METHODOLOGY AND MECHANISM: REINVESTIGATNG THE ULLMANN REACTION

A Dissertation Presented

by

DEREK VAN ALLEN

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Organic Chemistry

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DEDICATION

For Mom and Dad

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ABSTRACT

METHODOLGY AND MECHANISM: REINVESTIGATING THE ULLMANN REACTION

FEBRUARY 2004

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Directed by: Professor D. Venkataraman

We have combined the tools of organometallic chemistry with those of organic chemistry, and explored methodology and mechanism of palladium and copper-based catalysis. Organometallic chemistry plays a prominent role in industrial and academic laboratories, and developments in this field continue to expand our fundamental understating of chemical reactions. Herein, we report on a specific failure of a palladium-catalyzed coupling reaction, and the subsequent development of alternative copper-based methodologies. We have developed a new cross coupling protocol for the synthesis of unsymmetrical triarylphosphines, using copper-based catalysis. Furthermore, we conducted a thorough investigation into the mechanism of the century-old Ullmann coupling. Our mechanistic research is based on rational experimental design intended to address fundamental questions regarding copper-based catalysis. One such question is: *what is the nature of the reaction intermediate(s)*; our data is inconsistent with copper(III) intermediates.

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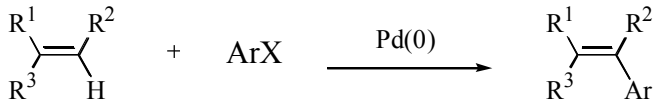
CHAPTER 1

PROLOGUE

1.1 Introduction:

The development of organometallic catalysts has had a dramatic influence on organic chemistry of the past several decades. During this time, there have been significant advances in metal catalyzed cross-coupling reactions for the formation of aryl-carbon and aryl-heteroatom bonds, which have led to more efficient synthetic protocols for many compounds that have important biological, pharmaceutical, and/or materials properties.[1-5] Traditionally, the construction of these bonds involved nucleophilic aromatic substitution (S_NAr) reactions, and were limited to electron deficient aryl halides and diazonium reactions. One of the most significant advancements in the field was the development of palladium(0)-catalyzed cross-coupling reactions, which have dominated the synthetic protocols for the construction of aryl-carbon and aryl-heteroatom bonds.[6-12] Several well-known palladium(0) protocols include, but are not limited to reactions such as the Heck, Sonogashira, Suzuki-Miyaura, and the more recent Hartwig-Buchwald coupling(Scheme 1.1).[13]

HECK:



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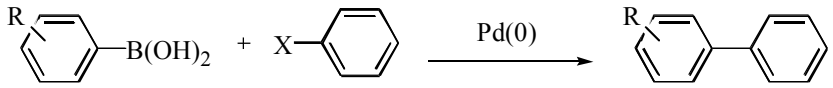

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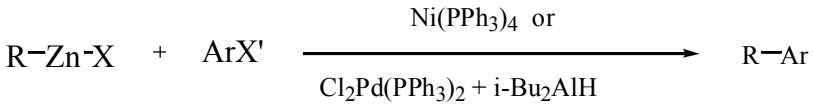
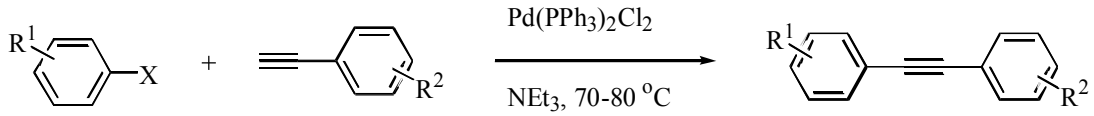


SONOGASHIRA:



HARTWIG-BUCHWALD:

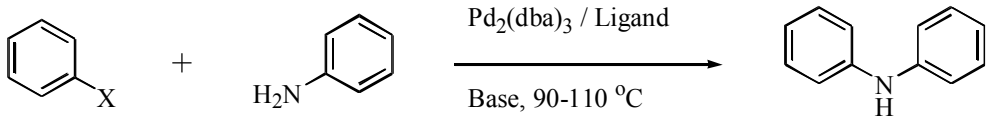


Figure 1.1: Examples of palladium catalyzed cross-coupling reactions.

Before the advent of palladium catalysts, copper mediated cross-coupling reactions, *Ullmann condensations*, were widely used for the formation of aryl-carbon and aryl-heteroatom bonds. These reactions suffer several limitations, such as harsh reaction conditions, high temperature, strong bases, and often the use of toxic polar solvents such as hexamethylphosphoramide (HMPA). These drawbacks commonly result in low

functional group tolerance and low and/or irreproducible yields. Despite these limitations and the success of palladium-catalyzed reactions, copper-based protocols remain the reactions of choice in large and industrial scale reactions. Furthermore, Ullmann-type reaction conditions are often successful where palladium-based procedures have failed.

Given the industrial and synthetic importance of copper-based protocols, we set out to develop *well-defined* copper catalysts to overcome the limitations of the Ullmann condensation. We also use these copper complexes as the basis for a mechanistic investigation of copper-catalyzed cross-coupling reactions in general. This dissertation will examine a specific example of the limitation of palladium(0)-catalyzed reactions, the subsequent development of alternative copper-catalyzed methodology, and the kinetic and mechanistic investigation of the copper-catalyzed Ullmann condensation.

In chapter two, we address a specific case of the failure of palladium catalysis to effectively couple an aryl amine with an aryl halide, and instead, initiated a unique cyclization reaction. This failure of palladium prompted two research efforts within our group; the first was to develop alternative copper-based methodology, and the second was to further explore the cyclization, resulting from the failed coupling reaction. Chapter two addresses this unique cyclization, resulting from the geometrical and steric constraints of the starting aryl amine, found to proceed via C-H activation palladium.

Chapter three focuses on the development of alternative copper-based methodology, for the synthesis of unsymmetrical triarylphosphines. The synthesis of triarylphosphines is often harsh, and insensitive to functional groups. The development

of our copper-catalyzed methodology is general, mild, tolerant to a variety of aryl iodides, and is palladium free.

Finally, chapter four addresses the long-standing, unresolved mechanism of the copper-catalyzed Ullmann coupling. We expand upon our experiences with palladium catalysis and copper- methodology, to a mechanistic investigation based on *chemically well-defined* copper catalysts, many of which were prepared specifically for our study. Our mechanistic investigation focuses on rationally defined experiments, which address fundamental questions, regarding the operative reaction mechanism in the Ullmann coupling.

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CHAPTER 2

FORMATION OF AN UNUSUAL INTRTAMOLECULAR C-N BOND: POSSIBLE C-H ACTIVATION

2.1 Introduction:

The synthesis of complex natural products exemplifies the modern synthetic chemists ability to carry out chemical transformations on almost any organic substrate. Although complex molecules can be synthesized, modification of the simplest organic molecules has continually been a problem, despite all of tools of modern synthetic chemistry. Saturated hydrocarbons, alkanes, are the most fundamental unit in organic chemistry, containing only carbon and hydrogen single bonds. However, few synthetic methodologies have been developed that are capable of carrying out selective chemical reactions on alkanes, because of their lack of reactivity. And in fact, C-H activation has been called one of the "holy grails" of modern synthetic chemistry.[1]

Saturated hydrocarbons are the main component of oil and natural gas, and therefore represent an important resource for the chemical industry. The ability to carry out chemical transformations of alkanes to more useful chemical products is important for supplying the chemical industry, as well as the potential to make use of industrial pollutants, such as methane. More importantly, the selective activation of the C-H bond is critical to our fundamental understanding of chemical reactivity.

The robust nature of the C-H bond, and therefore unreactivty, is often attributed to their high bond energies (~ 90–100 kcal/mol) and low acidity and basicity (pKa ~ 45-60).[1] There are however other contributing factors to alkanes lack of chemical reactivity,

such as the increased *s-character*, compared to other compounds made exclusively from carbon and hydrogen bonds. For example ethylene, acetylene, and benzene (C-H bond energies of 106, 120, and 109 kcal/mol respectively) are much more reactive than methane (C-H bond = 104 kcal/mol).[2] Although C-H bonds are relatively inert to most chemical reactions, they are known to undergo reactions with, oxygen, free radicals, and carbenes.[2] However, most of the observed reactivity of alkanes occurs at high temperature, under heterogeneous conditions, and without much chemical selectivity. Therefore, the goal of this area of research is to produce a catalyst and/or chemical reagent that will *selectively* activate the C-H bond at low temperatures.

2.2 Background:

There has been much worked carried out in the area of C-H activation. More recently, transition metal catalysis has emerged as viable method for the selective activation of C-H bonds.[1-9] Several of the most important examples of C-H activation to date have been catalyzed by ruthenium and iridium catalysts, exemplified by the work of Bergman, and Murai.[1,10-15] Recentyl, Harwig has shown that transition-metal boryl complexes can be used to catalytically to selectively activate C-H bonds in alkanes.[6-8,16-20] It has been noted that C-H activation, catalyzed by metal complexes, can occur through several different mechanisms, including oxidative addition, electrophilic substitution, and radical mechanisms. However, this chapter will focus on very specific homogenous conditions in which *pre-coordinated* metals are used to activate *intramolecular* C-H bonds, through oxidative addition.

Lewis and Smith established the initial results in this area of C-H activation in 1986, with the successful arylation of phenol with ethylene in both *ortho* positions using a ruthenium catalyst (Figure 2.1).[21]

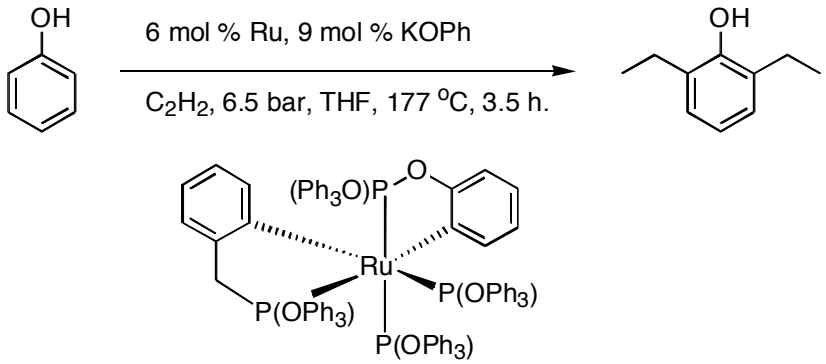


Figure 2.1: Initial study on the *intramolecular* C-H activation by metal complexes.

This reaction resulted in high yield and selectivity, because the ruthenium was *pre-coordinated* to the alcohol, and therefore in proximity to activate the ortho positions of phenol.

Later, in 1993, Murai developed a more versatile system based on the results of Lewis and Smith, in which a ketone was used to precoordinate ruthenium in order to active the ortho C-H aromatic bond, for the addition of alkenes (Figure 2.2).[13] In addition, these reaction conditions were extended to lactones and heteroaromatic ketones.[14,15]

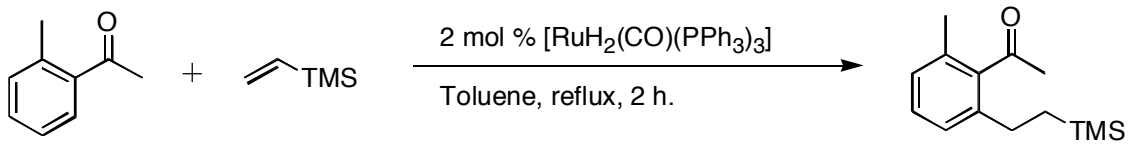


Figure 2.2: Extension of C-H activation of aromatic C-H bonds via precoordination.

Similar precoordination to pyridine derivatives, and subsequent aromatic C-H activation and alkene addition has been shown to be effective using rhodium catalysts.[22]

2.3 Activation of C-H bonds by palladium:

There has however been limited research on similar palladium catalyzed activations, and only recently has palladium begun to emerge as a viable metal catalyst for C-H activation. Miura et al. have used palladium complexes to precoordinate phenolates for the addition of alkenes or aryl halides, through activation of the *ortho* aromatic C-H bond (Figure 2.3).[23,24]

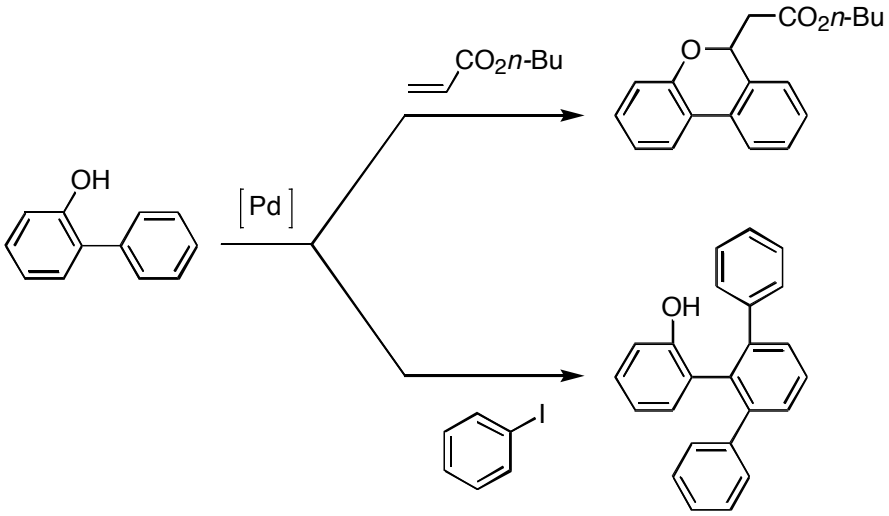


Figure 2.3: Palladium catalyzed activation of *ortho* aromatic C-H bonds.

Miura has further extended this methodology to the activation of the aldehyde C-H bond, according to the proposed catalytic cycle (Figure 2.4).[25]

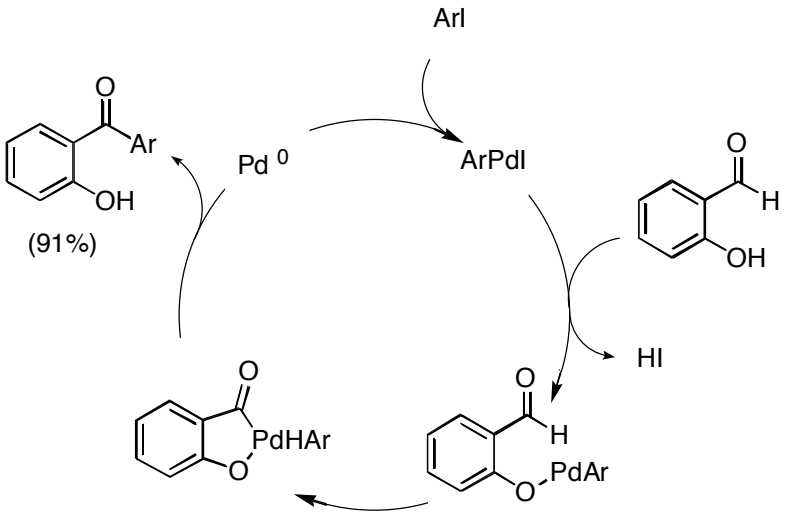


Figure 2.4: Proposed catalytic cycle for palladium-catalyzed activation of the aldehyde C-H bond. Reaction conditions: 5 mol % $PdCl_2$, 2 eq. ArI, 2 eq. Na_2CO_3, 0.2 eq. LiCl, DMF, 100 ^oC, 3.5 h.

The proposed catalytic cycle involves oxidative addition of the aryl iodide as the first step, as is the case for many palladium-catalyzed reactions in general. The second step involves coordination of the palladium to the alcohol, producing an aryl(alyloxy)palladium intermediate in which the palladium is now in close proximity to the aldehyde hydrogen. The next step involves a second oxidative addition to the aldehyde C-H bond, producing the palladium(IV) palladacycle, which subsequently reductively eliminates the product, and regenerating the active palladium(0) catalyst.

2.4 Activation of C-H bonds by palladium specifically at sp^3 centers:

The palladium catalyzed C-H activation reactions discussed thus far, have involved activation at sp^2-hybridized centers. Methods for palladium-catalyzed C-H activation at sp^3 centers however, have not been as well developed. Recently there have been a few reports of C-H activation of sp^3 systems, catalyzed by palladium. In 1992, Dyker reported on the synthesis of 6*H*-Dibenzo[b,*d*]pyrans by palladium catalyzed C-H activation of the methoxy group of Iodoanisole.[26-28] He later extended this methodology to include the activation of *tert*-butyl groups for the synthesis of 1,2-dihydrocyclobutabenzene derivatives.[4,29] In these reactions the regioselectivity does not arise through coordination, but rather from the oxidative addition of palladium(0) to the aryl halide bond. There have also been similar reports of palladium-catalyzed activation of benzylic C-H bonds using an aryl halide coupled with norbornene.[30] More recently, Zucca reported a 2,2'-bipyrimidal ligating system that activates sp^3-hybridized C-H bonds.[31] They have even reported the crystal structures of compounds based on bipyridine ligands (Figure 2.5).

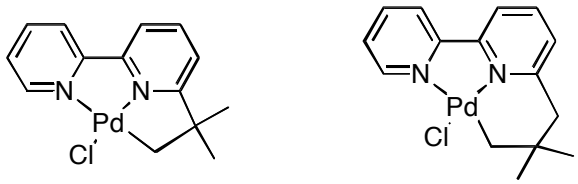


Figure 2.5: Crystal structures of activated sp^3-hybridized C-H bonds using 2,2'-byprimidal complexes.

2.5 From materials to organometallic chemistry:

We have been interested in strategies for the construction of electroactive materials based on substituted di- and triarylamines. Toward this end we utilized palladium-based chemistry for the formation of C-N bonds, developed independently by Hartwig[32] and Buchwald.[33] During the course of this research we have encountered an unusual intramolecular cyclization. In this chapter we report on our investigation into this unprecedented cyclization, most likely resulting from C-H activation at a geometrically constrained sp^3 center, and subsequent formation of an intramolecular C-N bond.

The initial reaction conditions found to facilitate cyclization of the secondary amine (diester), **X** employed $Pd_2(dba)_3$, diphenylphosphinobutane (DPPB), potassium bis(trimethylsilyl)amine (KHMDS), and methyl-2-bromobenzoate (Figure 2.6).

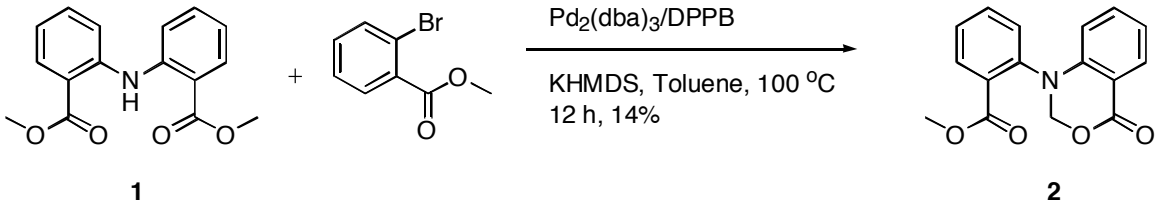


Figure 2.6: Our intial experimental conditions for cyclization *via* C-H activation.

These conditions are a slight modification to the generally accepted conditions for coupling reactions involving aryl amines with aryl halides. Although our initial goal was to couple **1** with the aryl halide to obtain a triarylamine substituted with *ortho* esters, we focused on optimizing the conditions for cyclization.

We conducted a series of control experiments and found that in the absence of any catalyst, base, or aryl halide the cyclization was not observed by GC. Similar control experiments indicated that the cyclization was not dependant on the aryl halide used, and several aryl halides are capable of promoting the cyclization, including bromobenzene, iodobenzene, methyl-2-bromobenzoate, and 4-bromotoluene. However, because GC analysis indicated that the yield was not dependent on the specific aryl halide used, we therefore continued to use methyl-2-bromobenzoate.

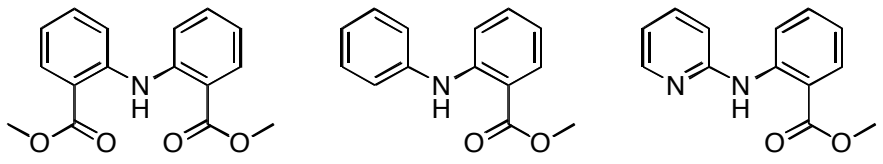
During our initial attempts to cyclize **1** to yield the C-H activated product **2**, several bases were studied; including NaOMe, NaO*t*-Bu, KO*t*-Bu, Cs_2CO_3, KHMDS, and LDA. However, only potassium bis(trimethylsilyl)amine (KHMDS) and cesium carbonate were found to facilitate the cyclization, KHMDS being more effective. Interestingly, LDA failed to promote cyclization, and was found to attack nucleophilically at the carbonyl center. Moreover, the cyclization is dependant on the amount of base used. The addition of excess KHMDS (5 equivalents) resulted in only starting materials after 24 hours. Subsequent experiments demonstrated that varying the amount of KHMDS from 1.2 equivalents to as low as a catalytic amount resulted in a small amount of cyclized product. This aspect of the reaction caused us to speculate about the role of the base, specifically hexamethyldisilazide. We suspected that KHMDS, after deprotonation of the amine was acting as a ligand, and as a result facilitating the cyclization.

Consequently, several experiments were conducted employing the free base, hexamethyldisila*zane* (HMDS) with, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$, to determine if, after

deprotonation, the free base was ligating to the catalyst, and possibly facilitating the cyclization. No cyclized product was observed by GC under these conditions. Furthermore, the palladium species were effectively killed in the presence of HMDS alone, indicated by a clear solution with mirrored palladium coated to the reaction flask. We therefore titrated KHMDS using a literature procedure,[34] and used the titrated base for subsequent reactions. The isolated yield of 14% was found when 1.2 equivalents of KHMDS were used with $Pd_2(dba)_3$/DPPF as the catalyst.

A variety of catalysts and their respective ligands were then tested while continuing to use KHMDS as the base. The equivalents of palladium were held constant at 5 and 10 mol percent, while the ligand to palladium ratio was varied from 0.75 to 3.0. The ligand to palladium ratio was monitored by GC and was not found to have a dramatic effect on the cyclization. Additional experiments were conducted using both $Pd_2(dba)_3$ and $Pd_3(dba)_5$, with $Pd_2(dba)_3$ being the most effective palladium(0) source when diphenylphosphine ferrocene (DPPF), diphenylphosphino butane (DPPB), or triphenylphosphine were used. Two biphenyl ligands were also tested, 2-(di-*t*-butylphosphino)biphenyl and 2-(dicyclohexylphosphino)biphenyl, both formed only a small amount of the cyclized product by GC. Finally, 1,2-Bis(dicylcohexylphosphino)ethane nickel(II) chloride was tested, with DPPF, but no cyclized product was observed. The most effective conditions for cyclization were when $Pd_2(dba)_3$/DPPB or $Pd_2(dba)_3$/DPPF were employed, with 5 or 10 mol percent palladium, resulting in isolated yields of 10-15%.

Compound **1** was prepared in 91% yield by slight modification of standard palladium coupling conditions employing DPPB as the ligand. Compounds **3,** and **4** were then considered as a means to explore the scope of the cyclization (Figure 2.7).



1 **3** **4**

Figure 2.7: Diphenylamines used to explore the scope of the cyclization conditions.

We were unable to prepare the monoester derivative, **3**, using typical palladium conditions. Based on our earlier success in using a soluble copper catalyst, $Cu(PPh_3)_3Br$, for the formation of diaryl ethers, we have recently been extending that methodology to the formation of aryl amines. Compound **4** was prepared in good yields using the copper catalyst, but subsequent cyclization resulted in only starting materials. Methylanthranilate, and 2-bromopyridine were subjected to the optimized cyclization conditions and resulted in mainly starting materials and another unusual product in 10% yield (Figure 2.8), which was identified by X-ray.

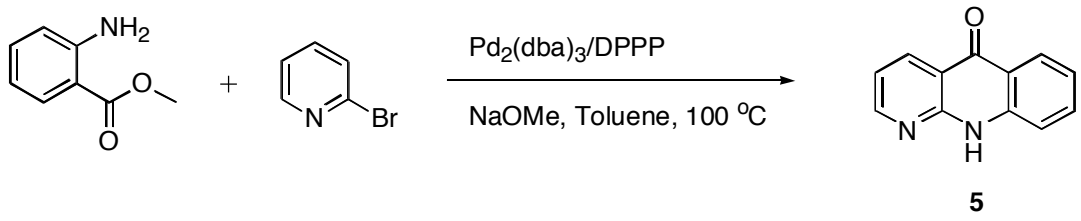


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Figure 2.8: Additional cyclization product identified by x-ray while attempting to prepare compound **4**.

Based on established mechanistic information for the coupling of aryl halides and amines, and cyclopalladation resulting in C-H activation, we have proposed a plausible mechanism as illustrated (Figure 2.9).

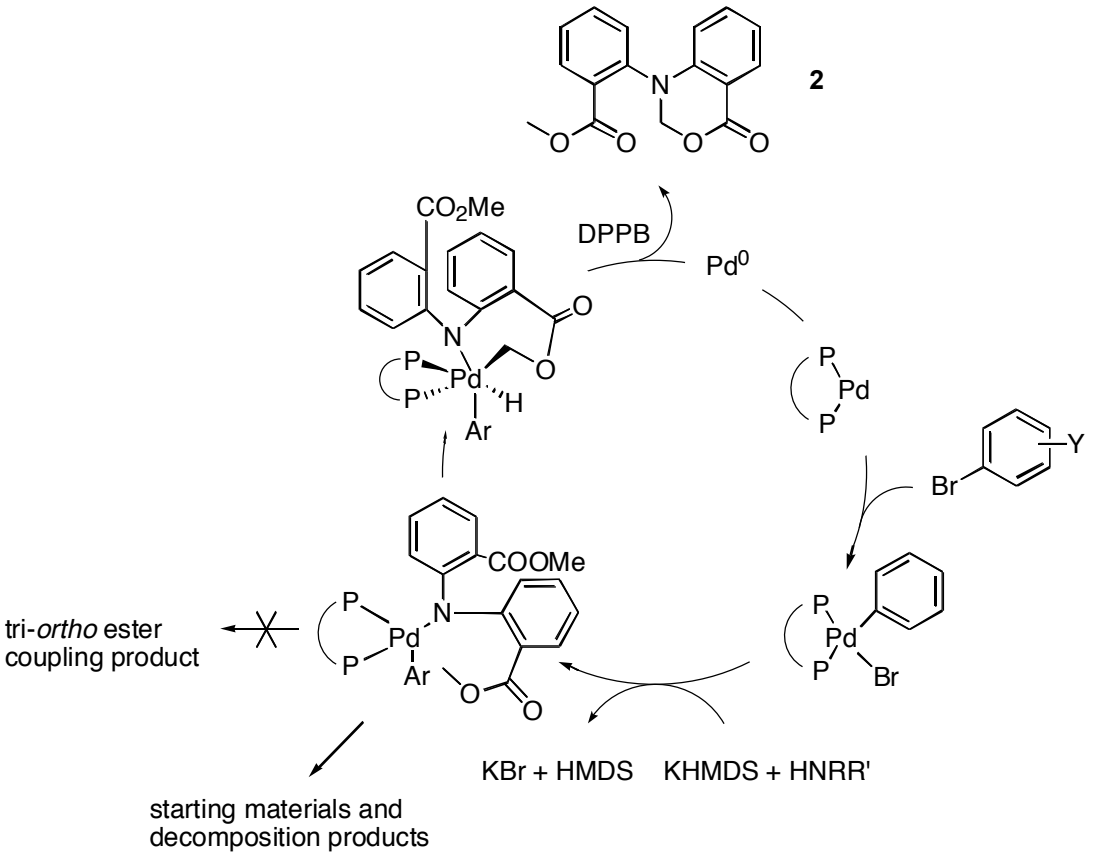

Figure 2.9: A plausible mechanistic cycle for the observed C-H activation resulting in cyclized products.

An important issue with the mechanism of this unique cyclization is: *what is the fate of the hydrogen*? The answer to this question would provide a definitive explanation of the observed C-H activation, and is well beyond the scope of this dissertation. However, we have conducted several control experiments in which formaldehyde and paraformaldehyde were added to the reaction mixture, to test the possibility that the cyclization is not a result of C-H activation. Had the added formaldehyde catalyzed the cyclization, or resulted in and increased yield, the process of C-H activation would be ruled out. The cyclization would then be occurring through oxidation of the ester to formaldehyde, and subsequent cyclization in the absence of palladium. We did not observe any product formation upon addition of formaldehyde or paraformaldehyde, and we therefore conclude the cyclization is proceeding via C-H activation by palladium at an sp^3 center.

Ryabov has shown cyclopalladation to be a favorable process for the activation of C-H bonds at palladium(II) centers. The groups of Hartwig and Amatore have conducted extensive mechanistic studies on palladium-catalyzed coupling of aryl amines. Our proposed mechanism accounts for the observations that mainly starting materials are recovered, the coupling product is not obtained, and a small amount of the cyclized product is produced.

We have also invoked a seven-membered palladacycle for reductive elimination to the six-membered cyclized product. This is reasonable, because we have invoked an octahedral palladium(IV) intermediate, and d^6 metals favor octahedral coordination geometry. In addition, the proposed mechanism accounts for the fact that both aryl halide

and base are required for the reaction to proceed. We therefore feel that the cyclization has occurred as a direct result of C-H activation facilitated by the geometrical constraints of the starting diester **1**.

2.6 Conclusion:

To summarize, the geometrical constraints of the secondary aryl amine **1** prevent further coupling to the *ortho*- substituted triarylamine, and result in the cyclized product **2**, *via* C-H activation at the sp^3 carbon of the methyl ester. The palladium catalyzed C-H activation at the sp^3 center of the ester group is facilitated by the geometrical constraints of the starting secondary amine. The yield of this anomalous cyclization reaction is dependent on the base and catalyst used. To date, KHMDS and $Pd_2(dba)_3$/DPPF have proven to be the most effective conditions for cyclization, yet still result in mainly starting materials after 24 hours. Further insight into the mechanism of this cyclization may allow the scope of this procedure to be extended to other systems.

As aforementioned, we were unable to prepare the tri-coupled product using standard palladium-based methodology. However, this failure of palladium provided the impetus for our group to develop alternate copper-based methodology, which was used to continue the materials aspect of this research project. The development of copper-based methodology has developed into a major research area for our group. We have subsequently shown copper-based methods to be effective for the cross-coupling of aryl halides with a variety nucleophiles in C-C, C-O, C-S, C-Se, C-P as well as C-N bond forming reactions [35-41] Upon completion of the C-H activation project, the similarity of

palladium and copper-based methodology allowed for an easy transition to developing copper-based methodology, and studying the mechanism of copper-catalyzed reactions, as the following chapters will discuss.

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CHAPTER 3

SYNTHESIS OF UNSYMMETRICAL TRIARYLPHOSPHINES

3.1 Introduction:

Aryl phosphine ligands are extremely important for many reactions catalyzed by transition metals and are ubiquitous in organometallic chemistry.[1-3] Triarylphosphine ligands are well known for their use in asymmetric catalysis as well as general metal-catalyzed procedures for aryl-carbon and aryl-heteroatom bond-forming reactions (Figure 3.1).[4-8] In addition, with the advent of general palladium-catalyzed cross-coupling reactions to construct aryl-carbon and aryl-heteroatom bonds, triphenylphosphine-based ligands have become increasingly important to systematically modify and tune the catalytic activity.

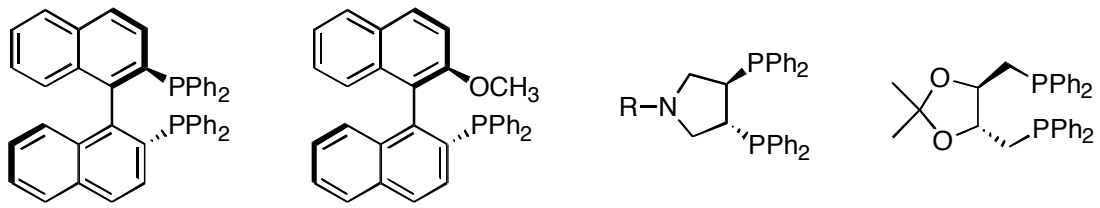

Figure 3.1: Examples of aryl phosphines used in asymmetric catalysis.

Over the years, several synthetic routes have emerged for the formation of the aryl-phosphorous bond. The classical methods of preparation of aryl phosphines often involve aryl-Grignard or aryl-lithium reagents with phosphine halides (Figure 3.2).[1,3]

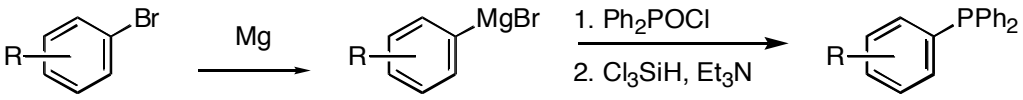

Figure 3.2: Example of a classical Grignard synthesis of aryl phosphines.

Many of these methods suffer the disadvantage of significant, if not exclusive oxidation to the phosphine oxide, and therefore require an additional reductive step to produce the aryl phosphine. As a result of the sensitivity of aryl-Grignard and aryl-lithium reagents, these reactions are intolerant to a wide variety of functional groups.

3.2 Emergence of palladium and nickel catalyzed procedures:

A significant advancement in the synthesis of triaryl phosphines came with the development of transition metal catalysis based on palladium(0) or nickel(0) complexes. These catalysts have been shown effective for the formation of aryl-carbon, and aryl-heteroatom bonds. However, the development of similar protocols for the formation of aryl-phosphorous bonds has been limited, and only recently have reports of palladium and nickel-catalyzed procedure emerged in the literature. The advent of palladium and nickel catalyzed procedures has helped to dramatically increase functional group tolerance in the synthesis of triaryl phosphines. In 1986 Stille demonstrated an effective synthesis of triarylphosphines using organotin reagents in the presence of a palladium catalyst.[9] No further reports using palladium catalysis emerged until 1996,[10,11] when Herd et. al developed methodology using palladium(0)-based protocols in the absence of added reagents. They have been successful in coupling a range of aryl iodides and

diphenylphosphine using a combination of bases and solvents. Similarly, nickel(0)-catalyzed protocols have also been employed in the synthesis of several tertiary phosphines (Figure 3.3).[12]

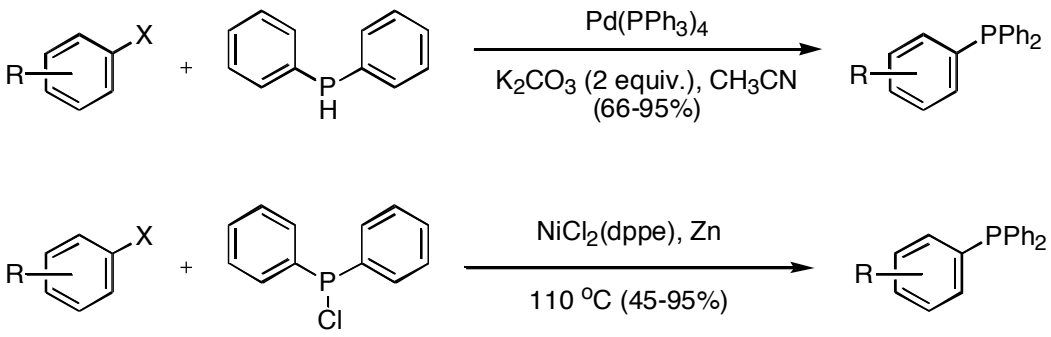

Figure 3.3: Examples of palladium(0) and nickel(0)-catalyzed protocols for the synthesis of triarylphosphines.

However, in contrast to the volume of literature that exists for the formation of aryl-nitrogen and aryl-oxygen bonds using cross-coupling reaction with palladium catalysts, only a very few reports exist for the formation of aryl phosphines, particularly unsymmetrical phosphines.[9,10,12-21]

3.3 Efficacy of copper-based catalysts:

In recent years, our group,[22-28] Buchwald group,[6,29-35] and others[36-40] have been developing copper-catalyzed cross-coupling reactions. These methods have demonstrated increased functional group tolerance and improvement over the traditional Ullmann-type reactions conditions. In addition, there exists an economic attractiveness to develop copper-based methods, since they are the methods of choice for large and

industrial scale reactions. We have extended copper-based methodology for the cross coupling of aryliodides with diphenylphosphine for the synthesis of unsymmetrical triaryl phosphines.

In order to demonstrate the efficacy of copper-based catalysts in the synthesis of triaryl phosphines, we first studied the cross-coupling reaction between iodobenzene and diphenylphosphine using a variety of *well-defined* copper complexes. These complexes can be classified based on the ligands coordinated to copper. First, those containing only monodentate, phosphine ligands of the type $[Cu(PPh_3)_3X]$, where X can be I, Br, or Cl. Second, those incorporating bidentate nitrogen-based chelating ligands such as 1,10-phenanthroline (phen) and 2,9-dimethyl-1,10-phenanthroline (dmp), such as $[Cu(phen)PPh_3Br]$ and $[Cu(dmp)PPh_3Br]$.

The synthesis of mononuclear phosphine bromide complex was readily synthesized from $CuBr_2$ and triphenylphosphine in methanol, $[Cu(PPh_3)_3Br]$, following a modification to Costa's protocol (Figure 3.4).[41]

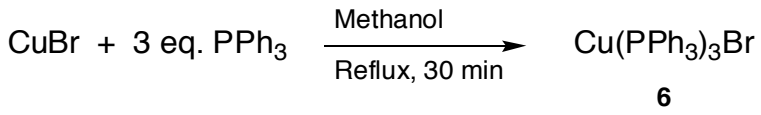

Figure 3.4: Preparation of $[Cu(PPh_3)_3Br]$ and general method for other corresponding halides.

Similarly, mononuclear tris-triphenylphosphine complexes containing chloride and iodide can be synthesized from CuCl and CuI. However, the iodide complexes required extending reflux time (See Appendix 1), and only the bromide complex was

studied for the synthesis of aryl phosphines. The complex, copper(I) tris-triphenylphosphine bromide, was effective for coupling iodobenzene with diphenylphosphine.

The synthesis of bidentate complexes $Cu(Phen)PPh_3Br$ and $Cu(dmp)PPh_3Br$ based on the chelating ligands 1,10-phenanthroline (Phen) and 2,9-dimethyl-1,10-phenanthroline (dmp) respectively are readily prepared from the mononuclear $[Cu(PPh_3)_3Br]$ complex, and were both found to facilitate the coupling of iodobenzene with diphenylphosphine. Although only the bromide derivatives were studied for the synthesis of triaryl phosphines, the corresponding chloride and iodide compounds can also be prepared using a similar protocol (Figure 3.5).

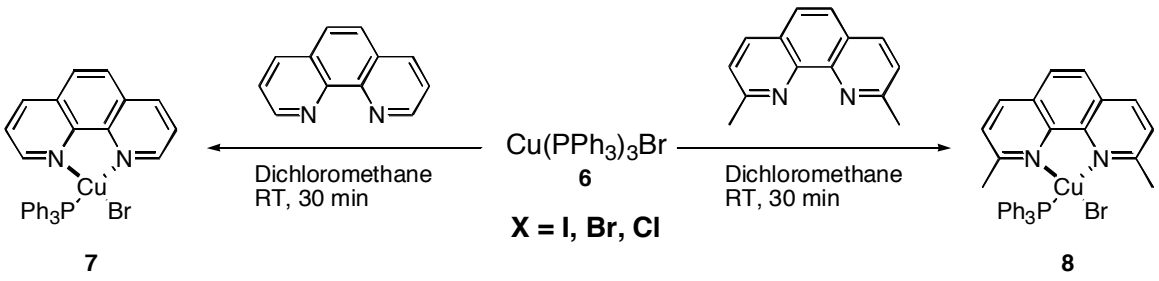

Figure 3.5: Synthesis of $[Cu(Phen)PPh_3Br]$ and $[Cu(dmp)PPh_3Br]$.

Furthermore, to determine the effect of phosphine ligand on the *well-defined* catalysts, a *phosphine-free* copper(I) complex was prepared, $Cu(dmp)_2Br \cdot H_2O$ (Figure 3.6). This copper complex was also successful for the cross-coupling of iodobenzene with diphenylphosphine.

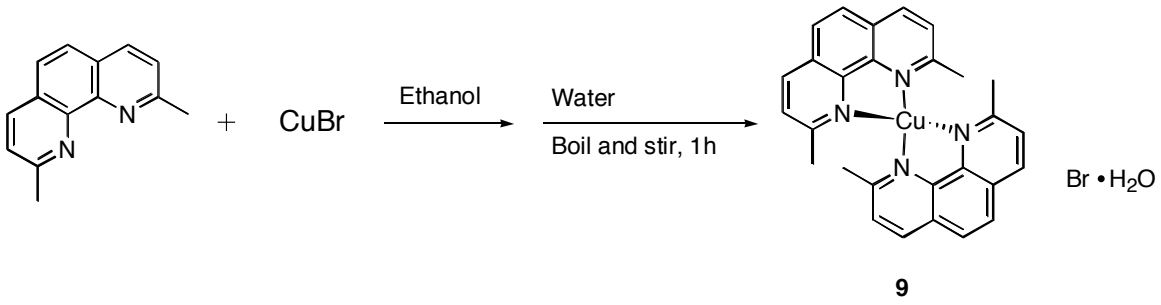

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Figure 3.6: Synthesis of the *phosphine-free* copper(I) complex, $[Cu(dmp)_2]Br \cdot H_2O$

All of the *well-defined* complexes were found to facilitate the cross-coupling of iodobenzene with diphenylphosphine. As part of our general optimization protocol we also studied the effects of ligand additives to copper(I) salts, as well as copper(I) salts alone. A comparison of additives to complexes and copper salts alone reveals that, although they all facilitate the reaction of iodobenzene with diphenylphosphine, the *well-defined* complexes, while effective, were not as effective CuI/phen and CuI alone (Table 3.1).

Table 3.1: A comparison of *well-defined* copper(I) complexes, additives, and copper(I) salts.

Catalyst	GC Yield (%)
Well-defined catalysts	
$Cu(PPh_3)_3Br$	83
$Cu(Phen)PPh_3Br$	69
$Cu(dmp)PPh_3Br$	61
$Cu(dmp)_2Br\,H_2O$	68
Additives	
CuI/Phenanthroline	99
CuI/Neocuproine	60
CuI/DMAP	54
Copper(I) Salts	
CuI	99
CuBr	34
CuCl	58

The most effective catalysts for the coupling of iodobenzene and diphenylphosphine were CuI/Phen and CuI alone. These results were contrary to our observation in other copper-catalyzed coupling reactions where there were substantial rate accelerations due to the ligands. We surmised that the product triphenylphosphine might form copper-triphenylphosphine complexes in situ, which in turn can accelerate the reaction rate. If this were true, then we should observe substantial differences between reactions catalyzed by $Cu(PPh_3)_3Br$ and CuBr in the rate of formation of the product during the initial stages of the reaction. However, we found no differences in the rate of formation of triphenylphosphine in these reactions. Hence, we speculate that instead of triphenylphosphine, diphenylphosphine may be acting as a ligand throughout the

reaction, contributing to the active catalytic species.[42-46] Surprisingly, we have found no reports on the use of copper halides for the coupling of diphenylphosphine to aryl halides in the literature. For reaction simplicity, we chose to employ ligand-free catalyst conditions, and therefore used CuI for the remainder of the optimization process.

3.4 Effect of base in the synthesis of unsymmetrical triarylphosphines:

We then screened various bases using CuI as the catalyst for the cross coupling of iodobenzene with diphenylphosphine (Table 3.2).

Table 3.2: Optimization of base for coupling of iodobenzene with diphenylphosphine, using CuI as the catalyst.

Base	GC Yield (%)
K_2CO_3	99
K_3PO_4	94
Cs_2CO_3	88
NaOMe	63
NaO*t*-Bu	52
NaOAc	43
KO*t*-Bu	23
NEt_3	0

We found that K_2CO_3, K_3PO_4, and Cs_2CO_3 were the most effective bases while NEt_3, KO*t*-Bu, NaOMe, and NaOAc were less effective (often resulting in little or no yield of triphenylphosphine).

Despite excellent yields obtained when potassium carbonate, K_2CO_3, was used in the coupling of iodobenzene and diphenylphosphine, significantly lower yield were

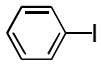
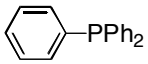
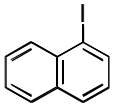
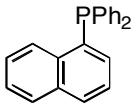
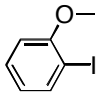
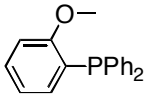
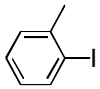
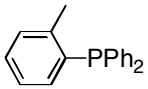
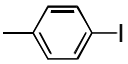
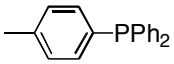
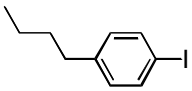
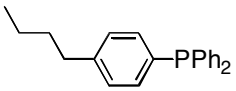
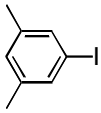
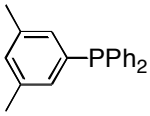
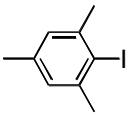
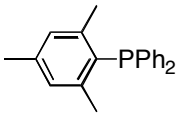
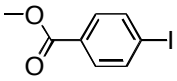
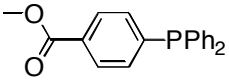
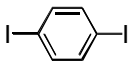
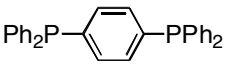
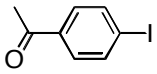
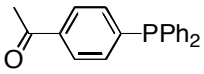
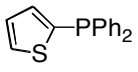
obtained while coupling several substituted aryl iodides using the same conditions. In these cases, we found significant amounts of triarylphosphine oxide were observed, which accounted for lower observed yields when K_2CO_3 was used with substituted aryl iodides. Similarly, potassium phosphate, K_3PO_4, was found to be very effective for coupling iodobenzene with diphenylphosphine. However, we again observed significant amounts of triarylphosphine oxide, when substituted aryl iodides were used with K_3PO_4 as the base.

We found that the production of triphenylphosphine oxide was minimized if Cs_2CO_3 was used as the base, in place of K_2CO_3 and K_3PO_4, for the coupling of substituted aryl iodides with diphenylphosphine. Hence, we decided to use CuI (10 mol %) as the catalyst, Cs_2CO_3 as the base, and toluene as the solvent as a more general protocol for the synthesis of triaryl phosphines, than was previously reported in the literature.

3.5 Optimized protocol and results:

We used the aforementioned protocol to couple various electron-withdrawing and electron-donating aryl iodides to diphenylphosphine in good yields (Table 3.3).

Table 3.3: Results of the cross coupling of aryl iodides with diphenylphosphine.

Compound	Aryl iodide	Product	Base	Isolated Yield (%)
10			K_2CO_3	83
11			Cs_2CO_3	91
12			Cs_2CO_3	64
13			Cs_2CO_3	76
14			Cs_2CO_3	42
15			Cs_2CO_3	70
16			Cs_2CO_3	77
17			Cs_2CO_3	71
18			Cs_2CO_3	70
19			Cs_2CO_3	71
20			Cs_2CO_3	67
21			K_2CO_3	63

As can be seen in Table 3.3, our protocol tolerates a variety of functional groups on the aryl iodide, including both electron-donating and electron-withdrawing groups. Base-sensitive functional groups such as methyl ketones (entry 11) and methyl esters (entry 9) are tolerated by this method. Ortho-substituted iodides also coupled well with this protocol (entries 3, 4, and 8), as well as bulky groups and multiple substitutions of the aryl iodide. In the case of entry 5, although the GC indicated the complete consumption of the starting materials our isolated yield of product was moderate. Since the boiling point (68 ^{o}C) of this compound is low, we incur loss of the product during isolation process. We also found that bromobenzene can be coupled with diphenylphosphine under the same conditions to form triphenylphosphine, but only in 10 % yield.

3.6 Conclusion:

To summarize our results, we have developed a new synthetic protocol for the synthesis of unsymmetrical triaryl phosphines starting from aryl iodides and diphenylphosphine, using CuI as the catalyst and Cs_2CO_3 and K_2CO_3 bases. Furthermore, we have demonstrated this new methodology to be tolerant to a variety of functional groups, including both electron withdrawing and electron-donating groups. Moreover, this protocol tolerates base sensitive groups on the starting aryl iodides. This method is palladium free and has demonstrated a dramatic improvement in overall yields, and the reaction conditions are much less harsh than similar protocols based on phosphination.

Shortly after our protocol was published, the group of Prof. Stephen Buchwald published a similar procedure, that required the use of an additive ligand, *N, N'*-dimethylethylenediamine to copper iodide.[47] This protocol was found to be effective for the cross coupling of a variety of aryl, as well as vinyl halides. However, they also reported that for coupling aryl iodides under *ligand-free* conditions, the use of Cs_2CO_3 and copper iodide were optimal.

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CHAPTER 4

MECHANISM OF THE MODIFIED ULLMANN REACTION

4.1 Introduction:

In recent years there has been a substantial research effort in developing copper-based catalysis for cross-coupling reactions of aryl halides with various nucleophiles to supplant the traditional Ullmann-type reaction conditions. Traditional copper-catalyzed reactions were pioneered by the work of Fritz Ullmann and Irma Goldberg in the early 1900's.[1] These reactions typically involve the coupling of aromatic halides with amines and phenols, for the synthesis of aryl ethers and aryl amines (Figure 4.1).

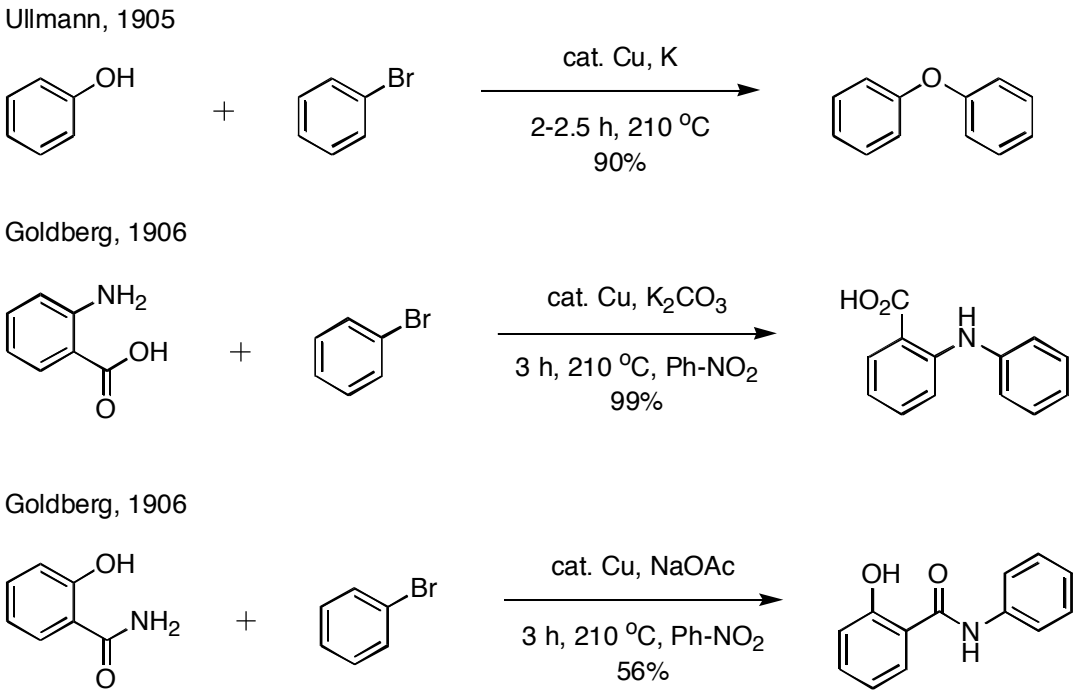

Figure 4.1: Examples of Ullmann and Goldberg coupling reactions.[1]

As a point of note, the term, Ullmann "condensation", is used to describe the copper-catalyzed reaction of aromatic halides with phenol salts, or anilines, to synthesize aryl ethers and amines. The terminology, Ullmann "coupling", however, is used to describe the synthesis of biaryls from aromatic halides. Typical reaction conditions suffer the disadvantages of high reaction temperatures, the used of toxic solvents such as HMPA, and intolerance to a wide-variety of functional groups.[2,3] The biggest drawback of the classical Ullmann reaction arises from inconsistent results obtained from the use of different copper sources. Despite these drawbacks and the development of palladium-based methodology, copper-mediated reactions remain the reactions of choice in large and industrial scale reactions.

More importantly, copper-based methods have been used in cases where palladium methodology has failed.[4-9] For example, the presence of functional groups in the *ortho* position to aromatic halides has led to considerable decreases in reaction rates, as well as substantially lower overall yields. And, palladium-catalyzed reactions often do not tolerate heterocyclic substrates, such as thiols, selenides, and active methylene compounds.

Recently, our group,[5,10-15] the Buchwald group,[16-31] and others have been developing methodology that improves upon the typical Ullmann-type reaction conditions to provide a more general and tolerate methodology based on copper catalysts.[1,32] We have subsequently demonstrated our methodology to be effective for the construction of C-C, C-O, C-S, C-P, C-Se, as well as C-N bonds.

4.2 Background:

Despite wide spread use and century old procedures, there has been limited research into the mechanism of copper-catalyzed Ullmann-type coupling reactions. In a pioneering study in 1964, Harold Weingarten made the critical observation that bromobenzene reacted rapidly with potassium phenoxide salts in the presence of copper(I), only when *impure* diglyme was used as the solvent.[33] After careful analysis, he determined that the diglyme solvent was contaminated with and ester. Weingarten concluded that "the function of the ester is not clearly understood, but it appears to be related to the *solubility* of the catalyst". He also conducted e.p.r. experiments using radical traps, such as 2,6-di-*t*-butyl-4-methoxyphenol, 2,5-di-*t*-butylhydroquinone, and phenothiazine, and found that although the e.p.r. signal changed dramatically from one reaction to another, there were no observable differences in the reaction rate. This was the first conclusive evidence *against* a free-radical mechanism. In addition to the e.p.r. studies, he also investigated the kinetics of the Ullmann condensation, and found the reaction to be first order in bromobenzene, and first order in copper catalyst. Based on theses results, Weingarten proposed a catalytic cycle involving a π-complex intermediate (Figure 4.2). Weingarten's pioneering investigation provided the first conclusive evidence indicating that copper(I) was the active catalytic species in the Ullmann condensation.

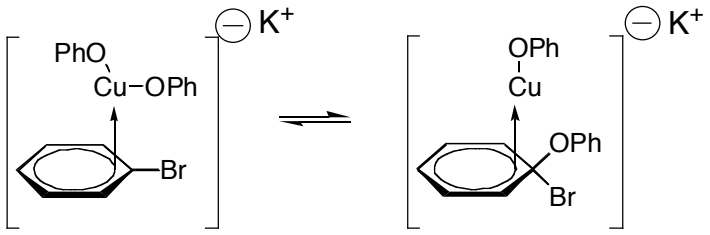

Figure 4.2: Weingarten's proposed intermediate in the Ullmann condensation.

In 1974, Cohen provided further evidence that Cu(I) catalysts do not proceed through a free radical mechanism. In this investigation he demonstrated that the addition of benzoic acid to the reaction of *o*-iodo-*N, N*,-dimethylbenzamide with CuCl in DMF resulted in the formation of *N, N*-dimethylbenzamide (Figure 4.3).

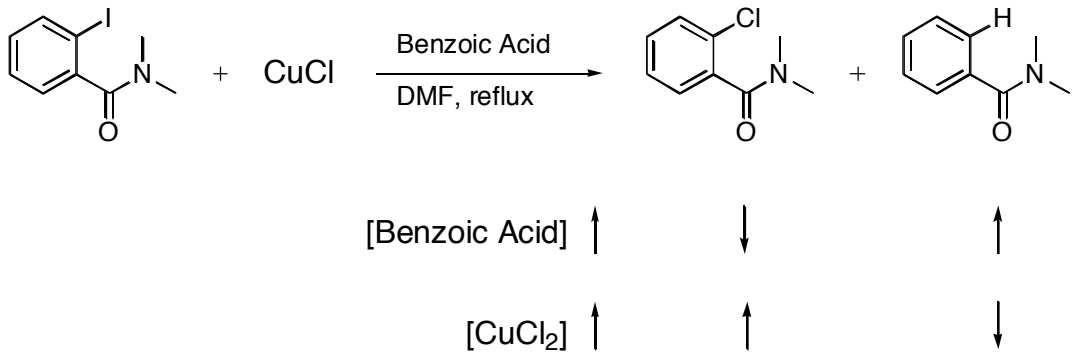

Figure 4.3: Competitive protonation and chlorination experiments conducted by Theodore Cohen in 1974.

Cohen observed that an increased concentration of benzoic acid resulted in an increase in the formation of *N, N*-dimethylbenzamide and a decrease of the chloro-substituted product, *o*-chloro-*N, N*,-dimethylbenzamide. Upon addition of increased concentration of CuCl however, produced and increase in *o*-chloro-*N, N*,-dimethylbenzamide, and a decrease in the formation of *N, N*-dimethylbenzamide. Based

on the results of these competitive protonation and chlorination experiments, Cohen concluded that an organocopper intermediate must be present in order to explain the results. An organocopper intermediate thus ruled out the possibility of arene-Cu π-complexes, arene free radicals, and arene-halide-nucleophile-Cu 4-centered intermediates.

Cohen therefore proposed a catalytic cycle involving the oxidative addition of Cu(I) into the aryl-halogen bond, to form a copper(III) intermediate which then undergoes an exchange of the halide with the nucleophile and subsequent reductive elimination to form the coupled product, and regenerate the active copper(I) species (Figure 4.4).

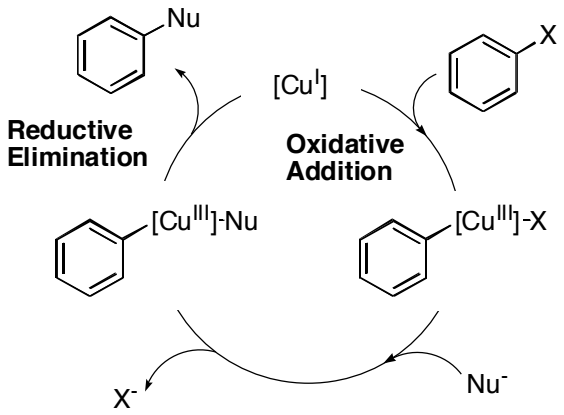

Figure 4.4: Proposed catalytic cycle involving a copper(III) intermediate.

In 1976 however, van Koten disputed Cohen's conclusion,[34] mainly because Cohen had failed to account for well-established chemistry of arene-copper intermediates. For example, arene-copper intermediates have been shown to produce Ar-

Ar coupled products, which Cohen did not observe. Furthermore, van Koten cites the instability of arene-copper intermediates under Cohen's reaction conditions, and uses themolysis studies to demonstrate that arene-copper π-complexing type intermediates are therefore unlikely in copper-catalyzed reactions.

In 1982, Russell Bowman further elaborated on copper-catalyzed reactions, by conducting a mechanistic comparison with the $S_{RN}1$ reaction.[35] One critical experiment was the reaction of dihalobenzenes, which can be used as a test for the intermediacy of aryl radical-anions, and therefore the $S_{RN}1$ reaction mechanism. The reaction of 1-chloro-4-iodobnezene with phenylthiolate exclusively yielded monocoupled products using catalytic CuI, whereas polymeric material was obtained under $S_{RN}1$ reactions conditions (Figure 4.5).

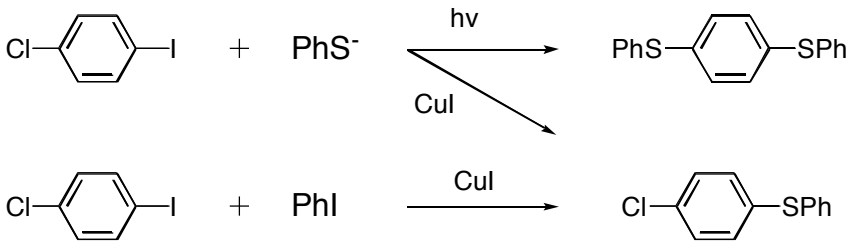

Figure 4.5: Dihalobenzenes as a test for the $S_{RN}1$ reaction mechanism.

A second technique for testing the possible intermediacy of aryl radicals is the ring closure reaction between and olefin and an *aryl radical*, which yield the cyclized product (Figure 4.6).

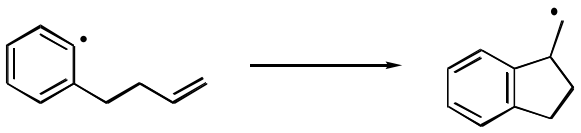

Figure 4.6: Cyclization reaction resulting from $S_{RN}1$ reaction conditions.

Bowman used this cyclization to study the possibility of aryl radicals as intermediates in copper-catalyzed coupling reactions, by comparing copper-catalyzed reaction with that of the $S_{RN}1$ reaction conditions. The copper-catalyzed reaction yielded the coupled product exclusively, and no cyclized product was observed under these conditions, while the same reaction run under $S_{RN}1$ conditions yielded the cyclized product (Figure 4.7). The absence of ring closure using CuI provides conclusive evidence against aryl radicals as intermediates in copper-catalyzed coupling reactions.

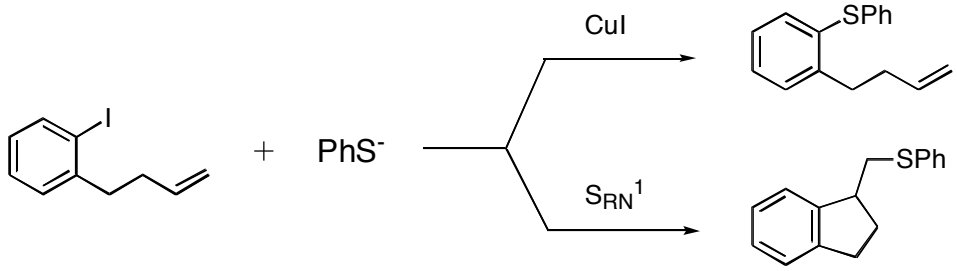

Figure 4.7: Bowman's comparison of $S_{RN}1$ and copper-catalyzed reaction mechanisms using a ring closing reaction.

The latest mechanistic report in the literature appeared in 1987, when Paine conducted a thorough investigation on several sources of copper, and concluded that there was *a single catalytic species* in the Ullmann coupling. Comparing homogeneous

and heterogeneous reactions, Paine showed that the active catalytic species was indeed, *soluble cuprous ion*, namely copper(I).[36]

To summarize, aryl radical intermediates in the reaction mechanism have been ruled out by Bowman's study, and aryl-copper intermediates have been proposed as intermediates by Cohen. More importantly, Weingarten, Cohen, and Paine demonstrated, using different experimental techniques, that the active catalytic species in the Ullmann coupling is indeed copper(I).

4.3 Modern improvements to the Ullmann coupling:

In 1997, Leibeskind showed dramatic improvements to reaction conditions in the Ullmann coupling, with the use of 2-thiophene carboxylate copper(I) (Figure 4.8).[37]

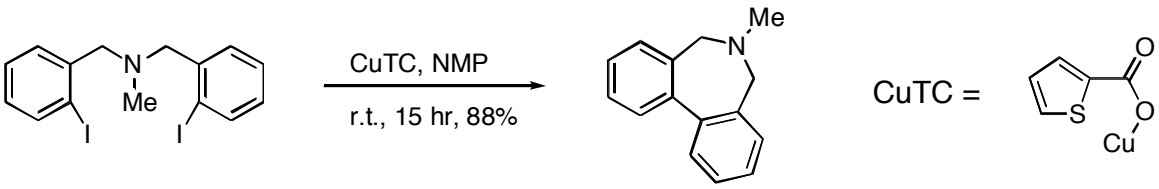

Figure 4.8: Improvements made to traditional Ullmann reaction conditions by Leibeskind et. al., with the use of CuTC.

These reactions are run at room temperature, and are effective for a variety of substrates. However, greater than stoichiometric amounts of the copper thiocarbamate are required in order to facilitate coupling.

More importantly, Buchwald reported the coupling of aryl bromides with various phenols, using a soluble copper salt, copper(I) trifluoromethylsulfonate as a *catalyst* with ethyl acetate and 1-napthoic acid as additives in 1997 (Figure 4.9).[16]

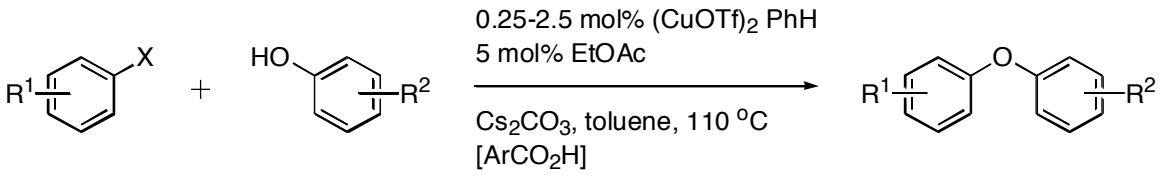

Figure 4.9: Buchwald's solubilization of copper by using trifluoromethylsulfonate.

Concurrently, Goodbrand independently reported that the used of certain additives in the synthesis of triphenylamines, greatly enhances the rate of copper-mediated reactions (Figure 4.10).[38]

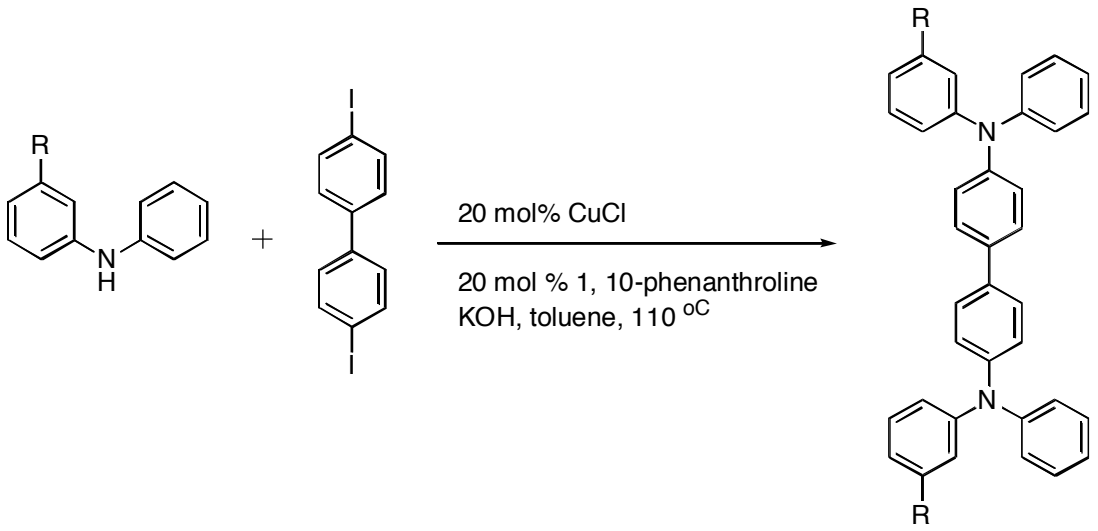

Figure 4.10: The use of additives such as 1,10-phenanthroline greatly increases the rate of copper-catalyzed reactions, as shown by Goodbrand.

The pioneering studies by Weingarten,[33] Cohen,[39-41], van Koten,[34] Bowman,[35] and Paine,[36] established that the active catalytic species in the copper-catalyzed Ullmann coupling is Cu^{I}. Based on these results, and recent improvements to the Ullmann coupling by Liebeskind,[37] Buchwald,[16] and Goodbrand,[38] we initiated a study of *chemically well-defined and soluble* copper(I) complexes that can be *systematically modified* as catalysts for the formation of aryl-carbon and aryl-heteroatom bonds, and for use in thorough mechanistic studies.

4.4 Mechanistic insights:

Despite van Koten's disagreement, recent papers on copper-catalyzed cross-coupling reactions refer to Cohen's investigation, and accept the formation of copper(III) intermediates as the most probable mechanism for these reactions. Cohen's proposed mechanism for copper(I)-catalyzed reaction is very similar to palladium(0) and gold(I)-catalyzed reactions,[42] and is quite attractive based upon this similarity. Although the very existence of copper(III) has been questioned, there are 60 structures in the recent edition of the Cambridge Crystallographic Database in which copper is formally assigned copper(III). Copper(III) intermediates have also been invoked in other copper-catalyzed mechanisms, such as the aziridation reaction. And, Stack recently reported the formation of copper(III) by the activation of aryl C-H bonds by copper(II).

There are however, several experimental details that do not bore well with copper(III) intermediates in modified Ullmann reactions. Most reactions involve the coupling of aryl iodides using either copper(I), or bromo complexes of copper(I). Although a transient copper(III) intermediate may be theoretically plausible; in the

presence of I^-, the ability to form copper(III) in the presence of iodide ions will be *unprecedented*. Furthermore, copper-catalyzed cross-coupling methodology tolerates *ortho* substituents on both the aryl halide and nucleophile. This is in stark contrast to palladium(0)-catalyzed reactions, in which the mechanism of oxidative addition/reductive elimination is well established. Moreover, aryl triflates are common substrates in palladium(0) methodology, but are inactive when subjected to modified Ullmann reaction conditions. To date, there have been no reports with conclusive evidence for the formation of copper(III) intermediates in any copper-catalyzed reactions.

In order to be able to modify and synthesize more active copper catalyst, it is imperative that we thoroughly understand the mechanistic aspects of copper-catalyzed reactions. This chapter reports on our investigation of the mechanism of copper-based catalysis in the synthesis of triarylamines. Our goal has been to determine the possible role of copper(III) intermediates in these cross-coupling reactions and experimentally determine the most likely mechanistic pathway by which copper-based catalysis occurs.

4.5 Catalytic cycles involving oxidation state change on the copper catalyst:

Based upon the abovementioned mechanistic information, we have outlined four possible reaction mechanisms, which based on earlier studies in the literature cannot be ruled out.[35,36,41,43] The mechanisms can be classified into two categories; those in which the oxidation state of copper changes throughout the mechanistic cycle, and two in which the oxidation state of copper remains constant throughout the reactions. Figure 4.11

illustrates two possible mechanistic pathways in which the oxidation state on copper must change.

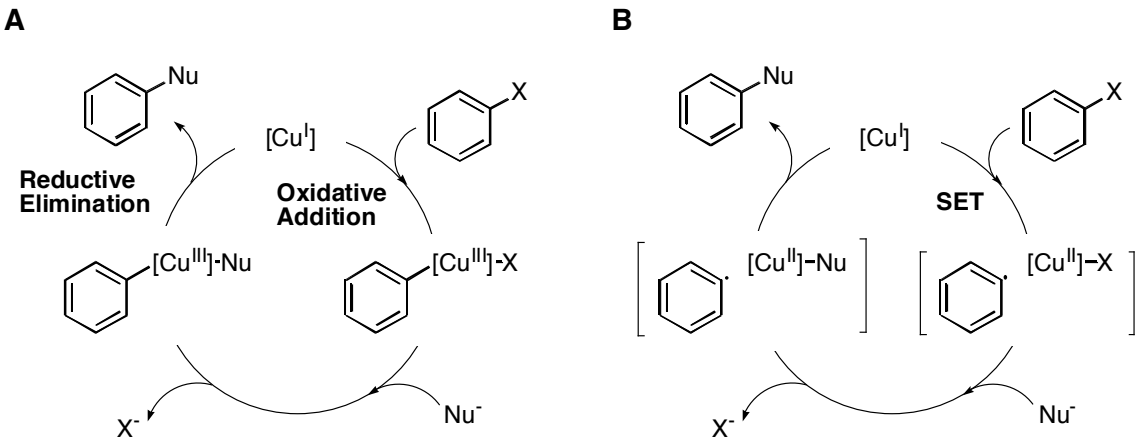

Figure 4.11: Reaction mechanisms in which the oxidation state of copper must change throughout the catalytic cycle.

The first catalytic cycle, path **A** is an *oxidative addition* path in which the aryl halide oxidatively adds to copper, resulting in a copper(III) intermediate. This type of cycle has been shown to be operative in palladium catalyzed cross-coupling reactions. After a nucleophile halogen exchange on copper the resulting intermediate reductively eliminates the coupled product, regenerating the active copper(I) catalyst. Path **B** also changes oxidation state but does so via *single-electron transfer* within the coordination sphere, and is therefore not a free radical mechanism. In this case, the intermediate is a copper(II) radical, which undergoes similar displacement of halide by the nucleophile, followed by radical combination to form the product and subsequent regeneration of the catalyst. These two pathways are very similar and are therefore difficult to distinguish

from one another experimentally. However, they both require equilibrium between copper and dissociated ligand to generate the active 16-electron complex.

4.6 Catalytic cycles involving no oxidation state change on the copper catalyst.

Similar to the previous two catalytic cycles, Figure 4.12 illustrates two additional mechanistic possibilities in which the oxidation state of copper does not change.

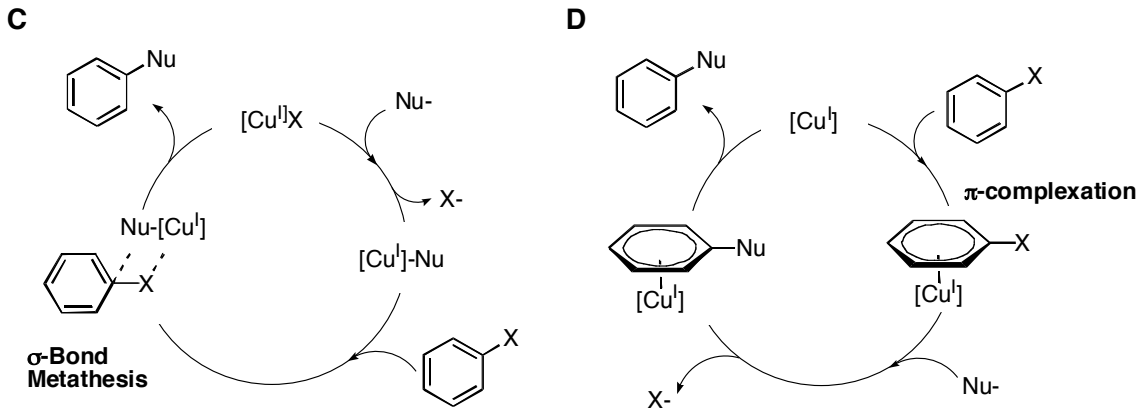

Figure 4.12: Catalytic cycles in which the oxidation state of the copper catalysts does not change throughout the reaction.

We have designated these two cycles σ-bond metathesis (**C**) and π-complexation (**D**). In both cases the copper catalyst remains in the +1 oxidation state throughout the reaction. These two mechanisms do however coordinate to copper differently. We have designated mechanism **C**, σ-bond metathesis. It is important to note however, σ-bond metathesis is a common reaction mechanism involving d^0 metal complexes, which cannot undergo an oxidation state change. Although our copper catalysts are d^{10}, mechanism **C** is similar to traditional σ-bond metathesis mechanism, in that it involves a four-centered

intermediate without an oxidation state change. We have therefore chosen the designation σ-bond metathesis. The first step of this reaction is displacement of the halide to form a [Cu]-Nu species that subsequently catalyzes the coupling. The copper catalyst must then coordinate to the aryl halide *via* a 4-centered intermediate. The orientation of the coordination can be readily determined by assigning partial charges to the copper catalyst and the aryl halide. Indeed, the halide is electronegative and creates a partial positive charge on the aromatic ring ipso to the halide, similar to the partial charges assigned in aromatic nucleophilic substitution reactions. The copper catalyst is of course in the +1 oxidation state and therefore the nucleophile can be assigned a partial negative charge. This type of orientation/coordination should therefore exhibit no substantial differences in rate or reactivity as a function of substitution. That is, we should observe similar reactivity patterns for both electron withdrawing and electron donating aryl iodides.

In the case of π-complexation however, there is no displacement of the aryl halide by the copper catalyst. Here, the copper catalyst coordinates to the aromatic ring of the aryl halide, which is polarized as a direct result of the substitution of the aryl halide. This polarization facilitates the coordination and subsequent exchange with the nucleophile to produce the coupled product, coordinated to copper. Consequently, the interaction of the aromatic ring of the product with copper, is much weaker than with the aryl halide, and the catalyst is therefore regenerated, releasing the coupled product. Hence, this mechanism should exhibit a pronounced substitution effect and show substantial differences in both rate and reactivity of electron donating and electron withdrawing aryl

iodides. We have ruled out the possibility of simple nucleophilic aromatic substitution *via* a Meisenheimer complex, because no reaction occurs in the absence of a copper catalyst.

Using the abovementioned catalytic cycles as a guide, we have conducted a series of experiments testing the conditions of each mechanism. Each mechanism raises important questions about the reaction mechanism, and the following section details the testing of these mechanistic possibilities.

4.7 Proof by elimination:

This section outlines our experimental approach to distinguishing between the four previously described mechanisms. Figure 4.13 outlines the experiments and rational described below. We begin with a *well-defined* copper complex based on the bidentate nitrogen-based ligand, 2,9-dimethyl-1,10-phenanthroline. The flow chart presents our experimental outline for elucidating the operative mechanism of copper-based catalysis in the Ullmann coupling.

We have outlined a set of conditions that test the validity of the aforementioned mechanisms. These conditions express our questions regarding different aspects of each mechanism, and it's potential as the most likely reaction pathway. To generalize our approach, the questions we have posed regarding the mechanism are the following:

- *What is the effect of the halide on the copper catalyst, and how does this impact the possibility of certain reaction mechanisms?*
- *What are the effects of added phosphine to the reaction?*

- *What are the effects of substituents on the aryl halide, and how does this information correspond to mechanistic insight?*
- *What is the impact of different oxidation states of copper catalysts, and how the effect the rate and conversion of reaction?*

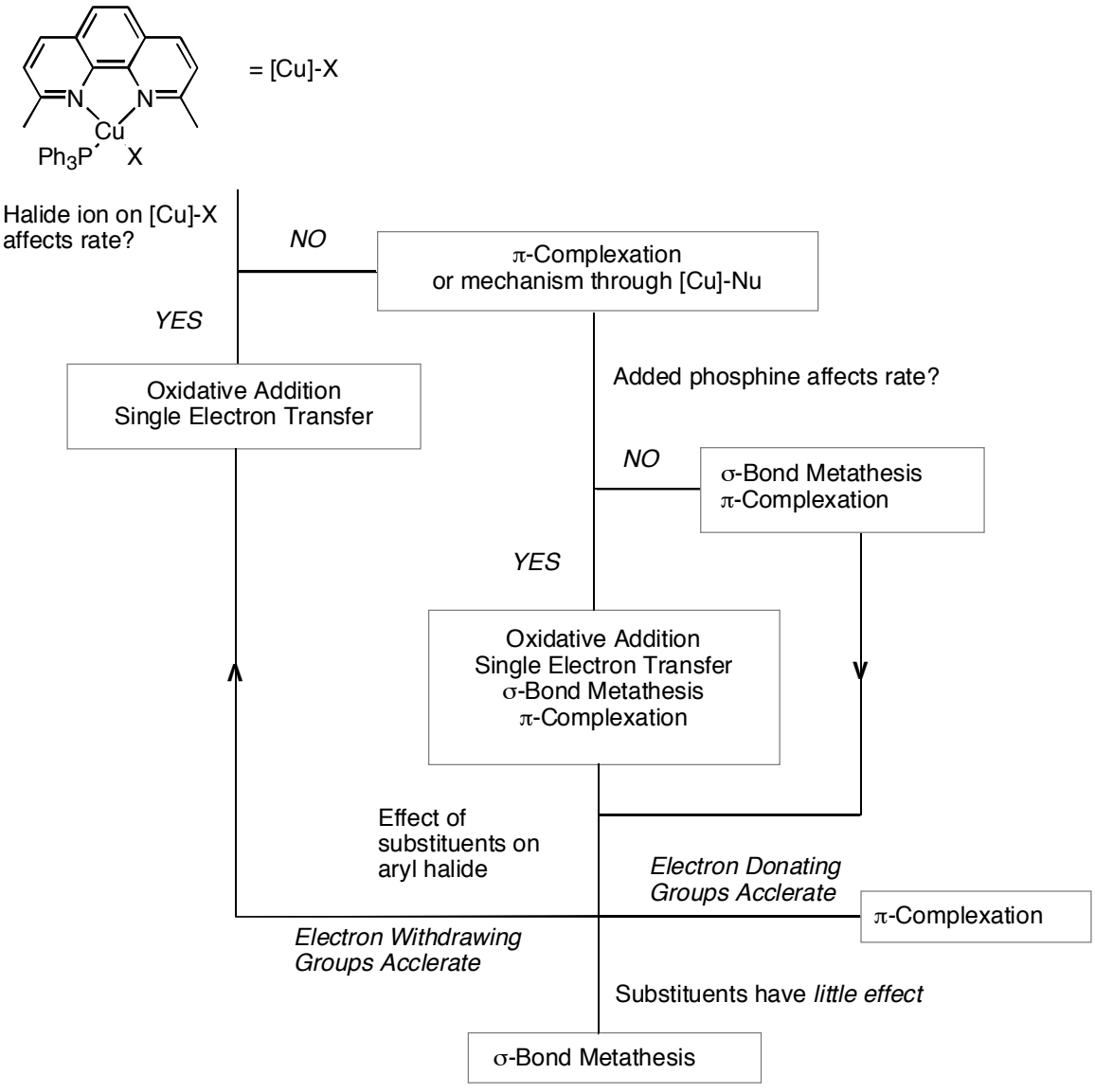

Figure 4.13: Flow chart of our experimental outline to distinguish between the four possible reaction mechanisms in the modified Ullmann coupling.

4.8 Details of kinetics experiments:

We have investigated copper-catalyzed cross coupling of diphenylamine with various substituted iodobenzenes as well as various catalyst oxidation states to explore several possible mechanisms, and to experimentally eliminate the likelihood of certain pathways. The reaction conditions employed use diphenylamine, 1.2 equivalents of KO*t*-Bu as the base, and 10 mol % copper catalyst in toluene. Our kinetics runs were all *pseudo-first order* in iodobenzene, and the rate expression for all of these experiments is therefore: Rate = k[IB]. All reactions were run at 110 ^{o}C, and monitored analytically by GC. As abovementioned, we have outlined an experimental approach to discerning which mechanism is most likely, based on the differences in the mechanisms, by eliminating the other possibilities experimentally.

4.9 Effect of halides on the *well-defined* complexes:

The first question we asked was: *does the halide counter ion on the copper complex has any effect on the rate of the cross coupling*?

Substantial differences in rate between a copper-chloro and copper-iodo complex should be observed in the case of mechanisms **A/B**, which involve a change in oxidation state of copper, especially in mechanism **A**, in which oxidative addition is most likely the rate determining step of the reaction.

The catalyst most commonly used, [Cu(dmp)PPh_3Br], has been very effective in the Ullmann coupling. In order to understand the effect of the halide counter ion we synthesized the corresponding iodo and chloro complexes, [Cu(dmp)PPh_3I] and

[Cu(dmp)PPh_3Cl], to complete the halide series. The two mechanisms, σ-bond metathesis and π-complexation do not involve an oxidation state change, and should exhibit little or no effect upon changing the halide counter ions on the catalyst. Whereas, the oxidative addition and SET mechanisms should show dramatic differences in reaction rates as a result of the different electronic and steric environment on copper. Using this series of catalysts. The reaction profile and reaction rates again indicated that the halide has no effect on the coupling, as shown in Figure 4.14.

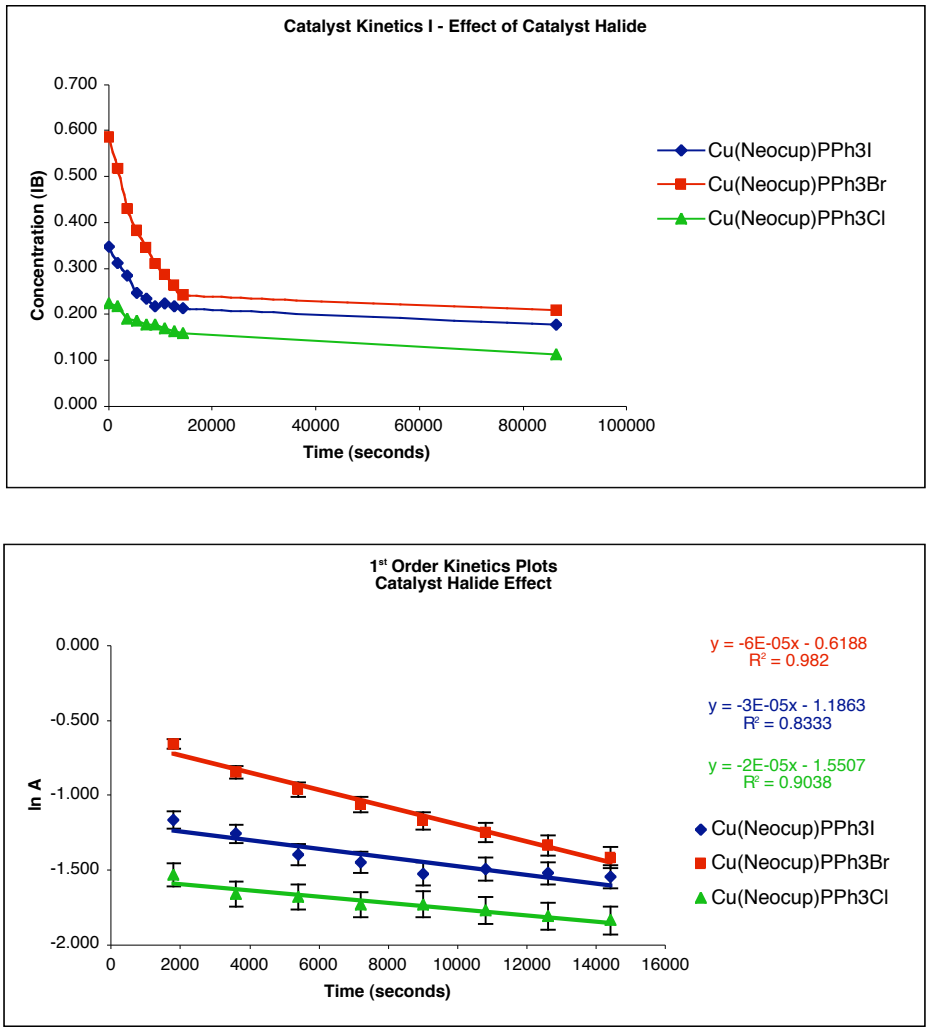

Figure 4.14: Effect of halide counter ion on several copper catalysts.

As can be seen, the reaction profiles for the series of catalysts containing iodo, bromo, and chloro counter ions are very similar, indicating that there is in fact *no effect* of the halide counter ion on the copper catalyst. Furthermore, the reaction rates for this series of catalysts are also nearly identical. The results of these experiments are inconsistent with both the oxidative addition and SET mechanisms, because each should be affected by the electronic changes to the catalyst, as a result of the required change in oxidation state.

4.10 Effect of added ligands:

The next question that we posed was: *How does the addition of triphenylphosphine effect the reaction rate and conversion?*

Our most commonly used and effective catalyst, [Cu(dmp)PPh_3Br], is a coordinatively saturated 18-electron complex and would have to form a coordinatively unsaturated 16-electron complex to further react. There are two possible pathways by which this could happen. One possibility is that there is an equilibrium dissociation of phosphine ligand to form the catalytically active 16-electron complex (Figure 4.15).

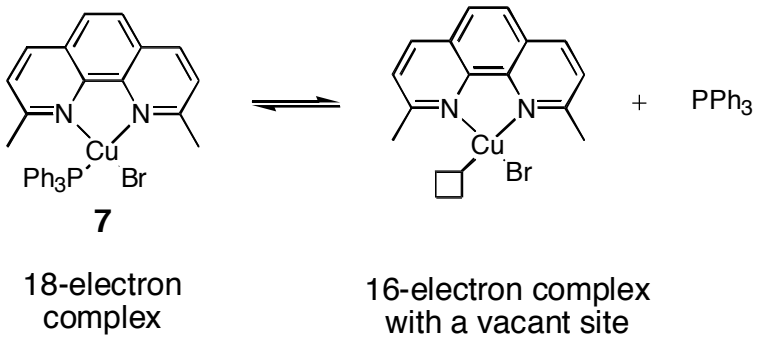

Figure 4.15: Dissociation of phosphine from *well-defined* copper complexes.

The effect of added triphenylphosphine will be to drive this equilibrium towards the 18-electron complex, if such an equilibrium exists, thus shutting down the reaction. Therefore, similar to palladium-catalyzed reactions where oxidative addition/reductive elimination is the established mechanism, we should observe a rate *decrease* with the addition of triphenylphosphine.[44-46]

Alternatively, the copper complex may undergo rapid exchange between the halogen on copper and the nucleophile, to generate [Cu]-Nu as the active catalytic species (Figure 4.16).

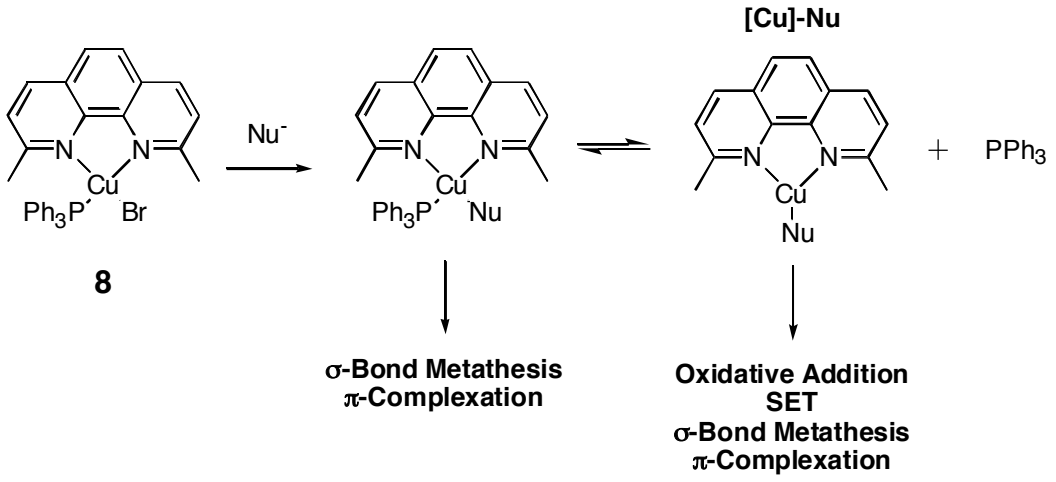

Figure 4.16: An alternate pathway to create a 16-electron complex, in which the complex may undergo rapid exchange between halogen and nucleophile on the copper catalyst.

Under these circumstances the addition of triphenylphosphine to the reaction will enable us to distinguish the active catalytic species, between the 18-electron complex and the coordinatively unsaturated 16-electron complex. In both the σ-bond metathesis and π-complexation mechanisms, the active catalytic species is an 18-electron complex, and

the addition of phosphine should therefore have *no effect* on the reaction. If however, there is a rapid exchange of the halide to form the coordinatively unsaturated 16-electron complex, [Cu]-Nu, there will be a *decrease* in the rate of reaction.

We again employed [Cu(dmp)PPh_3Br] as the catalyst and added triphenylphosphine ligand to the reaction, ranging from 0.5 equivalents to 2.0 equivalents, and observed *no effect* of added phosphine (Figure 4.17).

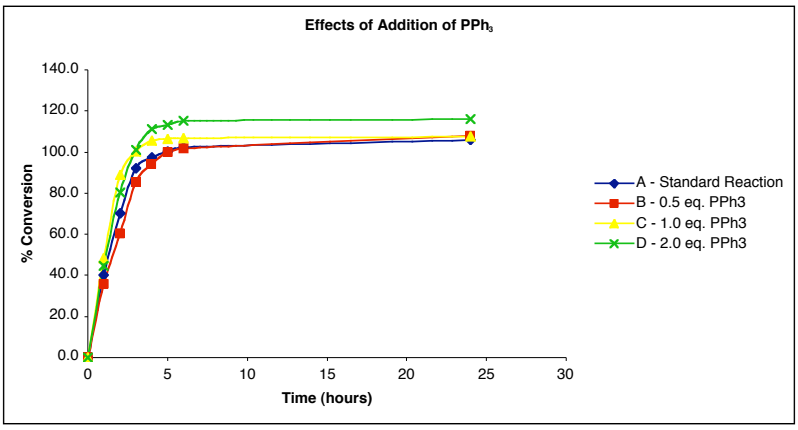

Figure 4.17: Effect of addition of triphenylphosphine to the coupling.

In order to more fully understand the effect of added ligand on the catalyst, as well as the reaction mechanism, we conducted similar experiments using 2,9-dimethyl-1,10-phenanthroline (neocuproine (dmp)) in place of phosphine. The addition of neocuproine to [Cu(dmp)PPh_3Br] would likely produce the copper species, [Cu(dmp)$_2$], which we have also found to be active in the Ullmann reaction. However, the catalyst [Cu(dmp)$_2$] is coordinatively unsaturated, and would need to dissociate a neocuproine ligand for a reaction to occur (Figure 4.18). The addition of neocuproine to the reaction,

will favor [Cu(dmp)$_2$] and keep this equilibrium from going towards the formation of products.

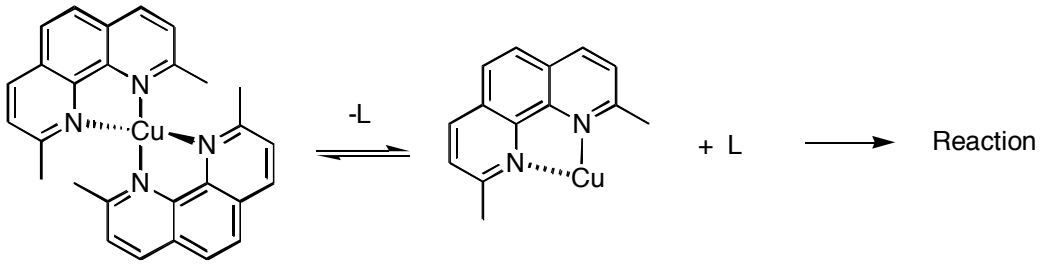

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Figure 4.18: Equilibrium conditions of [Cu(dmp)$_2$] required for reaction to occur.

We found that the rate of reaction was not affected by the addition of the neocuproine ligand, but the conversion was reduced. This observation means that the species formed in the presence of added neocuproine is not in the rate equation, that is, a copper species is formed that is not *catalytically* active. The can be attributed to the formation of [Cu(dmp)$_2$], or possibly [Cu(dmp)], which are only active stoichiometrically (Figure 4.19).

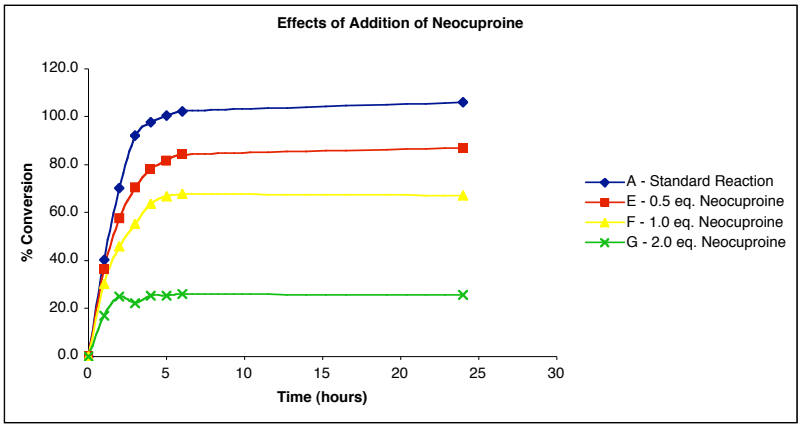

Figure 4.19: Effect of the addition of neocuproine to the coupling.

To summarize, we do not observe any effect of added phosphine to the reaction, which is consistent with a four-centered intermediate (σ-bond metathesis) and π-complexation mechanisms, and inconsistent with oxidative addition and SET. The addition of neocuproine to the reaction illustrates that a strongly binding ligand can shut down the reaction by preferentially coordinating to the copper catalyst, therefore preventing any reaction from occurring. The results of added phosphine are inconsistent with both *oxidative addition* and *SET*, whereas *σ-bond metathesis* and *π-complexation* are consistent with our experimental observations.

4.11 Substituent effects – part 1:

Our experiments thus far are consistent with only two of the four proposed mechanisms, *σ-bond metathesis* and *π-complexation*. The question then arises: *What is the substituent effect in the Ullmann coupling?* These questions address the issue of the

effects of substitution of the aryl halides, and may also be used to confirm or disconfirm our previous conclusions about the reaction mechanism.

Recall that electron-withdrawing groups on the aryl iodide will hasten oxidative addition and hence *increase* the rate of reaction, which is consistent with palladium reactions. The same effect would occur if an *SET* mechanism were operative. The possibility of the reaction proceeding through the *π-complexation* mechanism, in which the formation of a Meisenheimer complex is the first step, has already been ruled out. However, it may be possible that the aryl halide and the copper complex exist in equilibrium (Figure 4.20).

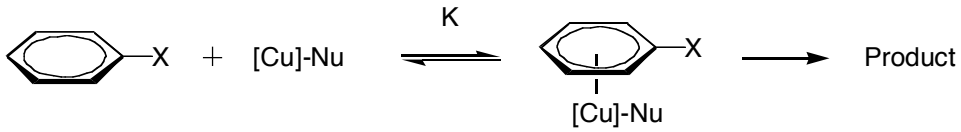

Figure 4.20: Possible equilibrium in the π-complexation mechanism.

If such an equilibrium were to exist, the reaction rate should depend on the concentration of the aryl-copper complex, [Cu]-Nu, which would depend on the equilibrium constant, K. Therefore, electron deficient aryl halides will result in a low equilibrium constant, and a *lowered* rate of reaction. If on the other hand, the equilibrium constant is high and independent of the functional groups on the aryl halide, then the electronics of the aryl halide will have *no effect* on the reaction rate. Electron withdrawing groups will *decrease* the reaction rate when K is small, which is the opposite effect of *oxidative addition* and *SET*, mechanisms **A** and **B**. A reaction

mechanism that is not affected by the substituents on the aromatic ring must have a transition state does not have charge build-up on the aromatic ring. This type of transition state is consistent with the *σ-bond metathesis* reaction mechanism.

To summarize, acceleration of the reaction rate by *electron withdrawing* groups is indicative of oxidative addition and SET (and would therefore contradict the results of added phosphine). Acceleration of the rate by *electron donating* groups is consistent with a mechanism that proceeds *via* π-complexation, and *little or no effect* in the rate, regardless of substitution on the aryl halide, is consistent with σ-bond metathesis.

4.12 Substituent effects – part 2:

In order to establish whether or not there is a substantial substituent effect in the reaction, we ran several kinetics experiments in order to plot our reaction rates against tabulated Hammett σ values. Our kinetics experiments were conducted on a variety of substrates ranging from electron donating to electron withdrawing groups. The first of which was 4-Iodotoluene. It is important to note that the consumption of the iodide corresponds to the production of the corresponding triphenylamine product, for all aryl iodide substrates. In general, we sampled over the first three hours because during this period of the reaction, the slope of the curve is linear, and first order with respect to the iodide.

The aryl iodides studied, in order of increasing electron-withdrawing character, is 4-iodotoluene, iodobenzene, 4-fluoroiodobenzene, 4-iodoanisole, 4-iodobenzotrifluoride,

4-iodobenzonitrile, and finally, 1-iodo-4-nitrobenzene.[47] These experiments were conducted with an excess of diphenylamine, to simulate 1st order kinetics with respect to the aryl iodides, and the rate data generated is used to quantitatively evaluate the substituent effect (Table 4.1)

Table 4.1: Substituted aryl iodides and their corresponding rate coefficients (k).

Aryl Iodide	Rate coefficient (k)
4-Iodotoluene	$9.00 \times 10^{-5}\ s^{-1}$
Iodobenzene	$6.00 \times 10^{-5}\ s^{-1}$
4-Fluoroiodobenzene	$7.00 \times 10^{-5}\ s^{-1}$
4-Iodoanisole	$1.00 \times 10^{-4}\ s^{-1}$
4-Iodobenzotrifluoride	$7.00 \times 10^{-5}\ s^{-1}$
1-Iodo-4-nitrobenzene	$2.00 \times 10^{-5}\ s^{-1}$

Our study of the substituent effect of aryl iodides in the modified Ullmann reaction is summarized in table 4.2. The established method of evaluating the substituent effect of a particular reaction is to plot the $\log(k/k_0)$ vs. σ-values. The resulting graph will be a straight line, providing there is a marked substituent effect. The slope of this curve is the reaction parameter, ρ, and is indicative of the magnitude of the substituent effect. We have used sigma values that have recently been tabulated in *Chemical Reviews*, for a variety of substituted halides by Taft.[48]

Table 4.2: Tabulated Hammett parameters from our study, and sigma parameters from Taft; where: k_0 is the rate coefficient of iodobenzene and k is the rate coefficient of the respective aryl iodide.

Iodide	σ_p : From Taft	Rate (k)	k_{sub} / k_H	log (k/k_0)
4-CH_3	-0.19	9.00×10^{-5} s^{-1}	1.50	1.76×10^{-1}
4-H	0.00	6.00×10^{-5} s^{-1}	1.00	0.00
4-F	0.04	7.00×10^{-5} s^{-1}	1.17	6.69×10^{-2}
4-OCH_3	0.40	1.00×10^{-4} s^{-1}	1.67	2.22×10^{-1}
4-CF_3	0.50	7.00×10^{-5} s^{-1}	1.17	6.69×10^{-2}
4-NO_2	0.75	2.00×10^{-5} s^{-1}	0.33	-4.77×10^{-1}

It is important to note that the rate coefficient, k, is very similar for all substrates studied. This indicates that there is *little or no effect* of electronics on the cross coupling of aryl iodides with diphenylamine, and therefore little or no Hammett correlation. Moreover, the logarithm data emphasizes that there is no effect of substituent on the aryl iodide, which would be consistently increasing or decreasing, depending upon the effect electronics had on the coupling. Our data clearly indicates there is no such correlation of Hammett parameters. To illustrate this point, a plot of $\log(k/k_0)$ vs. σ-values, using our data further illustrates that substituents on the aryl iodides have little or no effect on the modified Ullmann coupling (Figure 4.21). This figure clearly illustrates that there is little or no effect of substituents on the reaction rate, and as a result, the data cannot be reasonably fit to a straight line.

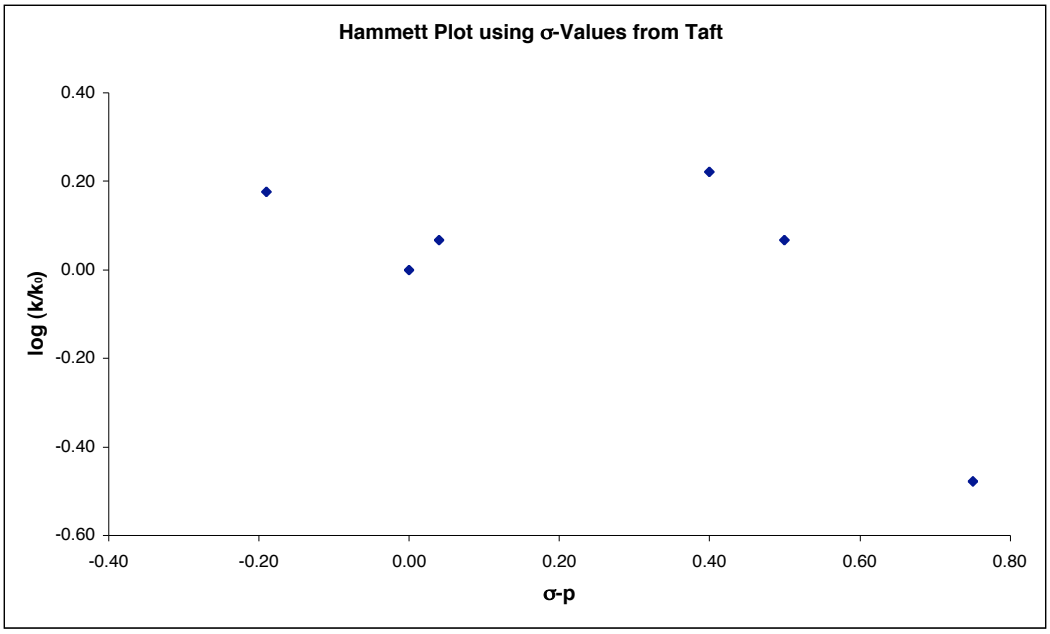

Figure 4.21: A Hammett plot of our substituent data.

In summary, we do not observe a pronounced substituent effect, even in the case of strongly electron withdrawing groups. As aforementioned, three of the four possible reaction mechanisms should exhibit substituents effects. The only mechanism that should not exhibit an effect is σ-bond metathesis. We also did not observe an effect of added phosphine, which is independently consistent with σ-bond metathesis and π-complexation. Therefore, our experimental results are redundantly inconsistent with oxidative addition, SET, and π-complexation, and consistent only with σ-bond metathesis.

4.13 Oxidation state of the catalyst - effects on catalysis:

The Ullmann reaction, and the modified Ullmann are catalyzed by copper(I) catalysts. To further support our assertion that oxidative addition is not a likely

mechanistic pathway, we have shown experimentally, that several oxidation states of copper can catalyze the modified Ullmann coupling. We have synthesized complexes that are formally copper(II) and copper(III), that facilitate reaction as well as copper(I) catalysts (Figure 4.22).

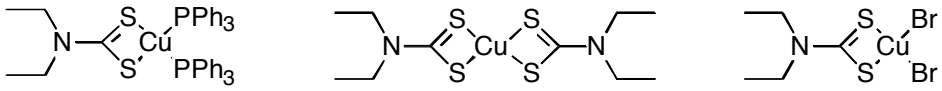

Figure 4.22: Copper complexes of three different oxidation states synthesized in our laboratory based on the ethylene dithiocarbamate (edtc) ligand.

The ethylene dithiocarbamate (edtc) ligand helps to stabilize copper(III), and for that reason we have prepared copper(I), copper(II), and copper(III) complexes based on the edtc ligand. In addition to [Cu(edtc)PPh_3], [Cu(edtc)$_2$], and [Cu(edtc)Br_2] we have also studied the reaction of the copper(II) complex, Cu(phen)Br_2, which is also an effective catalyst for the modified Ullmann reaction. During our mechanistic investigation, we have compared our standard catalyst for the modified Ullmann coupling, [Cu(dmp)PPh_3Br], with [Cu(phen)Br_2], and [Cu(edtc)Br_2] to explore the effect of oxidation state of copper in the cross coupling of iodobenzene with diphenylamine. All three different oxidation states of copper catalyze the reaction, and the consumption of iodobenzene is equal in all cases. The reaction profiles are identical, as well as the reaction rates, 6 x10^{-5} s^{-1}, 4 x10^{-5} s^{-1}, 7 x10^{-5} s^{-1}, for copper(I), copper(II), and copper(III), respectively. These reaction rates are, within experimental error, the same. This data is

therefore *inconsistent* with a catalytic cycle that involves a change in oxidation state of copper, and therefore precludes the oxidative addition and SET mechanisms. It is however, *consistent* with the σ-bond metathesis mechanism, and is further support of our previous studies, including the effects of added phosphine, and substituent effects.

4.14 Conclusion:

In this chapter we have reported on our investigation into the copper-catalyzed modified Ullmann reaction. Copper-catalyzed reactions are commonly believed to proceed *via* oxidative addition of a copper(I) catalyst to a copper(III) intermediate, similar to the established mechanism of palladium(0)-catalyzed reactions. Based on previous studies of copper-catalyzed reactions, we described, in detail, four reaction mechanisms that may be operative in the modified Ullmann reaction. We have rationalized and designed experiments that we've used to differentiate between these four reaction mechanisms.

Our experiments are based on the concept of proof by elimination; whereby we experimentally test the precepts of the four possible catalytic cycles, namely oxidative addition, single electron transfer, π-complexation, and σ-bond metathesis. We have tested various conditions of each reaction mechanism and experimentally shown that the three mechanisms, oxidative addition, SET, and π-complexation are not operative mechanisms in the modified Ullmann reaction.

Most importantly, we have provided experimental data that is inconsistent with the oxidative addition reaction mechanism, which for many years was believed to be the

operative process in copper-catalyzed reactions. Through careful experimental design, and the use of *chemically well-defined* copper complexes, we have concluded that the mechanism we have designated, σ-bond metathesis, which is consistent with all of our experimental observations, is the most likely reaction mechanism in copper-catalyzed reactions.

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CHAPTER 5

CONCLUSIONS

There has been thorough development of organometallic catalysts over the past half-century. In particular, palladium(0)-based catalysts have had a dramatic impact in the fields of biological, pharmaceutical, and materials chemistry. It was our intent at the outset of this research, to transition from palladium-based couplings, to develop copper-based methodology, and to conduct a thorough mechanistic investigation into the century old Ullmann coupling.

We have developed a novel carbon-nitrogen bond forming reaction resulting from a cyclization reaction facilitated by palladium-catalyzed C-H activation at an sp^3 center. The experimental conditions have been thoroughly investigated, including several palladium and nickel catalysts, as well as a variety of bases. The cyclization was found to be limited in scope, and this unusual observation is a direct result of the geometrical constraints of the starting secondary amine. Despite the limited scope of the observed cyclization, the use of geometrically constrained molecules has excellent potential as a tool for the investigation of organometallic reaction mechanisms.

The development of copper-catalyzed methodology in our research group was initiated as a means to address specific and general limitations of palladium-based methods, including the geometrically constrained secondary amine. As part of our ongoing research effort to develop copper-based methodology, we have reported on the synthesis of unsymmetrical triarylphosphines. This new methodology uses CuI as the

catalyst, and K_2CO_3 as the base, for coupling aryl iodides with diphenylphosphine. This protocol is tolerant to a variety of functional groups, including electron withdrawing and electron donating groups. We have also demonstrated this methodology to be effective with base sensitive groups, a dramatic improvement to traditional methods.

Through mechanistic investigations, using the concept of proof by elimination, we have shown that the only mechanism consistent with all of our experimental observations in the Ullmann reaction is σ-bond metathesis. Our rationale was based on several important experiments that tested various conditions of possible reaction mechanisms, while providing answers to several fundamental questions regarding each mechanism. In order to answer the specific questions we posed regarding the mechanism of the Ullmann coupling, we synthesized a variety of copper complexes. Several of these complexes were prepared with different halide counter ions, and of others with differing oxidation states, including copper(I), copper(II), and copper(III).

The first experiment tested the effects of different halides on copper complexes, the results of which were inconsistent with the oxidative addition mechanism. Another of these experiments explored the effects of added ligands, such as triphenylphosphine and neocuproine, which again were inconsistent with oxidative addition and single electron transfer mechanisms. We also studied the effects of substituents on aryl iodides in the cross coupling with diphenylamine, and found that there was not a dramatic effect, indicating that charged intermediates are not present in the transition state. These experiments were inconsistent with a π-complex mechanism, and along with the aforementioned experiments, supported a *four-centered intermediate*, and hence the σ-

bond metathesis mechanism. Additionally, we conducted kinetics experiments using several copper complexes of different oxidation states. We found that catalysts of three oxidation states of copper, (Cu^{I}, Cu^{II}, Cu^{III}), have no effect on the cross coupling of iodobenzene with diphenylamine, providing further evidence that is inconsistent with mechanisms involving oxidation state changes on copper.

In summary, we have explored a unique cyclization that results from the failure of palladium in certain cross coupling reactions. The failure of palladium prompted investigation into new copper-based methodology, in which we subsequently developed new methodology for the cross coupling of aryl iodides with diphenylphosphine, to synthesize a variety of unsymmetrical triarylphosphines. Finally, we conducted a thorough mechanistic investigation into the mechanism of the century-old copper-catalyzed Ullmann coupling, and provided conclusive evidence that is inconsistent with copper(III) intermediates. There is great potential to use this mechanistic information in the design of new highly active copper-based catalysts. However, to achieve this ultimate goal, further investigation in the laboratory is required to determine the optimal catalyst structure and properties.

APPENDIX

EXPERIMENTAL

General Information:

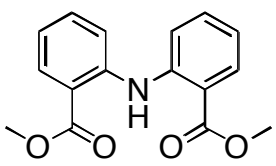
All chemicals were purchased from major chemical suppliers and were used without further purification. Flash chromatography was performed using ICN flash silica gel, 230-400 mesh. All ^{1}H and ^{13}C NMR spectra were recorded on a Brucker DPX300 MHz spectrometer. Chemical shifts (δ) and coupling constants (*J*) are reported in parts per million (relative to internal TMS) and Hertz, respectively. The abbreviations for splitting patterns are s, singlet; br s, broad singlet; d, doublet, t, triplet; q, quartet; and combinations therein (i.e. dd, doublet of doublets). Elemental analyses were performed in the Microanalysis Laboratory, University of Massachusetts at Amherst, by Dr. Greg Dabkowski. Mass spectral data were obtained at the University of Massachusetts Mass Spectrometry Facility, which is supported, in part, by the National Science Foundation. Xray crystallographic data was obtained at the X-ray Structural Characterization Laboratory and the University of Massachusetts Mass Spectrometry Facility, which is supported by the National Science Foundation, grant CHE-9974648. X-ray data were collected using a Nonius kappa-CCD diffractometer with MoKα (λ=0.71072 Å) as the incident radiation. Diffraction data were collected at ambient temperature unless otherwise stated. The raw data were integrated, refined, scaled, and corrected for Lorentz polarization and absorption effects, if necessary, using the programs DENZO and SCALEPAK, supplied by Nonius. Structure solutions and refinements were done (on F_o^2) using a suite of programs such as SIR97, SIR92, LSQ, SHELXS and SHELXL that are

contained within the Nonius MAXUS module. All structures were checked for any missing symmetry using MISSYM of PLATON.

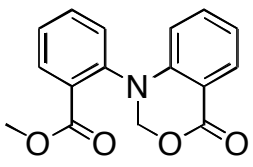
FORMATION OF AN UNUSUAL INTRAMOLECULAR C-N BOND: POSSIBLE C-H ACTIVATION?

General Procedure (A) using KHMDS. In a 50 mL Schlenk flask, $Pd_2(dba)_3$ (5 mol% with respect to **1**) was combined with a ligand (30 mol% with respect to **1**) and diester **(1)**. The flask was degassed and back-filled with argon several times. Methyl-2-bromobenzoate was added followed by toluene. After stirring for 10 min at room temperature, potassium bis(trimethylsilyl)amine (0.5 mol% with respect to **1**) was added. The reaction mixture was stirred at 110 ^{o}C for 12 h. The reaction mixture was filtered and the filtrate extracted in ether. A 1 mL sample was used for GC analysis.

General Procedure (B) for Bases other than KHMDS. In an argon-filled glove box, a 50 mL Schlenk flask equipped with a Teflon stir bar and a rubber septum, was charged with base (1.2 eq with respect to **1**), $Pd_2(dba)_3$ (5 mol% with respect to **1**), ligand (30 mol% with respect to **1**), and diester **(1)**. The sealed tube was taken out of the box and the aryl halide and toluene were injected into the tube through the septum under a flow of argon. The reaction mixture was stirred at 110 ^{o}C for 12 h. The reaction mixture was filtered and the filtrate extracted in ether. A 1 mL sample was used for GC analysis.



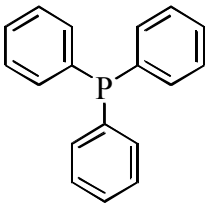
2, 2'-azanediyl-bis-methylbenzoate (1). In a 100 mL Schlenk flask, $Pd_2(dba)_3$ (0.637g, 0.70 mmol) was combined with 1,4-bis(diphenylphosphino)butane (0.446g, 1.05 mmol) and sodium methoxide (1.884g, 34.9 mmol). The flask was degassed and back-filled with argon several times. Methyl-2-bromobenzoate (3.9 mL, 27.8 mmol) was added followed by 20 mL of toluene. After stirring for 10 min at room temperature, methylanthranilate (3.0 mL, 23.2 mmol) was added. The reaction mixture was stirred at 110 ^oC for 8 h. The reaction mixture was filtered and the filtrate was extracted with water, brine, and then dried over sodium sulfate. Concentration in vacuo gave the crude product which was then purified by flash chromatography using a 2:1 ratio of diethyl ether to hexane as the eluent to give 4.48g (90% yield). Product can be further purified by re-crystallization from boiling hexane (m.p. 102-104 ^oC). 1H NMR: ($CDCl_3$) d 7.55 (dd, J=0.96, 8.49 Hz, 2H, H_1), 6.90 (td, J=1.29, 7.14 Hz, 2H, H_2), 7.37 (td, J=1.68, 7.62 Hz, 2H, H_3), 7.98 (dd, J=1.68, 7.92 Hz, 2H, H_4), 3.94 (s, 6H, H_5), 11.06 (br s, 1H, H_6). ^{13}C NMR: ($CDCl_3$) d 168.1 (C_7), 144.6 (C_6), 133.6 (C_2), 132.2 (C_4), 120.2 (C_3), 118.0 (C_1), 117.4 (C_5), 52.5 (C_8). HRMS calcd for $C_{16}H_{15}O_4N$ 285.30, found 285.3002. Anal. Calcd for $C_{16}H_{15}O_4N$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.44; H, 5.30; N, 4.84.



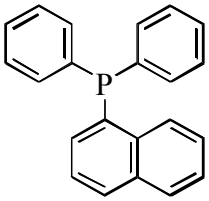
2-(4-Oxo-4H-benzo[d][1,3]oxazin-1-yl)-benzoic acid methyl ester (2). In a 50 mL Schlenk flask, $Pd_2(dba)_3$ (0.166 g, 0.18 mmol) was combined with triphenylphosphine (0.293 g, 1.1 mmol) and **(1)** (1.04 g, 3.65 mmol). The flask was degassed and back-filled with argon several

times. Methyl-2-bromobenzoate (0.60 mL, 4.3 mmol) was added followed by 40 mL of toluene. After stirring for 10 min at room temperature, potassiumbis(trimethylsilyl)amine (4.3 mL, 0.42M) was added. The reaction mixture was stirred at 110 ^{o}C for 12 h. The reaction mixture was filtered and the filtrate was extracted with water, brine, and then dried over sodium sulfate. Concentration in vacuo gave the crude product, which was then purified by flash chromatography using a 1:2 ratio of diethyl ether to hexane as the eluent to give 0.154 g (15% yield). ^{1}H NMR: (CDCl3) δ 3.77 (s, 3H), 5.48 (s, 2H), 6.69 (d, *J* = 8.3 Hz, 1H), 7.06 (dt, *J* = 1.1 and 7.7 Hz, 1H), 7.25 (dd, *J* = 1.3 and 7.9 Hz, 1H), 7.37 (m, 2H), 7.55 (td, *J* = 1.7 and 7.3 Hz, 1H), 8.00 (dd, *J* = 1.7 and 7.9 Hz, 1H), 8.07 (dd, *J* = 1.7 and 7.9 Hz, 1H). Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.95. Found: C, 67.76; H, 4.51; N, 4.92.

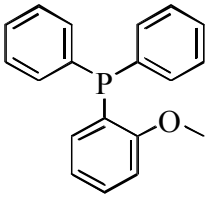
SYNTHESIS OF UNSYMMETRICAL TRIARYLPHOSPHINES



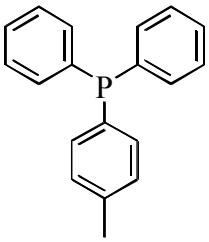
Triphenylphosphine (10): The general procedure was used to convert iodobenzene and diphenylphosphine to the title product. Purification by flash chromatography (pentane / dichloromethane [2:1] as the eluent) gave the analytically pure product as a white solid (435 mg, 83% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.34-7.22 (m, 15 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 137.2, 137.1, 133.8, 133.9, 128.8, 128.5, 128.4. ^{31}P NMR (121 MHz, $CDCl_3$) d -4.96 (s). Anal. for $C_{18}H_{15}P$: C, 82.43; H, 5.76; P, 11.81; Found: C, 82.13; H, 5.78.



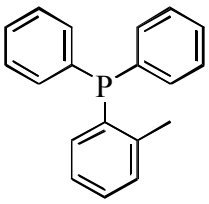
Naphthalen-1-yl-diphenyl-phosphane (11): The general procedure was used to convert 1-iodonapthanlene and diphenylphosphine to the title product. Purification by flash chromatography (dichloromethane as the eluent) gave the analytically pure product as a white solid (567 mg, 91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.51-7.28 (m, 15 H), 7.85 (t, 2H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 134.3, 134.1, 133.4, 133.4, 132.0, 129.5, 128.8, 128.7, 128.6, 128.5, 126.3, 126.0, 125.9, 125.5. ^{31}P NMR (121 MHz, $CDCl_3$) d -16.66 (s). Anal. for $C_{22}H_{17}P$: C, 84.60; H, 5.49; Found: C, 84.35; H, 5.49. Crystal data: Monoclinic, $P2_1/c$, a = 9.8830(2) Å, b = 10.0326(2) Å, c = 18.5657(5) Å, V = 1683.86(7) Å, Z = 4, number of unique reflections = 2957, number of parameters = 208, R_1 = 0.0474 (all data), GOF =



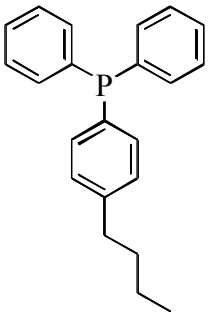
(2-Methoxy-phenyl)-diphenyl-phosphane (12): The general procedure was used to convert 2-iodoanisole and diphenylphosphine to the title product. Purification by flash chromatography (dichloromethane as the eluent) gave the analytically pure product as a white solid (373 mg, 64% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.35-7.26 (m, 11 H), 6.90-6.82 (m, 2 H), 6.69-6.65 (t, 1 H), 3.73 (s, 3H; methyl protons). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 161.2, 161.0, 136.7, 136.6, 134.0, 133.7, 133.6, 130.3, 128.6, 128.4, 128.3, 125.6, 125.5, 121.0, 110.2, 110.2, 55.6. ^{31}P NMR (121 MHz, $CDCl_3$) d -16.35 (s). Anal. for $C_{19}H_{17}OP$: C, 78.07; H, 5.86; P, 10.60, O, 5.47; Found: C, 78.19; H, 6.03; P, 10.4.



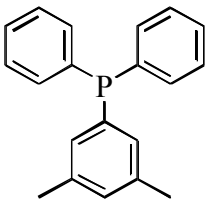
Diphenyl-*p*-tolyl-phosphane (13): The general procedure was used to convert 4-iodotoluene and diphenylphosphine to the title product. Purification by flash chromatography (pentane / dichloromethane [3:1] as the eluent) gave the analytically pure product as a white solid (232 mg, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.31-7.14 (m, 14 H), 2.34 (s, 3H; methyl protons). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 138.8, 137.6, 137.5, 134.0, 133.8, 133.7, 133.5, 133.5, 133.4, 129.8, 129.4, 129.3, 128.6, 128.5, 128.4, 128.2, 128.2, 128.1, 21.3. . ^{31}P NMR (121 MHz, $CDCl_3$) d -5.87 (s). Anal. for $C_{19}H_{17}P$: C, 82.59; H, 6.20; P, 11.21; Found: C, 82.62; H, 6.37; P, 11.4.



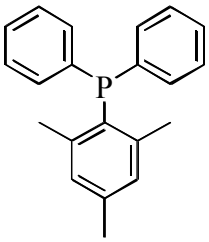
Diphenyl-*o*-tolyl-phosphane (14): The general procedure was used to convert 2-iodotoluene and diphenylphosphine to the title product. Purification by flash chromatography (pentane / dichloromethane [3:1] as the eluent) gave the analytically pure product as a white solid (420 mg, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.32-7.21 (m, 12 H), 7.09-7.04 (t, 1H), 6.79-6.75 (m, 1H), 2.39 (s, 3H; methyl protons). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 142.3, 142.0, 136.3, 136.2, 135.9, 134.1, 133.9, 132.7, 130.1, 130.0, 128.7, 128.6, 128.5, 126.0, 21.1. ^{31}P NMR (121 MHz, $CDCl_3$) d -13.23 (s). Anal. for $C_{19}H_{17}P$: C, 82.59; H, 6.20; P, 11.21; Found: C, 82.44; H, 6.11; P, 11.1.



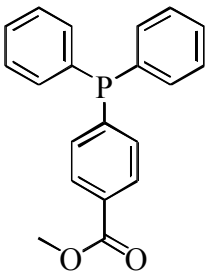
(4-Butyl-phenyl)-diphenyl-phosphane (15): The general procedure was used to convert 1-Butyl-4-iodo-benzene and diphenylphosphine to the title product. Purification by flash chromatography (hexane / dichloromethane [10:1] as the eluent) gave the analytically pure product as a colorless oil (443 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.29-7.12 (m, 14 H), 2.59 (t, 2H), 1.59 (t, 2H), 1.34 (m, 2H), 0.91 (t, 3H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 143.2, 137.1, 137.0, 133.4, 133.2, 133.1, 133.0, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 124.8, 34.9, 32.9, 22.1, 13.6. ^{31}P NMR (121 MHz, $CDCl_3$) d -16.73 (s). Anal. for $C_{22}H_{23}P$: C, 82.99; H, 7.28; Found: C, 82.72; H, 7.30.



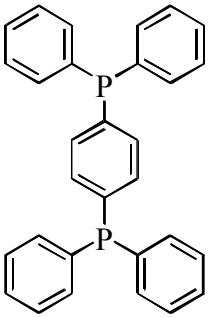
(3,5-Dimethyl-phenyl)-diphenyl-phosphane (16): The general procedure was used to convert 1-Iodo-3,5-dimethyl-benzene and diphenylphosphine to the title product. Purification by flash chromatography (pentane / dichloromethane [3:1] as the eluent) gave the analytically pure product as a colorless oil (447 mg, 77 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.31-7.30 (m, 10 H), 6.96-6.92 (m, 3 H), 2.24 (s, 6H; methyl protons). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 138.0, 137.9, 137.5, 137.4, 136.7, 136.6, 133.8, 133.6, 131.6, 131.4, 130.6, 128.5, 128.3, 128.4. ^{31}P NMR (121 MHz, $CDCl_3$) d -5.20 (s). Anal. for $C_{20}H_{19}P$: C, 82.74; H, 6.60; Found: C, 82.55; H, 6.69.



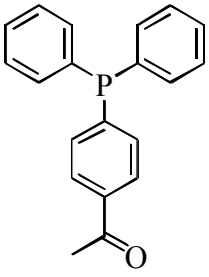
Diphenyl-(2,4,6-trimethyl-phenyl)-phosphane (17): The general procedure was used to convert 2-Iodo-1,3,5-trimethyl-benzene and diphenylphosphine to the title product. Purification by flash chromatography (pentane / dichloromethane [3:1] as the eluent) gave the analytically pure product as a colorless oil (432 mg, 71% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.37-7.20 (m, 10 H), 6.90 (s, 2 H), 2.27 (s, 3H; methyl protons), 2.18 (s, 6H; methyl protons). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 145.6, 145.4, 140.0, 139.9, 136.7, 136.5, 131.6, 131.3, 129.9, 129.9, 129.0, 128.3, 128.3, 127.4, 23.8, 23.6, 21.1. ^{31}P NMR (121 MHz, $CDCl_3$) d -16.39 (s). Anal. for $C_{21}H_{21}P$: C, 82.87; H, 6.95; Found: C, 82.70; H, 7.25.



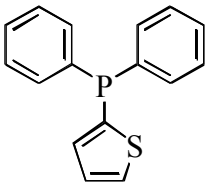
4-Diphenylphosphanyl-benzoic acid methyl ester (18): The general procedure was used to convert 4-Iodo-benzoic acid methyl ester and diphenylphosphine to the title product. Purification by flash chromatography (pentane / ethyl acetate [3:1] as the eluent) gave the analytically pure product as a white solid (448 mg, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.98-7.95 (d, 2 H), 7.36-7.32 (m, 12 H), 3.89 (s, 3H; methyl protons). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 166.8, 144.1, 143.9, 136.2, 136.1, 134.1, 133.8, 133.3, 133.0, 130.0, 129.3, 129.2, 129.1, 128.7, 128.6, 52.1. ^{31}P NMR (121 MHz, $CDCl_3$) d -5.04 (s). Anal. for $C_{20}H_{17}OP$: C, 74.99; H, 5.35; P, 9.67; Found: C, 74.99; H, 5.46, P, 9.7.



1,4-Bis-diphenylphosphanyl-benzene (19):[16] The general procedure was used to convert *p*-diiodobenzene and diphenylphosphine to the title product. Purification by flash chromatography (pentane / dichloromethane [2:1] as the eluent) gave the title product as an off-white solid (634 mg, 71 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.36-7.31 (m, 24 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 138.0, 136.8, 136.7, 136.5, 134.0, 133.7, 133.3, 133.2, 128.9, 128.6, 128.5. ^{31}P NMR (121 MHz, $CDCl_3$) d -5.20 (s). HRMS EI calcd for $C_{30}H_{24}P_2$, 446.1353; found: 446.1353.

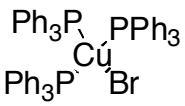


1-(4-Diphenylphosphanyl-phenyl)-ethanone (20): The general procedure was used to convert 4-iodoacetophenone and diphenylphosphine to the title product. Purification by flash chromatography (pentane / dichloromethane [1:6] as the eluent) gave the title product as an off-white solid (409 mg, 67 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.29-7.38 (m, 12 H), 7.86-7.89 (dd, 2 H; *J*=1.51 and 6.97), 3.89 (s, 3H; methyl protons). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 197.8, 144.5, 144.3, 136.8, 136.1, 136.0, 134.1, 133.8, 133.4, 133.2, 129.2, 129.0, 128.8, 128.7, 128.0, 127.9, 26.6. ^{31}P NMR (121 MHz, $CDCl_3$) d -3.81 (s). Anal. for $C_{20}H_{17}OP$: C, 78.93; H, 5.63; P, 10.18; Found: C, 78.73; H, 5.70, P, 10.0.

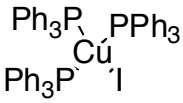


Diphenyl-thiophen-yl-phosphane (21): The general procedure was used to convert 2-iodothiophene and diphenylphosphine to the title product. Purification by flash chromatography (pentane / dichloromethane [3:1] as the eluent) gave the analytically pure product as an off-white solid (338 mg, 63% yield). ^{1}H NMR (300 MHz, $CDCl_3$) d 7.58-7.10 (m, 13 H). $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) d 138.0, 137.8, 136.5, 136.2, 133.2, 132.9, 132.0, 128.8, 128.6, 128.5, 128.4, 128.1, 127.9. ^{31}P NMR (121 MHz, $CDCl_3$) d -19.49 (s). Anal. for $C_{16}H_{13}PS$: C, 71.62; H, 4.88; P, 11.54; Found: C, 71.71; H, 5.00; P, 11.6.

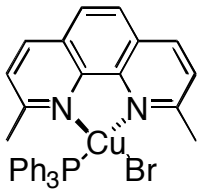
SYNTHESIS OF COPPER COMPLEXES



Synthesis of bromo(tristriphenylphosphine) copper(I): In an Erlenmeyer flask equipped with a Teflon stir bar, methanol (400 mL) was heated to boiling and triphenylphosphine (Acros, 28.2 g, 108 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, $CuBr_2$ (Acros, 99+%, 6.0 g, 27 mmol) was added as a solid, in portions. No special precautions were taken for the exclusion of air. Upon addition of the copper bromide, a white precipitate was formed. After the completion of the addition, the contents were refluxed for 30 min and the flask was allowed to cool to ambient temperature. The reaction mixture was then filtered through a Buchner funnel and the white residue was washed repeatedly with ethanol and then with diethyl ether. The resultant white solid was dried under dynamic vacuum to give 1 (24.4 g, 98% yield, mp. 164 ^{o}C). It can also be recrystallized as white needles from hot methanol. Crystal data for 1: Trigonal, *P*3 (no. 143), *a*=19.2150(3) Å, *b*=19.2150(3) Å, *c*=10.6220(3) Å, *V*=3396.39 Å^3, *Z*=3. The cell constants, contents and the space group are identical to that of the already reported structure of $Cu(PPh_3)_3Br$ (Cambridge Structural Database Refcode-FEYVAG). Although is stable to air and ambient moisture, we stored it in an argon-filled glove box. This is primarily due to the ease of setting up reactions, since Cs_2CO_3 is extremely hygroscopic and had to be stored in a dry atmosphere.

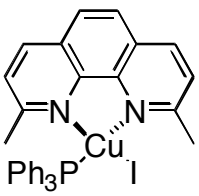


Synthesis of iodotris(triphenylphosphine) copper(I): In an Erlenmeyer flask equipped with a Teflon stir bar, methanol (100 mL) was heated to boiling and triphenylphosphine (Acros, 10.49 g, 40 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, CuI (Acros, 99+%, 1.904 g, 10 mmol) was added as a solid, in portions. No special precautions were taken for the exclusion of air. Upon addition of the copper iodide, a white precipitate was formed. After the completion of the addition, the contents were refluxed for 20 h and the flask was allowed to cool to ambient temperature. The reaction mixture was then filtered through a Buchner funnel and the white residue was washed repeatedly with ethanol and then with diethyl ether. The resultant white solid was dried under dynamic vacuum to give 1 (8.00 g, 82% yield). The product wsa recrystallized from dichloromethane/diethylether. It can also be recrystallized as white needles from hot methanol. Although stable to air and ambient moisture, we stored it in an argon-filled glove box. This is primarily due to the ease of setting up reactions, since Cs_2CO_3 is extremely hygroscopic and had to be stored in a dry atmosphere.

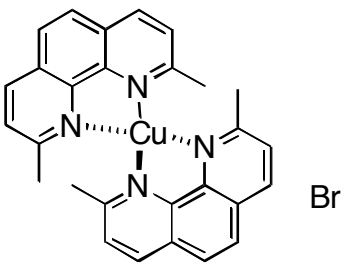


Synthesis of Cu(dmp)(PPh_3)Br: In an Erlenmeyer flask equipped with a Tefloncoated magnetic stirrer, Cu (PPh_3)$_3$Br (9.30 g, 10 mmol) was dissolved in 150 mL of dichloromethane. The complex dissolved immediately. To this stirring dichlormethane solution, neocuproine (2.09, 10 mmol) was added. The solution instantly turned orange red and was allowed to stir for 25 minutes. Afterwards the solvent was removed under dynamic vacuum to afford an orange-yellow

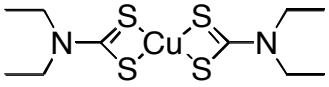
solid. Recrystallization was achieved by dissolving the solid 60 mL of dichloromethane and layered with 20 mL of diethylether; yellow needles (5.59g, 91% yield) Crystal data: Monoclinic, $P2_1/n$, a = 17.7710 (5) Å, b = 9.6250(3) C, c = 22.1092(8) Å, $\alpha = 90°$, $\beta = 99.5198°$, $\gamma = 90.00°$, V=3729.6, $Å^3$, $D_c = 1.436$ g cm^{-3}, Z = 4, number of unique reflections = 6500, number of parameters = 370, R1 = 0.4752 (all data), wR2 (for Fo > 4) = 0.4510, GOF = 1.731, residual electron density = +2.726e $Å^3$.



Synthesis of Cu(dmp)(PPh_3)I: In an Erlenmeyer flask equipped with a Tefloncoated magnetic stirrer, Cu $(PPh_3)_3I$ (4.89 g, 5.0 mmol) was dissolved in 75 mL of dichloromethane. The complex dissolved immediately. To this stirring dichlormethane solution, neocuproine (1.04, 5.0 mmol) was added. The solution instantly turned orange red and was allowed to stir for 18 hours. Afterwards the solvent was removed under dynamic vacuum to afford an yellow solid. Recrystallization was achieved by dissolving the solid 60 mL of dichloromethane and layered with 20 mL of diethylether; yellow needles (2.61g, 79% yield). Crystal data: Monoclinic, C2/c, a = 23.4582 (3) Å, b = 9.88350(3) Å, c = 25.0612 (3) Å, $\alpha = 90°$, $\beta = 97.4163°$, c = 90.00°, V = 5761.81, $Å^3$, $D_c = 1.333$ g cm-3, Z = 7, number of unique reflections = 4966, number of parameters = 334, R1 = 0.1013 (all data), wR2 (for Fo > 4) = 0.0953, GOF = 1.060, residual electron density = +0.740 e $Å^3$.



Copper(I) bis(neocuproine)bromide monohydrate: In an Erlenmeyer flask equipped with a Tefloncoated magnetic stirrer, $CuBr_2$ (0.456g, 2.0 mmol) was dissolved in minimal ethanol. The solution turned light green with a green precipitate upon addition. The solution was allowed to stir for 1 hour. Afterwards the solvent was removed under dynamic vacuum to afford a green solid, which was immediately diluted with 150 mL H_2O and the mixture was boiled in an Erlenmeyer flask. The mixture turned red upon heating. The mixture was allowed to boil for 5 minutes and cooled to ambient temperature. Upon cooling red crystals formed. The reaction mixture was then filtered through a Buchner funnel and the red crystals were collected (1.06 g, 90 % yield). Crystal data: Monoclinic, $P2_1/c$, a = 14.2216 (3) Å, b = 17.6126(3) Å, c = 10.3544 (3) Å, $\alpha = 90°$, $\beta = 91.175°$, c = 90.00°, V = 2593.0, $Å^3$, D_c = 1.111 g cm-3, Z = 4, number of unique reflections = 2404, number of parameters = 316, R1 = 0.1603 (all data), wR2 (for Fo > 4) = 0.1356, GOF = 1.042, residual electron density = +1.043e $Å^3$.



Bis(ethylenedithiocarbamate) copper(II): In an Erlenmeyer flask equipped with a Tefloncoated magnetic stirrer, $CuSO_4$ $5H_2O$ (0.627 g, 2.5 mmol) was dissolved in 25 mL distilled water. The solution turned light blue upon addition and was allowed to stir for 18 hours. Afterwards the reaction mixture was filtered through a Buchner funnel and the brown precipate washed with water. The solid was immediately dissolved in benzene and filtered to remove

impurities. Recrystallization was achieved by layering the benzene solution with ethanol; black crystals (0.73 g, 81 % yield). Crystal data: Monoclinic, $P2_1/c$, a = 9.9022 (3) Å, b = 10.6283(3) Å, c = 16.5789 (3) Å, $\alpha = 90°$, $\beta = 11.(18) \times 10^{1}°$, c = 90.00°, V = 1597.09, $Å^3$, D_c = 1.498 g cm-3, Z = 4, number of unique reflections = 2770, number of parameters = 155, R1 = 0.0697 (all data), wR2 (for Fo > 4) = 0.0663, GOF = 1.092, residual electron density = +0.220 e $Å^3$.

MECHANISM OF THE MODIFIED ULLMANN REACTION

A. Correction factors – general:

Equimolar amounts of sample and dodecane (internal standard) were analytically weighed into 10 mL vial and diluted with dichloromethane. The correction factor calculations are as follows:

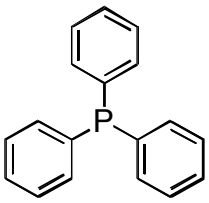
Correction factor = (I_x/I_s) (M_s/M_x)

Where: I_x = peak area of sample

I_s = peak area of standard

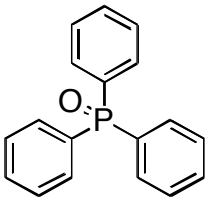
M_x = peak area of standard

M_s = peak area of sample



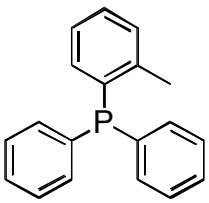
Triphenylphosphine: Triphenylphosphine (0.26309, 1.003 mmol) and dodecane (0.17428, 1.023 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.77



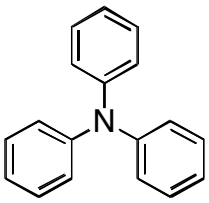
Triphenylphosphine oxide: Triphenylphosphine oxide (0.28073, 1.009 mmol) and dodecane (0.17106, 1.004 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.84



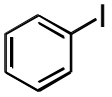
Diphenyl-*o*-tolyl-phosphane: Diphenyl-*o*-tolyl-phosphane (0.07065, 0.25569 mmol) and dodecane (0.04627, 0.25569 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.80



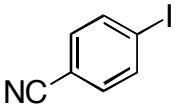
Triphenylamine: Triphenylamine (0.24516, 1.000 mmol) and dodecane (0.17031, 1.000 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 1.16



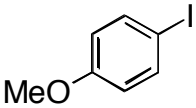
Iodobenzene: Iodobenzene (0.20480, 1.000 mmol) and dodecane (0.17130, 1.000 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.478



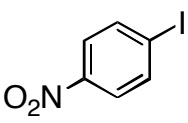
4-Iodobenzonitrile: 4-iodobenzonitrile (0.11421g, 0.49869 mmol) and dodecane (0.09074g, 0.532699 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.431



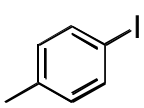
4-Iodoanisole: 4-iodoanisole (0.11787, 0.503653 mmol) and dodecane (0.08788, 0.515909 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.445



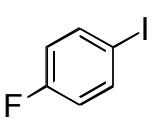
1-Iodo-4-nitrobenzene: 1-iodo-4-nitrobenzene (0.12457, 0.500261 mmol) and dodecane (0.08691, 0.510214 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.318



4-Iodotoluene: 4-iodotoluene (0.10979, 0.503554 mmol) and dodecane (0.08835, 0.518668 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.505



4-Fluoroiodobenzene: 4-Fluoroiodobenzene (0.22190, 0.9954 mmol) and dodecane (0.17264, 1.0140 mmol) were weighed into a 10 mL vial and diluted with dichloromethane. A small sample was taken into another 10 mL vial and further diluted with dichloromethane, and subsequently injected in the GC.

Correction factor = 0.465

B. Effect of halides on the copper complexes:

All times are recorded in seconds.

Dodecane = internal standard.

OIB = corrected iodobenzene concentrations using dodecane internal standard.

OTPA = corrected triphenylamines concentrations using dodecane internal standard.

0.268075 mmol Iodobenzene w/Cu(dmp)PPh_3I

Time (s)	Dodecane	Iodobenzene	OIB (A)	ln A
0	18.74040	3.19490	0.34808	-1.05531
1800	16.28304	2.48585	0.31171	-1.16570
3600	16.27700	2.26638	0.28429	-1.25776
5400	15.99789	1.93928	0.24750	-1.39633
7200	15.99638	1.83964	0.23481	-1.44898
9000	16.21366	1.72579	0.21733	-1.52636
10800	16.17384	1.77768	0.22441	-1.49427
12600	15.98055	1.70918	0.21837	-1.52154
14400	**16.07815**	**1.67711**	**0.21298**	**-1.54658**
86400	15.49343	1.34276	0.17695	-1.73188

0.53615 mmol Iodobenzene w/Cu(dmp)PPh_3Br

Time (s)	Dodecane	Iodobenzene	OIB (A)	ln A
0	19.14590	5.85787	0.58531	-0.53561
1800	16.69625	4.51973	0.51787	-0.65804
3600	16.26167	3.65088	0.42949	-0.84515
5400	16.34941	3.26863	0.38246	-0.96113
7200	16.07179	2.90704	0.34603	-1.06123
9000	15.93891	2.58642	0.31043	-1.16979
10800	16.06603	2.41089	0.28707	-1.24802
12600	15.95630	2.19730	0.26344	-1.33393
14400	**16.00383**	**2.02415**	**0.24196**	-1.41898
86400	15.89657	1.72930	0.20811	-1.56969

0.268075 mmol Iodobenzene w/Cu(dmp)PPh_3Cl

Time (s)	Dodecane	Iodobenzene	OIB (A)	ln A
0	18.49518	2.19196	0.22400	-1.49611
1800	18.03247	2.06515	0.21645	-1.53040
3600	18.21458	1.82741	0.18962	-1.66273
5400	18.22944	1.79338	0.18594	-1.68233
7200	18.16032	1.70066	0.17700	-1.73161
9000	17.87098	1.67588	0.17724	-1.73025
10800	17.98930	1.61849	0.17005	-1.77166
12600	18.06244	1.56306	0.16356	-1.81058
14400	**18.05368**	**1.52125**	**0.15926**	**-1.83722**
86400	17.38966	1.03543	0.11254	-2.18445

C. Effects of added ligands:

All times are recorded in hours.

Dodecane = internal standard.

% Conversions are uncorrected.

Diphenylamine / Iodobenzene

Time (h)	Triphenylamine	Dodecane	% Conversion
0	0.00000	46.56225	0.0
1	36.14260	63.8574	40.2
2	49.71756\	50.28244	70.2
3	56.45703	43.54297	92.0
4	57.87849	42.12151	97.5
5	58.57715	41.42285	100.4
6	59.04790	40.9521	102.3
24	57.93866	38.81581	105.9

Diphenylamine / Iodobenzene + 0.5 equivalents PPh_3

Time (h)	Triphenylamine	Dodecane	% Conversion
0	0.00000	39.67377	0.0
1	19.12807	37.89503	35.8
2	33.34766	39.26580	60.3
3	40.81790	33.91799	85.4
4	41.87223	31.54456	94.2
5	43.76333	31.07766	99.9
6	44.43505	30.96660	101.8
24	48.08965	31.61619	107.9

Diphenylamine / Iodobenzene + 1.0 equivalents PPh_3

Time (h)	Triphenylamine	Dodecane	% Conversion
0	0.00000	38.38549	0.0
1	20.76151	30.41475	48.4
2	32.11038	25.66076	88.8
3	35.37718	25.00573	100.4
4	36.71701	24.72135	105.4
5	36.64307	24.43773	106.4
6	37.43034	24.85523	106.9
24	38.61890	25.47925	107.6

Diphenylamine / Iodobenzene + 2.0 equivalents PPh_3

Time (h)	Triphenylamine	Dodecane	% Conversion
0	0.00000	15.48006	0.0
1	12.76192	20.31218	44.6
2	21.09363	18.58479	80.5
3	25.14297	17.63749	101.2
4	27.08512	17.29388	111.1
5	27.83081	17.43635	113.3
6	28.08932	17.30075	115.2
24	29.85132	18.25488	116.1

Diphenylamine / Iodobenzene + 0.5 equivalents Neocuproine

Time (h)	Triphenylamine	Dodecane	% Conversion
0	0.00000	48.46089	0.0
1	22.23908	43.69651	36.1
2	33.32132	41.11049	57.5
3	40.09976	40.42856	70.4
4	44.83507	40.79930	78.0
5	52.02677	45.23365	81.6
6	49.93946	42.07716	84.2
24	55.04542	44.95458	86.9

Diphenylamine / Iodobenzene + 1.0 equivalents Neocuproine

Time (h)	Triphenylamine	Dodecane	% Conversion
0	0.00000	100	0.0
1	29.84048	70.15952	30.2
2	39.25773	60.74227	45.9
3	43.69983	56.30017	55.1
4	47.24685	52.75315	63.6
5	48.50221	51.49779	66.8
6	48.79442	51.20558	67.6
24	48.61508	51.38492	67.1

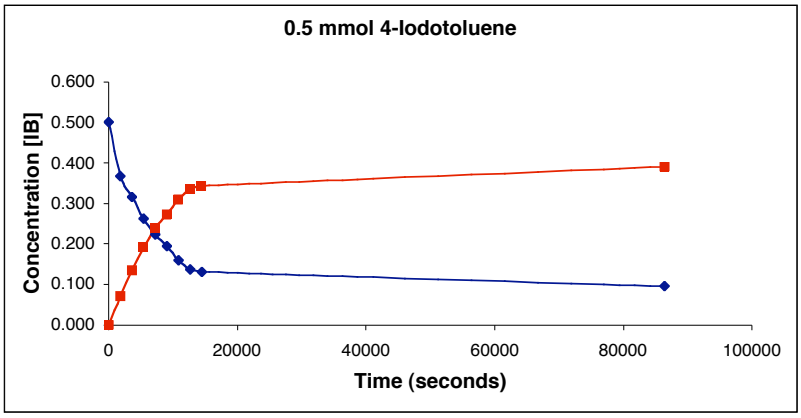
Diphenylamine / Iodobenzene + 2.0 equivalents Neocuproine

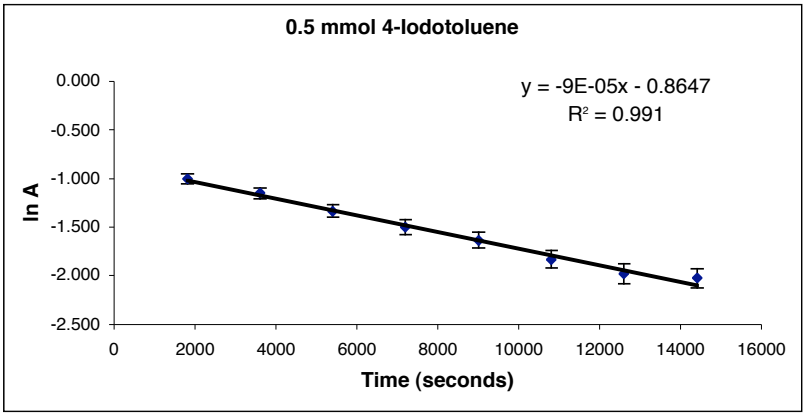
Time (h)	Triphenylamine	Dodecane	% Conversion
0	0.00000	41.73079	0.0
1	19.43259	80.56741	17.1
2	17.54853	50.24412	24.8
3	23.94209	76.05791	22.3
4	26.35383	73.64617	25.4
5	26.31062	73.68938	25.3
6	26.75264	73.24736	25.9
24	26.48753	73.51247	25.6

D. Substituent effects – data:

0.5 mmol 4-Iodotoluene

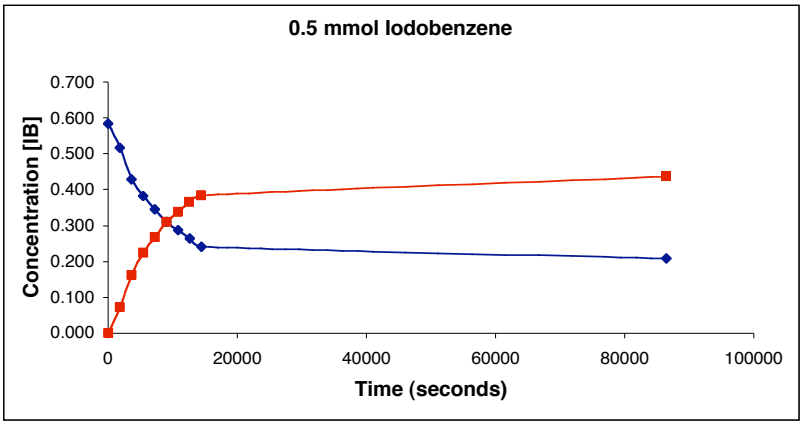
Time (s)	Dodecane	I-Tol	TPA	OIB (A)	OTPA	ln A
0	15.93197	4.11547	0.00000	0.501765	0.00000	-0.68962
1800	16.03894	3.37693	1.59412	0.36689	0.07054	-1.00269
3600	15.96517	2.89486	3.01931	0.31597	0.13421	-1.15211
5400	15.96862	2.41335	4.31126	0.26336	0.19160	-1.33425
7200	15.93702	2.04392	5.34662	0.22348	0.23809	-1.49841
9000	15.92417	1.78287	6.10019	0.19510	0.27186	-1.63425
10800	15.95094	1.46733	6.95237	0.16030	0.30932	-1.83071
12600	15.90332	1.26083	7.51178	0.13815	0.33521	-1.97939
14400	**16.00742**	**1.21060**	**7.73531**	**0.13179**	0.34294	-2.02657
86400	15.75376	0.86231	8.65961	0.09538	0.39010	-2.34986

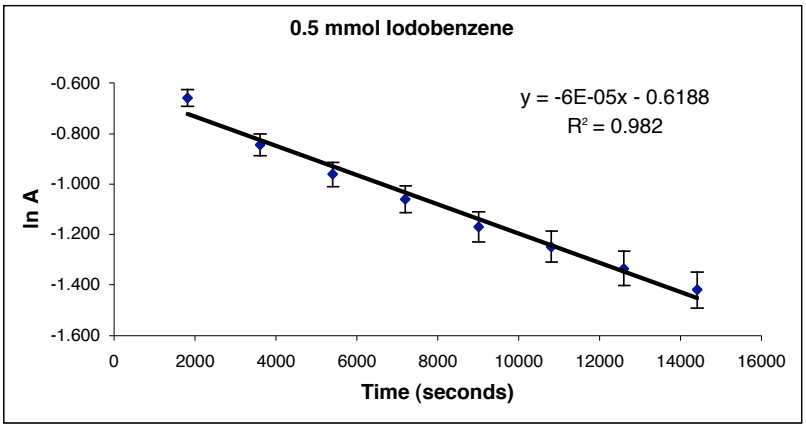




0.5 mmol Iodobenzene

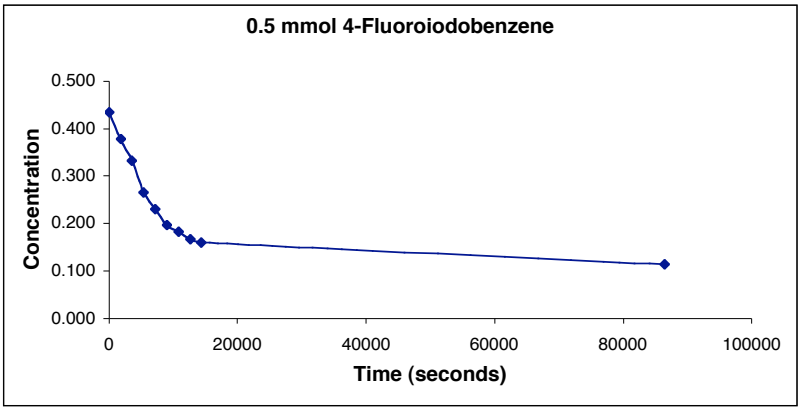
Time (s)	Dodecane	Iodobenzene	TPA	OIB	OTPA	ln A
0	19.14590	5.85787	0.00000	0.58531	0.00000	-0.53561
1800	16.69625	4.51973	1.68372	0.51787	0.07157	-0.65804
3600	16.26167	3.65088	3.71374	0.42949	0.16207	-0.84515
5400	16.34941	3.26863	5.17214	0.38246	0.22451	-0.96113
7200	16.07179	2.90704	6.05639	0.34603	0.26743	-1.06123
9000	15.93891	2.58642	6.95736	0.31043	0.30978	-1.16979
10800	16.06603	2.41089	7.66006	0.28707	0.33836	-1.24802
12600	15.95630	2.19730	8.22245	0.26344	0.36570	-1.33393
14400	**16.00383**	**2.02415**	**8.66892**	**0.24196**	**0.38442**	**-1.41898**
86400	15.89657	1.72930	9.77745	0.20811	0.43650	-1.56969

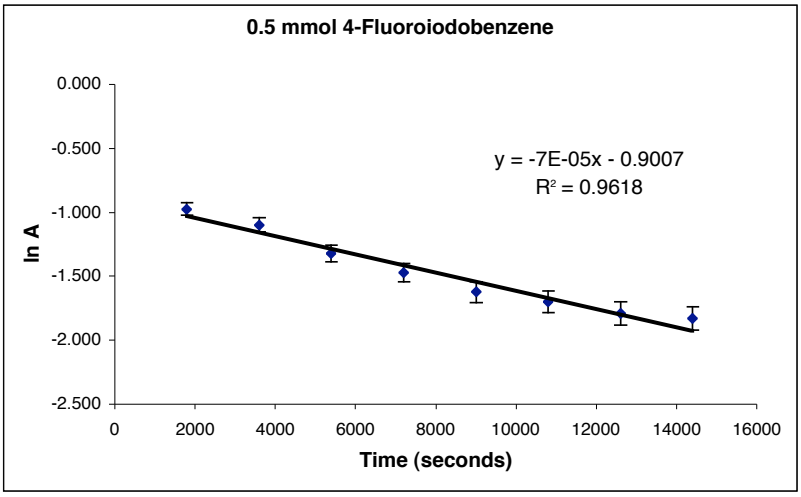




0.5 mmol 4-Flouroiodobenzene

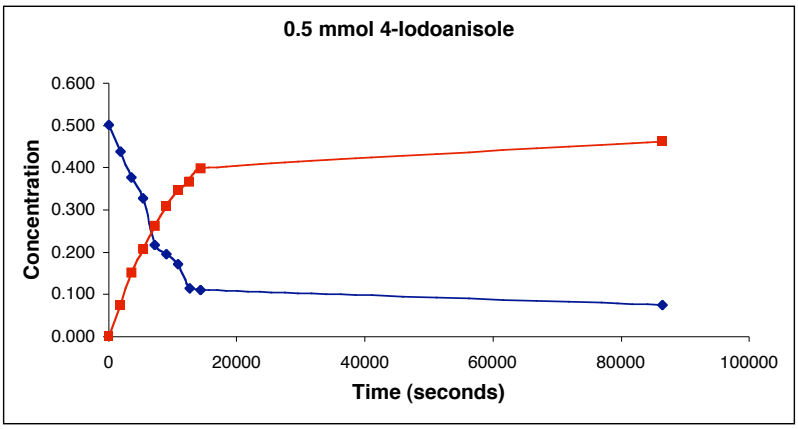
Time (s)	Dodecane	IB	TPA	OIB	OTPA	ln A
0	16.70800	4.16536	0.00000	0.43355	0.00000	-0.83575
1800	16.90947	3.37902	2.38912	0.37769	0.10027	-0.97369
3600	16.91156	2.97988	3.58099	0.33303	0.15027	-1.09952
5400	16.56297	2.33206	5.41406	0.26612	0.23198	-1.32382
7200	16.15036	1.96417	6.18778	0.22986	0.27190	-1.47028
9000	16.33202	1.70599	7.05968	0.19743	0.30677	-1.62239
10800	16.47397	1.59022	7.34455	0.18244	0.31639	-1.70131
12600	16.42566	1.45103	7.84397	0.16696	0.33890	-1.78998
14400	**16.51459**	**1.39746**	**8.12147**	**0.15993**	**0.34900**	**-1.83299**
86400	15.83441	0.95325	8.98536	0.11378	0.40271	-2.17347

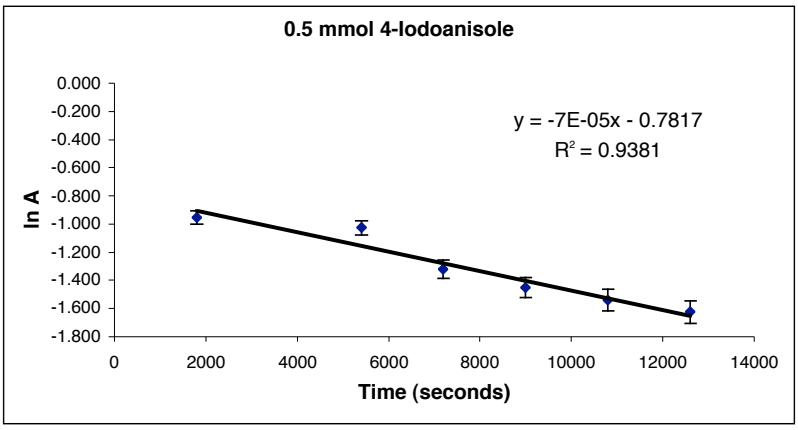




0.5 mmol 4-Iodoanisole

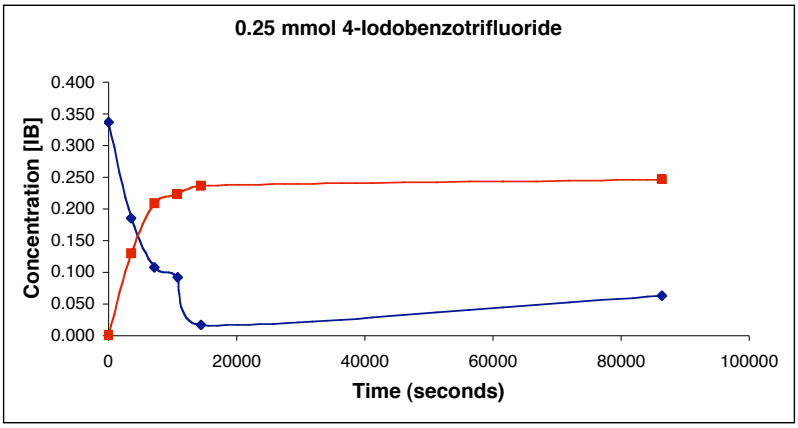
Time (s)	Dodecane	IB	TPA	OIB	OTPA	ln A
0	19.32916	4.39706	0.00000	0.501645	0.00000	-0.68986
1800	16.76457	3.72240	1.76410	0.43909	0.07468	-0.82305
3600	16.33167	3.11933	3.46953	0.37771	0.15077	-0.97364
5400	15.92931	2.63853	4.65357	0.32756	0.20732	-1.11609
7200	16.07836	1.77081	5.92406	0.21780	0.26148	-1.52419
9000	15.87023	1.56737	6.89299	0.19530	0.30824	-1.63320
10800	15.56847	1.34490	7.58907	0.17083	0.34594	-1.76708
12600	16.16745	0.93605	8.35958	0.11449	0.36695	-2.16724
14400	**15.78069**	**0.88490**	**8.85282**	**0.11089**	**0.39812**	**-2.19922**
86400	15.51214	0.58580	10.11217	0.07468	0.46263	-2.59455

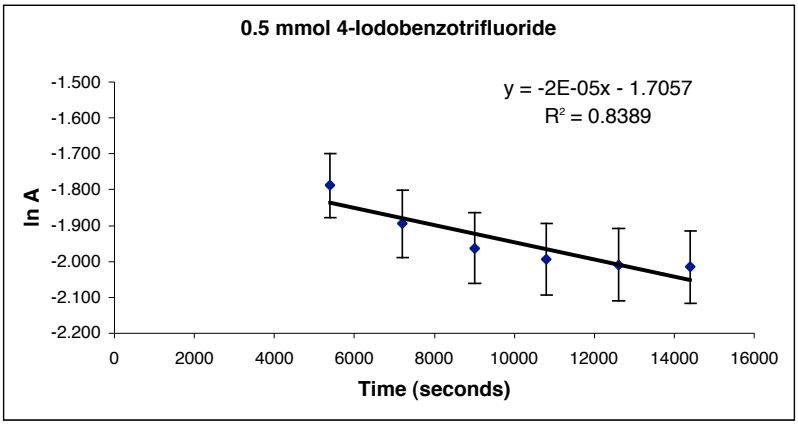




0.25 mmol 4-Iodobenzotrifluoride

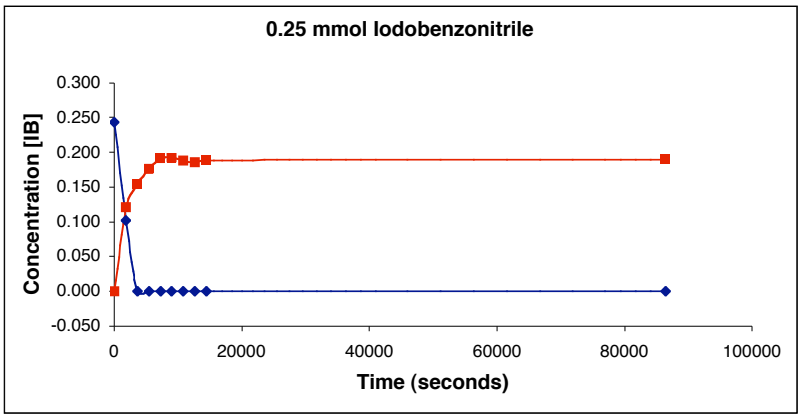
Time (s)	Dodecane	IB	TPA	OIB	OTPA	ln A
0	15.88015	2.62047	0.00000	0.33692	0.00000	-1.08790
3600	15.99118	1.45474	2.92253	0.18574	0.12970	-1.68340
7200	15.66049	0.82685	4.61594	0.10780	0.20918	-2.22746
10800	15.71238	0.70267	4.93364	0.09131	0.22284	-2.39350
14400	**16.12657**	**0.12814**	**5.37931**	**0.01622**	**0.23673**	**-4.12129**
86400	15.32037	0.46776	5.32541	0.06234	0.24669	-2.77517





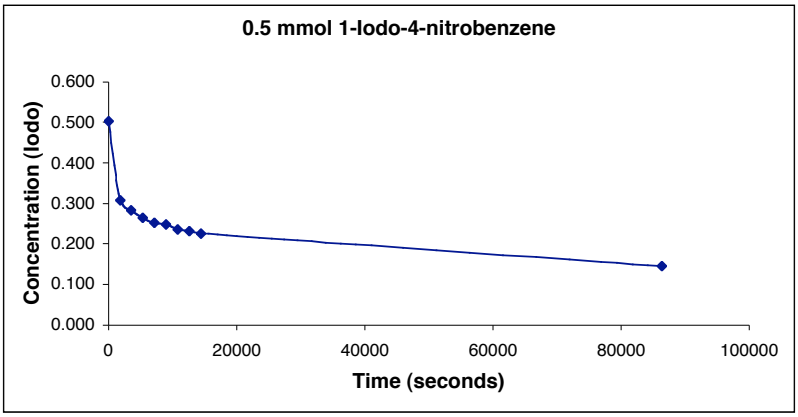
0.25 mmol 4-Iodobenzonitrile

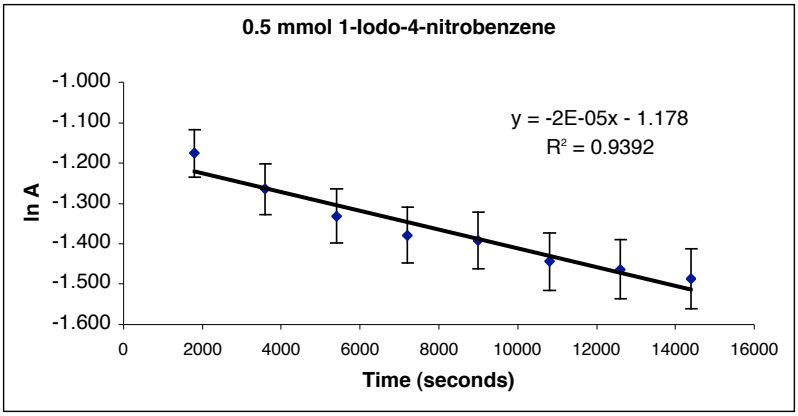
Time (s)	Dodecane	IB	Product	OIB	OTPA	ln A
0	16.90100	2.01839	0.00000	0.24384	0.00000	-1.41126
1800	15.25589	0.76422	2.59174	0.10228	0.12056	-2.28005
3600	15.77923	0.00000	3.42006	0.00000	0.15382	#NUM!
5400	15.58174	0.00000	3.86943	0.00000	0.17623	#NUM!
7200	15.40276	0.00000	4.14138	0.00000	0.19081	#NUM!
9000	15.24745	0.00000	4.13319	0.00000	0.19238	#NUM!
10800	15.45818	0.00000	4.09442	0.00000	0.18797	#NUM!
12600	15.54573	0.00000	4.05942	0.00000	0.18532	#NUM!
14400	**15.34315**	**0.00000**	**4.07075**	**0.00000**	**0.18829**	#NUM!
86400	14.81052	0.00000	3.95878	0.00000	0.18969	#NUM!



0.5 mmol 1-Iodo-4-nitrobenzene

Time (s)	Dodecane	I-NO2Bz	TPA	OIB (A)	OTPA	ln A
0	17.72547	2.04333	0.00000	0.502791	0.00000	-0.68758
1800	16.08652	1.79420	0.20433	0.30865	0.00901	-1.17555
3600	16.28034	1.66113	0.23672	0.28236	0.01032	-1.26459
5400	16.37760	1.56312	0.26332	0.26412	0.01141	-1.33136
7200	16.02339	1.45780	0.28004	0.25177	0.01240	-1.37925
9000	15.96249	1.43380	0.31468	0.24857	0.01399	-1.39204
10800	16.10833	1.37293	0.36128	0.23586	0.01592	-1.44452
12600	16.09976	1.34565	0.37519	0.23130	0.01654	-1.46406
14400	**16.00164**	**1.30611**	**0.36253**	**0.22588**	**0.01608**	**-1.48777**
86400	15.86268	0.83299	0.38752	0.14532	0.01734	-1.92883





F. Effect of oxidation state of the catalyst:

0.53615 mmol IB w/Cu(Neocup)PPh_3Br

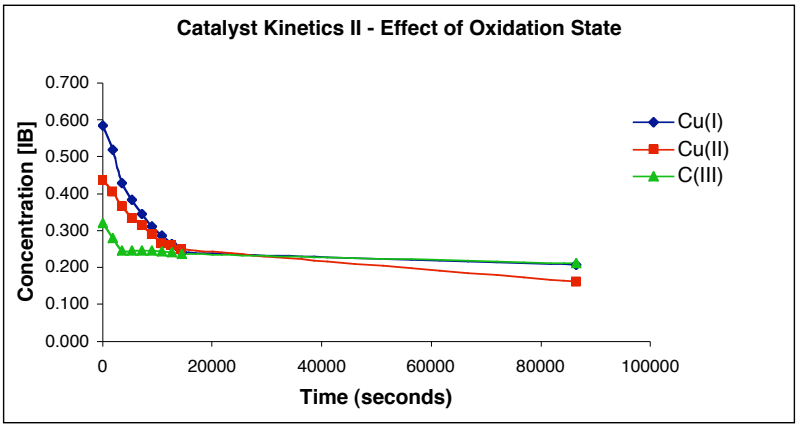
Time (s)	Dodecane	IB	TPA	OIB	OTPA	ln A
0	19.14590	5.85787	0.00000	0.58531	0.00000	-0.53561
1800	16.69625	4.51973	1.68372	0.51787	0.07157	-0.65804
3600	16.26167	3.65088	3.71374	0.42949	0.16207	-0.84515
5400	16.34941	3.26863	5.17214	0.38246	0.22451	-0.96113
7200	16.07179	2.90704	6.05639	0.34603	0.26743	-1.06123
9000	15.93891	2.58642	6.95736	0.31043	0.30978	-1.16979
10800	16.06603	2.41089	7.66006	0.28707	0.33836	-1.24802
12600	15.95630	2.19730	8.22245	0.26344	0.36570	-1.33393
14400	**16.00383**	**2.02415**	**8.66892**	**0.24196**	**0.38442**	**-1.41898**
86400	15.89657	1.72930	9.77745	0.20811	0.43650	-1.56969

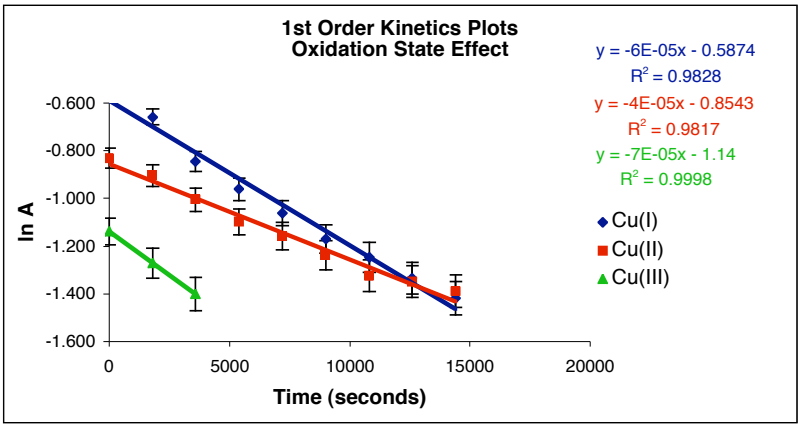
0.25 mmol IB w/Cu(Phen)Br_2

Time (s)	Dodecane	IB	TPA	OIB	OTPA	ln A
0	17.33784	3.69764	0.00000	0.43545	0.00000	-0.83138
1800	16.32168	3.23811	0.68644	0.40507	0.02985	-0.90369
3600	16.04789	2.87694	1.55869	0.36603	0.06893	-1.00504
5400	16.10238	2.63141	2.31579	0.33366	0.10206	-1.09763
7200	15.89279	2.44504	2.71087	0.31412	0.12105	-1.15799
9000	15.97179	2.26609	3.41297	0.28969	0.15165	-1.23895
10800	16.46307	2.14327	4.02995	0.26581	0.17372	-1.32497
12600	15.67061	1.99163	4.00182	0.25949	0.18123	-1.34902
14400	**15.6819**	**1.91408**	**4.31061**	**0.24921**	**0.19507**	**-1.38946**
86400	15.29963	1.20579	6.202	0.16091	0.28768	-1.82688

0.5 mmol IB w/Cu(Edtc)Br_2

Time (s)	Dodecane	IB	TPA	OIB	OTPA	ln A
0	17.59379	2.98000	0.00000	0.32013	0.00000	-1.13903
1800	17.87369	2.64862	1.10182	0.28008	0.04375	-1.27270
3600	17.90621	2.33496	1.77134	0.24646	0.07020	-1.40056
5400	17.60800	2.28147	1.82865	0.24489	0.07370	-1.40694
7200	17.28889	2.25344	1.71015	0.24635	0.07020	-1.40101
9000	17.51725	2.26753	1.70245	0.24466	0.06897	-1.40790
10800	17.44723	2.24460	1.77553	0.24315	0.07222	-1.41406
12600	17.69364	2.24812	1.81971	0.24014	0.07299	-1.42652
14400	**17.12768**	**2.15355**	**1.73316**	**0.23764**	**0.07181**	**-1.43698**
86400	17.60839	1.96985	1.87382	0.21144	0.07552	-1.55382


Catalyst Kinetics II - Effect of Oxidation State
Concentration [IB]
0.700
0.600
0.500
0.400
0.300
0.200
0.100
0.000
0
20000
40000
60000
80000
100000
Time (seconds)
Cu(I)
Cu(II)
C(III)


1st Order Kinetics Plots
Oxidation State Effect
ln A
-0.600
-0.800
-1.000
-1.200
-1.400
-1.600
0
5000
10000
15000
20000
Time (seconds)
y = -6E-05x - 0.5874
R2 = 0.9828
y = -4E-05x - 0.8543
R2 = 0.9817
y = -7E-05x - 1.14
R2 = 0.9998
Cu(I)
Cu(II)
Cu(III)

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