Formation of Aryl-Carbon and Aryl-Heteroatom Bonds Using Copper(I) Catalysts

A Dissertation Presented
by
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Organic Chemistry

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DEDICATION

To the Memory of the Eternal, Compassionate, and Omnipresent Guru.

To my parents Randhir and Neelam, and my wife, Sweta.

ACKNOWLEDGEMENTS

Completing a Ph.D. is one of life's greatest experience. I have been privileged over these last four years to have had the opportunity to have met some truly inspiring people. Coming to contact with them during my time at UMASS has given me a new perspective about the complexities of the both life and science, and this indubitably imprints one with a new set of values, to face life and its ever forthcoming intricacies. I immediately think of my research adviser, Professor D. Venkataraman, as I write down these lines. I am deeply grateful to him to have simply transformed my thought process in science and showed me the true meaning of the words, 'searching for excellence'. His unending energy and guidance has been the main driving force of this project. I am very grateful to all those who helped me in many ways over these past years. My generous lab colleagues, my committee members (Prof P.C. Uden, Prof J. Penelle, Prof P.M. Lahti, and Prof M. Maroney) have always tried to answer my questions and guide me through the project. I am indebted to my parents and Sweta, whose constant and gentle 'waves' of encouraging emails, phone calls, and talks have motivated me to keep searching. My father's spiritual guidance has also been a major turning point over these last few years. I still remember my harrowing time in the hospital in South Africa where I was at the lowest point in my life and was struggling to hang on to life. I look back now with a smile on my face and feel strong that I have conquered these strange times and am now graduating with the prize of all prizes. Special words of thanks to Dr A. Chandrasekaran and Dr G. Dabkowski for their help with the characterization of my products. I also wish to thank Prof B. Coughlin, who although not part of my committee, has always been open for discussion and guidance over the years.

I end with words from the perennial song of the Bhagavadgeeta:

" O Spirit, I am awestruck at this wondrous sight. I see in it, no beginning, no middle and no end "

ABSTRACT

The Formation of Aryl-Carbon and Aryl-Heteroatom Bonds Using Copper(I) Catalysts
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Copper(I) complexes of type $[Cu(PPh_3)_3X]$ (where X: Br, Cl), $[Cu(PPh_3)_2NO_3]$, $Cu(L)(PPh_3)_2X$ (where X: PF_6, NO_3, ClO_4 and L: phenanthroline, diimine, neocuproine), $Cu(L)(PPh_3)X$ (where X: Br and L: phenanthroline, di-imine, neocuproine) are synthesized and characterized to study their catalytic activities in carbon-heteroatom bond formation reactions. The geometrical parameters illustrate that there is a correlation between bite angles and copper-phosphorous bond lengths in mononuclear chelated copper(I) complexes. These complexes had wider bite angles than mononuclear non-chelated copper(I) complexes. Screening of the mononuclear copper(I) complexes in aryl-oxygen bond formation reactions show that the complexes $[Cu(PPh_3)_3Br]$ and $[Cu(neocup)(PPh_3)Br]$ catalyzed the formation of a range of substituted diphenyl ethers at 20 mol% and 10 mol% catalyst loadings respectively. The polynuclear copper(I) complexes fail to catalyze the same reaction. In aryl-nitrogen bond formation reactions, the same complexes $[Cu(PPh_3)_3Br]$ and $[Cu(neocup)(PPh_3)Br]$ enable the formation of a range of diaryl and triaryl amines. The protocol with $[Cu(PPh_3)_3Br]$ is used for the successful synthesis of *o*.*o*'.*o*''-amino-trisbenzoic acid-trimethylester at 170 ^{o}C in *o*-dichlorobenzene. This molecule is eluded by the Hartwig-Buchwald protocol. The well-defined complex $[Cu(neocup)(PPh_3)Br]$ is further investigated for the formation of aryl-sulfur and aryl-selenium bonds. Optimization and control experiments in this area show that using neocuproine as an additive with CuI, in the presence of NaO*t*-Bu, in toluene

allows the development of protocols for a range of aryl-sulfides and aryl-selenides. In the second protocol, the change of base to K_2CO_3 allows the coupling of a range of electron-poor iodides to the respective diaryl selenides. The observed results point to the potential of copper(I) catalysts as alternatives to palladium-based protocols, for the formation of aryl-O, N, S and Se bonds under mild conditions.

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Formation of Aryl-Carbon and Aryl-Heteroatom Bonds using Copper(I) Catalysts

1.1 Introduction

Aryl-carbon and aryl-heteroatom bonds are prevalent in many compounds that have important biological, pharmaceutical and/or materials properties (Chart 1.1).[1] Today, routes to the formation of these bonds are indispensable tools in synthetic chemistry.[2]

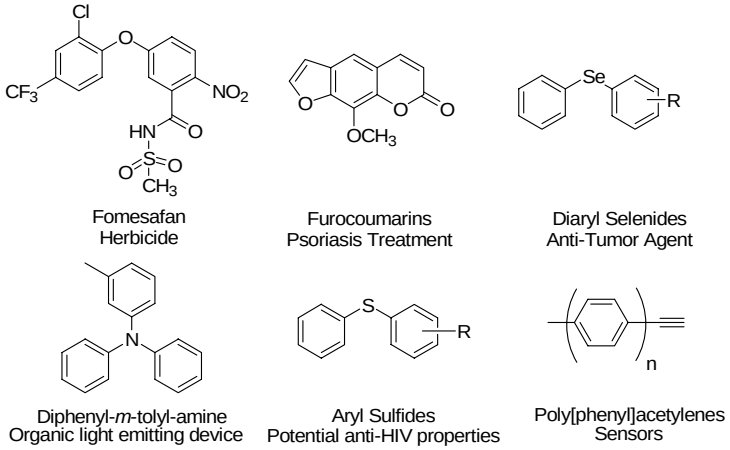
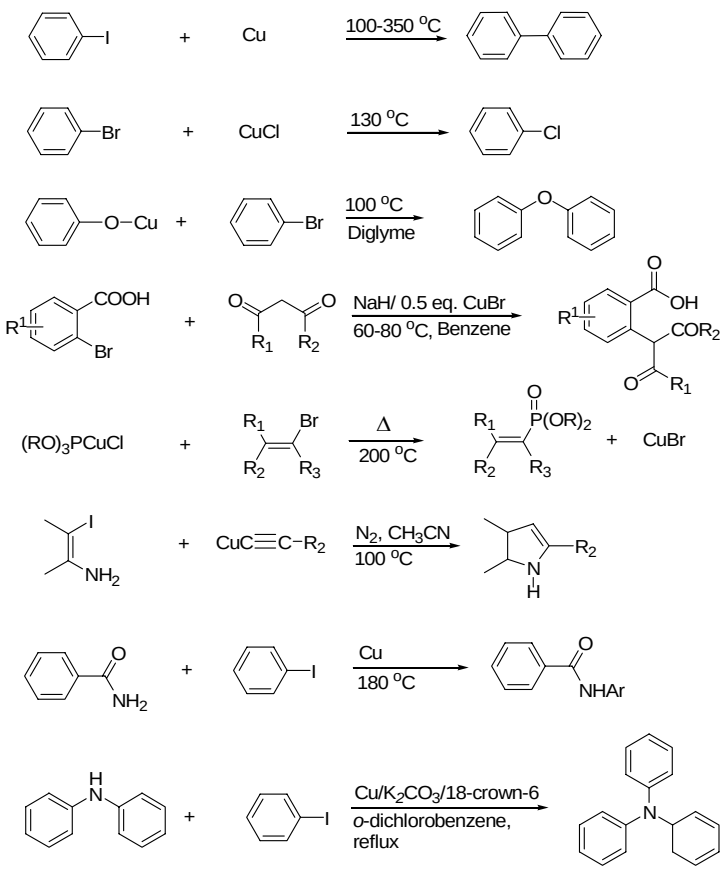


Chart 1.1: Examples of Compounds with Aryl-Carbon and Aryl-Heteroatom bonds and their Uses

Over the years, a number of synthetic routes have emerged for the formation of aryl-carbon and aryl-heteroatom bonds. A classical method for the formation of these bonds is the reaction of aryl halides with appropriate nucleophiles. This reaction,

however, is limited to highly electron-deficient aromatic halides. Other leaving groups such as N_2^+ have been used instead of the halide and form the basis of well-known reactions such as the Sandmeyer reaction and Schiemann reaction.[3]



Scheme 1.1: Examples of Copper-Catalyzed Cross-Coupling Reactions of Aryl Halides. (1959 to 1987)

In 1960`s, a new approach based on the complexation of metal carbonyl to the aromatic halides was examined towards developing a general method for the nucleophilic aromatic substitution (S_NAr) in aromatic halides. For example, η^6-arene-$Cr(CO)_3$ complexes are known to undergo S_NAr under mild conditions when compared with uncomplexed aromatic halides.[4,5] Concurrently, the use of transition metals as mediators

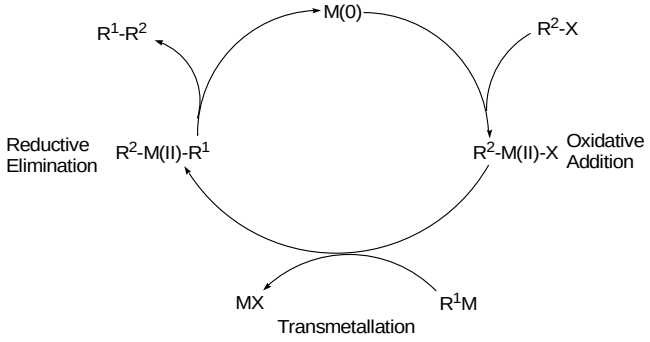
or as catalysts were also examined for the formation of aryl-carbon and aryl-heteroatom bonds from aryl halides. In this regard, the copper-mediated Ullmann reaction was shown to be extremely useful, for the formation of a range of aryl-carbon and aryl-heteroatom bonds (Scheme 1.1). Most copper(I) salts are insoluble in organic solvents, and hence the reactions are often heterogeneous. Therefore, the reactions are often conducted at high reaction temperatures (~200 °C) and require the use of toxic polar solvents such as hexamethylphosphoramide (HMPA). Moreover, the reaction rates are sensitive to functional groups on aryl halides and the yields are often irreproducible.

1.2 Emergence of palladium and nickel catalyzed cross-coupling reactions

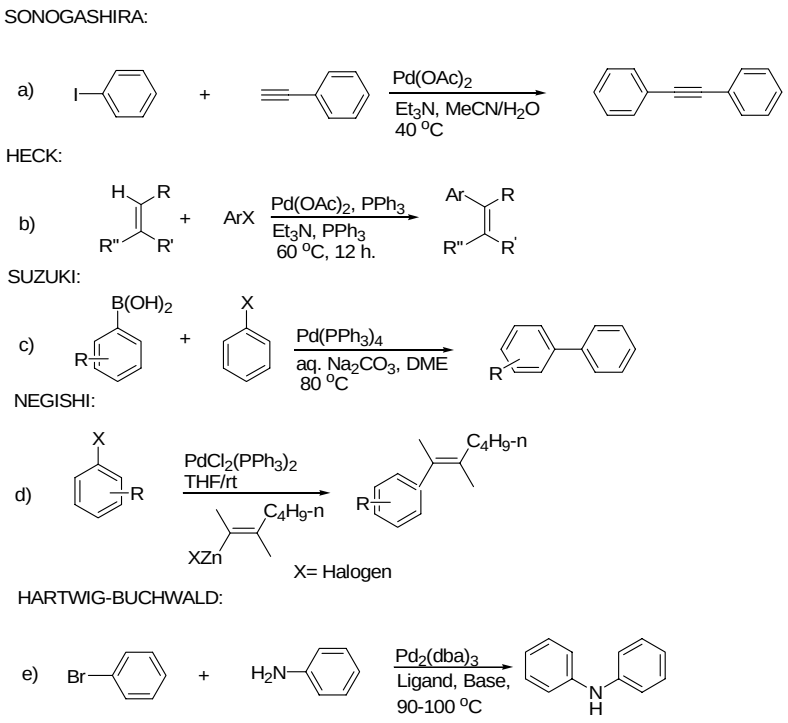
A major advancement in the formation of aryl-carbon and aryl-heteroatom bonds came with the development of transition metal-based catalysts such as nickel(0) and palladium(0) complexes. Mechanistically, palladium(0) oxidatively adds across the aryl-halogen bond to form aryl-palladium species. Then a nucleophile-halogen exchange ensues followed by a reductive elimination of the aryl-nucleophile species and the regeneration of the catalytically active Pd(0) (Scheme 1.2). This mechanistic cycle forms the basis of a class of reactions termed as cross-coupling reactions.

Cross-coupling reactions began with the use of nickel in substoichiometric amounts in an Ullmann-like procedure, but was eventually improved to totally catalytic conditions with diphosphine complexes and Grignard reagents.[6,7] The latter method launched a number of changes allowing the use of more efficient catalysts, including

palladium complexes and simultaneously more reactive and selective nucleophilic reagents.[8-14] In the past two decades, palladium(0)-based cross-coupling reactions have dominated the synthetic protocols for the formation of aryl-carbon and aryl-heteroatom bonds. Examples of well-known palladium(0)-catalyzed reactions include the Suzuki reaction, Heck coupling, Sonogashira-Miyaura, Negishi coupling and more recently the Hartwig-Buchwald coupling.[15] (Scheme 1.3)



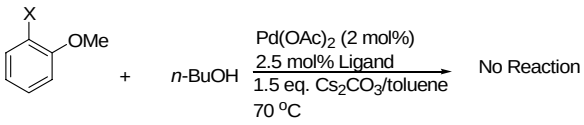
Scheme 1.2: A General Catalytic Cycle for Cross-Coupling Reactions



Scheme 1.3: Examples of Palladium Catalyzed Cross-Coupling Reactions

Despite the widespread use of palladium(0)-catalysts, it is not uncommon to find substrates or functional groups that do not undergo coupling by Pd-catalysts. For example, in the aromatic halides, the presence of functional groups in the *ortho* position leads to considerable decrease in the rate of the reactions and the yield of the final products. Palladium(0)-based reactions condition often do not tolerate heterocyclic substrates, as well as substrates such as aliphatic amines, aliphatic alcohols, active methylene compounds, thiols, and selenols. We summarize recent cases of the limitations of Pd(0)-catalyzed cross-coupling reaction below (Chart 1.2).

Recently, there have been attempts to circumvent the aforementioned problems in palladium catalysts with the use of phosphine ligands with large Tolman cone angles.[16,17] Ligands such as *tert*-butylphosphine have allowed the coupling of a broader range of substrates using consistent reaction conditions. They have also provided access to couple aryl chlorides, which are often unreactive under cross-coupling conditions. Although this approach has its own downside because the ligands themselves are very air sensitive and expensive, it can be argued that fine-tuning the conditions of palladium catalysts may eventually lead to a broadening of the scope of existing protocols. Despite these improvements, a pertinent question arises and *forms the essential basis for this thesis.* In the event of the failure of the well-established palladium chemistry, is there a viable alternative ?



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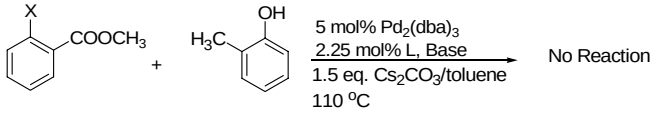

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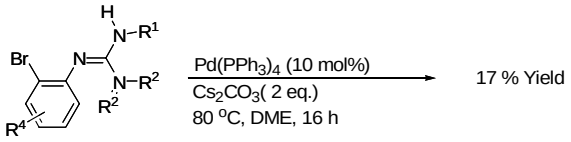

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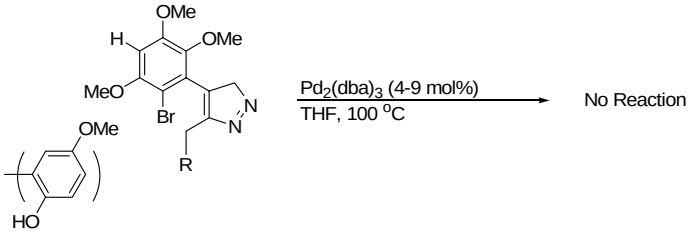

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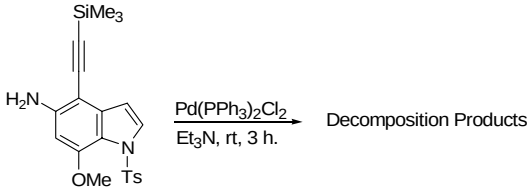

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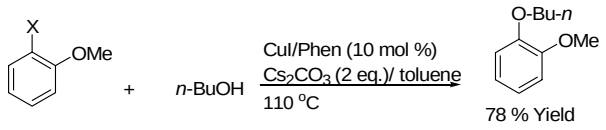
Chart 1.2: Some Recent Synthetic Problems Encountered in Palladium Cross-Coupling Reactions.

1.3 Modified Ullmann Type Reactions

In this thesis, we explore the use of copper(I)-based catalysts as an alternative to palladium(0) catalysts. The basis for the choice of copper for cross-coupling reactions is well-founded. As mentioned before, copper has been used in the Ullmann reactions for the formation of aryl-carbon and aryl-heteroatom bonds. More importantly, it has been shown in the literature that in cases where palladium has failed to catalyze a cross-coupling reaction, the Ullmann reaction was successful (see Chart 1.3). It is also noteworthy to point out similarities between Pd(0) and Cu(I). Since they belong to adjacent groups in the periodic table, Pd(0) and Cu(I) are isoelectronic. Also, in palladium(0)-catalyzed cross-coupling reactions, it is now well-established that the formal oxidation state of palladium oscillates between 0 and +2 during the course of the catalytic cycle.[18] If a similar mechanism is assumed in the Ullmann reaction, then the formal oxidation state of copper should oscillate between +1 and +3. Though the mechanistic aspects of the Ullmann reaction have still not been elucidated, stable copper(III) complexes have been structurally characterized.[19] As aforementioned, copper-mediated reactions are often heterogeneous and require the use of high temperature and polar but toxic solvents such as HMPA. In 1964, Harold Weingarten from Monsanto observed that if impure diglyme was used as a solvent then the rate of the reaction between potassium phenoxide and bromobenzene was enhanced.[20] He attributed the rate enhancement to the solubilization of copper(I) ions by the impurities in diglyme.



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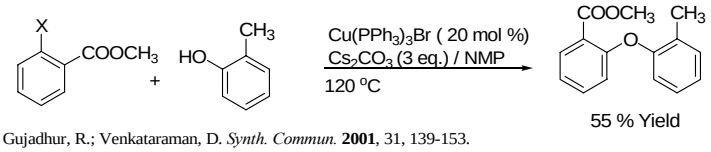

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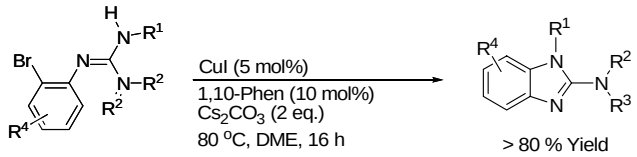

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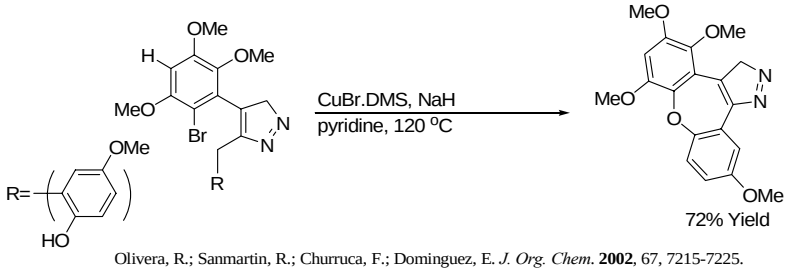

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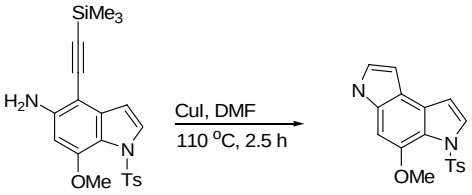


Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Perez, M.; Angel Garcia-Martin, M.; Gonzalez, J. M. *J. Org. Chem.* **1996**, 61, 5804-5812.

Chart 1.3: Examples of Copper-Catalyzed Reactions used as an Alternative Where Pd(0) Cross-Coupling fails.

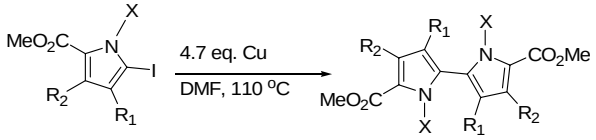
In 1976, Cohen and co-workers showed that *o*-bromonitrobenzene can homocouple to form 2,2'-dinitrobiphenyl at *room temperature* in the presence of a copper salt (copper(I) trifluoromethanesulfonate) that was soluble in the solvent, acetone/ammonia.[21] The observations by Weingarten and Cohen indicate that milder reactions conditions were indeed possible in copper-based cross coupling reactions, if the

solubility of the copper salts were increased. Furthermore, in 1987, Paine established that the active catalytic species in Ullmann reactions was indeed the *soluble cuprous* ion.[22] In 1997, Buchwald reported a general method for the formation of diaryl ethers using copper(I) triflate in catalytic amounts.[23] Despite its limitations in substrates, this protocol was much simpler than the reported palladium-based protocol reported by the Buchwald group. In 1999, Snieckus successfully explored the use of tetrakis(acetonitrile)copper(I) hexafluorophosphate, a complex soluble in organic solvents, for the formation of diaryl ethers.[24] Concurrently, Liebeskind and Goodbrand, reported that the use of certain additives in the reaction enhances the rate of certain copper-mediated reactions.[25,26] Liebeskind showed that traditional Ullmann biaryl coupling can be done at room temperature by the addition of a Cu(I) thiophene-2- carboxylate. In comparison, the reaction temperature for the traditional protocol was 110 ^{o}C (Scheme 1.4).[27]

Liebeskind et al.

Zhang, S.; Zhang, D.; Liebeskind, L.S. *J. Org. Chem*, **1997**, *62*, 2312-2313.

Sessler et al.



X= *tert*-butoxycarbonyl

Sessler, J. L.; Hoehner, M.C. *Synlett*, **1994**, *3*, 211-212.

Scheme 1.4: Comparison of the protocols used by Liebeskind et al vs. Sessler et al.

1.4 Organization of this dissertation

Based on the above precedences, we initiated a study of *chemically well-defined, stable and soluble* copper(I) complexes. Our objective was to create a family of well-defined copper(I) complexes that can be systematically modified to act as catalysts for the formation of *Aryl-O, Aryl-N, Aryl-S and Aryl-Se and Aryl-C bonds*.

In chapter 2 we describe the synthesis of the well-defined Cu(I)-Phosphine and Cu(I)-Phenanthroline complexes. Chapter 3 describes the development of a general protocol for the formation of diaryl ethers. In this chapter we also compare our protocol with the palladium-based methods. Chapter 4 deals with the development of a mild protocol for the synthesis of aryl amines. We also compare our protocol with palladium-based methods for the synthesis of specific aryl amines in this chapter. In chapter 5, we detail new protocols for the synthesis of diaryl sulfides and diaryl selenides using additives instead of well-defined copper(I) catalysts. We summarize all the results discussed in chapters 2-5, as well as discuss the future prospects for this chemistry, in the final chapter.

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Chapter 2

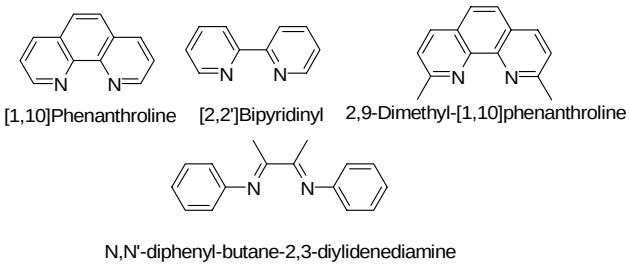
Synthesis of Copper(I) Complexes

2.1 Introduction

We began our investigation with a search for copper(I) complexes that were stable, well-defined and soluble in common organic solvents. In this regard many stable complexes with soft ligands such as triphenylphosphine and/or acetonitrile are known in the literature. These complexes have been studied for their charge-transfer and photophysical effects.[1] Copper(I)-acetonitrile complexes are the preferred source of copper(I) ions in the construction of many interesting supramolecular networks.[2,3] However, these complexes had not been studied for their catalytic properties towards cross-coupling reactions. We reasoned that copper(I)-phosphine complexes such as $[Cu(PPh_3)_3Br]$ are a good starting point to probe the catalytic activity of copper(I) complexes since they bear close structure resemblance to the widely used palladium(0) catalyst, $[Pd(PPh_3)_4]$. The triphenylphosphine ligands in palladium-based complexes stabilizes the zero oxidation state of the metal. Also, the lability of the Pd-PPh_3 bond provides a pathway to generate the catalytically active, $14e^-$, $Pd(PPh_3)_2$ species.

In 1999, Goodbrand and co-workers reported that the rate of formation of aryl amines were accelerated if phenanthroline was used as an additive to copper(I) salts.[4] Motivated by this observation, we also decided to synthesize a variety of well-defined copper(I) complexes using nitrogen-based chelating ligands such as phenanthroline,

neocuproine, and diimines[5] and 2,2'-bipyridine.(Scheme 2.1). During the course of this thesis many complexes were synthesized using phosphine- and/or nitrogen-based ligands. We chose to broadly classify them as mononuclear complexes with one copper atom and polynuclear complexes – complexes with more than one copper atom.

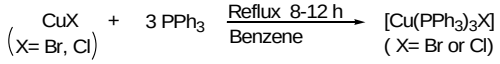


Scheme 2.1: Nitrogen-Based Chelating Ligands

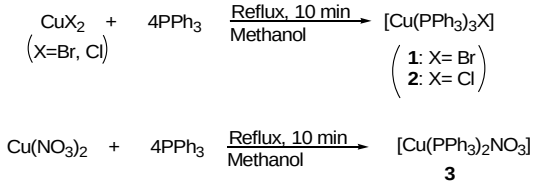
2.2 Mononuclear Triphenylphosphine Complexes of Copper(I)

A common method to synthesize copper(I)-phosphine complexes is to react copper(I) halides with triphenylphosphine in benzene at elevated temperatures for 8-12 h[6-8] (Scheme 2.2). In 1971, Jardine reported the synthesis of nitratobis(triphenylphosphine)copper(I) by the *in situ* reduction of copper(II) nitrate by triphenyphosphine and methanol (Scheme 2.3).[9] This method was very attractive since the starting material was the readily available copper(II) salts and the time required to make this complex was extremely short. Hence, we adapted this methodology to synthesize $[Cu(PPh_3)_3Br]$ (**1**) and $[Cu(PPh_3)_3Cl]$ (**2**) (Scheme 2.3 and Figures 2.1/2.2). The structures of these complexes are similar with those previously reported in literature (see experimental section). In these complexes, in addition to triphenylphosphine, the

counterion was also bound to the tetrahedral copper(I). However, in the case of complex (**3**), the nitrate ion acted as a bidentate ligand and hence only two triphenylphosphines are bound to the copper(I). These complexes are soluble in toluene, benzene, NMP, acetonitrile and insoluble in ether and ethanol. Bis(triphenylphosphine)copper(I) bromide, **4**, was obtained serendipitiously when we attempted to replace the phosphine ligands in $[Cu(PPh_3)_3Br]$ with 8-hydroxyquinoline. The cell constants, contents and the space group are identical to that of the already reported structure of $[Cu(PPh_3)_2Br]$ in the Cambridge Structural Database.



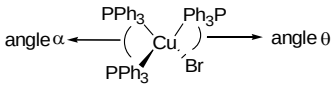
Scheme 2.2: General Procedure for Synthesis of $[Cu(PPh_3)_3X]$ (where X= Br, Cl) reported by Costa.[7]



Scheme 2.3: Synthesis of complexes **1, 2** by modification of the Jardine methodology used to make complex **3**

Table 2.1: Bite Angles and Cu-P Bond Lengths of Copper(I)-Phosphine Cu(I) Complexes

Phosphine Complexes



Entry	Complex	Dist Cu-P (Å)	Angle α (deg)	Angle θ (deg)
1	$[Cu(PPh_3)_3Br]$	2.323 (3)	115.27 (6)	103.03 (9)
2	$[Cu(PPh_3)_3Cl]$	2.349 (13)	110.04 (4)	108.89 (4)
3	$[Cu(PPh_3)_2NO_3]$	2.235 (2)	131.11 (13)	108.50 (18)
4	$[Cu(PPh_3)_2Br]$	2.262 (4)	126.20 (2)	116.95 (16)

The geometrical parameters for these complexes are tabulated in Table 2.1. A search of the Cambridge Structural Database indicates that the mean Cu-P distance in copper(I)-triphenylphosphine complexes is around 2.258 (± 0.05). As can be seen from Table 2.1, complexes 1,2 have Cu-P lengths slightly longer than the mean bond length. This can be attributed to the increased steric crowding around the copper(I) center. Indeed, longer Cu-P have been observed in copper(I) complexes with multiple triphenylphosphine ligands. For example, in $[Cu(PPh_3)_4]ClO_4$ the Cu-P bond length is 2.6 Å. We discuss the efficacy of these complexes to act as catalysts in the ensuing chapters.

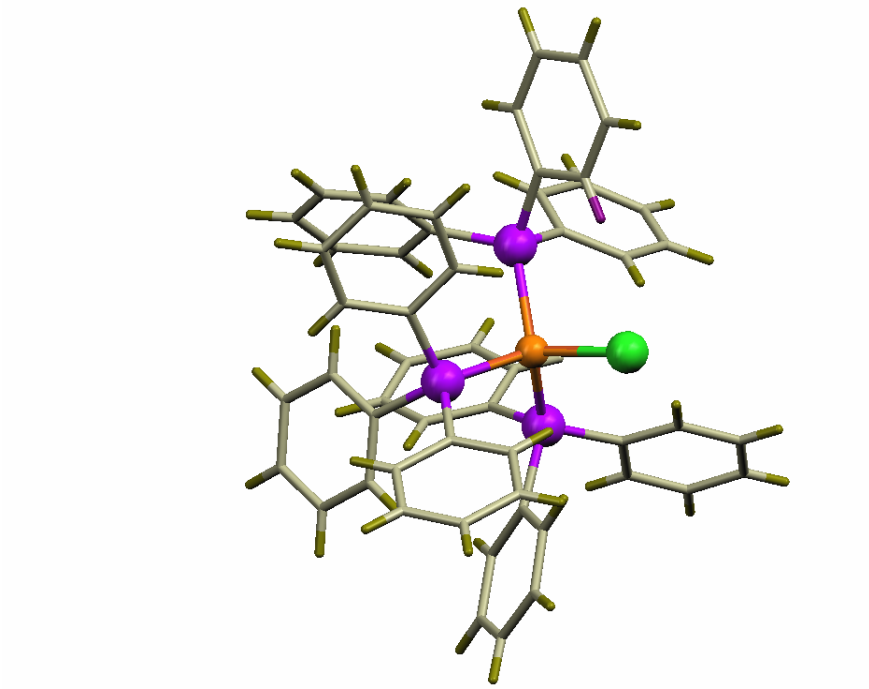


Figure 2.1: X-Ray Crystal Structure of $[Cu(PPh_3)_3Cl]$

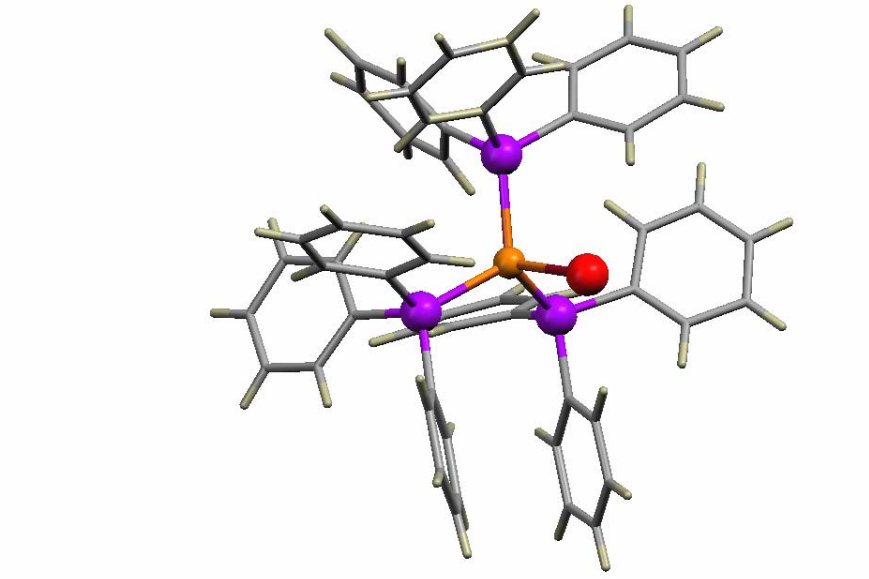


Figure 2.2: X-Ray Crystal Structure of $[Cu(PPh_3)_3Br]$

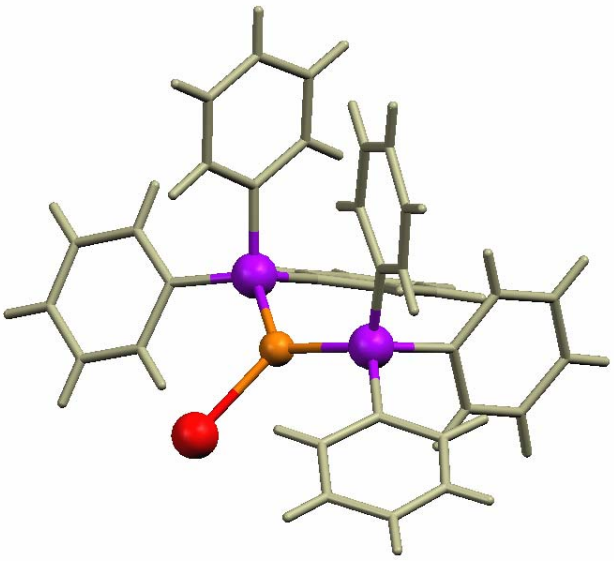


Figure 2.3: X-Ray Crystal Structure of $[Cu(PPh_3)_2Br]$

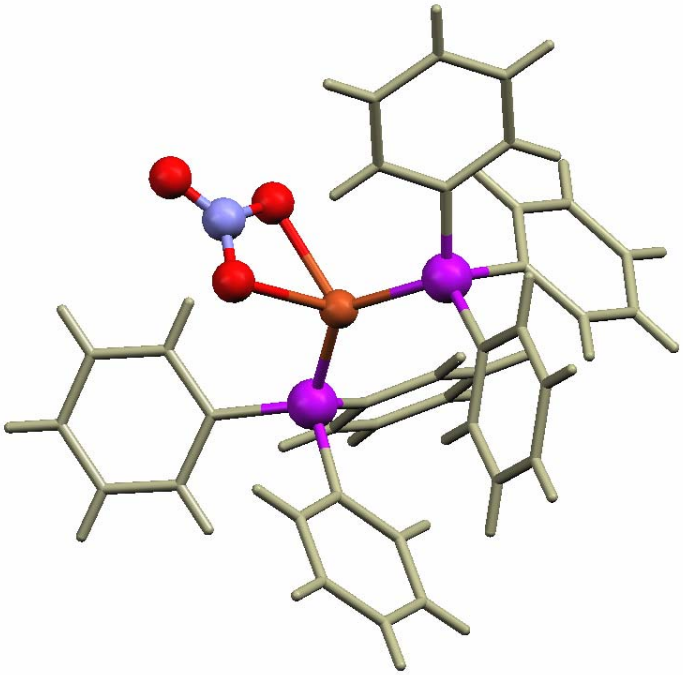
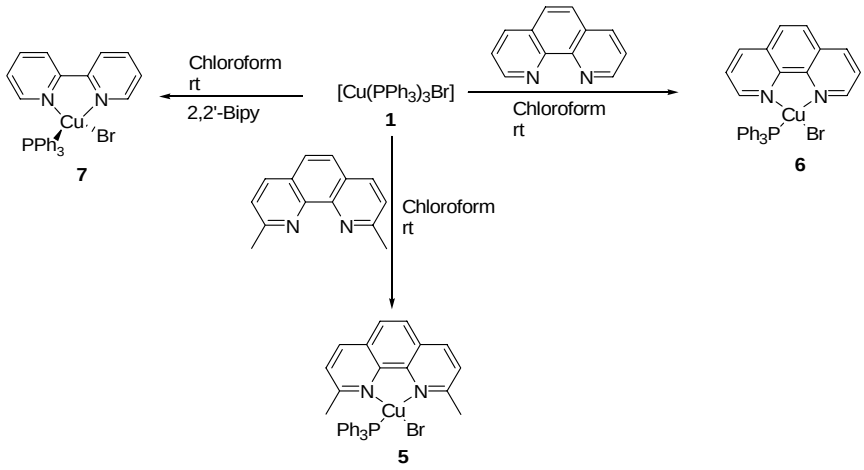


Figure 2.4: X-Ray Crystal Structure of $[Cu(PPh_3)_2NO_3]$

2.3 Copper(I) Complexes with Bidentate Ligands

Copper(I) complexes of phenanthroline, 2,2'-bipyridine and neocuproine ligands are known in literature and have been generally synthesized by the substitution of copper(I) tetrafluoroborate salts of type $[Cu(PPh_3)_4BF_4]$.[1,10] We first attempted to make these complexes by exchanging the phosphine ligands with complexes **1-3** with the ditopic ligands. We found that phenanthroline, 2,2'-bipyridine and neocuproine ligands readily exchanged with two of the three phosphine ligands in $[Cu(PPh_3)_3Br]$ to give complexes **5-7** (see Scheme 2.4 and Figures 2.5-2.7). These complexes were bright orange solids, stable to air and moisture.



Scheme 2.4: Synthesis of Phenanthroline Substituted Copper(I) Complexes (**5-7**) from $[Cu(PPh_3)_3Br]$

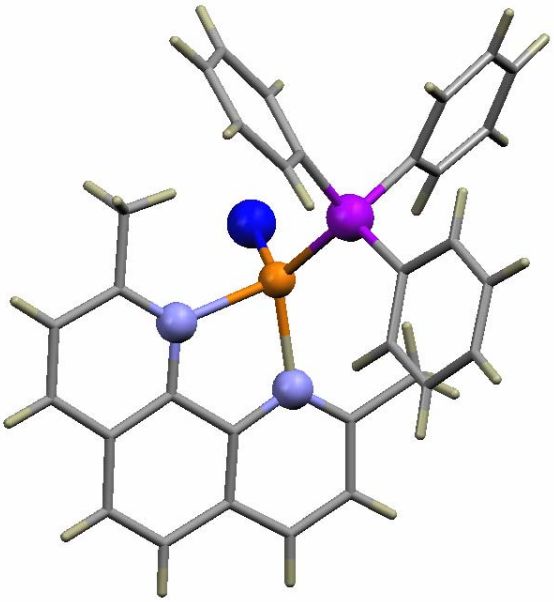


Figure 2.5: X-Ray Crystal Structure of [Cu(neocup)(PPh_3)Br] (**5**)

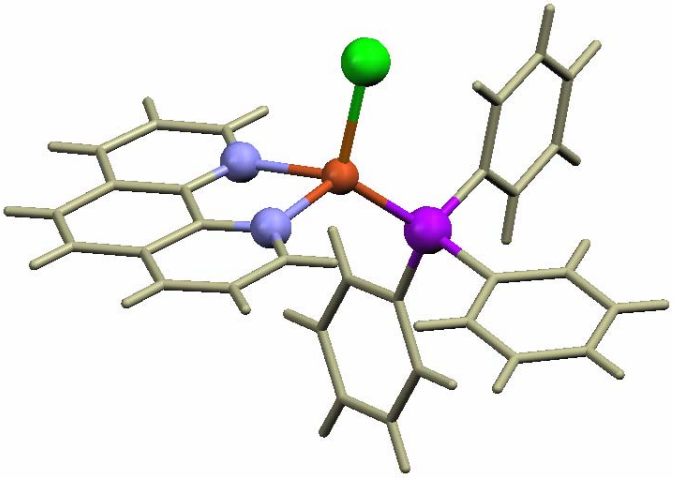


Figure 2.6: X-Ray Crystal Structure of [Cu(phen)(PPh_3)Br] (**6**)

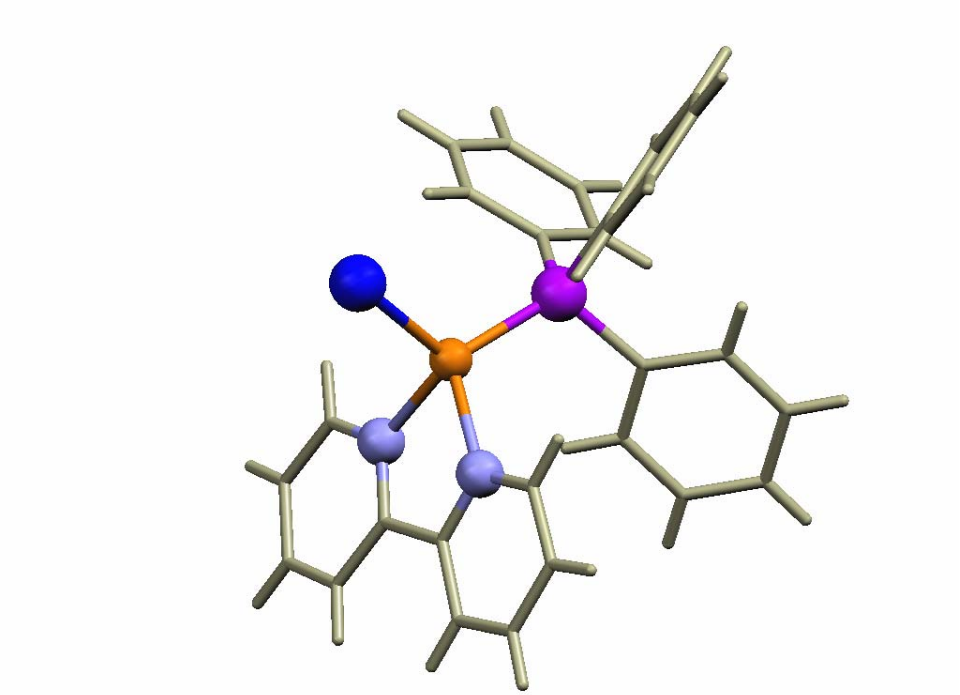
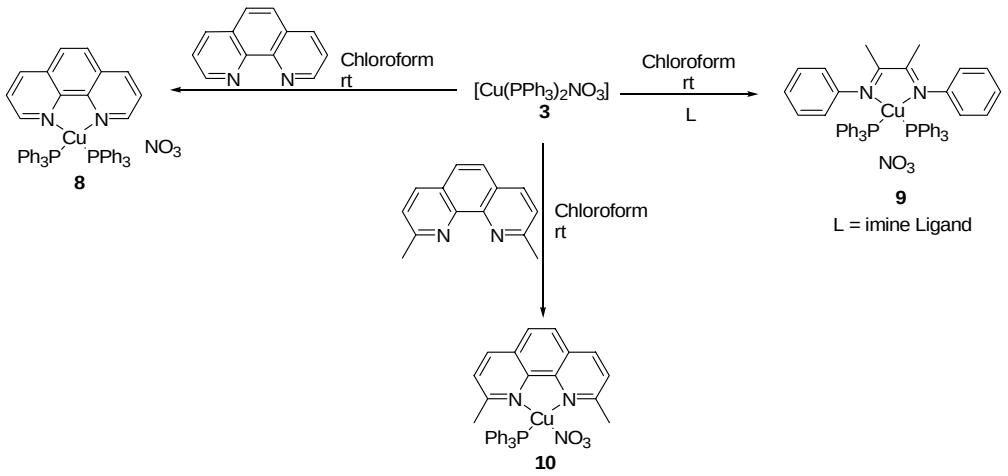


Figure 2.7: X-Ray Crystal Structure of [Cu(bipy)(PPh_3)Br] (**7**)

With [Cu(PPh_3)$_2NO_3$], we found that phenanthroline and one diimine ligand replaced the two triphenylphosphine ligands to give complexes **8** and **9** (See Scheme 2.5 and Figures 2.8 and 2.9). However, neocuproine replaced only one triphenylphosphine to give complex **10** (Figure 2.10). Although we initially reasoned that this may be due to the steric bulk imposed by the methyl groups in the 2 and 9 positions, we were able to successfully synthesize the bis triphenylphosphine complex, [Cu(neocup)(PPh_3)$_2$]PF_6, using [Cu(CH_3CN)]PF_6. At present we attribute this observation to a confluence of sterics and the presence of the coordinating ion.



Scheme 2.5: Synthesis of (**8**, **9, 10**) from $[Cu(PPh_3)_2]NO_3]$

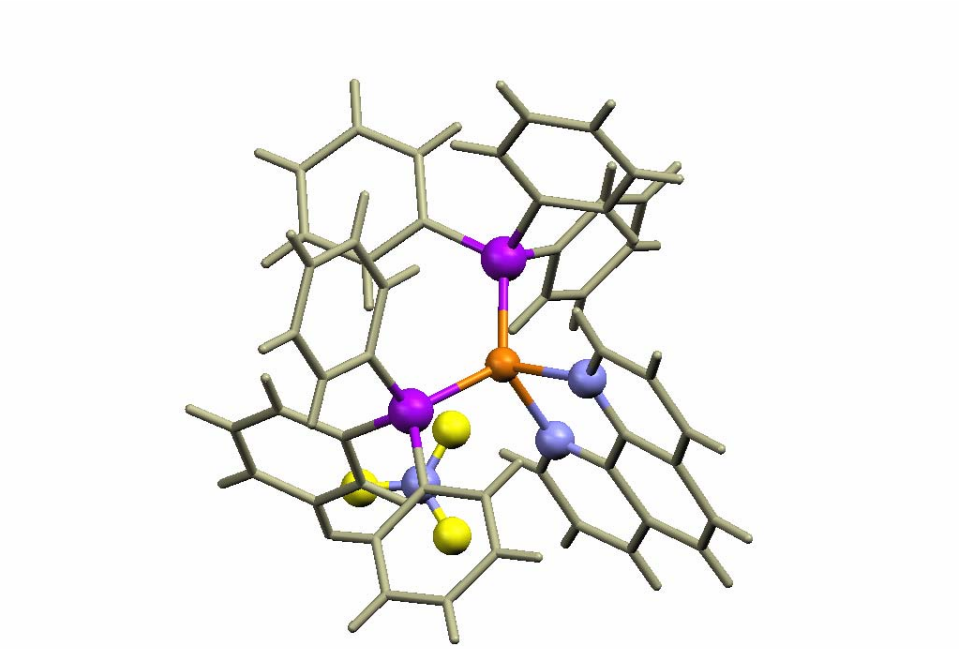


Figure 2.8: X-Ray Crystal Structure of $[Cu(phen)(PPh_3)_2](NO_3)$ (**8**)

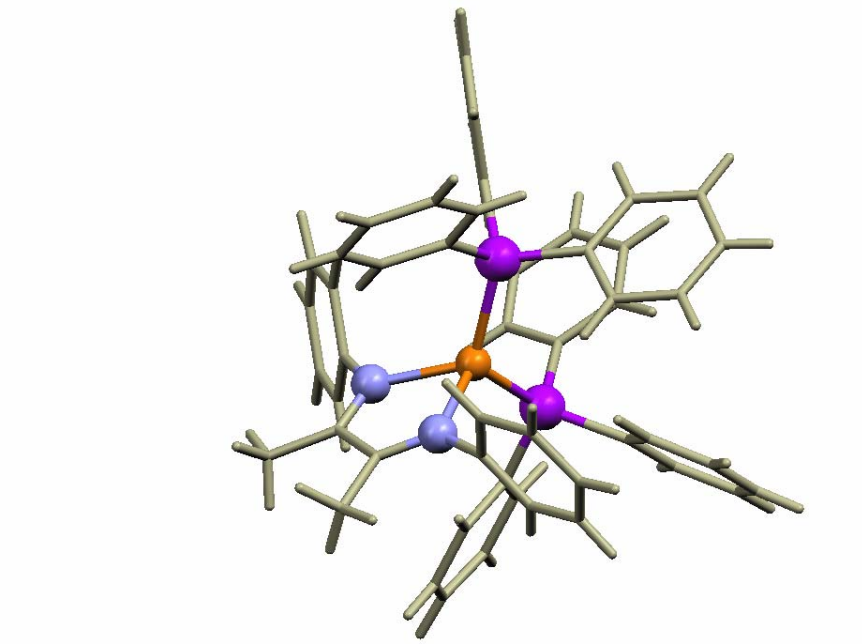


Figure 2.9: X-Ray Crystal Structure of $[Cu(C_{16}H_{16}N_2)(PPh_3)_2]NO_3$(**9**)

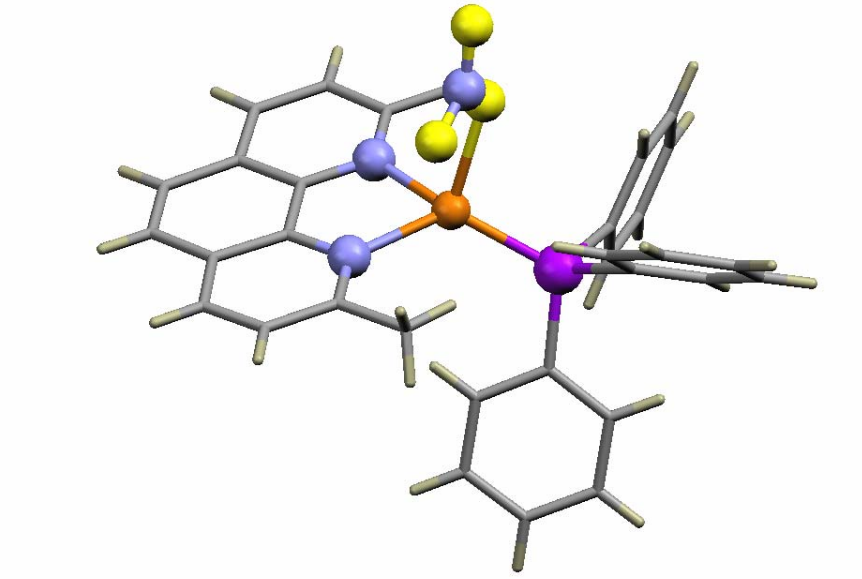
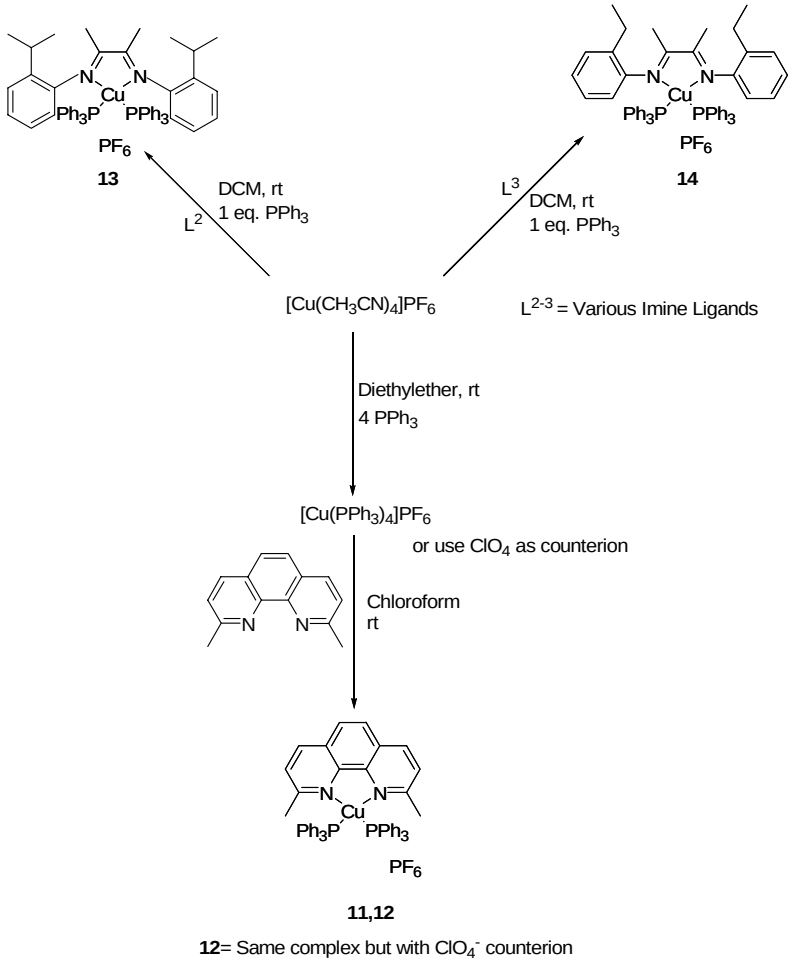


Figure 2.10: X-Ray Crystal Structure of $[Cu(neocup)(PPh_3)NO_3]$ (**10**)

The complex $[Cu(CH_3CN)_4]PF_6$ was made according to the procedure by Kubas[11]. This procedure involves the addition of HPF_6 to a magnetically stirred suspension of copper(I) oxide in acetonitrile. Full experimental details of this procedure have been given in the experimental section. This complex was used to isolate complexes (**11, 12, 13, 14**) which could not be obtained by the procedures detailed in both of the above synthetic schemes (Scheme 2.6 and Figures 2.11-2.14). All the complexes isolated were bright orange and were stable under ambient conditions. Complex **12** contains the same chelating ligand as compound **11**, but differs in the use of the counterion ClO_4^-.



Scheme 2.6: Synthesis of Phenanthroline and Diimine Substituted Copper(I) Complexes (**11-14**) from $[Cu(CH_3CN)_4]PF_6$

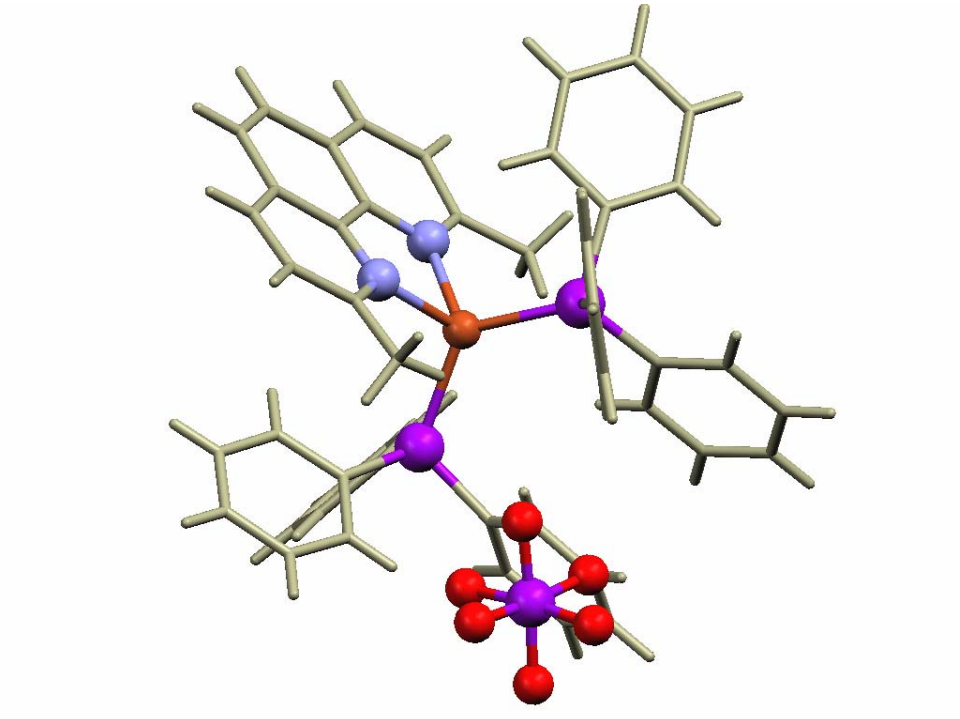


Figure 2.11: X-Ray Crystal Structure of $[Cu(neocup)(PPh_3)_2]PF_6$ (**11**)

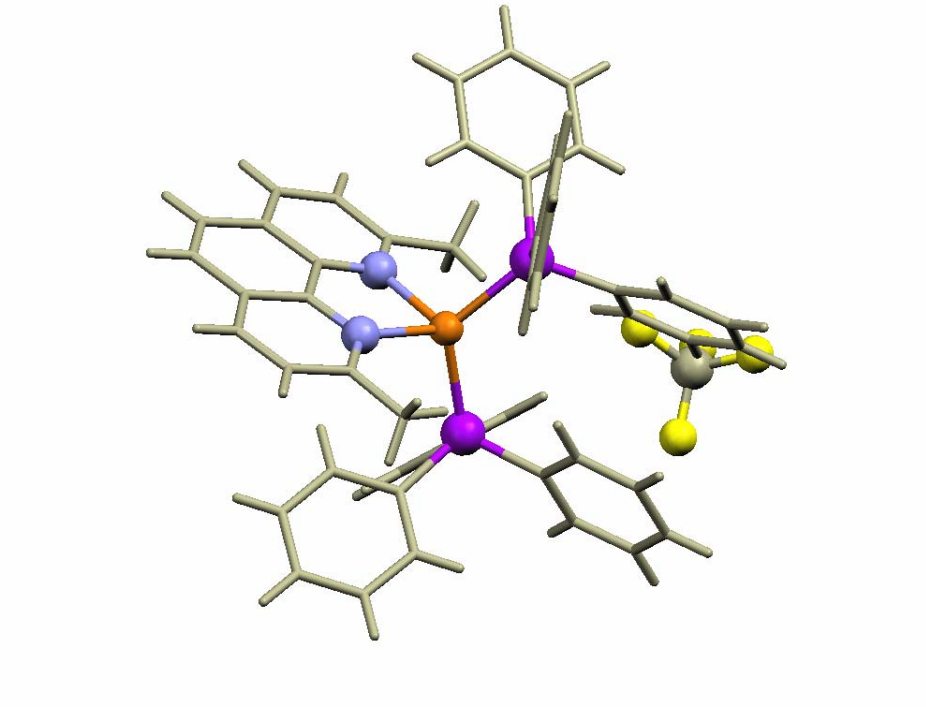


Figure 2.12: X-Ray Crystal Structure of $[Cu(neocup)(PPh_3)_2](ClO_4)$ **(12)**

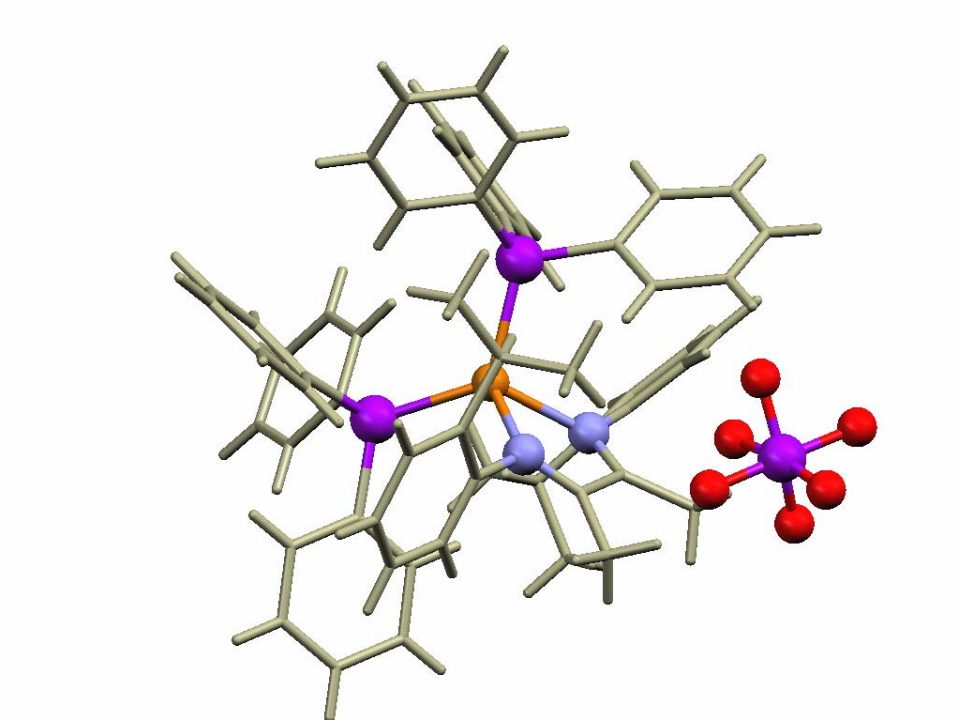


Figure 2.13: X-Ray Crystal Structure of $[Cu(C_{22}H_{26}N_2)(PPh_3)_2]PF_6$ (**13**)

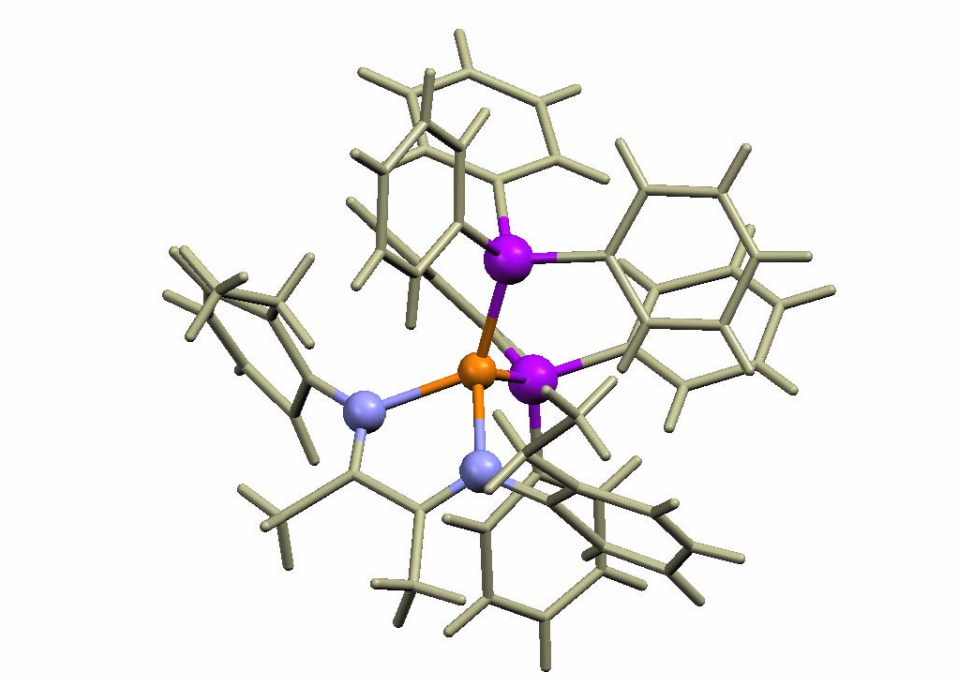
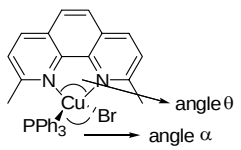


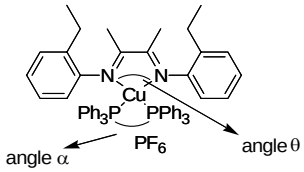
Figure 2.14: X-Ray Crystal Structure of $[Cu(C_{20}H_{24}N_2)(PPh_3)_2]PF_6$ (**14**)

Table 2.2: Bite angles and Cu-P bond Lengths of Chelated Cu(I) Complexes

Phenanthroline/Neocuproine Complexes



Diimine Complexes



Entry	*Complex*	*Dist Cu-P (Å)*	*Angle α (deg)*	*Angle θ (deg)*
1	[Cu(neocup)PPh_3Br]	2.207 (5)	114.50 (15)	79.70 (5)
2	[Cu(phen)(PPh_3)Br]	2.188 (9)	118.43 (3)	79.69 (9)
3	[Cu(neocup)(PPh_3)NO_3]	2.195 (7)	104.73 (6)	80.48 (7)
4	[Cu(bipy)(PPh_3)Br]	2.192 (16)	118.31 (5)	78.70 (2)
5	[Cu($C_{16}H_{16}N_2$)(PPh_3)$_2$]PF_6	2.270 (19)	119.93 (7)	76.10 (2)
6	[Cu(neocup)(PPh_3)$_2$]ClO_4	2.288 (8)	123.22 (3)	80.60 (10)
7	[Cu(phen)(PPh_3)$_2NO_3$]	2.285 (10)	123.98 (4)	79.92 (4)
8	[Cu(neocup)(PPh_3)$_2$]PF_6	2.280 (9)	124.66 (4)	80.25 (13)
9	[Cu($C_{20}H_{24}N_2$)(PPh_3)$_2$]PF_6	2.313 (3)	110.24 (10)	76.40 (3)
10	[Cu($C_{22}H_{26}N_2$)(PPh_3)$_2$]PF_6	2.310 (2)	120.35 (8)	77.30 (2)

The geometrical parameters for these complexes are tabulated in Table 2.2 below. It can be seen the the Cu-P bond is longer than the mean value of 2.258 Å for complexes with more than one phosphine ligand. In addition, the increase in the bulkiness of the ligand also lengthens the Cu-P bonds. At the present time, we have not established if longer Cu-P bonds translate into lower dissociation temperatures and increased lability for the triphenylphosphine ligands. This is currently being studied using ^{31}P NMR by Nestor Chavez-Trinidad in our research group. It can also be seen from Table 2.2 that the N-Cu-N angle denoted by theta varies from 76 to 81 deg. This short range in this angle

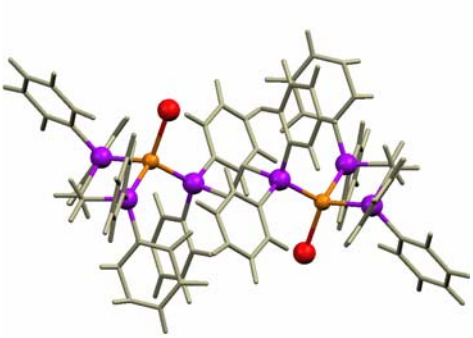
provides us with the opportunity to systematically study the electronic effects of the ligand on the activity of these complexes.

2.4 Polynuclear Cu(I) Complexes.

In 1998, Hartwig and co-workers reported the use of ditopic phosphines such as diphenylphosphinoferrocene (DPPF) as ligands for palladium(0)-catalyzed formation of aryl-nitrogen bonds. With an intent to use ditopic phosphines as ligands in our copper chemistry, we pursued the synthesis of well-defined copper(I) complexes using diphenylphosphinoethane (DPPE) as the ligand. Our first attempt to synthesize these mononuclear copper(I) complexes, using modified literature procedures[12] from copper bromide (1 mmol) and DPPE (1 mmol) dissolved in chloroform in the presence of PPh_3, lead to the formation of a binuclear Cu(I) complex. This complex comprised of DPPE ligand chelated to each of the copper and a third DPPE ligand bridging the two metal centers (Compound **15**, Table 2.3). To counteract the formation of the dinuclear species, we decided to make use of $[Cu(PPh_3)_3Br]$ as the starting material. We anticipated that the triphenylphosphine would act as a deterrent for aggregation. To our surprise, we found out that this did not take place. The end product was a polynuclear Cu(I)-DPPE complex (**16**). This compound contained three DPPE molecules and three copper centers. One of the copper centers adopted a trigonal planar geometry, whilst the two other metal centers were in a tetrahedral conformation (Compound **14**, Table 2.3).

Table 2.3: Polynuclear Cu(I)-DPPE Complexes (**15** and **16**)

Dinuclear Cu(I)-DPPE Complex (**15**)



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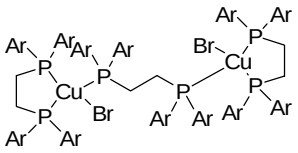

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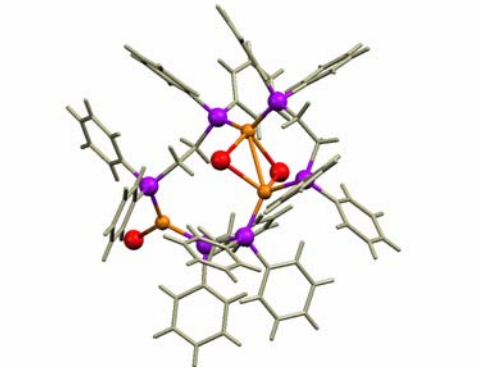
Polynuclear Cu(I)-DPPE Complex (**16**)



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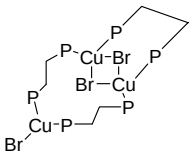

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In addition to the formation of polynuclear complexes with non-rigid chelating ligands, we also observed a surprising similar trend with non-chelating ligands such as PPh_3, and tri-*o*-tolyl-phosphane. In our earlier attempts to synthesize mononuclear bulky diimine complexes, one strategy adopted was to make use of method by Costa (Scheme 2.2). This method involved refluxing CuBr and the appropriate ligands for 24 h. Instead of the expected mononuclear chelated Cu(I)-diimine complex supported by two triphenylphosphine ligands, we isolated a tricyclic polynuclear Cu(I) compound (Figure

2.15). Morever, such an unexpected compound was not restricted to Costa`s methodology. Using Jardine's protocol, we have also identified a binuclear Cu(I)- tri-*o*-tolyl-phosphane bridged by two bromine atoms, instead of the expected mononuclear (tris tri-*o*-tolyl-phosphane)copper(I) complex (Figure 2.16). The increased bulk of the tri-*o*-tolyl-phosphane may possibly explain the occurrence of this dinuclear species.

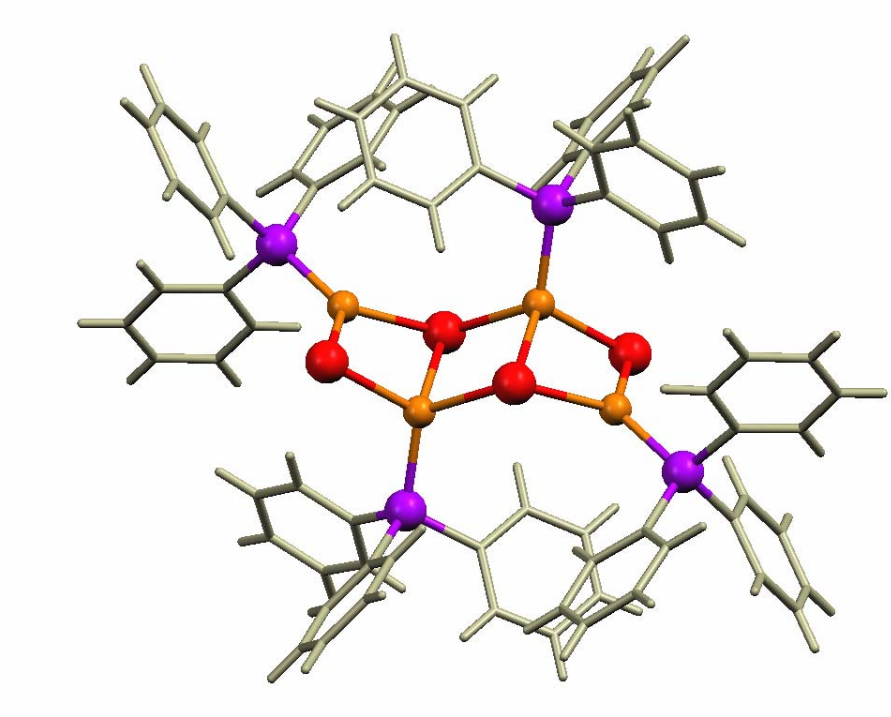

Figure 2.15: Polynuclear Tricyclic Cu(I) Complex

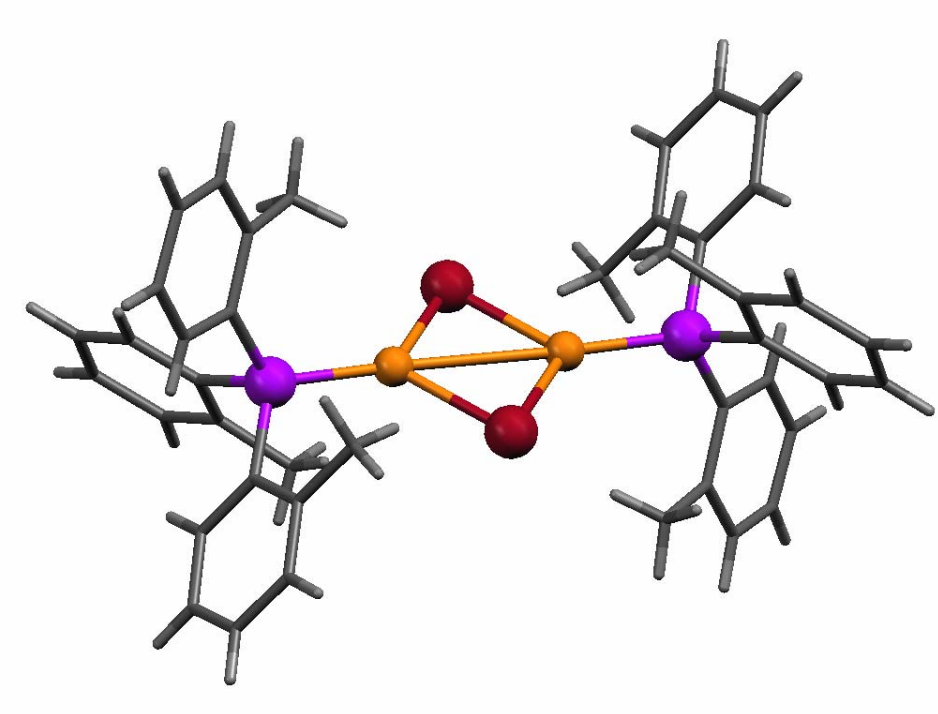

Figure 2.16: Dinuclear Cyclic Cu(I) Complex

In general, we found that the polynuclear complexes were inactive as catalysts in cross-coupling reactions.

2.5 Conclusions

A number of observations can be made from the above results. They are summarized as follows:

- The protocol by Jardine can be modified to make complexes of type $[Cu(PPh_3)_3X]$, where X=Cl, Br

- Mononuclear complexes such as $[Cu(PPh_3)_3Br]$ and $[Cu(PPh_3)_3Cl]$ $[Cu(PPh_3)_2NO_3]$ as well as $[Cu(CH_3CN)_4]PF_6$ can be easily substituted, under ambient conditions, into a range of N-based chelating ligands. (i.e. 1,10-phenanthroline, 2,2'-bipyridine, neocuproine, diimine). There is a correlation between increasing bite angles (α) and weakening of the Cu-P in these mononuclear Cu(I) complexes.
- Polynuclear complexes are obtained instead of mononuclear complexes when using DPPE in presence of Cu(I) salts or soluble Cu(I) complex.
- Both the methods of Costa and Jardine can lead to polynuclear Cu(I) species, with non-chelating aryl phosphine ligands such as PPh_3 and tri-*o*-tolyl-phosphane.

In the next three chapters we explore the synthetic potential of the above mononuclear and polynuclear complexes in the formation of aryl-heteroatom bonds.

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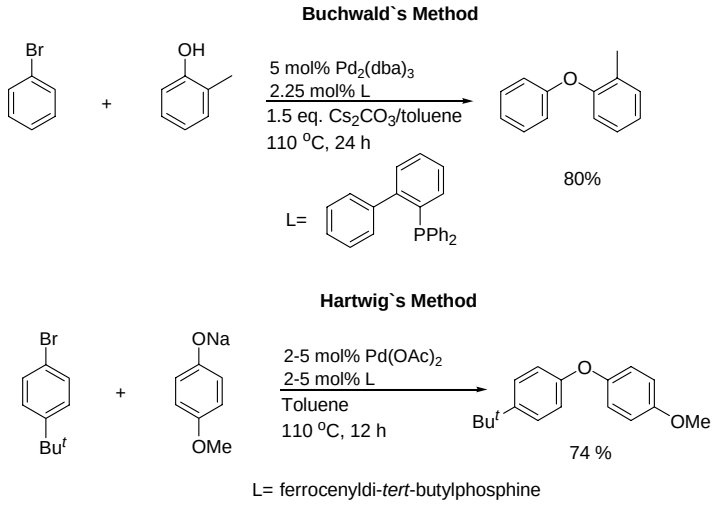
Chapter 3

Synthesis of Diaryl Ethers using Copper(I) Catalysts

3.1 Background

Aromatic ethers are compounds of increasing importance in the pharmaceutical and materials industries.[1] A classical method for the synthesis of alkyl aryl ethers is the reaction of phenoxides with alkyl halides. This reaction proceeds by the S_N2 mechanism and is termed as the Williamson reaction. Since most aryl halides do not undergo nucleophilic substitution reaction without the presence of a catalyst, the Williamson reaction is not successful for the formation of diaryl ethers. Until recently, the copper-mediated Ullmann reaction was the method of choice for the synthesis of diaryl ethers. However, these reactions often require high temperatures (~200 °C) and the use of copper salts in greater than stoichiometric amounts.[2,3] Over the last 10 years there has been a resurging interest in the development of new and milder methods to synthesize diaryl ethers. The Buchwald and Hartwig research groups have been prominent in developing palladium-based methods for diaryl ether synthesis (see Scheme 3.1).[4,5] This methodology involves the use of bulky phosphine ligands, with catalytic amounts of palladium, in the presence of a base. Although successful these protocols have inherent limitations, which we discussed in Chapter 1. We detail our efforts below to provide a new protocol for diaryl ether synthesis using copper catalysts, as an alternative to existing palladium-based protocols.



Scheme 3.1: The Hartwig-Buchwald Protocol for the Formation of Diaryl Ethers

3.2 Introduction

In 1997, Buchwald and co-workers reported the first copper-based protocol for the formation of diaryl ethers.[6] The reported protocol calls for the use of $[Cu(CF_3SO_3)\bullet 0.5C_6H_6]$ as the catalyst, cesium carbonate as the base, 5 mol % of ethyl acetate as an additive and toluene as the solvent. In certain cases, 1-napthoic acid was also required as an additive. In 1999, Snieckus and co-workers reported the use of $[Cu(CH_3CN)_4]PF_6$ as a catalyst for the formation of diaryl ethers from *o*-halobenzamides and *o*-halosulfonamides.[7] Although $[Cu(CH_3CN)_4]PF_6$ is slightly more stable than $[Cu(CF_3SO_3)\bullet 0.5C_6H_6]$ in air, it still requires the use of harsh conditions, such as the use of HPF_6 for its preparation. Our intent was to develop a very general and mild protocol for the formation of diaryl ethers that dispenses with the need for additives and/or air-sensitive copper(I) complexes. In this regard, we chose to probe the efficacy of copper(I)-phosphine complexes (**1-8)** as catalysts for the formation of diaryl ethers. As a test reaction, we chose the cross-coupling reaction of 4-bromotoluene and *p*-cresol in NMP

as solvent, in the presence of 1.5 eq. of Cs_2CO_3 at 120 ^oC. The choice of NMP as the solvent and cesium carbonate as the base were made because of literature precedents on their applications. NMP had been shown to be an efficient coordinating solvent for copper catalyzed aryl-carbon bond formation reactions, under ambient conditions[8], while cesium carbonate had shown its use as an effective inorganic base for crown ether synthesis.[9,10]

We found by TLC that mononuclear complexes (**1-4**) were effective as catalysts and bi- and polynuclear complexes (**5-8**) were ineffective. Among the mononuclear complexes, $[Cu(PPh_3)_3Br]$ (**1**) was noted to be the most effective (Chart 3.1).

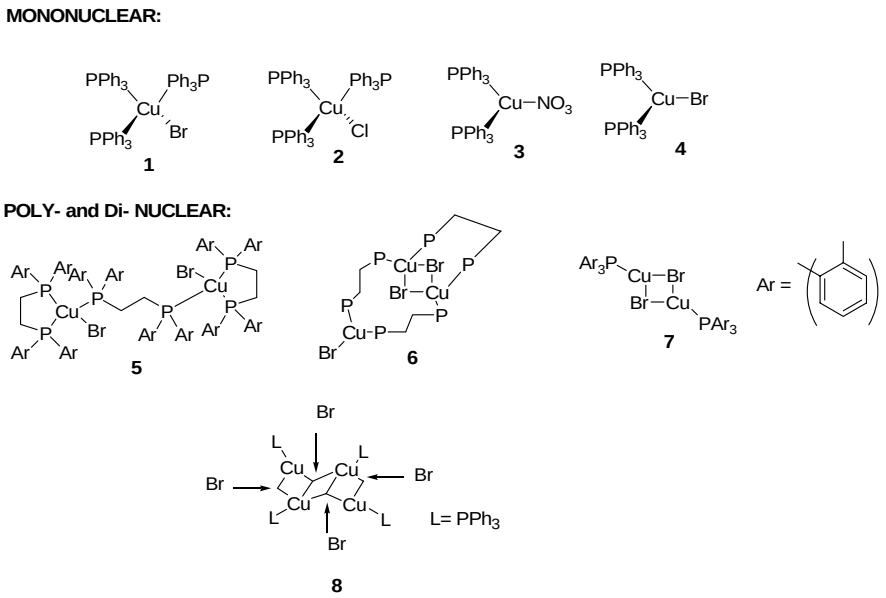


Chart 3.1: Mononuclear (**1-4**), Dinuclear (**5,7**) and Polynuclear (**6,8**) Copper(I) Complexes

3.3 Optimization and Results with tris(triphenylphosphine) Copper(I) bromide

We then examined the propensity of **1** to act as a catalyst for the formation of diaryl ethers using solvents such as toluene and N-methylpyrrolidinone (NMP). In NMP, we discovered that *o*- and *p*-cresol react with electron deficient aryl bromides such as 1-bromo-4-nitrobenzene and 4-bromobenzonitrile with Cs_2CO_3 to form the corresponding diaryl ether at 70 °C and in 6 h, *even in the absence of the copper catalyst* (see Table 3.1, entries 1-4). The reaction was however, incomplete in 6 h when Cs_2CO_3 was replaced with K_2CO_3 and does not occur if 4-*N*,*N*-dimethylaminopyridine (DMAP) was used as the base. In comparison, when the reaction was carried out in toluene, in addition to Cs_2CO_3, the copper catalyst was also required for the formation of the diaryl ether. These observations suggest that the formation of diaryl ethers from electron-deficient aryl bromides and electron-rich phenols might not require any catalysts such as Pd(0), if Cs_2CO_3 is used as a base and NMP as the solvent. This is very surprising owing to the fact that a number of authors have published protocols for electron-deficient ethers using transition metal catalysts.[6,7] Our procedure to couple electron-poor iodides is a Cu-free protocol.

Furthermore, for electron-rich aryl bromides, the reactions were complete in 48 h in the presence of 5 mol% of **1** and 3 eq. of Cs_2CO_3, in NMP. The reactions do not proceed when K_2CO_3, KO*t*-Bu or DMAP were used as bases. Also, in contrast to the reactions with electron-deficient aryl bromides, the copper catalyst was necessary for

diaryl ether formation. In general, we observed that the reactions were faster in NMP than in toluene.

Table 3.1: Reactions of Aromatic Bromides with Phenols in NMP or in Toluene

Entry	R	R'	Catalyst (mol%)	Solvent	Time (in h)	Temp (^oC)	Isolated Yields* (%)
1	*p*-NO_2	*p*-CH_3	0	NMP	6	70	88
2	*p*-NO_2	*o*-CH_3	0	NMP	6	70	86
3	*p*-CN	*p*-CH_3	0	NMP	6	70	80
4	*p*-CN	*o*-CH_3	0	NMP	6	70	85
5	*p*-CH_3	*o*-CH_3	20	NMP	17	100	75
6	*p*-CH_3	*p*-CH_3	20	NMP	17	100	70
7	*p*-$N(CH_3)_2$	*p*-CH_3	20	NMP	19	100	76
8	*p*-OCH_3	*p*-CH_3	20	NMP	24	100	75
9	*o*-OCH_3	*p*-CH_3	20	NMP	24	100	61
10	*o*-CH_3	*p*-CH_3	20	NMP	24	100	75
11	*o*-CH_3	*o*-CH_3	20	NMP	24	100	72
12	*p*-CH_3	*p*-CN	20	NMP	24	100	0
13	*p*-CH_3	*o*-$COOCH_3$	20	NMP	24	100	0
14	*o*-$COOCH_3$	*o*-CH_3	20	NMP	24	100	55
15	*p*-CN	H	20	Toluene	24	100	60
16	*p*-CH_3	*o*-CH_3	20	Toluene	24	100	27

*Cs_2CO_3 was used as the base. For all entries, catalyst loading: 20 mol% [$Cu(PPh_3)_3Br$], solvent: toluene, temperature: 110 ^oC

We then probed the effect of the catalyst concentration on the reaction time. We found that when **1** was increased to 20 mol%, the reactions were complete (by TLC) in 24 h, and gave good yields (entries 5-11, Table 3.1). Similar reaction times and yields

were observed, when **1** was used in stoichiometric amounts. We observed that the reaction mixtures needed to be very well stirred owing to the low solubility of Cs_2CO_3 in NMP.

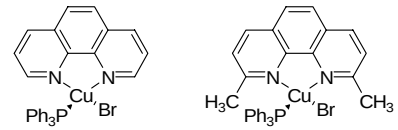
All of the diaryl ethers reported in Table 3.1 have been characterized by ^{1}H NMR, ^{13}C NMR and elemental analyses. The products from entry 1 and entry 6 in Table 3.1 have also been characterized by single crystal X-ray analyses.

From Table 3.1, it can be surmised that **1** is a very effective catalyst for the coupling of electron-rich phenols and electron-rich aryl bromides (entries 5-11). It is also effective in the coupling of *o*-substituted aryl bromides and *o*-substituted electron-rich phenols (entry 11), which have been derivatized to the carboxylic analogs for use in supramolecular topology studies.[11] In addition, another product that could not be obtained by well-known palladium chemistry (entry 14) was also isolated. However, **1** is ineffective in the coupling of electron-deficient phenols with electron-rich bromides (entries 12 and 13). This may be attributed to the delocalization of the charge on the phenoxide ion, making it a poor nucleophile. In fact, most general methods that have been reported in the literature have focused on phenols with electron donating substituents[6,7,12,13] although Song and co-workers have recently published a protocol with electron-poor phenols, using 2,2,6,6-tetramethylheptane-3,5-dione as the ligand.[14]

We also found that 4-bromobenzonitrile can couple with phenol, in toluene, to form the corresponding diaryl ether in 60 % yield (entry 15). In direct comparison, when

[$Cu(CF_3SO_3)$•$0.5C_6H_6$] was used as the catalyst, 1-naphthoic acid was required as an additive for the diaryl ether formation.[6]

3.4 Improved Protocol for Diaryl Ethers using [$Cu(neocup)(PPh_3)Br$]



[$Cu(phen)(PPh_3)Br$] [$Cu(neocup)(PPh_3)Br$]

9 **10**

Figure 3.1: Copper(I)-Phenanthroline Complexes

As aforementioned in Chapter 2, Goodbrand and co-workers reported the rate of formation of aryl-nitrogen bonds was accelerated when 1,10-phenanthroline was added to copper(I) salts. This observation had motivated us to prepare well-defined copper(I) phenanthroline and copper(I) neocuproine complexes. These complexes are soluble in organic solvents such as dichloromethane, chloroform, toluene (warm), benzene, NMP, DMF and DMSO. However, they are insoluble in diethylether or hexane. We were interested to see whether or not these complexes were effective catalysts in the formation of aryl-oxygen bonds. In this regard, we chose to study the formation of ditolylether from *p*-cresol and *p*-bromotoluene with 10 mol% of the complexes **9** and **10** and 3.0 eq. Cs_2CO_3 as the base. With [$Cu(PPh_3)_3Br$], we had observed that NMP was a better solvent than toluene for the formation of diaryl ethers. However, since toluene is a commonly used solvent in palladium-catalyzed protocols, we chose to use it as the solvent to probe the efficacy of the complexes **9** and **10** to act as catalysts in the reaction. We found by GC that [$Cu(neocup)(PPh_3)Br$] was the most effective catalyst and provided ditolylether

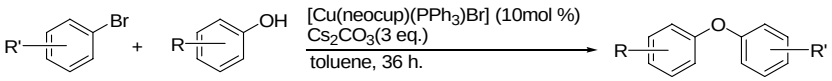
in almost quantitative yield in 36 h. Under similar conditions the yield was only 53% when [$Cu(PPh_3)_3Br$] was used as the catalyst. The use of neocuproine as an additive was not as effective as the well-defined catalyst.

Table 3.2: Comparison of Conversion to Aryl Ethers Using Various Copper(I) Complexes.

Entry	Cu(I) Catalyst	*p*-Tolylether Yield[a]	
		20 hours	**36 hours***
1	[$Cu(neocup)(PPh_3)Br$]	70	99
2	[$Cu(phen)(PPh_3)Br$]	21	53
3	[$Cu(PPh_3)_3Br$]	40	53
4	CuBr/neocuproine	43	65
5	CuBr/1,10-Phenanthroline	20	46
6	[$(CuOTf)_2 \cdot PhH$]	40	46

a-GC Yields
*Cs_2CO_3 was used as the base. For all entries, catalyst loading: 10 mol % of catalyst, solvent: toluene, temperature: 110 ^oC. We made use of 1 mmol of *p*-bromotoluene and 1 mmol of *p*-cresol in the controls.

Using this protocol (Scheme 3.2) we were able to couple various aryl bromides and phenols to form diaryl ethers in good yields using 10 mol% of **10** as a catalyst and Cs_2CO_3 as a base in toluene at 110 °C (entries 1-6, Table 3.3). This protocol tolerates base-sensitive functional groups such as ketones (entry 2). However, yields of diaryl ethers are substantially lower for aryl bromides bearing *ortho* substituents (entries 5 and 6). Two months after this protocol[15] was published, Wolter et al[16], developed a similar protocol for the coupling of aryl iodides and aliphatic alcohols using a catalytic amount of copper iodide and 1,10-phenanthroline, in the presence of cesium carbonate at 110 ^oC.



Scheme 3.2: General Protocol for Diaryl Ether Synthesis using [Cu(neocup)(PPh_3)Br]

Table 3.3: Reactions of Aryl Halides with Phenols with 10 mol% of complex **10**

Entry	R	R[1]	Yields[a]
1	*p*-CH_3	*p*-CH_3	>99
2	*p*-CH_3	*p*-$COCH_3$	>99
3	*o*-CH_3	*p*-CH_3	83
4	H	*p*-NO_2	95
5	*o*-CH_3	*o*-CH_3	36
6	*p*-CH_3	*o*-CH_3	31

[a]GC Yields

*Cs_2CO_3 was used as the base. For all entries, catalyst loading: 10 mol% [Cu(neocup)PPh_3Br], solvent: toluene, temperature: 110 ^oC

3.5 Conclusions

In conclusion, we have shown that both [Cu(PPh_3)$_3$Br] and [Cu(neocup)(PPh_3)Br] are effective catalysts for the formation of diaryl ethers from electron-rich bromides and phenols. A number of compounds have been made which are difficult to obtain using known palladium protocols (entry 11 & 14, Table 3.3). In contrast to other Cu(I) catalysts like Cu(I) triflate, **1** and **10** are extremely easy to prepare and are both air-stable. We have

also shown that electron-deficient aryl bromides couple with phenols in the presence of Cs_2CO_3, with NMP as the solvent, and do not require any catalyst .

3.6 References

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Chapter 4

Formation of Aryl-Nitrogen Bonds using Copper(I) Catalysts

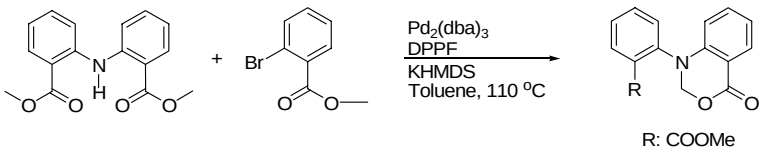
4.1 Background

Aromatic amines play a pivotal role in a number of fields. These include pharmaceuticals[1], agrochemicals[2], photography[3], xerography[4], pigments[5], and electronic materials[6]. The obvious importance of aryl amines and the past scarcity of general methods for their synthesis has provided an impetus for the development of catalysts for the formation of aryl nitrogen bonds. Among the most important developments in organic synthesis related to aryl-nitrogen bond formation in the last 20 years, has been the advent of palladium and nickel-catalyzed cross-coupling procedures. In the formation of aryl-nitrogen bonds, palladium catalysts have been tailored with the aim to furnish high turnover numbers[7], faster reaction rates[8], and high functional group compatibility[9]. To date, the best amination methods in this chemistry include the use of either bulky and sterically hindered alkyl phosphines[10] or P,N ligand containing a biphenyl backbone[11]. Both these systems allow the room temperature amination of aryl bromides and chlorides. Despite the meteoric success of palladium catalyzed chemistry, there has been over the recent years a revival in the use of copper-catalyzed methods for the formation of aryl-nitrogen bonds.[12,13] The focus on copper has been as a result of the increasing cost of palladium protocols[14], as well as the recent awareness by the scientific community that

copper catalysts may provide an alternative approach to the cross-coupling of a range of substrates, previously eluded by palladium chemistry.[15,16]

4.2 Introduction

As part of a project in our research group to develop well-ordered electroactive molecules based on triphenylamines an attempt was made to synthesize *o.o'.o''*-amino-trisbenzoic acid-trimethylester. It was found that when the Hartwig-Buchwald protocol was used to cross couple 2,2'-azanediyl-bis-methylbenzoate with 2-iodo-benzoic acid methyl ester in presence of $Pd_2(dba)_3$ as catalyst, DPPF as ligand and potassium hexamethyl disilazane as base, in toluene at 120 ^oC[17], a cyclized product was isolated instead of the expected triarylamine product (see Scheme 4.1).



Scheme 4.1: Attempted Cross-Coupling of Substituted Aryl Amine Using the Hartwig-Buchwald Cross-Coupling

This result pointed to a limitation in the Hartwig-Buchwald cross-coupling protocol. This added to the growing list of failures of palladium catalyzed reactions (see Chart 1.3). The failure to cross-couple aromatic halides with electron withdrawing groups, was not unknown in the palladium repertoire. The result obtained by our research group as well as other examples in the literature on the limitations of palladium cross-coupling protocols, gave us an incentive to start developing an alternative approach using copper(I) catalysts. With our previous success in using $[Cu(PPh_3)_3Br]$ and

[Cu(neocup)(PPh_3)Br] as catalysts for the formation of diaryl ethers[18], described in Chapter 3, we decided to explore the efficacy of the same soluble copper(I) complexes in the formation of aryl-nitrogen bonds. Our main intent was to attempt to develop a mild copper-catalyzed protocol that allowed the coupling of a wide range of substrates ranging from diphenyl amine to more sterically and electronically demanding substrates i.e. *o*.*o*'.*o*''-amino-trisbenzoic acid-trimethylester.

4.3 Application of [Cu(PPh_3)$_3$Br] in Aryl-Nitrogen Bond Formation Reactions

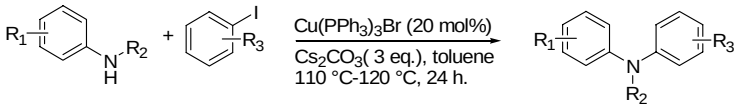
We first examined the propensity of [Cu(PPh_3)$_3$Br] to act as a catalyst for the formation of triphenylamine from diphenylamine and bromobenzene or iodobenzene. We found that the reactions were complete in 24 h (by TLC) at 120 °C when the aryl halide was iodobenzene. The reaction procedure required 20 mol% of the copper(I) catalyst, 1.5 eq. of cesium carbonate as the base, in toluene as the solvent (Scheme 4.2).

Using this protocol, we were able to synthesize a variety of functionalized triphenylamines in good yields from aryl amines and aryl iodides (Tables 4.1 and 4.2). However, the reactions were incomplete in 24 h (by TLC) if NMP was used as the solvent or if the aryl halide was bromobenzene. Also, we did not observe the formation of triphenylamine if *N*,*N*-dimethylaminopyridine (DMAP), potassium carbonate or sodium methoxide was used as the base instead of Cs_2CO_3.

In general, except for entry 5, electron-deficient aryl iodides provided better yields of triarylamines than electron-rich aryl iodides (Table 4.1, Entries 1-9). Entries 6

and 7 have lower yields possibly because of the large steric strain involved in the cross-coupling of the substrates.

While we are unable to explain the low reactivity of methyl-4-iodobenzoate in entry 4, after various trials, we found that if diphenylamine, [$Cu(PPh_3)_3Br$], and KO*t*-Bu (instead of Cs_2CO_3) were heated in toluene for 5 min at 120 °C, cooled to room temperature and then methyl-4-iodobenzoate was added and reheated to 120 °C for 24 h, the corresponding triphenylamine was obtained in 62 % yield (Entry 5). Furthermore, to our satisfaction, we were able to synthesize a triphenylamine, *functionalized at the ortho positionsof each phenyl group by ester groups* (Entry 7), a molecule that had could not be obtained by the Hartwig-Buchwald palladium chemistry (Figures 4.1).



Scheme 4.2: General Protocol for the Formation Aryl-Nitrogen Bonds using [$Cu(PPh_3)_3Br$]

Table 4.1: Reactions of Aryl Amines with Electron-Deficient Aryl Iodides with 20 mol% of $[Cu(PPh_3)_3Br]$

Entry	R_1	R_2	R_3	Time (in h)	Temp (°C)	Yields (%)
1	H	Ph	*o*-$COOCH_3$	24	120	69
2	H	Ph	*p*-$COCH_3$	24	120	68
3	H	Ph	*p*-NO_2	24	120	78
4	H	Ph	*p*-$COOCH_3$	24	120	25
5	H	Ph	*p*-$COOCH_3$	24	120	62[a]
6	*o*-$COOCH_3$	C_6H_4-*o*-$COOCH_3$	*o*-$COOCH_3$	32	120	10
7	*o*-$COOCH_3$	C_6H_4-*o*-$COOCH_3$	*o*-$COOCH_3$	32	175	40[b]
8	*o*-$COOCH_3$	H	*o*-$COOCH_3$	24	110	83
9	*o*-$COOCH_3$	H	H	24	110	70

[a] with KO*t*-Bu as the base instead of Cs_2CO_3 , [b] *o*-dichlorobenzene was used as a solvent.
*Cs_2CO_3 was used as the base. For all entries, catalyst loading: 20 mol% $[Cu(PPh_3)_3Br]$, solvent: toluene, temperature: 110 °C

With Cs_2CO_3 as the base, we were able to use base-sensitive functional groups such as ketones and esters (see Table 4.1). Using our protocol, we were also able to selectively aminate aryl iodide in the presence of a bromide as well as with electron-rich aryl iodides (Entries 10-15, Table 4.2).

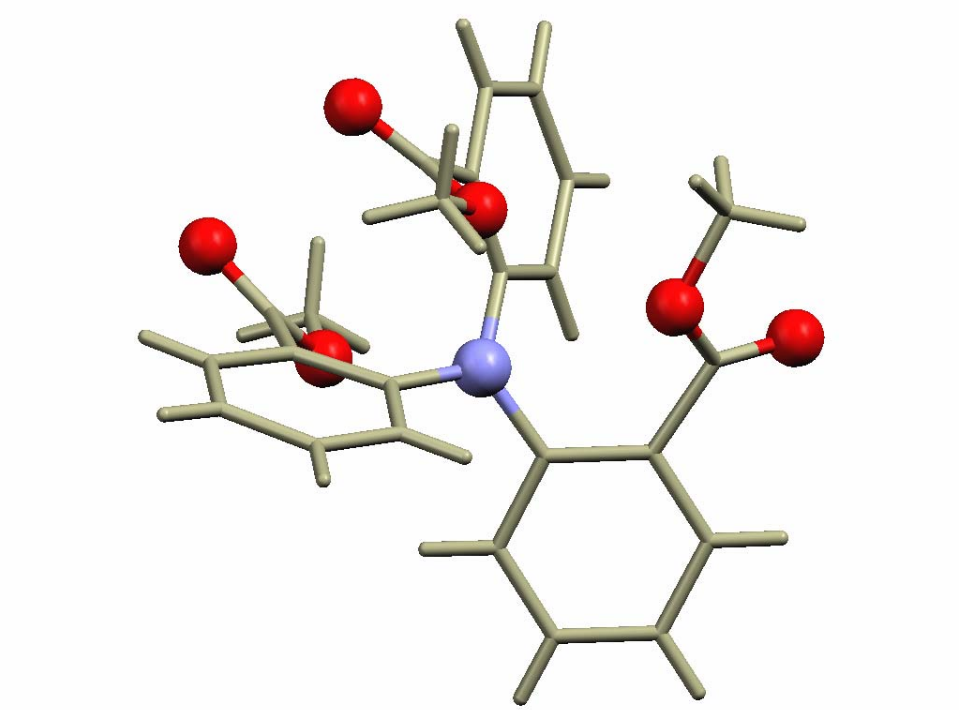


Figure 4.1: X-Ray Crystal Structure of o.o'.o''-amino-trisbenzoic acid trimethylester

Table 4.2: Reactions of Aryl Amines with Electron-Rich Aryl Iodides with 20 mol% of $[Cu(PPh_3)_3Br]$

Entry	R_1	R_2	R_3	Time (in h)	Temp (°C)	Isolated Yield* %
10	H	Ph	H	24	120	70
11	H	Ph	*p*-Br	24	120	54
12	H	H	H	24	110	75
13	*p*-CH_3	H	H	24	110	88
14	H	Ph	*p*-CH_3	24	120	52
15	H	Ph	*o*-CH_3	24	120	52

*Cs_2CO_3 was used as the base. For all entries, catalyst loading: 20 mol% $[Cu(PPh_3)_3Br]$, solvent: toluene, temperature: 110 ^oC

We also found that [$Cu(PPh_3)_3Br$] can be used as catalyst for the formation of diphenylamine from *substituted anilines* and aryl iodides (Entries 8 & 9, Table 4.1 and Entry 13, Table 4.2). Surprisingly, we found that these reactions were successful only if the amine, the catalyst and the base are stirred at 110 °C for few minutes (~ 5 min for the formation of an yellow color) *before* the addition of the aryl iodide. If all the starting materials were added at room temperature and heated to 110 °C, we observed a black precipitate without the formation of the diphenylamine.

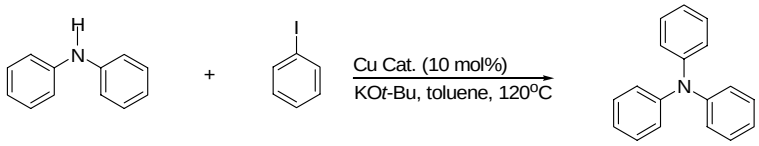
4.4 Controls and Comparison with other Protocols

Further controls were carried out to test the effectiveness of our catalyst in our proposed synthetic protocol. We replaced our catalyst with 20 mol% of CuI, CuBr, or 20 mol% of CuBr/60 mol% of PPh_3. In each of these reactions, we failed to observe the formation of triphenylamine, proving that well-defined complexes were necessary under the conditions of our protocol. Recent work[19] by Kelkar et al. using our catalyst indicated that the reactivity of [$Cu(PPh_3)_3Br$] was dramatically improved when KO*t*-Bu was used as the base. This supported our earlier observations about the improvement in yield with methyl-4-iodobenzoate when we used KO*t*-Bu (entry 5, Table 4.1). They also made the observation that adding PPh_3 and CuI in a 3:1 ratio, *or using our complex [$Cu(PPh_3)Br$]*, gave a 93% yield of triphenylamine, from aniline and 2 eq. of iodobenzene in the presence of KO*t*-Bu as the base.

Recently, Goodbrand and Hu reported[12] that when 1,10-phenanthroline/CuCl was used as the catalyst and 8 eq. KOH as the base, the rate of formation of aryl-nitrogen bonds was accelerated and the reactions were complete in 6 h, at 125 °C, in toluene. To accomodate nucleophile-sensitive functional groups like esters, we replaced KOH with cesium carbonate in Goodbrand's protocol. However, we found that the reaction of diphenylamine and iodobenzene was incomplete even after 15 h. This confirmed the usefulness of our protocol as it allowed the coupling of more nucleophile-sensitive functional groups on the aryl halide substrate.

All of the compounds listed in Table 4.1 and 4.2 were individually isolated and characterized by ^{1}H NMR, ^{13}C NMR and elemental analyses. Additionally, products obtained under entries 1, 3, 4, 6, 11 were also characterized by single crystal X-ray analyses.

4.5 Comparison with Phenanthroline-Substituted Cu(I)-Phosphine Complexes



Scheme 4.3: General Protocol used for Cu(I) Catalyst Screening

With the success of the above protocol between aryl amines and aryl iodides with [$Cu(PPh_3)_3Br$], we began a study to investigate the possible cross-coupling of aryl bromides or chlorides, instead of the aryl iodide in the above protocol (Scheme 4.3). Efforts in the scientific community in this endeavour have been greatly encouraged by

the lower costs of aromatic chloride and bromides. Our initial starting point was to make use of some of the well-defined monomeric copper(I) chelated complexes whose synthesis have been described earlier (see Chapter 2). Goodbrand's observation of the accelerating effect of 1,10-phenanthroline in aryl-nitrogen bond formation prompted us to test the well-defined copper(I)-phenanthroline complexes. A first attempt was made to compare the rate of conversion of diphenylamine to triphenylamine, using 10 mol% of $[Cu(PPh_3)_3Br]$ versus either 10 mol% of $[Cu(neocup)PPh_3Br]$ or 10 mol% of $[Cu(phen)PPh_3Br]$. Initial reactions showed that $[Cu(neocup)PPh_3Br]$ was the most active catalyst, giving an isolated yield of 78 % of triphenylamine in only 6 hours, in the presence of 1.5 eq. KO*t*-Bu as the base. When used in the presence of 1.5 eq. of Cs_2CO_3 the yield of the product with $[Cu(neocup)PPh_3Br]$ as the catalyst was 45 %, compared to 70 % with $[Cu(PPh_3)_3Br]$. This meant that the success of the conversion with $[Cu(neocup)PPh_3Br]$ was extremely base dependent. This base sensitive behavior is very analogous to that observed with palladium-based catalysts.[20] Other controls carried out showed that the reaction was much faster with KO*t*-Bu instead of NaH, Cs_2CO_3, N-ethylmorpholine, NaO*t*-Bu, K_3PO_4, K_2CO_3, CsF, $NaOCH_3$.

In light of the above results we decided to extend the optimization experiment carried out with $[Cu(neocup)PPh_3Br]$ to the range of phenanthroline, neocuproine, di-imine copper(I) complexes (see Chart 2.3). Our aim was to attempt to find the best catalytic system that could be exploited in future aryl-nitrogen bond formation reactions. The results obtained are summarized and discussed below (See Figure 4.3).

We proposed to take aliquots of the individual reaction mixtures at each hour for a six hourly period, as well as at an extended period of time i.e. 24 h. Comparison of the yields of triphenylamine showed that [Cu(neocup)PPh_3Br] gave slightly higher yields than all the other complexes at 6 and 24 hour intervals. The GC yield was 76 % for [Cu(neocup)PPh_3Br] vs. 55-74 % for all the other catalysts. One trend observed in these reactions is the loss of catalytic activity for all the complexes from 3-6 hours. This is shown by a leveling of all the curves (Figure 4.3) at this specific time period. What is causing the slight gain in yield with [Cu(neocup)PPh_3Br] ?

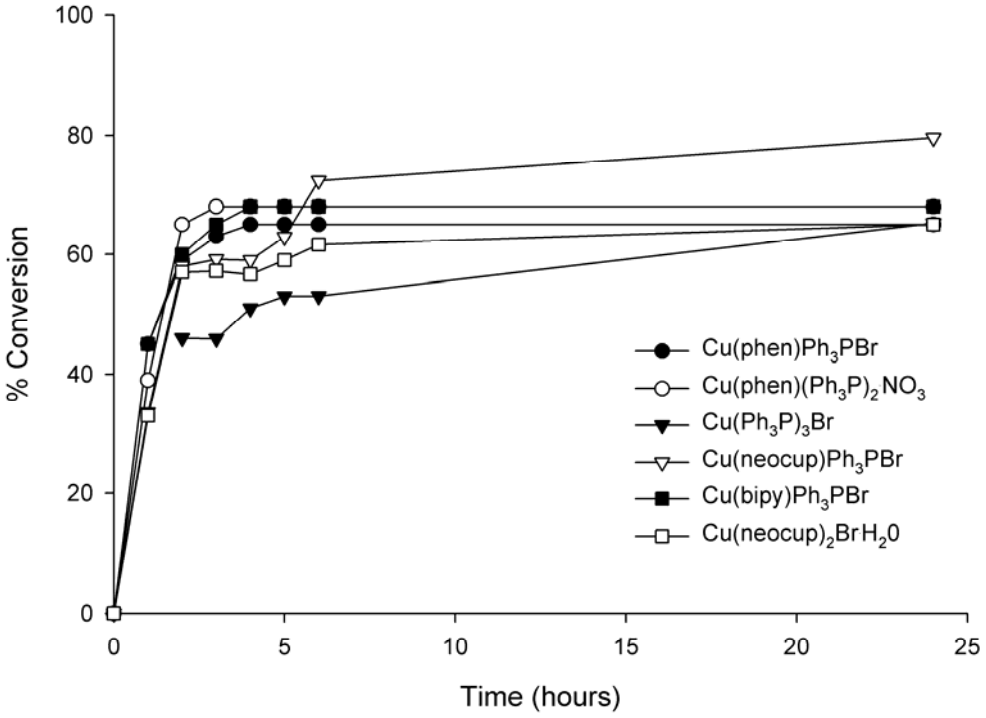


Figure 4.3: Comparison of the Rates of Conversion to Triphenylamine using various Chelated Cu(I) Complexes.

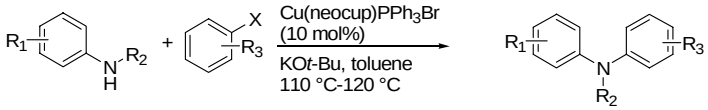
A possibly related observation with the above that was obtained from mass balance calculations for starting and final products showed a consistent trend of rapid iodobenzene loss of up to 70 % the initial concentration as from 2 hours onwards in all the reactions. We were unable to account for this rapid lost of iodobenzene. Efforts to identify benzene by GC, in order to prove a dehalogenation side reaction, were not fruitful. In addition, biphenyls were not identified which discounted a radical pathway for the loss of the aryl halide. *Is it possible that in the case of [Cu(neocup)PPh$_3$Br], the catalyst itself is less active in triggering the side reaction which entails massive loss of iodobenzene, and eventual collapse of the catalyst.* Control experiments were carried out for [Cu(neocup)PPh$_3$Br] and [Cu(phen)PPh$_3$Br] to check for reactivity of the catalysts after the 6 hour period, by charging the reaction with another 1 mmol of iodobenzene and diphenylamine. There were no improvement in yield of triphenylamine after either 6 or 24 h. The increased acidity of neocuproine as reported by other research groups and the higher stability constant of [Cu(neocup)(PPh$_3$)Br] compared to the other N-based chelated copper(I) complexes, may further support the argument proposed above. [21,22] The complex [Cu(neocup)$_2$Br].H$_2$O was also included in our optimization controls, because we wanted to test the behavior of a complex with low accessibility to the copper center. This complex gave a yield of 64 % after 24 h. However, constant addition of free neocuproine in the reaction had a detrimental effect on the yield of triphenylamine. This result proved that monomeric chelated copper(I) species might be the active entity in these reactions. The previous inactivities of poly- and di-nuclear species with diaryl ether synthesis also pointed towards this observation. (See Chapter 3).

In our optimization experiments we also considered testing other non-chelated copper(I) complexes to compare with the above results. Other complexes like $[Cu(CH_3CN)_4]PF_6$ and $[Cu(CF_3SO_3)\bullet 0.5C_6H_6]$ both gave low yields of 34-56 % when tested under similar conditions (see Scheme 4.3).

The complexes $[Cu(PPh_3)_2NO_3]$ and $[Cu(PPh_3)_2Br]$ were also tested to gain an insight on the effect of trigonal planar copper(I) systems. They both gave similar yields of 65 % and 67 % respectively

Based on the above investigations we decided to proceed with the use of $[Cu(neocup)(PPh_3)Br]$ as a catalyst for the formation of aryl-nitrogen bonds.

4.6 $[Cu(neocup)(PPh_3)Br]$: A New Amination Catalyst



Scheme 4.4: General Protocol for Aryl Amines Using $[Cu(neocup)(PPh_3)Br]$

Using the above results we proposed a new protocol for the conversion of aryl iodides in 6 h using $[Cu(neocup)PPh_3Br]$ as a catalyst (Scheme 4.4 and Table 4.3). Using this protocol, we were able to couple bromobenzene with diphenylamine to form triphenylamine in 36 h. We were also able to couple chlorobenzene with diphenylamine in moderate yields in 36 h. The protocol was successfully used to couple electron-rich

aryl halides with diphenylamine. Furthermore, the reaction of *p*-toluidine with two equiv. of bromobenzene yielded the corresponding triphenylamine in 70 % yield (entry 7).

Table 4.3: Reactions of Aryl Halides with Diphenylamine with 10 mol% of [Cu(neocup)(PPh_3)Br].

Entry	R_1	R_2	X	Time (in h)	Yield* (%)
1	H	Ph	I	6	78
2	H	Ph	Br	36	73
3	H	Ph	Cl	36	49[a]
4	*o*-CH_3	Ph	I	6	88
5	*p*-CH_3	Ph	I	6	70
6	*o*-CH_3	Ph	Br	36	50[a]
7	*p*-CH_3	H	Br	24	70[b]

[a]GC Yields, [b]used 2 eq. of bromobenzene
*KO*t*-Bu was used as the base. For all entries, catalyst loading: 10 mol% [Cu(neocup)(PPh_3)Br], solvent: toluene, temperature: 110 °C

4.7 Conclusions

In conclusion, we have shown that soluble, stable and an easy-to-prepare copper(I) complexes, [Cu(PPh_3)$_3$Br] and [Cu(neocup)PPh_3Br], can be used as catalysts for the formation of aryl-nitrogen bonds under mild conditions. [Cu(PPh_3)$_3$Br] is selective for a range of activated and deactivated aryl iodides. An electron-poor diphenylamine, i.e. 2,2'-azanediyl-bis-methylbenzoate, and anilines were also successfully coupled to form the related aromatic amines. Using this catalyst, the product *o.o'.o''*-amino-trisbenzoic acid-trimethylester was also synthesized, albeit in low yields. This product was not

obtained by current Hartwig-Buchwald protocols, which gave a cyclized amine product in the presence of $Pd_2(dba)_3$, DPPF and KHMDS at 110 ^oC. Recent findings in the literature have shed light on the utility of [$Cu(PPh_3)_3Br$], which was found useful in the formation of triphenylamines in a one-pot reaction from aryl iodide and aniline in presence of KO*t*-Bu in a few hours.[19] The accelerating effect of KO*t*-Bu was previously identified by ourselves during the cross-coupling of 4-iodo-benzoic methyl ester with diphenylamine.

With the catalyst [Cu(neocup)PPh_3Br], we showed that the rate of cross-coupling of aryl iodides with diphenyl amine can be accelerated (i.e 6 h) even at reduced catalyst loading (10 mol%). This catalyst proved successful in the cross-coupling aniline to triphenylamine in one pot, as well as in the conversion of bromobenzene and chlorobenzene to the desired products, albeit in low yields. Optimization studies with this catalyst and a wide range of N-based chelating and non-chelating catalyst showed a rapid loss of 70 % of iodobenzene as from 2-6 hours during the reaction. This phenomenon has not been fully elucidated during this study. Future works to understand this behaviour might entail an in-depth analysis of side products in this reaction using isotope labeling and NMR studies and GC analysis. An understanding of the reasons for the loss of catalytic activity may be valuable to design highly active and robust copper-based catalysts for aryl-nitrogen bond formation reactions.

4.8 References

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Chapter 5

Synthesis of Aryl-Sulfur and Aryl-Selenium Bonds Using Copper(I) Catalysts

5.1 Background

Methods for the formation of aryl-sulfur and aryl-selenium bonds are indispensable tools in synthetic chemistry. Their importance stems from the prevalence of aryl-sulfur bonds in many molecules that are of biological, pharmaceutical and materials interest.[5,18,26,44,45,49]. Similarly, diaryl selenides have also attracted considerable interest because of their potential as anticancer and antioxidant agents.[10,13,15,20-25] They are also key intermediates in the synthesis of a plethora of biologically and pharmaceutically important selenium compounds such as selenonium salts, selenoxides, selenimines, and selenide dihalides.[29,31,40]

5.2 Existing Methods for the Formation of Aryl-Sulfur Bonds

Traditional methods for the synthesis of aryl-sulfur bonds often require harsh reactions conditions. For example, coupling of copper thiolates with aryl halides requires polar solvents such as HMPA and temperatures around 200 °C. Reduction of aryl sulfones or aryl sulfoxides requires strong reducing agents such as DIBAL or $LiAlH_4$.[19,30,50,52] Synthetic routes to the formation of aryl alkyl sulfides have also been designed that require a procedure to dediazonate diazosulfides[7], or the use of other

strategies, such as, Phase Transfer Catalyst conditions (PTC)[11], [Cr_2CO_3]-activated aryl halides[3], or polar solvents (diglyme)[39]. In 1980, Migita and co-workers[28,35] first reported the cross-coupling reaction of aryl halides and aryl and alkyl thiols with $Pd(PPh_3)_4$ as the catalyst, NaO*t*-Bu as the base, in polar solvents such as refluxing ethanol or DMSO at 90 °C. However, only few reports have appeared in the literature for the formation of aryl-sulfur bonds using transition metal catalysts (Pd(0) or Ni(0)) since Migita's report.[6,12,17,32,33,47,53] This is in sharp contrast to the volume of literature that exists for the formation of aryl-nitrogen and aryl-oxygen bonds. Following Hartwig's mechanistic studies[17,32,33] on the reductive elimination of palladium(II) arylthiolate complexes with chelating phosphines, in 1996, Zheng and co-workers reported the first general palladium-based protocol for the synthesis of aryl sulfides from aryl triflates.[53] More recently, in 2001, Schöpfer and Schlapbach reported a general palladium catalyzed method for the synthesis of aryl sulfide from aryl iodides, in toluene, using DPEPhos as the ligand.[47]

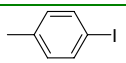
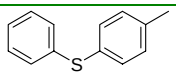
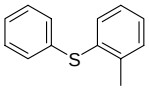
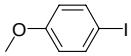
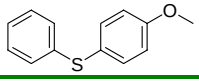
5.3 Optimization and Development of Aryl-Sulfur Bond Formation Using Copper(I) Catalysts

We first chose to study the efficacy of copper(I)–based catalysts in the cross-coupling reaction between iodobenzene and *n*-butanethiol, in toluene, using [Cu(phen)(PPh_3)Br] and [Cu(neocup)(PPh_3)Br] complexes. We had previously shown the utility of these complexes in the formation of aryl-nitrogen, aryl-oxygen, aryl-acetylene bonds. Our initial choice for the base was Cs_2CO_3. We based this choice on the observations by Buchwald, Snieckus, and our group that Cs_2CO_3 was essential in copper-

based protocols for the formation of aryl-oxygen bonds.[16,27,34] When we replaced Cs_2CO_3 with NaO*t*-Bu, we observed complete consumption of the starting materials when [Cu(neocup)(PPh_3)Br] was the catalyst. However, if [Cu(phen)(PPh_3)Br] was used as the catalyst, GC traces showed the presence of starting materials in trace amounts in the same time period.[1] Trace amounts of starting materials were also observed if KO*t*-Bu was used as the base.

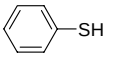
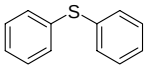
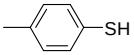
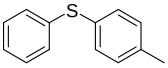
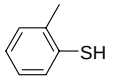
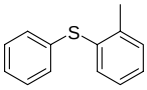
The coupled product was formed only in trace amounts if bromobenzene was used indicating that the reaction was selective to iodides. As a part of our control experiments, we replaced [Cu(neocup)(PPh_3)Br] with 10 mol% of CuI, CuI/neocuproine or CuCl/neocuproine as the catalyst. We found that CuI/neocuproine was as effective as [Cu(neocuproine)(PPh_3)Br]. However, only a trace amount of the coupled product was observed if CuI alone was used as the catalyst. This indicated that neocuproine was essential to accelerate the reaction. Also, GC traces indicated the presence of 5 mol% of iodobenzene and *n*-butanethiol if CuBr or CuCl/neocuproine was the catalyst. Other bases like K_3PO_4, KO*t*-Bu, triethylamine and K_2CO_3 were ineffective in the coupling of iodobenzene with *n*-butanethiol. Based on the aforementioned observations, we decided to use CuI (10 mol%)/neocuproine (10 mol%) as the catalyst, NaO*t*-Bu as the base and toluene as the solvent, as a standard protocol for the formation of aryl-sulfur bonds. These procedures were optimized by Craig Bates in our group. He was successful in using the same optimization procedures and protocol in designing the cross-coupling of substituted aryl iodides with thiophenols, to synthesize a range of diaryl sulfides.[8] (Examples in Tables 5.1 and 5.2)

Table 5.1: Reactions of Substituted Aryl Iodides with Thiophenol.

Entry	Aryl Iodide	Product	Isolated Yield* (%)
1			94
2			96
3			96

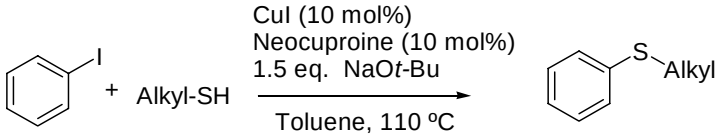
* NaO*t*-Bu as the base. For all entries, catalyst loading: 10 mol% CuI and 10 mol%, neocuproine , Solvent: toluene, Temperature: 110 °C

Table 5.2: Reactions of Aryl Iodides with Substituted Thiophenol.

Entry	Thiophenol	Product	Isolated Yield* (%)
1			98
2			97
3			95

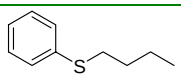
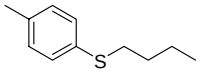
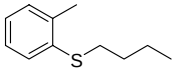
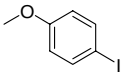
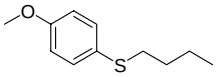
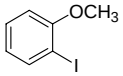
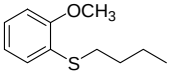
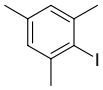
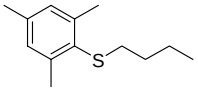
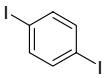
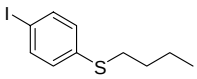
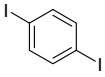
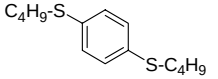
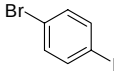
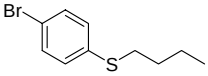
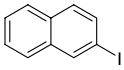
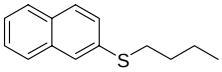
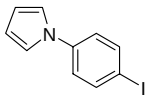
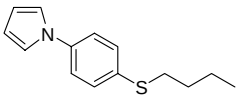
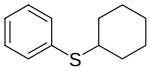
* NaO*t*-Bu as the base. For all entries, catalyst loading: 10 mol% CuI and 10 mol%, neocuproine , Solvent: toluene, Temperature: 110 °C

In brief, using our protocol, we were also able to couple alkyl aryl thiols with a range of aryl iodides in excellent yields (Scheme 5.1 & Table 5.3). The protocol is successful with the following; a) sterically bulky iodides (entry 6), b) diiodo-substituted benzene (entry 8), c) *n*-heteroatom substituted aryl iodide (entry 11) and d) cyclic thiols. It is also palladium-free and avoids the use of expensive and/or air-sensitive ligands.



Scheme 5.1: General Protocol for the Cross-Coupling of Alkyl thiols with Aryl Iodides

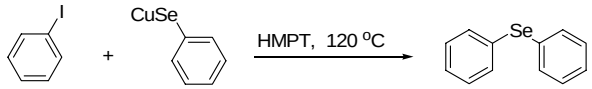
Table 5.3: Reactions of Iodobenzene with readily available Mercaptans.

Entry	Aryl Iodide	Product	Isolated Yield* (%)
1			95
2			94
3			93
4			95
5			84
6			98
7			88
8			98
9			92
10			95
11			95
12			77

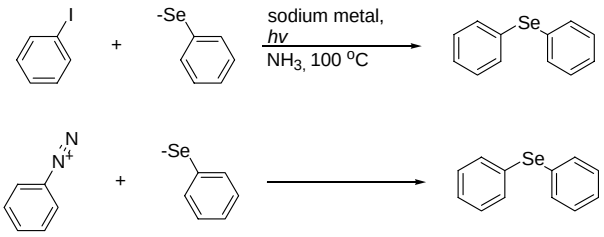
* NaO*t*-Bu as the base. For all entries, catalyst loading: 10 mol% CuI and 10 mol%, neocuproine , Solvent: toluene, Temperature: 110 ºC

5.4 Existing Methods for the Synthesis of Aryl-Selenium Bonds

Various synthetic methods for the formation of diaryl selenides have been reported in the literature.[2,5,44,51] Earlier methods often require photochemical or harsh reaction conditions such as the use of polar, toxic solvents such as HMPA and high reaction temperatures.[38,48](see Scheme 5.2) Other reported protocols include the reaction of aryl halide and benzeneselenate anion in liquid ammonia under UV light and the reaction of sodium selenide with arenediazonium salts.[4,41-43,46](see Scheme 5.3)



Scheme 5.2: Synthesis of Diaryl Selenides using the Suzuki Protocol



Scheme 5.3: Synthesis of Diaryl Selenides using Methods by Pierini and Rossi

In recent years, only a handful of reports have appeared in the literature with synthetic protocols for the formation of aryl-selenium bonds that are general, mild and tolerant. In 1985, Cristau and co-workers first showed that aryl selenides can be obtained by a cross-coupling reaction of aryl halides and sodium benzeneselenolate using Ni(II)-based catalysts.[14] In 2000, Millois and Diaz modified and extended Cristau's method to

accommodate diaryl diselenide as a starting material instead of sodium benzeneselenolate.[36] Very recently, the groups of Nishiyama and Beletskaya have independently reported protocols for the cross coupling reaction of aryl iodides and $PhSeSnBu_3$ using palladium-based catalysts.[9,37]

With the success of the earlier coupling of nucleophiles with alkyl aryl sufides, we attempted to extend the utility of the copper-based catalysts for the formation of aryl-selenium bonds.

5.5 Optimization of Aryl-Selenium Bond Formation Using Copper(I) Catalysts

We began the investigation of the cross-coupling reaction between aryl iodides and phenyl selenol using 10 mol% CuI/neocuproine with NaO*t*-Bu as the base and toluene as the solvent. Using this protocol the reaction between iodobenzene and phenyl selenol was complete in 24 h. The ligand, neocuproine, was found to be essential for the reaction, since its absence gave no conversion to the desired product. If in the reaction protocol, neocuproine was replaced by phenanthroline, was obtained in a lower yield (70 % by GC). Moreover, the reaction with the well-defined complex [Cu(neocup)(PPh_3)Br] showed complete conversion to the product after the same period of time. We chose to use CuI/neocuproine as our catalyst instead of the well-defined [Cu(neocup)(PPh_3)Br], since it gave identical results and dispenses with the need to synthesize the complex. After having established the efficacy of the CuI/neocuproine catalytic system for the

formation of aryl-selenium bonds, we then studied the effect of the base on these reactions (see Table 5.4).

Table 5.4: Optimization of the Reaction between Aryl Iodide and Phenyl Selenol

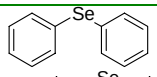
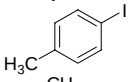
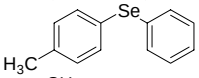
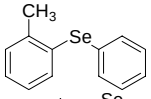
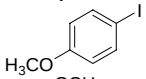
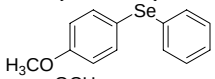
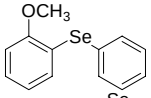
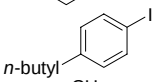
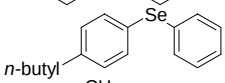
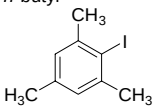
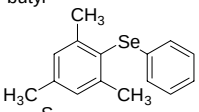
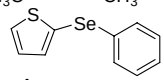
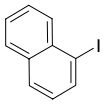
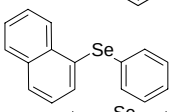
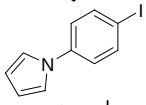
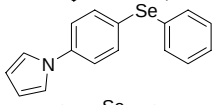
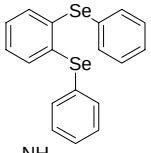
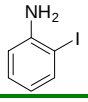
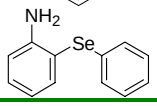
Entry	Base	GC Yield* (%)
1	CsF	<5
2	Cs_2CO_3	<5
3	KO*t*-Bu	<10
	K_2CO_3	70
5	Na_2CO_3	70
6	K_3PO_4	82
7	NaO*t*-Bu	92

* For all entries, catalyst loading: 10 mol% CuI and 10 mol%, neocuproine , Solvent: toluene, Temperature: 110 ^oC. We made use of 1 mmol of iodobenzene and 1 mmol of *n*-butanethiol in the reactions.

We found that NaO*t*-Bu was the most effective base for this reaction. In contrast, KO*t*-Bu was not an effective base in our protocol, similar to what we had observed for the formation of aryl-sulfur bonds. Milder bases such as K_3PO_4, K_2CO_3 and Na_2CO_3 provided diphenyl selenide in moderate yields. Other mild bases such as CsF and Cs_2CO_3 were ineffective. In our protocol, we then replaced iodobenzene with bromobenzene. By GC, in addition to both the starting materials, significant amount of diphenyl diselenide was observed, presumably from the oxidation of phenyl selenol. This indicated that the reaction was selective to iodides.

Using our protocol, we were able to couple phenyl selenol with electron-rich aryl iodides in very good yields (Table 5.5). We were able to couple sterically hindered iodides such as those with *ortho*-functionalities (entries 3, 5, 7 & 11), as well as aryl iodides containing heteroatoms (entry 8 & 10). When *o*-iodoaniline was used as the aryl halide, in addition to the desired selenide, we observed products arising from the self-coupling of *o*-iodoaniline. This problem also persisted with K_3PO_4. However, when K_2CO_3 was used as the base, we were able to isolate 1-amino-2-phenylselanylbenzene in 60 % yield (entry 12). With electron-poor aryl iodides, in addition to the desired diaryl selenides, we observed diaryl diselenides if NaO*t*-Bu or K_3PO_4 was used. In addition, with NaO*t*-Bu, transesterifcation products were observed when aryl halides with ester groups were used. We found that these problems can be avoided if K_2CO_3 was used instead of NaO*t*-Bu or K_3PO_4. Using this modified protocol we were able to obtain a variety of diaryl selenides from electron-poor aryl halides (Table 5.6). The protocol tolerates even base sensitive groups such as esters and ketones (entries 3, 4, 6). Similar to the previously described thiol coupling the protocol allows the coupling of a) sterically bulky iodides (entry 7), b) *ortho* diiobenzene (entry 11), c) n-heteroatom substituted aryl iodide (entry 10). It is a palladium-free methodology that avoids the use of $PhSeSnBu_3$ as a aromatic selenium source.

Table 5.5: Reaction of electron-rich Aryl Iodides and Phenyl Selenol

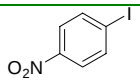
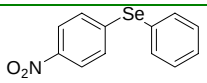
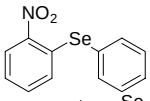
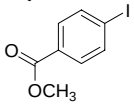
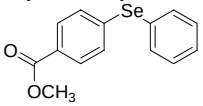
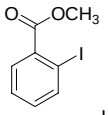
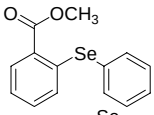
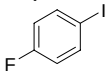
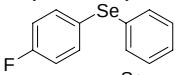
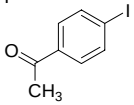
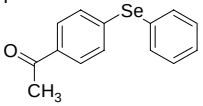
Entry	Aryl Iodide	Product	Isolated Yield (%)
1			90
2			84
3			80
4			88
5			78
6			80
7			82
8			68
9			82
10			76
11			81
12			60*

*K_2CO_3 was used instead of NaO*t*-Bu as the base. For all entries, catalyst loading: 10 mol % CuI & 10 mol % neocuproine, solvent: toluene, temperature: 110 ^oC

5.6 Conclusions

In summary, we have described above general synthetic protocols for the formation of aryl alkyl sulfides and diaryl selenides, using copper(I)-catalysts. In both of these protocols, we recommend the use of 10 mol% CuI, 10 mol% neocuproine, NaO*t*-Bu as the base, and toluene as the solvent. In the protocol for the formation of diaryl selenides from electron-poor aromatic iodides, we recommend the use of K_2CO_3 in the place of NaO*t*-Bu. These protocols are palladium-free and avoid the use of expensive and/or air-sensitive ligands, and make use of readily available starting materials.

Table 5.6: Reaction of Electron-Poor Aryl Iodides and Phenyl Selenol

Entry*	Aryl Iodide	Product	Isolated Yield (%)
1			75
2			81
3			78
4			76
5			92
6			78

* For all entries, catalyst loading: 10 mol % CuI & 10 mol % neocuproine, solvent: toluene, temperature: 110 ^{o}C

5.7 References

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Chapter 6

Conclusions and Future Work

6.1 Conclusions

In this dissertation we started with the aim to develop a range of stable, well-defined and soluble copper(I) complexes for potential use in cross-coupling reactions. A series of well-defined mononuclear and polynuclear copper(I) complexes stabilized by a varied combination of the following ligands (i.e. triphenylphosphine, 1,10-phenanthroline, neocuproine, diimines, halides, nitrate) were synthesized. These complexes were screened for their catalytic activities in the formation of aryl-oxygen, aryl-nitrogen, aryl-sulfur and aryl-selenium bonds. Geometrical parameters (i.e bite angles and Cu-P bond distance) of all the mononuclear complexes were gathered and analyzed. Further work is underway in our research group to establish a correlation between the longer Cu-P distances observed in chelating copper(I) complexes to the possible lower dissociation temperatures and increased lability of the triphenylphosphine ligands.

The copper(I)-phosphine complexes were synthesized by the modification of Jardine`s protocol used for the synthesis of $[Cu(PPh_3)_2NO_2]$. This synthesis was found to be more versatile than the route proposed by Costa. It allowed the formation of the copper(1) phosphine complexes (i.e $[Cu(PPh_3)_3Br]$, $[Cu(PPh_3)_3Cl]$, $[Cu(PPh_3)_2NO_3]$ in 10 minutes at room temperature, via an *in situ* reduction of the copper(II) halides.

Substitution of the complexes [$Cu(PPh_3)_3Br$] and [$Cu(PPh_3)_2NO_2$] thereafter lead to the facile conversion to a range of Cu(I)-phenanthroline complexes (**5-10**, Chapter 2). Bis(triphenylphosphine) complexes of neocuproine and bulkier diimines which we were unable to synthesize using either [$Cu(PPh_3)_2NO_3$] or [$Cu(PPh_3)_3Br$], were made by an alternative protocol involving the use of [$Cu(CH_3CN)_4$]PF_6, as starting material.

[$Cu(PPh_3)_3Br$] and [Cu(neocup)(PPh_3)Br] were shown to be effective catalysts for the formation of diaryl ethers from electron-rich bromides and phenols. In contrast to previously reported Cu(I) catalysts used for diaryl ether formation like Cu(I) triflate, both these complexes were easy to prepare and air-stable. We have also shown that electron-deficient aryl bromides could couple with substituted phenols in the presence of 3 eq. Cs_2CO_3, with NMP as the solvent without the need for any catalysts. With electron-rich aryl bromides it was interesting to note that the protocol with [$Cu(PPh_3)_3Br$] allowed the formation of sterically hindered compounds such as 1-Methyl-2-(2-methylphenoxy)benzene and 2-*o*-tolyloxy-benzoic acid methyl ester. These compounds are presently eluded by current palladium-catalyzed cross coupling reactions. The use of the complex [Cu(neocup)(PPh_3)Br] was an improvement to our earlier discovery as the catalyst loading could be reduced to 10 mol%. This protocol also allowed the coupling of aryl bromides with *ortho* functionalities.

In addition, we also extended the use of complexes [$Cu(PPh_3)_3Br$] and [Cu(neocup)PPh_3Br] to the formation of aryl-nitrogen bonds under mild conditions. [$Cu(PPh_3)_3Br$] was found to be selective for aryl iodides, whilst [Cu(neocup)PPh_3Br]

could be used, albeit under prolonged reaction times, to couple aryl bromides and aryl chlorides. The synthetic protocol with [$Cu(PPh_3)_3Br$] was found to tolerate various functional groups. It was also shown to be valuable by others[2] in the synthesis of triphenylamines in a one pot reaction from aryl iodide and aniline, in presence of KO*t*-Bu. Optimization and controls carried out with [$Cu(neocup)PPh_3Br$] as well as with a range of other N-based chelating ligands showed that a possible degradation of the catalysts took place as from 3-6 h in a typical amination reaction between diphenyl amine and iodo benzene, in presence of KO*t*-Bu as the base. Although we could not understand the origins of this loss of catalytic activity in the amination reaction we interpreted these results, as well as other data indicating unaccounted loss of iodobenzene, as evidence of the N-based chelating catalysts acting as precursors to promote other competing side reactions. An understanding of this behaviour is invaluable to building more robust and active copper(I) catalysts in the future.

We have also developed general synthetic protocols for the formation of aryl alkyl sulfides and diaryl selenides, using copper(I)-catalysts. In both of these protocols, we recommended the use of 10 mol% CuI, 10 mol% neocuproine, 1.5 eq. of NaO*t*-Bu as the base, and toluene as the solvent. In the protocol for the formation of diaryl selenides from electron-poor aromatic iodides, we recommend the use of K_2CO_3 in place of NaO*t*-Bu.

All the above protocols for aryl-O, N, S and Se described above are palladium-free and avoid the use of expensive and/or air-sensitive ligands, and make use of readily available starting materials.

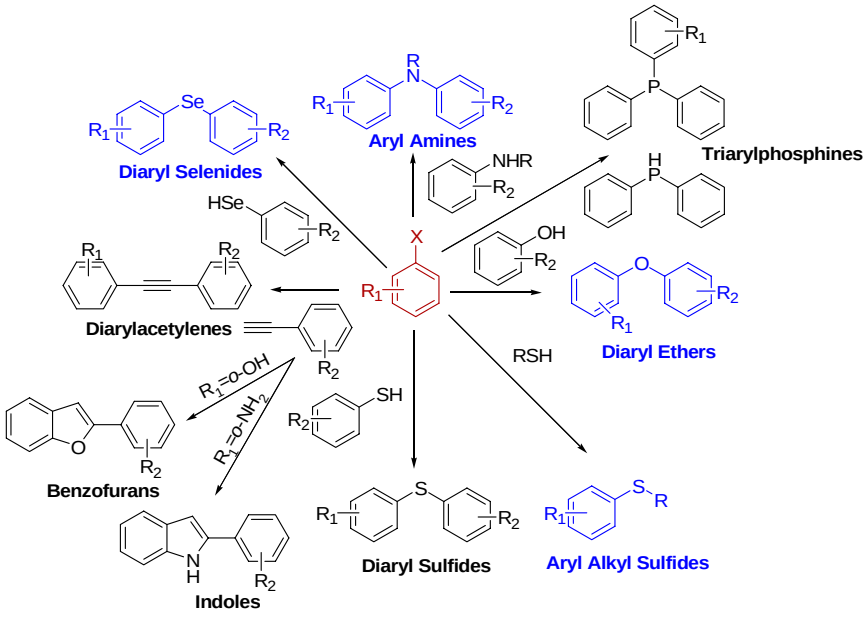
6.1 Future Work

The discovery of new methodologies for bond formation reactions using copper catalysts have been described in this dissertation. A number of other bond formation reactions catalyzed by copper(I)-based catalysts have also been developed and published by other colleagues in our research groups (i.e copper(I) catalyzed synthesis of benzofurans and triarylphosphines)[1,3]. Other works are presently in progress to develop new protocols for substrates such as indoles or benzothiophenes. Scheme 6.0 below summarizes some of the achievements as well as future work in progress in our research group. In addition to development of new protocols, a number of other projects are possible offshoots of the bulk of data that have been gathered by our research group. They are summarized below:

a). In-depth mechanistic studies of copper(I) catalyzed formation of Aryl-O, Aryl-N, Aryl-S and Se reactions. The use of Cu and P NMR as tools to investigate both the fate of the well-defined copper complexes and the lability of the triarylphosphines are possible options in this endeavour. The existence of well-defined copper(I)-aryl selenolates and copper-phenoxides can also be used to develop a better understanding of the mechanism of these reactions.

b). Comparison and understanding of the differences in yields from amination reactions is another project which is already being tackled in our research group. Redox studies of the copper(I)-phosphine and copper(I)-phenanthroline and neocuproine

complexes, P NMR monitoring of dissociation constants of the ligated phosphines, are in progress.



Scheme 6.0: Cross-Coupling Reactions using Copper(I) Chemistry in the D.V. Group

6.2 References

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(2) Kelkar, A.; Nandkumar, M. P.; Chaudari, R. V. "Copper-Catalyzed Amination of Aryl Halides: Single Step Synthesis of Triarylamines," *Tetrahedron. Lett.* **2002**, *43*, 7143-7146.

(3) Van Allen, D.; Venkataraman, D. "Copper-Catalyzed Synthesis of Unsymmetrical Triarylphosphines," *J. Org. Chem.* **2003**, *68*, 4590-4593.

Experimental

Synthesis of Copper(I)-Phosphine and Copper(I)-Phenanthroline Complexes

X-Ray Studies:

The X-ray crystallographic studies were performed using an Nonius Kappa CCD diffractometer and graphite monochromated MoK_α radiation (λ=0.71073 Å). Data were collected at 23±2°C for $\theta_{MoK\alpha} \leq 25°$. All data were included in the refinement. The structures were solved by direct methods and difference Fourier techniques and were refined by full-matrix least-squares. Refinements were based on F^2 and computations were performed on a 600 MHz Pentium III computer using SHELXS-86 for solution and SHELXL-97 for refinement. All of the non-hydrogen atoms, except those of disordered solvents, were refined anisotropically. The hydrogen atoms of the OH groups were located from difference Fourier techniques and refined isotropically, except for the hydrogens of water in 2 which were not included in the calculations. The hydrogens attached to disordered atoms were not included in the calculations. The remaining hydrogen atoms were included in the refinement as isotropic scatterers riding in either ideal positions or with torsional refinement (in the case of methyl hydrogen atoms) on the bonded atoms. The final agreement factors are based on the reflections with $I \geq 2\sigma_I$. Crystallographic data are summarized in Table 6.0.

Copper(I) Phosphine Complexes

Synthesis of bromotris(triphenylphosphine) copper(I): (Figure 2.2)

In an Erlenmeyer flask equipped with a Teflon stir bar, methanol (100 mL) was heated to boiling and triphenylphosphine (Acros, 7.9 g, 30.4 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, $CuBr_2$ (Acros, 99+%, 1.6 g, 7.6 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 stirred for 10 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 (5.73 g, 85% yield, mp. 164 ^{o}C). It can also be recrystallized as white needles from hot methanol. Anal calc. for $[Cu(PPh_3)_3Br]$: C, 69.71; H, 4.64; Cu, 6.83. Found: C, 69.67; H, 4.66; Cu, 6.20. We wish to point out that copper was analyzed using colorimetry, since there was a large interference from phosphorous in the ICP. For the same reason, we were unable to obtain a satisfactory P analysis. ^{31}P NMR (121 MHz) δ -0.5 (s). Crystal data for compound: Trigonal, *P*-3 (no. 143), *a*=19.2150(3)Å, *b*=19.2150(3)Å, *c*=10.6220(3)Å, α=90.00°, β=90.00°, γ=120.00°, *V*=3396.4 (3) Å^3, D_c=1.364 g cm^{-3}, *Z*=3, number of unique reflections=7487, number of parameters=519, *R*1 (for $F_o > 4\ \sigma$)=0.0397 and 0.0581 (all data), *wR*2 (for $F_o > 4\ \sigma$)=0.1040 and 0.1183 (all data), GOF=0.868, residual electron density=+0.340. 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). Selected bond lengths (Å): Cu-Br: 2.466 (3), Cu-P: 2.323 (3). Although 1 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 had to be stored in a dry atmosphere as it is extremely hygroscopic.

Synthesis of chloro tris(triphenylphosphine) copper(I): (Figure 2.1)

In an Erlenmeyer flask equipped with a Teflon stir bar, methanol (100 mL) was heated to boiling and triphenylphosphine (Acros, 2.46 g, 9.4 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, $CuCl_2$ (Acros, 99+%, 0.4 g, 2.35 mmol) was added as a solid, in portions. No special precautions were taken for the exclusion of air. Upon addition of the copper chloride, a white precipitate was formed. After the completion of the addition, the contents were stirred for 10 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 (1.18 g, 95% yield, mp. 170 ^oC). It can also be recrystallized as white needles from hot methanol. Anal. calcd. for [$Cu(PPh_3)_3Cl$]: C, 73.21; H, 5.12; Cu, 7.17. Found: C, 73.36; H, 5.26; Cu, 7.50. X-Ray data given in Table 6 below. Selected bond lengths (Å): Cu-Cl: 2.350 (2), Cu-P: 2.349 (13).

Synthesis of nitrato bis(triphenylphosphine) copper(I): (Figure 2.4)

In an Erlenmeyer flask equipped with a Teflon-coated stir bar, methanol (100 mL) was heated to boiling and triphenylphosphine (Alfa Aesar, 24.22 g, 92.34 mmol) was slowly added to the stirring methanol. After the complete dissolution of triphenylphosphine, $[Cu(NO_3)_2].2.5H_2O$ (Fisher Scientific, 7.16 g, 30.78 mmol) was added in small portions. No special precautions were taken for the exclusion of air. Upon addition of the copper(II) nitrate, a white precipitate formed. After the completion of the addition, the contents were stirred for 30 minutes 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 $[Cu(PPh_3)_2NO_3]$ (12.37 g, 62% yield). m.p. : 238-240 ^oC. The cell constants, contents and the space group are identical to that of the already reported structure of $[Cu(PPh_3)_2NO_3]$ (Cambridge Structural Database Refcode-NITPPC01). Selected bond lengths (Å): Cu-O: 2.214 (7), Cu-P: 2.237 (3).

Synthesis of bromo bis(triphenylphosphine) copper: (Figure 2.3)

$[Cu(PPh_3)_3Br]$ (1.0 g, 1.07 mmol) and 8-hydroxyquinoline (Acros, 0.14 g, 1 mmol). were added in an Schlenk flask equipped with a Teflon stir bar and filled with THF (15 mL). After the complete dissolution of both the compounds, K_2CO_3 (Aldrich, 99+%, 0.27 g, 2.00 mmol) was added as a solid, in portions. The flask was purged under

a stream of nitrogen and stirred over a magnetic plate at room temperature for 2 h. After the said time, diethyl ether (20 ml) was added and the solution was filtrated to remove the excess base. A yellow crystalline solid appeared in the filtrate which was revealed by melting point to be unreacted 8-hydroxyquinoline. This ligand was recovered quantitatively (0.13g). The filtrate solution was left overnight in the fume hood and the next day clear transparent crystals were spotted in the flask. These crystals were scraped out from the flask and washed with ethanol (10 ml) followed by ether (10 ml). X-Ray data was collected for this compound (0.57 g, 90 % yield) and is tabulated below (Table 6). Selected bond lengths (Å): Cu-Br: 2.341 (3), Cu-P: 2.264 (4).

Synthesis of copper-diphenylphosphinoethane complexes: (Table 2.3: Figures 15 and 16)

In an Erlenmeyer flask, CuBr (Aldrich, 0.7 g, 4.8 mmol) was added followed by DPPE (Acros, 4.0 g, 10 mmol). Chloroform (50 ml) was added to the flask and the contents stirred for a 24 h. Hexanes (100 ml) was added after 24 h, and a colourless precipitate instantly appeared. This precipitate was filtered and then crystallized from a 40 ml solution of hexane/chloroform (1:1). The crystals (77% yield) were filtered and recystallized in THF. Melting point: 210 ^{o}C. X-Ray crystallographic data was collected for the compound (**15**) is tabulated below. Another approach was taken to prevent aggregation into polynuclear complexes: In an Erlenmeyer flask, 20 ml of chloroform was added, followed by [$Cu(PPh_3)_3Br$] (0.930 g, 1mmol). Using a 50 ml addition funnel, DPPE (0.19 g, 0.5 mmol) was slowly added to the stirring solution of the catalyst over 24 h. A white precipitate was observed after addition. This precipitate was washed with

ethanol and ether, and crystallized from hexane/chloroform (62% yield). X-Ray data crystallographic gathered for this compound (**16**) is given in Table 6 below.

Synthesis of bridged copper(I)- tri-*o*-tolyl-phosphane.complex: (see Figure 2.16)

In an Schlenk flask purged with argon equipped with a Teflon stir bar, dry methanol (20 mL) was heated to boiling and tri-*o*-tolyl-phospane (Acros, 3.3 g, 10.92 mmol) was slowly added to the stirring methanol. After the complete dissolution of *o*-tolyl phosphine, $CuBr_2$ (Acros, 99+%, 0.61 g, 2.73 mmol) was added as a solid, in portions. Care was taken to add the copper salt under a constant stream of argon. Upon addition of the copper bromide, a yellowish-white precipitate was formed. After addition, the contents were stirred for 10 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 followed by diethyl ether. The resultant white solid was dried under dynamic vacuum to give the compound (Figure 2.16). The white solid was recrystallized from a 10:1 solution of hexane and dichloromethane. X-Ray data was collected for the compound (58%) and is tabulated in Table 6 below.

Synthesis of copper(I)-triphenylphosphine bromide polynuclear compounds: (Figure 2.15)

In an Schlenk flask purged with argon equipped with a Teflon stir bar, dry methanol (20 mL) was heated to boiling and triphenylphosphine (Acros, 1.04 g, 4 mmol) was slowly added to the stirring methanol. After the complete dissolution, 1,2-dimethyl

diphenyl diimine ligand (made available by Prof B Coughlin, PSE, UMASS, 0.236 g), $CuBr_2$ (Acros, 99+%, 0.61 g, 2.03 mmol) were added as a solids, in two portions. Care was taken to add the copper salt under a constant stream of argon. Upon addition of the copper bromide, a white precipitate was formed. After the completion of the addition, the contents were stirred for 10 min and the flask was refluxed for 1 1/2 h after which it 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 followed by diethyl ether. The resultant white solid was dried under dynamic vacuum to give compound. The white solid (32%) was recrystallized from a 1:1 solution of hexane and dichloromethane. X-Ray data was collected for the compound and is tabulated in Table 6 below.

Copper(I)-Phenanthroline Complexes

Synthesis of [Cu(Neocup)(PPh_3)Br]: (Figure 2.5) In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, Neocuproine hydrochloride (0.244 g, 1 mmol) and Na_2CO_3 (0.116g, 1 mmol) was added to dichloromethane (50 mL). After 2 hrs the mixture was filtered to remove the inorganic salts and the solvent removed under dynamic vacuum to yield neocuproine as a white solid (0.149 g, 72% yield). Then [Cu (PPh_3)$_3$Br] (0.66 g, 0.71 mmol) was dissolved in 50 mL of chloroform. The complex dissolved immediately. To this stirring chloroform solution, neocuproine (0.149, 0.71 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 (0.33g, 78% yield) Crystal data for 1: Monoclinic, *C*2/*c*, a=23.882 (3) Å, b=9.553 (3) Å, c=24.780 (3) Å, a=90°, b=98.091 (5)°, c=90.00°, V=5597.20 (5) $Å^3$, D_c=1.364 g cm^{-3}, Z=8, number of unique reflections=2599, number of parameters=334, R1 (for $F_o > 2$)=0.1224 (all data), wR2 (for $F_o > 4$)=0.2345, GOF=1.138, residual electron density=+0.623. Selected bond lengths (Å): Cu-Br: 2.458 (3), Cu-P: 2.207 (5), Cu1-N1: 2.114 (12), Cu1-N2: 2.127 (12).

Synthesis of [Cu(Phen)(PPh_3)Br]: (Figure 2.6) In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, tris(triphenylphosphine)copper(I)bromide (0.59g, 0.5 mmol) was added to chloroform (50 mL). After complete dissolution, 1,10-phenanthroline (0.07g, 0.5 mmol) was then added. The colorless solution immediately changed to orange. The contents of the flask were allowed to stir for 25 minutes at room temperature. Afterwards the solvent was removed under dynamic vacuum (rotovap) to afford an orange-yellow solid. Recrystallization was achieved by dissolving the solid 60 mL of dichloromethane and layered with 20 mL of diethylether. Crystal data for 1: Triclinic, *P*-1, a=8.394 (3) Å, b=9.366 (3) Å, c=18.205 (3) Å, a=78.55°, b=77.04°, c=70.39°, V=1302.26 (5) $Å^3$, D_c=1.364 g cm^{-3}, Z=3, number of unique reflections=7487, number of parameters=317, R1 (for $F_o > 2$)=0.0631(all data), wR2 (for $F_o > \sigma 4$)=0.0883, GOF=1.075, residual electron density=+0.416. The cell constants, contents and the space group are identical to that of the already reported structure of [Cu(Phen)(PPh_3)Br] (Cambridge Structural Database). Selected bond lengths (Å): Cu-Br: 2.442 (5), Cu-P: 2.183 (9), Cu1-N1: 2.084 (2), Cu1-N2: 2.101 (2).

Synthesis of [Cu(Bipy)(PPh_3)Br]: (Figure 2.7) In an Erlenmeyer flask equipped with a Teflon-coated magnetic stir bar, tris(triphenylphosphine)copper(I) bromide (7.45 g, 8.00 mmol) was added to chloroform (100 mL). After complete dissolution, 2,2'-bipyridine (1.27 g, 8.00 mmol) was then added. The colorless solution immediately turned orange. The contents of the flask were allowed to stir for 30 minutes at room temperature. Afterwards the solvent was removed *in vacuo* to afford an orange solid. Recrystallization was achieved by layering 80 mL of diethyl ether onto a solution of the solid dissolved in 40 mL of dichloromethane (3.06 g, 68% yield). m.p.: 215-217 ^{o}C. The cell constants, contents and the space group are identical to that of the already reported structure of [Cu(Bipy)(PPh_3)Br] (Cambridge Structural Database Refcode-COYNOT). Selected bond lengths (Å): Cu-Br: 2.415 (10), Cu-P: 2.204 (16), Cu1-N1: 2.071 (5), Cu1-N2: 2.102 (5).

Synthesis of [Cu(Phen)(PPh_3)$_2$$NO_3$]: (Figure 2.8) In an Erlenmeyer flask equipped with a Teflon-coated magnetic stir bar, Nitratobis(triphenylphosphine)copper(I) (977 mg, 1.50 mmol) was added to chloroform (20 mL). After complete dissolution, triphenylphosphine (393 mg, 1.50 mmol), followed by 1,10-phenanthroline (270 mg, 1.50 mmol) was then added. The colorless solution immediately turned yellow. The contents of the flask were allowed to stir for 30 minutes at room temperature. Afterwards the solvent was removed in vacuo to afford a yellow solid. Recrystallization was achieved by vapor diffusion of diethyl ether into a solution of the solid dissolved in 30 mL of dichloromethane (931 mg, 75% yield). m.p.: 202-204 ^{o}C. Crystal data for compound:

Table 6.0: Crystallographic Data for Mononuclear and Polynuclear Copper-Phosphine Complexes

Compound (see Chapter 2)	2.2	2.1	2.4	2.3	15 in Table 2.3	16 in Table 2.3	2.16	2.15
Formula	$[Cu(PPh_3)_3Br]$	$[Cu(PPh_3)_3Cl]$	$[C_{36}C_{30}CuBrP_2]$	$[C_{36}H_{30}CuNO_3P_2]$	$[C_{78}H_{84}Cu_2Br_2P_6]$	$[C_{84}H_{96}Cu_3Br_2P_6]$	$[C_{42}H_{42}Br_2Cu_2P_2]$	$[C_{72}H_{60}Br_4Cu_4P_4]$
Formula Weight	930.326	885.875	668.034	650.134	1677.898	1444.917	895.646	1622.968
Crystal System	Triclinic	Triclinic	Triclinic	Monoclinic	Triclinic	Monoclinic	Triclinic	Monoclinic
Space Group	*P*-3	*P*3	*P*-1	*C* 2/*c*	*P*-1	*P* 2_1/a	*P*-1	*C* 2/*c*
a (Å)	19.213 (5)	19.283 (4)	9.021 (2)	24.550 (2)	11.561 (7)	18.891 (3)	9.220 (6)	25.770 (5)
b (Å)	19.213 (5)	19.283 (4)	13.247 (4)	9.209 (7)	12.244 (10)	16.794 (2)	10.213 (7)	16.113 (4)
c (Å)	10.627 (3)	10.473 (2)	15.379 (4)	15.466 (10)	15.796 (2)	25.309 (4)	11.299 (9)	17.833 (4)
α (^{0})	90.00	90.00	115.51 (2)	90.00	78.071 (4)	90.00	101.535 (3)	90.00
β (^{0})	90.00	90.00	89.710 (10)	116.566 (4)	71.866 (4)	109.898 (5)	100.731 (3)	110.913 (10)
γ (^{0})	120.00	120.00	110.140 (10)	90.00	68.853 (5)	90.00	99.223 (6)	90.00
V (Å^3)	3396.40 (3)	3373.03 (12)	1534.90 (7)	3127.50 (4)	1970.80 (3)	7631.20 (2)	1002.50 (10)	6917.30 (3)
Z	3	4	2	4	2	4	1	4
D_{calc} (Mg/m^{-3})	1.364	1.744	1.446	1.381	2.828	1.258	1.484	1.558
Total No. Parameters	519	532	361	181	221	820	217	380
Total Reflns	7487	7759	2567	2773	3583	13370	1853	6029
GOF	0.868	0.868	1.18	1.17	1.126	0.928	1.023	1.068
R[a]	0.0581	0.0888	0.1497	0.0903	0.1741	0.0424	0.072	0.0408
R_w[b]	0.1183	0.1685	0.2338	0.1653	0.4050	0.0994	0.1694	0.0839

monoclinic, $P2_1$, a=10.0266 (2) Å, b=19.7098 (5) Å, c=10.6355 (3) Å, a=90°, b=103.2034 (9)°, c=90.00°, V=2046.25 (9) $Å^3$, D_c=1.348 g cm^{-3}, Z=2, number of unique reflections=3523, number of parameters=514, R_1 (for $F_o > 2$)=0.0228 (all data), wR2 (for $F_o > 4$)=0.0593. Selected bond lengths (Å): Cu1-P1: 2.253 (10), Cu1-P2: 2.284 (10), Cu1-N1: 2.082 (3), Cu1-N2: 2.101 (3).

Synthesis of $[Cu(C_{16}H_{16}N_2)(PPh_3)_2]PF_6$:(Figure 2.9) In an Erlenmeyer flask equipped with a Teflon-coated magnetic stir bar, Nitratobis(triphenylphosphine)copper(I) (977 mg, 1.50 mmol) was added to chloroform (20 mL). After complete dissolution, triphenylphosphine (393 mg, 1.50 mmol), followed the diimine (made available by Prof B Coughlin, PSE, UMASS) (270 mg, 0.354 mmol) was then added. The colorless solution immediately turned yellow. The contents of the flask were allowed to stir for 30 minutes at room temperature. Afterwards the solvent was removed in vacuo to afford a yellow solid. Recrystallization was achieved by vapor diffusion of diethyl ether into a solution of the solid dissolved in 30 mL of dichloromethane (931 mg, 85% yield). m.p.: 205-207 °C. Crystal data for compound: monoclinic , $P2_1/c$, a=13.897 (2) Å, b=13.799 (3) Å, c=25.915 (2) Å, a=90°, b=104.291 (9)°, c=90.00°, V=4538.35 (7) $Å^3$, D_c=1.297 g cm^{-3}, Z=4, number of unique reflections=3523, number of parameters=559, R1 (for $F_o > 2$)=0.0591 (all data), wR2 (for $F_o > 4$)=0.1010. The other diimines (also supplied by Prof B. Coughlin, PSE, UMASS) were made from $[Cu(CH_3CN)_4]PF_6$ in presence of 4 eq. of phosphine using the same procedures detailed above. The crystal data of both the complexes (**Figures 2.13 and 2.14, Chapter 2**) were compared and successfully matched with the cell constants, contents and the space group of similar structures already reported

in the Cambridge Structural Database. Selected bond lengths for compound in Figure 2.9 (Å): Cu1-P1: 2.262 (19), Cu1-P2: 2.269 (2), Cu1-N1: 2.091 (6), Cu1-N2: 2.091 (5). Selected bond lengths for compound in Figure 2.13 (Å): Cu1-P1: 2.294 (2), Cu1-P2: 2.313 (2), Cu1-N1: 2.129 (6), Cu1-N2: 2.097 (6). Selected bond lengths for compound in Figure 2.14 (Å): Cu1-P1: 2.285 (3), Cu1-P2: 2.310 (3), Cu1-N1: 2.142 (9), Cu1-N2: 2.145 (8).

Synthesis of [Cu(Neocup)(PPh_3)NO_3]: (Figure 2.10) In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, Neocuproine hydrochloride (1.7 g, 6.9 mmol) and Na_2CO_3 (1.13 g, 9.7 mmol) was added to dichloromethane (50 mL). After 2 hrs the mixture was filtered to remove the inorganic salts and the solvent removed under dynamic vacuum to yield neocuproine as a white solid (1.58 g, 92 % yield). Then [$Cu(PPh_3)_3N0_3$] (2.2 g, 3.5 mmol) was dissolved in 50 mL of chloroform. The complex dissolved immediately. To this stirring chloroform solution, neocuproine (0.73 g, 3.4 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 (0.78 g, 92% yield) Crystal data for 1: monoclinic , *C*2/c, a=24.368 (3) Å, b=9.475 (10) Å, c=24.907 (3) Å, a=90°, b=95.820 (6) °(6), c=90.00°, V=5721.75 (13) $Å^3$, D_c=1.246 g cm^{-3}, Z=5, number of unique reflections=5025, number of parameters=361, R1 (for $F_o > 2$)=0.0454 (all data), wR2 (for $F_o > 4$)=0.1005, GOF=1.007, residual electron density=+0.404.

Selected bond lengths (Å): Cu1-P1: 2.195 (7), Cu-O: 2.184 (19), Cu1-N1: 2.121 (2), Cu1-N2: 2.081 (18).

Synthesis of $[Cu(Neocup)(PPh_3)_2]PF_6$: (Figure 2.11) In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, Neocuproine hydrochloride (1.7 g, 6.9 mmol) and Na_2CO_3 (1.13 g, 9.7 mmol) was added to dichloromethane (50 mL). After 2 hrs the mixture was filtered to remove the inorganic salts and the solvent removed under dynamic vacuum to yield neocuproine as a white solid (1.58 g, 92 % yield). Then $[Cu(PPh_3)_4PF_6]$ {obtained by stirring $[Cu(CH_3CN)_4PF_6]$ and 5 eq. of PPh_3 in ether for 18 h} (0.5 g, 0.4 mmol) was dissolved in 50 mL of chloroform. The complex dissolved immediately. To this stirring chloroform solution, neocuproine (0.08 g, 0.37 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 (0.83 g, 90% yield) Crystal data for 1: triclinic, *P-1*, a=10.951 (3) Å, b=13.410 (10) Å, c=15.840 (3) Å, a=87.348°, b=86.889 (6)°, c=81.276°, V=2294.37 (8) $Å^3$, D_c=1.363 g cm^{-3}, Z=2, number of unique reflections=7957, number of parameters=559, R1 (for $F_o > 2$)=0.0403 (all data), wR2 (for $F_o > 4$)=0.1603, GOF=1.036, residual electron density=+0.404. Selected bond lengths (Å): Cu1-P1: 2.280 (9), Cu1-P2: 2.282 (10), Cu1-N1: 2.089 (3), Cu1-N2: 2.122 (3).

Synthesis of $[Cu(Neocup)(PPh_3)_2]ClO_4$: (Figure 2.12) In an Erlenmeyer flask equipped with a Teflon-coated magnetic stirrer, Neocuproine hydrochloride (1.7 g, 6.9

mmol) and Na_2CO_3 (1.13 g, 9.7 mmol) was added to dichloromethane (50 mL). After 2 hrs the mixture was filtered to remove the inorganic salts and the solvent removed under dynamic vacuum to yield neocuproine as a white solid (1.58 g, 92% yield). Then $[Cu(PPh_3)_4ClO_4]$ (1.2 g, 82 % yield) obtained by adding a solution of cupric perchlorate (1.86 g, 0.005 moles) to triphenylphosphine (6.55 g, 0.025 moles) stirring in absolute ethanol (35 mL) was added to a solution of diethyl ether at rt. To this stirring solution of the tetrakis(triphenylphosphine)copper(I) perchlorate salt, neocuproine (0.08 g, 0.37 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 (0.83 g, 90% yield). Crystal data for 1: monoclinic , $P2_1/c$, a=15.667 (10) Å, b=15.639 (10) Å, c=21.448 (3) Å, a=90°, b=115.37° (6), c=90°, V=4748.90 (9) $Å^3$, D_c=1.363 g cm^{-3}, Z=4, number of unique reflections=6691, number of parameters=568, R1 (for $F_o > 2$)=0.0592 (all data), wR2 (for $F_o > 4$)=0.1331, GOF=1.036, residual electron density=+0.404. Selected bond lengths (Å): Cu1-P1: 2.282 (8), Cu1-P2: 2.283 (8), Cu1-N1: 2.114 (2), Cu1-N2: 2.102 (2).

Synthesis of $[Cu(CH_3CN)_4]PF_6$: (Scheme 2.6) This product was supplied to me by Craig Bates (D.V. group) who followed the following procedure by Kubas. To a magnetically stirred suspension of 2.0 g (14 mmol) of copper(I) oxide in 40 mL of acetonitrile in a 125 mL Erlenmeyer flask is added 5 mL of 60-65% HPF_6 (about 113 mmol of HPF_6) in 2 mL portions. The reaction is very exothermic and may cause the

solution to boil. However, the reaction temperature is not critical and the warming is beneficial in that the product remains dissolved. After addition of the final portion of HPF_6, the solution is stirred for about 3 min. and is then filtered hot through a medium-porosity frit to remove small amounts of undissolved black solid. The pale blue solution is cooled in a freezer to about -20 ^oC for several hours. After about 12 h a blue-tinged white microcrystalline solid of $[Cu(CH_3CN)_4]PF_6$ forms. The solid is collected by filtration and washed with diethyl ether, and immediately redissolved in acetonitrile to remove Cu^{2+} species. Analysis calculated for $C_8H_{12}N_4PF_6Cu$: C, 25.9: H, 3.3; N, 15.1; P; 8.1; Cu, 16.7.

Formation of Aryl-Oxygen Bonds using Cu(I) Catalysts

General. All reactions for the synthesis of diaryl ethers were performed under an inert atmosphere of argon in oven-dried glassware. All reagents and solvents were purchased from Acros or from Aldrich and were used without further purification. Cesium carbonate (Acros, 99%) was stored in a glove box filled with argon. Flash chromatography was performed using ICN Flash Silica Gel, 230-400 mesh. The reported yields refer to isolated yields of the compounds, deemed pure by elemental analysis, ^1H NMR and ^{13}C NMR. All products were characterized by ^1H NMR, ^{13}C NMR and elemental analyses. NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Chemical shifts were recorded in parts per million (δ). The peak patterns are indicated as s, singlet; d, doublet; t, triplet; dd, doublet of doublets; and m, multiplet. The coupling constants, *J*, are reported in Hertz (Hz). The residual solvent peak was used

as the internal reference. Elemental analyses were preformed at the Microanalysis Laboratory, University of Massachusetts at Amherst by Dr. Greg Dabkowski. The reported melting points are uncorrected. X-ray data were collected using a Nonius kappa-CCD diffractometer with Mo K_α (λ=0.71073 Å) as the incident radiation. Diffraction data were collected at ambient temperature. 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. Structures solutions and refinements were done (on F_o^2) using suite of programs such as 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.

Cu-Catalyzed Coupling of Phenols with Aryl Halides

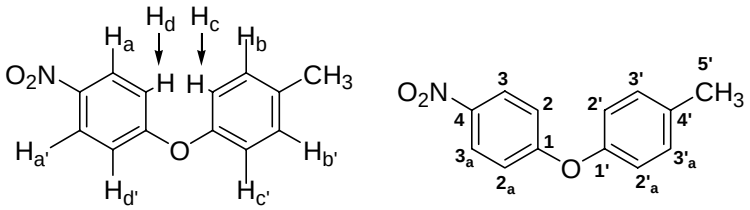
General Procedure A: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar and a rubber septum, was charged with cesium carbonate (Acros, 3.0 mmol) and [$Cu(PPh_3)_3Br$] (20 mol% with respect to the aryl halide) and was sealed with a rubber septum. The sealed tube was taken out and the phenol (2 mmol), the aryl halide (2 mmol) and N-methylpyrrolidinone (15 mL) were injected into the tube through the septum. The tube was then degassed and backfilled with argon three times using a long needle. The contents were then stirred at 100 ^oC for times indicated in Table 1. Care was taken to make sure the contents were well stirred. The reaction mixture was then cooled and filtered to remove any insoluble residues. Water was then added to the filtrate, and the aryl ether was extracted in hexane. The

combined extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was then purified with by flash column chromatography on silica gel to obtain the analytically pure product.

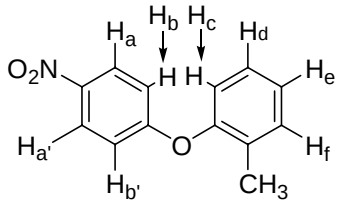
General Procedure B (without the catalyst): In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar, was charged with cesium carbonate (Acros, 3.0 mmol) and was sealed with a rubber septum. The sealed tube was taken out and the phenol (2 mmol), the aryl halide (2 mmol) and N-methylpyrrolidinone (15 mL) were injected into the tube through the septum. The tube was then degassed and backfilled with argon three times using a long needle. The contents were then stirred at 70 ^oC for times indicated in Table 1. Care was taken to make sure the contents were well stirred. The reaction mixture was then cooled and filtered to remove any insoluble residues. Water was then added to the filtrate, and the aryl ether was extracted in hexane. The combined extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was then purified with by flash column chromatography on silica gel to obtain the analytically pure product.

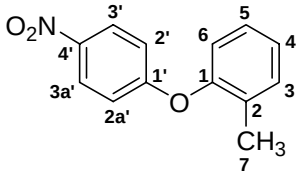
1-Methyl-4-(4-nitrophenoxy)benzene (entry 1, Table 3.1). Procedure B was used to convert *p*-cresol and 1-bromo-4-nitrobenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as white solid (0.40 g, 88% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (dd, *J*=7.0, 2H- H_a, $H_{a'}$), 7.22 (dd, *J*=7.2, 2H; H_b, $H_{b'}$), 6.96 (m, 4H; H_d, $H_{d'}$, H_c, $H_{c'}$), 2.31 (s, 3H- methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (C_1), 152.1 ($C_{1'}$), 142.2 (C_4), 135.1 ($C_{4'}$),

130.7 ($C_{3'}$, $C_{3a'}$), 125.7 (C_3, C_{3a}), 120.3 (C_2, C_{2a}), 116.6 ($C_{2'}$, $C_{2a'}$), 20.7 (C_5). Anal. Calcd. for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.80. Found: C, 68.04; H, 4.91; mp 65 °C. Crystal data: Orthorhombic, *Pbca* (no. 61), *a*=7.439 (2) Å, *b*=12.440 (3) Å, *c*=24.850 (7) Å, *V*=2299.8 (1) Å^3, *Z*=8, number of unique reflections=1573, number of parameters=154, *R*1=0.077 (all data), *wR* (w=1/($\sigma^2(F_o^2)$ + 0.0300* F_o^2)=0.064 (all data), GOF=2.04, residual electron density=+0.27.

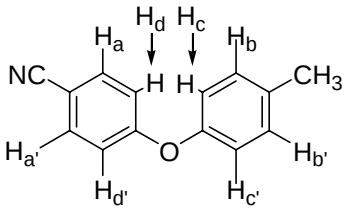


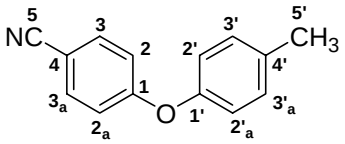
1-Methyl-2-(4-nitrophenoxy)benzene (entry 2, Table 3.1). Procedure B was used to convert *o*-cresol and 1-bromo-4-nitrobenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as yellow oil (0.39 g, 86% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (dd, *J*=7.0, 2H; H_a, $H_{a'}$), 7.34-7.16 (m, 3H; H_d, H_e, H_f), 7.02 (dd, *J*=7.7, 1H; H_c), 6.92 (dd, *J*=7.0, 2H; H_b, $H_{b'}$), 2.22 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C_1), 152.2 ($C_{1'}$), 142.1 ($C_{4'}$), 131.9 (C_3), 130.4 (C_2), 127.6 (C_5), 125.9 ($C_{3'}$, $C_{3a'}$), 125.8 (C_4), 121.0 (C_6), 115.8 ($C_{2'}$, $C_{2a'}$), 15.9 (C_7). Anal. Calcd. for C_{13} $H_{11}NO_3$: C, 68.12; H, 4.80. Found: C, 68.10; H, 4.85; mp 35 °C.





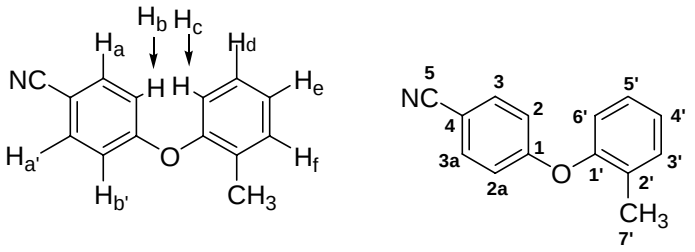
4-(4-Methylphenoxy)benzonitrile (entry 3, Table 3.1). Procedure B was used to convert *p*-cresol and 1-bromo-4-cyanobenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as white solid (0.3 g, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, *J*=8.8, 2H; H_a, $H_{a'}$), 7.24 (dd, *J*=8.1, 2H; H_b, $H_{b'}$), 6.90 (m, 4H; H_c, $H_{c'}$, H_d, $H_{d'}$), 2.41 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9 (C_1), 152.2 ($C_{1'}$), 134.8 ($C_{4'}$), 133.9 (C_3, C_{3a}), 130.6 ($C_{3'}$, $C_{3a'}$), 120.2 (C_2, C_{2a}), 118.8 (C_5), 117.4 ($C_{2'}$, $C_{2a'}$), 105.3 (C_4), 20.7 ($C_{5'}$). Anal. Calcd for $C_{14}H_{11}NO$: C, 80.38; H, 5.26; N, 6.69. Found: C, 79.93; H, 5.65; N, 6.24; mp 65 °C.



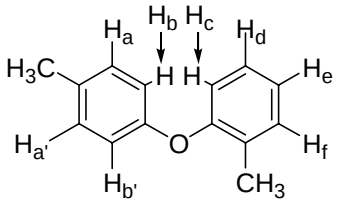


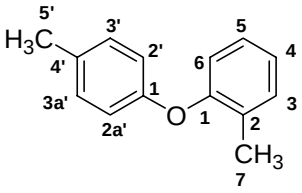
4-(2-Methylphenoxy)benzonitrile (entry 4, Table 3.1). Procedure B was used to convert *o*-cresol and 1-bromo-4-cyanobenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a white solid (0.35 g, 85% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, *J*= 6.9, 2H; H_a,

$H_{a'}$), 7.32-7.14 (m, 3H; H_d, H_e, H_f), 6.99 (dd, *J*=6.9, 1H; H_c), 6.91 (dd, *J*=6,97, 2H; H_b, $H_{b'}$), 2.41 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2 (C_1), 150.8 ($C_{1'}$), 132.6 (C_3, C_{3a}) 130.4 ($C_{3'}$), 128.9 ($C_{2'}$), 126.0 ($C_{5'}$), 124.1 ($C_{4'}$), 119.6 ($C_{6'}$), 117.3 (C_5), 115.1 (C_2, C_{2a}), 103.6 (C_4), 14.4 ($C_{7'}$). Anal. Calcd for $C_{14}H_{11}NO$: C, 80.38; H, 5.26. Found: C, 80.17; H, 5.40. ; mp 70 °C.

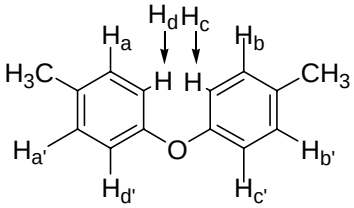


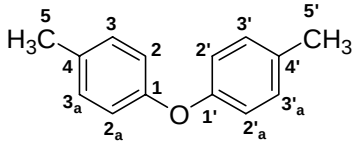
1-Methyl-2-(4-methylphenoxy)benzene (entry 5, Table 3.1). Procedure B was used to convert *o*-cresol and 1-bromo-4-methylbenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a colorless oil (0.29 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, *J*=8.5, 1H; H_c), 7.07 (m, 3H; H_f, H_b, $H_{b'}$), 6.83 (m, 4H; H_e, H_d, H_a, $H_{a'}$), 2.11 (s, 3H- methyl protons), 2.10 (s, 3H- methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (C_1), 154.9 ($C_{1'}$), 131.8 ($C_{4'}$), 131.3 (C_3), 130.1 ($C_{3'}$, $C_{3a'}$), 129.6 (C_2), 127 (C_5), 123.5 (C_4), 119.1 ($C_{2'}$, $C_{2a'}$), 117.5 (C_6), 20.6 ($C_{5'}$), 16.1 (C_7). Anal. Calcd. for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 84.62; H, 7.22.





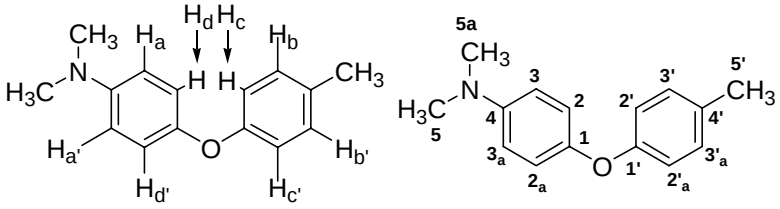
1-Methyl-4-(4-methylphenoxy)benzene (entry 6, Table 3.1). Procedure A was used to convert *p*-cresol and 1-bromo-4-methylbenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a white solid (0.27 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (dd, *J*=6.5, 4H; H_a, H_a, H_b, H_b), 7.1 (dd, *J*=6.5, 4H; H_c, H_c, H_d, H_d), 2.21 (s, 6H; C_5, $C_{5'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (C_1, $C_{1'}$), 132.3 (C_4, $C_{4'}$), 130 (C_3, C_{3a}, $C_{3'}$, $C_{3a'}$), 118.5 (C_2, C_{2a}, $C_{2'}$, $C_{2a'}$). Anal. Calcd. for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 84.62; H, 7.07; mp 50 °C. Crystal data: Orthorhombic, $P2_12_12_1$ (no. 19), *a*=5.9138(1) Å, *b*=7.8364(2) Å, *c*=24.6388(8) Å, *V*=1141.83(5) Å^3, *Z*=4, number of unique reflections=2167, number of parameters=136, *R*1=0.091 (all data), *wR* (w=1/($\sigma^2(F_o^2)$ + 0.0300* F_o^2)=0.047 (all data), GOF=2.04, residual electron density=+0.33.



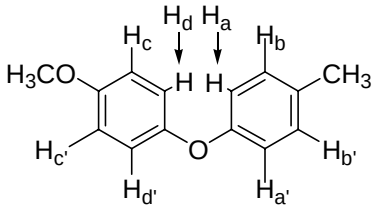


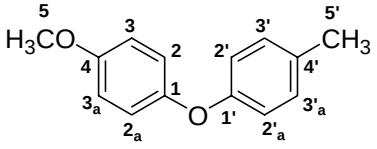
***N, N*-Dimethyl-4-(4-methylphenoxy)aniline (entry 7 , Table 3.1).** Procedure A was used to convert *p*-cresol and 4-bromo-*N, N*-dimethylaniline to the title product.

Purification by flash chromatography (1:1, dichloromethane/hexane) gave the analytically pure product as a white solid (0.34 g, 76% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, 2H; H_b, H_b), 6.96 (dd, 2H; H_c, H_c), 6.81 (dd, 2H; H_d, H_d), 6.66 (dd, 2H; H_a, $H_{a'}$), 2.91 (s, 6H; dimethyl protons), 2.21 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1 ($C_{1'}$), 146.4 (C_4), 145.8 (C_1), 129.8 ($C_{4'}$), 128.4 ($C_{3'}$), 118.9 (C_2), 115.7 ($C_{2'}$), 112.5 (C_3), 39.7 (C_5, C_{5a}), 19.0 ($C_{5'}$). Anal Calcd for $C_{15}H_{17}NO$: C, 79.29; H, 7.48. Found: C, 79.25; H, 7.68; mp 180 °C.

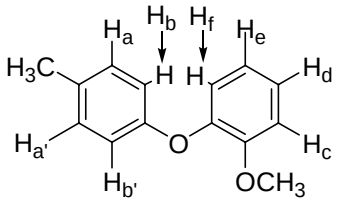


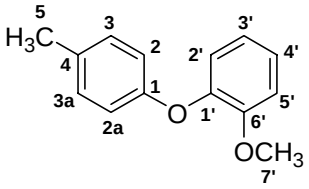
1-Methoxy-4-(4-methylphenoxy)benzene (entry 8, Table 3.1). Procedure A was used to convert *p*-cresol and 4-bromoanisole to the title product. Purification by flash chromatography (30% dichloromethane/hexane) gave the analytically pure product as a white solid (0.428 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (dd, *J*= 8.3, 2H; H_b, $H_{b'}$), 7.04 (dd, *J*= 8.9, 2H; H_d, $H_{d'}$), 6.99-6.89 (m, 4H; H_c, $H_{c'}$, H_a, $H_{a'}$), 3.91 (s, 3H; methoxy protons), 2.41 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (C_4), 155.5 ($C_{1'}$), 150.6 (C_1), 131.9 ($C_{4'}$), 129.9 ($C_{3'}$, $C_{3a'}$), 120.2 (C_2, C_{2a}) 117.6 ($C_{2'}$, $C_{2a'}$), 114.6 (C_3, C_{3a}). Anal Calcd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.54. Found: C, 78.33; H, 6.66; mp 63 °C.





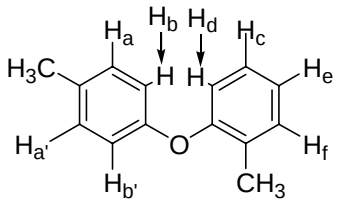
1-Methoxy-2-(4-methylphenoxy)benzene (entry 9, Table 3.1). Procedure A was used to convert *p*-cresol and 2-bromoanisole to the title product. Purification by flash chromatography (30% dichloromethane/hexane) gave the analytically pure product as a white solid (0.26 g, 61% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13-7.05 (m, 3H, H_f, H_e, H_d), 7.00 (dd, *J*= 8.00, 1H; H_c), 6.95-6.83 (m, 4H, H_a, $H_{a'}$, H_b, $H_{b'}$), 3.91 (s, 3H; methoxy protons), 2.2 (s, 3H; methyl protons); ^{13}C NMR δ 155.4 (C_1), 151.1 ($C_{6'}$), 145.6 ($C_{1'}$), 132.0 (C_4), 129.9 (C_3, C_{3a}) 124.2 ($C_{3'}$), 120.9 ($C_{4'}$), 120.2 ($C_{2'}$), 117.4 (C_2, C_{2a}), 112.6 ($C_{5'}$), 55.8 ($C_{7'}$), 20.6 (C_5). Anal Calcd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.54. Found: C, 78.2; H, 6.59; mp 75 °C.

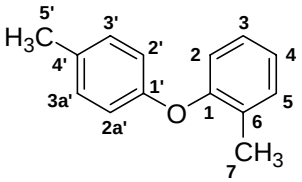




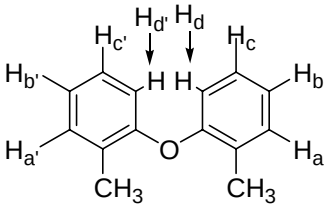
1-Methyl-2-(4-methylphenoxy)benzene (entry 10, Table 3.1). Procedure B was used to convert *o*-cresol and 1-bromo-2-methyltoluene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a colorless oil (0.29 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (dd, *J*=8.5, 1H; H_c),

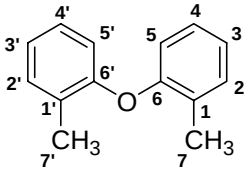
7.16-6.96 (m, 4H; H_f, H_b, $H_{b'}$, H_e), 6.86-6.76 (m, 3H; H_d, H_a, $H_{a'}$), 2.11 (s, 3H; methyl protons), 2.0 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5 (C_1), 154.9 ($C_{1'}$), 131.8 ($C_{4'}$), 131.3 (C_3), 130.1 ($C_{3'}$, $C_{3a'}$), 129.6 (C_2), 127 (C_5), 123.5 (C_4), 119.1 ($C_{2'}$, $C_{2a'}$), 117.5 (C_6), 20.5 ($C_{7'}$), 16.1 (C_7). Anal Calcd for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 84.83; H, 7.25; mp 155 °C.



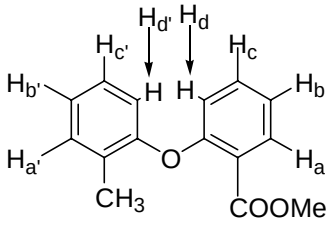


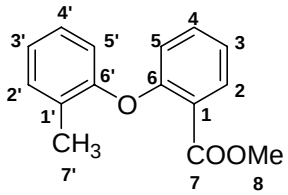
1-Methyl-2-(2-methylphenoxy)benzene (entry 11, Table 3.1). Procedure B was used to convert *o*-cresol and 1-bromo-2-methyltoluene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a colourless oil. (0.29 g, 72% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (dd, *J*= 7.3, 2H; H_a, $H_{a'}$), 7.33 (dd, *J*= 7.3, 2H; H_c, $H_{c'}$), 7.23 (dd, *J*=7.2, 2H; H_b, $H_{b'}$), 6.96 (dd, *J*=7.5, 2H; H_d, $H_{d'}$), 2.51 (s, 6H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (C_6, $C_{6'}$), 131.3 (C_2, $C_{2'}$), 128.8 (C_1, $C_{1'}$), 127.0 (C_4, $C_{4'}$), 123.0 (C_3, $C_{3'}$), 117.6 (C_5, $C_{5'}$), 16.1 (C_7, $C_{7'}$). Anal Calcd for $C_{14}H_{14}O$: C, 84.84; H, 7.07. Found: C, 84.82; H, 7.14.



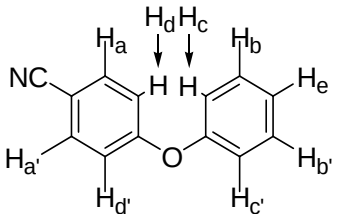


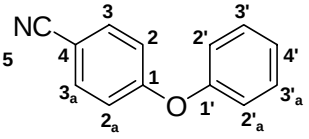
1-Methyl-2-(2-methylphenoxy)benzoate (entry 12, Table 3.1). Procedure A was used to convert *p*-cresol and 1-methyl-2-bromobenzoate to the title product. Purification by flash chromatography (1:1, dichloromethane/hexane) gave the analytically pure product as a colorless oil. (0.13 g, 55% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, *J*= 8.1 Hz, 2H; H_a), 7.34 (t, *J*= 7.91 Hz, 1H; $H_{c,}$), 7.28 (d, *J*=7.72 Hz, 1H; H_b), 7.22 (m, *J*=7.72 Hz, 3H), 7.11 (t, *J*= 7.75 Hz, 2H; $H_{d'}$, $H_{c'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8 (C_7), 157.2 (C_1), 155.0 ($C_{6'}$), 133.8 (C_4), 132.2 (C_2), 131.8 ($C_{2'}$), 129.9 ($C_{1'}$), 127.5 ($C_{4'}$), 124.3 ($C_{3'}$), 122.8 (C_3), 122.2 (C_6), 119.1 ($C_{5'}$), 118.8 (C_5), 52.48 (C8), 16.57 ($C_{7'}$). Anal. Calcd. for $C_{13}H_9ON$: C, 74.38; H, 5.78. Found: C, 74.10; H, 5.83.





4-Phenoxybenzonitrile (entry 13, Table 3.1). Procedure A was used to convert phenol and 1-bromo-4-cyanobenzene to the title product. However, toluene was used as the solvent instead of NMP. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a white solid. (0.12 g, 60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, *J*=8.1 Hz, 2H; $H_{d,,}H_{d'}$), 7.33 (dd, *J*= 7.91 Hz, 2H; $H_{a,}$ $H_{a'}$), 7.03 (t, *J*=7.72 Hz, 2H; H_e), 6.95 (d, *J*=7.72 Hz, 2H; $H_{b,}$ $H_{b'}$), 6.85 (d, *J*= 7.75 Hz, 2H; H_c, $H_{c'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.5 ($C_{1'}$), 154.6 (C_1), 134.0 ($C_{3'}$ $C_{3a'}$), 130.1 (C_3 C_{3a}), 125 ($C_{4'}$), 120.3 (C_2 C_{2a}), 118.7 (CN), 117.8 ($C_{2'}$, $C_{2a'}$), 105.6 (C_4). Anal. Calcd. for $C_{13}H_9ON$: C, 80.0; H, 4.61. Found: C, 79.86; H, 4.66.





1-Methoxy-2-(4-methylphenoxy)benzene (entry 14, Table 3.1). Procedure A was used to convert *p*-cresol and 2-bromoanisole to the title product. However, toluene was used as the solvent instead of NMP. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a white solid (0.047 g, 27% yield). The ^{1}H and ^{13}C NMR was identical to that of entry 5.

[Cu(neocup)(PPh_3)Br] Catalyzed Coupling of Phenols with Aryl Halides

General Procedure A: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar and a rubber septum, was charged with cesium carbonate (Acros, 3.0 mmol) and Cu(Neocup)(PPh_3)Br (10 mol% with respect to the aryl halide) and was sealed with a rubber septum. The sealed tube was taken out and the phenol (2 mmol), the aryl halide (2 mmol) and dry toluene (15 mL) were injected into the tube through the septum. The tube was then degassed and backfilled with argon three times using a long needle. The contents were then stirred at 110 ^{0}C for times indicated in Table 1. Care was taken to make sure the contents were well stirred. The reaction mixture was then cooled and filtered to remove any insoluble residues. Water was then added to the filtrate, and the aryl ether was extracted in hexane. The combined extracts

were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was then purified with by flash column chromatography on silica gel to obtain the analytically pure product.

1-Methyl-4-(4-methylphenoxy)benzene (entry 1, Table 3.3). Procedure A was used to convert *p*-cresol and 1-bromo-4-methylbenzene to the title product. An aliquot of the reaction mixture was extracted after 36 hours and compared against an authentic sample of 1-Methyl-4-(4-methylphenoxy)benzene purchased from Aldrich (GC yield: > 99 %). GC Correction factors used for calculation of the GC yield in this entry are as follows (*p*-cresol: 0.442; 1-bromo-4-methylbenzene; 0.457; 1-Methyl-4-(4-methylphenoxy)benzene: 1.077).

1-(4-phenoxyphenyl) ethanone (entry 2, Table 3.3). Procedure A was used to convert phenol and 4-bromoacetophenone to the title product. An aliquot of the reaction mixture was extracted after 36 hours and compared against an authentic sample of 1-(4-phenoxyphenyl)ethanone from Aldrich (GC yield: > 99 %). GC Correction factors used for calculation of the GC yield in this entry are as follows (*p*-cresol: 0.442; 4-bromoacetophenone: 0.481; 1-(4-phenoxyphenyl)ethanone: 1.066).

1-Methyl-2-(4-methylphenoxy) benzene (entry 3, Table 3.3). Procedure A was used to convert *o*-cresol and 1-bromo-4-methylbenzene to the title product. An aliquot of the reaction mixture was extracted after 36 hours and compared against a previously isolated and characterized sample of 1-Methyl-2-(4-methylphenoxy)benzene (GC yield: > 83 %).

GC Correction factors used for calculation of the GC yield in this entry are as follows (*o*-cresol: 0.441; 1-bromo-4-methylbenzene: 0.457; 1-Methyl-2-(4-methylphenoxy)benzene: 0.977).

4-nitrophenyl phenylether (entry 4, Table 3.3). Procedure A was used to convert phenol and 4-bromonitrobenzene to the title product. An aliquot of the reaction mixture was extracted after 36 hours and compared against an authentic sample of 4-nitrophenyl phenylether purchased from Aldrich (GC yield: > 95 %). GC Correction factors used for calculation of the GC yield in this entry are as follows (phenol: 0.424; 4-bromonitrobenzene: 0.742; 4-nitrophenyl phenylether: 0.754).

Diphenylether (entry 4, Table 3.3). Procedure A was used to convert phenol and bromobenzene to the title product. An aliquot of the reaction mixture was extracted after 36 hours and compared against an authentic sample of diphenylether purchased from Aldrich (GC yield: > 51 %). GC Correction factors used for calculation of the GC yield in this entry are as follows (phenol: 0.424; bromobenzene: 0.461; Diphenylether: 0.882).

1-Methyl-2-(2-methylphenoxy)benzene (entry 5, Table 3.3). Procedure A was used to convert *o*-cresol and 1-bromo-2-methyltoluene to the title product. An aliquot of the reaction mixture was extracted after 36 hours and compared against a previously isolated and characterized sample of 1-Methyl-2-(2-methylphenoxy)benzene (GC yield: > 36 %). GC Correction factors used for calculation of the GC yield in this entry are as follows (o-

cresol: 0.441; 1-bromo-2-methylbenzene: 0.541; 1-Methyl-2-(2-methylphenoxy)benzene: 0.965).

1-Methyl-2-(4-methylphenoxy)benzene (entry 6, Table 3.3). Procedure A was used to convert *p*-cresol and 1-bromo-2-methyltoluene to the title product. An aliquot of the reaction mixture was extracted after 36 hours and compared against a previously isolated and characterized sample of **1-Methyl-2-(4-methylphenoxy)benzene (GC yield: > 31 %).** GC Correction factors used for calculation of the GC yield in this entry are as follows (p-cresol: 0.442; 1-bromo-2-methylbenzene: 0.541; 1-Methyl-2-(4-methylphenoxy)benzene: 0.971).

Formation of Aryl-Nitrogen Bonds using Copper(I) Catalysts

General. All reactions for the synthesis of *N, N*-diphenylaniline were performed under an inert atmosphere of argon in oven-dried glassware. All reagents and solvents were purchased from Acros or from Aldrich and were used without further purification. Cesium carbonate (Acros, 99%) was stored in a glove box filled with argon. Flash chromatography was performed using ICN Flash Silica Gel, 230-400 mesh. The reported yields refer to isolated yields of the compounds, deemed pure by elemental analysis, ^{1}H NMR and ^{13}C NMR. All products were characterized by ^{1}H NMR, ^{13}C NMR and elemental analyses. NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Chemical shifts were recorded in parts per million (□). The peak patterns

are indicated as s, singlet; d, doublet; t, triplet; dd, doublet of doublets; and m, multiplet. The coupling constants, J, are reported in Hertz (Hz). The residual solvent peak was used as the internal reference. Elemental analyses were preformed at the Microanalysis Laboratory, University of Massachusetts at Amherst by Dr. Greg Dabkowski. The reported melting points are uncorrected. X-ray data were collected using a Nonius kappa-CCD diffractometer with MoKα (λ=0.71073 Å) as the incident radiation. Diffraction data were collected at ambient temperature. 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. Structures solutions and refinements were done (on F_o^2) using suite of programs such as 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.

Cu-Catalyzed Coupling of *N*-phenylaniline with Aryl Halides

General Procedure A: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar and a rubber septum, was charged with cesium carbonate (Acros, 1.5 mmol) and [$Cu(PPh_3)_3Br$] (20 mol% with respect to the aryl halide) and diphenylamine (1 mmol) and was sealed with a rubber septum. The sealed tube was taken out of the box and the aryl halide (1 mmol) and toluene (15 mL) were injected into the tube through the septum. Note that for entries 4-8 in Table 2, the solid aryl halides were weighed and added in the glove box itself such that only toluene was finally added outside of the box. The tube was then degassed and backfilled with argon

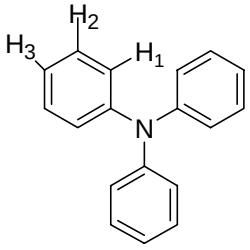
three times using a long needle. Care was taken to make sure the contents were well stirred. The reaction mixture was then cooled, mixed with 15 mL of diethyl ether, and filtered to remove any insoluble residues. The combined extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was then purified by flash column chromatography on silica gel to obtain the analytically pure product.

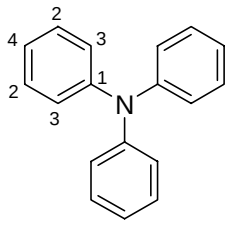
Cu-Catalyzed Coupling of Functionalized Anilines with Aryl Halides

General Procedure B: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar and a rubber septum, was charged with cesium carbonate (Acros, 1.5 mmol) and $[Cu(PPh_3)_3Br]$ (20 mol% with respect to the aryl halide) and was sealed with a rubber septum. The sealed tube was taken out and the aryl amine (entries: 12, 14, 15) (1 mmol), and toluene (15 mL) were injected into the tube through the septum. In the case of entry 13, *p*-toluidine was weighed and added in the box. The tube was then degassed and backfilled with argon three times using a long needle. The contents were then stirred at 110 ^oC for about 15 minutes. After 15 minutes, the tube was removed from the oil bath and cooled at room temperature for another 10 minutes. After cooling, the aryl iodide (entries 12-15) (1 mmol) was injected. The contents were then stirred at 110 ^oC for times indicated in Table 1. The reaction mixture was then cooled, mixed with 15 mL of diethyl ether, and filtered to remove any insoluble residues. The combined extracts were dried with anhydrous Na_2SO_4. The solvent was

removed under reduced pressure and the residue was then purified by flash column chromatography on silica gel to obtain the analytically pure product.

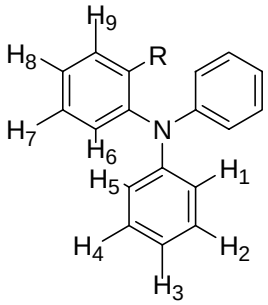
Triphenylamine (entry 10, Table 4.2). Procedure A was used to convert diphenylamine and iodobenzene to the title product. Purification by flash chromatography (1:4 dichloromethane/hexane) gave the analytically pure product as a white solid (0.17 g, 70% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, 6H- H_2), 7.07 (dd, J_{ortho}=6.97, 6H- H_1), 6.6 (t, J_{ortho}= 7.0, 6H- H_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.82 (C_1), 129.08 (C_2), 124.08 (C_3), 122.58 (C_4). Anal. Calcd. for $C_{18}H_{15}N$: C, 88.16; H, 6.12; N, 5.71. Found: C, 88.05; H, 6.18; N, 5.70.



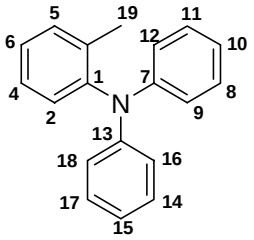


2-Methyl-*N*, *N*-diphenylaniline (entry 15, Table 4.2). Procedure A was used to convert *N*-phenylaniline and 1-iodo-2-methylbenzene to the title product. Purification by flash chromatography (1:4 dichloromethane/hexane) gave the analytically pure product as white solid (0.13 g, 52% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11- 7.24 (m, 6H- H_3, H_6, H_7, H_8, H_9), 6.90-7.00 (m, 8H- H_1, H_2, H_4, H_5,), 2.04 (methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.38 (C_7, C_{13}), 136.48 (C_1), 131.58 (C_5), 129.6 (C_4), 128.98 (C_8, C_{11},

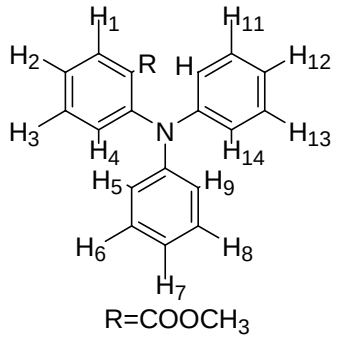
$C_{14,}$ C_{17}), 127.28 (C_{10}), 125.88 (C_{15}), 121.48 ($C_{9,}$ $C_{12,}$ $C_{16,}$ C_{18}), 121.32 (C_2), 18.48 (C_{19}). Anal. Calcd. for C_{19} $H_{17}N$: C, 88.03; H, 6.56; N,5.40. Found: C, 88.05; H, 6.56; N,5.33.

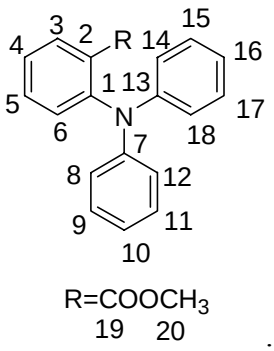


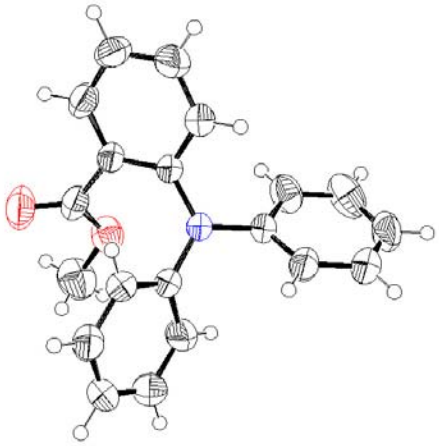
R=CH_3 (H_{10})



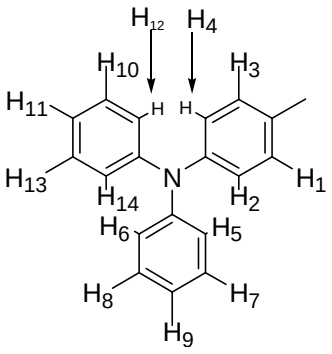
Methyl 2-(diphenylamino) benzoate (entry 1, Table 4.1). Procedure A was used to convert *N*-phenylaniline and methyl 2-iodobenzoate to the title product. Purification by flash chromatography (1:10 diethylether/hexane) gave the analytically pure product as a white solid (0.20 g, 69% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (dd, *J*=6.97, 1H; H_1), 7.42 (t, *J*=6.9, 1H; H_3), 7.15-7.30 (m, 6H), 6.90-7.05 (m, 6H), 3.41 (s, 3H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C_{19}), 147.7 ($C_{7,}$ C_{13}), 132.6 (C_5) 131.2 (C_3), 129.07 (C_9, C_{11}, C_{15}, C_{16}), 129.01 (C_6), 124.2 (C_{10}, C_{16}), 122.8 (C_8, C_{12}, C_{14}, C_{18}), 122.2 (C_4), 118.7 (C_2), 51.8 (C_{20}). Anal. Calcd for $C_{20}H_{17}NO_2$: C, 79.23; H, 5.61. Found: C, 79.23; H, 5.67. Crystal data: Orthorhombic, $P2_12_12_1$ (no. 19), *a*=5.9138 (1) Å, *b*=7.8364 (2) Å, *c*=24.6388 (8) Å, *V*=1141.83(5) Å^3, *Z*=4, number of unique reflections=2167, number of parameters=136, *R*1=0.091 (all data), *wR* (w=1/($\sigma^2(F_o^2)$ + 0.0300* F_o^2)=0.047 (all data), GOF=2.04, residual electron density=+0.33.

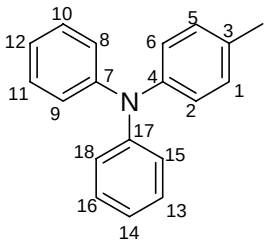




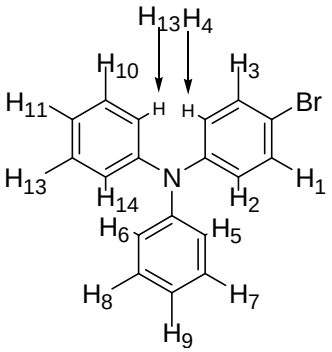


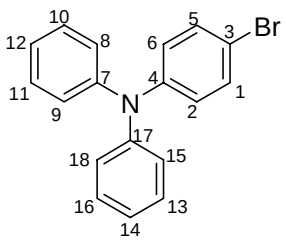
4-Methyl-*N*,*N*-diphenylaniline (entry 14, Table 4.2). Procedure A was used to convert *N*-phenylaniline and 1-iodo-4-methylbenzene to the title product. Purification by flash chromatography (1:4, dichloromethane/hexane) gave the analytically pure product as a white solid (0.17, 52 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08-7.17 (t, *J*=7.47), 6.83-7.00 (m), 2.2 (methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148 ($C_{7,}$ C_{17}), 145.17 (C_4), 132.67 (C_3), 129.8 (C_1), 129.07 ($C_{10,}$ $C_{11,}$ $C_{13,}$ C_{16}), 124.8 ($C_{2,}$ C_6), 123.57 ($C_{8,}$ $C_{9,}$ $C_{15,}$ C_{18}), 122.17 (C_5), 20.77 (methyl protons). Anal Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.56; N, 5.40. Found: C, 87.46; H, 6.62; N, 5.34.

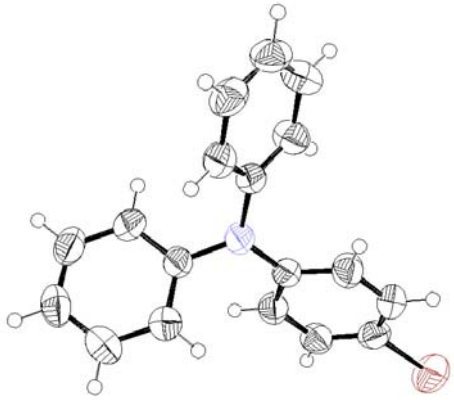




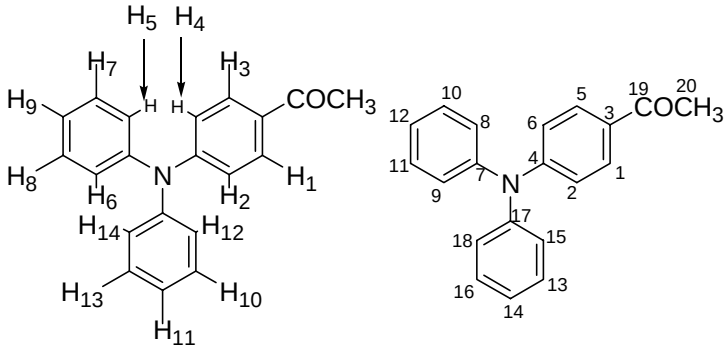
4-Bromo-*N*,*N*-diphenylaniline (entry 11, Table 4.2). Procedure A was used to convert *N*-phenylaniline and 1-bromo-4-iodobenzene to the title product. Purification by flash chromatography (1:1, dichloromethane/hexane) gave the analytically pure product as a white solid (0.17 g, 54% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.35 (m, 6H; H_1, H_3, H_{10}, H_{13}, H_7, H_8), 6.85-7.10 (m, 8H; H_6, H_5, H_{12}, H_{14}, H_9, H_{11}, H_2, H_4). Anal Calcd for $C_{18}H_{14}NBr$: C, 66.6; H, 4.32. Found: C, 66.35; H, 4.31. Crystal data: Monoclinic, *P21/c*, *a*=7.9963 (3) Å, *b*=18.2307 (7) Å, *c*=10.2278 (3) Å, *V*=1491.0 (1) Å^3, *Z*=4, number of unique reflections=2431, number of parameters=181, *R*1=0.0460 (all data), *wR* (w=1/[$\sigma^2(F_o^2)$+(0.0370p)^2+2.1279p] where p=(F_o^2+2F_c^2)/3)=0.1151 GOF=1.047, residual electron density=+0.586.



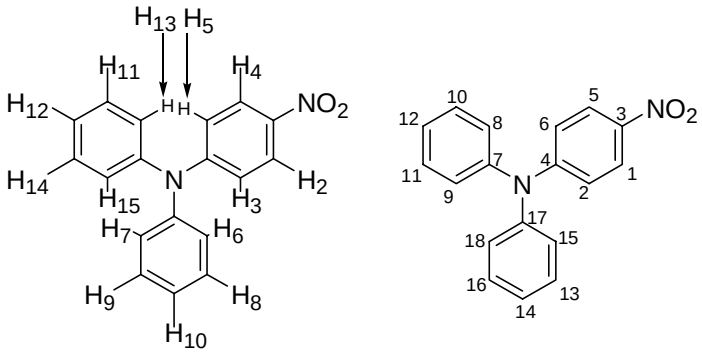


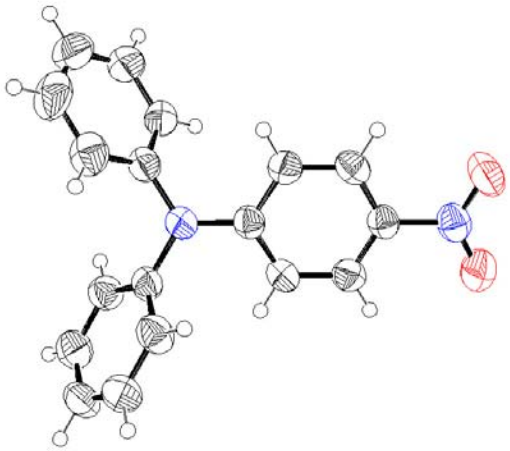


1-[4-(diphenylamino)phenyl]ethanone (entry 2, Table 4.1). Procedure A was used to convert *N*-phenylaniline and 1-(4-iodophenyl)ethanone to the title product. Purification by flash chromatography (1:2 ether/hexane) gave the analytically pure product as a pale yellow solid (0.19 g, 68% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J*=8.5, 1H; $H_{1,}$ H_3), 7.25 (d, 2H; $H_{6,}$ H_5, H_{12}, H_{14}), 7.02 (m, 6H; $H_{7,}H_{10,}H_{8,}H_{13,}H_{9,}$ H_{11}), 6.90 (d, *J*=8.5 4H; $H_{5,\ 6,12,\ 14}$) 2.54 (methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.5 (C_{19}), 152 (C_4), 146.38 ($C_{7,}$ C_{17}), 129.8 ($C_{1,}$ C_5), 129.7 (C_3), 129.6 ($C_{10,}$ $C_{13,}$ $C_{11,}$ C_{16}), 125.8 ($C_{8,}$ $C_{9,}$ $C_{15,}$ C_{18}), 124.56 ($C_{12,}$ C_{14}), 119.56 ($C_{2,}$ C_6), 26.16 (C_{20}). Anal. Calcd. for $C_{20}H_{17}ON$: C, 83.62; H, 5.92. Found: C, 83.06; H, 6.07.

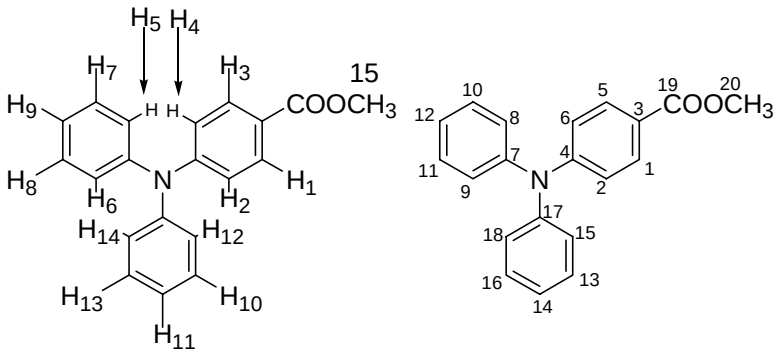


4-Nitro-*N*, *N*-diphenylaniline (entry 3, Table 4.1). Procedure A was used to convert *N*-phenylaniline and 1-iodo-4-nitrobenzene to the title product. Purification by flash chromatography (1:3 dichloromethane/hexane) gave the analytically pure product as a white solid (0.22 g, 78% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, *J*=9.23, 2H; $H_{2,}$ $H_{,4}$), 7.10-7.40 (m, 10H; $H_{14,}$ $H_{11,}$ $H_{15,}$ $H_{13,}$ $H_{7,}$ $H_{6,}$ $H_{8,}$ $H_{9,}$ $H_{10,}$ H_{12}), 6.90 (dd, *J*=9.23, 2H; C_5, C_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.3 (C_4), 145.57 ($C_{7,}$ C_{17}), 140.0 (C_3), 129.8 ($C_{10,}$ $C_{11,}$ $C_{13,}$ C_{16}), 126.47 ($C_{1,}$ C_5), 125.67 ($C_{8,}$ $C_{9,}$ $C_{15,}$ C_{18}), 125 ($C_{2,}$ C_6), 118.0 ($C_{12,}$ C_{14}). Anal. Calcd. for $C_{18}H_{14}N_2O_2$: C, 74.48; H, 4.82. Found: C, 74.23; H, 4.81. Crystal data: Orthorhombic, *Pbca*, *a*=12.9966(5) Å, *b*=13.0469(5) Å, *c*=17.3593(6) Å, *V*=2943.5(2) Å^3, *Z*=8, number of unique reflections=1336, number of parameters=199, *R*1=0.052 (all data), *wR* (w=1/(σ^2(F_o^2) + 0.0300* F_o^2)=0.0961 (all data), GOF=1.151, residual electron density=+0.12.

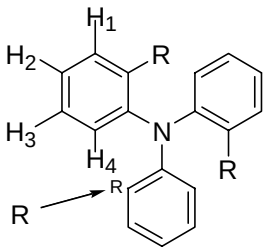




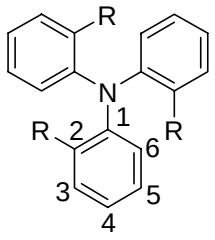
Methyl 4-(diphenylamino)benzoate (entry 5, Table 4.1). Procedure B was used to convert *N*-phenylaniline and methyl 4-iodobenzoate to the title product, with the exception that potassium *tert*-butoxide was used in place of cesium carbonate as base. Purification by flash chromatography (1:4 ether/hexane) gave the analytically pure product as a pale yellow solid (0.18 g, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, *J*=8.67, 2H; $H_{1,}$ H_3), 7.90 (d, *J*=8.67, 2H; $H_{2,}$ H_4), 7.15 (m, 5H; $H_{5,}H_{7,}H_{9,}H_{8,}H_6$), 7.33 (m, 5H; $H_{12,}H_{10,}H_{11,}H_{13,}H_{14}$), 3.90 (s, 3H- methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.77 (C_{19}), 152.0 (C_4), 146.5 ($C_{7,}C_8$), 130.77 ($C_{1,}C_5$), 129.4 ($C_{9,}C_{12}$), 129.1 ($C_{15,}C_{18}$), 125.77 ($C_{11,}C_{13,}$ $C_{14,}$ C_{17}), 124.3 ($C_{2,}$ C_6), 119.9 ($C_{10,}$ C_{16}), 117.6 (C_3), 51.67 (C_{20}). Anal. Calcd. for $C_{20}H_{17}O_2N$: C, 79.20; H, 5.61; N, 4.62. Found: C, 79.17; H, 5.62; N, 4.59.



o.o'.o''-amino-trisbenzoic acid-trimethylester (entry 7, Table 4.1). Procedure A was used to convert the 2,2'-azanediyl-bis-methylbenzoate and methyl 2-iodobenzoate to the title product, except for the following: 1,2 dichlorobenzene was used as the solvent. The reaction time was 30 h and the temperature was set at 170 ^{o}C instead of 120 ^{o}C. After the required time, the reaction mixture was transferred into a 50 mL round bottom flask and the contents of the flask were vacuum distilled at 135 ^{o}C to remove *o*-dichlorobenzene. After distillation, the remaining crude residue was purified by flash column chromatography using a 3:1 hexane/ethyl acetate solvent system on silica gel to obtain the analytically pure product as a pale yellow solid (0.17 g, 40 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (dd, J_{meta}=1.7, J_{ortho}=7.7, 3H; H_1), 7.36 (dt, J_{meta}=1.7, J_{ortho}=7.7, 3H; H_2), 7.06 (m, 6H; H_3, H_4), 3.51 (s, 9H; methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6 (C_7), 146.8 (C_1), 132.12 (C_5), 130.9 (C_3), 127.3 (C_6), 126.0 (C_2), 123.40 (C_4), 51.6 (C_8). Anal. Calcd for $C_{24}H_{21}O_6N$: C, 68.73; H, 5.01; N, 3.34. Found: C, 68.25; H, 5.01; N, 3.72. Crystal data: Triclinic, *P*-1 (2), *a*=8.2076(8) Å, *b*=8.8702 (8) Å, *c*=15.687 (2) Å, α= 102.00°, β= 91.05 (3) °, γ= 103.99°, *V*=1081.1(2) Å^3, *Z*=2, number of unique reflections=1974, number of parameters=280, *R*1=0.0942 (all data), wR2=0.1334, GOF=1.067, residual electron density=+0.131.

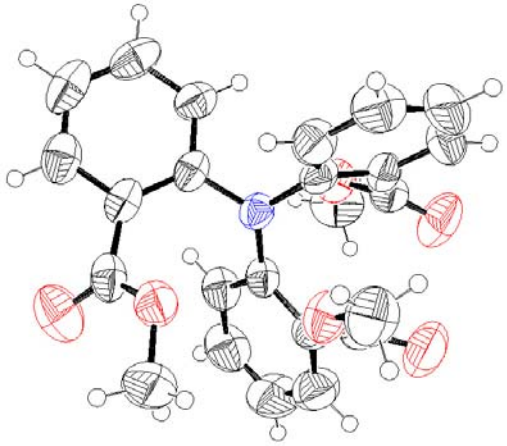


R=$COOCH_3$

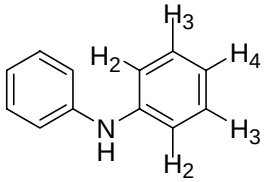


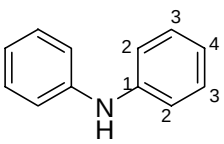
R=$COOCH_3$

7 8

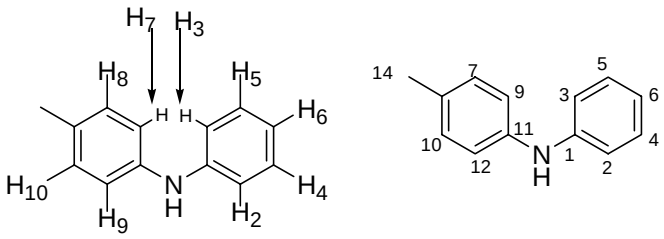


Diphenylaniline (entry 12, Table 4.2). Procedure B was used to convert phenylamine and iodobenzene to the title product. Purification by flash chromatography (1:4 dichloromethane/hexane) gave the analytically pure product as a pale yellow solid (0.12 g, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (m, 2H- H_4), 7.15 (dd, 4H; H_3), 7.02 (t, 4H; $H_{2,}$), 5.8 (amine proton); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143 (C_1), 129.2 (C_3), 120.8 (C_4), 117.4 ($C_{2,}$). Anal Calcd for $C_{12}H_{11}N$: C, 85.2; H, 6.5. Found: C, 85.16; H, 6.45.

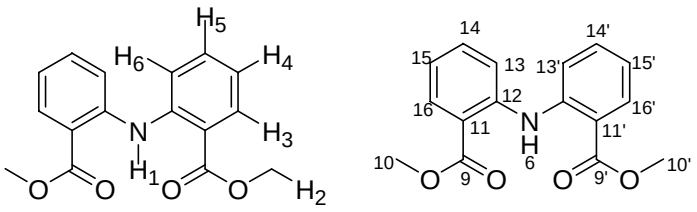




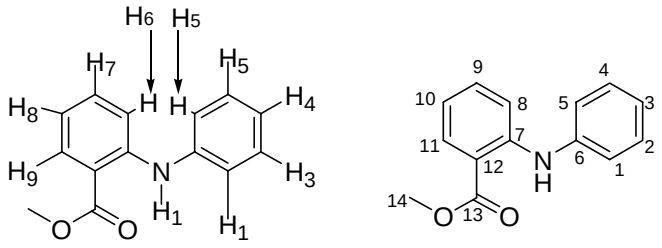
4-methyl-*N*-phenylaniline (entry 13, Table 4.2). Procedure B was used to convert *p*-toluidine and iodobenzene to the title product. Purification by flash chromatography (1:4 dichloromethane/hexane) gave the analytically pure product as a white solid (0.16 g, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (t, *J*=8.1, 2H- H_2, H_3), 6.9-7.10 (m, 6H- H_4, H_5, H_7, H_8, H_9, H_{10}), 6.8 (t, *J*=7.35, 1H- H_6), 5.5 (s, amine proton), 2.2 (s, 3H; methyl protons); ^{13}C NMR δ 143.88 (C_1), 140.18 (C_{11}), 130.88 (C_8), 129.7 (C_4,C_5), 129.2 (C_7, C_{10}) 120.1 (C_6), 118.7 (C_9,C_{12}), 116.7 (C_2,C_3), 20.58 (C_{13}). Anal Calcd for $C_{13}H_{13}N$: C, 85.2; H, 7.10. Found: C, 84.93; H, 7.16.



2,2'-azanediyl-bis-methylbenzoate (entry 8, Table 4.1). Procedure B was used to convert methyl 2-amino benzoate and methyl 2-iodobenzoate to the title product. Purification by flash chromatography (3:1, hexane/ethyl acetate) gave the analytically pure product as a pale yellow solid (0.236 g, 83 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) □ 8.0 (d, *J*=7.9, 2H- H_3), 7.55 (d, *J*=7.9, 2H- H_4), 7.35 (t, *J*=7.9, 2H- H_5), 6.9 (t, *J*=7.4, 2H- $H_{,6}$), 5.0 (amine proton), 4.0 (methyl protons); ^{13}C NMR δ 167.6 (C_9, $C_{9'}$), 144.0 (C_{12}, $C_{12'}$), 133.17 (C_{15}, $C_{15'}$), 131.6 (C_{14}, $C_{14'}$), 119.7 (C_{13}, $C_{13'}$), 117.5 (C_{16}, $C_{16'}$), 116.9 (C_{11}, $C_{11'}$), 52.0 (C_{10}, $C_{10'}$). Anal Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.26; N, 4.91. Found: C, 67.37; H, 5.33; N, 4.69.



Methyl 2-anilinobenzoate (entry 9, Table 4.1). Procedure B was used to convert methyl 2-amino benzoate and iodo benzene to the title product. Purification by flash chromatography (3:1, hexane/ethyl acetate) gave the analytically pure product as a pale yellow liquid. (58 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (dd, J_{0rtho}=8.05, J_{meta}=1.5, J_{para}, 1H- H_9); 7.20-7.40 (m, 6H- H_1, H_2, H_3,H_4, H_5, H_7), 7.08 (t, J=6.6, 1H- H_6), 6.62 (t, J_{ortho}=8.0, J_{meta}, 1H- H_8), 5.1 (amine proton), 4.0 (methyl proton); ^{13}C NMR δ 169.33 (C_{13}), 148.3 (C_{12}), 141.1 (C_6), 134.5 (C_9), 132.0 (C_8), 129.7 (C_4, C_5), 123.9 (C_{10}), 122.9 (C_2, C_3), 117.5 (C_{11}), 114.4 (C_7), 112.2 (C_1), 52.1 (C_{14}). Anal Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.84; H, 5.70; N, 6.02.

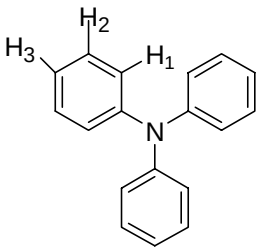


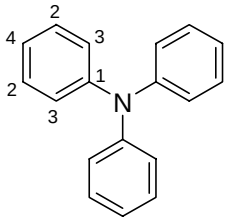
[Cu(neocup)(PPh_3)Br] Coupling of *N*-phenylaniline with Aryl Halides

General Procedure A: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar, was charged with potassium *tert*-butoxide

(Acros, 1.5 mmol) and [Cu(neocup)(PPh_3)Br] (10 mol% with respect to the aryl halide) and diphenylamine (1 mmol) was sealed with a rubber septum. The sealed tube was taken out of the box and the aryl halide (1 mmol) and toluene (15 mL) were injected into the tube through the septum. The tube was then degassed and backfilled with argon three times using a long needle. Care was taken to make sure the contents were well stirred. The reaction mixture was then heated at 110-120 ^{0} C at times indicated in Table 1. After the allowed time, the reaction mixture was then cooled, mixed with 15 mL of diethyl ether, and filtered to remove any insoluble residues. The combined extracts were dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was then purified by flash column chromatography on silica gel to obtain the analytically pure product. For entries 3, 6 a small sample of the reaction mixture was extracted after the specified time (see Table 1), and then run through a GC and compared against pure isolated sample of the expected product.

Triphenylamine (entry 1, Table 4.3). Procedure A was used to convert diphenylamine and iodobenzene to the title product. Purification by flash chromatography (1:4 dichloromethane/hexane) gave the analytically pure product as a white solid (0.19 g, 78 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, 6H- H_2), 7.07 (dd, J_{ortho}=6.97, 6H- H_1), 6.6 (t, J_{ortho}= 7.0, 6H- H_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.82 (C_1), 129.08 (C_2), 124.08 (C_3), 122.58 (C_4). Anal. Calcd. for $C_{18}H_{15}N$: C, 88.16; H, 6.12; N, 5.71. Found: C, 88.05; H, 6.18; N, 5.70.



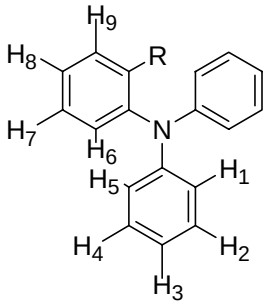


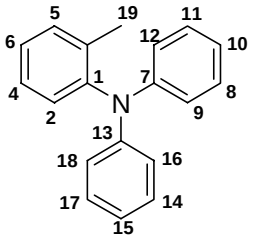
Triphenylamine (entry 2, Table 4.3). Procedure A was used to convert diphenylamine and bromobenzene to the title product. Purification by flash chromatography (1:4 dichloromethane/hexane) gave the analytically pure product as a white solid (0.19 g, 73 % yield). Same characterization data as entry 1.

Triphenylamine (entry 3, Table 4.3). Procedure A was used to convert diphenylamine and chlorobenzene to the title product. A aliquot of the reaction mixture was extracted after 36 hours and compared against a previously isolated and characterized sample of the expected product: triphenylamine (49 % GC yield). GC Correction factors used for calculation of the GC yield in this entry are as follows: (chlorobenzene: 0.467, Diphenylamine: 0.738, triphenylamine: 1.831). The product has the same characterization data as entry 1.

2-Methyl-*N*, *N*-diphenylaniline (entry 4, Table 4.3). Procedure A was used to convert *N*-phenylaniline and 1-iodo-2-methylbenzene to the title product. Purification by flash chromatography (1:4 dichloromethane/hexane) gave the analytically pure product as white solid (0.23 g, 88 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11- 7.24 (m, 6H- H_3, H_6, H_7, H_8, H_9), 6.90-7.00 (m, 8H- H_1, H_2, H_4, H_5,), 2.04 (methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.38 (C_7, C_{13}), 136.48 (C_1), 131.58 (C_5), 129.6 (C_4), 128.98 (C_8, C_{11},

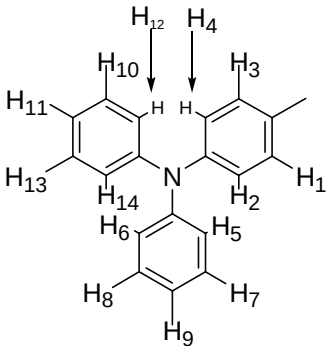
$C_{14,}$ C_{17}), 127.28 (C_{10}), 125.88 (C_{15}), 121.48 ($C_{9,}$ $C_{12,}$ $C_{16,}$ C_{18}), 121.32 (C_2), 18.48 (C_{19}). Anal. Calcd. for C_{19} H_{17}N: C, 88.03; H, 6.56; N,5.40. Found: C, 88.05; H, 6.56; N,5.33.

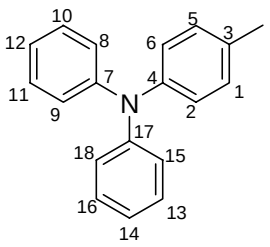




$R=CH_3$ (H_{10})

4-Methyl-*N*,*N*-diphenylaniline (entry 5, Table 4.3). Procedure A was used to convert *N*-phenylaniline and 1-iodo-4-methylbenzene to the title product. Purification by flash chromatography (1:4, dichloromethane/hexane) gave the analytically pure product as a white solid (0.18, 70 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08-7.17 (t, *J*= 7.47), 6.83-7.00 (m), 2.2 (methyl protons); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148 ($C_{7,}$ C_{17}), 145.17 (C_4), 132.67 (C_3), 129.8 (C_1), 129.07 ($C_{10,}$ $C_{11,}$ $C_{13,}$ C_{16}), 124.8 ($C_{2,}$ C_6), 123.57 ($C_{8,}$ $C_{9,}$ $C_{15,}$ C_{18}), 122.17 (C_5), 20.77 (methyl protons). Anal Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.56; N, 5.40. Found: C, 87.46; H, 6.62; N, 5.34.





2-Methyl-N, N-diphenylaniline (entry 6, Table 4.3). Procedure A was used to convert *N*-phenylaniline and 1-bromo-2-methylbenzene to the title product. An aliquot of the reaction mixture was extracted after 36 hours and compared against a previously isolated sample of 2-Methyl-*N*, *N*-diphenylaniline (GC yield: 50%). GC Correction factors used for calculation of the GC yield in this entry are as follows (1- bromo-2-methylbenzene: 0.541, 2-Methyl-N, N-diphenylamine: 0.883, Diphenylamine: 0.738). The product has the same characterization data as entry 4.

Diphenylaniline. Procedure A was used to convert phenylamine and bromobenzene to the title product. An aliquot of the reaction mixture was extracted and compared against a previously isolated and characterized sample of diphenylaniline (GC Yield: 54%). GC Correction factors used for calculation of the GC yield in this entry are as follows (bromobenzene: 0.461, aniline: 0.392, diphenylamine: 0.738).

4-Methyl-N,N-diphenylaniline. Procedure A was used to convert *p*-toluidine and bromobenzene to the title product. An aliquot of the reaction mixture was extracted and compared against a previously isolated and characterized sample of 4-Methyl-*N*,*N*-diphenylaniline (GC Yield: 54%). GC Correction factors used for calculation of GC yield in this entry are as follows: (1- bromo-4-methylbenzene: 0.457, 4-Methyl-N, N-diphenylamine: 1.243, *p*-toluidine: 0.452). The product has the same characterization data as entry 5.

A General Method for the Formation of Alkyl Thioethers using Copper(I) Catalysts

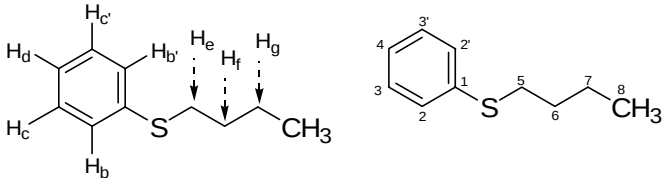
General. All of the reactions reported herein were conducted under an inert atmosphere of argon in oven-dried glassware. All reagents and solvents were obtained from Acros or from Aldrich and were used without further purification. Sodium *tert*-Butoxide (Acros, 99%) was stored in an argon filled glove box. Purification was performed by flash chromatography using ICN Flash Silica Gel, 230-400 mesh. The yields given refer to isolated yields of the characterized compounds, deemed pure by elemental analyses, ^{1}H NMR and ^{13}C NMR. NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Chemical shifts were reported in parts per million (δ). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; and m, multiplet. The coupling constants, *J*, are reported in Hertz (Hz). The residual solvent peak was used as the internal reference. Elemental analyses were performed at the Microanalysis Laboratory, University of Massachusetts at Amherst by Dr. Greg Dabkowski.

Cu-Catalyzed Coupling of *n*-Butyl sulfides with Aryl Iodides.

General Procedure: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar, was charged with sodium *tert*-butoxide (Acros, 3.0 mmol), CuI (10 mol% with respect to the aryl iodide), and neocuproine (10 mol % with respect to the aryl iodide). The tube was then sealed with a rubber septum, taken out of the glove box and *n*-butyl sulfide (2.2 mmol), the aryl iodide (2.00 mmol) and toluene

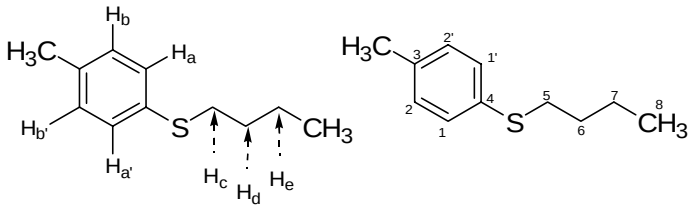
(5.0 mL) were injected into the tube through the septum. The contents were then stirred at 110 °C for 24 hours. The reaction mixture was then cooled to room temperature and filtered to remove any insoluble residues. The filtrate was concentrated in vacuo; the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product. Due to the stench of the *n*-butyl sulfides, all glassware and syringes used were washed with bleach to reduce the odor of the thiols.

***n*-Butyl Phenyl Sulfide (entry 1, Table 5.3):** The general procedure was used to convert iodobenzene and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (310 mg, 95 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.09 (m, 5H; H_b, $H_{b'}$, H_c, $H_{c'}$, H_d), 2.88-2.82 (t, *J*= 4.0, 2H; H_e), 1.60-1.46 (m, 2H; H_f), 1.42-1.30 (m, 2H; H_g), 0.88-0.82 (t, *J*= 3.9, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9 (C_1), 128.7 ($C_{3'}$, C_3 , C_2 , $C_{2'}$), 125.5 (C_4), 33.1 (C_5), 31.1 (C_6), 21.9 (C_7), 13.6 (C_8). Anal. Calcd. for $C_{10}H_{14}S$: C, 72.23; H, 8.49; S, 19.28; Found C, 71.97; H, 8.67; S, 19.07.

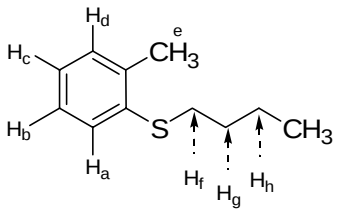


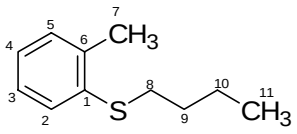
***n*-Butyl 4-Methylphenyl Sulfide (entry 2, Table 5.3):** The general procedure was used to convert 4-iodotoluene and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil

(331 mg, 94 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15-7.12 (d, *J*= 8.2, 2H; H_a, $H_{a'}$), 6.98-6.96 (d, *J*= 7.9, 2H; H_b, $H_{b'}$), 2.79-2.74 (t, *J*=7.1, 2H; H_c), 2.20 (Methyl Protons), 1.55-1.45 (m, 2H; H_d), 1.39-1.15 (m, 2H; H_e), 0.83-0.78 (t, *J*=7.1, 3H; H_f). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (C_4), 133 (C_3), 129.6 (C_1, $C_{1'}$), 129.47 (C_2, $C_{2'}$), 33.8 (methyl protons), 31.2 (C_5), 21.8 (C_6), 20.8 (C_7), 13.54 (C_8). Anal. Calcd. for $C_{11}H_{16}S$: C, 73.27; H, 8.94; S, 17.78; Found C, 73.21; H, 9.15; S, 17.57.

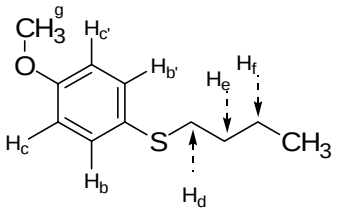


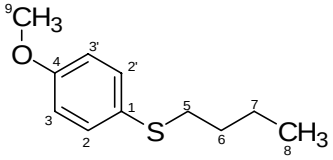
***n*-Butyl 2-Methylphenyl Sulfide (entry 3, Table 5.3):** The general procedure was used to convert 2-iodotoluene and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (331 mg, 93 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-6.97 (m, 4H; H_a, H_b, H_c, H_d), 2.80-2.78 (t, *J*= 7.3, 2H; H_f), 2.27 (s, 3H; H_e), 1.61-1.51 (m, 2H; H_g,), 1.44-1.17 (m, 2H; H_h), 0.87-0.82 (t, *J*= 7.3, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137 (C_1), 136.3 (C_6), 129.9 (C_5), 127.1 (C_2), 126.2 (C_3), 125.1 (C_4), 32.3 (C_8), 31 (C_9), 22 (C_{10}), 20.2 (C_7), 13.6 (C_{11}). Anal. Calcd. for $C_{11}H_{16}S$: C, 73.27; H, 8.94; S, 17.78; Found C, 73.23; H, 9.16, S, 17.57.





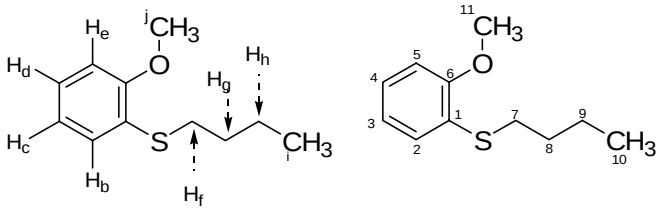
***n*-Butyl 4-Methoxyphenyl Sulfide (entry 4, Table 5.3):** The general procedure was used to convert 4-methoxy iodobenzene and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (370 mg, 95 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.23 (d, *J*= 9.0. 2H; H_b, $H_{b'}$), 6.76-6.73 (d, *J*= 8.8, 2H; H_c, $H_{c'}$), 3.69 (s, 3H; H_g), 2.75-2.70 (t, 2H; H_d), 1.50-1.43 (m, 2H; H_e), 1.36-1.28 (m, 2H; H_f), 0.83-0.78 (t, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.62 (C_4), 132.81 (C_1), 126.85 (C_2, $C_{2'}$), 114.39 (C_3, $C_{3'}$), 55.21 (C_9), 35.04 (C_5), 31.63 (C_6), 21.75 (C_7), 13.59 (C_8). Anal. Calcd. for $C_{11}H_{16}SO$: C, 67.30; H, 8.22; S, 16.33; Found C, 66.87; H, 8.28; S, 16.21.



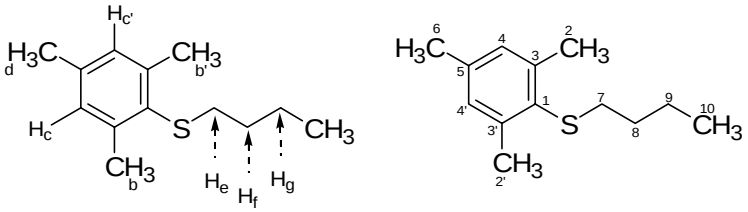


***n*-Butyl 2-Methoxyphenyl Sulfide (entry 5, Table 5.3):** The general procedure was used to convert 2-iodoanisole and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a light yellow oil (329 mg, 84 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-6.75 (m, 4H; H_b, H_c, H_d, H_e), 3.82 (s, 3H; H_j), 2.84-2.79 (t, *J*= 7.3, 2H; H_f), 1.60-1.52 (m, 2H; H_g), 1.43-1.36

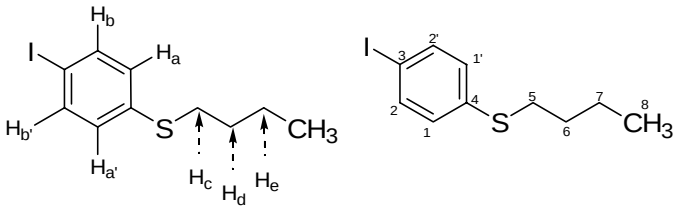
(m, 2H; H_h) 0.87-0.82 (t, *J*= 7.3, 3H; H_i). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.98 (C_6), 128.56 (C_2), 126.54 (C_4), 125.22 (C_1), 120.98 (C_3), 110.28 (C_5), 55.73 (C_{11}), 31.49 (C_7), 30.94 (C_8), 22.06 (C_9), 13.66 (C_{10}). Anal. Calcd. for $C_{11}H_{16}OS$: C, 67.30; H, 8.22; S, 16.33; Found C, 67.43; H, 8.28; S, 16.10.



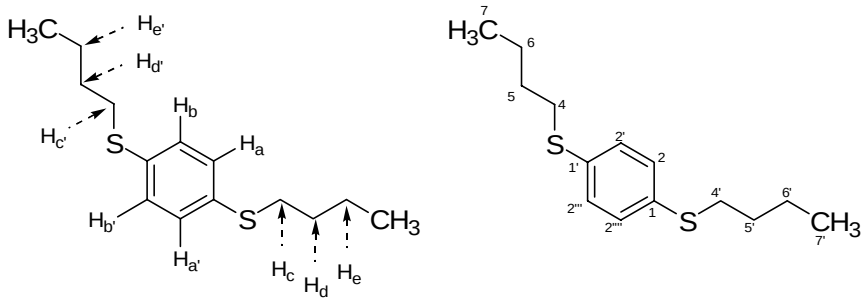
***n*-Butyl 2,2'-Dimethyl-4-methylphenyl Sulfide (entry 6, Table 5.3): The** general procedure was used to convert 2,2'-Dimethyl-4-methyl iodobenzene and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (405 mg, 98 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 2H; H_c, $H_{c'}$), 2.64-2.59 (t, *J*= 7.1, 2H; H_e), 2.50 (s, 6H; H_b, $H_{b'}$), 2.26 (s, 3H; H_d), 1.39-1.51 (m, 4H; H_f, H_g), 0.91-0.86 (t, *J*= 7.1, 3H; H_h). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8 (C_5), 137.7 (C_3, $C_{3'}$), 130.5 (C_1), 128.8 (C_4, $C_{4'}$), 35.2 (C_2, $C_{2'}$), 31.9 (C_6), 22.0 (C_7), 21.9 (C_8), 20.9 (C_9), 13.69 (C_{10}). Anal. Calcd. for $C_{13}H_{20}S$: C, 74.94; H, 9.67; S, 15.39; Found C, 74.66; H, 9.90; S, 15.32.



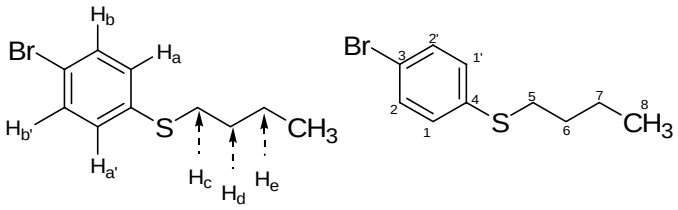
***n*-Butyl 4-Iodophenyl Sulfide (entry 7, Table 5.3**): The general procedure was used to convert diiodobenzene and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a pale yellow oil (512 mg, 88 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.55 (d, *J*=8.4, 2H; H_a, $H_{a'}$), 7.05-7.02 (d, *J*= 8.2, 2H; H_b, $H_{b'}$), 2.91-2.86 (t, *J*=7.3, 2H; H_c), 1.67-1.49 (m, 2H; H_d), 1.42-1.30 (m, 2H; H_e), 0.94-0.89 (t, *J*=7.3, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6 (C_1, $C_{1'}$), 137.2 (C_4), 130.2 (C_2, $C_{2'}$), 90.0 (C_3), 32.9 (C_5), 30.9 (C_6), 21.9 (C_7), 13.6 (C_8). High Resolution Mass. Spec. for $C_{10}H_{13}S$; Expected, 291.9783; Found, 291.9796



1,4-Bis-Butylsulfanyl-benzene (entry 8, Table 5.3): The general procedure was used to convert Diiodobenzene and 2 equiv. of *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a transparent oil (497 mg, 98 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, J_p=0.3, 4H; H_a, $H_{a'}$, H_b, $H_{b'}$), 2.83-2.78 (t, *J*= 7.3, 4H; H_c, $H_{c'}$), 1.56-1.48 (m, 4H; H_d, $H_{d'}$), 1.39-1.18 (m, 4H; H_e, $H_{e'}$), 0.86-0.81 (t, *J*=7.3, 6H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2 (C_1, $C_{1'}$), 129.5 (C_2, $C_{2'}$, $C_{2'''}$, $C_{2''''}$), 33.5 (C_4, $C_{4'}$), 31.1 (C_5, $C_{5'}$), 21.8 (C_6, $C_{6'}$), 13.5 (C_7, $C_{7'}$). High Resolution Mass. Spec. for $C_{14}H_{22}S_2$; Expected, 254.1163; Found, 254.1162

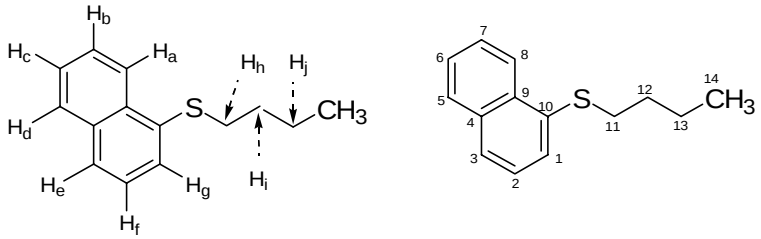


***n*-Butyl 4-Bromophenyl Sulfide (entry 9, Table 5.3):** The general procedure was used to convert 4-iodo bromobenzene and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (450 mg, 92 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.36 (d, *J*=8.6, 2H; H_a, $H_{a'}$), 7.19-7.15 (d, *J*= 8.28, 2H; H_b, $H_{b'}$), 2.91-2.86 (t, *J*=7.1, 2H; H_c), 1.57-1.47 (m, 2H; H_d), 1.41-1.31 (m, 2H; H_e), 0.94-0.89 (t, *J*=7.3, 3H; H_f). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.2 (C_4), 131.7 (C_1, $C_{1'}$), 130.2 (C_2, $C_{2'}$), 119.2 (C_3), 33.2 (C_5), 30.9 (C_6), 21.8 (C_7), 13.5(C_8). Anal. Calcd. for $C_{10}H_{13}Br$ C, 48.99; H, 5.34; S, 13.08; Found C, 49.09; H, 5.44; S, 12.96.

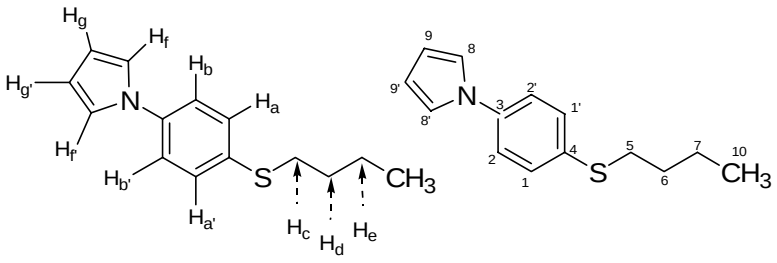


***n*-Butyl 2-Naphthalene Sulfide (entry 10, Table 5.3):** The general procedure was used to convert 2-Iodonaphthalene and *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane) gave the analytically pure product as a clear oil (410 mg, 95 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46-8.44 (d, *J*=8.1, 1H; H_a), 7.88-7.85 (d, *J*= 7.1,

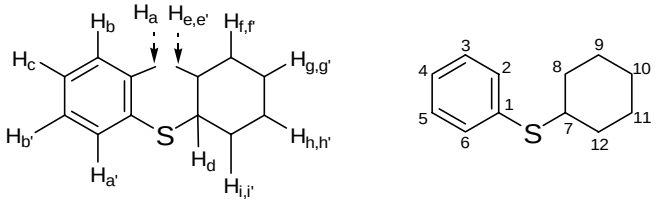
1H; H_d), 7.75-7.73 (d, 1H; H_e), 7.61-7.40 (m, 4H; H_g, H_f, H_b, H_c), 2.89-2.84 (t, 2H; H_h), 1.60-1.50 (m, 4H; H_i), 1.42-1.30 (m, 4H; H_j), 0.98-0.93 (t, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.17 (C_4), 133.81 (C_{10}), 132.78 (C_9), 128.47 (C_8), 127.27 (C_5), 126.72 (C_2) , 126.17 (C_6), 126.09 (C_7), 125.50 (C_1), 124.95 (C_3), 33.7 (C_{11}), 31.16 (C_{12}), 21.98 (C_{13}), 13.63 (C_{14}). Anal. Calcd. for $C_{14}H_{16}S$: C, 77.72; H, 7.45; S, 14.82; Found C, 77.44; H, 7.63; S, 14.56.



4-Pyrrole *n*-Butyl phenyl sulfide (entry 11, Table 5.3): The general procedure was used to convert Diiodobenzene and 2 equiv. of *n*-butyl sulfide to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a white solid (430 mg, 95% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.37 (d, *J*=8.8, 2H; H_a, H_a), 7.32-7.25 (d, *J*= 8.8, 2H; H_b, $H_{b'}$), 7.07-7.05 (t, *J*=2.2, 2H; H_g, $H_{g'}$), 6.35-6.33 (t, *J*=2.07, 2H; H_f, $H_{f'}$), 2.95-2.90 (t, *J*=7.15, 2H; H_c), 1.59-1.52 (m, 2H; H_d), 1.45-1.18 (m, 2H; H_e), 0.95-0.90 (t, *J*=7.3, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.8 (C_3), 130.5 (C_4), 120.8 (C_1, $C_{1'}$), 119.2 (C_2, $C_{2'}$), 118.2 (C_8, $C_{8'}$), 110.4 (C_9, $C_{9'}$), 33.9 (C_5), 31.1 (C_6), 21.9 (C_7), 13.5 (C_{10}). High Resolution Mass. Spec. for $C_{14}H_{17}NS$; Expected, 231.1082; Found, 231.1099.



Cyclohexyl-phenyl sulfide (entry 12, Table 5.3): The general procedure was used to convert iodobenzene and cyclohexylmercaptan to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (297 mg, 77% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, *J*=6.97, 2H; H_a, $H_{a'}$), 7.35-7.22 (m, 3H; H_b, $H_{b'}$, H_c,), 3.19-3.11 (m, 1H; H_d), 2.04 (m, 2H; H_e, H_i), 1.82 (m, 2H; $H_{e'}$, $H_{i'}$), 1.65 (m, 1H; H_g), 1.48-1.26 (m, 5H; H_h, H_f, $H_{h'}$, $H_{f'}$, $H_{g'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.11 (C_1), 131.75 (C_3, C_5), 128.64 (C_2, C_6), 126.46 (C_4), 46.44 (C_7), 33.26 (C_8, C_{12}), 25.97 (C_{10}), 25.69 (C_9, C_{11}). Anal. Calcd. for $C_{12}H_{16}S$: C, 74.94; H, 8.39; S, 16.67; Found C, 75.06; H, 8.40; S, 16.54.



General Method for the Formation of Aryl-Selenium Bonds using a Copper(I) Catalyst

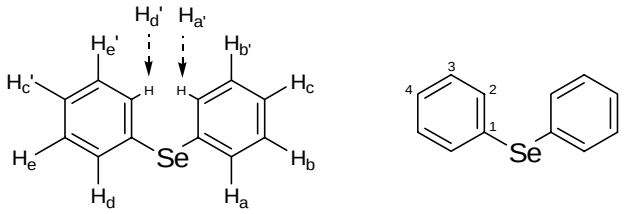
General. All of the reactions reported herein were conducted under an inert atmosphere of argon in oven-dried glassware. All reagents and solvents were obtained from Acros or from Aldrich and were used without further purification. Sodium *tert*-Butoxide (Acros, 99%) and Potassium Phosphate (Aldrich) and Potassium Carbonate (Aldrich) were stored in an argon filled glove box. Purification was performed by flash chromatography using ICN Flash Silica Gel, 230-400 mesh. The yields given refer to isolated yields of the characterized compounds, deemed pure by elemental analyses, ^{1}H NMR and ^{13}C NMR. NMR spectra were recorded on a Bruker AVANCE 300 MHz spectrometer. Chemical shifts were reported in parts per million (δ). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; and m, multiplet. The coupling constants, *J*, are reported in Hertz (Hz). The residual solvent peak was used as the internal reference. Elemental analyses were performed at the Microanalysis Laboratory, University of Massachusetts at Amherst by Dr. Greg Dabkowski. The reported melting points were uncorrected.

Cu-Catalyzed Coupling of Phenyl Selenols with Aryl Iodides

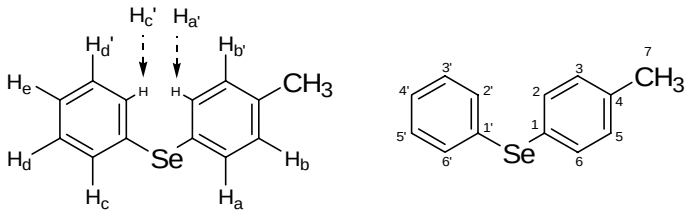
General Procedure: In an argon-filled glove box, a Pyrex glass tube (2.5 cm in diameter) equipped with a Teflon stir bar, was charged with sodium *tert*-butoxide (Acros, 3.0 mmol), CuI (10 mol% with respect to the aryl iodide), and neocuproine (10 mol% with respect to the aryl iodide). The tube was then sealed with a rubber septum, taken out

of the glove box and phenolselenol (2.2 mmol), the aryl iodide (2.00 mmol) and toluene (4.0 mL) were injected into the tube through the septum. The contents were then stirred at 110 °C for 24 hours. The reaction mixture was then cooled to room temperature and filtered to remove any insoluble residues. The filtrate was concentrated in vacuo; the residue was purified by flash column chromatography on silica gel to obtain the analytically pure product. Due to the stench and toxicity of the selenols, all glassware and syringes used were washed with bleach to reduce the odor. Phenyl Selenol must strictly be handled under argon at all times or the yield of the reactions is lowered and diphenyldiselenide is formed. All waste (both solid and liquid) generated from the reactions were stored in waste bottles and containers kept inside the fume hood.

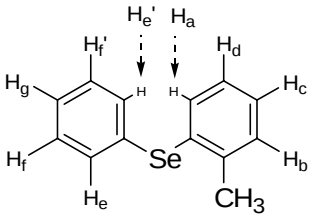
Diphenylselenide (entry 1, Table 5.5): The general procedure was used to convert iodobenzene and phenylselenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (410 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.36 (m, 4H; H_a, $H_{a'}$, H_d, $H_{d'}$), 7.20-7.15 (m, 6H; H_b, $H_{b'}$, H_e, $H_{e'}$, H_c, $H_{c'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.70 (C_1), 130.94 (C_2), 129.10 (C_3), 126.94 (C_4). Anal. Calcd. for $C_{12}H_{10}Se$: C, 61.81; H, 4.32; Found C, 62.19; H, 4.38.

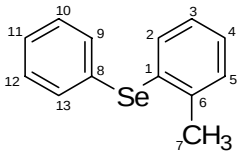


Phenyl-*p*-tolyl-selenide (entry 2, Table 5.5): The general procedure was used to convert 4-iodotoluene and phenylselenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (410 mg, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.30 (m, 4H; H_c, $H_{c'}$, H_a, $H_{a'}$), 7.17-7.01 (m, 3H; H_d, $H_{d'}$, H_e), 7.01 (d, *J*=8.4, 2H; H_b, $H_{b'}$), 7.04 (d, *J*= 7.9, 2H; H_b, $H_{b'}$), 2.23 (s, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.61 ($C_{1'}$), 133.85 (C_4), 131.99 (C_2, C_6), 132.06 (C_1), 130.16 (C_3, C_5), 129.17 ($C_{2'}$, $C_{6'}$), 126.82 ($C_{3'}$, $C_{5'}$), 126.72 ($C_{4'}$), 21.12 (C_7). Anal. Calcd. for $C_{13}H_{12}Se$: C, 63.16; H, 4.89; Found C, 63.29; H, 5.07.

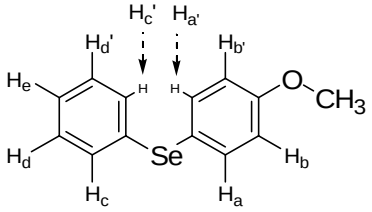


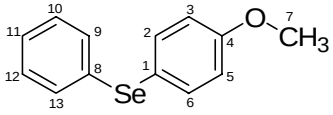
Phenyl-*o*-tolyl-selenide (entry 3, Table 5.5): The general procedure was used to convert 2-iodotoluene and phenylselenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a pale yellow oil (386 mg, 80 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-6.94 (m, 9H; H_a, H_b, H_c, H_d, H_e, $H_{e'}$, H_f, $H_{f'}$, H_g), 2.29 (s, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.75 (C_8), 133.56 (C_6), 132.68 (C_1), 130.67 (C_2), 130.17 (C_5), 129.30 (C_9, C_{13}), 127.70, (C_{10}, C_{12}), 127.07 (C_3), 126.66 (C_{11}), 126.27 (C_4), 20.30 (C_7). Anal. Calcd. for $C_{13}H_{12}Se$: C, 63.16; H, 4.89; Found C, 63.23; H, 5.14.





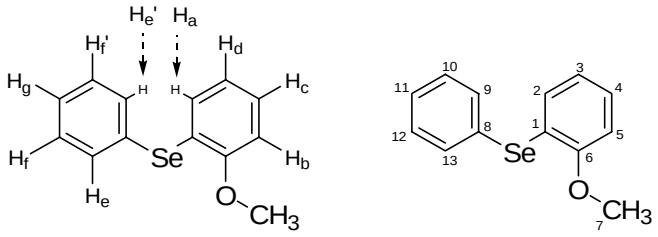
1-Methoxy-4-phenylselanyl-benzene (entry 4, Table 5.5): The general procedure was used to convert 4-iodoanisole and phenylselenol to the title product. Purification by flash chromatography (hexane/CH_2Cl_2 [4:1] as the eluent) gave the analytically pure product as a clear oil (460 mg, 88 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J*= 8.8, 2H; H_a, $H_{a'}$), 7.25-7.09 (m, 5H; H_c, $H_{c'}$, H_d, $H_{d'}$, H_e), 6.76 (d, *J*=8.8, 2H; H_b, $H_{b'}$), 3.70 (s, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7 (C_4), 136.5 (C_8), 133.1 (C_2, C_6), 130.8 (C_9, C_{13}), 129.1 (C_{10}, C_{12}), 126.3 (C_{11}), 119.8 (C_1), 115.1 (C_3, C_5), 55.23 (C_7). Anal. Calcd. for $C_{13}H_{12}OSe$: C, 59.32; H, 4.60; Found C, 59.44; H, 4.61.



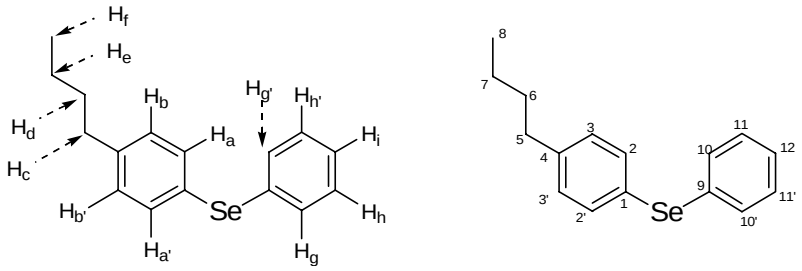


1-Methoxy-2-phenylselanyl-benzene (entry 5, Table 5.5): The general procedure was used to convert 2-iodoanisole and phenylselenol to the title product. Purification by flash chromatography (hexane/CH_2Cl_2 [4:1] as the eluent) gave the analytically pure product as a clear oil (430 mg, 78 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.05 (m, 6H; H_c, H_e, $H_{e'}$, H_f, $H_{f'}$, H_g), 7.12 (dd, *J*=7.5, 1H; H_a), 6.75-6.65 (m, 2H; H_b, H_d), 3.76 (s, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.48 (C_6), 135.34 (C_8), 130.65 (C_2), 129.35

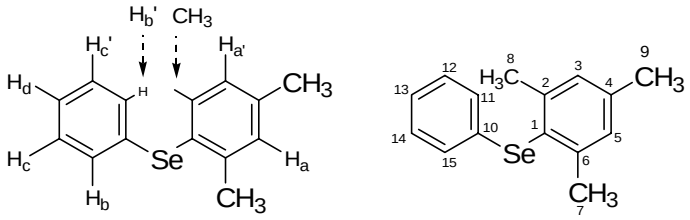
(C_9, C_{13}), 128.13 (C_{10}, C_{12}), 128.01 (C_4), 127.61 (C_{11}), 121.80 (C_1), 121.52 (C_3), 110.28 (C_5), 55.75 (C_7). Anal. Calcd. for $C_{13}H_{12}OSe$: C, 59.32; H, 4.60; Found C, 59.28; H, 4.65.



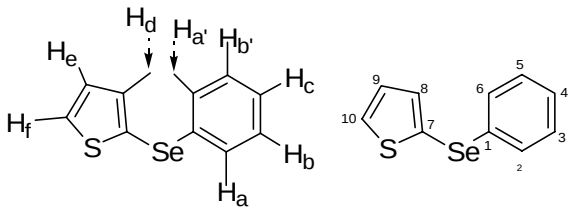
4-*n*-Butylselanyl-benzene (entry 6, Table 5.5): The general procedure was used to convert 4-*n*-butyl-iodobenzene and phenylselenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a transparent oil (463 mg, 80 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.31 (m, 4H; H_a, $H_{a'}$, H_b, $H_{b'}$), 7.18-7.13 (m, 3H; H_h, $H_{h'}$, H_i), 7.03-6.99 (m, 2H; H_g, $H_{g'}$), 2.53 (t, 2H; H_c), 1.53-1.18 (m, 4H; H_d, H_e), 0.87 (t, 3H; H_f). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.56 (C_4), 133.65 (C_9), 132.14 (C_2, $C_{2'}$), 131.93 (C_1), 129.49 (C_3, $C_{3'}$), 129.17 (C_{10}, $C_{10'}$), 127 (C_{11}, $C_{11'}$), 126.86 (C_{12}) , 32.25 (C_5), 33.46 (C_6) , 22.31 (C_7) , 13.92 (C_8). Anal. Calcd. for $C_{16}H_{18}Se$: C, 66.43; H, 6.27; Found C, 66.68; H, 6.54.



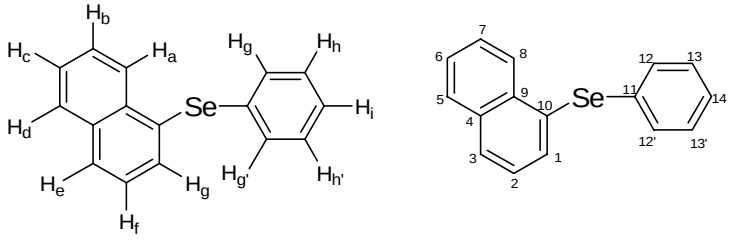
(2,4,6-trimethyl-phenyl)-phenyl selenide (entry 7, Table 5.5): The general procedure was used to convert 2,4,6-trimethyliodobenzene and phenylselenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a clear oil (451 mg, 82 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (s, 2H; H_a, $H_{a'}$), 6.96-6.87 (m, 3H; H_c, $H_{c'}$, H_d, H_b, $H_{b'}$) 2.26 (s, 6H; *ortho* methyl protons), 2.13 (s, 3H, *para* methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.06 (C_2, C_6), 139.51 (C_4), 133.87 (C_1), 129.53 (C_{10}), 129.27 (C_{11}, C_{15}), 128.82 (C_{12}, C_{14}), 127.15 (C_3, C_5), 125.76 (C_{13}), 24.70 (C_7, C_8), 21.49 (C_9). Anal. Calcd. for $C_{15}H_{16}Se$: C, 65.45; H, 5.86; Found C, 65.31; H, 5.86.



2-phenylselanyl-thiophene (entry 8, Table 5.5): The general procedure was used to convert 2-iodophenol and phenylselenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a pale yellow oil (320 mg, 68 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (dd, *J*=6.5, 1H; H_f), 7.26-7.23 (m, 3H; H_a, $H_{a'}$, H_e), 7.16-7.11 (m, 3H; H_b, $H_{b'}$, H_c), 6.98-6.94 (dd, *J*=8,85, 1H; H_d). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.02 (C_1), 133.39 (C_7), 132.05 (C_9), 129.84 (C_2, C_6), 129.18 (C_3, C_5), 129.84 (C_8), 128.30 (C_{10}), 126.68 (C_4). Anal. Calcd. for $C_{10}H_8SSe$: C, 50.21; H, 3.37; S, 13.41; Found C, 50.37; H, 3.37; S, 13.62.

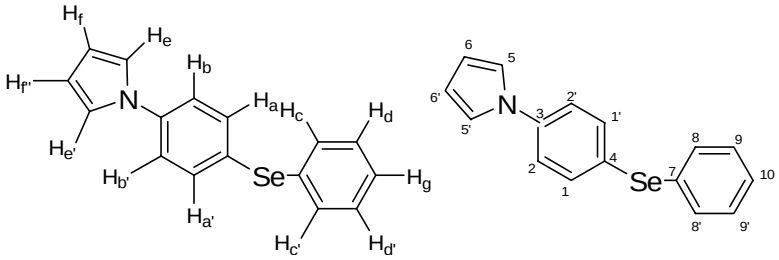


1-phenylselanyl-naphthalene (entry 9, Table 5.5): The general procedure was used to convert 2-iodonaphthalene and phenylselenol to the title product. Purification by flash chromatography (hexane) gave the analytically pure product as a clear oil (400 mg, 82 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25-8.22 (m, 1H; H_a), 7.74-7.64 (m, 3H; $H_{e,}$ H_f, H_g), 7.42-7.36 (m, 2H; $H_{g,}$ $H_{g'}$), 7.27-7.21 (m, 3H; $H_{b,}$ H_c, H_d), 7.24-7.21 (m, 3H; $H_{h,}$ $H_{h'}$, H_i). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.06 (C_4), 134.03 (C_9), 133.79 (C_{10}), 131.66 (C_3), 131.61 (C_8), 129.31 (C_5) , 129.24 (C_6), 129.14 (C_7), 128.53 (C_1), 127.59 (C_2), 126.89 (C_{11}), 126.75 ($C_{12,}$ $C_{12'}$), 126.31 ($C_{13,}$ $C_{13'}$), 125.97 (C_{14}). Anal. Calcd. for $C_{16}H_{12}Se$: C, 67.85; H, 4.27; Found C, 67.72; H, 4.24.

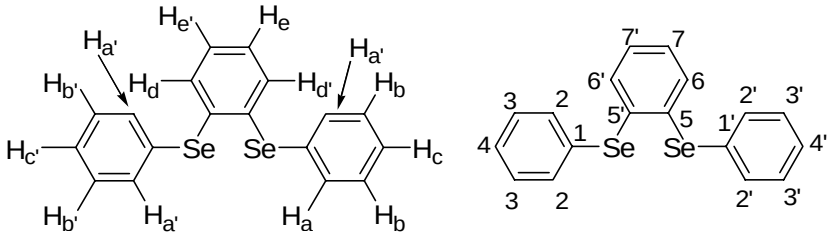


4-Pyrrole 1-selanylbenzene (entry 10, Table 5.5): The general procedure was used to convert 1-(4-iodophenyl)pyrrole and phenylselenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a white solid (450 mg, 76 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48-7.38 (m, 3H; H_d, $H_{g,}$ $H_{d'}$),

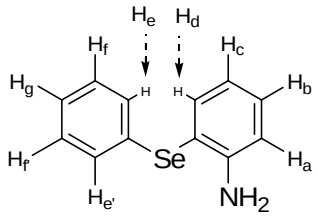
7.26-7.19 (m, 6H; $H_{b,}$ $H_{b'}$, $H_{a,}$ $H_{a'}$, $H_{c,}$ $H_{c'}$), 7.07 (t, *J*=4.3, 2H; $H_{e,}$ $H_{e'}$), 6.28 (t, *J*=4.3, 2H; H_f, $H_{f'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.54 (C_3), 133.35 (C_{10}), 132.68 (C_1, $C_{1'}$), 131.85 (C_2, $C_{2'}$), 129.40 (C_8, $C_{8'}$), 127.38 (C_9, $C_{9'}$), 125 (C_7), 121.16 (C_4), 119.13 ($C_{5,}$ $C_{5'}$), 110.70 ($C_{6,}$ $C_{6'}$). Anal. Calcd. for $C_{16}H_{13}NSe$: C, 64.43; H, 4.39; Found C, 64.35; H, 4.56. Melting Point: 86-88 ^{o}C .

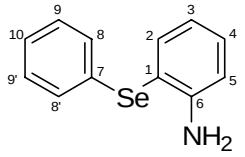


1,2-bis(phenylseleno)benzene (entry 11, Table 5.5): The general procedure was used to convert 1,2-diiodo-benzene and 2.2 equiv. of phenylselenol to the title product. Purification by flash chromatography (hexane as the eluent) gave the analytically pure product as a transparent oil (310 mg, 81 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.40 (m, 4H; H_a, $H_{a'}$), 7.23-7.20 (m, 6H; $H_{b,}$ $H_{b'}$, $H_{c,}$ $H_{c'}$), 7.12-7.09 (m, 2H; $H_{d,}$ $H_{d'}$), 6.99-6.94 (m, 2H; H_e, $H_{e'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.80 (C_1), 133.90 ($C_{2,}$ $C_{2'}$), 132.90 (C_6, $C_{6'}$), 130.55 (C_5, $C_{5'}$), 129.48 (C_3, $C_{3'}$), 127.87 (C_4, $C_{4'}$), 127.82 ($C_{7,}$ $C_{7'}$). Anal. Calcd. for $C_{18}H_{14}Se_2$: C, 55.69; H, 3.63; Found C , 55.50; H, 3.62.

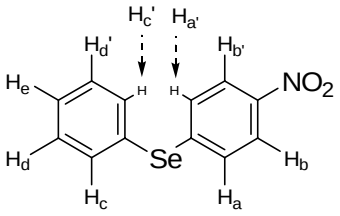


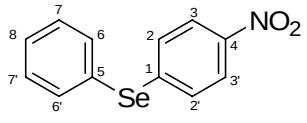
2-aniline-phenyl-phenyl selenide (entry 12, Table 5.5): The general procedure was used to convert 2-iodoaniline and phenylselenol to the title product. Purification by flash chromatography (hexane/dichloromethane [4:1] as the eluent) gave the analytically pure product as a white solid (300 mg, 62 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, *J*=7.7, H; H_a), 7.16-7.08 (m, 6H; H_g, $H_{f'}$, $H_{f''}$, H_e, $H_{e'}$, H_d), 6.75 (dd, J=7.9, 1H; H_c), 6.63 (dd, *J*=7.5, 1H; H_a). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.9 (C_6), 138.4 (C_1), 131.5 (C_3), 130.9 (C_4), 129.4 (C_9, $C_{9'}$), 129.2 (C_8, $C_{8'}$), 126.1 (C_2), 119.1 (C_5), 115.3 (C_{10}), 113.1 (C_7). Anal. Calcd. for $C_{12}H_{11}NSe$: C, 58.07; H, 4.47, N, 5.64. Found C, 58.35; H, 4.61; N, 5.53.



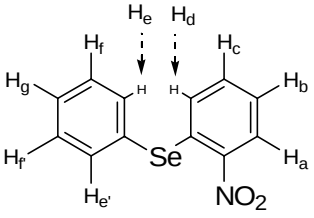


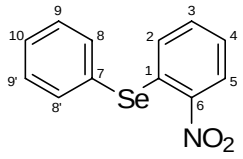
4-nitro-phenyl-phenyl selenide (entry 1, Table 5.6): The general procedure was used to convert 4-nitro iodobenzene and phenylselenol to the title product. Purification by flash chromatography (hexane/dichloromethane [4:1] as the eluent) gave the analytically pure product as a white solid (290 mg, 75 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (dd, *J*=8.4, 2H; H_b, $H_{b'}$), 7.63 (dd, *J*=8.1, 2H; H_a, $H_{a'}$), 7.45-7.25 (m, 5H; H_d, $H_{d'}$, H_e, H_c, $H_{c'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6 (C_4), 134.8 (C_3, $C_{3'}$), 129 (C_2, $C_{2'}$), 128.6 (C_6, $C_{6'}$), 128.3 (C_7, $C_{7'}$), 126.1 (C_1), 130.1 (C_5), 128.4 (C_8). Anal. Calcd. for $C_{12}H_9NO_2Se$: C, 51.81; H, 3.26; N, 5.04. Found C, 52.05; H, 3.34; N, 4.88.





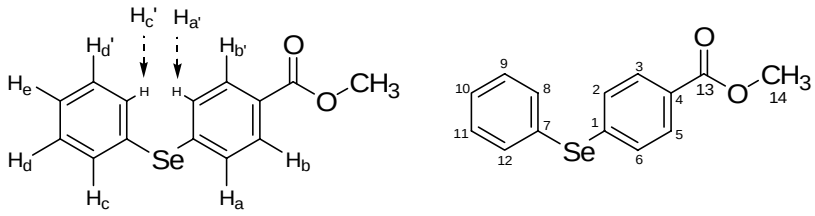
2-nitro-phenyl-phenyl selenide (entry 2, Table 5.6): The general procedure was used to convert 2-nitro iodobenzene and phenylselenol to the title product. Purification by flash chromatography (hexane/dichloromethane [4:1] as the eluent) gave the analytically pure product as a white solid (450 mg, 81 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (dd, *J*=7.5, H; H_a), 7.62 (d, *J*=6.5, 2H; H_b, H_c), 7.45-7.35 (m, 3H; H_f, $H_{f'}$, H_g), 7.24-7.15 (m, 2H; H_e, $H_{e'}$), 6.92 (d, *J*=7.53, 1H; H_d). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9 (C_6), 137.3 (C_8, $C_{8'}$), 135.8 (C_3), 133.6 (C_1), 130.1 (C_9, $C_{9'}$), 130 (C_4), 129.8 (C_5), 128 (C_{10}), 126 (C_2), 125.7 (C_7). Anal. Calcd. for $C_{12}H_9NO_2Se$: C, 51.81; H, 3.26, N, 5.04. Found C, 51.96; H, 3.38; N, 4.98.



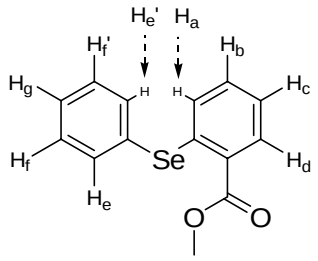


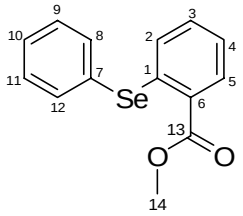
Methyl *p*-(phenylseleno)benzoate (entry 3, Table 5.6): The general procedure was used to convert methyl-4-iodobenzoate and phenylselenol to the title product. Purification by flash chromatography (hexane/dichloromethane [3:2] as the eluent) gave the analytically pure product as a white solid (481 mg, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, *J*=8.2, 2H; H_b, $H_{b'}$), 7.59-7.56 (m, 2H; H_a, $H_{a'}$), 7.38-7.35 (m, 5H; H_d, $H_{d'}$, H_e, H_c,

$H_{c'}$), 3.88 (s, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7 (C_{13}), 136.1 (C_1), 135.9 (C_4), 134.9 (C_8, C_{12}), 129.6 (C_7), 130.3 (C_9, C_{11}), 130.1 (C_3, C_5), 128.4 (C_{10}), 128.1 (C_2, C_6), 52.5 (C_{14}). Anal. Calcd. for $C_{14}H_{12}O_2Se$: C, 57.74; H, 4.15; Found C, 57.92; H, 4.39. Melting Point; 79-80 ^oC

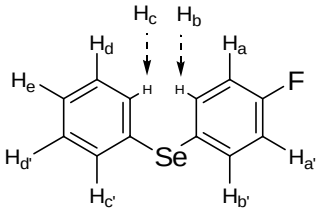


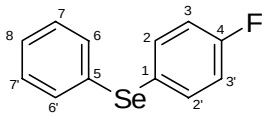
Methyl *o*-(phenylseleno)benzoate (entry 4, Table 5.6): The general procedure was used to convert methyl-2-iodobenzoate and phenylselenol to the title product. Purification by flash chromatography (hexane/dichloromethane[3:2] as the eluent) gave the analytically pure product as a clear oil (401 mg, 76 % yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J*=6.22, 1H; H_d), 7.47 (m, 2H; H_a, H_b), 7.33 (m, 3H; H_e, $H_{e'}$, $H_{f'}$), 7.14 (td, *J*=5.4, 1H; H_c), 7.04 (td, *J*=6.02, 1H; H_f), 6.73 (dd, *J*=6.7, 1H; H_g), 3.85 (s, 3H; methyl protons). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.79 (C_{13}), 143.15 (C_1), 135.47 (C_6), 132.39 (C_3), 132.22 (C_2), 130.93 (C_5), 129.65 (C_7), 129.02 (C_8, C_{12}), 127.28 (C_9, C_{11}), 126.58 (C_{10}), 124.19 (C_4), 52.10 (C_{14}). Anal. Calcd. for $C_{14}H_{12}O_2Se$: C, 57.74; H, 4.15; Found C, 57.85; H, 4.31.





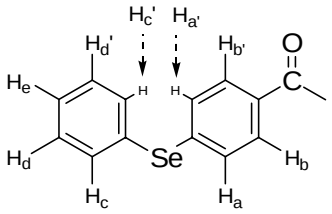
4-fluoro-phenyl-phenyl selenide (entry 5, Table 5.6): The general procedure was used to convert 2-nitro iodobenzene and phenylselenol to the title product. Purification by flash chromatography (hexane/dichloromethane [4:1] as the eluent) gave the analytically pure product as a white solid (460 mg, 92 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14-7.27 (m, 4H; H_a, $H_{a'}$, H_b, $H_{b'}$), 7.16-7.13 (m, 3H; H_d, H_e, $H_{d'}$), 6.87 (dd, *J*=8.6, 2H; H_c, $H_{c'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (C_4), 135.7 (C_2, $C_{2'}$), 135.6 (C_3, $C_{3'}$), 132.1 (C_6, $C_{6'}$), 129.3 (C_1), 127.1 (C_5), 116.6 (C_7, $C_{7'}$), 116.3 (C_8). Anal. Calcd. for $C_{12}H_9FSe$: C, 57.39; H, 3.61. Found C, 57.54; H, 3.65.

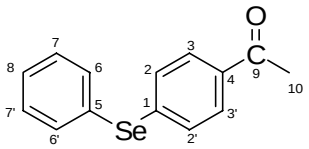




4-aceto-phenyl-phenyl selenide (entry 6, Table 5.6): The general procedure was used to convert 4-iodo-acetophenone and phenylselenol to the title product. Purification by flash chromatography (hexane/dichloromethane [4:1] as the eluent) gave the analytically pure product as a white solid (420 mg, 78 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (dd, *J*=8.2, 2H; H_b, $H_{b'}$), 7.59 (dd, *J*=7.7, 2H; H_a, $H_{a'}$), 7.38-7.35 (m, 5H; H_d, $H_{d'}$, H_e, H_c,

$H_{c'}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7 (C_9), 140.7 (C_4), 135.5 (C_2, $C_{2'}$), 134.1 (C_5), 130.6 (C_3, $C_{3'}$), 130.1 (C_7, $C_{7'}$), 129.3 (C_1), 129 (C_6, C_6'), 128.8 (C_8), 26.8 (C_{10}). Anal. Calcd. for $C_{14}H_{12}OSe$: C, 61.10; H, 4.40. Found C, 61.38; H, 4.63.





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