The Reductive Couplings of Enones and Alkynes and Application to Heterocycle Synthesis

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Chemistry)
in the University of Michigan
2012

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Dedication

I dedicate this dissertation to my parents, Cynthia and Jeffery, and to Amanda.

Acknowledgements

I'd like to thank my advisor John Montgomery for his guidance and mentorship. Under his supervision, I have learned to be a more creative thinker and a dedicated researcher. I'd also like to thank my dissertation committee for all of their helpful comments and advice.

I'd also like to thank the members of the Montgomery lab past and present who have helped me during my time in the group. Through my discussions and interactions with them, I've grown as a chemist, and they have helped make graduate school a more enjoyable experience. The efforts of Zach Miller, Taylor Haynes, and Aireal Jenkins are greatly appreciated with regards to proof-reading this dissertation.

Last and certainly not least, I'd like to thank my family, friends, and my fiancée, Amanda for their support throughout my graduate career.

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Abbreviations

Ac	acetyl
acac	acetylacetone
Ar	aryl
BINOL	1,1'-bi-2-napthol
n-Bu	butyl
t-Bu	*tert*-butyl
°C	degrees celsius
COD	cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
DIBALH	diisobutyl aluminum hydride
DMP	dimethoxy propane
DP-IPr	4,5-diphenyl-1,3-bis(2,4,6-triisopropylphenyl)-4,5-dihydro-imidazolium
DP-I*t*-Bu	1,3-bis(3,5-di-tert-butylphenyl)-4,5-diphenyl-4,5-dihydro-imidazolium
Dppe	1,2-Bis(diphenylphosphino)ethane
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
n-hex	hexyl
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
IMes	1,3-bis-(1,3,5-trimethylphenyl)imidazol-2-ylidene
IPr	1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene
IPrBAC	N^1,N^1,N^2,N^2-tetraisopropylcycloprop-1-ene-1,2-diamine

ITol	1,3-bis-(4-methylphenyl)imidazol-2-ylidene
KHMDS	potassium bis(trimethylsilyl)amide
Me	methyl
Mes	mesityl
min	minute(s)
MOM	methoxymethyl
MS	molecular sieves
μW	microwave
NHC	N-heterocyclic carbene
n-pent	pentyl
Ph	phenyl
pin	pinacol
i-Pr	isopropyl
n-Pr	propyl
rt	room temperature
SIPr	1,3-bis(2,6-diisopropylphenyl)-4,5-dihydro-imidazolium
sty	styrene
TBAF	tetrabutyl ammonium fluoride
TES	triethylsilyl
TESH	triethylsilane
Tf	triflate
THF	tetrahydrofuran
TIPSH	triisopropylsilane
TMDSO	tetramethyldisiloxane
TMEDA	Tetramethylethylenediamine
TMS	trimethylsilyl
Ts	tosyl

Abstract

A new method for the reductive coupling of alkynes to enones has been developed. This method provides an alternative to more traditional methods of conjugate addition and provides advances in terms of regioselectivity. Other methods rely on the use of preformed organometallic reagents that must be generated *in situ* stoichiometrically, while this approach utilizes simpler, more readily available starting materials. This method also offers an improved substrate scope over analogous methodologies.

Pyrroles, furans and thiophenes make up a class of heterocycles that are present in a broad range of biologically active natural products and pharmaceutically relevant molecules. There is a wide variety of methods for their synthesis, and one of the most widely used strategies, the Stetter-Paal-Knorr sequence, relies on access to 1,4-diketones. The reductive coupling of enones and alkynes allows for access to products that, upon oxidative cleavage, can be used as precursors to five-membered heterocycles. This process allows access to a wide variety of diversely substituted and polycyclic products.

The development of regiocontrol for a variety of coupling reactions was examined. Being able to selectively hydroborate or hydrosilylate π-systems such as dienes or alkynes provides access to useful synthetic intermediates. In an attempt to

develop regiocontrol for the enone-alkyne reductive coupling, a new reaction was discovered, allowing for the stereoselective synthesis of 1,4-skipped dienes.

Chapter 1

Introduction to Metal-Catalyzed Reductive Couplings

1.1 Introduction to the Metal-Catalyzed Conjugate Addition Reaction

1.1.1 Relevance of C-C Bond Forming Conjugate Addition

The conjugate addition reaction is one of the older known reactions in chemistry, and the carbon-carbon bond-forming variant has been widely used in organic synthesis. The addition of a nucleophile to an α,β-unsaturated carbonyl-containing compound results in the formation of an enolate, which can be protonated to form the γ,δ-unsaturated carbonyl directly, or be used to trap a different electrophile, functionalizing the starting material further. Unlike the conjugate addition of non-carbon nucleophiles, the carbon-carbon bond forming conjugate addition reaction is not reversible, making it an excellent method for coupling two organic fragments.

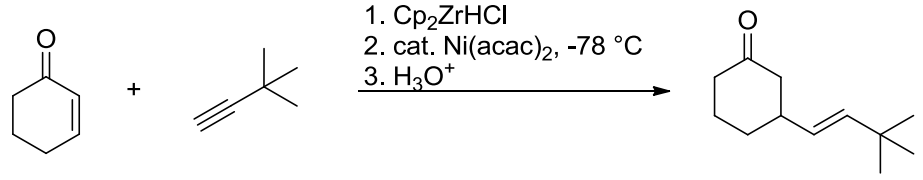
1.1.2 Methods for C-C Bond Forming Conjugate Addition

One of the seminal examples of a carbon-carbon bond-forming conjugate addition involves the addition of a vinyl halide to an α,β-unsaturated carbonyl with the aid of a cuprate reagent. In the presence of a lithium reagent, the vinyl halide undergoes lithium halogen exchange and forms a cuprate, which can then add to an electrophile. While this approach works well for a large variety of substrates, it does require the prior synthesis of the appropriately substituted vinyl halide, which in the case of more complicated targets

may not be trivial to synthesize. Terminal alkynes can also be utilized as the nucleophile for carbon-carbon bond-forming conjugate additions with enones using a nickel catalyst[1] or cuprate reagent (Scheme 1.1).[2] Using the Schwartz reagent, the alkyne undergoes a stereoselective hydrometallation to form an organometallic species that can then transmetallate with the copper reagent and add to the enone, giving the γ,δ-unsaturated ketone. The stereoselectivity observed in the product is controlled by the selective hydrozirconation the alkyne undergoes. This particular approach only works with high selectivity in the case of terminal alkynes, and can be accomplished using a nickel catalyst. In the case of internal alkynes, the yield is poor, due the lower reactivity towards zirconium hydride reagents.

Scheme 1.1 Conjugate Addition of Alkynes and Enones

Schwartz:



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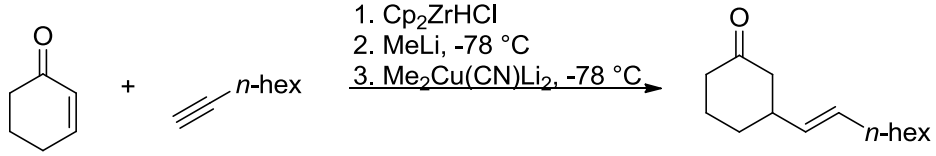
Lipshutz:



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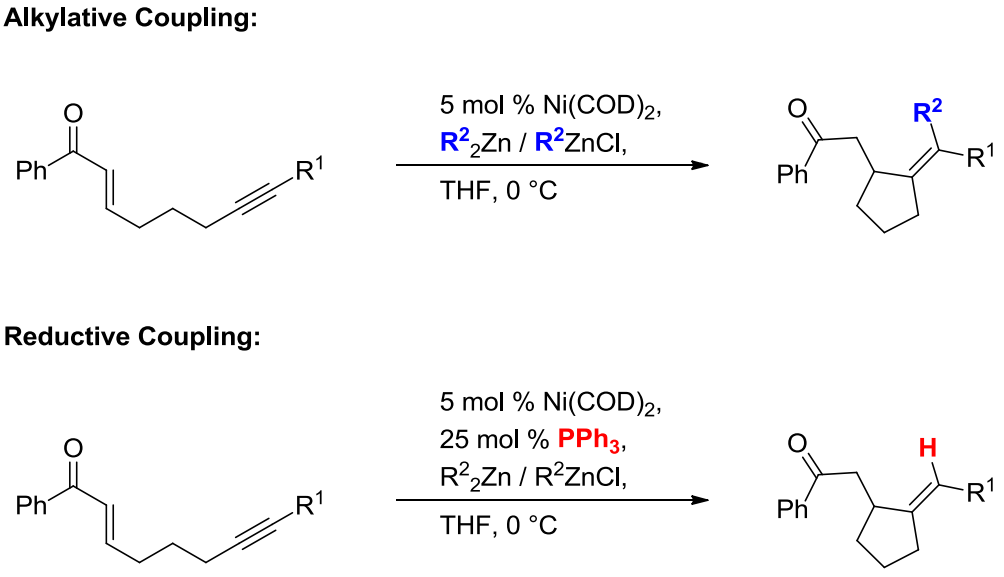
1.2 Reductive Coupling Background

1.2.1 Introduction to Enone-Alkyne Reductive Couplings

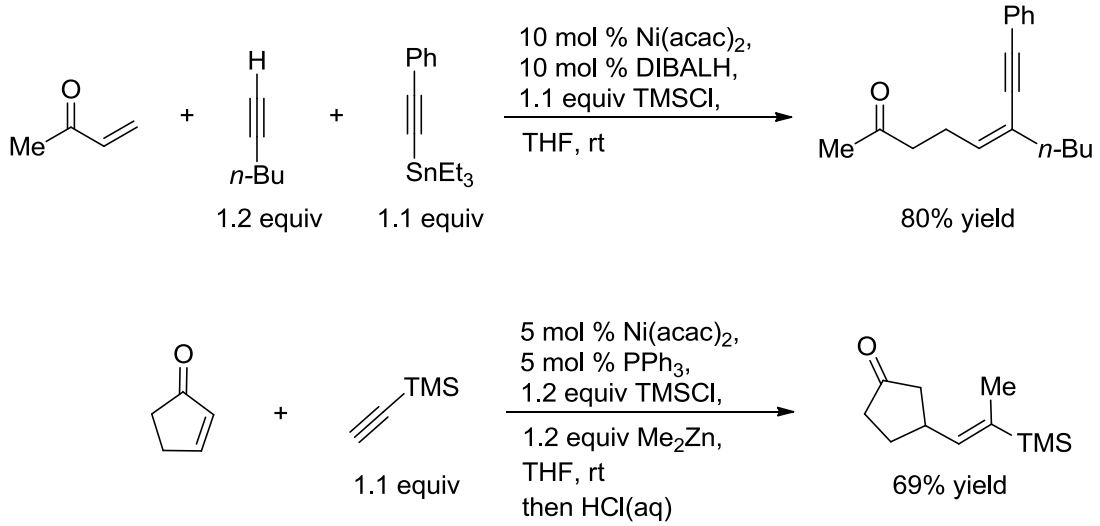
An early example of a reductive coupling of an enone and an alkyne was reported in our lab.[3] This transformation is limited to intramolecular reactions, and requires the use of an alkyl or aryl zinc reducing agent. In the presence of a nickel(0) catalyst and a zinc reducing agent, the tethered alkynyl-enone cyclizes with incorporation of the R-group from the zinc reagent (Scheme 1.2). In the presence of a phosphine ligand, the same reaction proceeds with incorporation of hydrogen instead of alkylation. The addition of the phosphine ligand allows for the reaction to proceed with β-hydride elimination and subsequent reductive elimination, as opposed to the ligand free conditions, in which the catalyst undergoes reductive elimination immediately resulting in alkylative coupling. This method was also applied to the synthesis of bicyclic, heterocycle-containing compounds.[4]

Scheme 1.2 Nickel-Catalyzed Alkylative and Reductive Couplings



These conditions were also examined in an intermolecular setting.[5] These reactions proceeded in lower yields than the intramolecular case, and even in the presence of a triphenylphosphine ligand gave the alkylative coupling product. When excess alkyne was used, incorporation of multiple equivalents of alkyne into the product was observed. Ikeda and coworkers had shown previously that this conjugated enyne product was also obtainable from a three component coupling of enones, alkynes and alkyl-tin reagents (Scheme 1.3).[6] The Ikeda group has also demonstrated the intermolecular coupling of enones and alkynes using a nickel(0)/triphenylphosphine catalyst with trimethylsilyl chloride and dimethylzinc.[7] This reaction proceeded in moderate yield for a limited scope of substrates.

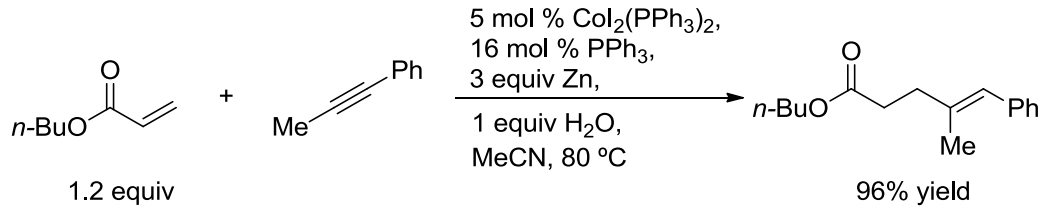
Scheme 1.3 Alkylative Reductive Coupling with Alkynyltin Reagents and Me_2Zn



The Cheng group developed a method for the reductive coupling of alkynes and conjugated alkenes (Scheme 1.4).[8] This system utilizes a cobalt catalyst with a phosphine ligand with zinc acting as a reducing agent to allow catalytic turnover. This transformation works for a broad scope of conjugated alkenes, including alkenes

conjugated to esters, sulfones and nitriles. The reactions gave only one regioisomer of the product in all cases examined.

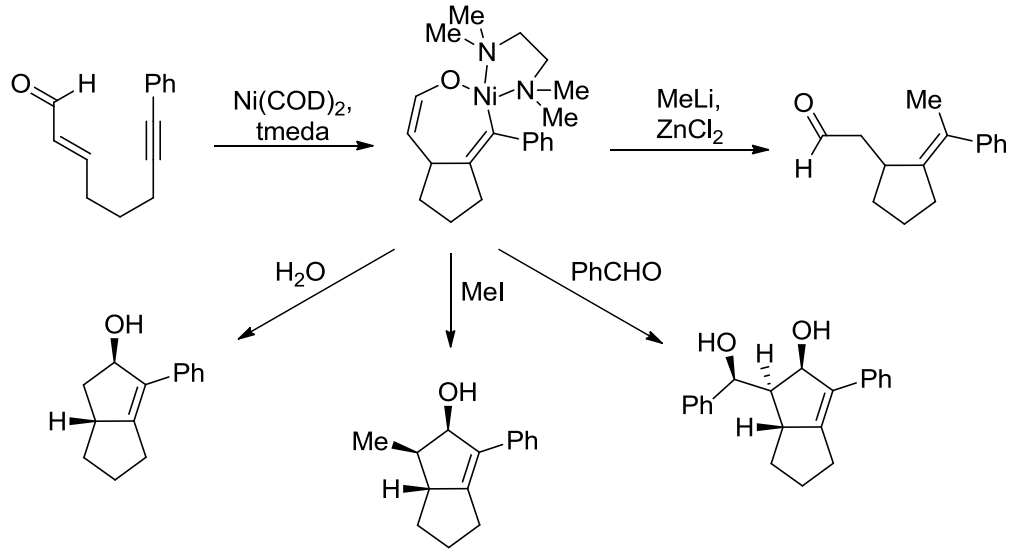
Scheme 1.4 Cobalt-Catalyzed Reductive Coupling



1.2.2 [3+2] Cycloaddition of Enals and Alkynes

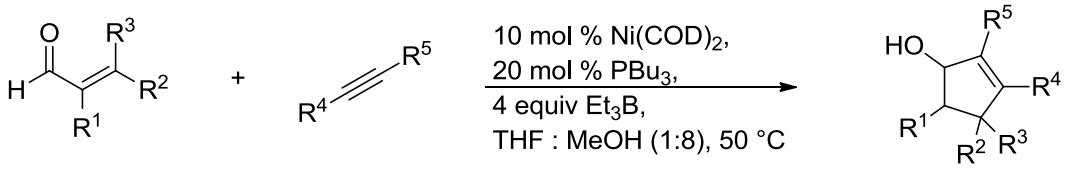
During the course of computational and mechanistic studies of the intramolecular enone-alkyne reductive coupling, alkynyl-enals were examined (Scheme 1.5).[9] In these investigations, the intramolecular substrates were subjected to $Ni(COD)_2$ and TMEDA, and the resulting metallacycle was formed and isolated. The reactivity of this intermediate was then probed by exposing it to different electrophiles. When an enal was used and the resulting metallacycle was treated to water, the cyclopentenol product was formed in high yield. Despite the high yield, this process suffered from the fact that stoichiometric nickel was required.

Scheme 1.5 Metallacycle Capture by TMEDA



Eventually, an intermolecular, catalytic variant was developed (Scheme 1.6).[10] With $Ni(COD)_2$, tri-*n*-butylphosphine, triethylborane, and methanol as a co-solvent, the intermolecular reductive [3+2] cycloaddition of enals and alkynes was achieved. This reaction proved efficient for a broad range of substrates giving moderate to high yields with good regioselectivities and diastereomeric ratios. This transformation represents a major step forward in the development of reductive coupling reactions, allowing for an efficient intermolecular coupling reaction with the use of a milder reducing agent (when compared to alkyl zinc reagents).

Scheme 1.6 Enal-Alkyne [3+2] Cycloaddition



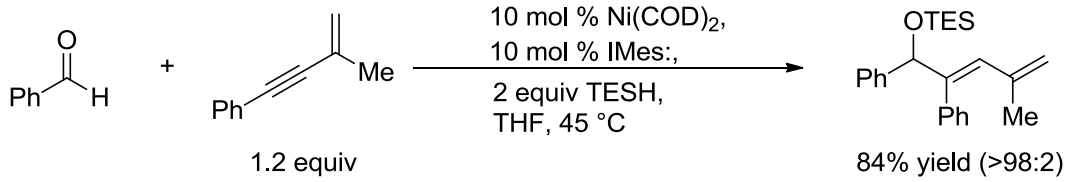
1.3 Introduction to Regiocontrol

1.3.1 Regiocontrol through Substrate Direction

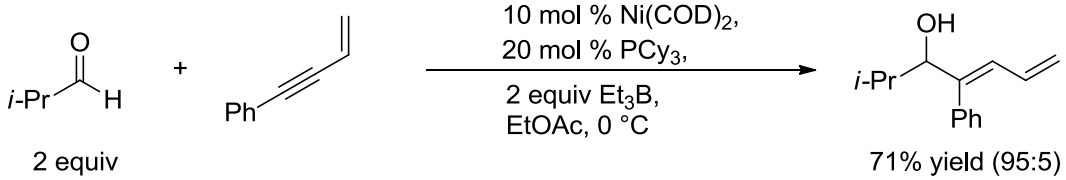
In the development of regioselective coupling reactions, such as the aldehyde-alkyne reductive coupling, there has also been an interest in developing a means to reverse the selectivity to the other regioisomer. This is due to the fact that the regiochemical outcome of these reactions is determined by the bias of the substrates. The method works well for symmetrically substituted internal alkynes since there is only one possible regioisomer of the product. However, when unsymmetrically substituted alkynes are used, the regioselectivity of the reaction is dependent on the inherent (electronic and steric) bias of the alkyne. The use of directing groups covalently attached to one of the substrates has been demonstrated as a means of accomplishing regiocontrol. During a mechanistic investigation of the nickel-catalyzed aldehyde-alkyne reductive coupling by our group,[11] conjugated enyne substrates were used (Scheme 1.7). It was found that the isopropene group was able to control the regiochemistry of the product completely, overriding the bias of the strongly directing phenyl group for the distal position.

Scheme 1.7 Alkenes as Directing Groups for Alkyne Coupling Reactions

Montgomery:



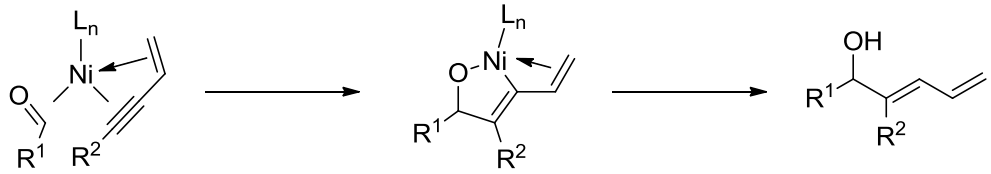
Jamison:



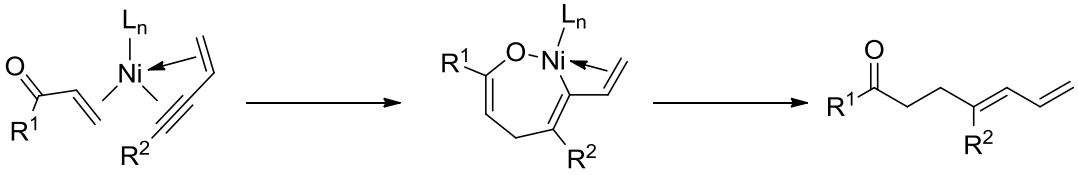
The Jamison group[12] also used enynes as substrates for aldehyde-alkyne reductive couplings, and found that the conjugated alkene provided high selectivity for one product, regardless for the substitution on the other terminus of the alkyne. They also demonstrated that unconjugated alkenes on the alkyne, further away from the carbon-carbon triple bond, could also exert great regiocontrol in the absence of a phosphine ligand.[13] The regiocontrol observed in the coupling of aldehydes and enynes likely arises from the coordination of the alkene of the enyne to the nickel center of the catalyst before the oxidative cyclization. This orientation of the enyne is consistent with the observed product (Scheme 1.8). From this, it seems likely that this method would be applicable to the enone-alkyne reductive coupling as well since it also proceeds via an irreversible, regioselectivity-determining oxidative cyclization.

Scheme 1.8 Rationalization for Alkene Directing Group

Aldehyde-Alkyne Coupling:

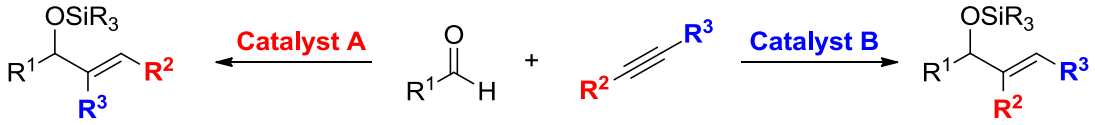


Enone-Alkyne Coupling:



While effective in some cases, this strategy has a major disadvantage of requiring that a directing group be covalently attached to one of the substrates, limiting the scope of the reaction. A noncovalent approach, such as developing a selective catalyst for the formation of each regioisomer, is much more attractive (Scheme 1.9).

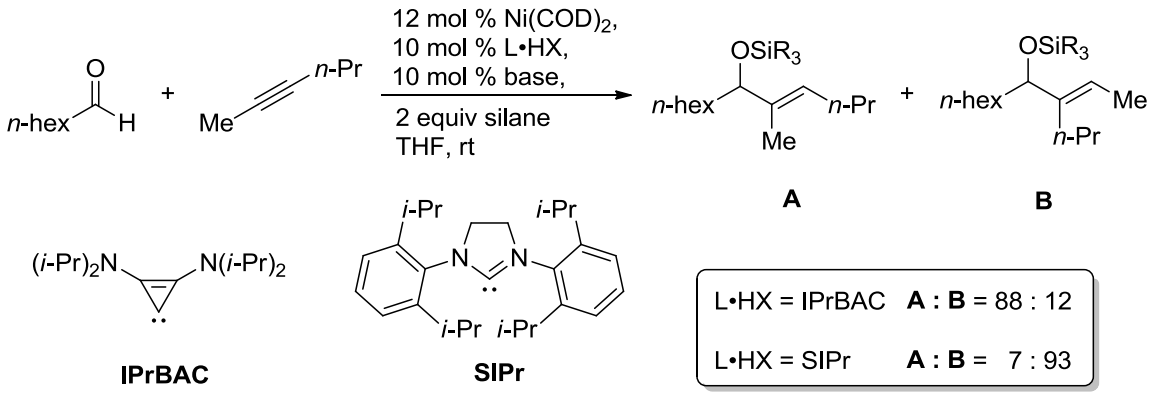
Scheme 1.9 Catalyst Control of Regiochemistry



1.3.2 Regiocontrol through Catalyst Design

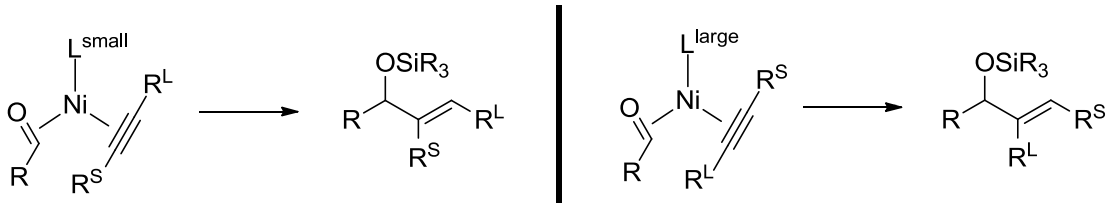
It has been shown previously in our laboratory that such control of regiochemistry through catalyst design is possible.[14] Through the use of sterically differentiated NHC ligands, the nickel-catalyzed aldehyde-alkyne coupling can efficiently yield either regioisomer of the allylic alcohol product (Scheme 1.10). In the reaction of heptaldehyde with 2-hexyne, the use of the less sterically hindered IPrBAC ligand gives primarily product **A** and the use of the bulky SIPr ligand favors product **B**.

Scheme 1.10 Regiocontrol of the Aldehyde-Alkyne Coupling



The steric effects of the ligands are able to influence the regiochemical outcome of the reaction due to how they interact with the substrates during the oxidative cyclization. In the case of a small ligand such as IPrBAC, the alkyne orients its larger group away from the aldehyde in order to minimize the steric interaction between the aldehyde and alkyne (Scheme 1.11). In the case of a larger ligand such as SIPr, the smaller group of the alkyne is oriented closer to the ligand in order to minimize the steric interaction between the alkyne and ligand. Once the substrates undergo this oxidative cyclization, the regiochemistry is set, and the intermediate undergoes σ-bond metathesis with a silane reducing agent to produce the desired silyl-protected allylic alcohol. This approach has been applied to a wide variety of substrates, allowing for the selective synthesis of a single allylic alcohol regioisomer. Following the optimization of the enone-alkyne reductive coupling, both substrate-directed and catalyst-directed strategies for regiocontrol were investigated.

Scheme 1.11 Ligand Control of Regiochemistry in the Aldehyde-Alkyne Coupling



1.4 The Development of Enone-Alkyne Reductive Couplings and Applications

1.4.1 Statement of Thesis Content and Scope

This dissertation describes the development of the reductive coupling of enones and alkynes. This approach to conjugate addition products avoids some of the limitations of previously established conjugate addition methods, namely the use of stoichiometric preformed organometallic reagents, and allows for increased functional group tolerance relative to other techniques. While the first iteration of this methodology allowed for high selectivity for one regioisomer of the product in the case of more biased substrates, regioselectivities suffered when less differentiated substrates were used. Building on techniques discovered in our group for controlling the regiochemistry of the aldehyde-alkyne reductive coupling reaction, the establishment of methods for regiocontrol of the enone-alkyne coupling as well as a broad range of other reactions was investigated. It was realized that the γ,δ-unsaturated carbonyl products from this reaction could serve as precursors to pyrrole heterocycles, providing access to a wide variety of substitution patterns of these molecules included polycyclic targets. During the regiocontrol studies, a new reductive coupling of enones and alkynes to form 1,4-dienes was also discovered.

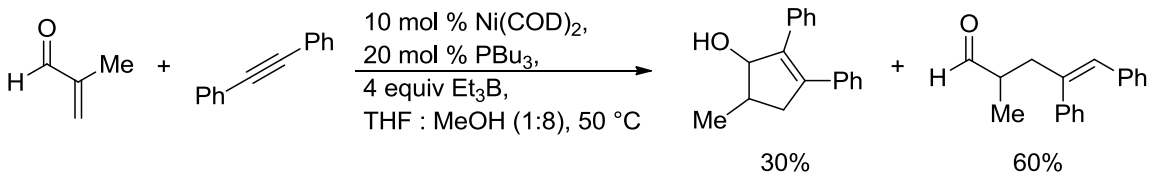
Chapter 2

Reductive Coupling of Enones and Alkynes

2.1 Development of the Intermolecular Enone-Alkyne Coupling

2.1.1 Discussion of Mechanism

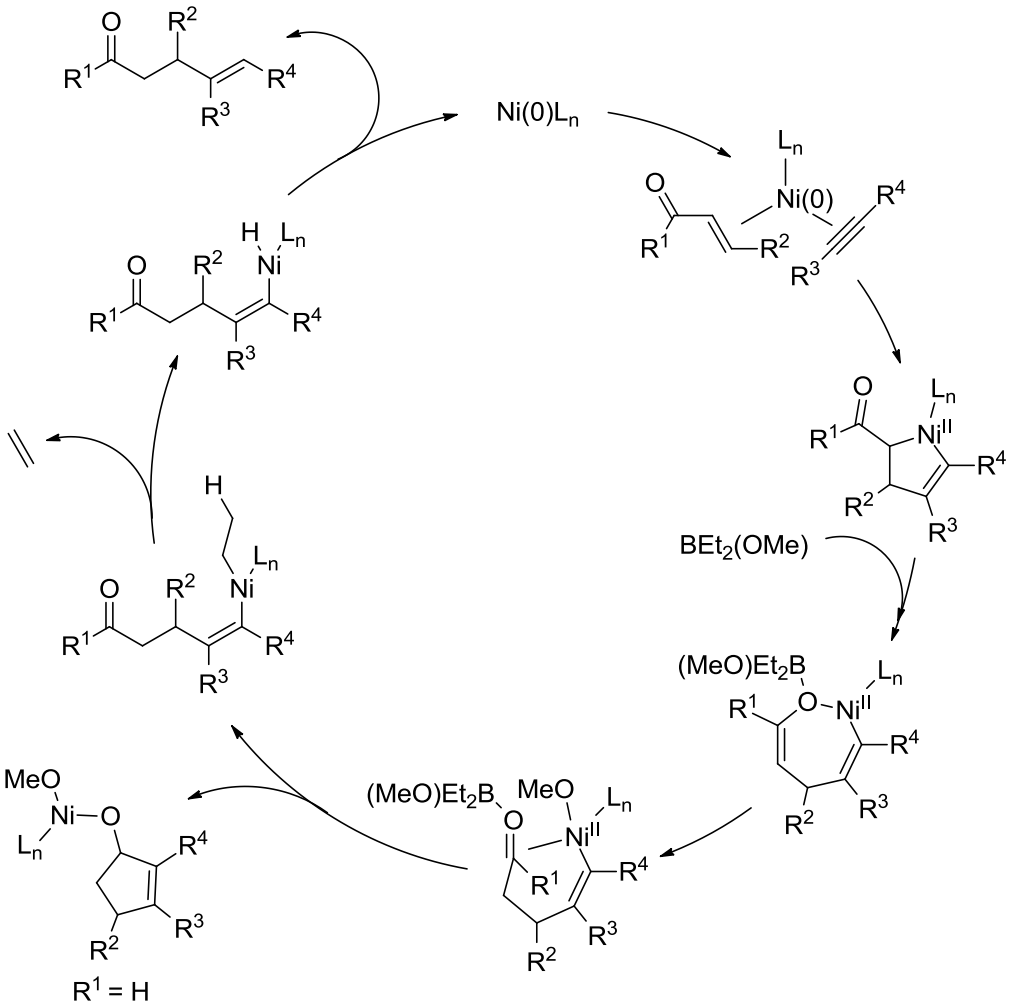
Scheme 2.1 Formation of γ,δ-Unsaturated Carbonyl Product



While examining the [3+2] cycloaddition of enals and alkynes, it was found that when a sterically hindered enal substrate was used, a γ,δ-unsaturated carbonyl product was observed in addition to the expected cyclopentenol product (Scheme 2.1). A mechanistic rationale for this result is shown in Scheme 2.2. The substrates coordinate to Ni(0) and undergo oxidative cyclization to form a five-membered metallacycle that would then undergo an isomerization to the more stable seven-membered metallacycle. Protonation of the enolate by methanol leads to a vinyl nickel intermediate with the carbonyl coordinated to the nickel center. In the case of an enal substrate, the carbonyl is less hindered and can undergo addition by the vinyl nickel species to furnish the [3+2] cycloaddition product. In the case of a more sterically hindered carbonyl such as an α-substituted aldehyde or an enone, addition of the nickel vinyl unit would be less facile when compared to an unhindered aldehyde. Instead, the same intermediate would then

proceed with exchange of an ethyl group from triethylborane to nickel, leading to an ethyl nickel species which could undergo β-hydride elimination producing a nickel hydride. This intermediate can then reductively eliminate to give the γ,δ-unsaturated carbonyl product. This unexpected side reaction was then further investigated and developed as a method for the reductive coupling of enones and alkynes.

Scheme 2.2 Enone-Alkyne Reductive Coupling Mechanism

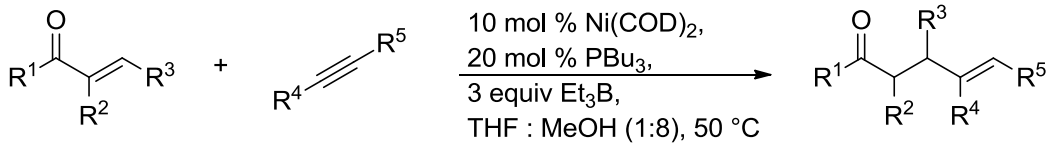


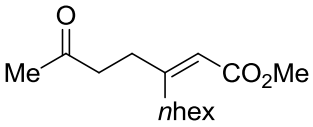
2.1.2 Methodology Development and Substrate Scope Investigation

The reductive coupling of alkynes and enones to form γ,δ-unsaturated ketones compliments existing conjugate addition technology by avoiding the use of pre-formed stoichiometric organometallic reagents, and allowing for greater substrate scope flexibility. Upon optimization of reaction conditions, substrate scope was investigated in collaboration with Ananda Herath (Table 2.1).[15] Typically, more sterically or electronically differentiated alkynes gave one regioisomer (Table 2.1, entry 5), and less sterically differentiated alkynes gave a mixture of regioisomers (Table 2.1, entry 6 and 7). Functional groups that are usually problematic for traditional cuprate additions, such as esters and unprotected hydroxyl groups, were tolerated well in the nickel catalyzed reductive coupling (Table 2.1, entries 1-4 and 6-8). It can also be seen that this coupling proceeds well with alkynoate substrates, which is interesting, since such substrates are considered good Michael acceptors.

Table 2.2 further explores the substitution patterns that are tolerated at different positions on the substrates. Aryl and alkyl substitution was found to work well at most positions. While methyl substitution was tolerated at the α-position of the enone (Table 2.2, entry 9), α,β-disubstitution of acyclic enones and α-substitution of cyclic enone prevented efficient coupling from occurring. Greater steric bulk, such as silyl ethers, around the α'-position of the enone was well tolerated (Table 2.2, entry 4 and 5). Overall, this method provides a powerful alternative to traditional 1,4-addition strategies. The reductive coupling of enones and alkynes allows for the synthesis of conjugate addition products under catalytic conditions without the use preformed organometallic reagents.

Table 2.1 Enone-Alkyne Reductive Coupling Scope I





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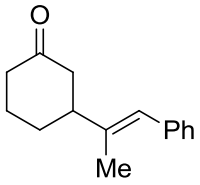

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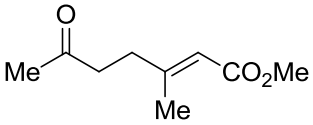

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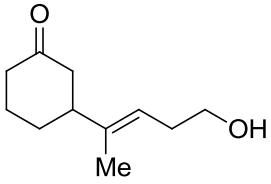

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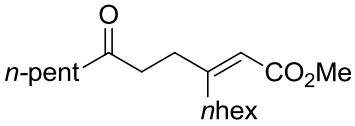

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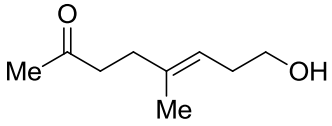

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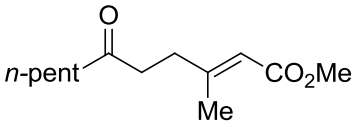

4
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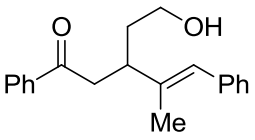
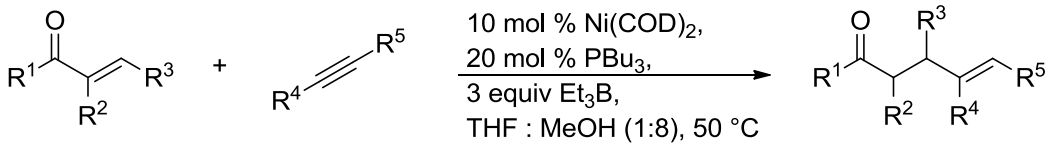
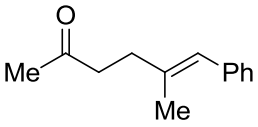


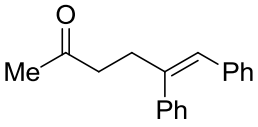
8
84% (>95:5)

Table 2.2 Enone-Alkyne Reductive Coupling Scope II

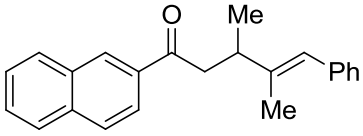




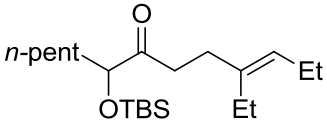
1
85% (>95:5)



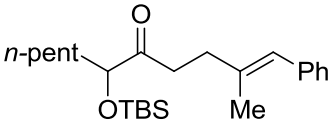
2
63%



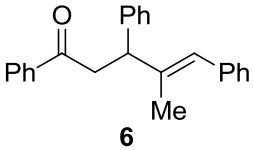
3
66% (>95:5)



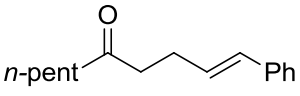
4
72%



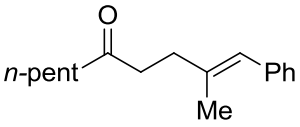
5
72% (>95:5)



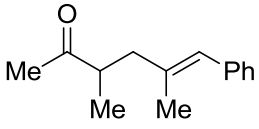
6
90% (>95:5)



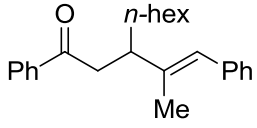
7
74% (>95:5)



8
78% (>95:5)



9
80% (>95:5)



10
65% (>95:5)

2.2 Investigation of Asymmetric Variant and Directing Group for Regiocontrol

2.2.1 Development of Asymmetric Variant of Enone-Alkyne Coupling

Due to the extensive use of the metal-catalyzed carbon-carbon bond forming conjugate addition reaction in organic synthesis, there has also been an extensive body of work towards the development of asymmetric variants.[16] One of the first methods involves the use of stoichiometric chiral ephedrine-derived ligands for cuprate additions of organolithium reagents to enones.[17] The first example of a highly enantioselective (>90% ee) catalytic conjugate addition to enones utilized a chiral phosphine ligand for the addition of Grignard reagents.[18]

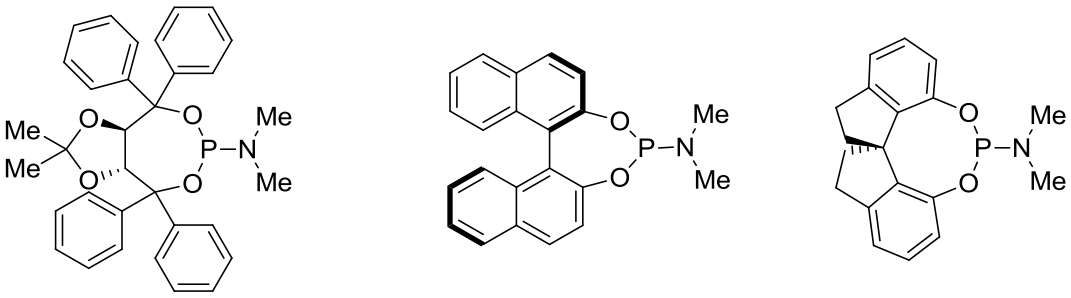
Building on these accomplishments, Ikeda and coworkers developed an asymmetric nickel-catalyzed addition of alkynes to cyclic enones using a chiral oxazoline ligand and dimethylzinc reducing agent.[19] While in the best cases these conditions provided modest enantioselectivies, it provides a basis for asymmetric nickel-catalyzed additions of alkynes to enones. Chiral monodentate phosphoramidites have also been shown to be excellent ligands for the asymmetric conjugate addition reaction.[20] In the presence of a copper catalyst and alkylzinc reagents, these ligands can yield very high enantiomerically enriched products for a broad range of substrates. For the most part these methods have been limited to use with stoichiometric organometallic reagents such as organozincs, organolithium reagents, and Grignard reagents.

More recently, an asymmetric reductive coupling of enones and alkynes has been achieved using a cobalt catalyst with chiral phosphine ligands.[21] While this method does provide some impressive enantioselectivities, its scope is limited to cyclic enones and a

few symmetric or electronically biased unsymmetric alkynes. There is still a need for a method to produce γ,δ-unsaturated ketones from enones and alkynes via an asymmetric conjugate addition.

Previously in our group, during the investigation of the enal-alkyne [3+2] cycloaddition, chiral ligands were screened in an attempt to induce enantioselectivity.[22] However, the ligands gave poor yields and very low enantioselectivities (10-20% ee). Given the success with phosphoramidite ligands in conjugate addition reactions, this ligand class seemed like a good starting place for investigating an asymmetric variant of the nickel-catalyzed enone-alkyne reductive coupling discussed earlier.

Scheme 2.3 Phosphoramidite Ligands

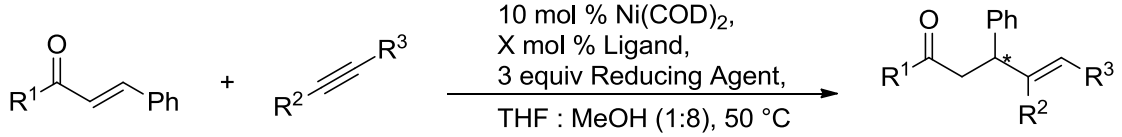


TADDOLPNMe$_2$ (*R*)-MONOPHOS (*R*)-SIPHOS

In the chiral ligand screen for the enal-alkyne coupling, a BINOL-derived phosphoramidite ligand had been tried and it was found to give a low yield of the desired product in only 10% ee. Nonetheless, we first chose a few commercially available phosporamidite chiral ligands (Scheme 2.3) to screen in the enone-alkyne reductive coupling (Table 2.3). MONOPHOS and SIPHOS gave only trace amounts of product (Table 2.3, Entries 1 and 3). A promising result was seen with a TADDOL-derived phosphoramidite ligand (Table 2.3, Entry 5) using benzylidene acetone and

phenylpropyne giving 44% ee. This ligand was then tried using a terminal alkyne, giving up to 54% ee (Table 2.3, Entry 7) at room temperature with a milder silane reducing agent. TADDOL-based phosphoramidite ligands are relatively simple to synthesize (Scheme 2.4), and provide several opportunities for ligand tuning. The aryl groups on the phosphoramidite can be varied simply by changing the aryl Grignard reagent used, and there are many possible amines that can be coupled to the phosphorus center. Enantioselectivity can likely also be enhanced by using chiral groups on the amine portion of the ligand, which has been used with some success in other methodologies using these ligands. In some cases, this reaction still worked relatively efficiently using a silane reducing agent instead of the typical triethylborane reducing agent (Table 2.3, Entries 5 and 7).

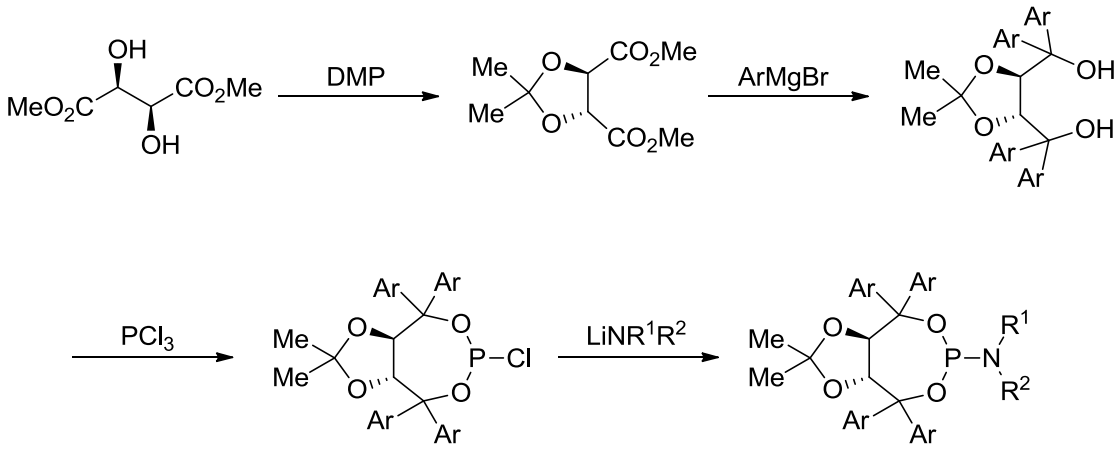
Table 2.3 Chiral Phosporamidite Ligand Screen



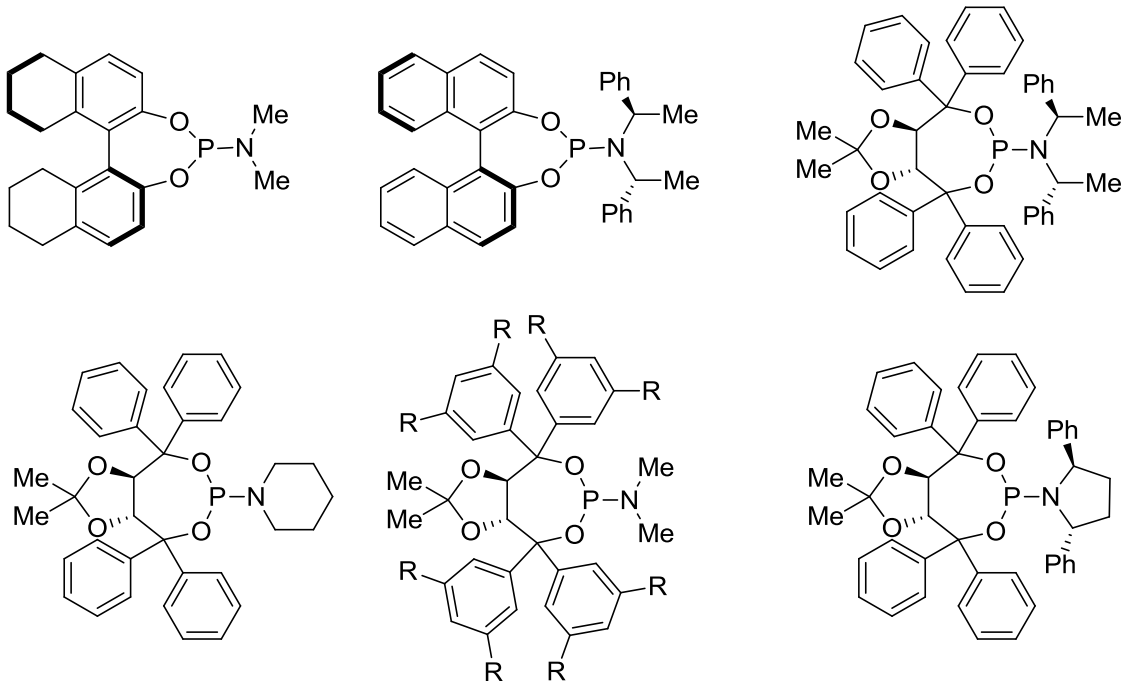
Entry	R^1	R^2	R^3	X mol % Ligand	Red. Agent	%Yield	%ee
1	Ph	Me	Ph	12 mol % *R*-MONOPHOS	Et_3B	0	N.D.
2	Me	H	Ph	12 mol % *R*-SIPHOS	Et_3B	0	N.D.
3	Me	Me	Ph	12 mol % *R*-SIPHOS	Et_3B	0	N.D.
4	Me	Me	Ph	10 mol % $TADDOLPNMe_2$	Et_3B	23	N.D.
5	Me	Me	Ph	10 mol % $TADDOLPNMe_2$	TESH	20	44
6	Me	H	*n*-hex	10 mol % $TADDOLPNMe_2$	Et_3B	53	39
7*	Me	H	*n*-hex	10 mol % $TADDOLPNMe_2$	TESH	N.D.	54

*used 8:1 THF:MeOH at r.t.

Scheme 2.4 General TADDOL-derived Phosphoramidite Synthesis



Scheme 2.5 Potential Phosphoramidite Ligands



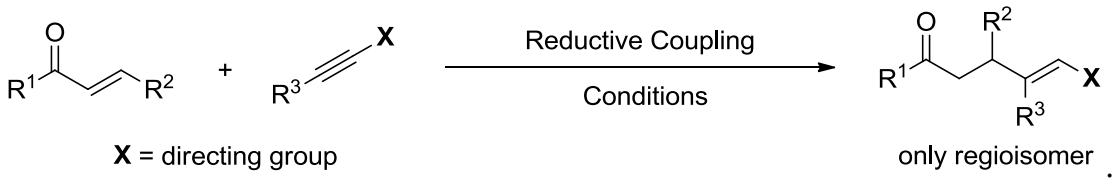
These initial results are promising, and with further optimization of the ligand and reducing agent could lead to high yielding couplings with high enantioselectivity, which would be the first example of an enantioselective enone-alkyne reductive coupling with acyclic enones. The next step in optimizing this procedure is synthesizing a more diverse

group of TADDOL-derived ligands varying the substitution on the aryl ring and the groups on the amine portion (Scheme 2.5).

2.2.2 Development of Directing Group for Regiocontrol

As discussed earlier (Section 1.4.2), one potential strategy for controlling the regioselectivity of this reaction is the development of a directing group on the alkyne substrate that would interact with the metal catalyst, favoring the formation of one regioisomer of the product over the other (Scheme 2.6).

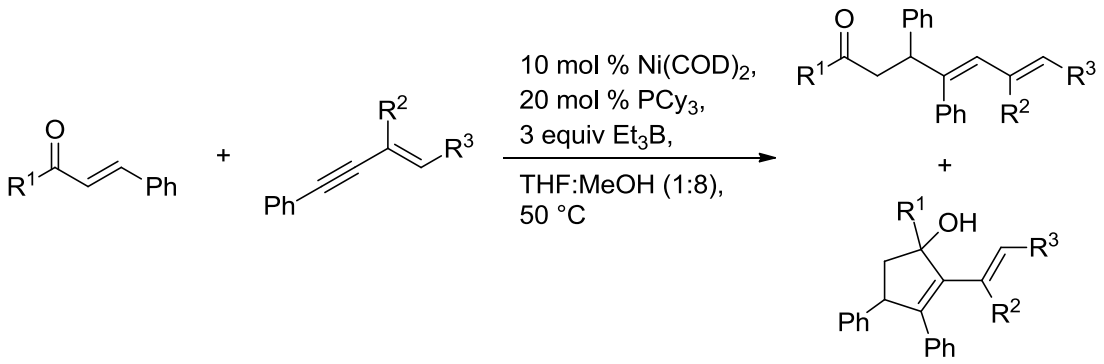
Scheme 2.6 Directing Group Control of Regiochemistry



Initially, a variety of conjugated enynes were screened under enone-alkyne reductive coupling conditions (Table 2.4). Most interestingly, significant amounts of [3+2] cycloaddition products were observed in several cases (Table 2.4, Entries 1,2, and 5). This is surprising because it was previously thought that observing the [3+2] product was not possible under catalytic conditions with enones due to steric constraints. The extra stabilization of the vinyl-nickel intermediate by the extra coordination of the alkene portion of the enyne may increase the nucleophilicity of the nickel-carbon bond, allowing it to attack the carbonyl group of the enone. The electronics of the enone carbonyl may also play a role in this result. It can be seen that when the R^1 substitution of the enone is changed from phenyl to methyl, the amount of [3+2] product observed drops dramatically (Table 2.4, Entries 1 and 2, 3 and 4). The increased electrophilicity provided by the

phenyl-substituted enone compared to a methyl-substituted enone could also be contributing to the high amount of cycloaddition product observed.

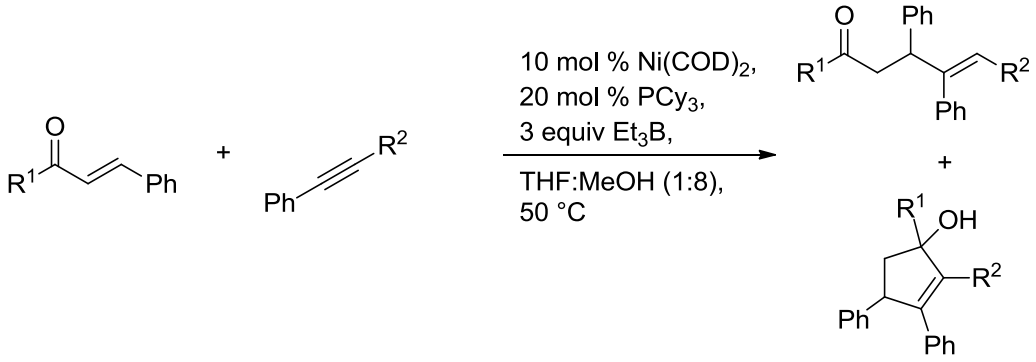
Table 2.4 Investigation of Enyne Substitution on Enone-Alkyne Reductive Coupling

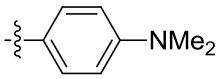
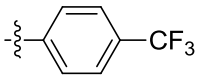
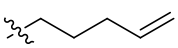
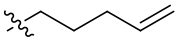


Entry	R^1	R^2	R^3	% Yield Reductive Coupling	% Yield [3+2]
1	Ph	H	H	0	80
2	Me	H	H	30	25
3	Ph	Me	H	25	20
4	Me	Me	H	19	0
5	Ph	*i*Pr	H	25	28
6	Ph	*t*Bu	H	0	0
7	Me	*t*Bu	H	0	0
8	Ph	Ph	H	0	0
9	Me	Ph	H	0	0
10	Ph	H	Ph	40	20
11	Me	H	Ph	43	10

It can also be see that increasing steric bulk at the R^2 position decreases yields, eventually shutting down the reaction completely. Phenyl substitution at the R^3 position also gave a mixture of reductive coupling and [3+2] products with only modest yields (Table 2.4, Entries 10 and 11). Due to the results seen from reactions with conjugated enynes, it was thought that the electronics of the substrates might have more of an effect on the outcome of the reaction than previously thought.

Table 2.5 Investigations of Alkyne Electronic Effects

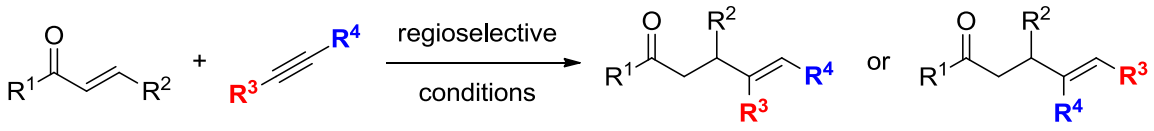


Entry	R^1	R^2	% Yield Reductive Coupling	% Yield [3+2]
1	Ph	Ph	80	0
2	Me		34	23
3	Me		80	5
4	Ph		27	5
5	Me		6	0

A brief study of the electronics of the alkyne substrate was undertaken (Table 2.5). One aryl ring of diphenylacetylene was substituted at the para position with both

electron-donating and electron-withdrawing groups. From this study, it was observed that an electron-withdrawing group, such as $–CF_3$, gave roughly the same results as unsubstituted diphenylacetylene, whereas substitution with an electron-donating group, such as $–NMe_2$, gave a drastically lower reductive coupling yield and a higher amount of the cycloaddition product. Tethered, non-conjugated enynes were also examined, but were found to give extremely low yields, and were not examined further (Table 2.5, Entries 1 and 2).

Scheme 2.7 Ligand Controlled Regioselectivity



From this study of the possible development of potential directing groups for controlling the regiochemistry of the enone-alkyne reductive coupling, it can be observed that while enynes may not be very effective at controlling regioselectivity, their electronic effects can have a profound, unexpected impact on the reaction pathway. Further investigation of developing regiocontrol for this transformation focused on using catalyst design to favor formation of one regioisomer of the product over another, as this would allow for a broader substrate scope by not being limited to those possessing a specific moiety required for controlling regiochemistry (Scheme 2.7).

2.3 Regiocontrol through Catalyst Design

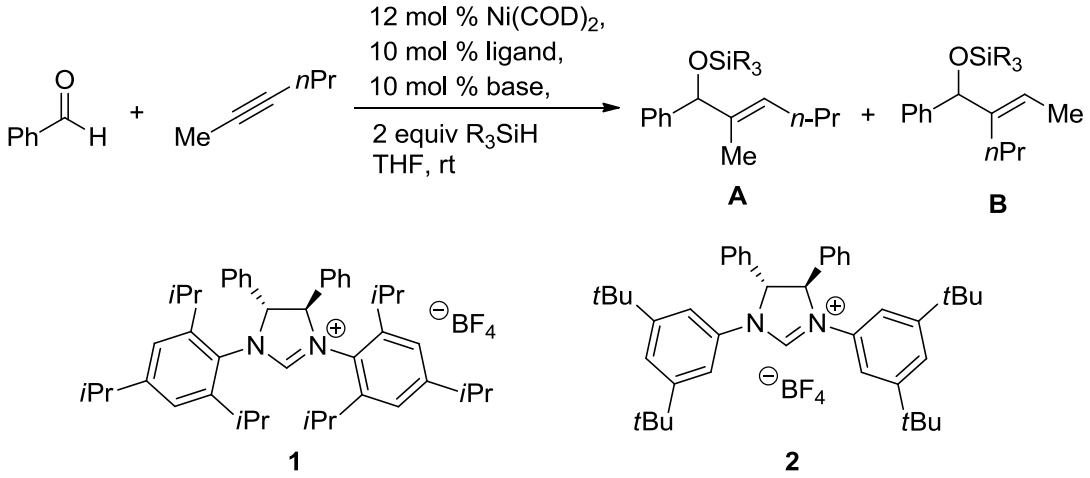
2.3.1 Development of Catalyst Generation Techniques

The development of regiocontrol strategies for the aldehyde-alkyne coupling provides a basis for the development of further regioselective reactions. In addition to applying this approach to a broad range of different reactions, there is also a need for the improvement of this methodology as it applies to the aldehyde-alkyne coupling. The development of high-yielding, highly regioselective standard large and small ligands with the potential for enantiocontrol would be a key advance in this area. With the current methodology, the large and small ligands as well as the silane reducing agent needed to be optimized for each substrate. In addition to being effective with regards to regiocontrol, NHC ligands with saturated backbones also provide a handle for the development of an asymmetric variant of this reaction (Scheme 2.8).[23] DP-IPr (Scheme 2.8, Structure **1**) has been shown to be a high yielding, highly regioselective large ligand for the aldehyde-alkyne coupling, but demonstrates poor enantiocontrol. Bis-(3,5-di-*tert*-butylphenyl)-di-phenyl-imidazolinium tetrafluoroborate (Scheme 2.8, Structure **2**) is an example of a highly regioselective small ligand that also affords high enantioselectivities.

Different procedures for generating the catalyst *in situ* via deprotonation of the carbene salt were sometimes required in order to optimize the yield. In most cases, the NHC salt is deprotonated using potassium *tert*-butoxide, which is weighed out with the ligand and $Ni(COD)_2$ in the glove box. However, in certain cases *n*-butyl lithium was optimal for catalyst formation. While this led to higher yields, organolithium reagents are more difficult to handle and raise the question of whether or not the lithium ion plays a role in catalyst formation. Overall, this methodology could be potentially improved by

investigating other means of generating the catalyst either though different *in situ* techniques or through ligand design.

Scheme 2.8 Development Regioselective and Enantioselective NHC Ligands



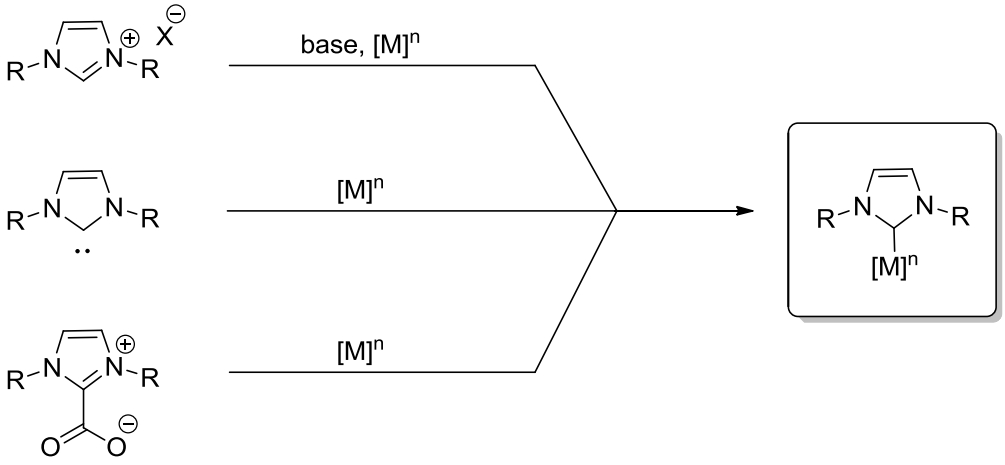
Entry	Ligand	Silane	Yield	A : B	ee (A)	ee (B)
1	**1**	Et_3SiH	79%	5 : 95	75%	36%
2	**2**	tBu_2SiH_2	10%	88 : 12	79%	73%

2.3.2 Catalyst Generation Strategies

There are many different ways to generate NHCs for the use of making complexes with transition metals (Scheme 2.9).[24] One of the most common methods for generating carbenes is the *in situ* deprotonation of a carbene salt. This is an attractive approach due to the high stability of carbene salts. Most of them are bench stable and relatively easy to isolate. The use of tetrafluoroborate salts in particular can allow for chromatographic isolation of carbene salts. These salts can be added to a metal reagent along with an appropriate base, and upon deprotonation can form a metal-carbene complex. There are a few drawbacks to this method. Depending on the base used, the

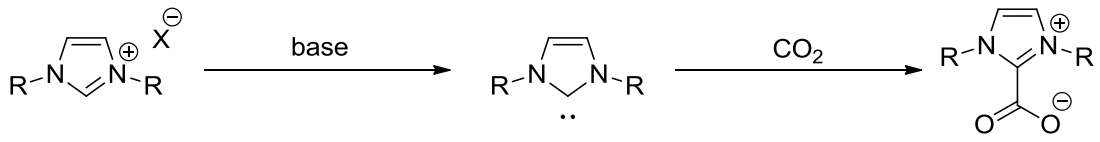
coordination chemistry could be complicated by the counter ions present as well as the protonated base. For example, when using KO*t*-Bu to deprotonate a hydrochloride salt of an NHC, *t*-BuOH and KCl are produced. Provided that a catalytic amount of the metal-carbene complex is being used in the reaction, there will be a minimal amount of *t*-BuOH and KCl present in solution, but in some cases they could participate in the reaction unproductively. Using *n*-butyl lithium as the base partially solves this problem by producing butane as a side product, which is fairly inert and can evaporate.

Scheme 2.9 Metal-Carbene Complex Generation Techniques



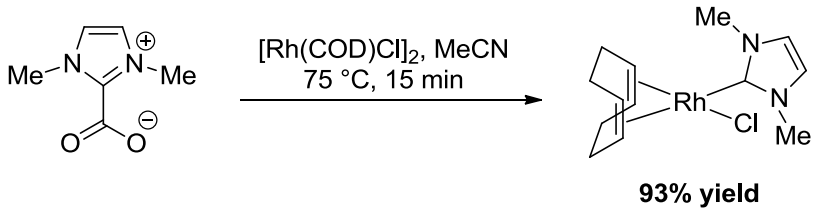
The *in situ* deprotonation side products can be avoided by using another approach to metal-carbene complex generation, such as adding free carbenes to a solution containing the metal of interest. Free carbenes can be isolated, stored in the absence of moisture in oxygen,[25] and added to metals to form complexes directly.[26] A major advantage of using free carbenes is that no side products are made in the formation of the metal-carbene complex other than the ligands that were present on the metal precursor. The main disadvantage of using free carbenes is that they can be difficult to isolate and must be stored carefully.

Scheme 2.10 Generation of NHC-Carboxylates



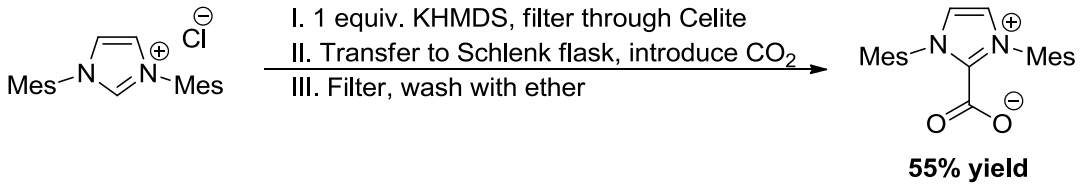
Another approach that avoids the side product generation and the stability issues of using free carbenes is the use of NHC carboxylates. In the presence of carbon dioxide, an NHC can form a zwitterionic imidazolium carboxylate species that can be isolated (Scheme 2.10).[27] While stable to air once isolated, NHC-carboxylates can decompose in aerated solutions and must be made under an inert atmosphere. The basic procedure for synthesizing these reagents is simple: a free carbene is generated, and the carbon dioxide is added. It has also been shown that these adducts of NHCs can be used to generate metal-carbene complexes through decarboxylation in the presence of a metal (Scheme 2.11).[28] Carbon dioxide is the only side product in this process. NHCs bearing isobutyl carboxylate esters have also shown similar reactivity.[29]

Scheme 2.11 Synthesis of Metal-carbene Complexes from NHC-Carboxylates



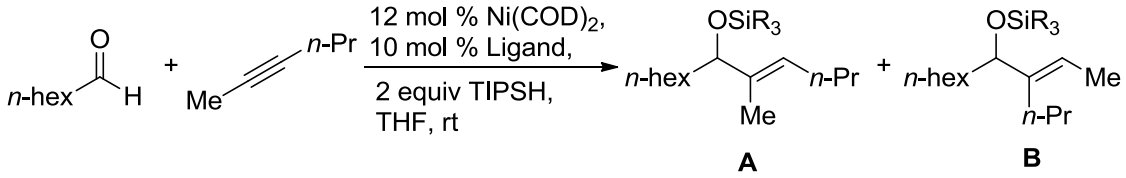
2.3.3 Catalyst Generation Data

Scheme 2.12 NHC-Carboxylate Synthesis



The effects of different metal-carbene generation techniques were compared using the nickel-catalyzed aldehyde-alkyne reductive coupling reaction. The IMes carboxylate was synthesized using the most current preparation (Scheme 2.12).[30] With the IMes carboxylate in hand, the impact of the catalyst generation technique on the aldehyde-alkyne coupling was examined (Table 2.6).

Table 2.6 Comparison of Metal-Carbene Complex Generation Methods



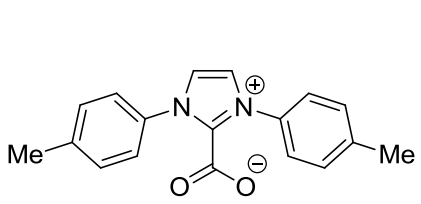
Entry	Ligand	Yield (A : B)
1	10 mol % IMes•HCl 10 mol % KO^{t}Bu	83% (67 : 33)*
2	10 mol % IMes:	78% (66: 34)
3	10 mol % IMes•CO_2	84% (77 : 23)

* Reference 14

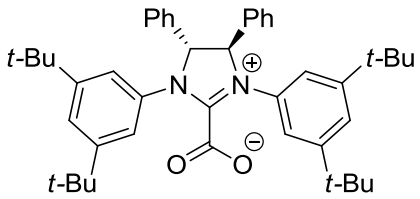
Compared to the *in situ* deprotonation, the free carbene and NHC-carboxylate methods gave similar results in terms of yield and regioselectivity. The free carbene gave almost identical regioselectivity at a slightly lower yield (Table 2.6, Entry 2). The NHC-carboxylate gave about the same yield and somewhat improved regioselectivity for

regioisomer A (Table 2.6, Entry 3). With the success of the IMes-carboxylate, the synthesis of other carboxylates was undertaken.

Scheme 2.13 Small NHC Carboxylates



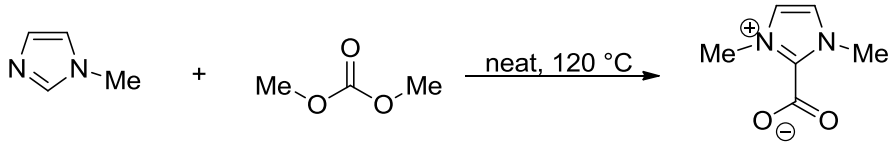
ITol•CO_2



DP-I*t*-Bu•CO_2

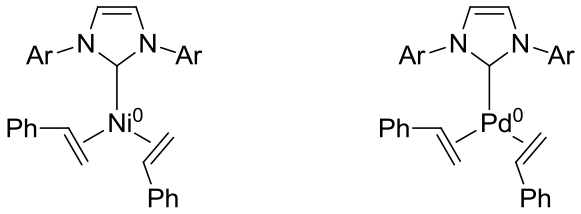
Previously, ITol and DP-I*t*-Bu (Scheme 2.13) had been shown to be highly regioselective for small ligand products in the aldehyde-alkyne coupling with the latter also providing good enantioselectivities. The main problem with both of these ligands is that they often lead to poor chemical yields. It was thought that making the carboxylate variants of these ligands might provide a means of more efficient catalyst generation resulting in better yields. Unfortunately, these carboxylates could not be isolated using the same procedure, and were not pursued further. A sterically unhindered methyl-substituted carbene carboxylate was made using a different synthesis (Scheme 2.14).[31] This ligand was also ineffective in the aldehyde-alkyne coupling, producing none of the desired product.

Scheme 2.14 Synthesis of N,N-Dimethyl Carboxylate



While NHC-carboxylates may provide another option for generating nickel-NHC catalysts, difficulties in their synthesis prevented further study. While not technically a method for metal-carbene complex generation, preformed metal-carbene complexes could also provide an alternative to generating a carbene *in situ*. The Perez group has recently synthesized nickel and palladium NHC complexes, and generously donated some of each for testing with our group's chemistry (Scheme 2.15).

Scheme 2.15 Metal-Carbene Complexes



IPrNi(sty)$_2$ **IPrPd(sty)$_2$**

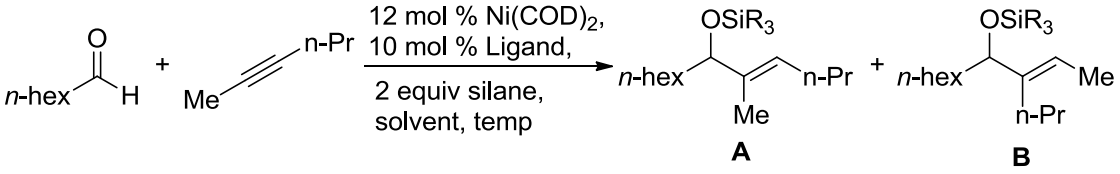
Ar = 2,6-diisopropylphenyl

Since only the complexes bearing the IPr ligand were available, we chose to compare the effect of the Perez complexes to other methods for catalyst generation using the same ligand (Table 2.7). Much lower catalyst loadings of the Perez complex were used due to the limited amount of material available. Entries 1 and 2 compare the literature procedure of *in situ* carbene formation to the use of a free carbene. While they both provide similar regioselectivities, the free carbene gave a much lower yield. Using the literature procedure with the Perez nickel complex gave no discernible yield of the desired products (Table 2.7, Entry 3). Increasing the temperature and changing the solvent only resulted in trace product (Table 2.7, Entry 4). However, changing the triisopropyl silane to the more reactive triethyl silane resulted in similar yields to those

reported previously and slightly higher regioselectivity for the large ligand product, B (Table 2.7, Entry 5). The palladium variant of the Perez complex was also tried under these conditions, but gave no detectable products (Table 2.7, Entry 6).

From these studies, it can be seen that NHC-carboxylates may provide a solution for improving catalyst generation techniques for the regioselective aldehyde-alkyne coupling, provided the problems with their synthesis can be solved. The development of ligand-based regiocontrol provides an exciting opportunity to apply this strategy to a broad range of reactions such as alkyne and 1,3-diene hydroboration and hydrosilylation, the coupling of aldehydes and 1,3-dienes, and the reductive coupling of enones and alkynes.

Table 2.7 Comparison with Perez Complex



Entry	Ligand	Silane	Solvent/temperature	Yield (A : B)
1	10 mol % IPr•HCl 10 mol % KO^{t}Bu	i-Pr$_3$SiH	THF, rt	84% (20 : 80)*
2	10 mol % IPr:	i-Pr$_3$SiH	THF, rt	21% (16 : 84)
3	1 mol % IPrNi(sty)$_2$	i-Pr$_3$SiH	THF, rt	N.R.
4	1 mol % IPrNi(sty)$_2$	i-Pr$_3$SiH	PhMe, 80 °C	trace
5	1 mol % IPrNi(sty)$_2$	Et$_3$SiH	PhMe, 80 °C	83% (12 : 88)
6	1 mol % IPrPd(sty)$_2$	Et$_3$SiH	PhMe, 80 °C	N.R.

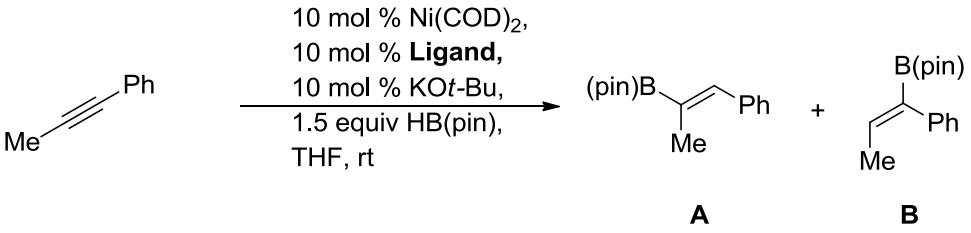
*Reference 14

2.4 Developing Regiocontrol for Hydroboration and Hydrosilylation Reactions

2.4.1 Hydroboration of Alkynes and Dienes

The regioselective hydroboration of alkynes and dienes can provide access to vinyl borane derivatives, which can be extremely useful in cross-coupling reactions, and allyl boranes, which are also useful for cross-coupling reactions as well as for the synthesis of allylic alcohols. Phenyl propyne and pinacol borane were chosen as model substrates for studying the regioselective hydroboration of alkynes (Table 2.8). These substrates were then subjected to a range of NHC ligands in the presence of a catalytic amount of nickel. Under these conditions, one regioisomer predominated (**A**), with increasing steric bulk having little effect on the ratio of **A** to **B**.

Table 2.8 Ligand Effect on Alkyne Hydroboration

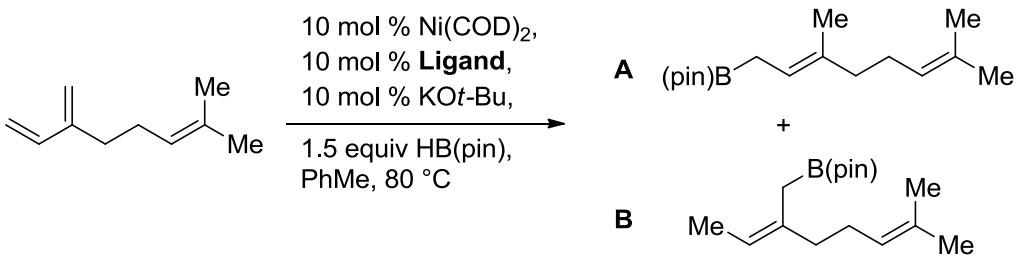


Ligand	A : B
IMes	94:6
SIPr	88:12
DP-IPr	>95:5

Hydroboration of 1,3-dienes also provides an opportunity for the development of regiocontrol. The 1,4-hydroboration of dienes has been previously reported using a

nickel catalyst,[32] however, it only works well for terminal dienes. Another example of 1,4-hydroboration of dienes, utilizing an iron catalyst,[33] is successful with 2-substituted and 2,3-disubstituted dienes. This particular method also has limited examples of regioselectivity reversal through the use of different ligands. While there are effective methods for the selective 1,4-hydroboration of 1,3-dienes, there is still a need for a method that can selectively form either regioisomer of the product for a range of diversely substituted substrates. To conduct a test of whether this was possible using the regiocontrol technique developed previously for the aldehyde-alkyne coupling, myrcene and pinacol borane were subjected to a range of NHC ligands in the presence of a nickel catalysts (Table 2.9). As the steric bulk of the ligand is increased from IMes to DP-IPr, the ratio of linear (**A**) to branched (**B**) decreases. While the selectivity for **B** with the bulkiest NHC is not perfect, this data does display a definite trend. Further optimization of this reaction may potentially lead to the development of regiocontrol for the hydroboration of dienes.

Table 2.9 Regioselective Hydroboration of 1,3-Dienes

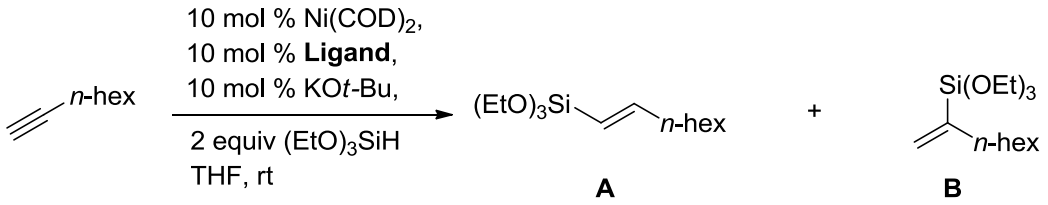


Ligand	Yield	A : B
IMes	71%	68 : 32
SIPr	74%	28 : 72
DP-IPr	32%	19 : 81

2.4.2 Hydrosilylation of Alkynes and Dienes

Before the discovery of regiocontrol for the aldehyde-alkyne coupling using sterically differentiated NHC ligands, our group had examined the regioselective hydrosilylation of alkynes.[34] While developing regioreversal for internal alkynes had been shown to be difficult, terminal alkynes showed more promise. To see if the more recent understanding of regiocontrol would apply, 2-octyne and triethoxysilane were screened against a range of NHC ligands in the presence of a nickel catalyst (Table 2.10). While a trend for regioreversal with increasing ligand sterics was found, the selectivities for the largest and smallest ligands were not perfect.

Table 2.10 Regioselective Hydrosilylation of Alkynes



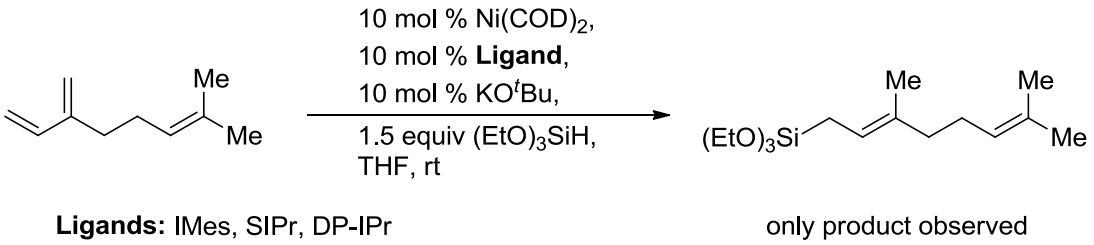
Ligand	Yield	A : B
ITol	34%	20 : 80
IPr-BAC*	N.D.	23 : 73
IMes**	72%	25 : 75
IPr**	70%	83 : 17

*Hasnain Malik, unpublished results
**Reference 66

The development of regiocontrol for the 1,4-hydrosilylation of conjugated dienes was also investigated. This reaction has been precendented using an iron-based catalyst, but with no examples of regioreversal.[35] Using the standard screen of NHC ligands and a

nickel catalyst, the hydrosilylation of myrcene was examined (Scheme 2.16). Despite the increasing steric bulk of the ligand, only the linear product was observed in modest yield.

Scheme 2.16 Regioselective Alkyne Hydrosilylation

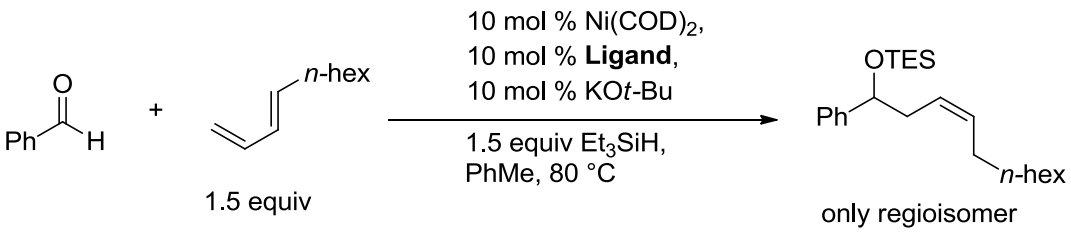


2.4 Investigation of Regiocontrol for Three Component Couplings

2.4.1 Aldehyde-Diene Coupling

The three component coupling of aldehydes, 1,3-dienes, and silanes has been demonstrated using a nickel catalyst with an NHC ligand.[36] However, this only works for a limited substrate scope and does not provide a means for regiocontrol. To see if we could develop regiocontrol for this reaction, benzaldehyde and a terminal diene were screened against a range of increasingly bulky NHC ligands in the presence of a nickel catalyst (Table 2.11). In all cases, only one regioisomer was observed.

Table 2.11 Regioselective Aldehyde-Diene Reductive Coupling



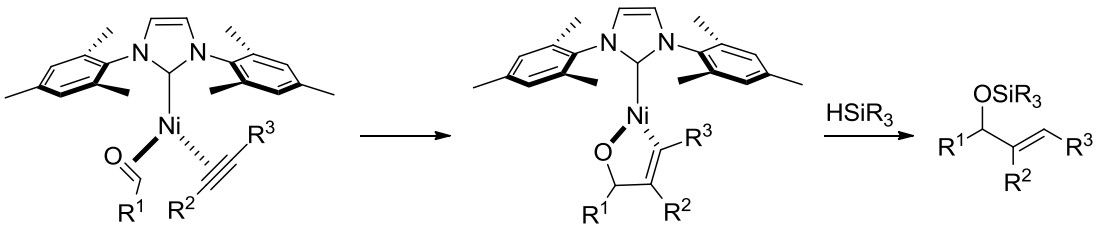
Ligand	Yield
IMes	76%
SIPr	89%
DP-IPr	60%

2.4.2 Enone-Alkyne Coupling

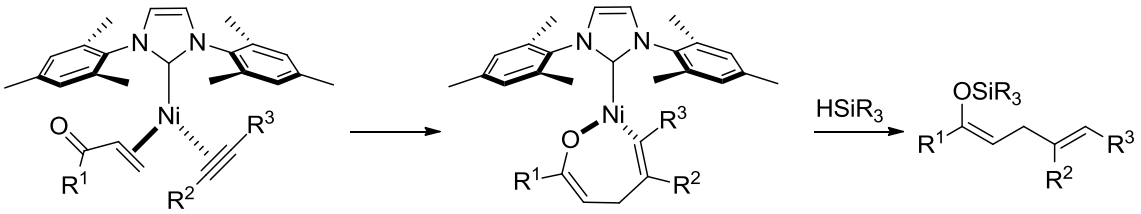
The nickel-catalyzed reductive coupling of enones and alkynes provides access to a broad range of γ,δ-unsaturated carbonyl products in good yields with high regioselectivity in most cases. The cases where regioselectivity suffers occur when the two functional groups on an internal alkyne are not sterically or electronically differentiated. Adaptation of this reaction to use a carbene-based catalyst could lead to improved regioselectivities for such substrates and the potential for developing regioreversal. The enone-alkyne coupling shares some similarities with the aldehyde-alkyne coupling. Both reactions undergo a regiochemistry-determining oxidative cyclization to form a metallacycle that is then intercepted by a reducing agent to generate a nickel hydride species that can reductively eliminate to give the product (Scheme 2.17).

Scheme 2.17 Similarities between Enone-Alkyne and Aldehyde-Alkyne Couplings

Aldehyde-Alkyne Reductive Coupling:



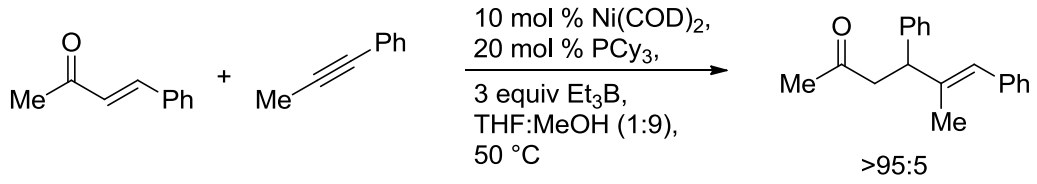
Enone-Alkyne Reductive Coupling:



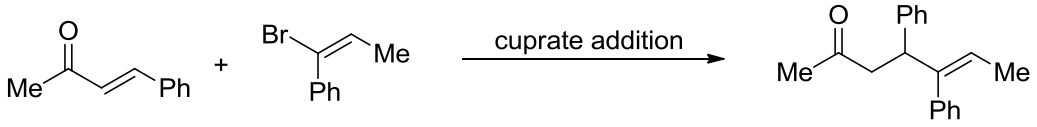
Being able to control the regioselectivity of this reaction would extend its utility in accessing conjugate addition products as well as in synthesizing precursors for pyrroles, thiophenes and furans. Currently, to access such products, one has to rely on the inherent selectivity of the alkyne to control which product is formed (Scheme 2.18). To get the opposite regioisomer, one would have to resort to a cuprate addition requiring the prior synthesis of a vinyl halide. Being able to simply switch the ligand in the enone-alkyne coupling would provide much more direct access to either of the possible regioisomers.

Scheme 2.18 Regiocontrol of Conjugate Addition Reactions

Enone-Alkyne Coupling with Biased Substrates:



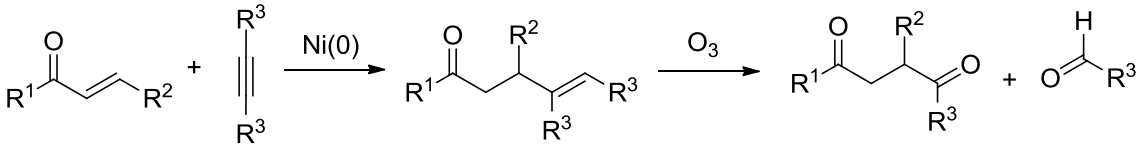
Cuprate Addition:



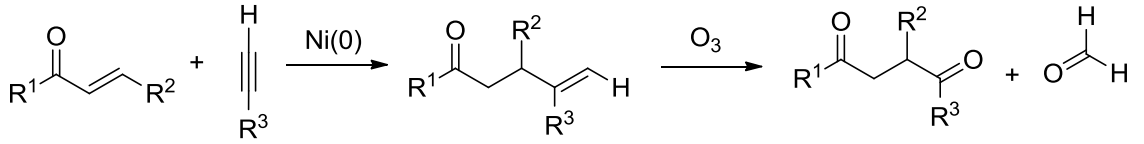
The development of regiocontrol for this reaction would also have an impact on the efficiency of the previously described route to heterocycles from γ,δ-unsaturated carbonyl compounds (Chapter 3). Currently, this approach requires the use of a symmetrical alkyne in the initial reductive coupling or one that is biased to give the desired functional group at the internal position of the resulting alkene (Scheme 2.19). Upon oxidative cleavage to form the dicarbonyl intermediate, one of the functional groups originating from the alkyne is effectively wasted. Being able to use a terminal alkyne and controlling the regioselectivity to produce the exo alkene product would ultimately result in the waste of only an equivalent of formaldehyde in the subsequent oxidative cleavage step.

Scheme 2.19 Utility for Heterocycle Synthesis

Current Dicarbonyl Synthesis:



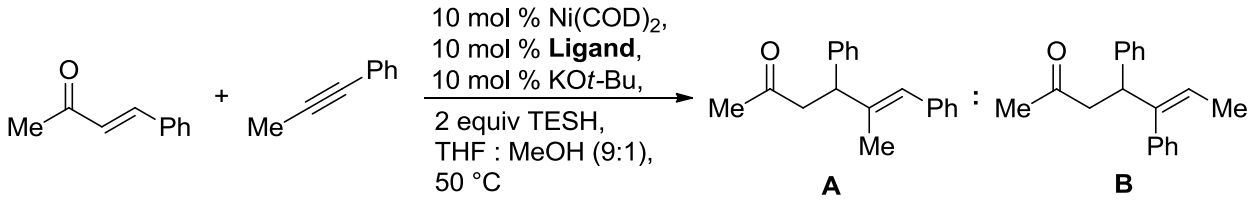
Dicarbonyl Synthesis with Regiocontrol:

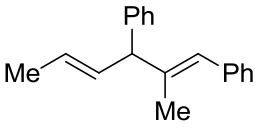


To begin the investigation of developing regiocontrol for the enone-alkyne coupling, benzylidene acetone and phenyl propyne were screened against a range of NHC ligands in the presence of triethylsilane and a nickel catalyst (Table 2.12). The ITol ligand under these conditions gave only a small amount of the expected small ligand product, A (Table 2.12, Entry 1). It also gave a significant amount of an unexpected 1,4-diene product which will be discussed in the Chapter 4. The IMes ligand gave a modest yield of the product, largely favoring product A (Table 2.12, Entry 2). Increasing the steric bulk of the ligand to SIPr gave a low yield of the ketone products, showing a shift in regioselectivity to slightly favor the large ligand product, B (Table 2.12, Entry 3). Increasing the steric bulk of the ligand further to DP-IPr gave only trace amounts of product, with the very confusing product distribution favoring product A (Table 2.12, Entry 4). This was a surprise since normally it is expected that increasing the steric bulk further would continue to favor product B. The data from this table is somewhat underwhelming as the regioreversal displayed by SIPr is very small. In the aldehyde-alkyne coupling, SIPr and DP-IPr often displayed similar regioselectivities, with the latter usually only being slightly better. So the fact that the regioselectivity displayed by the

second largest NHC ligand was poor and that the most sterically encumbered ligand gave the opposite regioselectivity in very low yield suggests that this reaction may not be amenable to this regiocontrol strategy. However, the yields were low and only one substrate pair was examined; so it is possible that with some yield optimization and using other substrates a better example of regioreversal may be found.

Table 2.12 NHC Screen of Enone-Alkyne Coupling

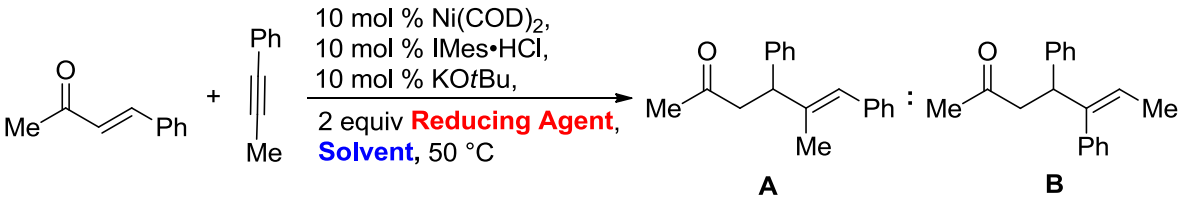


Entry	Ligand	Yield	A : B
1	ITol•HCl	 42% + A 4%	A only
2	IMes•HCl	33%	87 : 13
3	SIPr•HCl	28%	46 : 54
4	DP-IPr•BF_4	trace	65 : 35

Previously, the enone-alkyne reductive coupling had been optimized to use phosphine ligands and triethylborane as the reducing agent, and further experiments were needed to effectively adapt the reaction to use NHC ligands and silane reducing agents (Table 2.13). It was found that with an NHC ligand and triethylsilane reducing agent, the

exclusion of methanol led to no yield of the desired product (Table 2.13, Entry 2). Surprisingly, changing the silane to the more reactive triethoxysilane while still excluding methanol gave a significant amount of the enolsilane reductive coupling product (Table 2.13, Entry 3). One drawback to relying on a more reactive silane for high conversion is that it limits the regioselectivity optimization process. During the aldehyde-alkyne coupling optimization, both ligand and silane were adjusted to get the best regioselectivities. In the next entry, methanol was probed as the reducing agent, so no silane was added (Table 2.13, Entry 4). This provided the products in a slightly lower yield than the corresponding example with silane (Table 2.13, Entry 1) and with similar regioselectivity. The ratio of THF to methanol was then switched, which resulted in only trace amounts of product (Table 2.13, Entry 5). Finally, triethylborane was tried as a reducing agent, which gave a decent yield of the [3+2] product (Table 2.13, Entry 6), which can be accounted for by the more nucleophilic nickel-carbon bond formed during the course of the reaction due the increased σ-donating capacity of the NHC ligand relative to a phosphine ligand.

Table 2.13 Adaptation of Enone-Alkyne Coupling to NHC/Silane Conditions



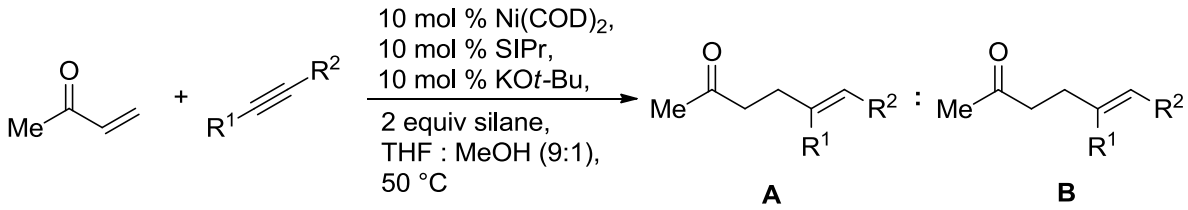
Entry	Reducing Agent	Solvent	Yield (A:B)
1	Et_3SiH	THF:MeOH (9:1)	33% (87:13)
2	Et_3SiH	THF	N. R.
3	$(EtO)_3SiH$	THF	high conversion enol silane of A**
4	MeOH	THF:MeOH (9:1)	24% (84:16)*
5	MeOH	THF:MeOH (1:9)	trace
6	Et_3B	THF:MeOH (9:1)	68% [3+2]

* IMes: was used with no base
**chalcone was used

Due to the poor regiocontrol observed previously using benzylidene acetone and phenyl propyne with different NHC ligands, other substrate combinations were investigated to see if the selectivities were substrate dependent (Table 2.14). When methyl vinyl ketone and phenyl propyne with SIPr as the ligand were used, a high yield of product was observed, with a high regioselectivity for the large ligand product, **B** (Table 2.14, Entry 1). Next, the alkyne was changed to 2-octyne, and under the same conditions as Entry 1 gave a low yield with the regioselectivity favoring product **B**, similar to what was observed in the aldehyde-alkyne coupling (Table 2.14, Entry 2). With this promising regiochemical result, triethoxysilane was then tried to see if it would increase the yield; however, it did not (Table 2.14, Entry 3). Despite the low yields these

results with different substrates provide interesting leads for further development of regiocontrol for the enone-alkyne coupling.

Table 2.14 Substrate Scope of NHC/Silane-Mediated Enone-Alkyne Coupling



Entry	R^1	R^2	Silane	Yield	A : B
1	Me	Ph	Et_3SiH	78%	25 : 75
2	Me	*n*-pent	Et_3SiH	18%	12 : 88
3*	Me	*n*-pent	$(EtO)_3SiH$	15%	15 : 85

*no MeOH added

2.4.3 Summary of Enone-Alkyne Reductive Coupling

In summary, an effective nickel-catalyzed reductive coupling of enones and alkynes has been described. This procedure works well for a broad scope of substrates. Areas for future development include the further development of an asymmetric variant and the establishment of a method for controlling the regiochemistry of the products. This reaction complements existing conjugate addition strategies for the synthesis of γ,δ-unstaturated ketones by allowing for the use of simple, readily accessible substrates without the need for prefunctionalizing the alkyne with a hydrometallating agent or synthesizing a functionalized vinyl halide. This method also allows for the use of substrates that are not compatible with traditional organocuprate technology such as

esters and free alcohols. One weakness of this method is the reliance on triethylborane for the reducing agent, which is a pyrophoric reagent. Subsequent work in our lab has addressed this issue by developing this reaction to use methanol as a reducing agent.[37]

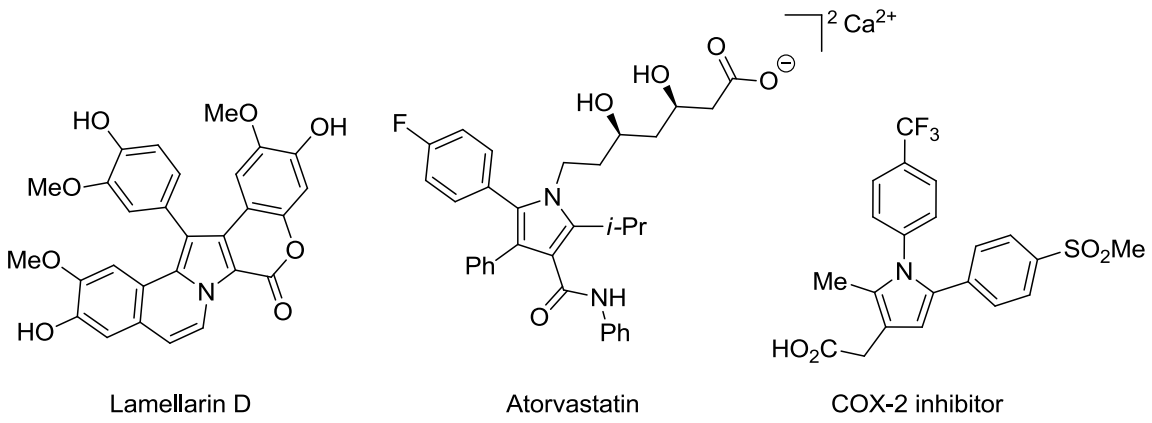
Chapter 3

The Synthesis of Pyrroles via the Reductive Coupling of Enones and Alkynes

3.1 Introduction to Pyrrole Synthesis

3.1.1 Relevance of Pyrrole-Containing Compounds

Scheme 3.1 Biologically Active Pyrrole-Containing Molecules



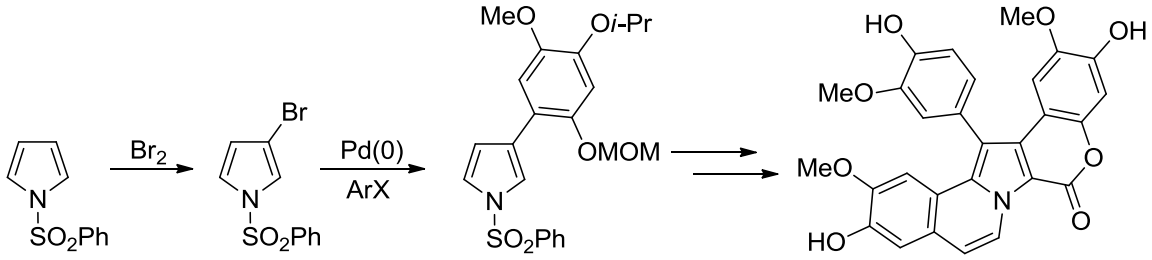
The pyrrole heterocycle is an important structural motif that is prevalent in a wide variety of natural products and other pharmaceutically relevant, biologically active molecules (Scheme 3.1).[38] Pyrrole-containing natural products such as lamellarins and ningalins show diverse biological activity, including antitumor properties, multi-drug resistance reversal, and HIV-1 integrase inhibition. Non-natural pyrrole-containing

compounds have also shown pharmaceutically relevant activity, such as atorvastatin, a potent HMG-CoA reductase inhibitor.[39] Due to the numerous interesting properties of pyrrole-containing molecules, diverse methods have been established for their synthesis.

3.1.2 Methods for the Synthesis of Pyrroles

There are many different ways to access the varying substitution patterns of these heterocycles;[40] however, there are few general methods for making a broad scope of pyrroles. Most methods of pyrrole synthesis fall into two main categories: stepwise functionalization of a simple pyrrole precursor, such as a mono-halogenated, N-protected pyrrole; or the coupling of more functionalized molecules to directly form the pyrrole ring (Scheme 3.2). The former strategy has been used successfully in the synthesis of complex, biologically active molecules, such as lamellarin D.[41] However, this strategy usually requires several sequential steps using expensive metal catalysts, necessitating functional group manipulation and leading to longer, linear synthetic sequences.

Scheme 3.2 Representative Stepwise Functionalization of a Pyrrole Ring



3.1.3 Cyclization and Cycloaddition Methods

Alternatively, there are methodologies that form the pyrrole ring directly from functionalized components. One strategy that was successfully applied to the total syntheses of several related pyrrole-containing natural products involved the use of an

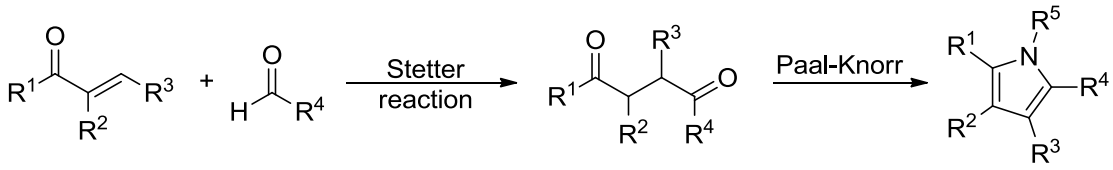
azadiene hetero-Diels-Alder reaction followed by a reductive ring contraction to form the pyrrole core.[42] This cycloaddition method allows for the effective coupling of moderately complex fragments, resulting in an efficient route to complicated, polycyclic pyrroles. Two other cyclization methods for the formation of pyrroles involve the copper mediated cyclization of a propargyl imine[43] or dithioacetal.[44] Using this procedure, 2-, 2,5-, 2,3,5-, and polycyclic pyrroles are obtained. Approaches utilizing 1,3-dipolar cycloadditions have also been developed. In one example, an azomethine ylide can be formed from an imine and a diazoacetonitrile in the presence of a rhodium catalyst, which then undergoes a [3+2] cycloaddition with dimethyl acetylenedicarboxylate to form 1,2-diaryl pyrroles in good yields with low catalyst loadings.[45] Another approach involves the formation of a 1,3-dipole from a TMSOTf-catalyzed coupling of acid chlorides, imines, and phosphites, which reacts with electron-deficient alkynes to afford a variety of pyrroles in a one-pot procedure.[46] Finally, more difficult to access *N*-acyl 3,4-trisubstituted pyrroles can be made through a sigmatropic rearrangement of an azine formed from an aldehyde and hydrazine using microwave irradiation.[47] These diverse methods can be used to access a broad range of diversely substituted pyrroles; however, each individual method has its own limitations with regards to substrate scope, the specific substitution patterns of pyrroles that can be produced, and ease of access of starting materials and required reagents.

3.1.4 Stetter Paal-Knorr Heterocycle Synthesis

One of the most versatile and popular strategies for synthesizing pyrroles is the classic Stetter Paal-Knorr sequence (Scheme 3.3). This strategy for pyrrole synthesis uses a Stetter reaction[48] to form a functionalized dicarbonyl compound from an aldehyde

and an α,β-unsaturated carbonyl, followed by a Paal-Knorr[49,50] cyclization with an amine under acidic conditions to form the pyrrole ring.

Scheme 3.3 Stetter Paal-Knorr Pyrrole Synthesis

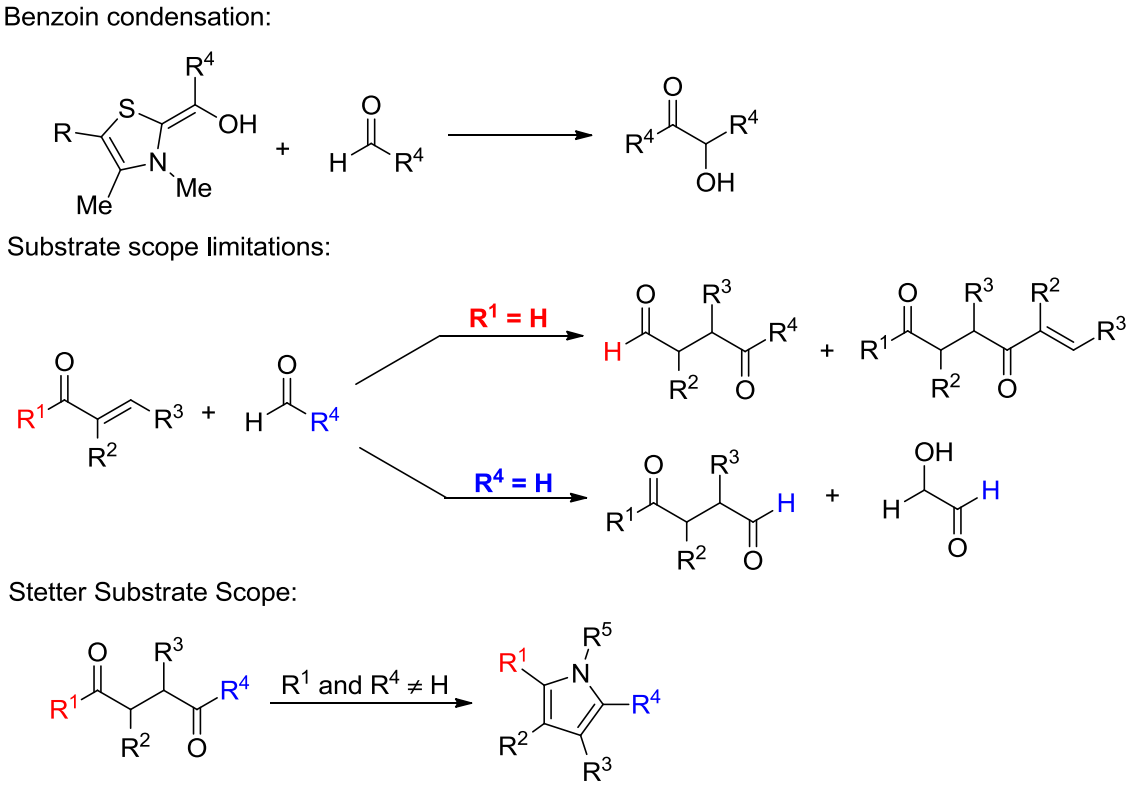


The Stetter reaction relies on the use of a carbene catalyst that can react with the aldehyde substrate to form an acyl anion equivalent, which can then undergo a 1,4-addition to the α,β–unsaturated carbonyl substrate. This method is also easily amenable to furan and thiophene[51] synthesis from the common dicarbonyl precursor. A key advantage of the Stetter Paal-Knorr sequence is the ability to produce many different substitution patterns of pyrroles from diverse and easy to access starting materials using relatively inexpensive and robust catalysts and reagents.

However, like all methods, it does have several limitations (Scheme 3.4). In the Stetter reaction, undesired benzoin-type condensations can occur where an acyl-anion derived from the aldehyde can add to another equivalent of itself. Typically, 1,4-dicarbonyls containing an aldehyde are difficult to synthesize via this route, as enals and formaldehyde make poor coupling partners since either component can readily homocouple[52] or form other undesired products.[53] Also, any products formed containing either an aldehyde or an α,β–unsaturated carbonyl can undergo further couplings with the starting materials or other products. Under certain conditions, enals have been used as the aldehyde coupling partner with specially modified chalcones,[54] but other than this

case, enals generally do not work well in the Stetter reaction. Formaldehyde is also a challenging coupling partner, and to the best of our knowledge, there are no examples where it is has been used successfully in a Stetter reaction. Ultimately, the Stetter Paal-Knorr sequence cannot efficiently produce pyrroles with hydrogen substituents at the 2 or 5 positions, due to limitations in the synthesis of the requisite 1,4-dicarbonyl intermediates.

Scheme 3.4 Limitations of the Stetter Reaction



3.1.5 1,4-Dicarbonyl Synthesis

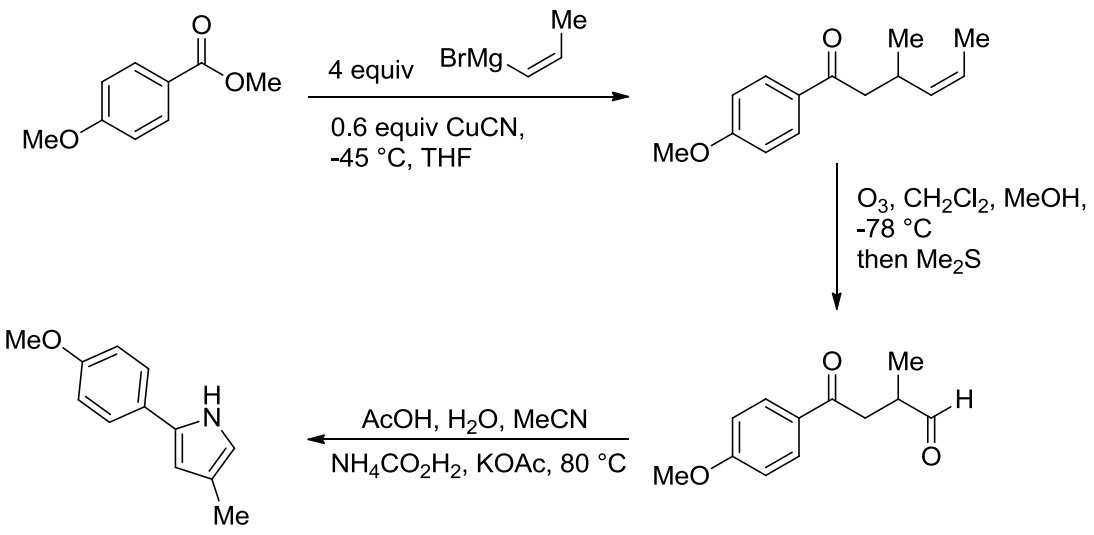
Due to the ease of access to pyrroles, furans, and thiophenes that the Paal-Knorr cyclization provides and the limitations of the Stetter reaction, there has been considerable effort made towards improving methods for 1,4-dicarbonyl synthesis. One

variant of the Stetter reaction involves the use of acyl silanes in place of aldehydes as a coupling partner, allowing for the synthesis of aromatic substituted 1,4-dicarbonyl compounds while preventing undesired benzoin condensation.[55] This reaction was also later combined with a Paal-Knorr cyclization into a one-pot procedure to produce pyrroles.[56] Another approach to the synthesis of these molecules is the oxidative heterocoupling of enolates.[57] This procedure allows for the selective coupling of an acyl oxazolidinone with another carbonyl unit in the presence of base and an oxidant. While this works well for an impressive variety of products and can be done asymmetrically, it requires the installation of the oxazolidone moiety on one of the substrates to ensure chemoselectivity for heterocoupling. Lastly, a conjugate addition/oxidative coupling strategy has recently been developed where an enolate generated from a Grignard addition to an enone adds to a (chloro)silylenol ether, and the resulting compound can be treated with an oxidant to produce the desired 1,4-dicarbonyl compound.[58] Although it requires the incorporation of a Grignard reagent, this method has been successfully applied to the synthesis of 2,3,5-trisubstituted pyrroles and the marine natural product metacycloprodigiosin. Despite these advances in overcoming some of the limitations of the Stetter reaction in 1,4-dicarbonyl synthesis, there is still a need for a versatile method for accessing different substitution patterns of these molecules, particularly examples containing an aldehyde as one of the carbonyls.

An approach involving the oxidative cleavage of a γ,δ-unsaturated ketone and subsequent Paal-Knorr cyclization has been previously utilized for the synthesis of pyrroles (Scheme 3.5). Lubell and coworkers have shown that adding excess vinyl Grignard reagents to a methyl ester can also produce γ,δ-unsaturated ketones, which upon

ozonolysis of the alkene, provide 1,4-dicarbonyl compounds that can then be cyclized to pyrroles using Paal-Knorr conditions.[59] This method allows for controlling substitution at the 1, 2, and 5 positions. For functionalization of the 3 and 4 positions, a substituted vinyl Grignard reagent must be used, and depending on the substitution pattern of the organometallic reagent, 2,4-disubstituted, 2,3,5-trisubstituted, and 2,3,4,5-tetrasubstituted pyrroles can be obtained.[60] This sequence is one of the few methods that allows for the incorporation of an aldehyde into the 1,4-dicarbonyl intermediate; however, it is limited overall by the substitution pattern of the Grignard reagent.

Scheme 3.5 Lubell's Pyrrole Synthesis



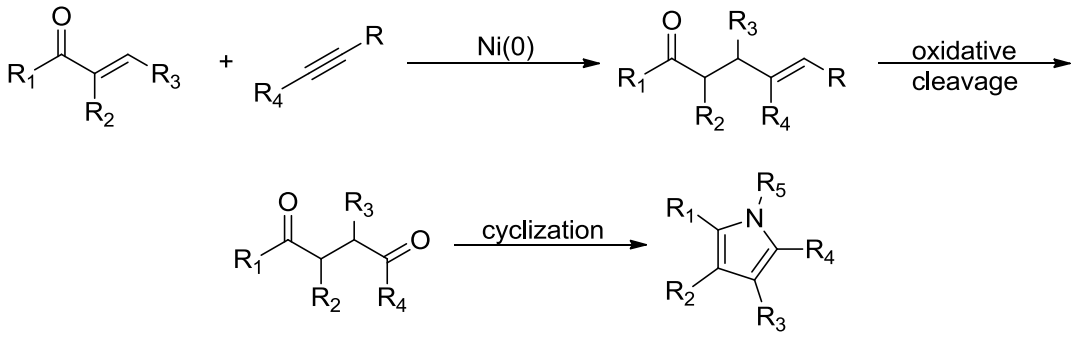
3.2 Enone-Alkyne Reductive Coupling as an Entry to Pyrroles

3.2.1 Route to 1,4-Dicarbonyl Compounds

The nickel-catalyzed reductive coupling of α,β-unsaturated carbonyls and alkynes developed in the Montgomery lab provides convenient access to γ,δ-unsaturated carbonyl compounds with high regioselectivity, and upon oxidative cleavage of the alkene, these

products furnish the corresponding dicarbonyl compounds, which in the presence of an amine can then be cyclized under Paal-Knorr conditions to pyrroles (Scheme 3.6). This approach allows for the synthesis of diversely substituted pyrroles through either the reductive coupling of enones and terminal alkynes[11] or enals and alkynes,[61] and provides access to those dicarbonyl compounds unattainable by the Stetter reaction.

Scheme 3.6 Nickel-Catalyzed Reductive Couplings as a Versatile Entry to Pyrroles



3.2.2 Condition Optimization

For the first step in the sequence, two different reductive coupling reactions were used. The first reaction, for the coupling of enones and alkynes, uses triethylborane as the reducing agent, resulting in the formation of the γ,δ-unsaturated ketone directly. This reaction tolerates a broad scope of substrates, including terminal alkynes, which allows for incorporation of hydrogen at the 2 or 5 position in the final pyrrole product. The second reductive coupling reaction allows for the coupling of enals and alkynes, producing the *Z*-enol silane product, which upon deprotection with mild acid,[62] provides efficient access to a γ,δ-unsaturated aldehyde. Deprotection of the enol silane with TBAF resulted in further reaction of the newly formed aldehyde with other enolates in the reaction mixture, decreasing the yield of the desired product. The enal-alkyne coupling

provides more flexibility for incorporating hydrogen at the 2 or 5 positions, and with the coupling of an enal with a terminal alkyne, permits hydrogen substitution at both positions.

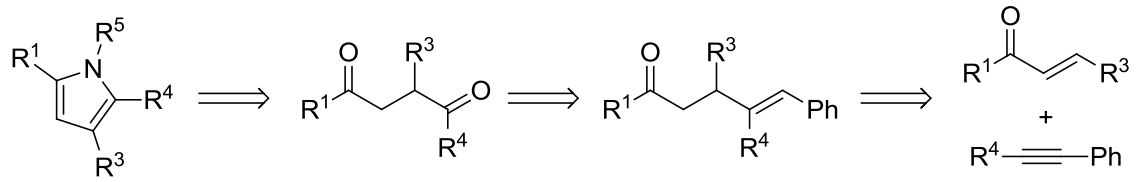
Ozonolysis was chosen for the oxidative cleavage of γ,δ-unsaturated carbonyls due to ease of handling and work-up, as opposed to osmium-mediated dihydroxylation and subsequent periodate cleavage. Methanol is typically used in ozonolysis reactions as a cosolvent to assist in a safer degradation of the unstable ozonide intermediate, but was not used in our conditions due to inconvenient hemi-acetal formation when the 1,4-dicarbonyl product contained an aldehyde. To compensate, triphenyl phosphine was used as a reducing agent for the work-up of the reaction.[63]

For the Paal-Knorr cyclization, conditions using microwave irradiation as a heating source were chosen to reduce reaction times.[64] Acetic acid is often used as a solvent for these reactions to provide an acidic medium to promote dehydration, but we found that a solvent system of 1:1 tetrahydrofuran to acetic acid was necessary to ensure solubility of some substrates. The reactions were heated to 170 °C as that was the maximum temperature that could be sustained by the microwave reactor without risking explosion of the reaction vessel. Microwave heating allowed for the reaction time to be short while still ensuring good conversion of substrate.

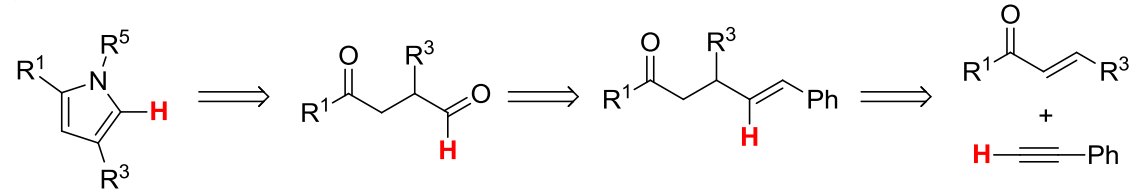
3.2.3 Substitution Pattern Scope

Scheme 3.7 Substitution Pattern Scope

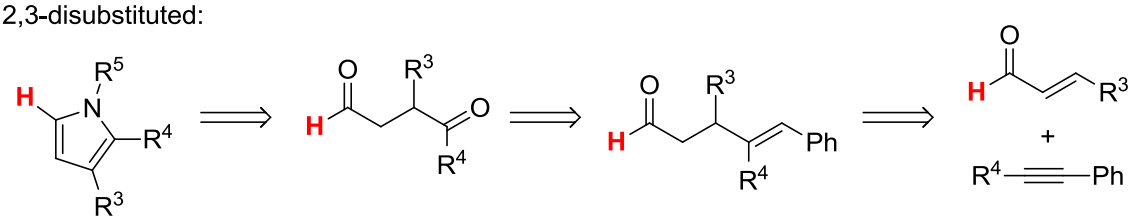
2,3,5-trisubstituted:



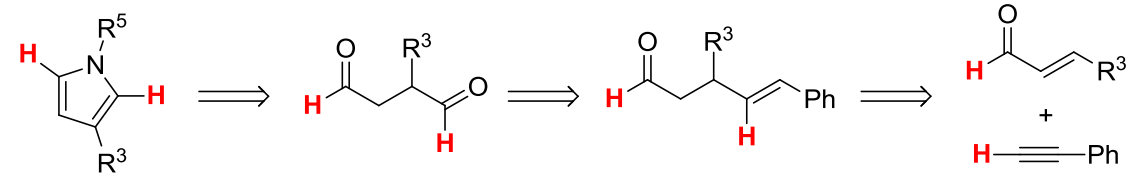
2,4-disubstituted:



2,3-disubstituted:



3-monosubstituted:

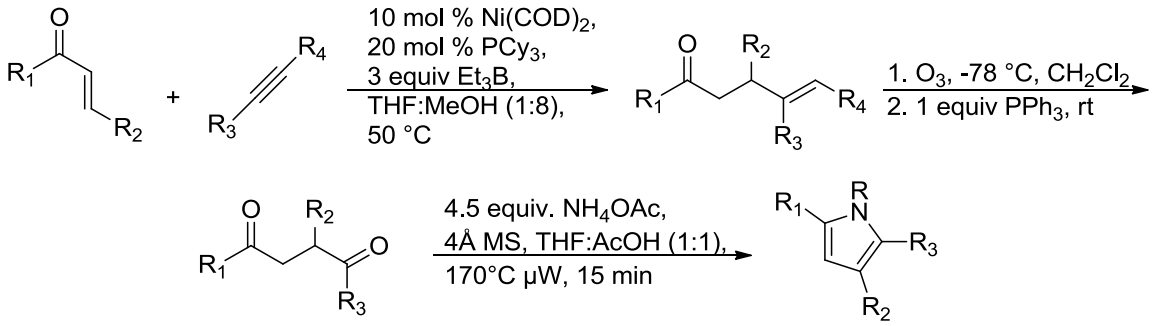


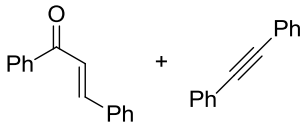
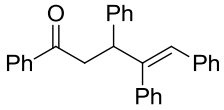
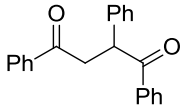
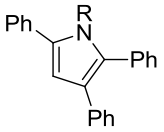
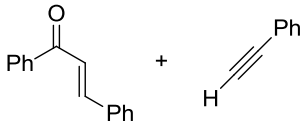
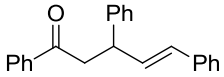
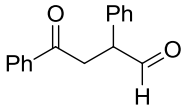
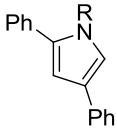
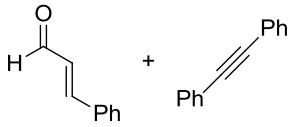
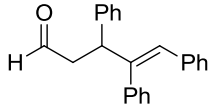
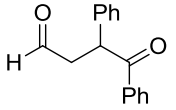
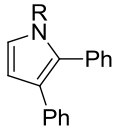
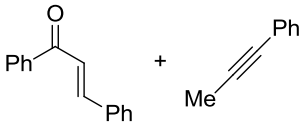
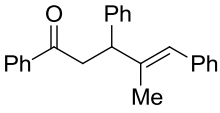
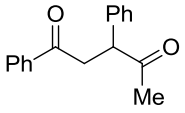
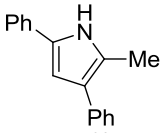
The nickel-catalyzed reductive coupling of enones and alkynes provides an entry point to a great diversity of substituted pyrroles from simple starting materials. One key advantage this approach has over the Stetter reaction and other related methodologies for 1,4-dicarbonyl synthesis is that it is capable of producing pyrroles with hydrogen at the 2 or 5 positions (Scheme 3.7). Using a terminal alkyne or enal in the reductive coupling would produce 2,4- or 2,3- disubstituted pyrroles, respectively. Coupling an enal with a terminal alkyne would allow for hydrogen substitution at both positions adjacent to the nitrogen, however, this was unachievable due to the instability of the intermediate 1,4-

dialdehyde. Also, the substitution at the α-position of the starting enone was not varied, as there is little substitution that is tolerated at the position by the reductive coupling reaction.

Initially, the intermolecular coupling of simple enones and alkynes were examined to demonstrate the diverse pyrrole substitution patterns that can produced using this method (Table 3.1). The coupling of an enone and an internal alkyne ultimately results in 2,3,5-trisubstituted pyrroles in good yields (Table 3.1, Entries 1a-c). Combining an enone and terminal alkyne gives one regioisomer of the product (Table 3.1, Entry 2a) in high yield, which can be used to make 2,4-disubstituted pyrroles. Using triethylsilane as the reducing agent and excluding methanol, an enal can be reacted with an internal alkyne, and upon removal of the silyl protecting group from the resulting *Z*-enol silyl ether, can furnish the γ,δ-unsaturated aldehyde (Table 3.1, Entry 3a), in modest yield. Upon oxidative cleavage of the alkene, this intermediate can be cyclized into a 2,3-disubstituted pyrrole. Aliphatic substituents are also tolerated by this procedure (Table 3.1, Entries 4a-c). From these results, it can be seen that a variety of di- and trisubstituted pyrroles that are difficult to make by other means can be obtained in high yield from simple starting materials.

Table 3.1 Substrate Scope



Substrates	RC Product	Dicarbonyl Product	Pyrrole
	 1a 81%	 1b 94%	 1c R = H 97% 1d R = ptol 62%
	 2a 88%	 2b 83%	 2c R = H 61% 2d R = Ph 71%
	 3a 50%*	 3b 77%	 3c R = H 76% 3d R = Ph 75%
	 4a 92%	 4b 64%	 4c 99%

*10 mol % $Ni(COD)_2$, 20 mol % PCy_3, 2 equiv Et_3SiH, THF, 50 °C

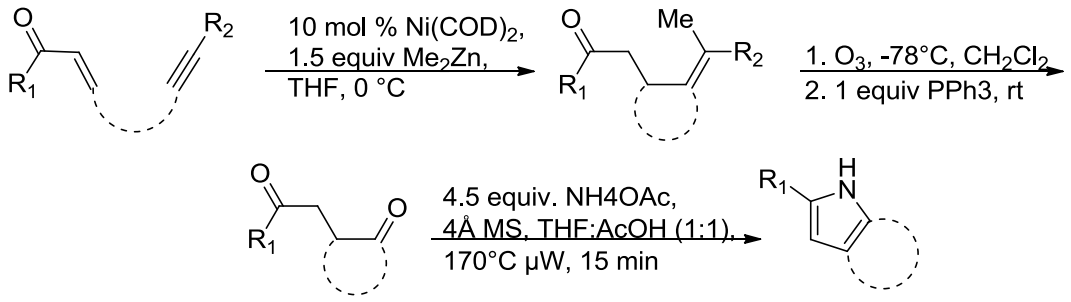
3.2.4 Complex Examples

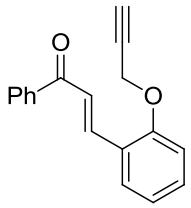
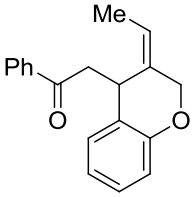
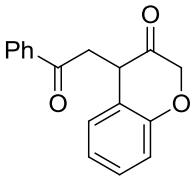
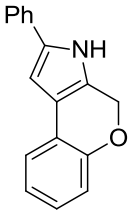
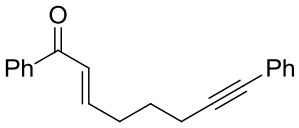
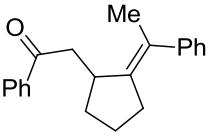
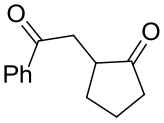
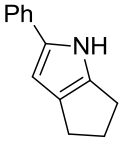
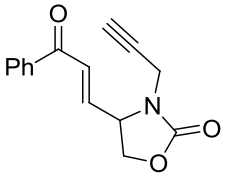
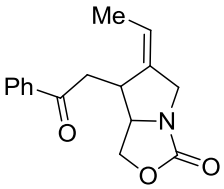
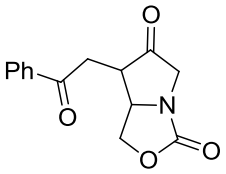
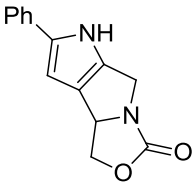
Having demonstrated the substitution pattern scope for this process, more complex polycyclic examples were pursued (Table 3.2). Surprisingly, it was found that

the phosphine based catalyst used for the intermolecular reductive couplings was ineffective for intramolecular coupling processes. Conditions reported previously[65] using no additional ligand and dimethylzinc as reducing agent gave the desired products in moderate yields. This may be due to the possibility that substrates for intramolecular couplings are less flexible in adapting the conformation necessary for metallacycle formation. Entry 1c is similar to the lamellarin core, and required different Paal-Knorr conditions to avoid product decomposition. Simple, bicyclic pyrroles can be made readily using this approach using an alkyl tether connecting the enone and alkyne (Table 3.2, Entry 2c). This method also provides efficient access to heteroaryl proline precursors (Table 3.2, Entry 3c).

Upon hydrolysis of the amide bond and oxidation of the C-O bond to a carboxylic acid, 3c can be converted to the proline residue (Scheme 3.8). There are very few methods for making this class of compounds,[66] and this route allows for complete selectivity of the isomer shown, allowing also for the thiophene and furan analogues to be made from the common intermediate 3b. The route used to make the starting material begins with serine, which is commercially available in either enantiomer, making synthesis of enantiopure heteroaryl prolines possible. When used in place of normal proline residues, these modified prolines were found to preserve peptide conformation in common β-turn motifs.[67]

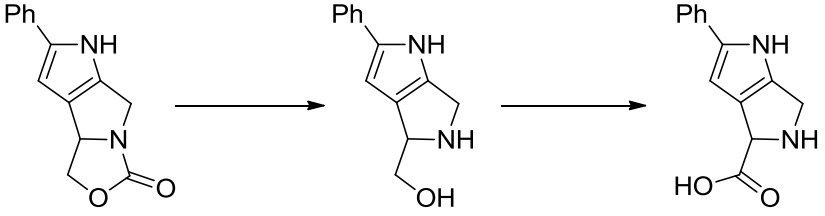
Table 3.2 Complex Pyrrole Synthesis



Substrates	RC Product	Dicarbonyl Product	Pyrrole
	 1a 47%	 1b 59%	 1c 35%*
	 2a 45%	 2b 96%	 2c 92%
	 3a 69%	 3b 62%	 3c 99%

*3 equiv NH_4OAc, 2 equiv TsOH, 4Å MS, THF:EtOH (1:2), reflux

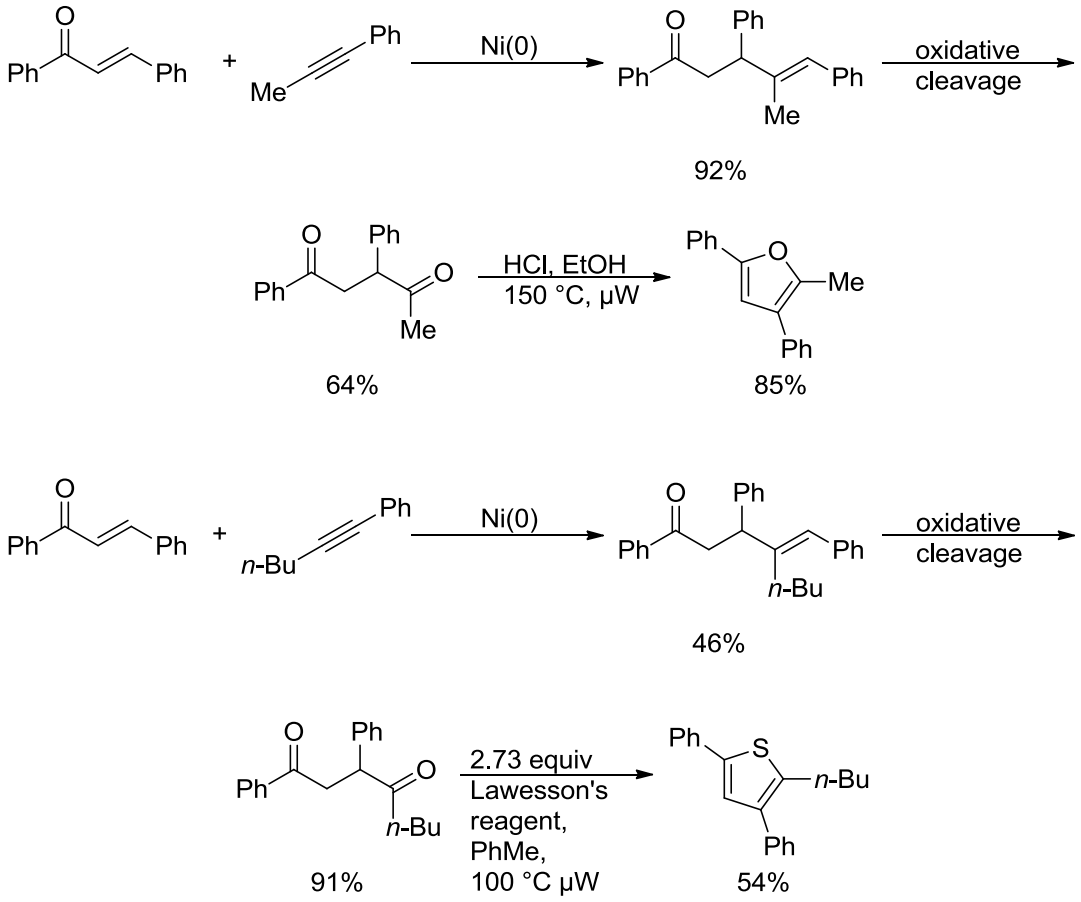
Scheme 3.8 Access to Heteroarylprolines



3.2.5 Furan and Thiophene Synthesis

The nickel-catalyzed reductive coupling approach to pyrrole synthesis also provides an efficient route to furans and thiophenes from the common dicarbonyl intermediate (Scheme 3.9). Under acidic conditions with microwave heating, furans can be made with the same broad substitution scope that was previously demonstrated with pyrroles. Similarly, thiophenes can be made from 1,4-dicarbonyl compounds simply with heating in the presence of Lawesson's reagent.

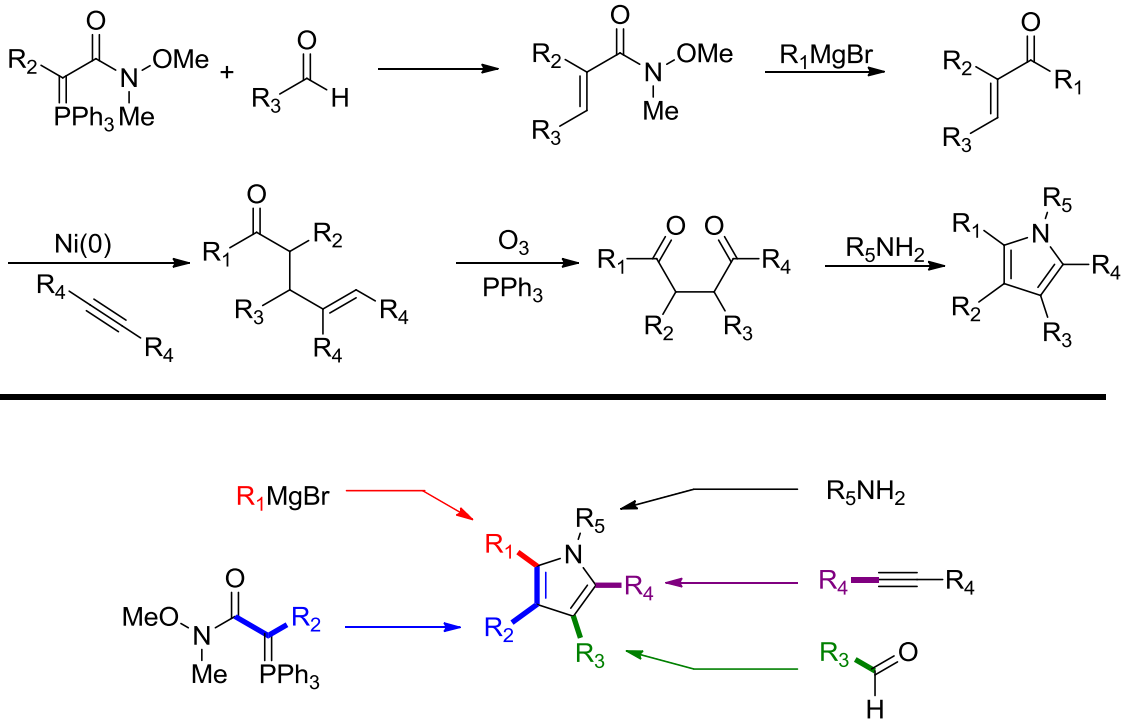
Scheme 3.9 Application to Furan and Thiophene Synthesis



3.2.6 Potential for Library Development

Given the diverse biological activity of pyrroles, furans and thiophenes, screening libraries of these compounds could be valuable. Complexity can be built up quickly from only a few, easily accessed reagents (Scheme 3.10). Enones can be made readily from a Weinreb amide/phosphorus ylide precursor. By simply varying the aldehyde and Grignard reagent, a wide variety of substitution could be introduced at the R^1 and R^3 positions. Some limited substitution, such as methyl could be incorporated at the R^2 position, however, this would require the R^3 to be hydrogen, as α,β-disubstituted enones typically do not work well in the reductive coupling with an alkyne. The alkyne used would also provide another position for more variation, but would require either that the alkyne be symmetrical in its substitution or be functionalized such that it would only form one regioisomer of the reductive coupling product to prevent mixtures from forming. Upon oxidative cleavage to form the dicarbonyl intermediate, various amines could be used to form pyrroles, or the dicarbonyl compound could be cyclized into a furan or thiophenes. This approach to library generation would allow for a great diversity of products to be made, while also allowing for the incorporation of complex functionality through a convergent synthetic route.

Scheme 3.10 Library Potential



3.3 Summary and Future Directions

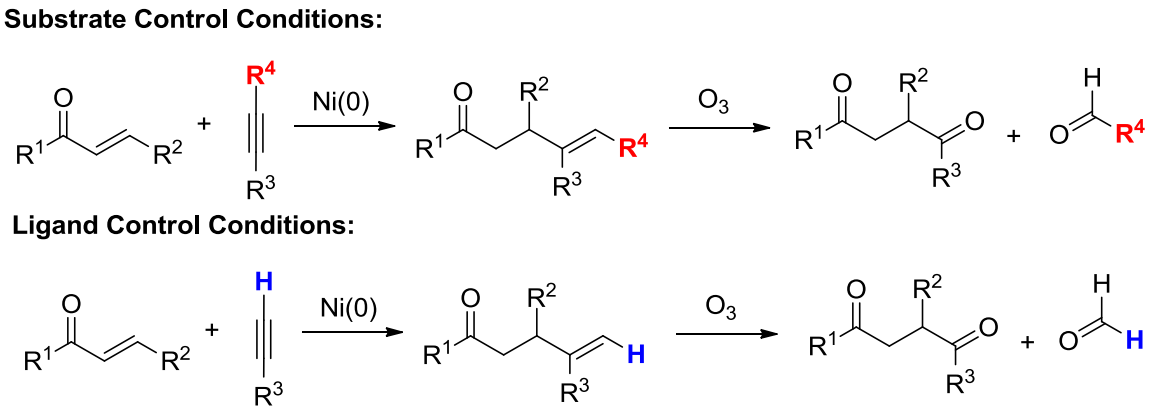
3.3.1 Context of this Method in Heterocycle Synthesis

One of the challenges in the synthesis of pyrroles and related heterocycles is that there are few single methods that can make a wide variety of substitution patterns of the desired products. The nickel-catalyzed reductive coupling entry to heterocycle synthesis allows for the convergent synthesis of a dicarbonyl precursor that can be efficiently converted into a pyrrole, furan or thiophene. This method also avoids some of the common limitations of one of the most popular pyrrole syntheses, the Stetter reaction, specifically, allowing incorporation of hydrogen at either the 2 or 5 positions. The reductive coupling approach allows for a more convergent synthesis, addressing one of the main disadvantages of the linear cross-coupling approach to heterocycle synthesis.

3.3.2 Future Directions

In summary, the development of an efficient method for the coupling of enones and alkynes to form γ,δ-unsaturated ketones and its application to the synthesis of diversely substituted pyrroles via 1,4-dicarbonyls has been described. Ongoing work in this area includes the investigation of developing processes with regiochemical reversal, where the regiochemical bias of the alkyne substrate could be overridden or directed by ligand choice, as demonstrated in the coupling of aldehydes and alkynes.[68] Current conditions require the use of an alkyne coupling partner with a strong regiochemical bias or one that is identically substituted at either end to ensure the dominance of one regioisomer of the product. Developing reaction conditions would allow for the selective incorporation of a substituent into the dicarbonyl scaffold, while only wasting a formaldehyde fragment from the oxidative cleavage (Scheme 3.11).

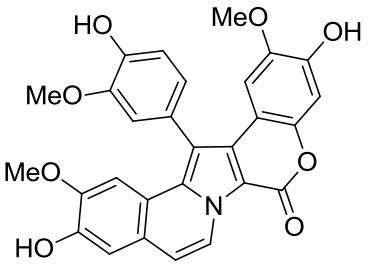
Scheme 3.11 Developing Regiocontrol for the Synthesis of 1,4-Dicarbonyl Compounds



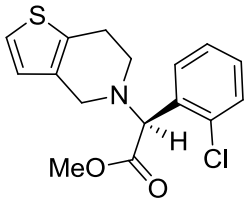
This methodology is ideally suited for the total synthesis of natural products and heterocycle-containing compounds with valuable biological activity as well as their analogues. As demonstrated by the complex example that resembles the lamellarin core

(Table 3.2 Entry 1d), the reductive coupling approach allows for a quick entry to other members of the lamellarin family. Clopidogrel is another example of a biologically active molecule that could be made efficiently using the reductive coupling approach. It would also provide simplified access to anologues by simply varying the starting enone.

Scheme 3.12 Total Synthesis Targets



Lamellarin D



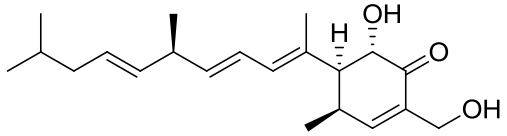
Clopidogrel (Plavix)

Chapter 4

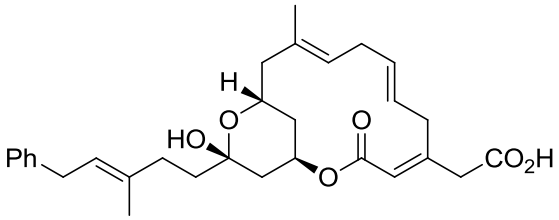
New Pathways for Enone-Alkyne Coupling

4.1 Synthesis of 1,4-Dienes

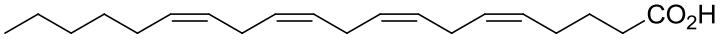
Scheme 4.1 Interesting Molecules Containing 1,4-Dienes



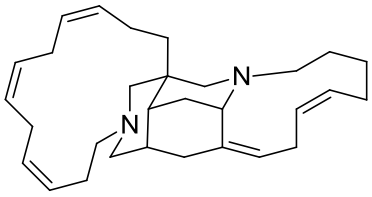
Phorbasin C



Ripostatin A



Arachidonic Acid

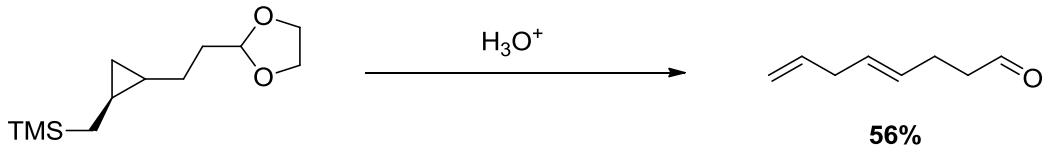


Madangamine A

The 1,4-skipped diene is an important structural motif in organic synthesis and is present in many natural products and other molecules with interesting biological activity (Scheme 4.1).[69] There are diverse methods for making 1,4-dienes; however, there are few methods for efficiently synthesizing them with sufficient levels of *E/Z* selectivity. One of the earliest methods for the selective synthesis of 1,4-dienes arose from the

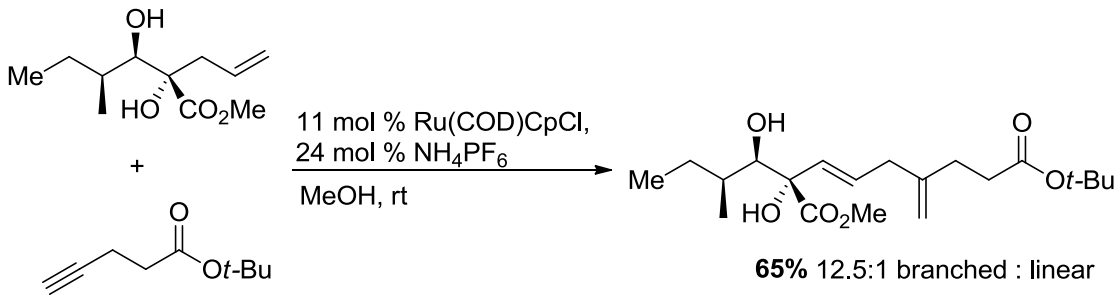
interest in synthesizing analogues of arachidonic acid.[70] This strategy utilizes the elimination of a silyl group adjacent to a cyclopropane, which can then open forming a 1,4-diene (Scheme 4.2). The selectivity is controlled by the stereochemistry of the cyclopropane ring. This approach only allows for control of the stereochemistry of one of the olefins formed.

Scheme 4.2 Wilson 1,4-diene synthesis



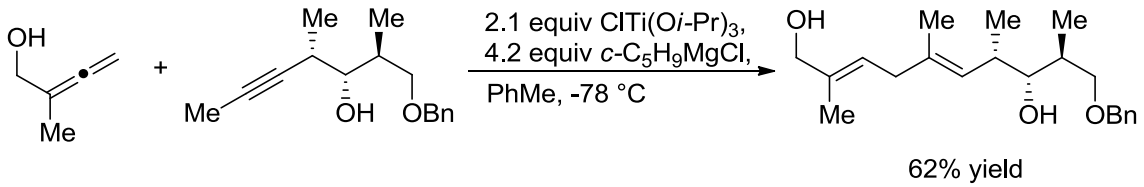
Another approach, developed by the Trost group for the synthesis of alternaric acid, involves the coupling of an alkene and alkyne to form the 1,4-skipped diene (Scheme 4.3).[71] The coupling reaction proceeds with metallacycle formation, with the regiochemistry of the alkyne is thought to be determined by its sterics. β-Hydride elimination forms the *E*-olefin and subsequent reductive elimination gives the 1,4-diene product. The branched product is favored due to the steric interactions between the ester component on the alkyne and the ruthenium complex.

Scheme 4.3 Trost 1,4-diene synthesis



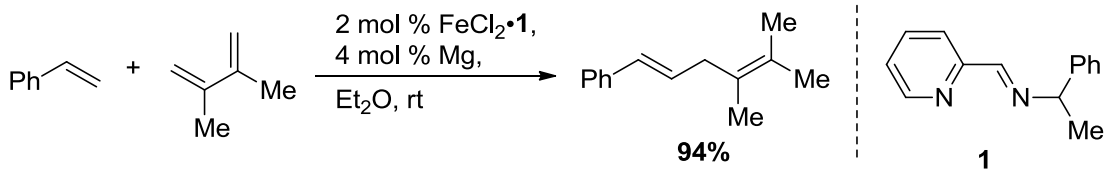
1,4-Dienes can also be synthesized from allenes and alkynes (Scheme 4.4).[72] This transformation proceeds with formation of a titanium-complexed allenic alkoxide, which can undergo directed carbometallation when added to an alkyne. The scope of the reaction is limited to symmetrical internal alkynes, trimethylsilyl-substituted alkynes, and internal alkynes with highly sterically differentiated groups. This reaction also suffers from a competing side reaction to form a conjugated triene product.

Scheme 4.4 Allenic Alkoxide-Directed Coupling with Alkynes



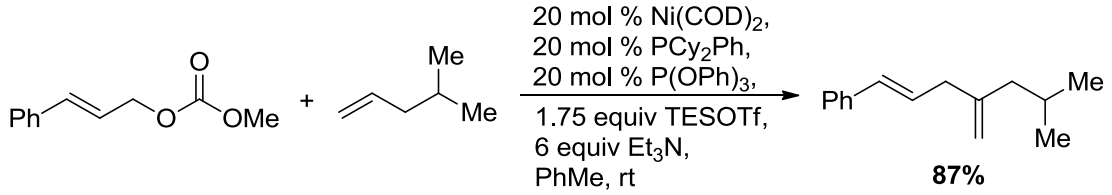
1,3-Dienes also provide a facile entry into the synthesis of 1,4-dienes through coupling with terminal alkenes (Scheme 4.5).[73] This method uses an iron catalyst with an iminopyridine ligand. The transformation is thought to proceed via an oxidative cyclization that adopts a conformation that minimizes steric interactions between the two substrates. A syn-β-hydride elimination and subsequent reductive elimination effectively transfers a hydride from the terminal alkene to the diene. This reaction produces linear 1,4-dienes in high yield and with good control of regioselectivity. The substrate scope is limited to terminal alkenes (mostly styrene derivatives) and tri- and tetra-substituted 1,3-dienes.

Scheme 4.5 Coupling of Dienes and Terminal Alkenes



Another strategy for the synthesis of 1,4-dienes is the allylic substitution of alkenes (Scheme 4.6).[74] This method employs the use of a nickel catalyst with a phosphine ligand that can form an η^3 species with the allylic-alcohol derived substrate, which can then undergo insertion by the alkene and subsequent β-hydride elimination to give the branched 1,4-diene product in most cases. When terminal alkenes are used, the reaction works well with high selectivity for the branched product over a broad range of substrates.

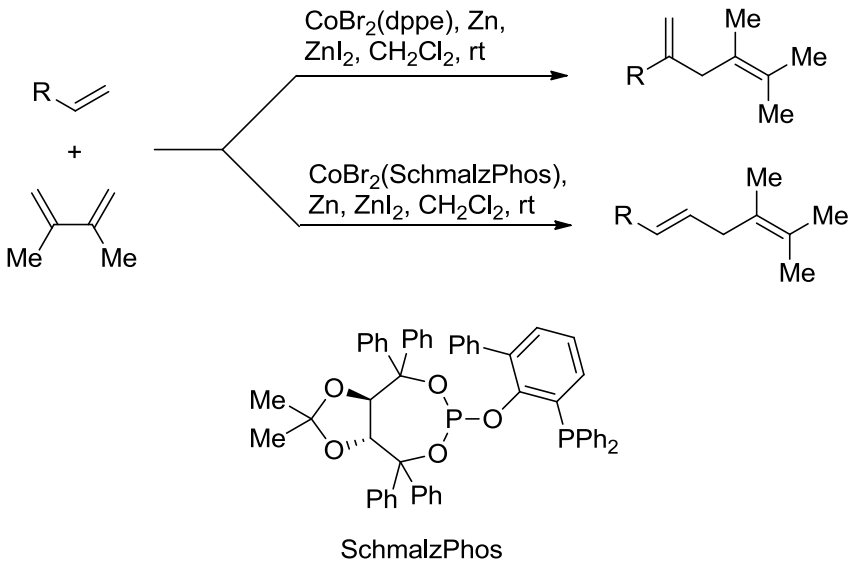
Scheme 4.6 Allylic Substitution Reaction with Alkenes



More recently, a method has been developed allowing for the coupling of 1,3-dienes and terminal alkenes to form either the branched or linear 1,4-diene selectively through the use of different ligands (Scheme 4.7).[75] Using a cobalt catalyst with a phosphine ligand, a terminal alkene and diene can be coupled to selectively give either the branched or linear 1,4-diene product, depending on the ligand used. The reaction is limited to terminal alkenes and symmetrically substituted 1,3-dienes. While there are many methods for making 1,4-dienes, there are fewer methods for making linear 1,4-

dienes with large substrate scope as well as dienes containing substitution at the methylene between the two alkenes.

Scheme 4.7 Selective Coupling of 1,3-Dienes and Terminal Alkenes

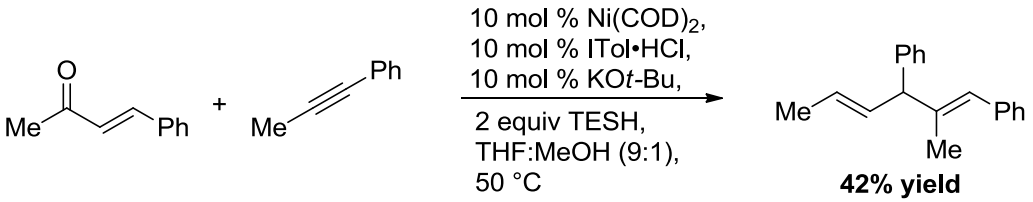


SchmalzPhos

4.2 Optimizations of Reaction Conditions

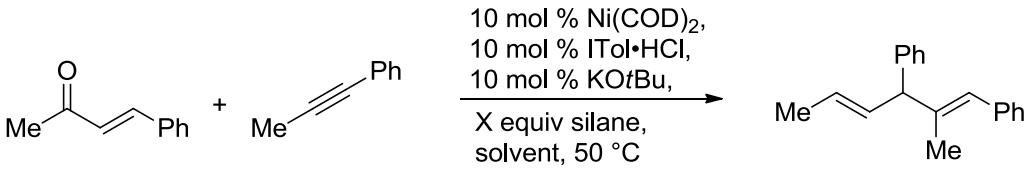
As described earlier (Table 2.12), the reductive coupling of enones and alkynes to form 1,4-dienes was initially discovered when screening ligands in the pursuit of developing a regioselective variant of the γ,δ-unsaturated ketone-forming enone-alkyne coupling reaction. When the ITol ligand in conjunction with triethylsilane was used, the 1,4-diene product was produced in modest yield (Scheme 4.8). This was quite an interesting result, as the product implies a net four electron reduction of the substrates. Before exploring mechanistic studies, some basic optimization of reaction conditions was pursued.

Scheme 4.8 Initial 1,4-Diene Result



It was found that triethylsilane was the optimal reducing agent for this reaction, and that four equivalents were required for a higher yield (Table 4.1, Entry 2). Triethoxysilane produced results similar to triethylsilane (Table 4.1, Entry 3), and the more sterically hindered triisopropylsilane produced none of the desired 1,4-diene (Table 4.1, Entry 4). Initially, it was thought that methanol was a necessary co-solvent for this transformation (Table 4.1, Entry 5), but upon closer examination, it was found that the reaction could still proceed, although in lower yields, in the absence of methanol when more equivalents of silane were used (Table 4.1, Entry 6). Heating was also required for optimal yield, as running the reaction at room temperature under otherwise ideal conditions led to a lower yield of the desired product (Table 4.1, Entry 7).

Table 4.1 Reaction Optimization for 1,4-Diene Synthesis

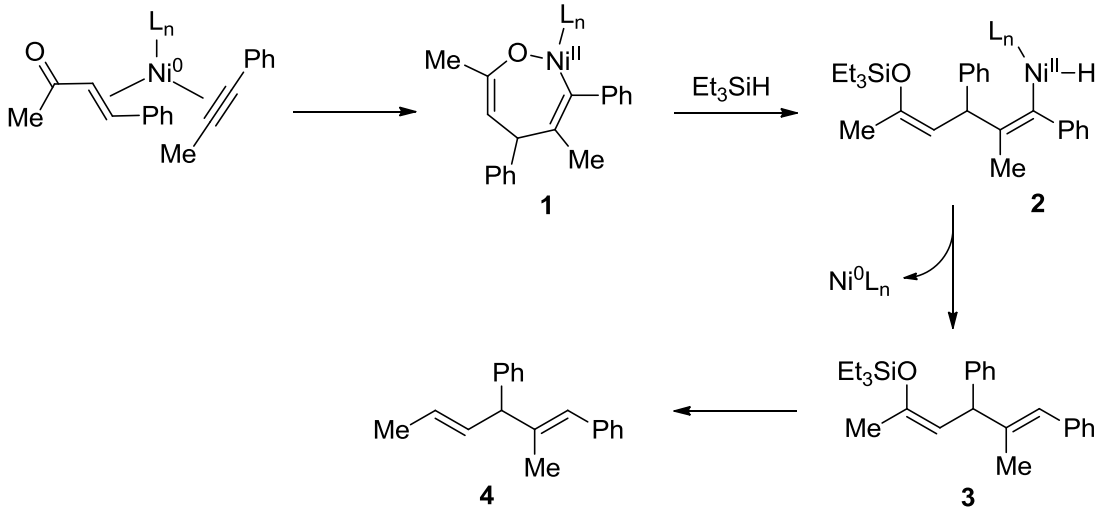


Entry	X equiv Silane	Solvent	Yield
1	2 equiv Et_3SiH	THF:MeOH (9:1)	42%
2	4 equiv Et_3SiH	THF:MeOH (9:1)	68%
3	2 equiv $(EtO)_3SiH$	THF:MeOH (9:1)	40%
4	4 equiv iPr_3SiH	THF:MeOH (9:1)	0%*
5	2 equiv Et_3SiH	THF only	trace
6	4 equiv Et_3SiH	THF only	26%
7	4 equiv Et_3SiH	THF:MeOH (9:1)	44%**

*reaction performed by David Todd
**reaction run at room temperature

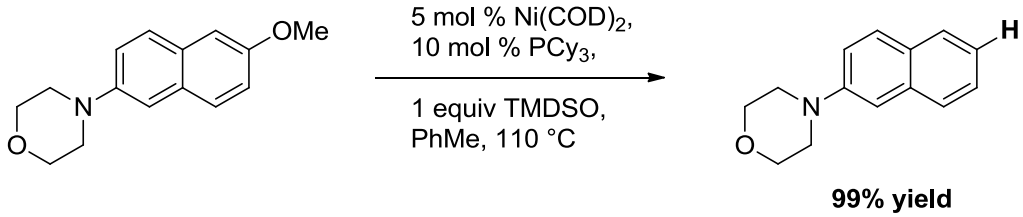
4.3 Mechanistic Investigations

Scheme 4.9 C-O Reduction Mechanism



There are several possible mechanisms for this reaction. In the first potential mechanism (Scheme 4.9), the substrates undergo an oxidative cyclization to form a seven-membered metallacycle (**1)** that can then participate in a σ-bond metathesis with the silane, forming an enol silane and a nickel hydride (**2**), which could undergo reductive elimination to give the enol silane product (**3**). This intermediate could then undergo a nickel-mediated reduction of the carbon-oxygen bond to give the diene product (**4**).

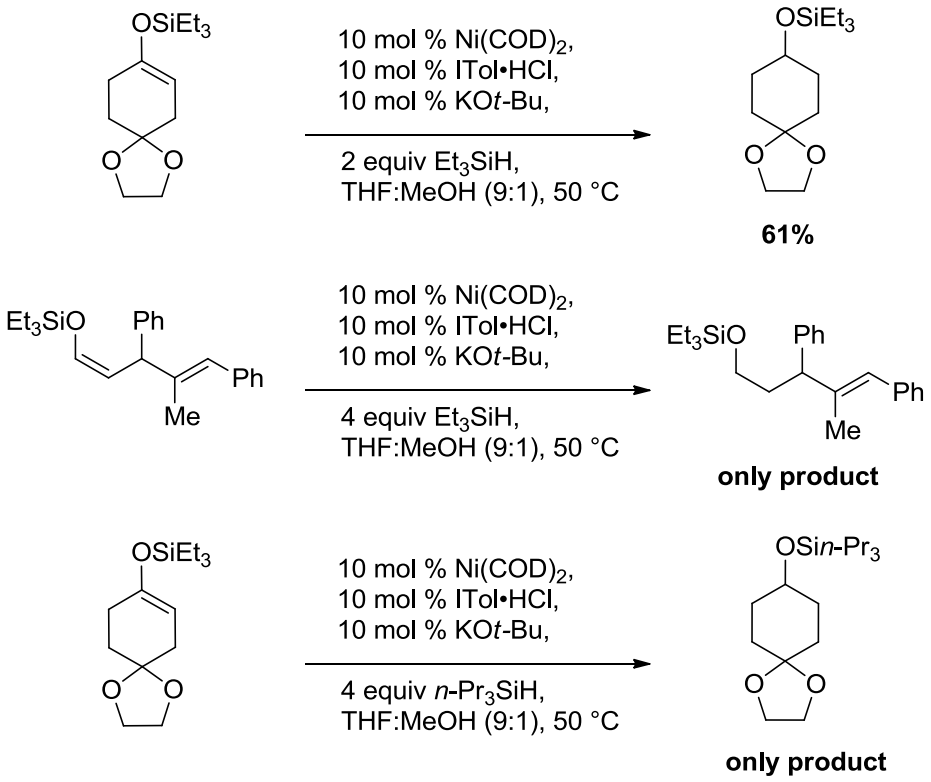
Scheme 4.10 Reduction of Aryl Ethers



Oxidative addition of a nickel catalyst to a carbon-oxygen bond and subsequent σ-bond metathesis with a silane is precedented (Scheme 4.10),[76] although only for aryl C-OMe bonds. If this mechanism were operative, one would expect that submitting an enol silane to the reaction conditions would result in reduction of the C-O bond, giving the alkene product. To test this, enol silanes were prepared and submitted to the reaction conditions optimized for the 1,4-diene-forming reaction (Scheme 4.11). In all cases, it was found that the enol silanes were not reduced to alkenes, but instead the alkene of the starting material was reduced without loss of the silyloxy group. To determine the mode of reduction of the enol silane, a TES-protected enol silane was submitted to the standard reaction conditions using *n*-propylsilane as the reducing agent. The only product observed from this reaction was the *n*-propylsilyl-protected alcohol, indicating that the starting material hydrolyzes to the ketone and then undergoes 1,2-reduction by the silane,

giving the observed product. From this data, it seems unlikely that the mechanism involves the formation and subsequent reduction of an enol silane.

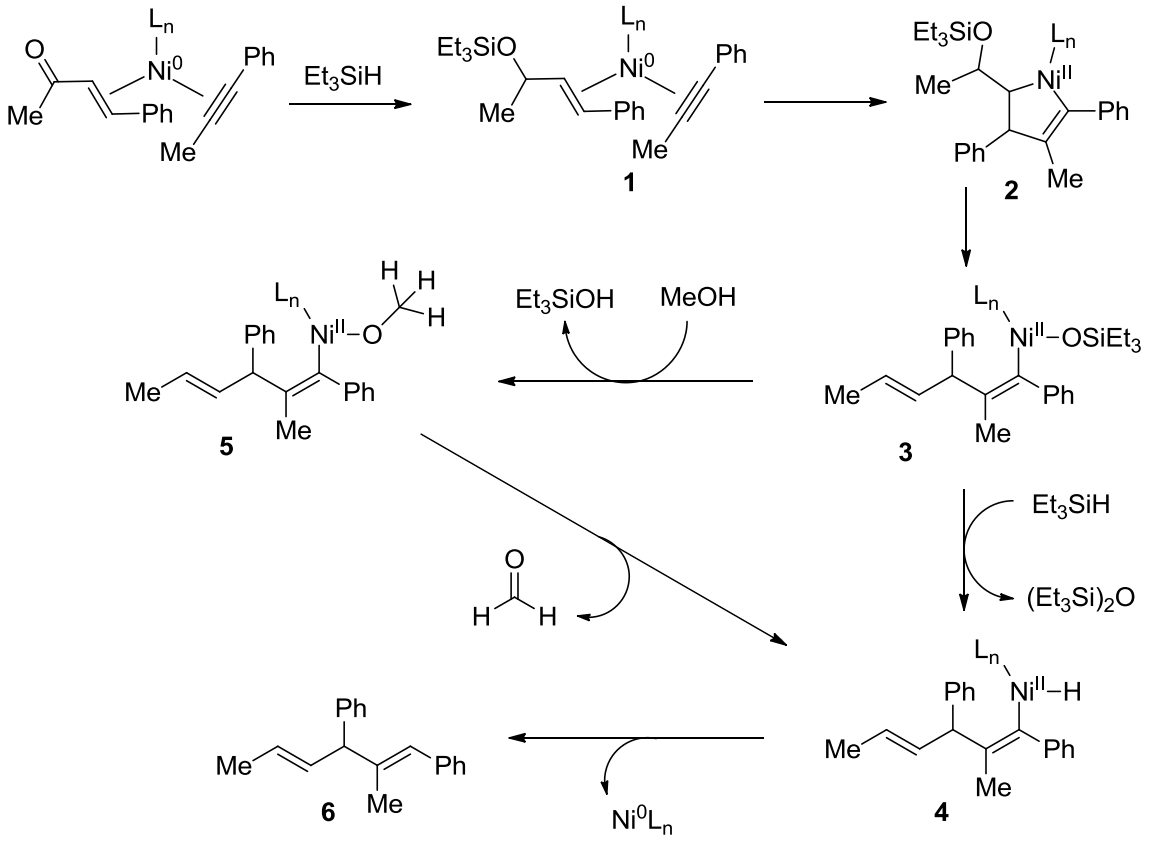
Scheme 4.11 Test of Enol Silane Reduction



Another potential mechanism involves the initial 1,2-reduction of the enone to form a silyl-protected allylic alcohol (**1**), which can then undergo an oxidative cyclization with the alkyne and nickel catalyst to form a five-membered metallacycle (**2**) (Scheme 4.12). The newly formed nickel-carbon bond could then participate in a σ-bond metathesis with the adjacent carbon-oxygen bond, forming the alkene and delivering a silyloxy group to the nickel center (**3**). From this intermediate, there are two possibilities for generating the nickel hydride (**4**) necessary to complete the catalytic cycle. One possibility is a σ-bond metathesis between another equivalent of silane and the nickel-

oxygen bond, which would give a nickel hydride (**4**) and an equivalent of bis-silyl ether. Another possibility is an equivalent of methanol eliminating an equivalent of silanol, creating a nickel-methoxy species (**5**). This intermediate could then undergo β-hydride elimination to create the nickel hydride intermediate (**4**), which could then reductively eliminate and give the product (**6**).

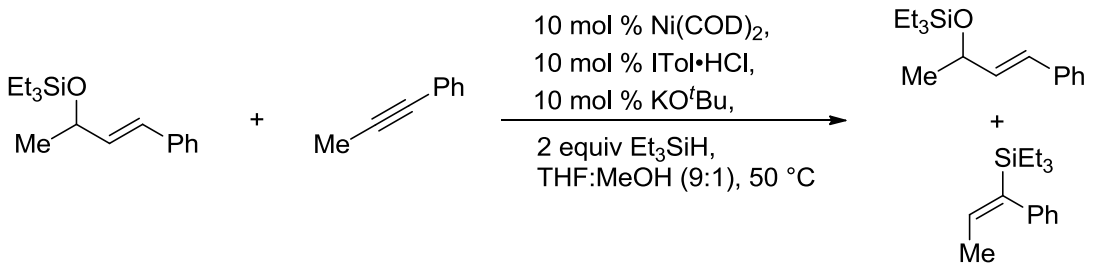
Scheme 4.12 Mechanism Involving Formation of Allylic Alcohol



The first step of this mechanism was probed by submitting a silyl-protected allylic alcohol to the reaction conditions to see if the 1,4-diene product was formed (Scheme 4.13). However, none of the desired product was observed; only starting material and hydrosilylated alkyne were detected. From this, it can be assumed that the mechanism

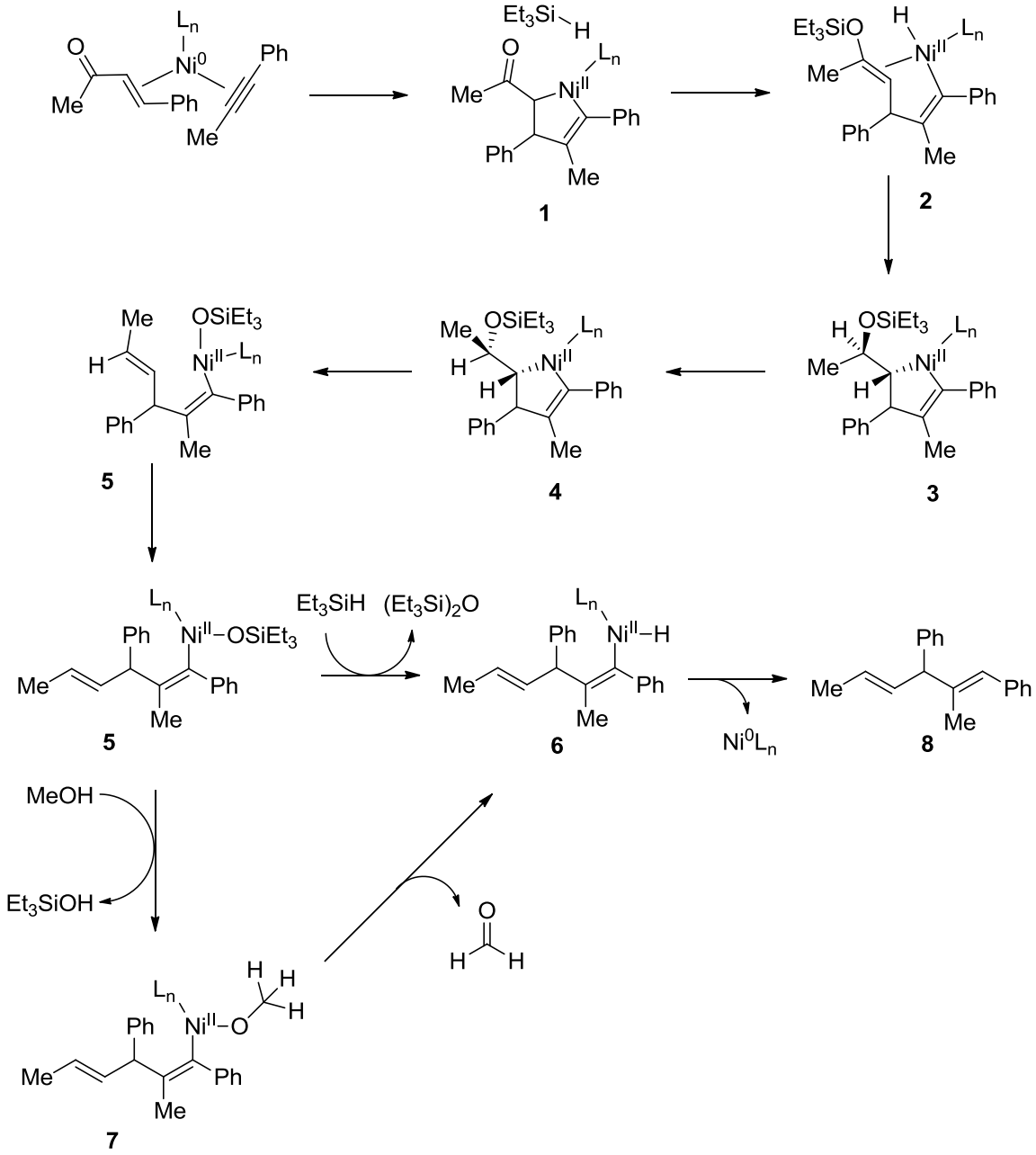
probably does not proceed with the formation of an allylic alcohol from a 1,2-reduction of the enone substrate.

Scheme 4.13 Allylic Alcohol as a Substrate



The third potential mechanism begins with oxidative cyclization of the substrates with the nickel catalyst to form a five-membered metallacycle (**1**) (Scheme 4.14). This metallacycle could then be intercepted by the silane, forming an enol silane and a nickel hydride that remains coordinated to the alkene (**2**). The alkene of the enol silane could then insert into the nickel hydride, reforming a new five-membered metallcycle (**3**), effectively hydrosilylating the carbon-oxygen bond. This intermediate would orient the carbon-oxygen bond *syn* to the nickel-carbon bond (**4**), allowing a β-silyloxy elimination that would form the *Z*-alkene present in the product and a nickel-silyloxy species (**5**). This intermediate can form a nickel hydride species (**6**) by either exchange with another equivalent of silane, or by coordination of a methoxy group (**7**) and subsequent β-hydride elimination. The nickel hydride species (**6**) can then undergo reductive elimination to give the product (**8**).

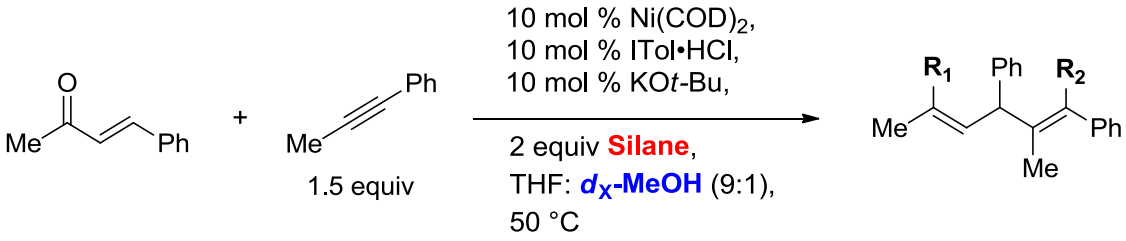
Scheme 4.14 Current Proposed Mechanism



While some of the substrate studies described earlier (Schemes 4.11 and 4.13) provided evidence against the first two mechanistic proposals, deuterium labeling studies were undertaken to improve our understanding of the mechanism for this transformation (Table 4.2). Since the substrates effectively undergo two hydride additions to form the product, determining which reagents they were coming from was investigated. First, the

reaction was performed using triethylsilyl deuteride in place of triethyl silane (Table 4.2, Entry 1). The 1,4-diene product was formed in 40% yield, nearly identical to the non-deuterated case, with complete deuterium incorporation at the former carbonyl position (R^1) and only 33% deuterium incorporation at the other vinyl position (R^2). This result implies that the hydride equivalent that is incorporated at the carbonyl position comes from the silane while the hydride that is incorporated at the other position can come from either the silane or another source. This finding fits with the mechanism proposed earlier (Scheme 4.14), where either a second equivalent of silane or methanol can provide the hydride that reduces the alkyne.

Table 4.2 Deuterium Labeling Studies

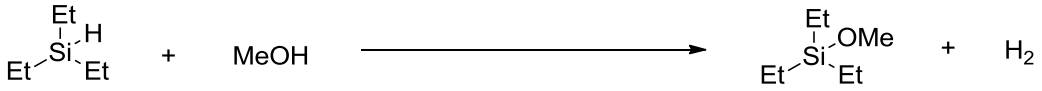


Entry	Silane	d_X-MeOH	Yield of Diene	R_1	R_2
1	Et_3SiD	MeOH	40%	>95% D	33% D
2	Et_3SiD	CD_3OD	47%	>95% D	>95% D
3	Et_3SiH	CD_3OD	29%	H	H
4	Et_3SiH	MeOD	29%	H	H
5*	Et_3SiH	MeOH	29%	H	H
6*	Et_3SiD	MeOH	37%	>95% D	53% D

*Performed under 1 atm H_2
**H denotes <5% D incorporation

Next, the experiment was tried with both triethylsilyl deuteride and fully deuterated methanol (Table 4.2, Entry 2). These reaction conditions gave the 1,4-diene product in 47% yield with complete deuterium incorporation at both the R^1 and R^2 positions. Again, this result corroborates the proposed mechanism where the hydride R^2 position can come from either the silane or methanol. To further confirm this mechanism, the reaction was repeated with triethylsilane and fully deuterated methanol, with the expectation that this would lead to at least partial deuteration at the R^2 position (Table 4.2, Entry 3). However, it was found that this was not the case, with only the completely undeuterated product being observed in 29% yield. This implies that the hydride equivalent that is incorporated at the R^2 position could be coming from another source. From the mechanism proposed earlier (Scheme 4.14), it was suggested that either methanol or the silane could provide the hydride that adds to the R^2 position. In the case of Entry 3 with TESH and CD_3OD, an isotope effect may be responsible for complete incorporation of hydrogen instead of deuterium at this position as either reagent can act as the reducing agent.

Scheme 4.15 Hydrogen as a Hydride Source



One possibility is that hydrogen gas is being formed during the course of the reaction and is being used as a reductant (Scheme 4.15). Methanol and silane could react to form hydrogen and Et_3SiOMe. If hydrogen is being generated from methanol and used in the reaction, it would be expected that methanol deuterated at the hydroxyl position would result in at least partial incorporation of deuterium at R^2 (Table 4.2, Entry 4).

Again, this is not the case, and only a 29% yield of the undeuterated product was observed. Next, the effect of conducting the reaction under an atmosphere of hydrogen was examined. If D-D or H-D is being generated and used in these reactions, it is expected that having an atmosphere of hydrogen would diminsh the degree of deuteration observed in the products. First, a control was run without any deuterium labeling (Table 4.2, Entry 5), and it was observed that the desired 1,4-diene was produced in 29% yield in the presence of hydrogen gas. Then, the reaction was repeated using triethylsilyl deuteride (Table 4.2, Entry 6). The product observed had full deuterium incorporation at the R^1 position and 47% incorporation at the R^2 position, which is inconsistent with hydrogen gas is being used in the reaction as a reductant. If it were, one would expect a decrease in the amount of deuterium incorporation at the R^2 position under a hydrogen atmosphere.

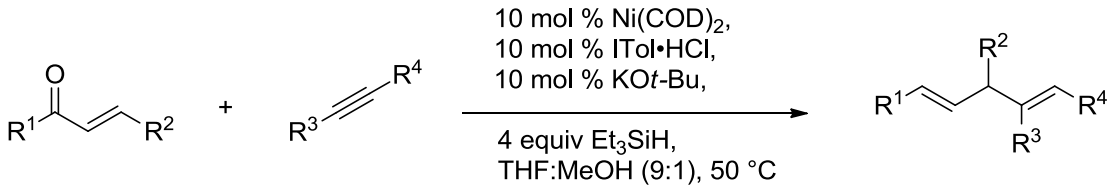
The substrate studies and deuterium labeling experiments suggest that the first two proposed mechanisms (Schemes 4.9 and 4.12) are not operative and that it is unlikely that hydrogen is being produced under these conditions and used a hydride source. The third proposed mechanism (Scheme 4.14) is consistent with all mechanistic data that has been acquired. The inability for cyclic enones to undergo the productive 1,4-diene forming reaction also supports the third mechanism as the intermediate formed from this substrate cannot undergo the bond rotation required to adopt the necessary *syn* conformation for the elimination of the silyloxy group (Table 4.3, Entry 4).

4.4 Substrate Scope

Under the optimized reaction conditions (Table 4.3, Entry 1), benzylidene acentone and phenyl-propyne give the corresponding 1,4-diene in modest yield. These

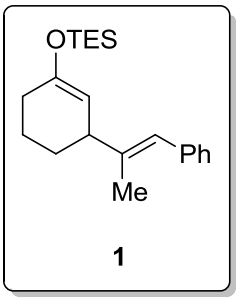
conditions were used to further explore the substrate scope of this reaction (Table 4.3). Changing the enone to trans-chalcone resulted in a high yield of the desired product (Table 4.3, Entry 2). Employing diphenyl acetylene as the alkyne in the coupling with benzylidene acetone led to dramatically lower yields (Table 4.3, Entry 3), suggesting that too much steric congestion around the site of C-C bond formation inhibits the reaction. Methyl vinyl ketone resulted in none of the desired diene product, with alkyne hydrosilylation being the only observed product (Table 4.3, Entry 4). Cyclohexenone and phenyl propyne gave none of the 1,4-diene product, but instead resulted in a low yield of the enol-silane coupled product (Table 4.3, Entry 5). It can also be seen that methyl substitution of the enone at the β-position does not seem to be well tolerated (Table 4.3, Entry 6). From this brief examination of the substrate scope of the 1,4-diene forming reaction, it seems that the substitution pattern of the enone substrate may be relatively narrow, but more investigation is needed.

Table 4.3 Substrate Scope



Entry	R^1	R^2	R^3	R^4	Yield
1	Me	Ph	Me	Ph	68%
2	Ph	Ph	Me	Ph	80%
3	Me	Ph	Ph	Ph	33%
4	Me	H	Me	Ph	N.R.
5	$-(CH_2)_3-$		Me	Ph	31% **1***
6	Ph	Me	Me	Ph	N.R.*

*Reaction performed by David Todd



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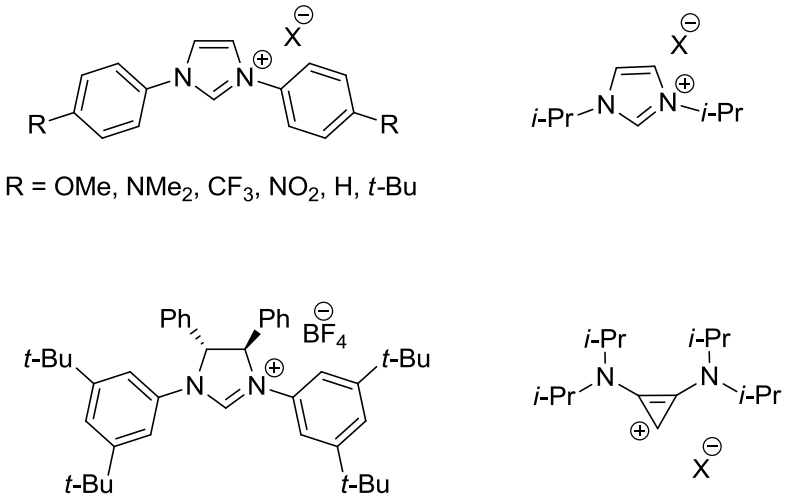
4.5 Summary of 1,4-Diene Synthesis and Future Directions

These initial results from the investigation of the reductive coupling of enones and alkynes to form 1,4-dienes are encouraging and will be pursued further. With a reasonable understanding of what the mechanism is for this transformation, the next step in this project is more extensively investigating the scope of substrates tolerated by this reaction. The data from Table 4.3 show that cyclic enones and enones containing β substitution that is not a phenyl group do not work well under current conditions. Further

exploration of what aryl groups can be tolerated is needed as well as which alkynes are amenable to this reaction.

Thus far it is not well understood why the ITol ligand is optimal for this transformation. The 1,4-diene product was not observed in other reactions using other carbene ligands, even in low yield, and to the best of our knowledge, has never been noticed at significant levels during previous studies of enone-alkyne reductive coupling. A more extensive screen of ligands for this reaction should be undertaken. Other less sterically hindered NHC ligands will be an appropriate starting point (Scheme 4.16). Chiral carbene ligands, such as the bis-(3,5-di-*t*-butylphenyl)-imadazolinium tetrafluoroborate will also be investigated.

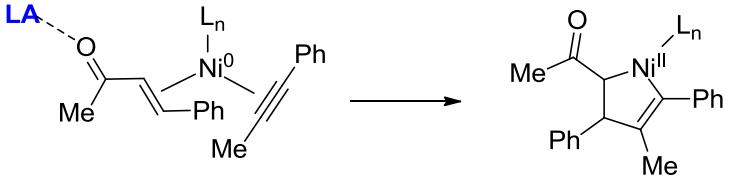
Scheme 4.16 Ligand Optimization



The reducing agent used in this reaction also needs further development. Thus far the best performing silane has been triethylsilane, however, in some cases, this can produce significant amounts of alkyne hydrosilylation as a side reaction. Increasing the steric bulk of the silane may decrease the amount of this undesired side reaction, but as

shown earlier, bulkier silanes can also decrease the yield of the desired reaction (Table 4.1, Entry 4). Other reducing agents that have been successful in the reductive enone-alkyne coupling, such as alkylzinc reagents and triethylborane, would result in undesired reactivity as they would be unlikely to be able to remove the oxygen from the enone as in the silane case. The addition of a Lewis acid may also increase yields (Scheme 4.17). In the triethlyborane-mediated enone-alkyne coupling, the formation of borate intermediates may aid in the necessary oxidative cyclization.

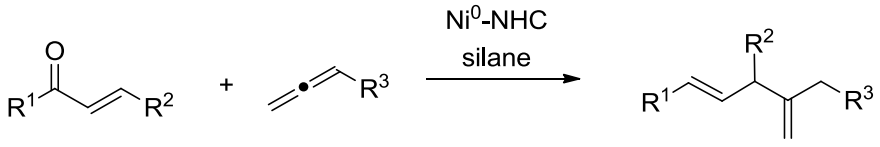
Scheme 4.17 Lewis Acid Additive Investigation



LA = BF_3•Et_2O, $TiCl_4$, $Ti(O\textit{i}\text{-}Pr)_4$, $Al(O\textit{i}\text{-}Pr)_3$, BPh_3, BEt_3OMe

Expanding this reaction to other coupling partners, such as allenes, could provide access to branched 1,4-dienes (Scheme 4.18). The nickel-catalyzed reductive coupling of enones and allenes has been demonstrated in our lab.[77] This manifold would allow for the synthesis of either the linear or branched product simply by changing one of the coupling partners.

Scheme 4.18 Reductive Coupling of Allenes and Enones to form Branched 1,4-Dienes



4.6 Overall Summary and Outlook for Development of Reductive Coupling Reactions

A broad range of different reactions have been examined with the goal of discovering strategies for regiocontrol. The initial results from the hydroboration of dienes provide promising leads for further development of this useful transformation. Similarly, the data collected thus far on the regiocontrol of the enone-alkyne reductive coupling warrant further investigation of this reaction, as it would provide convenient access to a broad range of conjugate addition products and precursors for heterocycle synthesis. The discovery of the reductive coupling of enones and alkynes to form 1,4-dienes is very exciting and encourages further development of this unique reaction.

Chapter 5

Experimental

5.1 General Experimental Details

Unless otherwise noted, all reactions were conducted in flame-dried or oven dried (120 °C) glassware with magnetic stirring under an atmosphere of dry nitrogen. THF and CH_2Cl_2 were purified under nitrogen using a solvent purification system (Innovative Technology, inc., Model # SPS-400-3 and PS-400-3). Methanol (Acros, extra dry with molecular sieves) was used as received without further purification. Aldehydes were distilled prior to use. Silanes were passed through alumina. $Ni(COD)_2$ (Strem Chemicals, Inc.) and tricyclohexyl phosphine (Aldrich) were stored and weighed in an inert atmosphere glovebox. Triethylborane and dimethylzinc (Aldrich, 2M in toluene) were used as received using standard Schlenk techniques. 4 Å molecular sieves (Aldrich, <5 micron powder) were heated under vacuum and purged with nitrogen prior to use. Ozone for ozonolysis reactions was generated using an Azcozon Ozone generator.

Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F254 (250 μm silica gel) glass plates and compounds were visualized with UV light and *p*-anisaldehyde stain. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh) silica gel. Eluent mixtures are reported as v:v percentages of the minor

constituent in the major constituent. All compounds purified by column chromatography were sufficiently pure for use in further experiments unless otherwise indicated.

^{1}H NMR spectra were measured at 400 MHz on a Varian MR400 instrument, at 500 MHz on a Varian Inova 500 instrument or at 700 MHz on a Varian vnmrs 700 instrument. The proton signal of the residual, nondeuterated solvent (δ 7.24 for $CHCl_3$) was used as an internal reference for ^{1}H NMR spectra. ^{13}C NMR spectra were completely heterodecoupled and measured at 175, 125 or 100 MHz. Residual chloroform (δ 77.0) was used as an internal reference. High resolution mass spectra were recorded on a VG 70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory.

5.2 Chapter 2 Experimental

5.2.1 General Procedure

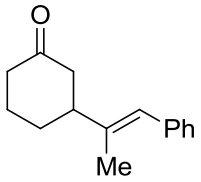
General Procedure for the $Ni(COD)_2/PBu_3$ Promoted Reductive Coupling of Enones and Alkynes:

To a solution of $Ni(COD)_2$ (0.1 equiv) in THF (0.6 mL) was added dropwise tributylphosphine (PBu_3) (0.2 equiv) at room temperature. After stirring for 5-10 min at rt, the reaction mixture became bright yellow. A solution of enone (1.0 equiv) and alkyne (1.5 equiv) at rt in MeOH (4.4 mL) was added, and then Et_3B (3.0 equiv) was added. The reaction mixture was stirred at 50 ºC until TLC analysis indicated disappearance of the enone. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated and residue was

purified by column chromatography on silica gel. Regioisomeric ratios were determined on crude reaction mixtures using ^{1}H NMR. The alkene stereochemistry was determined by NOE.

5.2.2 Table 2.1 Products

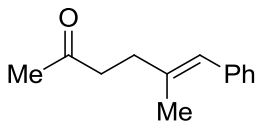
(*E*)-3-(1-Phenylprop-1-en-2-yl)cyclohexanone (Table 2.1, entry 5)



Following the general procedure, 2-cyclohexen-1-one (29 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 6 h at 50 °C. The product (52 mg, 80 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (20% Et_2O in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (m, 2H), 7.23 (m, 3H), 6.33 (s, 1H), 2.57-2.41 (m, 4H), 2.34 (m, 1H), 2.15 (m, 1H), 2.01 (m, 1H), 1.87 (d, *J* = 1.2 Hz, 3H), 1.75 (m, 2H); ^{13}C NMR (100 MHz, CDCl3): 211.4, 140.3, 137.9, 128.9, 128.0, 126.2, 124.8, 48.3, 46.7, 41.2, 30.1, 25.2, 15.7; IR (film, cm^{-1}) 3054, 2937, 1710, 1599; HRMS (EI) *m/z* calcd for $C_{15}H_{18}O$ [M+] 214.1358, found 214.1358.

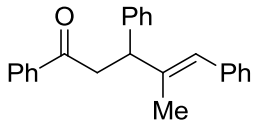
5.2.3 Table 2.2 Products

(*E*)-5-Methyl-6-phenylhex-5-en-2-one (Table 2.2, entry 1)



Following the general procedure, 3-buten-2-one (25 μL, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 1 h at 50 °C. The product (48 mg, 85 %, >95:5) wasobtained as a colorless oil after SiO_2 chromatography (20% Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 2H), 7.22 (m, 3H), 6.29 (s, 1H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.6 Hz, 2H), 2.20 (s, 3H), 1.87 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 208.3, 138.1, 137.3, 128.7, 128.0, 126.0, 125.3, 42.2, 34.4, 29.9, 17.8; IR (film, cm^{-1}) 3055, 2917, 1714, 1599, 1442; GCMS calcd for $C_{13}H_{16}O$ [M+] 188, found 188.

(*E*)-4-Methyl-1,3,5-triphenylpent-4-en-1-one (Table 2.2, entry 6)



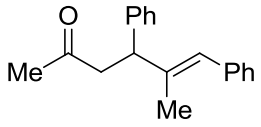
Following the general procedure, (*E*)-chalcone (62 mg, 0.30 mmol), 1-phenyl-1-propyne (52 mg, 0.45 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), PBu_3 (16 μL, 0.06 mmol), and Et_3B (130 μL, 0.90 mmol) were stirred for 12 h at 50 °C. The product (88 mg, 90 %, >95:5) was obtained as a colorless oil after SiO_2 chromatography (10-15% Et_2O in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 7.38-7.19 (m, 10H), 6.48 (s, 1H), 4.27 (t, *J* = 7.2 Hz, 1H), 3.65 (dd, *J* = 7.6, 16.4 Hz, 1H), 3.54 (dd, *J* = 7.2, 16.4 Hz, 1H), 1.80 (d, *J* = 1.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 198.5, 142.6, 140.0, 138.0, 137.2, 133.0, 128.9, 128.6, 128.4, 128.0, 127.96, 127.8, 126.5, 126.1, 125.3, 49.6, 42.4, 17.0; IR (film,cm^{-1}) 3058, 2912, 1687, 1448; HRMS (ESI) *m/z* calcd for $C_{24}H_{22}ONa$ $[M+Na]^+$ 349.1568, found 349.1562.

5.2.4 Table 2.3 Products

General Procedure for Table 2.3:

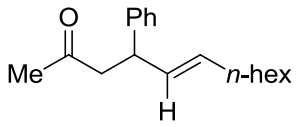
$Ni(COD)_2$ (0.1 mmol) and chiral ligand (0.1 mmol) were dissolved in 0.6 mL THF and allowed to stir at room temperature for ten minutes. The substrates were then added as a solution in 4.4 mL extra dry MeOH, followed by subsequent addition of triethylsilane (3 equiv). The reaction was heated to 50 ºC and allowed to stir overnight. The crude reaction mixture was diluted in EtOAc and washed twice with pH 8 NH_4Cl/NH_4OH buffer and once with brine. The organic layer was then dried over $MgSO_4$ and filtered. The solvent was then concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography.

(*E*)-5-methyl-4,6-diphenylhex-5-en-2-one (Table 2.3, Entries 4&5)



Following the general procedure, 44 mg of benzylidene acetone, 52 mg of phenyl propyne, 16.2 mg of $TADDOLPNMe_2$, and 143 μL of triethylsilane gave a crude reaction mixture that was purified by flash chromatography (20% EtOAc in hexanes) to give the product (15 mg, 20% yield). The product was found to have an enantiopurity of 44 %*ee*, which was ascertained using an OJ column in an eluent of 95/5 hexanes/isopropyl alcohol at a rate of 1 mL/min.

(*E*)-4-phenyldodec-5-en-2-one (Table 2.3, Entries 6&7)



Following the general procedure, 44 mg of benzylidene acetone, 50 mg of phenyl propyne, 16.2 mg of TADDOLPNMe$_2$, and 143 μL of triethylsilane gave a crude reaction mixture that was purified by flash chromatography (10% EtOAc in hexanes) to give the product. The product was found to have an enantiopurity of 54 %*ee*, which was ascertained using an OD-H column in an eluent of 99/1 hexanes/isopropyl alcohol at a rate of 0.75 mL/min.

5.2.5 Table 2.4 Enone-Enyne Products

General Procedure for Table 2.4 and 2.5

Ni(COD)$_2$ (0.1 equiv) and tricyclohexyl phosphine (0.2 equiv) were dissolved in 0.3 mL THF and allowed to stir at room temperature for ten minutes. The substrates were then added as a solution in 0.3 mL THF and 4.4 mL extra dry MeOH, followed by subsequent addition of triethylborane (3 equiv). The reaction was heated to 50 ºC and allowed to stir overnight. The crude reaction mixture was passed through a plug of silica using 1:1 EtOAc:hexane and then concentrated *in vacuo*. The resulting mixture was purified via flash chromatography.

5.2.6 Table 2.8 Products

General Procedure for Table 2.8 Alkyne Hydroboration

Ni(COD)$_2$ (0.1 equiv), NHC•HX (0.1 equiv), and KO*t*-Bu (0.1 equiv) were dissolved in 2 mL THF and allowed to stir at room temperature for ten minutes. Pinacol borane (1.5

equiv) was then added and the solution was allowed to stir for another ten minutes. The alkyne was then added as a solution in 3 mL THF via syringe drive over one hour. The reaction was run until TLC show disappearance of starting materials. The reaction was quenched with water and extracted with Et_2O and concentrated *in vacuo*. The crude reaction mixture was purified via flash chromatography.

5.2.7 Table 2.9 Products

General Procedure for Table 2.9 Diene Hydroboration

$Ni(COD)_2$ (0.1 equiv), NHC•HX (0.1 equiv), and KO*t*-Bu (0.1 equiv) were dissolved in 2 mL THF and allowed to stir at room temperature for ten minutes. Pinacol borane (1.5 equiv) was then added, the diene was subsequently added as a solution in 3 mL THF. The reaction was heated to 80 ºC for three hours. The reaction was quenched with water and extracted with Et_2O, passed through a pad of silica, and concentrated *in vacuo*. The crude reaction mixture was purified via flash chromatography. The ^{1}H NMR spectrum matched the published spectra.[33]

5.2.78 Table 2.10 Products

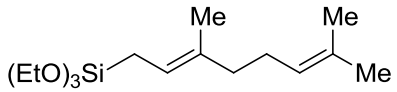
General Procedure for Table 2.10 Alkyne Hydrosilylation

$Ni(COD)_2$ (0.1 equiv), NHC•HX salt (0.1 equiv), and KO*t*-Bu (0.1 equiv) were dissolved in 2 mL THF and allowed to stir at room temperature for ten minutes. Triethoxysilane (2 equiv) was then added and the solution was allowed to stir for another ten minutes. The alkyne was then added as a solution in 3 mL THF via syringe drive over one hour. The reaction was run until TLC show disappearance of starting materials. The reaction mixture was passed through silica with 1:1 EtOAc:hexanes and concentrated *in vacuo*.

The crude reaction mixture was purified via flash chromatography. The ^{1}H NMR spectrum matched the published spectra.[34]

5.2.9 Scheme 2.16

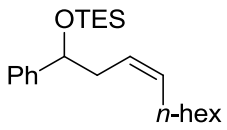
(*E*)-(3,7-dimethylocta-2,6-dien-1-yl)triethoxysilane



Following the same procedure used for Table 3.4 with the substitution of triethoxysilane for pinacol borane, the reactants gave a crude residue which was purified by flash chromatography to give the product as a mixture of regioisomers. The ^{1}H NMR spectrum matched the published spectra.[35]

5.2.10 Table 2.11 Products

(*Z*)-triethyl((1-phenyldec-3-en-1-yl)oxy)silane



$Ni(COD)_2$ (0.1 equiv), NHC•HX (0.1 equiv), and KO*t*-Bu (0.1 equiv) were dissolved in 2 mL THF and allowed to stir at room temperature for ten minutes. Triethylsilane (1.5 equiv) was then added to the reaction mixture. The diene (1 equiv) and alkyne (1.5 equiv) were subsequently added as a solution in 3 mL THF. The reaction was heated to 80 ºC overnight. The reaction was passed through a pad of silica with EtOAc, and concentrated *in vacuo*. The crude reaction mixture was purified via flash chromatography.

5.2.11 Table 2.12 Products

General Procedure for Table 2.12 Enone-Alkyne Regioselectivity Screen

$Ni(COD)_2$ (0.1 equiv), NHC•HX (0.1 equiv), and KO*t*-Bu (0.1 equiv) were dissolved in 1.5 mL THF and allowed to stir at room temperature for ten minutes. The enone (1 equiv) and alkyne (1.5 equiv) were added as a solution in 3 mL THF. Triethylsilane (2 equiv) and 0.5 mL MeOH were added subsequently, and the reaction was heated to 50 °C overnight. The crude reaction mixture was passed through a pad of silica with 1:1 EtOAc:hexane, and concentrated *in vacuo*. The crude reaction mixture was purified via flash chromatography, and the product was isolated as a mixture of regioisomers. See 4.2.4 for spectral data.

5.2.12 Table 2.14 Products

Following the general procedure for Table 2.12, $Ni(COD)_2$ (0.1 equiv), NHC•HCl (0.1 equiv), KO*t*-Bu (0.1 equiv), methylvinylketone (1 equiv), phenylpropyne (1.5 equiv) and triethysilane (2 equiv), gave a crude residue which was purified by flash chromatography. Regioisomeric ratios were determined by ^1H NMR analysis.

5.3 Chapter 3 Experimental

5.3.1 General Procedures

General Procedure A for the $Ni(COD)_2/PCy_3$ promoted coupling of Enones and Alkynes with Et_3B:

A solid mixture of 10 mol % $Ni(COD)_2$ and 20 mol % PCy_3 were dissolved in 0.1 M THF. This was allowed to stir at room temperature for 10 minutes. Enone (1.0 equiv) and alkyne (1.5 equiv) were added together as a solution in 0.5 M THF. Methanol (0.07

M) was then added, followed by addition of Et_3B (3.0 equiv), and the reaction mixture was heated to 50 °C and allowed to stir until starting materials were consumed. The reaction mixture was then filtered through a plug of silica with EtOAc. The solvent was then removed *in vacuo*, and the crude reaction mixture was purified via flash chromatography to afford the desired product.

General Procedure B for Ozonolysis:

The substrate was dissolved in methylene chloride (0.03 M), and cooled to -78 °C. Ozone was then bubbled through the solution until it turned bright blue. Oxygen was then bubbled through the solution until the blue color faded. PPh_3(1.0 equiv) was then added, and the reaction mixture was allowed to warm to room temperature overnight. The solvent was then removed *in vacuo*, and the crude reaction mixture was purified via flash chromatography to afford the desired product.

General Procedure C for Paal-Knorr Cyclization of 1,4-dicarbonyl Compounds to Pyrroles:

The substrate was placed in a microwave vial charged with a stir bar and dissolved in THF (0.15 M). Ammonium acetate or amine (4.5 equiv), 4 Å molecular sieves (a small spatula tip full), and acetic acid (0.15 M) were added sequentially. The vial was then sealed and heated at 170 °C for 15 minutes in a microwave reactor. The crude reaction mixture was filtered through Celite with EtOAc, and then washed with aqueous saturated sodium bicarbonate and then brine. The organic layer was then dried over $MgSO_4$ and the solvent was then removed *in vacuo*. The crude reaction mixture was purified via flash chromatography to afford the desired product.

General Procedure D for the $Ni(COD)_2/PCy_3$ promoted Coupling of Enals and Alkynes with Triethylsilane:

Same as procedure A, just using additional THF instead of methanol, and Et_3SiH instead of Et_3B. After purification via flash chromatography, the silylated product was then dissolved in THF (0.1 M), and cooled to 0 °C. Aqueous HCl (0.2 M) was added, and the reaction mixture was allowed to stir overnight, warming to rt. The crude reaction mixture was then extracted with ether, and the organic phase was washed three times with diethyl ether, once with brine, and then dried over $MgSO_4$. The solvent was then removed *in vacuo*, and the crude reaction mixture was purified via flash chromatography to afford the desired product.

General Procedure E for the $Ni(COD)_2/Me_2Zn$ promoted Cyclizations:

$Ni(COD)_2$ (10 mol %) was dissolved in THF (0.02 M) and cooled to 0 °C. Me_2Zn (2 M in toluene, 1.5 equiv) was then added dropwise, and allowed to stir for 10 minutes. The substrate was added to the reaction mixture via cannula using THF (0.1 M), and allowed to stir overnight at 0 °C. The reaction mixture was diluted with EtOAc and washed with a pH 8 solution of NH_4OH/ NH_4Cl and then brine. Organic phase was dried over $MgSO_4$, and the solvent was then removed *in vacuo*. The crude reaction mixture was purified via flash chromatography to afford the desired product.

General Procedure F for Paal-Knorr Cyclization of 1,4-dicarbonyl Compounds to Pyrroles:[78]

The substrate was placed in a 5mL round bottom flask charged with a stir bar and dissolved in 1 mL THF. Ammonium acetate (3 equiv) was added. Then a solution of *p*-

toluenesulfonic acid (2 equiv) was added in 2 mL dry ethanol followed by 4 Å molecular sieves (a small spatula tip full). A condenser was attached and the reaction was heated at reflux overnight. After cooling to rt, the crude reaction mixture diluted with EtOAc, washed with water and then brine. The organic layer was then dried over Na_2SO_4 and the solvent was then removed *in vacuo*. The crude reaction mixture was purified via flash chromatography to afford the desired product.

5.3.2 Table 3.1 Products

(Z)-1,3,4,5-tetraphenylpent-4-en-1-one.

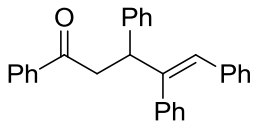


Table 3.1, Entry 1a: Following procedure A, $Ni(COD)_2$ (28 mg, 0.1 mmol), PCy_3 (56 mg, 0.2 mmol), trans-chalcone (208 mg, 1 mmol), diphenylacetylene (276 mg, 1.5 mmol), and Et_3B (434 μL, 3 mmol) gave a crude residue which was purified by flash chromatography (5% EtOAc in hexanes) to give the product (314 mg, 0.81 mmol, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (m, 2H), 7.57 (m, 1H), 7.46 (m, 2H), 7.29 (m, 4H), 7,22 (m, 4H), 7.06 (m, 3H), 6.97 (m, 2H), 6.86 (m, 2H), 6.56 (s, 1H), 4.62 (t, *J* = 7.5 Hz, 1H), 3.66 (dd, *J* = 17.0 Hz, 7.5 Hz, 1H), 3.51 (dd, *J* = 17.0 Hz, 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 144.7, 141.8, 140.4, 137.2, 136.9, 133.0, 129.2, 129.1, 128.6, 128.4, 128.3, 128.0, 127.8, 127.3, 127.0, 126.6, 126.4, 49.8, 42.5. IR (thin film): ν 3056, 3026, 2927, 1685, 1493, 1448 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{29}H_{24}O$, 388.1827, found 388.1823.

1,2,4-triphenylbutane-1,4-dione.[79]

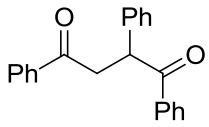


Table 3.1, Entry 1b: Following procedure B, (Z)-1,3,4,5-tetraphenylpent-4-en-1-one (116 mg, 0.3 mmol) and PPh_3 (79 mg, 0.3 mmol) yielded a crude residue which was purified by flash chromatography (10% EtOAc in hexanes) to give the product (92 mg, 0.29 mmol, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (m, 2H), 8.01 (m, 2H), 7.57 (m, 1H), 7.52 - 7.38 (m, 7H), 7.33 (m, 2H), 7.25 (m, 1H), 5.37 (dd, *J* = 10.0 Hz, 3.5 Hz, 1H), 4.25 (dd, *J* = 18.0 Hz, 10.0 Hz, 1H), 3.34 (dd, *J* = 18.0 Hz, 3.5 Hz, 1H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 198.9, 198.0, 138.7, 136.5, 136.5 133.2, 132.9, 129.2, 128.9, 128.6, 128.5, 128.2, 128.2, 127.4, 48.7, 43.9. IR (thin film): ν 3059, 2927, 1679, 1597, 1580, 1447, 1231 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{22}H_{18}O_2Na$, 337.1204, found 337.1204.

2,3,5-triphenyl-1H-pyrrole.[78]

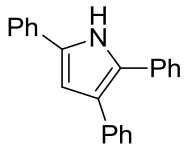


Table 3.1, Entry 1c: Following procedure C, 1,2,4-triphenylbutane-1,4-dione (44 mg, 0.14 mmol) and ammonium acetate (49 mg, 0.63 mmol) yielded a crude residue which was purified by flash chromatography (10% EtOAc in hexanes) to give the product (40 mg, 0.135 mmol, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (bs, 1H), 7.58 (d, *J* = 7.0 Hz, 2H), 7.46 – 7.24 (m, 13H), 6.74 (d, *J* = 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 133.1, 132.3, 132.2, 129.3, 129.0, 128.8, 128.4, 128.3, 127.5, 127.0,

126.6, 126.0, 123.9, 123.8, 108.6. IR (thin film): ν 3433, 3060, 2919, 1606, 1486, 1263 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{17}NNa$, 296.1439, found 296.1433.

2,3,5-triphenyl-1-(p-tolyl)-1H-pyrrole.

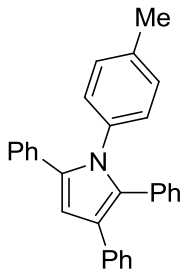


Table 3.1, Entry 1d: Following procedure C, 1,2,4-triphenylbutane-1,4-dione (44 mg, 0.14 mmol) and *p*-methylaniline (67 mg, 0.63 mmol) yielded a crude residue which was purified by flash chromatography (5% EtOAc in hexanes) to give the product (31 mg, 0.081 mmol, 58% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 – 7.13 (m, 13H), 7.06 (dd, *J* = 8.0 Hz, 1.5 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.70 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 136.2, 136.1, 134.8, 133.0, 132.8, 132.2, 131.5, 129.1, 128.7, 128.5, 128.2, 128.1, 127.9, 127.8, 126.8, 126.2, 125.4, 123.3, 109.8, 21.1. IR (thin film): ν 3045, 2923, 1680, 1601, 1514, 1484 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{29}H_{23}N$, 385.1830, found 385.1834.

(E)-1,3,5-triphenylpent-4-en-1-one.[80]

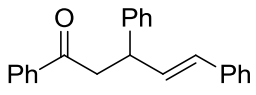


Table 3.1, Entry 2a: Following procedure A, $Ni(COD)_2$ (28 mg, 0.1 mmol), PCy_3 (56 mg, 0.2 mmol), trans-chalcone (208 mg, 1 mmol), phenylacetylene (153 mg, 1.5 mmol), and

Et_3B (434 μL, 3 mmol) gave a crude residue which was purified by flash chromatography (10% EtOAc in hexanes) to give the product (276 mg, 0.88 mmol, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (m, 2H), 7.57 (m, 1H), 7.47 (m, 2H), 7.35 – 7.18 (m, 10H), 6.42 (m, 2H), 4.32 (dt, *J* = 5.5 Hz, 7.0 Hz, 1H), 3.55 (dd, *J* = 16.5 Hz, 7.5 Hz, 1H), 3.50 (dd, *J* = 16.5 Hz, 6.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 143.3, 137.14, 137.1, 133.0, 132.5, 130.0, 128.6, 128.5, 128.4, 128.0, 127.7, 127.2, 126.6, 126.2, 44.5, 43.9. IR (thin film): ν 3059, 3024, 2923, 1685, 1597, 1493, 1448 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{23}H_{20}ONa$, 335.1412, found 335.1412.

4-oxo-2,4-diphenylbutanal.[81]

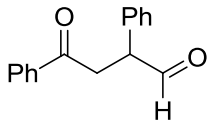


Table 3.1, Entry 2b: Following procedure B, (E)-1,3,5-triphenylpent-4-en-1-one (245 mg, 0.785 mmol) and PPh_3 (206 mg, 0.785 mmol) yielded a crude residue which was purified by flash chromatography (20% EtOAc in hexanes) to give the product (173 mg, 0.73 mmol, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.99 (m, 2H), 7.58 (m, 1H), 7.47 (m, 2H), 7.40 (m, 2H), 7.34 (m, 1H), 7.28 (m, 2H), 4.47 (dd, *J* = 8.5 Hz, 5.0 Hz, 1H), 3.97 (dd, *J* = 18.0 Hz, 8.5 Hz, 1H), 3.24 (dd, *J* = 18.0 Hz, 5.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 197.2, 136.4, 135.4, 133.3, 129.2, 129.1, 128.6, 128.1, 127.9, 53.6, 39.4. IR (thin film): ν 2923, 1723, 1683, 1599, 1493, 1449 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{14}O_2Na$, 261.0891, found 261.0883.

2,4-diphenyl-1H-pyrrole.[82]

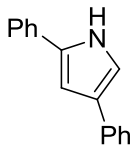


Table 3.1, Entry 2c: Following procedure C, 4-oxo-2,4-diphenylbutanal (80 mg, 0.34 mmol) and ammonium acetate (118 mg, 1.53 mmol) yielded a crude residue which was purified by flash chromatography (20% EtOAc in hexanes) to give the product (53 mg, 0.24 mmol, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 (bs, 1H), 7.60 (d, *J* = 7.0 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.40 (m, 4H), 7.27 (m, 2H), 7.15 (t, *J* = 2.0 Hz, 1H), 6.85 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 133.1, 132.5, 129.9, 128.9, 128.7, 126.5, 125.7, 125.2, 123.9, 115.6, 104.0. IR (thin film): ν 3441, 1585, 1454, 1156, 1134 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{16}H_{13}N$, 219.1048, found 219.1050.

1,2,4-triphenyl-1H-pyrrole.[83]

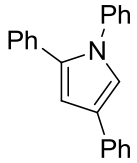


Table 3.1, Entry 2d: Following procedure C, 4-oxo-2,4-diphenylbutanal (85 mg, 0.36 mmol) and aniline (151 mg, 1.62 mmol) yielded a crude residue which was purified by flash chromatography (20% EtOAc in hexanes) to give the product (75 mg, 0.254 mmol, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (m, 2H), 7.41-7.20 (m, 14H), 6.77 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 135.2, 134.8, 132.8, 129.1, 128.8, 128.4, 128.2, 126.8, 126.6, 125.9, 125.7, 125.6, 125.2, 120.9, 108.8. IR (thin film): ν

3061, 1691, 1598, 1497, 1450, 1366 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{22}H_{17}N$, 295.1361, found 295.1360.

(Z)-3,4,5-triphenylpent-4-enal.

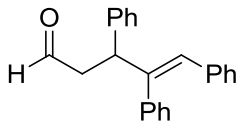


Table 3.1, Entry 3a: Following procedure D, $Ni(COD)_2$ (55 mg, 0.2 mmol), PCy_3 (112 mg, 0.4 mmol), cinnamaldehyde (264 mg, 2 mmol), phenylacetylene (534 mg, 3 mmol), and Et_3B (638 μL, 4 mmol) gave a crude residue which, after silyl group removal, was purified by flash chromatography (20% EtOAc in hexanes) to give the product (359 mg, 1.15 mmol, 57% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.31-7.21 (m, 8H), 7.06 (m, 3H), 6.86 (m, 4H), 6.52 (s, 1H), 4.39 (t, *J* = 7.5 Hz, 1H), 3.04 (ddd, *J* = 17.0 Hz, 8.0 Hz, 2.0 Hz, 1H), 2.93 (ddd, *J* = 17.0 Hz, 8.0 Hz, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 144.0, 140.8, 139.8, 136.5, 129.1, 129.0, 128.5, 128.4, 128.2, 127.9, 127.8, 127.2, 126.9, 126.7, 48.9, 47.2. IR (thin film): ν 3056, 3025, 2919, 1723, 1598, 1493, 1448 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{23}H_{20}O$, 312.1514, found 312.1512.

4-oxo-3,4-diphenylbutanal.[84]

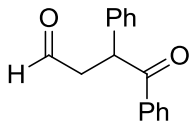


Table 3.1, Entry 3b: Following procedure B, (Z)-3,4,5-triphenylpent-4-enal (50 mg, 0.16 mmol) and PPh_3 (42 mg, 0.16 mmol) yielded a crude residue which was purified by flash chromatography (10% EtOAc in hexanes) to give the product (29 mg, 0.12 mmol, 75%

yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (s, 1H), 7.98 (m, 2H), 7.49 (m, 1H), 7.39 (m, 2H), 7.30 (m, 4H), 7.23 (m, 1H), 5.15 (dd, *J* = 9.5 Hz, 4.0 Hz, 1H), 3.63 (dd, *J* = 18.5 Hz, 9.5 Hz, 1H), 2.85 (dd, *J* = 18.5 Hz, 4.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.9, 198.1, 138.2, 136.0, 133.0, 129.3, 129.0, 128.5, 128.0, 127.4, 48.3, 47.6. IR (thin film): ν 3061, 2922, 2835, 2721, 1718, 1681, 1597, 1492, 1448 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{16}H_{14}O_2$, 238.0994, found 238.1007.

2,3-diphenyl-1H-pyrrole.[85]

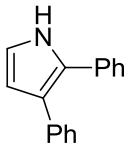


Table 3.1, Entry 3c: Following procedure C, 4-oxo-3,4-diphenylbutanal (72 mg, 0.3 mmol) and ammonium acetate (104 mg, 1.35 mmol) yielded a crude residue which was purified by flash chromatography (20% EtOAc in hexanes) to give the product (58 mg, 0.26 mmol, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (bs, 1H), 7.26-7.07 (m, 10H), 6.79 (m, 1H), 6.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 133.4, 128.7, 128.5, 128.3, 128.2, 127.5, 126.8, 125.7, 122.0, 118.1, 111.1. IR (thin film): ν 3415, 3060, 1601, 1507, 1443, 1289 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{16}H_{13}NNa$, 220.1126, found 220.1117.

1,2,3-triphenyl-1H-pyrrole.[86]

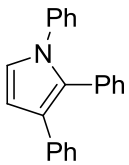


Table 3.1, Entry 3d: Following procedure C, 4-oxo-3,4-diphenylbutanal (72 mg, 0.3 mmol) and aniline (125 mg, 1.35 mmol) yielded a crude residue which was purified by flash chromatography (20% EtOAc in hexanes) to give the product (67 mg, 0.226 mmol, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.06 (m, 15H), 7.00 (d, *J* = 3.0 Hz, 1H), 6.56 (d, *J* = 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.3, 136.4, 132.3, 131.0, 129.9, 128.7, 128.3, 128.1, 128.0, 126.9, 126.4, 125.9, 125.4, 124.2, 123.0, 110.0. IR (thin film): ν 3057, 2926, 1596, 1496, 1362 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{22}H_{17}N$, 295.1361, found 295.1351.

(E)-4-methyl-1,3,5-triphenylpent-4-en-1-one.

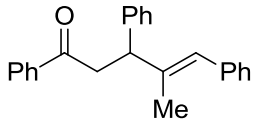


Table 3.1, Entry 4a: Following procedure A, $Ni(COD)_2$ (28 mg, 0.1 mmol), PCy_3 (56 mg, 0.2 mmol), trans-chalcone (208 mg, 1 mmol), phenylpropyne (176 mg, 1.5 mmol), and Et_3B (434 μL, 3 mmol) gave a crude residue which was purified by flash chromatography (5% EtOAc in hexanes) to give the product (300 mg, 0.92 mmol, 92% yield). Spectral data matched that previously reported.[11]

1,3-diphenylpentane-1,4-dione.

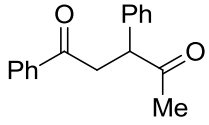


Table 3.1, Entry 4b: Following procedure B, (E)-4-methyl-1,3,5-triphenylpent-4-en-1-one (228 mg, 0.88 mmol) and PPh_3 (231 mg, 0.88 mmol) yielded a crude residue which was

purified by flash chromatography (10% EtOAc in hexanes) to give the product (143 mg, 0.57 mmol, 64% yield). Spectral data matched that previously reported.[78]

2-methyl-3,5-diphenyl-1H-pyrrole.

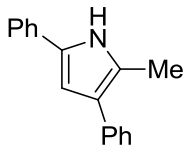


Table 3.1, Entry 4c: Following procedure C, 1,3-diphenylpentane-1,4-dione (74 mg, 0.29 mmol) and ammonium acetate (102 mg, 1.23 mmol) yielded the product without further purification (68 mg, 0.288 mmol, 99% yield). Spectral data matched that previously reported.[87]

5.3.3 Table 2.2 Products

(E)-2-(3-ethylidenechroman-4-yl)-1-phenylethanone.

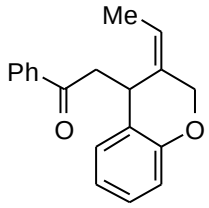


Table 3.2, Entry 1a: Following procedure E, (E)-1-phenyl-3-(2-(prop-2-yn-1-yloxy)phenyl)prop-2-en-1-one (262 mg, 1.0 mmol), $Ni(COD)_2$ (28 mg, 0.1 mmol), and dimethyl zinc (750 μL, 2M in toluene, 1.5 mmol) yielded a crude residue which was purified by flash chromatography (10% EtOAc in hexanes) to give the product (142 mg, 0.51 mmol, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (m, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.21 (m, 1H), 7.13 (m, 1H), 6.89 (m, 1H), 6.84 (d, *J* = 8.5

Hz, 1H), 5.64 (q, *J* = 7.0 Hz, 1H), 4.74 (dt, *J* = 11.5 Hz, 1.5 Hz, 1H), 4.48 (t, *J* = 7.0 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 3.40 (m, 2H), 1.67 (dd, *J* = 7.0 Hz, 1.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 154.4, 137.0, 133.2, 132.1, 129.4, 128.7, 128.2, 127.9, 125.8, 124.5, 120.8, 117.0, 69.231, 46.9, 33.2, 13.5. IR (thin film): ν 2971, 1683, 1596, 1580, 1486, 1448, 1234 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{19}H_{18}O_2Na$, 301.1204, found 301.1206.

4-(2-oxo-2-phenylethyl)chroman-3-one.

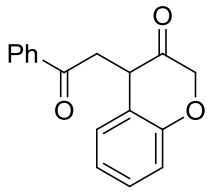


Table 3.2, Entry 1b: Following procedure B, (E)-2-(3-ethylidenechroman-4-yl)-1-phenylethanone (169 mg, 0.605 mmol) and PPh_3 (159 mg, 0.605 mmol) yielded a crude residue which was purified by flash chromatography (20% EtOAc in hexanes) to give the product (95 mg, 0.357 mmol, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.61 (m, 1H), 7.50 (m, 2H), 7.25 (m, 1H), 7.10 (m, 1H), 7.04 (m, 2H), 4.66 (d, *J* = 17.5 Hz, 1H), 4.53 (d, *J* = 17.5 Hz, 1H), 4.23 (t, *J* = 5.0 Hz, 1H), 3.92 (dd, *J* = 18.0 Hz, 4.5 Hz, 1H), 3.74 (dd, *J* = 18.0 Hz, 6.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.2, 196.4, 136.2, 133.5, 128.7, 128.3, 128.2, 126.4, 124.7, 124.6, 123.2, 117.9, 72.5, 44.4, 37.0. IR (thin film): ν 3064, 2916, 1732, 1685, 1597, 1582, 1488, 1458, 1229 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{17}H_{14}O_3Na$, 289.0841, found 289.0835.

2-phenyl-3,4-dihydrochromeno[3,4-b]pyrrole.

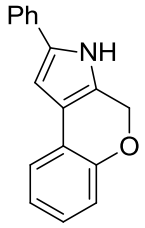


Table 3.2, Entry 1c: Following procedure F, 4-(2-oxo-2-phenylethyl)chroman-3-one (84 mg, 0.314 mmol), ammonium acetate (73 mg, 0.942 mmol), *p*-toluenesulfonic acid (119 mg, 0.628 mmol) yielded a crude residue which was purified by flash chromatography (20% EtOAc in hexanes) to give the product (37 mg, 0.151 mmol, 48% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (bs, 1H), 7.49 (m, 2H), 7.38 (m, 3H), 7.23 (m, 1H), 7.05 (m, 1H), 6.96 (m, 1H), 6.91 (m, 1H), 6.71 (d, *J* = 2 Hz, 1H), 5.37 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 133.1, 132.3, 129.0, 126.6, 126.3, 123.8, 123.7, 122.1, 121.9, 121.5, 116.2, 100.3, 63.8. IR (thin film): ν 3324, 3063, 2925, 1622, 1456, 1226 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{17}H_{13}NO$, 247.0997, found 245.0841.

(E)-1-phenyl-2-(2-(1-phenylethylidene)cyclopentyl)ethanone.

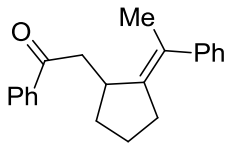


Table 3.2, Entry 2a: Following procedure E, (E)-1,8-diphenyloct-2-en-7-yn-1-one (274 mg, 1.0 mmol), $Ni(COD)_2$ (28 mg, 0.1 mmol), and dimethyl zinc (750 μL, 2M in toluene, 1.5 mmol) yielded a crude residue which was purified by flash chromatography (10% EtOAc in hexanes) to give the product (133 mg, 0.46 mmol, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.60 (m, 1H), 7.51 (m, 2H), 7.33 (m, 2H), 7.22 (m, 3H), 3.46 (m, 1H), 3.21 (dd, *J* = 16.5 Hz, 3.5 Hz, 1H), 3.07 (dd, *J* = 16.5 Hz, 10.5 Hz, 1H),

2.32 (m, 1H), 2.22 (m, 1H), 2.04 (s, 3H), 1.98 (m, 1H), 1.71 (m, 1H), 1.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 144.8, 142.8, 137.4, 133.0, 128.6, 128.1, 127.9, 127.8, 126.0, 43.0, 38.2, 32.5, 31.7, 24.6, 24.5, 21.0. IR (thin film): ν 2952, 1685, 1597, 1448, 1352 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{21}H_{20}O$, 290.1671, found 290.1673.

2-(2-oxo-2-phenylethyl)cyclopentanone.[88]

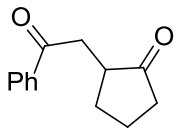


Table 3.2, Entry 2b: Following procedure B, (E)-1-phenyl-2-(2-(1-phenylethylidene)cyclopentyl)ethanone (132 mg, 0.45 mmol) and PPh_3 (119 mg, 0.45 mmol) yielded a crude residue which was purified by flash chromatography (10% EtOAc in hexanes) to give the product (89 mg, 0.44 mmol, 98% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.98 (m, 2H), 7.58 (m, 1H), 7.48 (m, 2H), 3.55 (dd, *J* = 18.0 Hz, 3.5 Hz, 1H), 3.06 (dd, *J* = 18.0 Hz, 8.0 Hz, 1H), 2.66 (dtdd, *J* = 11.5 Hz, 8.2 Hz, 3.3 Hz, 1.5 Hz, 1H), 2.40 (m, 2H), 2.30 (ddd, *J* = 19.0 Hz, 11.0 Hz, 8.6 Hz, 1H), 2.10 (dqt, *J* = 10.0 Hz, 6.5 Hz, 2.0 Hz, 1H), 1.88 (tdq, *J* = 11.5 Hz, 8.4 Hz, 7.5 Hz, 1H), 1.63 (qd, *J* = 12.0 Hz, 6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.4, 198.0, 136.6, 133.2, 128.6, 128.0, 45.1, 38.7, 37.6, 29.7, 20.8. IR (thin film): ν 2963, 2878, 1737, 1685, 1597, 1580, 1449, 1263 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{13}H_{14}O_2$, 202.0994, found 202.1003.

2-phenyl-1,4,5,6-tetrahydrocyclopenta[b]pyrrole.[89]

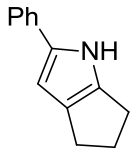


Table 3.2, Entry 2c: Following procedure C, 2-(2-oxo-2-phenylethyl)cyclopentanone (82 mg, 0.41 mmol) and NH_4OAc (142 mg, 1.845 mmol) yielded a crude residue which showed only product by ^1H NMR (75 mg, 0.408 mmol, 99% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 (bs, 1H), 7.43 (m, 2H), 7.34 (m, 2H), 7.17 (m, 1H), 6.32 (d, *J* = 2.0 Hz, 1H), 2.77 (t, *J* = 7.0 Hz, 2H), 2.674 (t, *J* = 7.0 Hz, 2H), 2.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 133.7, 128.8, 128.6, 125.5, 123.3, 101.7, 29.0, 25.5. IR (thin film): ν 3439, 2953, 2860, 1684, 1604, 1512, 1466, 1444 cm^{-1}. HRMS (EI) (*m/z*): $[M]^+$ calcd for $C_{13}H_{13}N$, 183.1048, found 183.1043.

(E)-6-ethylidene-7-(2-oxo-2-phenylethyl)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one.

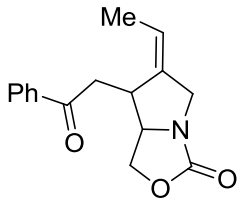


Table 3.2, Entry 3a: Following procedure E, (E)-4-(3-oxo-3-phenylprop-1-en-1-yl)-3-(prop-2-yn-1-yl)oxazolidin-2-one[90] (102 mg, 0.4 mmol), $Ni(COD)_2$ (11 mg, 0.04 mmol), and dimethyl zinc (300 μL, 2M in toluene, 0.6 mmol) yielded a crude residue which was purified by flash chromatography (50% EtOAc in hexanes) to give the product (78 mg, 0.29 mmol, 72% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 5.55 (m, 1H), 4.71 (dd, *J* = 9.4 Hz, 8.2 Hz, 1H), 4.637 (dd, *J* = 9.4 Hz, 4.2 Hz, 1H), 4.22 (d, *J* = 14.4 Hz, 1H), 3.76 (dt, *J* = 8.0 Hz, 4.4 Hz, 1H), 3.70 (ds, *J* = 14.6 Hz, 2.2 Hz, 1H), 3.51 (m, 1H), 3.10 (m, 2H), 1.63 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 161.3, 139.0, 136.1, 133.7, 128.8, 127.9, 118.8, 70.3, 66.1, 51.4, 42.4, 42.3, 14.2.

IR (thin film): ν 2917, 1754, 1680, 1596, 1580, 1449, 1395, 1201 cm^{-1}. HRMS (ESI) (*m/z*): $[M+H]^+$ calcd for $C_{16}H_{17}NO_3$, 272.1287, found 272.1297.

7-(2-oxo-2-phenylethyl)dihydropyrrolo[1,2-c]oxazole-3,6(1H,5H)-dione.

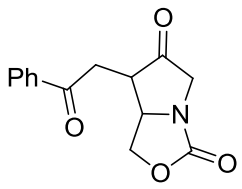


Table 3.2, Entry 3b: Following procedure B, (E)-6-ethylidene-7-(2-oxo-2-phenylethyl)tetrahydropyrrolo[1,2-c]oxazol-3(1H)-one (55 mg, 0.203 mmol) and PPh_3 (53 mg, 0.203 mmol) yielded a crude residue which was purified by flash chromatography (75% EtOAc in hexanes) to give the product (34 mg, 0.13 mmol, 64% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 7.96 (m, 2H), 7.63 (m, 1H), 7.51 (m, 2H), 4.75 (dd, *J* = 9.5 Hz, 7.5 Hz, 1H), 4.72 (dd, *J* = 9.5 Hz, 4.0 Hz, 1H), 4.21 (m, 2H), 3.72 (dd, *J* = 18.5 Hz, 4.0 Hz, 2H), 3.27 (dd, *J* = 18.5 Hz, 8.0 Hz, 1H), 2.78 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.4, 196.7, 160.2, 135.5, 134.0, 128.9, 128.1, 68.6, 61.3, 52.6, 48.8, 36.8. IR (thin film): ν 2919, 1756, 1682, 1597, 1401, 1221 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{13}NO_4Na$, 282.0742, found 282.0739.

2-phenyl-3b,4-dihydro-1H-pyrrolo[3',2':3,4]pyrrolo[1,2-c]oxazol-6(8H)-one.

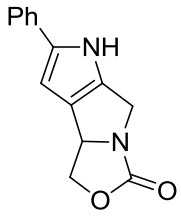
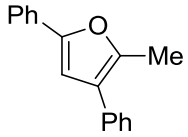


Table 3.2, Entry 3c: Following procedure C, 7-(2-oxo-2-phenylethyl)dihydropyrrolo[1,2-c]oxazole-3,6(1H,5H)-dione (43 mg, 0.167 mmol) and NH_4OAc (58 mg, 0.75 mmol) yielded a crude residue which showed only product by ^1H NMR (40 mg, 0.166 mmol, 99% yield). ^1H NMR (500 MHz, $CDCl_3$): δ 8.36 (bs, 1H), 7.44 (m, 2H), 7.39 (m, 2H), 7.25 (m, 1H), 6.33 (d, *J* = 2.0 Hz, 1H), 5.16 (m, 1H), 4.77 (m, 2H), 4.43 (dd, *J* = 8.5 Hz, 6.0 Hz, 1H), 4.31 (dd, *J* = 13.5 Hz, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 133.8, 132.5, 129.0, 126.8, 123.8, 99.1, 70.3, 59.4, 48.2. IR (thin film): ν 3300, 2918, 1733, 1604, 1512, 1387 cm^{-1}. HRMS (ESI) (*m/z*): $[M+Na]^+$ calcd for $C_{14}H_{12}N_2O_2Na$, 263.0796, found 263.0788.

5.3.4 Scheme 3.9 Products

2-methyl-3,5-diphenylfuran.



Following a procedure from Taddei and coworkers[91] 1,3-diphenylpentane-1,4-dione (78 mg, 0.31 mmol) was dissolved in 1.33 mL of 200-proof ethanol and transferred to a microwave vial charged with a stir bar. 0.33 mL of 1M HCl was added, and after vial was sealed, the mixture was heated in a microwave at 150 °C for 15 minutes. The crude reaction mixture was then diluted with EtOAc, and washed with aqueous saturated sodium bicarbonate and then brine. The organic layer was then dried over Na_2SO_4 and the solvent was then removed *in vacuo*, yielding the product without further purification (61 mg, 0.26 mmol, 85% yield). Spectral data matched that previously reported.[78]

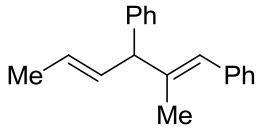
5.4 Chapter 4 Experimental

5.4.1 Table 4.1

General Procedure for Table 4.1

$Ni(COD)_2$ (0.1 equiv), ITol•HCl (0.1 equiv), and KO*t*-Bu (0.1 equiv) were dissolved in 1.5 mL THF and allowed to stir at room temperature for ten minutes. The substrates were then added as a solution in 3 mL THF. 0.5 mL of extra dry MeOH was added, followed by subsequent addition of silane (2-4 equiv). The reaction was heated to 50 ºC and allowed to stir overnight. The crude reaction mixture was passed through a plug of silica using 1:1 EtOAc:hexane and then concentrated *in vacuo*. The resulting mixture was purified via flash chromatography.

((1*E*,4*E*)-2-methylhexa-1,4-diene-1,3-diyl)dibenzene

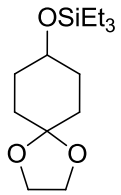


Following the general procedure, $Ni(COD)_2$ (16.5 mg, 0.06 mmol), ITol•HCl (17 mg, 0.06 mmol), KO*t*-Bu (6.7 mg, 0.06mmol), benzylidene acetone (88 mg, 0.6 mmol), phenylpropyne (105 mg, 0.9 mmol), and TESH (192 μL, 1.2 mmol) gave a crude residue which was purified by flash chromatography (hexanes) to give the product (70 mg, 41% yield). ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.25 (m, 8H), 7.19 (m, 2H), 6.42 (s, 1H), 5.81 (ddq, *J* = 15.1 Hz, 7.7 Hz, 1.6 Hz, 1H), 5.47 (dqd, *J* = 15.1 Hz, 6.53 Hz, 1.0 Hz, 1H), 4.07 (d, *J* = 7.7 Hz, 1H), 1.75 (d, *J* = 1.2 Hz, 3H), 1.75 (d, *J* = 7.7 Hz, 3H). ^{13}C NMR

(175 MHz, $CDCl_3$): δ 142.9, 140.8, 138.4, 132.2, 128.9, 128.3, 128.3, 128.0, 126.9, 126.5, 126.2, 126.0, 57.8, 18.1, 17.3.

5.4.2 Scheme 4.11 Products

(1,4-dioxaspiro[4.5]decan-8-yloxy)triethylsilane

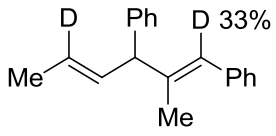


Following the general procedure from Table 4.1 with the omission of alkyne, $Ni(COD)_2$ (16.5 mg, 0.06 mmol), ITol•HCl (17 mg, 0.06 mmol), KO*t*-Bu (6.7 mg, 0.06mmol), benzylidene acetone (88 mg, 0.6 mmol), and TESH (384 μL, 2.4 mmol) gave a crude residue which was purified by flash chromatography (hexanes) to give the product (99 mg, 61% yield). ^{1}H NMR (700 MHz, $CDCl_3$): 3.95 (m, 4H), 3.80 (m, 1H), 1.85 (m, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.55 (m, 2H), 0.95 (t, 9H), 0.60 (q, 6H).

5.4.3 Table 4.2 Products

Deuterium incorporation was measured by comparing the ^{1}H NMR integration observed to the expected proton integration in the non-deuterated case.

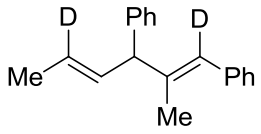
Table 4.2, Entry 1



Following the general procedure from Table 4.1, $Ni(COD)_2$ (16.5 mg, 0.06 mmol), ITol•HCl (17 mg, 0.06 mmol), KO*t*-Bu (6.7 mg, 0.06mmol), benzylidene acetone (88

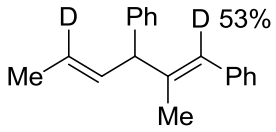
mg, 0.6 mmol), phenylpropyne (105 mg, 0.9 mmol), and TESD (192 μL, 1.2 mmol) gave a crude residue which was purified by flash chromatography (hexanes) to give the product (60 mg, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.20 (m, 10H), 6.45 (s, 0.67H), 5.83 (d, *J* = 6.5 Hz, 1H), 4.10 (d, *J* = 80 Hz, 1H), 1.77 (m, 6H).

Table 4.2, Entry 2



Following the general procedure from Table 4.1, $Ni(COD)_2$ (16.5 mg, 0.06 mmol), ITol•HCl (17 mg, 0.06 mmol), KO*t*-Bu (6.7 mg, 0.06mmol), benzylidene acetone (88 mg, 0.6 mmol), phenylpropyne (105 mg, 0.9 mmol), 0.5 mL CD_3OD and TESD (192 μL, 1.2 mmol) gave a crude residue which was purified by flash chromatography (hexanes) to give the product (71 mg, 47% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.20 (m, 10H), 5.83 (d, *J* = 7.5 Hz, 1H), 4.10 (d, *J* = 7.5 Hz), 1.80 (s, 4H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 142.9, 140.7, 138.3, 132.1, 128.9, 128.3, 128.3, 128.1, 128.0, 126.2, 126.0, 57.7, 17.3.

Table 4.2, Entry 6

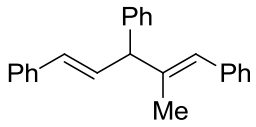


Following the general procedure from Table 4.1, $Ni(COD)_2$ (16.5 mg, 0.06 mmol), ITol•HCl (17 mg, 0.06 mmol), KO*t*-Bu (6.7 mg, 0.06mmol), benzylidene acetone (88 mg, 0.6 mmol), phenylpropyne (105 mg, 0.9 mmol), and TESD (192 μL, 1.2 mmol) under a hydrogen atmosphere (balloon) gave a crude residue which was purified by flash

chromatography (hexanes) to give the product (55 mg, 37% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.20 (m, 10H), 6.45 (s, 0.47H), 5.83 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 4.1 (d, *J* = 8.0 Hz, 1H), 1.77 (m, 6H).

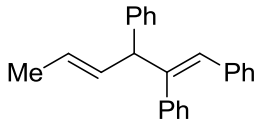
5.4.4 Table 4.3 Products

((1*E*,4*E*)-2-methylpenta-1,4-diene-1,3,5-triyl)tribenzene Table 4.3, Entry 2



Following the general procedure from Table 4.1, $Ni(COD)_2$ (16.5 mg, 0.06 mmol), ITol•HCl (17 mg, 0.06 mmol), KO*t*-Bu (6.7 mg, 0.06mmol), trans-chalcone (125 mg, 0.6 mmol), phenylpropyne (105 mg, 0.9 mmol), and TESH (384 μL, 2.4 mmol) gave a crude residue which was purified by flash chromatography (5% EtOAc/hexanes) to give the product (149 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 15H), 6.58 (dd, *J* = 16.0 Hz, 7.6 Hz, 1H), 6.42 (s, 1H), 6.39 (d, *J* = 15.6 Hz, 1H), 4.30 (d, *J* = 7.6 Hz, 1H), 1.81 (s, 3H).

(1*Z*,4*E*)-hexa-1,4-diene-1,2,3-triyltribenzene Table 4.3, Entry 3



Following the general procedure from Table 4.1, $Ni(COD)_2$ (16.5 mg, 0.06 mmol), ITol•HCl (17 mg, 0.06 mmol), KO*t*-Bu (6.7 mg, 0.06mmol), benzylidene acetone (88 mg, 0.6 mmol), diphenylacetylene (160 mg, 0.9 mmol), and TESH (384 μL, 2.4 mmol) gave a crude residue which was purified by flash chromatography (hexanes) to give the

product (61 mg, 33% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.5-6.6 (m, 15H), 6.54 (s, 1H), 5.89 (m, 1H), 5.41 (m, 1H), 4.42 (d, *J* = 7.5 Hz, 1H), 1.76 (d, *J* = 6.5 Hz, 3H).

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