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XV
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ABSTRACT

Asymmetric carbon-carbon bond forming processes and catalytic one-pot reactions remain challenges in organic synthesis. Since the discovery of the Diels-Alder reaction over eighty years ago, it has been one of the most important tools for synthetic organic chemists to synthesize as many as three carbocyclic rings in intermolecular and intramolecular reactions. Its versatility can provide up to four contiguous asymmetric centers with good yields. The majority of the Diels-Alder additions are endo selective, and reports of exo selective Diels-Alder reactions are few in the literature. Our goal is development of methodologies for catalytic, regioselective, exo selective, enantioselective Diels-Alder reactions and subsequent Hiyama-Denmark and Negishi cross couplings to make highly substituted cyclohexenoids with controlled relative and absolute stereochemistries. Diterpenoids containing the clerodane carbon skeleton are prevalent as secondary metabolites. Synthetic approaches to the trans-clerodanes are known, but cis-clerodanes are rare. This proposed methodology will also allow the scientific community to construct biologically important core structures like cis clerodanes and their derivatives.

Our research is based on syntheses of stable silicon dienes that would participate in catalytic, regioselective, exo selective, enantioselective Diels-Alder reactions. Earlier we have reported syntheses of 2-silicon substituted 1,3-dienes that participated in Diels-Alder reactions and obtained cycloadducts that also took part in sequential and tandem Hiyama cross couplings. Part of this dissertation is based on syntheses of novel 2-silicon substituted 1,3-butadienes made by one of the three protocols i) Grignard chemistry ii)
enynhydrosilylation and iii) ene-ynecross metathesis. We investigated efficacy and limitations for each of the three routes.

One of the key steps for the cross coupling chemistry is transmetallation. Previously, we have prepared 2-silyl-1, 3-dienes containing alkoxy groups on the silicon. Silanols and in situ silanols are excellent candidates for transmetallation. Our proposed methodology is based on sequential transmetallation, Diels-Alder, oxidative addition and reductive elimination. We have performed an extensive study on syntheses of silicon dienes containing a variety of nontransferable groups on silicon known to promote transmetallation. We have successfully carried out syntheses of all plausible masked silanol dienes both by the Grignard chemistry and ene-ynecross metathesis. All these synthons participated in regioselective Diels-Alder reactions. The cycloadducts were cross coupled via Pd catalyzed Hiyama-Denmark couplings. We designed tandem metathesis, Diels-Alder, and Hiyama couplings of these synthons and observed very high regio and diastereoselectivity. Alkene: Alkyne ratio in the case of ene-ynecross metathesis was investigated and the experimental outcome provided optimized synthon concentrations and the rate limiting reagent. Electron rich alkenes reacted much faster than electron poor alkenes in the case of EYCM. Ethylene, a common promoter in the metathesis reaction, showed significant inhibition in EYCM. Different chiral Pd and Ni pincer complexes were prepared and their catalytic activity was studied.
CHAPTER 1: INTRODUCTION

The fundamental challenge of Organic Chemistry is carbon-carbon bond forming processes and catalytic stereoselective transformations. The Diels-Alder reaction was reported by Otto Paul Hermann Diels and his doctoral student Kurt Alder in 1928, for which they received the 1950 Nobel Prize in Chemistry "for their discovery and development of the diene synthesis". Based on the choice of reagents Diels-Alder reactions can yield up to 4 chiral centers in the product. That’s why the Diels-Alder reaction is still so relevant among organic chemists. In 2005 the Nobel Prize in chemistry was jointly awarded to Yves Chauvin, Robert Grubbs and Richard Schrock for their contributions in metathesis reactions as they opened a new horizon of C-C bond formations. The 2010 Nobel Prize in Chemistry was awarded to Richard Heck, Akira Suzuki, and Ei-ichi Negishi for their discovery of metal mediated C-C bond formations. This present dissertation is based upon these earlier mentioned three milestones to solve some fundamental challenges of organic chemistry.

1.1 Diels-Alder Reaction

Since the discovery of the Diels-Alder reaction over eighty years ago\(^1\), it has been one of the most important tools for synthetic organic chemists to synthesize as many as three carbocyclic rings in intermolecular and intramolecular reactions. Its versatility can provide up to four contiguous asymmetric centers with good yields (Scheme 1.1).
1.2 Reaction Mechanism of Diels-Alder Reactions

In Diels-Alder reactions 3 π bonds are broken, and 2 σ and 1 π bonds are made. This thermodynamic favorability is known to be the driving force for the reaction. The mechanism of Diels-Alder reactions has been long debated by researchers. In a cycloaddition reaction two extremes are possible. One is concerted (synchronous or asynchronous) and the other is stepwise. The latter can be subdivided in two categories, diradical and zwitterionic (Figure 1.1).

Although the first report of the mechanism was known to be concerted, there were many opinions available. It’s safe to say the mechanism depends on substrates and the majority of the Diels-Alder reactions are known to be concerted. In 1959 Woodward et al reported two step reaction mechanisms where they hypothesized the rate determining step to be the single bond formation from the tertiary carbon of the diene to one of the sp² carbons of the dienophile. Woodward-Hoffmann’s orbital symmetry and Fukui’s frontier molecular orbital theory have been widely used by the scientific community to interpret the mechanistic pathway(s) for the Diels-Alder reaction. In summary, based on these two theories it can be said that the majority of the Diels-Alder reactions occur in a concerted fashion.
1.3 Rate of Diels-Alder reactions

The Diels-Alder reaction can be intermolecular or intramolecular, and it is performed under different reaction conditions. In many cases the reaction can be done at slightly elevated temperature and in some cases it requires drastic reaction conditions. Reactivity of the Diels-Alder reaction is governed by both sterics and electronics of the diene and the dienophile.
1.3.1 Steric Effects in Diels-Alder Reaction Rates

It has been observed that cyclic dienes react much faster than acyclic dienes. Under normal conditions aliphatic dienes largely exist in the $s$-$trans$ conformation and the Diels-Alder reaction requires dienes to be in the $s$-$cis$ conformation.

![Scheme 1.2](image)

**Scheme 1.2 s-Cis and s-Trans Conformations of 1, 3-Dienes**

Cyclic dienes are locked in $s$-$cis$ conformations, which is reflected in the rate of DA reactions (Scheme 1.2). Any substituent on the diene that would favor the $s$-$trans$ conformation would slow down the reaction. Substituents on the dienophile also play a pivotal role; higher number of alkyl substituents present on the dienophile would slow down the reaction.

1.3.2 Electronic Effects in Diels-Alder Reaction Rates

Electronics of diene and dienophile govern the success of Diels – Alder reactions. Electron rich dienes and electron poor dienophiles are the best possible combination. Dienes containing $\pi$ electron donating groups and dienophile containing electron withdrawing groups enhance reactivity in Diels-Alder reactions.
1.4 Molecular Orbital Theory and Diels-Alder Reactions

Molecular orbital theory states the overlap between the Highest Occupied Molecular Orbital (HOMO) of the diene and the Lowest Unoccupied Molecular Orbital (LUMO) of the dienophile will define the Diels-Alder product; the lower the HOMO-LUMO energy gap, the faster the reaction. Electron donating groups on the diene and electron withdrawing groups on the dienophile help to match the energy levels. In the case of electron poor diene and electron rich dienophile (inverse electron demand DA$^6$) it is the interaction between the diene LUMO and dienophile HOMO (Figure 1.2). Frontier Molecular Orbital (FMO) theory also successfully explains the effect of substituents on rate, any substituent that would hinder alignment of FMOs would slow down the reaction.

1.5 Stereoselectivity in Diels-Alder Reactions

The Diels-Alder reaction is a very important reaction for synthetic organic chemists, and is very popular due to the following stereoselective outcomes: regioselectivity, diastereoselectivity, and enantioselectivity.

1.5.1 Regioselectivity in Diels-Alder Reactions

In the case of unsymmetrical dienes and dienophiles, the Diels-Alder reaction shows preferential formation of one regioisomer over the other. For 1- substituted dienes the ortho adduct (Figure 1.3) is the major product (4 to 10 times) and for 2- substituted dienes the para adduct is the major product (4 to 10 times). Researchers often use transition metal Lewis acid catalysts to further enhance the regioselectivity.$^7$
Figure 1.2 Orbital Diagram of Diels-Alder Reaction
Figure 1.3 Rationale for Regioselectivity in Diels-Alder Reactions
1.5.2 Diastereoselectivity in Diels-Alder Reactions

The majority of Diels-Alder adducts show endoselectivity over exo cycloadducts formation, which is largely attributed to the secondary orbital overlap\textsuperscript{8,9} (Figure 1.4) of the incoming dienophile with the cisoid diene in the transition state. Scientists have adopted different strategies to reverse the endo selectivity in Diels-Alder reactions. If the secondary orbital interaction in the kinetically controlled endo transition state can be disturbed, then exo selectivity should be favored. Yamamoto et al showed the use of bulky recognition specific Lewis acids that would complex with the carbonyl group of a dienophile and destabilize the endo product.\textsuperscript{10} If the approaching dienophile encounters a stronger 1,3 dipolar interaction with a sterically demanding diene, that can also lead to exo selectivity.\textsuperscript{11} Transition metals are electron rich and d electrons often participate in electron donation. Our group reported the synthesis of cobalt substituted 1,3-dienes that gave exo products (Figure 1.5).\textsuperscript{12-15} Probably steric interactions of metal-ligand and dienophile disfavored the endo transition state.

\textbf{Figure 1.4 MO Picture of Endo and Exo Transition State} (Secondary orbital overlap is shown in blue)
\section*{1.5.3 Enantioselectivity in Diels-Alder Reactions}

There are several reports of chiral Lewis acid catalysts used in enantioselective (\textgt 25:1) Diels-Alder reactions\textsuperscript{16} which often also enhanced the diastereoselectivity by coordinating with the electron donating group on the dienophile. Dr. Corey provided a detailed description in his 2002 review article\textsuperscript{16} about the different types of enantioselective Diels-Alder additions. Chiral diazaaluminolidines\textsuperscript{17} and chiral oxazaborolidines\textsuperscript{18} were very popular in the nineties. Another approach was using chiral catalysts that would interact with the dienophile and make the unreactive diene react in enantioselective fashion.\textsuperscript{19} Mikami catalyst (Ti/ Binol) was used by many researchers.\textsuperscript{20,21}

\section*{1.6 Exo-Selective Diels-Alder Reactions Carried Out by the Welker Group}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ Welker_diagram.png}
\caption{Destabilized \textit{Endo} Transition State and Stabilized \textit{Exo} Transition State}
\end{figure}
In 1993 the Welker group first reported how pyr(glyoxime)$_2$-cobalt anions reacted with allenic electrophiles to produce cobalt substituted 1,3 dienes via a $S_N2'$ pathway (Scheme 1.3).\textsuperscript{22} The resultant $\sigma$ bonded 2-cobalt-1, 3-butadiene participated in DA reactions under very mild conditions. This rate enhancement was due to the combined effect of stercics and electronics. The bulky pyr(glyoxime)$_2$ group favored the $s$-cis conformation of the diene, and the metal d electrons of Co favored the cycloaddition. All these synthons were air stable, solid, and were prepared in multi gram scales. In the next year the same group reported exo selective Diels-Alder reactions of cobalt substituted 1, 3-dienes.\textsuperscript{23} With increase in glyoxime ligand set sizes the diastereoselectivity increased. They also developed demetallation methods to cleave the C-Co bond.
Later work from the same group demonstrated several examples of this methodology with a large number of variables. Now the challenge was whether it was possible to establish a methodology for \textit{exo} selective and enantioselective Diels-Alder reactions. They adopted two fundamentally different strategies.\textsuperscript{24} First, they used dienes that were known to participate in \textit{exo} selective DA reactions and screened a variety of chiral Lewis acid catalysts to obtain enantioselectivity.\textsuperscript{25} However reactions that showed reasonable yields failed to demonstrate enantioselectivity. One catalyst showed 62\% ee but the yield was 27\%. They prepared optically pure salen ligand substituted Co dienyl complexes (\textbf{1.16}) and were successful in obtaining crystal structures. In 2000 Chapman \textit{et al} reported enantioselective Diels-Alder reactions of optically active Co (III) salen dienyl complexes.\textsuperscript{26,27} A subsequent demetallation process also worked very well. Syntheses of chiral dienyl complexes, followed by DA reactions and demetallation were achieved in one pot reactions. After the demetallation process, the original Co-salen complex was quantitatively recovered with optical purity (\textbf{Scheme 1.5}). Clearly at this point methodology to prepare \textit{exo} selective, enantioselective DA cycloadducts has been established.
Scheme 1.5 *Exo* Selective Enantioselective Diels-Alder Reactions Reported by the Welker Group
The Welker group also prepared 2-cobaloxime-3-substituted-1, 3-dienyl complexes (1.20) but these complexes were incapable of attaining $s$-$cis$ conformations. Then they attempted and were successful in the preparation of 1-cobaloxime-3-substituted-1, 3-dienyl complexes (Scheme 1.6).

![Scheme 1.6 Preparation of 1-Cobaloxime-3-Substituted-1, 3- Dienes](image)

Water solubility is a major issue in the case of organic compounds, and to tackle this problem Tucker et al prepared water soluble Co substituted 1,3-dienes and successfully carried out DA reactions with different dienophiles in organic solvents as well as in water with good yields. Apart from metal mediated DA reactions, the Welker group at Wake Forest University also explored other nontraditional DA reactions. Once the metal substituted diene and its [4+2] additions were explored the next challenge was whether it is possible to prepare main group element substituted dienes that would transmetallate to transition metal catalysts and allow catalytic, $exo$ selective, enantioselective Diels-Alder reactions (Scheme 1.7).
Scheme 1.7 Proposed Methodology for Catalytic, Exo Selective, Enantioselective Diels-Alder Reactions

1.7.1 Main Group Element Substituted Boron Dienes

Till this date there are not many reports of main group element substituted dienes. Among them 2-substituted 1, 3 dienes are less prevalent than 1-substituted-1, 3 dienes. There are two\textsuperscript{32,33} reports of aluminium substituted cyclopentadienes but their synthetic reaction chemistry was not explored. In 2005 the Welker group first reported syntheses of 1, 3-dienyl-2-trifluoroborates (Scheme 1.8). These dienes were synthesized by preparing the Grignard reagent of chloroprene followed by its quenching with trimethylborate and aqueous KHF\textsubscript{2}. These dienes participated in regioselective DA reactions and cycloadducts were cross coupled with aryl halides and Pd catalysts.\textsuperscript{34,35} Later work from the same group established Rh (I) as a catalyst for Diels-Alder reactions and more importantly the Rh catalyst played a major role in the protodemetalation process (Figure 1.6).\textsuperscript{36} However 2-BF\textsubscript{3} substituted-1, 3-dienes had a limitation of solubility in organic solvents. To overcome
the solubility problem in 2012, the Welker group reported a new class of organic soluble boron dienes and their one pot Diels-Alder and cross coupling chemistry (Scheme 1.9).³⁷

Scheme 1.8 Preparation of Boron Dienes and Their Diels-Alder/ Cross Coupling Reactions³⁴,³⁵
Figure 1.6 Catalytic Cycle of Rh catalyzed Diels-Alder Reactions\textsuperscript{36}

Scheme 1.9 One Pot Pd catalyzed Diels-Alder/ Cross Coupling Reactions of Novel Boron Diene\textsuperscript{37}
1.7.2 2-Silyl-1, 3-Dienes

Reports of main group element substituted 1,3-dienes and their reaction chemistry are not widespread in organic chemistry. The first report of 2-triethylsilyl-1,3-butadiene and a few of its Diels-Alder reactions was made in 1978.\textsuperscript{38} Paquette and Daniels reported some 2-silyl-substituted-1,3-cyclohexadienes in 1982 but none of their Diels-Alder chemistry was investigated.\textsuperscript{39} Wang \textit{et al} published synthesis of 2-trimethylsilyl-1,3-butadiene by lithium aluminum hydride reduction of \(\alpha\)-allenic alcohols.\textsuperscript{40,41} First reports of 2-trimethoxysilyl-1,3-butadiene and 2-triethoxysilyl-1,3-butadiene were made in 1984.\textsuperscript{42}

In this section we will discuss syntheses and reaction chemistry of silicon dienes, and we have sub classified it into three sections.

1.7.2.1 Synthesis and Reaction Chemistry of 2 Silicon Dienes Prepared by Grignard Chemistry or Substitution at the 2 Position

\begin{align*}
\begin{array}{c}
\text{Cl} \quad \begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array} \\
\text{Cl} \\
\text{Cl}
\end{array} & \xrightleftharpoons{\text{Me}_3\text{SnLi}} \begin{array}{c}
\text{Sn} \\
\text{Sn}
\end{array} \\
1.34 & \xrightarrow{\text{Cl} \quad \text{Si} \quad \text{Si} \quad \text{Cl} \\
\text{MeLi}} \begin{array}{c}
\text{Si} \\
\text{Si}
\end{array} \\
1.35 & \xrightarrow{\text{1.36}}
\end{align*}

\textbf{Scheme 1.10 Synthesis of 2,3-bissilyl-1, 3- Dienes Reported by Reich \textit{et al} \textsuperscript{43}}

In 1993 Dr. Reich’s group at the University of Wisconsin, Madison synthesized 1,1,3,3-tetramethyl-4,5-dimethylene-1,3-disilolane from 2,3-dichloro-1,3-butadienes but the reaction chemistry was not reported (\textbf{Scheme 1.10}).\textsuperscript{43}
Ikeda et al reported a carbonickelation pathway of arylnickel halides to prepare 2-aryl-3-silyl-1,3-butadienes. The silyl dienes were cross coupled to make aryl substituted polyenes (Scheme 1.11). In 2007 Pidaparthi et al first reported synthesis of three 2- silicon substituted dienes using Grignard chemistry and their subsequent Diels-Alder reaction chemistry. Cross coupling of all those cycloadducts was studied and later published in 2009 (Scheme 1.12). Based on the 2009 study they concluded DA adducts of the catechol exchanged diene were the best candidates for cross coupling.

1.7.2.2 Synthesis of 2-Silyl-1, 3-Dienes via Hydrosilylation of 1, 3-Enynes
It is known that alkynes are more reactive than alkenes towards hydrosilylation.\textsuperscript{47} Equimolar mixture of alkene and alkynes when reacted with triethoxysilane in the presence of the active Karstedt Pt catalyst produced alkyne: alkene addition product in a ratio of 80:20. It is possible to selectively react the alkyne triple bond over the alkene double bond. Alami \textit{et al} showed unsymmetrical internal alkynes could be regioselectively hydrosilylated in the presence of highly active catalysts like PtO\textsubscript{2} and H\textsubscript{2}PtCl\textsubscript{6}.\textsuperscript{48} When they screened terminal alkynes with the same catalysts, the regioselectivity was poor.\textsuperscript{49} They fine-tuned the reactivity of PtCl\textsubscript{2} with Xphos, and were able to synthesize the \(\beta\) isomer. There are also reports of milder Rh catalysts for \textit{cis} hydrosilylation of enynes.\textsuperscript{50-52} Pt and Rh catalysts were a popular choice as the catalytic cycle involved oxidative addition of the transition metal to the Si-H bond. The addition of the Si-M-H species on the alkyne was governed by steric\textsuperscript{53} and it selectively produced the \(\beta\) isomer. On the other hand, Ru catalysts were reported to go via transmetallation pathways and produced the other \(\alpha\) isomer. Combining all above facts on alkene and alkyne hydrosilylation, it seems 1,3-ene hydrosilylation could be a possible alternative for the preparation of silicon substituted 1, 3-dienes. In 2007 the Welker group published syntheses of siloxacyclopentene containing 1, 3-dienes by intramolecular hydrosilylation of the siloxy substituted enynes (Scheme 1.13 Hydrosilylation of 1,3-Enynes)

\begin{equation}
\begin{align*}
\text{R}_1\text{C}≡\text{CR}_2 & \quad \text{H-SiL}_3 & \quad \text{R}_1\text{C}≡\text{CR}_2
\end{align*}
\end{equation}

\text{1.45} \quad \text{1.46} \quad \text{1.47} \quad \text{1.48}

\(\beta\) (Z) \quad \(\beta\) (E) \quad \alpha
They also reported Diels-Alder reactions of some of those dienes. However, cyclohexenyl dienes didn’t give any cycloadduct.

Scheme 1.14 Silicon Dienes prepared by Hydrosilylation of 1, 3-Enynes

Scheme 1.15 Hydroboration to Bisalkynes yielded Silyl Dienes

In 2012 Fujihara et al prepared 2-silicon dienes by Cu catalyzed silacarboxylation of internal alkynes where they used 1.57 as silicon source.

Scheme 1.16 Silicon Dienes Prepared by Fujihara et al
1.7.2.3 Synthesis and Reaction Chemistry of Silicon Dienes Prepared by Ene Yne Cross Metathesis

After studying preparation and reaction chemistry of simple unsubstituted 2-silyl-1, 3-butadienes the Welker group focused on substituted ones synthesized by ene-yne cross metathesis (Scheme 1.17). All these dienes participated well in thermal Diel-Alder reactions. Some of the cycloadducts also participated in Hiyama cross couplings. They also reported domino reactions of ene-yne metathesis, Diels-Alder and Hiyama cross couplings. Later work showed the Ru methathesis catalyst also catalyzed the Diels-Alder reaction and enhanced the diastereoselectivity (Scheme 1.18). Lee and co-workers synthesized a number of siloxacycles that were part of a 1,3-diene unit via a condensation/metathesis strategy using alkenyl alcohols and alkynyl silanes.

![Scheme 1.17 Mechanism for Ene-Yne Cross Methathesis](image)

**Scheme 1.17 Mechanism for Ene-Yne Cross Methathesis**
Scheme 1.18 Tandem Metathesis, Diels-Alder, and Hiyama Couplings

In 2010 Dixneuf et al reported synthesis of 2,3-bis(silyl)-1,3-dienes by the Ru catalyzed ene-yne metathesis involving stoichiometric addition of two molecules of diazo carbene to one molecule of alkyne.\textsuperscript{60}

Scheme 1.19 Preparation of Silicon Dienes Stoichiometric to Chromium

Patel et al reported synthesis of 2-silicon dienes by coupling propargyl silanes with Fischer carbene chromium complexes.\textsuperscript{61}
1.8.1 Organosilicon Chemistry

Scheme 1.19 Transition Metal Catalyzed Cross Couplings (Adapted and Modified from Reference 62)

Availability, low cost, and non-toxicity of silicon made the Hiyama coupling one of the most popular choices for organic chemists among other available cross coupling methodologies (Scheme 1.20). Cross coupling reactions between two sp² carbons is an important tool for carbon-carbon bond forming processes. Suitably substituted Diels-Alder adducts can also be cross coupled with aryl or alkenyl halides to make substituted cyclohexenoids. For cross coupling chemistry one of the most important steps is transmetallation (Scheme 1.21). As Professor Hiyama stated, “Having had a good number of highly effective palladium catalysts developed mainly for cross-coupling reactions, the development of the silicon-based protocols relies heavily on the design of organosilicon reagents which effectively undergo transmetalation, a key elemental step of the silicon-based cross coupling reaction.”

\[
\text{TG-} \begin{array}{c} L^1 \\ L^2 \\ L^3 \end{array} \text{Si-L}^2 + \text{PdL}^2X_2 \xrightarrow{\Theta \text{ activator}} \begin{array}{c} L^1 \\ L^2 \\ L^3 \end{array} \text{Pd-TG} \]

TG transferable group
L¹, L², L³ non-transferable group
Scheme 1.21 Transmetallation from Si to Pd(II) in the Presence of Fluoride Source\textsuperscript{64}

Less polarity of the C-Si bond usually adds to the stability of organosilicon reagents. Tetravalent organosilicon compounds are less nucleophilic towards organometallic or other electrophiles. To transmetallate a transferrable group from Si to Pd the reaction conditions usually require a nucleophilic activator. This criterion also enhances chemoselectivity.\textsuperscript{63} Hiyama \textit{et al} made a significant step forward from Kumada’s\textsuperscript{65} use of pentafluoro silicates for cross coupling by \textit{in situ} generating pentacoordinate active species (\textbf{Figure 1.7}) for transmetallation from stable tetravalent alkenyl\textsuperscript{66} and aryl halosilanes.\textsuperscript{67}
The presence of an electronegative F atom was presumed to facilitate the formation of penta coordinate Si species. Cl substituted halo silanes also worked well in place of F. Though halo silanes cross coupled well, they were not stable and cost effective. Tamao-Ito first reported the use of mono, di and trialkoxy silanes in Pd catalyzed cross coupling reactions. Alkoxy silanes gained popularity due to their stability and low cost. In addition to using fluorides and bases (nonfluoride), other synthetic strategies were

Figure 1.7 Catalytic Cycle of Hiyama Cross Couplings
employed to activate the C-Si bond. Taguchi \textit{et al} described an intramolecular activation approach of having a proximal hydroxyl group that would coordinate to the Si, and the resulting species would transmetallate to Cu. The new Cu intermediate would transmetallate to Pd and would cross couple with aryl halides.$^{72}$

1.8.2 Organosilanols and Masked Silanols

Hiyama and Hatanaka demonstrated that organosilanes, when suitably functionalized (with heteroatoms) and in the presence of a nucleophilic activator can undergo cross coupling reactions with palladium catalysts. The crucial feature for the success of Hiyama coupling was believed to be the ability to generate reactive penta-coordinate siliconate intermediates that were needed to effect the rate determining transmetallation. The Denmark group tried using siletanes as coupling partners as they are chemically more stable than halo silanes and they have a higher propensity to make penta-coordinate species in the presence of Lewis bases.$^{73}$ Siletanes (silacyclobutanes) are strained molecules. In the sp$^3$ hybridized state the angle strain is 79° vs 109°. Denmark \textit{et al} thought upon treatment with TBAF (tetrabutylammoniumfluoride) they would generate pentacoordinate trigonal bipyramidal species (Scheme 1.22) which would relieve angle strain and thus be the driving force for the forward reaction.

![Scheme 1.22 Release in Angle Strain of Siletanes in the Presence of Fluoride](image-url)

angle strain 79° vs 109°

angle strain 79° vs 90°
Further investigation revealed the strain release was not the sole reason for very fast transmetallation and excellent stereospecificity. Kinetic studies (Scheme 1.23) revealed disiloxane (1.76) and H bonded TBAF-silanol complex (1.77) were key species for the fast C-C bond formation. But silanols are not very stable and often dimerize to disiloxanes. To solve this problem silanolates were made which have longer shelf life but low solubility in some organic solvents. Masked silanols can be a good precursor which upon treatment with TBAF (activator) would in situ generate silanols (Scheme 1.25) which would transmetallate rapidly to Pd (Scheme 1.24, 1.25, 1.26, 1.27). The Hiyama group reported Pd (0) and Ag (I) assisted TBAF free cross coupling of aryl and alkenyl silanols. Later the Denmark group independently reported another example of fluoride free cross coupling of silanols.
In 2013 Gordillo et al reported NaOH promoted Hiyama cross couplings of vinylalkoxysilanes. The alkoxy bond got hydrolyzed in the strong basic medium and was converted to silanols, which participated in the Hiyama-Denmark coupling.  

![Diagram of the catalytic cycle for the Hiyama-Denmark coupling of silanlates.](image)

**Figure 1.8 Catalytic Cycle for the Hiyama-Denmark Coupling of Silanlates**

![Scheme 1.24 Hiyama and Hiyama-Denmark Cross Couplings.](image)

**Scheme 1.24 Hiyama and Hiyama-Denmark Cross Couplings**
The favorable O-Pd interaction in the Hiyama-Denmark reaction is believed to be a key factor in the cross coupling. A group from China reported cross coupling of arenesulfinates with organosilanes where they proposed bond formation between the sulfine O and the Pd prior to transmetallation.  

Scheme 1.25  2-Pyridyl-(dimethyl)-Silyl group in the Hiyama Cross Coupling

After Denmark’s initial report of using silatanes as silanol precursors Itami et al reported 2-pyridyl silyl group that in situ generated silanols and participated in cross coupling. Similarly 2-thienyl, benzyl and allyl groups were reported as silanol precursors.

Scheme 1.26  2-Thienyl-(dimethyl)-Silyl group in the Hiyama Cross Coupling
In 2012 the Moberg group from Sweden reported syntheses of 2-silanol substituted 1,3-dienes but they didn’t report any Diels-Alder reactions for these dienes, rather they used them in different cross coupling reaction conditions (Scheme 1.28). Han et al reported relay catalytic cascade reactions of (2-(but-3-en-1-ynyl)phenyl) silanols with quinones.
1.8.3 Hiyama Couplings with Conventional Pd Catalysts and the Significance of Pd Pincer Catalysts

We pursued organosilicon diene chemistry to achieve our ultimate research goal to develop methodologies for catalytic, *exo* selective, enantioselective Diels-Alder reactions. Previously we have successfully demonstrated that σ bonded cobalt dienyl complexes can yield aforementioned goals for stoichiometric transition metals. We hoped silicon or boron main group substituted dienes would transmetallate (TM) to the metal catalyst and then participate in sequential Diels-Alder (DA), oxidative addition (OA) and reductive elimination (RE) processes. However when we attempted sequential TM, DA, OA, and RE we did not observe any cycloadduct formation instead we observed dienyl-aryl cross coupled product (Scheme 1.29).

![Scheme 1.29 Attempted sequential TM, DA, OA, and RE](image)

We wanted our dienyl species to be long lived enough to participate in DA first and then cross couple. Instead of a Pd (II)/ Pd (0) system we wanted to focus on a Pd (IV)/ Pd (II) system as Pd (II) in the pincer complex is reluctant to undergo reductive elimination.\(^{86,87}\) Figure 1.9 demonstrates energy profiles for oxidative additions of Pd pincer complexes to aryl halides (bottom) and hypervalent aryl iodonium salts (top). The aryl halide OA to Pd NCN pincer complexes are endothermic and the TS is higher in energy than the corresponding hypervalent iodonium salts, and in the case of the latter the energy
of activation is lower and the process is exothermic. We hypothesized using Pd pincer complexes would be our best bet.

Figure 1.9 DFT Reaction Profiles of Oxidative Addition of Iodonium Salt (top) and Aryl Iodide (bottom) to the Pincer Complex.86
1.8.4 Proposed Stereoselective Methodology

Scheme 1.30 Proposed Catalytic Cycle for Catalytic, Exo Selective, Enantioselective Diels-Alder Reactions

In 2000 Stark et al first reported the synthesis of 1.97. They reacted 1, 3-dicyanobenzene with β-amino alcohols; the resultant bis-oxazolinyl complex was treated with LDA/TMEDA and Pd (II) complex to yield palladium phebox pincer complex 1.97. It was used for enantioselective Michael reactions. Later in 2008 Bugarin et al prepared the same compound with better yields by oxidative addition of Pd (0) precursors. They also reported the Lewis acidity of these complexes. We want to prepare silicon dienes that would transmetallate to optically active palladium pincer complexes (1.97) and the resultant Pd-dienyl species would be long lived enough to participate in regioselective,
diastereoselective, enantioselective Diels-Alder (Figure 1.10) reaction followed by cross coupling of hypervalent aryl iodonium salts.

**Figure 1.10 Possible Models for Stereoselectivity** (Blue is Preferred over Red)
Scheme 1.31 Ni Catalyzed Chemistry
1.9 Nickel Chemistry

The Fu group reported (Eq 1 and Eq 2) Ni catalyzed enantioselective Negishi cross coupling reactions\textsuperscript{90,91} of activated electrophiles but no mechanistic work nor reaction pathways were reported. Both reactions worked at low temperatures and relied on excellent transmetallation from Zn to Ni. Based on our hypothesis and relevant literature\textsuperscript{92-94} we think these two reactions (Eq 1 and Eq 2) go via radical pathways (Scheme 1.31). With this idea we also propose Zn diene chemistry to pursue our ultimate research goal.

1.10 Specific Aim

The long standing goal of our research is based on development of methodologies for catalytic, \textit{exo} selective, enantioselective Diels-Alder reactions. We want to synthesize silicon dienes containing nontransferable groups that are known to promote transmetallation via Grignard chemistry, hydrosilylation, and ene-yne metathesis. We hope to cross couple these Diels-Alder cycloadducts to prepare substituted cyclohexenoids with absolute or relative stereochemistries which are not easily available via \textit{endo} selective dienes.
2.1.1 Synthesis of 2-Silyl-1,3-Dienes by Grignard Chemistry

In the past we have reported methodology for multi gram scale synthesis of unsubstituted 2-silicon-1,3-dienes from 2-halo-1,3-dienes. In the majority of these preparations the halo diene was converted to the corresponding Grignard reagent and then reacted with organo silanes. When we tested dienes 2.2, 2.3, and 2.4 in sequential transmetallation, Diels-Alder (DA), oxidative addition, and reductive elimination reactions we learned there was no DA reaction and we just obtained cross coupled product. Silanols are known to be excellent candidates for transmetallation. We decided to prepare silanol substituted dienes and to pursue Hiyama-Denmark coupling instead of Hiyama coupling.

Scheme 2.1 Preparation of Unsubstituted Silicon Dienes via Grignard Reaction
2.1.2 Results and Discussion

We heated chloroprene with Mg to prepare the corresponding Grignard reagent and then reacted it with dimethyldichlorosilane to make buta-1, 3-dien-2-ylchlorodimethylsilane. *In situ* hydrolysis from the former to prepare the corresponding silanol 2.6 was the trickiest part. In the $^1$H NMR of the crude product of this reaction we observed another set of alkene peaks right next to the silanol diene peaks. With time these additional peaks tend to increase in intensity and in some cases peak broadening took place. Unlike alcohols silanols have a strong tendency to make Si-O-Si linkage (disiloxanes).\(^99\) We attempted different hydrolysis conditions from pH 2 to pH 10 with different reaction times and always saw the small peaks right next to larger peaks in the alkene region both in $^1$H and $^{13}$C NMR spectra. We observed higher occurrence (29 %) of the small peaks at pH 12 and lower occurrence (15 %) at the lower acidic pH 2. From mass spectrometric data we couldn’t determine the identity of this side product (proposed as 2.7). Finally after reviewing available literature on silanol chemistry\(^100\) we decided to use a buffer instead of acid or base for the hydrolysis. Eventually after screening different hydrolysis conditions we were able to minimize the intensity of additional peaks with 1M acetate buffer. Once we were able to minimize the byproduct formation by the right choice of buffer our next goal was to separate it from the target molecule.
Scheme 2.2 Preparation of Silanol Substituted Diene and Attempted Preparation of Silanolate

Silica gel and acidic, basic and neutral alumina were used to separate the silanol from the impurity using different mobile phases but it was literally impossible to separate these two products on TLC. We then focused on their thermal properties and after enough attempts finally we were able to isolate buta-1, 3-dien-2-yldimethylsilanol (2.6) by Kugelrohr distillation (Scheme 2.2). Although it may look like a very simple molecule, it was one of toughest ones to isolate. We have successfully isolated and characterized this unstable molecule for the first time. We attempted converting the silanol to corresponding silanolate (2.8) by reacting it with alkali metal hydrides but it led to the decomposition of the starting material. We also investigated the impurity, and based on the spectroscopic data it seems to us the impurity is the dimerized (polymerized in some cases) product 2.7 analogous to 2.11 and formation of which is thermodynamically favorable (Scheme 2.3).\(^{64}\)

Scheme 2.3 Formation of Silanol and Disiloxane from the Siletane\(^{101}\)
Denmark et al serendipitously discovered that silacylobutanes or siletanes in situ can generate silanols.\textsuperscript{64} 1-Chloro-1-methylsiletane is a commercially available reagent so we wanted to prepare 2-siletane substituted 1, 3-diienes. The chloroprene Grignard reagent was added to 1-chloro-1-methylsiletane at 0 °C and was reacted for 12 h, but we didn’t see any product formation. From our previous experience we know the carbanion of the 2-halo-1, 3 butadiene Grignard reagent is much less reactive than the corresponding aryl magnesium halides and vinyl magnesium bromide carbanions, so we modified Dudley’s protocol\textsuperscript{102} with longer time and higher temperature, and finally were able to prepare to diene 2.12. Chloroprene comes as a 50% solution in xylenes to prevent polymerization; when we attempted to separate diene 2.12 from xylenes we did not succeed as they have very close \( R_f \) values. When we attempted distillation under reduced pressure we observed cycloadduct formation (2.12 a, 2.12 b evident from the \(^1\)H NMR spectrum).

Scheme 2.4 Synthesis of the Siletane Substituted Diene
In an attempt to prepare 4-aryl substituted 2-silyl-1, 3-diene we made molecule 2.14 from commercially available starting material 2.13 following a reported literature procedure. When we attempted to prepare the Grignard reagent from the diene it decomposed during this reaction. A thorough examination of all our attempts on boron and silicon dienes revealed we never succeeded to try Umpolung (reversal of the polarity) on these higher substituted halo dienes.

![Scheme 2.5 Umpolung of the Silicon-Halogen Bond](image)

Precedently we were able to prepare 2.17 and 2.19 from their halo diene analog. The key difference between Scheme 2.1 and 2.5 is Umpolung of the Si-halogen bond.

### 2.1.3 Conclusion

We observed that in the case of unsubstituted 2-silyl 1, 3-dienes making the Grignard reagent from the corresponding halo diene and treating it with silyl electrophiles is probably the best path to products. However in the case of more substituted dienes
preparation of the Grignard reagent from halo silanes worked better probably due to the thermal instability of halo diene precursors.

2.2.1 Synthesis of 2-Silyl-1, 3-Dienes via Hydrosilylation of 1,3-Enynes

Previously, our group has carried out Ru and Cu catalyzed hydrosilylation reactions of 1,3-enynes and the results were not expected. In both cases we got a mixture of both regio-isomers.\textsuperscript{104}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme2_6}
\caption{Scheme 2.6 Metal Catalyzed Hydrosilylation of 1,3-Enynes}
\end{figure}

We next turned our attention to organic nucleophile/ base catalyzed \textit{trans} hydrosilylation. We have successfully extended Lee’s\textsuperscript{105} methodology for syntheses of siloxapentene containing 2-silyl-1, 3-dienes. The first step requires silylation of alkynes. Compounds \textbf{2.28a} – \textbf{2.28c} were isolated in good yields (\textbf{Scheme 2.7}). The second step is an example of unusual \textit{trans} hydrosilylation of enynyl silanes involving one pot carbonyl
condensation and silyl migration (Scheme 2.8). Compound **2.30a** was isolated with an overall yield (for two steps) of 72%. The yield for compound **2.30c** was 53%. $^1$H NMR and mass spectrometry data confirmed the formation of compound **2.30b** but it did not survive chromatographic separation on silica or alumina.

Scheme 2.7 Preparation of Silicon Dienes by Hydrosilylation

In the case of alkynyl silanes Maifeld *et al* used 95% potassium tert butoxide and reaction was completed within 20 min at room temperature.$^{105}$ When we attempted to do the same with reagent grade potassium tert butoxide the reaction did not work and we observed predominantly the alcohol product (**2.31**). Only when we used 95% pure potassium tert butoxide only then the reaction worked. In the case of aliphatic enynes we obtained siloxapentene containing dienes but in the case of aromatic enynes we predominantly observed the alcohol product instead of dienes.
Scheme 2.8 Proposed Mechanism for Hydrosilylation\textsuperscript{106}

**Diels-Alder reaction:** Diene 2.30\textsuperscript{a} was refluxed with N-phenylmaleimide for 72 h and no reaction was observed. The diene was recovered without any decomposition. We also observed dienes 2.30\textsuperscript{a} and 2.30\textsuperscript{b} can be stored for more than six months on the bench top at RT without any decomposition. Earlier we had prepared simple siloxapentene containing dienes from siloxy substituted enynes (Scheme 2.9 top) that participated in DA reactions.\textsuperscript{54} Enyne (2.31) was converted to the alcohol (2.32) by reaction with formaldehyde.
When we compared our present observation with previous results (Scheme 2.9) we concluded that probably due to steric interactions due to the methyl substituent the cycloaddition was not taking place.

**Scheme 2.9 Attempted Diels-Alder Reaction of Siloxapentene Containing Dienes**
2.2.3 Conclusion

Our results showed transition metal catalyzed hydrosilylation of enynes was not the best way to prepare 2-silyl-1, 3-dienes as the regio-selectivity was very poor. In contrast, 95% pure KO'Bu catalyzed trans-hydrosilylation of alkynyl silanes yielded much better results. These reactions require relatively inexpensive catalysts and reaction conditions are much more forgiving and mild.

2.3.1 Synthesis of 2-Silyl-1,3-Dienes by Intramolecular Enyne Metathesis

The Welker group has been interested in the preparation and reaction chemistry of main group element, boron and silicon substituted dienes for many years. In 2010 we reported the synthesis of a number of benzylidimethylsilyl substituted 2-silicon 1,3-dienes by cross metathesis. All these dienes reacted in Diels-Alder chemistry in highly diastereoselective fashion, and cycloadducts were cross coupled with aryl halides by Pd catalyzed reactions. Later, it was established that isolation of the diene is not required for the Diels-Alder chemistry, and the cycloadducts can be further cross coupled without purification.108

Scheme 2.10 One Pot Metathesis, DA, and Hiyama Couplings
The one pot metathesis, DA, and Hiyama coupling (Scheme 2.10) was preferred over sequential reactions because the Ru catalyst enhanced diastereoselectivity.\textsuperscript{108} With the same idea we proceeded to investigate intramolecular enyne cross metathesis reactions involving silyl alkynes and alkenes, silyl alkenes and alkynes, silyl alkenes and silyl alkynes. As outlined in Scheme 2.11 we wanted to pursue intramolecular enyne metathesis in three parallel pathways.

\textbf{Scheme 2.11 Intramolecular Enyne Metathesis Route for the Synthesis of Silicon Dienes}
2.3.2 Results and Discussion

Scheme 2.12 Intramolecular Enyne Metathesis

Intramolecular reactions are entropically favorable over intermolecular reactions. Therefore we decided to begin our investigation of the reaction pathways outlined in Scheme 2.11 by looking at the intramolecular enyne metathesis of silyl alkynes. There are very few examples of intramolecular ring closing enyne metathesis reactions that did not exploit the Thorpe Ingold effect\textsuperscript{109} or angle compression effect. We wanted to balance these two parameters. In order to do that, enynes \textbf{2.45} and \textbf{2.49} were prepared according to published literature procedures.\textsuperscript{110} These enynes did not contain quaternary carbons or bulky pendant groups on heteroatoms; which would facilitate the formation of four
membered ruthenacyclobutane rings. Enynesilanes 2.46 and 2.50 were obtained in good yields from their enyne precursors. Terminal silyl-eneyne 2.46 participated in the intramolecular enyne cross metathesis and diene 2.47 was isolated in moderate yield. The next higher homolog was then attempted using enyne silane 2.50, different types of Ru carbene catalysts, catalyst loadings, and solvents. But in each case decomposition of starting material took place. We have observed a significant inhibitory effect of ethylene on these cross metatheses reactions. We did not observe any product formation (appearance of characteristic dienyl peaks in the 1H NMR, more explanation in chapter 3 section 3.2.5) and observed decomposition of the reaction mixture whenever we ran this reaction under ethylene. Failure to synthesize diene 2.35 answered a very important question that it is possible to achieve intramolecular ring closing metathesis in the case of a 5 membered ring (Scheme 2.12) but addition of another CH₂ unit would require additional sterics to bring both ends in the same plane.₁¹¹-₁¹³

**Attempted Diels-Alder reaction:** Diene 2.47 was screened with mono (methylvinylketone) and disubstituted (N-phenylmaleimide) dienophiles at reflux temperatures in THF and DCM but NMR studies revealed diene decomposition.

### 2.3.3 Conclusion

To the best of our knowledge we first achieved and demonstrated intramolecular enyne metathesis reaction for the synthesis of 2 silicon substituted 1, 3-dienes. Both intermolecular and intramolecular metathesis seems to be an effective pathway for diene
preparation. For syntheses of 4-aryl-2-silyl-1, 3-butadienes intermolecular metatheses is probably the best pathway.

2.4 Experimental Section and Characterization Data

**General Procedures** The proton nuclear magnetic resonance ($^1$H NMR) spectra were obtained using a Bruker Avance 300 MHz spectrometer operating at 300.1 MHz or a Bruker Avance 500 MHz spectrometer operating at 500.1 MHz. $^{13}$C NMR spectra were obtained using a Bruker Avance 300 MHz spectrometer operating at 75.5 MHz. $^1$H and $^{13}$C NMR spectra were referenced to the residual proton or carbon signals of the respective deuterated solvents. All elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High-resolution mass spectrometry was performed at the UNC Mass Spectrometry Facility, Chapel Hill, NC; University of Illinois Mass Spectrometry Laboratory, Urbana, IL 61801

All reactions were carried out under an atmosphere of argon. Tetrahydrofuran (THF) was degassed with argon and then passed through two 4 x 36 inch columns of anhydrous neutral A-2 alumina (8 x 14 mesh; activated under a flow of Ar at 350 °C for 3 hr) to remove water. Toluene (PhMe) was degassed with Ar. Water was deionized and distilled. Deuterated solvents were purchased from Cambridge Isotope Laboratories and dried over molecular sieves. Sodium sulfate, sodium hydroxide, magnesium small turnings, 1, 2-dibromoethane were purchased from Aldrich Chemical Company and used as received. 2-Chloro-1, 3-butadiene, 50% in xylene (Chloroprene) was
purchased from Pfaltz & Bauer, Inc and used as received. Dimethyldichlorosilane and 3-methyl-3-butene-1-yne were purchased from Acros Organics.

**General procedure for Grignard Chemistry:** An oven-dried 100 mL 2-neck round-bottom flask equipped with a magnetic stir bar, addition funnel and reflux condenser was charged with magnesium (1.6 eq) followed by the addition of dibromoethane (11.0 mol %) in THF (5 mL). After stirring ~ca. 5 min (initiation of magnesium activation can be noticed by its silver color and ethane gas liberation), 3.0 mol % of anhydrous ZnCl₂ in THF (5 mL) was added. This mixture was added with additional THF (30 mL) and resulted in a whitish-grey solution which was brought to gentle reflux over a period of 15 min. Chloroprene (in 50 % xylene) (1.0 eq) and dibromoethane (23.0 mol %) in THF (25 mL) was added drop-wise to the refluxing reaction mixture over 30 min. After the addition, refluxing was continued for another 45 min. The greenish-grey colored Grignard solution was transferred by cannula into a 250 mL, one-neck round-bottomed flask containing chlorosilane (0.95 eq) in THF (25 mL) at room temperature. The reaction mixture was refluxed (1 h), poured into 0.5M HCl solution (100 mL) and extracted with pentane (2 × 75 mL). The combined colorless clear organic layers were washed successively with 0.5M HCl (75 mL) and water (2 × 100 mL). After drying over MgSO₄, the solvent was removed under reduced pressure to yield 2-substituted silyl diene with xylene as a colorless liquid.

**Synthesis of (Buta-1, 3-dien-2-yl) dimethylsilanol (2.6):**

Chloroprene in 50% xylene (1.0mL, 5.15 mmol) and dichlorodimethylsilane (0.645 g, 5 mmol) were used according to the general procedure above (1M acetate buffer of pH 5 was used instead of 0.5M HCl for the quench) to yield a light yellow colored liquid. ¹H
NMR of the crude product (1.1g) showed a mixture of xylenes, diene and the corresponding disiloxane dimer. Kugelrohr distillation at 60°C (4mm Hg) of the crude product yielded the target compound (3) (0.300g, 2.3 mmol, 46%). $^1$H NMR (300 MHz CDCl$_3$) $\delta$ 6.46 (dd, $J = 17.8, 10.8$ Hz, 1H), 5.77 (d, $J = 3.0$ Hz, 1H), 5.56 (d, $J = 2.9$ Hz, 1H), 5.37 (d, $J = 18.2$ Hz, 1H), 5.12 (d, $J = 10.8$ Hz, 1H), 2.25 (bs,1H) 0.3 (s, 6H) ; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 148.65, 140.88, 129.58,116.56, 0.32; EIMS calcd for C$_{16}$H$_{13}$OSi (M+H)$^+$ 129.06, found 129.0

**Attempted synthesis of Sodiumbuta-1, 3-dien-2-yldimethylsilanolate (2.8):**

Following similar published literature$^{114}$ inside a glove box washed NaH (0.015g, 0.9 mmol) was added to a round bottom flask containing 3 mL of anhydrous THF. Then diene 2.6 (0.1 g, 0.8 mmol) was added to THF (6 mL). The dilute diene solution was drop wise added to NaH suspension. It was stirred for 1 h and filtered through a fritted glass funnel. The filtrate was condensed and the solid was washed with dry pentane (10 mL). NMR studies revealed decomposition of starting material.

Similarly KH was attempted instead of NaH but the reaction was unsuccessful.

**Synthesis of 1-(buta-1, 3-dien-2-yl)-1-methylsiletane (2.12):**

Chloroprene in 50% xylenes (1.0mL, 5.15 mmol) and 1-chloro-1-methylsiletane (0.53 mL, 4.3 mmol) were used according to the general procedure above to yield a light yellow colored liquid. $^1$H NMR of the crude product (1.1 g) indicated formation of the diene ($^1$H NMR characteristic peaks) (300 MHz, Chloroform-d) $\delta$ 6.50 (ddt, $J = 17.7, 10.5, 0.8$ Hz,
1H), 5.82 (dt, J = 3.1, 0.7 Hz, 1H), 5.57 (ddd, J = 3.5, 1.2, 0.6 Hz, 1H), 5.24 – 5.07 (m, 2H), 1.34 – 0.86 (m, 6H), 0.42 (s, 3H).

Attempted synthesis of (E)-1-methyl-1-(4-phenylbuta-1,3-dien-2-yl)siletane (2.15)

(E)-(3-bromobuta-1,3-dien-1-yl)benzene was prepared from 1-Phenyl-1-buten-3-one following a published procedure.103 Halo diene (1.2 g, 5.73 mmol) was treated with Mg (0.223 g, 9.2 mmol) to prepare corresponding Grignard reagent and the resultant reaction mixture was added to 1-chloro-1-methylsiletane (0.6 mL, 5 mmol). 1H NMR confirmed decomposition of the starting material of the halo diene.

Synthesis of diisopropyl(3-methylbuta-1-en-1-yn-1-yl)silane (2.28a):

In a 100 mL flame dried flask equipped with a magnetic stir bar, 3-methyl-3-buten-1-yne (1.39 g, 20.9 mmol) was added followed by anhydrous THF (20 mL). The solution was cooled to -78 °C and nBuLi (15.0 mL of a 1.6 M soln in hexanes, 23.0 mmol) was added slowly and stirred for 20 min. Chlorodiisopropylsilane (3.44 g, 23.0 mmol) in THF (10 mL) was added drop wise to the above reaction mixture. After stirring for 30 min at -78 °C it was allowed to warm and stirred 12 h at RT. The milky white reaction mixture was diluted with diethyl ether (100 mL) and washed with half saturated NH₄Cl solution (100 mL). The organic layer was dried over MgSO₄ and the solvent was evaporated under reduced pressure to give a light yellow colored liquid (2.28a) (3.279 g, 18.18 mmol, 87%): 1H NMR (300 MHz, CDCl₃) δ 5.37- 5.38 (m, 1H), 5.27 (p, J = 1.6 6 Hz, 1H), 3.75 (bs, 1H), 1.90 (t, J = 1.14 Hz, 3H), 1.06 (m, 14H); 13C NMR (75 MHz, CDCl₃) δ 126.79, 123.0
4, 109.17, 86.6 8, 23.88, 18.49, 18.24, 10.86; HRMS calcd for C_{11}H_{20}Si (M^+) 180.1333, found 180.1333.

Synthesis of 2, 2-diisopropyl-5, 5-dimethyl-3-(prop-1-en-2-yl)-2, 5-dihydro-1, 2-oxasilole (2.30a):

In a 20 mL flame dried flask, anhydrous THF (5 mL) was added followed by acetone (0.269 g, 4.64 mmol). To that solution, the silylation product (2.28a) (0.92 g, 5.11 mmol) was added followed by 95% KO'Bu (0.052 g, 0.464 mmol). The solution was stirred for 40 min at RT and then washed with half saturated NH₄Cl solution (20 mL) and diethyl ether (20 mL), and the organics were dried over MgSO₄. Upon removal of the solvent under reduced pressure and flash chromatography with 4% diethyl ether in pentane (Rf 0.44), the target compound (2.30a) was isolated as a clear liquid, (0.918 g, 3.85 mmol, 83%): ¹H NMR (300 MHz, CDCl₃) δ 6.51 (s, 1H), 4.98 (bs, 1H), 4.79 (bs, 1H), 1.91 (s, 3H), 1.35 (s, 6H), 0.98 (m, 14H); ¹³C NMR (75 MHz, CDCl₃) δ 151.04, 142.12, 137.93, 116.31, 82.43, 29.73, 20.7, 17.84, 17.4, 13.19; HRMS calcd for C_{14}H_{26}O_{1}Si (M^+) 238.1753, found 238.1755.

Synthesis of dimethyl(3-methylbut-3-en-1-yn-1-yl)silane (2.28b):

Similarly 3-methyl-3-buten-1-yne (1.38 g, 20.9 mmol) was reacted with nBuLi (15.0 mL of a 1.6 M soln in hexanes, 23.0 mmol) and dimethylchlorosilane (2.37g, 25 mmol) to prepare dimethyl(3-methylbut-3-en-1-yn-1-yl)silane (2.28b) as a colorless liquid (1.8 g, 14.5 mmol, 69%). ¹H NMR (300 MHz, CDCl₃) δ 5.38 (s, 1H), 5.27 (s, 1H), 4.18 (sept, J
= 3.7 Hz, 1H), 1.89 (s, 3H), 0.26 (d, J = 3.7 Hz, 6 H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 126.62, 123.35, 107.67, 89.91, 23.15, 2.99; HRMS calcd for C$_7$H$_{11}$Si (M-H)$^+$ 123.0630, found 123.0632.

**Attempted Synthesis of 2, 2, 5, 5-tetramethyl-3-(prop-1-en-2-yl)-2, 5-dihydro-1, 2-oxasilole (2.30b):**

Compound 2.28b (0.400 g, 3.22 mmol), acetone (0.157 g, 2.7 mmol), and 95% KO'Bu (0.032 g, 0.27 mmol) were used for the diene synthesis as described above for 2.28a. $^1$H NMR of the crude product indicated diene (2.30b) formation but it could not be purified by alumina or silica column chromatography.

**Preparation of (E)-dimethyl (4-phenylbut-3-en-1-yn-1-yl)silane (28c):**

(E)-4-Phenyl-3-buten-1-yn (2.26) was synthesized from trans cinnamaldehyde as described previously.$^{115}$ Enyne 2.26 (1.361 g, 0.61 mmol), nBu-Li (7.3 mL of a 1.6 M soln in hexanes, 11.7 mmol), and chlorodiisopropylsilane (1.76 g, 11.7 mmol) were combined and worked up as described above to yield crude 28c (2.343 g) as a dark brown liquid. Flash chromatography using 3% triethylamine in pentane (R$_f$ 0.6) produced 28c as a light yellow colored oil (1.906 g, 7.86 mmol, 74%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.28 - 7.40 (m, 5H), 7.03 (d, $J$ = 16.3 Hz, 1H), 6.20 (dd, $J$ = 16.3, 1.04 Hz), 3.80 (bs, 1H), 1.08 - 1.12 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 142.75, 136.05, 128.82, 128.71, 126.31, 107.96, 107.93, 99.56, 18.53, 18.30, 10.93; HRMS calcd for C$_{16}$H$_{12}$Si (M$^+$) 242.14 90, found 242.1486.
Synthesis of 2,2-diisopropyl-3-(1-phenylvinyl)-2,5-dihydro-1,2-oxasilole (2.30c):

Compound (2.28c) (0.05 g, 0.206 mmol), paraformaldehyde, (0.0051 g, 0.17 mmol), and 95% KO'Bu (0.002 g, 0.017 mmol)) were combined and worked up as described above to yield a crude product which was purified by preparative silica gel chromatography and eluted with (3:3:96) triethylamine : diethyl ether: pentane mixture (Rf 0.4). An orange colored liquid (27c) was isolated (0.030 g, 0.11 mmol, 53%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.23 -7.43 (m, 5H), 7.13 (d, J = 15.98 Hz, 1H), 6.85 (bs, 1H), 6.40 (d, J = 15.98 Hz, 1H), 1.06 - 1.12 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 146.4 4, 137.45, 137.40, 132.71, 128.61, 127.48, 126.24, 72.63, 17.36, 16.96, 13.27.

Attempted Diels-Alder reaction of Diene 2.28a:

Diene (0.05 g, 0.2 mmol) and N-phenylmaleimide (0.075g, 0.435 mmol) were heated under reflux condition for 72 h. $^1$H NMR showed no DA reaction and starting materials were recovered without any decomposition.

Synthesis of benzyl (hept-6-en-1-yn-1-yl)dimethylsilane (2.46):

6-Hept-1-yne (2.45) (0.6 g, 6.37 mmol) was synthesized from 5-bromo-1-pentene as described previously. The enyne (2.45) (0.6 g, 6.37 mmol) was treated with $^9$Bu-Li (4.5 mL of a 1.6 M soln in hexanes, 7 mmol) and benzylchlorodimethylsilane (1.404 g, 7.5 mmol) as described above for 28a-c. A light yellow colored liquid (2.46) was obtained (1.377 g, 5.68 mmol, 89%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.22 (t, J = 8.04 Hz, 2H), 7.09 (m, 3H), 5.8 (ddt, J = 17, 10.25, 6.7 Hz, 1H), 5.04 5 (dd, J = 17.1, 1.72 Hz, 1H), 5.0 (m, 1H), 2.24 (t, J = 7.1 Hz, 2H), 2.19 (s, 2H), 2.14 (q, J = 7.4 4 Hz, 2H), 1.61 (p, J = 8.04 Hz, 2H), 0.11 (s, 6H); $^{13}$C
NMR (75 MHz, CDCl$_3$) $\delta$ 139.22, 137.74, 128.33, 128.0 6, 124.21, 115.19, 108.55, 83.10, 32.6 8, 27.6 8, 26.51, 19.23, -1.91; HRMS calcd for C$_{16}$ H$_{22}$ Si (M$^+$) 242.1491, found 242.1492.

**Synthesis of benzyldimethyl(oct-7-en-1-yn-1-yl)silane (2.50):**

7-Octen-1-yn (2.49) was synthesized as described previously.$^{110}$ 7-Octen-1-yn (2.49) (1.00 g, 9.24 mmol), $^n$Bu-Li (6.5 mL of a 1.6M soln in hexanes, 10.16 mmol) and benzylchlorodimethylsilane (1.877 g, 10.16 mmol) were combined according to the general procedure used to make 28a-c to produce a crude product which was purified by flash chromatography ($R_f$ 0.4, 2% diethyl ether in pentane) to yield a clear liquid 32 (0.899 g, 3.5 mmol, 65%). $^1$H NMR CDCl$_3$ (500 MHz) $\delta$ 7.25 (t, $J = 8.1$ Hz, 2H), 7.09 – 7.12 (m, 3H), 5.84 (ddt, $J = 17.1$, 10.28, 6.67 Hz, 1H), 5.05 (dd, $J = 17.13$, 1.8 Hz, 1H), 4.98 (m, 1H), 2.25 (t, $J = 6.75$ Hz, 2H), 2.21 (s, 2H), 2.1 (q, $J = 7.15$ Hz, 2 H), 1.46 - 1.59 (m, 4H), 0.13 (s, 6H); $^{13}$C NMR (300 MHz, CDCl$_3$) $\delta$ 139.24, 138.53, 128.34, 128.05, 124.20, 114.57, 108.80, 82.58, 33.19, 27.96, 27.93, 26.53, 19.71, - 1.91; HRMS calcd for C$_{17}$H$_{24}$Si (M$^+$) 256.1647, found 256.1645.

**Synthesis of benzyl(1-(cyclopent-1-en-1-yl)vinyl)dimethylsilane (2.47):**

Hoveyda-Grubbs second generation catalyst (0.045g, 0.053mmol) was added to a flame dried flask equipped with stir bar and 4 Å molecular sieves (40 % w/w). DCM (3mL) was added and the solution was degassed. Silylenyne (2.46) (0.080g, 0.353 mmol) was added and refluxed for 12h under Ar. The reaction was monitored by $^1$H NMR spectroscopy. Upon completion of the reaction, solvent was removed under vacuum and the crude
product was purified by preparative silica gel TLC (Rf 0.66 (triethylamine/ Et2O/ pentane, 1:1:50) to yield 30 (0.034 g, 0.140 mmol, 40%). 1H NMR ((500 MHz, CDCl3) δ 7.19 (t, J=7.54 Hz, 2H), 7.06 (t, J=7.38 Hz, 1H), 6.98 (d, J = 8.1 Hz, 2H), 5.8 (bs, 1H), 5.66 (d, J= 2.66 Hz, 1H), 5.36 (d, J = 2.65 Hz, 1H), 2.48-2.51 (m, 4H), 2.26 (s, 2H), 1.9 (p, J= 7.64 Hz, 2H), 0.133 (s, 6H); 13C NMR (75 MHz, CDCl3) δ 145.15, 144.19, 140.11, 129.40, 128.27, 128.00, 125.66, 123.96, 33.68, 33.07, 29.7, 25.96, 22.44; HRMS calcd for C16H22Si (M+) 242.14 91, found 242.14 94.

Attempted synthesis of benzyl(1-(cyclohex-1-en-1-yl)vinyl)dimethylsilane (2.51):
Intramolecular enyne metathesis of 2.51 was attempted with different catalysts (Hoveyda-Grubbs 2nd generation catalyst, Zhan 1B catalyst) and different catalyst loadings from 10 mol % - 30 mol % in different solvents (DCM, DCE, THF, toluene) but no product was isolated and the 1H NMR of the reaction mixture indicated decomposition of starting material.
CHAPTER 3: PREPARATION AND REACTION CHEMISTRY OF NOVEL SILANOL SUBSTITUTED DIENES

In 2014 we first reported the preparation and isolation of buta-1,3-dien-2-yldimethylsilanol. We soon realized silanols work very well in the cross coupling chemistry but they often dimerize upon isolation. We also attempted to convert the silanol to the corresponding silanolate but it led to the decomposition of the starting material. So we focused our attention to molecules that would in situ generate silanols. In 1999 the Denmark group reported silacyclobutane-based Pd-catalyzed cross coupling reactions which eventually go via silanol intermediates. In 2000 Itami et al first reported use of the 2-PyMe₂Si group as a ‘Phase tag’, and in the next year they reported the same functional group would generate silanol upon treatment with TBAF in Pd-catalyzed cross couplings. Professor Tamejiro Hiyama’s group from Japan reported in 2002 incorporation of the 2-thienyldimethyl group on silicon enhanced transmetallation, also via a silanol intermediate. In 2005 the Denmark group reported the preparation of 1, 3-butadiene containing terminal dimethylsilanol and 2-thienyldimethylsilyl groups. However none of the cycloadditions were reported. They reported sequential cross coupling of silanol and masked silanol substituted dienes with aryl halides. In the presence of potassium trimethylsilanolate and Pd catalyst only the silanol substituted dienyl end cross coupled. But in the presence of TBAF and Pd catalyst both silicon groups cross coupled. In this chapter we will discuss the efficacy and limitations for the preparation of different masked silanol substituted dienes and their reaction chemistry.
3.1.1 Synthesis of Dimethylpyridyl Substituted Silicon Dienes

Scheme 3.1 Preparation of Dimethylpyridyl Substituted 2-Silicon diene via Grignard Chemistry

In 2007 we reported the synthesis of 2-silicon substituted 1, 3-butadienes from chloroprene via Lewis acid catalyzed Grignard chemistry from the corresponding halo silanes.45 We adopted the same strategy and successfully synthesized pyridyl substituted silicon diene 3.7. Reagent 3.6 was in situ prepared by the reaction of 2-bromopyridine with nBu-Li. First we tried to separate the diene from xylene using silica gel flash column chromatography but in both cases (regular silica gel, and 3% triethylamine deactivated silica gel) the diene decomposed. Finally we were able to purify it on neutral alumina stationary phase using pentane and ethyl acetate mixture as mobile phase.
3.1.2 One Pot Diels-Alder and Cross Coupling reactions of (Dimethylsilyl)Pyridyl Group Substituted Dienes

Scheme 3.2 One Pot DA and Cross Coupling Reactions

We monitored the reactivity of diene 3.7 with N-phenylmaleimide at 25 °C by observing the cycloadduct formation with $^1$H NMR, and calculated $t_{1/2}$ of 22 min. Previously, we reported that 2-triethoxysilyl-1,3-butadiene showed 2% conversion to cycloadduct formation with the same dienophile at 25 °C after 30 min. $^{45}$ Diene 2.3 when was reacted with N-phenylmaleimide at 0 °C and $t_{1/2}$ was found to be 18.8 min. We took diene 3.7 and reacted it with three types of dienophiles. We attempted to isolate and to purify the Diels-Alder adducts but we did not succeed as compounds streaked heavily on the silica surface. The pyridyl group was known for its ‘phase tag’ nature. $^{116,118}$ We proceeded with the acidic workups and the NMR data revealed 90% product purity. Instead
of isolating the Diels-Alder adducts in the same reaction pot we added Pd (II) catalyst, tetra-n-butylammonium fluoride (TBAF) and aryl halide. We obtained high yields (two step), and regioselectivity\textsuperscript{34} in the cross coupled product. Previously we have observed that Diels-Alder adducts of 2-silicon substituted dienes required additives to fine-tune the cross couplings, and during the process the maleimide or the anhydride ring of the dienophile opened up.\textsuperscript{45,107} But these synthons reacted cleanly and cross couplings were achieved using Pd (II) and TBAF only. As per cross coupling chemistry is concerned the 2-PyMe\textsubscript{2}Si group worked best among all other organosilanes (Hiyama or Hiyama-Denmark couplings) that we attempted before. We screened three Pd sources (PdCl\textsubscript{2}, Pd(OAc)\textsubscript{2}, and PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2}), and Pd (OAc)\textsubscript{2} worked best.

3.1.3 Synthesis of Dimethylthienyl Substituted Silicon Dienes

![Scheme 3.3 Preparation of Dimethyl-2-thienyl Substituted Silicon Diene](image)

Similar to the Scheme 3.1 we prepared Diene 3.17 from the corresponding halo Diene (Scheme 3.3). We also monitored reactivity of the diene 3.17 with N-phenylmaleimide at 25 °C by observing cycloadduct formation with \textsuperscript{1}H NMR, and calculated t\textsubscript{1/2} of 29 min. Diene 3.17 showed comparable t\textsubscript{1/2} with respect to diene 3.7 (t\textsubscript{1/2}}
22 min). It was reacted with three different types of dienophiles and we obtained cycloadducts in good yields (Scheme 3.4).

Scheme 3.4 Regioselective DA Reactions
At first we attempted cross coupling conditions following previously reported literature. \(^{75,81}\) 1.2 equivalent of Diels-Alder adduct was reacted with 1 equivalent of aryl halide, 4 mol% of Pd (0) catalyst and 2 equivalents of TBAF under Ar at 50 °C. \(^1\text{H NMR}\) of the crude reaction mixture indicated decomposition of the starting material. Due to ease of handling we screened Pd (II) catalyst (5 mol%) with 1 equivalent of Diels-Alder adduct, 1.2 equivalent of iodobenzene, 2 equivalents of TBAF at RT for 1-3 h, and were able to isolate cross coupled products in good yields.

Scheme 3.5 Cross Coupling Reactions
3.2.1 Ene-Yne Cross Metathesis

In 2010 we published a methodology based on ene-yne metathesis to prepare 4-aryl- and 4-alkyl-2-silyl-1, 3-butadienes.\textsuperscript{57} We wanted to synthesize 4-substituted 1, silicon dienes containing nontransferable groups on silicon known to promote transmetallation. Based on reported literature\textsuperscript{119} we planned to synthesize dienes 3.26, 3.30, 3.33, 3.36, 3.38, and 3.40. We started with optimized conditions described in reference 9 by using 5 eq of alkene, 1 eq of alkyne, and 10 mol\% of Hoveyda-Grubbs 2\textsuperscript{nd} generation catalyst in DCM solvent.

Scheme 3.6 Attempted Preparation of Dimethylsilanol Substituted Silicon Diene

We first tried to make ethynyl silanol (3.24) from dimethyldichlorosilane but it polymerized when we tried to isolate it. So, we attempted the preparation of 3.24 from the same starting material and reacted it \textit{in situ} in the ene-yne metathesis reaction. We did not see the expected molecule but we observed \textit{trans}-stilbene (olefin metathesis product). We followed a literature procedure\textsuperscript{120,121} using polydimethylsiloxane to prepare 3.24 but that also did not work. We recovered unreacted polydimethylsiloxane (3.27).
Our next attempt was using chloro(ethynyl)dimethylsilane as silanol precursor (Scheme 3.7) but it also polymerized during the isolation process. When we tried a one pot Grignard reaction followed by metathesis, we got a complex reaction mixture.

As silanols were not stable enough to work with we focused on molecules that would in situ generate silanols. Our next target was to make siletane and diisopropyl substituted dienes as those groups were known to promote transmetallation. We again ran into polymerization problems, and one pot Grignard and metatheses reactions did not work.
After exploring siletane and alkyl silanes we focused on the 2-PyMe₂Si group. We were able to obtain 90% pure alkyne 3.37 by vacuum distillation. We took that alkyne and used 10 mol% Ru catalyst in the metathesis reaction. When the reaction did not work we hypothesized that the pyridyl impurities are poisoning the Ru catalyst. Then we used one eq of catalyst but we did not see any metathesis product. We knew from the literature that 2-pyridyl group cross couples well but 3-pyridyl group behaves poorly in Rh (I) catalyzed cross coupling chemistry,\(^{118}\) possibly due to directing property of the former. In 2002 Prof Yoshida’s group studied relative reactivities of different dimethyl(pyridyl)silanes in the Rh catalyzed hydrosilylation of alkenes.\(^{122}\) They also reported the following reactivity order; 2-PyMe₂SiH >> 3-PyMe₂SiH, 4-PyMe₂SiH, PhMe₂SiH. It was described that the rate enhancement was due to the coordination of the nitrogen lone pair with the metal center. In our case we think the coordination between the nitrogen lone pair and Ru carbene hindered the ruthenacyclobutane ring formation, and shut down the metathesis pathway.

**Scheme 3.9 Attempted Preparation of Dimethyl-2-pyridyl Substituted Silicon Dienes by Ene-Yne Cross Metathesis**
Scheme 3.10 Ene-Yne Cross Metathesis of Silyl Alkynes

Among the entire family of masked silanols alkyne 3.39 only participated in ene-yne cross metathesis. In the crude reaction mixture of ethynyldimethyl(thiophen-2-yl)silane and styrene we observed the appearance of characteristic dienyl peaks; and disappearance of alkyne peak. However the separation of the olefin metathesis side product 3.41 was a difficult problem. We attempted different stationary and mobile phases to separate diene 3.40 from molecule 3.41 but it ended up in the decomposition of the diene. Our next challenge was to suppress olefin metathesis and exclusively promote ene-yne metathesis to avoid the chromatographic separation problem.

3.2.2 Alkene-Alkyne Ratio Optimization

We started reversing the alkene (styrene) alkyne (3.39) ratio with excess alkyne (Table I entry 1). We were not able to drive the reaction in the presence of excess alkyne (Table I entry 1 - 3). With 6 mol% of Hoveyda-Grubbs 2nd generation catalyst after 12 h reflux we were able to drive the reaction to completion for styrene. Once we determined the
optimized alkene alkyne ratio (1:0.83) we concentrated on Ru carbene catalysts optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene Alkyne Ratio</th>
<th>Cat loading (mol %)</th>
<th>Temp, Time</th>
<th>Progress of reaction ((^1)H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:5</td>
<td>3 mol % to 18 mol %</td>
<td>rt to reflux, 12 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>2</td>
<td>1:3</td>
<td>3 mol % to 18 mol %</td>
<td>rt to reflux, 12 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>3a</td>
<td>1:0.9</td>
<td>3 mol %</td>
<td>reflux, 12 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>3b</td>
<td>1:0.9</td>
<td>7 mol %</td>
<td>reflux, 12 h</td>
<td>13%</td>
</tr>
<tr>
<td>3c</td>
<td>1:0.9</td>
<td>10 mol %</td>
<td>reflux, 12 h</td>
<td>44%</td>
</tr>
<tr>
<td>3d</td>
<td>1:0.9</td>
<td>15 mol %</td>
<td>reflux, 12 h</td>
<td>48%</td>
</tr>
<tr>
<td>4a</td>
<td>1:0.83</td>
<td>3 mol %</td>
<td>rt, 12 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4b</td>
<td>1:0.83</td>
<td>3 mol %</td>
<td>reflux, 12 h</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>1:0.83</td>
<td>4 mol %</td>
<td>rt, 12 h</td>
<td>19%</td>
</tr>
<tr>
<td></td>
<td>1:0.83</td>
<td>4 mol %</td>
<td>reflux, 12 h</td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>1:0.83</td>
<td>6 mol %</td>
<td>rt, 12 h</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td>1:0.83</td>
<td>6 mol %</td>
<td>reflux, 12 h</td>
<td>reaction complete</td>
</tr>
</tbody>
</table>

Table I Optimization of the Alkene Alkyne Ratio
Figure 3.1 Different Ru Carbene Catalysts

3.42 First-generation Grubbs catalyst

3.43 Second-generation Grubbs catalyst

3.44 First-generation Hoveyda-Grubbs catalyst

3.45 Second-generation Hoveyda-Grubbs catalyst

3.46 Zhan-1B catalyst

3.47 Grubbs pyr solvate catalyst
3.2.3 Catalyst Optimization

Ene-yne cross metathesis catalysts can be divided into three categories. i) Fischer Carbene complexes (W, Mo, Cr), ii) Pd and Pt catalysts, and iii) Ru catalysts. Among them Ru catalysts (Figure 3.1) involving Grubbs’s carbene are most popular due to their high degree of chemoselectivity. All these catalysts are Ru$^{2+}$ 16 e complexes. The first generation Grubbs catalysts exhibited good catalytic activity towards ROMP, RCM, preparation of 1,3-dienes via enyne metathesis, etc. However, the 1st generation Grubbs catalyst demonstrated poor reactivity in comparison to the more active and more sensitive Schrock catalysts in cases of sterically hindered or electronically deactivated alkenes. The second generation Grubbs’ catalyst was first reported in 1999, and since then there were several types of Grubbs second generation catalysts developed and optimized for different organic transformations. We took alkene and alkyne in a ratio of 1:0.83 and screened different Grubbs Ru carbene catalysts with 6 mol% catalyst loading (Table II).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Loading</th>
<th>Olefin Metathesis</th>
<th>Ene-yne Metathesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs 1st gen</td>
<td>6 mol%</td>
<td>yes</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs 2nd gen</td>
<td>6 mol%</td>
<td>yes</td>
<td>22%</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda-Grubbs 1st gen</td>
<td>6 mol%</td>
<td>yes</td>
<td>11%</td>
</tr>
<tr>
<td>4</td>
<td>Hoveyda-Grubbs 2nd gen</td>
<td>6 mol%</td>
<td>yes</td>
<td>complete</td>
</tr>
<tr>
<td>5</td>
<td>Zhan 1B</td>
<td>6 mol%</td>
<td>yes</td>
<td>None</td>
</tr>
</tbody>
</table>

Table II Catalysts Screening for the Ene-Yne Cross Metathesis
All these reactions were carried out under Ar atmosphere from RT to reflux in DCM solvent. Progress of the reactions were determined by integrating alkyne and new dienyl peaks (if any) in the $^1$H NMR. Grubbs 1st and Hoveyda-Grubbs 1st generation catalysts did not work well. Hoveyda-Grubbs 2nd generation catalyst worked best. To our surprise Zhan 1 B which is very similar in structure (and slightly electron poor) to the Hoveyda-Grubbs 2nd generation catalyst did not participate in the ene-yne metathesis pathway. After careful examination of the structures of the all six Ru carbene metathesis catalysts (Figure 3.1) it seemed that the most electronically rich and the least accessible Ru center worked best for the ene-yne cross metathesis pathway.

3.2.4 Alkene Electronics

With these results we focused on alkene electronics. In our previous work with benzyl(ethynyl)dimethylsilane we performed tandem metatheses, Diels-Alder, and cross coupling chemistry.$^{57,58}$ In both cases we have used terminal silyl alkynes and similar catalysts (Table II). But the metathesis chemistry of 2-thienyldimethyl group behaved very differently than the dimethylbenzyl group (Table III). When we screened different types of alkenes we saw electron rich alkenes reacted much faster than electron poor alkenes. The reaction with $p$-vinylanisole was completed with 3 mol% catalyst within 2 h under reflux conditions, whereas $p$-chlorostyrene needed 6 mol% catalyst and was refluxed for 30 h.
Scheme 3.11 Screening of Different Alkenes in Ene-Yne Cross Metathesis

<table>
<thead>
<tr>
<th>R</th>
<th>catalyst loading (mol %)</th>
<th>temperature</th>
<th>time (disappearance of the alkyne peak in $^1$H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-OCH$_3$</td>
<td>7</td>
<td>RT</td>
<td>3 h</td>
</tr>
<tr>
<td>-OCH$_3$</td>
<td>3</td>
<td>reflux</td>
<td>2 h</td>
</tr>
<tr>
<td>-H</td>
<td>6</td>
<td>reflux</td>
<td>12 h</td>
</tr>
<tr>
<td>-Cl</td>
<td>6</td>
<td>reflux</td>
<td>30 h</td>
</tr>
</tbody>
</table>

Table III Role of Alkene Electronics in case of Ene-Yne Cross Metathesis

Giessert et al studied the effect of alkene electronics with Grubbs 2nd generation catalyst and their work revealed electron withdrawing groups on the phenyl ring facilitates ene-yne metathesis, and the reaction goes via arylidene first (Figure 3.2 right). We tried to isolate all three dienes but they all decomposed on the solid chromatography surface (silica, alumina).
3.2.5 Inhibitory Effect of Ethylene

Ethylene has been reported by researchers\textsuperscript{127,128} as a promoter of metathesis until recently Gregg et al reported an inhibitory effect of excess ethylene in ene-yne metathesis.\textsuperscript{129} When we attempted Scheme 3.12 in the presence of one atmosphere pressure of ethylene the ene-yne cross metatheses pathway shut down and this inhibitory effect of ethylene was more prominent in the case of electron poor alkenes than electron rich alkenes. For the \textit{p}-methoxystyrene in the presence of ethylene at RT after 3 h of reaction we observed only 47 \% conversion. After stirring it at RT for overnight under ethylene the progress of the reaction was 54 \%. For styrene in the presence of ethylene after 12 h of reflux we observed 30 \% product formation (by \textit{\textsuperscript{1}H NMR), with another 10 h reflux the
reaction was only 36% complete. In the case of 4-chlorostyrene under ethylene we did not see any product formation even after 30 h of reflux.

In the case of benzyl(ethynyl)dimethylsilane (3.49) we haven’t observed this inhibitory effect of ethylene, and rate dependence on the alkene electronics. We think there are two separate phenomena taking place. First, the sulfur lone pairs are coordinating with the Ru center (Scheme 3.13). This coordination inhibited the formation of the ruthenacyclobutane ring formation upon the addition of the alkene (Figure 3.2 left). Figure 3.2 also illustrated two possible catalytic cycles based on the structural features of the product. In our case the ene-yne cross metathesis product is similar to the one described on the left (Figure 3.2).
In 2013 the Diver group reported ‘Inhibitory Effect of Ethylene in Ene-Yne Cross Metathesis’. They described an equilibrium between the $\text{L}_n\text{Ru}=\text{CH}_2$ species and ethylene.
to form a simple ruthenacyclobutane (3.55), as a catalyst resting state (Scheme 3.13). Based on the regioselectivity of our ene-yne metathesis product we think it is going via the methylidene pathway and which happened to be the precursor of the resting state (3.55) in the catalytic cycle in the presence of ethylene.

Scheme 3.13 Formation of the Ruthenacyclobutane Resting State

3.2.6 Tandem Metathesis and Diels-Alder Reactions

Once we optimized reaction conditions we carried out one pot methatheses and DA reactions. All three dienes reacted in highly regio, and diastereoselective fashions. We did not observe any meta Diels-Alder adducts and in the case of 3.56 and 3.57 the observed syn:anti ratio was 27:1 (determined by 2D NMR spectroscopy). When we analyzed crude reaction mixtures of tandem metathesis and Diels-Alder by $^1$H NMR spectroscopy we did not observe any exo adduct formation for p-chlorostyrene and p-vinylanisole. Upon
purification on silica surface we exclusively obtained the *endo* adduct. Relative stereochemistry of the cycloadducts were determined by $^1$H NOE spectral data.

![Scheme 3.14 One Pot Metathesis and Diastereoselective Diels-Alder Reactions](image-url)
Figure 3.3 Superimposed NOESY and COSY spectra of Molecule 3.56

Figure 3.4 NOE Correlations (I) of the Cycloadduct 3.56
Figure 3.5 NOE Correlations (II) of the Cycloadduct 3.56

Figure 3.6 NOESY Spectrum of 3.56
In Figure 3.3 the through bond correlations were represented in red and the through space correlations were represented in blue. Hb showed correlations to Hd and Hf, which are in consistent with a cis (endo) geometry (Figure 3.4). The NOE correlations of the cyclohexene ring H(s) with the phenyl ring were represented in the Figure 3.5.

Figure 3.7 NOESY Spectrum of 3.57
The NOESY spectrum (Figure 3.7) of 3.57 showed correlation between Hg and Hf. (Figure 3.9). Hg also showed correlations with Hb, Hc and Hd. The Hg and Hd correlation was absent in the NOESY spectrum of 3.56.
3.2.7 Cross Coupling Reactions

We used the optimized reaction conditions from the Scheme 3.5 and tried the cross coupling chemistry at RT but we recovered only unreacted starting materials. Finally we

Scheme 3.15 Cross Coupling Chemistry of Diels-Alder Cycloadducts

We used the optimized reaction conditions from the Scheme 3.5 and tried the cross coupling chemistry at RT but we recovered only unreacted starting materials. Finally we
were able to cross couple all three cycloadducts after refluxing for 4 h in the presence Pd (II) catalyst and TBAF (2.4 eq) under Ar atmosphere.

3.3 Conclusion

We have successfully studied and evaluated the chemistry of safety catch silanol dienes. We found out in terms of transmetallation that 2-pyridyldimethylsilyl worked best followed by 2-thienyldimethylsilyl, and dimethylbenzylsilyl groups. Electron poor alkenes reacted slower than electron rich alkenes in the Ru catalyzed metatheses. The inhibitory effect of ethylene (generally known as a promoter) was more prominent in the case of electron poor alkenes.
3.4 Experimental Procedure and Characterization Data

2-(Buta-1,3-dien-2-yldimethylsilyl)pyridine (3.7):

100 mL flame dried two neck flask was equipped with a magnetic stir bar, addition funnel and reflux condenser under Ar. Mg turnings (1.00 g, 41.66 mmol) were added followed by anhydrous THF (5 mL), followed by 1,2-dibromoethane (266 µL, 3.1 mmol). Activation of Mg was confirmed by the evolution of ethane gas. Anhydrous ZnCl₂ (0.168 g, 1.23 mmol) was dissolved in THF (3 mL) and was added to the reaction mixture. After stirring for 5 minutes the color of the solution became milky white. Anhydrous THF (20 mL) was added and it was set to reflux under Ar. After refluxing for 30 minutes chloroprene in 50% xylenes (5.04 mL, 26 mmol) was loaded into the addition funnel. 1, 2-Dibromoethane (0.533 µL, 6.2 mmol) and THF (5 mL) were mixed with the chloroprene and it was slowly added over 30 min. Upon completion of the addition it was refluxed for 45 min. The color of the reaction mixture turned green and it was cooled to the room temperature. The reaction mixture was cannula transferred to a round bottom flask containing dimethyldichlorosilane (3.00 mL, 25 mmol) and diethyl ether (50 mL). It was stirred for 2 hours under Ar. In a separate flame dried one neck 250 mL flask containing a magnetic stir bar 2-bromopyridine (2.5 mL, 26 mmol) was added. Anhydrous diethyl ether (15 mL) was added to it and the flask was sealed with a septum. The entire mixture was kept at under positive pressure of Ar and cooled to -78 °C. At the same temperature n-butyllithium (17 ml of 1.6 M solution in hexanes, 27.3 mmol) was added and was stirred for 30 min. The color changed to orange. To this reaction mixture buta-1, za3-dien-2-
ylchlorodimethylsilane was cannula transferred at -78 °C. The solution was allowed to reach room temperature and it was stirred for 12 h. The resultant chemical mixture was diluted with diethyl ether (100 mL), washed with sat NaHCO₃ solution (20 mL) and 1 (M) HCl (20 mL). The organic layer was collected and dried over Na₂SO₄. It was concentrated by rotary evaporation and subsequently purified by column chromatography (neutral alumina stationary phase, 50:1 pentane: ethylacetate, Rₐ 0.5). Diene 3.7 was obtained as a colorless liquid (3.69 g, 19.5 mmol, 78%). ¹H NMR (300 MHz, Chloroform-d) δ 8.73 (ddd, J = 4.8, 1.7, 1.1 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.13 (ddd, J = 7.3, 4.9, 1.8 Hz, 1H), 6.44 (ddt, J = 17.8, 10.8, 0.8 Hz, 1H), 5.86 (dd, J = 3.0, 0.8 Hz, 1H), 5.52 (dd, J = 3.0, 0.7 Hz, 1H), 5.14 – 5.02 (m, 1H), 4.96 (dd, J = 10.7, 0.9 Hz, 1H), 0.44 (s, 6H); ¹³C NMR (75 MHz, Chloroform-d) δ 166.50, 150.21, 146.87, 141.07, 133.99, 130.79, 129.67, 122.79, 116.82, -2.6; HRMS calcd for C₁₁H₁₆NSi (M+H)⁺ 190.1052, found 190.1056.

**General procedure of one pot DA and cross coupling:**

Diene 3.7 (1 eq) was added to dienophile (1.1 eq) and heated in a round bottom flask with THF solvent for 24 h under Ar. Then 5 mol % of Pd (II) catalyst added with aryl halide (1 eq) and TBAF (1 eq). The reaction mixture was heated under Ar for 4 h at 60 °C. The reaction mixture was filtered through a silica gel pad and solvent (EtOAc) was removed under reduced pressure. The crude product was purified by silica gel column chromatography (dichloromethane mobile phase).
Methyl 2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-carboxylate (3.9) and methyl 2,3,4,5-tetrahydro-[1,1'-biphenyl]-3-carboxylate (3.10):

Following the general procedure Diene 3.7 (0.1 g, 0.53 mmol) and methyl vinyl ketone (0.48 g, 0.69 mmol), PdCl$_2$(PhCN)$_2$ (0.010 g, 0.026 mmol), iodobenzene (0.108 g, 0.53 mmol), and TBAF (0.53 mL of a 1 M soln in THF, 0.53 mmol) were reacted. The crude product was purified by silica gel flash column chromatography using pure DCM to yield 3.9 and 3.10 (R$_f$ 0.6, 0.073 g, 0.37 mmol, 69%), identical by $^1$H NMR comparison to previously reported material.$^{34}$ Ratio of para and meta regio-isomers were determined by $^1$H NMR (3.17:1).

2, 5-diphenyl-3a, 4, 7, 7a-tetrahydro-1H-isoindole-1, 3(2H)-dione (3.12):

Following the general procedure diene 3.7 (0.094 g, 0.5 mmol), N-phenylmaleimide (0.094 g, 0.55 mmol), PdCl$_2$(PhCN)$_2$ (0.010 g, 0.026 mmol), iodobenzene (0.102 g, 0.5 mmol), and TBAF (0.5 mL of a 1 M soln in THF, 0.5 mmol) were used. The crude product was purified using by silica gel flash column chromatography using pure DCM to yield 3.12 (R$_f$ 0.5, 0.112 g, 0.37 mmol, 74%), identical by $^1$H NMR comparison to previously reported material.$^{34}$
3a-methyl-2,6-diphenyl-3a,4,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (3.14) and 3a-methyl-2,5-diphenyl-3a,4,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (3.15):

Following the general procedure diene 3.7 (0.094 g, 0.5 mmol), 2 methyl-N-phenylmaleimide (0.103 g, 0.55 mmol), PdCl$_2$(PhCN)$_2$ (0.010 g, 0.026 mmol), iodobenzene (0.102 g, 0.5 mmol), and TBAF (0.5 mL, 1 M soln in THF, 0.5 mmol) in THF solution were used. The crude product was purified by silica gel flash column chromatography using pure DCM to yield 3.14 and 3.15 (R$_f$ 0.53, 0.095 g, 0.31 mmol, 62%), identical by $^1$H NMR comparison to previously reported material.$^{34}$ Ratio of para/meta product was found out to be 5:1 by $^1$H NMR studies.

2-(Buta-1, 3-dien-2-ylidimethylsilyl)thiophene (3.17):

A 250 mL two neck round bottom flask equipped with magnetic stir bar was flame dried and cooled under Ar. Mg (3.00 g, 123 mmol) was added to it and a reflux condenser and addition funnel were attached. The set up was kept under a positive pressure of Ar. THF (10 mL), and 1, 2-dibromoethane (0.8 mL, 9.28 mmol) was added the reaction mixture. Activation of Mg was confirmed by the evolution of ethane. ZnCl$_2$ (0.504 g, 3.7 mmol) was dissolved in THF (5 mL) and was added to the reaction mixture. After stirring for 5 min the color of the solution became milky white. THF (20 mL) was added and it was set to reflux under Ar. After refluxing for 30 min chloroprene in 50% xylenes (15.1 mL, 78 mmol) was loaded into the addition funnel. 1, 2-Dibromoethane (1.6 mL, 18.6 mmol) and THF (15 mL) were mixed with the chloroprene and it was slowly added over 30 min. Upon completion of the addition it was refluxed for 45 min. The color of the reaction mixture
turned green and it was cooled to room temperature. In a separate flame dried one neck 500 mL flask a magnetic stir bar was added. A rubber septum was attached. Dimethyldichlorosilane (9.1 mL, 75 mmol) was diluted with THF (50 mL) and were added through the septum. The halo diene Grignard reagent was cannula transferred under Ar and was stirred at room temperature for 2 h. The solution was then cooled to -78 °C and 2-lithiothiophene (75 ml of a 1M soln in THF/hexanes, 75 mmol) was added drop wise. The reaction mixture was stirred for 12 h. After overnight stirring it was diluted with diethyl ether (100 mL) and the reaction mixture was washed with 1M HCl (20 mL), saturated NaHCO₃ (20 mL) solution and brine (20 mL). The organic layer was collected, dried over sodium sulfate, and were concentrated using a rotary evaporator. The pure compound was isolated by vacuum distillation at 50 °C at 4 mm of Hg (12.2 g, 63 mmol, 84%).

¹H NMR (300 MHz, Chloroform-d) 1H NMR (300 MHz, Chloroform-d) δ 7.62 (dd, J = 4.6, 0.9 Hz, 1H), 7.31 (dd, J = 3.3, 1.0 Hz, 1H), 7.19 (dd, J = 4.6, 3.3 Hz, 1H), 6.49 (dd, J = 17.7, 10.8 Hz, 1H), 5.87 (d, J = 2.9 Hz, 1H), 5.53 (d, J = 3.0 Hz, 1H), 5.22 (d, J = 17.7 Hz, 1H), 5.06 (d, J = 10.7 Hz, 1H), 0.50 (s, 6H)

¹³C NMR (75 MHz, Chloroform-d) δ 147.38, 140.79, 137.57, 135.17, 130.99, 130.3, 128.12, 116.62, -1.07; LRMS calcd for C₁₀H₁₅SSi (M+H)+ 195.1, found 195.1
**General procedure for DA:**

Diene 3.17 (1.2 eq) was added to a pressure tube followed by anhydrous THF (4 mL). Dienophile (1 eq) was added to it and it was degassed for 4 min. The tube was sealed using a crimp cap. It was heated for the stipulated period of time.

1-(4-(dimethyl(thiophen-2-yl)silyl)cyclohex-3-en-1-yl)ethan-1-one (3.18) and 1-(3-(dimethyl(thiophen-2-yl)silyl)cyclohex-3-en-1-yl)ethan-1-one (3.19):

Diene 3.17 (1.111 g, 5.72 mmol) and methyl vinyl ketone (0.4 mL, 4.76 mmol) were reacted for 12 h at 66 °C. The reaction mixture was rotovaped and dried under vacuum. The crude product was purified by silica gel flash column chromatography using pure DCM as mobile phase (Rf 0.6). Compounds 3.18 and 3.19 were obtained as a colorless liquid (1.08 g, 4.09 mmol, 88% yield). Ratio of para: meta isomer was 3:1 (determined by $^1$H NMR)

Diagnostic $^1$H NMR peaks of the major isomer: $^1$H NMR (300 MHz, Chloroform-d) δ 7.59 (dd, $J = 4.6$, 0.8 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.18 (dd, $J = 4.6$, 3.3 Hz, 1H), 6.11 (m, 1H), 2.55 (m, 1H), 2.30 – 2.17 (m, 3H), 2.14 (d, $J = 6.7$ Hz, 3H), 2.12- 1.92 (m, 2H), 1.66 – 1.37 (m, 1H), 0.374 (s, 3H), 0.37 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl₃) δ 211.40, 137.81, 136.36, 135.96, 134.73, 130.73, 128.09, 47.07, 28.35, 27.92, 26.48, 24.96, -2.43, -2.54; HRMS calcd for C$_{14}$H$_{21}$OSSi (M+H)$^+$ 265.1082, found 265.1075
5-(dimethyl(thiophen-2-yl)silyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (3.20):

Diene 3.17 (0.116 g, 0.6 mmol) and N-phenylmaleimide (0.086 g, 0.5 mmol) were reacted using the general procedure. The crude product was purified using silica gel and pure DCM (Rf 0.37). A light yellow colored solid was obtained (0.151 g, 0.41 mmol, 82%)

$^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.60 (dd, $J = 4.6$, 0.9 Hz, 1H), 7.50 – 7.28 (m, 3H), 7.29 – 7.08 (m, 4H), 6.38 (ddd, $J = 6.2$, 3.5, 2.5 Hz, 1H), 3.28 – 3.19 (m, 2H), 2.91 – 2.71 (m, 2H), 2.39 – 2.22 (m, 2H), 0.38 (s, 6H); $^{13}$C NMR (75 MHz, Chloroform-d) $\delta$ 179.07, 178.67, 140.27, 138.69, 136.36, 135.09, 132.02, 131.05, 129.04, 128.47, 128.23, 126.34, 39.32, 39.21, 26.30, 25.07, -2.62; HRMS calcd for C$_{14}$H$_{21}$OSSi (M+Na)$^+$ 390.0960, found 390.0957

6-(dimethyl(thiophen-2-yl)silyl)-3a-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (3.21) and 5-(dimethyl(thiophen-2-yl)silyl)-3a-methyl-2-phenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (3.22):

Diene 3.17 (0.116g, 0.6 mmol) and 2 methyl-N-phenylmaleimide (0.094 g, 0.5 mmol) were used in a similar process described above. The crude was purified using column chromatography (silica gel, DCM, Rf 0.56). Compound 3.21 and 3.22 were obtained as 2:1 mixture. Major isomer $^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.53 (dd, $J = 4.6$, 0.9 Hz, 1H), 7.39 – 7.27 (m, 3H), 7.24 – 6.96 (m, 5H), 6.30 (dt, $J = 6.4$, 3.1 Hz, 1H), 2.90 – 2.59 (m, 3H), 2.23 (ddt, $J = 15.0$, 6.8, 2.5 Hz, 1H), 1.91 (ddt, $J = 15.1$, 3.7, 1.7 Hz, 1H), 1.36 (s,
$^{13}$C NMR (75 MHz, Chloroform-d) δ 181.90, 177.89, 140.58, 140.12, 139.29, 138.53, 136.49, 135.09, 132.10, 131.05, 129.02, 128.44, 128.24, 126.35, 47.27, 44.30, 33.85, 26.91, 24.77, -2.57, -2.67; HRMS calcd for C$_{21}$H$_{23}$NNaO$_2$SSi (M+Na)$^+$ 404.1116, found 404.1112

**General procedure for cross coupling of Diels Alder cycloadducts (3.23, 3.23 a, 3.12, 3.14, 3.15):**

In a 5 mL round bottom flask 1 equivalent of Diels-Alder adduct, 1.2 equivalents of iodobenzene, Pd(OAc)$_2$ catalyst (5 mol%), and THF (3 mL) was added. A rubber septum was attached and it was degassed for 5 min. 2 equivalents of TBAF were added and it was stirred at RT for 1-3 hr. The completion of the reaction was monitored with thin layer chromatography. Upon completion of the reaction it was washed with sat NaHCO$_3$ soln (15 mL) and extracted with ethyl acetate (10 mL). The organic layer was dried over Na$_2$SO$_4$ and concentrated with a rotary evaporator. The crude product was purified using silica gel and pure DCM.

1-(2,3,4,5-tetrahydro-[1,1'-biphenyl]-4-yl)ethan-1-one (3.23) and 1-(2,3,4,5-tetrahydro-[1,1'-biphenyl]-3-yl)ethan-1-one (3.23 a):

Mixture of cycloadducts 3.18 and 3.19 (0.05 g, 0.189 mmol), iodobenzene, (0.046 g, 0.226 mmol), Pd(OAc)$_2$ (0.002 g, 0.009 mmol) and TBAF (0.45 mL of a 1M soln in THF, 0.45 mmol) were reacted for an hour following the general procedure. Target compounds were
isolated as a colorless sticky liquid (0.034 g, 0.17 mmol, 91%), identical by $^1$H NMR comparison to previously reported material.$^{34}$

2,5-diphenyl-3a,4,7,7a-tetrahydro-1H-isooindole-1,3(2H)-dione (3.12):

Cycloadduct 3.20 (0.09 g, 0.25 mmol), iodobenzene, (0.06 g, 0.294 mmol), Pd(OAc)$_2$ (0.003 g, 0.013 mmol) and TBAF (0.49 mL of a 1 M soln in THF, 0.49 mmol) were reacted for 3 h following the general procedure. Target compound was isolated as a colorless solid (0.066 g, 0.22 mmol, 87%), identical by $^1$H NMR comparison to previously reported material.$^{34}$

3a-methyl-2,6-diphenyl-3a,4,7,7a-tetrahydro-1H-isooindole-1,3(2H)-dione (3.14) and 3a-methyl-2,5-diphenyl-3a,4,7,7a-tetrahydro-1H-isooindole-1,3(2H)-dione (3.15)

Mixture of cycloadducts 3.21 and 3.22 (0.115 g, 0.3 mmol, iodobenzene, (0.073 g, 0.36 mmol), Pd(OAc)$_2$ (0.004 g, 0.018 mmol) and TBAF (0.6 mL of a 1 M soln in THF, 0.6 mmol) were reacted for 3 h following the general procedure. Target compound was isolated as a colorless solid (0.084 g, 0.26 mmol, 88 %), identical by $^1$H NMR comparison to previously reported material.$^{34}$

2-(ethnyldimethylsilyl)pyridine (3.4):

To a 250 mL flame dried flask dimethyldichlorosilane (2.6 mL, 21 mmol) was added followed by anhydrous diethyl ether (15 mL). Ethynylmagnesiumbromide (44 mL of a
0.5M soln in THF, 22 mmol) was added and stirred at RT for 2 h. In a separate 50 mL round bottom flask 2-bromopyridine was added followed by THF (5 mL). nBuLi (14.5 mL of a 1.6 M soln in hexanes, 23.1 mmol) was added to the reaction mixture at – 78 °C and was stirred under Ar for 10 min. The 2-lithiopyridine soln was added to the previous flask and was stirred at RT for 10 h. The resultant reaction mixture was washed with sat NaHCO₃ (30 mL) soln. The organic layer was collected, dried over Na₂SO₄ and concentrated by rotary evaporation. The crude reaction mixture was distilled at 45 °C at 4 mm of Hg. Target compound was isolated with 90 % purity (2.43 g, 15.12 mmol)

Diagnostic ¹H NMR peak (300 MHz, Chloroform-d) δ 8.54 (d, J = 4.9 Hz, 1H), 7.52 (m, 2H), 7.39 (t, J = 8.4 Hz, 1H), 2.32 (s, 1H), 0.26 (s, 6H)

Ethynyldimethyl(thiophen-2-yl)silane (3.39): Alkyne 3.39 was prepared following published literature procedure.¹¹⁷

General procedure for ene-yne cross metathesis and tandem Diels-Alder reactions:

In 5 mL flame dried round bottom flask alkene (1 eq), alkyne (0.83 eq) and DCM (3 mL) were added. It was thoroughly degassed with Ar. 6 mol% Hoveyda-Grubbs 2nd generation catalyst was added. The reaction mixture was stirred under Ar for specified time and temperature. N-phenylmaleimide (0.9 eq) was then added and heated for 36 h. The reaction mixture was filtered through silica a plug using ice cold methanol to remove catalyst, and stilbene by product. The filtrate was condensed and residual methanol was removed by
using high vacuum. The crude product was purified by flash column chromatography on silica gel.

(3aR,4S,7aS)-6-(dimethyl(thiophen-2-yl)silyl)-2,4-diphenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindole (3.56):

Ethynyldimethyl(thiophen-2-yl)silane (0.28 g, 1.68 mmol), styrene (233 µL, 2 mmol), and catalyst (0.063 g, 0.1 mmol) were refluxed for 12 h under Ar. N-phenylmaleimide (0.262 g, 1.5 mmol) was added and refluxed for 40 h. After washing with cold methanol, the crude product was chromatographed on silica gel using 8:1 benzene and ethyl acetate ($R_f$ 0.5). The title compound was obtained as a white solid (0.456 g, 1.03 mmol, 69%).

$^1$H NMR (300 MHz, Chloroform-d) $\delta$ 7.63 (dd, $J = 4.6, 0.9$ Hz, 1H), 7.44 – 7.26 (m, 8H), 7.24 – 7.13 (m, 2H), 6.82 (d, $J = 7.8$ Hz, 2H), 6.67 (dd, $J = 4.8, 2.2$ Hz, 1H), 3.85 (t, $J = 5.9$ Hz, 1H), 3.47 (dd, $J = 9.1, 6.7$ Hz, 1H), 3.37 (td, $J = 8.7, 2.6$ Hz, 1H), 3.07 (dd, $J = 16.5, 2.6$ Hz, 1H), 2.51 (ddt, $J = 16.4, 8.4, 2.1$ Hz, 1H), 0.47 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 178.17, 176.11, 140.49, 139.61, 138.63, 136.28, 135.23, 131.75, 131.24, 129.12, 128.88, 128.86, 128.40, 128.32, 127.24, 126.29, 45.23, 42.29, 39.08, 25.65, -2.44, -2.60; HRMS calcd for C$_{26}$H$_{26}$NO$_2$SSi (M+H)$^+$ 444.1454, found 444.1449
(3aS,4S,7aR)-6-(dimethyl(thiophen-2-yl)silyl)-2,4-diphenyl-2,3,3a,4,7,7a-hexahydro-1H-isindole (3.57):

The remaining reaction mixture of 3.56 was chromatographed using 4:1 pentane ethyl acetate mixture ($R_f$ 0.42). Target compound was isolated as white solid (0.018 g, 0.04 mmol, 2.6 %)

$^1$H NMR (500 MHz, Chloroform-d) δ 7.63 (dt, $J$ = 4.8, 1.4 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.40 – 7.34 (m, 3H), 7.33 – 7.27 (m, 4H), 7.22 – 7.18 (m, 3H), 6.55 – 6.50 (m, 1H), 4.12 (dd, $J$ = 5.6, 3.6 Hz, 1H), 3.49 – 3.40 (m, 1H), 3.19 (dddd, $J$ = 9.7, 6.9, 4.7, 2.0 Hz, 1H), 2.64 – 2.47 (m, 2H), 0.45 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 178.57, 178.13, 141.22, 141.05, 139.86, 136.21, 135.19, 131.94, 131.24, 129.09, 128.86, 128.53, 128.35, 127.63, 126.86, 126.33, 46.60, 41.33, 39.09, 26.28, -2.63, -2.72; HRMS calcd for C$_{26}$H$_{26}$NO$_2$SSi (M+H)$^+$ 444.1454, found 444.1449

(3aR,4S,7aS)-6-(dimethyl(thiophen-2-yl)silyl)-4-(4-methoxyphenyl)-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isindole (3.60):

Ethynyldimethyl(thiophen-2-yl)silane (0.28 g, 1.68 mmol), $p$-vinyl-anisole (263 µL, 2 mmol), and catalyst (0.063g, 0.1 mmol) were refluxed under Ar for 3 h. $N$-phenylmaleimide (0.262 g, 1.5 mmol) was added and refluxed for 40 h. After washing with cold methanol the crude product was chromatographed on silica gel using 8:1 benzene and ethyl acetate ($R_f$ 0.48). The target compound was isolated as a light yellow solid (0.506 g, 1.07 mmol, 71%)
$^1$H NMR (300 MHz, Chloroform-d) δ 7.64 (dd, $J = 4.6$, 0.9 Hz, 1H), 7.39 – 7.28 (m, 4H), 7.21 (dd, $J = 4.6$, 3.3 Hz, 1H), 7.18 – 7.11 (m, 2H), 6.84 (m, 4H), 6.63 (dd, $J = 4.9$, 2.1 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.78 (s, 3H), 3.50 – 3.25 (m, 2H), 3.06 (dd, $J = 16.5$, 2.6 Hz, 1H), 2.52 (ddd, $J = 16.4$, 8.5, 2.2 Hz, 1H), 0.47 (s, 6H);

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 178.30, 176.36, 158.84, 140.83, 139.26, 135.24, 131.71, 131.25, 130.47, 130.15, 128.90, 128.34, 127.40, 126.30, 113.86, 77.01, 55.28, 45.30, 39.03, 25.50, -2.42, -2.59; HRMS calcd for C$_{27}$H$_{28}$NO$_3$SSi (M+H)$^+$ 474.1559, found 474.1557

(3aR,4S,7aS)-4-(4-chlorophenyl)-6-(dimethyl(thiophen-2-yl)silyl)-2-phenyl-3a,4,7,7a-tetrahydro-1H-isooindole-1,3(2H)-dione (3.61):

Ethynyl(dimethyl(thiophen-2-yl)silane (0.07 g, 0.42 mmol), p-chloro-styrene (60 µL, 0.5 mmol), and catalyst (0.016g, 0.025 mmol) were refluxed under Ar for 30 h. N-phenylmaleimide (0.066 g, 0.38 mmol) was added and refluxed for 40 h. After washing with cold methanol the crude product was chromatographed on silica gel using 8:1 benzene and ethyl acetate (R$_f$ 0.52). White colored solid was isolated (0.112g, 0.23 mmol, 61%).

$^1$H NMR (300 MHz, Chloroform-d) δ 7.64 (dd, $J = 4.6$, 0.9 Hz, 1H), 7.31 (m, 7H), 7.24 – 7.18 (m, 2H), 6.82 (dt, $J = 7.8$, 1.5 Hz, 2H), 6.67 (dd, $J = 4.7$, 2.1 Hz, 1H), 3.86 (t, $J = 5.7$ Hz, 1H), 3.48 (dd, $J = 9.1$, 6.7 Hz, 1H), 3.38 (td, $J = 8.8$, 2.6 Hz, 1H), 3.08 (dd, $J = 16.5$, 2.6 Hz, 1H), 2.52 (dd, $J = 16.5$, 8.5 Hz, 1H), 0.48 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 178.22, 176.16, 140.44, 139.59, 138.59, 136.24, 135.24, 131.64, 131.26, 129.11, 128.90,
128.41, 128.37, 128.34, 127.26, 126.05, 45.23, 42.26, 39.05, 25.64, -2.45, -2.61; HRMS calcd for C_{26}H_{24}ClNaO_{2}SSi (M+Na)^{+} 500.0883, found 500.0901

**General procedure for cross coupling of 3.56, 3.60, and 3.61:**

In a 5 mL round bottom flask 1 equivalent of Diels-Alder adduct, 1.2 equivalent of iodobenzene, Pd(OAc)$_2$ catalyst (5 mol%), and 3 mL of THF was added. A rubber septum was attached and it was degassed for 5 min. Then 2 equivalents of TBAF were added and it was stirred for at RT for 15 min. The septum was removed and a reflux condenser was attached. The reaction mixture was refluxed for 4 h. Upon completion of the reaction it was extracted with sat NaHCO$_3$ soln (15 mL) and ethyl acetate (10 mL). The organic layers were dried over Na$_2$SO$_4$ and concentrated via rotary evaporator. The crude product was purified using silica gel and pentane/ethyl acetate mobile phase.

**(3aR,4R,7aS)-2,4,6-triphenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (3.62):**

Cycloadduct **3.56** (0.1 g, 0.23 mmol), iodobenzene, (0.057 g, 0.28 mmol), Pd(OAc)$_2$ (0.003 g, 0.013 mmol) and TBAF (0.46 mL of 1 M soln in THF, 0.46 mmol) were reacted following the general procedure. Target compound was isolated as white a solid (0.065 g, 0.17 mmol, 72 %), identical by $^1$H NMR comparison to previously reported material.$^{57}$
(3aR,4R,7aS)-4-(4-methoxyphenyl)-2,6-diphenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (3.63):

Cycloadduct 3.60 (0.095 g, 0.2 mmol), iodobenzene, (0.049 g, 0.24 mmol), Pd(OAc)$_2$ (0.002 g, 0.01 mmol) and TBAF (0.4 mL of a 1 M soln in THF, 0.4 mmol) were reacted following the general procedure. Target compound was isolated as a white solid (0.064 g, 0.16 mmol, 78 %), identical by $^1$H NMR comparison to previously reported material.$^{57}$

(3aR,4R,7aS)-4-(4-chlorophenyl)-2,6-diphenyl-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione (3.64):

Cycloadduct 3.61 (0.106 g, 0.22 mmol), iodobenzene, (0.054 g, 0.26 mmol), Pd(OAc)$_2$ (0.003 g, 0.013 mmol) and TBAF (0.44 mL of a 1 M soln in THF, 0.44 mmol) were reacted following the general procedure. Target compound was isolated as white solid (0.058 g, 0.14 mmol, 65 %), identical by $^1$H NMR comparison to previously reported material.$^{57}$
CHAPTER 4: METAL MEDIATED CHEMISTRY

Previously we have reported methodologies for exo selective, enantioselective Diels-Alder reactions which were stoichiometric in cobalt. Our goal has been to determine a catalytic version of these reactions. We prepared Si$^{45,57,96}$ and B$^{34,37}$ containing main group element substituted dienes and reported their thermal cycloaddition chemistry. We attempted sequential TM, DA, OA, and RE on these substrates but we only observed cross coupled product.$^{45}$

Scheme 4.1 Proposed Methodology for Catalytic, Exo Selective, and Enantioselective Cycloadditions

We pursued chiral Lewis acid catalysis for enantioselective transformations, and experimental results showed Lewis acid catalysis$^{25}$ did not work well. Our aim is to generate chiral transition metal substituted dienes from main group element substituted dienes and chiral catalysts. The intermediate (4.3) will be long lived enough to participate in exo selective enantioselective Diels-Alder reactions, and the DA adduct will cross couple
with aryl halides to make substituted cyclohexenoids, and will regenerate chiral catalyst that will turn over the catalytic cycle.\textsuperscript{89}

### 4.1.1 Synthesis of Palladium Pincer Complexes

Previously we prepared silicon dienes hoping they would transmetallate to the Pd catalyst, and the transmetallated species would participate in DA reactions. But experimental results indicated cross coupling between the diene and aryl halides prior to the DA.\textsuperscript{45} After reviewing different chiral Pd catalysts we focused on Pd pincer complexes as the Pd\textsuperscript{1+2} in the pincer complexes is less susceptible to participate in OA and RE.\textsuperscript{86}

**Scheme 4.2 Synthesis of Palladium Phebox Pincer Complex**
We were also interested in synthesizing different chiral Pd pincer complexes, and our proposed enantioselective model (Chapter 1) depended on the bulk of the pendant alkyl groups attached to the chiral oxazoline carbon. We chose 4.7 as the starting material as it would allow us to synthesize a series of chiral bisoxazoline ligands by using different optically pure amino alcohols.

2-Bromo-\textit{m}-xylene was oxidized to 2-bromoisophthalic acid by KMnO\textsubscript{4} oxidation.\textsuperscript{131} The dicarboxylic acid was converted to the corresponding acid chloride by reacting with SOCl\textsubscript{2} following the work of Bugarin et al.\textsuperscript{89} The acid chloride was coupled with 2 equivalents of commercially available L-valinol to prepare the intermediate amino alcohol and which was successively converted to pincer ligands by MeSO\textsubscript{2}Cl and triethylamine promoted cyclization.\textsuperscript{89} The pincer ligand was reacted with Pd (0) complexes to prepare optically active Pd (II) phebox catalyst 4.11.

4.1.2 Attempts to Isolate Pd-dienyl Species

![Image of Scheme 4.3 Attempts to Isolate Transmetallated Species]

We first attempted to isolate the transmetallated metal dienyl complex by conventional Hiyama couplings, which require a fluoride source to enhance the nucleophilicity of the non-polar silicon carbon bond. In the presence of a nucleophilic
source the Si atom generates a penta coordinate species which is the key step for transmetallation. \(^{132}\) Wang et al reported \(^1\)H NMR studies of palladium dienyl complexes when they reacted boron dienes with Pd phebox complexes (Figure 4.1). \(^{37}\)

![Diagram of reaction](image)

**Figure 4.1 \(^1\)H NMR Spectra of Boron and Palladium Substituted Dienes** (Reproduced and Modified from the Reference 37)

They took boron dienes and added it to a NMR tube containing CD$_3$CN and Pd (0) catalyst. They did not attempt to remove oxygen and the solution was heated for 1.5 h at 50 °C. In the \(^1\)H NMR they observed a new sets of diene peaks (Figure 4.1). Then they screened a variety of Pd (II) sources including Pd phebox, and observed identical dienyl peaks. However, when they added dienophiles to the reaction mixture they did not observe any cycloadduct formation.
Scheme 4.4 Reaction of the Pd Pincer with Silicon Dienes

We took catechol exchanged (4.15) silicon diene and silatrane silicon diene (4.17)\textsuperscript{45} with the same equivalents of Pd phebox and treated with TBAF from RT to 60 °C (we observed decomposition of the Pd phebox beyond this temperature). But we did not observe any evidence of transmetallation from Si to Pd. At room temperature we recovered both unreacted starting materials, and after heating for 5 h we observed some decomposition of the Pd phebox (floating black nano particles) and unreacted dienes.

Scheme 4.5 Attempted Pd Phebox Assisted Cross Coupling of Silatrane Diene
We hypothesized that the Pd-dienyl complex might be very short lived and moved on to isolate the cross coupled product (Scheme 4.5). When we did not observe expected product 4.19 we changed our directions towards synthesis of silicon dienes containing nontransferable groups that are known to promote transmetallation.$^{64,133}$

![Scheme 4.5](image)

**Scheme 4.6 Attempted Transmetallation Using Boron Diene**

Previously our group reported transmetallation from boron to Pd metal complexes.$^{34,37}$ We took boron diene 4.20 and attempted transmetallation under different reaction conditions. We added 4.11 and 4.20 in a NMR tube containing CD$_3$OD. It was heated at 60 °C for 4 h. In the $^1$H NMR we did not observe any sign of transmetallation but observed unreacted starting materials. We then tried the same reaction in the presence
of 1 equivalent of base (4.21) after running the reaction at RT, and at higher temperature (60 °C). In both cases we recovered unreacted starting materials.

4.1.3 Fluoride Sources in Hiyama and Hiyama-Denmark Cross Couplings

Researchers have used different fluoride sources based on their reactivity, and the most commonly and widely used fluoride source in the Hiyama couplings is TBAF.\textsuperscript{134} We also screened different fluoride sources TBAT\textsuperscript{135}, TASF,\textsuperscript{132} TMAT\textsuperscript{136} and did not observe any reaction. In the case of TASF we observed decomposition of the starting materials.

<table>
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<th>Catalyst</th>
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<th>Fluoride Source</th>
<th>Solvent</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Pd-Phebox</td>
<td>Silatrane</td>
<td>TBAF</td>
<td>CD\textsubscript{3}CN</td>
<td>no reaction</td>
</tr>
<tr>
<td>Pd-Phebox</td>
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<td>TMAF</td>
<td>CD\textsubscript{3}OD</td>
<td>no reaction</td>
</tr>
<tr>
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<tr>
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<td>CDCl\textsubscript{3}</td>
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</tr>
<tr>
<td>Pd-Phebox</td>
<td>Silatrane</td>
<td>TBAT</td>
<td>CD\textsubscript{3}CN</td>
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<tr>
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<td>CD\textsubscript{3}CN</td>
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<tr>
<td>Pd-Phebox</td>
<td>Silatrane</td>
<td>TBAT</td>
<td>CD\textsubscript{3}CN</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Table IV Attempted Transmetallation Using Different Nucleophilic Activators
4.1.4 Reaction Chemistry of Metal Pincer Complexes with Silanol Substituted Dienes

We have prepared silicon dienes that would \textit{in situ} generate silanol substituted dienes. We tested silanol substituted dienes for the isolation of a Pd-dienyl complex. Dienes 4.25 and 4.30 were treated with TBAF in the presence of Pd pincer (4.11) but we did not observe any spectroscopic evidence of the metal dienyl complex formation in multiple attempts. Spectroscopic data revealed decomposition of the starting materials. We also tried to trap the Diels-Alder adduct by cross coupling it with aryl halides. But we did not see any cross coupled product. The TBAF addition also led to the maleimide ring opening. However, we were able to isolate thermal Diels-Alder cycloadducts and consecutive cross coupled products (\textit{Chapter Three}). These observations directed us to the conclusion that the Diels-Alder adducts of these dienes are stable in an excess TBAF media but the same dienophile does not survive the TBAF medium prior to the cycloaddition. We screened \textit{p}-benzoquinone as another dienophile, and obtained a complex reaction mixture with evidence ($^1$H NMR) of cycloaddition between the diene and dienophile.
Scheme 4.7 Pd Pincer Catalyzed Chemistry of 2-Pyridyl Substituted Dienes

Scheme 4.8 Palladium Pincer Catalyzed Reaction Chemistry of 2-Thienyl Substituted Diene
There are only very few reports of the Pd pincer catalyzed Hiyama coupling in the literature.\textsuperscript{137} In 2008 Arriortua \textit{et al} reported Pd pincer cross coupling between trimethoxyphenylsilane with aryl bromides using NaOH (140 °C, 3 h) or TBAF (80 °C, 4 h) as nucleophilic activators\textsuperscript{138}. Presumably these reactions were not catalyzed by the Pd pincer but by the Pd nano particles.\textsuperscript{87} In 2011 Domniguez \textit{et al} reported that there was no cross coupling reaction between phenylalkoxy silanes and aryl bromides in the presence of Pd pincer catalyst and TBAF in THF at RT for 14 h.\textsuperscript{137}

\subsection*{4.1.5 Attempted Kumada Couplings}

We hypothesized that to make the transmetallation happen we might need stronger nucleophiles so our next attempt was Pd catalyzed Kumada couplings. In 1972 the groups of Robert Corriu,\textsuperscript{139} and Makoto Kumada\textsuperscript{140} independently reported the Ni catalyzed cross coupling of Grignard reagents. In all three cases of the Pd catalyzed Kumada couplings we observed nucleophilic attack on the imine carbon of the Pd-phebox (evident from the up field shift of the methine $^1$H) but we did not succeed to isolate the target compounds.
While exploring transmetallation pathways we were also simultaneously attempting oxidative addition pathways too. Benyunes et al reported syntheses of σ bonded Pt and Pd complexes from the chloroprene and allene complexes respectively.\textsuperscript{141} We first
attempted oxidative addition on chloroprene with Pd (0) complexes (Scheme 4.10), but we did not see the expected σ bonded complex and recovered unreacted chloroprene.

![Scheme 4.10 Attemped Preparation of Transition Metal Substituted Dienes by Oxidative Additions](image)

Among organometallic chemists Pd (II) is often preferred over Pd (0) due to the ease of handling of the former. There are reports in the literature yielding better results by reducing Pd (II) to Pd (0) and using it in situ rather than using Pd (0) sources. Following the preparation scheme of 4.45 we attempted the synthesis of molecule 4.46 (Scheme 4.11) but we only recovered the unreacted halodiene.
Scheme 4.11 In situ Generation of Pt (0) from Pt (II) Species

In 1977 Roffia et al reported the preparation of triphenylphosphine zerovalent complexes of Pd using alkaline alkoxides as reducing agents. They also reported olefin and benzoquinone adducts of these complexes. We attempted base catalyzed reduction of the Pd (II) to the Pd (0) (Scheme 4.12) followed by the oxidative addition of chloroprene, and trapping the former by Diels Alder additions. Analysis of the reaction mixture revealed the oxidative addition did not take place, and we isolated the chloroprene benzoquinone cycloadduct.
Syntheses of compounds 4.52, and 4.55 were known. Both protocols involved reduction of Ni (II) to Ni (0) and oxidative addition of aryl halides. We reduced Ni (II) to Ni (0) and attempted the synthesis of molecule 4.56. The spectral analysis of the reaction mixture confirmed unreacted chloroprene.

We found two United States patents related to the oxidative addition products of commercially available Ni (0) species. In the US patent 4,101,566 the inventor mentioned possible interference from the polymerization inhibitors (phenothiazine 0.1%, xylenes 49.5%) present in the commercially available chloroprene. We also learned about the super sensitivity of these complexes towards oxygen, and moisture. The detailed experimental procedure for the preparation of these compounds revealed, that some of these compounds
are stable at room temperature but the preparative oxidative addition step often required low temperatures (0 °C to –72 °C), and prolonged time (up to 14 h), which is very different than Pd catalyzed oxidative additions as they often require higher temperatures and shorter reaction times.

4.3.1 Nickamine Catalyzed Chemistry of Haloprene

In 2013 we came across an article from the group of Dr. Xile Hu at the École Polytechnique Fédérale de Lausanne (EPFL) in Switzerland where they have reported mechanistic studies of Ni catalyzed sp³-sp³ Kumada cross couplings of unactivated alkyl halides. They reported formation of σ bonded Ni-alkyl complexes as important reaction intermediates necessary for the cross couplings. 152 We took molecule 4.57 (referred to in the literature as Nickamine 153) and reacted it with 4.31 but we could not isolate 4.61 (Scheme 4.15) and recovered unreacted 4.57.
4.3.2 Reaction Chemistry of Chiral Nickel Complexes

In 1991 the research group of Dr. Nishiyama first reported the synthesis of pybox and its Rh complex. Later in 1997 they reported syntheses of chiral phebox following a four step sequence similar to pybox ligands.

Phebox and pybox ligands are isoelectronic and isosteric. The Fu group reported Ni-pybox catalyzed asymmetric Negishi cross couplings. We prepared organozinc reagent 4.64 from the chloroprene and reacted it in situ with the
dienophile, Ni catalyst, and chiral pybox ligands. To slow down the cross coupling process and to enhance DA reaction we added the alkyl halide over a period of 16 h. However the $^1$H NMR data indicated decomposition of the starting materials.

Scheme 4.16 Ni Catalyzed Negishi Coupling

We also attempted Ni catalyzed Hiyama cross couplings (Scheme 4.17) with silanol substituted dienes but we did not observe any evidence of transmetallation followed by Diels-Alder reaction. We also noted that a majority of the Ni catalyzed enantioselective catalytic transformations were carried out at low temperatures (from -20 °C to –72 °C). Considering the poor feasibility of Diels-Alder cycloadditions at these extreme low temperatures we moved on to Ni catalyzed enantioselective transformations that were known to take place at room temperature.
Scheme 4.17 Ni/Pybox Catalyzed Hiyama Couplings
In 2008 the Fu group reported Ni catalyzed stereo convergent cross couplings of racemic α-bromoesters with trimethoxysilyl benzene in the presence of 2 equivalents of TBAT at RT.\textsuperscript{159} We hypothesized the excess TBAT was converting the trimethoxysilyl group to the corresponding silanols, which were the active species for the cross coupling. As the trimethoxynylchlorosilane is not commercially available, and we had previously prepared 2-triethoxysilyl-1, 3-butadienes by the Grignard chemistry we attempted Scheme 4.18, but we did not see the expected results. We synthesized 4.71 by reacting ethynylmagnesiumbromide with triethoxynylchlorosilane and after fractional distillation of the crude product we obtained 89% pure (determined by \textsuperscript{1}H NMR) target molecule (4.71). When we tried the metathesis reaction with triethoxy(ethynyl)silane we only observed the
olefin metathesis product. Triethoxychlorosilane is an extremely air and moisture sensitive compound, and probably the hydrolyzed impurity shut down the ene-yne cross metathesis pathway.

### 4.4 Future Work

Our goal has been development of methodologies for catalytic, *exo* selective, enantioselective Diels Alder reactions. Previously we demonstrated stoichiometric enantioselective, *exo* selective Diels-Alder reactions of cobalt substituted diene. When we attempted Lewis acid catalyzed pathway the enantioselectivity was poor. To design a catalytic pathway based on transmetallation we needed sequential transmetallation, followed by Diels-Alder, followed by oxidative addition and reductive elimination. However, experimental results demonstrated cross coupling was taking place prior to Diels-Alder. To tackle this problem we tried Pd pincer complexes but they didn’t cross couple at all. Second, Pd catalyzed reactions often required high basic conditions which led to the decomposition of the starting materials. Recently we have started investigating the Ni catalyzed enantioselective cross coupling chemistry as the majority of these reactions were performed under milder conditions. In the future we will focus on Ni catalyzed cross coupling chemistry that can take place at RT,\textsuperscript{160} or may require elevated temperatures.\textsuperscript{161}

The other possible alternative to the transmetallation pathway is the oxidative addition of transition metal complexes to the carbon-halogen bond of the haloprene. When
we attempted oxidative addition on the haloprene no reaction took place presumably due to the impurities (to prevent polymerization) present in the commercially available haloprene. We would like to synthesize different haloprenes in our laboratory, and try the oxidative addition pathway.

C-H functionalization is emerging as one of the pioneering fields in organic transformations. At present in our laboratory we are synthesizing transition metal (Ru, Rh) substituted dienes by directed C-H activation, and optimizing the thermal cycloaddition chemistry. We hope in the near future we can establish a methodology for catalytic, exo selective, enantioselective Diels-Alder reactions via directed C-H activation.
4.5 Experimental Procedure and Characterization Data

2-Bromoisophthalic acid (4.8):

\( \text{tBu-OH (58 mL) and DI water (58 mL) were added to a 500 mL two neck round bottom flask. 2-Bromometaxylene (13.8 g, 75.5 mmol) of was added to it. Potassium permanganate (30 g, 190 mmol) was added to it and it was set to heat at 70 °C for 2 h. After heating for 2 h it was allowed to cool to RT, and a second addition of potassium permanganate (30 g, 190 mmol) was done (total amount of 60 g, 380 mmol). It was heated at 70 °C with vigorous stirring for another 1.5 h. The hot reaction mixture was filtered through a celite pad and was washed with 3 X 200 mL (total 600 mL) of boiling water. The filtrate was removed under reduced pressure, and DI water (70 mL) was added to the solid. Then concentrated HCl was drop wise added keeping the reaction mixture on ice bath till the pH reached 2 (before the addition of the acid the pH of the reaction mixture was 12), plenty of white solid appeared. The slurry was extracted with 3 X 120 mL of ethyl acetate and dried over sodium sulfate. The organic layer was concentrated under reduced pressure and white colored solid was obtained (13.2 g, 54 mmol, 72%). The \(^1\)H NMR was recorded in CDCl\(_3\) and compared with the previously reported result.}^{89}\)

2-Bromoisophthaloyl dichloride (4.9):

In a 100 mL two neck round bottom flask benzene (52 mL) and 2-bromoisophthalic acid (1.261 g, 5.15 mmol) were added, and it was set to stir for 15 min. Then the suspension was placed in an ice bath, and one drop of DMF and of thionyl chloride (11.6 mL, 159
mmol) were added. The reaction mixture (suspension) was set to reflux for 4 h, and the reaction mixture became yellow colored clear solution. Then reflux condenser was removed, and the excess thionyl chloride and benzene was carefully distilled leaving approximately 5 mL of solvent. It was placed in the refrigerator for 2 h. An off white colored solid appeared. The solid was washed with pet ether and was air dried (0.857 g, 3.03 mmol, 59 %). ¹H NMR was recorded in d₆-DMSO and found identical to the previously reported result.⁸⁹

(4S, 4’S)-2, 2’-(2-Bromo-1, 3-phenylene)bis(4-isopropyl-4,5-dihydrooxazole) (4.10):

In a 150 mL round bottom flask containing DCM (17 mL), commercially available (from Acros Organics) L-valinol (0.764 g, 7.4 mmol) was added. The round bottom flask was placed on an ice bath, and triethylamine (6.86 mL, 50.85 mmol) was added to it. A solution of 4.8 (0.95 g, 3.37 mmol in DCM (17 mL)) was loaded to an addition funnel. It was added to the valinol-triethylamine reaction mixture at 0 °C for a period of 1 h. Then the ice bath was removed and it was stirred at RT for another 6 h. The reaction was monitored by TLC on silica gel stationary phase (mobile phase 10:1 mixture of ethyl acetate and methanol, Rf 0.3). Again the ice bath was replaced and methane sulfonyl chloride (0.6 mL, 7.75 mmol) was drop wise added. Upon the addition of methane sulfonyl chloride the color of the solution changed from white to light yellow. It was allowed to stir at RT for another 10 h. 1 (N) K₂CO₃ solution (40 mL) was added drop wise to the reaction mixture at 0 °C. The organic layer was extracted with 4 X 100 mL of ethyl acetate. The organic layers were dried over sodium sulfate and the solvent was removed under reduced pressure. The light yellow colored viscous crude was purified by silica gel column chromatography using ethyl
acetate as the mobile phase, $R_f 0.62 \ (0.491 \text{ g, 1.35 mmol, 40 \%}).$ The $^1\text{H NMR}$ was recorded and compared with the previously reported result.$^{89}$

**Palladium pincer (4.11):**

Molecule 4.11 was prepared from 4.10 following a previously published protocol.$^{89}$

**Attempted preparation of 4.16 from 4.15:**

5 mL of anhydrous THF, 4.11 (0.05 g, 0.103 mmol), and 4.15 (0.039 g, 0.103 mmol) were added to a 10 mL round bottom flask. It was thoroughly degassed for 5 min and TBAF (0.12 mL of 1 M soln in THF, 0.103 mmol) was added under Ar. The color changed to red and after 15 min it turned to yellow. The reaction mixture was stirred for 6 h and was extracted with 6 mL of ethyl acetate and 6 mL of water. The organic layer was dried and concentrated under reduce pressure. $^1\text{H NMR}$ indicated that no reaction had taken place.

**Attempted synthesis of 4.16 from 4.17:**

Following the procedure described above same equivalents (0.103 mmol) of 4.15, 4.17 and TBAF were reacted. $^1\text{H NMR}$ confirmed the presence of the unreacted starting materials.
Attempted preparation of 4.19:

In a 10 mL round bottom flask 5 mL of dry THF, 4-iodoacetopheneone (0.098 g, 0.4 mmol), 4.17 (.128 g, 0.6 mmol), 4.11 (0.01 g, 0.02 mmol) were added. It was degassed for 5 min, and TBAF (0.1 mL of 1 soln in THF, 0.1 mml) was added. It was stirred for 6 h at RT, and the $^1$H NMR of the reaction mixture indicated unreacted starting materials.

Attempted preparation of 4.16 from 4.17:

In a NMR tube containing d$_6$-DMSO, 4.11 (0.01 g, 0.02 mmol) and 4.20 (0.005 g, 0.02 mmol) were added. $^1$H NMR was recorded at RT, and after heating for 2 h at 60 °C. Spectroscopic data revealed that no reaction took place. In a separate NMR tube containing d$_6$-DMSO above mentioned quantities of all three reagents, and sodium t-butoxide (0.004g, 0.04 mmol) were added. $^1$H NMR spectra were recorded at RT and after heating for 6 h at 60 °C. $^1$H NMR indicated that no reaction took place.

Attempted synthesis of 4.16 from 4.25 and 4.30:

In a NMR tube containing d$_8$-THF, 4.11 (0.01 g, 0.02 mmol) and 4.25 (0.004 g, 0.02 mmol) and TBAF (0.02 mL of 1 M soln in THF, 0.02 mmol) were added. $^1$H NMR could not confirm the formation of 4.16. Similarly 4.30 (0.004 g, 002 mol) was reacted in d$_8$-THF with 4.11 (0.01 g, 0.02 mmol) and TBAF (0.02 mL of 1 M soln in THF, 0.02 mmol). $^1$H NMR could not indicate the formation of 4.16.
**Attempted preparation of 4.29 from 4.25 and 4.30:**

In a 10 mL flame dried flask 5 mL dry THF was added. Then 4.11 (0.05 g, 0.1 mmol), 4.25 (0.02 g, 0.11 mmol), 4.26 (0.019 g, 0.11 mmol), 4.28 (0.046 g, 0.11 mmol) and TBAF (0.1 mL of 1 M soln in THF, 0.1 mmol) were added. The reaction mixture was stirred for 4 h at RT under Ar. \(^1\)\text{H} NMR of the crude indicated decomposition of \(N\)-phenylmaleimide 4.30 (0.021 g, 0.11 mmol) was reacted with 4.11 (0.05 g, 0.1 mmol), 4.26 (0.019 g, 0.11 mmol), 4.28 (0.046 g, 0.11 mmol) and TBAF (0.1 mL of 1 M soln in THF, 0.1 mmol) for 3 h at RT under Ar. \(^1\)\text{H} NMR of the crude product indicated decomposition of 4.26.

**Attempted Kumada couplings to isolate 4.16, 4.33, and 4.35:**

In a 10 mL flame dried flask equipped with a magnetic stir bar dry THF (5 mL) was added. 4.11 (0.05 g, 0.1 mmol) was added and a septum was attached. It was kept under Ar. The Grignard reagent 4.32 (0.15 mL of 0.7 M soln in THF, 0.1 mmol) was added using a syringe. From light yellow the color changed to dark brown. It was stirred for 1 h. Then the reaction mixture wax extracted with 10 mL of diethyl ether and 7 mL of water. The organic layer was dried and concentrated. \(^1\)\text{H} NMR of the crude indicated nucleophilic addition to the imine carbon.

Similarly 4.32 and 4.34 were reacted with 4.11. In both cases spectroscopic evidence indication of the nucleophilic addition to the imine carbon.
**Attempted preparation of 4.42:**

Anhydrous CHCl$_3$ (10 mL) was added to a 25 mL flame dried flask followed by chloroprene (0.05 mL of 1:1 mixture in xylenes, 0.26 mmol). It was degassed for 15 min. Pd (PPh$_3$)$_4$ (0.1 g, 0.087 mmol) was added to the reaction mixture. Upon addition of yellow colored Pd (0) to the reaction mixture the colorless solution turned dark red. It was stirred for 12 h under Ar. The reaction mixture was rotovaped and was redissolved in toluene and filtered through a celite pad. The filtrate was concentrated under reduced pressure and the $^1$H NMR of the crude indicated unreacted chloroprene. We also attempted the above reaction under reflux conditions but we did not observe any product formation.

**Attempted synthesis of 4.45:**

In a 25 mL flame dried flask equipped with a magnetic stir bar dry DCM (5 mL) and anhydrous ethanol (5 mL) were added. It was degassed for 3 min. Then choroprene (0.15 mL 50:50 mixture in xylenes, 1.3 mmol) was added and the reaction mixture was degassed for 3 min. White colored 4.43 (0.06 g, 0.2 mmol) was added and it was degassed for 5 min. Upon the addition of sodium borohydride (0.038 g, 1 mmol) the color of the reaction mixture changed to yellow. It was stirred overnight under Ar. The reaction mixture was washed and extracted with water and ethyl acetate. The organic layer was dried and concentrated. $^1$H NMR showed unreacted chloroprene.
**Attempted preparation of 4.61:**

In a 2 mL flame dried flask dry THF (1 mL) was added followed by commercially available (obtained from the Sigma-Aldrich) 4.59 (0.05g, 0.164 mmol). A septum was attached and it was kept under Ar. The reaction was cooled with a dry ice – acetone bath and 4.31 (0.382 mL, 0.164 mmol) was added drop wise to the reaction mixture at -78 °C. It was stirred for 12 h at RT. The color changed from dark brown to red. A drop of the reacton mixture was redissolved in C₆D₆ and ¹H NMR confirmed unreacted 4.59. Another equivalent of 4.31 was added and it was stirred for 10 h under Ar. ¹H NMR indicated unreacted nickel complex.

**Attempted preparation of 4.67 by Negishi Coupling:**

Zn dust (0.54 g, 8.2 mmol) was added to a 100 ml two neck flame dried flask. A reflux condenser and an addition funnel were attached. To the reaction mixture anhydrous THF (5 mL) and dibromoethane (0.05 mL, 0.5 mmol) were added, and it was stirred for 5 min under Ar. Then anhydrous ZnCl₂ (0.033 g, 0.24 mmol) was added and it was stirred for another 5 min. THF (20 mL) was added and reaction mixture was set to reflux. Chloroprene (1mL, 5.2 mmol), dibromoethane (0.05 mL, 0.5 mmol), and THF (15 mL) were loaded into the addition funnel. The chloroprene mixture was added drop wise over a period of 30 min. Upon completion of the addition the reaction mixture was gently refluxed for 45 min. In a separate 250 mL flask dry THF (30 mL), N-phenylmaleimide (0.899, 5.2 mmol), NiCl₂·glyme (0.011g, 0.052 mmol), commercially available (obtained from the TCI America) 2,6-Bis[(4S)-(−)-isopropyl-2-oxazolin-2-yl]pyridine (0.2 g, 0.68 mmol) were
added and it was cooled to 0 °C. The Zn diene solution was cannula transferred to the 250 mL round bottom flask. Cyclohexylbromide (0.64 mL, 5.2 mmol) was added to the reaction mixture at 0°C over a period of 16 h using a syringe pump. The reaction mixture was washed with 50 mL of saturated NH₄Cl solution and was extracted with ethyl acetate (3 X 100 mL). ¹H NMR indicated decomposition of the N-phenylmaleimide.

**Attempted preparation of 4.67 by Ni Catalyzed Hiyama Coupling:**

In a 100 mL flame dried flask dry dioxane (20 mL), 4.69 (0.14 g, 0.65 mmol), cyclohexylbromide (0.06 mL, 0.5 mmol), NiCl₂·glyme (0.011 g, 0.05 mmol), chiral amine (0.014 g, 0.06 mmol), N-phenylmaleimide (0.086 g, 0.5 mmol) were added. The reaction mixture was degassed using freeze, pump and thaw cycles. TBAT (0.539 g, 1 mmol) was added to a separate 50 mL flame dried flask containing dry dioxane (15 mL). This was also degassed using freeze, pump and thaw cycles. The TBAT solution was added the previous reaction mixture using a syringe. Upon the addition of TBAT the color of the solution changed from white to light green to deep red. The reaction mixture was set to stir at RT for 20 h. Acetone (20 mL) and 0.5 N HCl (20 mL) were added to the reaction mixture and it was stirred for 2 h. The resultant mixture was extracted with diethyl ether and water. The organic layers were collected and dried over sodium sulfate. It was concentrated under reduced pressure. ¹H NMR did not confirm formation of any cycloaddition products.
Triethoxy(ethynyl)silane (4.71):

Ethynylmagnesiumbromide (50 mL of 0.5 M soln in THF, 25 mmol) was added to a 100 mL round bottom flask containing 10 mL of anhydrous THF. The solution was cooled to 0 °C. Triethoxychlorosilane (4.9 mL, 25 mmol) was added to the Grignard reagent. The ice bath was removed after the addition was complete, and it was allowed to stir at RT for 12 h under Ar. The reaction mixture was washed with 20 mL of 0.5 N HCl and 3 X 50 mL of diethyl ether. The organic layers were collected and dried over sodium sulfate and concentrated under reduced pressure. The crude reaction mixture was distilled at 47 °C and 6 mm of Hg. The target compound was isolated as a colorless liquid (3.66 g (89% purity by $^1$H NMR), 17.35 mmol, 69%)

Diagnostic $^1$H NMR (300 MHz, Chloroform-$d$) δ 4.11 (q, $J = 7.1$ Hz, 6H), 2.37 (s, 1H), 1.25 (t, $J = 6.5$ Hz, 9H).
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Ramakrishna Mission Residential College, Narendrapur,
University of Calcutta, India
B.Sc. (Chem Hons) 2004

GRADUATE STUDY:
Indian Institute of Technology, Kharagpur, India
M.Sc. in Chemistry, 2006
University of Miami, Florida
M.S. in Chemistry, 2008
Wake Forest University, Winston-Salem, North Carolina
Ph.D., Organic Chemistry 2015

SCHOLASTIC AND PROFESSIONAL EXPERIENCE:

PhD Candidate, Department of Chemistry, Wake Forest University, August 2009 to August 2015.


Predoctoral Intern, Bascom Palmer Eye Institute, Miami, September 2008 to May 2009.

Teaching Assistant, University of Miami, Coral Gables, August 2006 to May 2008.

AWARDS AND RECOGNITION:

Invited by the ACS –Central North Carolina to be the primary speaker for their annual meeting at the North Carolina A&T University, 2014

Graduate student travel award, ACS Central North Carolina, 2014

Andrews travel award, Mississippi State University, 2014

Graduate student travel award, Wake Forest University, 2013

Award of academic merit, University of Miami, 2008
PROFESSIONAL SOCIETIES:

American Chemical Society (ACS), Division of Organic Chemistry, Division of Polymer Chemistry, Division of Polymeric Materials: Science and Engineering Association of University Technology Managers (AUTM)

PUBLICATIONS:


PRESENTATIONS:

Choudhury, P. P.; Welker, M. E., Preparation and reaction chemistry of novel silanol and in situ silanol dienes. Oral presentation in the ACS Southeastern regional meeting in Nashville, TN. October, 2014

Choudhury, P. P.; Junker, C. S.; Pidaparthi, R. R.; Welker, M. E., Syntheses of 2-Silyl-1,3-Dienes. Poster presentation in the ACS Southeastern regional meeting in Atlanta, GA. November, 2013

Choudhury, P. P.; Welker, M. E., Synthesis of 2-siloxycyclopentene containing 1,3 dienes and their Diels-Alder/cross-coupling reactions. Poster presentation in the ACS Southeastern regional meeting in Raleigh, NC. November, 2012