A Reactivity and Mechanistic Study of the Sonogashira Coupling and Grignard-Sonogashira Coupling Reactions

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ABSTRACT

A Reactivity and Mechanistic Study of the Sonogashira Coupling and Grignard-Sonogashira Coupling Reactions

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The interest in studying enediyne systems was stimulated by the discovery of anti-cancer agents containing enediyne functionalities, such as esperamicin and dynemicin. These compounds have potential for use as anti-tumour antibiotics, however, they are not sufficiently selective to be used clinically. Many attempts to synthesize analogs of the natural enediynes with improved selectivity and reduced toxicity have been made. A number of synthetic methodologies have been employed toward the synthesis of the analogs, including Stephens-Castro Coupling and Sonogashira Coupling. In this thesis, a reactivity study involving coupling reactions using $Pd(PPh_3)_4$ and a series of electron donating and electron withdrawing substituted aryl halides is presented. The positions of these substituents relative to the coupled alkyne (i.e., *ortho*, *meta*, *para*) were studied and the changes these substituents had on reactivity (i.e., electronic and steric effects) were investigated. All of the substituted alkynyl benzenes were successfully synthesized in all positions and fully characterized. High yields were obtained for both electron withdrawing and electron donating substituents. In competitive reactions electron

withdrawing groups in the *para* position reacted preferentially over electron donating groups. In general, substituents in the *ortho* position decreased the rate of reaction. When the starting halides were converted to Grignard reagents, high yields were obtained for electron donating groups as well as some hindered electron withdrawing groups. Mechanistic studies for the Grignard coupling reaction reveal that a transmetallation reaction occurs, and the same catalytic intermediate that is present in the standard Sonogashira coupling reaction also exists in the modified Grignard coupling process.

ACKNOWLEDGEMENTS

First and foremost I would like to express my extreme gratitude to Dr. Gottardo for her encouragement, guidance and support without which this thesis could not be completed. Her insights and suggestions have been a supreme influence on the outcome of this thesis because without her inspiration this thesis would not have been a success. Secondly, I would like to thank Dr. Spivak for his input on the mechanistic approaches and possibilities regarding the Pd and Pt NMR spectroscopic studies. In addition, special thanks is also deserving of Debbie and Ainsley for their patience and expert assistance with the HPLC and various other techniques. Finally, I would like to express gratitude to all those that I have had the privilege of sharing the lab with over the years for making my experience relaxing and fun.

LIST OF ABBREVIATIONS

CuI	Cuprous Iodide
DNA	Deoxyribonucleic Acid
Et_3N	Triethylamine
EtOAc	Ethyl Acetate
FTIR	Fourier Transform Infrared
GC-MS	Gas Chromatography Mass-Spectrometry
GLC	Gas Liquid Chromatography
HPLC	High Performance Liquid Chromatography
ICP	Inductively Coupled Plasma
IR	Infrared
KI	Potassium Iodide
NCS	Neocarzinostatin
NMR	Nuclear Magnetic Resonance
$Pd(PPh_3)_4$	Tetrakistriphenylphosphine Palladium(0)
PPh_3	Triphenylphosphine
$Pt(PPh_3)_4$	Tetrakistriphenylphosphine Platinum(0)
TEMPO	2,2,6,6-Tetramethyl-1-Piperidinyloxy Free Radical
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl

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CHAPTER ONE

A REVIEW OF ENEDIYNE STRUCTURE AND ACTIVITY

1.1 Introduction

Medical, biological and chemical communities often focus their research on naturally occurring compounds. One class of compounds derived from bacterial sources, the enediynes, have the potential to be used as anticancer agents. Their antitumour activity is due to their selective and irreversible DNA cleaving ability, however, the high toxicity and instability shown by these compounds prevents their use in clinical applications.[1,2] As a consequence, a number of synthetic approaches for the development of enediyne analogs that are more selective and less toxic, yet still retain or even exceed the efficiency of their natural counterparts, have been attempted.[2,3,4,5,6,7,8] The designed analogous enediyne compounds must provide a stable form of the enediyne core that can be activated and deactivated in a controlled manner, as well as being synthetically practical.

1.2 Enediyne Anticancer Agents

Enediyne antitumour antibiotics have a characteristic cyclic structure consisting of a conjugated (Z)-1,5-diyn-3-ene unit embedded within their structural framework.[2,9] There are currently five known classes of enediyne containing natural products, each class having structural similarity to the following five enediyne natural products (Figure 1):[2] calicheamicin, **1**, esperamicin, **2**, dynemicin, **3**, kedarcidin chromophore, **4**, and C-1027 chromophore, **5**. The neocarzinostatin chromophore, **6**, (Figure 2),[2] shows similar reactivity to the enediyne family

once activated, however, it lacks a conjugated enediyne moiety, containing an enyne-cumulene core instead.

In all of the enediyne natural products the enediyne moiety is contained within a nine or ten membered ring.[2] The nine membered rings are commonly associated with an apoprotein through noncovalent interactions which serves to prevent the enediyne from decomposing and facilitates its delivery to the target, DNA. The ten membered rings, on the other hand, are stabilized by molecular components that do not allow the enediyne to function until it is biologically activated.[2,10] The core of these compounds consists of three main functional units: a delivery system which is responsible for the penetration of cellular membranes and intercalation between the minor grooves in DNA, a highly strained diacetylenic ring system, which, once activated, serves as the DNA cleaving device and finally a triggering device that allows the activation of the enediyne toward the Bergman cyclization reaction.[2,9] Such triggers in these molecules result in bioreductions or isomerizations that are activated by light,[11] base,[12] metal ions,[13] or nucleophiles.[1, 14] These three units together represent the molecular architecture responsible for the remarkable activity and fascinating mode of action associated with enediynes.

1.2.1 Mode of Action

One of the most intriguing features of enediyne antibiotics is that their reactivity is masked until they are activated. It is for this reason that enediynes can be considered prodrugs which, by definition, have to undergo an activation step before they can unfold their biological activity.[2,5,15] This feature is essential in order to minimize cytotoxic effects during their distribution within the body.

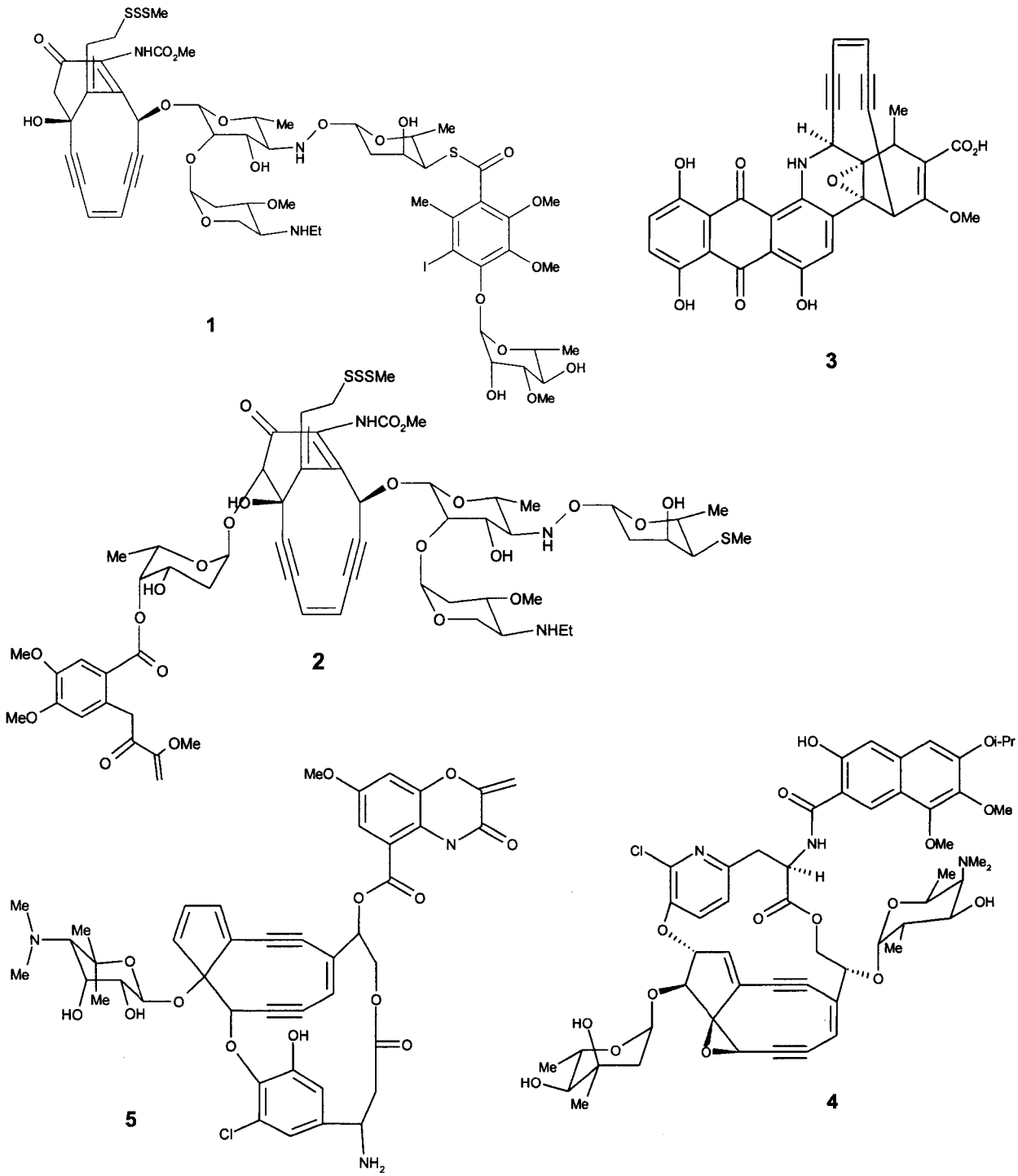


Figure 1[2]: Structures of enediyne natural products.

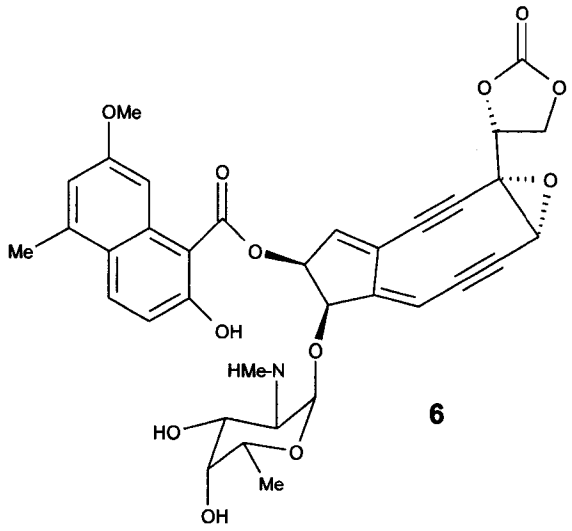


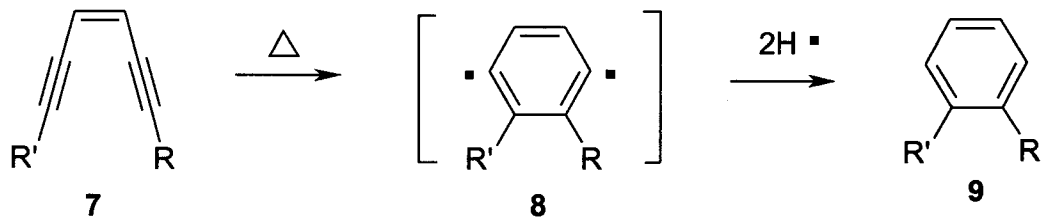
Figure 2[2]: Structure of the neocarzinostatin chromophore.

The irreversible cleavage of duplex DNA occurs in stages.[2,9,10] The first involves the recognition and binding of the enediyne to the minor groove of DNA through a structural feature that is bonded or complexed to it. Next, through a cascade of reactions, the enediyne becomes activated. Once the enediyne is activated, Bergman cyclization can occur (Scheme 1).[2,16,17,18,19] This process generates a highly reactive 1,4-benzenoid biradical, which strips hydrogen atoms from the sugar-phosphate backbone of the DNA causing permanent damage to the double helix.[20,21,22]

Bergman cycloaromatization is the key process imparting the DNA damage and has been the subject of considerable interest in recent years. Remarkably, in the early 1970's, Bergman designed, observed and studied this cycloaromatization reaction approximately fifteen years prior to the discovery of enediyne antibiotics.[18] Bergman is also credited with being the first to trap

and characterize the *para*-benzyne biradical intermediate.

Scheme 1[2]



It is through the biradical intermediate, **8**, that all of the members of the enediyne family are able to exhibit potent antitumour activity, however, reactivity of enediynes in the Bergman reaction can be affected by a number of factors. The distance between the two terminal acetylenic carbon atoms must be less than 3.2 Å in order for cyclization to occur.[2,23,24,25] Also the difference in strain energy between the enediyne and the transition state influences the rate of cyclization such that less strained enediyne systems cyclize faster. The concentration of the trapping agent is important as are substituent effects. Electronically, donating groups on the terminal acetylenic carbons have been shown to decrease the reactivity of enediynes, while withdrawing groups demonstrate the opposite effect.[2,3,26] Sterically, large groups on the terminal acetylenic carbons increase the distance between them leading to a decrease in reactivity toward cyclization.[2]

1.2.2 Calicheamicin/Esperamicin

Calicheamicin γ_1, **1**, and Esperamicin A_2, **2**, were the first enediyne natural products to be identified. Calicheamicin γ_1 has the greatest cytotoxicity among the natural enediynes and shares, with the esperamicin family, an intriguing mode of binding to the minor groove of DNA.[2,9,27] Both families contain two distinct structural regions that help provide the biological activity. The larger of the two regions consists of a carbohydrate residue comprising four monosaccharide units and one hexasubstituted benzene ring that are joined through a series of glycosidic, thioester, and hydroxylamine linkages. The second region, the aglycon, contains a compact, highly functionalised bicyclo[7.3.1]tridecenediyne core which houses a strained enediyne unit within a bridging ten-membered ring. The aryltetrasaccharide serves to deliver the drug to the target, double-stranded DNA. Calicheamicins bind predominantly in sequences such as TCCT or TTTT through hydrophobic interactions, while the esperamicins display less sequence specificity for causing single strand cuts between the bases T>C>A>G.[2,28] In addition, calicheamicins and esperamicins share a similar trigger within the aglycon moiety, an allylic trisulfide. A cascade of reactions occurs upon nucleophilic attack of the trisulfide, which results in the removal of the blocking device and triggers Bergman cyclization.[2,3,9]

1.2.3 Dynemicin

The dynemicins are a unique family of enediynes in that they are the only class of enediynes to be pigmented. They are violet in the solid state and deep blue in solution.[2] The dynemicins are also the only series to lack a sugar residue and contain a pentacyclic, anthraquinone based structure instead.[2,4,7,9] The anthraquinone region functions as the

intercalating agent, allowing the ten membered bridging enediyne moiety to be brought into the minor groove of DNA. Once bound, dynemicins are activated through a bioreduction of the quinone ring and a rearrangement to the quinone methide. The electron rich aromatic system simultaneously assists in the opening of the epoxide ring, blocking device, leading to a reactive intermediate that is able to undergo Bergman cyclization.[2,4,9] In turn, the duplex DNA is cleaved by both single and double stranded cuts with preference given to the 3' side of purine bases, specifically G and to a lesser extent A.[2,7]

1.2.4 Kedarcidin Chromophore

This enediyne natural product, **4**, is considered a chromoprotein consisting of a water soluble apoprotein and a highly unstable enediyne containing chromophore.[2,22] The enediyne unit is contained within a highly strained nine-membered ring, which is locked by an allylic epoxide that forms part of the fused bicyclic system. The DNA damaging properties reside principally in the chromophore, resulting in highly sequence specific single stranded cuts preferably between TCCT sites similar to the calicheamicins.[2]

1.2.5 C-1027 Chromophore

C-1027, **5**, consists of a carrier apoprotein containing 110 amino acids and a labile enediyne chromophore.[2,9,29] The apoprotein acts as a specific carrier to protect and transport the chromophore. Its most striking characteristic is the fact that the DNA cleavage mechanism proceeds in the absence of an activating agent, in contrast to other enediynes, and thus cleaves DNA through a non-bioreductive process. Instead, the reactive enediyne chromophore is released

from the apoprotein when it comes into contact with the target DNA through its benzoxazolinate and amino sugar moieties. In this protein free state, C-1027 is the most labile enediyne among all of the families of naturally occurring compounds. The constrained nine membered ring may contribute to lowering the barrier for interconversion between enediyne and biradical forms. The mechanism by which C-1027 chromophore remains inactive when associated to the apoprotein, but becomes activated when bound to DNA, is correlated to the structural changes and the activity of the chromophore itself. The free chromophore released from the apoprotein decreases in stability and is then converted to a reactive form due to removal of the conformational constraints of the apoprotein. By binding to DNA, the chromophore cyclizes and exposes the biradical to the DNA minor groove, whereupon simultaneous hydrogen abstraction occurs at specific TAT and AGA sites.

1.2.6 Neocarzinostatin Chromophore

Since the neocarzinostatin (NCS) chromophore, **6**, has an enyne-cumulene core instead of an enediyne core its mode of action is slightly different than the rest of the enediyne family. This compound consists of a heat, light and base labile chromophore bound to a 113 amino acid apoprotein with a naphthoate moiety that is essential for binding to DNA.[2,9,30] The biological activity of NCS resides in the chromophore while the apoprotein serves as a transporter and stabilizes the chemically sensitive chromophore. The apoprotein binds tightly and specifically to NCS and delivers the active chromophore between the base pairs via the naphthoate side chain.[31] DNA damage results primarily from single stranded DNA cuts at the A and T residues 80% of the time and proceeds via an oxygen free pathway.[22] It is usually activated by thiol attack on the

epoxide causing the ring to open prior to the rearrangement of the core, to form a biradical. This biradical acts in a similar manner to the biradical formed by the Bergman cyclization and abstracts hydrogens from the sugar-phosphate backbone to which it is bound, leading to strand cleavage and cell death.

1.2.7 Enediyne Analogs

Enediyne antibiotics are very unique in their biological function and mode of action. However, they are also too toxic and unstable to be applied clinically.[2] This unfortunate drawback has led researchers to design and synthesize enediyne analogs that display maximum biological activity while minimizing molecular complexity.[2,9] A number of research groups have focussed on improving the design of enediyne analogs in terms of binding capabilities, trigger mechanisms and potency in such a way that makes them more suitable for clinical use.[2,3,7,9] Ideally the analogs should exhibit structural simplicity so that they are relatively easy to synthesize. They should also be chemically stable under neutral conditions, but must also undergo cyclization once suitably activated. Another desirable strategy is to attach appropriate functionality to the enediyne system to achieve targeted delivery, as well as activation under biological conditions. Various studies have shown that structurally simplified analogs of natural enediynes can exhibit promising DNA cleaving ability.[4,7,9] The syntheses of the enediyne moieties have been accomplished either through elimination reactions including the generation of a double bond with the ethynyl groups already present, or through coupling reactions in which the triple bonds are connected to an already existing, typically halogenated, olefin.[32] These, as well as other methods, have been studied and employed in the preparation of enediynes, however, the

most common procedure for the construction of enediyne species is through a palladium-catalysed coupling reaction.

1.2.8 Synthesis of Enediynes

When designing and synthesizing a complex molecule, such as an enediyne analog, careful consideration to the reactions involved in the assembly of the molecule is important. One of the most common methods for the preparation of enediynes is the palladium cross-coupling reaction between a dihaloalkene and an acetylene, also known as the Sonogashira coupling.[33] This thesis investigates Pd cross-coupling reactions. In Chapter two of this thesis, a reactivity study of the palladium cross-coupling reaction is presented. In this section the reactivity at the site of carbon-carbon coupling between the halogenated carbon of the alkene and the acetylenic carbon is examined along with the influences different aryl halides, alkynes and catalyst systems have on coupling. Chapter three summarizes a reactivity study involving a different coupling procedure that is used to synthesize enynes, namely the Grignard-Sonogashira coupling. Finally, mechanistic studies of the Grignard-Sonogashira coupling are outlined in Chapter four.

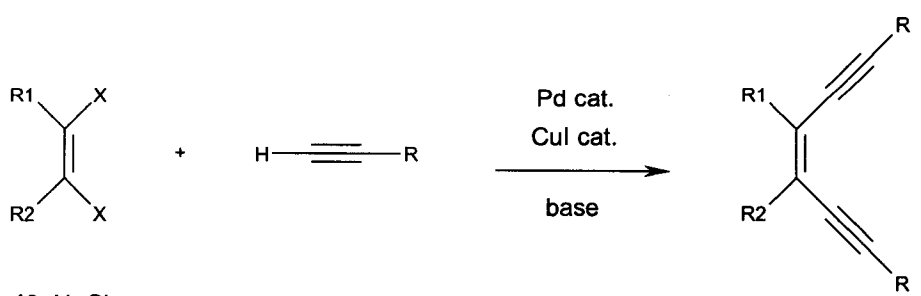
CHAPTER TWO

REACTIVITY STUDY INVOLVING THE PALLADIUM CROSS-COUPLING REACTION

2.1 Palladium Catalysed Coupling Reactions

In order to successfully synthesize a clinically viable analog of the enediyne natural products, a reliable method is needed to construct the enediyne core. To achieve this it is necessary to consider the various procedures for carbon-carbon coupling. A number of methods have been presented in the literature for carbon-carbon coupling, and many of these methods include the use of a metal catalyst.[32,34,35,36,37] Coupling reactions using nickel as the catalyst have been employed frequently,[32] however, a review of the literature indicates that most synthetic approaches to the assembly of enediyne moieties have used palladium-mediated coupling reactions between sp and sp^2 carbon centres. More specifically, reactions of haloalkenes with terminal acetylenes provide an efficient synthesis of the highly reactive core. A significant portion of the recent developments in this field have involved improvements or modifications of the versatile palladium-catalysed cross-coupling reaction (Scheme 2).[2]

Scheme 2[2]



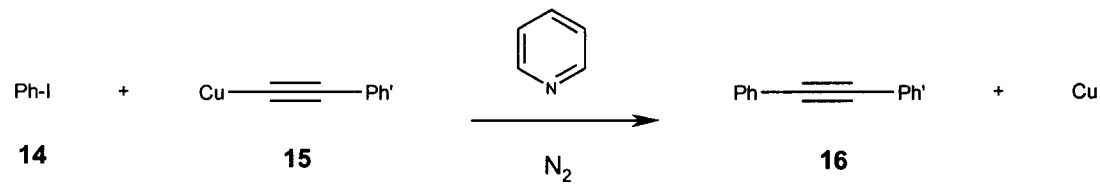
10; X=Cl
11; X=Br
12; X=I

13

2.1.1 Stephens-Castro Coupling

Stephens and Castro were the first to investigate the cross-coupling reaction in 1963.[35] Their research focussed on the formation of enynes by coupling cuprous acetylides with aryl halides in pyridine (Scheme 3).[35]

Scheme 3[35]



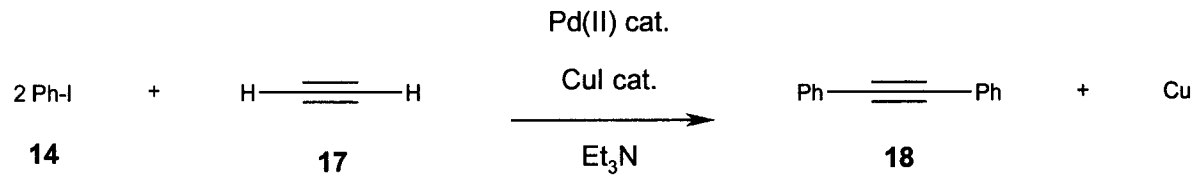
They have also studied the ease of reaction of *para*-substituted iodobenzenes with cuprous phenyl acetylide and found that *p*-NO_2 reacts better than *p*-H which reacts better than *p*-CH_3O.[35] A similar order of reactivity has been observed for the halogen exchange brought about by the action of CuI on *para*-substituted aryl halides. These reactions were also shown to work for alkenyl halides only if the leaving group (the halogen) is bonded to an sp^2 hybridized carbon atom. The iodide was the easiest to displace followed by the bromide and then the chloride with no displacement of the fluoride. Although this reaction worked to produce the desired product in high yields, it was not without major disadvantages. The violent reactivity of the cuprous acetylides and the extremely vigorous reaction conditions required to force the reactions to

completion allowed the possibility of improvements in the reaction conditions and thus, laid the ground work for the development of the Sonogashira Coupling method.[33]

2.1.2 Sonogashira Coupling Procedure

Sonogashira acknowledged the problems associated with the Stephens-Castro procedure and developed a modified version in which he generates the cuprous acetylides in situ, allowing for milder conditions and procedural simplicity. He also incorporated the use of a readily available Pd(II) catalyst in an amine solvent when he coupled iodoarenes, bromoalkenes and bromopyridines with acetylenes at room temperature (Scheme 4).[33]

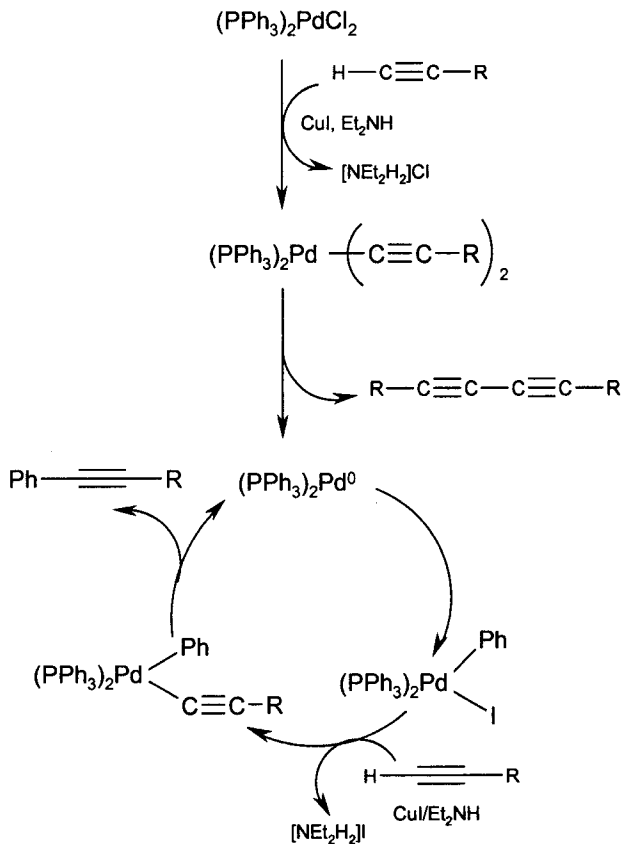
Scheme 4[33]



Although this set the framework for present research involving the palladium-catalysed coupling reaction, various problems associated with it affected the efficiency and practicality of the Sonogashira coupling of arylbromides with terminal alkynes. The low reactivity of the bromides required harsh conditions in order for the reaction to proceed. This issue was addressed by replacing the arylbromides with the more reactive aryliodides. The more polarizable C-I bond

facilitates the coupling in such a way that higher yields are obtained, however, the aryl iodides are more expensive and more difficult to prepare than the aryl bromides. Also, moderate yields are only obtained after purification of the reactants and strict exclusion of oxygen. If oxygen enters the reaction system, the oxidative homocoupling of the alkyne, also known as Glaser coupling,[2] occurs and thus, a large excess of the alkyne is sometimes necessary. This poses a potential problem, as the alkyne may be expensive and the undesired side product that results from the Glaser coupling is hard to separate from the desired products. A review of the literature indicates that although many have probed this mechanism, there is not a single comprehensive study that provides definitive evidence to support Sonogashira's suggested mechanism (Scheme 5).[33]

Scheme 5[33]

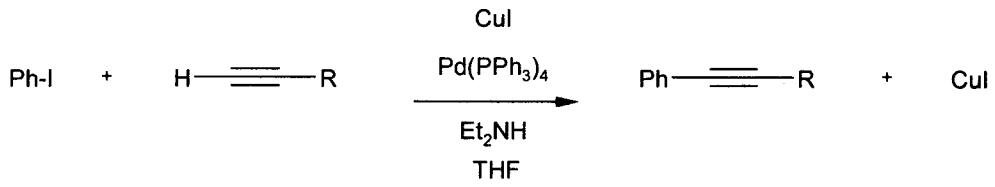


This mechanism suggests that in order to drive the reduction of the Pd(II) catalyst to the active Pd(0) catalyst, the oxidative homocoupling of the alkyne and alkynylation of the starting catalyst, catalysed by cuprous iodide in the presence of diethylamine, must occur. The Pd(0) catalyst that forms enters a catalytic cycle and undergoes oxidative addition with an aryl or vinyl halide. This oxidative addition is followed by the alkynylation of the adduct to give the aryl or vinyl alkynyl derivative of palladium which easily regenerates Pd(0) by the reductive elimination of the substitution product. This paper does not provide mechanistic proof regarding the role of CuI in the procedure despite the emphasized importance that its involvement has in order for the reaction to proceed. Studies done by Thorand and Krause attempted to solve these problems by incorporating slight changes to the reaction conditions.[36]

2.1.3 Coupling by Thorand and Krause

Modifications with respect to solvent, starting material, alkyne addition, and catalyst were made in an attempt to optimize the readily accepted Sonogashira reaction conditions. Out of a number of different solvent systems tried, the change to THF was the most successful in obtaining yields equal to, or higher than, Sonogashira's, after only one hour at room temperature with reagent grade reactants (Scheme 6).[36] The rate of reaction increases in THF and Glaser coupling is minimized, when combined with the slow, dropwise addition of the alkyne.[36,38] Various substituted aryl bromides as well as various alkynes were used along with a Pd(0) catalyst instead of Pd(II), giving yields ranging from 80-95%.

Scheme 6[36]



It is apparent in the literature that most of the enediyne work has been done using various modifications of the Sonogashira coupling procedure. Common starting material alkenes such as cis-1,2-dichloroethylene,[25,37,39,40,44] 1,2-dibromobenzene,[34,41,42] and 1,2-diiodobenzene[37,43] have been extensively studied in the literature. Typical alkynes are TMS acetylene,[37,41,43,44,45,46] and propargyl alcohol, or protected derivatives of it.[37,41,42] THF and benzene have been explored recently as the solvent, however, the preference still seems to be organic bases such as triethylamine, or n-butyl amine.[25,34,37,38,43,47,48] The catalyst system is also variable depending on the reaction conditions. Pd(II) catalysts are still used, however, Pd(0) catalysts are most commonly employed in combination with a CuI co-catalyst which remains constant throughout the literature. These include: $Pd^0(PPh_3)_4$, $Pd^{2+}Cl_2(PPh_3)_2$, and $Pd^{2+}(OAc)_2(PPh_3)_2$.[25,37,39,40,44,49,50]

In order to assemble enediyne molecules it is necessary to determine which method is most efficient. Understanding the chemistry at the site of carbon-carbon coupling is the key to achieving high yields. Substitution of an aromatic halide has an effect on the rate of coupling as well as the yield of desired coupled product. Experimental results concerning substitution along with results from varying the reaction conditions are presented and discussed in the next section.

2.2 Reactivity Study Toward the Synthesis of Alkynyl Aromatics Involving Sonogashira Coupling

This chapter focusses on three main issues concerning the Pd-catalysed coupling procedure. First, optimization of the coupling procedure was addressed by taking the electron density at the halogenated carbon, the site of carbon-carbon coupling, into consideration. In order to do this, substituents on the aromatic ring were varied along with the position that these electron withdrawing (EW) and electron donating groups (ED) were, with respect to an iodide, in one series and a bromide in another series. The steric and electronic effects associated with changing a substituent, relative to the displaced halogen, were studied in terms of their implication on reactivity. It is well known that electron withdrawing groups in the *ortho* and *para* positions to the halogen display a resonance effect. In fact, the ease of substitution has been found to increase with EW groups in the *para* position and decreases as the substituents become more ED, such that p-NO_2 > p-H > p-OCH_3.[35] The *ortho* position presents a problem, however, with steric hindrance affecting reactivity for bulky substituents. Both EW and ED groups at a *meta* position to a halogen exhibit minimal steric interactions and no resonance effects, however, inductive effects become an issue. The difference in reactivity was also compared between iodobenzenes and bromobenzenes. Secondly, different catalyst and co-catalyst systems were employed for the purpose of determining which catalyst system gives the most efficient coupling conditions. Finally, rate experiments were performed in order to determine competitive rates of reactivity between EW groups and ED groups as well as between the *ortho*, *meta*, and *para* substituted halobenzenes.

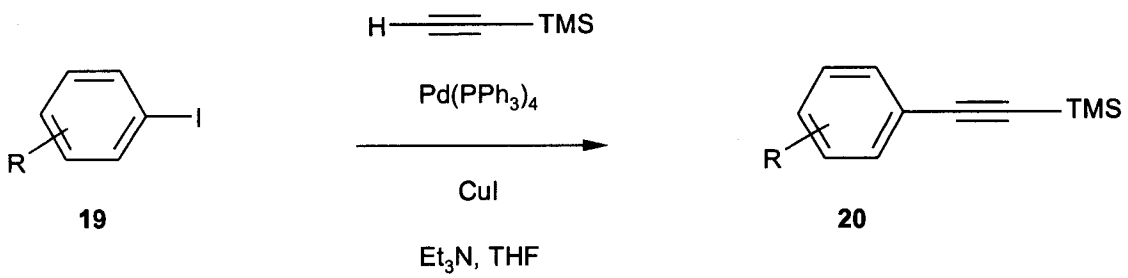
The analysis with respect to the combination of substituents that will give the most

favourable and efficient coupling conditions is based on GLC trends and experimental yield data. For preparation of samples for the GLC an internal standard, biphenyl, was chosen. This compound, as well as the starting materials, were run individually to determine what retention time they had using the same GLC method. The identification of the homocoupled alkyne peak was determined through previous experimentation. Four peaks were expected on the gas chromatographs, one peak each for the starting material (if not completely reacted), homocoupled alkyne, biphenyl and product. Through the process of elimination the product peak could be identified.

A series of substituted iodobenzenes and bromobenzenes were chosen as the starting materials for this set of experiments ranging from those that are strongly electron withdrawing to those that are strongly electron donating. The compounds investigated were selected based on their suitability in the chosen reaction environment, as well as the availability of all three iodo isomers and all three bromo isomers except for the ethyliodobenzenes and nitrobromobenzenes for which the *meta* isomers were unavailable. The reagents were chosen from those presented in the literature for the Sonogashira coupling.[33] Tetrakis(triphenylphosphine)palladium(0) was chosen as the catalyst along with cuprous iodide as the co-catalyst. Triethylamine was chosen as the base and TMS acetylene as the alkyne to be coupled. All reactions were performed in duplicate using identical amounts of each reactant in the ratios: 1 equivalent of the substituted iodo- or bromobenzene, 0.02 equivalents of $Pd(PPh_3)_4$, 0.04 equivalents of CuI, 1.5 equivalents of Et_3N, and 1.05 equivalents of TMS acetylene. Each reaction was run overnight for the same length of time. The starting halide was the only variable in these experiments to ensure that the effects being observed were due to the substituents and their relative positions. The general

reaction schemes, Procedure A in Section 4.3, for the synthesis of the alkynyl aromatics by palladium cross-coupling are shown in Scheme 7 and Scheme 8.

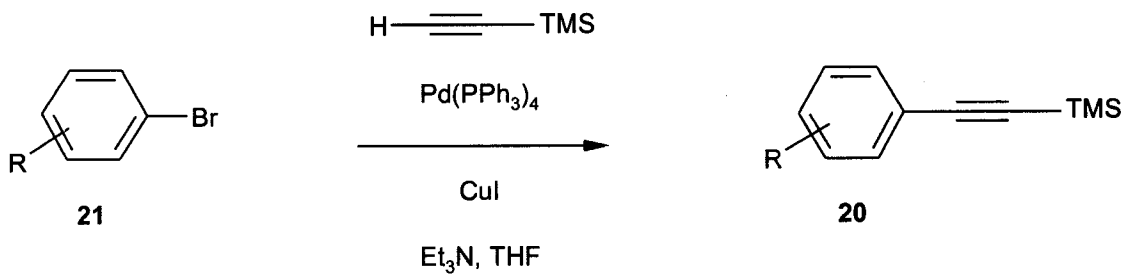
Scheme 7



R=CH_3,OCH_3, NH_2, OH, CH_2CH_3,

NO_2, CF_3, CO_2H, CO_2CH_3, OTf

Scheme 8



R= CH_3, OCH_3, NH_2, OH, CH_2CH_3,

NO_2, CF_3, CO_2H, CO_2CH_3

The next section describes a comprehensive investigation that encompasses a series of iodides and bromides with a variety of attached substituents. The effect that changing the position of the substituents from *ortho* to *meta* to *para* has on the outcome of the reaction was studied in an attempt to determine whether the substituent effects were steric or electronic.

2.3 Results and Discussion

The results of this reactivity study will be divided into three parts, the first involving observed trends with regard to percent yield of desired product obtained, the second involving the optimization of the catalytic system and the third involving rates of reactivity. Prior to beginning the investigation, a number of commercially unavailable starting materials were prepared. The *ortho*, *meta*, and *para*-iodophenols were converted to their corresponding triflates using the procedure found in Section 4.2.1 and the *ortho*, *meta*, and *para*-iodo and bromo esters were prepared using the procedure found in Section 4.2.2.

2.3.1 Percent Yield Trends

The yields between the substituted iodobenzenes, Table 1, and the substituted bromobenzenes, Table 2, for the standard coupling reaction are noticeably different. The yields of the substituted bromobenzenes are significantly lower than the corresponding substituted iodobenzenes. The exception is the substituted (trimethylsilyl)ethynylbenzene synthesized using 1-bromo-4-nitrobenzene (Table 2, Entry 6, R=*p*-NO_2), which provides a yield nearly the same as that using 1-iodo-4-nitrobenzene (Table 1, Entry 6, R=*p*-NO_2) as the starting material. The apparent increase in reactivity for the iodobenzenes can be explained, in part, by bond

polarization. The carbon-iodine bond is longer and more polarizable than the carbon-bromine bond which is more tightly bound. This allows the replacement of the iodide with the alkyne to occur more readily over the bromide as previously determined by Burdon.[51] It appears that with the exception of the iodobenzotrifluorides (Table 1, Entry 7) and the iodotriflates (Table 1, Entry 10) the *para* positions of electron withdrawing (EW) groups have reacted with the highest conversion to product in comparison to the *ortho* and *meta* positions. In fact, the *para* isomer of the iodotriflates (Table 1, Entry 10, R=*p*-OTf) was the least reactive compared to the *ortho* and *meta* isomers. Electron donating ethyl benzenes (Table 1, Entry 5) and the electron withdrawing trifluoromethylbenzene compounds (Table 1, Entry 10) seem to provide the highest yields despite the contrast to the pattern of reactivity observed by Stephens and Castro.[35] For all positions of the benzoic acids (Table 1, Entry 8) poor reactivity was observed in contrast to the other electron withdrawing substituents. The acidic hydrogen associated with these compounds must have interfered in the reaction through coordination with the metal catalyst leading to reduction of reactivity in the system. Once this compound was converted to the methyl ester (Table 1, Entry 9) the percent yield increased significantly. One unexpected trend observed in the yield data is that donators in the *ortho* position, in general, gave a higher yield compared to the *meta* position. If the *ortho* position presents a steric problem, in theory the *meta* position should offer relief from any steric strain and produce higher yields. Through experimentation, however, this was found not to be the case except for the *ortho* isomer of iodoaniline (Table 1, Entry 3, R=*o*-NH_2). The *meta* substituted aniline reacted better than the *ortho* and *para* isomers. From an electronic argument this result makes sense. The *meta* position of iodoaniline is inductively withdrawing and, thus, expected to react more readily than the resonance donating *ortho* position. Other

substituents that are inductively withdrawing, such as OH and NO_2 do not follow this expected trend. The hydrogen of the OH substituent may provide H-bond stabilization for the intermediate that forms when the OH substituent is in the *ortho* position allowing higher yields than the *meta* substituted iodophenol to be obtained. The NO_2 substituent is electron withdrawing in the *ortho* and *para* positions in addition to being inductively withdrawing in the *meta* position. The resonance effect of the *ortho* and *para* isomers seems to overpower the inductive effect of the *meta* isomer leading to higher yields obtained for these two positions. All of these observations lead to the fact that the iodo series was too reactive to differentiate between which donating substituents and withdrawing substituents are more or less reactive and to determine, with any certainty, which position is more favourable for reaction. These issues were addressed by considering the bromo series, which reduced the reactivity in a way that would allow trends between substituents to be more obvious and could also be correlated back to the iodo series. For the bromo substituted compounds, electron withdrawing groups in the *para* position resulted in the formation of coupled product in higher yields than the bromo substituted compounds with *para*-electron donating groups. This is especially true for 1-bromo-4-nitrobenzene (Table 2, Entry 6, R=*p*-NO_2) as it demonstrates similar reactivity to the more reactive iodo equivalent (Table 1, Entry 6, R=*p*-NO_2). These points together imply that electron withdrawing substituents *para* to the halide are the most reactive. This reactivity is true for all of the EW substituents that were used except for the bromo benzoic acids (Table 2, Entry 8). When these were converted to the bromo methyl ester (Table 2, Entry 9) a similar trend to that seen for the iodo benzoic acids (Table 1, Entry 8) was observed. An increase in yield from 0.0% to 11.8% in the *meta* position and 0.0% to 58.9% in the *para* position reinforces the theory that the inhibition of reactivity

displayed by the benzoic acids could be overcome by conversion to the ester. However, the yield for the *ortho* position remained 0.0%, possibly a result of steric interactions between the ester substituent and the alkyne, although, the *o*-iodoester compound does not support a steric argument, therefore other factors must be considered.

All positions for the electron donating substituted bromobenzenes resulted in extremely low yields. In this series, ED groups in the *meta* position proved to be slightly more reactive than the *ortho* substituted isomers. The bulky substituents that are positioned *ortho* to the site of reactivity hinder the coupling process and result in a low yield. Some of the electron donating groups are inductively withdrawing in the *meta* position resulting in a yield higher to that seen for the *ortho* and *para* positions, with the exception of the bromophenol. The OH substituent is resonance donating in the *para* position where the yield is the highest for this family of isomers. Since all of the bromophenol yields are very low this result is not necessarily significant.

2.3.2 Optimization of the Catalytic System and Coupling Reaction

The palladium-catalysed coupling procedure using $Pd(PPh_3)_4$ and CuI as the catalytic system is known to work well for the coupling of alkynes to aryl halides. A search for the most efficient method of assembling endiynes should consider all of the reagents involved in the reaction. The synthesis of enynes is the first logical step in doing so, and should not be limited to coupling through the above mentioned procedure alone. This interest in determining the most efficient reaction conditions was the impetus for employing the use of various catalytic systems and an attempt at a direct aromatic nucleophilic substitution reaction (Scheme 9).

Table 1: Sonogashira Reactivity Study: Yields for the Substituted Aryl Iodides*

Entry no.	R	I (Yield, %)		
		ortho	*meta*	*para*
1	CH_3	34.7	30.3	54.0
2	OCH_3	74.3	48.2	98.9
3	NH_2	60.1	65.7	42.3
4	OH	91.2	78.9	73.8
5	CH_2CH_3	> 99	NA	> 99
6	NO_2	90.4	61.5	94.1
7	CF_3	> 99	> 99	> 99
8	CO_2H	0.0	5.2	16.9
9	CO_2CH_3	73.4	87.1	89.4
10	OTf	74.9	37.6	16.3

*Note: Entries 1-10 were synthesized using Procedure A of Section 5.3.

Scheme 9

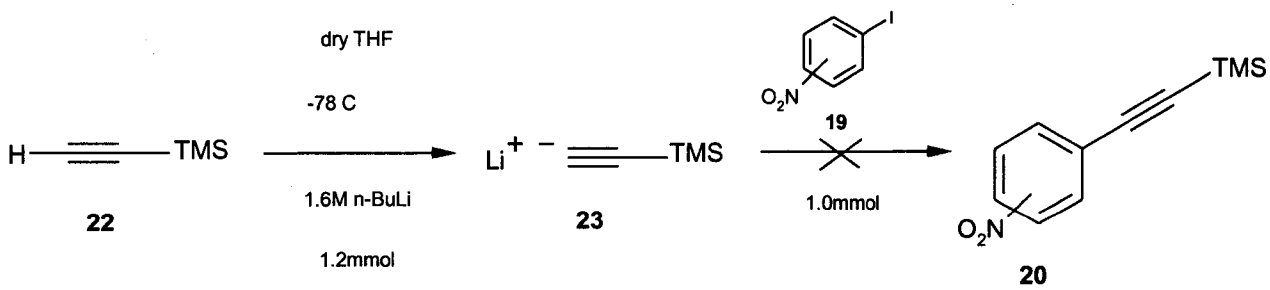


Table 2: Sonogashira Reactivity Study: Yields for the Substituted Aryl Bromides*

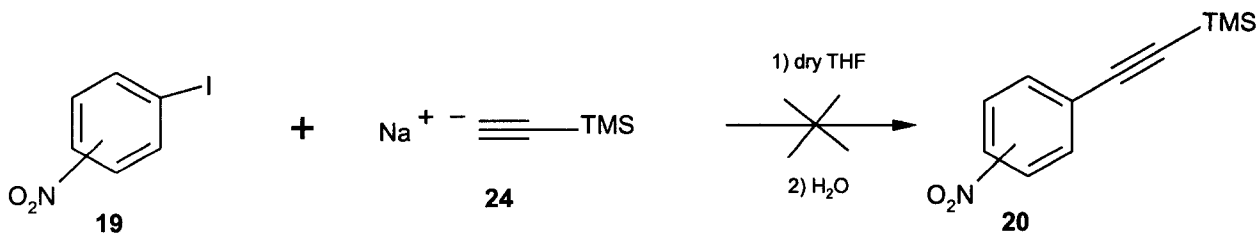
Entry no.	R	Br (Yield, %)		
		ortho	*meta*	*para*
1	CH_3	0.5	4.3	1.9
2	OCH_3	1.6	6.5	0.8
3	NH_2	1.6	0.0	0.0
4	OH	0.0	0.5	1.2
5	CH_2CH_3	NA	NA	NA
6	NO_2	74.4	NA	> 99
7	CF_3	0.3	5.5	20.3
8	CO_2H	0.0	0.0	0.0
9	CO_2CH_3	0.0	11.8	58.9
10	OTf	NA	NA	NA

*Note: Entries 1-10 were synthesized using Procedure A of Section 5.3.

The starting material, 1-iodo-2-nitrobenzene (Table 1, Entry 6, R=*o*-NO_2) was chosen for the aromatic nucleophilic substitution reaction, as electron withdrawing groups are known to undergo this type of reaction. The nucleophile was generated using TMS acetylene in the presence of butyllithium (Procedure K, Section 5.5). No product formation or starting material consumption was evident by GLC. This may be attributed to a lack of formation of the reactive TMS acetylide anion, thus addition of the anion directly into the reaction mixture was attempted (Scheme 10, Procedure L). However, direct addition of the anion also proved unsuccessful. It is believed that the formation of the anion is not the problem as product formation was not evident in the GLC.

Thus, it appears that this nucleophilic reaction does not work for the coupling of TMS acetylene to 1-iodo-2-nitrobenzene.

Scheme 10



The role of the CuI co-catalyst in the Sonogashira coupling has not been mechanistically proven, however, it has been shown in previous studies to be necessary for the coupling reactions to proceed.[2,33] In the absence of CuI, using a catalytic amount of $Pd(PPh_3)_4$, the reactions proceed very slowly, if at all. Varying the amount of CuI present does not alter the reactivity or the extent of the reaction. If the activity and interactions of CuI with the other reagents in the reaction mixture can be determined, there is a greater potential for elucidating the mechanism behind Pd cross-coupling reactions. This led us to explore experiments using Procedure M. They involved the replacement of CuI with KI to see which component of CuI, the Cu^+ or the I^-, is involved in the coupling mechanism. If it is the I^- component that is involved then the effect of the KI co-catalyst should be comparable to CuI. The 1-iodo-4-nitrobenzene (Table 1, Entry 6, R=*p*-NO_2)

substrate was chosen as it demonstrated high conversion to product using CuI. Unfortunately, KI did not show a similar effect by any means. Using this reagent in the place of CuI resulted in absolutely no conversion of starting material into product with a percent yield of 0.0%. Thus, CuI is not replaceable by KI. It would be beneficial to try the replacement of CuI with a different copper salt to confirm that it is the Cu^+ component that is involved in the coupling. We next questioned whether the yields would remain comparable if the $Pd(PPh_3)_4$ catalyst was replaced.

Four different catalysts were used in the place of $Pd(PPh_3)_4$ for Procedure A. The starting material used in this set of experiments was 4-iodoaniline (Table 1, Entry 3, R=*p*-NH_2) because this compound gave a moderate yield using $Pd(PPh_3)_4$ making an increase or decrease in yield easy to determine (Table 3). Each of the four catalysts were used with and without the addition of excess triphenylphosphine. The combination of Pd(II)Acetate / PPh_3 gave the highest cross coupling yield followed by the combination of Pd(II)Acetylacetonate / PPh_3. 1,1-Bis (diphenylphosphinoferrocenedichloro)Pd(II) without triphenylphosphine increased the yield slightly over the $Pd(PPh_3)_4$ catalysed reaction, however, not significantly. The difference between yields for 1,2-bis(diphenylphosphino)ethanedichloroPd(II) with PPh_3 and $Pd(PPh_3)_4$ without PPh_3 was negligible. It seems that the addition of excess triphenylphosphine with a Pd(II) catalyst has a positive effect on the outcome of the coupling reaction in general. The PPh_3 ligand serves to coordinate to the Pd centre, stabilizing the catalyst and reducing it to the reactive Pd(0) form. In its absence, the catalytic effect is diminished significantly. The exception was 1,1-bis diphenyl phosphinoferrocene dichloroPd(II) which decreased the yield when PPh_3 was present, while the other three catalysts demonstrated a decrease in yield when PPh_3 was absent.

Table 3: Yields for the Optimization of the Catalytic System Using 4-Iodoaniline as the Starting Material

Catalyst System*	Yield, %
$Pd(PPh_3)_4$	42.3
Pd(II)Acetate	4.8
Pd(II)Acetate / PPh_3	72.8
1,1-bis(diphenylphosphinoferrocenedichloro)Pd(II)	53.8
1,1-bis(diphenylphosphinoferrocenedichloro)Pd(II) / PPh_3	13.6
1,2-bis(diphenylphosphinoethanedichloro)Pd(II)	0.0
1,2-bis(diphenylphosphinoethanedichloro)Pd(II) / PPh_3	42.0
Pd(II)Acetylacetonate	0.0
Pd(II)Acetylacetonate / PPh_3	63.0

*Note: All systems were carried out using Procedure J of Section 5.3.

The reason for this may be that the reactive species formed using this catalyst is generated by an energetically uphill equilibrium involving PPh_3. The inhibition by excess phosphine may also suggest that a free coordination site is required to allow alkyne coordination in the next step when this bulky catalyst is used.

The final catalyst system employed was $PdCl_2(PPh_3)_2$. The procedure used in combination with this catalytic system was changed slightly. Procedure B and Procedure C were first attempted using 1-bromo-4-nitrobenzene (Table 2, Entry 6, R=*p*-NO_2) as the starting material due to its high degree of reactivity. The percent yields obtained were 88.2% and 74.8%

for Procedures B and C respectively. These yields were not comparable to the yields obtained using Procedure A, however, Procedure B still performed well enough to pursue. Reacting with 4-iodotoluene (Table 1, Entry 1, R=*p*-CH_3) and 4-bromotoluene (Table 2, Entry 1, R=*p*-CH_3) using Procedure B gave yields of 99.9% and 0.0%, respectively. Again, the trend in halogen reactivity was revisited and the iodide showed a significant enhancement over the bromide. Finally, an electron withdrawing compound, 4-bromobenzotrifluoride (Table 2, Entry 7, R=*p*-CF_3) and an electron donating compound, 4-bromoanisole (Table 2, Entry 2, R=*p*-OCH_3) were chosen and compared in terms of yield. As presented above, the compound with the electron withdrawing substituent gave a conversion to product of 25.4%, while the compound with the electron donating substituent showed no conversion at all.

An experiment was carried out to provide information regarding the mechanism of the cross-coupling reaction. Since not much is definitively known in terms of the mechanism and intermediates involved in the Pd- cross coupling reaction, a reaction using Procedure A was performed incorporating a well known radical trapping agent, TEMPO. The trapping agent did not interfere in the outcome of the reaction and the yield of product was comparable to the yield obtained without the trap, indicating that this coupling mechanism likely does not involve a radical intermediate. Without further investigations in this area, concrete suggestions can not be made as to the pathway this procedure follows.

2.3.3 Rates of Reactivity

In an effort to establish the reactivity pattern arising from changes in substitution in electron donating versus electron withdrawing groups and the attached halide, bromide versus

iodide, numerous rate reactions were carried out. The first set of experiments consisted of two rate reactions, one including an electron withdrawing substituent, 1-iodo-4-nitrobenzene (Table 1, Entry 6, R=*p*-NO_2) and another with an electron donating substituent, 4-iodotoluene (Table 1, Entry 1, R=*p*-CH_3). The progress of the reaction was tracked through GLC by the appearance and disappearance of product and starting material, respectively. It was found that there was no remaining 1-iodo-4-nitrobenzene thirty-five minutes after TMS acetylene addition and no disappearance of the 4-iodotoluene until seventy minutes after TMS acetylene addition. This time difference did not present enough of a contrast in reactivity, so the same rate comparison was attempted using the substituted bromides in the hope that the less reactive bromides would be able to slow down or moderate the reaction. The results for this set of experiments remain inconclusive in terms of reactivity differences between iodo and bromo compounds, as the EW substituted bromide species reacted within the same time frame as the EW substituted iodide compound and the ED substituted bromide did not completely react after one week. This may be attributed to the fact that the bromide species has a less reactive carbon-halogen bond. Further experimentation was necessary to provide resolution to this set of data. Instead of continuing to carry out the experiments on individual starting materials it was decided that better results may be obtained if they were set up to react in competition with each other. The first set in this series of experiments included 1-iodo-4-nitrobenzene (Table 1, Entry 6, R=*p*-NO_2) and 1-bromo-4-nitrobenzene (Table 2, Entry 6, R=*p*-NO_2) combined *in situ* as seen in Procedure E. 1-Iodo-4-nitrobenzene was considerably more reactive as it went to completion before any of the 1-bromo-4-nitrobenzene had a chance to react. Similarly, for the combination of 4-iodotoluene (Table 1, Entry 1, R=*p*-CH_3) and 4-bromotoluene (Table 2, Entry 1, R=*p*-CH_3) the 4-iodotoluene reacted

completely and 4-bromotoluene did not react at all. This comparison of reactivity provides greater evidence of the preferential displacement of iodides during the Pd cross-coupling reaction. Although both the iodide and bromide substituted with electron withdrawing substituents were reactive enough to convert to product within thirty-five minutes when they were tested individually, when placed in competition with each other the iodo compound with the electron withdrawing substituent proved to be considerably more reactive. A similar pattern of reactivity is seen when comparing the EW and ED substituted aryl iodides. This relative reactivity was tested using 1-iodo-4-nitrobenzene versus 4-iodotoluene in one reaction and 1-iodo-4-nitrobenzene versus 4-iodoanisole (Table 1, Entry 2, R=*p*-OCH_3) in another. The EW and ED substituted iodides exhibit similar reactivity when run individually, however, when placed in a competitive situation the aryl compound substituted with an electron withdrawing substituent reacts significantly faster. In order to determine which position is more reactive within a set of isomers, another series of reactions using HPLC was performed.

These experiments were similar to the competitive rate experiments previously explained in which one equivalent each of *ortho*, *meta* and the *para* starting materials of one iodobenzene isomer are placed in competition with each other in a reaction where only one equivalent of alkyne, (TMS acetylene) is present. Complete results for the HPLC rate experiments can be found in Tables 16-27 located in Appendix A along with the relative reactivity ratios contained in Tables 4 and 5. Concentration ratio versus time graphs were constructed and analysed; Graph1 shows the relative reactivity between *meta* vs *ortho* substituted aryl iodides and Graph 2 shows the relative reactivity between *para* vs *ortho* substituted aryl iodides.

Looking at the curve for iodoaniline (Table 1, Entry 3, R=*o*-NH_2 and *m*-NH_2) in Graph 1,

a slight increase in the *meta*/*ortho* concentration ratio at the beginning is apparent until the one hour mark is reached. At this point the curve levels off and continues for the remaining six hours. This indicates that initially the *ortho* isomer is more competitive than the *meta* until a certain point is reached where the reactivity of the *ortho* isomer can no longer compete with the concentration of the *meta* isomer. There are a number of possible explanations for this result. It is possible that once some of the *ortho*-iodoaniline is used up, its concentration in the reaction mixture decreases to a point where the *meta*-iodoaniline concentration is higher, thus, causing the *meta* isomer to become more competitive for reagents. The level part of the curve may indicate that the alkyne has been used up and is no longer available to react, however, this can not be proven using HPLC. The iodophenols (Table 1, Entry 4, R=*o*-OH and *m*-OH) show a steadily decreasing curve indicating that the *meta* isomer remains more competitive throughout the entire reaction. It has been determined that electron withdrawing substituents on aryl iodides are more reactive than aryl iodides substituted with electron donating groups. Even though OH is considered to be a resonance electron donating group, it is also inductively withdrawing in the *meta* position. The withdrawing property of the *meta* isomer along with the steric constraints of the *ortho* position, together, explain the enhanced reactivity of the *meta* substituted iodophenol. The graph for the iodonitrobenzenes (Table 1, Entry 6, R=*o*-NO_2 and *m*-NO_2) is essentially linear. The concentration ratios remain basically the same throughout the entire experiment. This may indicate that both the *ortho* and *meta* isomers are equally reactive or that the steric interactions presented by the *ortho* substituted NO_2 group are matched by the low reactivity exhibited by the aryl iodide when the NO_2 group is in the *meta* position.

Table 4: Concentration Ratios for Competitive Rate Reactions

Between *meta* and *ortho* Substituted Aryl Iodides*

Time (hrs)	R=OH	$R=CH_3$	$R=OCH_3$	$R=NH_2$	$R=CF_3$	$R=NO_2$
	[*m*]/[*o*]	[*m*]/[*o*]	[*m*]/[*o*]	[*m*]/[*o*]	[*m*]/[*o*]	[*m*]/[*o*]
0.0 hrs	0.890	0.642	1.015	1.014	0.970	1.000
0.5 hrs	0.885	0.131	0.323	1.106	0.801	1.009
1.0 hrs	0.894	0.130	0.284	1.107	0.390	1.005
1.5 hrs	0.850		0.285	1.105	0.253	1.007
2.0 hrs	0.805		0.318	1.114	0.198	1.006
2.5 hrs	0.777		0.278	1.115	0.198	0.997
3.0 hrs	0.755		0.286	1.115	0.167	1.008
3.5 hrs	0.595		0.279	1.114	0.182	1.006
4.0 hrs	0.553		0.289	1.115	0.176	1.005
4.5 hrs	0.495		0.279	1.113	0.174	1.007
5.0 hrs	0.453		0.311	1.109	0.170	1.006
5.5 hrs	0.400		0.279	1.118	0.168	0.983
6.0 hrs	0.350		0.276	1.119	0.164	0.981

*Note: The decrease in starting material concentration was monitored.

In contrast, the iodoanisoles (Table 1, Entry 2, R=*o*-OCH_3 and *m*-OCH_3) iodotoluenes (Table 1, Entry 1, R=*o*-CH_3 and *m*-CH_3) and iodobenzotrifluorides (Table 1, Entry 7, R=*o*-CF_3 and *m*-CF_3) exhibit a remarkable decrease within the first hour.

Table 5: Concentration Ratios for Competitive Rate Reactions Between *para* and *ortho* Substituted Aryl Iodides*

Time (hrs)	R=OH	$R=CH_3$	$R=OCH_3$	$R=NH_2$	$R=CF_3$	$R=NO_2$
	[*p*]/[*o*]	[*p*]/[*o*]	[*p*]/[*o*]	[*p*]/[*o*]	[*p*]/[*o*]	[*p*]/[*o*]
0.0 hrs	1.001	1.550	1.035	1.035	0.975	0.603
0.5 hrs	0.885	0.583	0.924	0.918	0.632	0.804
1.0 hrs	0.746	0.090	0.925	0.919	0.389	0.527
1.5 hrs	0.695	0.060	0.923	0.917	0.359	0.757
2.0 hrs	0.568	0.110	0.924	0.916	0.226	0.715
2.5 hrs	0.504		0.925	0.917	0.249	0.699
3.0 hrs	0.463		0.928	0.919	0.155	0.663
3.5 hrs	0.424		0.926	0.917	0.135	0.428
4.0 hrs	0.379		0.927	0.919	0.124	0.591
4.5 hrs	0.331		0.929	0.919	0.115	0.566
5.0 hrs	0.327		0.930	0.920	0.104	0.514
5.5 hrs	0.269		0.928	0.919	0.098	0.467
6.0 hrs	0.299		0.927	0.919	0.092	0.303

*Note: The decrease in starting material concentration was monitored.

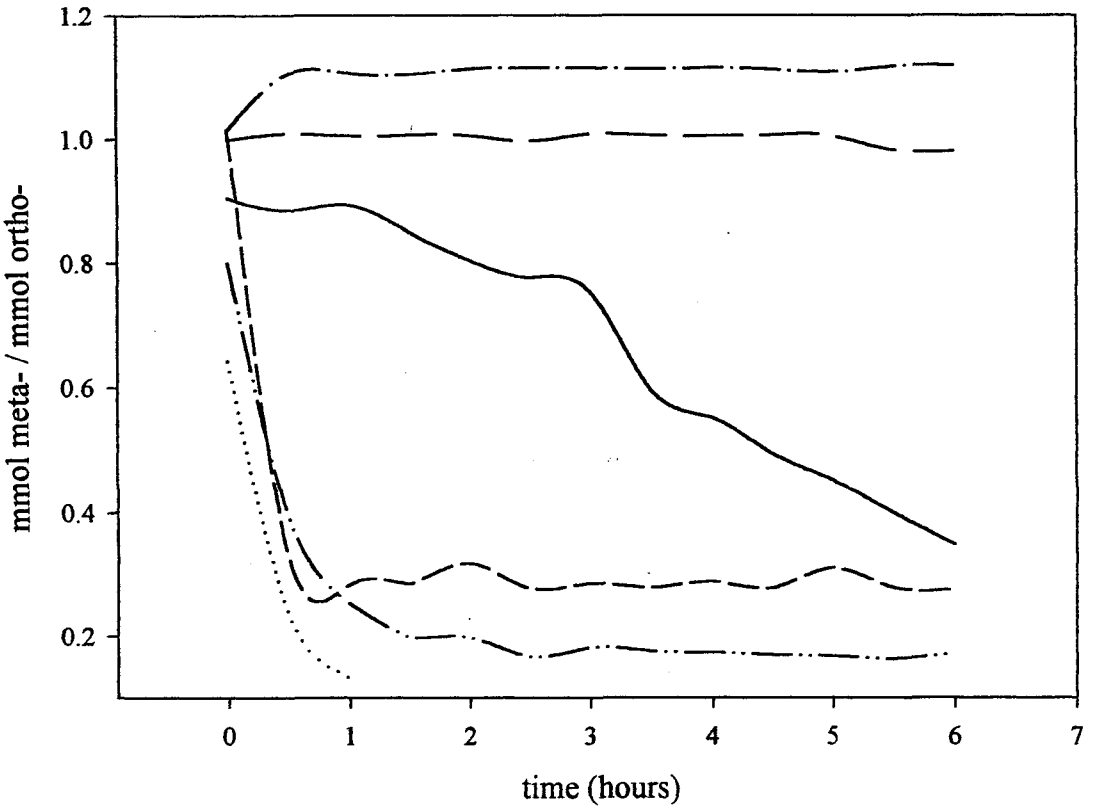
This trend shows that the concentration of the *meta* substituted species decreases quicker than the *ortho* substituted compound. After one hour the more reactive *meta*-iodotoluene has completely reacted and only *ortho*-iodotoluene remains in the reaction mixture, likely due to steric interactions. Furthermore, the inductive donating effects of the methyl group will decrease as the substituent moves from the *ortho* to the *meta* position. The iodoanisole and iodobenzotrifluoride

curves level off after the first hour and a half, likely indicating that there is no more alkyne available to react.

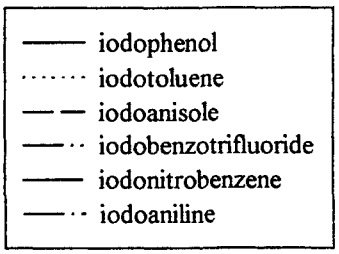
Similar reactivity is seen in the relative reactivity patterns for the *para* vs *ortho* substituted aryl iodides, Graph 2. The main differences are noticed for the iodoanilines, iodoanisoles and iodonitrobenzenes. In the case of *para* versus *ortho*-aniline, the *para*/*ortho* concentration ratio decreases initially. This means that the *para* isomer of this compound is more reactive than the sterically hindered *ortho* isomer. After one hour these curves also level off. Again the argument that all of the alkyne is used up and no longer present to react may be used to explain the cause of the level graph. A level plot is also seen for the iodoanisoles after a half hour. The slight initial decrease may indicate that *para*-iodoanisole is more reactive than the *ortho* isomer, however, the rapid levelling off of the curve reveals that once the concentration of the *para* isomer decreases to a certain point the concentration of *ortho*-iodoanisole is high enough, compared to the concentration of the *para* isomer, thus, allowing the *ortho* isomer to be more competitive. The nitrobenzene curve in Graph 2, on the other hand, does not level off as it did in the *meta* versus *ortho*-nitrobenzene case (Graph 1). A steady decrease in the concentration ratio between *para*-iodonitrobenzene and *ortho*-iodonitrobenzene occurs, implying that the *para* isomer is more reactive as steric problems are present when the NO_2 group is in the *ortho* position to the iodide. The plots for iodophenol, iodobenzotriflouride and iodotoluene are comparable to those seen in Graph 1. *Para*-iodobenzotrifluoride and *para*-iodotoluene are also more reactive than their corresponding, sterically hindered *ortho* isomers. In conclusion, it is apparent that all of the *para* substituted aryl iodides studied, excluding iodoanisole, react with a higher rate of reactivity than their *ortho* counterparts. Also, the *meta* substituted aryl iodides,

with the exception of iodoaniline and iodonitrobenzene, react faster than their corresponding *ortho* isomers.

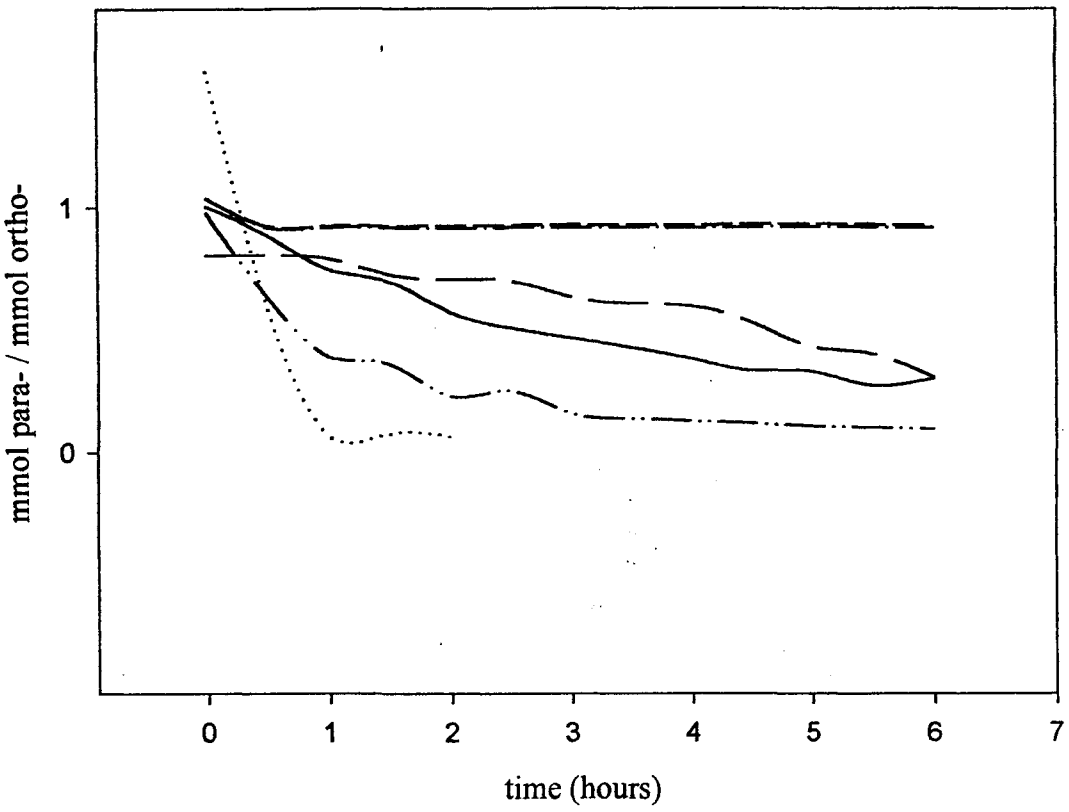
Graph 1
Relative Reactivity *meta-* vs *ortho*-Substituted Aryl Iodides*



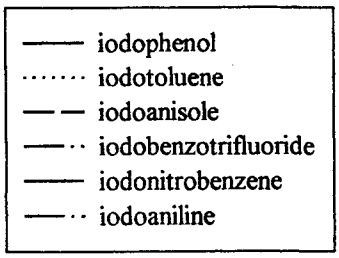
*Note: The decrease in starting material concentration was monitored.



Graph 2
Relative Reactivity *para-* vs *ortho*-Substituted
Aryl Iodides*



*Note: The decrease in starting material concentration was monitored.



The differences in reactivity between the *meta* and *para* substituted aryl iodides in this series cannot be determined from this set of data, and thus, presents an opportunity for further study in the future.

2.3.4 Conclusion

In summary, a number of conclusions can be drawn. It is obvious from yield trends and relative rates of reactivity that the most efficient means of coupling can be achieved using the palladium-catalysed cross-coupling reaction with a *para* substituted electron withdrawing aromatic starting materials. The best catalyst to use for the coupling of TMS-acetylene to 4-iodoaniline is Pd(II)acetate in combination with excess PPh_3 and CuI as the co-catalyst. Results from this section of the study do not provide any concrete mechanistic information aside from the speculation that the intermediates are not radical in nature. An interest in pursuing the unanswered questions regarding mechanism will possibly lead to the finding of an ideal route for the synthesis of enediynes. When this ideal route is found, it will promise an exciting future for enediyne anticancer applications.

This chapter includes the discussion of carbon-carbon bond formation using a palladium catalyst through a transmetallation reaction. It was shown that when an EW group is in the *para* position to the carbon at the site of coupling, the yield is the highest. An EW group on the aromatic ring withdraws electron density away from the site of reactivity causing the carbon at that site to be more electron deficient. From this trend, it can be concluded that a more electron deficient reaction site causes the reaction to proceed faster with higher yields under the Sonogashira coupling conditions. The opposite is true for ED substituents which change the

characteristics of the carbon at the site of reactivity, resulting in a higher electron density. The next chapter encompasses a study involving the formation of alkynyl aromatics through a transmetallation reaction when the site of reactivity is made electron rich, by formation of the Grignard reagent.

CHAPTER 3

REACTIVITY STUDY INVOLVING THE GRIGNARD-SONOGASHIRA REACTION

3.1 Grignard Coupling Reactions

The Sonogashira reaction is the coupling reaction that is most often employed in carbon-carbon bond formation between aryl and alkynyl compounds. However, organometallic acetylide derivatives, such as Sn-acetylides,[52,53,54] Zn-acetylides,[55,56,57,58] and Mg-acetylides,[59,60] have also been shown to participate in carbon-carbon coupling between two sp centres and between sp and sp^2 centres when Pd(0) is present. The carbanionic acetylides derived from alkali or alkaline earth metals undergo efficient addition to a wide variety of organic electrophiles such as imines, aldehydes, and acid chlorides to produce products that contain synthetic utility and versatility. Alkynes with terminal Grignard reagents have been used, conveniently, for the preparation of alkynyl arenes from aryl bromides and iodides. Specifically, they have been used for the cross-coupling of bromo aryl triflates with alkynyl Grignard reagents in the presence of the $PdCl_2$ catalyst to give high yields of alkynyl arenes formed by selective replacement of the triflate by the alkynyl group.[61,62,63,64] Another example in the literature includes the asymmetric cross-coupling of biaryl ditriflates with triphenylsilylethynyl magnesium bromide in the presence of a Pd catalyst to give selectively high yields of the corresponding chiral monoalkynylated biaryl systems.[65] MgBr acetylides have also been used to access Z-1,3-enynes through the condensation of Z-vinyl carbamates under Ni(0) catalysis.[66]

Coupling procedures using Grignard reagents, that are present in the literature, always proceed through the magnesium acetylide. Formation of the coupled product occurs when the

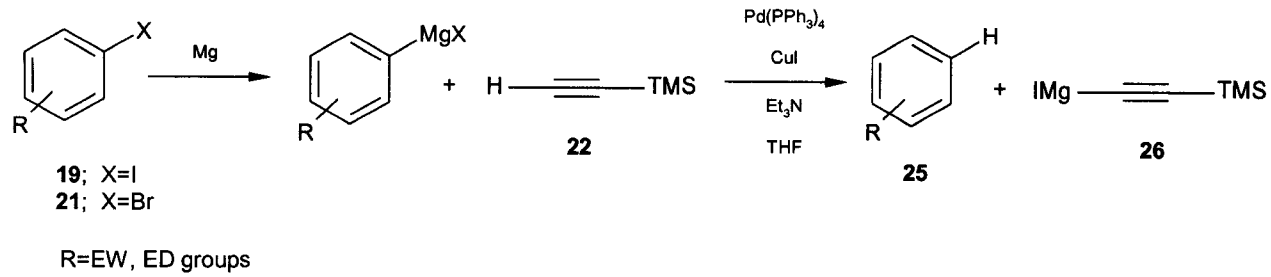
acetylenic Grignard reagent reacts with an aryl or alkenyl halide or triflate. An alternative method of achieve coupling by generating the Grignard reagent on the sp^2 hybridized carbon of the aryl halide, instead of the sp hybridized carbon of the acetylide, was considered.

3.2 Reactivity Study on the Synthesis of Alkynyl Aromatics Involving Grignard Coupling

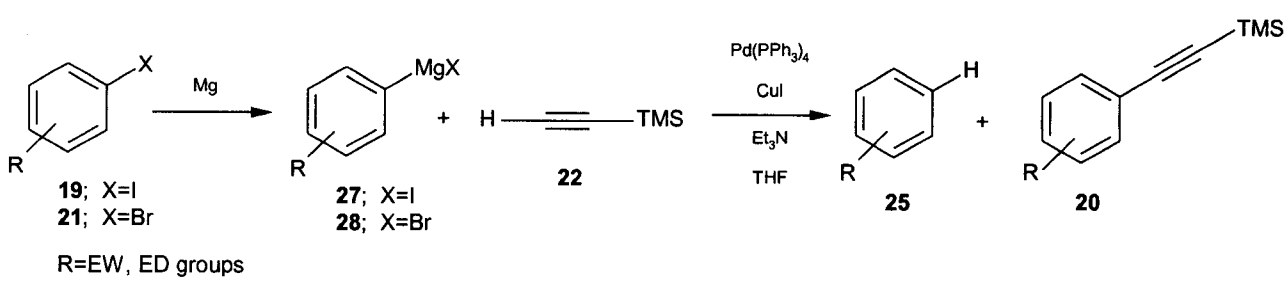
A number of issues concerning Grignard coupling are addressed in this chapter. It was necessary to determine whether the Grignard reagent actually forms on the aryl halide. It was also determined if prior formation of the Grignard reagent is essential to the outcome of the reaction or, if generation of the Grignard reagent throughout the course of the reaction is sufficient.

The conversion of the starting materials to Grignard reagents was done prior to the addition of the palladium and copper catalysts and alkyne. The same amounts of reagents used under the standard coupling conditions were used for the Grignard coupling: 1 equivalent of the substituted iodo- or bromobenzene, 1 equivalent of Mg, 0.02 equivalents of $Pd(PPh_3)_4$, 0.04 equivalents of CuI, 1.5 equivalents of Et_3N, and 1.05 equivalents of TMS acetylene. It was expected that once the Grignard was formed on the halobenzene, it would react with the acidic acetylenic hydrogen to give the reduced form of the Grignard reagent, **25**. If this was the case, the replacement of the hydrogen on the alkyne would occur instead of the formation of the desired coupled product, **20** (Scheme 12). However, when this reaction was actually attempted, only a trace amount of the reduced product, **25**, was obtained and the desired product, **20**, was the major product for all substituted aryl halides used (Scheme 12).

Scheme 11



Scheme 12



This observation raised two questions that will be addressed in the following section. Is the Grignard reagent really forming or is product formation the result of standard Sonogashira coupling? Is it important for the Grignard reagent to be generated before coupling takes place?

Once the answers to these questions were established, a number of reactions were carried out using the same series of compounds that were used in Chapter 2. Trends in the yield obtained

using this modified coupling procedure, in terms of differences in reactivity between electron donators and electron withdrawers, will be discussed in the next section along with a discussion of reactivity between substituted aryl iodides and substituted aryl bromides. The results from this set of data were compared to those obtained under standard conditions. Modifications to the catalyst system were made to determine the components necessary for the reaction to proceed. The effect of changing the alkyne on the reactivity of the Grignard coupling procedure was studied using 2-iodotoluene (Table 6, Entry 1, R=*o*-CH_3) as the starting material. Furthermore, an attempt at synthesizing simple enediynes by coupling TMS-acetylene to a number of already assembled enynes using the Grignard coupling procedure was performed.

3.3 Results and Discussion

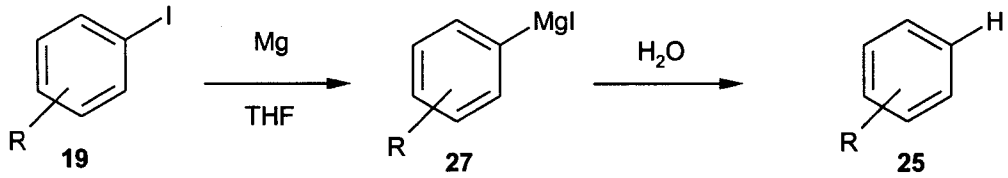
The results of this reactivity study will be divided into five parts: 1) establishing the importance of Grignard reagent formation; 2) outlining observed trends with regard to percent yield of desired product obtained; 3) the catalytic system; 4) coupling with various alkynes; and 5) the synthesis of enediynes. Prior to beginning the investigation a number of commercially unavailable starting materials were prepared. The *ortho*, *meta*, and *para*-iodo and bromo esters were prepared using the procedure found in section 4.2.2.

3.3.1 Importance of Grignard Formation

Two questions that were previously mentioned are addressed in this section. First and foremost, it was important to determine if the desired Grignard reagent forms or if the reaction proceeds without influence by added magnesium. A series of reactions were carried out on the

various substituted aryl halides using Procedure T, Section 5.5 (Scheme 13).

Scheme 13



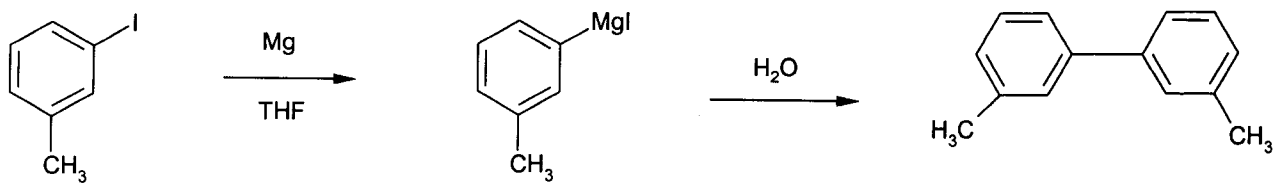
R=*o*-NH_2, *m*-CH_3, *m*-NO_2, *p*-OH,

m-CO_2H, *p*-OCH_3, *p*-CH_2CH_3

If the Grignard reagents do form then they could be quenched with water producing their reduced forms which are identifiable by GC-MS. Mass spectra for each of the above listed products formed using 2-iodoaniline (Table 6, Entry 3, R=*o*-NH_2), 4-iodophenol (Table 6, Entry 4, R=*p*-OH), 3-iodobenzoic acid (Table 6, Entry 8, R=*m*-CO_2H), 4-iodoanisole (Table 6, Entry 2, R=*p*-OCH_3), and 1-iodo-3-nitrobenzene (Table 6, Entry 6, R=*m*-NO_2) were obtained and compared to the mass spectra for aniline, phenol, benzoic acid, anisole, and nitrobenzene respectively. Ethylbenzene was not commercially available, thus a GC-MS comparison could not be made, however, the mass spectrum for the product of Grignard formation using 1-iodo-4-ethylbenzene was observed. A mass spectrum obtained for the product formed when 3-iodotoluene was used as the starting material did not match the spectrum for toluene as this reaction formed 3,3'-dimethylbiphenyl, **28**, instead of the reduced Grignard reagent (Scheme 14). The reduced

Grignard products formed for all of the above starting materials, although it was not quantitative. This indicates that Grignard formation on the aryl iodide definitely occurs. Evidence that the Grignard reagent forms for the iodo and bromotoluenes is given by the substantially higher yield obtained for the modified Grignard coupling reaction versus the standard coupling procedure. Under standard conditions the aryl halides with electron withdrawing substituents demonstrated significantly higher yields than the electron rich substituents. This result indicates that when the site of coupling is made electron rich, through the use of a Grignard reagent, the reactivity of compounds with electron donating substituents should increase since Grignards show carbanion-type reactivity. The yield for the compound containing an ED methyl group does increase, thus, the Grignard must be forming.

Scheme 14



19 **28**

To determine if Grignard formation before the addition of reagents is necessary, an experiment was carried out where one equivalent of Mg, and a catalytic amount of $Pd(PPh_3)_4$, and CuI were added simultaneously to the reaction mixture. Product formation was observed, however, in a

much lower yield than that obtained under standard Sonogashira conditions. Therefore, forming the aryl Grignard reagent prior to the addition of the catalysts, base and alkyne is important.

3.3.2 Percent Yield Trends

The yields obtained for the substituted aryl iodides, Table 6, and substituted aryl bromides, Table 7, are significantly different. It is evident that the iodides are much more reactive than the bromides for reasons previously discussed in Chapter 2. For all three isomers of the electron donating methyl group, significantly higher yields were obtained than those from the corresponding reaction using standard conditions. The reactivity of the Grignard modified reaction was not hindered by the expected steric effects of the *ortho*-methyl group. The OCH_3, NH_2, and NO_2 substituted aryl iodides are inductively withdrawing in the *meta* position yet they still produced a greater yield than the corresponding Sonogashira reaction. The yields for the *ortho* and *para* positions for the OCH_3, NH_2, and NO_2 substituted aryl iodides, on the other hand, were lower than those found in the previous study (Chapter 2), yet still comparable. The most unexpected aspect of our investigations was that functional groups such as, NO_2, OH, and CO_2CH_3, which usually interfere with Grignard reagents were only slightly affected since reactions including these substituents still resulted in the formation of product. However, the yields for these compounds were lower than those obtained under standard Sonogashira coupling conditions.

Table 6: Grignard Reactivity Study: Yields for Substituted Aryl Iodides*

Entry no.	R	I (Yield, %)		
		ortho	*meta*	*para*
1	CH_3	93.9	91.8	68.7
2	OCH_3	22.3	68.5	71.0
3	NH_2	55.6	72.9	38.4
4	OH	59.4	49.2	19.5
5	CH_2CH_3	87.7	NA	87.4
6	NO_2	6.6	97.4	40.9
7	CF_3	17.9	87.8	96.8
8	CO_2H	0.8	1.6	1.5
9	CO_2CH_3	9.1	65.4	42.8
10	OTf	NA	NA	NA

*Note: Entries 1-10 were synthesized using Procedure F of Section 5.3.

3.3.3 The Catalyst System

Using 2-iodotoluene as the starting material, a series of reactions were run to determine the combination of reagents necessary for the Grignard coupling reaction to proceed. When $Pd(PPh_3)_4$ is not present the coupling does not occur. In the absence of the CuI co-catalyst the reaction also does not proceed. A reaction excluding both the catalyst and the co-catalyst does not lead to product formation. It can be clearly stated from these results that the Grignard modified reactions will only proceed if catalytic amounts of both $Pd(PPh_3)_4$ and CuI are present.

The catalyst system including $PdCl_2$ and PPh_3 in a 1:2 ratio, along with the starting

material, 2-iodotoluene, was used for the Grignard coupling reaction. The yield obtained for this experiment was 42.9% compared to the 92.9% obtained by using $Pd(PPh_3)_4$.

Table 7: Grignard Reactivity Study: Yields for Substituted Aryl Bromides*

Entry	R	Br (Yield, %)		
no.		*ortho*	*meta*	*para*
1	CH_3	12.9	12.7	10.3
2	OCH_3	7.8	8.2	0.8
3	NH_2	0.0	0.0	0.0
4	OH	0.0	0.0	0.0
5	CH_2CH_3	NA	NA	NA
6	NO_2	0.7	NA	34.8
7	CF_3	0.0	15.5	42.7
8	CO_2H	0.0	0.0	0.0
9	CO_2CH_3	1.1	3.1	1.8
10	OTf	NA	NA	NA

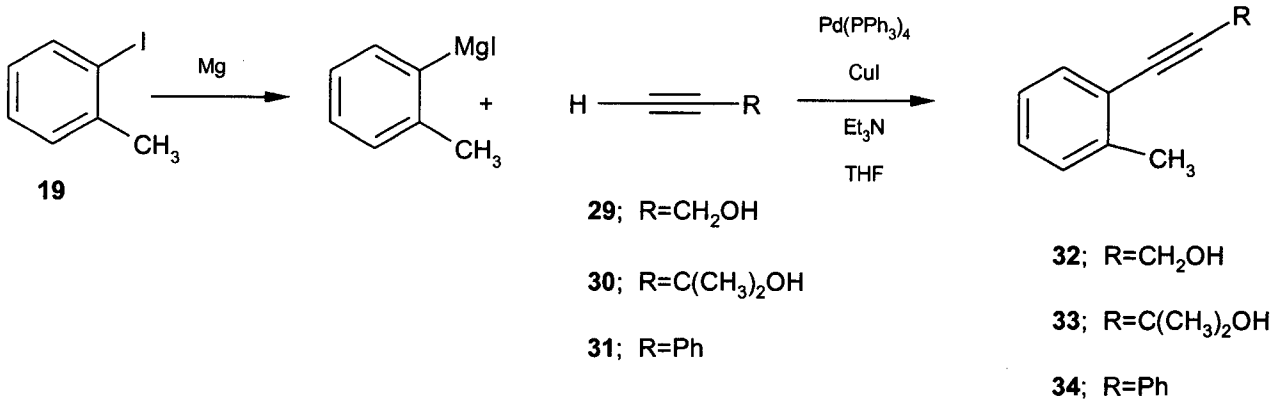
*Note: Entries 1-10 were synthesized using Procedure F of Section 5.3.

3.3.4 Grignard Coupling Using a Variety of Alkynes

The modified Grignard coupling procedure was attempted with alkynes other than TMS acetylene including: 2-propyn-1-ol, **29**, 2-methyl-3-butyn-2-ol, **30**, and phenylacetylene, (Scheme 15). All three iodophenol isomers produced unexpected moderately high yields through the Grignard reaction. Since alkynes **29**, and **30** are less acidic than the iodophenols it was thought

that they might not interfere in the Grignard reaction. However, compared to the yield obtained for the coupling of 2-iodotoluene to TMS-acetylene, 92.9%, those found using the other alkynes were significantly lower, 2.6%, 9.3% and 51.5% for 2-propyn-1-ol, **29**, 2-methyl-3-butyn-2-ol, **30**, and phenylacetylene respectively. Due to the small amount of desired product obtained for the former two compounds they were not isolable and thus, were not characterized. The conclusions drawn from this set of data were first, that TMS-acetylene provides the best coupling and second, the terminal alcohol groups on 2-propyn-1-ol, **29**, and 2-methyl-3-butyn-2-ol, **30**, have interfered in the Grignard reaction as expected, thus an attempt at protecting these alcohol groups prior to coupling may significantly improve the yields.

Scheme 15

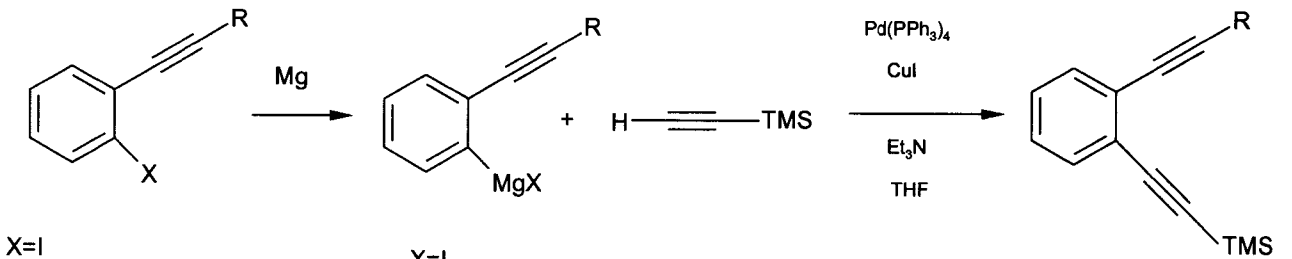


3.3.5 The Synthesis of Enediynes

To this point this thesis has focussed on the preparation of enynes. The ultimate goal of the research program is the synthesis of enediynes. A number of available enynes were coupled

to TMS-acetylene, the alkyne that exhibits the best coupling yield. These include various bromo and iodo enynes (Scheme 16).

Scheme 16



X=I
- **35**; R=CH_2OH
- **36**; R=$C(CH_3)_2OH$
- **37**; R=Ph
- **38**; R=TMS

X=Br
- **39**; R=CH_2OH
- **40**; R=$C(CH_3)_2OH$
- **41**; R=Ph
- **42**; R=TMS

X=I
- **43**; R=CH_2OH
- **44**; R=$C(CH_3)_2OH$
- **45**; R=Ph
- **46**; R=TMS

X=Br
- **47**; R=CH_2OH
- **48**; R=$C(CH_3)_2OH$
- **49**; R=Ph
- **50**; R=TMS

X=I
- **51**; R=CH_2OH
- **52**; R=$C(CH_3)_2OH$
- **53**; R=Ph
- **54**; R=TMS

X=Br
- **55**; R=CH_2OH
- **56**; R=$C(CH_3)_2OH$
- **57**; R=Ph
- **58**; R=TMS

Of the eight products only two were isolable and characterized, 1-[(2-phenyl-1-ethynyl)]-2-[(trimethylsilylethynyl)]benzene, **53**, and 1,2-Bis-(trimethylsilyl ethynyl)benzene, **54** (Table 8). Considering that alcohols can quench Grignard reagents, the low yields obtained for Entries 1,2,5, and 6 in Table 8 are not surprising. A possible way to improve these yields may be to protect the alcohol before coupling.

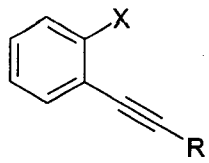


Table 8: Yields for the Synthesis of Enediynes

Entry no.	SM Enyne	Yield, %
1	R=CH_2OH; X=Br	0.0
2	R=$C(CH_3)_2OH$; X=Br	0.0
3	R=Ph; X=Br	0.0
4	R=TMS; X=Br	0.0
5	R=CH_2OH; X=I	3.9
6	R=$C(CH_3)_2OH$; X=I	2.5
7	R=Ph; X=I	56.7
8	R=TMS; X=I	13.3

3.3.6 Conclusion

In summary, it has been demonstrated that a modified set of palladium cross-coupling reactions which use aryl Grignard reagents react with an alkyne to give coupled products in good to exceptional yields in several instances. It is significant to note that the mild reaction conditions do not result in the formation of the expected magnesium acetylide compound. It is also particularly noteworthy that functional groups such as NO_2, OH and CO_2CH_3 still give reasonable yields of the desired coupled product, although, it is well known that they interfere in Grignard reactions. This modified Grignard-Sonogashira reaction provides a useful method for the formation of carbon-carbon bonds and thus, may have utility toward the synthesis of

enediynes. The next question to acknowledge is with regard to the mechanism. Does the palladium cross-coupling mechanism apply here or is there a different mechanism occurring? The answer to this question will be addressed in the next chapter.

CHAPTER 4

DETERMINATION OF MECHANISM

IN THE

GRIGNARD-SONOGASHIRA COUPLING REACTION

4.1 Mechanism for the Palladium Cross-Coupling Reaction

Sonogashira was the first to propose a mechanism for the palladium cross coupling reaction (Scheme 5).[33] He proposed that in order to drive the reduction of a Pd(II) catalyst to the active Pd(0) catalyst, the oxidative homocoupling of the alkyne and alkynylation of the starting catalyst, processes that are catalysed by cuprous iodide in the presence of diethylamine, have to occur. Next, the Pd(0) catalyst that forms enters a catalytic cycle where subsequent oxidative addition of an aryl or vinyl halide occurs. This process is followed by the alkynylation of the adduct to give the aryl or vinyl alkynyl derivative of palladium which regenerates Pd(0) by the reductive elimination of the substitution product.

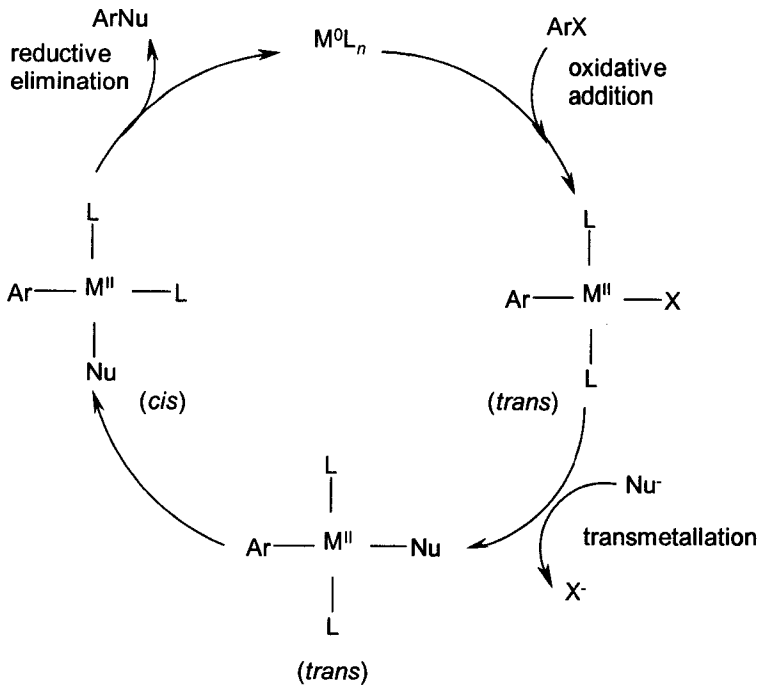
A slightly modified and generally accepted mechanism for the palladium cross coupling reaction proceeds through three steps.[49] The first step of the catalytic cycle is an oxidative addition of the aryl halide to the Pd(0) fourteen electron complex to give a *trans*-arylpalladium(II) complex. The second step involves a transmetallation reaction which complexes the alkyne to the Pd(II) centre. The final step generates the desired coupled product and regenerates the Pd(0) catalyst through a reductive elimination reaction (Scheme 17).[49] Most mechanistic investigations have not been performed in the context of a real catalytic cycle due to the instability of the intermediate complexes and the difficulty in looking at isolated catalytic

cycle segments. Recently a new proposal has been made from an investigation that studies cross coupling reactions in the context of their real catalytic cycles (Scheme 18).[49] Anions and halides were unexpectedly found to coordinate both Pd(0) and aryl Pd(II) complexes, forming tri- or penta-coordinated anionic intermediates. Amatore et al. have discovered through mechanistic studies that $Pd^0(PPh_3)_2$, formed after two successive decomplexations of PPh_3, is the reactive catalyst in the oxidative addition step. They propose that $ArPd^{II}X(PPh_3)_2$, (X=Cl, Br,I), ***A***, forms anionic complexes $Pd^0(PPh_3)_2(Ar)^-$, in which Ar^- anions coordinate the Pd(0) centre. These are key anionic tricoordinated intermediates in the palladium catalysed coupling of aryl halides which undergo oxidative addition to ArX. They also propose that *trans*-$ArPdX(PPh_3)_2$, ***B***, complexes can not be intermediates under catalytic conditions, instead the alkyne attacks an intermediate pentacoordinated neutral complex to give the anionic pentacoordinated complex, $ArPdX(alkyne)(PPh_3)_2^-$, ***C***. This brings the Ar and alkyne ligands into a favourable position which facilitates fast reductive elimination of the product and regeneration of the catalyst.

4.2 Results and Discussion

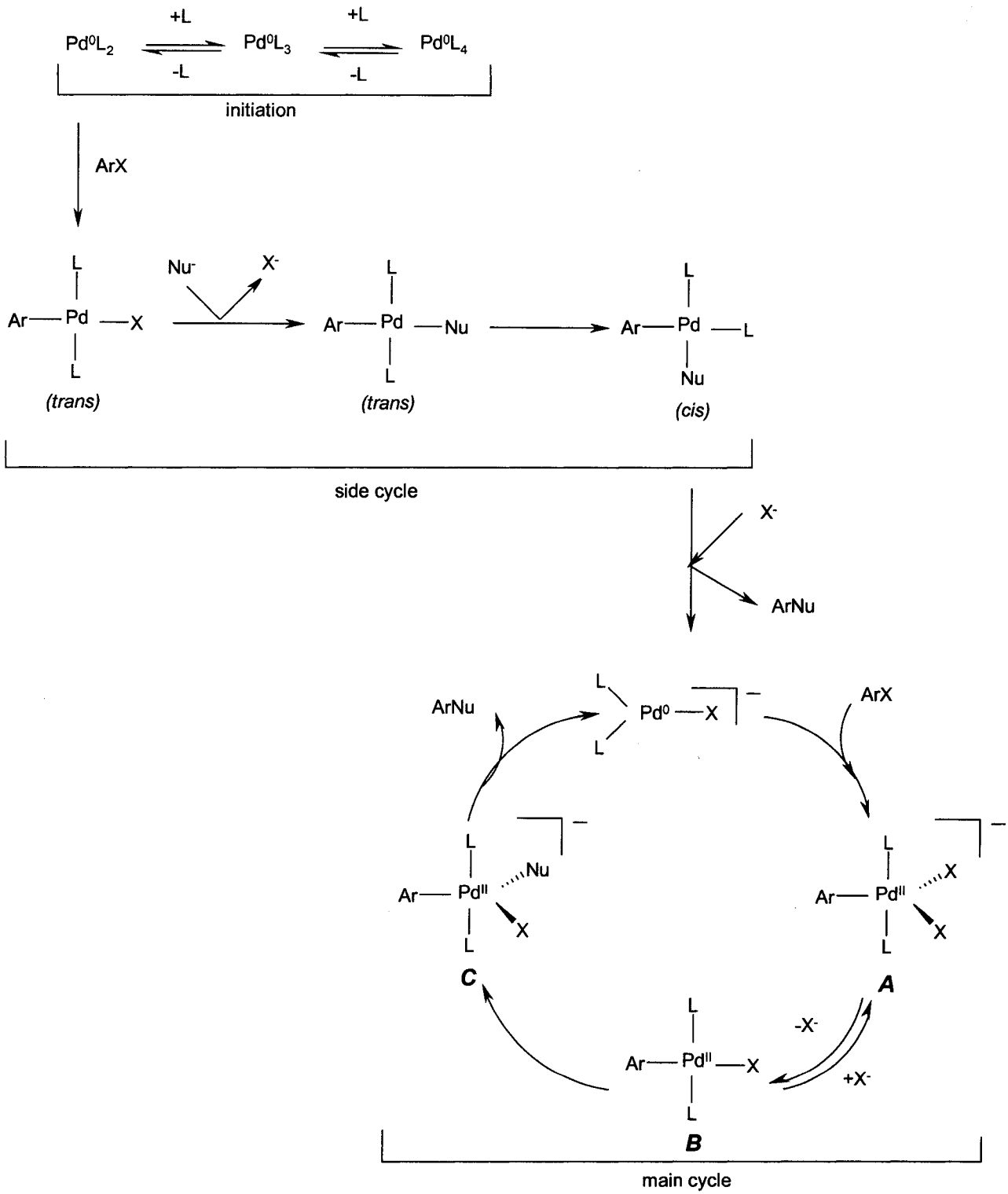
Mechanistic data for the Grignard modified coupling reaction is not present in the literature. Insight into the chemistry involved in this reaction was gained through the performance of a number of experiments. The first approach to determining the mechanism was the completion of a low temperature ^{31}P NMR experiment using the palladium coupling procedure under standard conditions, followed by a low temperature ^{31}P NMR experiment using the corresponding $Pt(PPh_3)_4$ catalyst under the same conditions, for comparison.

Scheme 17[49]



The initial thought, when designing the spectroscopy study, was that the Pt catalyst would slow down the reaction to a time scale which would allow the intermediates to be observed by NMR. The collection of ^{195}Pt NMR data was attempted, however, the signal for ^{195}Pt could not be detected. The low temperature experiments did not lead to any concrete conclusions, thus, another set of investigations was carried out. ^{31}P NMR studies of the intermediate complex for the standard Sonogashira coupling procedure and the Grignard-Sonogashira were performed and compared.

Scheme 18[49]



4.2.1 Mechanistic Studies Involving NMR Spectroscopy

^{31}P NMR studies show identical intermediates in both the standard Sonogashira reaction and the modified Grignard-Sonogashira reaction. A ^{31}P signal (relative to H_3PO_4 as the internal standard) at 23.8 ppm, present in both spectra, represents the *trans*-$ArPdX(PPh_3)_2$ species.[67] Other peaks observed were the $Pd(PPh_3)_4$ catalyst at 30.2 ppm and 23.7 ppm, and PPh_3 at -4.5 ppm.

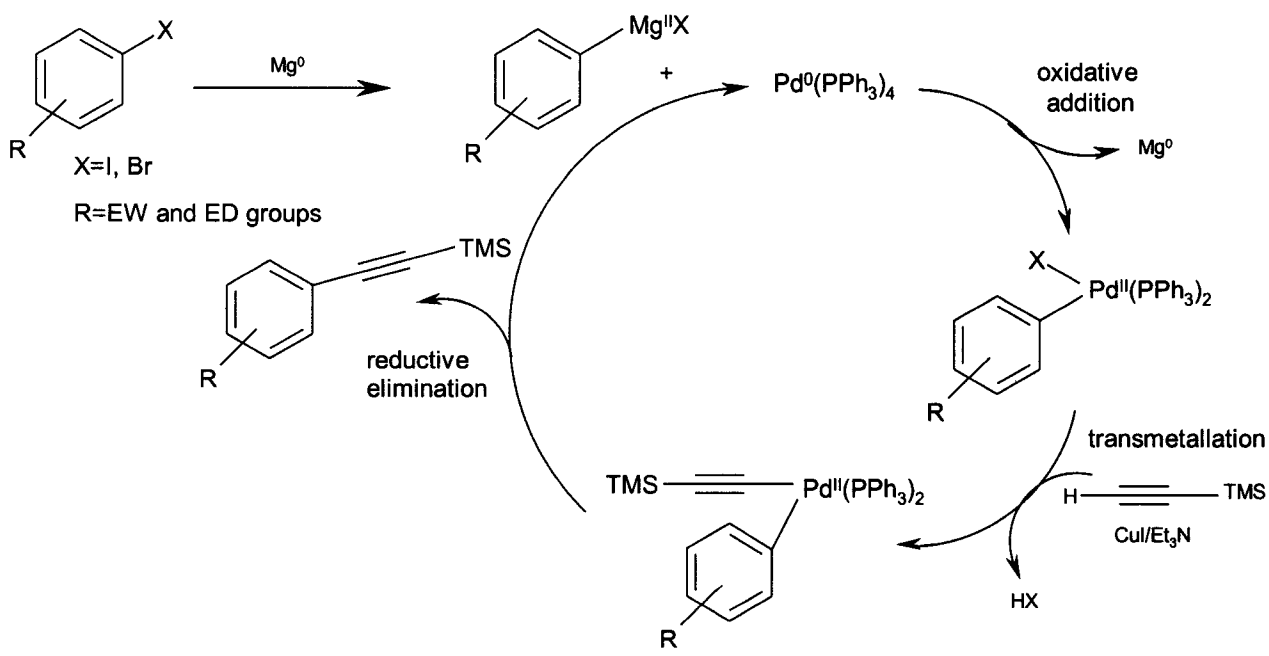
4.2.2 Mg Mass Balance Reaction

Due to the aqueous work up in the Grignard reaction, it is difficult to determine the nature of the magnesium by-product in the resulting reaction mixture. Although, it may be a slightly primitive method of determining the amount of Mg(0) regenerated once the reaction was complete, the physical removal of magnesium metal pieces within the reaction mixture was somewhat effective. Prior to the addition of the catalyst and alkyne, the products from the Grignard formation procedure were cannuled into a new flask, therefore, no magnesium metal was present before the Sonogashira reaction took place. This ensured that any magnesium metal recovered was generated after the Sonogashira reaction was completed. Once the organics were separated from the metals, ICP analysis was done. This method did exhibit a high margin of experimental error, however, 49.2% of the Mg(0) was recovered. This is almost exactly half of the magnesium that reacted according to the yield previously calculated for 2-iodotoluene, the starting material used. Since Mg(0) was recovered from the reaction mixture and the aryl Grignard reagent was proven to form, it can be concluded that the Mg(II) of the Grignard reagent is reduced back to its metallic form through the course of the reaction.

4.2.3 Proposed Mechanism

Similar to standard Sonogashira coupling, the Grignard coupling reactions undergo an oxidative addition, transmetallation, and reductive elimination reaction (Scheme 19). The carbon-magnesium bond of the aryl Grignard reagent shows a higher degree of polarization and is, thus, more reactive than the carbon-halogen bond. This enhanced reactivity facilitates the exchange of Mg with Pd at the oxidative addition step. The insertion of Pd(0) occurs with an oxidation state change to Pd(II) and it is proposed that this oxidation is coupled to the reduction of the Mg(II) to recoverable Mg(0).

Scheme 19



4.2.4 Conclusion

This modified Grignard coupling reaction proceeds through a transmetallation reaction similar to the Sonogashira coupling procedure. The intermediate, *trans*-$ArPdX(PPh_3)_2$, is the same for both procedures as suggested through ^{31}P NMR spectroscopic studies. Further investigation of the Pd-Mg exchange is necessary.

4.3 Future Work

This work has attempted to determine which combination of substituents, and relative positions to the halogen on the aromatic ring, give the most favourable conditions for the coupling of alkynes onto aryl rings. In the process of attempting to answer questions proposed in this thesis, the prospect of investigation into many new areas arose, which should be looked into in the future.

The ^{195}Pt experiments should be looked into further. Once the ^{195}Pt signal is found it may be used to analyse the point in the reaction that the coordination of Cu to the Pt catalyst occurs, if it does at all. The behaviour of the Cu co-catalyst observed in this experiment can then be applied to the corresponding Pd catalyst system. With regard to the role of CuI in the mechanism, it may also be beneficial to replace the CuI with a different copper salt to see if it has an effect on the outcome of the reaction. Mechanistic data concerning the Mg-Pd exchange for the Grignard modified reactions should continue to be obtained along with rate experiments for this series of reactions. Other experiments should be developed for studying the nature of the magnesium byproduct as the method used in this thesis has a high margin of error. In terms of optimization of the alkyne involved, 2-propyn-1-ol and 2-methyl-3-butyn-2-ol should be

protected to see if the yields obtained would be improved from those obtained using the unprotected alkynes. Finally, this thesis mainly encompasses the synthesis of enynes. The information obtained from these experiments has provided some insight into which coupling procedure is most effective for monocoupling. With some modification this data should be applied to the synthesis of enediynes.

CHAPTER 5

EXPERIMENTAL SECTION

5.1 General Materials, Experimentation Techniques, and Instrumentation Used

THF was distilled from potassium, while all other solvents, excluding those used for the HPLC experiments, were of reagent grade and used without further purification. All reactions were performed under nitrogen by insertion of a balloon through a rubber septum and carried out in flame dried glassware of varying sizes. Air and moisture sensitive reagents were transferred through the rubber septa on the flame dried reaction flask via syringe. Excess solvents were drawn off in vacuo using a Buchi rotary evaporator at pressures obtained by a water aspirator. The catalysts $Pd(PPh_3)_4$, $Pt(PPh_3)_4$, $PdCl_2$, Pd(II) acetyl acetonate, [1,1'-bis(diphenylphosphino)-ferrocene]dichloro Pd(II), [1,2-bis(diphenylphosphino)-ethane]dichloro Pd(II) were placed in parafilm sealed vials so as not to allow moisture to penetrate the contents, and wrapped in aluminum foil as they are light sensitive. All of these catalysts were purchased from Aldrich with the exception of $Pd(PPh_3)_4$ and $Pt(PPh_3)_4$ which were synthesized using previously described methods.[68,69] They were stored at -10 °C prior to and after use. Similarly, all other starting materials for which procedures are not listed were purchased. Trimethyl[(4-methylphenyl) ethynyl]silane,[70] 2-[(trimethylsilyl)ethynyl]phenol,[71] trimethyl[(2-methoxyphenyl)ethynyl] silane,[71] trimethyl[(4-methoxyphenyl)ethynyl]silane,[72] 2-[(trimethylsilyl) ethynyl]benzenamine,[73] 3-[(trimethylsilyl)ethynyl]benzenamine,[74] and 4-[(trimethylsilyl)ethynyl] benzenamine[75] were compared to previously reported literature values. The crude samples of compounds not reported in the literature were stored in vials in the refrigerator until further purification and analysis were

conducted.

Analytical thin layer chromatography was performed on silica gel 250 μm in thickness, with a 5-17 particle size and a 60 Å pore size. Spots were viewed under UV light as the plates contained a 254 nm fluorescence indicator. Solvents used for TLC are indicated in the procedure along with their concentration ratios determined by volume. Column chromatography was used to separate and purify the crude products. This was accomplished using 230-400 mesh recycled silica gel and a combination of hexane/EtOAc was the solvent system used. Gas-Liquid chromatography (GLC) was performed on a Hewlett Packard 5890 equipped with a flame ionization detector. The DB-5HT column consisted of 5% phenyl and methylpolysiloxane and the carrier gas was helium set at a flow rate of 2.0 ml/min. Samples of the pure *para*-substituted compounds were used to calculate response factors as all percent yields for the coupling reactions, with biphenyl as an internal standard, were reported by GLC. Similarly, gas chromatography-mass spectrometry (GC-MS) was carried out on a Hewlett Packard 5890 series II machine also using a DB-5HT column and helium as the carrier gas. The mass spectra were measured and recorded on a VG Micromass Autospec mass spectrometer and are presented as follows: parent ion (relative intensity), m/e of significant fragments (relative intensity). Elemental analyses were recorded on a CEC 240-XA Elemental Analyzer. Infrared spectra were measured on a Perkin Elmer 1320 Infrared Spectrometer. Samples were prepared either neat or as a nujol mull on NaCl plates, with the exception of trimethyl[(4-methoxyphenyl)ethynyl]silane, 3-[(trimethylsilyl)ethynyl]benzoic acid, and 4-[(trimethylsilyl)ethynyl]benzoic acid which were resolved on a Bruker IFS66 Fourier Transform Infrared Spectrometer (FTIR) and the data for both methods are reported in reciprocal centimetres. Proton nuclear magnetic resonance

(^{1}H NMR) spectra were acquired using a Bruker AC-E 200 MHz NMR spectrometer or a Varian Oxford AS 500 MHz NMR. The solvent used was $CDCl_3$ with a 1% TMS internal standard. Chemical shift values were reported in the following order: chemical shift for ^{1}H NMR; (multiplicity, coupling constant in Hz, integration). ^{13}C NMR spectra were also recorded on the same instruments using the same solvent. $CDCl_3$ was used as the internal standard (δ 77.0) and was reported in ppm downfield from TMS. ^{31}P NMR spectra were recorded on the same apparatus and are reported using phosphoric acid as the internal standard. For competitive rate reactions a Varian Prostar HPLC equipped with a model 410 autosampler, PDA detector, and a 220/230/240 solvent delivery module was used. The solvent system that was used depended on the compounds being separated and a C8 high performance column was used for all experiments except the *ortho*, *meta*, and *para* iodoaniline which used a C18. The peaks were displayed at a wavelength of 254 nm and a resolution factor of greater than or equal to one was considered to be sufficient separation between peaks for this series of experiments. Finally, a Jarrell Ash ICAP 9000 ICP with an operating power of 1150 W was used to determine magnesium concentration.

5.2 General Procedures for the Preparation of Starting Materials

5.2.1 Triflation of a monosubstituted iodophenol[76]

2-Iodophenol, 3-iodophenol or 4-iodophenol, (6.16 mmol) were added to separate flame dried round bottom flasks containing a stir bar. The flasks were sealed and placed under nitrogen. Dry methylene chloride (15.0 ml) was added to each flask along with Et_3N (0.9 ml, 1.23 g, 12.3 mmol) via syringe and the resulting mixtures were left to stir over an ice bath until they reached 0°C. At this point Tf_2O (1.20 ml, 715 mg, 7.13 mmol) was added dropwise over

fifteen minutes. The ice bath was removed following addition and the reaction was left to proceed overnight. No work up was necessary, only solvent removal, followed by column chromatography using 30% EtOAc in hexanes.

1-Iodo-2-trifluoromethanesulfonylbenzene

Yield: 96.4%; TLC (30% EtOAc in hexanes): $R_f = 0.64$; ^1H NMR ($CDCl_3$): δ 7.87 (dd, J=6.5,1.5 Hz, 1H), 7.40 (t, J=7.3 Hz, 1H), 7.31 (d, J=8.5 Hz, 1H), 7.08 (t, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 150.4, 140.9, 130.3, 129.8, 122.2, 117.8, 89.2 ; IR (neat, cm^{-1}): 3060, 1565, 1475, 1320, 1240, 1140, 1120, 1050, 1000, 640; MS: 352 (M^+, 95.3), 288 (17.5), 219 (91.5), 203 (13.0), 191 (70.5), 165 (11.5), 127 (14.5), 92 (98.6), 80 (18.6), 64 (100); C & H Anal. for $C_7H_4SO_3F_3I$: Calculated; C 23.89%, H 1.15%, Found; C 23.59%, H 1.39%.

1-Iodo-3-trifluoromethanesulfonylbenzene

Yield: 99.9%; TLC (30% EtOAc in hexanes): $R_f = 0.67$; ^1H NMR ($CDCl_3$): δ 7.55 (t, J=2.0 Hz, 1H), 7.21 (dd, J=1.0, 1.5 Hz, 1H), 7.19 (dd, J=1.0, 1.5 Hz, 1H), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 149.2, 137.8, 131.7, 130.4, 120.9, 93.8, 53.7; IR (neat, cm^{-1}): 3000, 1550, 1540, 1445, 1400, 1220, 1020, 880, 760, 620; MS: 352 (M^+, 100), 288 (4.0), 219 (22.0), 203 (4.1), 191 (20.0), 161 (40.2), 92 (55.5), 75 (5.3); C & H Anal. for $C_7H_4SO_3F_3I$: Calculated; C 23.89%, H 1.15%, Found; C 25.45%, H 1.42%.

1-Iodo-4-trifluoromethanesulfonylbenzene

Yield: 99.9%; TLC (30% EtOAc in hexanes): $R_f = 0.66$; ^1H NMR ($CDCl_3$): δ 7.65 (d, J=8.5 Hz,

2H), 6.90 (d, J=10.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 139.5, 123.4, 121.5, 118.9, 93.2; IR (neat, cm^{-1}): 3000, 1480, 1430, 1290, 1230, 1120, 1030, 875, 830, 740, 630; MS: 352 (M^+, 90.5), 219 (100), 203 (8.1), 191 (69.5), 161 (12.5), 142 (6.8), 92 (88.4), 75 (12.5); C & H Anal. for $C_7H_4SO_3F_3I$: Calculated; C 23.89%, H 1.15%, Found; C 26.65%, H 1.40%.

5.2.2 Esterification of a monosubstituted iodo or bromobenzoic acid

2-Iodobenzoic acid, 3-iodobenzoic acid, 4-iodobenzoic acid, 2-bromobenzoic acid, 3-bromobenzoic acid, and 4-bromobenzoic acid (8.0 mmol) were added to separate flame dried three necked round bottom flasks. Thionyl chloride (0.70 ml, 1.1 g, 9.6 mmol) was added dropwise via syringe to each flask over thirty minutes. These mixtures were refluxed in a hot water bath maintained at approximately 80°C for forty minutes. The reaction was cooled below 25°C, in an ice bath while dry methanol (1.56 ml, 38.4 mmol) was added dropwise. These mixtures were refluxed for fifteen minutes, and then cooled. Ice cold water (20 ml) was added and a diethyl ether (3 x 30 ml) extraction was performed on each sample. Saturated $NaHCO_3$ (1 x 20 ml) and NaCl (1 x 20 ml) were used to wash the organic layers. The resulting organics were dried with anhydrous Na_2SO_4 and filtered.

Methyl 2-iodobenzoate

Yield: 72.0%; TLC (20% EtOAc in hexanes): R_f = 0.55 ; ^1H NMR ($CDCl_3$): δ 7.99 (d, J=8.0 Hz, 1H), 7.79 (dd, J=6.5, 1.5 Hz, 1H), 7.40 (t, J=6.5 Hz, 1H), 7.15 (t, J=6.5 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.1, 141.5, 135.2, 132.8, 131.1, 128.0, 94.2, 52.6; IR (neat, cm^{-1}): 2800, 1740, 1580, 1440, 1295, 1255, 1190, 1130, 1100, 1040, 1010, 900, 740, 630 ; MS: 262

(M^+, 95.5), 231 (100), 203 (78.2), 127 (6.0), 92 (15.0), 76 (96.9); C & H Anal. for $C_8H_7O_2I$: Calculated; C 36.69%, H 2.70%, Found; C 38.16%, H 2.56%.

Methyl 3-iodobenzoate

Yield: 99.9%; TLC (20% EtOAc in hexanes): Rf = 0.49; ^1H NMR ($CDCl_3$): δ 8.13 (t, J=1.5 Hz, 1H), 7.75 (dd, J=6.5, 1.0 Hz, 1H), 7.63 (dd, J=6.5, 1.0 Hz, 1H), 7.00 (s, 1H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.9, 141.9, 138.6, 132.0, 130.2, 128.9, 93.4, 52.5; IR (neat, cm^{-1}): 3030, 2800, 1730, 1560, 1440, 1290, 1250, 1190, 1130, 1050, 900, 730, 640; MS: 262 (M^+, 95.0), 230 (93.8), 203 (77.5), 135 (19.8), 120 (18.0), 103 (27.9), 92 (8.8), 76 (100); C & H Anal. for $C_8H_7O_2I$: Calculated; C 36.69%, H 2.70%, Found; C 37.44%, H 2.93%.

Methyl 4-iodobenzoate

Yield: 87.3%; TLC (20% EtOAc in hexanes): R_f = 0.55; ^1H NMR ($CDCl_3$): δ 7.90 (dt, J=8.5, 2.0 Hz, 2H), 7.74 (dt, J=8.5, 2.0 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 180.2, 138.5, 137.9, 137.8, 131.9, 52.4; IR (neat, cm^{-1}): 3029, 2800, 1732, 1582, 1375, 1275, 900, 735; MS: 262 (M^+, 92.2), 231 (100), 203 (79.8), 135 (8.9), 104 (30.0), 76 (92.0); C & H Anal. for $C_8H_7O_2I$: Calculated; C 36.69%, H 2.70%, Found; C 36.99%, H 2.60%.

Methyl 2-bromobenzoate

Yield: 95.6%; TLC (25% EtOAc in hexanes): R_f =0.51; ^1H NMR ($CDCl_3$): δ 7.69 (dd, J=5.5, 1.5 Hz, 1H), 7.55 (dd, J=6.5, 1.5 Hz, 1H), 7.26 (t, J=6.0 Hz, 1H), 7.23 (t, J=5.5 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.7, 134.4, 132.7, 132.2, 131.4, 127.3, 121.7, 52.5;

IR (neat, cm^{-1}): 3030, 2800, 1730, 1585, 1460, 1430, 1295, 1250, 1190, 1130, 1100, 1030, 900, 740, 630; MS: 216 (M^+, 37.2), 183 (100), 155 (31.2), 139 (5.0), 76 (12.0); C & H Anal. for $C_8H_7O_2Br$: Calculated; C 44.69%, H 3.28%, Found; C 42.28%, H 3.19%.

Methyl 3-bromobenzoate

Yield: 37.3%; TLC (25% EtOAc in hexanes): $R_f = 0.58$; ^1H NMR ($CDCl_3$): δ 8.15 (s, 1H), 7.94 (d, J=2.5 Hz, 1H), 7.64 (d, J=2.0 Hz, 1H), 7.28 (t, J=8.0 Hz 1H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.9, 135.9, 132.7, 132.2, 130.1, 128.3, 122.6, 52.5; IR (neat, cm^{-1}): 3030, 2800, 1730, 1570, 1440, 1295, 1260, 1190, 1130, 1080, 1060, 900, 830, 750, 660; MS: 214 (M^+, 42.0), 183 (100), 155 (41.9), 76 (18.0); C & H Anal. for $C_8H_7O_2Br$: Calculated; C 44.69%, H 3.28%, Found; C 44.15%, H 3.28%.

Methyl 4-bromobenzoate

Yield: 84.9%; TLC (20% EtOAc in hexanes): $R_f = 0.52$; ^1H NMR ($CDCl_3$): δ 7.88 (d, J=8.0 Hz, 2H), 7.56 (d, J=8.5 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.5, 131.9, 131.2, 129.2, 128.2, 52.4; IR (neat, cm^{-1}): 3029, 2810, 1735, 1590, 1276, 1100, 1012, 905, 720; MS: 214 (M^+, 36.9), 183 (100), 155 (34.5), 75 (13.0); C & H Anal. for $C_8H_7O_2Br$: Calculated; C 44.69%, H 3.28%, Found; C 45.00%, H 3.45%.

5.3 General Procedures for Preparation of Substituted Trimethylsilylethynylbenzenes

Procedure A: Coupling Procedure #1

This procedure was run twice for each substituted iodo- and bromobenzene. $Pd(PPh_3)_4$

(46 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), and Et_3N (0.42 ml, 303 mg, 3.0 mmol) were added to a flame dried flask. The contents were sealed with a septum and placed under nitrogen. A substituted iodo or bromobenzene compound (2.0 mmol) in dry THF (5 ml) was introduced through the septum via syringe. The contents were stirred and cooled in an ice bath. After stirring for ten minutes TMS-acetylene (0.30 ml, 206 mg, 2.1 mmol) was added dropwise over thirty minutes. This reaction mixture was allowed to stir at room temperature overnight, upon which it was filtered through celite to remove the Pd and Cu catalysts. Excess solvent was removed from the filtrate in vacuo. All of the crude samples were spotted on TLC plates. A known mass of sample was combined with a known mass of biphenyl in 1 ml of methylene chloride for GLC and diluted further for GC-MS. The *ortho*, *meta*, and *para* substituted crude products were dissolved in diethyl ether for separation and purification by column chromatography.

Procedure B: Coupling procedure #2[36]

This procedure was run for selected substituted iodo and bromobenzenes. $PdCl_2$ (7.3 mg, 0.04 mmol), and PPh_3 (20 mg, 0.08 mmol) were added to a flame dried flask. The contents were sealed with a septum and placed under nitrogen. Dry THF (5 ml) was added via syringe and the mixture was left to stir for thirty minutes to allow the $Pd(PPh_3)_2Cl_2$ complex to form. After thirty minutes CuI (15.0 mg, 0.08 mmol) and THF (2.0 ml) were added to the flask along with a substituted phenyl halide (2.0 mmol) dissolved in THF (3 ml). Next, Et_3N (0.42 ml, 303 mg, 2.1 mmol) was syringed into the flask followed by the addition of TMS-acetylene (0.30 ml, 206 mg, 2.1 mmol) over 1 hour. Once all of the TMS-acetylene was added, the solvent was removed and

the resulting residue was treated with *n*-pentane (3 x 20 ml). The last washing of the crude product was filtered through celite and the resulting crude residue was rotovapped to remove the excess solvent. A known mass of the residue was combined with a known mass of biphenyl in 1 ml of methylene chloride and injected into the GLC for analysis.

Procedure C: Coupling procedure #3[36]

This procedure was run for selected substituted iodo- and bromobenzenes. $PdCl_2$ (17.1 mg, 0.1 mmol), and PPh_3 (65.1 mg, 0.25 mmol) were added to a flame dried flask. The contents were sealed with a septum and placed under nitrogen. Dry THF (5 ml) was added via syringe and the mixture was left to stir for thirty minutes to allow the $Pd(PPh_3)_2Cl_2$ complex to form. After thirty minutes a substituted benzene halide (2.0 mmol) dissolved in THF (3 ml), Et_3N (0.42 ml, 303 mg, 2.1 mmol) and TMS-acetylene (0.42 ml, 294 mg, 3.0 mmol) were introduced via syringe. This mixture was left to stir at room temperature for twenty minutes and CuI (15.0 mg, 0.08 mmol) was added by briefly opening the septum. The flask contents were left to stir for sixteen hours upon which the solvent was removed and the residue was treated with *n*-pentane (3 x 20 ml) and filtered through celite. A known mass of the residue was combined with a known mass of biphenyl in 1 ml of methylene chloride and injected into the GLC for analysis

Procedure D: Rate Reactions of Monosubstituted Iodobenzenes and Bromobenzenes using GLC

This procedure was run for selected substituted iodo and bromobenzenes (2.0 mmol). $Pd(PPh_3)_4$ (46 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), biphenyl (known weight) and Et_3N

(0.42 ml, 303 mg, 3.0 mmol) were added to a flame dried flask. The contents were sealed with a septum and placed under nitrogen. A substituted iodo or bromobenzene compound (2.0 mmol) in dry THF (5 ml) was introduced through the septum via syringe. The contents were stirred and cooled in an ice bath. A portion (15 μl) of this mixture was drawn out of the reaction flask through the septum via syringe, diluted with methylene chloride (0.25 ml) and 1 μl of this dilute solution was injected into the GLC. After stirring for ten minutes TMS-acetylene (0.30 ml, 206 mg, 2.1 mmol) was added over thirty-five minutes. Upon completion of this addition, another sample (15 μl) of the flask contents was immediately micro-syringed into methylene chloride (0.25 μl) and 1 μl of this dilute solution was injected into the GLC. At thirty-five minute intervals after this, samples were removed from the reaction mixture and GLCs were obtained until the starting material peak was not visible on the gas chromatograph.

Procedure E: Competitive Rate Reactions of Monosubstituted Iodobenzenes and Bromobenzenes using GLC

This procedure was run for selected substituted iodo and bromobenzenes (2.0 mmol). $Pd(PPh_3)_4$ (46 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), biphenyl (internal standard) and Et_3N (0.42 ml, 303 mg, 3.0 mmol) were added to a flame dried flask. The contents were sealed with a septum and placed under nitrogen. Dry THF (5 ml) and a combination of substituted benzene halide compounds (2.0 mmol each) were introduced through the septum via syringe, upon which the contents were stirred and cooled in an ice bath. A portion (15 μl) of this mixture was drawn out of the reaction flask through the septum via syringe, diluted in methylene chloride (0.25 ml) and 1 μl of this dilute solution was injected into the GLC. After stirring for ten minutes, TMS-

acetylene (0.30 ml, 206 mg, 2.1 mmol) was added over thirty-five minutes. Upon completion of this addition, another sample of the flask contents (15 μl) was immediately micro-syringed into methylene chloride (0.25 ml) and 1 μl of this dilute solution was injected into the GLC. At thirty-five minute intervals after this, samples were removed from the reaction mixture and GLCs were obtained until one of the starting material peaks was not visible on the gas chromatograph.

Procedure F: Grignard Coupling Procedure

This procedure was run twice for each substituted iodo or bromobenzene. To a flame dried flask was added Mg (49 mg, 2.0 mmol), a substituted iodo or bromobenzene (2.0 mmol), a small fragment of I_2 and dry THF (5 ml). The contents were sealed with a septum and placed under nitrogen. The resulting mixture was heated in a water bath at 40 °C and stirred over two nights. After the Mg was reacted, the septum was momentarily removed to introduce: $Pd(PPh_3)_4$ (46 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), and Et_3N (0.42 ml, 303 mg, 3.0 mmol). After this mixture had been stirring for ten minutes, TMS-acetylene (0.30 ml, 206 mg, 2.10 mmol) was added dropwise over ten minutes. This was left to stir at room temperature for four hours, whereupon it was quenched with water (4.0 ml), extracted with diethyl ether (3 x 10 ml), washed with water (5.0 ml) and saturated NaCl (5.0 ml), dried with $MgSO_4$, filtered and concentrated. A known mass of sample was combined with a known mass of biphenyl in 1 ml of methylene chloride for GLC and diluted further for GC-MS. The *ortho*, *meta*, and *para* substituted crude products were dissolved in diethyl ether for separation and purification by column chromatography.

Procedure G: Grignard coupling using $PdCl_2$ and PPh_3 in a 1:2 ratio

Procedure F was followed, however, the starting materials used in this procedure were 1-iodo-4-ethylbenzene and 2-iodotoluene and the catalyst system included $PdCl_2$ (0.05 mmol) and PPh_3 (0.09 mmol) in place of $Pd(PPh_3)_4$.

Procedure H: Grignard coupling between TMS-acetylene and an alkyne substituted halo benzene

Procedure F was followed, however, the starting material was an alkyne substituted halo benzene. This procedure was performed on a smaller scale as there was only a small amount of starting material available.

Procedure I: Grignard coupling of a series of alkynes to 2-iodotoluene

Procedure F was followed, however, 2-iodotoluene (1.0 mmol) was used as the starting material and a number of different alkynes were used instead of TMS-acetylene. These include: 2-propyn-1-ol (1.0 mmol), 2-methyl-3-butyn-2-ol (1.0 mmol) and phenylacetylene (1.0 mmol).

Procedure J: Coupling of TMS-acetylene with 4-iodoaniline using a number of different catalyst systems

Procedure A was followed, however, the catalyst system used was modified. This procedure uses 4-iodoaniline as the starting material and was repeated twice for four different catalyst systems, once including PPh_3 (0.16 mmol) and once excluding it. The catalysts are: 1) Pd(II) Acetate (0.04 mmol), 2) 1,1-bis diphenylphosphinoferrocenedichloroPd(II) (0.04 mmol),

3) 1,2-bis diphenylphosphinoethanedichloroPd(II) (0.04 mmol), and 4) Pd(II) Acetylacetonate (0.04 mmol).

5.4 Preparations

Trimethyl[(2-methoxyphenyl)ethynyl]silane

Refer to procedures A and F. 2-Iodoanisole (0.26 ml, 468 mg, 2.0 mmol) and 2-bromoanisole (0.25 ml, 374 mg, 2.0 mmol) were used to obtain the product by both methods. This compound was prepared, purified and compared to literature values.[36]

Yield: Procedure A: 2-iodoanisole 74.3%, 2-bromoanisole 1.6%;

Procedure F: 2-iodoanisole 22.3%, 2-bromoanisole 7.8%.

Trimethyl[(3-methoxyphenyl)ethynyl]silane

Refer to procedures A and F. 3-Iodoanisole (0.24 ml, 468 mg, 2.0 mmol) and 3-bromoanisole (0.25 ml, 374 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: 3-iodoanisole 48.2%, 3-bromoanisole 6.5%;

Procedure F: 3-iodoanisole 68.5%, 3-bromoanisole 8.2%;

TLC (20% EtOAc in hexanes): R_f= 0.64; ^{1}H NMR ($CDCl_3$): δ 7.39 (dd, J=9.0, 2.4 Hz, 1H), 7.26 (s, 1H), 7.13 (t, J=9.0, Hz, 1H), 7.06 (dd, J=8.5, 2.4 Hz, 1H), 3.36 (s, 3H), 0.37 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 139.5, 134.3, 130.1, 122.4, 120.3, 110.9, 101.1, 98.2, 56.0, 0.0; IR (neat, cm^{-1}): 2995, 2950, 2150, 1580, 1480, 1248, 1155; MS: 204 (M^+, 27), 189 (100), 146 (8.0); C & H Anal. for $C_{12}H_{16}OSi$: Calculated; C 70.53%, H 7.91%, Found; C 68.72%, H 7.74%.

Trimethyl[(4-methoxyphenyl)ethynyl]silane

Refer to procedures A and F. 4-Iodoanisole (460 mg, 2.0 mmol) and 4-bromoanisole (0.25 ml, 374 mg, 2.0 mmol) were used to obtain the product by both methods. This compound was prepared, purified and compared to literature values.[72] Procedure B was also followed using 4-bromoanisole as the starting material.

Yield: Procedure A: 4-iodoanisole 98.9%, 4-bromoanisole 0.8%;

Procedure B: 4-bromoanisole 0.0%

Procedure F: 4-iodoanisole 71.0%, 4-bromoanisole 0.8%.

Trimethyl[(2-methylphenyl)ethynyl]silane

Refer to procedures A and F. 2-Idotoluene (0.25, 436 mg, 2.0 mmol) and 2-bromotoluene (0.24 ml, 342 mg, 2.0 mmol) were used to obtain the product by both methods. Procedure G was also followed using 2-iodotoluene as the starting material.

Yield: Procedure A: 2-iodotoluene 34.7%, 2-bromotoluene 0.5%;

Procedure F: 2-iodotoluene 93.9%, 2-bromotoluene 12.9%;

Procedure G: 2-iodotoluene 42.9%;

TLC (20% EtOAc in hexanes): $R_f = 0.63$; ^{1}H NMR ($CDCl_3$): δ 7.52 (d, J=7.2 Hz, 2H), 7.29 (t, J=8.2 Hz, 1H), 7.26 (dd, J=5.0, 1.7 Hz, 1H), 2.51 (s, 3H), 0.34 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.6, 132.3, 129.4, 128.8, 125.6, 123.1, 104.0, 98.1, 34.9, 0.0; IR (neat, cm^{-1}): 3010, 2950, 2860, 2150, 1590, 1480, 1250; MS: 188 (M^+, 22.5), 173 (100), 145 (10.2); C & H Anal. for $C_{12}H_{16}Si$: Calculated; C 76.52%, H 8.56%, Found; C 76.32%, H 8.76%.

Trimethyl[(3-methylphenyl)ethynyl]silane

Refer to procedures A and F. 3-Iodotoluene (0.26 ml, 436 mg, 2.0 mmol) and 3-bromotoluene (0.24 ml, 342 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: 3-iodotoluene 30.3%, 3-bromotoluene 4.3%;

Procedure F: 3-iodotoluene 91.8%, 3-bromotoluene 12.7%;

TLC (20% EtOAc in hexanes): $R_f = 0.60$; ^1H NMR ($CDCl_3$): δ 7.36 (s, 1H), 7.40 (t, J=7.3 Hz, 1H), 7.18 (d, J=7.2 Hz, 1H), 7.14 (d, J=7.1 Hz, 1H) , 2.32 (s, 3H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 138.0, 132.4, 129.3, 129.0, 128.2, 128.0, 115.4, 93.8, 34.9, 0.0; IR (neat, cm^{-1}): 3030, 2970, 2845, 2145, 1595, 1483, 1248; MS: 188 (M^+, 17.8), 173 (100), 143 (5.4); C & H Anal. for $C_{12}H_{16}Si$: Calculated; C 76.52%, H 8.56%, Found; C 76.29%, H 8.86%.

Trimethyl[(4-methylphenyl)ethynyl]silane

Refer to procedures A and F. 4-Iodotoluene (436 mg, 2.0 mmol) and 4- bromotoluene (0.25 ml, 342 mg, 2.0 mmol) were used to obtain the product by both methods. This compound was prepared, purified and compared to literature values.[70] Procedures B, D and E were also followed using both starting materials.

Yield: Procedure A: 4-iodotoluene 54.0%, 4-bromotoluene 1.9%;

Procedure B: 4-iodotoluene 99.9%, 4-bromotoluene 0.0%;

Procedure D: 4-iodotoluene peak disappeared 70 min. after TMS-acetylene addition;

4-bromotoluene peak did not disappear up to 1 week after TMS-acetylene addition;

Procedure E: 4-iodotoluene vs. 4-bromotoluene: 4-iodotoluene peak disappeared first 70

min. after TMS-acetylene addition;

4-iodotoluene vs. 1-iodo-4-nitrobenzene: 1-iodo-4-nitrobenzene peak disappeared first 35 minutes after TMS-acetylene addition;

Procedure F: 4-iodotoluene 68.7%, 4-bromotoluene 10.3%.

2-[(Trimethylsilyl)ethynyl]phenol

Refer to procedures A and F. 2-Iodophenol (440 mg, 2.0 mmol) and 2-bromophenol (0.23 ml, 346 mg, 2.0 mmol) were used to obtain the product by both methods. This compound was prepared, purified and compared to literature values.[36]

Yield: Procedure A: 2-iodophenol 91.2%, 2-bromophenol 0.0%;

Procedure F: 2-iodophenol 59.4%, 2-bromophenol 0.0%.

3-[(Trimethylsilyl)ethynyl]phenol

Refer to procedures A and F. 3-iodophenol (440 mg, 2.0 mmol) as well as 3-bromophenol (346 mg, 2.0 mmol) were used to obtain the crude product by both methods.

Yield: Procedure A: 3-iodophenol 78.9%, 3-bromophenol 0.5%;

Procedure F: 3-iodophenol 49.2%, 3-bromophenol 0.0%;

TLC (30% EtOAc in hexanes): $R_f = 0.50$; ^{1}H NMR ($CDCl_3$): δ 7.07 (s, 1H), 6.96 (d, J= 7.0 Hz, 1H), 6.90 (t, J=7.5 Hz, 1H), 6.84 (d, J=8.0 Hz, 1H), 4.89 (br. s., 1H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$): 155.2, 129.5, 124.8, 124.3, 118.7, 116.2, 104.9, 94.5, 0.0; IR (neat, cm^{-1}): 3400, 2860, 2060, 1545, 1535, 1200, 1005, 800; MS: 190 (M^+, 19.5), 175 (100), 145 (4.6), 88 (3.6); C & H Anal. for $C_{11}H_{14}OSi$: Calculated; C 69.42 %, H 7.41%. Found; C 68.11%, H 7.06%.

4-[(Trimethylsilyl)ethynyl]phenol

Refer to procedures A and F. 4-Iodophenol (440 mg, 2.0 mmol) and 4-bromophenol (346 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: 4-iodophenol 73.8%, 4-bromophenol 1.2%;

Procedure F: 4-iodophenol 19.5%, 4-bromophenol 0.0%;

TLC (30% EtOAc in hexanes): $R_f = 0.46$; ^1H NMR ($CDCl_3$): δ 7.17 (dd, J=3.5, 2.5 Hz, 2H), 6.52 (dt, J=6.5, 3.0 Hz, 2H), 3.99 (br. s., 1H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): 155.8, 141.7, 133.6, 115.3, 105.0, 92.3, 0.0; IR (neat, cm^{-1}): 3300, 2880, 2080, 1470, 1210, 1120, 800; MS: 190 (M^+, 29), 175 (100), 145 (6.8), 88 (6.40); C & H Anal. for $C_{11}H_{14}OSi$: Calculated; C 69.42%, H 7.41%. Found; C 69.42%, H 7.24%.

2-[(Trimethylsilyl)ethynyl]aniline

Refer to procedures A and F. 2-Iodoaniline (438 mg, 2.0 mmol) and 2- bromoaniline (344 mg, 2.0 mmol) were used to obtain the product by both methods. This compound was prepared, purified and compared to literature values.[73]

Yield: Procedure A: 2-iodoaniline 60.1%, 2-bromoaniline 1.6%;

Procedure F: 2-iodoaniline 55.6%, 2-bromoaniline 0.0%;

3-[(Trimethylsilyl)ethynyl]aniline

Refer to procedures A and F. 3-Iodoaniline (0.24 ml, 438 mg, 2.0 mmol) and 3-bromoaniline (0.22 ml, 344 mg, 2.0 mmol) were used to obtain the product by both methods. This compound was prepared, purified and compared to literature values.[74]

Yield: Procedure A: 3-iodoaniline 65.7%, 3-bromoaniline 0.0%;

Procedure F: 3-iodoaniline 72.9%, 3-bromoaniline 0.0%.

4-[(Trimethylsilyl)ethynyl]aniline

Refer to procedures A and F. 4-Iodoaniline (438 mg, 2.0 mmol) and 4- bromoaniline (344 mg, 2.0 mmol) were used to obtain the product by both methods. This compound was prepared, purified and compared to literature values.[75] Procedure J was also followed using 4-iodoaniline as the starting material.

Yield: Procedure A: 4-iodoaniline 42.3%, 4-bromoaniline 0.0%;

Procedure F: 4-iodoaniline 38.4%, 4-bromoaniline 0.0%;

Procedure J: 1a) Pd(II)Acetate: 4.8%;

1b) Pd(II)Acetate / PPh_3: 72.8%;

2a) 1,1-bis diphenylphosphinoferrocenedichloroPd(II): 53.8%;

2b) 1,1-bis diphenylphosphinoferrocenedichloroPd(II) / PPh_3: 13.6%;

3a) 1,2-bis diphenylphosphinoethanedichloroPd(II): 0.0%;

3b) 1,2-bis diphenylphosphinoethanedichloroPd(II) / PPh_3: 42.0%;

4a) Pd(II)Acetylacetonate: 0.0%;

4b) Pd(II)Acetylacetonate / PPh_3: 63.0%.

2-[(Trimethylsilyl)ethynyl]benzoic acid

Refer to procedures A and F. 2-Iodobenzoic acid (496 mg, 2.0 mmol) and 2-bromobenzoic acid (402 mg, 2.0 mmol) were used to obtain the product by both methods. This

compound was prepared, however no pure product was obtained due to insufficient yields. Yield: Procedure A: 2-iodobenzoic acid 0.0%, 2-bromobenzoic acid 0.0%;

Procedure F: 2-iodobenzoic acid 0.8%, 2-bromobenzoic acid 0.0%.

3-[(Trimethylsilyl)ethynyl]benzoic acid

Refer to procedures A and F. 3-Iodobenzoic acid (496 mg, 2.0 mmol) and 3-bromobenzoic acid (402 mg, 2.0 mmol) were used to obtain the product by both methods. Yield: Procedure A: 3-iodobenzoic acid 5.2%, 3-bromobenzoic acid 0.0%;

Procedure F: 3-iodo benzoic acid 1.6%, 3-bromobenzoic acid 0.0%;

TLC (50% EtOAc in hexanes): Rf = 0.64; ^{1}H NMR ($CDCl_3$): δ 12.51 (s, 1H), 8.22 (s, 1H), 8.07 (d, J=6.0 Hz, 1H), 7.70 (d, J=6.1 Hz, 1H), 7.44 (t, J=9.6 Hz, 1H), 0.28 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.5, 136.9, 133.7, 130.0, 129.3, 128.5, 123.9, 103.6, 95.9, 0.0; IR (neat): 3447, 2960, 2159, 1701, 1299, 1090; MS: 218 (M^+, 12.2), 203 (100), 115 (4.2); C & H Anal. of $C_{12}H_{14}O_2Si$: Calculated; C 66.02%, H 6.46%, Found C 67.12%, H 6.79%.

4-[(Trimethylsilyl)ethynyl]benzoic acid

Refer to procedures A and F. 4-Iodobenzoic acid (496 mg, 2.0 mmol) and 4-bromobenzoic acid (402 mg, 2.0 mmol) were used to obtain the product by both methods. Yield: Procedure A: 4-iodobenzoic acid 16.9%, 4-bromobenzoic acid 0.0%;

Procedure F: 4-iodobenzoic acid 1.5%, 4-bromobenzoic acid 0.0%;

TLC (50% EtOAC in hexanes): R_f = 0.67; ^{1}H NMR ($CDCl_3$): δ 11.92 (s, 1H), 8.04 (d, J=3.2 Hz, 2H), 7.53 (d, J=3.2 Hz, 2H), 0.27 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.3, 132.1, 130.1, 128.9,

128.7, 104.0, 98.5, 0.0; IR (neat): 2953, 2156, 1729, 1459, 1292, 1126; MS: 218 (M^+, 9.1), 203 (100), 115 (6.0).

Trimethyl[(2-nitrophenyl)ethynyl]silane

Refer to procedures A and F. 1-Iodo-2-nitrobenzene (498 mg, 2.0 mmol) and 1- bromo-2-nitrobenzene (404 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: 1-iodo-2-nitrobenzene 90.4%, 1-bromo-2-nitrobenzene 74.4%;

Procedure F: 1-iodo-2-nitrobenzene 6.6%, 1-bromo-2-nitrobenzene 0.7%;

TLC (20% EtOAc in hexanes): $R_f = 0.60$; ^1H NMR ($CDCl_3$): δ 7.20 (d, J=3.4 Hz, 1H), 7.37 (t, J=0.6 Hz, 1H), 7.27 (d, J=3.0 Hz, 1H), 7.17 (t, J=3.0 Hz, 1H), 0.19 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 150.5, 135.5, 133.0, 129.2, 124.8, 118.7, 104.1, 99.7, 0.0; IR (neat): 2958, 2160, 1528, 1342, 1250; MS: 219 (M^+, 6.0), 204 (100), 159 (24.0), 143 (34.0); C & H & N Anal. of $C_{11}H_{13}O_2NSi$: Calculated; C 60.24%, H 5.98%, N 6.39%, Found C 59.79%, H 5.54%, N 6.10%.

Trimethyl[(3-nitrophenyl)ethynyl]silane

Refer to procedures A and F. 1-Iodo-3-nitrobenzene (498 mg, 2.0 mmol) was used to obtain the product by both methods. 1- Bromo-3-nitrobenzene starting material was unavailable.

Yield: Procedure A: 1-iodo-3-nitrobenzene 61.5%;

Procedure F: 1-iodo-3-nitrobenzene 97.4%;

TLC (20% EtOAc in hexanes): $R_f = 0.61$; ^1H NMR ($CDCl_3$): δ 8.18 (dt, J=8.2, 1.2 Hz, 1H), 7.75 (dt, J=7.8, 1.4 Hz, 1H), 7.49 (t, J=6.6 Hz, 1H), 7.22 (s, 1H), 0.26 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 148.0, 137.6, 129.3, 126.9, 125.0, 122.9, 102.1, 97.8, 0.0; IR (neat): 2900, 2840,

2155, 1455, 1245; MS: 219 (M^+, 7.0), 204 (100), 158 (22.0), 143 (13.0); C & H & N Anal. of $C_{11}H_{13}O_2NSi$: Calculated; C 60.24%, H 5.98%, N 6.39%, Found C 59.84%, H 5.74%, N 6.22%.

Trimethyl[(4-nitrophenyl)ethynyl]silane

Refer to procedures A and F. 1-Iodo-4-nitrobenzene (498 mg, 2.0 mmol) and 1- bromo-4-nitrobenzene were used to obtain the product by both methods. Procedures B and C were also followed using 1-bromo-4-nitrobenzene as the starting material. Procedures D and E were also followed using both 1-iodo-4-nitrobenzene and 1-bromo-4-nitrobenzene as the starting materials. Yield: Procedure A: 1-iodo-4-nitrobenzene 94.1%, 1-bromo-4-nitrobenzene 99.9%;

Procedure B: 1-bromo-4-nitrobenzene 88.2%;

Procedure C: 1-bromo-4-nitrobenzene 74.8%;

Procedure D: 1-iodo-4-nitrobenzene peak disappeared 35 min. after TMS-acetylene addition;

1-bromo-4-nitrobenzene disappeared 35 min. after TMS-acetylene addition;

Procedure E: 1-iodo-4-nitrobenzene vs. 1-bromo-4-nitrobenzene:1-iodo-4-nitrobenzene peak disappeared first 35 min. after TMS-acetylene addition;

1-iodo-4-nitrobenzene vs. 4-iodoanisole: 1-iodo-4-nitrobenzene peak disappeared first 35 min. after TMS-acetylene addition;

Procedure F: 1-iodo-4-nitrobenzene 40.9%, 1-bromo-4-nitrobenzene 34.8%

TLC (20% EtOAc in hexanes): $R_f = 0.63$; ^1H NMR ($CDCl_3$): δ 8.18 (d, J=6.6 Hz, 2H), 7.50 (d, J=6.7 Hz, 2H), 0.31 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 132.9, 129.2, 124.5, 123.6, 116.1, 114.9, 0.0;

IR (neat): 2950, 2850, 2165, 1460, 1252; MS: 219 (M^+, 11.0), 204 (100), 158 (28.0), 143 (9.0); C & H & N Anal. of $C_{11}H_{13}O_2NSi$: Calculated; C 60.24%, H 5.98%, N 6.39%, Found C 60.16%, H 5.94%, N 6.17%.

Methyl 2-(trimethylsilylethynyl)benzoate

Refer to procedures A and F. Methyl 2-iodobenzoate (524 mg, 2.0 mmol) and methyl 2-bromobenzoate (430 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: methyl 2-iodobenzoate 73.4%, methyl 2-bromobenzoate 0.0%;

Procedure F: methyl 2-iodobenzoate 9.1%, methyl 2-bromobenzoate 1.1%;

TLC (20% EtOAc in hexanes): $R_f = 0.55$; ^1H NMR ($CDCl_3$): δ 7.87 (t, J=1.0 Hz, 1H), 7.71 (dt, J=1.5, 5.0 Hz, 1H), 7.36 (dt, J=2.0, 5.0 Hz, 1H), 7.12 (t, J=8.0 Hz, 1H), 3.81 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 166.5, 136.2, 133.3, 130.4, 129.6, 128.5, 123.7, 103.9, 95.5, 52.4, 0.0; IR (neat): 2930, 2129, 1720, 1430, 1290, 1250, 1210, 1100, 900, 845; MS: 232 (M^+, 5.5), 217 (34.0), 187 (100), 143 (8.0); C & H Anal. of $C_{13}H_{16}O_2Si$: Calculated; C 67.21%, H 6.9%, Found C 67.80%, H 7.30%.

Methyl 3-(trimethylsilylethynyl)benzoate

Refer to procedures A and F. Methyl 3-iodobenzoate (524 mg, 2.0 mmol) and methyl 3-bromobenzoate (430 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: methyl 3-iodobenzoate 87.1%, methyl 3-bromobenzoate 11.8%;

Procedure F: methyl 3-iodobenzoate 65.4%, methyl 3-bromobenzoate 3.1%;

TLC (20% EtOAc in hexanes): $R_f = 0.49$; ^1H NMR ($CDCl_3$): δ 7.86 (s, 1H), 7.70 (dd, J=6.5, 1.0

Hz, 1H), 7.35 (dd, J=6.0, 1.5 Hz, 1H), 7.10 (t, J=8.0 Hz, 1H), 3.51 (s, 3H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 166.3, 136.1, 133.2, 130.5, 129.6, 128.6, 123.8, 104.1, 95.4, 52.3, 0.0; IR (neat): 2930, 2129, 1720, 1430, 1290, 1250, 1210, 1100, 890, 850, 750; MS: 232 (M^+, 14.6), 217 (100), 194 (6.0), 163 (23.4), 92 (82.5), 73 (26.2); C & H Anal. of $C_{13}H_{16}O_2Si$: Calculated; C 67.21%, H 6.90%, Found C 69.73%, H 7.10%.

Methyl 4-(trimethylsilylethynyl)benzoate

Refer to procedures A and F. Methyl 4-iodobenzoate (524 mg, 2.0 mmol) and methyl 4-bromobenzoate (430 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: methyl 4-iodobenzoate 89.4%, methyl 4-bromobenzoate 58.9%;

Procedure F: methyl 4-iodobenzoate 42.8%, methyl 4-bromobenzoate 1.8%;

TLC (20% EtOAc in hexanes): R_f = 0.55; ^1H NMR ($CDCl_3$): δ 7.71 (d, J=8.5 Hz, 2H), 7.26 (d, J=8.5 Hz, 2H), 3.62 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 166.7, 132.0, 129.8, 129.5, 127.9, 104.2, 97.9, 52.4, 0.0; IR (neat): 2800, 1730, 1272, 1175, 1105, 1020, 865; MS: 232 (M^+, 14.9), 217 (100), 163 (14.8), 92 (89.6), 73 (16.0), 63 (5.5); C & H Anal. of $C_{13}H_{16}O_2Si$: Calculated; C 67.21%, H 6.90%, Found C 69.29%, H 7.05%.

Trimethyl[(2-ethylphenyl)ethynyl]silane

Refer to procedures A and F. 1-Iodo-2-ethylbenzene (0.29 ml, 464 mg, 2.0 mmol) was used to obtain the product by both methods. 1-bromo-2-ethylbenzene starting material was unavailable.

Yield: Procedure A: 1-iodo-2-ethylbenzene 99.9%;

Procedure F: 1-iodo-2-ethylbenzene 75.4%;

TLC (20% EtOAc in hexanes): $R_f = 0.66$; ^1H NMR ($CDCl_3$): δ 7.16 (d, J=3.0 Hz, 1H), 6.96 (t J=7.0 Hz, 1H), 6.91 (d, J=6.5 Hz, 1H), 6.84 (t, J=6.0 Hz, 1H), 2.59 (q, J=7.0 Hz, 2H), 0.63 (t, 3H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 146.7, 132.4, 128.7, 127.9, 125.5, 122.2, 103.9, 97.7, 27.7, 14.6, 0.0; IR (neat, cm^{-1}): 2860, 2055, 1430, 1200, 819, 790, 704; MS: 202 (M^+, 74.4), 187 (100), 159 (11.5), 145 (15.5), 128 (17.5), 115 (10.5), 86 (39.9), 73 (27.6), 59 (94.0); C & H Anal. for $C_{13}H_{18}Si$: Calculated; C 77.16%, H 8.96%, Found; C 79.00%, H 9.07%.

Trimethyl[(4-ethylphenyl)ethynyl]silane

Refer to procedures A and F. 1-Iodo-4 ethylbenzene (0.29 ml, 464 mg, 2.0 mmol) was used to obtain the product by both methods. 1-Bromo-4-ethylbenzene starting material was unavailable. Procedure G was also followed.

Yield: Procedure A: 1-iodo-4-ethylbenzene 99.9%;

Procedure F: 1-iodo-4-ethylbenzene 99.9%;

Procedure G: 1-iodo-4-ethylbenzene 18.4%;

TLC (20% EtOAc in hexanes): $R_f = 0.66$; ^1H NMR ($CDCl_3$): δ 7.11 (d, J=3.2 Hz, 2H), 6.83 (d, J= 3.2Hz, 2H), 2.34 (q, J=8.5 Hz, 2H), 0.94 (t, J=3.0 Hz, 2H) , 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 144.8, 131.9, 127.7, 120.3, 105.4, 93.1, 28.8, 15.3, 0.0; IR (neat, cm^{-1}): 2860, 2061, 1455, 1200, 819, 790, 704; MS: 202 (M^+, 19.0), 187 (100), 149 (10.5), 133 (5.9), 92 (54.5), 75 (34.0); C & H Anal. for $C_{13}H_{18}Si$: Calculated; C 77.16%, H 8.96 %, Found; C 79.01%, H 8.80%.

Trimethyl[(2-trifluoromethanesulfonylphenyl)ethynyl]silane

Refer to procedure A. 1-Iodo-2-trifluoromethanesulfonylbenzene (704 mg, 2.0 mmol) was used to obtain the product.

Yield: Procedure A: 1-iodo-2-trifluoromethanesulfonylbenzene 74.9%;

TLC (20%EtOAc in hexanes): $R_f = 0.77$; ^1H NMR ($CDCl_3$): δ 7.64 (dd, J=6.5, 1.5 Hz, 1H), 7.29 (dd, J=5.5, 2.0 Hz, 1H), 7.15 (td, J=7.5, 1.5 Hz, 1H), 6.83 (td, J=7.5, 0.5 Hz, 1H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 150.6, 141.3, 134.6, 130.4, 128.5, 122.0, 118.6, 103.3, 97.7, 0.0; IR (neat, cm^{-1}): 2960, 2160, 1485, 1429, 1210, 1140, 1090, 895, 861, 760; MS: 322 (M^+, 8.0), 307 (81.0), 190 (68.5), 159 (100), 115 (71.0); C & H Anal. of $C_{12}H_{13}O_3F_3SSi$: Calculated; C 44.71%, H 4.06%, Found C 42.37%, H 3.73%.

Trimethyl[(3-trifluoromethanesulfonylphenyl)ethynyl]silane

Refer to procedure A. 1-Iodo-3-trifluoromethanesulfonylbenzene (704 mg, 2.0 mmol) was used to obtain the product.

Yield: 1-iodo-3-trifluoromethanesulfonylbenzene 37.6%;

TLC (20%EtOAc in hexanes): $R_f = 0.71$; ^1H NMR ($CDCl_3$): δ 7.39 (t, J=1.0 Hz, 1H), 7.28 (dt, J=8.0, 1.0 Hz, 1H), 7.07 (s, 1H), 7.03 (dt, J=8.5, 1.0 Hz, 1H), 0.20 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 149.7, 135.9, 132.3, 130.6, 126.3, 125.1, 121.9, 102.9, 97.7, 0.0; IR (neat, cm^{-1}): 2960, 2150, 1601, 1568, 1480, 1426, 1250, 1220, 1141, 1119, 948, 840, 730; MS: 322 (M^+, 15.5,), 307 (100), 189 (6.5), 174 (39.4), 146 (25.0); C & H Anal. of $C_{12}H_{13}O_3F_3SSi$: Calculated; C 44.70%, H 4.06%, Found C 45.84%, H 4.70%.

Trimethyl[(4-trifluoromethanesulfonylphenyl)ethynyl]silane

Refer to procedure A. 1-Iodo-4-trifluoromethanesulfonylbenzene (704 mg, 2.0 mmol) was used to obtain the product.

Yield: 1-iodo-4-trifluoromethanesulfonylbenzene 16.3%;

TLC (10%EtOAc in hexanes): $R_f = 0.84$; ^1H NMR ($CDCl_3$): δ 7.28 (dd, J=7.0, 1.5 Hz, 2H), 6.98 (d, J=9.0 Hz, 2H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 149.3, 134.0, 131.9, 121.6, 124.1, 123.4, 96.9, 0.0; IR (neat, cm^{-1}): 2820, 2159, 1498, 1430, 1250, 1213, 1144, 860, 840, 759; MS: 322 (M^+, 17.5), 307 (100), 189 (6.0), 174 (38.5), 146 (8.9); C & H Anal. of $C_{12}H_{13}O_3F_3SSi$: Calculated; C 44.71%, H 4.06%, Found C 46.61%, H 3.61%.

2-[(Trimethylsilyl)ethynyl]benzotrifluoride

Refer to procedures A and F. 2-Iodobenzotrifluoride (0.29 ml, 544 mg, 2.0 mmol) and 2-bromobenzotrifluoride (0.27 ml, 450 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: 2-iodobenzotrifluoride 99.9%, 2-bromobenzotrifluoride 0.3%;

Procedure F: 2-iodobenzotrifluoride 17.9%, 2-bromobenzotrifluoride 0.0%;

TLC (30% EtOAc in hexanes): $R_f = 0.86$; ^1H NMR ($CDCl_3$): δ 7.77 (d, J=8.0 Hz, 1H), 7.72 (d, J=8.5 Hz, 1H), 7.60 (t, J=10.5 Hz, 1H), 7.37 (t, J=10.0 Hz, 1H), 0.11 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 134.8, 131.9, 128.9, 126.4, 125.0, 122.9, 121.9, 101.0, 101.2, 0.0; IR (neat, cm^{-1}): 2761, 1981, 1499, 1469, 1387, 1350, 1219, 1150, 1118, 1040, 959, 932; MS: 242 (M^+, 16.0), 227 (100), 146 (24.2), 127 (18.5), 106 (9.6), 81 (9.4).

3-[(Trimethylsilyl)ethynyl]benzotrifluoride

Refer to procedures A and F. 3-Iodobenzotrifluoride (0.29 ml, 544 mg, 2.0 mmol) and 3-bromobenzotrifluoride (0.28 ml, 450 mg, 2.0 mmol) were used to obtain the product by both methods.

Yield: Procedure A: 3-iodobenzotrifluoride 99.9%, 3-bromobenzotrifluoride 5.5%;

Procedure F: 3-iodobenzotrifluoride 87.8%, 3-bromobenzotrifluoride15.5%;

TLC (30% EtOAc in hexanes): R_f = 0.84; ^{1}H NMR ($CDCl_3$): δ 7.76 (t, J=5.0 Hz, 1H), 7.36 (d, J=7.5 Hz, 1H), 7.32 (s, 1H), 7.27 (d, J=7.0 Hz, 1H), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 132.7, 127.5, 123.0, 122.6, 121.5, 120.9, 103.9, 101.9 100.7, 0.0; IR (neat, cm^{-1}): 2960, 2160, 2060, 1489, 1430, 1330, 1250, 1135, 1070, 895; MS: 242 (M^+, 8.5), 227 (100), 197 (5.1).

4-[(Trimethylsilyl)ethynyl]benzotrifluoride

Refer to procedures A and F. 4-Iodobenzotrifluoride (0.29, 544 mg, 2.0 mmol) and 4-bromobenzotrifluoride (0.28 ml, 450 mg, 2.0 mmol) were used to obtain the product by both methods. Procedure B was also followed using 4-bromobenzotrifluoride as the starting material.

Yield: Procedure A: 4-iodobenzotrifluoride 99.9%, 4-bromobenzotrifluoride 20.3%;

Procedure B: 4-bromobenzotrifluoride 25.4%;

Procedure F: 4-iodobenzotrifluoride 96.8%, 4-bromobenzotrifluoride 42.7%;

TLC (30% EtOAc in hexanes): R_f = 0.85; ^{1}H NMR ($CDCl_3$): δ 7.36 (d, J=5.5 Hz, 2H), 7.01 (d, J=6.0 Hz, 2H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 132.7, 127.5, 125.7, 103.9, 97.7, 88.8, 86.8, 0.0; IR (neat, cm^{-1}): 2960, 2160, 2060, 1410, 1202, 1132, 1050, 940, 870; MS: 242 (M^+, 12.4), 227 (100), 197 (6.6).

1,2-Bis-(trimethylsilylethynyl)benzene

Refer to Procedure I. 1-Iodo-2-(trimethylsilylethynyl)benzene (57.2 mg, 0.19 mmol) and 1-bromo-2-(trimethylsilylethynyl)benzene (11.9 mg, 0.05 mmol) were used to obtain product.

Yield: 1-iodo-2-(trimethylsilylethynyl)benzene 13.3%;

1-bromo-2-(trimethylsilylethynyl)benzene 0.0%;

TLC (20% EtOAc in hexanes): $R_f = 0.65$; ^1H NMR ($CDCl_3$): δ 7.44-7.39 (m, 2H), 7.20-7.16 (m, 2H), 0.26 (s, 18H); ^{13}C NMR ($CDCl_3$): δ 132.2, 127.9, 125.8, 88.2, 85.6, 0.0; IR (neat, cm^{-1}): 3068, 2159, 1574, 1457, 1412, 1251, 1128, 1035, 846, 748; MS: 270 (M^+, 55.0), 255 (74.0), 227 (8.5), 195 (16.5), 167 (19.0), 120 (28.4), 73 (100).

1-[(2-Phenyl-1-ethynyl)]-2-[(trimethylsilylethynyl)]benzene

Refer to Procedure I. 1-Iodo-2-[(2-phenyl-1-ethynyl)]benzene (479 mg, 1.6 mmol) and 1-bromo-2-[(2-phenyl-1-ethynyl)]benzene (148 mg, 0.57 mmol) were used to obtain product.

Yield: 1-iodo-2-[(2-phenyl-1-ethynyl)]benzene 56.7%;

1-bromo-2-[(2-phenyl-1-ethynyl)]benzene 0.0%;

TLC (22% EtOAc in hexanes): $R_f = 0.69$; ^1H NMR ($CDCl_3$): δ 7.48-7.44 (m, 6H), 7.29-7.20 (m, 3H), 0.19 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 132.4, 131.9, 128.5, 128.4, 128.3, 127.9, 123.5, 104.1, 98.9, 93.8, 88.5, 1.15, 0.0; IR (neat, cm^{-1}): 2956, 2923, 2219, 2158, 1599, 1494, 1471, 1442, 1249, 1211, 1094, 1068, 1017, 870, 843, 801, 753, 689; MS: 274 (M^+, 63.8), 259 (100), 243 (11.8), 229 (6.2), 215 (20.5), 130 (14.0).

5.5 Other Procedures

Procedure K: Nucleophilic Aromatic Substitution Reaction #1

This procedure was performed in duplicate for 1-iodo-2-nitrobenzene. To a solution of TMS-acetylene (0.155 ml, 108 mg, 1.1 mmol) in dry THF (5.0 ml) at -78 °C, was added 1.6M butyllithium (0.75 ml, 1.2 mmol). After stirring for one hour while warming to 0 °C, 1-iodo-2-nitrobenzene (249 mg, 1.0 mmol) dissolved in THF (1.0 ml) was added to the solution through the septum via syringe. The reaction mixture was stirred at this temperature for one hour and then warmed to room temperature while stirring further for one hour. Water (5.0 ml) was added very cautiously to quench the unreacted lithiated species. This reaction mixture was extracted with diethyl ether (3 x 10 ml), washed once with NaCl (5.0 ml), dried over $MgSO_4$ and filtered. The resulting crude residue was rotovapped to remove the excess solvent. A known mass of the residue was combined with biphenyl (internal standard) in 1 ml of methylene chloride and injected into the GLC for analysis.

Yield: trimethyl[2-(nitrophenyl)ethynyl]silane: 0.0%.

Procedure L: Nucleophilic Aromatic Substitution Reaction #2

A solution of 1-iodo-2-nitrobenzene (245 mg, 1.0 mmol) in THF (5 ml) was cooled as sodium acetylide (320 mg, 1.2 mmol) was added. After stirring for 1 hour H_2O (5 ml) was added dropwise to quench the unreacted sodium species. The mixture was extracted with diethyl ether (3 x 10 ml) and washed with saturated NaCl (5 ml). The resulting organic mixture was dried over magnesium sulphate, filtered and excess solvent was removed. A known mass of residue was combined with biphenyl (internal standard) in 1 ml of methylene chloride and injected into

the GLC for analysis.

Yield: trimethyl[2-(nitrophenyl)ethynyl]silane: 0.0%.

Procedure M: Replacement of CuI with KI

Procedure A was followed using 1-iodo-4-nitrobenzene (489 mg, 2.0 mmol) as the starting material. The catalyst system used included Pd $(PPh_3)_4$ (46.0 mg, 0.04 mmol) and KI (13.3 mg, 0.08 mmol).

Yield: trimethyl[4-(nitrophenyl)ethynyl]silane: 0.0%.

Procedure N: Reaction using a sealed vessel

Procedure F was followed, however, 2-iodotoluene (2.0 mmol) was used as the starting material and instead of using a round bottom flask in which to perform the experiment, a pressure tube was used.

Yield: trimethyl[2-(methylphenyl)ethynyl]silane: 27.4%.

Procedure O: Exclusion of $Pd(PPh_3)_4$

Procedure F was followed, however, the $Pd(PPh_3)_4$ catalyst was absent. This procedure uses 2-iodotoluene (2.0 mmol) as the starting material.

Yield: trimethyl[2-(methylphenyl)ethynyl]silane: 0.0%.

Procedure P: Exclusion of CuI

Procedure F was followed however, the CuI cocatalyst was absent. This procedure uses

2-iodotoluene (2.0 mmol) as the starting material.

Yield: trimethyl[2-(methylphenyl)ethynyl]silane: 0.0%.

Procedure Q: Exclusion of both $Pd(PPh_3)_4$ and CuI.

Procedure F was followed however, both the $Pd(PPh_3)_4$ catalyst and the CuI cocatalyst were absent. This procedure uses 2-iodotoluene (2.0 mmol) as the starting material.

Yield: trimethyl[2-(methylphenyl)ethynyl]silane: 0.0%.

Procedure R: Simultaneous Grignard Formation and Pd coupling of 2-iodoaniline

$Pd(PPh_3)_4$ (46 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), 2-iodoaniline (439 mg, 2.0 mmol), Mg (49 mg, 2.0 mmol) and a few crystals of I_2 were added to a flame dried flask. The contents were sealed with a septum and placed under nitrogen. THF (5.0 ml) and Et_3N (0.42 ml, 303 mg, 2.1 mmol) were added via syringe. As this mixture was stirring at room temperature TMS-acetylene (0.30 ml, 202 mg, 2.0 mmol) was introduced dropwise via syringe over ten minutes. This mixture was left to stir at room temperature for four hours when it was quenched with water (4ml), extracted with diethyl ether (3 x 20 ml), washed once with water and once with saturated NaCl. Then it was filtered and concentrated. A known mass of the residue was combined with a biphenyl (internal standard) in 1 ml of methylene chloride and injected into the GLC for analysis.

Yield: 2-[(trimethylsilyl)ethynyl]aniline: 23.9%.

Procedure S: Magnesium Mass Balance Reaction

To a flame dried flask was added Mg (490 mg, 20.0 mmol), 2-iodotoluene (20.0 mmol), a small fragment of I_2 and dry THF (50 ml). The contents were sealed with a septum and placed under nitrogen. The resulting mixture was heated in a water bath at 40 °C and stirred over two nights. After the Mg was dissolved, the septum was momentarily removed to introduce: $Pd(PPh_3)_4$ (460 mg, 0.40 mmol), CuI (150 mg, 0.8 mmol), and Et_3N (4.2 ml, 3030 mg, 30 mmol). After this mixture had been stirring for ten minutes, TMS-acetylene (3.0 ml, 2060 mg, 21.0 mmol) was added dropwise over ten minutes. This was left to stir at room temperature for four hours. Using a spatula the reaction mixture was scooped out onto a watch glass and solid Mg was picked out with tweezers. The resulting sample was suction filtered using methylene chloride to remove the organics. The left over Mg and catalysts were boiled in aqua regia and cooled. The solution was transferred to a 1L volumetric flask and brought up to volume using deionized distilled water. This solution was further diluted by half and used for ICP analysis.

% recovery of Mg^0: 49.2%.

Procedure T: Proof of Grignard Formation

Mg (0.05 mg, 2.0 mmol), a selected substituted iodobenzene (1.0 mmol), and I_2 were added to a flame dried flask. Dry THF (5 ml) was added via syringe after the flask was sealed with a septum and placed under nitrogen. The contents of the flask were left to stir in a water bath maintained at 40°C for two days whereupon water (4 ml) was added to quench the reaction. A diethyl ether work up was performed washing once with water and once with saturated NaCl. The solvent was not drawn off but a GC-MS was taken of the organic layer. A GLC was also

done of pure aniline, toluene, nitrobenzene, benzoic acid, and phenol and compared to the GLC of the organic layer the reactions involving 2-iodoaniline, 3-iodotoluene, 1-iodo-3-nitrobenzene, 3-iodobenzoic acid, and 4-iodophenol respectively.

MS: aniline: 93 (M^+, 100), 73 (31.5), 63 (12.9), 50 (15.0); phenol: 94 (M^+, 100), 66 (49.5), 55 (10.5); toluene: (No MS as this reaction formed the methylphenyl dimer instead of toluene); benzoic acid: 122 (M^+, 16.5), 95 (18.0), 81 (31.2), 69 (100); anisole: 108 (M^+, 100), 93 (13.9), 78 (52.0), 65 (57.5); nitrobenzene: 123 (M^+, 44.5), 93 (31.5), 77 (100), 65 (12.9); ethylbenzene: 103 (M^+, 31.0), 91 (100), 65 (7.5).

Procedure U: NMR Experiment to study the formation of the Pd complex in the coupling reaction

$Pd(PPh_3)_4$ (46 mg, 0.04 mmol), 2-iodotoluene (5 μl, 9.4 mg, 0.04 mmol) and THF (2.5 ml) were added to a flame dried round bottom flask and placed under nitrogen. This reaction was left to stir for twenty-four hours. The solvent was removed.

^{31}P NMR ($CDCl_3$): δ 30.11 (catalyst), 24.28, 23.78, -4.35 (TPP).

Procedure V: NMR Experiment to study the formation of the Pd-Mg complex in the Grignard coupling reaction

Mg (40 mg, 16 mmol), 2-iodotoluene (5 μl, 9.4 mg, 0.04 mmol), and a few crystals of I_2 were added to a flame dried round bottom flask. Anhydrous ether (2.5 ml) was added and the flask was placed under nitrogen. This mixture was stirred over heat (40 °C) for two days and was then cannuled into another flask containing $Pd(PPh_3)_4$ (50 mg, 0.04 mmol) dissolved in

anhydrous ether. This new solution was left

3.81 (TPP); t=0 hrs: ^{31}P NMR ($CDCl_3$): δ 32.15, 23.41, 21.00, 13.70, -3.77; t=1.5 hrs: ^{31}P NMR ($CDCl_3$): δ 32.64, 26.85, 23.39 (reduced), 21.00, 18.25, 18.09; t=2.5 hrs ^{31}P NMR ($CDCl_3$): δ 32.75, 23.31 (enhanced again), 21.00, 13.76 (came back), -9.01; t=3.5 hrs: ^{31}P NMR ($CDCl_3$): δ 32.71, 23.35, 21.00, 13.62 (enhanced), -9.01; t=24 hrs: ^{31}P NMR ($CDCl_3$): δ 44.15, 32.60, 23.64, 21.10, 20.84 (reduced), 13.55.

$Pt(PPh_3)_4$: before TMS-acetylene addition: ^{31}P NMR ($CDCl_3$): δ 30.29, 16.88, 13.48, 13.39, 12.97, 11.96, -3.90; t=0 hrs: ^{31}P NMR ($CDCl_3$): δ 32.05, 24.13, 21.73, 18.27, 16.83, 13.58, 13.49, 12.06, 11.97, -3.65; t=1.5 hrs: ^{31}P NMR ($CDCl_3$): δ 32.05, 21.73, 18.27, 16.83, 16.17, 13.48, 9.52, -3.71; t=2.5 hrs: ^{31}P NMR ($CDCl_3$): δ 32.03, 24.16, 19.95, 12.83, 9.53, -3.72; t=3.5 hrs: ^{31}P NMR ($CDCl_3$): δ 32.02, 19.94, 18.26, 16.82, 12.82, 9.52, -3.74; t=24 hrs: ^{31}P NMR ($CDCl_3$): δ 32.03, 20.80, 19.94 (enhanced), 18.26 16.83, 13.00, 9.52, -3.75.

Procedure X: HPLC Rate Experiments

Procedure A was followed however, the amounts of reagents were reduced to exactly half of that used in procedure A. *Ortho* substituted iodobenzenes were used competitively with the *meta* substituted equivalent in one reaction and the *para* substituted equivalent in a separate reaction except all three positions of the iodoanilines which were reacted together. Once all of the reagents, except for TMS-acetylene were added to the flask, a portion (7.5 μl) of the reaction mixture was removed via syringe and diluted with acetonitrile (0.5 ml) and injected into the HPLC. Immediately after the TMS-acetylene was added another sample was removed (7.5 μl), diluted with acetonitrile (0.5 ml) and injected into the HPLC. Every half hour up to six hours after TMS-acetylene addition, a sample was removed from the reaction mixture, diluted and

injected into the HPLC. Samples that were not injected immediately were stored in the freezer until analysed. Upon completion of the experiment a calculation was made at each half hour interval using the following formula, $A_0/C_0 = A_x/C_x$, where A_0 and C_0 are the area and concentration of starting material at time = 0 minutes, and A_x and C_x are the area and concentration of starting material at the half hour time intervals. A graph of concentration ratio vs. time was constructed. See Tables 4-5 and Graphs 1-2.

Table 9: Method of Separation for the Iodophenols

Time	% MeOH	% H_2O	Flow Rate (ml/min)
initial	65%	35%	1.1
5 minutes	65%	35%	1.1
30 minutes	75%	25%	1.1
40 minutes	100%	0%	1.1

Table 10: Method of Separation for the Iodotoluenes

Time	% Acetonitrile	% H_2O	Flow Rate (ml/min)
initial	38%	62%	1.3
5 minutes	38%	62%	1.3
30 minutes	42%	58%	1.3
45 minutes	46%	54%	1.3
50 minutes	80%	20%	1.3
60 minutes	100%	0%	1.3

Table 11: Method of Separation for the Iodoanilines

Time	% Acetonitrile	% H_2O	Flow Rate (ml/min)
initial	40%	60%	1.1
5 minutes	40%	60%	1.1
30 minutes	55%	45%	1.1
40 minutes	100%	0%	1.1

Table 12: Method of Separation for the Iodoanisoles

Time	% Acetonitrile	% H_2O	Flow Rate (ml/min)
initial	60%	40%	0.8
5 minutes	60%	40%	0.8
30 minutes	75%	25%	0.8
40 minutes	100%	0%	0.8

Table 13: Method of Separation for the Iodobenzotrifluorides

Time	% Acetonitrile	% H_2O	Flow Rate (ml/min)
initial	65%	35%	0.8
5 minutes	65%	35%	0.8
30 minutes	100%	0%	0.8

Table 14: Method of Separation for the Iodonitrobenzenes

Time	% Acetonitrile	% H_2O	Flow Rate (ml/min)
initial	44%	56%	1.1
5 minutes	44%	56%	1.1
30 minutes	79%	21%	1.1
35 minutes	100%	0%	1.1

Table 15: Method of Separation for the Iodoethylbenzenes

Time	% Acetonitrile	% H_2O	Flow Rate (ml/min)
initial	48%	52%	1.1
18 minutes	48%	52%	1.1
25 minutes	49%	51%	1.1
50 minutes	100%	0%	1.1

APPENDIX A

Table 16: Competitive Rate Experiment Data

ortho vs. *meta* Iodophenol

Time	Retention Time (min)		Peak Area		Ratio
	***o*-phenol**	***m*-phenol**	***o*-phenol**	***m*-phenol**	**[*m*]/[*o*]**
before TMS-acetylene addition	4.49	4.99	10.8	11.4	
0.0 hrs	4.45	4.95	9.55	9.90	0.890*
0.5 hrs	4.47	4.97	8.94	9.22	0.885
1.0 hrs	4.47	4.98	9.39	9.81	0.894
1.5 hrs	4.45	4.95	8.35	8.35	0.850
2.0 hrs	4.49	5.01	9.20	8.66	0.805
2.5 hrs	4.47	4.97	8.47	7.64	0.777
3.0 hrs	4.47	4.98	8.28	6.80	0.755
3.5 hrs	4.48	4.99	8.63	6.00	0.595
4.0 hrs	4.48	4.99	8.58	5.53	0.553
4.5 hrs	4.47	4.99	8.18	4.75	0.495
5.0 hrs	4.47	4.98	7.84	4.19	0.453
5.5 hrs	4.48	4.91	3.09	1.44	0.400
6.0 hrs	4.47	4.94	7.67	3.15	0.348

*$C_n=A_nC_0/A_0$

o-iodophenol: C_n=(9.55)(1.195mmol)/(10.8) =1.056689815

m-iodophenol: C_n=(9.90)(1.083mmol)/(11.4) =0.982

$C_n(meta)/C_n(ortho)$ = 0.890

Table 17: Competitive Rate Experiment Data

***ortho* vs. *para* Iodophenol**

Time	Retention Time (min)		Peak Area		Ratio
	o-phenol	*p*-phenol	*o*-phenol	*p*-phenol	[*p*]/[*o*]
before TMS-acetylene addition	4.52	5.09	10.6	18.4	
0.0 hrs	4.53	5.09	9.12	15.6	1.001
0.5 hrs	4.51	5.06	8.82	13.6	0.885
1.0 hrs	4.53	5.09	9.35	12.1	0.746
1.5 hrs	4.52	5.08	9.79	11.8	0.695
2.0 hrs	4.54	5.10	8.80	8.70	0.568
2.5 hrs	4.54	5.11	8.56	7.55	0.504
3.0 hrs	4.51	5.07	8.11	6.56	0.463
3.5 hrs	4.52	5.07	8.93	6.61	0.424
4.0 hrs	4.52	5.07	8.57	5.61	0.379
4.5 hrs	4.50	5.05	8.28	4.76	0.331
5.0 hrs	4.51	5.07	8.78	5.12	0.327
5.5 hrs	4.49	5.04	8.00	3.81	0.269
6.0 hrs	4.48	5.04	8.48	4.52	0.299

Table 18: Competitive Rate Experiment Data

***ortho* vs. *meta* Iodotoluene**

Time	Retention Time (min)		Peak Area		Ratio
	***o*-toluene**	***m*-toluene**	***o*-toluene**	***m*-toluene**	**[*m*]/[*o*]**
before TMS-acetylene addition	27.52	28.71	3.99	5.79	
0.0 hrs	27.31	28.47	6.42	8.98	0.642
0.5 hrs	26.99	27.97	3.51	1.34	0.131

Table 19: Competitive Rate Experiment Data

***ortho* vs. *para* Iodotoluene**

Time	Retention Time (min)		Peak Area		Ratio
	***o*-toluene**	***p*-toluene**	***o*-toluene**	***p*-toluene**	**[*p*]/[*o*]**
before TMS-acetylene addition	26.88	27.53	3.62	12.16	
0.0 hrs	23.90	24.55	4.32	11.08	1.550
0.5 hrs	23.64	24.17	3.74	6.90	0.583
1.0 hrs	23.52	24.14	3.62	0.736	0.062
1.5 hrs	24.06	24.66	2.84	0.820	0.070
2.0 hrs	24.86	25.70	0.10	0.036	0.060

Table 20: Competitive Rate Experiment Data

***ortho* vs. *meta* Iodoanisole**

Time	Retention Time (min)		Peak Area		Ratio
	o-anisole	*m*-anisole	*o*-anisole	*m*-anisole	[*m*]/[*o*]
before TMS-acetylene addition	7.60	8.31	7.97	9.11	
0.0 hrs	7.49	8.18	15.10	14.3	1.015
0.5 hrs	7.55	8.25	13.0	4.69	0.323
1.0 hrs	7.54	8.23	12.7	4.06	0.284
1.5 hrs	7.53	8.22	14.7	4.76	0.285
2.0 hrs	7.50	8.18	5.45	1.98	0.318
2.5 hrs	7.51	8.19	13.0	3.95	0.278
3.0 hrs	7.51	8.19	16.0	5.21	0.286
3.5 hrs	12.43	13.39	19.2	5.72	0.279
4.0 hrs	10.23	11.14	19.6	6.26	0.289
4.5 hrs	11.06	11.94	17.9	5.43	0.279
5.0 hrs	7.49	8.18	5.76	2.13	0.311
5.5 hrs	7.44	8.21	13.3	4.05	0.279
6.0 hrs	7.42	8.09	13.3	3.99	0.276

Table 21: Competitive Rate Experiment Data

***ortho* vs. *para* Iodoanisole**

Time	Retention Time (min)		Peak Area		Ratio
	***o*-anisole**	***p*-anisole**	***o*-anisole**	***p*-anisole**	**[*p*]/[*o*]**
before TMS-acetylene addition	7.74	8.29	17.8	18.6	
0.0 hrs	7.65	8.21	16.3	17.3	1.035
0.5 hrs	7.64	8.19	15.5	15.6	0.924
1.0 hrs	7.61	8.16	14.8	14.3	0.925
1.5 hrs	7.59	8.14	14.4	13.3	0.923
2.0 hrs	7.58	8.13	13.0	11.7	0.924
2.5 hrs	7.63	8.18	12.5	11.1	0.925
3.0 hrs	7.62	8.17	12.0	10.4	0.928
3.5 hrs	7.61	8.15	12.5	10.5	0.926
4.0 hrs	7.59	8.13	12.8	10.4	0.927
4.5 hrs	7.58	8.13	11.9	9.72	0.929
5.0 hrs	7.59	8.13	11.8	9.65	0.930
5.5 hrs	7.61	8.16	11.9	9.68	0.928
6.0 hrs	8.84	9.47	14.1	11.3	0.927

Table 22: Competitive Rate Experiment Data

***ortho* vs. *meta* Iodobenzotrifluoride**

Time	Retention Time (min)		Peak Area		Ratio
	o-BTF	*m*-BTF	*o*-BTF	*m*-BTF	[*m*]/[*o*]
before TMS-acetylene addition	8.62	9.71	28.7	20.9	
0.0 hrs	8.53	9.61	25.1	15.08	0.801
0.5 hrs	8.53	9.59	26.8	7.81	0.390
1.0 hrs	8.48	9.54	25.4	4.80	0.253
1.5 hrs	8.46	9.50	12.8	1.90	0.198
2.0 hrs	8.41	9.46	24.6	3.65	0.198
2.5 hrs	8.41	9.45	12.9	1.62	0.167
3.0 hrs	8.50	9.55	26.7	3.64	0.182
3.5 hrs	8.44	9.49	24.9	3.27	0.176
4.0 hrs	8.31	9.33	26.8	3.51	0.174
4.5 hrs	8.42	9.46	27.5	3.51	0.170
5.0 hrs	8.42	9.46	27.3	3.43	0.168
5.5 hrs	8.40	9.43	28.7	3.54	0.164
6.0 hrs	8.44	9.48	29.4	3.78	0.172

Table 23: Competitive Rate Experiment Data

***ortho* vs. *para* Iodobenzotrifluoride**

Time	Retention Time (min)		Peak Area		Ratio
	o-BTF	*p*-BTF	*o*-BTF	*p*-BTF	[*p*]/[*o*]
before TMS-acetylene addition	8.52	9.45	23.0	32.5	
0.0 hrs	8.50	9.43	19.1	25.8	0.975
0.5 hrs	8.50	9.42	20.4	17.8	0.632
1.0 hrs	8.46	9.38	20.8	11.2	0.389
1.5 hrs	8.41	9.32	9.36	4.66	0.359
2.0 hrs	8.42	9.32	19.3	6.04	0.226
2.5 hrs	8.46	9.38	9.53	3.29	0.249
3.0 hrs	8.45	9.37	20.4	4.36	0.155
3.5 hrs	8.41	9.31	20.3	3.79	0.135
4.0 hrs	8.42	9.33	21.1	3.62	0.124
4.5 hrs	8.45	9.36	22.5	3.55	0.115
5.0 hrs	8.49	9.39	21.2	3.07	0.104
5.5 hrs	8.35	9.26	19.5	2.63	0.098
6.0 hrs	8.47	9.39	20.9	2.64	0.092

Table 24: Competitive Rate Experiment Data

***ortho* vs. *meta* Iodonitrobenzene**

Time	Retention Time (min)		Peak Area		Ratio
	o-nitro	*m*-nitro	*o*-nitro	*m*-nitro	[*m*]/[*o*]
before TMS-acetylene addition	9.81	11.54	18.4	32.2	
0.0 hrs	9.91	11.62	16.1	28.6	1.000
0.5 hrs	9.85	11.56	12.9	23.0	1.009
1.0 hrs	9.82	11.53	15.0	26.5	1.005
1.5 hrs	9.94	11.64	15.0	26.6	1.007
2.0 hrs	9.81	11.52	13.3	23.5	1.006
2.5 hrs	9.79	11.50	14.5	25.4	0.997
3.0 hrs	9.81	11.52	9.22	16.8	1.008
3.5 hrs	9.85	11.54	10.1	18.3	1.006
4.0 hrs	9.78	11.49	10.0	18.1	1.005
4.5 hrs	10.07	11.79	8.44	15.2	1.007
5.0 hrs	9.86	11.57	10.4	18.6	1.006
5.5 hrs	9.82	11.54	15.7	27.0	0.983
6.0 hrs	9.81	11.53	15.3	26.4	0.981

Table 25: Competitive Rate Experiment Data

***ortho* vs. *para* Iodonitrobenzene**

Time	Retention Time (min)		Peak Area		Ratio
	o-nitro	*p*-nitro	*o*-nitro	*p*-nitro	[*p*]/[*o*]
before TMS-acetylene addition	10.06	11.56	16.6	25.9	
0.0 hrs	10.01	11.51	14.0	13.6	0.603
0.5 hrs	9.86	11.35	13.0	16.8	0.804
1.0 hrs	9.85	11.34	12.6	10.7	0.527
1.5 hrs	9.84	11.33	12.5	15.2	0.757
2.0 hrs	9.82	11.31	12.6	14.5	0.715
2.5 hrs	9.85	11.34	14.1	15.7	0.699
3.0 hrs	9.78	11.27	15.1	16.1	0.663
3.5 hrs	9.83	11.31	13.1	9.02	0.428
4.0 hrs	9.83	11.31	14.3	13.6	0.591
4.5 hrs	9.84	11.31	14.5	13.2	0.566
5.0 hrs	9.86	11.33	13.9	11.5	0.514
5.5 hrs	9.85	11.32	15.6	11.7	0.467
6.0 hrs	9.84	11.31	12.5	6.07	0.303

Table 26: Competitive Rate Experiment Data

***ortho* vs. *para* Iodoethylbenzene**

Time	Retention Time (min)		Peak Area		Ratio
	o-ethyl	*p*-ethyl	*o*-ethyl	*p*-ethyl	[*p*]/[*o*]
before TMS-acetylene addition	27.48	28.76	1.64	3.91	
0.0 hrs	27.41	28.68	6.28	14.07	0.995
0.5 hrs	26.85	28.03	5.91	2.29	0.172
1.0 hrs	25.53	26.64	3.49	0.75	0.095
1.5 hrs	25.23	26.26	3.76	0.70	0.083
2.0 hrs	25.12	26.19	6.46	1.81	0.125
2.5 hrs	25.68	26.80	6.31	1.75	0.123
3.0 hrs	25.94	27.04	6.11	1.51	0.109

Table 27: Competitive Rate Experiment Data

***ortho* vs. *meta* vs. *para* Iodoaniline**

Time	Retention Time (min)			Peak Area		
	***o*-aniline**	***m*-aniline**	***p*-aniline**	***o*-aniline**	***m*-aniline**	***p*-aniline**
before TMS-acetylene addition	13.94	15.55	14.47	34.8	18.4	21.3
0.0 hrs	17.03	18.91	17.64	39.8	19.4	22.7
0.5 hrs	15.30	17.00	15.85	33.5	17.2	19.6
1.0 hrs	14.35	16.02	14.88	32.4	16.9	18.7
1.5 hrs	14.27	15.89	14.80	31.0	16.4	17.6
2.0 hrs	12.73	14.33	13.23	30.8	16.3	17.3
2.5 hrs	12.31	13.84	12.79	26.4	13.6	14.2
3.0 hrs	12.12	13.64	12.60	27.3	14.5	15.1
3.5 hrs	12.06	13.59	12.54	26.9	14.2	14.6
4.0 hrs	12.76	14.31	13.25	27.8	13.5	10.4
4.5 hrs	12.61	14.15	13.10	27.2	14.4	14.6
5.0 hrs	11.79	13.24	12.23	24.9	13.3	14.7
5.5 hrs	11.17	12.59	11.59	25.0	13.4	14.1
6.0 hrs	11.25	12.66	11.67	25.2	13.6	14.3

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