REGIOSELECTIVE RHODIUM-CATALYZED ALKYNE HYDROTHIOLATION
WITH ALKANE THIOLS: SUBSTRATE SCOPE AND MECHANISTIC
INVESTIGATIONS

by

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Abstract

The optimization and substrate scope of ClRh(PPh₃)₃-catalyzed alkyne hydrothiolation with alkane thiols producing E-linear vinyl sulfides is presented. The reactions generally proceed in good yields with good selectivities for a variety of alkane thiols and alkynes. Bulky aliphatic alkynes result in the best selectivity, while aryl alkynes with para-substituted electron donating groups give the best yields. The presence of coordinating functional groups in either the substrate or solvent negatively affects the reaction both in yield and selectivity. Deuterium-labeling studies indicate that the reaction proceeds via thiol oxidative addition, migratory alkyne insertion into the Rh-H bond, followed by reductive elimination.

Investigations into the mechanism of Tp*Rh(PPh₃)₂-catalyzed alkyne hydrothiolation are discussed. Five mechanisms are identified as being the most likely for this process; experiments were designed to support or refute each of these possibilities. Two mechanisms are definitively dismissed and another is dismissed as highly unlikely. The results cannot distinguish between the remaining two. The product distribution of hydrothiolation is analyzed and compared to other precatalysts. Stoichiometric reactivity of Tp*Rh(PPh₃)₂ with benzyl thiol is presented. Two new complexes, proposed to be Tp*Rh(PPh₃)₂(HSBn) and Tp*Rh(H)(SBn)(PPh₃), are generated. Presumed Tp*Rh(H)(SBn)(PPh₃), prepared in situ, does not catalyze alkyne hydrothiolation. Kinetic analysis was complicated by reaction inhibition at high thiol concentrations and competing side-reactions at high alkyne concentrations. Kinetic isotope effect experiments indicate that the alkyne is not involved in the rate-determining step; however, differences in the reactivity of several para-substituted phenyl acetylenes suggest that the rate-determining step is influenced by alkyne electronics. Overall, the reaction appears to obey the following rate law under normal catalytic reaction conditions

\[ \text{rate} = k[Tp*Rh(PPh₃)₂][\text{thiol}]^{1/2}[\text{alkyne}]^0. \]

The reaction is hypothesized to proceed by thiol oxidative addition, migratory alkyne insertion into the Rh-S bond, followed by reductive elimination.
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<td>κ</td>
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Chapter 1: Introduction

1.1 Importance of Sulfur Containing Molecules

Sulfur is ubiquitous in nature and can be found in natural products, bioactive molecules and agrochemicals. Sulfur can also play an important role as an auxiliary functionality or as a synthetic intermediate. In particular, elemental sulfur is one of the oldest known pesticides; thus, it is not surprising that many organic agrochemicals contain sulfur, some examples of which are shown in Figure 1.1. Malathion is an organophosphate insecticide used extensively in agricultural and horticultural applications. It is also used in regional programs to control mosquitoes. The use of malathion by ground application and aerial spraying is generally the preferred method of eradicating adult mosquitoes associated with West Nile Virus because of its relatively low toxicity to humans, other mammals, and birds compared with other organophosphate insecticides.

![Chemical structures]

Thiocarbamate (herbicide)  Thiodicarb (insecticide, molluscicide)  Malathion (insecticide)

Figure 1.1: S-containing agrochemicals.

Many natural products and pharmaceuticals also contain sulfur. A few representative examples are shown in Figure 1.2. Griseoviridin is a streptogramin antibiotic, characterized by a cyclic structure encompassing a vinyl sulfide moiety. Several synthetic approaches to this molecule have been reported,$^{1-6}$ including a total synthesis.$^7$
Another example of a sulfur-containing pharmaceutical is K11777 – an irreversible cysteine protease inhibitor, currently in preclinical development as a potential drug candidate for Chagas disease.\(^8\) Chagas disease is the leading cause of heart disease in Latin America, caused by a protozoan parasite \textit{Trypanosoma cruzi}. Inhibition of the parasite’s cysteine protease Cruzain has shown promise as a therapeutic treatment of the disease. K11777 is providing support that inhibition of Cruzain can eradicate the parasite. It is believed that the vinyl sulfone functionality of K11777 is the source of efficacy of the drug.\(^9\) This orally bioavailable, non-toxic pharmaceutical has also been investigated for the treatment of various other diseases that are likely caused by parasitic cysteine proteases including schistosomes (flatworms).\(^10\)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{S-containing pharmaceuticals.}
\end{figure}

Montelukast, the active component of Singulair, is a leukotriene receptor antagonist. It is used for the treatment of asthma and for the relief of seasonal allergy symptoms. This drug, containing a distinctive thioether functionality, was discovered and developed by scientists at the Merck Frosst Centre for Therapeutic Research in Montreal.

Two of the examples shown above include a vinyl sulfide moiety. Vinyl sulfides are an important class of compounds both for their presence in biologically active
molecules and their use as synthetic intermediates. The next section will highlight the synthetic utility of vinyl sulfides.

1.1.1 Vinyl Sulfides

Vinyl sulfides are useful synthons as they can easily survive the conditions for many synthetic reactions prior to their selective manipulation. Vinyl sulfides and their oxidized derivatives have also evolved as useful synthetic intermediates because they can act as masked carbonyls, enolate equivalents, and Michael acceptors.\(^{11-13}\) They can also be used as cross-coupling partners in reactions such as the Kumada coupling.\(^{14}\) Additionally, as seen in Figure 1.3, vinyl sulfides can undergo many other transformations to form new value-added or functionalized molecules.\(^{13}\)

![Figure 1.3: Transformations of vinyl sulfides.\(^{13}\)](image)

Vinyl sulfides are particularly important not only as synthetic targets as highlighted above but also as synthetic intermediates, as illustrated in Figure 1.4. They have been used as part of total syntheses for natural products (+)-Laurencin\(^{15}\) and Lapidilectine B\(^{16,17}\). In a total synthesis of the natural product (-)-Coriolin, alkyl vinyl sulfides are used both as starting materials and later on as a key synthetic intermediate.\(^{18}\)
Vinyl sulfides can be prepared in a number of ways\textsuperscript{13} including: Wittig reactions,\textsuperscript{19,20} elimination from thioketals/thioacetals,\textsuperscript{21,22} and nucleophilic substitution of vinyl halides\textsuperscript{23-25}. Typically, these methods require preparation of the starting material – Wittig reagent, thioacetal, or vinyl halide. Some of these methods suffer from issues of selectivity when substituted vinyl sulfides are formed. Issues with selectivity between the $E$ and $Z$ forms can be overcome by preparing the appropriate $E$ or $Z$ vinyl halide.\textsuperscript{23-25} Nucleophilic substitution at the halide with thiolates then forms the analogous $E$ or $Z$ vinyl sulfide. Of course, this method necessitates pre-forming the desired vinyl halide.

A more simple method of preparing vinyl sulfides from commercially available starting materials is desirable. One such method – alkyne hydrothiolation – constitutes a simple, 100% atom-economic method of forming vinyl sulfides, as illustrated in the next section.

\textbf{Figure 1.4: Natural product syntheses involving vinyl sulfides.}
1.2 Hydrothiolation

Alkyne hydrothiolation is a convenient and efficient method for preparing vinyl sulfides. This reaction involves the addition of an S-H bond across the π-system of an alkyne as shown in equation 1.1. This transformation affords three possible isomers. The two linear isomers result from anti-Markovnikov addition in a syn (E-isomer, E) or anti (Z-isomer, Z) fashion. Conversely, the branched isomer (B) results from Markovnikov addition. For this reaction to be useful synthetically, one isomer should be able to be generated exclusively. Hence, regio- and stereoselectivity are important considerations in the design of this reaction.

![Diagram showing three isomers of hydrothiolation products](image)

This reaction has been shown to occur via three major pathways: nucleophilic attack, free radical addition, and transition metal catalysis. Depending on the methodology employed, different isomers are produced. Until the early 1990’s, the first two pathways were the only known routes for hydrothiolation.

1.2.1 Nucleophilic Hydrothiolation

The nucleophilic addition of a thiol to an unsaturated compound was first published over 100 years ago in 1905.26 Preformed thiolate, RS⁻, was added to alkynes to generate Z-linear vinyl sulfides. This selectivity prompted Truce et al. to coin and investigate the “Rule of trans-Nucleophilic Addition”.27-34 It was later demonstrated that all three vinyl sulfide isomers were accessible depending on the R group of the alkyne.35

Typically, nucleophilic methods for hydrothiolation have used stoichiometric amounts of base, high temperatures and occasionally toxic metals. Recent advances have made nucleophilic methods more effective at catalytically forming a single isomer – the Z-linear vinyl sulfide. At the present time, this is the only hydrothiolation route to selectively form this isomer.
Recently, catalytic amounts of base have been used to selectively form the Z-linear product. One of the first examples was the use of cesium carbonate, Cs$_2$CO$_3$, to produce the Z-linear product selectively.$^{36}$ This example is of particular importance as it is effective for alkane thiols, which have proven to be reluctant substrates in hydrothiolation. Since this initial report, other examples of catalytic nucleophilic hydrothiolation have been reported, but with poor E:Z selectivity between the linear vinyl sulfides.$^{37,38}$ Catalytic amounts of In(OTf)$_3$ have been used to affect alkene hydrothiolation. However, in this case, the Markovnikov product is formed.$^{39}$

### 1.2.2 Radical Hydrothiolation

The first example of free radical addition of a thiol was first reported in 1949.$^{40,41}$ Thioacetic acid adds to 1-hexyne under mild conditions to form mono- and di-adducts (equation 1.2). The monoadduct (the vinyl sulfide) formed is the linear product; however, the stereochemistry of the product (E:Z) was not examined.

$$\text{O} + \text{nC}_4\text{H}_9\equiv \xrightarrow{\text{neat}} \text{nC}_4\text{H}_9\equiv \text{S} + \text{nC}_4\text{H}_9\text{O}(1.2)$$

In 1964, Oswald et al. studied the reaction of phenyl acetylene with a variety of thiols to determine their stereochemical outcomes.$^{35}$ By using $^1$H NMR spectroscopy, IR spectroscopy and gas chromatography, the authors were able to determine that a mixture of E and Z linear vinyl sulfides was formed, with the Z isomer typically formed as the major product. The reaction with arene thiols occurred at room temperature without the need of an initiator. Alkane thiols, conversely, required the addition of peroxides or UV irradiation to react.

Free radical addition of thiols to unsaturated compounds proceeds through a typical radical chain mechanism (Figure 1.5). Hydrothiolation can be initiated by peroxides, azo compounds, or UV radiation. The primary step is the addition of the thiol radical to the alkyne at the less substituted end to form a vinyl radical. The chain transfer step involves proton abstraction from another thiol molecule by the vinyl radical. This is
believed to be the rate-determining step. The anti-Markovnikov selectivity for the radical addition reaction is thought to arise from the formation of the more stable vinyl carbon-based radical.

![Radical chain mechanism.](image)

Figure 1.5: Radical chain mechanism.

Oswald et al. also tried to determine why the Z isomer was formed in excess. They found that the Z:E ratio of a mixture of isomers did not change with extended reaction times at room temperature. However, when the products of hydrothiolation with arene thiols were exposed to high temperatures through distillation, the Z isomer was converted to the E isomer. In contrast, no isomerization occurred for the vinyl sulfides produced from alkane thiols. However, if benzene thiol is added to a mixture of these isomers at high temperature, the Z isomer is converted. Hence, it was postulated that arene thiols are post isomerization catalysts. In the absence of post isomerization, the control of stereoselectivity could be due to three different factors. The formation of the Z vinyl radical could be favoured over the E radical, or the isomerization of the vinyl radical could favour the Z radical. Finally, abstraction from the Z thyl radical could be favoured due to the sterics of approach of the thiol.

Free radical hydrothiolation eliminates the formation of the branched isomer; however, this mechanism exerts limited control over the two linear isomers. Furthermore, alkenes are more reactive towards thiols than alkynes; hence, it is difficult to stop the reaction simply at the vinyl sulfide. In 1987, it was discovered that the addition of 4 equivalents of MeOH to the hydrothiolation reaction stopped diaddition and increased reaction rates and yields. A variety of terminal alkynes reacted with benzene thiol or butane thiol to produce only the linear vinyl sulfides (a mixture of Z and E isomers were formed).
Many other reports of radical-initiated hydrothiolation have been published over the years including examples of alkene hydrothiolation. An interesting example is that of Ranu and Mandal who reported the anti-Markovnikov addition of thiols to unactivated alkenes in water. This reaction is high yielding with terminal, internal, cyclic and acyclic olefins and arene and alkane thiols.

Overall, free radical addition of thiols to \( \pi \)-systems is effective for both arene and alkane thiols. It is selective for the anti-Markovnikov product but does not distinguish between the \( E \) and \( Z \) vinyl sulfides. Furthermore, since alkenes are more reactive to radical addition processes than alkynes, it is difficult to prevent diaddition of a thiol to an alkyne.

### 1.3 Transition-Metal-Catalyzed Hydrothiolation

Transition metals can be useful for the catalytic construction of new carbon-element bonds. They hold significant advantages over radical and nucleophilic methods – they are effective in controlling regio- and stereoselectivity and avoid the use of toxic metals. Though transition metals have been exploited for forming many C-E bonds, the development of strategies for metal–sulfur bond formation has lagged far behind that of other M-E bonds. This lack of knowledge stems partly from the fact that sulfur tends to be a catalyst poison as it makes strong bonds to many late transition metals (strong coordinating and adsorbtive properties).

Despite this fear of catalyst poisoning, transition-metal-catalyzed synthetic reactions with thiols have been reported. Some of the early work with thiols as substrates in transition-metal-catalyzed reactions, rather than as ancillary ligands, was the desulfurization and carbonylation reactions of thiols by Alper and coworkers in the 1980’s. Dicobalt octacarbonyl was found to catalyze the transformation of benzyl and arene thiols to esters in the presence of carbon monoxide and alcohols with concomitant formation of \( \text{H}_2\text{S} \) as the sulfur byproduct (Scheme 1.1a). The following year, they reported that the same reaction in the presence of a diene rather than an alcohol resulted in the formation of a thioester and COS (Scheme 1.1b). They also reported that a
rhodium carbonyl complex could catalyze the desulfurization of thiiranes to olefins (Scheme 1.1c).[^47]

![Scheme 1.1](image)

Furthermore, in the last 10-15 years, organosulfur compounds have proven to be versatile reagents in many transition-metal-catalyzed reactions. There are many examples of additions of sulfur compounds to unsaturated C-C bonds – the simplest example being hydrothiolation.

### 1.3.1 Early Work

The first reported transition-metal-catalyzed alkyne hydrothiolation was reported in 1976 using a molybdenum catalyst.[^48] In the presence of catalytic amounts of MoOL₂ or MoO₂L₂ (L = dithiocarbamate), 1 equivalent of thiophenol reacts with 1 equivalent of dimethylacetylenedicarboxylate (DMAD) to give Z-dimethyl-2-(phenylthio)fumarate (Scheme 1.2). Further reaction with a second equivalent of benzene thiol gives the alkene hydrothiolation product, dimethyl-2,3-bis(phenylthio)succinate. Stoichiometric reactions indicated that the reaction involves some metal alkyne complexation.
The next fundamental step toward transition-metal-catalyzed hydrothiolation was Ogawa and coworkers’ pioneering work with the addition of dichalcogenides (RS-SR and RSe-SeR) to alkynes in 1991. Bisaryl disulfides were reacted with terminal alkynes in the presence of a catalytic amount of Pd(PPh₃)₄, which produced vicinal bis(aryltio)alkenes (equation 1.3). The reactions proceeded in good yields and with regiospecific formation of the Z isomer. The reaction was tolerant to functionalities on the sulfide or alkyne but was unsuccessful with internal alkynes or alkyl disulfides. Wilkinson’s catalyst, ClRh(PPh₃)₃, and Pt(PPh₃)₄ also showed some catalytic activity. In 2001, this work was extended to include alkyl disulfides. For these substrates, a rhodium catalyst was necessary. Terminal alkynes reacted with alkyl disulfides in the presence of a catalytic amount of Rh(H)(PPh₃)₄, triflic acid, and dppf or P(p-MeOC₆H₄)₃. The reaction was tolerant of functional groups on both the alkyne and the disulfide.

The disulfide addition reaction ultimately led to the discovery of several metal catalysts for the addition of thiols to alkynes in 1992 by the same research group. In this seminal paper, the reaction between 1-octyne and benzene thiol was investigated in the presence of various transition metal complexes. Four different products were observed (equation 1.4): the linear vinyl sulfide isomers (E and Z), the branched vinyl sulfide (B) and the product of double-bond isomerization from the branched vinyl sulfide (B’). In
this study, the two anti-Markovnikov products (E and Z) were not distinguished. The authors found that the addition of benzene thiol to 1-octyne in the absence of catalyst, or even in the presence of acetic acid, resulted in a mixture of the anti-Markovnikov products. However, in the presence of a catalytic amount of Pd(OAc)$_2$, the branched vinyl sulfides were formed selectively. The reaction with Pd(OAc)$_2$ was successful with a variety of alkynes, both terminal and internal, and with several arene thiols. It was noted that the reaction was unsuccessful with nBuSH and MeO$_2$CCH$_2$SH – a result that started the belief that alkane thiols are unreactive substrates for transition-metal-catalyzed alkyne hydrothiolation.

Interestingly, Pd(PPh$_3$)$_4$, Pd(PhCN)$_2$Cl$_2$, Pt(PPh$_3$)$_4$ and Ni(PPh$_3$)$_2$Cl$_2$ produced the isomerization product B' as the major product.$^{52,53}$ It was suggested that with these precatalysts, the branched vinyl sulfide is initially formed but then isomerized in situ. It was later noted that the some of the phosphine complexes also formed Z-bis(arylthio)alkenes as another byproduct. In contrast, ClRh(PPh$_3$)$_3$ produced the E-linear vinyl sulfide as the major product, though with poor selectivity over the branched vinyl sulfide and its isomerized product.

Since then a number of groups have investigated transition-metal-catalyzed hydrothiolation. The use of transition metals has significantly improved the selectivity of this reaction. In general, it was found that nickel, palladium and platinum complexes produce the branched vinyl sulfides selectively, whereas rhodium and iridium complexes produce the E-linear vinyl sulfides selectively.

The next few sections will discuss the successes in this field. Alkyne and allene hydrothiolation reactions producing the linear isomer will be discussed first, followed by those producing the branched isomer. These sections will be followed by a short discussion of intramolecular alkyne hydrothiolation followed by alkene hydrothiolation. Finally, the related RS-G additions will be briefly discussed.
### 1.3.2 Linear Vinyl Sulfides

The first transition metal catalyst precursor to selectively produce the $E$-linear vinyl sulfide was reported by Ogawa and coworkers in 1992.\(^5\)\(^1\) It was noted that Wilkinson’s catalyst catalyzes alkyne hydrothiolation favouring the anti-Markovnikov product albeit with poor selectivity. Optimization of this reaction was subsequently reported with a tremendous increase in selectivity for the trans ($E$) isomer (equation 1.5).\(^5\)\(^2\)

\[
\text{ArSH} + \text{R} = \text{ClRh(PPh}_3\text{)}_3 \xrightarrow{3 \text{ mol\%, EtOH, } 40^\circ\text{C}} \text{R} - \text{SAr}
\]  

The newly optimized reaction with Wilkinson’s catalyst works for a variety of alkynes, including both terminal and internal alkynes. When enynes are employed, hydrothiolation occurs selectively at the alkyne. Unfortunately, the reaction was only successful with arene thiols – two examples other than benzene thiol were shown. The authors reported that “hydrothiolation with alkane thiols such as cyclohexanethiol did not proceed”. This second report of incompatibility with alkane thiols seemingly cemented the belief that alkane thiols are unreactive in transition-metal-catalyzed alkyne hydrothiolation.

A variety of rhodium and iridium complexes with bidentate N-N and P-N ligands were investigated by Messerle and coworkers for alkyne hydrothiolation.\(^5\)\(^4\) The substrate scope of these studies, however, was small with only four alkynes examined and only one thiol (benzene thiol). These complexes also produced the linear vinyl sulfides. The iridium complexes were found to be more effective than their rhodium counterparts (Figure 1.6). \([\text{Ir(PyP)(CO)}_2]B\text{Ph}_4\) (PyP = 1-(2-diphenylphosphinoethyl)pyrazole) was found to be the most effective catalyst precursor. In contrast to Wilkinson’s catalyst, in this study both linear vinyl sulfides were produced with the Z-linear vinyl sulfide as the major product. This report was followed up in 2009, but the newly investigated complexes were less successful (Figure 1.6b).\(^5\)\(^5\)
A related report of hydrothiolation of 1-alkynylphosphines is another rare example of selective anti-addition. When thiols are reacted with 1-alkynylphosphines in the presence of 5 mol% Pd(OAc)$_2$ neither the typical $E$-linear isomers nor the “branched-type” isomers were produced; instead, $Z$-1-phosphino-2-thio-1-alkenes were produced (equation 1.6).$^{56}$ This procedure was successful for both arene and alkane thiols. The reaction was also effective using PdCl$_2$ and Pd$_2$(dba)$_3$. This is the only example of a palladium precatalyst resulting in the formation of a linear vinyl sulfide, though it is arguable that this result is primarily due to the nature of the substrate: an alkyne vs. a 1-alkynylphosphine.

$$\text{RSH} + \text{R}^1\equiv\text{PR}^2_3 \xrightarrow{5 \text{ mol}\% \text{Pd(OAc)}_2} \text{SAr} \text{ PR}^2_3 \quad (1.6)$$

There are few examples of alkyne hydrothiolation to form the $E$-linear vinyl sulfide selectively. However, as illustrated above, Wilkinson’s catalyst is highly selective, and the other rhodium and iridium precatalysts are selective for the linear vinyl
sulfides. These catalyst precursors work well for arene thiols but, prior to our contributions (discussed in Chapter 2), are unreactive towards aliphatic thiols.

### 1.3.3 Branched Vinyl Sulfides

Most of the work on transition-metal catalyzed hydrothiolation has focused on palladium and nickel catalyst precursors providing the branched vinyl sulfide. The range of π-systems investigated is broad including terminal, internal and conjugated alkynes, as well as allenes. However, until our group’s work in 2005, there were no reports of hydrothiolation with alkane thiols, perhaps due to reports that alkane thiols were unreactive.51,52 This section highlights systems that provide branched vinyl sulfides chronologically, including the contributions by our group.

The scope of the Pd(OAc)₂-catalyzed reaction reported by Ogawa and coworkers in 199251 was further expanded by Bäckvall and Ericsson to include enynes.57 As expected, the precatalyst was completely selective for addition of benzene thiol to the triple bond over the double bond. Furthermore, the branched isomer was still produced with these substrates. Both acyclic and cyclic enynes (the triple bond is exocyclic) underwent alkyne hydrothiolation; however, only when the alkyne was in the terminal position. These resulting dienes could also be subsequently oxidized to 2-(phenylsulfonyl)-1,3-dienes or 2-(phenylsulfinyl)-1,3-dienes selectively (Scheme 1.3), further illustrating the utility of the products of hydrothiolation.

![Scheme 1.3](image)

Ogawa and coworkers noted that allene hydrothiolation with benzene thiol was also possible using 3 mol% Pd(OAc)₂, affording vinyl sulfides (equation 1.7).58 This route is highly regioselective for the branched vinyl sulfide and for addition at the
terminal double bond of the allene, unlike the radical catalyzed reaction, which results in a mixture of isomers. This methodology was high yielding for aliphatic allenes and no double-bond isomerization was noted.

\[
\text{PhSH} + R \quad 3 \text{ mol\% Pd(OAc)}_2 \quad \text{R} \quad \text{SPh} \quad (1.7)
\]

As was previously mentioned, when complexes such as Pd(PhCN)\(_2\)Cl\(_2\) were used for hydrothiolation, double-bond isomerization of the branched product occurred resulting in a mixture of products. Further exploration of this phenomenon several years later resulted in a procedure for sequential Markovnikov addition and double-bond isomerization to form internal vinyl sulfides (equation 1.8). Use of this precatalyst resulted in good yields of only the internal (isomerized) vinyl sulfide; most aliphatic alkynes reacted successfully. There is little to no selectivity, however, between the \(E\) and \(Z\) forms of the resulting olefin. Of course, since a methylene group adjacent to the alkyne is required for isomerization to be possible, the use of aromatic alkynes results in only the branched vinyl sulfide.

\[
\text{PhSH} + R \quad 5 \text{ mol\% Pd(PhCN)\(_2\)Cl\(_2\) benzene, 80 °C} \quad \text{R} \quad \text{SPh} \quad (1.8)
\]

A preliminary study in 2004 suggested that nickel complexes, like palladium complexes, also favor Markovnikov addition. The addition of benzene thiol to 1-octyne in the presence of 5 mol\% Ni(PPh\(_2\)Me)\(_4\) and 10 mol\% Ph\(_2\)P(O)OH resulted in the formation of the branched vinyl sulfide in high yield and with high selectivity. It is also worth noting that the use of this nickel catalyst precursor circumvents the use of elevated temperatures needed for palladium precatalysts.

The following year, Beletskaya and coworkers found that metal chloride complexes (NiCl\(_2\), PdCl\(_2\), K\(_2\)PtCl\(_4\), and RuCl\(_3\)) catalyzed hydrothiolation but with poor selectivity forming the Markovnikov product and its isomerization product as well as the anti-Markovnikov products. Interestingly, the metal chloride complexes all favoured the anti-Markovnikov products, with K\(_2\)PtCl\(_4\) giving complete selectivity for the linear vinyl sulfides. The authors do not comment on \(E:Z\) ratios but state that the formation of the
anti-Markovnikov products is probably due to a background, non-metal catalyzed reaction, suggesting a mixture of E and Z isomers was formed.

Of particular interest was the observation that upon addition of NEt₃, the selectivity changed completely and the branched isomer (and its isomerization product) were significantly favoured (equation 1.9). This reversal in selectivity is believed to be due to the base suppressing the background reaction. The addition of 1 equivalent of γ-terpene as a radical trap promoted excellent selectivity of the branched vinyl sulfide (including any isomerized product) over the linear vinyl sulfides when NiCl₂ was used as the catalyst precursor. This result suggests that the formation of the linear vinyl sulfides was a radical-initiated reaction.

\[
\begin{align*}
\text{PhSH} + n\text{C}_6\text{H}_{13} \xrightarrow{3 \text{ mol}\% \text{NiCl}_2, 6 \text{ mol}\% \text{NEt}_3, \ \gamma\text{-terpene (1 equiv), CHCl}_3, 95 \text{ °C}} & n\text{C}_6\text{H}_{13} \text{SPh} + n\text{C}_6\text{H}_{11} \text{SPh} \\
\end{align*}
\] (1.9)

In 2005, our group reported the first examples of transition-metal-catalyzed alkyne hydrothiolation with alkane thiols (equation 1.10). It was found that the electron-rich Tp*Rh(PPh₃)₂ (Tp* = hydrotris(3,5-dimethylpyrazolyl)borate) catalyzes the hydrothiolation of a range of alkynes, both terminal and internal, with both arene and alkane thiols in high yields. The reactions with alkane thiols proceeded with excellent selectivity, while the reactions with arene thiols were less selective. Of particular interest, however, is that the vinyl sulfide produced is not the linear isomer expected from previous examples of rhodium catalysis but rather the branched vinyl sulfide.

\[
\begin{align*}
\text{RSH} + \text{R'}\equiv \xrightarrow{3 \text{ mol}\% \text{Tp*Rh(PPh}_3)_2 \text{ DCE/Tol (1:1)}} \text{R'}\text{SR} \\
\end{align*}
\] (1.10)

The following year Mizobe and coworkers found that a similar complex, Tp*Rh(coe)(MeCN) (coe = cyclooctene), also catalyzes alkyne hydrothiolation to
selectively produce the branched vinyl sulfide.\textsuperscript{61} Their report does not examine substrate scope, using only benzene thiol and three alkynes, but does examine the mechanism of this reaction, which will be further discussed in Section 1.4.

Another new feat in alkyne hydrothiolation was achieved by Beletskaya and coworkers in 2006 with the first solvent-free transition-metal-catalyzed hydrothiolation.\textsuperscript{62} With 2 mol\% Ni(acac)\textsubscript{2}, hydrothiolation proceeded with high selectivity and yields for the branched product with little or no isomerization. Under these conditions, the nickel complex is polymeric in nature and takes on nanosized structural units. The active catalyst is believed to be [Ni(SPh)]\textsubscript{n}. Aliphatic alkynes with a variety of functional groups were well tolerated with this methodology; however, the selectivity was poor when phenyl acetylene was used. The reaction could be scaled up to produce 50 g of product. In the initial report, a 2:1 ratio of PhSH:alkyne was necessary for high yields and selectivity (equation 1.11). However, later that year, the authors reported that with slow addition of the alkyne, one equivalent of thiol could be used without affecting yield or selectivity.\textsuperscript{63}

\[
2 \text{ equiv. PhSH} + nC_6H_{13} \xrightarrow{2 \text{ mol}\% \text{ Ni(acac)}_2} nC_6H_{13}SPh (\text{solvent-free}) 40 \degree C
\] (1.11)

Another example of selective Markovnikov addition of thiols to alkynes without double-bond isomerization or formation of bis(arylthio)alkenes was reported by Beletskaya and Nolan.\textsuperscript{64} A series of N-heterocyclic carbene (NHC) complexes of the type CpNi(NHC)Cl were investigated for the addition of PhSH to 1-heptyne. With all complexes, the branched vinyl sulfide was the major product and no isomerization product was observed. Of the NHC complexes investigated, CpNi(IMes)Cl gave the best yield and selectivity.

In the course of this study another byproduct was observed, which the authors speculate is a diene resulting from the insertion of a second equivalent of alkyne (equation 1.12). The identity of this byproduct, and the mechanism of its formation, will be further discussed in section 1.4. The addition of NEt\textsubscript{3} and use of excess thiol improved the reaction yield and suppressed formation of the undesired diene. This precatalyst was
effective for the hydrothiolation of aliphatic terminal alkynes with arene thiols with good-to-excellent selectivity.

\[
\text{PhSH} + R\equiv \xrightarrow{3 \text{ mol\%}} \begin{array}{c}
\text{PhSH} \\
\text{PhSH}
\end{array} + \begin{array}{c}
R\equiv \\
R\equiv
\end{array}
\]

Following the report of Ni nanoparticles effecting selective hydrothiolation, Beletskaya and coworkers reported that Pd nanoparticles formed from Pd(OAc)$_2$ were also successful hydrothiolation precatalysts.$^{65}$ Once again, the active catalyst is believed to have a [Pd(SR)$_2$]$_n$ structure. This solvent-free system is effective for aliphatic alkynes and results in better yields and selectivity than the nickel system but requires microwave irradiation. Furthermore, this catalytic system is effective for hydrothiolation with the alkane thiols cyclohexanethiol and benzyl thiol.

A recent investigation into allene hydrothiolation by Ogawa and coworkers revealed that Pd(PPh$_3$)$_4$ is an excellent catalyst precursor for the addition of benzene thiol to cyclohexyl allene (Scheme 1.4).$^{66}$ This methodology results in high yields and high selectivity for the branched vinyl sulfides (Markovnikov addition at the terminal allene double bond). A similar reaction with phenyl allene resulted in a mixture of isomers. Of note, the Pt congener produced a mixture of the anti-Markovnikov addition products (with addition at the terminal allene double bond).

\[
\text{PhSH} + \xrightarrow{5 \text{ mol\% Pd(PPh}_3)_4} \begin{array}{c}
\text{PhSH} \\
\text{PhSH}
\end{array} + \begin{array}{c}
\text{PhSH} \\
\text{PhSH}
\end{array}
\]

Scheme 1.4
Most recently, Marks and coworkers published a report on organoactinide-mediated hydrothiolation.\textsuperscript{67} Th(IV) and U(IV) complexes, $\kappa$-(Me$_2$SiCp)$_2$An(CH$_2$TMS)$_2$, are highly active catalyst precursors for the addition of both arene and alkane thiols to aliphatic, aryl and vinyl alkynes to produce branched vinyl sulfides in high yield and with excellent selectivity.

Unlike the $E$-linear vinyl sulfides, there are many transition metal complexes that catalyze hydrothiolation to produce branched vinyl sulfides, as illustrated above. For example, many Ni and Pd complexes, such as Pd(OAc)$_2$, CpNi(IMes)Cl, nanosized Ni(acac)$_2$ and nanosized Pd(OAc)$_2$, are able to perform this reaction with high regioselectivity. In addition, some rhodium complexes, Tp*Rh(PPh$_3$)$_2$ and Tp*Rh(coe)(MeCN) also produce the branched vinyl sulfide selectively. Interestingly, this selectivity is contrary to the literature precedence for rhodium. Finally, f-element complexes, specifically actinide complexes, can also catalyze this formation.

However, some of these catalyst precursors do suffer from limitations. Double-bond isomerization was observed with Pd(PhCN)$_2$Cl$_2$ and NiCl$_2$ resulting in the formation of new internal vinyl sulfides, whereas, a new undesired diene was observed with certain CpNi(NHC)Cl precatalysts. Poor regioselectivity plagues other complexes that have not been discussed herein. Substrate scope is also a limitation for some of these complexes; in particular, aromatic alkynes still present regioselectivity challenges for many catalyst precursors. Furthermore, prior to our group’s work in 2005, there were no reports of transition-metal-catalyzed hydrothiolation with alkane thiols to form either isomer.

1.3.4 Intramolecular Alkyne Hydrothiolation

There are only a few examples of metal-catalyzed intramolecular alkyne hydrothiolation. The first example was published in 1999 by McDonald and coworkers and features the only chromium precatalyst developed for hydrothiolation. (THF)Cr(CO)$_5$, in the presence of NEt$_3$, promoted the thiacyclosimerization of an alkynyl thiol to form a 4,5-dihydrothiophene (equation 1.13).\textsuperscript{68} Thiophenes are very important synthetic targets for biologically active compounds,\textsuperscript{69} conducting polymers\textsuperscript{70} and nonlinear optical materials\textsuperscript{71}. 
Another example of intramolecular hydrothiolation has been used to access highly substituted thiophenes (equation 1.14). Z-2-en-4-yn-1-thiols undergo cycloisomerization in the presence of PdI₂ and KI to form thiophenes from terminal and internal alkynes. ⁷²

\[
\begin{align*}
R - \text{SH} & \quad \text{(THF)Cr(CO)₅} \rightarrow \quad R - \text{S} - \text{H} \\
& \quad \text{NEt₃, Et₂O, THF} \quad \text{(1.13)}
\end{align*}
\]

In 2006, the first example of gold-catalyzed hydrothiolation was reported. The gold catalyst precursor allowed for the formation of 2,5-dihydrothiophenes via the stereoselective cycloisomerization of α-thioallenes (equation 1.15). ⁷³ The reaction occurs with full transfer from the allenic chirality axis to the new stereogenic center. Au(I) and Au(III) precatalysts can affect this transformation, with AuI and AuCl being the most active.

\[
\begin{align*}
R^1 - \text{SH} & \quad \text{1 mol% PdI₂, 2 mol% KI} \quad \text{DMA, 100 °C} \\
& \rightarrow \quad R^1 - \text{S} - R^4 \\
& \quad \text{(1.14)}
\end{align*}
\]

1.3.5 Alkene Hydrothiolation

Following the report of gold-catalyzed intramolecular allene hydrothiolation, He and coworkers reported that another Au(I) complex, (Ph₃P)Au(BF₄), can catalyze the hydrothiolation of conjugated olefins. ⁷⁴ The addition of both arene and alkane thiols to cyclic and acyclic 1,3-dienes afforded allylic sulfides, with Markovnikov addition selectivity (equation 1.16). An unactivated olefin, vinylcyclohexane, could also be successfully reacted with an alkane thiol (equation 1.17). Unfortunately, double bond isomerization seems to occur resulting in a 1:1 mixture of two products: addition at the
secondary or tertiary carbon. Nevertheless, this result is very promising for the possibility of selective alkene hydrothiolation.

\[
\text{RSH} + \text{alkene} \xrightarrow{5\text{ mol}\% \text{(Ph}_3\text{P)}\text{Au(BF}_4)} \text{CH}_2\text{Cl}_2} \xrightarrow{5\text{ mol}\% \text{(Ph}_3\text{P)}\text{Au(OTf)}} \text{CH}_2\text{Cl}_2, 80^\circ\text{C}} \xrightarrow{1.16} \text{SR} + \text{alkene}
\]

In the same year, Gunnoe and coworkers reported that a copper complex catalyzes the hydrothiolation of activated alkenes. Both benzene thiol and benzyl thiol add to a variety of mono-, di- and trisubstituted electron-deficient alkenes to produce the anti-Markovnikov sulfide (equation 1.18). The reactions are catalyzed by (IPr)Cu(SR), an NHC copper(I) complex, with high yields and excellent selectivity. A later report suggests that the copper-catalyzed reactions resemble simple base-catalyzed alkene hydrothiolation via intermolecular nucleophilic addition.

\[
\text{RSH} + \text{alkene} \xrightarrow{5\text{ mol}\% \text{(IPr)}\text{Cu(SR)}} \text{CH}_2\text{Cl}_2, 80^\circ\text{C}} \xrightarrow{1.18} \text{SR} + \text{alkene}
\]

There are also examples of alkene hydrothiolation by radical-initiated or nucleophilic methods. To the best of our knowledge, however, these are the only examples of catalytic transition-metal-mediated alkene hydrothiolation. This is a relatively new field that has the potential to open up many new possibilities including enantioselective hydrothiolation.

1.3.6 RS-G Additions

In addition to the hydrothiolation and bisthiolation reactions discussed earlier, other examples of transition-metal-catalyzed thiolations (RS-G additions) were reported. The earliest example is thioboration – the addition of a S-B bond across an alkyne π-bond. Pd(PPh\textsubscript{3})\textsubscript{4} successfully catalyzes the reaction between 9-(alkylthio)-9-BBN and
terminal alkynes with excellent selectivity. The resulting vinylboranes are shown to be useful coupling partners for cross-coupling reactions (Scheme 1.5).

![Scheme 1.5](image)

A few other thiolation reactions behave similarly to thioboration. Thiophosphorylation (the addition of a S-P(O) bond across a π-system), thioesterification (the addition of a S-C(O) bond across a π-system) and cyanothiolation (the addition of a S-CN bond across a π-system) are all examples of RS-G additions to alkynes. All three of these reactions are catalyzed by palladium(0) phosphine complexes and produce vinyl sulfides consistent with syn addition of the RS-G molecule, giving the same selectivity as thioboration, as shown in equation 1.19.

\[
RS-G + R'\equiv \xrightarrow{Pd(0)} \xrightarrow{3 \text{ mol}\% \text{Pd(PPh}_3\text{)}_4} \xrightarrow{\text{THF, 50 °C}} \xrightarrow{\text{MeOH}} R'SR \xrightarrow{R''X} R''SR \\
R= \text{Ph, Bn, Bu}
\]

**Thioformylation** – the addition of an arene thiol to an alkyne in the presence of CO – is catalyzed by rhodium and platinum precatalysts, producing complimentary isomers (Scheme 1.6). These products differ in the position of carbon monoxide incorporation. Ogawa has referred to the platinum-catalyzed reaction as hydrothiocarboxylation to distinguish between products. It is interesting that the two active precatalysts for this reaction, Rh(H)(CO)(PPh₃)₃ and Pt(PPh₃)₄, do not catalyze the highly related hydrothiolation reaction.⁵¹,⁵²
Finally, carbothiolation involves the addition of a S-C(O) bond across a π-system followed by decarbonylation. Pt(PPh₃)₄ catalyzes the addition of thioesters to alkynes followed by decarbonylation to produce substituted vinyl sulfides (equation 1.20).⁷⁹

\[
\text{RSO}_2 \text{R''} + \text{R'\text{==\text{===}}} \xrightarrow{5 \text{ mol\% Pt(PPh}_3)_4} \text{Tol, reflux} \xrightarrow{} \text{R''SPh}
\] (1.20)

As discussed above, several thiolations are known where RS-G adds to an alkyne resulting in a vinyl sulfide. In these reactions, the thio group adds to the internal carbon of the alkyne and the other group adds to the terminal end in a \textit{syn} fashion. Interestingly, all of the reported examples are catalyzed by Pd(0) or Pt(0) catalysts, as well as HRh(CO)(PPh₃)₃ – all of which are unreactive towards hydrothiolation. It is also curious that while alkylthio groups were used for some of these reactions prior to our work in 2005 (such as thioboration and thioformylation), successful hydrothiolation reactions with alkane thiols had not been reported. Since authors other than Ogawa did not report on hydrothiolation results with alkane thiols, it is unknown whether alkane thiols were unreactive in other systems or simply not investigated. Since Ogawa had effectively established that alkanethiols were unreactive towards hydrothiolation, it is possible no one else investigated their use until our 2005 report with Tp*Rh(PPh₃)₂.

1.3.7 Summary of Successes and Failures of Alkyne Hydrothiolation

As mentioned earlier, the two major challenges with alkyne hydrothiolation are the control of regio- and stereoselectivity and the inability to use alkane thiols. When
starting the research described in this thesis, the selectivity challenge was mostly solved—though improvements can always be made. *E*-linear vinyl sulfides could be selectively prepared from arene thiols using a rhodium catalyst. *Z*-linear vinyl sulfides could be selectively prepared using recent nucleophilic methods. Finally, branched vinyl sulfides are prepared from arene thiols using palladium, nickel, actinide, and certain rhodium catalysts.

The use of alkane thiols still presents a challenge. The challenge was solved for branched vinyl sulfides using Tp*Rh(PPh₃)₂, and other catalysts since the start of this thesis. Furthermore, the nucleophilic method for *Z*-linear vinyl sulfides also works with alkane thiols. The preparation of *E*-linear vinyl sulfides by alkyne hydrothiolation with alkane thiols still remained a challenge.

1.4 Hydrothiolation Mechanisms

The elucidation of the mechanism of hydrothiolation is important to the understanding of the limitations of the reaction. In transition-metal-catalyzed hydrothiolation, two regioisomers can be formed selectively under appropriate conditions; therefore, there are at least two operable mechanisms for this reaction, depending on the conditions. The different proposed mechanisms of transition-metal-catalyzed hydrothiolation are presented in this section and are outlined by the metal involved.

The catalytic cycle for the Pd(OAc)₂-catalyzed hydrothiolation was first proposed in the original transition-metal-catalyzed hydrothiolation report. This mechanism has been supported by later reports of Pd-catalyzed hydrothiolation and is shown in Figure 1.7. The first step of the mechanism involves ligand exchange to produce the active catalyst [Pd(SPh)₂]. This step was proposed based on stoichiometric reactions between Pd(OAc)₂ and 3 equivalents of PhSH, which produced a dark brown precipitate and 2 equivalents of AcOH. The uncharacterized precipitate, believed to be [Pd(SPh)₂]ₙ, was not catalytically active. However, a similar brown precipitate formed under the same conditions but in the presence of allene or alkyne showed moderate catalytic activity. This solid also reacted with allenes and alkynes to produce the expected vinyl
sulfide. Elemental analysis of this solid suggests that it is \([\text{Pd} \text{(SPh)}_2]_n\). No explanation is provided to explain the requirement for an equivalent of alkyne.

![Proposed mechanism for Pd(OAc)\(_2\)-catalyzed hydrothiolation.](image)

Figure 1.7: Proposed mechanism for Pd(OAc)\(_2\)-catalyzed hydrothiolation.

After ligand exchange, insertion of the alkyne into one of the Pd-S bonds provides the correct vinyl palladium intermediate. Protonation by another equivalent of thiol releases the vinyl sulfide from the palladium center and regenerates the active species. Evidence for the insertion of an alkyne into a Pd-S bond was reported by Kuniyasu and Kurosawa.\(^8^3\) They were able to isolate the product of such an insertion by using less reactive reagents. Reaction of (dppe)Pd(SAr)\(_2\) with DMAD generated the \(\text{cis}\)-insertion product (equation 1.21). Its structure was confirmed by X-ray crystallographic analysis. Heating of this product to 50 °C generated the \(E\)-isomer as assigned by NMR spectroscopy.
Likewise, the hydrothiolation/double-bond isomerization by PdCl$_2$(PhCN)$_2$ is proposed to operate by a very similar mechanism. Ligand exchange is proposed as the first step to generate the active catalyst, L$_n$Pd(SPh)Cl. This is also supported by a stoichiometric reaction between PdCl$_2$(PhCN)$_2$ and 2 equivalents of PhSH, which resulted in a red-brown precipitate whose elemental analysis is consistent with a formula of [PdCl(SPh)(PhSH)]$_n$ (n = 1 or 2). This precipitate shows moderate catalytic activity for hydrothiolation/double-bond isomerization.

The next steps of the catalytic cycle – insertion and protonation – are the same as the above cycle. However, following protonation, the vinyl sulfide binds to palladium and double-bond isomerization occurs via a cationic intermediate. The mechanism for this process is shown in Figure 1.8.$^{51}$
The nickel catalysts are believed to proceed through an analogous mechanism to the palladium catalysts. A stoichiometric reaction between Ni(acac)$_2$ and PhSH once again produced a polymeric species with an elemental analysis consistent with [Ni(SPh)$_2$]$_n$. The polymer was shown to react with alkynes to produce the expected vinyl sulfide and shows catalytic activity. In contrast to the palladium species, the nickel polymer did not need to be prepared in the presence of an alkyne.

Similarly, ligand exchange was found to produce the active catalyst when CpNi(IMes)Cl was used as well. In this case, NEt$_3$ is needed to accelerate the ligand exchange by producing thiolate in situ. Thus, reaction with ArS$^-$, formed in situ, and CpNi(IMes)Cl produced isolable, nonpolymeric CpNi(IMes)(SAr). The structure was assigned by NMR spectroscopy and XRay crystallographic data. This complex reacts
with alkynes to produce the branched vinyl sulfide and can be used as a catalyst for hydrothiolation.

In this same study, the diene byproduct mentioned in Section 1.3.3 was also reported. The diene is believed to be the product of double alkyne insertion with both alkyne equivalents adding in a *syn* fashion, as shown in Figure 1.9. The structure of the diene is proposed based on the presence of vinylic resonances present in the $^1$H NMR spectrum. However, the vinyl species in the first nickel intermediate I seemed to have undergone double bond isomerization with the addition of the second alkyne equivalent in II. It is unlikely that double-bond isomerization would have occurred with this second addition and the isomerization is not mentioned in the text. Thus, if we assume that double-bond isomerization does not occur, the nickel intermediate and, thus, the diene are incorrectly drawn. We suggest the structures for intermediate II and the diene shown in parentheses next to the reported structures. Both the reported diene and our suggested structure match the 1D NMR spectroscopic data provided.

![Proposed mechanism for diene formation. Our suggested structures are in brackets.](image)

The actinide precatalysts discussed earlier also proceed through an active disulfide catalyst. The catalytic cycle goes through insertion of the alkyne into the An-S bond. Protonation by another equivalent of thiol releases the branched vinyl sulfide.
When Wilkinson’s catalyst\textsuperscript{52} and Messerle’s Rh and Ir complexes\textsuperscript{54,55} are used for hydrothiolation, the opposite regioisomer (linear vinyl sulfide) is produced. To probe the mechanism, Ogawa performed a stoichiometric reaction between ClRh(PPh\textsubscript{3})\textsubscript{3} and PhSH.\textsuperscript{52} This reaction resulted in trans-HRhCl(SPh)(PPh\textsubscript{3})\textsubscript{2}, a complex which effectively catalyzes hydrothiolation. Hence, a mechanism was proposed that involved oxidative addition of the thiol to rhodium, followed by stereoselective insertion of the alkyne into the Rh-H bond. Subsequent reductive elimination, in the presence of thiol, releases the product and regenerates the active catalyst, HRhCl(SPh)(PPh\textsubscript{3})\textsubscript{2}, as shown in Figure 1.10.

![Figure 1.10: Proposed mechanism for ClRh(PPh\textsubscript{3})\textsubscript{3}-catalyzed hydrothiolation.](image)

Both Tp*Rh(PPh\textsubscript{3})\textsubscript{2} and Tp*Rh(coe)(MeCN) generate the branched vinyl sulfide through hydrothiolation, opposite to the other rhodium and iridium precatalysts. During the course of our investigations into the mechanism of Tp*Rh(PPh\textsubscript{3})\textsubscript{2}-catalyzed hydrothiolation, Mizobe and coworkers published their efforts towards elucidating the mechanism for their catalyst precursor. In their study, they observed that oxidative addition of the thiol can occur to form Tp*Rh(H)(SPh)(MeCN). This species was found to be catalytically inactive towards hydrothiolation. When two equivalents of benzene
thiol are added to the initial rhodium complex, however, a new species is formed that is catalytically active. This crystallographically characterized complex is the disulfide species $\text{Tp}^*\text{Rh}(\text{SPh})_2(\text{MeCN})$. The proposed mechanism, therefore, involves double thiol addition to form the disulfide. The alkyne then inserts into the Rh-S bond, similar to the palladium and nickel catalyzed mechanisms. Protonation with another equivalent of thiol releases the vinyl sulfide and regenerates the active catalyst, as shown in Figure 1.11.$^{61}$

Two major mechanisms emerge from these studies as the mechanisms for transition-metal-catalyzed hydrothiolation. When the linear isomer is formed, a catalytic cycle involving S-H activation, alkyne insertion into a M-H bond and reductive elimination seems to be operating. The catalytic cycle for formation of the branched isomer seems to involve formation of a M(SR)$_2$ species, followed by alkyne insertion into a M-S bond and then protonation. However, other mechanisms could be involved, as rigorous kinetic and mechanistic analyses have not been performed in most cases.
1.5 Scope of Thesis

As illustrated in this chapter, transition-metal-mediated alkyne hydrothiolation is an attractive method for preparing \(E\)-linear or branched vinyl sulfides. The existing methods for the preparation of \(E\)-linear vinyl sulfides are limited to arene thiols, typically benzene thiol. Chapter 2 illustrates a method for stereoselective formation of \(E\)-linear vinyl sulfides from alkyne hydrothiolation with alkane thiols. This method is the first reported transition-metal-catalyzed alkyne hydrothiolation with alkane thiols to selectively produce this vinyl sulfide. The scope of the reaction is examined and a mechanism for the reaction is proposed. The cause of the reversal of the regioselectivity between ClRh(PPh\(_3\))\(_3\) and Tp\(^*\)Rh(PPh\(_3\))\(_2\) is investigated in Chapter 3. The mechanism of Tp\(^*\)Rh(PPh\(_3\))\(_2\)-catalyzed hydrothiolation is examined through product and substrate scope analysis, stoichiometric reactivity and kinetic analysis. Insights into the mechanism of Tp\(^*\)Rh(PPh\(_3\))\(_2\)-catalyzed hydrothiolation are presented, allowing a number of possible mechanisms to be excluded from further consideration. The conclusions and future work are discussed in Chapter 4.
Chapter 2: ClRh(PPh₃)₃-Catalyzed Alkyne Hydrothiolation with Alkane Thiols

2.1 Introduction

The presence of sulfur in natural products and the utility of sulfur-based reagents as synthetic intermediates illustrate the need for efficient and versatile methods for the construction of sulfur-containing molecules. One such method is through transition metal catalysis. However, metal-catalyzed reactions involving thiols have been explored to a lesser extent than that of other functional groups such as amines and alcohols. This is because of a prejudice that sulfur would behave as a catalyst poison due to the strong interaction of sulfur with late transition metals. It was believed that the strong coordinating ability of sulfur would block reactive metal coordination sites or prevent the release of the sulfur containing molecule from the metal. Nevertheless, some catalytic reactions involving thiols, including alkyne hydrothiolation, have been developed.

Metal-catalyzed alkyne hydrothiolation, the formal addition of an S-H bond across a π-system, is an attractive, atom-economic method of preparing vinyl sulfides (equation 2.1). There are two major challenges for this reaction. Alkyne hydrothiolation can produce three different vinyl sulfide products; therefore, one of the challenges has been to develop regioselective hydrothiolation conditions. The second challenge is the difficulty in using alkane thiols. As discussed in Chapter 1, radical, nucleophilic and metal-catalyzed alkyne hydrothiolation using arene thiols is well precedented; however, reactions with alkane thiols are less common. Prior to 2005, transition-metal-catalyzed alkyne hydrothiolation was believed to be ineffective with alkane thiols. In 1992, the ability of Wilkinson’s catalyst to effectively catalyze the hydrothiolation of alkynes with arene thiols was reported. The combination of 1-octyne and benzene thiol in the presence of 2 mol% ClRh(PPh₃)₃ at 80 °C resulted in the formation of 89% yield of the corresponding vinyl sulfides (Scheme 2.1a), with the linear...
isomer being the major product (52% yield; E/Z ratio of 98/2). The remaining 37% was composed of the branched isomer B (14%) and an isomer B’, presumably resulting from isomerization of the double bond of the initially formed branched product (23%). This preliminary study was followed up in 1999 by a full discussion of optimization and substrate scope.\textsuperscript{52} It was reported that with increased catalyst loading, lower temperature and a change in solvent, the yield and selectivity of the reaction was vastly improved. The same reaction with the optimized conditions now resulted in 80% yield of the E-linear vinyl sulfide and only 4% yield of the branched vinyl sulfide isomerization product B’ (Scheme 2.1b). Furthermore, the authors found that this reaction was successful with a variety of aromatic and aliphatic alkynes, both terminal and internal. However, when alkane thiols such as cyclohexane thiol were used under similar reaction conditions (ethanol, 25 °C, 5 mol% catalyst), no reaction occurred.

This finding, in addition to a similar result with Pd(OAc)\textsubscript{2},\textsuperscript{51} led to the general belief that alkane thiols could not be used for transition-metal-catalyzed alkyne hydrothiolation. The authors did not speculate on the cause for this disparity in reactivity between arene and alkane thiols. Our hypothesis was that differences in S-H bond strengths – either homolytic (PhS-H BDE = 83 kcal/mol vs. CH\textsubscript{3}S-H BDE = 89 kcal/mol) or heterolytic (PhSH pKa (H\textsubscript{2}O) = 8 vs. PhCH\textsubscript{2}SH pKa (H\textsubscript{2}O) = 15) – could be the cause of this discrepancy.\textsuperscript{87} The differences in reactivity with arene and alkane substrates is not limited to thiols; the same holds true with amines in hydroamination\textsuperscript{88} and transmetallation in certain cross-coupling reactions, such as Suzuki coupling.\textsuperscript{89}
Despite the notion that alkane thiols could not be used in previously published reports, we surmised that a more active catalyst could achieve hydrothiolation with the less reactive alkane thiols. In 2005, our group reported that Tp*Rh(PPh₃)₂ (Tp* = hydrotris(3,5-dimethylpyrazolyl)borate) was able to catalyze alkyne hydrothiolation with a variety of alkane and arene thiols giving the branched vinyl sulfide (B) in high yield and with high regioselectivity.⁶⁰ Excited by this discovery, a series of poly(pyrazolyl)borate rhodium complexes were selected to explore their ability to promote alkyne hydrothiolation with alkane thiols.⁹⁰

In the course of our work comparing other Rh(I) complexes for the alkyne hydrothiolation of alkane thiols, we tested Wilkinson’s catalyst, ClRh(PPh₃)₃, as a control experiment.⁹¹ We discovered that contrary to published results,⁵¹,⁵² it does indeed catalyze alkyne hydrothiolation with alkane thiols under similar conditions⁶⁰ as those used with the poly(pyrazolyl)borate rhodium complexes. Furthermore, it is complementary to Tp*Rh(PPh₃)₂ as it produces the E-linear vinyl sulfide. This chapter discusses the advancement of this discovery.

### 2.2 Results and Discussion

The reaction between 2,2,2-trifluoroethane thiol (1) and phenylacetylene (12) using 3 mol% of ClRh(PPh₃)₃ in 1,2-dichloroethane (DCE) unexpectedly resulted in the formation of the E-linear and branched vinyl sulfides in 90% yield as a 9:1 mixture, favouring the E-linear product. The vinyl sulfide products were identified by the diagnostic chemical shifts and coupling patterns of the olefinic protons in the ¹H NMR spectra. The olefinic protons of the linear isomers appear as two doublets (in most cases) in the ¹H NMR spectrum, typically between 6 and 7 ppm in CDCl₃. The E and Z isomers can be distinguished by their coupling constants: trans (E) olefins have larger coupling constants (12-18 Hz) than cis (Z) olefins (8-12 Hz).⁹² For these vinyl sulfides, the olefinic protons of the E-linear vinyl sulfides have coupling constants of 15-16 Hz and those of the Z-linear vinyl sulfides have coupling constants around 10-12 Hz. The olefinic proton resonances for the branched isomer typically appear between 5 and 6 ppm as two singlets. Geminal proton coupling in unsaturated systems is quite small (<1 Hz) and in most cases is not visible in the ¹H NMR spectra for these compounds.
The reactivity of Wilkinson’s catalyst toward alkane thiols in hydrothiolation was unexpected. Spurred on by this discovery, the reaction was then optimized for selectivity, time and yield and its limits tested through an evaluation of the substrate scope and functional group compatibility. The thiols and alkynes examined are shown in Charts 2.1 and 2.2.

Chart 2.1: Thiols examined for hydrothiolation activity.

Chart 2.2: Alkynes examined for hydrothiolation activity.
2.2.1 Optimization

The first reaction condition we were interested in examining was the solvent given that both yield and selectivity using arene thiols were highly solvent-dependent. Curious as to whether appropriate solvent selection was also important with respect to hydrothiolation of alkane thiols, solvent influence was examined for our test reaction between 2,2,2-trifluoroethane thiol and phenylacetylene (Table 2.1).

Table 2.1: Solvent Optimization Study.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. Amt. (mol %)</th>
<th>Solvent</th>
<th>Isolated Yield (%)</th>
<th>E:Z:B&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Toluene</td>
<td>70</td>
<td>5:0:1</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Benzene</td>
<td>85</td>
<td>5:0:1</td>
</tr>
<tr>
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<td>3</td>
<td>Hexane</td>
<td>&lt;10</td>
<td>2:0:1</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>THF</td>
<td>51</td>
<td>10:0:1</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>DCE</td>
<td>90</td>
<td>9:0:1</td>
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<td>0</td>
<td>DCE</td>
<td>0</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
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<td>50</td>
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</tr>
<tr>
<td>8</td>
<td>0</td>
<td>EtOH</td>
<td>50</td>
<td>1:4:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 0.3 mmol alkyne, 0.33 mmol thiol, 0.009 mmol catalyst, and 1.8 mL solvent. <sup>b</sup> Isomeric ratios determined by <sup>1</sup>H NMR spectroscopy.

Solvent screening was performed at room temperature using 3 mol% catalyst. All reactions were stopped after 3 hours for direct comparison. The reaction proceeded in good yield (70-85%) in both benzene and toluene with good regioselectivity of 5:1 (entries 1 and 2). The reaction was also attempted in non-polar hexanes (entry 3). Very little product formation was observed in this case, presumably because the rhodium complex was not soluble in this solvent. When the reaction was performed in polar solvents such as THF and DCE (entries 4 and 5) the selectivity was greatly enhanced to
10:1 and 9:1, respectively. Unfortunately, the yield of the reaction in THF was only moderate at 51%, possibly due to inhibition by solvent coordination to the rhodium centre. In DCE, however, the yield of the reaction was still very high (90%). In all cases, no Z-linear isomer formation was observed, which was a good indication that no radical-initiated reaction was taking place. To ensure the reaction was indeed metal catalyzed, the reaction between thiol and alkyne was performed in DCE in the absence of the Rh catalyst (entry 6). After 3 hours, no product formation was observed, proving that the catalyst is necessary for hydrothiolation to occur in DCE.

DCE may play a more significant role in catalysis. Recently, cationic Rh(I) and Ir(III) complexes with bound DCE have been reported.\textsuperscript{93,94} In both complexes, \([\text{Rh(P}^3\text{Bu}_3)_2(\text{DCE})][\text{BAR}_4^4]\) and \([\text{Ir(PPh}_3)_2(\text{H})_2(\text{DCE})][\text{BAR}_4^4]\), the solvent is bound through both chlorines. A study of the iridium complex revealed that DCE forms a stronger adduct than dichloromethane. The DCE adduct improved resistance to decomposition but retarded the rate of catalysis for olefin hydrogenation. Unlike these cationic complexes, decomposition of Tp*Rh(PPh\textsubscript{3})\textsubscript{2} occurred in pure DCE,\textsuperscript{95} requiring a co-solvent to be used for hydrothiolation. Decomposition of ClRh(PPh\textsubscript{3})\textsubscript{3} in DCE was not found to be an issue.

The reaction was also attempted using ethanol, the optimal solvent in the studies of hydrothiolation with arene thiols\textsuperscript{52} (entry 7). We expected no reaction in ethanol, thereby explaining the lack of reactivity of alkane thiols observed in that study. Interestingly, the reaction did proceed in this solvent. However, the Z-isomer was formed predominantly in this case, suggesting a background-uncatalyzed reaction. Indeed, when compared to the reaction performed in ethanol without the Rh catalyst (entry 8), the yield and selectivity were identical. Our observation of a background reaction in ethanol is inconsistent with the previous report. However, cyclohexane thiol and an unspecified alkyne (most likely 1-octyne) were used in that study and it is possible that there is no reaction between cyclohexane thiol and 1-octyne. We did not attempt to make the direct comparison to cyclohexane thiol as this particular thiol has a terrible stench even from the sealed, unopened bottle and was not opened. However, catalytic hydrothiolation with the related cyclopentane thiol (11) and diphenyl acetylene (25) was observed (vide infra Table 2.6).
Catalyst loading was also examined in DCE (reactions were allowed to run for 4.5 hours). Increasing catalyst loading to 10 mol% did not affect the reaction yield or selectivity. Decreasing the loading down to 1 mol% decreased the selectivity slightly to 6:1 but the yield was still high. However, at 0.5 mol% loading, the yield decreased slightly and some Z-isomer formation was observed (6:1 linear:branched; 10:1 E:Z). The formation of this isomer suggests that some background reaction may occur after 3 hours (further support of this is shown in section 2.2.3) and that at low catalyst loading the background reaction begins to compete with the catalytic reaction. This suggests that high selectivity for the E-linear vinyl sulfide necessitates the use of higher catalyst loading.

In addition to catalyst loading, the optimal reagent ratio was also investigated. Ogawa and coworkers observed that PhS-SPh was formed as a byproduct if excess thiol (2 equiv.) was not added drop-wise to the reaction. In our system, drop-wise addition was not necessary and disulfide formation was not observed. However, we found that if a slight excess of alkyne (1.1 equiv.) was used in the hydrothiolation reactions, a new product was observed in the $^1$H NMR spectrum of the crude reaction mixture. The $^1$H NMR data for this product is consistent with literature values for enyne formation from alkyne dimerization. The dimerization of terminal alkynes is a known reaction for Wilkinson’s catalyst (equation 2.2). Alkyne dimerization is suppressed in the presence of a slight excess of thiol (1.1 equiv.).

$$\text{Ph} = \text{ClRh(PPh}_3\text{)}_3 \rightarrow \text{Ph} = \text{Ph}$$

The effect of temperature on the reaction was examined as well. For this study, reactions were run in sealed NMR tubes. As $d_4$-DCE is quite expensive, CDCl$_3$ was used for the reactions conducted in an NMR tube ($\$125/5g$ $d_4$-DCE vs. $\$110/10g$ CD$_2$Cl$_2$ vs. $\$28/100g$ CDCl$_3$). Reactions in CDCl$_3$ occur with comparable yield and selectivity as in DCE. The reaction was monitored at 4 different temperatures: 0 °C, room temperature (20-25 °C), 40 °C and 80 °C. No significant effect was observed – the reaction was slightly slower at lower temperature and no selectivity change was noticed at higher temperature, contrary to published results with benzene thiol and 1-octyne.
It seems that the key to the success of ClRh(PPh$_3$)$_3$ catalyzed hydrothiolation with alkane thiols was the choice of the appropriate solvent: 1,2-dichloroethane. The polar, non-coordinating nature of this solvent makes it ideal for the reaction. Furthermore, heating does not seem to be required for the reaction to occur. The optimized reactions are thus: 3 mol% ClRh(PPh$_3$)$_3$, room temperature, DCE, and 1.1 equiv. of thiol.

### 2.2.2 Substrate Scope

Having found the optimal reaction conditions, we next set out to determine the scope of this reaction. Substrate scope was determined by first performing the reactions in a sealed NMR tube in CDCl$_3$. Reactions were initially tested at room temperature. If no reaction occurred or the yield of the reaction was very low, the reaction was repeated at increased temperature. All thiol/alkyne combinations were tested in the absence of catalyst on the same time scale as the catalyzed reaction to assess whether or not any background radical reaction was occurring. In some cases, a background reaction did occur, which was always considerably slower than the catalytic reaction and always favoured the Z-linear isomer. Fortunately, background reactions could be suppressed by wrapping the NMR tubes in foil to block any light-initiated radical reactions. Reaction progress was monitored by $^1$H NMR spectroscopy. Once general substrate scope was established, selected reactions that seemed most promising were performed on a larger scale to isolate the products. Full characterization was then performed on these products.$^{101}$ The results of the initial screening and larger scale studies are shown below.

We first tested the scope of this reaction with aryl alkynes, as shown in Table 2.2. The hydrothiolation of phenyl acetylene (12) with 2,2,2-trifluoroethane thiol (1) and benzyl thiol (2) (entries 1 and 2) occurred in high yield (90%). Both reactions were highly selective (9:1 and 19:1 selectivity, respectively). The preparative scale hydrothiolation in DCE (“Isol. Yield” in Table 2.2) produced similar results to the NMR tube reactions in CDCl$_3$ in both cases. The yield and/or selectivity for the E-linear vinyl sulfide were further improved, as the linear isomer was isolated as the only product.
Table 2.2: Hydrothiolation of Phenyl Acetylene with Alkane Thiols Using Wilkinson’s Catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thiol</th>
<th>Product</th>
<th>Temp, Time</th>
<th>NMR Yield\textsuperscript{a,b}, Lin:Br Ratio\textsuperscript{d}</th>
<th>Isol. Yield\textsuperscript{c}, Lin:Br Ratio\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Ph-S-S-\text{CF}_{3}</td>
<td>rt, 1h</td>
<td>90%, 9:1</td>
<td>90%, E only</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Ph-S-S-Ph</td>
<td>rt, 20h</td>
<td>90%, 19:1</td>
<td>91%, E only</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Ph-S-S-</td>
<td>rt, 24h</td>
<td>55%, 4:1</td>
<td>n/a</td>
</tr>
<tr>
<td>4\textsuperscript{e}</td>
<td>3</td>
<td>28</td>
<td>rt, 3h</td>
<td>74%, 4:1</td>
<td>n/a</td>
</tr>
<tr>
<td>5\textsuperscript{e}</td>
<td>3</td>
<td>28</td>
<td>rt, 24h</td>
<td>n/a</td>
<td>72%, 3:1</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>Ph-S-</td>
<td>rt, 9h</td>
<td>8%, B only</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>N.R.</td>
<td>rt, 20h</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>Ph-S-\text{OH}</td>
<td>70°C, 26h</td>
<td>52%, &gt;19:1</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
<td>Ph-S-\text{OR}</td>
<td>rt, 31h</td>
<td>&lt;16%, &gt;19:1</td>
<td>n/a</td>
</tr>
<tr>
<td>10\textsuperscript{g}</td>
<td>7</td>
<td>Ph-S-\text{CO}_{2}\text{Bu}</td>
<td>rt, 24h</td>
<td>n/a</td>
<td>72%, 8:1</td>
</tr>
<tr>
<td>11\textsuperscript{g}</td>
<td>8</td>
<td>Ph-S-\text{O}\text{C}_{6}</td>
<td>65°C, 24h</td>
<td>n/a</td>
<td>93%, 8:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Averaged yields of multiple runs determined by \textsuperscript{1}H NMR spectroscopy relative to internal standard. \textsuperscript{b} CDCl\textsubscript{3} \textsuperscript{c} DCE \textsuperscript{d} Isomeric ratios determined by integration of vinyl signals in \textsuperscript{1}H NMR spectra. \textsuperscript{e} 10 mol% catalyst used. \textsuperscript{f} E:Z ratio 1:1 \textsuperscript{g} Reactions performed by Paul Bichler.
n-Propane thiol (3) also reacts with phenyl acetylene (entries 3 and 4), although with lower selectivity than trifluoroethane thiol (1) and benzyl thiol (2) (entries 1 and 2). When 3 mol% catalyst is used, the reaction does not proceed beyond 55% yield. The reaction proceeds with a selectivity of 4:1, though 10 mol% of the catalyst was needed to achieve a reasonable combined yield (74%). The isolated yield for the reaction performed in DCE is similar (entry 5); however, in this case, the two isomers could not be separated by column chromatography.

The importance of thiol sterics was examined with the reaction between t-butyl thiol (4) and phenyl acetylene, which produced only the undesired branched isomer in very poor yield (entry 6). Higher catalyst loading and increased temperatures were not attempted to see if the reaction yield increased or if the selectivity improved. This thiol has an overpowering stench that quickly escapes from the glovebox. Thus, it was felt that our efforts were better focused on optimizing reactions that would avoid exposing the lab and building to the stench of t-butyl thiol.

To probe the chemoselectivity of our hydrothiolation methodology, 2-mercapto-1-ethanol (5) was reacted with phenyl acetylene. In this case, hydroalkoxylation – the addition of an O-H bond across a π-system – could also occur. Intermolecular hydroalkoxylation is not very common, so we did not expect the alcohol to react. Indeed, no reaction occurred at room temperature (entry 7); however, at elevated temperature (entry 8), new olefinic products were observed. Based on comparison to literature values, it was determined that the thiol reacted exclusively (no product of hydroalkoxylation was observed). The reaction proceeded in moderate yield (52%). Hydrothiolation occurred with excellent selectivity for the linear isomer over the branched but with poor selectivity between the E and Z forms (1:1). It is possible that the pendant alcohol could coordinate to the rhodium centre and affect the mechanism to allow the formation of the Z-linear isomer.

To test our proposal that the presence of a coordinating group causes the formation of the Z-linear isomer, we next used a thiol with an ether moiety. The reaction of bis(2-mercaptoethyl) ether (6) and phenyl acetylene did not proceed in good yield (entry 9). This substrate has two thiol groups and as such hydrothiolation could occur exclusively on one end of the molecule or on both ends. With such low reactivity and the
presence of starting material in the NMR tube, it was not possible to distinguish the product of single hydrothiolation from double hydrothiolation. The yield is calculated based on the assumption that each 2-mercaptoethyl ether molecule reacted only once with the alkyne (single hydrothiolation) so that the maximum yield of this reaction is 16% (as determined by $^1$H NMR spectroscopy). Isolation of the reaction products was not attempted, as the yield was not high enough to pursue further. Like the reaction with 2-mercapto-1-ethanol (5), the linear isomer was favoured (>19:1) but without selectivity between the two linear isomers (1:1 E:Z). This result further supports the possibility discussed above that the presence of a coordinating group results in the formation of the Z-linear isomer (vide infra section 2.2.3).

The last two reactions shown in Table 2.2 (entries 10 and 11) were performed by Paul Bichler, a fellow graduate student in the Love group, and are included to show the full functional group tolerance of this methodology. Bichler found that both an ester moiety (7) and a furan group (8) on the thiol were tolerated when reacted with phenyl acetylene. Both reactions resulted in the E-linear isomer being produced in 8:1 excess over the branched isomer with good to excellent yields (72 and 93%, respectively). Formation of the Z-linear vinyl sulfide was not observed in DCE.

Substituted aryl alkynes with electron-donating and electron-withdrawing groups in the para position were also tested to examine the effect of alkyne electronics. In Table 2.3, benzyl thiol (2) is shown to react with three para-substituted aryl alkynes. In DCE, all three reactions produce the E-linear vinyl sulfide exclusively. When the electron-donating methoxy-substituted alkyne is used (13, entry 1), hydrothiolation occurs in moderate yield (57%). When the methyl substituent is used (14, entry 2), excellent yield is observed (94%) but elevated temperature was required. Better reactivity – higher yield at room temperature – is obtained when the electron-withdrawing bromo-substituted alkyne is used (15, entry 3). This is opposite to the trend observed when Tp*Rh(PPh$_3$)$_2$ is used as the catalyst (vide infra Chapter 3).
4-Ethynylanisole (13) was reacted not only with benzyl thiol, but also with alkane thiols with ester and ether functionalities, as well as a simple alkane thiol. The yield for the reaction between propane thiol (3) and 4-ethynylanisole (13) (entry 4) is similar to that with phenyl acetylene at 50% yield when 3 mol% catalyst was used; likewise, similar selectivity was essentially achieved. Increased catalyst loading may have improved the reaction yield (as with phenyl acetylene), but was not examined.
The reaction between $n$-butyl-3-mercaptopropionate (7) and 4-ethynylanisole proceeded in good yield (78%) and good selectivity (entry 5). 2-Phenoxyethane thiol (10) reacted with 4-ethynylanisole in moderate yield and with good selectivity (entry 6). The yield of the $E$-linear isomer increased in DCE. A small amount of the $Z$-linear isomer (~10%) was observed in the $^1$H NMR spectra of the reactions with 4-ethynylanisole (13) (Table 2.2, entries 4-6). This was expected for $n$-butyl-3-mercaptopropionate (7) and 2-phenoxyethane thiol (10) because of the coordinating ability of the ether and ester moieties but unexpected for propane thiol (3). It is possible that the ether moiety on the alkyne can coordinate to the rhodium centre and thus can affect the reaction selectivity (vide infra Section 2.2.3). The $Z$-linear vinyl sulfide was not observed in the larger scale reactions in DCE.

The larger scale hydrothiolation in DCE produced similar results to the NMR tube reactions in CDCl$_3$ in most cases. In some cases, the yield and selectivity for the $E$-linear vinyl sulfide were even improved (Table 2.2 entries 1-2 and Table 2.3 entries 2 and 6). This trend shows that DCE is a superior solvent for this reaction compared to CDCl$_3$, especially since the isolated yields are obtained after purification by column chromatography. Furthermore, column chromatography allowed isolation of only the linear vinyl sulfide in many cases. The isolated products were fully characterized by NMR spectroscopy and mass spectrometry. Elemental analysis was not performed, as most of the vinyl sulfide products were present as viscous oils.

Having shown that ClRh(PPh$_3$)$_3$ effectively catalyzes hydrothiolation of aryl alkynes with a variety of alkane thiols, we were interested in testing the scope of alkynes that could be used. We started by investigating conjugated alkynes, as shown in Table 2.4. Conjugated alkynes are interesting substrates since the S-H bond can potentially add across the $\pi$-bond of both the alkyne and the alkene. Given that transition-metal-catalyzed hydrothiolation of alkenes is rare, we expected that the S-H bond would add preferentially to the alkyne C-C bond. Of further interest is that the 1,3-diene products resulting from alkyne hydrothiolation should yield potential Diels-Alder substrates.
Table 2.4: Initial Screen of Hydrothiolation of Conjugated Alkynes with Alkane Thiols Using Wilkinson’s Catalyst.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thiol</th>
<th>Alkyne</th>
<th>Product</th>
<th>Temp, Time</th>
<th>NMR Yield&lt;sup&gt;a,b&lt;/sup&gt;, Lin:Br Ratio&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Isol. Yield&lt;sup&gt;c&lt;/sup&gt;, Lin:Br Ratio&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>16</td>
<td><img src="image" alt="40" /></td>
<td>rt, 1h</td>
<td>46%, 6:1</td>
<td>n/a</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>16</td>
<td>40</td>
<td>rt, 2h</td>
<td>n/a</td>
<td>41%, 8:1</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>17</td>
<td>N.R.</td>
<td>rt, 9h</td>
<td>N.R.</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>18</td>
<td><img src="image" alt="41" /></td>
<td>rt, 5h</td>
<td>30%, 1:1</td>
<td>n/a</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2</td>
<td>16</td>
<td><img src="image" alt="42" /></td>
<td>rt, 24h</td>
<td>n/a</td>
<td>67%, 8:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Averaged yields of multiple runs determined by <sup>1</sup>H NMR spectroscopy relative to internal standard. <sup>b</sup> CDCl<sub>3</sub> <sup>c</sup> DCE <sup>d</sup> Isomeric ratios determined by integration of vinyl signals in <sup>1</sup>H NMR spectra. <sup>e</sup> Reaction performed by Paul Bichler.

In the reaction with CF<sub>3</sub>CH<sub>2</sub>SH (1) and 1-ethynylcyclohexene (16) (entry 1), hydrothiolation occurred exclusively at the alkyne position as expected. The yield of this reaction, however, was only 46% with a selectivity of 6:1 of the E-linear isomer over the branched. The selectivity was slightly improved, but the yield remained the same, when the reaction was performed in DCE (entry 2). Bichler also tested the reactivity of this enyne with benzyl thiol (2) and found the reaction occurred in higher yield and with similar selectivity (entry 5). In the reaction between benzyl thiol and 1-ethynylcyclohexene, an unidentified byproduct was observed in the crude reaction.
mixture. It is possible that some of this vinyl sulfide is reacting with unreacted alkyne to form the Diels-Alder product.

An acyclic enyne, 2-methyl-1-buten-3-yne (17), did not react with ethyl mercaptoacetate (9) (entry 3). Ethyl propiolate (18), on the other hand, does react with 2,2,2-trifluoroethanethiol (1) though in poor yield (30%) and without selectivity between the $E$-linear and branched vinyl sulfide (entry 4). The ester functional group is untouched by the reaction. The optimization of these reactions was not examined in depth but given the results seen with other substrates; future investigations could focus on higher temperature reactivity and higher catalyst loading.

In previous reports, aliphatic alkynes undergo hydrothiolation with arene thiols more readily than aromatic alkynes. The ability to use aliphatic alkynes with this methodology was also examined. A total of four aliphatic alkynes were reacted with 8 different alkane thiols, as shown in Table 2.5. Overall, these reactions were not as effective as those with aryl alkynes, presumably owing to the less activated nature of the alkynes. This was also found to be the case when Tp*Rh(PPh$_3$)$_2$ is used as the catalyst.
Table 2.5: Initial Screen of Hydrothiolation of Aliphatic Alkynes with Alkane Thiols Using Wilkinson’s Catalyst.

\[
R\text{-SH} + R' \quad \overset{\text{3 mol% } \text{ClRh(PPh}_3\text{)3}}{\text{CDCl}_3 \text{ OR DCE}} \quad E + B
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thiol</th>
<th>Alkyne</th>
<th>Product</th>
<th>Temp.</th>
<th>NMR Yield(^a,b), Lin:Br Ratio(^d)</th>
<th>Isol. Yield(^c), Lin:Br Ratio(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>19</td>
<td><img src="43" alt="Image" /></td>
<td>rt, 28h</td>
<td>72%, &gt;19:1</td>
<td>32%, E only</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>19</td>
<td>N.R.</td>
<td>rt, 72h</td>
<td>N.R.</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>20</td>
<td>TMS<img src="44" alt="Image" /></td>
<td>rt, 2h</td>
<td>50%, &gt;19:1</td>
<td>65%, E only</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>20</td>
<td>TMS<img src="45" alt="Image" /></td>
<td>70°C, 19h</td>
<td>41%, &gt;19:1</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>20</td>
<td>45</td>
<td>80°C, 24h</td>
<td>n/a</td>
<td>48%, E only</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>20</td>
<td>N.R.</td>
<td>70°C, 19h</td>
<td>N.R.</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>21</td>
<td>N.R.</td>
<td>65°C, 36h</td>
<td>N.R.</td>
<td>n/a</td>
</tr>
<tr>
<td>8(^e)</td>
<td>1</td>
<td>22</td>
<td><img src="46" alt="Image" /></td>
<td>rt, 4h</td>
<td>61%, 1:2</td>
<td>44%, 1.2:1</td>
</tr>
<tr>
<td>9(^f)</td>
<td>2</td>
<td>22</td>
<td><img src="47" alt="Image" /></td>
<td>rt, 16h</td>
<td>90%, 1:5(^g)</td>
<td>n/a</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>22</td>
<td><img src="48" alt="Image" /></td>
<td>rt, 4h</td>
<td>&lt;5%</td>
<td>n/a</td>
</tr>
<tr>
<td>11</td>
<td>3</td>
<td>22</td>
<td>48</td>
<td>70°C, 24h</td>
<td>&lt;10%</td>
<td>n/a</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>22</td>
<td>N.R.</td>
<td>rt, 72h</td>
<td>N.R.</td>
<td>n/a</td>
</tr>
</tbody>
</table>

\(^a\) Averaged yields of multiple runs determined by \(^1\)H NMR spectroscopy relative to internal standard. \(^b\) CDCl\(_3\). \(^c\) DCE. \(^d\) Isomeric ratios determined by integration of vinyl signals in \(^1\)H NMR spectra. \(^e\) Additional 3 mol% catalyst added after 2h. \(^f\) 10 mol% catalyst used. \(^g\) Double bond isomerization of branched product occurred.
Hydrothiolation of several aliphatic alkynes with 2,2,2-trifluoroethane thiol (1) was successful. Reaction with t-butyl acetylene (19) and trimethylsilyl acetylene (20) (entries 1 and 3) resulted in excellent selectivity for the E-linear isomer, presumably owing to the bulk of the alkyne, and in moderate to good yields. While the yield for the reaction with trimethylsilyl acetylene increased when performed in DCE, the isolated yield with t-butyl acetylene decreased significantly. This is most probably due to the high volatility of this substrate (bp 37-38 °C), rather than an inherent problem in reactivity. The reaction between ethyl mercaptoacetate (9) and trimethylsilyl acetylene (20) at elevated temperature (entry 4) resulted in exclusive formation of the E-linear isomer, supporting the hypothesis that alkyne bulk improves selectivity. The isolated yield of this reaction was similar in DCE at 48%.

1-Octyne (22) does not possess considerable steric bulk and as such the selectivity of the reaction with 2,2,2-trifluoroethane thiol (1) (entry 8) was poor (1:2 linear:branched) although the reaction proceeded in good overall yield. The yield increased in DCE but the selectivity remained low. Despite the poor selectivity between the linear and branched products, it is noteworthy that no double bond isomerization of the branched vinyl sulfide is observed. This is a common problem when using long straight chain aliphatic alkynes. However, isomerization to the corresponding internal vinyl sulfide does occur when benzyl thiol (2) is reacted with 1-octyne (entry 9). In fact, the major product of the reaction is the isomerization product (72% yield) in a 1:1 ratio of the E and Z isomerized products, as shown in equation 2.3. It is interesting that the reactions with 1-octyne are the only thiol/alkyne combinations to give the branched vinyl sulfide (or its isomerization product) as the major product. The mechanistic implications of this result will be discussed in Section 2.2.3. Characterization of these vinyl sulfides was a little more challenging, as the vinyl protons are no longer simple doublets as for the linear isomer or singlets for the branched isomer. Luckily these products were prepared and isolated in our group by another method. Assignments are based on comparison of the vinyl proton resonances to the reported literature values.
Recently, our group noted that this isomerization is suppressed by running the reaction in benzene instead of chloroform.\textsuperscript{103} It was hypothesized that trace HCl in the chloroform mediates this isomerization.\textsuperscript{64} The benzyl thiol reaction, however, was not pursued further since the undesired branched vinyl sulfide was the major product.

It is not surprising that \textit{n}-propane thiol (3) reacts with 1-octyne only to a limited extent (entries 10 and 11), as neither the thiol nor the alkyne possess any activating functionalities. Unfortunately, none of the other screened thiol/alkyne combinations were found to react with the aliphatic alkynes tested. This is perhaps not surprising for 2-mercaptoethyl ether (6) (entries 2 and 12), which was not very reactive with aryl alkynes. \textit{3}-Dimethylamino-1-propyne (21) did not react with \textit{n}-butyl-3-mercaptopropionate (7) (entry 7), even at elevated temperatures. The aminoalkyne could bind to the rhodium centre and preclude reactivity. This will be further discussed in Section 2.2.3.

Finally, the hydrothiolation of internal alkynes with different alkane thiols was examined (Table 2.6). Benzyl thiol (2) reacts with the unsymmetrical 1-phenylpropyne (23) at elevated temperature (50 °C) with a higher catalyst loading (10 mol\%) resulting in a good yield (entry 1). The two possible \textit{E}-linear isomers were formed in a 4:1 ratio, favouring the less sterically-hindered isomer. When this reaction was performed in DCE, the \textit{E}-isomer shown (49) was isolated in 57\% yield.
Table 2.6: Hydrothiolation of Internal Alkynes with Alkane Thiols Using Wilkinson’s Catalyst.

\[
R-SH + R\equiv\equiv R' \xrightarrow{3 \text{ mol}\% \text{ClRh(PPh}_3\text{)_3}} \text{CDCl}_3 \quad \text{R'} \equiv \equiv \text{R''} \quad \text{SR}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Thiol</th>
<th>Alkyne</th>
<th>Product</th>
<th>Temp, Time</th>
<th>NMR Yield</th>
<th>Lin:Br Ratio</th>
<th>Isol. Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{b}</td>
<td>2</td>
<td>23</td>
<td>Ph\equiv\equiv CH\equiv\equiv Ph</td>
<td>50 °C, 24h</td>
<td>87%, 4:1</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>24</td>
<td>N.R.</td>
<td>70 °C, 5d</td>
<td>N.R</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>3\textsuperscript{f}</td>
<td>11</td>
<td>25</td>
<td>Ph\equiv\equiv Ph</td>
<td>65 °C, 5d</td>
<td>54%</td>
<td>n/a</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Averaged yields of multiple runs determined by \textsuperscript{1}H NMR spectroscopy relative to internal standard. \textsuperscript{b} CDCl\textsubscript{3} \textsuperscript{c} DCE \textsuperscript{d} Isomeric ratios determined by integration of vinyl signals in \textsuperscript{1}H NMR spectra. \textsuperscript{e} 10 mol\% catalyst used. \textsuperscript{f} Reaction performed by Paul Bichler.

Unfortunately, the reaction between \textit{n}-propane thiol (3) and 3-hexyne (24) did not occur (entry 2). This is presumably due to the lack of activating functionalities in both substrates, similar to the reaction with 1-octyne (22). Diphenyl acetylene (25), on the other hand, reacts with cyclopentane thiol (11) at elevated temperature to obtain the \textit{E}-vinyl sulfide in 54\% yield (entry 3).\textsuperscript{104}

Overall, Wilkinson’s catalyst is effective for the hydrothiolation of alkynes with alkane thiols. The reaction is selective for the \textit{E}-linear isomer in most cases. The reaction is tolerant of various alkane thiols with different functional groups and is successful with aryl and aliphatic terminal and internal alkynes. Aryl alkynes with \textit{para}-substituted electron donating groups give the best yields. Bulky aliphatic alkynes result in the best selectivity. Conjugated alkynes and internal alkynes do not undergo hydrothiolation as readily. The presence of coordinating functional groups on either substrate or solvent negatively affects the reaction both in yield and selectivity. The reaction proceeds very poorly, if at all, when both the alkane thiol and the aliphatic alkyne do not possess
activating functionalities. To better understand the generality of the scope of this methodology, the mechanism of the reaction was investigated.

2.2.3 Mechanistic Studies

In the original report of ClRh(PPh\textsubscript{3})\textsubscript{3}-catalyzed alkyne hydrothiolation with arene thiols, the mechanism of the reaction was explored\textsuperscript{52}. The postulated mechanism is shown in Scheme 2.2. Oxidative addition of the arene thiol onto ClRh(PPh\textsubscript{3})\textsubscript{3} forms a rhodium hydrido sulfide, species A. After coordination of the alkyne, insertion into the Rh-H bond with \textit{syn} addition occurs thus forming a \textit{trans}-vinylrhodium species, C. Reductive elimination from this intermediate produces the \textit{E}-linear vinyl sulfide. Intermediate A is regenerated following addition of another equivalent of thiol. According to this mechanism, the \textit{E}-linear vinyl sulfide should be the product of \textit{syn} addition, meaning the H and R groups from the alkyne are on the same of the resulting olefin.
As our methodology makes use of the same rhodium complex for catalysis and produces the same isomer, it seems logical that ClRh(PPh3)3-catalyzed alkyne hydrothiolation with alkane thiols occurs by a similar mechanism as that with arene thiols. Nevertheless, two other mechanisms are feasible.

The first involves nucleophilic attack of the thiol on the alkyne. After initial alkyne coordination to the rhodium centre, the thiol could externally attack at the terminal or internal alkyne carbon via path a or b, as shown in Scheme 2.3. Protonation by a second equivalent of thiol would release the vinyl sulfide from the resulting vinylrhodium species. Both pathways occur via anti addition so that pathway a would produce the Z-linear vinyl sulfide and pathway b would produce the branched vinyl sulfide product. Both pathways of this mechanism are considered unfeasible as they would not produce the major product.

![Scheme 2.3](image)

Of course, it is possible that the Z-linear vinyl sulfide (pathway a) is initially produced in the course of the reaction and subsequently undergoes isomerization to the E-linear vinyl sulfide. This possibility was examined by preparing a sample enriched in the Z-isomer. 2,2,2-Trifluoroethane thiol (1) was combined with phenyl acetylene (12) in CDCl₃, in the absence of the rhodium catalyst. After a few days, light-induced hydrothiolation occurred producing the Z and E isomers in 38% and 16% yield, respectively, with respect to an internal standard. At this time, 3 mol% of ClRh(PPh3)3 was added to the reaction mixture, as shown in Scheme 2.4.
No evidence for isomerization was observed. The yield of the $Z$ isomer remained the same at 38%. An extra 36% of the $E$ isomer was produced as well as 2% of the branched isomer. This can be attributed to the catalyzed reaction between the unreacted thiol and alkyne. The ratio of the extra 40% product at 18:1 $E$-linear to branched is consistent with the catalyzed reaction.

The second alternative mechanism involves a rhodium vinylidene (Scheme 2.5). In this mechanism, oxidative addition of the alkyne occurs first to form a rhodium hydrido acetylide. This intermediate can then isomerize to form a rhodium vinylidene. Attack by the thiol, followed by reductive elimination, produces the linear vinyl sulfide. This mechanistic pathway, however, would not distinguish between the $E$ and $Z$ isomers, most likely producing a mixture of the two, which is not the case for our system. Furthermore, this mechanism would result in the phenyl group and the H’ from the alkyne (Scheme 2.5) being on the same carbon.
Having eliminated the nucleophilic attack mechanism, we wanted to distinguish between the oxidative addition and vinylidene mechanisms. The use of an isotopically labeled reagent would allow the determination of which mechanism is operable. Since deuterophenylacetylene, PhCCD, is commercially available, and no D-labelled thiols are commercially available, we attempted to examine the addition with deuterated alkyne. Reaction of benzyl thiol (2) with PhCCD (2% D) in the presence of Wilkinson’s catalyst led to the formation of the E-linear isomer with syn addition of the alkyne (equation 2.4).

\[
\text{PhCH}_2\text{SH} + \text{Ph} \begin{array}{c} \equiv \text{D} \end{array} \xrightarrow{3 \text{ mol}\% \text{ ClRh(PPh}_3\text{)}_3, \text{CDCl}_3} \text{Ph} \begin{array}{c} \equiv \text{D} \end{array} \text{S} \text{Bn} \quad (2.4)
\]

This simple experiment lends supports to the oxidative addition mechanism. Furthermore, this experiment and the fact that the E-linear vinyl sulfide is the major product of the reaction help to eliminate the other mechanistic possibilities. Based on this evidence, we propose that ClRh(PPh\(_3\))\(_3\)-catalyzed alkyne hydrothiolation with alkane thiols occurs by the mechanism shown in Scheme 2.2, which in turn allows rationalization of the substrate scope of the reaction.

Bulky thiols, such as t-butyl thiol (4), show no reactivity towards hydrothiolation. Given the proposed mechanism, this is expected, as after S-H activation, it would be difficult for the alkyne to get close enough to the metal center for coordination or insertion to occur. Likewise, any thiol with pendant groups that can coordinate to the metal center after oxidative addition would also hinder the approach of the alkyne. In the reaction of 2-mercapto-1-ethanol (5) and phenyl acetylene (12) (Table 2.2), no reaction occurred at room temperature but increased temperature improved reactivity. It is possible that the pendant alcohol was released from the metal center at higher temperature, allowing the alkyne to coordinate to the metal.

Furthermore, when substrates with alcohols or ethers are used, there is formation of the Z-linear vinyl sulfide. A small amount of this isomer is produced when reactions with 4-ethynylanisole (13) are performed in CDCl\(_3\) (Table 2.2), though it is unclear whether this also occurs in DCE since the isolated yield of the E-linear vinyl sulfide is
higher than the NMR yield in CDCl$_3$. The cis olefin is produced in equal amounts to the trans olefin when the coordinating ether or alcohol is on the thiol. It is not possible for the cis olefin to be prepared via the proposed mechanism; therefore we believe that with these thiols, another mechanism such as the one shown in Scheme 2.3 is operable. Since the yields of these reactions were not very high with these thiols, the mechanism was not examined further.

Coordination of pendant functionalities can also be a problem when these exist on the alkyne. If the alkyne irreversibly coordinates to the rhodium center prior to S-H activation, hydrothiolation would not occur. Irreversible alkyne coordination is more likely in cases when the alkyne can coordinate in a bidentate fashion, such as with 3-dimethylamino-1-propyne (21) (Table 2.5). This may also explain why reaction yields are lower in THF, which is a coordinating solvent.

Alkyne bulk, unlike thiol bulk, is advantageous for this reaction. The selectivity between the $E$-linear and branched vinyl sulfide is determined by directionality of the coordinated alkyne prior to insertion. In Scheme 2.2, the R group from the alkyne is shown as pointing away from the ligands on rhodium. This positioning is what leads to the formation of the $E$-linear product. If the alkyne were to coordinate in the other direction, the branched product would be formed. These two possibilities are shown in Scheme 2.6. Because of sterics, the alkyne will normally orient as shown in Scheme 2.6a and hence, the steric bulk of the alkyne essentially determines the regioselectivity of the reaction. The exception to this rule is 1-octyne.

![Scheme 2.6](image-url)
Reaction with 1-octyne (22) results in the formation of either a 1:1 mixture of the $E$-linear and branched isomer (with CF$_3$CH$_2$CH, 1) or an excess of the branched isomer (with PhCH$_2$SH, 2). The sterics of the long carbon chain of the alkyne act differently than other groups. The chain most likely does not lie only on one side of the alkyne. The chain most probably will curl up in solution; thus, there is no steric difference between the sides of the alkyne.

A similar finding was observed with the dimerization of terminal alkynes catalyzed by Wilkinson’s catalyst. It was observed that while the dimerization of phenyl acetylene led to the formation of the linear enyne, the dimerization of unsubstituted aliphatic alkynes, such as 1-octyne, led to the formation of the branched enyne.$^{97,99}$

The relative reactivity of the thiols and alkynes discussed above supports the mechanism shown in Scheme 2.2. The selectivity issues discussed also support this mechanism. Therefore, we propose that ClRh(PPh$_3$)$_3$-catalyzed alkyne hydrothiolation with alkane thiols occurs by oxidative addition of the thiol, followed by insertion of the alkyne into the Rh-H bond and subsequent reductive elimination of the $E$-linear vinyl sulfide, just as proposed for arene thiols.$^{52}$

2.3 Conclusions

We have shown that commercially available Wilkinson’s catalyst is effective for the catalytic hydrothiolation of alkynes with alkane thiols, contrary to literature reports. This methodology is selective for the $E$-linear vinyl sulfide product. The reaction is tolerant of various alkane thiols with different functional groups.

The methodology is most robust for the hydrothiolation of aryl alkynes and works for a variety of thiols with different functional groups. The selectivity is modest, however, when aliphatic unsubstituted alkane thiols are used. The hydrothiolation of aliphatic alkynes works best for bulky alkynes. Terminal and conjugated alkynes can be used in this reaction successfully. Internal alkynes bearing one arene ring can be used but necessitate the use of higher temperatures. Overall, the reaction works for a variety of alkynes and thiols with good-to-excellent yields and regioselectivities.
Several mechanisms were considered for ClRh(PPh₃)₃-catalyzed alkyne hydrothiolation. The proposed mechanism involves oxidative addition of the thiol, followed by insertion of the alkyne into the Rh-H bond, and subsequent reductive elimination. This mechanism was also proposed for alkyne hydrothiolation with arene thiols catalyzed by ClRh(PPh₃)₃, although limited data was presented in support of this hypothesis.⁵²

2.4 Experimental

2.4.1 General Procedures

Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled Vacuum Atmospheres drybox (O₂ < 2 ppm). NMR spectra were recorded on Bruker Avance 300 or Bruker Avance 400 spectrometers. ¹H, ¹³C and ¹⁹F NMR spectra are reported in parts per million and ¹H and ¹³C NMR spectra were referenced to residual solvent. Coupling constant values were extracted assuming first-order coupling. All spectra were obtained at 25 °C. 1,3,5-Trimethoxybenzene was used as an internal standard for NMR yields. Mass spectra were recorded on a Kratos MS-50 mass spectrometer.

2.4.2 Materials and Methods

Hexane, benzene, diethyl ether, THF and toluene were dried by passage through solvent purification columns.¹⁰⁵ 1,2-Dichloroethane and ethanol were distilled from molecular sieves and degassed prior to use. CDCl₃ was purified by vacuum transfer from P₂O₅ and was degassed prior to use. All organic reagents were obtained from commercial sources and distilled before use. 1,3,5-Trimethoxybenzene was sublimed prior to use. ClRh(PPh₃)₃ was purchased from Strem Chemicals and was used without further purification. Spectroscopic data for known vinyl sulfides 27E,²⁴ 27B,⁶⁰ 28B,⁶⁰ 30E,²⁴ 47E,⁶⁰ 47B,⁶⁰ 47B’,⁶⁰ and 49⁶⁰ were consistent with literature values. Compounds 32, 33, 42, and 49 were prepared by Paul Bichler.⁹¹
2.4.3 General Experimental Procedure for Hydrothiolation

NMR Tube Reactions:
RhCl(PPh$_3$)$_3$ (4 mg, 0.0045 mmol, 3 mol %) and 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol) were dissolved in CDCl$_3$ (0.9 mL) in the glove box in a screw cap NMR tube. To this solution, thiol (0.165 mmol) followed by alkyne (0.15 mmol) were added. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. If necessary, the tube was heated in an oil bath. Reaction progress was monitored by $^1$H NMR spectroscopy. Product yield and isomeric ratio were determined by comparison of the integration of the product vinylic proton peaks to the internal standard peak.

Note: When possible, a freshly prepared standard solution containing RhCl(PPh$_3$)$_3$ and 1,3,5-trimethoxybenzene in CDCl$_3$ was used.

Solvent Optimization Reactions:
RhCl(PPh$_3$)$_3$ (14 mg, 0.015 mmol, 3 mol %) was dissolved in a given solvent (3 mL) in the glove box in a 5 mL vial equipped with a magnetic stir bar and a screw cap. To this solution, thiol (0.55 mmol) followed by alkyne (0.50 mmol) were added. The vial was removed from the glove box and the reaction was stirred at the indicated temperature. The reaction was monitored by TLC. After the reaction was completed, hexanes or petroleum ether (boiling range 35-60 °C) was added to the reaction mixture to precipitate the rhodium complex. The resulting mixture was filtered through silica gel, and washed with hexanes to remove the catalyst.

Preparative Scale Reactions:
RhCl(PPh$_3$)$_3$ (14 mg, 0.015 mmol, 3 mol %) was dissolved in 1,2-dichloroethane (3 mL) in the glove box in a 5 mL vial equipped with a magnetic stir bar and a screw cap. To this solution, thiol (0.55 mmol) followed by alkyne (0.50 mmol) were added. The vial was removed from the glove box and the reaction was stirred at the indicated temperature. The reaction was monitored by TLC. After the reaction was completed, hexanes or petroleum ether (boiling range 35-60 °C) was added to the reaction mixture to precipitate the rhodium complex. The resulting mixture was filtered through silica gel, washed by
hexanes or petroleum ether, and concentrated under vacuum. Flash chromatography (SiO$_2$, hexane or a mixture of hexane:ethyl acetate as eluent) provided the product.

### 2.4.4 Analytical data for hydrothiolation products

**26E**: Yellow Oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.33 – 7.25 (m, 5H), 6.73 (d, 1H, $J = 15.6$ Hz), 6.65 (d, 1H, $J = 15.6$ Hz), 3.32 (q, 2H, $J = 9.6$ Hz). $^{19}$F/$^1$H NMR (CDCl$_3$, 300 MHz): δ –66.8. $^{13}$C/$^1$H NMR (CDCl$_3$, 300 MHz): δ 136.0, 131.8, 128.7, 127.8, 126.0, 121.0, 36.0 (q, $J = 33$ Hz), 29.7. HRMS (EI) m/z calcd for C$_{10}$H$_9$SF$_3$: 218.0377; found: 218.0377.

**26B**: Observed *in situ* as mixture with E-linear product. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.33 – 7.25 (m, 5H), 5.61 (s, 1H), 5.54 (s, 1H), 3.10 (q, 2H, $J = Hz$). $^{19}$F/$^1$H NMR (CDCl$_3$, 300 MHz): δ –66.4.

**28E**: Yellow oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.55 – 7.20 (m, 5H), 6.72 (d, 1H, $J = 15.6$ Hz), 6.46 (d, 1H, $J = 15.6$ Hz), 2.77 (t, 2H, $J = 7.3$ Hz), 1.72 (q, 2H, $J = 7.3$ Hz), 1.03 (t, 3H, $J = 7.3$ Hz).

**29B**: Diagnostic vinyl peaks observed *in situ*.

$^1$H NMR (CDCl$_3$, 300 MHz): δ 5.98 (s, 1H), 5.76 (s, 1H).

**30Z**: Observed *in situ* as mixture with E-linear product.

$^1$H NMR (CDCl$_3$, 300 MHz): δ 7.50 – 7.27 (m, 5H), 6.47 (d, 1H, $J = 10.8$ Hz), 6.20 (d, 1H, $J = 10.8$ Hz), 3.82 (t, 2H, $J = 6$ Hz), 2.95 (t, 2H, $J = 6$ Hz), 2.18 (s, br, 1H).
31E: Diagnostic vinyl peaks observed *in situ* as mixture with Z-linear product.  

$^1$H NMR (CDCl$_3$, 300 MHz): δ 6.67 (d, 1H, $J = 15.7$ Hz), 6.46 (d, 1H, $J = 15.7$ Hz).

31Z: Diagnostic vinyl peaks observed *in situ* as mixture with E-linear product.  

$^1$H NMR (CDCl$_3$, 300 MHz): δ 6.39 (d, 1H, $J = 10.7$ Hz), 6.21 (d, 1H, $J = 10.7$ Hz).

34E: Pale yellow - white solid. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.40 – 7.27 (m, 5H), 7.21 (d, 2H, $J = 8.8$ Hz), 6.85 (d, 2H, $J = 8.8$ Hz), 6.58 (d, 1H, $J = 15.6$ Hz), 6.53 (d, 1H, $J = 15.6$ Hz), 4.00 (s, 2H), 3.81 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 400 MHz): δ 158.8, 137.4, 129.8, 128.8, 128.6, 128.4, 127.2, 126.8, 121.5, 114.0, 37.6, 55.2.

35E: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.40-7.30 (m, 5H), 7.17 (d, 1H, $J = 8.2$ Hz), 7.10 (d, 1H, $J = 8.2$ Hz), 6.66 (d, 1H, $J = 15.6$ Hz), 6.53 (d, 1H, $J = 15.6$ Hz), 4.01 (s, 2H0, 3.17 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 400 MHz): δ 137.3, 136.8, 134.2, 128.3, 128.8, 129.6, 128.4, 127.3 125.5, 123.0, 37.5, 21.1. HRMS (EI) m/s calcd for C$_{16}$H$_{16}$S: 240.09727; found: 240.09717.

35B: Observed *in situ* as mixture with E-linear product.  

$^1$H NMR (CDCl$_3$, 300 MHz): δ 7.09-6.99 (m, 4H), 5.35 (s, 1H), 5.10 (s, 1H), 3.81 (s, 3H), 2.29 (s, 2H).
36E: Off-white solid. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.39 (d, 2H, $J = 8.5$ Hz), 7.36 – 7.30 (m, 5H), 7.10 (d, 2H, $J = 8.4$ Hz), 6.71 (d, 1H, $J = 15.6$ Hz), 6.44 (d, 1H, $J = 15.6$ Hz), 4.01 (s, 2H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 300 MHz): δ 131.7, 131.4, 128.8, 128.7, 128.5, 127.4, 127.2, 127.0, 126.3, 125.5, 37.4. HRMS (EI) m/s calcd for C$_{15}$H$_{13}$SBr: 303.9921; found: 303.9917.

37E: Diagnostic vinyl peaks observed in situ as mixture with Z-linear and branched products.
$^1$H NMR (CDCl$_3$, 300 MHz): δ 6.49 (d, 1H, $J = 15.6$ Hz), 6.38 (d, 1H, $J = 15.6$ Hz).

37Z: Diagnostic vinyl peaks observed in situ as mixture with E-linear and branched products.
$^1$H NMR (CDCl$_3$, 300 MHz): δ 6.31 (d, 1H, $J = 11$ Hz), 6.03 (d, 1H, $J = 11$ Hz).

37B: Diagnostic vinyl peaks observed in situ as mixture with E- and Z-linear products.
$^1$H NMR (CDCl$_3$, 300 MHz): δ 5.31 (s, 1H), 5.03 (s, 01H).

38E: Diagnostic vinyl peaks observed in situ as mixture with Z-linear and branched products.
$^1$H NMR (CDCl$_3$, 300 MHz): δ 6.45 (s, 2H).

38Z: Diagnostic vinyl peaks observed in situ as mixture with E-linear and branched products.
$^1$H NMR (CDCl$_3$, 300 MHz): δ 6.36 (d, 1H, $J = 10.8$ Hz).
**38B:** Diagnostic vinyl peaks observed *in situ* as mixture with *E-* and *Z-*linear products.

$^1$H NMR (CDCl$_3$, 300 MHz): δ 5.38 (s, 1H), 5.13 (s, 1H).

**39E:** Solid. $^1$H NMR (CDCl$_3$, 400 MHz):

δ 7.30–7.22 (m, 4H), 6.96 (t, 1H, $J = 5.5$ Hz), 6.91 (d, 2H, $J = 6.0$ Hz), 6.83 (d, 2H, $J = 6.0$ Hz), 6.60 (d, 2H, $J = 15.6$ Hz), 6.55 (d, 1H, $J = 15.6$ Hz), 4.20 (t, 2H, $J = 6.9$ Hz), 3.80 (s, 3H), 3.14 (t, 2H, $J = 6.9$ Hz).

$^{13}$C{$^1$H} NMR (CDCl$_3$, 400 MHz): δ 158.9, 158.3, 129.6, 129.5, 128.8, 126.9, 121.3, 121.1, 114.6, 114.1, 67.1, 55.3, 32.0. HRMS (EI) m/s calcd for C$_{17}$H$_{18}$SO$_2$: 286.1028; found: 286.1031.

**39Z:** Diagnostic vinyl peaks observed *in situ* as mixture with *E-*linear and branched products.

$^1$H NMR (CDCl$_3$, 300 MHz): δ 6.38 (d, 1H, $J = 10.6$ Hz), 6.10 (d, 1H, $J = 10.6$ Hz).

**39B:** Diagnostic vinyl peaks observed *in situ* as mixture with *E-* and *Z-*linear products.

$^1$H NMR (CDCl$_3$, 300 MHz): δ 5.37 (s, 1H), 5.22 (s, 1H).

**40E:** Oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 6.40 (d, 1H, $J = 15.2$ Hz), 5.99 (d, 1H, $J = 15.2$ Hz), 5.75 (m, 1H), 3.22 (q, 2H, $J = 9.7$ Hz), 2.12 (m, 4H), 1.63 (m, 4H). $^{19}$F{$^1$H} NMR (CDCl$_3$, 300 MHz): δ -66.8.

**40B:** Diagnostic vinyl peaks observed *in situ* as mixture with *E-*linear product.

$^1$H NMR (CDCl$_3$, 300 MHz): δ 5.40 (s, 1H), 5.35 (s, 1H).
41E: Diagnostic vinyl peaks observed *in situ* as mixture with branched product.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.55 (d, 1H, $J = 15.3$ Hz), 5.94 (d, 1H, $J = 15.3$ Hz)

41B: Diagnostic vinyl peaks observed *in situ* as mixture with *E*-linear product.

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.53 (s, 1H), 5.93 (s, 1H).

43E: Yellow Oil. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 5.94 (d, 1H, $J = 15.2$ Hz), 5.85 (d, 1H, $J = 15.2$ Hz), 3.17 (q, 2H, $J = 9.7$ Hz), (s, 9H). $^{19}$F{$^1$H} NMR (CDCl$_3$, 300 MHz): $\delta$ -66.7. $^{13}$C{$^1$H} NMR (CDCl$_3$, 300 MHz): $\delta$ 162.4, 146.5, 116.4, 36.1 (q, $J = 33$Hz), 34.3, 29.2. HRMS (EI): calcd for C$_8$H$_{13}$SF$_3$: 198.0690; found: 198.06912.

44E: Yellow Oil. $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 6.42 (d, 1H, $J = 18.0$ Hz), 5.93 (d, 1H, $J = 18.0$ Hz), 3.31 (q, 2H, $J = 9.7$ Hz), 0.08 (s, 9H). $^{19}$F{$^1$H} NMR (CDCl$_3$, 300 MHz): $\delta$ -66.8. $^{13}$C{$^1$H} NMR (CDCl$_3$, 300 MHz): $\delta$ 135.9, 129.0, 34.3 (q, $J = 33$ Hz), -1.2. HRMS (EI) m/z calcd for C$_7$H$_{13}$SSiF$_3$: 214.0459; found: 214.0459.

45E: Yellow Oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 6.60 (d, 1H, $J = 18.1$ Hz), 5.80 (d, 1H, $J = 18.1$ Hz), 4.21 (q, 2H, $J = 7.1$ Hz), 3.48 (s, 2H), 1.29 (t, 3H, $J = 7.1$ Hz), 0.08 (s, 9H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 400 MHz): $\delta$ 169.5, 136.5, 126.7, 61.5, 33.5, 14.1, -1.3. HRMS (EI) m/z calcd for C$_9$H$_{18}$SSiO$_2$: 218.0797; found: 218.0802.
**46E+46Z**: Yellow Oil. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 5.97–5.87 (m, 2.2H, E), 5.17 (s, 1H, Z), 4.99 (s, 1H, Z), 3.99 (q, 2H, $J = 7.2$ Hz, Z), 3.16 (q, 2.4H, $J = 7.6$ Hz, E), 2.26 (t, 2H, $J = 7.6$ Hz, Z), 2.08 (q, 2.4H, $J = 6.7$ Hz, E), 1.58-1.28 (m, 17.6H, 1.2E+Z), 0.91-0.84 (m, 6.6H, 1.2E+Z).

$^{19}$F{$^1$H} NMR (CDCl$_3$, 300 MHz): $\delta$ -66.3 (1.2F, E), -66.9 (1F, Z).

$^{13}$C{$^1$H} NMR (CDCl$_3$, 400 MHz): $\delta$ 143.0, 136.6, 120.3, 109.9, 36.8, 36.2 (q, $J = 33$ Hz), 33.9 (q, $J = 33$ Hz), 32.9, 31.6, 28.8, 28.7, 28.5, 28.3, 22.6, 14.0. HRMS (EI) m/z calcd for C$_{10}$H$_{17}$SF$_3$: 226.1003; found: 226.0999.
Chapter 3: Mechanism of Tp*Rh(PPh₃)₂-Catalyzed Alkyne Hydrothiolation

3.1 Introduction

Transition metal complexes have become essential to the synthetic organic community as reaction catalysts. They not only catalyze or accelerate reactions that otherwise would not occur but they can also control the selectivity of a particular reaction. In alkyne hydrothiolation, shown in equation 3.1, the use of transition metals has allowed control of regioselectivity. Rhodium and iridium complexes generally catalyze the formation of the E-linear vinyl sulfide (equation 3.1);⁵²,⁵⁴,⁵⁵,⁶¹,⁹¹ while the use of palladium, nickel or actinide complexes typically allow the formation of the branched vinyl sulfide B as the major product.⁵¹,⁵³,⁶²-⁶⁵,⁶⁷,¹⁰⁶ Until recently, this trend has held for the reported catalysts of alkyne hydrothiolation with arene thiols.

\[
\begin{align*}
\text{RSH} + & \quad \text{E-linear} \quad \text{SR} + \quad \text{Z-linear} \quad \text{R}^1\text{SR} + \quad \text{Branched} \\
\text{R}^1\equiv & \quad \text{SR} + \quad \text{SR}
\end{align*}
\]

The first example of metal-catalyzed alkyne hydrothiolation with alkane thiols was reported by our group in 2005 using a pyrazolylborate rhodium complex.⁶⁰ Tp*Rh(PPh₃)₂ (Tp* = hydrotris(3,5-dimethylpyrazolyl)borate) was shown to be a highly active catalyst for hydrothiolation. A variety of alkane thiols reacted with aromatic, aliphatic, terminal and internal alkynes in good yield and with excellent selectivity (selected examples are shown in Figure 3.1). Contrary to other rhodium-catalyzed hydrothiolations, the branched isomer was formed selectively. Furthermore, when Tp*Rh(PPh₃)₂ was used for hydrothiolation with arene thiols, the branched isomer was still formed as the major product, though with modest selectivity.
Motivated by the success of the Tp* ligand in affecting this transformation for rhodium, a variety of other polypyrazolylborate rhodium bis(triphenylphosphine)
complexes, (PPB)Rh(PPh$_3$)$_2$ (PPB = polypyrazolylborate), were prepared by Lauren Fraser, an M.Sc. student in the group.$^{90,107}$ The different ligands are shown in Figure 3.2.

![Polypyrazolylborate ligands](image)

**Figure 3.2: Polypyrazolylborate ligands screened for (PPB)Rh(PPh$_3$)$_2$-catalyzed hydrothiolation.**

Polypyrazolylborate ligands have gained popularity over the past few decades since they were first reported by Trofimenko in 1966.$^{108,109}$ These scorpionate ligands are commonly referred to as Cp (cyclopentadienyl) analogs due to their similar electronic properties: they are both monoanionic, 6-electron donor ligands, which can occupy up to three metal coordination sites.$^{109}$ However, PPBs have some advantages over Cp ligands in that they are more tunable with many sites of substitution on the pyrazolyl group, as well as the boron atom. Futhermore, they are easier to handle as the sodium and potassium salts of the PPBs are air stable. Polypyrazolylborate complexes gained notoriety for their ability to activate C-H bonds.$^{110-117}$ Moreover, rhodium polypyrazolylborate complexes have been used as catalyst precursors for alkyne polymerization,$^{118-120}$ hydrophosphinylation,$^{121}$ hydroformylation,$^{122}$ hydrosilylation,$^{123}$ hydroamination$^{124}$ and cyclopropanation$^{125}$.

These complexes were tested as precatalysts for hydrothiolation by Fraser.$^{90,107}$ We were interested in determining if the branched isomer is the major product when different polypyrazolylborates were used. Indeed, the branched vinyl sulfide was the
major product for all the active complexes screened (Table 3.1). It was found that ligand
denticity and pyrazolyl group substitution were important to reaction efficacy. The
corresponding bidentate ligand (Bp*) was inferior to the tridentate ligand (Tp*) in both
yield and selectivity. Furthermore, the unsubstituted ligands (Bp and Tp) were either
catalytically inactive or did not catalyze the reaction in good yield or promote selectivity.

Table 3.1: (PPB)Rh(PPh₃)₂-Catalyzed Alkyne Hydrothiolation.⁹⁰,¹⁰⁷

```
\[
\begin{array}{|c|c|c|}
\hline
\text{Entry} & \text{PPB} & \text{R = Ph} & \text{R = CF₃} \\
\hline
1 & \text{Tp*} & 2\text{h}, 93\%, 16:1 & 2\text{h}, 65\%, 3:1 \\
2 & \text{Bp} & 24\text{h}, 24\%, 1:1^b & 24\text{h}, \text{N.R.} \\
3 & \text{Bp*} & 2\text{h}, 55\%, 5:1 & 2\text{h}, 32\%, 1:1^b \\
4 & \text{Tp} & 24\text{h}, 7\%^c, \text{Z only} & 48\text{h}, 14\%, \text{E+Z only} \\
5 & \text{Tp}^{\text{Ph}} & 2\text{h}, 87\%, 11:1 & 2\text{h}, 64\%, 4:1 \\
6 & \text{Tp}^{\text{Ph,Me}} & 2\text{h}, 78\%, 6:1 & 2\text{h}, 84\%, 4:1 \\
\hline
\end{array}
\]

^a Isolated yields. ^b Z was also observed. ^c Conversion.
```

Based on Fraser’s work, we were curious as to how the polypyrazolylborate
ligand affects the regioselectivity of the reaction, and as such, we were interested in
comparing the mechanism of the Tp*Rh(PPh₃)₂-catalyzed reaction to other rhodium
hydrothiolation catalyst precursors, such as ClRh(PPh₃)₃. To this end, we postulated five
different mechanistic possibilities for Tp*Rh(PPh₃)₂-catalyzed alkyne hydrothiolation, as
described below.
3.1.1 S-H Activation Followed by Alkyne Insertion into the Rh-H Bond

As discussed in Chapter 2, following our discovery that Tp*Rh(PPh₃)₂ catalyzes hydrothiolation with alkane thiols, we discovered that ClRh(PPh₃)₃ also catalyzes alkyne hydrothiolation with alkane thiols. The two precatalysts, however, produce different regioisomeric products, with ClRh(PPh₃)₃ giving the E-linear vinyl sulfide. While this is of significant merit for the synthetic community, in that there are now two complimentary methods for forming the two different isomers from alkane thiols, we were still puzzled by the mechanistic basis of this change in regioselectivity. The two precatalysts differ simply in their anionic ligands: Cl vs. Tp*.

In a report by Ogawa and coworkers on ClRh(PPh₃)₃-catalyzed hydrothiolation with arene thiols, a mechanism involving oxidative addition of the thiol onto rhodium followed by syn insertion of the alkyne into the Rh-H bond was proposed. Subsequent reductive elimination generates the vinyl sulfide product (Scheme 3.1). Depending on the orientation of the alkyne prior to insertion, two different isomers could be formed. If the alkyne is oriented so that the R group points away from the ligands (1,2-insertion), as depicted in Scheme 3.1, then the E-linear vinyl sulfide is formed. When Wilkinson’s catalyst was used both with arene thiols and alkane thiols, the E-linear product was formed selectively. Mechanistic investigations with arene thiols suggest that Wilkinson’s catalyst goes through this mechanism for alkyne hydrothiolation. Our investigations with alkane thiols support this mechanism being operative for alkane thiols as well.
To form the branched product, the alkyne would have to be oriented in the opposite direction prior to insertion with the alkyne R group pointing toward the rhodium ligands (2,1-insertion), as shown in Scheme 3.2b. However, it is unlikely that the alkyne would orient itself this way when a bulkier ligand (Tp* vs Cl) is present, particularly since there is still good selectivity when bulky alkynes are used.

Scheme 3.1

Scheme 3.2
This type of oxidative addition – insertion – reductive elimination mechanism is very common in transition metal catalysis.\textsuperscript{126} It has also been proposed for alkene hydrogenation by Wilkinson’s catalyst.\textsuperscript{127} This series of steps is also commonly seen in many cross-coupling reactions, such as the Heck reaction.\textsuperscript{128,129} Furthermore, this mechanism is also invoked for other H-E additions to \( \pi \)-systems such as some hydroaminations and hydrophosphinylation.\textsuperscript{85}

\subsection*{3.1.2 S-H Activation Followed by Alkyne Insertion into the Rh-S Bond}

An alternative to the oxidative addition mechanism with insertion into the Rh-H bond, described in Section 3.1.1, is insertion of the alkyne into the Rh-S bond. If the alkyne is oriented in the more favourable orientation as dictated by sterics, insertion of the alkyne into the Rh-S bond followed by reductive elimination would produce the branched vinyl sulfide product, as shown in Scheme 3.3.
An early example of insertion of an alkyne into a Rh-S bond involves the addition of an electron deficient alkyne. Dimethyl acetylenedicarboxylate (DMAD) inserts into the Rh-S bond of a rhodium carbon disulfide complex, CpRh(PPh₃)(CS₂). The structure of the complex is shown below (equation 3.2). Examples of alkyne insertions into other Rh-S and other M-S bonds have also been reported for M = Mo, W, Ru, Co, Mn, Fe, Pd and Pt. The palladium and platinum reports are of particular interest as they relate directly to alkyne hydrothiolation and other alkyne thiolations (RS-G additions to alkynes).

In an effort to investigate the mechanism of RS-G additions to alkynes catalyzed by Pd and Pt complexes, the insertion of DMAD into a Pd-S bond was explored. The reaction between (dppe)Pd(SAr)₂ and excess DMAD definitively showed that single and double insertion of an alkyne into a Pd-S bond is possible (equation 3.3). Further study of the insertion product indicated that the insertion kinetically favours syn insertion of the alkyne. Evidence of alkyne insertion into a Pt-S bond was also investigated by the same research group. Terminal alkynes, such as phenyl acetylene, were observed to insert into the Pt-S bond of trans-(PPh₃)₂Pt(SAr)Cl (equation 3.4). The use of this complex allowed study of alkyne insertion without subsequent reductive elimination. Once again syn insertion was observed as the kinetic product.
As evidenced by the examples above, the insertion of an alkyne into a M-S bond is possible. Insertion into a M-X bond (X = heteroatom) in the presence of a M-H bond is more rare, but has also been reported. For example, the insertion of a carbonyl group into a Rh-Si bond preferably over a Rh-H bond in complexes of the type Rh(H)(SiR₃)X has been established as the key aspect of rhodium-catalyzed hydrosilylation (addition of an H-Si bond) of ketones and aldehydes. Likewise, catalytic alkyne hydrosilylation by an iridium complex has been proposed to proceed via selective alkyne insertion into the Ir-Si bond with no observed insertion into the Ir-H bond (Scheme 3.4). This proposal was made by the elimination of other hypothesized mechanisms based on product analysis and rational arguments. Moreover, insertion of an alkyne into an M-X bond in the presence of an M-H bond has been proposed to occur in Pd-catalyzed hydrostannation, Ru-catalyzed hydroamination, and Pt-catalyzed hydrothiocarboxylation.

Furthermore, examples of insertions of unsaturated molecules into a Pt-N or Pt-O bond in the presence of a Pt-H bond have been observed and definitively characterized, as reductive elimination of the organics requires elevated temperature. Phenyl isocyanate, CO₂, CS₂, acrylonitrile and methylacrylate all insert into the Pt-N bond of trans-(H)Pt(NHPh)(PEt₃)₂ selectively. Phenyl isocyanate was also shown to insert selectively into the Pt-O bond of (H)Pt(OPh)(PEt₃)₂.

3.1.3 Disulfide Intermediate

The generally accepted mechanism for nickel and palladium hydrothiolation catalysts involves a metal disulfide species, LnM(SR)₂, as the active catalyst. This mechanism was also proposed for the actinide hydrothiolation precatalysts. The mechanism involves initial ligand exchange from the catalyst precursor to form the
catalytically active species $L_nM(SR)_2$. Alkyne insertion into one of the M-S bonds yields a metal vinyl species. Protonolysis by another equivalent of thiol yields the branched vinyl sulfide and regenerates the active catalyst. This mechanism is shown in Scheme 3.5.

Scheme 3.5

Shortly after our report on the catalytic activity of Tp*Rh(PPh$_3$)$_2$ towards hydrothiolation, Mizobe and coworkers reported that another rhodium polypyrazolylborate complex, Tp*Rh(coe)(MeCN) (coe = cyclooctene), catalyzes alkyne hydrothiolation with arene thiols.$^{61}$ The branched vinyl sulfide is again the major product, indicating that the polypyrazolylborate ligand is indeed the source of the change in regioselectivity. Hydrothiolation with alkane thiols was not reported.

In this report, the catalytic mechanism was investigated and the results eliminated the possibility of the two S-H activation mechanisms and indicated the intermediacy of a rhodium disulfide complex. The precatalyst initially reacts with two equivalents of the thiol to form a disulfide species Tp*Rh(SR)$_2$(MeCN), with concomitant loss of H$_2$ (Scheme 3.6). Loss of the acetonitrile ligand is then followed by insertion of the alkyne into one of the Rh-S bonds. Protonation by another equivalent of thiol releases the
branched vinyl sulfide and coordination of the resulting deprotonated thiol reforms the active rhodium species.

![Scheme 3.6](image)

### Alkyne C-H Activation/Vinylidene Intermediate

It is also possible to envision a catalytic cycle starting with oxidative addition of the alkyne onto rhodium. C-H activation would result in a rhodium hydrido acetylide. This intermediate would then quickly isomerize to the rhodium vinylidene.\textsuperscript{154-158} Attack by thiol and subsequent release from rhodium would result in a mixture of the two linear isomers, as shown in Scheme 3.7.

![Scheme 3.7](image)

Metal vinylidenes have been invoked as intermediates in catalysis to rationalize anti-Markovnikov additions of nucleophiles to alkynes,\textsuperscript{159} such as rhodium-catalyzed alkyne hydroalkoxylation\textsuperscript{85} and hydroboration\textsuperscript{160}. A key drawback of reactions that occur through this mechanism is that only terminal alkynes can form vinylidenes; therefore, additions to internal alkynes cannot occur via this mechanism. A vinylidene intermediate was proposed for another polypyrazolylborate rhodium complex for a different hydroelement addition reaction. TpRh(C\(_2\)H\(_4\))\(_2\)/PPh\(_3\) was used to catalyze alkyne hydroamination, the addition of an N-H bond across a C-C triple bond.\textsuperscript{124} This catalyst
produces the anti-Markovnikov enamine for secondary amines or imines for primary amines.

3.1.5 Transition-Metal-Assisted Nucleophilic Attack

It is also possible that the hydrothiolation mechanism does not involve oxidative addition at all. One such possibility involves external nucleophilic attack of the thiol, sometimes referred to as a Wacker-type mechanism. Initial coordination, but not C-H activation, of the alkyne would activate the alkyne toward nucleophilic attack. The thiol could then attack at either the terminal or internal carbon of the alkyne. Release of the vinyl sulfide product would then occur by protonation. This mechanism could produce two different vinyl sulfides depending on which carbon is attacked, as shown in Scheme 3.8. If the terminal carbon is attacked (pathway a, Scheme 3.8), the Z-linear isomer is produced. If the internal carbon is attacked (pathway b, Scheme 3.8), the branched isomer is produced. Both of these products would occur via anti addition.

Scheme 3.8

This type of mechanism has been proposed for the hydrothiolation of 1-alkynylphosphines catalyzed by Pd(OAc)$_2$\textsuperscript{56}. The phosphine coordinates to the palladium center thereby activating the alkyne towards nucleophilic attack by the thiol. The thiol attacks at the terminal carbon with anti-addition to afford Z-1-phosphino-2-thio-1-alkenes.

This mechanism is also commonly proposed for intramolecular hydrothiolation. The intramolecular hydrothiolation of Z-2-en-4-yn-1-thiols to form substituted thiophenes is also postulated to occur through electrophilic activation of the alkyne by
PdI$_2$ and intramolecular nucleophilic attack by the thiol group.

Metal-assisted nucleophilic attack is also proposed for gold-catalyzed $\alpha$-thioallene hydrothiolation. In this reaction, the gold catalyst coordinates to the terminal allenic double bond to promote intramolecular attack of the thiol group.

3.1.6 Summation of Mechanistic Possibilities

Five possible mechanisms for Tp*Rh(PPh$_3$)$_2$-catalyzed alkyne hydrothiolation of alkane thiols have been proposed. Other mechanisms may be possible; however, the mechanisms presented above were identified as being the most likely, based on comparison to related reactions. These mechanisms thus serve as a starting point for our analysis. A summary of the vinyl sulfides that can be produced by these mechanisms is shown below (see Table 3.2). In the following sections, some of these mechanistic possibilities will be eliminated based on product distribution and steric arguments. Following analysis of product distribution, a series of stoichiometric reactions are examined. Finally, kinetic analysis of the reaction and substrate scope analysis were performed to elucidate the mechanistic details of this transformation. These results permitted a number of the likely possible mechanisms to be dismissed. However, definitively distinguishing between the remaining mechanisms proved to be difficult. Nevertheless, these studies provide a strong foundation for future mechanistic exploration of this intriguing ligand effect on regioselectivity. Suggestions for future directions, to be pursued by a new graduate student joining this summer, are presented in Chapter 4.
3.2 Results and Discussion

3.2.1 Product Analysis

Two of the mechanistic possibilities mentioned in the introduction – S-H activation followed by alkyne 1,2-insertion into the Rh-H bond (Section 3.1.1) and C-H activation of the alkyne (Section 3.1.4) – can be eliminated as possibilities based on the vinyl sulfides formed when Tp*Rh(PPh₃)₂ is used as the catalyst (see Table 3.2). As mentioned earlier, the branched vinyl sulfide is the major product of the reaction and the E-linear vinyl sulfide is sometimes produced as a minor product. In the first mechanism, the sterically favoured alkyne insertion route would produce only the observed minor product. This mechanism may account for the formation of the E-linear vinyl sulfide as a minor product but is not the predominant mechanism. S-H activation followed by alkyne 2,1-insertion into the Rh-H bond would produce the correct vinyl sulfide, however, due to steric considerations, we do not believe that 2,1-insertion would occur with a substituted trispyrazolylborate ligand present when it does not occur for a small chloride ligand.

### Table 3.2: Products Expected from Proposed Mechanisms.

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>R(^1)SR</th>
<th>E</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-H Activation/Rh-H Insertion</td>
<td>minor</td>
<td>major</td>
<td>--</td>
</tr>
<tr>
<td>S-H Activation/Rh-S Insertion</td>
<td>major</td>
<td>minor</td>
<td>--</td>
</tr>
<tr>
<td>Disulfide Intermediate</td>
<td>major</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>C-H Activation</td>
<td>--</td>
<td>possible</td>
<td>possible</td>
</tr>
<tr>
<td>TM-Assisted Nucleophilic Attack</td>
<td>possible</td>
<td>--</td>
<td>possible</td>
</tr>
</tbody>
</table>
There are examples of the steric barrier to 2,1-insertion being overcome by an electronic preference, such as in styrene polymerization.\(^{161}\) However, there are also examples of unsaturated substrates with an electronic preference for 2,1-insertion, such as acrylates, inserting in a 1,2-fashion when bulky ligands are present on the metal.\(^{162}\) Furthermore, an examination of alkene insertions into Rh-X bonds \((X = N, O, C)\) found that there is a large activation barrier difference between 1,2- and 2,1-alkene insertions into these bonds.\(^{163}\) For example, the calculated difference in energy for these two processes into Rh-NH\(_2\) is 5.4 kcal/mol and it is 7.6 kcal/mol for insertion into Rh-OH. It was also found that the barrier to insertion was higher for Rh-CH\(_3\). It is suggested that the reason the barrier is much higher for insertion into the Rh-C bond over the Rh-N or Rh-O bond has to do with the ability of N and O to coordinate dative. This increases the bond order of the metal in the transition state and lowers the activation barrier to insertion.

The C-H activation mechanism does not lead to formation of the branched vinyl sulfide but instead leads to a mixture of the linear isomers. In Tp*Rh(PPh\(_3\))\(_2\)-catalyzed alkyne hydrothiolation, formation of the Z-linear isomer is not observed at all and the E-linear isomer is only observed as a minor product. Furthermore, hydrothiolation of internal alkynes is catalyzed by Tp*Rh(PPh\(_3\))\(_2\), which would not be possible by this mechanism. Moreover, a postdoctoral fellow in our group, Changsheng Cao, isolated the Rh hydrido acetylide and treated it with thiol (Scheme 3.9).\(^{164}\) No reaction occurred, indicating that the rhodium hydrido acetylide complex cannot enter the catalytic cycle.

\[
\text{Scheme 3.9}
\]

Thus, the S-H activation/Rh-H insertion and C-H activation mechanisms can be eliminated as mechanistic possibilities. The remaining three possibilities are: S-H oxidative addition with alkyne insertion into the Rh-S bond, formation of a L\(_n\)Rh(SR)\(_2\) complex as the active catalyst, and transition-metal-assisted nucleophilic attack. We therefore set out to differentiate between these mechanisms.
The mechanistic investigations into Tp*Rh(PPh₃)₂-catalyzed hydrothiolation were performed using benzyl thiol and phenylacetylene. These particular substrates were chosen because of their relatively low volatility (compared to propane thiol or tert-butylacetylene). This combination was also chosen because of its high yield and selectivity at room temperature. Furthermore, this allows more direct comparison to ClRh(PPh₃)₃, whose mechanistic analysis was performed with the same thiol/alkyne pair (Chapter 2).

3.2.1.1 Syn vs Anti Addition

Of the three remaining mechanisms proposed for Tp*Rh(PPh₃)₂-catalyzed alkyne hydrothiolation, two provide vinyl sulfides solely from syn insertion (the S-H activation/Rh-S insertion and the disulfide intermediate mechanisms). The other would produce some or only anti addition products (transition-metal-assisted nucleophilic attack). Based on this distinction, we anticipated that a deuterium-labeling experiment could eliminate one or two of these proposals.

![Figure 3.3: Syn vs. anti addition](image)

To determine whether the product is the result of syn or anti addition, the olefinic resonances of the proteo-product needed to be assigned. This assignment was done using NOE experiments by a Chemistry 449 student in our group, Baldip Kang. It was determined that the downfield vinyl resonance at 5.11 ppm correlated to the H cis to the sulfide group. Kang verified these results using molecular modeling and the Tobey-Simmons rule, which predicts chemical shift values based on the additive effects of substituents on unsaturated aliphatics.

Deuterium-labeled phenyl acetylene, PhCCD (2% D), was used for this experiment, as it is commercially available. This alkyne was reacted with benzyl thiol in the presence of 3 mol% Tp*Rh(PPh₃)₂ in d₈-toluene, as shown in equation 3.5. Three
different outcomes were possible: the deuterium could be cis to the phenyl group from the alkyne, it could be cis to the sulfur, or there could be a mixture of the two products.

\[
\begin{align*}
&\text{Ph}^\text{SH} + \text{Ph} = \text{D} \xrightarrow{3 \text{ mol}\% \text{Tp}^*\text{Rh(PPh}_3)_2}\text{d}_8\text{-tol} \quad \text{D} \quad \text{H} \\
&\quad \text{Ph}^\text{S}^\text{Bn} \quad \delta 5.34 \quad \text{and} \quad 5.11 \text{ ppm (in } \sim 5\% \text{ yield)} \quad \delta 5.10 \text{ ppm. Based on these and the NOE results, it was determined that hydrothiolation mediated by Tp*Rh(PPh}_3)_2 \text{ occurred in a syn fashion – eliminating transition-metal-assisted nucleophilic attack as a possible mechanism. The remaining two mechanistic possibilities were investigated through an examination of substrate scope, stoichiometric reactions and kinetic analysis.}
\end{align*}
\]

3.2.1.2 Minor Products

At first glance, one would assume that Tp*Rh(PPh}_3)_2 and Tp*Rh(coe)(MeCN) would catalyze hydrothiolation by the same mechanism. The two complexes differ only in their ancillary ligands: two PPh}_3 ligands vs. coe and MeCN ligands. If we assume that the two complexes catalyze the reaction by entering the same catalytic cycle proposed for Tp*Rh(coe)(MeCN)\textsuperscript{61} then both species would initially react with two equivalents of thiol to form the disulfide species Tp*Rh(SR)_2L. Once Tp*Rh(SR)_2L is formed, the ancillary ligand L must dissociate for the alkyne to be able to coordinate and subsequently insert into the Rh-S bond. Thus, after ligand dissociation, the active catalyst Tp*Rh(SR)_2 would be the same in the two systems.
Figure 3.4: Catalytic cycle comparison for Tp*Rh(PPh₃)₂ and Tp*Rh(coe)(MeCN) assuming the intermediacy of a Rh disulfide complex.

If the two complexes involve the same catalytic cycle with identical intermediates then their product distributions should be the same. However, while both catalysts produce the branched vinyl sulfide from alkyne hydrothiolation, there is a difference in the minor product produced. Catalysis with Tp*Rh(PPh₃)₂ yields the E-linear vinyl sulfide as the only minor product while catalysis with Tp*Rh(coe)(MeCN) yields the Z-linear vinyl sulfide and the thioketal as minor products (Scheme 3.10). Mizobe and coworkers attribute the formation of the Z-linear isomer as the minor product to a small amount of background nucleophilic or radical-initiated reaction occurring (which generally favour formation of Z, as discussed in Chapter 1).
The mechanistic study of Tp*Rh(coe)(MeCN) and Tp*Rh(SPh)₂(MeCN) as hydrothiolation precatalysts was performed with benzene thiol and 4-ethynyl anisole. While the Z-linear vinyl sulfide was never observed in Tp*Rh(PPh₃)₂-catalyzed hydrothiolation with alkane thiols, it was sometimes observed in trace amounts when arene thiols were used. The reaction of benzene thiol and 4-ethynyl anisole in C₆D₆ was repeated in the presence of catalytic Tp*Rh(PPh₃)₂ and reaction progress was monitored by ¹H NMR spectroscopy to determine if any of the Z-linear vinyl sulfide was produced. The reaction was performed both under our conditions (3 mol% catalyst, 165 mM [thiol], 150 mM [alkyne], room temperature) and under the conditions for Tp*Rh(coe)(MeCN) (14 mol% catalyst, 70 mM [thiol], 70 mM [alkyne], 50 °C). Light was not excluded from these reactions to better mimic the conditions for Tp*Rh(coe)(MeCN) (i.e., the NMR tubes were not wrapped in foil). After one hour, exclusive formation of the branched vinyl sulfide was observed. Under our conditions, the reaction had reached 94% completion within one hour. Under the conditions for Tp*Rh(coe)(MeCN), the reaction was slower, presumably due to the lower concentration.

The light-induced reaction between benzene thiol and 4-ethynyl anisole (without catalyst present) was also monitored by NMR spectroscopy. In one hour, roughly 70% of the Z-linear vinyl sulfide is formed exclusively (one of the olefinic doublets overlapped with the internal standard peak thus the yield is approximate). The reported hypothesis that the formation of the Z-linear vinyl sulfide is a background reaction may be correct. However, when Tp*Rh(PPh₃)₂ is used, this background reaction is suppressed, presumably because the catalytic reaction is faster than the light-induced reaction.
The formation of the \(E\)-linear vinyl sulfide possibly occurs through another catalytic cycle (such as that entered by Wilkinson’s catalyst) that only \(\text{T}\text{p}^*\text{R}\text{h}(\text{PPh}_3)_2\) can access. Formation of the \(E\)-linear vinyl sulfide as the minor product is best explained by the S-H activation/Rh-S insertion mechanism. In this mechanism, after oxidative addition of the thiol, the alkyne could insert into not only the Rh-S bond, but also into the Rh-H bond to a lesser extent, producing the \(E\)-linear vinyl sulfide (Scheme 3.11).

\[
\begin{align*}
\text{Scheme 3.11} \\
\text{In addition to the } Z\text{-linear vinyl sulfide minor product, } \text{T}\text{p}^*\text{R}\text{h(coe)(MeCN)}\text{-catalyzed alkyne hydrothiolation also produces a thioketal as another minor product. This minor product is not observed in the } \text{T}\text{p}^*\text{R}\text{h(PPh}_3)_2\text{ system. The thioketal is the product of Markovnikov addition of the thiol to the branched vinyl sulfide. The authors do not speculate on whether this is a transition-metal-promoted side reaction or if the complex is active toward hydrothiolation of other alkenes.}
\end{align*}
\]

The sharp contrast in minor products between \(\text{T}\text{p}^*\text{R}\text{h(PPh}_3)_2\) and \(\text{T}\text{p}^*\text{R}\text{h(coe)(MeCN)}\) suggests that the two complexes may promote hydrothiolation by different mechanisms. The formation of the \(E\)-linear vinyl sulfide in the \(\text{T}\text{p}^*\text{R}\text{h(PPh}_3)_2\)-catalyzed reaction is best supported by the oxidative addition mechanism. The formation of the \(Z\)-linear vinyl sulfide as a minor product with \(\text{T}\text{p}^*\text{R}\text{h(coe)(MeCN)}\) and not \(\text{T}\text{p}^*\text{R}\text{h(PPh}_3)_2\) can be explained as a background reaction that is competitive with the metal-catalyzed reaction in the former case and suppressed in the latter. The mechanism of formation of the thioketal in the \(\text{T}\text{p}^*\text{R}\text{h(coe)(MeCN)}\) system is unclear.
3.2.1.3 Diene Byproduct

Nolan, Beletskaya and coworkers reported the formation of a diene as a byproduct of CpNi(IMes)Cl-catalyzed alkyne hydrothiolation.\(^{64}\) They suggest the byproduct arises from a second equivalent of alkyne inserting into the Ni-C bond of the nickel vinyl species prior to protonolysis, as shown below (Scheme 3.12). As discussed in Chapter 1, their proposed structure necessitates double-bond isomerization as well. The use of NEt\(_3\) as an additive and an excess of thiol prevented diene formation.

\[
\text{Scheme 3.12}
\]

We observed a similar byproduct in Tp*Rh(PPh\(_3\))\(_2\)-catalyzed hydrothiolation as well. This byproduct was initially observed in certain catalytic reactions performed on an NMR scale, shown below (Chart 3.1).\(^{90,103}\) The observed resonances in the \(^1\)H NMR spectra of three singlets in the olefinic range at roughly 5.5, 5.8 and 6.7 ppm suggested a diene structure for this byproduct as well. The byproduct is typically observed in 5-10% yield based on NMR integration. When two equivalents of phenyl acetylene and one equivalent of benzyl thiol are used in hydrothiolation, the diene is formed in 30% yield (Figure 3.5). Based on comparison to the diagnostic resonances for the diene reported by Beletskaya and coworkers, we suggest a similar structure, without double-bond isomerization, for the byproduct.
The formation of this diene in our system could give further insight into the mechanism of alkyne hydrothiolation. The mechanism of diene formation must involve one thiol equivalent and two alkyne equivalents. This ratio is supported by the reaction of benzyl thiol with PhCCD (equation 3.6). Only one of the three expected olefinic resonances was observed suggesting that the other two resonances correspond to protons originating from the alkyne.
We first considered the mechanistic possibility of initial C-H activation of the alkyne, despite knowing that the complex formed after alkyne addition to rhodium is unreactive toward thiol (\textit{vide supra}). However, it is possible that this complex would react with the second equivalent of alkyne to produce an alkyne dimer and that this enyne could then undergo hydrothiolation. This possibility was examined by reacting phenyl acetylene with a catalytic amount of Tp*Rh(PPh\textsubscript{3})\textsubscript{2} (equation 3.7). No appreciable amount of the alkyne dimer was observed over the time scale of the hydrothiolation reaction (formation of the rhodium hydrido acetylide is observed); thus, the mechanism of diene formation does not involve alkyne C-H activation.

This is consistent with the catalytic cycle for diene formation sharing intermediates with the hydrothiolation catalytic cycle. Analysis of the different pathways involving S-H activation of the thiol, followed by 1,2- or 2,1-alkyne insertion into the Rh-H or Rh-S bond, followed by insertion of a second equivalent of alkyne into either Rh bond shows 8 possible mechanisms that would produce one of two dienes consistent with the NMR data. Analysis of the different pathways commencing with formation of Tp*Rh(SR)\textsubscript{2} followed by two sequential alkyne insertions results in two catalytic cycles each producing one of the same two dienes (Figure 3.6 and Figure 3.7). NOE experiments on the diene sulfide should distinguish between the three possible structures shown in Figure 3.7. In conclusion, analysis of the diene byproduct does not help distinguish between the two S-H activation/insertion mechanisms or the mechanism involving a disulfide intermediate for alkyne hydrothiolation.
Figure 3.6: Possible mechanisms for diene formation.
Figure 3.7: Diene byproduct structure possibilities.

Although analysis of this byproduct does not give us mechanistic insight, its formation may. There is a discrepancy in the byproducts formed from hydrothiolation catalyzed by Tp*Rh(PPh₃)₂ and Tp*Rh(coe)(MeCN). The authors do not mention the diene byproduct in the report on Tp*Rh(coe)(MeCN)-catalyzed hydrothiolation. Formation of the diene is not mentioned even when three equivalents of alkyne are used (for kinetic experiments); therefore we conclude that Tp*Rh(coe)(MeCN) does not produce such a product. This discrepancy suggests that the two complexes may catalyze hydrothiolation by differing mechanisms or simply that Tp*Rh(PPh₃)₂ can access a different competing catalytic cycle that Tp*Rh(coe)(MeCN) cannot.

3.2.1.4 Vinyl Disulfides

The addition of chalcogenides to π-systems can be achieved in two ways: RY-YR addition (such as bisthiolation) and H-YR addition (such as hydrothiolation), where Y= S or Se. Transition-metal-catalyzed hydrothiolation was summarized in chapter 1 and bisthiolation was mentioned. Bisthiolation was not explored in depth in this thesis because, contrary to expectations, the two reactions behave differently. Disulfide addition is catalyzed by Pd(0) catalysts, which are inactive towards hydrothiolation. Furthermore, hydrochalcogenation of internal alkynes is well established, whereas dichalcogenide addition to internal alkynes was not reported until this year.

The widely accepted mechanism for transition-metal-catalyzed addition of disulfides to alkynes includes the following steps: oxidative addition of the S-S bond, ligand dissociation and alkyne coordination, alkyne insertion into the M-S bond, followed
by C-S reductive elimination to form vinyl disulfides (Scheme 3.13). Oxidative addition/Rh-S insertion and the disulfide intermediate mechanism for hydrothiolation both correspond to the proposed mechanism for the addition of disulfides to alkynes.

Thus, if Tp*Rh(PPh₃)₂-catalyzed hydrothiolation occurs via a rhodium disulfide intermediate, both hydrothiolation and bisthiolation would share three of the four catalytic intermediates in their catalytic cycles. If this were the case, one would expect to witness some vinyl disulfide product in hydrothiolation reactions. However, vinyl disulfides are not observed in Tp*Rh(PPh₃)₂-catalyzed hydrothiolation. This discrepancy has led some hydrothiolation researchers, such as Beletskaya and coworkers,¹⁶⁸ to stop reporting the mechanism involving a disulfide intermediate as their proposal for the catalytic cycle. Instead, they have begun to suggest the S-H activation/Rh-S insertion mechanism as the catalytic pathway for alkyne hydrothiolation producing the branched vinyl sulfide.

Scheme 3.13
3.2.1.5 Summary of Product Analysis

We considered five mechanistic possibilities for Tp*Rh(PPh$_3$)$_2$-catalyzed alkyne hydrothiolation. Of these five, two – S-H activation/Rh-H insertion and C-H activation – were eliminated because they would not generate the same products as those observed experimentally under catalytic conditions. A simple deuterium-labelling study eliminated a third Wacker-type mechanism, by showing that the reaction occurs with syn addition. The two remaining possibilities – oxidative addition followed by insertion into a Rh-S bond and formation of L$_n$Rh(SR)$_2$ as the active catalyst – were further examined based on the minor products of the Tp*Rh(PPh$_3$)$_2$-catalyzed reaction.

Comparison to a similar catalyst, Tp*Rh(coe)(MeCN), reveals a discrepancy in the minor products formed relative to those formed with Tp*Rh(PPh$_3$)$_2$. The $E$-linear vinyl sulfide is the minor product from the Tp*Rh(PPh$_3$)$_2$-catalyzed reaction. This product would be expected if the oxidative addition mechanism was the mechanism for hydrothiolation. However, when Tp*Rh(coe)(MeCN) is used as a hydrothiolation catalyst, the $Z$-linear vinyl sulfide and a thioketal are observed as the minor products of the reaction. Tp*Rh(coe)(MeCN) is reported to catalyze hydrothiolation by formation of a L$_n$Rh(SR)$_2$ species. This implies that Tp*Rh(coe)(MeCN) and Tp*Rh(PPh$_3$)$_2$ may promote hydrothiolation by different mechanisms. This analysis suggests that S-H oxidative addition followed by alkyne insertion into the Rh-S bond is the more probable mechanism for our catalytic system.

Analysis of the diene byproduct does not further our understanding of the mechanism as either mechanism could produce the diene byproduct. The absence of any vinyl disulfide byproduct, however, suggests that the mechanism involving L$_n$Rh(SR)$_2$ is not the operable mechanism for this reaction. Overall, while both [S-H activation/Rh-S insertion and disulfide intermediate] are still possibilities, these analyses suggest that the S-H activation/Rh-S insertion mechanism may be more probable for Tp*Rh(PPh$_3$)$_2$-catalyzed alkyne hydrothiolation.
3.2.2 Stoichiometric Reactions

During the course of our mechanistic investigations, the mechanism of alkyne hydrothiolation by the related polypyrazolylborate rhodium complex – Tp*Rh(coe)(MeCN) – was reported.\(^1\) The proposed mechanism involves the initial formation of Tp*Rh(SR)\(_2\)(MeCN), which is hypothesized to be the active catalyst. The authors used stoichiometric reactions to eliminate the oxidative addition mechanism and to support the disulfide mechanism. The authors prepared two new complexes, Tp*Rh(H)(SAr)(MeCN) and Tp*Rh(SAr)\(_2\)(MeCN), and screened them as hydrothiolation catalysts. The first complex is an intermediate in the oxidative addition pathway and the second is an intermediate in the disulfide mechanism. The hydride complex was used as a catalyst for hydrothiolation and found to be catalytically inactive. This result suggests that this complex is neither part of the catalytic cycle nor able to enter into it. The disulfide complex, however, was able to catalyze hydrothiolation.

Based on comparison of the products formed from Tp*Rh(PPh\(_3\))\(_2\)-catalyzed hydrothiolation and Tp*Rh(coe)(MeCN)-catalyzed hydrothiolation, we hypothesized that the two complexes operate by different mechanisms. The more likely mechanism for the Tp*Rh(PPh\(_3\))\(_2\) precatalyst begins with oxidative addition of the thiol onto the metal center \((\text{vide supra} \ Scheme \ 3.5)\). Using Tp*Rh(PPh\(_3\))\(_2\), this step would yield \(k^3\)-Tp*Rh(H)(SR)(PPh\(_3\)). We propose that this complex is the active catalyst for alkyne hydrothiolation. This hypothesis is contrary to that proposed for Tp*Rh(coe)(MeCN),\(^1\) but in accord with the mechanism proposed for ClRh(PPh\(_3\))\(_3\)-catalyzed hydrothiolation, as \(\text{trans-}HRh(Cl)(SPh)(PPh\(_3\))\(_3\) was found to catalyze alkyne hydrothiolation.\(^2\)

To test our mechanistic hypothesis, we set out to investigate the oxidative addition of benzyl thiol onto Tp*Rh(PPh\(_3\))\(_2\). This step was initially investigated by NMR spectroscopy in C\(_6\)D\(_6\). The starting metal complex, Tp*Rh(PPh\(_3\))\(_2\), appears in the \(^{31}\text{P}\{^1\text{H}\}\) NMR spectrum as a doublet centered at 43.0 ppm with \(J_{\text{Rh-P}} = 176\) Hz. Five minutes after addition of one equivalent of benzyl thiol to Tp*Rh(PPh\(_3\))\(_2\), a new set of resonances appear in the \(^{31}\text{P}\{^1\text{H}\}\) NMR spectrum. Two doublets of doublets appear at 53.2 ppm \((J_{\text{Rh-P}} = 175\) Hz, \(J_{\text{P-P}} = 41\) Hz) and 44.8 ppm \((J_{\text{Rh-P}} = 175\) Hz, \(J_{\text{P-P}} = 41\) Hz) in a 1:1 ratio. This coupling pattern is consistent with a rhodium complex with two inequivalent phosphines that are \(\text{cis}\) to one another.\(^{169-171}\) We believe this is a 5-coordinate rhodium complex with
coordinated, unactivated, thiol (A, equation 3.8). This reaction was also performed with two equivalents of thiol and the same NMR spectra were observed.

\[
\begin{align*}
\text{Tp}^*\text{Rh(PPh}_3\text{)}_2 & \quad + \quad \text{BnSH} & \quad \text{rt, C}_6\text{D}_6 & \quad \rightarrow & \quad \text{Tp}^*\text{Rh(PPh}_3\text{)}_2\text{(HSBn)} & \quad + & \quad \text{PPh}_3 \\
\text{(possible structure)}
\end{align*}
\]

Within the next 10 minutes, a new complex B is formed, as evidenced by a new doublet in the \(^{31}\text{P}\{^1\text{H}\}\) NMR spectrum at 44.6 ppm (\(^{1}\text{J}_{\text{Rh-P}} = 173\) Hz), as well as a singlet at -4.5 ppm corresponding to free PPh\(_3\) (Figure 3.9). By the end of one hour (total), the starting material doublet and the set of doublet of doublets disappear, leaving only the signals corresponding to B and free PPh\(_3\). The course of this reaction, as determined by \(^{31}\text{P}\{^1\text{H}\}\) NMR spectroscopy is shown in Figure 3.10. The \(^{31}\text{P}\) NMR spectrum looks similar and does not display any further splitting of the resonances.

\[
\begin{align*}
\text{Figure 3.8:} & \quad \text{Possible structures for B.}
\end{align*}
\]
Figure 3.9: $^{31}P\{^1H\}$ NMR spectrum of reaction of Tp*Rh(PPh$_3$)$_2$ and benzyl thiol (400MHz, C$_6$D$_6$, 14 °C).

Figure 3.10: Time plot of reaction of Tp*Rh(PPh$_3$)$_2$ with benzyl thiol (lines are provided as a visual guide).
A $^1$H NMR spectrum taken when only B remains shows a resonance at -16.4 ppm (dd, $^1$J$_{Rh-H} = 16$ Hz, $^2$J$_{P-H} = 31$ Hz) consistent with a rhodium hydride coupled to a cis-phosphine. This assignment is further supported by the doublet of doublets signal in the $^1$H NMR spectrum collapsing to a doublet in the $^1$H{$^3$P} NMR spectrum of the same sample. Whether or not the hydride complex corresponds to the species that exhibits the doublet at 44.6 ppm in the $^3$P{$^1$H} NMR spectrum is not yet clear; additional 2D NMR experiments will be conducted to obtain more information. It is not uncommon to observe coupling of a rhodium hydride to a phosphine ligand in the $^1$H NMR spectrum but not in the $^3$P NMR spectrum.\(^{172}\) The chemical shift of this hydride is consistent with the value of -16.4 ppm reported for trans-(H)Rh(Cl)(SPh)(PPh$_3$)$_3$, prepared from a stoichiometric reaction between ClRh(PPh$_3$)$_3$ and benzene thiol.\(^{52}\)

Tris(pyrazolyl)borate ligands can bind in both a $\kappa^2$ and $\kappa^3$ fashion. In most cases, it is found to bind to three metal coordination sites occupying three facial positions. In 16-electron square planar complexes, however, it can bind to two or three coordination sites.\(^{109,173}\) Distinguishing between the two binding modes by $^1$H NMR spectroscopy can be difficult, particularly for the 16-electron complexes. These complexes can have three different geometries: two square planar structures (SP1 and SP2) and a trigonal bipyramid (TBP) (Figure 3.11). Both the square planar structures and the trigonal bipyramid structure would display a 2:1 ratio in the $^1$H NMR spectrum for the pyrazolyl groups if the ancillary ligands are the same. However, in many cases, only one pyrazolyl signal is observed due to rapid exchange of the pyrazolyl arms. It is believed that this exchange occurs via a turnstile mechanism in the trigonal bipyramid structure and via a $\kappa^3$ intermediate for the square planar case.\(^{174}\) For example, Tp*Rh(PPh$_3$)$_2$, displays one set of signals for the pyrazolyl groups at 25 °C. For the coordinated thiol complex A, the two pyrazolyl groups coordinated to rhodium are also equivalent. Therefore, we would expect to observe 4 sets of methyl signals in a 2:2:1:1 ratio and two pyrazolyl H signals in a 2:1 ratio if pyrazolyl exchange is not occurring.
In an octahedral Rh\textsuperscript{III} complex of the type Tp*Rh(L\textsuperscript{1}L\textsuperscript{2}L\textsuperscript{3}), such as the product of oxidative addition of a thiol onto Tp*Rh(PPh\textsubscript{3})\textsubscript{2}, the three pyrazolyl arms are inequivalent and should display distinct NMR resonances. Therefore, for $\kappa^3$-Tp*Rh(H)(SBn)(PPh\textsubscript{3}), one would expect 3 singlets for the 4-H-pyrazolyl protons ($\delta$ 5 – 6 ppm) and 6 singlets for the methyl groups ($\delta$ 0.5 – 3 ppm). The oxidative addition of other H-X organics such as alkynes,\textsuperscript{95,175} aldehydes,\textsuperscript{95,175} and triphenyltin hydride\textsuperscript{175} onto Tp*Rh(PPh\textsubscript{3})\textsubscript{2} display distinct pyrazolyl resonances in the $^1$H NMR spectra as described above, as well as doublets of doublets for the rhodium hydride. The B-H signal is observed as a broad singlet at ~4.5ppm in some cases. The $^1$H NMR spectrum of Tp*Rh(H)(SPh)(MeCN) displays signals corresponding to three inequivalent pyrazolyl groups and a hydride signal at $-13.79$ (d $J = 11.0$ Hz).\textsuperscript{61}

The $^1$H NMR spectra obtained during the course of the stoichiometric reaction between Tp*Rh(PPh\textsubscript{3})\textsubscript{2} and benzyl thiol are not very helpful for structure determination. The spectrum of Tp*Rh(PPh\textsubscript{3})\textsubscript{2} is very broad at room temperature. Once thiol is added, the peaks sharpen and resonances corresponding to equivalent pyrazolyl groups are observed at $\delta$ 5.62 (s, 3H), 2.21 (9H) and 2.01 (9H), as well as a singlet for the methylene signal for benzyl thiol at 3.28 ppm. The thiol proton is not observed during the course of the reaction. This suggests activation or deprotonation of the thiol occurs since, in the absence of a metal complex, the thiol methylene is observed as a doublet and the thiol proton is observed as a triplet in the NMR spectrum. Despite changes being observed in the $^{31}$P{$^1$H} NMR spectra for this reaction, the $^1$H NMR spectrum does not change. Furthermore, while we can observe up to three different rhodium complexes in solution
by $^{31}$P{$^1$H} NMR spectroscopy, there is only one dominant set of signals in the $^1$H NMR spectra. In some instances, a small amount (~10%) of another complex with three inequivalent pyrazolyl groups can be observed in the $^1$H NMR spectrum. This minor product is present throughout the course of the reaction in roughly the same concentration in the trials for which it is observed.

There may be other rhodium hydride species in the reaction mixture as well. The $^1$H NMR spectrum also displays two other dd resonances in the hydride region at -15.8 ppm ($J = 13.0, 27.8$ Hz) and at -14.4 ($J = 18.8, 18.8$ Hz). Both of these signals appear as doublets in the $^1$H{$^{31}$P} NMR spectrum indicating coupling to phosphorus and have coupling constants consistent with a cis-orientation between the hydride and phosphine. Therefore, these two signals are also consistent with a $L_n$Rh(H)(PPh$_3$) species. The proposed structure for B, Tp*Rh(H)(SBn)(PPh$_3$), has no diastereomers so the other signals do not correspond to an isomer of B. It is possible that the other hydride species are similar to B but with a $\kappa^2$-Tp* ligand, where one pyrazolyl ring has dissociated from the rhodium center, however this is rare for an 18-electron complex.$^{173}$ While the resonance at -16.4 ppm is always present in this reaction, the other two signals are not consistently reproducible. The resonance at -14.4 ppm is very weak and appears infrequently.

Certain possibilities for other hydride complexes observed by other research groups may be eliminated as structures for the extra hydride complexes. The addition of $C_6F_5SH$ to Tp*Rh(PPh$_3$)$_2$ in methylene chloride was previously investigated and exhibited interesting reactivity.$^{172}$ The reaction resulted in fragmentation of the Tp* ligand to give a neutral pz* (1,3-dimethylpyrazole) ligand and the formation of a sulfide bridged dimer with Rh(I) and Rh(III) centres (Scheme 3.14). Each PPh$_3$ ligand is inequivalent in this complex and this was reflected in the $^{31}$P NMR spectrum. We do not observe any resonances in the $^{31}$P NMR spectrum of the reaction with benzyl thiol that would indicate that a similar process is occurring in that reaction. The addition of triphenylsilane, Ph$_3$SiH, to Tp*Rh(PPh$_3$)$_2$ in methylene chloride also results in fragmentation of the Tp* ligand, and reaction with the solvent to form Rh(Cl)$_2$(H)(PPh$_3$)$_2$(pz*) and Rh(Cl)(H)$_2$(PPh$_3$)$_2$(pz$^*$).$^{172}$ The rhodium hydrides in these complexes display coupling to rhodium and two equivalent phosphines (dt in the $^1$H
NMR spectrum). The same reaction in toluene formed Tp*Rh(H)\(_2\)(PPh\(_3\)) instead. The \(^{31}\)P NMR spectrum of this complex displays a doublet at 58.58 ppm (\(J = 151.3\) Hz). The NMR spectra of the reaction with benzyl thiol are not consistent with any of these products. However, when this reaction is performed in CD\(_2\)Cl\(_2\), many new signals appear in the \(^{31}\)P\{\(^1\)H\} NMR spectrum and in the hydride region of the \(^1\)H NMR spectrum, indicating that similar reactivity in methylene chloride is possible. It is interesting that the reaction of Tp*Rh(PPh\(_3\))\(_2\) with triphenyltin hydride in methylene chloride does not result in fragmentation of the Tp* ligand or reaction with the solvent and instead forms the expected oxidative addition product Tp*Rh(H)(SnPh\(_3\))(PPh\(_3\)).

\[\text{Scheme 3.14}\]

\(^1\)H NMR spectroscopy can be ambiguous for determining the denticity of the Tp* ligand. A study of a series of Tp*ML\(_n\) complexes (M = Rh, Ir and Pt) complexes demonstrated that the \(^{11}\)B NMR chemical shift of the Tp* ligand can be used to
distinguish between κ² and κ³ coordination.¹⁷⁴ κ²-Tp*MLₙ complexes exhibited ¹¹B NMR chemical shifts between -5.90 and -6.99 ppm; whereas the resonances for κ³-Tp*MLₙ complexes fell between -8.44 and -9.76 ppm. This trend was independent of the metal center and its oxidation state. Furthermore, infrared spectroscopy can also be used to distinguish the two binding modes.¹⁷⁶ The frequency of the B-H stretch has also been found to correlate with denticity with ν_{B-H} < 2500 cm⁻¹ indicative of κ² binding and ν_{B-H} > 2500 cm⁻¹ indicative of κ³ binding. This study was performed with Tp⁸, where R = iPr, however, subsequent analysis of other Tp*MLₙ complexes have shown that the trend holds for other tris(pyrazolyl)borate ligands.¹⁷⁴ Finally, denticity in the solid-state can be obtained from X-ray crystallography.

To determine Tp* denticity, ¹¹B NMR spectroscopy was performed. Tp*Rh(PPh₃)₂ displays a singlet at -9.4 ppm. This signal is in the range for a κ³-Tp* ligand. However, previous reports on the structure of Tp*Rh(PPh₃)₂ suggest the Tp* ligand is bound in a bidentate fashion.¹⁰⁷,¹⁷⁵,¹⁷⁷ Though the report on ¹¹B NMR spectroscopy as a handle for denticity compared a large number of complexes, no triphenylphosphine complexes were studied. Unfortunately, Tp*Rh(PPh₃)₂ does not seem to follow the published trend; hence, the ¹¹B NMR spectra may not be of as much use in determining denticity as hoped. In the stoichiometric reaction of Tp*Rh(PPh₃)₂ and benzyl thiol, when only complex B and PPh₃ remain (according to ³¹P{¹H} NMR spectroscopy), there appear to be three ¹¹B NMR resonances at -1.4, -10.6 and -13.9 ppm. These signals lie outside the diagnostic chemical shift ranges for κ² and κ³ binding. However, since two signals are upfield of the the Tp*Rh(PPh₃)₂ signal, we propose that they correspond to two κ³-Tp*RhLₙ complexes. The signal at -1.3 ppm may correspond to a κ⁰- or κ¹-Tp* ligand.¹¹⁴

Further characterization of complex B was complicated by the fact that after 2-3 hours, the doublet in the ³¹P{¹H} NMR spectrum disappears and only a signal for free PPh₃ remains. However, the hydride signals remain. The transient nature of complex A and the disappearance of B over a short period of time makes further characterization of A or B, such as ¹³C NMR analysis, 2D or variable temperature NMR experiments and solid-state IR spectroscopy, difficult or impossible. For example, ¹³C NMR spectroscopy
was not attempted, as the two complexes would have been consumed in the time it takes to acquire the spectrum.

Variable temperature NMR spectroscopy was next considered. Since product decomposition can occur at high temperatures, only low temperature NMR spectroscopy was investigated.\textsuperscript{95,172} Tp*Rh(PPh\textsubscript{3})\textsubscript{2} was reacted with one equivalent of benzyl thiol for 40 minutes at room temperature in \textit{d}\textsubscript{8}-toluene. At this time, the \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectrum indicated that complex B and Tp*Rh(PPh\textsubscript{3})\textsubscript{2} were present in the reaction mixture. The NMR tube was then placed into the pre-cooled NMR spectrometer. After 15 minutes at \(-80\) °C, the \textsuperscript{31}P\{\textsuperscript{1}H\}, \textsuperscript{11}B and \textsuperscript{1}H NMR spectra were obtained. The spectrometer temperature was then increased and spectra were acquired at \(10^\circ\) increments. The low temperature NMR spectroscopy was repeated with a sample that contained only complex B and free PPh\textsubscript{3} according to the \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectrum.

The \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectra of both samples did not change at low temperature until \(-60\) °C. At temperatures below \(-60\) °C, the \textsuperscript{31}P signal for complex B disappears, probably due to poor solubility at low temperatures. Low temperature \textsuperscript{11}B NMR spectroscopy did not yield any useful information. Below \(0\) °C, only the signal at \(-1.4\) ppm is observed. However, the signal is very broad and it is possible that the other two signals are present but not observed. The \textsuperscript{11}B nucleus is quadrupolar and can exhibit severe line broadening. Moreover, regular borosilicate glass NMR tubes were used for these experiments and the glass gives a very broad signal across most of the spectral window creating a wavy baseline, further complicating the spectrum.

The variable temperature \textsuperscript{1}H NMR spectra are a bit more complicated and difficult to decipher. Furthermore, the \textsuperscript{31}P\{\textsuperscript{1}H\} NMR spectra suggest that in both samples, the concentration of the species in solution is changing. In the first sample, the concentration of Tp*Rh(PPh\textsubscript{3})\textsubscript{2} decreased from the first low temperature spectrum to the last. In the second sample with only complex B and PPh\textsubscript{3}, the signal for complex B had almost disappeared by the end of the variable temperature experiments. It appears that at low temperature (-60 °C), there are three sets of 4-H pyrazolyl signals: 5.73 (s); 5.57 and 5.52 (s, 1:2); 5.28 and 5.15 (s, 1:2). As the temperature increases, the two sets of 1:2 signals coalesce into one signal each at 5.52 and 5.36 ppm. The 5.73 signal is the dominant signal. The methyl region is too complicated for analysis. The hydride region
displays two doublets of doublets at -15.8 ppm and -16.4 ppm. The hydride at -16.4 ppm is the dominant signal.

The assignment of B as Tp*Rh(H)(SBn)(PPh$_3$) is based on the single phosphine resonance coupled to rhodium, as well as the dd hydride resonance. However, the $^1$J$_{Rh-P}$ value of 173 Hz for B is more typical of a Rh(I) species rather than a Rh(III) species.$^{95,172,175}$ Furthermore, the intensity of the hydrides observed in the $^1$H NMR spectrum are very small and it is possible that the hydride resonances correlate with a different minor rhodium phosphine complex, which is not observed in the $^{31}$P NMR spectrum. A 2D heteronuclear correlation NMR spectrum of B would indicate if the observed hydride resonances correspond to a hydride on the same rhodium centre as the phosphine with a resonance at 44.6 ppm in the $^{31}$P{$^1$H} NMR spectrum. An alternative structure for B is Tp*Rh(HSBn)(PPh$_3$) while the observed hydride signals correspond to Tp*Rh(H)(SBn)(PPh$_3$).

To further study this species, preparative scale reactions were attempted to isolate the hypothesized reaction intermediate. Tp*Rh(PPh$_3$)$_2$ was reacted with one or two equivalents of benzyl thiol in a variety of solvents: benzene, toluene, 1:1 benzene:hexanes, DCE, and 1:1 DCE:Toluene. After one hour, the mixture changed from yellow/orange to orange/brown. The reaction was concentrated and the crude reaction mixture was analyzed by $^{31}$P{$^1$H} NMR spectroscopy. In all attempts either no phosphorus signal or only a signal for uncoordinated PPh$_3$ was observed. The $^1$H NMR spectra were too complicated to decipher. Unfortunately, the reaction seems to have undergone the same secondary reaction as was observed in the NMR tube reaction after a few hours. Attempts at crystallization of the resulting rhodium species in various solvent combinations were unsuccessful.

It should be noted that the analogous oxidative addition product in Tp*Rh(coe)(MeCN)-catalyzed hydrothiolation, Tp*Rh(H)(SR)(MeCN), was not isolated cleanly either.$^{61}$ The reaction of Tp*Rh(coe)(MeCN) with an equimolar amount of benzene thiol yielded a 6:3:1 mixture of Tp*Rh(H)(SPh)(MeCN), Tp*Rh(SPh)$_2$ and Tp*Rh(coe)(MeCN) (equation 3.9). This mixture of products was used to test the catalytic viability of Tp*Rh(H)(SPh)(MeCN). However, with a resultant 3:2 ratio of the hydrido sulfide and active precatalysts, some amount of hydrothiolation should have
occurred. The authors do not mention if any vinyl sulfide is formed, nor do they comment on how they arrived at the conclusion that the hydrido sulfide complex is inactive toward hydrothiolation.

$$\text{Tp}^*\text{Rh(MeCN)(coe)} + \text{PhSH} \rightarrow \text{Tp}^*\text{Rh}^{-}\text{H} + \text{PhSH} + \text{Tp}^*\text{Rh(MeCN)(coe)} \quad (3.9)$$

Despite our lack of success in complex isolation, we were still interested in evaluating the catalytic ability of B toward alkyne hydrothiolation. To this end, we prepared complex B in situ and tested its catalytic viability. Tp*Rh(PPh$_3$)$_2$ was reacted with 2 equivalents of benzyl thiol (to ensure the reaction went to completion) in C$_6$D$_6$. The reaction progress was monitored by $^{31}$P{$^1$H} NMR spectroscopy until only the signal for B remained (45 min). At this time, an aliquot of the reaction mixture equivalent to 3 mol% of complex was syringed into another NMR tube charged with internal standard and solvent. Benzyl thiol and phenyl acetylene were added to the NMR tube as in other hydrothiolation reactions (equation 3.10). The reaction progress was monitored by $^1$H NMR spectroscopy. After two hours, the reaction had only proceeded to 8% completion (compared to >80% when Tp*Rh(PPh$_3$)$_2$ is used). There was no change after 24 hours. This reaction was performed three times with different batches of Tp*Rh(PPh$_3$)$_2$ with the same result.

$$\text{PhSH} + 1.0 \text{ equiv.} \rightarrow \text{PhS} + 3 \text{ mol}\% \text{ B} \rightarrow \text{PhS} \quad (3.10)$$

The lack of catalytic ability of B does not support our hypothesis that catalysis occurs via S-H activation followed by alkyne insertion. However, it is possible that complex C (the decomposition product of complex B) was already present in solution when catalytic ability was examined. This product does not catalyze hydrothiolation and this product could inhibit the catalytic ability of complex B. Furthermore, the assignment of B may be incorrect; if future analysis indicates that B is not Tp*Rh(H)(SPh)(PPh$_3$), then this analysis would not exclude the S-H activation/Rh-S insertion mechanism as a
hypothesis. However, because of the lack of catalytic ability of $B$, we turned our efforts to investigating the possibility that the reaction proceeds through a disulfide intermediate.

Studies on hydrothiolation using nickel and palladium catalyst precursors, whose mechanisms involve disulfide intermediates as active catalysts, focused on isolating the product of the metal precatalyst and the thiol.$^{51,58,62,64,65}$ This intermediate was found to be of the form $L_nM(SR)_2$. We attempted to prepare $\text{Tp}^*\text{Rh(SR)}_2(\text{PPh}_3)$ and test its ability to catalyze hydrothiolation. Direct addition of a thiol to $\text{Tp}^*\text{Rh(PPH}_3)_2$ could result in formation of a mixture of products (as it did with $\text{Tp}^*\text{Rh(coe)(MeCN)}$), including the intermediate from the oxidative addition mechanism. Therefore, $\text{Tp}^*\text{Rh(PPH}_3)_2$ was instead treated with an equimolar amount of dibenzyl disulfide in $d_8$-toluene to try to form the disulfide species (Scheme 3.15). After 12 days at room temperature, no change was observed by $^{31}P$ NMR spectroscopy. The reaction mixture was then heated to 80 °C for 24 hours. Heating resulted only in decomposition via orthometalation of a PPh$_3$ ligand. This type of decomposition has been previously reported by our group.$^{95}$ The lack of reactivity is not surprising as dibenzyl disulfide is not easily cleaved.$^{178,179}$

\[
\begin{align*}
\text{Tp}^*\text{Rh(PPH}_3)_2 + \text{Ph-S-S-Ph} & \xrightarrow{d_8\text{-toluene} \text{ rt, 12 d}} \text{N.R.} \xrightarrow{80 ^\circ \text{C}} \text{24 h} \xrightarrow{} \text{Tp}^*\text{Rh(PH}_2\text{Ph)}
\end{align*}
\]

Scheme 3.15

Our focus changed to formation of the arene thiol analog. This time, $\text{Tp}^*\text{Rh(PPH}_3)_2$ was treated with an equimolar amount of diphenyl disulfide in $d_6$-benzene.$^{180}$ The $^{31}P\{^1H\}$ NMR spectrum of the reaction showed the appearance of a new species in solution along with free PPH$_3$, and the consumption of $\text{Tp}^*\text{Rh(PPH}_3)_2$ within 24 hours. The new singlet appeared at 25.8 ppm in the NMR spectrum; this chemical shift is consistent with a P(V) species such as triphenylphosphine sulfide or triphenylphosphine di(phenyl sulfide). It is likely that the disulfide reacted with dissociated PPH$_3$ in solution. To test this hypothesis, PPH$_3$ was combined with an equimolar amount of diphenyl disulfide in $d_6$-benzene. The $^{31}P\{^1H\}$ NMR spectrum displays the same singlet.
Based on literature, the new species is presumed to be triphenylphoshine di(phenyl sulfide), as shown in equation 3.11.\textsuperscript{178}

\[
PPh_3 + PhS-SPh \xrightarrow{\text{C}_6\text{D}_6} \text{Ph}_3\text{R} \text{SPh} \text{SPh}
\]

(3.11)

To avoid the consumption of the disulfide by free PPh\textsubscript{3}, Tp*Rh(PPh\textsubscript{3})\textsubscript{2} was next treated with an excess (10 equivalents) of diphenyl disulfide in \textit{d}_6-benzene. After 28 hours at room temperature, the same signals were observed in the \textsuperscript{31}P\{}\textsuperscript{1}H\} NMR spectrum corresponding to Ph\textsubscript{3}P(SPh)\textsubscript{2} and free PPh\textsubscript{3}. Additionally, the doublet corresponding to Tp*Rh(PPh\textsubscript{3})\textsubscript{2} had disappeared. Based on this data, it is unlikely that Tp*Rh(SPh)\textsubscript{2}(PPh\textsubscript{3}) was produced. Furthermore, the \textsuperscript{1}H NMR spectrum displays resonances corresponding to three equivalent pyrazolyl groups. If Tp*Rh(SPh)\textsubscript{2}(PPh\textsubscript{3}) was present in solution, one would expect a 2:1 ratio of pyrazolyl signals corresponding to the two pyrazolyl groups \textit{trans} to the sulfides and one group \textit{trans} to the phosphine. The \textsuperscript{1}H NMR data reported for Tp*Rh(SPh)\textsubscript{2}(MeCN) display a 2:1 ratio of pyrazolyl resonances, as expected.\textsuperscript{181}

Since it was not possible to prepare Tp*Rh(SPh)\textsubscript{2}(PPh\textsubscript{3}) by addition of a disulfide to Tp*Rh(PPh\textsubscript{3})\textsubscript{2}, we attempted to prepare the disulfide species by addition of excess thiol to Tp*Rh(PPh\textsubscript{3})\textsubscript{2}. As discussed above, addition of one or two equivalents of benzyl thiol to the rhodium complex resulted in formation of the thiol coordinated complex \textbf{A} and the rhodium hydrido sulfide \textbf{B}. Therefore, the reaction was performed with 30 equivalents of thiol. The reaction was performed in \textit{C}_6\textit{D}_6 and reaction progress was monitored by \textsuperscript{31}P\{}\textsuperscript{1}H\} NMR spectroscopy. As observed with addition of one equivalent of thiol, complex \textbf{A} is observed in the spectrum within minutes of the thiol addition. However, unlike the reaction with stoichiometric thiol addition, complex \textbf{B} is not observed. Instead, a new doublet is observed at 28.8 ppm (\textit{J} = 107 Hz) within 10 minutes. The concentration of this complex (\textbf{D}) and of \textbf{A} increase with respect to the Tp*Rh(PPh\textsubscript{3})\textsubscript{2} signal over the next hour (Figure 3.12). Over the following hour, the concentration of all three complexes decreases in comparison to free PPh\textsubscript{3} and by 2 hours, only free PPh\textsubscript{3} remains (Figure 3.13). At this time, the \textsuperscript{1}H NMR spectrum displays signals for equivalent pyrazolyl groups: 5.61 (s, 3H), 2.20 (s, 9H), 2.01 (s, 9H). These
signals are the same as those observed in the stoichiometric reaction. Furthermore, the three hydride signals observed in the stoichiometric reaction are also observed.

Figure 3.12: $^{31}\text{P}_{\text{t}}^{1}\text{H}$ NMR Spectrum of Tp*Rh(PPh$_3$)$_2$ + 30 equiv. BnSH (400MHz, C$_6$D$_6$, 14 °C)
Figure 3.13: Time plot of reaction of Tp*Rh(PPh$_3$)$_2$ with excess benzyl thiol (lines are provided as a visual guide)

We were unable to isolate complex D, even on a preparative scale. With limited characterization data, we are only able to speculate on the identity of this complex. We propose that complex D is Tp*Rh(SBn)$_2$(PPh$_3$). Unfortunately, we were unable to test its catalytic ability as we were neither able to isolate the complex, nor form it exclusively \textit{in situ}.

Despite complicated characterization of the product of thiol addition to the catalyst precursor, investigation of the alkyne insertion product could possibly distinguish between the two hypothesized mechanisms. Tp*Rh(PPh$_3$)$_2$ was reacted with one or two equivalents of benzyl thiol until only complex B was observable by $^{31}$P NMR spectroscopy. At this time, one equivalent of phenyl acetylene was added to the reaction mixture. After 30 minutes, the $^{31}$P{$^1$H} NMR spectrum remained unchanged. However, in one trial there were new small signals in the methyl region of the $^1$H NMR spectrum but no corresponding new signals in the 4H-pyrazolyl region. The hydride region of the spectrum displayed the same two hydrides at -15.8 and -16.4 ppm. The new methyl signals were not reproducible. A similar experiment combined Tp*Rh(PPh$_3$)$_2$, 1 equivalent of benzyl thiol and 1 equivalent of phenyl acetylene at the same time in C$_6$D$_6$. In this reaction, the branched vinyl sulfide is produced. A complex with equivalent
pyrazolyl groups is observed in the $^1$H NMR spectrum (5.62, 2.21, 2.01 ppm), in addition to signals corresponding to a new complex with three inequivalent pyrazolyl groups (complex E). There are three 4H-pyrazolyl signals at 5.80, 5.65 and 5.21 ppm in a 1:1:1 ratio and six methyl groups at 2.64, 2.57, 2.55, 2.35, 2.29, 1.57 ppm, integrating to 3H. Resonances corresponding to complex A and later complex B were observed in the $^{31}$P{$^1$H} NMR spectrum. The $^1$H NMR spectrum did not change significantly over the course of the reaction. Characterization of the new complex (E) was not possible.

In Pd(OAc)$_2$-catalyzed alkyne hydrothiolation, the product of Pd(OAc)$_2$ and thiol did not catalyze hydrothiolation. However, a similar product obtained in the presence of alkyne, did catalyze hydrothiolation.$^{52,57}$ Perhaps, an analogous process is occurring in Tp*Rh(PPh$_3$)$_2$-catalyzed hydrothiolation. The active catalyst may not form until one turnover has occurred.

Ideally, stoichiometric reactions aid in the characterization of catalytic intermediates. The ability of the intermediates to catalyze the same reaction would lend support to a particular mechanism. Unfortunately, deciphering the mechanism of this reaction seems to be more complicated than anticipated. We were unable to isolate or unambiguously characterize any proposed intermediates in Tp*Rh(PPh$_3$)$_2$-catalyzed hydrothiolation due to competing side reactions. The reaction between Tp*Rh(PPh$_3$)$_2$ and benzyl thiol was monitored by $^1$H, $^{31}$P{$^1$H}, and $^{11}$B NMR spectroscopy. Two new complexes A, proposed to be Tp*Rh(PPh$_3$)$_2$(HSBn), and B are formed in the stoichiometric reaction, according to $^{31}$P{$^1$H} NMR spectroscopy.$^{52}$ $^{11}$B NMR spectroscopy suggests there are three different inequivalent Tp* ligands in solution but was unhelpful in determining the denticity of the Tp* ligand. The $^1$H NMR spectra were too complicated to aid in characterization, but indicated that two or three rhodium hydride complexes exist in solution. Isolation was not possible due to further reaction of complex B.

Complex B formed in situ was not able to catalyze hydrothiolation at an appreciable rate. This result suggests that B is not an intermediate in the catalytic cycle. However, NMR spectroscopy suggests that while complex B may be the only complex observed by $^{31}$P NMR spectroscopy, there may be other uncharacterized products in solution. The characterization of complex B was performed in situ without purification. It
is possible that the other uncharacterized products present in solution inhibited catalysis. Alternatively, the assignment of B as Tp*Rh(H)(SBn)(PPh₃) could be incorrect. In this case, the lack of activity of B does not refute the validity of the S-H activation/Rh-S insertion mechanism.

The reaction of Tp*Rh(PPh₃)₂ and thirty equivalents of benzyl thiol produced A and a new complex D, proposed to be Tp*Rh(SR)₂(PPh₃). The catalytic ability of D was not assessed because we were unable to prepare the complex cleanly. Furthermore, the characterization of this complex is based solely on the ³¹P{¹H} NMR spectrum.

3.2.3 Kinetic Analysis

In preparative scale hydrothiolation, the ideal solvent was a 1:1 mixture of toluene and DCE. DCE alone presented the best initial reaction rates empirically, however this was accompanied by decomposition of the metal complex. Orthometalation of a PPh₃ ligand on Tp*Rh(PPh₃)₂ occurs within a few hours in DCE at room temperature. The addition of toluene precludes catalyst decomposition, presumably by sufficiently lowering the solvent polarity. The role of the solvent in catalytic hydrothiolation was examined to determine the effect of solvent polarity on hydrothiolation.

The reaction of benzyl thiol with phenyacetylene in the presence of 3 mol% of Tp*Rh(PPh₃)₂ was examined in a series of deuterated solvents: C₆D₆, d₅-toluene, CDCl₃, CD₂Cl₂, d₅-acetone, MeOD, CD₃CN and d₅-DMSO. Deuterated DCE was not used because of cost considerations. The dielectric constant of DCE (10.42) is close to that of CD₂Cl₂ (9.08); therefore, CD₂Cl₂ can be used to approximate the effect of DCE. A 1:1 mixture of CD₂Cl₂ and d₅-toluene was also examined to approximate the dielectric constant of the preparative scale hydrothiolation reactions. The results are shown in Table 3.3.
Table 3.3: Solvent Effect on Alkyne Hydrothiolation

\[
\text{BnSH} + \text{Ph} \xrightarrow{3 \text{ mol\% Tp*Rh(PPh}_3)_2} \text{ solv, rt} \rightarrow \text{Ph}^{-}\text{SPh}
\]

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Dielectric Constant</th>
<th>(t_{1/2}) (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{C}_6\text{D}_6)</td>
<td>2.28</td>
<td>7</td>
</tr>
<tr>
<td>(d_6)-tol</td>
<td>2.38</td>
<td>7</td>
</tr>
<tr>
<td>CDCl(_3)</td>
<td>4.81</td>
<td>7</td>
</tr>
<tr>
<td>CD(_2)Cl(_2)</td>
<td>9.08</td>
<td>7</td>
</tr>
<tr>
<td>CD(_2)Cl(_2)/(d_6)-tol</td>
<td>--</td>
<td>n/a</td>
</tr>
<tr>
<td>(d_6)-acetone</td>
<td>20.7</td>
<td>n/a</td>
</tr>
<tr>
<td>MeOD</td>
<td>32.6</td>
<td>n/a</td>
</tr>
<tr>
<td>CD(_3)CN</td>
<td>37.5</td>
<td>n/a</td>
</tr>
<tr>
<td>(d_6)-DMSO</td>
<td>47</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Monitoring hydrothiolation in the 1:1 mixture of CD\(_2\)Cl\(_2\) and \(d_6\)-toluene was not possible because it was very difficult to lock on the deuterium signal in this solvent mixture. By the time the first NMR spectrum could be obtained, the reaction was more than 50% complete. Additionally, Tp*Rh(PPh\(_3\))\(_2\) is sparingly soluble in \(d_6\)-acetone, MeOD, CD\(_3\)CN and \(d_6\)-DMSO, thus, most of the complex did not dissolve in these solvents even with heating and sonication. Reaction rates could therefore not be determined in these solvents. Interestingly, solvent polarity has no measurable effect on Tp*Rh(PPh\(_3\))\(_2\)-catalyzed alkyne hydrothiolation except that Tp*Rh(PPh\(_3\))\(_2\) is only soluble in solvents with a dielectric constant less than 20. This is suggestive of low polarity of the reaction transition state. Furthermore, the regioselectivity of the reaction was the same in all four solvents; therefore, regioselectivity is not driven by electrostatics. These results suggest selectivity is mainly driven by steric considerations and thermodynamics.

To gain further insight into the reaction mechanism, the kinetics of the reaction were examined. A kinetic profile of the overall reaction was obtained to compare product formation and substrate consumption, as shown in Figure 3.14. Kinetic experiments were performed with benzyl thiol and phenyl acetylene. This reaction is too fast at room
temperature to obtain useful kinetic data; thus, the reactions were run at 14 °C. The precatalyst, thiol and internal standard were premixed in a screw cap NMR tube and cooled to 14 °C for 10 minutes. The alkyne was then added via syringe. Reaction progress at was 14 °C monitored by $^1$H NMR spectroscopy. Concentrations of species in solutions were determined through comparison to an internal standard.

**Figure 3.14: Kinetic profile of hydrothiolation**

Product formation follows a linear trend, whereas thiol consumption follows an exponential decay, suggesting first-order dependence on [thiol]. Alkyne concentration starts low and increases before following a linear consumption decay. Omitting the induction period, the linear decay of alkyne concentration suggests the reaction is zero-order in [alkyne]. A first order dependence on [thiol] and zero order dependence on [alkyne] and [product] indicate that the rate-determining step of the reaction only involves one equivalent of thiol (and presumably of the metal complex). This would suggest that the rate-determining step is either oxidative addition (to form either $L_n$Rh(H)(SR) or $L_n$Rh(SR)$_2$) or protonolysis (disulfide intermediate mechanism). While this profile gives a good starting point for understanding the kinetic dependence of the reaction, more rigorous kinetic experiments were attempted for more concrete analysis.
There appears to be an induction period for the alkyne, as evidenced by the first 10 minutes of the time plot (Figure 3.14). The alkyne concentration is very low 2 minutes after alkyne addition and slowly increases over the next 5 minutes and then decreases linearly. The initial decrease in alkyne concentration suggests a possible competition between alkyne and thiol for metal coordination. It is not probable that alkyne C-H activation is occurring as we have previously shown this is an irreversible process. It is more likely that until S-H activation of the thiol occurs, the alkyne is in competition for coordination to the Rh(I) center.

The reaction was performed under pseudo-first order conditions for the alkyne to verify the reaction’s zero-order dependence on alkyne concentration, where the reaction progress was monitored with both 30 and 50 equivalents of thiol. Less than 10% of the product was formed under these conditions. Unfortunately, running the reaction with even 10 equivalents of thiol inhibits reactivity. Despite this setback, we were able to rule out the alkyne’s involvement in the rate-determining step of the catalytic cycle. The rates of reaction for benzyl thiol with deutero-phenyl acetylene were compared against that with proteo-phenyl acetylene, as shown in Figure 3.15. Since there is no observable primary kinetic isotope effect, we conclude the alkyne is not involved in the rate-determining step; furthermore, this result is consistent with zero order dependence on alkyne concentration.
Figure 3.15: Kinetic isotope effect for alkyne in hydrothiolation

To verify the reaction’s first-order dependence on [thiol], it would be desirable to run the reaction with a large excess of alkyne. Unfortunately, it was not possible to examine the reaction under pseudo-first order conditions because with increasing amounts of alkyne, the amount of the diene byproduct increased (vide supra Section 3.2.1.3). We reasoned that any data collected under these conditions would not truly reflect alkyne hydrothiolation due to the competing side reaction generating the diene sulfide.

To avoid this side reaction, the reaction was monitored with varying amounts of thiol closer to normal reaction conditions, while maintaining an excess of thiol. Hydrothiolation reactions were monitored with 1.1, 2.2, 5.5 and 10.5 equivalents of thiol. Another problem encountered with this method was that alkyne consumption changes from a linear decay to an exponential decay when the equivalents of thiol used changes from 2.2 to 5.5 equivalents (Figure 3.16). Furthermore, the reaction rate decreases with even 5.5 equivalents of thiol suggesting that whatever inhibits the reaction with a large excess of thiol is beginning to occur at this concentration of thiol. Additionally, with 10.5 equivalents of thiol, no observable product formation occurs within 3 hours.
Varying thiol concentration

However, when the thiol concentration is doubled from 1.1 to 2.2 equivalents relative to alkyne concentration, the reaction rate also doubles. This trend suggests that when the concentration of thiol is similar to that of the alkyne (such as in catalytic conditions), the reaction rate is first-order in [thiol]. When thiol concentration is at least five times greater than alkyne concentration then a different term in the rate law involving alkyne concentration dominates and slows down the reaction.

To determine if the rate-determining step involves a mono- or dinuclear rhodium intermediate, the reaction rate at various catalyst loadings was also examined. As shown in Figure 3.17, the rate increases exponentially with increasing catalyst loading. This plot shows that the reaction is second-order in [catalyst], suggesting a dinuclear intermediate in the rate-determining step. However, it is possible that this is only occurring at high catalyst concentration. In fact, if the highest catalyst loading (10 mol%) is ignored, then the rate appears to increase linearly, indicating the reaction is first order in [Tp*Rh(PPh₃)₂] at low catalyst loading as expected and that at 10 mol% loading, the rate law is altered.
The competing side reaction forming the diene byproduct and the reaction inhibition at higher thiol concentrations greatly hinder the study of the kinetics of catalytic alkyne hydrothiolation, with the reaction kinetics being more complicated than anticipated. However, some conclusions can be drawn from the data presented. At or near regular Tp*Rh(PPh₃)₂-catalyzed hydrothiolation reaction conditions, the rate seems to obey the following equation: rate = \(k[\text{Tp*Rh(PPh₃)₂}]^{1}[\text{thiol}]^{1}[\text{alkyne}]^{0}\). This rate equation agrees with the rate equation supported by the kinetic data for Tp*Rh(SPh)₂(MeCN), the active catalyst derived from Tp*Rh(coe)(MeCN). However, the time plots of product formation for the two precatalysts are different – the Tp*Rh(PPh₃)₂ system shows linear growth and the Tp*Rh(coe)(MeCN) system shows logarithmic growth.

In comparison to the rate equation for the Tp*Rh(PPh₃)₂ system, the actinide catalyst precursors discussed earlier⁶⁷ – which operate by a disulfide mechanism like Tp*Rh(coe)(MeCN) – obey a different rate equation. The kinetic studies of the actinide system are consistent with rate = \(k[\text{catalyst}]^{1}[\text{thiol}]^{0}[\text{alkyne}]^{x}\). The reaction between \(n\)-pentane thiol and 1-hexyne was found to be first-order in [alkyne] at low alkyne
concentrations but zero-order in [alkyne] at high alkyne concentrations. The authors postulate that insertion of the alkyne is therefore the rate-determining step of the reaction.

The complicated nature of Tp*Rh(PPh₃)₂-catalyzed hydrothiolation prevented a detailed investigation into the kinetics of the reaction. However, a general rate law was approximated from the data presented. The difference in the kinetic behaviour of Tp*Rh(PPh₃)₂-catalyzed hydrothiolation from complexes which catalyze hydrothiolation via a LₐM(SR)₂ intermediate suggest that Tp*Rh(PPh₃)₂-catalyzed hydrothiolation does not go through a disulfide intermediate.

### 3.2.4 Substrate Scope Analysis

#### 3.2.4.1 Substrate Compatibility

Subsequent to the communication of Tp*Rh(PPh₃)₂-catalyzed alkyne hydrothiolation, the full scope and limitations of the use of Tp*Rh(PPh₃)₂ as a precatalyst for alkyne hydrothiolation with alkane thiols was reported by our group (vide supra Figure 3.1). It was found that catalytic hydrothiolation was high yielding and highly selective for a wide range of thiols and alkynes. Both aryl and aliphatic alkynes react in high yields and internal alkynes also react in high yields, though with elevated temperatures. The reaction is tolerant to functional groups on the thiol or alkyne except if the functional group can coordinate to the metal. Strongly coordinating groups on the alkyne, such as pyridine, were found to inhibit catalysis by accelerating irreversible alkyne C-H activation. These complexes are catalytically inactive toward alkyne hydrothiolation.

Allyl thiol also inhibits hydrothiolation but by a different mechanism. Allyl thiol reacts with Tp*Rh(PPh₃)₂ to form a new phophine-free rhodium complex without a rhodium hydride signal in the ¹H NMR spectrum. This new complex was not isolated but is hypothesized to be a rhodium disulfide species because of the concomitant formation of a small amount of diallyl disulfide. However, a variety of other functional groups on the alkyne or thiol, such as nitriles, halogens and esters, were well tolerated. Furthermore, electron rich alkynes were found to react more rapidly than electron
deficient alkynes.

To learn more about the effect of alkyne electronics on catalytic hydrothiolation, the reactivity and selectivity of several para-substituted phenyl acetylenes was examined. The reaction progress between benzyl thiol and six alkynes was monitored at 14 °C in the presence of 3 mol% Tp*Rh(PPh₃)₂. Three para-substituted phenyl acetylenes with electron donating groups (NMe₂, OMe and Me) and two with electron withdrawing groups (Br and CF₃) were compared to phenyl acetylene. These reactions were first reported in the aforementioned paper; however, the reactions were all stopped after 2 hours and no kinetic data was obtained.

The alkyne substitution does not play a role in regioselectivity as only the branched vinyl sulfides were produced. However, alkyne substitution does affect reaction rate and yield, which is in agreement with the previous report. The reactions do not proceed to further completion after 2 hours. After obtaining the $k_{obs}$ for these reactions, we attempted to construct a Hammett plot. The electron rich alkynes were compared separately from the electron deficient alkynes for two reasons. First, the reaction between benzyl thiol and 1-ethynyl-4-trifluoromethylbenzene does not proceed past 40% yield; therefore, only the reaction with 1-bromo-4-ethynylbenzene was examined in detail. Second, the order in [thiol] and in [alkyne] changes with electron deficient alkynes to second order in [thiol] and first order in [alkyne]; thus, the two sets of rates cannot be directly compared. This change in the reaction profile suggests that electron deficient alkynes slow down the alkyne insertion step sufficiently to make it the rate-determining step.

From the rates of vinyl sulfide formation, a Hammett plot was constructed. Using $\sigma$, $\sigma^+$ or $\sigma^-$ values for NMe₂, OMe, Me and H, a straight line was not obtained and no trend was observed. However, if unsubstituted phenyl acetylene is omitted from the analysis as well, the rates correlate with the $\sigma^-$ values (Figure 3.18). Care must be taken in interpreting this result as only three data points have been used and these are only electron rich phenyl acetylenes. Without a correlation between the rates and the sigma values, no information can be extracted from this set of experiments. The lack of correlation with the unsubstituted phenyl acetylene, as well as the complication using electron-donating groups in the para position could be indicative of a change in the
mechanism or the kinetics of the reaction, but there is insufficient information to postulate further. Qualitatively, it is apparent that substitution at the para-position of phenyl acetylene plays an undefined role in reactivity but not selectivity.

Figure 3.18: Hammett plot for Tp*Rh(PPh₃)₂-catalyzed hydrothiolation

3.2.4.2 Arene Thiols

In our initial report on Tp*Rh(PPh₃)₂-catalyzed alkyne hydrothiolation, we reported that hydrothiolation with alkane thiols occurred with high regioselectivity, whereas hydrothiolation with arene thiols occurred with only modest selectivity. The five hydrothiolation reactions with arene thiols examined in this paper range in selectivity from 6:1 down to 1.4:1. The worst selectivity was displayed by substituted arene thiols. Since we used benzene thiol as well as benzyl thiol in our stoichiometric studies, we were curious to know the source of this discrepancy between the alkane and arene thiols, particularly relating to mechanistic differences.
Table 3.4: Reported Alkyne Hydrothiolation with Arene Thiols\textsuperscript{60}

\[
\text{ArSH} + R' \xrightarrow{3 \text{ mol}\% \text{Tp}^*\text{Rh(PPh}_3\text{)_2}} \xrightarrow{\text{DCE:Tol (1:1), rt}} \text{R'}\text{SAr} + \xrightarrow{E}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Time (h)</th>
<th>Yield\textsuperscript{a}, Br:Lin Ratio\textsuperscript{b}</th>
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<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>2</td>
<td>84%, 6:1</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>\textit{p}-CH\textsubscript{3}OC\textsubscript{6}H\textsubscript{4}</td>
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<td>89%, 3.2:1</td>
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<td>\textit{o},\textit{p}-F\textsubscript{2}C\textsubscript{6}H\textsubscript{4}</td>
<td>2</td>
<td>90%, 2.6:1</td>
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<tr>
<td>4</td>
<td>\textit{p}-CH\textsubscript{3}C\textsubscript{6}H\textsubscript{4}</td>
<td>Ph</td>
<td>1.5</td>
<td>83%, 1.4:1</td>
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<tr>
<td>5</td>
<td>\textit{p}-BrC\textsubscript{6}H\textsubscript{4}</td>
<td>Ph</td>
<td>23</td>
<td>85%, 1.7:1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yields. \textsuperscript{b} Small amounts of Z were observed.

When repeating some of the reported reactions in a sealed NMR tube, we found that the reactions produced only the branched vinyl sulfide. None of the \textit{E}-linear vinyl sulfide was observed. This was surprising to us as the only difference between the NMR scale reaction and the preparative scale reaction is the solvent: \textit{d}_8\text{-toluene vs. 1:1 DCE:toluene}. Therefore, the reaction between benzene thiol and phenyl acetylene was run on a preparative scale in both toluene and a 1:1 DCE:toluene mixture. In both cases, the crude reaction mixture resulted in a 6:1 mixture of the branched and \textit{E}-linear vinyl sulfides, as previously reported. These results suggest that the mechanism of alkyne hydrothiolation with arene thiols and with alkane thiols is probably the same. The cause of reduced selectivity with arene thiols is associated with preparative scale reactions in proteo solvents (possibly a mass transfer effect).
Table 3.5: “New” Alkyne Hydrothiolation with Arene Thiols

\[
\text{ArSH} + \text{R} = \text{S} \xrightarrow{3 \text{ mol% Tp*Rh(PPh\textsubscript{3})\textsubscript{2}}} \text{rt} \quad \text{R} - \text{SSA}r + \text{R} = \text{S} \text{Ar}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R'</th>
<th>Time (h)</th>
<th>NMR Yield\textsuperscript{a,b}, B:E Ratio</th>
<th>Isolated Yield\textsuperscript{c,d}, B:E Ratio</th>
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<td>Ph</td>
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<td>Ph</td>
<td>1</td>
<td>&gt;95%, &gt;19:1</td>
<td>n/a</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yields determined by \textsuperscript{1}H NMR spectroscopy relative to internal standard. \textsuperscript{b} d\textsubscript{6}-Tol \textsuperscript{c} 1:1 DCE:Tol or Tol \textsuperscript{d} Isomeric ratios determined by integration of vinyl signals in \textsuperscript{1}H NMR spectra

3.3 Conclusions

Five mechanistic possibilities for Tp*Rh(PPh\textsubscript{3})\textsubscript{2}-catalyzed alkyne hydrothiolation were considered. Product analysis and a deuterium-labeling study eliminated three mechanisms because they would not generate the same products as those observed experimentally under catalytic conditions. The two remaining mechanistic possibilities – oxidative addition followed by alkyne insertion into a Rh-S bond or a mechanism involving a L\textsubscript{n}Rh(SR)\textsubscript{2} intermediate – were considered based on substrate scope, further product analysis, stoichiometric reactivity and kinetic analysis.

Comparison to a similar hydrothiolation precatalyst, Tp*Rh(coe)(MeCN), exposes a discrepancy in the minor products formed from the two Tp*RhL\textsubscript{n} complexes that have proven useful in alkyne hydrothiolation. The \textit{E}-linear vinyl sulfide and a diene byproduct are the minor product from the Tp*Rh(PPh\textsubscript{3})\textsubscript{2}-catalyzed reaction; however, when Tp*Rh(coe)(MeCN) is used as a hydrothiolation precatalyst, the \textit{Z}-linear vinyl sulfide and a thio-ketals are observed as the minor products of the reaction. Tp*Rh(coe)(MeCN) is reported to catalyze hydrothiolation by formation of a L\textsubscript{n}Rh(SR)\textsubscript{2} species. This analysis suggests Tp*Rh(PPh\textsubscript{3})\textsubscript{2} probably catalyzes hydrothiolation via a different mechanism.
Analysis of stoichiometric reactivity was more complicated than originally anticipated. The identification and characterization of the complexes formed were rendered difficult because of competing side reactions. The stoichiometric reaction between Tp*Rh(PPh$_3$)$_2$ and benzyl thiol was monitored by $^1$H, $^{31}$P{$^1$H}, and $^{11}$B NMR spectroscopy. Two new complexes, A and B, are formed in the stoichiometric reaction; according to $^{31}$P{$^1$H} NMR spectroscopy these are proposed to be Tp*Rh(PPh$_3$)$_2$(HSBn) and Tp*Rh(H)(SBn)(PPh$_3$), respectively. $^{11}$B NMR spectroscopy suggests there are three different inequivalent Tp* ligands in solution but was unhelpful in determining the denticity of the Tp* ligand. The $^1$H NMR spectra were too complicated to aid in characterization, but indicated that two or three rhodium hydride complexes exist in solution. Isolation was not possible due to further reaction of complex B. The identity of B needs to be investigated further. The reaction of Tp*Rh(PPh$_3$)$_2$ and thirty equivalents of benzyl thiol produced Tp*Rh(PPh$_3$)$_2$(HSBn) and a new complex D, proposed to be Tp*Rh(SR)$_2$(PPh$_3$).

Despite not isolating the catalytic intermediates, the catalytic ability of B was examined in situ and found to be inactive towards alkyne hydrothiolation. However, NMR spectroscopy suggests that while complex B may be the only complex observed by $^{31}$P NMR spectroscopy, there may be other uncharacterized products in solution. If B is Tp*RH(H)(SBn)(PPh$_3$), this result would nullify the hypothesis that the reaction occurs via oxidative addition of the thiol followed by alkyne insertion. However, if B is a different species, such as Tp*Rh(HSBn)(PPh$_3$), then this mechanism would still be valid.

Kinetic analysis of catalytic hydrothiolation was also problematic. Determination of the rate law was complicated because of competing side reactions at high alkyne concentration and inhibition at high thiol concentration. Furthermore, it seems that the catalytic reaction conditions are close to the limit for a change in the rate-determining step; increased catalyst loadings, increased thiol concentrations, or the use of electron-deficient alkynes alter the rate law for the reaction making kinetic analysis very complicated. The rate law is approximated as rate = $k[\text{Tp*Rh(PPh}_3)_2]^1[\text{thiol}]^1[\text{alkyne}]^0$ close to catalytic conditions for benzyl thiol and phenyl acetylene.

Unfortunately, the data presented does not fully support or refute either possible mechanism. The complications from side reactions in the stoichiometric reactivity studies
and kinetic analysis hampered our ability to obtain conclusive evidence for deciphering the mechanism of Tp*Rh(PPh₃)₂-catalyzed alkyne hydrothiolation with alkane thiols. However, we believe that the results presented herein point more toward a mechanism involving oxidative addition of the thiol onto rhodium, followed by alkyne insertion into the Rh-S bond and subsequent by reductive elimination of the branched vinyl sulfide. While this is a provocative mechanism, others have proposed analogous mechanisms for other H-E addition reactions using similar methods for mechanistic analysis. Nevertheless, it is obvious that the Tp* ligand plays a role in changing the mechanism of rhodium-catalyzed alkyne hydrothiolation when compared to Wilkinson’s catalyst. The trispyrazolylborate ligand is a hard 6-electron donor when bound in a κ³-fashion, which creates a very electron-rich rhodium centre. It is doubtless this difference which alters the mechanism of the reaction. Overall, these studies provide the foundation for further exploration of the mechanism by which Tp*Rh(PPh₃)₂ catalyzes alkyne hydrothiolation.

3.4 Experimental

3.4.1 General Procedures

Manipulation of organometallic compounds was performed using standard Schlenk techniques under an atmosphere of dry nitrogen or in a nitrogen-filled Vacuum Atmospheres drybox (O₂ < 2 ppm). NMR spectra were recorded on Bruker Avance 300 or Bruker Avance 400 spectrometers. ¹H, ¹¹B, ¹³C and ³¹P NMR spectra are reported in parts per million and ¹H and ¹³C NMR spectra were referenced to residual solvent. Coupling constant values were extracted assuming first-order coupling. All spectra were obtained at 25 °C unless otherwise noted. 1,3,5-Trimethoxybenzene was used as an internal standard for NMR yields and kinetic experiments. Mass spectra were recorded on a Kratos MS-50 mass spectrometer.

3.4.2 Materials and Methods

Benzene and toluene were dried by passage through solvent purification columns. ¹⁰⁵ 1,2-Dichloroethane was distilled from molecular sieves and degassed prior to use. CDCl₃ was
purified by vacuum transfer from P₂O₅ and was degassed prior to use. C₆D₆ and d₅-toluene were degassed prior to use. All organic reagents were obtained from commercial sources and distilled before use. 1,3,5-Trimethoxybenzene was sublimed prior to use. ClRh(PPh₃)₃ was purchased from Strem Chemicals and was used without further purification. Tp*Rh(PPh₃)₂ was prepared as previously reported.⁶⁰

3.4.3 General Experimental Procedures for Hydrothiolation and Stoichiometric Reactions

General Procedure for Alkyne Hydrothiolation (NMR Tube Reactions):
Tp*Rh(PPh₃)₂ (4 mg, 0.0045 mmol, 3 mol %) and 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol) were dissolved in C₆D₆ or d₅-toluene (0.9 mL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Thiol (0.165 mmol) was added to the NMR tube solution using a microsyringe followed by alkyne (0.15 mmol) addition using a microsyringe. Reaction progress was monitored by ¹H NMR spectroscopy. Product yield and isomeric ratios were determined by comparison of the integration of the product vinylic proton peaks to the internal standard peak.

Note: When possible, a freshly prepared standard solution containing Tp*Rh(PPh₃)₂ and 1,3,5-trimethoxybenzene in the given solvent was used.

D-Labeling Experiment:
Tp*Rh(PPh₃)₂ (4 mg, 0.0045 mmol, 3 mol %) and 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol) were dissolved in C₆D₆ (0.9 mL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Benzyl thiol (0.165 mmol, 19.5 µL) was added to the NMR tube solution using a 25 µL microsyringe followed by d-phenyl acetylene (0.15 mmol, 16.5 µL) addition using a 25 µL microsyringe. Reaction progress was monitored by ¹H NMR spectroscopy.

Vinyl sulfide-D diagnostic peaks observed in situ: ¹H NMR (C₄D₆, 400 MHz): δ 5.10 (s, 1H), 3.62 (s, 2H).
**Preparation of Diene Byproduct:**

Tp*Rh(PPh₃)₂ (4 mg, 0.0045 mmol, 3 mol %) and 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol) were dissolved in C₆D₆ (0.9 mL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Benzyl thiol (0.075 mmol, 8.8 µL) was added to the NMR tube solution using a 25 µL microsyringe followed by phenyl acetylene (0.15 mmol, 16.5 µL) addition using a 25 µL microsyringe. Reaction progress was monitored by ¹H NMR spectroscopy. Product yield was determined by comparison of the integration of the product vinylic proton peaks to the internal standard peak. 68% yield vinyl sulfide. 30% yield diene.

Diene diagnostic peaks observed *in situ* with vinyl sulfide: ¹H NMR (C₆D₆, 300 MHz): δ 6.66 (s, 1H), 5.75 (s, 1H), 5.49 (s, 1H), 3.44 (s, 2H).

**D-Labeling Experiment:**

Tp*Rh(PPh₃)₂ (4 mg, 0.0045 mmol, 3 mol %) and 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol) were dissolved in C₆D₆ (0.9 mL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Benzyl thiol (0.075 mmol, 8.8 µL) was added to the NMR tube solution using a 25 µL microsyringe followed by ⁴-phenyl acetylene (0.15 mmol, 16.5 µL) addition using a 25 µL microsyringe. Reaction progress was monitored by ¹H NMR spectroscopy.

Diene-D diagnostic peaks observed *in situ* with vinyl sulfide: ¹H NMR (C₆D₆, 300 MHz): δ 5.50 (s, 1H), 3.44 (s, 2H).

**Alkyne Dimerization Experiment:**

Tp*Rh(PPh₃)₂ (4 mg, 0.0045 mmol, 3 mol %) and 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol) were dissolved in C₆D₆ (0.9 mL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Phenyl acetylene (0.3 mmol, 33 µL) was added to the NMR tube solution using a 25 µL microsyringe. Reaction progress was monitored by ¹H NMR spectroscopy. No dimer was observed in the ¹H NMR spectrum in the timescale of hydrothiolation (45 min).
Stoichiometric Reaction of Tp*Rh(PPh$_3$)$_2$ and Benzyl Thiol:

NMR Tube Reaction:

Tp*Rh(PPh$_3$)$_2$ (18.5 mg, 0.02 mmol) was dissolved in C$_6$D$_6$ or d$_8$-toluene (1 mL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. 1 equivalent of benzyl thiol (0.02 mmol, 2.35 µL) or 2 equivalents of benzyl thiol (0.04 mmol, 4.7 µL) was added to the NMR tube solution using a 5 µL microsyringe. Alternatively, a standard solution of benzyl thiol was prepared (23.5 µL benzyl thiol in 1 mL d$_8$-toluene) and 100 µL of the solution was added via a 250 µL microsyringe for the addition of 1 equivalent of benzyl thiol. Reaction progress was monitored by $^{31}$P{$^1$H} and/or $^1$H NMR spectroscopy every 5 minutes (for the time plot, the “multi_zgvd” command was used).

Complex A, Tp*Rh(PPh$_3$)$_2$(HSBn), is observed within 10 minutes. $^{31}$P{$^1$H} NMR (C$_6$D$_6$, 400 MHz): δ 53.2 (dd, $^1$J$_{Rh-P}$ = 175 Hz, $^2$J$_{P-P}$ = 41 Hz, 1P), 44.8 ppm ($^1$J$_{Rh-P}$ = 175 Hz, $^2$J$_{P-P}$ = 41 Hz, 1P).

Complex B, Tp*Rh(H)(SBn)(PPh$_3$) is observed within 20 minutes with free PPh$_3$. 

$^{31}$P{$^1$H} NMR (C$_6$D$_6$, 400 MHz): δ 44.6 (d, $^1$J$_{Rh-P}$ = 173 Hz).

$^1$H NMR (C$_6$D$_6$, 400 MHz): δ 5.62 (s, 3H), 2.21 (s, 9H), 2.01 (s, 9H), -16.4 (dd, $^1$J$_{Rh-H}$ = 16 Hz, $^2$J$_{P-H}$ = 31 Hz).

$^{11}$B NMR (d$_8$-toluene, 400 MHz): δ -1.4 (s, br), -10.6 (s, br), -13.9 (s, br).

Other resonances are also observed in the $^1$H NMR spectrum of certain trials including $^1$H NMR (C$_6$D$_6$, 400 MHz): δ -14.4 (dd, $^1$J$_{Rh-H}$ = $^2$J$_{P-H}$ = 18.8 Hz), -15.8 (dd, $^1$J$_{Rh-H}$ = 13 Hz, $^2$J$_{P-H}$ = 27.8 Hz).

Preparative Scale Reaction:

This reaction was performed in various solvents, for varying amounts of time, and with one or two equivalents of thiol. Furthermore, various work up procedures were attempted.

Tp*Rh(PPh$_3$)$_2$ (104 mg, 0.114 mmol) was dissolved in a given solvent (benzene, toluene, 1:1 toluene/DCE, CH$_2$Cl$_2$, benzene/hexanes) in the glove box in a round bottom Schlenk flask equipped with a magnetic stir bar. The flask was sealed with a septum and removed
from the glove box. Benzyl thiol (14 µL, 0.12 mmol) was added with a microsyringe. The reaction was stirred for 1-24 hours. Subsequently, the orange/brown reaction mixture was either layered with hexanes or concentrated and dissolved in toluene or benzene and layered with hexanes to hopefully afford crystals.

**Test of Catalytic Ability of Tp*Rh(H)(SBn)(PPh₃):**

Tp*Rh(H)(SBn)(PPh₃) was prepared *in situ:* Tp*Rh(PPh₃)₂ (16.6 mg, 0.018 mmol) was dissolved in C₆D₆ (796 µL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Benzyl thiol (0.036 mmol, 4.2 µL) was added to the NMR tube solution using a 5 µL microsyringe. The reaction progress was monitored by ³¹P{¹H} NMR spectroscopy until only the signal for Tp*Rh(H)(SBn)(PPh₃) and PPh₃ remained (45 min).

200 µL of this solution (equivalent to 0.0045 mmol Tp*Rh(H)(SBn)(PPh₃)) was removed from the NMR tube using a 250 µL microsyringe. This was added to a screw cap NMR tube containing 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol) and 364 µL C₆D₆. Benzyl thiol (0.165 mmol, 19.5 µL) was added to the NMR tube solution using a microsyringe followed by phenyl acetylene (0.15 mmol, 16.5 µL) addition using a microsyringe. Reaction progress was monitored by ¹H NMR spectroscopy. 8% yield vinyl sulfide (3h).

**Stoichiometric Reaction of Tp*Rh(PPh₃)₂ and Dibenzyl Disulfide:**

Tp*Rh(PPh₃)₂ (18.5 mg, 0.02 mmol) was dissolved in C₆D₆ (800 µL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Dibenzyl disulfide (5 mg, 0.02 mmol), dissolved in C₆D₆ (200 µL), was added to the NMR tube solution using a microsyringe. The reaction progress was monitored by ³¹P{¹H} NMR spectroscopy. After 12 days at room temperature, the NMR tube was heated to 80 °C for 24 hours. Only the orthometalation product was observed.
**Stoichiometric Reaction of Tp*Rh(PPh$_3$)$_2$ and Diphenyl Disulfide:**

Tp*Rh(PPh$_3$)$_2$ (18.5 mg, 0.02 mmol) was dissolved in C$_6$D$_6$ (900 µL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Diphenyl disulfide (4 mg, 0.02 mmol), dissolved in C$_6$D$_6$ (200 µL), was added to the NMR tube solution using a microsyringe. The reaction progress was monitored by $^{31}$P{$^1$H} NMR spectroscopy.

$^{31}$P{$^1$H} NMR (C$_6$D$_6$, 400 MHz): $\delta$ 25.8 (s).

**Reaction of PPh$_3$ and Diphenyl Disulfide:**

Recrystallized PPh$_3$ (13.1 mg, 0.05 mmol) was dissolved in C$_6$D$_6$ (500 µL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Dibenzyl disulfide (11 mg, 0.05 mmol), dissolved in C$_6$D$_6$ (400 µL), was added to the NMR tube solution using a microsyringe. The reaction progress was monitored by $^{31}$P{$^1$H} NMR spectroscopy.

$^{31}$P{$^1$H} NMR (C$_6$D$_6$, 400 MHz): $\delta$ 25.8 (s).

**Reaction of Tp*Rh(PPh$_3$)$_2$ with Excess Diphenyl Disulfide:**

Tp*Rh(PPh$_3$)$_2$ (18.5 mg, 0.02 mmol) was dissolved in C$_6$D$_6$ (600 µL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Diphenyl disulfide (44 mg, 0.2 mmol), dissolved in C$_6$D$_6$ (400 µL), was added to the NMR tube solution using a microsyringe.

$^{31}$P{$^1$H} NMR (C$_6$D$_6$, 400 MHz): $\delta$ 25.8 (s, Ph$_3$P(SPh)$_2$), -4.5 (s, PPh$_3$).

Diagnostic $^1$H NMR (C$_6$D$_6$, 400 MHz): $\delta$ 5.61 (s, 3H), 2.20 (s, 9H), 2.01 (s, 9H).

**Reaction of Tp*Rh(PPh$_3$)$_2$ with Excess Benzyl Thiol**

Tp*Rh(PPh$_3$)$_2$ (18.5 mg, 0.02 mmol) was dissolved in C$_6$D$_6$ (930 µL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Benzyl thiol (0.6 mmol,
70.5 µL) was added to the NMR tube solution using a microsyringe. Reaction progress was monitored by $^{31}$P{$^1$H} NMR spectroscopy.

Complex A, Tp*Rh(PPh$_3$)$_2$(HSBn), is observed within 10 minutes. Complex D, Tp*Rh(SBn)$_2$(PPh$_3$), is also observed within 10 minutes. $^{31}$P{$^1$H} NMR (C$_6$D$_6$, 400 MHz): δ 28.8 (d, $^1$J$_{Rh-P}$ = 110 Hz). $^1$H NMR (C$_6$D$_6$, 400 MHz): δ 5.61 (s, 3H), 2.20 (s, 9H), 2.01 (s, 9H), -14.4 (dd, $^1$J$_{Rh-H}$ = $^2$J$_{P-H}$ = 18.8 Hz), -15.8 (dd, $^1$J$_{Rh-H}$ = 13 Hz, $^2$J$_{P-H}$ = 27.8 Hz), -16.4 (dd, $^1$J$_{Rh-H}$ = 16 Hz, $^2$J$_{P-H}$ = 31 Hz).

**Stoichiometric reaction of Tp*Rh(PPh$_3$)$_2$, benzyl thiol and phenyl acetylene**

**Method A**

Tp*Rh(PPh$_3$)$_2$ (18.5 mg, 0.02 mmol) was dissolved in C$_6$D$_6$ or $d_8$-toluene (1 mL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. 1 or 2 equivalents of benzyl thiol (0.02 mmol, 2.4 µL or 0.04 mmol, 4.7 µL) was added to the NMR tube solution using a 5 µL microsyringe. The reaction progress was monitored by $^{31}$P{$^1$H} NMR spectroscopy until only the signal for Tp*Rh(H)(SBn)(PPh$_3$) remained (45 min – 75 min). Phenyl acetylene (0.02 mmol, 2.2 µL) was then added using a 25 µL microsyringe. Alternatively, a standard solution of benzyl thiol was prepared (23.5 µL benzyl thiol in 1 mL $d_8$-toluene) and 100 µL of the solution was added via a 250 µL microsyringe for the addition of 1 equivalent of benzyl thiol; and a standard solution of phenyl acetylene was prepared (22.0 µL phenyl acetylene in 1 mL $d_8$-toluene) and 100 µL of the solution was added via a 250 µL microsyringe for the addition of 1 equivalent of phenyl acetylene. Reaction progress was monitored by $^{31}$P{$^1$H} and $^1$H NMR spectroscopy.

$^{31}$P{$^1$H} NMR (C$_6$D$_6$, 400 MHz): same as prior to alkyne addition

**Method B**

Tp*Rh(PPh$_3$)$_2$ (18.5 mg, 0.02 mmol) were dissolved in C$_6$D$_6$ (1 mL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Benzyl thiol (0.02 mmol, 2.4 µL) was added to the NMR tube solution from a standard solution using a microsyringe followed by phenyl acetylene (0.02 mmol, 2.2 µL) addition from a standard solution
using a microsyringe. Reaction progress was monitored by $^{31}\text{P}\{^{1}\text{H}\}$ and $^{1}\text{H}$ NMR spectroscopy.

$^{31}\text{P}\{^{1}\text{H}\}$ NMR ($C_6D_6$, 400 MHz): same as without alkyne addition

$^{1}\text{H}$ NMR ($C_6D_6$, 400 MHz): 5.80 (s, 0.3H), 5.65 (s, 0.3H), 5.62 (s, 3H), 5.21 (s, 0.3H), 2.64 (s, 0.9H), 2.57 (s, 0.9H), 2.55 (s, 0.9H), 2.35 (s, 0.9H), 2.29 (s, 0.9H), 2.21 (s, 9H), 2.01 (s, 9H), 1.57 (s, 0.9H), -15.8 (dd, $^{1}J_{\text{Rh-H}} = 13$ Hz, $^{2}J_{\text{P-H}} = 27.8$ Hz), -16.4 (dd, $^{1}J_{\text{Rh-H}} = 16$ Hz, $^{2}J_{\text{P-H}} = 31$ Hz).

### 3.4.4 General Experimental Procedures for Kinetic Studies

#### General Procedure for Solvent Study

Tp*Rh(PPh$_3$)$_2$ (4 mg, 0.0045 mmol, 3 mol %) and 1,3,5-trimethoxybenzene (8 mg, 0.05 mmol) were dissolved in the appropriate solvent (600 µL) in the glove box in a vial and transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then removed from the glove box. Benzyl thiol (19.5 µL, 0.165 mmol) was added to the NMR tube solution using a 25 µL microsyringe followed by alkyne (16.5 µL, 0.15 mmol) addition using a 25 µL microsyringe. Reaction progress was monitored by $^{1}\text{H}$ NMR spectroscopy every 5 minutes at 25 °C using the “multi_zgvd” command. Substrate and product concentration were determined by comparison of the integration of the internal standard peak to the thiol methylene, alkylnyl proton or the product vinylic and methylene proton peaks. The concentrations were plotted against time in Microsoft Excel.

#### General Procedure for Kinetic Runs

(Example provided for 1.1 equivalents of benzyl thiol and 1 equivalent of phenyl acetylene)

Standard solutions of Tp*Rh(PPh$_3$)$_2$ (0.015 mmol, 14 mg) and 1,3,5-trimethoxybenzene (0.17 mmol, 28 mg) in $C_6D_6$ (2.00 mL) were prepared in the glove box on the day the experiments were prepared. 600 µL of the standard solution (corresponding to 0.0045 mmol Tp*Rh(PPh$_3$)$_2$, 0.05 mmol 1,3,5-trimethoxybenzene) were transferred to a screw cap NMR tube. The tube was sealed with a cap fitted with a septum and was then
removed from the glove box. Benzyl thiol (19.5 \(\mu\)L, 0.165 mmol, 1.1 equivalent) was added to the NMR tube solution using a 25 \(\mu\)L microsyringe. The NMR tube was then placed in the pre-cooled 400 MHz NMR spectrometer (13.9 °C) to equilibrate. At 10 minutes after thiol addition, phenyl acetylene (16.5 \(\mu\)L, 0.15 mmol) was added to the NMR tube using a 25 \(\mu\)L microsyringe. The NMR tube was placed back in the spectrometer. After 2 minutes, reaction progress was monitored by \(^1\)H NMR spectroscopy every 5 minutes using the “multi_zgvd” command. Substrate and product concentration were determined by comparison of the integration of the internal standard peak to the thiol methylene, alkynyl proton or the product vinylic and methylene proton peaks. The concentrations were plotted against time in Microsoft Excel to obtain the reaction rate. Each experiment was performed in triplicate.

**Procedure for Determination of Reactant Order**

Experiments were performed as in the general case with the following exceptions: New standard solutions were prepared so that the total volume in the NMR tube (including thiol and alkyne) was equal to 600 \(\mu\)L. The amount of benzyl thiol was also different: 2.2 equivalents (39.0 \(\mu\)L, 0.33 mmol), 5.5 equivalents (96.9 \(\mu\)L, 0.825 mmol), 10.5 equivalents (185 \(\mu\)L, 0.1575 mmol), 30 equivalents (19.5 \(\mu\)L, 0.165 mmol), 50 equivalents (19.5 \(\mu\)L, 0.165 mmol). The experiments for 2.2 and 5.5 equiv. thiol were performed in triplicate and those for 10.5, 30 and 50 equiv. were performed in duplicate.

**Procedure for Determination of Catalyst Order**

Experiments were performed as in the general case with the following exceptions: New separate standard solutions were prepared. 200 \(\mu\)L of the 1,3,5-trimethoxybenzene standard solution (59 mg, 0.35 mmol, dissolved in 1.40 mL \(\text{C}_6\text{D}_6\)) was added to the NMR tubes for 5 mol%, 7.5 mol% and 10 mol% catalyst loading.

*5 mol% catalyst loading:* 300 \(\mu\)L of the Tp*Rh(PPh$_3$)$_2$ standard solution (17 mg, 0.018 mmol, dissolved in 750 \(\mu\)L \(\text{C}_6\text{D}_6\)) and 64 \(\mu\)L of \(\text{C}_6\text{D}_6\) were added to the NMR tube prior to thiol addition.

*7.5 mol% catalyst loading:* Tp*Rh(PPh$_3$)$_2$ (10 mg, 0.011 mmol) was dissolved in 364 \(\mu\)L of \(\text{C}_6\text{D}_6\) was added to the NMR tube prior to thiol addition.
10 mol% catalyst loading: Tp*Rh(PPh₃)₂ (14 mg, 0.015 mmol) was dissolved in 364 μL of C₆D₆ was added to the NMR tube prior to thiol addition.
Each experiment was performed in duplicate.

**Procedure for Kinetic Isotope Effect Study**
Experiments were performed as in the general case with the following exception: 
*d*-phenyl acetylene (16.5 μL, 0.15 mmol) was used instead of phenyl acetylene. This experiment was performed in triplicate.

**General Procedure for the Hammett Study:**
Experiments were performed as in the general case with the following exceptions:
Standard solutions of Tp*Rh(PPh₃)₂ and 1,3,5-trimenthoxybenzene were prepared so that the total volume in the NMR tube would equal 600 μL (including thiol and alkyne).
For alkynes that are oils, the addition of phenyl acetylene was substituted as follows: 4-ethynylanisole (19.5 μL, 0.15 mmol) or 4-ethynyltoluene (19.0 μL, 0.15 mmol) was used.
For alkynes that are solid, the addition of phenyl acetylene was substituted as follows: N,N-dimethyl-1-ethynylaniline (22 mg, 0.15 mmol) or 1-ethynyl-4-bromotoluene (27 mg, 0.15 mmol) was dissolved in 200 μL and added to the NMR tube using a 250 μL microsyringe.
Experiments were not repeated since yields correlated with reported yields.
Chapter 4: Conclusions and Future Work

4.1 Conclusions

Transition-metal-catalyzed alkyne hydrothiolation is a useful method for selectively preparing vinyl sulfides. Prior to the onset of this thesis, the Love group had reported the only example of transition-metal-catalyzed hydrothiolation with alkane thiols using Tp*Rh(PPh₃)₂. Moreover, there were no methods for preparing $E$-linear alkyl vinyl sulfides. We have successfully developed a methodology for selectively preparing $E$-linear vinyl sulfides from alkynes and alkane thiols using Wilkinson’s catalyst [ClRh(PPh₃)₃] as a catalyst precursor, contrary to literature reports. This method is analogous to the existing methodology for arene thiols with the same catalyst precursor, and simply required optimization of conditions to extend the reaction scope to include alkane thiols. Furthermore, the reaction is also complementary to the aforementioned methodology developed by our group for the formation of branched vinyl sulfides. The reaction is tolerant of various alkane thiols with a wide range of functional groups, but is negatively affected by the presence of coordinating functional groups. The reaction is successful with aryl and aliphatic terminal and internal alkynes, with electron-rich aryl alkynes resulting in the highest yields and bulky aliphatic alkynes promoting the best selectivity. This contribution to the field of transition-metal-catalyzed hydrothiolation addresses the two hydrothiolation challenges presented in the introduction, namely, control of regio- and stereoselectivity and the ability to use alkane thiols.

Investigations into the mechanisms of the two catalytic hydrothiolation methodologies for alkane thiols developed by the Love group were presented in this thesis. It is proposed that ClRh(PPh₃)₃-catalyzed hydrothiolation with alkane thiols occurs by the same mechanism proposed for arene thiols, namely: oxidative addition of the thiol onto the rhodium center, followed by insertion of the alkyne into the Rh-H bond, and subsequent reductive elimination of the linear vinyl sulfide.

Several mechanisms were considered for Tp*Rh(PPh₃)₂-catalyzed alkyne hydrothiolation and all but two were eliminated. One possible mechanism is oxidative addition of the thiol onto the rhodium center, followed by insertion of the alkyne into the
Rh-S bond, and subsequent reductive elimination of the branched vinyl sulfide. The second possibility is oxidative addition of two equivalents of thiol to form Tp*Rh(SR)$_2$(PPh$_3$)$_2$, followed by insertion of the alkyne into a Rh-S bond and subsequent protonolysis by another thiol to produce the branched vinyl sulfide. However, determination of the mechanism was more difficult than anticipated.

Comparison of the product distribution to another hydrothiolation catalyst precursor, Tp*Rh(coe)(MeCN)$_6$, which catalyzes hydrothiolation by the latter mechanism, indicated that the complexes probably catalyze hydrothiolation by different mechanisms. The stoichiometric reactivity of the metal complex with benzyl thiol was investigated. Two new complexes were observed by $^{31}$P($^1$H) NMR spectroscopy over the course of the reaction; they are proposed to be Tp*Rh(PPh$_3$)$_2$(HSBn) and Tp*Rh(H)(SBn)(PPh$_3$). $^{11}$B NMR spectroscopy indicated that there may be multiple κ$_3$-Tp*RhL$_n$ species in solution, which may be different isomers of κ$_3$-Tp*Rh(H)(SBn). The pyrazolyl groups on the Tp* ligand appear to be equivalent by $^1$H NMR spectroscopy, most likely from rapid exchange. In addition, there appears to be more than one Rh-H species according to the $^1$H NMR spectrum. Isolation of B was not possible despite numerous attempts under a variety of conditions; the complex is only present for a few hours during the course of the reaction. Complex B, formed in situ, did not catalyze alkyne hydrothiolation, suggesting that it is not part of the catalytic cycle. While this evidence would appear to refute the oxidative addition mechanism, the other species in solution may be inhibiting catalysis or the proposed identity of B may be incorrect.

Attempts to form Tp*Rh(SR)$_2$(PPh$_3$)$_2$ from dibenzyl disulfide and diphenyl disulfide were unsuccessful. A new compound was observed in the reaction of Tp*Rh(PPh$_3$)$_2$ with a large excess of benzyl thiol that is hypothesized to be Tp*Rh(SR)$_2$(PPh$_3$)$_2$; however, this compound was not isolable and its catalytic ability was not tested.

Kinetic experiments were performed to gain insight into the reaction mechanism. A time plot of the reaction progress by $^1$H NMR spectroscopy indicates that the reaction rate is first order in [thiol] and zero order in [alkyne]. Pseudo-first order reaction conditions for further kinetic analysis were not possible due to a competing side-reaction at high alkyne concentrations and reaction inhibition at high thiol conditions. Kinetic
isotope experiments indicate that the alkyne is not involved in the rate-determining step. However, kinetic monitoring of hydrothiolation of different \textit{para}-substituted phenyl acetylenes indicated that the rate equation for the reaction is different for electron-rich and electron-deficient alkenes. Finally, the order in [catalyst] seems to change from first-order to second-order at high catalyst loading.

Attempts at deciphering the reaction mechanism for Tp*Rh(PPh$_3$)$_2$-catalyzed alkyne hydrothiolation were ambiguous. This demonstrates that mechanistic analysis is a difficult and complicated process. However, these initial forays into mechanism determination can be supplemented with experiments described in the next section, and comparisons to future reports on transition-metal-catalyzed hydrothiolation, to create a more complete mechanistic picture. In the meantime, we hypothesize that the data presented best supports a mechanism involving thiol S-H oxidative addition, followed by migratory alkyne insertion into the Rh-S bond and reductive elimination.

\textbf{4.2 Future Work}

A more thorough investigation of the substrate scope of ClRh(PPh$_3$)$_3$-catalyzed alkyne hydrothiolation with arene and alkane thiols is currently underway in the Love group. This investigation is focusing on potential directing group effects of alkyne substituents on hydrothiolation as well as functional group tolerance. A one-pot procedure for the functionalization of $E$-linear vinyl sulfides prepared from alkyne hydrothiolation will also be investigated. In addition, the use of Rh-catalyzed alkyne hydrothiolation for the synthesis of K11777,\textsuperscript{8} which is a promising therapeutic for the treatment of Chagas disease (considered by the World Health Organization to be a Neglected Global Disease), is being investigated in the Love group.

More detailed mechanistic investigations into the mechanism of this reaction would also be worthwhile. Kinetic analysis, such as that described in Chapter 3, for ClRh(PPh$_3$)$_3$ could provide insight into other rhodium-catalyzed alkyne hydrothiolation mechanisms, such as that for Tp*Rh(PPh$_3$)$_2$. Stoichiometric reactions with ClRh(PPh$_3$)$_3$ would also be an interesting avenue of research.
Several approaches for mechanistic analysis of the Tp*Rh(PPh₃)₂-catalyzed alkyne hydrothiolation remain and will be pursued by a new graduate student, Matthew Wathier. The effect of thiol electronics could be investigated by comparing the rates of reaction of different para-substituted benzene thiols. Furthermore, Tp*Rh(H)(SR)(PPh₃) and Tp*Rh(SR)₂(PPh₃) could be prepared from a method independent of oxidative addition of the thiol onto Tp*Rh(PPh₃)₂. For example, the MeCN congeners could be prepared as described in the literature and the acetonitrile ligand could be subsequently substituted with PPh₃. Alternatively, the less reactive Tp*Ir(PPh₃)₂ could be prepared and used for stoichiometric investigations. Additionally, monitoring of the reaction between Tp*Rh(PPh₃)₂ and benzyl thiol by IR spectroscopy could provide additional information for the characterization of the products of that reaction. The B-H stretching frequency could give support to the ¹¹B NMR data indicating the denticity of the Tp* ligand. In addition, the number of Rh-H frequencies could indicate the number of species in solution. Furthermore, monitoring of this reaction by ¹⁰³Rh NMR spectroscopy could also provide mechanistic insight.

Investigation of the insertion step could be performed by a route similar to that performed for platinum. For example, synthesis of Tp*Rh(SR)(X)(PPh₃) and Tp*Rh(H)(X)(PPh₃) where X = halide would be valuable for selective examination of alkyne insertion without allowing subsequent reductive elimination to occur. This investigation would definitively show whether alkyne insertion into the Rh-S or Rh-H bond is possible. An initial attempt at preparing Tp*Rh(SR)(I)(PPh₃) was unsuccessful. Tp*Rh(PPh₃)₂ was reacted with I₂, according to a similar literature procedure, and resulted in Rh(0), as evidenced by a black coating on the reaction flask. Further attempts at preparing these complexes should be examined.

Furthermore, examination of the kinetic isotope effect for insertion of an electron-deficient alkyne into Tp*Rh(H)(SR)(PPh₃) against Tp*Rh(D)(SR)(PPh₃) could distinguish between 1,2-alkyne insertion into the Rh-S bond or 2,1-insertion into the Rh-H bond. Moreover, the catalytic hydrothiolation of a thioalkyne substrate could also provide evidence to distinguish between insertion into the Rh-H or Rh-S bond. Depending on the chain length, the alkyne should only be able to insert into one of the bonds in the correct orientation to provide the branched vinyl sulfide. However, the
intramolecular reaction could occur by an entirely different mechanism, as intramolecular hydrothiolation typically occurs through transition-metal-mediated nucleophilic attack.\textsuperscript{68,72,73}

Additionally, LRh(PPh\textsubscript{3})\textsubscript{2} complexes with other scorpionate ligands, such as poly(phosphino)borates\textsuperscript{185,186}, poly(amine)borates\textsuperscript{187} and the neutral Tp* analog HC(pz*)\textsubscript{3}, ligand will be prepared. These complexes will be examined as hydrothiolation catalyst precursors to further our understanding of the role of a scorpionate ligand.

Finally, alkene hydrothiolation catalyzed by Tp*Rh(PPh\textsubscript{3})\textsubscript{2} will be examined. Moreover, Tp*Rh(PPh\textsubscript{3})\textsubscript{2} was found to be an effective catalyst precursor not only for alkyne hydrothiolation with arene and alkane thiols but also for alkyne hydrophosphinylation.\textsuperscript{60,121} Therefore, the examination of the catalytic ability of Tp*Rh(PPh\textsubscript{3})\textsubscript{2} for other H-X additions, such as hydroselenation and hydroalkoxylation, should also be examined in the future.
References

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(96) Reaction rate may have been affected – this was not tested.
(101) NMR spectroscopy (¹H, ¹³C, ¹⁹F) and high resolution mass spectrometry were performed. Elemental analysis was not performed, as most of the vinyl sulfide products are oils.
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Cao, C. Unpublished results


(180) This reaction was performed with both kosher and non-kosher diphenyl disulfide.