# STUDIES IN COPPER CATALYZED AMINATION OF ARYLHALIDES

A THESIS
SUBMITTED TO
THE UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

**NANDKUMAR MANIKRAO PATIL**

AT

HOMOGENEOUS CATALYSIS DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE-411 008
INDIA

MARCH 2007

राष्ट्रीय रासायनिक प्रयोगशाला
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद)
डॉ. होमी भाभा मार्ग पुणे – 411 008. भारत
NATIONAL CHEMICAL LABORATORY
(Council of Scientific & Industrial Research)
Dr. Homi Bhabha Road, Pune - 411 008. India.

# CERTIFICATE

This is to certify that the work incorporated in the thesis, **"Studies in Copper Catalyzed Amination of Arylhalides"** submitted by **Mr. Nandkumar M. Patil,** for the Degree of **Doctor of Philosophy,** was carried out by the candidate under my supervision in the Homogeneous Catalysis Division, National Chemical Laboratory, Pune – 411 008, India. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

**Dr. R. V. Chaudhari**

**(Research Supervisor)**

# DECLARATION

I hereby declare that the thesis **“Studies in Copper Catalyzed Amination of Arylhalides”** submitted for the degree of Doctor of Philosophy to the University of Pune has not been submitted by me for a degree to any other University.

March, 2007 **Nandkumar M. Patil**

Pune

*Dedicated to*

*My Parents*

*…For the beautiful life they*
*have bestowed on me*

# *ACKNOWLEDGEMENT*

*I wish to express my sincere gratitude to my research guide, Dr. R. V. Chaudhari, former Head, Homogeneous Catalysis Division, National Chemical Laboratory (NCL) for his constant support and encouragement during the course of this work. I am grateful for his teaching, guidance. His enthusiastic attitude, innovative ideas and scientific knowledge have inspired me profoundly. I truly feel privileged to have joined his research group.*

*I would like to express my sincere gratitude and respect to Dr. S. P. Gupte, for his constant support, valuable help and suggestions during my research work. I am and will remain grateful to him for his teaching, guidance, friendship and wonderful personality.*

*I would like to gratefully acknowledge Dr. A. A. Kelkar for his guidance, constant support and encouragement during the course of this work.*

*I would like to express my sincere gratitude and respect to Dr. B. D. Kulkarni, Deputy Director and Head, CEPD & Homogeneous Catalysis Division, NCL, for his constant support, valuable help, guidance and suggestions during my research work.*

*I am grateful to Council of Scientific and Industrial Research (CSIR), India for the research fellowship. I am thankful to former Director Dr. Paul Ratnasamy, present Director Dr. S. Sivaram, NCL for allowing me to carry out research work and extending me all the possible infrastructural facilities.*

*I sincerely acknowledge Dr. R. M Deshpande, Dr. C. V. Rode, Dr. R. Jaganathan, Dr. G. S. Grover, Dr. V. V. Ranade, Dr. V. H. Rane, Dr. Sengupta, Mr. P. B. Jadkar, Dr. V. M.Bhandari, Mr.Ozarde, Mr. S. S. Joshi, Dr. S. H. Vaidya, Mrs. Savita S., Dr. A. A. Kulkarni and Mr. H. M. Raheja for their valuable help and co-operation during my research stay in NCL. I would like to thank all other members of homogeneous catalysis division, for a healthy working atmosphere.*

*I take this opportunity to express my sincere gratitude to Dr. Mrs. V.G. Puranik, Dr. Rajmohanan, Dr. Mandale, Mr. Gaikwad A. B., Dr. Mrs. Kulkarni S., Dr. Bhadbhade, Dr. D. Srinivasan, Dr. Rajesh, Mrs. Renu Parischa, Dr. Shubhangi U., Dr. P. P. Wadgaonkar, Dr. M. K. Dongre, Dr. U.R. Kolkote, Dr. B. M. Bhawal, and Mr. S. Chandrahas for their valuable help and guidance during my research work.*

*I also wish to thank my senior and more over my friend Dr. Sunil D., Dr. Vinod, Dr. S. P. Mathew, Dr. A. Seayad, Dr. S. Jayasree, Dr. Kausik, Dr.Yogesh, Dr. Sunil, Dr Manish (badi), Dr. Shrikant, Dr. Tushar, Dr. Charu, Dr. Manisha (choti) and Avinash M. I would like to express my deepfelt gratitude to my colleagues and friends Nitin, Makarand, Pipalad, Sunil Shinde, Anamika, Debu, Bibhas, Shashi, Rangeet, Jaypraksh, Vikas, Amit, Mahesh B., Anand, Mahesh, Rajesh, Rashmi, Ruta, Kapil, Abhishek, Kausik, Himadri, Ankush Biradar, Sangeeta, Lalita, Umar, Tejeshwani, Vabhavi and Geeta for their friendship and helping hands.*

*I would like to express my sincere gratitude to Dr. D. P. Sabde and Dr. Jayant Kandare, for his constant support and valuable help during this research work.*

*I would like to acknowledge to Bennur, Eshwar, Dr. Mrugan, Bapu, Uma, Subbu, Arindam, Mahesh K. Nagendra K., Nitin D., Ramesh Kale, Dumbre, Ram Ambre, Santosh, Suresh, Bhrate G., Satish, Hemant, Sunita, Dr. Shubhangi, Ankush Mane, Prtap Patil and many in NCL who are not named in person, for their valuable suggestions and helping hand.*

*I would like to gratefully acknowledge to Subbu, Radha, Ravi, Shaker (Electrical), Dure, Nrawde, Shinde ,Mr. A.M. Patil, Mr. Mahajan, Mr. More, (work shop) Mr. Borkar, Mr. Tapan Sah, Mrs. Shintre, Mr. Jadhav, administration and other supporting staff of NCL for their co-operation.*

*I also wish to thank my school and forever friends, Dr. V.V. Bhade, Dr. Dayanad More, Dr. Madhav Chambule and Dr. Narayan S. for their valuable suggestions, support and encouragement during this research work.*

*No thanks can be enough to acknowledge the encouragement of my parents, my wife Suchitra and my daughter Tejal. They have been my constant source of strength. Needless to say it was because of the efforts of my family today I stand where I am.*

*I would like to acknowledge to my sister Kanchan O. Dongaonkar for her support and encouragement during this research work.*

***March 2007*** ***Nandkumar M. Patil***

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# List of Abbreviations

| | |
|---|---|
| 5-nitroPhen | 5-nitri-1, 10-phenanthroline |
| Ar | Aryl |
| Bu | n-butyl |
| Cat | Catalyst, catalytic |
| $CDCl_3$ | Deuterated chloroform |
| $Cs_2CO_3$ | ciesium Carbonate |
| $Cu(OAC)_2$ | Copper accetate |
| CuBr | Copper (I) bromide |
| CuCl | Copper (I) chloride |
| $CuCO_3$ | Copper carbonate |
| CuI | Copper (I) Iodide |
| dba | Dibenzylideneacetone |
| DBU | 1,8 diazabicyclo [5.4.0] undec-7-ene |
| DhDMDbPhen | 6,7-dihydro-5,8-dimethyl dibenzo-1,10-phenanthroline |
| DMF | N,N-Dimethyl foramide |
| DPPE | 1,2- bis (diphenylphsophino) ethylene |
| DPPH | 1,5-bis (diphenylphsosphino) hexane |
| DPPM | 1,1-bis (diphenylphsophino) methane |
| DPPP | 1,3-bis (diphenylphsosphino) propane |
| DPPT | 1,4-bis (diphenylphsosphino) pentane |
| EDATA | Ethylene diamine tetra acetic acid |
| EDATE | Ethylene diamine tetra ethane |
| EDATM | Ethylene diamine tetra methane |
| EDX | Energy dispersive X-ray |
| EPR | Electron paramagnetic resonance |
| equiv | Equivalent (s) |
| Et | Ethyl |
| FID | Flame ionization detector |

| | |
|---|---|
| FTIR | Fourier transform infrared |
| GC | Gas chromatography |
| GC-MS | Gas chromatography-Mass spectrometry |
| h | Hour (s) |
| $K_2CO_3$ | Potassium carbonate |
| KOH | potassium hydroxide |
| KOt-Bu | Potassium t-butaoxide |
| LUMO | Lowest unoccupied molecular orbital |
| MASNMR | Magic angle spinning nuclear magnetic resonance |
| MCM-41 | Mobile crystalline materials –41 |
| Me | Methyl |
| ml | Milliliter |
| Mol | Mole |
| $NaHCO_3$ | Sodium bicarbonate |
| NaOH | Sodium hydroxide |
| NaOMe | Sodium methoxide |
| NaOt-Bu | Sodium t-butaoxide |
| Neocup | neocuprine |
| NMP | N-methyl pyrolodine |
| NMR | Nuclear magnetic resonance |
| PDATE | Propylene diamine tetra ethane |
| Ph | Phenyl |
| Phen | 1,10-phenanthroline |
| $PPh_3$ | Triphenylphosphine |
| RT | Room temperature |
| SEM | Scanning electron microscopy |
| *t*-Bu | tert-butyl |
| TEA | Tetra ethylamine |
| TEM | Transmission electron microscopy |
| TG | Thermogravimetry |
| TGA | Thermogravimetric analysis |

| | |
|---|---|
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMPhen | Tetramethyl-1,10-phenanthroline |
| TOF | Turn over frequency |
| UV-Vis | Ultra violet visible |
| XPS | X-ray photoelectron spectroscopy |
| XRD | X-ray diffraction |

# Abstract of the Thesis

The growth of chemical industry is influenced by several factors including economics, availability of feedstock, development of new competitive technologies and environmental acceptance. Catalysis has played a vital role in developing new technologies as well as in solving environmental problems. The need of catalytic technologies in conversion of cheaper feedstock to chemicals, new routes for fine chemicals, pharmaceuticals and specialties, removal of pollutants, waste minimization and global preservation and supply of energy is obvious. The conventional manufacturing using the stoichiometric synthetic routes often involves toxic and corrosive reagents, byproducts and waste products consisting of inorganic salts. The conventional routes were less efficient and more polluting but were able to make products that meet the specifications required by industry at viable cost and hence were acceptable due to non-availability of alternative greener routes. In this context, both homogeneous and heterogeneous catalysis have played an important role in the development of new chemistry and technology towards clean synthesis.

Copper-catalyzed C-N bond formation has long been a practical and efficient method for the construction of aryl C-N bonds in both academic and industrial field.[1] The classical technique for the preparation of triarylamines is based on the Ullmann reaction originally reported in 1901.[2] The original Ullmann reactions were carried out at high temperatures (~483 K) using stoichiometric amount of copper and yields obtained were only moderate. Efforts were concentrated towards reducing the harsh reaction conditions and Pd containing catalysts were found to be effective in bringing down the reaction temperature below ~ 393 K. However, Pd is an expensive catalyst and further work was concentrated in replacing Pd by cheaper transition metals like Ni or Cu. In this connection, N or P containing ligands were most effective in making copper as effective as palladium under mild reaction conditions. However, very high concentrations of inorganic bases (such as KOH, etc.) were necessary to effectively carry out amination.

Arylamines are commonly encountered in natural products, pharmaceuticals, xerographic and photographic materials as well as conducting polymers**.** Arylamines

have a large number of other applications and are thus attractive targets for chemical synthesis. One of their earliest applications was in the production of brightly colored synthetic dyes, introduced in the late nineteenth century. They are found in biologically active compounds such as pharmaceuticals, agrochemicals, and several commonly occurring DNA lesions. Arylamines have also been employed as ligands for transition metals, and in the design of conducting polymers and other electronically interesting materials.[1]

Traditionally, the preparation of alkyl aryl amines has been carried out by the reductive amination of aniline derivatives or arene nitration/reduction protocols. These methods, although effective; suffer from drawback of a relatively limited substrate generality and functional group tolerance. Additionally, these synthetic strategies often require multiple steps or the use of expensive reagents in stoichiometric amounts. The preparation of aryl ethers has most often been achieved *via* Ullmann ether synthesis. Though useful, Ullmann reaction suffers from a limited substrate scope; the reaction typically works best for the coupling of electron-deficient and sterically unhindered aryl halides.[2] Moreover, Ullmann condensation requires stoichiometric or even more than stoichiometric amount of copper salts to bring about the reaction.

Thus, the transition metal catalyzed arylation reactions of amines and alcohols would constitute powerful tools for synthetic chemists. John Hartwig and coworkers have been developing practical procedures for the palladium-catalyzed arylation of amines and alcohols with aryl halides or sulfonates.[1] During the course of their investigation the substrate scope of these transformations has been incrementally expanded. With each cycle of this catalyst improvement process, advances in mechanistic understanding and ligand design have also been made. Most of the work was done on palladium-catalyzed amination reactions. Palladium-catalyzed amination is costly; because palladium is costly metal and required exotic ligand such as BINAP, Xantphos, etc. but at the same time have wide range of substrate tolerance ability. It is desirable to develop a cheaper catalyst system with good activity and selectivity for commercial applications. There is an economic attractiveness for using copper over noble metals such as palladium but the yields were low.[3] Goodbrand reported preliminary work on copper-catalyzed amination using ligands. The problem with this system is that it works only with 1,10-

phenanthroline ligand.[2d] Buchwald also reported copper-catalyzed amination using diol as the ligands, but no detailed study had been done on this important topic.[2e]

Chapter 1 presents a detailed literature review on catalysis and synthesis of various amine derivatives for amination reaction. The importance of C-N coupling in organic synthesis and related chemical industries such as pharmaceuticals and fine chemicals is enormous. For example, in a recent report on twenty top-selling drugs all of them involve at least at one stage C-N bond coupling chemistry in their synthesis.[1d] The palladium-catalyzed arylation of amines has been under the focus of intensive research in recent years.[1] Buchwald and Hartwig have made considerable contribution towards the development of general, reliable, and practical catalysts for the formation of aromatic carbon-nitrogen bonds by the cross-coupling of amines and aryl (and heteroaryl) iodides, bromides, chlorides and triflates. Most of the work was done on palladium-catalyzed amination reaction, and there were very few reports on other metals such as nickel and copper. Finally, the amination reactions and the current trends in their catalytic route and synthesis of industrially important amines have been discussed. This review covers details of catalytic studies and other relevant synthesis of amine aspects.[1] The following observations emerged from the literature review:

- $Pd_2(dba)_3$ as catalyst precursor in combination with ligands the most suitable catalysts for the amination of aryl halides. Palladium-catalyzed amination reaction required exotic ligand such as BINAP, Xantphos, etc. This catalyst system was found to be most suitable for inactivated amines, such as morpholine, piperazene and hetero amines and aryl chlorides.
- $Pd_2(dba)_3$ and $(t\text{-Bu})_3P$ catalyst system has been reported for the amination of piperazene, which has medicinal value.
- The palladium-catalyzed amination of aryl bromides, iodides and triflates with primary and secondary amines and anilines has provided a new route to a wide variety of arylamines. Buchwald and his group’s expanded the aryl amination methodology to include aryl chlorides, which is the least expensive, and most widely available aryl halides.

- There is no report on other noble metals like Platinum, Rhodium, and Iridium for the amination of arylhalides.
- Very few reports are available on nickel-catalyzed amination reaction. $Ni(COD)_2$ and DPPF or 1,10-phenanthroline or 2,2'-bipyridine catalyst systems are available for the amination of aryl iodides, bromides and chlorides.
- There are some reports on copper-catalyzed amination reaction, which is cheaper compared to palladium. Also there is no need to use exotic ligand such as BINAP, Xantphos for copper-catalyzed amination reaction for aryl bromide and aryl iodides. No detailed study has been done on copper-catalyzed amination reaction with respect to effect of ligands and parameters on the behavior of reaction.
- There is a considerable increase in the publication rate in the field of copper- catalyzed amination in the last five years. Majority of these reports are on homogeneous copper-catalyzed amination, wherein the catalyst recycle issue is not satisfactorily addressed. Therefore, stability and separation of the catalyst is a field of interest to the current researchers working in the area of catalysis. The significance of heterogenised homogeneous catalyst needs to be investigated.

Chapter 2 presents a experimental study on ligand-free copper-catalyzed amination reaction. System was standardized for copper-catalyzed reaction and various bases, solvents, arylhalides and arylamines were screened. The effect of temperature on reaction was also studied. We reported for the first time that catalytic amount of copper (I) iodide, KO*t*-Bu as a base and toluene as a solvent at 408 K temperature gives high yield (80-82%)of triphenylamine. It is observed that copper-catalyzed amination reactions in presence of ligand is significantly accelerated and selectivity towards triphenylamines increases sharply. Various ligands such as *N*-containing and *P*-containing heterocycles were screened. Chelating *N*-containing ligands such as 1,10-phenenthroline and 2,2'-bipyridine give 100 % conversion of aniline and more than 90 % yield of TPA. Monodentate *N*-containing ligand such as 2,6-diphenypyridine in presence of catalyst to ligand ratio of 1:1 gave excellent yield (94%) of TPA. We observed that for copper-catalyzed amination, CuI/2,6-diphenypyridine catalyst system is one of the excellent catalyst systems so far reported. Copper-catalyzed amination reaction with diphosphine ligands shows promising results

From the results obtained, it is clear that in chelating diphosphines, activity as well as yield of TPA increased with increase in carbon chain length initially ($C_1$-$C_3$) and thereafter decreased with further increase in carbon chain length between the phosphines. It is likely that the ligands (DPPT and DPPH) behave as monodentate ligands leading to lower activity and the best results were obtained with DPPP as a ligand. A similar trend was observed for alkyldiamine ligands. Various catalyst precursors and bases were also screened. However the *N*-containing ligands such as 1,10-phenanthroline, 2,2'-bipyridine and 2,6-diphenylamine alone with KO*t*-Bu as a base and toluene as solvent at 385 K temperature are the best for the amination of arylhalides. Industrially as well as academically important amine derivatives such as 4-phenyl morpholine and *n*-phenylpiperazene were synthesized using non-ligated and ligated copper-catalyst system resulting in promising to excellent yields of triphenylamine. These amine derivatives were characterized by using various characterization techniques such as NMR ($^1$H, $^{13}$C), FT-IR, GC-MS, elemental analysis and melting point. Activity of ligand-assisted reaction was explained on the steric and electronic effect of ligands. And also on the ability of ligand to influence the Cu(I) –Cu(II) equilibrium during the oxidative addition step.

Chapter 3 describes the well-defined copper (I) complexes amination reactions. There are only two reports on the well-defined copper (I) complexes for the amination of arylhalides.[2] However, there is much scope to synthesize and characterize several copper (I) complexes and test their catalytic applications for the amination of arylhalides. It is desirable to develop robust, cheaper and easy to synthesis well-defined copper (I) complexes for the amination of arylhalides. Six copper (I) complexes were synthesized (including three new) and tested for amination reactions. All copper (I) complexes were characterized by NMR ($^1$H, $^{13}$C, $^{31}$P), IR, Far-IR, elemental analysis, TGA-DTA, EDX and SEM. Complexes Cu-1, Cu-2 and Cu-3 were known and Cu-4, Cu-5 and Cu-6 are new. Cu-4, Cu-5 and Cu-6 are characterized also by single crystal X-ray analysis.

These copper (I) complexes were tested for the bis-amination of arylhalides and gave promising yields of products. Cu-6 complex gave comparable activity, 73 % yield of product (DPA+TPA) with reference to previous report[2] (52-60 % yield) Cu-1 and Cu-6 gave excellent activity for the amination of arylhalides.

Cu-2 is a representive catalyst for the amination reaction. Using this catalyst, the detailed study of effect of reaction parameters, such as type of base, solvent, temperature and arylhalides on the activity and selectivity of the amination reaction has been carried out. Using Cu-2 catalyst various industrially important amines were synthesized and characterized by NMR ($^1$H, $^{13}$C), FT-IR, GC-MS, elemental analysis and melting point. The activity of copper complex catalyst was explained on the basis of complex structure and ligand properties such as co-ordination ability etc.

Chapter 4 presents the heterogenised copper complexes for the amination of arylhalides. Amination reaction using homogeneous copper catalyst system is not a shape selective reaction and the maximum TON reported is 20.7. It is difficult to recover catalyst in homogeneous system or recycle it. To overcome these difficulties, our efforts are directed towards the development of a cheaper heterogeneous catalyst system, which can be easily recovered and recycled and thus increase the TON. For solving these major issues heterogenised homogenous complexes were prepared on support like zeolite-Y, silica, charcoal, clay, etc. In this chapter two types of heterogenised catalyst (a) encapsulated copper complexes in zeolite-Y and (b) tethered copper complexes on various supports were prepared.

Copper/1,10-phenanthroline, copper/2,2'-bipyridine were encapsulated in zeolite-Y and MCM-41. These encapsulated copper catalysts were characterized by using EPR, Solid U.V, FT-IR, Surface area, elemental analysis, XRD, TGA, IAS and ICPES, and from these characterizations, it was confirmed that the copper complexes were encapsulated in zeolite-Y.

Encapsulated copper complexes were tested for amination of aryl iodide and selectively diphenylamine was obtained. For this aniline and iodobenzene was used in the molar ratio of 1:1. Thus encapsulated copper complexes in zeolite-Y are shape selective catalyst for the synthesis of diphenylamine (DPA). This could be due to the fact that the pore diameter of zeolite-Y is ~7A$^o$, while diameter of TPA is greater than 7A$^o$ and diameter of DPA is less than 7A$^o$. This catalyst is stable and there was no leaching up to five recycles.

Encapsulated copper catalyst in MCM-41 for amination of aryl iodide gives selectively triphenylamine (TPA). But supported catalyst is not stable, it leaches out and catalyst activity goes down after every recycle. This may be due to the leaching of the complex from large (35A$^o$) pore channel of MCM-41, leached catalyst promote reaction leading to TPA formation.

Copper complexes were tethered on various supports such as zeolite-Y, silica, alumina, charcoal, titanium oxide and clay. These tethered catalysts were fully characterized by using XPS, Solid U.V, FT-IR, Surface area, XRD, TGA, IAS and ICPES, SEM and TEM. Eight different tethered copper catalysts were synthesized using reported method.[3] These eight tethered catalysts were tested for amination reactions. These catalysts show promising activity and selectivity for the synthesis of triarylamines. Out of these, Cu(Phen)($PPh_3$)Br-PTA-Y gives best activity. Using this catalyst various bases and solvent were screened. The effect of temperature on activity and selectivity was also investigated. The recycle study of Cu(Phen)($PPh_3$)Br-PTA-Y indicated that there is no loss in activity even after five recycles and at the end of fifth recycle ~ 72 % yield of TPA is realized. No leaching of copper metal was observed in the organic phase. Thus, heterogenised copper catalyst shows build up TON of 69 at the end of fifth recycle compared to its homogenous counter part Cu(Phen)($PPh_3$)Br, which gave TON of 20.7 (recycling was not possible).

Thus, heterogenised form of copper catalyst overcomes the major issues such as catalyst separation and recycles which generally involves tedious procedures for homogenously catalyzed amination of arylhalides. These heterogenised copper catalysts are stable up to five recycles without any leaching of metal for the amination of arylhalides.

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# CHAPTER 1

# INTRODUCTION AND LITERATURE SURVEY

## 1.1 Introduction

Syntheses of amines have perhaps received more attention than the preparation of many other functional groups in organic synthesis.[1] With the growing repertoire of biologically relevant nitrogenous molecules, so is the need of efficient synthetic methods to prepare amines as useful intermediates.[2,3] Due to their interesting physiological activities, secondary amines in particular are extremely important pharmacophores in numerous biologically active compounds, which have greatly been touted in the area of drug discovery.[4]

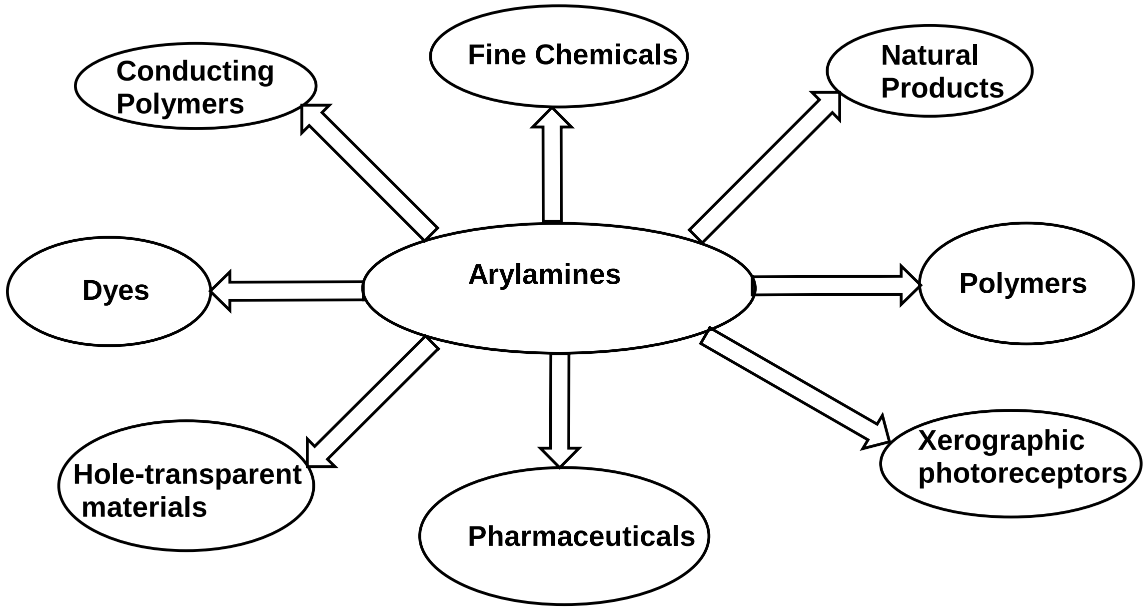
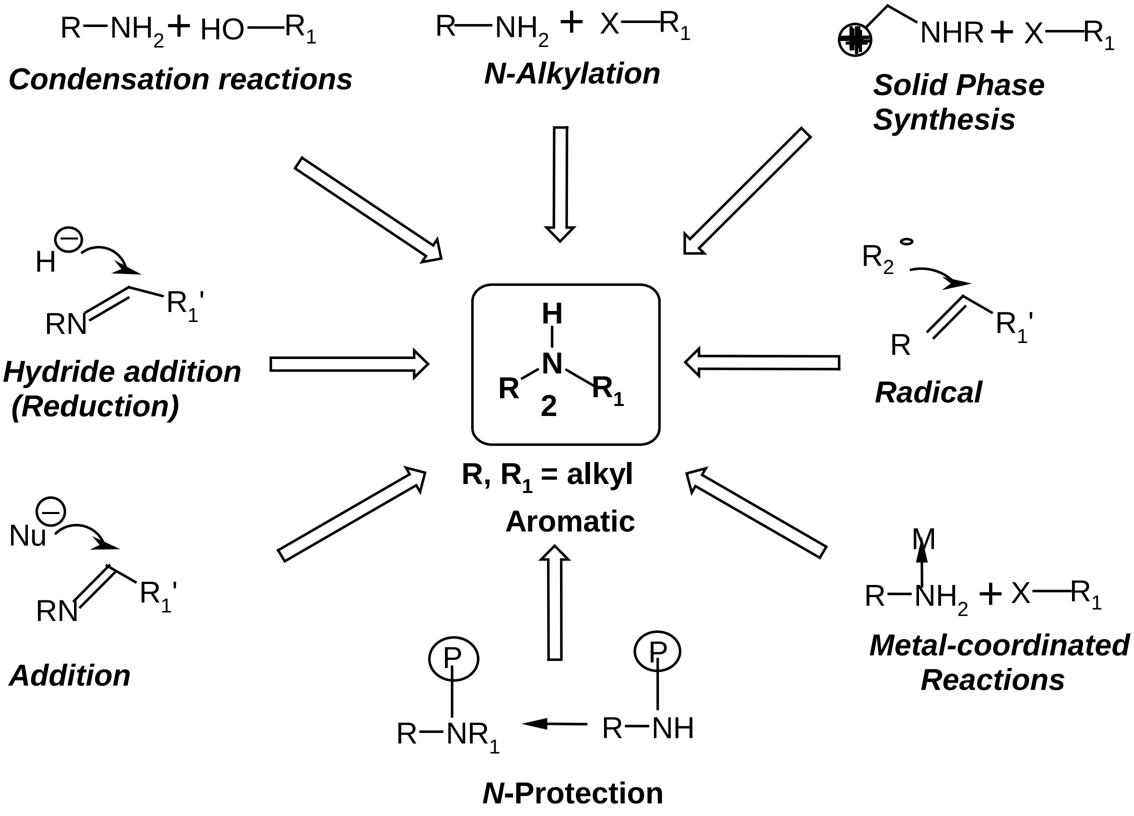


**Figure1.1:** Application of arylamines

Arylamines are ubiquitous in numerous fields of chemistry. Arylamines are commonly encountered in natural products,[5] pharmaceuticals,[6] xerographic and photographic materials,[7] as well as conducting polymers. Traditionally, the preparation of alkylarylamines has been carried out by the reductive amination of aniline derivatives or arene nitration/reduction protocols.[8,9] These methods, although often effective, suffer from a relatively limited substrate generality and functional group tolerance. Additionally these synthetic strategies often require multiple steps or the use of expensive reagents in stoichimetric amounts. The Ullmann reaction also gives the arylamines. The Ullmann reaction suffers from a limited substrate scope; the reaction typically works best for the coupling of electron-deficient and sterically unhindered arylhalides.

This filed has also spurred intense activity on solid phase synthesis[10] as well as combinational library generation,[11] where the secondary amine can be utilized as an important scaffolding for further manipulations. However, despite the widespread interest, traditional methods for secondary amine formation are often problematic because of harsh reaction conditions, generally poor yields, and/or low chemical slectivities.[12] Illustrated in *Scheme 1.1* is a brief classification for the synthesis of secondary amines, among which suitable procedures and conditions can be properly chosen to prepare the desired amines efficiently.

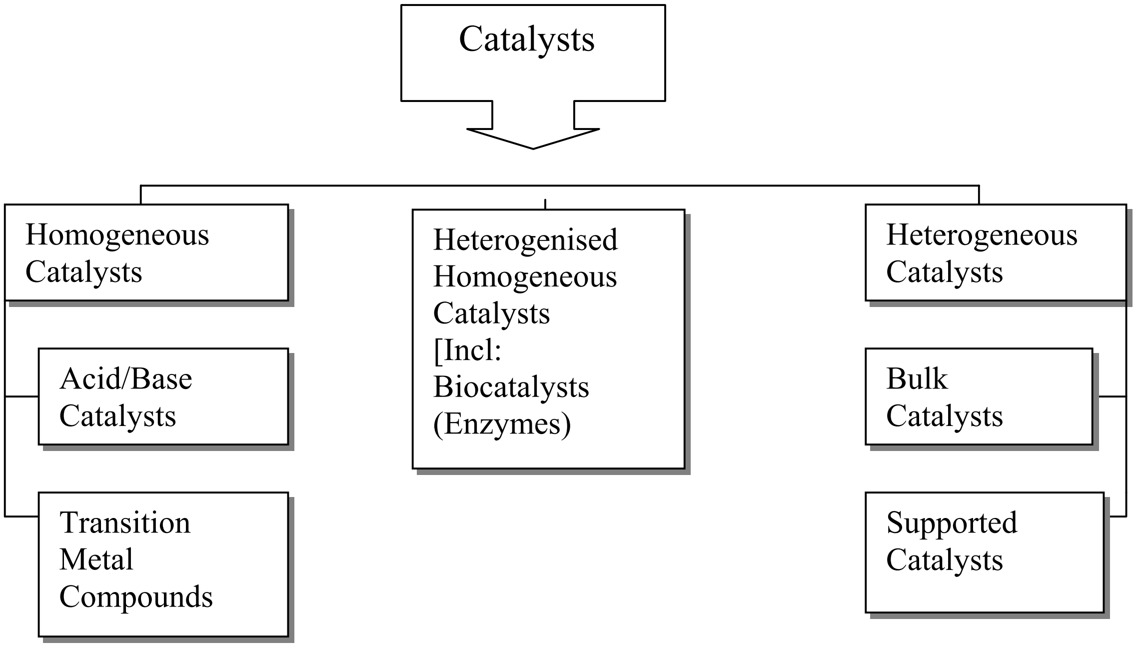


**Scheme1.1:** Various routes for synthesis of secondary amines

Thus, the transition metal catalyzed arylation reactions of amines and alcohols would constitute powerful tools for synthetic chemists. Hartwig and coworkers have been developing practical procedures for the palladium-catalyzed arylation of amines and alcohols with aryl halides or sulfonates.[13] During the course of their investigation the substrate scope of these transformations has been incrementally expanded. With each cycle of this catalyst improvement process, advances in mechanistic understanding and ligand design have also been made. In this topic we will discuss about catalyst and catalytic process in very short.

The growth of chemical industry is influenced by several factors including economics, availability of feedstock, development of new competitive technologies and environmental acceptance.[14] Catalysis has played a vital role in developing new technologies as well as in solving environmental problems. The need of catalytic technologies in conversion of cheaper feedstock to chemicals, new route for fine chemicals, pharmaceuticals and specialties, removal of pollutants, waste minimization and global preservation and supply of energy is obvious.

**Table 1.1:** Classification of catalysts



Catalysis is generally classified into two types depending on the physical nature of the catalyst employed: as homogenous, in which the catalyst is soluble in the reaction medium, and heterogeneous in which the catalyst is immiscible with the reaction medium or present as a separate phase. Homogenous catalysis by soluble metal complex catalysts has been practiced in industry for several years for a number of processes involving carbonylation, hydroformylation, oligomerization, isomerization, polymerization and oxidation.[15] The unique features of these catalysts are high activity and selectivity at mild operating conditions, ability to activate commercially available and cheaper substrates such as CO, hydrogen, olefins and alcohols and plausible characterization at a molecular level. While the industrial significance of homogenous catalysis was realized several decades ago with the development of hydroformylation technology (oxo process), Wacker process, carbonylation of methanol to acetic acid, ethylene polymerization by Zeigler-Natta catalysts and *p*-xylene oxidation of terephthalic acid, it is only in recent years that the true potential of homogenous catalysts has become evident with widely expanding applications for the synthesis of fine chemicals, pharmaceuticals and specialty chemicals. The performance of homogenous catalysts depends on type of the metal, ligands, promoters and co-catalysts. The main drawback of homogenous catalysis is the separation of the catalyst and products, which is often a tedious task involving precipitation of the catalyst by adding non-polar solvents, high vacuum distillation or extraction of products into a second phase, etc. subsequently, only 20% of the industrial

**Table 1.2:** Homogenous vs. Heterogeneous Catalysis

| Process | Homogenous Catalysis | Heterogeneous Catalysis |
|---|---|---|
| Activity (relative to metal content) | High | Variable |
| Selectivity | High | Variable |
| Reaction Conditions | Mild | Harsh |
| Service life of catalysis | Variable | Long |
| Sensitivity towards catalyst poisons | Low | High |
| Diffusion problems | None | May be important |
| Catalyst recycling | Expensive | Not necessary |
| Variability of steric and electronic properties of catalysis | Possible | Not possible |
| Mechanistic understanding | Plausible under random conditions | More or less important |

catalytic reactions involve homogenous catalysis, 80% employing the classical heterogeneous catalysis involving supported metal catalysts.

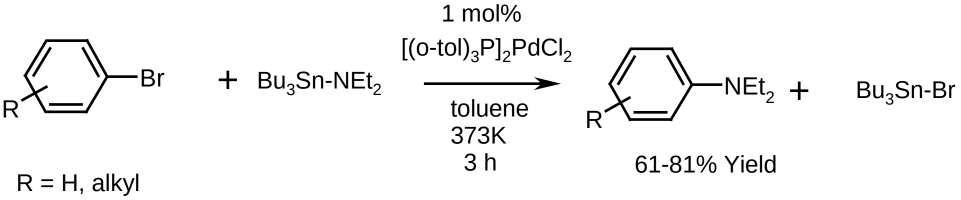
## 1.2 Palladium catalyzed amination

Palladium gives the best results for major organic transformations such as C-C, C-O and C-N coupling reactions. One of the most revealing facts is that in 1994's list of the twenty top-selling pharmaceuticals, a significant number contained aromatic carbon-nitrogen bonds.[15] The palladium-catalyzed arylation of amines have been under the focus of intensive research in recent years.[16] Buchwald and Hartwig have made considerable contribution towards the development of general, reliable, and practical catalysts for the formation of aromatic carbon-nitrogen bonds by the cross-coupling of amines and aryl (and heteroaryl) iodides, bromides, chlorides and triflates. Due to these contributions now a day this amination reaction is known as ***Buchwald-Hartwig amination.***

### 1.2.1 History of palladium-catalyzed amination

#### 1.2.1.1 Early Palladium-Catalyzed amination

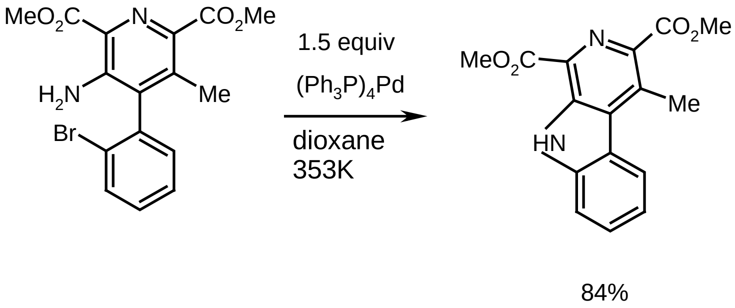
In the 1980s a few results suggested that a general metal-catalyzed method to form arylamines from arylhalides would be possible. In 1983 Kosugi[17] published a short paper on the reaction of tributyltin amides with aryl bromides catalyzed by $[(o\text{-}tol)_3P]_2PdCl_2$ as shown in (*Scheme1.2).*[18]



**Scheme1.2:** Pd-catalyzed amination using tributyltin

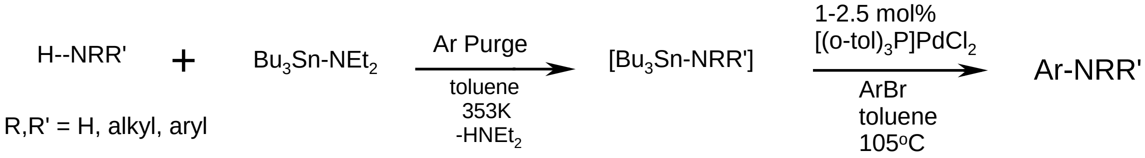
The scope of this reaction appeared to be limited to dialkylamides and electron-neutral arylhalides. For examples, the use of arylhalides with nitro, acyl, methoxy, and dimethylamino substituents gave poor yields upon palladium-catalyzed reaction with tributyltin diethylamide. Furthermore, aryl bromides were the only aryl halides that provided any reaction product. Only unhindered dialkyltin amides gave substantial amounts of amination product.

Boger[19] reported studies on palladium-mediated cyclization to form the CDE ring system of lavendamycin (*Scheme1.3)*. These reactions were conducted with stoichimetric amounts of [Pd($PPh_3$)$_4$]. However, when used in 1mol % quantity of catalyst failed to catalyze these reactions, presumably because of the absence of base.[20, 21]



**Scheme1.3:** Synthesis of lavendamycin

Until almost ten years later, no palladium-catalyzed amination chemistry was reported. Guram and Buchwald[22] showed that the chemistry could be extended beyond electron-neutral aryl halides. With tin amides derived in situ this chemistry was extended to aryl halides bearing alkoxycarbonyl, amino, and alkoxo groups *(Scheme1.4).* However, reactions that proceeded with 80% yield or greater were still limited to tin amides derived from secondary amines.



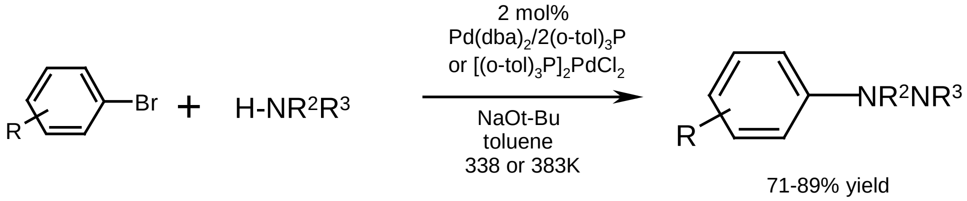
**Scheme1.4:** Synthesis of alkoxyamine for amination

### 1.2.1.2 The Limitation of early palladium-catalyzed amination

The initial results concerning arylhalides amination and related results in chemistry forming aryl sulfides and phosphanes strongly suggested that a mild, convenient route to arylamines from arylhalides could be developed. However, a source of amido group must be less toxic, more thermally stable, and less air-sensitive than tin amides. The type of aryl halides that can undergo this reaction must extend beyond electron-neutral arylhalides, for example to aryl chlorides, iodides and aryl triflates and heteroaromatic amines. Perhaps most important are reaction of primary amines; since the arylhalide amination with primary amines would give secondary alkylarylamines. In addition, it will be highly desirable to extend this type of reaction to the formation of aryl ethers and phenols, since there are no truly mild and convenient methods for this transformation. These substrates are tedious to prepare by classical methods. Finally, the rates and turnover numbers provided by the catalysts must be much higher than those in Kosugi's chemistry and Boger's stoichimetric cyclization reaction.[18,20]

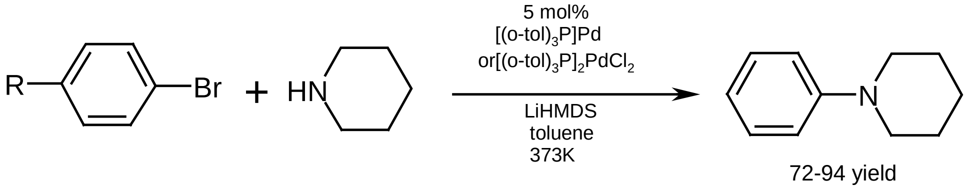
### 1.2.1.3 Tin free amination

In 1995 the research groups of Buchwald[23] and Hartwig[24] published concurrently their results on tin-free amination of arylhalides. Instead of isolation or generation of a tin amide in situ, the amination reactions were conducted by reaction of an arylhalides with amines (*Scheme 1.5).* These reactions were typically carried out between 353 K and 373 K in toluene. The catalyst used initially were a combination of $Pd_2dba_3$ and two equivalents of $(o\text{-}tol)_3P$.



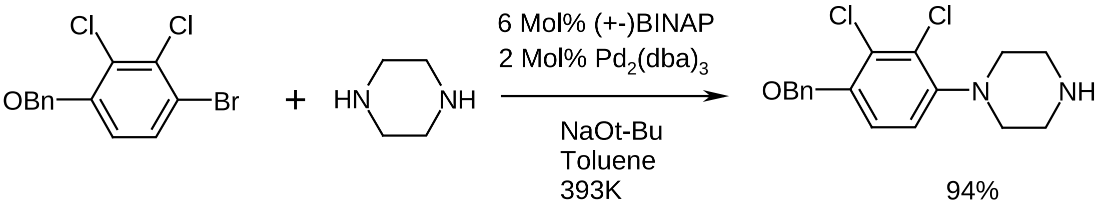
**Scheme 1.5:** Pd-catalyzed amination of substituted bromobenzene

Similarly, Hartwig and Louie[23] reported that LiHMDS was also useful base for such transformations (*Scheme1.6).* They also reported two different complexes as catalysts; $[(o\text{-tol})_3P]_2PdCl_2$ and $[(o\text{-tol})_3P]_2Pd$ effectively catalyzed the amination reaction.



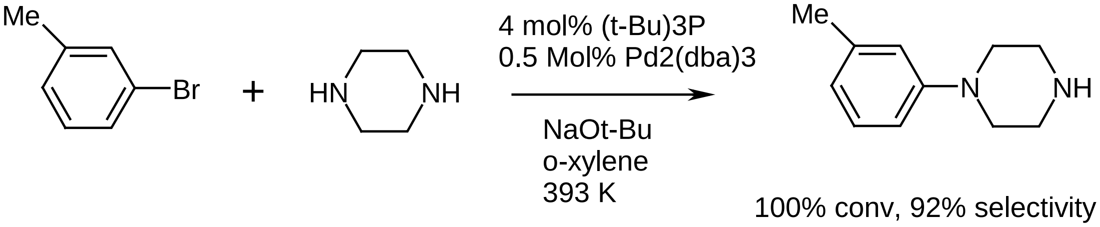
**Scheme1.6:** Amination of bromobenzene with cyclohexane

Morita[25] have utilized the BINAP/Pd- catalyst system to prepare arylpiperazine, which are metabolites of *Aripiprazole*, an anti-psychotic agent (*Scheme 1.7).*



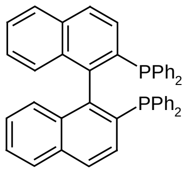
**Scheme 1.7:** BINAP/Pd for amination of bromobenzene with arylpiperazine

Other ligands are useful in C-N bond coupling of aryl bromides and cyclic amines. In 1998, Nishiyama[26] at Tososh Corporation reported that tri-*tert*-butylphosphine is an effective supporting ligand for the palladium- catalyzed arylation of piperazine, *Scheme 1.8.* The ($t$-Bu)$_3$P/Pd-catalyst provide the product with 1 mol% Pd in high selectivity.

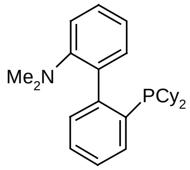


**Scheme 1.8:** ($t$-Bu)$_3$P/Pd for amination of bromobenzene with arylpiperazine

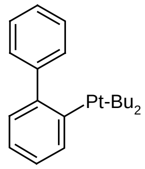
The Buchwald[27,28] subsequently disclosed that sterically hindered Phosphine based ligands (such as **1, 2,3** and **4**) and ferocene-based monophosphines such as **5** was useful ligand that acyclic secondary amines and amination of aryl/alkyl halides. These ligands gives very high yield for normal amination and good yield for heteroamines also.[29,30]



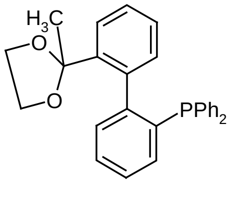
**1**



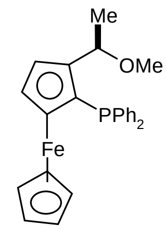
**2**



**3**



**4**



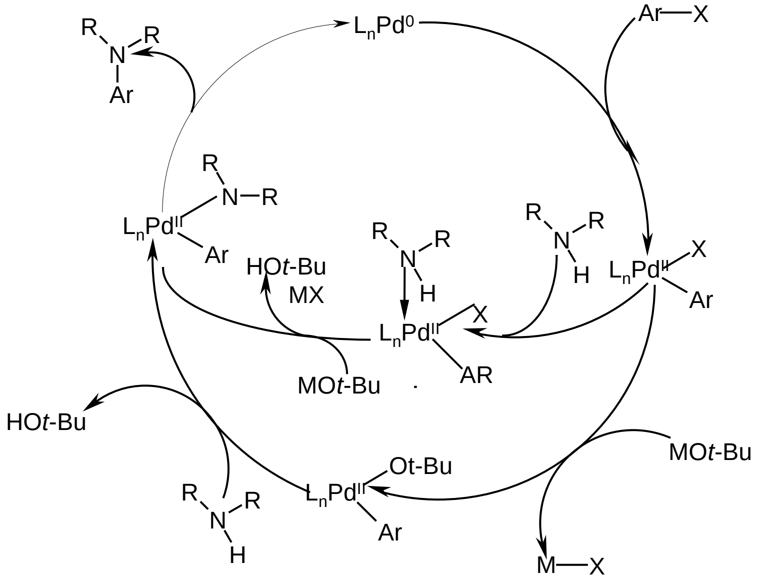
**5**

### 1.2.2 Mechanism of palladium-catalyzed amination

Although these reports greatly expanded the scope and utility of the amination reaction, these catalytic systems enjoyed a relatively narrow substrate scope compared to subsequent generations of catalysts developed both by the Buchwald[31] and Hartwig[32] groups. Through iterative cycles of ligand design, methodology studies, and mechanistic investigations, highly active and broadly useful catalyst system have been developed.

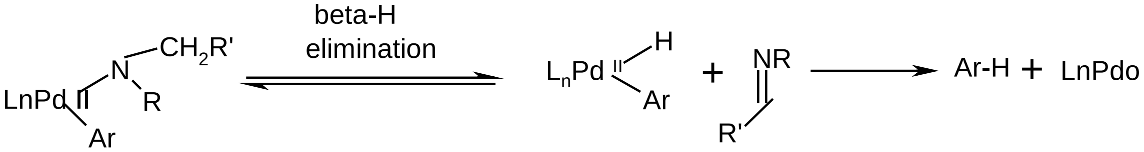
The accepted mechanism for the amination reaction is shown in *Scheme 1.9.* The catalytic cycle begins with the oxidative addition of arylhalides by Pd (0). The palladium (II) aryl amide can be formed either by direct displacement of the halide by the amide or via the intermediacy of a palladium (II) alkoxide.[33] Reductive elimination of the C-N bond results in the formation of the desired arylamine and regeneration of the Pd (0) catalyst.[34,35]

In the coupling of more challenging substrate, e.g. chlorobenzene, hetero-cyclic amines etc, reduction of arylhalide is frequently observed.[36]



**Scheme 1.9:** Reaction mechanism of palladium-catalyzed amination

Specifically, in the reaction of electron-rich arylhalides, reduced arene is a major by-product arises when the palladium amide can undergo β-hydride elimination to generate an imine and a palladium (II) arylhalides (*Scheme1.10).* Subsequent reductive elimination yields the reduced arene and regenerates the Pd (0) catalyst. Thus one of the major challenges confronted in the development of more efficient amine arylation catalysts was to shut down this unwanted side reaction.



**Scheme 1.10:** β- H elimination mechanism

The above examples indicate that important development of palladium catalyzed amination of arylhalides reported in literature. *Table 1.3* shows an exhaustive account of Pd-catalyzed amination reactions.

**Table 1.3:** Literature survey of palladium catalyzed amination of aryl halides

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 1 | [(o-tol)$_3$P]$_2$PdCl$_2$ | (o-tol)$_3$P | Bu$_3$Sn-NEt$_2$ | 373 | | Toluene | Using electronically neutral aryl bromide | 61-81 | Migita et. al.[17] (1983) |
| 2 | (Ph$_3$P)$_4$Pd | PPh$_3$ | Intramolecular amine (lavendamycin) | 353 | | Dioxane | Total Synthesis of lavendamycin | 84 | Boger et. al.[19] (1984) |
| 3 | Pd$_2$(dba)$_3$ | DPPFOMe<br>(+-)-PPFA | 4-tert-butylbromobenzene & di-n-butylamine | 353 | NaOt-Bu | Toluene | This system give high activity for aliphatic amines | 97<br>92 | Togni et. al.[37] (1990) |
| 4 | [(o-tol)$_3$P]$_2$PdCl$_2$ | (o-tol)$_3$P | Ar-Br & Bu$_3$Sn-NEt$_2$ | 353-378 | | Toluene | In situ by amine exchange reaction | 55-88 | Buchwald et. al. [22] (1994) |
| 5 | Pd(dba)$_2$/2(o-tol)$_3$P | (o-tol)$_3$P | Ar-Br & H-NR$^2$R$^3$ | 338-383 | NaOt-Bu | Toluene | Use first time tin free substrate | 71-89 | Buchwald et. al.[24] (1995) |
| 6 | Pd | (o-tol)$_3$P | Ar-X & H-NR$_2$ | 373 | MOt-Bu | Toluene | Mechanistic study, Regenerate Pd$^o$ | 75-90 | Hartwig et. al.[23] (1995) |
| 7 | Pd$_2$(dba)$_3$ | (o-tol)$_3$P<br>(+-)BINAP | 3,5 dimethyl bromobenzene & *N*-methylpiperazine | 353 | NaOt-Bu | Toluene | 2 mol % ligand | 47-98 | Hartwig et. al.[33](1996) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 8 | $DPPFPdCl_2$ | DPPF | Br-Br & cyclic amine | 373 | NaOt-Bu | THF | $DPPFPdCl_2$ added DPPF improves the yield | 87 | Hartwig et. al.[36] (1996) |
| 9 | $Pd_2(dba)_3$ | BINAP | Aryl bromide & acyclic secondary amines | 353 | NaOt-Bu | Toluene | Substituted group on aryl bromides varies the yields | 79 | Buchwald et. al.[38] (1996) |
| 10 | $Pd_2(dba)_3$ | $(o\text{-}tol)_3P$ | 4-iodotoluene & secondary amines | 373 | NaOt-Bu | Dioxane | This protocol useful for cyclic and acyclic secondary amines | 78 | Buchwald et. al[39] (1996) |
| 11 | $Pd(OAc)_2$ | Ferrocene based diphosphines | Aryl chloride & aliphatic amine | 358 | NaOt-Bu | Toluene | Using new ferrocene based diphosh For aliphatic amine | 94 | Zanetti et. al.[40] (1996) |
| 12 | $Pd_2(dba)_3$ | (+-)-PPF-OMe | Ester substituted Ar-Br & Cyclic amine | 373 | $Cs_2CO_3$ | Toluene | Ester group aryl halides were used | 80 | Buchwald et. al.[27] (1997) |
| 13 | $Pd_2(dba)_3$ | (+-)-BINAP | Aryl iodide & secondary amine | R T | NaOt-Bu | Dioxane | In this system used 18-C-6 for the improvement | 90 | Buchwald et. al.[41a] (1997) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition |  |  | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | Temp. K | Base | Solvent |  |  |  |
| 14 | Palladacycle | PdCycle | Aryl chloride & cyclic amine | 408 | KOt-Bu | Toluene | Using palladacycle shows that good activity for aryl chloride | 74 | Beller et. al.[42] (1997) |
| 15 | $(Cy_3P)_2PdCl_2$ | $Cy_3P$ | Aryl chloride & Cyclic amine | 393 | NaOt-Bu | Toluene | This Protocol active for aryl chlorides | 65 | Reddy et. al.[43] (1997) |
| 16 | $Pd_2(dba)_3$ | BINAP | 1,3-dibromobenzene & 1,3 diaminophenyl | 373 | NaOt-Bu | Toluene | Synthesis of poly(imino-1,3-phenylene) | 86 | Kanbara et. al.[44] (1997) |
| 17 | $Pd_2(dba)_3$ | DPPF | Substituted aryl bromide & aniline | 373 | NaOt-Bu | THF | Synthesis of new ligand through this method. | 95 | Frost et. al.[45] (1997) |
| 18 | $Pd_2(dba)_3$ | DPPF | Aryl bromide & Aniline | 363 | NaOt-Bu | Toluene | Bis-amination synthesis of tryarylamine | 72 | Marder et. al.[46] (1997) |
| 19 | $Pd(OAc)_2$ | Ferrocene based diphosphines | Aryl chloride & aliphatic amine | 358 | NaOt-Bu | Toluene | Using new ferrocene based diphosh For aliphatic amine | 89 | Imwinkelried et. al.[47] (1997) |
| 20 | $Pd_2(dba)_3$ | (+-)BINAP | Piperazine & Ar-Br | 393 | NaOt-Bu | Toluene | Synthesis of arylpiperazines | 94 | Morita et. al.[25] (1998) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition |  |  | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | Temp. K | Base | Solvent |  |  |  |
| 21 | $Pd_2(dba)_3$ | BINAP | TBS- Protected compound | 358 | NaOt-Bu | Toluene | Total Synthesis of hydroxitraconazole, as a antifungal agent | 81 | Tanoury et. al.[48] (1998) |
| 22 | $Pd_2(dba)_3$ | $(t\text{-}Bu)_3P$ | Ar-Br & Piperazine | 393 | NaOt-Bu | *o*-xylene | Gives 100 % conv. | 92 | Nishiyama et. al.[26] (1998) |
| 23 | $Pd_2(dba)_3$ | 2-dicyclohexyl phosphine 2'-dimethyl amine bipheny | Ar-Br & Morpholine | 353 | $K_3PO_4$ | DME | -COOMe<br>-COMe group on aryl halides | 81-82 | Buchwald et. al.[49] (1998) |
| 24 | 1 mol % Pd $(OAc)_2$ | 2,2'-di-t-butyl feroccen | Aryl chloride & Cyclic amine | 373 | NaOt-Bu | Toluene | Feroccen based phosphine ligand gives good activity for aryl chlodies | 81-85 | Hamann et. al.[50] (1998) |
| 25 | $Pd_2(dba)_3$ | BINAP | Aniline & substituted arylbromide | 363-373 | NaOt-Bu | Toluene | Synthesis of acridone derivatives | 81 | Snieckus et. al.[51] (1998) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 26 | $Pd(dba)_2$ | Substituted BINAP | Amino BINAP & bromobenzene | 333 | NaOt-Bu | Toluene | 100% conv. Of amino BINAP and synthesis new ligand | 99 | Kocovsky et. al.[52] (1998) |
| 27 | $Pd(OAc)_2$ | DPEphos | 2,6-dimethyl bromobenzene & 2,6-di-iso-propyl aniline | 373 | NaOt-Bu | Toluene | This system useful for the satirically hindered aryl halides & aryl amines | 90 | Buchwald et. al.[53] (1998) |
| 28 | $Pd(OAc)_2$ | DPPF | Aryl bromide & pyrrole | 393 | NaOt-Bu | Toluene | Amination of N-containing heterocyclic compound | 87 | Hartwig et. al.[54] (1998) |
| 29 | $Pd(OAc)_2$ | DPPF | Benzophenone hydrazone & aryl bromide | 363 | $Cs_2CO_3$ | Toluene | Amination of Benzophenone hydrazone | 81 | Hartwig, et. al.[32] (1998) |
| 30 | $Pd_2$ | BINAS-6 | Aryl halides & arylamines | 348-383 | NaOH | Water-methanol | Two-phase protocol | 70-91 | Boche et. al.[55] (1998) |
| 31 | $Pd_2(dba)_3$ | (+-)BINAP | 2-bromo Napthalene | 353 | NaOt-Bu | Toluene | Synthesis of quinazoline, as a antbacterial agent | 59 | Kung et. al.[56] (1999) |
| 32 | $Pd_2(dba)_3$ | P,N & O,P chelating ligands | Br-Br & cyclic amine | 373 | NaOt-Bu | Toluene | Using P,N and O,P-Chelating ligands | 98 | Guram et.al.[57] (1999) |
| 33 | 1 mol % $Pd(OAc)_2$ | 0.8 mol % $(t\text{-}Bu)_3P$ | 2-metyl bromobenzene & Morpholine | R T | NaOt-Bu | Toluene | This system active at room temperature for aryl bromide & aryl chloride | 96 | Hartwig et. al.[58] (1999) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 34 | $Pd_2(dba)_3$ | Heterocyclic carbene ligands | 4-metyl bromobenzene & Cyclohexylamine | R T | KOt-Bu | Dioxane | Using heterocyclic carbene ligands reaction goes at room temperature | 83 | Nolan et. al.[59] (1999) |
| 35 | $Pd_2(dba)_3$ | Xantphos | 4-bromobenonitrile & N-ethylaniline | 353 | $Cs_2CO_3$ | Toluene | This ligand is particularly effective in the coupling of electron – deficient alkylamines & electron – deficient arylbromides | 85 | Buchwald et. al.[30] (1999) |
| 37 | $Pd(dba)_2$ | $(t\text{-Bu})_3P$ | 2-bromotoluene & diphenylamine | R T | NaOt-Bu | Toluene | Synthesis of arylamines | 97 | Hartwig et. al.[60] (1999) |
| 39 | $Pd(dba)_2$ | New cyclic phosphine ligand | N-phenylpiperazene & 4-chlorobenzonitrile | 378 | NaOt-Bu | Toluene | New ligand using for aryl chloride | 90 | Guram, et. al.[61] (1999) |
| 40 | $Pd_2(dba)_3$ | (+-)BINAP | 1,2-diphenyl ethylenediamine 2-iodonaphthalene | 383 | NaOt-Bu | Dioxane | β-hydride elimination type | 70 | Denmark et. al.[62] (1999) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 41 | $Pd(OAc)_2$ | Xantphos | Benzophenone hydrazone & aryl bromide | 353 | NaOt-Bu | Toluene | Amination of Benzophenone hydrazone | 98 | Buchwald et. al.[63] (1999) |
| 42 | $Pd_2(dba)_3$ | (+-) BINAP | 2,4-diethylazetidine and ortho-bromo toluene | 343 | KOt-Bu | Toluene | N-arylation of chiral azetidines with high yield | 85 | Maritetti et. al.[64] (2000) |
| 43 | $Pd_2(dba)_3$ | 2-dicyclohexyl phosphine 2'-dimethyl amine bipheny | 4- bromotoluene & Di-n-butylamine | R T | NaOt-Bu | DME | Phosphine amine ligands gives high activity at room temperature. | 96 | Buchwald et. al.[65] (2000) |
| 44 | $Pd_2(dba)_3$ | 2-dicyclohexyl phosphine 2'-dimethyl amine bipheny | Aza-crown ethers & aryl bromide | 353 | NaOt-Bu | Toluene | Amination aza-crown ethers Pata-postion gives high yield & o- position gives low yield | 41-87 | Buchwald et. al.[66] (2000) |
| 45 | $Pd_2(dba)_3$ | 2-dicyclohexyl phosphine 2'-dimethyl amine bipheny | *N*-methyl piperazine & Ar-Br | 353 | NaOt-Bu | Toluene | Synthesis of chiral bidentate ligands | 95 | Kranich et. al.[67] (2000) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition |  |  | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | Temp. K | Base | Solvent |  |  |  |
| 46 | $Pd(OAc)_2$ | (+-)BINAP | Ar-Br & cyclic amine | 373 | $Cs_2CO_3$ | Toluene | Using 10 mol % 18-crown-6 | 93 | Torisawa et. al.[68] (2000) |
| 47 | $Pd_2(dba)_3$ | (+-)BINAP | Aniline derivatives & 4-iodoethylbenzoate | 373 | NaOt-Bu | Toluene | Synthesis of retinoic nuclear receptor ligand | 84 | Kagechika et. al.[69] (2000) |
| 48 | $Pd_2(dba)_3$ | DPPF | 4-bromobenezonitrile & diphenylamine | 343 | NaOt-Bu | o-xylene | Synthesis of 4-diphenylaminostysene | 83 | Stupp et. al.[70] (2000) |
| 49 | Pd $(OAc)_2$ | Dicyclohexyl-o-biphenyphosphine | Fictionalized aryl chloride & cyclic amines | 373 | $K_3PO_4$ | DME | Dicyclohexyl-o-biphenyphosphine is an excellent supporting ligand | 90 | Buchwald et. al.[71] (2000 |
| 50 | $Pd_2(dba)_3$ | (+-)-BINAP | 1,2-dibromobenzene & α-methylbenzylamine | 408 | NaOt-Bu | Toluene | Formation of C2-symmetric diamine. | 61 | River et. al.[72] (2000) |
| 51 | $Pd(OAc)_2$ | BINAP | Substituted Aniline & substituted aryl bromide | 373 | $Cs_2CO_3$ | Toluene | Synthesis of phenazine derivatives | 99 | Kamikawa et. al.[73] (2000) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 52 | Pd | 3 mol % $(t\text{-}Bu)_3P$ | Ar-Br & Indoles | 373 | $Cs_2CO_3$ | Toluene | Amination of indoles | 77 | Watanable et. al.[74] (2000) |
| 53 | $Pd_2(dba)_3$ | BINAP Type Phosphine ligand | Ar-Br & Indoles | 353-393 | NaOt-Bu | Toluene | Amination of indoles | 87 | Old et. al.[75] (2000) |
| 54 | $Pd(OAc)_2$ | $(t\text{-}Bu)_3P$ | Bromothiophene & diphenyl amine | 393 | NaOt-Bu | Toluene | Amination of Bromothiophene | 69 | Yamamoto T, et. al.[76] (2000) |
| 55 | $Pd(OAc)_2$ | BINAP | Electron deficient thiophene & secondary amine | 383 | $Cs_2CO_3$ | Toluene | Using Electron deficient thiophene | 94 | Luker et. al.[77] (2000) |
| 56 | $Pd(OAc)_2$ | DPPP | 1-methyl piperazine & substituted aryl abromide | 358 | NaOt-Bu | Toluene | Synthesis on new ligands | 97 | Lopez R, et. al,[78] (2000) |
| 57 | $Pd_2(dba)_3$ | aminophosphine ligand | Vinylogous amide & aryl bromide | 353 | $Cs_2CO_3$ | Toluene | Amination of Vinylogous amide | 87 | Edmonson et. al.[79] (2000) |
| 58 | | | Aryl chloride & secondary amines | 373 | KOt-Bu | Toluene | Amination reaction without catalyst and ligand. | 74-92 | Beller et. al,[80] (2001) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 59 | Pd | Feroccen, diphos | Aryl bromide & amine | 353 | NaOt-Bu | Toluene | Kinetic study | 50-74 | Guari et. al.[81] (2001) |
| 60 | $Pd[P(t\text{-}Bu)_3]_2$ | $P(t\text{-}Bu)_3$ | Aryl chloride & amines | 363 | NaOt-Bu | Toluene | Mechanism of aryl chloride amination: base induced | 90 | Hartwig, et. al.[82] (2001) |
| 61 | Pd | BINAP & 18-C-6 | Aryl halides & Piperazine | 383 | $K_2CO_3$ | Toluene | Synthesis of various piperazine derivatioves, | 78 | Torisawa et. al.[83] (2002) |
| 62 | $Pd(OAc)_2$ | BINAP | Aryl halides & arylamines | 363 | NaOt-Bu | Toluene | Synthesis of thienocarbazole | 30-75 | Queiroz et. al.[84] (2002) |
| 63 | $[PdBr(PR_3)]_2$ | | Aryl halides & amines | R T | NaOt-Bu | THF | Amination of aryl chloride and bromides & study of their rates | 82-98 | Hartwig et. al.[85] (2002) |
| 64 | $Pd_2(dba)_3$ | BINAP | Aryl halides & aryl amines | 383 | NaOt-Bu | Toluene | Synthesis of tridentate Bis(Oxazoline) ligand | 30-72 | Guiry et. al.[86] (2002) |
| 65 | Pd | | Amino acids & aryl halides | Microwave | $Na_2CO_3$ | $H_2O$/ MeCN | Synthesis of 4-aryl phenylalanines using microwave radiation. | 86 | Gong et. al.[87] (2002) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 67 | $Pd_2(dba)_3$ | Bulky electron rich ligands | Aryl halides & secondary amines | 338 | $LiNTMS_2$ | THF | Amination of keto, ester substituted aryl halides | 85-95 | Buchwald et. al.[88] (2002) |
| 68 | $Pd(dba)_2$ | $(t\text{-}Bu)_3P$ | Five member heterocyclic halides & secondary amines | R T- 393 | NaOt-Bu | Toluene | Amination of five member hetrocyclic halides | 90 | Hartwig, et. al.[89] (2002) |
| 69 | Pd | BINAP | Aryl halides & Triflates | 323 | NaOt-Bu | Toluene | Mechanistic studay of aryl halides & triflates | 85-92 | Hartwig[90](2002) |
| 70 | $Pd_2(dba)_3$ | BINAP | Aryl bromide & amine resins | 353 | NaOt-Bu | Dioxane | Amination of amine resins | 63 | weigand, et. al.[91] (2002) |
| 71 | Pd | $PPh_3$ | Intramolecular amine | 383 | $K_2CO_3$ | Toluene | Intramolecular amination. | 91 | Brain et. al.[92] (2003) |
| 72 | $Pd_2(dba)_3$ | BINAP | 2-bromopyridine & cyclohexeneimine | 353 | KOt-Bu | Toluene | Arylation of azidrines | 53-95 | Yudin et. al.[93] (2003) |
| 73 | $Pd(OAc)_2$ | BINAP | Primary amine & aryl halides | 373 | Cs2CO3 | Toluene | Sulpher containing reactant used | 50-90 | Ferreira et al.[94] (2003) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 74 | $Pd_2(dba)_3$ | BINAP | Aryl iodides derivatives & halide derivative | 373 | $Cs_2CO_3$ | Toluene | Synthesis of anthranilic acids | 40-65 | Csuk et. al.[95] (2003) |
| 75 | Pd-Crbene complex | Bulky electron rich ligands | Aryl chlorides & aryl amines | 338 | KOt-Bu | Ionic Liquid | Using ionic liquid and new pd- carbene complex | 80-94 | Ismail et. al.[96] (2004) |
| 76 | $Pd_2(dba)_3$ | P(i-$BuNCH_2CH_2$ | Aryl chloride & heterocyclic amine | 373 | NaOt-Bu | Toluene | Amination of aryl chlorides . | 81-88 | Urgaonkar et. al.[97] (2004) |
| 77 | Pd-Cu | $PPh_3$ | Aryl iodide & amino acids | Microwave | | | Reaction in microwave | 55-90 | Xu et. al.[98] (2004) |
| 78 | Pd | BINAP | Aryl halides & amine | 393 | NaOt-Bu | Toluene | Good yield for Chloride | 65-92 | Beller et. al.[99] (2004) |
| 79 | Pd | BINAP<br>New Ligand | Aryl halides & amines | 373 | NaOt-Bu | Toluene | Novel ligands | 60-95 | Singer et. al.[100] (2004) |
| 80 | Pd di-nuclear complex | | Aryl chloride & secondary amines | RT | KOt-Bu | THF | Novel Pd-complex. | 76-86 | Vilar et. al.[101] (2004) |

| No. | Catalyst | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 81 | $Pd_2(dba)_3$ | Phospha-adamantanes | Aryl halides & Amines | 298-383 | NaOt-Bu | Toluene | New ligand | 93-98 | Capretta et. al.[102] (2004) |
| 82 | Pd $(OAc)_2$ | Phosphine | Aryl chloride & amine | MW | NaOt-Bu | Toluene | Controlled MW used | 60-90 | Maes et. al.[103] (2004) |
| 83 | $Pd_2(dba)_3$ | Phosphine | Aryl halides & aryl amine | 373 | NaOt-Bu | Toluene | C-N & C-C coupling | 60-87 | Verkade et. al.[104] (2005) |
| 84 | Pd(Pt-$Bu_3$) | $(t\text{-}Bu)_3P$ | Heterocyclic aryl chloride & amine | R T- 393 | NaOt-Bu | DME | Activation of aryl chlorides | 85-99 | Hartwig et. al.[105] (2005) |

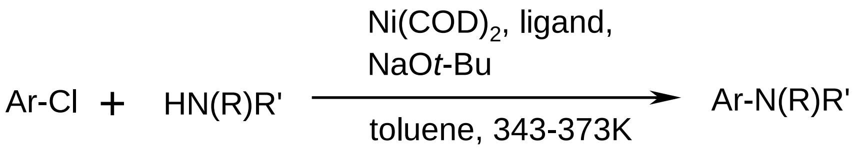
## 1.3 Nickel Catalyzed Amination of Arylhalides

The palladium catalyzed amination of aryl bromides,[8-14] iodides,[15-17] and triflates[14] with primary and secondary amines and anilines has provided a new route to a wide variety of arylamines. Buchwald and his group has expanded the aryl amination methodology to include aryl chlorides, stems from the fact that they are both the least expensive and most widely available aryl halides. Many of the methods used to extend the scope of palladium-catalyzed C-C and C-N bond forming reactions to include aryl chlorides are limited by the need for substrate that activated by electron-withdrawing groups or by complexed transition metal fragments.[106] While electron rich phosphines have been utilized,[27,28] these do not appear to be viable ligands for palladium-catalyzed aminations; increased electron density on the metal center decrease the rate of reductive elimination relative to $\beta$-hydride elimination, leading to lower yields of coupled products and increased amount of arene side products.

To overcome these limitations of palladium-catalyzed amination, nickel is the alternative catalyst.

### 1.3.1 History of Nickel-Catalyzed Amination

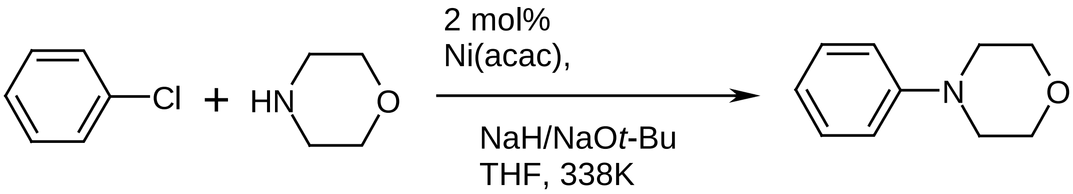
In 1997 Buchwald and Wolfe[41b] shown that amination of aryl chlorides using catalytic amounts of $Ni(COD)_2$ and DPPF or 1,10-phenanthroline in the presence of sodium *tert*-butoxide. This procedure has a broad substrate scope: electron-rich or electron-poor aryl chlorides, as well as chloropyridines derivatives can be combined with primary and secondary amines to give desired arylamine products in moderate to excellent yields (63 to 91%) (*Scheme1.11).* Additionally a procedure which utilizes the air-stable pre-catalysts (DPPF)$NiCl_2$ or (phen.)$NiCl_2$ is also used.



$$\text{Ar-Cl} + \text{HN(R)R'} \xrightarrow[\text{toluene, 343-373K}]{\text{Ni(COD)}_2\text{, ligand, NaO}t\text{-Bu}} \text{Ar-N(R)R'}$$

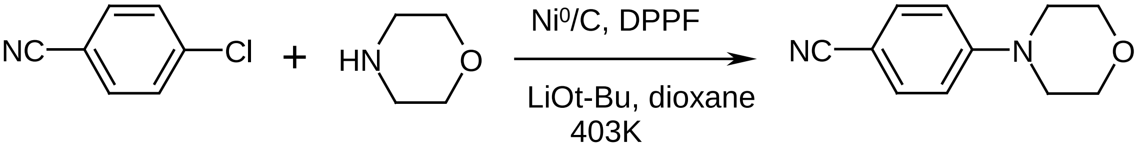
**Scheme1.11:** Amination of chlorobenzene using $Ni(COD)_2$ catalyst

1998 to 2002 Yves Fort[107-111] has published nickel-catalyzed amination of aryl chlorides results. Fort used Ni(COD) and 2,2'-bipyridine as a ligand for amination of aryl chlorides as well as substituted aryl chlorides such as electron-rich and electro-poor with aryl amine as well as heteroamines. A new aryl amination protocol has been developed using catalyst combination prepared from $Ni(acac)_2$ associated a sterically hindered dihydroimidazoline carbene ligand. A high acitivity (yields75-98%) was attained using, 2 mol% Ni/carbene cluster *(Scheme 1.12).*



**Scheme 1.12:** Ni-catalyzed amination of chlorobenzene

Lipshutz B.H.[112] reported $Ni^0/C$ heterogeneous catalyst with DPPF for the aromatic aminations (*Scheme 1.13).* He varies bases the LiO*t*-Bu (91% yield) gave statistically significant grater rates of coupling and ultimately isolated yields than NaOt-Bu (16% yield) or KO*t*-Bu (15% yield). He has not discussed about recycle of catalyst.



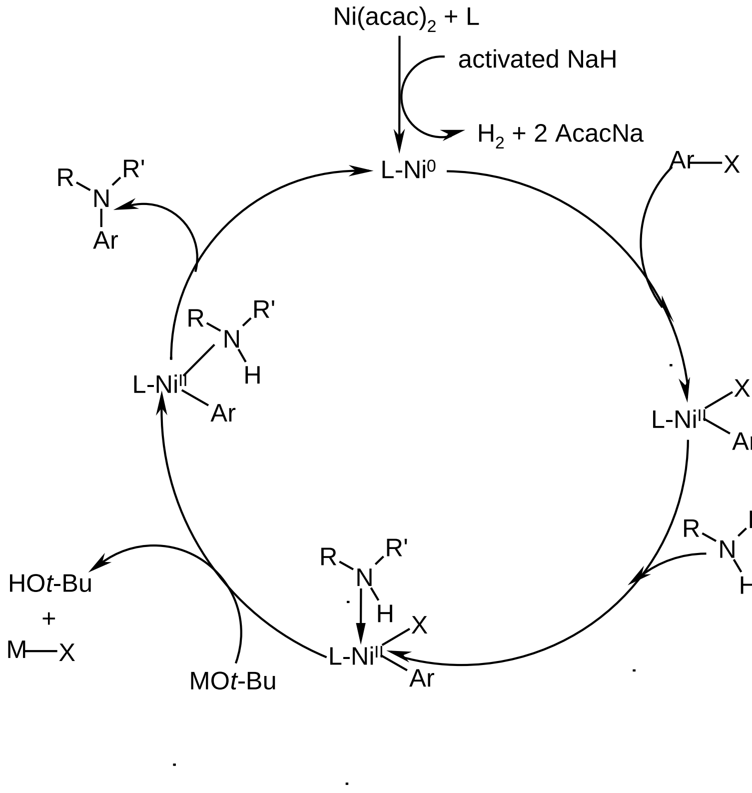
**Scheme 1.13:**Ni-catalyzed amination of chlorobenzene with morpholine

A detailed account of nickel-catalyzed amination of arylhalide is presented in *Table 1.4.*

### 1.3.2 Mechanism of Nickel-Catalyzed Amination

Yves Fort proposed mechanism for the amination of aryl chlorides.[107] There is little mechanistic information about coupling conducted with the Ni(0)/SIPr.HCl/NaO*t*-Bu catalyst combination, but the catalytic cycle for the amination reaction is presumably similar to that postulated for the palladium-catalyzed amination of arylhalides using

Pd/carbene system.[35] The first step involves formation of Ni(0) by reduction of Ni(acac)$_2$ with NaOt-Bu activated sodium hydride followed by coordination of the carbene generated form SIPr.HCl to the metal center. Transmission electron spectroscopy coupled energy-dispersive X-ray spectra of the Ni/carbene catalyst thus obtained revealed a homogeneous distribution of uniformly sized amorphous and subnanometrical Ni(0) particles. The strong electron donating property of the carbene ligand facilitates the oxidative addition of the aryl chloride to Ni(0). From results obtained with anilines and primary amines. Aryl amido nickel species are involved in the second step of the catalytic cycle.



**Scheme1.14:** Proposed mechanism of nickel-catalyzed amination

Finally stric bulk of the carbene generated from SIPr.HCl may accelerate the C-N bond forming reductive elimination. On the basis of these observations, a likely pathway, shown in *Scheme1.14.*

**Table 1.4:** Literature survey of nickel-catalyzed amination of arylhalides

| No. | Catalyst system | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 1 | Ni(COD)$^2$ | DPPF | Aryl chlorides & aryl amines | 373 | NaOt-Bu | Toluene | Use of various ligand for chloro activation | 62-85 | Buchwald et al.,[106] (1997) |
| 2 | Ni (0) | $PPh_3$ / Bipy /Phen. | Aryl halide & Piperidine | 326 | NaOMe | THF | Using Ni As a reagent form | 40-90 | (1)Fort Y, et. al.[110] (1998) |
| 3 | Ni/C | $PPh_3$ / Bipy /Phen. / o-toly / DPPF | Aryl chloride & amine | 403 | $Cs_2CO_3$ | Toluene / Dioxane | Supported Ni using for chloro activation | 78-91 | (2) Lipshutz B.H, et. al.[112] (2000) |
| 4 | Ni(0) | Bipy | Piperazine & aryl chloride | 343 | NaH / t-AmONa | THF | Mono as well as bis amination of piperazene | 41-86 | (3) Fort Y, et.al,[109] (2000) |
| 5 | Ni (0) | Bipyridine | Aryl chlorides and amines | 338 | NaH/ NaOt-Am | THF | Using Bipyridine as a ligand for piperazine amination. | 23-90 | Zhang Ze,[113] (2000) |

| No. | Catalyst system | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 6 | Ni(0) | Bipy | Secondary amine & aryl dichloride | 343 | NaH / t-AmONa | THF | Mono as well as di-amination of aryl dichloride | 44-85 | (4) Fort Y, et.al.[111] (2001) |
| 7 | 2 mol % $Ni(acac)_2$ | 8 mol %Carbene | Morpholine & Aryl chloride | 340 | NaH/ NaOt-Bu | THF | Using various carbenes are the ligands | 12-99 | (5) Fort Y, et.al,[108] (2001) |
| 8 | Ni Complex | Carbene | Morpholine & Aryl chloride | 340 | NaOt-Bu | THF | Using various ligands | 55-99 | (6) Fort Y, et.al,[107] (2002) |
| 9 | Ni/C | DPPF | Aryl chlorides & amines | 423 | LiOt-Bu | Toluene | Supported catalyst and varies ligand | 70-80 | Lipshutz B.H, et. al.[114] (2003) |

## 1.4 Copper-catalyzed amination

The classic technique for the construction of triarylamines has been the hallmark of Ullmann condensation.[115] As usually practiced, the reaction involves the condensation of a diphenylamine and an unactivated aryl halide with catalysis by some form of copper (metal, alloy, Cu (I) or (II) salt) in the presence of added base. The reaction is noted for its unreliable nature and sensitivity to catalyst type. Strongly aggressive conditions involving high temperature and extended reaction times are generally needed to secure best moderate yields. In an variant, bis (arylation) of a substituted aniline with 2 equivalents of an aromatic halide in which two or perhaps all three of the aromatic rings are identically substituted. Yields tend to be substantially poorer in these cases.[115]

Attempts have been made to moderate the harshness of the reaction conditions. Frechet and Gauthier reported that crown ethers induce rate accelerations and improve yields in certain Ullmann condensations.[116] The procedure however, does not obviate the requirement for high temperature, and the long reaction times (15 h in the best case) make it unattractive for large-scale industrial applications.

An area of research showing rapid progress is the application of transition metal catalysis to the formation of aromatic carbon-nitrogen bond. Aromatic amines with a wide structural variation have been successfully synthesized under exceptionally mild reaction conditions.[117] It is as yet premature to judge whether this chemistry will supplant the Ullmann condensation as the robustness and economics of a method requiring noble metal catalysis in a large scale industrial application requires demonstration, particularly in the commodity chemicals arena.[118]

### 1.4.1 Comparison with Pd-catalyzed C-N cross-coupling reactions

A serious drawback of palladium catalyzed amination protocol has been the necessity to use strong bases such as NaO*t*-Bu, which essentially limited the overall tolerance of the method to base-insensitive functional groups. In this respect Cu-catalyzed procedures requiring milder bases are an improvement, particularly for base sensitive reagents. However, with the recent introduction of special bulky ligands allowing for Pd-catalyzed amination reactions to be carried out under much milder conditions and employ soft bases, such as $K_2CO_3$, etc., there has been considerable expansion of the synthetic potential of the Buchwald-Hartwig method. Generally, in synthetic applications Pd-catalyzed amination so far has no rival. However, the potential of new ligand-assisted copper catalyzed reactions is considerable. The advantage of copper-catalyzed amination chemistry, besides the cost of metal and ligands, and the overall cost of synthetic procedure (Pd-catalyzed amination reactions, particularly those involving high-performance ligands, require a higher level of experimental work, place more stringent requirements to the quality of solvents and reagents, benefit from the use of special expensive techniques, such as inert atmosphere glove box, etc.) are associated with a different reactivity profile. Though the scope of Pd-catalyzed amination reaction is currently wider, copper catalysts permit us to address different synthetic targets. In general, copper catalysts show a better tolerance to reactive functionality, which is vulnerable to palladium catalysts. Pd and Cu catalyzed reactions may show complementary chemoselectivity. While Pd catalysis preferentially attacks aromatic amino-group, copper catalyzed reaction have richer choice of targets including amide, azole, or aliphatic amine nitrogen, which makes it possible to perform selective reactions with unprotected compounds bearing several different centers.[118,119]

### 1.4.2 History of copper-catalyzed amination

mportant information on the kinetics of amine Ullmann condensations is available. The reaction is zero order in amine with rate determining step being the loss of halide from the substrate with the reactivity order being I > Br > Cl >> F.[120] Detailed kinetics has proven difficult to extract under the heterogeneous conditions normally employed. Paine,[120] by studying a homogeneous but synthetically nonviable reaction surrogate, concluded that only copper (I) states actively participate as catalysts regardless of the oxidation level of the added copper. Additionally, despite the apparent heterogeneity of the reaction, the nucleophillic species is considered to be a soluble amine cuparate.

Rate accelerations have been reported in the related, industrially important Ullmann condensation of phenols leading to diphenyl esters. Careful work by Weingarten[121] clearly demonstrated that impurities present in his reaction solvent, diglyme, imparted enhanced catalytic activity. Such activity was destroyed by LAH treatment and distillation of the solvent. Subsequently, this impurity was identified as diester and several related simple diesters are found to invoke this positive effect. Paradoxically, other structurally similar diesters produced no such effect. A mechanistic rationale for this phenomenon was not identified but increased catalyst solubility was suspected and catalyst competency appeared to be related to the ligating ability of the ligand. Bryant and Dadeville[122] have extended the usefulness of the effect to the copper (I) catalyzed methanolsis of aryl bromides to form methyl aryl esters. Here the effect was explained on the basis of stabilization and solubilization of the copper (I) catalyst. Unfortunately, the direct transfer of such approaches to the amine Ullmann condensation is not possible. Since the presence of large excesses of hydroxide together with the production of water of reaction would ensure the rapid hydrolytic destruction of these ligands. A subsequent patent reported that the copper (I) ligand, 8-hydroxyquinoline, produced a similar effect in aromatic ether formation.

Ullmann condensation of diarylamines with iodobenzene has been investigated under homogeneous and heterogeneous catalytic conditions with cuprous and cupric salts, as well as powdered copper metal. Copper catalyzed condensation of diarylamines with iodoaromatics is relatively insensitive to substituent (for substituted iodobenzenes $\rho = -0.25$; for substituted diphenylamines $\rho= 1.09$) but quite sensitive to halogen ($k_I/k_{Br} > 200$). The first direct evidence for solution catalysis after filtration of a metal catalyzed reaction was obtained. Quantitative analysis of reaction rates, product yields and catalyst characteristics leads to a comprehensive picture of the formation of soluble cuprous ion as the single active catalytic species under all conditions investigated. The hypothesis rationalizes many of the perplexing results, which typify the literature associated with copper catalyzed nucleophillic aromatic substitution.[120]

$$\mathrm{Ph_2N^-} + \mathrm{CuI} \xrightarrow{\text{fast ; irreversible}} \mathrm{Ph_2NCu} + \mathrm{I^-}$$

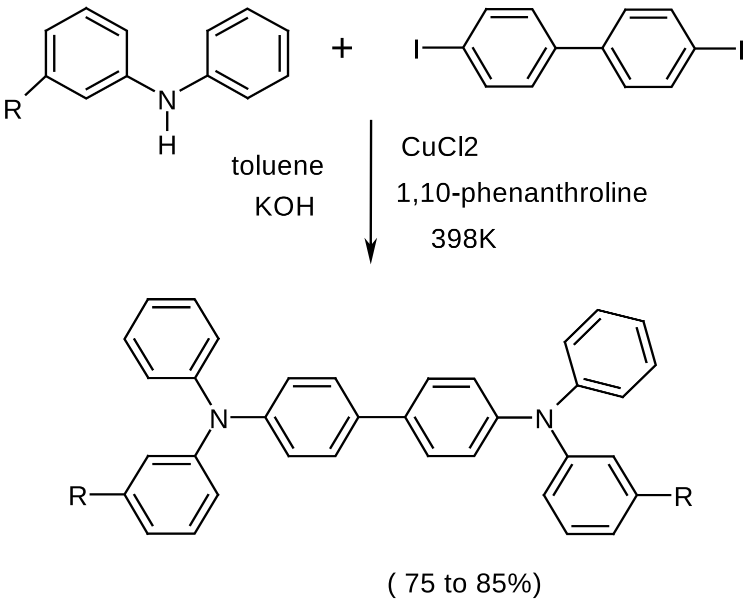
$$\mathrm{Ph_2NCu} + \mathrm{PhI} \xrightarrow{\text{slow;}k_2} \mathrm{Ph_3N} + \mathrm{CuI}$$

**Scheme 1.15:** Copper catalyzed mechanism proposed by Paine

In their investigation of copper mediated halogen exchange reactions, Bacon and Hill found that the rates varied by a factor of 200 in 13 solvents. Generally, they found that better cation complexing solvents, such as pyridines and benzonitrile, or added anions (e.g., $Cl^-$, $PhS^-$) lowered the rates, while more polar, aprotic media (dimthylaceatmide, DMF, $Me_2S$, and HMPA) gave similar rates, about 100-200 times faster than the others. There is no correlation of this kind of data with any solvent polarity parameter, so it is not clear at this time whether good copper complexing agents accelerate or retard reaction and what, if any, effect "pure solvent" polarity has.

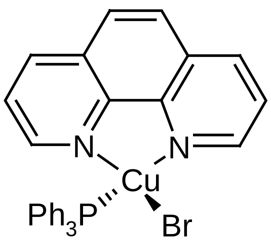
In dipolar aprotic solvents, nitranions[120] derived from anilines of enhanced *N*-acidity displace fluorine from activated aromatic compounds at room temperature. Diaryl amines thus produced are free from triarylamines, which are formed at higher temperatures when diarylamines, after *N*- deprotonation by Potassium *t*-butoxide or by the heavier alkali metal carbonates, similarly displace activated fluorine. Certain diarylamines can also be prepared by chlorine displacement in the presence of alkali metal carbonates. It is confirmed that such carbonates play only an auxiliary role in the Ullmann (copper assisted) diarylamine synthesis conducted in dipolar aprotic solvents; they may indeed impede the reaction in some instances.

In 1999 Goodbrand first time showned the ligand accelerated amination of arylhalides.[123] The ligands comprised alkyl and aryl monodentate and bidentate nitrogen-containing compounds added in an equimolar amount with respect to cuprous chloride 93.5 mol %) using KOH as a base (8 equimolar) as shown in *Scheme 1.16.* This reaction carried out at 398 K temperature in toluene, gives 75 to 85% yield of required product.



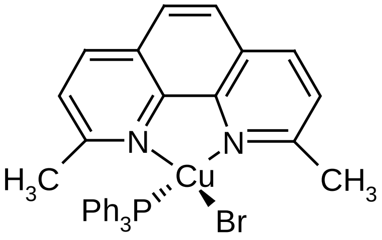
**Scheme 1.16:** Copper catalyzed amination of 4.4'-diiodobiphenyl

*Gujadhur et al,* [124] reported the mild synthetic protocols for the formation of aryl-carbon, aryl-nitrogen, and aryl-oxygen bonds based on soluble, well defined copper (I) catalysts. These protocols do not require the use of Palladium and/or expensive ligands. The catalysts **6** and **7** shown below were prepared by the addition of 1,10 phenanthroline to a solution of tris(triphenylphosphine) copper (I) bromide in chloroform at room temperature. They were the first to show these complexes as catalysts for the formation of aryl nitrogen-bonds. They found that the reaction of the diphenylamine with iodobenzene using **6** as catalyst and KO*t*-Bu as the base in toluene at 383 K was complete in 3h. However the same was completed in 90 min when **7** was used as a catalyst, *Scheme 1.17*.



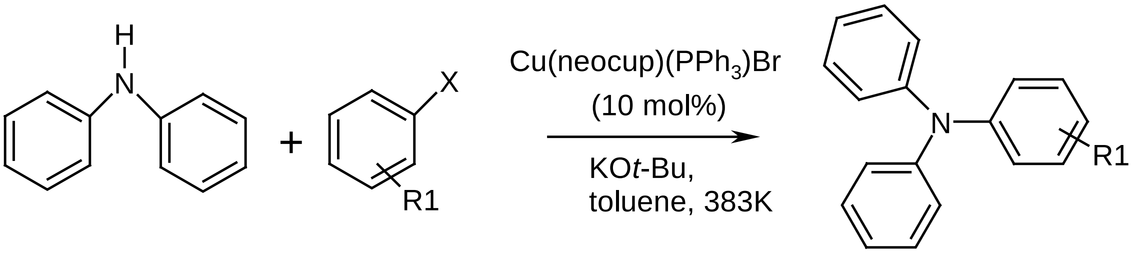
Cu(Phen)(PPh$_3$)Br

**6**



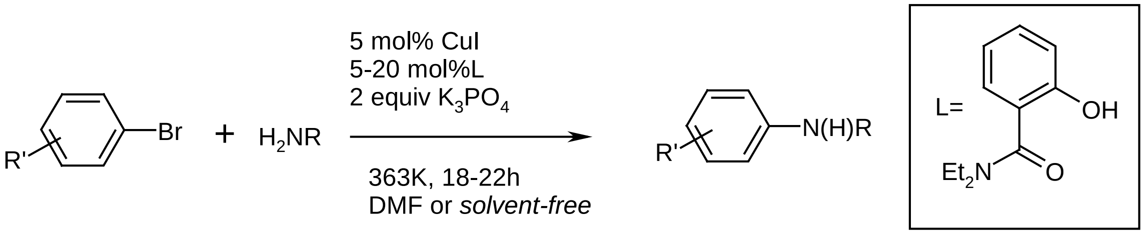
Cu(neocup)(PPh$_3$)Br

**7**



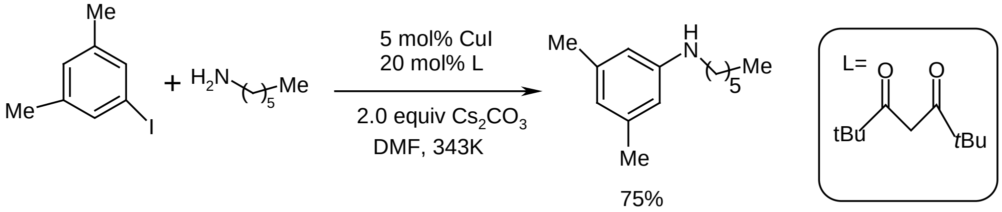
**Scheme 1.17:** Amination of arylhalides using copper (I) complex

Buchwald[125] developed an efficient copper-catalyzed amination of aryl bromides with primary alkyl amines, that uses commercially available diethylsalicylamide as the ligand, (*Scheme 1.18).* This amination reaction can be performed at 363 K in good yield. A verity of functional groups is compatible with these reaction conditions. Preliminary results show that this reaction can be carried out under solvent-free conditions with comparable yields.



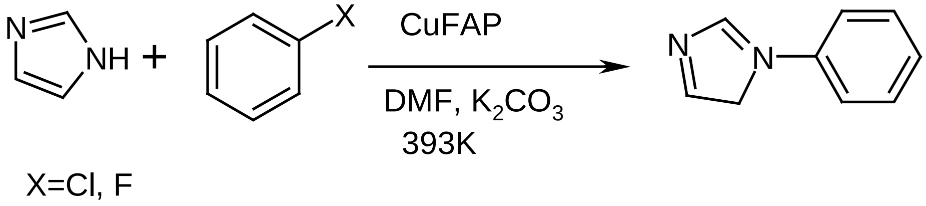
**Scheme 1.18:**Copper catalyzed amination of bromobenzene using *O*-containing ligands

Buchwald[126] examined different 2-acetylcyclohexanones as a ligand for copper-catalyzed C-N bond formation in the reaction between 5-iodo-m-xylene and n-hexylamine. While no coupling occurred at 343 K in the absence of ligand, addition of 20% of ligand resulted in the formation of the desired coupling product in 75% yield after 10h.



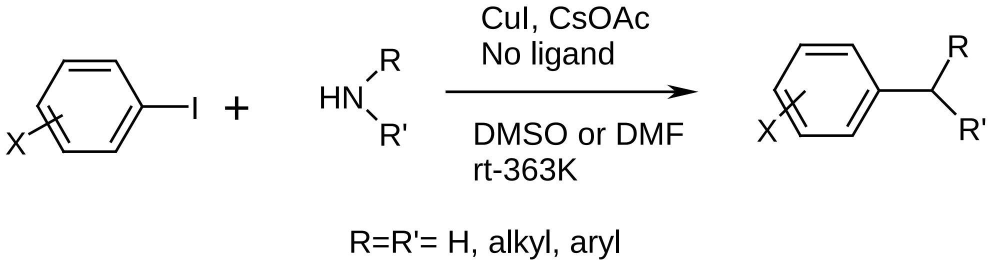
**Scheme 1.19:**Copper catalyzed amination of arylhalides using glycol as ligand

Choudary[127] successfully showed to the N-arylation of the imidazole with a wide range of chloro- and fluoroarenes using copper heterogeneous catalyst, and the yield of products in the rage of 62 – 100% was realized *(Scheme 1.20).*



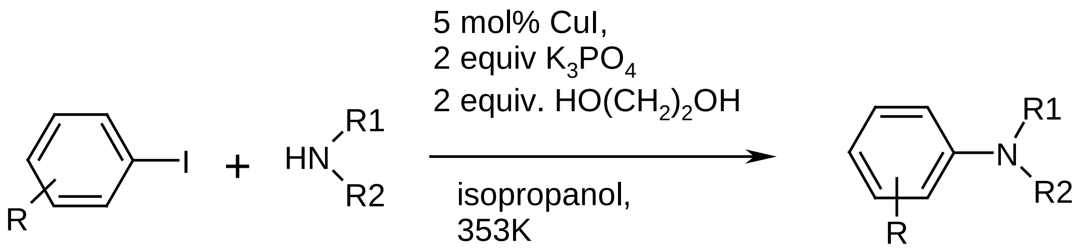
**Scheme1.20:** Heterogenised copper catalyst for the amination of arylhalides

A mild intermolecular copper-mediated amination of aryl iodides has been developed.[128] The reaction takes place at room temperature or heating at 363 K and tolerates halogen attached to the aromatic ring, *Scheme 1.21*. Its synthetic applications include a synthetic protocol for unsymmetrical *N, N'*-dialkylated phenylenediamines and both a stepwise and a general synthetic method for *N*-aryl secondary amines.



**Scheme 1.21:** Copper catalyzed amination of arylhalides using DMF as a solvent

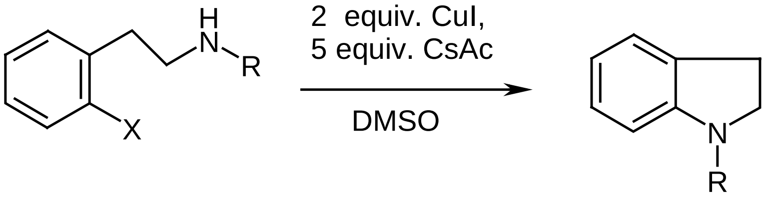
Buchwald has reported a mild method for the copper-catalyzed amination of aryl iodides.[125] This operationally simple C-N bond-forming protocol uses CuI as the catalyst and ethylene glycol as ligand in 2-propanol.[129] A variety of functionalized aryl iodides as well as several amines were efficiently coupled using this method (*Scheme 1.22.)* This catalytic amination procedure is relatively insensitive to moisture and can be performed under an air atmosphere with comparable yield.



**Scheme 1.22:** Copper catalyzed amination of arylhalides using isopropanol as a solvent

Seung Uk Son[130] synthesized uniform $Cu_2O$ coated Cu nanoparticles from the thermal decomposition of copper acetylacetonate in oleyamines followed by air oxidation and used these nanoparticles as catalyst for Ullmann type amination coupling reaction of aryl chlorides and imidazole. High catalytic activity of the $Cu_2O$ coated Cu nanoparticles seems to results from high surface area derived from nanoparticles. In addition the coordination of oleylamine on the nanoparticles might affect the catalytic activity. It is noteworthy that commercially available bulk $Cu_2O$ power shown only 16% conversion of 4-chloroacetophenone under same conditions. In the case of un-activated aryl chlorides such as chlorobenzene and 4-methoxy chlorobenzene, reaction doesn't go. Interestingly, in the case of 1,4-dichlorobenzene, only one chloride of 1,4-dichlorobenzene would participate in the coupling reaction because the initial product, 4-chloroimidazolylbenzene can be regarded as an electron-donating chlorobenzene substrate. As expected, the single imidazole coupled product, 4-chloroimidazolylbenzene, was selectively produced in 69 % yield. The freshly prepared nanoparticles also showed good activity for this amination (95% isolated yields for 4-chlorofluorobenzene).

F. Tohru shown that a unique combination of copper iodide and cesium acetate catalyze intramolecular amination of arylhalides with primary or *N*-benzyl amines and at moderately elevated temperatures with other amine derivatives.[131] The reaction has been applied to the formation of 5-, 6-, and 7-memered rings, *Scheme1.23*. Remarkably, halogens at the *meta*-position were retained, providing a definitive advantage over palladium-catalyzed systems.



**Scheme 1.23:** Intramolecular amination of arylhalide

*Table 1.5* summarizes the literature reports on copper-catalyzed amination of arylhalides

**Table1.5:** Literature survey of copper-catalyzed amination of arylhalides

| No. | Catalyst system | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 1 | $CuCl_2$ | 1,10-phenanthroline | Aryl halides & aryl amines Or dihalo aryls & diamino aryls | 398 | KOH | Toluene | Amination of mono or di halo compounds | 78-85 | (1) Goodbrand et. al.[123] (1999) |
| 2 | CuI | | Aryl halides & β-amino acid | 373 | $K_2CO_3$ | DMF | Synthesis of SB-214857 | 69 | (3) Dawei M, et. al.[132] (2001) |
| 3 | $Cu(OAc)_2$ | Mystric acid | Aryl boranic acid & secondary amine | R T | | 2,6-Lutidine | Using aryl boranic acid for the C-N coupling | 58-91 | (4) Buchwald S. L, et. al.[133] (2001) |
| 4 | n-BuLi | 10 mol % TMEDA | Olefine & amines | 393 | | THF | Base catalyzed amination of olefine | 89 | (5) Beller M, et. al.[134] (2001) |
| 5 | CuI | 1,10-phenanthroline | Aryl iodide & N-Boc hydrazine | 353 | $Cs_2CO_3$ | DMF | A reversal in regioselectivity is observer for the arylation of benzoic hydrazine | 97 | (6) Buchwald S. L, et. al.[135] (2001) |
| 6 | 5-10 mol % CuI | 5-20 mol % Diamines | Aryl halides & amides | 353 | $K_2CO_3$ | Toluene | Study of various diamine ligands | 60-95 | (7) Buchwald S. L, et. al.[136] (2002) |

| No. | Catalyst system | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 7 | 5 mol % CuI | 2 Equiv. $OH(CH_2)_2OH$ | Aryl iodide & secondary amine | 353 | $K_2PO_4$ | Isopropanol | This catalyst system insensitive for moisture and stable for air atmosphere | 80-93 | (8) Buchwald S. L,$^{141}$ (2002) |
| 8 | 2 equiv. CuI | 20 mol % Diamines | Intramolecular amination | 363 | CsOAc | DMSO | Intramolecular amination . Study of various substrate and temerature effect | 92 | (9) Fukuyama T, et. al.$^{137}$ (2002) |
| 9 | 5 mol % CuI | Diethylsalicyl amide | Aryl bromide & primary aryl amine | 363 | $K_2PO_4$ | DMF or Solvent free | Amination of primary amine | 70-91 | (13) Buchwald S. L,$^{125}$ (2003) |
| 10 | | | Aryl halides & secondary amine | Micro wave | KOt-Bu | DMSO | Amination aryl halide without transition metal using microwave | 94 | (18) Tu Y-Q, et. al.$^{138}$ (2003) |
| 11 | CuI | Diamines | Aryl bromides & Oxazolidinones | 383 | $K_2CO_3$ | Dioxane | Amination of aryl bromide with oxazolidinones | 90 | (19) Trehan S, et. al.$^{139}$ (2003) |

| No. | Catalyst system | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 12 | CuI | Ligand | Aryl halides & amines | 373 | KOt-Bu | - | Solvent free reaction | 75-99 | (23) Gajre A.S., et.al.[140] (2004) |
| 13 | Cu nanoparticles | | Imidazole & aryl chloride | 423 | $Cs_2CO_3$ | DMSO | Amination of aryl chlodie with Imidazole using Cu-nanoparticales | 95 | (25) Hyeon T, et. al.[130] (2004) |
| 14 | Cu nanoparticles | | Imidazole & aryl chloride | 423 | $Cs_2CO_3$ | DMSO | Amination of aryl chlodie with Imidazole using Cu-nanoparticales | 95 | (25) Hyeon T, et. al.[130] (2004) |
| 15 | CuFAP or CuTBAP | | Chloro & Floro arnenes & imidazole | 393 | $K_2CO_3$ | DMF | Heterogeneous catalysts | 85-100 | (27) Chaudhary B.M. et. al.[127] 2005) |
| 16 | CuI | Amino acids | Aryl halides and aliphatic amines as well as aromatic amines | 320-383 | $K_3PO_4$ | DMSO | Explain mechanism in two ways | 80-97 | Ma, et.al [142] (2005) |

| No. | Catalyst system | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 17 | CuI | Diketones | Aryl halides and aliphatic amines as well as aromatic amines | R.T. | $Cs_2CO_3$ | DMF | Reaction at room temperature | 90-98 | Buchwald, S.L. et. al.[126] (2006) |
| 18 | CuI | Amino acids | Aryl halides and aliphatic amines as well as aromatic amines | 383 | $Cs_2CO_3$ | DMF | Explain mechanism | 70-90 | Guo et. al.[143] (2006) |
| 19 | CuI | BINAP | Hetrocyclic amine and arylhalides | 363 | $Cs_2CO_3$ | DMF | Synthesis of heterocyclic amines | 70-90 | Zhang, et. al.[144] (2006) |
| 20 | CuI | Diamine and amine | Aryl halides and aliphatic amines as well as aromatic amine, phenols | 353 | $K_3PO_4$ | $CH_3CN$ | Ether synthesis | 20-100 | Ouali, et.al.[145] (2006) |
| 21 | CuI | Different diamines | Aryl halides and aliphatic amines as well as aromatic amine, | 393 | KO*t*-Bu | Toluene | Various amine synthesis | 80-95 | Liu, et. al.[146] (2006) |
| 22 | Cu-complexes | Perform complex | Aryl halides and aliphatic amines as well as aromatic amine | 393 | KO*t*-Bu | Toluene | Complex activity | 80 | Zhang, et. al.[147] (2006) |

| No. | Catalyst system | Ligand | Substrate | Reaction Condition | | | Other Details | Yield, % | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Temp. K | Base | Solvent | | | |
| 23 | Cu complexes | CuI | Aryl halides and aliphatic and $NH_3$ | R.T. | CsOAc | DMSO | Synthesis of specialist chemicals | 40-80 | Sarkar, M,[148] (2006) |
| 24 | CuI | Diamines | Aryl halides and aliphatic amines as well as aromatic amine | 383 | $K_3PO_4$ | Dioxane | Synthesis of various aminederivatives | 50-70 | Filipski et. al.[149](2006) |

## 1. 5 Scope and Objectives of Thesis

Copper catalyzed amination of arylhalides has relevance to industry because of the cost effectiveness of copper as catalyst over palladium. However, the development of catalyst system based on copper catalyst is challenging, as this chemistry is not well understood like that of palladium. Most of the work reported for copper catalyzed system employ homogeneous catalyst, the system is highly complex due to use of solid base and recycle of catalyst is not simple. Heterogenization of copper catalyst is important from point of view of using minimum amount of expensive ligand. Therefore, there is a need to understand the behaviors of copper catalyzed system for amination of arylhalides. Keeping this in mind, work on the thesis was focused an following aspects.

- To develop a cheaper catalyst system with high activity and selectivity
- Role of the monodentate and chelating N-containing ligands
- Role of monodentate phosphine and diphos ligands
- Effect of reaction parameters such as base, solvent, temperature on the activity and selectivity of the amination reaction.
- Synthesis of different amine derivatives.
- Synthesis and testing of well defined copper complex catalyst
- Development of heterogeneous catalyst:
    - i) Encapsulation of copper complexes in zeolite-Y
    - ii) Tethered copper complexes on various supports

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# CHAPTER 2

# HOMOGENEOUS COPPER CATALYZED AMINATION OF ARYLHALIDES

# Ligand Free Copper-Catalyzed Amination of Arylhalides

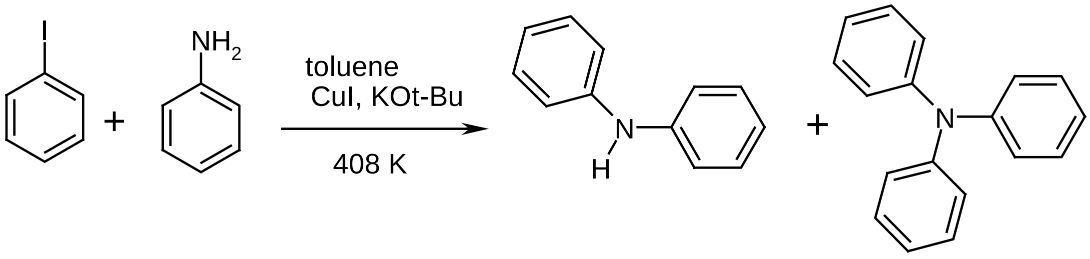
## 2.1 Introduction

Arylamines are attractive targets for chemical synthesis because of their wide utility in fine chemicals, dyes and polymers.[1] Based on the important developments by Buchwald[1] and Hartwig,[2] the Pd-catalyzed C-N coupling reaction of arylhalides has recently become the most important method for laboratory scale synthesis of substituted arylamines. High purity triarylamines find applications in xerographic photoreceptors and as a constituent of non-linear optical chromophores useful in the design of integrated electro-optic switches and modulators.[3] Recently, extensive research has been directed towards development of triarylamines as hole-transport materials for organic electro-luminescent (EL) display devices.[3,4]

Conventionally, triarylamines are produced by Ullmann coupling of aryliodides and diarylamines with stoichiometric amount of copper in the form of metal, alloy, Cu(I) or Cu (II) salt.[4] Major drawbacks of this method are high temperature, strong bases, stoichiometric amount of copper or copper salts, long reaction times and low to moderate yields of triamine.[3,4,5] Bis-arylation of substituted aniline with two equivalents of an aromatic halide to produce triarylamine derivatives has been reported with conventional Ullmann catalyst, however yields are substantially poor (30-50 %).[3,4]

Efforts have been made to improve the yield and employ milder reaction conditions as compared to Ullmann coupling reaction. Gauthier and Frechet[6] used more than the stoichiometric amount of copper with for 18-crown-6 ether as a phase transfer promoter and eight times excess base with respect to diphenylamine in *o*-dichloro benzene as a solvent. The yields of mono substituted triarylamine obtained were in the range of 78 to 90 %, the reaction was carried out 18 to 21 hours. Even though, catalytic activity and yield of triarylamine increased with the use of 18-crown-6 prompter, drawback of this work is the requirement of copper in stoichiometric quantity and high temperature (453 K). Yamanoto[7] has reported amination of iodobenzene at 503 K using six equivalent of copper powder as a catalyst as well as HX acceptor to eliminate the use of base, good yields (63% of TPA) were obtained in this case too. Paine[4] investigated Ullmann condensation reaction of diarylamines with iodobenzene, under homogeneous and heterogeneous catalytic conditions with cuprous and cupric salts, as well as powdered copper metal. The first direct evidence of reaction catalyzed by copper ion that is soluble in the reaction media and insoluble copper metal do not contribute to catalysis was shown by this researcher. Quantitative analysis of reaction rates, product yields and catalyst characteristics lead to comprehensive picture of the formation of soluble cuprous ion as the single active catalytic species under all conditions investigated. Thus literature reports indicate that conventional Ullmann condensation have major drawbacks such as the requirement of high reaction temperature (443 to 513 K), stoichiometric or more than stoichiometric amount of copper, use of large excess of base with respect to reactant and limited scope of substrates.

High purity triarylamines find applications in various emerging technologies and hence our aim was to develop a facile and single step catalytic route for the synthesis of triarylamines. It is desirable to develop a cheaper catalyst system with high activity and selectivity for triarylamine synthesis and there is also an economic attractiveness for using cheaper copper based catalyst over noble metals such as palladium.[8] strong bases are required in conventional Ullmann coupling for the quenching the halides from arylhalides and formation of product. We have found out that the use of KO*t*-Bu as a base was very crucial in the development of ligand free catalyst for selective and efficient synthesis of triarylamines in a single step. We have studied the effect of temperature, solvent, substrate concentrations and catalyst concentration on activity and selectivity. The reaction of aryliodide and aromatic amine in the presence of catalytic amount of CuI and a base (potassium tertiary butoxide) lead to the formation of diaryl amine (1) and triaryl amine (2) as products *(Scheme 2.1).*



**1 (DPA)** **2 (TPA)**

**Scheme 2.1:** Ligand free copper catalyzed amination of iodobenzene

## 2.2 Experimental

### 2.2.1 Materials

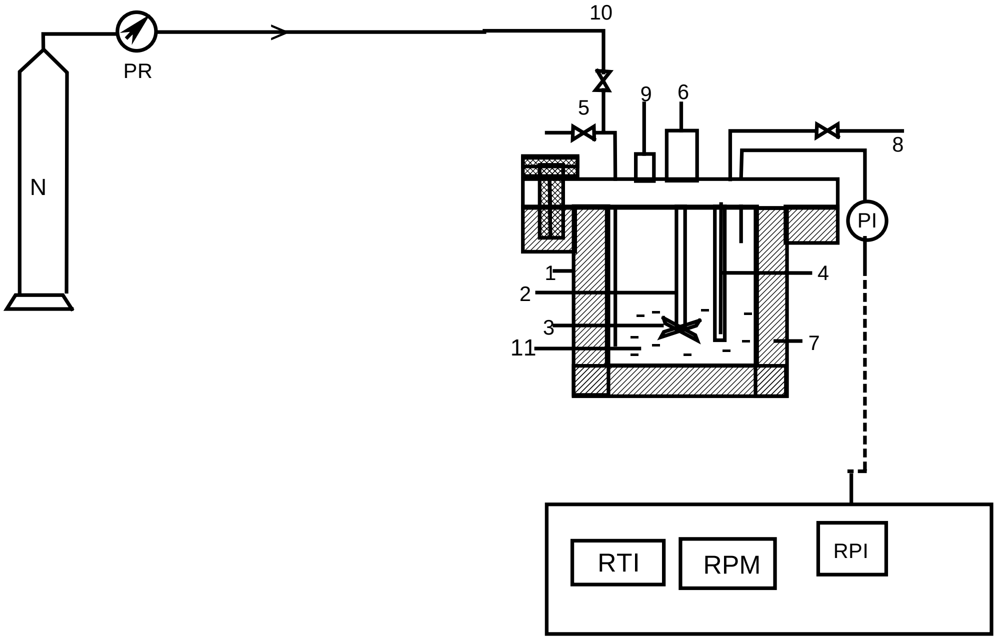
Aniline, substituted anilines, Copper (I) Iodide (CuI), toluene, and chlorobenzene, were purchased from *s. d.* Fine Chemical Ltd. India. Iodobenzene, bromobenzene, Copper (II) bromide, Copper (II) carbonate basic ($Cu(II)CO_3$. $Cu(OH)_2$ were purchased from Aldrich, USA. KO*t*-Bu, NaO*t*-Bu, KOH, NaOH, $K_2CO_3$, $Cs_2CO_3$, NaOMe, TEA, tri-*t*-butylamine, $NaHCO_3$, were purchased from *s. d.* Fine chem. Ltd India. 1,8-Diazabicyclo [5.4.0] undec-7-ene (DBU); 1,5-Diazabicyclo [2.2.0] non-5-ene (DBN); 1,4- Diazabicyclo [2.2.2] octane (DABCO) 1,5-Diazabicyclo [4.3.0] none-5-ene and *N,N*-Dimethylbenzylamine were purchased from Aldrich Chem. Ltd, USA. Aniline and toluene were distilled and dried using literature procedures

### 2.2.2 General Experimental Procedure

All amination reactions were carried out in a 50 ml capacity Hast 'C' high-pressure autoclave (Model number: 2430HC2). The autoclave system was supplied by M/S Parr Instruments Co., USA, and was provided with arrangement for sampling of liquid and gaseous contents, automatic temperature control and variable stirred speed control. A safety rupture disc was also fitted to the reactor. The reactor was designed for working pressure of 2000 psi and temperature up to 523 K. A typical experimental setup is shown in *Figure 2.1*.

20 ml of toluene as a solvent was charged to the autoclave followed by arylamine (4 mmol), arylhalide (12 mmol), CuI (0.08 mmol) and base (12 mmol). The reactor was flushed twice with nitrogen to ensure complete removal of air. The autoclave was then heated to 408 K. Reaction was initiated by switching the stirrer on (800 rpm) and the reaction was continued for 14 hours. Autoclave was cooled to room temperature and liquid sample was withdrawn for GC analysis. Reaction solution was filtered to remove the precipitated base and washed with toluene few times. The solution was concentrated to obtain crude product, which was chromatographed using silica gel and eluted with pet ether and ethyl acetate (98 : 2 ) to obtain pure product. The products

separated, were characterized by IR, GC-MS and NMR analysis and compared with authentic samples by GC analysis whenever possible.



**A Schematic representation of the reactor setup**
(1) Reactor, (2) Stirrer shaft, (3) Impeller, (4) Thermowell, (5) Sampling valve, (6) Magnetic stirrer, (7) Furnace, (8) Outlet, (9) Rupture disc, (10) Gas inlet, (11) Reaction mixture, P1: Pressure transducer, PR: Pressure regulator, RTI: Reactor temperature indicator, RPM: Revolution per minute, RPI: Reactor pressure indicator

**Figure 2.1:** Experimental Setup

### 2.2.3 Analytical methods

Liquid samples were analyzed on a Hewlett Packard (Model 6890, with auto sampler) GC, controlled by the HP chem-station software. A Capillary Column, HP-5; 5% phenyl methylsiloxane (30m x 0.32mm x 0.25μm film thickness) was used to analyzed volatile liquid phase reactants and products. The FT-IR spectra were recorded on a Bio-Rad FTS-175 spectrometer in the range 4000-400cm$^{-1}$. The samples were made as KBr pellets (1 % w/w). The spectra were recorded in transmittance (%T) mode. NMR was obtained from a Brucker 500MHz, MSL300 and Brucker- AC200 machines. Elemental analysis of the compounds was carried out on a CHNS-O EA1108, elemental analyzer of Carlo Erbo Instruments, Italy. Mass spectra were recorded on Hewlett

Packard GC-MS Model HP 6890N (with auto sampler) fitted with HP-5 column with 5973N mass selective detector.

**The Standard conditions for GC analysis were as follows**

| | |
|---|---|
| Injector (split) temperature | 523K |
| Flame ionization detector temperature | 523K |
| Column temperature | 313K – 553K (ramp, 30 K/min) |
| Carrier gas (He) flow | 1.4 ml/min |
| Inlet Pressure (He) | 8.00 psig |
| Split ratio | 50:1 |

The conversion, selectivity and yield (based on aniline) were calculated as follows

$$\%\ \text{Conversion of aniline} = \frac{\text{Initial moles of aniline} - \text{Final moles of aniline}}{\text{Initial moles of aniline}}\ \text{X}\ 100$$

$$\%\ \text{Selectivity of DPA (TPA)} = \frac{\text{No. of moles of DPA (TPA) formed}}{\text{No. of moles of DPA (TPA) expected based on Aniline converted}}\ \text{X}\ 100$$

$$\%\ \text{Yield of DPA (TPA)} = \frac{\text{No. of moles of DPA (TPA) formed}}{\text{No. of moles of theoretical possible DPA (TPA)}}\ \text{X}\ 100$$

*(Yield based on aniline charged, mol)*

## 2.3 Results and Discussion

The objective of this work was to develop cheaper and easily available copper-catalyst system for the amination of arylhalides, to triarylamines in single step. In the ligand free amination of arylhalides we have studied effect of various process parameters on activity and selectivity. We have also synthesized few triarylamine derivatives, important for academic as well as industrial view point.

### 2.3.1 Preliminary Experiments

Few preliminary experiments were carried out using aniline and iodobenzene as reactants, KO*t*-Bu as a base, CuI as a catalyst and toluene as a solvent at 408 K, to check feasibility of the amination reaction, material balance, separation and characterization of the products. GC analysis of the initial and final sample of reaction mixture indicated that reactants aniline and iodobenzene in small quantities were present at the end of reaction and two main products were formed with few by-products. Authentic samples of diphenylamine (DPA) and triphenylamine (TPA) were injected and it was found that TPA was the major product. GC-MS analysis of the sample was carried out and formation of DPA and TPA was conformed by MS fragmentation pattern. Formation of benzene, biphenyl and *t*-butyl phenyl ether as by-product was conformed by GC-MS analysis. Benzene can form by dehalogenation of iodobenzene; biphenyl can be form by Ullmann coupling under reaction conditions while *t*-butyl phenyl ether can form by the reaction of KO*t*-Bu with iodobenzene.

It was observed that about 80 to 90 % material balance was accounted for amination of iodobenzene. Other byproducts could not be characterized. Further work was carried out using this methodology to investigate the amination of arylhalides on activity and selectivity.

### 2.3.2 Screening of Catalyst precursor

Various copper-catalyst precursors were screened for the amination of iodobenzene. The results are presented in *Table 2.1,* these results show that copper (I) salts, such as CuI, CuBr and CuCl give good activity and selectivity for the synthesis of TPA as a product *(Table 2.1, sr. no. 1,2 and 3).* Copper (II) salts such as $CuBr_2$ and

$CuCl_2$ gave lower activity as compared to copper (I) salts. It was found that CuI gave the best results for the amination of iodobenzene with 72% yield of TPA *(Table 2.1, sr. no. 1).* Ullmann condensation of aryliodides and diarylamines with stoichiometric amount of copper in the form of a metal alloy or Cu(I)/Cu(II) salts at 473 K temperature gave low to moderate yield (20 to 60 %) of amines.[4,7] In order to check the catalytic effect of CuI, a non-catalytic reaction was carried out *(Table 2.1, sr. no. 7)* under similar conditions, which showed 51% conversion of aniline with a poor yield of triphenylamine (7 % yield of TPA) was obtained with many by-products such as benzene and trace amount of biphenyl. Comparisons of the results *(Table 2.1, sr. no. 1 and 7)* clearly show that CuI enhances the conversion as well as selectivity of triphenylamine.

**Table 2.1:** Copper catalyzed amination of iodobenzene: Effect of catalyst precursor

| Sr. No. | Catalyst Precursor | Conv. of Aniline, (%) | Yield, (%) | |
|---|---|---|---|---|
| | | | TPA | DPA |
| 1 | CuI | 88 | 72 | 8 |
| 2 | CuBr | 85 | 68 | 9 |
| 3 | CuCl | 80 | 62 | 7 |
| 4 | $CuBr_2$ | 78 | 59 | 8 |
| 5 | $CuCO_3.Cu(OH)_2$ | 64 | 41 | 9 |
| 6 | $CuCl_2$ | 67 | 40 | 10 |
| 7 | No catalyst | 51 | 7 | 12 |

***Reaction conditions:*** *Aniline: 4.0 mmol; Iodobenzene: 12.0 mmol; Catalyst Precursor: 0.08 mmol; KOt-Bu: 12.0 mmol; Toluene: 20 ml; Temperature: 408 K; Time: 14 h; Agitation Speed: 800 rpm; Pressure: reaction under autogenous pressure.*

Thus copper (I) and (II) salts are active for the amination of arylhalides, but copper (I) salts gave higher yield of TPA compared to Copper (II) salts. Further work was carried out using CuI as a catalyst.

### 2.3.3 Effect of Solvents

Various solvents were screened for the amination of iodobenzene using CuI as a catalyst, at 408 K temperature. *Table 2.2* clearly shows that all solvents work very well for the ligand free amination of arylhalides using copper-catalyst reactions. A non-polar solvent such as toluene gives best yield of TPA *(Table 2.2, sr. no. 1)*. Polar, non-polar, protic solvents gave good yield of TPA. In polar solvent formation of byproducts such as benzene was observed by the dehalogenation of iodobenzene. Thus 2 to 5 % benzene formation was observed when polar solvent such as NMP and THF were used, while with non-polar solvent such as toluene trace amount of benzene was observed. Buchwald and Alex[1] found that polar solvent like THF, NMP and DMF give dehalogenation product form arylhalides in Pd-catalyzed amination reaction. Buchwald and Alex[1] and Hartwig[2] have also found that toluene is suitable solvent for Pd-catalyzed amination reaction. Results are presented in *Table 2.2* in descending order of conversion of aniline. Thus toluene was found to be the best solvent for the amination of iodobenzene *(Table 2.2, sr. no. 1)* and further work was carried out using toluene as a solvent.

**Table 2.2:** Copper-Catalyzed Amination: Effect of Solvent

| Sr. No | Solvent | Conv. of Aniline, (%) | Yield, (%) | |
|---|---|---|---|---|
| | | | TPA | DPA |
| 1 | Toluene | 87 | 71 | 8 |
| 2 | NMP | 80 | 58 | 7 |
| 3 | 1,4 dioxane | 79 | 51 | 8 |
| 4 | Tetrahydrofuran | 77 | 54 | 13 |
| 5 | Cyclohexane | 75 | 59 | 9 |
| 6 | *t*- Butanol | 75 | 52 | 11 |
| 7 | Acetonitrile | 72 | 49 | 8 |

***Reaction conditions:*** *Aniline: 4.0 mmol; Iodobenzene: 12.0 mmol; CuI: 0.08 mmol; KOt-Bu: 12.0 mmol; Solvent: 20 ml; Temperature: 408 K; Time: 14 h; Agitation Speed: 800 rpm; Pressure: reaction under autogenous pressure.*

### 2.3.4 Effect of Temperature

Amination of iodobenzene using CuI catalyst was carried out in a temperature range of 358 K to 433 K (*Table 2.3).* At lower temperature (358 K) conversion of aniline was 46 % with 19 % yield of TPA and 9 % yield of DPA. Conversion as well as yield of TPA increased with increasing temperature up to 423 K *(Table 2.3, sr. no. 1 to5)* with further increase in temperature, marginal drop in TPA yield was observed (69 % yield of TPA at 423 K against 72 % at 408 K). Optimum results (88 to 89 % conversion of aniline and 72 to 73 % yield of TPA) were obtained in a temperature range of 408 to 423 K. Therefore, further work was carried out using 408 K temperature.

**Table 2.3:** Copper catalyzed amination of iodobenzene: Temperature effect

| Sr. No. | Temperature, (K) | Conv. of Aniline, (%) | Yield, (%) | |
|---|---|---|---|---|
| | | | TPA | DPA |
| 1 | 358 | 46 | 19 | 9 |
| 2 | 373 | 57 | 24 | 8 |
| 3 | 388 | 62 | 30 | 10 |
| 4 | 408 | 88 | 72 | 8 |
| 5 | 423 | 89 | 73 | 6 |
| 6 | 433 | 83 | 69 | 7 |

***Reaction conditions:*** *Aniline: 4.0 mmol; Iodobenzene: 12.0 mmol; CuI: 0.08 mmol; KOt-Bu: 12.0 mmol; Toluene: 20 ml; Time: 14 h; Agitation Speed: 800 rpm; Pressure: reaction under autogenous pressure.*

### 2.3.5 Effect of Catalyst (CuI) Loading

The effect of CuI loading was studied in the range of 0.008 mmol to 4 mmol CuI (see *Figure 2.2*). All the reactions were carried out for 14 h reaction time. At lower CuI loading (0.008 mmol) 59 % conversion of aniline was observed with 9 % yield of TPA and 16 % yield of DPA respectively. Conversion of aniline and yield of TPA increased while yield of DPA decreased with increasing CuI loading up to 0.08 mmol (*Table 2.4, sr. no. 3, 4 and 5).* However, further increase in CuI loading, did not improve the results. Best results were obtained at a CuI loading of 0.08 mmol (88 % conversion of aniline and

**Table 2.4:** Copper catalyzed amination of iodobenzene: Effect of CuI loading

| Sr. No. | CuI, (mmol) | Conv. of Aniline, (%) | Yield, (%) | |
|---|---|---|---|---|
| | | | TPA | DPA |
| 1 | 4 | 90 | 74 | 7 |
| 2 | 2 | 90 | 74 | 9 |
| *3 | 0.08 | 88 | 72 | 8 |
| 4 | 0.02 | 61 | 22 | 13 |
| 5 | 0.008 | 59 | 9 | 16 |

***Reaction conditions:*** *Aniline: 4.0 mmol; Iodobenzene: 12.0 mmol; KOt-Bu: 12.0 mmol; Toluene: 20 ml; Temperature: 408 K; Time: 14 h; Agitation Speed: 800 rpm; Pressure: reaction under autogenous pressure. * Standard reaction condition*

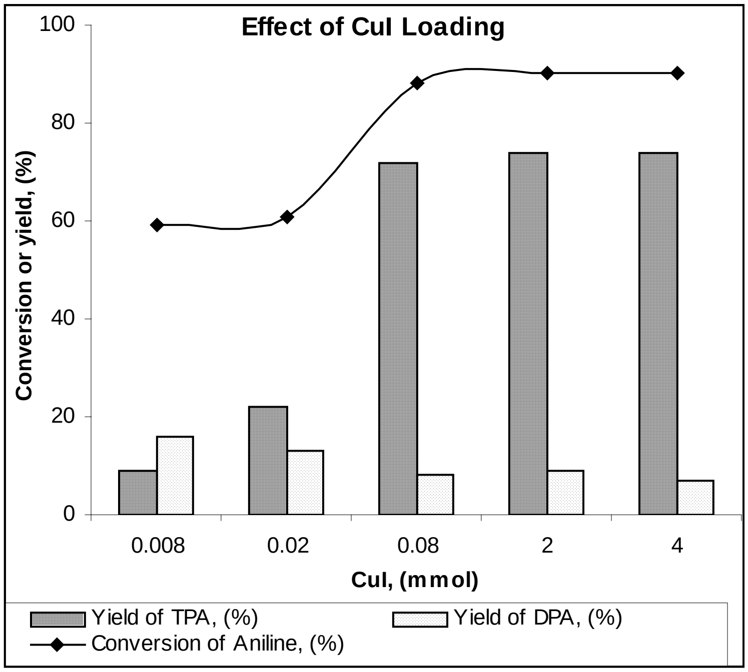


**Figure 2.2:** Copper Catalyzed Amination of Iodobenzene: Effect of CuI Loading (**Reaction Conditions:** see *Table 2.4*)

72 % yield of TPA). Even the use of stoichiometric amount of CuI (4 mmol) *(Table 2.4, sr. no. 1)* did not lead to higher conversion of aniline and higher yield of TPA. At higher catalyst loading it is likely that part of catalyst may not be soluble in the reaction media

(>0.08 mmol), resulting in no further improvement in activity and yield of TPA. However this explanation is probable, since in autoclave reaction we could not measure the solubility of catalyst and hence a definitive reasoning cannot be made out of these experiments at this stage.

### 2.3.6 Effect of Substrate Concentration

According to scheme 2.1, one mol of iodobenzene reacts with one mole of aniline to give one mole of DPA as a product and two moles of iodobenzene react with one mole of aniline to give one mole of TPA as a product. Thus the stoichiometric ratio of aniline : iodobenzene for the synthesis of DPA and TPA is 1 : 1 and 1: 2 respectively. Amination reactions were carried out using CuI as a catalyst and varying the ratio of aniline : iodobenzene in the range of 1 : 1 to 1 : 3 *(see Table 2.5).* Best results were obtained at aniline : iodobenzene ratio of 1 : 3 see *Table 2.5* and *Figure 2.3* (88 % conversion of aniline with 72 % yield of TPA and 8 % yield of DPA). With increase in aniline : iodobenzene ratio from 1 : 1 to 1 : 3, conversion of aniline increases from 69 % to 88 % and TPA yield increase significantly from 8 % to 72 % while DPA yield decrease marginally from 14 % to 8 %. Results clearly indicate the dependence of activity of the catalyst on iodobenzene concentration. As per mechanism proposed for Ullmann condensation, by Paine,[4] $Ph_2N^-$ reacts with CuI giving rise to species of the type "$Ph_2NCu$" which reacts with PhI leading to TPA formation to regenerate copper iodide. Step two is assumed to be the slowest step (RDS) in the mechanism *(Scheme 2.2)*

$$Ph_2N^- + CuI_{(insol)} \xrightarrow{\text{Fast: irreversible}} Ph_2NCu + I^-$$

$$Ph_2NCu + PhI \xrightarrow{\text{Slow}} Ph_3N + CuI$$

**Scheme 2.2:** Reaction mechanism

Our observed trend can also be explain based on the mechanism suggested by Paine. Concentration of iodobenzene used is crucial in deciding the selectivity as well as yield of the products. At higher iodobenzene concentration, DPA formation will be faster and excess iodobenzene is available, leading to the formation of TPA as the major product.

**Table 2.5:** Copper catalyzed amination: Effect of substrate concentration

| Sr. No. | Aniline: Iodobenzene mmol: mmol | Conv. of Aniline, (%) | Yield, (%) | |
|---|---|---|---|---|
| | | | TPA | DPA |
| 1 | 4:4 | 69 | 8 | 14 |
| 2 | 4:8 | 80 | 31 | 17 |
| 3* | 4:12 | 88 | 72 | 8 |

***Reaction conditions:*** **Aniline: 4.0 mmol; *Iodobenzene: 12.0 mmol; KOt-Bu: 12.0 mmol; Toluene: 20 ml; Temperature: 408 K; Reaction Time: 14 h; Agitation Speed: 800 rpm; Pressure: reaction under autogenous pressure. (All other charges were constant, except Aniline and Iodobenzene)*

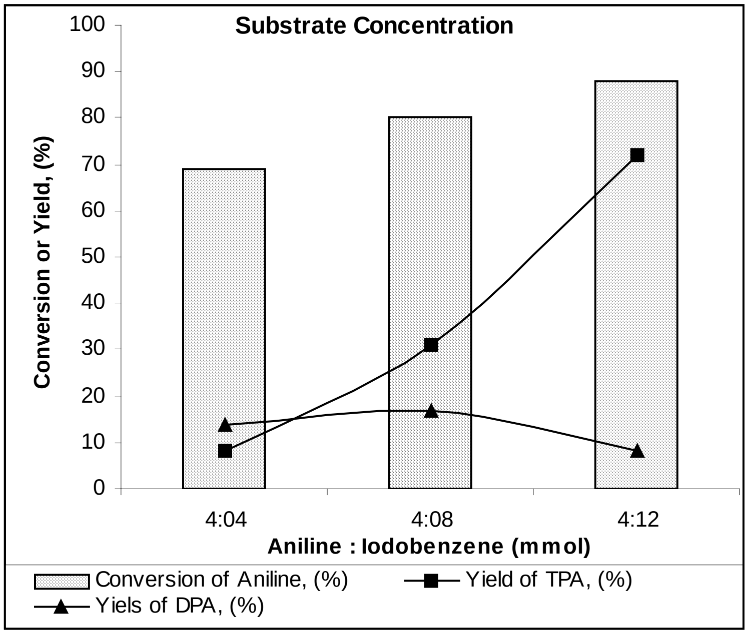


**Figure 2.3: C**opper Catalyzed Amination: Effect of Substrate Concentration (**Reaction Conditions:** see in *Table 2.5*)

### 2.3.7 Effect of Base

The selection of the correct base is crucial for the success of C-N coupling process. This is particularly true with respect to functional group tolerance and reaction rate.[1] Various bases were screened for the amination of arylhalides using CuI as a catalyst and the results are presented in *Table 2.6.* With, NaO*t*-Bu and DBU as bases *(Table 2.6, sr. no. 2 and 3),* 50 and 21 % conversion of aniline was obtained respectively with 6 and 4 % yield of triphenylamine and 19 and 4 % yield of diphenylamine respectively. With all other bases studied (NaOMe, $Cs_2CO_3$, KOH, $NaHCO_3$, NaOH and TEA) trace amount of triphenylamine formation were observed. Best results were obtained using KO*t*-Bu as a base *(Table 2.6, sr. no. 1)* 88 % conversion of aniline and 72 % yield of TPA. It is well known that amination reaction requires strong bases like NaO*t*-Bu for Pd-catalyzed amination reaction.[9] However, in the CuI catalyzed amination KO*t*-Bu gave very good yield of TPA while NaO*t*-Bu gave very poor yield of DPA or TPA indicating that the role of base is complex in nature. KO*t*-Bu was found to be the best (72 % yield of TPA) base for the amination of iodobenzene using CuI catalyst.

**Table 2.6:** Copper catalyzed amination of iodobenzene: Screening of bases

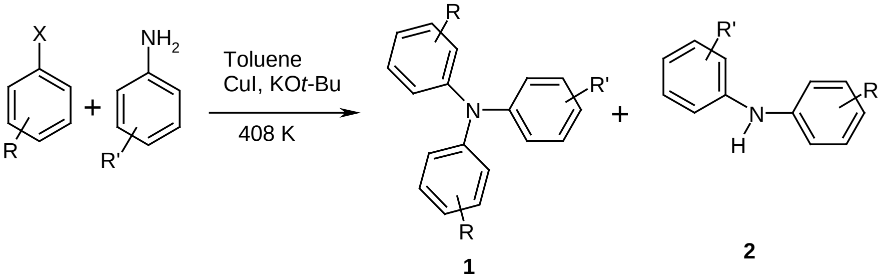
| Sr. No | Base | Conv. of Aniline, (%) | Yield, (%) | |
|---|---|---|---|---|
| | | | TPA | DPA |
| 1 | KOt-Bu | 88 | 72 | 8 |
| 2 | NaOt-Bu | 50 | 6 | 19 |
| 3 | DBU$ | 21 | 4 | 4 |
| 4 | $K_2CO_3$ | 20 | 2 | Trace |
| 5 | NaOMe | 25 | Trace | Trace |
| 6 | TEA | 26 | Trace | Trace |
| 7 | $Cs_2CO_3$ | 17 | Trace | Trace |
| 8 | $NaHCO_3$ | 16 | Trace | Trace |
| 9 | NaOH | 15 | Trace | Trace |
| 10 | KOH | 19 | Trace | Trace |

***Reaction conditions:** Aniline: 4.0 mmol; Iodobenzene: 12.0 mmol; CuI: 0.08 mmol; Base: 12.0 mmol; Toluene: 20 ml; Temperature: 408 K; Time: 14 h; Agitation Speed: 800 rpm; $ 1,8 diazabicyclo [5.4.0] undec-7-ene; Pressure: reaction under autogenous pressure.*

### 2.3.8 Screening of Arylhalides and Aniline Derivatives

A few arylhalides were screened as substrates and it was observed that aryliodides gave higher yields (70 to 80 %) of triarylamines *(Table 2.7)*. Activity varies with arylhalides in the order I>Br>Cl. The higher yield of triarylamines was obtained with *p*-iodoanisole as the reactant *(82 %; Table 2.7, sr. no. 4)*. A few substitute aniline derivatives were also tested and the catalyst was found to be tolerant to substituents present on the ring except for a nitro group. Higher yields of triarylamines were obtained

**Table 2.7:** Synthesis of Different Amine Derivatives Without Ligand



**Scheme 2.3:** Synthesis of various amine derivatives

| Sr. No. | R | R’ | X | Conv. of aryl amine, (%) | Yield, (%)* | |
|---|---|---|---|---|---|---|
| | | | | | 1 | 2 |
| 1 | H | H | I | 89 | 70 | 7 |
| 2 | H | H | Br | 81 | 45 | 12 |
| 3 | H | H | Cl | 57 | 28 | 12 |
| 4 | *p*-$OCH_3$ | H | I | 99 | 81 | 8 |
| 5 | H | *p*-$OCH_3$ | I | 99 | 82 | 12 |
| 6 | *p*-$OCH_3$ | *p*-$OCH_3$ | I | 96 | 79 | 9 |
| 7 | H | *o*-NO2 | I | 14 | 0 | 0 |
| 8 | H | *p*-$NO_2$ | I | 17 | 0 | 0 |

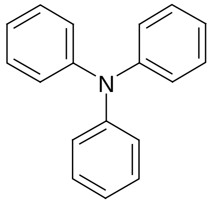
***Reaction conditions:*** *Arylamine: 4.0 mmol; Arylhalide: 12.0 mmol; CuI: 0.08 mmol; KOt-Bu: 12.0 mmol; Toluene: 20 ml; Temperature: 408 K; Time: 14 h; Agitation Speed: 800 rpm; Pressure: reaction under autogenous pressure; *: Isolated yield* with the electron donating *p*-methoxy group as a substituent for both arylhalides and aniline as the reactants *(Table 2.7, sr. no. 4, 5 and 6),* but the reaction did not proceed with *o*- and *p*-nitro aniline as reactants *(Table 2.7, sr. no.7 and 8).* All amine derivatives synthesized are important in conducting polymers and fine chemicals.[10,11]

## 2.4 Conclusions

Amination of iodobenzene with aniline has been investigated using copper catalyst. In ligand free system satisfactory catalyst activity can be obtained using strong base such as KO*t*-Bu. Reactivity of aniline was decreasing with electron withdrawing substituent on aryl ring. The optimized reaction conditions for CuI-KO*t*-Bu system is 408 K temperature, 14 h contact time, aniline : iodobenzene : KO*t*-Bu : CuI in proportion 1 : 3 : 3: 1/50 gave aniline conversion of 88 % and TPA yield of 72 %. Electron donating substituents on aniline (e.g. –$OCH_3$) improve the yield of triphenylamine.

## 2.5 Characterizations of amine Derivatives

### (i) Triphenylamine



**(i) NMR:**

**$^1$H NMR**( $CDCl_3$ 200 M Hz) δ 6.63 – 7.68 (m, 15 H)

**$^{13}$C NMR** ( $CDCl_3$ 125 M Hz) δ 122.6, 124.1, 129.2, 147.8

**(ii)GC MS:** M/Z 245 (base peak), 217, 204, 191, 167, 152, 141, 128, 115, 102, 89, 77, 65, 51

**(iii) IR:** 1373 $cm^{-1}$ C-N stretching of tertiary amine

**(iv) Elemental analysis:** calculated for $C_{18}H_{15}N$: C 88.20, H 6.24, N 5.39; found C 88.13, H 6.16, N 5.71.

**(v)Melting Point:** 126-128$^o$C (127$^o$C Literature)

**Figure 2.4:** $^{1}$H NMR of triphenylamine

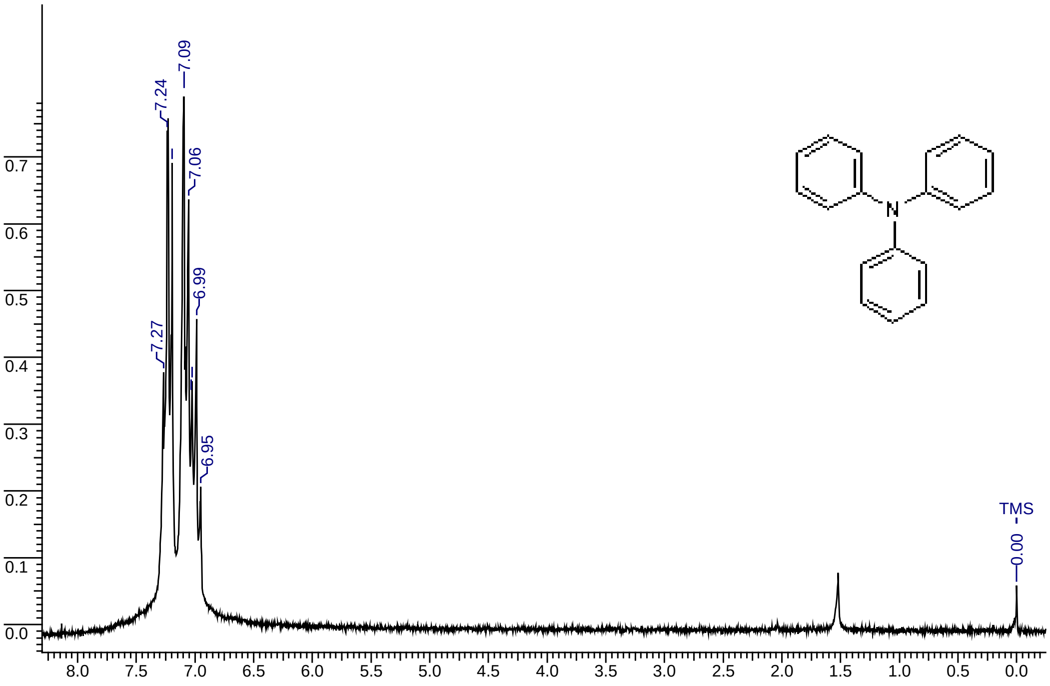


**Figure 2.5:** $^{13}$C NMR of triphenylamine

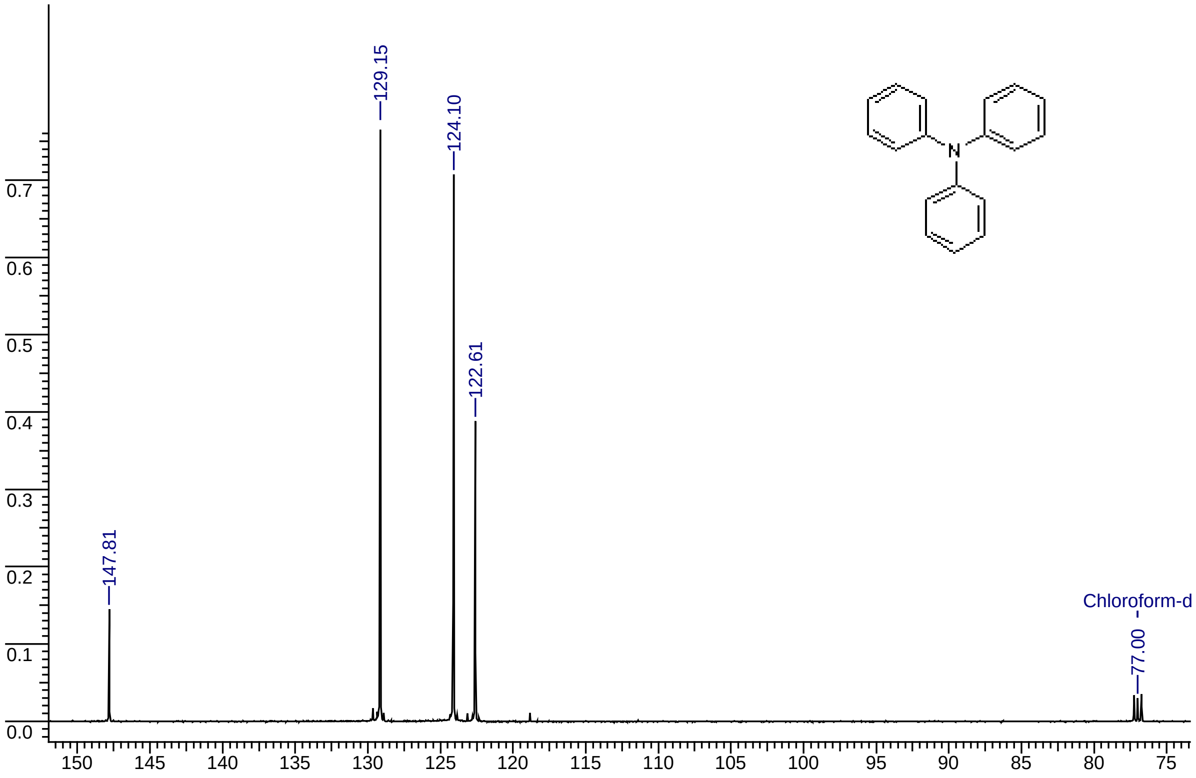
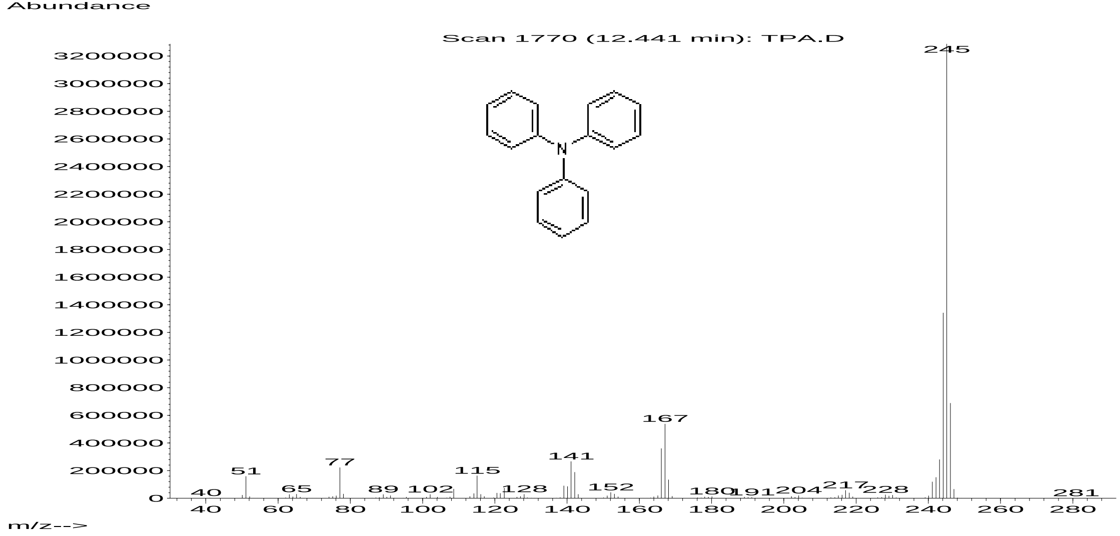
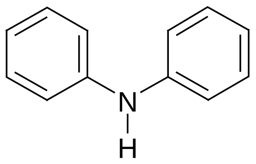


**Figure 2.6:** GC-MS of triphenylamine



## (ii) Diphenylamine



**(i) NMR:**

**$^{1}$H NMR** (CDCl$_3$ 200 M Hz) δ 5.68 (bs, 1H), 6.92 (t, J= 8Hz, 2H), 7.06 (d, J= 8Mz, 4H), 7.26 (t, J= 8Mz, 4H)

**$^{13}$C NMR** ( CDCl$_3$ 125 M Hz) δ 117.7, 120.8, 129.2, 143.0

**(ii)GC MS:** M/Z 169 (base peak), 154, 141, 128, 115, 104, 83, 76, 66, 51

**(iii) IR:** 3383 cm$^{-1}$ N-H stretching (aromatic secondary amine)

1319 cm$^{-1}$ C-N stretching of secondary amine

**(iv)Elemental analysis:** Calculated for C$_{12}$H$_{11}$N: C 84.03, H 9.30, N 6.58; found C 85.17, H 8.75, N 6.98.

**(v)Melting Point:** 53-56$^{o}$C (52-54$^{o}$C Literature)

**Figure 2.7:** $^{1}$H NMR of diphenylamine

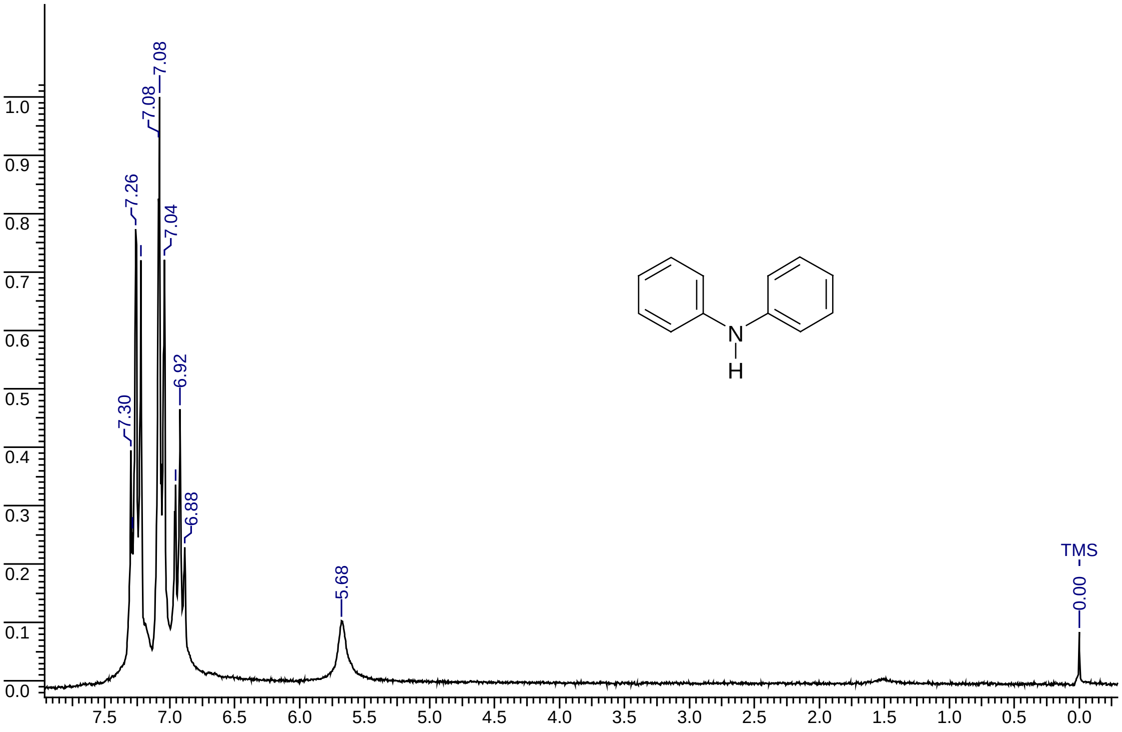


**Figure 2.8:** $^{13}$C NMR of diphenylamine

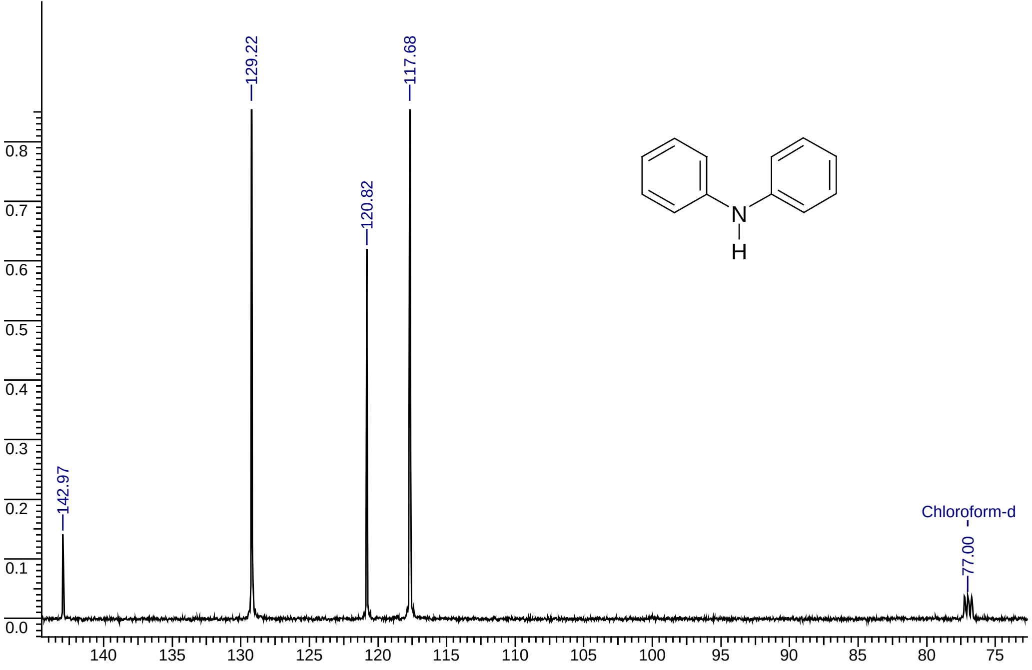
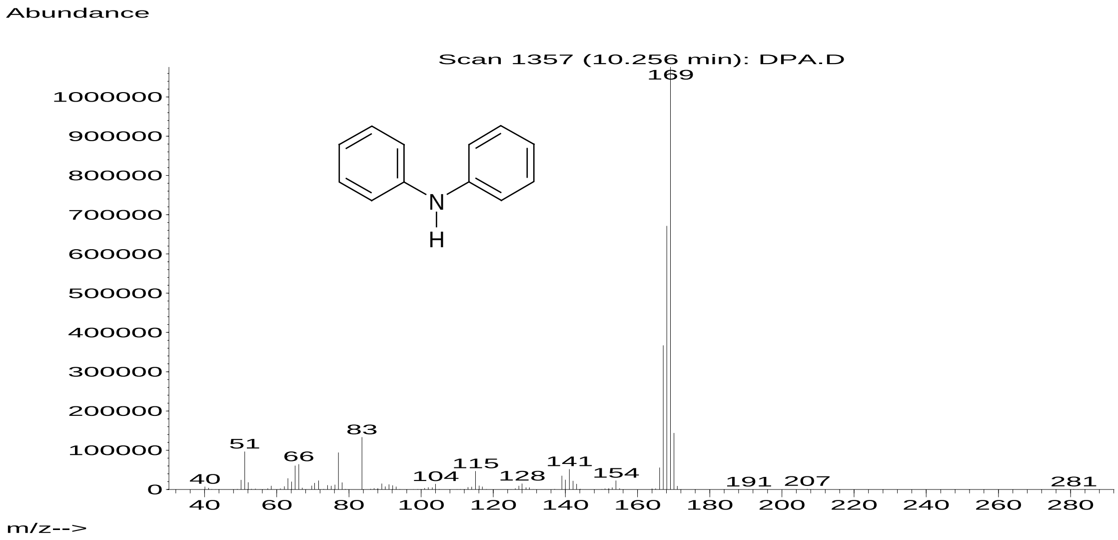
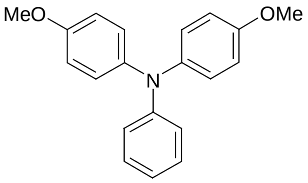


**Figure 2.9:** GC-MS of diphenylamine



### (iii) 4,4'-dimethoxy triphenylamine



**(i) NMR:**

$^{1}$**H NMR** ($CDCl_3$ 200 M Hz) δ 3.78 (s, 6H), 6.77 – 6.87 (m, 5H), 6.93 (d, J= 8Mz, 2H), 7.04 (d, J= 8Mz, 4H), 7.16 (t, J= 8Mz, 2H)

$^{13}$**C NMR** (CDCl3 125 M Hz) δ 55.4, 114.6, 120.5, 120.9, 126.3, 128.9, 141.1, 148.7, 155.6

**(ii)GC MS:** M/z 305 (base peak), 290, 275, 260, 246, 230, 218, 198, 182, 169, 152, 140 128, 115, 103, 92, 77, 64, 51

**(iii) IR:**1244 cm$^{-1}$ C-O-C starching (asymmetric)

835 cm$^{-1}$ C-O stretching

**(iv)Elemental analysis:** Calculated for $C_{20}H_{19}NO_2$: C 78.99, H 6.61, N 4.66; found C 78.66, H 6.27, N 4.59.

**(v) Melting Point:** 108-112°C

**Figure 2.10:** $^1$H NMR of 4,4'-dimethoxy triphenylamine

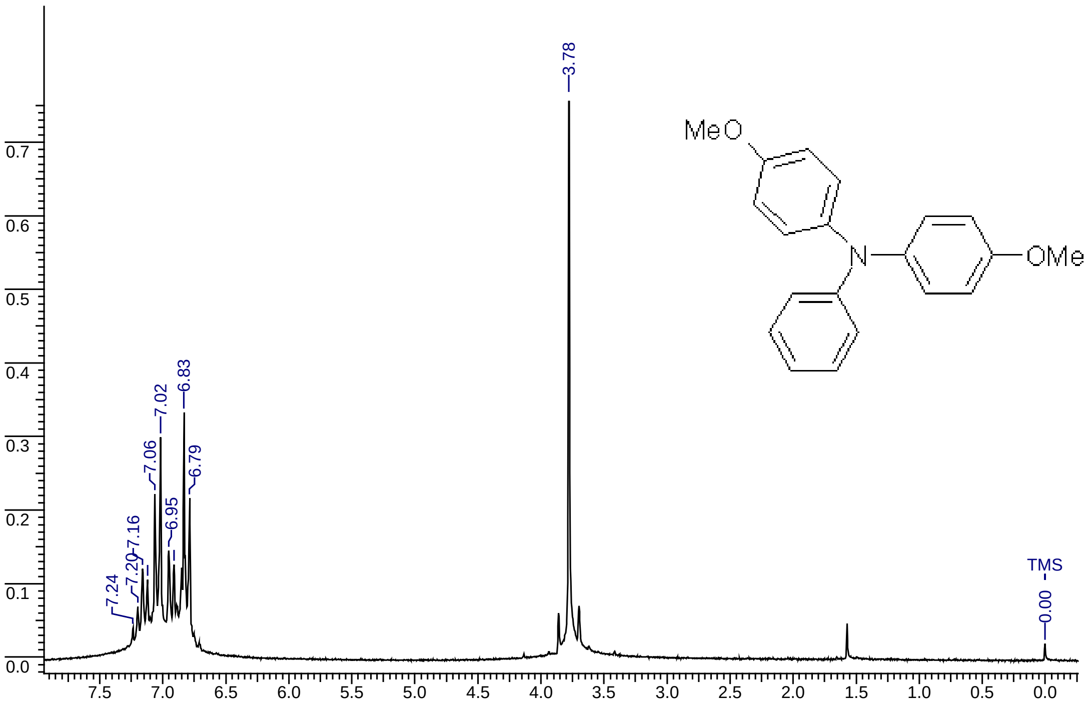


Figure 2.11: $^{13}$**C NMR** of 4,4'-dimethoxy triphenylamine

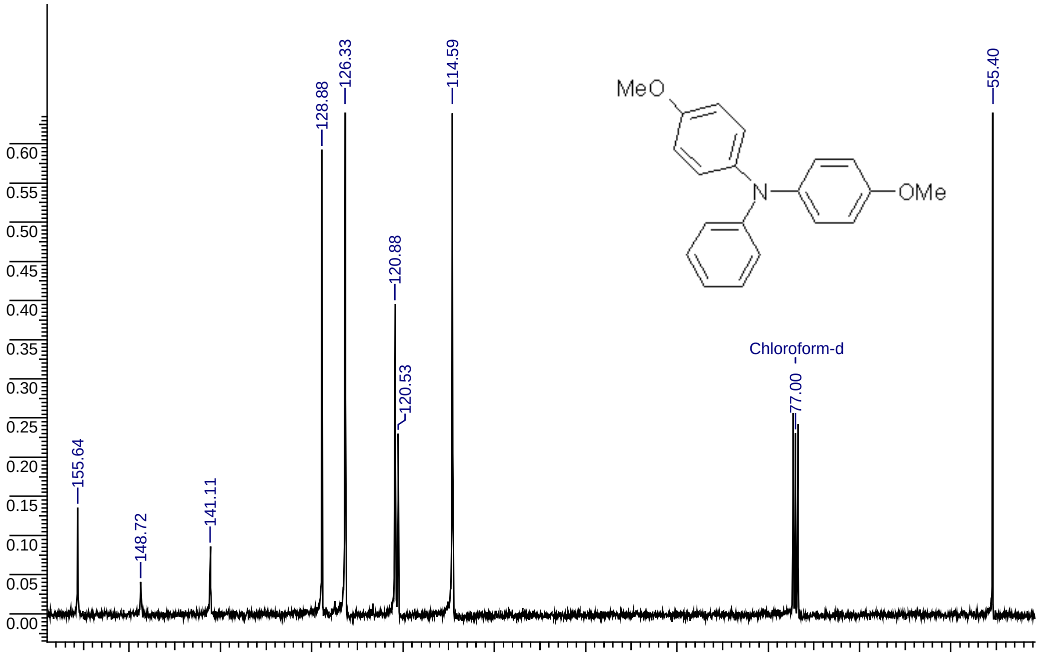
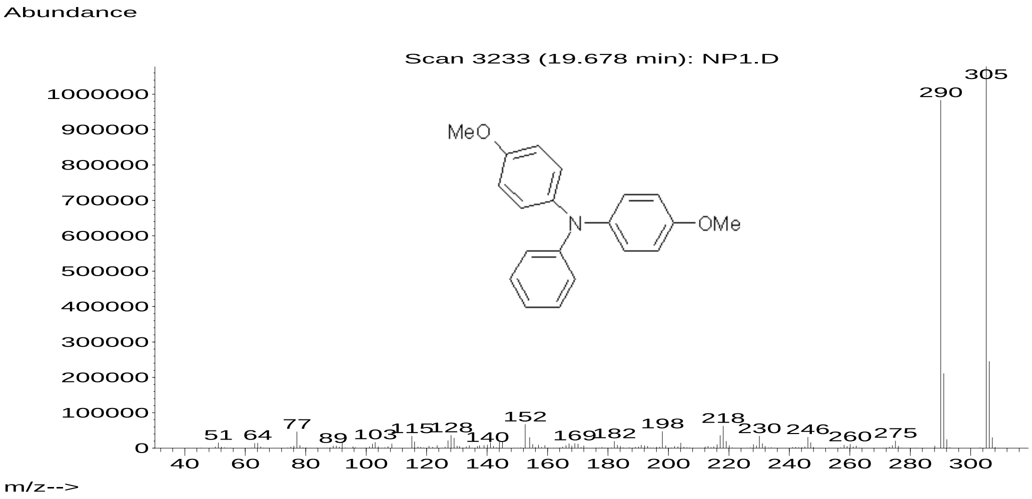
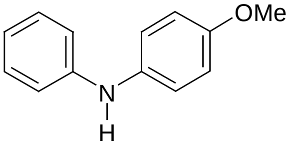


Figure 2.12: **GC-MS** of 4,4’-dimethoxy triphenylamine



## (iv) 4-Methoxy diphenylamine



**(i) NMR:**

**$^1$H NMR** ($CDCl_3$ 200 M Hz) δ 3.79 (s, 3H), 5.49 (bs, 1H), 6.72-6.9 (m, 5H), 7.07 (d, J= 8Hz, 2H), 7.21 (t, J= 8Hz, 2H)

**$^{13}$C NMR** (CDCl3 125 M Hz) δ 55.5, 114.6, 115.6, 119.5, 112.1, 129.3, 135.7, 145.1, 155.2

**(ii)GC MS:** M/z 199, 184 (base peak), 167, 154, 140, 128, 117, 103, 92, 77, 63, 51

**(iii)IR:** 3388 cm$^{-1}$ N-H stretching (secondary amine)
1249 cm$^{-1}$ C-O-C stretching (asymmetric)
751 cm$^{-1}$ C-O stretching
1317 cm$^{-1}$ C-N stretching (secondary amine)

**(iv) Elemental analysis:** Calculated for $C_{13}H_{13}NO$: C 78.36, H 7.45, N 6.83; found C 78.36, H 6.58, N 7.03.

**(v) Melting Point:** 100-104°C

**Figure 2.13:** $^1$H NMR of 4-Methoxy diphenylamine

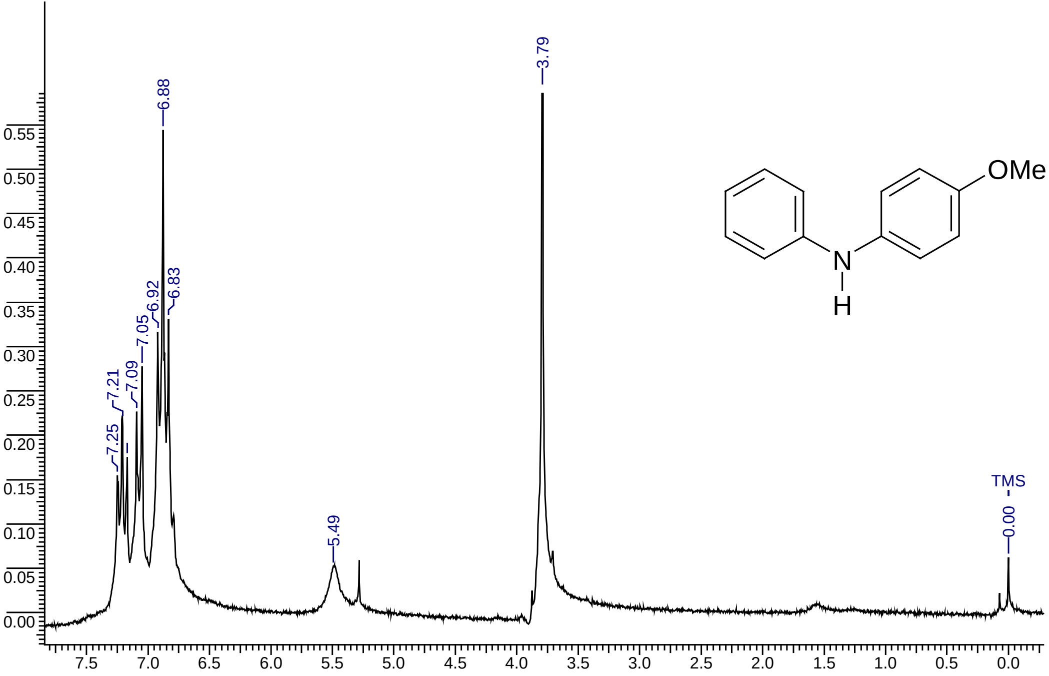


**Figure 2.14:** $^{13}$C NMR of 4-Methoxy diphenylamine

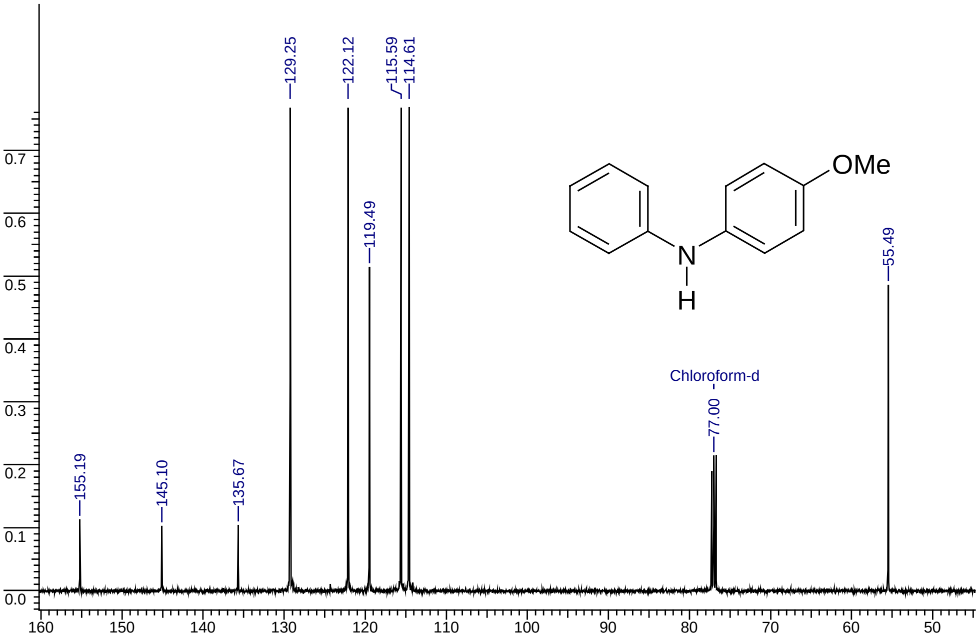
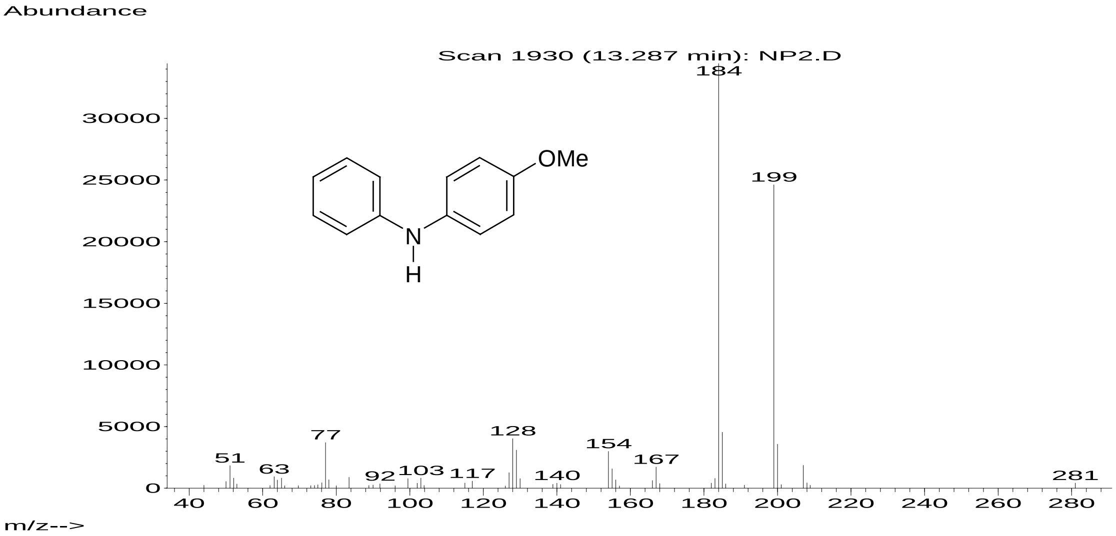
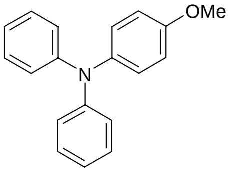


**Figure 2.15:** GC-MS of 4-Methoxy diphenylamine



### (v) 4-Methoxy triphenylamine



**(i) NMR:**

**$^1$H NMR** (CDCl$_3$ 200 M Hz) δ 3.79 (s, 3H), 6.83 (d, J= 8Mz, 2H), 6.94 (t, J= 8Mz, 2H), 6.99 – 7.11 (m, 6H), 7.21 (t, J= 8Mz, 4H)

**$^{13}$C NMR** (CDCl$_3$ 125 M Hz) δ 55.4, 114.7, 121.8, 122.8, 127.3, 129.0, 140.7, 148.1, 156.1

**(ii) GC MS:** M/z 275 (base peak), 260, 241, 230, 217, 204, 193, 182, 167, 154, 139, 128, 115, 103, 89, 77, 63, 51

**(iii) IR:**1246 cm$^{-1}$ C-O-C stretching (asymmetric)

1290 cm$^{-1}$ C-N stretching (tert-amine)

836 cm$^{-1}$ C-O stretching

**(iv) Elemental analysis:** Calculated for $C_{19}H_{17}NO$: C 83.00, H 5.82, N 5.13; found C 82.88, H 6.22, N 5.09.

**(v) Melting Point:** 103-105°C

**Figure 2.16:** $^{1}$H NMR of 4-Methoxy triphenylamine

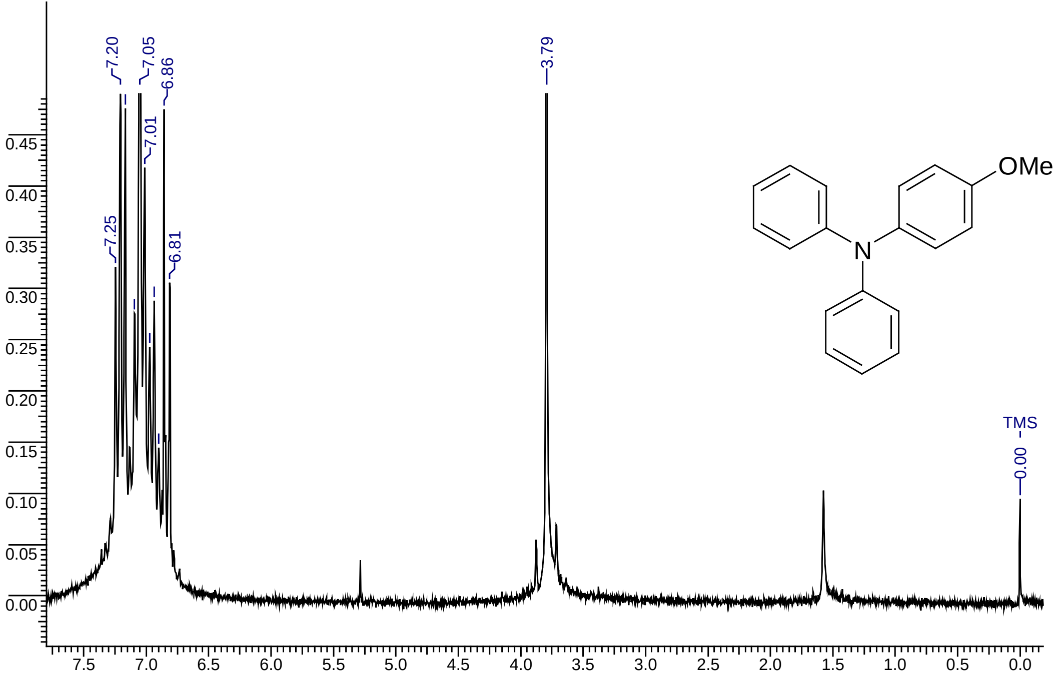


**Figure 2.17:** $^{13}$C NMR of 4-Methoxy triphenylamine

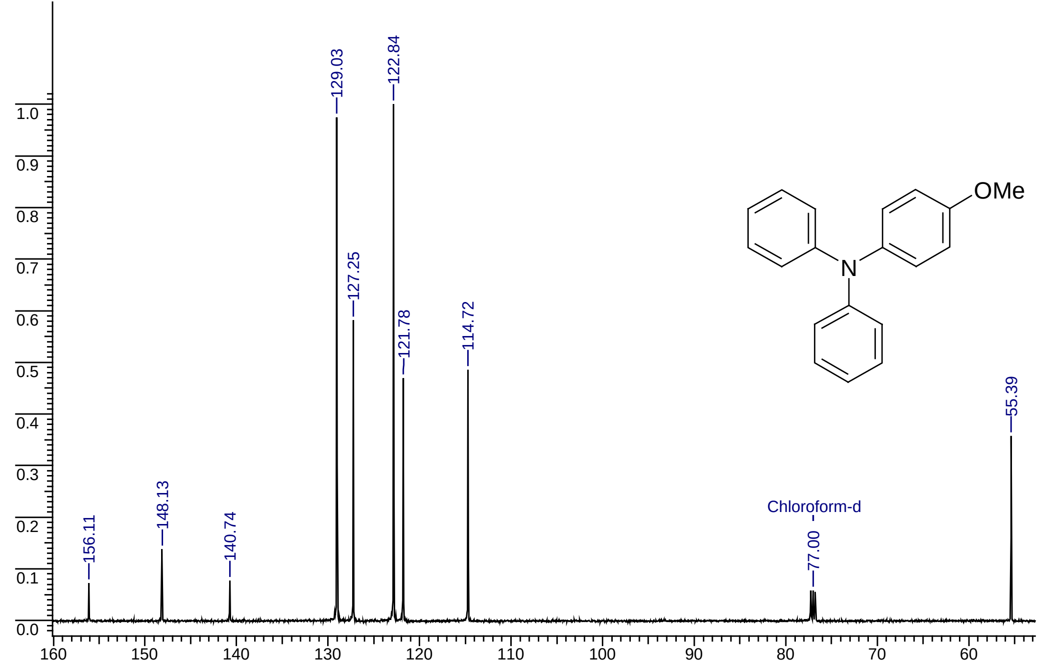
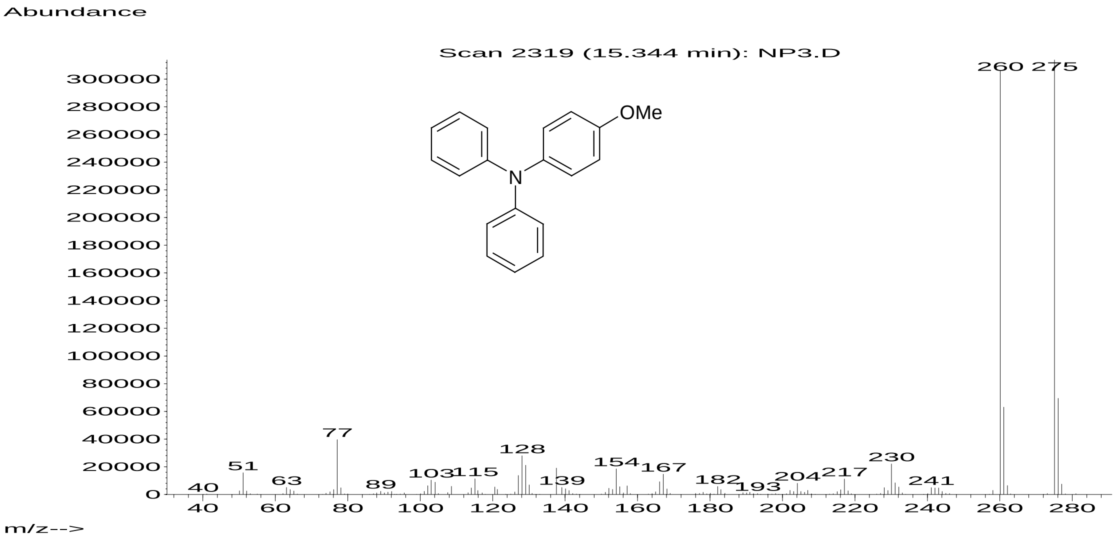
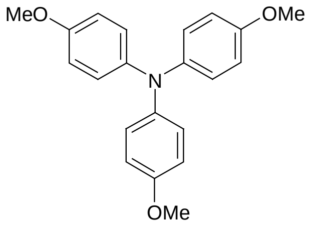


**Figure 2.18:** GC-MS of 4-Methoxy triphenylamine



### (vi) 4, 4', 4''-trimethoxy triphenylamine



**(i) NMR:**

**$^1$H NMR** (CDCl$_3$ 200 M Hz) δ 3.78 (s, 9H), 6.79 (bs, 12H)

**$^{13}$C NMR** ( CDCl$_3$ 75 M Hz) δ 55.5, 114.6, 124.9, 141.8, 155.0

**(ii) GC MS:** M/z 335 (base peak), 320, 305, 290, 276, 262, 248, 234, 212, 198, 184, 167, 144, 128, 115, 92, 77, 64, 51

**(iii) IR:** 1244 cm$^{-1}$ C-O-C stretching (asymmetric)

828 cm$^{-1}$ C-O stretching

1319 cm$^{-1}$ C-N stretching (tret-amine)

**(iv) Elemental analysis:** Calculated for $C_{21}H_{21}NO_3$: C 75.11, H 6.45, N 4.13; found C75.20, H 6.31, N 4.18.

**(v) Melting Point:** 94-97°C

**Figure 2.19:** $^1$H NMR of 4, 4’, 4’’-trimethoxy triphenylamine

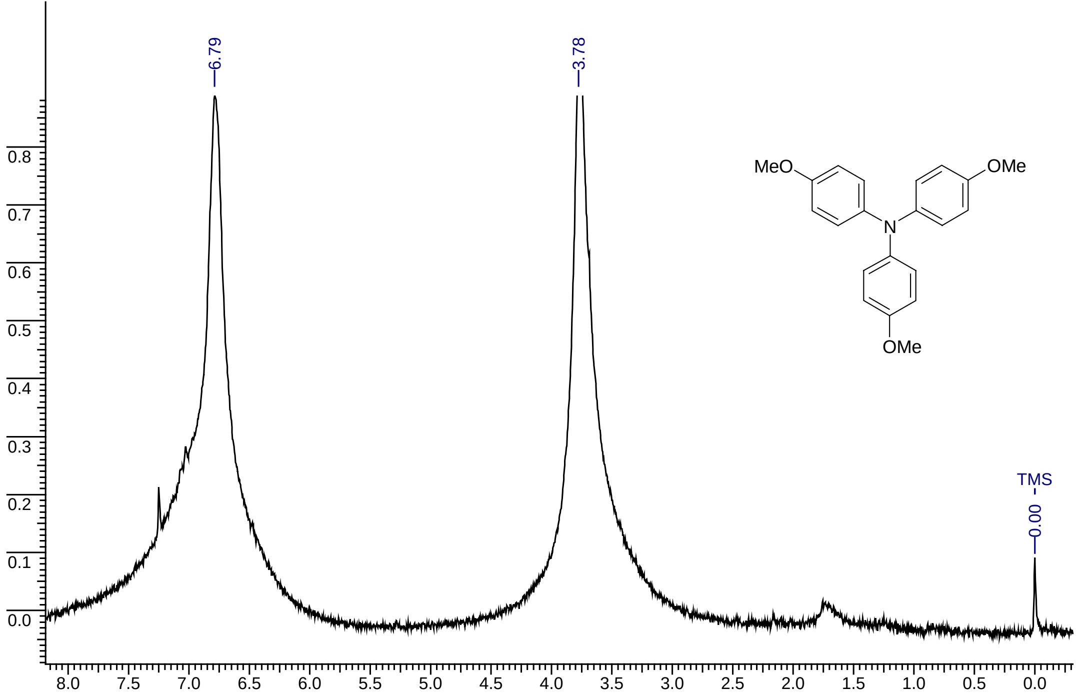


**Figure 2.20:** $^{13}$C NMR of 4, 4’, 4’’-trimethoxy triphenylamine

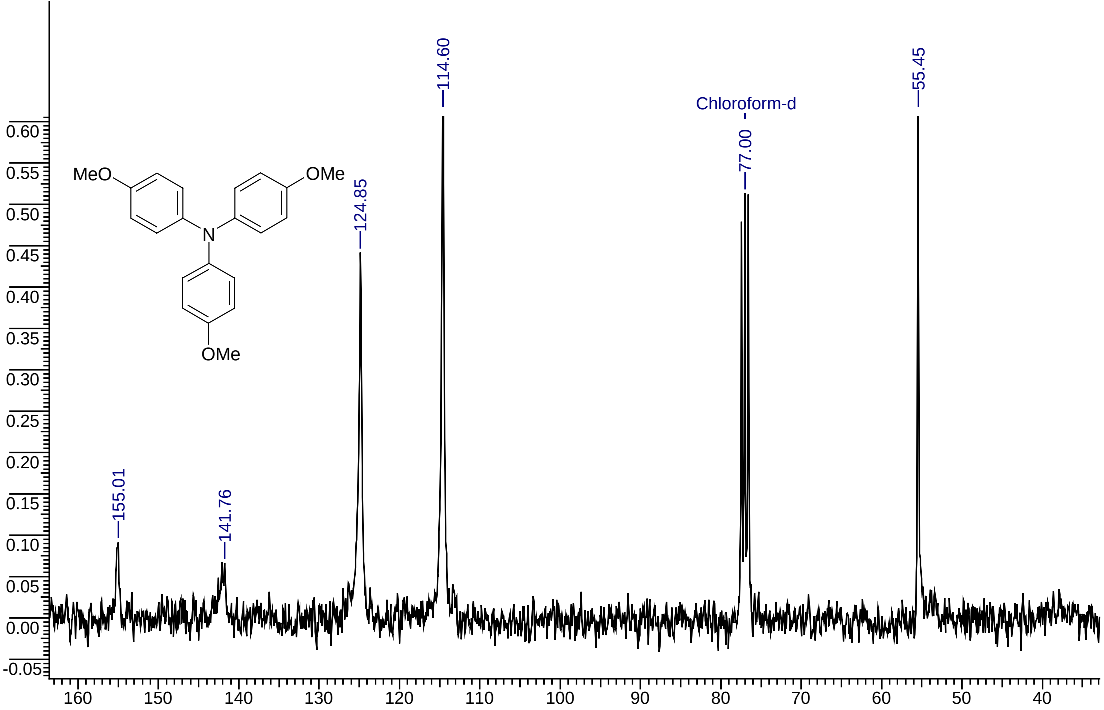
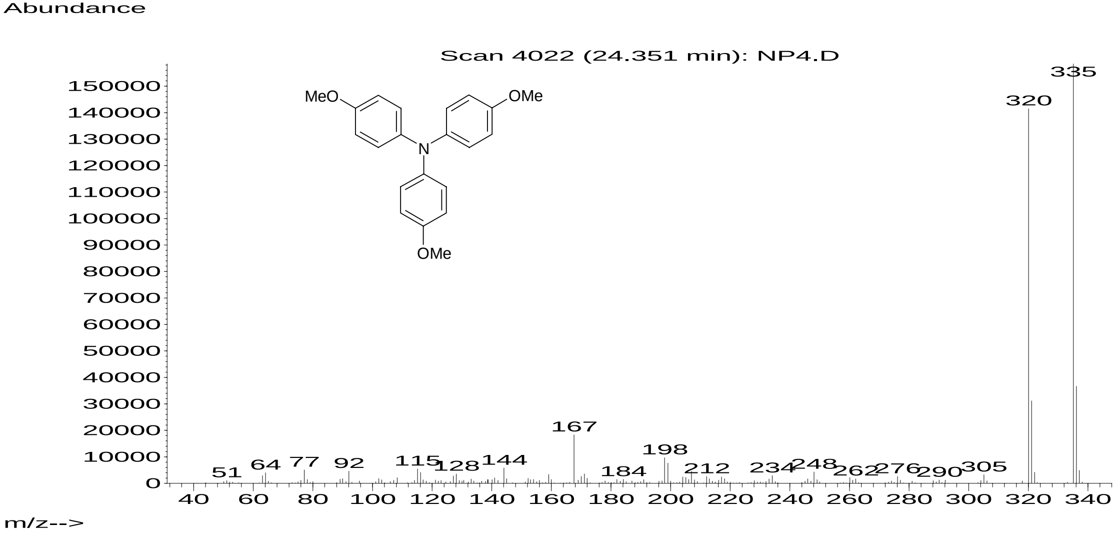
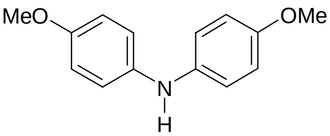


**Figure 2.21:** GC-MS of 4, 4’, 4’’-trimethoxy triphenylamine



## (vii) 4, 4’-dimethoxy triphenylamine



### (i) NMR:

**$^1$H NMR** (CDCl$_3$ 200 MHz) δ 3.77 (s, 6H), 6.84 (bs, 8H)

**$^{13}$C NMR** (CDCl3 75 MHz) δ 55.6, 114.7, 119.8, 121.4, 130.3

**(ii) GC MS:** M/z 229, 214 (base peak), 207, 199, 171, 154, 143, 115, 77, 44

**(iii) Elemental analysis:** Calculated for $C_{14}H_{15}NO_2$: C 73.34, H6.59, N 6.11; found C 73.90, H 6.14, N 6.38.

**Figure 2.22:** $^{1}$H NMR of 4, 4’-dimethoxy triphenylamine

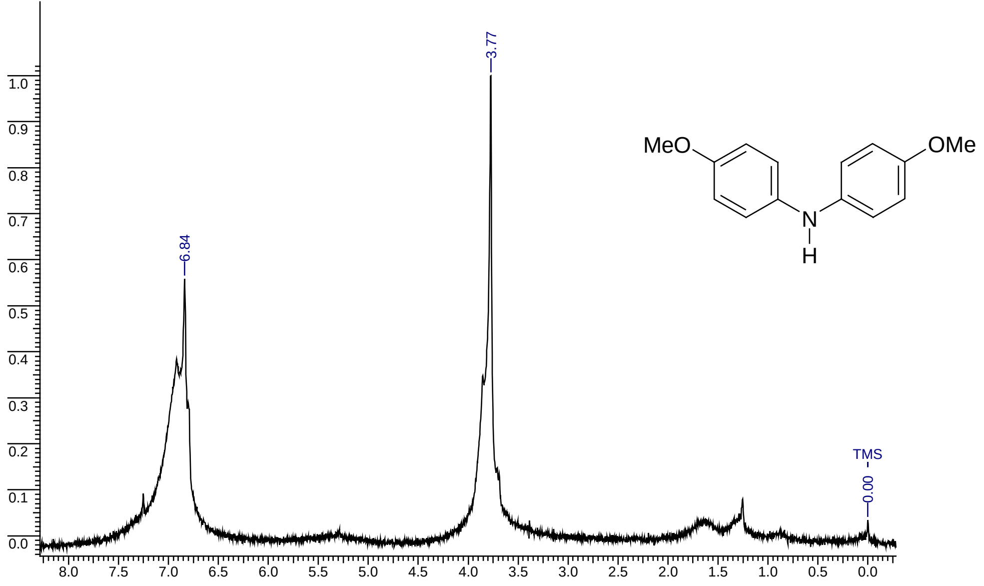


**Figure 2.23:** $^{13}$C NMR of 4, 4’-dimethoxy triphenylamine

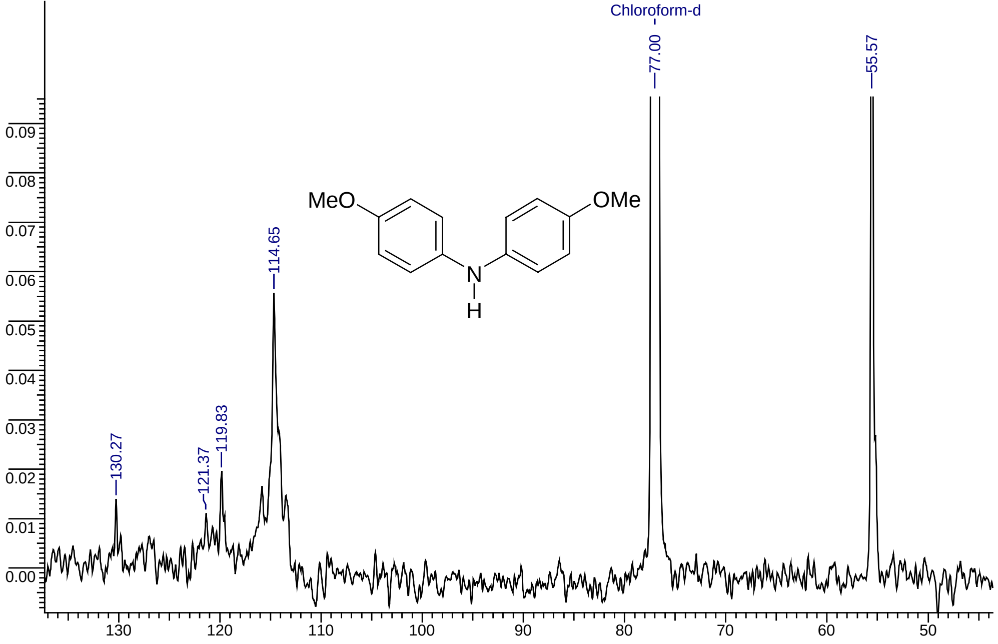
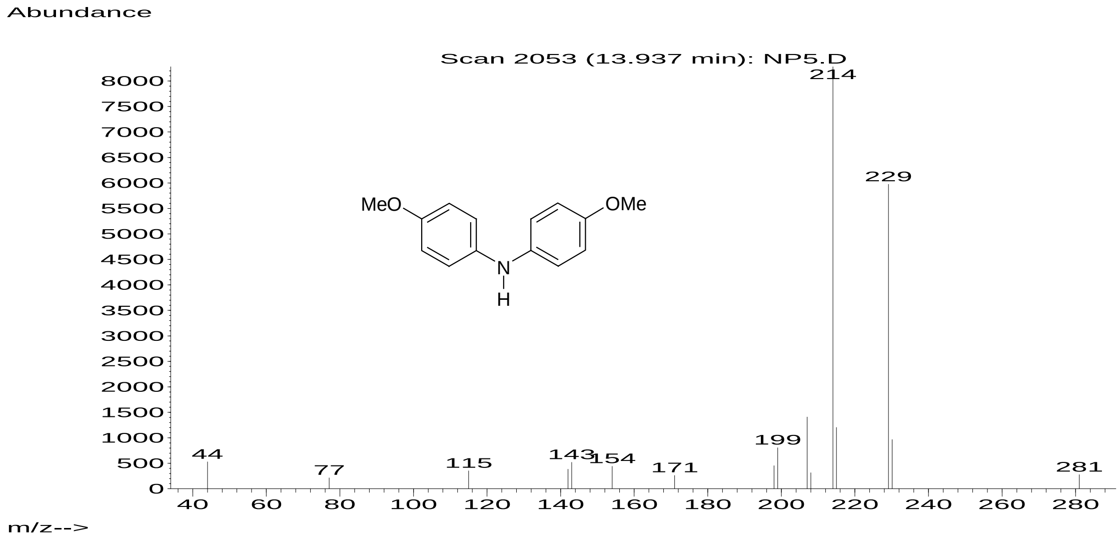


Figure 2.24: **GC-MS** of 4, 4’-dimethoxy triphenylamine



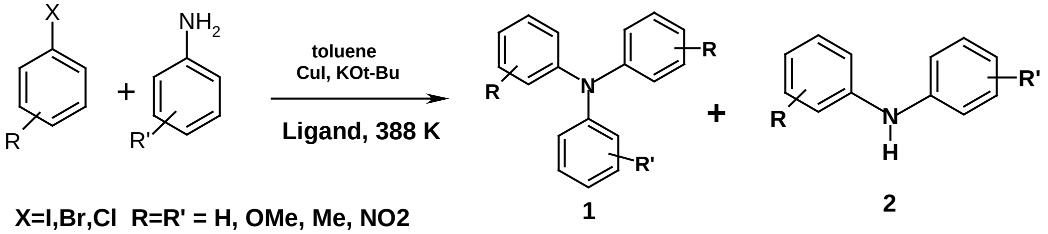
# Copper-Catalyzed Amination of Arylhalides with Ligand

## 2.6 Introduction

Arylamines are ubiquitous in numerous fields of chemistry.[1b] Conventional methods of synthesis of triarylamines; drawbacks of Ullmann coupling and their applications have been presented in *section 2.1.*

Even though Ullmann coupling was discovered in early nineteenth century,[12] there was no major improvement in copper catalyst until 1999. Goodbrand and Hu[3] successfully developed highly active and selective catalyst for amination of arylhalides, with the use of CuCl/1,10-phenanthroline catalyst system and KOH as a base, reaction proceeds smoothly at 398 K temperature (as against >493 K for conventional Ullmann synthesis) to give 70 to 85 % yield of triaryl amines. Extensive research is being carried on the development of improved copper based catalyst using various ligands and bases. Gujadhur *et. al.*[13] have found that copper complex Cu $(PPh_3)_3Br$, is active for amination of mono- and di-arylamines to di- and tri-arylamines respectively using $Cs_2CO_3$ as a base at 393 K. Gujadhur *et. al.*[14] have shown that the well define copper (I) complexes such as $Cu(Phen)(PPh_3)Br$ and $Cu(neocup)(PPh_3)Br$ are active for mono-amination as well as bis-amination of aryliodide, yields in the range of 70 to 85 % of triarylamines as products were reported. Jerphagon *et. al.*[15] have investigated amination of alkylamines using aminoarenethiolate-copper (I) complexes as catalyst. They got yields in the range of 40 to 90 % of desired products, in 16 hours at 433 K. Buchwald systematically investigated *O*-containing ligands for the arylhalides and alkylamines as the reactants.[16,17,18] Kwong *et. al.*[16] have investigated the use of various glycols as ligand and found that ethylene glycol as ligand gave 70 to 90 % yield of desire product in 18 hours reaction time at 353 K. However 20 equivalents of ethylene glycol is required with respect to CuI for excellent catalytic activity. Kwong *et. al.*[17] have reported the use of diethylsalicymide as ligand (catalyst to ligand ratio: 1 : 4) and yields obtained were in the range of 80 to 90 % in 18 to 22 hours reaction time at 363 K. A significantly higher activity was obtained using β-diketones as ligands at room temperature for alkyl amine.[18] Yields obtained were in the range of 90 to 99 % in 1 to10 hours. Research work carried out for last few years has led to the development of improved copper catalyst for *N*-arylation of various substrate such as anilines[19], imidazoles[20], amides[21] and nitrogen heterocycles[22,23] etc. have been reported. However most of the advancement in the improvement of yields were made for alkylamines as substrate and there is no major improvement on industrially important arylamines for the improvement of yields in last seven years. Hoverer the research on ligand-assisted copper catalyzed reaction showed that presence of ligand increases catalyst solubility, stability, and except few cases prevents aligomerization of metal. Further it was noticed that judicious choice of promoters and catalytic conditions reactions could be efficiently performed at moderate conditions as against drastic conditions that were necessary in absence of ligand.

Our goal was to develop a facile and single step catalytic system for synthesis of triarylamines. It is desirable to develop a cheaper catalyst system with high activity and selectivity for synthesis of triarylamines. For this purpose various *N*- and *P*- containing mono dentate as well as chelating ligands have been screened. Detail investigation on the effect of various process parameters such as temperature, solvent, substrate concentrations and catalyst concentration on activity and selectivity have been carried out and described in this section.



**Scheme 2.4:** Copper catalyzed amination of arylhalides

## 2.7 Experimental Section

### 2.7.1 Materials

Aniline, substituted aniline derivatives, Copper (I) Iodide (CuI), toluene, chlorobenzene KO*t*-Bu, NaO*t*-Bu, KOH, NaOH, $K_2CO_3$, $Cs_2CO_3$, NaOMe, TEA, tri-*t*-butylamine, and $NaHCO_3$ were purchased from *s. d.* Fine Chemical Ltd. India. Iodobenzene, bromobenzene, Copper (II) bromide, Copper carbonate basic ($Cu(II)CO_3.Cu(OH)_2$), $Ph_2P$-$CH_2$-$PPh_2$ [Bis (diphenyl phosphino) methane (DPPM)], $Ph_2P$-CH=CH-$PPh_2$ [Cis1, 2 Bis (diphenylphoshino) ethylene (DPPE)], $Ph_2P$-$(CH_2)_3$-

$PPh_2$ [1,3-bis(diphenyl phosphino )propane (DPPP)], $Ph_2P-(CH_2)_4-PPh_2$ [1,4--bis(diphenyl phosphino)butane (DPPB)], $Ph_2P-(CH_2)_5-PPh_2$ [1,5--bis(diphenyl phosphino)pentane (DPPT)], $Ph_2P-(CH_2)_6-PPh_2$ [1,6-bis(diphenyl phosphino)hexane (DPPH)], (*o*-tolyl)$_3$P (Tri-*o*-tolyl phosphine), P(Bu)$_3$(Tri-n-butyl phosphine), $PPh_3$(Triphenyl phosphine), Pyridine, Bipyridine, terpyridine, quinoline, isoquinoline, 1,10-phenanthroline, 2,6-diphenyl pyridine, 4-phenyl pyridine, 2-phenylpyridine, 8-hyroxy quinoline, 2-chloropyridine, neocuprine, 2,2'-bipyridil, 3,4,7,8-tetramethyl-1,10-phenanthroline, 6,7-dihydro,5,8 dimethyl dibenzyl-1,10-phenanthroline, *N, N, N', N'*-tetra ethyl ethylene diamine, *N, N, N', N'*- tetramethyl ethylene diamine, *N, N, N', N'*-tetra ethyl 1, 3 propane diamine, 1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU); 1,5-Diazabicyclo[2.2.0] non-5-ene (DBN); 1,4-Diazabicyclo[2.2.2] octane (DABCO) 1,5-Diazabicyclo[4.3.0] none-5-ene, and *N,N*-Dimethylbenzylamine all these were purchased from Aldrich Chemical Ltd USA.

### 2.7.2 Analytical methods

Analytical method was same as discussed in *section 2.2.3* of this chapter.

### 2.7.3 General Experimental Procedure

Amination reactions were carried out in a 50 ml capacity two neck round bottom flask. In a typical experiment, Toluene (23 ml) was charged to the round bottom flask followed by catalyst (0.28mmol), ligand (0.28mmol), arylamine (7.85mmol), aryl halides (16.48mmols), and base (23.5mmol). Reflux condenser was attached to the flask and the round bottom flask was flushed twice with nitrogen or argon to ensure removal of air. Nitrogen balloon was attached to the condenser, to maintain inert atmosphere during the reaction. The round bottom flask was then stirred by magnetic needle and heated to 388 K in oil bath and the reaction was continued for 2 to 5 hours. After cooling to room temperature, the reaction solution was filtered (liquid sample taken for GC analysis) to remove the precipitated base and washed with toluene few times. Solution was concentrated to obtain crude product, which was chromatographed to obtain pure products. The products separated, were characterized by IR, GC-MS and NMR analysis and compared with authentic samples whenever possible.

The sequence of addition during charging the reactants was as follow:

Solvent → Substrate → Catalyst + Ligand → Base

A typical experimental setup is shown in *Figure 2.25*.

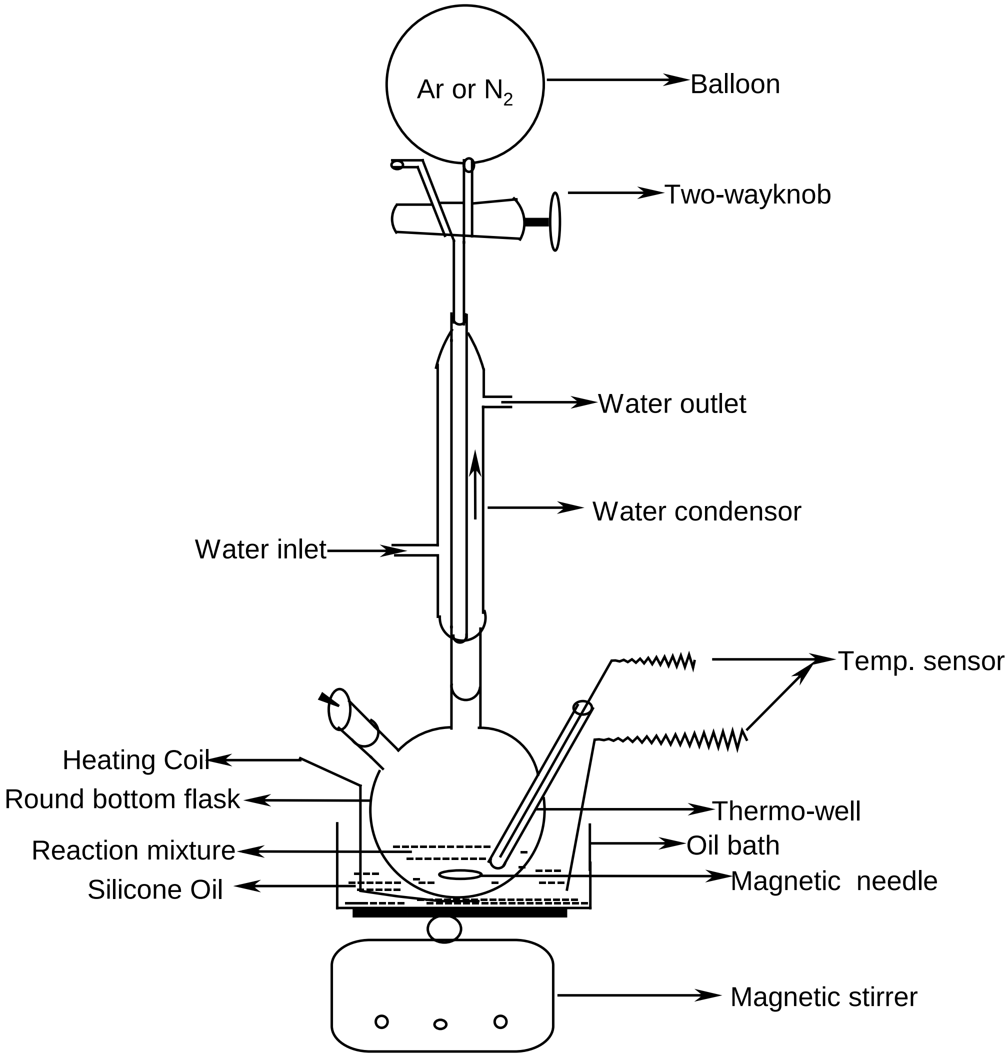


**Figure 2.25:** Schematic diagram of reaction setup

## 2.8 Results and Discussion

Objective of the work was to develop copper catalyst system with high activity and selectivity for triarylamine synthesis. In previous section results obtained on ligand free copper-catalyst have been presented. Recent literature on amination reaction clearly shows improved results for palladium and copper-catalyst system. In present work various *N*- and *P*-containing ligands have been screened to improve activity of CuI catalyst. Effect of various reaction conditions such as base, solvent and temperature etc. on the conversion and yield has been investigated in detail. The results are present below.

### 2.8.1 Effect of Catalyst precursors

Various copper-catalyst precursors were screened using 1,10-phenanthroline as a ligands and potassium tertiary butoxide (KO*t*-Bu) as a base, and the results are presented in *Table 2.8.* CuI was found to be the best catalyst precursor for1,10-phenanthroline ligand *(Table 2.8, sr. no. 1).* With 1,10-phenanthroline as a ligand, yield of TPA decreased with catalyst precursors in the order: CuI>CuBr~CuCl>CuOt-Bu. Activation of amine is proposed to be the first step in the conventional Ullmann condensation reaction mechanism,[4] and the observed drop in activity may be due to lower activity of other catalyst precursors compared to CuI. Cu (II) salts also gave lower yield of TPA *(Table 2.8, sr. no. 3 and 6)* compared to CuI. Cu (I) compounds are proposed to be active species in the amination reaction and Cu (II) salts used as catalyst precursors have to be reduced to give active Cu (I) intermediate leading to lower catalytic activity and lower yield of TPA. Thus best results were obtained using CuI as a catalyst precursor and further work was carried out using CuI.

**Table 2.8:** Effect of catalyst precursors

| Sr. No. | Catalyst | Reaction Time, (h) | Conv. of Aniline, (%) | TPA, (%) | | DPA, (%) | |
|---|---|---|---|---|---|---|---|
| | | | | Sele. | Yield | Sele. | Yield |
| 1 | CuI | 3.5 | 98 | 93 | 91 | 4 | 4 |
| 2 | CuBr | 3.5 | 90 | 82 | 74 | 9 | 9 |
| 3 | $CuCO_3.Cu(OH)_2$ | 3.5 | 90 | 71 | 64 | 19 | 17 |
| 4 | $Cu(OAC)_2$ | 3.5 | 89 | 73 | 56 | 20 | 18 |
| 5 | CuCl | 3.5 | 85 | 61 | 52 | 35 | 29 |
| 6 | $CuBr_2$ | 3.5 | 83 | 75 | 62 | 20 | 17 |
| 7 | CuO*t*-Bu | 5 | 85 | 58 | 49 | 11 | 10 |

***Reaction conditions:*** *Aniline: 7.85 mmol; Iodobenzene: 16.48 mmol; Catalyst: 0.28 mmol; 1,10-phenanthroline: 0.28 mmol; KOt-Bu: 23.5 mmol; Toluene: 23 ml; Temperature: 385 K.*

### 2.8.2 Effect of Base with Respect to Ligands

Arylation of aniline is more difficult as compared to aliphatic amines.[24] Generally strong bases are required for the reaction. Therefore, selection of base is very important for C-N coupling process. During the screening work of ligand, strong base KO*t*-Bu was used, however it was not clear if one base which is good for ligand. Therefore, present investigation of screening of bases was carried out with three different ligands. The results obtained are presented in *Table 2.9.* KO*t*-Bu base is most efficient amongst bases investigated and it can be seen that ligand do not show much it in alternating the activity of base system. The yield of DPA and TPA are not affected to great extent. Except the ligand 1,10-phenanthroline, where in KOH as a base shows exceptionally high activity and TPA-DPA yield compared to alter two ligands *(Table 2.9, entry 3 and 5).* It may be due to better efficiency of $K^+$ as seen in KO*t*-Bu *(Table 2.9, entry 1).* Compared to $K^+$ as cation $Na^+$ show poor activity (Table 2.9, entry, 2 and 5). From this point of view our results on KOH as base and 1,10-phenathroline as ligand show interesting yield of TPA and DPA (~ 30 % for KOH as against nil in NAOH, *Table 2.9, entry 3 and 5*).

**Table 2.9:** Effect of bases with ligands

| Sr. No. | Base | Aniline conv., (%) | | | Yield of TPA, (%) | | | Yield of DPA, (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Bipy | Phen | 2,6DPP | Bipy | Phen | 2,6DPP | Bipy | Phen | 2,6DPP |
| 1 | KO*t*-Bu | 100 | 98 | 100 | 95 | 91 | 94 | 2 | 4 | 1 |
| 2 | NaO*t*-Bu | 59 | 42 | 39 | 13 | 16 | 12 | 41 | 21 | 22 |
| 3 | KOH | 22 | 74 | 20 | 4 | 35 | 1 | 13 | 29 | 3 |
| 4 | NaOMe | 18 | 17 | 18 | 8 | 0 | 0 | 8 | 0 | 0 |
| 5 | NaOH | 16 | 19 | 16 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | DBU$^\$$ | 18 | - | 16 | 0 | - | 0 | 0 | 0 | 0 |
| 7 | TEA | 15 | - | - | 0 | - | - | 0 | - | - |

***Reaction conditions:*** *Aniline: 7.85 mmol; Iodobenzene: 16.48 mmol; CuI: 0.28 mmol; 2,6-diphenyl pyridine: 0.28 mmol; Base: 23.5 mmol; Toluene: 23 ml; Time: 3.5h; Temperature: 385 K;* $^\$$ *= 1,8 diazabicyclo [5.4.0] undec-7-ene.;* ***Bipy*** *= 2,2'-bipyridine;* ***Phen*** *= 1,10-phenanthroline;* ***2,6DPP*** *= 2,6-diphenylpyridine;*

### 2.8.3 Effect of Substrate Concentration

Effect of aniline: iodobenzene ratio was investigated to optimize the yield of TPA. As presented in *section 2.3.6,* the stoichimetric ratio of aniline : iodobenzene for TPA formation is 1:2. We have taken one, two and three equivalent of iodobenzene with respect to aniline. It was found that two equivalent of iodobenzene gave 98 % conversion of aniline and 91 % yield of TPA *(Table 2.10, sr. no 2).* Three equivalents of iodobenzene with respect to aniline gave 99 % conversion of aniline and 93 % yield of TPA *(Table 2.10, sr. no. 3).* These results were shown that using three equivalent of iodobenzene, marginal improvement in yield (*Table 2.10, sr. no. 2 and 3)* is realized. With iodobenzene concentration increase their was increase in yield and decrease in concentration results in decrease in yield of TPA *(Table 2.10, sr. no. 1,2 & 3).* This indicates that the yield of TPA depends upon the concentration of iodobenzene. Goodbrand and Hu [3] and Gujadhar *et. al.*[13] have also obtained similar results. Hence to avoid excess use of costly iodobenzene, further work was carried out using two equivalent of iodobenzene with respect to aniline. *Figure 2.26* shows the impact of iodobenzene concentration on selectivity of TPA, however, the conversions are not greatly affected by iodobenzene concentration (85, 98 and 99 %, conversion, *Table 2.10, sr. no. 1, 2 and 3).*

**Table 2.10:** Effect of substrate concentration

| Sr. No | Aniline: Iodobenzene | Conv. of Aniline, (%) | TPA, (%) | | DPA, (%) | |
|---|---|---|---|---|---|---|
| | | | Sele. | Yield | Sele. | Yield |
| 1 | 1:1 | 85 | 23 | 20 | 18 | 15 |
| 2* | 1:2.1 | 98 | 93 | 91 | 4 | 4 |
| 3 | 1:3 | 99 | 94 | 93 | 2 | 2 |

***Reaction conditions:*** **Aniline: 7.85 mmol; *Iodobenzene: 16.48 mmol; CuI: 0.28 mmol; 2,2'-bipyridine: 0.28 mmol; KOt-Bu: 23.5 mmol; Toluene: 23 ml; Time: 3.5 h; Temperature: 385 K.*

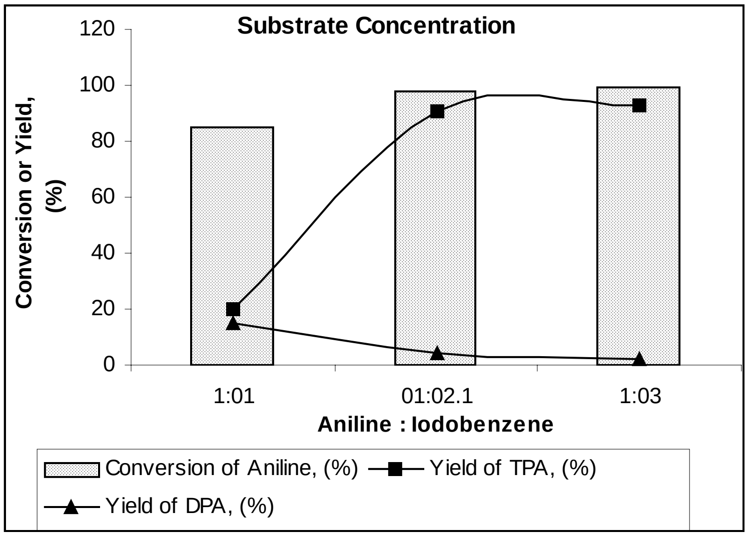


**Figure 2.26:** Effect of Substrate Concentration

(**Reaction Conditions:** see *Table 2.10*)

### 2.8.4 Effect of Solvents

Various solvents were screened using CuI/2,2'-bipyridine as a catalyst system as shown in *Table 2.11*. Low yields of TPA were obtained with polar solvents like *N*, *N'*-dimethyl formamide, tetrahydrofuran and non-polar solvents like cyclohexane. The formation of benzene (~4 %) by reduction of iodobenzene was also observed for THF and DMF solvents. Similar results have also been obtained for Pd-catalyzed amination reaction using NaO*t*-Bu as a base and DMF, THF as solvents.[1] Best results were obtained with toluene as a solvent *(Table 2.11, sr. no. 1)*. The screened solvents can be arranged in decreasing order of TPA yield as: toluene>1,4-dioxane>acetonitrile>*N,N'*-dimethylformamide>2-methyl-propane-2-ol> tetrahydrofuran >cyclohexane. Thus less polar solvents like toluene are suitable for copper catalyzed amination reaction.

**Table 2.11:** Effect of solvents

| Sr. No | Solvent | Conv. of Aniline, (%) | TPA, (%) | | DPA, (%) | |
|---|---|---|---|---|---|---|
| | | | Sele. | Yield | Sele. | Yield |
| 1 | Toluene | 99 | 95 | 94 | 2 | 2 |
| 2 | 1,4 dioxane | 84 | 63 | 53 | 20 | 17 |
| 3 | DMF* | 60 | 15 | 9 | 68 | 41 |
| 4 | Tetrahydrofuran | 52 | 6 | 3 | 50 | 26 |
| 5 | Acetonitrile | 47 | 30 | 14 | 61 | 29 |
| 6 | *t*-Butanol | 34 | 24 | 8 | 50 | 17 |
| 7 | Cyclohexane | 30 | 6 | 2 | 24 | 7 |

***Reaction conditions:*** *Aniline: 7.85mmol; Iodobenzene: 16.48mmol; CuI: 0.28mmol; 2,2'-bipyridine: 0.28mmol; Base: 23.5mmol; Solvent: 23ml; Time: 3.5h; Temperature: reflex temperature. * 388K.*

### 2.8.5 Effect of Ligands

Extensive ligand screening has been done recently by Buchwald,[22,23] Scholz,[25] Cristau[26] and by us.[27,28] Scholz et al.[25] have shown that the selectivity and productivity of mono arylation of aniline can be carefully tuned by ligand variation. This type of fine-tuning by copper catalyzed system is rare and is more common for palladium system. Various *N*- and *P*- containing ligands were screened for amination of iodobenzene and the results are present bellow

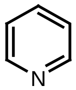
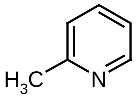
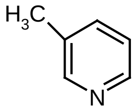
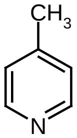
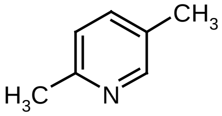
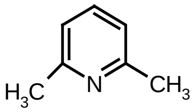
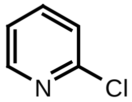
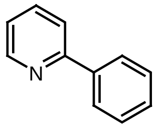
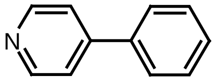
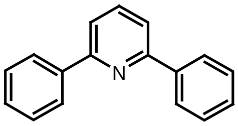
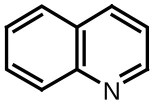
#### 2.8.5.1 *N*-containing ligands

Screening of various *N*-containing ligands was carried out using CuI as a catalyst precursor and KO*t*-Bu as a base *(Table 2.12).* Pyridine as a ligand gave 58 % yield of TPA while 2,2'-bipyridine as a ligand gave complete conversion of aniline with 95 % yield of TPA *(Table 2.12, sr. no. 1 and 16).* Various substituted pyridines were screened and it was observed that electron-donating groups (methyl, phenyl and carboxylate) led to increase in catalytic activity. Thus with 2-phenyl pyridine and 4-phenyl pyridine 62 and 63 % yield of TPA was obtained respectively, while with 2,6-diphenyl pyridine complete conversion of aniline with 94 % yield of TPA was obtained *(Table 2.12, sr. no. 8 to 10).* Similar trends were observed with methyl and acetyl groups on the pyridine ring *(Table*

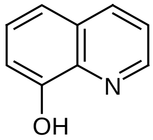
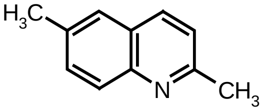
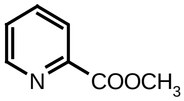
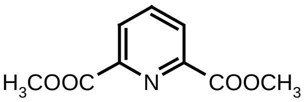
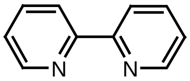
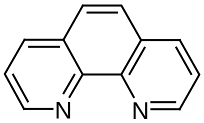
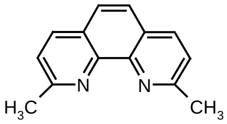
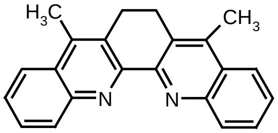
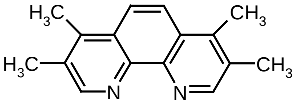
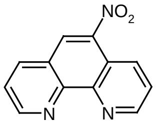
*2.12, sr. no. 2 to 6 and 14, 15).* With electron withdrawing group like Cl *(2-chloropyridine, Table 2.12, sr. no. 7),* low yield (33 %) of TPA was obtained. For other ligands *(Table 2.12, sr. no. 21 to 25 and 28)* the yields of TPA obtained were in a range of 43 to 83 %. For 2,2'-dithiobis(5-nitropyridine) poor yield of TPA (20 %) was obtained due to electron withdrawing nitro group as well as thio bridge between the pyridine rings *(entry 26)*. With 2,6-dimethyl quinoline and 8-hyroxy-quinoline as ligand 78 % and 73 % yields of TPA were obtained respectively which is slightly better than 61 % obtained with quinoline as a ligand *(Table 2.12, sr. no. 11, 12 and 13).*

It can be seen from the results obtained on screening of *N*-containing ligands that, the activity of copper catalyst formed in-situ can be qualitatively explained on the nature of ligand. On the basis of steric and electronic effects involved in the coordination of nitrogen atom to copper the strength of Cu-N bond may be one of the important factors that decide the activity of copper catalyst.[25] For example, in pyridine and picolines as ligand, the activity of copper complexes catalyst is lowest with 2-Me and 2-chloro pyridine as ligand *(entry 2 and 7)*, while 3 and 4 methyl pyridine shows comparable activity to pyridine *(Table 2.12 entry 2, 7 and 3, 4)*. The lower activity observed for 2-Me pyridine is due to steric factor of methyl group in ortho position to N, and in chloro derivative of pyridine both electron withdrawing as well as steric hindrance make Cu-N bond weaker that result in poor stability of complex leading decomposition to inactive copper.[25] Dimethyl substituted pyridines *(Table 2.12, entry 5, 6)* and phenyl substituted pyridines. *(Table 2.12, entry 8, 9 and 10)* show higher activity compared to mono methyl pyridine due to better donating ability of these ligands compared to methyl pyridines and the steric factor may be of less important in this case. Similar explanation for bidentate and tridentate pyridines are possible for their catalytic activity. It may be noted however, that the results on activity of catalyst describe the importance of steric and electronic effect but, catalyst activity can depend on many factors other than strength of metal ligand bond, e.g. too strong or weak bond (Cu-N) may be deterrent to catalyst activity. A similar approach for explaining the effect of salen ligand in copper catalyzed amination has been adopted earlier.[26] Their investigation showed that improvement of the catalyst activity can be explained on the basis of binding efficiency of ligand and it`s stabilizing ability of copper coordination number.

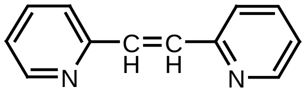
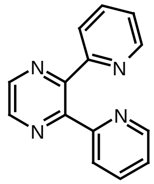
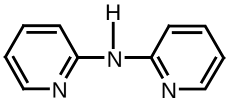
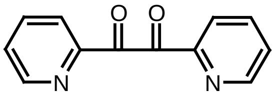
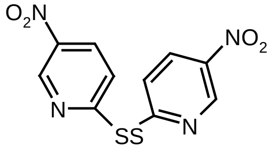
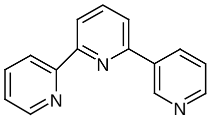
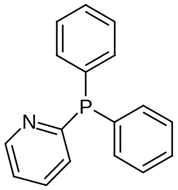
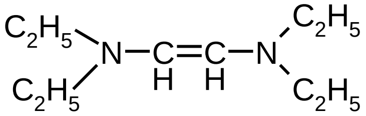
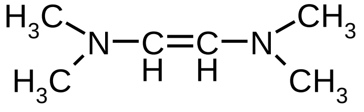
**Table 2.12:** Copper catalyzed amination: effect of *N*-containing ligands

| Sr. No. | Ligand | Conv. of Aniline, (%) | DPA, (%) | | TPA, (%) | |
|---|---|---|---|---|---|---|
| | | | Sele. | Yield | Sele. | Yield |
| 1 |  | 84 | 18 | 15 | 69 | 58 |
| 2 |  | 68 | 14 | 10 | 76 | 52 |
| 3 |  | 87 | 15 | 13 | 79 | 69 |
| 4 |  | 89 | 7 | 6 | 80 | 71 |
| 5 |  | 91 | 9 | 8 | 84 | 76 |
| 6 |  | 96 | 7 | 6 | 88 | 84 |
| 7 |  | 56 | 8 | 5 | 59 | 33 |
| 8 |  | 100 | 15 | 15 | 62 | 62 |
| 9 |  | 91 | 17 | 15 | 69 | 63 |
| 10 |  | 100 | 1 | 1 | 94 | 94 |
| 11 |  | 87 | 25 | 22 | 74 | 62 |

Continue ………

| Sr. No. | Ligand | Conv. of Aniline, (%) | DPA, (%) | | TPA, (%) | |
|---|---|---|---|---|---|---|
| | | | Sele. | Yield | Sele. | Yield |
| 12 |  | 91 | 14 | 13 | 80 | 73 |
| 13 |  | 97 | 11 | 11 | 80 | 78 |
| 14 |  | 91 | 7 | 6 | 68 | 62 |
| 15 |  | 99 | 13 | 12 | 74 | 73 |
| 16 |  | 100 | 2 | 2 | 95 | 95 |
| 17 |  | 98 | 4 | 4 | 93 | 91 |
| 18 |  | 98 | 3 | 3 | 92 | 90 |
| 19 |  | 89 | 10 | 9 | 86 | 77 |
| 20 |  | 99 | 5 | 5 | 91 | 90 |
| 21 |  | 90 | 10 | 9 | 78 | 70 |

Continue ………

| Sr. No. | Ligand | Conv. of Aniline, (%) | DPA, (%) | | TPA, (%) | |
|---|---|---|---|---|---|---|
| | | | Sele. | Yield | Sele. | Yield |
| 22 |  | 97 | 5 | 5 | 85 | 83 |
| 23 |  | 89 | 15 | 13 | 78 | 70 |
| 24 |  | 76 | 19 | 14 | 71 | 54 |
| 25 |  | 68 | 40 | 27 | 63 | 43 |
| 26 |  | 53 | 25 | 13 | 38 | 20 |
| 27 |  | 100 | 5 | 5 | 90 | 90 |
| 28 |  | 92 | 7 | 6 | 90 | 83 |
| 29 |  | 88 | 12 | 11 | 82 | 72 |
| 30 |  | 92 | 10 | 9 | 80 | 74 |

***Reaction conditions:*** *Aniline: 7.85 mmol; Iodobenzene: 16.48 mmol; CuI: 0.28 mmol; Ligand: 0.28 mmol; KOt-Bu: 23.5 mmol; Toluene: 23 ml; Time: 3.5 h; Temperature: 385 K.*

Thus, the activity of the catalyst can be improved by using pyridine-based ligands and with fine-tuning of electron donating substituents on ligands. The best results were obtained with 2,6-diphenyl pyridine as a ligand (94 % yield of TPA). The increase in yield may be due to electron donating groups on the pyridine ring as well as steric effects.

Various phenanthroline derivatives were screened however, no such significant change in the catalytic activity *(Table 2.12, sr. no. 17 to 21),* was observed. The alkyl amine ligand series such as EDATE, EDATM, and PDATE showed that, good yield of TPA was obtained (yields in the range of 72 to 74 % *Table 2.12, sr. no 29 and 30*).

### 2.8.5.2 *P*-Containing Ligands

Further the effect of monodentate and bidentate phosphine ligands were investigated. For this purpose few monodentate and bidentate ligands were screened and the results are presented below.

#### i) Monodentate phosphine ligands

Few monodentate phosphine ligands were tested for the amination of iodobenzene as shown in *Table 2.13.* Results obtained clearly show that activity as well as yield of TPA depends upon the CuI : ligand ratio. With CuI : ligand ratio of 1 : 1, reaction did not proceed and TPA formation was not observed for $PPh_3$ as a ligand.

While reaction proceeds smoothly with tri-*o*-toly phosphine and tri-*n*- butyl phosphine to give 24, 48 % yield of TPA and 18, 16 % yield of DPA respectively. With increasing ratio of CuI : ligand from 1: 1 to 1: 3 increase yield of TPA for $PPh_3$ as well as tri-*o*-toly phosphine *(Table 2.13, sr. no. 2,3,5 and 6)* were obtained. Best results were obtained at CuI : ligand ratio 1: 2 (80 % yield of TPA) using tri-*n*-butyl phosphine as a ligand. Further increase in ratio led to marginal decrease TPA yield (76 %). The observed results indicate that increase in electron density on phosphorous led to enhance catalytic activity. Schloz *et. al.*[25] earlier observed similar effect of phosphorous containing ligand on copper catalyzed arylation of aniline by chloro nitro benzene, their observation showed that reaction was accelerated by a factor of almost two by electron rich triscyclopentylphosphine compared to triphenyl phosphine which has poor electron donating ability compared to triscyclopentylphosphine.

Table 2.13: Effect Monodentate Phosphine Ligands

| Sr. No. | Ligand | CuI: Ligand Ratio | Conv. of aniline, (%) | Product Yield, (%) | |
|---|---|---|---|---|---|
| | | | | TPA | DPA |
| 1 | $PPh_3$* | 1:1 | 12 | 0 | 0 |
| 2 | $PPh_3$ | 1:2 | 62 | 15 | 17 |
| 3 | $PPh_3$ | 1:3 | 73 | 19 | 25 |
| 4 | (*o*-tol)$_3$P* | 1:1 | 67 | 24 | 18 |
| 5 | (*o*-tol)$_3$P | 1:2 | 86 | 43 | 15 |
| 6 | (*o*-tol)$_3$P | 1:3 | 89 | 51 | 9 |
| 7 | $P(Bu)_3$* | 1:1 | 80 | 48 | 16 |
| 8 | $P(Bu)_3$ | 1:2 | 95 | 80 | 3 |
| 9 | $P(Bu)_3$ | 1:3 | 91 | 76 | 6 |

***Reaction condition:*** *Aniline: 7.85 mmol; Iodobenzene: 16.48 mmol; CuI: 0.28 mmol; *Ligand: 0.028 mmol; Toluene: 23 ml; KOt-Bu: 23.5 mmol; Temperature: 385 K; Time: 3.5 h.*

### ii) Bidentate diphos ligands

Various bidentate diphos ligands have been screened for amination reaction and results are presented in *Table 2.14*. All the diphosphine ligands screened were active for amination of iodobenzene and the best results were obtained using DPPP as a ligand (80 % yield of TPA, *Table 2.14 sr. no 3).* Activity as well as yield of triphenylamine increased with increase in carbon chain length initially ($C_1$-$C_3$) and decreased with further increase in carbon chain length between the phosphines (See *Figure 2.27).* It is likely that the ligands (DPPT and DPPH) behave as monodentate ligands leading to lower the activity.[29] Thus in the case of diphos, formation of *cis*-chelating with CuI in reaction media is possible and this active catalytic species increase the catalytic activity and selectivity for the amination of iodobenzene.

The results on ligand screening show that bidented ligands having *N*- as well as *P*- atom give better activity compare to monodentate ligands. Improved results obtained can be explained on the formation of cis-chelating complex, using bidentate ligands. 2,6-diphenyl pyridine gave excellent catalytic activity compare to pyridine as a ligand. The

**Table 2.14:** Effect of Diphos Ligands

| Sr. No. | Ligand | Conv. of Aniline, (%) | Yield, (%) | |
|---|---|---|---|---|
| | | | TPA | DPA |
| 1 | $Ph_2P$-$CH_2$-$PPh_2$ (DPPM) | 83 | 30 | 22 |
| 2 | $Ph_2P$-$CH_2$=$CH_2$-$PPh_2$ (DPPE) | 86 | 63 | 19 |
| 3 | $Ph_2P$-$(CH_2)_3$-$PPh_2$ (DPPP) | 90 | 80 | 6 |
| 4 | $Ph_2P$-$(CH_2)_5$-$PPh_2$ (DPPT) | 72 | 36 | 24 |
| 5 | $Ph_2P$-$(CH_2)_6$-$PPh_2$ (DPPH) | 40 | 10 | 24 |

***Reaction conditions:*** *Aniline: 7.85 mmol; Iodobenzene: 16.48 mmol; CuI: 0.28 mmol; Ligand: 0.28 mmol; KOt-Bu: 23.5 mmol; Toluene: 23 ml; Time: 3.5 h; Temperature: 385 K.*

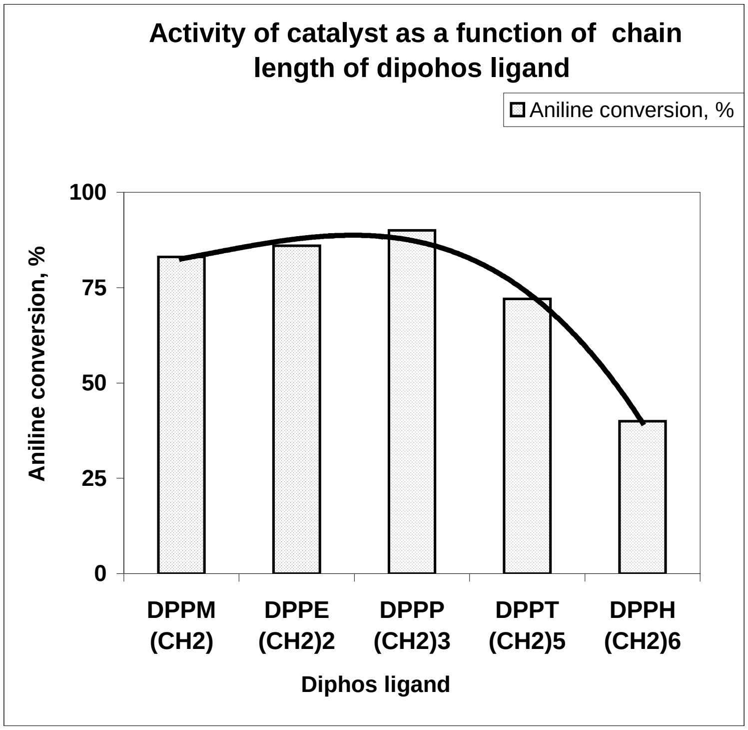
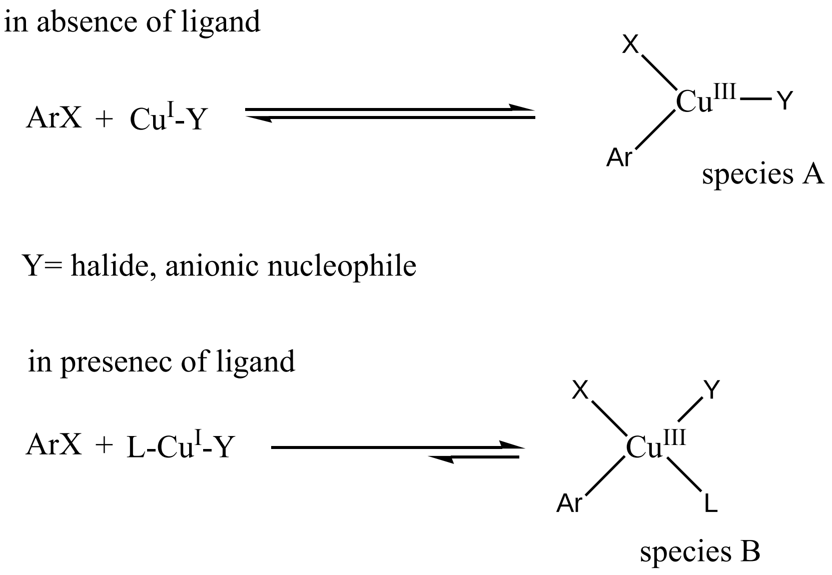


**Figure 2.27:** Activity of catalyst as a function of chain length of diphos ligand (**Reaction Condition:** see *Table 2.14*)

observed results may be due to electron donating group present in *o*-position as well as steric effects. Buchwald has also observed similar effects in the *N*-arylation of hexylamine using CuI catalyst and phenol base ligands.[16]

The results on ligand effect confirm that addition of suitable ligand improves the catalytic system of copper over that without addition of such ligands. The ligands are shown to assist the crucial oxidative addition of aryl halide to Cu(I) in Ullmann condensation reactions.[26] These investigators have speculated the possible role played by the addition of ligand in favoring the otherwise equilibrium reaction between oxidative addition of aryl halide to the Cu(I) precursor.[26] The well-documented copper catalyzed halogen exchange in aryl halides is also an indicative of this reversibility,[30,31,32] seeing that the reverse reaction is equivalent to reductive elimination of aryl halide from copper(III). Hard donor ligands (Lewis bases with nitrogen or oxygen binding sites) are expected to be better, since they can display a higher affinity toward hard copper (III) than soft copper (I).[33,34] Due to their suitable σ-donor and π--acceptor properties, as well as their chelating nature, they might exhibit a superior ability to stabilize the oxidative addition product (species B), thus shifting to the right the position of the equilibrium in *Scheme 2.5*



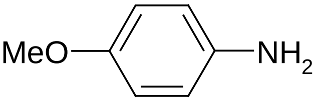
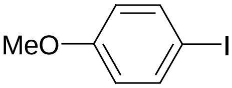
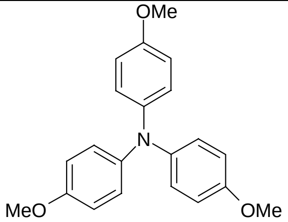
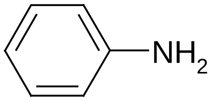
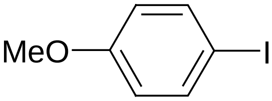
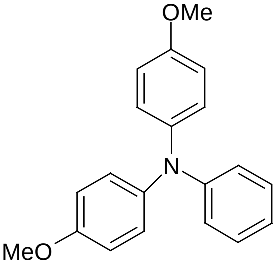
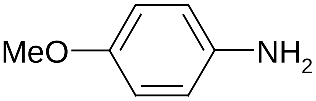
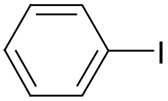
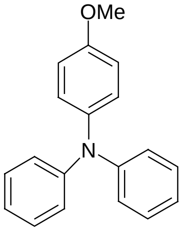
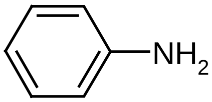
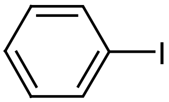
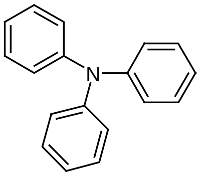
**Scheme 2.5 Plausible role of ligand in Ullmann condensation reaction[26,30]**

Thus it can be envisage that, in presence of ligand more amounts of $Cu^{III}$ catalytic species can be present which is responsible for C-N coupling reaction than in absence of ligand.

### 2.8.6 Synthesis of Amine Derivatives

A few arylhalides and substituted anilines were screened using CuI-2,2'-bipyridine as a catalyst system *(Table 2.17)*. In all these reactions an isolated yield of

**Table 2.17:** CuI/2,2'- bipyridine Catalyzed Amination: Screening of Arylhalides and Arylamines

| Sr. No. | Aryl amine | Arylhalide | Product | Yield*, (%) |
|---|---|---|---|---|
| 1 |  |  |  | 95 |
| 2 |  |  |  | 95 |
| 3 |  |  |  | 94 |
| 4 |  |  |  | 90 |

***Reaction conditions:*** *Arylamines: 7.85 mmol; Arylhalides: 16.48 mmol; CuI: 0.28 mmol; 2,2'-bipyridine: 0.28 mmol; KOt-Bu: 23.5 mmol; Toluene: 23 ml; Time: 3.5 h; Temperature: 385 K; *: isolated yields.*

95 % triarylamine was achieved in 3.5h. This is the first report of synthesis of triarylamine in a single step with very high yield in a reaction time 3.5 hours at 388 K. All these amine derivatives are important for industry.[1,2] These derivatives are characterized by NMR, IR, and GCMS, elemental analysis, as (*see section 2.5* ).

## 2.9 Conclusion

The results obtained clearly shows a significant improvement in the yield of triarylamine with use of bidentate ligand (1 equivalent to Cu) and KO*t*-Bu as base. Best result were obtained using 1,10-phenanthroline and 2,2'-bipyridine (91 to 95 % yield of TPA) as ligands. The higher activity obtained using bidentate ligand (1 equivalent to Cu) may be due to blocking of adjacent *cis* sites of the Cu catalyst. Thus coordination of the amine and aryl group of arylhalide in *cis* position may be favorable for the amination reaction. Monodentate *N*-containing ligand such as 2,6-diphenylpyridine gives high (94 %) yield of TPA (1 equivalent to Cu). Various amine derivatives were synthesized with high yield (90 to 95 %) of triarylamines, which are important in industrially as well as academically. Diphos ligands were showing to give high TPA (80 %) and selectivity for triphenylamine (88 %). Monodentate alkyl phosphine such as *o*-toly phosphine, *t*ri-*n*-butyl phosphine, gives high yield (80 %) of TPA (2 equivalents of Cu). An interesting finding is that promising yield of TPA and DPA (35 and 29 % respectively) are obtained with KOH as base and 1,10-pheanthroline as ligand.

In summary, we have demonstrated for the first time higher yields in ligand free copper-catalyzed amination of primary amines to triarylamines. The role of KO*t*-Bu is important in the development of ligand free copper-catalyst system. Use of bidentate and monodentate ligands (1 equivalent to Cu) gave triarylamines with high activity and selectivity.

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# CHAPTER 3

# SYNTHESIS AND CHARACTERIZATIONS OF COPPER (I) COMPLEXES AND ITS CATALYTIC APPLICATION FOR THE AMINATION OF ARYLHALIDES

## 3.1 Introduction

The importance of C-N coupling in organic synthesis and related chemical industries such as pharmaceuticals and fine chemicals is enormous. For example, in a recent report that involves the synthesis of twenty top-selling drugs the C-N bond coupling chemistry has been used in at least one step.[1] The palladium-catalyzed arylation of amines have been under the focus of intensive research in recent years.[1,2,3] Buchwald[4] and Hartwig[5] have made considerable contribution towards the development of general, reliable, and practical catalysts for the formation of aromatic carbon-nitrogen bonds by the cross-coupling of amines and aryl (and heteroaryl) iodides, bromides, chlorides and triflates.[6-9] Most of work was done on palladium-catalyzed amination reaction, while few reports were published on the usage of other metals such as nickel and copper.[9-16]

Metal catalyzed arylation of amine for the synthesis of structurally demanding amines has been investigated in detailed using palladium in conjunction with exotic ligands such as Xantphos, BINAP. These Pd- complexes have been extensively used for the arylation of amines such as piperazine.[17-22]

The efficiency of catalyst system depends on several parameters such as nature of central metal atom, ligand, base, solvent, etc.[4a] In Pd-catalyzed C-N bond formation reactions, Pd(0) is believed to be the active species. The Pd(II) precursors such as $Pd(OAc)_2$ is reduced to Pd(0) by amines.[4a] It has been reported in the literature that *p*-anisole is more reactive than aniline in amidation reactions. Similarly nature of ligand also plays a key role in Pd-catalyzed C-N bond formation. Electron rich ligands are expected to increase the electron density on Pd there by facilitating oxidative addition. However, bulky ligand favors the formation of lower coordination complexes (e.g. LPd is favorable to $L_2Pd$) and is believed to be more active catalyst. Further, ligands with sterically hindered structure are assumed to accelerate the rate of reductive elimination. Though, simple increase in the bulkiness of ligand may lead to weak binding of ligand to metal, thus precipitating the metal, under reaction conditions. Similarly, choice of base also plays an important role. Strong organic base such as NaO*t*-Bu are likely to be more effective in deprotonation of coordinated amine compared to $K_2CO_3$. Moreover, NaO*t*-Bu as a base is effective under milder conditions (at room temperature), required for structurally demanding amines. There have been efforts to develop catalyst systems with less expensive bases such as KOH and NaOH. Boche[23] has demonstrated the effective uses of these bases in toluene and butanol as solvent. Buchwald has shown that $CsCO_3$ can be an efficient base having increased functional group compatibility. Further, this base tolerates chelating ligands such as BINAP, Xantphos and DPEphos[4b] Pd-catalyzed C-N coupling reactions are air sensitive and need degassed solvent. Toluene has been shown to be preferred choice among all solvents. Many other solvents such as butanol, dioxane, DMF, and NMP have been employed for Pd-catalyzed reactions.

Thus, it may be noted that there is no common choice of parameters that can be advocated for the use of C-N bond formation reactions. Depending on the choice of the substrates to be used and the product to be formed, one has to work out their components of the catalytic system. However, with a broad understanding of nature of reactant and product, one can decide the choice of central metal atom (i.e. palladium or copper) and ligand system that can be used. Since copper is harder than palladium, the use of a hard ligand and strong base may be more suitable when a catalyst system based on Cu is used.

In this present chapter we focus on the efficiency of various preformed complexes. Attempts have been made to explain the activity and selectivity profile of these complexes. Since attempt to isolate the catalytic complex was unfruitful, we have carried out several stoichiometric reactions of catalyst and bases with aniline and iodobenzene to elucidate the plausible steps in reaction mechanism as well.

It may be noted that no attempt has been made earlier to explain the effect of catalytic activity of copper system based on the structure of well defined copper complexes. Therefore, in absence of any prior literature, the explanation of parameter effects on catalyst activity and selectivity has been restricted to qualitative level only.

## 3.2 Experimental Section

### 3.2.1 Materials

Aniline, toluene, chlorobenzene, dichloromethane, diethyl ether, ethanol, chloroform, methanol, triphenyl phosphine, morpholine, and *p*-anisidene all from *s.d.* Fine Chemical Ltd. India. Iodobenzene, bromobenzene, Copper (II) bromide, 1,10-phenanthroline, neocuprine, 3,4,7,8-tetramethyl-1,10-phenanthroline, 6,7-dihydro,5,8 dimethyl dibenzyl-1,10-phenanthroline, 5-nitro1,10-phenanthroline were purchased from Aldrich Chemical Ltd USA. KO*t*-Bu, NaO*t*-Bu, KOH, $K_2CO_3$, TEA, were purchased from *s. d.* Fine chem. Ltd India. 1,5-Diazabicyclo[2.2.0] non-5-ene (DBN), 2-methoxy iodobenzene, 3-methoxt iodobenzene, 4-methoxt iodobenzene, di-iodobenzene, 2,4-dimethyl iodobenzene, 4-iodo-napthalene,and diphenylamine were purchased from Aldrich Chem. Ltd, USA.

### 3.2.2 General Experimental Procedure

Amination reaction was carried out in a 50 ml two neck round bottom flask as shown in experimental setup *(chapter two, Figure2.29).* In a typical experiment, toluene (23 ml) was added to the round bottom flask followed by arylamine (7.85mmol), aryl iodide (16.48mmols), catalyst (copper (I) complex) (0.28mmol) and base (23.5mmol). Naphthalene (250mg) was added as a internal standard for GC analysis. Reflux condenser was attached to the flask and the system was flushed twice with argon to ensure removal of air. Argon balloon was attached to the condenser, to maintain inert atmosphere during the reaction. The round bottom flask was then stirred by magnetic stir-bar and heated to 385 K in oil bath. The reaction was allowed to proceed for 3.5 h to 7 hours. After cooling to room temperature, the reaction solution was filtered to remove the precipitated base and washed with toluene few times. Solution was concentrated to obtain crude product, which was chromatographed using a solvent mixture of hexane and ethyl acetate to obtain pure products. The products separated, were characterized by IR and NMR analysis and compared with authentic samples by GC analysis whenever possible.

The sequence of addition while reaction charged as follow:

Solvent ⟶ Substrate ⟶ Cu-complex ⟶ Base

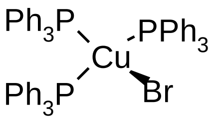
A typical experimental setup shown in chapter two *Figure 2.29*

### 3.2.3 Analytical Method

Analytical method was same as discussed in chapter two, *section 2.2.4.*

## 3.3 Synthesis of Copper (I) Complexes

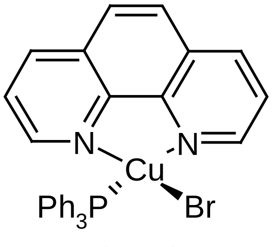
### 3.3.1 Synthesis of $Cu(PPh_3)_3Br$ [tris(triphenylphosphine)copper(I)bromide][10]



***(Cu-1)***

In an Erlenmeyer flask equipped with a Teflon stir bar, methanol (100ml) was heated to boiling and triphenyl phosphine (Across. 6g, 22.4 mmol) was slowly added to stirring methanol. After the complete dissolution of triphenyl phosphine, $CuBr_2$ (Across, 99+%, 1.24g, 5.27 mmol) was added as a solid, in portions. No special precautions were taken for the exclusion of air. Upon addition of the copper bromide, a white precipitate was formed. After the completion of addition, the contents were stirred for 10 minutes and the flask was allowed to cool to ambient temperature. The reaction mixture filtered through a Buckner funnel and the white residue was washed repeatedly with ethanol and than with diethyl ether. The resultant white solid was dried under dynamic vacuum to give $Cu(PPh_3)_3Br$ (tris(triphenylphosphine)copper(I)bromide) (5.46g, 81% yield, mp 164°C).

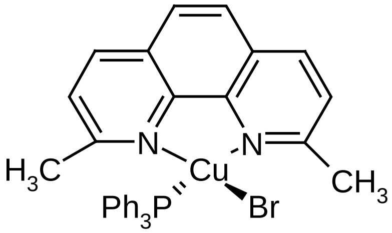
### 3.3.2 Synthesis of $Cu(Phen)(PPh_3)Br$[12]



***(Cu-2)***

In an Erlenmeyer flask equipped with a teflon-coated magnetic stirrer, tris(triphenylphosphine)copper(I)bromide (1.77g, 1.5mmol) was added to chloroform (150 ml). After complete dissolution, 1,10-phenanthroline (0.21g, 1.5 mmol) was then added. The colorless solution immediately changed to orange. The contents of the flask were allowed to stir for 30 to 35 minutes at room temperature. The solvent was then removed under dynamic vacuum (rotavapor) to afford an orange-yellow solid. Recrystallization was achieved by dissolving the solid in 150 ml of dichloromethane and layered with 50 ml of diethyl ether (1.25g, 71.5% yield).

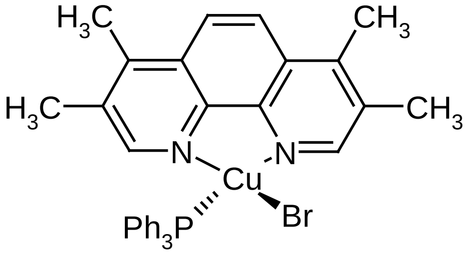
### 3.3.3 Synthesis of Cu(neocup)(PPh$_3$)Br[12]



***(Cu-3)***

In an Erlenmeyer flask equipped with a teflon-coated magnetic stirrer, tris(triphenylphosphine)copper(I)bromide (1.98g, 2.13 mmol) was added to chloroform (150 ml). After complete dissolution, neocuproine (0.447g, 2.13 mmol) was added. The colorless solution immediately changed to red. The contents of the flask were allowed to stir for 30 to 35 minutes at room temperature. After worlds the solvent was then removed under dynamic vacuum (rotavapor) to afford an orange-yellow solid. Recrystallization was achieved by dissolving the solid in 150 ml of dichloromethane and layered with 50 ml of diethyl ether (1.03g, 81% yield).

### 3.3.4 Synthesis of Cu(TMPhen)(PPh$_3$)Br

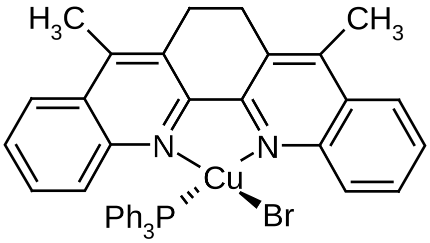


***(Cu-4)***

In an Erlenmeyer flask equipped with a teflon-coated magnetic stirrer, Tris(triphenylphosphine)copper(I)bromide (1.98g, 2.13 mmol) was added to chloroform

(150 ml). After complete dissolution, 3,4,7,8-Tetramethyl-1,10-phenanthroline (0.507g, 2.13 mmol) was then added. The colorless solution immediately changed to red. The contents of the flask were allowed to stir for 30 to 35 minutes at room temperature. After worlds the solvent was then removed under dynamic vacuum (rotavapor) to afford an yellow solid. Recrystallization was achieved by dissolving the solid in150 ml of dichloromethane and layered with 50 ml of diethyl ether (1.23g, 80% yield)

### 3.3.5 Synthesis of Cu(DhDmDbPhen)($PPh_3$)Br

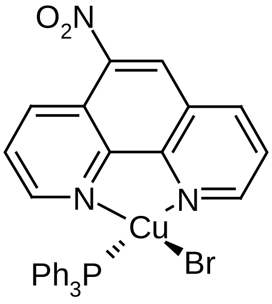


***(Cu-5)***

In an Erlenmeyer flask equipped with a teflon-coated magnetic stirrer, Tris(triphenylphosphine)copper(I)bromide (3.54g, 3 mmol) was added to chloroform (200 ml). After complete dissolution, 6,7-Dihydro-5,8-dimethyldibenzo[1,10] phenanthroline (0.9312g, 3 mmol) was then added. The colorless solution immediately changed to dark brown. The contents of the flask were allowed to stir for 30 to 35 minutes at room temperature. The solvent was then removed under dynamic vacuum (rotavapor) to afford a dark brown solid. Recrystallization was achieved by dissolving the solid in 200 ml of dichloromethane and layered with 80 ml of diethyl ether (1.82g, 85% yield)

### 3.3.6 Synthesis of Cu(5-nitroPhen)($PPh_3$)Br

In an Erlenmeyer flask equipped with a teflon-coated magnetic stirrer, Tris(triphenylphosphine)copper(I)bromide (3.54g, 3 mmol)was added to chloroform (200 ml). After complete dissolution, 5-nitro-1,10-phenanthroline (0.676g, 3 mmol) was then added. The colorless solution immediately changed to brick red. The contents of the flask were allowed to stir for 30 to 35 minutes at room temperature. The solvent was removed under dynamic vacuum (rotavapor) to afford a brick red solid. Recrystallization was achieved by dissolving the solid in 200 ml of dichloromethane and layered with 80 ml of diethyl ether (1.70g, 89% yield).



***(Cu-6)***

## 3.4 Characterization of Copper (I) Complexes

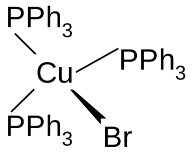
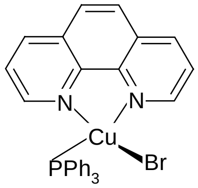
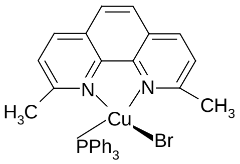
### 3.4.1 Characterization of Copper (I) Complexes Cu-1 to Cu-3:

The synthesis and characterization of Cu-1, Cu-2 and Cu-3 copper (I) complexes have been reported in literature, we have also characterized these complexes by using various analytical techniques.

Elemental analysis of the complexes was carried out on a CHNS-O EA1108, Elemental analyzer of Carlo Erbo Instruments, Italy. The FT-IR spectra were recorded on a Bio-Rad FTS-175 spectrometer in the range 4000-400cm$^{-1}$. The samples were made as KBr pellets (1% w/w). The spectra were recorded in transmittance (%T) mode. Far–IR spectra was recorded in the range of 550 to 50 cm$^{-1}$. EDX analysis of the complex was carried out on SEM-Leica Stereoscan 440 made in Leo Cambridge. The EDX gave the information on the elemental composition of the material under examination. $^{1}$H, $^{13}$C and $^{31}$P NMR was obtained from Brucker 500 MHz, MSL300 and Brucker AC200 machines. TGA/DTA analysis of the complex was carried out on TGA/DTA-32 Seiko instrument. This sample was carried out in the temperature range 35$^{o}$C to 715$^{o}$C, at the rate of 10$^{o}$C/min, in static air.

All above characterization of Cu-1, Cu-2 and Cu-3 are presenting in *Table 3.1*

**Table 3.1:** Copper (I) Complex Catalyst Characterization

| Copper (I) Complex | Elemental | IR[24-27] | NMR | TGA/ DTA |
|---|---|---|---|---|
|  | Calc. C 69.72, H 4.88 Found C 69.85, H 5.25 | Normal ν = 3048, 1481, 1434, 1365, 1091, 871, 744, 693, 508 cm$^{-1}$ Far-IR ν = 57 (Cu-P), 149 (Cu-Br) | $^{1}$H δ (7.1-7.4) m for 45 Ar, H, $^{13}$C δ 128.24, 128.41, 129.41, 133.63, 133.79, 134.09, $^{31}$P δ –4.86 s, b | 157 to 351ºC 82% loss of PPh$_3$, 351 to 603ºC 9% loss of Br, 603 to 750ºC 8 % CuO Remain. |
|  | Calc. C 61.5, H 3.96, N 4.78, Found C 61.23, H 4.53, N 4.90 | Normal ν = 3050, 1585, 1508, 1479, 1434, 1093, 840, 746, 695, 552, 508 cm$^{-1}$ Far-IR ν = 57 (Cu-P), 151 (Cu-Br), 490 (Cu-N) | $^{1}$H δ 8.95 (6H, bs), 8.32 (1H, bs), 7.86 (1H, bs), 7.67-6.65 (2H, m), 7.43 (6H, bs), 7.34-7.24 (12H, m) $^{13}$C δ 128.26, 129.67, 131.94, 132.13, 133.70 $^{31}$P δ –4.89 s, b | 145 to 324ºC 49% loss of PPh$_3$, 324 to 531ºC 12.5 % loss of Br, 531 to 690ºC 29 % loss of L & 8% CuO Remain. |
|  | Calc. C 62.6, H 4.43, N 4.56, Found C 62.99, H 4.81, N 4.70 | Normal ν = 3054, 1589, 1500, 1481, 1434, 1361, 1091, 871, 741, 694, 526, 508 cm$^{-1}$ Far-IR ν =59 (Cu-P), 156 (Cu-Br), 508 (Cu-N) | Solvent DCM+CDCl$_3$ $^{1}$H δ 2.83 s (6H, 2CH$_3$), 7.27-7.14 m (10H, Ar), 7.48-7.38 m (7H-Ar), 7.74 s (2H, Ar), 8.18-8.14 d (2H, Ar, J = 8Hz) $^{13}$C δ 53.58, 124.49, 124.91, 126.66, 127.84, 128.87, 132.93, 133.06, 135.94 $^{31}$P δ –5.07 s,b | 198.9 to 282.8 ºC 39 % loss of PPh$_3$, 282.8 to 684 ºC 50 % loss of L and Br 550 to 750ºC 12 % loss of Br & 9.5 % CuO Remain. |

### 3.4.2 Characterization of Cu(TMPhen)(PPh$_3$)Br

#### 3.4.2.1 Elemental Analysis

Elemental analysis: calculated for $C_{34}H_{31}BrCuN_2P$: C 63.60, H 4.87, N 4.36 found C 63.34, H 5.07, N 4.95

### 3.4.2.2 IR

The samples were made as KBr pellets (1% w/w). The spectra were recorded in transmittance (%T) mode. ν = 3045, 1585,1517, 1479, 1434, 1383, 1093, 820, 748, 696, 524 and 527 $cm^{-1}$

**Far-IR**

Bond starching of frequency of copper–phosphrous, Copper-bromide and copper- nitrogen are as ν =54 (Cu-P),[25] 159 (Cu-Br),[26] 490, 508 (Cu-N)[27] $cm^{-1}$

### 3.4.2.3 EDX (Energy Dispersive X-ray Analysis)

Presence of C, N, Br, Cu and P elements in Cu-4 complex was conformed by EDX analysis.

### 3.4.2.4 NMR

**Solid state $^{31}P$ HPDC MAS NMR:**

Solid-state High Power Decoupled MAS 31P NMR spectra recorded on BrukerDRX500 spectrometer of Copper (I) Complex (Cu-4). The HPDEC MAS $^{31}P$ NMR spectra for the complex Cu(TMPhen)($PPh_3$)Br (Cu-4) complex are shown in *Figure 3.1.* These spectra contain asymmetric quartet splitting patterns of the type, which has been reported previously for a range of copper (I) complexes with phosphine ligands.[28-31] This asymmetric splitting is due to the combined effects of scalar and dipolar spin-spin coupling between the phosphorus nucleus ($^{31}P$, nuclear spin = ½) and the copper nucleus ($^{63}Cu$, $^{65}Cu$, nuclear spin I = 3/2) and the copper nuclear quadrupole coupling. This has been discussed previously by Menger and Veeman,[32] who presented calculations of the line positions for the components of this quartet in terms of the various coupling constants involved. These are the copper nuclear

Zeeman interaction $\gamma_{cu}\,\hbar\,\mathbf{B}$, the copper nuclear quadrupole coupling constant $e^2qQ$, and the phosphorus-copper scalar and dipolar coupling constants and $\mu_o\gamma_p\gamma_{Cu}\,\hbar / 4\pi a r^3$ (r = the Cu-P bond length). Menger and Veeman[32] carried out their calculations for the case in which the ratio R of the dipolar to the scalar-coupling constant (eq. 1) is equal to 0.5 and calculated the quartet line positions as

$R = \mu_o \gamma_p \gamma_{Cu}\, \hbar / 4\pi a r^3$ (eq.1)

A function of the dimensionless parameter K (eq. 2), which is

$K = 3\, e^2 qQ / 4I\,(2I-1)\, \gamma_{cu}\, \boldsymbol{\hbar}\, \mathbf{B}$ (eq. 2)

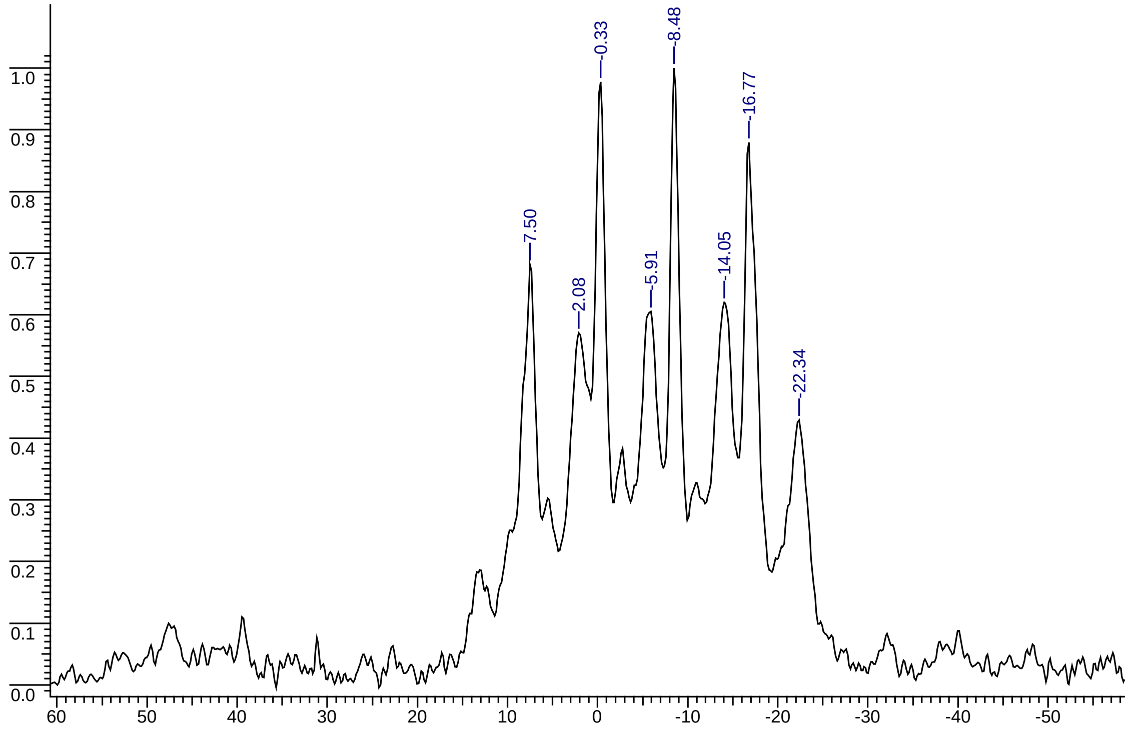


**Figure 3.1:** HPDEC MAS $^{31}$P NMR spectra for the complex Cu-4

$^{31}$P spectra theoretically shows four peaks for copper (I) complexes according to this equation (2nI + 1) where n = copper valiancy in this complex, Cu=1 and I = 3/2 for $^{63}$Cu and $^{65}$Cu. In *Figure 3.1* eight peaks were observed. Four high intensity NMR shifts are shown in Figure 3.1 viz δ 7.50, -0.33, -8.48, -16.77 and four low intensity NMR shifts are shown in Figure 3.1 viz δ 2.08, -5.91, -14.05 and -22.34. In this case the lines are sufficiently narrow to allow resolution of the splitting arising from coupling of $^{31}$P to $^{63}$Cu (natural abundance 69.09%) and $^{65}$Cu (30.91) in the outermost lines in the quartet. Although this type of copper isotope splitting has been reported previously,[32] the resolution obtained in such spectra is not normally sufficient to allow its observation.

That the splitting is due to coupling of the phosphorus nucleus to different isotopes of copper can be demonstrated by applying the method of analysis described above to the separate quartet splitting.

The Scalar phosphorus-copper coupling constants a/ ħ determined by the above procedure is in all cases almost exactly equal to the mean of the three-line spacing. [29]

a/ ħ calculated by using eq. 3.[29]

$a/\hbar = \Delta_1 + \Delta_2 + \Delta_3 / 3$ (eq. 3)

$\Delta_1 + \Delta 2 + \Delta_3$ are from spectra

$a/\hbar = 1587.01 + 1648.05 + 1678.57 / 3 = 1637.877$ Hz

**$^1$H NMR** ($CDCl_3$, 500MHz) δ 1.83 (s, 6H, $CH_3$) 2.17 (s, 6H, $CH_3$) 7.24 -7.70 (m, 19H, Ar-H)

**13C NMR** ($CDCl_3$, 125MHz) δ 30.67, 128.18, 129.25, 130.49, 131.86, and 133.55

### 3.4.2.5 Single Crystal X-ray Crystallographic Studies

The X-ray data of **Cu-4 to Cu-6** were collected on a SMART APEX CCD single crystal X-ray diffractometer with omega and phi scan mode and different number of scans and exposure times for different crystals using λ $MoK_\alpha$ = 0.71073 Å radiation, at T = 293(2) K with Oscillation / frame -0.3º, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24. All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs. The crystal structures were solved by direct method using SHELXS-97 and the refinement was performed by full matrix least squares of $F^2$ using SHELXL-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Göttingen, Germany, 1997).

### Crystal Data for Cu-4

$[2(C_{34}H_{31}N_2PBrCu).CH_2C_{l2}.H_2O]$, $M$ = 1387.00, Crystal dimensions 0.56 x 0.10 x 0.03 mm, quadrant data acquisition. Total scans = 4, total frames = 2424, exposure / frame = 10.0 sec / frame, θ range = 1.78 to 25.0º, completeness to θ of 25.0 º is 99.8 %, Triclinic, space group $P^{-1}$, a = 9.5591(5), $b$ = 19.1206(11), $c$ = 19.1900(11) Å, α =

100.385(1) ° $\beta$ = 103.339(1)°, $\gamma$ = 103.750(1) ° $V$ = 3210.8 (3) $Å^3$, $Z$ = 2, $D_c$ = 1.435 mg $m^{-3}$, $\mu$ (Mo $K_\alpha$) = 2.086 $mm^{-1}$, 31353 reflections measured, 11279 unique [I>2σ(I)], R value 0.0609, wR2 = 0.1431

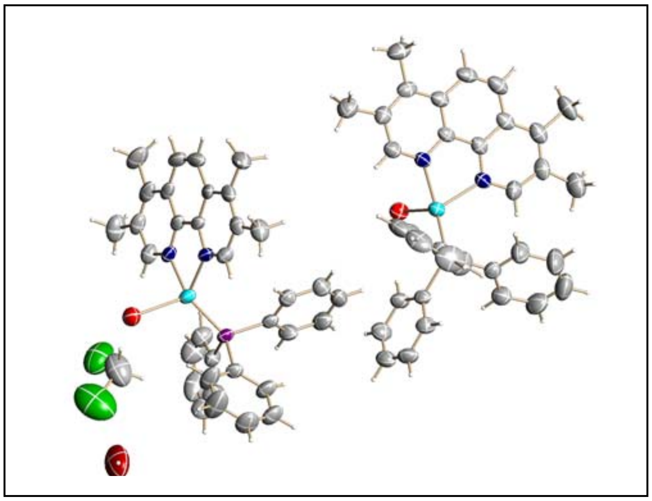


**Figure 3.2:** Two molecules of Cu-4, DCM and water molecules

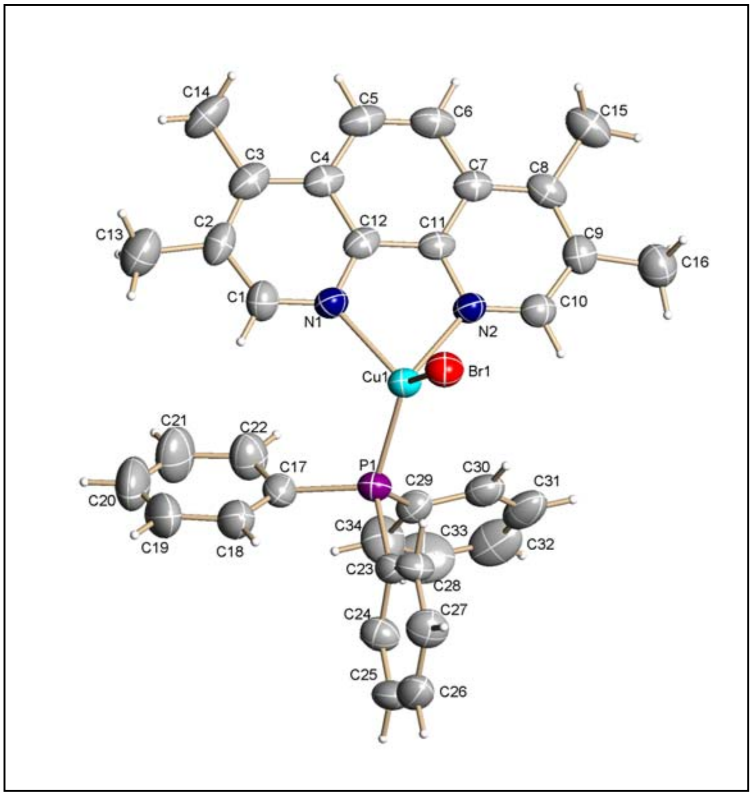


**Figure 3.3:** ORTEP Figure of Cu-4

There are two molecules in the asymmetric unit along with one molecule of dichloromethane and one molecule of water as solvent of crystallization.

Copper is tetra-coordinated to bromine, phosphorus atom of the triphenyl phosphine and two nitrogen atoms of 3,4,7,8-Tetramethyl-1,10-phenenthroline ligand in a tetrahedral manner.

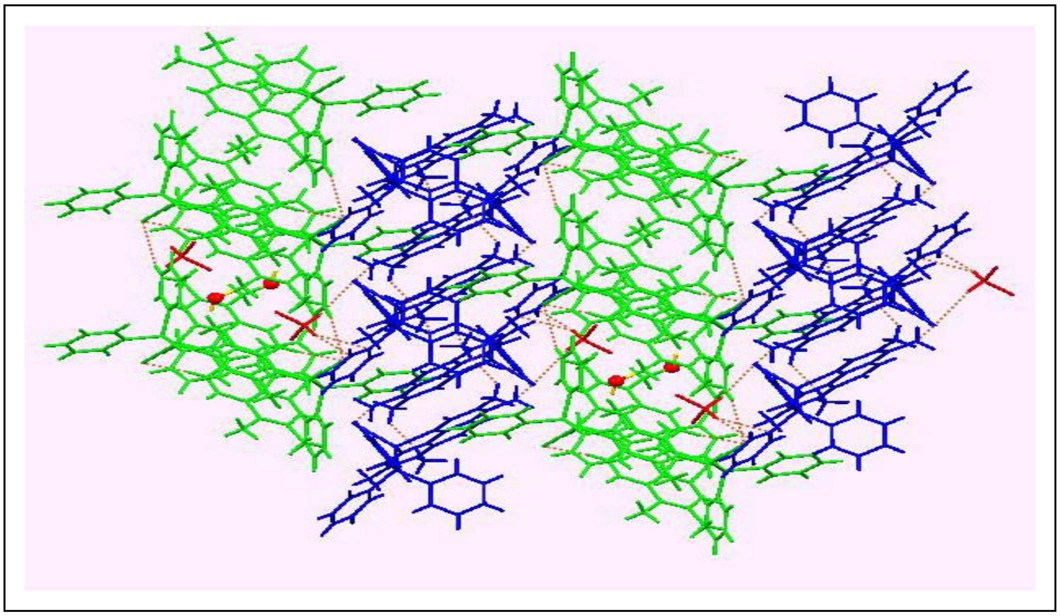


**Figure 3.4:** Packing of complex Cu-4 down “c” axis

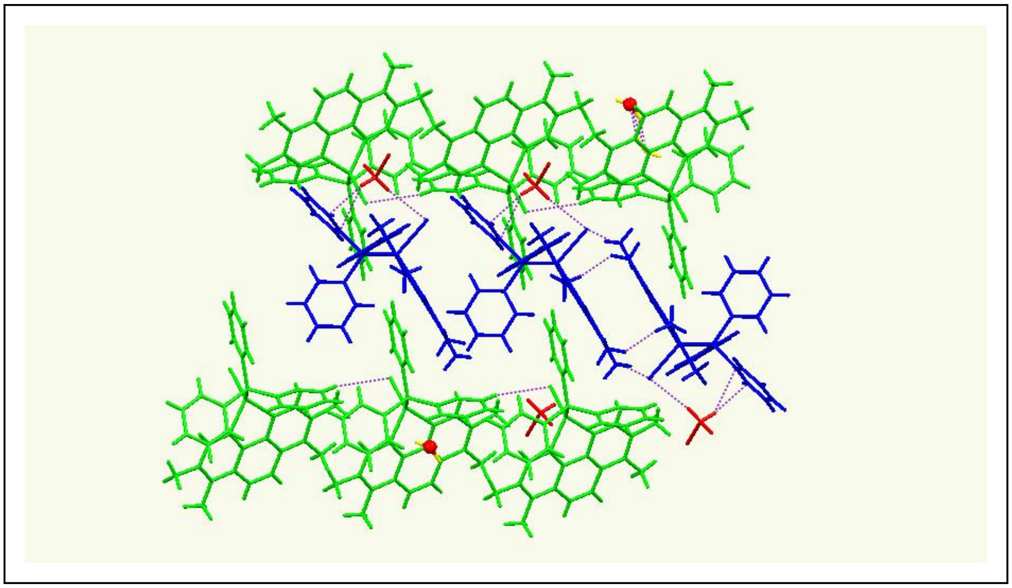


**Figure 3.5:** Packing of complex Cu-4 down “c”-axis: Interaction of DCM molecule

The geometry around both the Cu atoms in the asymmetric unit is tetrahedral. Dichloromethane molecule makes CH-π contacts while the bromine has CH-Br contacts with other neighboring symmetric related molecules. Water molecule has no interaction with other neighboring molecules. Packing of the molecule in the asymmetric unit are due to the CH-π interaction.

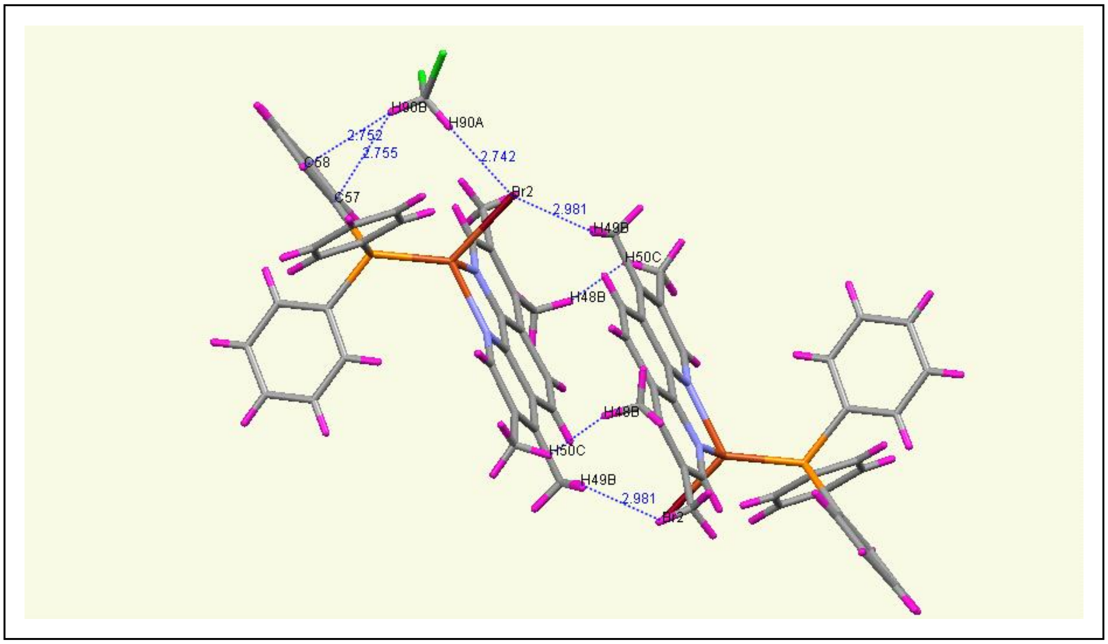


**Figure 3.6:** Interaction of Cu-4 complex molecules

**Table 3.2:** Selected Bond Length and Bond Angles of Complex Cu-4

| Bond Lengths (Å) | | Bond Angles (º) | |
|---|---|---|---|
| Cu(1)-N(2) | 2.110 (5) | N(1)-Cu(1)-N(2) | 78.67 (19) |
| Cu(1)-N(1) | 2.109 (5) | N(1)-Cu(1)-P(1) | 113.14 (14) |
| Cu(1)-P(1) | 2.1891 (17) | N(2)-Cu(1)-P(1) | 126.22 (14) |
| Cu(1)-Br(1) | 2.4276(10) | N(1)-Cu(1)-Br(1) | 109.62 (14) |
| | | N(2)-Cu(1)-Br(1) | 100.08 (14) |
| | | P(1)-Cu(1)-Br(1) | 121.11 (5) |

**Table 3.3:** Crystal Data and Structure Refinement Parameters for Complex Cu-4

| Sr. No. | Parameters | Data |
|---|---|---|
| 1 | Empirical Formula | $[2(C_{34}H_{31}N_2PBrCu).CH_2C_{l2}.H_2O]$ |
| 2 | Formula Weight | 1387 |
| 3 | Temperature | 293 (2) K |
| 4 | Wavelength | 0.71073 Å |
| 5 | Crystal System | Triclinic |
| 6 | Space Group | $P^{-}1$ |
| 7 | Unit Cell Dimensions | a = 9.5591 (5) Å α = 100.385(1)°<br>b = 19.1206 (11) Å β = 103.339 (1)°<br>c = 19.1900 (11) Å γ = 103.750 (1)° |
| 8 | Volume | 3210.8 (3) $Å^3$ |
| 9 | Z | 2 |
| 10 | Density, (Calculated) | 1.435 mg $m^{-3}$ |
| 11 | Absorption Coefficient | 2.086 $mm^{-1}$ |
| 12 | F(000) | 1416 |
| 13 | Crystal Size | 0.56 x 0.10 x 0.03 mm |
| 14 | θ range for data collection | 1.78 to 25° |
| 15 | Index ranges | -11<=h<=11, -22<=k<=22, -22<=l<=22 |
| 16 | No. of reflections collected | 31353 |
| 17 | No. of ind reflections | 11279 [R (int) = 0.0628] |
| 18 | Completeness to θ of 25° | 99.8 % |
| 19 | Maximum transmission | 0.9344 |
| 20 | Minimum transmission | 0.3880 |
| 21 | Refinement method | Full –matrix least-squares on $F^2$ |
| 22 | No. of data / restraints / parameters | 11279 / 3 / 753 |
| 23 | Goodness-of-fit on $F^2$ | 1.032 |
| 24 | Final R indices [I>2sigma (I)] | R1 = 0.0609, wR2 = 0.1431 |
| 25 | R indices (all data) | R1 = 0.1066, wR2 = 0.1651 |
| 26 | Largest difference peak and hole | 0.947 and –0.593 e. $Å^3$ |

### 3.4.3 Characterization of Cu(DhDmDbPhen)($PPh_3$)Br

#### 3.4.3.1 Elemental analysis

Elemental analysis: calculated for $C_{40}H_{33}N_2CuBrP$: C 67.09, H 4.64, N 3.91 found C 65.50, H4.64, N 4.09

#### 3.4.3.2 IR

The samples were made as KBr pellets (1% w/w). The spectra were recorded in transmittance (%T) mode. ν = 3048, 1577, 1504, 1480, 1434, 1381, 1091, 964, 763, 694, 520 and 506 $cm^{-1}$

**Far-IR**

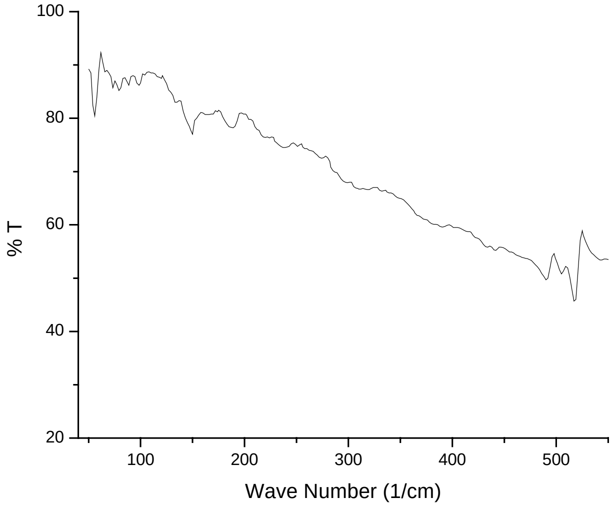


**Figure 3.7:** Far-IR spectra of Cu-5 complex

Bond starching of frequency of copper–phosphorus, copper-bromide and copper-nitrogen are as ν =55 (Cu-P),[25] 151 (Cu-Br),[26] 490, 518 (Cu-N)[27] $cm^{-1}$

#### 3.4.3.3 EDX (Energy Dispersive X-ray Analysis)

Presence of C, N, Br, Cu and P elements in Cu-4 complex was conformed by EDX analysis.

### 3.4.3.4 NMR

**Solid state $^{31}$P HPDC MAS NMR:**

$^{31}$P high power decoupled NMR spectra of Cu-5 complex as shown in *Figure 3.8.* This asymmetric quartet splitting has been observed in a wide range of Cu(phen)(PPh$_3$)Br complexes and is due to the combined effects of scalar and dipolar spin-spin coupling between the phosphorus nucleus ($^{31}$P, nuclear spin I = ½) and the copper nucleus (63Cu, 65Cu, nuclear spin S = 3/2) and the copper nuclear quadrupole coupling. This has been discussed previously in *section 3.4.2.4.*

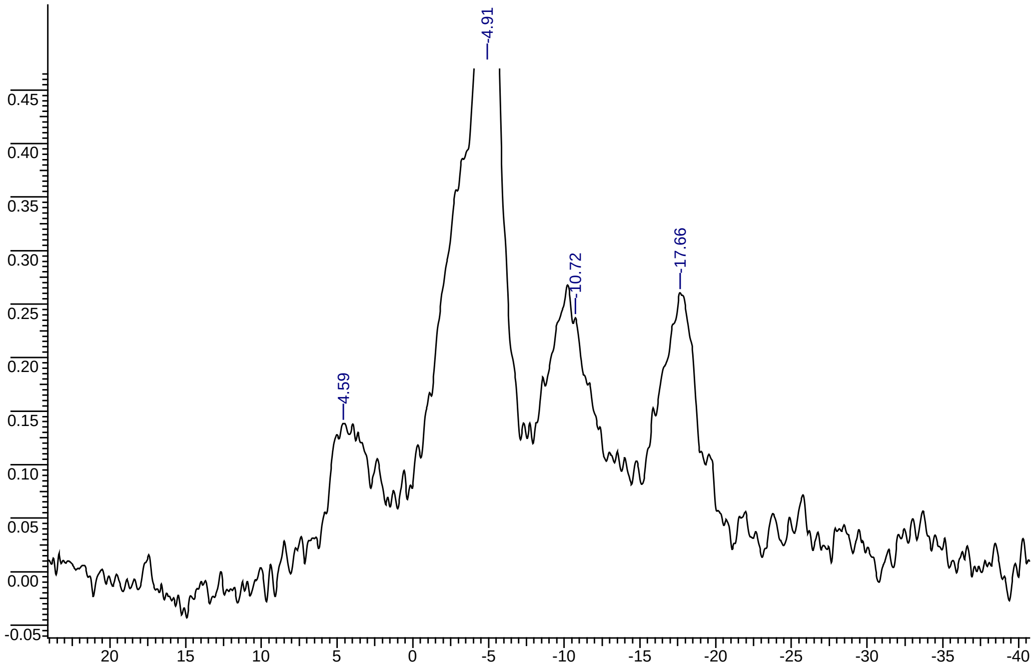


**Figure 3.8:** Solid state $^{31}$P HPDC MAS NMR spectra of Cu-5

**$^{1}$H NMR** (CDCl$_3$, 500MHz) δ 1.56 s (4H, CH$_2$), 2.49 s (3H, CH$_3$), 3.13 s (3H, CH$_3$), 7.07-7.30 m (18H, Ar), 7.79-7,84 m (1H, Ar), 9.05-9.09 m (1H, Ar)

**13C NMR** (CDCl$_3$, 125MHz) δ 14.03, 24.04, 123.08, 127.61, 128.09, 128.18, 12.13, 131.70, 133.40, 133.55

### 3.4.3.5 Single Crystal X-ray Crystallographic Studies

**Crystal Data for Cu-5**

($C_{40}$ $H_{33}$ Br Cu $N_2$ P), $M$ = 716.10, Crystal dimensions 0.24 x 0.16 x 0.10 mm, Hemisphere data acquisition. Total scans = 3, total frames = 1271, exposure / frame = 10.0 sec / frame, $\theta$ range = 1.98 to 25.0º, completeness to $\theta$ of 25.0 º is 99.9 %, Monoclinic, space group $P2_1/n$, a = 15.2649 (12), $b$ = 13.3661(10), $c$ = 16.0847 (13)Å, $\beta$ = 90.363(1)º, $V$ = 3281.7(4) Å$^3$, $Z$ = 4, $D_c$ = 1.449 mg m$^{-3}$$_,$ $\mu$ (Mo $K_{\alpha}$) = 1.449 mm$^{-1}$, 16327 reflections measured, 5764unique [$I>2\sigma(I)$], R value 0.0471, wR2 = 0.0996

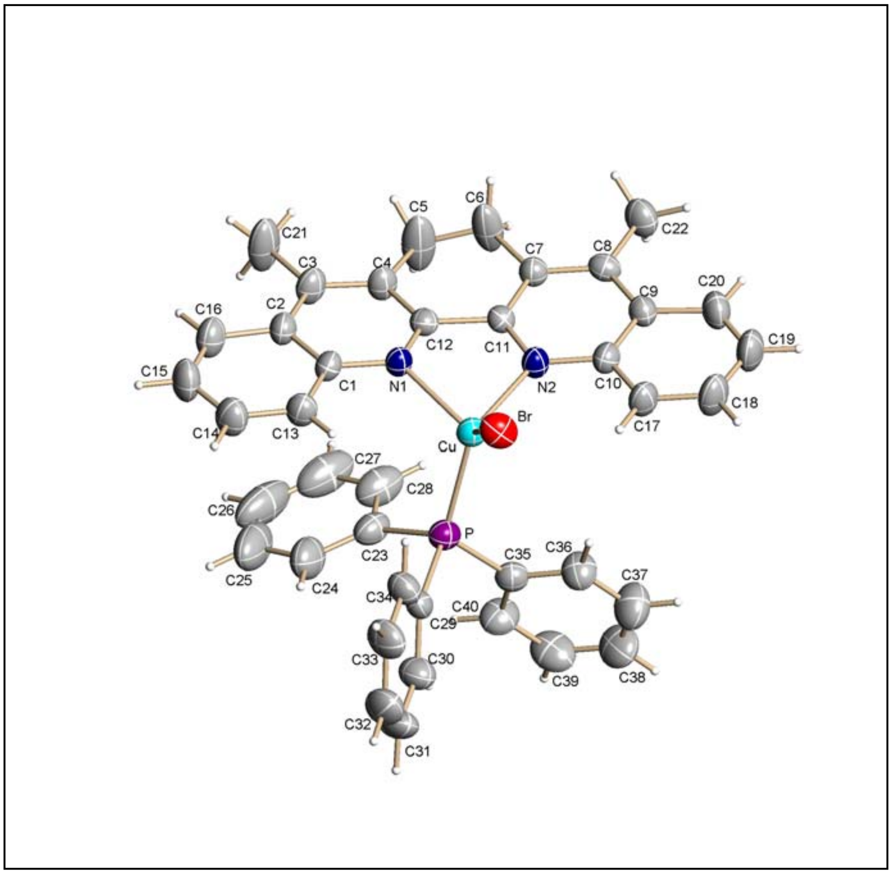


**Figure 3.9:** ORTEP Figure of Cu-5

Copper is tetra-coordinated to bromine, phosphorus atom of the triphenyl phosphine and two nitrogen atoms of 6,7-Dihydro-5,8-dimethyldobenzo [1,10] phenanthroline ligand in a tetrahedral geometry.

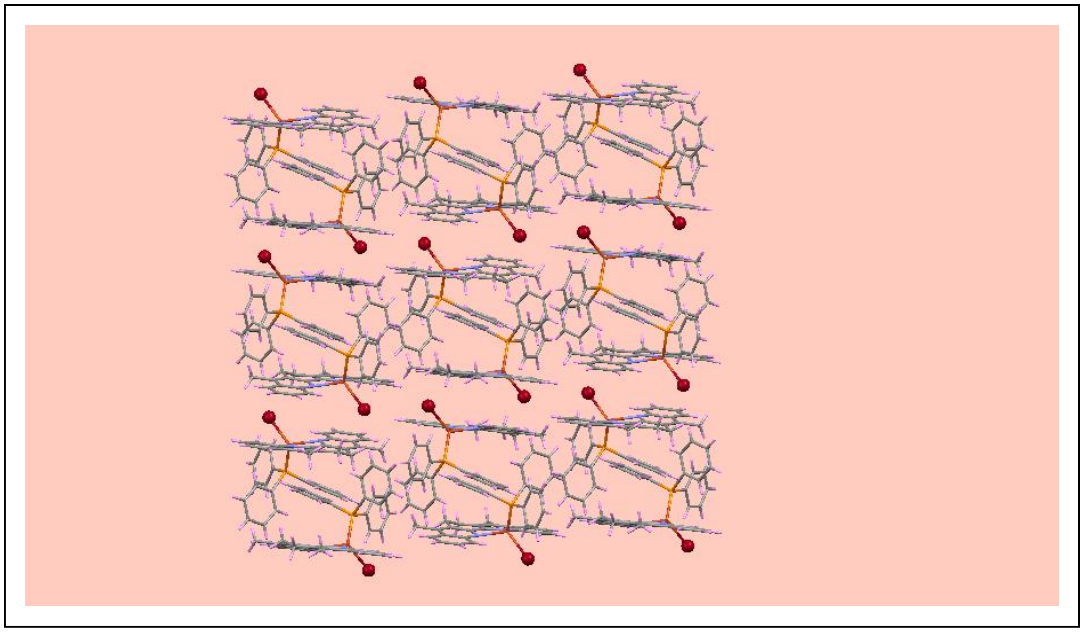


**Figure 3.10:** Packing of complex Cu-5 down "b"-axis

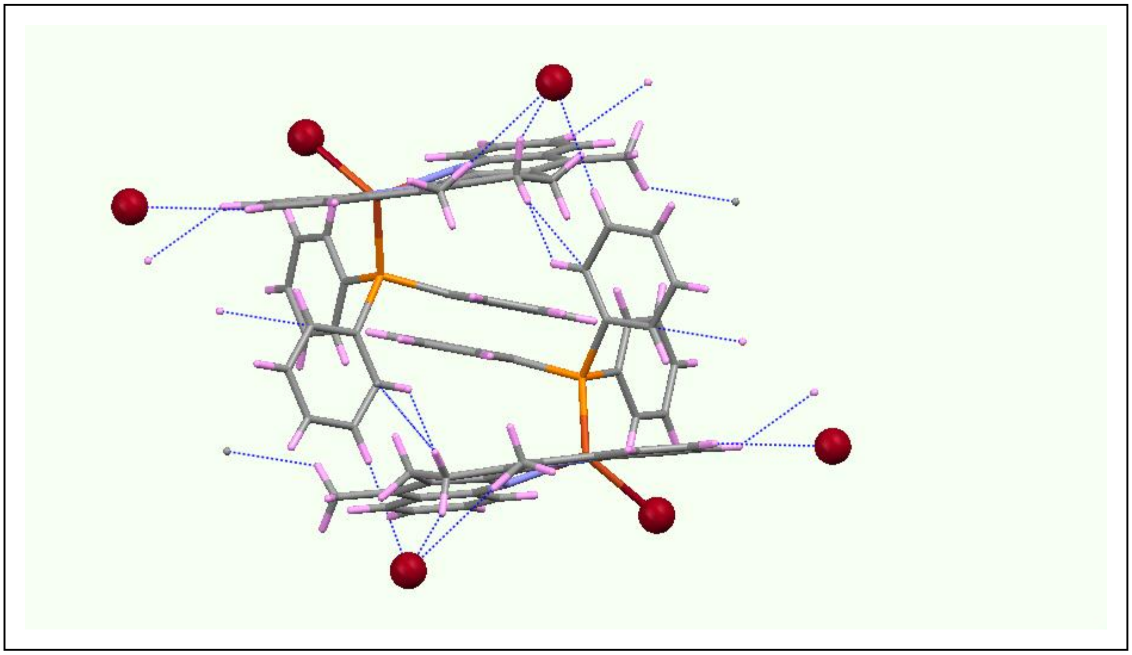


**Figure 3.11:** Interaction of molecules complex Cu-5

The two L-shape molecules pack in cubic fashion (cube brand fashion), which form the pillars. All the bromine atoms lies insides the channels formed by such pillars. In *Figure 3.10* the red ball is the bromine atom and it lies in between the two layers of complex.

**Table3.4:** Crystal Data and Structure Refinement Parameters for Complex Cu-5

| Sr. No. | Parameters | Data |
|---|---|---|
| 1 | Empirical Formula | $C_{40}H_{33}BrCuN_2P$ |
| 2 | Formula Weight | 716.10 |
| 3 | Temperature | 293 (2) K |
| 4 | Wavelength | 0.71073 Å |
| 5 | Crystal System | Monoclinic |
| 6 | Space Group | $P2_1/n$ |
| 7 | Unit Cell Dimensions | a = 15.2649 (12) Å<br>b = 13.3661 (10) Å β = 90.363 (1)º<br>c = 16.0847 (13) Å |
| 8 | Volume | 3281.7 (4) $Å^3$ |
| 9 | Z | 4 |
| 10 | Density, (Calculated) | 1.449 mg $m^{-3}$ |
| 11 | Absorption Coefficient | 1.964 $mm^{-1}$ |
| 12 | F(000) | 1464 |
| 13 | Crystal Size | 0.24 x 0.16 x 0.10 mm |
| 14 | θ range for data collection | 1.98 to 25º |
| 15 | Index ranges | -9<=h<=18, -15<=k<=15, -19<=l<=19 |
| 16 | No. of reflections collected | 16327 |
| 17 | No. of ind reflections | 5764 [R (int) = 0.0519] |
| 18 | Completeness to θ of 25º | 99.9 |
| 19 | Maximum transmission | 0.8324 |
| 20 | Minimum transmission | 0.6458 |
| 21 | Refinement method | Full –matrix least-squares on $F^2$ |
| 22 | No. of data / restraints / parameters | 5764 / 0 / 408 |
| 23 | Goodness-of-fit on $F^2$ | 0.972 |
| 24 | Final R indices [I>2sigma (I)] | R1 = 0.0471, wR2 = 0.0996 |
| 25 | R indices (all data) | R1 = 0.0921, wR2 = 0.01189 |
| 26 | Largest difference peak and hole | 0.529 and –0.284 e. $Å^3$ |

**Table 3.5:** Selected Bond Length and Bond Angles of Complex Cu-5

| Bond Lengths (Å) | | Bond Angles (º) | |
|---|---|---|---|
| Cu-N(2) | 2.088 (3) | N(2)-Cu-N(1) | 78.36 (13) |
| Cu-N(1) | 2.098 (3) | N(2)-Cu-P | 212.28 (10) |
| Cu-P | 2.2158 (13) | N(1)-Cu-P | 106.03 (10) |
| Cu-Br | 2.4191 (7) | N(2)-Cu-Br | 110.32 (10) |
| | | N(1)-Cu-Br | 119.24 (9) |
| | | P-Cu-Br | 116.31 (4) |

### 3.4.4 Characterization of Cu(5-nitroPhen)($PPh_3$)Br

#### 3.4.4.1 Elemental analysis

Elemental analysis: calculated for $C_{30}H_{22}N_3CuBrPO_2$: C 57.11, H 3.51, N 6.66 found C 56.98, H 3.68, N 7.10

#### 3.4.4.2 IR

The samples were made as KBr pellets (1% w/w). The spectra were recorded in transmittance (%T) mode. ν = 3053, 1622, 1535, 1509, 1478, 1434, 1358, 1094, 836, 745, 697, 522 and 499 $cm^{-1}$

**Far-IR:**

Bond starching of frequency of copper–phosphorus, copper-bromide and copper-nitrogen are as ν =57 (Cu-P),[25] 159 (Cu-Br),[26] 438, 495, 523 (Cu-N)[27] $cm^{-1}$

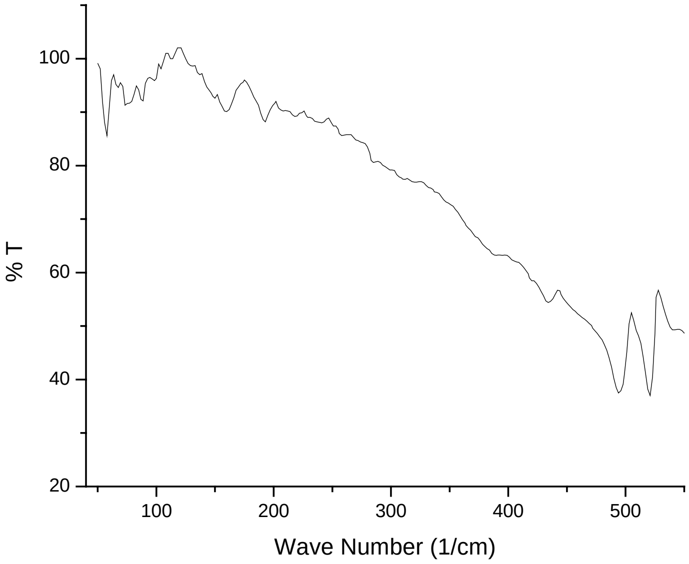


**Figure 3.12:** Far-IR spectra of Cu-6 complex

### 3.4.4.3 EDX (Energy Dispersive X-ray Analysis)

Presence of C, N, Br, Cu and P elements in Cu-4 complex was conformed by EDX analysis as shown in *Figure 3.13.*

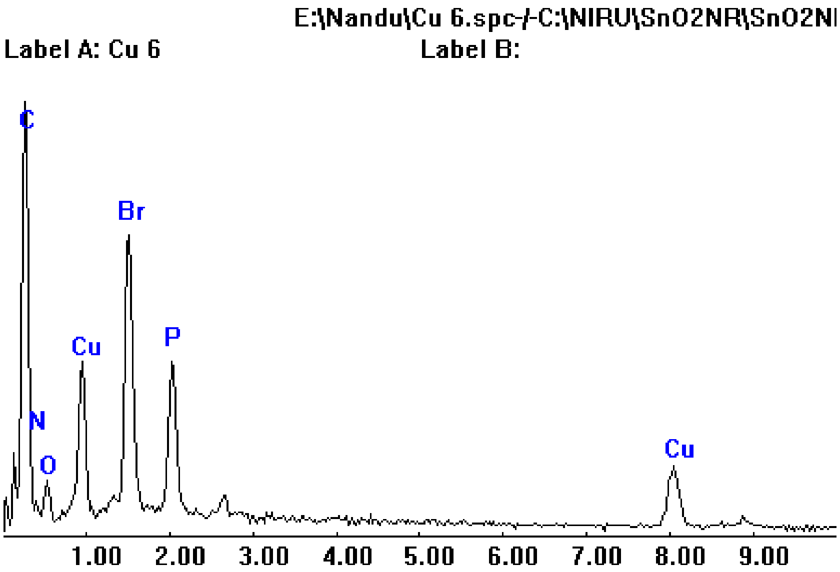


**Figure 3.13:** EDX spectra of Cu-6 complex

### 3.4.4.4 NMR

**Solid state $^{31}$P HPDC MAS NMR**

$^{31}$P high power decoupled MAS NMR shift are δ –13.38, -5.30, 2.12 and 9.20 of Cu-6 complex are shown in *Figure 3.14.* This has been discussed previously in *section 3.4.2.4 and section 3.4.3.4.*

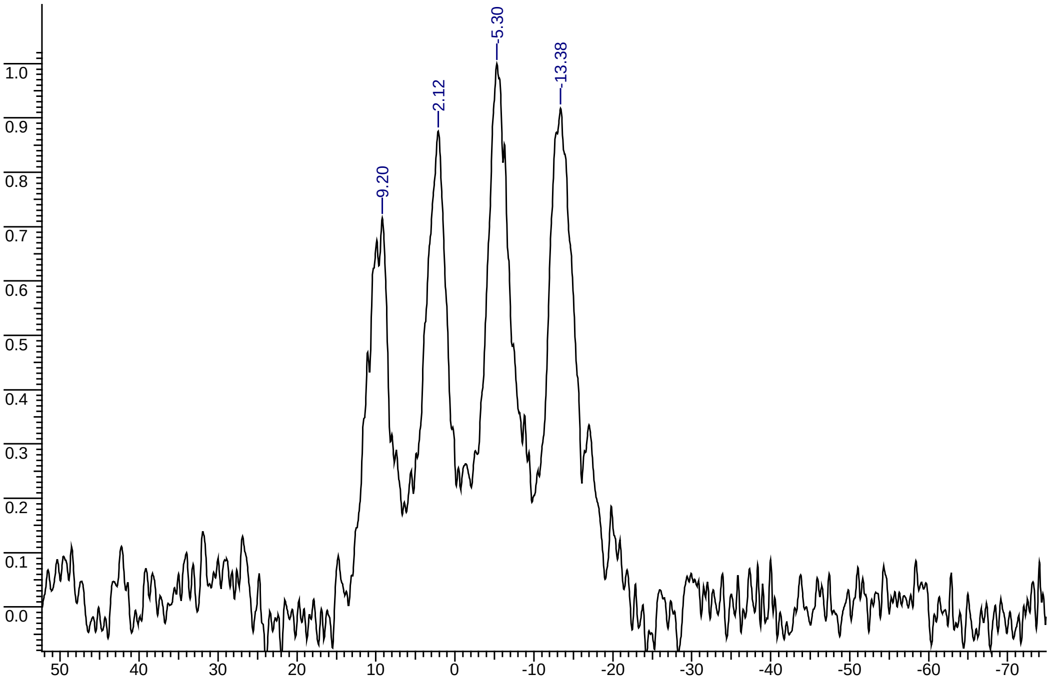


**Figure 3.14:** Solid state $^{31}$P HPDC MAS NMR spectra of Cu-5

**$^{1}$H NMR** ($CDCl_3$, 500MHz) δ 7.26-9.10 m (22H, Ar)

**13C NMR** ($CDCl_3$, 125MHz) δ 127.78, 128.75, 128.83, 135.44, 172.28

### 3.4.4.5 X-Ray Single Crystal Analysis

**Crystal Data for Cu-6**

($C_{30}$ $H_{22}$ Br Cu $N_3$ $O_2$ P), *M* = 630.93, Crystal dimensions 0.10 x 0.08 x 0.02 mm, θ range = 2.41 to 23.75°, completeness to θ of 23.75 ° is 99.9 %, Triclinic, space group P$^{-}$ $^{1}$, a = 9.4090(13), *b* = 9.733(13), *c* = 17.199 (2) Å, α = 90.772(3)° , β = 104.382(3)°, γ =

118.393 (2)º $V$ = 1326.1(3) Å$^3$, $Z$ = 2, D$_c$ = 1.580 mg m$^{-3}$, $\mu$ (Mo K$_\alpha$) = 2.424 mm$^{-1}$, 11410 reflections measured, 4041unique [I>2σ(I)], R value 0.0855, wR2 = 0.1446

Copper is tetra-coordinated to bromine, phosphorus atom of the triphenyl phosphine and two nitrogen atoms of 5-nitro-1,10-phenanthroline ligand in a tetrahedral manner.

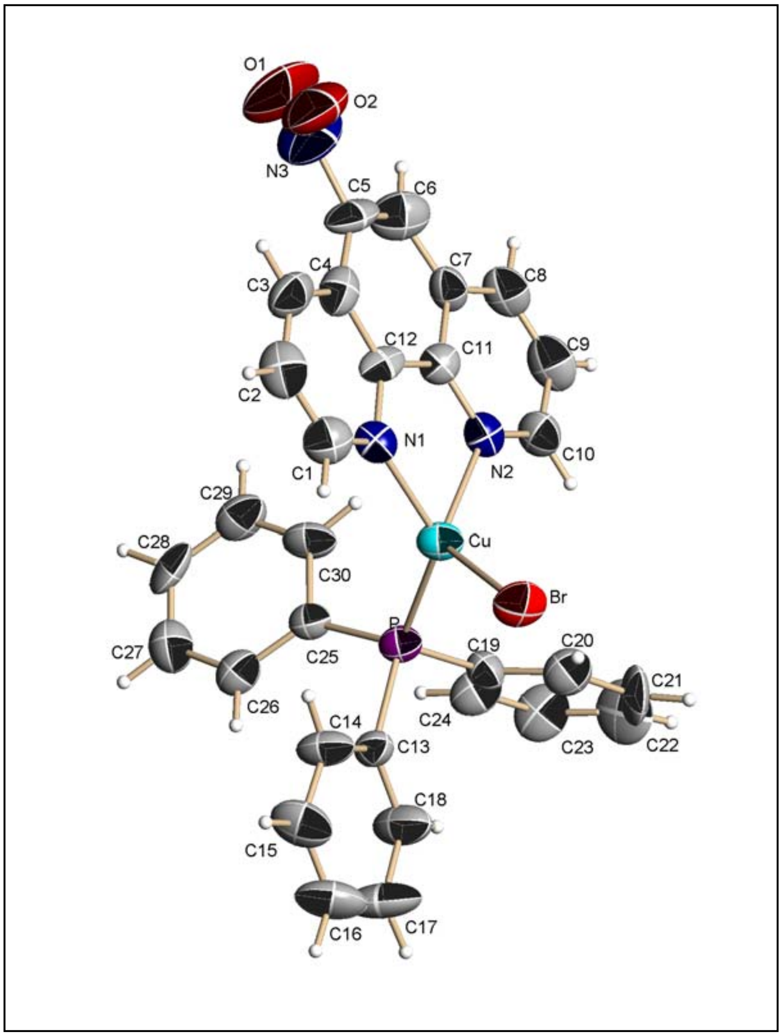


**Figure 3.15:** ORTEP Figure of Cu-6

The ligands of the symmetry related molecules come closer to form CH-π and π-π interactions. PPh$_3$ group separates the H-bonding layer. Formation of dimmer and distances of two atoms are shown in *Figure 3.16.*

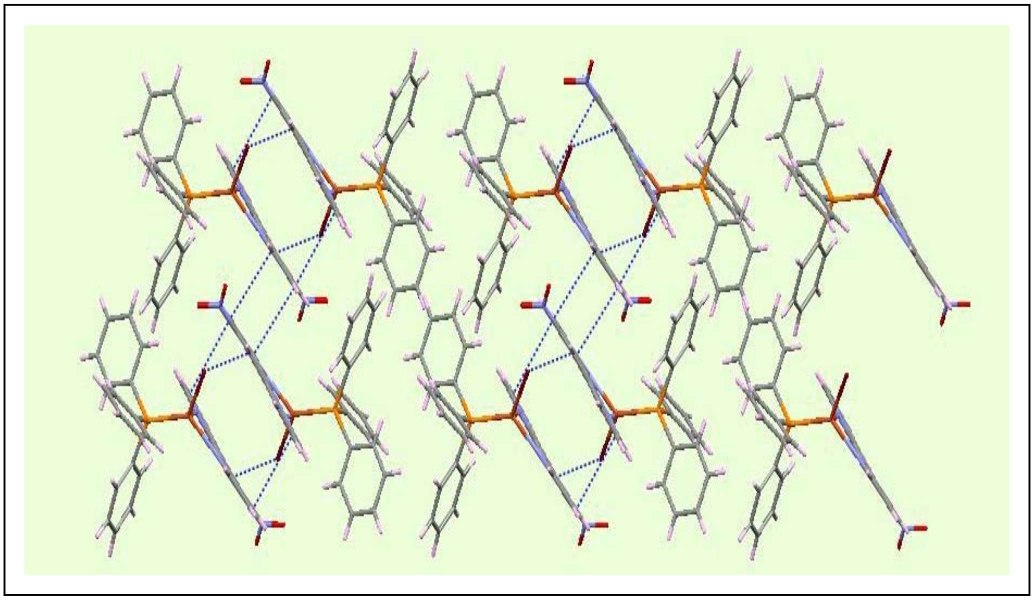


**Figure 3.16:** Packing of complex Cu-6 down "b"-axis

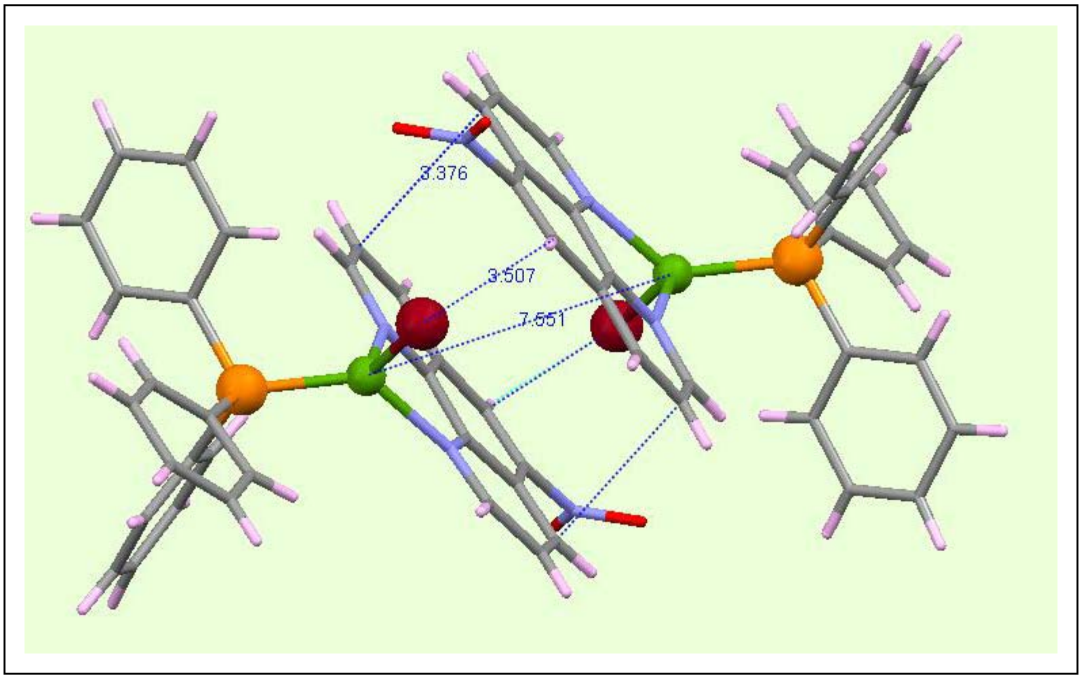


**Figure 3.17:** Formation of the dimmer of complex Cu-6

**Table3.6:** Crystal Data and Structure Refinement Parameters for Complex Cu-6

| Sr. No. | Parameters | Data |
|---|---|---|
| 1 | Empirical Formula | $C_{30}H_{22}BrCuN_3O_2P$ |
| 2 | Formula Weight | 630.93 |
| 3 | Temperature | 293 (2) K |
| 4 | Wavelength | 0.71073 Å |
| 5 | Crystal System | Triclinic |
| 6 | Space Group | $P^{-1}$ |
| 7 | Unit Cell Dimensions | a = 9.4090 (13) Å α = 90.772 (3)°<br>b = 9.7330 (13) Å β = 90.363 (1)°<br>c = 17.199 (2) Å γ = 118.393 (2)° |
| 8 | Volume | 1326.1 (3) $Å^3$ |
| 9 | Z | 2 |
| 10 | Density, (Calculated) | 1.580 mg $m^{-3}$ |
| 11 | Absorption Coefficient | 2.424 $mm^{-1}$ |
| 12 | F(000) | 636 |
| 13 | Crystal Size | 0.10 x 0.08 x 0.02 mm |
| 14 | θ range for data collection | 2.41 to 23.75° |
| 15 | Index ranges | -10<=h<=10, -11<=k<=11, -19<=l<=19 |
| 16 | No. of reflections collected | 11410 |
| 17 | No. of ind reflections | 4041[R (int) = 0.1165] |
| 18 | Completeness to θ of 23.75° | 99.9 |
| 19 | Maximum transmission | 0.9609 |
| 20 | Minimum transmission | 0.8017 |
| 21 | Refinement method | Full –matrix least-squares on $F^2$ |
| 22 | No. of data / restraints / parameters | 4041 / 0 / 343 |
| 23 | Goodness-of-fit on $F^2$ | 1.048 |
| 24 | Final R indices [I>2sigma (I)] | R1 = 0.0855, wR2 = 0.1446 |
| 25 | R indices (all data) | R1 = 0.1589, wR2 = 0.1713 |
| 26 | Largest difference peak and hole | 0.646 and –0.549 e. $Å^3$ |

**Table 3.7:** Selected Bond Length and Bond Angles of Complex Cu-6

| Bond Lengths (Å) | | Bond Angles (º) | |
|---|---|---|---|
| Cu-N(1) | 2.050 (8) | N(1)-Cu-N(2) | 79.1 (13) |
| Cu-N(2) | 2.132 (8) | N(1)-Cu-P | 133.0 (2) |
| Cu-P | 2.197 (3) | N(2)-Cu-P | 108.7 (2) |
| Cu-Br | 2.3968 (17) | N(1)-Cu-Br | 103.5 (2) |
| | | N(2)-Cu-Br | 123.5 (2) |
| | | P-Cu-Br | 108.70 (9) |

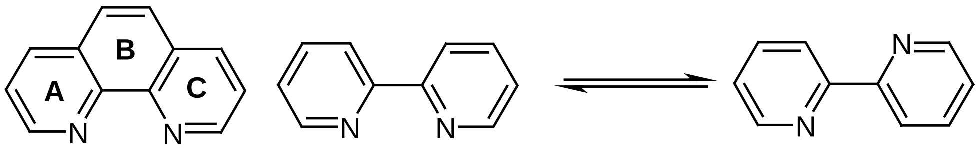
### 3.5 Results and Discussion:

Chapter two describes the copper-catalyzed amination reactions with in-situ formation of catalyst from copper precursor and ligand. There are only two reports on the use of well-defined copper (I) complexes for the amination of arylhalides.[10,12] Thus, there is much scope to explore copper (I) complexes of various N and P containing heterocyclic ligands. For the purpose of investigating these three entirely new complexes having N-containing ligands have been synthesized, characterized and tested for C-N coupling reaction. There are several advantages of using well-defined copper (I) complexes:

- Use of copper as catalyst has cost advantage over Pd
- These copper (I) complexes are not air sensitive (robust)
- Soluble in major solvents such as chloroform, dichloromethane and warm toluene
- Ligands used are cheaper and commercially available
- Easy to synthesize and are well defined copper (I) complexes
- Useful for understanding mechanistic study

These advantages can be considered as alternatives to palladium and do not require the use of expensive and/or air-sensitive phosphine ligands such as tributyl phosphine, tri-*t*-butylphosphine that are often required in the palladium chemistry.[12]

Copper (I) complexes containing phenanthroline are highly active for C-N coupling, because 1,10 phenanthroline and its family have some special features, which are discussed here. 1,10 phenanthroline (a) is the parent compound of an important class of chelating agents.



(a) (b) (c)

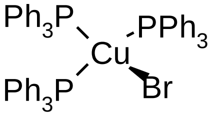
Compared to the more common 2,2'-dipyridyl system (b, c). 1,10-phenanthroline has several distinct properties: the rigid structure imposed by the central ring B means that the two nitrogen atoms are always held in juxtaposition, whereas, in structure (b,c) free rotation about the linking bond allows the two nitrogen to separate (b & c ), in particular under basic or strongly acidic conditions. This entropic advantage for 1,10-phenanthroline means that complexes with metal ions can form more rapidly, a property of importance, for catalysis.[33,34] The nitrogen atom in this case (having aromatic system) is in $sp^2$-hybridized state.[35] The nitrogen donors ligands of this type exhibit extensive coordination chemistry especially in bi and terdentate form. This property of N-containing heterocyclic ligands has particular relevance to the activity of catalyst for C-N bond formation reaction. It has been shown in Chapter 2 that copper (I) species are found to be more active for Ullmann condensation reactions. The excessive electron density on Cu(I) species can be stabilized by the use of ligands capable of reducing electron density on metal. Oligopyridines are ideally suited for this role,[36] as they possess a filled highest occupied molecular orbital and a vacant lowest unoccupied molecular orbital of suitable energies for interactions with metal d orbital.[37] Staking interaction in metal complexes of oligopyridine also plays important part in enhancing the activity of complexes due to weak interactions of ven der Waals kind.

Nitrogen ligands are known to bring about the change in coordination of copper, e.g. it is known that Cu(II) forms a square planar complex $[CuL_2]^{2+}$ with 1,10 phenanthroline. However, neocuprene can not coordinate with Cu(II) in this fashion because of steric hindrance of dimethyl groups in 2,9 position. Instead, neocuprene transforms $d^9$ $Cu^{2+}$ to $d^{10}$ $Cu^+$ with four Cu-N bonds arranged in a tetrahedron with two ligands lying in mutually perpendicular planes.[38] Although, this copper complex is inactive for catalysis due to strong chelating nature of ligands, forming complex with single phenanthroline ligand in coordination with a other ligands like phosphine and halide can make copper complex more labile for catalyst purpose. Similar kind of Cu(II)-Cu(I) transformations are known in terpyridine as ligands.[39] In this chapter such types of copper complexes have been prepared and tested for their activity.

### 3.5.1Catalyst activity of well-defined copper (I) complexes

This chapter describes synthesis of six copper (I) complexes (including three new ones) and testing their activity for amination reactions (See Section 3.1). Copper complexes of nitrogen containing electron rich ligands have been prepare as they are known to increases the activity of copper, nickel and palladium complex catalysts in amination of arylhalides.[4,13,14] In complexes Cu-3 to Cu-6, substitution on 1,10-phnanthroline ligand has been purposely varied in order to see the effect of ligand coordination to copper metal with respect to unsubstituted phenanthroline (complex Cu-2) complex as a reference. These copper (I) complexes are shown below:

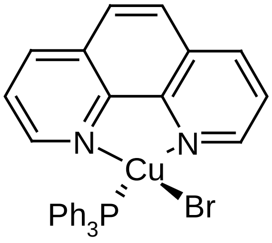
**1) $Cu(PPh_3)_3Br$ :**



**(Cu-1)**

**$PPh_3$:** Triphenylphosphine

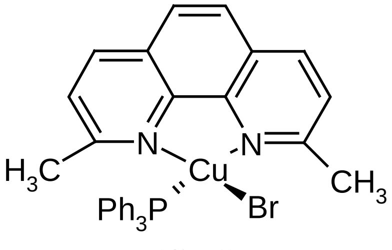
**2) $Cu(Phen)(PPh_3)Br$:**



**(Cu-2)**

**Phen:** 1,10-phenanthroline

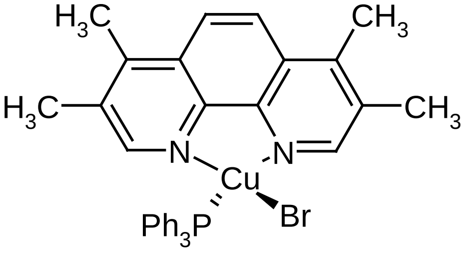
**3) $Cu(neocup)(PPh_3)Br$:**



**(Cu-3)**

**neocup:** neocuprine

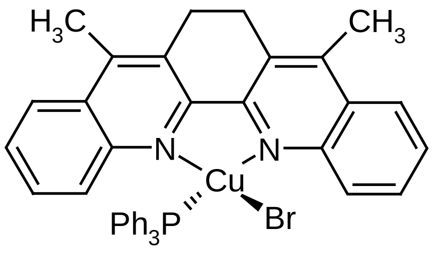
**4) $Cu(TMPhen)(PPh_3)Br$:**



**(Cu-4)**

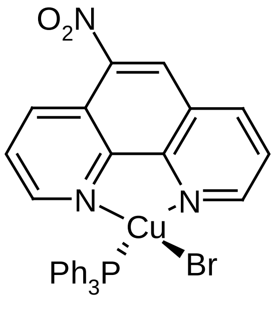
**TMPhen:** Tetramethyl-1,10-phenanthroline

**5) Cu(DhDmDbPhen)(PPh$_3$)Br :**



**(Cu-5)**

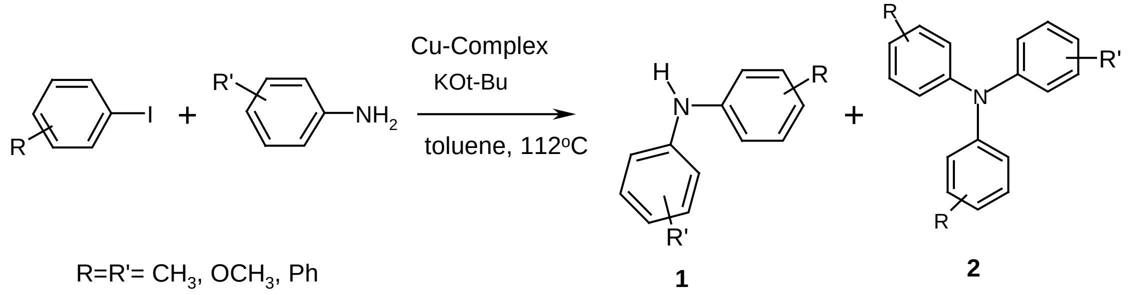
**6) Cu(5-nitroPhen) (PPh$_3$)Br:**



**(Cu-6)**

**DhDMDbPhen:** 6,7-dihydro-5,8-dimethyl dibenzo-1,10-phenanthroline

**5-nitroPhen:** 5-nitri-1, 10-phenanthroline



**Scheme 3.1:** Reaction scheme for the amination of arylhalides using copper complexes

*Table 3.8* shows the results obtained using these complexes. These results indicate that the conversion of aniline at 3.5h is more but selectivity is low, largely because of non-catalytic reaction of aniline and KO*t*-Bu giving rise to potassium salt of aniline (intermediate), which reacts with copper species giving rise to DPA and TPA (see the *section 3.6 for details*). At 5.5h contact time, most of the aniline salt intermediate is converted into products improving selectivity based on aniline. Table 3.8 shows some interesting results, Catalysts Cu-1 and Cu-6 shows good activity, which is accompanied by exceptionally good selectivity as well (activity ~ 75% and selectivity ~ 94% or more and yield ~ 74%). Catalyst Cu-5, shows lowest activity (conversion 60%) but good selectivity (91%). Catalyst Cu-2 and Cu-4 show good activity (conversion 80 %) with poor selectivity and yield (~ 86 and ~ 57 respectively), while catalyst Cu-3 shows average of these two cases.

Several factors play crucial role in deciding the activity of ligand modified copper complex catalyst,[40,41] on a broader basis these are:

- Electronic effect influencing ligand donating ability
- Steric hindrance of ligand that influence Cu-L bond strength
- Trans effect
- Cone angle or bite angle
- Ability of ligand in stabilizing Cu(I)

Bite angle is one of the major factors that affect the catalyst activity but in the copper (I) complexes studied the single crystal X-ray analysis show that no major change in bond angle of N1-Cu-N2 is observed (N1-Cu-N2 angle ~ 78.36-79.30°; see *Table 3.2, 3.5 and 3.7*). Hence it is presumed that bite angle does not play a crucial role in deciding catalytic activity in these complexes. Second factor is trans effect, in this well-defined copper (I) complex bidentate phenanthroline is in cis position, and one of the nitrogen atoms of ligand 1,10-phenanthroline is in trans position to bromide, the effect of bromide is weak[42] and since Cu(I) complexes are not likely to have square planar structure, the effect is assumed to be unimportant.

It is assumed that, Cu-N bond is sensitive to electronic and steric properties of ligands and is playing the major role in deciding the activity of copper (I) complex catalyst in this case. This assumption is based on the facts that the strength of M-N bond is affected more by steric effects in metal-N heterocyclic ligand containing complexes than corresponding effects in metal phosphorous ligands.[35] Although the activity difference in copper (I) complexes shown in *Table 3.8* is not much, complex Cu-5 shows the lowest activity (aniline conversion 60 %). Other five complexes are highly active (in comparison to Cu-5) but show poor selectivity of amination products except complex Cu-6 and Cu-1. It may be noted here that, the rate-determining step as per widely accepted mechanism *(section 3.7 and scheme 3.8)* is oxidative addition of iodobenzene. One of the most important factors that influence this step is oxidation state of copper. It is believed that copper (I) complexes or salts are more efficient in oxidative addition compared to Cu(II).[1c,36,43] The presence of ligands also contributes immensely in the process. Oxidative addition of aryl halide to Cu(I) species oxidize it to Cu(III) species, the stability of this species depends on the ligands present in copper coordination. Thus, their exist an equilibrium between Cu(I) and Cu(III) species, and then amine elimination can take place from Cu(III) species. The nature of ligand controls these steps during catalysis *(Section 2.8.5.2 chapter 2 for details).*

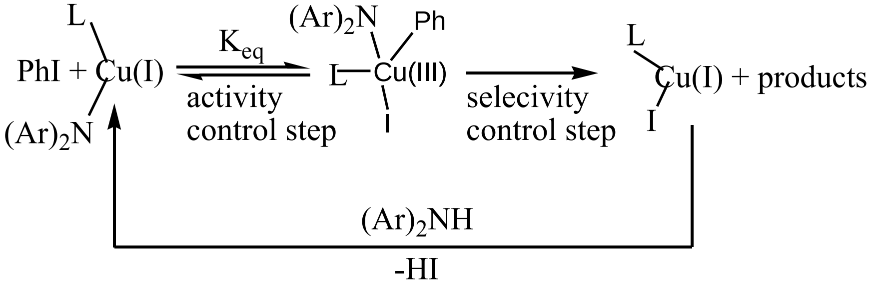
**Table3.8:** Catalyst activity for amination of aryl halide

| Sr. No. | Catalyst | Time, (h) | Conv. of Aniline, (%) | Selectivity, (%) (DPA+TPA) | Yield, (%) | |
|---|---|---|---|---|---|---|
| | | | | | DPA | TPA |
| 1 | Cu-1 | 3.5 | 62 | 45 | 12 | 16 |
| | | 5.5 | 74 | 100 | 17 | 57 |
| 2 | Cu-2 | 3.5 | 76 | 75 | 11 | 46 |
| | | 5.5 | 80 | 86 | 9 | 60 |
| 3 | Cu-3 | 3.5 | 60 | 60 | 13 | 23 |
| | | 5.5 | 77 | 81 | 16 | 47 |
| 4 | Cu-4 | 3.5 | 67 | 46 | 9 | 22 |
| | | 5.5 | 80 | 75 | 12 | 54 |
| 5 | Cu-5 | 3.5 | 58 | 59 | 15 | 31 |
| | | 5.5 | 60 | 91 | 20 | 35 |
| 6 | Cu-6 | 3.5 | 75 | 68 | 15 | 36 |
| | | 5.5 | 77 | 94 | 23 | 50 |

***Reaction Condition:*** *Iodobenzene: 0.66 Kmol/$m^3$; Aniline: 0.295 Kmol/$m^3$; copper (I) complex: 0.01056 Kmol/$m^3$; toluene: 23 x $10^{-6}$ $m^3$; KOt-Bu: 0.8838 Kmol/$m^3$; temperature: 385 K.*

The results on activity and selectivity pattern of these complexes *(Table 3.8)* show that, there is not much difference in activity and selectivity pattern except for Cu-5 catalyst, which shows slightly reduced activity compared to others and similar selectivity. However, for complex Cu-1 and Cu-6 both factor are good, therefore these complexes are the best for C-N coupling reaction from our study. The activity and selectivity pattern can be in part explained by elementary steps proposed earlier *section (2.8.5.2)*. However, the overall activity shown by these complex can be more complex and could be the net results of several factors affecting the catalytic cycle.[40,41]

If it is assumed that the activity of catalyst is controlled by the oxidative addition of PhI to Cu(I) species. And thus oxidized Cu(III) species, via reductive elimination produce amination products accounting for selectivity of reaction. These steps are shown in *Scheme 3.2.*



**Scheme 3.2**: Role of ligand in tuning the activity and selectivity in amination reaction

Thus, the value of $K_{eq.}$ in first step of *Scheme 3.2* represents the activity of copper catalyst as the next step is assumed to be fast and the rate at which aryl halide react with Cu(I) species decides the conversion of aryl halide (since addition of aniline is not rate determining). The results shown in *Table 3.8* are qualitatively discussed based on electronic and steric effects point of view:

The lowest activity (but high selectivity) obtained for Cu-5 having sterically hindered 6,7-dihydro-5,8-dimethyl dibenzo-1,10-phenanthroline ligand could be due to poor ability of aryl halide to oxdatively add on to Cu(I) species, but better stabilization with Cu (III) oxidation state by ligand might be the result of good selectivity (also see text).

In complex Cu-3, Cu-4 and Cu-5 methyl substituted 1,10-phenanthroline is ligated to copper, this substitutions increases the electron density on N compared to 1,10-phenathroline (i.e. complex Cu-2). The complex Cu-5 has position of N in phenanthroline ring, which is more hindered compared to unsubstituted phenanthroline. The fused benzene rings in the position 2,3 and 8,9 is fix in space which makes the ligand 6,7-dihydro-5,8-dimethyl dibenzo-1,10-phenanthroline sterically more hindered as compared to 1,10-phenathroline. Next, the ligand neocuprene has also substituted methyl groups at similar position like 6,7-dihydro-5,8-dimethyl dibenzo-1,10-phenanthroline, but these are not as rigid as the ligand of complex Cu-5 (since like phenyl ring, methyl groups can not be fused to 1,10 phenanthroline molecule). Thus hindered nature of ligand 6,7-dihydro-5,8-dimethyl dibenzo-1,10-phenanthroline make the catalyst Cu-5 least active in comparison to other copper containing complexes.

It may be recalled that in earlier Section 2, screening of ligands indicated that in-situ formation of catalytic complex from weakly donating ligands such as triphenyl phosphine as ligand gave poor activity compared to pyridine, however amount of $PPh_3$ greatly improved the conversion of aniline *(Chapter 2; Section 2.7.5, Table 2.13).* Thus too much weakening of ligand-copper bond reduces the copper-phosphine ligands, which is a poor electron donating compared to nitrogen. Complex Cu-1 having three phosphine ligands also contributes in an excellent way in making catalyst activity almost at par with Cu-2. Here, probably contribution of three $PPh_3$ ligand makes copper catalyst stable compared to that formed in-situ examined earlier *(Chapter 2, Table 2.13),* giving very poor activity. Finally, complex Cu-2 was selected for further investigation since; it shows reasonably good activity and selectivity amongst other complexes and ligand is easily available. Comparison of activity of 1,10-phenanthroline complexes of copper with phosphine containing ligands indicates that cheap ligand such as triphenyl phosphine is quite effective compared to *N*-containing expensive ligands. Since *P*-containing ligand from weaker bonding with metal compare to *N*-containing ligand, too much strong nature of ligand is not necessary for good activity but amount of *P*-containing ligand may be crucial to optimize catalyst efficiency. The explanation given here is qualitative in nature and more work needs to be done for better understanding of these effects.

Thus, fine-tuning of bond strength of copper and nitrogen is necessary for the optimum activity of these catalysts. More detail work on this subject may help in explaining the activity of different copper complexes as well as help in designing of new complexes with cheaper metals such as copper and nickel.

### 3.5.2 Effect of Catalyst Concentration

The catalyst concentration effect is studied using Cu(Phen) ($PPh_3$)Br between the catalyst loading range of 0 – 1.07 x $10^{-2}$ $Kmol/m^3$. In absence of catalyst almost 40%

conversion of aniline is observed, however corresponding product is not form to that extent (15% DPA + TPA). As the catalyst concentration is increased, conversion of aniline also increases along with amination products. At higher loading of catalyst both conversion and yield are became independent of catalyst amount (beyond 0.34 x $10^{-2}$ Kmol/$m^3$ catalyst loading). It may be noted here that as the catalyst loading is increased, selectivity of amination products improves and maximum yield of 80% of TPA and DPA are obtained. Catalyst concentration of 0.703 x $10^{-2}$ Kmol/$m^3$ was chosen for further exploration purpose.

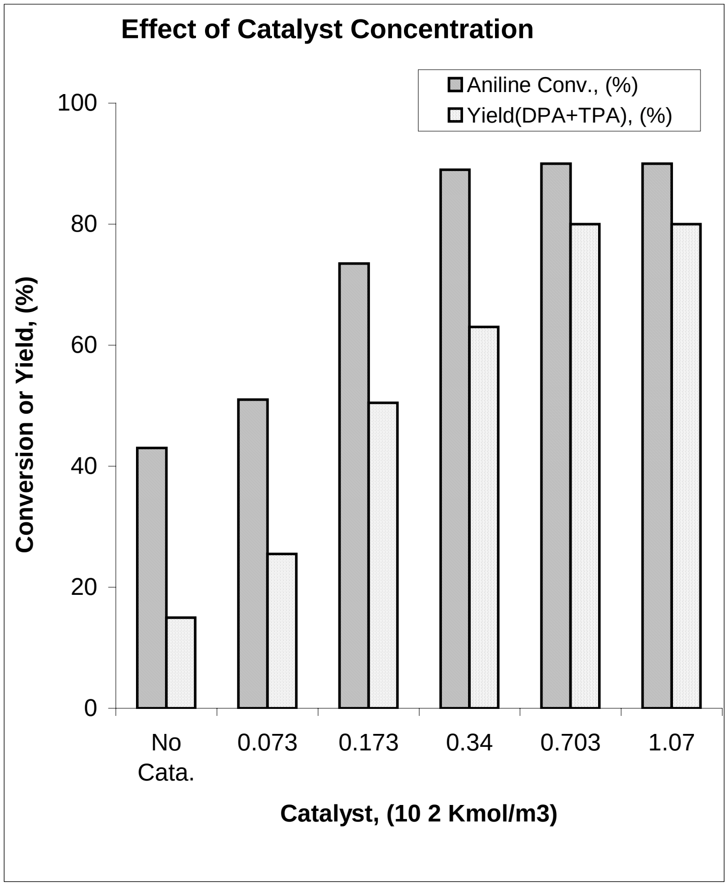


**Figure 3.18:** Effect of catalyst concentration

***Reaction Condition:*** *Iodobenzene: 0.66 Kmol/$m^3$; Aniline: 0.295 Kmol/$m^3$; toluene: 23 x $10^{-6}$ $m^3$; KOt-Bu: 0.8838 Kmol/$m^3$; temperature: 385 K; time 6h.*

### 3.5.3 Base Effect

Various bases were tested for the amination reaction using Cu-2 as catalyst. It was found that KO*t*-Bu was the best base for the amination of aryl halides. KO*t*-Bu gave best activity since it is a strong inorganic base. NaO*t*-Bu gave more selectivity towards DPA as compare to KO*t*-Bu, due to the less activity of NaO*t*-Bu. The bases $CH_3COONa$, DBN (1,5-Diazabicyclo [4.3.0] non-5 ene), TEA show no activity *(Table 3.9, entries 5,6 and 7)*. In absence of base no conversion of aniline and no amination product are formed *(Table 3.9, entry 8)*. Gujadhur *et.al.*[12] reported KO*t*-Bu as the best base for the mono-amination of arylhalides using Cu(Phen)($PPh_3$)Br as catalyst. For the further study we have used KO*t*-Bu as a base and Cu-2 as a catalyst.

**Table3.9:** Effect of base for amination of aryl halide

| Sr. No. | Base | Conv. of Aniline, (%) | Yield of DPA, (%) | Yield of TPA, (%) |
|---|---|---|---|---|
| 1 | KOt-Bu | 80 | 9 | 60 |
| 2 | NaOt-Bu | 45 | 11 | 4 |
| 3 | $K_2CO_3$ | 10 | 1 | 3 |
| 4 | KOH | 37 | 3 | 4 |
| 5 | $CH_3COONa$ | 21 | 0 | 0 |
| $^{\$}6$ | DBN | 21 | 0 | 0 |
| 7 | TEA | 23 | 1 | 0 |
| 8 | No Base | 0 | 0 | 0 |

***Reaction Condition:*** *Iodobenzene: 0.66 Kmol/m$^3$; Aniline: 0.295 Kmol/m$^3$; Cu(Phen)($PPh_3$)Br: 0.01056 Kmol/m$^3$; toluene: 23 x 10$^{-6}$ m$^3$; KOt-Bu: 0.8838 Kmol/m$^3$; temperature 385 K; time 5.5h.; \$ DBN: 1,5-Diazabicyclo[4.3.o]non-5 ene*

### 3.5.4 Effect of Base Concentration

Effect of KO*t*-Bu base was studied in the range 0.299 – 1.385 Kmol/m$^3$ using Cu-2 as a catalyst. *Figure 3.19* show that plot of base to aniline ratio versus conversion of aniline and yield of amination products. The conversion of aniline increases with increase in base concentration due to the aniline salt formation. However, even at base to aniline ratio of 5 (mol/mol) conversion of aniline do not reach 100%. The yield of DPA and TPA increase as the ratio of base salt to aniline is increased and levels off at 80 % yield beyond the ratio of ~3. At this stage, the combined selectivity of DPA and TPA is only 82 %. Since yield and conversion did not improve beyond ratio of 3, this ratio was taken as standard in all other investigation.

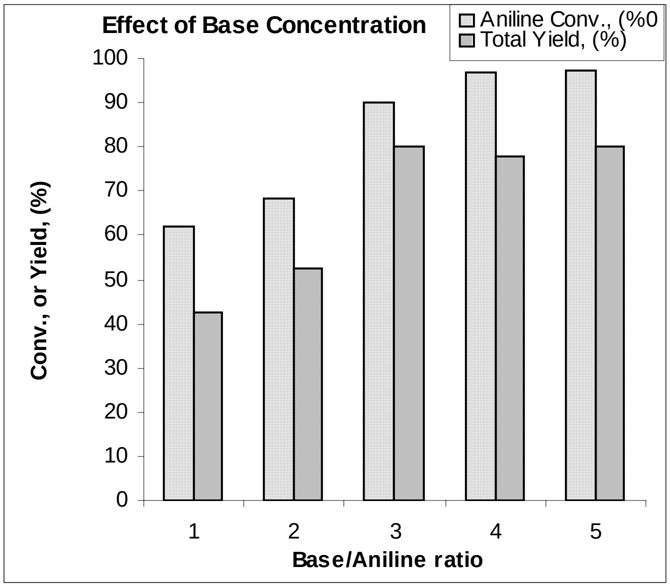


**Figure 3.19:** Effect of base concentration

***Reaction Condition:*** *Iodobenzene: 0.66 Kmol/m*$^3$*; aniline: 0.295 Kmol/m*$^3$ *(constant); Cu(Phen)(PPh*$_3$*)Br: 0.00703 Kmol/m*$^3$*; toluene: 23 x 10*$^{-6}$*; temperature: 385 K; time 6h.*

### 3.5.5 Effect of Solvent

Various solvents were screened using Cu(Phen)(PPh$_3$)Br (Cu-2) as a catalyst and KOt-Bu as a base *(Table 3.10)*. In amination of arylhalides most of the work done is on palladium as catalyst and for this reaction Buchwald[4] and Hartwig[5] used toluene as a solvent. They have also tested other solvents like 1,4-dioxane, NMP, THF, DMF, xylene.

Our previous report on copper catalyzed amination of aryl halides shows that toluene is the best solvent.[44,45] Our aim was, to investigate the effect of solvent on well defined copper (I) complexes and here also we found toluene is the best solvent for the amination of aryl halides. Reactions were carried out at 385 K using toluene, *N,N'*-dimethyl formamide (DMF), *m*-xyelene as solvents *(Table 3.10, entries 1,3 and 7).* For other solvents reactions were carried out at reflux temperatures. No yields of TPA and DPA were obtained with polar solvent like Acetonitrile, DMF *(Table 3.10, entry 6 and 7).*

Less polar solvent *m*-xylene and non-polar solvent cyclohexane gave less yield of TPA *(Table 3.10, entry 3 and 4).* 1,4-dioxane gives moderate yield of TPA and *t*-BuOH gives no yield of TPA *(Table 3.10, entry 2 & 5).* Solvent can be arranged in decreasing order of TPA yield as: toluene >1,4-dioxane > *m*-xylene > Cyclohexane > *t*-butanol > MeCN = DMF

**Table 3.10:** Effect of solvents for amination of aryl halide

| Sr. No. | Solvent | Conv. of Aniline, (%) | Yield of DPA, (%) | Yield of TPA, (%) |
|---|---|---|---|---|
| 1 | Toluene | 80 | 9 | 60 |
| 2* | 1,4-dioxane | 71 | 10 | 55 |
| 3 | *m*-xylene | 69 | 14 | 27 |
| 4* | Cyclohexane | 61 | 14 | 10 |
| 5* | *t*-BuOH | 37 | 6 | 0 |
| 6* | MeCN | 27 | 0 | 0 |
| 7 | DMF | 2 | 0 | 0 |

***Reaction Condition:*** *Iodobenzene: 0.66 Kmol/m$^3$; Aniline: 0.295 Kmol/m$^3$; Cu(Phen)(PPh$_3$)Br: 0.01056 Kmol/m$^3$; solvent: 23 x 10$^{-6}$ m$^3$; KOt-Bu: 0.8838 Kmol/m$^3$; temperature: 385 K time 5.5h.*: reflux temperature*

Thus less polar solvent like toluene is suitable for the well define copper (I) complex for the amination of arylhalides.

### 3.5.6 Effect Of Aniline Concentration

The effect of concentration of aniline was investigated in the range of 0.104 – 0.84 Kmol/m$^3$ under constant concentration of base. *Figure 3.20* shows the plot of conversion of aniline and yield of amination products versus ratio of base to aniline. At low concentration aniline (ratio = 8.7, base : aniline) almost 100 % conversion of aniline is achieved with 80 % yield of amination products. As the concentration of aniline is increases conversion and yields remain almost constant in the beginning, however at high concentration of aniline (ratio = 1) very poor conversion of aniline and yield of product is obtained (40 % conversion and yield). This is because at high concentration of aniline the stoichiometric requirement of base (which is two times that of aniline on molar basis) is not satisfied. Hence at base/aniline ratio of 1, the reaction is limited by base, resulting poor conversion and yields.

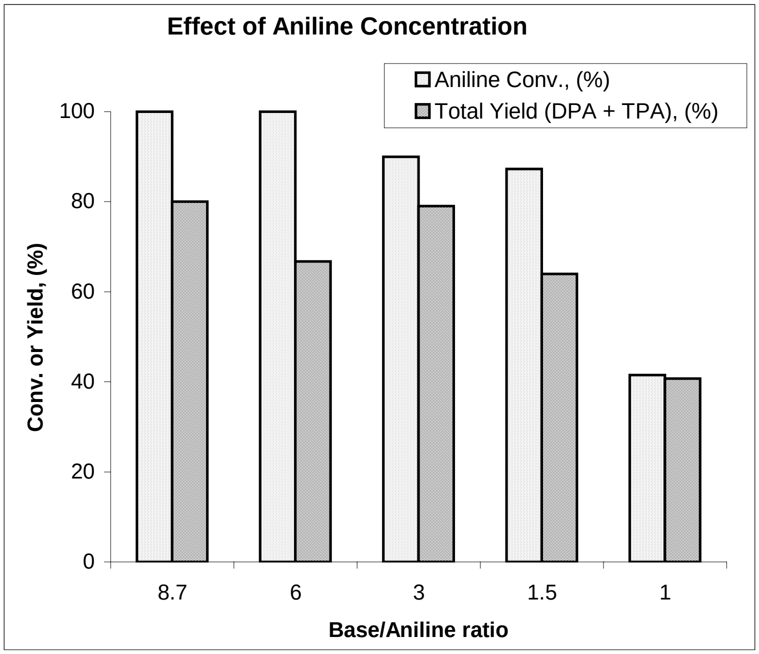


**Figure 3.20:** Effect of aniline Concentration

***Reaction Condition:*** *Iodobenzene: 0.66 Kmol/m*$^3$*; Cu(Phen)(PPh*$_3$*)Br: 0.00703 Kmol/m*$^3$*; toluene: 23 x 10*$^{-6}$ *m*$^3$*; KOt-Bu: 0.8838 Kmol/m*$^3$*(constant); temperature: 385 K; time 6h.*

### 3.5.7 Effect of Temperature

Temperature effect was investigated using Cu(Phen)(PPh$_3$)Br as a catalyst, KOt-Bu as a base and toluene as a solvent at various temperature *(Table 3.11)* and the best results were obtained at 385 K temperature. Activity of catalyst decreases with decrease in the temperature of reaction, *(Table 3.11, entries 1,2 and 3).*

**Table 3.11:** Effect of temperature for amination of arylhalides

| Sr. No. | Temperature, (K) | Conv. of Aniline, (%) | Yield of DPA, (%) | Yield of TPA, (%) |
|---|---|---|---|---|
| 1 | 385 | 80 | 9 | 60 |
| 2 | 373 | 63 | 16 | 33 |
| 3 | 363 | 60 | 18 | 18 |

***Reaction Condition:*** *Iodobenzene: 0.66 Kmol/m$^3$; Aniline: 0.295 Kmol/m$^3$; Cu(Phen)(PPh$_3$)Br: 0.01056 Kmol/m$^3$; toluene: 23 x 10$^{-6}$ m$^3$; KOt-Bu: 0.8838 Kmol/m$^3$; time 5.5h.*

In *Table 3.11* we observed that decrease in reaction temperature leads to increase in yield of DPA. The conversion of aniline at 363 K temperature was 60%, with poor selectivity to amination products; however, improvements in yields were observed at high temperatures.

### 3.5.8 Effect of arylhalides

*Table 3.12* shows that chlorobebenzene gave least yield of TPA and bromobenzene gave very poor yield of TPA. Iodobenzene gave best yield of TPA, *(Table 3.5 entry 1).* Aryl chlorides are usually inert and the order of reactivity, ArI> ArBr>ArCl is consistent with the Ar-X bond strength.[46]

**Table 3.12:** Effect of arylhalides

| Sr. No. | Aryl halide | Conv. of Aniline, (%) | Yield of DPA, (%) | Yield of TPA, (%) |
|---|---|---|---|---|
| 1 | Iodobenzene | 80 | 9 | 60 |
| 2 | Bromobenzene | 47 | 13 | 4 |
| 3 | Chlorobenzene | 46 | 4 | 1 |

***Reaction Condition:*** *Arylhalides: 0.66 Kmol/m$^3$; Aniline: 0.295 Kmol/m$^3$; Cu(Phen)(PPh$_3$)Br: 0.01056 Kmol/m$^3$; toluene: 23 x 10$^{-6}$ m$^3$; KOt-Bu: 0.8838 Kmol/m$^3$; temperature: 385 K; time 5.5h.*

Experimentally found bond dissociation energies for phenyl halide at 298 K for Cl, Br and I are 96, 81 and 65 Kcal/mol respectively.[47] Also it is known that metal center coordinated by electron-rich phosphine ligands can effectively activate C-Cl bonds of aryl chlorides.[47]

### 3.5.9 Effect of Iodobenzene Concentration

It is believed that oxidative addition of iodobenzene to copper complex is the slowest step in amination reaction.[46] Hence concentration of iodobenzene is important for enhancing the rate of reaction. Concentration of iodobenzene was studied in the range 0.167 – 1.154 Kmol/$m^3$ and the graph of conversion or yield versus PhI concentration is depicted in the *Figure 3.21 (a).* The yield of TPA and combined yield of DPA + TPA is based on PhI conversion. It can be seen from this figure that, when PhI is less than the stoichiometric requirement (i.e. PhI concentration of 0.167 and 0.32 Kmol/$m^3$) compared

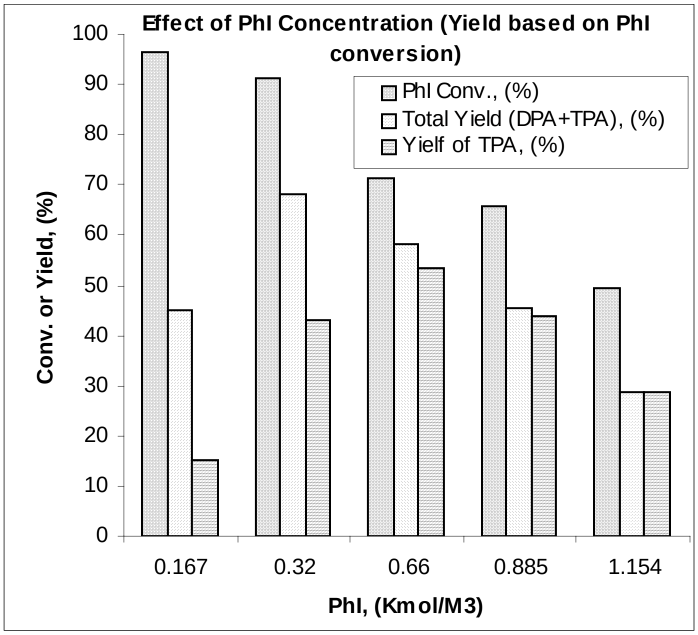


**Figure 3.21 (a):** Effect of Iodobenzene concentration

***Reaction Condition (for Figure 3.21 (a) and (b):*** *Aniline: 0.295 Kmol/$m^3$; Cu(Phen)($PPh_3$)Br: 0.00703 Kmol/$m^3$; toluene: 23 x $10^{-6}$ $m^3$; KOt-Bu: 0.8838 Kmol/$m^3$; temperature: 385 K; time 6h.*

to aniline, PhI conversion in the range 93 to 96 % is obtained as PhI in this case is a limiting reactant. It may be noted in this case that low concentration of PhI, large amount of side products, which are polymeric in nature and resinous in nature are formed, decreasing the yield of DPA and TPA. At PhI concentration of 0.66 Kmol/m$^3$ and above, amination reaction proceeds without any starvation of PhI. Under this condition aniline becomes limiting reactant and PhI conversion are limited by aniline concentration.

A maximum yield of amination products can obtained when PhI is slightly in excess of stoichiometric requirement compared to aniline (PhI concentration is 0.66 Kmol/m$^3$). The Figure 3.21 (a) is thus showing the importance of PhI concentration in amination reaction, indicating that PhI concentration lower then stoichiometric requirement leads to side product formation, while higher concentration of PhI than stoichimetric requirement does not help to a great extent.

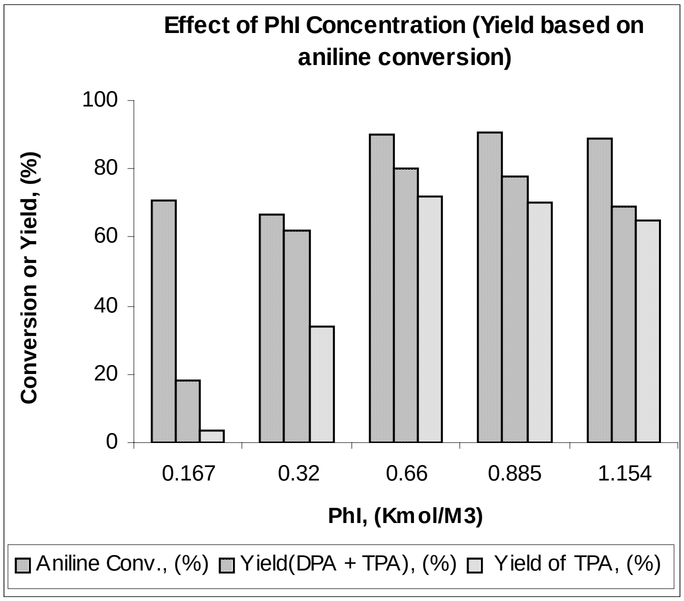


**Figure 3.21 (b):** Effect of iodobenzene concentration

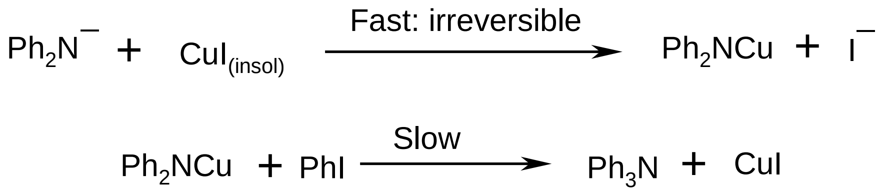
[**Reaction condition:** see Figure 3.21 (a)]

Therefore, the optimum concentration of PhI is 0.66 Kmol/m$^3$ (PhI/ aniline ratio 2.24). These facts are more clearly seen in *Figure 3.21 (b)*, where PhI concentration is plotted against the aniline conversion and yields are based on aniline. The aniline conversion in the range 70 – 90 % is obtained indicating that aniline conversion is not sensitive to PhI concentration, this is expected as aniline is converted due to reaction with base KO*t*-Bu forming potassium salt or adduct of aniline. The increase in PhI concentration enhance the conversion of this adduct or salt into DPA and TPA in presence of copper catalyst [Figure 3.21 (b)].

### 3.6 Investigation of Reaction Mechanism

The Ullmann condensations mechanism involving oxidative addition and reductive elimination was earlier proposed by Cohen in 1974.[48] and later supported by several literature reports[49,50,51] indicating Cu(I) and Cu(III) intermediates. The mechanistic information on copper-catalyzed amination of arylhalide is however limited due to the complexities involved during product formation leading to salts and precipitation of copper in many cases. In this regard, use of well-defined copper complexes of phenanthroline ligands have been successfully explored to understand the mechanism.[52] Moreover, the information that is available on Pd catalyzed mechanism may be of limited use when it comes to copper catalyzed system. This is because the electronic and stabilization demand for copper catalyzed system may be entirely different for that established for palladium.[53]

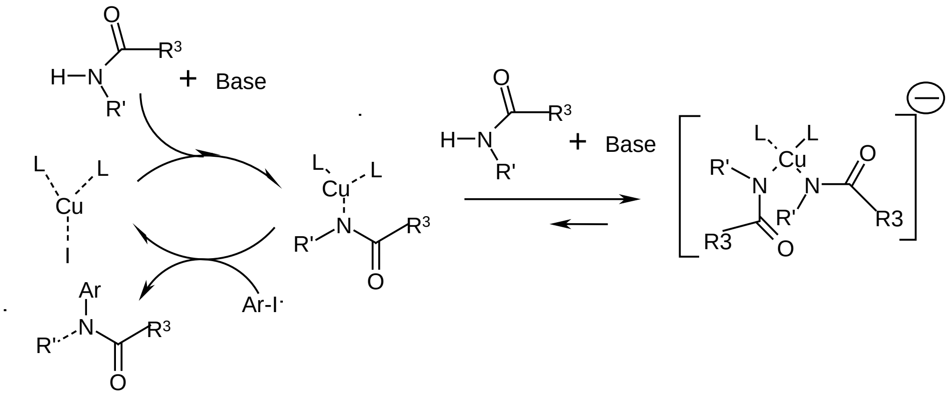
As per mechanism proposed for Ullmann condensation, by Paine,[46] $Ph_2N^-$ reacts with CuI giving rise to species of the type "$Ph_2NCu$" which reacts with PhI leading to TPA formation to regenerate copper iodide. Step two is assumed to be the slowest step (RDS) in the mechanism *(Scheme 3.3)*



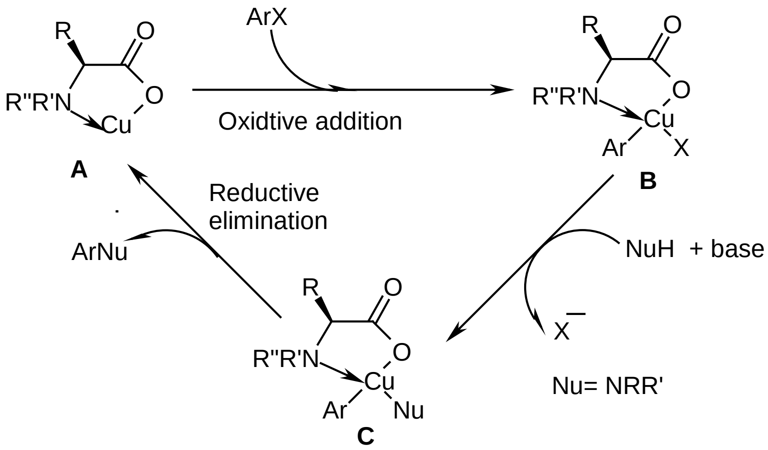
**Scheme 3.3:** Reaction mechanism proposed by Paine

Paine has further proposed that only soluble copper catalyst is responsible for Ullmann condensation.

Buchwald and co-workers have reported a proposed a reaction mechanism in presence of strong base (*Scheme 3.4).*[54] These authors conclude that presence of diamine ligand facilitates amidation even at room temperature, while, without this ligand temperature up to 353 K is required. The role of salt in *Scheme 3.4* is not clarified in this work.



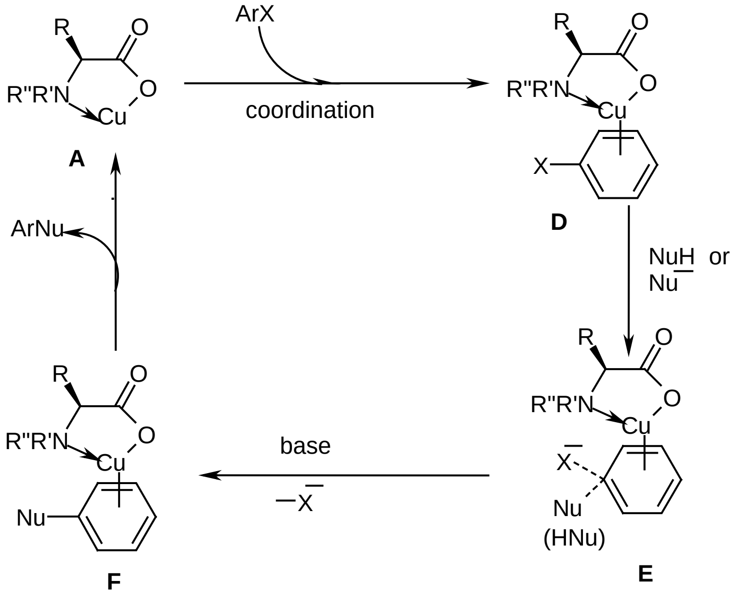
**Scheme 3.4:** Copper-catalyzed amidation reaction mechanism proposed by Buchwald



**Scheme 3.5:** Copper catalyzed amination of arylhalides proposed by Ma (route 1)

On basis of above two proposed mechanism Dawei Ma[55] proposed mechanisms for copper catalyzed amination of arylhalide. They put forward two possible catalytic cycle see *Scheme 3.5 and 3.6.* In *Scheme 3.5,* the chelation of Cu(I) with an amino acid makes Cu(I) species more reactive towards the oxidative addition, and also able to stabilize the oxidative addition intermediate **B,** thereby promoting the coupling reaction.

In *Scheme 3.5,* chelated Cu(I) might make the aromatic ring of the π-complex **D** more electron –deficient, thereby facilitating the nucleophilic attack of amines or nitro anions generated from *N*-containing heterocycles. In both these mechanism, it may be noted that oxidative addition of PhI to copper complex catalyst has been shown to be the first step.



**Scheme 3.6:** Copper catalyzed amination of arylhalides proposed by Ma (route 2)

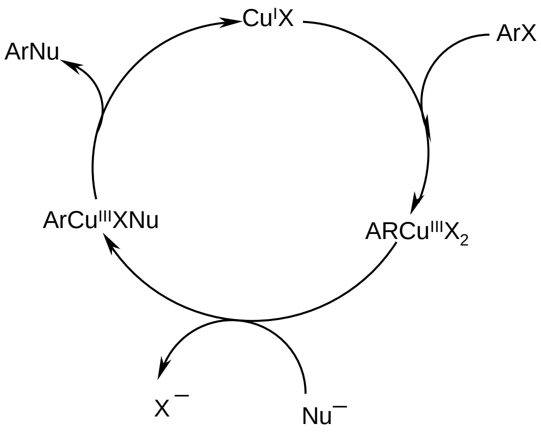
Recently Cristau et al., have investigated the mechanistic aspects of copper catalyzed amination reaction of 1,4 diiodo benzene by pyrazole as a model system.[43] Their mechanism was based on oxidative addition and reductive elimination steps. Following experimental observations were made on the model system for choosing this mechanism:

1) The reactivity sequence found is ArI>ArBr>ArCl which parallels the leaving-group ability of the halide ions,
2) Couplings are slightly favored by electron-withdrawing groups on aryl halides and slightly disfavored by electron-releasing ones,
3) Steric hindrance on either coupling partner is rate depressing, and
4) Unactivated aryl halides do not react in the absence of the copper catalyst.

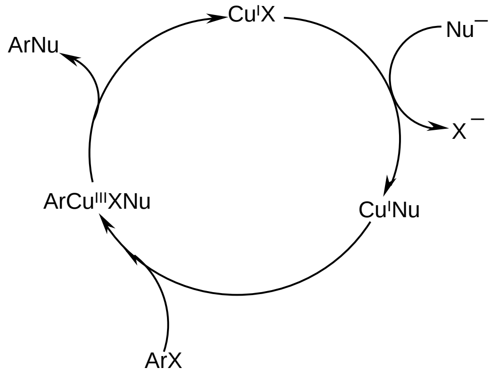
This mechanism involves following elementary steps:

1. Oxidative addition of the aryl halide to copper (I) generating a transient Cu(III) species,
2. Nucleophilic substitution of copper-bound halide by amine anion, and
3. Reductive elimination of the coupling product,
4. Regenerating the active catalyst.

Although a monomeric copper complex has been shown here to undergo oxidative addition, a dinuclear oxidative addition process could also be envisaged to occur. Similarly it may be noted that it is not certain as to which step is first nucleophilic substitution or the oxidative addition step. Both possibilities are depicted on *Scheme 3.7 and 3.8.*[43]



**Scheme 3.7:** Mechanism of Cu-catalyzed amination: Oxidative addition is first step

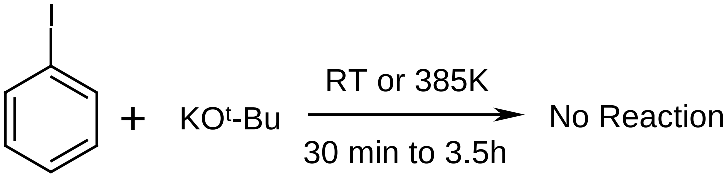


**Scheme 3.8:** Mechanism of Cu-catalyzed amination: Nucleophilic substitution of amine as first step

The above discussion on reaction mechanism of amination of arylhalide indicates that oxidative addition of copper (I) catalyst is the slowest step according to many researchers. And that reaction is catalyzed by soluble copper catalyst formed in-situ. However, the reaction of aniline and base to form PhNHK type salt or adducts is not well understood. Following experiments were carried out for to understand this step.

**a) Reaction with Iodobenzene and potassium t-butoxide**

In this experiment we have taken iodobenzene and KO*t*-Bu base without solvent and stirred the mixture for three and half hour, with heating and we found that there was no reaction. This indicates that there is no interaction between iodobenzene and KO*t*-Bu base.

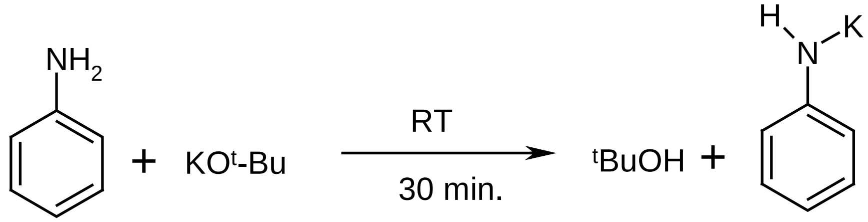


**Scheme 3.9:** Reaction with iodobenzene and KOt-Bu

**b) Reaction with aniline and potassium t-butoxide**

Reaction of aniline and KO*t*-Bu was carried out under inert atmosphere and at room temperature for about 30 min. It was observed that upon addition of solid KO*t*-Bu (white) to aniline solution, KO*t*-Bu salt immediately turns into a shining white gelatinous solid liberating t-butanol *(See Scheme3.10)*. GC analysis of the reaction solution confirmed the formation of t-butanol. Quantity analysis indicated ~70 % conversion of KO*t*-Bu base. The formation of potassium salt of aniline as per *Scheme 3.10* could not be confirmed due to its reactive nature. However, such types of salt have been postulated earlier for Pd-catalyzed amination of arylhalides.[54] An indirect approach to confirm the formation of potassium salt of aniline was adopted. In this approach, aniline salt was first dried by removing volatile components, butanol and unreacted aniline by distillation under reduced pressure (60 mm Hg pressure and 358

K temperature) in a rotavap. The dried powder also contains small amount of unreacted KOt-Bu along with potassium salt of aniline. Hydrolyzing dried solid by water produce aniline and KOH *(See Scheme 3.11)* which separated into organic and aqueous layers. GC analysis of organic layer showed the presence of aniline and trace of t-butanol, obviously the formation of aniline can only occurred due to the hydrolysis of potassium salt by water *(see Scheme 3.11)*, while some *t*-butanol is also seen due to unconverted KO*t*-Bu base. The aqueous layer showed strong basic pH, conforming formation of KOH. However formation of KOH is not confirmative test in this case as it could be formed via unreacted KO*t*-Bu as well. *Figure 3.22* shows the NMR signals of organic layer wherein the presence of aniline is confirmed.



**Scheme 3.10:** Reaction with iodobenzene and KO*t*-Bu

**Scheme 3.11:** Reaction with potassium salt of aniline with water

Amination of iodobenzene was carried out using perform aniline salt following the procedure shown in experimental section for standard reaction. It was observed that the concentration-time reaction profile was similar to that observed under standard conditions. This experiment indicates that aniline is first activated by KO*t*Bu forming potassium salt of aniline.

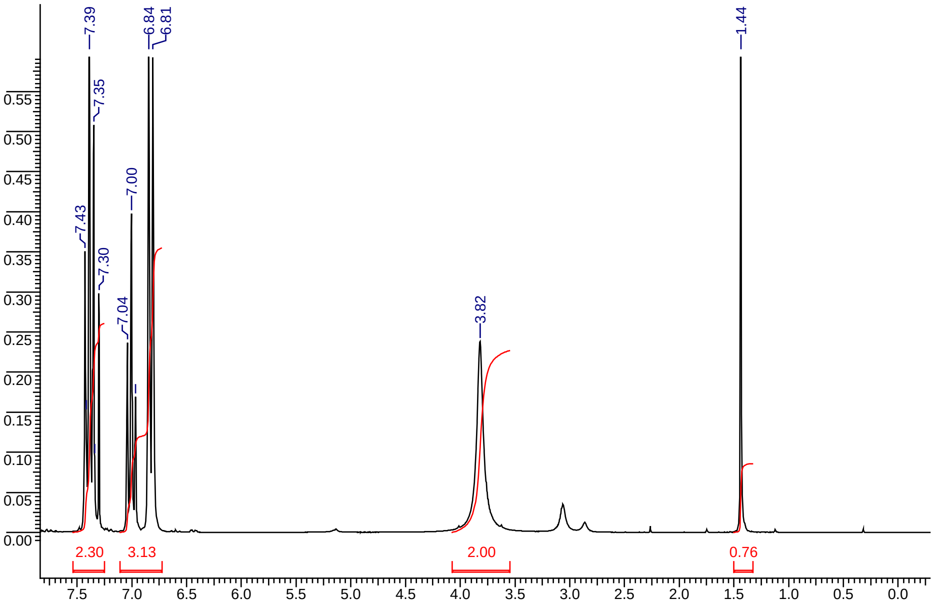


**Figure 3.22:** $^1$H NMR of organic phase

### Observation Made During Amination of Iodobenzene by Perform Copper Complex Catalyst

1. Aniline activation by KO*t*-Bu is the first step, and activated aniline reacts with copper complex is the next step
2. Iodobenzene is not activated by KO*t*Bu
3. Copper acetate (copper hydroxyl carbonate) as catalyst shows lower activity than Cu(Phen)($PPh_3$)Br complex
4. Preformed complexes of copper (I) are less active than similar complexes formed in-situ
5. Catalyst activity of in-situ formation of copper catalyst from CuI and $PPh_3$ is very poor compare to that formed from CuI and 1,10-phenathroline

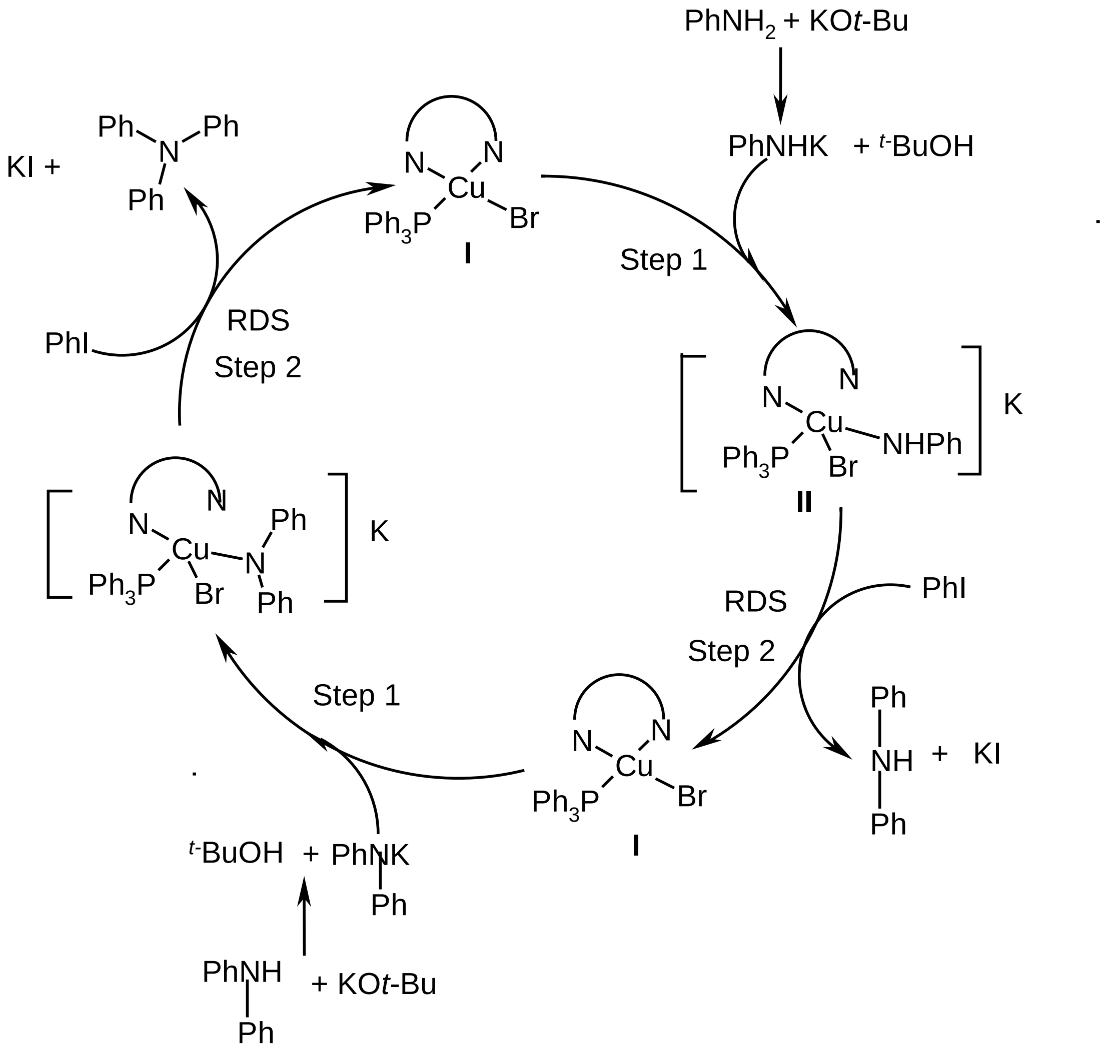
Lower activity of $Cu(OAc)_2$ as against copper (I) complexes (complex Cu-2) suggest that oxidative addition is facilitated more by copper (I) complexes than copper (II) complexes.[55]

A tuning of Cu-ligand bond is important for obtaining optimum activity of copper (I) complexes. Cu-P bond in copper (I) phosphine complex is weaker in comparison to Cu-N bond in copper (I) phenanthroline complex.[53] The weaker bond of Cu-P makes these complexes highly reactive and hence there is a possibility of copper being precipitated in this case under reaction conditions to metallic copper. While in copper-phenanthroline complexes the bond strength is correct.

Preformed Cu(I) complexes are coordinatively saturated confirm and in order to activate these complexes a dissociation step is required so that the substrate can enter into the copper coordination sphere to initiate the reaction. This can become an energy intensive step, compare to the case where copper complexes are formed in-situ. In the later case both ligand and reactant can compete for the copper center, and since molar concentration of reactants is in far excess compared to the ligand, the probability of forming active copper complex with coordination of reactant is very high, thus initiating the reaction in more efficient manner compare to perform complex. This is a qualitative explanation and ligand basicity values, steric and other factors needs to be considered while evaluating efficiencies of catalytic reactions.

## Postulated Reaction Mechanism

Based on observations made in this chapter a postulated reaction mechanism of amination of iodobenzene catalyzed by well-defined Cu(Phen)($PPh_3$)Br complex is depicted in *Scheme 3.12.* Here it has been shown that copper complex (species I) irreversibly reacts with mono potassium salt of aniline forming anionic species [II]. Oxidative addition of iodobenzene to species [II], liberate diphenylamine and starting complex is regenerated. The diphenylamine generated can react with KO*t*-Bu producing potassium salt of diphenylamine. This potassium salt of diphenylamine reacts in similar fashion as shown in step 1 and 2 generating triphenylamine and species [I] i.e. original copper complex. It may be noted here that the mechanism is based on mono potassium salt of anilines (PhNHK and $(Ph)_2NK$) and not dipotassium salt ($PhNK_2$). This is a speculated reaction mechanism for amination of arylhalides using well-define copper (I) complex. More work is required to be done in order to confirm step postulated here.

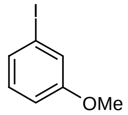
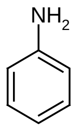
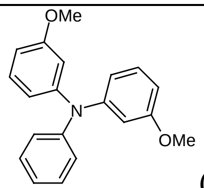
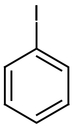
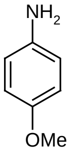
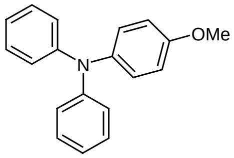
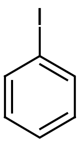
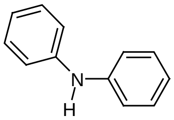
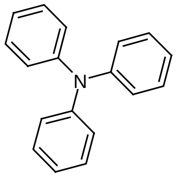
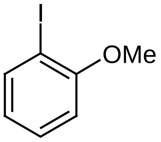
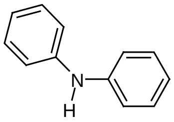
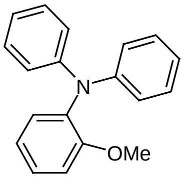
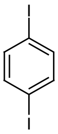
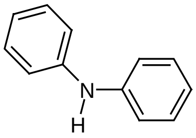
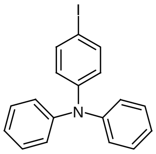
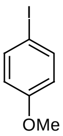
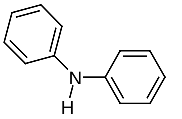
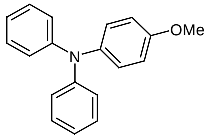
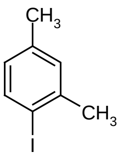
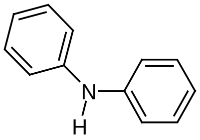
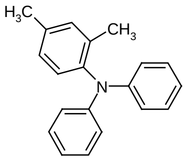


**Scheme 3.12:** Proposed mechanism well-defined copper (I) complex catalyzed amination of arylhalides

### 3.7 Synthesis of various amine derivatives:

Synthesis of various amine derivatives using Cu-2 as a catalyst was carried out, KO*t*-Bu was used as a base, toluene as a solvent at 385 K temperature and 7h reaction time. Gujadhur *et al*[12] reported 78% yield of TPA using same catalyst system and 6h reaction time. In this work we have synthesized industrially as well as academically important amine derivatives. 4-methoxy triphenylamines, 3-methoxy triphenylamines and 2-methoxy triphenylamines are useful in conducting polymers as well as optical switches.[57] 4-Phenymorpholine and its series are used in pharmaceuticals.

**Table 3.13:** Synthesis of various amine derivatives

| Sr. No. | Arylhalides | Amines | Product$^{\$}$ | Yield, (%) |
|---|---|---|---|---|
| 1* |  |  |  (a) | 78 |
| 2* |  |  |  (b) | 69 |
| 3 |  |  |  (c) | 82 |
| 4 |  |  |  (d) | 84 |
| 5 |  |  |  (e) | 86 |
| 6 |  |  |  (f) | 71 |
| 7 |  |  |  (g) | 67 |

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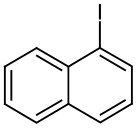
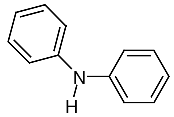
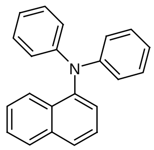
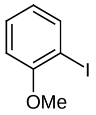
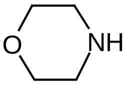
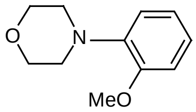
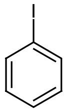
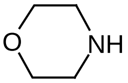
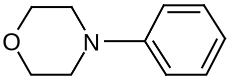
| 8 |  |  |  (h) | 70 |
| 9 |  |  |  (i) | 58 |
| 10 |  |  |  (j) | 65 |

***Reaction Condition:*** *Arylhalides: 0.30 Kmol/m$^3$; amine: 0.33 Kmol/m$^3$; Cu(Phen)(PPh$_3$)Br: 0.01056 Kmol/m$^3$; toluene: 23 x 10$^{-6}$m$^3$; KOt-Bu: 0.66Kmol/m$^3$; temperature: 385 K; time: 7h; *arylhalides: 0.66 Kmol/m$^3$; amine: 0.295 Kmol/m$^3$;; KOt-Bu: 0.8838 Kmol/m$^3$; $^\$$Isolated yields*

The electron donating substituents on aromatic ring of aniline or iodobenzene increase the amination activity. Thus aromatic ring substituents –OCH$_3$ and –CH$_3$ on aniline shows higher activity compared to aniline or iodobenzene *(Table 3.13, entries 1,2,4,6 Vs entry 7).* Cu(Phen)(PPh$_3$)Br catalyst gives good activity for the synthesis of 4-phenylmorpholine and 2'-methoxy 4-phenylmorpholine *(Table 3.13, entry 9 and 10).* 4-iodo triphenylamine was synthesized by using same methodology; it is important product for polymerizations and further coupling. These substrates were earlier investigated for amination activity using Pd-catalyzed amination, but not for copper catalyzed amination reactions.

Thus this robust catalyst system is useful for the synthesis of various type amine derivatives.

## 3.8 Conclusion

Three new copper (I) complexes have been reported for amination of aryl iodide. These new complexes of phenanthroline family ligands have been well characterized and their crystal structure determined by single crystal X-ray analysis. A competitive study of well-defined six copper (I) complexes (including three new) have been made and their activity and yield pattern have been compared. Also, the effect of copper (I) complexes formed in-situ and that preformed were compared for amination activity.

The activity of copper (I) complexes was explained on the ability of phenanthroline family ligands to bind with copper center. It was found that electron-donating substituents on phenanthroline ring were found to favor amination, while steric hindrance of ligands was found to reduce its activity. It was concluded that, a fine tuning of electron donating ability of ligand and structural property would be necessary to optimize the activity of copper (I) catalyst for amination. It was also found that compared to Pd-catalyzed system copper catalyst is much robust and is less sensitive to type of ligands, particularly when strong base such as KO*t*-Bu is used. The activity of well-defined copper (I) complexes was found to be slightly less compared to that formed in-situ. This was attributed to kinetic effect involving dissociation of ligand, which is a pre requesit in this case. Cu(Phen)($PPh_3$)Br was the best copper (I) complex catalyst amongst the complexes examined in this study, although activities and yield were not too different in these complexes. The process parameter effect showed that non polar media is favorable to amination reaction with complex Cu(Phen)($PPh_3$)Br showing sensitivity to amination products depending on reaction parameters.

## 3.9 Characterizations of amine Derivatives

### 3.9.1 (a) 3,3'-dimethoxy triphenylamine

**(i) NMR:**

**$^1$H NMR** ($CDCl_3$, 200 MHz) δ 3.68 (s, 6H), 6.52 – 6.67 (m, 6H Ar), 6.97- 7.25 (m, 7H Ar)

**$^{13}$C NMR** ($CDCl_3$, 50 MHz) δ 55.03, 108.09, 109.95, 116.60, 122.90, 124.51, 129.09, 129.68, 147.5, 148.87, 160.35

**(ii) GC MS:** M/Z 305 (base peak), 298, 273, 259, 246, 230, 217, 204, 187, 167, 152, 145, 128, 115, 102, 92, 77, 64, 51.

**(iv) IR:**1247 cm$^{-1}$ C-O-C starching (asymmetric)

847 cm$^{-1}$ C-O stretching

1317 cm$^{-1}$ C-N stretching of tertiary amine

**(v)Melting Point:**Yellow colored gel type solid.

**Figure3.23:** $^{1}$H NMR of 3,3'-dimethoxy triphenylamine

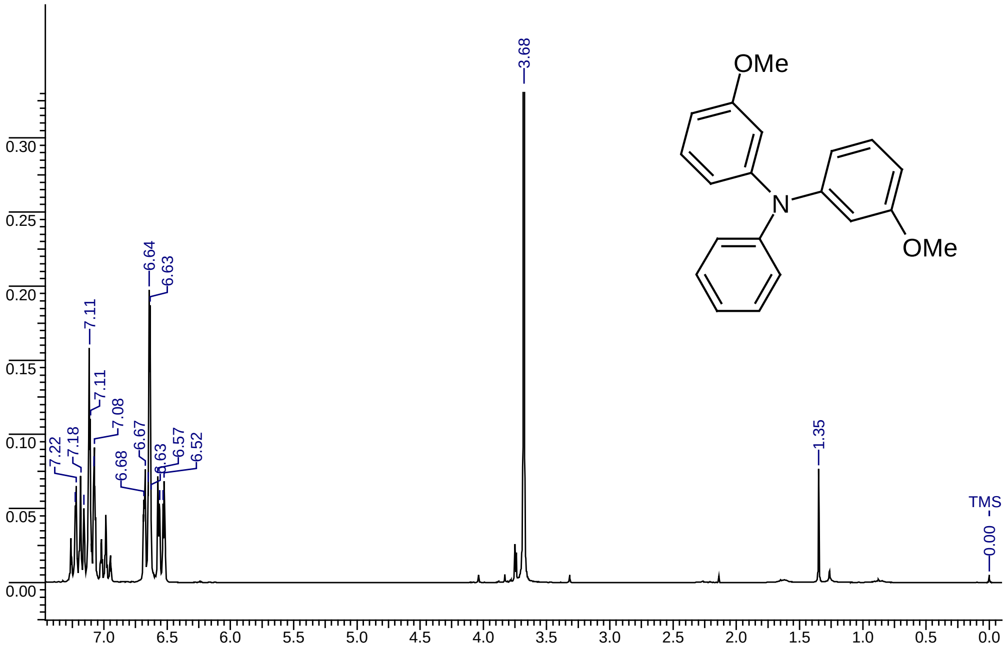


**Figure3.24:** $^{13}$C NMR of 3,3'-dimethoxy triphenylamine

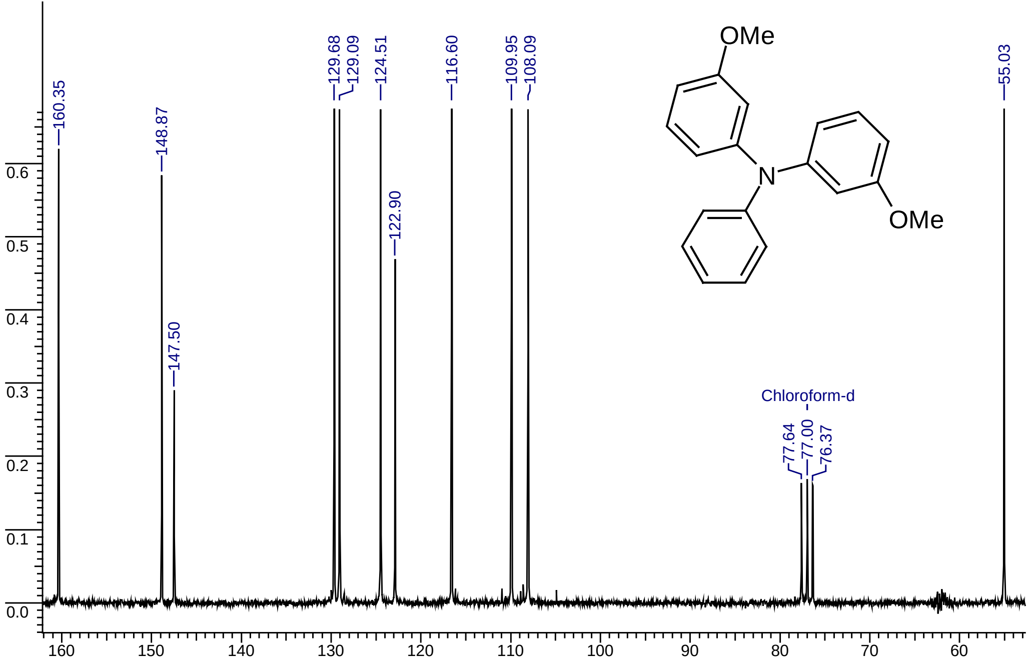
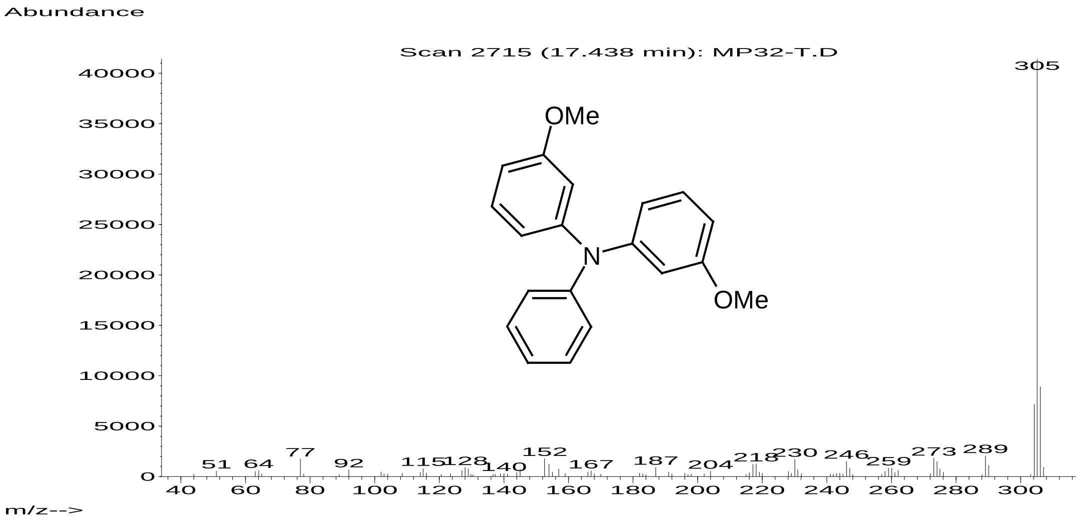


**Figure3.25:** GCMS of 3,3'-dimethoxy triphenylamine



### 3.9.2 (b) 4-methoxy triphenylamine

Detail characterizations are discussed in *chapter two section 2.3.7.1.*

### 3.9.3 (c) Triphenylamine

Detail characterizations are discussed in *chapter two section 2.3.7.1.*

### 3.9.4 (d) 2-methoxy triphenylamine

**(i) NMR:**

**$^1$H NMR** (CDCl$_3$ 200 M Hz) δ 3.62 (s, 3H), 6.87 – 7.01 (m, 8H Ar), 7.14 - 7.22 (m, 6H Ar)

**$^{13}$C NMR** (CDCl$_3$, 50 MHz,) δ 55.79, 113.30, 121.37, 121.55, 126.69, 128.76, 130.12, 135.53, 147.68

**(ii) GC MS:** M/Z 275 (base peak), 259, 244, 230, 217, 204, 182, 167, 154, 137, 128, 120, 104, 92, 77, 64, 51.

(iii)**IR:**1236 cm$^{-1}$ C-O-C starching (asymmetric)

841 cm$^{-1}$ C-O stretching

1275 cm$^{-1}$ C-N stretching of tertiary amine

**(iv)Elemental analysis:** calculated for $C_{19}H_{17}NO$: C 82.88, H 6.28, N 5.09; found C 82.50, H 6.89, N 5.28.

**(v)Melting Point:** 73-78°C

**Figure 3.26:** $^{1}$H NMR of 2-methoxy triphenylamine

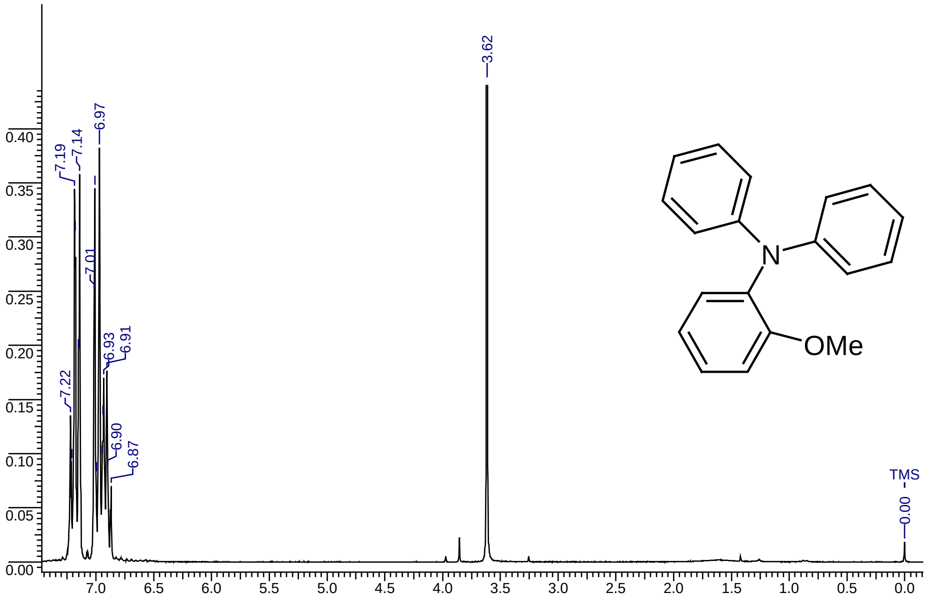


**Figure 3.27:** $^{13}$C NMR of 2-methoxy triphenylamine

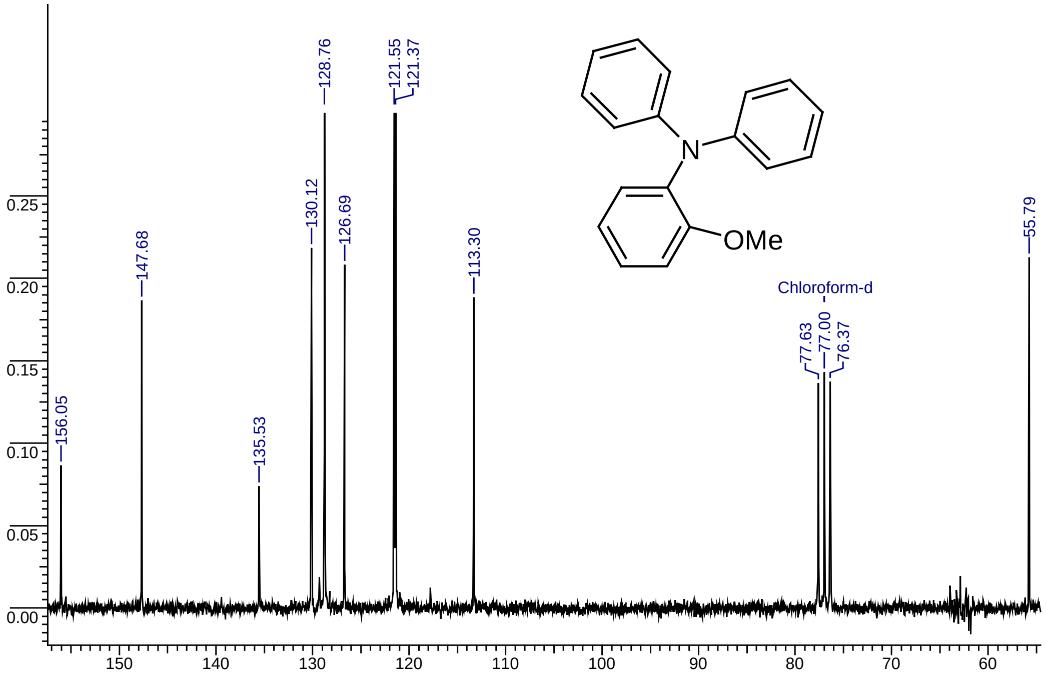
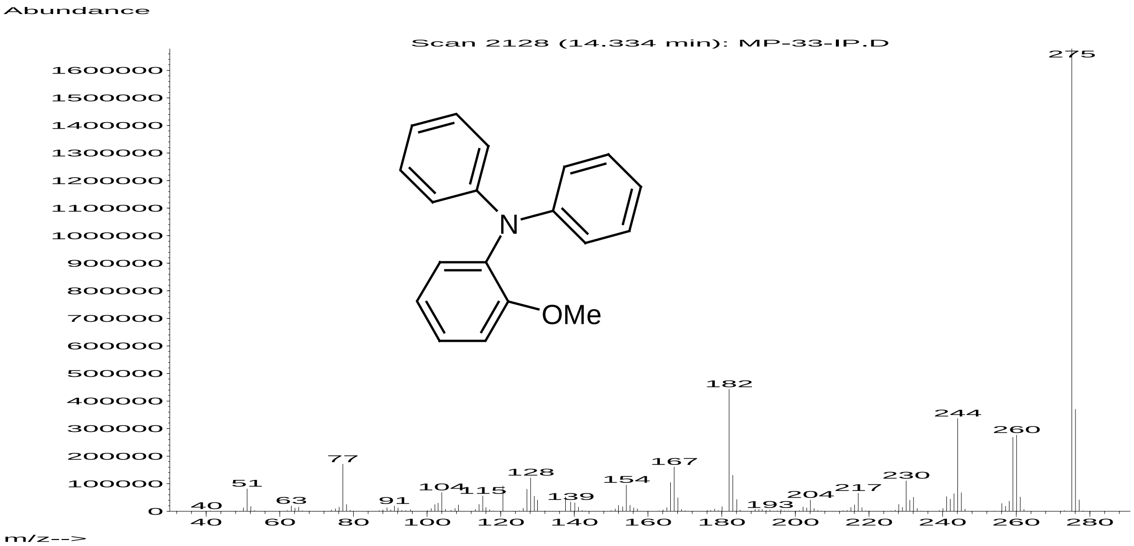


**Figure 3.28:** GCMS of 2-methoxy triphenylamine



### 3.9.5 (e) 4-iodo triphenylamine

**(i) NMR**

**$^1$H NMR** (CDCl$_3$ 200 M Hz) δ 6.85 – 6.85 m (2H, Ar), 6.98 -7.09 m (6H, Ar), 7.20 – 7.30 m (4H, Ar), 7.45 – 7.52 m (2H, Ar)

**$^{13}$C NMR** (CDCl$_3$, 50 MHz) δ 123.29, 124.51, 125.26, 129.34, 138.00, 147.20, 147.67

**(ii) GC MS:**M/Z 371 (base peak), 356, 345, 306, 268, 243, 228, 217, 204, 185, 167, 152, 139, 122, 108, 99, 89, 77, 64, 51.

**iii) IR:**1280 cm$^{-1}$ C-N stretching of tertiary amine

**iv) Elemental analysis:**calculated for $C_{18}H_{14}NI$: C 58.24, H 3.80, N 3.77; found C59.08, H 4.37, N 4.95.

**v) Melting Point:**100-104°C

**Figure 3.29:** $^{1}$H NMR of 4-iodo triphenylamine

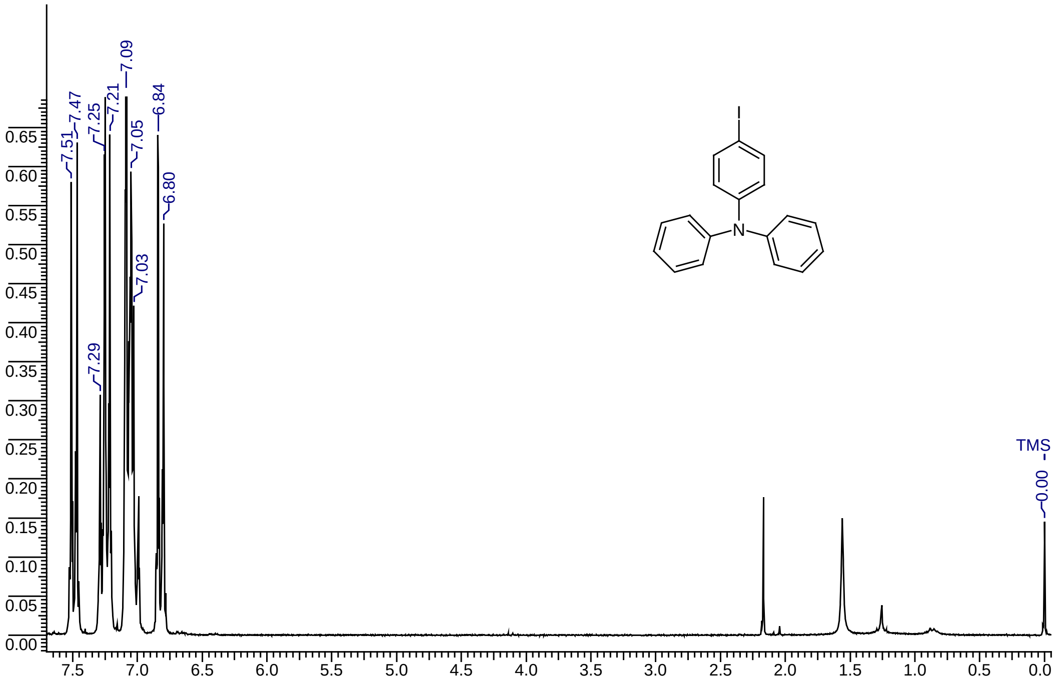


**Figure 3.30:** $^{13}$C NMR of 4-iodobenzene triphenylamine

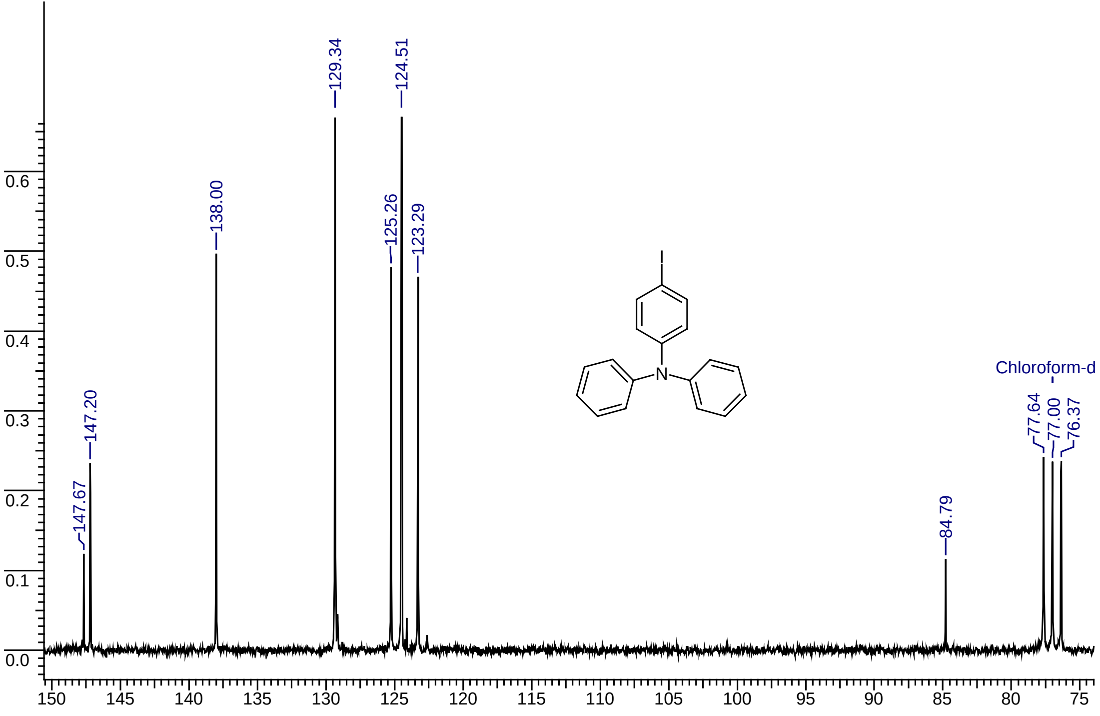
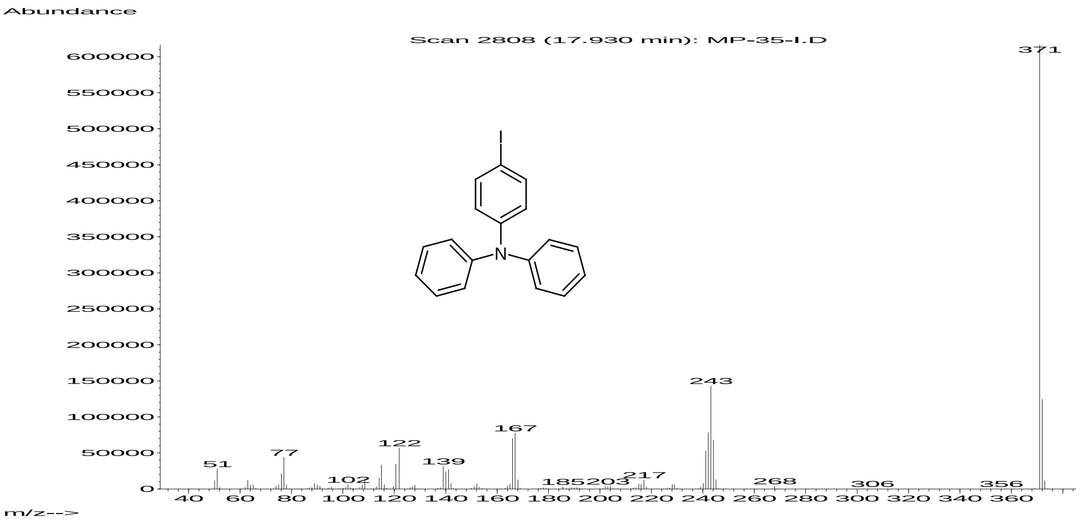


**Figure 3.31:** GCMS of 4-iodo triphenylamine



### 3.9.6 (f) 4-methoxy triphenylamine

(Compound b and f are the same). Detail characterizations are discussed in *chapter two section 2.3.7.1.*

### 3.9.7 (g) 2,4-dimethyl triphenylamine

**(i) NMR**

**$^1$H NMR** (CDCl$_3$, 200 M Hz) δ 2.00 (s, 3H), δ 2.33 (s, 3H), 6.89 – 7.22 (m, 13H Ar)

**$^{13}$C NMR** (CDCl$_3$, 50 MHz) δ 18.38, 20.97, 121.12, 121.28, 128.94, 132.32, 135.67, 136.24, 142.70

**(ii) GC MS:** M/Z 273 (base peak), 266, 258, 243, 230, 217, 207, 194, 180, 167, 152, 144, 136, 128, 115, 103, 91, 77, 65, 51.

**(iii) IR:**1232 cm$^{-1}$ C-N stretching of tertiary amine

**(iv)Elemental analysis:** calculated for $C_{20}H_{19}N$: C 87.87, H 7.01, N 5.12; found C 87.50, H 7.33, N 5.12.

**(v) Melting Point:** 72-76°C

**Figure 3.32:** $^1$H NMR of 2,4-dimethyl triphenylamine

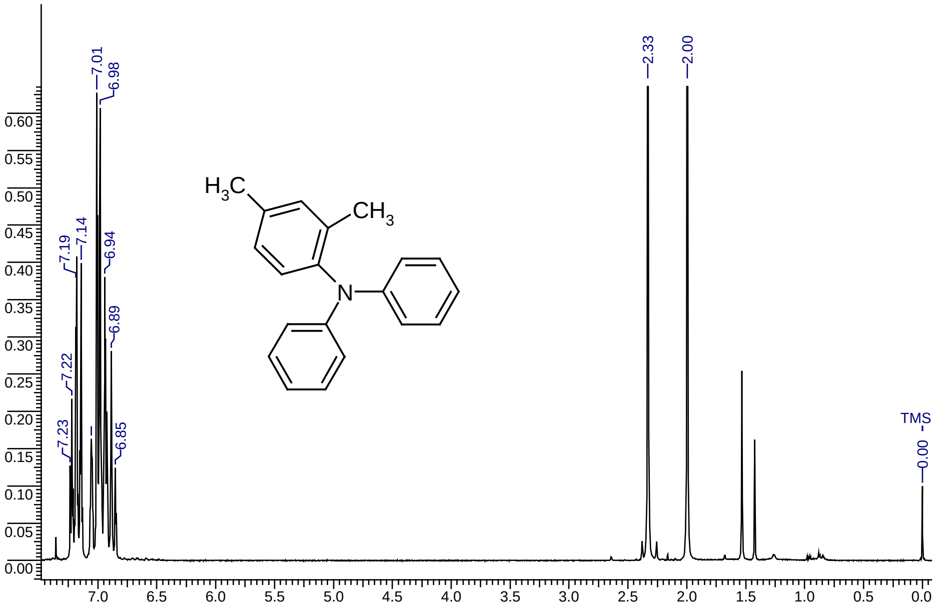


**Figure 3.33:** $^{13}$C NMR of 2,4-dimethyl triphenylamine

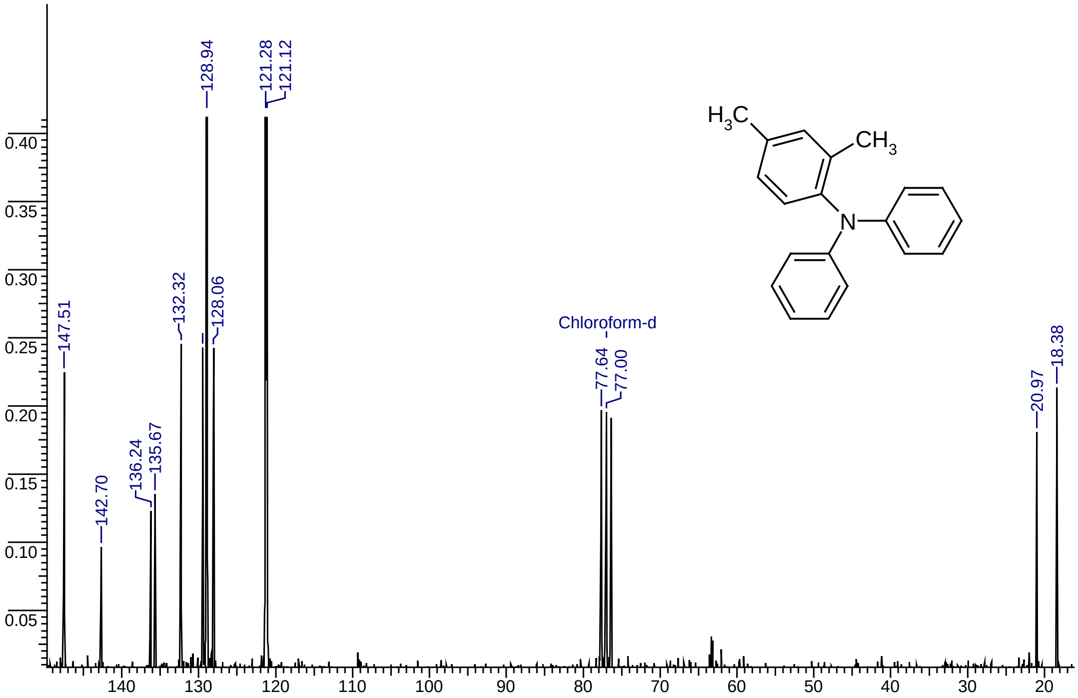
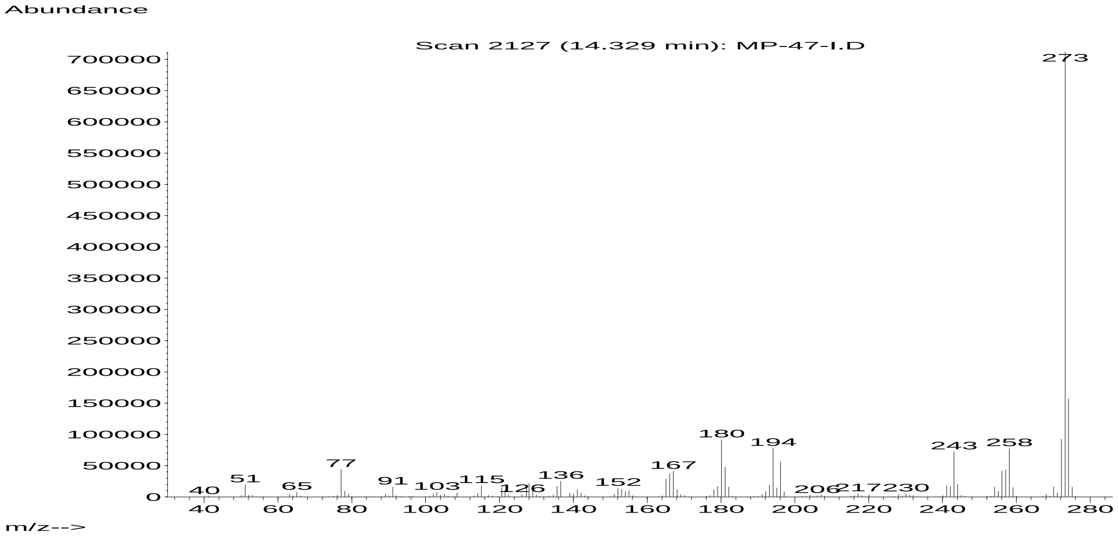


**Figure 3.34:** GCMS of 2,4-dimethyl triphenylamine



### 3.9.8 (h) 1-diphenylamine naphthalene

**(i) NMR**

$^{1}$**H NMR** ($CDCl_3$, 200 M Hz) δ 6.89 – 7.98 (m, 17H Ar)

$^{13}$**C NMR** ($CDCl_3$, 50 MHz) δ 212.61, 121.81, 124.24, 124.34, 126.07, 126.32, 127.19, 128.33, 129.04, 131.24, 135.25, 143.56

**(ii) GC MS:** M/Z 295 (base peak), 278, 267, 254, 241, 228, 217, 202, 191, 180, 166, 147, 139, 127, 115, 101, 89, 77, 63, 51.

**(iii) IR:**1177 $cm^{-1}$ C-N stretching of tertiary amine

**(iv)Elemental analysis:** calculated for $C_{22}H_{17}N$: C 89.46, H 5.80, N 4.74; found C 88.43, H 6.09, N5.4.

**(v)Melting Point :**121-125°C

**Figure 3.35:** $^{1}$H NMR of 1-diphenylamine naphthalene

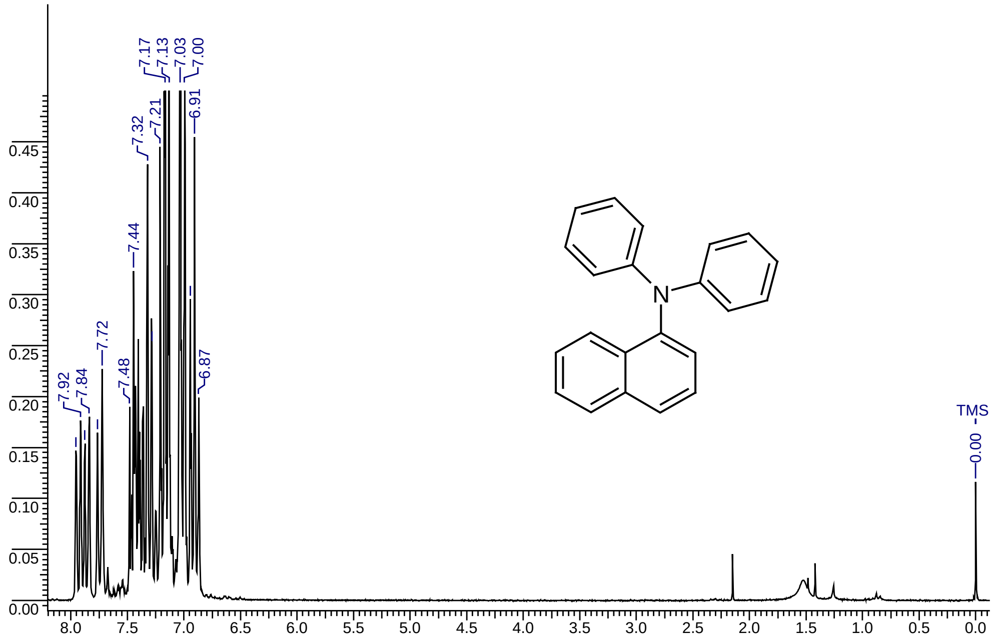


**Figure 3.36:** $^{13}$C NMR of 1-diphenylamine naphthalene

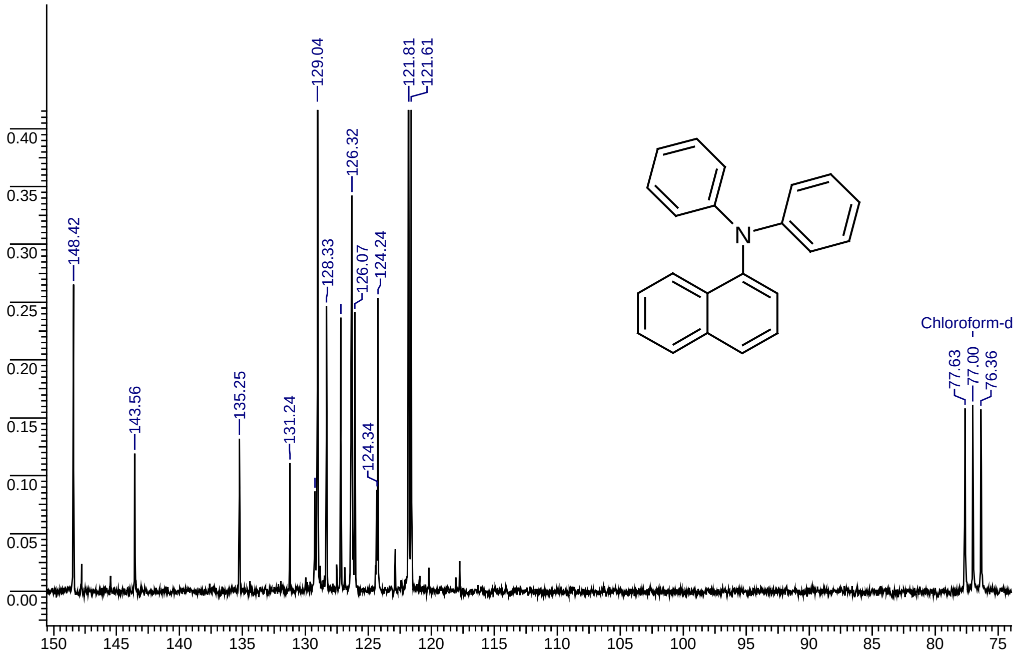
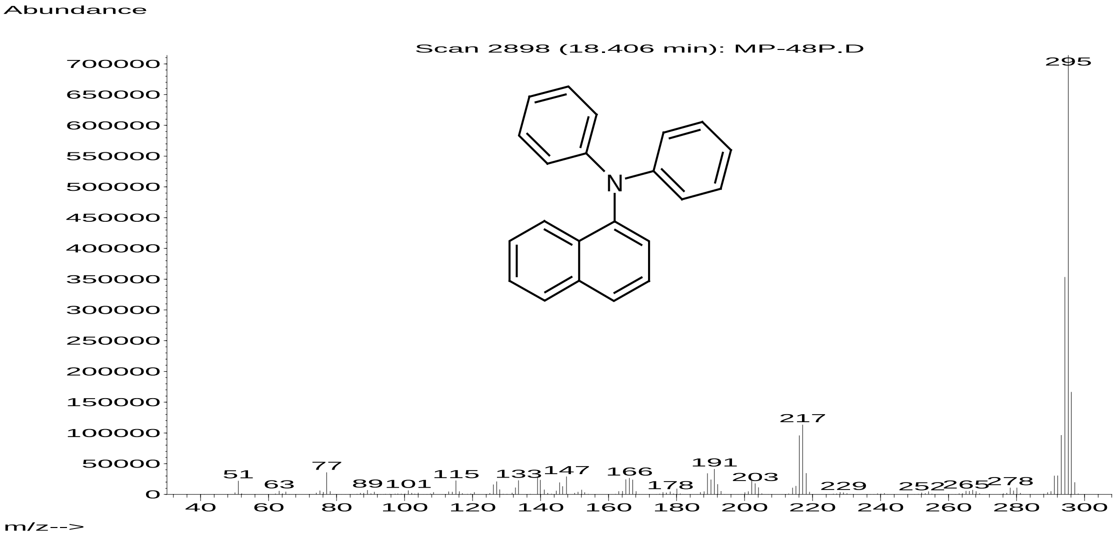


**Figure 3.37:** GCMS of 1-diphenylamine naphthalene



### 3.9.9 (i) 2'-methoxy 4-phenylmorpholine

**(i) NMR:**

**$^1$H NMR** ($CDCl_3$, 200 M Hz) δ 3.12 – 3.17 t (4H, Morpholine ring), 3.79 s (3H, $OCH_3$), 3.82 – 3.87 t (4H, Morpholine ring), 6.42 – 6.55 (3H, Ar), 7.14 -7.26 (1H, Ar)

**$^{13}$C NMR** (CDCl3, 50 MHz) δ 49.20, 55.11, 66.81, 102.14, 104.64, 108.40, 129.79, 152.63, 160.55

**(ii) GC MS:** M/Z 193, 178, 162, 148, 135(base peak), 130, 121, 107, 102, 92, 86, 77, 65, 57, 51

**(iii) IR :**1246 cm$^{-1}$ C-O-C starching (asymmetric)

1048 cm$^{-1}$ C-O stretching

1266 cm$^{-1}$ C-N stretching of tertiary amine

**(iv)Elemental analysis:** calculated for $C_{11}H_{15}NO_2$: C 68.37, H 7.82, N 7.25; found C 68.09, H 7.90, N 7.46.

**Figure 3.38:** $^1$H NMR of 2’-methoxy 4-phenylmorpholine

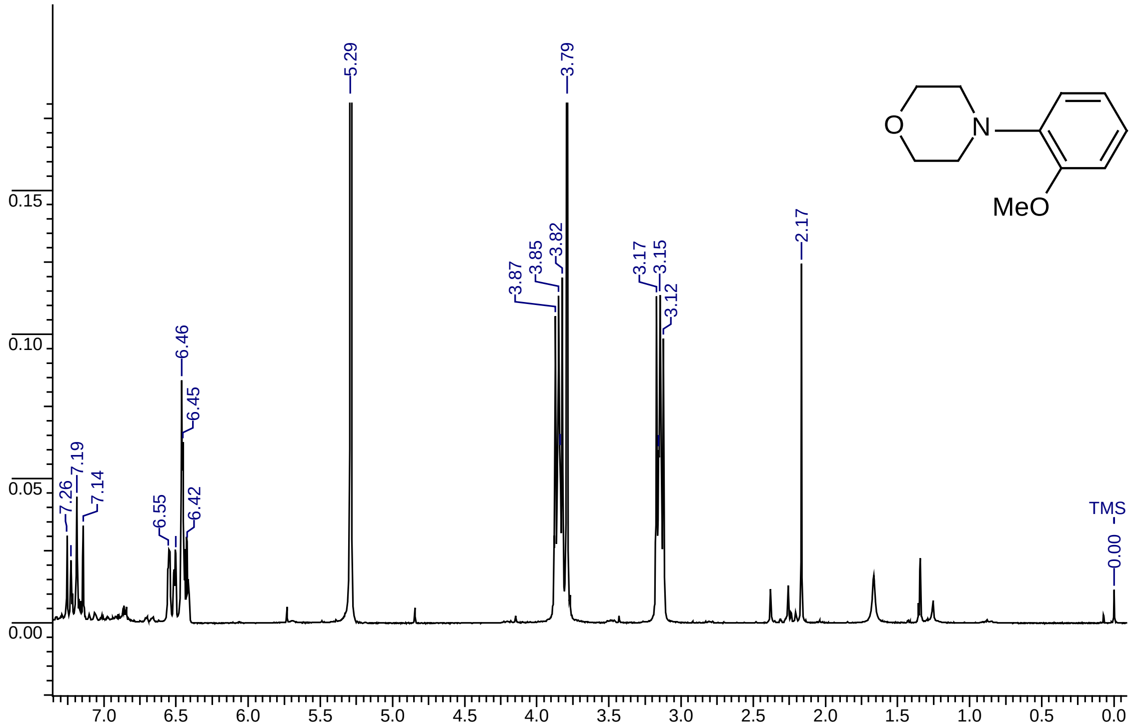


**Figure 3.39:** $^{13}$C NMR of 2’-methoxy 4-phenylmorpholine

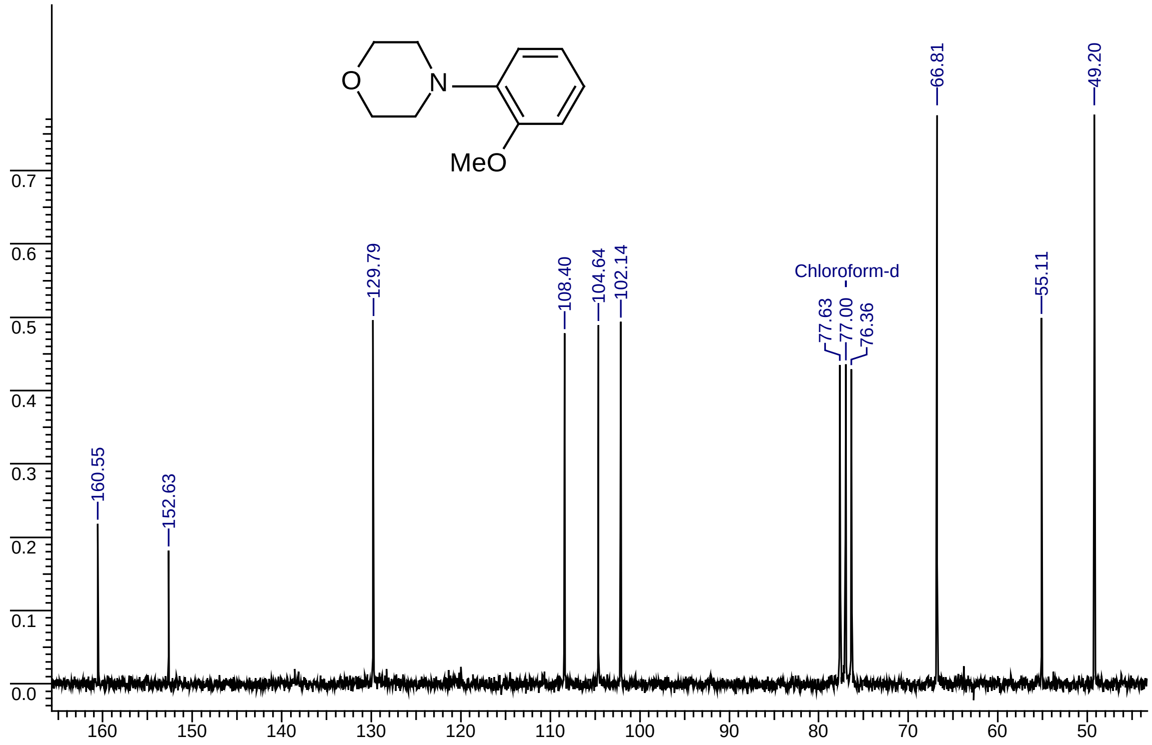
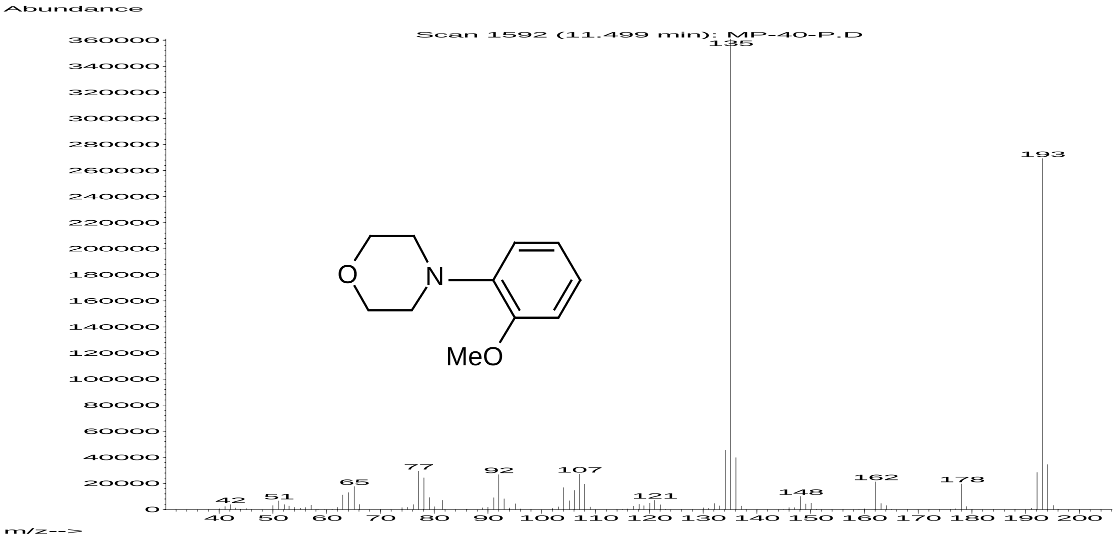


**Figure 3.40:** GCMS of 2'-methoxy 4-phenylmorpholine



### 3.9.10 (j) 4-phenylmorpholine

**(i) NMR:**

**$^1$H NMR** ($CDCl_3$, 200 M Hz) δ 3.17 (dd, 4H; N-$CH_2$), 3.85 (dd, 4H; O-$CH_2$), 6.88 – 6.94 (m, 3H Ar), 7.24-7.30 (dd, 2H, Ar, J= 8 Hz)

**$^{13}$C NMR** ($CDCl_3$, 100 MHz) δ 27.71, 10.16, 38.63, 42.95, 52.09, 74.21

**(ii) GC MS:** M/Z 163, 148, 144, 132, 128, 121, 117, 105 (base peak), 91, 86, 81, 77, 61, 51.

**(iii) IR:**1260, 1230 cm$^{-1}$ C-N stretching of tertiary amine

1100, 1065 cm$^{-1}$ C-O stretching

**(iv)Elemental analysis:** calculated for $C_{10}H_{13}NO$: C 73.55, H 8.03, N 8.58; found C 73.11, H 8.34, N 9.48.

**(v)Melting Point:** 50-53°C (51-54°C Literature)

**Figure 3.41:** $^{1}$H NMR of 4-phenylmorpholine

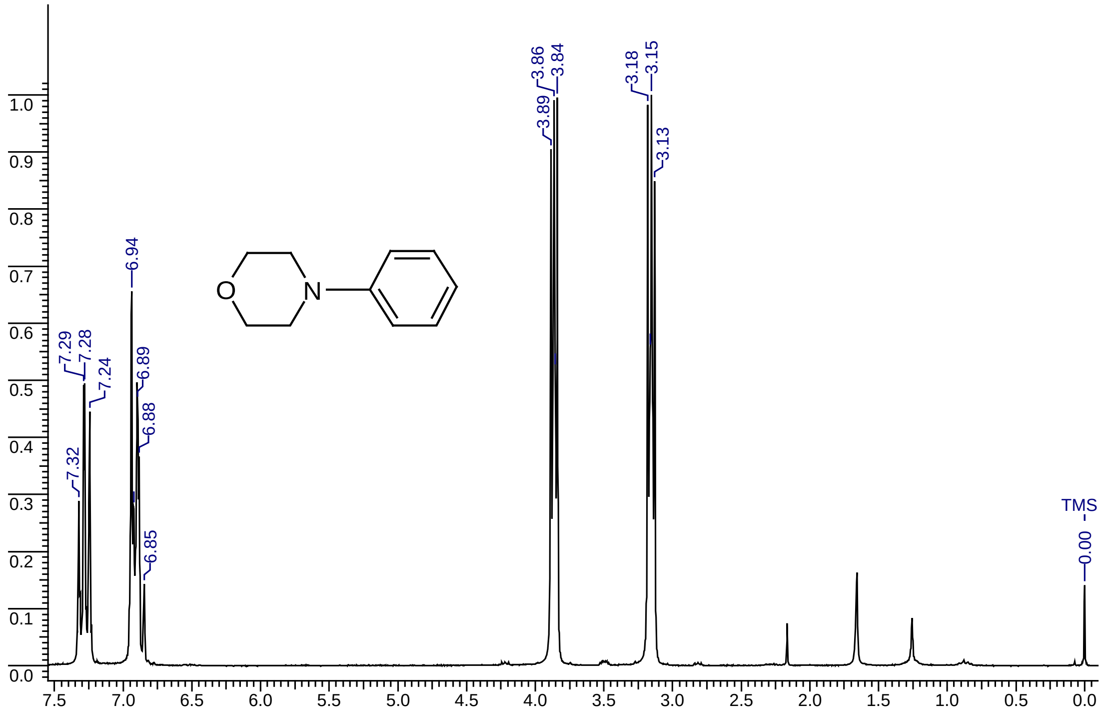


**Figure 3.42:** $^{13}$C NMR of 4-phenylmorpholine

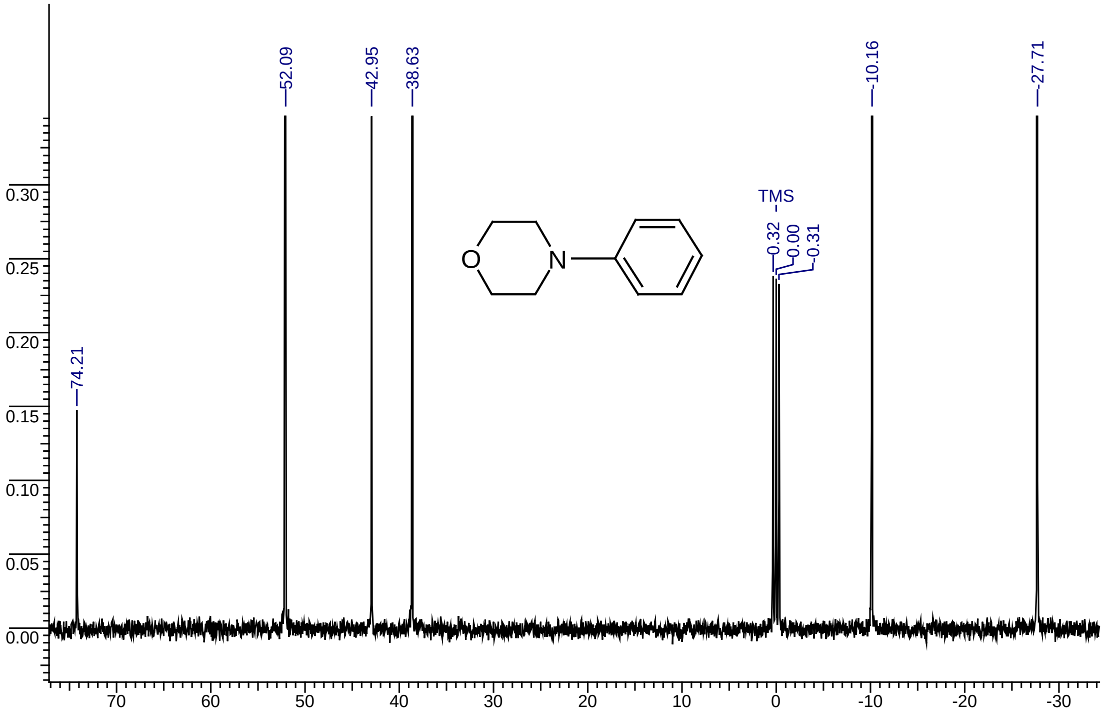
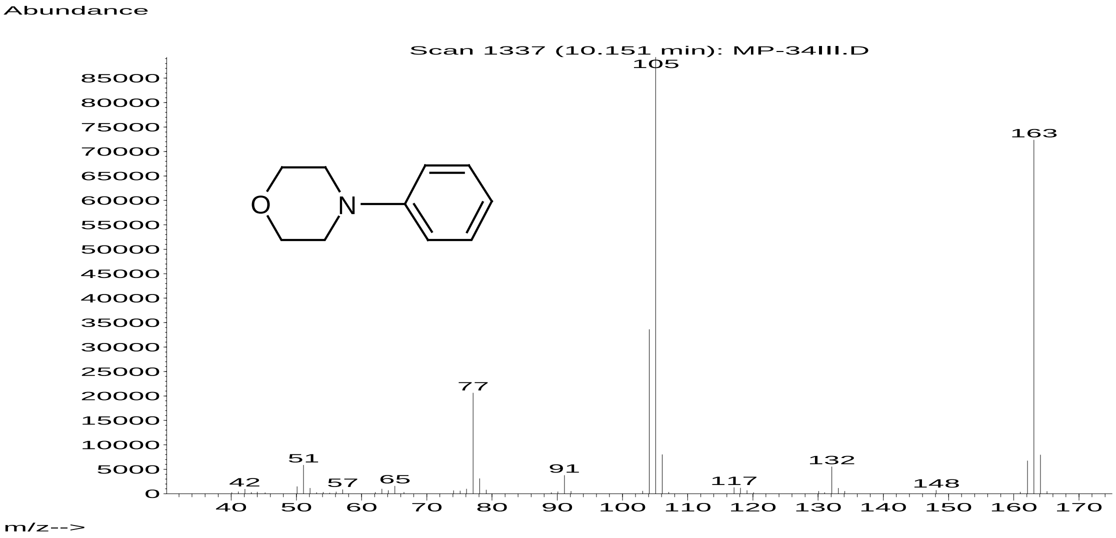


**Figure 3.43:** GCMS of 4-phenylmorpholine



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# CHAPTER- 4

# SYNTHESIS, CHRACTRIZATION AND CATALYTIC APPLICATIONS OF THE HETEROGENISED HOMOGENOUS COPPER CATALYSTS FOR THE AMINATION OF ARYLHALIDES

## 4.1 Introduction

Aryl amines are attractive targets for chemical synthesis, because of their numerous applications such as pharmaceuticals, fine chemicals, agrochemicals, photography, xerography, pigments and electronic materials.[1] Aromatic C-N bond formation method through homogenous Pd-catalyzed reaction is well established, but there is no report on heterogeneous catalyzed method.[2] Many homogenous catalytic systems, through have many attractive properties, viz. high selectivity and activity, yet they can not be commercialized because of difficulties associated with the catalyst-product separation from the catalyst system, procurement in usual conditions, thermally sensitive and reusability of the catalyst.[3] Hence, the homogenous reactions that have been commercialized either involve volatile substrates and products or do not contain thermally sensitive organic liquids. The term ***'heterogenization'*** refers to a process, where by a homogeneous transition metal complex (including free metal particles, biological molecules, organic species etc.) is either immobilized, or anchored, or incorporated or encapsulated in an inert organic (polymer) or inorganic support. These heterogeneous catalysts have a lot of advantages over their homogenous analogues:

(i) fixed-bed and continues flow through operations,

(ii) complete commercial utility on a large scale owing to economic debits of batch type operations and / or expense of catalyst recovery and recycle,

(iii) maintaining high selectivities and conversions (turn over frequency) of their homogeneous analogues for many reactions, and

(iv) preventing other side reactions e.g. dimerization, alkylation and aggregate formation of the catalyst complex, which normally occurs in batch mode.

To solve the problem occurring in homogenous catalyst system, new processes and catalyst designing are under investigation, which can be broadly divided in two types. In the first case, a catalysts system is designed so that it is solubilized in a solvent that, under some conditions, is immiscible with the reaction products. These reactions involve two phases and are often referred to as ***Biphasic Systems.***[4] The other type involves the metal complex catalyst or metal (in form of nanaoparticles) anchored to some kind of soluble or insoluble support, and the separation is carried out by a filtration procedure. This type of process is known as ***Heterogenizing Homogeneous Catalysts.***[5]

It is in this context, immobilization of metal complexes has particular significance. In this approach, the organometallic complex is encapsulated or anchored inside or tethered to the pores and wall of the inorganic inert matrices, e.g. zeolite, MCM-41, materials, clay etc. in such a way that the complex is tightly bound inside the pores.[6] The prime requirement is the stability of catalyst in liquid phase, while retaining high activity, selectivity and the original configuration.

In several reports, heterogeneous catalysis by encapsulated materials, have been addressed for oxidation[7], hydrogenation[8] and asymmetric epoxidation[9] reactions, but attempts to heterogenize some of the industrially relevant homogeneous catalysts with their homogeneous counterparts has not been well investigated with meaningful quantitative data.

To our knowledge, there was only two truly heterogeneous catalyst with high activity and selectivity for copper catalyzed amination reaction.[10] Most significant development in the amination reaction has been the development of Pd catalyst by Buchwald[11] and Hartwig.[12] Development of palladium catalyst has widened the scope of amination reaction for the synthesis of large number of substituted diaryl- and triaryl amines with very high selectivity. Yet, copper-mediated coupling (Ullmann coupling) is still the reaction of choice for large and industrial scale production of these compounds. Recently, milder Ullmann-type methodologies for the N-arylation of anilines, imidazoles, amides, and nitrogen heterocycles have been reported. However, in these reports also, triarylamines are obtained as predominant products and diaryl amine cannot be obtained with high selectivity.[2] Thus, Ullmann coupling is selective only for the synthesis of triaryl amines and so far there are no reports on the synthesis of diaryl amines with high selectivity using copper catalyst. Also, in spite of the recent developments, separation of catalyst and product remains a challenge in copper catalyzed amination reaction. Given the importance of aryl amines in a variety of applications development of a heterogeneous catalyst, which utilizes inexpensive copper catalyst rather than palladium may provide a complementary development to existing protocols. Herein, we describe our initial work leading to an expedient method for effecting amination of aryl iodides to give either diaryl amines and triaryl amines with very high selectivity using the heterogeneous catalysts prepared from copper-1,10-phenanthroline catalyst system.

Heterogeneous catalysts developed show high selectivity and activity even after several recycle experiments.

Heterogeneous catalysts were prepared by encapsulation CuI/1,10-phenanthroline encapsulated in Zeolite Y, and tethering $Cu(PPh_3)$( 1,10-phenanthroline)Br, tethered on Zeolite Y using phosphotungstic acid as a tethering agent. Catalysts were prepared by known literature methods[13] and characterized by XRD, ESCA, EPR, IR, UV, surface area and SEM. Characterization, clearly indicated that heterogeneity of copper complexes.

Few reactions were carried out using CuI/1,10 phenanthroline and 2,2'-bipyridine as a catalyst system and KO*t*-Bu as a base *(see section 2.8.5.1 and 2.8.3)*. From the results obtained it can be clearly seen that even with iodobenzene: aniline molar ratio of 1:1, diphenylamine and triphenylamine were obtained as major products. From the reaction scheme *(Scheme 2.1),* diphenylamine is obtained as a product of reaction of iodobenzene and aniline. Diphenylamine reacts further with second mole of iodobenzene to give triphenylamine as the product. In the present case, even though the molar ratio of iodobenzene and aniline is same, triphenylamine is formed as a major product. This clearly shows that even the ligated copper catalyst is not selective for the formation of diphenylamine as a product. At higher ratios of iodobenzene: aniline, triphenylamine formation increased substantially and >95% triphenylamine was formed at a ratio of 3:1. In order to develop heterogenised catalysts for the synthesis of arylamines, zeolite Y was chosen as a support. The pore diameter of the zeolite Y is ~7 Å, which will ensure entrapment of Cu-1,10-phenanthroline complex in the zeolite matrix. Also, the pore diameter constraints will inhibit reaction of diphenylamine (formed by amination of aniline and iodobenzene) with another molecule of iodobenzene to form triphenylamine as the product (observed predominantly in the homogeneously catalyzed reactions). With this strategy in mind, we prepared various encapsulated catalyst systems. Other set of catalysts was prepared using tethering method, in which catalyst is essentially present in the surface of the support and hence size restrictions may not affect performance of the catalyst. Catalysts were characterized in detail by various techniques such as XRD, ESCA, TEM, TGA, IR, NMR, UV-Visible spectroscopy.

## 4.2 Encapsulated Copper Catalyst

### 4.2.1 Introduction

Homogeneous catalysis is gaining considerable interest due to its high activity and selectivity at milder reaction conditions for a wide variety of reactions.[14] However, their practical applications have been limited by difficulties in achieving industrially viable catalyst-product separation. [15] In this context, encapsulation of metal complexes as a mean of “heterogenization” has particular significance. Zeolite and Zeotypes (molecular sieves), owing to their varied intrinsic properties (e.g., acidity, bacicity, redox behavior, etc.), channel sizes, high surface areas, thermal and chemical stabilities, and channel structures (shape selectivities), have been extensively used in oil refining, petrochemical, and fine chemical industries for the past couple of decades.[16]

The prime requirement is stability of encapsulated complex, so that it does not leach out of the catalyst pores to the liquid phase in the course of a reaction, while retaining high activity, selectivity, and original configuration. In several reports, heterogeneous catalysis by encapsulated supports has been addressed for carbonylation, oxidation, hydrogenation, epoxidation, and heck reactions, [17] but not for amination reaction.

Here we are reporting synthesis of 1%, 4%, and 8% Cu(Phen)-Y , 4% Cu(Bipy)-Y and 4% Cu(Bipy)-MCM-41 catalyst for the amination of arylhalides. The encapsulated catalyst 4% Cu(Phen)-Y reporting that was characterized by all possible characterization tequiences. We an also encapsulated copper complex in Zeolite-Y and MCM-41 material is the shape selective catalyst for the amination of arylhalides.

### 4.2.2 Materials

The materials required for the synthesis of catalyst and reactions were taken from the following sources

$Cu(OAc)_2$. $H_2O$, 1,10 phenanthroline, 2,2’ bipyridine Iodobenzene and copper acetate all were purchased from Aldrich. Acetonitrile and acetone were purchased from Merck; Chlorobenzene, bromobenzene, toluene, aniline, and potassium tertiary butoxide, phosphotungstic acid (PTA), Copper (I) Iodide (CuI), neutral alumina, charcoal, NaO*t*-

Bu, KOH, NaOH, $K_2CO_3$, $Cs_2CO_3$, NaOMe, TEA, tri-t-butyl amine, $NaHCO_3$, methanol, pet ether, were purchased from *s. d*. Fine Chemicals. Aniline and toluene were distilled and dried using literature procedures

### 4.2.3 Synthesis of Encapsulated Copper Catalyst

Our aim to select to chose material for the encapsulation of copper complex in Zeolite-Y and MCM-41 was to check the shape selectivity and activity, which, depends upon pore channel diameter. Pore channel diameter of Na-Y is ~7 A° and MCM-41 is ~35A°. This large difference in pore channels diameter gave the shape selectivity for the amination of aryl halides.

### 4.2.3.1 Synthesis of Cu-Y

To prepare the 1% Cu-Y, 0.020gm of copper acetate was dissolved in 10 ml of distilled water. To this was added 2gms of Na-Y and the mixture was stirred for 12 hrs. The solid was filtered, washed repeatedly with distilled water and $Cu^{+2}$-Y thus obtained by exchange method was dried at $120^0$C for 12 h. Powder XRD showed that there was no change in the structure of the zeolite matrix. The exact amount of copper loaded on the zeolite was determined by ICP-AES analysis.

### 4.2.3.2 Synthesis of Cu (Phen.)-Y catalyst

In a typical procedure to prepare 1% Cu (phen)-Y catalyst 1.5 gm of 1% Cu-Y was crushed well with phenanthroline ligand (0.225mmol, 3 times the number of moles of Cu loaded) in a mortar and heated in a glass reactor under nitrogen atmosphere. The temperature was slowly raised to $200^oC$ and heated at this temperature for 6 hrs. It was cooled and the un-reacted ligand and complex on the surface was removed by soxhlet extraction with acetonitrile and acetone for 4 h. The catalyst was dried at $120^oC$ for 5 h and used for the reaction.

Similar procedures were adopted for 4% and 8% copper catalyst preparation

#### 4.2.3.3 Synthesis of Cu (bipy.)-Y Catalyst

This catalyst was prepared by using the same procedure as used for the preparation of Cu (Phen)-Y catalyst as discussed in *section 4.2.3.2.*

#### 4.2.3.4 Synthesis of Cu (bipy.)-MCM-41 Catalyst

This catalyst was prepared by using the same procedure as used for the preparation of Cu (Phen)-Y catalyst as discussed in *section 4.2.3.2.*

### 4.2.4 Characterization of Encapsulated Copper complexes in Zeolite-Y

Synthesized 4% Cu(Phen)-Y catalyst characterized by various tequiences such as UV, IR, TGA/DTA, EPR, XRD and BET surface area. All characterization results conform that Cu-phenanthroline complex encapsulated in zeolite-Y.

#### 4.2.4.1 Powder X-ray diffraction (XRD)

The Phase purity and crystallinity of the zeolite–Y encapsulated copper complexes were determined by using a computer-controlled automatic Rigaku RINT 2000 X-ray diffract meters. The Ni-filtered Cu- Kα radiation ($\lambda$ = 1.5404Å) was used with a curved graphite crystal monochromator and NaI scintillator. XRD data at 298K was collected in the $2\theta$ range 5-50˚ at a scan rate of 4 deg/min or lower. The Sample was prepared as thin layers on metal slides. The relative peaks intensities of (331), (311) and (220) reflections of Zeolite-Y samples indicated the cation distribution in the lattice. [13]

No major changes, except reduction in peak intensity, were observed in the X-ray diffraction patterns of zeolite-Y upon formation (encapsulation) of copper complexes inside the zeolite cages (cavities). This indicates that the encapsulation of the copper complexes did not alter the zeolite framework structure.

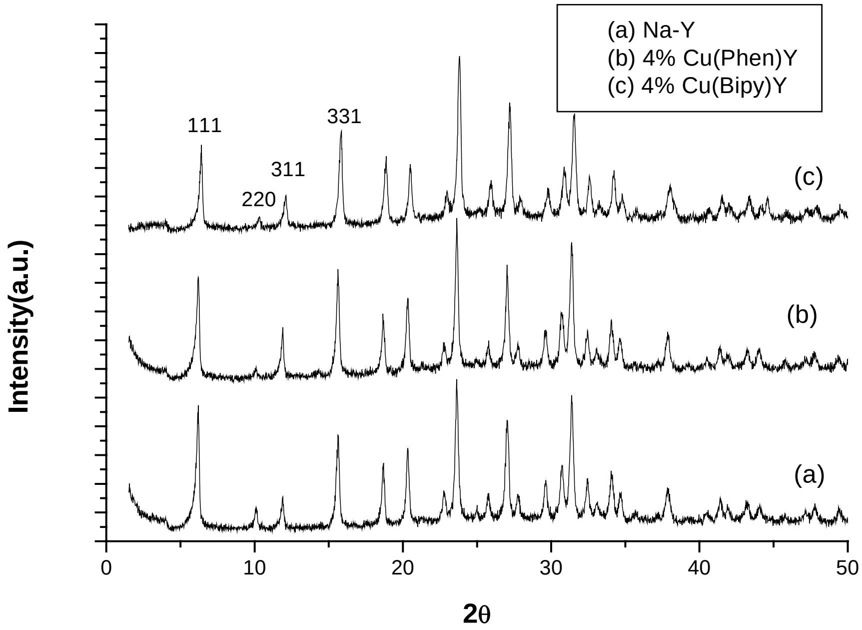


**Figure 4.1:** XRD of (a) Na-Y, (b) 4% Cu(Phen)-Y, (c) 4% Cu(Bipy)-Y

### 4.2.4.2 UV-Visible Spectra

The UV-visible spectra of the encapsulated copper complexes were recorded using the UV-2101 and UV-2550 spectrometers in the range 200-800nm. The UV-visible spectra of the Cu-Y and encapsulated complexes are as shown in *Figure 4.2*. 4% Cu-exchanged Y showed a broad absorption band in the range of 300-700nm due to *d-d* transitions of $Cu^{+2}$ ions present in different geometric modes. 4% Cu (Phen)-Y showed a ligand-centered transition (LMCT bands) at 345nm and two-resolved *d-d* transitions at 490 and 560nm. These bands respectively occurred at 335nm and 485nm for 4% Cu (bipy)-Y, which shift towards the higher energy side. This shows that Cu (bipy) is more stable than Cu(Phen) complex.

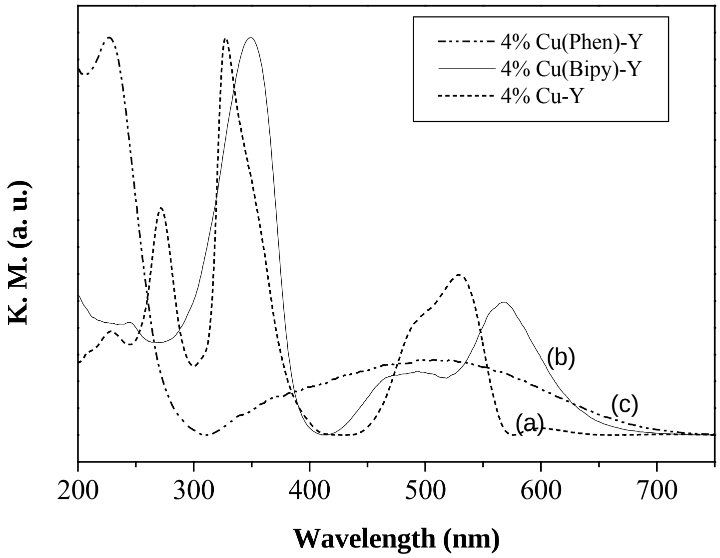


**Figure 4.2:** UV Spectra of (a) 4% Cu(Phen)-Y, (b) 4% Cu(Bipy)-Y, (c) 4% Cu-Y

### 4.2.4.3 Electron Paramagnetic Resonance (EPR)

The EPR spin Hamiltonian parameters provide information about the molecular and electronic structure of the metal complexes. EPR spectroscopy in ideal case can differentiate the encapsulated metal complexes from the surfaces absorbed species. It provides information about the electron spin density distribution and any structural changes, which may have taken place after the complex is encapsulated inside the zeolite pores. The EPR spectra of the zeolite-Y-encapsulated copper complexes were recorded using a Bruker EMX X-band spectrometer with 100 KHz field modulations. Frequency calibration was done using a microwave frequency counter fitted in an ER 041 XG-D microwave bridge EPR spectra with a well-resolved parallel hyperfine features point out that the complexes are isolated and intermolecular interactions are negligible. The spin Hamiltonian parameter $g_{\|}$=2.233, $g_{\perp}$=2.094, $A_{\|}$ (Cu)=181G for Cu (phen) and $g_{\|}$=2.221, $g_{\perp}$=2.097, $A_{\|}$ (Cu) =160 G are well within range for a penta coordinated molecular structure for $Cu^{+2}$ species, where in two positions are occupied by nitrogen atoms of the

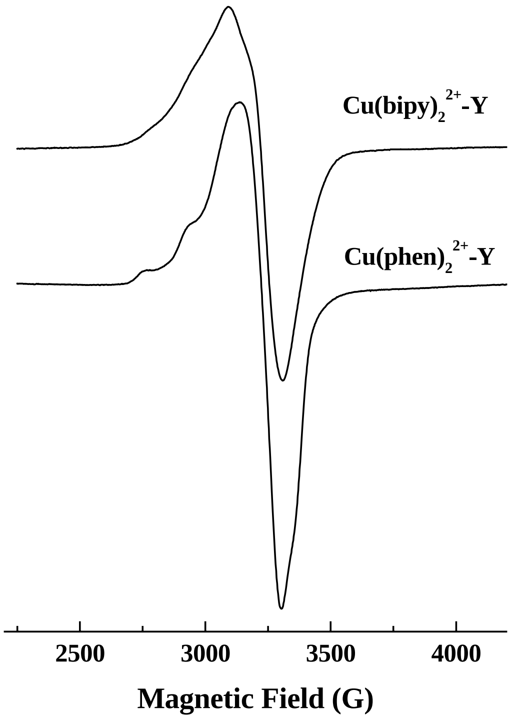


**Figure 4.3:** EPR spectra of copper 1,10-phenethroline and 2,2'-bipyridine encapsulated in Zeolite-Y

nitrogen ligand and fifth coordination is provided by the zeolite frame work.

The absence of signals at $g_{\parallel}$=2.395, $g_{\perp}$=2.0836, $A_{\parallel}$ (Cu)=126.4G indicate the $Cu^{+2}$ ions exchanged formed complexes with the phenanthroline and bipyridine ligands.

### 4.2.4.4 BET Surface Area

Surface area of 4% Cu-Y was decreased on encapsulation. This is one of the direct evidences to show that the complexes are encapsulated in the cages of the zeolite-Y. $S_{BET}$ decreased from 543m$^2$/g for 4%Cu-Y to 332m$^2$/g for 4%Cu (bipy)-Y. It further decreased to 310m$^2$/g for 4% Cu (phen)-Y due to increase in the molecular dimensions of the ligand. The decrease is smaller in the present case compared to the encapsulated Cu-Phthalocyamine complexes 203m$^2$/g due to comparatively smaller dimensions of the ligand.

### 4.2.4.5 Infra-Red Spectroscopy (IR)

Formation and encapsulation of metal complexes inside the super cages is confirmed by elemental analysis. IR, UV, EPR and Thermal analysis (TGA/DTA) where the Cu-exchanged Y showed a broad absorption band in the range 300-700nm due to *d-d* transitions at 490 and 560nm. These bands for 4%Cu (bipy)-Y occurred at 335nm 485 & 530nm respectively. Although peaks due to metal complexes are masked by the broad intense zeolite bands their presence can be ascertained in the spectra of samples containing 8% Cu compositions (8% Cu (phen)-Y; 1523, 1433, 850, 788, 790, 648), Cu(bipy)-Y; 1475, 1446, 793, 769).

### 4.2.4.6 Thermal Gravimetric analysis (TGA/DTA)

The thermal stabilities of encapsulated copper complexes were examined using thermo gravimetric and differential thermal analysis (TGA-DTA). Thermogravimetry (TG) involves recording the weight of a substance in the presence of controlled heating or cooling as a function of time or temperature. The TG curve is characterized by two prominent features viz., the flat portion s, which indicates temperature ranges, wherein the thermal stability of compound is assured and the curved portions, which indicate weight loss. From the weight loss observed, it is possible to determine the chemical composition of the compound. In differential thermal analysis (DTA) the temperature difference of the material of interest and a reference material under identical controlled conditions of heating or cooling with respect to time or temperature are recorded. TGA-DTA analysis was done on a Mettler-Toledo 851 system in nitrogen atmosphere and scan rate 10 deg/min.

These experiments show that the catalyst is stable up to 200$^{o}$C. TGA/DTA profile is as shown in *Figure 4.4.* The weight loss observed around 100$^{o}$C corresponds to loss of water present in the zeolite. The broad peak around 220$^{o}$C is attributed to the decomposition of ligands.

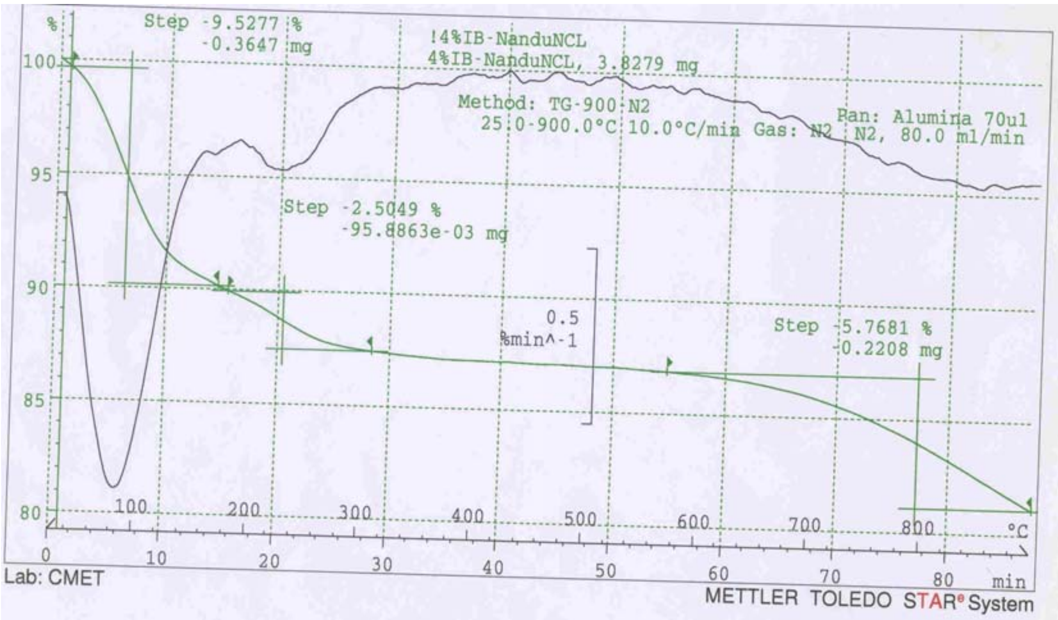


**Figure 4.4:** TGA-DTA of 4% Cu(Phen)-Y

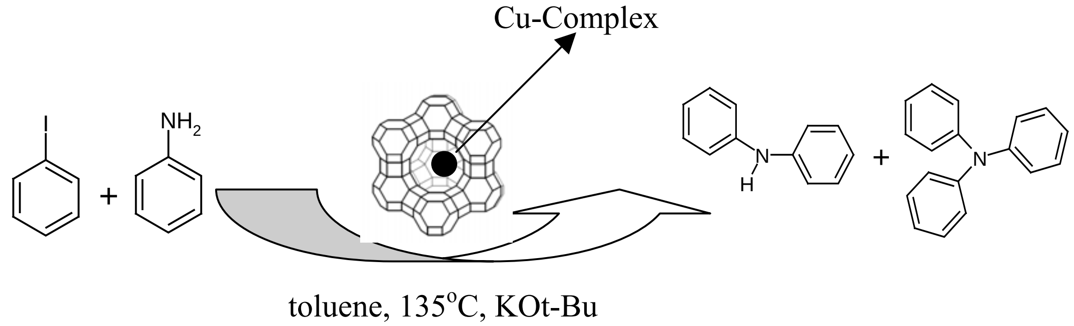
### 4.2.4.7 Inductive Coupled Plasma Atomic Emission Spectroscopy (ICP-AES)

The metal ion content in zeolite samples was determined by inductive coupled plasma-atomic emission spectroscopy. In a typical sample preparation for ICP-AES analysis, 50 mg of solid zeolite-Y encapsulated copper complex material was dissolved in a 1:1 mixture of con. $HNO_3$ (3ml) and 40% HF (3ml) or conc. $H_2SO_4$ (3ml) was taken in a polypropylene beaker. The resultant homogeneous solution was transferred to a 100 ml polypropylene volumetric flask and made up to the mark using de-ionized water. The ICP-AES analysis was done on a Perkin Elmer PE-1000 system in Ar atmosphere and $\lambda$ = 190 to 775 nm.

The copper ion contains in the zeolite-Y and encapsulated copper complexes were determined using a Hitachi (Z 8000) atomic absorption

All above characterization conformed that Cu-Phenanthroline encapsulated in the zeolite Na-Y. These characterized encapsulated copper catalyst used for the amination of iodobenzene, with recycle study.

### 4.2.5 Experimental Section



**Scheme 4.1:** Amination of aryl iodide using Cu-complex encapsulated in zeolite Y

#### 4.2.5.1 Analytical Method

A similar analytical methods used in chapter two section 2.2.4 were employed to characterize and estimate reactants and products.

#### 4.2.5.2 Experimental procedure

Amination reactions were carried out in a 50 ml capacity high-pressure autoclave (Parr Instruments, USA. Model number: 2430HC2). Toluene used as a solvent (20 ml) was charged to the reactor followed by aniline (2.10 mmol), iodobenzene (2 mmol), encapsulated 4% Cu(Phen)-Y catalyst (225mg) and KOt-Bu (16.5 mmol). The reactor was flushed twice with nitrogen to ensure complete removal of air. The autoclave was then stirred and heated to 408 K and the reaction was continued for 14 hours. After cooling to room temperature, the reaction solution diluted 50% with toluene and injected to GC for the calculation of conversion of aniline and yield of desired products. Reaction setup was shown in chapter two in *Figure 2.1.*

#### 4.2.5.3 Catalyst Recycle Procedure

After completion of the reaction, the reaction mixture was filtered. The solid part, which contained precipitated base (KI) and catalyst was washed with large quantity of toluene. It was then washed with little amount of distilled water and again by toluene thrice. The catalyst was dried under vacuum for 3 to 4 hours. After drying catalyst it was kept in furnace under nitrogen flow at 393 K for 5 to 6 hours, cooled under nitrogen flow and weighed. This catalyst was then reused for reaction charge as given in the above experimental procedure. In the recycle studies, the copper contain of the catalyst and subsequent amination reaction matures were analyzed for metal contents by ICP-AES analyzes.

### 4.2.6 Results and Discussion

Synthesized encapsulated copper complex in Zeolite–Y and MCM-41 material were tested for amination of arylhalides and recycle studies for the catalyst was also carried out. Our aim was to entrap the copper complex in the zeolite Y and enhance the activity as well as selectivity towards DPA.

#### 4.2.6.1 Catalyst Activity

*Table 4.1* shows the results of various types of encapsulated catalysts tested for the amination of arylhalides. Only zeolite Na-Y encapsulated catalyst show that good activity and selectivity for the amination of iodobenzene. There is only one repot on *N*-alkylation's of aniline[18] using zeolite Y, this report show that shape selectivity towards diphenylamine and lesser amount of triarylamines were obtained. In the present work using Na-Y catalyst we obtained 8% TPA in presence of KO*t*-Bu (see Table 4.1, entry 1). 4% Cu-Y catalyst without 1,10-phenanthroline ligand show high activity and selectivity for the formation of DPA as compare to only Na-Y as a catalysts (Table 4.1, entry 1, 2). However, the activity of 4% Cu-Y activity and selectivity were lower than a Cu(Phen)-Y catalyst *(Table 4.1 entries 1-6).* Other catalysts screened were 1%, 4%, 8% Cu(Phen) and 4% Cu(Bipy) encapsulated in the zeolite Y. The amount of copper contain in these was kept to equimolar quantity. It was found that 4% Cu(Phen)-Y and 4% Cu(Bipy)-Y gave the best activity and selectivity for the synthesis of DPA. 8% Cu(Phen)-Y gave the highest conversion but less selectivity for DPA and comparative high selectivity for TPA as compare to 4% Cu(Phen)-Y and Cu(Bipy)-Y catalysts (table 4.1 entries 4, 5 and 6). 8% Cu(Phen)-Y gave high yield of TPA, because of high loading of copper in zeolite-Y which was leached and that leached catalyst gave enhanced selectivity for TPA formation. These experiments indicate that high loading of metal complex lead to leaching, that due to the improper entrapment of metal complex in zeolite Y. 4%

Cu(Bipy)-Y and Cu(Phen)-Y gave high activity and selectivity for diphenylamine, because of channel diameter of Na-Y zeolite is ~7A° and previous reports shows that the same type of shape selectivity for the zeolite Y catalyst.[18] These results are also shown in *Figure 4.5.*

**Table 4.1:** Reaction with iodobenzene and aniline using copper complex encapsulated in Na-Y Zeolite

| Sr. No. | Catalyst | Con. of Aniline, (%) | Selectivity of DPA, (%) | Yield of DPA, (%) | Yield of TPA, (%) |
|---|---|---|---|---|---|
| 1[a] | Na-Y | 40 | 58 | 23 | 8 |
| 2[b] | 4% Cu-Y | 60 | 69 | 41 | 7 |
| 3[a] | 1% Cu(phen)-Y | 85 | 80 | 68 | 4 |
| 4[b] | 4% Cu(phen)-Y | 88 | 84 | 74 | 3 |
| 5[b] | 4% Cu(bipy)-Y | 89 | 87 | 78 | 2 |
| 6[c] | 8% Cu(phen)-Y | 90 | 66 | 60 | 15 |

***Reaction Condition:*** *Iodobenzene: 2.0mmol; Aniline: 2.105mmol; KOt-Bu: 6.451 mmol; Catalyst: $^{a}$ = 900, $^{b}$ = 225, $^{c}$ = 115 mg; Toluene: 20 ml; Temperature: 408 K; Time: 14h*

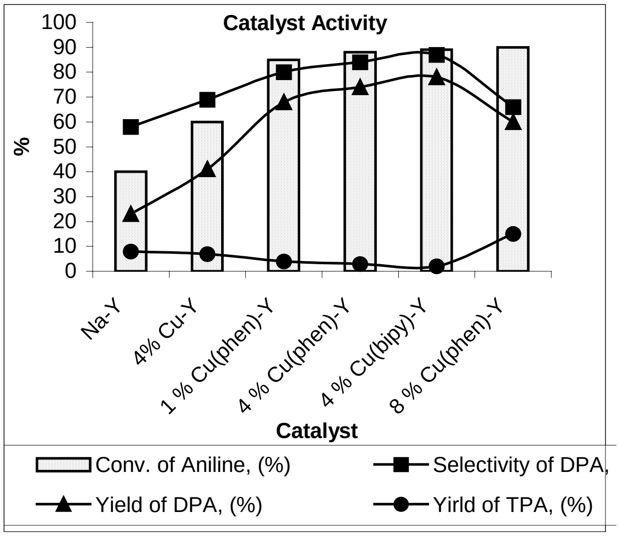


**Figure 4.5:** Catalyst activity for the amination of iodobenzene (**Reaction Condition:** see *Table 4.1*)

Thus 4% Cu(Phen)-Y and 4% Cu(Bipy)-Y gave the best activity as well as selectivity for the formation of DPA and Cu(Phen)Y catalyst was chosen for the recycle study.

### 4.2.6.2 Recycle Study of Cu(Phen)-Y catalyst for the amination of Iodobenzene

To check the catalyst stability recycles study was carried out and it was observed that even after 5th recycle the catalysts activity and selectivity remains same, it shows the catalyst is very active and stable *(see the Figure 4.6)*. Reaction mixture and the catalysts thus recovered (dissolved in conc. $HNO_3$) were also analyzed for determination of copper content by ICP-AES analyses, the solution shows no copper contain. Also the overall TON obtained at the end of five recycle was 200, which is much more as compare to the best reported for homogeneous catalyst, which is 40.

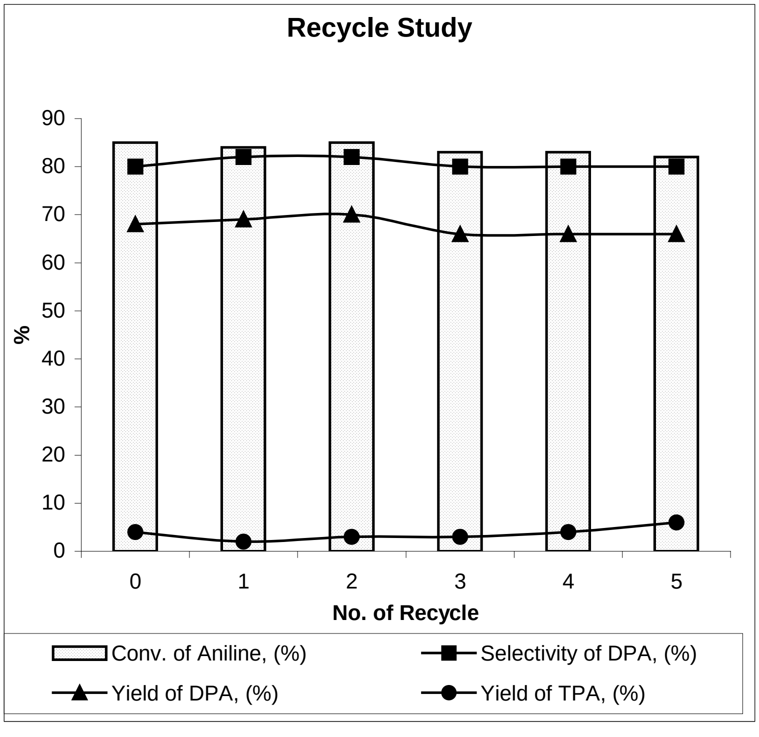


**Figure 4.6:** Recycle study of 4% Cu(Phen) encapsulated in zeolite Y

***Reaction Condition:*** *Iodobenzene: 2.0mmol; Aniline: 2.105mmol; KOt-Bu: 6.451 mmol; 4% Cu(Phen)-Y: 225 mg; Toluene: 20 ml; Temperature: 408 K; Time: 14h*

Thus this encapsulated catalysts is stable and active even after 5th recycle under same reaction conditions. This encapsulated copper catalyst is shape selective and recyclable for the synthesis of DPA with high TON.

### 4.2.6.3 Cu(Bipy) Encapsulated in MCM-41 Catalyst

To develop heterogeneous shape selective catalyst for the synthesis of triphenylamines, MCM-41 or MCM-48 was thought to be the best material for encapsulation of copper complex. MCM-41 having pore diameter ~35A° is more suitable for TPA synthesis.

### 4.2.6.3.1 Surface Area

Surface area of 4% Cu-MCM-41 was decreased on encapsulation. This is one of the direct evidences to show that the complexes are encapsulated in the cages of the zeolite-Y. $S_{BET}$ decreased from 1180m$^2$/g for 4%Cu-MCM-41 to 1035m$^2$/g for 4%Cu (bipy)-MCM-41. It further decreased to 928m$^2$/g due to increase in the molecular dimensions of the ligand. The decrease is smaller in the present case compared to the encapsulated, but as shown in *section 4.2.4* Cu(Bipy) encapsulated in the MCM-41.

### 4.2.6.3.2 Catalyst Activity

The above synthesized 4% Cu(Bipy)-MCM-41 catalyst, MCM-41 (without catalyst and ligand) and one with only copper exchange with MCM-41 catalyst, were screened for the amination of iodobenzene. Here we obtained very high activity and selectivity for triphenylamines (see Table 4.3 and Figure 4.7), MCM-41 gave 6 % of TPA (*Table 4.3 sr. no. 1*) and 4% Cu-MCM-41 catalyst gave 15 % yield of TPA. Best results were obtained for 4% Cu(Bipy)MCM-41 catalyst (71 % TPA).

**Table 4.2:** Activity of catalysts for the amination of iodobenzene using Cu(Bipy) encapsulated in MCM-41

| Sr. No. | Catalyst | Conv. of aniline, (%) | Sele. of TPA, (%) | Yield of TPA, (%) | Yield of DPA, (%) |
|---|---|---|---|---|---|
| 1 | MCM-41 | 18 | 33 | 6 | 3 |
| 2 | 4% Cu-MCM-41 | 32 | 46 | 15 | 9 |
| 3 | 4% Cu(Bipy)-MCM-41 | 80 | 89 | 71 | 5 |

***Reaction Condition:*** *Iodobenzene: 4.45mmol; Aniline: 2.10mmol; KOt-Bu: 6.45mmol; 4% Cu (Bipy.)-MCM-41: 225mg; Toluene: 20 ml; Temperature: 408 K; Time: 14h;*

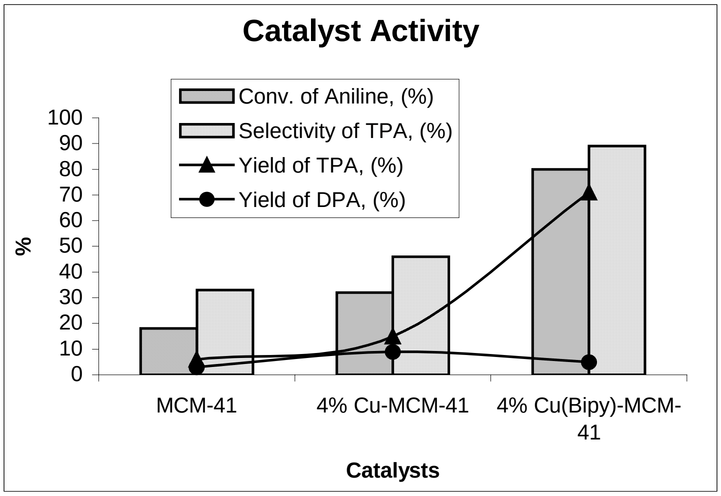


**Figure 4.7:** Catalyst activity for the amination of iodobenzene (**Reaction Condition:** see table 4.2)

### 4.2.6.3.3 Recycle study

Recycle study of the Cu(Bipy)-MCM-41 catalyst is shown in *Figure 4.8,* the catalytic activity decreases after each recycle experiments. Which shows that the considerable amount catalyst is leached out in the reaction mixture. Catalyst leaching is expected because of pore and channel diameter of MCM-41 is ~35A$^{o}$ and this encapsulated copper complex comes out from the MCM-41 metrics under in reaction conditions. However encapsulated Cu(Bipy) in MCM-41 selectively from triphenylamine, this is due to the large pore diameter of MCM-41 and leaching of copper complex in reaction solution Thus Cu(Bipy)-MCM-41 catalyst is not useful as a heterogeneous catalyst.

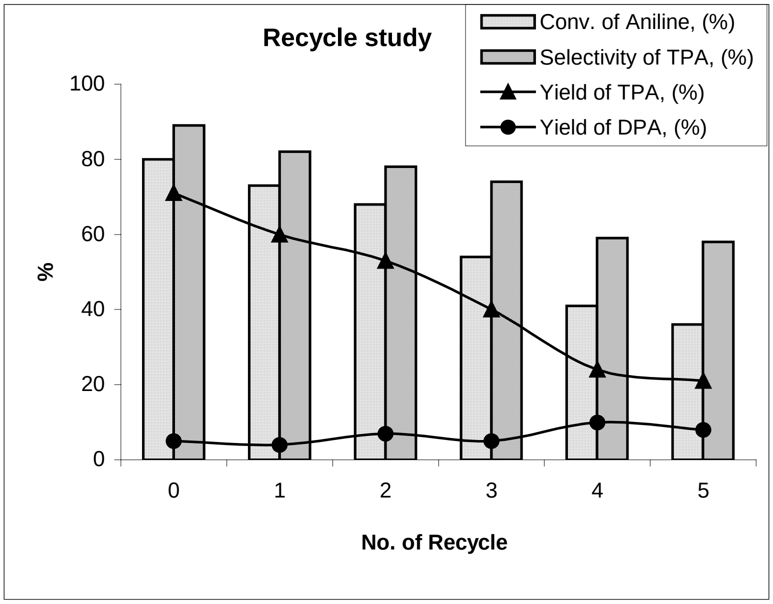


**Figure 4.8:** Recycle study of 4% Cu(Bipy)MCM-41 catalysts

***Reaction Condition:*** *Iodobenzene: 4.45mmol; Aniline: 2.10mmol; KOt-Bu: 6.45mmol; 4% Cu (Bipy.)-MCM-41: 225mg; Toluene: 20 ml; Temperature: 408 K; Time: 14h;*

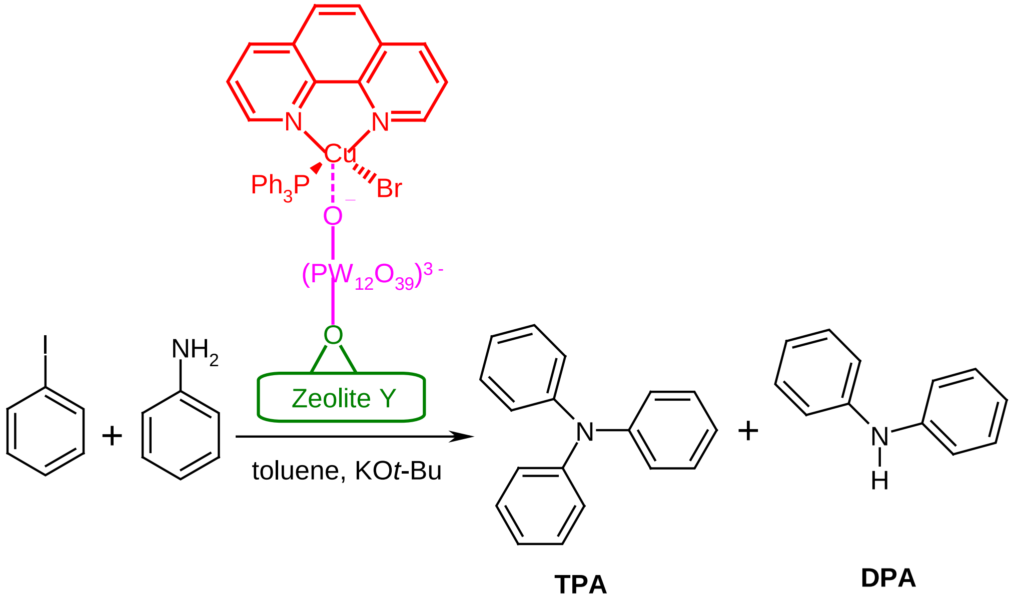
To develop true heterogeneous copper catalyst to give selectively triphenylamines with high TON is a major challenge.

## 4.3 Tethered Copper (I) Complexes

### 4.3.1 Introduction

Past three decades of catalysis saw various efforts to supports metal complexes on inert, insoluble, inorganic, matrices for '*heterogenization'* of soluble metal complexes to solid catalyst active for the variety of industrially important reactions.[19] Numerous methods of heterogenization have been investigated [20-22] for applications to various reactions. However lower activity-selectivity, leaching of metals, limitations of the support-pore size and deactivation of the catalysts have limited the actual use of 'heterogenised' catalyst in industry asking for challenges to look for newer versions or modification of the heterogenised catalyst.[23] recently novel approaches to immobilize homogeneous catalysts on solid supports (Clay, $Al_2O_3$, $SiO_2$, zeolite) has been proposed in which, the organometallic complex was tethered to inorganic matrices[24,25] for asymmetric hydrogenation. One of the advantages of this approach is to anchor homogenous catalysts, this procedure can be used to anchor a variety of pre-formed active homogenous catalysts onto a number of different supports. It is shown that the tethering technique leads to a true heterogeneous catalyst, which gives enhanced catalytic activity and stability compared to other method including encapsulation. There is no report on heterogenised homogenous catalyst, for the amination of arylhalides, but there is one report on heterogeneous copper catalyst for the amination of arylhalides.[10]

The objective of this work was to extend and explore the tethering method for heterogenizing metal complex catalysts for catalytic applications in amination (aromatic C-N bond) reactions. Particularly heterogenised Cu(Phen)($PPh_3$)Br and Cu(neocup)($PPh_3$)Br complex catalysts were prepared by tethering to zeolite Na-Y and other supports (e.g. $SiO_2$, $Al_2O_3$, MgO, Clay, Charcoal, and $TiO_2$) through heteropolyacid [e.g. phosphotungstic acid ($H_3PW_{12}O_{40}$. $xH_2O$, where $x = 6 – 240$)] as a tethering agent. It is demonstrated that these heterogeneous catalysts thus prepared, gave higher activity and stability for the amination of aryl iodide.



**Scheme 4.2.** Amination of aryl iodide using Cu(Phen)($PPh_3$)Br tethered to PTA on zeolite Na-Y

Zeolite Na-Y was our obvious choice as the support owing to its large cavity (12-14 A° supercage) accessible through four 7.4 A° windows, high surface area (~ 700 $m^2$/g). Moreover, zeolite Y particles are highly monodisperse in morphology (especially in size) with about 95% monodispersity for 300nm particle-size. This feature obviously helps in tethering the phosphotungstic acid (PTA) molecule on zeolite surface in a uniform manner and hence, maximum loading of PTA molecules (hence, more of metal complex can also be anchored to the PTA surface) can be achieved on the uniform and nano-sized zeolite particles. A few catalyst tethered to alumina were also prepared to compare the activities of the Na-Y supported catalysts. A detailed characterization of the heterogeneous catalysts using powder X-ray diffraction, X-ray photoelectron spectra (XPS), Transmission Electron Microscopy (TEM), Infra-red spectroscopy (IR), BET Surface area, Scanning Electron Microscopy (SEM), Energy dispersive X-ray analysis (EDX) and Inductive coupled plasma atomic emission spectroscopy is also reported to prove the catalyst heterogeneity.

### 4.3.2 Material

Iodobenzene, bromobenzene, 1,10-phenanthroline, copper (II) bromide, 1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU); 1,5-Diazabicyclo[2.2.0] non-5-ene (DBN); 1,4-Diazabicyclo[2.2.2] octane (DABCO) 1,5-Diazabicyclo[4.3.0] none-5-ene, N,N-Dimethylbenzylamine and neocuprene all were purchased from Aldrich chemical USA. Toulene, N,N-dimethyl formaamide, THF, 1,4-dioxane, Cyclohexane, triethylamine, potassium t-butoxide, sodium t-butoxide, potassium carbonate, phosphotungstic acid, triphenyl phosphine, naphthalene, diethyl ether, dichloromethane, chloroform, ethanol, and aniline all were purchased from *s.d.* fine chem. India.

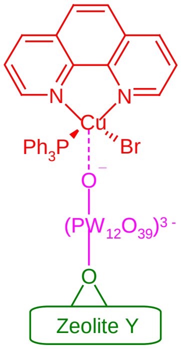
### 4.3.3 Synthesis of Tethered Copper complex catalyst

#### 4.3.3.1 Synthesis of Cu(Phen)($PPh_3$)Br and Cu(neocup)($PPh_3$)Br complexes

Synthesis of Cu(Phen)($PPh_3$)Br and Cu(neocup)($PPh_3$)Br complexes were carried out as described in *chapter 3 (section 3.2.2.2 and 3.2.2.3)* respectively.

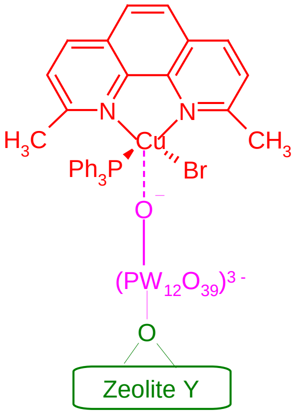
#### 4.3.3.2 Synthesis of tethered 3.76% Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to zeolite Y

The tethered catalyst was prepared following the procedure reported by Augustine and co-workers.[23,24] To a solution of phosphotungstic acid (2.81 mmol) in 250 ml of methanol, a slurry of zeolite Y (10.5g of Na-Y) in 320 ml of methanol was added and stirred vigorously for 6 h. the white solid (PTA-Y) obtained was filtered, washed thoroughly with methanol to ensure complete removal of phosphotungstate anion from the solid and dried at 373 K for 6 h. Part of this solid (10g) was suspended in 400 ml methanol and 2.56 mmol of Cu(Phen)($PPh_3$)Br complex was added and reflux under stirring for 18 h. The pale yellow solid product [Cu(Phen)($PPh_3$)Br-PTA-Y] was then washed with repeatedly (Soxhlet extraction for 18 h) to remove unanchored Cu-complex to PTA-Y, dried at 373 K, and used as such for amination reactions.



### 4.3.3.3 Synthesis of tethered Cu(neocup)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to zeolite Y

The tethered catalyst was prepared following the procedure reported by Augustine and co-workers.[24,25] To a solution of phosphotungstic acid (3.90 mmol) in 300 ml of methanol, a slurry of zeolite Y (10.5g of Na-Y) in 320 ml of methanol was added and stirred vigorously for 6 h. the white solid (PTA-Y) obtained was filtered, washed thoroughly with methanol to ensure complete removal of phosphotungstate anion from the solid and dried at 373 K for 6 h. Part of this solid (10g) was suspended in 400 ml methanol and 3.66mmol of Cu(neocup)($PPh_3$)Br complex was added and reflux under stirring for 18 h. The pale yellow solid product [Cu(neocup)($PPh_3$)Br-PTA-Y] was then washed with repeatedly (Soxhlet extraction for 18 h) to remove unanchored Cu-complex to PTA-Y, dried at 373 K, and used as such for amination reactions.



### 4.3.3.4 Synthesis of tethered Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to Titanium oxide

The tethered catalyst was prepared using the same procedure of Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to zeolite Y, here only the support is titanium oxide instead of zeolite Y.

### 4.3.3.5 Synthesis of tethered Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to Montmorillonite Clay

The tethered catalyst was prepared as same procedure of Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to zeolite Y, here used support is montmorillonite Clay instead of zeolite Y.

### 4.3.3.6 Synthesis of tethered Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to Alumina

The tethered catalyst was prepared as same procedure of Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to zeolite Y, here used support is alumina instead of zeolite Y.

### 4.3.3.7 Synthesis of tethered Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to Charcoal:

The tethered catalyst was prepared as same procedure of Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to zeolite Y, here used support is charcoal instead of zeolite Y.

### 4.3.3.8 Synthesis of tethered Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to Silica

The tethered catalyst was prepared as same procedure of Cu(Phen)($PPh_3$)Br on phosphotungstic acid(PTA) anchored to zeolite Y, here used support is silica instead of zeolite Y.

### 4.3.4 Characterization of tethered Cu(Phen)(PPh$_3$)Br on phosphotungstic acid(PTA) anchored to zeolite Y

#### 4.3.4.1 Powder X-ray diffraction (XRD)

The microporous phase of zeolite-Y, PTA-Y, 3.76% Cu(Phen)(PPh$_3$)Br-PTA-Y catalyst were characterized by powder XRD. The distinct reflections and crystallinity remained unaltered from one another, as observed by powder XRD patterns in fig. 4.9.

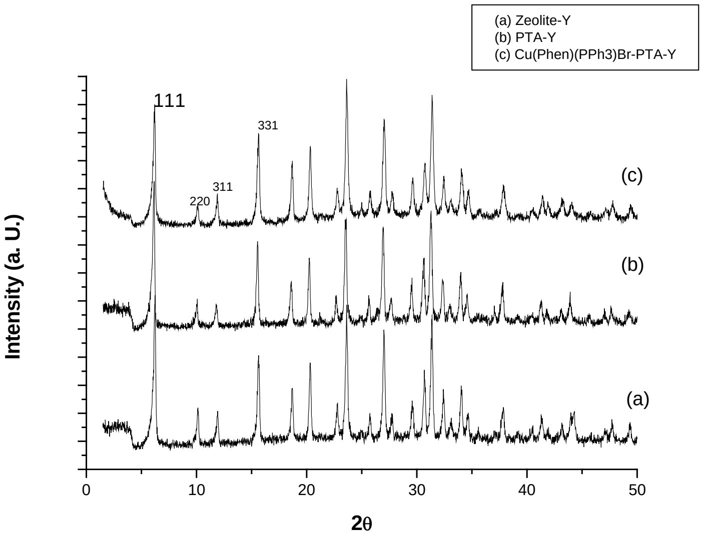


**Figure 4.9:** XRD of (a) Zeolite -Y, (b) PTA-Y,
(c) 3.76% Cu(Phen)(PPh$_3$)BrPTA-Y

This shows that: (a) there is no change in crystallinity or morphology (determined by peak position) of zeolite Y embedded with PTA compared to that neat zeolite Y sample and (b) the porous framework of Cu(Phen)(PPh$_3$)Br-PTA-Y catalyst were not affected or damaged during the complex formation Cu(Phen)(PPh$_3$)Br complex were tethered to the PTA-Y support.

#### 4.3.4.2 Scanning Electron Microscopy (SEM)

This is important tool for morphological characterization of microporous and mesoporous molecular sieve materials. Different types of morphology of the synthesized materials as well as the presence of any amorphous phase in the samples can be characterized using this technique. The major advantage of SEM is that bulk samples can also be studied directly by this technique. The ESM micrographs of the samples were determined on Leica Stereoscan 440 scanning electron microscope. The samples were prepared with isopropanol as like solid gel. The sample were loaded on stubs and sputtered with thin gold film to prevent surface charging and also to protect from thermal damage from the electron beam, prior to scanning. Powder X-ray diffreaction shown that there was no alteration of crystaillinity of zeolite Y after tethered 3.76% Cu(Phen)(PPh$_3$)Br-PTA.

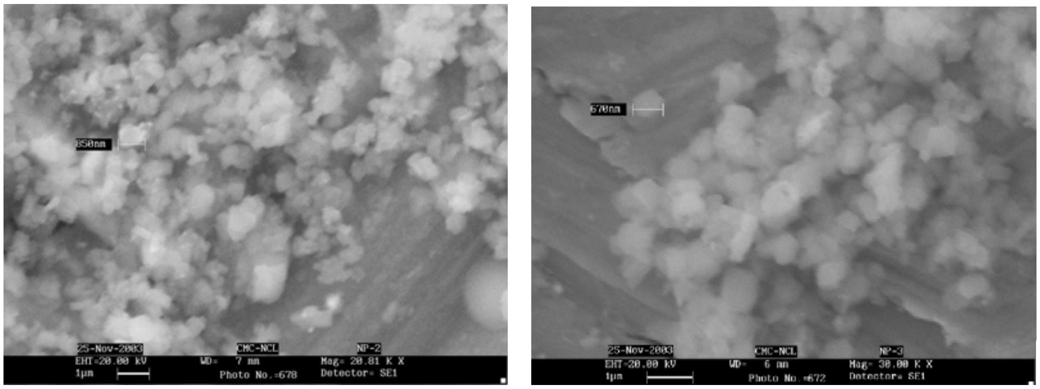


**Figure 4.10.** SEM of (NP-2) 3.76% Cu(Phen)(PPh$_3$)Br-PTA-Y before reaction and (NP-3) 3.76% Cu(Phen)(PPh$_3$)Br-PTA-Y after reaction

To further consolidate this fact, we also scanned 3.76% Cu(Phen)(PPh$_3$)Br-PTA-Y catalyst before and after amination of iodobenzene reaction by SEM *(Figure. 4. 10)*. The crystalline patterns of the catalysts as well as the parent material zeolite Na-Y remained unaffected even after 5th recycle. This conclusion further supports the integrity of the Cu-complex tethered by PTA to the zeolite matrix and retaining the crystallinity and morphology of Zeolite Y even after reuse.

### 4.3.4.3 IR Spectra

The FT-IR spectra were recorded on a Bio-Rad FTS-175 spectrometer in the range 4000-400cm$^{-1}$. The samples were made as KBr pellets (1% w/w). The spectra were recorded in transmittance (%T) mode.

Infrared Transmittance Spectra gives valuable information for all the functional groups of the catalyst system. See the ***Figure 4.11*** for IR spectra of 3.76% Cu(Phen)(PPh$_3$)Br-PTA-Y and Cu(Phen)(PPh$_3$)Br. PTA shows the band at 1079 $\nu_{(P\text{-}O)}$, 981 $\nu_{(W=O)}$, 899 $\nu_{(W\text{-}O\text{-}W)}$, 595 and 509 cm$^{-1}$ for $\nu_{(O\text{-}P\text{-}O).}$[26,27] Cu(Phen)(PPh3)Br shows the characteristic band in the range 1600 – 1430 cm$^{-1}$ $\nu_{(C\text{-}C,\ C\text{-}N\ aromatic)}$[28] The bands placed at 509 and 595 $\nu_{(O\text{-}P\text{-}O)}$ are masked by support bands[29] in the spectrum so the information is obtained from the less affected regions. Thus, by FT-IR spectroscopy it was possible to elucidate the bonding interactions present as well as the typical spectral vibrations for the complex and the supports, while the complex was tethered on support of zeolite-Y.

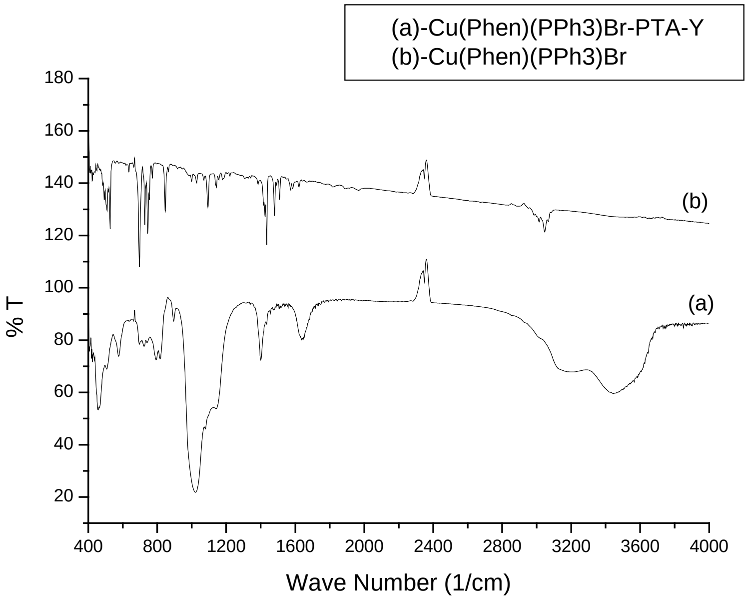


**Figure 4. 11:** IR Spectra of (a) 3.76% Cu(Phen)(PPh$_3$)Br-PTA-Y and (b) Cu(Phen)(PPh$_3$)Br

### 4.3.4.4 X-ray Photoelectron Spectroscopy (XPS)

X-ray photoelectron spectroscopy (XPS) studies of the PB film before and after cycling (i.e. on the as-deposited films and the reduced films) were carried out on a VG Microtech ESCA 3000 electron spectrometer with an Mg-K$_\alpha$ X-ray source (unmonochromatized). For the present measurements the anode was operated at 140 W (14kV, 10mA) and the analyzer was operated at constant pass energy of 50 eV. All the spectra were recorded with similar spectroscopic parameters. The binding energy (B.E.)

scale was calibrated using determining the B.E. of Au4$f_{7/2}$ (84 eV), Ag3$d_{3/2}$ (368.4 eV) and pure metal form Johnson-Matthey, London. The B.E. values (measured to an accuracy of 0.2eV) are in a good agreement with the literature values. The resolution in terms of the full width at half maximum (FWHM) of the Au4$f_{7/2}$ level is 1.6 eV.

**Table 4.3:** XPS Binding Energy Valves [a] for Different Elements Present in 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y Catalyst

| | Elements | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | $C_{1s}$ | $Br_{3d}$ | $Al_{2p}$ | $Si_{2p}$ | $P_{2p}$ | $N_{1s}$ | $O_{1s}$ | W | | Cu | |
| | | | | | | | | 4$f_{7/2}$ | 4$f_{5/2}$ | 2$p_{3/2}$ | 2$p_{1/2}$ |
| PTA-Zeolite Y | 285 | - | 75 | 103.5 | 132 | - | 532.5 | 36.3 | 38.4 | - | - |
| Cu(Phen)(PPh3)Br-PTA-Y | 285 | 68 | 75 | 103.5 | 133 | 403.5 | 532.5 | 36.3 | 38.5 | 932.6 | 952.4 |
| Literature Values * | 285 | 68.5 | 75 | 103.4 | 133 | 402.5 | 531 | 36.4 | 38.6 | 932.4 | 952.5 |

[a] *All the values were corrected to C $_{(1s)}$ with binding energy of 285 eV using adventitious carbon. * Handbook of X-ray Photoelectron Spectroscopy, Physical electronics, Perkin Elmer,* ***1979.***

Surface analysis by XPS spectra was carried out in terms of the binding energy values of various elements present (Copper, Tungsten, Bromine, Aluminum, Phosphorus, Silica, Carbon, Nitrogen and Oxygen) in the catalyst supports after the necessary $C_{1s}$ correction *Figure 4.12*. The B.E. and the oxidation state values for all the elements agree very well with the proposed interaction of HPA to alumina. It also suggests that all copper is present as Cu(I) without undergoing any irreversible change from its original state in Cu(Phen)($PPh_3$)Br. Copper (I) complex shows the binding energy at 932.6, which is reported in literature.[30] This is clearly show that oxidation sate of copper is 1. B.E. of phosphorus of PTA is in literature 131.2 and $PPh_3$ of copper complex is nearly 133 to 133.5, here we found broad peak of phosphorus and which is merge the two peaks in one peak at 133. B.E. of all other elements are all most same which are reported in literature.

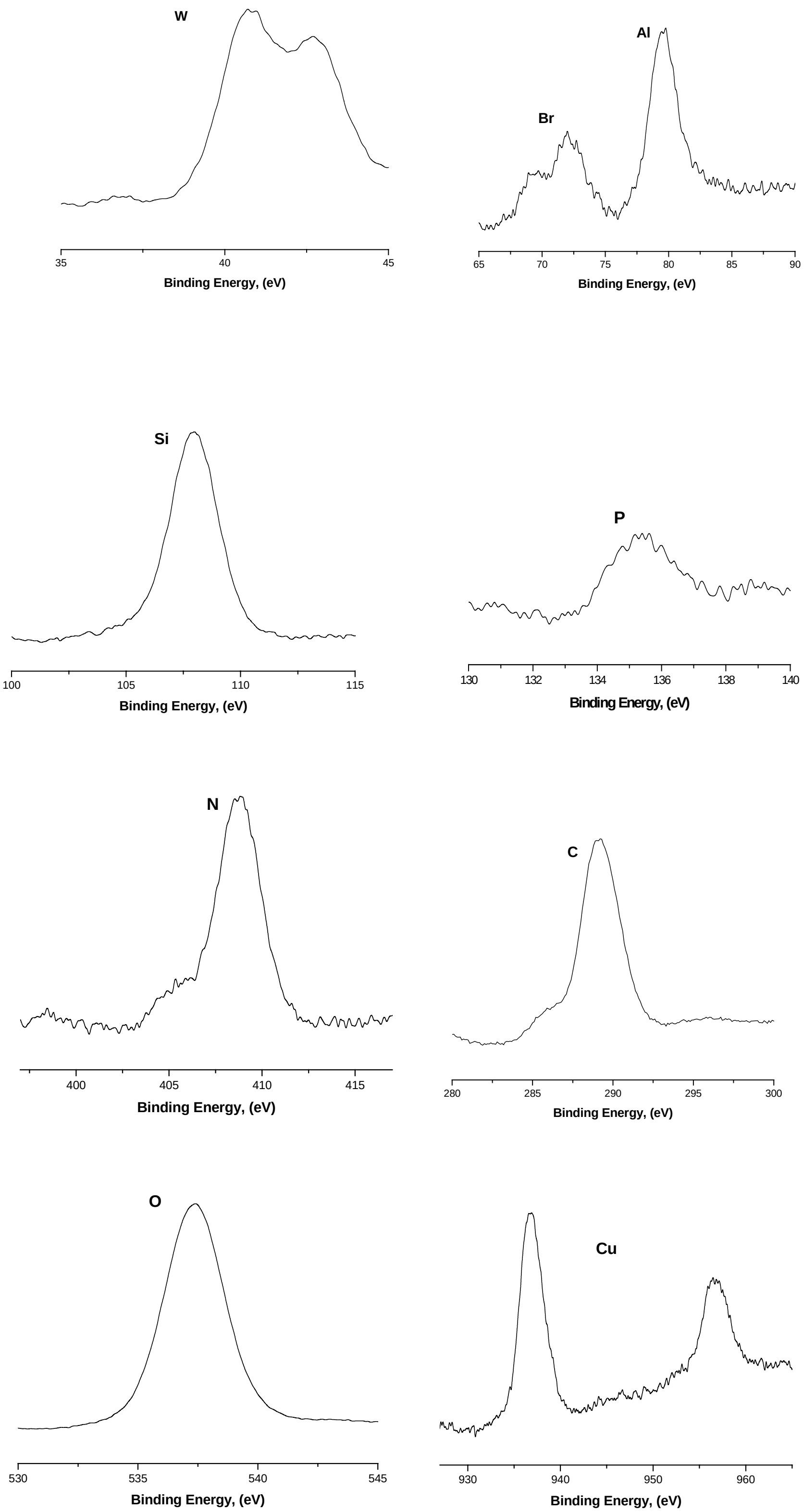


**Figure 4.12:** XPS Spectra of 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y Catalyst

### 4.3.4.5 Transmission Electron Microscopy (TEM)

The TEM images were scanned on a JEOL JEM-1200EX instrument with 100kVof acceleration voltage. Tem samples were prepared by placing a drop of the mixture of catalyst and isopropanol solution onto a gold-coated copper TEM grid. We have used TEM analysis to estimate the size of catalyst particles and how dispersed copper complex on the surface of Na-Y. These images show that on the support (Na-Y) copper complex tethered with phosphotungstic acid (PTA). In this image black color is of support (Na-Y), on the surface, copper complexes (Which is white in this image) with PTA as a tethering agent. This is direct structural evidence for copper complex tethered on Na-Y.

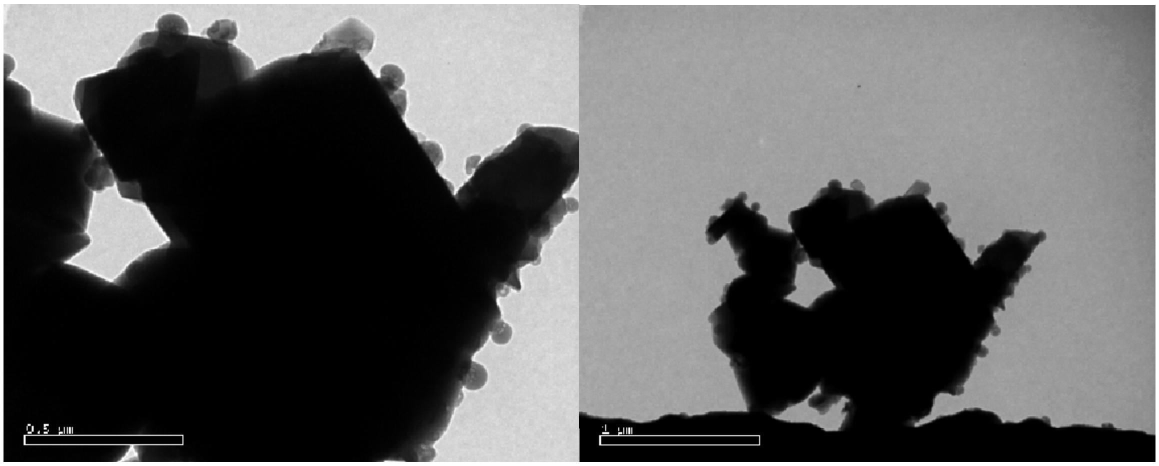


**Figure 4.13:** TEM of 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y catalyst

### 4.3.4.6 Energy dispersive X-ray analysis (EDX)

The Energy dispersive X-ray analysis (EDX) of the Cu(phen)($PPh_3$)Br-PTA-Y tethered catalyst was carried out on a Leica Stereoscan-440 SEM equipped with a Phoenix EDX attachment. The samples were prepared as like SEM, but film was little thicker than SEM samples. The EDX spectra were gives the elemental composition of Cu(Phen)($PPh_3$)Br-PTA-Y catalyst. In this EDX spectra of all (Cu, Br, P, N, Si, O, W, and Al) elements give the exact percentage of respective elements in this catalyst. The EDX determined percentage compositions of elements are 4 to 5 % lower than ICPES or AS.

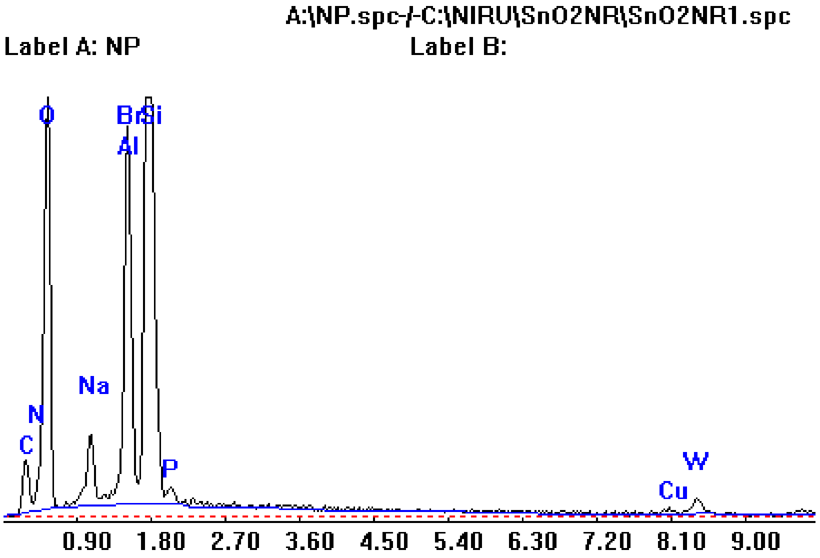


**Figure 4.14:** EDX spectra of Cu(Phen)($PPh_3$)Br-PTA-Y

### 4.3.4.7 Inductive coupled plasma atomic emission spectroscopy

The metal ion content in zeolite samples was determined by inductive coupled plasma-atomic emission spectroscopy. In a typical sample preparation for ICP-AES analysis, 50 mg of solid zeolite-Y tethered copper complex material was dissolved in a 1:1 mixture of con. $HNO_3$ (3ml) and 40% HF (3ml) or conc. $H_2SO_4$ (3ml) was taken in a polypropylene beaker. The resultant homogeneous solution was transferred to a 100 ml polypropylene volumetric flask and made up to the mark using de-ionized water. The ICP-AES analysis was done on a Perkin Elmer PE-1000 system in Ar atmosphere and $\lambda$ = 190 to 775 nm. The copper ion contains tethered copper complexes on the surface of zeolite-Y, were determined using a Hitachi (Z 8000) atomic absorption. The results of ICP-AES analysis showed 3.76 % Cu in the sample of Cu(Phen)($PPh_3$)Br-PTA-Y tethered catalyst.

## 4.3.5 Experimental Section

### 4.3.5.1 Experimental Procedure

Amination reaction was carried out in a 50 cc capacity two neck round bottom flask as shown in experimental setup. In a typical experiment, Toluene (23 ml) was charged to the round bottom flask followed by aniline (7.85mmol), iodobenzene (16.48mmol), tethered copper catalyst (0.28mmol) and base (23.5mmol). Naphthalene (250mg) was added as a internal standard for GC analysis. Reflux condenser was attached to the flask and the round bottom flask was flushed twice with argon to ensure removal of air. Argon balloon was attached to the condenser, to maintain inert atmosphere during the reaction. The round bottom flask was then stirred by magnetic needle and heated to 112°C in oil bath and the reaction was continued for 10 to 12 hours. After cooling to room temperature, the reaction solution was filtered to remove the precipitated base and washed with solvent few times. For this standard run, reaction mixture diluted in nearly 50% and injected to GC for calculations of conversion and yields of product.

The sequence of addition while reaction charged as follow:

$$\text{Solvent} \longrightarrow \text{Substrate} \longrightarrow \text{Catalyst} \longrightarrow \text{Base}$$

Experiments were carried out using glass reactor of capacity 50 CC. The details of the setup are shown in chapter two *fig. 2.29*

$$Cu\ TON = \frac{(\text{Number of mole of DPA} + \text{Number of mole of TPA})}{\text{Number of mole of copper}}$$

#### 4.3.5.2 Leaching and Recycle Experiments with the tethered catalysts, Cu(Phen)(PPh$_3$)Br-PTA-Y

Catalyst leaching experiments have been performed by hot filtration of the reaction mixture and subsequently testing the catalytic activity of the filtered solution for the amination without addition of catalyst no amination activity. The catalysts thus recovered (dissolved in conc. $HNO_3$) was also analyzed for determination of copper and tungsten content by ICP-AES analyses, which matched with the original Cu and W contain of the catalyst. For catalyst recycle experiments, the tethered catalyst was filtered and wash three times with toluene. Filtered and dried catalyst under vacuum for three to four hours was used for further recycle runs.

### 4.3.6 Results and Discussion

Our direction of the research was towards the development heterogeneous copper catalyst for the synthesis of triphenylamines selectively. It has been observed that an encapsulated copper complex in MCM-41 was not stable and cannot be recycled. So seven different tethered copper catalysts were synthesized applied for the amination of arylhalides. The activity and selectivity study of each catalyst was carried out. An effect of various parameters on reaction was also studied. Best-tethered catalyst was studied for the stability and recycle study e.g. metal leaching experiments.

#### 4.3.6.1 Catalysts Activity

Various tethered copper complexes on different inert supports were screened for the amination of iodobenzene. Cu(Phen)($PPh_3$)Br and Cu(neocup)($PPh_3$)Br copper complexes tethered on zeolite Y and various inorganic supports using phosphotungstic acid as a tethering agent. *Table 4.4* shows that copper complexes tethered on zeolite Y and alumina gave high activity and selectivity for the synthesis of triphenylamine as compare to other inorganic supports titanium oxide, clay, charcoal and silica *(Table 4.4 entries 1-7).* Zeolite Na-Y was best support, because of high surface area (~ 700 $m^2$/g). Moreover, zeolite Y particles are highly monodisperse in morphology (especially in size) with about 95% monodispersity for 300nm particle-size. This feature obviously helps in tethering the phosphotungstic acid (PTA) molecule on zeolite surface in a uniform manner and hence, maximum loading of PTA molecules (hence, more of metal complex can also be anchored to the PTA surface). 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y catalyst gave best result as compare to 3.76% Cu(neocup)($PPh_3$)Br-PTA-Y and same trends observed in neat homogenous complexes.

Thus 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y is the best heterogeneous catalyst for the synthesis of triphenylamines and this is the first report of heterogenised catalyst for the amination of arylhalides. Further detailed study of catalysts stability and recycliablity was carried out using this catalyst.

**Table 4.4:** Activity of tethered catalysts on amination of iodobenzene

| Sr. No. | Catalysts | Conv. of Aniline, (%) | Sele. of TPA, (%) | Yield of TPA, (%) | Yield of DPA, (%) |
|---|---|---|---|---|---|
| 1 | 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y | 86 | 84 | 72 | 9 |
| 2 | ~ 4% Cu(neocup)($PPh_3$)Br-PTA-Y | 70 | 85 | 60 | 12 |
| 3 | ~ 4% Cu(Phen)($PPh_3$)Br-PTA-Alumina | 78 | 71 | 55 | 8 |
| 4 | ~ 4% Cu(Phen)($PPh_3$)Br-PTA-Titanium Oxide | 74 | 35 | 26 | 13 |
| 5 | ~ 4% Cu(Phen)($PPh_3$)Br-PTA-Clay | 80 | 40 | 32 | 7 |
| 6 | ~ 4% Cu(Phen)($PPh_3$)Br-PTA-Charcoal | 50 | 49 | 25 | 24 |
| 7 | ~ 4% Cu(Phen)($PPh_3$)Br-PTA-Silica | 56 | 40 | 22 | 20 |

***Reaction Conditions:*** *Aniline: 4.0mmol, Iodobenzene: 8.25mmol, ~ 4 % Catalysts: 0.550g, KOt-Bu: 16.0mmol, Toluene: 20.0ml, Naphthalene: 0.250g, Time: 10h, Temperature: 385 K.*

### 4.3.6.2 Recycle Study

The recycle experiments were carried out by a procedure as described in *chapter 4 (section 4.3.5.2)* for the amination of iodobenzene using 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y. After 5th recycle the catalysts activity and selectivity remain same without leaching of copper and tungsten metals. Reaction mixture and the catalysts thus recovered (dissolved in conc. $HNO_3$) were also analyzed for determination of copper and tungsten content by ICP-AES analyses. 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y catalyst was active and stable after 5th recycle and this is first repots on amination of arylhalides to use recycle heterogeneous catalyst with high TON. Best homogenous copper catalyst gave

20.7 TON *(Table 2.12, entry 17)*, but 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y tethered heterogeneous catalysts gave 69 TON.

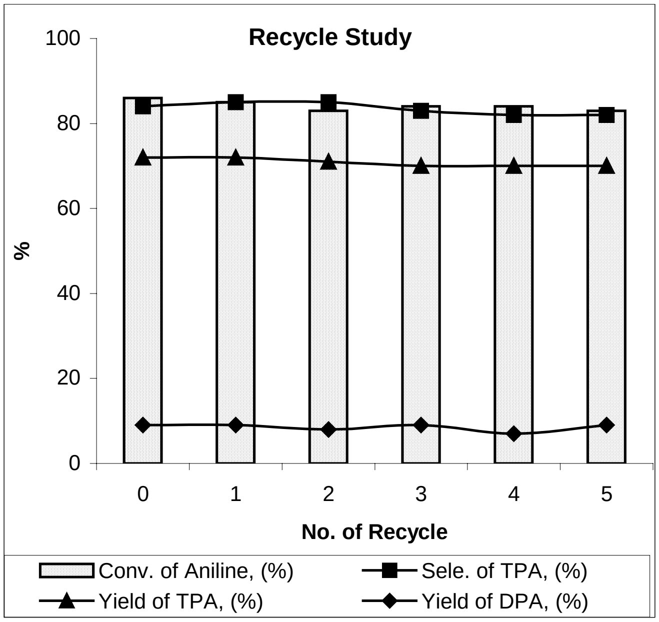


**Figure 4.15:** Recycle study of 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y catalyst for the amination of iodobenzene

***Reaction Conditions:*** *Aniline: 4.0 mmol, Iodobenzene: 8.25 mmol,* 3.76% Cu(Phen)($PPh_3$)Br-Y*: 0.550g, KOt-Bu: 16.0mmol, Toluene: 20.0ml, Naphthalene: 0.250g, Time: 10h, Temperature: 385 K.*

Thus the tethered catalyst 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y is stable and active even after 5th recycle under same reaction conditions. This tethered copper catalyst is selective, recyclable catalyst for the synthesis of TPA with high TON.

### 4.3.6.3 Base Effect

Various bases were tested for the amination reaction using 3.76% Cu(Phen)(PPh3)Br-PTA-Y as a catalyst. Strong bases such as KO*t*-Bu and NaO*t*-Bu gave high activity and selectivity for the amination of arylhalides. NaO*t*-Bu gives more selectivity towards DPA as compare to KO*t*-Bu, due to the less activity of NaO*t*-Bu. There is one more reason may be possible, KO*t*-Bu react with aniline forming $KNHC_6H_5$ salt which react with iodobenzene and TPA is obtained. KO*t*-Bu is the best base for the amination of arylhalides using 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y as a catalyst. Other bases such as $K_2CO_3$, KOH, and DBN (1,5-Diazabicyclo [4.3.0] non-5 ene), show no activity (*Table 4.5 entries 3,4 and 5*). Gujadhur [31] reported KOt-Bu is the best base for the mono-amination of arylhalides using homogenous Cu(Phen)($PPh_3$)Br as a catalyst. For the further study was carried out using KO*t*-Bu as a base and Cu(Phen)(PPh3)Br-PTA-Y as a catalyst.

**Table 4.5:** Effect of Base on amination of iodobenzene

| Sr. No. | Base | Conv. of Aniline, (%) | Sele. of TPA, (%) | Yield of TPA, (%) | Yield of DPA, (%) |
|---|---|---|---|---|---|
| 1 | KO*t*-Bu | 86 | 84 | 72 | 9 |
| 2 | NaO*t*-Bu | 63 | 2 | 1 | 5 |
| 3 | KOH | 27 | 0 | 0 | 1 |
| 4 | DBN$^{\$}$ | 9 | 0 | 0 | 0 |
| 5 | $K_2CO_3$ | 7 | 0 | 0 | 0 |

***Reaction Conditions:*** *Aniline: 4.0mmol, Iodobenzene: 8.25mmol, 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y: 0.550g, Base: 16.0mmol, Toluene: 20.0ml, Naphthalene: 0.250g, Time: 10h, Temperature: 385 K, $^{\$}$= 1,5-Diazabicyclo [4.3.0] non-5 ene*

### 4.3.6.4 Solvent Effect

Various solvents were screened using 3.76% Cu(Phen)($PPh_3$)Br-PTA-Y as a catalyst and KO*t*-Bu as a base for the amination of arylhalides *(Table 4.6and Figure 4.16).* In homogenous palladium catalyzed amination reaction toluene was found to be the best solvent.[11,12] other solvents like 1,4-dioxane, DMF and xylene, were also effective

Our pervious report on copper catalyzed amination of aryl halides shows that toluene is the best solvent.[32] The aim of this study is to see the effect of the solvent polarity on well define copper (I) complexes tethered on zeolite Y using phosphotungstic acid as a tethering agent for the amination of arylhalides, here also we found toluene as the best solvent for the amination of aryl halides. Reactions were carried out at 385 K for toluene, *N,N'*-dimethyl formamide (DMF), *m*-xylene solvents *(Table 4.6, entries 1,3 & 5),* in other solvents reactions were carried out at reflux temperatures. Very poor yields of

TPA and DPA were obtained with polar solvent like DMF and Acetonitrile *(Table 4.6, entry 5 & 6).* Less polar solvent *m*-xylene gives less yield of TPA *(Table 4.6, entry 3).* 1,4-dioxane gives moderate yield of TPA and *t*-BuOH gives poor yield of TPA (Table 4.6, entry 2 & 4). Solvent can be arranged in decreasing order of TPA yield as: toluene >1,4-dioxane > *m*-xylene > *t*-butanol

**Table 4.6:** Effect of solvent on amination of iodobenzene

| Sr. No. | Solvent | Conv. of Aniline, (%) | Sele. of TPA, (%) | Yield of TPA, (%) | Yield of DPA, (%) |
|---|---|---|---|---|---|
| 1 | Toluene | 86 | 84 | 72 | 9 |
| 2 | *1,4-dioxane | 54 | 44 | 24 | 19 |
| 3 | *m*-xylene | 63 | 25 | 16 | 15 |
| 4 | **t*-butanol | 35 | 12 | 4 | 27 |
| 5 | DMF | 28 | 8 | 3 | 2 |
| 6 | *Acetonitrile | 30 | 5 | 1 | 8 |

***Reaction Conditions:*** *Aniline: 4.0mmol, Iodobenzene: 8.25mmol,* 3.76 % *Cu(Phen)(PPh$_3$)Br-PTA-Y: 0.550g, Base: 16.0mmol, Solvent: 20.0ml, Naphthalene: 0.250g, Time: 10h, Temperature: 385 K, *: reflux temperature*

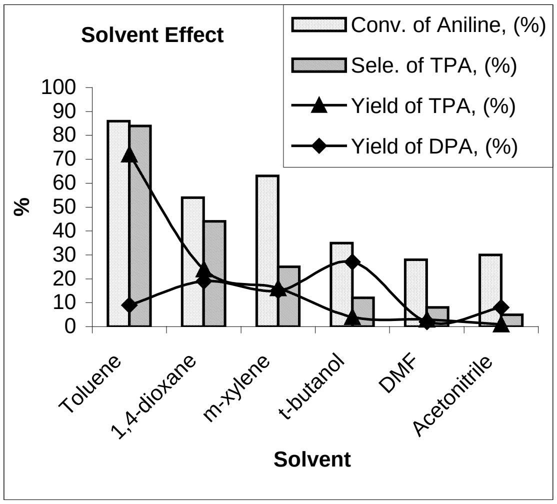


**Figure 4.16:** Effect of solvent on the amination of iodobenzene using 3.76% Cu(Phen)(PPh$_3$)Br-PTA-Y as a catalyst

(**Reaction Condition:** see Table 4.6)

Thus less polar solvent like toluene is suitable for the3.76 % Cu(Phen)($PPh_3$)Br-PTA-Y for the amination of arylhalides.

### 4.3.6.5 Temperature Effect

Choosing 3.76 % Cu(Phen)($PPh_3$)Br-PTA-Y as a catalyst, KO*t*-Bu as a base and toluene as a solvent the reaction was carried out at various temperature *(Table 4.7 and Figure 4.17).* Best results were obtained at 385 K temperature. Activity of catalyst is decreases with temperature, *(Table 4.7, entries 1,2 & 3).* Interestingly it is observed that the decrease in reaction temperature increases the yield of DPA.

**Table 4.7:** Effect of temperature on amination of iodobenzene

| Sr. No. | Temperature, (K) | Conv. of Aniline, (%) | Sele. of TPA, (%) | Yield of TPA, (%) | Yield of DPA, (%) |
|---|---|---|---|---|---|
| 1 | 385 | 86 | 84 | 72 | 9 |
| 2 | 373 | 73 | 48 | 35 | 13 |
| 3 | 363 | 67 | 30 | 20 | 15 |

***Reaction Conditions:*** *Aniline: 4.0mmol, Iodobenzene: 8.25mmol,* 3.76 % *Cu(Phen)(PPh$_3$)Br-PTA-Y: 0.550g, KOt-Bu: 16.0mmol, Toluene: 20.0ml, Naphthalene: 0.250g, Time: 10h.*

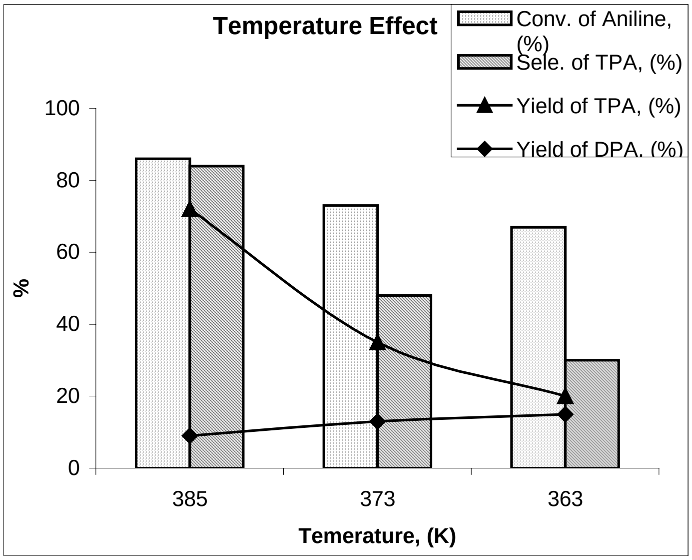


**Fig. 4.17:** Effect of temperature on the amination of iodobenzene using 3.76 % Cu(Phen)($PPh_3$)Br-PTA-Y as a catalyst
(**Reaction Condition:** see Table 4.7)

The conversion of aniline was 67%, at 363 K, but mass balance is off as compare to reaction at 385 and 373 K temperature, because initially aniline reacts with KO*t*-Bu and further reaction carried is efficiently proceeds only at temperature ~385.

Thus at 385 K temperature best results were obtained for the amination of iodobenzene using heterogeneous 3.76 % Cu(Phen)($PPh_3$)Br-PTA-Y catalyst and KO*t*-Bu as a base. Hence high temperature is favorable for synthesis of triphenylamine.

## 4.4 Conclusion

The problem of catalyst recyclability encountered in homogeneously catalyzed reaction has been solved by heterogenizing copper catalysts. These catalysts were shown to give good activity and recyclability.

Na-Y encapsulated copper complexes catalyst for amination of aryl iodide showed high selectively for diphenylamine formation. This catalyst was stable and their was no leaching up to five recycles.

Encapsulated copper catalyst in MCM-41 for amination of aryl iodide gave selectively triphenylamine (TPA), but this catalyst is not stable, it leaches and activity goes down after every recycle.

The major challenge to develop heterogeneous copper catalyst to give selectively triphenylamines with high TON was achieved by preparing tethered copper complex using phosphotungstic acid as a tethering agent on various inorganic supports e.g. zeolite Y, alumina, clay etc. These tethered catalyst fully characterized by using XPS, Solid U.V, FT-IR, Surface area, XRD, TGA, IAS and ICPES, SEM and TEM. These catalysts show promising activity and selectivity for the synthesis of triarylamines. Cu(Phen)($PPh_3$)Br-PTA-Y gave the best activity. Using this catalyst various bases and solvent were screened. The effect of temperature on activity and selectivity was also investigated. The recycle study of 3.76 % Cu(Phen)($PPh_3$)Br-PTA-Y indicated that there was no loss in activity even after five recycles and at the end of fifth recycle ~ 72 % yield of TPA is realized. No leaching of copper metal was observed in the organic phase. Thus, heterogenised copper catalyst shows build up TON up to 69 at the end of fifth recycle compared to its homogenous counter part CuI/ 1,10 phenanthroline which gave TON of 20.7.

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# APPENDIX 1

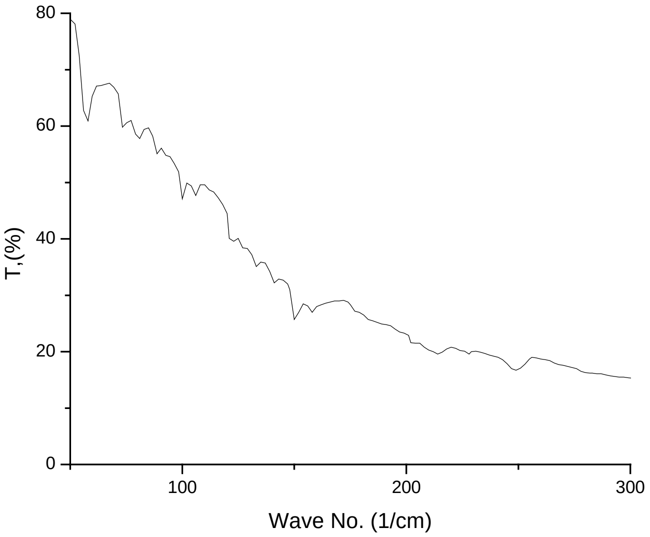

**Figure A1.1:** Far-IR of Cu-1 complex

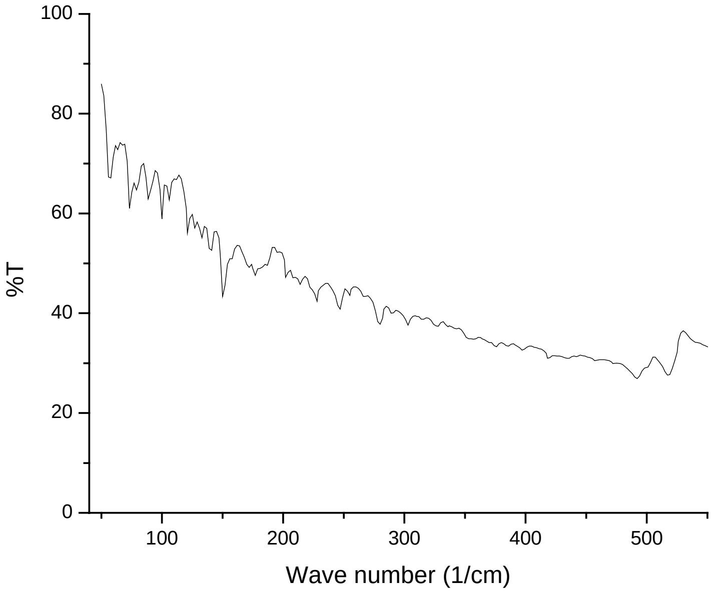

**Figure A1.2:** Far-IR of Cu-2 complex

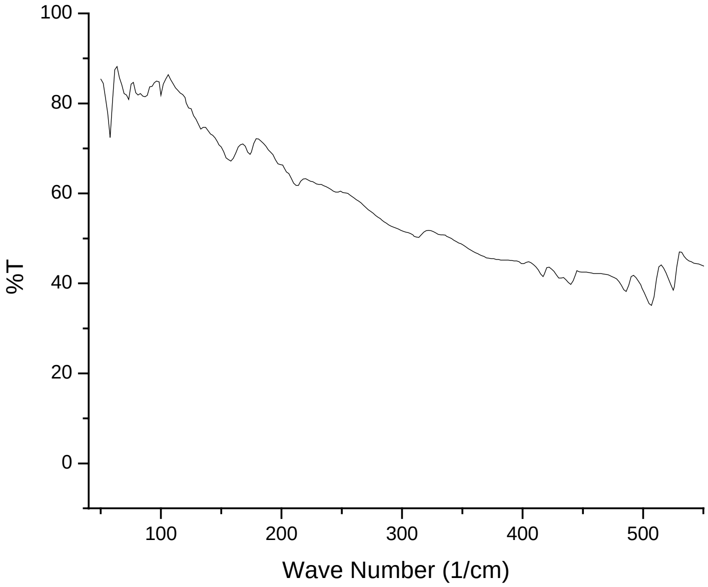

**Figure A1.3:** Far-IR of Cu-3 complex

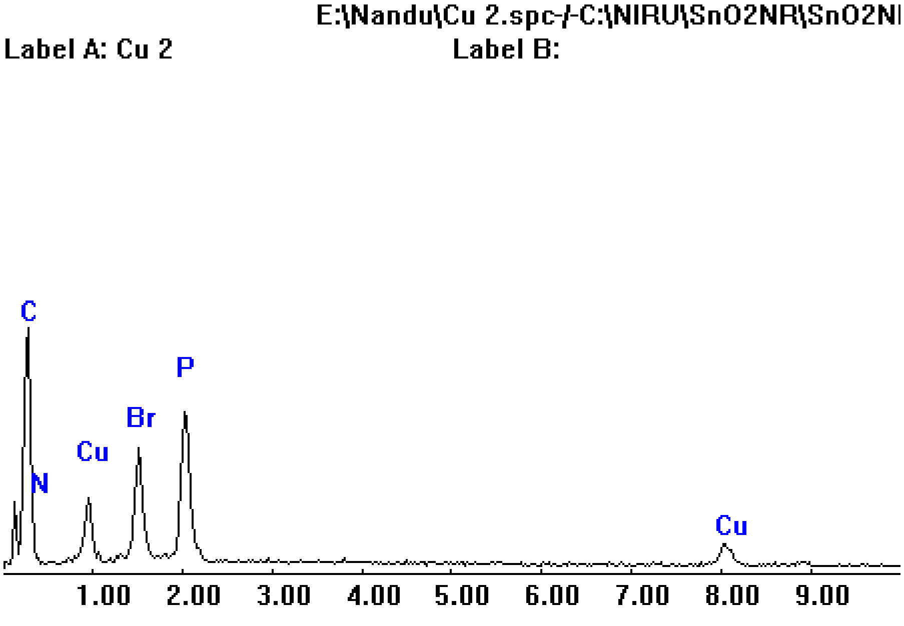

**Figure A1.4:** EDX spectra of Cu-2

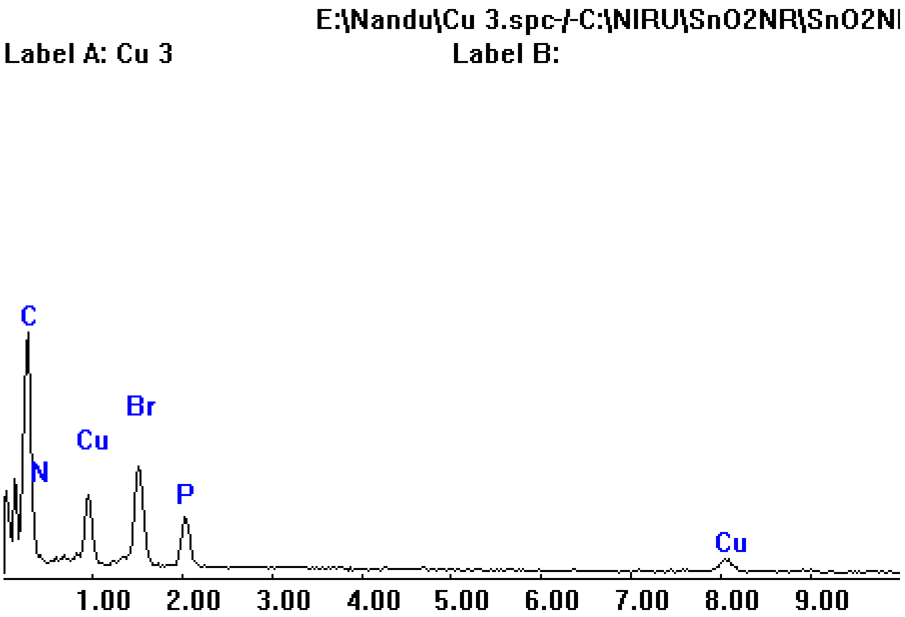

**Figure A1.5:** EDX spectra of Cu-3

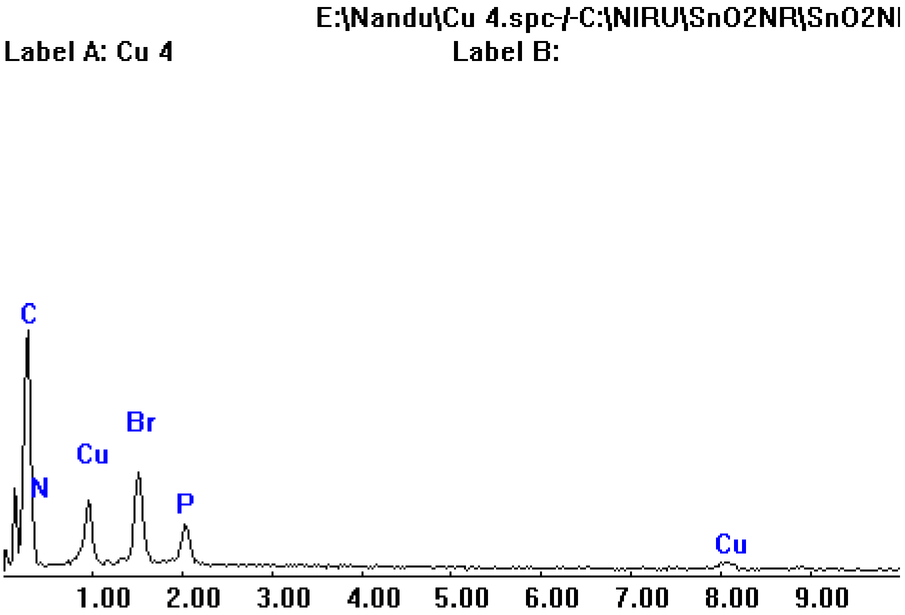

**Figure A1.6:** EDX spectra of Cu-4

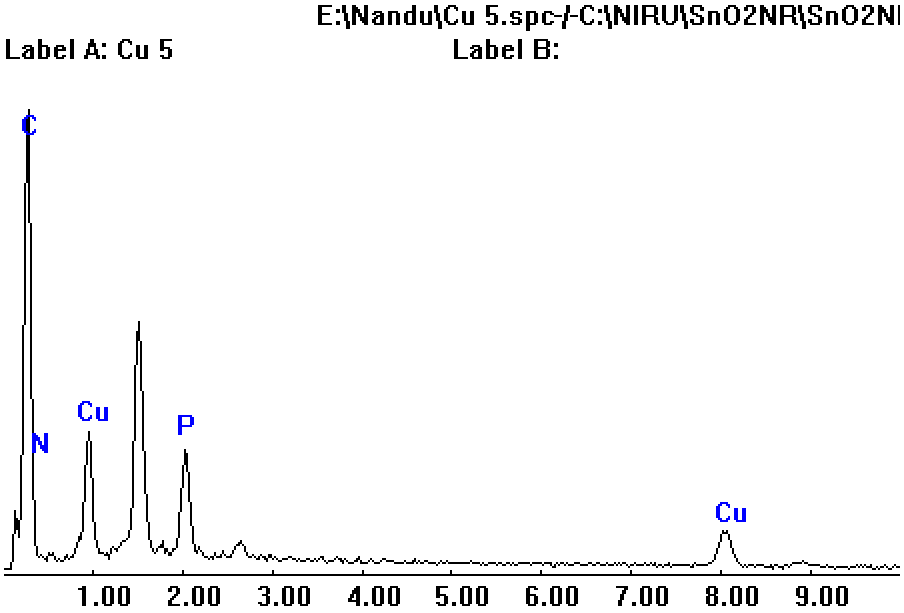

**Figure A1.6:** EDX spectra of Cu-5

# Publication & Symposia

## Publication

1. Copper-catalysed amination of aryl halides: single-step synthesis of triarylamines
   Ashutosh A. Kelkar, **Nandkumar M. Patil** and Raghunath V. Chaudhari
   **Tetrahedron Letters *43***, 2002, 7143-7146 **(42 Citation)**

2. Synthesis of triarylamines by copper catalysed amination of aryl halides
   **Nandkumar M. Patil**, Ashutosh A. Kelkar and Raghunath V. Chaudhari
   **J. Mol. Cata. A: Chem**. ***223,*** 2004, (1-2), 45-50

3. Highly efficient sulfimidation of 1,3-dithianes by Cu (I) complesex
   L Giribabu, S.P. Singh, **Nandkumar M. Patil,** S.P. Gupte, R.V. Chaudhari and M.L. Kantam.
   Communicated: **J. Mol. Cata. A: Chem.**

4. Synthesis, characterized of well-defined copper (I) complexes and its catalytic activity for amination of arylhalides
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## Patent

1. An improved process for the preparation of Arylamines
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1. Copper catalysed amination reactions
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3. ***Oral Presentation:*** **‘**Heterogenised homogeneous copper complexes for the amination of arylhalides’
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