Optimization and Development of Nickel-Catalyzed [3+2]-Reductive and Alkylative Cycloadditions

by

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Dedication

To my grandparents whom I think of and remember fondly

Lloyd Foley (In Memory)
Ora Foley (In Memory)
James R. Haley (In Memory)
Ruth Haley

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List of Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
BEt_3	triethylborane
Bn	benzyl
t-Bu	tert-butyl
°C	degrees centigrade
Cp	cyclopentyl
COD	cyclooctadienyl
Cy	cyclohexyl
dba	dibenzylideneacetone
DMF	dimethylformamide
DPEphos	bis(2-diphenylphosphinophenyl)ether
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene

equiv	equivalent
Et	ethyl
EWG	electron withdrawing group
Hex	hexyl
HMDS	hexamethyldisilazane
h	hour
IMes	1,3-bis-(1,3,5-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene
ITol	1,3-bis-(tolyl)imidazole-2-ylidene
IPrBAC	2,3-Bis(diisopropylamino)cycloprop-2-en-1-ylium
L	ligand
Me	methyl
min	minute
MCR	multicomponent reaction
µw	microwave
NHC	N-Heterocyclic Carbene
Nu	nucleophile

Oct	octyl
PBu_3	tributylphosphine
PCy_3	tricyclohexylphosphine
PMe_3	trimethylphosphine
PPh_3	triphenylphosphine
Ph	phenyl
PhMe	toluene
i-Pr	isopropyl
$P\textit{t}Bu_3$	tritertbutylphosphine
RT	room temperature
SD	syringe drive
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
Tf	triflyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
tmeda	tetramethylethylenediamine

TMS	trimethylsilyl
Tol	toluene
Ts	tosyl

Abstract

Optimization and Development of Nickel-Catalyzed [3+2]-Reductive and Alkylative Cycloadditions

Five-membered carbocycles are important structural motifs in natural products and biologically active compounds. One way to construct these rings is to combine a two-atom component and a three-atom component together in a [3+2] cycloaddition. Many traditional cycloaddition methodologies make use of polar reagents, vinyl carbenoids, or strained rings. Unfortunately, these methodologies require special substrates that may be difficult to carry through a synthesis or difficult to install in a late stage of a synthesis. It is therefore desirable to use simple, readily available π-components for these purposes similar to more conventional cycloaddition reactions such as Diels Alder processes. Other methodologies have been developed that circumvent the problems of traditional methodologies and the complications of combining simple π-components by changing the substrate oxidation state or rearranging the atomic connectivity of the molecule. The Montgomery group has long worked on methodologies that take advantages of changes in substrate oxidation state.

This dissertation presents the development and optimization of nickel-catalyzed [3+2]-reductive cycloadditions for the synthesis of cyclopentenone products. This methodology utilizes enoate and alkyne simple π-components and combines them with a nickel catalyst under mild conditions. This methodology is also tolerant of a variety of functional groups and substitution patterns. Reductive coupling products isolated from some reactions lend support to our proposed

mechanism. Interesting trends in product selectivity for reductive coupling vs. [3+2]-reductive cycloadditions were also rationalized.

Sometimes further functionalization of carbocyclic products is necessary, but functionalization requires further reaction and purification steps. Multicomponent reactions offer a solution to this difficulty by combining many reactants in a single pot to form a highly functionalized product. The reactants are assembled in a sequential cascade of simple reactions. A major challenge of multicomponent couplings is to conduct the reaction in such a way that all reactants funnel down to a single product. There are many examples of [3+2] cycloadditions involving polar reagents, but these methods suffer from the same difficulties as the two-component cycloadditions. Methods that make use of simple π-components for multicomponent cycloadditions are rare. Catalytic intermolecular multicomponent methodologies would be a welcome advance for several two-component methodologies.

This dissertation describes the optimization and development of nickel-catalyzed multicomponent [3+2]-alkylative cycloadditions for the synthesis of highly functionalized cyclopentenones. This methodology is an extension of the enoate-alkyne [3+2]-reductive cycloaddition methodology and adds an aldehyde as the third component. While the yields are lower for this chemistry, it is a welcome advance for [3+2] cycloaddition methodology. The mechanism of the reaction is presently unclear. Internal redox products isolated from some reactions suggest a mechanism similar to that of the [3+2]-reductive cycloadditions. On the other hand, experiments conducted in aprotic solvents by the Ogoshi group are suggestive of a mechanism involving a ketene intermediate.

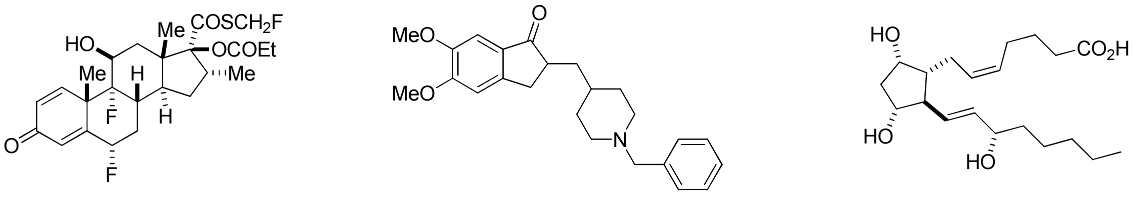
Chapter 1

[3+2] Cycloadditions: Methods for the Formation of Five-Membered Rings

1.1 Introduction

Five-membered rings are an important structural motif in biologically active compounds and considerable study has been devoted to the synthesis of five membered rings.[1-4] Common methods used to make five-membered rings involves a [3+2] cycloaddition where a two-atom component is combined with a three-atom component to form a five-membered ring. Many of the oldest [3+2] cycloaddition methodologies use 1,3-dipolar reagents for the synthesis of heterocycles. Other methodologies have developed that are exclusively focused on carbocycle synthesis. Many of these carbocycle methodologies have developed within the last thirty years. This work focuses primarily on these carbocycle methodologies and presents new two-component and multicomponent methods for the synthesis of carbocycles.

Scheme 1. Biologically Active Molecules Containing Five-Membered Carbocycles



Advair

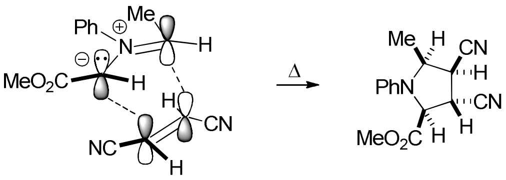
Aricept

Prostaglandin $PGF_{2\alpha}$

1.2 Traditional Methods: Dipolar Cycloaddition FMO Theory

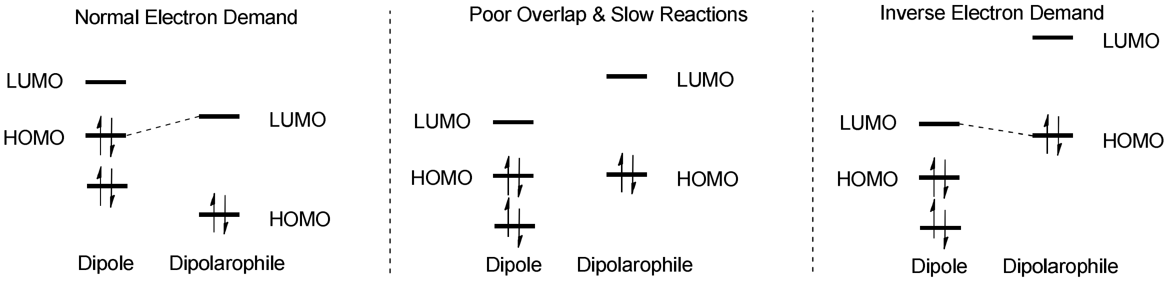
1,3-Dipoles can react with two-atom components to yield five-membered ring products. The 1,3-dipole has a resonance structure with a formal positive charge on one terminus and a formal negative charge on the opposite terminus. Most 1,3-dipoles have a heteroatom in the center to stabilize the electron deficient terminus of the dipole (Scheme 2).[5]

Scheme 2. [3+2] Cycloaddition with a 1,3-Dipole



1,3-dipoles can preferentially react with either electron-rich or electron-poor dipolarophiles. This reactivity is due to a move from HOMO$_{dipole}$/LUMO$_{dipolarophile}$-controlled (normal electron demand) to LUMO$_{dipole}$/HOMO$_{dipolarophile}$-controlled (inverse electron demand) reactions as the dipolarophile goes from electron rich to electron-poor (Scheme 3). Reactions with substrates of intermediate electronic character react slowly as neither HOMO/LUMO sets of orbitals are close together in energy.

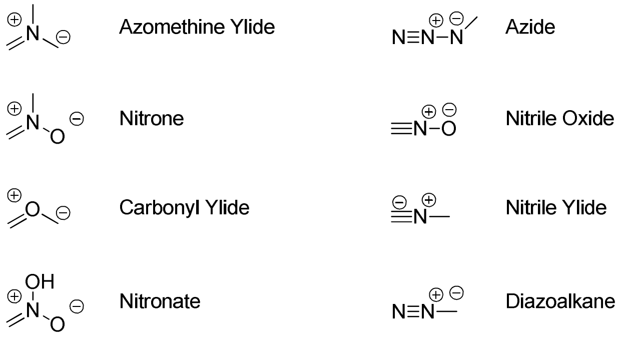
Scheme 3. HOMO and LUMO in 1,3-Dipolar Cycloaddition



1.2.1 Traditional Methods: Dipolar Cycloadditions

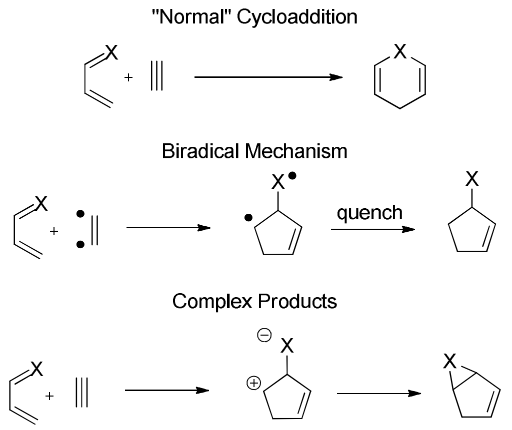
Dipolar reagents are the most widely used reagents in [3+2] cycloadditions, and most of these result in the formation of heterocycles. A few recent reviews have focused on their use in intramolecular[6] and asymmetric reactions.[7] A recent book focuses on the use of azomethine ylides, nitrones, carbonyl ylides, azides, nitrile oxides, nitrile ylides, nitronates, diazoalkanes and several other dipolar reagents for heterocycle and natural product synthesis (Scheme 4).[8]

Scheme 4. Common 1,3-Dipolar Reagents



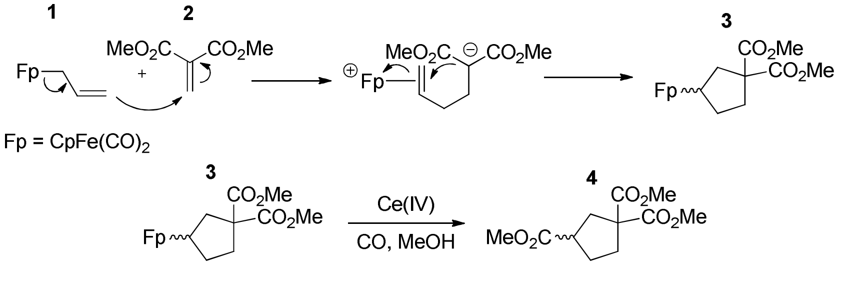
More specialized methods are necessary for the synthesis of carbocyclic five-membered rings. It would be advantageous to use simple π-components such as alkenes, alkynes, dienes, unsaturated carbonyls and others for a two-component cycloaddition reaction because of the ease of access and the ability to advance these precursors through a complex linear synthesis compared with specialized or reactive reagents. Unfortunately, the direct formation of a five-membered carbocycle from these simple precursors would require the formation of a biradical species or result in the formation of a fused bicyclic product (Scheme 5)

Scheme 5. Use of simple precursors complicates formation of carbocycles



In order to get around this complexity, specialized reagents that form 1,3-dipoles can be used. Some of the earliest examples of this involved metallated iron and cobalt reagents that undergo cycloadditions with π-systems.[9] For example, Baker and co-workers synthesized allyl iron reagent **1** to react with electron deficient olefin **2** to form metallated cyclopentane **3** (Scheme 6).[10] Cyclopentane **3** can be demetallated under oxidative carboxylation conditions to form highly substituted cyclopentane product **4**. This is one of many examples from an extensive review in this area of chemistry by Welker.[9]

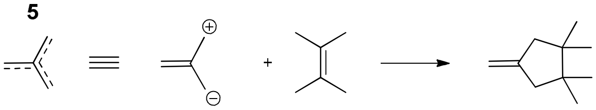
Scheme 6. Early Dipolar Cycloadditions with Metallated Substrates



Another way to access these carbocyclic products is to use a trimethylenemethane intermediate **5**, which is an all carbon 1,3-dipole (Scheme 7).[3,11,12] Accessing this species was originally difficult and its reactivity was difficult to control.[13,14] There was some success in synthesizing an iron-tricarbonyl TMM complex, but it was unfortunately not very reactive.[15-17]

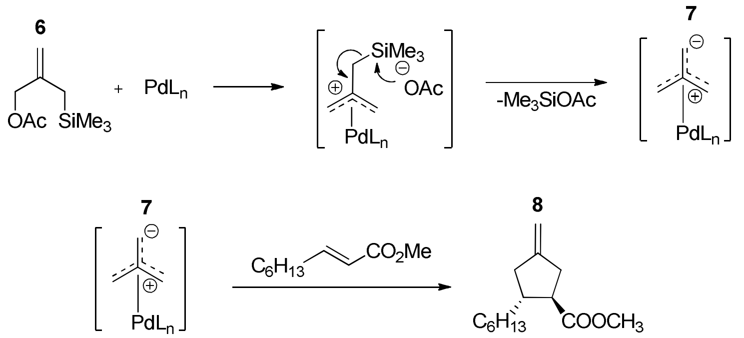
Scheme 7: Trimethylenemethane for the Synthesis of Carbocycles

5



Due to the problems in developing the TMM synthon **5**, much of the initial excitement about its synthetic potential disappeared. Many groups turned to the use of synthetic TMM equivalents. Some of the trouble with generating TMM equivalents is that the synthon has to have a functional group that acts as anion equivalent and a functional group that acts as a cation equivalent. Groups that are mutually compatible may not have the desired reactivity. This problem was solved by using a palladium complex as an activator which could ionize poor leaving groups (Scheme 8).[3] In this solution, the palladium coordinates to the trimethylenemethane reagent **6** resulting in the ionization of the acetate group. The acetate group can then attack the silyl group resulting in the fleeting TMM intermediate **7**. This intermediate can then react with an electron deficient olefin in the generic example shown to form the cyclopentene product **8**.[18] Many different TMM scaffolds can be made which broadens the range of products available.[3] There have also been several reviews[3,11] and a book chapter[12] on the use of these TMM synthons.

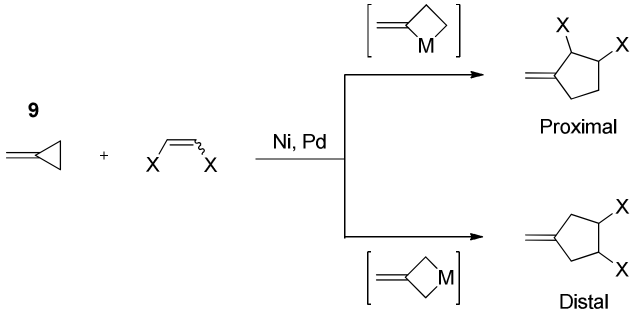
Scheme 8. Generation of the TMM reagent and Reaction with Electron Deficient Olefins



1.2.2. Strained Rings

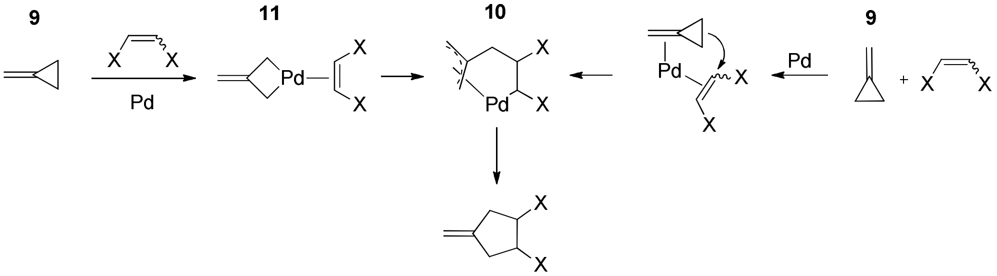
Strained rings have long been used to access cyclopentyl rings. Earlier examples make use of methylene cyclopropane derivatives **9**. Reactions of **9** with olefins have been catalyzed by either nickel or palladium.[3,19] The regioselectivity of the reaction depends on if the metal inserts into the distal or proximal end of the cyclopropane ring (Scheme 9). With palladium catalysts the regioselectivity is distal only.

Scheme 9. Distal vs. Proximal Addition Determines Regioselectivity



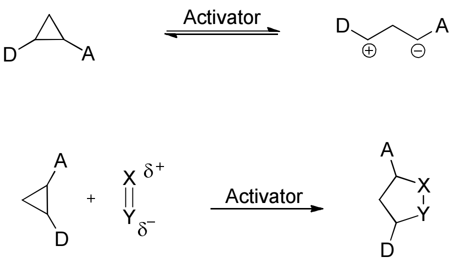
There is some disagreement about the mechanism of the palladium catalyzed reaction. Trost proposes that instead of oxidative addition of the metal to the distal end of the methylene cyclopropane, that the palladium coordinates to both the methylene cyclopropane and the alkene and then undergoes an oxidative cyclization to generate the palladium η^3-intermediate **10** (Scheme 10).[3] Reductive elimination of palladium from the intermediate then forms the product. Alternatively, the metal undergoes oxidative addition to the cyclopropane ring forming a metallacyclobutane intermediate **11**.[19] The metallacycle then coordinates to the olefin and inserts into the olefin forming an η^3 intermediate **10** which can then undergo reductive elimination to form the product. The chemistry of this reagent has been well explored and is the subject of several reviews.[3,19]

Scheme 10. Mechanistic Uncertainty about Oxidative Addition Step



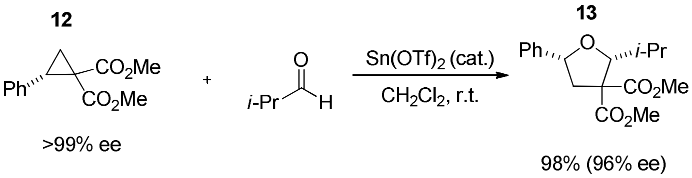
Donor-acceptor (DA) cyclopropanes provide another popular way to make cyclopentanoid and heterocycle products. The DA cyclopropane acts as a 1,3-dipole equivalent in these reactions and activation of the ring is necessary to achieve the desired reactivity (Scheme 11).[20] The electron-donating and electron-withdrawing groups on the ring can serve to make these polar processes more favorable. After activation, these rings react with a polarized two-component group to form the five-membered ring.

Scheme 11. Donor Acceptor Cyclopropane Basics



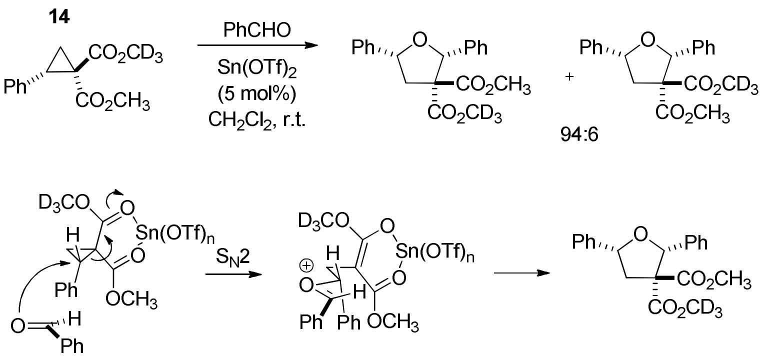
Donor-acceptor cyclopropanes have been commonly used in heterocycle synthesis. There are many examples of reactions of DA cyclopropanes with substrates such as aldehydes, nitrones, isocyanates, imines as well as other double bond containing functionality.[20] In a recent example by Johnson and co-workers, they demonstrated that they could transfer the stereochemistry of the cyclopropane ring **12** to the tetrahydrofuran product **13** without the use of a chiral ligand (Scheme 12).[21] This reaction was general with respect to both aromatic and aliphatic aldehydes.

Scheme 12. Donor-Acceptor Cyclopropane Transfer of Substrate Stereochemistry to Products



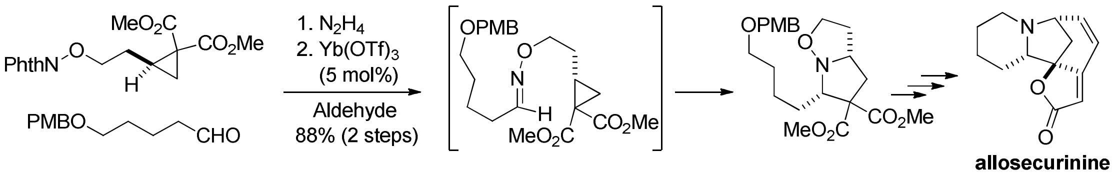
Further investigation of this reaction with the use of a deuterium labeled substrate **14** led Johnson and co-workers to conclude that the reaction occurred by an S_N2 process where the aldehyde attacks the activated cyclopropane, inverting the stereochemistry at the C2 carbon (Scheme 13). A concerted mechanism was ruled out because experiments with electron-poor aldehydes were sluggish, and it would be expected that electron-poor aldehydes have lower LUMO energies with better interaction with the dipole HOMO for faster reactions.

Scheme 13. Deuterium Studies Indicate S_N2 Pathway



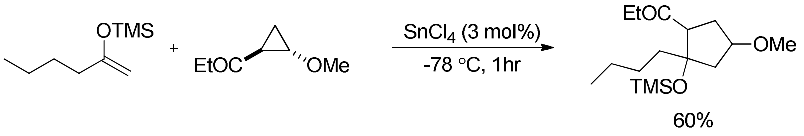
The Kerr group has developed a class of intramolecular reactions of DA cyclopropanes with nitrones formed in situ. They were able to apply their chemistry to the synthesis of allosecurinine from the Securinega alkaloid family (Scheme 14).[22,23] The cycloaddition was a key step at the beginning of the synthesis and was conducted on multigram scale with excellent yields.

Scheme 14. Donor-Acceptor Cyclopropanes in Allosecurinine Synthesis



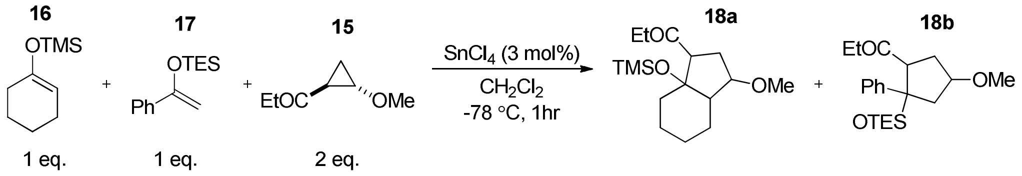
Donor-acceptor cyclopropanes have also been used to form cyclopentenoid rings, but these reactions are less common. In an early example, the Kuwajima group demonstrated that they were able to react cyclic and acyclic silyl enol ethers with donor-acceptor cyclopropanes in the presence of a catalytic amount of $SnCl_4$ to form monocyclic and bicyclic products (Scheme 15).[24]

Scheme 15. Donor-Acceptor Cyclopropanes in Carbocycle Synthesis



In a separate experiment the DA cyclopropane **15** was shown to epimerize under the reaction conditions as evidence for a zwitterionic intermediate. A scrambling experiment was performed to determine if the silicon-oxygen bond is cleaved during the cycloaddition (Scheme 16). A mixture of TMS-protected cyclohexyl enol ether **16** and TES protected enol ether **17** was reacted with the DA cyclopropane **15** with no silyl scrambling in the products **18**.

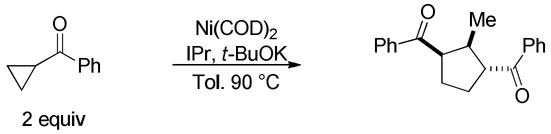
Scheme 16. Silyl Scrambling Experiment



Other examples have appeared involving electron deficient alkynes[25] and alkenes[26], silyl ynol[27] and enol[28] ethers, terminal alkynes,[29] and glycal-derived[30] DA cyclopropanes.

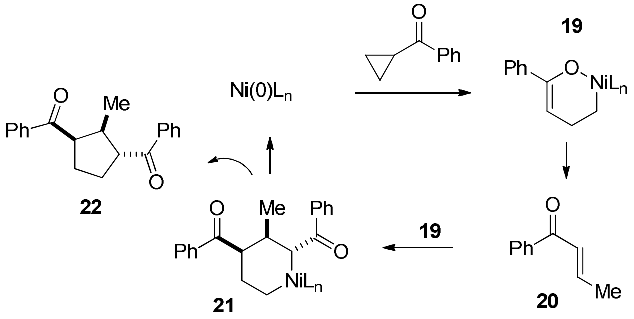
Despite the usefulness of DA cyclopropane chemistry, the Lewis acid activated cyclization of simple cyclopropyl ketones is inefficient. The Montgomery group has developed a dimerization reaction of simple cyclopropyl ketones, such as **22**, using nickel catalysts to form trisubstituted cyclopentane rings (Scheme 17).[31]

Scheme 17. Dimerization of Cyclopropyl Ketones to Form Trisubstituted Cyclopentane Rings



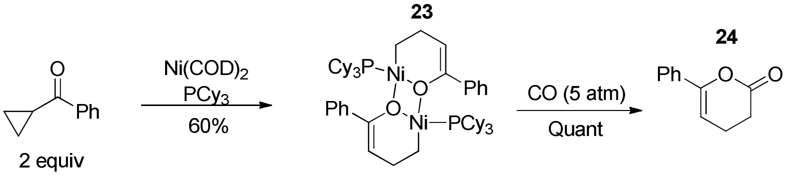
The reaction proceeds by oxidative addition of the nickel into the cyclopropyl group and expansion to a six-membered metallacycle **19** (Scheme 18). The metallacycle can then undergo β-hydride elimination to form enone product **20**. The enone then adds to another equivalent of metallacycle **19** in solution to form **21**. Reductive elimination of **21** then forms the product **22**. After further development and careful syringe drive optimization, Montgomery and co-workers were able to expand the scope of this methodology to crossed reactions.

Scheme 18. Mechanism of Nickel-Catalyzed Cyclopropyl Ketone Dimerization



The Ogoshi group also reported the same reactivity of cyclopropyl ketones with nickel catalysts.[32] They reported the isolation and characterization of a dimeric metallacycle **23** as well as an enone dimer coordinated to the nickel catalyst. They were able to treat **23** with carbon monoxide (5 atm) to form a lactone product **24** (Scheme 19).

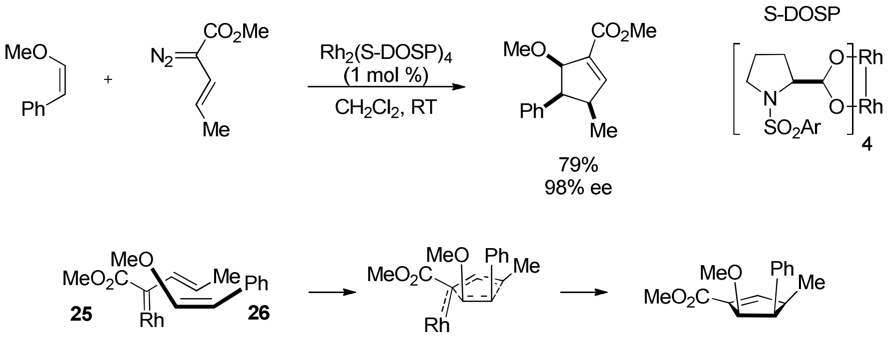
Scheme 19. Dimerization and Interception of Metallacycle with CO



1.2.3 Vinyl Carbenoids

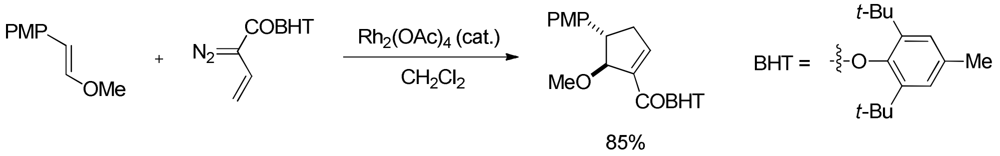
Vinyl carbenoids have also been useful for the production of cyclopentenoid products. The Davies group has been involved in the development of this chemistry with rhodium catalysts.[33,34] They found that they could combine a vinyldiazoacetate with an electron rich olefin in the presence of a chiral catalyst to form enantiomerically pure, highly-substituted cyclopentenoid products (Scheme 20).[33] The products were further transformed with a variety of other known reactions to demonstrate the synthetic utility of the products. The mechanistic details of the reaction are unclear, but the cis product stereochemistry is indicative of a concerted attack on the front face of the carbenoid **25** by the vinyl ether **26** followed by elimination of the metal. Alternatively, the reaction could be proceeding through a [4+2] mechanism followed by reductive elimination.

Scheme 20. Rhodium Vinyl Carbenoid Transformation of Vinyl Ethers



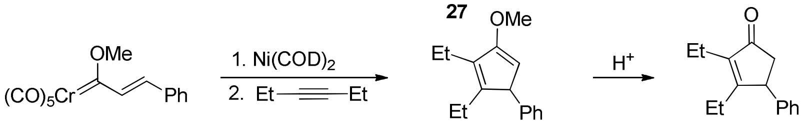
There have also been earlier reports by the Davies group with vinyldiazoacetates, vinyl ethers, and rhodium catalysts, but these reactions are thought to be mechanistically different than the ones previously discussed (Scheme 21).[34] On the basis of substitution and solvent effects, these reactions are thought to proceed through a step-wise ionic mechanism.

Scheme 21. Rhodium-Catalyzed Vinyl Carbenoid Cycloaddition



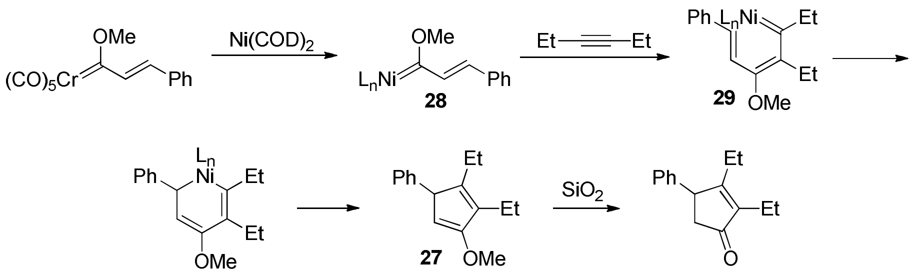
Barluenga and co-workers have demonstrated that chromium vinyl carbenoids can be used to form cyclopentenone products from alkynes (Scheme 22).[35] The initial product formed is methyl ether **27** which upon exposure to acidic conditions forms the cyclopentenone product. Ynol ethers as well as boron and tin-substituted alkynes were demonstrated to be suitable reaction partners for the vinyl carbenoid reagent. Products featuring a boron or tin functional group could be carried through further synthetic transformations.

Scheme 22. Formation of Cyclopentenones from Chromene Vinyl Carbenoids



Barluenga proposes that the reaction starts by transmetallation of the chromium carbenoid with nickel (Scheme 23). Next, regioselective insertion of the vinyl-nickel carbenoid **28** into the alkyne forms a new nickel carbenoid **29**. After formation of carbenoid **29**, a [3,3] electrocyclic ring closure can occur followed by reductive elimination to form the vinyl methoxy ether **27**. Exposure to or acidic silica converts the ether into the cyclopentenone.

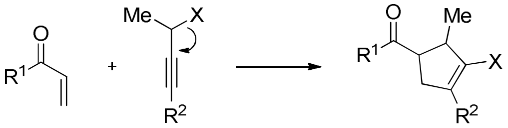
Scheme 23. Mechanism of Cyclopentenone Formation



1.3 Simple π-Components

While several of the previous methods are very well developed for forming cyclopentanoid products, there are some challenges to the use of such methods. Many of these methods require the use of specialized reagents that can be difficult to install at a late stage in a synthesis or may be difficult to carry through a synthesis. Some of these methods also involve prior reagent preparation or the use of highly polarized functional groups. It would be ideal to use simple, readily available, and easily installed π-components, but the use of these suffers from the complications of trying to perform a simple cycloaddition reaction to form a five-membered ring. One way to circumvent these difficulties is to rearrange the atomic connectivity of the three-atom component during the cycloaddition (Scheme 24). There are methods which involve a 1,2-silicon or 1,2-hydride shift to accomplish this.

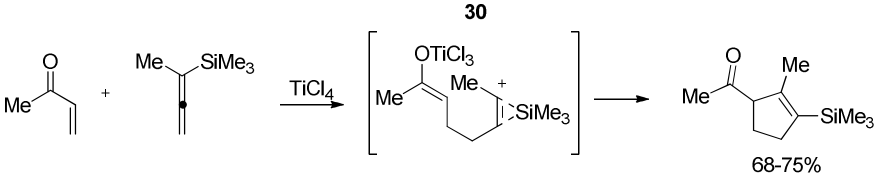
Scheme 24. Rearranging Atomic Connectivity



1.3.1 1,2-Silyl Shifts

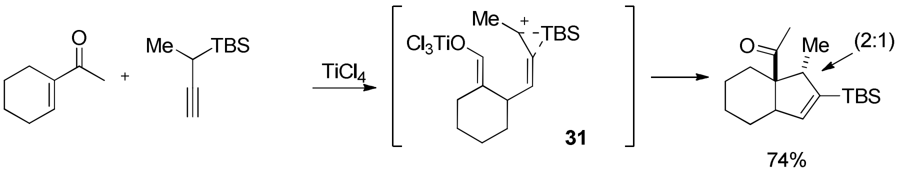
Much methodological development has surrounded allyl silane, allenyl silane, and propargyl silane reagents.[36-38] This methodological work has been accompanied by the development of [3+2] cycloadditions for the formation of carbocycles. In 1981, the Danheiser group developed a [3+2] cycloaddition with allenyl silanes and cyclic and acyclic enones to form cyclic and bicyclic products (Scheme 25).[39] Reaction of the enone oxygen with $TiCl_4$ generates an allylic carbocation which is attacked by the allenyl silane. The vinyl cation is stabilized by the silicon group, and intramolecular attack of this cation by the titanium enolate **30** closes the ring. The reaction has since been expanded to reactions with acyl silanes to form similar carbocyclic products.[40] This reaction has also been expanded to form heterocyclic products from aldehydes,[41] N-acylium ions,[41] imines,[42] and ethyl glyoxylate.[43]

Scheme 25. [3+2] Cycloaddition of Allenyl Silanes



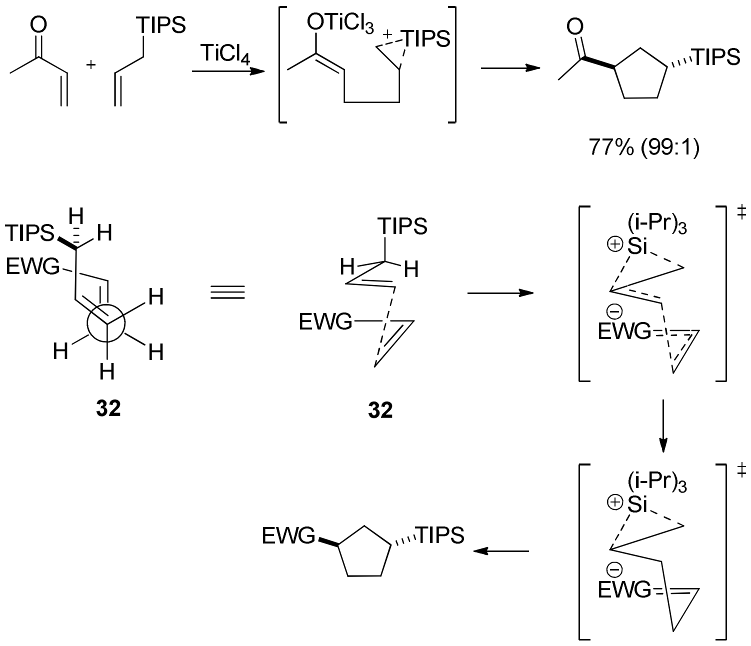
In 1992, the Danheiser group applied this reactivity to propargyl silanes (Scheme 26).[44-47] Cycloadditions with propargyl silanes with is thought to proceed by the same mechanism as allenyl silanes starting with reaction of the enone with $TiCl_4$. Attack of the titanium enolate **31** on the stabilized vinyl cation closes the ring. It was necessary to use bulky silane groups in this reaction to suppress desilylation which leads to allenes. They also demonstrated that propargyl silanes can be reacted with an N-acyliminium substrate to form a heterocycle or with a tropylium substrate to form a bicyclic carbocycle.

Scheme 26. [3+2] Reaction of Propargyl Silanes with Enones



Danheiser and co-workers also disclosed the reaction of allyl silanes with enones to form cyclopentane products within the same report as the propargyl silanes.[44] The reaction is highly diastereoselective, which arises from a preference for the synclinal transition state **32** (Scheme 27).[45-48] The electron withdrawing group shows a preference for the endo rather than exo transition state, which minimizes charge separation and benefits from secondary orbital interactions. The reaction has since been expanded to an asymmetric variant. Considerable study has also been devoted to the use of allyl silanes for the [3+2] cycloadditions of various heterocycles.[36-38]

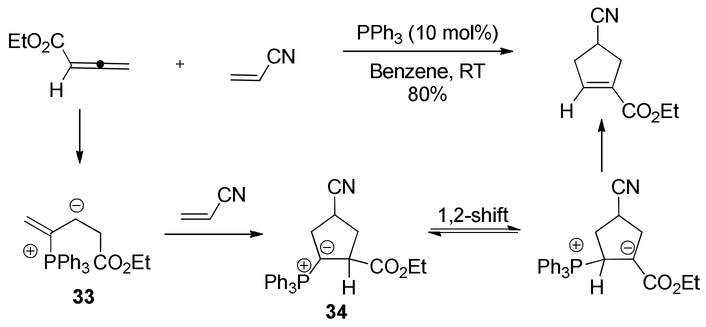
Scheme 27. [3+2] Cycloadditions of Allyl Silanes and Diastereoselectivity



1.3.2. 1,2-Hydrogen Shifts

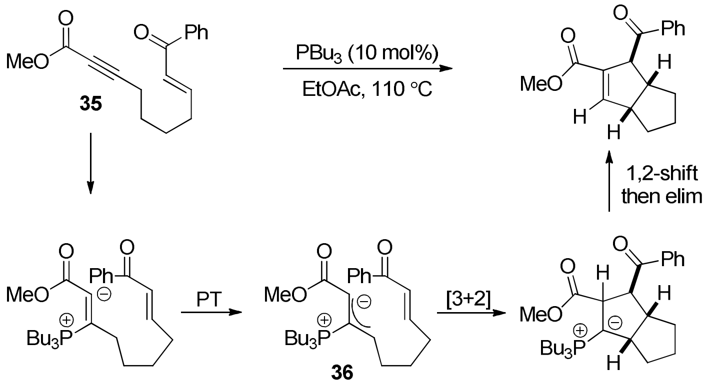
Similar to 1,2-silyl shifts, 1,2-hydrogen shifts have been used in phosphine-catalyzed transformations.[49] In 1995, Lu and co-workers demonstrated that 2,3-butadienoates or 2-butynoates could be treated with a phosphine catalyst in the presence of an electrophilic olefin to form cyclopentene products (Scheme 28).[50] It was proposed that the reaction started with addition of the phosphine into the allene to form a 1,3-dipole **33**. This dipole then reacts with the olefin to form a cyclic intermediate **34**. A 1,2-hydrogen shift then enables the phosphine catalyst to be eliminated forming the product. Zhang and co-workers later developed an asymmetric version of this reaction with chiral phosphine catalysts.[51] Nitrogen heterocycles can also by synthesized by the phosphine-catalyzed reaction of allenoates and imines,[52,53] and alkynoates and imines.[54]

Scheme 28. Phosphine-Catalyzed [3+2] Cycloaddition of Allenoates and Olefins



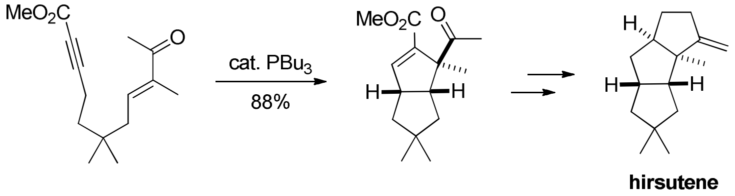
Inspired by Lu’s work, the Krische group developed an intramolecular version of the phosphine-catalyzed alkynoate and olefin cycloaddition (Scheme 29).[55] They found that increased temperatures were necessary because the dipolarophile was more highly substituted than those that Lu had used. The alkynones were also tolerated in the reaction, and aryl, cyclopropyl, and ester groups were tolerated on the dipolarophile. The reaction is thought to proceed in a stepwise fashion starting with addition of the phosphine into the alkynoate **35**. A proton transfer generates the 1,3-dipole **36** which then undergoes an intramolecular cycloaddition with the enone. A 1,2-hydrogen shift followed by elimination of the phosphine affords the product.

Scheme 29. Intramolecular Phosphine-Catalyzed [3+2] Cycloaddition



Krische was able to apply his group's methodology to the synthesis of hirsutene, a member of the triquinane family known for its biological activity (Scheme 30).[56] They were able to maintain the previously developed conditions for the cyclization, which occurred in good yield. A highlight of the synthesis is that the annulation yields a single stereoisomer. Further elaboration of the annulation product yielded hirsutene.

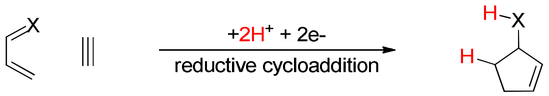
Scheme 30. Phosphine-Catalyzed Annulation in the Synthesis of Hirsutene



1.3.3. Reductive Cycloadditions

Other strategies for making five-membered rings by two component processes involve a change in substrate oxidation state during the cycloaddition. For example, in a reductive cycloaddition, a net two-electron reduction occurs that allows a stable five-membered intermediate to be formed without any changes in the original atomic connectivity of the starting reagents (Scheme 31).

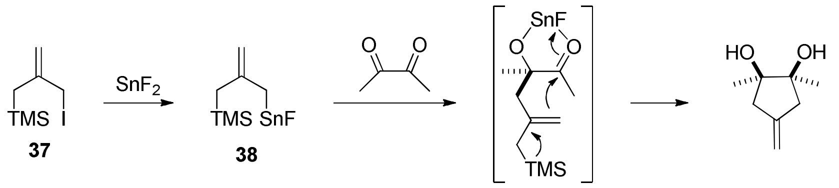
Scheme 31. General Scheme for Reductive Cycloadditions



1.3.3.1 Dianion Synthons

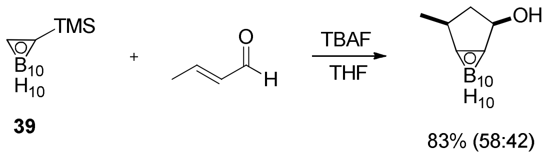
An early example of this reaction was demonstrated by the Molander group. They demonstrated that 3-halo-2-[(trimethylsilyl)methyl]propene **37** could be treated with a metal to create a dianionic synthon **38** (Scheme 32).[57] Synthon **38** could then be reacted with a dione to yield cyclopentenoid products. Zinc was originally tried as a reducing agent with no success. However, when SnF_2 was employed the reaction was successful, presumably because of the greater Lewis acidity of Sn(IV), and the fluoride ion increased the nucleophilicity of the allyl silane. The stereochemistry of the product is chelation controlled.

Scheme 32. Reductive Cycloadditions with Allyl Silanes



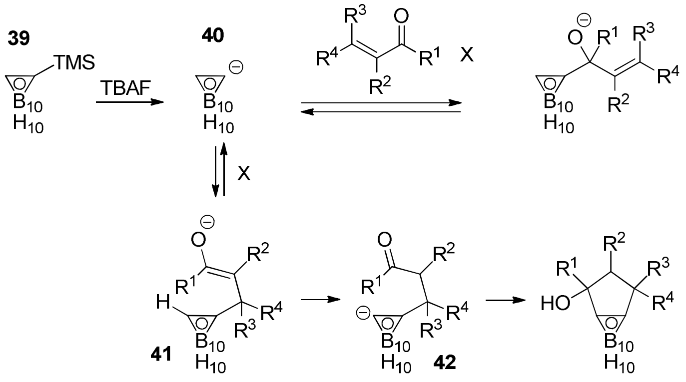
The Yamamoto group has also demonstrated this sort of reactivity with carboranyltrimethyl silane **39** and conjugated carbonyl compounds to form cyclopentenoid products (Scheme 33). The stereoselectivity was poor however.[58]

Scheme 33. Dianionic Reaction of Carboranyl Silanes



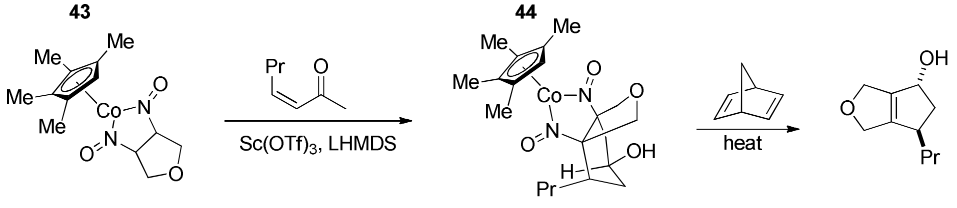
The reaction is thought to proceed by attack on the carboranyltrimethyl silane **39** by TBAF to generate a carboranyl anion **40** (Scheme 34). This anion then reacts with the enal or enone in solution to form an enolate **41**. Intramolecular deprotonation of the carboranyl intermediate **42** by the enolate and addition into the newly formed carbonyl revealed the carbocyclic product. Reactions stopped prematurely reveal the presence of allylic alcohols. Silane-protected allylic carboranyl alcohols treated with TBAF also yield carbocyclic products.

Scheme 34. Mechanism of Carboranyl Annulation



A much later example by Bergman and Toste demonstrates that cobalt dinitrosyl complex **43** can be used for [3+2] annulations of unsaturated enones and ketimines in the presence of Sc(OTf)$_3$ and LHMDS (Scheme 35).[59] Initially, reactions with enones were developed, and an X-ray structure of the polycyclic tertiary alcohol was obtained. The reaction was also applied to ketimines which yielded tertiary amines. Exposure of the intermediate cobalt complex **44** to norbornadiene under microwave conditions yielded bicyclic cyclopentenol products. The reaction likely proceeds by deprotonation of the α-nitrosyl hydrogen of **43** which undergoes 1,4 addition with the carbonyl or iminyl compound. A second deprotonation of the α-nitrosyl hydrogen is responsible for closing the ring and yielded the polycyclic cobalt intermediate **44**.

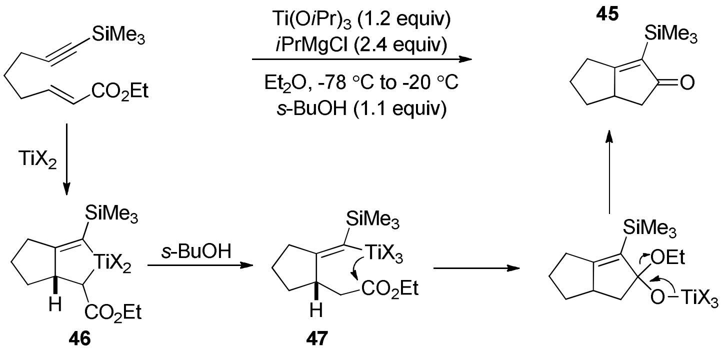
Scheme 35. [3+2] Cycloaddition of Cobalt Nitrosyl Complexes



1.3.3.2. Other Metal-Mediated Reductive Cycloadditions

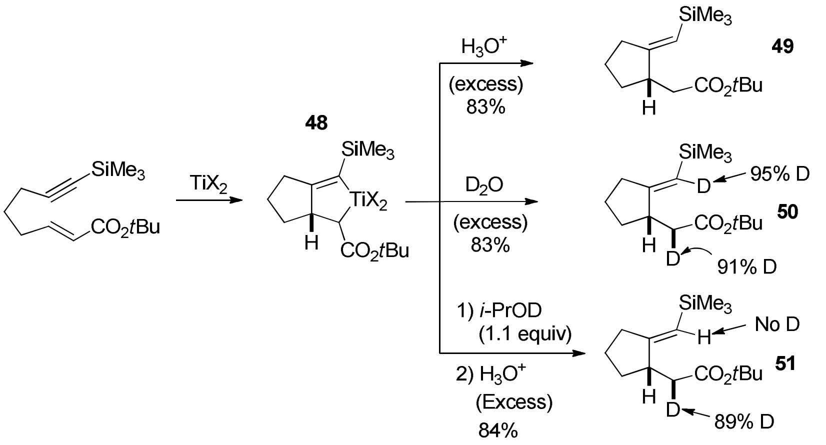
Other methods have made use of very simple, easily accessible π-components. In 1996, Sato reported titanium-mediated [3+2]-reductive cycloadditions of acetylenic enoates to yield bicyclic ketones (Scheme 36).[60] This reaction was originally uncovered while attempting to optimize the reaction for a related monocyclic side product. They found that when a limited amount of acid (1.1 equiv) was used in the reaction, the unexpected bicyclic ketone product **45** could be obtained in high yields. The authors proposed that after oxidative cyclization by the titanium, the bicyclic metallacycle **46** could be protonated yielding **47**. If this bicyclic metallacycle was exposed to excess acid, then monocyclic products resulted (from vinyl protonation of **47**). However, if the amount of acid is limited, then a second ring closure takes place yielding the bicyclic ketone.

Scheme 36. Titanium-Mediated [3+2]-Reductive Cycloaddition



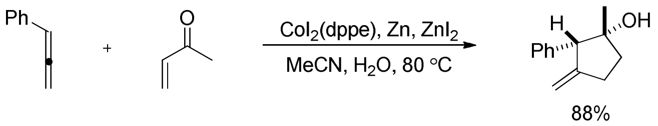
A subsequent report published by Sato broadened the substrate scope of this reaction.[61] This reaction was general with respect to tethered alkynyl and alkenyl enoates. Additional experiments with deuterated alcohols elucidated further clues about the mechanism of the reaction. When metallacycle **48** was treated with excess acid or D_2O, monocyclic products **49** and **50** from with incorporation of the deuterium at the α-carbon adjacent to the carbonyl and at the alkenyl position (Scheme 37). However, if **48** is treated with 1.1 equiv of *i*PrOD and then with excess acid, they found that only the α-carbon was deuterated in product **51**. This indicates that the titanated-ester portion of the molecule is more reactive than the alkenyl-titanium moiety. The difference in reactivity of titanium-carbon bonds is responsible for the divergent product selectivity in presence of excess or a limited amount of acid.

Scheme 37. Deuterium Experiment for Titanium-Mediated [3+2] Cycloaddition



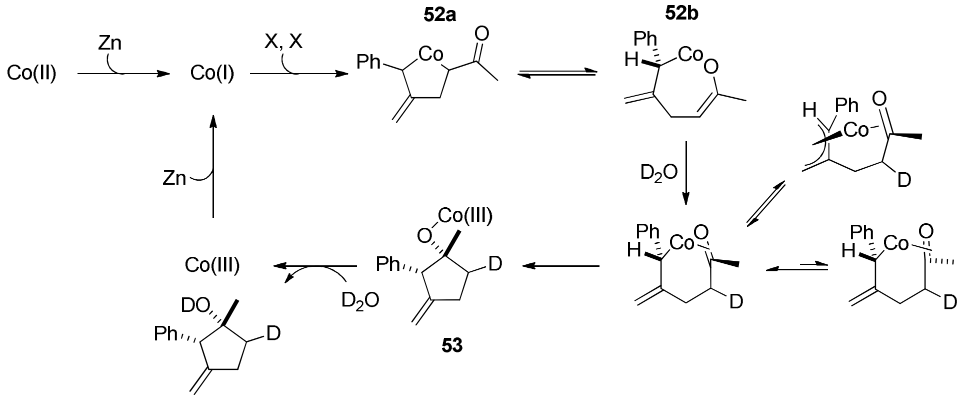
In recent studies, the Cheng group has published an intermolecular cobalt-catalyzed [3+2] reductive cycloaddition with allenes and enones (Scheme 38).[62] This cobalt-catalyzed reaction yields cyclopentenol products with exclusive regioselectivity and good diastereoselectivity. This reaction is tolerant of aliphatic and aromatic allenes and unsubstituted aliphatic enones. This reaction also yields lactone products when ester-substituted allenes are employed.

Scheme 38. Cobalt-Catalyzed [3+2] Cycloaddition of Allenes and Enones



Cheng proposes that the reaction begins by reduction of Co(II) to Co(I) by zinc dust (Scheme 39). Next the Co(I) undergoes cyclometallation with the allene and enone to form a mixture of O- and C-enolate metallacycles (**52a** & **52b**), which are proposed to be in equilibrium. Protonation of **52** and intramolecular insertion of the cobalt into the carbonyl yields alkoxide **53**. The alkoxide is then protonated yielding the observed product. The use of D_2O instead of H_2O in the reaction supports this mechanism as the deuterium atom is incorporated in the 5-position of the cyclopentenol ring and the oxygen in the product is deuterated.

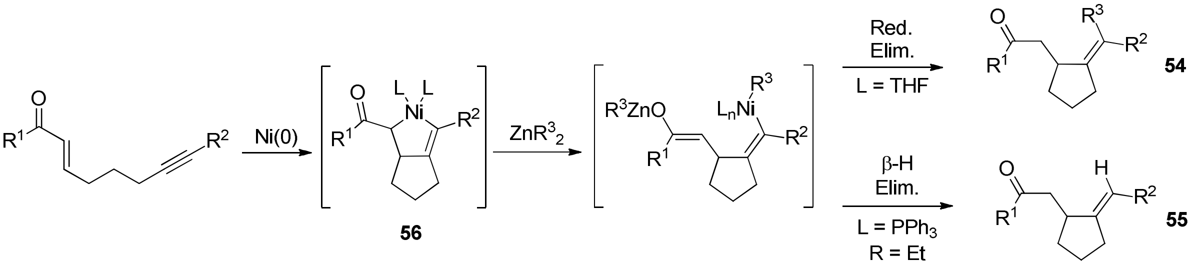
Scheme 39. Mechanism of Cobalt-Catalyzed [3+2] Cycloadditions



1.3.4. Montgomery Group [3+2]-Reductive Cycloaddition History

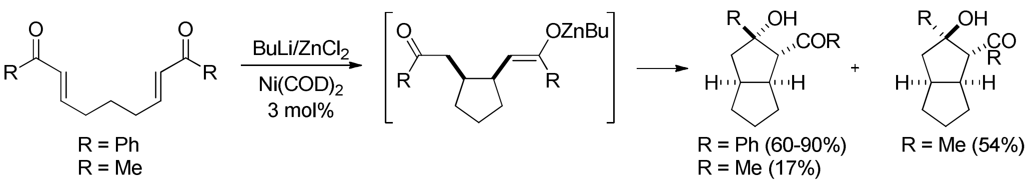
The Montgomery group has had a long-standing interest in [3+2] cycloaddition chemistry and carbocycle synthesis. In 1996, Savchenko and Montgomery were studying the reactivity of alkynyl enones and demonstrated that intramolecular coupling reactions that yielded carbocyclic products were possible with a catalytic amount of nickel and an organozinc reducing agent (Scheme 40). The cyclization reaction was either accompanied by alkylation (**54**) or reduction (**55**) depending on the structure of the organozinc reagent and if phosphine ligand was present.[63] Later Montgomery and co-workers discovered that the phosphine ligands, because of their electron-donating ability, promoted β-hydride elimination processes. After β-hydride elimination, reductive elimination yields reductive coupling product **55**. This was only possible with organozincs containing a β-hydrogen.[64,65] Similar to Sato's chemistry, the reaction is thought to proceed through a metallacycle intermediate **56**. Unlike, Sato's titanium mediated cyclizations, intermediate **56** is intercepted with a reducing agent which regenerates the catalyst.

Scheme 40. Nickel-Catalyzed Cyclizations



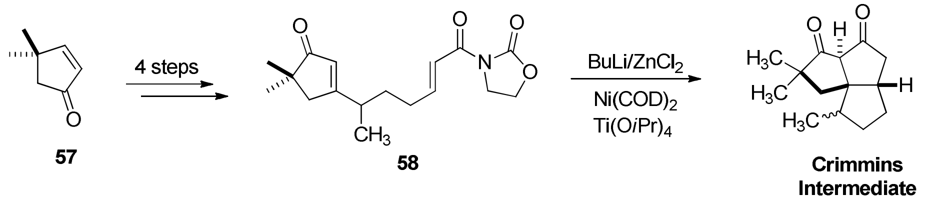
They were probing the substrate scope of this reaction with bis-enone substrates and obtained bicyclooctenol products when dibutylzinc was used (Scheme 41).[63] Unlike the reductive cyclizations, the organozinc is not incorporated into the product and the organozinc reagent must be sp^3 hybridized for the reaction to be productive.[63,64] It is speculated that this reaction proceeds through a metallacycle based pathway initiated by the nickel catalyst, and this metallacycle is intercepted by the organozinc.[65]

Scheme 41. Nickel-Catalyzed [3+2] Cycloadditions with Bis-Enones



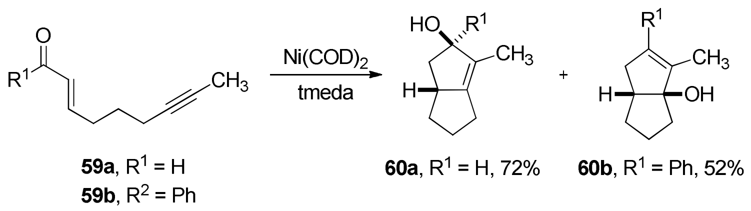
This bis-enone cycloaddition methodology was later expanded to include oxazolidinone moieties for the synthesis of the Crimmins key triquinane intermediate.[66] The Crimmins intermediate is a common synthetic intermediate in the synthesis of the pentalenene family of triquinane natural products. The cycloaddition precursor was available in four steps from **57**. Treatment of the dicarbonyl intermediate **58** with a nickel catalyst yielded the Crimmins intermediate (Scheme 42).

Scheme 42. Synthesis of Crimmins Intermediate from Dicarbonyl Precursor



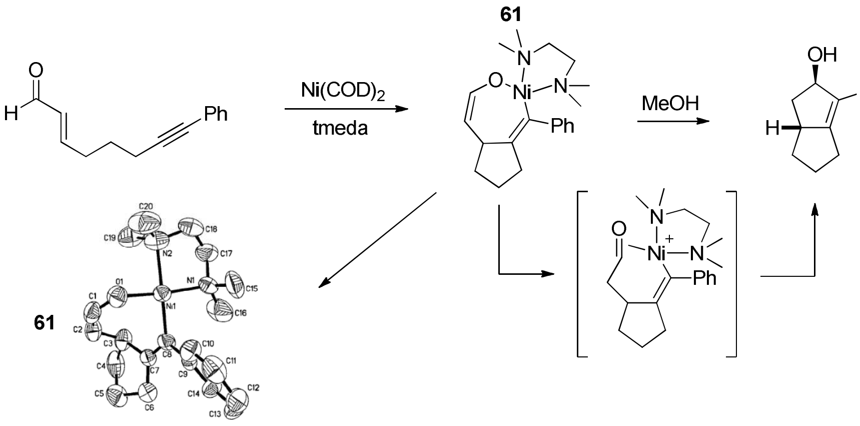
The Montgomery group also experimented with alkynyl α,β-unsaturated carbonyl substrates **59** and discovered that these bicyclooctenol products **60** were also accessible, albeit with stoichiometric amounts of nickel and TMEDA ligand (Scheme 43).[67] Treatment of alkynyl enone substrates also yielded these reductive cycloaddition products, but upon workup with diluted acid, rearranged tertiary alcohol products emerged (**60b**).

Scheme 43. Nickel-Mediated [3+2] Cycloadditions



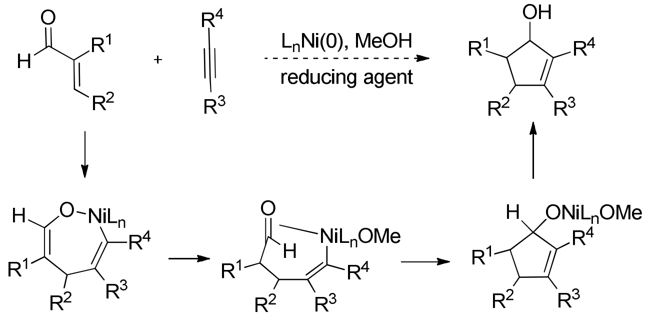
The mechanism was proposed to proceed via an oxidative cyclization with the nickel to yield a C- or O-nickel enolate. Protonation of the enolate followed by insertion of the metal into the carbonyl and protonation of the metal alkoxide affords the product (Scheme 44). This proposed nickellacycle intermediate **61** was later isolated and characterized by X-ray crystallography.[68] The substrate scope of the [3+2] cycloaddition was expanded in later papers to include tricyclic products, but all attempts to make this reaction catalytic were unsuccessful.[69]

Scheme 44. Mechanisms of Nickel-Mediated [3+2] Cycloaddition and X-ray



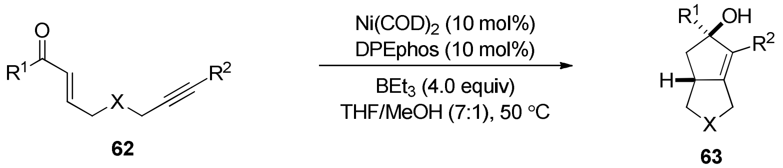
They key problem in enabling a catalytic reaction was to have a suitable electrophile or Brønsted acid co-exist with a suitable reducing agent to convert the Ni(II) alkoxide to a Ni(0) species and a cyclopentenol product. The problem with the stoichiometric reactions was that no suitable reducing agent could be found that could satisfy these criteria (Scheme 45). There were a couple of reports involving a organoborane reducing agent in a protic solvent that offered the solution to this problem.[70,71]

Scheme 45. Strategy for Nickel-Catalyzed Reductive Cycloadditions



In order to explore potential catalytic reductive cycloadditions, a simple substrate **62**, was synthesized and screened against several ligands.[72] The organoborane reducing agent with a THF/methanol co-solvent system enabled catalytic reductive cycloadditions of substrate **62**. Furthermore, this transformation was possible with a number of monodentate and bidentate ligands. The best yields were possible with DPEphos, so the substrate scope was expanded to include aliphatic alkynes and oxygen linkers to yield heterocyclic products **63** (Table 1). In short, the organoborane and protic solvent system allowed access to products that had only been previously accessible with stoichiometric amounts of nickel.

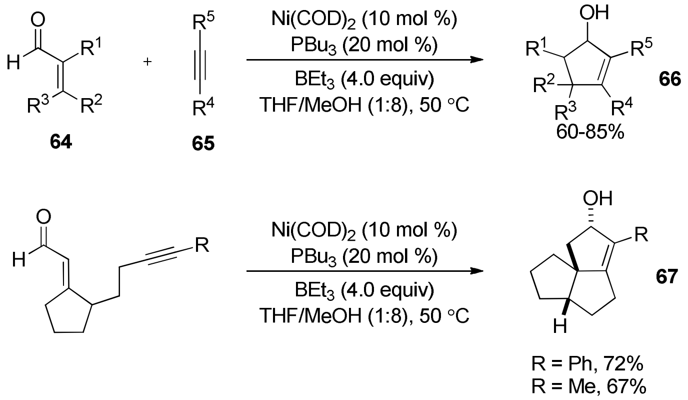
Table 1: Substrate Scope of Intramolecular Nickel-Catalyzed [3+2]-Reductive Cycloadditions



Entry	R^1	R^2	X	**63** Yield (%)
1	H	Ph	CH_2	87
2	H	Me	CH_2	78
3	H	Ph	O	44

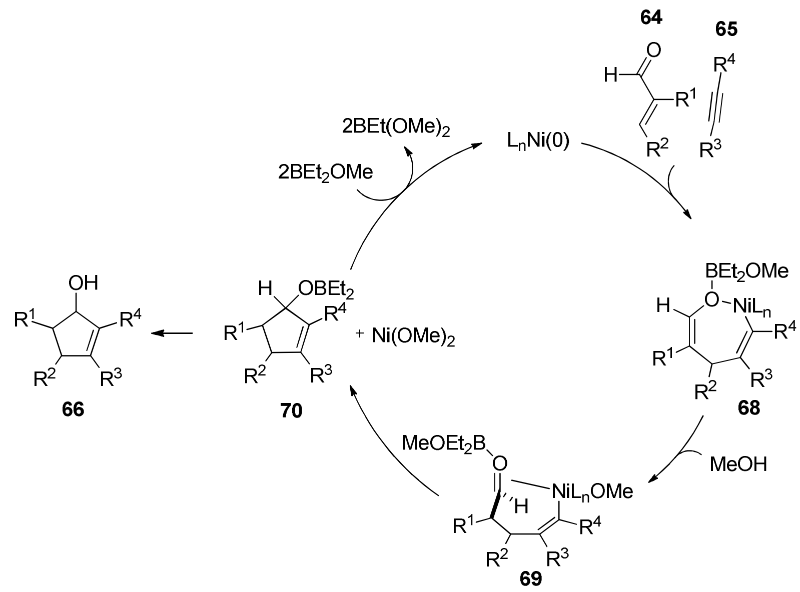
This nickel-catalyzed [3+2]-reductive cycloaddition was next expanded to intermolecular reactions (Scheme 46). DPEphos was not an efficient ligand for intermolecular transformations, so after further ligand screening, it was found that PBu_3 was a much more effective ligand. The procedure was re-optimized, and a broad range of enal substrates **64** and alkynes **65** could be transformed into cyclopentenol products **66** with this catalyst system.[73] These conditions were even applicable to tethered substrates for the synthesis of triquinane ring systems **67** (Scheme 46).

Scheme 46. Nickel-Catalyzed Intermolecular [3+2]-Reductive Cycloadditions



The mechanism of this reaction is thought to be similar to that of the stoichiometric nickel-mediated intramolecular [3+2] cycloadditions.[72,73] The mechanism is proposed to involve oxidative cycloaddition to form complex **68** (Scheme 47). It is known that triethylborane undergoes partial methanolysis to $Et_2B(OMe)$ which is depicted instead of BEt_3 in reactions conducted in co-solvent systems with methanol.[74] Complexation of the Lewis acidic borane to enal **64** accelerates oxidative cyclization, and fast protonation of the enolate **68** by methanol affords a vinyl-nickel intermediate **69**. Insertion of vinyl-nickel intermediate **69** into the tethered aldehyde closes the cyclopentene ring affording alkoxide intermediate **70**. Release of the product **66** along with the nickel (II) species followed by regeneration the nickel catalyst with the borane restarts the catalytic cycle with another substrate pair.

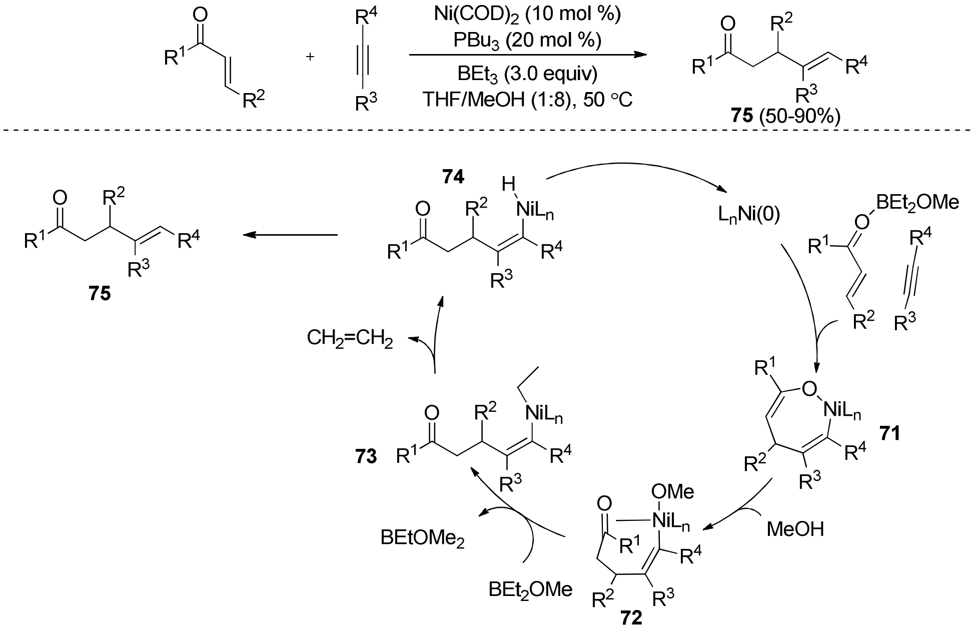
Scheme 47. Mechanism of Nickel-Catalyzed Enal-Alkyne Reductive Cycloaddition



It is unclear exactly how the organoborane interacts with enal **64** or the metallacycle **68**. However, computational studies of similar metallacycles in the presence of organozincs when no phosphines or N-heterocyclic carbenes are present suggest a complex interaction.[75,76] Organoboranes have also been the subject of recent computational studies involving oxidative cyclizations.[77] There are also several possibilities for the initial structure of the product alkoxide **70** as the initial product can be also envisioned as the nickel alkoxide. The borane is essential for ring closure because acyclic products are formed when there is no reducing agent.[78]

In the context of some of our findings in later chapters, a report by our group that immediately followed the catalytic [3+2] cycloaddition communication is particularly relevant. The protic-cosolvent system and organoborane reducing agent also allowed access to intermolecular, catalytic reductive couplings of enones and alkynes yielding γ,δ-unsaturated ketones as products.[79] These transformations had been limited to intramolecular reactions,[64,80] or had required the formation of metallated coupling partners for intermolecular reactions,[81-84] so the development of this methodology was a welcome advance. The proposed mechanism shared several steps with the proposed mechanism of the [3+2] cycloadditions. Coordination of the metal to the enone and alkyne was followed by oxidative cyclization to yield the seven-membered metallacycle **71**. Protonation of the metal enolate then gives acyclic intermediate **72**. Unlike the proposed cycloaddition mechanism, intermediate **72** is intercepted with the organoborane reducing agent and transmetallates to give a dialkyl nickel (II) intermediate **73** which can undergo β-hydride elimination to yield a nickel hydride species **74** (Scheme 48). The nickel-hydride then reductively eliminates to form the γ,δ-unsaturated carbonyl product **75**.

Scheme 48. Nickel-Catalyzed Reductive Coupling with Enones and Alkynes



1.4 Metal-Mediated [3+2] Cycloaddition Cascade

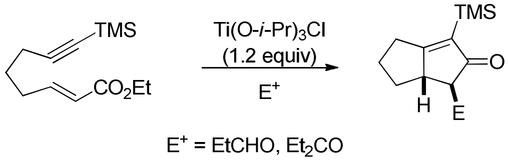
Several of the metal-mediated [3+2] cycloadditions that require protonation prior to the final cyclization can also be intercepted with an electrophile under aprotic conditions. These transformations are uncommon and yield highly functionalized cycloaddition products.

Moreover, these transformations have synthetic utility since multiple rings, bonds, and stereocenters can be constructed in a single-pot. One of the main drawbacks to these transformations is that they require stoichiometric amounts of metal and are generally limited to intramolecular examples.

1.4.1 Titanium-Mediated [3+2]-Alkylative Cycloadditions

Sato also reported interception of these titanacycles with electrophiles such as aldehydes and ketones along with [3+2]-reductive cycloadditions of alkynyl enoates (Scheme 49).[60,61] This was possible with both alkynyl enoates and alkenyl enoates. In some examples E1cb elimination of the hydroxyl group was observed. In the reactions with aldehydes the reaction was not diastereoselective at the hydroxyl position (63:37).

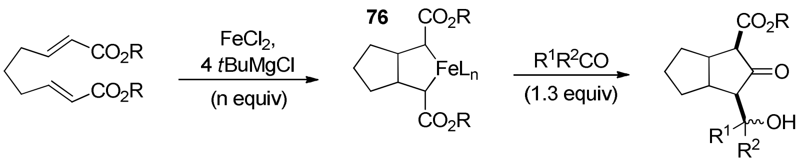
Scheme 49. Metal-Mediate [3+2]-Alkylative Cycloaddition with Titanium



1.4.2 Iron-Mediated [3+2]-Alkylative Cycloadditions

In 2008, Urabe reported similar reactivity with iron and tethered bis-enoate substrates.[85,86] Deuterium-labelling indicated that the iron-carbon bonds had similar reactivity to the titanium carbon bonds and a similar mechanism was proposed to Sato's mechanism for titanium-mediated [3+2] cycloadditions. Like Sato's work, the reaction was limited to stoichiometric amounts of iron. Urabe's group demonstrated both protonation (not shown) and alkylation (Table 2) of the proposed iron metallacycle **76**.

Table 2. Iron- Mediated [3+2]-Alkylative Cycloaddition

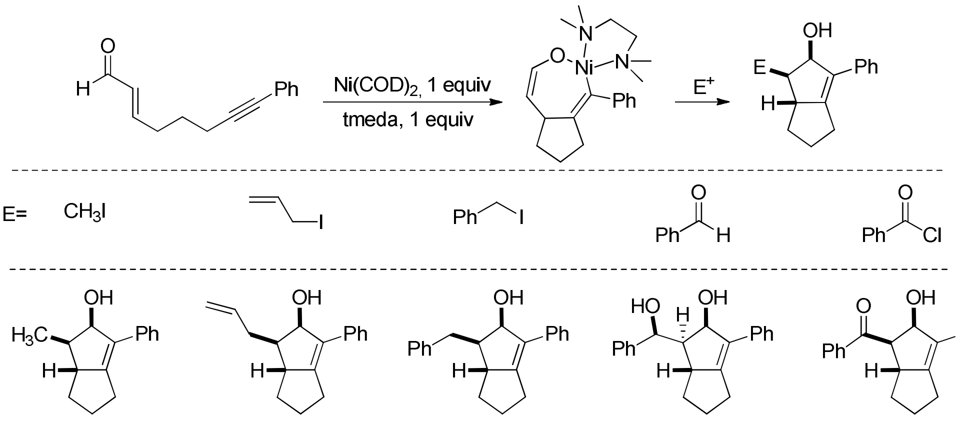


R	*n*	R^1	R^2	Yield
Et	1.5	Me	Me	55
Me	1.25	Et	H	70
Et	1.5	Et	H	46
iPr	1.5	Et	H	62

1.4.3. Nickel-Mediated [3+2]-Alkylative Cycloadditions

Similar to the iron and titanium-mediated [3+2] cyclizations, in 2003 the Montgomery group also expanded their [3+2]-reductive cyclizations to include alkylative examples.[69] Our group's substrate scope was more expansive and included the use of acyl halides, alkyl halides, α,β-unsaturated carbonyl components, and aldehydes (Scheme 50). Our group also demonstrated that tricyclic products, including spirocycles, could be accessed. Unfortunately, like all other metal-mediated examples, these transformations could not be performed with catalytic amounts of metal. The fundamental problem was creating an environment in which the metal enolate can be protonated, but the metal catalyst must also be reduced from the nickel (II) to the nickel (0) species.

Scheme 50. Nickel-Mediated [3+2]-Alkylative Cycloadditions

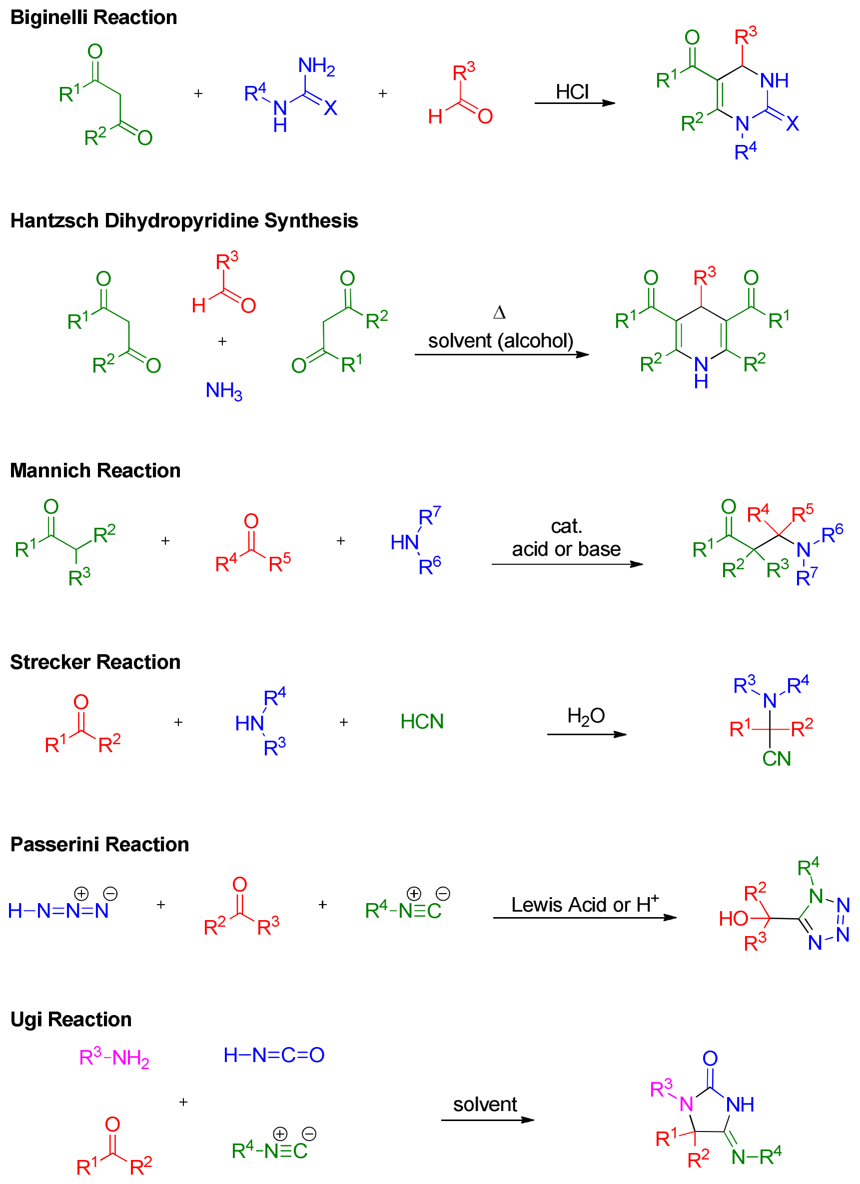


The cycloaddition chemistry previously discussed involves at most two components that are brought together in a single pot to form the five-membered ring. The alkylative intramolecular cyclizations are two-component processes. However, if intermolecular variants of these are developed, the reaction becomes a multicomponent coupling reaction (MCR).

1.5 Multicomponent Couplings

Multicomponent reactions are reactions in which three or more reactants come together to form a single product. These reactants are assembled in a sequential cascade of simple reactions which eventually funnels down to a single product. The challenge is to conduct the reaction in such a way that side products are minimized and each new bond formed is high yielding. There are several common named multicomponent reactions (Scheme 51).[87] Several of these have many variants, such as the Ugi reaction.

Scheme 50. Common Named Multicomponent Reactions



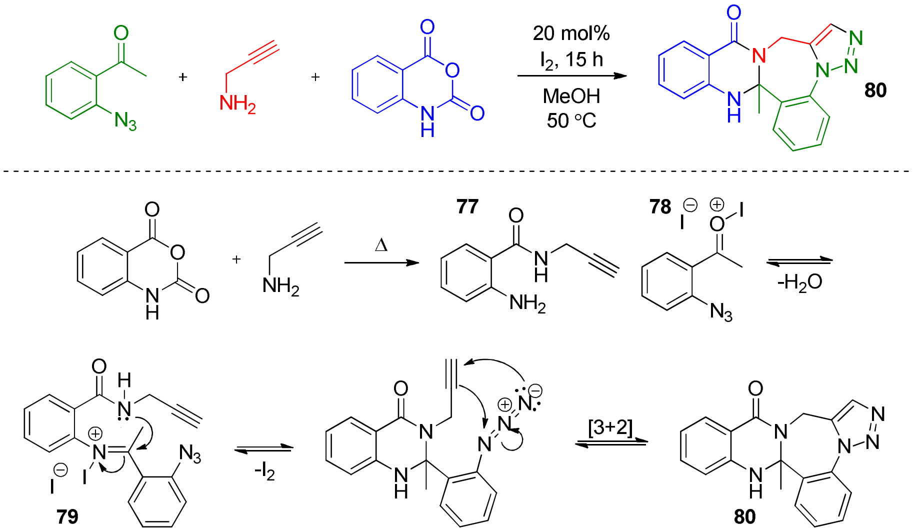
1.5.1 1,3-Dipolar Reagents

While there are several common named MCRs, multicomponent cycloaddition reactions are less common. Most MCR [3+2] cycloadditions involved the use of dipolar reagents, which is not surprising given their widespread use. As a result, most MCR cycloadditions result in highly functionalized heterocycles. The use of MCR cycloadditions for the synthesis of highly functionalized carbocycles is not well developed.

1.5.1.1 Azide Alkyne Couplings

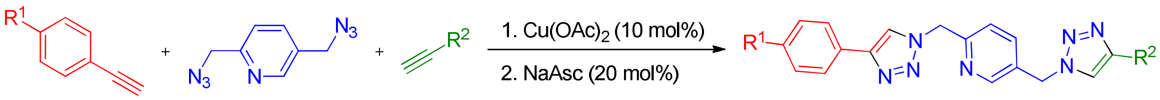
Multicomponent cascades involving azide-alkyne [3+2] cycloadditions are some of the most common dipolar multicomponent cycloadditions. There have been a few recent examples of these types of couplings. The Kurth group demonstrated that they could couple propargyl-amines, isatoic anhydride, and aromatic azides in a single pot to form benzodiazepines (Scheme 52).[88] The reaction proceeds by addition of the propargyl alkyne into the isatoic anhydride followed by decarboxylation to form intermediate **77**. The aniline **77** then condenses with the activated ketone **78** to form imine intermediate **79**. Molecular iodine promotes nucleophilic attack of the amine in **79**, but Kurth also suggests that it acts as an activator for the ketone **78**. A dipolar azide-alkyne [3+2] cycloaddition forms the final two rings and yields the triazole product **80**.

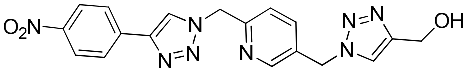
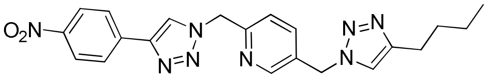
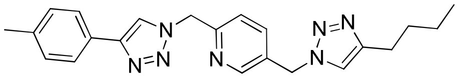
Scheme 52. Multicomponent Azide-Alkyne Cycloadditions to Form Triazolodiazepene Products



The Zhu group has also demonstrated a three-component copper-catalyzed azide-alkyne coupling (CuAAC) to form bis-triazoles.[89] The reaction between the bis-azide and the different alkynes is chemoselective and chelation controlled. They found chelating azides possessed unusually high reactivity in CuAAC reactions. In the presence of both chelating and non-chelating azides, alkynes selectively react with the chelating azide. Addition of sodium ascorbate to the reaction after the first cyclization increases the concentration of the Cu(I) catalyst and enables triazole formation with non-chelating azides. This group first developed a one-pot, two-step sequence where both alkynes were separated by time of addition, but they eventually developed a one pot protocol that took advantage of differences in alkyne reactivity. The first CuAAC [3+2] cycloaddition occurs between the alkyne of greater reactivity and the selectively chelating azido group. Next sodium ascorbate is added, and the less reactive alkyne undergoes another CuAAC reaction with the non-chelating azide to generate the product (Table 3)

Table 3. CuAAC Reactions to Form Bistriazoles

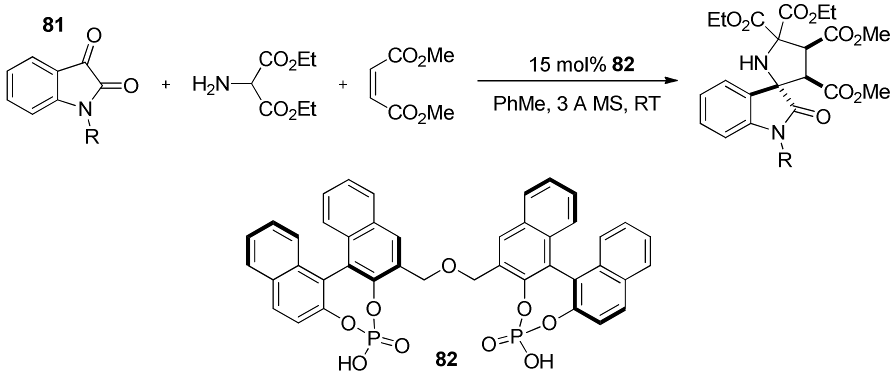


Entry	bistriazole	Yield
1		70%
2		98%
3		74%

1.5.1.2 Azomethine Ylides

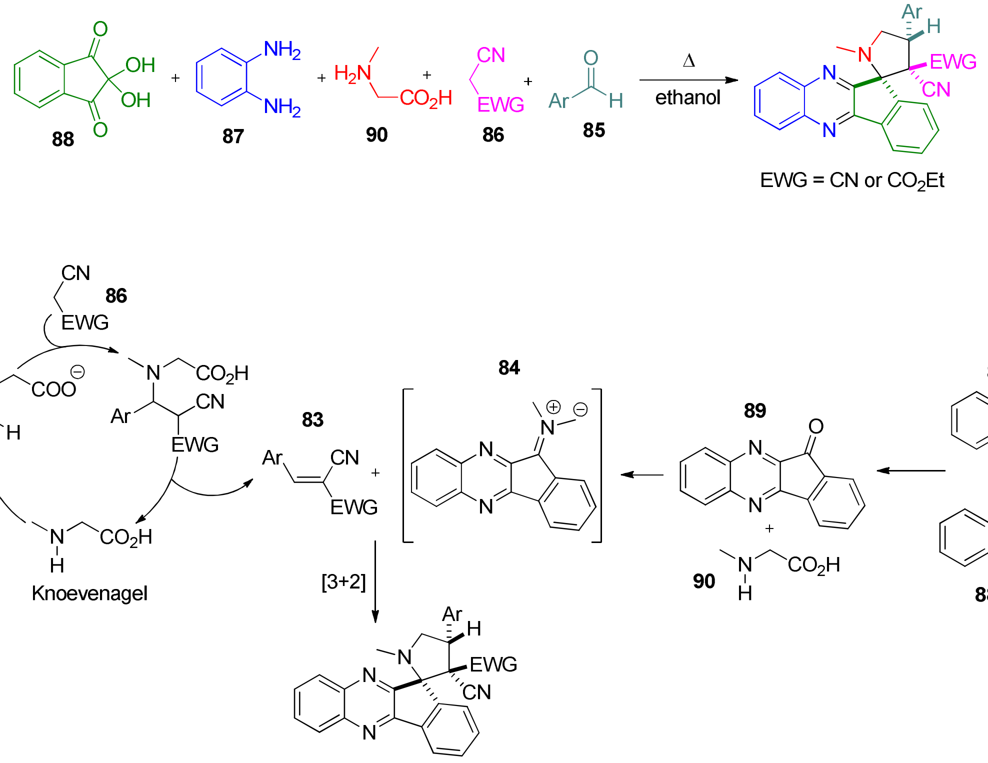
MCR cycloadditions with azomethine ylides are also common. Azomethine ylides are often formed in situ by reaction with a carbonyl moiety followed by reaction with a dipolarophile to yield the coupling product. Recently the Gong and Luo groups demonstrated catalytic-asymmetric assembly of spiro[pyrrolidin-3,2’-oxindole] scaffolds using isatin-based azomethine ylides.[90] Several of the product compounds showed cytotoxicity in bioassays. The reaction is proposed to proceed by phosphoric acid-catalyzed azomethine ylide formation from the amine and ketone followed by the [3+2] cycloaddition with the electron deficient olefin (Scheme 53). The reaction was amenable to a number of different esters, olefins, and substitution on the nitrogen atom of the isatin **81**.

Scheme 53. MCR Enantioselective Azomethine Ylides for Spirooxindole Scaffolds



In a similar example, Wen and Li synthesized spiropyrrolidine derivatives in good yield from a five-component reaction that involves a [3+2] cycloaddition with an olefin **83** and azomethine ylide **84** which were both generated in situ (Scheme 54).[91] This reaction was also catalytic, but unlike Gong and Luo’s report was not asymmetric. The olefin **83** is generated by a catalytic Knovenagel condensation between an aldehyde **85** and nitrile **86**. The azomethine ylide is generated from condensation of an aromatic diamine **87**, with ninhydrin **88** to form a ketone **89**. Condensation of ketone **89** with the amine catalyst **90** followed by thermal decarboxylation generates the azomethine ylide **84**. This reaction was conducted with a variety of aromatic aldehydes and either malonitrile or cyanic ester.

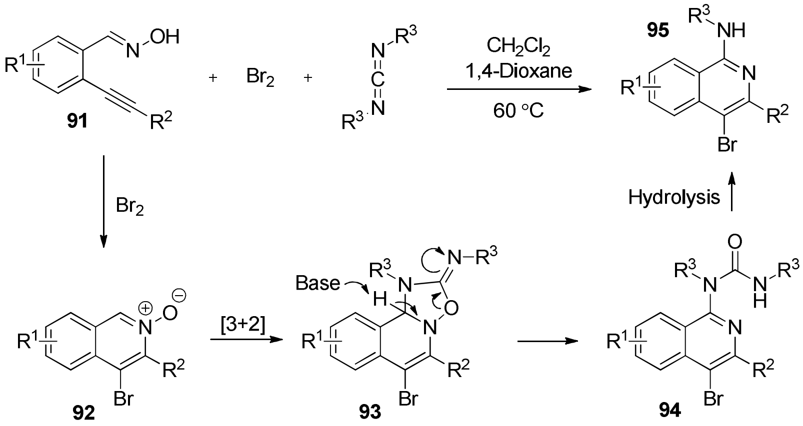
Scheme 54. Five-Component Azomethine Ylide [3+2] Cycloaddition



1.5.1.3 Nitrones

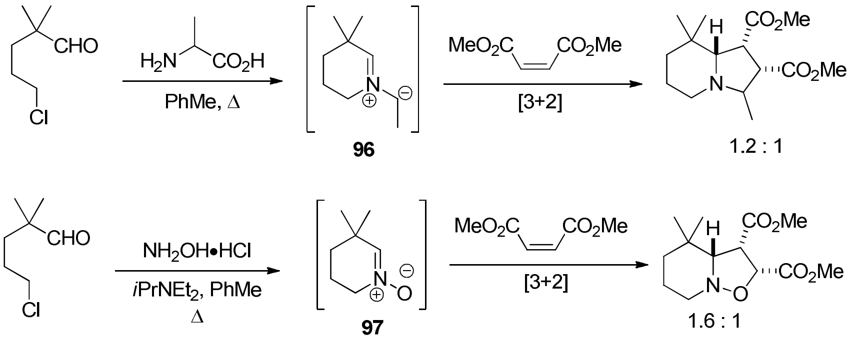
Multicomponent couplings using azomethine ylides and azide/alkyne combinations are the most common, but nitrones have also been used in multicomponent [3+2] cycloadditions. The Wu and Ye groups have demonstrated these multicomponent [3+2] cycloaddition reactions with nitrones to synthesize 1-aminoisoquinolines.[92] They reported that an alkynyl-benzaldoxime **91**, could be combined with molecular bromine and a carbodiimide under milder conditions and with milder reagents than had been previously used to access such structures. The authors propose that the oxime **91**, undergoes a 6-endo cyclization with the bromine to form a bicyclic intermediate oxide **92** (Scheme 55). Intermediate **92** undergoes a [3+2] cycloaddition with the diimide to yield cycloadduct **93**, which rearranges to form urea **94**. This urea is hydrolyzed to form the final product **95**. Aliphatic and aromatic substituents were tolerated on the oxime as well as both cyclohexyl and isopropyl substituents on the carbodiimide.

Scheme 55. Multicomponent [3+2] Cyclizations of Nitrile-Oxides



In another example, Coldham demonstrated that bicyclic amines could be accessed by treating halo-alkyl aldehydes with amino acids or esters, which after cyclization forms an azomethine ylide **96** in situ (Scheme 56).[93] This azomethine ylide then reacts with an olefin to form a bicyclic product. These bicyclic products are ordinarily accessible using stannylated or silylated amines, but this option provides a much simpler route. This methodology was also extended to hydroxyl amine which forms nitrone **97** in situ. Nitrone **97** reacts with the olefin in the same way the azomethine ylide does and yields oxazole products.

Scheme 56. Multicomponent Cycloadditions with Nitrones and Olefins

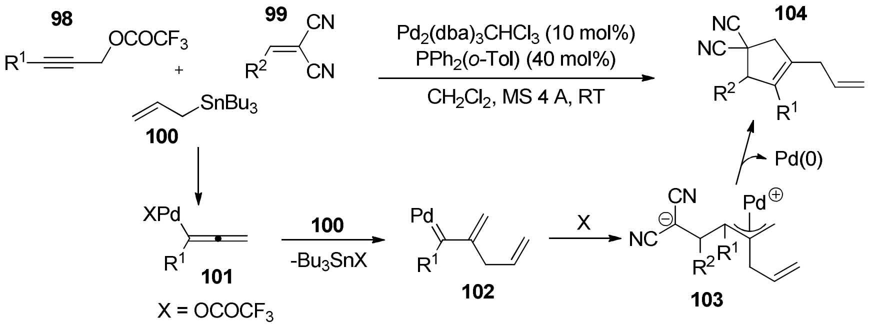


Like the reductive [3+2] cycloadditions most of the dipolar reagents used for this transformation result in the formation of heterocycles. Accessing carbocycles is much more difficult, and multicomponent [3+2] cycloadditions for carbocycle synthesis are uncommon. There have been a few reports involving carbenoids, strained rings, and 1,2-silyl shifts.

1.5.2. Carbenoids

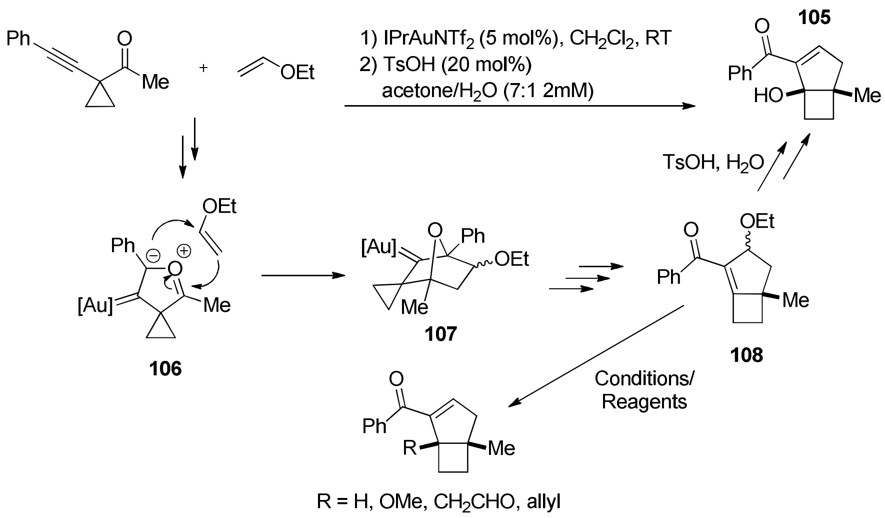
Recently the Jin and Yamomoto groups reported a palladium-catalyzed [3+2] cycloaddition involving a palladium carbenoid intermediate **102**.[94] The authors had noted that propargyl compounds react with hard nucleophiles in the presence of palladium to form allenes.[95-97] They reasoned that they could intercept the purported allenyl palladium intermediate **101** with a soft nucleophile to form a vinyl carbenoid **102**. Carbenoid **102** could then be intercepted by a third component and cyclize to form a five membered ring. After some experimentation, they found that treatment of propargyl trifluoroacetates **98**, ethylidene malonitriles **99**, and allylstannane **100** with a palladium catalyst yielded cyclopentene products. The reaction was high yielding with both aliphatic and aromatic olefins and alkynes. The authors propose that the propargyl compound **98** reacts with palladium to form an allenyl palladium intermediate **101**, which is attacked by the allyl stannane **100** (Scheme 57). A vinyl palladium carbenoid compound **102** is formed, which reacts with the malonitrile to form π-allyl palladium complex **103**. This allyl palladium complex undergoes C-alkylation to give the cyclopentene product **104**.

Scheme 57. Palladium-Catalyzed Multicomponent [3+2] Cycloaddition



Gold catalysts have also been employed in [3+2] cycloadditions involving carbenoid species. Zhang and co-workers have demonstrated that treatment of alkynyl ketones and electron rich olefins with gold catalysts results in the formation of bicyclo[3.2.0]heptanes **105**.[98] One of the initially proposed intermediates is a gold carbenoid species **106** which undergoes a dipolar cycloaddition with the olefin to form a complex bicyclic intermediate **107** (Scheme 58). Intermediate **107** then goes through a series of rearrangements to yield an unstable intermediate **108**. This intermediate converts to product **105** under acidic conditions. The crude reaction mixture could also be treated with a nucleophile under various conditions to yield a variety of three component coupling products.

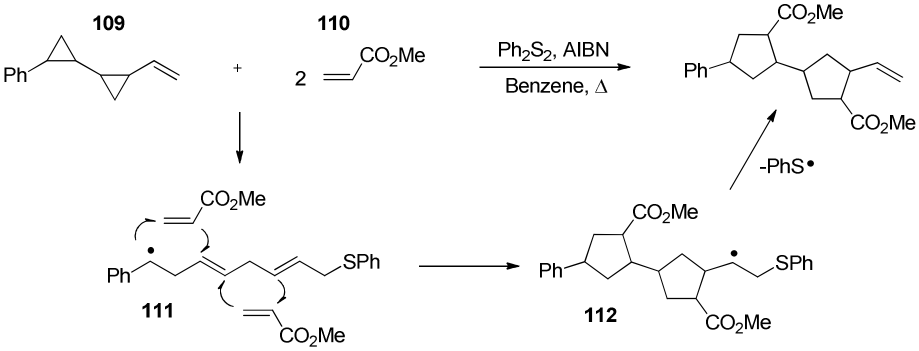
Scheme 58. Gold-Catalyzed Multicomponent Cycloadditions



1. 5. 3. Strained Rings

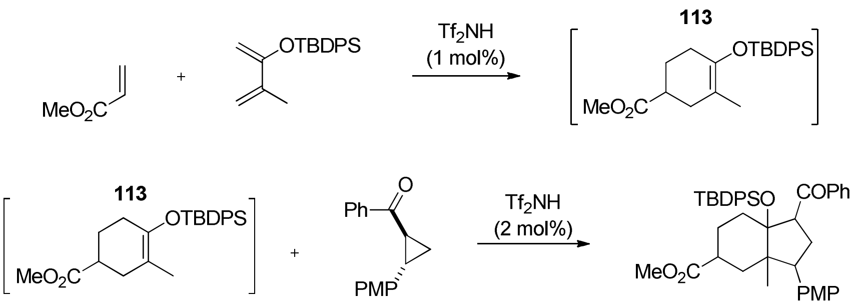
There have also been a few reports of strained rings in multicomponent [3+2] cycloadditions. Feldman reported radical-mediated cycloadditions of vinylcyclopropanes with olefins.[99] These reactions yielded allyl-cyclopentane products. In an effort to exploit the chain-nature of radical mediated cyclizations, they synthesized cyclopropane substrate **109** and subjected it to reaction conditions in the presence of olefin **110**. This reaction delivered the cyclopentyl product in modest yields, but with little stereocontrol. The reaction is initiated by AIBN which reacts with Ph_2S_2 to create a thiophenyl-radical (Scheme 59). The thiophenyl radical ring-opens the cyclopropyl rings in a chain process that affords an acyclic homoallylic radical intermediate **111**. The homoallylic radical then reacts in a chain-like fashion with the olefin to form the carbinyl radical intermediate **112**. Radical elimination of the thiophenyl group yields the product and regenerates the thiophenyl radical.

Scheme 59. Radical Mediated Multicomponent [3+2] Cycloadditions with Strained Rings



Donor-acceptor cyclopropanes have also been used in multicomponent cycloadditions. Cycloadditions with donor-acceptor cyclopropanes usually require stoichiometric amounts of Lewis acid for a productive reaction. The Takasu group discovered that triflic imide (Tf_2NH) reacts with silanes to form R_3SiNTf_2 in situ to catalyze [2+2] cycloadditions with silyl enol ethers.[72] They extended this methodology to [3+2] cycloadditions of silyl enol ethers with donor-acceptor cyclopropanes and found that they could form cyclopentane products in good yield.[101] Cyclic enol ethers could be used to form bicyclic products in good yield. When they tried to expand the bicyclic method to a [4+2]/[3+2] cascade where the cyclic enol ether **113** is constructed by a [4+2] cycloaddition, the reaction gave a complex mixture of products. They were able to access the desired tricyclic products in modest yield when the DA cyclopropane is added sequentially (Scheme 60).

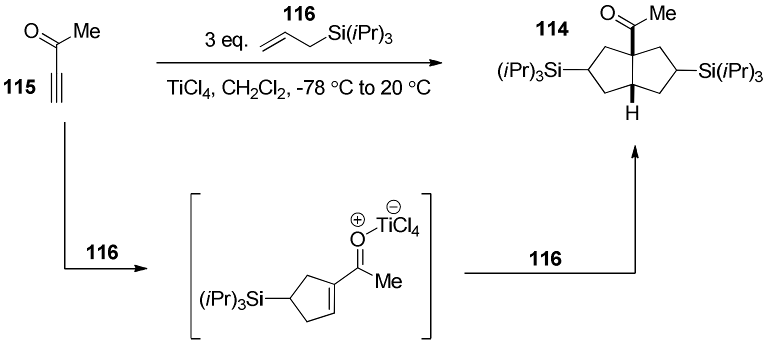
Scheme 60. Multicomponent Cycloadditions with DA Cyclopropanes



1.5.4 1,2-Silicon Shifts

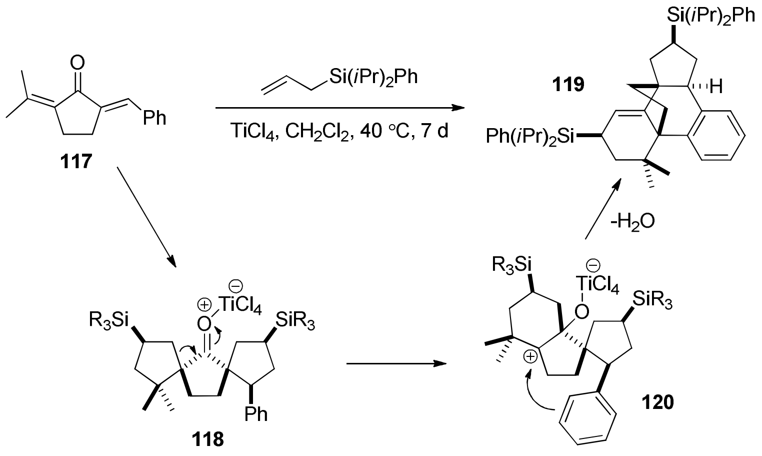
Allyl silanes have been successfully used in multicomponent [3+2] cycloaddition reactions for the construction of bicyclic ring systems. Knölker previously demonstrated transformations similar to Danheiser's allylsilane olefin cyclizations (Scheme 27) to form cyclopentane products.[102] Specifically, they had demonstrated this transformation with cyclopentenes which resulted in the formation of bicyclic products similar to **114**. Knölker then reasoned that similar products could be accessed by reacting two equivalents of allylsilane with an alkyne substrate in a multicomponent [3+2] cycloaddition (Scheme 61).[103] Experiments with alkyne **115** and allylsilane **116** demonstrated that this hypothesis was correct and these products were accessible in good yields. The reaction was not very efficient with the bulky phenyl substituted allylsilane (Si(*i*Pr)$_2$Ph).

Scheme 61. Multicomponent Allylsilane Cycloadditions with Alkynes



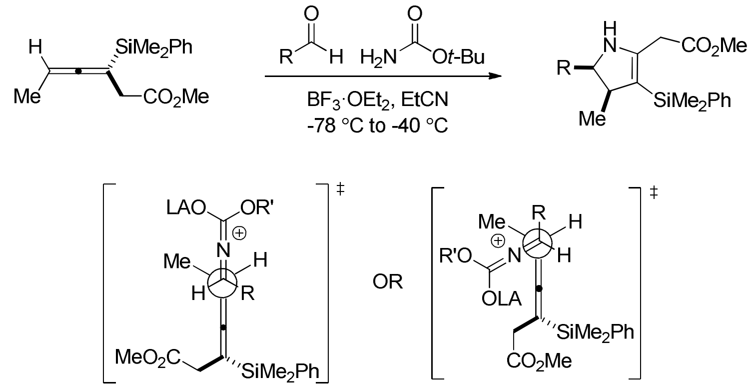
Knölker later reported a multicomponent coupling with allylsilanes and bis-enone substrate **117**.[104] Similar to his previous work, he intended to di-annulate the bis-enone **117** and form a spirocyclic product **118** this time. Treatment of bis-enone **117** with the allylsilane instead afforded a complex polycyclic product **119** (Scheme 62). The desired product, **118**, does form, but coordination of the Lewis acid to the ketone causes a Wagner-Meerwein rearrangement to form cationic intermediate **120**. Freidel-Crafts alkylation of this carbocation and elimination of water upon workup affords the observed product.

Scheme 62. Multicomponent Reactions with Allylsilanes and Bis-olefins



Allenylsilanes have been used in multicomponent coupling reactions for the formation of heterocyclic products. Recently, Panek demonstrated that iminium ions formed in situ could be treated with allenylsilanes to form pyrrole products (Scheme 63).[105] Carbamates were the optimum amine source and $BF_3 \cdot OEt_2$ was the optimal Lewis acid for iminium ion formation. The reaction was highly diastereoselective. The diastereoselectivity is thought to arise from either an antiperiplanar or synclinal transition state where the axial chirality of the allene transfers to the *si* face of the iminium ion. Gauche interactions are minimized in the antiperiplanar transition state, but the synclinal transition state places the R group of the iminium furthest from the allene.

Scheme 63. Multicomponent Allenylsilane [3+2] Cycloadditions



1.6. Conclusion

There are many methods available to access five-membered carbocycles and heterocycles. Accessing cyclopentenoid products is more difficult than accessing heterocyclic products, although many methodologies have been developed to address these difficulties. Many of these methods use 1,3-dipolar reagents, vinyl carbenoid species, or strained rings and have enjoyed widespread use. Despite the success of these methodologies, some of the drawbacks include the use of specialized reagents or conditions. It may also be difficult to install some of these groups at a late stage in a synthesis or carry it through a synthesis. Other methods have evolved to address these difficulties and these methods rearrange the skeleton of the reagent or change the oxidation state of the substrate. Alkylative variants of metal-catalyzed reactions unfortunately require stoichiometric amounts of metal. Multicomponent variants of these methodologies offer ways to further functionalize the carbocyclic products without additional isolation and purification steps. While reports involving 1,3-dipolar reagents are more common, they suffer from the drawbacks of the two-component coupling processes. Unfortunately, multicomponent variants of methodologies that take advantage of rearrangements or changes in oxidation state are much less common and this area would benefit from additional research.

Chapter 2

Nickel-Catalyzed [3+2]-Reductive Cycloadditions of Enoates and Alkynes

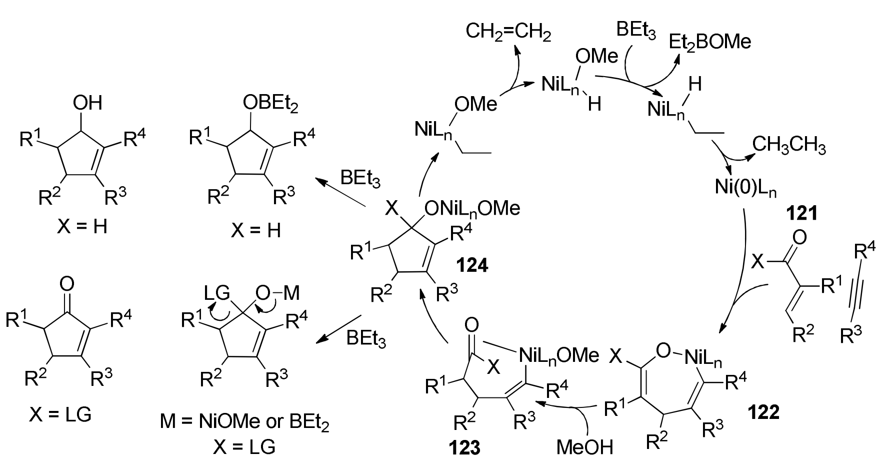
2.1. Introduction

The [3+2] cycloaddition is a common way to construct five-membered rings. Methodologies for accessing carbocycles make use of dipolar reagents, vinyl carbenoid species, or strained rings. These methods suffer from drawbacks such as the need for specialized reagents or conditions. These specialized groups may not be easily installed at a late stage in a synthesis or carried through a synthesis. Methods that use simple, readily available π-components that can be easily installed or easily carried through a synthesis offer a way to circumvent these difficulties. Combining these π-components to form a five-membered ring requires rearrangement of the skeleton of the reagent or a change in substrate oxidation state. The work of the Montgomery group over the last decade falls into the latter category. Our group has made use of enone or enals and coupled them with alkynes to form cyclopentenol products. Initially, this chemistry was limited to intramolecular, stoichiometric reactions, but methodologies were eventually developed that enabled both nickel-catalyzed intra- and intermolecular couplings of enals and alkynes to form cyclopentenol products. This chapter details the development of nickel-catalyzed enoate and alkyne couplings to form the corresponding cyclopentenone products. This methodology is complementary to the enal-alkyne couplings and enjoys the use of more stable enoate starting materials than the enals used in the enal-alkyne coupling methodology.

2.2 Leaving Group Screen

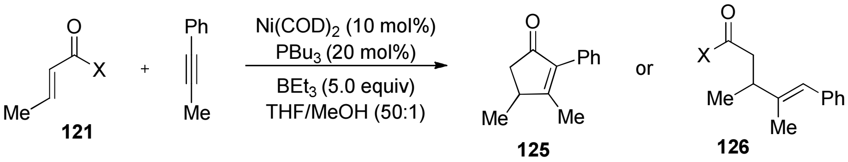
After the nickel-catalyzed enal-alkyne reductive cycloadditions had been developed, we sought to access the corresponding cyclopentenones. These cyclopentenones could be accessed by performing a nickel-catalyzed enal-alkyne reductive cycloaddition and then oxidizing the product; this requires multiple steps including purifying unstable enal starting materials. After some study of the proposed catalytic cycle, we realized that we could change the X group on the α,β-unsaturated carbonyl starting material **121**, to a leaving group, which would allow access to the desired cyclopentenone products (Scheme 64). The proposed pathway would be much the same as the proposed pathway for the nickel-catalyzed enal-alkyne reductive cycloaddition. Coordination of nickel to **121** and the alkyne followed by oxidative cyclization gives the seven-membered metallacycle **122**. The metallacycle is next protonated by methanol to give acyclic vinyl-nickel intermediate **123**. Insertion of the vinyl-nickel moiety into the carbonyl closes the ring to give intermediate **124**. Next, instead of transmetallation to yield the product, a labile leaving group can be eliminated from either the metallated ro borylated intermediate **124** to give the cyclopentenone product.

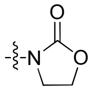
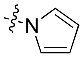
Scheme 64. Leaving Groups Allow Access to Cyclopentenone Products



We began by screening several leaving groups for this transformation and found that while methyl enoates were unreactive (entry 1), oxazolidinones, phenyl enoates, and N-acylpyrroles all yielded the desired cyclopentenone (Table 4). The oxazolidinone and phenyl enoate were efficient for conversion to the desired product, but phenyl enoates gave the best overall yield (entry 2). The N-acylpyrroles were very efficient at yielding acyclic reductive coupling products, **126**, and afforded the cyclopentenone, **125**, as a minor side product. Oxazolidinones also gave acyclic reductive coupling products in low yields.

Table 4. Enoate Derivative Leaving Group Screen for Reductive Cycloadditions

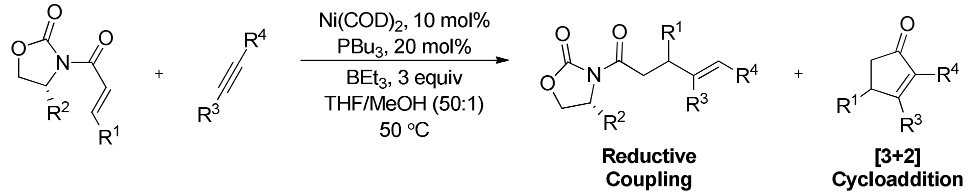


Entry	X	Product, Yield
1	OMe	- - -
2	OPh	**125** (75%)
3		**125**(64%)
4		**125**(5%) + **126d** (90%)

2.2.1 Oxazolidinone Notes: A Brief Aside

We conducted a brief, but noteworthy study on oxazolidinone substrates and believe this chemistry has potential for further development. We discovered that the yield of the reductive coupling product and the reductive cycloaddition product varies from substrate to substrate, with the reductive coupling product forming in 10% yield or less and the reductive cycloaddition product forming in less than a 50% yield (Table 5). The yield of the reductive coupling product increased when a substrate with a large benzyl substituent on the oxazolidinone ring was used (Entry 4). Mechanistically, the reductive coupling product is thought to emerge when ring closure does not occur from intermediate **123**, and instead the acyclic intermediate transmetallates with reducing agent then β-hydride and reductively eliminates to afford the acyclic reductive coupling product. This is similar to the reductive coupling methodology developed by our group in 2007 (See Scheme 48, Chapter 1).[79]

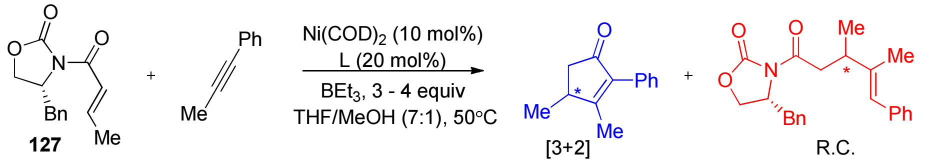
Table 5. Reductive Coupling and [3+2]-Reductive Cycloadditions with Oxazolidinones

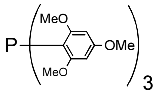


	Substituent				Product Yield	
Entry	R^1	R^2	R^3	R^4	**R.C.**	**[3+2]**
1	H	H	Me	Ph	10%	27%
2	Me	H	Me	Ph	5%	51%
3	Me	H	Et	Et	11%	35%
4	Me	Bn	Me	Ph	38%	16%

Oxazolidinones are perhaps best known for their use as chiral auxiliaries in Evans aldol methodology.[106,107] Because these imide derivatives gave reductive coupling products, albeit in low yield, we sought to use chiral auxiliaries for diastereoselective reactions. Like Evans chemistry, we could potentially separate both product diastereomers after a diastereoselective reaction and cleave the auxiliaries to yield enantiopure products. Our examination of this area was brief and we only studied a single oxazolidinone derivative. This is a plausible avenue for future research as few publications have emerged on enantioselective reductive coupling of enones and alkynes.[108-111] In general, we found it difficult to optimize for a diastereoselective reaction while also maintaining selectivity for the reductive coupling product (Table 6). Many reactions were not diastereoselective, low yielding, or were not selective for the reductive coupling product.

Table 6. Optimizing for Diastereoselective Reactions with Oxazolidinones



Entry	L	**(X)**	[3+2]	R.C.	dr
1	PMe_3	0.8	1	0.1	ND
2	PBu_3	1.5	1	1.7	> 9:1
3	PPh_3	2.7	1	1.8	1:2
4		4.7	1	1	ND
5	PCy_3	0.3	1	13	2.1:1
6	DPEphos	0.3	1	8.3	1.4:1
7	dppf	32	1	5	1:1.2

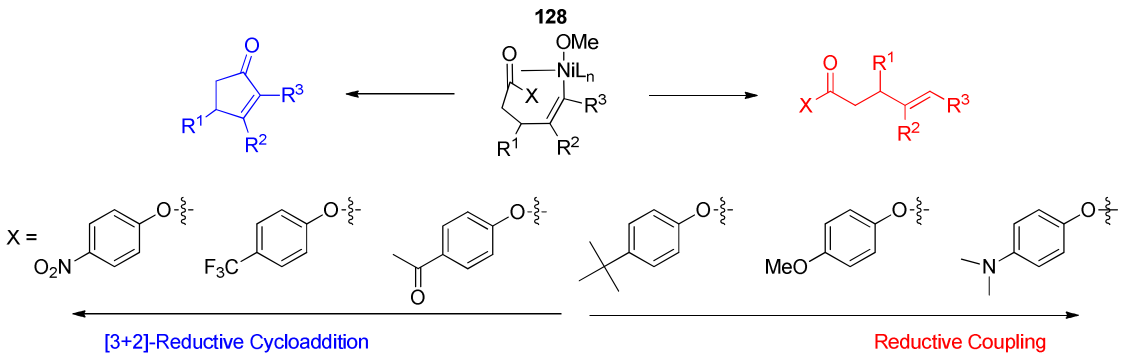
127 : [3+2] : R.C.
~4% : 16% : 38%

Products are given in GC Ratios

2.2.2 Electrophilicity of Phenoxy Group

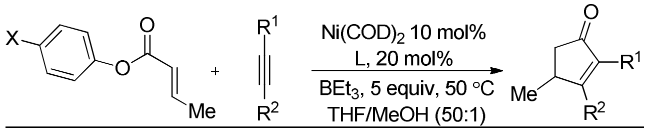
Based upon our early understanding of the reaction mechanism and our experience with the oxazolidinone chemistry, we sought to control the reductive cycloaddition vs. reductive coupling product selectivity or make the reaction more efficient by altering the electronics of intermediate **128**. If the phenoxy group were more electron deficient, then it should make the carbonyl more electron deficient making the insertion into intermediate **128** more facile and resulting in higher yields of the product (Scheme 65). Alternatively, if the ring becomes electron-rich, then insertion into the carbonyl may become disfavored resulting in selectivity for reductive coupling products.

Scheme 65. Does Electrophilicity of the Phenoxy Group Control Product Selectivity?



We tested a few different electron-deficient and electron-rich phenoxy groups. However, no trends were evident (Table 7). In general, several of the electron-deficient groups were reactive under the reaction conditions; the nitro group was reduced to the amine and the ketone substituent reacted to form several side products (Entry 2 & 3). Less reactive groups such as the CF_3 group or the methoxy group did not give substantial difference in yield in most cases. The reductive coupling product was not observed in any of these cases either. It could be that the size or type of X group on the α,β-unsaturated carbonyl component plays a larger role in the product selectivity than the electronics of the ring.

Table 7. Effects of Phenoxy Electronics on [3+2]-Reductive Cycloaddition



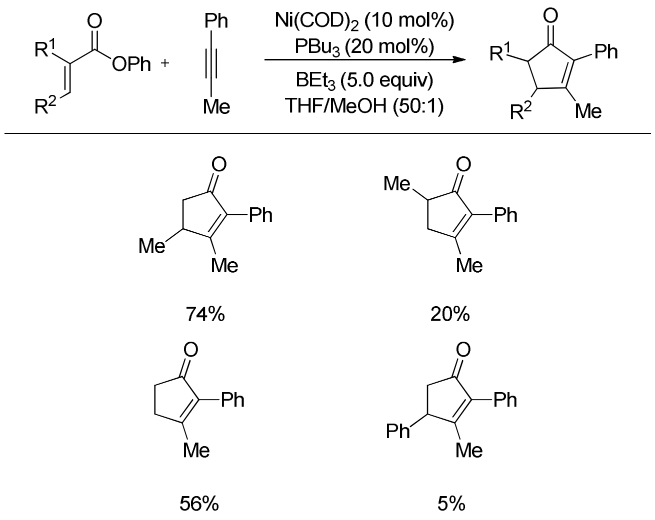
Entry	L	X	R^1	R^2	Yield
1	PBu_3	CF_3	Ph	Me	29%[a]
2	PBu_3	NO_2	Ph	Me	<5%[a]
3	PBu_3	$COCH_3$	Ph	Me	52%[a]
4	PBu_3	H	Ph	Me	74%
5	PBu_3	OMe	Ph	Me	72%[a]
6	PCy_3	CF_3	*n*-Hex	*n*-Hex	71%
7	PCy_3	H	*n*-Hex	*n*-Hex	81%
8	IMES[b]	CF_3	*n*-Hex	*n*-Hex	~78%
9	IMES[b]	H	*n*-Hex	*n*-Hex	86%

a) NMR Yield; *b)* 10 mol%, 10 mol% *t*-BuOK

2.3 Substituents on the Enoate and Alkyne

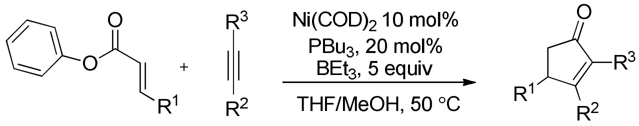
After we realized that phenoxy group electronics do not have a significant impact on the reaction, we further explored the substrate scope with respect to the substitution pattern on the enoate (Scheme 66). We found that β-methyl and unsubstituted enoates gave higher yields while reactions with the β-phenyl and α-methyl substituted enoates were inefficient. Because reactions were inefficient with the α-methyl and β-phenyl substituted enoates, we decided to move forward and begin optimizing the better yielding substrates first.

Scheme 66. Enoate Substitution Screen



Optimization was initiated by examining the alkyne substrate scope (Table 8). Reactions of the β-methyl substituted enoate were low yielding with any other alkyne than phenyl-propyne (entry 1). However, reaction of the unsubstituted enoate with terminal alkynes (entry 4) was similar to reactions with phenyl-propyne (entry 2), and good reactivity was seen with diphenyl acetylene (entry 8). The reaction yield of unsubstituted enoate and aliphatic alkynes (entry 6) was lower. We decided to move forward with the optimization of the β-methyl enoate with the aliphatic alkyne because of the intermediate nature of the yield. We also decided to optimize the reaction of the terminal alkyne with the unsubstituted enoate because this presented an opportunity to optimize a higher yielding example and gave additional opportunity to study regioselectivity.

Table 8. Initial Alkyne Substrate Scope for Reductive Cycloadditions



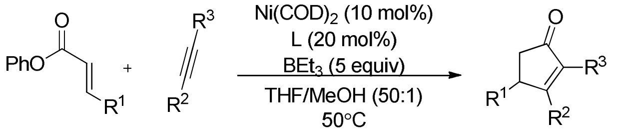
Entry	R^1	R^2	R^3	Yield
1	Me	Me	Ph	74%*
2	H	Me	Ph	56%
3	Me	H	*n*-oct	15%
4	H	*n*-oct	H	59%*
5	Me	*n*-hex	*n*-hex	~39%
6	H	*n*-hex	*n*-hex	~39%
7	Me	Ph	Ph	10%
8	H	Ph	Ph	66%

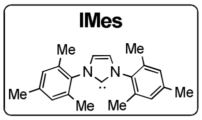
*NMR Yield

2.4 Ligand Optimization

Ligands were screened to optimize reaction efficiency for substrate pairs from Table 9 (entries 4 & 5). In general, bulky and basic ligands worked best for the more sterically encumbered β-methyl enoate and internal aliphatic alkyne. Unfortunately, yields were low with the most sterically encumbered ligands, which slowed the desired reaction (entries 8 & 10), and conjugate addition of the ethyl group to the enoate predominates (see Section 72). The reaction trend of the smaller unsubstituted enoate and terminal aliphatic alkyne is more complex. It appears that the oxidative addition into the unsubstituted enoate is far more facile than the β-methyl enoate, therefore, reaction efficiency is not highly dependent upon the basicity of the ligand. The size of the unsubstituted enoate and alkyne makes the reaction amenable to a variety of ligand sizes. The regioselectivity of the reaction seems to be high with very small and large ligands. It was confusing to us that the yields of unsubstituted enoates with the PCy_3 were so low (entry 7). We initially wondered if this was a steric effect, so we also screened ligands of intermediate size between PPh_3 and PCy_3 (entries 4-6) since the yields were good with PPh_3 (entry 4). These ligands revealed no steric trend, and repetition of the PCy_3 result gave inconsistent results. Also notable is the extremely high selectivity that the NHC ligand IPr affords when it is used with unsubstituted enoates and terminal alkynes.

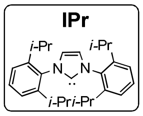
Table 9. Ligand Screen for Optimization of Reductive Cycloadditions





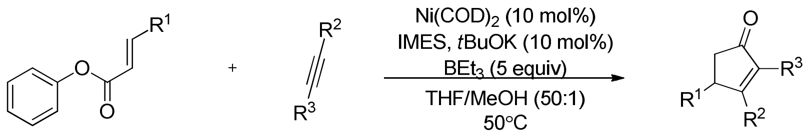
		R^1 = Me R^2 = *n*-Hex R^3 = *n*-Hex	R^1 = H R^2 = *n*-Oct R^3 = H	
Entry	L	Yield	Yield	(rs^c)
1	PMe_3	~24%	~12%	ND
2	PBu_3	44%	53%	(9:91)
3	DPEphos^a	63%	~36%	(15:85)
4	PPh_3	~35%	65%	(21:79)
5	$PCyPh_2$		58%	(12:88)
6	PCy_2Ph		55%	(6:94)
7	PCy_3	81%	47%	(1:99)
8	$P(tBu)_3$	<10%	~12%	ND
9	IMes^{a,b}	86%	62%	(15:85)
10	IPr^{a,b}	46%	66%	(1:99)

a 10 mol %, *b* 20 mol %, *c* GC ratio,



With the IMes ligand in hand, the generality of the substrate scope was investigated. The reaction was successful with simple substrates (Table 10). The yields did not improve when phenyl-propyne was used as the alkyne coupling partner. It was also noted that a substrate mismatch occurs with the β-methyl enoate and terminal alkyne. Also notable is the lack of selectivity with any asymmetric aliphatic alkyne. This is not surprising given the difficulty of enabling regioselective reactions with alkynes without electronic or steric bias.

Table 10. Simple Substrate Scope for Reductive Cycloadditions



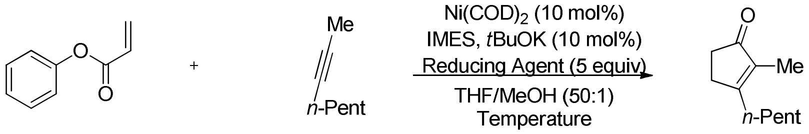
Entry	R^1	R^2	R^3	Yield	rs
1	Me	Me	Ph	74%	7:1
2	H	Me	Ph	65%	12:1
3	Me	H	*n*-oct	~21%	2:1
4	H	*n*-oct	H	62%	9:1
5	Me	*n*-hex	*n*-hex	86%	NA
6	H	*n*-hex	*n*-hex	71%	NA
7	Me	*n*-pent	Me	61%*	2:1
8	H	*n*-pent	Me	56%	2:1

*5-10% impurities

2.5 Reducing Agent/Temperature Optimization

Different reducing agents and temperatures were also examined for this transformation (Table 11). Silanes have typically been used in combination with NHC ligands instead of boranes. Attempts to use silane reducing agents, in this chemistry, resulted in very low yields, while yields were similar with various boranes. We propose that this is because the rate-determining step of the reaction occurs before the proposed transmetallation and reduction of the catalyst. Therefore, the type of borane should have little impact upon the reaction itself. The mechanism of the reaction or the catalyst resting state could be changed when silanes are used which would explain the low yields with the use of triethylsilane. We also briefly examined the effects of higher temperature on the reaction. However, a small increase in reaction temperature had little effect on yield. Only slightly higher temperatures were tried because during the ligand screening for this reaction, the temperature was mistakenly left at 60 °C instead of 50° C and about 10% higher yields resulted. Further experimentation revealed that higher yields were not experimentally different.

Table 11. Reducing Agents and Temperature for Reductive Cycloadditions

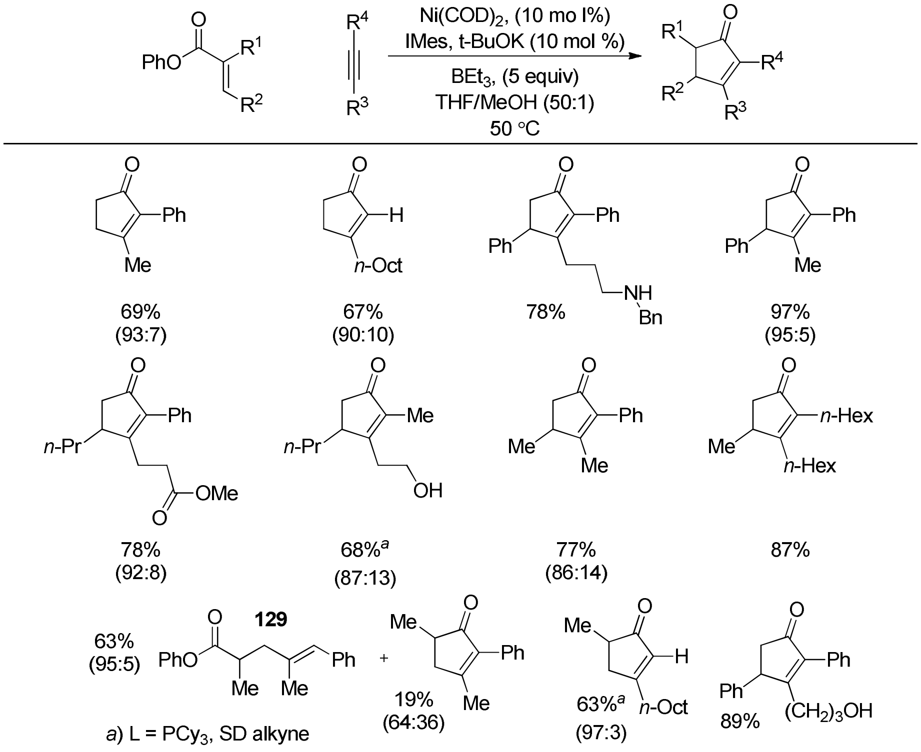


Entry	Reducing Agent	Temperature	Yield	rs
1	Et_3SiH	50 °C	<5%	ND
2	BBu_3	50 °C	43%	1.5:1
3	BEt_3	60 °C	51%	1:1.7
4	BEt_3	50 °C	56%	2:1

2.6 Substrate Scope

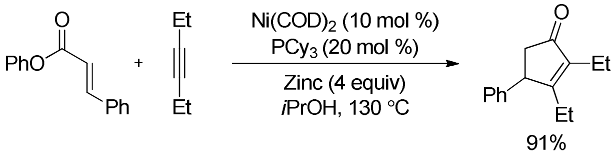
The substrate scope of this reaction was further investigated and expanded to include all substitution patterns on the enoate and a variety of functionalized alkynes. This reductive cycloaddition is efficient with simple unsubstituted enoates with either terminal or internal alkynes (Scheme 67). Cycloadditions with the α-methyl substituted enoate and 1-decyne are also efficient, but when the internal alkyne, phenyl-propyne is used, reductive coupling products predominate. The reductive coupling product, **129**, has mechanistic implications (discussed in Section 2.9). A number of functional groups such as free hydroxyls, esters, and free amines are also tolerated under the reaction conditions. In general regioselectivity (in parentheses) tends to be good with IMes and in some cases, better with IPr (see Table 9), but IPr was not efficient with all substrates (discussed in Section 2.7). Also notable are the high yields with β-phenyl enoate under optimized conditions. Regiochemical outcomes were determined by 2D NMR experiments: gCOSY, gHSQC, and gHMBC.

Scheme 67. Substrate Scope of Reductive Cycloadditions



It should also be noted at the time of our publication of this work, a similar publication from the Ogoshi group appeared (Scheme 68).[112] Ogoshi's conditions for this transformation were not the same as the conditions we developed for this methodology. Ogoshi used PCy_3 as the ligand for this transformation, and the reaction was performed in isopropanol at 130 °C. During our ligand screening exercise (section 2.4, Table 9), we found that PCy_3 enabled good yields when β-methyl enoate was used, but the results were not very consistent with the unsubstituted enoate and 1-decyne. IMes was chosen over PCy_3 because it gave the best overall yields consistently. Ogoshi's methodology also included the use of isopropanol not only as a proton source, but also presumed to act as the reducing agent for the nickel (II) species that is liberated after product formation. Our own group has used methanol as the reducing agent in related nickel-catalyzed couplings.[113] Ogoshi and co-workers proposed that the role of the zinc dust is either to reduce the nickel (II) species back to the nickel (0) catalyst or to promote the reduction of the nickel catalyst by the isopropanol. The zinc dust is not necessary for a catalytic reaction, but yields are better when it is used.

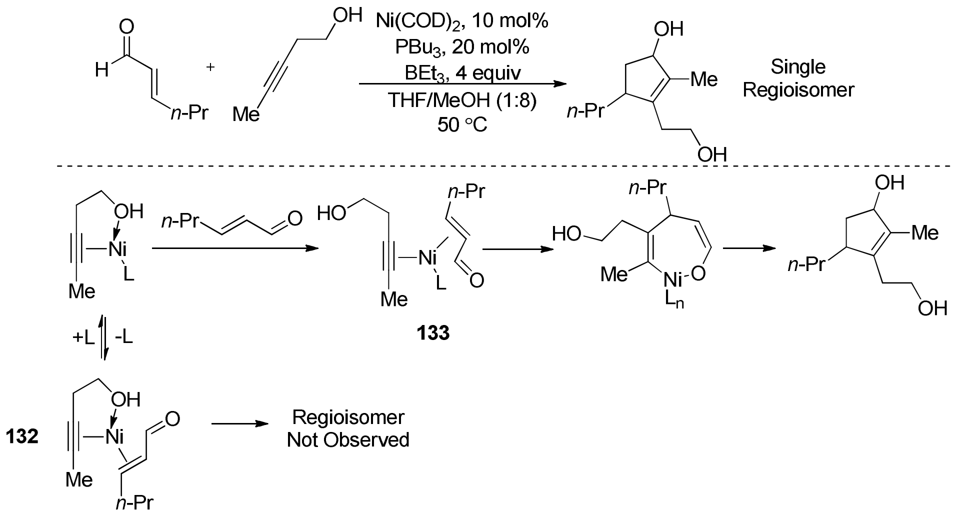
Scheme 68. Ogoshi's Nickel-Catalyzed [3+2] Cycloadditions with Enoates and Alkynes



2.6.1 Alkynol Optimization

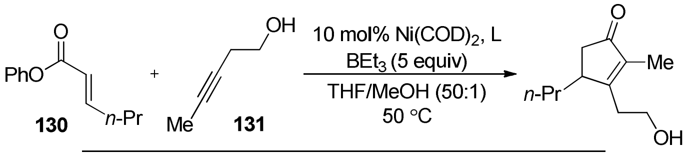
The reductive cycloaddition of β-*n*-propyl enoate **130** with alkynol **131** required special optimization for good yields and selectivity (See Table 12). The pursuit of this particular substrate combination grew out of the desire to emulate a similar example presented in Ananda Herath's dissertation[114] with a hydroxyl directing effect (Scheme 69). In Ananda's example, it was proposed that the hydroxyl group was acting as a labile ligand. If the hydroxyl group were coordinated to the metal when oxidative addition in intermediate **132** occurred, then the opposite regioisomer is predicted. However, dissociation of the hydroxyl group and coordination of the enal with retention of configuration on the nickel (**133**) makes the regioselectivity of the observed product highly favorable.

Scheme 69. Perfect Regioselectivity with Alkynols in Enal-Alkyne Reductive Cycloaddition



Using the enoate **130** in place of the hexenal, we sought to use the hydroxyl group on the alkyne as a labile ligand to direct the regiochemistry of the reaction. However, the reactivity of **131** proved to be entirely different than that of the hexenal (Table 12). Yields were initially low, but were improved with slow addition of the alkyne. It appears that there is no hydroxyl directing effect. The smaller ligands such as PBu_3 and ITol were not regioselective. As the bulk of the ligand increased, the reaction was more regioselective, with IPr and PCy_3 providing the best regioselectivity.

Table 12. Alkynol Optimization

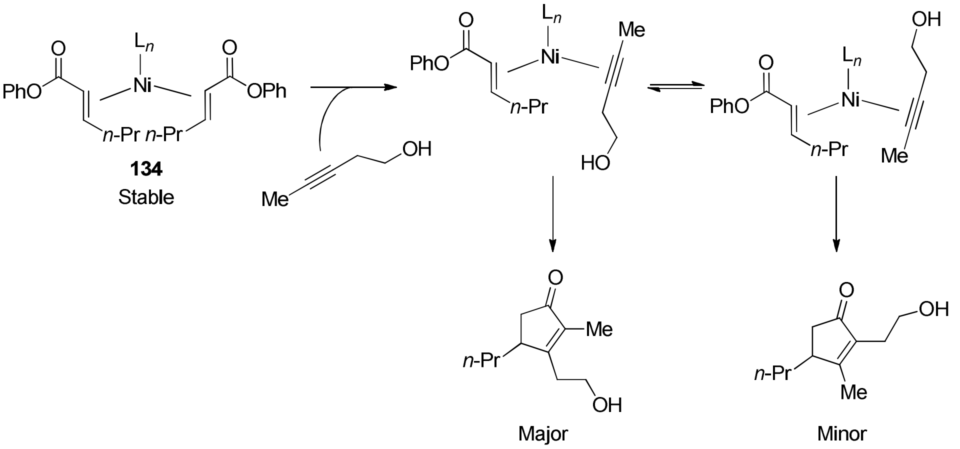


Entry	L	Yield	RS
1	PBu_3[a]	~10%	73:27
2	PCy_3[a]	73%	87:13
3	ITol[*b*] (*n*-BuLi)	~12%	~50:50
4	IMES[*b*] (*t*-BuOK)	57%	73:27
5	IPr[*b*] (*t*-BuOK)	~47%[*c*]	88:12

a) 20 mol %, *b)* 10 mol % L, Base,
c) No alkyne syringe drive

We propose that the absence of the directing effect is due to the formation of a tetrahedral bis-enoate complex **134**. Ni(0) tetrahedral bis-enone complexes have been studied by our group in the past and are characteristically stable.[75] The Ogoshi group has managed to obtain X-ray crystals of similar dienoate complexes.[115] Treatment of these complexes with alkyne yielded the desired cycloaddition product. The enoates could act in a similar fashion and prevent simultaneous coordination of the hydroxyl group and the π-bond of alkynol **131** (Scheme 70). Oxidative cyclization would have to be preceded by dissociation of one of the enoates followed by coordination of the alkynol at the triple bond. This proposed sequence of events would not allow for hydroxyl group of the alkynol to direct the regiochemistry of the cycloaddition.

Scheme 70. Rationale for Alkynol Regioselectivity

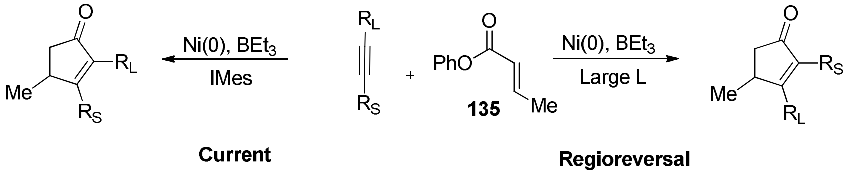


2.7 Limitations

2.7.1 Regioreversals and Ligand Size Effects

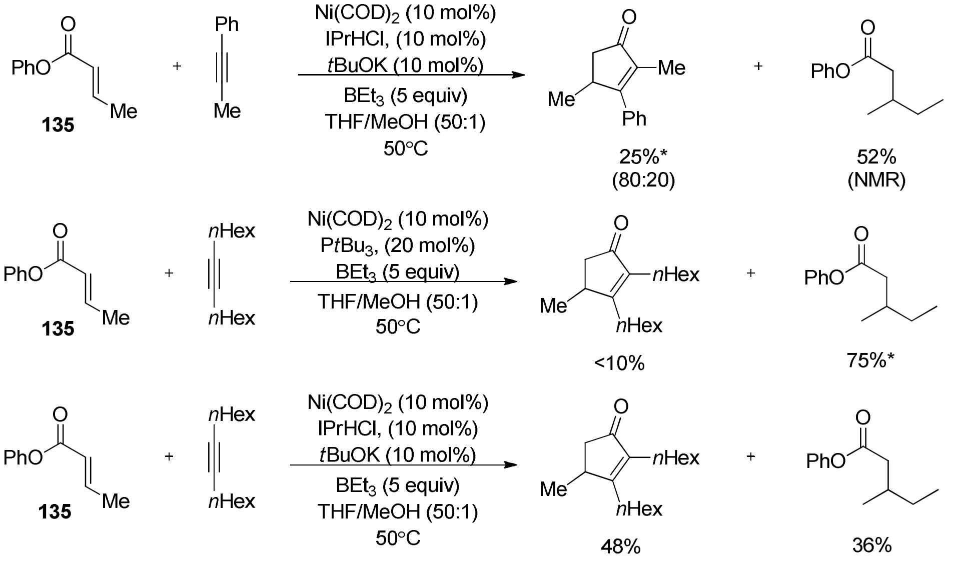
Due to our experiences with ligand based regiocontrol in the aldehyde-alkyne reductive couplings,[116] we attempted to exert the same regiocontrol to obtain products with reversed regioselectivity on our reductive cycloadditions using larger ligands (Scheme 71).

Scheme 71. Regioreversal with Large NHCs.



We attempted this transformation with phenyl propyne, β-methyl enoate, and the large NHC IPr and the selectivity for the regioisomer was good. Unfortunately, yields were low because 1,4-addition of an ethyl group into **135** predominates when the ligand is large (Scheme 72). This is also evident in the reaction of **135** with an aliphatic alkyne with large ligands such as P*t*Bu$_3$ or IPr. The larger ligand likely makes the energy barrier for oxidative addition too high and reduction of the enoate becomes faster than oxidative addition so enoate reduction products predominate.

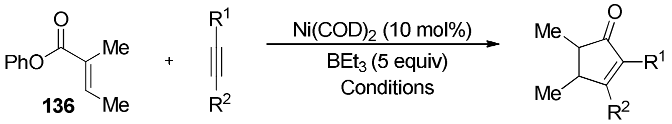
Scheme 72. Large Ligands and Regioreversals



*10% impure

We also sought to repeat analogous examples from the enal-alkyne substrate series to demonstrate complementary of the enoate methodology to the enal-alkyne reductive cycloaddition methodology. In doing so, limitations of the enoate-alkyne reductive cycloadditions emerged. Initial optimization was attempted with disubstituted enoate **136** and a variety of alkynes and conditions (Table 13). Reactions of disubstituted enoate **136** with phenyl-propyne only gave trace products, visible only on the GC. The reaction was unproductive even with smaller ligands. Smaller terminal alkyne, 1-decyne, was also tried, but the reaction was unproductive. The reaction was slightly more productive with an internal aliphatic alkyne, but yields remained very low even at higher reaction temperatures.

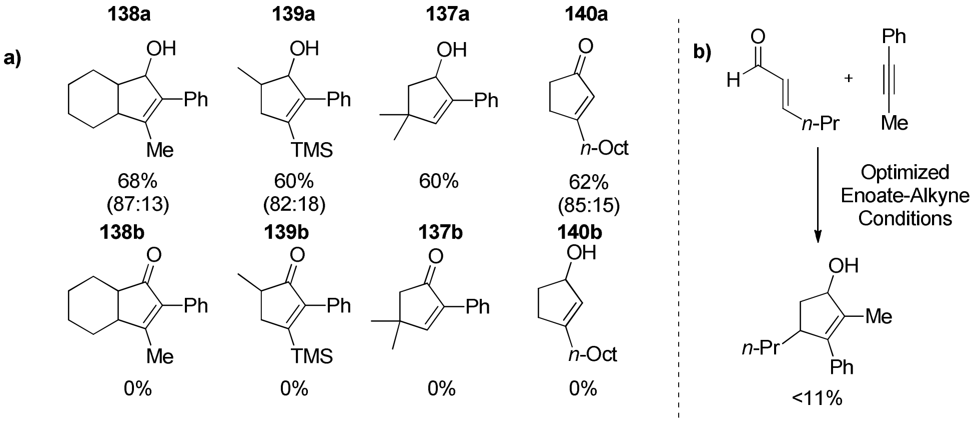
Table 13. Attempted Optimization of Disubstituted Enoates



Entry	Alkyne	Conditions	Yield
1	Me—≡—Ph	IMES, *t*BuOK (10 mol%) THF/MeOH (50:1), 50°C	Trace (GC)
2		PBu_3 (20 mol%) THF/MeOH (50:1), 50°C	0%
3		PBu_3 (20 mol%) THF/MeOH (50:1), 50°C SD Alkyne	0%
4		PCy_3 (20 mol%) THF/MeOH (50:1), 50°C	0%
5	H—≡—*n*Oct	IMES, *t*BuOK (10 mol%) THF/MeOH (50:1), 50°C	Trace (GC)
6	*n*Hex—≡—*n*Hex	IMES, *t*BuOK (10 mol%) THF/MeOH (50:1), 50°C	<5%
7		IMES, *t*BuOK (10 mol%) Tol/BnOH (50:1), 90°C	<5%
8		IMES, *t*BuOK (10 mol%) Dioxane/MeOH (50:1), 90°C Sealed Tube	<5%

Other limitations of this methodology were evident when we sought to compare the reactivity of other substrates (Scheme 73a). For example, β-dimethyl enals reacted favorably with phenyl-acetylene, but when this reaction was tried with a β-dimethyl enoate, no productive reaction occurred (products **137**). When this result is considered in the context of unproductive reactions disubstituted enoate **136** and the cyclohexyl enoate (products **138b**), it is evident that where reactions with disubstituted enals are favorable, those with disubstituted enoates are not favorable. The β-dimethyl group seems to seriously impede the oxidative cyclization which is why the yield is very low. Reactions with a TMS substituted alkyne was also unproductive (product **139b**). Ogoshi experienced similar limitations with his substrates. We further probed the similarities between the enal-alkyne couplings and enoate-alkyne couplings by comparing regioselectivity of terminal alkyne couplings (products **140**). The enal-alkyne coupling with acrolein and 1-decyne however only yielded alkyne reduction products (product **140a**). There were no examples of enal-alkyne couplings with acrolein in the 2006 communication,[73] and the only example with a terminal alkyne was with a β-disubstituted enal. This suggests that the substrate pair is not well matched for the desired reaction. We also attempted to apply the enoate-alkyne coupling conditions to the enal-alkyne couplings, but were only met with limited success (Scheme 73b). Yields were low, and the opposite regioisomer was formed when the IMes ligand was used.

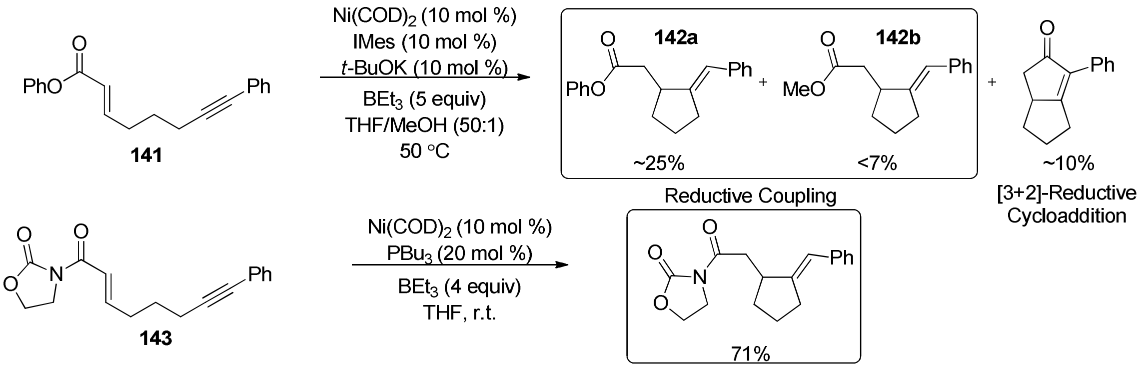
Scheme 73. Limitations in Comparison of Reactivity of Enoates and Enals



2.7.2 Intramolecular Examples

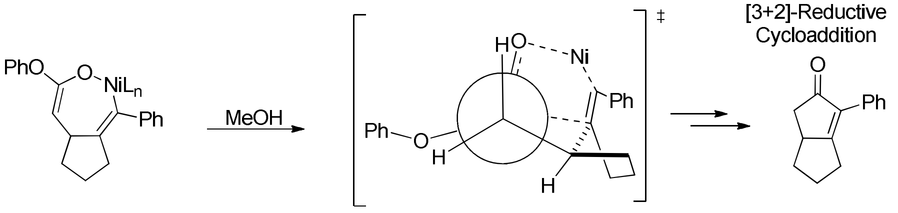
We also tried to perform intramolecular examples with tethered alkynyl enoate **141**. However, the reaction yields were low and the reductive coupling product **142** was favored. Transesterfication of the product with methanol was also problematic. Interestingly, this has not been observed in intermolecular couplings, especially when reduced enoate products predominate. The selectivity for the monocyclic reductive coupling product, instead of the bicyclic reductive cycloaddition product has also been observed with a tethered alkynyl imide **143** (Scheme 74).[117,119] The reaction of the phenoxy enoate was also attempted using bidentate ligands such as TMEDA and bipyridine, however yields only decreased with these ligands. These bicyclic products can be accessed more easily through the nickel-catalyzed enal-alkyne intramolecular reductive cycloadditions.[72,73] Simple oxidation of the product alcohol would yield the cyclopentenone cycloadduct.

Scheme 74. Intramolecular Reactions with Enoates and Imides



Inspection of hand-held molecular models of the transition state for the insertion of the vinyl-nickel species into the carbonyl helped to understand and justify the formation of reductive coupling products (Scheme 75). This analysis illustrated that this transition state is eclipsed, which may be why the reductive cycloaddition product is disfavored.

Scheme 75. Hand-Held Model Justification for Low Yield of Reductive Cycloaddition Products



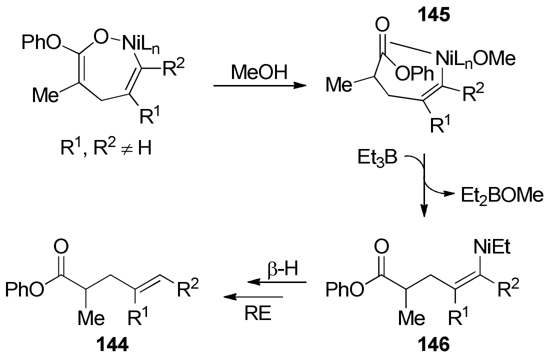
2.7.3 Other Substrates

We also examined the reactivity of enoates with other substrates, however these reactions for were unproductive. Reactions of tethered bis-enoates only resulted in ethyl reduction of one of the enoates. Reactions of allenes instead of alkynes with enoates, resulted in low yields, and the reaction was not regioselective. Reactions with alkenes instead of alkynes were also tested, but were found to be unproductive. Phenoxy aldehydes and ketones were also examined for their reactivity with alkynes, but these substrates did not yield coupling products.

2.8 Trends with α-Methyl Enoates

The α-methyl enoate substrate showed interesting reactivity that merits discussion. Reactions with 1-decyne gave the expected cycloaddition product in good yields. However, when these substrates were reacted with other alkynes, the yield of the reductive cycloaddition product was depressed and the reductive coupling product **144** emerged. The reductive coupling product **144** is formed when the vinyl-nickel species **145** does not insert into the carbonyl and is instead intercepted by the reducing agent. Transmetallation of **145** with reducing agent forms another acyclic intermediate **146** which can β-hydride eliminate and then reductively eliminate to form the product **144** (Scheme 76).

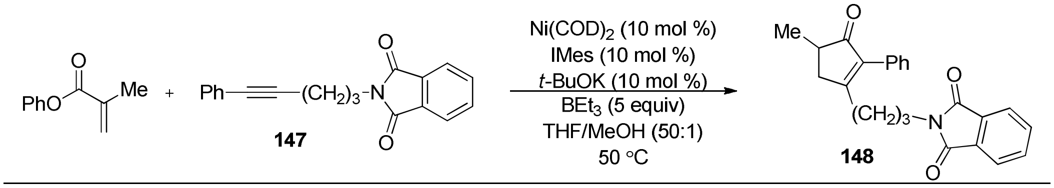
Scheme 76. Proposed Mechanism for the Formation of Reductive Coupling Products



2.8.1 Phthalimide Series Optimization

The special reactivity of the α-methyl enoate was first noted while examining its reaction with a phthalimide alkyne derivative **147**. Initially we tried to focus on improving the yields of the cycloadduct, however the yield of the reductive cycloaddition product **148** could not be improved beyond 50% (Table 14). Despite not being able to optimize for the reductive cycloaddition product, this study provided some insights about the reductive cycloaddition methodology. We reasoned that if we used the Lewis acid Al(OiPr)$_3$ it could favor insertion of the vinyl nickel species into the carbonyl by coordinating the carbonyl and activating it for addition, but yields decreased with the use of this additive. We also thought that lowering the concentration of borane may slow the transmetallation step and disfavor the reductive coupling product, but that resulted in either lower yields or significantly longer reaction times.

Table 14. Optimization for Cycloaddition Products with Phthalimide Substrates



147 **148**

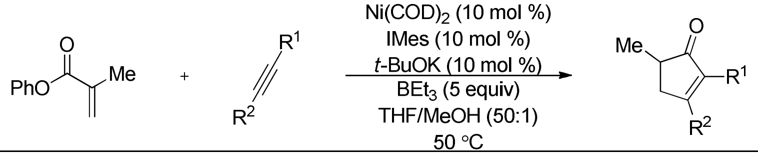
Entry	Conditions	Isolated Yield [3+2], RC	Prod Ratio^a [3+2] : RC
1	Optimized [3+2]	43%, <8%	77:23
2	Syringe-pump Enoate	~22%, ND	ND
3	Syringe-pump Alkyne	38%, 29%	63:37
4	Catalyst 20 mol %	46%, ND	>94:6
5	Syringe-pump BEt_3	~31%, <4%	84:16
6	$Al(O\textit{i}Pr)_3$ (1.5 equiv)	43%, ~10%	76:24
7	$Al(OiPr)_3$, Syringe-Pump BEt_3	<10%, ND	~81:19
8	BEt_3 (3 equiv)	~49%, ND	~94:6

a) NMR Ratio

2.8.2 Reductive Coupling Products and General Observations

Because of low yields in the phthalimide cycloadduct **148**, we decided to turn our attention to a simpler substrate system for optimization. Attempts at optimizing the reaction with the highly reactive phenyl-propyne for the reductive cycloaddition product were not successful (Table 15). Using a smaller ligand such as PBu_3 did result exclusively in the formation of the cycloaddition product, however yields were very low. Conversely, we discovered when terminal alkynes are used, the reductive cycloaddition product is the only product observed. Yields were initially low with the terminal alkyne but could be improved by slow addition of the alkyne.

Table 15. Divergent Reactivity of Alkynes with the α-Methyl Enoates

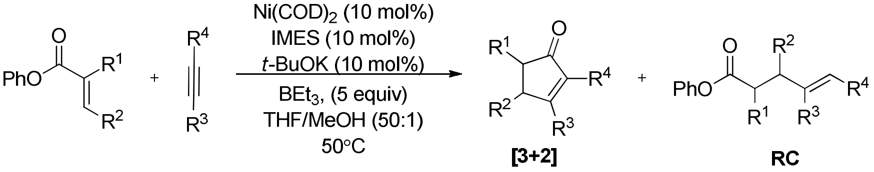


Entry	Conditions	R^1	R^2	Yield [3+2], RC	Prod Ratio [3+2], RC
1	Optimized [3+2]	Ph	Me	19%, 63% (64:36), (95:5)	31:69
2	L = PBu_3	Ph	Me	20%, ---	NA
3	Standard	H	*n*-Oct	51%*, ---	NA
4	Catalyst 20 mol %	H	*n*-Oct	46%*, ---	NA
5	Syringe-pump Alkyne	H	*n*-Oct	60%*, ---	NA

*10-15% impure

When the reactivity patterns of different substituents of the enoate are mapped out, a trend emerges (Table 16). Reactions with β-methyl enoate give exclusively reductive cycloaddition products. Conversely, reactions with α-methyl enoate give predominantly reductive coupling products when reacted with internal alkynes. The regioselectivity is low for the cycloaddition product, but high for the reductive coupling product. But when these α-methyl enoate is reacted with a terminal alkyne, only the reductive cycloaddition product is observed.

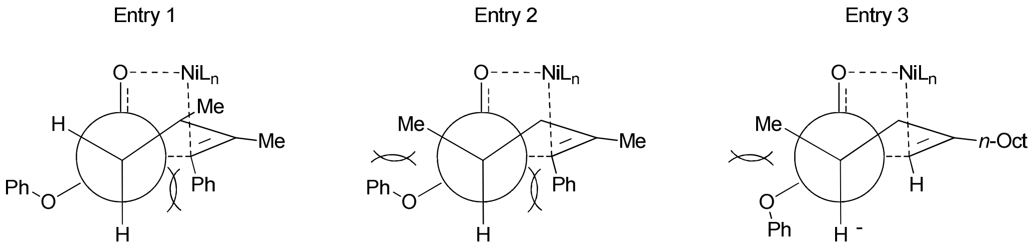
Table 16. Enoate Substituent Trends for Reductive Coupling and Reductive Cycloaddition Product Formation



					Yield		
Entry	R^1	R^2	R^3	R^4	[3+2]	RC	RS
1	H	Me	Me	Ph	76%	_	(86:14)
2	Me	H	Me	Ph	16%	63%	(64:36);(95:5)
3	Me	H	*n*-Oct	H	~60%	_	(97:3)

We propose that both the α-methyl and the alkynyl phenyl group sterically encumber the vinyl-nickel coordinated intermediate (Scheme 77). In entry 1, there are steric repulsions between the alkenyl phenyl group and the phenoxy group. The phenoxy group has room to orient away from this large substituent so the reductive cycloaddition product forms. In entry 2, the same steric repulsion is present between the alkenyl phenyl group and the phenoxy group, but the phenoxy group also encounters steric repulsions from the α-methyl group. These unfavorable steric interactions disfavor the 1,2-insertion into the carbonyl resulting in the formation of the reductive coupling product. The reductive cycloaddition product regioselectivity (entry 2) is low compared to other substrates on the table (entries 1 & 3). Conversely, the reductive coupling product regioselectivity is very high. These ratios are consistent with our model in that when the phenyl group is geminal to the nickel, 1,2-insertion is less favored and the reductive coupling product is easily formed. When the methyl group of the phenyl propyne is geminal to the nickel, the reductive cycloaddition product is favored which is why so little of the minor reductive coupling regioisomer is observed and also why the regioselectivity is low for the reductive cycloaddition products. In entry 3, a terminal alkyne is used, so there is no alkenyl-phenyl group present and the vinyl-nickel coordinated intermediate is less sterically encumbered. It is much easier for the 1,2-insertion to occur because the phenoxy group can orient away from the α-methyl group, so the reductive cycloaddition product is favored.

Scheme 77. Substitution Patterns and Reductive Coupling Rational


Entry 1 — Entry 2 — Entry 3

[3+2]-Reductive Cycloaddition Favored

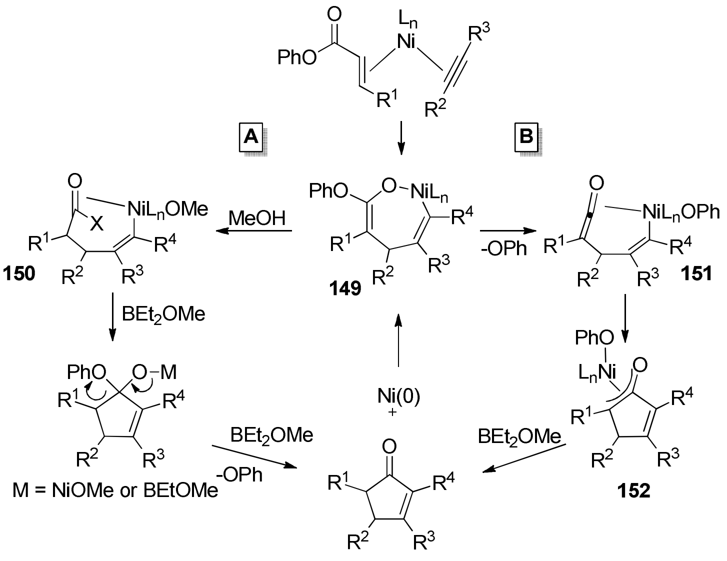
Reductive Coupling Favored

[3+2]-Reductive Cycloaddition Favored

2.9 Mechanism

The mechanism of this reaction likely proceeds by coordination of the nickel catalyst to the enoate and alkyne followed by oxidative cyclization to form a seven-membered metallacycle (Scheme 78). We believe that the metal-bound enolate **149** is then protonated by the methanol in solution to yield an acyclic intermediate **150** (path A). The vinyl-nickel species can then undergo an intramolecular insertion into the carbonyl to close the ring followed by α-elimination of the phenoxy group and regeneration of the catalyst with the borane in solution. Alternatively, after metallacycle formation, the phenoxy group could undergo α-elimination to form an acyclic ketene intermediate **151** (path B). The vinyl-nickel species then inserts into the ketene intermediate closing the five-membered ring. The metal enolate **152** is protonated by the methanol in solution and the catalyst is regenerated with the reducing agent to reform the Ni(0) species.

Scheme 78. Mechanism of [3+2] Cycloadditions

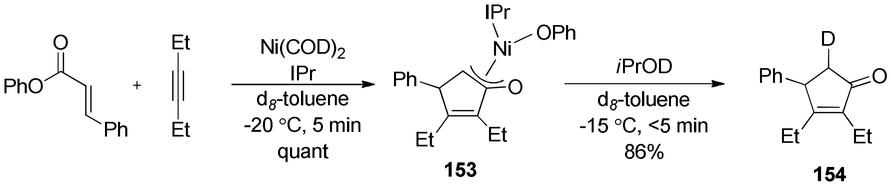


2.9.1 Metallacycle vs. Ketene

We strongly favor path A because protonation is very fast and because of the reductive coupling products we have seen with some substrates. These reductive coupling products are still accessible through the ketene mechanism, however, the phenoxy group must reinsert back into the ketene for the product to form. This seems unlikely as no transesterfication products were observed in intermolecular examples. It is also notable that experiments with unsaturated acyl oxazolidinones, which undergo reductive couplings, have been demonstrated to undergo proposed metallacycle based mechanisms without extrusion of the oxazolidinone unit.[117-119]

The Ogoshi group has published evidence in support of the ketene mechanism B. They performed a low temperature NMR experiment in which they treated β-phenyl enoate and 3-hexyne with stoichiometric amounts of nickel (Scheme 79). They observed and characterized by NMR the nickel enolate complex **153**. When this enolate **153** was treated with deuterated isopropanol, the α-deuterated cyclopentenone **154** formed in high yield. While this experiment demonstrates the possibility of the ketene mechanism, it should be noted that this experiment was performed in an aprotic solvent, toluene, with stoichiometric amounts of nickel. Our catalytic reductive cycloaddition is performed in a protic co-solvent system. In Ogoshi's catalytic reductive cycloaddition methodology, the reaction is performed in isopropanol instead of a co-solvent system.

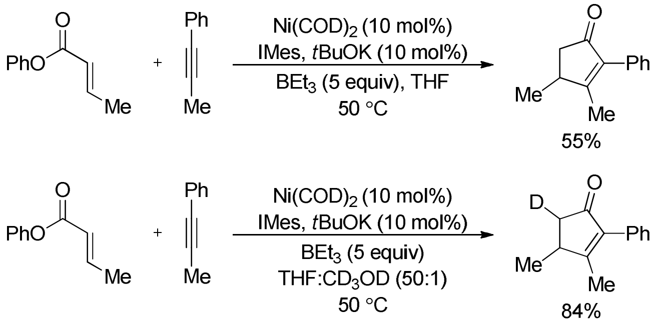
Scheme 79. Ogoshi's NMR Experiment



2.9.2 Probing Metallacycle vs. Ketene

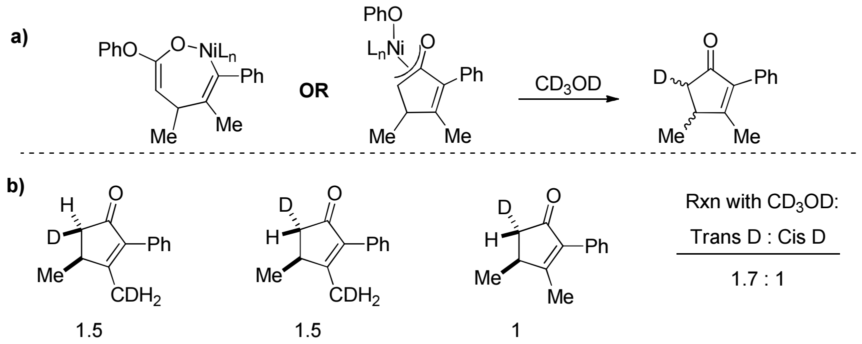
We also sought to verify whether the reaction proceeds by mechanistic path A or B. We found that the reaction was productive in the absence of methanol, but the yields were significantly lower (Scheme 80). This finding indicates that the ketene mechanism is viable under aprotic conditions. We used deuterated methanol (CD_3OD) in place of methanol, and witnessed deuteration of the product at the α-position, with the product forming in much higher yields.

Scheme 80. Probing Mechanism without Methanol and with CD_3OD



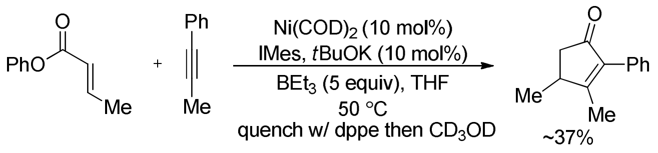
We thought that it might be possible to differentiate the mechanism by studying the product stereochemistry at the deuterated position (Scheme 81a). The 7-membered metallacycle might yield different stereochemistry than the cyclopentene-metal enolate. We performed this experiment with CD_3OD under the same conditions as Scheme 80 and found that deuterium incorporation most often occurred trans to the methyl group, but this was not highly selective (Scheme 81b). We also witnessed some deuterium scrambling of the alkynyl methyl group.

Scheme 81. Deuterium Experiments with Metal-Enolates



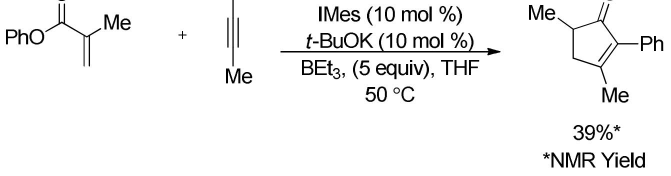
However, when we tried quenching with CD_3OD, when the reaction proceeds through path B, there was no deuterium incorporation in the product (Scheme 82). The proton source must come from somewhere else in the reaction. Mechanisms could be drawn in which the hydrogen is derived from the borane. Probing this mechanistic possibility would require complex synthesis of a deuterated borane reagent.

Scheme 82. Quench with CD_3OD Results in No Deuterium Incorporation



We also conducted an experiment with the α-methyl enoate substrate to probe if the reductive coupling product was accessible under conditions that were known to favor the ketene mechanism. We conducted the reaction with the α-methyl enoate and phenyl-propyne under aprotic conditions (Scheme 83). Under protic conditions, the reductive coupling product is favored with the reductive cycloaddition product forming in low yields. However, when the reaction is conducted under aprotic conditions the reductive coupling product does not form and the reductive cycloaddition product forms in higher yield than observed under protic reaction conditions.

Scheme 83. Reaction α-Methyl Enoate Under Aprotic Conditions Favors Reductive Cycloaddition Product



2.10 Conclusion

In conclusion, a reductive cycloaddition has been developed with enoates and alkynes. This methodology is complementary to the nickel-catalyzed enal-alkyne cycloadditions, however accessing the cyclopentenone products in some substrates still requires a nickel-catalyzed enal-alkyne cycloaddition followed by oxidation of the product. The mechanism of this reaction is thought to proceed through protonation of a metallacycle, but we acknowledge that the ketene mechanism is also possible. Further development of this chemistry should aim to alkylate the in situ metal enolate instead of protonate to form a [3+2]-alkylative cycloaddition product (discussed in Chapter 3). Other future directions for this project include the development of allene-enoate couplings. Alternatively, diastereoselective reductive coupling reactions could be further investigated. Our examination of this area was brief and there is potential for accessing enantiopure products from diastereoselective reactions.

Chapter 3

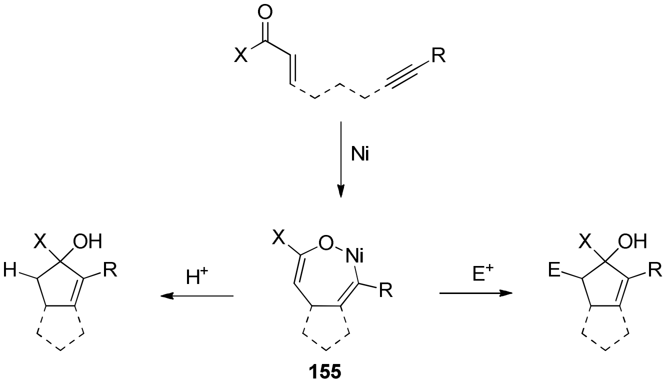
Nickel-Catalyzed [3+2]-Alkylative Cycloadditions

3.1 Introduction

Sometimes further functionalization of carbocyclic [3+2] products is necessary, but functionalization requires further reaction and purification steps. Multicomponent reactions offer a solution to this difficulty by combining many reactants in a single pot to form a highly functionalized product. The reactants are assembled in a sequential cascade of simple reactions. There are many examples of [3+2] cycloadditions involving polar reagents, but these methods suffer from the same difficulties as the dipolar two-component cycloadditions. Methods that make use of simple π-components for multicomponent cycloadditions are rare, and variants only exist for methodologies that take advantage of rearrangements. Methods that use changes in oxidation state are limited to two-component processes. However, there is another way to create an MCR cycloaddition reaction. Several of the reductive cycloaddition methods involve an intramolecular reaction between the two π-components to form the five-membered ring. Alkylation instead of protonation introduces a second component to the methodology. If the tether between the two π-components is removed, then three-components are required. All of these two-component alkylative cycloadditions require stoichiometric amounts of metal and development of catalytic conditions would be an advance for these methodologies. This chapter details the development of nickel-catalyzed [3+2]-alkylative cycloadditions with enoates, alkynes and aldehydes to form highly functionalized cyclopentenones. This methodology expands on the previously developed nickel-catalyzed enoate-alkyne methodology and offers a solution to the limitations of stoichiometric [3+2]-alkylative cycloadditions. It is also one of the few examples of a multicomponent cycloaddition reaction with simple π-components.

While we were developing the nickel-catalyzed reductive cycloadditions, we decided to test the reactivity of the proposed metal-enolate **155** with a carbon-based electrophile instead of an acidic hydrogen to yield an alkylated product (Scheme 84). Interception of these metal enolates with other electrophiles had been accomplished previously, however, these transformations were only possible with stoichiometric amounts of nickel.[69]

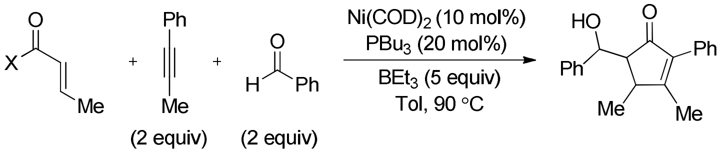
Scheme 84. Protonation and Alkylation of Nickel-Enolates

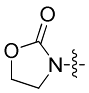
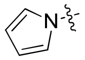


3.2 Initial Optimization of [3+2]-Alkylative Cycloaddition

Similar transformations had been attempted with aldehydes after catalytic conditions had been developed for enal-alkyne reductive cycloadditions. Unfortunately, the reaction led to complex mixtures of products, presumably because of the similar reactivity of aldehydes and enals. Enoates, on the other hand, are not as reactive as aldehydes. During the development of the reductive cycloadditions we saw an additional opportunity to develop transformations employing catalytic quantities of metal based upon existing methodology requiring stoichiometric amounts of metal. At the same time that we screened leaving groups for the enoate reductive cycloaddition (Chapter 2, Table 4), we also screened leaving groups for the alkylative transformation (Table 17). The reactivity of the alkylative cycloaddition paralleled that of the reductive cycloaddition transformations, with the phenyl enoate giving the best yields (Entry 2). Reductive coupling products were not observed with any of the leaving groups screened for the alkylative cycloadditions.

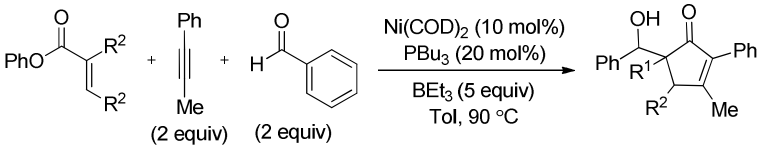
Table 17. Comparison of Enoate Derivative for Alkylative Cycloadditions



Entry	X	Yield
1	MeO	---
2	PhO	58%
3		48%
4		30%

After the phenyl enoate had been selected as the best enoate derivative, other substrates were screened, however, yields of other substrates were either similar or very low (Table 18). The β-methyl enoate (entry 1) gave the best yields overall, followed by α-methyl enoate (entry 2). However, unsubstituted and β-phenyl substituted enoates gave low yields (entries 3 & 4).

Table 18. Initial Substrate Screen for Alkylative Cycloadditions

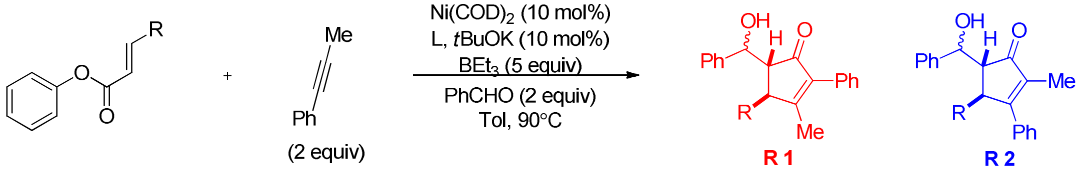


Entry	R^1	R^2	Yield
1	H	Me	58%
2	H	H	~25%
3	Me	H	45%*
4	H	Ph	25%

**p*-OMe enoate

A short ligand screen was performed on the best-yielding substrate and an intermediate-yielding substrate to see if the reaction could be easily optimized (Table 19). Generation of *t*-BuOH from the deprotonation of the IMes·HCl salt could act as a proton source for the metallacycle in solution, therefore free carbenes were also examined for any difference in reactivity. However, there was little difference between the HCl salt and free carbene. Tributylphosphine, IMes, and IPr gave similar yields, and PCy_3 gave lower yields. The diastereoselectivity of the reaction was somewhat complex. The PBu_3 ligand gave the best regioselectivity, with the products being epimeric at the –OH position. The diastereoselectivity deteriorated slightly with the IMes ligand and IPr gave regioisomeric mixtures. Because PBu_3 provided the best yields and regioselectivity, optimization of the reaction was continued with this phosphine as the ligand of choice.

Table 19. Initial Short Ligand Screen for Alkylative Cycloaddition

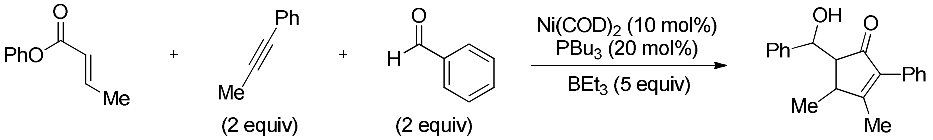


L	R = Me	(rs) (d1:d2 : d1:d2)	R = H	(rs) (d1:d2 : d1:d2)
PBu_3[a]	58%	~(67:33)	~25%	~(58:42)
IMes·HCl	55%	~(54:38 : 8)	~32%	~(67:33)
IPr	~62%	~(18:11 : 53:18)	~45%	~(19:13 : 17:51)
IMes[b]	38%[c]	~(61:27 :12)	36%	~(67:33)
PCy_3	29%	~(63:31 : 6)	<12%	~(94 : 6)

a) 20 mol%, *b)* free carbene c) ~60% with 1.5 equiv of aldehyde and alkyne - 38% not experimentally representative

Optimization of the reaction solvent, temperature, substrate equivalents, catalyst concentration and order or time of addition can lead to improved yields. Conditions similar to the reductive cycloadditions were examined first since the reductive cycloadditions had been optimized, however, the yield did not vary significantly (Table 20). After several attempts to improve the yield at this lower temperature, we noticed that a minor diastereomer was forming that was not observed when higher temperatures had been used. This diastereomer is presumed to be the cis-alkylated diastereomer since both major diastereomers of each regioisomer could be accounted for. It was noted that the yields (entries 5 & 8) and selectivity (entry 1) improved under certain conditions. A combination of these conditions can be seen in entry 12, with no substantial change in yield, indicating the higher yields could arise from experimental variations. We also noted that the equivalents of alkyne and aldehyde could be decreased with no decrease in yield (entry 10).

Table 20. Alkylative Cycloaddition Optimization with PBu$_3$ as Ligand



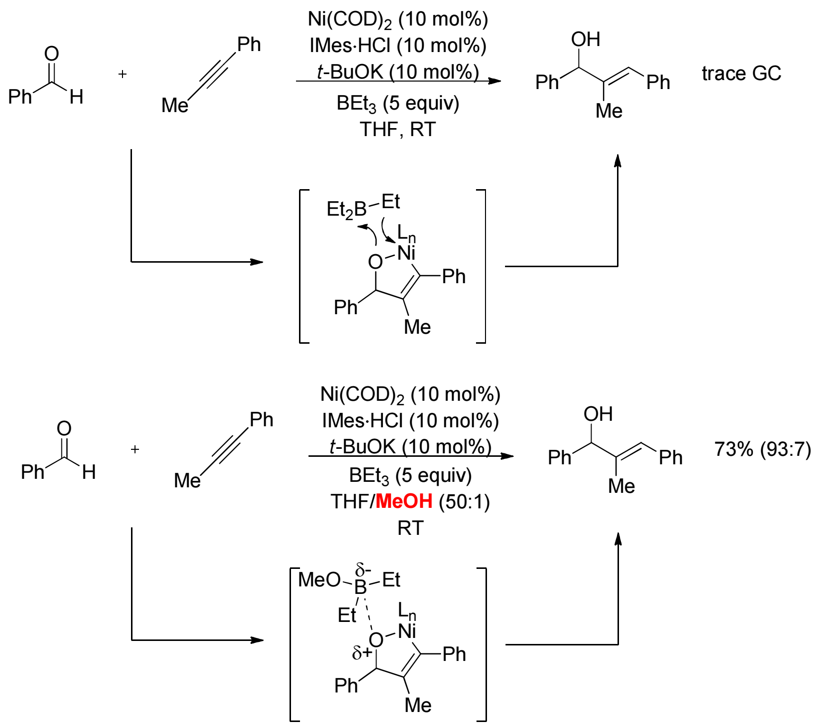
Entry	Solvent	Temp	Yield	other	dr (Major Regioisomer)	All isomers (currently known)
1	Tol	90 °C	52%	(57% avg.)	74 : 26	74 : 26
2	Tol	50 °C	58%		64 : 29 : 7	64 : 29 : 7
3	THF	50 °C	58%		65 : 29 : 6	65 : 29 : 6
4	THF	50 °C	63%*	IMes·HCl (10 mol%) tBuOK (10 mol%)	~51 : 35 : 14	~ 44 : 30 : 11 : 8 : 7
5	Tol	50 °C	62%	SD Alkyne	60 : 30 : 10	60 : 30 : 10
6	Tol	50 °C	57%	SD PhCHO	61 : 31 : 8	61 : 31 : 8
7	Tol	50 °C	58%	Ni(COD)$_2$ (20 mol%) PBu$_3$ (40 mol%)	60 : 30 : 10	60 : 30 : 10
8	Tol	50 °C	63%	10 mol% extra cat. after 1 hr	64 : 28 : 7	64 : 28 : 7
9	THF/DMF	50 °C	18%*		~71 : 29	
10	Tol	90 °C	57%	1.5 equiv alkyne & aldehyde	73 : 27	69 : 26 : 5
11	THF	100 °C	23%*	µv 100 °C, 15min	~50:50	
12	Tol	90 °C	~57%	SD Alkyne 10 mol% cat after 1hr	69 : 25 : 6	

Blue: Major Regioisomer
Red: Minor Regioisomer
*NMR Yield

3.2.1 Lewis Acid/Reducing Agent Optimization

We had also observed that in a protic co-solvent system, boranes could be effective at promoting aldehyde-alkyne reductive couplings. These couplings have been shown to proceed efficiently in the presence of silane reducing agents and inefficiently with borane alone. However, when a protic co-solvent system is used, the reaction becomes productive (Scheme 85).

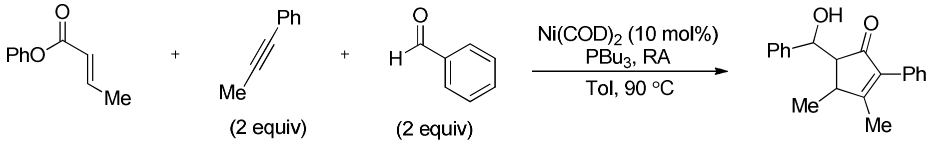
Scheme 85. Lewis Acid Improves Efficiency of Aldehyde Alkyne Couplings



Observations from these experiments and related observations from the reductive cycloadditions[72,73] and other methodologies[78,120] gave inspiration for trying Lewis acids to improve reactivity. The yields in the reductive cycloadditions were significantly higher than the yields for the alkylative cycloaddition. However, the conditions for the alkylative cycloaddition are different than for the reductive cycloaddition. The reductive cycloaddition works best in a THF/MeOH protic co-solvent system and it is understood that the borane undergoes methanolysis to form a BEt_2OMe species.[74] Furthermore, we knew that the Lewis acidic borane species is likely responsible for promoting the intramolecular insertion of the vinyl-nickel species into the carbonyl, because in related transformations in the absence of borane, acyclic products predominate.[78] We also suspected that the Lewis acidic borane species may also play a role in promoting the initial oxidative addition of the catalyst to the substrates.[72,73]

Because of these observations, it was thought that inclusion of borane Lewis acids that presumably formed in the reductive cycloaddition may improve the yield of the alkylative cycloadditions. Unfortunately, protic solvents could not be used, as the reductive cycloaddition product would predominate. The use of BEt_2OMe or BEt_2OPh (in situ) resulted in very low yields, but showed high diastereoselectivity (Table 21). Adding more reducing agent only marginally improved diastereoselectivity, but had no impact upon the reaction yield (entry 2). Aluminum triisopropoxide has also been successfully used in nickel-catalyzed reactions,[120] but led to low yields of both E1cb elimination products and reductive cycloaddition product (entry 3). It was also noted that using diethyl zinc could result in higher yields,[121] but both the selectivity and yields were diminished (entry 6).

Table 21. Lewis Acid/Reducing Agent Screen

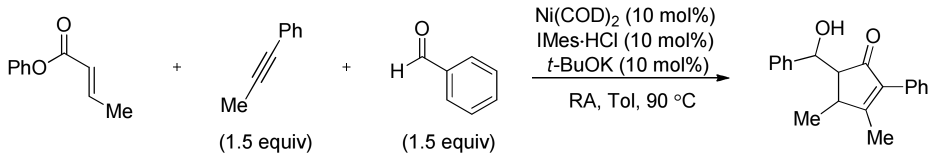


Entry	RA	Equiv	Yield	dr
1	BEt_3	5	58%	72:27
2	BEt_3	10	~58%	76:24
3	$BEt_3/Al(O\mathit{i}Pr)_3$[a]	5	0%	---
4	BEt_2OMe	5	<4%	89:11
5	BEt_2OPh	5	<5%	92:8
6	Et_2Zn[b]	3	41%[c]	42:58

a) 2 equiv, *b*) 0 °C to RT, *c*) NMR Yield

We also attempted to improve the yield by trying different reducing agents (Table 22). Other reducing agents have been shown to be successful in other nickel-catalyzed transformations. For example, in Ogoshi's nickel-catalyzed reductive cycloadditions zinc dust was used as the reducing agent (entry 2).[115] Trimethylaluminium and Et_3SiH have also been successfully used in nickel-catalyzed transformations (entry 4).[116,65] Triethoxysilane was also tried because it is known to be more reactive than triethylsilane, but those conditions resulted primarily in alkyne hydrosilylation (entry 5). Unfortunately, changes in reducing agent resulted in no productive reaction. These reactions were not performed chronologically, but intermittently after IMes had been selected as the best overall ligand for the alkylative cycloaddition.

Table 22. Reducing Agent Screen



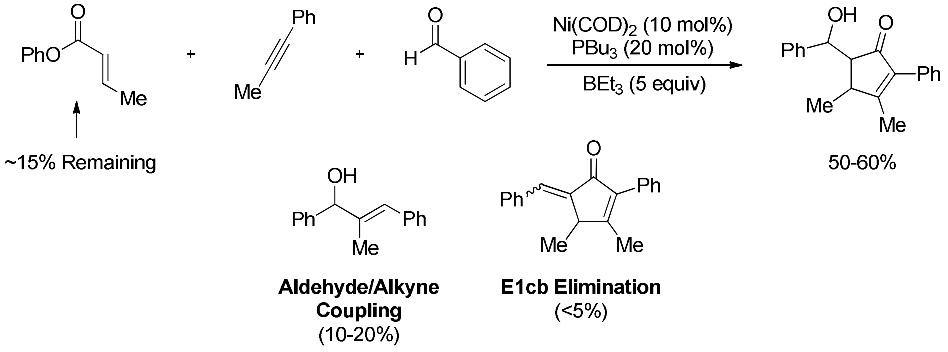
Entry	RA	Equiv	Yield	dr/rs
1	BEt_3	5	~60%[a]	54 : 38 : 8
2	Zn dust	5	trace	ND
3	$AlMe_3$[b]	3	0%	--
4	Et_3SiH	5	0%	--
5	Et_3OSiH	5	0%	--
6	BPh_3	5	<7%	ND

a) Free IMes, *b*) 0 °C to RT

3.2.2 Model Substrate Pair Discussion

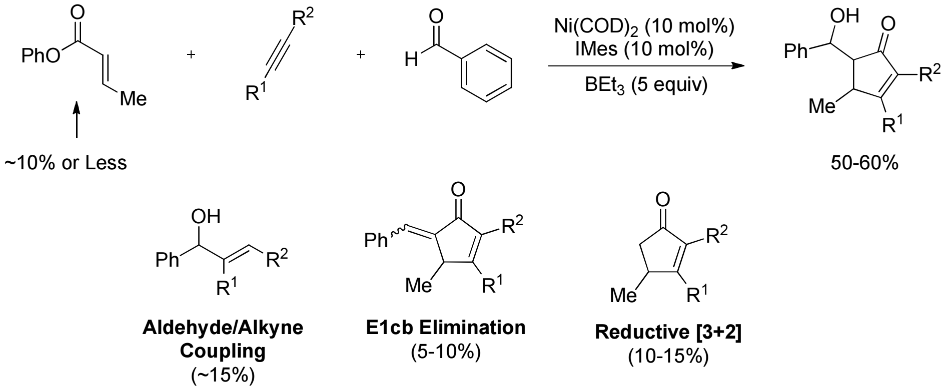
The β-methyl enoate is a good model substrate and consistently gave good yields when coupled with phenyl-propyne and benzaldehyde. However, after optimization, the yield could not be improved beyond 60%. Analysis of this reaction using PBu_3 as the ligand reveals that there is unreacted β-methyl enoate, benzaldehyde, and phenyl-propyne when the reaction is stopped (even after long reaction times) (Scheme 86). Side reactions include reduction of the enoate, alkyne, and aldehyde, along with other unidentified side products that form from reaction of the enoate. The alkyne and aldehyde do undergo reductive coupling, but the yield for this reaction is low. The β-hydroxy enone product also undergoes E1cb elimination, but not to an appreciable extent.

Scheme 86. Thorough Analysis of Alkylative Cycloaddition Employing PBu_3 as the Ligand



Under conditions employing IMes as the ligand, reactions with phenyl-propyne and 4-octyne were also thoroughly analyzed (Scheme 87). When IMes is used, there is little to no enoate remaining at the end of the reaction. However, one of the main differences between the use of IMes and PBu_3 is an increase in the amount of reductive cycloaddition products formed. Experiments conducted with free IMes and the IMes·HCl salt reveal that this is not due to the *t*-butanol generated from deprotonating the HCl salt as there is still reductive cycloaddition product forming in the reaction when the free NHC is used. Reductive coupling between the aldehyde and alkyne does not increase substantially in yield when IMes is used. The yield of E1cb elimination of the product does increase, but this side product typically does not form in over 10% yield. It should be noted that one of the two main diastereomers could eliminate preferentially to form the E1cb elimination product. Therefore, the measured diastereo- and regioselectivity may not be entirely accurate. Exogenous water is a concern, but when molecular sieves were added to the reaction, a greater percentage of reductive cycloaddition product forms. However, E1cb elimination products did not increase, which indicates that the formation of reductive cycloaddition products is not linked to E1cb elimination. Repetition of this experiment gave the expected yield but did not reduce the amount of reductive cycloaddition product formed. A product inhibition experiment was performed, and there was no decrease in yield, so product inhibition is not responsible for the low yields. If the reductive cycloaddition product and E1cb elimination products are counted towards the yield, then in some cases the yield begins to look closer to the yields in the reductive cycloadditions.

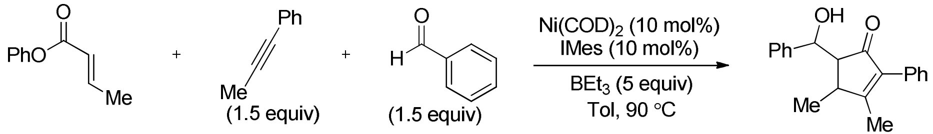
Scheme 87. Thorough Analysis of Alkylative Cycloaddition when IMes is Employed as the Ligand



3.2.3 Syringe Drive Experiments with Model Substrate Pair

It is suspected that because there are a large amount of side products (alkyne trimerization, alkyne reduction, aldehyde reduction, enoate reduction, and other unidentified side products in low yields) generated from this reaction that perhaps some small quantity of side product is inhibiting the catalyst. Nearly all reactions slow or show little change after two hours, so this may be likely. It was thought that syringe drive experiments or dilution could improve the yield by lowering the concentration of substrates in solution and increasing the lifetime of catalyst. Furthermore, when IMes is employed the alkyne was not observed in the crude GC trace in some cases, so slow addition of the alkyne could prevent the alkyne from being converted to undesired side products. A dilution experiment did not improve the yield. Syringe drive experiments with a variety of addition techniques also did not lead to improvement of the yield (Table 23). In some cases with longer times, the yield actually decreased. It was also noticed that there were side products that presumably formed as side reactions with the borane in the crude NMR. Borane was slowly added, but it had no impact upon yields (entry 2).

Table 23. Alkyne Syringe Drive Experiments



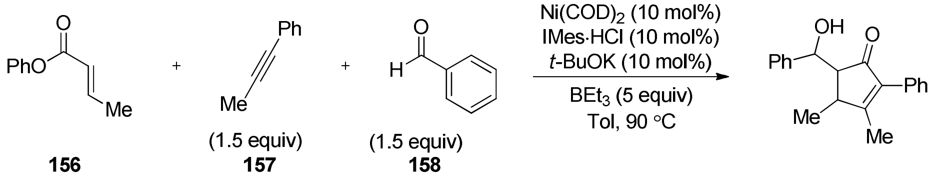
156 **157** **158**

Entry	Time	SD	Yield
1	10 min	**157**	47%
2	10 min	**157**, BEt_3	43%*
3	30 min	**157**	38%
4	90 min	**157**	32%

*IMes·HCl = ligand

More syringe drive experiments were conducted with the intent of lowering the concentration of all reaction constituents except for the catalyst in an effort to slow down side reactions or catalyst degradation (Table 24). These experiments did not lead to improvements in yield, but the yields were higher than the previous syringe drive experiments in most cases.

Table 24. Syringe Drive Experiments for All Substrates



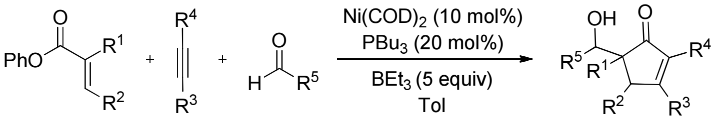
156 **157** **158**

Entry	Time	SD	Yield
1	10 min	**156**, **157**, **158** BEt$_3$	55%
2	10 min	**156**, **157** BEt$_3$	51%
3	60 min	**156**, **157**, **158** BEt$_3$	50%
4	90 min	**156**, **157**, **158** BEt$_3$	39%

3.2.4 Pre-Optimized Alkylative Substrate Scope

The substrate scope was further expanded to test the generality of the reaction (Table 25). However, experimentation with other substrates revealed that this reaction was not general with respect to aliphatic alkynes, even if the β-methyl enoate is used. Aliphatic aldehydes were also tolerated.

Table 25. Substrate Scope of Alkylative Cycloaddition



Entry	R^1	R^2	R^3	R^4	R^5	Yield
1	H	H	Me	Ph	Ph	~25%
2	H	Me	Me	Ph	Ph	58%
3	H	Me	Me	Ph	Ph	25%
4	Me	H	Me	Ph	Ph	54%
5	H	Me	*n*Pr	*n*Pr	Ph	9%^{a,b}
6	H	Me	Me	Ph	*n*Hex	52%^{b}

a) NMR Yield; *b*) Rxn at 50 °C

3.3 Optimizing Alkylative Substrate Scope

3.3.1 Ligand Optimization

Looking back to the reductive cycloaddition project, it was noticed that yields for other substrates dramatically improved when the IMes ligand was used (Table 9). Notably the yields for reductive cycloadditions employing aliphatic alkyne substrates doubled when switching from PBu_3 to IMes. We wondered if we could apply this advance to the alkylative cycloaddition chemistry, and if it worked, how much the yield would improve (Scheme 88).

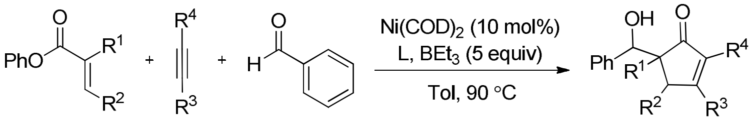
Scheme 88. Applications of Lessons from Reductive Cycloadditions

L	Yield
PBu_3	~39%
IMes	82%

L	Yield
PBu_3	9%
IMes	?

When we tested our hypothesis by employing IMes as the ligand for a transformation using 4-octyne, gratifyingly we found that the yield improved (Table 26, entry 5). The yields of other substrates classes such as the unsubstituted enoate (entry 6) and the β-phenyl substituted enoate (entry 4) also improved but only by ten percent. Unfortunately the yields of other high yielding substrates did not improve and yields with terminal alkynes were also low (entry 7).

Table 26. IMes improves yields of inefficient Alkylative Cycloadditions

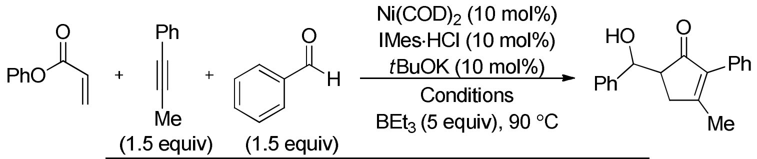


Entry	L	R^1	R^2	R^3	R^4	Yield
1	PBu_3	H	Ph	Me	Ph	~25%
2	PBu_3	H	Me	*n*Pr	*n*Pr	9%
3	PBu_3	H	H	Me	Ph	~25%
4	IMes	H	Ph	Me	Ph	43%
5	IMes	H	Me	*n*Pr	*n*Pr	52%
6	IMes	H	H	Me	Ph	~35%
7	IMes	Me	H	*n*Oct	H	17%

3.3.2 Syringe Drive Optimization

The cycloaddition yields of some substrates, such as β-phenyl enoate, unsubstituted enoate, and reactions with 1-decyne, were still low. Based upon the syringe drive experiments performed with the model substrate pair, we decided that despite the lack of improvement in the model substrate, slow addition may improve the yield. The 10 minute syringe drive had the least impact upon the yield with the model substrate. Gratifyingly, a variation of the syringe drive addition was found that improved the yields by 10% across several substrates (Table 27), but had no effect on the model substrate pair (Table 24, entry 2). The reductive cycloaddition proceeds in much better yields than the alkylative cycloaddition, and there is some reductive cycloaddition product formed in these reactions. It may be that the formation of the C-C bond is a high energy step in the reaction which may be why the yields are lower for the alkylative cycloaddition chemistry. Increasing the concentration of aldehyde in the reaction relative to the other components has led to slightly better yields, which supports the initial hypothesis.

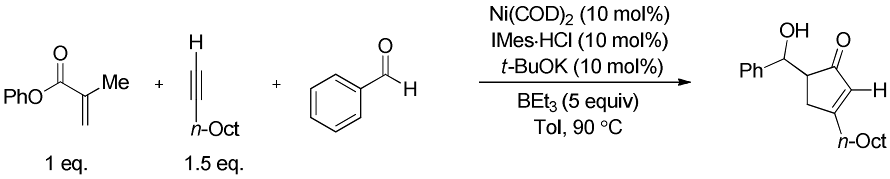
Table 27. Syringe Drive Optimization of Lower Yielding Substrates



Entry	Conditions	Yield
1	No Syringe Drive (SD)	~35%
2	SD enoate, alkyne, aldehyde, and borane into catalyst	~35%
3	SD enoate, alkyne, and borane into catalyst + aldehyde	47%

Yields with the terminal alkyne were still very low (<30%), so additional syringe drive experiments with variable amounts of aldehyde and alkyne were devised (Table 28). It was thought that since the alkylation step is difficult and because yields were low with terminal alkynes that increasing the concentration of the aldehyde would improve the yields as it did in syringe drive experiments with other substrates. Unfortunately, greater concentrations of aldehyde either did not affect product yields or further inhibited the reaction. The concentration of the alkyne was also increased in case alkyne trimerization was limiting yields, but this also did not improve yields.

Table 28. Optimization of Alkylative Cycloadditions with Terminal Alkynes

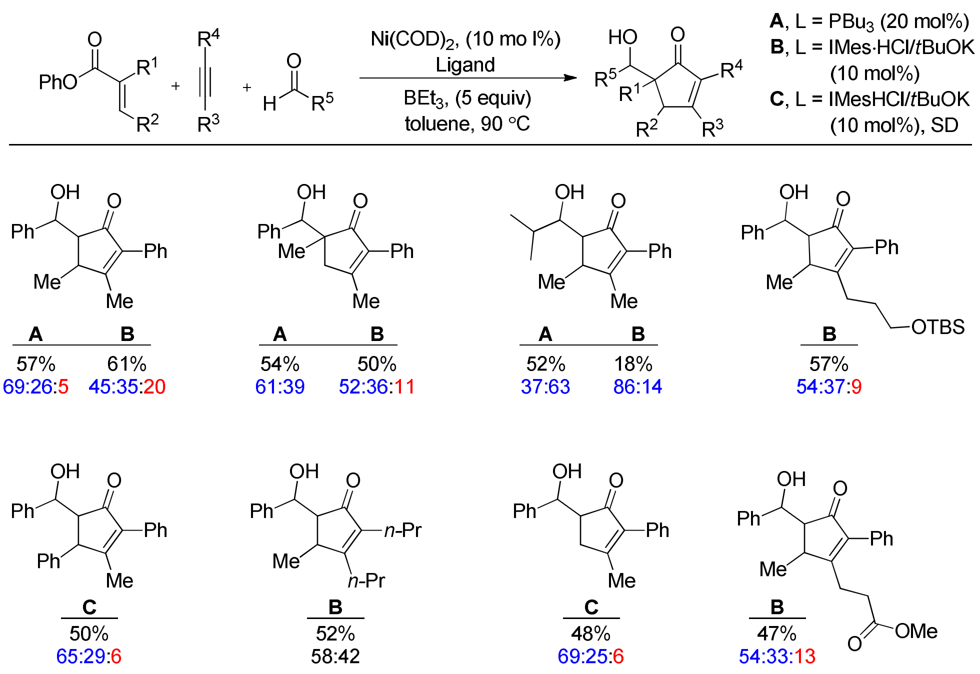


Entry	Conditions	Eq. Aldehyde	Yield
1	No SD	1.5	~17%
2	SD enoate, alkyne, and borane into catalyst + aldehyde	1.5	27%
3	SD enoate, alkyne, and borane into catalyst + aldehyde	3	27%
4	SD enoate, alkyne, and borane into catalyst + aldehyde	5	<7%
5	SD enoate, alkyne, and borane into catalyst + aldehyde	1.5 (3 eq. Alkyne)	28%

3.3.3 Alkylative Cycloaddition Substrate Scope

Since terminal alkynes were low yielding, we decided to further investigate the substrate scope of the reaction. Several substrate combinations had not been subjected to reaction conditions when IMes was employed and some of those reactions led to further insights into alkylative cycloaddition chemistry (discussed in later sections). The nickel-catalyzed alkylative cycloaddition proceeds in good yield with respect to substitution pattern (Scheme 89). Both aliphatic and aromatic alkynes, aldehydes, and enoates are tolerated. The reaction was also tolerant of functionality such as esters and protected alcohols. The diastereoselectivity is slightly higher when PBu_3 is employed as the ligand, but the reaction is not efficient with all substrates. The IMes ligand offers the best generality with slightly diminished regioselectivity and diastereoselectivity. The yields of reactions with aliphatic aldehydes are also significantly diminished when IMes is employed as the ligand. Part of the reason for the lower yields is the selective conversion of one diastereomer to form E1cb elimination products. This result is not entirely reproducible and repetition of the reaction results in variable amounts of the minor diastereomer and the amount of E1cb elimination product forming. However, the sum of the yields of both diastereomers and the amount of elimination product is lower than the yields of many of the other products. Also of note is the formation of a small amount of acyclic redox product (~20%) when the α-methyl enoate is reacted in the presence of the IMes ligand.

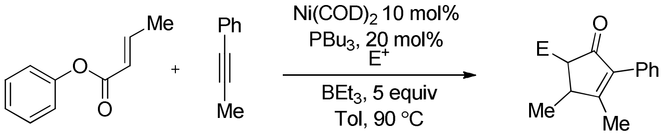
Scheme 89. Nickel-Catalyzed Alkylative Cycloaddition Substrate Scope

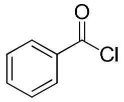
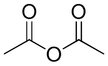


3.3.4 Electrophiles and Other Substrates

Other substrates such as alkyl and acyl halides were used in the stoichiometric alkylative cycloadditions. We decided to briefly investigate some of these substrates as electrophiles for the alkylative cycloaddition (Table 29). One of our concerns was that the halogens on many of these substrates could be problematic for the nickel catalyst. To circumvent this problem, we used syringe drive addition to lower the concentration of these potentially reactive electrophiles so that we could intercept the metal-enolate in situ. Base was added to each reaction to soak up any acid. However, none of these substrates led to a productive reaction. Small amounts (<10%) of reductive cycloaddition products were noted in some cases. The reaction was also attempted with an epoxide and a ketone, but these reactions were not productive. Alkylative cycloadditions with different electrophiles was not extensively investigated or developed, so this area should be the subject of future investigations.

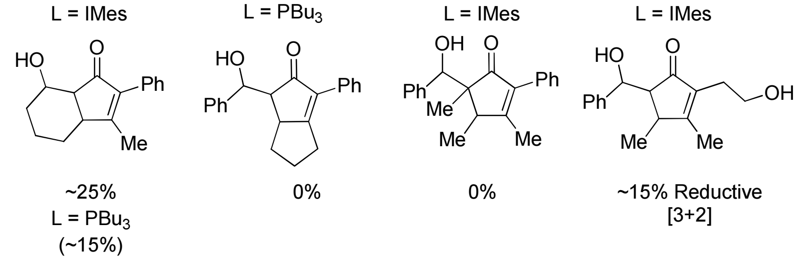
Table 29. Alkylative Cycloadditions with Different Electrophiles



Electrophile	(1 equiv) Additive	Procedure	Yield
BnBr	None		0%
BnBr	None	SD BnBr	0%
BnBr	NEt*i*Pr$_2$	SD BnBr	0%
	NEt*i*Pr$_2$	SD PhCOCl	0%
	NEt*i*Pr$_2$	SD Ac$_2$O	0%
TMSCl	None	Sealed Tube	0%
TMSCl	NEt*i*Pr$_2$	Sealed Tube	0%

Substrates that would undergo intramolecular reactions were also investigated (Scheme 90). Unfortunately, substrates that undergo intramolecular alkylations were inefficient while substrates that underwent intramolecular cyclization were unproductive. Reactions with these tethered alkynyl enoates were unproductive and unreacted starting material as well as reductive cycloaddition product was recovered from the reaction. Similar to the reductive cycloaddition chemistry, reactions with disubstituted enoates were completely unproductive. Reactions with alkynes with unprotected alcohol led to reductive cycloaddition products.

Scheme 90. Intramolecular Alkylative Cycloadditions and Misc. Substrates

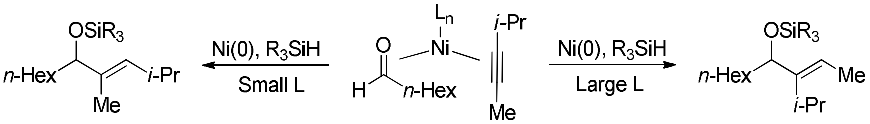


3.4 Regioselectivity and Diastereoselectivity

3.4.1 Regioreversals

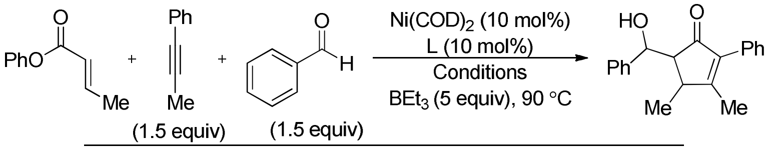
In 2010, we reported that we could control the regioselectivity of aldehyde-alkyne couplings with carbene ligands (Scheme 91).[116] If large NHC ligands were used, the large substituent of the alkyne would be forced to orient towards the aldehyde and the C-C bond forms at that the more hindered terminus of the alkyne. With smaller carbene ligands, the large substituent orients away from the aldehyde and the C-C bond forms at the less hindered terminus of the alkyne.

Scheme 91. Regiocontrol with Carbene Ligands

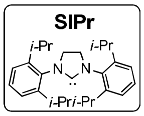


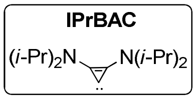
We decided to see if we could improve regioselectivities with smaller carbenes than IMes or reverse regioselectivity with larger carbenes than IPr. Also, since IMes and IPr had worked well for most substrates we also thought that we might see better substrate yields with different carbenes (Table 30). Unfortunately smaller carbenes gave poor yields and did not improve on the selectivity of the reaction. Larger ligands than IPr also gave poor yields, but could reverse the regioselectivity of the reaction. Overall, there does seem to be a trend from smaller to larger ligands where the terminus of the alkyne with the small substituent forms a C-C bond with the enoate when the ligand is small and the terminus of the alkyne with the larger substituent forms a C-C bond with the enoate when the ligand is large. There were significant amounts of uncharacterized side products formed when larger ligands such as SIPr were used. There is potential for optimization of regioselectivity with the larger ligands as a possible future avenue of research.

Table 30. Regioreversals with Carbenes



L	Conditions	Yield	Selectivity
PBu$_3$	Toluene	57%	69:26:5
IPrBAC	20 mol% cat BuLi, Dioxane	5%*	~74:26 ~70 : 23 : 7
ITol	tBuOK (10 mol%) Toluene	10%*	~78 : 20 : ND : 2
IMes	*t*BuOK (10 mol%) Toluene	61%	~56:44 ~45 : 35 : 20
IPr	*t*BuOK (10 mol%) Toluene	~62%	18 : 11 : 53 : 18
SIPr	*t*BuOK (10 mol%) Toluene	36%*	~11 : 65 : 23
SIPr	*t*BuOK (10 mol%) Dioxane	22%*	~20 : 60 : 20





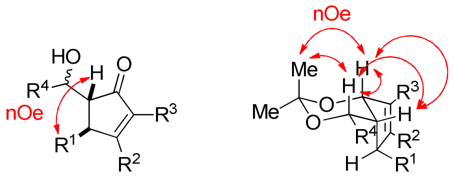
3.4.2 Diastereoselectivity

The isomeric ratio of the products reflects the formation of two major diastereomers of the major regioisomer of the reaction with the minor regioisomer forming in small quantities (Scheme 2). The stereochemistry is epimeric at the hydroxyl position. The substituent at the α-position is oriented trans to the methyl (or phenyl) substituent at the β-position. There are a few exceptions to this selectivity, with the α-substituent and β-substituent being oriented *cis* to one another. The first exception appears as a minor product when the reaction is conducted at 50 °C which is suggestive of isomerism of the products at higher temperatures. The second case is when aliphatic aldehydes are used, the cis isomer forms in minor quantities.

3.4.2.1. Determining Diastereoselectivity

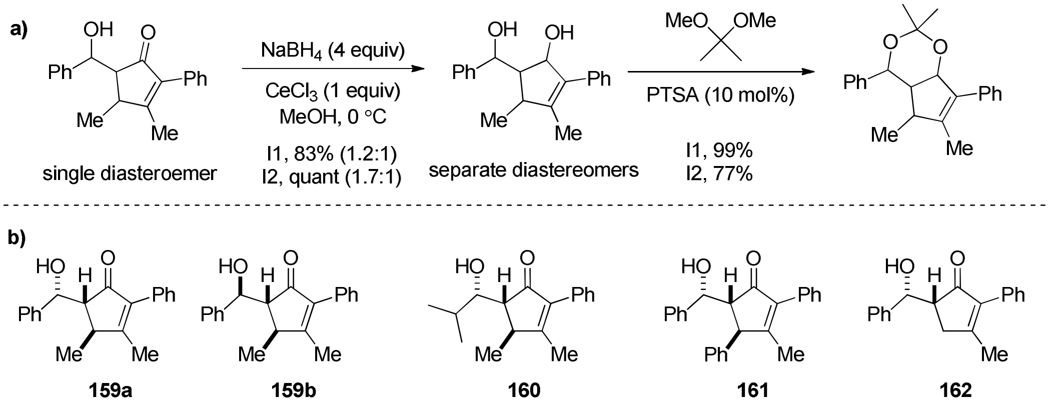
This stereochemistry was established by an nOe relationship between the β-substituent of the ring and the α-hydrogen. The stereochemistry at the epimeric position was more difficult to determine and involved Luche reduction and acetal cyclization of the resulting diol (Scheme 92). The acetal was then subjected to nOe experiments and the nOe relationships of the protons geminal to the acetal oxygens and the methyl group of the acetal were indicative of the relative stereochemistry.

Scheme 92. Relative Stereochemistry is Determined by Product nOe Relationships



A representative example is shown in Scheme 93a of the reduction to the diol and protection to form the acetalide. The reduction to the diol was performed on the purified diastereomer and the diol diastereomers were separated before acetal protection. Scheme 93b shows all the cases where the relative stereochemistry was determined. The relative stereochemistry was determined for both diastereomers of the model substrate **159**, but was determined for only one diastereomer of the other substrates **160** (minor diast.), **161** (major diast.), and **162** (major diast.). The J-values of these protons were also evaluated and found to be consistent with the stereochemistry indicated by the nOe experiments (see Chapter 5). The J-values of the protons in the product (before acetal cyclization) were also calculated and compared to known examples (See Chapter 5).[72] Most of these J-values were found to be similar.

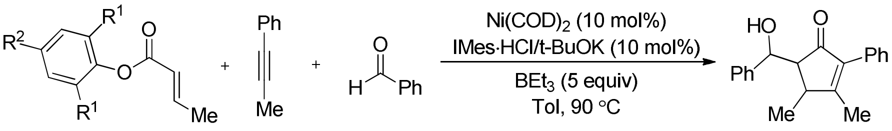
Scheme 93. Luche Reduction and Acetal Formation Reveals Relative Stereochemistry



3.4.1.2 Improving Diastereoselectivity

A few different Lewis acids such as TiF_4 and $Sn(OTf)_2$ were added to the model reaction to improve the diastereoselectivity. Unfortunately, with as little as two equivalents of these acids, the reaction was completely unproductive. Aluminum triisopropoxide was also used but resulted in low yields of reductive cycloaddition and E1cb elimination products. We also tried to improve the diastereoselectivity by increasing the bulk on the phenyl ring of the phenoxy group. The use of the mesityl phenoxy group led to a slight improvement in selectivity, but significantly lower yields (Table 31). The use of the di-tert-butyl phenoxy group led to an unproductive reaction.

Table 31. Modification of Phenoxy Group to Improve Diastereoselectivity

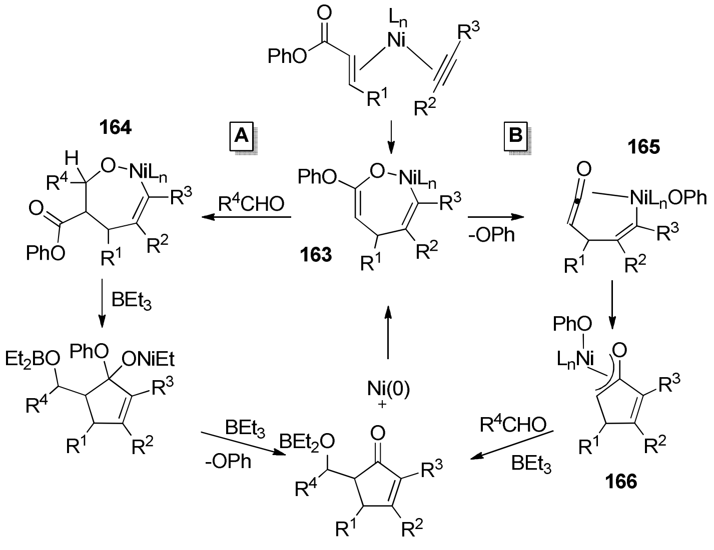


Entry	R^1	R^2	Yield	Selectivity
1	H	H	61%	45 : 35 : 20
2	Me	Me	36%	67 : 24 : 8
3	*t*-Bu	H	---	---

3.5 Mechanism

The alkylative cycloaddition could proceed through two different mechanistic pathways (Scheme 94). The pathways proposed are the same as is proposed for the reductive cycloaddition. Oxidative addition of the metal to the enoate and alkyne yields the metallacycle **163**, which can follow path A and alkylate the metal-enolate to yield a second metallacycle **164**. Transmetallation with the borane in solution followed by intramolecular insertion of the vinyl-nickel species into the ester closes the five-membered ring. The phenoxy group is extruded and the catalyst is regenerated with the reducing agent. Alternatively if the reaction proceeds through path B, the phenoxy group can be eliminated from metallacycle **163**, resulting in the formation of a ketene intermediate **165**. Intramolecular insertion of the vinyl-nickel species into the ketene closes the five membered ring and alkylation of the metal enolate **166** with the aldehyde yields the product. The reducing agent in solution regenerates the catalyst to start the catalytic cycle again. There is evidence supporting both mechanisms.

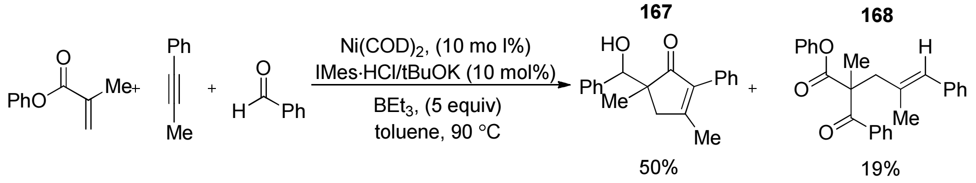
Scheme 94. Proposed Mechanism of Alkylative Cycloaddition



3.5.1 Redox Products

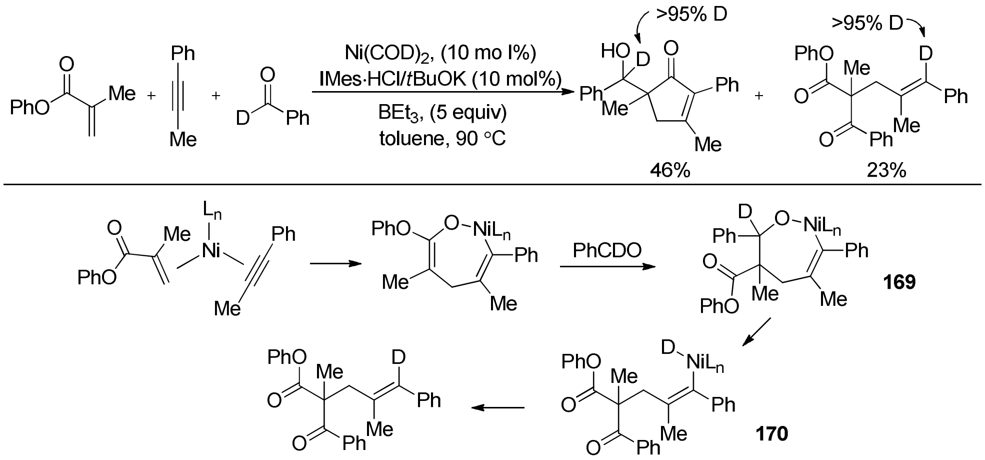
When α-methyl enoates were used, a small amount of acyclic product **167** forms along with the expected cycloaddition product **168** (Scheme 95).

Scheme 95. Formation of Acyclic Redox Products



The acyclic product that forms when α-methyl enoates are used can only form through pathway A. After oxidative cyclization and alkylation, β-hydride elimination from **169** can occur yielding an acyclic nickel-hydride intermediate **170**. This can then reductively eliminate forming an acyclic internal redox product.[78] Experiments with deuterated-benzaldehyde confirm this result (Scheme 96). This has been previously demonstrated in internal redox couplings utilizing α-substituted and unsubstituted enones, aldehydes, and alkynes in the absence of reducing agent.[78] This product was also formed in the absence of reducing agent, albeit in significantly lower yields, and the alkylative cycloaddition product was also not formed in the absence of reducing agent.

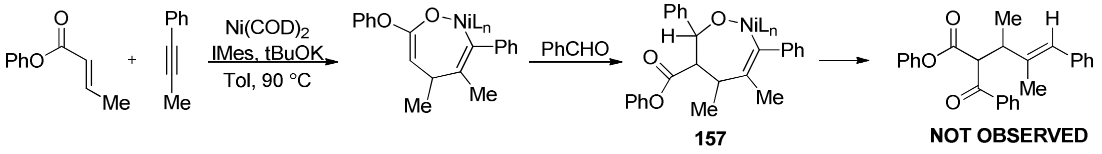
Scheme 96. Proposed Mechanism of Redox Product Formation



3.5.2 Probing the Mechanism

It was thought that we could probe the mechanism of the reaction by excluding the reducing agent. Without reducing agent, if the reaction was proceeding through path A, we would expect to see acyclic redox products predominate, because the structure of these intermediate **169** is not significantly different than the structures of the intermediates proposed from the studies of Herath, Li, and Montgomery.[78] However, in reactions without reducing agent, and with β-methyl enoates, these products do not form (Scheme 97).

Scheme 97. No Redox Products Form in the Absence of Reducing Agent with β-methyl Enoate



Ogoshi has demonstrated that in the absence of electrophiles in aprotic solvent conditions, that five-membered nickel-enolates can be observed by using low temperature NMR experiments (See Chapter 2, Scheme 79).[112] Upon quenching with *i*-PrOD, the reductive cycloaddition product forms. It is possible that the alkylative cycloaddition is therefore proceeding through pathway B and that the acyclic redox products are afforded exclusively as a consequence of the special reactivity of the α-methyl enoate. Furthermore, it is noteworthy that in the multicomponent redox paper, β-substituted substrates were unreactive. Interestingly, after constructing hand-held molecular models, the orbital overlap for insertion of the vinyl-nickel into the ketene intermediate seems to be poor.

3.6 Conclusion

In conclusion the first catalytic, intermolecular [3+2]-alkylative cycloaddition has been developed. This reaction is general with regard to substitution pattern of the enoate and is tolerant of both aryl and alkyl alkynes and aldehydes. The actual mechanism is presently unclear. This methodology expands the reductive cycloaddition chemistry to a multicomponent alkylative reaction. It also advances to the metal-mediated alkylative cycloadditions to catalytic alkylative cycloadditions. Further development of this chemistry should aim to expand the scope of electrophiles, as conditions for alkylation with other electrophiles were not extensively investigated. Regioreversals could also be optimized as yields were low because of the formation of side products when SIPr was employed as the ligand. Large NHC ligands were also not extensively explored. Other π-components such as allenes or alkenes could also be substituted for alkynes.

Chapter 4

Context and Conclusions

Five-membered rings are important structural motifs in a variety of biologically active molecules. One way to access these five-membered rings is to combine a two-atom component with a three-atom component in a [3+2] cycloaddition. It would be efficient and beneficial to use the same simple π-components that are used in Diels-Alder type processes in [3+2] cycloadditions. Unfortunately, the synthesis of five-membered rings is complicated by the inability to combine these simple π-components together because a five-membered ring is formed. In order to combine simple π-components to form the five-membered ring together, it would require a bi-radical process or complex bicyclic products would have to be formed. Alternate strategies with different types of reagents have been developed to work around this complication. One additional complication of these strategies is that methods to form carbocycles are less well developed than those that form heterocycles, and it is carbocycle synthesis that this work is exclusively focused on.

Many synthetic strategies utilize 1,3-dipolar reagents for the synthesis of five-membered rings. Many of these dipolar strategies have been developed exclusively for heterocycle synthesis however. There are a few methodologies that have been developed for the synthesis of carbocycles that take advantage of dipolar reagents. Older methodologies make use of iron or cobalt metallated reagents that react with electron deficient olefins. This suffers from the drawback of having to pre-synthesize the metallated reagent and then the products must be demetallated. A newer method makes use of the dipolar trimethylenemethane intermediate, which also reacts with electron deficient olefins to form cyclopentene products. A major drawback of this method is that several synthetic steps are necessary to synthesize the precursor to this intermediate.

Other methods use strained rings or vinyl carbenoid reagents to access cyclopentanoid products. Some of these methods, such as those that utilize the methylenecyclopropanes, are quite well developed. Methodologies that utilize donor-acceptor cyclopropanes are also well developed, but these methodologies are mostly focused on heterocycle synthesis; a few examples of these reagents being used in carbocycle synthesis do exist, however. The methods that make use of vinyl carbenoid reagents, make use of a vinyl diazo compounds that are metallated by a catalyst or use a pre-metallated carbenoid reagent for cyclopentenoid synthesis. The use of strained rings or carbenoid reagents also requires special synthetic manipulations to install these structural motifs. It may be difficult to carry some of these motifs through a synthesis or install them at a late stage in a synthesis.

There are some ways to circumvent the difficulties that surround the use of dipolar, carbenoid, and strained rings for the synthesis of five-membered rings. It would be ideal to use simple π-components that are readily available, easily installed, or easily carried through a synthetic sequence. There are some ways to get around the complications of using these reagents for the synthesis of five-membered rings. One method is to rearrange the atomic-connectivity of the reagent, a 1,2-shift, during the formation of the five-membered ring. There have been several classes of silane reagents that have been used for the synthesis of five-membered rings. Other methods use phosphine catalysts to effect a 1,2-hydrogen shift during a cascade sequence for the formation of the five-membered ring.

Another distinct strategy is to change the substrate oxidation state during the cycloaddition. This strategy is becoming increasingly general and is an excellent method for carbocycle synthesis. Some of these methods use dianionic intermediates. Others use stoichiometric or catalytic quantities of metal in the reductive cycloaddition of simple π-components. The Montgomery group has been focused on these types of transformations throughout much of the group history. Initial development in this area involved nickel-mediated reductive and alkylative cycloadditions of tethered π-components, which are similar to related titanium- and iron-mediated reductive and alkylative cycloadditions. The use of organoborane reducing agents enabled intramolecular and intermolecular nickel-catalyzed reductive cycloadditions of enals and alkynes to form cyclopentenol products. Unfortunately, these new conditions did not allow for the same advances for catalytic alkylative or intermolecular-catalytic alkylative cycloadditions involving aldehydes or electrophiles, which is a challenge for forming highly functionalized cyclopentenoid products. The intermolecular-alkylative cycloaddition is a multicomponent reaction which presents its own special challenges.

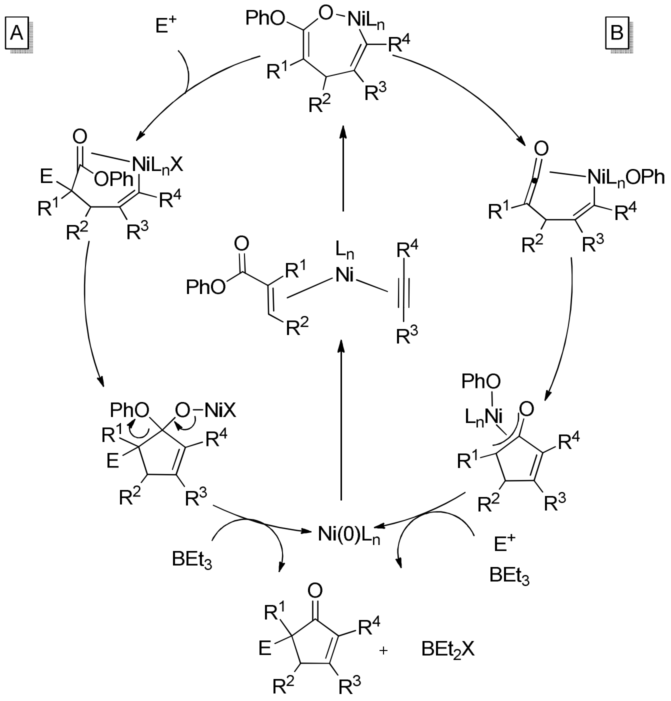
Multicomponent reactions are especially useful for forming multiple bonds in a single pot. This usually happens in a cascade sequence of simple reactions. A major challenge of multicomponent reactions is to get all reactants to funnel down to a single product. Most multicomponent cycloaddition reactions utilize dipolar reagents, mostly for heterocycle synthesis. Variants for carbocycle synthesis are less common and these strategies make use of strained rings or carbenoid intermediates. Three-component processes have also been developed for methodologies involving silane reagents that rearrange their atomic-connectivity during the cycloaddition. More strategies for forming highly functionalized carbocycles through multicomponent processes are needed.

Nickel-catalyzed enal-alkyne reductive cycloadditions provided cyclopentenol products. We sought to find a way to access the corresponding cyclopentenone products. These products were still accessible through oxidation of the cyclopentenol products, but first the nickel-catalyzed enal-alkyne coupling has to be performed with enal reagents which are unstable and require purification prior to use. We believed that these products might be accessible if we used an α,β-unsaturated carbonyl component with a leaving group that could be eliminated during the coupling process to form the cyclopentenone product. After screening different α,β-unsaturated carbonyl components, we found that phenyl enoates provided the best overall yields. The reaction was insufficiently general and yields were low with other substrate pairs or substitution patterns. The generality of the reaction was greatly improved when IMes was used as the ligand for the reaction. We also discovered that when we were exploring the substrate scope of the reaction, acyclic reductive coupling products dominated when we coupled the α-substituted enoate with internal alkynes. When we discovered that when the same enoate was reacted with terminal alkynes to yield cycloaddition products, we attributed this special reactivity to steric effects. We propose that this reaction proceeds through a similar mechanism as the enal-alkyne couplings and believe that the formation of this reductive coupling product, which would be difficult to envision forming through other mechanistic pathways, is evidence towards this pathway. Other mechanisms involving a ketene intermediate could be envisioned. A publication emerged, shortly after our own publication on this project, showing that the proposed products could form under aprotic conditions demonstrating the viability of this mechanism. We performed a few of our own experiments and confirmed this result, and the viability of this pathway, but experimental difficulties made it difficult to determine which pathway predominates. However, we were able to demonstrate that the reaction that favors the formation of the reductive coupling producgt under protic conditions only forms the reductive cycloaddition product under aprotic conditions. This may indicate a change in mechanism depending on solvent conditions, where under aprotic conditions, the ketene pathway is operative. Conversely, because protonation is a very fast event, and because our reactions are performed under protic conditions, we believe this ketene mechanism to be unlikely under our “normal” protic reaction conditions. Also, the emergence of reductive coupling products in some reactions would be more difficult to form in reactions involving a ketene intermediate.

We saw additional opportunity to expand this enoate-alkyne coupling to a three component process involving alkylation with aldehydes instead of protonation. The three-component enal-alkyne and aldehyde coupling was unsuccessful largely because of the similar reactivity of enals and aldehydes. These reactions resulted in a large number of different products. Enoates and aldehydes are sufficiently different that a cascade process will funnel down to a single product. We tested this three-component process and found that alkylated products formed as a mixture of two favored diastereomers, but in somewhat lower yields than the enoate-alkyne couplings. Initial optimization revealed that the reaction could not be readily expanded to differently substituted enoates or different types of alkynes. We found that when we used IMes as the ligand, the generality of the reaction improved. There were some substrates that were still low yielding and the yields could be improved with the use of a syringe drive. There were a few reasons as to why the yields were low. When tributylphosphine was used as the ligand, there was unreacted enoate leftover. However, while IMes improved conversion, formation of small amounts of reductive coupling and E1cb elimination product caused the yields to still be lower than the corresponding enoate-alkyne reductive cycloadditions. The mechanism of the reaction is presently unclear. We witnessed the formation of acyclic coupling products which could only be formed through a redox pathway involving a seven-membered metallacycle that is also proposed in the pathway of the enoate-alkyne reductive cycloadditions. Deuterium labeling experiments confirmed this result. This acyclic redox product was only seen when the α-methyl enoate substrate was used however. Experiments with other substrates revealed no redox products and experiments without borane reducing agent – which should favor the formation of the acyclic products also did not produce acyclic redox products. We therefore believe that the ketene mechanism may be operative under these conditions, because there is no proton source in solution and our experiments along with results published by others demonstrate the viability of this pathway.

If we compare both the reductive and alkylative cycloadditions, it is likely that the reductive cycloaddition proceeds through pathway A because the reductive cycloaddition is performed under protic reaction conditions (Scheme 98). The alkylative cycloaddition is conducted under aprotic conditions somewhat similar to the conditions that Ogoshi used in his NMR experiment. There are a few notable differences however. Ogoshi's experiment was conducted using stoichiometric amounts of nickel and at lower temperatures than the conditions that are used for the alkylative cycloaddition. He also never intercepted his metal enolates with aldehydes. Despite the similarity in conditions, the mechanism of the reaction is unclear. The ketene mechanism is entirely plausible because Experiments with other substrates revealed no redox products, and experiments without borane reducing agent, which should favor the formation of the acyclic products, also did not produce acyclic redox products. It should also be noted that the α-methyl enoate may be a special substrate that biases the reaction pathway towards pathway A, as redox and reductive coupling products are not observed with other substrates.

Scheme 98. Overview of Mechanistic Conclusions



Chapter 5

Supporting Information

5.1. Nickel-Catalyzed Reductive Cycloaddition Procedure

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, inc. Model # SPS-400-3 and PS-400-3. Enoates were distilled prior to use. Ni(COD)$_2$ (Strem Chemicals, Inc., used as received), 1,3-Bis(2,4,6-trimethyl-phenyl)imidazolium chloride (IMes·HCl), tricyclohexylphosphine, DPEphos, and potassium *tert*-butoxide was stored and weighed in an inert atmosphere glovebox. Tri-N-butylphosphine was freshly distilled and used under an inert atmosphere. Methanol (Acros SureSeal Extra Dry with molecular sieves) was used as received. All reactions were conducted in flame-dried or oven dried (120 °C) glassware under nitrogen atmosphere. ^{1}H and ^{13}C spectra were obtained in CDCl$_3$ at rt (25 °C), unless otherwise noted, on a Varian Mercury 400 MHz, Varian Unity 500 MHz instrument, or Varian Unity 700 MHz Instrument. Chemical shifts of ^{1}H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of CDCl$_3$ (77.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory. Regioisomeric ratios were determined on crude reaction mixtures using NMR or

GC. GC analyses were carried out on an HP 6980 Series GC System with an HP-5MS column (30m x 0.252mm x 0.25 μm)

General Procedure A: Enoate-Alkyne Cycloaddition with IMes

$Ni(COD)_2$ (8.3 mg, 0.03 mmol, 0.1 equiv), 1,3-bis(2,4,6-trimethyl-phenyl)imidazolium chloride, (IMes·HCl) (10.2 mg, 0.03 mmol, 0.1 equiv), and KO-*t*-Bu (3.4 mg, 0.03 mmol, 0.1 equiv) were combined under an inert atmosphere and dissolved in 3 mL of THF at rt. The catalyst solution was stirred 10-15 min. at rt. until a deep blue solution resulted. Enoate (0.3 mmol, 1 equiv), alkyne (0.45 mmol, 1.5 equiv) and methanol (0.1 mL) were then cannulated over from a nitrogen purged vial in 2 mL of THF. BEt_3 (217 μL) was then added via syringe and the reaction was placed in a 50 °C oil bath until TLC analysis indicated disappearance of the enoate. After reaction completion the general procedure for workup was followed.

General Procedure B: Enoate-Alkyne Cycloaddition with PCy_3

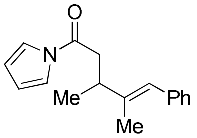
$Ni(COD)_2$ (8.3 mg, 0.03 mmol, 0.1 equiv) and tricyclohexylphosphine (16.8 mg, 0.06mmol) were combined under an inert atmosphere and dissolved in 1.5 mL of THF at rt. The catalyst solution was stirred 10-15 min. at rt. until an orange/yellow solution resulted. Enoate (0.3 mmol, 1 equiv) and methanol (0.1 mL) were then cannulated over from a nitrogen purged vial in 1.5 mL of THF. The alkyne (0.45 mmol, 1.5 equiv) was then dissolved in 2 mL of THF. BEt_3 (217 μL) was then added via syringe. A small amount (0.2 mL) of the alkyne solution was then added followed by placement of the reaction in a 50 °C oil bath, and by 1.5 hour syringe-pump addition of the alkyne. The reaction was monitored until TLC analysis indicated disappearance of the enoate. The general workup procedure was then followed.

General Workup Procedure for Nickel-Catalyzed [3+2] Cycloaddition Product Formation

Upon completion of the reaction the septum was punctured with an needle to allow air in, and the reaction was stirred at rt. for 30 min. Saturated NH_4Cl (2.5 mL) was then added and the aqueous layer was extracted 3x with 5mL methylene chloride. The combined organic layers were then washed with 0.5 M NaOH (20 mL) followed by a brine wash (20 mL). The organic layers were then dried over anhydrous Na_2SO_4 followed by filtration through a pad of silica and concentration via rotary evaporation. The products were then purified via flash column chromatography.

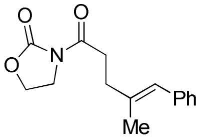
5.2 Nickel-Catalyzed [3+2]-Reductive Cycloaddition Product Characterization

(E)-3,4-dimethyl-5-phenyl-1-(1H-pyrrol-1-yl)pent-4-en-1-one (Table 4, Entry 4)



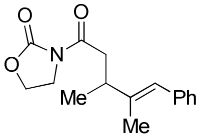
$Ni(COD)_2$ (8.3 mg, 0.03 mmol, 0.1 equiv) was weighed out under an intern atompshoere and 1.5 mL of THF was added after the vial was transferred to a schlenk line. Next, tributylphosphine (12 mg, 0.06mmol) was added dropwise to the pale yellow solution resulting in a bright yellow solution after 10-15 min. The rest of the setup follows General Procedure A with (E)-1-(1H-pyrrol-1-yl)but-2-en-1-one (0.041 g, 0.3 mmol) and and phenyl-propyne (0.056 mL, 0.45 mmol). The product was isolated after column chromatography (0.075 g, 90%). ^1H NMR (500 MHz $CDCl_3$): δ 7.34-7.39 (m, 4H), 7.23-7.28 (m, 3H), 6.40 (s, 1H), 6.35 (t, J = 2.3 Hz, 2H), 3.05-3.10 (m, 2H), 2.89-2.92 (m, 1H), 1.92 (s, 3H), 1.30 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 141.0, 137.9, 128.9, 128.0, 126.1, 125,1, 119.0, 113.1, 40.5, 39.8, 19.3, 15.1.

(E)-3-(4-methyl-5-phenylpent-4-enoyl)oxazolidin-2-one (Table 5, Entry 1)



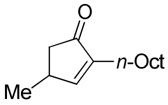
Ni(COD)$_2$ (8.3 mg, 0.03 mmol, 0.1 equiv) was weighed out under an intern atompshoere and 1.5 mL of THF was added after the vial was transferred to a schlenk line. Next, tributylphosphine (12 mg, 0.06mmol) was as a solution dropwise to the pale yellow solution resulting in a bright yellow solution after 10-15 min. The rest of the setup follows General Procedure A with (E)-1 3-acryloyloxazolidin-2-one (0.04 g, 0.28 mmol) and and phenyl-propyne (0.050 mL, 0.43 mmol) and triethylborane (0.124 mL, 0.85 mmol). The product was isolated after column chromatography as an impure product (0.007 g, 10%). ^{1}H NMR (400 MHz CDCl$_3$): δ 7.29-7.33 (m, 2H), 7.17-7.23 (m, 3H), 6.33 (s, 1H), 4.39-4.44 (m, 2H), 4.02-4.06 (m, 2H), 3.15-3.19 (m, 2H), 2.54 (t, J = 8.0 Hz, 2H), 1.90 (d, J = 1.2 Hz, 3H).

(E)-3-(3,4-dimethyl-5-phenylpent-4-enoyl)oxazolidin-2-one (Table 5, Entry 2)



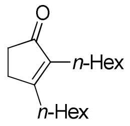
Ni(COD)$_2$ (8.3 mg, 0.03 mmol, 0.1 equiv) was weighed out under an intern atompshoere and 1.5 mL of THF was added after the vial was transferred to a schlenk line. Next, tributylphosphine (12 mg, 0.06mmol) was as a solution dropwise to the pale yellow solution resulting in a bright yellow solution after 10-15 min. The rest of the setup follows General Procedure A with (E)-3-(but-2-enoyl)oxazolidin-2-one (0.05 g, 0.32 mmol) and and phenyl-propyne (0.060 mL, 0.49 mmol) and triethylborane (0.13 mL, 0.96 mmol). The product was isolated after column chromatography (0.004 g, 5%). ^{1}H NMR (400 MHz $CDCl_3$): δ 7.26-7.30 (m, 2H), 7.14-7.20 (m, 3H), 6.31 (s, 1H), 4.33-4.38 (m, 2H), 3.97 (t, J = 8.0 Hz, 2H), 3.17 (dd, J = 15.6 Hz, 6.8 Hz, 1H), 2.87-3.10 (m, 2H), 1.83 (d, J = 1.2 Hz, 3H), 1.16 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 153.5, 141.6, 138.1, 128.8, 127.9, 126.0, 124.7, 61.9, 42.5, 40.5, 39.6, 19.4, 14.9.

4-methyl-2-octylcyclopent-2-enone (Table 8, Entry 3)



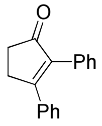
Ni(COD)$_2$ (8.3 mg, 0.03 mmol, 0.1 equiv) was weighed out under an internal atmosphere and 1.5 mL of THF was added after the vial was transferred to a schlenk line. Next, tributylphosphine (12 mg, 0.06mmol) was added dropwise to the pale yellow solution resulting in a bright yellow solution after 10-15 min. The rest of the setup follows General Procedure A with phenyl 3-butenoate (0.049 g, 0.3 mmol) and and 1-Decyne (0.081 mL, 0.45 mmol). The product was obtained as an impure single regioisomer after column chromatography (10% EtOAc/Hexanes) as a colorless oil (0.011 g, 17%). ^{1}H NMR (400 MHz $CDCl_3$): δ 7.16 (s, 1H), 2.88 (m, 1H), 2.62 (dd, J = 18.8 Hz, J = 6.4 Hz, 1H), 2.13 (tt, J = 7.8 Hz, J = 1.6 Hz, 2H), 1.95 (dd, J = 18.8 Hz, J = 2.0 Hz, 1H), 1.43-1.48 (m, 2H), 1.25-1.31 (m, 10H), 1.16 (d, J = 7.2 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H). The minor regioisomer could be isolated using General Procedure B. The products form in roughly a 2:1 ratio isolation yields the impure regioisomers (0.016 g, 27%). Minor Regioisomer: ^{1}H NMR (400 MHz $CDCl_3$): δ 5.89 (s, 1H), 2.86 (quin, J = 6.8 Hz, 1H), 2.64 (dd, J = 18.8 Hz, J = 6.8 Hz, 1H), 2.44 (ddd, J = 17.6 Hz, J = 8.8 Hz, J = 7.6 Hz, 1H), 2.27 (ddd, J = 15.6 Hz, J = 10.0 Hz, J = 6.0 Hz, 1H), 2.00 (dd, J = 18.8 Hz, J = 2.4 Hz, 1H), 1.50-1.63 (m, 2H), 1.32-1.39 (m, 10H), 1.19 (d, J = 7.2 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H).

2,3-dihexylcyclopent-2-enone (Table 8, Entry 6)



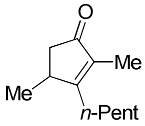
Ni(COD)$_2$ (8.3 mg, 0.03 mmol, 0.1 equiv) was weighed out under an intern atompshoere and 1.5 mL of THF was added after the vial was transferred to a schlenk line. Next, tributylphosphine (12 mg, 0.06 mmol) was added dropwise to the pale yellow solution resulting in a bright yellow solution after 10-15 min. The rest of the setup follows General Procedure A with pheny acrylate (0.044 g, 0.3 mmol) and and 7-tetradecyne (0.10 mL, 0.45 mmol). The product was obtained after column chromatography as an impure colorless oil (0.034 g, 39%). ^{1}H NMR (500 MHz CDCl$_3$): δ 2.47-2.49 (m, 2H), 2.40 (t, J = 7.5 Hz, 2H), 2.34-2.36 (m, 2H), 2.15 (t, J = 8.0 Hz, 2H), 1.52 (quin, J = 8.0 Hz, 2H), 1.27-1.36 (m, 14H), 0.90 (t, J = 7.0 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H).

2,3-diphenylcyclopent-2-enone (Table 8, Entry 10)



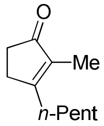
Ni(COD)$_2$ (8.3 mg, 0.03 mmol, 0.1 equiv) was weighed out under an intern atompshoere and 1.5 mL of THF was added after the vial was transferred to a schlenk line. Next, tributylphosphine (12 mg, 0.06 mmol) was added dropwise to the pale yellow solution resulting in a bright yellow solution after 10-15 min. The rest of the setup follows General Procedure A with pheny acrylate (0.044 g, 0.3 mmol) and and diphenylacetylene (0.08 g, 0.45 mmol). The product was isolated after column chromatography (0.046 g, 66%). ^{1}H NMR (400 MHz CDCl$_3$): δ 7.24-7.34 (m, 8H), 7.19-7.22 (m, 2H), 3.03-3.05 (m, 2H), 2.68-2.71 (m, 2H).

2,4-dimethyl-3-pentylcyclopent-2-enone (Table 10, Entry 7)



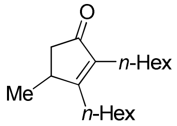
General procedure A was followed with phenyl 3-butenoate (0.049 g, 0.3 mmol) and 2-octyne (0. 065 mL, 0.45 mmol). TLC indicated disappearance of phenyl 3-butenoate after 1 hour. The product was obtained as an impure colorless oil after column chromatography (5% EtOAc/Hexanes) (0.033 g, 61%). Major Regioisomer (contains 20% minor regioisomer): ^{1}H NMR (500 MHz CDCl$_3$): δ 2.82 (quin, J = 6.5 Hz, 1H), 2.60 (dd, J = 19.0 Hz, J = 7.0 Hz, 1H), 2.46 (ddd, J = 13.5 Hz, J = 9.5 Hz, J = 7.0 Hz, 1H), 2.31 (ddd, J = 14.5 Hz, J = 9.0 Hz, J = 5.5 Hz, 1H), 1.95 (dd, J = 18.5 Hz, J = 2.0 Hz, 1H), 1.68 (s, 3H), 1.51-1.56 (m, 1H), 1.38-1.46 (m, 1H), 1.22-1.37 (m, 4H), 1.14 (d, J = 7.0 Hz, 3H), 0.90 (t, J = 7.0 Hz, 3H). Minor Regioisomer (contains 1:1 mixture of regioisomers): ^{1}H NMR (500 MHz CDCl$_3$): δ 2.71 (quin, J = 6.5 Hz, 1H), 2.62 (dd, J = 19.0 Hz, J = 7.0 Hz, 1H), 2.15 (t, J = 8.0 Hz, 2H), 1.99 (s, 3H), 1.97 (dd, J = 19.0 Hz, J = 2.5 Hz, 1H), 1.25-1.35 (m, 6H), 1.15 (d, J = 7.0 Hz, 3H), 0.86 (t, J = 7.5 Hz, 3H).

2-methyl-3-pentylcyclopent-2-enone (Table 10, Entry 8)



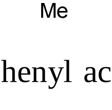
General procedure A was followed with phenyl acrylate (0.044 g, 0.3 mmol) 2-octyne (0. 065 mL, 0.45 mmol). The product was formed as a mixture of regioisomers (2:1) which could be partially separated to yield the pure product (0.028 g, 56%). Major Regioisomer: ^{1}H NMR (500 MHz CDCl$_3$): δ 2.49-2.50 (m, 2H), 2.42 (t, J = 8.0 Hz, 2H), 2.36-2.39 (m, 2H), 1.70 (s, 3H), 1.54 (quin, J = 7.5 Hz, 2H), 1.29-1.39 (m, 4H), 0.92 (t, J = 7.0 Hz, 3H).

2,3-dihexyl-4-methylcyclopent-2-enone (Scheme 67)



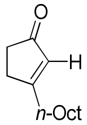
General procedure A was followed with phenyl 3-butenoate (0.049 g, 0.3 mmol) and 7-tetradecyne (0.10 mL, 0.45 mmol). TLC indicated disappearance of phenyl 3-butenoate after 1 hour. The product was obtained as a colorless oil after column chromatography (5% EtOAc/Hexanes) (0.069 g, 87%). ^{1}H NMR (500 MHz CDCl$_3$): δ 2.82 (quin, *J* = 6.8 Hz, 1H), 2.59 (dd, *J* = 19.0 Hz, 6.8 Hz, 1H), 2.49 (ddd, *J* = 13.5 Hz, 10.0 Hz, 6.8 Hz 1H), 2.30 (ddd, *J* = 14.0 Hz, 8.8 Hz, 4.9 Hz, 1H), 2.08-2.17 (m, 1H), 2.13 (q, *J* = 6.7 Hz, 1H), 1.94 (dd, *J* = 18.5 Hz, 2.0 Hz, 1H), 1.5 – 1.63 (m, 1H), 1.19-1.48 (m, 15H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ, 209.0, 177.7, 140.1, 43.1, 34.5, 31.63, 31.56, 29.5, 29.3, 28.6, 28.4, 27.4, 23.2, 22.6, 22.5, 19.3, 14.03, 14.00. IR (thin film): ν 2956, 2928, 2858, 1702, 1639, 1458, 1412, 1377, 1361, 1293, 1194, 1163, 1114, 1054, 888, 725, 548 cm^{-1}. HRMS (EI) (*m/z*): [M]$^+$ calc for $C_{18}H_{32}O$, 264.2453; found, 264.2452.

3-methyl-2-phenylcyclopent-2-enone (Scheme 67)



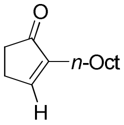
General procedure A was followed with phenyl acrylate (0.044 g, 0.3 mmol). TLC indicated disappearance of phenyl 3-butenoate after 1.5 hours. The product was obtained as a mixture of regioisomers after column chromatography (10% EtOAc/Hexanes) as a colorless oil (93:7 crude regioselectivity) (36 mg, 69%). The spectra of the purified major[122] and minor[123] isomer matched those from the literature.

3-octylcyclopent-2-enone (Major Regioisomer) (Scheme 67)



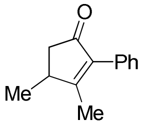
General procedure A was followed with phenyl acrylate (0.044 g, 0.3 mmol) and 1-Decyne (0.081 mL, 0.45 mmol). TLC analysis indicated disappearance of the phenyl acrylate after 1 hour (90:10 crude regioselectivity). The product was obtained as a single regioisomer after column chromatography (10% EtOAc/Hexanes) as a colorless oil (0.039 g, 67%). ^{1}H NMR (500 MHz CDCl$_3$): 5.94 (m, 1H), 2.57-2.58 (m, 2H), 2.39-2.41 (m, 4H), 1.58 (quin, *J* = 7.5 Hz, 1H), 1.27-1.35 (m, 11H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 210.2, 183.3, 129.4, 35.3, 33.5, 31.8, 31.5, 29.29, 29.26, 29.1, 27.0, 22.6, 14.0. IR (thin film): v 2927, 2856, 1710, 1676, 1618, 1466, 1439, 1410, 1378, 1337, 1284, 1232, 1182, 1144, 1072, 985, 840, 723, 691, 622, 487, 434 cm^{-1}. HRMS (EI) (m/z): [M]$^+$ calc for $C_{13}H_{22}O$, 194.1671; found, 194.1677.

2-octylcyclopent-2-enone (Minor Regioisomer) (Scheme 67)



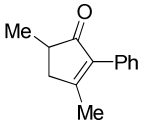
In the above experiment, the minor regioisomer was obtained as a single regioisomer after column chromatography (5% EtOAc/Hexanes). ^{1}H NMR (400 MHz CDCl$_3$): δ 7.30 (m, 1H), 2.54-2.57 (m, 2H), 2.38-2.41 (m, 2H), 2.16 (t, *J* = 7.6 Hz, 2H), 1.43-1.49 (m, 1H), 1.26.1.31 (m, 11H), 0.88 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 210.12, 157.2, 146.6, 34.6, 31.9, 29.42, 29.36, 29.2, 27.7, 26.4, 24.8, 22.7, 14.1. IR (thin film): v 2925, 2855, 1706, 1633, 1465, 1407, 1345, 1296, 1254, 1197, 1057, 1001, 922, 790, 723 cm^{-1}. HRMS (EI) (m/z): $[M]^+$ calc for $C_{13}H_{22}O$, 194.1671; found, 194.1673.

3,4-dimethyl-2-phenylcyclopent-2-enone (Scheme 67)



General procedure A was followed with phenyl 3-butenoate (0.049 g, 0.3 mmol) and 1-phenyl-1-propyne (0.056 mL, 0.45 mmol). TLC indicated disappearance of phenyl 3-butenoate after 2 hours. TLC analysis indicated disappearance of the phenyl acrylate after 1 hour The product was obtained as a single regioisomer after column chromatography (10% EtOAc/Hexanes) as a colorless oil (0.043 g, 77%) (86:14 crude regioselectivity). ^{1}H NMR (400 MHz $CDCl_3$): δ 7.32-7.40 (m, 2H), 7.26-7.30 (m, 3H), 2.86 (quin, *J* = 7.1 Hz, 1H), 2.77 (dd, *J* = 18.2 Hz, 6.6 Hz, 1H), 2.14 (d, *J* = 18.4 Hz, 1H), 2.12 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 226.2, 175.5, 139.8, 131.8, 129.1, 128.1, 127.5, 43.5, 37.3, 19.1, 15.9. IR (thin film): ν 3056, 2964, 2872, 1694, 1634, 1599, 1496, 1443, 1413, 1379, 1339, 1296, 1241, 1206, 1185, 1142, 1078, 1031, 948, 926, 894, 823, 762, 701, 671, 628, 586, 560, 519, 496 cm^{-1}. HRMS (EI) (m/z): $[M]^+$ calc for $C_{13}H_{14}O$, 186.1044; found, 186.1046. The minor regioisomer matched spectra from the literature.[35]

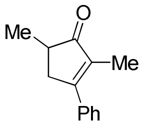
3,5-dimethyl-2-phenylcyclopent-2-enone (Major Regioisomer) (Scheme 67)



General procedure A was followed with phenyl methacrylate (0.049 g, 0.3 mmol) and phenyl-1-propyne (0.056 mL, 0.45 mmol). TLC indicated disappearance of the phenyl methacrylate after 1 hour (64:36 crude regioisomer mixture). The product was obtained after column chromatography

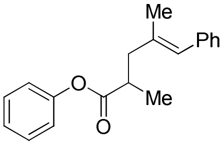
(10% EtOAc, Hex) as a regioisomeric mixture (0.01 g, 19%). Further purification by column chromatography (3% acetone/hexanes) separated the regioisomers giving colorless oils. ^{1}H NMR (400 MHz $CDCl_3$): δ 7.42-7.39 (m, 2H), 7.29-7.33 (m, 3H), 2.91 (dd, *J* = 18.4 Hz, 6.8 Hz, 1H), 2.54 (quind, *J* = 7.3 Hz, 2.7 Hz, 1H), 2.27 (d, *J* = 18.8 Hz, 1H), 2.17 (s, 3H), 1.26 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 209.9, 169.8, 139.0, 132.0, 129.1, 128.2, 127.5, 40.9, 40.0, 18.2, 16.7. IR (thin film): ν 3056, 2929, 1700, 1641, 1495, 1433, 1381, 1344, 1236, 1211, 1136, 924, 888, 854, 773, 739, 701, 623, 594, 544, 470 cm^{-1}. HRMS (EI) (m/z): $[M]^+$ calc for $C_{13}H_{14}O$, 186.1045; found, 186.1043.

2,5-dimethyl-3-phenylcyclopent-2-enone (Minor Regioisomer) (Scheme 67)



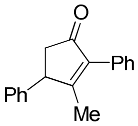
In the above experiment the minor regioisomer was obtained after further purification by column chromatography (3% acetone/hexanes). ^{1}H NMR (400 MHz $CDCl_3$): δ 7.52-7.54 (m, 2H), 7.42-7.48 (m, 3H), 3.16 (dd, *J* = 18.0 Hz, 5.4 Hz, 1H), 2.51-2.56 (m, 2H), 1.97 (s, 3H), 1.27 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ, 212.3, 164.7, 136.4, 135.3, 129.4, 128.6, 127.6, 39.4, 38.4, 16.7, 10.1. IR (thin film): ν 3057, 2925, 1696, 1626, 1495, 1445, 1378, 1346, 1223, 1114, 1004, 962, 915, 765, 743, 697, 585, 455 cm^{-1}. HRMS (EI) (m/z): $[M]^+$ calc for $C_{13}H_{14}O$, 186.1045; found, 186.1041

(Z)-phenyl 2,4-dimethyl-5-phenylpent-4-enoate (Scheme 67)



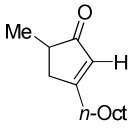
In the above experiment, the acyclic coupling product was obtained as a colorless oil (0.053g, 63%) after column chromatography (5% EtOAc/Hexanes). ^{1}H NMR (500 MHz CDCl$_3$): δ 7.32-7.36 (m, 4H), 7.20-7.26 (m, 4H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.05 (s, 1H), 3.01 (sext, *J* = 7.2 Hz, 1H), 2.72 (dd, *J* = 13.5 Hz, 8.0 Hz), 2.40 (dd, *J* = 13.5 Hz, 7.0 Hz, 1H), 1.94 (s, 3H), 1.35 (d, *J* = 8.5 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.8, 150.8, 138.0, 135.6, 129.4, 128.9, 128.1, 127.6, 126.2, 125.7, 121.5, 45.0, 38.3, 17.6, 16.9. IR (thin film): v 3024, 2976, 2936, 1946, 1757, 1652, 1595, 1493, 1457, 1361, 1279, 1196, 1139, 1106, 1026, 919, 838, 747, 700, 501 cm^{-1}. HRMS (ESI+) (m/z): [M+Na]$^+$ calc for $C_{19}H_{20}O_2Na$, 303.1356; found, 303.1351.

3-methyl-2,4-diphenylcyclopent-2-enone (Scheme 67)



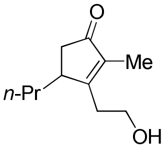
General procedure A was followed with phenyl cinnamate (0.067 g, 0.30 mmol) and phenyl-1-propyne (0.056 mL, 0.45 mmol)**.** TLC analysis indicated disappearance of phenyl cinnamate after 1 hour. Purification by column chromatography (10% EtOAc/Hexanes) gave the product as a colorless oil and as a 95:5 mixture of regioisomers (0.072 g, 97%) (95:5 crude regioisomer mixture). ^{1}H NMR (500 MHz CDCl$_3$): δ 7.40-7.35 (m, 2H), 7.33-7.38 (m, 5H), 7.25-7.31 (m, 1H), 7.16-7.20 (m, 2H), 3.96 (d, *J* = 6.5 Hz, 1H), 3.07 (dd, *J* = 19.0 Hz, 7.0 Hz, 1H), 2.55 (dd, *J* = 19.0 Hz, 2.5 Hz, 1H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 206.6, 173.2, 141.7, 140.7, 131.5, 129.1, 129.0, 128.2, 127.8, 127.3, 127.1, 49.1, 44.9, 16.6. IR (thin film): v 3380, 3058, 3026, 2924, 1952, 1884, 1810, 1699, 1636, 1599, 1495, 1454, 1444, 1407, 1378, 1338, 1309, 1279, 1227, 1199, 1137, 1076, 1030, 1002, 946, 934, 919, 847, 761, 699, 673 cm^{-1}. HRMS (ESI+) (m/z): $[M+Na]^+$ calc for $C_{18}H_{16}ONa$, 271.1099; found, 271.1095. The minor regioisomer matched the spectra from the literature.[5]

5-methyl-3-octylcyclopent-2-enone (Scheme 67)



General procedure B was followed with phenyl methacrylate (0.049 g, 0.3 mmol) and 1-Decyne (0.081 mL, 0.45 mmol). TLC analysis indicated disappearance of the phenyl methacrylate upon completion of the 1.5 hour syringe drive (97:3 crude regioselectivity). Purification with column chromatography (5% EtOAc/Hexanes) gave the product as a colorless oil and as a single regioisomer (90-95% pure, 0.041g, 63%). ^{1}H NMR (400 MHz $CDCl_3$):): 5.89 (m, 1H), 2.81 (dd, *J* = 18.4 Hz, 6.8 Hz, 1H), 2.36-2.41 (m, 3H), 2.16 (d, *J* = 18.8 Hz, 1H), 1.55-1.58 (m, 2H), 1.20-1.30 (m, 10H), 1.17 (d, *J* = 7.6 Hz), 0.88 (t, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.70, 181.37, 128.12, 40.68, 40.37, 33.47, 31.80, 29.32, 29.30, 29.15, 27.02, 22.62, 16.48, 14.07. . IR (thin film): v 2927, 2856, 1707, 1618, 1458, 1432, 1371, 1337, 1265, 1174, 1019, 875, 780, 723, 621 cm^{-1}. HRMS (EI) (m/z): $[M]^+$ calc for $C_{14}H_{24}O$, 208.1827; found, 208.1831.

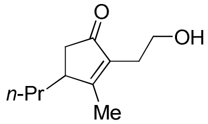
3-(2-hydroxyethyl)-2-methyl-4-propylcyclopent-2-enone (Major Regioisomer) (Scheme 67)



General procedure B was followed with (E)-phenyl hex-2-enoate (0.057 g, 0.30 mmol) and 3-pentyn-1-ol (0.041 mL, 0.45 mmol). TLC analysis indicated disappearance of the (E)-phenyl hex-2-enoate 2 hours after syringe drive completion. Purification with column chromatography

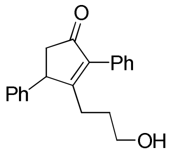
(50% EtOAc/Hexanes) gave the product as a colorless oil and as a mixture of regioisomers (0.037 g, 68%) (87:13 crude regioisomer mixture). Further purification by column chromatography (15% acetone/hexanes) gave the major regioisomer. ^{1}H NMR (500 MHz $CDCl_3$): δ 3.83 (m, 2H), 2.78-2.84 (m, 2H), 2.60 (dt, *J* = 10.0 Hz, 6.6 Hz, 1H), 2.53 (dd, *J* = 19.0 Hz, 6.5 Hz, 1H), 2.07 (dd, *J* = 18.5 Hz, 2.0 Hz, 1H), 1.73-1.79 (m, 4H), 1.48 (t, *J* = 5.0 Hz, 1H), 1.24-1.39 (m, 2H), 1.16 (dtd, *J* = 13.0 Hz, 9.8 Hz, 4.9 Hz, 1H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.0, 172.4, 138.1, 60.4, 40.8, 40.5, 35.3, 32.1, 20.5, 14.1, 8.2. IR (thin film): ν 3423, 2956, 2872, 1697, 1638, 1466, 1408, 1383, 1342, 1205, 1148, 1049, 963, 912, 862, 747, 556 cm^{-1}. HRMS (EI) (m/z): $[M]^+$ calc for $C_{11}H_{18}O_2$, 182.1307; found, 182.1305.

2-(2-hydroxyethyl)-3-methyl-4-propylcyclopent-2-enone (Minor Regioisomer) (Scheme 67)



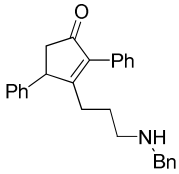
The minor regioisomer was obtained in an enriched form (66:34 major:minor) from a mixture of regioisomers after further purification by column chromatography (15% acetone/hexanes). ^{1}H NMR (400 MHz $CDCl_3$): δ 3.83 (m, $2H_{major}$), 3.67 (q, *J* = 5.9 Hz, $2H_{minor}$) 2.78-2.84 (m, $2H_{major}$ + $1H_{minor}$), 2.68-2.75 (m, $1H_{minor}$) 2.50-2.63 (m, $2H_{major}$ +$1H_{minor}$), 2.46 (t, *J* = 5.8 Hz, $2H_{minor}$) 2.11 (dd, *J* = 18.8 Hz, 1.6 Hz, $1H_{minor}$) 2.07 (dd, *J* = 18.5 Hz, 2.0 Hz, $1H_{major}$), 2.03 (s, $3H_{minor}$) 1.73-1.79 (m, $4H_{major}$ + $1H_{minor}$), 1.48 (t, *J* = 5.0 Hz, $1H_{major}$), 1.09-1.40 (m, 3H), 0.943 (t, *J* = 7.2 Hz, $3H_{minor}$) 0.937 (t, *J* = 7.3 Hz, $3H_{major}$). ^{13}C NMR (126 MHz, C_6D_6): δ 208.5, 206.7, 173.7, 170.8, 138.6, 138.0, 61.5, 60.2, 42.8, 40.7, 40.5, 40.4, 35.3, 35.0, 32.1, 27.9, 20.6, 20.3, 14.6, 14.19, 14.16, 8.3. IR (thin film): ν 3423, 2956, 2872, 1697, 1638, 1466, 1408, 1383, 1342, 1205, 1148, 1049, 963, 912, 862, 747, 556 cm^{-1}. HRMS (EI) (m/z): $[M]^+$ calc for $C_{11}H_{18}O_2$, 182.1307; found, 182.1305.

3-(3-hydroxylpropyl)-2-4-diphenylcyclopent-2-enone (Scheme 67)



General procedure A was followed with phenyl cinnamate (0.067 g, 0.30 mmol) and 5-phenylpent-4-yn-1-ol (0.072 g, 0.45 mmol). TLC analysis indicated disappearance of the phenyl cinnamate after 1 hour. Purification by column chromatography (35% EtOAc/Hex) gave a single regioisomer (0.078 g, 89%).^{1}H NMR (400 MHz CDCl$_3$): δ 7.39-7.435 (m, 2H), 7.24-7.35 (m, 6H), 7.17-7.19 (m, 2H), 4.10 (dd, *J* = 7.2 Hz, 2.0 Hz, 1H), 3.39-3.45 (m, 2H), 3.04 (dd, *J* = 19.0 Hz, 7.0 Hz, 1H), 2.62 (ddd, *J* = 14.0 Hz, 9.5 Hz, 4.9 Hz, 1H), 2.51 (dd, *J* = 18.5 Hz, 2.3 Hz, 1H), 2.12 (ddd, *J* = 14.0 Hz, 9.5 Hz, 4.9 Hz, 1H), 1.62-1.78 (m, 1H), 1.50-1.60 (m, 1H), 1.37-1.44 (bs, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 207.0, 176.2, 141.6, 141.4, 131.5, 129.07, 129.06, 128.4, 127.9, 127.4, 127.2, 62.1, 46.5, 45.1, 30.1, 25.8. IR (thin film): v 3430 br, 3027, 2930, 1697, 1632, 1598, 1494, 1454, 1348, 1139, 1058, 929, 757, 700, 505 cm^{-1}. HRMS (ESI+) (m/z): [M+Na]$^+$ calc for $C_{20}H_{19}O_2Na$, 315.1361; found, 382.1355.

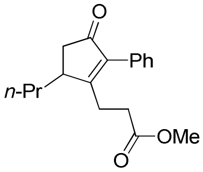
3-(3-(benzylamino)propyl)-2,4-diphenylcyclopent-2-enone (Scheme 67)



General procedure A was followed with phenyl cinnamate (0.067 g, 0.30 mmol) and N-benzyl-5-phenylpent4-yn-1-amine (0.112 g, 0.45 mmol). TLC analysis indicated disappearance of the phenyl cinnamate after 1 hour. Purification by column chromatography (30% EtOAc/Hex, 2% NEt$_3$) gave the product as a colorless oil and as a single regioisomer (0.089 g, 78%).^{1}H NMR (400 MHz CDCl$_3$): δ 7.42-7.45 (m, 2H), 7.24-7.37 (m, 9H), 7.19-7.21 (m, 4H), 4.11 (dd, *J* = 8.5

Hz, 1.8 Hz, 1H), 3.63 (s, 2H), 3.06 (dd, *J* = 19.2 Hz, 7.2 Hz, 1H), 2.63 (ddd, *J* = 13.6 Hz, 9.6 Hz, 6.7 Hz, 1H), 2.53 (dd, *J* = 19.0 Hz, 2.0 Hz, 1H), 2.43-2.55 (m, 2H), 2.12 (ddd, *J* = 14.0 Hz, 9.5 Hz, 5.5 Hz, 1H), 1.54-1.64 (m, 1H), 1.49-1.53 (m, 1H), 0.9-1.05 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.5, 176.4, 141.7, 141.4, 140.1, 131.6, 129.11, 129.10, 128.4, 128.3, 128.0, 127.9, 127.4, 127.2, 126.9, 53.6, 48.7, 46.5, 45.1, 27.5, 27.1. IR (thin film): v 3326, 3082, 3058, 3025, 2928, 2817, 1950, 1876, 1810, 1698, 1631, 1598, 1493, 1453, 1407, 1346, 1305, 1277, 1224, 1135, 1075, 1029, 1001, 926, 736, 698, 617, 600, 577, 538, 508 cm^{-1}. HRMS (ESI+) (m/z): $[M+Na]^+$ calc for $C_{27}H_{27}NONa$, 382.2171; found, 382.2159.

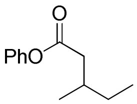
Methyl 3-(3-oxo-2-phenyl-5-propylcyclopent-1-enyl)proponoate (Major Regioisomer) (Scheme 67)



General procedure A was followed with (E)-phenyl hex-2-enoate (0.057 g, 0.30 mmol) and methyl 5-phenylpent-4-ynoate (0.085 mL, 0.45 mmol). TLC analysis indicated disappearance of the (E)-phenyl hex-2-enoate after 1 hour. Purification by column chromatography (20% EtOAc/Hexanes) gave the product as a mixture of regioisomers (0.067 g, 78%) (92:8 crude regioisomer mixture). Further purification by column chromatography gave yielded the major regioisomer. ^{1}H NMR (400 MHz $CDCl_3$): δ 7.36-7.42 (m, 2H), 7.30-7.35 (m, 1H), 7.20-7.22 (m, 2H), 3.63 (s, 3H), 3.01 (ddd, *J* = 14.8 Hz, 9.4 Hz, 7.0 Hz, 1H), 2.90-2.94 (m, 1H), 2.68 (dd, *J* = 18.4 Hz, 6.8 Hz, 1H), 2.65-2.73 (m, 1H), 2.52 (ddd, *J* = 16.0 Hz, 9.6 Hz, 6.2 Hz, 1H), 2.41 (ddd, *J* = 16.4 Hz, 9.4 Hz, 7.0 Hz, 1H), 2.25 (dd, *J* = 18.8 Hz, 2.4 Hz, 1H), 1.77-1.85 (m, 1H), .125-1.45 (m, 3H), 0.98 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.6, 175.2, 172.4, 141.3, 131.5, 128.9, 128.3, 127.7, 51.7, 40.8, 39.7, 35.0, 31.3, 24.2, 20.3, 14.0. IR (thin film): v

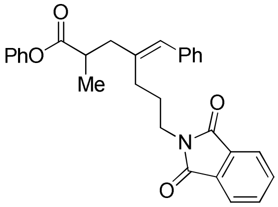
3056, 2956, 2931, 2872, 1738, 1703, 1634, 1598, 1495, 1438, 1345, 1260, 1175, 1030, 990, 949, 929, 893, 866, 765, 701, 604, 578, 500 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{18}H_{23}O_3$, 287.1642; found, 287.1642. Diagnostic peaks for the minor isomer seen in an attached enriched 1H NMR spectrum are as follows: 3.58 (s, 3H), 3.23 (m, 1H), 1.02-1.15 (m, 1H), 0.82 (t, *J* = 7.4 Hz, 3H).

Phenyl 3-methylpentanoate, (Scheme 72)



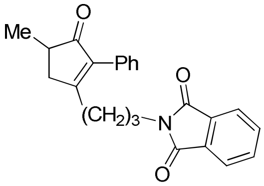
$Ni(COD)_2$ (8.3 mg, 0.03 mmol, 0.1 equiv) and tri-tert-butylphosphine (12 mg, 0.06mmol) were weighed out separately under an inert atmosphere. After placement on a schlenk line, $Ni(COD)_2$ was solvated in 1 mL of THF and the phosphine was cannulated over in 1.5 mL of THF. The catalyst was stirred for 10-15 min and the rest of the procedure follows General Procedure A using phenyl 3-butenoate (0.049 g, 0.3 mmol) and 7-tetradecyne (0.10 mL, 0.45 mmol). The product was obtained as an impure colorless oil after column chromatography (5% EtOAc/Hexanes) (0.043 g, 75%). ^1H NMR (500 MHz $CDCl_3$): δ 7.38-7.41 (m, 2H), 7.24 (m, 1H), 7.08-7.10 (m, 2H), 2.58 (dd, J = 14.5 Hz, J = 6.0 Hz, 1H), 2.37 (dd, J = 14.5 Hz, J = 8.0 Hz, 1H), 2.05 (oct, J = 6.5 Hz, 1H), 1.47 (dqd, J = 13.8 Hz, J = 7.5 Hz, J = 5.5 Hz, 1H), 1.33 (dquin, J = 13.5 Hz, J = 7.5 Hz, 1H), 1.06 (d, J = 6.5 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 150.7, 129.4, 125.7, 121.6, 41.4, 32.1, 29.3, 19.3, 11.3.

(E)-phenyl 4-benzylidene-7-(1,3-dioxoisoindolin-2-yl)-2-methylheptanoate (Table 14, Entry 1)



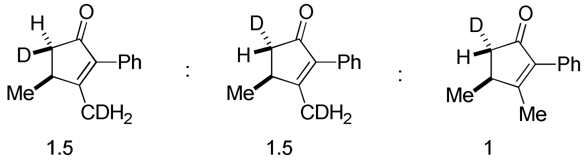
General Procedure A was followed using phenyl methacrylate (49 mg, 0.3 mmol, 1.0 equiv), 2-(5-phenylpent-4-yn-1-yl)isoindoline-1,3-dione (130 mg, 0.45 mmol, 1.5 equiv). The reaction was complete after 1 hour. Column chromatography yielded impure reductive coupling product (0.01 g, 8%). ^{1}H NMR (500 MHz CDCl$_3$): δ 7.81-7.83 (m, 2H), 7.70-7.71 (m, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.18-7.21 (m, 3H), 7.09-7.14 (m, 3H), 7.03 (d, J = 7.5 Hz, 2H), 6.43 (s, 1H), 3.66 (t, J = 7.0 Hz, 2H), 2.97 (sept, J = 7.0 Hz, 1H), 2.73 (dd, J = 14.0 Hz, J = 8.5 Hz, 1H), 2.31-2.42 (m, 3H), 1.90 (quin, J = 8.0 Hz, 2H), 1.35 (d, J = 6.5 Hz, 3H).

2-(3-(4-methyl-3-oxo-2-phenylcyclopent-1-en-1-yl)propyl)isoindoline-1,3-dione (Table 14, Entry 1, 148)



General Procedure A was followed using phenyl methacrylate (49 mg, 0.3 mmol, 1.0 equiv), 2-(5-phenylpent-4-yn-1-yl)isoindoline-1,3-dione (130 mg, 0.45 mmol, 1.5 equiv). The reaction was complete after 1 hour. Column chromatography yielded impure reductive coupling product (0.06 g, 43%). ^{1}H NMR (500 MHz CDCl$_3$): δ 7.82-7.83 (m, 2H), 7.72-7.73 (m, 2H), 7.33-7.36 (m, 2H), 7.26-7.30 (m, 1H), 7.18-7.20 (m, 2H), 3.67 (t, J = 7.5 Hz, 2H), 2.94 (dd, J = 18.5 Hz, J = 7.0 Hz, 1H), 2.59 (t, J = 7.0 Hz, 2H), 2.54 (quind, J = 7.3 Hz, J = 5.0 Hz, 1H), 2.29 (d, J = 18.5 Hz, 1H), 1.95 (quin, J = 7.5 Hz, 2H), 1.25 (d, J = 7.5 Hz, 3H).

Scheme 81



General procedure A was followed with phenyl 3-butenoate (0.049 g, 0.3 mmol) and 1-phenyl-1-propyne (0.056 mL, 0.45 mmol) and CD_3OD (0.1 mL) in place of methanol. The reaction was run for 2 hours then worked up using the general workup procedure. The product was obtained as a single regioisomer after column chromatography (10% EtOAc/Hexanes) as a colorless oil (0.047 g, 84%). ^{1}H NMR (500 MHz C_6D_6): δ 7.42-7.43 (m, 2H), 7.26 (t, J = 7.5 Hz, 2H), 7.14-7.16 (m, 1H), 2.34-2.40 (m, 0.5H), 2.07 (m, 1H), 1.79-1.83 (m, 0.75H), 1.6 (s, 1.5H), 1.58 (m, 0.8H). 0.69 (d, J = 7.0 Hz, 3H).

3,4-dimethyl-2-phenylcyclopent-2-enone (Scheme 82)

General procedure A was followed with phenyl 3-butenoate (0.049 g, 0.3 mmol) and 1-phenyl-1-propyne (0.056 mL, 0.45 mmol) without the use of methanol. The reaction was run for 3 hours and was then quenched by adding dppe (60 mg, 50 mol %) followed by CD_3OD after stirring 1 min. The general workup procedure was then used. The product was obtained as an impure single regioisomer after column chromatography (10% EtOAc/Hexanes) as a colorless oil (0.02 g, 37%). ^{1}H NMR (500 MHz C_6D_6): δ 7.42-7.43 (m, 2H), 7.26 (t, J = 7.5 Hz, 2H), 7.14-7.16 (m, 1H), 2.37 (dd, J = 18.0 Hz, J = 6.5 Hz, 1H), 2.08 (quin, J = 7.0 Hz, 1H), 1.80 (d, J = 18.5 Hz, 1H), 1.60 (s, 3H), 0.69 (d, J = 7.0 Hz, 3H).

5.3. Nickel-Catalyzed Alkylative Cycloaddition Procedure

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, inc. Model # SPS-400-3 and PS-400-3. Enoates were distilled prior to use. $Ni(COD)_2$ (Strem Chemicals, Inc., used as received), 1,3-Bis(2,4,6-trimethyl-phenyl)imidazolium chloride (IMes·HCl), and potassium *tert*-butoxide was stored and weighed in an inert atmosphere glovebox. Tri-N-butylphosphine was freshly distilled and used under an inert atmosphere. Aldehydes were freshly distilled using a Buchi GKR-51 kuegelrhor. All reactions were conducted in flame-dried or oven dried (120 °C) glassware under nitrogen atmosphere. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at rt (25 °C), unless otherwise noted, on a Varian Mercury 400 MHz, Varian Unity 500 MHz instrument, or Varian Unity 700 MHz Instrument. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.26 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory. HPLC purification was conducted using either a Shimadzu LC-8A HPLC with a Grace PN 81116 Alltima Silica 5µm 250 x 10mm prep column or a Waters Delta 600 Agilent Zorbax RX-SIL Prep HT 21.2 x 250 mm 7µm column.

General Procedure A:

$Ni(COD)_2$ (8 mg, 0.03mmol, 0.1 equiv) was added to a vial in the glovebox and the vial was then plugged a rubber septum, removed from the glovebox and attached to a nitrogen atmosphere filled schlenk line. Toluene (1.5 mL) was then added to the vial and the catalyst was allowed to stir for a few minutes before tri-N-butylphosphine (15µL, 0.06 mmol, 0.2 equiv) was added dropwise turning the pale yellow catalyst solution to bright yellow. Next, enoate (0.3 mmol, 1 equiv) was weighed out into a separate vial and the vial was placed under a nitrogen atmosphere and purged three times with nitrogen. Alkyne (0.45 mmol 1.5 equiv) and aldehyde (0.45 mmol, 1.5 equiv) were then added to the substrate vial via syringe and the vial was purged with nitrogen twice more. Toluene (0.5 mL) was added to the combined substrates and this solution was cannulated over to the catalyst solution washing twice with toluene (0.5 mL) resulting in a red reaction. Triethylborane (217µL, 1.5 mmol, 5 equiv) was then added immediately to the reaction via syringe and the reaction was placed in a preheated 90 °C oil bath and stirred for 2 hours before quenching with 1.5 mL saturated NH_4Cl.

General Procedure B:

$Ni(COD)_2$ (8 mg, 0.03mmol, 0.1 equiv), IMes·HCl (10 mg, 0.03 mmol, 0.1 equiv), and t-BuOK (3 mg, 0.03 mmol, 0.1 equiv) were added sequentially to a flame dried vial in the glovebox. The vial was then plugged with a rubber septum, removed from the glovebox and attached to a nitrogen atmosphere filled schlenk line. Toluene (1.5 mL) was then added to the catalyst resulting in a black-yellow or brown solution after 10 minutes of stirring. The rest of the procedure is identical to procedure A.

General Procedure C:

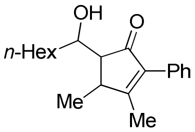
$Ni(COD)_2$ (8 mg, 0.03mmol, 0.1 equiv), IMes·HCl (10 mg, 0.03 mmol, 0.1 equiv), and t-BuOK (3 mg, 0.03 mmol, 0.1 equiv) were added sequentially to a flame dried vial in the glovebox. The vial was then plugged with a rubber septum, removed from the glovebox and attached to a nitrogen atmosphere filled schlenk line. Toluene (2.0 mL) was then added to the catalyst resulting in a black-yellow or brown solution after 10 minutes of stirring. Next, enoate (0.3 mmol, 1 equiv) was weighed out into a separate vial and the vial was placed under a nitrogen atmosphere and purged three times with nitrogen. Alkyne (0.45 mmol 1.5 equiv) was then added to the substrate vial and the vial was purged twice more with nitrogen. Toluene (0.5 mL) was added to the substrate vial followed by addition of triethylborane (217µL, 1.5 mmol, 5 equiv) by syringe. The substrate and reducing agent solution was drawn up into a syringe and the vial was washed with toluene twice (0.25 mL) resulting in a substrate solution volume of 1.0 mL. Aldehyde (0.45 mmol, 1.5 equiv) was then added via syringe to the stirred catalyst solution and the vial was placed in a pre-heated 90 °C oil bath followed by a 10 min addition of the 1 mL solution of substrates and reducing agent with a syringe drive. The reaction was stirred for 2 hours before quenching with 1.5 mL of saturated NH_4Cl.

General Workup Procedure:

The reaction is quenched with 1.5 saturated NH_4Cl and then washed into a separatory funnel. The organic and aqueous layers are then separated and the aqueous layer is extracted twice with methylene chloride (2 mL). The organic layers were then combined and washed with 10 mL of 0.5 M NaOH followed by brine (10 mL). The organic layers are then dried with Na_2SO_4 and filtered through a pad of silica washing with 50/50 EtOAc/Hex. The solution was then concentrated to yield the crude isolate.

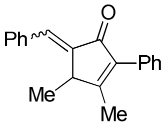
5.4 Nickel-Catalyzed [3+2]-Alkylative Cycloaddition Product Characterization

5-(1-hydroxyheptyl)-3,4-dimethyl-2-phenylcyclopent-2-enone (Table 25, Entry 6)



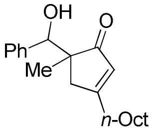
General Procedure A was followed using phenyl 3-butenoate (49 mg, 0.3 mmol, 1 equiv) and 1-phenyl-1-propyne (75 µL, 0.6 mmol, 2.0 equiv), and heptaldehyde (84 µL, 0.6 mmol, 2.0 equiv) at 50 °C. The reaction was run overnight then worked up using the general workup procedure. Column chromatography yielded the product as a mixture of diastereomers contaminated with reductive cycloaddition product (calc. 0.046 g, 51%). Major Diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.44 (m, 2H), 7.36-7.38 (m, 1H), 7.28-7.32 (m, 2H), 4.40 (s, 1H), 3.74 (t, J = 8.5 Hz, 1H), 2.52-2.53 (m, 1H), 2.10-2.15 (m, 4H), 1.61-1.62 (m, 2H), 1.40-1.44 (m, 1H), 1.25-1.35 (m, 10H), 0.89 (t, J = 6.5 Hz, 3H). Minor Diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.41 (m, 2H), 7.28-7.33 (m, 3H), 4.20 (d, J = 3.0 Hz, 1H), 2.84-2.85 (m, 1H), 2.24 (t, J = 2.5 Hz, 1H), 2.15 (s, 3H), 2.09 (d, J = 5.5 Hz, 1H), 1.52-1.60 (m, 3H), 1.30-1.34 (m, 10H), 0.89 (t, J = 6.5 Hz, 3H).

Elcb Elimination Product, Mixture of Diastereomers (Scheme 86)



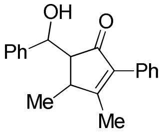
The E1cb elimination product could be isolated from the reaction by column chromatography. Extremely impure compounds were isolated so no spectra will be given. Characteristic peaks of each diastereomer are given as follows: ^{1}H NMR (500 MHz, CDCl$_3$): Major Diastereomer: δ 3.83 (q, J = 6.5 Hz, 1H), 2.26 (s, 3H), 1.33 (d, J = 7.0 Hz, 3H). Minor Diastereomer: δ 3.73 (q, J = 7.0 Hz), 2.22 (s, 3H), 1.07 (d, J = 7.5 Hz, 3H).

5-(hydroxy(phenyl)methyl)-5-methyl-3-octylcyclopent-2-enone (Table 26, Entry 7)



General Procedure B was followed using phenyl methacrylate (49 mg, 0.3 mmol, 1.0 equiv), 1-Decyne (81 µL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was allowed to go overnight and then worked up using the general workup procedure. Column chromatography yielded the product as a mixture of impure diastereomers (0.017 g, 17%, ~2:1 ratio). Major Diastereomer: ^{1}H NMR (400 MHz, CDCl$_3$):): δ 7.28-7.36 (m, 5H), 5.88 (s, 1H), 4.87 (d, J = 3.6 Hz, 1H), 3.02 (d, J = 18.4 Hz, 1H), 2.58 (d, J = 4.0 Hz, 1H), 2.34 (t, J = 7.6 Hz, 2H), 1.97 (d, J = 18.0 Hz, 1H), 1.48-1.51 (m, 2H), 1.20-1.28 (m, 10H), 1.03 (s, 3H), 0.87 (t, J = 6.4 Hz, 3H). Minor Diastereomer: ^{1}H NMR (400 MHz, CDCl$_3$):): δ 7.27-7.35 (m, 5H), 5.79 (s, 1H), 4.74 (s, 1H), 3.96 (s, 1H), 2.72 (d, J = 18.8 Hz, 1H), 2.29 (t, J = 7.6 Hz, 2H), 2.01 (d, J = 18.8 Hz, 1H), 1.44-1.50 (m, 3H), 1.20-1.29 (m, 12H), 0.87 (t, J = 6.8 Hz, 3H).

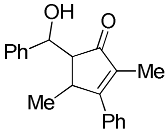
5-(hydroxy(phenyl)methyl)-3,4-dimethyl-2-phenylcyclopent-2-enone (Scheme 89)



General Procedure A was followed using phenyl 3-butenoate (49 mg, 0.3 mmol, 1 equiv) and 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and NMR of the crude isolate revealed the product in an isomeric ratio of 69:26:5. Column chromatography (5 to 20% EtOAc/Hex) yielded the products 20 mg and 30 mg of product whose NMR matched that previously published (50 mg, 57%).[72]

General Procedure B was followed using phenyl 3-butenoate (49 mg, 0.3 mmol, 1 equiv) and 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and NMR of the crude isolate revealed the product in an isomeric ratio of 45:35:20. Column chromatography (5 to 20% EtOAc/Hex) yielded the products 16.5 mg and 37 mg of product whose NMR matched that previously published (54 mg, 61%).

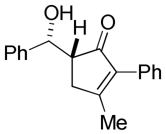
5-(hydroxy(phenyl)methyl)-2,4-dimethyl-3-phenylcyclopent-2-enone (Scheme 89, Minor Regioisomer, Major Diastereomer)



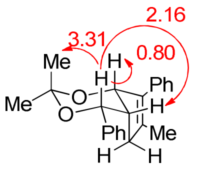
^{1}H NMR (700 MHz, CDCl$_3$): δ 7.39-7.46 (m, 4H), 7.36-7.38 (m, 3H), 7.32-7.33 (m, 2H), 7.27 (t, J = 4.2 Hz, 1H), 5.53 (t, J = 3.5 Hz, 1H), 3.37 (m, 1H), 2.57 (d, J = 4.9 Hz, 1H), 2.45 (t, J = 2.8 Hz, 1H), 1.86 (d, J = 1.4 Hz, 3H), 0.63 (d, J = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, CDCl$_3$): δ

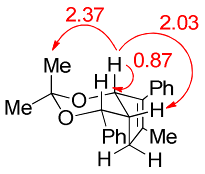
209.2, 173.4, 142.2, 135.9, 135.0, 129.1, 128.4, 128.4, 127.9, 127.3, 125.4, 71.9, 36.3, 18.9, 9.5. IR (thin film) v: 3423, 2963, 1684, 1625, 1495, 1450, 1383, 1347, 1053, 773, 740, 705 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{20}H_{20}O_2$, 293.1536; found, 279.1537.

trans-5-hydroxy(phenyl)methyl)-3-methyl-2-phenylcyclopent-2-enone (Major Diastereomer, Scheme 89)

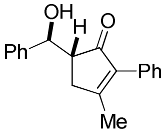


General Procedure C was followed using phenyl acrylate (44 mg, 0.3 mmol, 1 equiv), 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and purified by column chromatography (10 to 30% EtOAc/Hex) to yield an impure mixture of isomers (69:25:6). Purification of the products on the Shimadzu HPLC yielded the products as a mixture of diastereomers (84:16) (40 mg, 48%). The diastereomers could be separated after additional HPLC runs revealing the major diastereomer as a white solid and the minor as an oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.28-7.42 (m, 10H), 5.47 (t, J = 3.9 Hz, 1H), 2.94 (m, 1H), 2.73 (d, J = 18.2 Hz, 1H), 2.58 (d, J = 4.9 Hz, 1H), 2.45 (dd, J = 18.9 Hz, J = 7.4 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 207.8, 172.8, 142.4, 140.2, 131.5, 129.1, 128.4, 128.2, 127.7, 127.4, 125.6, 71.9, 52.8, 33.0, 18.4. IR (thin film) v: 3441, 3056, 2907, 1695, 1635, 1597, 1494, 1448, 1380, 1346, 1209, 1135, 1006, 964, 912, 762, 744, 701, 668, 586 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{19}H_{18}O_2$, 279.1380; found, 279.1377.



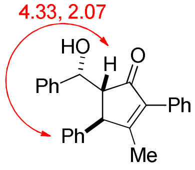


cis-5-hydroxy(phenyl)methyl)-3-methyl-2-phenylcyclopent-2-enone (Minor Diastereomer, Scheme 89)



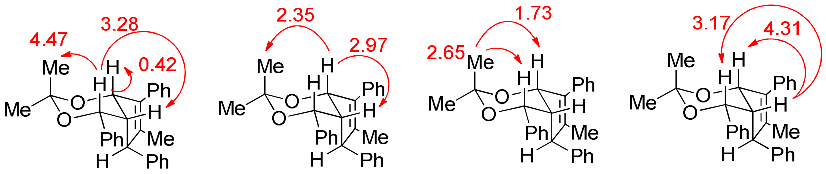
^{1}H NMR (700 MHz, CDCl$_3$): δ 7.30-7.45 (m, 10H), 4.98 (s, 1H), 4.74 (d, 9.8 Hz, 1H), 2.91 (ddd, J = 9.8 Hz, 7.0 Hz, 2.8 Hz), 2.49 (dd, J = 19.3 Hz, J = 7.3 Hz, 1H), 2.26 (d, J = 18.9 Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (176 MHz, CDCl$_3$): δ 210.3, 172.7, 141.5, 139.5, 130.1, 129.1, 128.6, 128.4, 128.2, 128.0, 75.7, 51.3, 35.7, 18.3. IR (thin film) ν: 3442, 1676, 1635, 1494, 1429, 1381, 1346, 1205, 1140, 1040, 911, 737, 701 cm^{-1}. HRMS (ESI+) (m/z): [M+Na]$^+$ calc for $C_{19}H_{18}O_2$, 301.1199; found, 301.1199.

(4R,5R)-5-((R)-hydroxy(phenyl)methyl)-3-methyl-2,4-diphenylcyclopent-2-enone (Major Diastereomer, Scheme 89)

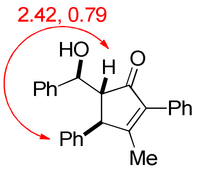


General Procedure C was followed using phenyl cinnamate (67 mg, 0.3 mmol, 1 equiv), 1-phenyl-1-propyne (56 μL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 μL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and purified by column chromatography (10 to 20% EtOAc/Hex) to yield an impure mixture of isomers

(65:29:6). Further column chromatography and HPLC purification on the Waters HPLC yielded the major diastereomer as a white solid (28 mg) and the minor diastereomer as a colorless oil (10 mg) and mixture of isomers (15 mg, 50:29:15:6) (53 mg, 50%). ^{1}H NMR (700 MHz, CDCl$_3$): δ 7.44 (t, J = 7.4 Hz, 2H), 7.34-7.39 (m, 5H), 7.28 (t, J = 7.7 Hz, 2H), 7.23 (t, J = 7.7 Hz, 1H), 7.12-7.13 (m, 3H), 6.70-6.72 (m, 2H), 5.51 (t, J = 4.2 Hz, 1H), 3.88 (d, J = 2.1 Hz, 1H), 2.92 (t, J = 3.2 Hz, 1H), 2.68 (d, 4.9 Hz, 1H), 1.91 (s, 3H). ^{13}C NMR (176 MHz, CDCl$_3$): δ 207.4, 174.4, 141.6, 141.2, 141.1, 131.4, 129.2, 128.6, 128.3, 128.2, 127.9, 127.4, 127.3, 126.7, 125.6, 72.2, 62.5, 50.3, 16.8. IR (thin film) v: 3445, 3026, 1682, 1630, 1495, 1379, 1149, 1054, 908, 763, 728, 698, 602, 574 cm^{-1}. HRMS (ESI+) (m/z): [M+H]$^+$ calc for $C_{25}H_{22}O_2$, 355.1693; found, 355.1693.

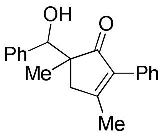


(4R,5R)-5-((S)-hydroxy(phenyl)methyl)-3-methyl-2,4-diphenylcyclopent-2-enone (Minor Diastereomer, Scheme 89)



^{1}H NMR (700 MHz, CDCl$_3$): δ 7.45-7.47 (m, 2H), 7.38-7.39 (m, 3H), 7.26-7.30 (m, 5H), 7.10-7.13 (m, 3H), 6.52 (d, J = 7.0 Hz, 2H), 4.82 (d, J = 9.8 Hz, 1H), 4.75 (s, 1H), 3.45 (s, 1H), 2.85 (dd, J = 9.8 Hz, J = 2.8 Hz, 1H), 1.91 (s, 3H). ^{13}C NMR (176 MHz, CDCl$_3$): δ 209.7, 174.5, 140.7, 140.2, 140.1, 130.8, 129.2, 128.7, 128.5, 128.4, 128.3, 128.2, 127.4, 127.3, 126.9, 75.9, 61.4, 52.7, 16.9. IR (thin film) v: 3449, 3028, 2916, 1679, 1635, 1599, 1494, 1454, 1377, 1334, 1203, 1146, 1039, 912, 761, 735, 699, 572 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{25}H_{22}O_2$, 355.1693; found, 355.1693.

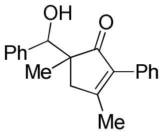
5-(hydroxy(phenyl)methyl)-3,5-dimethyl-2-phenylcyclopent-2-enone (Major Diastereomer, Scheme 89)



General Procedure A was followed using phenyl methacrylate (49 mg, 0.3 mmol, 1.0 equiv), 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was worked up using the general workup procedure and the NMR revealed the isomeric ratio of the crude to be (61:39). This crude isolate was then subjected to column chromatography (10 to 20% EtOAc/Hex) and 30 mg and 18 mg of product was isolated (48 mg, 54%). The diastereomers could be separated with additional flash chromatography revealing the major diastereomer as a white solid and the minor as a colorless oil. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.28-7.42 (m, 10H), 4.97 (d, J = 4.9 Hz, 1H), 3.12 (d, J = 18.2 Hz, 1H), 2.70 (d, J = 4.2 Hz, 1H), 2.13 (s, 3H), 2.10 (d, J = 18.2 Hz, 1H), 1.15 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 211.3, 171.2, 141.0, 138.5, 131.7, 129.1, 128.2, 128.1, 127.8, 127.6, 127.2, 76.8, 52.3, 41.7, 22.9, 18.3. IR (thin film) v: 3443, 2928, 1689, 1639, 1495, 1380, 1044, 909, 744, 700 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{20}H_{20}O_2$, 293.1536; found, 293.1533.

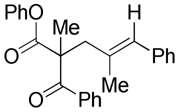
General Procedure B was followed using phenyl methacrylate (49 mg, 0.3 mmol, 1.0 equiv), 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and NMR spectroscopy revealed a 46:36:12:6 distribution of isomers. Column chromatography (10 to 20%) of the crude concentrate yielded the product as an oil in a 52:36:11 ratio (44 mg, 50%).

5-(hydroxy(phenyl)methyl)-3,5-dimethyl-2-phenylcyclopent-2-enone (Minor Diastereomer, Scheme 89)



^{1}H NMR (700 MHz, CDCl$_3$): δ 7.38-7.40 (m, 4H), 7.26-7.34 (m, 4H), 7.18 (d, J = 7.7 Hz, 2H), 4.85 (s, 1H), 3.95 (s, 1H), 2.86 (d, J = 19.6 Hz, 1H), 2.15 (d, J = 18.9 Hz, 1H), 2.08 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (176 MHz, CDCl$_3$): δ 212.4, 171.0, 140.0, 138.0, 131.3, 129.0, 128.2, 127.9, 127.8, 127.7, 127.3, 76.7, 51.2, 43.3, 18.9, 18.1. IR (thin film) v: 3443, 2929, 1688, 1638, 1495, 1452, 1381, 1046, 739, 700 cm^{-1}. HRMS (ESI+) (m/z): [M+H]$^+$ calc for $C_{20}H_{20}O_2$, 293.1536; found, 293.1532.

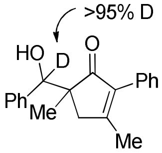
(E)-phenyl 2-benzoyl-2,4-dimethyl-5-phenylpent-4-enoate (Scheme 95, 168)



General Procedure B was followed using phenyl methacrylate (49 mg, 0.3 mmol, 1.0 equiv), 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and the crude was subjected to column chromatography (10 to 20% EtOAc/Hex). Further column chromatography (35% CH_2Cl_2/Hex) of the impure isolate yielded the pure product as a white solid (22 mg, 19%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.98 (d, J = 7.6 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.46 (t, J = 7.6

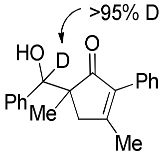
Hz, 2H), 7.11-7.30 (m, 8H), 6.69 (d, J = 8.0 Hz, 2H), 6.36 (s, 1H), 3.17 (d, J = 13.6 Hz, 1H), 3.08 (d, J = 14.0 Hz, 1H), 1.83 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (133 MHz, $CDCl_3$): δ 197.0, 172.9, 150.3, 137.7, 135.8, 133.6, 133.0, 130.9, 129.4, 129.0, 128.8, 128.6, 128.1, 126.4, 126.1, 121.0, 57.5, 47.5, 21.6, 19.6. IR (thin film) ν: 2919, 1752, 1685, 1597, 1491, 1446, 1379, 1276, 1236, 1192, 1162, 1084, 1001, 970, 923, 795, 747, 699, 689, 671, 498 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{26}H_{24}O_3$, 385.1798; found, 385.1809.

5-(1-deutero,1-hydroxy(phenyl)methyl)-3,5-dimethyl-2-phenylcyclopent-2-enone (Major Diastereomer, Scheme 96)



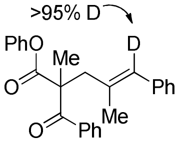
General Procedure B was followed using phenyl methacrylate (49 mg, 0.3 mmol, 1.0 equiv), 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and D-benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and the crude was subjected to column chromatography (10 to 20% EtOAc/Hex). Further purification on the Waters HPLC yielded the pure major diastereomer as a white solid (25 mg) and the minor diastereomer as a colorless oil (15 mg) (40 mg, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26-7.42 (m, 10H), 3.12 (d, J = 18.4 Hz, 1H), 2.69 (s, 1H), 2.08-2.12 (m, 4H), 1.14 (s, 3H). ^{13}C NMR (176 MHz, CD_3CN): δ 211.3, 172.3, 143.0, 138.7, 133.6, 130.2, 129.1, 128.8, 128.5, 128.5, 128.4, 77.0 (t, J = 22.4), 53.1, 41.7, 22.9, 18.3. IR (thin film) ν: 3445, 3056, 1688, 1638, 1598, 1494, 1446, 1380, 1345, 1221, 1117, 1057, 901, 779, 743 cm^{-1}. $[M+H]^+$ calc for $C_{20}H_{19}O_2D$, 294.1599; found, 293.1598.

5-(1-deutero,1-hydroxy(phenyl)methyl)-3,5-dimethyl-2-phenylcyclopent-2-enone (Major Diastereomer, Scheme 96)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (t, J = 6.8 Hz, 4H), 7.27-7.34 (m, 4H), 7.16 (d, J = 7.2 Hz, 2H), 3.92 (s, 1H), 2.84 (d, J = 19.2 Hz, 1H), 2.13 (d, J = J = 19.2 Hz, 1H), 2.06 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (176 MHz, CD_3CN): δ 211.5, 172.6, 142.3, 139.3, 133.2, 130.0, 128.9, 128.5, 128.3, 128.3, 127.8, 77.2 (J = 22.1 Hz), 53.6, 42.3, 21.6, 17.8. IR (thin film) v: 3443, 3056, 2928, 1684, 1637, 1597, 1495, 1447, 1380, 1345, 1232, 1089, 1058, 1031, 904, 873, 776, 737, 701, 666, 546 cm^{-1}. $[M+H]^+$ calc for $C_{20}H_{19}O_2D$, 294.1599; found, 293.1592.

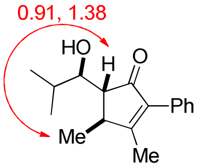
(E)-5-Deutero-Phenyl-2-benzoyl-2,4-dimethyl-5-phenylpent-4-enoate (Scheme 96)



General Procedure B was followed using phenyl methacrylate (49 mg, 0.3 mmol, 1.0 equiv), 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and D-benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and the crude was subjected to column chromatography (10 to 20% EtOAc/Hex). Further column chromatography (2.5% Acetone/Hex) of the impure isolate yielded the pure product as a white solid (26 mg, 23%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.33 (t, J = 7.8 Hz, 2H), 7.17-7.29 (m, 6H), 6.74 (d, J = 8.0 Hz, 2H), 3.22 (d, J =

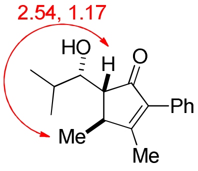
14.0 Hz, 1H), 3.13 (d, J = 14.0 Hz, 1H), 1.89 (s, 3H), 1.80 (s, 3H). NMR (176 MHz, CDCl$_3$): δ 197.0, 172.9, 150.3, 137.6, 135.9, 133.5, 132.9, 130.6 (t, J = 22.8 Hz) 129.4, 129.0, 128.8, 128.6, 128.1, 126.4, 126.1, 121.0, 57.5, 47.4, 21.6, 19.6. IR (thin film) v: 3057, 1753, 1684, 1597, 1492, 1446, 1378, 1304, 1192, 1089, 1024, 1001, 969, 936, 796, 748 cm^{-1}. HRMS (ESI+) (m/z): [M+H]$^+$ calc for $C_{26}H_{23}O_3D$, 386.1861; found, 386.1861.

(4S,5R)-5-((R)-1-hydroxy-2-methylpropyl)-3,4-dimethyl-2-phenylcyclopent-2-enone (Major Diastereomer, Scheme 89)

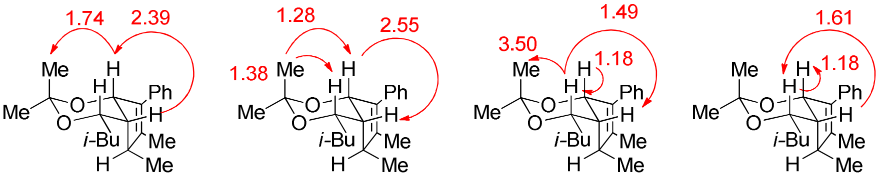


General Procedure A was followed using phenyl 3-butenoate (49 mg, 0.3 mmol, 1 equiv) and 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and isobutyraldehyde (41 µL, 0.45 mmol, 1.5 equiv). Procedural Note: This reaction was conducted in a sealed tube instead of a vial. The reaction was worked up using the general workup procedure and NMR of the crude reaction revealed a (37:63) ratio of isomers. The crude isolate was subjected to column chromatography (5 to 20% EtOAc/Hex) followed by purification on a Waters HPLC (97:3 Hex/(20% *i*-PrOH/Hex) yielding 18 mg of the major diastereomer as a colorless oil and 22 mg of the minor diastereomer as a white solid (40 mg, 52%). ^{1}H NMR (700 MHz, CDCl$_3$): δ 7.41 (t, J = 7.7 Hz, 2H), 7.33 (t, J = 6.3 Hz, 1H), 7.28 (d, J = 7.7 Hz, 2H), 4.39 (s, 1H), 3.58 (d, J = 9.1 Hz, 1H), 2.53 (q, J = 6.5 Hz, 1H), 2.22 (d, J = 9.8 Hz, 1H), 2.15 (s, 3H), 1.86 (quin, J = 6.3 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, CDCl$_3$): δ 210.5, 176.0, 139.2, 131.2, 129.1, 128.3, 127.8, 76.6, 55.4, 41.5, 31.4, 20.4, 18.0, 15.9, 14.9. IR (thin film) ν: 3455, 2963, 1675, 1635, 1598, 1493, 1419, 1380, 1342, 1270, 1154, 1003, 733, 699 cm^{-1}. HRMS (ESI+) (m/z): [M+H]$^+$ calc for $C_{17}H_{22}O_2$, 259.1693; found, 259.1694.

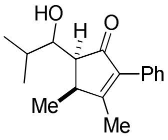
(4S,5R)-5-((S)-1-hydroxy-2-methylpropyl)-3,4-dimethyl-2-phenylcyclopent-2-enone (Minor Diastereomer, Scheme 89)



^{1}H NMR (700 MHz, $CDCl_3$): δ 7.40 (t, J = 7.7 Hz, 2H), 7.27-7.35 (m, 3H), 3.90 (ddd, J = 8.5 Hz, J = 5.5 Hz, J = 2.5 Hz, 1H), 2.95 (q, J = 5.4 Hz, 1H), 2.37 (t, J = 2.8 Hz, 1H), 2.15 (s, 3H), 1.90 (dsept, J = 2.5 Hz, J = 6.5 Hz, 1H), 1.73 (d, J = 5.0 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.1, 176.2, 139.9, 131.9, 129.2, 128.2, 127.6, 76.8, 56.8, 38.5, 31.8, 19.7, 19.1, 18.6, 15.9. IR (thin film) ν: 3439, 2961, 1685, 1635, 1598, 1444, 1379, 1341, 1152, 1079, 997, 751, 700 cm^{-1}. HRMS (ESI+) (m/z): [M+H]$^+$ calc for $C_{17}H_{22}O_2$, 259.1693; found, 259.1698.



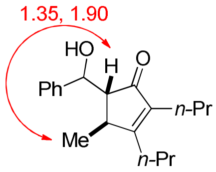
Cis-1-hydroxy-2-methylpropyl)-3,4-dimethyl-2-phenylcyclopent-2-enone (Minor Diastereomer, Scheme 89)



^{1}H NMR (700 MHz, $CDCl_3$): δ 7.40 (t, J = 7.7 Hz, 2H), 7.29-7.32 (m, 3H), 3.98 (dt, J = 7.0 Hz, 5.6 Hz, 1H), 3.06 (quin, J = 7.0 Hz, 1H), 2.79 (t, J = 6.3 Hz, 1H), 2.35 (sept, J = 7.0 Hz, 1H), 2.17 (s, 3H), 1.82 (d, J = 5.6 Hz, 1H), 1.40 (d, J = 7.7 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 206.9, 175.4, 138.5, 131.7, 129.2, 128.2, 127.6, 75.1, 53.6, 41.8, 30.4, 19.8, 18.0, 16.6, 16.3. IR (thin film) ν: 3499, 2960, 1690, 1639, 1600, 1493, 1444, 1382, 1341, 1082, 993, 923, 760, 700 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{17}H_{22}O_2$, 259.1693; found, 259.1697.

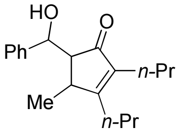
General Procedure B was followed using phenyl 3-butenoate (49 mg, 0.3 mmol, 1 equiv) and 1-phenyl-1-propyne (56 µL, 0.45 mmol, 1.5 equiv), and isobutyraldehyde (41 µL, 0.45 mmol, 1.5 equiv). Procedural Note: This reaction was conducted in a sealed tube instead of a vial. The reaction was worked up using the general workup procedure and was then subjected to column chromatography (5 to 20% EtOAc/Hex) revealing the single minor diastereomer product along with a small amount of the cis-diastereomer (86:14). Further purification on the Waters HPLC (97:3 Hex/(*i*-PrOH/Hex)) yielded the final product as a white solid (14 mg, 18%).

trans-5-(hydroxy(phenyl)methyl)-4-methyl-2,3-dipropylcyclopent-2-enone (Major Diastereomer, Scheme 89)



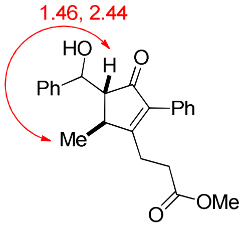
General Procedure B was followed using phenyl 3-butenoate (49 mg, 0.3 mmol, 1 equiv) and 4-octyne (66 µL, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was then worked up using the general workup procedure and NMR revealed two diastereomers (58:42). The crude reaction mixture was subjected to column chromatography (10 to 20% EtOAc/Hex) to yield an impure and unseparated diastereomers. Further column chromatography (0.5% MeOH/CH_2Cl_2) resulted in purification and partial separation of the product diastereomers yielding 14 mg of the minor diastereomer, 16 mg of the major diastereomer, and 15 mg of both diastereomers (58:42) all as colorless oils (44 mg, 52%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.32-7.33 (m, 4H), 7.25-7.26 (m, 1H), 5.33 (t, J = 4.2 Hz, 1H), 2.83 (d, J = 5.6 Hz, 1H), 2.75 (q, J = 7.0 Hz, 1H), 2.40 (ddd, J = 14.0 Hz, 9.1 Hz, 7.7 Hz, 1H), 2.31 (t, J = 2.8 Hz, 1H), 2.23 (ddd, J = 14.0 Hz, 9.1 Hz, 4.9 Hz, 1H), 2.08-2.16 (m, 2H), 1.48-1.56 (m, 1H), 1.39 (sext, J = 7.7 Hz, 2H), 1.28-1.36 (m, 1H), 0.86 (t, J = 5.6 Hz, 3H), 0.86 (t, J = 6.0 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 209.6, 178.8, 142.1, 140.0, 128.2, 127.3, 125.6, 72.3, 60.0, 35.8, 30.3, 25.1, 21.8, 20.7, 18.1, 14.1, 14.0. IR (thin film) ν: 3402, 2959, 1684, 1635, 1450, 1372, 1084, 701, 556 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{19}H_{26}O_2$, 287.2006; found, 287.2007.

5-(hydroxy(phenyl)methyl)-4-methyl-2,3-dipropylcyclopent-2-enone (Minor Diastereomer, Scheme 89)



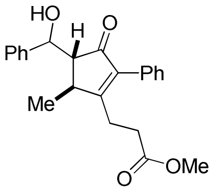
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.29-7.39 (m, 5H), 5.09 (s, 1H), 4.57 (d, J = 9.8 Hz, 1H), 2.43 (ddd, 14.0 Hz, 9.1 Hz, 7.0 Hz, 1H), 2.32 (q, J = 7.0 Hz, 1H), 2.23 (ddd, J = 14.0 Hz, 9.1 Hz, 4.9 Hz, 1H) 2.11-2.20 (m, 3H), 1.52-1.57 (m, 1H), 1.42 (quind, J = 7.0 Hz, 3.5Hz, 2H), 1.36-1.39 (m, 1H), 0.93 (t, J = 7.7 Hz, 3H), 0.90 (t, J = 7.7 Hz, 3H), 0.63 (d, J = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 211.7, 178.8, 141.6, 139.2, 128.4, 128.1, 126.9, 75.9, 59.1, 38.4, 30.3, 25.0, 21.8, 20.8, 17.5, 14.2, 14.0. IR (thin film) v: 3436, 2961, 2872, 1676, 1630, 1454, 1383, 1048, 703 cm^{-1}. HRMS (ESI+) (m/z): [M+H]$^+$ calc for $C_{19}H_{26}O_2$, 287.2006; found, 287.2007.

Methyl-3-trans-4-(hydroxy(phenyl)methyl)-5-methyl-3-oxo-2-phenylcyclopent-1-en-1-yl)propanoate (Major Diastereomer, Scheme 89)



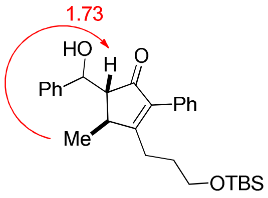
General Procedure B was followed using phenyl 3-butenoate (49 mg, 0.3 mmol, 1 equiv) and methyl-5-phenylpent-4-ynoate (85 mg, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was worked up using the general workup procedure and NMR spectroscopy revealed a 54:33:13 mixture of isomers. This product was further purified using column chromatography (10 to 40% EtOAc/Hex) yielding impure unseparated isomers. These isomers could be further purified and separated using the Waters HPLC (85:15 (Hex/(*i*-PrOH/Hex)) yielding 13 mg of pure major diastereomer as a white solid, 13 mg of the pure minor diastereomer, as a colorless oil, and 25 mg of mixed isomers (62:17:14:7) as a colorless oil (51 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.43 (m 8H), 7.20-7.22 (m, 2H), 5.45 (dd, J = 5.0 Hz, J = 3.5 Hz, 1H), 3.63 (s, 3H), 2.91-2.97 (m, 2H), 2.59-2.66 (m, 2H), 2.51 (t, J = 3.0 Hz, 1H), 2.44 (ddd, J = 16.0 Hz, 10.0 Hz, 5.5 Hz, 1H), 2.32 (ddd, J = 15.5 Hz, 8.5 Hz, 7.0 Hz, 1H), 0.90 (d, J = 7.5 Hz, 3H). ^{13}C NMR (176 MHz, CD_3CN): δ 207.0, 177.9, 173.5, 144.5, 141.4, 133.4, 130.2, 129.2, 129.1, 128.6, 127.9, 126.5, 72.2, 62.0, 52.3, 36.3, 32.1, 24.8, 18.5. IR (thin film) v: 3465, 2959, 1736, 1699, 1493, 1443, 1345, 1197, 765, 703. HRMS (ESI+) (m/z): [M+H]$^+$ calc for $C_{23}H_{24}O_4$, 365.1747; found, 365.1750.

Methyl-3-trans-4-(hydroxy(phenyl)methyl)-5-methyl-3-oxo-2-phenylcyclopent-1-en-1-yl)propanoate (Minor Diastereomer, Scheme 89)



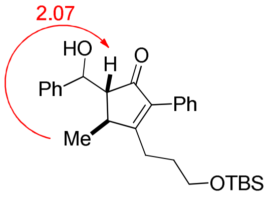
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.34-7.44 (m, 8H), 7.22 (d, J = 6.8 Hz, 2H), 4.83 (s, 1H), 4.75 (d, J = 9.6 Hz, 1H), 3.63 (s, 3H), 2.98 (ddd, J = 14.6 Hz, 9.1 Hz, 7.1 Hz, 1H), 2.62 (ddd, J = 14.8 Hz, 9.2 Hz, 5.6 Hz, 1H), 2.52 (qd, J = 6.8 Hz, 2.4 Hz, 1H), 2.39-2.47 (m, 2H), 2.33 (ddd, J = 16.0 Hz, 9.4 Hz, 7.0 Hz, 1H), 0.78 (d, J = 7.2 Hz, 3H). ^{13}C NMR (133 MHz, CDCl$_3$): δ 209.3, 177.2, 172.2, 141.2, 140.2, 130.8, 129.0, 128.6, 128.5, 128.3, 128.2, 126.9, 75.5, 59.5, 51.9, 38.4, 31.4, 24.0, 17.5. IR (thin film) v: 3454, 2961, 1734, 1695, 1635, 1597, 1493, 1436, 1345, 1199, 1048, 913, 765, 736, 702 cm^{-1}. HRMS (ESI+) (m/z): [M+Na]$^+$ calc for $C_{23}H_{24}O_4$, 387.1569; found, 387.1571.

trans-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-5-(hydroxy(phenyl)methyl)-4-methyl-2-phenylcyclopent-2-enone (Major Diastereomer, Scheme 89)



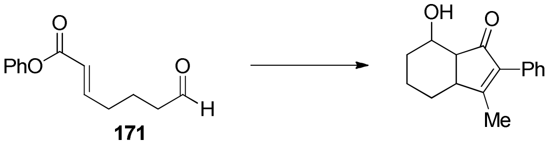
General Procedure B was followed using phenyl 3-butenoate (49 mg, 0.3 mmol, 1 equiv) and tert-butyldimethyl((5-phenylpent-4-yn-1-yl)oxy)silane (123 mg, 0.45 mmol, 1.5 equiv), and benzaldehyde (46 µL, 0.45 mmol, 1.5 equiv). The reaction was worked up using the general workup procedure and subjected to column chromatography yielding a crude mixture of isomers (54:37:9). These isomers were able to be further purified and separated using the Shimadzu HPLC yielding 19 mg of pure minor diastereomer as a colorless oil, 44 mg of pure major diastereomer as a white solid, and an additional 14 mg of mixed isomers (22:68:10) as a colorless oil (77 mg, 57%). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.35-7.41 (m, 6H), 7.31 (t, J = 7.0 Hz, 1H), 7.28 (t, J = 7.0 Hz, 1H), 7.22 (d, J = 6.8 Hz, 2H), 5.44 (d, J = 1.4 Hz, 1H), 3.56 (dt, J = 10.5 Hz, 5.6 Hz, 1H), 3.47 (ddd, J = 10.5 Hz, 7.0 Hz, 5.6 Hz, 1H), 2.96 (qd, J = 7.0 Hz, 2.8 Hz, 1H), 2.75 (s, 1H), 2.68 (ddd, J = 7.0 Hz, 10.5 Hz, 5.6 Hz, 1H), 2.49 (t, J = 2.8 Hz, 1H), 2.37 (ddd, J = 13.3 Hz, 10.0 Hz, 4.4 Hz, 1H), 1.69 (dtt, J = 16.1 Hz, 7.7 Hz, 5.6 Hz, 1H), 1.50 (dquin, J = 18.2 Hz, 5.6 Hz, 1H), 0.89 (d, J = 7.7 Hz, 3H), 0.84 (s, 9H), -0.01 (s, 3H), -0.02 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 207.4, 180.1, 142.0, 140.1, 131.7, 129.1, 128.3, 128.2, 127.7, 127.4, 125.6, 72.2, 62.3, 60.6, 35.9, 30.6, 25.8, 25.3, 18.2, 17.9, -5.4, -5.5. IR (thin film) ν: 3446, 2955, 2856, 1684, 1630, 1597, 1495, 1471, 1360, 1255, 1152, 1099, 959, 835, 776, 702 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{28}H_{38}O_3Si$, 451.2663; found, 451.2672.

trans-3-(3-((tert-butyldimethylsilyl)oxy)propyl)-5-(hydroxy(phenyl)methyl)-4-methyl-2-phenylcyclopent-2-enone (Major Diastereomer, Scheme 89)



^{1}H NMR (700 MHz, $CDCl_3$): δ 7.38-7.44 (m, 6H), 7.33-7.35 (m, 2H), 7.25 (d, J = 7.0 Hz, 2H), 5.01 (s, 1H), 4.74 (d, J = 9.8 Hz, 1H), 3.57 (dt, J = 5.6 Hz, 10.5 Hz, 1H), 3.52 (ddd, J = 9.8 Hz, 7.0 Hz, 5.6 Hz, 1H), 2.71 (ddd, J = 13.3 Hz, 10.5 Hz, 5.6 Hz, 1H), 2.53 (qd, J = 7.0 Hz, 4.2 Hz, 1H), 2.36-2.41 (m, 2H), 1.70 (dtt, J = 16.8 Hz, 7.7 Hz, 5.6 Hz, 1H), 1.50-1.56 (m, 1H), 0.84 (s, 9H), 0.75 (d, J = 7.0 Hz, 3H), -0.01 (s, 3H), -0.01 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$): δ 209.0, 180.2, 141.4, 139.3, 131.1, 129.1, 128.5, 128.4, 128.2, 127.9, 126.9, 75.7, 62.4, 59.5, 38.5, 30.6, 25.8, 25.5, 18.2, 17.2, -5.4, -5.4. IR (thin film) ν: 3443, 2927, 2855, 1679, 1631, 1597, 1494, 1471, 1360, 1256, 1149, 1099, 956, 834, 775, 700 cm^{-1}. HRMS (ESI+) (m/z): $[M+H]^+$ calc for $C_{28}H_{38}O_3Si$, 451.2663; found, 451.2662.

7-hydroxy-3-methyl-2-phenyl-3a,4,5,6,7,7a-hexahydro-1H-inden-1-one (Scheme 90)



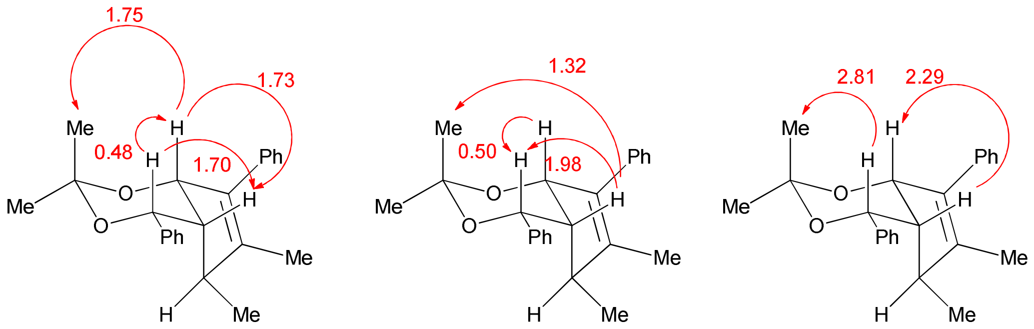
General procedure B was followed with 0.043 g or 0.05 g of enoate derivative **171**. After overnight reaction impure product was isolated (0.01 g or 0.019 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.42 (m, 5H), 3.98 (dt, J = 12.8 Hz, J = 4.8 Hz, 1H), 3.07 (s, 1H), 3.01 (dt, J = 10.0 Hz, J = 6.8 Hz, 1H), 2.50 (t, J = 8.0 Hz, 1H), 2.15 (s, 3H), 1.97-2.01 (m, 1H), 1.86-1.91 (m, 1H), 1.64-1.77 (m, 2H), 1.24-1.33 (m, 2H).

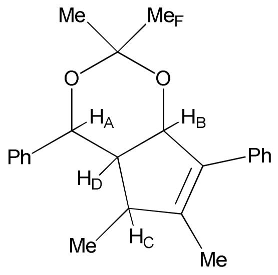
5.5 General Procedure for Acetalide Formation and Characterization

Purified diastereomer (1 equiv) and $CeCl_3$ (1 equiv) were dissolved in 1 mL MeOH. This solution was cooled to 0 °C and $NaBH_4$ (4.5 equiv) was added in portions. The reaction was stirred until completion of the reaction was confirmed by TLC. The reaction was quenched with 1 mL NH_4Cl and extracted 3x with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. Flash chromatography of the crude isolate separated the product diastereomers.

Each diastereomer was dissolved in 1 mL DMP (dimethoxypropane) and a 1 mol % PTSA was added as a 1 mg/ 100 µL solution. After 30 min, the reaction was quenched with 1 mL sat. $NaHCO_3$ and extracted 3x with EtOAc. The organic layers were washed with brine and dried over Na_2SO_4. The crude product was purified by flash chromatography yield. Only one diastereomer will yield the desired acetalide. The other diastereomer will initially yield an acetalide product, but this product is unstable and will rapidly decompose. Multiple spots on the TLC plate or a reaction that turns yellow indicates this.

Diastereomer 159a (Scheme 93b)





ppm

noe obs		5.45 A	5.05 B	1.85 D
5.45	A	---	0.50	1.98
5.05	B	0.48	---	2.29
1.85	D	1.70	1.73	---
1.61	F	2.81	1.75	1.32

ppm

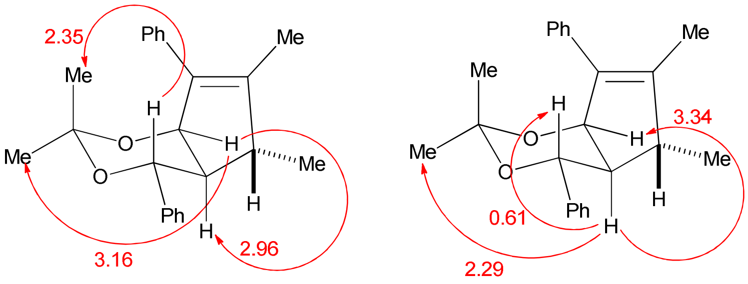
J obs		5.45 A	5.05 B	1.85 D
5.45	A	---	---	4.3
5.05	B	---	---	4.4
1.85	D	4.2	4.9	---

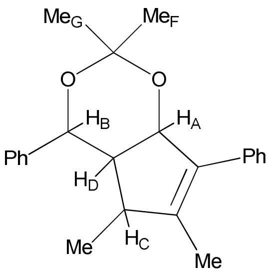
Purified diastereomer **159a** (20 mg, 0.07 mmol), $CeCl_3$ (25 mg, 0.07 mmol), and $NaBH_4$ (12 mg, 0.3 mmol) were reacted according to the general procedure. Flash chromatography of the crude isolate (1.2:1) separated the product diastereomers (9.0 mg and 7.5 mg, 83%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.45-7.47 (m, 2H), 7.36-7.39 (m, 6H), 7.28 (m, 1H), 5.38 (d, J = 3.2 Hz, 1H), 5.14 (d, J = 6.4 Hz, 1H), 3.48 (s, 1H), 3.12 (quin, J = 6.8 Hz, 1H), 2.28 (td, J = 7.2 Hz, J = 3.2 Hz, 1H), 2.18 (s, 1H), 1.76 (s, 3H), 0.66 (d, J = 7.2 Hz, 3H).

The major diol diastereomer (9.0 mg, 0.03 mmol) was protected according to the general procedure using 0.6 mg (0.003 mmol) of PTSA as acid. The crude product was purified by flash chromatography yielding a white solid (9.9 mg, 99%).

^{1}H NMR (700 MHz, C_3D_6O): δ 7.46 (d, J = 7.7 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.37 (t, J = 7.7 Hz, 2H), 7.33 (t, J = 8.1 Hz, 2H), 7.26 (t, J = 7.7 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 5.45 (d, J = 4.2 Hz, 1H), 5.04 (d, J = 4.9 Hz, 1H), 2.80 (dt, J = 8.4 Hz, J = 4.4 Hz, 1H), 1.85 (ddd, J = 8.4 Hz, J = 4.4 Hz, J = 4.3 Hz, 1H), 1.75 (s, 3H), 1.61 (s, 3H), 1.43 (s, 3H), 0.25 (d, J = 6.8 Hz, 3H). ^{13}C NMR (176 MHz, C_3D_6O): δ 146.5, 142.7, 138.2, 136.4, 128.8, 128.8, 128.7, 127.8, 127.1, 126.6, 98.3, 79.3, 70.9, 49.7, 42.5, 30.3, 20.4, 17.6, 13.9.

Diastereomer 159b (Scheme 93b)





noe obs		ppm 5.08 A	4.65 B	2.24 D
5.08	A	---	---	2.34
4.65	B	---	---	0.61
2.24	D	2.96	0.23	---
1.53	F	3.16	1.75	---
1.48	G	---	1.48	---

J obs		ppm 5.08 A	4.65 B	2.24 D
5.08	A	---	---	5.6
4.65	B	---	---	10.5
2.24	D	7.7	10.5	---

ϕAD ≈ 0° or 140°
ϕBD ≈ 40° or 120°

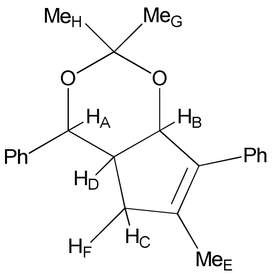
Purified diastereomer **159b** (10 mg, 0.03 mmol), $CeCl_3$ (11 mg, 0.03 mmol), and $NaBH_4$ (5 mg, 0.14 mmol) were reacted according to the general procedure. Flash chromatography of the crude isolate (1.7:1) separated the product diastereomers (7 mg and 4.5 mg, 100%). Major

Diastereomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.46-7.48 (m 2H), 7.27-7.39 (m, 8H), 5.11 (s, 1H), 4.97 (dd, J = 7.6 Hz, J = 3.2 Hz, 1H), 3.39 (d, J = 4.4 Hz, 1H), 2.75 (quin, J = 6.8 Hz, 1H), 2.25 (d, J = 4.0 Hz, 1H), 2.19 (q, J = 8.0 Hz, 1H), 1.77 (s, 3H), 0.66 (d, J = 6.8 Hz, 3H).

The major diol diastereomer (7 mg, 0.03 mmol) was protected according to the general procedure using 0.5 mg (0.003 mmol) of PTSA as acid. The crude product was purified by flash chromatography yielding a white solid (7 mg, 77%).

^{1}H NMR (700 MHz, CDCl$_3$): δ 7.46 (d, J = 7.0 Hz, 2H), 7.44 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 7.23-7.35 (m, 1H), 5.08 (d, J = 7.7 Hz, 1H), 4.65 (d, J = 10.5 Hz, 1H), 2.68 (m, 1H), 2.24 (ddd, J = 10.2 Hz, J = 10.5 Hz, J = 5.6 Hz, 1H), 1.84 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 0.75 (d, J = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, CDCl$_3$): δ 146.5, 141.2, 137.0, 133.5, 128.5, 128.3, 128.0, 127.9, 127.4, 126.6, 100.6, 79.1, 75.5, 54.1, 47.3, 25.9, 24.3, 19.0, 14.1.

Diastereomer 162, (Scheme 93b)



		ppm		
noe obs		5.34 A	5.04 B	2.31 D
5.35	A	---	0.87	3.83
5.25	B	0.80	---	3.74
2.54	D	2.16	2.03	---
1.65	H	3.31	2.37	---

		ppm		
J obs		5.34 A	5.04 B	2.31 D
5.35	A	---	---	4.5
5.25	B	---	---	4.5
2.54	D	4.0	4.5	---

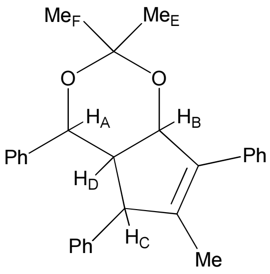
$\phi \approx 45°$ or $120°$

Purified diastereomer **162** (15 mg, 0.05 mmol), CeCl$_3$ (19 mg, 0.05 mmol), and NaBH$_4$ (8 mg, 0.2 mmol) were reacted according to the general procedure. Flash chromatography of the crude mixture of diastereomers (1.5:1) yielded the purified diols (6 mg and 4 mg, 76%). Major diastereomer: ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44-7.46 (m, 2H), 7.35-7.39 (m, 5H), 7.27-7.29

(m, 1H), 5.31 (d, J = 3.2 Hz, 1H), 5.13 (d, J = 4.8 Hz, 1H), 2.99 (dd, J = 16.8 Hz, J = 8.0 Hz, 1H), 2.68 (td, J = 8.0 Hz, J = 3.6 Hz, 1H), 2.10-2.17 (m, 2H), 1.86 (s, 3H).

The major diol diastereomer (6 mg, 0.02 mmol) was protected according to the general procedure using 0.4 mg (0.002 mmol) of PTSA as acid. The crude product was purified by flash chromatography yielding the acetalide.^{1}H NMR (700 MHz, $CDCl_3$): δ 7.40-7.43 (m, 4H), 7.36 (t, J = 7.7 Hz, 2H), 7.35 (t, J = 7.7 Hz, 2H), 7.28 (m, 1H), 7.23 (t, J = 7.0 Hz, 1H), 5.34 (d, J = 4.0 Hz, 1H), 5.04 (d, J = 4.5 Hz, 1H), 2.64 (dd, J = 16.5 Hz, J = 9.5 Hz, 1H), 2.31 (ddt, J = 9.5 Hz, J = 7.8 Hz, J = 4.5 Hz, 1H) 1.88 (s, 3H), 1.70 (dd, J = 16.3 Hz, J = 7.3 Hz, 1H), 1.66 (s, 3H), 1.56 (s, 3H).

Diastereomer 161 (Scheme 93b)



noe obs		5.35 A	5.25 B	2.54 D	1.65 E
5.35	A	---	0.28	3.17	2.65
5.25	B	0.42	---	4.31	1.73
2.54	D	3.28	2.97	---	---
1.65	E	4.47	2.35	---	---

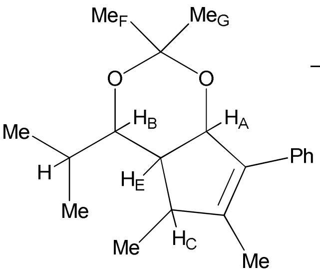
J obs		5.35 A	5.25 B	2.54 D
5.35	A	---	---	4.4
5.25	B	---	---	4.4
2.54	D	4.0	5.2	---

$\phi AD \approx 43°$ or $123°$
$\phi BD \approx 43°$ or $123°$

Purified diastereomer **161** (8 mg, 0.02 mmol), $CeCl_3$ (8 mg, 0.02 mmol), and $NaBH_4$ (3 mg, 0.09 mmol) were reacted according to the general procedure. Flash chromatography of the crude mixture of diastereomers yielded the desired diastereomer as the minor diastereomer (1.1 mg, 14%). Minor Diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.45 (m, 8H), 7.22-7.26 (m, 1H), 7.15-7.19 (m, 1H), 7.03-7.09 (m, 3H), 6.70-6.72 (m, 2H), 5.39-5.42 (m, 2H), 4.11 (m, 1H), 3.15 (m, 1H), 2.81 (m, 1H), 2.25 (d, J = 5.6 Hz, 1H), 1.57 (s, 3H).

The minor diol diastereomer (1 mg, 0.003 mmol) was protected according to the general procedure using 0.06 mg (0.0003 mmol) of PTSA as acid. The crude product was purified by flash chromatography yielding the acetalide (0.7 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.50 (m, 2H), 7.36 (t, 8.0 Hz, 2H), 7.09-7.10 (m, 2H), 7.00-7.01 (m, 3H), 6.91-6.92 (m, 3H), 6.48-6.49 (m, 2H), 5.38 (d, J = 4.0 Hz, 1H), 5.28 (d, J = 5.2 Hz, 1H), 3.85 (d, J = 8.0 Hz, 1H), 2.54 (dt, J = 8.4 Hz, J = 4.4 Hz, 1H), 1.64 (s, 3H), 1.60 (s, 3H).

Diastereomer 160 (Scheme 93b)



ppm (C_6D_6)

noe obs		1.34 F	3.45 B	4.80 A	1.53 E
1.34	F	---	3.41	1.64	---
3.45	B	1.02	---	---	1.61
4.80	A	1.28	---	---	2.39
1.53	E	---	1.49	2.55	---

ppm ($CDCl_3$)

noe obs		1.43 F	3.59 B	4.94 A
1.43	F	---	3.50	1.74
3.59	B	1.38	---	1.37
4.80	A	0.79	1.18	---

ppm (C_6D_6)

J obs		1.53 E	3.45 B	4.80 A
1.53	E	---	2.5	6.0
3.45	B	3.0	---	---
4.80	A	6.0	---	---

$\phi AE \approx 30°$ or $130°$
$\phi BE \approx 40°$ or $130°$

Purified minor diastereomer **160** (15 mg, 0.06 mmol), $CeCl_3$ (22 mg, 0.06 mmol), and $NaBH_4$ (9 mg, 0.2 mmol) were reacted according to the general procedure. Flash chromatography of the crude mixture of diastereomers (1.5:1) yielded the pure major diastereomer (6 mg, 39%) and impure minor diastereomer (4 mg). Minor Diastereomer (impure): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.38 (m, 5H), 5.08 (d, J = 7.0 Hz, 1H), 3.75 (dd, J = 9.0 Hz, J = 2.5 Hz, 1H), 3.10 (quin, J

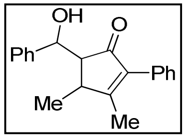
= 6.5 Hz, 1H), 2.92 (s, 1H), 2.23 (td, J = 6.9 Hz, J = 2.5 Hz, 1H), 1.91 (m, 1H), 1.81 (s, 3H), 1.21 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H), 0.99 (d, J = 6.5 Hz, 3H).

The minor diol diastereomer (4 mg, 0.02 mmol) was protected according to the general procedure using 0.3 mg (0.002 mmol) of PTSA as acid. The crude product was purified by flash chromatography yielding the acetalide.^{1}H NMR (500 MHz, C_6D_6): δ 7.59-7.61 (m, 2H), 7.25 (t, J = 8.0 Hz, 2H), 4.8 (d, J = 6.0 Hz, 1H), 3.45 (dd, J = 10 Hz, J = 2.5 Hz, 1H), 3.08 (quin, J = 7.0 Hz, 1H), 1.83 (septd, J = 6.0 Hz, J = 3.5 Hz, 1H), 1.65 (s, 3H), 1.53 (ddd, J = 7.5 Hz, J = 6.0 Hz, J = 3.0 Hz, 1H), 1.46 (s, 3H), 1.34 (s, 3H), 1.08 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H).

5.6 Alkylative Cycloaddition Product J-Table

Substrate	Diaster.	H_A δ	H_A J	H_B δ	H_B J	H_C δ	H_C J	H_C δ	H_C J
1	Major	5.5	t, 3.8	2.46	t, 3	2.88	q, 5.0		
2	Major	5.47	t, 3.9	2.94	m	2.73	d, 18.2	2.45	dd 18.9, 7.4
3	Major	5.5	t, 4.2	2.92	t, 3.2	3.88	d, 2.1		
4	Major	4.97	d, 4.9	N/A	N/A	3.12	d, 18.2	2.1	d, 18.2
5	Major	5.33	t, 4.2	2.31	t, 2.8	2.75	q, 7.0		
6	Major	3.9	ddd, 8.5, 5.5, 2.5	2.37	t, 2.8	2.95	q, 5.4		
7	Major	5.3	t, 3.5	2.4	m	3.02	qd, 7.7, 2.8		
8	Major	5.44	d, 1.4	2.49	t, 2.8	2.96	qd, 7.0, 2.8		
1	Minor	4.73	d, 9.6						
2	Minor	4.74	d, 9.8	2.91	ddd, 9.8, 7, 2.8	2.49	dd, 19.3, 7.3	2.26	d, 18.9
3	Minor	4.82	d, 9.8	2.85	dd, 9.8, 2.8	3.45	s		
4	Minor	4.85	s	N/A	N/A	2.86	d, 19.6	2.15	d, 18.9
5	Minor	4.57	d, 9.8			2.32	q, 7.0		
6	Minor	3.58	d, 9.1	2.22	d, 9.8	2.53	q, 6.5		
7	Minor	4.75	d, 9.6	2.51	t, 3				
8	Minor	4.74	d, 9.8	2.2	dd, 8.8, 2	2.53	qd, 7, 4.2		

1



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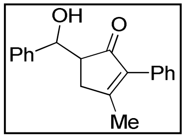

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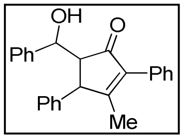

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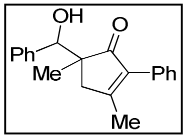

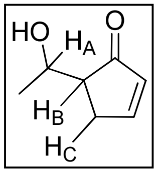

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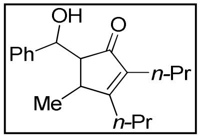

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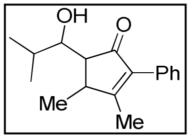

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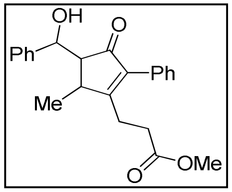

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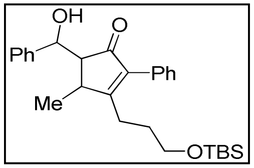
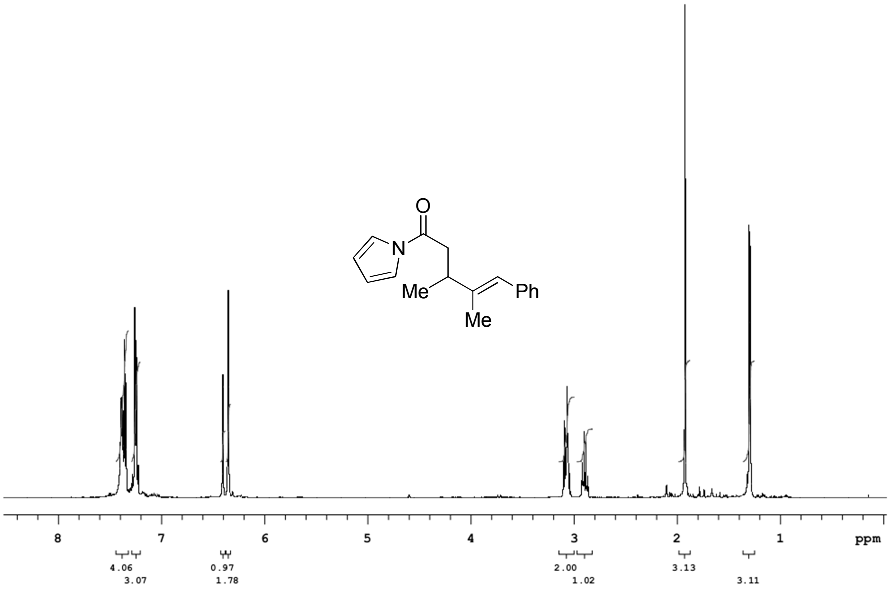


5.7 Chapter 2 Product Spectra (Excludes Published Spectra)

Table 4, Entry 4



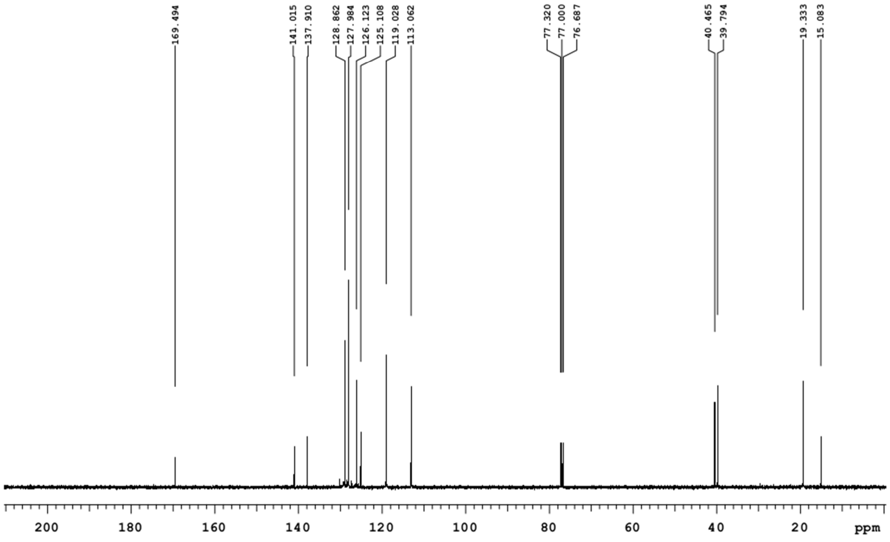
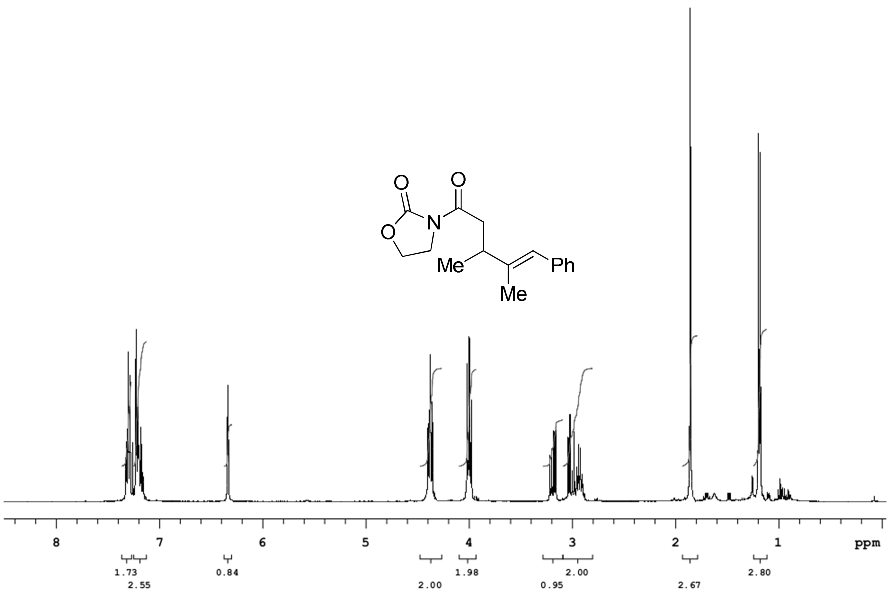


Table 5, Entry 2



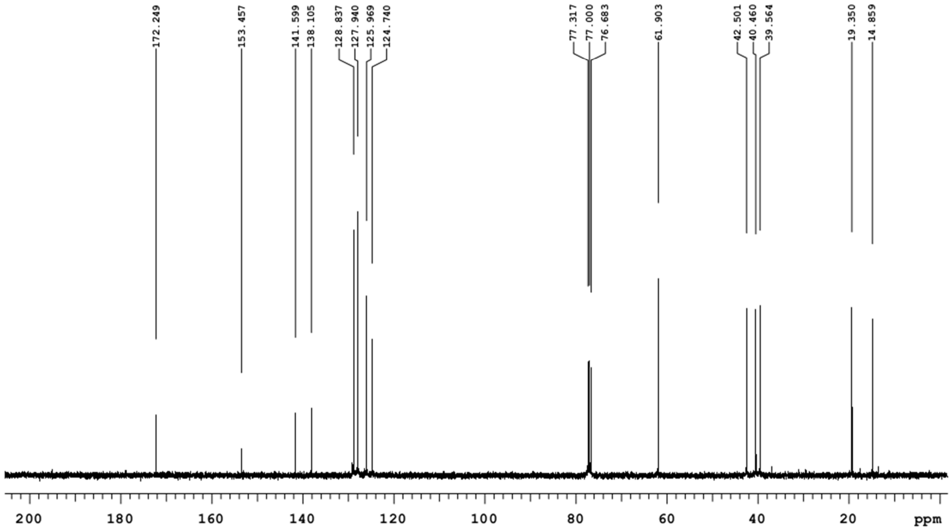


Table 5, Entry 1

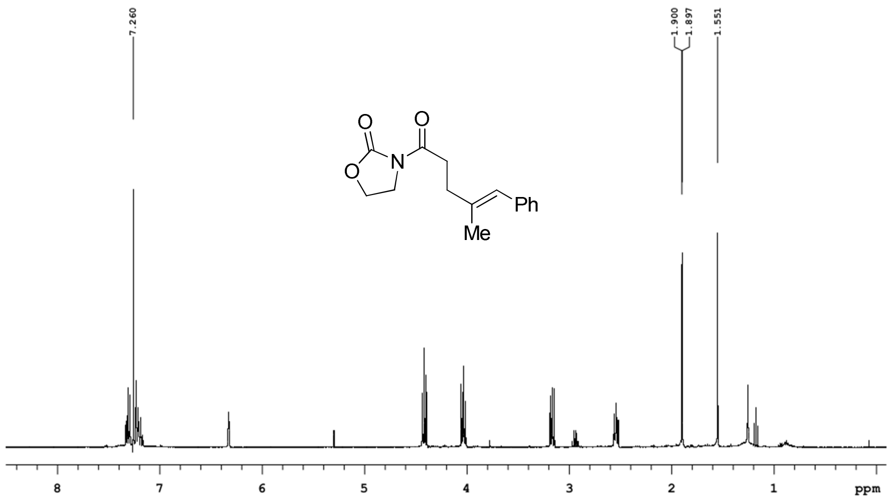


Table 8, Entry 10

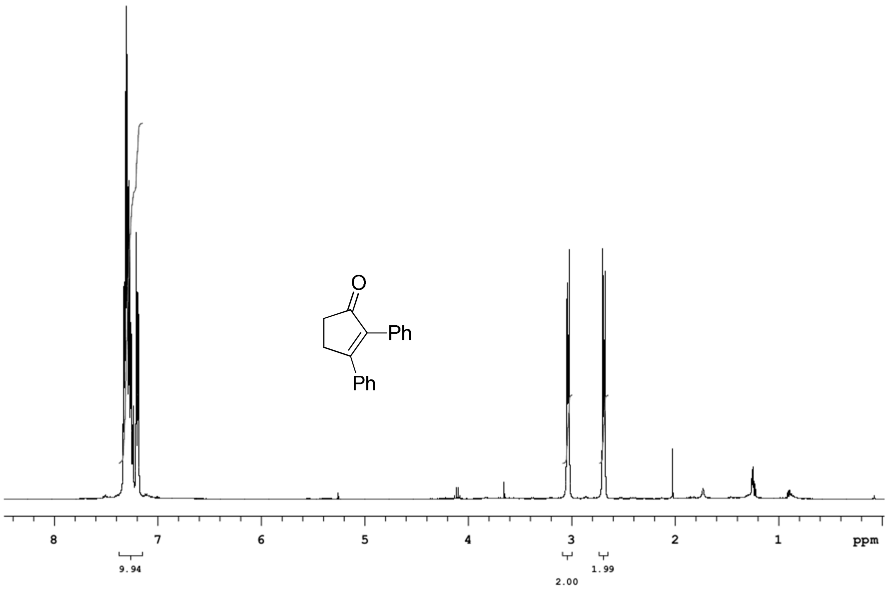


Table 8, Entry 3, Major Regiosisomer

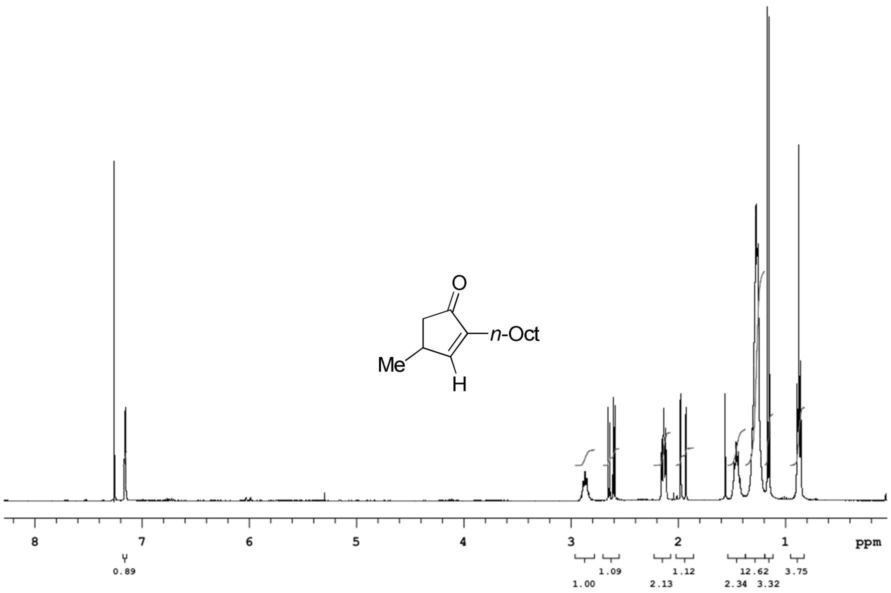
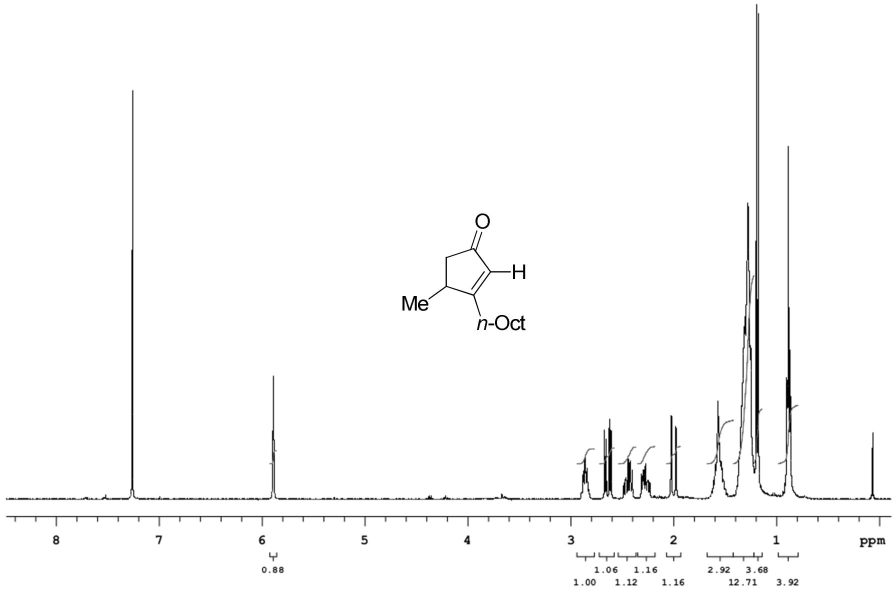


Table 8, Entry 3, Minor Regioisomer



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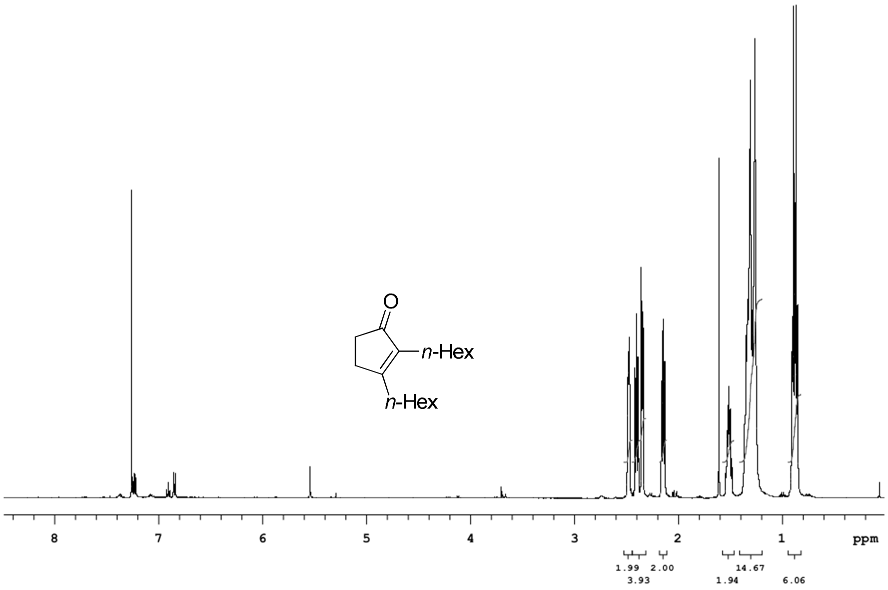


Table 10, Entry 8

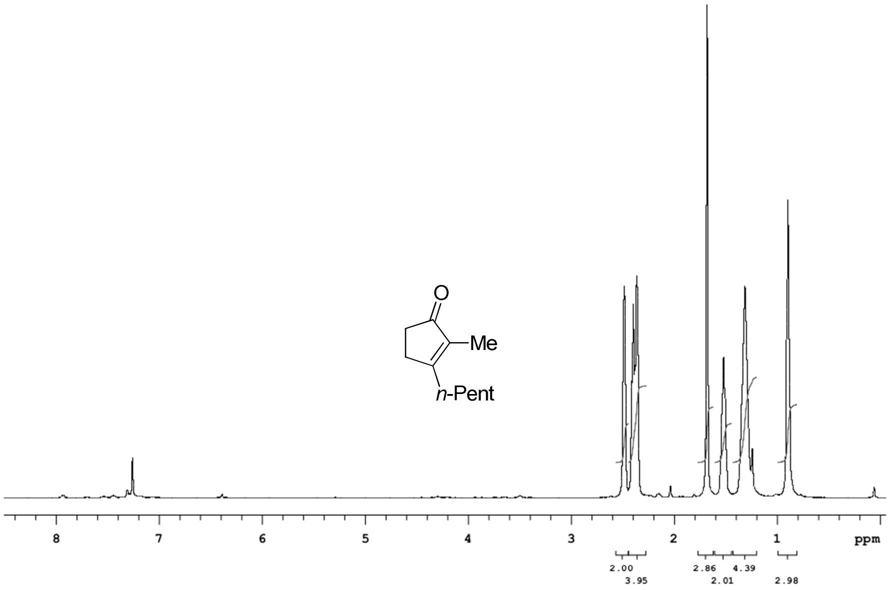


Table 10, Entry 7, Major Regioisomer

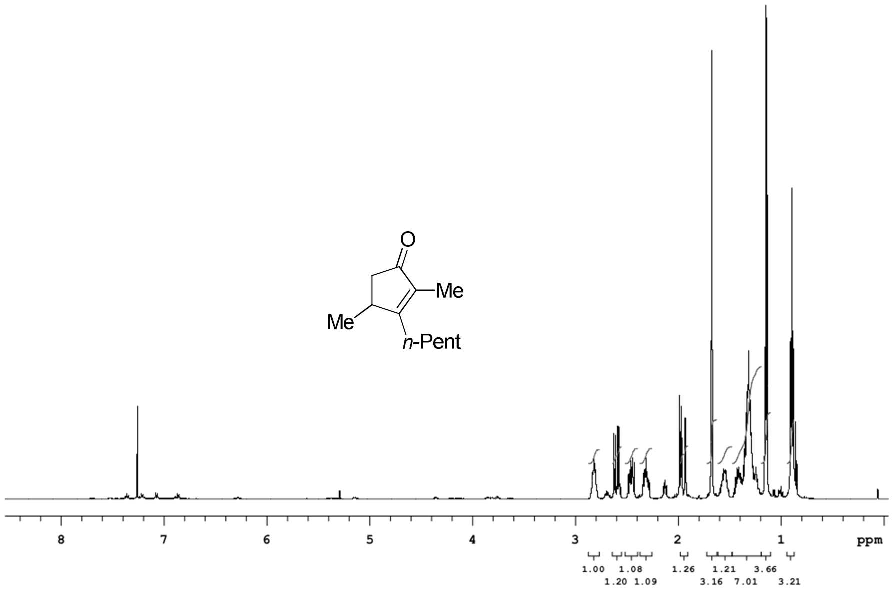


Table 10, Entry 7, Minor Regioisomer

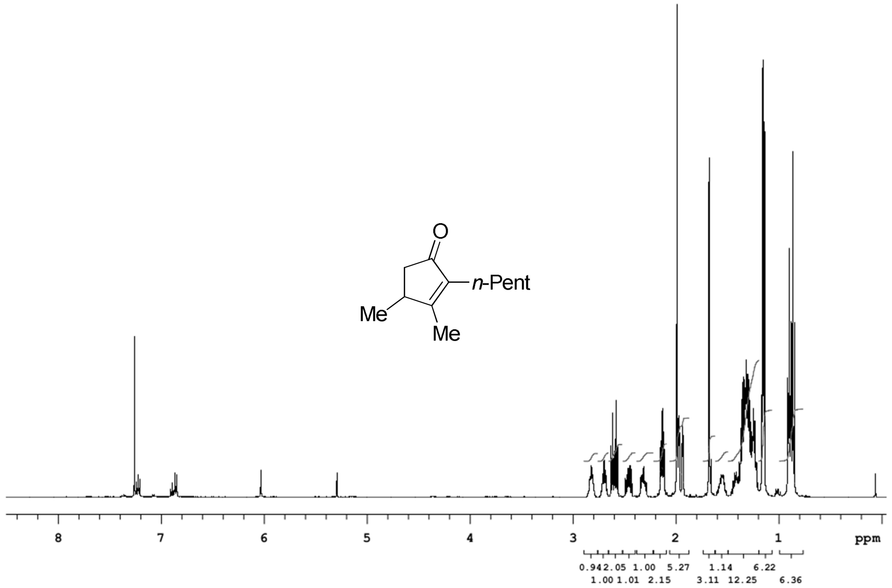


Table 14, Entry 1, 148

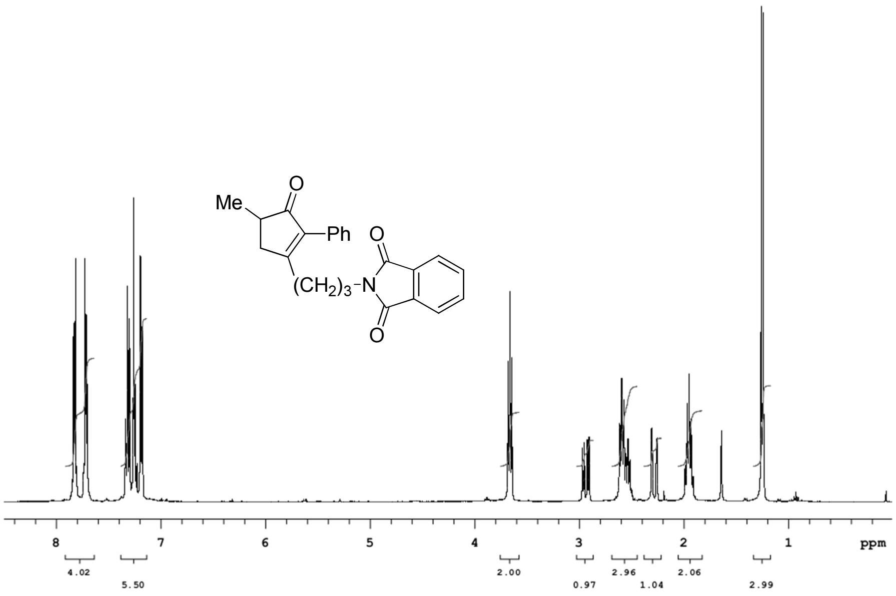
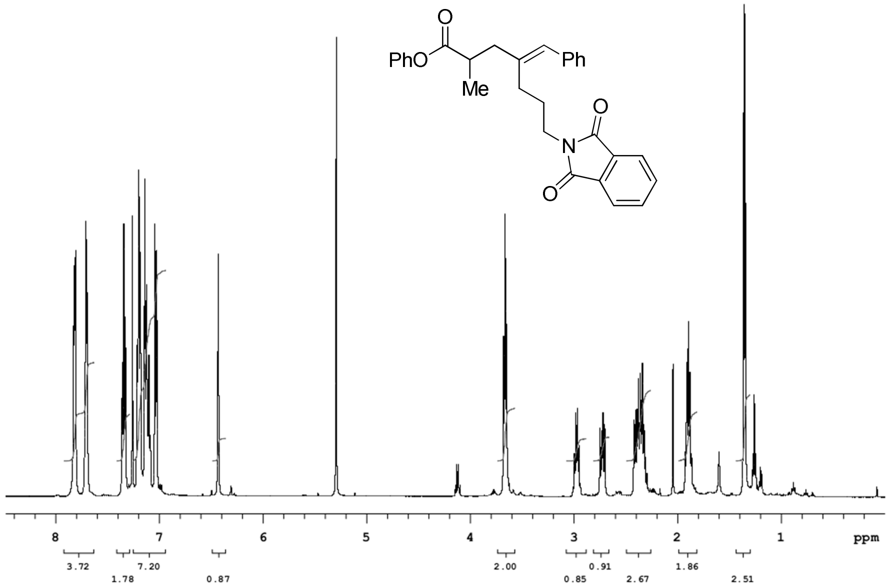
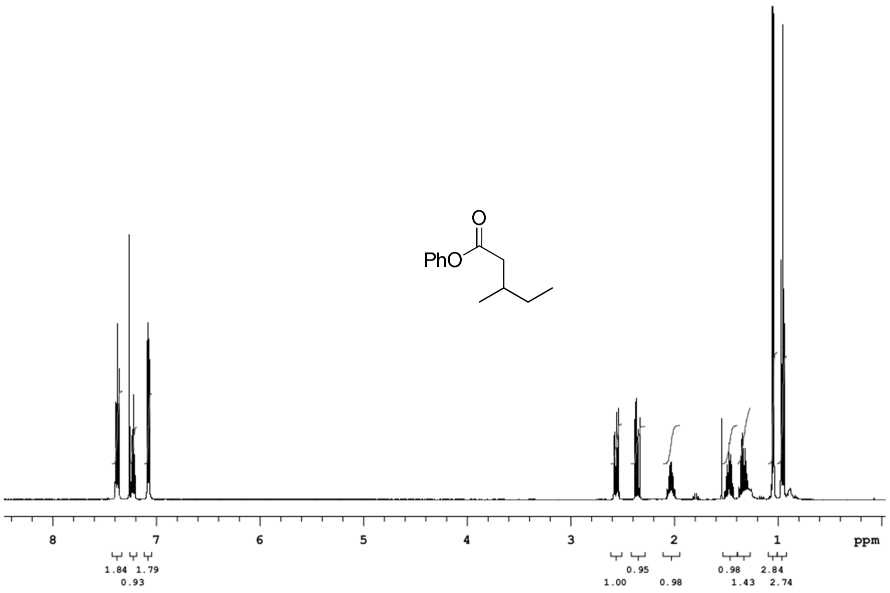


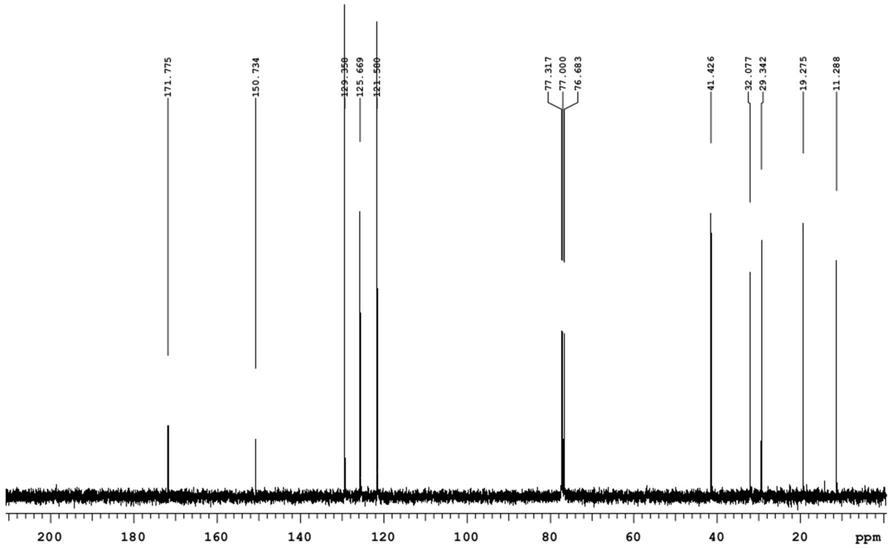
Table 14, Entry 1



Scheme 72

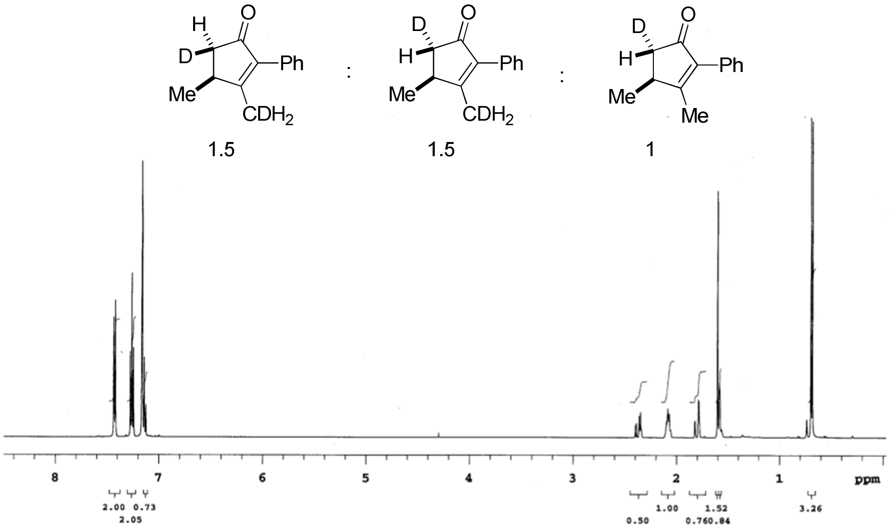


O
PhO
8
7
6
5
4
3
2
1
ppm
1.84
0.93
1.79
1.00
0.95
0.98
0.98
1.43
2.84
2.74

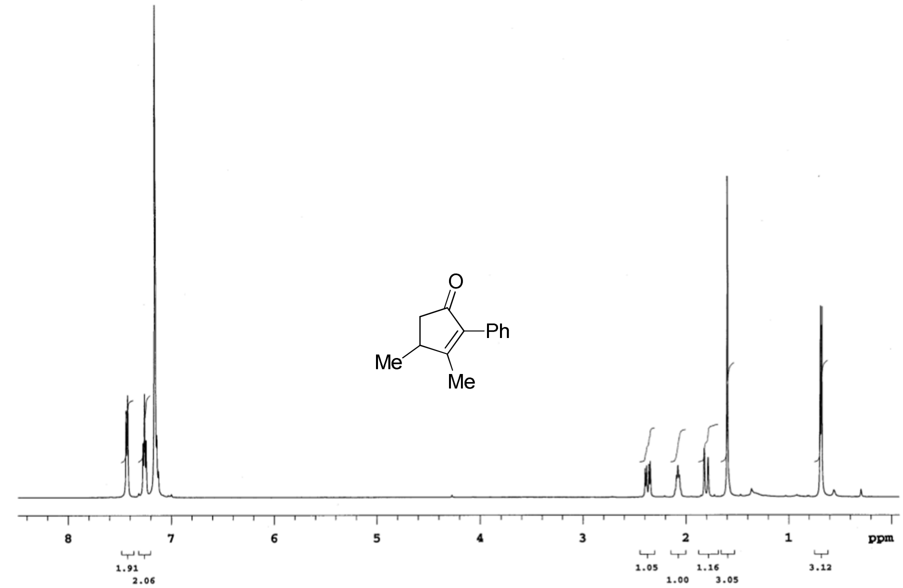


171.775
150.734
129.350
125.669
121.580
77.317
77.000
76.683
41.426
32.077
29.342
19.275
11.288
200
180
160
140
120
100
80
60
40
20
ppm

Scheme 81



Scheme 82



5.8 Chapter 3 Product Spectra

Table 25, Entry 6, Major Diastereomer

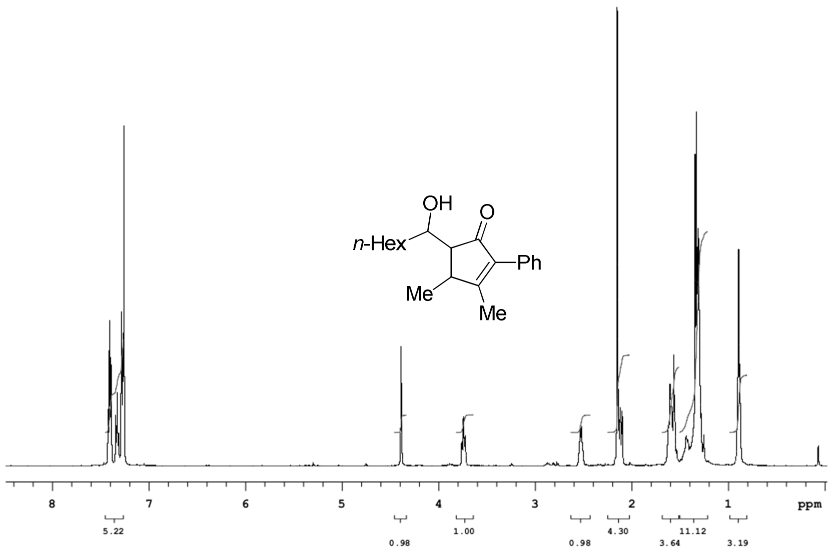


Table 25, Entry 6, Minor Diastereomer

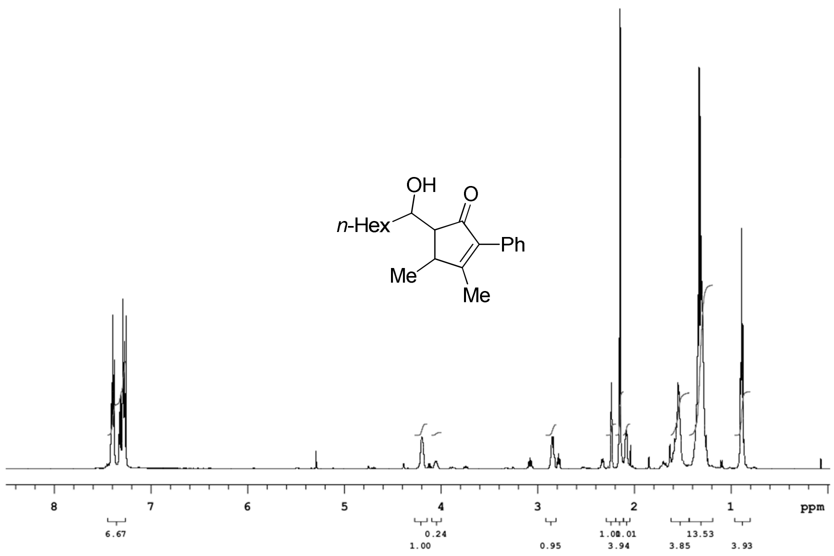


Table 26, Entry 7, Major Diastereomer

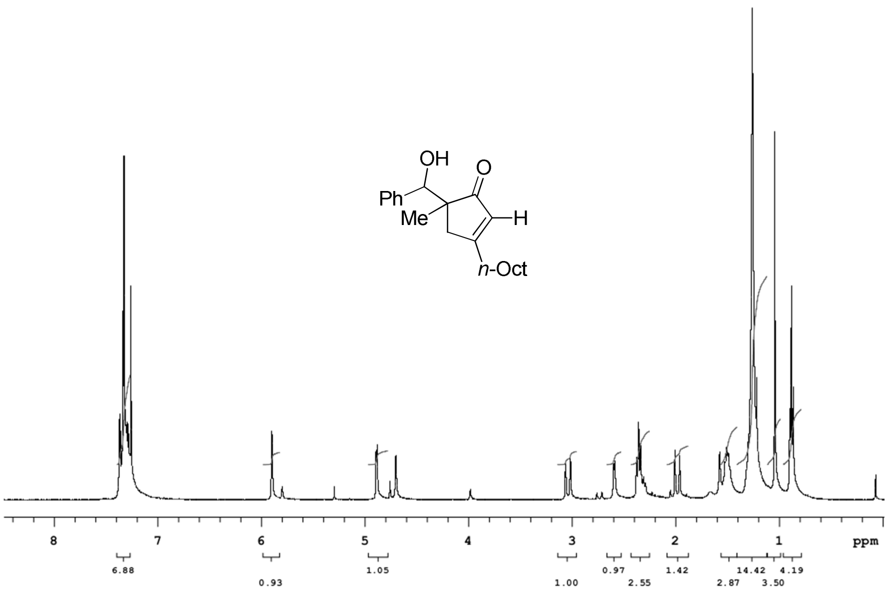
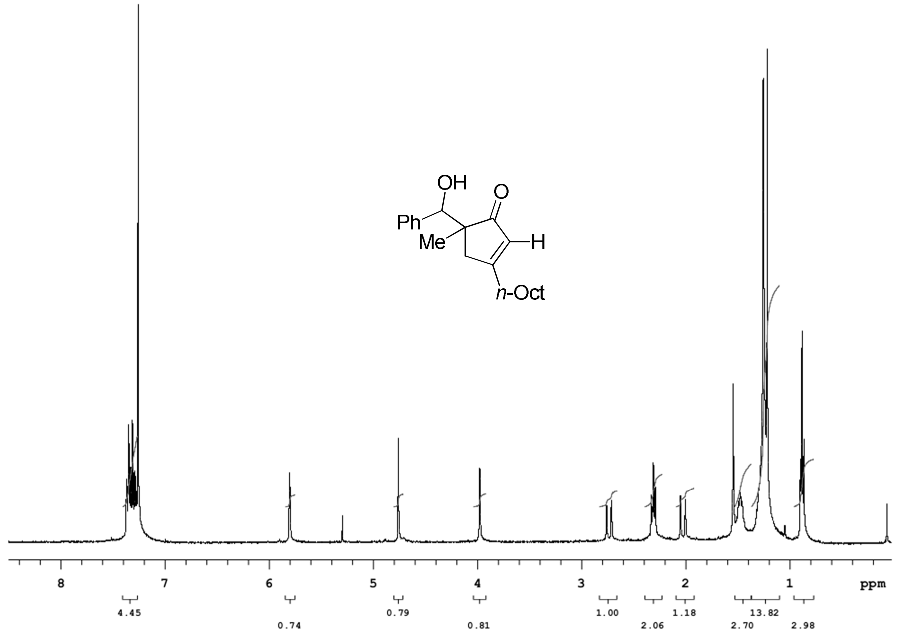
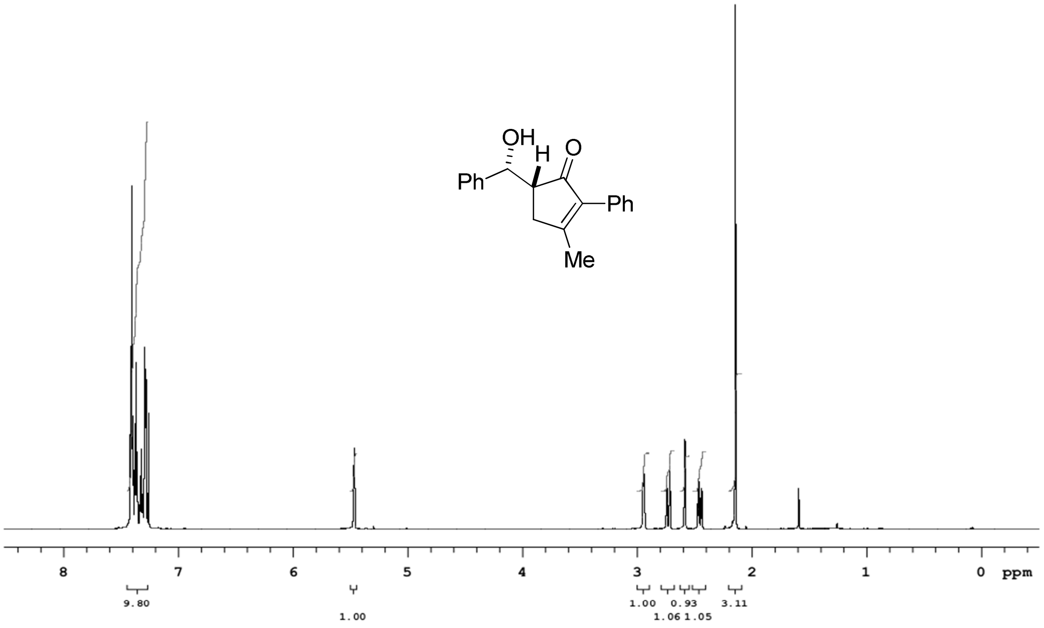
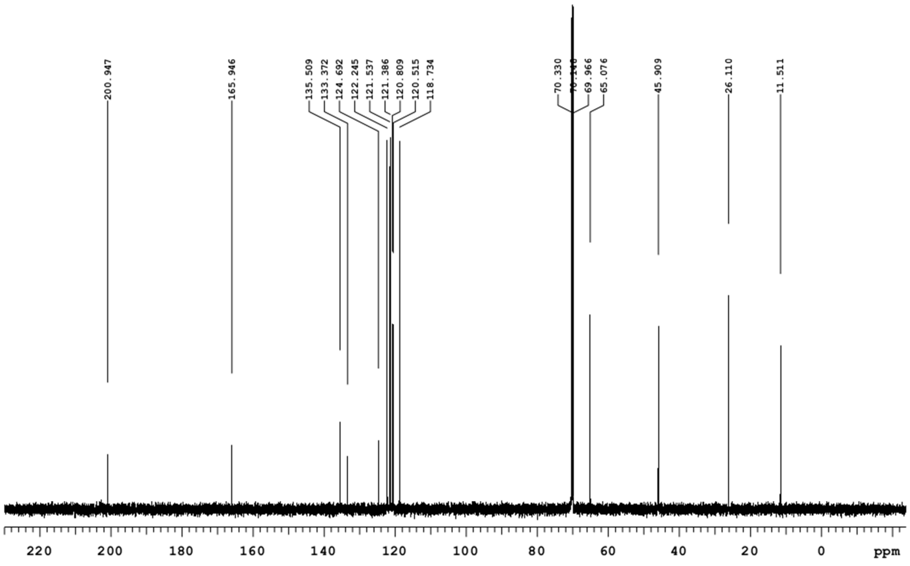


Table 26, Entry 7, Minor Diastereomer

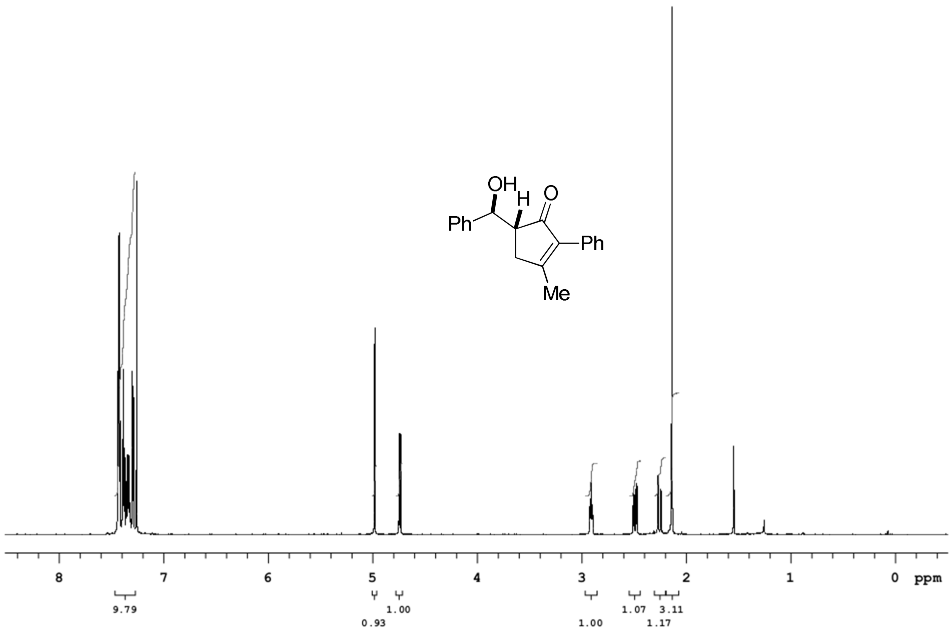


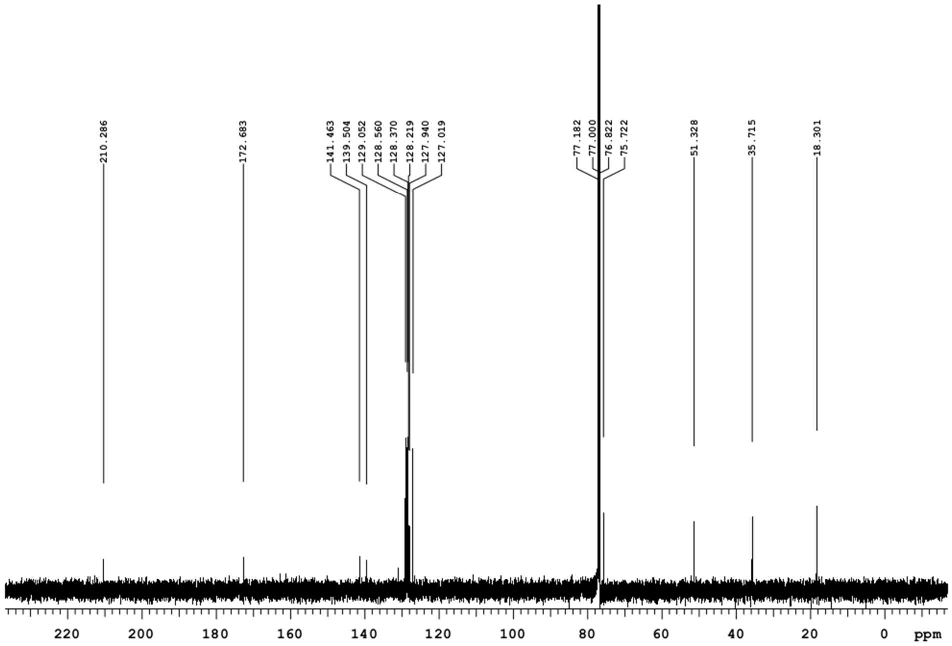
Scheme 89, Major Diastereomer



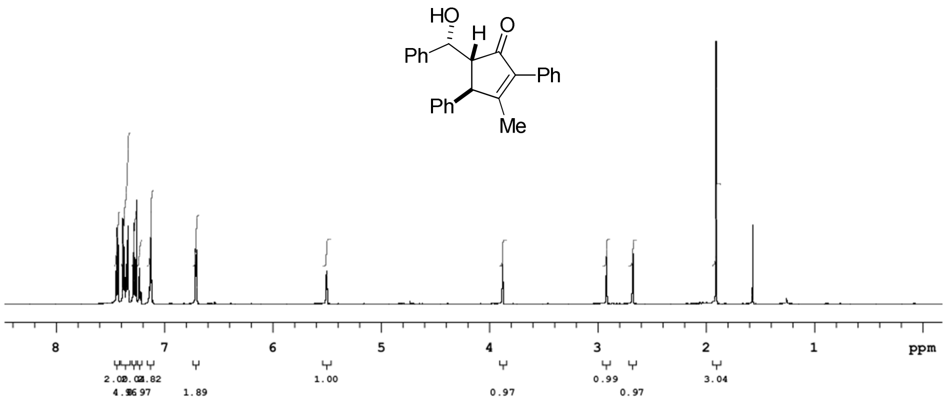


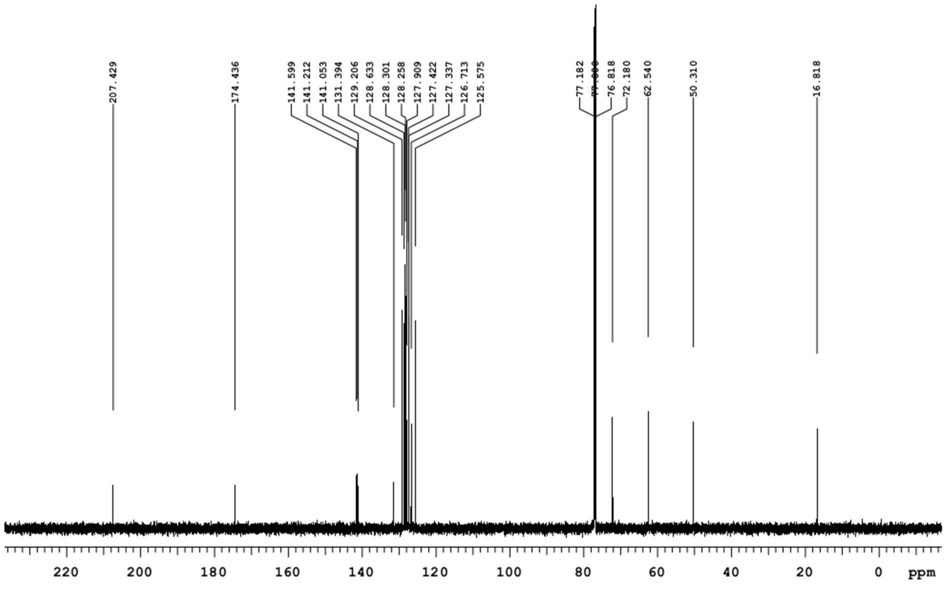
Scheme 89, Minor Diastereomer



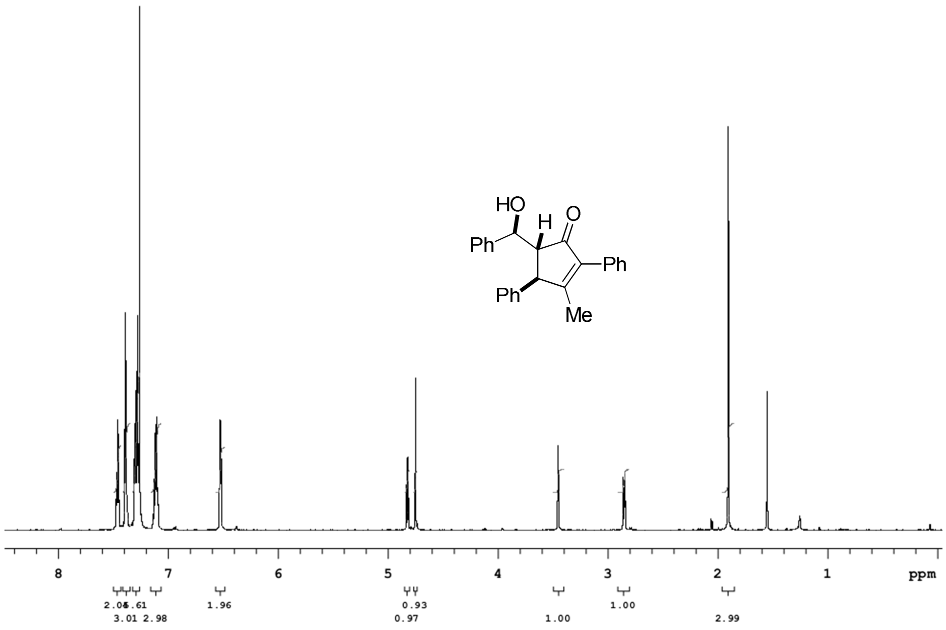


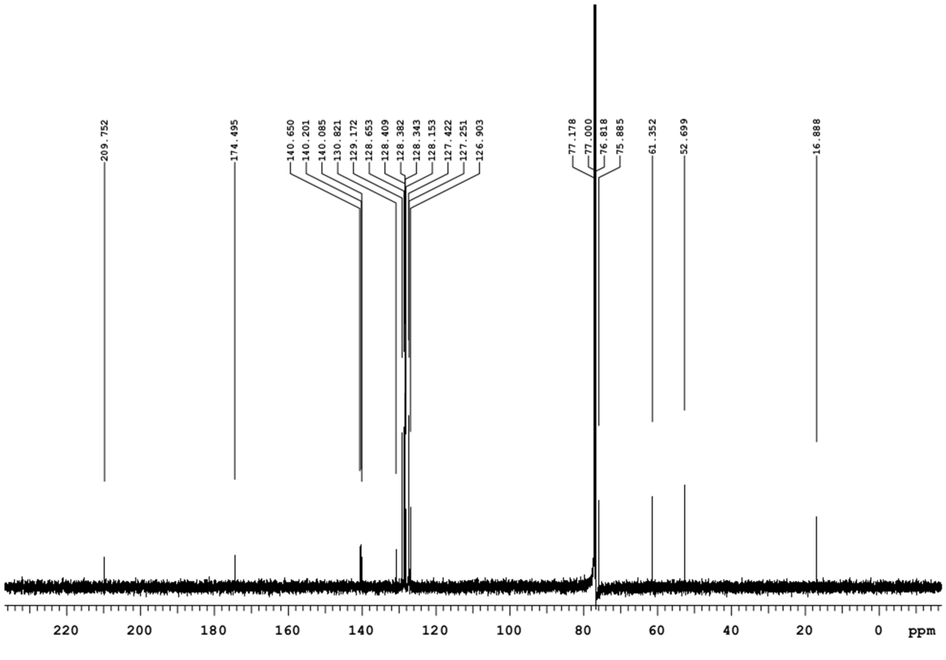
Scheme 89, Major Diastereomer



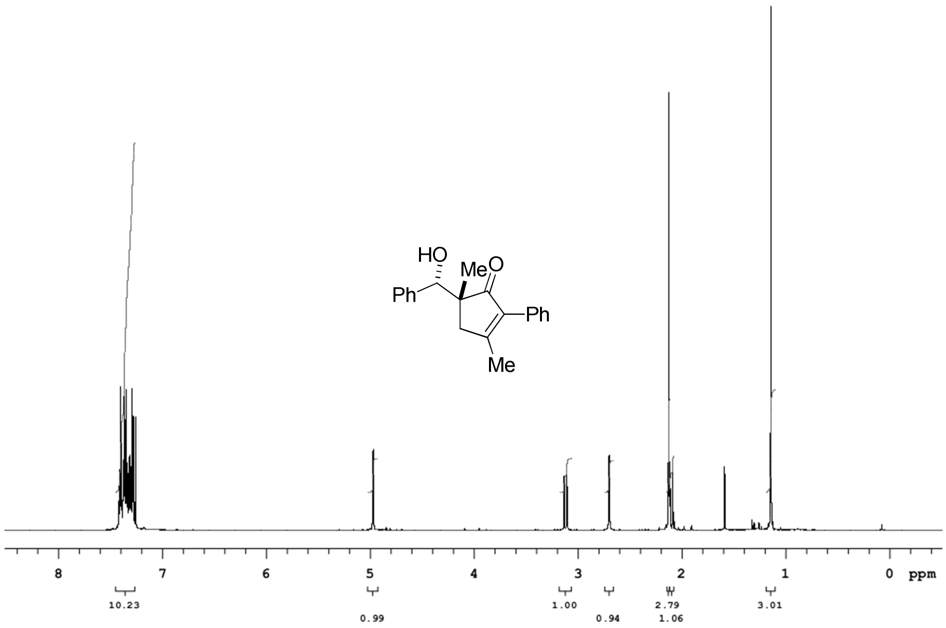


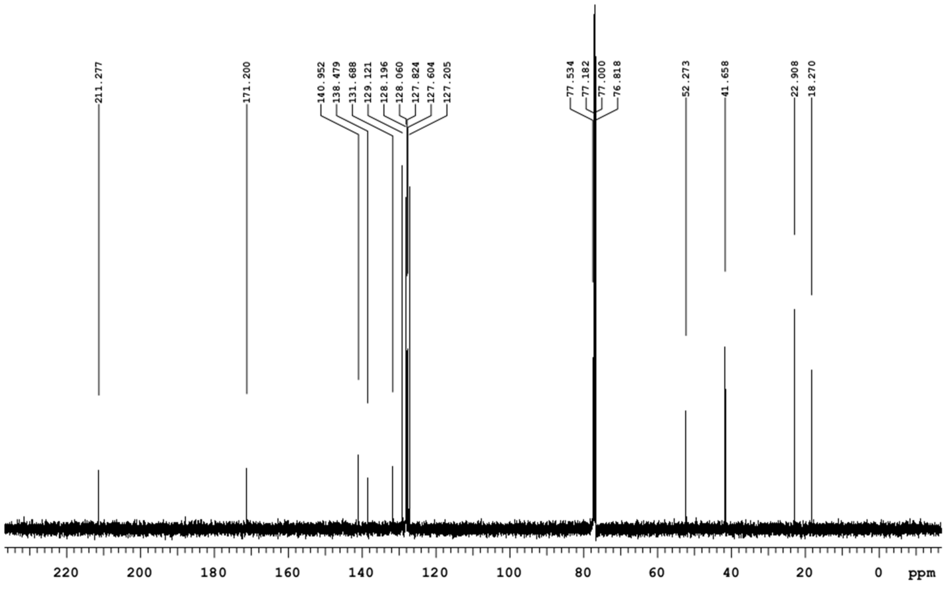
Scheme 89, Minor Diastereomer



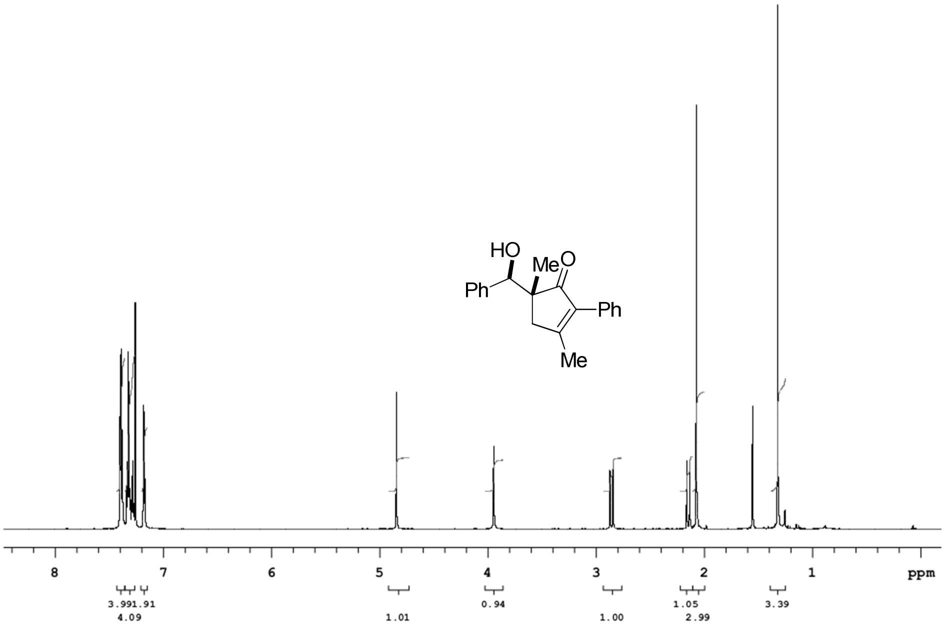


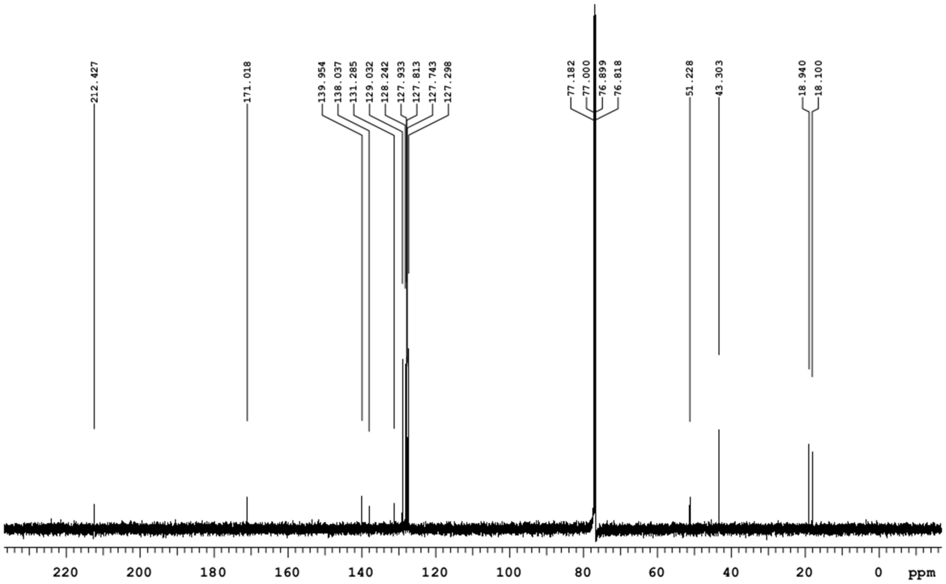
Scheme 89, Major Diastereomer



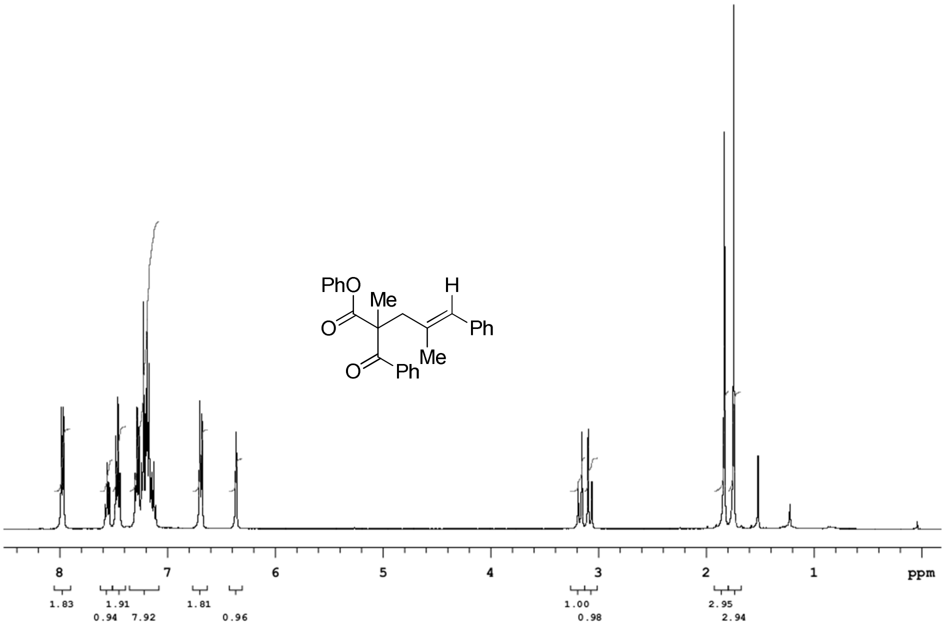


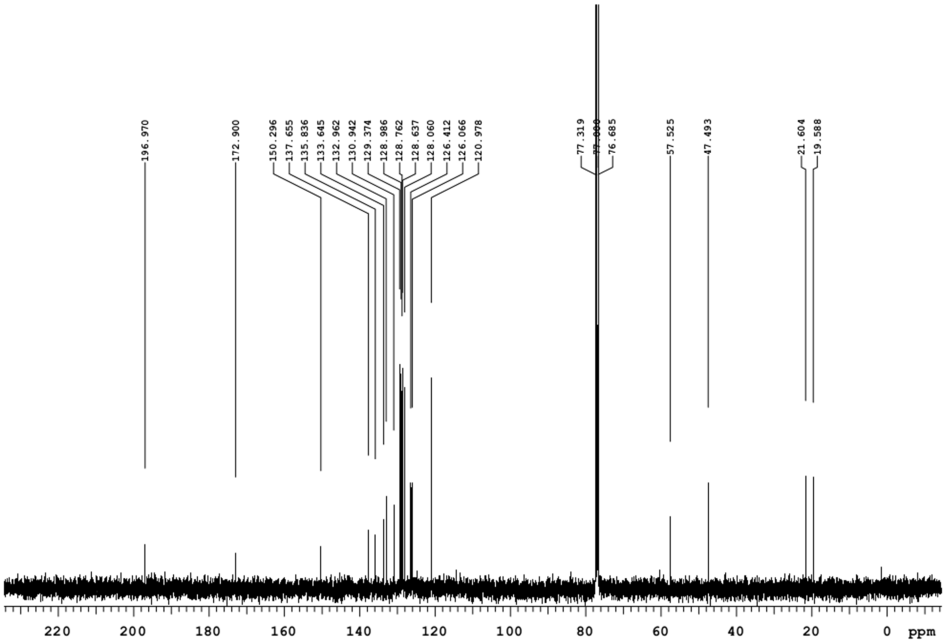
Scheme 89, Minor Diastereomer



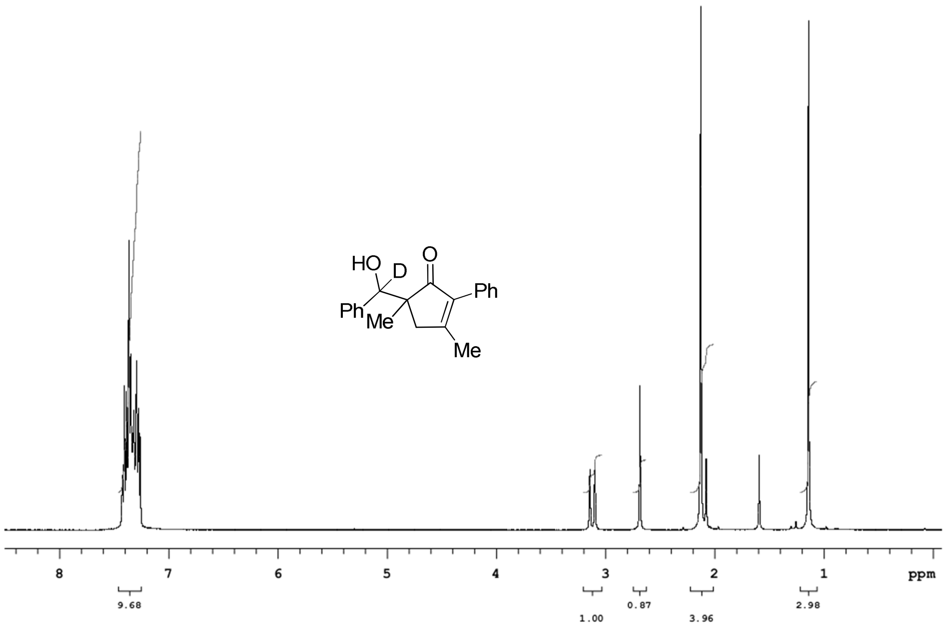


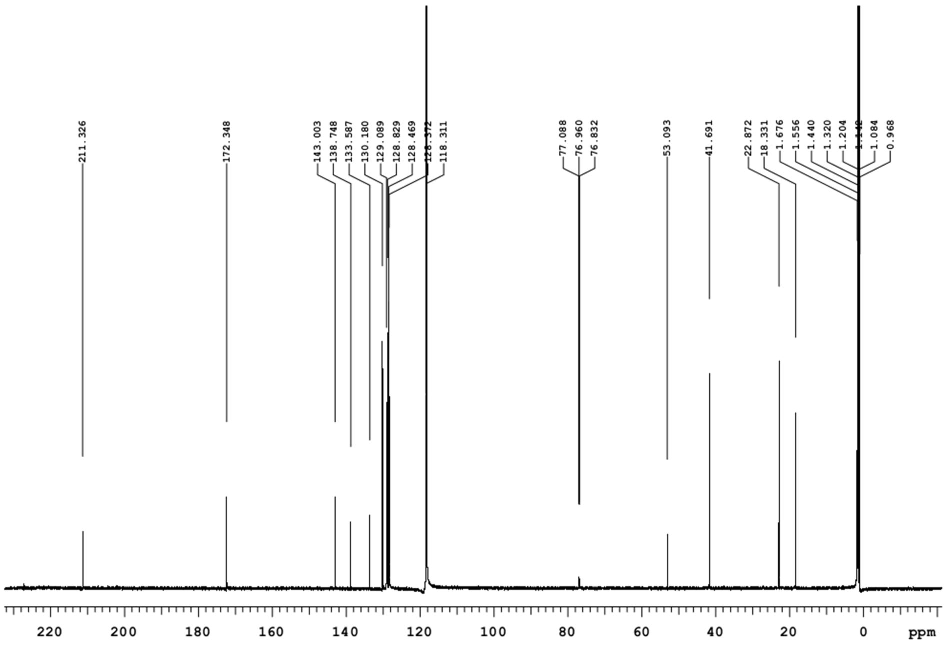
Scheme 95, 168



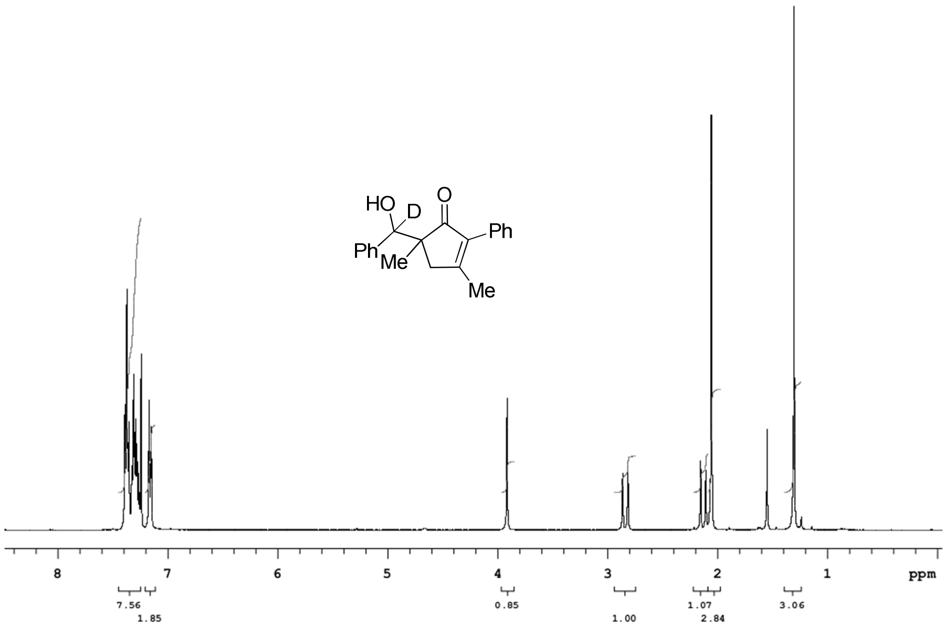


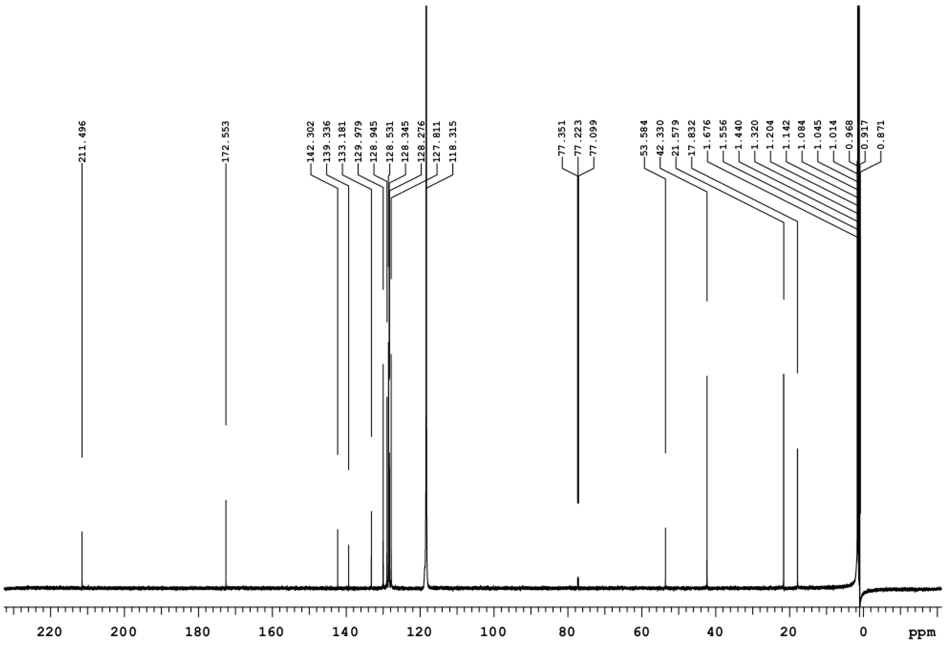
Scheme 96, Major Diastereomer



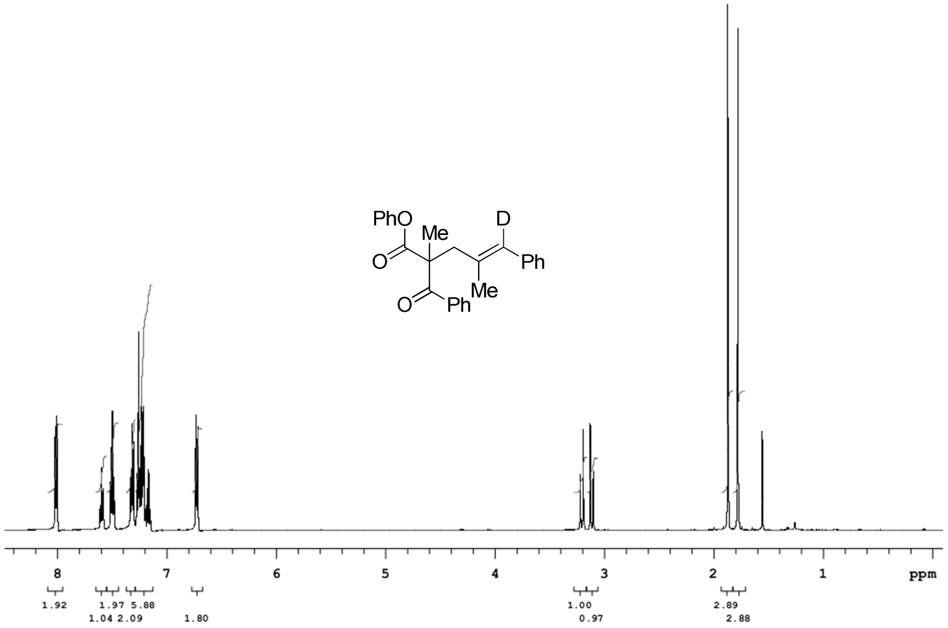


Scheme 96, Minor Diastereomer





Scheme 96


PhO
Me
D
O
Ph
Me
O
Ph
8
7
6
5
4
3
2
1
ppm
1.92
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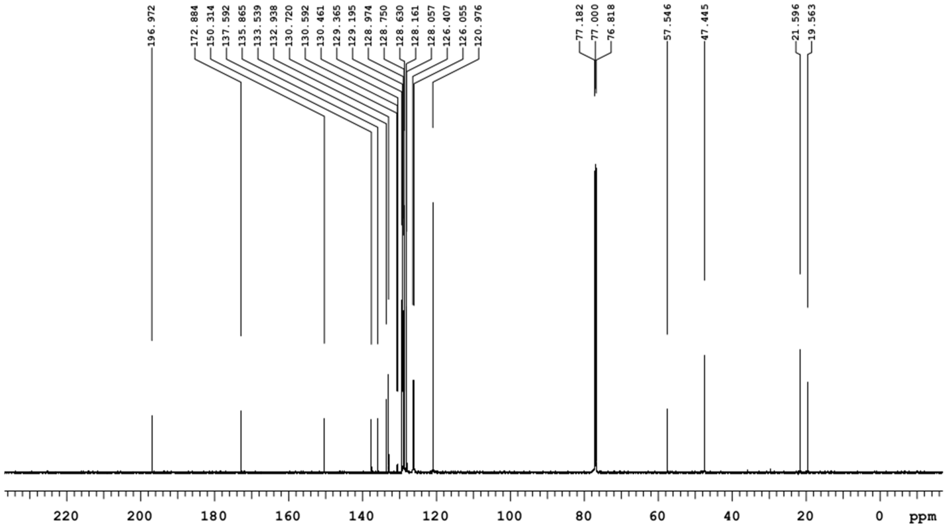
1.00
0.97
2.89
2.88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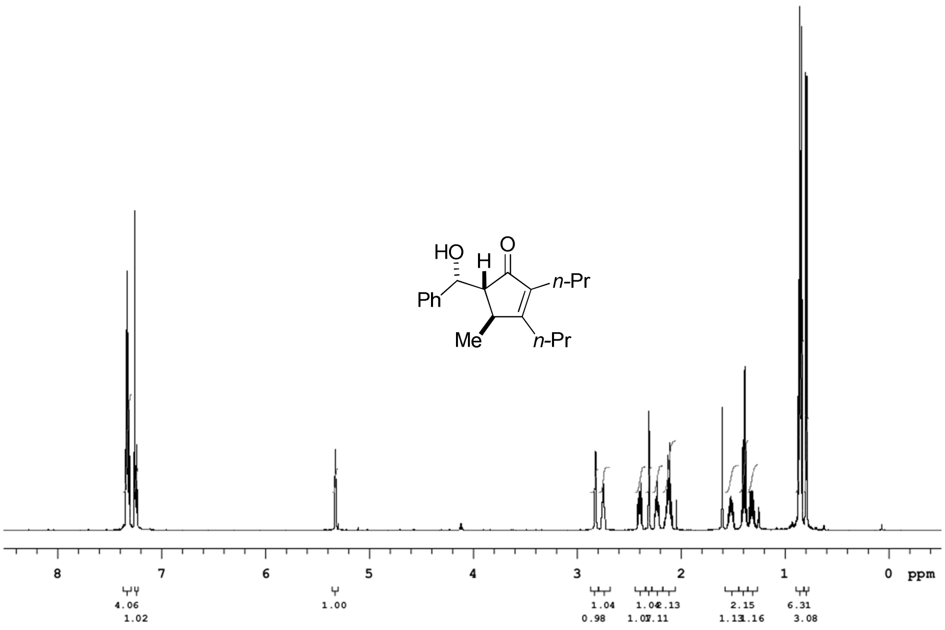
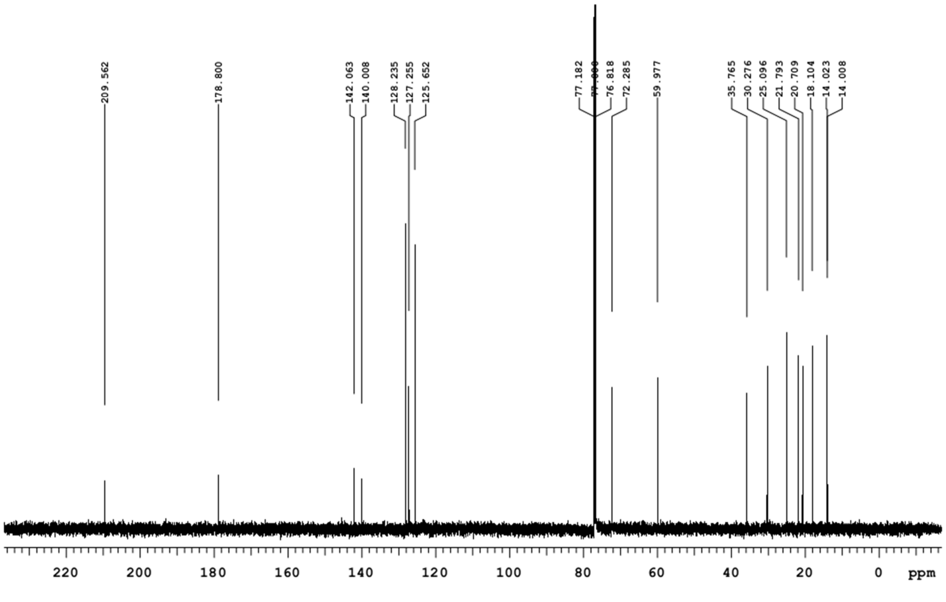
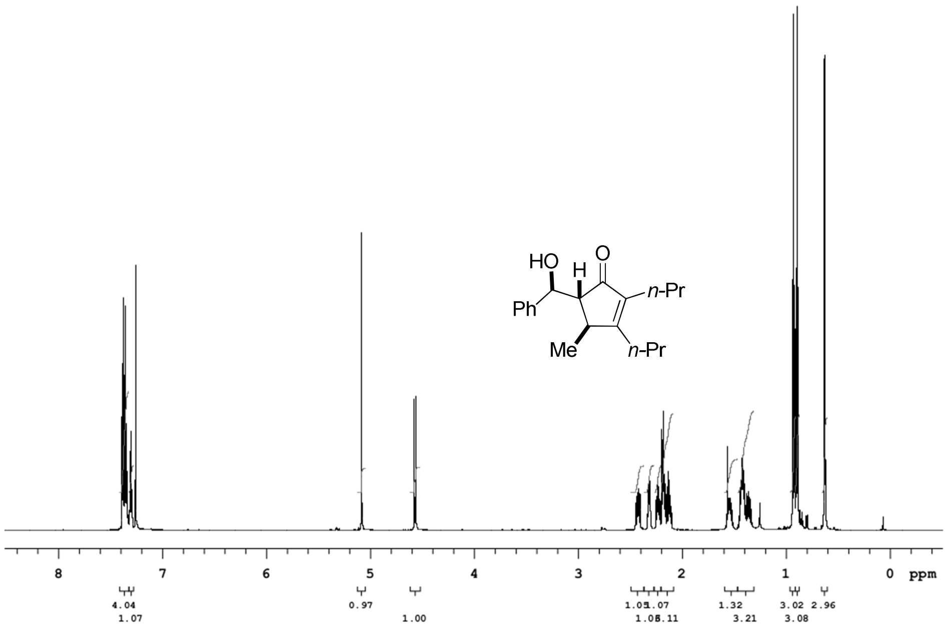
172.884
150.314
137.592
135.865
133.539
132.938
130.720
130.592
130.461
129.365
129.195
128.974
128.750
128.630
128.161
128.057
126.407
126.055
120.976
77.182
77.000
76.818
57.546
47.445
21.596
19.563
220
200
180
160
140
120
100
80
60
40
20
0
ppm

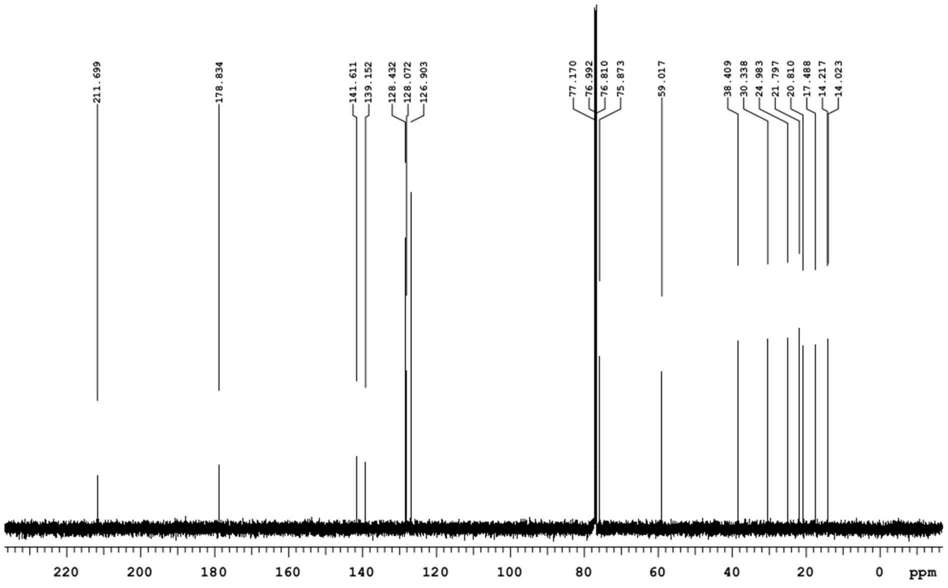
Scheme 89, Major Diastereomer



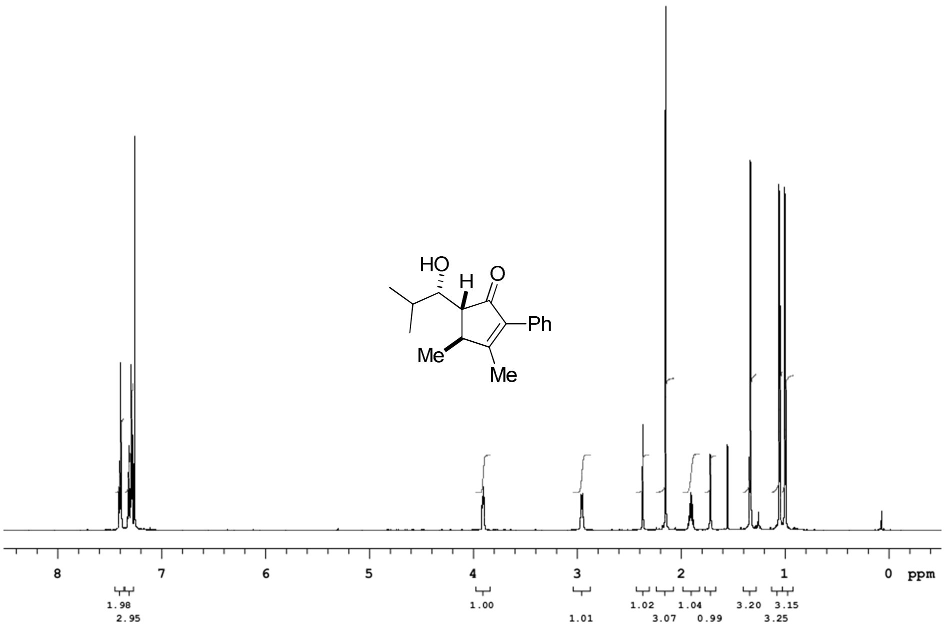


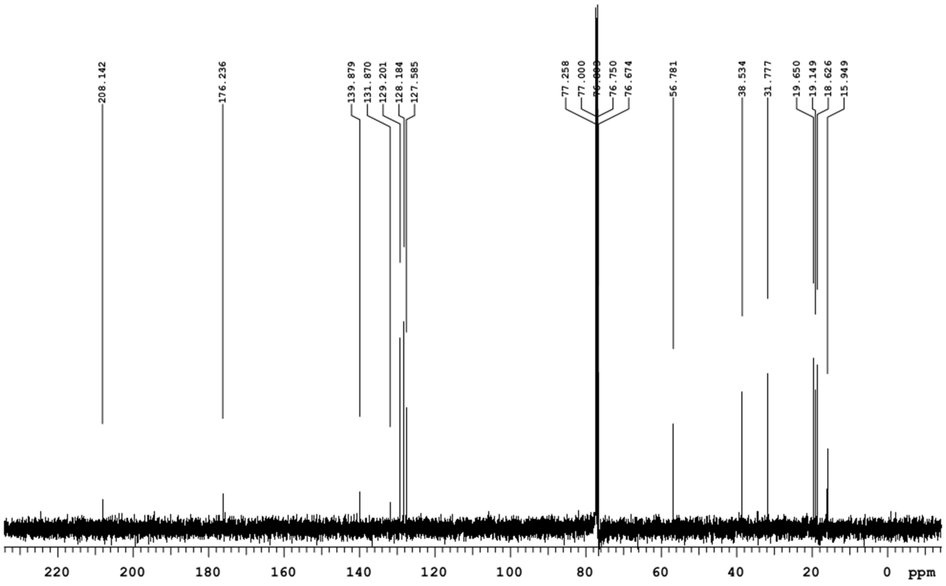
Scheme 89, Minor Diastereomer



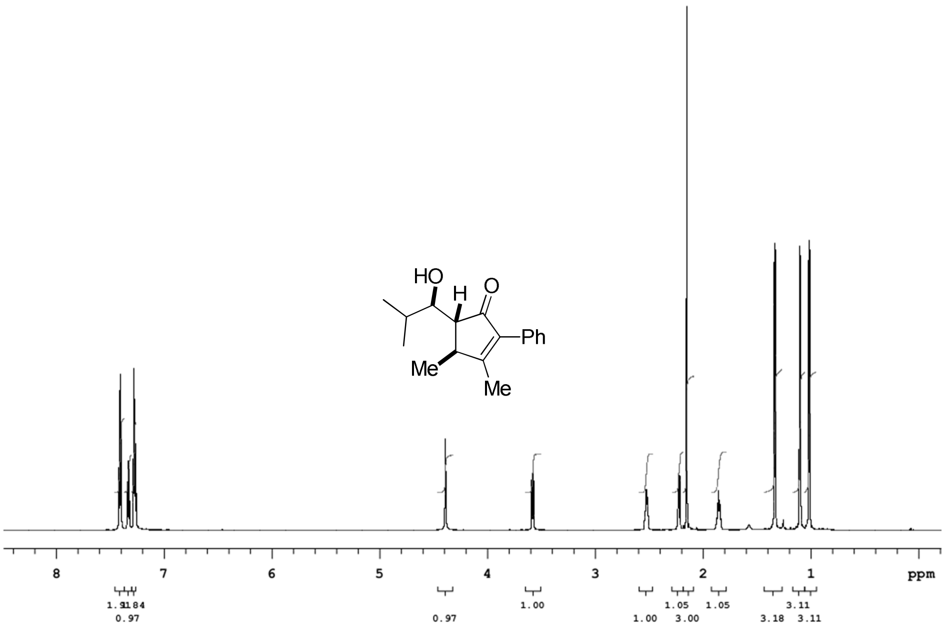


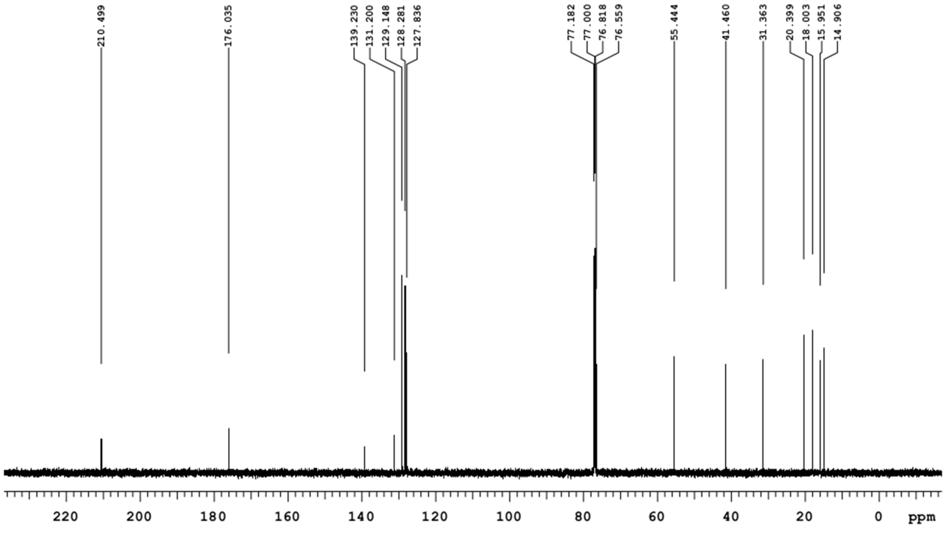
Scheme 89, Minor Diastereomer



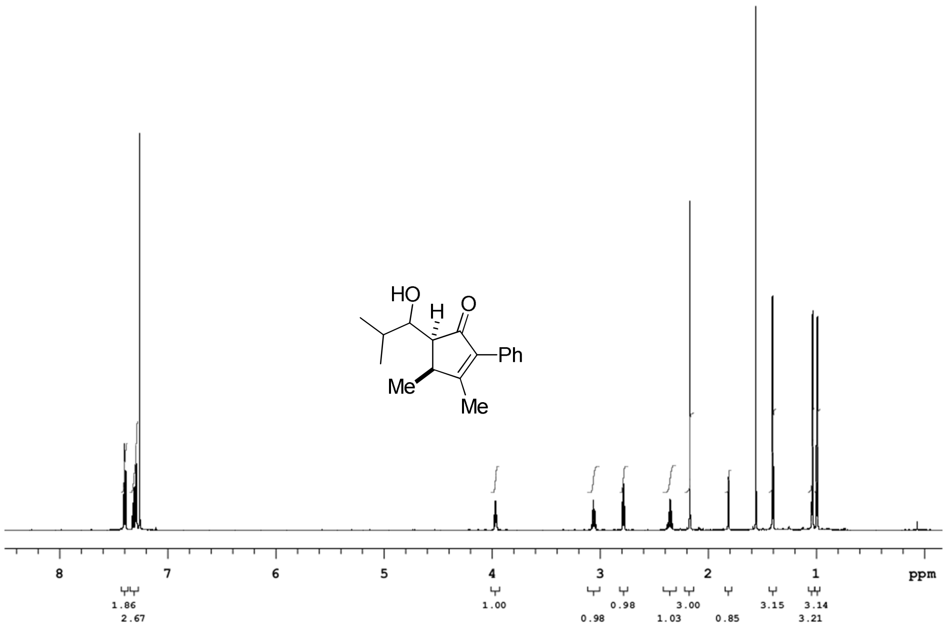


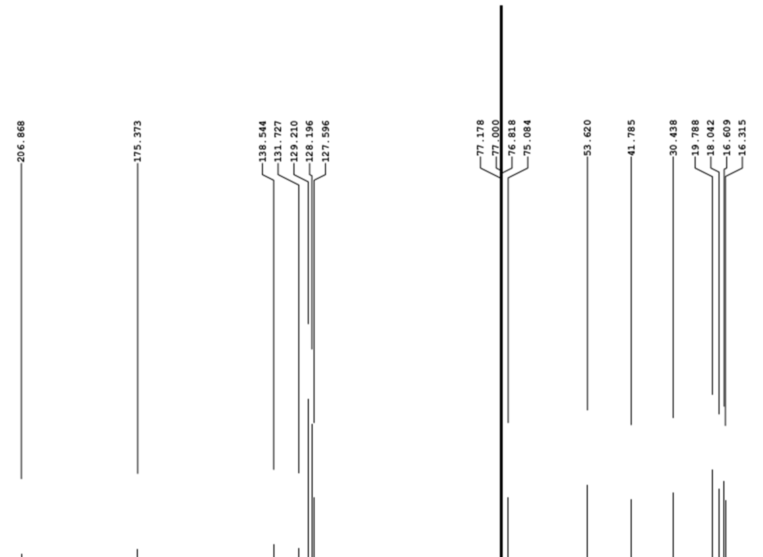
Scheme 89, Major Diastereomer



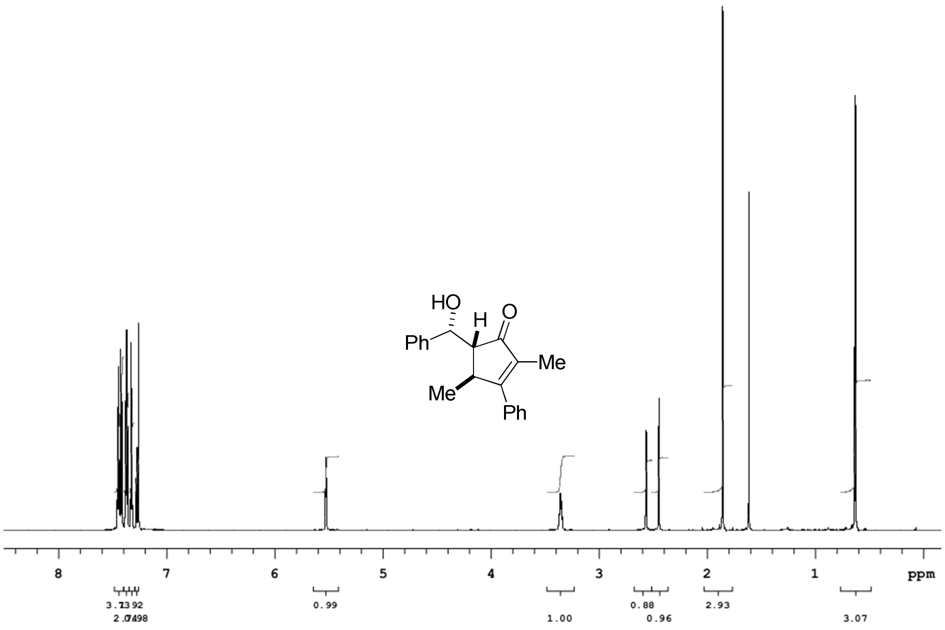


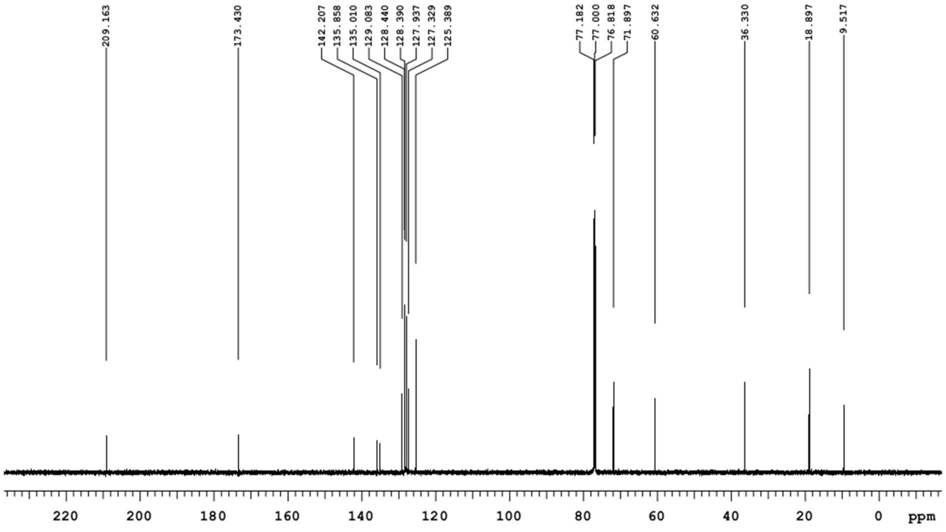
Scheme 89, Cis Diastereomer



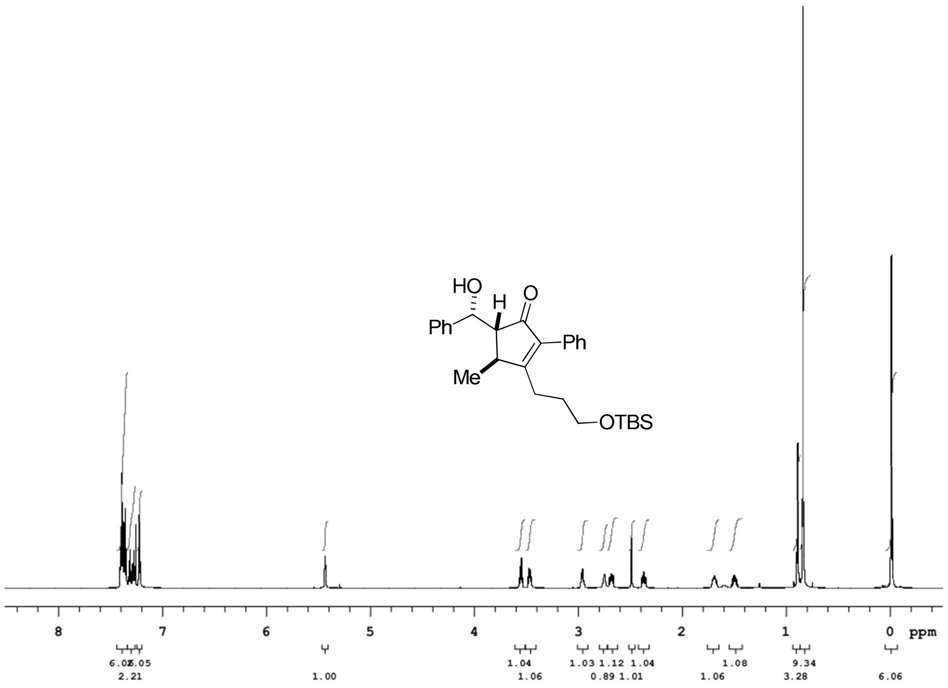


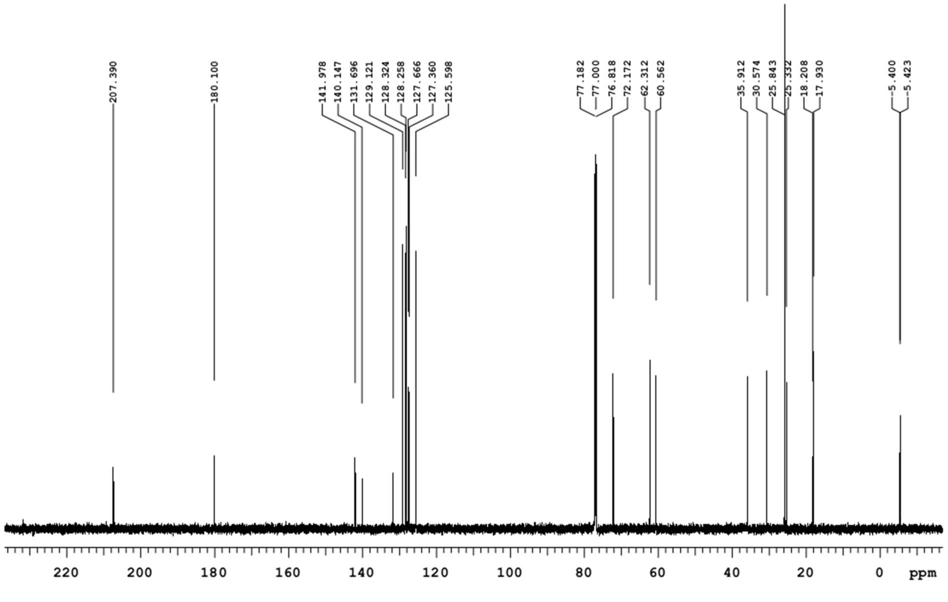
Scheme 89, Minor Regioisomer



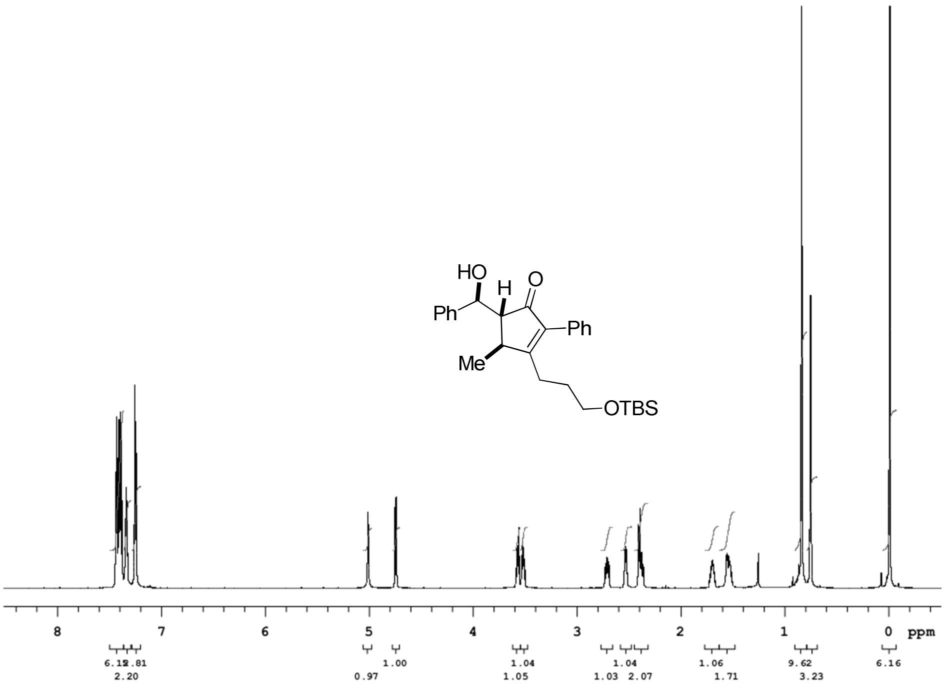


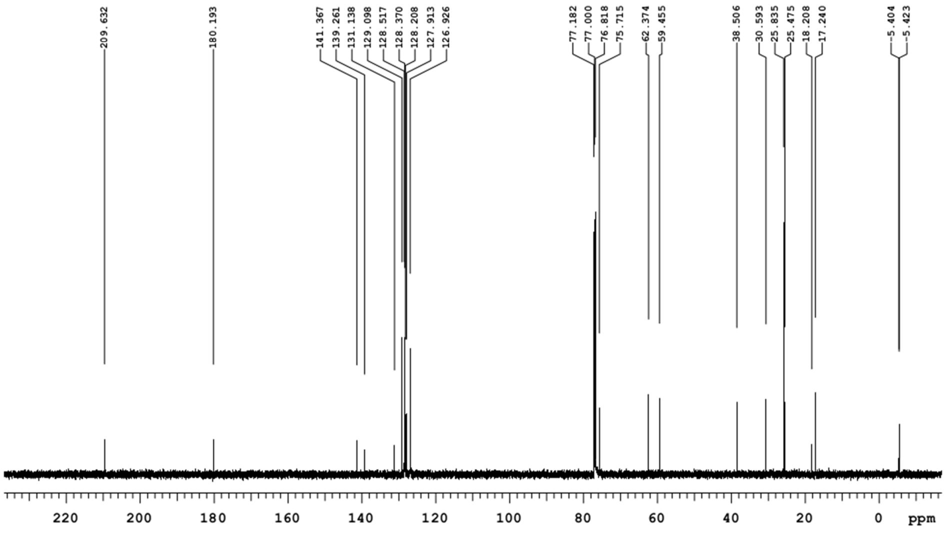
Scheme 89, Major Diastereomer



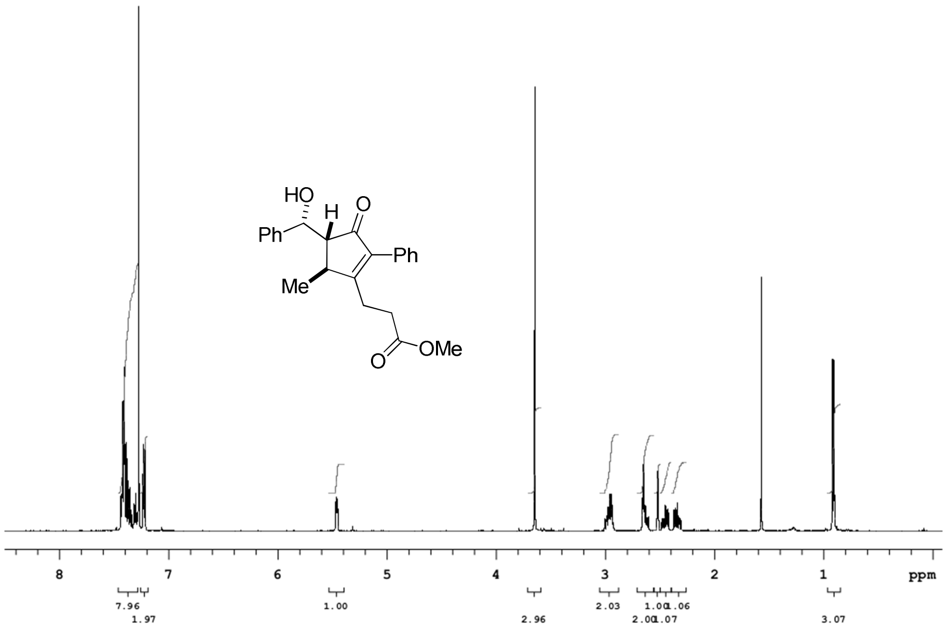


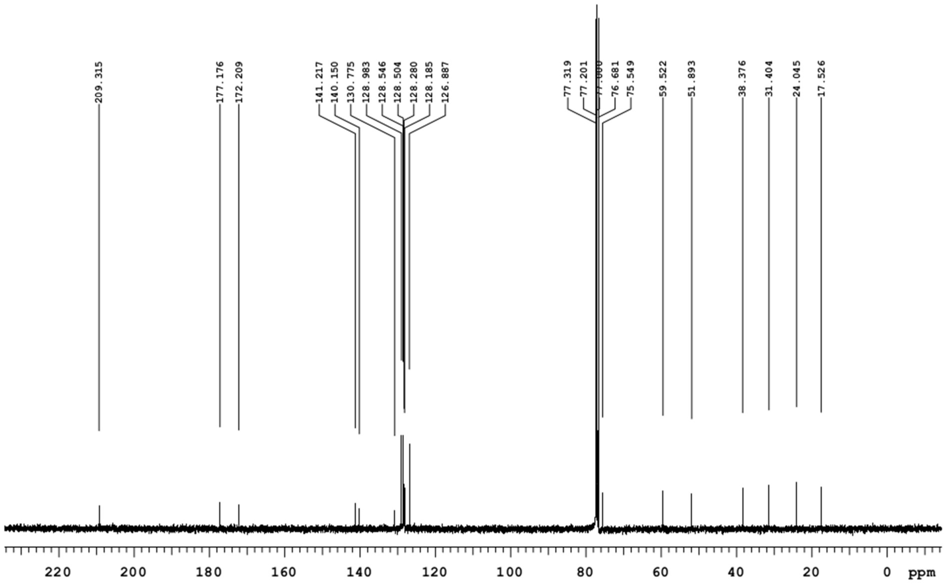
Scheme 89, Minor Diastereomer



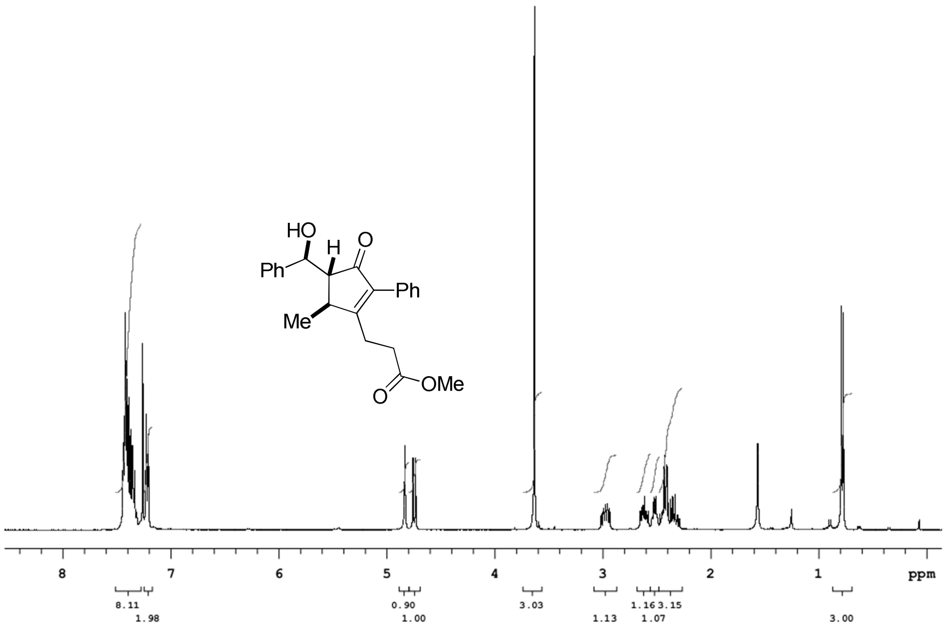


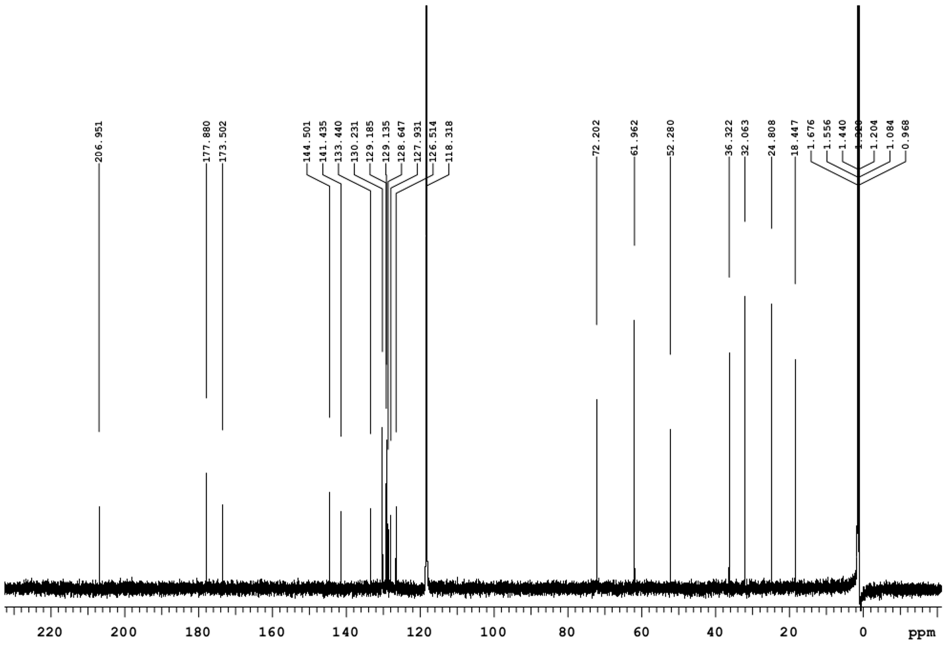
Scheme 89, Major Diastereomer



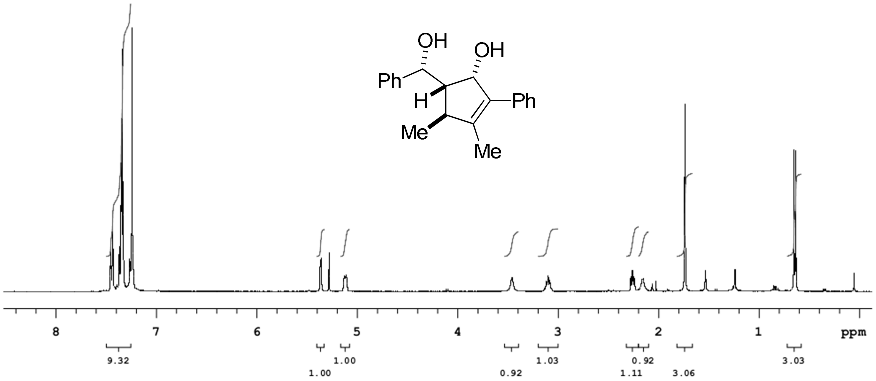


Scheme 89, Minor Diastereomer

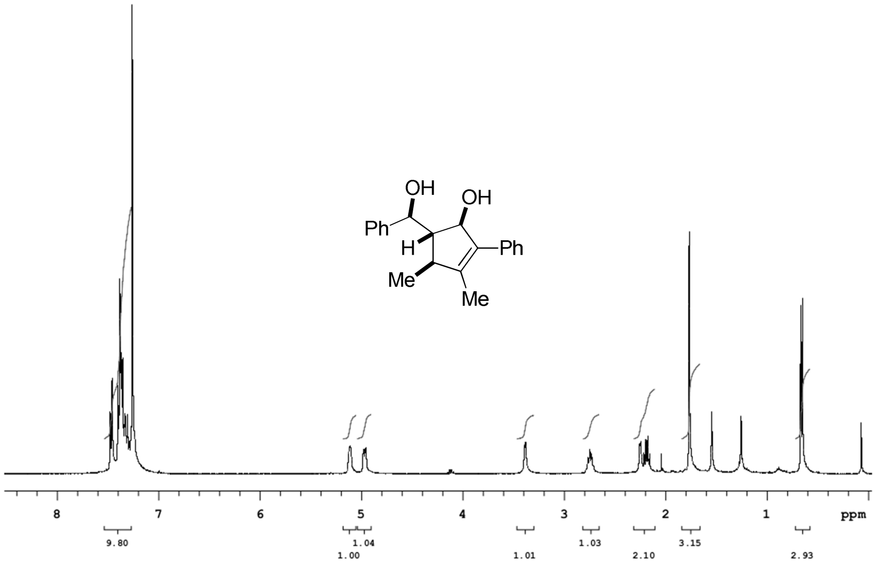




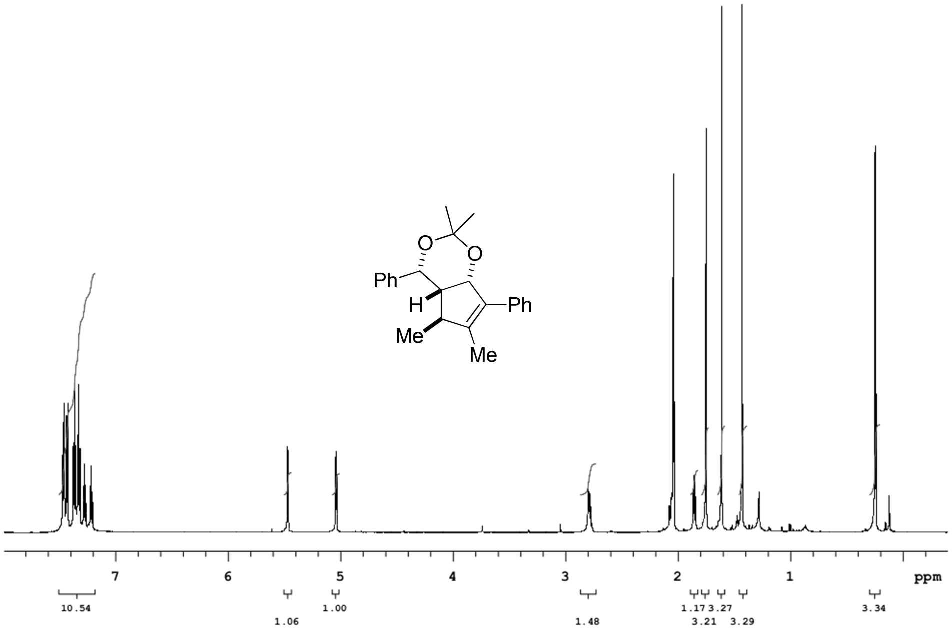
Scheme 93b, Major Diol Diastereomer 159a

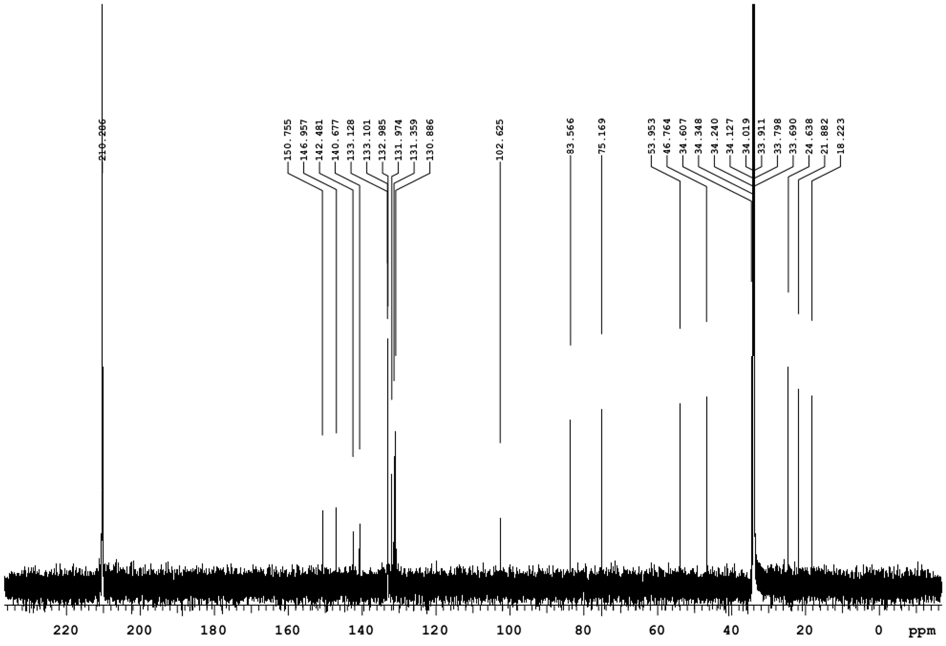


Scheme 93b, Major Diol Diastereomer 159b

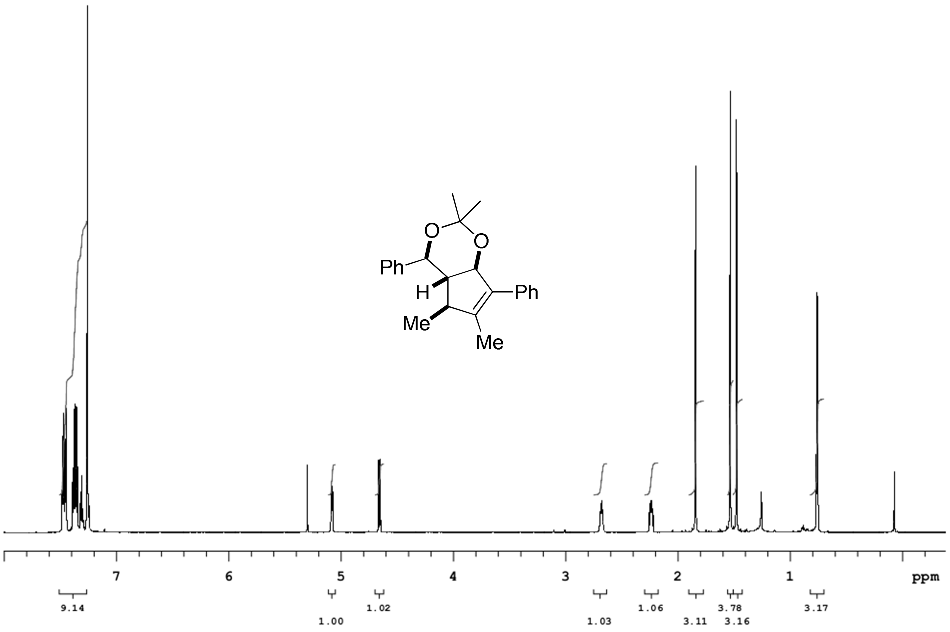


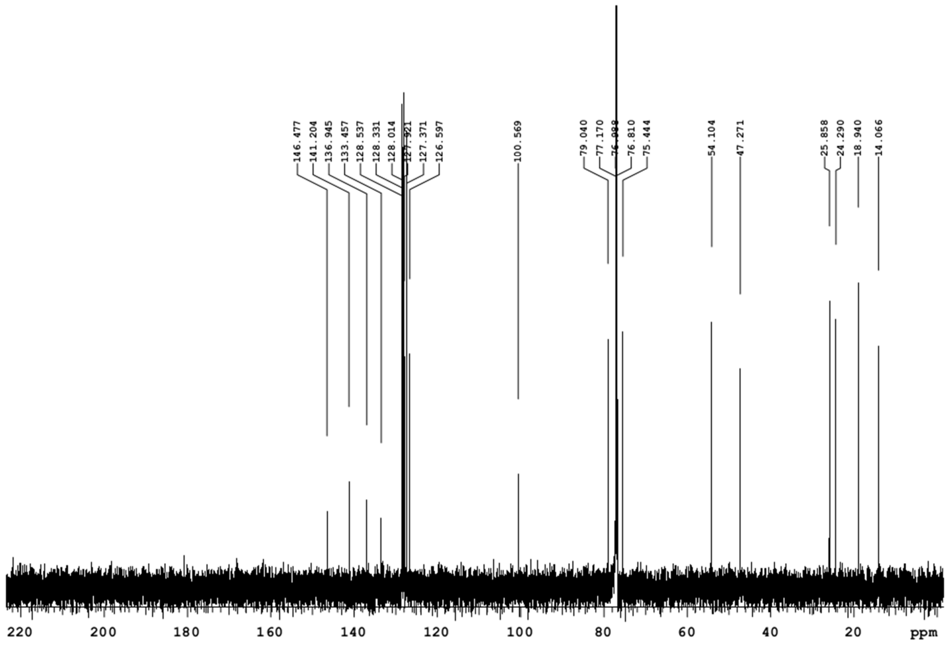
Scheme 93b, Acetalide Diastereomer 159a



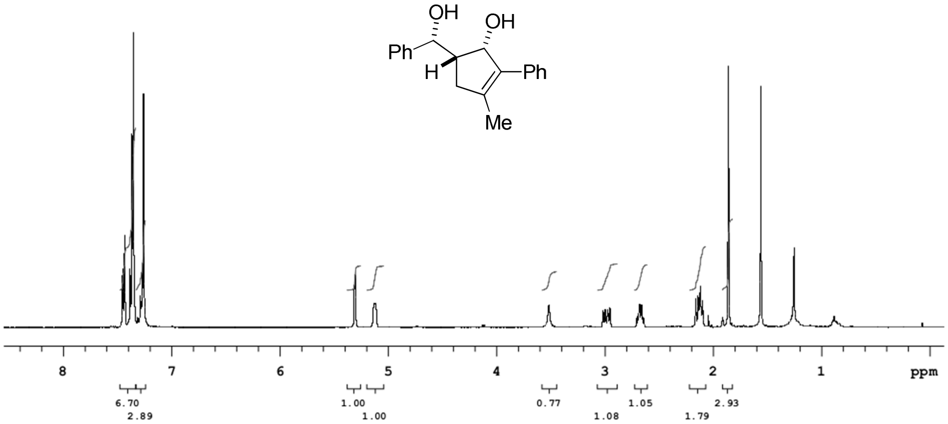


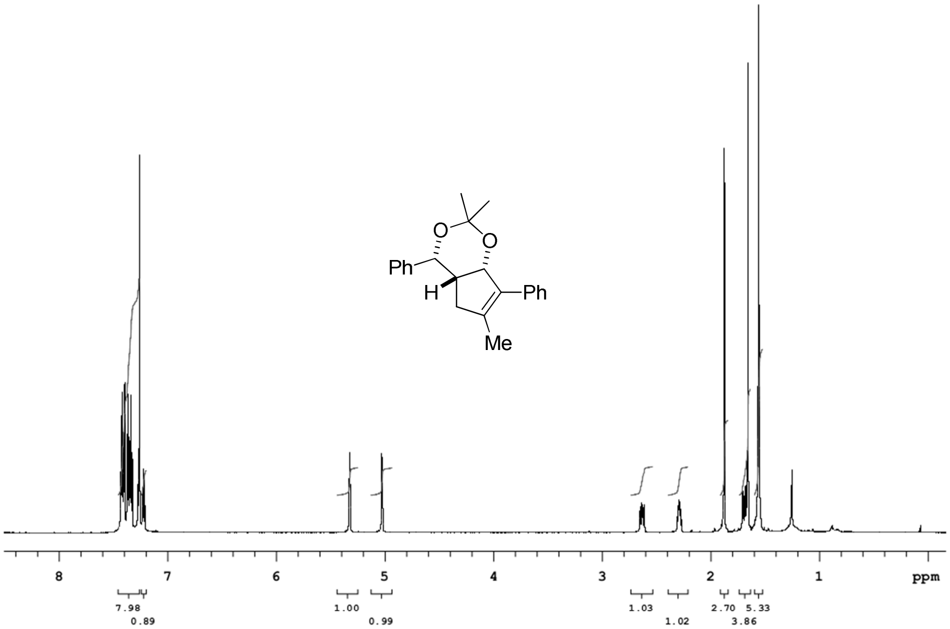
Scheme 93b, Acetalide Diastereomer 159b



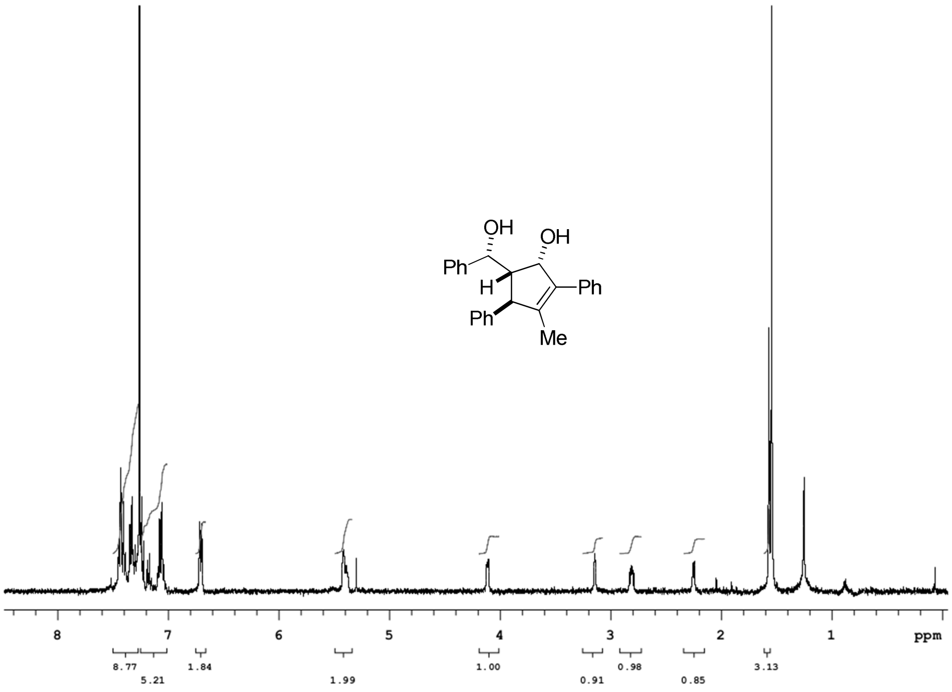


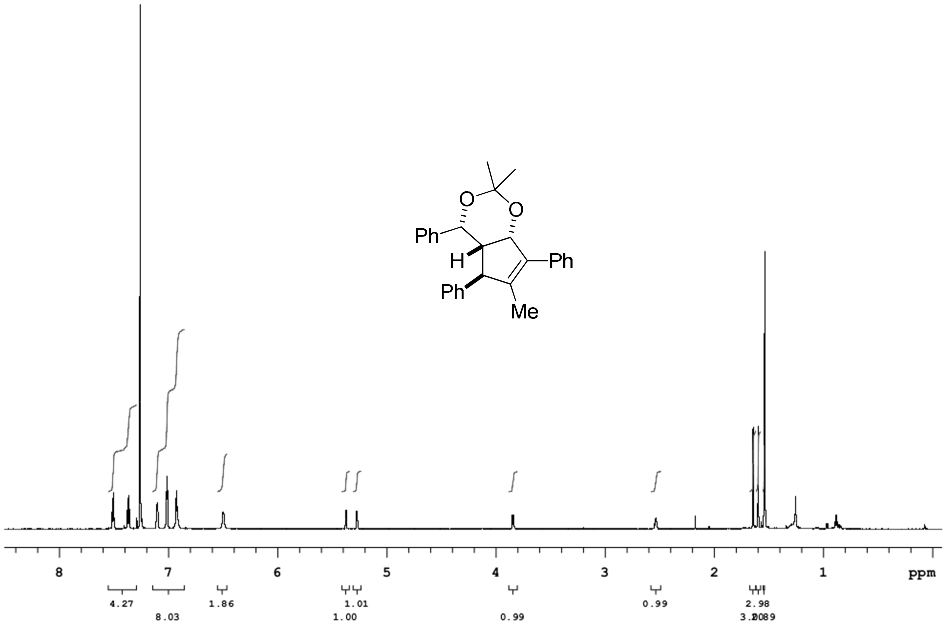
Scheme 93b, Diastereomer 162



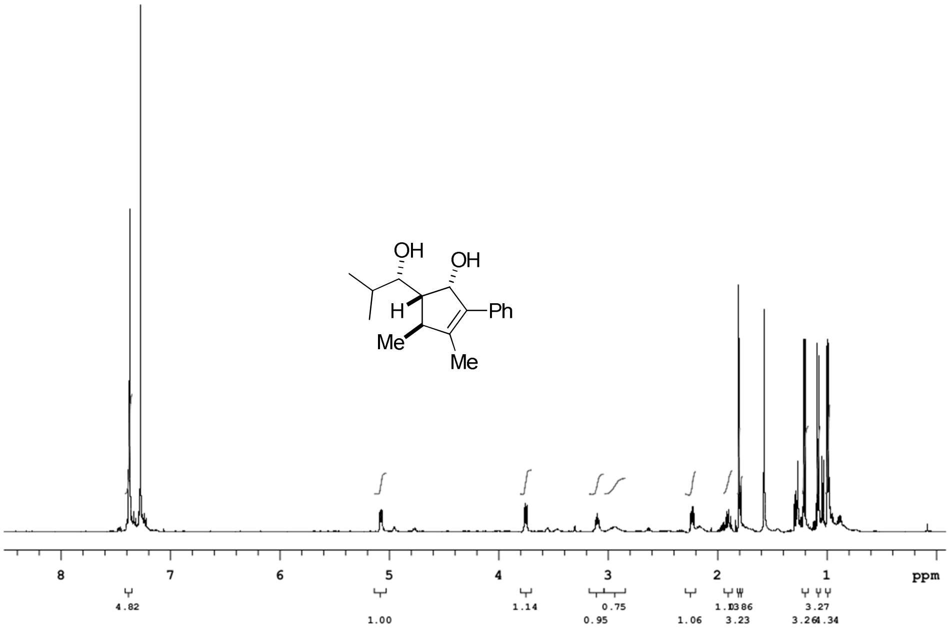


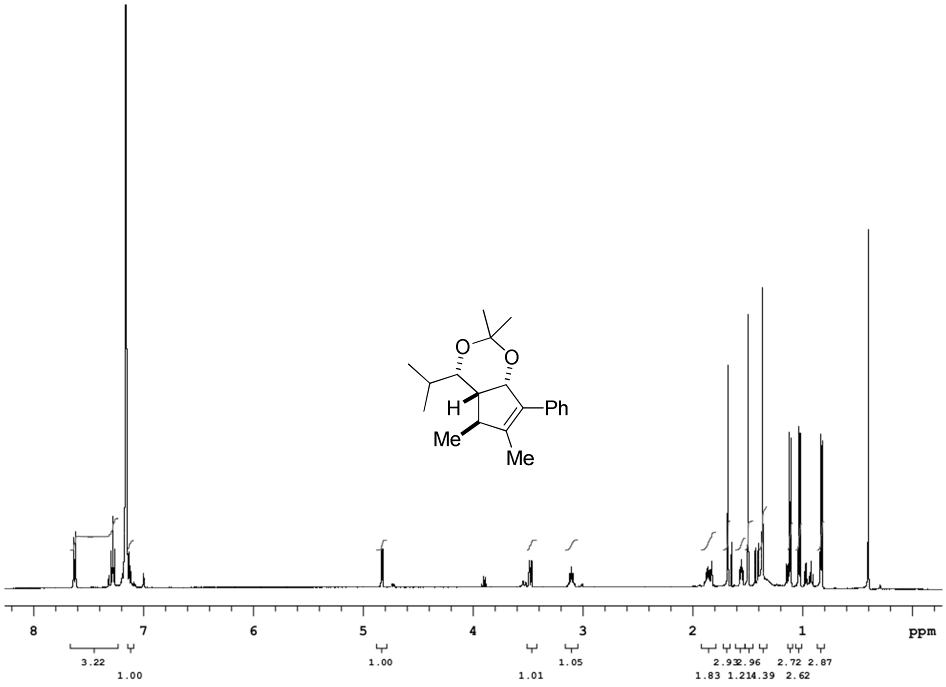
Scheme 93b, Diastereomer 161



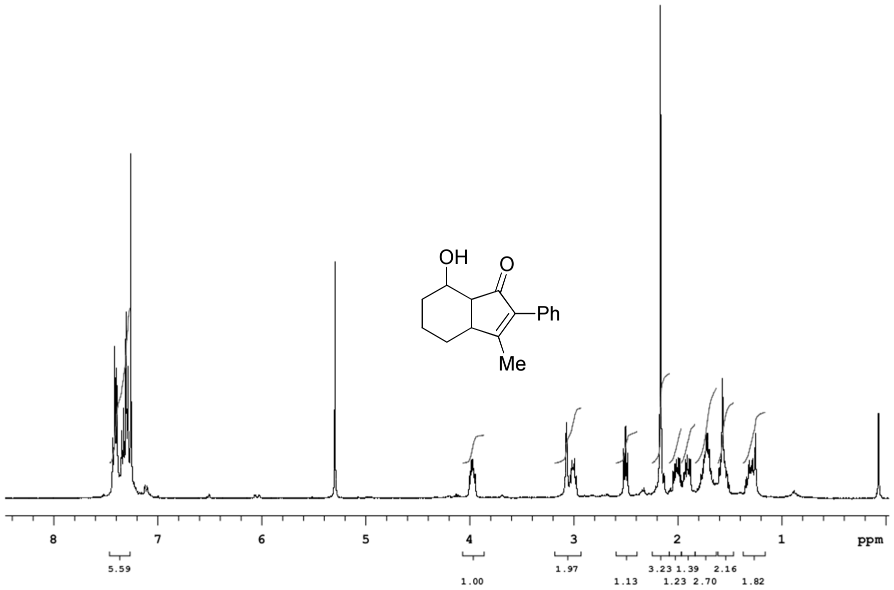


Scheme 93b, Diastereomer 160





Scheme 90



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