STRATEGIES TOWARDS CARBON-CARBON BOND FORMATION VIA TANDEM HYDROTHIOLATION/KUMADA CROSS-COUPLING

by

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Abstract

Using recently developed methodology from our group, a variety of aryl and aliphatic terminal alkynes were reacted with *n*-propanethiol to undergo catalytic alkyne hydrothiolation in the presence $Tp^*Rh(PPh_3)_2$. The alkynes examined afforded the branched isomer with high regioselectivity and moderate-to-high yield. Unsubstituted aryl alkynes, or those containing an electron-donating substituent at the *para* position, gave the branched vinyl sulfide in good isolated yield. In contrast, vinyl sulfides derived from aryl alkynes containing an electron-withdrawing substituent at the *para* position showed a decrease in reactivity and yield. The aliphatic alkynes that were investigated gave the desired branched vinyl sulfide in good yield. The isolated vinyl sulfides were then subjected to Kumada cross-coupling in the presence of $NiCl_2(PPh_3)_2$ with various aryl and aliphatic Grignard reagents, affording the corresponding 1,1-disubstituted olefins. While benzyl-, phenyl- and trimethylsilylmagnesium halides were shown to be suitable cross-coupling partners, phenylethynyl-, vinyl- and *n*-butylmagnesium halides were not. Once the viability for the Kumada cross-coupling of vinyl sulfides was established, a one-pot protocol was investigated. It was shown that the one-pot procedure afforded the desired 1,1-disubstituted olefin from readily available terminal alkynes in similar, and in some cases superior, yields than the two-step process.

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Å	angstroms (10^{-10} meters)
μ	mu, micro
Ac	acetate
acac	acetylacetonate
α	alpha
Bn	benzyl
β	beta
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
br	broad
Bu	butyl
calcd	calculated
cat.	catalyst
CNS	central nervous system
J	coupling constant
°	degrees
°C	degrees Celcius
D	deuterium
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAC	dimethyl acetylenedicarboxylate
dppf	diphenylphosphinoferrocene
d	doublet
dd	doublet of doublets
EI	electron impact
E	entgegen
eq	equation
equiv.	equivalent
Et	ethyl
δ	gamma
g	gram
Hz	hertz
HMTA	1,3-hexamethylenetetramine
HRMS	high resolution mass spectroscopy
h	hour
Tp*	hydrotris(3,5-dimethylpyrazolylborate)
L	litre

MHz	mega hertz
Me	methyl
mg	milligram
mL	millilitre
mmol	millimol
min	minute
M	molar (mol L^{-1})
m	multiplet
NMP	*N*-methylpyrrolidone
n	normal
NMR	nuclear magnetic resonance
ppm	parts per million
Ph	phenyl
pip	piperidine
q	quartet
quin	quintet
rt	room temperature
sxt	sextet
s	singlet
t	tertiary
t-Bu	tertiary butyl
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
tol	toluene
TFP	tri(2-furyl)phosphine
TMS	trimethylsilyl
t	triplet
td	triplet of doublets
PPh_3	triphenylphosphine
Z	zusammen

Acknowledgements

I would first like to thank my supervisor Dr. Jennifer Love for all her support and encouragement in the past three years. Her kindness, patience, and advice in times of personal and research related struggles, has been a huge contribution to my success as a graduate student. I would also like to thank my fellow group members in the Love Lab; Paul Bichler, Heather Buckley, Alex Dauth, Lauren Fraser, Shiva Shoai, Alex Sun, Sara van Rooy, Tongen Wang and Jun Yang for all their help and support throughout these past few years.

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"The LORD is my rock, my fortress and my deliverer;

my God is my rock, in whom I take refuge.

He is my shield and the horn of my salvation, my stronghold."

Chapter 1 – Introduction

1.1 Background

Substituted olefins are present in many biologically active molecules and synthetic intermediates.[1-3] Consequently, strategies for their synthesis and functionalization has been an area of continued interest and development. In particular, the 1,1-disubstituted double bond motif is present in several natural products such as dysidiolide[4] (antitumor agent), kainic acid[5] (CNS stimulant), laulimalide[6] (microtubule stabilizer) and pinnatoxin A[7] (potent neurotoxin) (Figure 1.1). Methods for the construction of 1,1-disubstituted olefins have been developed to a much lesser degree than those for 1,2-disubstituted olefins. Even so, a number of methods have emerged, but all have significant limitations.

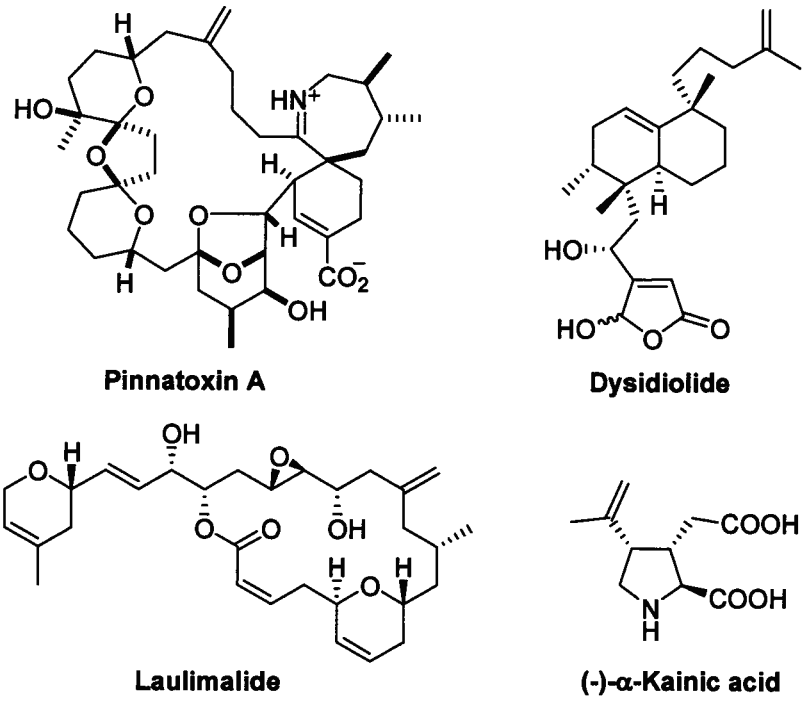
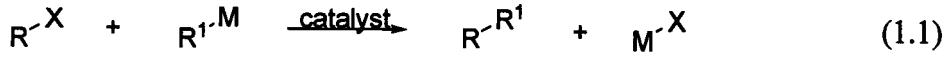


Figure 1.1. Natural products containing 1,1-disubstituted olefins

Transition-metal catalysis is widely used in organic synthesis, and can be used in the synthesis of 1,1-disubstituted olefins. One example is the cross-coupling of an aryl halide with an organometallic reagent, which can be obtained from the corresponding vinyl halide.[8] The disadvantage of starting with vinyl halides lies in the often harsh conditions needed in their synthesis. These conditions typically require the use of a strong Lewis or Bronsted-Lowry acid, such as BBr_3 or HBr, and therefore, present functional group incompatibility. An alternative to the use of vinyl halides in cross-coupling is the use of vinyl triflates; however, their synthesis also presents some functional group incompatibility.[8,9] Another widely used transition-metal catalyzed reaction in the formation of 1,1-disubstituted olefins is the cationic Heck reaction.[10] This typically involves the reaction of an aryl halide with a mono-substituted olefin. One

disadvantage to this reaction is that it is mainly limited to the use of aryl halides, activated alkyl halides or alkyl halides lacking β-hydrogens.[11] It can be seen that by exploring different potential cross-coupling partners, milder methods for the synthesis of 1,1-disubstituted olefins can be realized.

One of the uses of vinyl sulfides is their ability to act as substrates in metal-catalyzed reactions, allowing for the stereospecific functionalization of olefins. Sulfur-containing substrates have had use as electrophilic cross-coupling partners in reactions with organotin reagents (Stille-type), arene and heteroarene boronic acids (Suzuki-Miyaura type), organozinc chloride (Negishi-type), and Grignard reagents (Kumada-type) in the presence of nickel or palladium to give the corresponding unsaturated or saturated carbon-carbon bond (eq 1.1).[12]

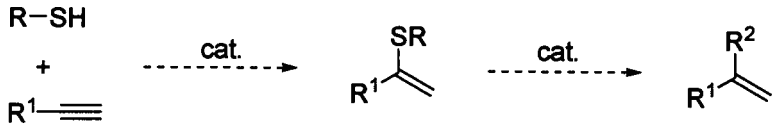


(1.1)

M = B : Suzuki-Miyaura
M = Sn : Stille
M = Zn : Negishi
M = Mg : Kumada

We proposed that transition-metal catalyzed cross-coupling involving vinyl sulfides could be a useful route for the synthesis of 1,1-disubstituted olefins (Scheme 1.1). Furthermore, we anticipated that a one-pot procedure for 1,1-disubstituted olefin synthesis may be possible by combining the vinyl sulfide synthesis and cross-coupling reactions. While recent progress has been made in the area of catalytic C-S bond formation, a general and dependable synthetic method for the formation of 1,1-disubstituted vinyl sulfides from alkynes has been comparatively evasive. The use of

carbon-sulfur bonds in cross-coupling reactions can be an effective route to the synthesis of 1,1-disubstituted olefins; however, this method requires that the corresponding 1,1-disubstituted vinyl sulfide starting material be available. Consequently, a versatile procedure for the formation of branched vinyl sulfides from alkynes is needed. As our proposed strategy involves the formation of 1,1-disubstituted olefins from terminal alkynes, the metal-catalyzed formation of branched vinyl sulfides will first be outlined. This will be followed by a review of the use of C-S bond cleavage in cross-coupling chemistry.



Scheme 1.1. Proposed strategy for 1,1-disubstituted olefin synthesis

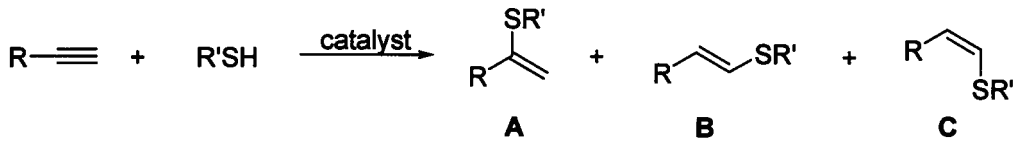
1.2 Hydrothiolation

1.2.1 Transition-Metal Catalyzed Alkyne Hydrothiolation

Due to the widespread belief that thiols and sulfides act as catalyst "poisons," their reactivity in metal-catalyzed reactions have been studied to a much lesser extent than other heteroatom-containing nucleophiles, such as amines, alcohols and phosphines. Nonetheless, metal-catalyzed hydrothiolation of both aryl and alkylthiols as substrates has been successful. The formation of carbon-sulfur bonds has been achieved through several ways, which include radical,[13] nucleophilic[14] and transition-metal[15] catalyzed

alkyne hydrothiolation. The products of these reactions can then be used as building blocks in total synthesis and are precursors to more complex molecular structures.[16]

In 1976, Newton and co-workers showed that $MoO_2[S_2C(1\text{-pip})]_2$ can catalyze the addition of thiophenol to dimethyl acetylenedicarboxylate (DMAC), affording the addition product as a mixture of *E* and *Z*-isomers (19:1) in 25 % yield.[15a] Since then, several other metal catalysts have been found to successfully add an S-H bond across terminal and internal alkynes. There are three possible products resulting from the addition of the S-H bond across a terminal alkyne: the branched product (**A**), and the linear isomers (*E* and *Z*, **B** and **C** respectively) (eq 1.2). The formation of the branched isomer will be covered in the following section as it is directly related to this thesis.

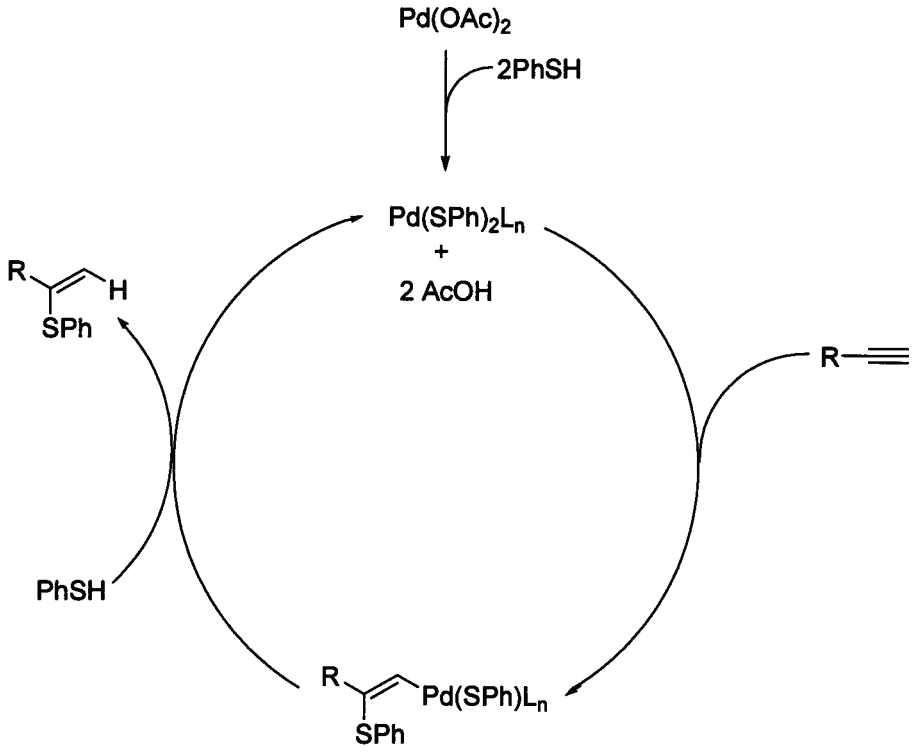


(1.2)

1.2.1-1 Formation of the Branched Hydrothiolation Product

In 1992, Ogawa and co-workers showed that various palladium, platinum, nickel and rhodium complexes could catalyze the reaction of thiophenol and 1-octyne to afford the corresponding vinyl sulfides.[15f] From the metal complexes that were examined, they found that $Pd(OAc)_2$ gave the branched product (**A**) with high regioselectivity for a variety of terminal alkynes with aryl thiols. The alkynes used included hydroxyl, trimethylsilyl aryl alkynes, as well as amino substituted aliphatic alkynes. In order to gain a better understanding of the mechanism of this reaction, the stoichiometric reaction

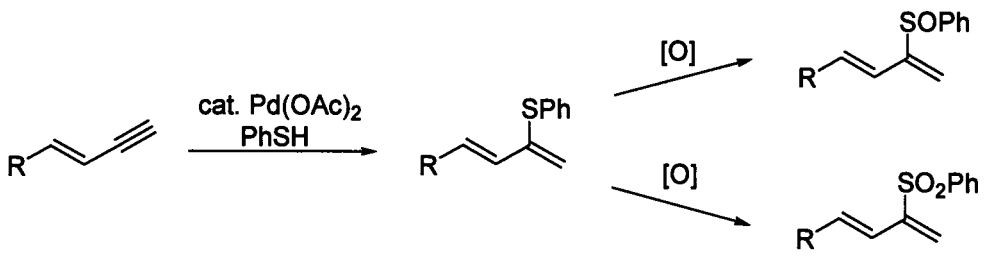
of $Pd(OAc)_2$ and thiophenol was carried out. From the reaction between $Pd(OAc)_2$ and thiophenol, it was observed that a palladium sulfide species ($[Pd(SPh_2]_n$) and AcOH was produced. Furthermore, this palladium-sulfide species was capable of catalyzing the hydrothiolation of alkynes with thiophenol. Based on these observations, a catalytic pathway for $Pd(OAc)_2$-catalyzed hydrothiolation was proposed (Scheme 1.2).[15f]



Scheme 1.2. Proposed catalytic cycle for $Pd(OAc)_2$-catalyzed hydrothiolation

In 1994, Bäckvall and co-workers showed that thiophenol can add to terminal enynes in the presence of $Pd(OAc)_2$ to afford the corresponding 2-(phenylthio)-1,3-dienes (Scheme 1.3).[15b] The resulting vinyl sulfides, depending on the oxidizing agent and reaction conditions, were then selectively converted to sulfoxides and/or sulfones. For

the thiophenol addition to conjugated enynes, the optimal conditions [enyne (1.00 mmol), PhSH (1.00 mmol), $Pd(OAc)_2$ (0.02 mmol) in THF (0.5 mL) at 50 °C] gave 41–75 % yield of the branched product across the alkyne, leaving the alkene untouched.



Scheme 1.3.[15b] Addition of thiophenol to conjugated enynes

In 2005, our group showed that $Tp^*Rh(PPh_3)_2$ [Tp* = hydrotris(3,5-dimethylpyrazolylborate)] (Figure 1.2) can regioselectively catalyze alkyne hydrothiolation to give the branched addition product.[15m] Although alkyl thiols have been reportedly ineffective in metal-catalyzed alkyne hydrothiolation,[15g] we rationalized that a highly active metal catalyst would permit the use of alkyl thiols. The ability of $Tp^*Rh(PPh_3)_2$ to activate C-H,[17] Sn-H, Si-H[18] and S-H[18] bonds prompted us to select this complex for the initial study. The exploratory reaction of phenylacetylene and benzylthiol in the presence of $Tp^*Rh(PPh_3)_2$ gave exclusively the branched isomer in 90% isolated yield after just 20 min. A variety of aliphatic thiols were then reacted with both aryl and aliphatic alkynes, affording the desired branched vinyl sulfides in excellent regioselectivities and good-to-excellent yields (eq 1.3). For the different substrate pairs that were explored, it was found that while the reaction involving aryl thiols with aryl alkynes gave excellent isolated yields (83-90%), a diminished branched:linear product ratio was observed (6:1 to 1.4:1).

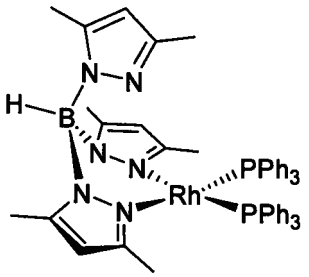
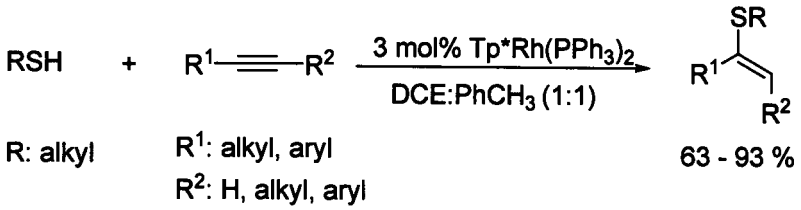


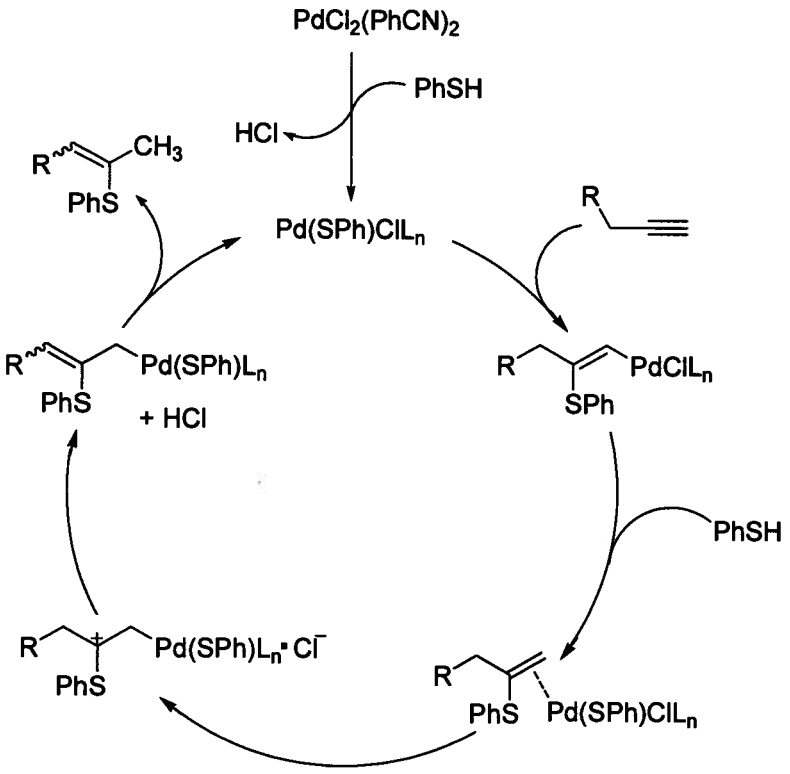
Figure 1.2. $Tp^*Rh(PPh_3)_2$ catalyst



(1.3)

1.2.1-2 Branched Product Isomerization

In 1999, Ogawa[15g] and co-workers reported the use of $PdCl_2(PhCN)_2$ as catalyst in the formation of internal vinyl alkynes. This occurred via initial formation of the branched hydrothiolation product of terminal aliphatic alkynes, followed by sequential double-bond isomerization. In order to gain some understanding about the mechanism of this reaction, Ogawa and co-workers carried out the stoichiometric reaction of $PdCl_2(PhCN)_2$ with 2 equiv of PhSH to afford palladium complex, $[PdCl(SPh)(PhSH)]_n$ (where n = 1 or 2). The palladium complex was found to catalyze the reaction of thiophenol and 1-octyne to afford the corresponding addition/isomerisation product. Furthermore, if the branched product was treated with a catalytic amount of the palladium complex, the double-bond isomerization product could be afforded in almost quantitative yield. From these results, a catalytic cycle for the hydrothiolation/isomerization with $PdCl_2(PhCN)_2$ was proposed (Scheme 1.4).

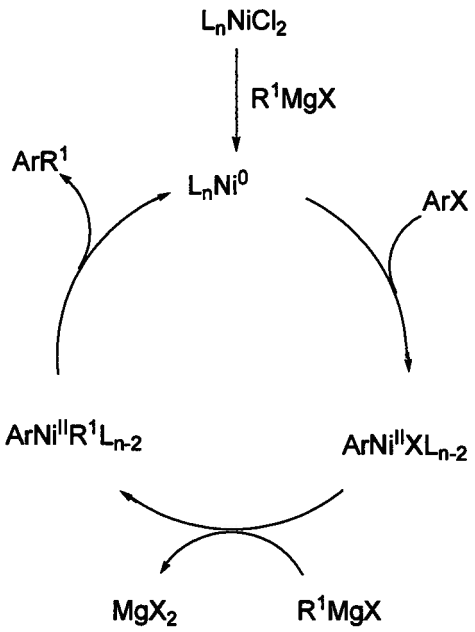


Scheme 1.4.[15g] Proposed catalytic cycle of $PdCl_2(PhCN)_2$-catalyzed hydrothiolation

1.3 Metal-Catalyzed Cross-Coupling of C-S Bonds for C-C Bond Formation

Transition-metal catalyzed cross-coupling reactions for carbon-carbon bond formation began with Kumada[19] and Corriu[20] and their co-workers in 1972. Independently of one another, these two groups found that Grignard reagents can be coupled with vinyl or aryl halides in a stereospecific manner in the presence of a nickel catalyst. Shortly after this initial discovery, Murahashi[21] *et al.* introduced the use of palladium instead of nickel in the cross-coupling reaction. The catalytic cycle for Kumada cross-coupling (Scheme 1.5) involves the reduction of the Ni(II) precatalyst by the Grignard reagent. The resulting Ni(0) species then oxidatively adds to the

organohalide, affording a halo(organo)nickel complex. Transmetallation then takes place to afford a diorganonickel complex which undergoes reductive elimination, affording the desired cross-coupling product and regenerating the active catalyst.[53] A radical process for the cross-coupling is also a possible pathway. Although the coupling of an organometallic reagent with organohalides had been recognized as one of the most valuable methods for carbon-carbon bond formation, the attention had been mostly limited to organohalides. It was not until 1979 that organosulfur compounds were used as electrophilic partners in nickel-catalyzed cross-coupling reactions.

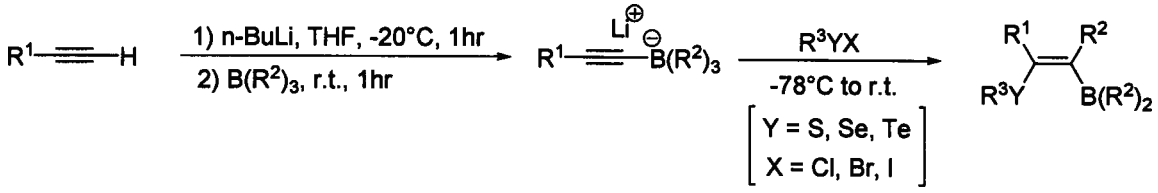


Scheme 1.5.[53] Catalytic cycle for Kumada-catalyzed cross-coupling

Takei[22] and Wenkert[16d] and their coworkers found that 1,2-disubstituted vinyl sulfides could be reacted with various Grignard reagents in the presence of a nickel catalyst to afford the corresponding 1,2-disubstituted olefins. Wenkert also found that the

carbon-sulfur bond of sulfoxides and sulfones are capable of being replaced by carbon-carbon bonds using this type of chemistry.[16d] Since this initial discovery, a variety of sulfur containing substrates have been used as coupling partners in the formation of more highly functionalized molecules.

One example is the synthesis of tri[23]- and tetrasubstituted[24] olefins. In 2001, Hevesi and coworkers reported the rearrangement of 1-alkynyltrialkyl borates, triggered by chalcogen (S, Se, Te) electrophiles in high stereoselectivity (Scheme 1.6). These β-chalcogeno vinylboranes then undergo sequential protodeborylation followed by Kumada cross-coupling to afford the corresponding trisubstituted vinyl sulfides, -selenides or –tellurides.[24] Later, the same group showed that carbodeborylation of the β-chalcogenovinyl borane is possible to afford the corresponding tetrasubstituted vinyl sulfide. These tetrasubstituted vinyl sulfides were then subjected to nickel-catalyzed cross-coupling to afford a variety of tetrasubstituted olefins.[24a] The use of the carbon-sulfur bond in metal-catalyzed cross-coupling will be discussed in the following section.

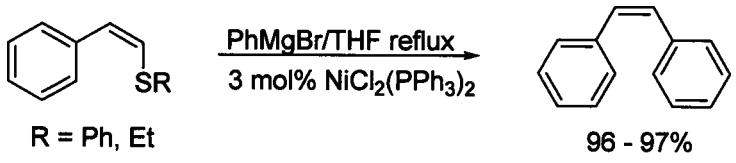


Scheme 1.6. Formation of β-chalcogeno alkenylboranes

1.3.1 Kumada Cross-Coupling of C-S Bonds

1.3.1-1 Cross-Coupling of Sulfides with Grignard Reagents

Takei and co-workers[22] reported the reaction of phenylmagnesium bromide with phenyl styryl sulfide in the presence of $NiCl_2(PPh_3)_2$ affording stilbene as the cross-coupling product, and biphenyl (homo-coupled product) (eq 1.4). Using phenyl styryl sulfide and PhMgBr as a model reaction in order to optimize the cross-coupling conditions, they found that 3 mol% catalyst loading afforded the desired substituted olefin in the highest yields. Increasing the catalyst loading did not improve the yield of the reaction, but instead led to larger amounts of the by-product resulting from the homo-coupling of the Grignard reagent. $NiCl_2(PPh_3)_2$ was also reportedly necessary for the reaction to take place, and that organolithium reagents were not suitable partners in the cross-coupling reaction. The optimized conditions were determined to involve 2.1 equiv. of Grignard reagent in the presence of 3 mol% $NiCl_2(PPh_3)_2$ and refluxing for 6-20 hours in THF or Et_2O. A variety of vinyl sulfides were successfully reacted with aryl and alkylmagnesium bromides in moderate to high yield under these reaction conditions (Table 1.1).

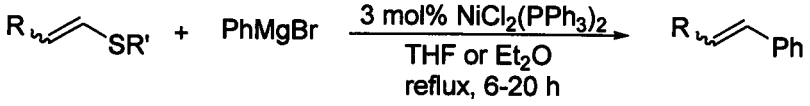


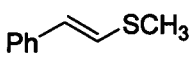
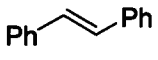
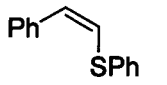
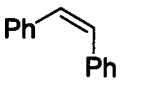
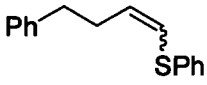
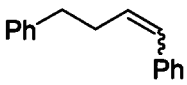
R = Ph, Et

96 - 97%

(1.4)

Table 1.1.[16d] $NiCl_2(PPh_3)_2$-catalyzed cross-coupling of 1,2-disubstituted vinyl sulfides



Sulfide	Grignard	Product	Yield (%)
	PhMgBr		60
	PhMgBr		85
	PhMgBr		97
	PhMgBr		81

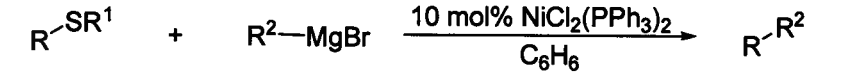
The use of 2.0 equiv. of Grignard reagent was required when vinyl arylsulfides were used as coupling partners, while vinyl alkylsulfides required only 1.0 equiv. Dialkyl thioethers were not suitable substrates for this reaction. In general, the use of an excess amount of Grignard reagent produced the cross-coupled products in higher yields. The reaction was found to be highly stereospecific and only proceeded when vinyl or aryl sulfide substrates were coupled with Grignard reagents.

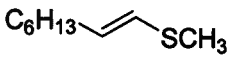
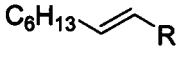
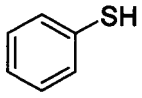
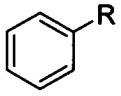
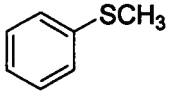
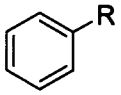
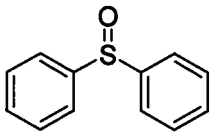
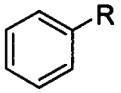
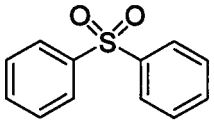
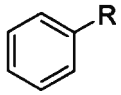
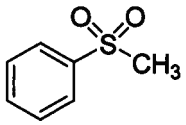
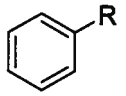
Although their initial studies showed that the cleavage of the C_{sp^3}-S bond of an alkyl sulfide did not occur, Takei and co-workers later reported the use of allylic sulfides as suitable cross-coupling partners with Grignard reagents in the presence of either $NiCl_2(PPh_3)_2$ or $NiCl_2$(dppp).[25] Both nickel complexes were successful in catalyzing the coupling reaction; however, $NiCl_2$(dppp) was less reactive than $NiCl_2(PPh_3)_2$ when sterically hindered allylic sulfides were used. The reaction conditions for allylic sulfides with Grignard reagents were carried out in the presence of 3 mol% $NiCl_2(PPh_3)_2$ and 1.5-2.4 equiv. of Grignard reagent, refluxing in Et_2O for 8-10 hours. In general, the cross-

coupling of allylic sulfides was faster than for vinyl or aryl sulfides when a 1:1 ratio of Grignard to sulfide was used.

In 1979, Wenkert and co-workers[16d] showed that methylmagnesium and aryl-magnesium bromides could be successfully cross-coupled with vinyl and aryl thiols, sulfides, sulfoxides and sulfones in the presence of $NiCl_2(PPh_3)_2$ (Table 1.2). The cross-coupling reactions of the sulfides were carried out in refluxing benzene for 1-30 hours with 2-5 equiv. of Grignard reagent and 10 mol% of $NiCl_2(PPh_3)_2$.

Table 1.2.[16d] $NiCl_2(PPh_3)_2$-catalyzed cross coupling of sulfides, sulfoxides and sulfones.

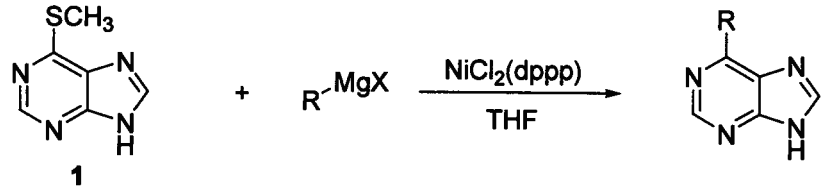


Sulfide	Grignard	Product	Yield %
	R = CH_3 R = Ph		71 80
	R = CH_3 R = *p*-$CH_3C_6H_4$		64 50
	R = CH_3 R = *p*-$CH_3C_6H_4$		97 74
	R = CH_3 R = *p*-$CH_3C_6H_4$		77 57
	R = CH_3 R = *p*-$CH_3C_6H_4$		70 53
	R = CH_3 R = *p*-$CH_3C_6H_4$		97 45

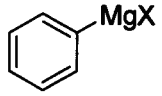
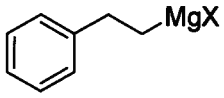
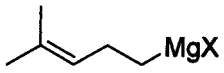
The results also showed that the sulfur displacement process was faster for vinyl sulfides than for aryl sulfides, while alkyl sulfides could not undergo cross-coupling at all. In agreement with what was found by Takei and co-workers, Wenkert found that the nickel complex was necessary in order for the reaction to take place. Furthermore, although $NiCl_2(PPh_3)_2$ gave high yields in various different reactions involving methyl and aryl Grignard reagents, no reaction took place when EtMgBr was used as cross-coupling partner. In this case, $NiCl_2$(dppp) was shown to have better reactivity, presumably due to the ability of the bidentate ligand to better facilitate the reductive elimination step, leading to the cross-coupled product.[26] Wenkert and Takei both showed that alkyl and aryl magnesium halides could be used in nickel-catalyzed cross-coupling reactions with aryl, vinyl and allylic sulfides with retention of configuration. Since these first reports by Wenkert and Takei, the use of low-valent nickel in the cross-coupling of sulfides with Grignard reagents has been extended to a variety of different sulfur-containing substrates.

In 1985, Takei and co-workers extended this strategy for the synthesis of substituted 6-alkyl and 6-aryl purine derivatives.[27] Starting from 6-(methylthio)purine **1** and various alkyl and aryl Grignard reagents, the cross-coupled product could be obtained in good yields in the presence of $NiCl_2$(dppp) (Table 1.3).

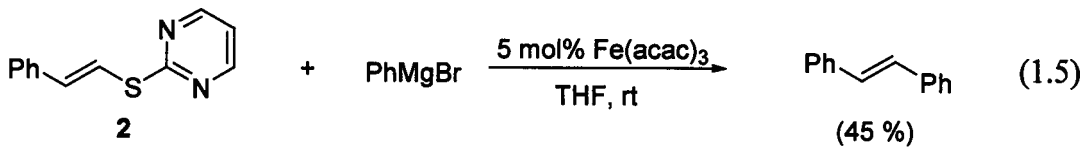
Table 1.3.[27] Nickel-catalyzed cross-coupling of 6-alkyl and 6-aryl purine derivatives.



1

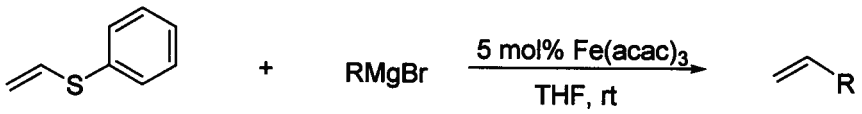
Grignard	Yield %	Grignard	Yield %
	68	*n*-C_4H_9MgX	74
		n-$C_5H_{11}MgX$	62
	72	*n*-$C_6H_{13}MgX$	62
		n-$C_7H_{15}MgX$	67
	71	*n*-$C_8H_{17}MgX$	68

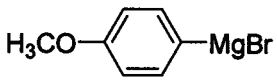
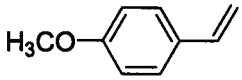
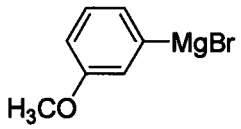
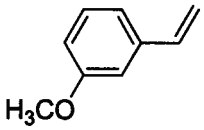
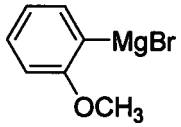
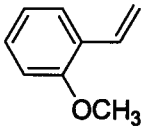
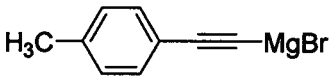
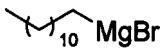
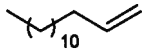
In 2005, Itami and co-workers[28] reported an iron-catalyzed cross-coupling reaction of vinyl sulfides with various Grignard reagents. It was found that the cross-coupling between styryl 2-pyrimidyl sulfide (**2**) and PhMgBr could be catalyzed by $Fe(acac)_3$ at room temperature to afford *trans*-stilbene (45%) (eq 1.5). To determine whether or not the 2-pyrimidal group was necessary for the cross-coupling to take place, phenyl vinyl sulfide was reacted with various Grignard reagents in the presence of $Fe(acac)_3$ (Table 1.4).



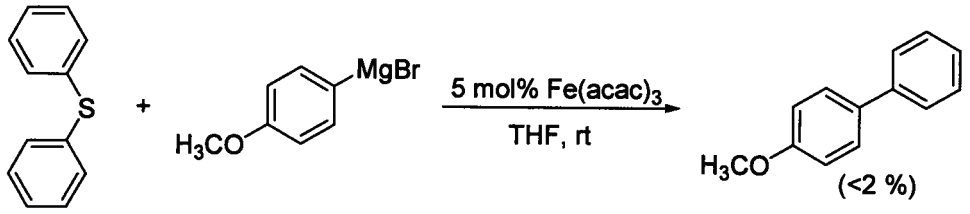
2 (45 %) (1.5)

Table 1.4.[28] $Fe(acac)_3$-catalyzed cross-coupling of phenyl vinyl sulfide



entry	Grignard	Product	Yield (%)
1			74
2			40
3			11
4		-	0
5			65

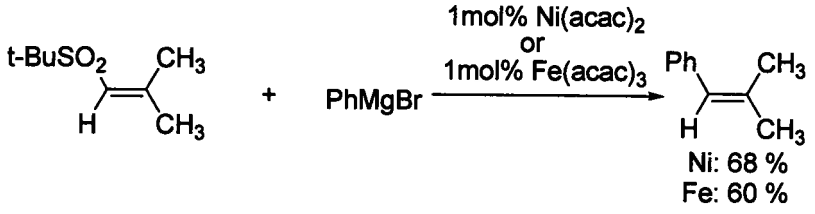
When *p*-$MeOC_6H_4MgBr$ was used in the cross-coupling reaction, the desired substituted olefin, resulting from the vinyl-S bond cleavage, was obtained in 74 % yield. The product obtained from the cross-coupling at the aryl-S bond was produced in only 2 % yield. These results have shown that the reactivity at the vinyl-S position far exceeds that of the aryl-S position. This observation was supported by the reaction of diphenyl sulfide with *p*-$MeOC_6H_4MgBr$, affording the cross-coupled product in less than 2 % yield (eq 1.6).[28] Other iron complexes were also investigated for the cross-coupling, and while $FeCl_3$, $FeCl_2$ and $Fe(OAc)_2$ were all capable of catalyzing the reaction of phenyl vinyl sulfide and *p*-$MeOC_6H_4MgBr$, $Fe(acac)_3$ gave the highest yields.



(1.6)

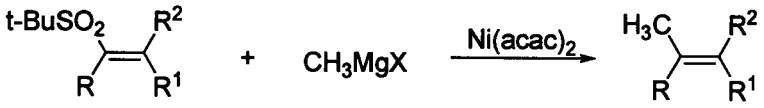
1.3.1-2 Cross-Coupling of Sulfones and Sulfonates with Grignard Reagents

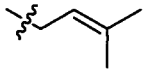
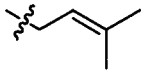
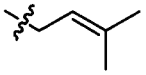
In 1982, Julia and co-workers reported the cross-coupling of vinyl *t*-butyl sulfones[29] with Grignard reagents in the presence of $Ni(acac)_2$ or $Fe(acac)_3$ catalysts (eq 1.7). While both $Ni(acac)_2$ and $Fe(acac)_3$ were successful in the cross-coupling involving a variety of vinyl sulfones with PhMgBr, only $Ni(acac)_2$ was shown to be reactive when methyl Grignard was used as a coupling partner (Table 1.5). Julia and co-workers later reported the use of aryl *t*-butyl sulfones as suitable coupling substrates under similar conditions.[30,31] Arylmagnesium halides afforded the desired cross-coupling product for both vinyl and aryl *t*-butyl sulfones while isopropylmagnesium chloride afforded the reduced product in high yield.



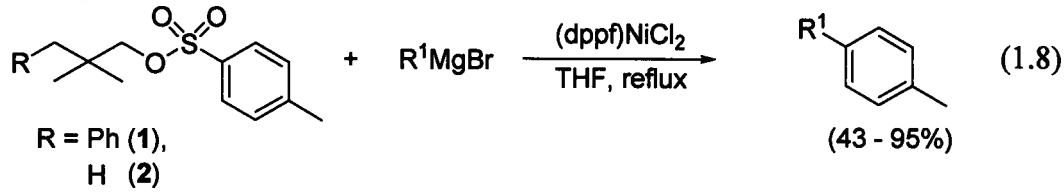
(1.7)

Table 1.5. $Ni(acac)_2$-catalyzed cross-coupling of vinyl *t*-butyl sulfones



R	R^1	R^2	X	Yield (%)
	CH_3	H	Cl	71
	CH_3	H	Br	80
	CH_3	H	I	80
n-C_6H_{13}	H	CH_3	Cl	55
n-C_6H_{13}	H	CH_3	Br	68
n-C_6H_{13}	H	CH_3	I	51

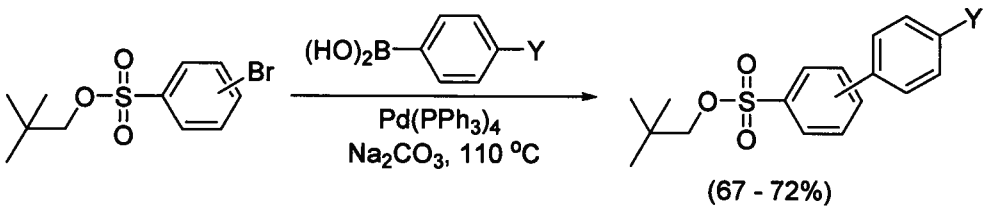
In 2003, Park and co-workers showed that the cross-coupling of alkyl arenesulfonates with aryl Grignard reagents in the presence of $NiCl_2$(dppf) is an excellent method for the synthesis of unsymmetrical biaryls.[32] Although $NiCl_2$(dppf) was not capable of catalyzing the reaction when alkylmagnesium halides were used as coupling partners, the reaction took place in high yields when $NiCl_2$(dppe) was used instead.[33] A wide variety of alkyl and aryl arenesulfonates were synthesized and used in the reaction; however, for the purposes of developing a reactivity profile, sulfonates **1** and **2** were reacted with various aryl and vinyl Grignard reagents (eq 1.8).



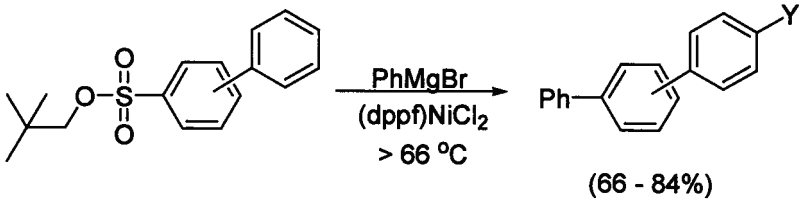
(1.8)

Due to the loss of SO_2 from the neopentyloxysulfonyl leaving group, the reactions were usually accompanied by the production of the corresponding neopentyl alcohol in the same amount as the desired cross-coupled product. In these reactions, it was found that *para*-substituted alkyl phenylmagnesium bromides could afford the desired biaryl product in high yields, while sterically hindered vinyl or *ortho*-substituted alkyl phenylmagnesium bromides gave the desired coupling product in lower yields. Due to competitive insertion at the C-O bond of the product, *p*-methoxyphenylmagnesium bromide gave lower yields of the desired biaryl product, and Grignard reagents with electron withdrawing substituents, such as CF_3, were found to be unreactive.[33]

In 2004, Park and co-workers applied very similar reaction conditions as those described for the cross-coupling of alkyl arenesulfonates with Grignard reagents, in order to synthesize unsymmetrical terphenyls.[34] The low reactivity of alkyloxysulfonyl groups to typical palladium catalysts allowed for the chemoselective reaction of neopentyl bromobenzene sulfonates with arylboronic acids (eq 1.9). This was followed by sequential cross-coupling reaction with arylmagnesium bromides, to give unsymmetrical terphenyls in high yields (eq 1.10).



(1.9)



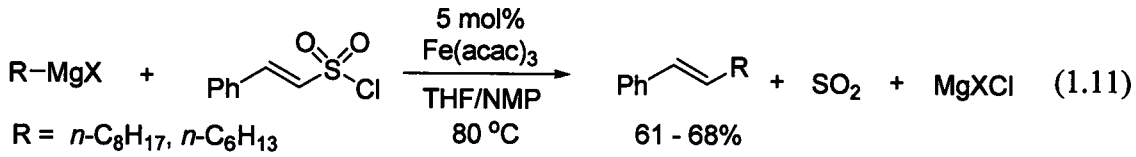
(1.10)

1.3.1-3 Cross-Coupling of Sulfonyl Chlorides with Grignard Reagents

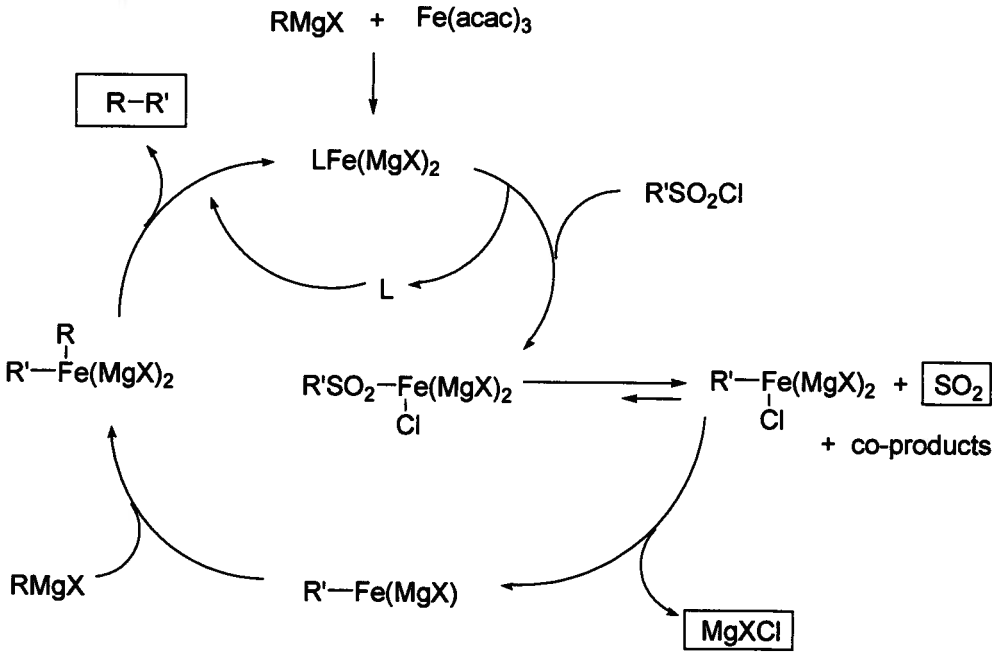
Although the use of palladium in carbon-carbon cross-coupling of sulfonyl chlorides has been reported, when applied to Kumada-Corriu type cross-coupling involving Grignard reagents, palladium or nickel based catalyst were shown to be unsuccessful.[35] In 2006, Vogel and co-workers attempted the use of a palladium based catalyst in order to carry out the cross-coupling of sulfonyl chlorides with Grignard reagents; however, the desired Kumada-Corriu cross-coupling reaction failed, and only the homo-coupled product from the Grignard reagent was obtained. This led to the investigation of other metals to carry out the reaction. While the reaction of vinyl *t*-butyl sulfones[29] and aryl *t*-butyl sulfones[30,31] are known to undergo nickel and iron-catalyzed cross coupling with Grignard reagents, the first use of sulfonyl chlorides in these iron-catalyzed Kumada-type reactions was reported by Vogel and co-workers in 2008.[36]

The carbon-carbon cross-coupling of various aryl, vinyl and alkyl magnesium halides were successfully reacted with alkane- and alkenesulfonyl chlorides in the presence of $Fe(acac)_3$ without the use of any additional ligands. The model reaction involved *n*-octanesulfonyl chloride with PhMgBr in the presence of 5 mol% $Fe(acac)_3$. When the cross-coupling reaction was carried out in THF at 80 °C, the desired *n*-octylbenzene was afforded in only 28 % yield, accompanied by the corresponding sulfone product in 5 % yield. The reaction carried out in refluxing Et_2O or 1,2-dimethoxyethane also gave poor yields due to Grignard homo-coupling, while the reaction carried out at room temperature afforded large amounts of sulfone. Although the addition of TMEDA and HMTA did increase the yield slightly, the optimal conditions for the reaction were carried out in THF and *N*-methylpyrrolidone (NMP) at 80 °C in the

presence of $Fe(acac)_3$ with no additional ligands.[36] Once these conditions were obtained, the reaction of various sulfonyl chloride and Grignard reagent combinations were carried out. In the case of alkenesulfonyl chlorides, the cross-coupling proceeded in moderate yields with retention of configuration (eq 1.11). A proposed mechanism for the desulfinylative Kumada cross-coupling is shown below (Scheme 1.7), and follows Fürstner's[37] suggestion that low-valent iron species react much like Pd^0 catalysts.



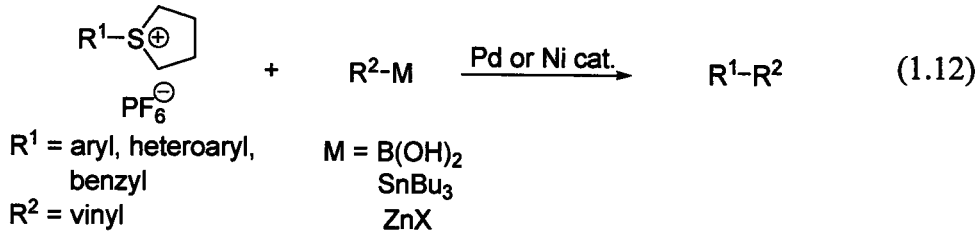
(1.11)



Scheme 1.7.[36] Proposed catalytic cycle of Fe-catalyzed cross-coupling of sulfonyl chlorides

1.3.2 Negishi Cross-Coupling Involving C-S Bond Cleavage

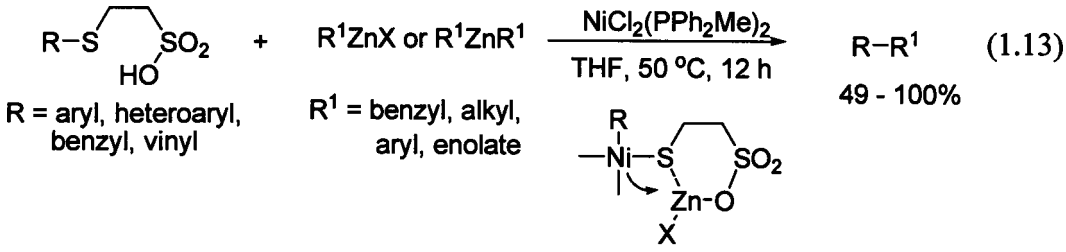
In 1997, Liebeskind[38] and co-workers showed that aryl, heteroaryl, vinyl and benzylsulfonium salts could undergo Negishi, Mizoroki-Heck, Suzuki-Miyaura, and Stille-type cross-coupling reactions in the presence of Ni or Pd catalysts for carbon-carbon bond formation (eq 1.12). From the numerous reactions that were performed, it was found that when benzylic and heterobenzylic sulfonium salts were used as coupling partners, the organostannane reaction worked slightly better than the organoboron counterpart for the metal-catalyzed reaction. This observed trend was reversed when aryl and heteroarylsulfonium salts were used.



(1.12)

In 1999, Liebeskind[39] and co-workers reported that *S*-(substituted)thioglycolic acids could undergo Ni-catalyzed cross-coupling with organozinc reagents in good-to-excellent yield. In order for the reaction to take place at a reasonable rate, a zinc cofactor was necessary. They proposed that the zinc ion could be intramolecularly bound in order that the proposed nickel-thiolate intermediate could be activated, thus facilitating transmetallation (eq 1.13). To determine which zinc reagent (the "internally" bound or an "external" zinc reagent) was responsible for the transmetallation process, the following experiments were carried out. An equimolar amount of thioglycolic acid was reacted with $ZnMe_2$ in the presence of $NiCl_2(PPh_3)_2$ at room temperature, and no cross-

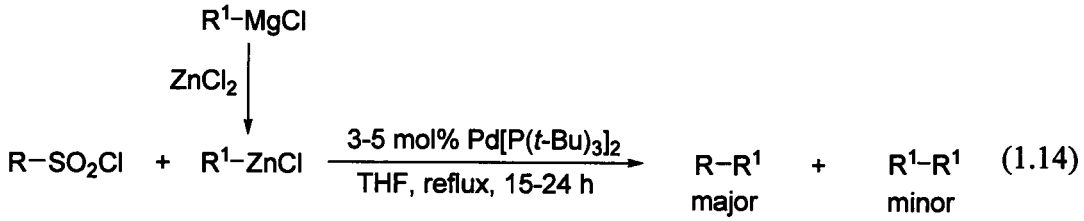
coupling took place after 50 h; however, vigorous gas evolution was observed. When a second equiv. of $ZnMe_2$ was added to this reaction mixture, the R-Me cross-coupled product was afforded in good yield. Furthermore, when $ZnEt_2$ was added to the preformed MeZn-thioglycolate species, the R-Et cross-coupled product was obtained as the major product. From these experiments, it was concluded that an "external" zinc reagent is mainly responsible for the transmetallation to nickel, and not the alkylzinc that is internally bound.[39]



(1.13)

In 2006, Vogel and Dubbaka developed a palladium-catalyzed cross-coupling reaction of sulfonyl and organozinc chlorides (eq 1.14).[35] Their initial attempts to cross-couple sulfonyl chlorides with Grignard reagents in the presence of 1-20 mol% Pd[P(*t*-Bu)$_3$]$_2$ only gave the homo-coupled Grignard reagent with a small amount of sulfone. The investigation of the cross-coupling reaction under Negishi cross-coupling conditions was also carried out. The reaction of 1-naphthalenesulfonyl chlorides and 2-methylphenylzinc chloride in the presence of 3-5 mol% Pd[P(*t*-Bu)$_3$]$_2$ as catalyst in boiling THF were found to give the highest yields. The reaction of various other sulfonyl chloride and Grignard reagent combinations were carried out using the optimized

reaction conditions. It was shown that, in general, arylsulfonyl chlorides gave better yields than for allyl and alkylsulfonyl chlorides.[35]



(1.14)

1.3.3 Stille Cross-Coupling Involving C-S Bond Cleavage

Liebeskind and co-workers showed that a variety of tetramethylene, benzylic, heterobenzylic and alkenylsulfonium salts can undergo Stille cross-coupling with *n*-Bu_3Sn in the presence of Pd or Ni catalyst.[38] Very low catalyst loading (0.01-0.5% Pd_2dba_3) was required in order for the benzylic and heterobenzylic sulfonium salt to undergo cross-coupling with *n*-Bu_3SnR. Furthermore, the addition of $Ph_2P(O)O^-$/*n*-Bu_4N^+ to act as a "*n*-Bu_3Sn" scavenger greatly increased the efficiency of the reaction. In 1999, Liebeskind and co-workers reported that unlike the corresponding heterobenzylic halides, sulfonium salts are suitable cross-coupling substrates in Stille cross-coupling in the presence of palladium.[40] The exploratory reactions revealed that for the substrates of interest (Figure 1.3), the typical reaction conditions that had previously been obtained,[38] were not very effective in the general cross-coupling reaction of heterobenzylic sulfonium salts with organometallic reagents.

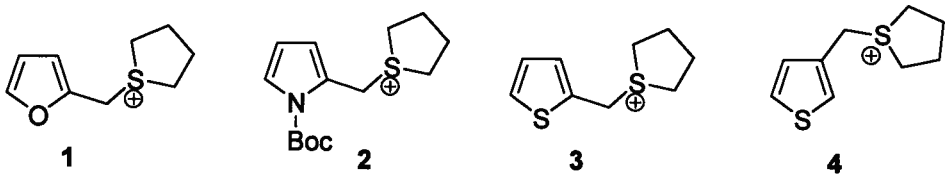
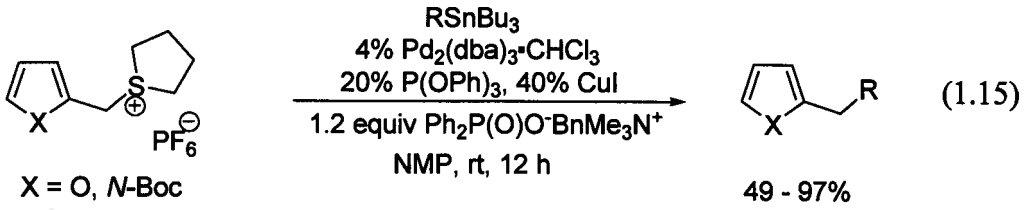


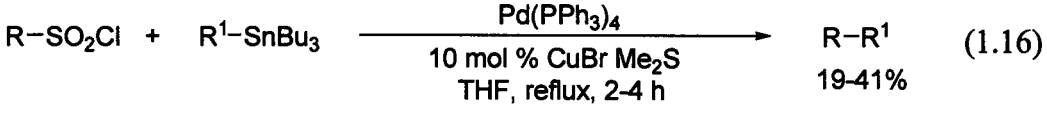
Figure 1.3. Heterobenzylic sulfonium salts

The catalytic system that needed to be developed was one which could catalyze the cross-coupling reaction at low enough temperature to minimize the possibility of competitive decomposition of the heterobenzylic coupling partner and catalyst deactivation. It was concluded that in order to attain the desired catalytic system, a support ligand was needed that could bind the metal well enough to prevent catalyst decomposition, but weak enough not to interfere with the transmetallation step.[40] Furthermore, the support ligand should not be alkylated by the heterobenzylic halide or sulfonium salt. Various support ligands were surveyed, and it was found that the use of either $P(PPh_3)$ or $P(OPh)_3$ gave excellent yields of the cross-coupled product. Further investigation of solvent, organostannane scavenger and additives revealed that the optimum conditions for the cross-coupling reaction required NMP solvent, $Pd_2(dba)_3 \cdot CHCl_3/(PhO)_3P/CuI$ as the catalyst system, and $Ph_2P(O)O^-BnMe_3N^+$ as a *n*-Bu_3Sn scavenger (eq 1.15).[40] In the case where an unhindered vinylstannane was used, CuI was omitted from the reaction due to the Cu(I)-induced homocoupling that occurred. Liebeskind and co-workers also applied the use of $P(OPh)_3$ as a support ligand with $Pd(PhCN)_2Cl_2$ to cross-couple heterobenyzlic sulfonium salts under Suzuki and Negishi cross-coupling conditions.[40]

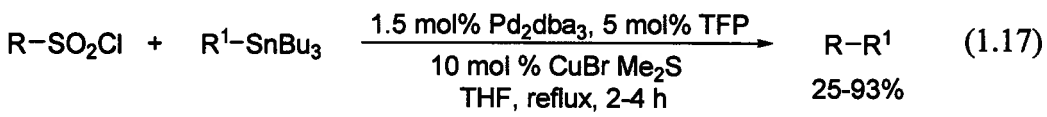


(1.15)

In 2003, Vogel and Dubbaka showed for the first time, that phenylmethanesulfonyl chloride can undergo Stille cross-coupling with organostannanes in the presence of palladium and copper.[41] When $Pd(PPh_3)_4$ was used as catalyst, the self-coupling of the organostannanes and diarylsulfides were the major products formed, with only moderate-to-poor yields of the desired cross-coupling product (eq 1.16). When the Pd source was changed to Pd_2dba_3 (1.5 mol%) with TFP (5 mol%) and $CuBr{\cdot}Me_2S$ (10 mol%), the reaction worked successfully with a variety of sulfonyl chloride and organostannane combinations (eq 1.17).[41]



(1.16)



(1.17)

1.4 Conclusions

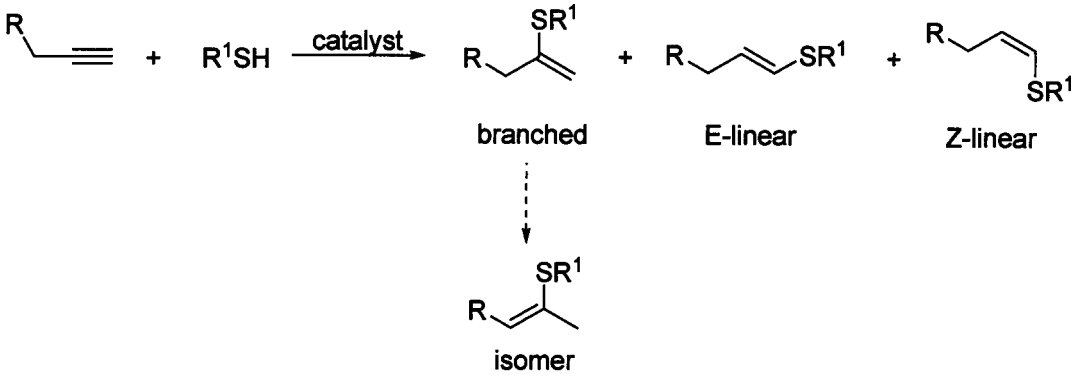
The development of strategies for olefin functionalization is an active area of synthetic chemistry as substituted double bonds are present in many biologically active molecules and synthetic intermediates. In this chapter, catalytic alkyne hydrothiolation affording the branched product was discussed, as well as the use of C-S bond cleavage in

transition-metal catalyzed cross-coupling reactions. We have previously disclosed a convenient method for the regioselective formation of branched vinyl sulfides from alkynes via catalytic alkyne hydrothiolation using $Tp^*Rh(PPh_3)_2$.[15m] We anticipated that these vinyl sulfides could act as pseudo vinylhalides to undergo subsequent cross-coupling to afford 1,1-disubstituted olefins in two steps from readily available alkyne precursors. In the following chapters, the synthesis of a series of branched *n*-propylthiovinyl sulfides will be discussed, followed by their subsequent use in Kumada cross-coupling to afford 1,1-disubstituted olefins. Furthermore, we envisioned a one-pot procedure for the catalytic alkyne hydrothiolation and cross-coupling steps to improve the efficiency of the reaction.

Chapter 2 – Catalytic Alkyne Hydrothiolation Using $Tp^*Rh(PPh_3)_2$

2.1 Introduction

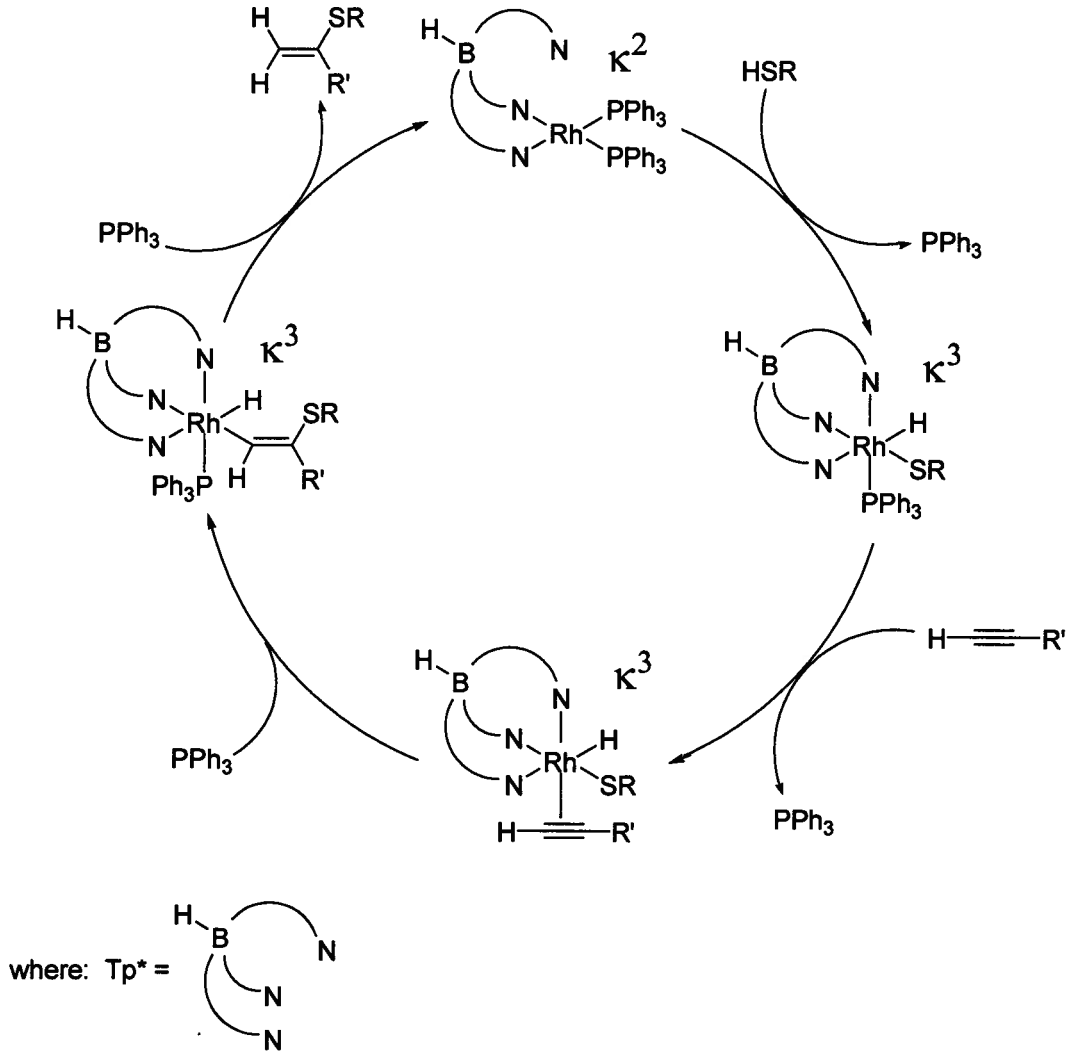
Alkyne hydrothiolation is the addition of an S-H bond across an alkyne. In the case of terminal alkynes, three addition products are possible (Scheme 2.1). The formation of C-S bonds have been achieved through several ways which include radical[13], nucleophilic[14] and transition-metal[15] catalyzed hydrothiolation; however, until recently, the use of alkyl thiols in alkyne hydrothiolation has been quite limited.



Scheme 2.1. Possible products of alkyne hydrothiolation

Previous work done by our group has shown that $Tp^*Rh(PPh_3)_2$ [Tp* = hydrotris(3,5-dimethylpyrazolylborate)] catalyzes alkyne hydrothiolation of a wide range of aliphatic, aromatic and internal alkynes with a variety of thiols. The structure of $Tp^*Rh(PPh_3)_2$ is shown in Figure 1.2. When $Tp^*Rh(PPh_3)_2$ was used as catalyst, the branched isomer (Markovnikov product) was afforded in high yields and selectivity.[15m]

Based on preliminary mechanistic investigations, a catalytic cycle for the Tp*Rh(PPh_3)$_2$-catalyzed reaction has been proposed (Scheme 2.2); however, further mechanistic studies are currently underway.[54] We have also recently reported that Wilkinson's catalyst, in the appropriate solvent, affords the hydrothiolation product in high yield and selectivity, with the *E*-linear isomer as the major product.[15o]



Scheme 2.2. Proposed catalytic cycle for Tp*Rh(PPh_3)$_2$-catalyzed hydrothioltion

Recently, the investigation of the reactivity of bis- and tris(pyrazolyl)borate complexes (Figure 2.1) towards catalytic hydrothiolation was carried out, and tris(pyrazolyl)borate complexes were shown to be superior than the corresponding bis(pyrazolyl)borate complexes.[15p] In addition, complexes that contained substitution on the pyrazolyl rings gave higher yield and selectivity than those that contained unsubstituted rings, affording the branched isomer as the major product.

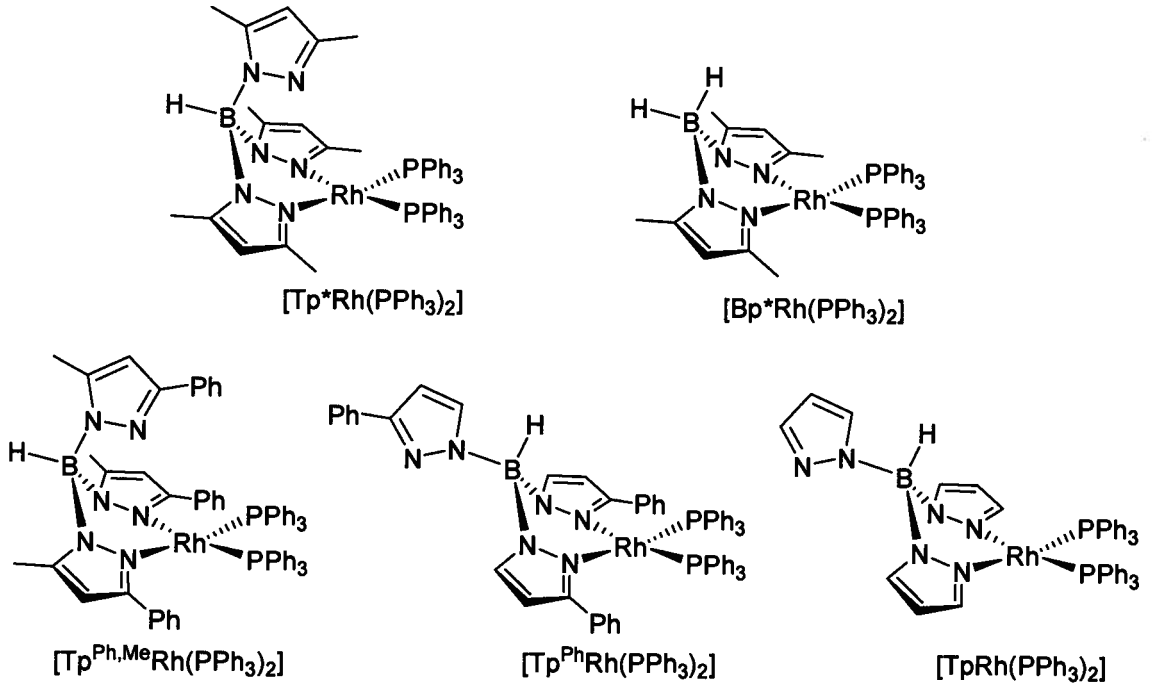


Figure 2.1. Rhodium pyrazolylborate complexes

As previously discussed, one of the synthetic uses of vinyl sulfides is their ability to act as precursors to a variety of functionalized molecules. For example, vinyl sulfides can undergo cross-coupling with an appropriate nucleophile to generate substituted olefins. We envisioned that we could use our recently developed methodology in the synthesis of 1,1-disubstituted vinyl sulfides as a synthetic route to 1,1-disubstituted

olefins from terminal alkynes. In order for efficient cross-coupling to take place, the vinyl sulfide cross-coupling partner should be easily obtained, and have a leaving group of low molecular weight to minimize waste. We thought that *n*-propanethiol would be a suitable candidate for the reaction with various alkynes to afford the corresponding vinyl sulfides. Propanethiolate would act as the leaving group in the subsequent cross-coupling reaction. The molecular weight of this leaving group is similar to that of bromide, a commonly used leaving group in cross-coupling reactions. Furthermore, we had established in our original communication on catalytic hydrothiolation using $Tp^*Rh(PPh_3)_2$, that *n*-propanethiol reacts with high yield and selectivity in hydrothiolation; however, only one example using *n*-propanethiol was reported. Therefore, our first goal was to establish that hydrothiolation could proceed with a broader range of alkynes in selectivity and with acceptable yields. This chapter describes the reaction of *n*-propanethiol with functionalized aryl and aliphatic alkynes.

2.2 Results and Discussion

2.2.1 Procedure and Optimization of Hydrothiolation Reactions

Hydrothiolation reactions were carried out in a nitrogen-filled Vacuum Atmospheres glovebox (O_2 < 2 ppm) unless otherwise specified. $Tp^*Rh(PPh_3)_2$ (0.03 equiv.) was weighed out in the glove box using a spatula into a 20 mL vial equipped with a magnetic stir bar. A 1:1 mixture of DCE:toluene was then added by syringe, followed by sequential addition of *n*-propanethiol (1.1 equiv.) and alkyne (1 equiv.) via micropipette. The vial was then sealed using a screw cap with a foil liner, removed from

glove box and wrapped in foil. The solution was stirred for the desired reaction time (2-16 h), and then concentrated. The residue was subjected to flash chromatography to afford the desired product. In general, the resulting hydrothiolation products were quite volatile, making their isolation somewhat difficult.

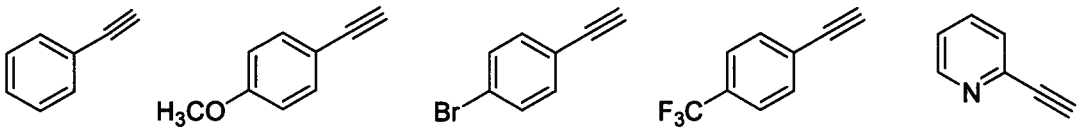
The optimization of the catalytic hydrothiolation reaction involving $Tp^*Rh(PPh_3)_2$ was carried out previously by our group, and revealed that $Tp^*Rh(PPh_3)_2$ gave the highest yields in a 1:1 mixture of 1,2-dichloroethane and toluene as solvent.[15m] It was also found that if left for prolonged periods of time (>2 d) in THF, $Tp^*Rh(PPh_3)_2$ decomposes, forming an inactive complex for hydrothiolation. The use of a 1:1 mixture of DCE and toluene circumvented this potential problem. Using previously established optimized reaction conditions, *n*-propanethiol was reacted with various alkynes in order to broaden the substrate scope of its use in alkyne hydrothiolation.

2.2.2 Substrate Scope of Hydrothiolation with *n*-Propanethiol

It has been previously reported by our group that $Tp^*Rh(PPh_3)_2$ is an excellent catalyst for the hydrothiolation of aliphatic and arylthiols with a variety of aliphatic, aryl and internal alkynes, giving good-to-excellent yields. The hydrothiolation results of *n*-propanethiol with various aryl and aliphatic alkynes (Chart 2.1) are summarized in Table 2.1.

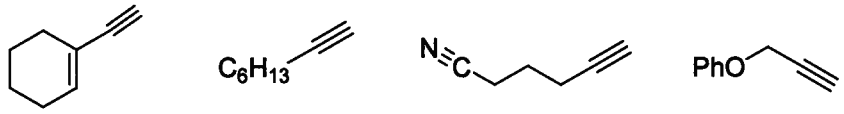
Chart 2.1. Alkyne substrates for hydrothiolation

Aryl Alkynes



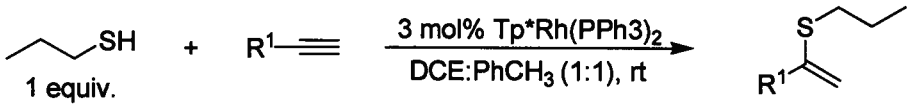
1 **2** **3** **4** **5**

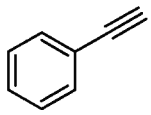
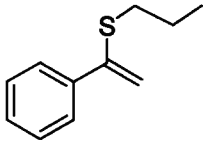
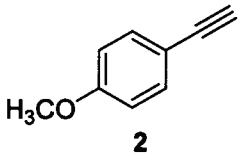
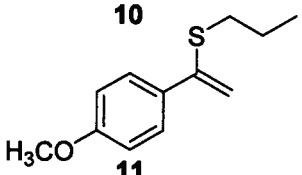
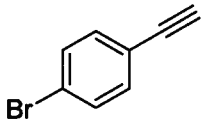
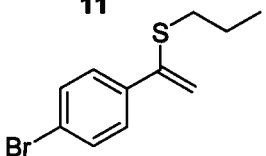
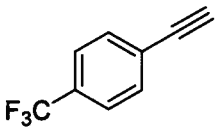
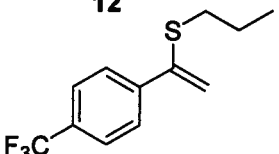
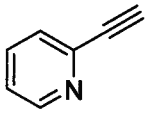
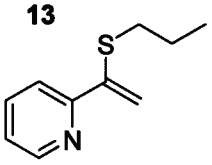
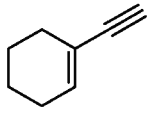
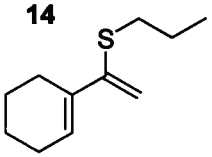
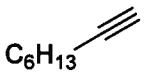
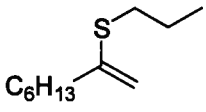
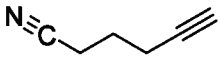
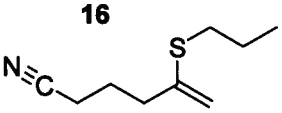
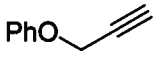
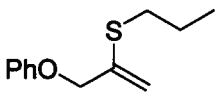
Aliphatic Alkynes



6 **7** **8** **9**

Table 2.1. Substrate scope alkyne hydrothiolation of *n*-propanethiol



Entry	Alkyne	Product	Time	Yield[a]
1	 **1**	 **10**	2 h	74%
2	 **2**	 **11**	2 h	72%
3	 **3**	 **12**	16 h	69%
4	 **4**	 **13**	16 h	15%
5	 **5**	 **14**	16 h	0%
6	 **6**	 **15**	2 h	83%
7	 **7**	 **16**	16 h	86%
8	 **8**	 **17**	16 h	65%
9	 **9**	 **18**	16 h	0%

[a] Isolated yield.

The reaction of *n*-propanethiol with phenylacetylene (**1**) in the presence of 3 mol% $Tp^*Rh(PPh_3)_2$ was carried out first. The reaction was complete after 2 h; the formation of product was indicated by the appearance of the two singlet resonances for the olefinic protons of the branched product (**10**) at δ 5.47 and δ 5.19. The emergence of the olefinic protons of the branched product was used as a diagnostic tool to indicate the formation of all the hydrothiolation products investigated. Vinyl sulfide **10** was isolated via flash chromatography; however, while removing solvent, a portion of the product was also lost due to the volatility of the product. Furthermore, if left neat at room temperature, the product starts to decompose within hours and a change from a clear, colorless oil, to a clear yellow oil is observed. Therefore, to minimize the decomposition, vinyl sulfide **10** was stored in the freezer as a solution in petroleum ether, and to avoid the loss of product during isolation, vacuum rotary evaporation was carried out at room temperature. A visual change in all of the isolated hydrothiolation products of alkynes (**1-4, 6-8**) with *n*-propanethiol is observed if left neat at room temperature, indicating product decomposition.

The reaction of *n*-propanethiol with 4-ethynyl anisole (**2**) was also complete after 2 h, with the singlet resonances for the olefinic protons of the branched product appearing at δ 5.39 and δ 5.11. For the reaction of aryl alkynes **3** and **4,** a decrease in reactivity was observed, requiring 16 h to reach completion. The reaction involving 2-ethynylpyridine (**5**) did not undergo the hydrothiolation reaction. A possible reason for this reaction could be caused by competitive C-H activation of the alkyne. For the aliphatic alkynes that were investigated, 1-ethynylcyclohexene (**6**) showed the highest reactivity, reaching completion after 2 h and afforded the branched product in high selectivity and isolated

yield. The hydrothiolation reactions of 1-octyne (**7**) and 5-cyanohexyne (**8**) were complete after 16 h; affording the branched product in moderate-to-high isolated yields. Vinyl sulfides **16** and **17** were prone to isomerisation; however, the avoidance of the use of chloroform as solvent in either chromatography or NMR spectroscopy could circumvent this problem. Phenylpropargyl ether (**9**) showed no reaction after 16 h at room temperature to form the corresponding vinyl sulfide.

2.3 Conclusions

The hydrothiolation of *n*-propanethiol with various aryl and aliphatic alkynes in the presence of $Tp^*Rh(PPh_3)_2$ has been carried out. The alkynes that underwent the hydrothiolation reaction afforded the branched vinyl sulfide in high selectivity. For the aryl alkynes that were investigated we found that vinyl sulfides derived from either unsubstituted or electron-rich aryl alkynes (**1** and **2** respectively) were isolated in high yields. Vinyl sulfides derived from aryl alkynes containing electron withdrawing substituents (**3** and **4**) led to a significant decrease in reactivity. Aliphatic alkynes (**6-8**) also reacted with *n*-propanethiol with high selectivity and good isolated yields (entries 6,7 and 8). While product decompostion was observed, dilution in petroleum ether and storage at -2 °C minimized decomposition. The use of the isolated branched vinyl sulfides in Kumada cross-coupling to generate 1,1-disubstituted olefins will be discussed in the following chapter.

2.4 Experimental Procedures

2.4.1 General Methods

The synthesis and manipulation of air and moisture sensitive organometallic compounds was carried out in a nitrogen-filled Vacuum Atmospheres glovebox ($O_2 < 2$ ppm). Reactions were carried out at room temperature and stirred with a Teflon-coated magnetic stir bar. Reaction mixtures were concentrated using rotary evaporation methods combined with a high vacuum pump line. Glassware was cleaned in the following manner: submersion in a base bath (500 g KOH, 2 L deionized water, 8 L isopropanol) for 16 h, rinsing with copious amounts of deionized water, followed by rinsing with acetone. Flash chromatography was used to separate products (Silicycle, 60-200μm, 70-230 mesh), and the solvent was eluted using air pressure.

2.4.2 Reagents and Solvents

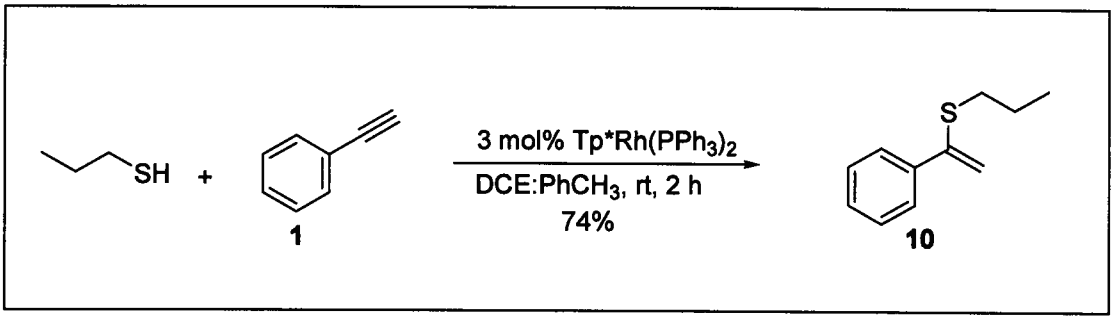
$Tp^*Rh(PPh_3)_2$ [Tp* = hydrotris(3,5-dimethylpyrazolylborate)] was prepared by a published procedure.[15m] Hexanes, 1,2-dichloroethane (DCE), THF and toluene were dried by passage through solvent purification columns. All other commercial reagents and solvents were used without further purification. Deuterated chloroform was dried using activated molecular sieves (4Å) and d_8-toluene was used from 1 g ampules.

2.4.3 Physical and Spectropscopic Measurements

NMR spectra were recorded on Bruker Avance 300 or Bruker Avance 400 spectrometers. ^1H and ^{13}C NMR spectra are reported in parts per million and referenced

to residual solvent. Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, m = multiplet, dd = doublet of doublets, td = triplet of doublets. All spectra were obtained at 25 °C. Mass spectra were recorded on a Kratos MS-50 mass spectrometer. Higher yields and elemental anlyses of the compounds were impeded by product volatility.

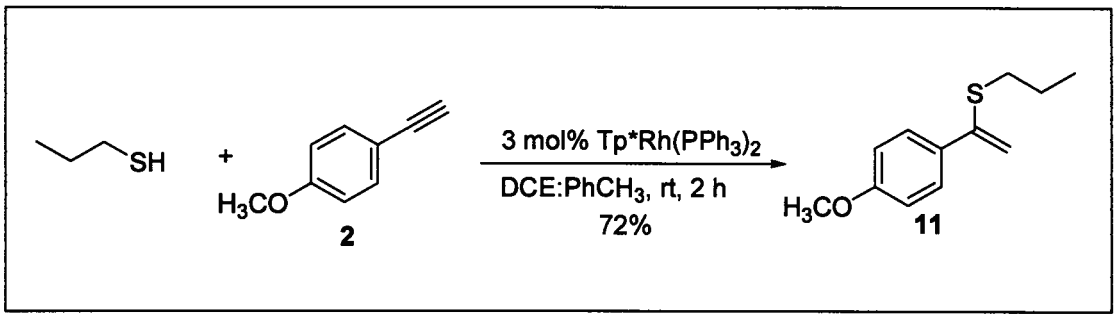
Reaction of *n*-Propanethiol and Phenylacetylene (1)



$Tp^*Rh(PPh_3)_2$ (82 mg, 0.089 mmol) was weighed out in the glove box using a spatula into a 20 mL vial equipped with a magnetic stir bar. A 1:1 mixture of DCE:toluene (5 mL) was then added by syringe, followed sequentially by *n*-propanethiol (296 μL, 3.26 mmol) and phenylacetylene (325 μL, 2.96 mmol) via micropipette. The vial was then sealed using a screw cap with a foil liner, removed from glove box and wrapped in foil. After stirring for 2 h at room temperature, the solution was concentrated and the residue was subjected to flash chromatography using petroleum ether as eluent to afford the product as a clear, colorless oil with yellow tint (390 mg, 2.19 mmol, 74% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 – 7.50 (m, 2 H), 7.42 – 7.29 (m, 3 H), 5.47 (s, 1 H), 5.19 (s, 1 H), 2.69 (t, *J*=7.3 Hz, 2 H), 1.69 (sxt, *J*=7.3 Hz, 2 H), 1.03 (t, *J*=7.3 Hz, 3 H).

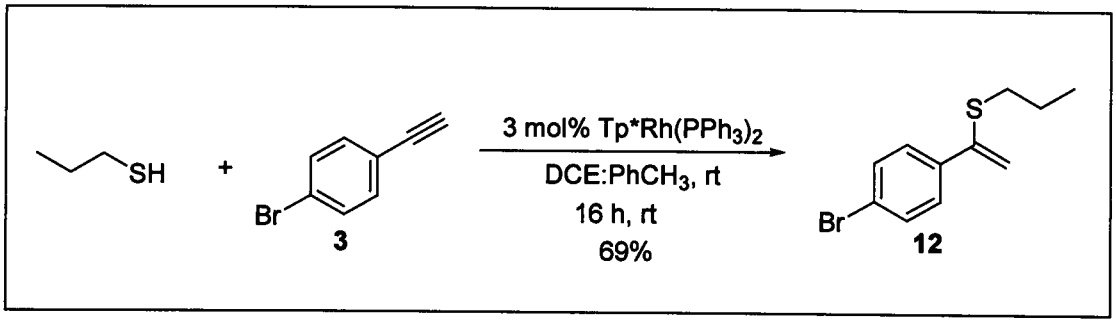
$^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 145.2, 139.8, 128.3, 128.3, 127.1, 110.4, 34.1, 21.9, 13.5. HRMS (EI) m/z calcd for $C_{11}H_{14}S$: 178.0816; found: 178.0815.

Reaction of *n*-Propanethiol and 4-ethynylanisole (2)



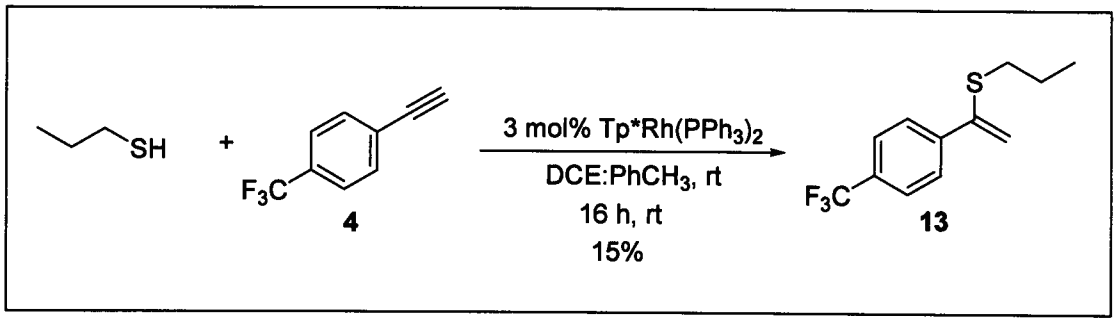
$Tp^*Rh(PPh_3)_2$ (75 mg, 0.081 mmol) was weighed out in the glove box using a spatula into a 20 mL vial equipped with a magnetic stir bar. A 1:1 mixture of DCE:toluene (5 mL) was then added by syringe, followed sequentially by *n*-propanethiol (269 μL, 2.97 mmol) and 4-ethynylanisole (350 μL, 2.7 mmol) via micropipette. The vial was then sealed using a screw cap with a foil liner, removed from glove box and wrapped in foil. After stirring for 2 h at room temperature, the solution was concentrated and the residue was subjected to flash chromatography, using a 4:1 petroleum ether:DCM mixture as eluent, to afford the product as a clear, colorless oil with yellow tint (405 mg, 1.94 mmol, 72% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J*=9.1 Hz, 2 H), 6.88 (d, *J*=9.1 Hz, 2 H), 5.39 (s, 1 H), 5.11 (s, 1 H), 3.83 (s, 3 H), 2.72 - 2.62 (t, *J*=7.3 Hz, 2 H), 1.67 (sxt, *J*=7.3 Hz, 2 H), 1.02 (t, *J*=7.3 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 159.7, 144.6, 132.3, 128.3, 113.6, 109.1, 55.3, 34.1, 21.9, 13.5. HRMS (EI) m/z calcd for $C_{12}H_{16}OS$: 208.0922; found: 208.0926.

Reaction of *n*-Propanethiol and 4-Ethynyl-1-Bromobenzene (3)



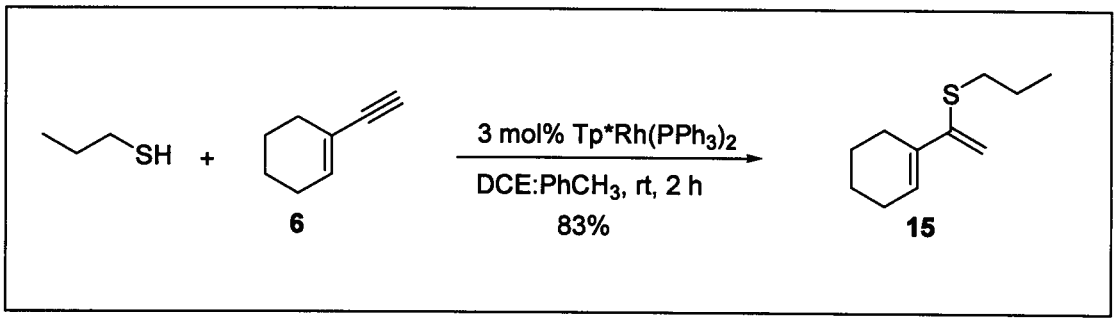
$Tp^*Rh(PPh_3)_2$ (84 mg, 0.09 mmol) was weighed out in the glove box using a spatula into a 20 mL vial equipped with a magnetic stir bar. A 1:1 mixture of DCE:toluene was then added (3 mL), followed sequentially by *n*-propanethiol (302 μL, 3.33 mmol) and 4-ethynyl-1-bromobenzene (549 mg, 3.03 mmol), which was weighed out in a 5 mL vial and transferred to the reaction mixture using 3 mL of a 1:1 mixture of DCE:toluene. The vial was then sealed using a screw cap with foil liner, removed from glove box and wrapped in foil. After stirring for 16 hours at room temperature, the solution was concentrated and the residue was subjected to flash chromatography using petroleum ether as eluent to afford the product as a white solid (538 mg, 2.09 mmol, 69% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.15 - 7.45 (m, 2 H), 7.45 - 7.39 (m, 2 H), 5.45 (s, 1 H), 5.19 (s, 1 H), 2.67 (t, *J*=7.1 Hz, 2 H), 1.66 (sxt, *J*=7.3, 2 H), 1.02 (t, *J*=7.5 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 144.1, 138.8, 131.4, 128.7, 122.3, 111.0, 34.1, 21.9, 13.5. HRMS (EI) m/z calcd for $C_{11}H_{13}SBr$: 255.9921; found: 255.9924.

Reaction of *n*-Propanethiol and 4-Ethynyl-*α,α,α*-Trifluorotoluene (4)



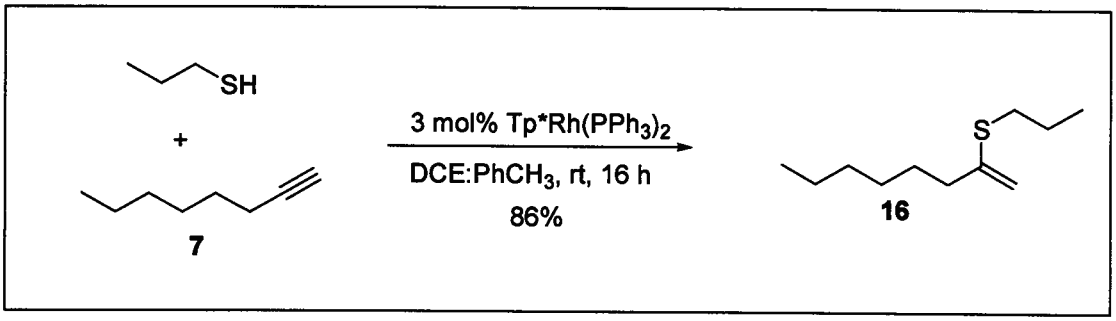
$Tp^*Rh(PPh_3)_2$ (50 mg, 0.054 mmol) was weighed out in the glove box using a spatula into a 20 mL vial equipped with a magnetic stir bar. A 1:1 mixture of DCE:toluene was then added (4 mL), followed sequentially by *n*-propanethiol (181 μL, 1.98 mmol) and 4-ethynyl-*α,α,α*-trifluorotoluene (293 μL, 1.8 mmol) via micropipette. The vial was then sealed using a screw cap with foil liner, removed from glove box and wrapped in foil. After stirring for 24 hours at room temperature, the solution was concentrated and the residue was subjected to flash chromatography using petroleum ether as eluent to afford the product as a clear, colorless oil (71 mg, 0.288 mmol, 16% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 - 7.54 (m, 4 H), 5.52 (s, 1 H), 5.27 (s, 1 H), 2.69 (t, *J*=7.3 Hz, 2 H), 1.77 - 1.59 (m, 2 H), 1.03 (t, *J*=7.3 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 144.1, 143,4, 130.2, 127.5, 125.3 (q, *J*=3.4 Hz), 122.7, 112.2, 34.2, 21.9, 13.5. HRMS (EI) m/z calcd for $C_{12}H_{13}SF_3$: 246.0690; found: 246.0689.

Reaction of *n*-Propanethiol and 1-Ethynylcyclohexene (6)



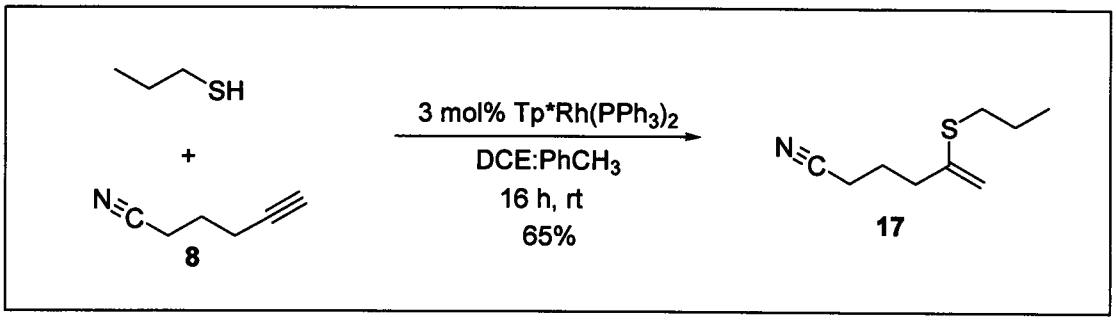
$Tp^*Rh(PPh_3)_2$ (75 mg, 0.081 mmol) was weighed out in the glove box using a spatula into a 20 mL vial equipped with a magnetic stir bar. A 1:1 mixture of DCE:toluene (5 mL) was then added by syringe, followed sequentially by *n*-propanethiol (269 μL, 2.97 mmol) and 1-ethynylcyclohexene (317 μL, 2.7 mmol) via micropipette. The vial was then sealed using a screw cap with a foil liner, removed from glove box and wrapped in foil. After stirring for 2 h at room temperature, the solution was concentrated and the residue was subjected to flash chromatography using petroleum ether as eluent to afford the product as a clear, colorless oil (409 mg, 2.24 mmol, 83% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (t, *J*=4.1 Hz, 1 H), 5.26 (s, 1 H), 4.89 (s, 1 H), 2.66 (t, *J*=7.3 Hz, 2 H), 2.23 (td, *J*=4.1, 1.94 Hz, 2 H), 2.14 (dt, *J*=3.9, 2.26 Hz, 2 H), 1.73 - 1.51 (m, 6 H), 1.01 (t, *J*=7.4 Hz, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 145.6, 135.4, 127.1, 106.6, 33.8, 26.9, 25.7, 22.8, 22.1, 21.9, 13.7. HRMS (EI) m/z calcd for $C_{11}H_{18}S$: 182.1129; found: 182.1133.

Reaction of *n*-Propanethiol and 1-Octyne (7)



$Tp^*Rh(PPh_3)_2$ (30 mg, 0.033 mmol) was weighed out in the glove box using a spatula into a 20 mL vial equipped with a magnetic stir bar. A 1:1 mixture of DCE:toluene (4 mL) was then added by syringe, followed sequentially by *n*-propanethiol (108 μL, 1.19 mmol) and 1-octyne (159 μL, 1.08 mmol) via micropipette. The vial was then sealed using a screw cap with foil liner, removed from glove box and wrapped in foil. After stirring for 16 h at room temperature, the solution was concentrated and the residue was subjected to flash chromatography with petroleum ether as eluent to afford the product as a clear, colorless oil (173 mg, 0.93 mmol, 86% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (s, 1 H), 4.68 (s, 1 H), 2.68 (t, *J*=7.3 Hz, 2 H), 2.22 (t, *J*=7.5 Hz, 2 H), 1.68 (sxt, *J*=7.3 Hz, 2 H), 1.60 - 1.45 (m, 2 H), 1.30 (m, 6 H), 1.03 (t, *J*=7.54 Hz, 3 H), 0.95 - 0.82 (m, 3 H). $^{13}C\{^1H\}$ NMR (d^8-toluene, 100 MHz): δ 146.7, 104.7, 38.12, 33.3, 32.1, 29.3, 29.1, 23.0, 22.0, 14.3, 13.7. HRMS (EI) m/z calcd for $C_{11}H_{22}S$: 186.1442; found: 186.1447.

Reaction of n-propanethiol with 5-hexynenitrile (8)



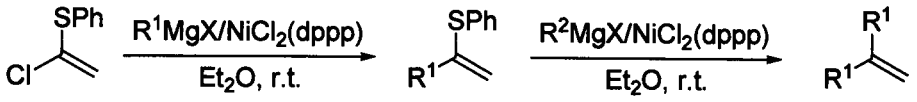
$Tp^*Rh(PPh_3)_2$ (100 mg, 0.108 mmol) was weighed out in the glovebox using a spatula into a 60 mL schlenck flask equipped with a magnetic stir bar and greased glass stopcock. A 1:1 DCE:toluene mixture was then added (4 mL) was then added by syringe. The flask was then sealed with a rubber septum, taken out of the glovebox and wrapped in foil. *n*-Propanethiol (360 μL, 3.97 mmol) was then added followed by 5-hexynenitrile (377 μL, 3.6 mmol) via micropipette. After stirring for 16 hours at room temperature, the solution was concentrated and the residue was subjected to flash chromatography with petroleum ether as eluent to afford the product as a clear, colorless oil (396 mg, 2.34 mmol, 65% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (s, 1 H), 4.76 (s, 1 H), 2.67 (t, *J*=7.31 Hz, 2 H), 2.43 - 2.29 (m, 4 H), 1.89 (quin, *J*=6.97 Hz, 2 H), 1.66 (sxt, *J*=7.31 Hz, 2 H), 1.01 (t, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 143.1, 119.3, 107.1, 36.0, 33.1, 24.1, 21.5, 15.8, 13.5. HRMS (EI) m/z calcd for $C_9H_{15}NS$: 169.0925; found: 169.0924.

Chapter 3 – Kumada Cross-Coupling of Vinyl Sulfides

3.1 Introduction

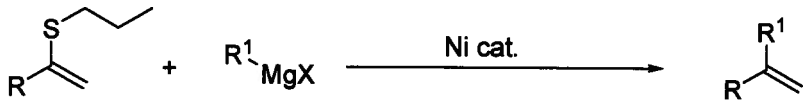
The development of strategies for the construction and substitution of olefins is an area of continued interest due to their presence in biologically active molecules and advanced synthetic intermediates. Traditional transition-metal catalyzed cross-coupling reactions for the synthesis of substituted olefins typically involve the use of vinyl halide or vinyl triflate starting material. The harsh conditions often required for the synthesis of these starting materials present functional group incompatibility, and have led to the investigation of alternate coupling partner substrates.

In 1987, Naso and co-workers reported the synthesis of 1,1-disubstituted olefins involving the use of 1-chloro-1-phenylthioethene;[42] however, the substrate scope that was developed for this reaction was limited to only two examples. The chemoselective introduction of different alkyl groups onto the double bond was possible due to the reactivity differences between the carbon-chloride and the carbon-sulfur bonds towards cross-coupling. When one equiv. of Grignard reagent was reacted with 1-chloro-1-phenylthioethene in the presence of $NiCl_2$(dppp), reaction occurred at the carbon-chloride bond first, affording the corresponding vinyl sulfide. If another equiv. of Grignard reagent was added, the cross-coupling at the carbon-sulfur bond occurred, affording the corresponding disubstituted olefin (eq 3.1). While a one-pot protocol was possible, higher yields were obtained when the vinyl sulfide resulting from carbon-chloride cleavage was actually isolated first before a second equiv. of Grignard reagent was added for cross-coupling at the carbon sulfur bond.



(3.1)

A convenient method for the regioselective synthesis of 1,1-disubstituted vinyl sulfides was developed by our group,[15m] and we have shown that *n*-propanethiol can undergo alkyne hydrothiolation with various alkynes in moderate to high isolated yields (Table 2.1). Due to the low molecular weight of *n*-propanethiol, we postulate that the corresponding vinyl sulfide would be a suitable cross-coupling partner for the synthesis of a variety of 1,1-disubstituted olefins. In this chapter, the reaction of vinyl sulfides derived from the hydrothiolation of various alkynes with *n*-propanethiol with Grignard reagents in the presence of $NiCl_2(PPh_3)_2$ will be discussed (eq 3.2). Furthermore, we will show that a one-pot procedure for the synthesis of the 1,1-disubstituted olefins is possible from readily available alkynes.



(3.2)

3.2 Results and Discussion

3.2.1 Procedure and Optimization of Cross-Coupling Reactions

The test reaction was carried in Et_2O, using vinyl sulfide **10** (Chart 3.1) and benzylmagnesium chloride (Chart 3.2, **19**) in the presence of 5 mol% $NiCl_2(PPh_3)_2$. The reaction was allowed to reflux for 16 h; however, it did not go to completion. After varying the catalyst loading and changing solvents from Et_2O to THF, the optimal

conditions were found to require 10 mol% catalyst loading and refluxing in THF (75 °C) for 16 h. Although Et_2O was also a suitable solvent, THF was chosen due to its higher boiling point. When Et_2O was used, at the end of the required reaction time of 16 h, the reaction mixture became a thick black paste, and gave overall lower yields than in THF. For each of the reaction combinations, the vinyl sulfides (**10-13, 15-17**) were first combined with the $NiCl_2(PPh_3)_2$ in THF. When the Grignard reagent was added in one portion, an increased amount of the homo-coupled product of the Grignard reagent was observed. It was found that the best results were obtained when the Grignard reagent is added dropwise over a longer period of time (over a period of 1 h). The reaction mixture was passed through a plug of Celite, and the organic layer was extracted with Et_2O, dried over Mg_2SO_4 and concentrated. The residue was then subjected to column chromatography, and it was found that the cross-coupled products tended to be less volatile than their corresponding vinyl sulfide starting material.

3.2.2 Substrate Scope of Kumada Cross-Coupling Reactions

Chart 3.1. Vinyl sulfide substrates for Ni-catalyzed cross-coupling

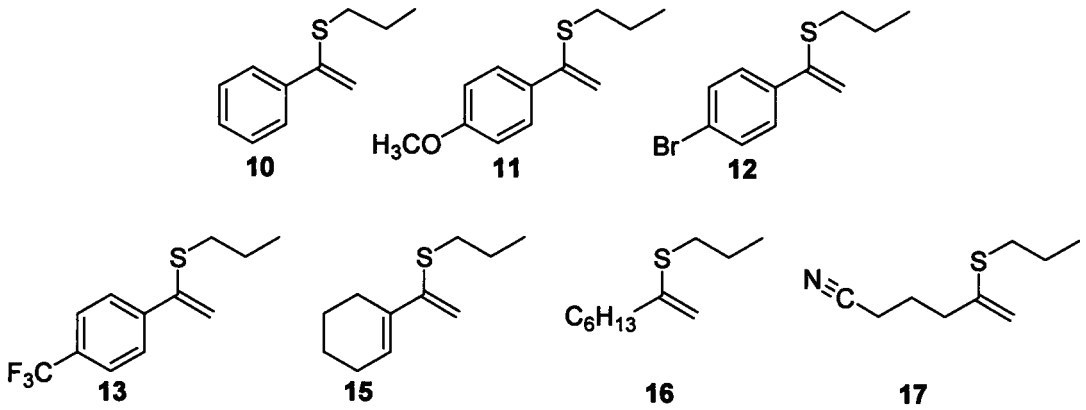
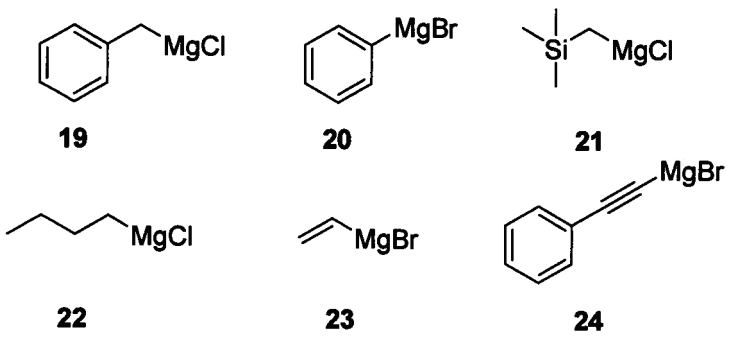
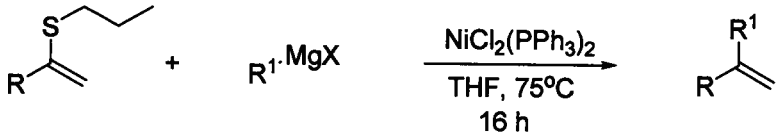


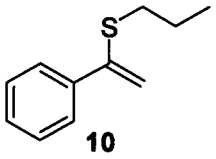
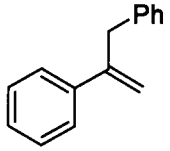
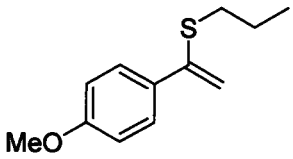
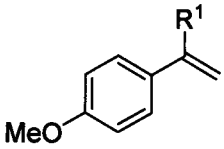
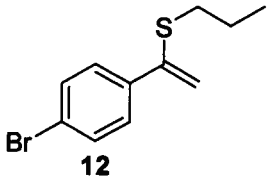
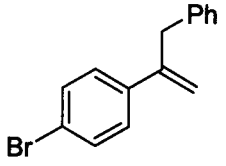
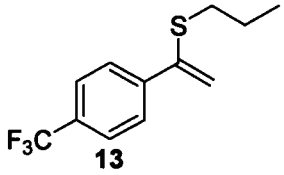
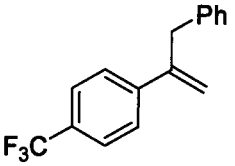
Chart 3.2. Grignard reagents for Ni-catalyzed cross-coupling



The results for the cross-coupling reactions of various aryl vinyl sulfides (**10-13**) with a variety of Grignard reagents (**19-24**) are summarized in Table 3.1 and the results for the cross-coupling involving aliphatic vinyl sulfides (**15-17**) are summarized in Table 3.2. One problem encountered was that the cross-coupling reactions involving vinyl sulfide **10** could not be separated from the homo-coupled Grignard reagent by column chromatography. As a consequence, the yield was calculated by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard. Based on ^{1}H NMR spectroscopic analysis, the cross-coupling of **10** with **19**, afforded the desired 1,1-disubstitued olefin in 51% yield. The disappearance of the vinyl proton singlet resonances (δ 5.47 and 5.19) of **10** indicated that the reaction had gone to completion, and the appearance of new singlet resonances (δ 5.53 and 5.05) indicated that a new 1,1-disubstituted olefin was formed.

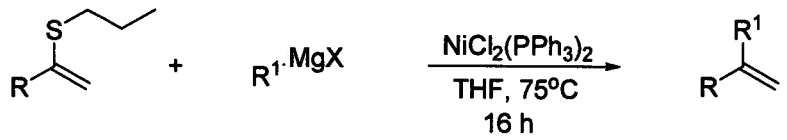
Table 3.1. Summary of $NiCl_2(PPh_3)_2$-catalyzed cross-coupling of aryl vinyl sulfides

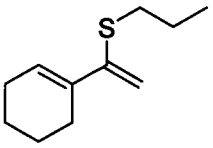
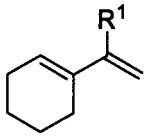
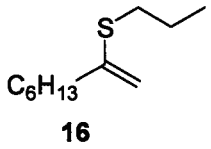
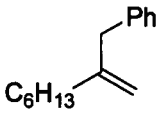
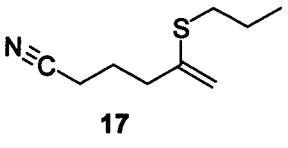
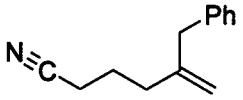


Entry	Vinyl Sulfide	Grignard	Product	Yield
1	 **10**	$PhCH_2MgCl$ (**19**)		51%[a] (**25**)
2	 **11**	$PhCH_2MgCl$ (**19**)		61% (**26**)
3		PhMgBr (**20**)		43% (**27**)
4		TMS-CH_2MgCl (**21**)		60%[b] (**28**)
5		*n*-BuMgCl (**22**)		0%
6		$CH_2CHMgBr$ (**23**)		0%
7		PhCCMgBr (**24**)		0%
8	 **12**	$PhCH_2MgCl$ (**19**)		0%
9	 **13**	$PhCH_2MgCl$ (**19**)		trace

[a] Yield determined by ^1H NMR spectroscopic analysis in $CDCl_3$. [b] $R^1 = CH_3$.

Table 3.2. Summary of $NiCl_2(PPh_3)_2$-catalyzed cross-coupling of aliphatic vinyl sulfides



Entry	Vinyl Sulfide	Grignard	Product	Yield
10		$PhCH_2MgCl$ (**19**)		55% (**29**)
11		PhMgBr (**20**)		41% (**30**)
12		TMS-CH_2MgCl (**21**)		81% (**31**)
13		*n*-BuMgCl (**22**)		0%
14	**15**	$CH_2CHMgBr$ (**23**)		0%
15		PhCCMgBr (**24**)		0%
16	 **16**	$PhCH_2MgCl$(**19**)		51% (**32**)
17	 **17**	$PhCH_2MgCl$(**19**)		0%

Reaction of vinyl sulfide **11** with Grignard reagents **19-21** gave the desired cross-coupling products. We found that vinyl sulfides derived from aryl alkynes containing an electron-donating substituent at the *para* position gave higher yields in the cross-coupling reaction with Grignard reagents than vinyl sulfides derived from unsubstituted aryl alkynes. Vinyl sulfides derived from aryl alkynes containing an electron-withdrawing substituent at the *para* position (**12-13**), gave no cross-coupling product or only trace amounts. This reactivity trend is consistent with what was previously reported by Wenkert and co-workers when aryl vinyl sulfides anethole, methylisoeugenol and isosafrole were synthesized.[43] It can be seen that with increasing electron donation from the aryl ring of the vinyl sulfide, the yield of the cross-coupling product also increases.

For the reaction with trimethylsilylmethylmagnesium chloride (**21**) with vinyl sulfide **11**, only the desilated cross-coupled product was obtained.

The cross-coupling reaction involving vinyl sulfide **12** was not successful in giving the desired substituted olefin, presumably due to the competitive cross-coupling reaction or metal-halogen exchange occurring at the carbon-bromide bond. While the reaction was not expected to be successful due to various possible side reactions, the reaction was carried out in order to test the limits of the coupling reaction. The product that was formed was not isolated; however, it has been shown that different leaving groups show different reactivities towards the cross-coupling reaction. One example of chemoselective Kumada cross-coupling is the reaction of Grignard reagents with chlorophenyl alkyl sulfides in the presence of $NiCl_2(PPh_3)_2$.[44] The reaction occurs first at the carbon-chloride bond. If a second equiv. of Grignard reagent is added, subsequent reaction occurs at the carbon-sulfur bond, and the disubstituted benzene can be obtained. Another example is the previously mentioned work of Naso and co-workers[42] in the synthesis of 1,1-disubstituted olefins from 1-chloro-1-phenylthioethene. Another reaction that was used in order to test the limit of the cross-coupling reaction was the reaction involving vinyl sulfide **17**, where the possible side reactions could have been the attack of the Grignard reagent on the cyano group or deprotonation of the proton α to the cyano group. The desired cross-coupling product was not obtained.

The reaction of vinyl sulfide **13** with benzylmagnesium chloride only gave trace amounts of the cross-coupled product, which was indicated by the appearance of new singlet resonances (δ 5.56 and 5.16) in the olefinic region of the ^1H NMR spectrum. Vinyl sulfide **15** reacted with Grignard reagents **19-21** affording the desired cross-

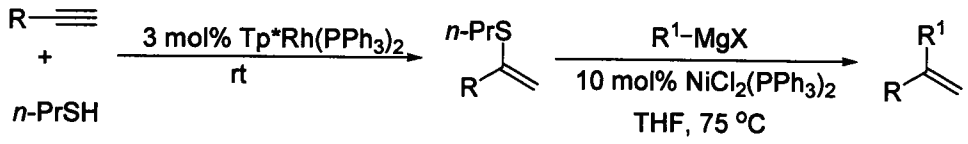
coupling product; however, in contrast to the reaction with vinyl sulfide **11**, the silylated product was obtained in high isolated yield when TMS-CH_2MgCl (**21**) was used as Grignard reagent. Although it was previously mentioned that primary and secondary Grignard reagents act as reducing agents in the cross-coupling reaction in the presence of $NiCl_2(PPh_3)_2$, the absence of β-hydrogens in TMS-CH_2MgCl allows it to act as a suitable nucleophile in the formation of the desired 1,1-disubstituted olefin. We should note that allyl silanes have been used in allylation reactions or as nucleophiles in other cross-coupling reactions.[45] Furthermore, all of the products of the cross-coupling reaction of **15** have potential to act as Diels-Alder substrates.[46]

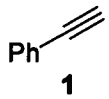
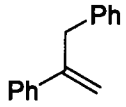
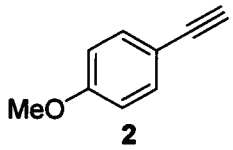
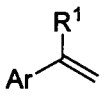
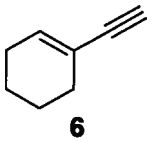
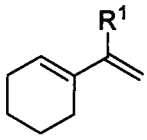
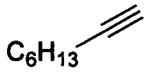
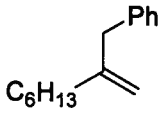
Reaction using phenylethynylmagnesium- or *n*-butylmagnesium bromide as cross-coupling partners did not give the desired substituted olefin when reacted with vinyl sulfides **11** and **15**, but instead gave unidentified by-products. It is known that primary and secondary Grignard reagents can serve as reducing agents in the reductive cleavage of carbon-sulfur bonds in the presence of $NiCl_2(PPh_3)_2$.[26,47] Wenkert and co-workers found that the reduction can be suppressed by changing catalysts from $NiCl_2(PPh_3)_2$ to $NiCl_2$(dppp) or $NiCl_2$(dppe). It was thought that the role of the ligand was crucial in determining the reactivity of the catalyst. By replacing the triphenylphosphine ligands with a bidentate dppp or dppe ligand, the reductive elimination step leading to cross-coupling could be accelerated, thus decreasing the chance for reductive cleavage to occur.[47] The use of other nickel-complexes containing bidentate ligands in the cross-coupling reaction is an area of future exploration in our group.

3.2.3 One-Pot Hydrothiolation and Kumada Cross-Coupling

Once the feasibility of vinyl sulfides to act as substrates in cross-coupling for the synthesis of 1,1-disubstituted olefins was established, we addressed the possibility of a one-pot procedure, combining the hydrothiolation and Kumada cross-coupling reactions. Although the hydrothiolation reaction was typically carried out in a 1:1 DCE:toluene mixture, while the cross-coupling was carried out in THF, THF was chosen in order to carry out the one-pot protocol. We previously mentioned that $Tp^*Rh(PPh_3)_2$ decomposes in THF if left for extended periods (>2 d); however, since the hydrothiolation step is complete within 16 h, we did not expect the use of THF to be problematic. The desired 1,1-disubstituted olefins obtained from the one-pot protocol (Table 3.3) gave comparable, and in some cases, superior isolated yields to those obtained from the two-step procedure. To determine what may be the cause of the superior yields, the hydrothiolation reaction was carried out using the $NiCl_2(PPh_3)_2$ as catalyst and the cross-coupling reaction was carried out using $Tp^*Rh(PPh_3)_2$ as catalyst. When the hydrothiolation was carried out using $NiCl_2(PPh_3)_2$ as catalyst, only unreacted starting material is observed. When $Tp^*Rh(PPh_3)_2$ was used as the catalyst for the cross-coupling reaction, a small amount of the cross-coupling product is formed, indicated by the emergence of new singlet resonances in ^1H NMR corresponding to the vinyl protons of the desired product. The superior yields that is sometimes observed in the one-pot protocol may the result of both the $NiCl_2(PPh_3)_2$ and $Tp^*Rh(PPh_3)_2$ complexes catalyzing the cross-coupling reaction. Alternatively, loss of the vinyl sulfide substrates from the hydrothiolation reaction in the isolation step may occur, thus lowering the overall yield of the two-step process.

Table 3.3. Summary of Results for One-Pot Protocol



Entry	Alkyne	Grignard	Product	Time	Yield
1	 **1**	$PhCH_2MgCl$ (**19**)		16 h	30%[a] (**25**)
2	 **2**	$PhCH_2MgCl$ (**19**)		16 h	65% (**26**)
3		PhMgBr (**20**)		16 h	37% (**27**)
4		TMS-CH_2MgCl (**21**)		16 h	63%[b] (**28**)
5	 **6**	$PhCH_2MgCl$(**19**)		16 h	66% (**29**)
6		PhMgBr(**20**)		16 h	30% (**30**)
7		TMS-CH_2MgCl(**21**)		16 h	60% (**31**)
8	 **7**	$PhCH_2MgCl$(**19**)		16 h	78% (**32**)

[a] Yield determined by ^1H NMR spectroscopic analysis in $CDCl_3$. [b] $R^1 = CH_3$.

3.3 Conclusions

We have found that vinyl sulfides derived from aryl and aliphatic alkynes and *n*-propanethiol, can undergo nickel-catalyzed Kumada-type cross-coupling with Grignard reagents to afford 1,1-disubstituted olefins. Furthermore, the vinyl sulfides derived from aryl alkynes that have an electron donating substituent at the *para* position gave higher yields than the unsubstituted variant, which in turn gave better yields than alkyl vinyl sulfides with an electron withdrawing substituent at the *para* position. While aryl and aliphatic Grignard reagents were found to be suitable cross-coupling partners, vinyl

Grignard reagents and those containing β-hydrogens did not afford the desired 1,1-disubstituted olefin. A one-pot protocol has also been established and provides comparable or better isolated yields than the two-step procedure, while improving efficiency in requiring only one workup step. In addition to improving the efficiency of the reaction, the avoidance of one purification step reduces the use purification solvents as well as reaction solvent.

3.4 Experimental Procedure

3.4.1 General Methods

The synthesis and manipulation of air and moisture sensitive organometallic compounds was carried out under N_2 atmosphere. Reactions were refluxed at 75 °C for 16 h and stirred with a Teflon-coated magnetic stir bar. Reaction mixtures were concentrated using rotary evaporation methods combined with a high vacuum pump line. Internal standard yields were obtained via ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as internal standard. A potassium hydroxide, isopropanol and water base bath was used to clean glassware, followed by subsequent rinsing with deionized water and acetone. Flash chromatography was used to separate products (Silicycle, 60-200μm, 70-230 mesh), and the solvent was eluted using air.

3.4.2 Reagents and Solvents

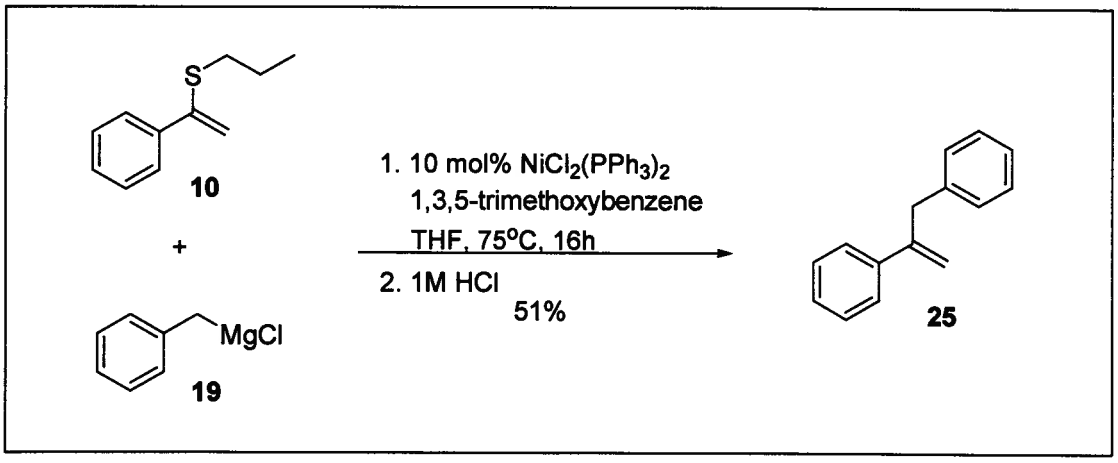
$NiCl_2(PPh_3)_2$ was prepared by a published procedure.[48] Hexanes, 1,2-dichloroethane (DCE), THF and toluene were dried by passage through solvent

purification columns. All other commercial reagents and solvents were used without further purification. Deuterated chloroform was dried using activated molecular sieves (4Å).

3.4.3 Physical and Spectropscopic Measurements

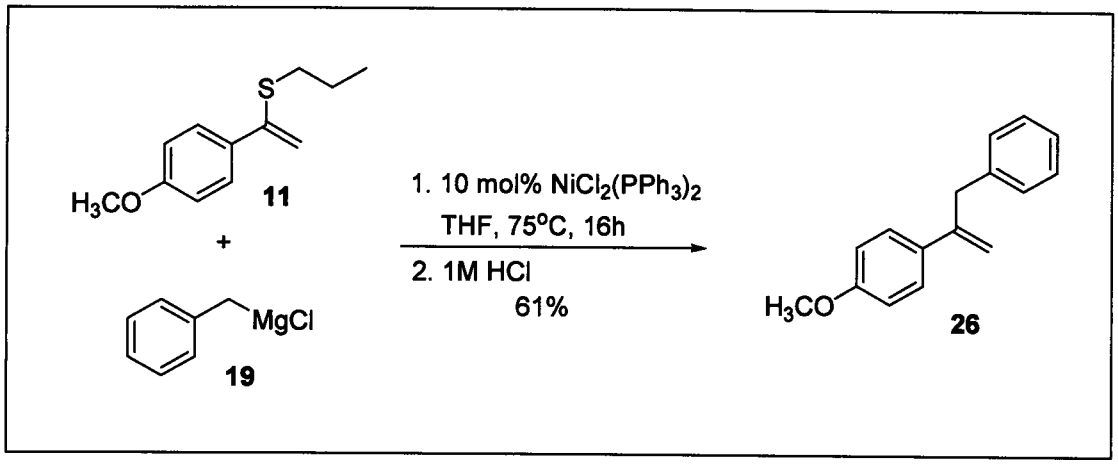
NMR spectra were recorded on Bruker Avance 300 or Bruker Avance 400 spectrometers. ^{1}H and ^{13}C NMR spectra are reported in parts per million and referenced to residual solvent. Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, m = multiplet, dd = doublet of doublets, td = triplet of doublets. All spectra were obtained at 25 °C. Mass spectra were recorded on a Kratos MS-50 mass spectrometer. Higher yields and elemental analyses of the compounds were impeded by homo-coupling of the Grignard reagent and product volatility.

Reaction of (10) with Benzylmagnesium Chloride (19)



The yield for the above reaction was determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard. $NiCl_2(PPh_3)_2$ (36 mg, 0.056 mmol) was weighed out using a spatula onto weighing paper and added to a flame-dried 25 mL 2-neck round-bottom flask containing vinyl sulfide **10** (100 mg, 0.56 mmol), 1,3,5-trimethoxybenzene (31.3 mg, 0.186 mmol) and a magnetic stir bar. The round-bottom flask was sealed using two rubber septa and flushed with N_2 gas. THF (6.8 mL) was then added and the mixture was stirred vigorously while a 1.0 M solution of benzylmagnesium chloride (2.2 mL) in Et_2O was added dropwise via syringe over a period of 1 h. The reaction flask was then equipped with a flame dried reflux condenser and glass stopper, and the resulting brown/black solution was heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution was added (4 mL) followed by Et_2O (4 mL). The solution was stirred for 5 min then filtered through a plug of Celite. The organic layer was extracted with Et_2O (3 x 5 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was dissolved in $CDCl_3$. ^{1}H NMR (300 MHz) spectroscopic analysis indicated the formation of the cross-coupled product[49] in 51 % yield. The spectrum shown in Appendix 2 contains residual toluene, bibenzyl and tetrahydrofuran.

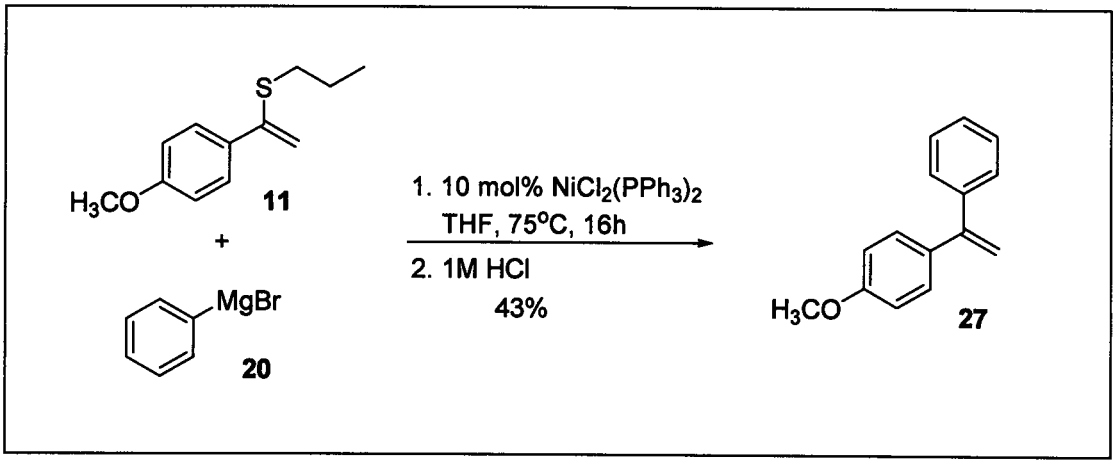
Reaction of (11) with Benzylmagnesium Chloride (19)



$NiCl_2(PPh_3)_2$ (16 mg, 0.026 mmol) was weighed out using a spatula onto weighing paper and added to a flame-dried 15 mL 2-neck round-bottom flask containing vinyl sulfide **11** (55 mg, 0.26 mmol) and a magnetic stir bar. The round-bottom flask was sealed using two rubber septa and flushed with N_2 gas. THF (3.7 mL) was then added and the mixture was stirred vigorously while a 1.0 M solution of benzylmagnesium chloride (1.1 mL) in Et_2O was added dropwise via syringe over a period 1 h. The reaction flask was then equipped with a flame dried reflux condenser and stopper, and the resulting brown/black solution was heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution was added (2 mL) followed by Et_2O (2 mL). The solution was stirred for 5 min then filtered through a plug of Celite. The organic layer was extracted with Et_2O (3 x 4 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was then subjected to flash chromatography to afford the product as a clear colorless oil (36 mg, 0.16 mmol, 61 %). ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J*=8.9 Hz, 2 H), 7.30 – 7.20 (m, 5 H), 6.83 (d, *J*=8.9 Hz, 2 H), 5.44 (s, 1 H), 4.96 (s, 1 H), 3.83 (s, 2 H), 3.80 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 159.0, 146.1, 139.7,

133.2, 128.8, 128.3, 127.2, 126.0, 113.6, 113.0, 55.2, 41.7. HRMS (EI) m/z calcd for $C_{16}H_{16}O$: 224.1201; found: 224.1202.

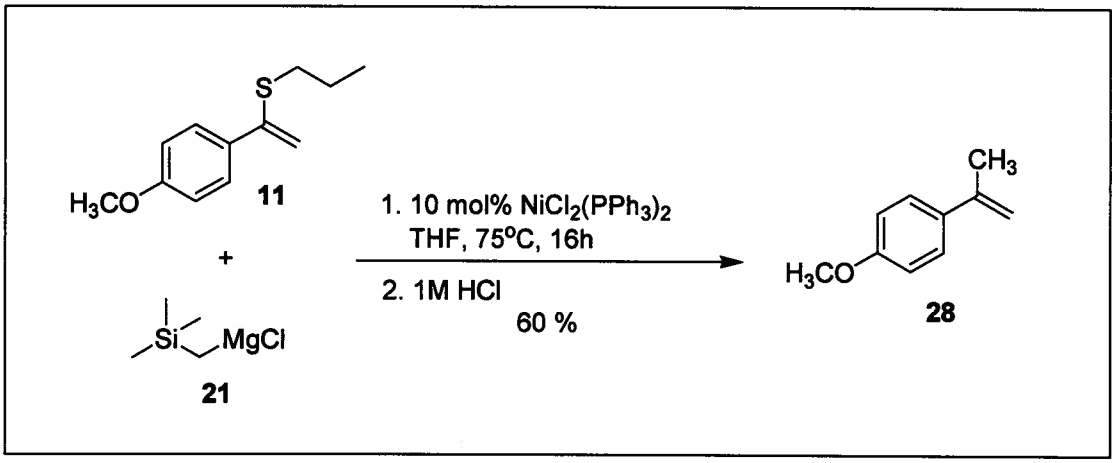
Reaction of (11) with Phenylmagnesium Bromide (20)



$NiCl_2(PPh_3)_2$ (30 mg, 0.048 mmol) was weighed out using a spatula onto weighing paper and added to a flame-dried 25 mL 2-neck round-bottom flask containing vinyl sulfide **11** (100 mg, 0.48 mmol) and a magnetic stir bar. The round-bottom flask was sealed using two rubber septa and flushed with N_2 gas. THF (6.0 mL) was then added and the mixture was stirred vigorously while a 1.0 M solution of phenylmagnesium bromide (2 mL) in THF was added dropwise via syringe over a period of 1 h. The reaction flask was then equipped with a flame dried reflux condenser and glass stopper, and the resulting brown/black solution was heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution was added (4 mL) followed by Et_2O (4 mL). The solution was stirred for 5 min then filtered through a plug of Celite. The organic layer was extracted with Et_2O (3 x 8 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography to afford the product as a white solid (44 mg, 0.21 mmol, 43 %). Characterization matches previously

reported data.[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 - 7.22 (m, 7 H), 6.85 (d, *J*=9.2 Hz, 2 H), 5.38 (s, 1 H), 5.34 (s, 1 H), 3.81 (s, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 159.3, 149.5, 141.8, 134.0, 129.4, 128.3, 128.1, 127.6, 113.5, 112.9, 55.3. HRMS (EI) m/z calcd for $C_{15}H_{14}O$: 210.1045; found: 210.1050.

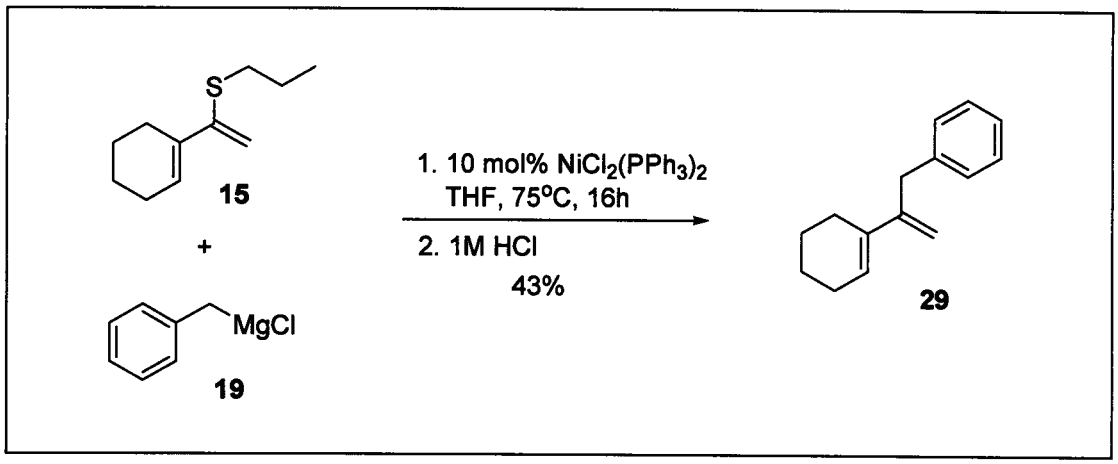
Reaction of (11) with Trimethylsilylmethylmagnesium Chloride (21)



$NiCl_2(PPh_3)_2$ (30 mg, 0.048 mmol) was weighed out using a spatula onto weighing paper and added to a flame-dried 25 mL 2-neck round-bottom flask containing vinyl sulfide **11** (100 mg, 0.48 mmol) and a magnetic stir bar. The round-bottom flask was sealed using two rubber septa and flushed with N_2 gas. THF (6.0 mL) was then added and the mixture was stirred vigorously while trimethylsilylmethylmagnesium chloride (2 mL of a 1.0 M solution in Et_2O) was added dropwise via syringe over a period of 1 h. The reaction flask was then equipped with a flame dried reflux condenser and glass stopper, and the resulting brown/black solution was heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution was added (4 mL) followed by Et_2O (4 mL). The solution was stirred for 5 min then filtered through a plug of Celite.

The organic layer was extracted with Et_2O (3 x 8 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography to afford the product as a colorless oil (43 mg, 0.29 mmol, 60 %). Up to 10 % of the reduced product is produced as observed by ^1H NMR. Characterization matches previously reported data.[51] ^1H NMR (300 MHz, $CDCl_3$) δ 7.44 (d, *J*=8.7 Hz, 2 H), 6.88 (d, *J*=8.7 Hz, 2H), 5.30 (s, 1 H), 5.01, (s, 1 H), 3.83 (s, 3 H), 2.15 (s, 3 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 159,0, 142.5, 133.7, 126.6, 113.5, 110.6, 55.3, 21.9. HRMS (EI) m/z calcd for $C_{10}H_{12}O$: 148.0888; found: 148.0885.

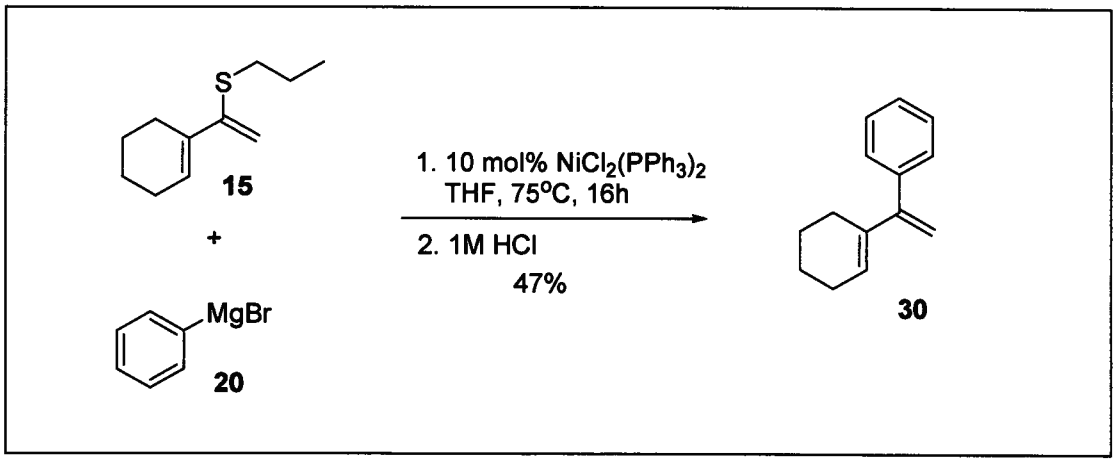
Reaction of (15) with Benzylmagnesium Chloride (19)



$NiCl_2(PPh_3)_2$ (34 mg, 0.055 mmol) was weighed out using a spatula onto weighing paper and added to a flame-dried 25 mL 2-neck round-bottom flask containing vinyl sulfide **15** (100 mg, 0.55 mmol) and a magnetic stir bar. The round-bottom flask was sealed using two rubber septa and flushed with N_2 gas. THF (7.7 mL) was then added and the mixture was stirred vigorously while benzylmagnesium chloride (2.2 mL of a 1.0 M solution in Et_2O) was added dropwise via syringe over a period of 1 h. The reaction flask was then

equipped with a flame dried reflux condenser and glass stopper, and the resulting brown/black solution was heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution was added (5 mL) followed by Et_2O (5 mL). The solution was stirred for 5 min then filtered through a plug of Celite. The organic layer was extracted with Et_2O (3 x 8 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography to afford the product as a clear, colorless oil (60 mg, 0.30 mmol, 43 %). ^1H NMR (300 MHz, $CDCl_3$) δ.7.32 - 7.24 (m, 2 H), 7.23 - 7.14 (m, 3 H), 5.93 (t, *J*=4.1 Hz, 1 H), 5.16 (s, 1 H), 4.74 (s, 1 H), 3.60 (s, 2 H), 2.26 - 2.18 (m, 2 H), 2.14 - 2.04 (m, 2 H), 1.73 - 1.62 (m, 2 H), 1.61 - 1.49 (m, 2 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ 147.0, 140.6, 135.5, 128.7, 128.2, 125.7, 125.5, 111.4, 40.1, 26.0, 25.9, 22.9, 22.1. HRMS (EI) m/z calcd for $C_{15}H_{18}$: 198.1409; found: 198.1409.

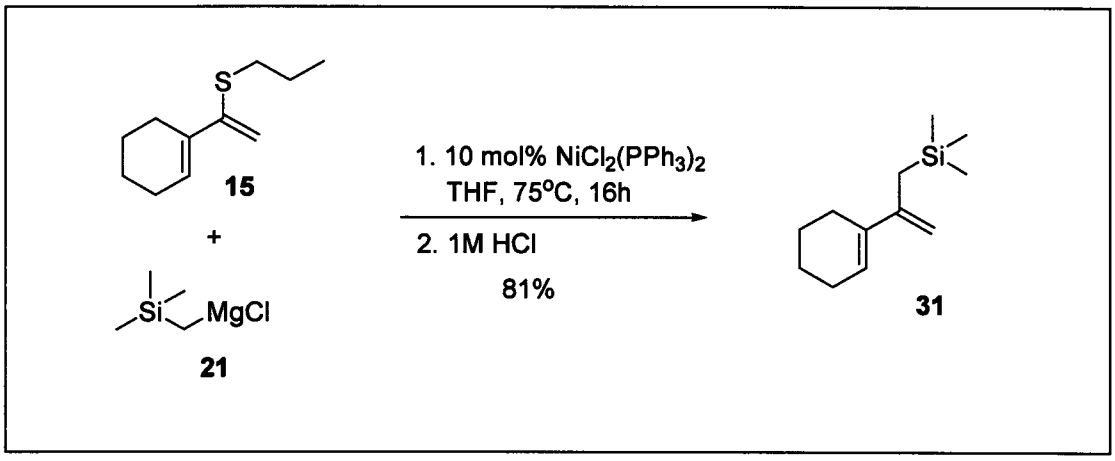
Reaction of (15) with Phenylmagnesium Bromide (20)



$NiCl_2(PPh_3)_2$ (33 mg, 0.052 mmol) was weighed out using a spatula onto weighing paper and added to a flame-dried 25 mL 2-neck round-bottom flask containing vinyl sulfide **15**

(95 mg, 0.52 mmol) and a magnetic stir bar. The round-bottom flask was sealed using two rubber septa and flushed with N_2 gas. THF (7.5 mL) was then added and the mixture was stirred vigorously while phenylmagnesium bromide (2.2 mL of a 1.0 M solution in THF) was added dropwise via syringe over a period of 1 h. The reaction flask was then equipped with a flame dried reflux condenser and glass stopper, and the resulting brown/black solution was heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution was added (5 mL) followed by Et_2O (5 mL). The solution was stirred for 5 min then filtered through a plug of Celite. The organic layer was extracted with Et_2O (3 x 8 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography to afford the product as a clear, colorless oil (45 mg, 0.24 mmol, 47 %). Characterization matches previously reported data.[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 - 7.21 (m, 5 H), 5.63 (t, *J*=4.1 Hz, 1 H), 5.20 (s, 1 H), 4.98 (s, 1 H), 2.32 - 2.19 (m, 2 H), 2.17 - 2.04 (m, 2 H), 1.80 - 1.67 (m, 2 H), 1.67 - 1.56 (m, 2 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 151.7, 142.1, 137.1, 129.0, 128.7, 127.8, 126.9, 110.9, 26.4, 25.9, 22.9, 22.2. HRMS (EI) m/z calcd for $C_{14}H_{16}$: 184.1252; found: 184.1251.

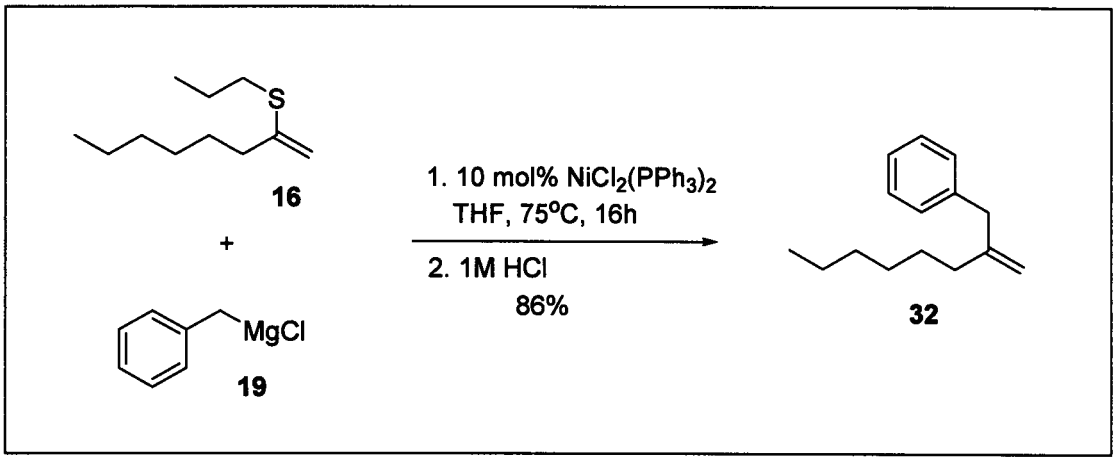
Reaction of (15) with Trimethylsilylmethylmagnesium Chloride (21)



$NiCl_2(PPh_3)_2$ (26 mg, 0.041 mmol) was weighed out using a spatula onto weighing paper and added to a flame-dried 25 mL 2-neck round-bottom flask containing vinyl sulfide **15** (75 mg, 0.41 mmol) and a magnetic stir bar. The round-bottom flask was sealed using two rubber septa and flushed with N_2 gas. THF (5.0 mL) was then added and the mixture was stirred vigorously while trimethylsilylmethylmagnesium chloride (1.7 mL of a 1.0 M solution in Et_2O) was added dropwise via syringe over a period of 1 h. The reaction flask was then equipped with a flame dried reflux condenser and glass stopper, and the resulting brown/black solution was heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution was added (5 mL) followed by Et_2O (5 mL). The solution is stirred for 5 min then filtered through a plug of Celite. The organic layer was extracted with Et_2O (3 x 8 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography to afford the product as a clear colorless oil (64 mg, 0.33 mmol, 81 %). ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (t, *J*=4.0 Hz., 1 H), 4.86 (s, 1 H), 4.62 (s, 1 H), 2.27 - 2.06 (m, 4 H), 1.77 (s, 2 H), 1.73 - 1.52 (m, 4 H), 0.00 (s, 9 H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz):

δ 146.4, 136.6, 125.1, 106.7, 26.1, 25.9, 23.9, 23.1, 22.2, 1.2. HRMS (EI) m/z calcd for $C_{12}H_{22}Si$: 194.1491; found: 194.1493.

Reaction of (16) with Benzylmagnesium Chloride (19)



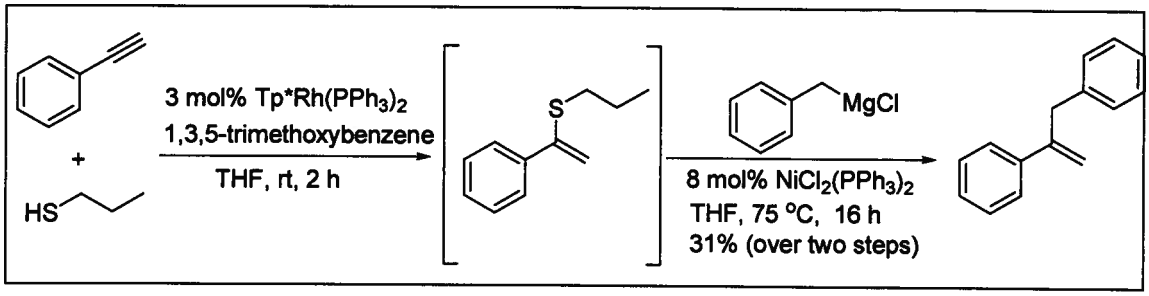
$NiCl_2(PPh_3)_2$ (31 mg, 0.062 mmol) was weighed out using a spatula onto weighing paper and added to a flame-dried 25 mL 2-neck round-bottom flask containing vinyl sulfide **16** (115 mg, 0.62 mmol) and a magnetic stir bar. The round-bottom flask was sealed using two rubber septa and flushed with N_2 gas. THF (7.0 mL) was then added and the solution was stirred vigorously while benzylmagnesium chloride (2.5mL of a 1.0 M solution in Et_2O) was added dropwise via syringe over a period of 1 h. The reaction flask was then equipped with a flame dried reflux condenser and glass stopper, and the resulting brown/black solution was heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution was added (5 mL) followed by Et_2O (5 mL). The solution is stirred for 5 min then filtered through a plug of Celite. The organic layer was extracted with Et_2O (3 x 8 mL), dried over Mg_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash chromatography to afford the product as a clear colorless oil (56 mg, 0.32 mmol, 51 %). 1H NMR (300 MHz, $CDCl_3$)

δ 7.37 - 7.13 (m, 5 H), 4.83 (s, 1 H), 4.74 (s, 1 H), 3.35 (s, 2 H), 1.98 (t, *J*=7.5 Hz, 2 H), 1.53 - 1.38 (m, 2 H), 1.38 - 1.20 (m, 6 H), 0.89 (t, *J*=6.9 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 175MHz): δ 149.3, 139.9, 129.0, 128.2, 126.0, 110.9, 43.0, 35.4, 31.7, 29.0, 27.6, 22.6, 14.1. HRMS (EI) m/z calcd for $C_{15}H_{22}$: 202.1722; found: 202.1716.

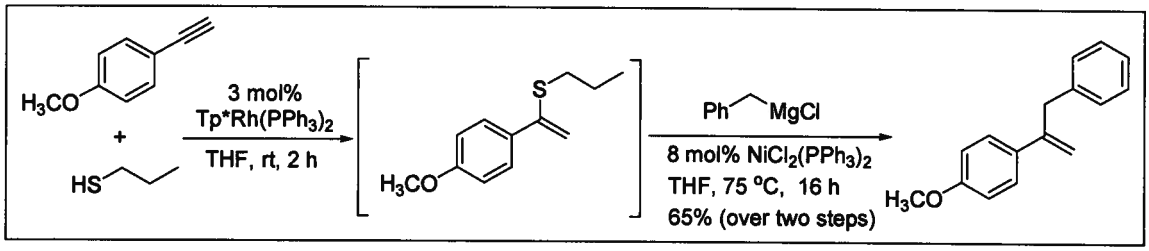
One-pot hydrothiolation/Kumada cross-coupling

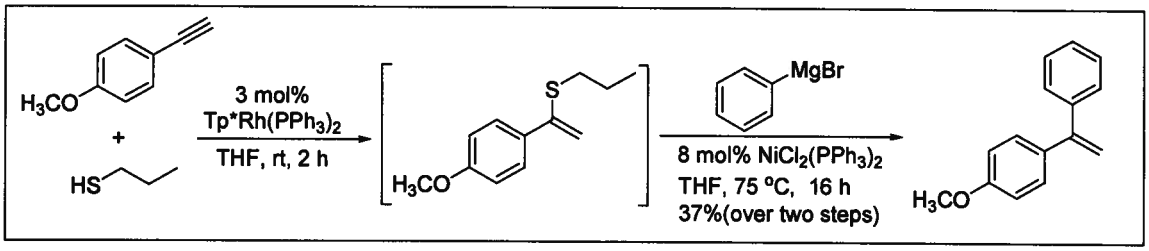
General procedure

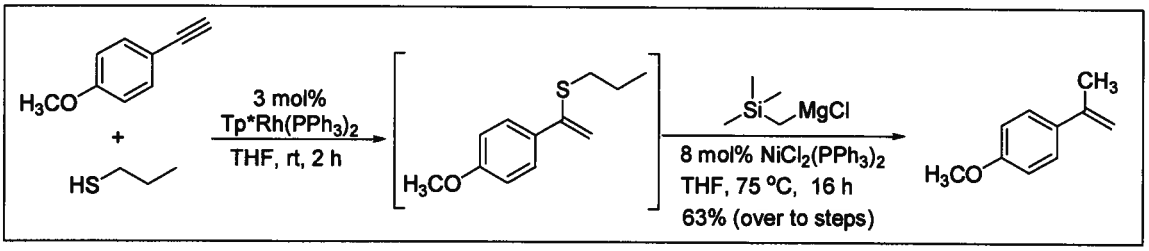
Tp*Rh(PPh_3)$_2$ (25 mg, 0.027 mmol) was weighed out in the glove box using a spatula into a 25 mL two-neck round bottom flask equipped with a magnetic stir bar. THF (2.5 mL) was then added by syringe, followed sequentially by *n*-propanethiol (90 μL, 0.99 mmol) and alkyne (0.9 mmol) via micropipette. The reaction flask was then sealed with rubber septa, removed from glove box and wrapped with foil. The solution was stirred at room temperature for 2 h unless otherwise specified. After 2 h the foil was removed and a solution of $NiCl_2(PPh_3)_2$ (45 mg, 0.072 mmol in 10 mL of THF) was added by syringe. While the solution was vigorously stirred, a 1.0 M solution of Grignard reagent (3.6 mL, 3.6 mmol) was added dropwise via syringe over 1 h. The reaction flask was then equipped with a flame dried reflux condenser and glass stopper, and heated to 75 °C for 16 h. The solution was then allowed to cool to room temperature and a 1 M HCl solution (4 mL) was added, followed by Et_2O (4 mL). After stirring for 5 min, the mixture was filtered through a plug of Celite. The organic layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were dried over Mg_2SO_4 for 10 min, filetered and then concentrated under reduced pressure. The residue was subjected to flash chromatography to afford the product. Yields given are isolated yields, unless otherwise specified.

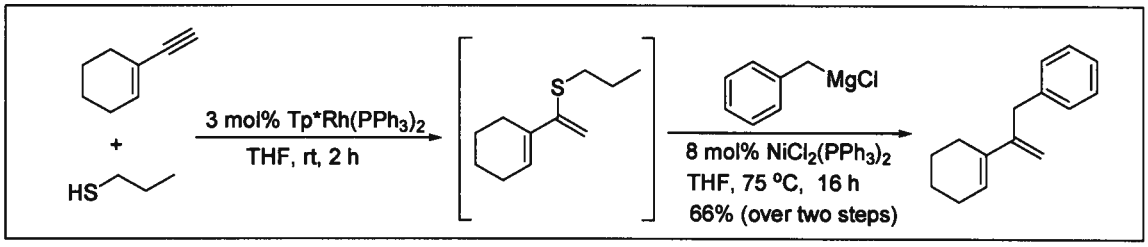


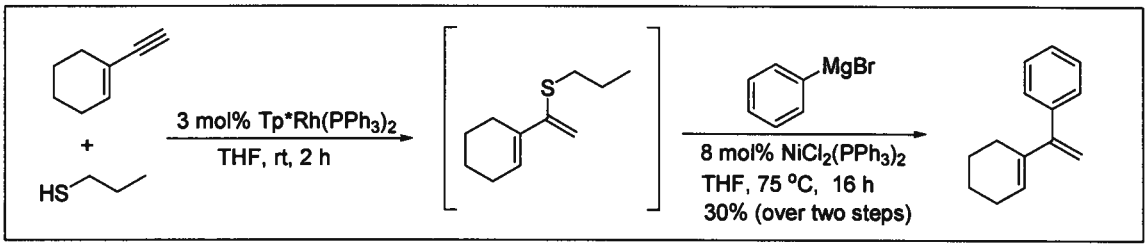
$Tp^*Rh(PPh_3)_2$ (27 mg, 0.029 mmol), *n*-propanethiol (95 μL, 1.05 mmol), alkyne (0.97 mmol), $NiCl_2(PPh_3)_2$ (45 mg, 0.072 mmol in 10 mL of THF), Grignard reagent (3.9 mL, 3.6 mmol), 1,3,5-trimethoxybenzene (53.2. mg, 0.316 mmol). The yield for the above reaction was determined by ^1H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

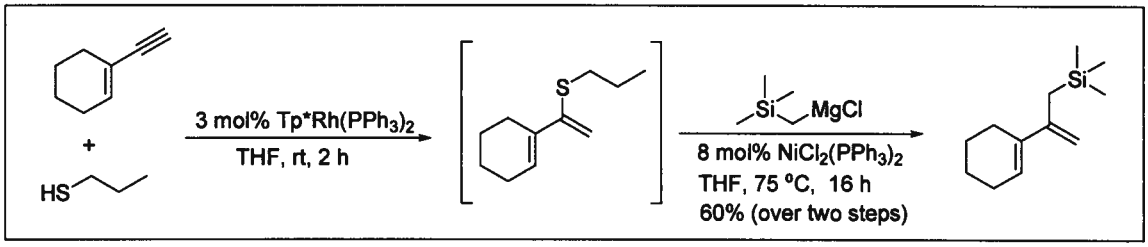


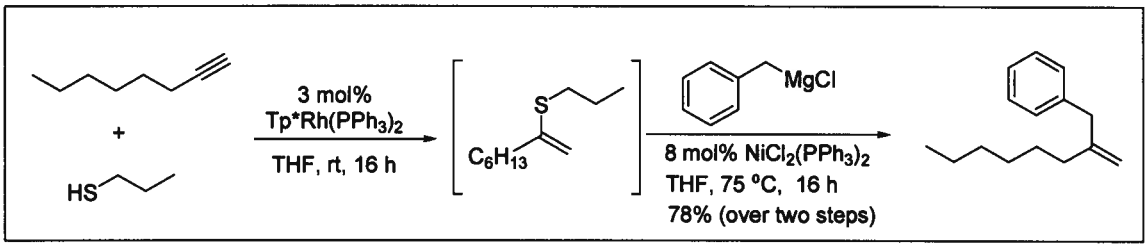





3 mol% Tp*Rh(PPh3)2
THF, rt, 2 h
HS
S
MgCl
8 mol% NiCl2(PPh3)2
THF, 75 °C, 16 h
66% (over two steps)


3 mol% Tp*Rh(PPh3)2
THF, rt, 2 h
HS
S
MgBr
8 mol% NiCl2(PPh3)2
THF, 75 °C, 16 h
30% (over two steps)


3 mol% Tp*Rh(PPh3)2
THF, rt, 2 h
HS
S
Si
MgCl
8 mol% NiCl2(PPh3)2
THF, 75 °C, 16 h
60% (over two steps)


3 mol%
Tp*Rh(PPh3)2
THF, rt, 16 h
HS
S
C6H13
MgCl
8 mol% NiCl2(PPh3)2
THF, 75 °C, 16 h
78% (over two steps)

Chapter 4 – Summary, Conclusions and Future Work

4.1 Summary

In this theses, we have shown a useful method for the synthesis of 1,1-disubstituted olefins from readily available terminal alkynes via hydrothiolation followed by nickel-catalyzed Kumada-type cross-coupling with various Grignard reagents. While our group previously reported the successful catalytic alkyne hydrothiolation of a variety of alkynes (aryl and aliphatic) with a series of thiols (aryl and aliphatic) in the presence of $Tp^*Rh(PPh_3)_2$, the use of *n*-propanethiol was limited to only one example. The expansion of previously established methodology was carried out using *n*-propanethiol as hydrothiolation substrate with a variety of alkynes to afford the corresponding vinyl sulfides in moderate-to-high isolated yields.

Vinyl sulfides derived from unsubstituted aryl alkynes or aryl alkynes containing an electron-donating substituent at the *para* position gave high isolated yields, while vinyl sulfides derived from aryl alkynes containing an electron-withdrawing substituent at the *para* position showed a significant decrease in reactivity and yield. Aliphatic alkynes **6**, **7** and **8** gave high isolated yields while alkyne **9** showed no reactivity to the hydrothiolation reaction. It should be noted that the vinyl sulfide products are relatively unstable should be used immediately or stored in the freezer as a solution in petroleum ether.

The Kumada coupling of the isolated vinyl sulfides from the reaction of aryl and aliphatic alkynes, with various Grignard reagents were then investigated to explore the

feasibility of their use as substrates for 1,1-disubstituted olefin synthesis. The cross-coupling of vinyl sulfides **10-17** with various Grignard reagents (**19-24**) was carried out, and it was found that 1,1-disubstitued olefins can be afforded by the reaction of aryl or aliphatic Grignard reagents with alkyl or aryl vinyl sulfides. We also found that vinyl sulfides derived from aryl alkynes containing an electron-donating substituent at the *para* position increased reactivity towards cross-coupling relative to the vinyl sulfide derived from the unsubstituted aryl alkyne. In contrast, vinyl sulfides derived from aryl alkynes containing an electron-withdrawing substituent at the *para* position had a significant decrease in reactivity towards cross-coupling. Alkynylmagnesium halides, vinyl magnesium halides, or Grignard reagents that contain β-hydrogens were found to be unproductive in the cross-coupling reaction in the presence of $NiCl_2(PPh_3)_2$. A one-pot protocol was also developed for the formation of 1,1-disubstituted olefins starting from readily available alkynes.

4.2 Future Work

In this thesis, the synthesis of a variety of 1,1-disubstituted olefins was discussed involving catalytic alkyne hydrothiolation and subsequent nickel-catalyzed Kumada cross-coupling. The vinyl sulfides obtained from the hydrothiolation involving *n*-propanethiol readily decompose at room temperature. Isolation and characterization of these decomposition products may be useful in further optimizing the hydrothiolation procedure. Furthermore, investigation of the cross-coupling reaction using nickel catalysts containing bidentate ligands, suchs as $NiCl_2$(dppp) and $NiCl_2$(dppf), may expand the scope of the cross-coupling reaction to more functionalized Grignard reagents

and aliphatic Grignard reagents containing β-hydrogens. Furthermore, once a more generalized cross-coupling is established using aliphatic Grignard reagents a possibility for an intramolecular cross-coupling can be explored.

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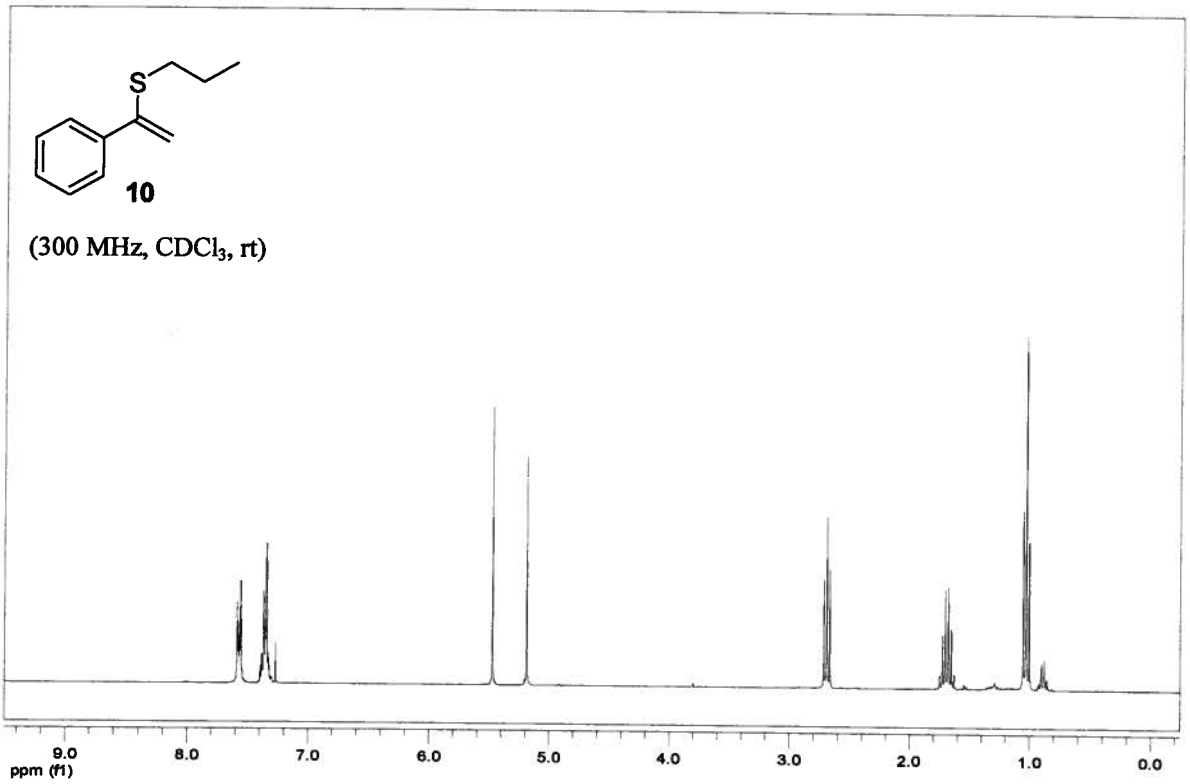
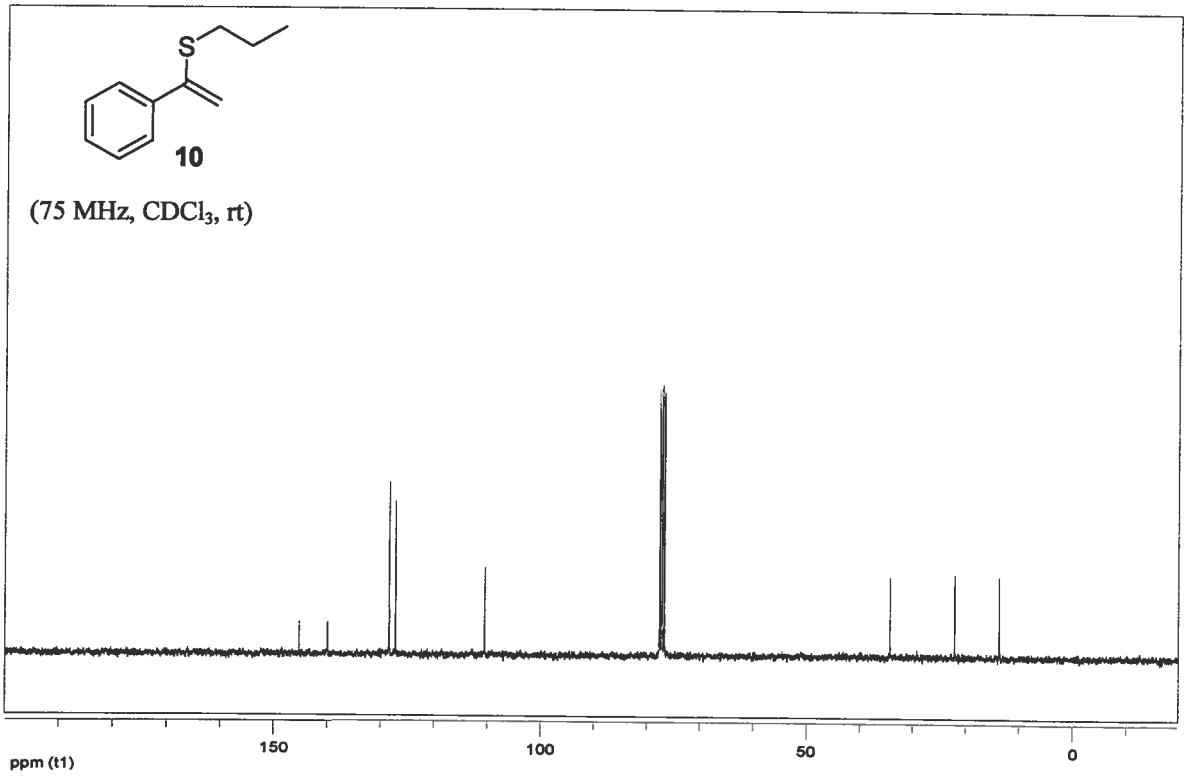
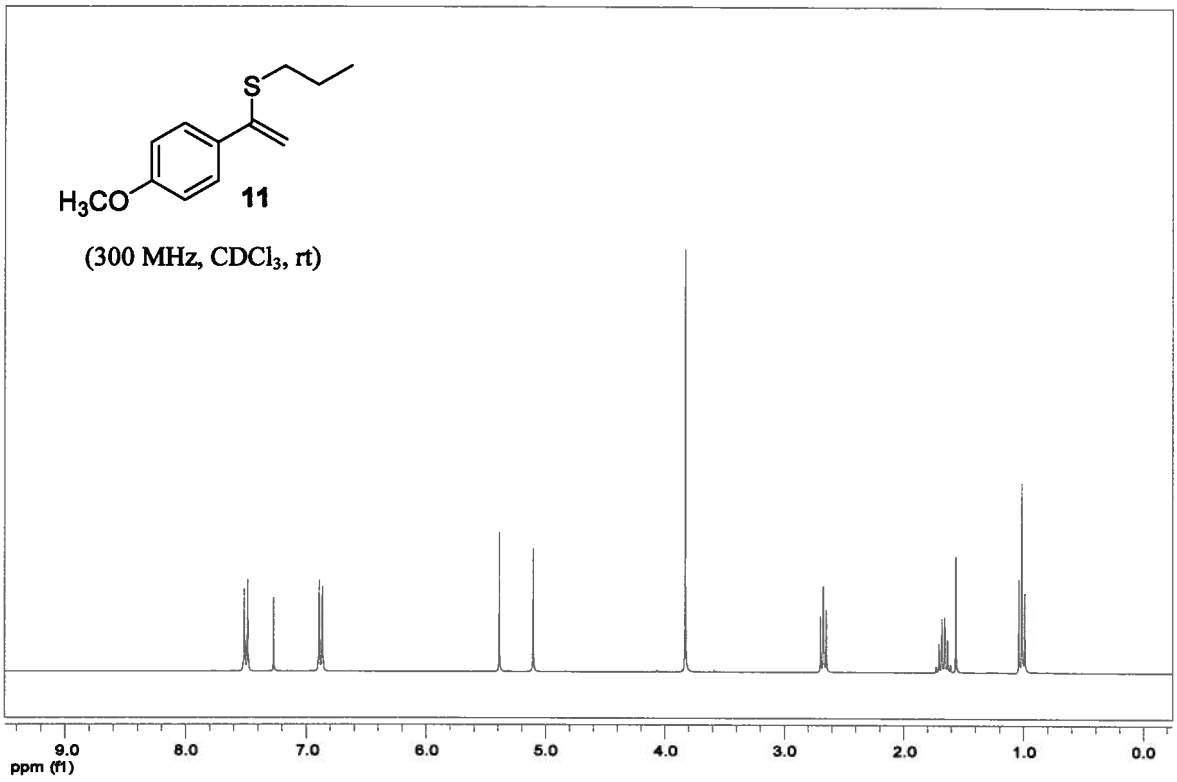
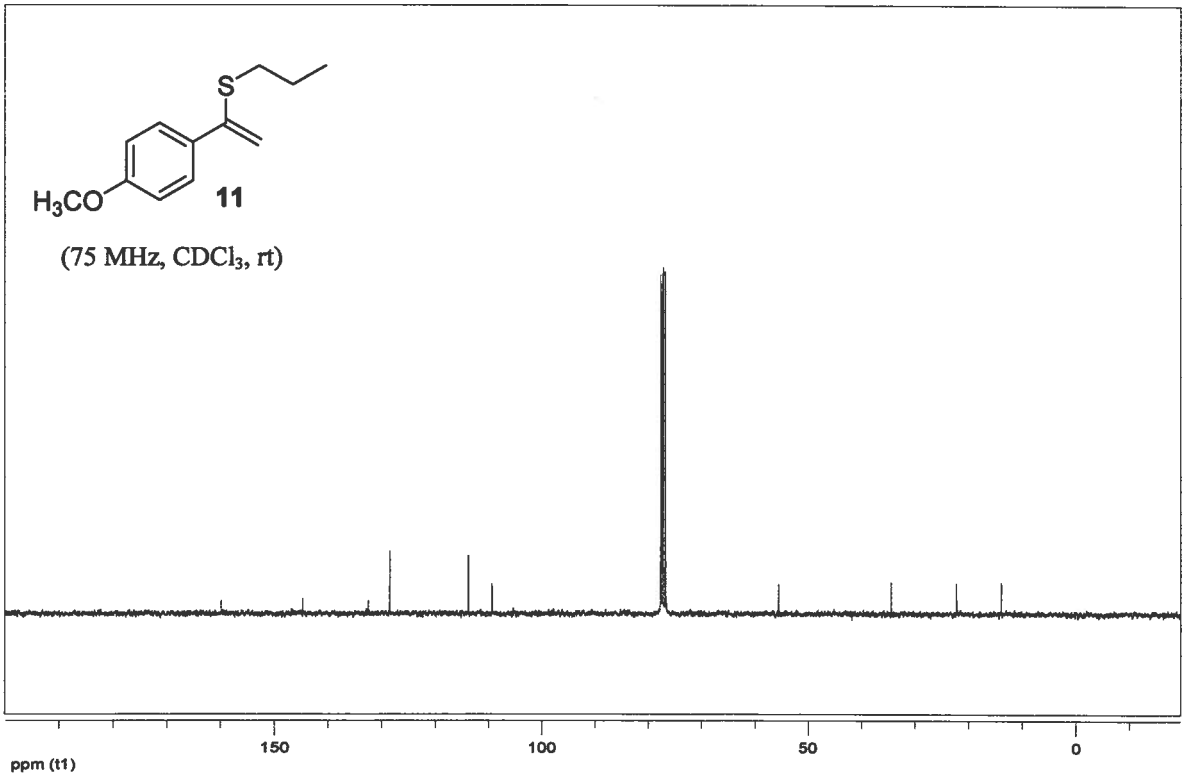
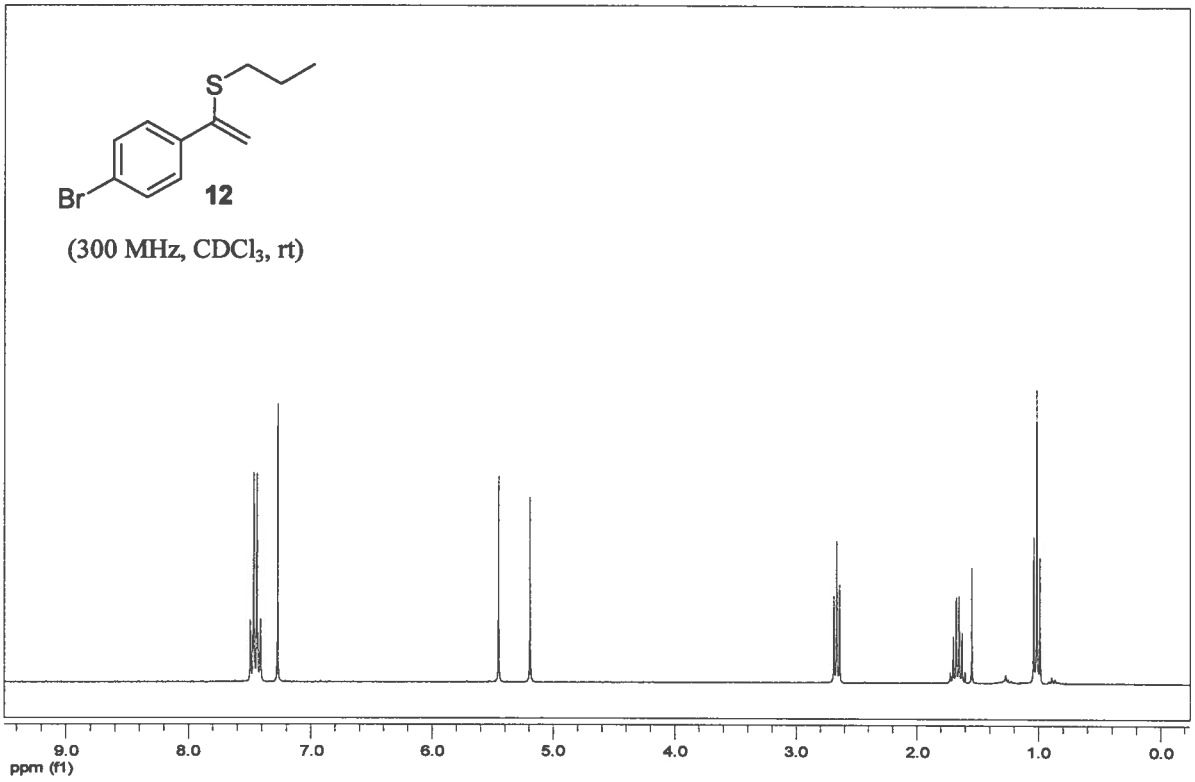
Appendix I: ^{1}H and ^{13}C NMR Spectra for Hydrothiolation Products

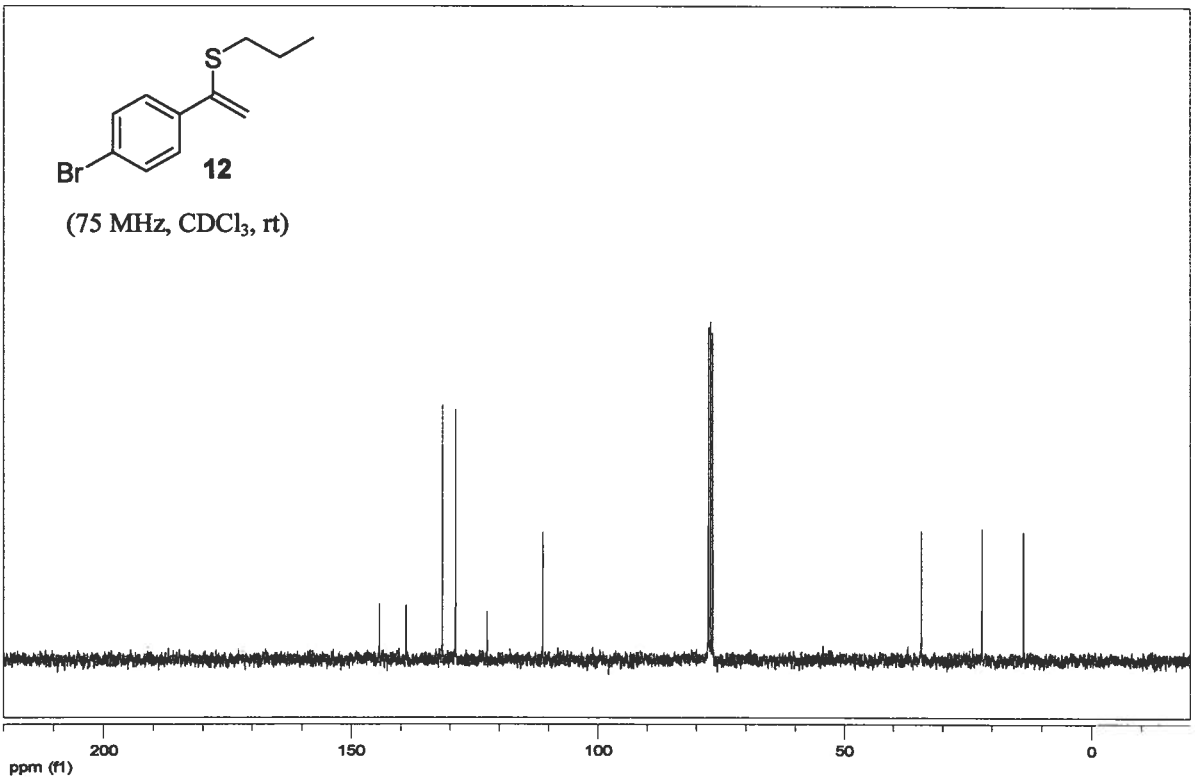


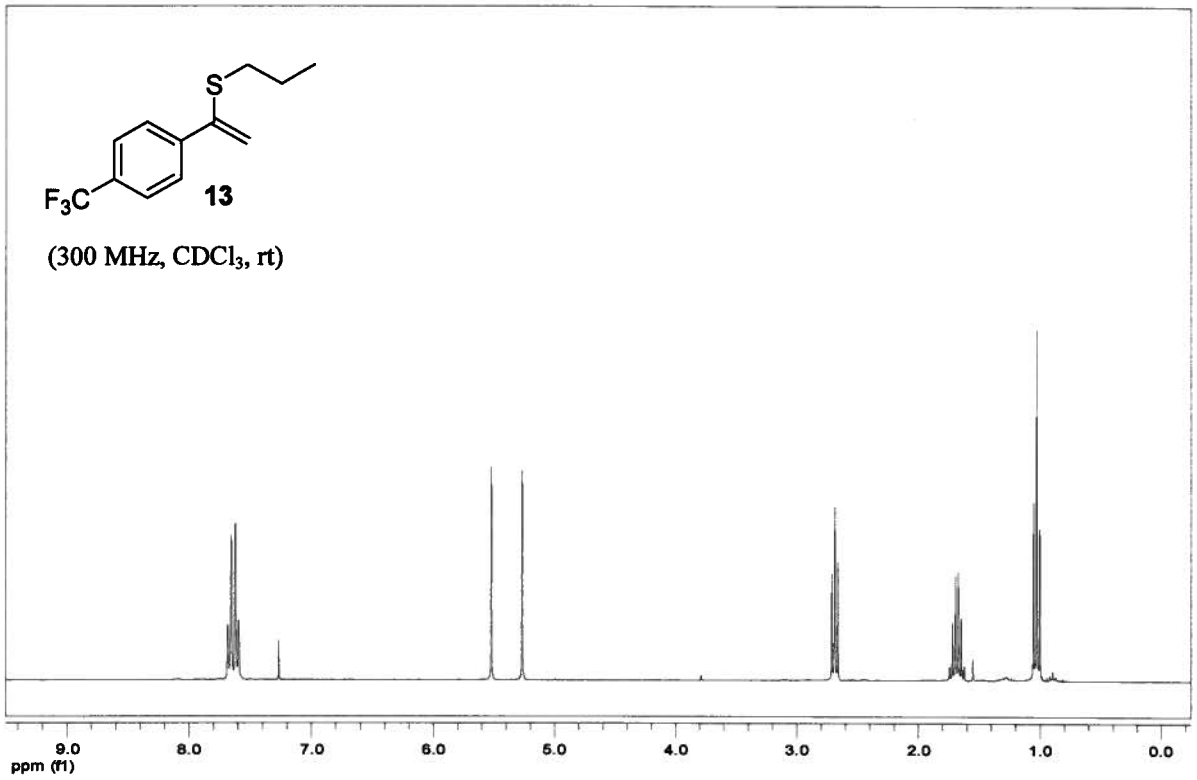


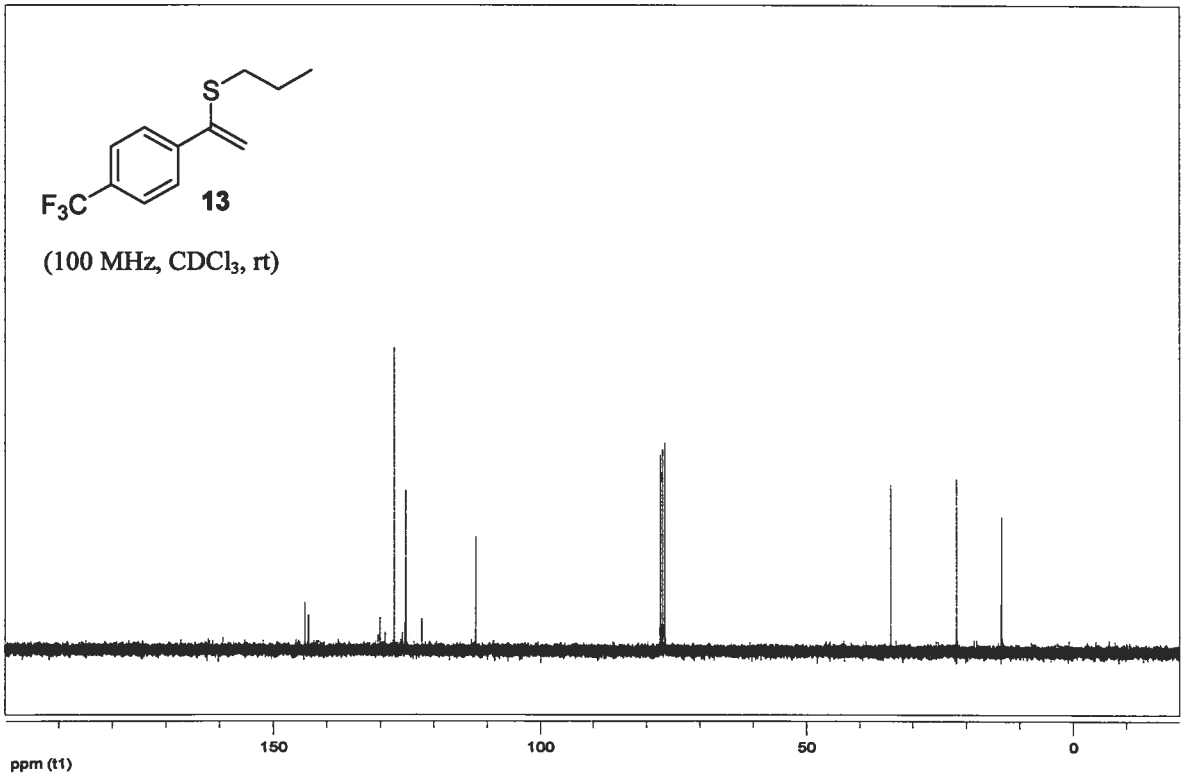

S
H3CO
11
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

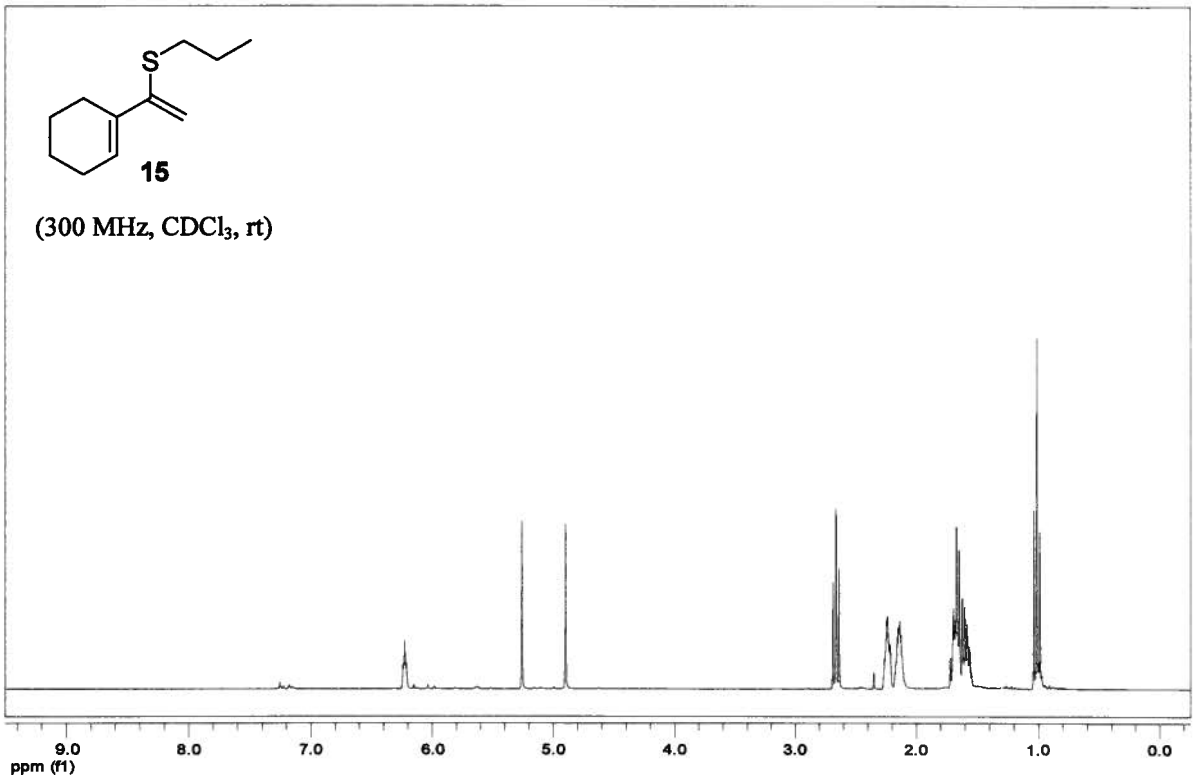

S
H3CO
11
(75 MHz, CDCl3, rt)
150
100
50
0
ppm (t1)

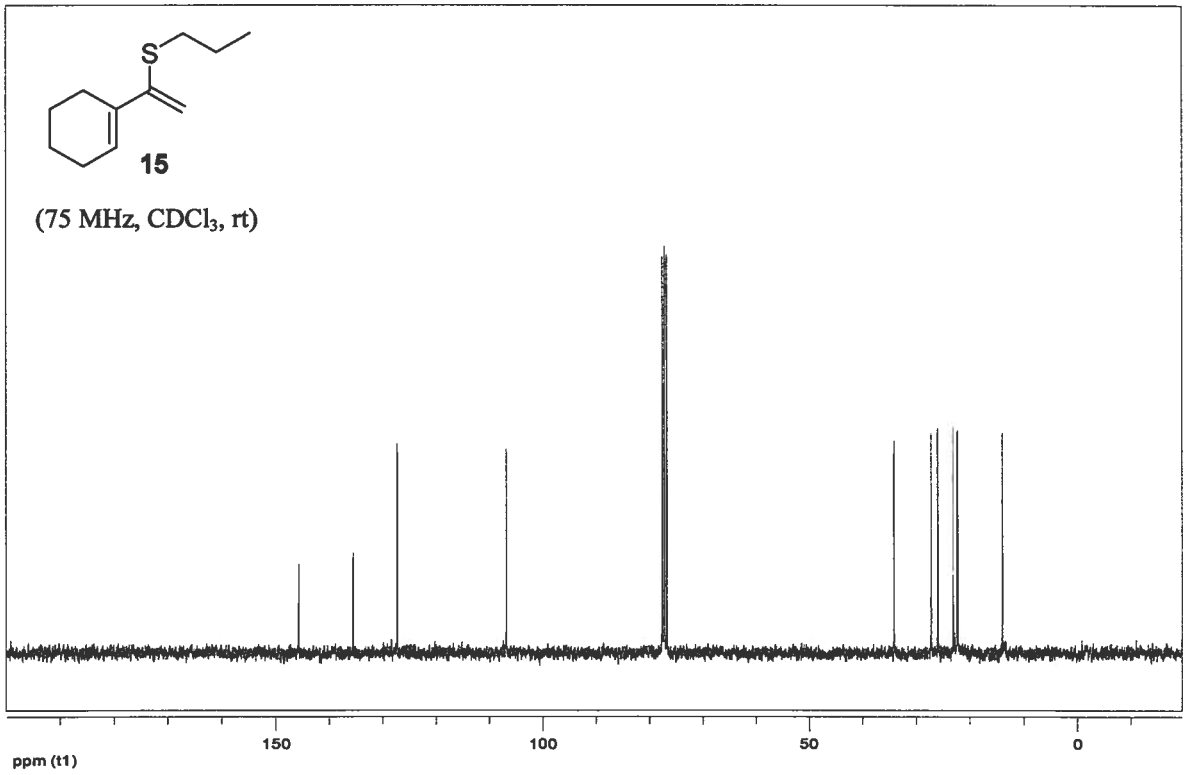

S
Br
12
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

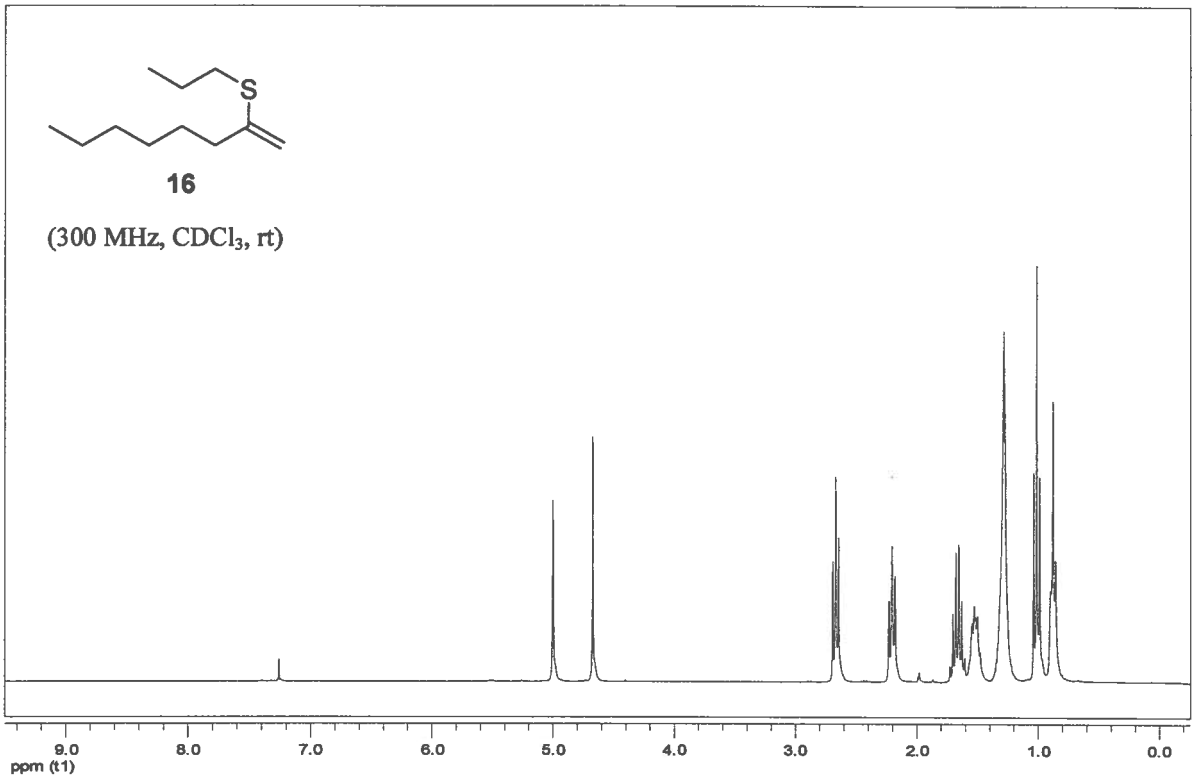

S
Br
12
(75 MHz, CDCl3, rt)
200
150
100
50
0
ppm (f1)

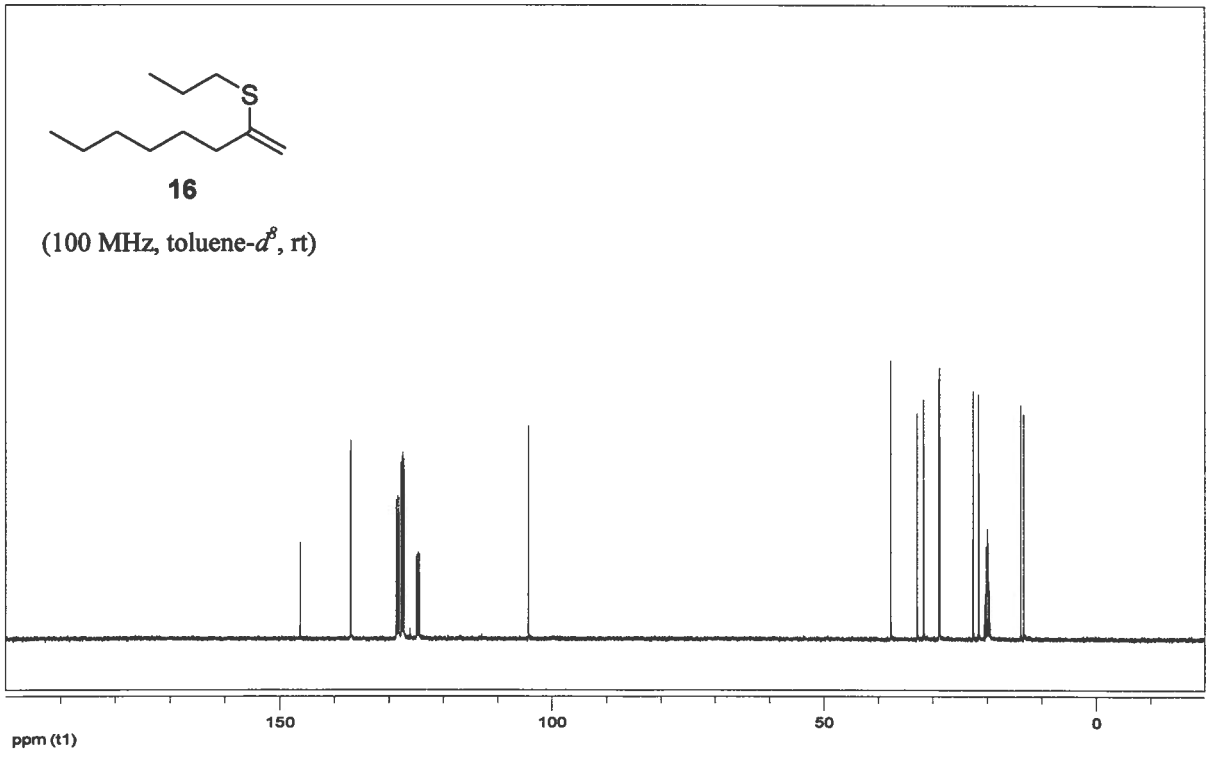

S
F3C
13
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

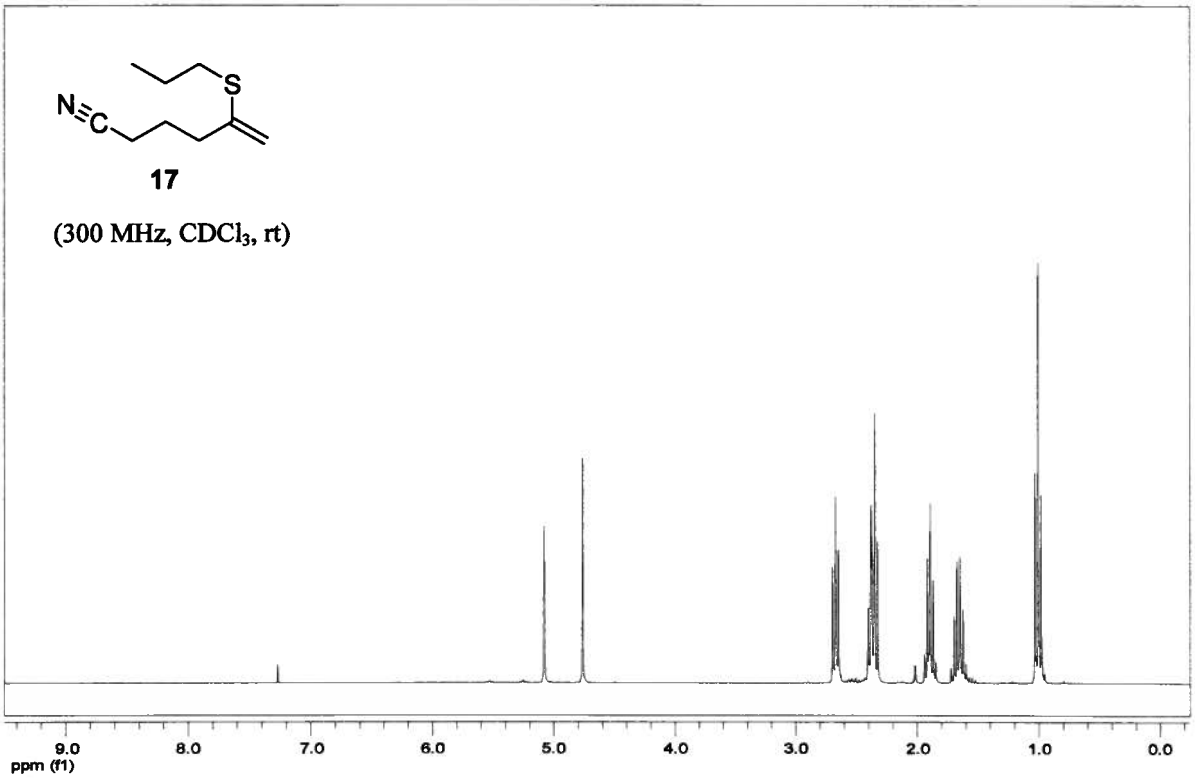

S
F3C
13
(100 MHz, CDCl3, rt)
150
100
50
0
ppm (t1)


S
15
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


S
15
(75 MHz, CDCl3, rt)
150
100
50
0
ppm (t1)

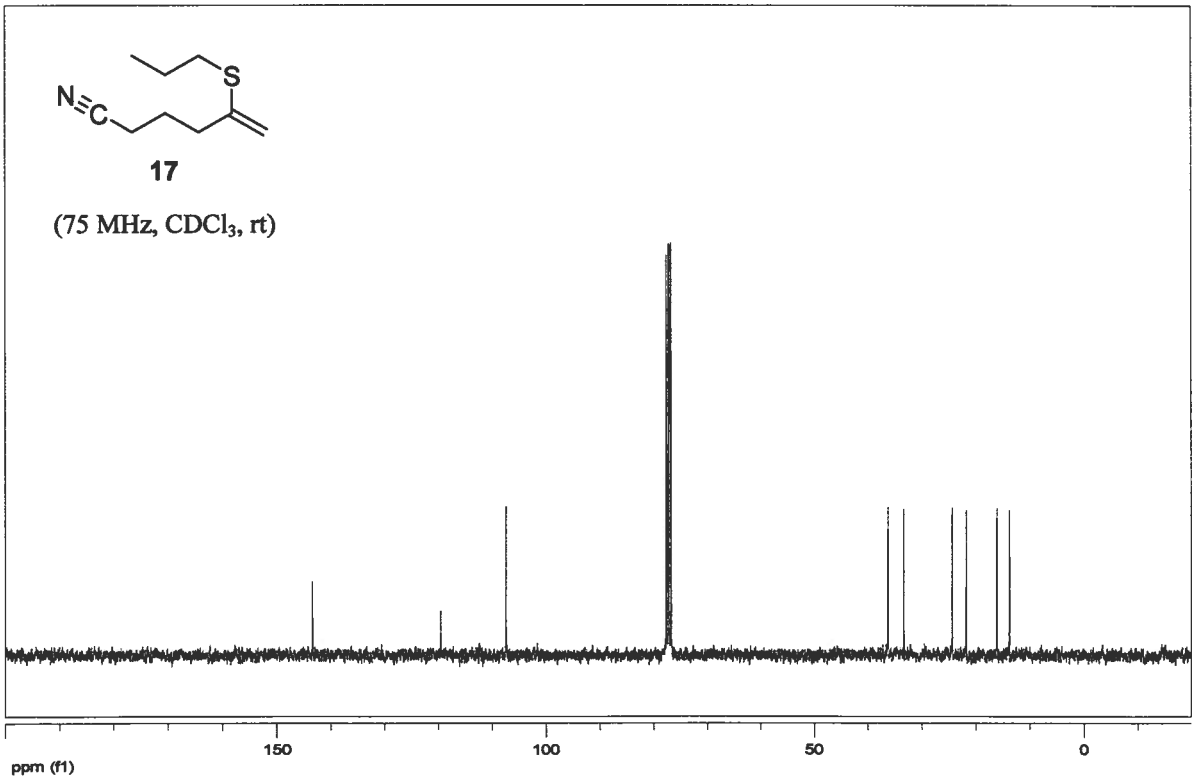

S
16
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


S
16
(100 MHz, toluene-d8, rt)
150
100
50
0
ppm (t1)



17

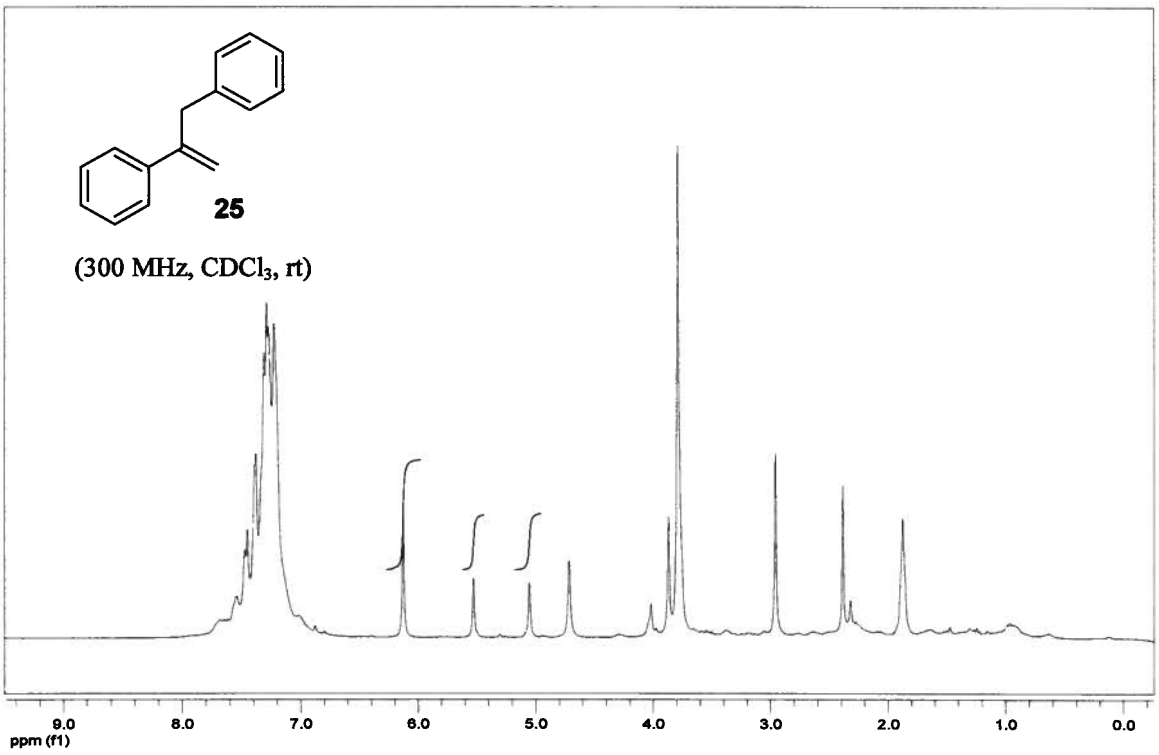
(300 MHz, $CDCl_3$, rt)



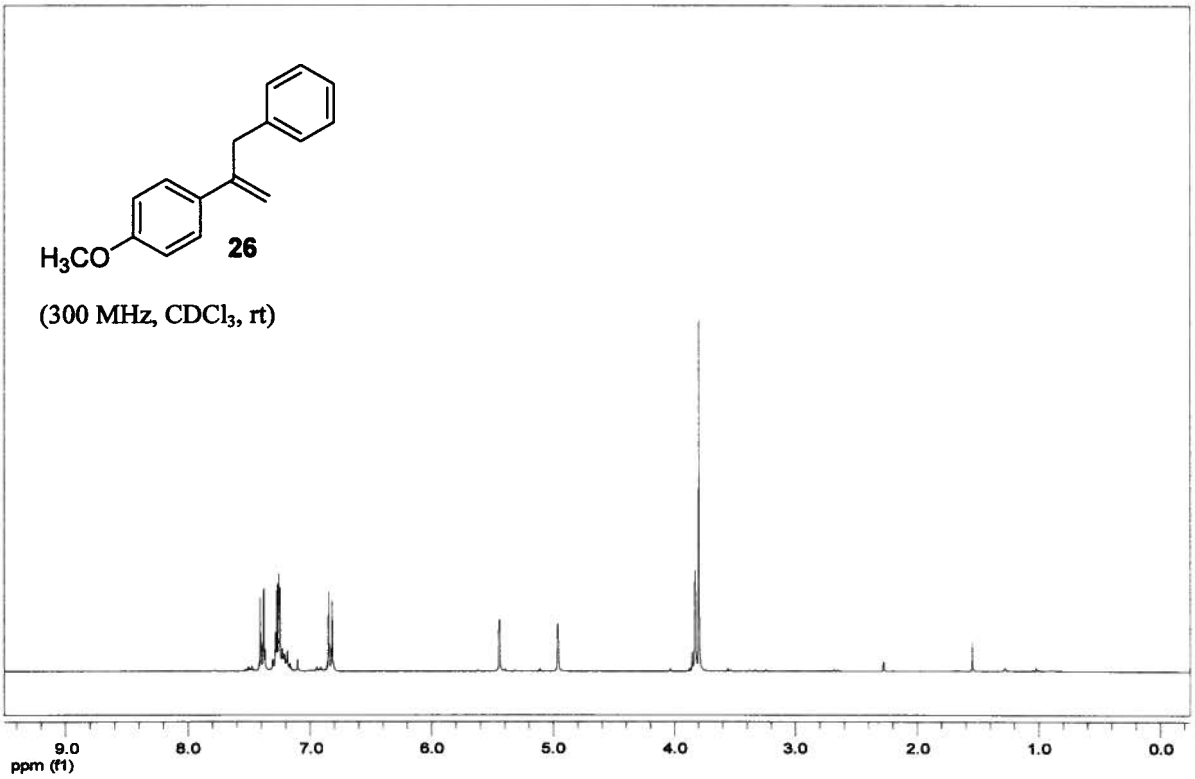
17

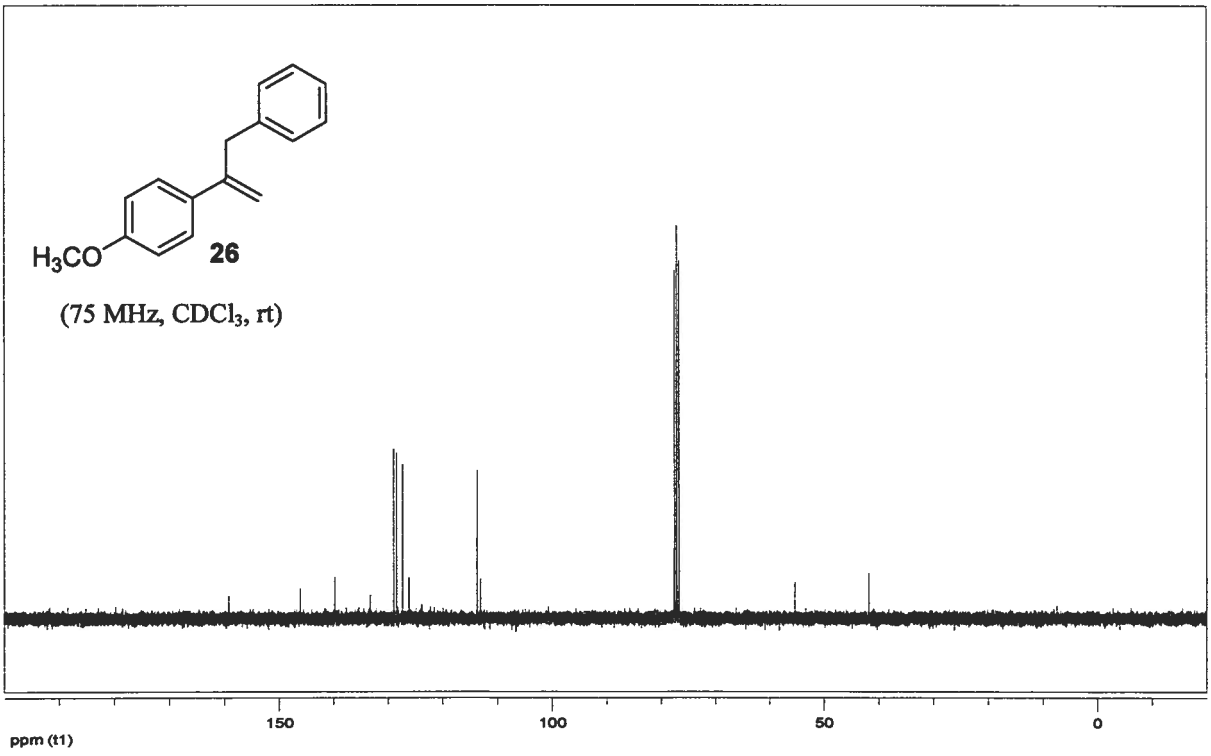
(75 MHz, $CDCl_3$, rt)

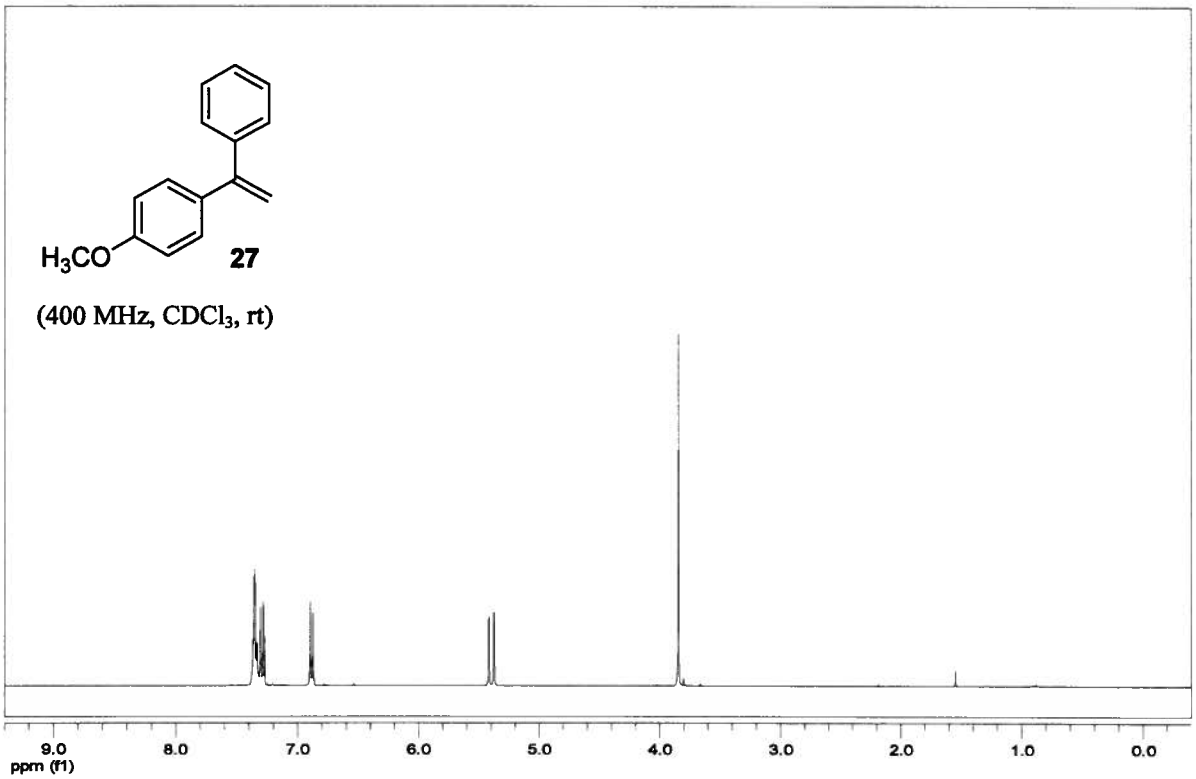
Appendix II: ^{1}H and ^{13}C NMR Spectra for Kumada Cross-Coupling Products

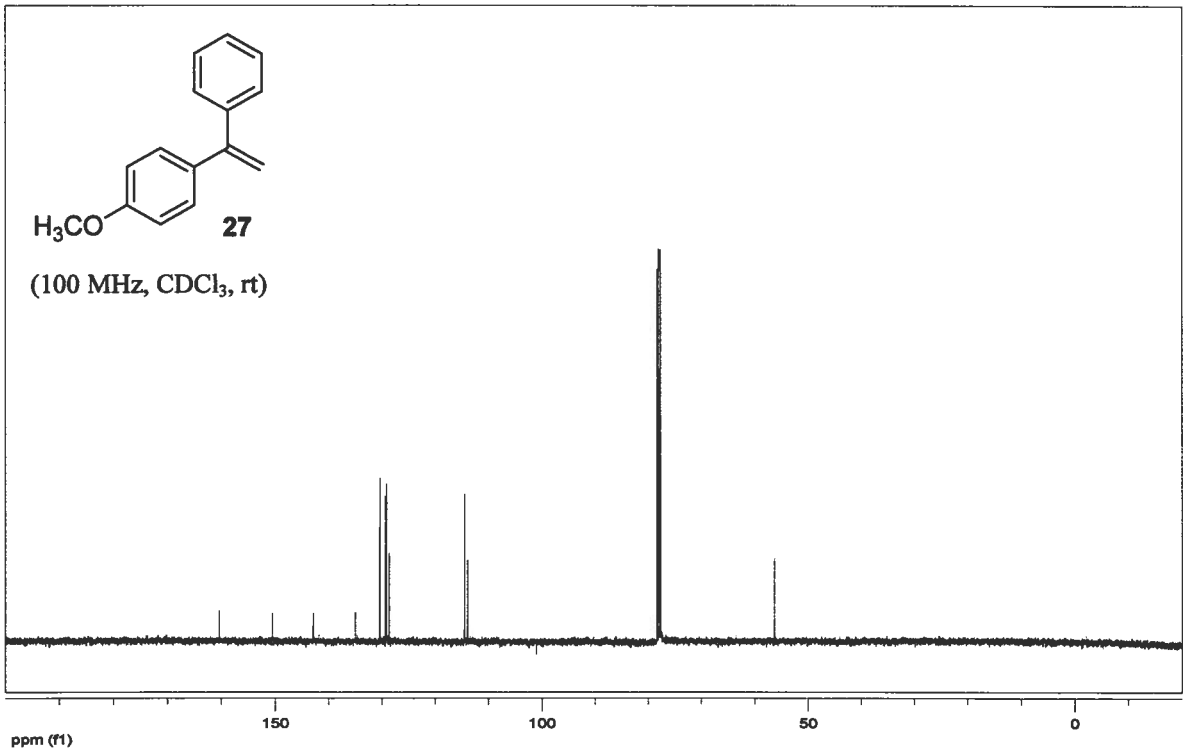


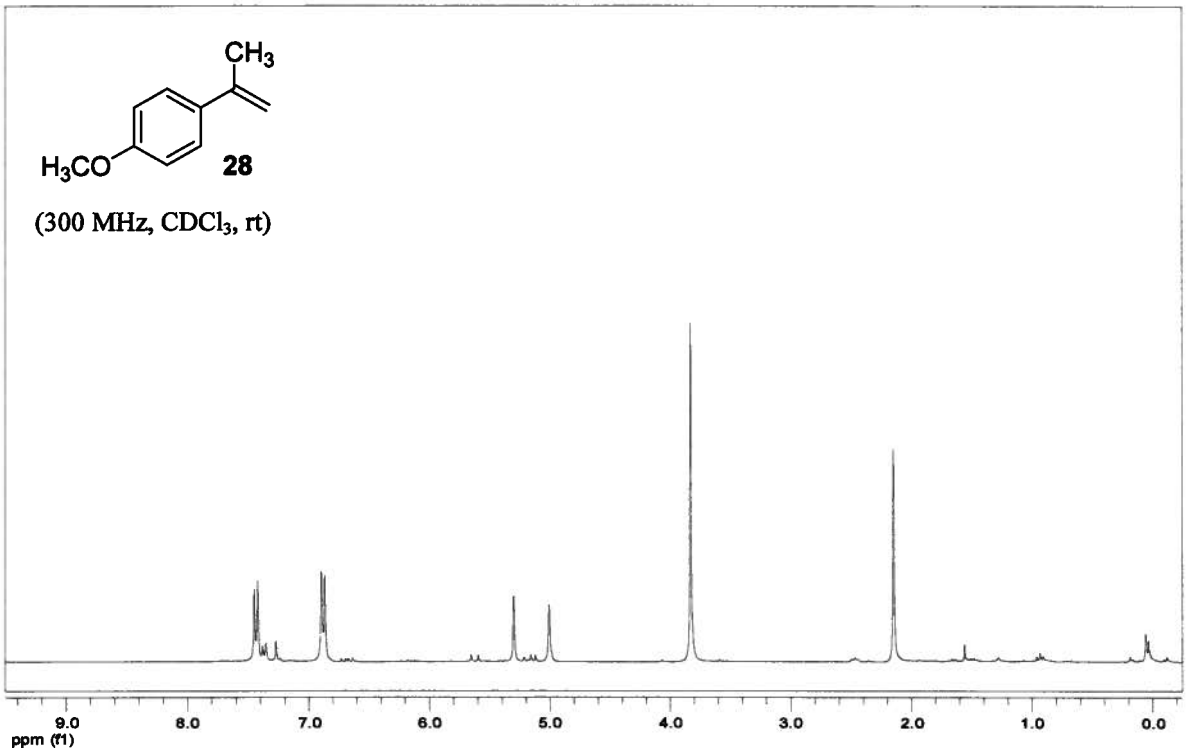
The spectrum above was taken from the crude product and contains the desired cross-coupling product as well as bibenzyl, toluene and tetrahydrofuran. The yield was determined by ^{1}H NMR spectroscopic analysis using 1,3,5-trimethoxybenzene as an internal standard.

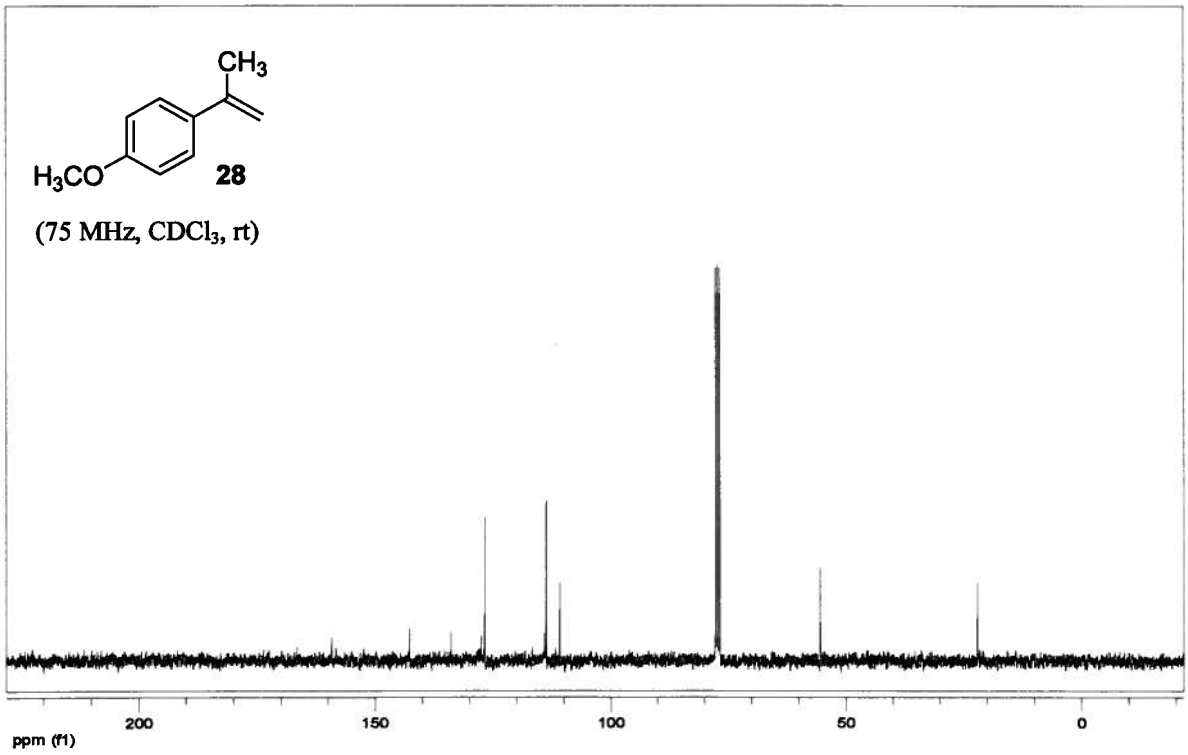

H3CO
26
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

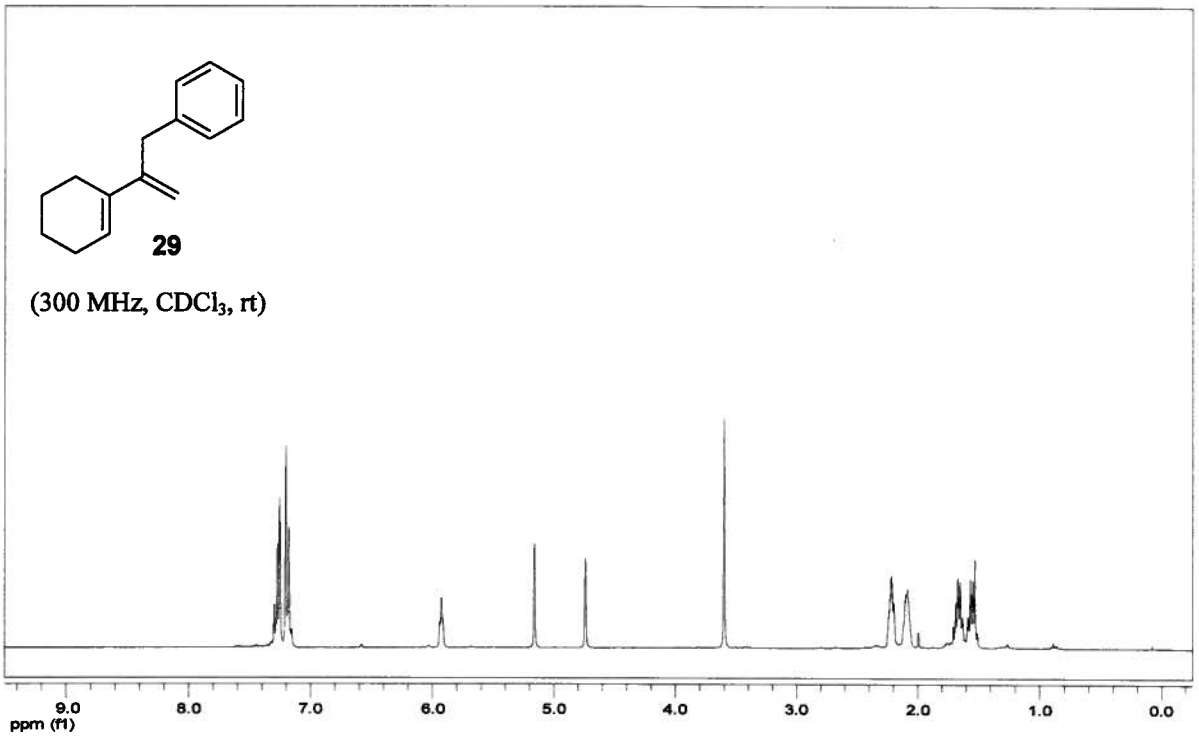

H3CO
26
(75 MHz, CDCl3, rt)
150
100
50
0
ppm (t1)

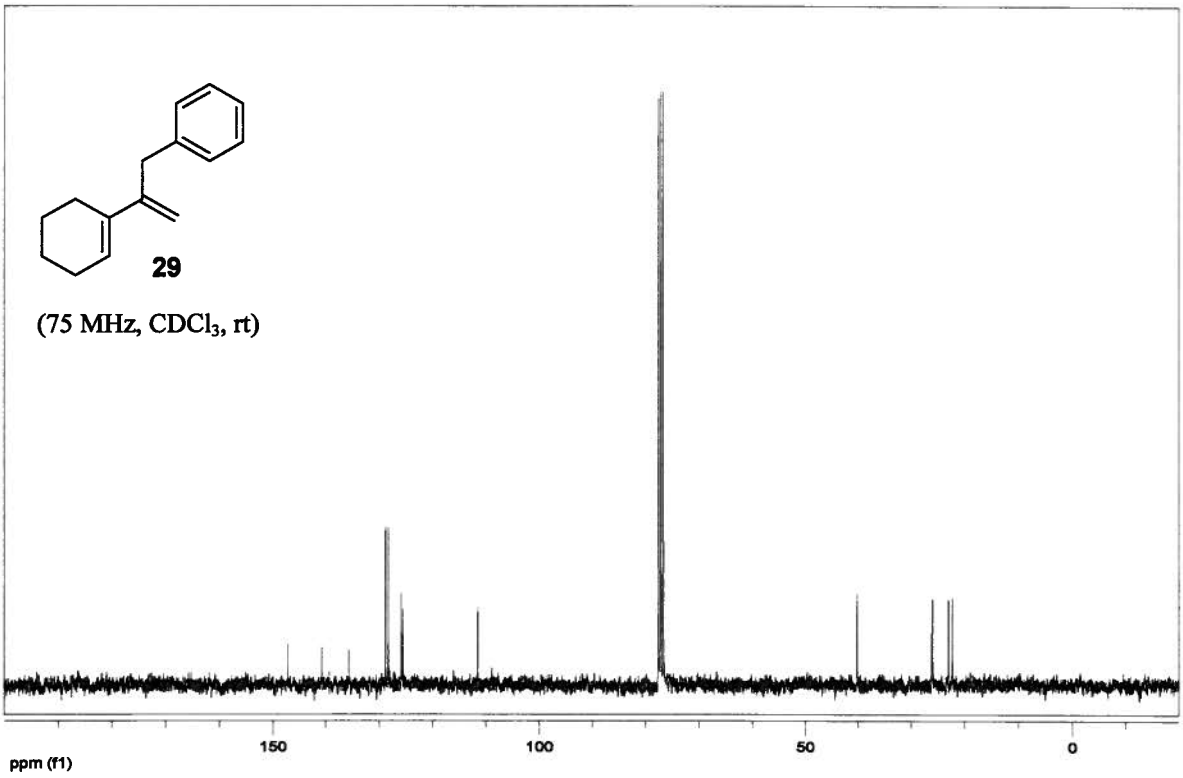

H3CO
27
(400 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

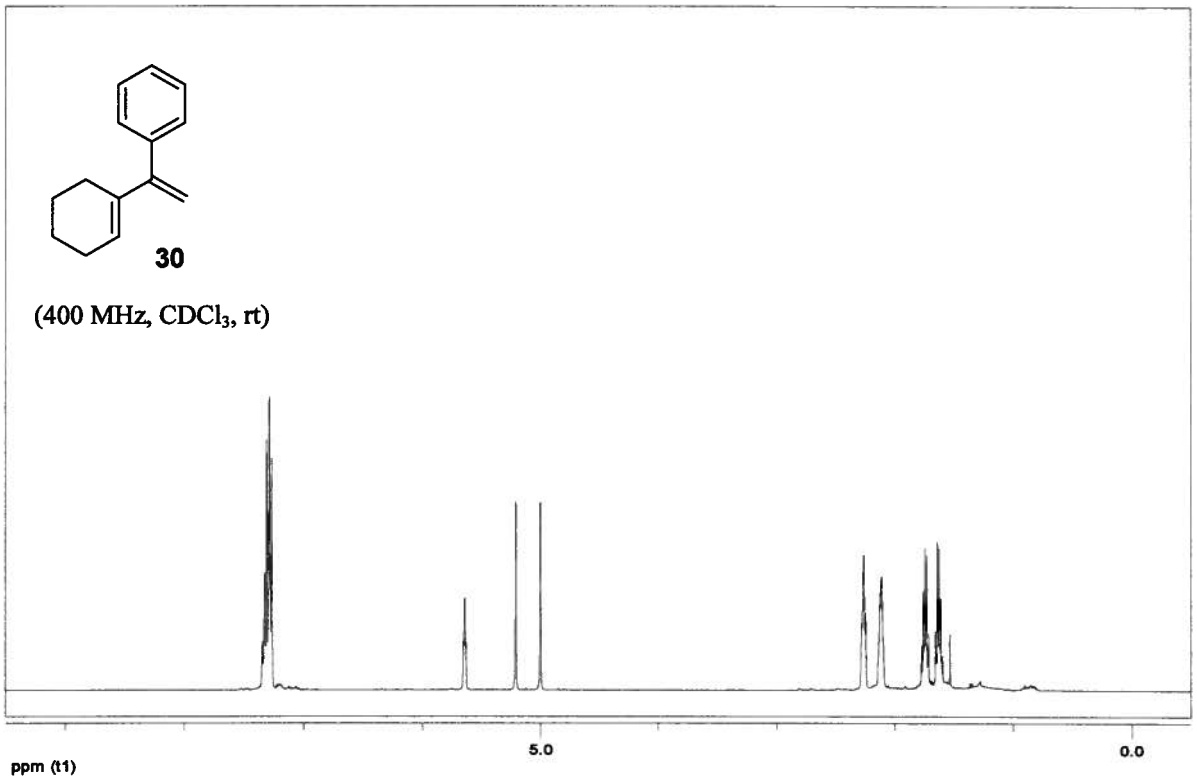

H3CO
27
(100 MHz, CDCl3, rt)
150
100
50
0
ppm (f1)

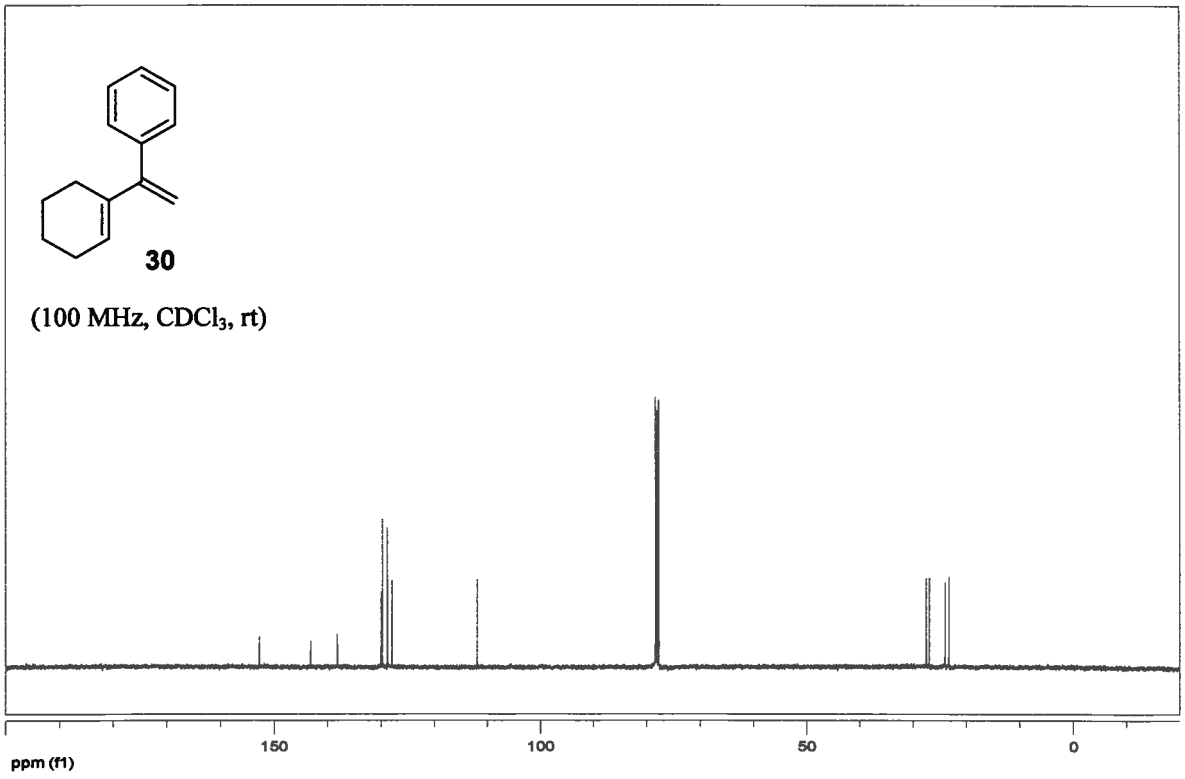

CH3
H3CO
28
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

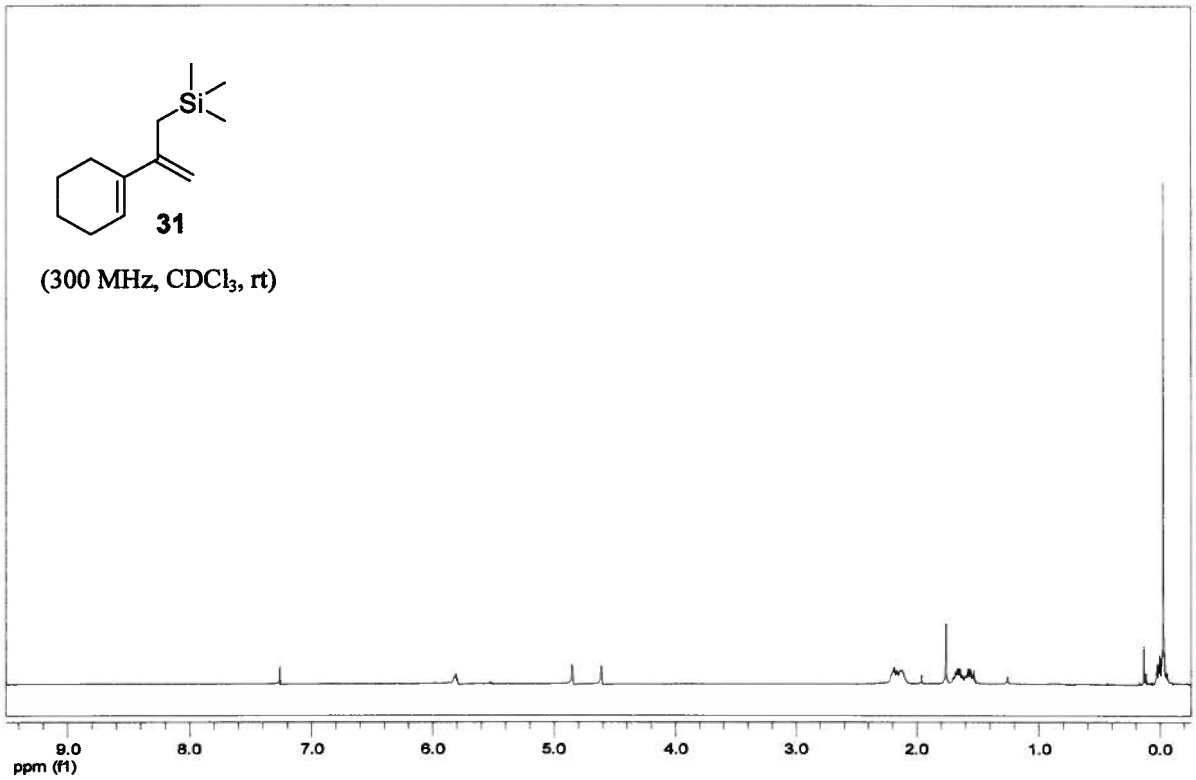

CH3
H3CO
28
(75 MHz, CDCl3, rt)
200
150
100
50
0
ppm (f1)

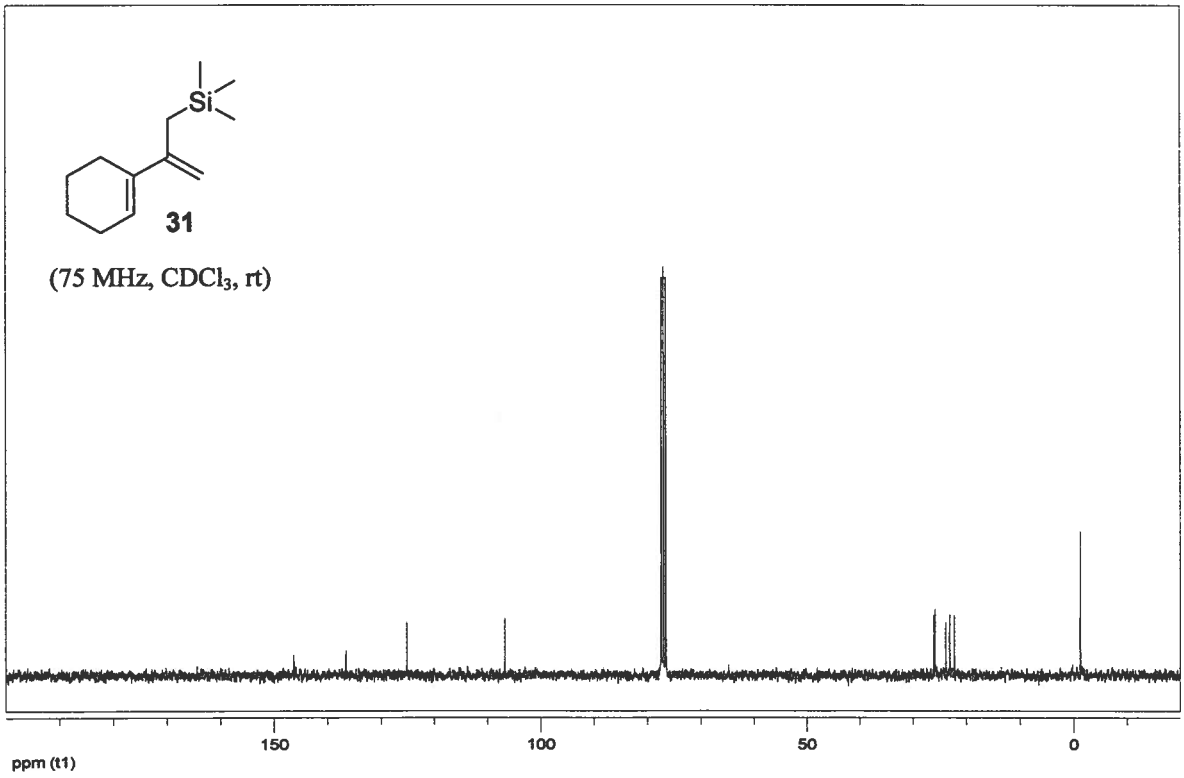

29
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)

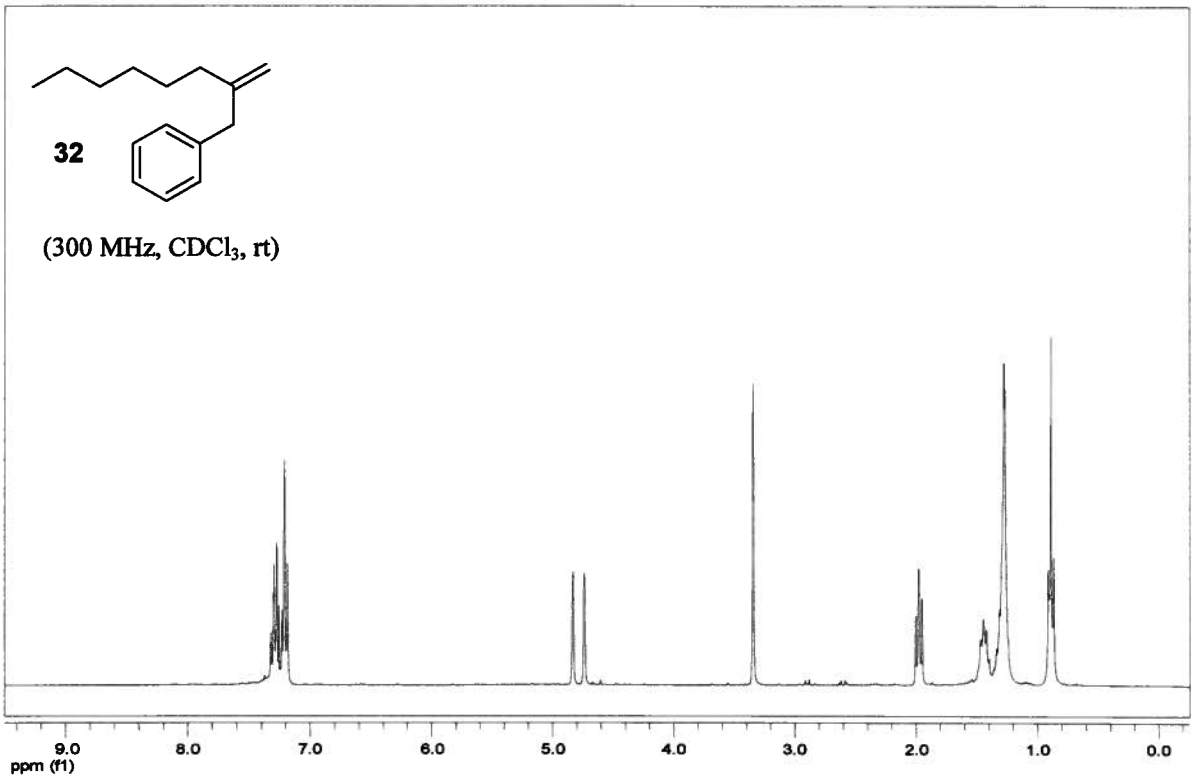

29
(75 MHz, CDCl3, rt)
150
100
50
0
ppm (f1)

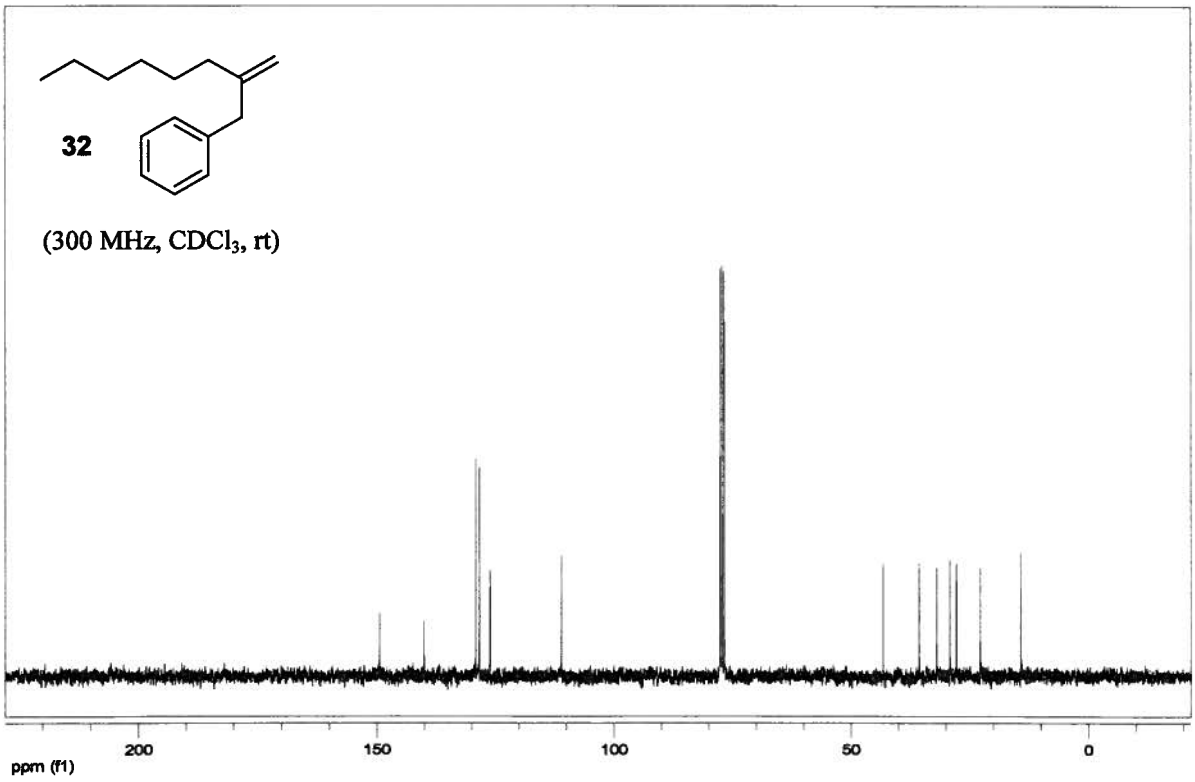

30
(400 MHz, CDCl3, rt)
5.0
0.0
ppm (t1)


30
(100 MHz, CDCl3, rt)
150
100
50
0
ppm (f1)


Si
31
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


Si
31
(75 MHz, CDCl3, rt)
150
100
50
0
ppm (t1)


32
(300 MHz, CDCl3, rt)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (f1)


32
(300 MHz, CDCl3, rt)
200
150
100
50
0
ppm (f1)