H), 4.56 (ddd, $J$ = 11.2, 5.5, 1.3 Hz, 1H), 4.31 (dd, $J$ = 11.2, 9.0 Hz, 1H), 3.89-3.84 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.2, 148.8, 137.1, 129.0, 127.9, 127.7, 121.2, 72.1, 40.2; IR (neat) 3030, 2893, 1730 cm$^{-1}$.  **43** was submitted for HRMS, however no signals could be obtained which correspond to the expected *m/z*.

**3-Diazo-5-phenyl-3,6-dihydro-2*H*-pyran-2-one** (**44**): Prepared following general procedure described in experimental of Scheme 2.11: orange oil (0.15 g, 0.74 mmol, 39%); 113-115 $^{\circ}$C; $^{1}$H NMR [400 MHz, (CD$_3$)$_2$CO] $\delta$ 7.60-7.30 (comp, 5H), 6.99 (t, $J$ = 1.2 Hz, 1H), 5.42 (d, $J$ = 1.2 Hz, 2H); $^{13}$C NMR [100 MHz, (CD$_3$)$_2$CO] $\delta$ 165.1, 137.1, 130.4, 129.3, 125.8, 125.3, 110.3, 71.9 (C=N$_2$ missing); IR (neat) 2924, 2085, 1685 cm$^{-1}$; HRMS-EI: [M]$^{+}$ calcd. for C$_{11}$H$_8$N$_2$O$_2$ 200.0516, found 200.0586.

**Dihydro-2*H*-pyran-2,4(3*H*)-dione** (**47**): An oven dried 500 mL round bottom flask under a nitrogen atmosphere was charged with a 60 wt% mineral suspension of NaH (3.61 g, 90 mmol).  The mineral suspension was washed with pentanes three times (10 mL), each time removing the solvent *via* cannula filtration. Anhydrous THF (200 mL) was added to the flask, which was then cooled to 0 $^{\circ}$C. The white suspension was stirred vigorously, and methyl acetoacetate (8.6 mL, 80 mmol) was added dropwise.  Upon completion of addition the reaction mixture was stirred for a further 10 minutes, during which time the white suspension turned to a clear light yellow solution.  A hexane solution of *n*-BuLi (32 mL, 80 mmol, 2.5 M) was added dropwise, the reaction mixture turned to a dark red colour.  After stirring a further ten minutes, acetone (5.9 mL, 80 mmol) was added all at once, causing the reaction solution to rapidly turn to a dark yellow solution.  After ten minutes, NaOH$_{aq}$ (80 mL, 200 mmol, 2.5 M) was added and the reaction solution was warmed to room temperature and allowed to stir overnight.  The rapidly stirring biphasic reaction mixture was acidified with 2.5 M

HCl$_{aq}$ to pH 7. Diethyl ether (200 mL) was added, and the layers were separated. Two further extractions with diethyl ether (200 mL each) were performed upon the aqueous layer, the combined organic phases were washed with brine (80 mL) and dried over anhydrous Na$_2$SO$_4$. The mixture was filtered and evaporated under reduced pressure to an orange oil. Recrystallization was performed by dissolving the crude oil in a minimal volume of dichloromethane and slowly adding pentanes. After cooling in a fridge overnight, the resulting crystals were isolated by filtration, washing three times with pentanes (10 mL) to provide **47** as a light yellow crystalline solid (4.21 g, 36 mmol, 37%). The ^{1}H NMR spectrum [(400 MHz, CDCl$_3$) $\delta$ 3.43 (s, 2H), 2.70 (s, 2H), 1.51 (s, 6H)] matched the previously reported ^{1}H NMR spectrum.[30]

**Reaction of 47 with PCl$_5$**: To a flame dried round bottom flask was added anhydrous dichloromethane (15 mL), followed by PCl$_5$ (0.91 g, 4.4 mmol). The solution was stirred at 0 $^o$C under a nitrogen atmosphere, and ketone **47** (0.26 g, 1.8 mmol) was added. The yellow solution was removed from the ice bath and heated to reflux. After one hour, the light yellow solution was cooled to 0 $^o$C, and water (10 mL) was added to quench the reaction. The solvent layers were separated, and the organic phase was washed with water (10 mL), brine (10 mL), and dried over anhydrous MgSO$_4$. The mixture was filtered, and the filtrate was evaporated to a yellow oil by rotary evaporation. The resulting yellow oil was filtered through a short plug of silica gel (2:1 hexanes/ethyl acetate) to provide a white crystalline solid tentatively identified by ^{1}H and ^{13}C NMR spectroscopy as

**49** (0.27 g, 1.7 mmol, 93%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.50-6.47 (m, 1H), 6.07 (s, 1H), 1.92 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.2, 150.9, 146.5, 120.5, 118.1, 27.3, 20.7.


*tert*-**Butyl 6-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (51)**: *N*-Boc valerolactam **50** (1.50 g, 7.5 mmol) was added to stirring anhydrous THF (50 mL) in a flame dried round bottom flask under a nitrogen atmosphere at -78 $^o$C. A THF solution of LHMDS (8.3 mL, 8.3 mmol, 1.0 M) was added dopwise and stirred for an additional 30 minutes, at which point a solution of phenylselenyl bromide (1.42 g, 8.5 mmol) in THF (10 mL) was rapidly added. The resulting clear orange reaction solution was stirred 15 minutes, then warmed to room temperature and quenched with water. Approximately two-thirds of the solvent was removed under reduced pressure, and the solution was diluted with water (60 mL). The solution was extracted three times with diethyl ether (50 mL each), and the combined organic extract was washed with water (40 mL), brine (40 mL), and dried over anhydrous MgSO$_4$. The mixture was filtered and concentrated under reduced pressure to produce an orange oil. Column chromatography on silica gel (4:1 hexanes/ethyl acetate) provided the desired selenide as a yellow oil (2.15 g, 6.07 mmol, 81%). The $^1$H NMR spectrum (400 MHz, CDCl$_3$) $\delta$ 7.66-7.62 (comp, 2H), 7.33-7.22 (comp, 3H), 3.98 (t, *J* = 5.8 Hz, 1H), 3.72-3.57 (comp, 2H), 2.27-2.73 (comp, 4H), 1.53 (s, 9H) is consistent with the desired selenide. The selenide (2.09 g, 5.9 mmol) was then stirred in dichloromethane (15 mL) at 0 $^o$C, *m*-CPBA (2.02 g, 9.0 mmol) in a solution of dichloromethane (10 mL) was

added, and the solution was allowed to warm to room temperature and stir for 3 h, over which time a white solid precipitated. Saturated NaHCO$_{3(aq)}$ (30 mL) was added, the aqueous and organic phases were separated and the aqueous layer was extracted a further two times with dichloromethane (30 mL each). The combined organic extract was washed with water (40 mL) and brine (30 mL), then dried over anhydrous MgSO$_4$. The solution was filtered and evaporated under reduced pressure to produce a colorless oil, which was purified *via* column chromatography on silica gel (4:1 hexanes/ethyl acetate) to provide **51** as a clear oil (0.80 g, 4.1 mmol, 69% yield from selenide). The ^{1}H NMR spectrum [(400 MHz, CDCl$_3$) δ 6.78 (dt, *J* = 9.9, 4.2 Hz, 1H), 5.98 (dt, *J* = 9.9, 1.8 Hz, 1H), 3.86 (t, *J* = 6.4 Hz, 2H), 1.55 (s, 9H)] matched the previously reported ^{1}H NMR spectrum.[42]

***tert*-Butyl 3-diazo-2-oxo-3,6-dihydropyridine-1(2*H*)-carboxylate (52)**: Prepared following the general procedure described for Scheme 2.11: orange oil (0.18 g, 0.42 mmol, 52%); ^{1}H NMR (400 MHz, CD$_3$CN) δ 6.21 (dt, *J* = 9.9, 1.9 Hz, 1H), 5.35 (dt, *J* = 9.9, 3.9 Hz, 1H), 4.30 (dd, *J* = 3.9, 1.9 Hz, 2H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, CD$_3$CN) δ 163.9, 152.4, 115.2, 113.5, 83.4, 48.2, 28.1 (C = N$_2$ missing); IR (neat) 2979, 2086, 1717, 1674 cm$^{-1}$; HRMS-ES [M+H]$^+$ calcd for C$_{10}$H$_{14}$N$_3$O$_3$ 224.1035, found 224.1029.

**1-Methyl-5,6-dihydropyridin-2(1*H*)-one (55)**: The lactam **53** (1.5 mL, 13 mmol) was added to anhydrous THF (120 mL) stirring in a flame dried round bottom

flask under a nitrogen atmosphere at -78 $^{\circ}$C.  A THF solution of LHMDS (31 mL, 31 mmol, 1.0 M) was added dopwise and stirred for 30 minutes, at which point a solution of phenylselenyl chloride (1.42 g, 8.5 mmol) in THF (20 mL) was quickly added.  The resulting clear orange reaction solution was stirred 15 minutes, then warmed to room temperature, and water was added.  Approximately two-thirds of the solvent was removed by reduced pressure and solution was diluted with water (100 mL).  The mixture was extracted three times with diethyl ether (70 mL each); and the combined organic extract was washed with water (60 mL), brine (40 mL), and dried over anhydrous $MgSO_4$.  The mixture was filtered and concentrated under reduced pressure to an orange oil.  The orange oil was purified by column chromatography on silica gel (2:1 hexanes/ethyl acetate) provided the desired selenide **54** as a colourless oil (3.30 g, 12.3 mmol, 90%).  The $^1$H NMR spectrum of selenide **54** [(400 MHz, $CDCl_3$) $\delta$ 7.69-7.66 (comp, 2H), 7.31-7.26 (comp, 3H), 4.02 (t, $J$ = 5.0 Hz, 1H), 3.27 (t, $J$ = 5.7 Hz, 2H), 2.93 (s, 3H), 2.13-1.69 (comp, 4H)] is consistent with the desired selenide.  The selenide (3.25 g, 12.1 mmol) was then stirred in dichloromethane (50 mL) at 0 $^{\circ}$C, *m*-CPBA (4.08 g, 77 wt%, 18.3 mmol) in a solution of dichloromethane (10 mL) was added; and the reaction was allowed to warm to room temperature and stir for three hours, over which time a white suspension formed.  Saturated $NaHCO_{3(aq)}$ (60 mL) was added and the phases were separated; the aqueous phase was extracted two times with dichloromethane (60 mL each).  The combined organic extract was washed with water (50 mL) and brine (30 mL), then dried over anhydrous $MgSO_4$.  The mixture was filtered and evaporated under reduced

pressure to a clear oil, which was purified *via* column chromatography on silica gel (1:1 hexanes/ethyl acetate) to provide **55** as a light yellow oil (1.20 g, 10.8 mmol, 89% yield from **54**). The $^1$H NMR spectrum [(400 MHz, CDCl$_3$) δ 6.54 (dt, $J$ = 9.9, 4.2 Hz, 1H), 5.92 (dt, $J$ = 9.9, 1.8 Hz, 1H), 3.42 (t, $J$ = 7.4 Hz, 2H), 2.99 (s, 3H), 2.42-2.37 (comp, 2H)] matched the previously reported $^1$H NMR spectrum.[42]

**2-Diazocyclohexane-1,3-dione** (**61**): Following a procedure reported by Moriarty and coworkers,[43] a THF (80 mL) solution of **60** (13.50 g, 120 mmol), mesyl azide (15.96 g, 132 mmol) was stirred in a round bottom flask at 0 $^{\circ}$C. Triethylamine (18 mL, 130 mmol) was added in one portion, rapidly turning the light yellow solution dark red. After 20 min, the resulting dark brown suspension was diluted with water (150 mL) and extracted three times with diethyl ether (80 mL). The combined organic extract was washed with brine (50 mL) and dried over anhydrous MgSO$_4$. The mixture was filtered and concentrated under reduced pressure to a brown oil, then passed through a plug of silica gel (2:1 hexanes/ethyl acetate). The diazo compound **61** eluted as a yellow band (14.23 g, 103 mmol, 86%). The $^1$H NMR spectrum [(400 MHz, CDCl$_3$) δ 6.20 (dt, $J$ = 10.0, 1.8 Hz, 1H), 5.38 (td, $J$ = 3.3, 10.0 Hz, 1H), 4.99 (dd, $J$ = 3.3, 1.8 Hz, 2H)] matches that previously reported.

**2-Diazocyclohex-3-en-1-one (59)**: The diazo compound **61** (4.12 g, 30 mmol) was vigorously stirred in methanol (75 mL), and a solution of NaBH$_4$ (0.39 g, 10

mmol) in water (10 mL) was added rapidly. After 5 minutes, the reaction solution was diluted with water (200 mL) and extracted three times with diethyl ether (80 mL each). The combined organic extracts were washed with water (50 mL), brine (50 mL), and dried over anhydrous $MgSO_4$. The mixture was filtered and concentrated by reduced pressure to a yellow oil (0.22 g). The crude alcohol was not further purified, but immediately subjected to dehydration conditions. The yellow oil (0.22 g) was stirred in anhydrous dichloromethane (30 mL each) with triethylamine (0.90 mL, 6.4 mmol) in a flame dried round bottom flask at 0 °C under a nitrogen atmosphere. A solution of $POCl_3$ (0.22 mL, 2.4 mmol) in anhydrous dichloromethane (5 mL) was added over 30 min, after which the reaction mixture was allowed to warm to room temperature overnight. The resulting brown reaction solution was quenched by pouring the reaction solution onto ice-water. After extracting three times with dichloromethane (30 mL each) from the aqueous phase, the combined extract was washed with brine (20 mL) and dried over anhydrous $MgSO_4$. Column chromatography on silica gel (2:1 ethyl acetate/hexanes) afforded **59** as an orange oil (0.13 g, 1.1 mmol, 3% yield from **61**): ^{1}H NMR (400 MHz, $CD_3CN$) δ 6.24 (br d, $J$ = 9.8 Hz, 1H), 5.55-5.50 (m, 1H), 2.48-2.44 (comp, 4H); ^{13}C NMR (100 MHz, $CD_2Cl_2$) δ 194.7, 120.6, 114.5, 37.0, 23.8 (C = $N_2$ missing); IR (neat) 3056, 2958, 2086, 1684 cm^{-1}. No *m/z* consistent with **59** observed in HRMS.

2.49
2.50
2.51
2.51
2.52
2.52

4.33
4.34
4.35

5.48
5.51
5.78
5.78
5.81

**35**

2.44

2.49

1.00

0.95

0.0

5.0

ppm (t1)

3.71
3.73
4.37
4.41
5.15
5.15
5.74
5.75
5.77
5.77
6.03
6.07
6.10
6.31
6.32
7.22
7.22
7.24
7.24
7.29
7.31

0.93
1.83
1.84
1.00
1.81
0.96
4.88

**41**

0.0

5.0

ppm (f1)

106

3.86
3.86
3.87
4.29
4.31
4.32
4.34
4.53
4.54
4.55
4.55
6.15
6.15
6.17
6.18
6.96
6.97
6.97
6.97
6.99
7.00
7.00
7.24
7.35
7.37

**43**

0.97
1.00
1.00
0.95
0.97
5.03

5.0

0.0

ppm (t1)

7.46
7.28
6.95

5.40

4.30
0.68
2.00

5.0
0.0

ppm (f1)

44

108

1.92
1.92

6.07
6.07
6.48
6.49
6.49
6.49

Cl

HO₂C

**49**

6.03

1.00

0.98

5.0

0.0

ppm (f1)

109

1.48

4.29
4.29
4.30
4.30
5.33
5.34
5.35
5.35
5.36
5.37
6.19
6.19
6.20
6.21
6.22
6.22

9.81

2.00

0.91

0.92

0.0

5.0

ppm (t1)

**52**

110

2.44
2.46
2.45

5.51
5.53
5.54

6.23
6.24
6.26

4.64

1.00

1.00

**59**

5.0

0.0

ppm (t1)

31.0

68.2

113.3

123.4

170.7

**35**

165.8

140.1
137.6
130.7
128.5
128.2
127.8
126.8
116.6

66.8

48.5

Ph

**41**

250   200   150   100   50   0
ppm (t1)

114

163.2
148.8
137.1
129.0
127.9
127.7
121.2

72.1

40.2

O=⟨ring⟩—Ph

**43**

250   200   150   100   50   0
ppm (t1)

115

128.01

93.32
91.07
88.28

73.23

34.88

O

N₂

Ph

**44**

ppm (t1)    200    150    100    50    0

116

21.2
27.7

118.6
120.9

147.0
151.4

169.7

HO₂C

Cl

**49**

250    200    150    100    50    0
ppm (f1)

117

28.1
48.2
83.4
113.5
115.2
152.4
163.9

**52**

250   200   150   100   50   0
ppm (t1)

118

194.7
120.6
114.5
37.0
23.8

**59**

250 200 150 100 50 0
ppm (t1)

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119

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# ASYMMETRIC CYCLOPROPANATION AND C-H INSERTION REACTIONS OF ENDOCYCLIC VINYLDIAZOCARBONYL COMPOUNDS

## I.    BACKGROUND

As was described in the preceding chapter, a series of endocyclic vinyldiazocarbonyls (**1-5**) were prepared to evaluate their utility in asymmetric carbene reactions. Having secured a supply of endocyclic vinyldiazocarbonyl compounds, we turned our attention to evaluating their utility in catalytic asymmetric metal carbene chemistry. Intermolecular C—H insertion and cyclopropanation reactions have formed associated products in good yields and high enantiomeric excess with acyclic metal vinylcarbenes.[1-4] Our investigations of endocyclic metal vinylcarbenes were therefore focused upon cyclopropanation and C—H insertion reactions. Of particular interest to us was whether the catalyst $Rh_2(S\text{-}DOSP)_4$ (**6**)[5] would provide similar levels of enantioselectivity in reactions with endocyclic vinylcarbenes as is observed with acyclic vinyldiazoacetates (commonly >90% ee in intermolecular cyclopropanation and

C—H insertion reactions).  Preliminary results of this study have recently been

accepted for publication.[6]

**Figure 3.1**. Endocyclic vinyldiazocarbonyl compounds.
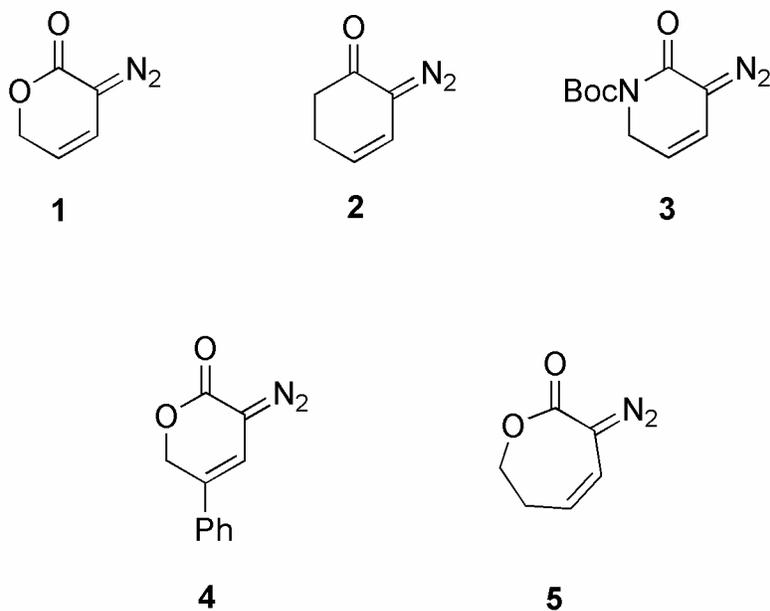
**Figure 3.2**. Asymmetric dirhodium catalysts.
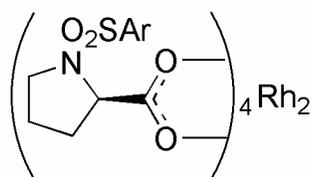


Ar = p-(C$_{12}$H$_{25}$)C$_6$H$_4$
Rh$_2$(S-DOSP)$_4$ (**6**)
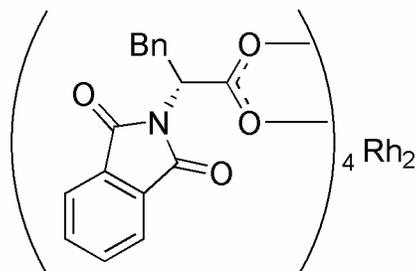
Rh$_2$(S-PTPA)$_4$ (**7**)
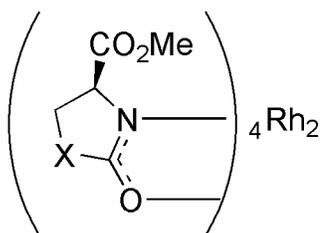


| X = CH$_2$ | Rh$_2$(S-MEPY)$_4$ | (**8a**) |
| X = O | Rh$_2$(S-MEOX)$_4$ | (**8b**) |
| X = NCOCH$_2$Bn | Rh$_2$(S-MPPIM)$_4$ | (**8c**) |



| R=Me | Rh$_2$(S-MEAZ)$_4$ | (**9a**) |
| R=i-Bu | Rh$_2$(S-IBAZ)$_4$ | (**9b**) |
| R=l-menthyl | Rh$_2$(S,S-MenthAZ)$_4$ | (**9c**) |
| R=d-menthyl | Rh$_2$(S,R-MenthAZ)$_4$ | (**9d**) |
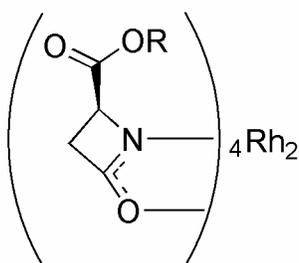
## II. RESULTS AND DISCUSSION

## Asymmetric Cyclopropanation of Endocyclic Vinyldiazocarbonyl Compounds

**Catalyst screening in the cyclopropanation of styrene by 1.** Initial studies of the reactivity of endocyclic vinyldiazocarbonyl compounds focused on screening asymmetric dirhodium catalysts in the cyclopropanation of styrene by the endocyclic vinyldiazocarbonyl compounds. Carboxylate[5,7] and carboxamidate[8-11] ligated asymmetric dirhodium catalysts, which have provided high levels of enantioselectivity in metal carbene cyclopropanation and C—H insertion reactions, were selected for this purpose. All reactions were run in dichloromethane; carboxamidate ligated catalysts were used in refluxing dichloromethane, while reactions of the more reactive carboxylate ligated catalysts were performed at room temperature. Reaction solutions were degassed with $N_{2(g)}$ prior to addition of **1** in all cases. In the initial catalyst screen, a dichloromethane solution of the vinyldiazolactone **1** was added to five equivalents of styrene and 1 mol% of catalyst over eight hours. The diastereoselectivity and enantioselectivity of the cyclopropanation reactions were determined by $^1$H NMR and GC, respectively, upon filtration of the reaction solution over silica gel and evaporation of the solution to an oil. Upon purification of **10**, NOE experiments (see experimental) show the major diastereomer of **10** to be *E*-**10**. Analysis of each reaction by $^1$H NMR spectral analysis prior to

purification of *E*-**10** showed *E*-**10** to be the only observable cyclopropane diastereomer, leading us to assign the diasteromeric ratio of **10** as >20:1.

**Table 3.1**. Catalyst Screen for Cyclopropanation of Styrene with **1**.[a]
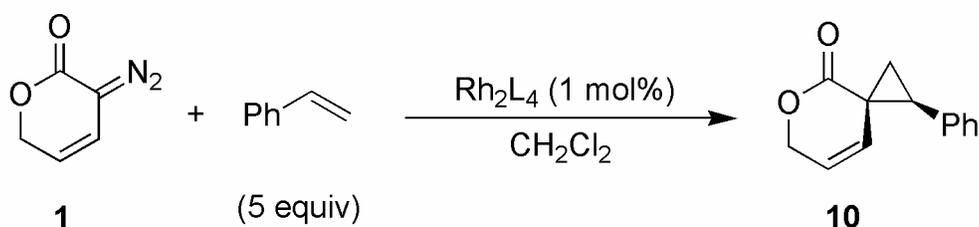


| Rh$_2$L$_4$ | Temperature | Yield (%) | ee (%)[b] |
|---|---|---|---|
| Rh$_2$(OAc)$_4$ | rt | 60 | - |
| Rh$_2$(*S*-DOSP)$_4$ (**6**) | rt | 60 | 14 |
| Rh$_2$(*S*-PTPA)$_4$ (**7**) | rt | 78 | 23 |
| Rh$_2$(*S*-MEPY)$_4$ (**8a**) | reflux | 69 | 10 |
| Rh$_2$(*S*-MEOX)$_4$ (**8b**) | reflux | 63 | 6 |
| Rh$_2$(*S*-MPPIM)$_4$ (**8c**) | reflux | 55 | 10 |
| Rh$_2$(*S*-MEAZ)$_4$ (**9a**) | reflux | 76 | 64 |
| Rh$_2$(*S*-IBAZ)$_4$ (**9b**) | reflux | 78 | 65 |
| Rh$_2$(*S*,*S*-MenthAZ)$_4$ (**9c**) | reflux | 71 | 82 |
| Rh$_2$(*S*,*R*-MenthAZ)$_4$ (**9d**) | reflux | 80 | 84 |

[a] To a dichloromethane solution of 5 equiv styrene and 1 mol% catalyst at the indicated temperature was added a solution of **1** over 8 h.
[b] %ee of **10** determined by GC.

It was immediately apparent that the carboxylate ligated catalyst Rh$_2$(*S*-DOSP)$_4$ (**6**), in almost all cases the optimal catalyst in asymmetric reactions of donor/acceptor substituted diazo compounds,[5] does not provide good levels of

asymmetric induction in the cyclopropanation of **1** by styrene. Only a low level of asymmetric induction was obtained, with 14% ee being measured for cyclopropane **10**. Although dichloromethane is not the optimal solvent for obtaining high levels of enantiomeric excess with $Rh_2$(S-DOSP)$_4$ (**6**),[5] vinyldiazolactone **1** is insoluble in nonpolar solvents such as pentanes and cyclohexanes. The inability to perform the cyclopropanation under solvent conditions generally recognized as optimal for $Rh_2$(S-DOSP)$_4$ (**6**) lends uncertainty to how direct a comparison may be drawn between the performance of $Rh_2$(S-DOSP)$_4$ (**6**) in reactions of acyclic vinyldiazoacetates versus vinyldiazolactone **1**. The carboxylate ligated catalyst $Rh_2$(S-PTPA)$_4$ (**7**)[7] also provided **10** with poor enantioselectivity.

The commonly used carboxamidate ligated catalysts $Rh_2$(S-MEPY)$_4$ (**8a**),[8] $Rh_2$(S-MEOX)$_4$ (**8b**),[9] and $Rh_2$(S-MPPIM)$_4$ (**8c**)[10] provided low levels of enantioselectivity. Upon use of the azetidinate ligated catalyst $Rh_2$(S-MEAZ)$_4$ (**9a**),[11] however, a substantial increase in enantoselectivity was observed; cyclopropane **10** was obtained with 66% ee. The increase in enantioselectivity obtained using the azetidinate ligated catalyst $Rh_2$(S-MEAZ)$_4$ (**9a**) in comparison to $Rh_2$(S-MEPY)$_4$ (**8a**) was surprising to us in view of previous studies of asymmetric dirhodium catalysts. In a previous study of intramolecular cyclopropanation and C—H insertion reactions of the diazoacetate **11**, the azetidinate ligated catalyst $Rh_2$(S-IBAZ)$_4$ (**9b**) provided **12** in 50% ee, in comparison to the 95% ee obtained with $Rh_2$(S-MEPY)$_4$ (**6a**).[12]

**Scheme 3.1.**
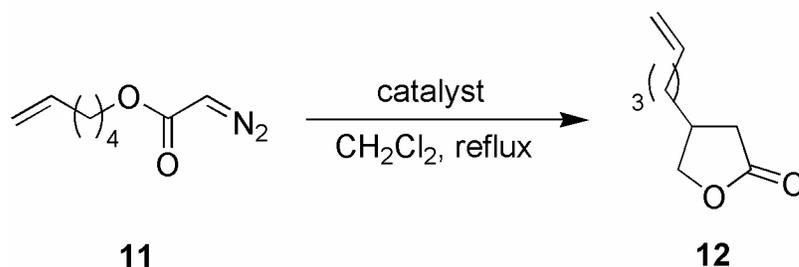


| Rh$_2$L$_4$ | | %ee **12** |
|---|---|---|
| Rh$_2$(S-MEPY)$_4$ | (**6a**) | 95 |
| Rh$_2$(S-IBAZ)$_4$ | (**9b**) | 50 |

     With the increased enantioselectivity of **10** obtained with Rh$_2$(S-MEAZ)$_4$ (**9a**), we investigated other azetidinate ligated dirhodium catalysts available to us. The azetidinate ligated catalyst Rh$_2$(S-IBAZ)$_4$ (**9b**) provided an enantiomeric excess comparable to that of Rh$_2$(S-MEAZ)$_4$ (**9a**). The diastereomeric catalysts Rh$_2$(S,S-MenthAZ)$_4$ (**9c**) and Rh$_2$(S,R-MenthAZ)$_4$ (**9d**),[13] however, increased the enantioselectivity of **10** to 80% and 84% ee, respectively. The isolated yields obtained with catalysts Rh$_2$(S,S-MenthAZ)$_4$ (**9c**) and Rh$_2$(S,R-MenthAZ)$_4$ (**9d**) were comparable to all other catalysts utilized. Previous studies of asymmetric cyclopropanation reactions of diazoacetates catalyzed by Rh$_2$(S,S-MenthAZ)$_4$ (**9c**) and Rh$_2$(S,R-MenthAZ)$_4$ (**9d**) have shown the diastereomer Rh$_2$(S,R-MenthAZ)$_4$ (**9d**) typically provides the highest levels of enantioselectivity, though the differences in enantioselectivities were modest.[13] In the cyclopropanation of **1** with styrene, there is no appreciable difference in asymmetric induction between the two catalysts.

The study of the asymmetric cyclopropanation of styrene with vinyldiazolactone **1** using a series of dirhodium catalysts demonstrated that only the azetidinate ligated dirhodium catalysts provided useful levels of asymmetric induction (>80% ee for **10**). The results of the catalyst screen in Table 3.1 have been reproduced within our research group by a colleague, Kou-Hui Wu.[14] Further asymmetric cyclopropanation reactions of endocyclic vinyldiazocarbonyl compounds **1-5** and a range of olefins focused upon the use of the catalyst Rh$_2$(*S,R*-MenthAZ)$_4$ (**9d**).

**Reaction conditions for cyclopropanation of styrene with vinyldiazolactone 1.** In the initial catalyst screen, a dichloromethane solution of the vinyldiazolactone **1** was added over eight hours to a solution of styrene and catalyst in refluxing dichloromethane. Throughout the course of the catalyst screening study and in subsequent reactions, exposure of the reaction mixture to air was observed to cause a rapid color change in the reaction solution. A reaction solution of the dirhodium catalyst Rh$_2$(*S,R*-MenthAZ)$_4$ (**9d**), for example, turns rapidly from a light purple solution to a brown solution within minutes if the reaction is unsealed. If vinyldiazolactone **1** is added subsequent to this color change, further reaction of **1** with the catalyst does not occur, despite refluxing for several hours. All reactions were therefore degassed with nitrogen prior to addition of the vinyldiazolactone and sealed under a nitrogen atmosphere.

The reaction conditions for the cyclopropanation of **1** with styrene had not been optimized for the catalyst screen (Table 3.1). Upon identifying Rh$_2$(*S,R*-

MenthAZ)$_4$ (**9d**) as providing the cyclopropane **10** in good enantioselectivity and yield, we turned our attention to further investigation of the reaction conditions. In an effort to further increase the enantioselectivity of the cyclopropanation reaction, we repeated the Rh$_2$(*S,R*-MenthAZ)$_4$ (**9d**) catalyzed reaction at room temperature and 0 $^o$C. All other variables were identical to the conditions described in the catalyst screen. When a dichloromethane solution of vinyldiazolactone **1** was added to a reaction solution at room temperature over ten hours, cyclopropane **10** formed in low, highly variable yields (less than 30%). In several instances, the formation of **10** was not observed, and vinyldiazolactone **1** failed to react with the catalyst. Cooling the solution at 0 $^o$C resulted in no reaction of **1** with the dirhodium catalyst.

The slow addition of the diazo compound to a reaction solution is commonly used in reactions of acceptor substituted diazo compounds to prevent the reaction of the diazo compounds and carbene intermediates. Donor/acceptor substituted diazo compounds do not readily dimerize, and the use of slow addition of the diazo compound to the catalyst solution is typically not required,[15] although exceptions do exist.[16-18] All reactions to this point were performed by slow addition of a dichloromethane solution of vinyldiazolactone **1** to the reaction solution; however, it was not known if this was in fact required. A cyclopropanation reaction of **1** and styrene was performed with Rh$_2$(*S,R*-MenthAZ)$_4$ (**9d**) in refluxing dichloromethane in which a dichloromethane solution of **1** was added all at once, as opposed to over eight hours. When **1** was added all at once, even after ten hours the vinyldiazolactone **1** remained the major

component of the reaction mixture. Analysis of the reaction mixture by $^{1}$H NMR and thin layer chromatography showed substantial amounts of **1**, with the formation of several minor products (including **10**). Components of the reaction solution other than **1** and **10** could not be identified. These results would indicate that if the diazo **1** is not added *via* slow addition, a reaction product occurs which suppresses the active catalyst species. It is not apparent what this may be, and further attempts were not made to investigate this. All subsequent reactions were performed using the initial conditions (Table 3.1) of slow addition of a diazo compound to a solution of dirhodium catalyst and substrate.

**Scheme 3.2**.
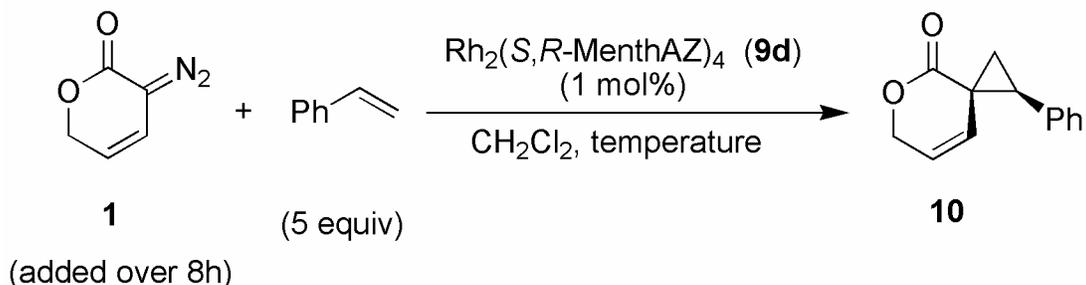


In evaluating the effect of temperature and rate of addition of **1** to the reaction solution, the initial conditions (Table 3.1) provided the highest yields of **10**, with good enantioselectivity obtained using the catalyst Rh$_2$(*S,R*-MenthAZ)$_4$ (**9d**). For all subsequent reactions of endocyclic vinyldiazocarbonyl compounds with olefins, slow addition of the diazo compound to a solution of catalyst and substrate in refluxing dichloromethane as described in the catalyst screen are used as standard reaction conditions.

**Cyclopropanation of styrene with endocyclic vinyldiazocarbonyl compounds 1-5.** The $Rh_2(S,R\text{-MenthAZ})_4$ (**9d**) catalyzed cyclopropanation of styrene with diazo compounds **1**-**5** was used to evaluate the generality of endocyclic vinyldiazocarbonyl compounds in asymmetric metal carbene reactions. Reaction conditions used in the cyclopropanation of **1**-**5** were identical to those described for the catalyst screening of the cyclopropanation of **1** (Table 3.1). As has been previously described, cyclopropane **10** is formed with high diastereoselectivity (>20:1 *E:Z*) in the reaction of styrene and **1** with $Rh_2(S,R\text{-MenthAZ})_4$ (**9d**), as determined by $^1H$ NMR spectral analysis of the reaction mixture prior to purification of **10**. In the reaction of endocyclic vinyldiazocarbonyl compounds **2**-**5** with styrene, only a single cyclopropane compound was identified by $^1H$ NMR spectral analysis of the reaction mixtures. By analogy to the reaction of **1** and styrene, the diastereoselectivity of the cyclopropane compounds obtained from diazo compounds **2**-**5** was assigned to be *E*.

**Table 3.2.** Cyclopropanation of Styrene with Vinyldiazo Compounds **1-5**.[a]



| Diazo | Product | Yield (%) | ee (%)[b] |
|---|---|---|---|
| **1** | **10** | 80 | 84 |
| **2** | **13** | 52 | 26 |
| **3** | **14** | 61 | 37 |
| **4** | **15** | 61 | 39 |
| **5** | **16** | 30 | 14 |

[a] To a dichloromethane solution of 5 equiv styrene and 1 mol% catalyst at the indicated temperature was added a solution of diazo compound over 8 h. [b] %ee of cyclopropane product determined by GC or HPLC, as described in experimental.

As has been previously described, the Rh$_2$(*S*,*R*-MenthAZ)$_4$ (**9d**) cyclopropanation reaction of **1** with styrene proceeds with high isolated yield and enantioselectivity (84% ee). Reaction of vinyldiazoketone **2** under identical reaction conditions provided the cyclopropane **13** in 26% ee,[19] indicating that the asymmetric cyclopropanation is highly sensitive to the carbonyl adjacent to the metal carbene.

The observation that the cyclopropanation of vinyldiazoketone **2** proceeds with poor enantioselectivity is consistent with previous research by our group and others in asymmetric intramolecular cyclopropanation reactions of diazocarbonyl compounds.[2,20,21] The development of catalytic systems which provide high enantiomeric excesses for metal carbenes derived from diazoketones has proven to be more difficult than the development of effective asymmetric catalysts for metal carbenes generated from diazoacetates.[20] A wide variety of asymmetric catalysts (i.e., **6**, **8**, **9**) promote cyclopropanation and C—H insertion reactions with diazoacetates in excellent enantiomeric excesses.[22-25] In contrast, asymmetric cyclopropanation and C—H insertion reactions with diazoketones that proceed in good enantiomeric excess are rare (i.e. Scheme 3.3). Although catalyst systems have been reported which provide good levels of enantioselectivity in the asymmetric cyclopropanation and C—H insertion reactions of diazoketone compounds, they have only been shown to be applicable to limited diazoketone compounds and the further examples of their use have not been described since the initial reports.[26-31]

**Scheme 3.3**.



**17a**

Rh$_2$($R$-MEPY)$_4$ (**6a**)

CH$_2$Cl$_2$, reflux

**18a** (75%), 95% ee



**17b**

Rh$_2$($R$-MEPY)$_4$ (**6a**)

CH$_2$Cl$_2$, reflux

**18b** (82%), 11% ee



**19a**

**19b**
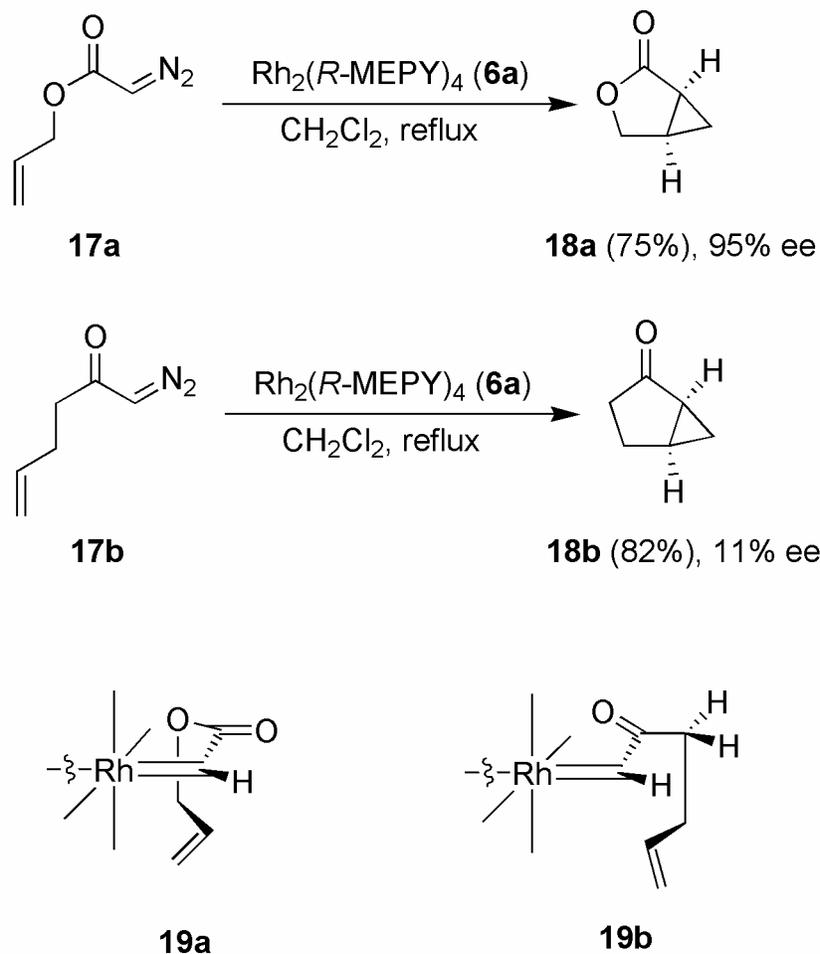
The general failure of metal carbenes derived from diazoketones to undergo reactions with good levels of enantiomeric excess has been the subject of some speculation.[2,21,32] Conformational factors have been implicated in the low levels of enantioselectivity that are typically observed in cyclopropanations of diazoketones. As shown in the proposed transition states **19a** and **19b**, carbenes derived from diazoacetates (i.e. **17a**) are believed to orient the carbonyl *anti* to the metal carbene bond (**19a**), as opposed to a *syn* orientation with carbenes derived from diazoketones (**19b**).[32] The conformation of carbene **19b**

results in cyclopropanation occurring at a greater distance from the catalyst as compared to **19a**, consequently the catalyst ligands exert considerably less enantiocontrol over **19b**. An alternative explanation of the superior enantioselectivities typically obtained with diazoacetate derived metal carbenes proposes that heteroatom resonance with the carbonyl stabilizes the electrophilic metal carbene, leading to improved selectivity.[2]

Cyclopropanation of the lactam **3** also proceeded with poor enantioselectivity; only 37% ee was obtained.[33] Previous research has established that diazoacetamides provide higher enantioselectivites in intramolecular cyclopropanation reactions than analogous diazoacetates (i.e., **20a** *versus* **20b**); in view of this, we found the lowered enantioselectivity in the reaction of lactam **3** in comparison to lactone **1** to be surprising. However, all examples of asymmetric diazoacetamide cyclopropanations that we are aware of utilize *N*,*N*-dialkyl diazoacetamides such as **20b**; the carbamate protecting group of **3** will reduce potential for resonance stabilization of the electrophilic carbene, which may lead to low enantioselectivity.

**Scheme 3.4**.



20a                              21a (88%), >94% ee



20b                              21b (94%), 90% ee
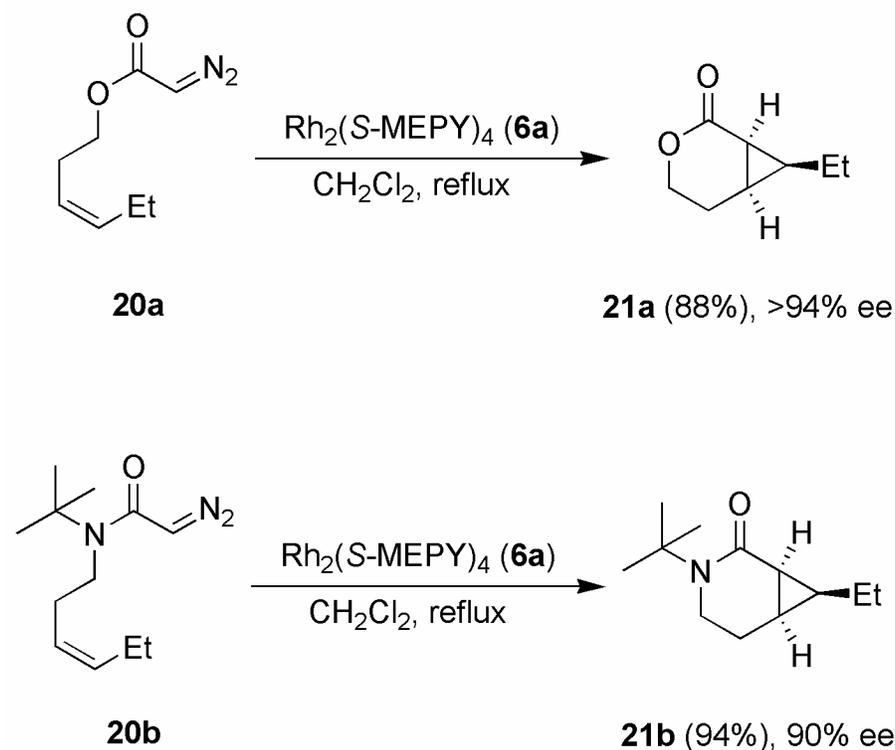
The vinyldiazolactone **4** is the only substituted endocyclic vinyldiazocarbonyl compound which was used in this study. $Rh_2(S,R\text{-MenthAZ})_4$ (**9d**) catalyzed cyclopropanation of **4** by styrene yields cyclopropane **15** in 39% ee. Purification of the cyclopropane compound **15** was complicated by several reaction byproducts; despite considerable efforts to isolate **15** by column chromatography, analytically pure **15** could not be obtained. Due to the difficulty in the isolation of **15** and the low enantiomeric excess of the cyclopropane product, further reactions with **4** were not carried out.

An enantiomeric excess of 14% was obtained for the cyclopropanation of the seven-membered lactone **5**, the reaction of which provided a significant number of uncharacterized byproducts and a low isolated yield of **16**. Several

byproducts were observed by $^1$H NMR of the reaction solution prior to purification. As the cyclopropane product **16** of the vinyldiazolactone **5** was formed in low yield and enantiomeric excess, further investigations of the vinyldiazolactone **5** were not performed.


**Scope of olefins in asymmetric cyclopropanation of 1.** Having determined that the optimal catalyst in the cyclopropanation of **1** with styrene was Rh$_2$(*S,R*-MenthAZ)$_4$ (**9d**), we applied this catalyst to the cyclopropanation of **1** with an expanded series of olefins. Reaction conditions were slightly modified from the conditions used in the catalyst screen of the cyclopropanation of **1** (Table 3.1), the olefin substrates were used at 2.5 equivalents instead of 5 equivalents. Upon completion of the reaction of **1** and an olefin, the reaction solution was filtered through a short plug of silica gel, eluting with dichloromethane, and evaporated to an oil. Analysis of the unpurified oil by $^1$H NMR allowed the determination of the *E:Z* selectivity of the cyclopropanation, and analysis by GC or HPLC was used to determine the enantiomeric excess of the cyclopropane product. Isolated yields of the cyclopropane compounds were obtained by purification using column chromatography on silica gel.

**Table 3.3.** Cyclopropanation of vinyldiazolactone **1**.[a]
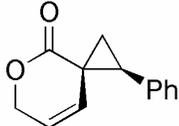


| **1** | (2.5 equiv) | | **10, 22-25** |

| R / R' (alkene) | Product | Yield (%) | $E{:}Z$[b] | % ee $(E)$[c] |
|---|---|---|---|---|
| (vinyl)–Ph | **10** | 80 | >20:1 | 84 |
| (indene) | **22** | 68 | >20:1 | 40 |
| (butadienyl)–Ph | **23** | 86 | 5:1 | 73 |
| (2-methyl dienyl)–Ph | **24** | 81 | 8:1 | 86 |
| (vinylcyclohexene) | **25** | 74 | >20:1 | 80 |

[a] To a dichloromethane solution of 5 equiv styrene and 1 mol% catalyst at the indicated temperature was added a solution of **1** over 8 h. [b] Determined by ¹H NMR spectroscopy. [c] Determined by GC or HPLC, as described in experimental.

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The reaction of 2.5 equivalents of styrene forms cyclopropane **10** with an enantioselectivity and yield that is comparable to that obtained with 5 equivalents (Table 3.1). The cyclopropanation of indene provides **22** in good yield, although the enantioselectivity is only 40%. Only a single diastereomer of **22** was observed in $^1$H NMR spectroscopic analysis of the reaction prior to purification. The relative stereochemistry of **22** was determined by NOE (see experimental).

Cyclopropanation of 1-phenyl-1,3-butadiene provides **23** in a 5:1 *E:Z* ratio, with the enantioselectivity of *E*-**23** measured to be 73% ee. Only the terminal olefin reacted with the metal carbene derived from **1**, no cyclopropane products resulting from the reaction of the internal olefin of 1-phenyl-1,3-butadiene were observed by $^1$H NMR prior to purification of **23**. Increasing the steric bulk of the substituent adjacent to the reacting olefin (cyclopropanes **24** and **25**) led to increases in enantioselectivity and diastereoselectivity of the cyclopropanation. Although the cyclopropane *E,Z* diastereomers of **23** and **24** could be separated, the use of multiple columns of silica gel were required.

**Scheme 3.5**.



**1**

**26** (<20%)
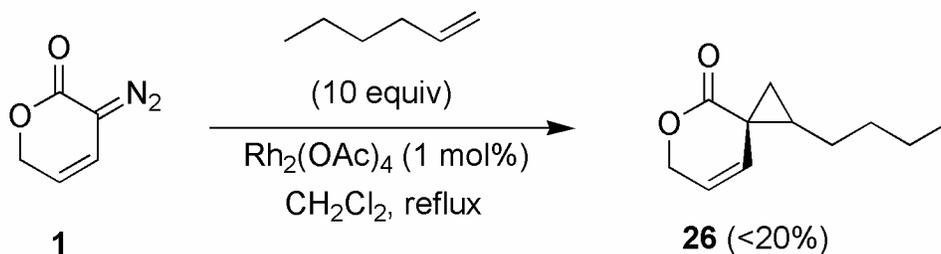
Simple alkenes such as 1-hexene are not as reactive toward metal carbenes as are electron rich olefins.[34] Consequently, the number of equivalents

of olefin to the diazo compound (**1**) was increased to ten; despite this, the cyclopropanation reaction with 1-hexene proceeded in low yield.  Byproducts were formed that were inseperable from **26** by column chromatography with silica gel, and attempts to purify **26** were discontinued when it became apparent that the yield of **26** would be less than 20%.

**Synthetic applications of vinylcyclopropanes.** *Cis*-divinylcyclopropanes are well known to undergo Cope rearrangement to hydroazulenes,[35] a reaction which had seen use in the construction of seven-membered ring carbocycles in the synthesis of natural products.[18,36-38]  The reaction of vinyldiazoacetates with dienes has provided the most general approach to the construction of *cis*-divinylcyclopropanes.[39]  The use of asymmetric catalysts which can provide the cyclopropane intermediate in an enantioselective fashion result in the formation of the corresponding hydroazulene without loss of enantioselectivity.  As is demonstrated by the reaction of 1-phenylbutadiene with vinyldiazoacetate **27**, the Cope-rearrangement of the cyclopropane intermediate **28** occurs following cyclopropanation.[39]  In some cases, the Cope-rearrangement proceeds at sufficiently slow rates that the *cis*-divinylcyclopropane intermediate is isolated and subjected to elevated temperatures to promote the Cope rearrangement.  For example, in the synthesis of tremulenolide A (**33**), cyclopropane **31** was isolated upon reaction of **30**; only upon heating to 140 $^{\circ}$C did the Cope rearrangement proceed to generate the key intermediate **32**.[18]

**Scheme 3.6**.



**27**

**28**

**29** (83%) 98% ee

**30**

**31**

140 °C

**32** (49%)

1) H₂, ClRh(PPh₃)₃

2) K₂CO₃

**33** (68%)

(+/–) - Tremulenolide A
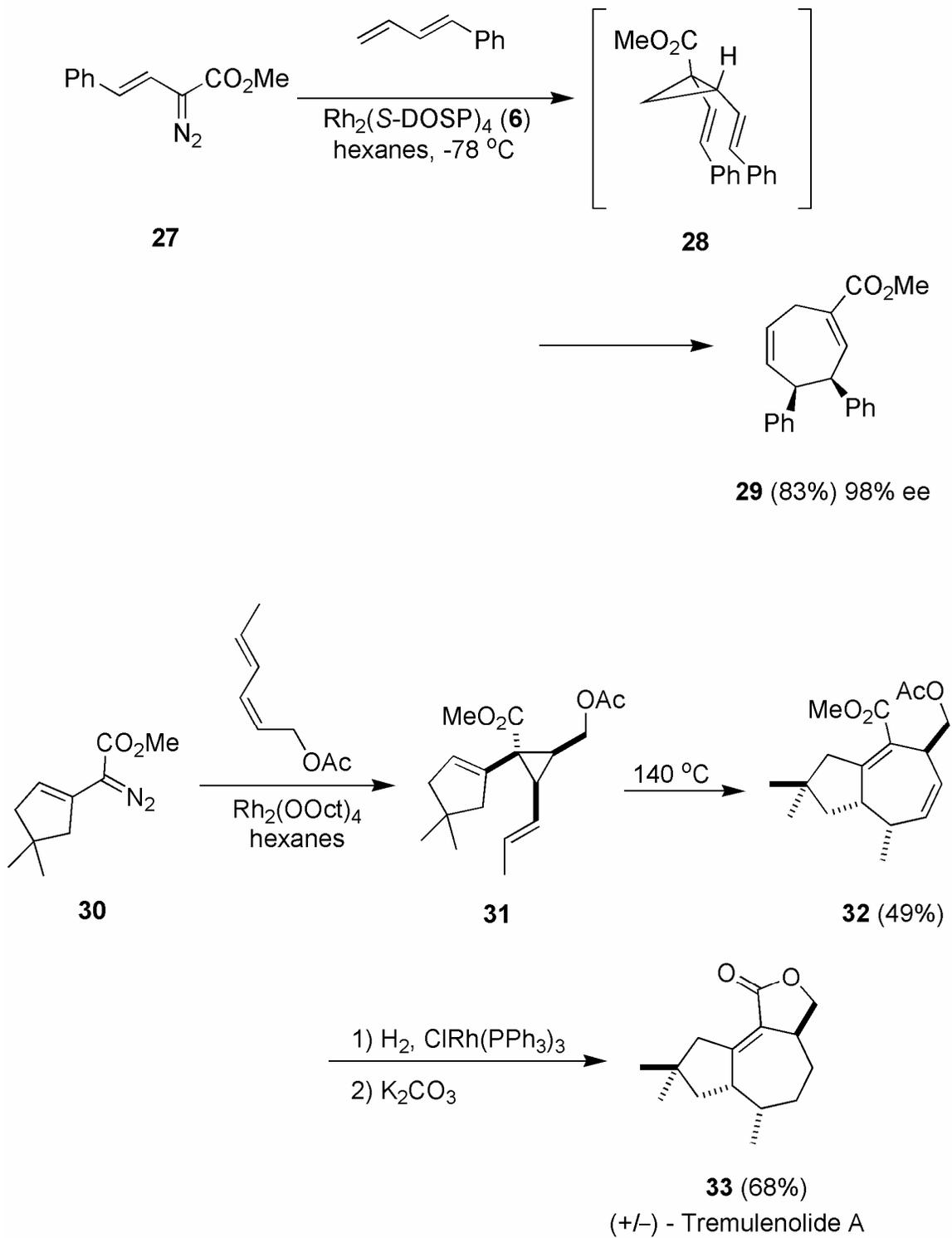
In a demonstration of this by Davies, the diastereomeric dienes **34a** and **34b** are reacted with *trans*-styryldiazoacetate **27** to provide the hydroazulene diastereomers **35a** and **35b**, respectively.[39]   However, stereoselective preparation of two olefin diastereomers is not always practical or possible (i.e., 1-vinylcyclohexene), limiting the hydroazulene diastereomers which may be obtained with *trans*-vinyldiazoacetates.   Control of the olefin geometry of the vinyldiazoacetate would have the same effect as control of that of the diene; but, as was previously discussed (Chapter 2), reactions of vinyldiazoacetates are generally limited to the *trans*-vinyldiazoacetate diastereomer.   Cope rearrangement of *cis*-divinylcyclopropanes derived from **1** would provide a diastereoselective substitution at the 3,4-position of the hydroazulene core that is complimentary to that available with *trans*-vinyldiazoacetates.

**Scheme 3.7**.



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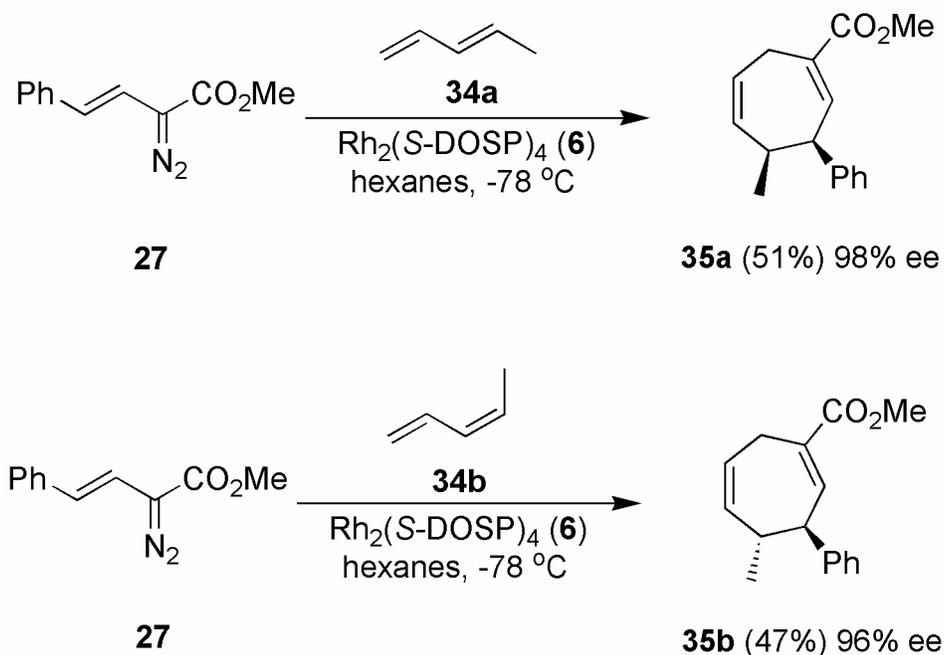
The *cis*-divinylcyclopropanes **23**-**25** prepared by cyclopropanation of dienes with vinyldiazolactone **1** are stable and do not undergo a spontaneous Cope rearrangement. This is easily understood upon consideration of the conformation of *cis*-divinylcyclopropanes **23**-**25**. The olefins of **23**-**25** are locked into an arrangement that prevents effective overlap of the $\pi$-orbitals, and consequently prevents Cope rearrangement. Cleavage of the lactone ring, however, should permit the Cope rearrangement to proceed.

**Figure 3.3**. Spirocyclic lactones **23**-**25**.



**23**-**25**
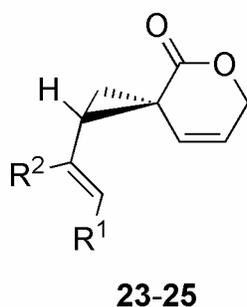
Lactone **23** was treated with LiAlH$_4$ in refluxing THF to effect reductive cleavage of the lactone. The Cope rearrangement proceeded in refluxing THF to yield hydroazulene **39**-**41**. As the *E,Z* diastereomers of **23** were not readily separated by column chromatography on silica gel, the unseparated *E,Z* diastereomers (5:1) were used in the hope that the resulting cyclopropane diol *Z*-**36** and the hydroazulene **39** obtained upon Cope rearrangement of *E*-**36** would be separable. Fortunately, hydroazulene **39** proved to be a highly crystalline material, and could be crystallized from the reaction mixture in good yield. An X-ray crystal structure of **39** was obtained, and confirmed the relative

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stereochemistry.   Crystallization leads to an enrichment of the enantiomeric excess of **39**; measurement of the enantiomeric excess of crystallized **39** by GC demonstrated it to be 92% ee.

**Table 3.4**. Preparations of Hydrozulenes.



**23-25**

**36** R$^1$ = Ph, R$^2$ = H
**37** R$^1$ = Ph, R$^2$ = Me
**38** R$^1$ = (CH$_2$)$_4$, R$^2$ = -

recrystallize

**39-41**
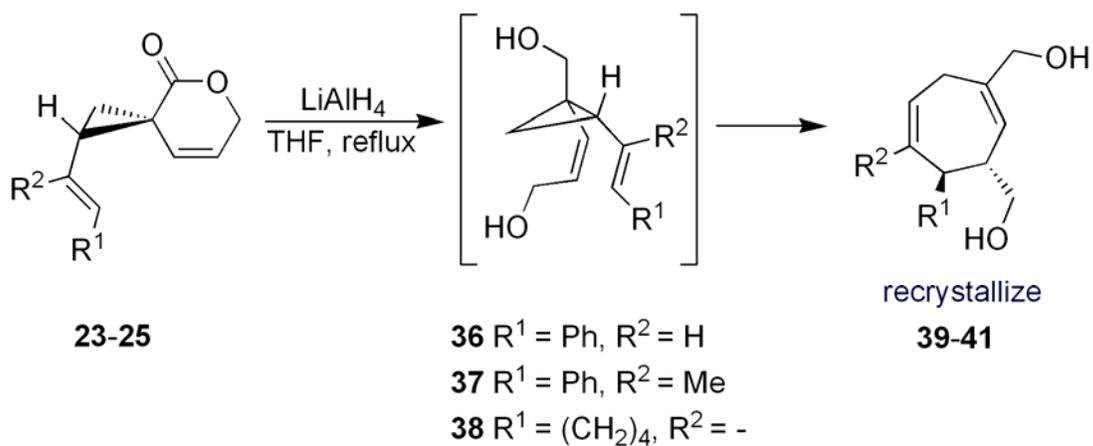
| Cyclopropane | Product |
| --- | --- |
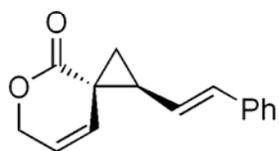


**23**
73% ee
5:1 *E:Z*
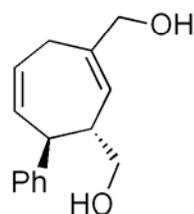
**39** (53%) 92% ee
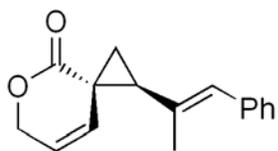


**24**
86% ee
8:1 *E:Z*
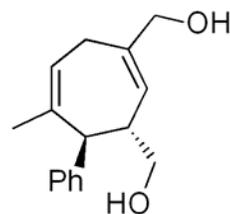
**40** (40%) % ee n.d.



**25**
80% ee

**41** (73%) 94% ee

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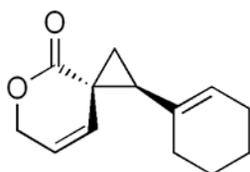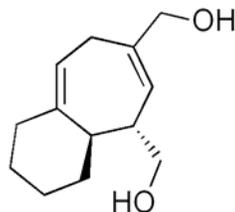
**Figure 3.4**. X-ray crystal structure of **39**.
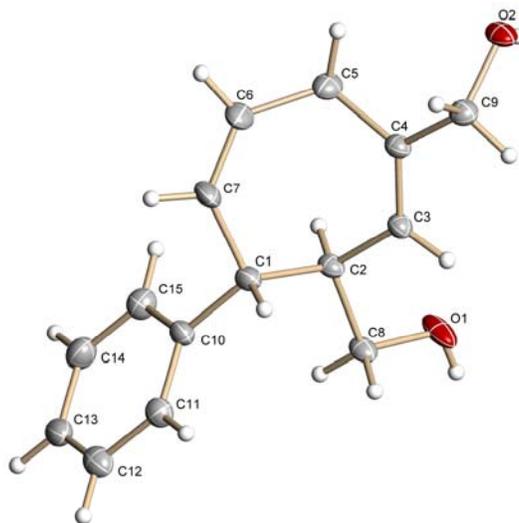


Similarly, treatment of *E,Z*-**24** and *E*-**25** with LiAlH$_4$ in refluxing THF provides the corresponding hydroazulenes upon crystallization. Hydroazulene **41** showed a enantiomeric excess of 94% upon crystallization, however the enantiomeric excess of **40** could not be determined despite considerable efforts to develop GC or HPLC conditions that allowed the separation of enantiomers. Recrystallization of the hydroazulenes **39-41** from the reaction mixture allows a convenient preparation of hydroazulenes from the cyclopropane products of **1** and dienes.

**Figure 3.5**. Natural products containing seven-membered ring carbocycle cores.



Phorbol

Resiniferatoxin

Ingenol

Huratoxin

Genkwanine A
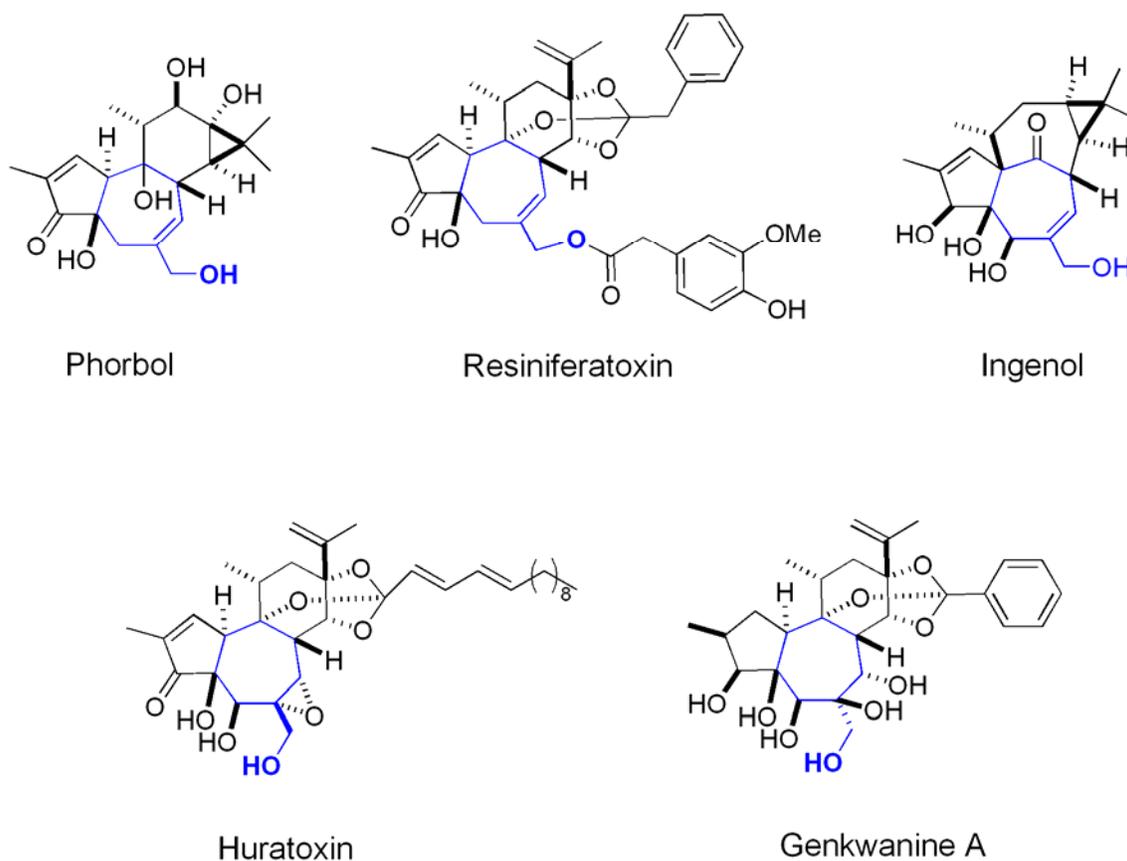
The development of a concise, asymmetric route to hydroazulenes has excellent promise as a future application of asymmetric cyclopropanation reactions of **1**. A wide range of biologically active natural products which posses a seven-membered carbocycle core similar to that present in hydroazulenes **39-41** has been described. The Cope rearrangement of cyclopropanes **23-25** has the potential to be utilized as a convenient approach to seven-membered rings of a variety of natural products or their structural analogues.

## Asymmetric C-H Insertion of Endocyclic Vinyldiazocarbonyl Compounds

**Catalyst screening of C—H insertion of 1,4-cyclohexadiene with 1.** The ability of donor/acceptor substituted diazo compounds to undergo intermolecular C—H insertion reactions has been the subject of considerable research over the past several years. The ability to perform catalytic asymmetric C—C bond formation by insertion of carbenes into unactivated C—H bonds offers considerable synthetic value. Our initial investigations into the intermolecular C—H insertion reaction of endocyclic vinyldiazocarbonyl compounds focused upon the screening of dirhodium catalysts in the reaction of **1** with the C—H insertion substrate 1,4-cyclohexadiene. Although 1,4-cyclohexadiene has been reported as an effective C—H insertion substrate in reactions with aryldiazoacetates,[40,41] no examples have been reported with vinyldiazoacetates. Reactions of the aryldiazoacetate **42** with 1,4-cyclohexadiene and $Rh_2(S\text{-DOSP})_4$ (**6**) are known to proceed with excellent chemoselectivity. Carbon-hydrogen insertion into the allylic methylene C—H bond is significantly favored over cyclopropanation.[41]

**Scheme 3.8**.



42 → 43a (50%, >98 : 2) 71% ee + 43b
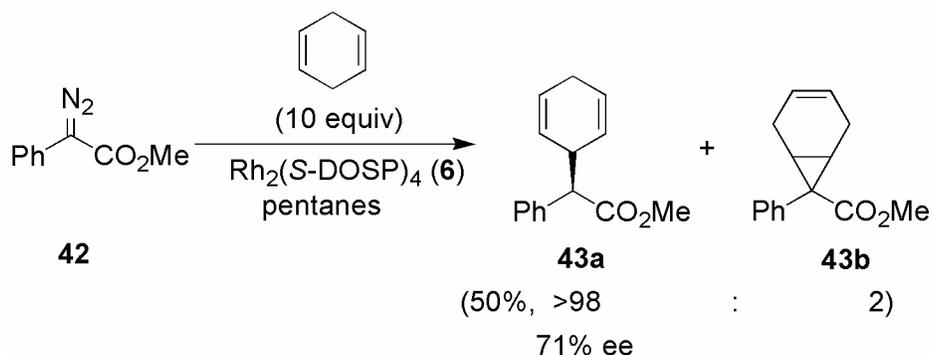
The addition of a dichloromethane solution of vinyldiazolactone **1** over eight hours to dichloromethane solution of 1,4-cyclohexadiene and Rh$_2$(OAc)$_4$ provided the C—H insertion product **44a** and cyclopropane **44b** in a 2:3 ratio, as measured by $^1$H NMR spectrum of the reaction solution prior to pufication.

**Scheme 3.9**.



1 + (5 equiv) → 44a (53%, 2 : 3) + 44b
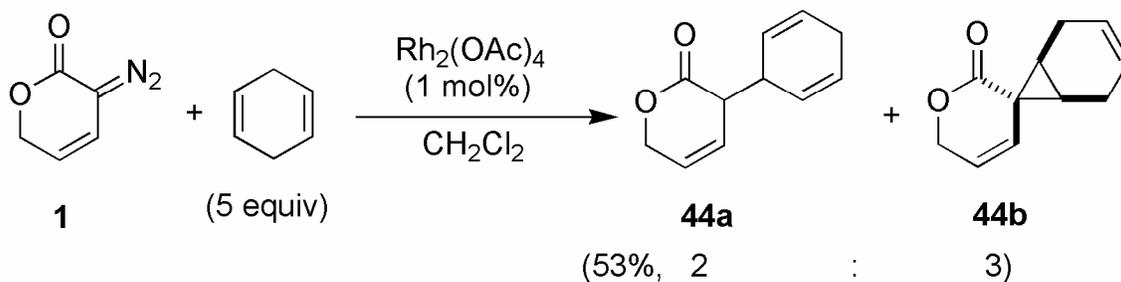
In the subsequent catalyst screen, the relative ratios of **44a:b** were determined by $^1$H NMR spectroscopy prior to purification *via* column chromatography, and the enantiomeric excess of **44a** was determined by GC. The catalyst screen of the C—H insertion reaction was performed in a manner similar to that of the catalyst screen described for the cyclopropanation of styrene

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by **1** (Table 3.1). As with the catalyst screen in the cyclopropanation reaction, the more reactive carboxylate ligated dirhodium catalysts **6-7** were used at room temperature, while carboxamidate ligated dirhodium catalysts **8-9** were used in refluxing dichloromethane.

**Table 3.5**. Catalyst Screen for C-H Insertion of **1** with 1,4-Cyclohexadiene.[a]
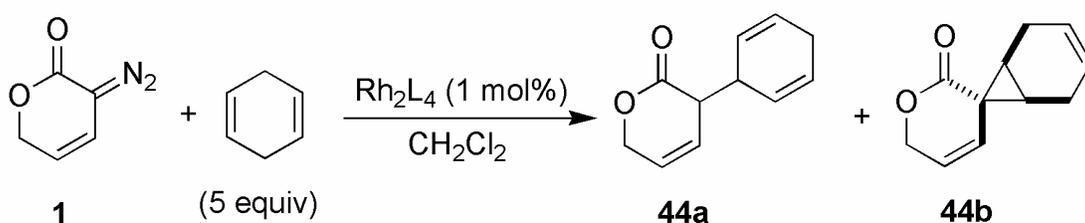


| Rh$_2$L$_4$ | Temperature | Yield (%) | 44a:b[b] | %ee (44a)[c] |
|---|---|---|---|---|
| Rh$_2$(S-DOSP)$_4$ (**6**) | rt | 56 | 1:9 | 18, R |
| Rh$_2$(S-PTPA)$_4$ (**7**) | rt | 46 | 1:4 | 26, S |
| Rh$_2$(S-MEPY)$_4$ (**8a**) | reflux | 47 | 4:1 | 8, R |
| Rh$_2$(S-MEOX)$_4$ (**8b**) | reflux | 34 | 9:1 | 10, R |
| Rh$_2$(S-MPPIM)$_4$ (**8c**) | reflux | 40 | 4:1 | 7, R |
| Rh$_2$(S-MEAZ)$_4$ (**9a**) | reflux | 43 | 9:1 | 60, R |
| Rh$_2$(S-IBAZ)$_4$ (**9b**) | reflux | 52 | 9:1 | 66, R |
| Rh$_2$(S,S-MenthAZ)$_4$ (**9c**) | reflux | 42 | 9:1 | 79, R |
| Rh$_2$(S,R-MenthAZ)$_4$ (**9d**) | reflux | 50 | 9:1 | 80, R |

[a] To a dichloromethane solution of 5 equiv diene and 1 mol% catalyst at the indicated temperature was added a solution of **1** over 8 h. [b] Determined by ^{1}H NMR spectroscopy prior to purification. [c] Determined by GC analysis as described in experimental.

Considering the well documented chemoselectivity exhibited by metal vinylcarbenes formed with Rh$_2$(S-DOSP)$_4$ (**6**) for C—H insertion,[1-3,42] it was with

surprise that we observed that formation of cyclopropane **44b** was the dominant reaction pathway using the catalyst Rh$_2$(S-DOSP)$_4$ (**6**). The small amount of **44a** which was observed was formed with only 18% ee. The preferential formation of cyclopropane **44b** was observed to be general for reactions catalyzed by the carboxylate ligated dirhodium catalysts Rh$_2$(OAc)$_4$, Rh$_2$(S-DOSP)$_4$ (**6**), and Rh$_2$(S-PTPA)$_4$ (**7**).

Fortunately, C—H insertion proved to be the dominant reaction pathway when carboxamidate ligated catalysts were used. Rh$_2$(S-MEPY)$_4$ (**8a**) provided a 4:1 ratio of **44a:b**; however, the enantiomeric excess of **44a** was only 8%. The catalysts Rh$_2$(S-MEOX)$_4$ (**8b**) and Rh$_2$(S-MPPIM)$_4$ (**8c**) also provided **44a** as the major product, but the observed enantioselectivities were similarly low. A significant increase in enantioselectivity of **44a** was observed upon use of the azetidinate ligated catalysts Rh$_2$(S-MEAZ)$_4$ (**9a**) and Rh$_2$(S-IBAZ)$_4$ (**9b**). Optimal levels of enantioselectivity and chemoselectivity were obtained with Rh$_2$(S,S-MenthAZ)$_4$ (**9c**) and Rh$_2$(S,R-MenthAZ)$_4$ (**9d**), providing **44a** with 79% ee and 80% ee respectively. It is notable that the enantioselectivities associated with all asymmetric catalysts used in the C—H insertion catalyst screen closely mirrored those observed for the cyclopropanation of styrene by **1** (Table 3.1).

**Scheme 3.10**.



**44a**
(80% ee)

1) DDQ, PhH

2) H$_2$, Pd/C (10 wt%) EtOAc/MeOH

**45**
$[\alpha]_D^{23}$ +14.1°
(c = 0.28, CHCl$_3$)
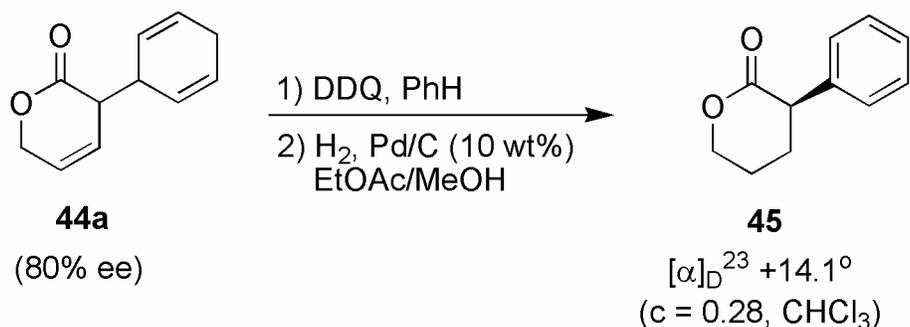
The absolute stereochemistry of **44a** was readily determined by chemical conversion to the known compound **45**.[43] A sample of **44a**, obtained in 80% ee by the Rh$_2$(*S,R*-MenthAZ)$_4$ (**9d**) catalyzed C—H insertion reaction was treated with DDQ to effect oxidative aromatization of the diene. Subseqent hydrogenation of the lactone olefin provided the known lactone **45**; the optical rotation was measured to be $[\alpha]_D^{23}$ +14.1° (*c* = 0.28, CHCl$_3$). The optical rotation of (*R*)-**45** in 72% enantiomeric excess has been reported to be $[\alpha]_D^{22}$ +32.6° (*c* = 0.424, CHCl$_3$),[43] allowing us to assign the absolute stereochemistry of **44a** formed by reaction of Rh$_2$(*S,R*-MenthAZ)$_4$ (**9d**) to be *R*. The reduced optical rotation observed for our sample of **45** relative to the literature value may have resulted from racemization during the process of converting **44a** to **45**, likely due to transposition of the lactone olefin upon aromatization of the diene.[44] Additionally, catalytic hydrogenation is known to result in racemization of stereocenters adjacent to carbonyls.[45]

Based on previous allylic C—H insertion reactions of metal vinylcarbenes we would not expect to obtain the direct C—H insertion product from a reaction

of 1,4-cyclohexadiene and a vinylcarbene.[46-48]  Instead, the product of a C—H insertion/Cope rearrangement (**46**) should be formed.  As has been previously discussed (Chapter 2), the insertion of acyclic metal vinylcarbenes into an allylic C—H bond occurs with concomitant Cope rearrangement.[46]  The failure to undergo concomitant Cope rearrangement, as is observed with acyclic vinylcarbenes ,indicates that the transition state structure for C—H insertion (**47**) places the olefin $\pi$ orbitals of the lactone and diene orthogonal to each other, and not aligned to undergo the Cope rearrangement.

**Scheme 3.11**.



**1**                                    **44a**                    **46**
                                                                (not observed)

**44a** *via*



**47**
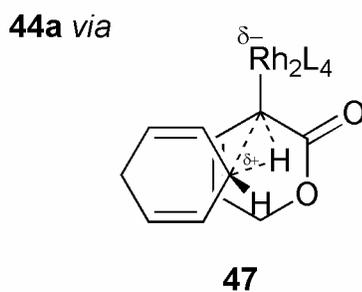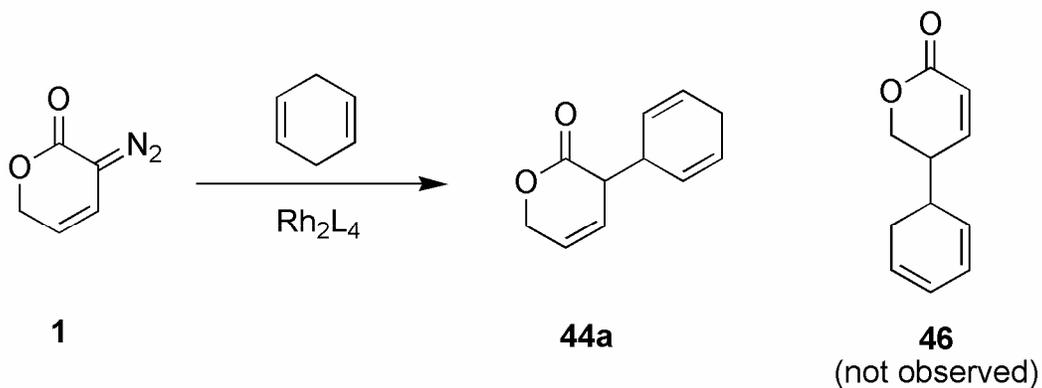
**Scope of C—H insertion substrate in reaction of 1.** Having demonstrated that the intermolecular C—H insertion reaction of **1** with 1,4-cyclohexadiene could be accomplished in good yield and enantioselectivity using dirhodium azetidinate ligated catalysts (**9**), we turned our attention to investigating the substrate scope of the C—H insertion reaction. As is indicated in the proposed transition state **47**, the C—H insertion reaction is believed to proceed through a transition state in which positive charge is developed at the reacting carbon of the C—H bond.[49,50] Consequently, substitution on the C—H insertion substrate which stabilizes the developing positive charge significantly increases the susceptibility of the C—H bond toward insertion by a metal carbene. Allylic and benzylic positions are activated toward C—H insertion, as are positions adjacent to heteroatoms.[50]

Reactions used in evaluating the scope of C—H insertion were performed using the general procedure which has been outlined for the catalyst screen of the C—H insertion reaction of **1** and 1,4-cyclohexadiene (Table 3.5). As a significant catalyst effect was observed for chemoselectivity in the reaction of 1,4-cyclohexadiene, the catalysts $Rh_2(OAc)_4$ and $Rh_2(S\text{-MEAZ})_4$ (**9a**) were utilized in the evaluation of all C—H insertion substrates. Though $Rh_2(S\text{-MEAZ})_4$ (**9a**) does not provide optimal enantioselectivities in the reaction of 1,4-cyclohexadiene, the chemoselectivity for C—H insertion as opposed to cyclopropanation of the diene matches or exceeds that of all other catalysts evaluated, and large quantities of $Rh_2(S\text{-MEAZ})_4$ (**9a**) were readily available for screening purposes.

**Scheme 3.12**.
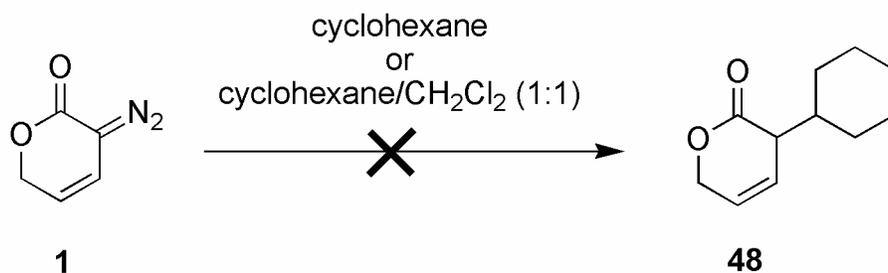


Conditions: a) (1 mol%) Rh$_2$(OAc)$_4$, rt
                b) (1 mol%) Rh$_2$(S-MEAZ)$_4$ (**9a**), reflux

The use of cyclohexane as a C—H insertion substrate was investigated, however the insolubility of the diazo **1** and catalyst in cyclohexanes prevent the reaction of **1** with catalyst. Solubilizing **1** and the catalyst by the addition of dichloromethane as a co-solvent allowed diazo decomposition of **1** to occur, but failed to provide appreciable amounts of **48**; a large number of products were formed, none in sufficient yield to be readily isolated and characterized.

Tetrahydrofuran (THF) is a viable C—H insertion substrate for reactions with aryldiazoacetates; activation by the oxygen of THF directs insertion of the metal carbene into the C—H bond $\alpha$ to oxygen.[15] Vinyldiazolactone **1** was added to a THF solution of dirhodium catalyst at room temperature or reflux. The C—H insertion product **49** could not be identified in any reaction; ^{1}H NMR analysis of the unpurified reaction indicated that several reaction products were formed. No product was formed with sufficient selectivity to be isolated and characterized.

**Scheme 3.13**.
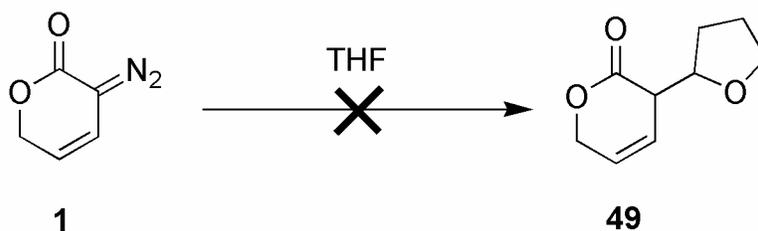


Conditions: a) (1 mol%) $Rh_2(OAc)_4$, rt
b) (1 mol%) $Rh_2(S\text{-}MEAZ)_4$ (**9a**), reflux

The evaluation of C—H insertion substrates was expanded to encompass substrates **50-56**. The intermolecular C—H insertion reactions of substrates **50-56** have been previously reported to occur with aryldiazoacetates and vinyldiazoacetates at the indicated C—H bond.[1,2] In no instance could C—H insertion products be identified in reactions of **50-56**; analysis of the reaction solutions by ^{1}H NMR spectroscopy and GC-MS showed that no major products were formed in the reactions of **50-55**. In all instances, a significant number of products were observed, although some C—H insertion products may be present none were. Olefins **51** and **54** not only failed to undergo C—H insertion with **1**, but cyclopropanation of the olefin was also not observed. This corresponds to prior reports of the scope of cyclopropanation reactions with aryldiazoacetates and vinyldiazoacetates; olefins possessing trans substitution are too sterically hindered to undergo cyclopropanation reaction with the metal carbenes of aryldiazoacetates and vinyldiazoacetates.[51,52]

**Scheme 3.14.**



Conditions: a) (1 mol%) Rh$_2$(OAc)$_4$, rt
b) (1 mol%) Rh$_2$(S-MEAZ)$_4$ (**9a**), reflux



**50**  **51**  **52**  **53**



**54**  **55**  **56**
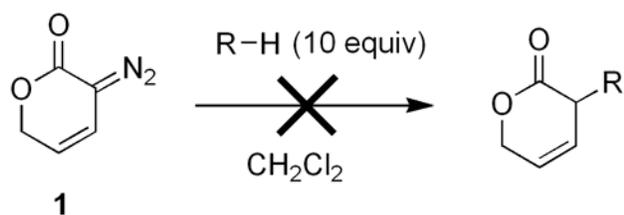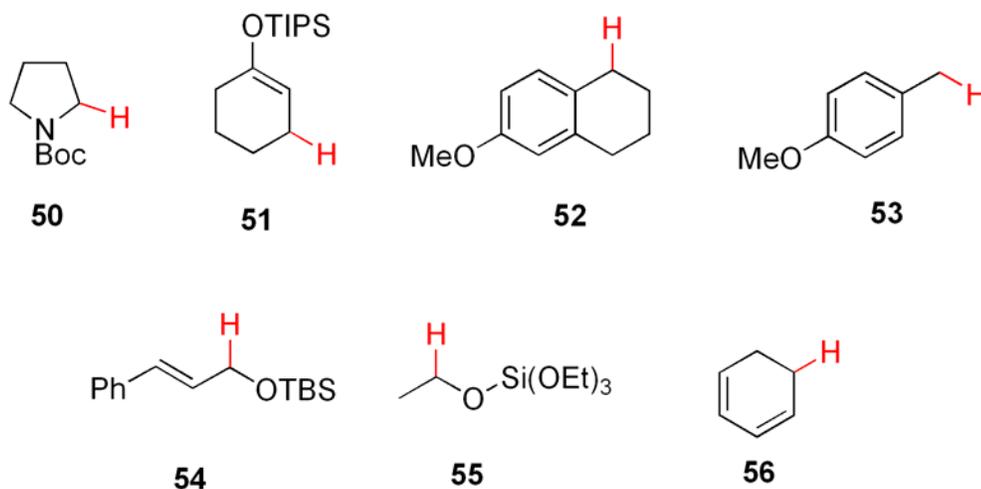
Diene **56** has been used as a C—H insertion substrate in reactions with vinyldiazoacetates; cyclopropanation of the diene does not effectively compete with C—H insertion at the allylic position by vinyldiazoacetates.[46] In the reaction of vinyldiazolactone **1** with **56**, however, cyclopropane **57a** is the exclusive product observed in reactions catalyzed by the catalysts Rh$_2$(OAc)$_4$ or Rh$_2$(S-MEAZ)$_4$ (**9a**). The relative stereochemistry of **57a** was assigned by analogy to the relative stereochemistry determined for cyclopropanes previously prepared from cis disubstituted olefins (**22** and **44b**). Attempts to measure the

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enantiomeric excess of **57a** were unsuccessful, separation of the enantiomers was not achieved by GC.

**Table 3.6**. Reaction of 1,3-Cyclohexadiene with Vinyldiazolactone **1**.[a]
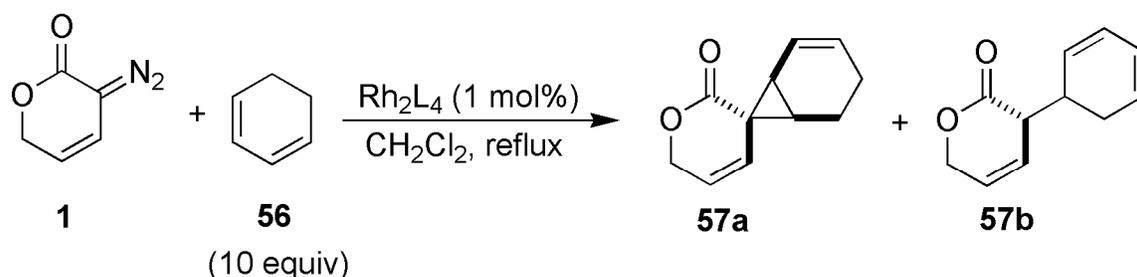


| Rh$_2$L$_4$ | Temperature | Yield (%) | **57a:b**[b] |
|---|---|---|---|
| Rh$_2$(OAc)$_4$ | rt | 70 | >20:1 |
| Rh$_2$(S-MEAZ)$_4$ **(9a)** | reflux | 63 | >20:1 |

[a] To a dichloromethane solutionof 10 equiv diene and 1 mol% catalyst at the indicated temperature was added a solution of **1** over 8 h. [b] Determined by ^{1}H NMR prior to puficiation.

Of the compounds evaluated as intermolecular C—H insertion substrates in reactions with vinyldiazolactone **1**, only 1,4-cyclohexadiene provides appreciable yields of C—H insertion product. The allylic C—H bond of 1,4-cyclohexadiene is highly activated toward insertion as it is activated by two olefins. At this point, no other compounds have been identified as viable intermolecular C—H insertion substrates in the reaction of vinyldiazolactone **1**.

## Asymmetric Cyclopropanation of Endocyclic Vinyldiazocarbonyl Compounds

Previous studies by our group of metal carbene cyclopropanation reactions have led to the development of reaction models to explain the product stereochemistry obtained with carboxamidate ligated dirhodium catalysts. Modeling studies of methyl diazoacetate bound to the catalyst $Rh_2(S\text{-MEPY})_4$ (**8a**) identified four conformational energy minima in which the carbene carboxyl moiety is placed in one of the four quadrants of the catalyst formed by the carboxamidate ligands.[53]  Scheme 3.21 shows the analogous conformations of the carbene derived from the vinyldiazolactone **1** about a generic carboxamidate ligated dirhodium catalyst.

A close correspondence of enantiomeric excesses in the asymmetric cyclopropanation and C—H insertion of **1** over a broad spectrum of dirhodium catalysts (Table 3.1 and Table 3.5) was observed.  This indicated to us that asymmetric induction in both reactions could be described by a single model, as well as emphasizing the reproducibility of asymmetric cyclopropanation and C—H insertion reactions of **1**.  As was earlier described, the catalyst $Rh_2(S,R\text{-}MenthAZ)_4$ (**9d**) provides the C—H insertion product **44a** as the $R$ enantiomer. All other $S$-configured carboxamidate ligated catalysts also provided (R)-**44a**.

The rhodium-bound carbene of **1** is depicted in Scheme 3.21 looking down the Rh—Rh bond axis; the bridging carboxamidate ligands define four quadrants. Four conformers are shown as the vinylcarbene rotates about the Rh—C bond (conformers A-D), in each conformer the carbene is shown bisecting the

carboxamidate ligands.  Attack of a substrate (i.e. 1,4-cyclohexadiene) upon the

carbene is blocked by the ligand esters positioned in quadrants 1 and 4, leaving

quadrants 2 or 3 open to attack.  The absolute stereochemistry which would be

obtained by attack of 1,4-cyclohexadiene upon the carbene is indicated below

the depiction of each conformer.  The putative transition state of the C—H

insertion reaction of 1,4-cyclohexadiene (**47**) is depicted in

Scheme 3.11.

**Scheme 3.15.**



cis − 2,2



**A)** (R)

**B)** (R)

**D)** (S)

**C)** (S)
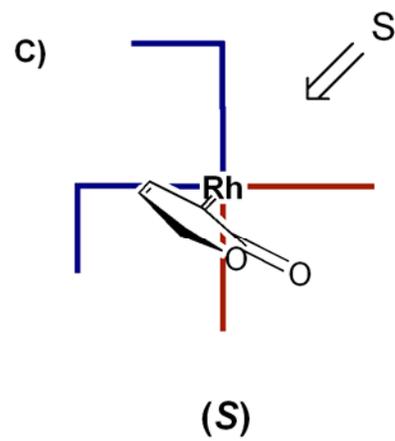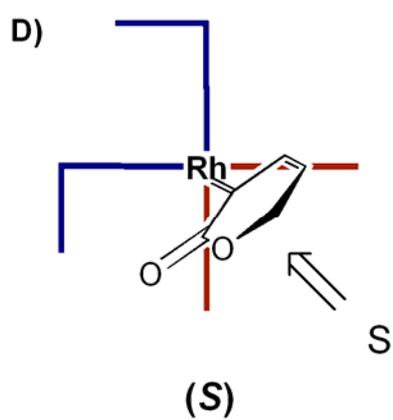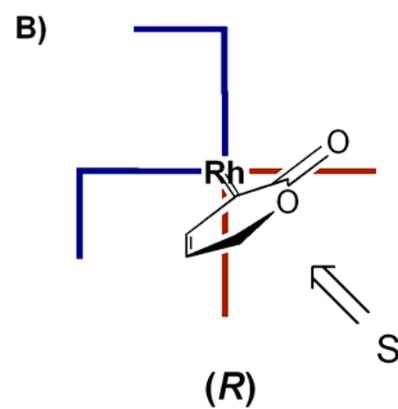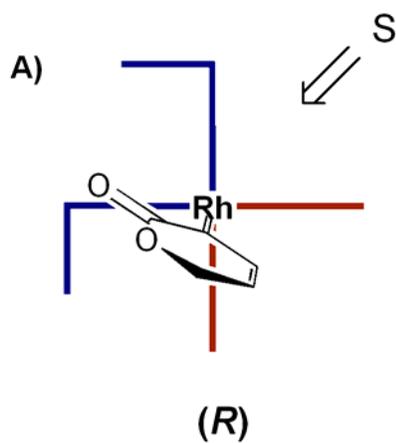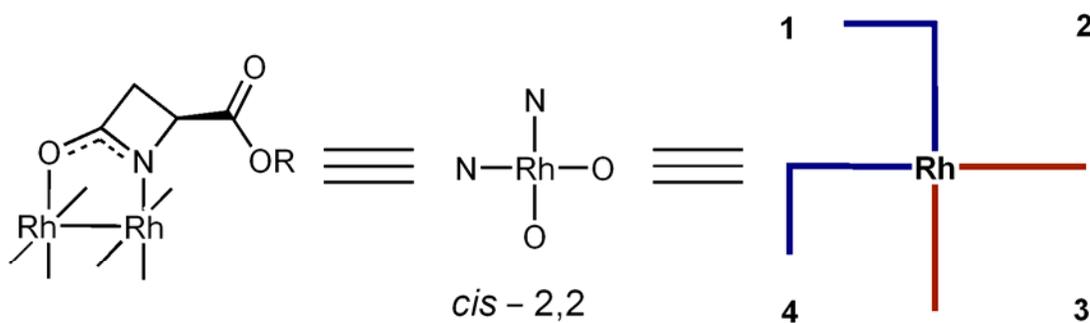
S = 1,4-cyclohexadiene

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It is unlikely that a large population of the rhodium-bound carbene would exist as conformers A or D; electrostatic interactions between the ligand ester and lactone oxygen atoms would disfavor these conformers relative to conformers B or C. Conformers B and C are therefore expected to be the major conformers accessed by the rhodium-bound carbene. The observed absolute stereochemistry of the C—H insertion product (*R*)-**44a** indicates B is the major reacting conformer; the same conclusion was reached in the previous model of the carboxamidate ligated dirhodium catalyzed cyclopropanation of diazoacetates.[53]

## III.   CONCLUSION

The objective of this study was to evaluate the suitability of endocyclic vinyldiazocarbonyl compounds in asymmetric metal carbene reactions which are known to be viable with vinyldiazoacetates. Endocyclic vinyldiazocarbonyl species were expected to be a stable class of vinyldiazocarbonyl compounds, unable to undergo the intramolecular cyclization to pyrazoles that vinyldiazoacetates are prone to. Over the course of this study, endocyclic vinyldiazocarbonyl compounds were observed to have good stability, over several days very little decomposition was observed if the endocyclic vinyldiazocarbonyl was stored at 4 $^{\circ}$C.

Good levels of enantioselectivity was observed for cyclopropanation and C—H insertion reactions with vinyldiazolactone **1**, Rh$_2$($S$,$R$-MenthAZ)$_4$ (**9d**) provided cyclopropanation and C—H insertion products with enantioselectivities of 80% ee and greater. The use of endocyclic vinyldiazocarbonyl compounds **2-5** did not proceed with comparable levels of enantioselectivity, indicating that the ultimate scope of endocyclic vinyldiazocarbonyl compounds in catalytic asymmetric reactions may be limited. These substrates were not investigated as thoroughly as vinyldiazolactone **1**, however, due to their more involved preparations (Chapter 2). A broad catalyst screen of reactions of **2-5** may yet demonstrate synthetically useful levels of enantioselectivity with these substrates.

The development of a model to explain the observed asymmetric induction obtained in the reaction of rhodium-bound carbenes generated from **1** has begun to be developed. An issue which this model should address as it is further developed is the selectivity difference observed in reaction of **1** with azetidinate ligated dirhodium catalysts and all other dirhodium catalysts investigated. Understanding the elements leading to good enantioselectivities with these catalysts may ultimately allow further catalyst development, and increase the scope of endocyclic vinyldiazocarbonyl compounds which may be used to provide good levels of enantioselectivity.

## IV.  EXPERIMENTAL

**General Information:** NMR spectra were recorded on a Bruker DRX-400 MHz instrument and obtained as solutions in deuterochloroform unless otherwise noted.  Chemical shifts of ^{1}H NMR are quoted relative to internal $Me_4Si$ (0.00 ppm), those of ^{13}C NMR are quoted relative to residual solvent (77.0 ppm).  High-resolution mass spectra were obtained on a JEOL SX102a spectrometer.  IR spectra were obtained on a JASCO FT/IR-4100 spectrometer.  Thin layer chromatography was performed on Merck Silica Gel 40 $F_{254}$ glass backed plates, visualization was achieved with UV or $KMnO_4$ stain. Column chromatography was performed on 40-63 $\mu$m, 230-400 mesh, 60 A silica gel.  All reagents were purchased from Aldrich unless otherwise specified.   Preparation of diazo compounds **1-5** detailed in Chapter 2.  Substrates 1-phenyl-1,3-butadiene,[54] 1-phenyl-3-methylbutadiene,[54] 1-vinylcyclohexene,[55] **50**[56] and **51**[57] were prepared by previously published procedures.  C—H insertion substrate **59** was provided by Jason Nichols.   Anhydrous dichloromethane and tetrahydrofuran were obtained by dried by nitrogen forced-flow over activated alumina as described by Grubbs.[58]

**General Procedure for Table 3.1:**  To a flame dried flask containing anhydrous dichloromethane (20 mL) dirhodium catalyst (.013 mmol) and olefin (6.6 mmol) were added.  The apparatus was degassed and heated to reflux under nitrogen. A solution of **1** (160 mg, 1.29 mmol) in 10 mL dichloromethane was added over

eight hours.  Upon completion of addition, the reaction mixture was refluxed for an additional one hour, then filtered through a short plug of silica gel to remove the dirhodium catalyst.  Diastereomer *E*-**10** was the only observable cyclopropane by $^1$H NMR spectroscopy, allowing the *E:Z* diasteromeric ration to be assigned as >20:1, gas chromatography was used to determine the enantiomeric excess of **10**.  Silica gel column chromatography (6:1 hexanes/ethyl acetate) of the reaction mixture provided:

(1*S*,3*S*)-1-Phenyl-5-oxaspiro[2.5]oct-7-en-4-one (**10**): white solid (189 mg, 0.95 mmol, 80%); mp 97-99 $^o$C; GC: (B-DM, 30m x 0.25 mm; 0.25 $\mu$m film, 140 $^o$C/10 min, 1 $^o$C/min ramp to 160 $^o$C), retention times of 45.3 min (-) and 47.3 min (+); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35-7.20 (comp, 5H), 5.72 (dt, *J* = 10.0, 2.8 Hz, 1H), 5.01 (dd, *J* = 2.8, 1.8 Hz, 2H), 4.96 (dt, *J* = 10.0, 1.8 Hz, 1H), 3.26-3.23 (m, 1H), 2.14 (dd, *J* = 9.0, 4.8 Hz), 1H), 1.56 (dd, *J* = 7.7, 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.9, 135.5, 129.1, 128.4, 127.2, 124.7, 121.2, 69.2, 35.2, 26.8, 22.7; IR (neat) 3021, 2885, 1716 cm$^{-1}$; HRMS (EI) calcd for C$_{13}$H$_{12}$O$_2$ 200.0837, found 200.0834 (M)$^+$.


**General Procedure for Table 3.2:**  General procedure described in Table 3.1 was followed, enantiomeric excesses of **13**-**17** determined prior to purification by silica gel column chromatography by GC or HPLC as indicated.

(1*S*,3*S*)-1-Phenylspiro[2.5]oct-7-en-4-one (**13**): (6:1 hexanes/EtOAc) clear oil (93 mg, 0.47 mmol, 52%); GC: (B-DM, 30m x 0.25 mm; 0.25 $\mu$m film, 180 $^o$C), retention times of 17.7 min (major) and 18.7 min (minor), 26% ee; [$\alpha$]$_D^{21}$ +35.1 (*c*

= 0.41, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.32-7.15 (comp, 5H), 5.83 (dt, $J$ = 10.2, 4.2 Hz, 1H), 4.96 (dt, $J$ = 10.2, 1.5 Hz, 1H), 3.05-3.01 (m, 1H), 2.63-2.2.05 (m, 4 H), 2.07 (dd, $J$ = 9.0, 4.3 Hz, 1H), 1.48 (dd, $J$ = 6.8, 4.3 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 209.3, 136.5, 128.3, 129.1, 127.7, 126.9, 126.4, 38.7, 36.8, 23.2, 23.7; IR (neat) 2845, 1697 cm$^{-1}$; HRMS (ESI$^+$) calc. for C$_{14}$H$_{14}$O: 198.1045, found 298.1055 (M+H)$^+$.

*tert*-Butyl (1*S*,3*S*)-4-oxo-1-phenyl-5-azaspiro[2.5]oct-7-ene-5-carboxylate (**14**): (8:1 hexanes/EtOAc) clear oil (142 mg, 0.47 mmol, 61%); HPLC [OD, 98:2 hexanes/2-propanol, 1 mL/min) retention times of 13.7 min and 15.7 min] 37% ee; [α]$_D^{23}$ +21.9 ($c$ = 0.13, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29-7.21 (comp, 5H), 5.62 (dt, $J$ = 10.3, 3.4 Hz, 1H), 4.90 (dt, $J$ = 10.3, 1.9 Hz, 1H), 4.35 (ddd, $J$ = 17.9, 3.4, 1.9 Hz, 1H), 4.29 (ddd, $J$ = 17.9, 3.4, 1.9 Hz, 1H), 3.24-3.20 (m, 1H), 1.56 (s, 9H), 1.46 (dd, $J$ = 7.5, 4.5 Hz, 1H) ; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.4, 152.8, 136.9, 129.6, 128.8, 127.4, 125.6, 120.5, 83.7, 47.9, 35.5, 31.2, 28.5, 23.1; IR (neat) 2988, 1766, 1716 cm$^{-1}$; HRMS (FAB$^+$) calcd for C$_{18}$H$_{21}$NO$_3$Li 306.1681, found 306.1679 (M+Li)$^+$.

(1*S*,3*S*)-1,7-Diphenyl-5-oxaspiro[2.5]oct-7-en-4-one (**15**): (5:1 hexanes/EtOAc) clear oil (94 mg, 0.34 mmol, 61%); HPLC [OD-H, 98:2 hexanes/2-propanol, 1 mL/min) retention times of 42.3 min and 46.5 min] 39% ee; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.25-7.05 (comp, 10H), 5.38 (dd, $J$ = 15.3, 1.2 Hz, 1H), 5.32 (dd, $J$ = 15.3, 1.2 Hz, 1H), 5.25 (br s, 1H), 3.35-3.31 (m, 1H), 2.23 (dd,$J$ = 9.1, 4.8 Hz,

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1H), 1.68 (dd, $J = 7.9$, 4.8 Hz, 1H); HRMS (ESI$^+$) calc. for $C_{19}H_{17}O_2$: 277.12285, found 277.12241 (M+H)$^+$.


(1$S$,3$S$)-1-Phenyl-5-oxaspiro[2.6]non-8-en-4-one (**16**): (6:1 hexanes/EtOAc) white solid (57 mg, 0.27 mmol, 30%); mp 138-139 $^o$C, GC: (G-TA, 30m x 0.25 mm; 0.25 $\mu$m film, 140 $^o$C), retention times of 50.2 min (minor) and 53.8 min (major), 14% ee; $[\alpha]_D^{21}$ +8.9 ($c = 0.50$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.17 (comp, 5H), 5.65 (dddd, $J = 11.8$, 4.5, 3.2, 1.0 Hz, 1H), 4.91 (dt, $J = 11.8$, 2.0 Hz, 1H), 4.62 (ddd, $J = 11.8$, 9.8, 2.0 Hz, 1H), 4.44 (dddd, $J = 12.0$, 5.5, 3.2, 1.0 Hz, 1H), 2.83 (dd, $J = 9.5$, 7.3 Hz, 1H), 2.58-2.49 (m, 1H), 2.36-3.28 (m, 1H), 2.17 (dd, $J = 9.5$, 5.0 Hz, 1H), 1.53 (dd, $J = 7.3$, 5.5 Hz, 1H); 4.5, 3.2, 1.010.3, 3.4 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 175.8, 136.4, 130.6, 128.9, 128.9, 127.5, 125.2, 65.9, 34.7, 32.2, 30.5, 21.9; IR (neat) 3061, 2845, 1697 cm$^{-1}$; HRMS (EI) calcd. for $C_{14}H_{14}O_2$ 214.0994, obs. 214.0991 (M)$^+$.


**General Procedure for Table 3.3:** General procedure described in Scheme 1 was followed, enantiomeric excess of **22**-**25** determined prior to purification by silica gel column chromatography by GC or HPLC as indicated. Relative stereochemistry of **22** determined by NOE.

**22**: (6:1 hexanes/EtOAc) pale yellow solid (205 mg, 0.96 mmol, 68%); mp 100-101 $^o$C; GC: (G-TA, 30m x 0.25 mm; 0.25 $\mu$m film, 160 $^o$C isotherm) retention times of 47.1 min (minor) and 51.5 min (major), 40% ee; $[\alpha]_D^{23}$ 17.5 ($c = 0.19$, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.19 (m, 5H), 5.80 (dt, $J = 10.3$, 3.0

Hz, 1H), 4.99 (dt, $J$ = 16.5, 2.1 Hz, 1H), 4.89 (ddd, $J$ = 16.5, 3.0, 1.8 Hz, 1H), 4.71 (dt, $J$ = 16.3, 2.1 Hz, 1H), 3.51 (dd, $J$ = 6.8, 2.1 Hz, 1H), 3.33 (dd, $J$ = 17.9, 6.8 Hz, 1H), 2.90 (d, $J$ = 17.9 Hz), 2.83 (t, $J$ = 6.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.5, 143.6, 139.7, 127.1, 126.9, 125.3, 124.1, 123.2, 120.4, 68.7, 42.6, 34.8, 32.5, 28.3; IR (neat) 2887, 1717 cm$^{-1}$; HRMS (EI) calcd for C$_{14}$H$_{12}$O$_2$ 212.0837, obs 212.0843 (M)$^+$.

**23**: (6:1 hexanes/EtOAc) clear oil (209 mg, 0.92 mmol, 86%); 5:1 mixture of *E,Z*-**23** diastereomers. Diastereomeric ratio determined by $^1$H NMR prior to chromatography (*E*-**23** 1.28 ppm, *Z*-**23** 1.45 ppm). Enantiomeric excess of *E*-**23** determined below performed prior to isolation of reaction solution. Isolated yield of *E,Z*-**23** obtained upon initial column chromatography (6:1 hexanes/EtOAc). Diastereomers separated by further chromatography (dichloromethane).

(1*R*,3*S*)-1-[(*E*)-2-Phenylvinyl]-5-oxaspiro[2.5]oct-7-en-4-one (*Z*-**23**): Clear oil, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.19 (comp, 5H), 6.59 (d, $J$ = 15.9 Hz, 1H), 6.34 (dd, $J$ = 15.9, 9.1 Hz, 1H), 5.84 (ddd, $J$ = 9.9, 3.6, 2.4 Hz, 1H), 5.31 (ddd, $J$ = 9.9, 2.4, 1.2 Hz, 1H), 5.03 (dt, $J$ = 16.5, 2.4, 1H), 4.95 (ddd, $J$ = 16.5, 3.6, 1.2 Hz, 1H), 2.16-2.10 (m, 1H), 2.05 (dd, $J$ = 7.6, 4.8 Hz, 1H), 1.45 (dd, $J$ = 8.5, 4.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 169.3, 136.9, 132.3, 128.7, 128.5, 127.3, 126.10, 126.06, 120.8, 69.1, 36.6, 28.8, 24.9; IR (neat) 3020, 1722 cm$^{-1}$; HRMS (EI) calcd for C$_{15}$H$_{14}$O$_2$ 226.0994, found 226.0989 (M$^+$).

(1*S*,3*S*)-1-[(*E*)-2-Phenylvinyl]-5-oxaspiro[2.5]oct-7-en-4-one (*E*-**23**): Clear oil, HPLC (OD-H, 90:10 hexanes/2-propanol, 1 mL/min) retention times of 15.0 min

(minor) and 18.9 min (major), 73% ee; $[\alpha]_D^{22}$ +59.3 ($c$ = 0.69, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.21 (comp, 5H), 6.60 (d, $J$ = 15.8 Hz, 1H), 5.96 (dd, $J$ = 15.8, 8.3 Hz, 1H), 5.86 (dt, $J$ = 10.0, 2.9, 1H) 5.46 (dt, $J$ = 10.0, 2.1 Hz, 1H), 5.02-5.01 (comp, 2H), 2.76-2.70 (m, 1H), 2.11 (dd, $J$ = 8.9, 4.6 Hz, 1H), 1.28 (dd, $J$ = 7.3, 4.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.6, 136.6, 133.7, 128.6, 127.6, 126.0, 125.7, 125.9, 121.7, 69.1, 34.4, 27.4, 25.0; IR (neat) 3024, 1721 cm$^{-1}$; HRMS (EI) calcd for C$_{15}$H$_{14}$O$_2$ 226.0994, found 226.0989 (M$^+$).


**24**: (6:1 hexanes/EtOAc) 81%, clear oil, 8:1 mixture $E$,$Z$-**24** diastereomers. Diastereomeric ratio determined by $^1$H NMR prior to chromatography ($E$-**24** 6.38 ppm, $Z$-**24** 6.47 ppm). Enantiomeric excess of $E$-**24** determined below performed prior to isolation of reaction solution. Isolated yield of $E$,$Z$-**24** obtained upon initial column chromatography (6:1 hexanes/EtOAc). Diastereomers isolated by further silica gel column chromatography (dichloromethane).

(1$S$,3$S$)-1-[($E$)-1-Methyl-2-phenylvinyl]-5-oxaspiro[2.5]oct-7-en-4-one ($E$-**24**): Clear oil, HPLC: (AD-H, 98:2 hexanes/2-propanol, 1 mL/min) retention times of 11.8 min (major) and 13.2 min (minor), 86% ee; $[\alpha]_D^{21}$ +77.8$^o$ ($c$ = 0.73, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36-7.23 (comp, 5H), 6.38 (s, 1H), 5.84 (dt, $J$ = 10.2, 2.8 Hz, 1H), 5.33 (br d, $J$ = 10.2 Hz, 1H), 5.05-5.03 (comp, 2H), 2.72 (fortuitous t, $J$ = 7.9 Hz, 1H), 1.96 (dd, $J$ = 8.7, 4.7 Hz, 1H), 1.91 (s, 3H), 1.47 (dd, $J$ = 7.4, 4.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.2, 137.1, 133.6, 128.8, 128.2, 128.0, 126.6, 124.6, 121.2, 69.1, 39.7, 25.8, 23.1, 19.1; IR (neat) 3050, 2884, 1722 cm$^{-1}$; HRMS (EI) calcd for C$_{16}$H$_{16}$O$_2$ 240.1150, found 204.1141 (M$^+$).

(1*S*,3*S*)-1-Cyclohex-1-en-1-yl-5-oxaspiro[2.5]oct-7-en-4-one    (**25**):    (6:1 hexanes/EtOAc) 77%, clear oil, GC: (B-DM, 30m x 0.25 mm; 0.25 $\mu$m film, 160 $^o$C isotherm)  retention times of 82.4 min (minor) and 96.0 min (major), 80% ee; $[\alpha]_D^{22}$ +68.2 (*c* = 0.63,  CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.80 (dt, *J* = 10.2, 2.8 Hz, 1H), 5.57-5.42 (m, 1H), 5.26 (dt, *J* = 10.2, 2.0 Hz, 1H), 5.01-4.99 (comp, 2H), 2.47-2.43 (m, 1H), 2.10-1.45 (comp, 9H), 1.27 (dd, *J* = 7.4, 4.4 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.5, 133.0, 125.1, 125.0, 120.6, 69.1, 37.5, 29.5, 25.2, 25.1, 22.7, 22.31, 22.25; IR (neat) 3020, 2879, 1716 cm$^{-1}$; HRMS (EI) calcd for C$_{13}$H$_{16}$O$_2$ 204.1150, found 204.1148 (M$^+$).

**Representative Procedure for Table 3.4, preparation of 39:**  Unseparated *E,Z-* **23** (5:1 *E:Z*) (203 mg, 0.90 mmol) was stirred in anhydrous THF (10 mL) at 0 $^o$C. LiAlH$_4$ (93 mg, 2.7 mmol) was added portionwise, and the reaction mixture was heated to reflux under nitrogen.  After 36 h the mixture was cooled to 0 $^o$C and quenched *via* dropwise addition of water until gas was no longer observed evolving.  An aqueous solution of NaOH (0.5 mL, 50 wt%) was added, and the mixture was allowed to stir for 10 min.  Anhydrous Na$_2$SO$_4$ was added and the mixture stirred 2h.  The resulting aluminium salts were removed by filtration through Celite, washing with Et$_2$O five times (20 mL each).  Solvent was removed from the filtrate by rotary evaporation, and the residue was crystallized from a minimal amount of dichloromethane and hexanes to yield [(3*S*,4*S*)-4-Phenylcyclohepta-1,5-diene-1,3-diyl]dimethanol (**39**) (110 mg, 53% yield, 92%

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ee) as a white crystalline solid: mp 114 °C, GC: (B-DM, 30m x 0.25 mm; 0.25 μm film, 140 °C/10 min, 1 °C/min ramp to 160 °C) retention times of 68.7 min (minor) and 70.5 min (major), 92% ee; $[\alpha]_D^{20}$ -60.6 ($c$ = 0.34, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30-7.20 (comp, 5H), 5.80-5.73 (comp, 2H), 5.61-5.57 (m, 1H), 4.05 (s, 2H), 3.58-3.53 (m, 1H), 3.43 (dd, $J$ = 10.4, 4.9 Hz, 1H), 3.37 (dd, $J$ = 10.4, 6.2 Hz, 1H), 3.13-3.08 (m, 1H), 2.95-2.89 (m, 1H), 2.77 (dd, $J$ = 18.9, 6.5 Hz, 1H), 1.99 (br s, 1H), 1.67 (br s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 144.0, 142.9, 133.8, 128.5, 128.2, 126.8, 126.5, 126.2, 68.0, 65.0, 45.6, 45.0, 28.6. Structure confirmed by X-ray crystallography.

[(3*S*,4*R*)-5-Methyl-4-phenylcyclohepta-1,5-diene-1,3-diyl]dimethanol (**40**): 40%, white crystalline solid, mp 90-91 °C; $[\alpha]_D^{20}$ -64.4 ($c$ = 0.44, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30-7.17 (comp, 5H), 5.67-5.58 (comp, 2H), 3.98 (s, 2H), 3.57 (d, $J$ = 6.9 Hz, 1H), 3.38-3.36 (m, 1H), 3.09-3.04 (m, 1H), 2.93-2.86 (m, 1H), 2.69 (dd, $J$ = 19.3, 6.7 Hz, 1H), 2.06 (br s, 2H), 1.52 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.6, 143.5, 136.9, 128.3, 126.3, 124.9, 122.3, 67.9, 65.0, 50.0, 45.6, 29.3, 26.4; HRMS (FAB$^+$) calcd for C$_{16}$H$_{20}$O$_2$Li 251.1623, obs 251.1629 (M+Li)$^+$.

(4a*R*,5*S*)-2,3,4,4a,5,8-Hexahydro-1*H*-benzo[7]annulene-5,7-diyldimethanol (**41**): 70%, white crystalline solid, mp 83-85 °C; GC: (B-DM, 30m x 0.25 mm; 0.25 μm film, 170 °C) retention times of 53.5 min (major) and 57.9 min (minor), 94% ee; $[\alpha]_D^{20}$ -42.9 ($c$ = 0.73, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.68-5.65 (m, 1H), 5.45-5.40 (m, 1H), 4.02 (s, 2H), 3.79 (dd, $J$ = 10.5, 4.6 Hz, 1H), 3.75 (dd, $J$ =

10.5, 7.0 Hz, 1H), 2.97-2.89 (m, 1H), 2.61-2.54 (m, 1H), 2.44 (dd, $J$ = 17.3, 7.2 Hz, 1H), 2.28 (br s, 2H), 2.14-1.99 (comp, 2H), 1.93-1.70 (comp, 4H), 1.45-1.16 (comp, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 145.1, 143.7, 125.8, 118.1, 67.3, 64.1, 43.7, 41.1, 39.9, 33.2, 28.9, 27.7, 26.7; HRMS (FAB$^+$) calcd for C$_{13}$H$_{20}$O$_2$Li 215.1623, obs 215.1625 (M+Li)$^+$.

**General Procedure for Table 3.5:** To a flame-dried flask containing anhydrous dichloromethane (20 mL), dirhodium catalyst (.013 mmol) and 1,4-cyclohexadiene (0.61 mL, 6.5 mmol) were added. The apparatus was degassed and heated to reflux under nitrogen. A solution of **1** (160 mg, 1.29 mmol in 10 mL dichloromethane) was added over eight hours. Upon completion of addition, the reaction mixture was refluxed for an additional hour, then filtered through a short silica gel plug to remove the dirhodium catalyst. Integration of diagnostic $^1$H NMR signals of **44a** (4.80 ppm) and **44b** (4.98 ppm) were used to determine the relative ratios of **44a,b**. GC was used to determine the enantiomeric excess of **44a** prior to column chromatographic purification. Silica gel column chromatography (3:1 hexanes/ethyl acetate) of the reaction mixture provided an unseparated mixture of **44a,b** from which isolated yields were calculated from the mass of the product. Pure samples of **44a** and **44b** were obtained by subsequent silica gel chromatography (10:1 hexane/ethyl acetate), but only partial separation was achieved.  Relative stereochemistry of **44b** was determined by NOE.

(3$R$)-3-Cyclohexa-2,5-dien-1-yl-3,6-dihydro-2$H$-pyran-2-one (**44a**) [from Rh$_2$($S$,$R$-MenthAZ)$_4$ catalyzed reaction]**:** Clear oil, GC: Chiraldex G-TA (30m x 0.25 mm),

140 $^{\circ}$C/10 min, 1 $^{\circ}$C/min ramp to 160 $^{\circ}$C), retention times 26.2 min (*R*) and 29.2

min (*S*), 80% ee *R*; $[\alpha]_D^{21}$ +29.5 (*c* = 0.31, CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ

5.97-5.76 (comp, 4H), 5.65-5.50 (comp, 2H), 4.83-4.78 (comp, 2H), 3.62-3.55 (m,

1H), 3.09-3.04 (m, 1H), 2.64-2.58 (comp, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) 170.6,

127.5, 127.1, 125.87, 123.9, 124.0, 122.9, 68.8, 44.4, 38.1, 26.2; IR (neat) 3018,

1733 cm$^{-1}$; HRMS (EI) calcd for C$_{11}$H$_{12}$O$_2$ 176.0837, found 176.0835 (M+).

6'*H*-spiro[bicyclo[4.1.0]hept-3-ene-7,3'-pyran]-2'-one (**44b**) [from Rh$_2$(*S*-DOSP)$_4$

catalyzed reaction]**:** Clear oil, $^1$H NMR (400 MHz, CDCl$_3$) δ 5.95 (dt, *J* = 10.5, 2.9

Hz, 1H), 5.63 (m, 2H), 5.42 (dt, *J* = 10.5, 1.9 Hz, 1H), 4.98 (dd, *J* = 2.9, 1.9 Hz,

2H), 2.54-2.42 (comp, 2H), 2.19-2.16 (m, 2H), 2.09-2.01 (m 2H); $^{13}$C NMR (100

MHz, CDCl$_3$) δ 172.5, 124.2, 122.9, 121.1, 68.5, 28.0, 26.1, 19.6; IR (neat) 2988,

1712 cm$^{-1}$; HRMS (EI) calcd for C$_{11}$H$_{12}$O$_2$ 176.0837, found 176.0837 (M+).


**Determination of absolute stereochemistry of 44a:** A sample of **44a**,**b** (9:1,

84 mg, 0.48 mmol) obtained from the Rh$_2$(4*S*,*R*-MenthAZ) catalyzed C-H

insertion (80% ee as measured by GC) was stirred in toluene (10 mL). 2,3-

Dichloro-5.6-dicyano-1,4-benzoquinone (216 mg, 0.96 mmol) was added. After 2

h, the toluene was evaporated and the reaction mixture was quickly passed

through a short silica gel plug (3:1 hexane/ethyl acetate) to remove a bright red

baseline impurity. The resulting solution was evaporated to a yellow oil. Ethyl

acetate (5 mL) was added, followed by 10% Pd/C (10 mg). The flask was then

placed under a balloon of hydrogen gas. After stirring 12 h, the mixture was

filtered through a Celite pad, washing with ethyl acetate, and evaporated.

Column chromatography (4:1 hexane:ethyl acetate) provided 2-phenyl-δ-valerolactone (71 mg, 86% yield).  The optical rotation of 2-phenyl-δ-valerolactone was measured: $[\alpha]_D^{23}$ +14.1 ($c$ = 0.28,  CHCl$_3$).  A previous report lists the optical rotation of the $R$ enantiomer (72% ee) to be: $[\alpha]_D^{22}$ +32.6 ($c$ = 0.424,  CHCl$_3$), indicating the absolute stereochemistry of the predominant enantiomer of **44a** to be $R$.

**Representative procedure for Scheme 3.14 and Table 3.6:** To a flame-dried flask containing anhydrous dichloromethane (10 mL), Rh$_2$(OAc)$_4$ (4 mg, 1.0 mmol) and 1,3-cyclohexadiene (0.45 mL, 4.8 mmol) were added. The apparatus was degassed with nitrogen, after which a solution of **1** (120 mg, 0.97 mmol in 2 mL dichloromethane) was added over two hours.  Upon completion of addition, the reaction mixture was stirred for an additional one hour, then filtered through a short silica gel plug to remove the dirhodium catalyst and concentrated under reduced pressure to a yellow oil. Analysis of the residue by $^1$H NMR spectroscopy shows excess 1,3-cyclohexadiene and **57a** as the only observable components of the mixture.   Purification of the residual oil by column chromatography on silica gel provided **57a**: clear oil (118 mg, 0.68 mmol, 70%); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.97-5.88 (comp, 2H), 5.83-5.78 (m, 1H), 5.51 (ddd, $J$ = 16.3, 3.5, 1.4 Hz, 1H), 5.00 (dt, $J$ = 16.3, 2.4 Hz, 1H), 4.92 (ddd, $J$ = 16.3, 3.5, 1.4 Hz, 1H), 2.47 (dd, $J$ = 8.9, 4.4 Hz, 1H), 2.25-2.69 (comp, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.7, 129.3, 122.7, 122.0, 121.7, 68.3, 31.9, 29.0, 27.4, 21.4,

15.8; IR (neat) 2988, 1712 cm$^{-1}$; HRMS (EI) calcd for $C_{11}H_{12}O_2$ 176.0837, found 176.0837 (M+).

**Determination of relative stereochemistry of 2b, 3a:**

nOe experiments were performed on a Bruker AM-400 instrument. Observed correlations were used to assign the relative stereochemistry of **2b**, **3a** as those shown.
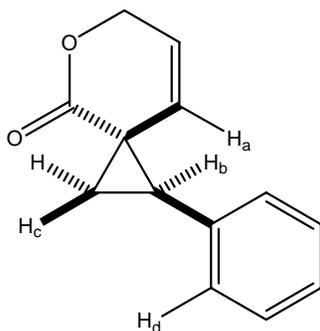


| Irradiated Signal (ppm)/$H_x$ | Correlated Signals (ppm)/$H_x$ | % Correlation |
|---|---|---|
| 4.96/$H_a$ | 1.56/$H_c$ | 1.3 |
| | 7.21 (d, $J$ = 7.3 Hz)/$H_d$ | 0.8 |
| | 3.25/$H_b$ | 0 |
| 3.25/$H_b$ | 7.21 (d, $J$ = 7.3 Hz)/$H_e$ | 1.1 |
| 1.56/$H_c$ | 4.96/$H_a$ | 0.9 |
| | 7.21 (d, $J$ = 7.3 Hz)/$H_d$ | 2.1 |

| Irradiated Signal (ppm)/$H_x$ | Correlated Signals (ppm)/$H_x$ | % Correlation |
|---|---|---|
| 5.63/$H_d$ | 5.42/$H_a$ | 0.1 |
| 5.42/$H_a$ | 5.63/$H_d$ | 0.3 |
| | 2.09-2.01/$H_c$ | 1.1 |
| | 2.19-2.16/$H_b$ | 0 |
| 2.09-2.01/$H_c$ | 5.42/$H_a$ | 0.7 |



| Irradiated Signal (ppm)/$H_x$ | Correlated Signals (ppm)/$H_x$ | % Correlation |
|---|---|---|
| 4.71/$H_a$ | 2.90/$H_d$ | 1.2 |
| 3.51/$H_c$ | No correlation | |
| 2.90/$H_d$ | 4.71/$H_a$ | 1.5 |
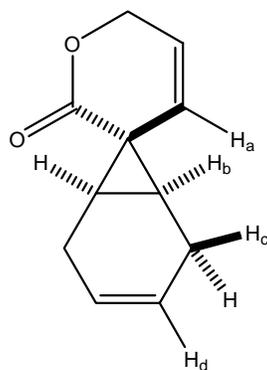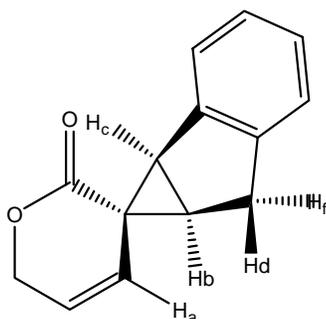
1.54
1.56
1.56
1.58
2.12
2.13
2.14
2.15
3.23
3.25
3.27
4.94
4.94
4.95
4.96
4.97
4.97
5.01
5.01
5.01
5.02
5.70
5.70
5.71
5.72
5.73
5.74
7.20
7.35

1.09
1.12
1.00
1.00
2.09
1.02
5.33

0.0
5.0

ppm (t1)

Ph

**10**
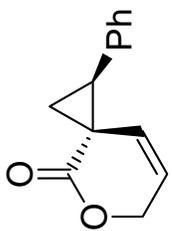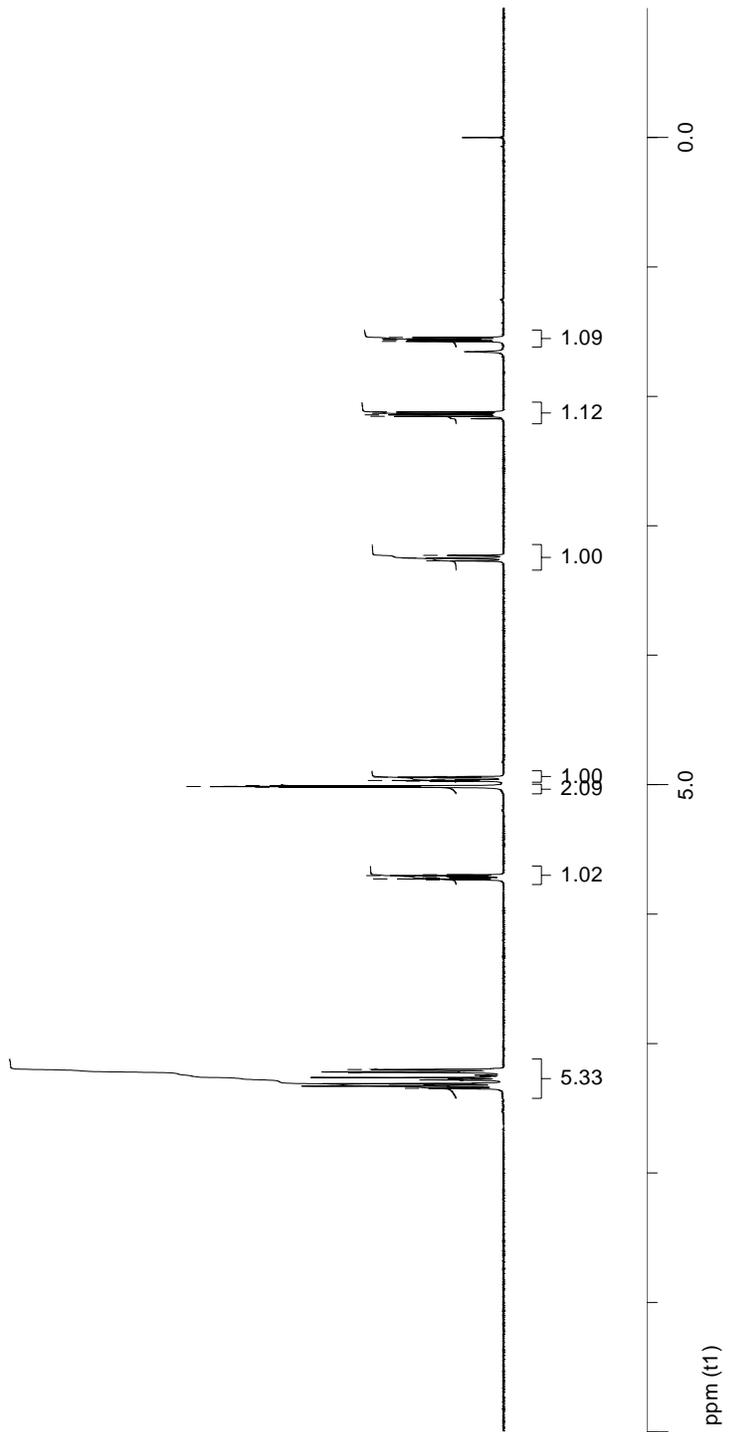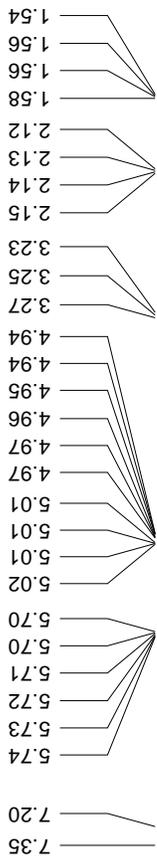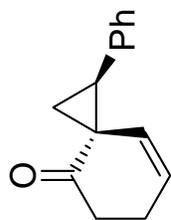
1.46
1.47
1.48
1.49
1.60
2.05
2.06
2.07
2.08
2.48
2.49
2.59
2.61

4.94
4.97

7.16
7.18
7.18
7.23
7.26
7.29
7.30
7.31

1.27
1.04
2.10
2.05
0.98
0.95
1.00
5.27

0.0

5.0

ppm (f1)

Ph

O

13

7.31
7.30
7.29
7.26
7.24
7.22
7.21
7.19

5.64
5.61

4.91
4.88

4.34
4.33
4.33
4.32
4.31
4.31
4.31
4.30

2.13
2.12
2.11
2.09

1.56

5.55

1.03

1.02

1.00

1.06

1.09
9.38

Ph

O

BocN

**14**

5.0

0.0

ppm (f1)

7.37
7.08

5.39
5.39
5.37
5.37
5.29

3.38
3.36
3.34

2.26

1.72
1.71
1.71

15.26

1.00
0.99
0.94

1.18

1.16

1.81

**15**

Ph

Ph

O

O

5.0

0.0

ppm (f1)

7.17
7.19
7.19
7.31
7.33

4.59
4.61
4.62
4.89
4.92

1.65
2.16
2.17
2.19
2.81
2.83
2.83

**16**

5.26

1.00

1.00
1.04
1.04

0.98
1.07
1.09
1.03

1.04

5.0

0.0

ppm (f1)

2.82
2.83
2.85
2.88
2.92
3.30
3.31
3.50
3.50
3.51
3.52
4.69
4.72
4.97
5.78
5.81
7.20
7.32
7.33
7.34

**22**

1.02
1.08
1.09
1.00
2.12
1.04
4.27

5.0

0.0

ppm (f1)

184

1.43
1.45
1.46
1.47
2.03
2.05
2.05
2.06
2.10
2.12
2.14
4.92
4.92
4.93
4.93
4.96
4.96
4.97
4.97
5.00
5.01
5.01
5.04
5.05
5.05
5.30
5.30
5.32
5.32
5.32
5.33
5.82
5.82
5.84
6.31
6.33
6.35
6.37
6.57
6.61
7.17
7.18
7.19
7.36

Ph

Z-23

1.12
1.07
1.12
2.33
1.00
0.93
0.96
1.04
5.33

0.0

5.0

ppm (t1)

1.27
1.28
1.28
1.30
2.09
2.10
2.11
2.12
2.70
2.70
2.72
2.72
2.74
2.74
2.76
2.76
5.01
5.45
5.45
5.45
5.47
5.48
5.48
5.84
5.85
5.86
5.87
5.87
5.88
5.93
5.95
5.97
5.99
6.58
6.62
7.23
7.33
7.34

Ph

*E-23*

1.27
1.12
1.00
2.12
1.01
1.01
1.01
1.04
5.48

5.0
0.0

ppm (t1)

186

E-24

1.45
1.46
1.47
1.48
1.91
1.95
1.96
1.97
1.98
2.70
2.72
2.74
5.04
5.32
5.35
5.82
5.82
5.83
5.84
5.85
5.86
6.38
7.23
7.25
7.32
7.34

2.88
1.07
0.94

2.07
0.98
0.98
1.00
5.30

0.0

5.0

10.0

15.0

ppm (t1)

187

1.25
1.27
1.27
1.28
1.49
1.50
1.50
1.51
1.83
1.84
2.03
2.03
2.45

5.00
5.00
5.01
5.24
5.25
5.26
5.27
5.27
5.55
5.55
5.56
5.56
5.78
5.78
5.79
5.80
5.81
5.82

**25**

1.20
10.00
0.91

2.00
1.02
1.04
1.02

0.0

5.0

ppm (t1)

**39**

2.66
2.67
2.70
2.72
2.86
2.88
2.90
2.92
2.93
3.04
3.05
3.09
3.09
3.36
3.38
3.56
3.57
3.98
5.58
5.60
5.64
5.67
7.17
7.30
7.30

40

2.99
2.19
1.07
1.04
0.98
1.00
1.91
1.89
1.91
5.51

5.0
0.0

ppm (t1)

190

1.17
1.40
1.41
1.44
1.87
1.88
2.90
2.91
2.46
2.43
2.45
2.47

3.75
3.77
3.77
4.02

5.42
5.43
5.43
5.66
5.66
5.67
5.68

3.28
4.16
2.21
1.96
1.10
1.08
1.04

2.07
1.97

1.00
1.00

0.0

5.0

ppm (f1)

**41**

2.59
2.60
2.60
2.61
2.61
2.62
3.06
3.06
3.07
3.56
3.57
3.57
3.58
4.80
4.80
4.81
5.45
5.58
5.74
5.74
5.88
5.88
5.89

44a

2.30
0.88
0.86
2.00
1.82
3.56

5.0

0.0

ppm (t1)

2.03
2.03
2.07
2.08
2.17
2.17
2.18
2.19
2.46
2.51
2.52

4.98
4.98
4.98
4.99
5.41
5.43
5.43
5.63
5.93
5.93
5.94
5.96

**44b**

2.07
1.89
2.00

1.95

0.98
1.95
1.00

0.0

5.0

ppm (t1)

57a

1.68
1.79
1.80
2.18
2.48
2.49

4.94
4.95
4.98
5.52
5.52
5.79
5.79
5.97

6.07
1.00

2.16
1.00
3.19

0.0

5.0

ppm (f1)

195

23.2
23.6
36.0
36.8
38.7

126.3
126.9
127.7
128.3
129.1
136.5

209.3

**13**

ppm (t1)

0

50

100

150

200

14

22.6
28.0
30.8
35.0

47.4

83.2

120.1
125.2
127.0
128.3
129.1
136.4

152.3

171.0

250 200 150 100 50 0
ppm (f1)

197

23.5
27.0
36.0
70.1
121.2
124.7
127.4
128.1
128.5
128.7
129.2
131.9
135.5
135.6
171.8

Ph

Ph

O

**15**

250   200   150   100   50   0
ppm (t1)

21.9
30.5
32.2
34.7

65.9

125.2
127.5
128.9
128.9
130.6
136.4

175.8

Ph

O

O

**16**

250    200    150    100    50    0
ppm (t1)

28.3
32.5
34.8
42.6

68.7

120.4
123.2
124.1
125.3
126.9
127.1
139.7
143.6

171.5

**22**

0

50

100

150

200

ppm (t1)

200

Z-**23**

24.9
28.8
36.6
69.1
120.8
126.1
126.1
127.3
128.5
128.7
132.3
136.9
169.3

250   200   150   100   50   0
ppm (t1)

25.0
27.4

34.4

69.1

121.7
124.9
125.7
126.0
127.6
128.6
133.7
136.6

171.6

Ph

*E-23*

ppm (t1)

0

50

100

150

200

202

19.1
23.1
25.8

39.7

69.1

121.2
124.6
126.6
128.0
128.2
128.8
133.6
137.1

172.2

Ph

*E-24*

O

250    200    150    100    50    0
ppm (t1)

22.3
22.3
22.7
25.1
29.5
37.5

69.1

120.6
125.0
125.1
133.0

172.5

**25**



ppm (t1)

250   200   150   100   50   0

**39**

28.6

45.0
45.6

65.0
68.0

126.2
126.5
126.8
128.2
128.5
133.8
142.9
144.0

0

50

100

150

200

250
ppm (f1)

205

26.43
29.33

45.61
49.99

65.00
67.85

122.28
124.86
126.27
128.29

136.93
143.47
143.59

**40**

0

50

100

150

200

ppm (t1)

206

**41**

26.6
27.5
28.7
33.0
39.7
40.9
43.5
63.9
67.2
118.0
125.7
143.5
144.9

0

50

100

150

200

250
ppm (f1)

207

44a

26.2
38.1
44.4
68.8
122.9
123.9
124.4
125.7
127.1
127.5
170.6

ppm (t1)

250 200 150 100 50 0

15.8
21.5
27.4
29.1
32.0

68.4

121.7
122.0
122.7
129.4

171.8

**57a**

250 200 150 100 50 0
ppm (f1)

209

HSQC of 44b

44b

210

**Table 1.** Crystal data and structure refinement for UM#1361.

| | |
|---|---|
| X-ray lab book No. | 1361 |
| Crystal ID | Doyle/Bykowsky DBXI-35-1 |
| Empirical formula | $C_{15}H_{18}O_2$ |
| Formula weight | 230.29 |
| Temperature | 220(2) K |
| Wavelength | 0.71073 Å |
| Crystal size | $0.47 \times 0.45 \times 0.08$ mm$^3$ |
| Crystal habit | colorless plate |
| Crystal system | Monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions | $a = 15.6008(15)$ Å $\quad \alpha = 90°$ |
| | $b = 8.1638(8)$ Å $\quad \beta = 103.468(2)°$ |
| | $c = 10.3918(11)$ Å $\quad \gamma = 90°$ |
| Volume | 1287.1(2) Å$^3$ |
| Z | 4 |
| Density, $\rho_{calc}$ | 1.188 g/cm$^3$ |
| Absorption coefficient, μ | 0.077 mm$^{-1}$ |
| F(000) | 496 e |
| Diffractometer | Bruker Smart1000 CCD area detector |
| Radiation source | fine-focus sealed tube, Mo$K\alpha$ |
| Generator power | 50 kV, 30 mA |
| Detector distance | 4.939 cm |
| Detector resolution | 8.33 pixels/mm |
| Total frames | 4230 |
| Frame size | 512 pixels |
| Frame width | 0.3 $°$ |
| Exposure per frame | 23 sec |
| Total measurement time | 35.43 hours |
| Data collection method | ω and φ scans |
| θ range for data collection | 2.69 to 27.50° |
| Index ranges | $0 \le h \le 20, -10 \le k \le 0, -13 \le l \le 13$ |
| Reflections collected | 18602 |
| Independent reflections | 4042 |
| Observed reflection, $I>2\sigma(I)$ | 3450 |
| Coverage of independent reflections | 99.5 % |
| Variation in check reflections | 0.05 % |
| Absorption correction | Semi-empirical from equivalents |
| | SADABS (Sheldrick, 1996) |
| Max. and min. transmission | 0.994 and 0.911 |
| Structure solution technique | direct |
| Structure solution program | SHELXS-97 (Sheldrick, 1990) |
| Refinement technique | Full-matrix least-squares on F$^2$ |
| Refinement program | SHELXL-97 (Sheldrick, 1997) |
| Function minimized | $\Sigma w(F_o^2 - F_c^2)^2$ |
| Data / restraints / parameters | 4042 / 2 / 180 |
| Goodness-of-fit on F$^2$ | 1.001 |
| $\Delta/\sigma_{max}$ | 0.000 |
| Final R indices: $R_1$, $I>2\sigma(I)$ | 0.0381 |
| $wR_2$, all data | 0.0762 |
| $R_{int}$ | 0.0320 |
| $R_{sig}$ | 0.0136 |
| Weighting scheme | $w = 1/[\sigma^2(F_o^2) + (0.01P)^2 + 0.579P]$, |
| | $P = [max(F_o^2,0) + 2F_o^2]/3$ |
| Extinction coefficient | 0.0131(6) |
| Largest diff. peak and hole | 0.139 and -0.133 e/Å$^3$ |

$R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $\quad wR2 = [\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$

**Table 2.** Atomic coordinates and equivalent[*] isotropic atomic displacement parameters ($\text{Å}^2$) for UM#1361.

| Atom | x/a | y/b | z/c | $U_{eq}$ |
|------|------|------|------|------|
| C1 | 0.29134(9) | 0.30942(17) | 0.34076(15) | 0.0368(3) |
| C2 | 0.19085(8) | 0.33976(15) | 0.30906(14) | 0.0327(3) |
| C3 | 0.14691(8) | 0.21731(16) | 0.38197(13) | 0.0340(3) |
| C4 | 0.13893(9) | 0.05930(16) | 0.35226(14) | 0.0340(3) |
| C5 | 0.16885(10) | -0.00835(18) | 0.23461(15) | 0.0430(4) |
| C6 | 0.26507(11) | 0.01845(18) | 0.24241(17) | 0.0486(4) |
| C7 | 0.31527(10) | 0.14630(19) | 0.28767(18) | 0.0486(4) |
| C8 | 0.16882(9) | 0.51446(16) | 0.34339(16) | 0.0384(3) |
| O1 | 0.07567(7) | 0.52903(13) | 0.31216(15) | 0.0589(4) |
| C9 | 0.10268(9) | -0.05951(17) | 0.43647(16) | 0.0398(3) |
| O2 | 0.03491(7) | -0.16271(11) | 0.36243(12) | 0.0438(3) |
| C10 | 0.34170(9) | 0.44686(17) | 0.29221(15) | 0.0362(3) |
| C11 | 0.39890(9) | 0.54601(18) | 0.37993(16) | 0.0419(3) |
| C12 | 0.44608(10) | 0.66995(19) | 0.33609(18) | 0.0478(4) |
| C13 | 0.43600(10) | 0.6967(2) | 0.20271(18) | 0.0495(4) |
| C14 | 0.37878(11) | 0.5996(2) | 0.11355(17) | 0.0538(4) |
| C15 | 0.33253(10) | 0.4752(2) | 0.15757(16) | 0.0459(4) |
| H1A | 0.3119 | 0.3055 | 0.4383 | 0.040(4) |
| H2A | 0.1674 | 0.3233 | 0.2129 | 0.028(3) |
| H3 | 0.1239 | 0.2554 | 0.4524 | 0.043(4) |
| H5A | 0.1565 | -0.1262 | 0.2279 | 0.048(4) |
| H5B | 0.1345 | 0.0436 | 0.1539 | 0.054(5) |
| H6 | 0.2939 | -0.0683 | 0.2105 | 0.074(6) |
| H7 | 0.3751 | 0.1344 | 0.2869 | 0.064(5) |
| H8A | 0.1928 | 0.5359 | 0.4377 | 0.034(4) |
| H8B | 0.1944 | 0.5936 | 0.2921 | 0.038(4) |
| H1 | 0.0598(12) | 0.6211(14) | 0.319(2) | 0.080(7) |
| H9A | 0.1509 | -0.1283 | 0.4852 | 0.048(4) |
| H9B | 0.0790 | 0.0021 | 0.5014 | 0.048(4) |
| H2 | -0.0028(9) | -0.108(2) | 0.3095(14) | 0.065(6) |
| H11 | 0.4061 | 0.5293 | 0.4713 | 0.056(5) |
| H12 | 0.4849 | 0.7356 | 0.3976 | 0.063(5) |
| H13 | 0.4678 | 0.7804 | 0.1727 | 0.054(5) |
| H14 | 0.3711 | 0.6180 | 0.0223 | 0.067(6) |
| H15 | 0.2944 | 0.4088 | 0.0957 | 0.056(5) |

[*] $U_{eq}$ is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

**Table 3.** Anisotropic atomic displacement parameters [*] ($\text{Å}^2$) for UM#1361.

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|------|----------|----------|----------|----------|----------|----------|
| C1  | 0.0319(7)  | 0.0343(7)  | 0.0431(8)  | 0.0041(6)  | 0.0063(6)  | 0.0019(6)  |
| C2  | 0.0327(7)  | 0.0239(6)  | 0.0400(7)  | -0.0018(6) | 0.0053(6)  | 0.0020(5)  |
| C3  | 0.0321(6)  | 0.0299(7)  | 0.0404(7)  | -0.0019(6) | 0.0093(6)  | 0.0026(5)  |
| C4  | 0.0332(7)  | 0.0281(6)  | 0.0397(8)  | 0.0001(6)  | 0.0063(6)  | 0.0023(5)  |
| C5  | 0.0551(9)  | 0.0281(7)  | 0.0483(9)  | -0.0045(7) | 0.0173(8)  | -0.0007(7) |
| C6  | 0.0569(10) | 0.0307(8)  | 0.0652(11) | 0.0005(8)  | 0.0283(9)  | 0.0115(7)  |
| C7  | 0.0376(8)  | 0.0376(8)  | 0.0732(11) | 0.0058(8)  | 0.0184(8)  | 0.0114(6)  |
| C8  | 0.0349(7)  | 0.0245(7)  | 0.0541(9)  | -0.0042(7) | 0.0070(7)  | 0.0007(5)  |
| O1  | 0.0353(5)  | 0.0287(6)  | 0.1068(11) | -0.0192(7) | 0.0047(6)  | 0.0054(4)  |
| C9  | 0.0418(8)  | 0.0314(7)  | 0.0457(8)  | 0.0003(7)  | 0.0091(7)  | -0.0023(6) |
| O2  | 0.0410(6)  | 0.0237(5)  | 0.0635(7)  | -0.0001(5) | 0.0056(6)  | -0.0002(4) |
| C10 | 0.0303(7)  | 0.0346(7)  | 0.0437(8)  | 0.0018(7)  | 0.0086(6)  | 0.0028(6)  |
| C11 | 0.0365(7)  | 0.0446(9)  | 0.0430(8)  | -0.0019(7) | 0.0061(7)  | 0.0000(6)  |
| C12 | 0.0383(8)  | 0.0409(9)  | 0.0622(10) | -0.0050(8) | 0.0074(8)  | -0.0048(7) |
| C13 | 0.0398(8)  | 0.0425(9)  | 0.0689(11) | 0.0079(9)  | 0.0180(8)  | -0.0012(7) |
| C14 | 0.0537(10) | 0.0611(11) | 0.0485(10) | 0.0084(9)  | 0.0157(8)  | -0.0033(8) |
| C15 | 0.0461(9)  | 0.0476(9)  | 0.0430(8)  | -0.0042(8) | 0.0080(8)  | -0.0070(7) |

[*] The anisotropic atomic displacement factor exponent takes the form: $-2\pi^2 [ h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12} ]$

**Table 5.** Bond lengths (Å) and angles (°) for UM#1361.

| | | | | | |
|---|---|---|---|---|---|
| C1-C7 | 1.521(2) | C1-C10 | 1.5216(19) | C1-C2 | 1.5450(17) |
| C1-H1A | 0.9900 | C2-C3 | 1.5117(18) | C2-C8 | 1.5286(17) |
| C2-H2A | 0.9900 | C3-C4 | 1.3255(18) | C3-H3 | 0.9400 |
| C4-C9 | 1.5023(19) | C4-C5 | 1.5111(19) | C5-C6 | 1.500(2) |
| C5-H5A | 0.9800 | C5-H5B | 0.9800 | C6-C7 | 1.324(2) |
| C6-H6 | 0.9400 | C7-H7 | 0.9400 | C8-O1 | 1.4182(16) |
| C8-H8A | 0.9800 | C8-H8B | 0.9800 | O1-H1 | 0.799(9) |
| C9-O2 | 1.4285(17) | C9-H9A | 0.9800 | C9-H9B | 0.9800 |
| O2-H2 | 0.833(9) | C10-C11 | 1.380(2) | C10-C15 | 1.392(2) |
| C11-C12 | 1.389(2) | C11-H11 | 0.9400 | C12-C13 | 1.376(2) |
| C12-H12 | 0.9400 | C13-C14 | 1.378(2) | C13-H13 | 0.9400 |
| C14-C15 | 1.384(2) | C14-H14 | 0.9400 | C15-H15 | 0.9400 |
| | | | | | |
| C7-C1-C10 | 109.64(12) | C7-C1-C2 | 112.68(12) | C10-C1-C2 | 112.81(11) |
| C7-C1-H1A | 107.1 | C10-C1-H1A | 107.1 | C2-C1-H1A | 107.1 |
| C3-C2-C8 | 110.32(11) | C3-C2-C1 | 110.07(11) | C8-C2-C1 | 111.84(11) |
| C3-C2-H2A | 108.2 | C8-C2-H2A | 108.2 | C1-C2-H2A | 108.2 |
| C4-C3-C2 | 123.77(12) | C4-C3-H3 | 118.1 | C2-C3-H3 | 118.1 |
| C3-C4-C9 | 121.35(13) | C3-C4-C5 | 120.94(13) | C9-C4-C5 | 117.67(12) |
| C6-C5-C4 | 113.37(13) | C6-C5-H5A | 108.9 | C4-C5-H5A | 108.9 |
| C6-C5-H5B | 108.9 | C4-C5-H5B | 108.9 | H5A-C5-H5B | 107.7 |
| C7-C6-C5 | 129.48(14) | C7-C6-H6 | 115.3 | C5-C6-H6 | 115.3 |
| C6-C7-C1 | 130.12(14) | C6-C7-H7 | 114.9 | C1-C7-H7 | 114.9 |
| O1-C8-C2 | 107.40(11) | O1-C8-H8A | 110.2 | C2-C8-H8A | 110.2 |
| O1-C8-H8B | 110.2 | C2-C8-H8B | 110.2 | H8A-C8-H8B | 108.5 |
| C8-O1-H1 | 112.3(14) | O2-C9-C4 | 113.51(12) | O2-C9-H9A | 108.9 |
| C4-C9-H9A | 108.9 | O2-C9-H9B | 108.9 | C4-C9-H9B | 108.9 |
| H9A-C9-H9B | 107.7 | C9-O2-H2 | 111.2(13) | C11-C10-C15 | 117.77(14) |
| C11-C10-C1 | 121.20(13) | C15-C10-C1 | 121.03(14) | C10-C11-C12 | 121.42(15) |
| C10-C11-H11 | 119.3 | C12-C11-H11 | 119.3 | C13-C12-C11 | 120.07(16) |
| C13-C12-H12 | 120.0 | C11-C12-H12 | 120.0 | C12-C13-C14 | 119.37(16) |
| C12-C13-H13 | 120.3 | C14-C13-H13 | 120.3 | C13-C14-C15 | 120.40(16) |
| C13-C14-H14 | 119.8 | C15-C14-H14 | 119.8 | C14-C15-C10 | 120.97(15) |
| C14-C15-H15 | 119.5 | C10-C15-H15 | 119.5 | | |
| | | | | | |
| C7-C1-C2-C3 | 66.09(16) | C10-C1-C2-C3 | -169.10(11) | C7-C1-C2-C8 | -170.92(13) |
| C10-C1-C2-C8 | -46.10(17) | C8-C2-C3-C4 | 165.68(13) | C1-C2-C3-C4 | -70.43(17) |
| C2-C3-C4-C9 | 173.88(12) | C2-C3-C4-C5 | -4.1(2) | C3-C4-C5-C6 | 59.72(18) |
| C9-C4-C5-C6 | -118.36(14) | C4-C5-C6-C7 | -37.9(2) | C5-C6-C7-C1 | -2.9(3) |
| C10-C1-C7-C6 | -140.47(19) | C2-C1-C7-C6 | -13.9(3) | C3-C2-C8-O1 | -56.52(16) |
| C1-C2-C8-O1 | -179.38(13) | C3-C4-C9-O2 | 130.59(14) | C5-C4-C9-O2 | -51.34(17) |
| C7-C1-C10-C11 | -120.07(15) | C2-C1-C10-C11 | 113.47(15) | C7-C1-C10-C15 | |
| 58.97(18) | C2-C1-C10-C15 | | -67.50(18) | C15-C10-C11-C12 | -0.1(2) |
| C1-C10-C11-C12 | 178.96(13) | C10-C11-C12-C13 | 0.4(2) | C11-C12-C13-C14 | 0.0(2) |
| C12-C13-C14-C15 | -0.7(3) | C13-C14-C15-C10 | 1.0(3) | C11-C10-C15-C14 | -0.5(2) |
| C1-C10-C15-C14 | -179.61(14) | | | | |

**Table 7.** Hydrogen bond information for UM#1361 (Å and °).

| D—H⋯A* | d(D—H) | d(H⋯A) | d(D⋯A) | ∠(DHA) |
|---|---|---|---|---|
| O1—H1⋯O2#1 | 0.799(9) | 1.885(10) | 2.6768(14) | 171(2) |
| O2—H2⋯O1#2 | 0.833(9) | 1.866(10) | 2.6945(16) | 173.0(18) |

* D - donor atom, H - hydrogen, A - acceptor.
Symmetry transformation codes: #1 x,y+1,z    #2 -x,y-1/2,-z+1/2

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