Development of Dipicolinic Acid Based Mono-Amides as New Ligands for Copper Catalyzed Carbon-Nitrogen and Carbon-Sulfur Bond Formation

A dissertation submitted to the Department of Chemistry,

Quaid-i-Azam University, Islamabad, in partial fulfillment

of the requirements for the degree of

Master of Philosophy

in

Organic Chemistry

by

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Islamabad

2016

DECLARATION

This is to certify that this dissertation entitled as **"Development of DipicolinicAcidBased Mono-Amides as New Ligands for Copper CatalyzedCarbon-Nitrogen and Carbon-Sulfur Bond Formation"** submitted by **BibiAmna**is accepted in its present form by the Department of Chemistry, Quaid-i-Azam University, Islamabad, Pakistan, as satisfying the dissertation requirements for the degree of **Master of Philosophy** in **Organic Chemistry.**

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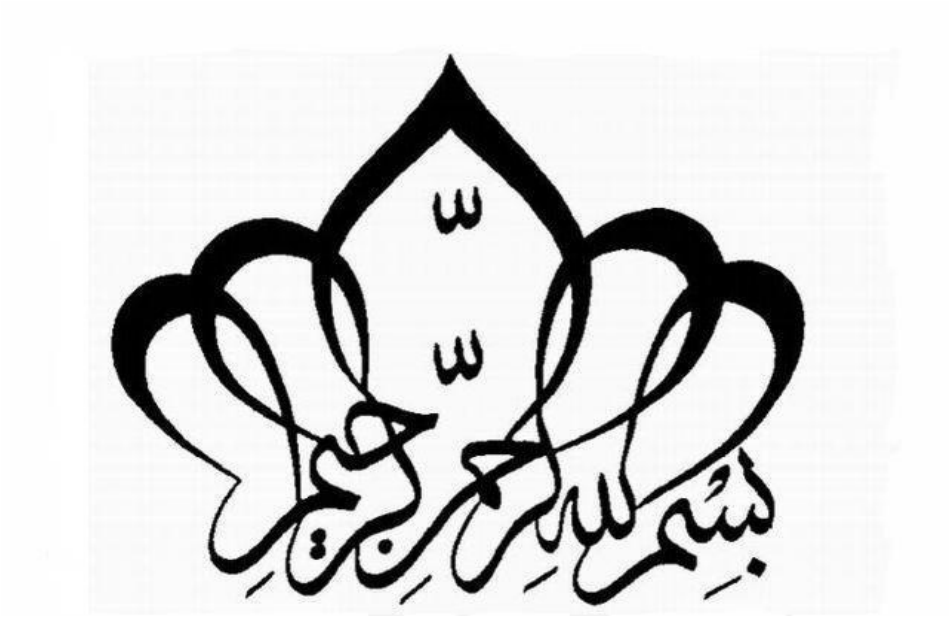

In the name of Allah, the most gracious, the most merciful

"He grants Hikmah to whom He pleases, and he, to whom Hikmah is granted is indeed granted abundant good. But none remember (will receive admonition) except men of understanding."

(Al-BAZARAH;269)

"O Allah, I ask Thee for Beneficial Knowledge, acceptable action,and good provision."
(Al-Tirmidhi Hadith 2487)

Dedication

This humble effort is dedicated to the martyrs of Army public school Peshawar and Bacha khan university Charsadda

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All praises to **Allah**, Almighty, Who is the entire source of knowledge and wisdom endowed to mankind; who gave me courage and potential to pursue this goal. All respect for His Last **Prophet Hazrat Muhammad (sallallaho*alaihewaalehewasallam*)**, who gave my conscience the essence of belief in Allah.

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I am very grateful to my family for their love, encouragement and constant support, both morally and financially, over the years. Words are just not enough to say thanks to, my beloved father for always standing by my side, encouraging me with the words of hope whenever I felt down and making a compromise on my lab timings, my loving and supportive mother who always prayed for my success and both of my brothers for their moral support.

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Bibi Amn

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Abbreviations and Acronyms

Å	Angstrorm
Ar	Aromatic substituent
acac	Acetylacetone
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Cu	Copper
DPA	Dipicolinic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	*N*,*N*-Dimethyl formamide
DMSO	Dimethylsulfoxide
DME	1,2-dimethoxyethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dba	Dibenzylideneacetone
DCM	Dichloromethane
DPA	Dipicolinic acid
HMPA	Hexamethylphosphoramide
i-PrOH/ IPA	iso-propanol
NMO	4-methylmorpholine-*N*-oxide
Ni	Nickel
OTf	Trifluoromethanesulphonate
OMs	Methane sulfonate

Phen	Phenanthroline
Pd	Palladium
Piv	Pivaloyl
r.t	Room temperature
TEA	Triethylamine
THF	Tetrahydrofuran
TEMPO	Tetramethyl pipiridinyloxy
TMEDA	Tetramethyl ethylenediamine
TLC	Thin layer chromatography
UV	Ultraviolet

Abstract

Carbon-heteroatom bonds are enormously found in both natural and synthetic products which play vital role in polymer chemistry, material science, agriculture and pharmaceutical industry. Due to prevalence of these bonds, development of new and efficient methods for their construction is of great significance. Transition metal catalysis has revolutionized the way these bonds are formed. Number of methodologies has been developed to form C-heteroatom bonds employing transition metals as catalysts. Transition metal mediated cross-coupling reactions to form C-N, C-O and C-S bonds have been greatly improved by using ligands. Mono-amides of dipicolinic acid are discovered to efficiently act as ligands for copper catalyzed C-N and C-S cross coupling reactions. These ligands are highly stable.

Mono-amide of ethylamine was found to be the most efficient ligand after the careful screening of all the available mono-amides of dipicolinic acid. Best working conditions for mono-amide of ethylamine were found after successful screening of each reaction parameter such as solvent, base, temperature and molar ratio of base. The scope of newly discovered catalytic system was investigated by the arylation of various amides and aromatic thiols using differently substituted iodobenzenes. All the coupled products were obtained in good to excellent yields. Synthesized products were characterized by physical and spectroscopic techniques.

CHAPTER-1

INTRODUCTION

Carbon-nitrogen, carbon-oxygen and carbon-sulfur bonds are an integral part of many compounds that show tremendous biological activities[1–5]. Due to ubiquity of these bonds in natural and synthetic compounds, there has always been a need to discover mild, general and efficient methodologies for the formation of these carbon-heteroatom bonds[6,7]. Traditionally, nucleophilic aromatic substitution reactions were used for the formation of aryl-N, aryl-O and aryl-S bonds, which in turn required electron-deficient aryl halides along with strong nucleophiles and nitrogen as a leaving group; in short, activated substrates were used by the classical methods[8,9].

Development of transition-metal catalysis was a great breakthrough in the field of synthetic organic chemistry as it enabled the chemists to carry out carbon-heteroatom bond synthesis under milder conditions[10–13]. Most popular amongst these transition-metal catalyzed methods are the ones that utilize palladium and copper as a catalyst[14].

1.1. Transition Metals as Catalysts

A catalyst is a substance that accelerates the rate of a reaction without being used up itself in the process. Catalysts are pretty important for many reactions as without them many of the industrial processes would be rendered commercially uneconomical.

Transition metals make very good catalysts[15], these are divided into two broad categories which are homogenous and heterogeneous catalysts.

I) Homogenous Catalysts:

A catalyst that exists in the same phase as the reactants is called a homogenous catalyst and this type of catalysis classified as homogenous catalysis[16]. Some well-known examples of homogenous catalysis include hydroformylation[17] and transfer hydrogenation[18] as well as certain kind of Ziegler-Natta polymerization[19] and

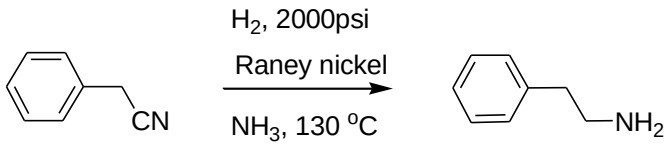
hydrogenation[20]. Homogenous catalysts have also been employed in a variety of industrial processes such as:

a) Monsanto process, which is an industrial process for manufacturing of acetic acid by catalytic carbonylation of methanol and "rhodium'' is employed as a catalyst in this method[21].
b) Cativa process, which is based on an "iridium'' containing catalyst, and is also used for the production of acetic acid through the carbonylation of methanol[22].
c) Wacker process is the first organomatellic and organopalladium reaction applied on an industrial scale. It involves oxidation of ethylene to acetaldehyde by oxygen in water using ''tetrachloropalladate'' as a catalyst[23].

II) Heterogeneous Catalysts:

If the catalyst is present in a different phase as the reactants, it is called heterogeneous catalyst and this type of catalysis is termed as heterogeneous catalysis[24]. Heterogeneous catalyst is often employed in industry due to ease of its separation from the products[25]. Examples are as following:

a) Synthesis of phenethylamine by the reduction of nitriles employs "Raney nickel'' as a catalyst[26].

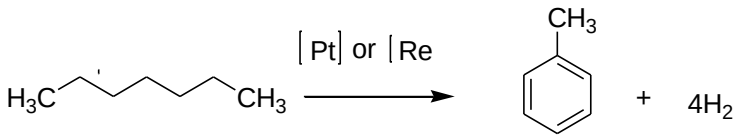


83%

b) Formation of sulfuric acid in contact process makes use of "vanadium oxide''as a catalyst[27].

$$SO_2(g) + 1/_2O_2(g) \xrightarrow{V_2O_5} SO_3(g)$$

c) Reforming of naphtha, utilizes "platinum or rhenium'' on silica or silica-alumina support base[28].



Transition metals belong to the d-block of periodic table and they contain partially filled d-orbitals[29]. Transition metals are considered as good catalysts because they can lend electrons or withdraw electrons from the reagent depending upon the nature of reaction. The ability of transition metals to exist in a variety of oxidation states, to interchange between different oxidation states, ability to form complexes and be a good source of electrons makes them a catalyst of choice. Incomplete d-orbitals allow the metal to facilitate the exchange of electrons. Transition metals can both give and except electrons easily[30].

Transition metals act by forming complexes with the reagents. Transition metals undergo oxidation or reduction to supply electrons if the transition state of the reaction demands electrons as well as the transition metals can hold excess electron density in case of excess buildup of electrons, thereby helping the reaction to take place[31].

Transition metals contain nine orbitals (one s, three p and five d) possessing suitable energies and geometrical features for bonding to maximum of nine ligands to attain maximum of 18 electrons according to 18-electron rule[32]. Transition metals can form covalent as well as coordinate covalent bond to the ligands. If all of the nine orbitals of the metal are completely filled, it is termed as coordinately saturated. Such a metal is resistant towards nucleophilic attack, so ligand replacement occurs by S_N1 type mechanism that is a ligand leaves before the attachment of another ligand and therefore metal converts to a 16-electron system. This switching between 16 and 18-electron system provides a driving force for a catalytic cycle[30].

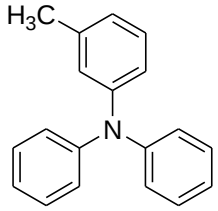
Recently modern synthetic methodologies are at their primitive stages and still there is a long way to go in order to develop efficient, high yielding, selective, economical and safe methods for the synthesis of fundamentally synthesizable compounds and transition metal catalysis has a great potential to help synthetic chemists in this regard[33].

1.2. Cross-Coupling Reactions

Metal catalyzed cross-coupling reactions are the one that join two molecular fragments using metal as a catalyst. The 2010 Nobel Prize in chemistry was awarded to pioneers of palladium-catalyzed carbon-carbon cross coupling reactions first disclosed over 40 years ago. Since then cross coupling reactions have become a staple of modern organic synthesis and have been developed for virtually every element in the first and second row of the p-block of the periodic table. Common examples of the transition metals used in cross coupling reactions include palladium[34], copper[35], nickel[36] and iron[37]. In general when cross-coupling reactions unite two fragments, one fragment serves as the electrophile while the other one as nucleophile. The elementary steps of a catalytic cycle are as following[38]:

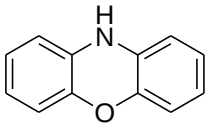
a) Oxidative addition, a metal inserts into σ-bond of the electrophile, this step increases the formal oxidation state of the metal and increases the number of ligands bound to the metal.
b) Transmetallation (ligand exchange), the nucleophile replaces ligand on a metal. After transmetallation, both molecular fragments to be coupled are bound to the metal.
c) Reductive elimination, the actual bond forming event that makes the organic product. Reductive elimination extrude the new organic molecule with both molecular fragments united by a σ-bond, leaving the metal in its original oxidation state and ready to start the catalytic cycle again.

The backbone of many organic compounds is composed of C-C bonds but the presence of heteroatom often derives the function of these molecules such as oxygen, nitrogen and sulfur which are held by C-heteroatom bonds in these compounds for example almost all natural products, pharmaceuticals and polymers contain ketone, ester or ether C-O bonds and C-N bonds of amine. Heterocyclic compounds containing C-O, C-N and C-S bonds in their ring structures find their applications in almost all areas of chemistry[39–42] (Figure 1.1, Figure 1.2).



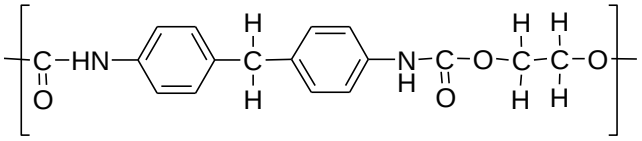
Diphenyl-m-tolyl amine

(Organic light emitting device)



Phenoxazine

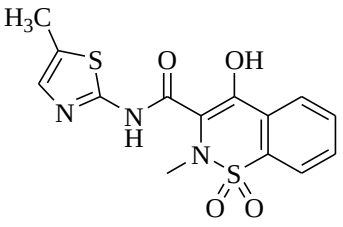
(Dye)



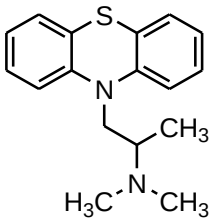
Polyurethane

(Versatile family of polymer)

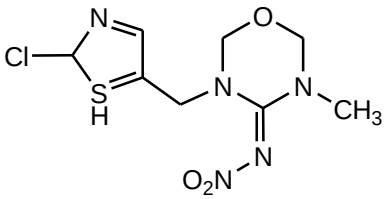
Figure 1.1. Synthetically important compounds containing C-heteroatom bonds



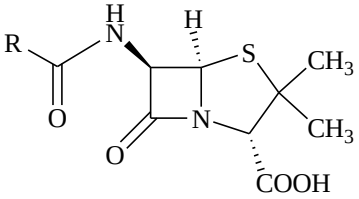
Meloxic
(anti-inflammatory drug)



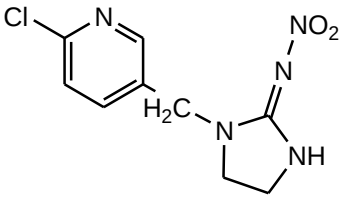
Promethazine
(Neuroleptic medication)
antihistamine



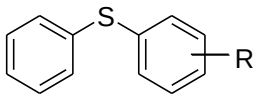
Thiamethoxam
(Insecticide)



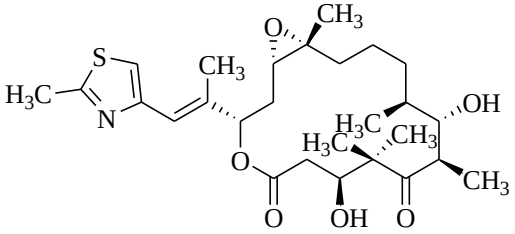
Penicillin
(Antibiotic)



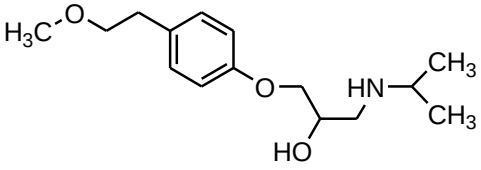
Imidacloprid
(Insect neurotoxin)



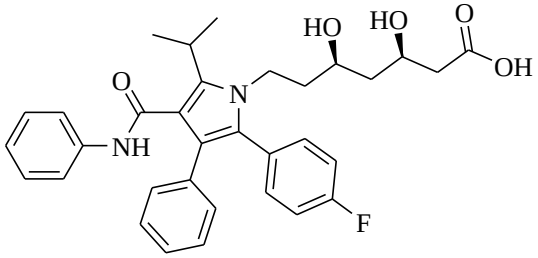
Aryl-sulfides
(Potential anti-HIV properties)



Epothilone
(potential cancer drug)



Metoprolol
(used for angina treatment)



Atorvastatin
(lowering blood cholesterol)

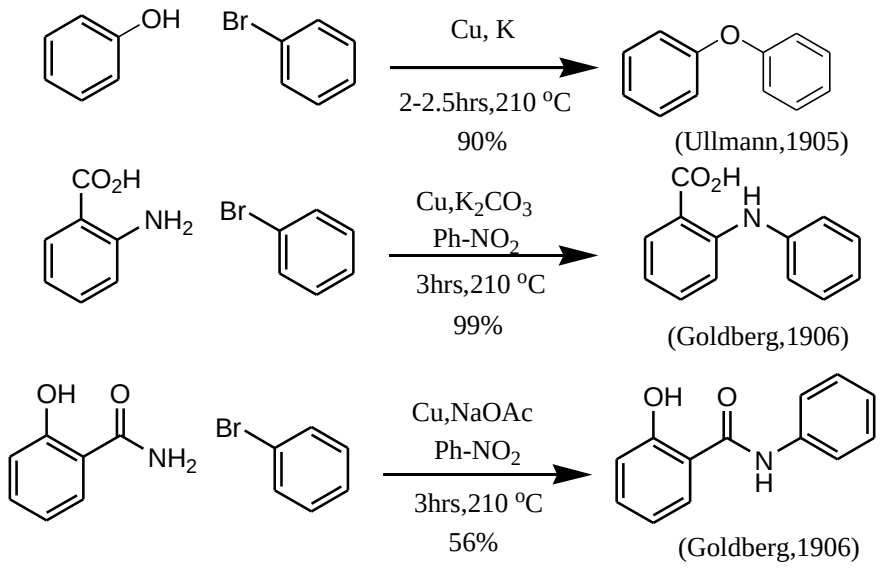
Figure 1.2. C-heteroatom bond containing drugs and insecticides

1.3. Emergence of Transition Metal Catalyzed Cross-Coupling Reactions

Tremendous work of Grignard on organomagnesium reagents[43] and synthesis of diethyl zinc by Frankland[44] in 1849 initiated the progress of modern organometallic chemistry. Some useful applications of nearly every metal present in periodic table have been demonstrated in synthetic organic chemistry. Selectivity and reactivity of organometallic reagent can be tuned according to the nature of the metal employed in a particular reaction. Development of transition metal catalysis during the last few years has brought a revolution in the field of synthetic organic chemistry for the formation of C-C and C-heteroatom bonds.

Many transition metals are effective promoters for the cross-coupling reactions such as palladium[34], nickel[36], iron[37], ruthenium[45], rhodium[46] and copper[35]. Transition metals posses low ionization energies. Compared to s- and p-orbitals, the d-orbitals is located farther away from nucleus so d-electrons are held quite loosely by the nucleus, therefore it is the d-electrons that make transition metals, special. The importance of transition metal chemistry is evident by the three Nobel prizes in chemistry to Ei-ichi Negishi, Akira Suzuki and Richard F.Heck for their pioneering work on the development of Pd-catalyzed cross-coupling reactions.

At the beginning of the 20th century, Fritz Ullmann and Irma Goldberg started off their pioneering work on copper catalyzed coupling reactions for the formation of aryl-C, aryl-O and aryl-N bonds. For the very first time they used unactivated aryl halides[47–49]. Ullmann was the first one to carry out copper catalyzed diaryl ether synthesis[47c] while copper catalyzed aryl amination and aryl amidation were both carried out by Goldberg[36], unintentionally using bidentate-coordinating substrate (Scheme 1.1).



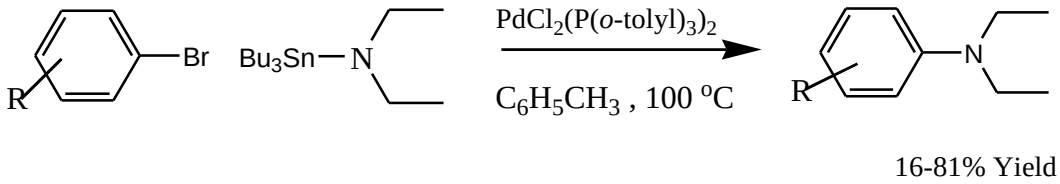
Scheme 1.1 Ullmann ether synthesis, Goldberg amination and Goldberg amidation

These reactions found their way into a number of industrial applications. However harsh reaction conditions particularly high temperatures have always been major restrictions of Ullmann and Goldberg protocol[47,48]. Most importantly with the evolution of green chemistry, the use of stoichiometric amount of copper, a heavy metal, in order to obtain high yield must be considered a major drawback[50].

1.4. Palladium-Catalyzed Amination Reactions

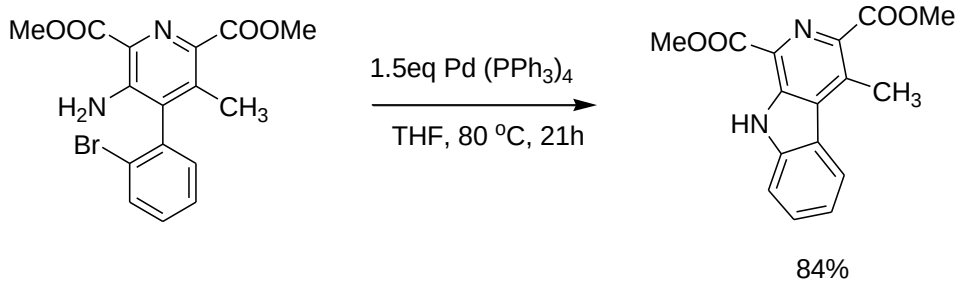
At the end of last century, the palladium based methodologies set out to solace the synthetic problems faced by the copper based approaches, initiated by Migita and mainly pushed by the efforts of Buchwald and Hartwig. Through the numerous efforts of these and other research groups, palladium catalysis came out to be the most sustainable and robust method for carrying out carbon-heteroatom bond formations[51–55].

In 1983, Migita, Kosugi and co-workers carried out Pd (0)-catalyzed amination of bromobenzenes using tin amides as nucleophiles[56] (Scheme 1.2).



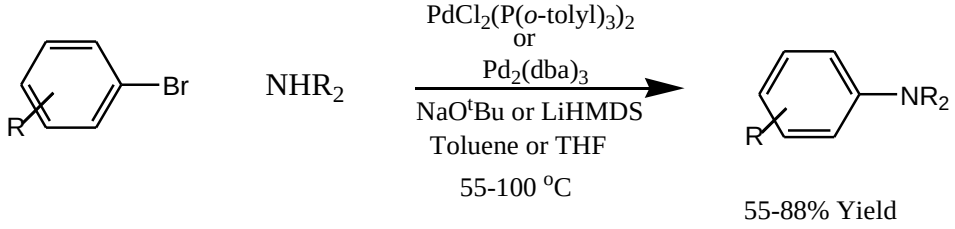
Scheme 1.2. First example of Pd-catalyzed aryl amine coupling

In 1984, Dale L. Boger and James S. Panek reported an example of C-N bond formation while working on the synthesis of lavendamycin making use of stoichiometric $Pd(PPh_3)_4$[57] (Scheme 1.3.).



Scheme 1.3. Pd-catalyzed synthesis of lavendamycin

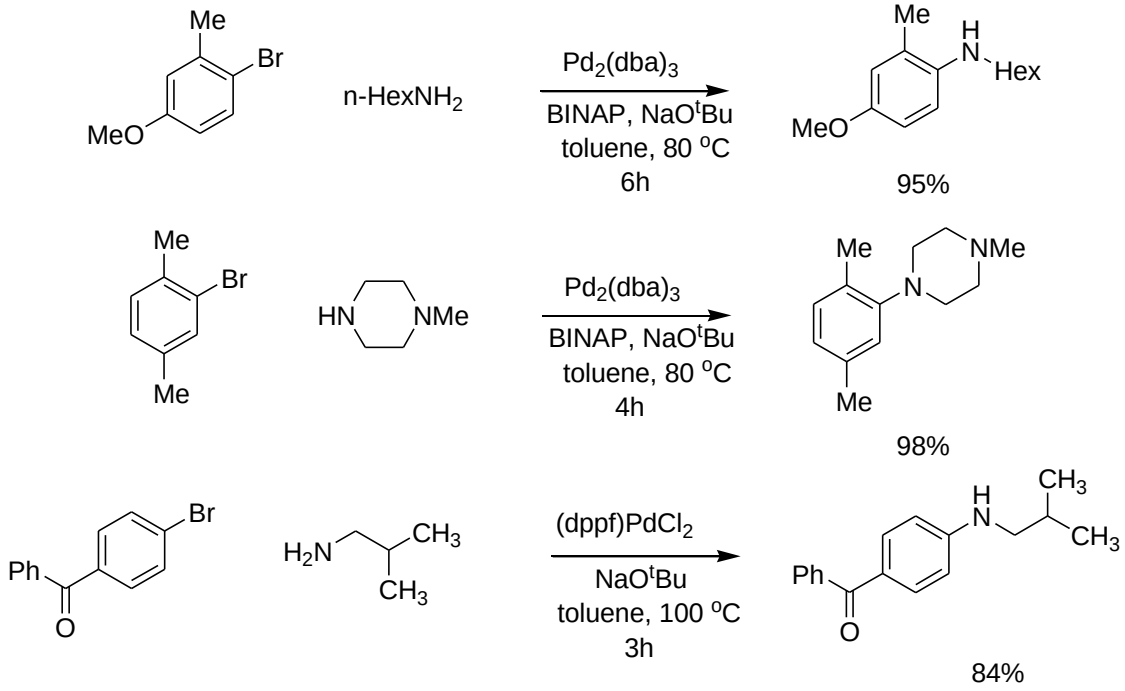
Buchwald and Hartwig in 1984, independently developed Pd (0)-catalyzed reactions which directly employed amines as nucleophiles in the presence of bases to synthesize variously substituted amines. These Pd-catalyzed amination reactions are popularly recognized as Buchwald-Hartwig amination reactions[58] (Scheme 1.4).



Scheme 1.4. Buchwald-Hartwig amination reactions

Buchwald and Hartwig,in their initial work, got succeeded to carry out amination of bromoarenes via secondary amines but found that, amination using primary amines was problematic due to the side reactions involving bis-arylation and *β*-hydride elimination.

Studies were therefore carried out to develop new ligands in order to solve these problems. Discovery of bidentate-phosphine ligands came out to be a major breakthrough in the development of palladium-catalysis[59,60]. Buchwald and Hartwig reported vast improvement in yield and scope by the use of phosphine ligands (Scheme 1.5).



Scheme1.5. Pd-catalyzed amination of bromoarenes

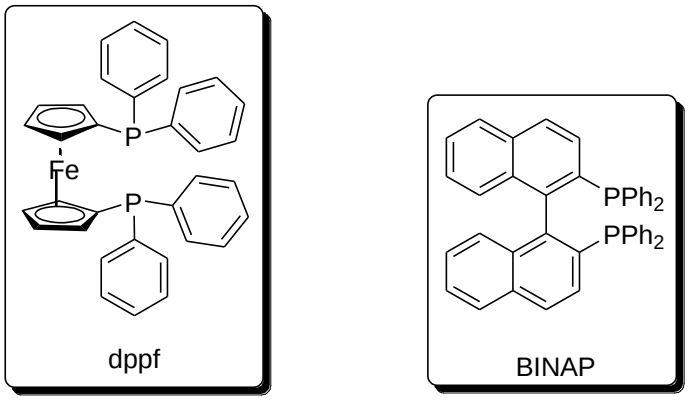
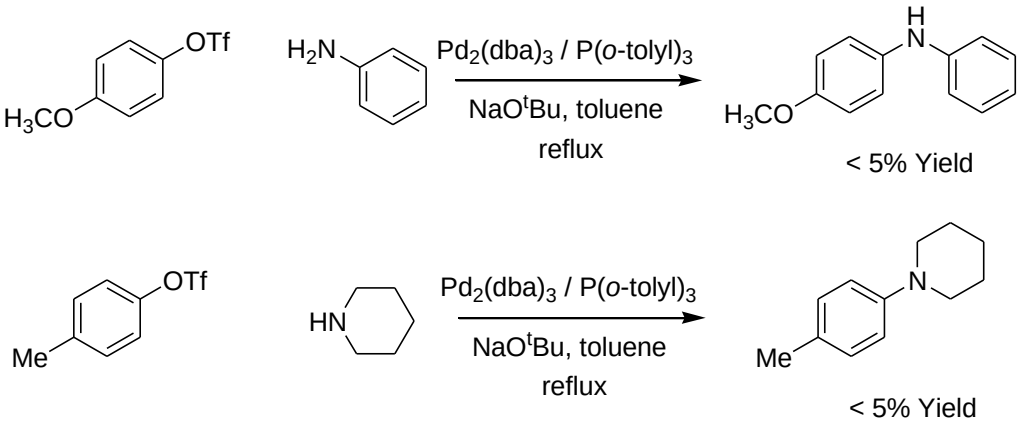


Figure 1.3. Structures of phosphine ligands

Buchwald proposed the ineffectiveness of mono-dentate ligands in the amination reactions of aryl iodides because they resulted in the formation of more stable iodide dimmers. Some experiments suggested that the steric difference of Br and I is also important (Figure 1.4). Pd-P and Pd-C rotation barriers were found to be greater for the large sized halides[61].

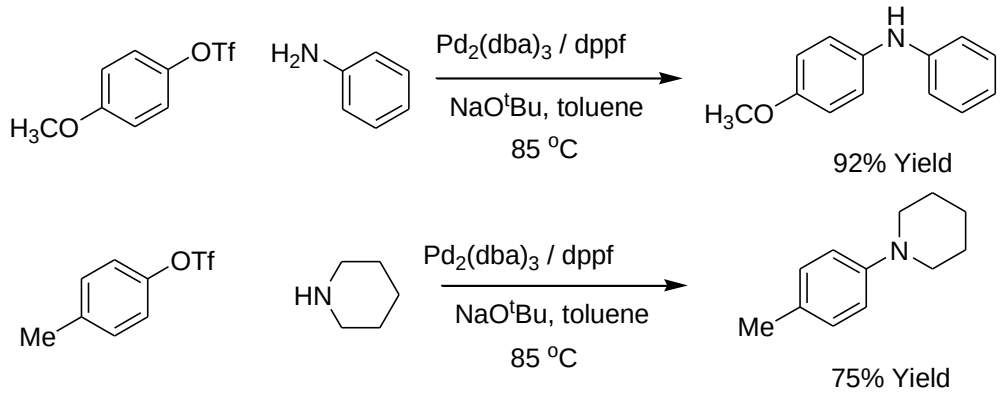
Figure 1.4. Palladium dimmers in catalytic cycle

Moreover nucleophilic bases tend to cleave triflates into phenols at the rate competitive to reductive elimination[62] (Scheme 1.6).

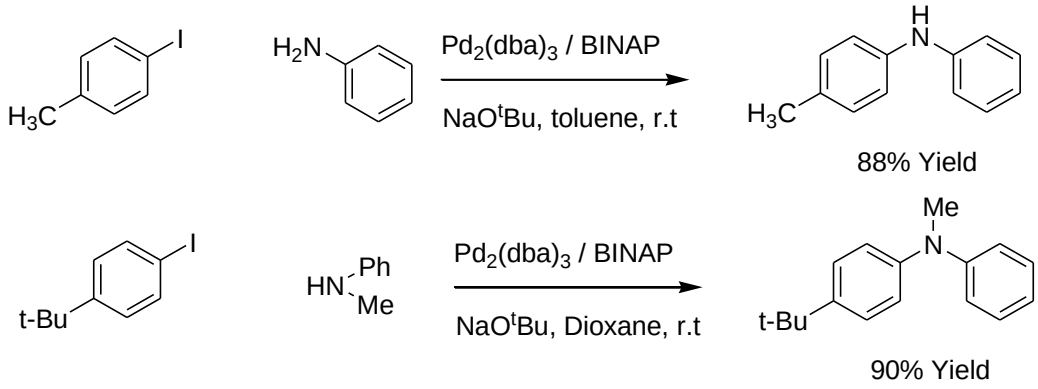


Scheme 1.6. Pd-catalyzed amination of triflates

The solution for these two challenging substrates (aryl iodides and triflates) lied in the use of bidentate phosphine ligand[63–65] (Scheme 1.7, 1.8).



Scheme 1.7. Pd-catalyzed amination of triflates using dppf ligand



Scheme 1.8 Pd-catalyzed amination of substituted iodobenzenes using BINAP ligand

Due to the tremendous efforts made by Buchwald and Hartwig, and through the numerous contributions made by other research groups Pd-catalysis got developed as the most sustainable and robust methodology for carrying out C-C and C-heteroatom bond transformations and ligand designing played a major role in this development[66] (Figure 1.5).

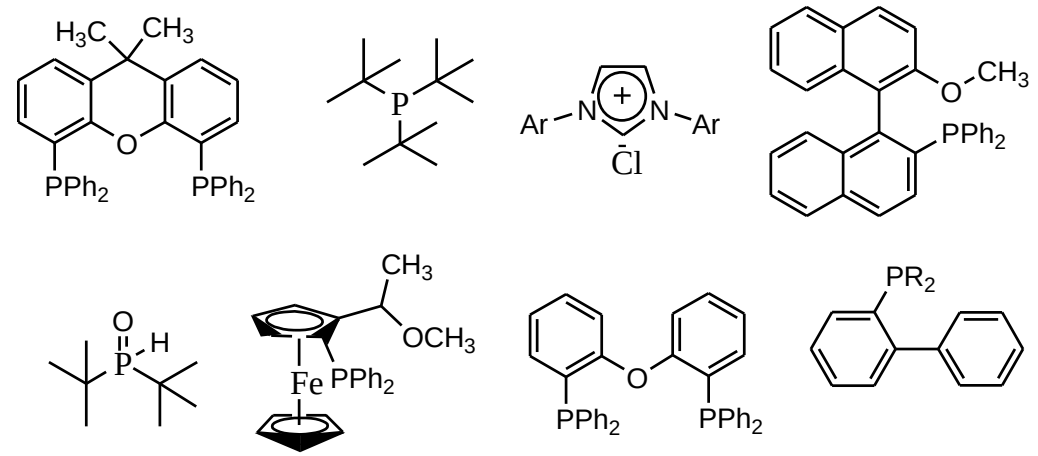


Figure 1.5. Structures of carbene and phosphine based ligands used in Pd-catalysis

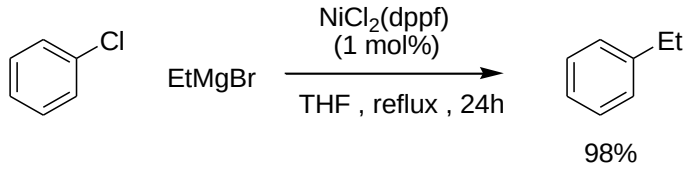
Although the palladium based methodologies are much developed to date, yet it is not rare to find the substrates that are not compatible with Pd-catalysis. There are also certain functional groups that are not tolerated in Pd-based methods such as amides, alcohols and carboxylic acids. Apart from these, other drawbacks include high cost of palladium, air and moisture sensitivity[67] of the ligands used and difficult removal of palladium residues during the workup of the reaction[68].

All above mentioned deficiencies of palladium, prompted researchers to think of some other alternatives of this expensive methodology, so they started considering Nickel and Copper once again.

1.5. Nickel as a Catalyst in Cross Coupling Reactions

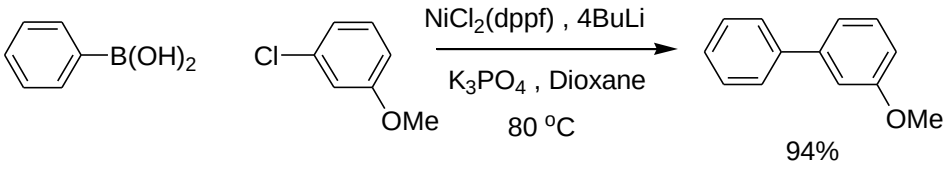
Nickel-catalysis has seen tremendous development during the last decade[69]. Certain key properties of nickel such as ease of access to multiple oxidation states and facile oxidative addition have resulted in the development of a range of innovative reactions.

In 1972 Kumada[70,71] and Corriu independently reported the cross-coupling of C (sp^2)-halides using organometallic compounds, thus by employing Nickel phosphine as a catalyst the reaction of chlorobenzene with EtMgBr resulted in almost quantitative yield of the product (Scheme 1.9).



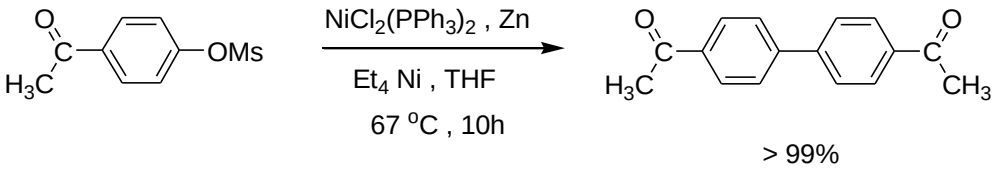
Scheme 1.9. Ni-catalyzed alkylation of chlorobenzene

Nickel catalysts are inexpensive and show high efficiency even when used with less reactive substrates in cross-coupling reactions. For instance, desired biaryl product was obtained in good yield by the $NiCl_2$(dppf) catalyzed cross-coupling of aryl borates with aryl chlorides/mesylates in the presence of butyl lithium, phosphines or zinc metal as a co-reductant (Scheme 1.10).



Scheme 1.10. Ni-catalyzed coupling reaction of aryl borates with aryl chlorides

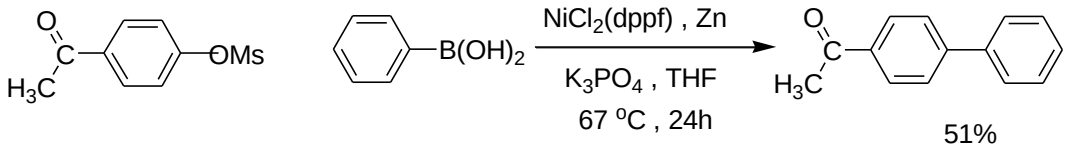
Aryl arenesulfonates and aryl mesylates are cross-coupled with aryl boronic acids in Suzuki type cross-coupling reactions in dioxane or THF, using Ni (0) as a catalyst. Ni (0) possesses higher nucleophilicity than Pd (0), hence arenesulfonates and aryl mesylates, despite of their low reactivity undergo oxidative addition in presence of Ni (0) complexes[72]. The Ni (II) species that results from oxidative addition reacts with another aryl mesylate in the presence of zinc to form symmetrical homocoupled biaryls (Scheme 1.11).



Scheme 1.11. Homocoupled biaryls synthesis using $NiCl_2(PPh_3)_2$ as catalyst

In 1995 Percec′s group reported that a catalyst comprising of Ni(0) species incorporating the 1,1′-bis(diphenylphosphino)ferrocene, this dppf ligand is effective in carrying out

cross coupling reactions[73]. Thus by using 10 mol% $NiCl_2$ (dppf), 3.0 equivalents of K_3PO_4 and 1.7 equivalents of Zn in presence of THF at 67 °C, moderate yields were obtained with high selectivity (Scheme 1.12).



Scheme 1.12. Ni-catalyzed cross-coupling reaction of aryl borate with aryl mesylate

Homocoupled product was formed only in traces. Thus by only a slight change in reaction conditions that is substitution of dppf for PPh_3 along with addition of K_3PO_4 and phenyl boronic acid virtually closed the pathway leading towards homocoupled product. This result is a first example of making use of Ni catalyst in Suzuki reaction.

Ni catalyzed Kumada reaction was also reported in 1995 by the Percec′s group[74] (Figure 1.6).

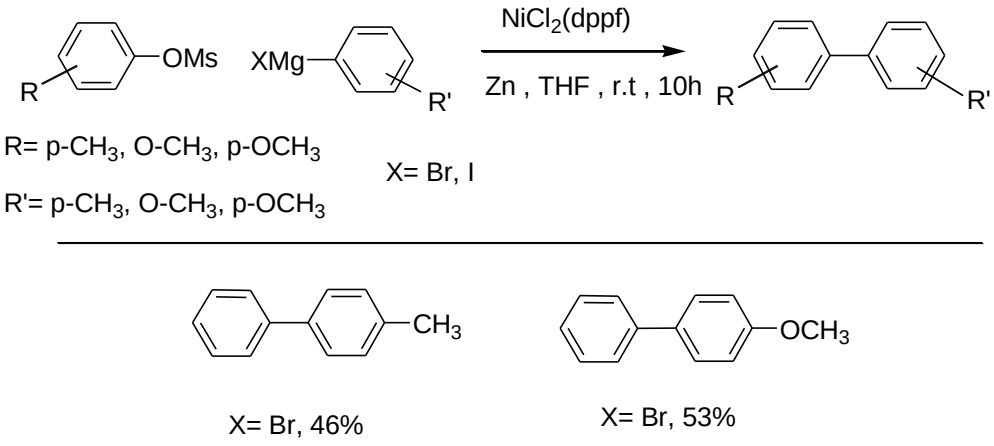
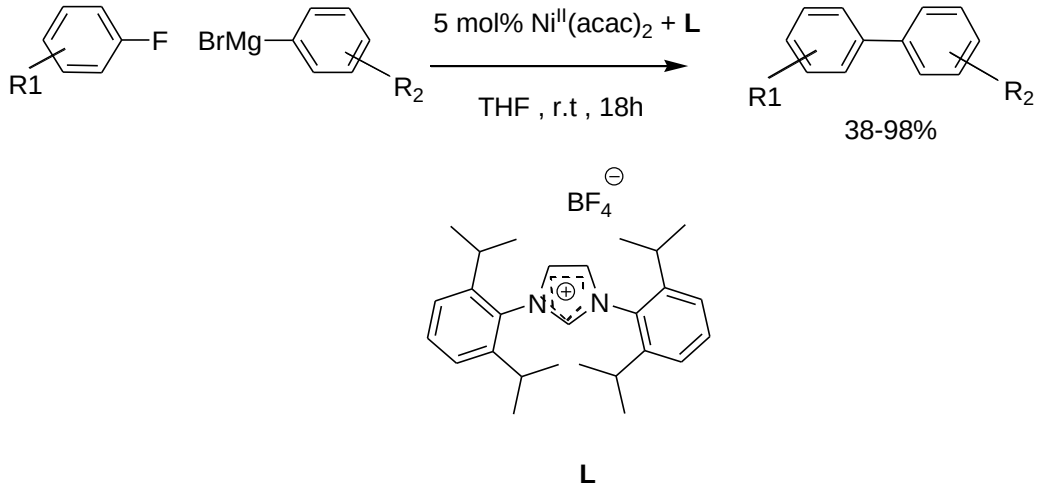


Figure 1.6. Scope of Ni-catalyzed kumada reaction

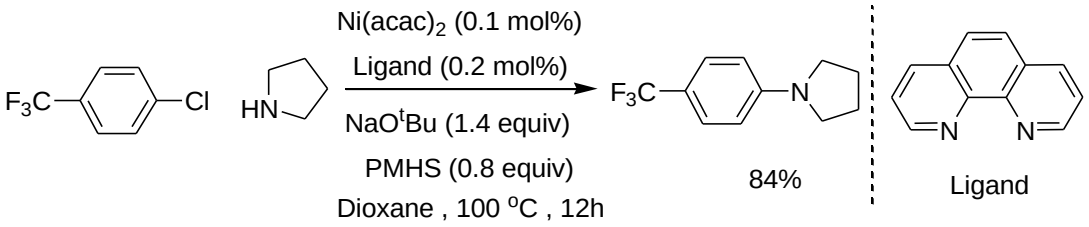
In 2001, Herrmann′s group reported the first successful cross-coupling of C-F electrophile[75] (scheme 1.13).



Scheme 1.13. Ni-catalyzed cross-coupling reaction of substituted flourobenzenes

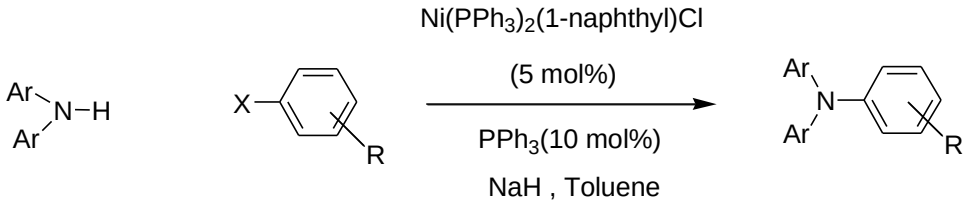
Nickel catalyzed aryl amination has received much less attention as compared to Pd-catalyzed amination reactions. Majority of the reported reactions need reducing agents which are incompatible with many functional groups.

The reaction of pyrrolidine with 1-chloro-4-trifluoromethylbenzene in the presence of catalytic amount of $Ni(acac)_2$ and 1,10-phenanthroline, employing polymethylhydrosiloxane (PMHS)[76] as a reducing agent yielded 84% product (Scheme 1.14).



Scheme 1.14. Ni-catalyzed arylation of pyrrolidine in presence of phenanthroline

Triarylamines were synthesized by the reaction of aryl bromides/ iodides with diaryl amines using Ni as a catalyst. In this reaction Ni (0)-Ni (II) shuttle in catalytic cycle and can be affected by the Ni(II)-(δ-aryl) complexes/ PPh_3/ NaH system for the cross-coupling reaction[77] (Scheme 1.15).



Scheme 1.15. Ni-catalyzed triarylamines synthesis

1.6. Copper as a Catalyst

Copper has been an ancestor of palladium in cross coupling reactions. Copper catalyzed Ullmann and Goldberg reactions served well for C-O, C-N and C-S bond formation[78]. However, copper suffered an increased degree of neglect after the tremendous development of palladium catalyzed processes[79,80]. Synthesis of arylamines by Ullmann and Goldberg reaction was the last stronghold of copper, which was also captured by the robust development of Pd-catalyzed amination reactions. However, it was not that easy to get rid of copper. Its earth abundance, ease of handling, stability and most importantly low price present it as a better alternative of palladium which is evident by a steady increase in its use during the last few years. Copper can help carrying out cross-coupling reactions in a way quite similar to palladium further it is more useful and versatile than its closest neighbour in the periodic table that is nickel.

For copper, the ease of accessibility to four oxidation states from 0 to +3 is the major character that distinguishes it from palladium which exists in only two stable oxidation states, 0 and +2. Palladium can also exist in +1, +3 and +4 oxidation state but these are extremely rare and play no significant role in coupling reactions[81]. Most likely, +1 and +3 oxidation states serve the catalytic cycle of copper in cross coupling reactions. Another notable feature of copper is its accessibility to odd-electron state which implies that copper can also take part in redox single electron processes, so an alternative free radical mechanism must also be considered. Sandmeyer reaction is believed to follow such mechanism where arenediazonium salts are used as electrophilic reagents in copper mediated nucleophilic substitution reactions.[82–85]

$$RX + Cu(I) \rightarrow R^{\cdot} + X^{-} + Cu(II)$$

$$R^{\cdot} + Nu^{-} \rightarrow RNu + e^{-}$$

One of the drawbacks of classical Ullmann and Goldberg reaction was the poor solubility of copper salts in the reaction medium. Certain observations made by scientists led to the idea that traditional copper-based protocols could be improved if copper could be made more soluble in the reaction medium. Some of the observations are enlisted over here:

1) Harold Weingarten, in 1964 reported that, in the coupling of potassium phenoxide and bromobenzene, presence of a diester as an impurity in the solvent lead to an increased reaction rate[86]. He believed that this diester helped making copper soluble in reaction medium.
2) In 1987, Paine reported that soluble cuprous ions are catalytically active species in Ullmann reaction[87].
3) In 1993 Capdevielle noticed increased rate of copper-catalyzed methanolysis of aryl bromides by the use of various esters[88].

All these observations show that it is very much possible to increase the yield of classical Ullmann reaction by carefully controlling the conditions.

Buchwald in 1997 reported the cross-coupling of aryl bromides with phenols using toluene as a solvent at 110 ^{o}C. He used soluble copper complex, copper (I) trifluromethanesulfonate-benzene with ethyl acetate and 1-naphthoic acid as the additives and Cs_2CO_3 was employed as a base[89]. This synthesis of diaryl ethers is exemplified by the following aspects:

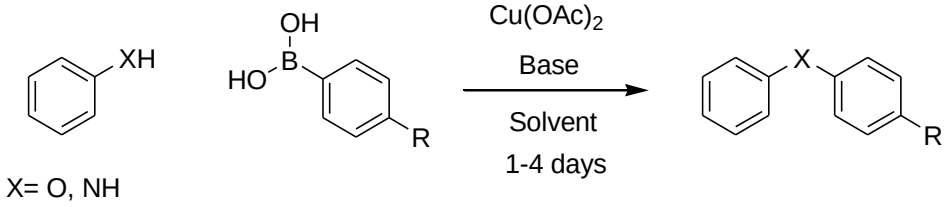
a) Use of copper in catalytic amount rather than stoichiometric amount, used for traditional copper-based methodologies.
b) The use of expensive and air sensitive ligands is avoided, required in palladium-based catalysis.

In 1999, rate enhancement effects of 1, 10-phenanthroline was reported in the copper-catalyzed synthesis of triarylamines by Goodbrand[90].

Based on these observations the researchers started considering use of Cu(I) complexes as catalysts for cross-coupling reactions. These complexes bear ligands that have been proved to be effective as additives in copper catalyzed coupling reactions as well as these complexes are soluble in variety of organic solvents, helping to increase the solubility of copper in reaction medium.

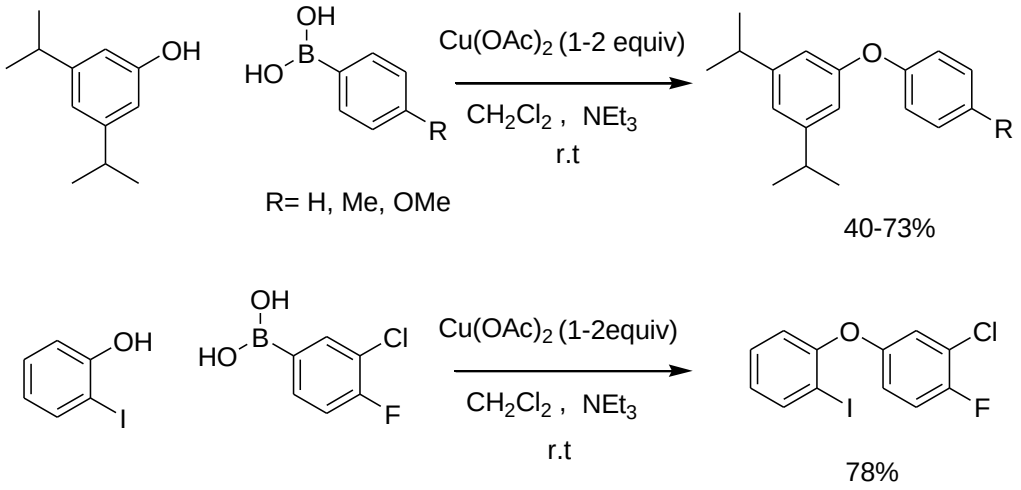
1.6.1. Copper Catalyzed C-O Bond Formation

In 1998, research groups of Chan[91], Evans[92] and Lam[93] independently reported the copper assisted arylation reactions for the formation of C-N and C-O bonds. These groups successfully devised milder methods for the construction of these C-heteroatom bonds (Scheme 1.16).



Scheme 1.16. Cu-catalyzed C-heteroatom bond formation

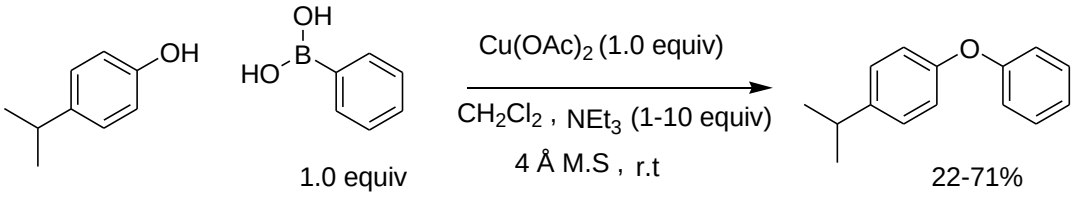
They discovered new conditions showing that, the use of Cu $(OAc)_2$, heteroatom donor and boronic acid, were ideal to effect classical Ullmann condensation. Chan and co-workers reported four examples of the synthesis of unsymmetrical tri-substituted diaryl ethers using two phenolic substrates. Both of these phenolic substrates underwent efficient cross-coupling with ortho substituted, electron-rich and electronically-poor boronic acids (Scheme 1.17).



Scheme 1.17. Cu-catalyzed arylation of substituted phenols

Evans and co-workers further evaluated the limitations and scope of the new stoichiometric copper-assisted procedure[94] (table 1.1).

Table 1.1 Optimization of conditions for arylation of 4-*i*-propyl phenol

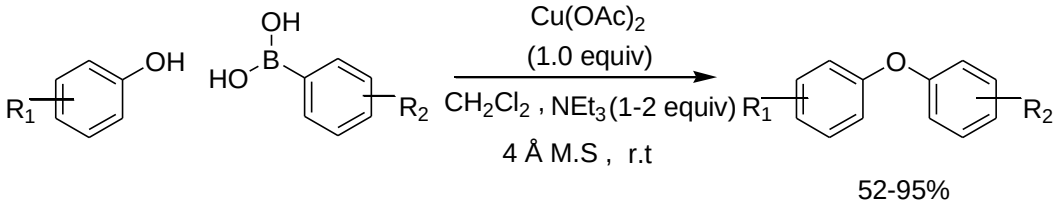


Atmosphere	NEt_3 [equiv.]	$Cu(OAc)_2$ [equiv.]	Yield [%]
Ar	1	1	22
Ar	10	1	34
air	1	1	41
air	10	1	71
O_2	5	1	71

They confirmed that reaction conditions mentioned above worked well in most of the cases. They reported that $Cu(OAc)_2$ was an optimal Cu(II) source and the use of other copper salts such as $Cu(NO_3)_2$, $Cu(OCOCF_3)_2$, $Cu(OPiv)_2$ and $Cu(acac)_2$ resulted in

inferior results. Neither did the use of $CuCl_2$, $Cu(ClO_4)_2$, $Cu(OTf)_2$ and $CuSO_4$ resulted in the formation of significant coupled product. It was observed that during the progress of the reaction significant amount of diphenyl ether and phenol were produced which might be due to the formation of water molecules during the course of reaction. Boronic acid could be the reason of this water formation. Boronic acid forms trimeric triaryl boroxine that may then take part in the reaction. Thus use of molecular sieves results in yield enhancement. It was reported that all type of electronically and structurally diverse phenols and boronic acids underwent efficient cross-coupling reactions to afford products in almost quantitative yields (table 1.2).

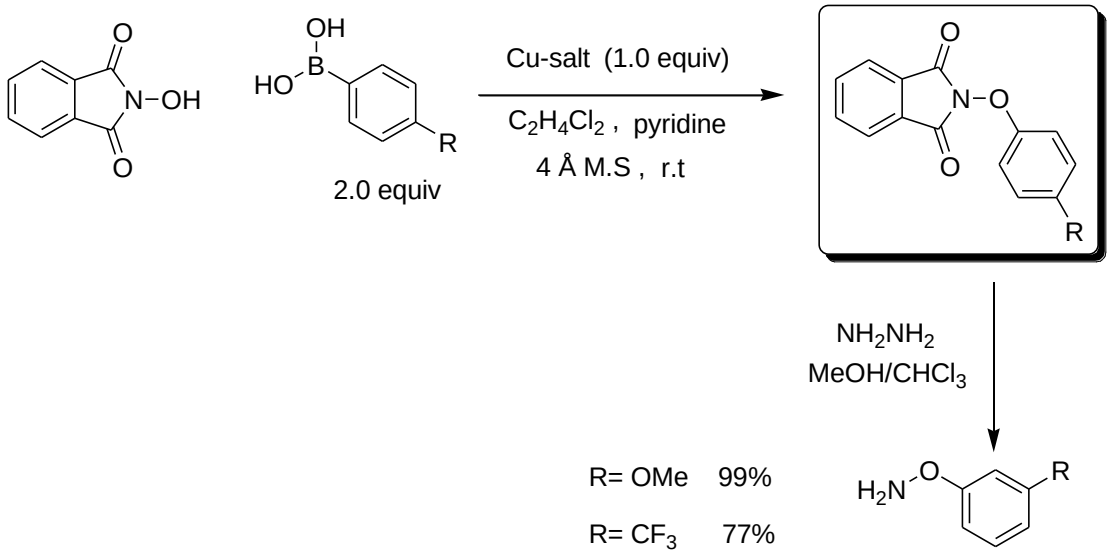
Table 1.2. Scope Cu-catalyzed diaryl ether synthesis



R_1	R_2	NEt_3 [equiv.]	Yield [%]
p-tBu	H	1.5	95
p-tBu	p-Me	2.0	87
p-tBu	p-OMe	2.0	85
o-Cl	H	2.0	95
o-Cl	p-Me	1.0	70
o-Cl	p-F	2.0	61
o-OMe	p-F	1.0	97
o-OMe	p-OMe	2.0	82
o-OMe	o-Me	1.0	52

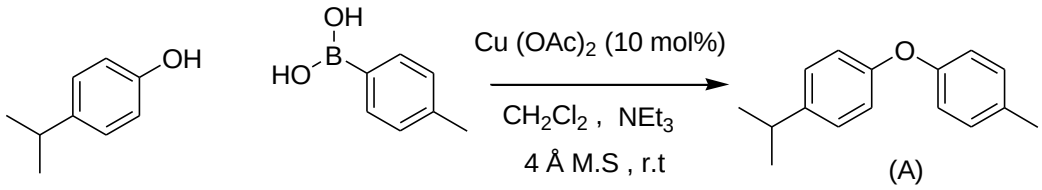
Sharpless, Petrassi and Kelly reported that N-hydroxyimides can also participate as nucleophilic reaction partner in copper-assisted arylation reactions. Coupling of various boronic acids with N-hydroxyimides was investigated at slightly modified conditions using 1,2-dichloroethane as a solvent with ambient air and molecular sieves. The coupled

product could be further converted to corresponding *o*-arylhydroxylamine after hydrazinolysis in methanol[95] (scheme 1.18).



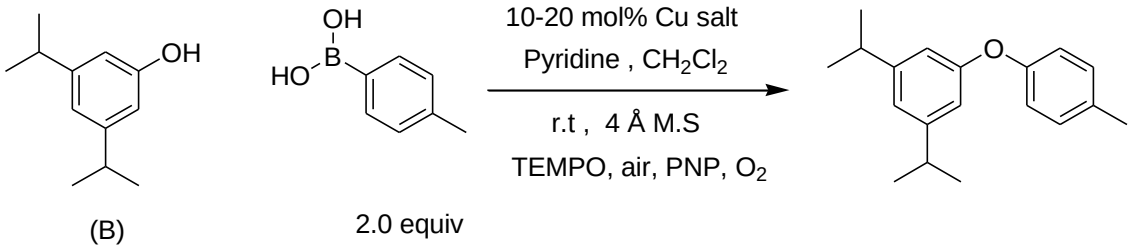
Scheme 1.18. Cu-catalyzed arylation of N-hydroxyimides and synthesis of *o*-arylhydroxylamine

The potential for the catalytic variant was observed during the synthesis of product (A). The product was obtained in low yield by using catalytic amount of $Cu(OAc)_2$ in DCM, in the presence of triethylamine under argon or oxygen[96] (scheme 1.19).



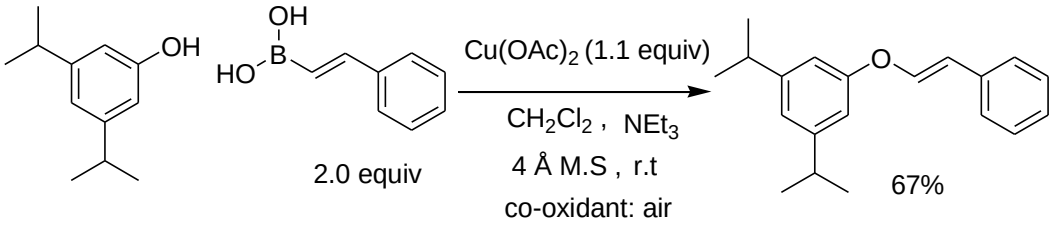
Scheme 1.19. Diaryl ether synthesis using copper in catalytic amount

Lam and co-workers made an improvement in the catalytic version by using a co-oxidant in the cross-coupling of *p*-tolylboronic acid with the phenol (B). The best yield (79%) was obtained when oxygen was used as oxidant however, it was also possible to use [{Cu (μ-OH) (TMEDA)}$_2$]Cl_2/oxygen, pyridinium N-oxide (1.1equiv)/air or TEMPO (1.1 equiv)/air in the presence of $Cu(OAc)_2$[97] (scheme 1.20).



Scheme 1.20. Cu-catalyzed diaryl ether synthesis aided by co-oxidant

Lam and co-workers reported that vinyl boronic acids could also function as coupling partner in C-O bond forming reactions[97] (Scheme 1.21).



Scheme 1.21. Cu-catalyzed cross-coupling reaction of styryl boronic acid

1.6.1.1. Aryl Halides as Aryl Donors in C-O Bond Formation

The introduction of Cs_2CO_3 as a base by Buchwald and co-workers for Ullmann arylation has led to much better results and much better procedures for diaryl ether synthesis by the coupling of aryl bromides or iodides with variety of phenols[98]. Ethyl acetate was found to be necessary as catalytic additive in these reactions. An equimolar amount of 1-naphthoic acid was required for the reaction of unreactive phenols. Transformation was greatly facilitated by the use of molecular sieves. Arylation of hindered or less reactive phenols via unactivated aryl halides was now possible under these new conditions (Figure 1.7).

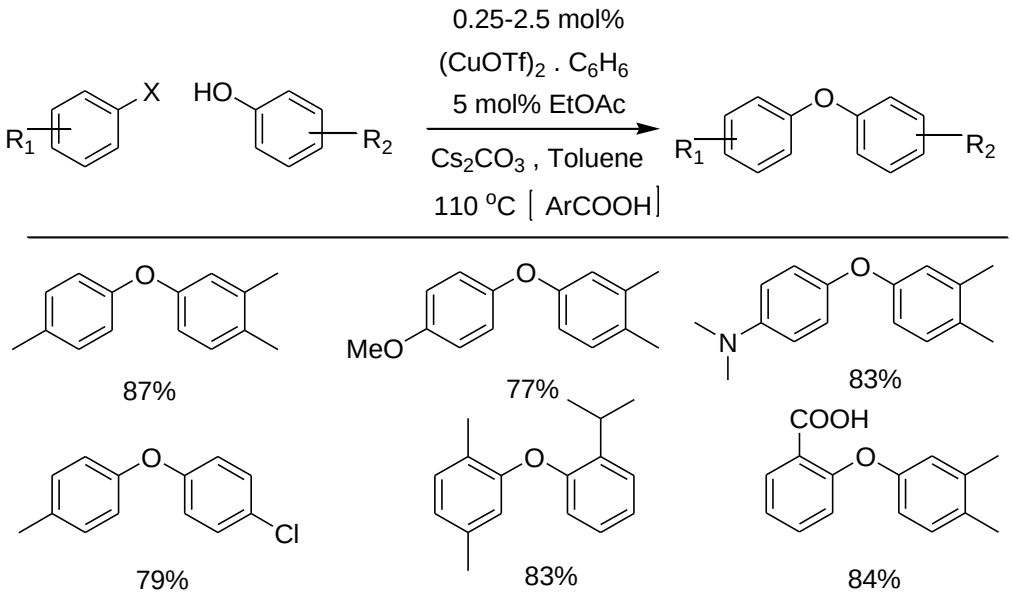


Figure 1.7. Scope of Cu-catalyzed diaryl ether synthesis

Use of 2,2,6,6-tetramethylheptane-3,5-dione (TMHD) as an additive along with Cs_2CO_3 as a base, resulted in high reaction rate of Cu-catalyzed diaryl ether synthesis[99]. The ligand, TMHD worked well with Cs_2CO_3 while gave no significant results with other bases (figure 1.8).

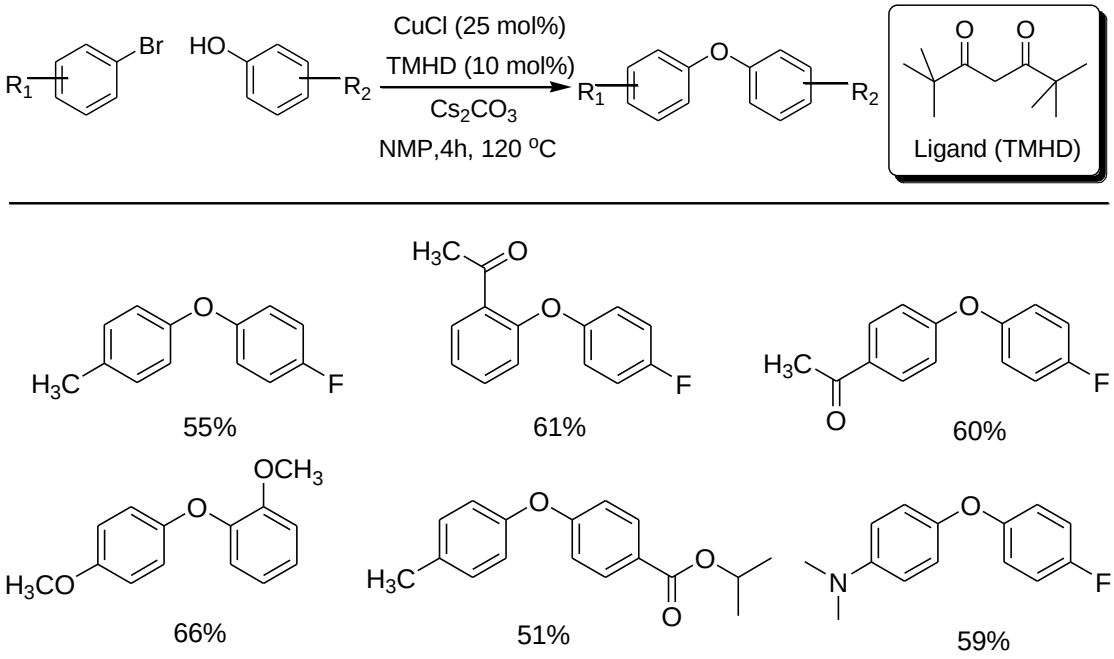


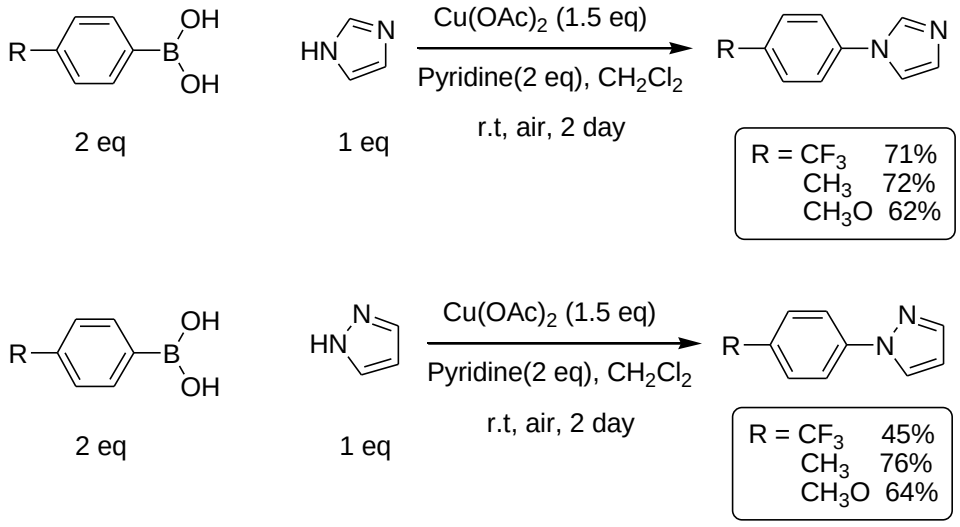
Figure 1.8. Scope of Cu-catalyzed diaryl ether synthesis using TMHD as a ligand

1.6.2. Copper-Catalyzed C-N Bond Forming Reactions

Copper-assisted arylation of amines has been known for a century, as classical Ullmann reaction[100]. This reaction required harsh conditions such as prolonged heating and long reaction time in presence of Cu(I) or Cu(II) salt, Cu bronze or oxides of Cu in polar high boiling solvents. Emergence of Pd-catalyzed amination was a major breakthrough in the chemistry of amines. A resurgence of interest in more practical and much cheaper Cu-catalysis has been brought about by the use of variety of ligands which can modulate the reactivity of a catalyst and thus make it possible to achieve more effective and versatile catalytic system.

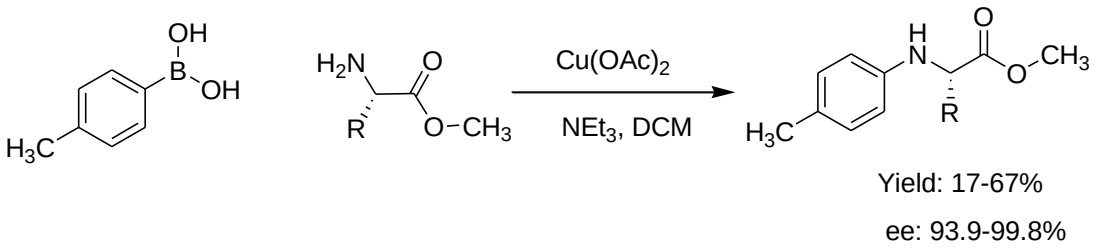
1.6.2.1. Boronic Acids as Aryl Donors in Cu-Catalyzed C-N Cross Coupling Reactions

Chan-Evans-Lam coupling had been applied in the cross-coupling reactions of nitrogen containing heterocycles and resulted in a good yield of *N*-arylated heteroarenes (Scheme 1.22).This reaction could be carried out under mild reaction conditions and in the presence of air. Use of DMF as a solvent gave good yield as compared to DMSO, ethyl acetate and toluene[101].



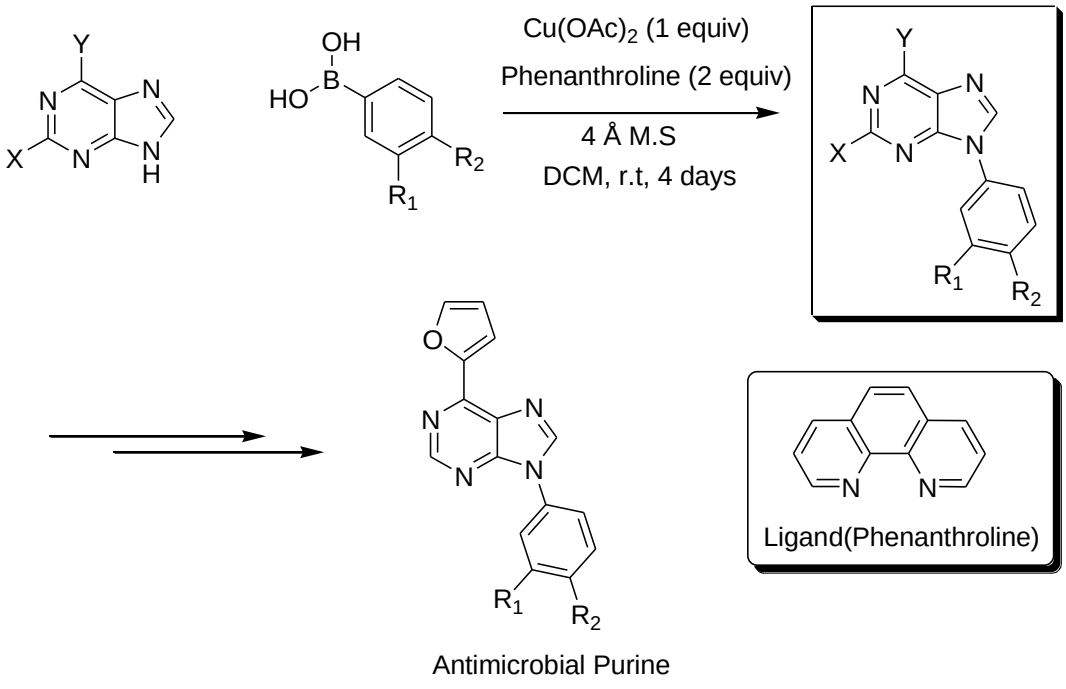
Scheme 1.22. Cu-catalyzed C-O cross coupling reactions of hetero aryls

Enantiomerically pure α-amino esters when treated with *p*-tolylboronic acid using $Cu(OAc)_2$ as a catalyst under mild reaction conditions give Enantiomerically pure product at room temperature[1o2] (Scheme 1.23).



Scheme 1.23. Cu-catalyzed arylation of α-amino esters

9-*N*-purines react with arylboronic acids to yield antimicrobial purines in the presence of $Cu(OAc)_2$ and molecular sieves. Phenanthroline is used as a ligand in this reaction[1o3]. Electron donating and electron withdrawing groups on arylboronic acid are tolerated very well (Scheme 1.24).



Scheme1.24. Cu-catalyzed synthesis of antimicrobial purines

1.6.2.2. Aryl Halides as Aryl Donors in Cu-catalyzed C-N coupling Reactions

The most important contribution for the introduction of general Ullmann type reaction of amines was made by Buchwald and co-workers[104a]. The first modern version was the reports that the arylation of imidazoles could be efficiently catalyzed by Cu $(OTf)_2$ which rejuvenated the area of research as indicated by an enrichment of scientific literature by increasing number of reports[104b] (Figure 1.9).

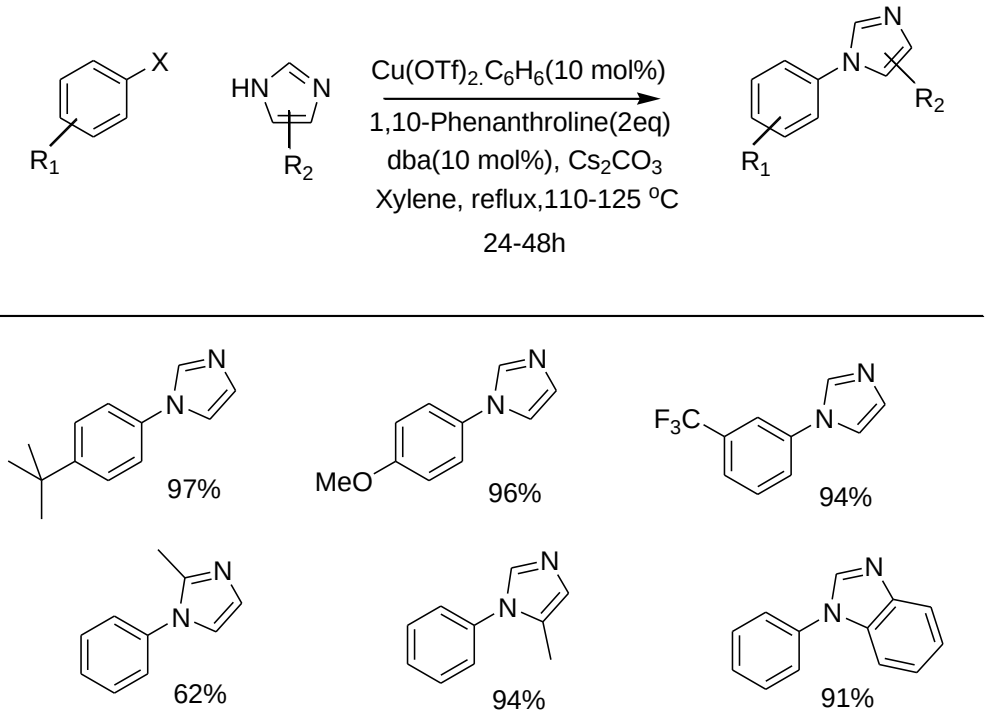
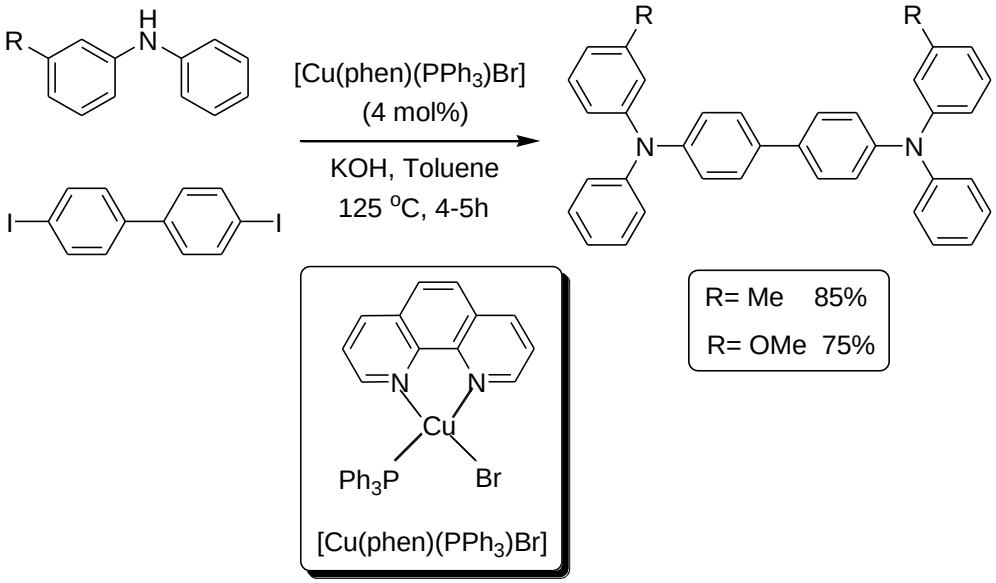


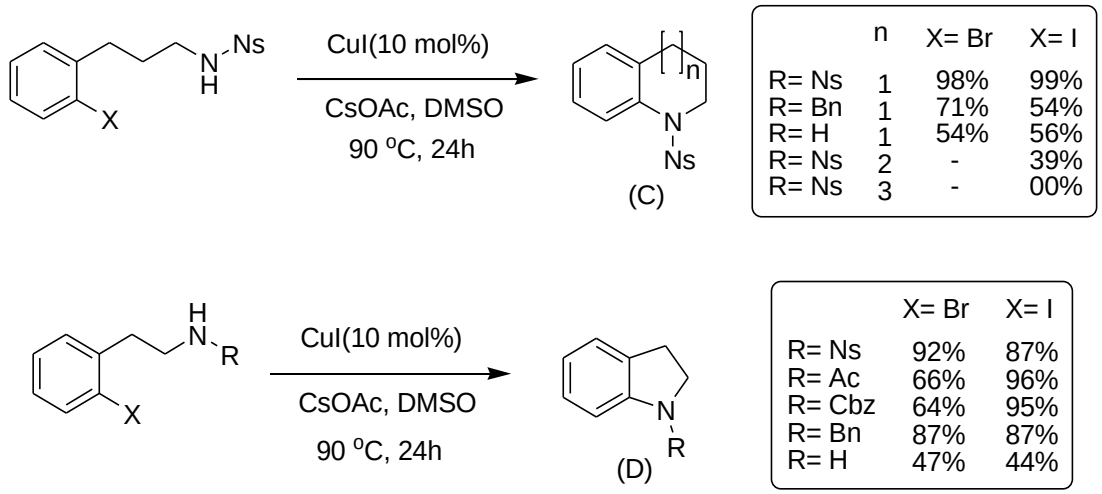
Figure 1.9. Scope of Cu-catalyzed arylation of imidazole

"Hole conducting" triaryl amines were prepared by Goodbrand and Hu in presence of [Cu(phen)(PPh_3)Br] as an accelerating ligand[105] (scheme 1.25).



Scheme 1.25. [Cu(phen)(PPh_3)Br] catalyzed synthesis of triaryl amines

A significant breakthrough in the modified Ullmann condensation was brought about by Fukuyama and co-workers. They reported an efficient intramolecular cyclization rout to tetrahydroquinoline (C) and dihydroindoles (D) at room temperature by using a combination of CuI and CsOAc[106] (Scheme 1.26).



Scheme 1.26. Cu-catalyzed intramolecular C-N coupling reactions

Venkataraman reported the use of soluble and air-stable Cu (I) catalysts E and F in the synthesis of triaryl amines from diaryl amines[107]. The synthesis of these stable copper complexes was inspired by the observations that soluble cuprous ions are the active catalytic species in Ullmann condensation reactions (figure 1.10).

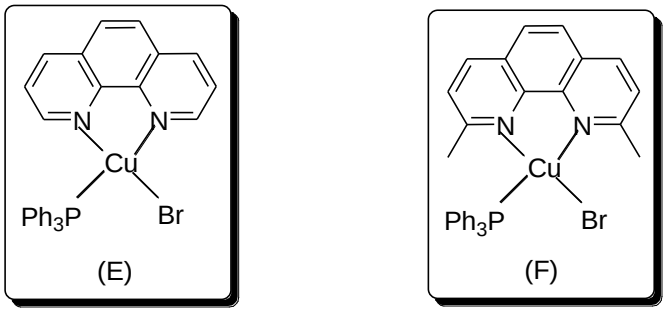
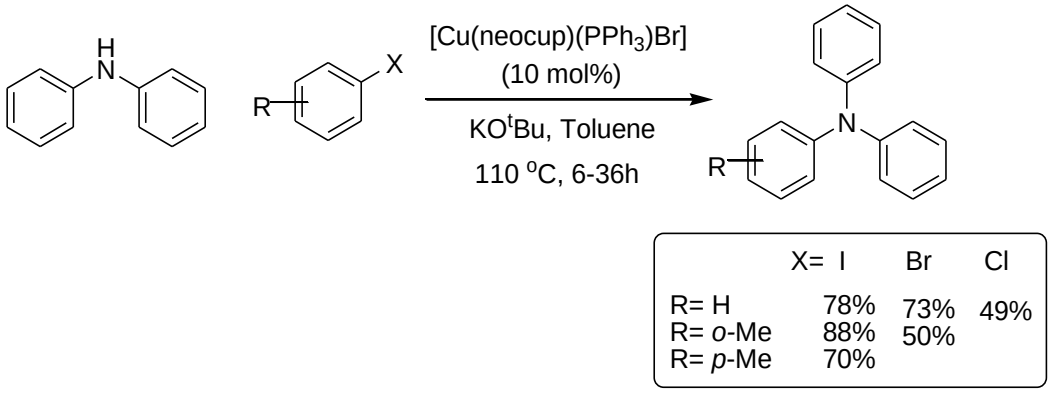


Figure 1.10. Complexes of copper salts with phenanthrolines

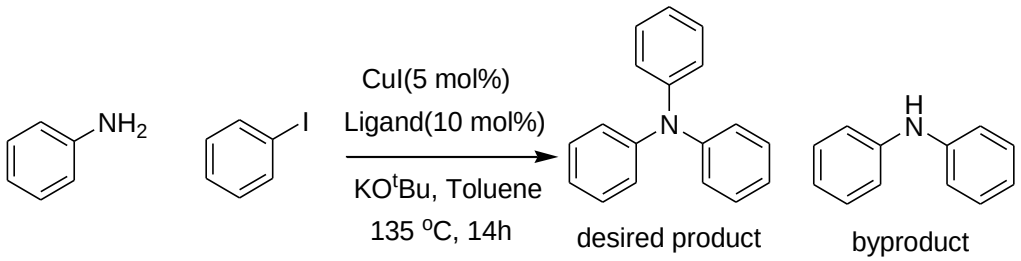
In mediating *N*-arylation the catalyst F was found to be twice as efficient as catalyst E and its use was reported in triaryl amines synthesis (Scheme 1.27).



	X= I	Br	Cl
R= H	78%	73%	49%
R= *o*-Me	88%	50%	
R= *p*-Me	70%		

Scheme 1.27. [Cu(neocup)(PPh_3)Br] catalyzed triaryl amine synthesis

A systematic study was carried out on mono and bidentate ligands **1-21** for their ability to form active copper catalyst with CuI in the reaction of aniline with iodobenzene for the synthesis of triphenylamine (Scheme 1.28).



Scheme 1.28. Cu-catalyzed arylation of aniline to form triphenylamine

Amongst all these ligands, pyridines and quinolines were shown to be less efficient ligands. PPh_3 accelerated the reaction rate only when PPh_3 /Cu ratio was greater than 2:1 while the dppf came out to be the most efficient ligand amongst all chelating bisphosphanes. The highest yield and selectivity was obtained in the presence of 2, 2′-bipyridine (Figure 1.11).

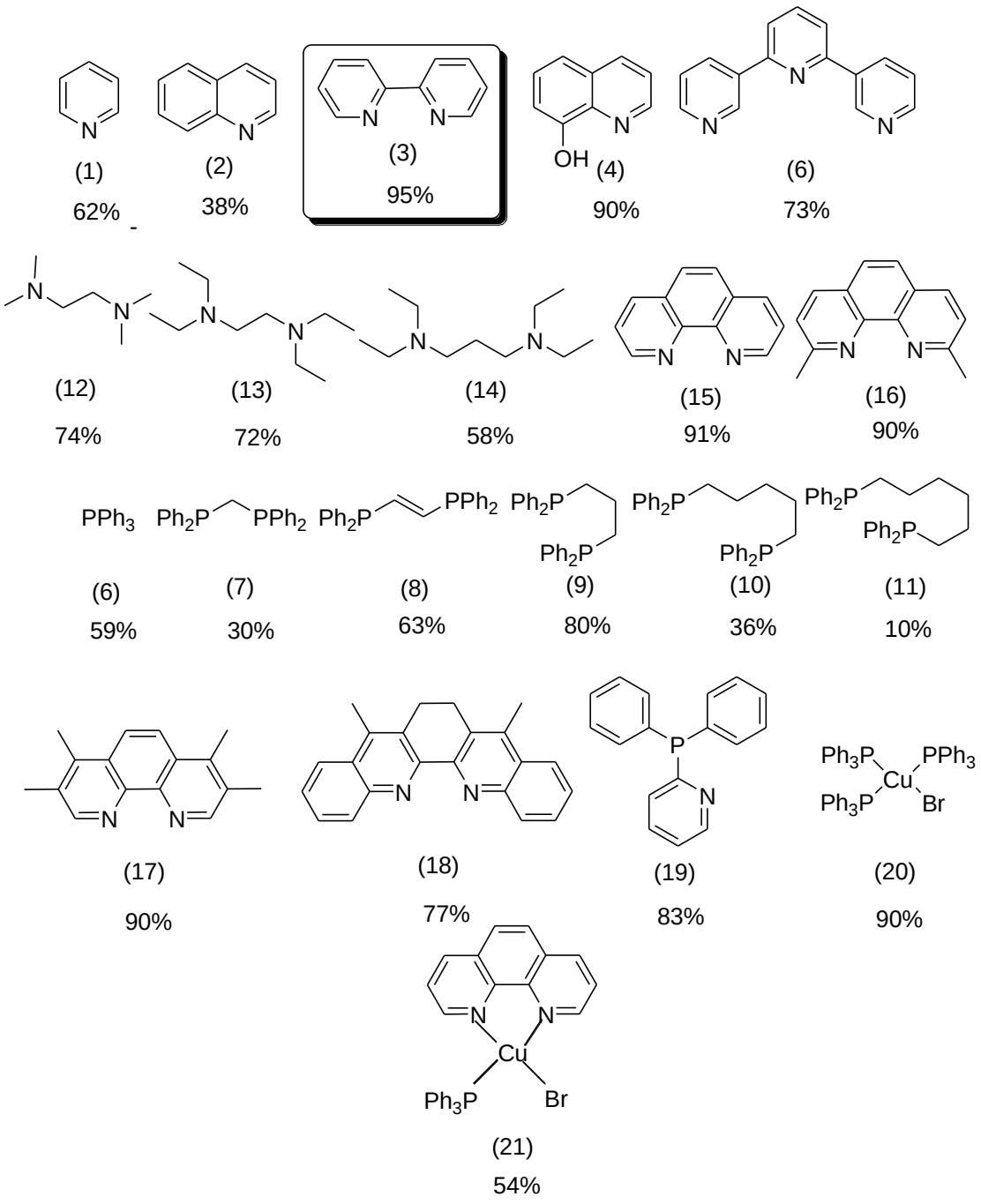


Figure 1.11. Collection of mono and bi-dentate ligands used for the synthesis of triphenylamine

In 2002 Buchwald and co-workers made a significant breakthrough in the aryl amidation reaction, classically known as Goldberg reaction. They introduced diamines as ligands for the amidation of aryl iodides and bromides[108]. These diamine-based ligands are the

most popular and efficient amongst all the ligands that have been designed so far (Figure 1.12).

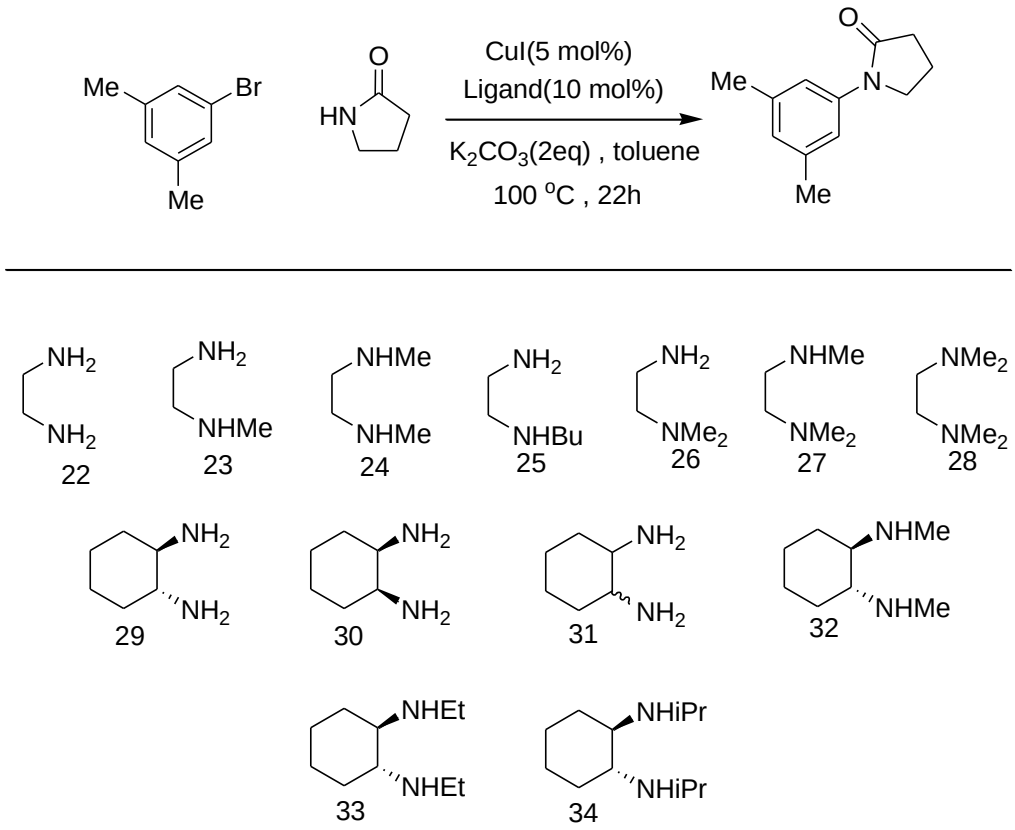


Figure 1.12. Diamine-based ligands

The diamine skeleton has pronounced effect on the ability to facilitate copper-catalyzed coupling reactions[109]. The steric bulk and degree of substitution on the diamine play the most critical role in bringing about the aryl amidation. The *N*, *N*′-dimethyl ethylene diamine (24) and *N, N*′-dimethyl cyclohexane diamine (32) show the higher activity[109,110]as compared to the unsubstituted ones. The presence of bulky substituents such as ethyl and isopropyl group hinders the activity. An increase in the number of substituents on nitrogen centre renders the ligand completely inactive *e.g.* tetramethyl ethylene diamine (TMEDA) (Figure 1.13).

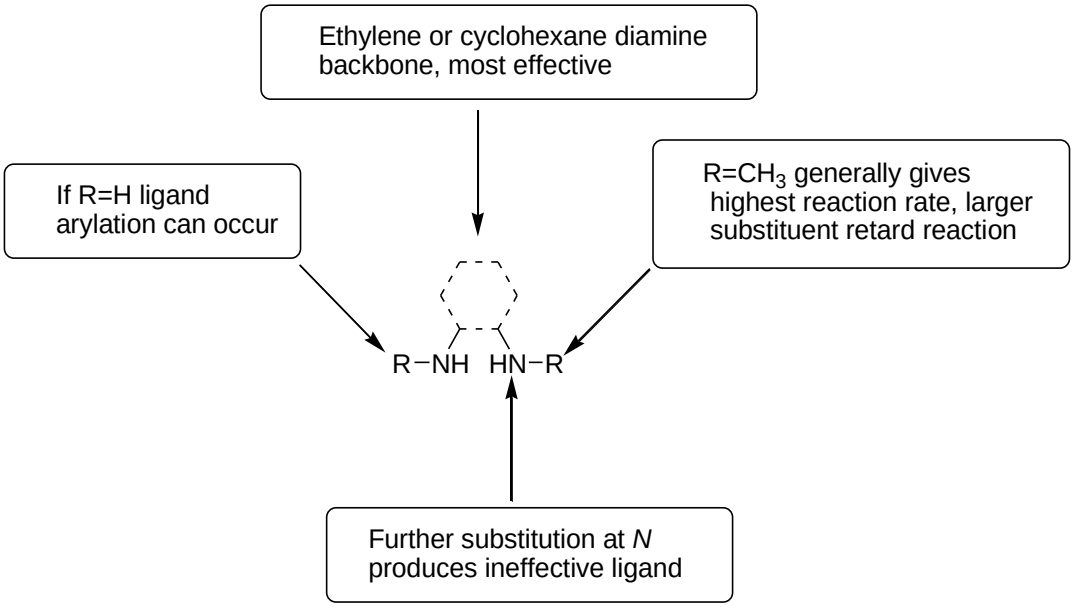


Figure 1.13. Critical features of diamine-based ligands

The nature of the base plays the most important role in the amidation of aryl iodides and bromides. Amidation of aryl iodides proceeds best in the presence of K_3PO_4 while the aryl bromides react faster when K_2CO_3 is employed as a base[111]. The obvious reason behind this interesting phenomenon is the fact that the rate of deprotonation of amide must be equal to the rate of amidation reaction. If deprotonated amide is formed in excess it would hinder the catalytic cycle presumably due to the formation of an unreactive multiply ligated cuprate complex (figure 1.14).

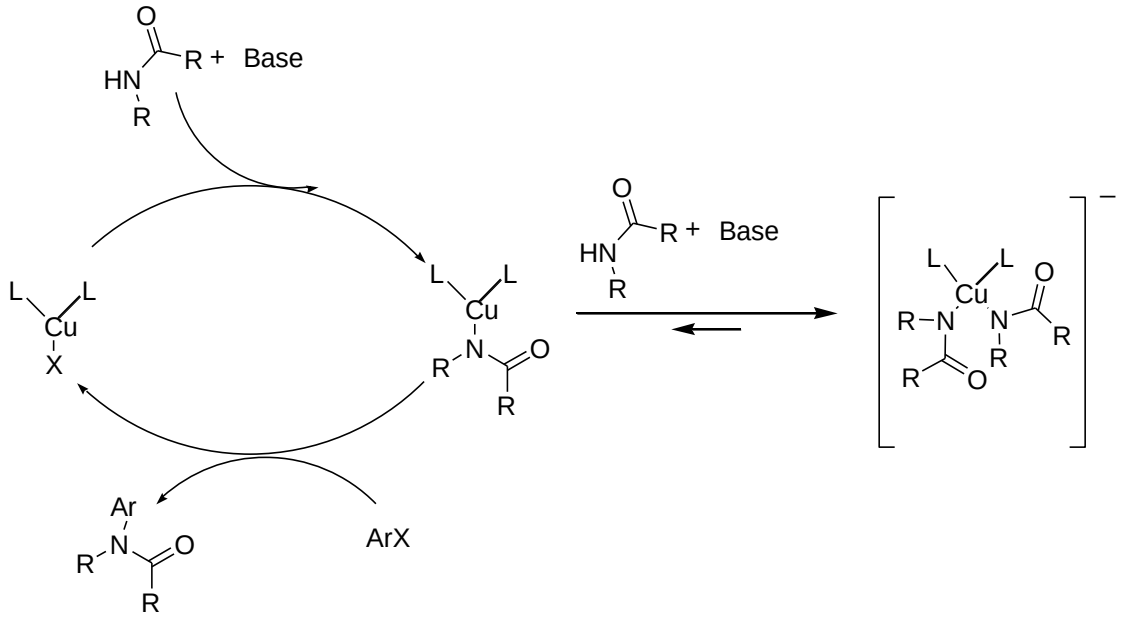


Figure 1.14. Formation of multiply ligated cuprate complex

Buchwald and co-workers also reported that diamine-based ligands help increasing the reaction rate of C-N coupling reactions by preventing the multiple ligations of amide to the copper[112–113] thus inhibiting copper from catalyst poisoning (figure 1.15).

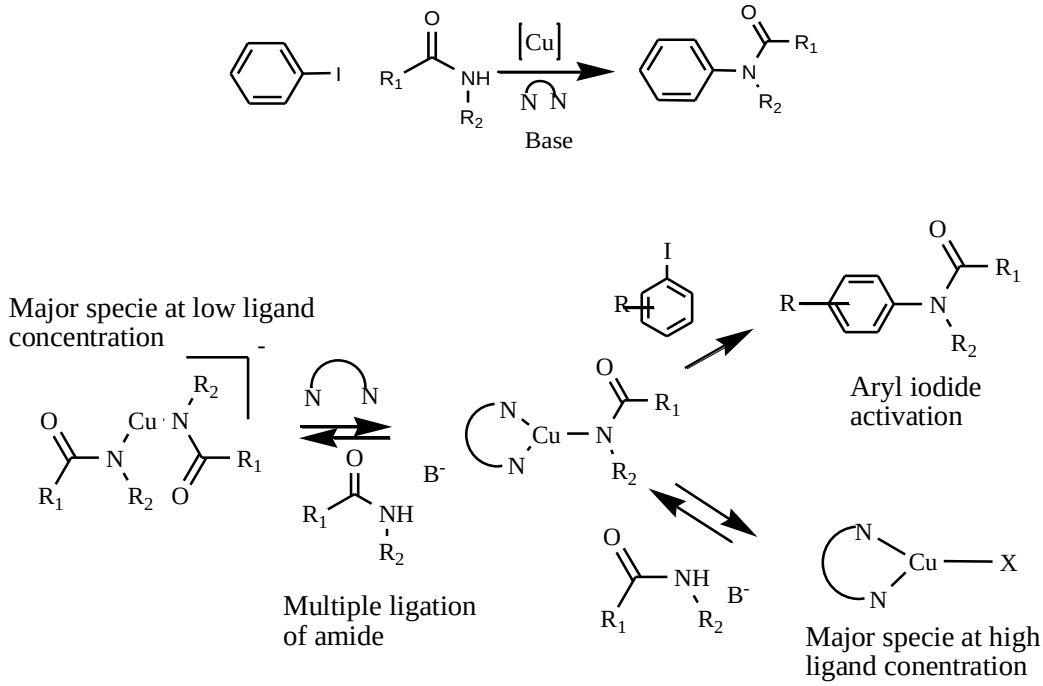


Figure 1.15. Mechanism followed by diamine-based ligands

Buchwald and co-workers also reported the *N*-arylation of indoles, using a diamine-based ligand *i.e. trans-N,N*-dimethyl cyclohexane diamine[114]. All the desired products were obtained in good to excellent yield.

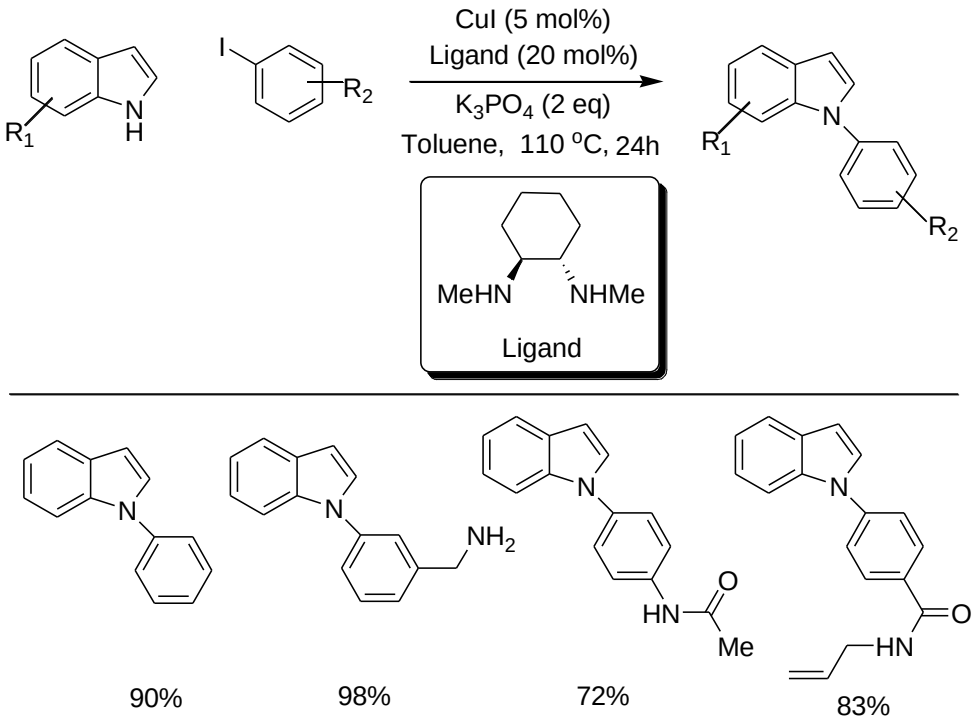


Figure 1.16. Scope of Cu-catalyzed N-arylation of indoles using *trans N, N*-dimethyl cyclohexane diamine as a ligand

Variety of diols has been reported to efficiently act as ligands for copper-catalyzed C-N coupling reactions.

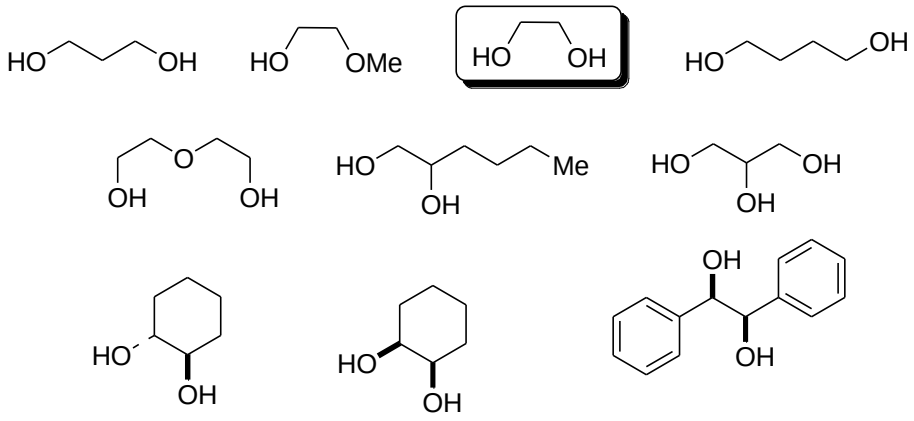


Figure 1.17. A collection of diol-based ligands used in Cu-catalyzed reactions

Amongst the diol ligands, the ethylene glycol was reported to be the most efficient one. All the products were obtained in good yields without any need to protect reaction mixture from moisture and air.

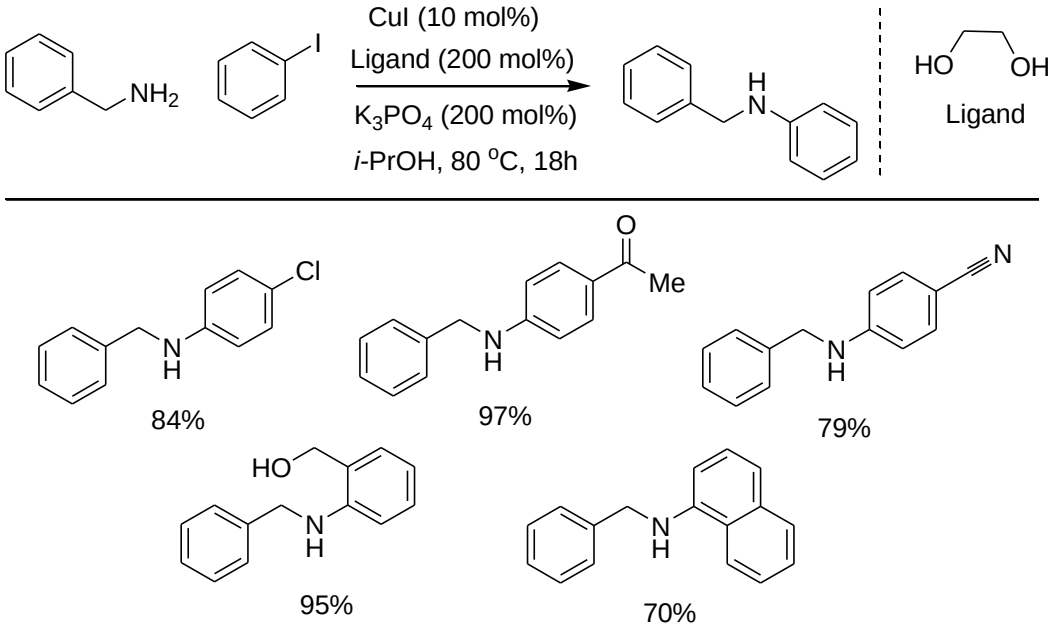


Figure 1.18. Scope of Cu-catalyzed N-arylation of iodobenzene using ethylene glycol as ligand.

Buchwald and co-workers reported a range of phenol ligands for the *N*-arylation of primary alkyl amines[115] (Figure 1.19).

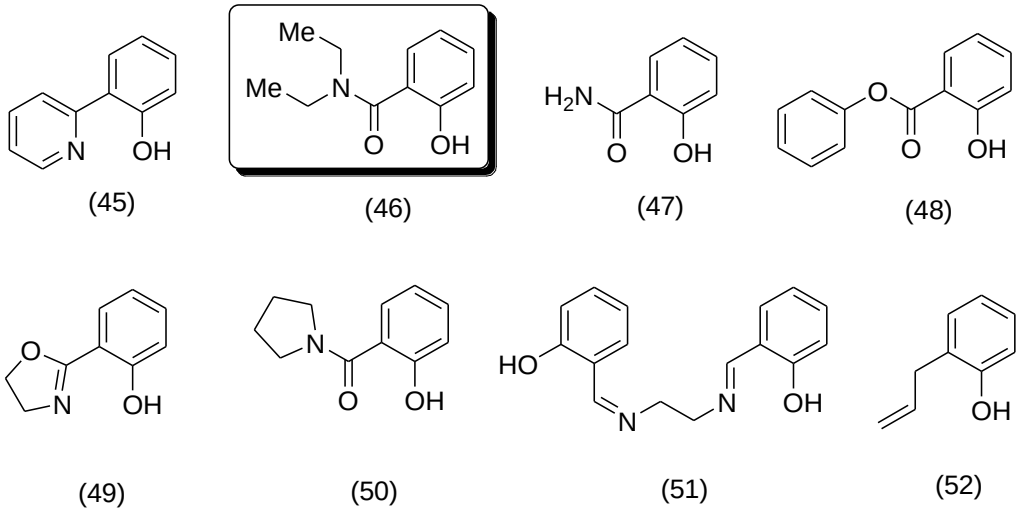


Figure 1.19. Collection of differently substituted phenol-ligands

N, N-diethylsalicylamide (46) was observed to be the most efficient amongst all the phenol ligands that were screened, in terms of yield and conversion. Variety of heteroaryl and ortho-substituted substrates gave satisfactory yields (Figure 1.20). This method worked well for primary amines but secondary amines gave poor yields under these conditions. Both K_2CO_3 and K_3PO_4 were found to be effective but the use of amine bases such as DBU and DABCO resulted in poor results.

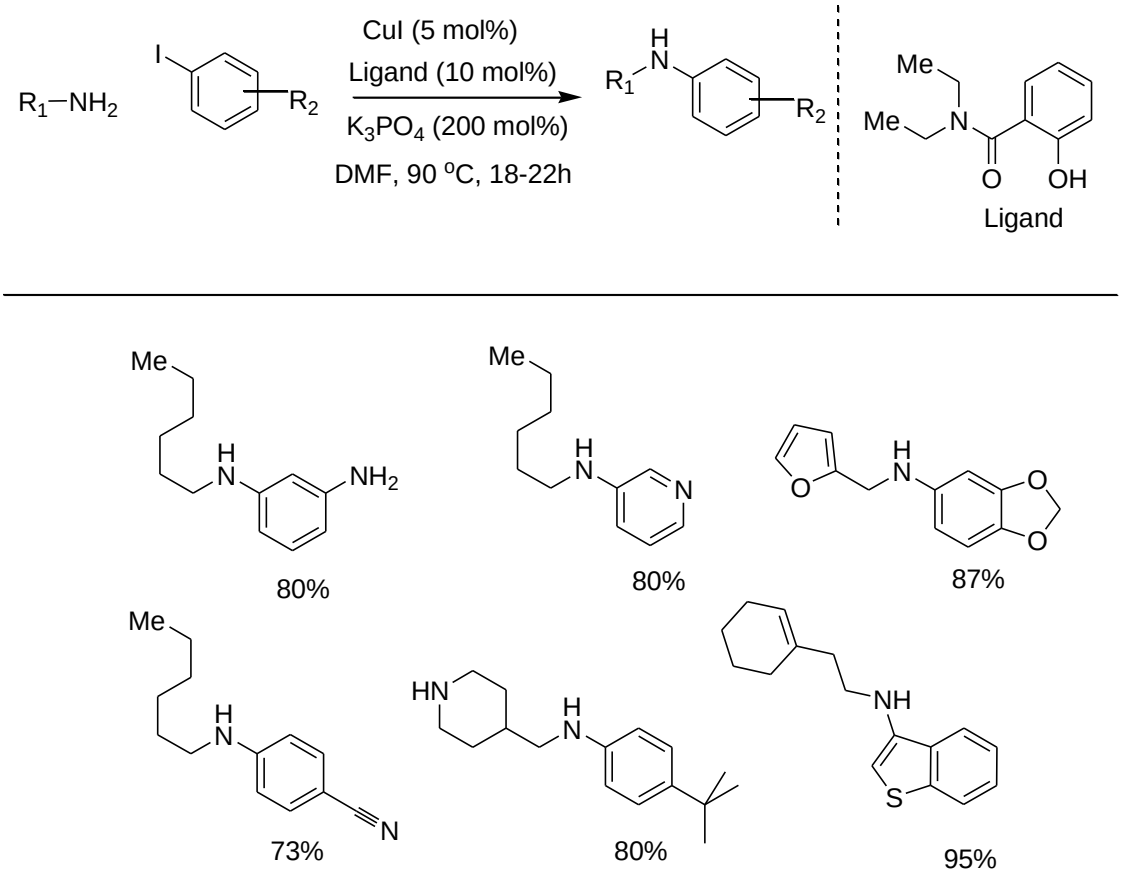


Figure 1.20. Substrate scope of Cu-catalyzed N-arylation of differently substituted iodobenzenes using phenol ligand

Coupling of aryl halides has also been reported with α-amino acids[116]. The accelerating effect of these α-amino acids has allowed Ullmann condensation to take place at lower temperatures than those under classical experimental conditions (Figure 1.21).

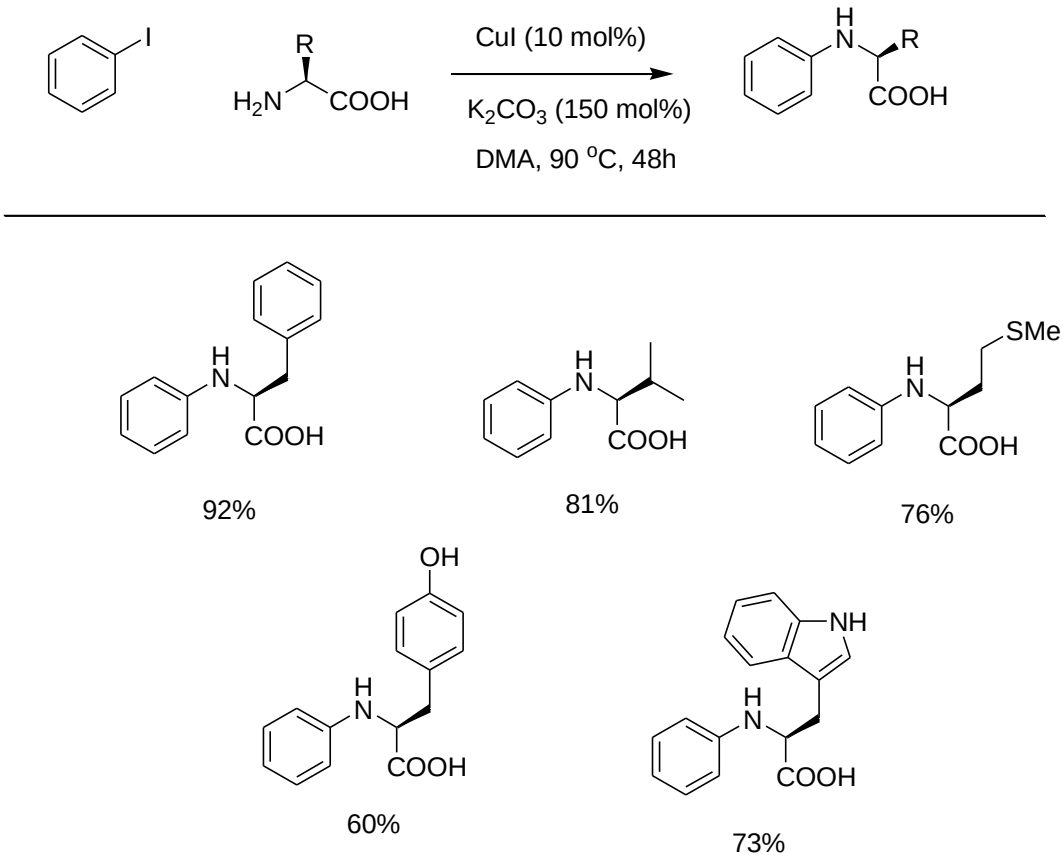
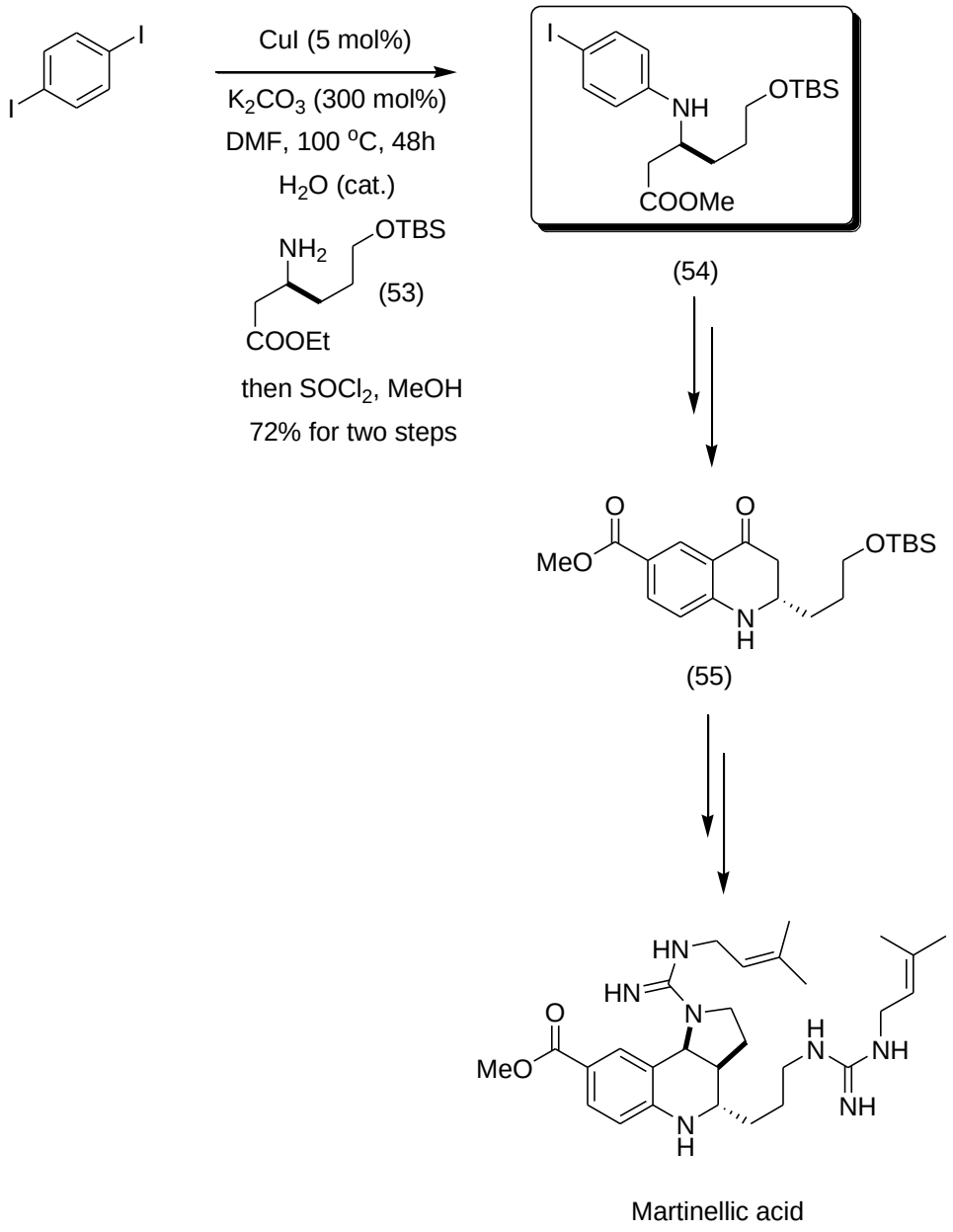


Figure 1.21. Cu-catalyzed arylation of α-amino acids

1, 4-diiodobenzene was reported to be a good electrophile by Ma and co-workers in arylation reaction with *β*-aminoester (53). Although the reaction time was quite longer (2 days) but it resulted in good yield and no diamination product was formed as a side product. The product (54) was used as a key intermediate in order to get (56) that were converted to martinellic acid, a natural product[117] (Scheme 1.29).

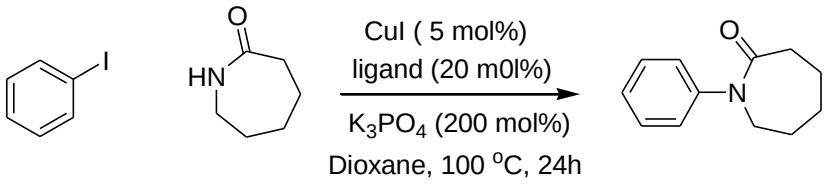


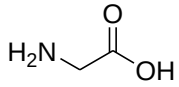
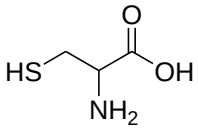
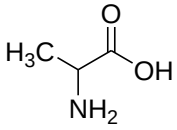
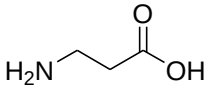
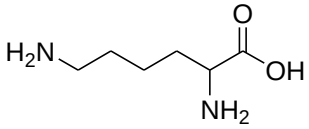
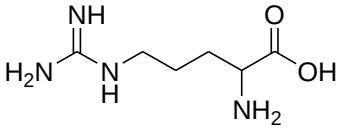
Scheme 1.29. Cu-catalyzed arylation of *β*-amino ester leading towards the synthesis of martinellic acid

Ma and co-workers reported that amino acids can also act as ligands for other nucleophiles instead of themselves, in C-N coupling reactions. Encouraged by this report W.Deng and co-workers in 2004 systematically studied the effects of amino acids as ligands in copper-catalyzed amidation reactions[118]. They screened seven different amino

acids for the arylation of caprolactam via iodobenzene. The yields they obtained for different ligands are given in the table 1.3.

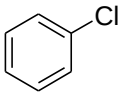
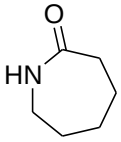
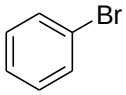
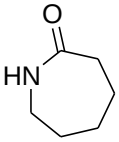
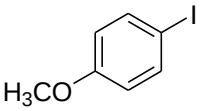
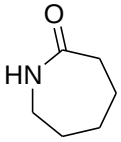
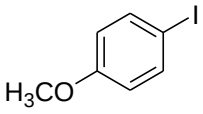
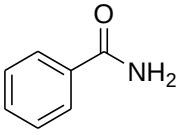
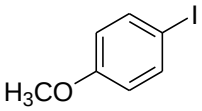
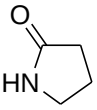
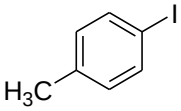
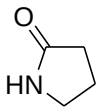
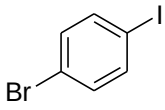
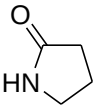
Table 1.3. Screening of different amino acids as ligands



Amino acid	Structure	%Yield
Glycine		97
Cystiene		92
α–Alanine		98
β-Alanine		99
Lysine		99
Arginine		97

Glycine was further used as a ligand to carry out coupling reactions of aryl halides with variety of different amides using 5 mol% CuI, 20 mol% glycine, 2 equivalent K_3PO_4 in dioxane at 100 °C for 24 hours. Respective yields are shown in the table 1.4.

Table 1.4 Yields of amidation reactions carried out using glycine as ligand

Aryl Halide	Amide	%Yield
		26
		62
		98
		71
		98
		93
		95

Mechanism of copper-catalyzed coupling reactions is not very well understood[119]. W.Deng and co-workers have proposed the following mechanism for amino acid catalyzed coupling reaction. According to the mechanism, the role of ligand is either to stabilize the Cu (III) intermediate or to promote the oxidative addition aryl iodide to Cu (I) species. This mechanism also explains that why it is the amide nitrogen and not the amino group of amino acid, that participate in the coupling reaction. It is so because the

amide nitrogen in the Cu (III) complex is more reactive due to its anionic nature whereas the amino (NH_2) group of amino acid ligand is neutral[118,119] (Figure 1.22).

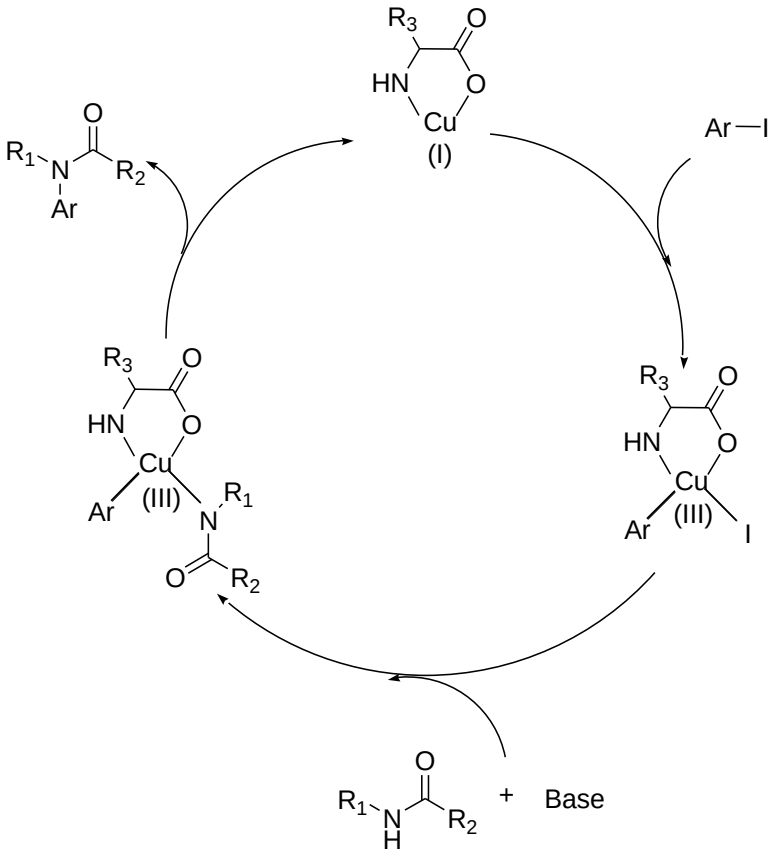


Figure 1.22. Proposed mechanism of Cu-catalyzed arylation using amino acids as ligand

1.7. Copper-Catalyzed C-S Coupling Reactions

C-S bond forming reactions are much less studied transformations as compared to the literature available for the C-O and C-N coupling reactions. The need for the development of carbon-sulfur bond forming reactions is endorsed by the prevalence of diary sulfides in natural and synthetic compounds that exhibit activities against HIV, Alzheimer's disease, cancer and asthma[120–125].

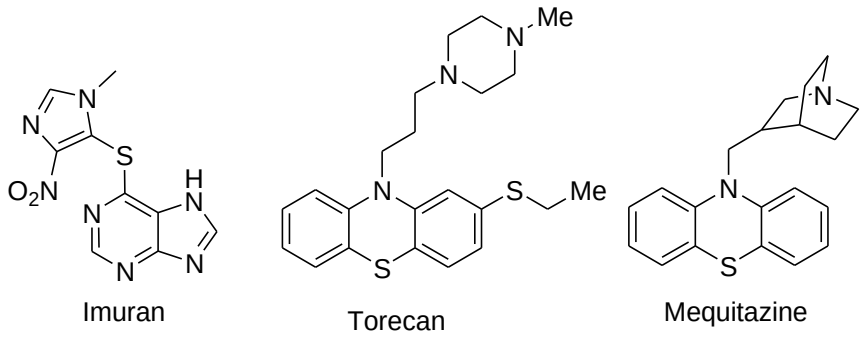
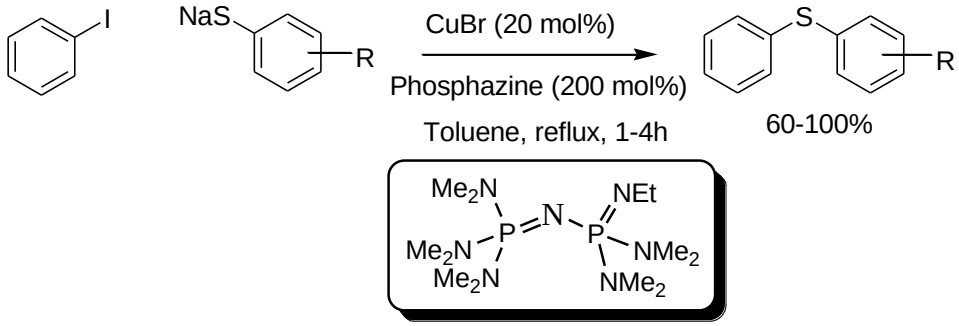


Figure 1.23. Pharmaceutically important drugs containing C-S bonds as their integral part

Methods used to synthesize aryl sulfides without the aid of transition metals are inefficient and exhibit low functional group tolerance. Some of these methods required nucleophilic aromatic substitution, nucleophilic attack on disulfides and metal-mediated reduction of disulfides. Transition metal catalysis has been realized to be an indispensible tool for the development of efficient methods to synthesize aryl sulfides. Two main challenges faced by the synthetic chemists, working with sulfur containing compounds are:

a) Remarkable self-coordination ability of sulfur that results in the formation of diphenyl disulfide instead of desired product.
b) Strong coordination of sulfur with the transition metal which plague the activity of metal catalyst and results in catalyst-poisoning[126].

The progress to develop the catalytic systems which are able to withstand the catalyst deactivation is on its way. Over the last decade copper has emerged as a viable catalyst for carrying out C-S coupling reactions. Palomo and co-workers reported the use of CuBr with phosphazine base to catalyze the arylation of thiol, using iodobenzene[127]. Despite of high catalyst loading and high cost of base this reaction was efficient and established the basis of Cu-catalyzed carbon-sulfur coupling reactions (Scheme 1.29).



Phosphazine Base

Scheme 1.30. Cu-catalyzed arylation of thiol using phosphazine base

The phosphazine was regarded as a special type of base that may also act as chelating ligand for copper.

The first practical synthesis of aryl sulfides using Cu as a catalyst was reported by Buchwald. Ethylene glycol was used as ligand to stabilize copper during the course of reaction[128] (Figure 1.24).

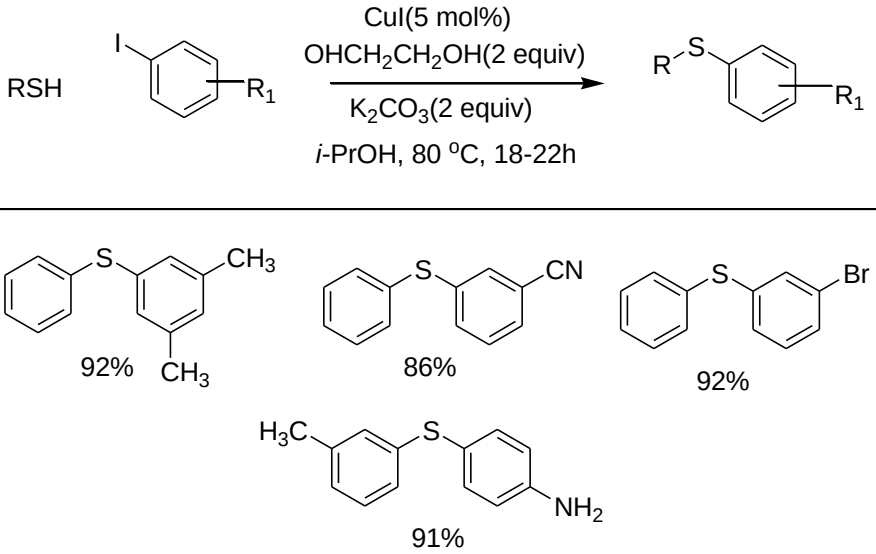
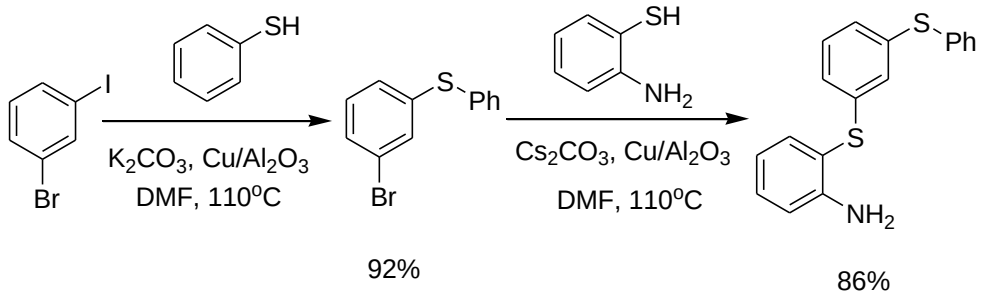


Figure 1.24. Cu-catalyzed thioether synthesis using ethylene glycol ligand

Ranu and co-workers reported a highly regioselective process for the arylation of thiols by using alumina-supported copper catalyst[129], which has previously been employed in the etherification and amination reactions. Under this protocol, reactivity of a copper

catalyst is significantly changed by simply changing the base. The use of Cs_2CO_3 allows the coupling of bromoarenes with thiols in the presence of aryl iodides. Switching the base to K_2CO_3 results in the chemoselective thiation of aryl iodides. This chemoselectivity is attributed to the ability of Cs_2CO_3, a strong base, to polarize the aryl bromide bond and allow Cu to undergo more facile oxidative addition. Notably, under these conditions, aryl amine is also not coupled with aryl bromide (Scheme 1.31).



Scheme 1.31. Cu-catalyzed arylation of thiol using alumina-supported copper catalyst

A new reaction sequence for the arylation of sulfinic acid using aryl iodides to synthesize diaryl and methyl aryl sulfones was reported by Baskin and Wang[130]. A wide range of functional groups are tolerated by this procedure but its scope is limited by the fact that aryl bromides do not react. The utility of this procedure relies heavily upon the ease of access to sulfinic acid salts (Figure 1.25).

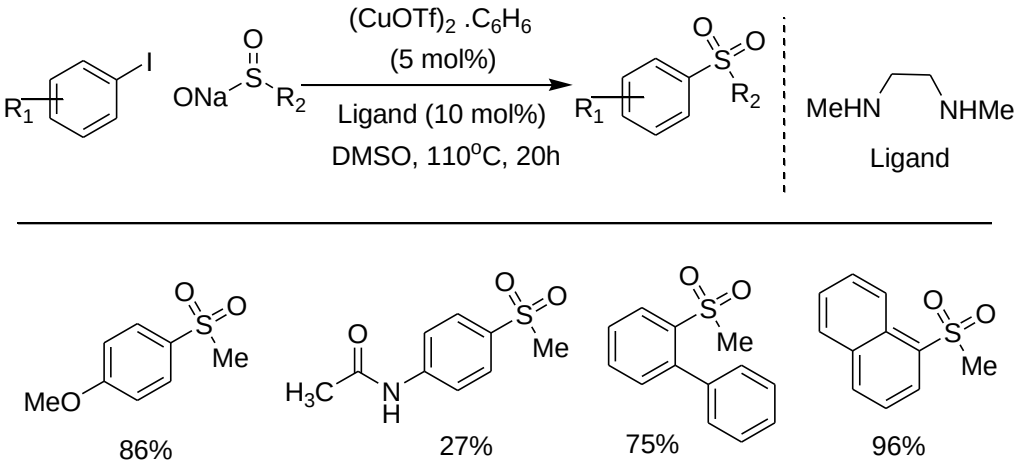


Figure 1.25. Cu-catalyzed arylation of sulfinic acids

Chiosis et al. carried out S-arylation of 8-mercaptoadenine with iodoarenes using CuI-Neocuproine system in DMF at 110 °C[131] (Figure 1.26).

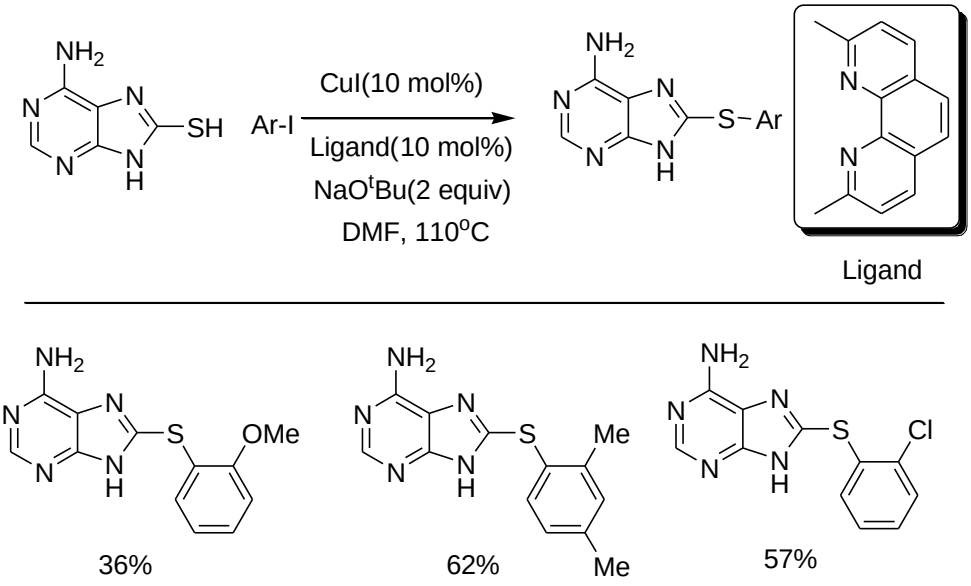
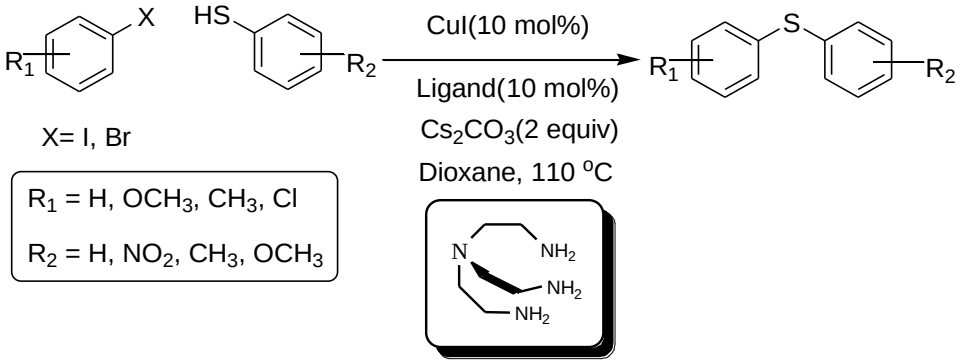


Figure 1.26. Scope of S-arylation of 8-mercaptoadenine

An efficient methodology for the arylation of thiols was developed by Shingare and co-workers, using a tripodal ligand, tris-(2-aminoethyl) amine[132] (Scheme 1.32).



Scheme 1.32. Cu-catalyzed arylation of thiol using tris-(2-aminoethyl) amine as ligand

Chen and co-workers reported N, N-dioxide as an effective ligand to carry out thiation of aryl iodides[133], using cesium carbonate as a base in DME at 80 °C (figure 1.27).

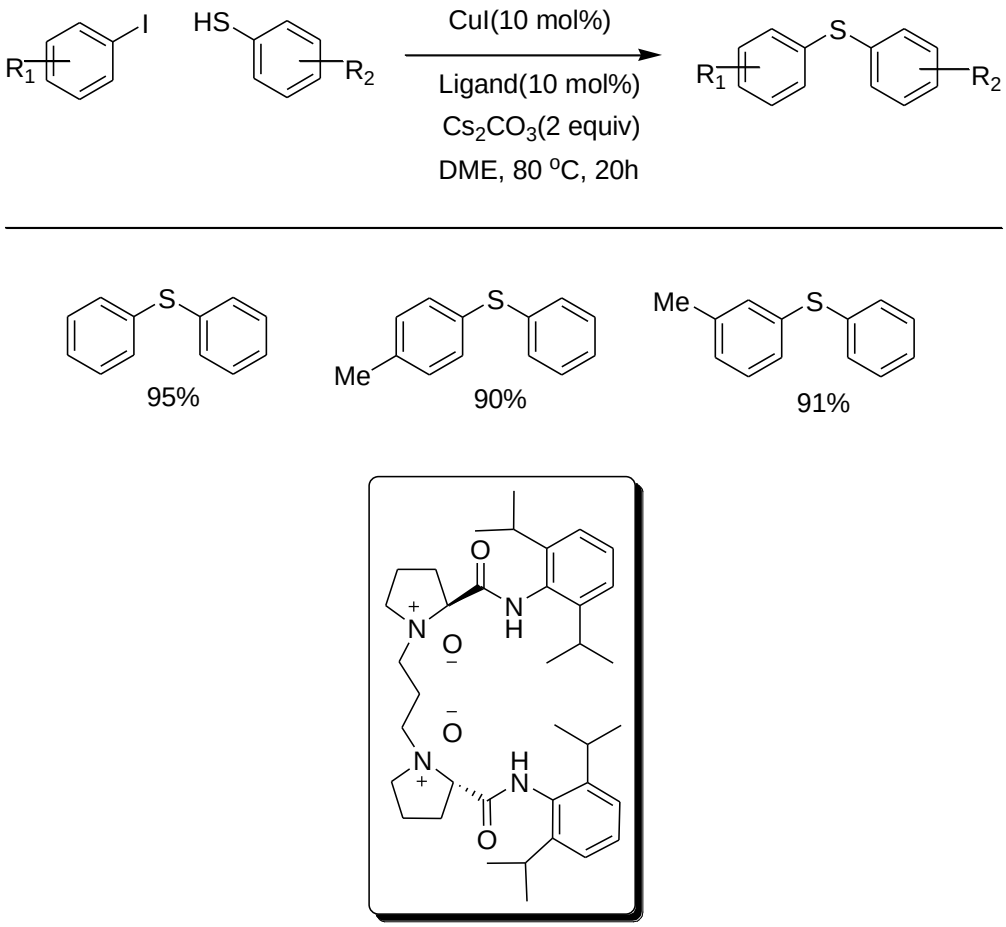


Figure 1.27. Cu-catalyzed arylation of thiophenols using N, N-dioxide as a ligand

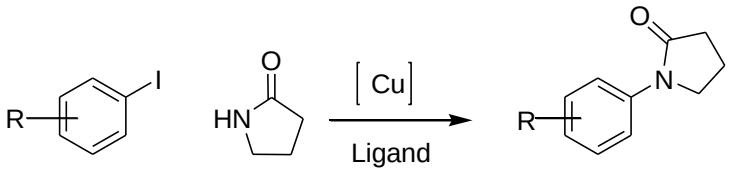
Concluding Remarks

It is evident from literature survey that major development witnessed by synthetic organic chemistry is credited to transition metal catalysis. For the last few decades transition metal catalysis has emerged as one of the most indispensable tools for carrying out carbon-heteroatom bond forming reactions. Different methods utilize different transition metals as catalysts, among these Pd, Ni, Ru, and Cu are most extensively used to catalyze C-C and C-heteroatom bond forming reactions. Use of Copper salts as catalyst has been known for more than a century since the findings of Ullmann and Goldberg. However, copper chemistry had been neglected for an extended period of time after the stupendous development of palladium-based procedures. Deficiencies of Pd-catalysis forced synthetic chemists to reconsider copper as a catalyst of choice. Various research groups have put their efforts to make these classical reactions work under milder conditions, mainly by the use of ligands. Ligand designing has played a vital role in the ongoing progress of Cu-catalysis and most promising results in this field have been demonstrated by Buchwald research group. Although the ligand designing for Cu-catalyzed procedures is at its infancy, still a variety of ligands is available which could be used for an efficient C-O, C-N and C-S bond construction.

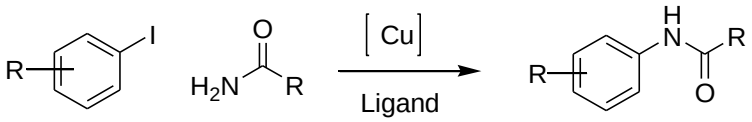
Plan of Work

Taking into consideration, the coordination ability of 2, 6-pyridine dicarboxylic acid also known as dipicolinic acid (DPA), it was planned to work out a new class of ligands by exploiting this chelation ability of DPA and to contribute towards the growing avalanche of ligands for copper catalyzed C-N and C-S coupling reactions. This idea was made to work by the synthesis of mono-amides of dipicolinic acid and their subsequent use to carry out arylation of amides and thiols in order to check the scope of this catalytic system (Cu (I) / mono-amide of DPA). It was also aimed to find out the most efficient mono-amide after the careful screening of all the available mono amides and to optimize reaction conditions for this mono-amide.

The present study consists of two parts. First part includes the arylation of cyclic and acyclic amides by mono and di-substituted iodobenzenes (modified Goldberg reaction)

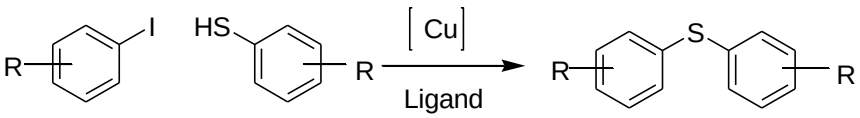


Scheme 1.33. Cu-catalyzed arylation of cyclic amide

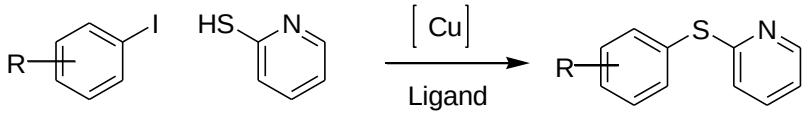


Scheme 1.34. Cu-catalyzed arylation of acyclic amides

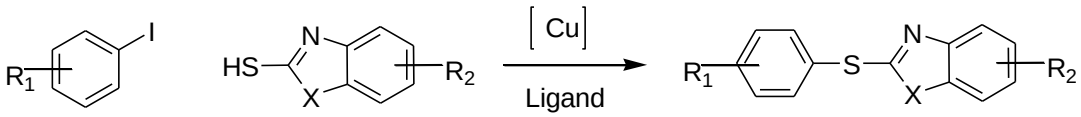
The second part includes the arylation of aromatic and hetero aromatic mono and bicyclic thiols by using the same variously substituted iodobenzens.



Scheme 1.35. Cu-catalyzed arylation of thiophenols



Scheme 1.36. Cu-catalyzed arylation of hetero aromatic mono cyclic thiols



Scheme 1.37. Cu-catalyzed arylation of bicyclic hetero aromatic thiols.

CHAPTER-2

RESULTS AND DISCUSSION

A wide range of compounds showing biological as well as many other useful properties contain either C-N or C-S bond as their integral part or sometimes a molecule comprises of both of these bond types. The prevalence of these bonds in a wide range of useful compounds demands mild, general and efficient methodologies for their construction. Classical Ullmann and Goldberg reactions for carbon-heteroatom bond synthesis could not gain much popularity to be used on large scale due to harsh reaction conditions. Development of the methodologies that could work under mild conditions was a major goal of synthetic chemists and accomplishment of this goal is largely attributed to the emergence of transition metal catalysis. Copper based procedures got neglected due to remarkable development of Pd-based methods. High cost and limited scope of Pd-catalysis helped copper, regain its lost field which was further backed by the observations that Cu-based methodologies could be made more efficient by increasing solubility of copper salts in the reaction medium. Observations that certain additives increase solubility of copper salts resulted in the deliberate addition of additives to increase yield. Since then different research groups have discovered and designed different classes of ligands that played a pivotal role towards the progress of Cu-catalysis and the process is still continued. Neutral bi- and tridentate chelators are used in variety of reaction protocols. The variety of donor combination include O, O-, N, N-, O,N-, N, O, N- and O,N,N- chelators. The wide choice of ligands increases the potential for optimization and fine-tuning of the given transformation. Apart from increasing solubility, ligands stabilize the metal catalyst during the course of reaction and control most of the properties of a metal-ligand complex. Phenanthrolines, amino acids, diol, phenols and diamine based ligands have been discovered so far for copper-catalyzed C-N and C-S coupling reactions and still there is much room for the development of inexpensive, experimentally simple and environmentally benign procedures.

2.1. Mono-Amides of Dipicolinic Acid

Dipicolinic acid possesses high coordination power and is reportedly known to form complexes with transition metals and lanthanides[134]. Amides of DPA are of great interest for their potential applications in catalysis and coordination chemistry and retain inherent chelation ability of DPA. Mono-amides DPA are quite rare but they show tremendous coordination ability. keeping in mind this high chelating power, we decided to use newly synthesized mono amides of dipicolinic acid as ligands for C-N and C-S cross coupling reactions, which were synthesized as novel compounds by one of my seniors as a part of his research project[135] (Figure 2.1).

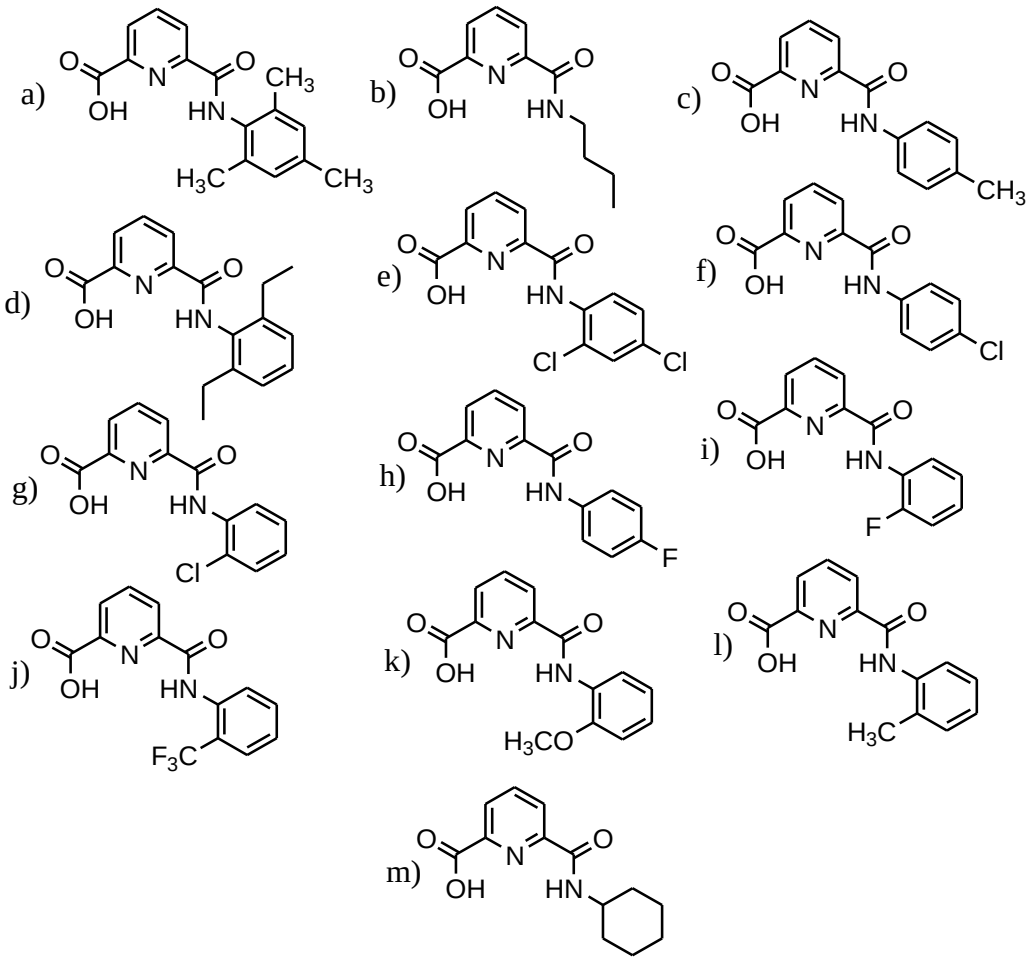


Figure 2.1. Mono-amides of Dipicolinic Acid

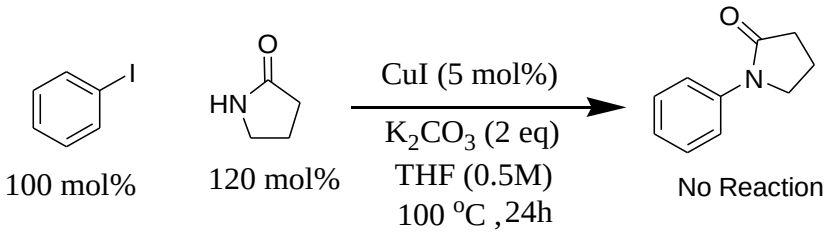
2.2. Arylation of Amides (Modified Goldberg Coupling Reaction)

The study of the use of mono-amides as new ligands for C-N and C-S coupling reactions began with the screening of all above mentioned amides for their coordination ability.

2.2.1. Ligand Screening

To carry out the ligand screening, cross coupling reaction of iodobenzene with 2-pyrolidinone was used as a model reaction in the presence of 5 mol% CuI, 10 mol% ligand, 200 mol% K_2CO_3 in THF at 100 ^oC for 24 hours.

A controlled reaction was also setup under the same conditions as the model reaction but without the addition of any ligand. This controlled reaction gave no product and both of the reactants were present in the reaction mixture as such which showed that ligand is necessary for the successful completion of reaction and to get desired coupled product (Scheme 2.1).

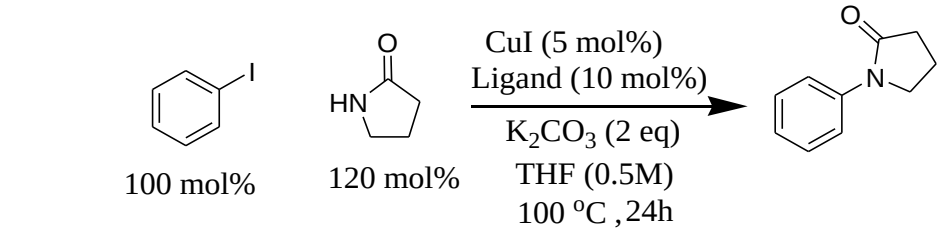


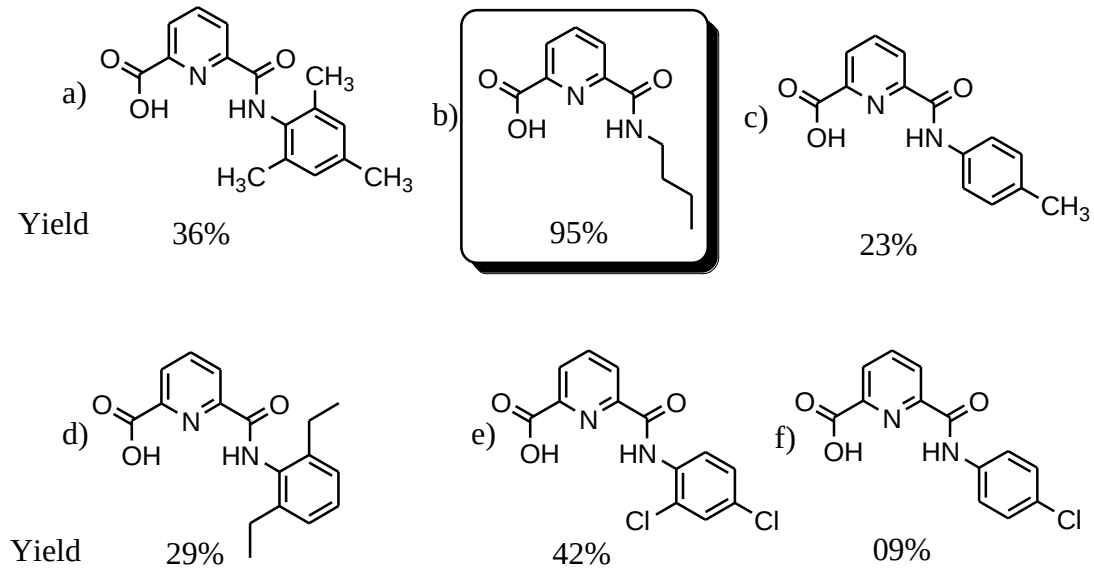
Scheme 2.1. Controlled Reaction.

The results of ligand screening showed that both, steric and electronic factors control the activity of mono-amides as ligands and there is always a compromise between these two factors in controlling the yield of a reaction *e.g.* mono-amide of butylamine gave highest yield while mono-amide of cyclohexyl amine resulted in only 15% yield the reason might be the steric hinderance faced by the metal during complex formation due to the axial hydrogens of cyclohexane ring. Mono-amide of 2,4,6-trimethylaniline gave 36% yield while that of toluene resulted in 23 % yield, the reason might be the increased electron density due to three electron donating groups in case of 2,4,6-trimethylaniline. In case of mono-amide of 2,6-diethylaniline yield decreased to 29% as compared to ligand (a). Although ethyl group is more activating than methyl group but it also offers more steric hindrance during the course of reaction. Amongst anilines substituted at *ortho* position,

mono-amide of trifluroaniline gave highest yield as compared to *ortho* methoxy and *ortho* methylaniline; the reason might be the decreased steric hindrance in case of -CF_3 group due to small size of fluorine. The most anomalous behavior was shown by mono-amide of *o*-chloroaniline. It resulted in highest yield as compared to *p*-chloroaniline while in case of flouroanilines, *p*-fluoraniline gave better yield as compared to *o*-fluoroanilines. diamide of DPA (p) gave no reaction due to increased steric hindrance offered by two aromatic rings of aniline. . Use of the mono-amide of ethylamine *i.e.* 6-(butylcarbamoyl) picolinic acid gave the coupled product in highest yield .Apart from using mono-amides of DPA as a ligands, diester of dipicolinic acid, diamide of dipicolinic acid and dipicolinic acid itself without any further modification were also investigated for their ligand activity. Diacid and diester resulted in quite low yield while use of the diamide as a ligand gave no reaction at all, probably due to high sterics.

(Scheme 2.3).





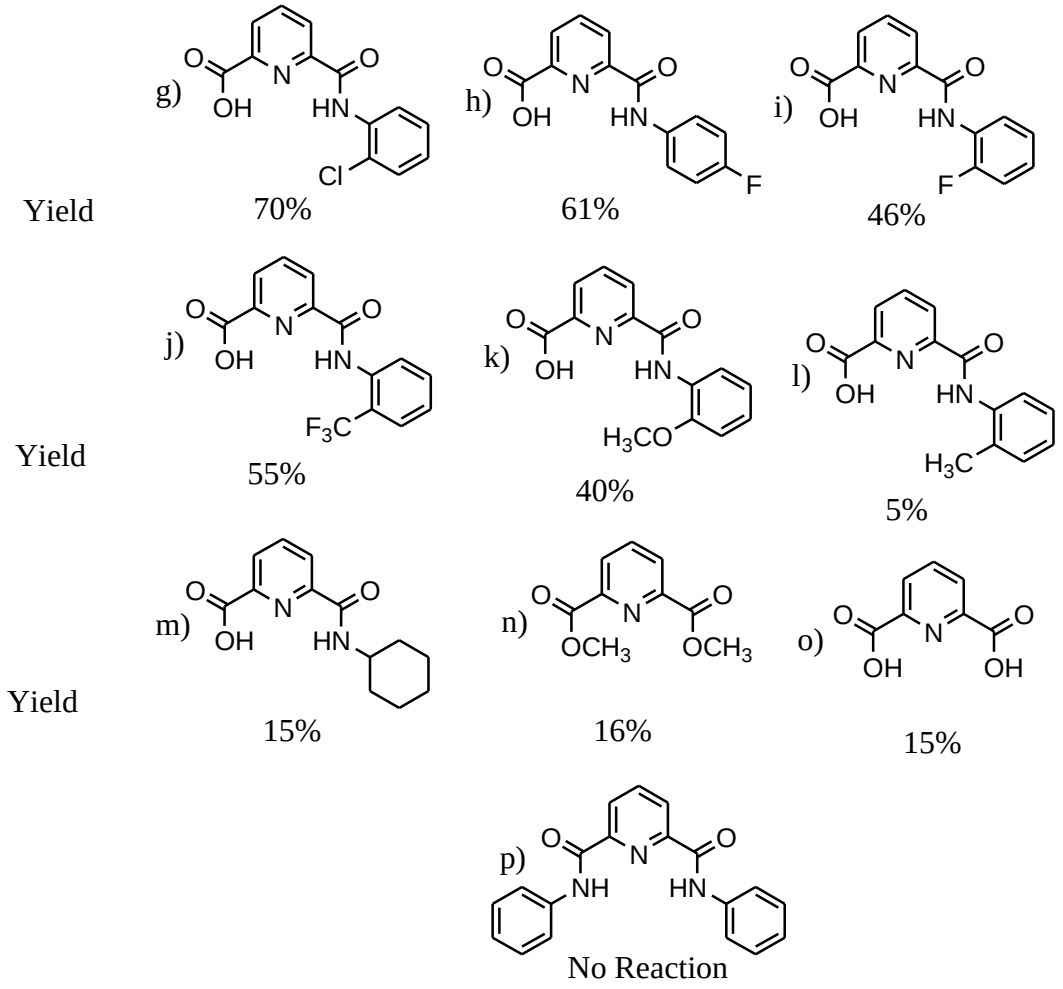


Figure 2.2. a) Model reaction **b)** results of ligand screening.

2.2.2. Scope of Reaction

Scope of the reaction was checked by the amidation of mono-substituted iodobenzenes, using mono-amide of butyl amine as a ligand (Figure 2.3).

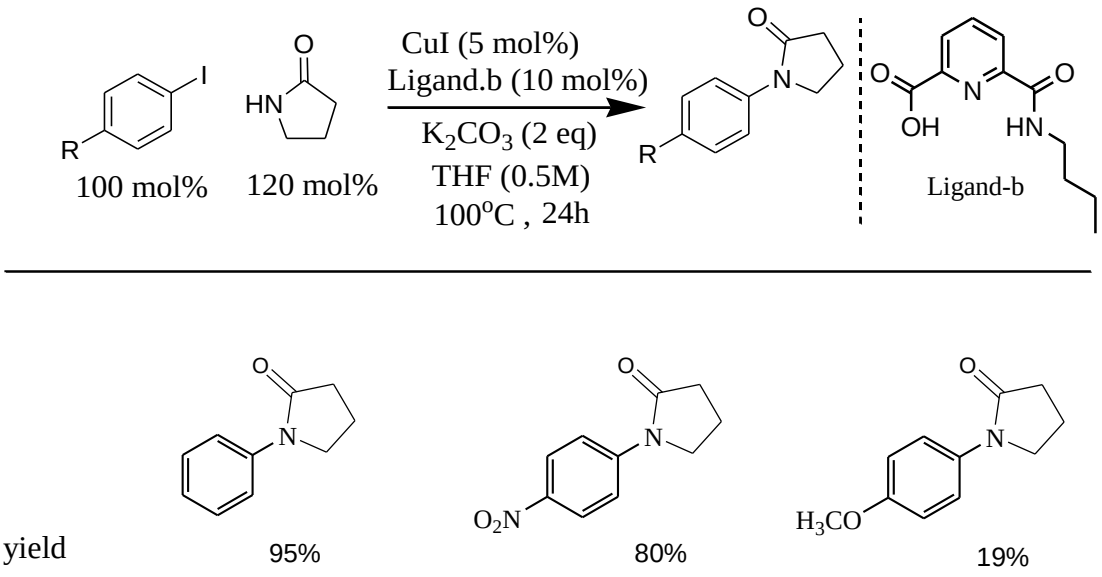


Figure 2.3. Scope of arylation of 2-pyrrolidinone using mono-amide of butyl amine as ligand.

Substitution of $-NO_2$ group on benzene ring resulted in good yield whereas the substitution of $-OCH_3$ group decreased the yield. The most obvious reason for this deference in yield is the fact that substitution of $-NO_2$ group on the benzene ring, makes the ring electron-deficient and hence make oxidative addition of copper-catalyst across Ar-I bond more facile. Amidation of 4-methoxy iodobenzene resulted in only 19% yield so it was decided to optimize reaction conditions for this substrate.

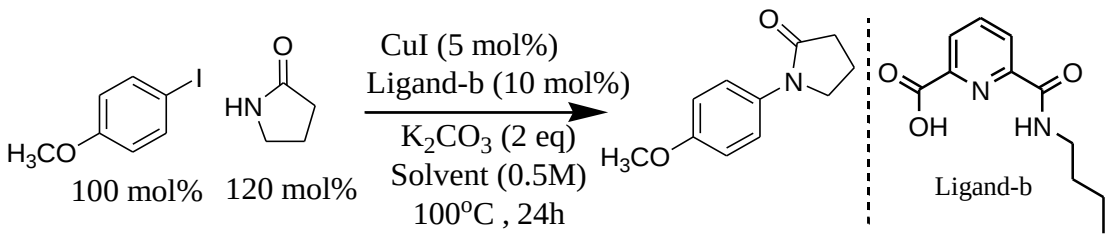
2.2.3. Reaction Conditions Optimization

Amidation of 4-methoxy iodobenzene was optimized using 2-pyrolidinone 120 mol% and 4-methoxy iodobenzene as a limiting reactant with 5 mol% CuI, 10 mol% ligand, 2 equivalents of K_2CO_3 in THF solvent at 100 °C for 24 hours, as initial conditions. Optimization was started with solvent screening.

2.2.3.(a) Solvent Screening

As the solvent plays a vital role in increasing or decreasing the efficiency of a reaction, it was decided to take start with solvent screening. Detailed literature survey showed that most commonly used solvents for C-N coupling reactions are toluene, THF, dioxane and DMF. We also performed solvent screening using these solvents (table 2.1).

Table 2.1. Solvent screening for Cu-catalyzed amidation of 4-methoxy iodobenzene



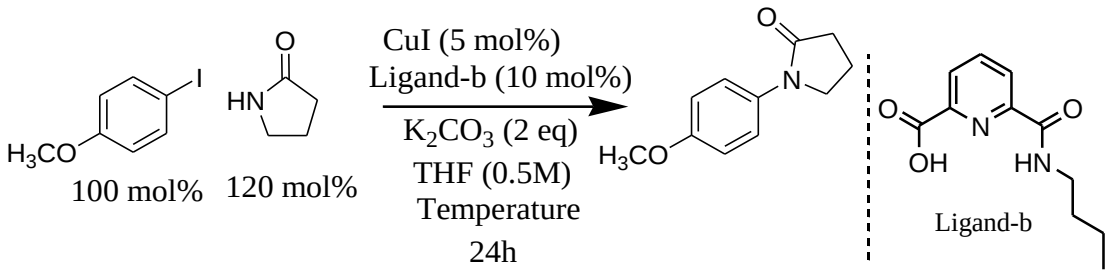
ENTRY	SOLVENT	YIELD (%)
1	THF	19
2	Toluene	10
3	Dioxane	17

Use of toluene as a solvent resulted in decreased yield probably due to its non polar nature it was not able to completely solubilize the ligand which possesses a polar acid group. Dioxane and THF gave comparable yields. As THF gave relatively higher yield, it was decided to proceed temperature screening using THF as a solvent.

2.2.3.(b) Temperature Screening Using THF as a Solvent

Temperature plays a very important role in determining the efficiency of the reaction. Increase in temperature generally increases the kinetic energy of molecules and hence reaction rate is also increased but sometimes increase in temperature results in decreased yield due the decomposition of any one of the components of reaction mixture. Thus it important to find out an optimum temperature for a given type of reaction.

Table 2.2. Temperature screening in THF



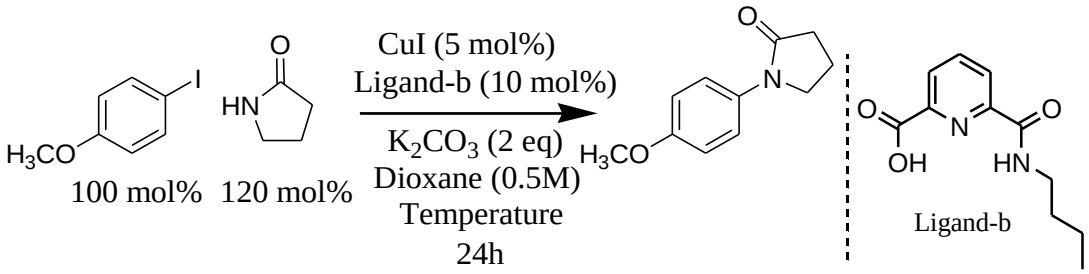
ENTRY	TEMP (°C)	YIELD (%)
1	100	19
2	110	15
3	120	11

Results of temperature screening showed that increasing temperature by 10 °C resulted in decreased yield. Increasing temperature up to 120 °C decreased the yield further. As the boiling point of THF is 66 °C, it could be speculated that increasing temperature up to 110 °C and further, caused decomposition of THF and resulted in decreased yield of the reaction (Table2.2).

2.2.3.(c) Temperature Screening Using Dioxane as a Solvent

During the solvent screening, along with THF, the other promising candidate for further screening was dioxane so we decided to carry out temperature screening in dioxane as well. The results of temperature screening are given in the table 2.3. It is evident from the table that yield got increased by increasing temperature up to 120 °C. Increasing temperature further up to 130 °C resulted in significance increase in yield. This increase in yield could be attributed to the polar nature of dioxane. Due to its polar nature, it could solubilize ligand pretty well and hence make the reaction more efficient. Boiling point of dioxane is 101°C so it can tolerate increase in temperature up to 120 °C and more.

Table **2.3.** Solvent screening in dioxane.

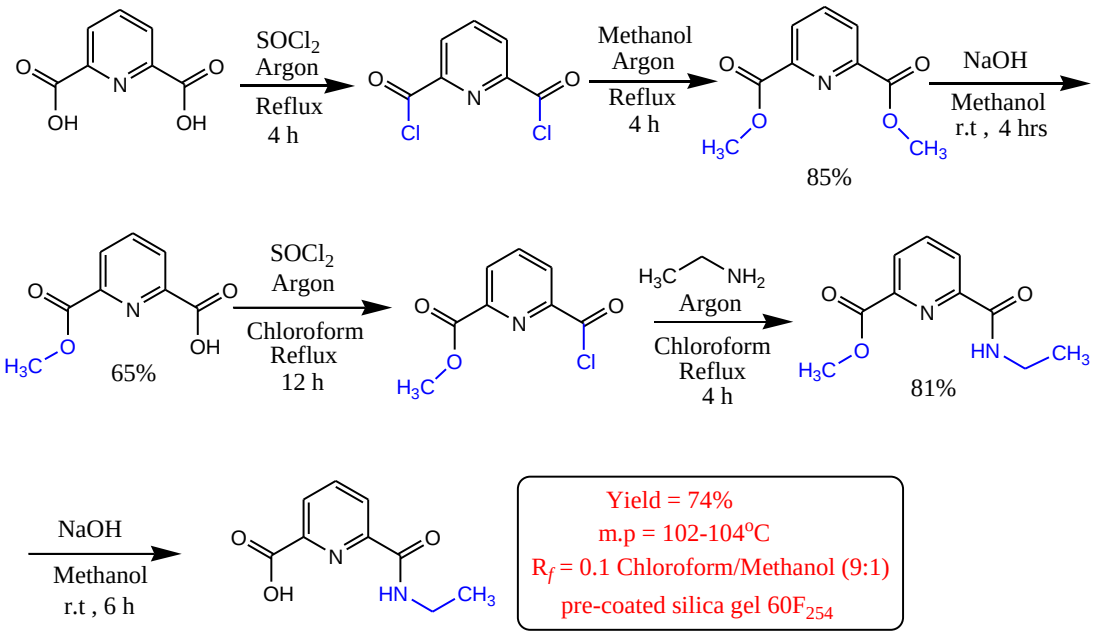


ENTRY	TEMP(°C)	YIELD (%)
1	100	19
2	110	41
3	120	60
4	130	62

After all the ligand screening done for 4-methoxy iodobenzene, maximum yield that could be achieved was 62%. At this point, keeping in mind the optimized ligand structure of diamine-based ligand, it was decided to decrease the chain length of the amide part of mono-amide of dipicolinic acid, which we believed would help us to increase the yield of iodoarenes substituted with electron-donating groups due to decrease in steric hindrance by decreasing length of alkyl chain (Table 2.3).

2.3. Synthesis of Mono-amide of Ethylamine

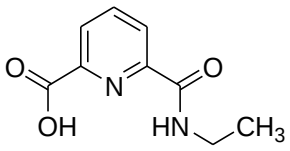
Mono-amide of ethylamine [6-(ethylcarbamoyl) picolinic acid] was synthesized with a view to decrease steric hindrance of the ligand. Decreasing chain length of alkyl group of amine would cause mono-amide to offer less steric hindrance and thus helps in effective coordination with CuI.



Scheme 2.2. Scheme for the synthesis of mono-amide of ethylamine

2.3.1. Characterization of Mono-amide of Ethylamine Using IR Spectroscopy

Table 2.4. IR data for the synthesis of mono-amide of ethylamine.

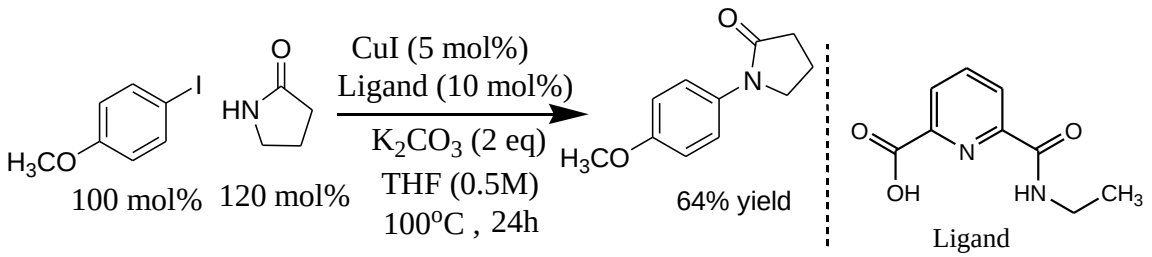


Functional group	O-H (acid)	-NH-	C=O (acid)	C=O (amide)	C-H (sp^3)
Frequency ($\bar{\upsilon}$) (cm^{-1})	3400-2416	3262	1728	1649	1361

Table 2.4 shows the characteristic stretching frequencies of the functional groups found in mono-amide of ethylamine. A broad band ranging from 3400-2416 cm^{-1} corresponds to –OH group of acid. Presence of absorption band with the sharp end at 3262 cm^{-1} indicates the presence of -NH- group, this characteristic band confirms the formation of

amide. Absorption band for the carbonyl of carboxylic acid appears at 1728 cm^{-1} while the band for carbonyl of amide appears at 1649 cm^{-1}. Appearance of two different absorption bands for carbonyl moiety, one corresponding to acid while other corresponding to amide shows that the dipicolinic acid has been converted to its mono-amide. The characteristic absorption bands for C-H (SP^3) appears around 1361 cm^{-1} and 2870 cm^{-1}.

After the synthesis of mono-amide of ethylamine, it was used as a ligand to carry out amidation of 4-methoxy iodobenzene. The conditions used were the same, used for the ligand screening *i.e.* 5 mol% CuI, 10 mol% ligand, 2 equivalents of K_2CO_3 in THF at 100^0C for 24h (Scheme 2.3).



Scheme 2.3. Arylation of 2-pyrrolidinone using mono-amide of ethylamine as ligand.

The use of newly synthesized ligand (mono-amide of ethylamine), enhanced the yield up to 64%, which was only 19% when mono-amide of butyl amine was used as a ligand under the same set of conditions. Hence the idea of using sterically less demanding mono-amide went up to our expectations really well.

Use of mono-amide of ethylamine resulted in 64% yield of the coupled product under the given set of conditions; it was important to find out the conditions for this ligand under which it works best so screening of different reaction parameters was done in order to find out the optimum working conditions for mono-amide of ethylamine.

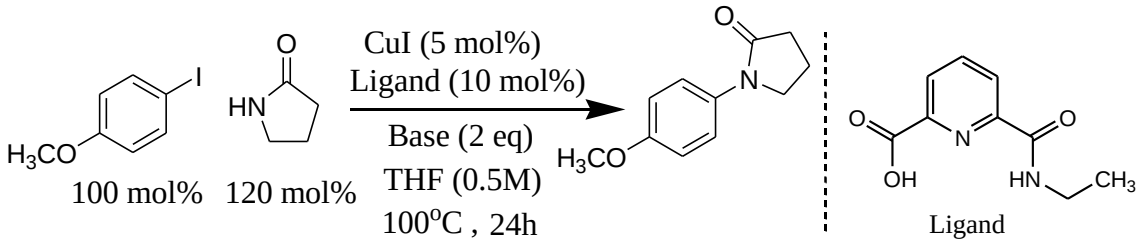
2.3.2. Reaction Conditions Optimization

The parameters which were screened for the amidation of 4-methoxy iodobenzene using mono-amide of DPA with ethylamine, included base, solvent and temperature.

2.3.2.(a) Base Screening

The optimization of the reaction conditions with new ligand was started with base screening. The most commonly used bases for C-heteroatom coupling reactions include K_2CO_3, K_3PO_4 and Cs_2CO_3 so base screening was carried out using these three bases. Same reaction was carried out using different bases while all other factors were kept constant (Table 2.5).

Table 2.5. Base screening for Cu-catalyzed amidation of 4-methoxy iodobenzene

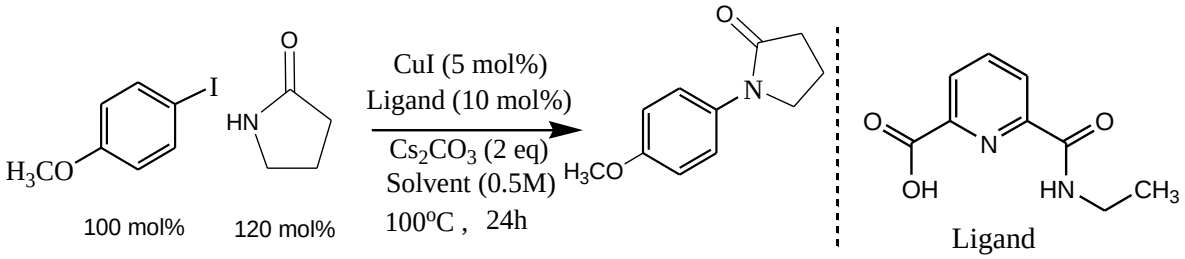


ENTRY	BASE	YIELD (%)
1	K_3PO_4	70
2	K_2CO_3	64
3	Cs_2CO_3	78

Use of K_3PO_4 improved the yield from 64% to 70%. Yield increased up to 78% when Cs_2CO_3 was added as a base. The obvious reason for this increase is the fact that a strong base increased the rate of deprotonation of amide and cesium salts are also more soluble in organic media as compared to potassium salts. Iodide is a very good leaving group so the rate of deprotonation of amide and rate of amidation of aryl iodide, both proceeded at the same rate, making the whole process rapid, helping to increase the rate of reaction which subsequently resulted in increased yield.

2.3.2.(b) Solvent Screening

Table 2.6. Solvent screening for Cu-catalyzed amidation of 4-meyhoxy iodobenzenes

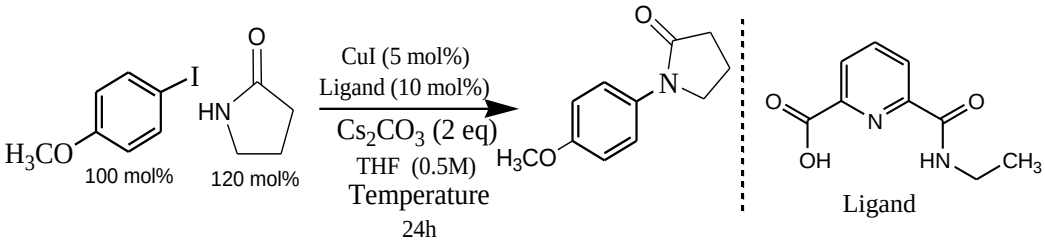


ENTRY	SOLVENT	YIELD (%)
1	DMF	34
2	Toluene	30
3	THF	78
4	Dioxane	71

The results shown in the table 2.5 are almost similar to the solvent screening done in case of mono-amide of butyl amine (table 2.1). Use of both highly polar solvent DMF and non polar solvent toluene decreased the yield whereas THF and dioxane again gave comparative yields. Although DMF is more polar than dioxane but still it resulted in the decreased yield of the reaction because it gets decomposed at 100 °C or higher temperatures. As in case of ligand screening for butyl amine, THF was chosen first for further temperature screening (Table 2.6).

2.3.2.(c) Temperature Screening Using THF as a Solvent

Table 2.7. Temperature screening for Cu-catalyzed amidation of 4-methoxy iodobenzene

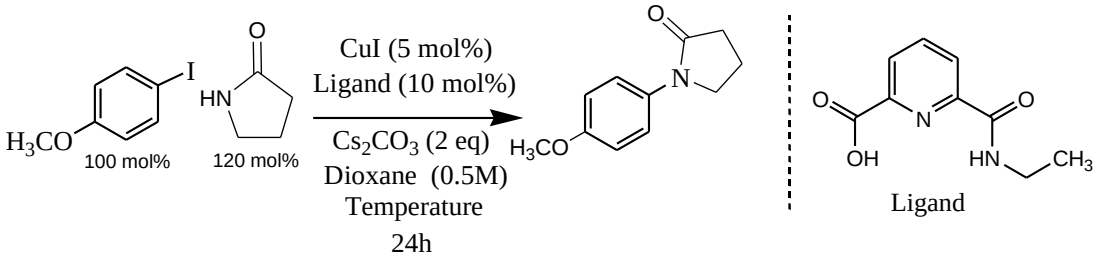


ENTRY	TEMP (°C)	YIELD (%)
1	90	71
2	100	78
3	110	75
4	120	52

Again by increasing temperature up to 120 °C, the yield of the coupled product got decreased to 52%. Whereas decreasing temperature from 100 °C to 90 °C also resulted in decreased yield. The reason might be that at low temperature the reaction does not get enough kinetic energy to proceed at satisfactory rate (Table 2.7).

2.3.2.(d) Temperature Screening Using Dioxane as a Solvent

Table 2.8. Temperature screening in dioxane

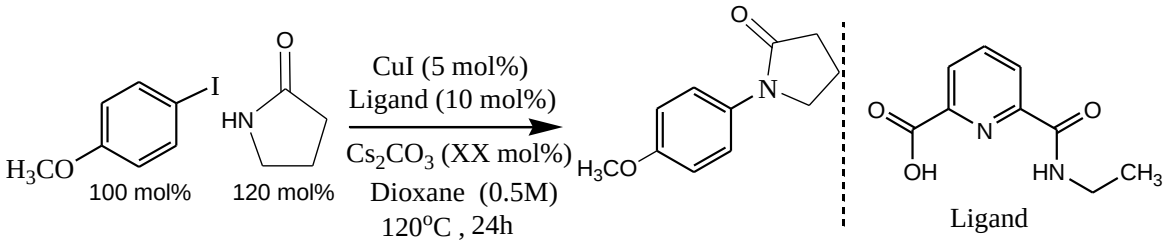


ENTRY	TEMP (°C)	YIELD (%)
1	100	65
2	110	97
3	120	99

An increase of temperature from 100 °C to 110 °C resulted in tremendous increase in yield. Almost quantitative yield was obtained when temperature was increased up to 120 °C (Table 2.8).

2.3.2.(e) Effect of Base Concentration on the Reaction

Table 2.9. Effect of changing base concentration on the amidation of 4-methoxy iodobenzene



ENTRY	mol%	YIELD (%)
1	100	91
2	200	99
3	300	99

After optimizing dioxane as a best solvent and Cs_2CO_3 as best base for the reaction, the concentration of the base was screened by increasing and decreasing concentration from initial 200 mol%. Results of base concentration screening showed that decreasing base concentration to 100 mol% decreased the yield. Increasing base concentration up to 300 mol% was ineffective as shown in table 2.8. The optimum concentration was found to be the initial 200 mol% (Table 2.8).

2.3.3. Reaction Scope for the Amidation of Variously Substituted Iodobenzenes

After the successful base, solvent and temperature screening, the optimum conditions for the N-arylation of 2-pyrolidinone were found to be 5 mol% CuI,10 mol% ligand (mono-amide of ethylamine), 200 mol% Cs_2CO_3 in dioxane solvent at 120 °C for 24 hours. With the optimized conditions in hand, the scope of the reaction was investigated for the amidation of mono and di-substituted iodobenzenes using cyclic and acyclic amides.

2.3.3.1. Amidation of Mono-substituted Iodobenzenes using 2-Pyrrolidinone

Amidation of mono-substituted iodobenzene was carried out using 100 mol% iodobenzenes, 120 mol% 2-pyrolidinone, 5 mol% CuI, 10 mol% ligand, 200 mol% Cs_2CO_3 in dioxane at 120 °C for 24 hours. All the coupled products were obtained in excellent yields irrespective of the substituent present on the benzene ring (Figure 2.4).

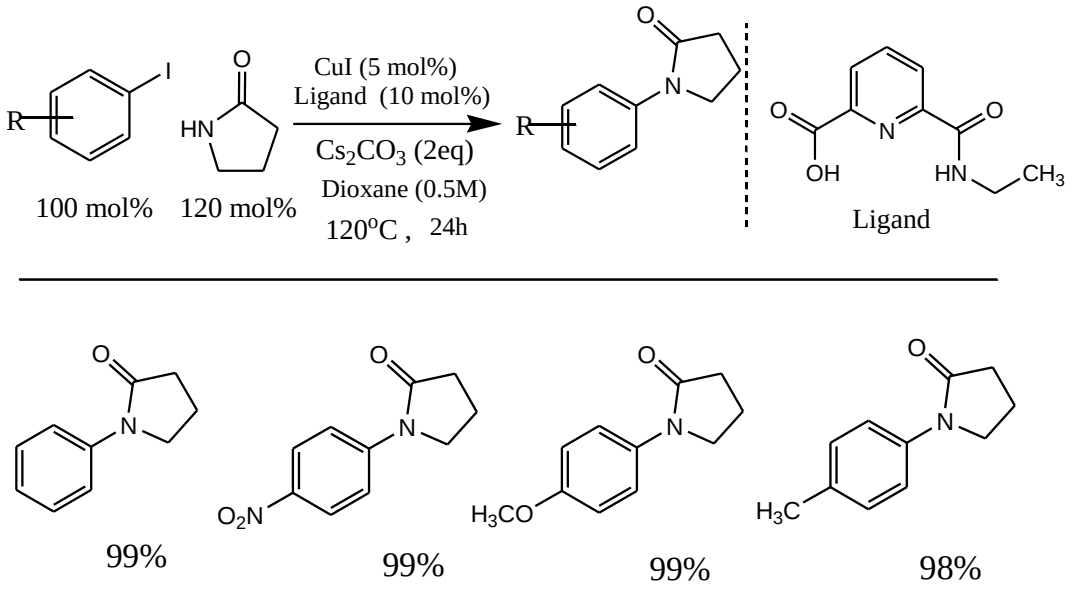


Figure 2.4. Amidation of mono-substitute iodobenzenes

2.3.3.2. Effect of Changing Catalyst and Ligand Loading on the Amidation of Mono-substituted Iodobenzenes

Amidation of mono-substituted iodobenzenes was also carried out under low concentration of copper and ligand in order to investigate the efficiency of the catalytic system. Concentration of CuI was decreased from 5 mol% to 2 mol% and ligand concentration was decreased from 10 mol% to 4 mol%.

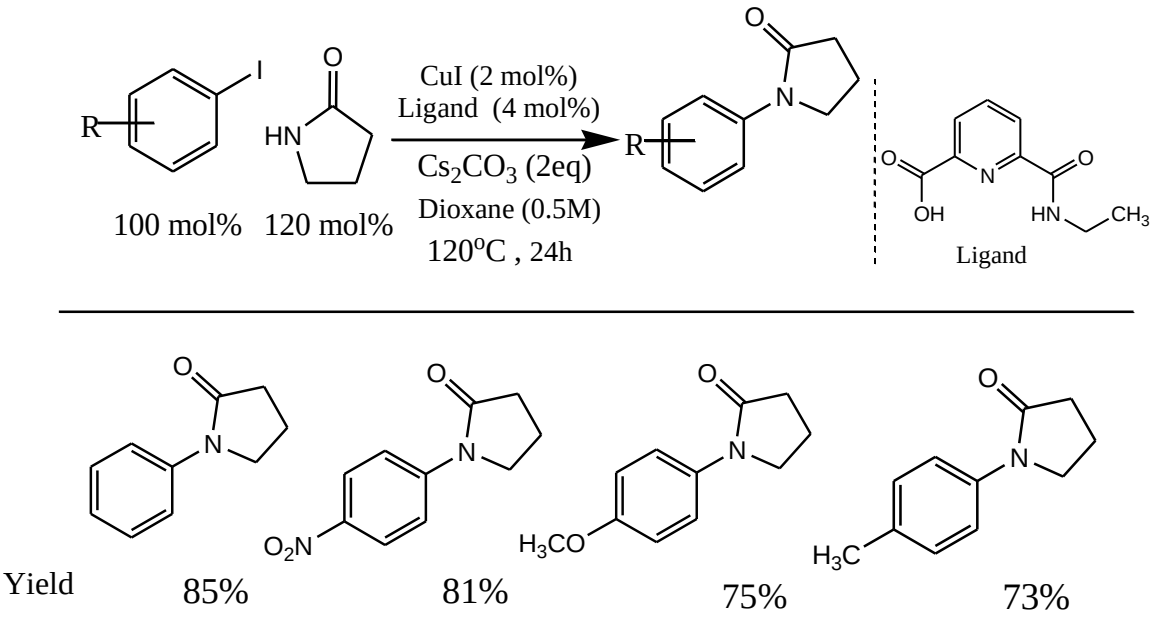


Figure 2.5. Cu-catalyzed amidation of mono-substituted iodobenzenes at low catalyst and ligand concentration.

2.3.3.3. Cu-catalyzed Amidation of Di-substituted Iodobenzenes using 2-Pyrolidinone

N-arylation of 2-pyrolidinone was also carried out using di-substituted iodobenzenes under the same conditions used for the amidation of mono-substituted iodobenzenes. Coupled products were obtained in fair to good yields (Figure 2.6)

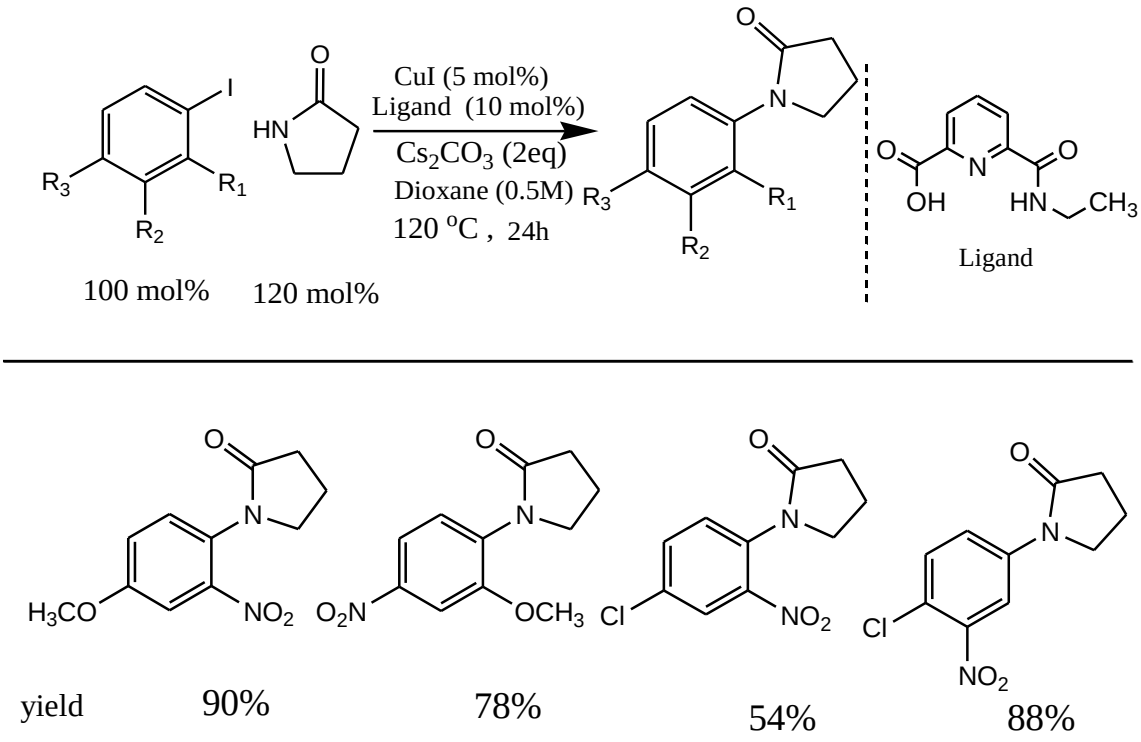


Figure 2.6. Cu-catalyzed amidation of di-substituted iodobenzenes

When 2-nitro-4-methoxy iodobenzene was used yield was 90% while the use of 2-methoxy-4-nitro iodobenzene decreased the yield to 78%. This difference in results is attributed to the strong electron donating effect of -OCH_3 group, which when substituted at ortho position effects the reaction more as compared to when it is substituted at para position. Yield is high in case of 3-nitro-4-chloro iodobenzene but it got decreased when 2-nitro-4-chlorobenzene was used, most probably due to steric hindrance offered by -NO_2 group at ortho position of iodobenzene.

2.3.3.4. Effect of Lowering Catalyst and Ligand Concentration on the Amidation of Di-substituted Iodobenzenes

Amidation of di-substituted iodobenzenes was also carried out at low catalyst and ligand concentration using 2 mol% CuI and 4 mol% ligand. Results are shown in the figure 2.7.

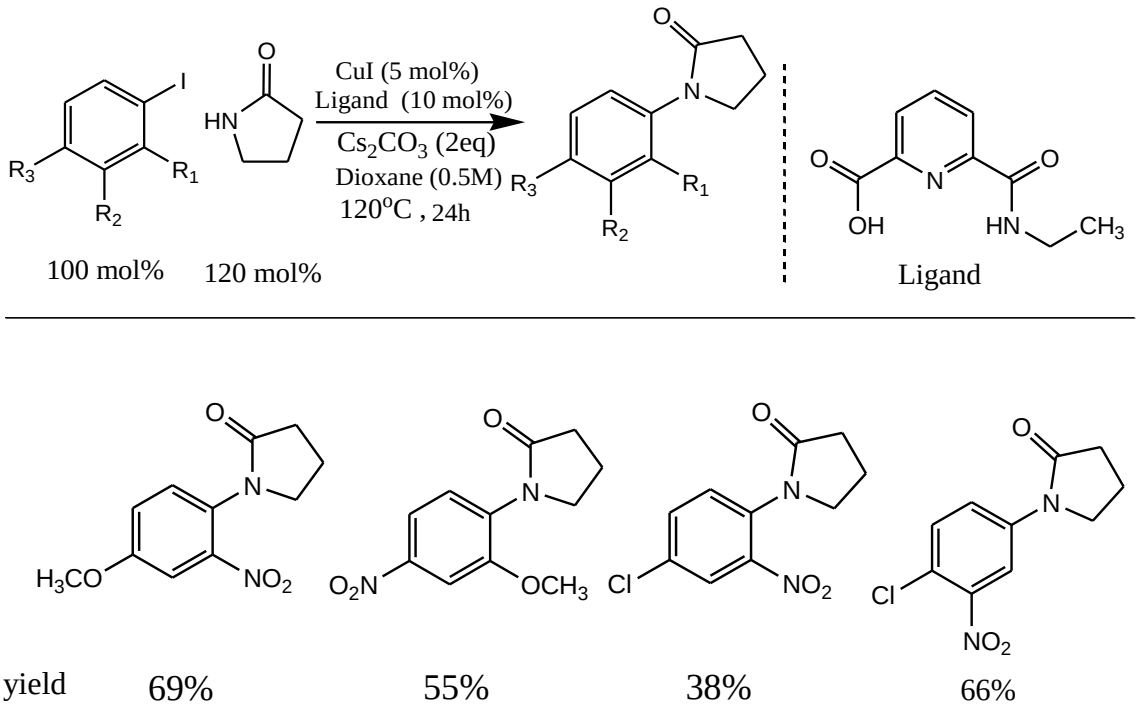


Figure 2.7. Amidation of di-substituted iodobenzenes under low concentration of CuI and ligand

2.3.3.5. Amidation of Mono and Di-substituted Iodobenzenes Using Acyclic Amides

In order to extend the scope of newly devised catalytic system, arylation of both mono and di-substituted iodobenzenes was carried out using acyclic amides such as acetamide and benzamide. Reaction conditions were comprised of 5 mol% CuI, 10 mol% ligand and 2 equivalents of Cs_2CO_3 in dioxane at 120 °C for 24 hours. All the coupled products were obtained in fair to good yields (Figure 2.8).

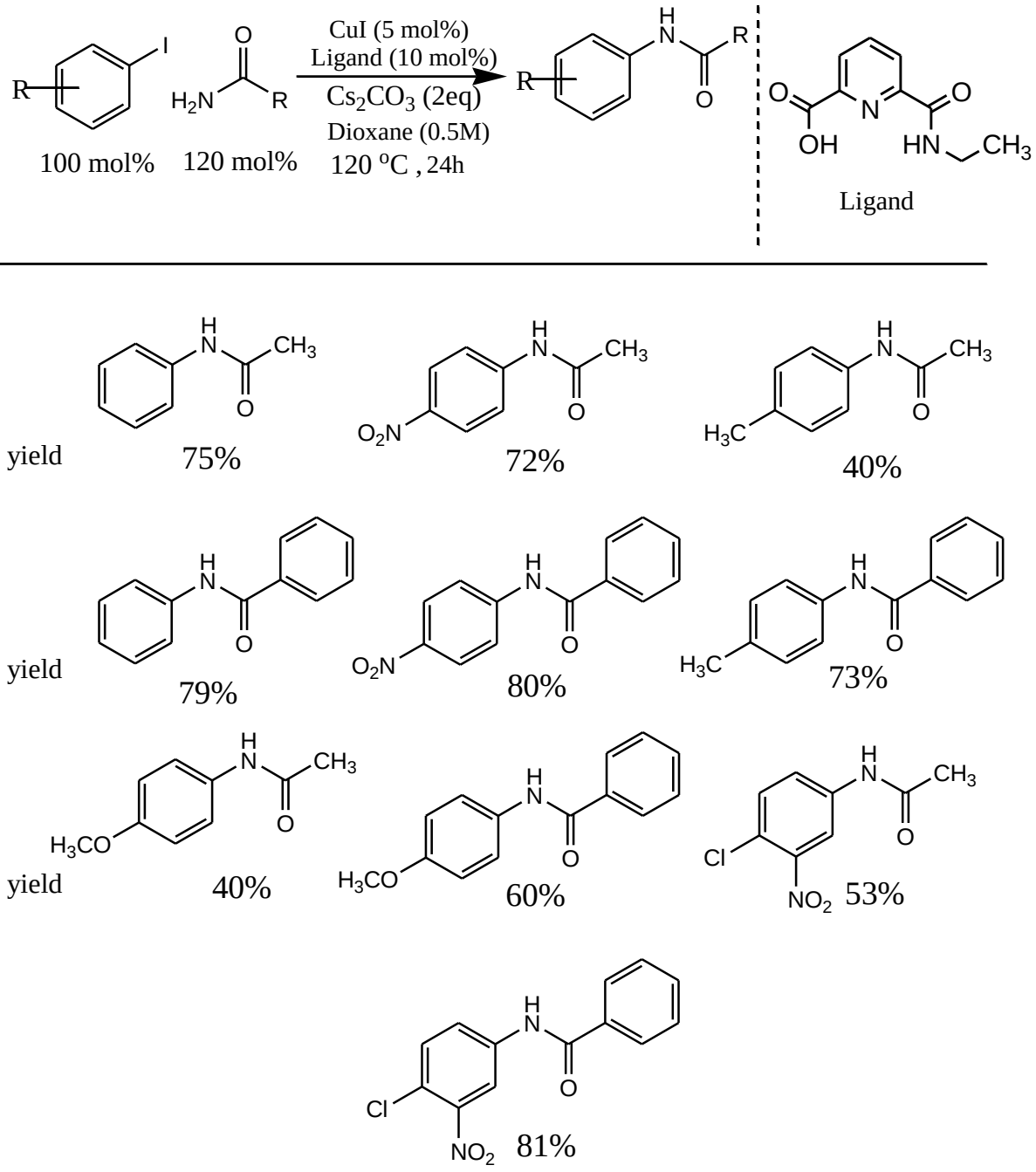


Figure 2.8. Cu-catalyzed N-arylation of acetamide and benzamide

It is evident from the figure 2.8 that the yields of N-arylation of acyclic amides are lower than that of cyclic amides. The reason of this disparity might be explained by the structural difference of cyclic and acyclic amides. Structure of cyclic amides is rigid hence the orbital containing the lone pair of nitrogen is not in perfect alignment with the

π* orbital of the carbonyl moiety so the lone pair of nitrogen cannot be put into the π* orbital of carbonyl group. This lone pair of electrons remains on the nitrogen and is available for donation, making cyclic amides good nucleophiles. In case of acyclic amides, the orbital containing lone pair of nitrogen and π* orbital of carbonyl group are in perfect alignment for the delocalization of lone pair of electrons from nitrogen to carbonyl. This delocalization of electrons results in lowering the nucleophilicity of acyclic amides.

2.3.4. Proposed Mechanism of Cu-catalyzed C-N Coupling Reactions

Mechanistically Cu-catalyzed coupling reactions are not very well understood. There is not a single mechanism upon which all the scientists are unanimously agreed. Different research groups have proposed different mechanisms depending on their observations. Mechanism proposed for the catalytic system, used in the present study is shown in the Figure 2.9.

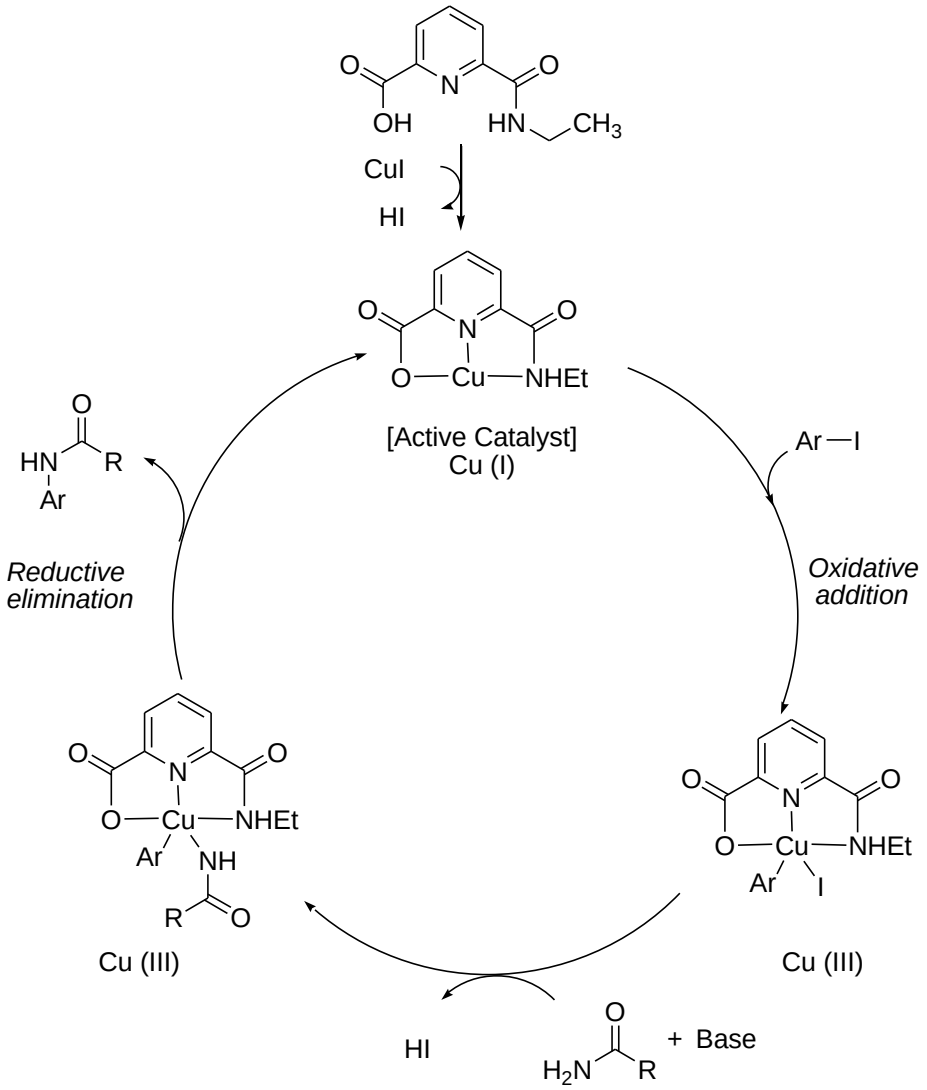


Figure 2.9. Proposed mechanism for the arylation of amides

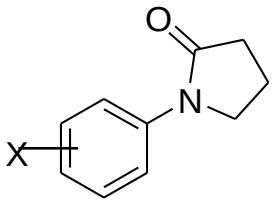
Catalytic cycle begins with a formation of an *in situ* complex between CuI and the ligand followed by the oxidative addition of this copper complex across aryl iodide. Oxidation state of Cu changes from +1 to +3 after oxidative addition step. Ligation of amide with the complex takes place after the deprotonation of amide *via* base. Regeneration of the active catalytic Cu (I) species is viable through C-N bond reductive elimination to afford the desired product.

2.3.5. Characterization of Products of C-N Coupling Reactions

2.3.5.1. Characterization by Physical Parameters

Physical state, melting point, R_f value and yield of all the synthesized compounds are entabulated over here. All the products of C-N coupling reactions are solid and are colorless to yellow in color.

Table 2.10. Physical data of products of arylation of cyclic amide.



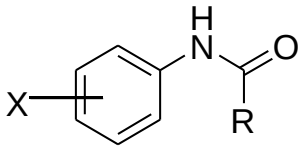
Code	X	Color	m.point	R_f*	Yield (%)	
					CuI/L*	CuI/L***
1a	H	White solid	105-109 °C	0.5	99	85
1b	4-NO_2	Pale yellow solid	122-126 °C	0.33	98	81
1c	4-OCH_3	White solid	113-115 °C	0.30	99	75
1d	4-CH_3	White solid	96-98 °C	0.51	99	73
1e	2-NO_2, 4-OCH_3	Pale yellow solid	88-89 °C	0.18	88	66
1f	2-NO_2, 4-Cl	Light Brown solid	41-45 °C	0.29	54	38
1g	3-NO_2,4-Cl	Pale yellow solid	133-135 °C	0.49	90	69
1h	2-OCH_3, 4-NO_2	Brown solid	142-145 °C	0.18	78	55

*n-Hexane : Ethyl acetate 1:1, Silica gel-60F_{254} under UV light at 254 nm.

** CuI (5 mol %), Ligand (10 mol %).

*** CuI (2 mol %), Ligand (4 mol %).

Table 2.11. Physical data of products of arylation of primary acyclic amides



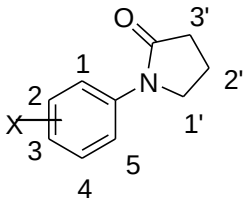
Code	R	X	Color	m.p	R_{f*}	Yield (%)
2a	CH_3	H	White solid	113-115 °C	0.47	75
2b	Ph	H	White solid	162-163 °C	0.84	79
2c	CH_3	4-NO_2	Yellow solid	208-211°C	0.14	72
2d	Ph	4-NO_2	Orange solid	190-19 1°C	0.43	80
2e	CH_3	4-OCH_3	White solid	130-132 °C	0.11	40
2f	Ph	4-OCH_3	White solid	153-157 °C	0.34	73
2g	CH_3	4-CH_3	White solid	150-152 °C	0.53	40
2h	Ph	4-CH_3	White solid	154-157 °C	0.82	60
2i	CH_3	3-NO_2,4-Cl	Brown solid	138-140 °C	0.34	53
2j	Ph	3-NO_2,4-Cl	Yellow solid	155-156 °C	0.83	81

*n-Hexane : Ethyl acetate 1:1, Silica gel-60F_{254} under UV light at 254 nm.

2.3.5.2. Characterization by ^{1}H NMR Spectroscopy

The synthesized compounds were characterized by ^{1}H NMR spectroscopy. Table 2.12 and 2.13 are showing ^{1}H NMR data of all the products of C-N cross-coupling reactions.

Table 2.12. ^{1}H NMR data of arylation of 2-pyrrolidinone.



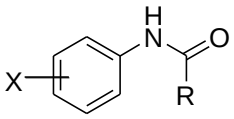
	1a	**1d**	**1e**	**1f**	**1g**
X =	H	4-CH_3	2-NO_2, 4-OCH_3	2-NO_2,4-Cl	3-NO_2,4-Cl

comp	**δ (ppm), Integration, multiplicity and coupling constants (J ; Hz)**				
	protons				
	Ar-H	**1′**	**2′**	**3′**	**X**
1a	7.62 (d, *J* = 7.8 Hz, 2 H), 7.39 - 7.41(m, 2 H), 7.16 (t, 1 H)	3.88 (t, *J* = 6.9 *Hz*, 2H)	2.18 (quint, *J* = 7.2 Hz, 2 H)	2.63 (t, *J* = 6.9 Hz, 2 H)	---
1d	7.49 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.1 Hz, 2 H)	3.82 (t, *J* = 6.9 Hz, 2 H)	2.18 (quint, *J* = 7.2 Hz, 2 H)	2.58 (t, *J* = 7.8 Hz, 2 H)	2.33 (s, 3 H)
1e	7.52 (d, *J* = 2.8 Hz, 1 H), 7.31 - 7.27(m, 1 H), 7.21 - 7.15 (m, 1 H)	3.84 (t, *J* = 6.9 Hz, 2 H)	2.11 (quint, *J* = 7.2 Hz, 2H)	2.26 (t, *J* = 7.6 Hz, 2 H)	3.88 (s, 3 H)

1f	7.97 (d, *J* = 2.40 Hz, 1 H), 7.60 (dd, *J* = 8.59, 2.40 Hz, 1 H), 7.30 (d, *J* = 8.59 Hz, 1 H)	3.92 (t, 6.9 Hz, 2 H	2.66 (quint, 7.4 Hz, 2 H)	2.23 (t, 7.6 Hz, 2 H)	___
1g	8.19 (d, *J* = 2.7 Hz, 1 H), 7.91(dd, J = 9,2.7 Hz, 1 H), 7.51 (dd, *J* = 13.2, 4.2 Hz, 1 H)	3.88 (t, J = 6.9 Hz, 2H)	2.68 (quint, 7.3 Hz, 2 H)	2.20 (t, J = 7.5 Hz, 2H)	___

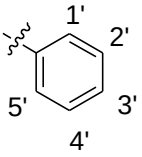
^{1}H NMR data reported in the table 2.12 is in complete agreement with the structure of coupled products. In all compounds, two protons next to nitrogen on the 2-pyrrolidinone ring indicated as 1′ are the most deshielded ones amongst all the protons of 2-pyrrolidinone ring due to the resonance of lone pair of electrons on nitrogen towards benzene ring. Deshielding of protons indicated at position 3′ is caused by the diamagnetic anisotropy of carbonyl group. There is no such deshielding effect present for protons at position 2′ so they are little shielded as compared to H-1′ and H-3′. In all these compounds, absence of the signal for amide proton (-NH-) confirms the formation of C-N bond between pyrolidinone and iodobenzene. For compounds 1a, chemical shift values of the aromatic protons are very close to each other and depend up on the substituent at position 4 and 2 on the benzene ring. Protons present at the *ortho* position of benzene ring in compound 1a are shielded due to resonance of lone pair of nitrogen. Resonance effect also cause shielding of *para* protons while *meta* protons are not affected by resonance. *Ortho* protons are shielded in 1d, 1e, 1f and 1g as well. The most deshielded protons in the aromatic region are the ones which are next to nitro (-NO_2) group.

Table 2.13 ¹ H NMR data of arylation of acyclic amides.



2f **2g**

X = OCH_3 CH_3

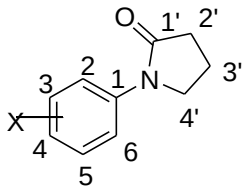
R =  OCH_3

Comp.	**δ (ppm), Integration, multiplicity and coupling constants (J ; Hz) protons**			
	Ar-H	**-NH-**	**R**	**X**
2f	7.75 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 9.1 Hz, 2H)	9.40 (s , 1H, N*H*)	8.02 - 7.95(m, 5H)	3.79 (s, 3H)
2g	8.18 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H)	9.88 (s, 1H, N*H*)	2.89 (s, 3H)	2.75 (s,3H)

¹H NMR data shown in table 2.13 confirms the arylation of acyclic amides. As in the case of 2-pyrolidinone, the amide proton is the most deshielded one. Unlike that of 2-pyrolidinone, the *ortho* protons are not shielded by the resonance of lone pair of nitrogen because in this case the lone pair of nitrogen is in a perfect position to resonate towards carbonyl group. So the *ortho* protons appear at higher chemical shift value as compared to *meta* protons. Signals for the protons of -OCH_3 and -CH_3 group appear at the chemical shift value of 3.79 ppm and 2.75 ppm respectively.

2.3.5.3. Characterization by ^{13}C NMR

Table 2.14. ^{13}C NMR data of C-N coupled products



1a **1e** **1f** **1g**

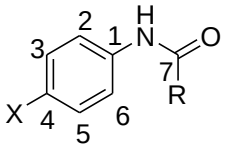
X = H 2-NO_2,4-OCH_3 2-NO_2,4-Cl 3-NO_2,4-Cl

Comp.	**δ (ppm), Integration, multiplicity and coupling constants (J ; Hz) carbons**							
	C-1	**C-2,C-3, C-5, C-6**	**C-4**	**C-1′(C=O)**	**C-2′**	**C-3′**	**C-4′**	**X**
1a	146.4	129.4,134.2,139.4, 128.8, 124.5, 119.9	124.5	175.1	32.7	18.0.	48.8	---
1e	146.4	129.4,125.0,120.1, 110.2	158.6	175.1	31.0	19.0	50.4	56.0
1f	133.7	133.7, 133.1, 130.7, 128.4, 125.7	130.7	175.1	31.1	19.0.	50.1	---

1g	140.7	149.1, 130.1,128. 9, 117.1	125.4	174.8	33.4	19.1.	50.1	---

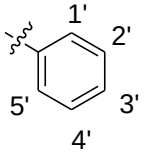
^{13}C NMR data shown in the table 2.14 confirms the formation of desired compounds. The carbon of the carbonyl group is the most deshielded one in all the compounds. The trend of chemical shift values for the carbons (C-2′, C-3′and C-4′) of 2-pyrolidinone ring is the same as we observed in the ^{1}H NMR. Ipso carbon is the most deshielded carbon of the aromatic region in all the compounds mentioned in the table except compound 1e, in which C-4 is the most deshielded carbon of the benzene ring due to presence of electronegative oxygen atom of methoxy group.

Table 2.15. ^{13}C NMR data of arylation of acyclic amides.



2f **2g**

X = OCH_3 CH_3

R =  OCH_3

Comp.	**δ (ppm), Integration, multiplicity and coupling constants (J ; Hz) carbons**					
	C-1	**C-2,C-3,C-5,C-6**	**C-4**	**C-7(C=O)**	**R**	**X**
2f	129.2	122.7, 114.6	157.1	166.0	136.5, 133.4, 132.1, 128.2	55.7

2g	137.8	133.9, 132.2, 129.9, 129.2, 128.3	136.4	166.1	21.1	20.9

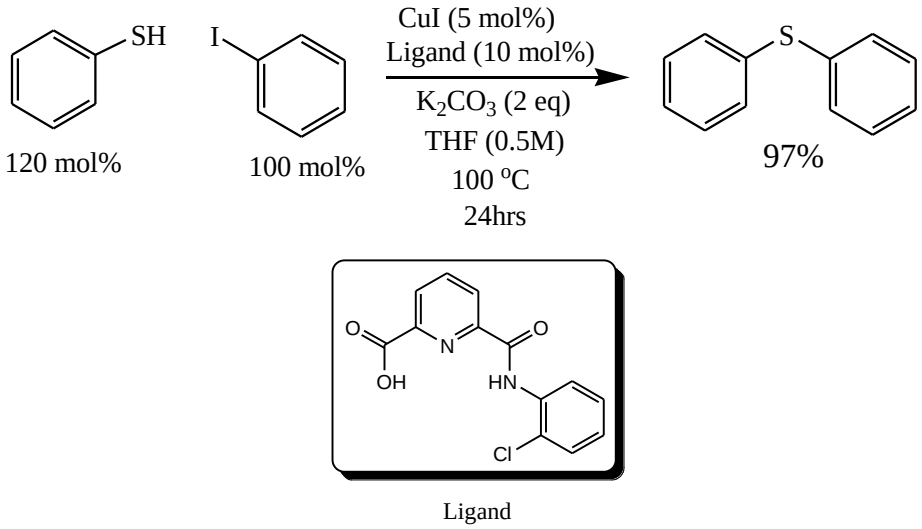
^{13}C NMR data of compounds 2f and 2g confirms their formation. Signal resonating around 166 ppm in both of the products corresponds to the carbonyl carbon of amide. C-4 in compound 2f resonates at higher chemical shift value than the ipso carbon probably due to the presence of electronegative oxygen atom of -OCH_3 group while in case of compound 2g, C-4 appears up field than C-1 due to electron donating effect of –CH_3 group. Although methoxy group is a strong electron donating group but carbon having methoxy group as a substituent resonates down field because it is directly attached to oxygen atom that shows electron withdrawing inductive effect. In compound 2f, the aromatic carbons of phenyl ring (C-1′to C-6′) of benzamide resonates down field as compared to carbons (C-1 to C-6) benzene ring due to diamagnetic anisotropy of carbonyl group located next to phenyl ring.

2.4. Copper-catalyzed C-S coupling Reactions for the Arylation of Thiols

Mono-amides of dipicolinic acid were also used as ligands for C-S coupling reactions in order to extend the scope of newly discovered catalytic system to more than one type of carbon-heteroatom bond forming reactions as there are only few ligands that could be employed for more than one type of coupling reactions.

As sulfur is a strong nucleophile compared to nitrogen, mono-amide of DPA with 2-chloroaniline was decided to be used as a ligand, which was shown to be a little less efficient than the mono-amide of DPA with butyl amine during the ligand screening for C-N coupling reactions. The idea behind using this ligand was the fact that the strong nucleophilicity of sulfur may compensate for the low efficiency of mono-amide of 2-chloroaniline. To check this idea arylation of thiophenol was chosen as a model reaction

using 5 mol% CuI, 10 mol% ligand, 200 mol% K_2CO_3 in THF solvent at 100^0C for 24 hours (Scheme 2.4).



Scheme 2.4. Cu-catalyzed arylation of thiophenol using mono-amide of DPA as a ligand

2.4.1. Reaction Scope of the Cu-catalyzed Arylation of Thiophenol

As the model reaction resulted in an excellent yield, same ligand was employed to check the scope of this catalytic system for the mono-substituted iodobenzenes (Figure 2.10).

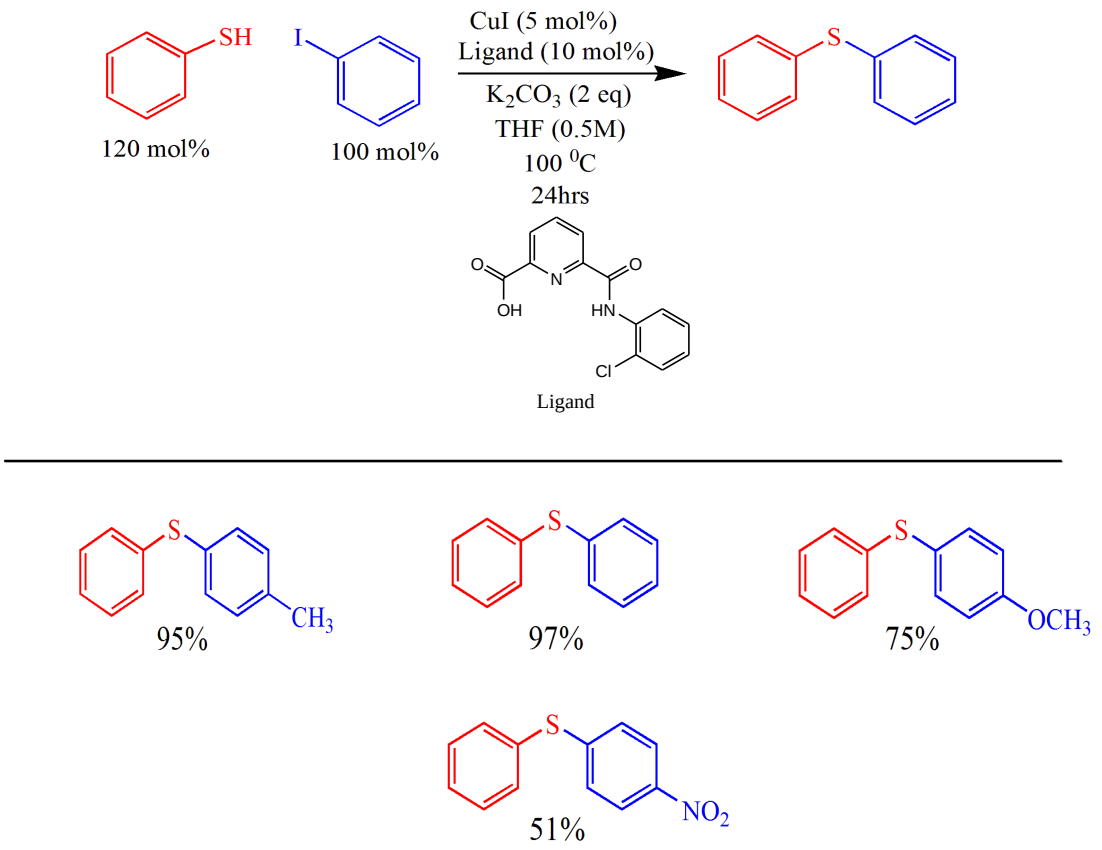
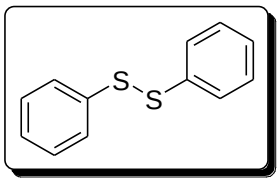


Figure 2.10. Thiation of mono-substituted iodobenzenes

All the iodobenzenes gave good yields except 4-nitro iodobenzene. In arylation of thiophenol with 4-nitro iodobenzene, diphenyldisulfide was also formed as a byproduct along with the desired product.

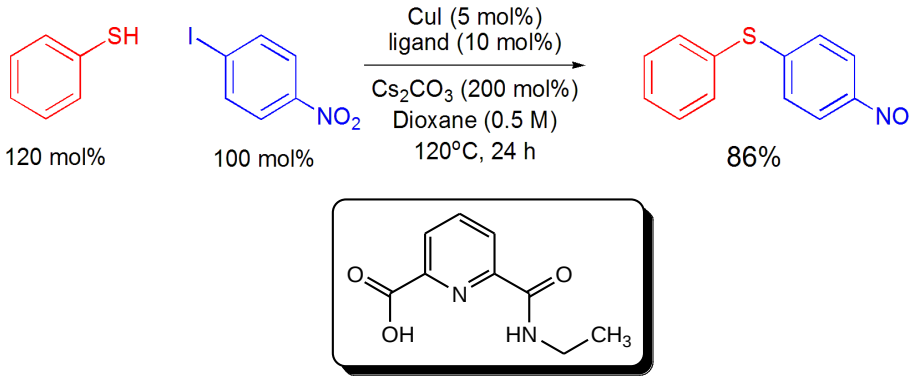


Byproduct

Formation of diphenyldisulfide showed the inefficiency of the catalytic system. The present catalytic system is not efficient enough to prevent the self coordination of sulfur to form S-S bond in case of 4-nitro iodobenzene hence the idea of using mono-amide of DPA with 4-chloroaniline as a ligand for C-S coupling reactions did not go well. Thiation of 4-nitro iodobenzene was carried out under the newly devised catalytic system which was used for the N-arylation of amides.

2.4.2. Effect of Changing Catalytic System

As the idea of using mono-amide of 4-chloroaniline did not work and resulted in the formation of byproduct diphenyldisulfide in case of 4-nitro iodobenzene. It was decided to use the catalytic system that was devised for the amidation of variously substituted iodobenzenes for the arylation of thiophenol *via* 4-nitroiodobenzene, in order to check whether this catalytic system does help to reduce the byproduct formation or not thus thiation of 4-nitro iodobenzene was carried out using 5 mol% CuI, 10 mol% ligand and 2 equivalents of Cs_2CO_3 in dioxane at 100 °C for 24 hours (Scheme 2.5).



Scheme 2.5. Cu-catalyzed arylation of thiol using mono-amide of ethylamine as ligand

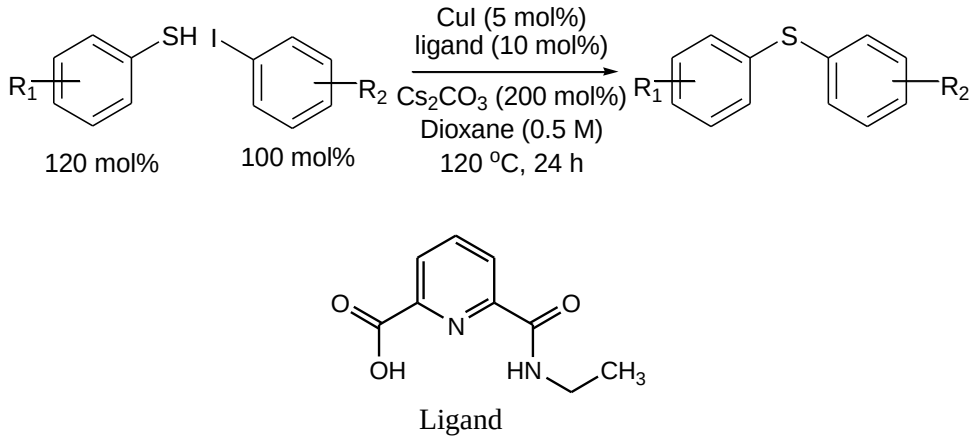
The yield of the reaction was improved from 51% to 86% under new conditions, showing that this catalytic system worked really well in reducing self coupling of thiophenol and can withstand the catalyst poisoning caused by the coordination of sulfur with copper metal.

2.4.3. Scope of Cu-catalyzed Arylation of Thiophenols Using Mono and Di-substituted Iodobenzenes

Arylation of substituted and unsubstituted thiophenols was carried out to extend the scope of this catalytic system for C-S coupling reactions as well.

2.4.3.1. Cu-catalyzed Arylation of Thiophenols using Mono-substituted Iodobenzenes

Arylation of substituted and unsubstituted thiophenols was carried out to extend the scope of our catalytic system. All the desired products were obtained in good to excellent yield. The substitution of $-NH_2$ group on thiophenol ring was expected to increase the yield of the reaction due to electron donating nature of $-NH_2$ group, but the yield got decreased. The reason for little decrease in yield in case of 2-amino thiophenol and 4-amino thiophenol might be the fact that $-NH_2$ can also act as a nucleophile which results in the formation of C-N coupled side product. Since sulfur is a stronger nucleophile compared to nitrogen, the major product is C-S coupled product. Use of naphthalene-2-thiol also afforded the desired product in excellent yield (Figure 2.11).



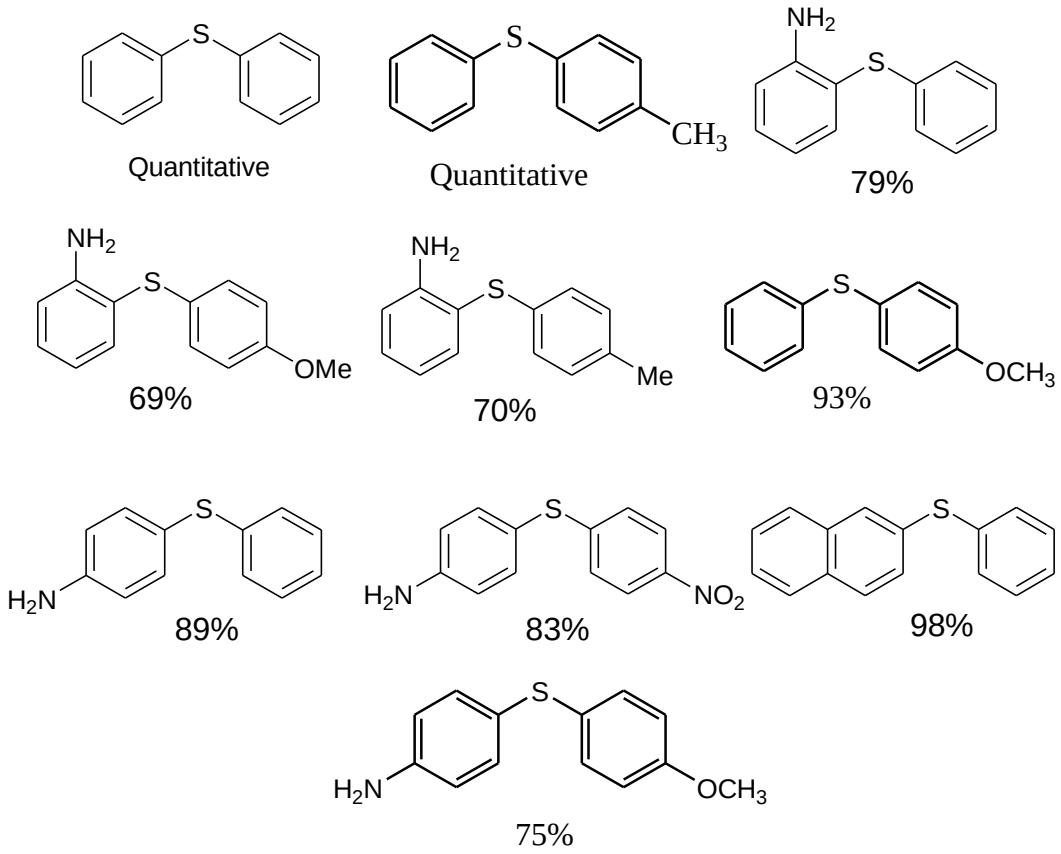


Figure 2.11. Cu-catalyzed arylation of substituted and unsubstituted thiophenols

2.4.3.2. Cu-catalyzed Thiation of Di-substituted Iodobenzenes

Cu(I) catalyzed synthesis of thioethers was carried out using 120 mol% thiophenol, 100 mol% di-substituted iodobenzene, 5 mol% CuI,10 mol% ligand and 2 equivalents of

Cs_2CO_3 in dioxane at 120 °C for 24 hours. All the coupled products were obtained in good to excellent yields irrespective of the nature of substituents and their respective position on the iodobenzene ring (Figure 2.12).

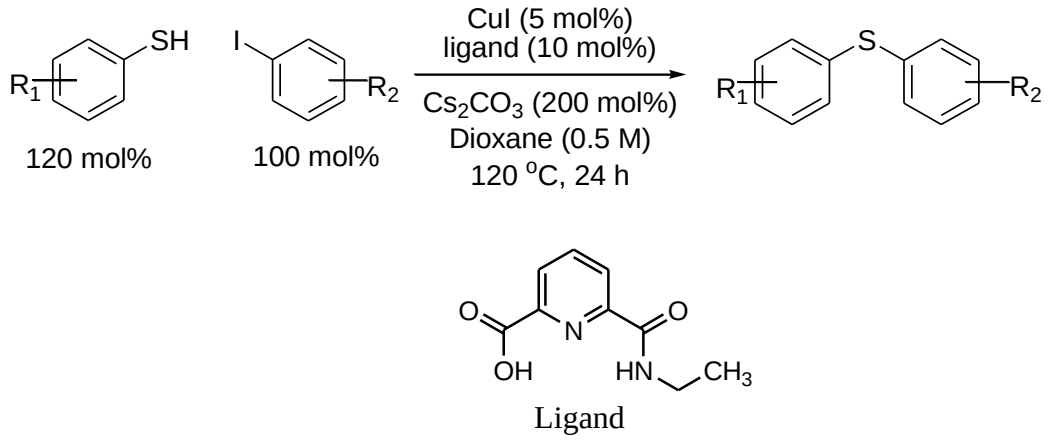


Figure 2.12. Cu-catalyzed thiation of di-substituted iodobenzenes

2.4.3.3. Cu-catalyzed Arylation of Hetero Aromatic Thiols

Hetero aromatic thiols coupled to haloarenes are found in many biologically active compounds therefore it was important to find out that how well, the catalytic system discussed in the present study, works with these type of coupling reactions. For this purpose arylation of three different hetero aromatic thiols was carried out using iodobenzene and 3-nitro-4-chloro iodobenzene. These hetero aromatic thiols included

pyridine-2-thiol (Scheme 2.18), 5-chloro benzothiazole and benzo imidazole-2-thiol (Scheme 2.19). All these substrates afforded appreciable yield of desired products.

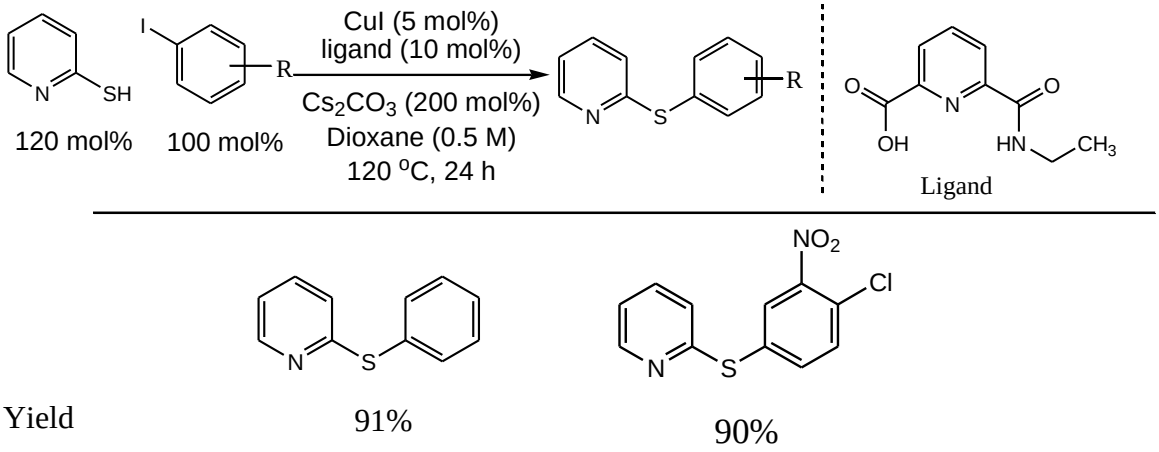


Figure 2.13. Cu-catalyzed arylation of 2-thiol pyridine

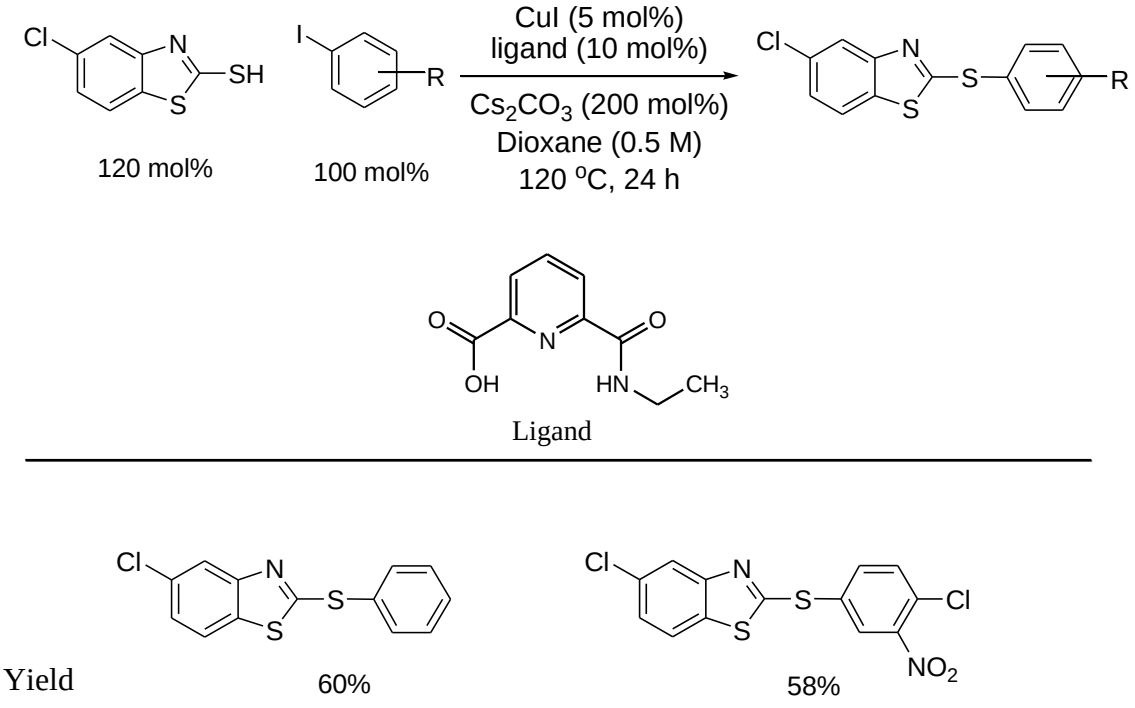


Figure 2.14. Cu-catalyzed arylation of 5-chloro benzothiazole

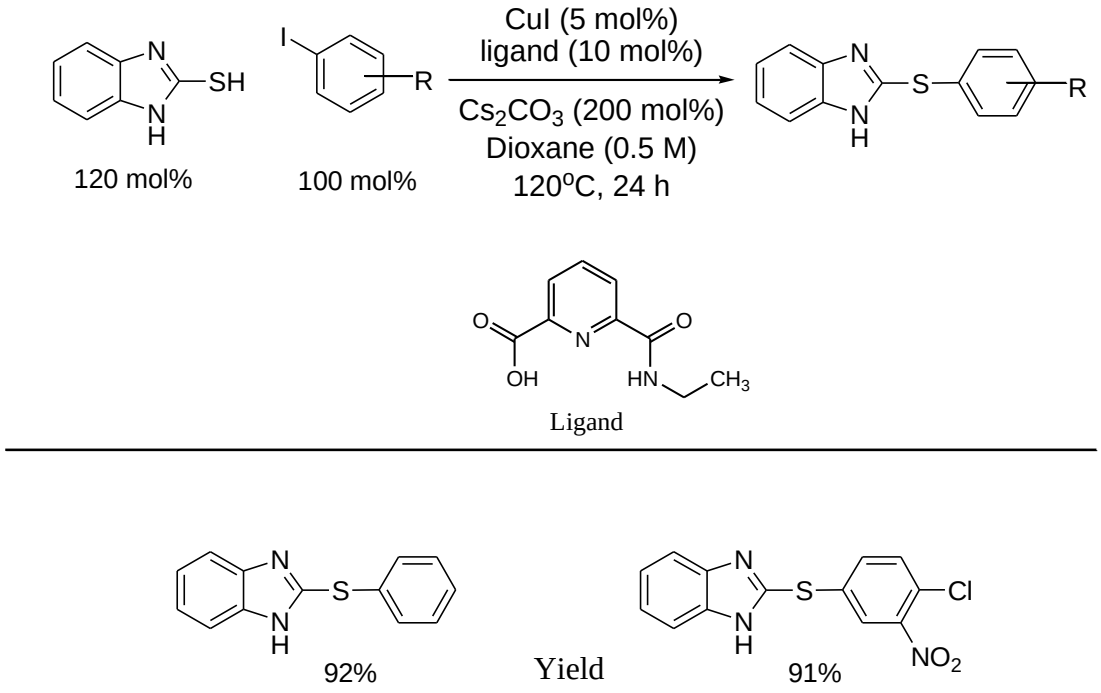


Figure 2.15. Cu-catalyzed arylation of benzo imidazole-2-thiol

2.4.4. Proposed Mechanism for the Arylation of Thiols

A plausible mechanism has been proposed for the arylation of thiols. The sequence of events is same as arylation of amides (Figure 9.16).

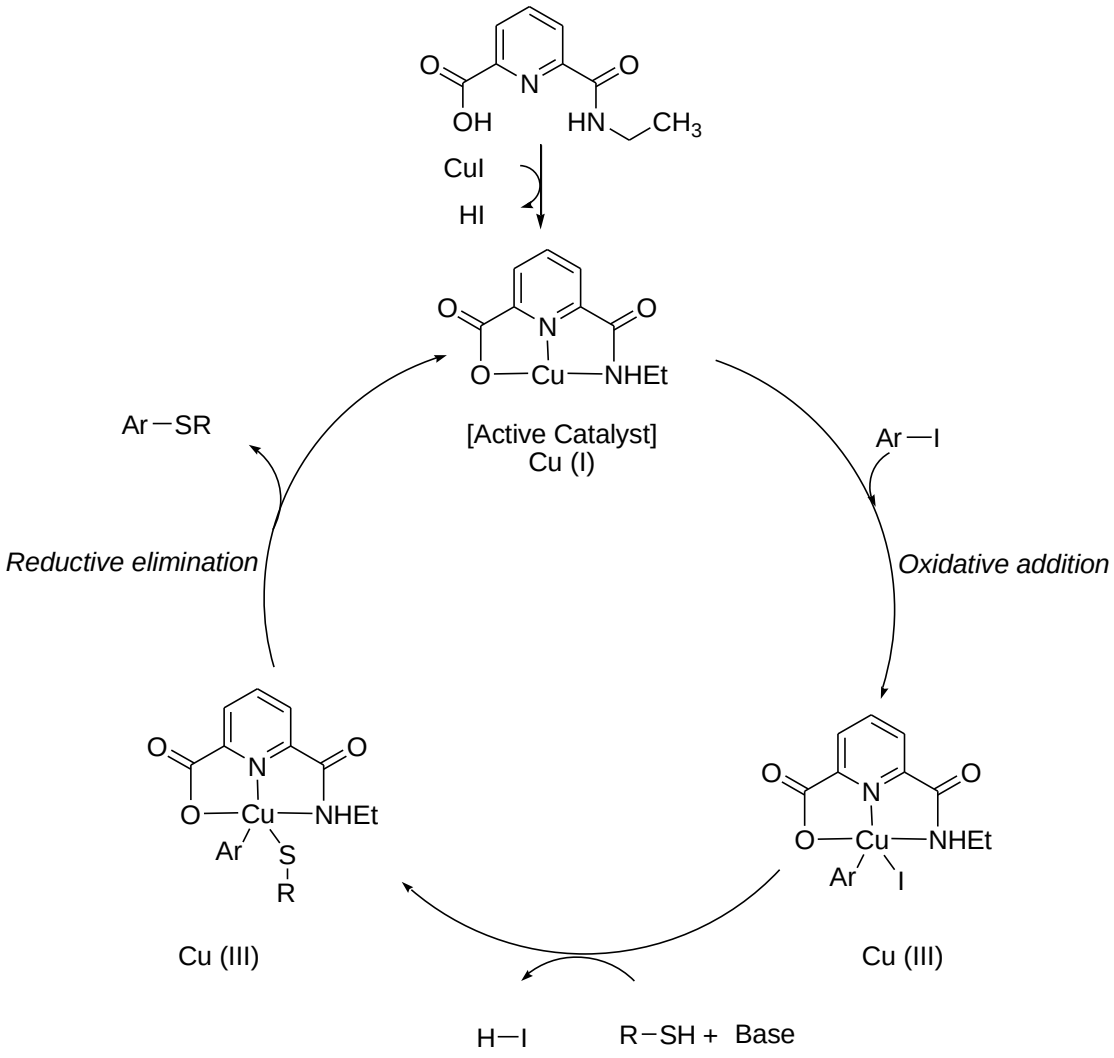
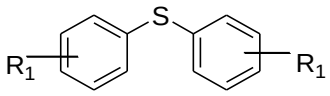


Figure 2.16. Proposed mechanism of arylation of thiols

2.4.5. Characterization of C-S Coupled Products

2.4.5.1. Characterization by Physical Parameters

Table 2.16. Physical data of products of arylation of thiophenols



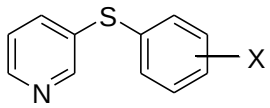
Code	X_1	X_2	Color	R_f	Yield (%)
3a	H	H	Colorless liquid	0.6*	quantitative
3b	H	4-CH_3	Colorless liquid	0.61*	quantitative
3c	H	4-OCH_3	Colorless liquid	0.06*	93
3d	4-NH_2	4-OCH_3	Dark brown sticky solid	0.06′	75
3e	2-NH_2	4-OCH_3	Dark purple sticky solid	0.16′	69
3f	2-NH_2	4-CH_3	Brown sticky solid	0.37′	70
3g	4-NH_2	4-NO_2	Pale yellow solid	0.09′	83
3h	4-NH_2	H	Brown sticky solid	0.11′	89
3i	2-NH_2	H	Dark green sticky solid	0.09′	79
3j	Ph	H	Sticky white solid	0.81′	98
3k	H	4-NO_2	Orange solid	0.05*	86
3l	H	3-NO_2,4-Cl	Pale yellow solid	0.51′	98
3m	4-NH_2	3-NO_2,4-Cl	Dark brown sticky solid	0.1′	84
3n	H	2-OCH_3,4-NO_2	Yellow solid	0.08′	94
3o	Ph	2-NO_2,4-OCH_3	Yellow sticky solid	0.19′	94

3p	Ph	3-NO_2,4-Cl	Pale Yellow sticky solid	0.47′	98
3q	H	2-NO_2,4-Cl	Yellow solid	0.56′	96
3r	H	2-NO_2,4-OCH_3	Light yellow sticky solid	0.27′	95

*n-Hexane, Silica gel-60-F_{254} under UV light at 254 nm.

′n-hexane: Ethylacetate 95: 5

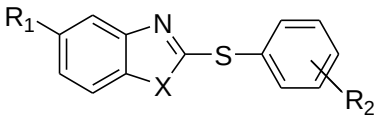
Table 2.17. Physical data of products of arylation of mono cyclic hetero aromatic thiols.



Comp.	**X**	**Color**	**R_f***	**Yield (%)**
3s	H	Colorless liquid	0.41	91%
3t	3-NO_2,4-Cl	Pale yellow solid	0.13	90%

*n-Hexane : Ethyl acetate 9:1, silica gel-60F_{254} under UV light at 254 nm.

Table 2.18. Physical data of products of arylation of bi cyclic hetero aromatic thiols.

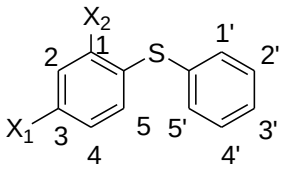


Comp.	**X**	**R_1**	**R_2**	**Color**	**R_f***	**Yield (%)**
3u	S	Cl	H	Off white sticky solid	0.42	60
3v	S	Cl	3-NO_2,4-Cl	Pale yellow solid	0.41	58
3w	N	H	H	White sticky solid	0.14	92
3x	N	H	3-NO_2,4-Cl	Pale yellow solid	0.12	91

*n-Hexane : Ethyl acetate 9:1, Silica gel-60F_{254} under UV light at 254 nm.

2.4.5.2. Characterization by ^{1}H NMR

Table 2.19. ^{1}H NMR data of arylation of thiophenols



3a **3b** **3c** **3k** **3n**

X_1 = H CH_3 OCH_3 NO_2 NO_2

X_2 = H H H H OCH_3

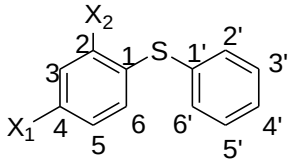
Code	**δ (ppm), Integration, multiplicity and coupling constants (J ; Hz) protons**		
	Ar-H	**X_1**	**X_2**
3a	δ (ppm): 7.26-7.57 (m, 10H)	---	---
3b	7.16 – 7.36 (m, 9H)	2.39 (s, 1H)	---
3c	7.44 -7.49 (m, 2H), 7.15 - 7.31 (m, 5H), 6.92 – 6.97 (m, 2H)	3.85 (s, 3H).	---
3k	8.07 (dd, J = 2.1,9 Hz, 2*H*), 7.51(dd, J = 1.2, 11.4 Hz, 2H), 7.45-7.48 (m, 3H), 7.18 (dd, *J* = 2.7,9.6 Hz, 2H)	---	---
3n	8.06 (dd, J = 2.7, 9 Hz, 1*H*), 7.70 (d, J = 2.7, Hz, 1H), 7.28-7.52 (m, 5H), 6.92 (d, *J* = 9 Hz, 1H)	---	4.01 (s, 3H).

^{1}H NMR data of the products of arylation of thiols shown in the table is in complete agreement with their structures. The chemical shift values of the aromatic protons of both the phenyl rings are very close to each other so it is very difficult to assign chemical shift values to these protons separately. In compound 3a and 3b all the aromatic protons

appear in a very close range so all of these are integrated together. In compound 3c protons H-2 and H-4 appears up field as compared to protons H-1 and H-5 due to strong electron donating effect of -OCH_3 group hence protons *ortho* to methoxy group are shielded while protons *meta* to methoxy group remain unaffected. In compound 3c, H-2 and H-4 appears around 8.07 ppm due to the presence of strong electron withdrawing -NO_2 group at position 4. In compound 3n, H-4 resonates at 8.06 ppm while H-2 resonates at 7.70 ppm because it is *ortho* to both -NO_2 and -OCH_3 group.

2.4.5.3. Characterization by ^{13}C NMR

Table 2.20. ^{13}C NMR data of arylation of thiophenols



	3a	**3b**	**3c**	**3k**	**3n**
X_1 =	H	CH_3	OCH_3	NO_2	NO_2
X_2 =	H	H	H	H	OCH_3

Comp.	**δ (ppm), Integration, multiplicity and coupling constants (J ; Hz)**				
	carbons				
	C_1	**C_1'**	**C_2 - C_6**	**X_1**	**X_2**
3a	135.8	135.8	131.1, 129.2, 129.1, 127.5, 127.2	---	---
3b	137.6	137.1	131.3, 131.3, 130.1, 129.7, 129.0, 127.5, 126.4	21.1	---
3c	128.1	138.6	159.8, 135.4, 128.9, 125.7, 124.2, 115.0	55.40	---

3k	145.3	134.8	148.5, 130.8, 130.0, 129.7, 126.6, 124.0	___	___
3n	123.1	134.1	160.4, 141.8, 130.6, 129.9, 129.1, 128.9, 123.6, , 109.6	___	56.8

^{13}C NMR values are in complete agreement with the structure of C-S coupled products. It is very difficult to differentiate between the chemical shift values of aromatic carbons of both phenyl rings except when they are in close proximity to some substituent. In compound 3a and 3b, ipso carbons resonate down field while both in 3 c and 3 k, signal for C-4 appears at higher chemical shift value than the rest of carbons. In compound 3n, C-2 resonates up field as compared to C-4 because C-2 is next to methoxy (-OCH_3) group while C-4 is attached to nitro (-NO_2) group which makes C-4 deshielded and shields the carbons next to it through space effect. Both oxygen of -NO_2 group push electrons towards carbon centre due to mutual repulsion between electrons in the space.

Conclusion

We have embarked on a project aiming at the development of the new ligands that are easy to synthesize, are of low cost and efficient in carrying out carbon-heteroatom cross-coupling reactions. Amide derivatives of dipicolinic acid were chosen to be investigated for their ability to work as ligands. It was found that CuI/6-(ethylcarbamoyl) picolinic acid can efficiently catalyze the coupling of aryl iodides with cyclic and acyclic amides. After this discovery it was found that this copper-assisted catalytic system based on mono-amide of ethylamine as a ligand could also be used to carry out the C-S cross-coupling reactions as well.

Reaction conditions were optimized for this new catalytic system and it was found that it worked best when 2 equivalents of Cs_2CO_3 are used as a base in 0.5 M dioxane at 120°C for 24 hours. Substrate scope for this catalytic system was investigated for both C-N and C-S coupling reactions. This newly devised catalytic system was found compatible with number of functional groups substituted on the substrates used. Arylation of secondary cyclic amides, primary acyclic amides, thiophenols, hetero aromatic mono and bicyclic thiols using differently substituted iodobenzenes, resulted in appreciable yields of desired coupled products.

The mono-amide derivatives of dipicolinic acid are highly stable and retain the high coordination ability of parent dipicolinic acid, therefore the discovery of this class of ligands is a valuable addition towards the growing field of ligand designing for Cu-catalyzed cross-coupling reactions. The catalytic system, discussed in the present study is highly general, inexpensive and environmentally benign. Although in present work, the use of mono-amides of DPA is restricted only to C-N and C-S coupling reactions but these ligands got a high potential to be used for other type of couplings especially C-O coupling reactions.

All the coupled products synthesized as a part of present study, were purified through flash column chromatograph and characterized by ^{1}H NMR and ^{13}C NMR while the synthesis of mono-amide of ethylamine was confirmed by employing IR spectroscopy

CHAPTER-3

EXPERIMENTAL

3.1. General Consideration

Clean and oven-dried apparatus was used to carry out all the reactions. Inert atmosphere of argon/nitrogen was used for all the reactions to be performed in non-aqueous solvents. Reactions were performed using dried-distilled solvents. Purification of commercially available reagents was carried out when found necessary. 13 x 100 mm oven-dried Pyrex sealed glass tubes were used for transition metal catalyzed reactions and freshly distilled solvents were used for carrying out these cross-coupling reactions. Pyridine-2,6-dicarboylic acid was purchased from Merck and employed for the synthesis of mono-amides of pyridine-2,6-dicarboxylic acid. Anhydrous magnesium sulphate /sodium sulphate was used for drying combined organic layers obtained after solvent extraction. Progress of the reactions was monitored by thin layer chromatography (TLC) 0.2 mm pre-coated plates of Merck silica gel-60 F_{254} were used for this purpose. UV- active spots were analyzed under UV lamp working at the wavelength of 254 nm. Different staining reagents such as ninhydrin, potassium permanganate ($KMnO_4$), anisaldehyde, poly phosphomolybdic acid (PMA) and iodine vapors were employed according to the functional groups contained in a molecule, for visualizing UV-inactive spots. Almost all the products were purified through flash column chromatography using silica-gel 60 F of 200-300 mesh size as a stationary phase.

3.2. Instrumentation

Gallenkamp melting point apparatus (MP-D) was used to take melting points of solid compounds. IR spectrum was recorded using schimadzu fourier transform model 270 1R spectrophotometer with the facility of attenuated total reflectance and absorption frequencies were reported in reciprocal centimeter (cm^{-1}) units. Bruker Avance 300 *MHz* spectrophotometer was used for recording ^{1}H NMR and ^{13}C NMR spectra of the synhthesized compounds. Coupling constants (*J*) were mentioned in Hertz (*Hz*) units while chemical shift values were quoted in delta (δ) units.

3.3. Drying and Distillation of Organic Solvents

All the organic solvents employed in reactions must be moisture free for the successful completion of a reaction. Different drying reagents were employed for drying organic solvents followed by distillation. A brief overview is given over here describing the drying and distillation of the solvents, commonly employed in organic synthesis.

3.3.1. 1, 4-Dioxane (b.p. 101 °C)

Drying of 1,4-dioxane is very difficult due to its complete miscibility with water. Calcium chloride ($CaCl_2$) was used to dry 1,4-dioxane. This pre-dried dioxane was refluxed in sodium metal with benzophenone and stored over activated 3 Å molecular sieves.

3.3.2. Toluene (b.p. 110.6 °C)

Toluene was pre-dried using calcium hydride (CaH_2). Pre-dried toluene was refluxed with sodium metal using benzophenone as an indicator, until color changed to deep blue. Distilled toluene was stored using activated 3 Å molecular sieves.

3.3.3. Tetrahydrofuran (b.p. 66 °C)

Analytical grade tetrahydrofuran was refluxed with sodium metal using benzophenone as an indicator until deep blue color appeared. Freshly distilled THF was used each time for setting up highly moisture sensitive transition metal catalyzed coupling reactions.

3.3.4. Dichloromethane (b.p. 39.6 °C)

DCM is easy to dry due to its low water content. It was distilled by refluxing over calcium hydride and stored over activated 3 Å molecular sieves.

3.3.5. Chloroform (b.p. 61.2 °C)

Calcium hydride is a effective desiccant for drying chloroform. $CHCl_3$ was distilled over CaH_2 and was stored, using 3 Å activated molecular sieves.

3.3.6. DMF (b.p. 153 °C)

DMF is stirred over Calcium hydride overnight and then it is filtered and distilled at reduced pressure. Distilled DMF is stored over activated 3 Å molecular sieves.

3.3.7. Methanol (b.p. 64.7 °C)

In order to dry methanol, magnesium (Mg) metal in presence of iodine (I_2) was used as a desiccant. It was refluxed until color turns milky white and stored over activated 3 Å molecular sieves.

3.4. Procedure for the Synthesis of Mono-amides of Dipicolinc acid With Ethylamine

Step-1: Synthesis of methyl di-ester of dipicolinic acid

Pyridine-2,6-dicarboxylic acid (3.3g, 20 m.moles) was refluxed with thionyl chloride (3.48mL, 48m.mol) After 4 hours of reflux thionyl chloride was distilled off and 40 mL dried methanol was added to the reaction mixture containing di-chloride of dipicolinic acid to synthesize di-ester of dipicolinic acid. Excess methanol was evaporated under reduced pressure. Crystalline diester of dipicolinic acid was obtained in 85% yield after solvent extraction.

Step- 2: Synthesis of mono-ester of dipicolinic acid

Diester (2.54g, 13 m.moles) was dissolved in methanol (120mL) and selectively hydrolyzed by the drop wise addition of 0.5 M aqueous solution of sodium hydroxide (NaOH). The reaction was monitored with TLC using 10% methanol in chloroform as a mobile phase. After the completion of the reaction (in 6 hours), the reaction mixture was concentrated under reduced pressure on rotary evaporator. Mono-ester of dipicolinic acid was obtained in 65% yield after multistep solvent extraction.

Step-3: Synthesis of amide of mono-ester of dipicolinic acid

Mono-ester of dipicolinic acid (2g, 11 m.moles) was dissolved in dried-distilled chloroform (40mL) and thionyl chloride (1.92mL) was added to it. After refluxing the reaction mixture for 4-5 hours, excess thionyl chloride was distilled off to get mono-chloride mono-ester of dipicolinic acid that was dissolved in dried-distilled chloroform and 2 equivalents of $CH_3CH_2NH_2$ were added to it. This reaction mixture was refluxed over night. The progress of the reaction was checked using TLC. After the completion of

reaction, chloroform was evaporated under reduced pressure and solidified product was afforded in 81% yield after solvent extraction using ethyl acetate as organic layer.

Step-4: Synthesis of amide of dipicolinic acid

Monoester monoamide (11.03m.moles) of DPA was then dissolved in dry methanol (40 mL) and hydrolyzed using aqueous solution of sodium hydroxide for 6 hours. Excess of methanol was evaporated under reduced pressure and crystalline, white colored mono-amide of DPA was obtained in 74% yield after solvent extraction using ethyl acetate as an organic layer.

Yield: 74%**, m.p:** 102-104 ℃**, R_f :** 0.1 (Chloroform/Methanol, 9:1)

IR: ($\bar{v}$, cm^{-1}) = 3400-2416 (O-H), 3262 (-NH-), 1728 (C=O acid), 1649 (C=O amide), 1361, 2870 (C-H sp^3).

3.5. General Procedure for the N-arylation of Cyclic and Acyclic Amides

A 13x100 mm oven-dried Pyrex glass sealed tube, equipped with magnetic stirrer was charged with amide (120 mol %), iodobenzene (100 mol %), Cs_2CO_3 (200 mol %), CuI (5 mol %) and ligand (10 mol %). After the addition of dioxane (0.5 M), the aperture of the sealed tube was covered with rubber septum and purged using an argon flow for few minutes. After purging, the septum was replaced by Teflon-coated screw cap quickly. The reaction mixture was stirred at 120 ℃ for 24 hours. After the completion of time the sealed tube is allowed to attain room temperature and TLC is taken to check whether the reaction has been completed or not. The dioxane was evaporated under reduced pressure. Pure coupled product was obtained by purification through flash column chromatography on silica gel as stationary phase using n-hexane/ethyl acetate (85:15) as eluting solvent system. All the coupled products were solid, ranging from colorless to dark brown color.

1-phenylpyrrolidin-2-one (1a)

White solid, **Yield:** 99%, m.p : 105-109 °C, R_f Value: 0.5 (n-Hexane : Ethyl acetate 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.8 Hz, 2 H), 7.39 - 7.41 (m, 2 H), 7.16 (m, 1 H), 3.88 (t, 2 H), 2.63 (t, *J* = 6.9 Hz, 2 H), 2.18 (quint, *J* = 7.2 Hz, 2 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.1, 158.6, 146.4, 129.4,174.2, 139.4, 128.8, 124.5, 119.9, 48.8, 32.7, 18.0.

1-(4-nitrophenyl)pyrrolidin-2-one (1b)

White solid, **Yield:** 99%, m.p : 122-126 °C, **R_f Value**: 0.33 (n-Hexane : Ethyl acetate 1:1).

1-(4-methoxyphenyl)pyrrolidin-2-one (1c)

White solid, **Yield:** 99%, m.p : 113-115 °C, **R_f Value**: 0.30 (n-Hexane : Ethyl acetate 1:1).

1-(4-methylphenyl)pyrrolidin-2-one (1d)

White solid, **Yield:** 98%, m.p : 96-98 °C, **R_f Value**: 0.51 (n-Hexane : Ethyl acetate 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2 H), 7.16 (d, *J* = 8.1 Hz, 2 H), 3.82 (t, *J* = 6.9 Hz, 2 H), 2.58 (t, *J* = 7.8 Hz, 2 H), 2.33 (s, 3 H), 2.08-2.18 (quint, 2 H).

1-(4-methoxy-2-nitrophenyl)pyrrolidin-2-one (1e)

White solid, **Yield:** 88%, m.p : 88-89 °C, **R_f Value**: 0.18(n-Hexane : Ethyl acetate 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.8 Hz, 1 H), 7.31 - 7.27(m, 1 H), 7.21 - 7.15 (m, 1 H), 3.88 (s, 3 H), 3.84 (t, *J* = 6.9 Hz, 2 H), 2.59 - 2.49 (quint, 2H), 2.26 (t, *J* = 7.6

Hz, 2 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.1, 158.6, 146.4, 129.4,125.0, 120.1, 110.2, 56.0, 50.4, 31.0, 19.0.

1-(4-chloro-2-nitrophenyl)pyrrolidin-2-one (1f)

Yellow solid, **Yield:** 54%, m.p : 41-45°C, **R_f Value**: 0.29 (n-Hexane : Ethyl acetate 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm): 7.97 (d, *J* = 2.40 Hz, 1 H), 7.60 (dd, *J* =8.59, 2.40 Hz, 1 H), 7.30 (d, *J* = 8.59 Hz, 1 H), 3.92 - 3.83 (m, 2 H), 2.61 - 2.50 (m, 2 H),2.34 - 2.21 (m, 2 H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ(ppm):175.1, 145.8, 133.7, 133.1, 130.7,128.4, 125.7, 50.1, 31.1, 19.0.

1-(4-chloro-3-nitrophenyl)pyrrolidin-2-one (1g)

Bright yellow solid, **Yield:** 90%, m.p : 133-135°C, **R_f Value**: 0.49 (n-Hexane : Ethyl acetate 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.19 (d, *J* = 2.7 Hz, 1 H), 7.91(dd, J = 9,2.7 Hz, 1 H), 7.51 (dd, *J* = 13.2, 4.2 Hz, 1 H), 3.88 (t, J = 6.9 Hz, 2H), 2.68-2.63 (m, 2 H), 2.20 (t, J = 7.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ (ppm): 174.8, 149.1, 140.7, 130.1,128.9, 125.4, 117.1, 50.1, 33.4, 19.1.

1-(2-methoxy-4-nitrophenyl)pyrrolidin-2-one (1h)

White solid, **Yield:** 78%, m.p : 142-145°C, **R_f Value**: 0.18 (n-Hexane : Ethyl acetate 1:1).

***N*-phenylacetamide (2a)**

White solid, **Yield:** 75%, m.p : 113-115°C, **R_f Value**: 0.47 (n-Hexane : Ethyl acetate 1:1).

***N*-phenylbenzamide (2b)**

White solid, **Yield:** 79%, m.p : 162-163 °C, **R_f Value**: 0.84 (n-Hexane : Ethyl acetate 1:1).

***N*-(4-nitrophenyl)acetamide (2c)**

yellow solid, **Yield:** 72%, m.p : 208-211 °C, **R_f Value**: 0.14 (n-Hexane : Ethyl acetate 1:1).

***N*-(4-nitrophenyl)benzamide (2d)**

orange solid, **Yield:** 80%, m.p : 190-191°C, **R_f Value**: 0.43 (n-Hexane : Ethyl acetate 1:1).

***N*-(4-methoxyphenyl)acetamide (2e)**

White solid, **Yield:** 40%, m.p : 130-132 °C, **R_f Value**: 0.11 (n-Hexane : Ethyl acetate 1:1).

***N*-(4-methoxyphenyl)benzamide (2f)**

White solid, **Yield:** 73%, m.p : 153-157 °C, **R_f Value**: 0.34 (n-Hexane : Ethyl acetate 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.40 (b, 1H, N*H*), 8.02 - 7.95 (m, 2H), 7.75 (d, *J* = 9.1 Hz, 2H), 7.59 - 7.44 (m, 3H), 6.92 (d, *J* = 9.1 Hz, 2H), 3.79 (s,3H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ (ppm): 166.0, 157.1, 136.5, 133.4, 132.1,129.2, 128.2, 122.7, 114.6, 55.7.

***N*-(4-methylphenyl)acetamide (2g)**

White solid, **Yield:** 40%, m.p : 150-152 °C, **R_f Value**: 0.53 (n-Hexane : Ethyl acetate 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.88 (b, 1H, N*H*), 8.18 (d, *J* = 8.5 Hz, 2H), 2.89 (S, 3H), 7.61 (d, *J* = 8.2 Hz, 2H), 2.75 (s, 3H). **^{13}CNMR (75 MHz, $CDCl_3$)** δ (ppm): 166.1, 137.8, 136.4, 133.9, 132.2, 129.9, 129.2, 128.3, 20.9.

***N*-(4-methylphenyl)benzamide (2h)**

Brown solid, **Yield:** 60%, m.p : 154-157 °C, **R_f Value**: 0.82 (n-Hexane : Ethyl acetate 1:1).

***N*-(4-chloro-3-nitrophenyl)acetamide (2i)**

Yellow solid, **Yield:** 53%, m.p : 138-140 °C, **R_f Value**: 0.34 (n-Hexane : Ethyl acetate 1:1).

***N*-(4-chloro-3-nitrophenyl)benzamide (2j)**

White solid, **Yield:** 81%, m.p : 155-156 °C, **R_f Value**: 0.83 (n-Hexane : Ethyl acetate 1:1).

3.6. General Procedure for the Arylation of Aromatic and Hetero Aromatic Thiols

A 13x100 mm oven-dried Pyrex glass tube, equipped with magnetic bar was charged with thiophenol (120 mol %), iodobenzene (100 mol %), Cs_2CO_3 (200 mol %), CuI (5 mol %) and ligand (10 mol %). After the addition of dioxane (0.5 M), the aperture of the sealed tube was covered with rubber septum and purged using an argon flow for few minutes. After purging, the septum was replaced by teflon-coated screw cap quickly. The

reaction mixture was stirred at 120 ℃ for 24 hours. After the completion of time the sealed tube was allowed to attain room temperature and TLC was taken to check whether the reaction has been completed or not. The dioxane was evaporated under reduced pressure. Pure coupled product was obtained by purification through flash column chromatography on silica gel as stationary phase using 5% ethyl acetate in n-hexane as a mobile phase. Most of the coupled products were liquid while few of them were sticky solids as well, ranging from colorless to brown and purple in color.

Diphenyl sulfide (3a)

Colorless liquid, **Yield:** quantitative, **R_f Value**: 0.6 (n-Hexane only).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.26-7.57 (m, 10H). **^{13}CNMR (75 MHz, $CDCl_3$)** δ (ppm): 135.84, 131.10, 129.2, 129.1, 127.5, 127.2.

4-methylphenyl phenyl sulfide (3b)

Colorless liquid, **Yield:** quantitative, **R_f Value**: 0.61 (n-Hexane only).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.16 – 7.36 (m, 9H), 2.39 (s, 1H). **^{13}CNMR (75 MHz, $CDCl_3$)** δ (ppm): 137.6, 137.1, 132.3, 131.3, 130.1, 129.7, 129.0, 127.5, 126.4, 21.1.

4-methoxyphenyl phenyl sulfide (3c)

Colorless liquid, **Yield:** 93%, **R_f Value**: 0.06 (n-Hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.44 -7.49 (m, 2H), 7.15 - 7.31 (m, 5H), 6.92 - 6.97 (m, 2H), 3.85 (s, 3H). **^{13}CNMR (75 MHz, $CDCl_3$)** δ (ppm): 159.8, 138.6, 135.4, 128.9, 128.1, 125.7, 124.2, 115.0, 55.4.

4-(4-methoxyphenyl thio) benzenamine (3d)

Dark brown sticky solid, **Yield:** 75%, **R_f Value**: 0.06 (n-Hexane : Ethyl acetate 95:5).

2-(4-methoxyphenyl thio) benzenamine (3e)

Dark purple sticky solid, **Yield:** 69%, **R_f Value**: 0.16 (n-Hexane : Ethyl acetate 95:5).

2-(4-methylphenyl thio) benzenamine (3f)

Brown sticky solid, **Yield:** 70%, **R_f Value**: 0.37 (n-Hexane : Ethyl acetate 95:5).

4-(4-nitrophenyl thio) benzenamine (3g)

Pale yellow solid, **Yield:** 83%, **R_f Value**: 0.09 (n-Hexane : Ethyl acetate 95:5).

4-(phenyl thio) benzenamine (3h)

Brown sticky solid, **Yield:** 89%, **R_f Value**: 0.11 (n-Hexane : Ethyl acetate 95:5).

2-(phenyl thio) benzenamine (3i)

Dark green sticky solid, **Yield:** 79%, **R_f Value**: 0.09 (n-Hexane : Ethyl acetate 95:5).

Naphthalene-2-yl (phenyl) sulfide (3j)

White sticky solid, **Yield:** 98%, **R_f Value**: 0.81 (n-Hexane : Ethyl acetate 95:5).

4-nitrophenyl phenyl sulfide (3k)

Pale yellow solid, **Yield:** 86%, **R_f Value**: 0.05 (n-Hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.07 (dd, J = 2.1,9 Hz, 2H), 7.51(dd, J = 1.2, 11.4 Hz, 2H), 7.45-7.48 (m, 3H), 7.18 (dd, *J* = 2.7,9.6 Hz, 2H). **^{13}CNMR (75 MHz, $CDCl_3$)** δ (ppm): 148.5, 145.3, 134.8, 130.8, 130.0, 129.7, 126.6, 124.0.

4-chloro-3-nitrophenyl phenyl sulfide (3l)

Pale yellow solid, **Yield:** 98%, **R_f Value**: 0.51 (n-Hexane : Ethyl acetate 95:5).

4-(4-chloro-3-nitrophenyl thio) benzenamine (3m)

Dark brown sticky solid, **Yield:** 84%, **R_f Value**: 0.1 (n-Hexane : Ethyl acetate 95:5).

2-methoxy-4-nitrophenyl phenyl sulfide (3n)

Yellow solid, **Yield:** 94%, **R_f Value**: 0.08 (n-Hexane : Ethyl acetate 95:5).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.06 (dd, J = 2.7, 9 Hz, 1H), 7.70 (d, J = 2.7, Hz, 1H), 7.28-7.52 (m, 5H), 6.92 (d, *J* = 9 Hz, 1H), 4.01 (s, 3H). **^{13}CNMR (75 MHz, $CDCl_3$)** δ (ppm): 160.4, 141.8, 134.1, 130.6, 129.9, 129.1, 128.9, 123.6, 123.1, 109.6, 56.8.

(4-methoxy-2-nitrophenyl)(naphthalen-2-yl) sulfide (3o)

Yellow sticky solid, **Yield:** 94%, **R_f Value**: 0.19 (n-Hexane : Ethyl acetate 95:5).

(4-chloro-3-nitrophenyl)(naphthalen-2-yl) sulfide (3p)

Pale yellow sticky solid, **Yield:** 98%, **R_f Value**: 0.47 (n-Hexane : Ethyl acetate 95:5).

2-nitro-4-chlorophenyl phenyl sulfide (3q)

Yellow solid, **Yield:** 96%, **R_f Value**: 0.56 (n-Hexane : Ethyl acetate 95:5).

4-methoxy-2-nitrophenyl phenyl sulfide (3r)

Light yellow sticky solid, **Yield:** 95%, **R_f Value**: 0.27 (n-Hexane : Ethyl acetate 95:5).

3-(phenyl thio) pyridine (3s)

Colorless liquid, **Yield:** 91%, **R_f Value**: 0.41 (n-Hexane : Ethyl acetate 9:1).

3-(4-chloro-3-nitrophenyl thio) pyridine (3t)

Pale yellow solid, **Yield:** 90%, **R_f Value**: 0.13 (n-Hexane : Ethyl acetate 9:1).

5-chloro-2-(phenyl thio) benzothiazole (3u)

Off white sticky solid, **Yield:** 60%, **R_f Value**: 0.42 (n-Hexane : Ethyl acetate 9:1).

5-chloro-2-(4-chloro-3-nitrophenyl thio) benzothiazole (3v)

Pale yellow solid, **Yield:** 58%, **R_f Value**: 0.41 (n-Hexane : Ethyl acetate 9:1).

2-(phenyl thio) benzimidazole (3w)

White sticky solid, **Yield:** 60%, **R_f Value**: 0.14 (n-Hexane : Ethyl acetate 9:1).

2-(4-chloro-3-nitrophenyl thio) benzimidazole (3x)

Pale yellow solid, **Yield: 91**%, **R_f Value**: 0.12 (n-Hexane : Ethyl acetate 9:1).

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