STUDIES IN CATALYTIC CARBONYLATION OF AMINES FOR THE SYNTHESIS OF DISUBSTITUTED UREAS AND CARBAMATES

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SUBMITTED TO
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BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis, **“Studies in Catalytic Carbonylation of Amines for the Synthesis of Disubstituted Ureas and Carbamates”** submitted by **Mr. Mahesh R. Didgikar,** for the Degree of **Doctor of Philosophy,** was carried out by the candidate under my supervision in the C.E. & P.D. 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. S. P Gupte

(Research Supervisor)

Declaration

I hereby declare that the thesis entitled "**Studies in catalytic carbonylation of amines for the synthesis of disubstituted ureas and carbamates**", submitted for the Degree of **Doctor of Philosophy** to the University of Pune, has been carried out by me at the National Chemical Laboratory, Pune under the supervision of Dr. S. P. Gupte. The work is original and has not been submitted in part or full by me for any other degree or diploma to this or any other University.

Date:
Place:

(Mahesh R. Didgikar)

Dedicated to

My Parents

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Abstract of the Thesis

The application of catalysis for synthesis of a variety of materials required to satisfy human needs right from food and clothing to drugs, plastics, detergents, fuels, agrochemicals and pesticides has been realized and exploited only in the past few decades, which now account for more than one sixth of the value of all goods manufactured worldwide. Catalysis has been widely used for providing cleaner alternative routes for stoichiometric organic synthesis and converting hazardous emissions to harmless streams. Stoichiometric organic reactions produce large amount of byproducts and mineral salts creating environmental threat. Thus, the importance of catalysis to society is not only in economic aspects but also from the environmental considerations.

Organic compounds containing carbonyl functionality like carbonates, carbamates and substituted ureas have been synthesized conventionally using phosgene and isocyanates, which are stoichiometric reagents, and are extremely toxic and hazardous. Carbamates and substituted ureas find their applications in several areas of chemistry, like agricultural industry, pharma industry, polymer industry as well as synthetic organic chemistry. For example, disubstituted ureas are important agricultural chemicals, resin precursors, dyes and additives to petroleum compounds and polymers.[1] The cyclic substituted urea functionality has been found to appear in drugs like HIV-protease inhibitors[2], FKBP12 inhibitors, and CCK-B receptor antagonists. Similarly, carbamates are very useful intermediates in organic synthesis and find several applications in many areas of chemistry[3] like agrochemicals, protecting groups in peptide chemistry, dyestuffs, linkers in combinatorial synthesis, etc. Carbamates have also gained immense significance in the combinatorial synthesis[4, 5] in the preparation of small chiral molecule libraries of pharmacological importance, which has contributed to the understanding of structure and folding, biological function, and therapeutic potential of biological macromolecules like polypeptides.

Several alternative phosgene-free synthetic routes to ureas and carbamates are currently explored, such as: (a) the oxidative carbonylation of amine in the presence of alcohols[7] (b) the reductive carbonylation of nitroaromatics[8] (c) the reaction of amines with CO_2 in the presence of alkylating agents[9] (d) the reaction of amines with urea and

alcohols or phenols, at high temperature (>473 K)[10] (e) alcoholysis of substituted urea[11] and (f) the aminolysis of organic carbonates.[12]

Out of these eco-friendly routes for the synthesis of ureas and carbamates, going by atom-economy and ease of operation, oxidative carbonylation of amines and methoxycarbonylation using DMC represent the most suitable alternatives. Several transition metal catalyst systems have been reported with good results for the oxidative carbonylation of amines. However, an effective catalyst system or form of the noble metal catalyst, which can satisfy the basic requirement of the convenience or ease in separation or recovery of the catalyst, which comprises the cost center of a transition metal catalyzed system, has not been reported. Also, there have been no reports on a Pd (II) catalyst in nano-form supported on an inert support like a zeolite. Similarly, though methoxycarbonylation of amines has been explored with lead catalysts in several reports, a detailed kinetic investigation of the reaction has not been undertaken.

The amine methoxycarbonylation route for carbamate synthesis has attracted a lot of attention in the last few years especially because of the development of a non-phosgene process for preparing DMC from methanol, carbon monoxide, and oxygen in liquid phase, in the year 1983.[13] Several catalyst systems have been successfully attempted for amine alkoxycarbonylation using organic carbonates, a larger part being investigated on methoxycarbonylation using DMC. The metal catalysts successfully explored for amine methoxycarbonylation involve lead salts and oxides, zinc salts, ytterbium triflates. Some other catalysts reported include K_2CO_3 and 18-crown-6, organophosphorous Brönsted acids, etc.

Among all the catalysts reported, in terms of reaction rates and product selectivity, lead compounds represent the best catalysts. However, there is no kinetic investigation of a lead catalyzed reaction system.

With these observations in mind, the following specific problems were chosen for the thesis work:

- ❖ Synthesis and characterization of various palladium complexes prepared by using laboratory synthesized and commercially available sulfonated *N*-ligands and evaluation of their catalytic activity for the oxycarbonylation of aliphatic and aromatic amines.

- Study of effect of reaction parameters on the catalytic activity of the water-soluble palladium complexes in the oxidative carbonylation of amines
- Synthesis, characterization and evaluation of the catalytic properties of nano-palladium immobilized on APTS modified NaY zeolite in the iodide promoted oxycarbonylation of amines for the selective synthesis of substituted ureas.
- Methoxycarbonylation of aniline using dimethyl carbonate, catalyzed by lead compounds, and a detailed kinetic investigation and evaluation of rate models based on empirical approach.
- Investigation of catalytic activity of Pb_3O_4 as a heterogeneous catalyst for the selective synthesis of carbamates using different classes of amines.

The research work carried out for this thesis has been presented in four chapters, the brief outline of which is given below.

Chapter 1: Introduction and Literature Survey

This chapter presents a detailed survey of the literature on synthesis of disubstituted ureas and carbamates by conventional, stoichiometric methods; and the evolution of their synthesis modes into homogeneous and heterogeneously catalyzed, safer, less energy intensive, better atom-economical and greener routes. In the context of the safe and eco-friendly routes with good atom-economy, oxidative carbonylation and alcoxycarbonylation of amines have emerged to be two of the most effective synthetic methods for substituted ureas and carbamates. Palladium catalysts comprise the most active transition metal catalysts for oxidative carbonylation, though several other noble metals are also active as catalysts. Use of highly active palladium complexes and the techniques to immobilize these complexes on various supports has been reviewed critically. Also, the mechanism and the kinetic studies on oxidative carbonylation have been discussed. Similarly, a detailed account of the various catalysts systems which range from transition metals, post-transition metals, bulk catalysts like zeolites and clays, and the relatively newer category of catalysts like ionic catalysts and phosphoric acid has been investigated.

The following observations emerged from the literature review:

- Though selenium, palladium, platinum, nickel, cobalt, rhodium, iridium, ruthenium, tungsten and gold complexes have been shown to be active catalysts for amine oxidative carbonylation reactions, most of the research focuses on palladium catalysts. Palladium in almost every form has been tried and tested for these reactions and has been found to be active to varying degrees.
- Most of the literature in amine oxycarbonylation deals with attempting transition metal catalysts in various forms, like homogeneous or heterogeneous catalysts. Heterogeneous catalysis has been investigated in greater details; with a larger emphasis on development of solid, heterogenized homogeneous catalysts, mostly of palladium.
- The literature shows lacunae in the research on amine oxycarbonylation in terms of development of a robust, easily separable (recoverable) catalyst. Ureas pose the problem of precipitation in reaction medium, in which case, the catalyst recovery becomes a tedious and costly affair.
- The methoxycarbonylation of amines for the synthesis of carbamates has attracted a lot of attention in recent years, owing to the advent of oxidative carbonylation method, a non-phosgene synthesis method for the industrial-scale synthesis of dimethylcarbonate (DMC) by EniChem in 1985.
- Several catalysts including metal catalysts like lead, zinc or bulk catalysts like phosphoric acids, ionic liquids, etc have been reported for the methoxycarbonylation of amines for the synthesis of carbamates.
- Lead is found to be the most effective catalyst for methoxycarbonylation, however, there is no report on the development of a kinetic model for such a system.

Chapter 2: Aqueous-Biphasic Oxidative Carbonylation of Amines Using Water-soluble Transition Metal Catalysts

The second chapter deals with exploring and evaluating the catalytic activity of water-soluble palladium catalysts; prepared using sulfonated nitrogen ligands, in an aqueous-biphasic solvent system for the oxidative carbonylation of amines for the synthesis of disubstituted ureas.

The ligands used in the study comprise of commercially available as well as laboratory-synthesized ligands using the methods reported in literature. The biphasic catalytic system consisting of a water-soluble catalyst system carries the unique advantage of separation of catalyst system from the reaction components. Previously reported palladium catalysts have either been homogeneous or heterogeneous, supported or metallic palladium catalysts.

The products of the present reaction system, which are disubstituted ureas, have sparing solubility in all commonly used organic solvents, and therefore the products precipitate out from reaction medium. In such cases, the heterogeneous catalyst has to be separated by relatively crude methods of separation such as sieving,[14] which may lead to the loss of precious catalyst. Although soluble catalysts are comparatively easy to separate in such cases, the catalysts still have a high probability of being contaminated with unreacted substrate or partially dissolved product. The degree of solubility of the product in the reaction medium depends on the aliphatic or aromatic amines employed for their synthesis. In either of the cases, the efficiency of catalyst recovery is low, considering the very small loadings of catalysts. In an atom economic and clean process like oxidative carbonylation, the cost center of the process is the catalyst, and therefore, efficient recovery of catalyst carries immense importance.

In the present study, the feasibility of oxidative carbonylation of aliphatic or aromatic amines in such a biphasic system was first established using a water-soluble palladium catalyst prepared from palladium acetate and disulfonated bipyridine ligand. The activity of this catalyst was compared with that of conventional homogeneous and heterogeneous palladium catalysts. Optimization of reaction conditions and parameters was then carried out, and also the optimum ratio of organic and aqueous phases was established. Thereafter, the recycle activity of the catalyst was confirmed by recovering the aqueous phase in each reaction and using it as the catalyst for further recycles. It was observed that the aqueous phase catalyst did not lose its catalytic activity upon five recycles. The parametric studies involved screening of transition metal catalysts, screening of sulfonated nitrogen ligands, screening of iodide promoters, solvents and amine substrates.

The amine screening study showed that, primary amines, both aliphatic as well as aromatic substrates gave good (>90%) yields of substituted ureas. The substituted ureas thus synthesized were thoroughly characterized by elemental analysis, IR and NMR characterization.

Chapter 3: Lead Oxide Catalyzed Methoxycarbonylation of Amines with Dimethylcarbonate

In this chapter, methoxycarbonylation of amines with dimethylcarbonate (DMC) to carbamate was carried out using lead compounds as catalysts. Aniline was chosen as model substrate for the detail investigation. A comparative account of the catalytic activity of lead and zinc compounds has been considered.

The parametric effect studies were carried out with aniline as substrate, lead oxide as catalyst and DMC as solvent in the temperature range of 423-443K. In a typical experiment, some induction was observed, as there was no reaction in the initial period. The detailed investigation of induction period was carried out and it was found that the induction period varies with reaction temperature, catalyst concentration and aniline concentration.

The kinetics of methoxycarbonylation of aniline to carbamate using the lead oxide as catalyst was carried out in the temperature range of 423 – 443 K. For the kinetic studies, the induction period was eliminated and the data points excluding the induction periods were considered. The effect of agitation speed, concentration of aniline and catalyst loading on the rate of reaction has been studied. Detailed analysis of liquid-solid and intraparticale mass transfer was carried out using initial rate data to ensure the kinetic regime. Based on these data, several rate equations were evaluated. To select the most suitable rate equation, an optimization method based on Marquardt’s algorithm combined with fourth order Runge-Kutta method was used. The kinetic parameters and activation energy were evaluated. The activation energy for the reaction, as found from the Arrhenius plot was 94 kJ/mol.

Chapter 4: Oxidative Carbonylation of Amines for the Synthesis of Disubstituted Ureas Catalysed by Pd Nanoparticles Immobilized on Amine-functionalized Zeolite

Among the various new concepts, catalysis by metal nanoparticles has received immense interest of the researchers because of its potential in achieving higher catalytic activity. At the same time, agglomeration at higher reaction temperature, separation and reuse of metal nanoparticles from the reaction systems are considered as the major challenges for their practical applications. In this chapter, palladium nanoparticles bound at high surface coverage on 3-aminopropyltrimethoxysilane (APTS)-functionalised Na-Y zeolites are presented as excellent heterogeneous catalysts ([Pd]-APTS-Y) for the oxidative carbonylation. A detailed characterization by UV-vis., FTIR, TGA, XRD, XPS and TEM has been done to understand the exact nature of the nanocomposites. It was observed from FTIR and TGA that the palladium metal nanoparticles were immobilized due to the amine functionality of the zeolite surface modifier. XRD results ensured that zeolite structure was not affected during the reaction. XPS analyses confirmed the metallic state of palladium (Pd^0), before and after the reaction. TEM images of the fresh and used catalysts indeed showed that the palladium nanoparticles supported on amine-functionalised zeolite remain unchanged at the end of the reactions.

All the reactions were carried out using atmospheric pressure of $CO+O_2$ ($CO:O_2$ in 8:1 ratio) mixture. Preliminary experiments to establish the catalytic activity as well as the reusability of [Pd]-APTS-Y were carried out. The recycle study showed that there was negligible leaching of Pd, and the recovered catalyst did not lose its catalytic activity on recycle.

The effect of reaction parameters on oxycarbonylation of aniline using the [Pd]-APTS-Y catalyst was then undertaken. The studies were carried out in a temperature range of 323-343K. Aniline was the model substrate for all these studies. The effect of variation in agitation speed, temperature, effect of substrate concentration, catalyst concentration and iodide concentration were investigated. Screening of solvents was carried out and DMF was found to be the best solvent. Screening of iodide promoters using various sources of iodide was carried out, and NaI was chosen as the promoter for the remaining studies. The effect of iodide concentration was also carried out to find out the optimum iodide concentration for oxycarbonylation of aniline.

In a nutshell, the outcome of the work done in the present thesis can be summarized as follows-

1. Synthesis and characterization of sulfonated water-soluble N-ligands has been done, and these ligands have been successfully investigated for the aqueous-biphasic oxidative carbonylation of amines. The present work is the first report for oxidative carbonylation of amines in a biphasic medium. The ligands have been found to be stable towards oxidizing conditions unlike the conventional sulfonated phosphine ligands, and the catalyst in aqueous medium was found to be easily recoverable and gave excellent recycle activity. Several disubstituted ureas were synthesized with high selectivity, using this water-soluble catalyst. The important objective of convenient separation of the catalyst from the reaction medium and the precipitated or dissolved product has been successfully achieved.
2. The methoxycarbonylation of amines using lead (IV) oxide as a solid, reusable catalyst has been investigated in detail. Mechanistic studies using stoichiometric reactions as well as IR spectroscopic investigation have been undertaken, based on which a probable mechanism for the reaction has been proposed. Based on the trends observed in the parametric investigations, a rate model has been proposed and the activation energy for the reaction has been calculated.
3. A novel immobilized Pd nanoparticle catalyst ([Pd]-APTS-Y) has been prepared using functionalized Na-Y zeolite, and a detailed characterization of the same has been carried out. This catalyst has been assessed for its activity for oxycarbonylation of amines at atmospheric pressure conditions of CO and O_2. The recycle activity of the catalyst has been established.

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Appendix I- List of abbreviations

Bipy	4,4’-Bipyridine
BipyDS	Disodium salt of bipyridine-4,4’-disulfonic acid
Conc.	Concentration
C-T	Concentration-time
DCM	Dichloro methane
DMF	N,N-Dimethyl foramide
eq.	Equation (s)
EtOH	Ethanol
FTIR	Fourier transform infrared
GC	Gas chromatography
GC-MS	Gas chromatography-Mass spectrometry
h	Hour (s)
i. e.	That is
ICP-AES	Inductive copuplled Plasma- atomic emission spectrophotometry
MEK	Methy Ethyl Ketone
MeOH	Methanol
ml	Milliliter
Mol	Mole
MPa	Megapascal
NMR	Nuclear magnetic resonance
ppm	Parts per million
RT	Room temperature
T	Temperature
t	Time
TEM	Transmission electron microscopy
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TOF	Turnover frequency
TON	Turnover number
TPA	Tons per annum
TPP or $P(Ph)_3$	Triphenyl phosphine
TPPDS	Triphenylphsosphine disulphonate disodium
TPPMS	Triphenyl phosphine monosulfonate monosodium
TPPO	Triphenyl phosphine oxide
TPPTS	Triphenyl phosphine trisulfonate trisodium
TRPTC	Thermo regulated phase-transfer catalysis
viz.	Namely
XPS	X-ray photoelectron spectroscopy
XRD	X-ray diffraction

Publications

1. Synthesis of Polyesteramides by Palladium-Catalyzed Carbonylation–Polycondensation of Aromatic Diiodides and Amino Alcohols S. M. Kulkarni, M. R. Didgikar and R. V. Chaudhari *J. Mol. Catal. A: Chem.* 207, 2004, 97.

2. Environmentally Benign Catalytic Hydroformylation-Oxidation Route for Naproxen Synthesis K. B. Rajurkar, S. S. Tonde, M. R. Didgikar, S.S. Joshi and R. V. Chaudhari, *Ind. Eng. Chem. Res.,* 46, *25*, 2007, 8480.

3. Selective Oxidation Of Toluene To Benzaldehyde Using Cu/Sn/Br Catalyst System N. D. Kulkarni, K. B. Rajurkar, M. R. Didgikar and S. S. Joshi (*Communicated to Int. J. Chem. Soc.*)

4. Biphasic Oxidative Carbonylation of Amines using Water-soluble Palladium Catalysts M. R. Didgikar, S.S. Joshi, S. P. Gupte, M. M. Diwakar, R. M. Deshpande and R. V. Chaudhari *(Communicated to J. Mo. Cat. A: Chem))*

5. Cobalt chloride-Containing Desiccant Silica Gel as a Reusable Catalyst for Oxidation of *p*-Cresol to *p*-Hydroxybenzaldehyde M. R. Didgikar, K. B. Rajurkar, N. D. Kulkarni, S.S. Joshi *J. Chem. Technol. Biotechnol.)*

6. Silica Sulfuric Acid as an Efficient Solid Acid Catalyst for Solvent-free Synthesis of Coumarins by Pechmann Condensation. M. R. Didgikar, A. L. Shete, S.S. Joshi *(Manuscript in preparation)*

Symposia/ conferences

- Kinetics of Methoxycarbonylation of Aromatic Amines with Organic Carbonates Catalyzed by Lead Compounds M. R. Didgikar, K. B. Rajurkar, S. S. Joshi, S.P. Gupte and R. V. Chaudhari; CAMURE-6 and ISMR-5, January 2007 (Poster Presentation)
- Silica Sulfuric Acid As A Heterogeneous Catalyst For The Synthesis of Coumarins Via Pechmann Condensation M. R. Didgikar, A. L. Shete, S. S. Joshi and R. V. Chaudhari; CAMURE-6 and ISMR-5, January 2007. (Poster Presentation)

- Environmentally Benign Catalytic Hydroformylation-Oxidation Route for Naproxen Synthesis' R.V. Chaudhari, K.B. Rajurkar, S.S. Tonde, M.R. Didgikar, S.S. Joshi; CAMURE-6 and ISMR-5, January 2007 (Oral Presentation)

- Selective Liquid Phase Oxidation of Ethyl Benzene Using Hydrotalcite-Like Compounds K. B. Rajurkar, M.R. Didgikar, and R.V. Chaudhari, APOGEE-2K7 conference at BITS-Pilani, India, March 2007 (Oral Presentation)

- Oxidative Carbonylation of Amines in a Biphasic medium Using Water-soluble Transition Metal Catalysts M. R. Didgikar, S. S. Joshi, S. P. Gupte, R. V. Chaudhari; NCFCE-2007 IIT-Guwahati, December 07 (Poster Presentation)

- Liquid Phase Oxidation of *p*-Cresol to *p*-Hydroxy Benzaldehyde M.R. Didgikar, K.B. Rajurkar and S.S. Joshi NCFCE-2007, IIT-Guwahati, December 07 (Poster Presentation)

- ‘Synthesis and Application of Catalytically Active Platinum and Palladium Nanoparticles Grafted on Surface Modified NaY Zeolite’ M. R. Didgikar and S. P. Gupte; International Conference on Drug Discovery and Nanotechnology - 2008, Yeshwant Mahavidyalaya, Nanded, (Oral Presentation)

Chapter 1

Introduction and Literature Survey

This chapter presents a detailed survey of literature relevant to the work done in this thesis. This includes the present modes of synthesis of substituted ureas and carbamates; as well as the evolution in the research in catalysis in this area. The development of the homogeneous, heterogeneous and heterogenized homogeneous carbonylation catalysts to facilitate effective catalyst–product separation and reuse has been described in this chapter. A thorough discussion of the different aspects of the existing state-of-the-art, and the understanding gained from this review has been presented; and thereby an orientation for the research work relevant to this thesis has been achieved.

1.1. INTRODUCTION

Catalysis has its implication in many fields, which include industry, energy, environment, and life sciences. Chemical industry has been one of the major economic activities in this century and will also be so in the coming century. About 80 per cent of processes in the chemical industry now depend on catalysts to work efficiently, and the number is rising. Since the chemical industry is one of the most important and competitive sectors of all developed economies, it is not surprising that catalysis is an extremely active research area. New catalysts are being designed and new catalytic processes being devised that aim to produce cleaner chemical processes. These use less energy, and environmentally acceptable agents (for example, air or oxygen as an oxidant instead of hydrogen peroxide) and perhaps water as a solvent, resulting in less noxious waste. Catalyst research is vital in combating pollution.

Virtually all the living processes depend on biological catalysts called enzymes, and understanding their role in molecular biology and human health must not be underestimated. Enzymes and enzyme-like materials are also being increasingly used as catalysts for industrial processes. Catalysis, since its origin, had an allure due to the inherent aspects of maximized output via energy and time-efficient alternative pathways and the use of non-conventional and eco-friendly resources.

The surge in chemical process industry and its application for the enhancement of the quality human life and health has in fact on the other hand caused serious damage to environment in the twentieth century, producing hazardous substances, which cause acid rain, unacceptably increased carbon dioxide levels in the atmosphere, a reduction of stratospheric ozone levels and so on. Therefore, much effort has been focused on eliminating or decreasing environmentally hazardous substances. In fact, the industry as a whole reduced its emissions to air, land, and water by 41% between 1987 and 1991, while the overall production increased by more than 10%.[1] NO_x, SO_x, fluorocarbons and perchlorinated benzene are some of the major targets in this respect. Besides these end-of-pipe problems, there are many processes, which may require environmental considerations. Much energy is consumed for disposing of by-products or converting them into environmentally non-hazardous substances. Production of extra-energies itself is the cause of the further production of carbon dioxide, NO_x, SO_x and so on. The processes requiring the handling of dangerous chemicals such as hydrogen fluoride, phosgene, and hydrogen cyanide require the special efforts for securing the safety. In the processes using sulfuric acid, sodium hydroxide or aluminum chloride, waste water must be neutralized, and a large amount of inorganic products such as ammonium sulfate and sodium chloride are formed as by-products. For example, in the synthesis of 1 ton of ε-caprolactam for Nylon 6, about 5.4 tons of ammonium sulfate is formed in the production of hydrazine and Beckmann rearrangement of cyclohexanone oxime. The processes using a large amount of solvents are also those consuming a lot of energy for purification and recycling of the solvents. Multi-step synthesis processes must be short cut. Non-selective reactions have to be replaced by highly selective reaction systems. In this respect, further development of shape-selective zeolites or highly enantioselective catalysts are extremely important. These processes, which give burdens on the environment, must be improved or essentially replaced by more environmentally friendly or compatible processes. The selection of the best synthesis and processes must be determined not only from the high rate of the production of the desired products, but also "environmental benignness". The importance of environmentally benign processes has been repeatedly stressed in recent years.[2]

Substituted ureas and carbamates are important classes of fine chemicals. They find numerous applications in agricultural, pharmaceutical and polymer industry. These are functional derivatives of carbonic acid (substituted ureas- amide derivatives and carbamates- ester-amide derivatives). Their reactivity towards specific functionalities and their interconvertability, which in turn is catalyst-specific, offers a wide array of reactions of synthetic importance. These active precursors have conventionally been synthesized by the potentially hazardous phosgenation route. There has been extensive research in exploring greener alternatives for their syntheses in the past few decades.

The aim of this thesis is to explore the chemistry and catalysis of the synthesis of disubstituted ureas and carbamates by catalytic carbonylation reactions. Hence the focus of this chapter is a detailed survey of the relevant literature on catalysis, kinetics and chemistry of homogeneous, heterogeneous and heterogenized homogeneous catalysts (biphasic and solid supported transition metal complex catalysis) for oxidative carbonylation and alcoxycarbonylation reactions as environmentally benign routes for the synthesis of ureas and carbamates.

1.2. CATALYSIS AND FINE CHEMICAL INDUSTRY

The widely accepted definition of a catalyst is ‘a substance that alters the rate at which reaction equilibrium is attained, without itself being consumed in the reaction processes’. By ‘not being consumed’, the statement implies that the catalyst is regained at the end of the chemical transformation unaltered in its chemical nature, although it may undergo several chemical changes during the course of the reaction. Catalysis is broadly classified into three categories depending on the physical nature of the catalyst employed:[3]

- Homogeneous catalysis: The reactants, products and catalyst are present in the same phase.
- Heterogeneous catalysis: Reactants/ products and catalyst are present in separate phases. Conventionally, the catalyst is generally solid and the reactants are either liquid or gas, however, the catalyst may even be in a liquid phase separate from that of the reactants/ products as in biphasic catalysis.
- Biocatalysis or enzymatic catalysis: It mainly involves all biological and related reactions.

Chemicals are broadly classified as commodities, fine and performance chemicals. Petrochemicals, basic chemicals, organic chemicals (large-volume), monomers, commodity fibers and plastics belong to the class of commodities, while advanced intermediates, building blocks, bulk drugs and bulk pesticides, active ingredients, bulk vitamins and flavor and fragrance chemicals are listed under fine chemicals. Performance chemicals encompass adhesives, diagnostics, disinfectants, electrochemicals, food additives, mining chemicals, pesticides, pharmaceuticals, photographic chemicals, specialty polymers and water treatment chemicals. In view of the shorter life cycles of fine and performance chemicals as compared to commodities, product innovation, which requires enormous resources, is highly knowledge based. The growth of the fine chemicals business is mainly fostered by the introduction of new pharmaceuticals, agrochemicals, engineering plastics and other specialties requiring high value organic intermediates. Fine and specialty chemicals are generally considered chemicals that are manufactured to high and well-defined standards of purity compatible to the desired performance as opposed to heavy chemicals made in large amounts to technical levels of purity. Catalytic science and technology were largely confined to petroleum and petrochemical industry until the seventies. Fine and specialty chemical industry had focused its attention mainly on product innovation and less on process development until recently. Consequently, every kg of product obtained in multi-step process generates 15–20 kg waste causing pollution in alarming levels that prompted strident public pressure on many of the governments to lay increasingly stringent environmental legislation. This has led to the adoption of clean technology in the fine and performance chemical industry. Chemical industry at the same time has focused its attention on development of cutting edge technologies to meet global competitiveness and zero emission of effluents. To meet these challenges, the industry requires innovative catalytic technologies that offer high space–time yield, improved yield of the desired product, high regio- and enantioselectivity for the market driven isomer, low water requirement and non-corrosivity of the reacting chemicals. Established chemical processes that are often based on technology developed in the first half of the 20th century may no longer be acceptable in these environmentally conscious days. Therefore, enviro-economics will become the driving force behind the development of new processes for existing and new products.[4] Earlier, it was the commodity industry which utilized catalytic processes, but now the above-mentioned constraints have forced the fine chemical industries to prefer catalytic processes thus cutting down the expenditure significantly, while keeping in stride with the environmental regulations laid out. The use of heterogeneous catalysts, in particular zeolites and clays, has significantly contributed to the development of new methodologies in organic synthesis targeted to dispense the conventional and waste generating reagents and achieve high atom economy to be applied in fine chemical sector.[5]

The application of a particular mode of catalysis and the choice of a catalyst in fine chemical syntheses depends on several factors. While most of the bulk or commodity chemicals are synthesized by the economical and robust heterogeneous catalysts, the fine and specialty chemicals segment has witnessed application of heterogeneous as well as homogeneous catalysts complexes. A new trend is the application of homogeneous catalysts for the synthesis and production of multifunctional, more complex molecules such as agrochemicals and pharmaceuticals.[6]

Table 1.1 illustrates a few chemical processes for the synthesis of fine chemicals and the relevant catalysts, which narrates the diversity of industrially applicable catalysis.

Table 1.1. Industrial processes using homogeneous and heterogeneous catalysts

Sr	Process	Type of catalysis	Catalyst	Company
1	Alkylation of benzene to ethylbenzene	Heterogeneous	H-ZSM-5	Mobil-Badger[7]
2	Alkylation of phenol to 2-cresol and 2,5-xylenol	Heterogeneous	Fe-V-O/SiO_2	Asahi Chemicals, Japan[7]
3	*n*-C_4 isomerization to *i*-C_4	Heterogeneous	Fe-Mn/ZrO_2-SO_4^{2-}	Sun Zeolite; BP-Chemicals[7]
4	Dehydration of ethanol to ethylene	Heterogeneous	Al_2O_3	Petrobrass[7]
5	Amination of phenol to aniline	Heterogeneous	MgO, B_2O_3, Al_2O_3 or TiO_2/SiO_2 or Al_2O_3	USS[7]
6	Etherification of olefins to MTBE/ TAME	Heterogeneous	Ion Exchange Resins	Erdoelchemi[7]
7	Amination of ethylene oxide to diethanolamine and ethanolamine	Heterogeneous	Al-Si-zeolite	Berol/ Nobel[7]
8	Cracking of heavy oil	Heterogeneous	MgO-Al_2O_3-zeolite	Nippon Oil[7]
9	Etherification of *i*-C'$_4$ to MTBE	Heterogeneous	Ion Exchange Resin	IFP, Arco[7]
10	Hydration of ethylene to ethanol	Heterogeneous	Solid phosphoric acid	Shell, BP[7]
11	Disproportionation of benzene to benzene and *p*-xylene.	Heterogeneous	Zeolites	UOP[7]
12	Oxidation of ethylene to acetaldehyde	Homogeneous	$PdCl_2$/$CuCl_2$	Wacker-Werke[8]
13	Oxidation of *p*-xylene to terephthalic acid/ester	Homogeneous	Co/Mn-salts	Imhausen
14	Polymerisation of ethylene to HDPE/LDPE	Homogeneous	Ni-complex	Shell[9]
15	Hydrocyanation of butadiene to adipic acid	Homogeneous	Ni-complex	Du Pont[10]

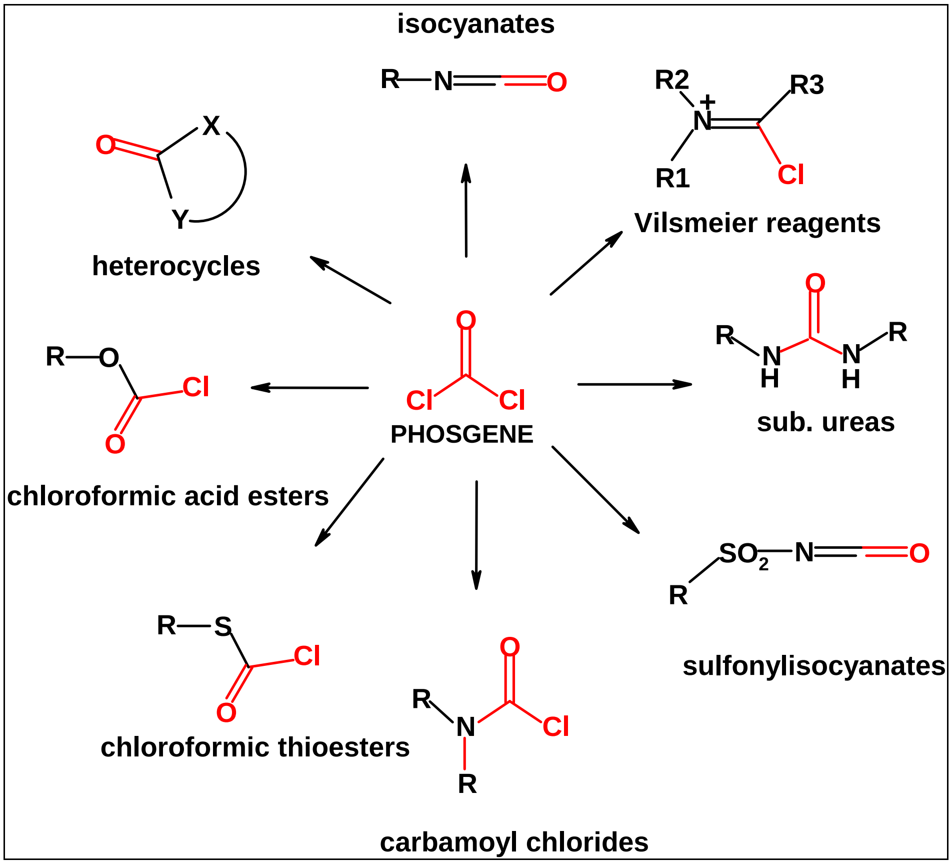
Sr	Process	Type of catalysis	Catalyst	Company
16	Asymmetric hydrogenation of acetamido cinnamicacid(3-methoxy -4-acetoxy derivative) (l-dopa process)	Homogeneous	Rh(diene)(solvent)] +/DIPAMP $NaCo(CO)_4$ $HCo(CO)_3PBu_3$	Monsanto[11] BASF[12] Shell[13]
17	Hydroformylation of propene to butyraldehyde	Homogeneous	$HRh(CO)(PPh_3)_3$; Rh/TPPTS	Union Carbide[14] Ruhrchemie-Rhone-Poulenc[15]
18	Hydroformylation of diacetoxybutene to 1-methyl-4-acetoxy butanal (Vitamin A intermediate)	Homogeneous	$HRh(CO)(PPh_3)_3$ Rh catalyst Rh/ Iodide	Hoffmann-La Roche[16] BASF[17] Monsanto[18]
19	Carbonylation of methanol to acetic acid	Homogeneous	$Co_2(CO)_8$ Ir/Iodide Rh/MeI	BASF[19] B.P. Chemicals[20] Halcon[21]
20	Carbonylation of methyl acetate to acetic anhydride	Homogeneous	Rh/MeI	Eastman Chemicals[22]
21	Carbonylation of ethylene to propionic acid	Homogeneous	$Ni(OCOC_2H_5)_2$	BASF[23]
22	Carbonylation of acetylene to acrylic acid	Homogeneous	Ni-salts or carbonyls	BASF[24]
23	Carbonylation of benzyl chloride to phenyl acetic acid	Homogeneous	$Co_2(CO)_8$	Montedison[25]
24	Carbonylation of 1-(4-isobutylphenyl)ethanol to Ibuprofen	Homogeneous	$PdCl_2(PPh_3)_2/HCl$	Hoechst-Celanese[26]
28	Oxidative carbonylation of methanol to dimethyl carbonate	Homogeneous	$PdCl_2$-$CuCl_2$	Assoreni[27]

1.3. CARBONYLATION USING PHOSGENE

Phosgene or carbonyl chloride, $COCl_2$ (CAS No. 75-44-5) is a toxic, highly reactive gas. Phosgene is electrophilic and undergoes attack by a variety of nucleophiles including primary and secondary amines, hydroxy groups, and thiols. In addition, it also reacts with macromolecules, such as enzymes, proteins, or other polar phospholipids, resulting in formation of covalent adducts that can interfere with molecular functions.

Phosgene is a facile source of carbon monoxide, and is primarily used in the polyurethane industry for the production of polymeric isocyanates. Phosgene is also used in the polycarbonate industry and in the manufacture of carbamates and related pesticides, dyes, perfumes, pharmaceuticals, and isocyanates. The majority of phosgene for industrial applications is made on site by the reaction of carbon monoxide and chlorine gas using an activated carbon catalyst. Phosgene may also be produced as a combustion product of carbon tetrachloride, methylene chloride, trichloroethylene, or butyl chloroformate, although these methods are not utilized industrially. Phosgene is a colorless gas at room temperature with an odor ranging from strong and stifling when concentrated to hay-like when diluted. Phosgene is slightly soluble in aqueous media, but, when dissolved, it is very rapidly hydrolyzed to carbon dioxide (CO_2) and hydrochloric acid (HCl), with a half-life at 37°C of approximately 0.026 seconds.

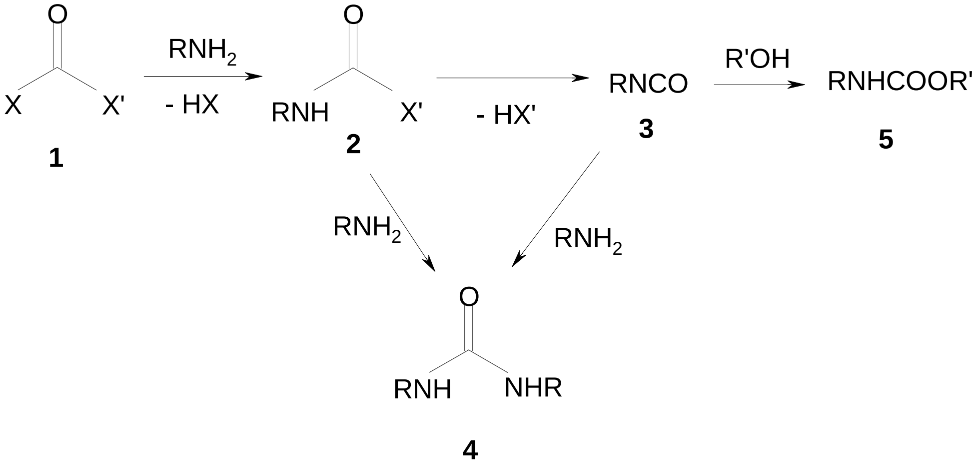
Phosgene has been used conventionally for the synthesis of a variety of fine and specialty chemicals, the most important classes being the polycarbonates, polyurethanes, substituted ureas and carbamates. Scheme 1.1 represents the various applications of phosgene in fine chemical industry.



Scheme 1.1. Fine chemical syntheses mediated by phosgene

1.3.1. Synthesis of substituted ureas and carbamates using phosgene

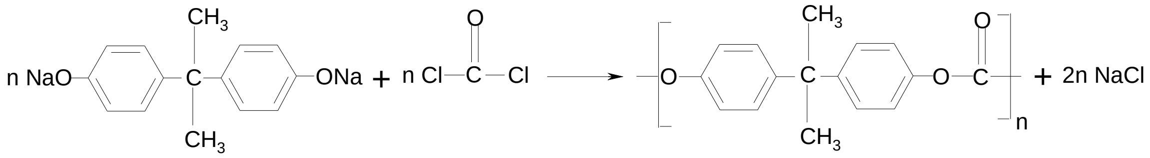
The simplest and direct synthesis of substituted ureas is described by the general and merely strategic Scheme 1.2. The process essentially involves two steps: (1) reaction of the selected amine with the reagent 1 containing the carbonyl group to form the intermediate 2, still possessing a leaving group linked to the carbonyl; (2) further reaction of the intermediate 2 with the same amine or with a different amine to form the symmetrical or the unsymmetrical substituted urea 4 directly or through the more reactive isocyanate 3. Apart from the preparation of the parent urea, commercially produced by dehydration of ammonium carbamate obtained by direct reaction of ammonia with carbon dioxide,[28] the most early and classical method for the preparation of *N,N'*-symmetrical substituted ureas involves the reaction of amines with phosgene (reagent 1, X, XA = Cl). The addition of amines to isocyanates 3 can be regarded as the main route for the synthesis of the more challenging *N,N'*-unsymmetrical substituted ureas 4. However, it is important to underline that isocyanates themselves are toxic and are usually prepared from phosgene.[29,30]. The isocyanate 3 in the presence of an alcohol yields a carbamate 5.



Scheme 1.2. Phosgene based synthesis of substituted ureas and carbamates

1.3.2. Synthesis of polycarbonates using phosgene

Polycarbonates (PCs) are important engineering thermoplastics with excellent mechanical, optical, electrical, and heat resistance properties.[31] Annual market growth for aromatic PCs has been more than 10% from the late 1990s. Currently, the worldwide production capacity of PC is more than 1.5 million TPA, and the construction of new PC plants is very likely to continue.[32,33] Currently, the interfacial polycondensation of bisphenol A (BPA) with phosgene (Scheme 1.3) is the primary commercial method for PC synthesis.[33,34] Apart from the problem of handling of the toxic phosgene, this process also involves use of copious amounts of methylene chloride as the solvent, which is 10 times the weight of the products. The major producers of PCs like GE (Cartagena, Spain), Bayer (Antwerp, Belgium), and Asahi Kasei (Taiwan) have introduced new non-phosgene-based manufacturing units using DPC as the carbonylation agent, which may lead to elimination of solvents and lowering fixed capital investment.[35] In 2002, about 12% of polycarbonates were produced by phosgene-free technology.



Scheme 1.3. Polycarbonate (PC) synthesis from interfacial polycondensation of bisphenol-A salt in an aqueous caustic solution and phosgene in an organic solution.

1.3.3. Synthesis of polyurethanes using phosgene

Polyurethane polymers are extremely important and versatile materials having numerous applications in foams, surface and textile coatings, adhesives and elastomers. They are used in a wide variety of industries such as furniture, construction, aircraft and automobile manufacture and mining equipment. The total market size for urethane intermediates in Europe is in excess of 3×10^6 tonnes of which diisocyanates make up over half. These materials are manufactured from hydroxy terminated polyester resins made by the high temperature Lewis acid catalysed condensation of a diacid and diol,[36] or hydroxy terminated polyethers derived from propylene oxide, in both cases the subsequent reaction with highly toxic diisocyanates produces the polyurethane polymer.[37] The toxicity and environmental hazard of the diisocyanates is such that the maximum allowable concentration in the emissions to atmosphere is as low as 0.005 ppm. All companies using toluene diisocyanate and any company using in excess of 100 tonnes per annum of diphenyl methane diisocyanate is regarded as such a risk to the environment that it has to be a registered isocyanate works with the Department of the Environment. The diisocyanates are synthesised by the reaction of phosgene and the corresponding diamine,[38] a process that involves the elimination of hydrogen chloride and uses a large volume of chlorinated solvent.

$$RNH_2 + COCl_2 \longrightarrow R\text{—}N{=}C{=}O + 2\,HCl \qquad 1.1$$

The synthesis of 1,000,000 tonnes of diisocyanate in Europe creates approximately 330,000 tonnes of hydrogen chloride requiring treatment and disposal. Thus, the production of a narrow range of toxic diisocyanates is limited to only the few companies in the world who are capable of operating the process safely. While there have been many attempts at non-phosgenation routes to diisocyanates and to the synthesis of polyurethanes without using diisocyanates,[39,40,41] none have been successful commercially.

1.3.4. Environmental concerns

Production and use of phosgene opens many worrying toxicological and environmental problems. Phosgene gas is highly toxic. Inhalation is the primary exposure route for phosgene. Suspected sources of atmospheric phosgene are fugitive emissions, thermal decomposition of chlorinated hydrocarbons, and photooxidation of chloroethylenes. Although the existence of atmospheric sinks for phosgene has been questioned, it is postulated that phosgene’s removal from the atmosphere is rather slow.

The American Conference of Governmental Industrial Hygienists (ACGIH, 2000) recommends a time-weighted average of 0.1 ppm (0.4 mg/m^3) to protect against irritation, anoxia, and pulmonary edema. The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit is 0.1 ppm, and the Occupational Safety and Health Administration (OSHA) has promulgated an 8-hour permissible exposure limit of 0.1 ppm connected with use and storage of large amounts of chlorine, production of a lot of waste constituted of aqueous solutions contaminated by chlorine by-products and high environmental risk in storage, transportation and use of a reagent characterized by high toxicity and volatility. Nevertheless, about 2 million tons per year of phosgene are produced and utilized worldwide.[42]

Despite these safety concerns arising out of the toxicity of phosgene and generation of huge amounts of salt wastes (use of 1 kg phosgene gives 1.17 kg of salt waste),[43] the chemical industry still uses about 2×10^6 ton/year of phosgene worldwide,[44] as process economy still favours the phosgenation process. Despite the stringent norms by environmental agenciesa and government regulations and the overall awareness for developing green technologies, the preference for using phosgene still prevails due to certain obvious advantages like extremely high reactivity towards nucleophiles like amines for selective syntheses of desired compounds, overall process economy and the convenience in usage.[45]

1.4. SYNTHESIS AND APPLICATIONS OF SUBSTITUTED UREAS

Substituted ureas are aliphatic or aromatic organic derivatives of urea, and depending on the substitution on N atom, they may be termed as mono-, di-, tri- or tetrasubstituted ureas; and could be symmetric or asymmetric in nature.

1.4.1. Applications of substituted ureas in fine and specialty chemicals

Substituted ureas constitute an important class of chemical compounds; and have found applications in diverse areas. Substituted ureas have found extensive applications in agriculture industry as plant growth regulators and pesticides, particularly herbicides. A systematic account and a survey of data on the effectiveness of ureas as plant growth regulators and herbicides have been given in a review,[46] in which certain regularities in the herbicidal activity of substituted ureas as a function of their structure have been established. Studies in this field are developing vigorously; new communications on the efficiency of substituted ureas as herbicides,[47] and plant growth stimulators,[48] as well as fungicides[49] insecticides,[50] bactericides,[51] and other pesticides,[52,53] promising for practical applications, are being published systematically. Yet another field in which substituted ureas are widely employed is that of the manufacture of physiologically active substances[54,55] and medicinal preparations, mainly with tranquillizing and anticonvulsant activities. Various *N*-alkyl-*N*'-aminophenoxyureas are used in the treatment of asthma and other diseases of the respiratory tract[56,57] and substituted ureas are used as components of medicinal preparations for the treatment of cardiac diseases.[58]

Certain nitroureas exhibit anticancer and antileukaemic properties,[59] heterylcarbonylureas dissolve gall stones,[60] while indolylureas, amidinoureas, *N*-aryl-*N′*-imidazolidineureas, aminoethylureas, and piperidinylureas possess hypotensive properties.[61] Sulphonylureas and l-amidino-3-phenylureas exhibit dermatological properties.[62,63] The latter can also be used to reduce blood pressure and in the treatment of increased acidity and stomach ulcers;[64,65] *N*-alkyl-*N′*- dialkylaminoethylureas[66] and pyrazinylureas can also be employed in the treatment of gastrointestinal diseases;[67] certain substituted ureas are used as agents for the protection of the skin against boils.[68]

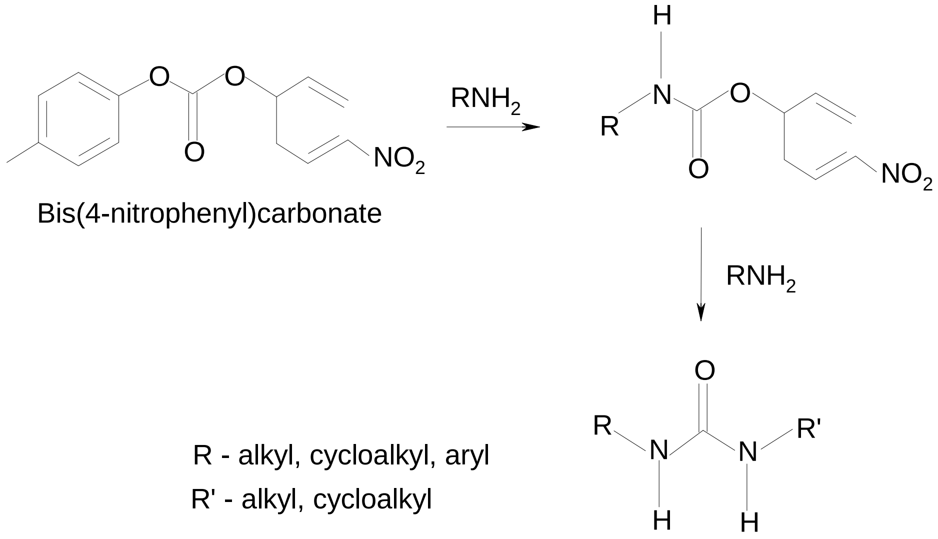
Certain phenylureas are capable of inhibiting the degradation of connective tissues in warm blooded animals and in man.[69] Ureas with nitrogen-containing heterocycles can be used as regulators of immune responses,[70] as antihelminthic preparations,[71,72] and as hypoglycaemic substances.[73,74] Data concerning the use of substituted ureas for the dyeing of hair and keratin and cellulose fibres have been described in the literature;[75,76] 3-hydroxy-2,4-dimethylphenylurea is the most effective.[77],[78] Substituted ureas are able to form complexes with certain metal ions and they are used in analytical chemistry as complex forming agents.[79,80] Certain urea derivatives (for example, the symmetrical diethylphenylurea under the name centramit) serve as stabilisers of smokeless powders;[81] 1,3-dialkylureas are used in the synthesis of sweetening agents and as sugar substitutes.[82] Tetramethylurea is used as a solvent in polarography.[83] Urea derivatives are also employed as solvents for quinone or hydroquinone in the manufacture of hydrogen peroxide[84] and as solvents and catalysts in chlorination reactions.[85] Substituted ureas can serve as the starting materials for the synthesis of polymers[86] and also surfactants.[87]

The substituted urea functionality has also been found to appear in drugs like HIV-protease inhibitors[88],[89] FKBP12 inhibitors,[90] and CCK-B receptor antagonists.[91] Some substituted ureas have been found to act as artificial receptors and self assembled supramolecules.[92] Besides these, disubstituted ureas are important agricultural chemicals, resin precursors, dyes and additives to petroleum compounds and polymers.[93]

1.4.2. Non-phosgene, reagent-based methods of synthesis

1.4.2.1. Using Bis(4-nitrophenyl)carbonate

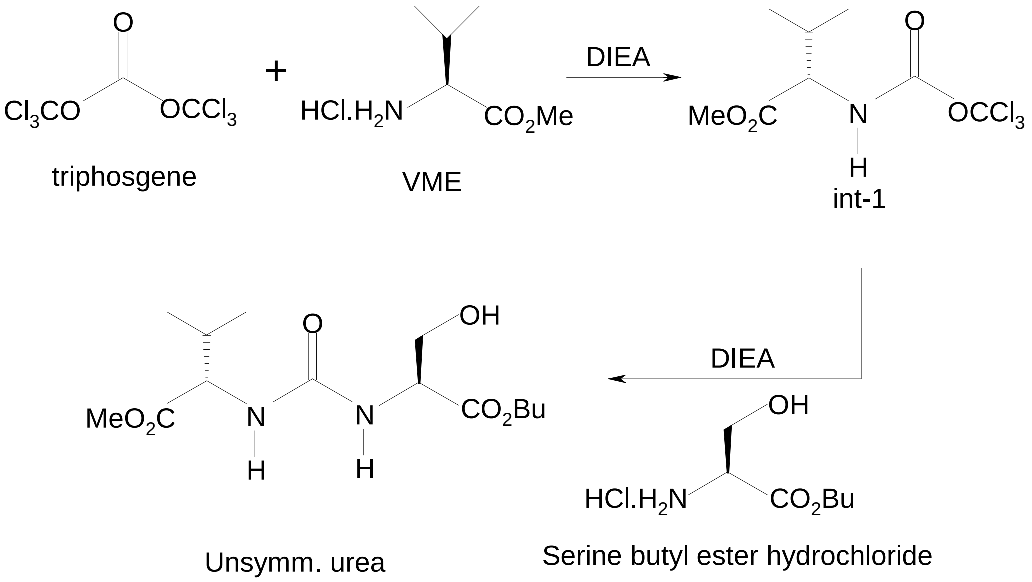
Bis(4-nitrophenyl)carbonate, a very stable reagent, can be converted into carbamates (44–78% yield) by reaction with equimolecular amounts of primary aliphatic or aromatic amines within 2 h in dichloromethane. Intermediate carbamate then reacts further with different primary amines giving the unsymmetrical ureas in good yields (50–96%) (Scheme 1.4). The second step is considerably slower that the first and requires a longer reaction time of approximately 4 hours.



Scheme 1.4 Synthesis of substituted urea using bis(4-nitrophenyl)carbonate

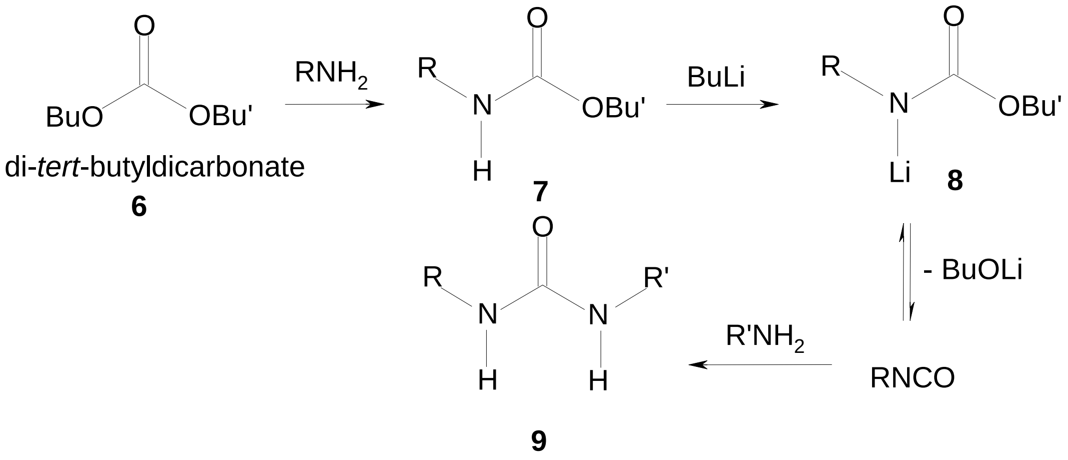
1.4.2.2. Using triphosgene

Triphosgene [bis(trichloromethyl)carbonate], a crystalline solid which represents a safe and stable replacement for phosgene and can be handled without special precaution,[9] is successfully utilized to the sequential synthesis of unsymmetrical ureas also bearing chiral amino acid derivatives, without having to purify the intermediates. Thus, in a model reaction valine methyl ester hydrochloride (VME) is reacted with triphosgene in the presence of diisopropylethylamine (DIEA) in dichloromethane at room temperature for 30 minutes giving the intermediate (int-1). Serine butyl ester hydrochloride and DIEA in dichloromethane are then added over 10 minutes. The product unsymmetrical urea is obtained in 89% yield via a typical sequential, three-component reaction (Scheme 1.5). The reaction is successfully applicable to different amines containing multiple functionalities such as unprotected primary and secondary alcohols (85–88% yield). An important application of this strategy is represented by the use of O-trimethylsilyl protected amino acid hydrogen chlorides to produce half-acid/half-ester urea dipeptides in 45–49% yield, starting materials for a variety of pharmacologically active compounds. Addition of the selected O-trimethylsilyl protected amino acid hydrogen chloride to a solution of triphosgene in chloroform and in the presence of DIEA results in the formation of the isocyanate intermediate which is converted in situ into the urea dipeptide upon reaction of a second amino acid methyl ester in methanol.



Scheme 1.5. Synthesis of ureas using triphosgene

Similar application is reported for di-*tert*-butyldicarbonate 6 [$(BOC)_2O$], a well known reagent utilized for protecting the amino group giving *N*-BOC-primary amines 8 with high yield and selectivity. Reagents 8 can be converted into unsymmetrical substituted ureas 9 by reaction with a second amine. The reaction requires the use of strong bases such as alkyllithiums, which convert 8 into the isocyanate capable of undergoing fast addition of a second amine affording the final unsymmetrical urea. (Scheme 1.6). Softer and more safely handled organic bases such as 4-dimethylaminopyridine (DMAP) can be utilized and eventually recovered at the end of the reaction, giving symmetrical as well as unsymmetrical ureas in 80–99% yield by stirring the reaction mixture for 14 h at 40 °C.[94] The crucial role of isocyanates as intermediates in this approach is confirmed by a detailed mechanistic study which demonstrates that carbamates are by-products which are not convertible into ureas.[95]

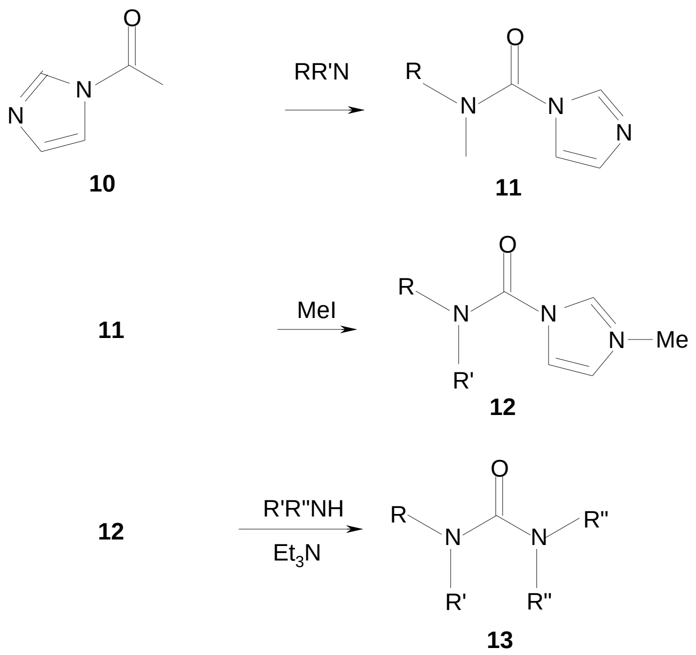


R- Aryl; R’- alkyl, cycloalkyl

Scheme 1.6. Synthesis of ureas using di-*tert*-buytl dicarbonate

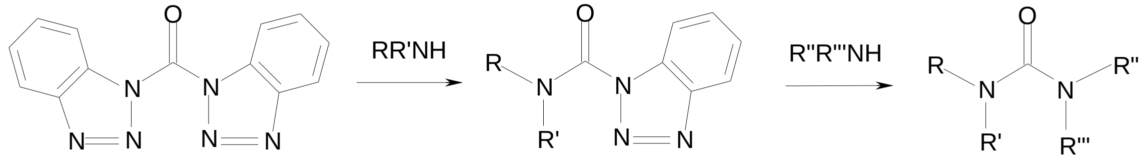
1.4.2.3. Using *N,N’*-carbonyldiimidazole

The commercially available and easily handled crystalline solid *N,N’*-carbonyldiimidazole 10 (CDI) is utilized as starting reagent for the general synthesis of unsymmetrical tetra- substituted ureas. The intermediate carbamoyl imidazole 11 is first obtained by reaction of CDI with a secondary amine. Compound 11 is successively converted into the more reactive and resonance-stabilized imidazolinium salt 12 by *N*-alkylation of the imidazole moiety. Addition of a different secondary amine to 12 furnishes *N,N,N’,N’’*-unsymmetrical tetrasubstituted ureas 13 in high yield (72–99%) (Scheme 1.7).



Scheme 1.7. Sequential synthesis of disubstituted urea starting from *N,N'*-carbonyldiimidazole

Imidazolinium salts 12 are produced quantitatively and do not require additional purification for the final conversion to the ureas 13. Although the salts 12 are hygroscopic, they can be stored for several weeks without detectable decomposition.[96] The carbonyldiimidazole-based approach is successfully applied also to the synthesis of some more sophisticated urea dipeptides, which represent building blocks for the preparation of inhibitors of HIV-protease. These compounds are simply obtained by mixing in sequence CDI with the selected amino acid ester hydrochloride salt in the presence of triethylamine, and avoiding use of strong bases such as BuLi or lithium diisopropylamide (LDA) utilized in the methodology described in Scheme 1.6, which can racemize the stereogenic centers. Similarly, *N,N'*-carbonyldibenzotriazole 14 can be utilized to synthesize *N,N,N',N''*-unsymmetrical tetrasubstituted ureas 16 by one-pot reaction with the first amine to produce the carbamoylbenzotriazole intermediate 15 that can react under more forceful conditions with a second amine giving the final urea in satisfactory to good yields (24–85%)[97] (Scheme 1.8). The reaction conditions and the yields of intermediate 19 are significantly affected by the steric hindrance of the substituents of the amines utilized. The procedure succeeds at room temperature in THF for 2 days in 40–71% yield for cyclic, aliphatic and aromatic amines, whereas harsher conditions are required and lower yields obtained from congested secondary amines. Unfortunately reagent 18 is not commercially available and must be synthesized directly by benzotriazole and phosgene. This drawback makes the above approach unattractive and utilizable only in lab-scale preparation.



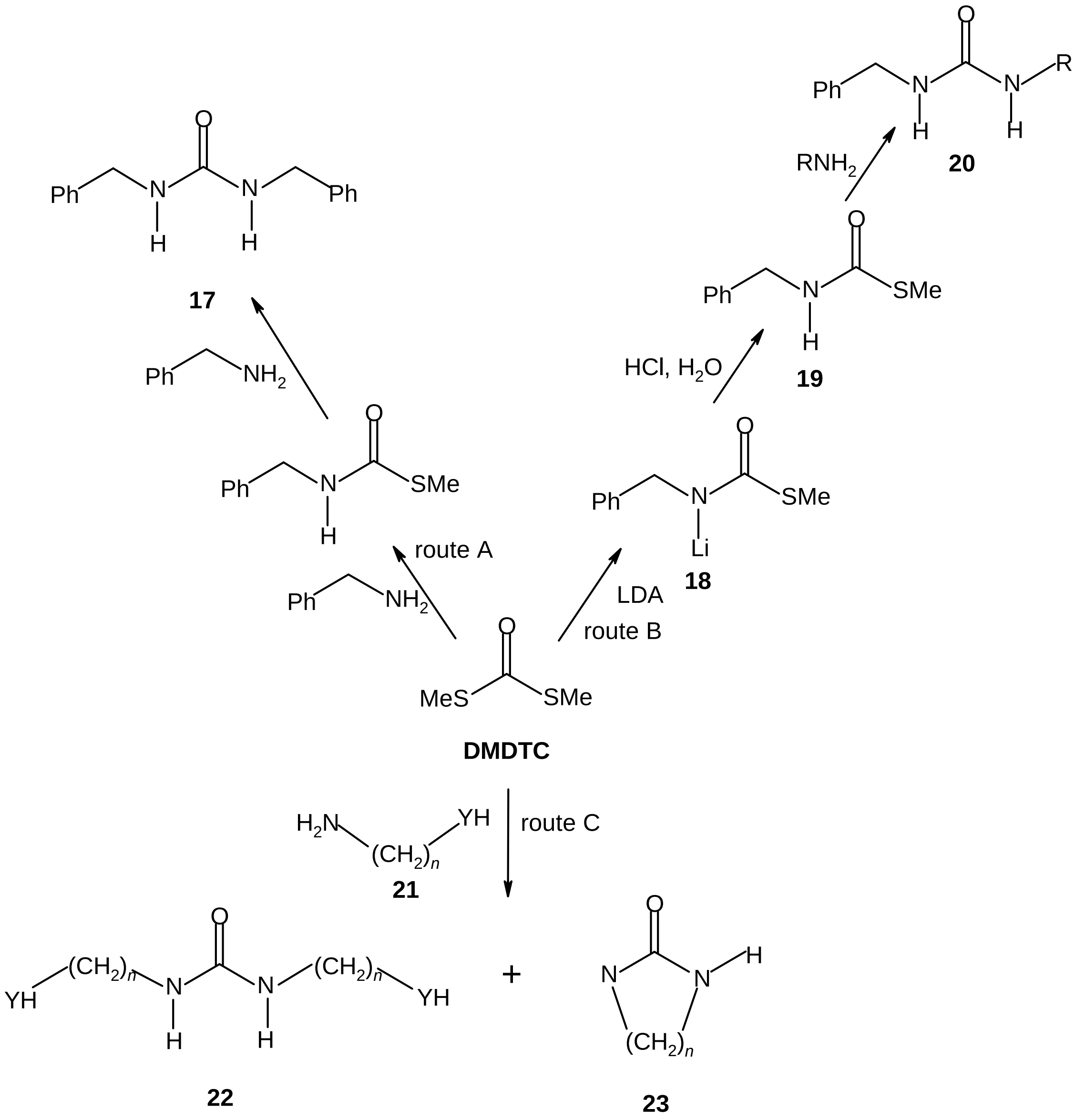
14 **15** **16**

R, R’, R”, R”’- alkyl, aryl or cycloalkyl

Scheme 1.8. One-pot synthesis of disubstituted urea starting from *N,N’*-carbonyldibenzotriazole

1.4.2.4. Using *S,S*-Dimethyldithiocarbonate (DMDTC)

S,S-Dimethyldithiocarbonate (DMDTC) represents a mild and safely handled reagent structurally similar to phosgene which is useful in the synthesis of ureas. DMDTC can be prepared from methanol, carbon disulfide and dimethyl sulfate by a two-step sequence.[98] Even if dimethyl sulfate is a suspected human carcinogen the substance is relatively nonvolatile and can be handled safely with care in the laboratory. In a representative example, DMDTC is allowed to react with 2 equivalents of benzylamine at 60°C for 24 h in methanol or ethanol giving symmetrical dibenzylurea 17 in 85% yield (Scheme 1.9, route A).[99] Results of mechanistic studies confirm that the second reaction stage is faster than formation of *N*-benzyl-*S*-methylthiocarbamate 19. By carrying out the reaction under basic conditions (LDA), DMDTC is deprotonated immediately after being formed giving the corresponding lithium salt 18 in quantitative yield, which is relatively stable toward nucleophilic substitution at ambient temperature and will not react further to give dibenzylurea (Scheme 1.9, route B). Treatment with aqueous HCl affords thiocarbamate 19 that can react further with different aliphatic amines furnishing the unsymmetrical ureas 20 (40–65% yield). Aliphatic amines 21 bearing an hydroxy or an amino substituent at the β or γ position react with DMDTC in dilute solution providing predominantly cyclic ureas or carbamates 23 (40–80% yield) (Scheme 1.9, route C). By increasing the concentration of the starting reagent 21 with respect to DMDTC, the symmetrical ureas 22 are obtained in high yield (75–100%) without need for protection and deprotection procedures.

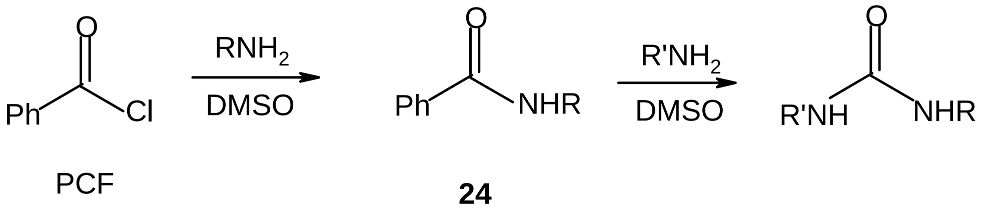


Where YH- NH_2, OH; R- alkyl

Scheme 1.9. Synthesis of symmetric (17), asymmetric (20) or cyclic (23) ureas starting with DMDTC.

1.4.2.5. Using phenyl chloroformate

Disubstituted ureas including some chiral compounds are efficiently synthesized by reaction of amines with carbamates 24, which in turn are prepared from phenyl chloroformate (PCF) (Scheme 1.10).[100] The reaction occurs at room temperature in 78–95% yield simply by mixing the reagents in DMSO, the only by-product being phenol which is easily removable by an aqueous NaOH wash. The method is also successfully applied to secondary amines to generate *N,N,N'*-trisubstituted ureas in 78–89% yield independent from the steric hindrance of the reagents. The reaction conditions are compatible with a number of functional groups such as chiral amines, amino acids and amino alcohols. A possible drawback of this approach is associated with the use of DMSO as solvent, which is toxic, a possible carcinogen and explosive when mixed with some organic and inorganic reagents.[101] The use of DMSO as solvent is critical to the mildness of the conditions. Compared to DMSO, the reaction is much slower in MeOH, dioxane, DME or CH_2Cl_2 in which the carbamate 24 is insoluble at the beginning of the reaction.

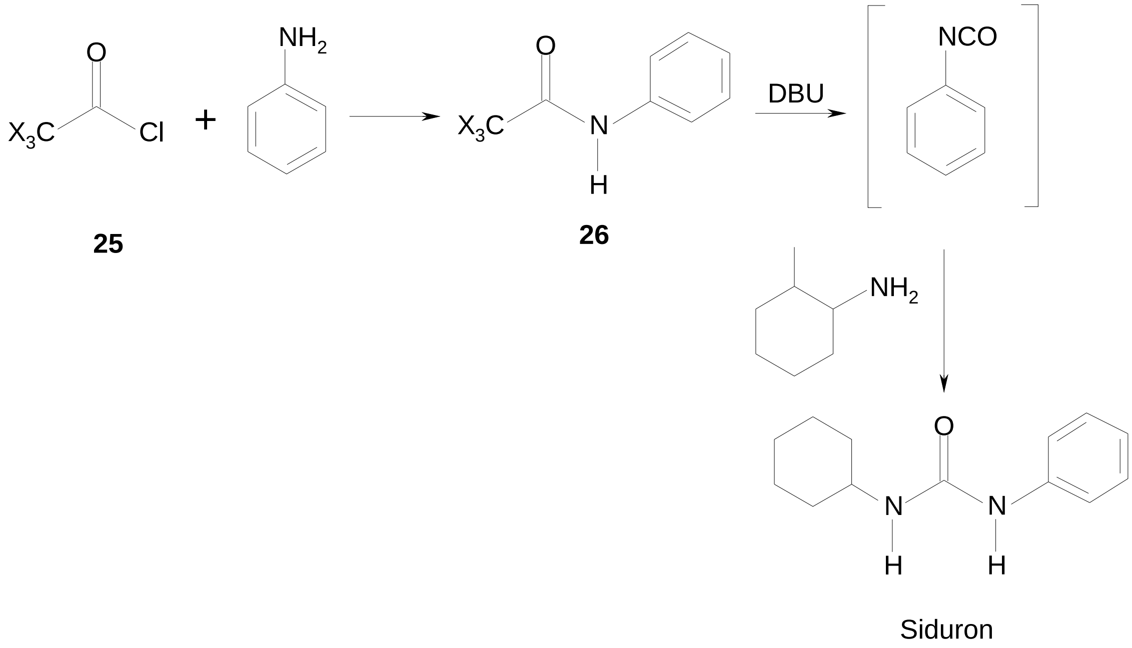


R, R' = alkyl, aryl, cycloalkyl

Scheme 1.10. Synthesis of ureas from phenyl chloroformate (PCF)

1.4.2.6. Using trihaloacetylchlorides

Trihaloacetylchlorides 25 are unsymmetrical reagents, which are commercially available at reasonable prices. They can be quantitatively converted into the corresponding trihaloacetamides 26 (80–90%) as easily handled crystalline solids with long shelf life by reaction with convenient aromatic or aliphatic amines. These compounds react with different aliphatic amines in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) giving unsymmetrical ureas such as Neburon and Siduron with biological activity (Scheme 1.11). As expected from the reaction mechanism, the rates of the reaction of intermediates 33 with bases exhibit a strong dependence on the nature of the trihalomethyl group according to the scale $RCOCF_3$ < $RCOCCl_3$ < $RCOCBr_3$. As for some other reported methodologies, this 'one-pot' synthesis of ureas from readily available trihaloacetanilides has the clear advantage that it avoids the need to isolate the highly toxic isocyanates. The crucial role of the isocyanates in the present reaction is confirmed by the unreactivity of trichloroacetamides derived from *N,N*-disubstituted amines which can not afford isocyanates.

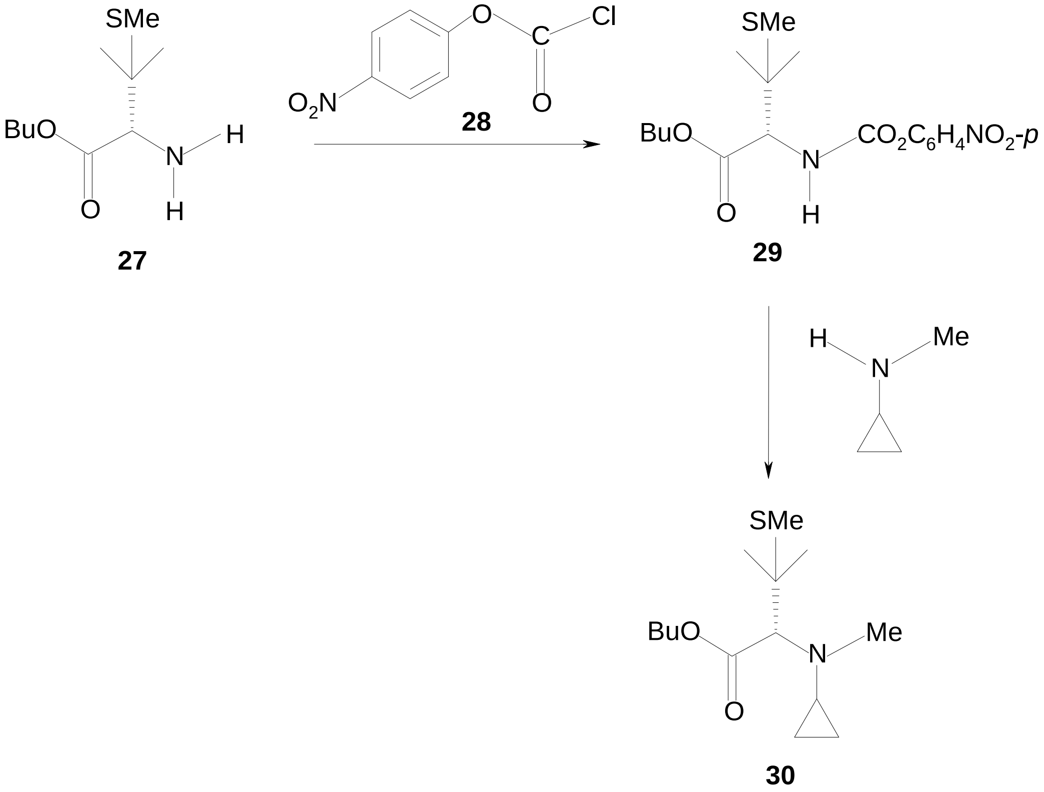


X- F, Cl or Br

Scheme 1.11. Synthesis of unsymmetric ureas starting with trihaloacetylchlorides

1.4.2.7. Using *p*-nitrophenylchloroformate

Ureas containing structurally complex frameworks, including amino acid derivatives, are efficiently prepared from *p*-nitrophenylchloroformate 28. To give an example, *S*-methyl-*O*-benzyl-L-penicillamine 27 reacts with 28 in acetonitrile at 0 °C for 30 min giving carbamate 29. Further addition of cyclopropylmethylamine in the same solvent and in the presence of $NaHCO_3$ gives the amino acidic urea 30 in 92% yield (Scheme 1.12). The reaction occurs under very mild conditions owing to the good leaving ability of the *p*-nitrophenyl group and hence is not applicable to tetrasubstituted ureas.[102]



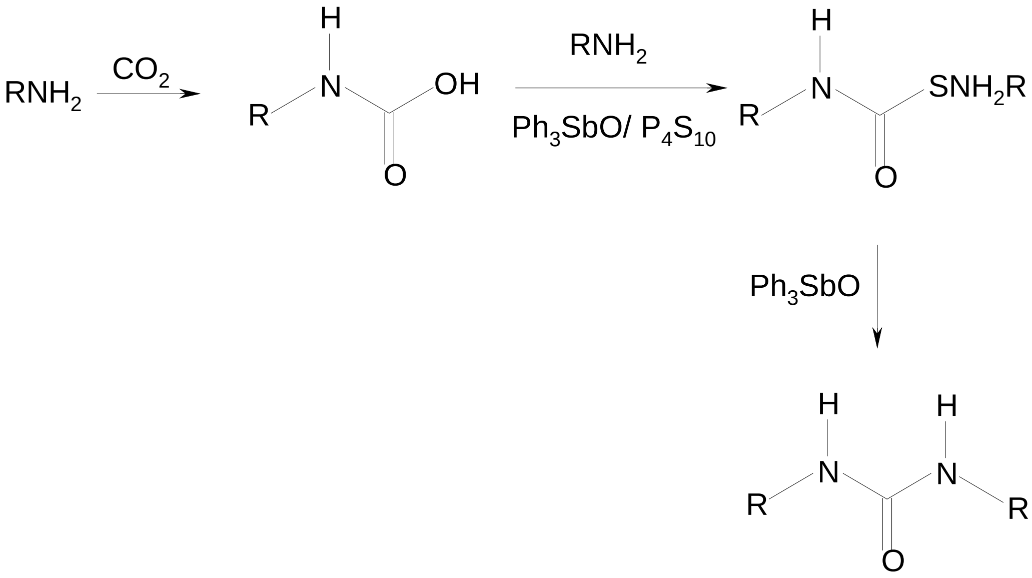
Scheme 1.12. Synthesis of amino acidic ureas starting from *p*-nitrophenylchloroformate (28)

1.4.3. Green methods of synthesis of substituted ureas

Owing to the increasing demand for specialty molecules with urea moieties, and also the global awareness for cleaner technologies, there has been a distinct rise in the efforts to synthesize substituted ureas by eco-friendly, atom-economical and economical routes apart from the above-mentioned reagent-based syntheses utilizing hazardous reagents or generating stoichiometric amounts of waste byproducts. Carbon dioxide activation for the syntheses of carbonylation reactions has been one of the most desired catalytic chemical transformations in the recent past, and substituted urea and carbamate synthesis via carbon dioxide-mediated carbonylations of amines and nitro compounds has attracted considerable attention. Other promising and more practical methods in terms of potential for process viability include transition metal catalyzed carbonylations of nitroaromatics or amines.

1.4.3.1. Carbonylation using carbon dioxide

The use of carbon dioxide in industrial applications represents an important goal since minimization of carbon dioxide emission can be achieved by direct fixation into the target compound. Triphenylstibine oxide (Ph_3SbO) catalyses the carbonylation of diamines $H_2N(CH_2)_nNHR$ (n = 2, 3; R = Me, CH_2CH_2OH, $CH_2CHMeOH$) with CO_2 in the presence of 3Å molecular sieves, giving the corresponding cyclic ureas in 83–98% yield.[103] The modified catalyst Ph_3SbO/P_4S_{10} utilized in the molar ratio amine/Ph_3SbO/P_4S_{10} 40/1.0/2.0 is highly effective for the carbonylation of both amines and diamines giving linear and cyclic ureas at 80–150°C for 12 h with CO_2 (4.9 MPa).[104] Monitoring the reaction by ^{13}C NMR spectroscopy revealed the reaction course as shown in Scheme 1.13.



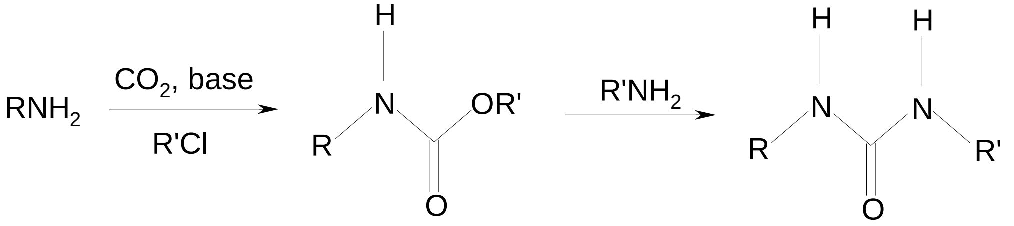
R- allyl, alkyl, phenyl

Scheme 1.13. Catalytic carbonylation of amines with carbon dioxide

In a more sophisticated manner propargyl alcohols are utilized in stoichiometric amounts as water scavengers. The reaction of aliphatic and aromatic primary amines with CO_2 is performed at 120–140 °C in the presence of a mixture of $RuCl_3{\cdot}H_2O$ and Bu_3P (amine/Ru molar ratio: 100) and an excess of the propargyl alcohol derivative (generally 2-methylbut-3-yn-2-ol) affording *N,N'*-disubstituted symmetrical ureas in 41–68%

yield.[105] However, both the triphenylstibine oxide and propargyl alcohol based processes seem to be exploitable only at the laboratory scale owing to the use of toxic and/or expensive reagents.

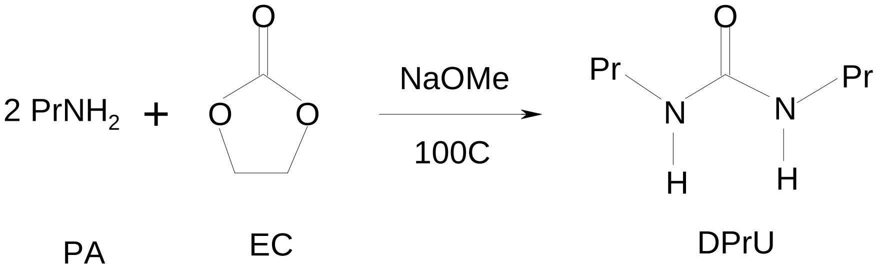
More conveniently carbamate esters can be synthesized by reaction of amines with carbon dioxide and alkyl halides in the presence of bases (Scheme 1.14).[106] Use of sterically hindered guanidine bases gives best results (80–99% yield with virtually 100% selectivity). Amino acids and diamines are efficiently converted into the corresponding carbamates, which can be utilized as intermediates to ureas. However, the use of stoichiometric amounts of bases represents a serious limit for the large-scale application of the process. A further drawback of this methodology is represented by the alkylation of the amine, which affords unwanted by-products. The above side reaction can be avoided by performing alkylation of alkylammonium *N*-alkylcarbamates, which are easily obtained from primary amines and CO_2 in the presence of 18-crown-6 which can be recovered quantitatively at the end of the reaction.[107] An advantage which increases the industrial interest of the methodology is represented by the possibility of reducing the production of chloride wastes. In fact, different alkylating agents instead of alkyl chlorides can also be employed. The entire process occurs with yields close to 100%.[108]



Scheme 1.14. Synthesis of ureas by carbonylation of amines with carbon dioxide in the presence of alkyl halides

1.4.3.2. Carbonylation using organic carbonates

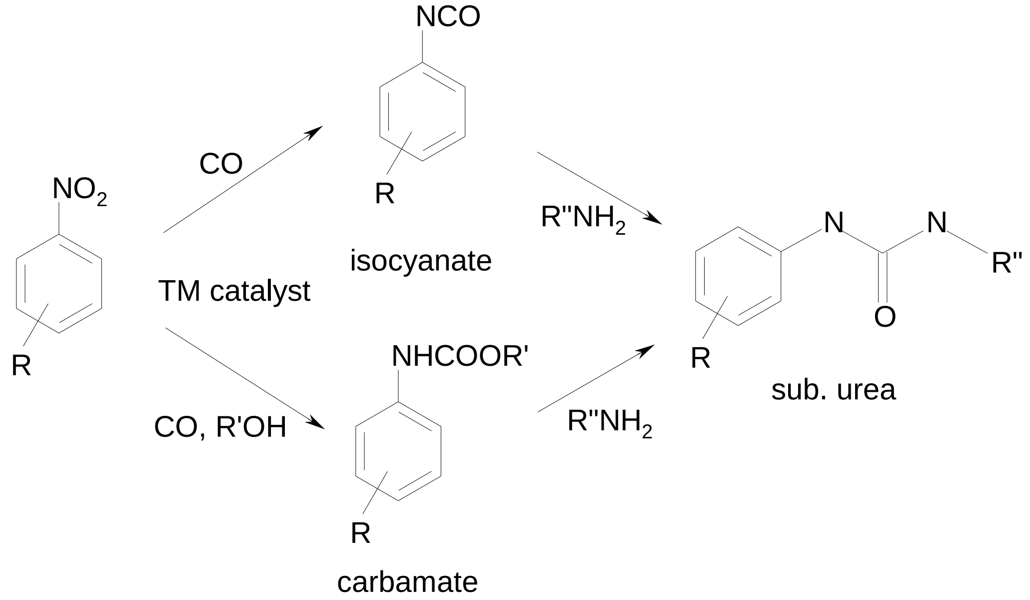
Carbonic acid diesters are very attractive reagents and of great economic interest because they represent safe, non-corrosive and environmentally acceptable alternative to phosgene for carbonylation and carboxylation reactions. For example, methoxycarboxylation with dimethylcarbonate offers a phosgene-free route for the production of carbamates and isocyanates[109] comparable, by the environmental point of view, with the transition metal catalysed carbonylation of nitro compounds and amines with CO. Ethylene carbonate (EC), which is prepared in large amounts by reacting ethylene oxide with CO_2,[110] represents an effective carbonylating reagent for conversion of propylamine (PA) into *N,N'*-dipropylurea (DPrU) (Scheme 1.15). Reaction of EC with an excess of PA in 28% methanolic NaOMe in autoclave at 100 °C for several hours affords the product DPrU in 85% yield.[111] The procedure can be efficiently applied to the large scale synthesis of both symmetrical and unsymmetrical *N,N'*-disubstituted ureas in high yield.



Scheme 1.15. Urea synthesis by carbonylation of amines with organic carbonates.

1.4.3.3. Carbonylation of nitro-aromatics

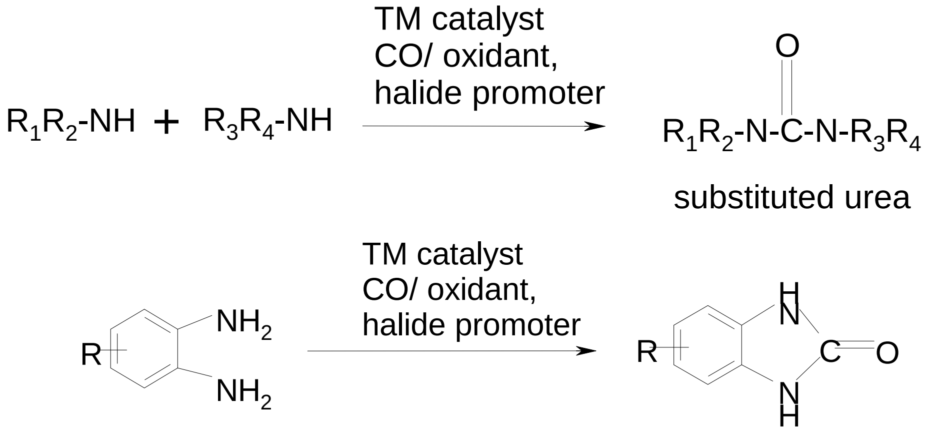
Since 1962, the catalytic carbonylation of nitro compounds with particular interest towards nitroaromatic compounds has been extensively studied with the main focus upon the production of isocyanates, which have achieved great commercial importance in the preparation of important industrial targets including ureas. Different catalysts have been used to promote the process including group 8–10 metal compounds (mainly Pd, Ru and Rh) combined with a Lewis acid co-catalyst (mainly $FeCl_3$, $MoCl_5$, V_2O_5 and Fe_2O_3) or Brönsted acid (e.g. trimethylbenzoic acid). The methodology was particularly studied and developed with the aim of producing methylenediphenyl isocyanates and phenyldiisocyanate, which are of commercial importance in the manufacture of polyurethanes. Concerning the synthesis of monoisocyanates, because of their instability under the reaction conditions, the process was better utilized in the production of *N*-phenylcarbamates by trapping isocyanates with alcohols (Scheme 1.16). Furthermore isocyanates can be converted in situ into symmetrical diphenyl ureas by reaction with amines either added to the reaction mixture or produced in situ by reduction of the nitro compound.[112] Diphenylurea (DPU) is synthesized in almost quantitative yield from nitrobenzene, aniline and CO in the presence of a Pd(II) complex with triphenylphosphine (0.2 mol% with respect to aniline) dissolved in a non-polar solvent such as toluene or xylene at 120°C. The carbamoyl complex [PhNCO(Pd)] or nitrene complex-[PhN(Pd)] can be formed depending on whether nitrobenzene or aniline interact with the catalyst. Unsymmetrical substituted ureas are likewise synthesized by reductive carbonylation of 4-substituted nitrobenzenes in the presence of an excess of an aliphatic secondary amine using palladium acetate, bipyridyl and copper tosylate as co-catalyst; the best selectivity is obtained by continuously adding the aliphatic amine during the period of reaction (approximately 10 hours).[113] Synthesis of para-substituted symmetrical diaryl ureas in satisfactory yield (27–88%) is performed by reaction of accessible aromatic nitrocompounds with CO in the presence of $Ru_3(CO)_{12}$ in cis-cyclooctene as the solvent (substrate/catalyst ratio 25).[114] *N,N'*-Substituted ureas are obtained in fairly low yields (45–55%) by dioxygen-induced carbonylation of amines in the presence of nickel carbonyl complexes (substrate/catalyst ratio 100)[115] or (h-methylcyclopentadienyl)manganese tricarbonyl irradiated with UV light,[37] which are less expensive than palladium-based catalysts.



Scheme 1.16. Synthesis of ureas by catalytic carbonylation of nitroaromatics

1.4.3.4. Oxidative carbonylation of amines

Oxidative carbonylation of amines is an attractive green route for the synthesis of substituted ureas and carbamates. The reaction involves carbonylation of amines catalyzed by a transition metal catalysts from Group VIII in the presence of an iodide-containing promoter like alkali metal iodide, quaternary ammonium iodide or iodine; and an oxidant like air, oxygen or nitro compounds. The general reaction scheme is shown in Scheme 1.17, wherein in the first equation, R_1, R_2, R_3 and R_4 are H, alkyl or aryl groups; and they may be same or different. A mixture of two different amines under these reaction conditions gives a mixture of two symmetric and an asymmetric urea, while a primary diamine like *o*-phenylene diamine gives a cyclic urea. The most effective catalyst has been found to be palladium, although several homogeneous transition metal catalysts have been reported, some of which include selenium compounds, palladium compounds, nickel, tungsten, Rhodium, gold, etc.



TM catalyst- transition metal catalyst

Scheme 1.17. Transition metal catalyzed oxidative carbonylation of amines

Among the earliest reports on transition metal catalyzed oxidative carbonylation is the reaction of carbonyl selenide with amines and amino alcohols to produce ureas and carbamates. Fukuoka et al. tried various supported transition metal catalysts for the oxidative carbonylation of amines, palladium being the preferred metal. Alper and Hartstock[116] introduced a homogeneous $PdCl_2$-$CuCl_2$ catalyst for oxidative carbonylation reaction at room temperature and atmospheric pressure. Wan et al.[117] have shown that the polymer-supported bimetallic catalyst (PVP-$PdCl_2$-$MnCl_2$) exhibits high activity and selectivity for the oxidative carbonylation of amines under atmospheric pressure in the presence of a base. Shi and Deng have reported a gold complex [(Au(PPh_3)Cl] as an active catalyst for oxidative carbonylation reaction for the first time.[118] Among the oxidants screened for oxidative carbonylation are oxygen, air, iodine, nitro compounds or peroxides. The temperatures for these reactions typically range from 298 to 493 K; while the pressures are in the range of 3 to 10 MPa. McCusker et al. have carried out extensive research in the tungsten carbonyl catalyzed oxycarbonylation of primary aliphatic, aromatic or cyclic amines for the synthesis of cyclic ureas.[119]

A more detailed account of the transition metal catalyzed oxidative carbonylation of amines is taken in section 1.6.

1.5. SYNTHESIS AND APPLICATIONS OF CARBAMATES

The esters of carbamic acid or carbamates display some of the characteristic properties of carboxylic acid esters and amides. Some of their reactions are those of esters, amides, enols, and apparently of cyanic acid. The most abundantly known carbamate is the ethyl carbamate or urethane, which has been used as a precursor to isocynates during the synthesis of polyurethanes. Carbamates have a wide range of applications in chemical industry, from the synthesis of commodity chemicals like polyurethanes, herbicides and pesticides[120] to several fine and specialty chemicals; like for the production of drug intermediates in pharmaceutical industry.[121] Recently, due to the development of combinatorial techniques in the field of drug discovery and due to their medicinal and biological properties, carbamates have gained considerable importance in the preparation of small molecule libraries.[122] In organic synthesis, carbamates are often used as protecting groups for amine functionality.[123] Carbamates have played a key role in understanding of DNA structures.[124] 'Rubisco', is the most abundant enzyme used in biological systems bearing a carbamate functionality, and plays an important part in fixation of CO_2 by photosynthesis, which probably is the most important biochemical reaction of an ecosystem.[125]

The commercial production of carbamate is almost exclusively based on conventional phosgene technology. Several attempts have been made to synthesize carbamates with non-phosgene routes, many of which are reagent based while others are catalytic, eco-friendlier alternatives.

1.5.1. Non-phosgene, reagent based methods for carbamate synthesis

Isocyanates are facile sources of carbamates and vice versa. Compounds containing hydrogen atoms attached to oxygen react with isocyanates. All types of alcohols-primary, secondary, tertiary, and polyhydric-react to give carbamates,[126,127] (Scheme 1.18) the only exception being triphenylcarbinol, which gives no reaction.[128]

$$R-N=C=O + R'-OH \longrightarrow RNHCOOR'$$

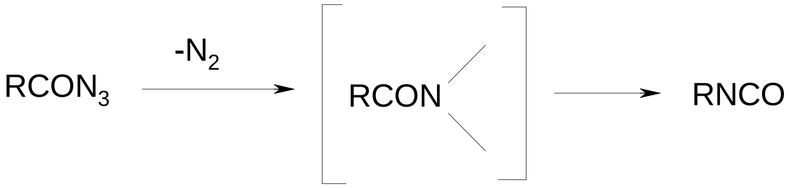
Scheme 1.18. General scheme for the synthesis of carbamates from isocyanate and alcohol

Phenols, including polyhydric phenols, react, especially in the presence of aluminum chloride.[129]Therefore, all the methods for the preparation of isocyanates are useful for the synthesis of the carbamates of choice, by the consequent reactions with appropriate alcohols.

The various reagent-based, non-phosgene methods of synthesis of isocyanates and carbamates are described below.

1.5.1.1. Curtius rearrangement of acid azide

The method other than the phosgene reaction, which has been used most, is the Curtius rearrangement of an acid azide in a neutral solvent.

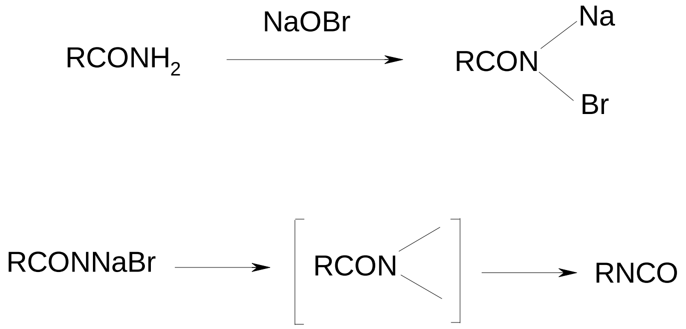


Scheme 1.19. Synthesis of isocyanates by Curtius Rearrangement of acid azides

Curtius used the method for the preparation of substituted ethylene diisocyanates. However, he prepared the diazide by treating substituted succinic hydrazides with nitrous acid. Yields from the reaction are usually good, as in the case of undecyl isocyanate, which was obtained in 81-86 per cent yield.

1.5.1.2. The Hofmann rearrangement of amides

This method is useful only for those isocyanates, which do not react readily with water, since an aqueous medium is required.



Scheme 1.20. Synthesis of isocyanates by Hofmann rearrangement

1.5.1.3. Double decomposition reactions

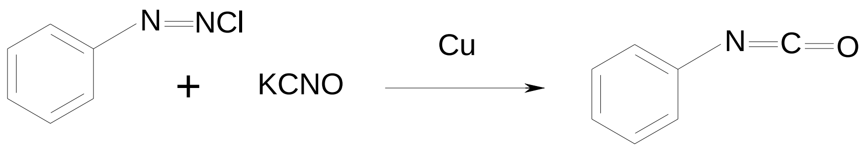
The reaction between organic halides or sulfates and salts of cyanic acid was one of the first methods used for the preparation of isocyanates. Wurtz in 1849, prepared alkyl isocyanates by this method.

$$R_2SO_4 + 2\,KCNO \longrightarrow 2\,RNCO + K_2SO_4 \qquad 1.2$$

The reaction between the alkyl sulfate and potassium cyanate was conventionally the best method for the synthesis of methyl or ethyl isocyanate. In addition, acyl isocyanates may be prepared in this way, using acid chlorides as shown in equation 1.2.

1.5.1.4. Other miscellaneous methods

Diazonium chlorides react with potassium cyanate in the presence of copper to give isocyanates.



Scheme 1.21. Synthesis of isocyanates from diazonium chlorides

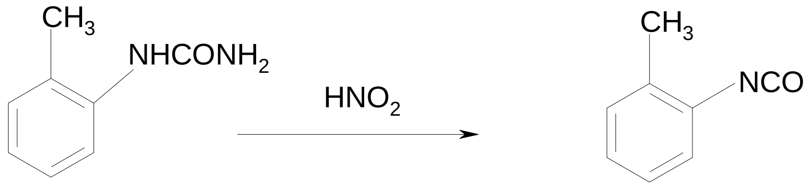
Degner and von Pechmann reported that the reaction between diazomethane and nitrourea produced methyl isocyanate.

$$H_2NCONHNO_2 + 3\ CH_2N_2 \longrightarrow [\ HCNO + H_2NNO_2 + 3\ CH_2N_2\ ]$$

$$CH_3NCO + (CH_3)_2NNO_2 \longleftarrow$$

Scheme 1.22. Synthesis of isocyanate from nitrourea

o-Tolylurea in the presence of nitrous acid is converted to the isocyanate.



Scheme 1.23. Synthesis of isocyanate from monosubstituted urea

Isocyanides and isothiocyanates are oxidized with mercuric oxide to give the isocyanate, as shown in equations 1.3 and 1.4.

$$RNC + HgO \longrightarrow RNCO \qquad 1.3$$

$$RCNS + HgO \longrightarrow RNCO \qquad 1.4$$

The Schmidt rearrangement of carboxylic acid gives isocyanates.

$$\mathrm{RCOOH} + \mathrm{HN_3} \longrightarrow \mathrm{R_2{-}N{=}C{=}O} \qquad 1.5$$

The routes mentioned above for carbamate synthesis either deals with handling of potentially hazardous chemicals or requires acid and bases in stoichiometric amount which produces inorganic salts that ends up with aqueous effluent.

Several efforts have been made for the preparation of carbamates using non-toxic reagents and for the development of novel environmentally friendly methodologies.

1.5.2 Eco-friendly methods for carbamate synthesis

In the past few decades, several catalytic, mild and eco-friendly routes have been explored for the synthesis of carbamates, involving the use of mild and less hazardous chemicals, for example, substrates like nitroaromatics, amines or substituted ureas and carbonylating agents like carbon monoxide and dioxide or DMC.

1.5.2.1 Carbonylation of nitroaromatics to carbamates

For nearly past 50 years, the carbonylation of nitroaromatics has been extensively studied as a means of replacing the traditional process principally for the production of isocyanates. The transformation, if carried out in alcohol media, leads to the formation of carbamates, which upon thermal degradation yield isocyanates. Industrially, aliphatic and aromatic isocyanates represent very important intermediates. Especially in polymer industries, poly isocyanates such as 2,4-toluene diisocyanate (TDI) or methylene 4,4'-diphenyl diisocyanate (MDI) are the starting materials for the synthesis of many polyurethanes.[130] For aromatic isocyanate producers, the advantages of carbonylation processes staring from nitroaromatics were foreseen quite some time ago and have attracted attention for more than 30 years.[131]

The carbon monoxide-mediated reduction of nitrogen-oxygen aromatic bonds was reported in 1949 by Buckeley and Ray who converted nitrobenzene in azobenzene under very harsh conditions (250°C, 3000 bar), forming carbon dioxide.[132] This discovery initiated the research on various reduction processes of the nitroso aromatic linkage assisted by transition metal complexes using CO. Subsequently, in 1967, Hardy and Bennet reported the catalytic generation of isocyanates from nitro compounds using rhodium, palladium or other metal salts in the presence of a Lewis acid promoter.[133] Catalytic systems comprising various transition metal salts were then systematically studied. The catalyst system typically consisted of a catalyst precursor used in conjunction with various promoters such as ligands or co-catalyst (mostly Lewis acid) or both. The selectivity and conversion of the carbonylation reaction was found to be dependant on the nature and properties of the precursors, ligands, promoters as well as on the temperature and CO pressure applied during the reaction. Typical reaction temperatures ranged between 393−493 K, with the pressures lying between 4 to 20 MPa. For the synthesis of carbamates, various catalysts such as metals deposited on various solid supports in the presence of ligands[134] or system as (MXn / ligand / Lewis acid) with $RhCl_3$ or $PdCl_2$ were active. New catalytic system with Ir or Pt complexes were also effective and performed like $PtCl_2(PPh_3)_2/SnCl_4$ precursors.[135]

Polynuclear precursors like carbonyl clusters of rhodium or ruthenium constituted much more active catalyst for carbonylation, especially when used with a co-catalyst like NEt_4Cl.[136] The presence of a co-catalyst was essential for the catalysis to proceed efficiently and specifically, for instance diamine ligand was required with Pd catalyst. Attempts to replace the diamine by diphosphine ligand or vice-versa in these systems often resulted in lower selectivity and yield.[137] Other new systems like ([Rh]/dppe),[138] ([Rh]/phen)[139] or ([Pd]phen/H^+)[140] have been thoroughly studied relative to the others. Very impressive results were obtained when Brönsted acid co-catalyst was replaced by Ce(IV) salt.[141] Other recently discovered active catalysts are ruthenium complexes of Schiff bases[142] or Pd salts with Keggin-type heteropolyanions ($PdCl_2$/HPA).[143]

1.5.2.2. Oxidative carbonylation of amines to carbamates in alcohol medium

The oxidative carbonylation of amines offers an immensely attractive route for the synthesis of substituted ureas and carbamates, owing to the cheap and abundantly available raw materials used in this route. Most importantly, this route employs carbon monoxide, which is much less toxic than phosgene. Another advantage is the ease with which CO can be activated using transition metal catalysts- a basis for vastly studied and exploited carbonylation chemistry.

A schematic presentation of this reaction is given in Scheme 1.24.

$$R\text{-}NH_2 + CO + 1/2\ O_2 + R'\text{-}OH \xrightarrow{\text{Catalyst}} RNHCOOR' + H_2O$$

Scheme 1.24 General scheme for catalytic oxycarbonylation of amines to carbamates

Oxidative carbonylation of aromatic amines to carbamate is reported to be effectively carried out using a variety of noble metal catalyst viz. Pd, Pt, Rh, Ir, Ru etc. in presence of promoters such as iodide ion and α.-benzoinoxim etc. under severe conditions of high pressure of $CO:O_2$ gas mixture and high temperature. The selectivity and conversion of the carbonylation reaction is dependant on the type of catalyst used, concentration of amine, CO: O_2 ratio and temperature. Typical reaction temperatures range between 353 to 493 K, whereas pressure usually lies between 3 to 10 MPa. Se, Te and Co catalysts have also been used for carbonylation of aliphatic and alicyclic amines, but these catalysts show very low activity towards the carbonylation of aromatic compounds.[144] Alper and Hartstock[116] described a homogeneous $PdCl_2$-$CuCl_2$ catalyst for the carbonylation reaction at room temperature and atmospheric pressure. Wan et al.[117] have shown that the polymer-supported bimetallic catalyst (PVP-$PdCl_2$-$MnCl_2$) exhibits high activity and selectivity for the oxidative carbonylation of amines under atmospheric pressure in presence of base. Shi and Deng have reported a gold complex [(Au(PPh_3) Cl] as an active catalyst for oxidative carbonylation reaction for the first time. These researchers have also developed a relatively simple catalyst system consisting of $PdCl_2$ and sulfated zirconia for the efficient synthesis of carbamates.[145] Recently F. Shi et al.[146] have developed an efficient catalyst system, Pd complex-ionic liquid, for the carbonylation of amines and shown the reusability of catalyst with slight loss in catalytic activity.

1.5.2.3. Carbon dioxide mediated carboxylation of amine to carbamate

The CO_2-based carbonylation chemistry holds the potential of being industrially the most attractive, due to the non-toxic nature and the abundant availability of carbon dioxide as the carbonylating agent. However, the major challenge associated with this route remains the activation of CO_2. The utilization of carbon dioxide in the synthesis of carbamates can represent an attractive alternate route to conventional phosgene or isocyanate based routes. (Scheme 1.25).

$$\text{R-NH}_2 + \text{CO}_2 + \text{R'-X} \xrightarrow{\text{Catalyst}} \text{RNHCOOR'} + \text{HX}$$

Scheme 1.25. Carboxylation of amine with carbon dioxide

Chisholm and Extine in 1977 showed that transition metal complexes of *N,N*-dimethyl amide $M(Me_2N)n$ add onto CO_2 giving metal-carbamato derivatives.[147] Later Tsuda et al.[148] reported the catalytic conversion of amines and carbon dioxide to carbamates. Kojima et al.70 found that aluminum porphyrine is able to activate CO_2 and the catalytic system thus generated yields carbamate from amine and epoxide under ambient condition with TON of ~ 35. Ruthenium catalyzed carboxylation of secondary amines and terminal alkynes has been reported to give enol carbamates in good yields with high regio and sterio selectivity.[149] Higher yields of carbamates were realized when alkyl halides and a suitable "host-guest" type of additives such as macrocyclic poly-ethers[107] or onium salts[150] or strong organic bases with the ability to delocalize their charge were employed as additives. However, the disadvantage of this methodology was that it requires stoichiometric amount of alkyl halide and produces equal amount of halide salts as a waste.

1.5.2.4. Carboxylation of amine to carbamate using organic carbonate

The alcoxycarbonylation of amines, which may also be termed as the aminolysis of organic carbonates (Scheme 1.26) is a facile and attractive synthetic route to carbamates.

$$\text{RR'NH} + \text{R''OCOOR''} \xrightarrow{\text{Catalyst}} \text{RR'NHCOOR''} + \text{R''OH}$$

Where R,R'= H, alkyl or aryl; R"= alkyl or aryl group

Scheme 1.26. General scheme for catalytic carboxylation of amine to carbamate using organic carbonate

1.5.2.4.1. Advantages of methoxycarbonylation route to carbamates

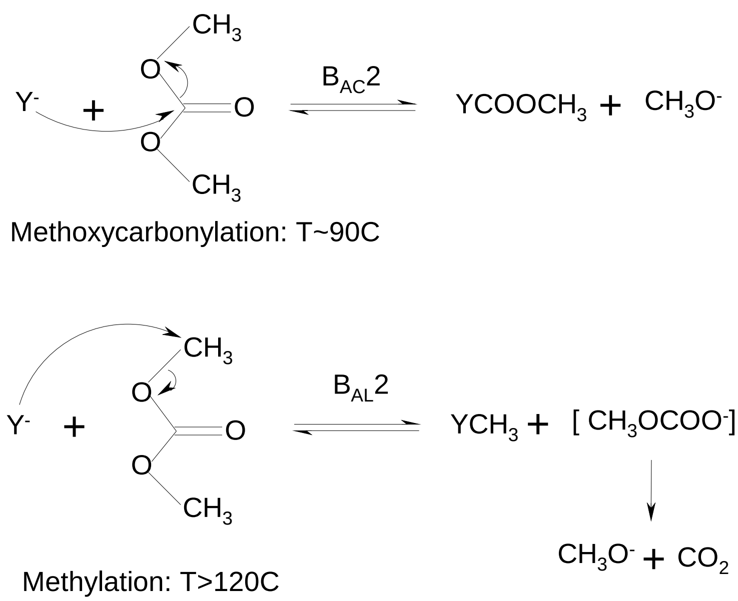
The major reasons for this route being under intense investigation since last three decades are as follows

1. This transformation requires an amine and an organic carbonate as substrates, which are easily available, and are much safer to handle as compared to those used in the conventional phosgene-based technology. Also, the process produces only an alcohol as a co-product, and is quite atom-economical.
2. The industrial production of DMC by oxidative carbonylation of methanol has been achieved by Enichem[151] and Ube[152]. Due to this, organic carbonates like DMC are now cheaply and abundantly available. The alcohol co-products generated in the alcoxycarbonylation reaction can therefore be reused for the synthesis of the organic carbonate, thereby improving the atom economy of the process. Besides, the organic carbonates of high boiling alcohols[153] or phenols[154] can be obtained easily by trans-esterification of DMC or diethyl carbonate. Thus, non-phosgene routes to carbonic acid diesters like dimethyl carbonate (DMC) and aromatic diesters like DPC are now available.
3. The conventional phosgenation route to carbamates generates large amounts of salts, which are generated when the hydrochloric acid formed in the process is neutralized with an alkali. Also, the process is highly exothermic, and requires elaborate cooling apparatus, which adds to the capital expenditure. The methoxycarbonylation does not generate any acidic or alkaline byproduct. Also, the reaction is only slightly exothermic.
4. Phosgene-based carbamate synthesis results in low chemoselectivity, and hydrolysable chlorinated byproducts are formed. Methoxycarbonylation can be tailored using appropriate catalyst and reaction conditions and parameters to get a high selectivity to carbamates.
5. Unlike the other routes for amine carbonylation, this route does not require the expensive transition metal catalysts, but much economical catalysts like salts or compounds of zinc, lead and tin. Also, no promoter or co-catalysts are required, thus eliminating the possibility of generation of salts or undesirable byproducts.

1.5.2.4.2. Chemoselectivity in alcoxycarbonylation reaction

Alcoxycarbonylation of amines has been reported with several acidic, basic catalysts, and aromatic carbonates like diphenyl carbonate (DPC) or aliphatic carbonates like dimethyl carbonates (DMC) have most frequently been employed as the carbonates. Owing to its easy availability, DMC has been used as the carbonate in several reports for investigation of activities of various catalysts. DMC is generally used as a carboxylating or methylating agent, and the chemoselectivity can be tuned using appropriate reaction conditions and catalysts.

The reagent chemistry of organic carbonate has been developed by Ono and Tundo for synthesis of several important organic intermediates, establishing DMC as a benign building block for organic synthesis. Alkyl carbonates e.g. DMC show two sites for interacting with nucleophilic reagents: a) a methyl sp^3 carbon atom b) the carbonylic sp^2 carbon. The attack of a nucleophile Y- either of the carbon atoms depends on the reaction temperature and the catalyst used (Scheme1.27). It should be noted, however, that there is not always a clear cutoff between the two pathways of Scheme 1.27. Nevertheless, it is generally observed that (i) at the reflux temperature (90°C), DMC acts primarily as a methoxycarbonylating agent by a $B_{AC}2$ (bimolecular, base-catalyzed, acyl cleavage, nucleophilic substitution) mechanism where the nucleophile attacks the carbonyl carbon of DMC, giving the transesterification product. (ii) at higher temperatures (usually >160°C), DMC acts primarily as a methylating agent by the $B_{AL}2$ (bimolecular, base-catalyzed, alkyl cleavage, nucleophilic substitution) mechanism, where the nucleophile attacks the methyl group of DMC.[155] Among methoxycaronylation and methylation, only the latter reaction is irreversible, because the CH_3OCO_2H that is formed decomposes to methanol and CO_2. Since both methylation and methoxycarbonylation generate CH_3O^-, both reactions can be conducted in the presence of catalytic amounts of base. This avoids the formation of unwanted inorganic salts as byproducts and the related disposal problems. In principle, the methanol produced can be recycled for the production of DMC.[156]



Scheme 1.27. Nucleophilic substitution on DMC by $B_{AC}2$ and $B_{AL}2$ mechanisms

Dialkyl carbonates are thus interesting examples of ambident electrophilic substrates and the regioselectivity of the attack by nucleophiles is an important feature of the chemistry of these compounds.

1.5.2.4.3 Catalysis of alcoxycarbonylation reaction

The literature on carboxylation of amine to carbamate using organic carbonate is summarized in Table 1.2. Most of the reported literature shows that this reaction has been carried out preferably using the organic carbonate as a substrate as well as solvent. The catalysts with moderate to good activities reported for methoxycarbonylation include strong bases[157] such as alkali metal alkoxides, or Pb, Zn, Co, Sn, Al, Mn and Ti organometallic complexes and compounds[158] have been widely used as catalyst in the carboxylation of anilines. Lewis acids, such as $AlCl_3$, $SnCl_2$, $ZnCl_2$, $Zn(OAc)_2$, $FeCl_3$ or metal (Rh, Ru) complexes have also proved to be effective catalysts.[159] Aresta et al. have demonstrated excellent catalytic activity of organophosphorus acids $Ph_2P(O)OH$, $(PhO)_2P(O)OH$, $(BuO)_2P(O)OH$ and $(BuO)P(O)(OH)_2$ towards the alcoxycarbonylation of aromatic monoamines with dimethyl carbonate (DMC) as well as diphenyl carbonate (DPC), with very high selectivity to the corresponding carbamates.[160] The authors have rationalized the catalytic role of the P-acid. The reaction mechanism shows intriguing analogies with the mechanism of formation, in living systems, of carbamate anion from ammonia and hydrogencarbonate catalyzed by the carhamylphcsphate synthase (CPS) enzyme. Aresta et al., in another report, have extended this investigation to aromatic diamines focussing the attention on 4,4'-methylendianiline (MDA) and 2,4-diaminotoluene (TDA), as the corresponding dicarbamates are suitable precursors to methylene diphenyl diisocyanate (MDI) and toluene diisocyanate (TDI), respectively.[161] These diisocyanates are useful monomers for the synthesis of industrially relevant polyurethanes. The authors have demonstrated that, in the presence of selected P-acids and under mild conditions, both MDA and TDA can react with DPC, affording the corresponding dicarbamates selectively and with high yields. Further, under controlled experimental conditions, the same reaction can be used for the selective synthesis of corresponding monocarbamates.[162]

Synthesis of carbamate from dialkyl carbonate and amines in the presence of γ-Al_2O_3,[168] MCM-41-TBD,[171] and Yb(OTf)[163] has been also reported. SiMa and co-workers have demonstrated alkoxy carbonylation of primary and secondary amines by DMC using ionic liquids (e.g. salts of substituted imidazolium). The ionic liquids function both as catalyst as well as solvents. In addition use of ionic liquid provides an efficient separation of products from catalyst components. Tundo et al. have also reported, CO_2 promoted Carboxylation of aliphatic amines to carbamate in excellent yield under super critical conditions (90 bar CO_2; 130ºC). Extensive screening study on micro porous and mesoporous zeolites and metal oxides catalysts has been reported for synthesis of methyl *N*-phenyl carbamate from DMC and aniline.

$Mn(OAc)_2.2H_2O$ catalyzed the reaction of butylamine with DMC to afford methyl N-butyl carbamate, which was obtained in a 91% yield (amine base) at 333K in 4 h when the DMC/butyl amine ratio was 2/1. This reaction was also catalyzed with ZrO_2-SiO_2 (Zr/Si = 5) mixed oxide. The yield of methyl N-butyl carbamate was 88% at 333K in 4 h.[164]

Table1.2. Literature on carboxylation of amine using organic carbonate

Sr	Substrate	Carbonate	Catalyst	Time, h	Temp, ºC	Amine conv, %	Carbamate yield, %	Ref.
1	C_6H_5-NH_2	DMC	$Zn(OAc)_2.H_2O$	1	160	98	97	165
2	*m*-Cl-C_6H_4-NH_2	DEC	NaH	1.5	25	-	70	166
3	C_6H_{13}-NH_2	DMC	$Pb(NO_3)_2$	2	25	-	93	166
4	C_3H_7-NH_2	DMC	$Pb(NO_3)_2$	2	120	99	99	167
5	C_6H_5-NH_2	DMC	γ-Al_2O_3	48	100	98	93	167
6	*p*-Cl-C_6H_4-NH_2	DMC	γ-Al_2O_3	48	90	100	95	168
7	$C_{10}H_{21}$-NH_2	DMC	$scCO_2$	17	90	100	85	168
8	$C_{10}H_{21}$-NH_2	DEC	$scCO_2$	20	130	96	83	169
9	n-C_4H_9-NH_2	DMC	$Yb(OTf)_3$	8	130	80	65	169
10	C_6H_5-NH_2	DMC	$Yb(OTf)_3$	8	80	-	93	170
11	*p*-NO_2-C_6H_4-NH_2	DMC	$Yb(OTf)_3$	8	80	-	96	170
12	C_6H_5-CH_2-NH_2	DEC	MCM-41-TBD	24	125	99	98	171
13	C_6H_{11}-NH_2	DEC	MCM-41-TBD	24	125	92	90	171
14	C_6H_{11}-NH_2	DMC	BMImCl	1	170	100	83	172
15	C_6H_5-CH_2-$N(CH_3)H$	DMC	BMImCl	1	170	100	99	172
16	H_2N-$(CH_2)_6$-NH_2	DMC	$Sc(OTf)_3$	40	20	100	80 (dicarbamate)	173
17	C_6H_5-NH_2	DMC	ZrO_2/SiO_2	7	170	89	53	174
18	1,5-naphthalene diamine	DMC	Anhydrous $Zn(OAc)_2$	3	170	100	95	175

1.6. OXIDATIVE CARBONYALTION OF AMINES

Oxidative carbonylations have acquired a growing importance during the last few years, owing to the development of new and selective catalytic systems, mainly based on palladium, which are able to promote ordered sequences of transformations under mild conditions with formation of highly functionalized carbonyl compounds in one step starting from very simple building blocks. Transition metal catalysts yield substituted ureas and carbamates from amines by oxidative carbonylation under mild reaction conditions. Also, the oxidative carbonylation of alcohols and phenols to carbonates can be catalyzed by palladium or copper species.[176] This reaction is of particular practical importance, since it can be developed into an industrial process for the phosgene-free synthesis of dimethyl carbonate (DMC) and diphenyl carbonate (DPC), which are important industrial intermediates for the production of polycarbonates. Moreover, DMC can be used as an eco-friendly methylation and carbonylation agent.[177] The industrial production of DMC by oxidative carbonylation of methanol has been achieved by Enichem[178] and Ube[179].

1.6.1. General features of oxidative carbonylation reaction

Carbonylation is a process in which carbon monoxide is inserted into an organic substrate under the action of a metal undergoing a reduction of its oxidation state [the reduction Pd(II) → Pd(0)] is the most common case]. In order to achieve a catalytic reaction, some way must be provided to reconvert the metal in its original oxidation state. In other words, an external oxidant is needed to allow a stoichiometric process (eq. 1.6) to become a catalytic one (eq. 1.7).

$$\mathrm{SH_2} + \mathrm{CO} + \mathrm{M\,(X)} \longrightarrow \mathrm{S(CO)} + \mathrm{M(X\text{-}2)} + 2\mathrm{H^+} \tag{1.6}$$

$$\mathrm{SH_2} + \mathrm{CO} + [\mathrm{OX}] \xrightarrow{\text{M cat}} \mathrm{S(CO)} + [\mathrm{OXH_2}] \tag{1.7}$$

1.6.1.1. Homogeneous catalysts for oxidative carbonylation of amines

Palladium (II) salts or complexes have been known to catalyze the formation of carbamates by the oxidative carbonylation of aliphatic or aromatic amines and aliphatic alcohols in the presence of CO and oxygen. In addition, hydrochloric acid and a cocatalyst such as $FeCl_3$ or $CuCl_2$ are generally added to the reaction mixtures.[180]

Mulla et al.[181] have screened several salts and complexes of transitin metals like ruthenium, rhodium and palladium. The complexes in this study were preformed, and the ligands studied included mostly monodentate ligands containing N, P or O as the donor atoms. It was found in this study that, the ligand variation does not substantially alter the rate of the reaction. Moreover, the product selectivity remains very high (>98%) with all the ligands. Surprisingly, the authors have found out that ruthenium complexes gave better catalytic activities than palladium complexes, and the best catalyst in terms of reaction rate was $[Ru(CO)_3I_3]$ NBu_4.

Giannoccaro et al. have reported soluble catalyst complexes of palladium[182] and nickel[115] for the oxidative carbonylation of aniline. The addition of copper salts in palladium catalyzed reactions have reported to enhance the reaction rate. Giannoccaro has found that, the choice of solvent is critical in terms carbon monoxide selectivity. It has been reported that the undesirable CO oxidation to CO_2 is almost suppressed when the reaction is carried out in alcohol media, while the CO_2 formation is marked when THF or dimethoxypropane wre used as solvents. Additionally, tailoring the reaction conditions becomes an important factor in deciding the product selectivity when alcohols are used as solvents, and more drastic reaction conditions, i.e., higher pressure and temperature result in the formation of carbamate esters instead of the substituted ureas. The author has therefore postulated that, it was likely that carbamates are formed not by direct interaction with aniline, CO, and alcohol; but rather by alcoholysis of the urea.

Research by Pri-Bar et al.[183] indicates that iodine or potassium iodide can be used as a promoter for the carbonylation of primary and secondary amines, instead of a copper (II) salt such as $CuCl_2$. Treatment of primary or secondary amines with carbon monoxide in acetonitrile, in the presence of iodine, potassium carbonate, and a catalytic amount of palladium (II) acetate for 3 hours at 95°C afforded di- and tetrasubstituted ureas. Iodine and the catalyst are needed for the reaction to occur. Absence of the base results in a lowering of the overall yields. This is believed to be due the partial conversion of the amine to the ammonium salt by the HI byproduct. In the presence of a small quantity of air or oxygen, the reaction results in the formation of an oxamide, a double carbonylation product, which is formed in addition to the urea.[184] This phenomenon is more prevalent with secondary amine substrates.

Studies by Calderazzo showed that decacarbonyldimanganese and pentacarbonylmethylmanganese can catalyze the carbonylation of primary aliphatic amines to disubstituted ureas.[185] On heating primary aliphatic amines to 180-200° under a pressure of CO (106 - 135 atm), in the presence of $Mn_2(CO)_{10}$ or $CH_3Mn(CO)_5$, the corresponding disubstituted ureas were obtained in moderate yields. Small yields of *N*-alkyl formamides were also obtained, but their formation is believed to be due to a reaction pathway unrelated to the one that produces ureas. Secondary aliphatic amines, however, were unreactive; and aromatic amines such as aniline gave very poor yields of the corresponding diphenylurea. Other manganese catalysts such as (η-methylcyclopentadienyl) manganese tricarbonyl have been also used in the carbonylation of primary amines to the corresponding disubstuted ureas.[186]

Other transition metals have been used for carbonylation of amines to ureas, but not commonly. Cobalt complexes, for example, can only catalyze anilines to form the corresponding diaryl ureas. The selectivity for the oxidative carbonylation of amines with cobalt catalysts is not very high. When *N, N'*-bis(salicylidene)ethylenediaminecobalt(II) was used to carbonylate amines in the presence of methanol, CO (1 atm) and dioxygen (1 atm); the oxidative carbonylation was found to produce a number of side products. Optimization work carried out by Bassoli et al.[187] at increased pressure of CO and O_2 using eventually obtained a higher selectivity of urea.

Nickel complexes, unfortunately, have not found a foothold in carbonylation catalysts because of their low reactivity. This is true of a number of complexes of other transition metals; such as platinum, rhodium, and iron. The issues with most transition metal complexes are the low yield of urea and formation of side products. In addition, most transition-metal catalysts cannot carbonylate both primary and secondary aliphatic amines. They are mainly successful in the formation of *N,N'*-diaryl ureas from the primary aromatic amines.

More recently, gold has been used to catalyze the carbonylation of amines to form carbamates. Alkyl ureas have been found to be formed in good yield when an Au(I) catalyst such as Au(PPh$_3$)Cl is used.[118] Low turnover frerquencies were obtained with these catalysts.

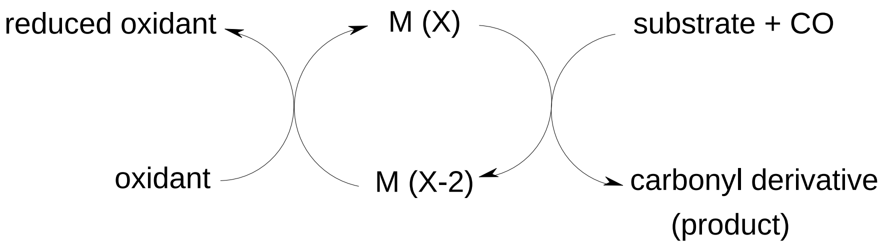
Tungsten complexes have been recently used to carbonylate amines to ureas. Studies carried out by McElwee-White et al.,[119] found that direct carbonylation of primary amines to *N, N'*-disubstituted ureas could be attained using the tungsten (IV) imido carbonyl complex $[(CO)_2W(NPh)I_2]_2$ in a stoichiometric reaction. Unfortunately, this method is not applicable to the carbonylation of secondary amines to form tetrasubstituted ureas because formamides are formed instead. Efforts to improve yields of ureas and the range of amines substrates led to the $W(CO)_6$/ I_2 catalytic system. In this particular catalytic system, the I_2 acts as the oxidant, CO is the carbonyl source, and potassium carbonate acts as the base to regenerate the free amine from the amine salt formed during the course of the reaction. This reaction was applicable to the carbonylation of both primary and secondary aliphatic amines to ureas; however, it fails for aromatic amines.[188]

1.6.1.2. Heterogeneous catalysts for oxidative carbonylation of amines

Fukuoka et al.[189] tried various supported transition metal catalysts for the oxidative carbonylation of amines, palladium being the preferred metal. Some other reports on heterogeneous palladium for oxidative carbonylation of amine include-metallic Pd;[190] Pd/C by Gupte et al;[191] immobilized Pd like montmorillonite-bipyridinepalladium(II) acetate;[192] sulfate modified zirconia supported,[193] i.e. Pd/ ZrO_2-SO_4^{2-}; etc. It is observed, however, that all these reports suffer from either low yields of ureas, high catalyst loading or non-applicability to all the classes of amines owing to very low conversions or yields. It is also important to note that substituted ureas obtained from high molecular weight or substituted aromatic amines with higher number of C atoms are sparingly soluble in most of the solvents and tend to precipitate out of the reaction mixture. In such cases, heterogeneous catalysts are not easy to separate from the product.

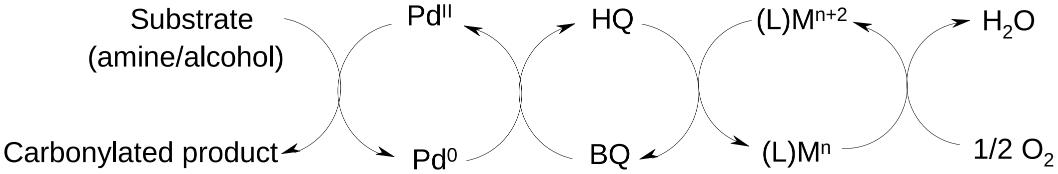
1.6.1.3. Reoxidation of transition metal catalyst in oxycarbonylation of amines

The metal reoxidation process has always been a major problem in oxidative carbonylation, in relation to which a large number of patents have been issued. These reactions involve the Pd^{2+}/Pd^0 redox couple, and the key problem is to avoid clustering of zerovalent Pd and its efficient reoxidation. Direct reoxidation with O_2 is also possible, and has proven particularly effective in the case of Pd(0) → PdI_4.



Scheme 1.28 Reoxidation of transition metal catalyst in oxidative carbonylation reaction

However, if the reduction of palladium in the cycle as shown in Scheme 1.28 is from Pd(II) to Pd(0), i.e. to metallic palladium, direct reoxidation with oxygen is rather slow. Further improvement of this palladium reoxidation process is a multi-step electron transfer system, which speeds up the oxidation stage[194] by using benzoquinone (BQ) and a redox-couple based on salts of Mn, Co, Ce or Cu.[195] In the case of $CuCl_2$, the resulting cuprous chloride in some cases has in its turn been reoxidized by means of oxygen or other oxidants such as alkyl nitrites. Such kind of catalyst systems (Pd-Cu) have been reported for oxidative carbonylation of amines and alcohols.[196,197] In these cases, the palladium reoxidation is generally done indirectly with oxygen and realized by means of an electron transfer chain consisting of a combination of two or more metallic and/or organic co-catalysts (Scheme 1.29).



HQ- hydroquinone; BQ- benzoquinone, M- metal co-catalyst

Scheme 1.29. Electron transfer chain between Pd and O_2.

Bäckvall et al. have developed “triple-catalysis” systems as shown in Scheme 1.29 for palladium catalyzed oxidation reactions, to enable the use of dioxygen as the stoichiometric oxidant.[198] The researchers propose that the co-catalyst/BQ systems are effective because certain thermodynamically favored redox reactions between reagents in solution (including the reaction of Pd^0 with O_2) possess high kinetic barriers, and the co-catalytic mixture exhibits highly selective kinetic control for the redox couples shown in Scheme 1.29.[199]

The reoxidation of the principle metal catalyst like palladium is favoured by stabilizing the Pd species through interaction with a chelating ligand.[200] In particular, substituted phenanthroline ligands are shown to have a positive influence on the catalyst performances in the oxycarbonylation of phenol.[201]

1.6.1.4. Carbon monoxide oxidation in oxidative carbonylation

A major point of concern in oxidative carbonylation is the presence in the reaction medium of water, which is even formed as a co-product when oxygen is used as reoxidant. In fact, in the presence of water, competitive metal-promoted oxidation processes, such as oxidation of CO to CO_2, may take place, which reduce the activity of the catalyst towards the desired carbonylation reaction and also cause low CO selectivity towards the desired carbonylation products. The oxidation of CO to CO_2 may be promoted by Ir(IV), Pt(IV, II), Rh(III), and especially by Pd(II), and can be stoichiometric (eq. 1.8) or catalytic (working in the presence of an oxidant such as O_2, Cu(II) or quinone, eq. 1.9). In the case of particularly water-sensible oxidative carbonylation processes, a dehydrating agent has proven necessary to achieve acceptable catalytic efficiencies and/or product yields. Several systems have been envisaged to eliminate water, such as acetals, enol ethers, orthoformates, etc.

$$MX_2 + CO + H_2O \longrightarrow M + CO_2 + 2HX \qquad 1.8$$

$$CO + H_2O + [OX] \longrightarrow CO_2 + [OXH_2] \qquad 1.9$$

1.6.1.5. Recovery and reuse of catalyst

The soluble forms like soluble salts or complexes of Group VIII transition metals, and in particular palladium, are well-established as highly active catalysts for the oxidative carbonylation of amines and alcohols.[202,203] However, effective recovery of the used metals remains a critical item.[196] Major emphasis has therefore been on the exploration of supported or immobilized forms of the catalysts. Fukuoka et al. reported excellent activity of insoluble palladium catalysts like metallic palladium, Pd/C, Pd/SiO_2, Pd/Al_2O_3 and Lindlar catalyst (Pd-Pb/$CaCO_3$) in conjunction with halide promoters. Gupte et al.[204] have done extensive research on the catalytic activity of supported palladium catalysts for amine oxycarbonylation, which includes the effect of reaction parameters like the effect of substituents in the amine substrates, solvents, halide promoters, the concentration of the iodide promoter, partial pressures of carbon monoxide and oxygen, etc.

Solubility of ureas- Substituted ureas are stable, less reactive molecules having low solubilities in even highly polar organic solvents.[92,205] Therefore, the mass transfer limitations and separation of the catalyst from the precipitated product mass can pose major problems. These situations create unique situation, where neither a homogeneous (soluble) nor a supported, heterogeneous catalyst can satisfy the goal of catalyst-procduct separation, which is the basic requirement of an efficient catalyst system to be practically applicable. Shi et al. have reported the separation of Pd/ZrO_2 catalyst by sieving;[92] in which case, there is a high probability of loss of the expensive transition metal catalyst. Therefore, developing a heterogeneous catalytic system that combines good catalytic performance with satisfactory recovery of the metals used is an extremely important milestone in the efforts to make the oxidative carbonylation route acceptable for industrial applications.

Table 1.3. Summary of literaure on catalytic oxidative carbonylation of amines

Sr. No.	Substrate	Catalyst Pkg	Solvent	Oxidant	Time, Hr	Temp, C/ Pressure, MPa	Amine conv, (%)	Product (sel, %)	Remarks	Ref.
10	*o*-phenylenediamine	Se (stoich/excess)	NMP	O_2/ DMSO	20	100C, 31kg/cm^2	99	*o*-phenyleneurea (98-99)	Several cyclic ureas synthesized in good yields	206
11	Ph-NH_2	2 % Pd/SiO_2, NaI	C_2H_5OH	O_2	3	160-170°C, 86 kg/cm^2	94.5	*N,N'*-Diphenylurea- 1 Ethyl-*N*-phenyl carbamate- 98	Screening of supported transition metal catalysts	207
	Ph-NH_2	5% Rh/C, NaI	C_2H_5OH	O_2	3	160-170°C, 86 kg/cm^2	97	*N,N'*-Diphenylurea- 2 Ethyl-*N*-phenyl carbamate- 84		
	Ph-NH_2	Ru-black, KI	C_2H_5OH	O_2	3	160-170°C, 86 kg/cm^2	67	*N,N'*-Diphenylurea- 21 Ethyl-*N*-phenyl carbamate- 76		
	Ph-NH_2	5% Pt/C, CsI	C_2H_5OH	O_2	3	160-170°C, 86 kg/cm^2	96	*N,N'*-Diphenylurea- 10 Ethyl-*N*-phenyl carbamate- 42		
12	P,S-amine	Pd $(OAc)_2$, K_2CO_3,I	CH_3CN	O_2	2	95°C, 2.7 atm	95	Sub. Urea (95)	High yields of urea	208
						RT	63	Sub. Urea (95)	High yields of urea	
13	R-NH_2	Pt-gr, halide	ROH	O_2	4	150 °C, 90 atm	98	carbamate (95)	-	209

Table 1.3. Summary of literaure on catalytic oxidative carbonylation of amines (cont'd)

Sr. No.	Substrate	Catalyst Pkg	Solvent	Oxidant	Time, Hr	Temp, C/ Pressure, MPa	Amine conv, (%)	Product (sel./yield %)	Remarks	Re f.
14	$PhNH_2$	Pd $(C_6H_7N)_2Cl_2$, NaI	CH_3OH	O_2	2	170° C, 41 atm	59	Urea- 23.2; carba-76.1	Screening of homogeneous transition metal complexes	210
	$PhNH_2$	$Rh(CO)_2acac$, NaI	CH_3OH	O_2	2	170° C, 41 atm	48.4	Urea- 24.3; carba-74.5		
	$PhNH_2$	$Ru(CO)_2(Py)_2Cl_2$, NaI	CH_3OH	O_2	2	170° C, 41 atm	38.8	Urea- 35.1; carba-62.4		
15	Ph NH_2	5% Pd/C, NaI	DMF	O_2	2	100C, 40.8 bar	97	*N,N'*-diphenylurea (97.8)	Parametric studies; mechanism proposed	191
16	$C_{12}H_{25}NH_2$	$PdCl_2$, $CuCl_2$, HCl	CH_3OH	O_2	2	RT, 1 atm	-	carbamate (99)	Acid addition benefitial but not essential	211
	$C_{12}H_{25}NH_2$	$PdCl_2$, $CuCl_2$, HCl	CH_3OH	Di-t-butyl peroxide	2	RT, 1 atm	-	carbamate (79)		
	Piperidine	$PdCl_2$, $CuCl_2$, HCl	CH_3OH	O_2	2	RT, 1 atm	-	carbamate (16) oxamate (12)	Oxamates obtained as Double carbonylation products	
	Piperidine	$PdCl_2$, $CuCl_2$, HCl	CH_3OH	Di-t-butyl peroxide	2	RT, 1 atm	-	carbamate (64) oxamate (16)		
17	$PhNH_2$	Pd-black, CsI	CH_3OH	O_2	2	170, 86 kg/cm^2	95	Methyl-N-phenyl carbamate (MPC) (98)	-	212
18	Me-NH_2	Pd metal, NaI	CH_3OH	O_2	2	443 K, 61 atm	98	Methyl-N-methyl carbamate (86); N,N'-dimethylurea	Screening of catalysts; parameter study	213

Table 1.3. Summary of literaure on catalytic oxidative carbonylation of amines (cont'd)

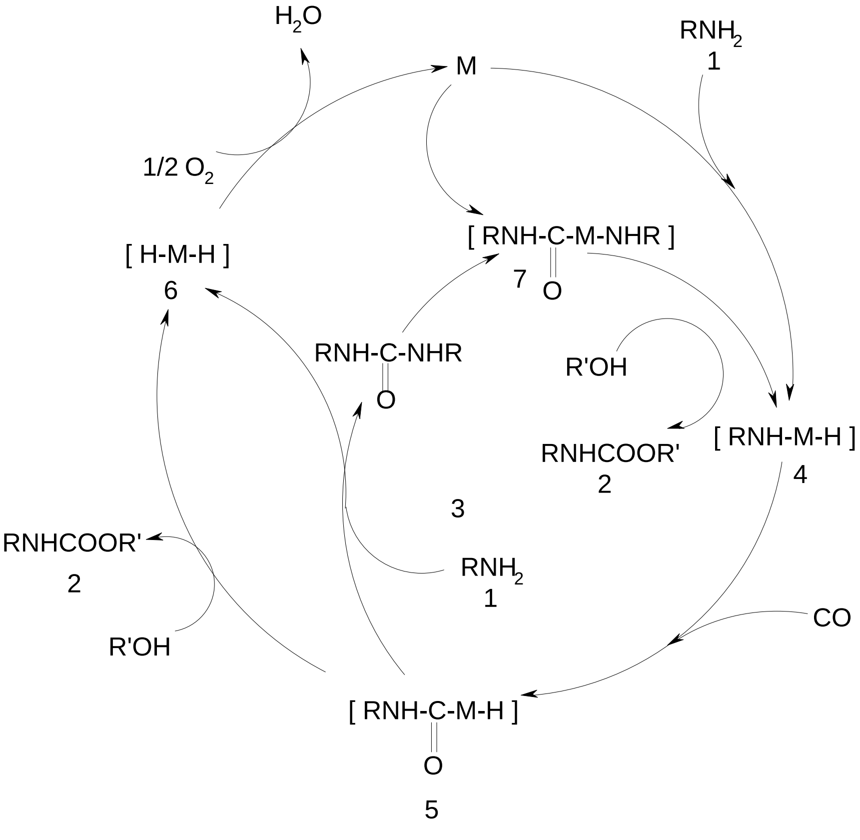
Sr. No.	Substrate	Catalyst Pkg	Solvent	Oxidant	Time, Hr	Temp, C/ Pressure, MPa	Amine conv, (%)	Product (sel./yield %)	Remarks	Ref.
19	P,S-amine or urea	IIIA-VA & VIII gr, Porphyrine or metal phthalocyanine	ROH	O-containing comp (O_2)	3	160, 5.0	93	Carbamate, 96	CO/O_2 1600 psig	214
20	$PhNH_2$	Rh/C or Rh/ZSM-5, LiI	C_2H_5OH	O_2	2	170, 5.17	~91	EPC, 96.7	Effect of support on CO_2 formation	215
21	$PhNH_2$	Pd/ ZSM-5, NaI	CH_3OH	O_2	2	150, 54 bar	99.4	MPC (98.2)	150° C	216
22	Cyclohexyl amine	Pd-clay, 2,2'-bipy, + montmorillnite (Pd-clay), NaI	--	O_2	8	130, 81 atm	100	Carbamate (isolated- 99)	130° C	217
23	*t*-$BuNH_2$	Co-(salen), NaI	EtOH	O_2	3	180, 1000 psi	100	Carbamate (99)	TOF 10-33	218
24	$PhNH_2$	Homo. Transition metal complexes, e. g. $[Ru(CO)_3I_3]NBu_4$	DMSO	O_2	5	100, 1 atm	65	DPU (96)	Activation energy 26.6 kcal/mol	219
25	$PhNH_2$	$(CO)_2W(NPh)I_2(pip)$ (piperidine complex)	CH_2Cl_2	air	24	RT, 1 atm	100	Isolated yield of DPU105%	-	119
26	$PhNH_2$	PVP-$PdCl_2$-$2MnCl_2$, NaI	C_2H_5OH	O_2	30	55, 1 atm	93	EPC (97)	-	117
27	$PhNH_2$	K_2SeO_3 (SeO_2+K_2CO_3)	CH_3OH	O_2	2	130, 6.8	95	Urea 68.8 Carbamate 30.5	High TOF (2082)	220
28	Propylamines	$W(CO)_6$, K_2CO_3	Ch_2Cl_2 / H_2O biphasic	I_2	24	90, 80 atm	90	Isolated yield of diisopropyl urea 90%	CO	119

Table 1.3. Summary of literaure on catalytic oxidative carbonylation of amines (cont'd)

Sr. No.	Substrate	Catalyst Pkg	Solvent	Oxidant	Time, Hr	Temp, C/ Pressure, MPa	Amine conv, (%)	Product (sel, %)	Remarks	Ref.
29	R-NH_2	$\gamma - TiPRh_{0.25}bipy^{d}_{0.33}$; $PhNH_3^+I^-$	--	O_2	1	150, 5	63	MPC (82); DPU (6)	Rh(III)–diamine complexes intercalated in γ-titanium phosphate; TOF~7.5	221
30	$C_{12}H_{25}NH_2$	Pd / ZrO_2-SO_4^{2-}	CH_3CN	O_2	1	135, 4	100	100	TOF 190, Catalyst recovered by sieving	92
31	2,4-diaminotoluene	$Au(PPh_3)Cl + PPh_3$	CH_3OH	O_2	3	200, 5	98	Dicarbamate (93)	Low TOFs (11-36), soluble Au complex catalysts	118
32	$PhNH_2$	[emim][$SeO_2(OCH_3)$]	CH_3OH	O_2	2	60, 1.36	97	*N,N'*-diphenylurea(99)	-	222
33	R-NH_2	$Pd(OAc)_2$ 5 mol %; $Cu(OAc)_2$ 50 mol %	Toluene	Air	2	Reflux, 1 atm	$PhNH_2$=100	Symmetric urea (94)	-	223
	Ph-CH_2-NH_2 + piperidine (1:2)	$Pd(OAc)_2$ 5 mol %; $Cu(OAc)_2$ 50 mol %	Toluene	Air	2	Reflux, 1 atm	$PhNH_2$=100	Asymmetric urea (93)	-	

1.6.2. Mechanism of oxidative carbonylation of amines

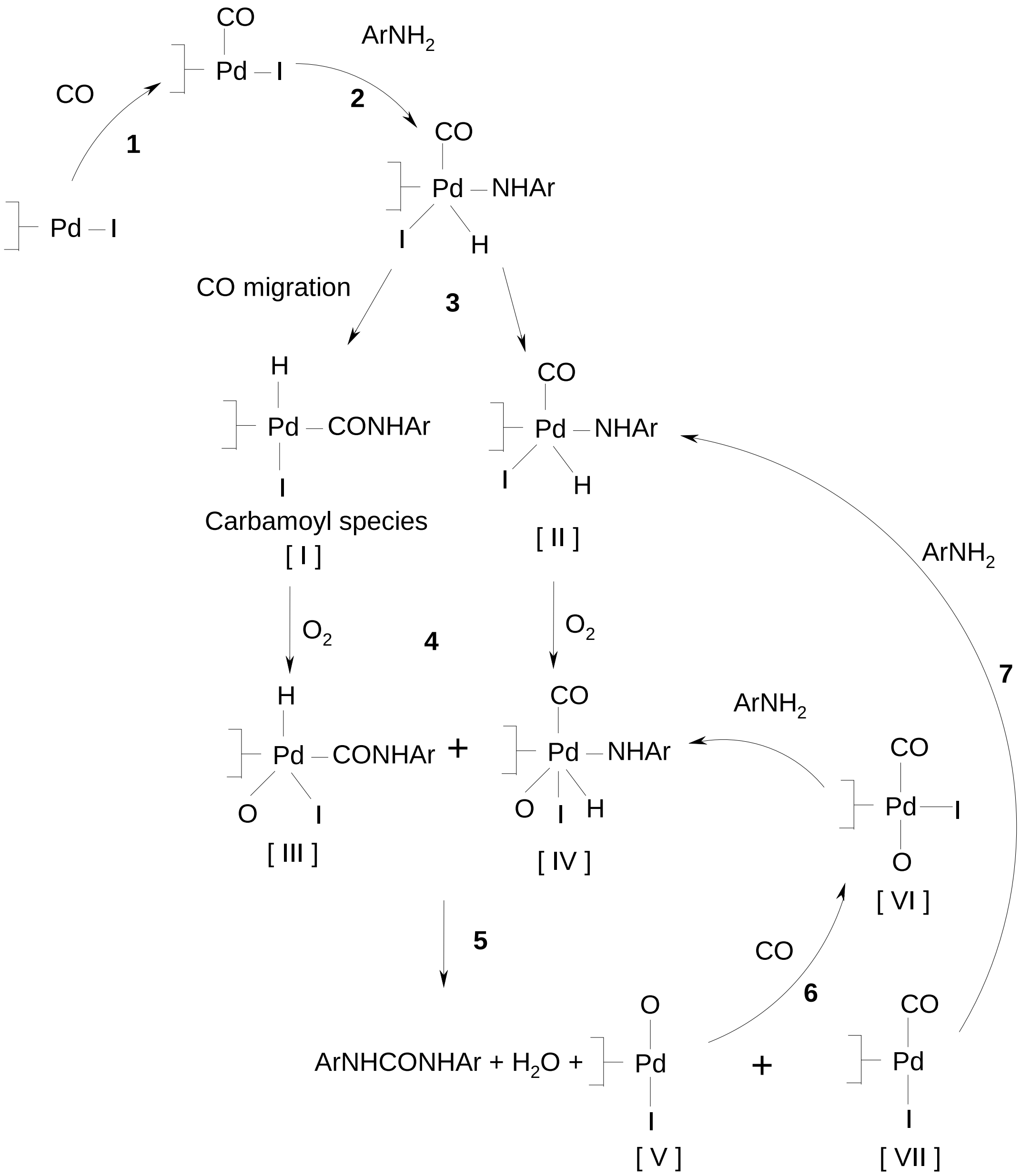
The mechanism of oxidative carbonylation of amines is not clearly understood. Fukuoka et al. investigated oxidative carbonylation of aniline using palladium metal catalyst promoted by iodides and in the presence of methanol as solvent.[224] The authors have proposed that the nucleophilic amine first coordinates with the palladium in metallic state (Pd(0)), which then binds with CO, followed by the insertion into the Pd-N bond to give the metal-carbamoyl species 5 (Scheme 1.30). The latter then reacts with either the amine to give the corresponding urea, or with alcohol to yield the carbamate. In this process, the catalyst forms the metal-hydride species upon the elimination of the urea or carbamate. This species is then reoxidized to metallic state, in the presence of an oxidant like oxygen. In this process, one mole of water is generated.



Scheme1.30. Mechanism for oxidative carbonylation of amine in alcohol

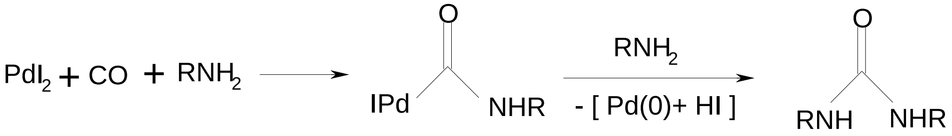
The mechanism proposed leaves some doubts unsolved. The formation of PdH_2 type species is relatively difficult; it may need a strong oxidant to convert the species immediately into Pd. Also, this mechanism does not elaborate the role of the iodide promoter which is essential for this particular catalyst-substrate combination. However, several plausible mechanisms are found in the literature. Vasapollo et al.[225] have demonstrated the synthesis of carbamoyl type of complexes by reacting the complexes of palladium and platinum with carbon monoxide and aniline. The complexes have been well characterized by spectroscopic techniques, and their reactivity has been studied. They found that these complexes react with aniline in the presence of a base and under CO atmosphere to yield *N,N'*-diphenylurea. This provides the basis for the hypothesis that the oxidative carbonylation of aniline proceeds via carbamoyl types of intermediates. Gupte et al.[204] have studied the oxycarbonylation of amines using Pd catalysts in detail. Based on their observations, they have proposed the mechanism illustrated in Scheme 1.2. The authors found that no amine conversion was observed in the absence of the iodide promoter, clearly indicating that palladium activation by iodide was essential for the nucleophilic attack by the amine.

According to the mechanism proposed by Gupte et al. (Scheme 1.31), the heterogeneous palladium is essentially modified by the iodide promoter, and the Pd-I species formed then helps stabilize the subsequent I-Pd-CO moiety. This is followed by the nucleophilic attack of the amine, which leads to the formation of a Pd-carbamoyl complex. The carbamoyl complex then rapidly reacts with oxygen to give the product, i.e. disubstituted urea. It has also been stated that both the Pd-CO and Pd-O type of complexes are formed on the surface of the catalyst, and they play key role in the overall activity of the catalyst.



Scheme 1.31. Proposed mechanism for supported Pd catalyzed oxycarbonylation of amine

The formation of isocynate type of species in the transition metal catalyst has also been proposed in several studies. The oxidative carbonylation of secondary amines and the effect of solvents on the progress of the reaction studied by Gabriele et al. in the PdI_2-KI-CO_2 type of catalyst system sheds light on the possibility of formation of isocyanato type of species. According to the authors, the reaction proceeds via formation of a carbamoylpalladium type of species, and generates two moles of HI and one mole of Pd(0).



Scheme 1.32(a). Formation of carbamoylpalladium species as the intermediate

The reoxidation of Pd(0) occurs by oxidative addition of I_2, which in turn is generated by the oxidation of HI by oxygen. The basicity of amines in this case, therefore, hinders the reaction progress due to the acid-base equilibrium as shown in Scheme 1.32(b).

$$RNH_2 + HI \longrightarrow R\overset{+}{N}H_3 + I^-$$

Scheme 1.32(b) The acid-base equilibrium between amine and HI

The equilibrium makes the amine unavailable for the catalytic carbonylation, and therefore the equilibrium needs to shift towards right if the reaction is to progress. The authors have found out that the intelligent choice of solvent such that the basicity of amine is suppressed as far as possible, and also allows for the dissolution of the PdI_2-KI catalyst system results in very high activity of the catalyst in terms of turnover numbers. The promoting effect of carbon dioxide has also been attributed to the lowering of the basicity of the amine substrate by the formation of a carbamate species. The authors have further reported detection of isocyanates in low conversion experiments, and also that secondary amines are unreactive with this catalyst system. These results suggest the carbamoyl-palladium species is in pre-equilibrium with the substrate, and is followed by the formation of an isocyanate as shown in Scheme 1.33.

$$PdI_2 + CO + RNH_2 \xrightarrow{-[\,Pd(0) + HI\,]} R{=}N{=}C{=}O \longrightarrow RNH(CO)NHR$$

Scheme 1.33. Formation of isocynate intermediate in the oxidative carbonylation of amine

Further, the authors have observed the formation of unsymmetrical ureas as predominant products when a slight excess of secondary amines were added in conjunction with the primary amine substrate, which again supports the claim about the formation of isocyanate intermediate in the catalytic cycle.

1.6.3 Safety Aspects in Oxidative Carbonylation

The oxidative carbonylation using oxygen or air as the oxidant deserves special attention in terms of safety. Not only is carbon monoxide a poisonous gas, but it also forms a highly explosive mixture with air or oxygen, when mixed in particular ratios. It is therefore a necessity to the potential hazards associated with oxidative carbonylation reaction.

1.6.3.1 The hazards associated with carbon monoxide

The toxicological effects of carbon monoxide, exposure limits and the symptoms associated with its exposure are well documented. Nevertheless, CO intoxication often presents a significant challenge, as treatment protocols, especially for hyperbaric oxygen therapy, remain controversial because of a paucity of definitive clinical studies.

The significant pathophysiological effects of exposure to carbon monoxide (CO) are-

- Impaired oxygen delivery and utilization at the cellular level
- It has profound impact on the organs with highest oxygen requirement, e.g. brain, heart.
- It binds reversibly with hemoglobin, resulting in relative anemia. The affinity of CO towards hemoglobin is 230-270 times more avid compared to oxygen; hence even small CO concentrations result in significant levels of carboxyhemoglobin (HbCO).
- It binds to cardiac myoglobin with great affinity, resulting in myocardial depression.
- Studies have indicated that CO may cause brain lipid peroxidation and leukocyte-mediated inflammatory changes in the brain, a process that may be inhibited by hyperbaric oxygen therapy.

The prominent symptoms caused by acute poisoning are malaise, fatigue, chest pain, palpitations, lethargy, confusion, depression, impulsiveness, nausea, vomiting, diarrhea, abdominal pain, headache, drowsiness, confusion, visual disturbance, fecal and urinary incontinence, memory and gait disturbances, bizarre neurologic symptoms and coma.

1.6.3.2 The hazards associated with mixtures of carbon monoxide with oxygen or air

Fire or explosions may occur in confined spaces which have an atmosphere within the explosive limits of the gas (or liquid vapour). Explosive limits (also known as “flammable limits”), expressed in percentage (%), may be defined as the minimum and maximum concentrations of a flammable gas or vapour between which ignition can occur. Concentrations below the lower explosive limit (LEL) are too lean to burn while those above the upper explosive limit (UEL) are too rich. The LEL and UEL for carbon monoxide in air are shown in Figure 1.1.

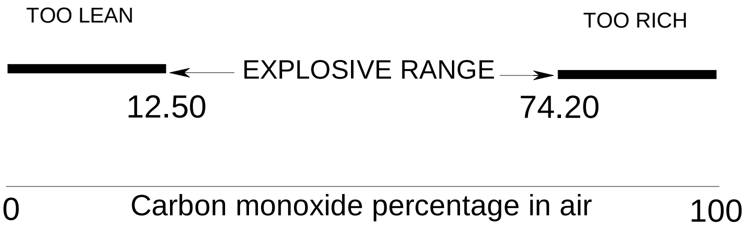


Figure 1.1 Lower Explosive Limit (LEL) and Upper Explosive Limit (UEL) for CO in air

This diagram explains why a percentage of CO in air in the range of 12.5 to 74.2 is explosive.[226] Similarly, the explosive limits of CO in pure oxygen are 15.50-93.90.

1.7. SCOPE AND OBJECTIVE OF THE THESIS

Disubstituted ureas and carbamates are examples of finechemical intermediates of immense importance in chemical indusrty that find applications in diverse areas such as agrochemical, pharmaceutical, polymer and fine chemical industry. They also exemplify a large section of the chemical industry still synthesized to a major extent using hazardous, non-eco friendly reagents like phosgene, isocyanates or chloroformates. Despite extensive studies in the catalysis of oxidative carbonylation, the limitations such as catalyst leaching and catalyst-product separation problems have not been addressed thoroughly. Very importantly, the research in catalysis in this area shows complete disregard on catalyst separation issue and its recovery when a multiphase catalytic reaction which results in a solid product formation is taken into account. Methoxycarbonylation of amines also presents an attractive route for the synthesis of carbamtes; however, a better understanding of the activity of economical, heterogeneous and most importantly reusable catalysts still lacks the understanding of the mechanism and kinetics, which is an integral part of the study of catalysis when taken up in a commercial application point of perspective.

The state of the art on transition metal catalyzed oxidative carbonylation and methoxycarbonylation of amines evidently shows good scope for a detailed understanding of the catalysis, and exploration of new, highly active and reusable catalysts to make these routes industrially attractive.

Keeping these observations from the literature survey in the background, following specific objectives were set for the research carried out in this thesis-

- Aqueous-biphasic oxidative carbonylation of amines using water-soluble transition metal catalysts.
- Lead oxide catalyzed methoxycarbonylation of amines with dimethylcarbonate.
- Oxidative carbonylation of amines for the synthesis of disubstituted ureas catalyzed by Pd nanoparticles immobilized on amine-functionalized zeolite.

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Chapter 2

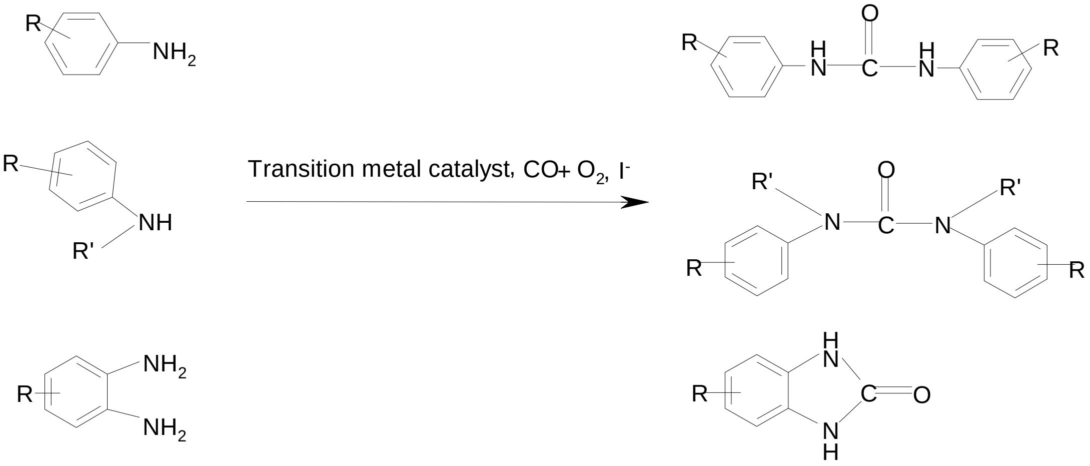
Aqueous-Biphasic Oxidative Carbonylation of Amines Using Water-soluble Transition Metal Catalysts

This chapter describes the synthesis of novel water-soluble transition metal catalysts by using sulfonated N-ligands, their characterization using IR, NMR and other conventional techniques; and their application for the oxidative carbonylation of amines in aqueous biphasic medium. The substituted urea products formed in oxidative carbonylation of amines have sparing solubility in majority of organic solvents, and therefore tend to contaminate the heterogeneous catalysts. In this context, the water-soluble catalysts carry the unique advantage of keeping the catalyst separated from both the organic phase as well as the precipitated products; thereby avoiding the contamination of precious catalyst. The catalyst sytem has been found to be useful for synthesizing disubstitued ureas by oxycarbonylation of a wide variety of amines, including cyclic ureas. The different parametric studies on the activity and selectivity of the reaction have been performed for the proper understanding and optimization of the catalyst system. The water soluble catalyst complexes were found to be highly active, selective, stable and recyclable, and thus were demonstrated to be efficient and truly heterogeneous in nature.

2.1. INTRODUCTION

The substituted ureas find vast number of applications. Disubstituted ureas are important agricultural chemicals, resin precursors, dyes and additives to petroleum compounds and polymers.[1] They are also useful in the synthesis of carbamates, which are important precursors to polyurethanes. Besides these, cyclic ureas also are important agricultural and pharmaceutical compounds. The cyclic substituted urea functionality has been found to appear in drugs like HIV-protease inhibitors,[2] FKBP12 inhibitors, and CCK-B receptor antagonists. Some substituted ureas have been found to act as artificial receptors and self-assembled supramolecules.

Substituted ureas have conventionally been produced by the reaction of amines with carbamyl halides, isocyanates or phosgene.[3] However, a few major problems are associated with the phosgenation technology. The phosgene gas itself is highly toxic and corrosive, and hence poses severe handling hazards. Besides, the reaction produces voluminous amounts of hydrolysable chlorinated compounds, which are difficult to separate from the desired product. The process being highly exothermic requires elaborate cooling apparatus and hence is expensive. A few previous reports mention the use of diphosgene and triphosgene[4] as safer substitutes for phosgene; however, their high costs make them industrially unattractive.



Scheme 2.1. Catalytic oxidative carbonylation of amines to substituted ureas

Oxidative carbonylation of amines (Scheme 2.1) is an attractive green route for the synthesis of di-, tri- or tetra-substituted ureas.

Several homogeneous transition metal catalysts have been reported, some of which include selenium compounds,[5] palladium compounds,[6] nickel;[7] tungsten;[8] Rhodium,[9] gold,[10] etc. Among all the transition metal catalysts explored for the reaction, palladium is found to be the most studied and most efficient catalyst. It has been tested for this reaction in both-homogeneous and heterogeneous forms. Some of the numerous reports on use of palladium catalyst for oxycarbonylation of amines include- Homogeneous palladium catalysts including $PdCl_2$ – by Becker;[11] Pd and Cu salts[12]: palladium complexes like $PdCl_2(PPh_3)_2$, Pd $(C_6H_5NH_2)$ Cl_2, Pd(ppen$_2$) Cl_2, $Pd(SbPh_3)_3$ Cl_2 by Mulla et al.[13] Homogeneous catalysts obviously pose the problem of catalyst separation from the product, and are therefore not applicable on industrial scale when it comes to synthesis of non-volatile products like substituted ureas. In this context, several heterogeneous and immobilized palladium catalysts have also been screened for amine oxycarbonylation. Fukuoka et al.[14] tried various supported transition metal catalysts for the oxidative carbonylation of amines, palladium being the preferred metal. Some other reports on heterogeneous palladium for oxidative carbonylation of amine include- metallic Pd;[15] Pd/C by Gupte et al;[16] immobilized Pd like montmorillonite-bipyridinepalladium(II) acetate;[17] sulfate modified zirconia supported,[18] i.e. Pd/ ZrO_2-SO_4^{2-}; etc. It is observed, however, that all these reports suffer from either low yields of ureas, high catalyst loading or non-applicability to all the classes of amines owing to very low conversions or yields. It is also important to note that substituted ureas obtained from high molecular weight or substituted aromatic amines with higher number of C atoms are sparingly soluble in most of the solvents and tend to precipitate out of the reaction mixture. In such cases, heterogeneous catalysts are not easy to separate from the product.

Biphasic catalysis is of much current interest owing to their unique advantage of providing homogeneous catalysis as well as the ease in separating the catalyst from the products.[19] Brink et al reported for the first time the aqueous-biphasic oxidation of alcohols using a water-soluble palladium complex catalyst synthesized using the water-soluble ligand-bathophenanthroline disulfonate.[20]

In the present study, water-soluble complexes of a few noble transition metal catalysts like Pd, Rh and Ru, prepared by using N-donor ligands, are applied to the oxidative carbonylation of amines to synthesize substituted ureas.

The distinct advantages of employing a water-soluble catalyst system for synthesis of substituted ureas via oxycarbonylation of amines are as follows-

1. The catalysis occurs in water, thus making the separation of catalyst from reaction medium convenient. This feature is of special significance, since the advantage of separation is not possible in case of both-homogeneous as well as heterogeneous (solid) catalysis. Substituted ureas have sparing solubility in most of the solvents, and therefore tend to precipitate in reaction medium, thus contaminating the solid catalyst, which has to be separated using techniques like sieving[19a], resulting in the loss of precious metal catalysts. Similarly, homogeneous catalysts cannot be separated from reaction medium easily, as they are contaminated by the unreacted amines and by-products, if any.
2. The catalyst is reusable, and there is no significant drop in the activity of the catalyst upon recycle.
3. Recovery and reuse of the water-soluble halide promoter is possible.
4. Aliphatic as well as aromatic amines of varying solubilities in water give excellent yields of substituted ureas with the present catalyst system.
5. The substituted ureas owing to their sparing solubility in the organic phase crystallize out of the reaction medium, and can be isolated by simple filtration.

2.2. EXPERIMENTAL SECTION

2.2.1. Materials

2.2.1.1. Chemicals

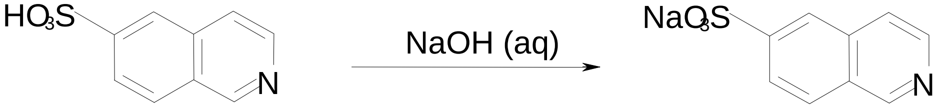
Aniline, substituted anilines and aliphatic amines, ethyl iodide, and the solvents, all GR grade, were purchased from Merck Chemicals India Ltd. Palladium acetate, ruthenium chloride hydrate, rhodium trichloride hydrate, bathophenanthrolinedisulfonic acid disodium salt hydrate, bathocuproinedisulfonic acid disodium salt hydrate, and the iodides sodium iodide, potassium iodide, cesium iodide and tetraethyl ammonium iodide; and Dowex 50W-X8 20-50 mesh were purchased from Aldrich Chemicals, Milwaukee (WI), U.S.A. Hydriodic acid (56%) was procured from Fluka Chemicals. 2,2'-Bipyridine, ammonium metavanadate, iodine and sodium hydroxide were purchased from Loba Chemie, Mumbai, India. Sodium sulfite, sodium chloride, sodium bicarbonate and zinc dust were purchased from SD Fine Chemicals (Mumbai, India). Solvents were freshly distilled before use. Amines were freshly distilled or recrystallized prior to use. Carbon monoxide (99.99%) and oxygen (99.90%) were purchased from Matheson Gas Company, U.S.A. Water used for the synthesis of water-soluble complexes and for oxidative carbonylation reactions was double distilled through a glass water-distillation unit and deionised using a Mili-Q (Millipore) membrane filter.

2.2.1.2. Synthesis of *N*-ligands

The chelating bidentate *N*-ligands Bathophenanthrolinedisulfonic acid disodium salt and Bathocuproinedisulfonic acid disodium salt hydrate were procured from Aldrich Chemicals, U.S.A., and were used as received. The procedures for the ligands synthesized in the laboratory are given below.

2.2.1.2.1. Isoquinoline-5-sulfonic acid, sodium salt (IQS-Na)

This monodentate ligand was conveniently prepared from commercially available, isoquinoline-5-sulfonic acid (IQSA) (Spectrochem, AR grade, 99.0%). The reaction for the synthesis is as shown in Scheme 2.2.



Scheme 2.2. Synthesis of sodium salt of isoquinoline-5-sulfonic acid

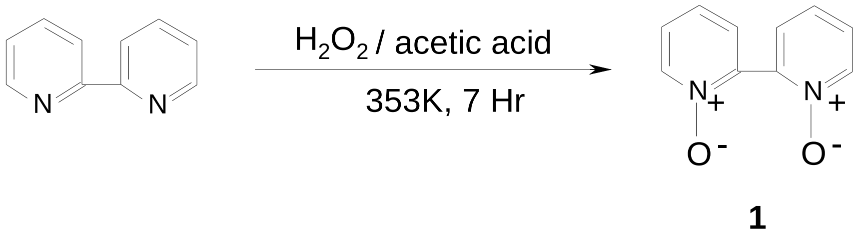
To an aqueous solution of IQSA (1.0 gm, i.e. 4.779 mmol in 5 gm deionised water), a cold aqueous solution of sodium hydroxide (0.172 gm, 4.779 mmol, 20% w/v) was added dropwise with continuous stirring. After the addition was complete, the solution was stirred for 2 more hours at room temperature under inert atmosphere. During this period, the turbid solution became clear and colourless. The resultant solution was then concentrated on rotavap at 333 K for 4 hours to get a white solid. The resulting IQS-Na was washed with 90% methanol several times and the vacuum dried. The water-soluble ligand was analysed by elemental analysis; calculated- C- 46.75%, H- 2.62%, N- 6.06%, S- 13.87%; Found- C- 45.84%, H- 2.33%, N- 5.96%, S- 14.54%.

2.2.1.2.2. Disodium 2,2'-bipyridine-4,4'-disulfonate (bipy-DS)

The synthesis of this ligand was carried out with minor modifications to literature procedure.[21] The procedure involved a sequential five-step synthesis, as follows-

I. Synthesis of 2,2'-bipyridine-*N,N'*-dioxide, 1

2, 2'-bipyridine (10gm, 64mmol), hydrogen peroxide (13 ml) and glacial acetic acid (75 ml) were heated at 353 K for 3 hours (Scheme 2.3). Hydrogen peroxide (9 ml) was added and heating was continued for 4 hours. The colourless solution was cooled to room temperature and added slowly to acetone (1 Lit), precipitating a white solid of 2,2'-bipyridine-*N,N'*-dioxide, **1**. It was filtered and vacuum dried. The isolated yield of the *N*-oxide was 90%, based on the 2,2'-bipyridine charged. M.P. of the compound was found to be 585 K (decomp.); elemental analysis- calculated- C- 63.83%, H- 4.26%, N- 14.89%; Found- C- 63.92%, H- 4.20%, N- 15.05%.

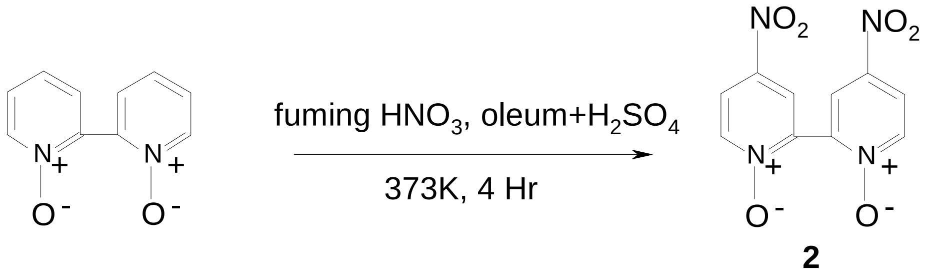


Scheme 2.3. Synthesis of 2,2'-bipyridine-*N,N*'-dioxide

II. Synthesis of 4,4'-dinitro-2,2'-bipyridine *N,N'*-dioxide, 2

To a mixture of 1 and oleum (60%)-sulfuric acid (1:2 v/v, 15 ml) in an ice bath, 10 cc fuming nitric acid was added slowly (Scheme 2.4). The mixture was heated to 373 K for 4 hours, with the reflux condenser fitted with a calcium chloride drying tube. After the reaction, it was cooled to room temperature and poured onto crushed ice-water mixture cautiously, to get a yellow precipitate.

This precipitate was filtered, washed and dried to give 4,4’-dinitro-2, 2’-bipyridine *N.N*’-dioxide, **2**. M. P. = 545K; elemental analysis- calculated- C- 43.17%, H- 2.16%, N- 20.14%; Found- C- 47.40%, H- 2.17%, N- 22.22%.



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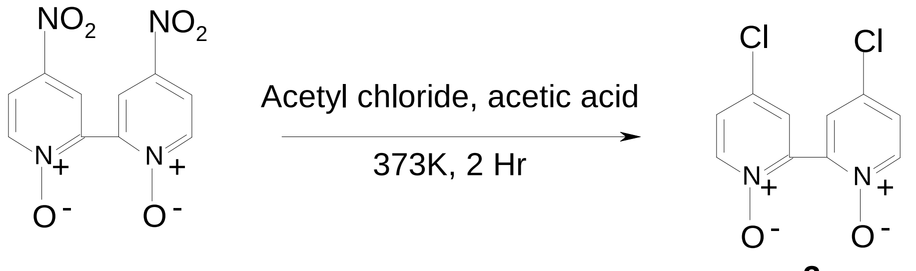
Scheme 2.4. Synthesis of 4,4’-dinitro-2,2’-bipyridine *N,N*’-dioxide

III. Synthesis of 4,4’-dichloro-2,2’-bipyridine *N,N’*-dioxide, 3

Glacial acetic acid (120 ml), acetyl chloride (80 ml, 1.02 mmol) and **2** (7.5 gm, 27 mmol) were heated at 373 K for 2 hours (Scheme 2.5). The cooled mixture was poured onto ice carefully, and the solution neutralized with sodium hydroxide solution (30 %, w/v) to give a white solid of 4,4’-dichloro-2,2’-bipyridine *N,N’*-dioxide, **3**. This was collected by filtration, washed with water and vacuum dried (7 gm, 98%). M.P. = 553K; elemental analysis- calculated- C- 46.69%, H- 2.33%, N- 10.89%, Cl- 27.58%; Found- C- 46.73%, H- 2.21%, N- 12.41%, Cl- 26.98%.



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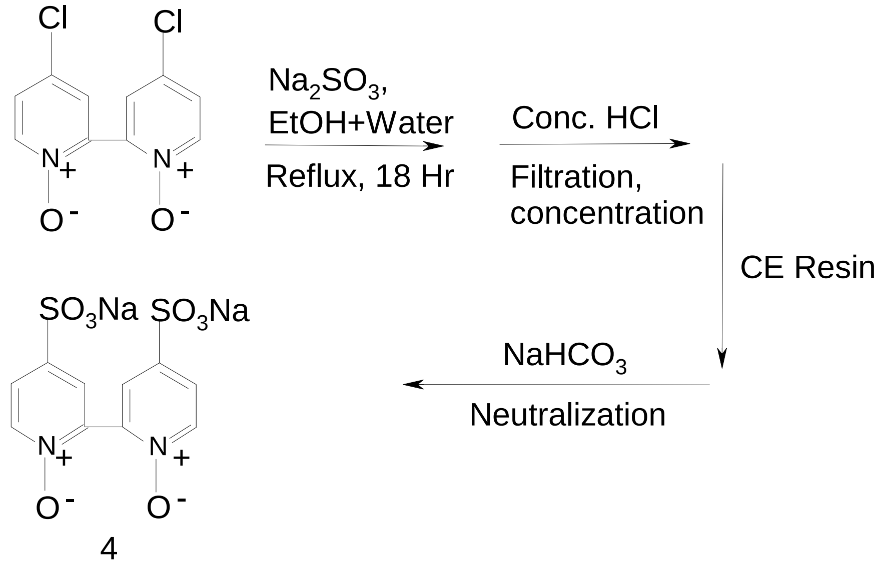
Scheme 2.5. Synthesis of 4,4’-dichloro-2,2’-bipyridine *N,N’*-dioxide

IV. Synthesis of 2,2’-bipyridine-4,4’-disulfonic acid-*N,N’*-dioxide, 4

Sodium sulfite (25 gm, 0.16 mol) and **3** (7 gm, 26 mmol) were heated to reflux in ethanol-water (1:1 v/v, 100 ml) for 18 hours under nitrogen (Scheme 2.6). The resultant solution was evaporated to dryness to give a white solid, which was dissolved in

10 ml water. Concentrated HCl (10 ml) was added, precipitating a white solid of sodium chloride. This was removed by filtration, the colourless filtrate evaporated to dryness and precipitation of sodium chloride repeated twice.

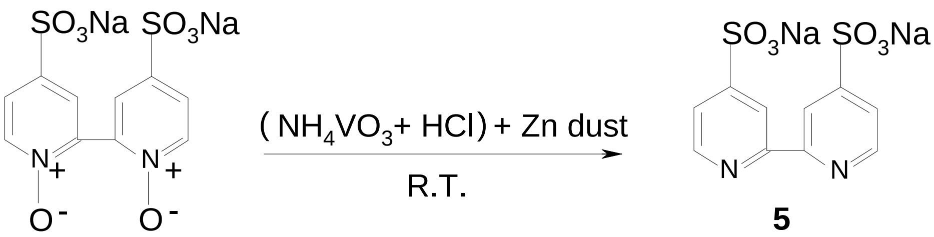
The solution was evaporated to dryness, and dissolved in minimum amount of water, and passed through a Dowex 50W-X8 20-50-mesh cation exchange resin. The eluate was concentrated to approximately 20 ml, and neutralized with $NaHCO_3$. The final colourless filtrate was evaporated to dryness to get the disodium salt of 2,2'-bipyridine-4, 4'-disulfonic acid-*N, N*'-dioxide, **4** (4 gm, 80%). Elemental analysis- calculated- C- 34.48%, H- 2.30%, N- 8.05%, S- 18.39%; Found- C- 33.47%, H- 3.25%, N- 8.51%, S- 16.71%.



Scheme 2.6. Synthesis of 2,2'-bipyridine-4,4'-disulfonic acid-*N,N*'-dioxide

V. Synthesis of Disodium 2,2'-bipyridine-4,4'-disulfonate, 5

The sodium salt of 4 (2 gm, 5.5 mmol) was dissolved in water (20 ml). Ammonium metavanadate, NH_4VO_3, (5 gm, 43 mmol) was added to HCl (60 ml, 6 mol.dm^{-3}), and the mixture was degassed. Zinc dust (8 gm, 0.12 mol) was added to the orange vanadium solution, as the colour of the solution changed through blue and green to violet. The reaction is shown in Scheme 2.7.



Scheme 2.7. Synthesis of disodium 2,2'-bipyridine-4,4'-disulfonate

This solution was added, under nitrogen, to the sulfonic acid solution, when an instantaneous colour change to green occurred. This solution was then neutralized by sodium hydroxide solution (4 mol. dm^{-3}), and the pale green precipitate was formed was removed by filtration and washed with hot water. The filtrate and washing were combined and concentrated, and recrystallized from water, to yield white solid of disodium 2,2'-bipyridine-4,4'-disulfonate **5** (1.1 gm, 65%). Elemental analysis-calculated- C- 33.34%, H- 1.68%, N- 7.78%, S- 17.80%; Found- C- 29.91%, H- 3.27%, N- 6.34%, S- 17.49%. The final ligand thus obtained was then characterized by elemental analysis, IR, ^{1}H NMR (Figure 2.1) and ^{13}C NMR (Figure 2.2).

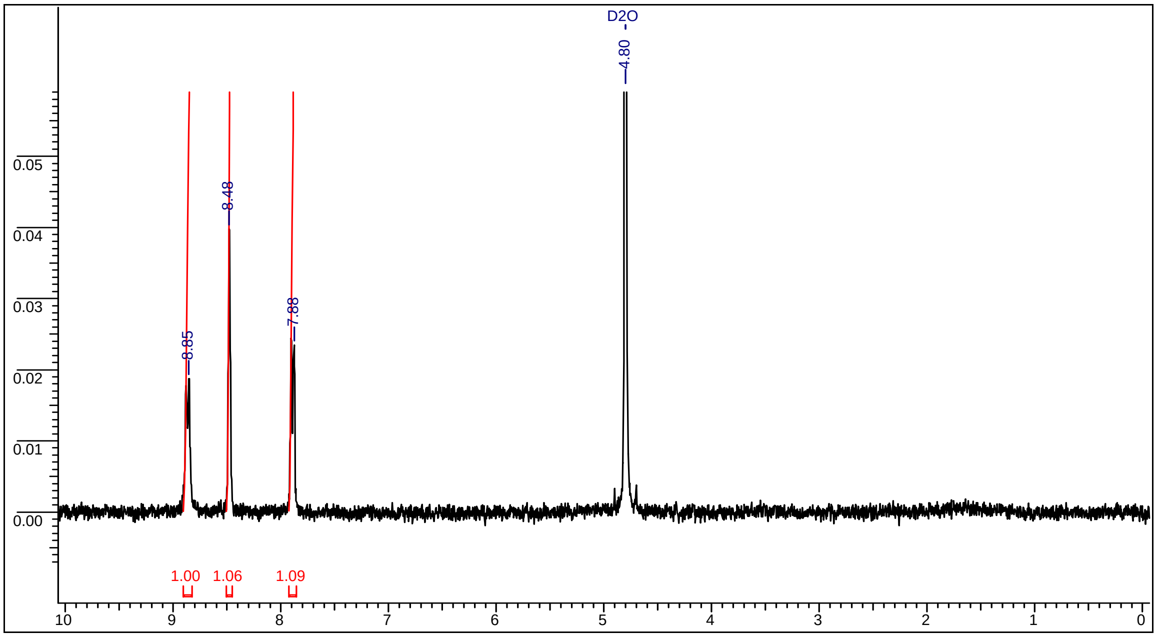


Figure 2.1. ^{1}H NMR spectrum of bipyDS

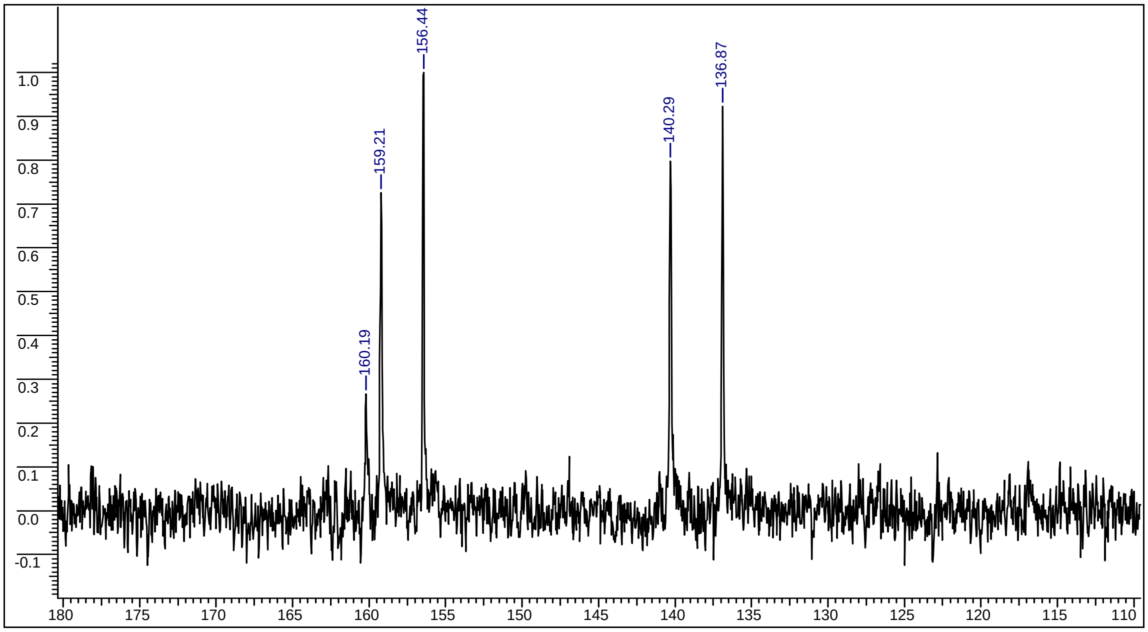


Figure 2.2. ^{13}C NMR spectrum of bipyDS

2.2.1.2.3. Synthesis of triphenylphosphine trisulfonate, sodium salt (TPPTS)

Sulfonation reactor set up

For synthesis of triphenyl phosphine trisulfonate (TPPTS)**,** a double-jacketed 1 L glass reactor equipped with a high-speed half-moon stirrer was used. This reactor was designed so that operation under argon atmosphere was possible. The temperature was controlled by circulation of water using a cryostat. A similar reactor of larger volume was used for neutralization of the crude reaction mixture. The procedure used was similar to that reported in the literature.[22]

Reaction charge for the synthesis of TPPTS

- SO_3/TPP =12 (molar ratio)
- $SO_3/(SO_3 + H_2SO_4 +$ TPP) = 34% (w/w)
- $H_2SO_4/ (SO_3 + H_2SO_4 +$ TPP) = 56%(w/w)

200 g of 98% pure sulfuric acid was introduced into the sulfonation reactor. The acid was cooled under constant stirring to 285-288K by means of a cryostat. 50 g of triphenyl phosphine (TPP) (190.75 mmol) was introduced slowly at 288K over a period of 30-45 min. This gave a homogeneous yellow coloured solution of TPP in sulfuric acid.

280 g (141.48 ml, d=1.98 at 308K) of 65% oleum (SO_3 content: 2.275 mol) was transferred into the addition funnel from the oleum receiver. This oleum was then introduced in the sulfonation reactor containing TPP solution in sulfuric acid, over a period of 40-45 minutes maintaining a maximum temperature of 288K with rapid stirring. The temperature of the reaction mixture was then raised to 295 K and was maintained for 76 hours using a cryostat. This step of keeping the reaction mixture at 295 K is critical for optimum yield of TPPTS. Thereafter, the temperature of the reactor was lowered to ~283 K and 50 g of distilled water was introduced while maintaining the temperature at 283 K. This addition is necessary to quench the excess SO_3 present after the sulfonation reaction is complete. The addition of water is highly exothermic, and hence temperature was maintained at < 283 K while adding water. This gave a solution of sulfonated triphenyl phosphine in sulphuric acid. This reaction mixture was further diluted to approximately 800 ml under cooling (283K). This diluted solution was then transferred into a neutralization reactor under argon atmosphere. The reactor was similar to the reaction vessel, but of a larger capacity (approx. 3 litres). The solution was neutralized using 50% (w/w) degassed sodium hydroxide solution, maintaining the temperature constant at 283K. The reaction mixture obtained was in a slurry form. The neutralized mixture was then filtered and the filtrate was evaporated under reduced pressure at 323-333 K till the volume reduced to about 250 ml from the initial two liters. 1.5 liters of methanol was added to the above solution and the mixture was refluxed under argon atmosphere for 2 hours. TPPTS dissolved in methanol completely, which was filtered hot, with the solid residue comprising only sodium sulphate. The filtrate was evaporated under reduced pressure. The solid TPPTS obtained was recrystallized from ethanol, weighed and stored under argon atmosphere. The yield was found to be 80-85%.

2.2.1.3. Synthesis of $Pd(OAc)_2(bipy)$

A solution of palladium acetate (100mg, 0.4455mmol) was prepared in 10 ml chloroform, and a solution of 2,2'-bipyridine (84mg, 0.5378mmol; 1.2 equivalent of Pd) in 5 ml chloroform was added to it drop-wise, as the complex started precipitating out gradually. The solution was stirred at room temperature for 1 hr. The solvent was removed by filtration, and the yellow solid obtained was dried using vacuum at room temperature, and a yellow crystalline solid of $Pd(OAc)_2(bipy)$ was obtained. This complex was characterized by elemental analysis. Calculated: C-43.94%, H-4.21%, N-7.32%, O-16.72%, Pd- 27.80%; obtained: C-35.73%, H-4.83%, N-5.87%.

2.2.1.4. Synthesis of water-soluble transition metal catalysts

It should be noted that, the water-soluble catalysts synthesized by the procedures given in the following section were prepared as aqueous solutions, and were used as such.

2.2.1.4.1. Preparation of $PdCl_2(TPPTS)_2$

This complex was prepared by simple overnight mixing of the catalyst precursor, i.e. $PdCl_2$ and TPPTS under inert atmosphere of argon. The ligand (641.2 mg, 1.128 mmol; 2 equivalent of Pd) was dissolved in water (5 ml), and palladium chloride (100mg, 0.564 mmol) was added to it. The contents of the flask were stirred overnight using a magnetic needle at room temperature. The homogeneous catalyst formed had a faint brown colour.

2.2.1.4.2. Preparation of Pd-N water-soluble complexes

The palladium precursor used in all the reactions was $Pd(OAc)_2$. For every reaction, the catalyst was freshly prepared; by the following procedure- bipyDS (192.6 mg, 0.5345 mmol; 1.2 equivalent of Pd) was dissolved in 5 ml distilled water in a round-bottomed flask with the help of a magnetic needle. The solution appeared faint pink in colour. 100 mg (0.4454 mmol) palladium acetate was added to this liquid under stirring. The solution was kept under vigorous stirring at room temperature for 12 hours. At the end of 12 hours, a clear, homogeneous, brownish solution was obtained. This solution was diluted to 10 ml using distilled water.

For the synthesis of water-soluble complexes of rhodium and ruthenium, similar procedure as above was followed.

2.2.2. GENERAL PROCEDURE FOR OXIDATIVE CARBONYLATION OF AMINES

2.2.2.1. Experimental set-up

The reactions were carried out in a 600ml Parr Hastelloy-C-276. The autoclave was provided with gas inlet, gas outlet, a safety rupture disc (gold faced-14 MPa), digital temperature, pressure and agitation speed indicators with temperature control (±1K) and magnetically driven stirrer having variable agitation speed adjustment (Figure 2.3). The carbon monoxide and oxygen gases were supplied through high-pressure gas reservoirs made of SS-316.

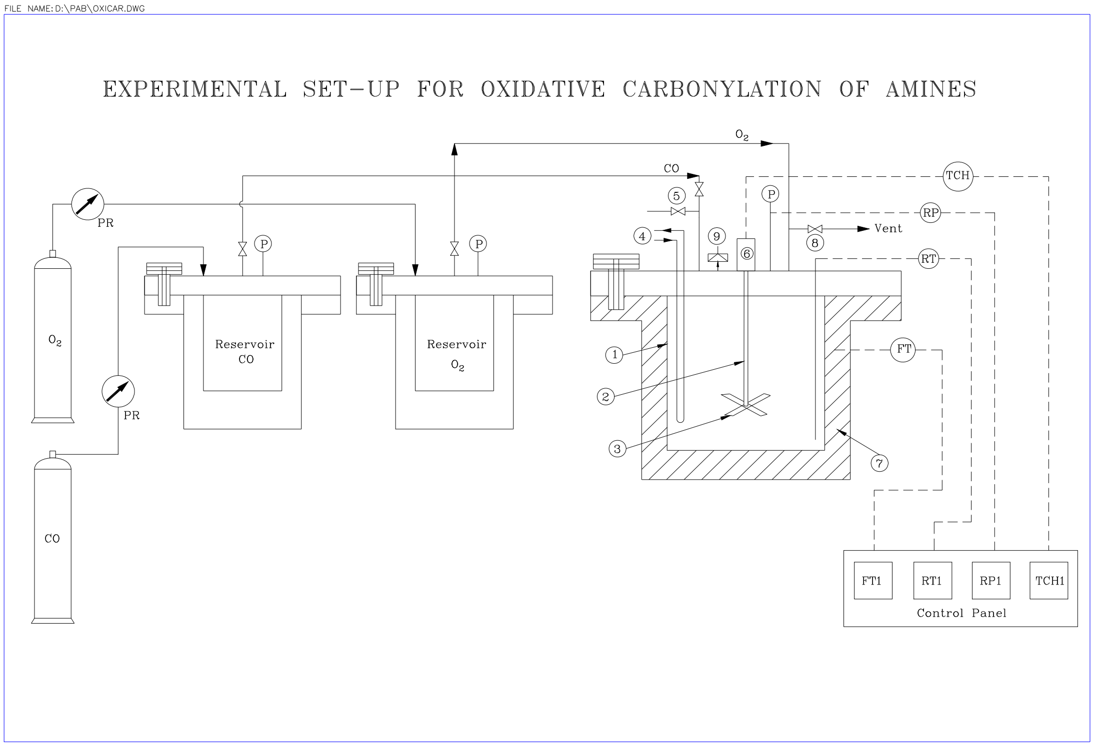


Figure 2.3. A schematic of reactor set-up for biphasic oxidative carbonylation

Reactor components- 1. Reactor 2. Stirrer Shaft 3. Impeller 4. Cooling loop 5. Sampling valve 6. Magnetic Drive 7. Furnace 8. Gas Vent Valve 9. Rupture Disc; FT-Furnace Temperature; RT-Thermocouple; PR-Transducer; TCH-Tachometer; TCH1- RPM Indicator; FT1-Furnace Temperature Indicator; RT1-Reactor Temperature Indicator; RP1: Reactor Pressure Indicator; P: Pressure Gauge;PR: Pressure Regulator.

2.2.2.2. Typical procedure for oxidative carbonylation of amines

The requisite amounts of amine, organic solvent, sodium iodide and the water-soluble catalyst were charged and the reactor was sealed. The autoclave was purged once with nitrogen and thrice with carbon monoxide; and then pressurized with the same under constant stirring. Oxygen was then pressurized into the reactor, so as to make the ratio of carbon monoxide to oxygen 13:1. The heating was started, and an agitation speed of 16.66 Hz (1000 R.P.M.) was reached as the temperature reached 423K.

The progress of the reaction was monitored by observing the pressure drop in the autoclave, and a 2:1 mixture of CO and O_2 was fed to the reactor intermittently, to maintain the reaction pressure between 5.52-6.90 MPa (980-1000 psig). The reaction was carried out for specific time duration, at the end of which, the contents were cooled to room temperature and the gas was vented off in a hood under continuous vacuum after analyzing by gas chromatography (GC). The autoclave was then opened. The residue formed in the reaction was filtered off, washed, dried and weighed. The two phases in the filtrate were separated using a separating funnel. The organic phase was then analyzed by G. C. for estimating the unreacted amine. The organic phase was then concentrated using rotavap at 323K to remove the solvent. The residue and the concentrate from organic layer of the filtrate were then dissolved in dimethylformamide, and the solution was analyzed by HPLC to determine the amount of disubstituted urea formed in the reaction.

2.2.3. ANALYTICAL METHODS

The ligands and catalysts were characterized by IR spectral and elemental analysis. The IR spectra were recorded using Bio-rad FTS 175C machine in transmission mode using KBr pellets. The elemental analyses were done on a CHNS-O EA 1108, Elemental analyzer of Carlo-Erba Insrtuments, Italy. Pd metal analysis was done using AAS.

The liquid samples obtained from the reaction were analyzed for amine quantification by gas chromatographic analysis of the organic phase at the end of the reaction on a Hewlett Packard 6890 Series Gas Chromatograph using an HP-5 (Crosslinked 5% phenyl methyl siloxane stationary phase) column and FID, and controlled by HP Chemstation Software. The details of GC analysis conditions are given in Table 2.1. Gas samples were analyzed using a thermal conductivity detector (TCD) on Hayesep (10 feet, 8/100 mesh) and Molecular AR Sieves (13 feet, 45/60 mesh) packed columns, which were operated through a programmed valve switching. The details of GC analysis conditions and valve programming are given in Table 2.2 and Table 2.3 respectively. The separation and quantification of *N*,*N'*-diphenylurea (DPU) was done by HPLC analysis of liquid samples on an Agilent Series 1100 High Performance Liquid Chromatograph using a Symmtery Shield^{TM} RP_8 (Waters) RP-18 column (250 mm × 0.5 mm ID × 0.21 μ film thickness) using a Quaternary LC Pump. The detector used was a UV-DAD and the monitoring wavelength used in typical analysis was 254 nm. The analysis was done with injection volume of 20 μl, using methanol-water as the mobile phase under gradient conditions as detailed in Table 2.4.

Table 2.1. Standard conditions for GC analysis of liquid samples

Parameter	**Conditions**
Injector temperature	523 K
Pressure (He)	20 psig
Mode	Split, split ratio- 25:1
Carrier gas	He, flow rate- 2 ml/min
Detector	Flame ionization detector (FID) temperature- 573K
Column	HP-5 capillary column, temperature- 313 K–563K (programmed)

Table 2.2. Standard conditions for GC analysis of gas

Parameter	**Conditions**
Injector temperature	523 K
Pressure (He)	20 psig
Mode	Splitless
Carrier gas	He, flow rate- 2 ml/min
Detector	Thermal conductivity detector (TCD) temperature- 573K
Column	Molecular Sieve, Hyasep packed column, 13×45/60 mesh; temperature 323 K–498 K (programmed)

Table 2.3. Valve Programming for analysis of gases

Time, min	Parameter	Set point
0.01	1	ON
0.02	2	OFF
0.15	1	OFF
3.00	2	ON
6.50	2	OFF

Table 2.4. Mobile phase gradient programme for HPLC

Ramp	Time, min	Hold Time, min	ACN (%)	Water (%)	Flow rate (ml/min)
1	0.00	0.00	40	60	1
2	5.00	5.00	40	60	1
3	10.00	5.00	50	50	1
4	12.00	02.00	60	40	1
5	15.00	03.00	60	40	1
6	20.00	05.00	80	20	1
7	25.00	05.00	90	10	1
8	30.00	05.00	100	0	1
9	35.00	05.00	100	0	1
10	40.00	05.00	80	20	1
11	42.00	02.00	60	40	1
12	45.00	03.00	40	60	1
13	50.00	05.00	40	60	1

The conversion, selectivity, yields and turn over numbers (TON) were calculated as follows

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

$$\%\text{Selectivity} = \frac{(2 \times \text{moles of DPU formed})}{\text{Converted moles of aniline}} \times 100$$

$$\%\text{Yield} = \frac{\%\ \text{Conversion} \times \%\ \text{Selectivity}}{100}$$

$$\text{TON} = \frac{\text{moles of DPU formed}}{\text{moles of catalyst charged}}$$

$$\text{TOF} = \frac{\text{moles of DPU formed}}{\text{moles of catalyst charged} \times \text{time in hours}}$$

2.3. RESULTS AND DISCUSSION

2.3.1. Preliminary experiments to establish the activity of water-soluble catalyst

A few reactions were carried out to establish catalytic activity of the water-soluble catalyst $Pd(OAc)_2$(bipyDS) using aniline as the substrate and NaI as the promoter. An experiment carried out in absence of any iodide promoter resulted in no aniline conversion, conforming to the literature reports that amine oxycarbonylation essentially requires an iodide promoter.

The preliminary studies included a comparison of the conventional and the proposed aqueous-biphasic catalytic system for the oxidative carbonylation of aniline as the model substrate. The results are as shown in Figure 2.4. First of all, the conventional homogeneous Pd- NaI catalyst system was applied for oxidative carbonylation of aniline in toluene as the solvent. As expected, excellent aniline conversion and yield of *N,N'*-diphenyl urea (DPU) were obtained. It was observed that the catalytic activity of the water-soluble complex made from palladium acetate and bipyDS-sodium salt was comparable to its organic analogue, that is, Pd(bipy)$(OAc)_2$. The Reactions where $Pd(OAc)_2$(bipy) was used as catalyst in toluene as the solvent; and the experiment in which a mixture of toluene and water in a volume ratio of 5:1 was taken along with Pd $(OAc)_2$(bipyDS) as the catalyst resulted in similar yields of DPU. However, it has been observed that the yields and the selectivity depend a lot on the volume ratios of aqueous and organic phases. This result is justified by the fact that the reaction rates depend largely on the diffusion of the substrate from organic phase into the aqueous phase, which in turn is based on the miscibility of organic solvent in water, as well as concentration gradient of amine in the two phases. The optimum ratio of organic to aqueous phase was found to be 5:1. Increase in the amount of water resulted in the formation of tar and lower conversions of amine. It is also interesting to note from the Figure 2.4 that, the yield of DPU as well as the selectivity and activity of the catalyst in terms of TOF is considerably low when Pd(OAc)$_2$(bipy) is used as the catalyst with water as the reaction medium.

In the context of green chemistry, the use of the water-soluble catalyst for oxidative carbonylation in water only as the reaction medium would be most rewarding. However, as it can be observed from Figure 2.4, the use of an organic solvent is essential to achieve moderate TOF values, and the best solvent composition is 20% water in toluene, which offers a maximum TOF of 208 with Pd(OAc)$_2$(bipyDS).

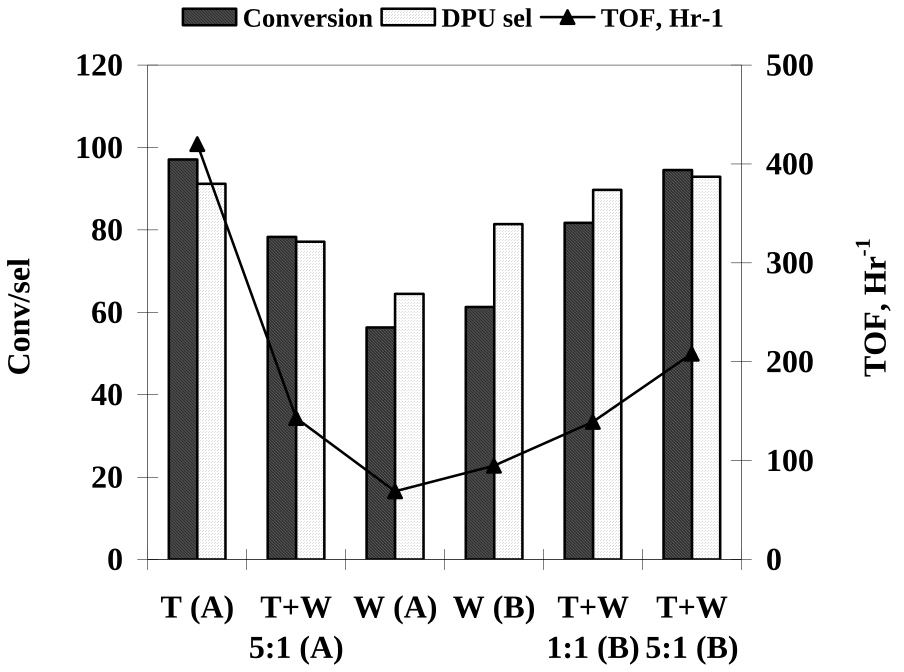


Figure 2.4. Preliminary studies for development of an aqueous-biphasic reaction system for oxidative carbonylation of aniline

Reaction conditions: aniline 74 mmol, Pd 0.078 mmol, NaI 0.63 mmol, T 423 K, P 6.89 MPa, CO:O$_2$ 13:1, Time 120min, Agitation 16.66 Hz. Catalysts: A= Pd(OAc)$_2$(bipy), B= Pd(OAc)$_2$(bipyDS); T= toluene as reaction medium; W= water as reaction medium; T+W= toluene+water as reaction medium, in the volume ratio given.

2.3.2. Effect of agitation speed

It was important to check the effect of agitation speed on aniline conversion in the present study, because mass transfer resistances play a very important role in heterogeneous as well as biphasic catalytic systems. The effect of agitation speed was studied in the range of 10 to 25 Hz, under standard conditions. All the reactions were carried out up to partial conversions of aniline, for a fixed amount of time, i.e. 60 minutes to assess the effect properly. As it is evident from the Figure 2.5, the minimum agitation speed required for the aqueous-biphasic system was 13.33 Hz, beyond which, there was no effect on the rate of aniline conversion. All the further studies were therefore carried out at the agitation speed of 16.66 Hz.

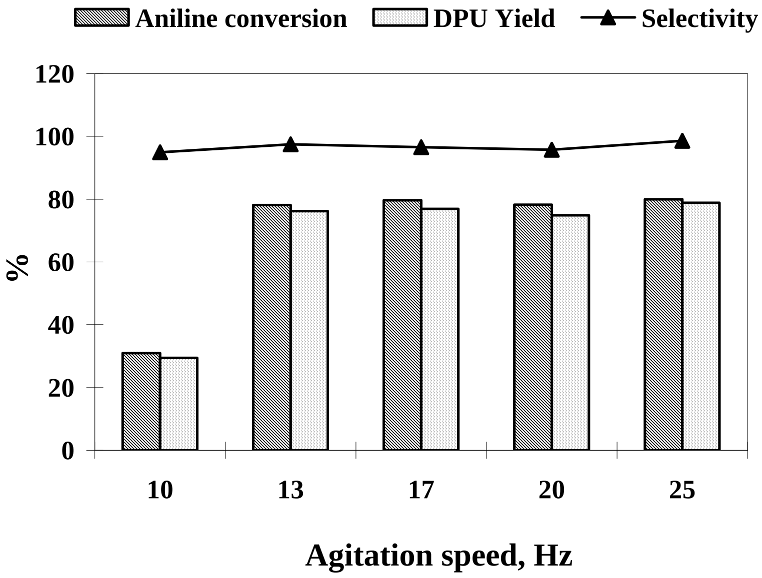


Figure 2.5. Effect of agitation speed on oxidative carbonylation of aniline

Reaction conditions: Aniline 74 mmol, $Pd(OAc)_2$(bipyDS) 0.078 mmol, ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, Total P 6.89 MPa, $CO:O_2$ 13:1, Time 60 min

2.3.3. Typical oxidative carbonylation reaction and concentration-time profile

The concentration-time (C-T) profile for aniline and product DPU was plotted. The experiments for various time intervals were carried out, and the reaction mixtures were analyzed for quantification of aniline and DPU. The gas phase in these reactions was analyzed for CO_2 formation by gas chromatography using TCD. Figure 2.6 shows the typical C-T profile for aniline oxycarbonylation in the biphasic system.

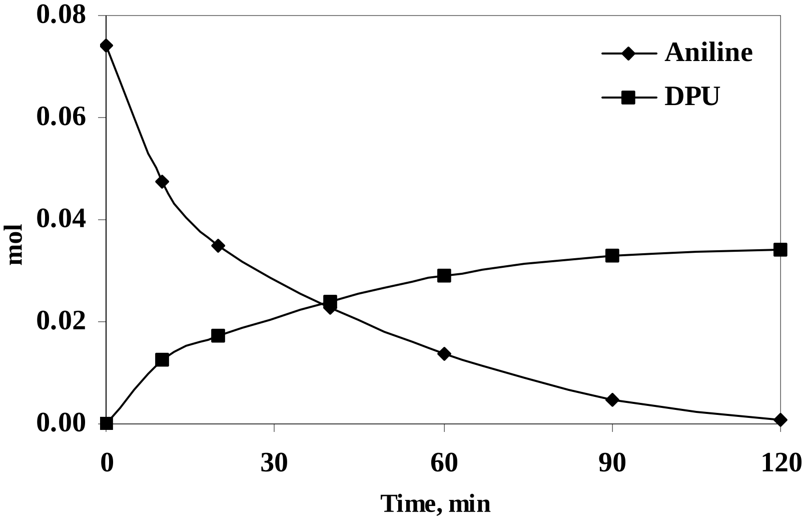


Figure 2.6. Concentration-time profile for biphasic oxidative carbonylation of aniline
Reaction conditions: Aniline 74 mmol, $Pd(OAc)_2(bipyDS)$ 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423K, P 6.89 MPa, $CO:O_2$ 13:1, Agitation 16.66 Hz.

As it can be noticed from the C-T profile, the formation of DPU in the reaction is commensurate with the consumption of aniline with respect to stoichiometry. However, the reaction also shows formation of carbon dioxide, which is well known in transition metal catalyzed reactions involving CO and water.

For example, such CO oxidation catalyzed by transition metal has been demonstrated involving Pd[23] and Ni.[24] The typical water-gas shift reaction is shown in scheme 2.8.

$$PdX_2L_2 + CO + H_2O = Pd^0 + CO_2 + 2L + 2HX$$

Scheme 2.8. The palladium catalyzed water-gas shift (WGS) reaction

The formation of CO_2 by such oxidation of CO takes place due to the nucleophilic attack of water molecule on the CO molecule coordinated to the transition metal center.

The formation of CO_2 in the reaction is adverse due to the fact that it decreases the selectivity of the CO towards DPU. It has also been reported that the formation of CO_2 increases with prolonged reaction times,[25] which was also observed in the present study, as can be seen from Figure 2.7. The CO_2 formed in the biphasic oxidative carbonylation of aniline reaction was quantified by carrying out experiments for fixed reaction times, and analyzing the gas samples from the autoclave at the end of each experiment. The GC analysis was done on a Hyasep packed column using a TCD, and the quantification was based on standard calibration curve.

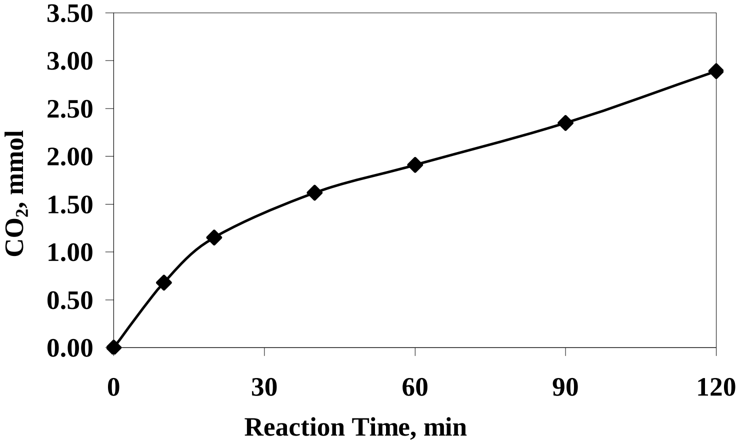


Figure 2.7. Formation of CO_2

Reaction conditions: Aniline 74 mmol, $Pd(OAc)_2$(bipyDS) 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423K, P 6.89 MPa, $CO:O_2$ 13:1, Agitation 16.66 Hz.

It was found that the amount of CO_2 formed in the reaction increased with reaction time. The CO_2 selectivity based on total CO charged in the reaction was calculated, and it was found to be 6.9%

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2.3.4. Screening of water-soluble transition metal complexes

The water-soluble complexes of palladium, rhodium and ruthenium were compared for the catalytic activity for oxidative carbonylation of aniline under aqueous-biphasic reaction conditions. The results obtained are shown in Table 2.5.

The palladium complex was found to be most active in terms of the yield of DPU as well as turnover frequency. However, the selectivity of aniline towards DPU remained high in all the cases.

Table 2.5. Screening of water-soluble metal complexes for aniline oxidative carbonylation

Sr	**Catalyst Precursor***	**Aniline Conversion, %**	**DPU Selectivity, %**	**DPU Yield, %**	**TOF, h^{-1}**
1	$Pd(OAc)_2$	97.18	95.59	88.64	220.5
2	$RhCl_3.xH_2O$	86.45	92.77	80.20	190.0
3	$RuCl_3.xH_2O$	77.14	90.48	69.80	165.5

Reaction conditions: Aniline 74 mmol, Catalyst precursor 0.078 mmol, BipyDS 0.156 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423 K, P 6.89 MPa, $CO:O_2$ 13:1, Agitation 16.66 Hz, time 120 min.

*- The precursors and the ligand were stirred at room temperature in deionized water overnight to make the water-soluble complex, which was charged in to the reaction.

2.3.5. Effect of solvents

Several organic solvents were screened for the aqueous-biphasic reaction in the optimized solvent composition (organic solvent: water = 5:1 v/v). The effect of the organic solvent in an aqueous-biphasic gas-liquid reaction depends on several factors like- 1) polarity of the solvent 2) solubility of the substrate (amine in this case) 3) The solubility of gases in the organic phase 4) The miscibility or solubility of the organic solvent in water 5) the solubility of products in the organic and aqueous phases. The results of solvent screening study are presented in Table 2.6.

In the solvent variation study, it was observed that the conversion was good in all the cases, although slight variation in the DPU yields was noted. The marginal differences in DPU yields for example in case of toluene (entry 2) and heptane (entry 6) is due to the lower water-solubility of the latter. It was found that the solvent variation did not affect the selectivity to *N, N'*-diphenylurea.

Table 2.6. Effect of various solvents

Sr	Solvent	Wm*	Conv., %	Sel., %	Yield, %	TOF, Hr^{-1}
1	Cyclohexane	0.01	89.5	96.0	85.9	203.8
2	Toluene	0.051	96.8	98.1	95.0	225.3
3	Diethylether	6.89	88.4	97.2	85.9	203.8
4	Benzene	0.18	87.0	96.3	83.8	198.7
5	Chlorobenzene	N.A.	93.4	96.0	89.7	212.7
6	Heptane	0.0003	93.0	93.1	86.6	205.4
7	Xylene	0.018	73.0	96.8	70.7	167.6

Reaction conditions: Aniline 74 mmol, $Pd(OAc)_2(bipyDS)$ 0.078 mmol ($10^{-5}m^3$), Solvent $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423 K, P 6.89 MPa, $CO:O_2$ 13:1, Agitation 16.66 Hz, Time 120 min; Wm* solubility in water (%w/w)

2.3.6. Effect of iodide promoters

Several iodide compounds were screened for their activity as promoters for the biphasic oxycarbonylation of aniline. The results are illustrated graphically in Figure 2.8. From the iodide-screening results, it is quite visible that in case of all the iodide sources, which have good solubility in water, good to excellent yields of urea have been obtained. In case of iodine, for example, there is partitioning of the promoter in the two phases, and therefore the lack of required concentration of iodide in aqueous phase results in lower yield of DPU. Accordingly, ethyl iodide has scanty solubility in water, and the conversion of aniline is much lower, although the selectivity to DPU is at par with other iodide promoters (>90%). It was observed that all the alkali metal iodides as well as tetraethylammonium iodide were excellent promoters for the reaction, as they resulted in aniline conversions of > 95% and DPU yields of >90%. NaI was used as the iodide promoter for further exploration of the water-soluble palladium complex catalyzed aqueous-biphasic oxidative carbonylation of aniline.

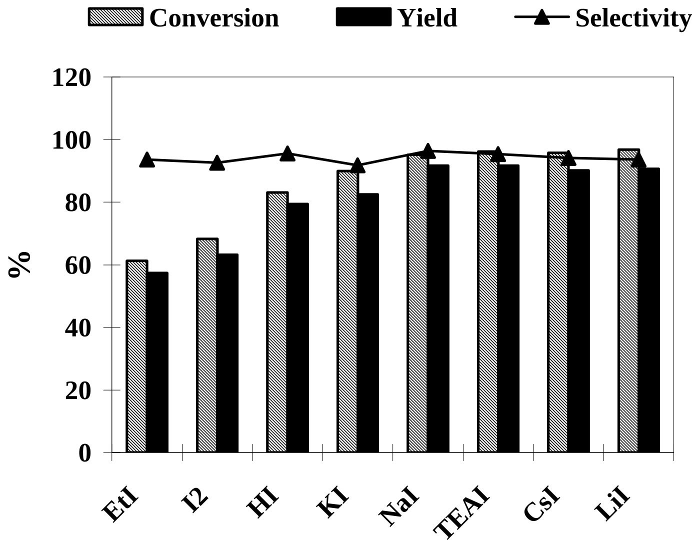


Figure 2.8. Screening of iodide promoters for aniline oxycarbonylation

Reaction conditions: Aniline 74 mmol, Pd(OAc)$_2$(bipyDS) 0.078 mmol (10^{-5}m^3), Toluene 5×10^{-5}m^3, Iodide promoter 0.90 mmol, T 423 K, P 6.89 MPa, CO:O$_2$ 13:1, Agitation 16.66 Hz, time 120 min

2.3.7. Effect of iodide concentration

As reported by Gupte et al.,[26] the proposed mechanism suggests requirement of one mole of iodide per mole of palladium for the catalytic cycle to proceed. The optimum iodide:palladium molar ratio (I^-:Pd) as observed by the authors report is 1, which has been justified by the observations in the experimental results. The optimum I^-:Pd ratio in the present study was found to be higher than the one-phase oxidative carbonylation of amines using supported palladium catalysts reported earlier by Gupte et al (See Figure 2.9). This observation is attributed to the possible partitioning of iodide in organic and aqueous phases. The dependence of reaction rate on the I^-:Pd ratio shows a maxima at 4, after which, slight decrease is observed. The higher concentrations of iodide are known to form inactive Pd complexes, which retard the desired reaction,[26] and hence a maxima is usually observed in this study.

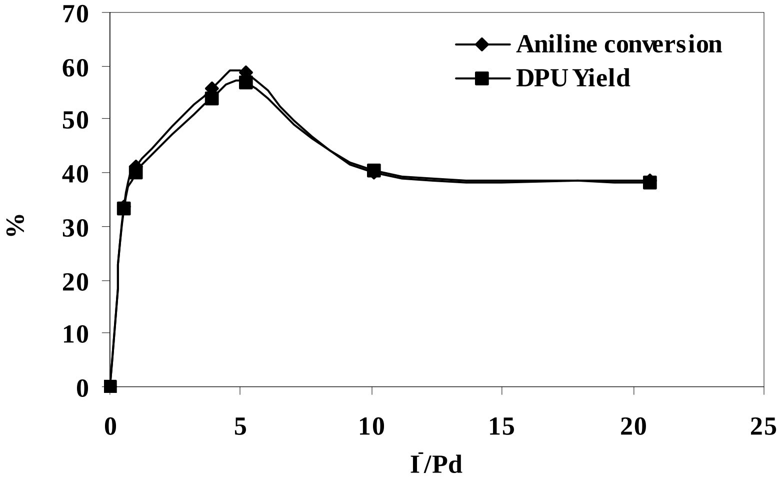


Figure 2.9. Effect of iodide concentration

Reaction conditions: Aniline 74 mmol, Pd(OAc)$_2$(bipyDS) 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423 K, P 6.89 MPa, CO:O$_2$13:1, Agitation 16.66 Hz, time 120 min

2.3.8. Recycle studies

2.3.8.1. Catalyst recycle

The recovery and reusability of the catalyst are obviously the biggest advantages of a two-phase catalytic reaction, even as the catalyst used can be tailor-made by manipulating the ligands. In the present study also, the reusability of the water-soluble palladium complex was critically checked. Figure 2.10 shows the performance of Pd(OAc)$_2$(bipyDS) for oxidative carbonylation of aniline upto 5 recycles.

In each of the recycles, the catalyst phase was separated and used as such for the next reaction. As it can be observed from the above table, the loss in the activity of the catalyst in terms of DPU yields is negligible. The AAS analysis of the recovered organic phase showed that <0.1 ppm Pd had leached into it. These observations consolidate the applicability of water-soluble Pd-N chelate complexes as robust and reusable catalysts in the aqueous-biphasic oxidative carbonylation of amines. The aqueous solutions of Pd(OAc)$_2$(bipyDS) as well as PdbathDS were found to be stable for several days, and no discoloration or palladium precipitation was observed.

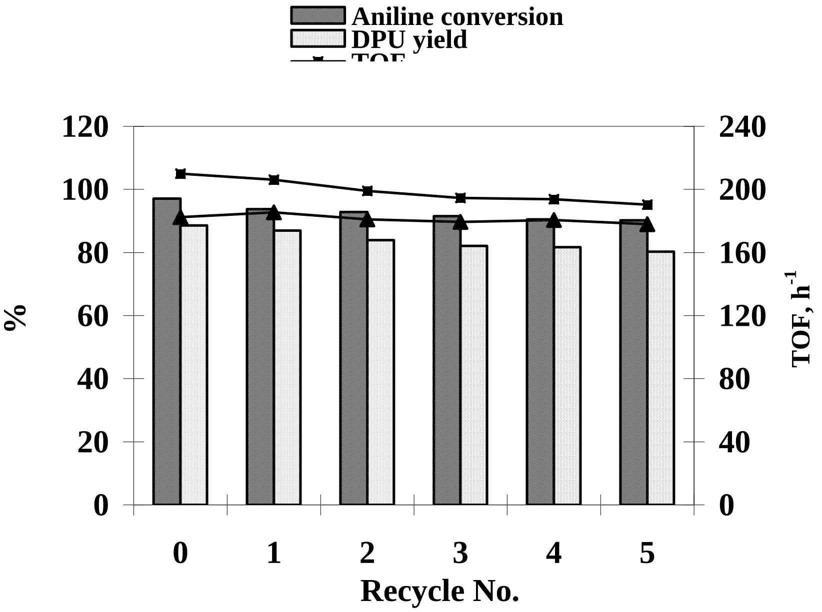


Figure 2.10. Recycle study for $Pd(OAc)_2$(bipyDS)

Reaction Conditions: aniline 70 mmol, $Pd(OAc)_2$(bipyDS) 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, NaI 0.63 mmol, T 423 K, P 6.89 MPa, $CO:O_2$ 13:1, Agitation 16.66 Hz, Time 120 min.

2.3.8.2. Promoter recycle

Since the water-soluble complex was completely recovered after the reaction, it was expected that the iodide promoter could be recovered as well at the end of the reaction. Therefore, a comparative account of the concentration of iodide in the initially charged as well as recovered aqueous phase was carried out using potentiometric estimation. It was observed, however, that the iodide was lost upto 75% of its original loading at the end of second recycle. The loss was attributed to the possible formation trace amounts of iodinated products of aniline, or as iodine into the organic phase. The recycle reactions also indicated decline in aniline conversions and yields of DPU when no fresh iodide was charged into recycle experiments. Good conversion and yields were obtained again when iodide was replenished into the aqueous catalyst phase.

2.3.8.3. Catalyst recycle: Oxidation state of Pd

The X-ray photoelectron spectroscopy was used for the determination of the oxidation states of the respective elements present in the catalyst composites. The X-ray actually removes the core orbital electrons of the elements at specific binding energies, which are fingerprints for particular oxidation states of the element. The XPS data also delivers some information about the immediate local electronic environment of the selected element incorporating the perturbation of the electron density due to the neighboring functional groups and/or ligands. Figure 2.11 (a) shows the full-scale spectrum of the fresh $Pd(OAc)_2$(bipyDS) catalyst.

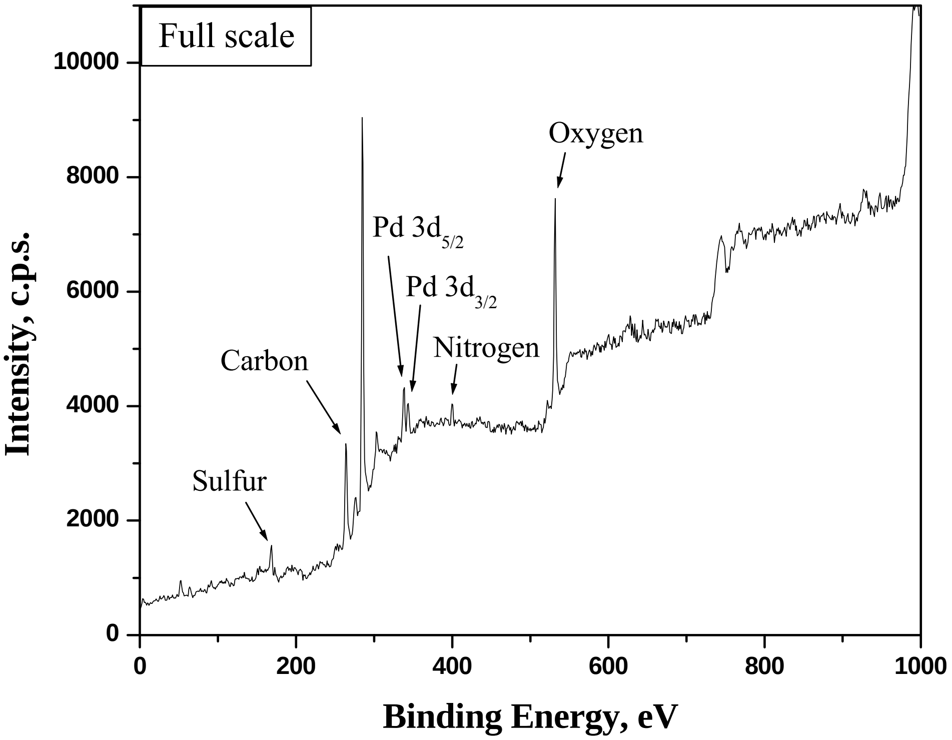


Figure 2.11 (a). XPS Spectrum of $Pd(OAc)_2$(bipyDS), whole spectrum

The freshly prepared catalyst $Pd(OAc)_2$(bipyDS) as well as that recovered after the recycle experiments was concentrated at low temperature (323K) on rotavap into a dry, amorphous powder and characterized by XPS for sulfur, nitrogen, carbon and palladium atoms for their respective binding energies (B. E.) and oxidation states. The B. E. values of the elements present in $Pd(OAc)_2$(bipyDS) (Table 2.7 and Figure 2.11(a) and 2.11 (b)) catalyst complied well with literature values obtained from similar Pd-complexes- homogeneous or heterogeneous. The data for each element was corrected with respect to signal of the adventitious carbon at 285 eV.

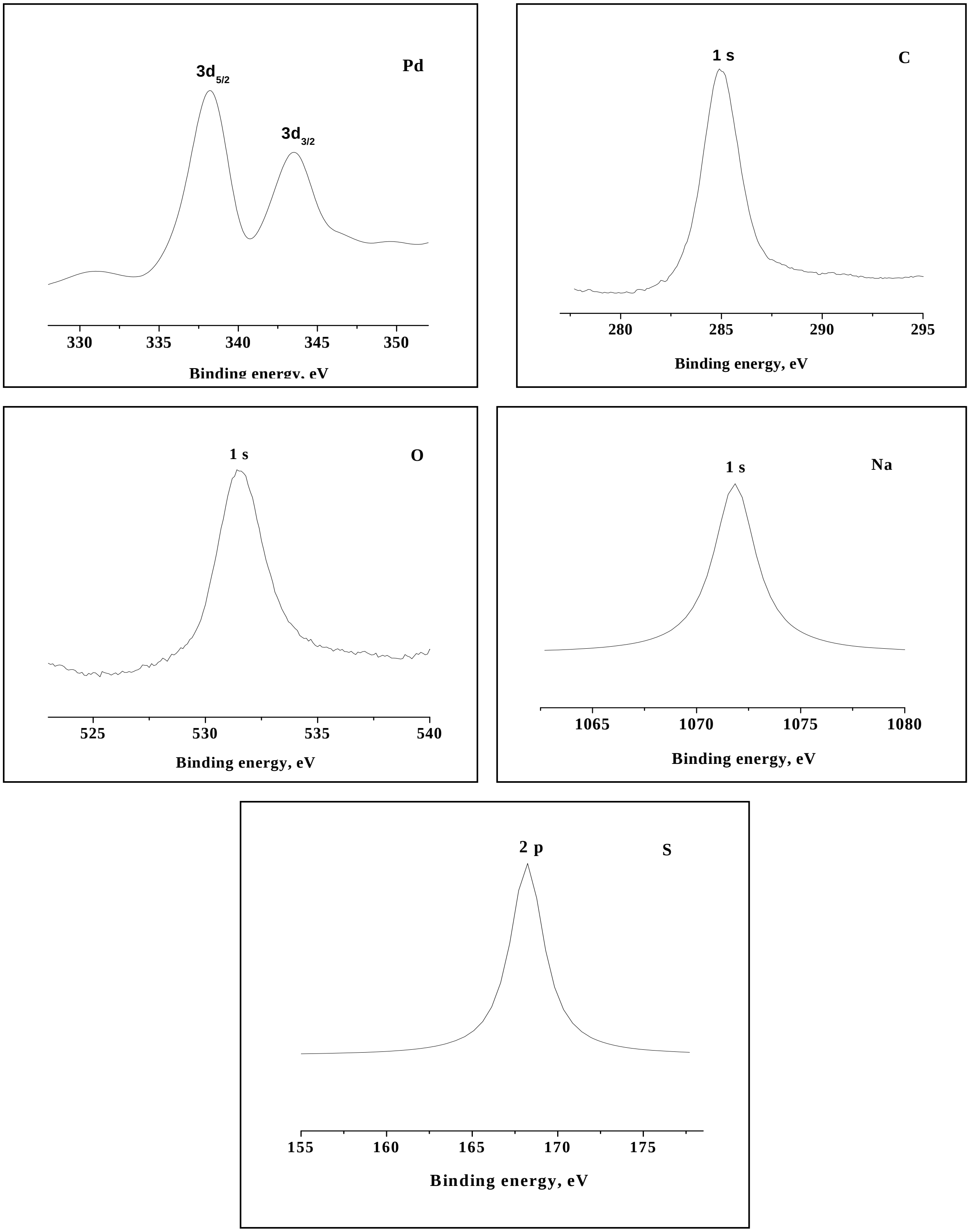


Figure 2.11 (b). XPS Spectrum of Pd(OAc)$_2$(bipyDS), binding energies of important elements

The binding energies of the other elements like N 1s, O 1s and S 2p also matched very well with the electronic condition of the water-soluble complex. For example, O 1s state occurs at 533.1 eV, which is similar to the +2 oxidation state of oxygen in an anion, e.g. carboxylate, or sulphonate; binding energy value for N 1s is 400.5 eV, which is slightly higher than the binding energy for N in pyridine (~398.7 eV) due to the chelation through the N-atom in the complex and consequent depletion of electron density.

The binding energy value of sulphur 2p, which was found to be 169.3 eV also matched closely with the S 2p value in sulfate group like in Na_2SO_4, which is 169.6 eV. All these binding energy values indirectly support the molecular composition of the water-soluble $Pd(OAc)_2$(bipyDS) complex. A comparison of the XPS pattern of the recovered and fresh complex also confirms that the molecular nature of the complex and more particularly the oxidation state of palladium remains unchanged after the reaction.

Table 2.7. XPS data for $Pd(OAc)_2$(bipyDS) (values in eV)

	Element						
	C	**N 1s**	**O 1s**	**S $2p_{3/2}$**	**Na 1s**	**Pd $3d_{5/2}$**	**Pd $3d_{3/2}$**
Uncorrected	288.9	404.4	537.0	173.2	1075.8	342.3	347.4
Corrected	285.0	400.5	533.1	169.3	1071.9	338.4	343.5
Literature[a]	285.0	400.0	532.1	169.6[27]	1071.5[28]	338.6[29]	343.9

a- B.E. values for comparison for elements are based on literature values comparison with analogous molecules; there is no precedent of XPS analysis of $Pd(OAc)_2$(bipyDS)

For pure $Pd(OAc)_2$ the $3d_{5/2}$ state occurs at around 338.5 eV, while the palladium is in the +2 oxidation state. The soft and resonating character of the OAc- anion imparts lesser electron density to the Pd center and hence Pd binding energy is slightly higher for $Pd(OAc)_2$. While in the case of other complexes of palladium coordinated by 2,2'-bipyridine- like in $PdCl_2$(bipy)- $3d_{5/2}$ state occurs at lower values like 338.0 eV. The $3d_{5/2}$ state in the $Pd(OAc)_2$(bipyDS) occurs at 338.4 eV, indicating that the OAc group in the complex is intact, while the sulfonated bipyridine is coordinated to palladium. A characteristic band gap of 5.1 eV was also observed between the $3d_{5/2}$ and $3d_{3/2}$ signals of palladium for the palladium complex. Also, since no peak is observed at B. E. value of 335.0 eV, which is the characteristic B. E. value for Pd $3d_{5/2}$, it is also confirmed that no palladium in 0 (zero) oxidation state is present in the fresh or recovered catalyst (Figure 2.12).

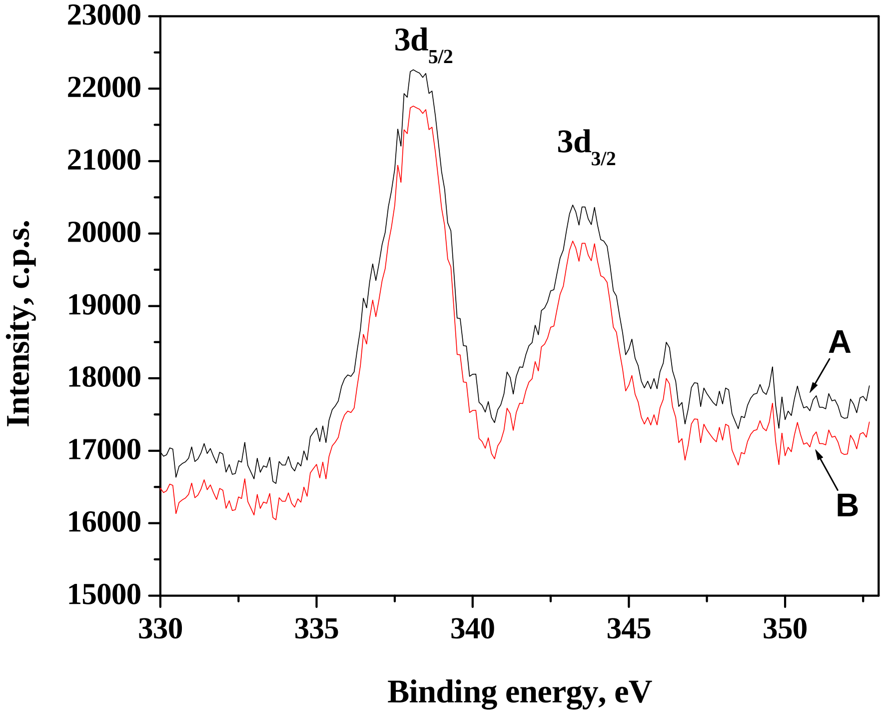


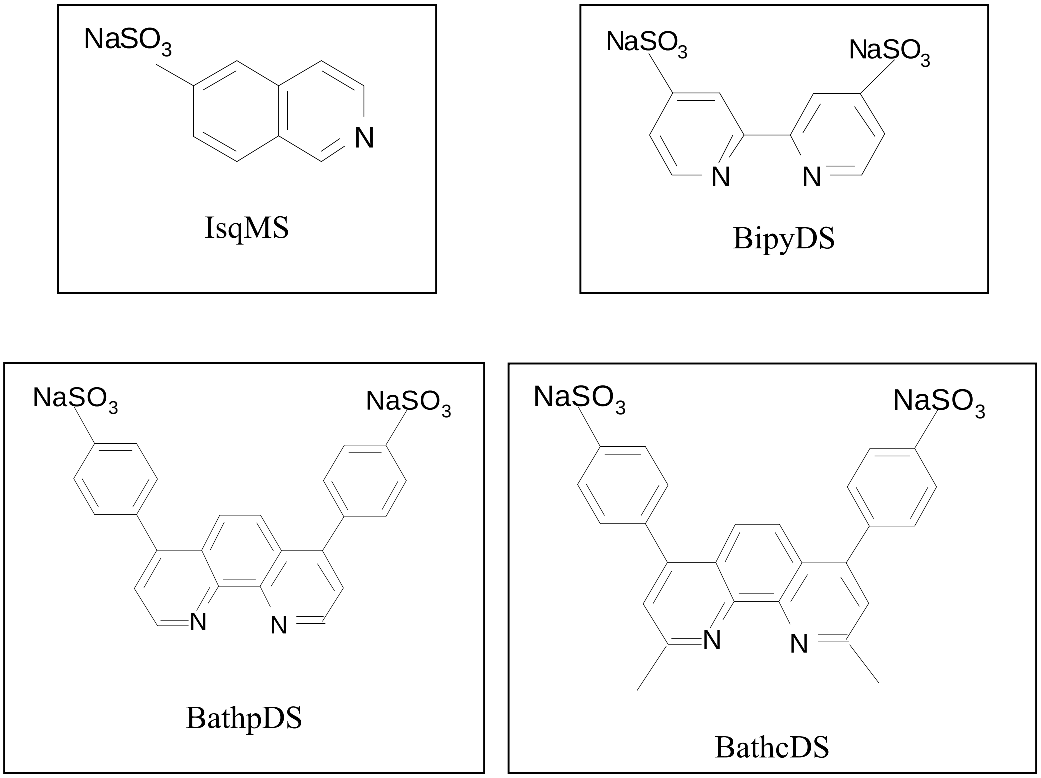
Figure 2.12. XPS Spectra of A) Fresh Pd(OAc)$_2$(bipyDS) and B) Pd(OAc)$_2$(bipyDS) recovered from aniline oxidative carbonylation experiment

2.3.9. Screening of water-soluble *N*-ligands

A few sulfonated water-soluble *N*-ligands were screened for the oxidative carbonylation of aniline using Pd(OAc)$_2$ precursor. The palladium complexes were prepared as aqueous solutions, and then charged into the reaction. The effect of ligand variation on conversion levels of aniline was assessed to study the effect on the reaction rate.

Various commercially available or laboratory synthesized sulfonated N-ligands were used. The yields of DPU lowered with increasing steric hindrance in the ligand, as can be observed from Table 2.8. This observation appears contradictory to the ligand variation effect observed by Ishii et al.[30] in the oxidative carbonylation of phenol, where the authors have speculated that the bulkier bidentate N-ligands cause faster the cleavage of the Pd–C bond in the phenoxycarbonyl intermediate (which would be the carbamoyl intermediate in the present reaction), thus giving higher reaction rate. The rate, however, was better when a bidentate N-ligand was used instead of the monodentate water-soluble IsqMS ligand.

The ligands screened were isoqunoline sulfonic acid, sodium salt as a monodentate ligand; and bipyridine disulfonic acid, disodium salt, bathophenanthroline disulfonic acid, disodium salt and bathocuproine disulfonic acid, disodium salt as bidentate ligands, for oxycarbonylation of aniline (Figure 2.13).



IsqMS

BipyDS

BathpDS

BathcDS

Figure 2.13. Sulfonated *N*-ligands screened for biphasic oxidative carbonylation of aniline

Table 2.8. Screening of water-soluble ligands

Sr	WS N-ligand	Aniline conversion, %	DPU Selectivity, %	DPU Yield, %	TOF
1	IsqMS[a]	32.7	96.5	31.6	74.8
2	BipyDS	58.7	97.5	57.2	135.7
3	BathpDS	59.1	94.8	56.0	132.9
4	BathcDS	55.9	96.7	54.1	128.2

Reaction conditions: Aniline 74 mmol, Pd complex catalyst 0.078 mmol ($10^{-5}m^3$), L:Pd = 1.2, Toluene $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423 K, P 6.89 MPa, CO:O_2 13:1, Agitation 16.66 Hz, time 30 min. [a] L:Pd = 2.2

The results obtained are given in Table 2.8. The ligand screening confirmed that all the catalysts prepared using the variety of sulfonated *N*-ligands resulted in selective synthesis of DPU (selectivity >95%), although the rates obtained were different.

2.3.10. Effect of reaction parameters on the reaction

The effect of variations in reaction parameters were studied using aniline as model substrate and $Pd(OAc)_2$(bipyDS)-NaI as the catalyst system. Following parameters were studied-

1. Temperature Effect
2. Aniline Concentration Effect
3. Effect of Variation of *p*CO
4. Effect of Variation of pO_2

2.3.10.1. Effect of reaction temperature

The effect of temperature on oxycarbonylation of aniline was studied in the range of 373-443 K. The reactions were taken for short period of 30 minutes, to get a visible effect on the aniline conversion and DPU yield. The results obtained are as follows-

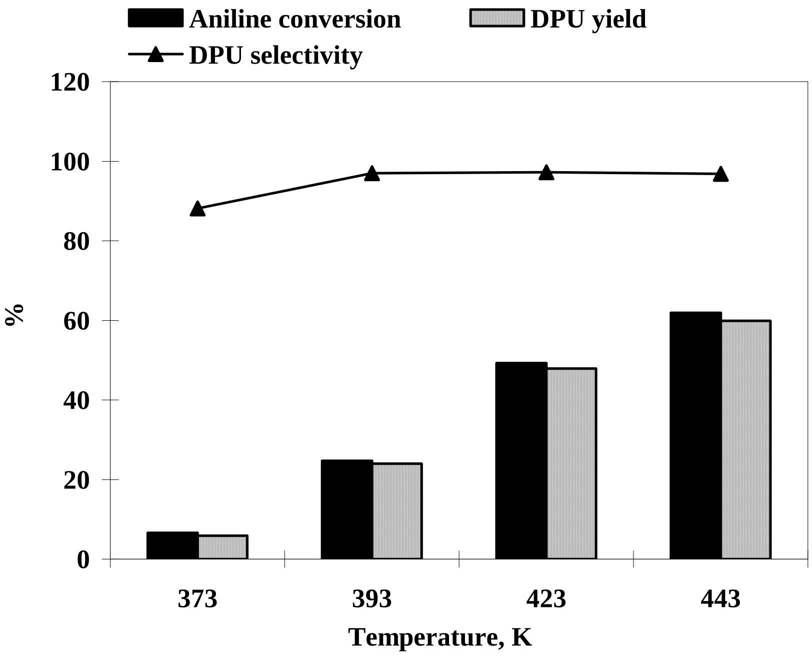


Figure 2.14. Effect of reaction temperature on biphasic oxycarbonylation of aniline **Reaction conditions**: Aniline 74 mmol, Pd(OAc)$_2$(bipyDS) 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423 K, P 6.89 MPa, CO:O$_2$ 13:1, Time 30 min, Agitation 16.66 Hz.

2.3.10.2. Effect of aniline concentration

These experiments were taken with the same substrate to catalyst and iodide to catalyst molar ratios as in the typical experiment; in the aniline concentration range of 0.063 mol to 0.097 mol. It was found that the conversion of aniline increased with the increase in aniline concentration. The results obtained are shown in Figure 2.15. There was no effect of aniline concentration on the selectivity to DPU.

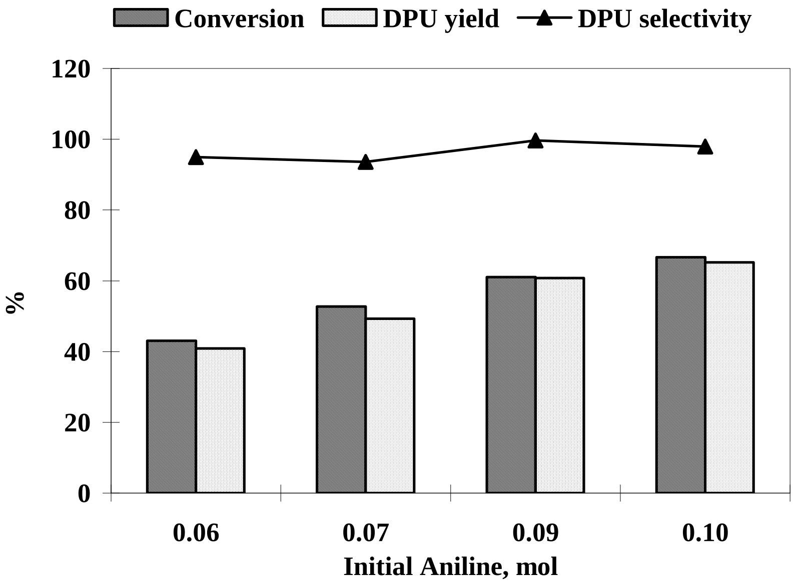


Figure 2.15. Aniline concentration effect on aniline conversion and yield of DPU **Reaction conditions**: Pd(OAc)$_2$(bipyDS) 0.078 mmol (10^{-5}m^3), Toluene 5×10^{-5}m^3, NaI 0.90 mmol, T 423 K, P 6.89 MPa, CO:O$_2$ 13:1, Stirring 16.66 Hz, Reaction Time 30 min.

2.3.10.3. Effect of variation in P_{CO}

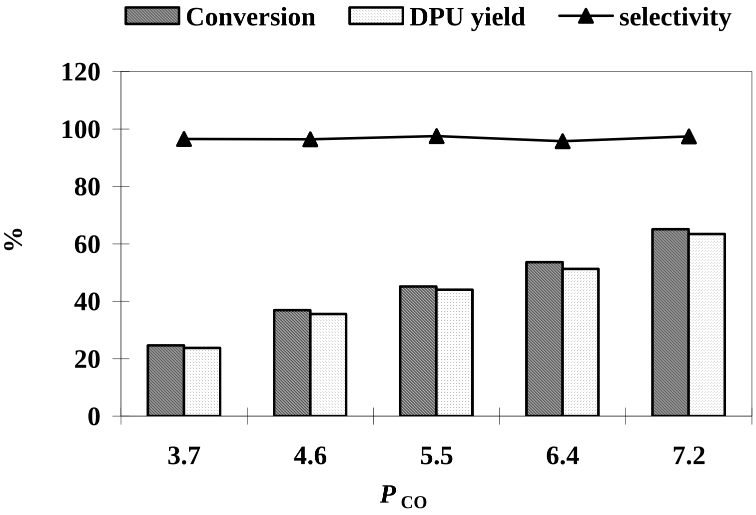


Figure 2.16. Effect of CO partial pressure

Reaction conditions: Aniline 74 mmol, Pd(OAc)$_2$(bipyDS) 0.078 mmol (10^{-5}m^3), Toluene 5×10^{-5}m^3, T 423 K, pO$_2$ 0.482633 MPa, CO:O$_2$ 13:1, Agitation 16.66 Hz, time 30 min

The effect of variation of partial pressure of carbon monoxide was carried out under model reaction conditions, at 423 K, while keeping the partial pressure of oxygen fixed at 0.483 MPa. The results of this study can be seen in Figure 2.16. The effect of increasing CO partial pressure was found to be linear, and the yield of DPU increased with increase in *p*CO.

2.3.10.4. Effect of variation in P_{O2}

The effect of change in the partial pressure of oxygen was studied in the P_{O2} range of 0.414-0.689 MPa, while keeping the CO partial pressure at 6.412 MPa. The effect of variation in the partial pressure of oxygen on the biphasic oxidative carbonylation of aniline can be seen from Figure 2.17.

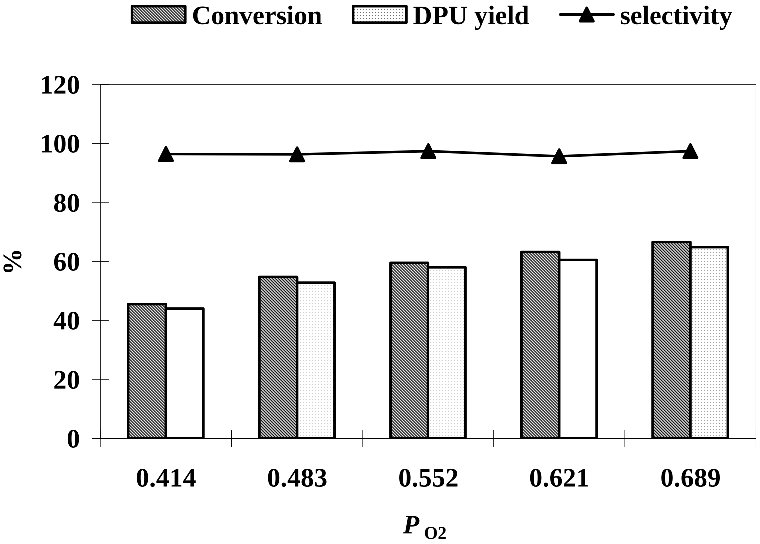


Figure 2.17. Effect of O_2 partial pressure

Reaction conditions: Aniline 74 mmol, Pd complex catalyst 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, T 423K, *p*CO 6.412124 MPa, CO:O_2 13:1, Stirring 16.66 Hz, time 30 min

The most important purpose of this particular study was to check for the oxygen starvation effect, i.e., depletion of oxygen in the reaction resulting in mass-transfer limitation, thereby resulting in lowering of DPU yields. Within the permissible variation range of oxygen concentration in gas phase, the partial pressure variation showed a consistent rise in the conversion of aniline as well as the yield of DPU, although the effect was not very drastic. This confirmed that the typical reaction conditions were not in the mass-transfer regime, but are in the kinetic regime, and that there was no oxygen starvation in the reaction.

2.3.11. Proposed mechanism

The oxidative carbonylation of amine to urea (or carbamate) involves transfer of hydrogen from amine to the metal centre of the catalyst, which results in reduction of oxidation state of metal upon formation of hydride species. The reduced catalytic species generally is reoxidized by promoter and in the process metal coordinated hydride is either abstracted by the promoter (e.g. in the case of quinone as the promoter) or converted into water as commonly observed when oxygen is used as the oxidant.[2] The generated water competes with substrate amine giving rise to a side reaction of carbon monoxide oxidation to carbon dioxide. Therefore, designing catalytic system involving water as a solvent and at the same time minimizing CO oxidation is challenging. In order to minimize the CO oxidation, amine should be preferably be activated by the catalyst rather than water. The water-soluble palladium catalyst presumably makes the Pd catalyst more reactive towards amine. Also, it seems likely that quaternized amine which was readily soluble in aqueous medium makes quaternary amine more susceptible to be attacked by water-soluble Pd catalyst. The mechanism speculated in Figure 2.18 is based on the alternation of oxidation states of palladium between I and II (which is consistent with XPS results shown earlier). A stoichiometric reaction between the $Pd(OAc)_2(BipyDS)$ complex 1 and NaI showed formation of the active catalytic intermediate species 2, which has also been reported previously by Mueller et al.[31] The need of charging higher equivalents of sodium iodide in the reaction was evident from the reversible nature of this particular step of reaction. It was observed that this reaction takes place at room temperature and with immediate effect, which was evident from the immediate color change from faint yellow to dark brown. The rate-determining step in this pathway may be speculated to be the oxidative transition of the amino-carbamoyl palladium complex to the active catalytic complex 2, with the release of the carbamoyl moiety as the substituted urea.

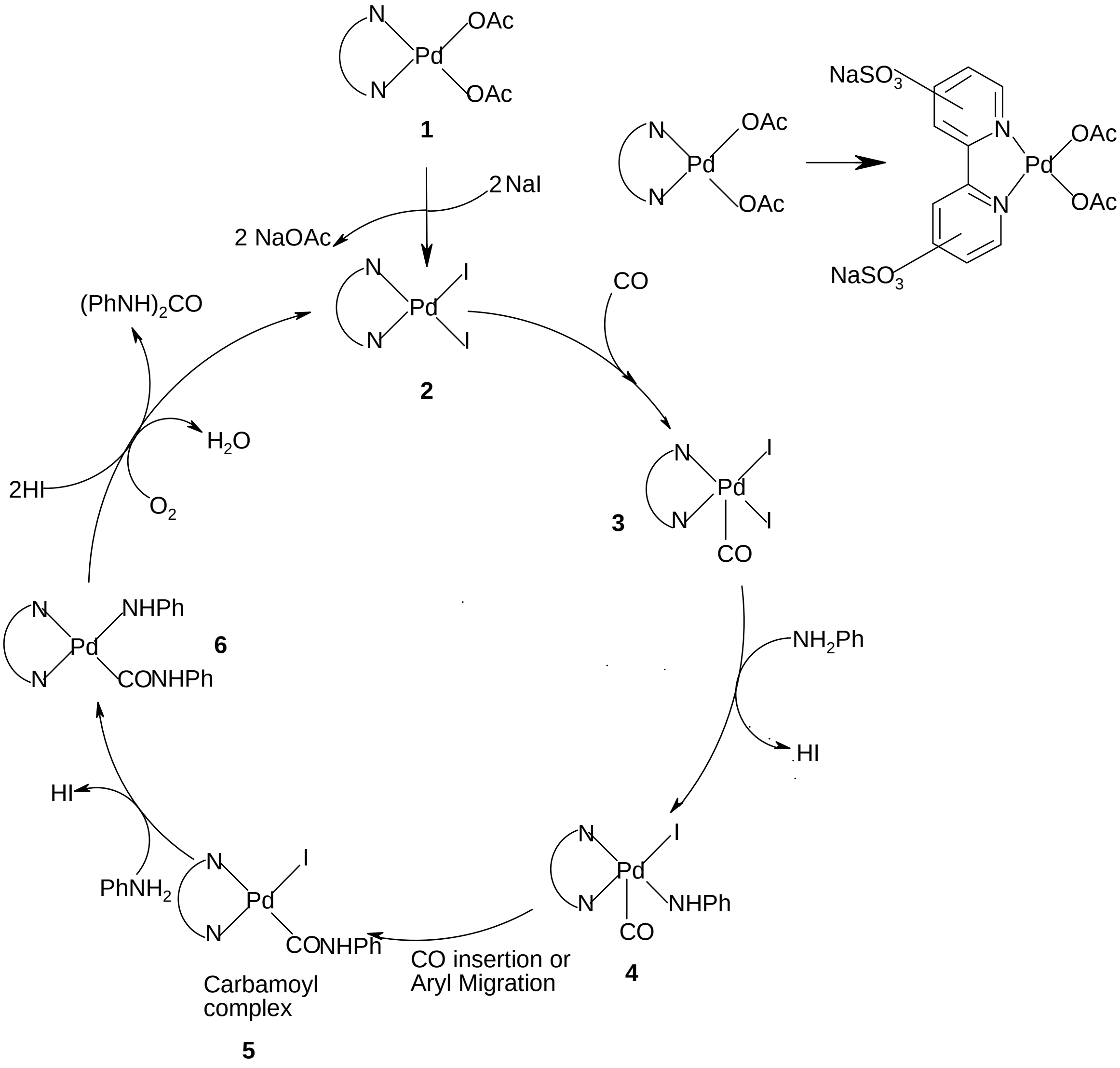


Figure 2.18. Proposed mechanism for aqueous-biphasic oxidative carbonylation of aniline

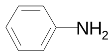
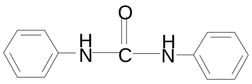
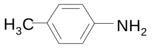
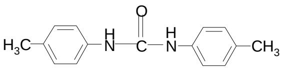
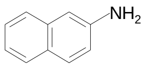
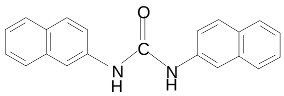
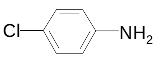
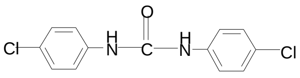
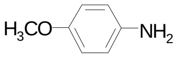
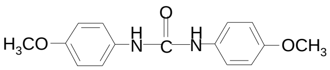
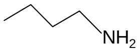
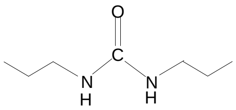
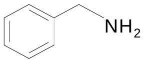
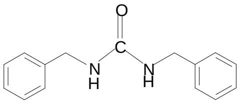
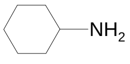
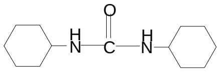
2.3.12. Screening of amine substrates

The applicability of the biphasic catalytic system was investigated for a range of amines, under model reaction conditions, and the results are listed in Table 2.9. Low yields of disubstituted ureas were obtained where chloroaniline, *p*-aminophenol, *p*-anisidine and nitroaniline were used as substrates. Good to excellent yields of ureas were obtained in cases of aniline, *p*-toluidine, benzylamine, butylamine, cyclohexylamine and *o*-phenylene diamine. Although cyclic urea could be obtained with satisfactory yield in case of *o*-phenylenediamine, no amine conversion or cyclic urea was observed when ethylene diamine was used as a substrate, which also happened in case when 3% Pd/C was used as catalyst in place of the water-soluble Pd(OAc)$_2$(bipyDS) catalyst.

2.3.12.1. Primary monoamines as substrates

Primary aliphatic, aromatic and cyclic monoamines gave excellent results upon the biphasic oxidative carbonylation with Pd(OAc)$_2$(bipyDS) catalyst.

Table 2.9. Screening of primary monoamines

Sr.	**Amine**	**Disubstituted urea**	**Results**		
			Conversion, %	**Selectivity, %**	**Yield$^{\bullet}$, %**
1			94.5	92.9	87.8
2			96.8	97.5	94.4
3			95.6	85.6	81.8
4			54.1	88.7	48.0
5			98.3	81.0	79.6
6			97.4	94.6	92.2
7			96.8	83.8	81.1
8			98.2	93.8	92.1

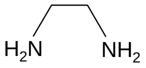
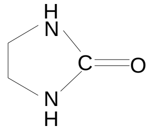
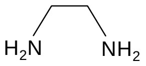
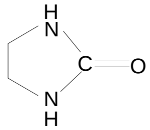
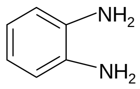
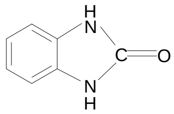
Reaction conditions: amine 74 mmol, Pd(OAc)$_2$(bipyDS) 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423 K, P 6.89 MPa, CO:O$_2$ 13:1, Agitation 16.66 Hz, Time 120min • = Isolated yields.

It was observed that in all the reactions, the aqueous layer containing the water-soluble catalyst retained a clear yellow colour after the reaction. Also, no palladium precipitation was observed in these reactions. In general, the amines having high electron density at nitrogen gave better yields of respective ureas.

2.3.12.2. Primary diamines as substrates

Primary diamines were also screened, to check for the formation of cyclic substituted ureas. EDA and OPDA were used as substrates, and the results obtained are presented in Table 2.10.

Table 2.10. Screening of primary diamines

Sr	Amine	Urea	Amine conversion, %	Urea selectivity, %	Urea yield, %
1			-	-	-
2*			-	-	-
3			96.60	87.4	84.50

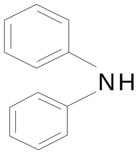
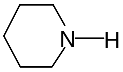
Reaction conditions: amine 74 mmol, $Pd(OAc)_2$(bipyDS) 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, * catalyst= 3% Pd/C and no water in solvent phase; NaI 0.90 mmol, T 423 K, P 6.89 MPa, $CO:O_2$13:1, Agitation 16.66 Hz, Time 120min

The aromatic diamine, 1,2-phenylene diamine (entry 3) was found to be an excellent substrate for the present study. The *o*-phenyleneurea obtained in this case could be conveniently isolated and characterized by conventional spectroscopic techniques. The aliphatic amine, ethylene diamine did not show any conversion under the similar experimental conditions. In order to understand whether the reason for the failure of amine conversion in this case was a limitation of the biphasic catalyst system or the low reactivity of the aliphatic diamine, a similar experiment was carried out using the conventional 5% Pd/C catalyst, with toluene as the solvent and in absence of water in the reaction medium. Neither any absorption of the CO+O_2 mixture, nor any conversion of amine was observed in this experiment also, indicating that ethylene diamine, under the present set of experimental conditions, is not a good substrate for oxidative carbonylation. A probable reason for the no formation of cyclic urea form ethylene diamine could be the thermodynamic non-feasibility, owing to the high steric strain in the cyclic urea molecule.

2.3.12.3. Secondary amines as substrates

Reactions were taken with standard charge and with dibenzylamine and piperidine as the substrates.

Table 2.11. Screening of secondary amines

Sr	Substrate	Amine Conv, %	Urea Yield, %	Remark
1		0	0	No gas absorption/ residue formation observed. M. S. of org layer showed absence of urea.
2		87	0	Gas absorption/ amine conversion was observed, but no residue formation was observed. M. S. of org layer showed absence of urea.

Reaction conditions: amine 74 mmol, $Pd(OAc)_2(bipyDS)$ 0.078 mmol ($10^{-5}m^3$), Toluene $5\times10^{-5}m^3$, NaI 0.90 mmol, T 423 K, P 6.89 MPa, CO:O_2 13:1, Agitation 16.66 Hz, time 120 min.

It was observed that, there was no amine conversion in case of dibenzylamine, but considerable conversion of piperidine was observed, however, urea formation was not observed in any of the cases. It should be noted that palladium precipitation was observed in both the cases. The results obtained are given in Table 2.11. A summary of the characterization of the disubstituted ureas obtained is given in Table 2.12.

Table 2.12. Characterization of disubstituted ureas

Sr.	Disubstituted urea	Molecular formula	IR $\nu_{(C=O)}$, cm^{-1}	Microanalysis, %		
				Ele.	**Calc.**	**Obtained**
1	1,3-Diphenyl urea	$C_{13}H_{12}N_2O$	1649	C H N	73.56 5.70 13.20	73.47 6.33 12.99
2	1,3-di-*p*-tolylurea	$C_{15}H_{16}N_2O$	1640	C H N	74.97 6.71 11.66	74.18 6.70 11.87
3	1,3-bis (4-methoxyphenyl)urea	$C_{15}H_{16}N_2O_3$	1634	C H N	66.17 5.88 10.29	66.28 6.37 10.31
4	1,3-di (naphthalen-2-yl)urea	$C_{21}H_{16}N_2O$	1632	C H N	80.77 5.13 8.97	79.59 5.32 8.94
5	1,3-dibutylurea	$C_9H_{20}N_2O$	1623	C H N	62.79 11.63 16.28	62.77 10.41 15.32
6	1,3-dibenzylurea	$C_{15}H_{16}N_2O$	1627	C H N	74.97 6.71 11.66	74.90 6.54 11.73
7	1,3-dicyclohexylurea	$C_{13}H_{24}N_2O$	1626	C H N	69.60 10.78 12.49	69.17 11.91 12.08
8	*o*-phenylene urea (1H-benzo[d]imidazol-2(3H)-one)	$C_7H_6N_2O$	1742	C H N	62.60 4.47 20.90	61.67 4.15 21.39
9	1,3-bis (4-chlorophenyl)urea	$C_{13}H_{10}Cl_2N_2O$	1633	C H N Cl	55.54 3.59 9.96 25.22	55.49 4.12 10.01 24.98

2.4. CONCLUSIONS

A robust and active catalyst system employing the conventional transition metal precursors has been devised for oxidative carbonylation of amines. The present work is the first report on oxidative carbonylation of amines for the selective synthesis of disubstituted ureas *via* the transition-metal catalysis in water, carried out in a water-organic solvent biphasic system. The complexes are rendered water-soluble by making their complexes with water-soluble *N*-ligands. The moiety making the nitrogen ligands is a sulfonate group, and such ligands have been synthesized by sulfonation of the *N*-heterocycles. Various such ligands, both monodentate and bidentate have been screened for the oxidative carbonylation of aniline as a model substrate in the presence of iodide promoters and oxygen gas as the oxidant. Palladium metal complexes of bidentate *N*-ligands have been found to be highly active for the reaction. The significance of such a system lies in the advantage gained in the catalyst-product separation. None of the prior reports mention the separation of catalyst in a satisfactory manner, owing to the scarce solubility of the substituted urea products even in highly polar solvents.

The aqueous-biphasic oxycarbonylation of amines using such water-soluble noble metal complexes have been found to yield substituted urea products of a range of primary amines, however, the catalyst system fails to yield substituted urea from secondary amines.

The cyclic urea products could also be synthesized from aromatic diamines, certain derivatives of which have significant importance in medicinal chemistry as HIV-protease inhibitors.

In summary, following major aspects have been achieved in the study illustrated in this chapter-

- Synthesis and characterization of water-soluble complexes prepared from sulfonated N-heterocyclic ligands.
- Successful application of the water-soluble catalyst system in aqueous-biphasic reaction medium, and optimisation of reaction parameters. The catalyst is reusable, and there is no significant drop in the activity of the catalyst upon recycle.
- Partial recovery and reuse of the water-soluble halide promoter is possible.

- Aliphatic as well as aromatic primary amines have been found to give excellent yields of substituted ureas with the present catalyst system.
- The substituted ureas owing to their sparing solubility in the organic phase crystallize out of the reaction medium, and can be isolated by simple filtration.

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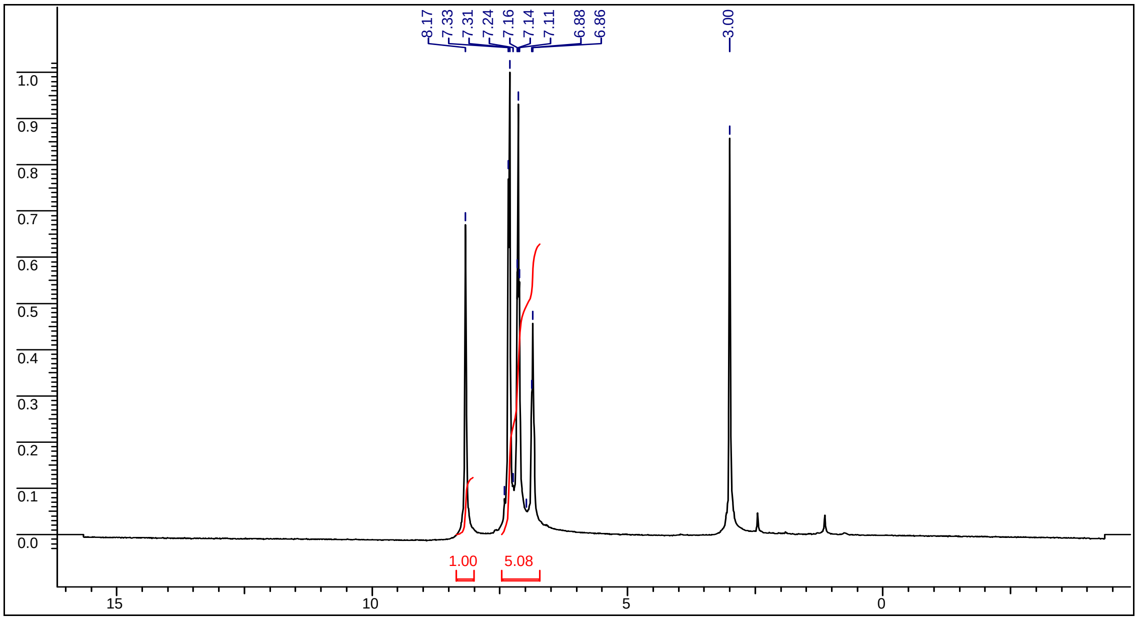
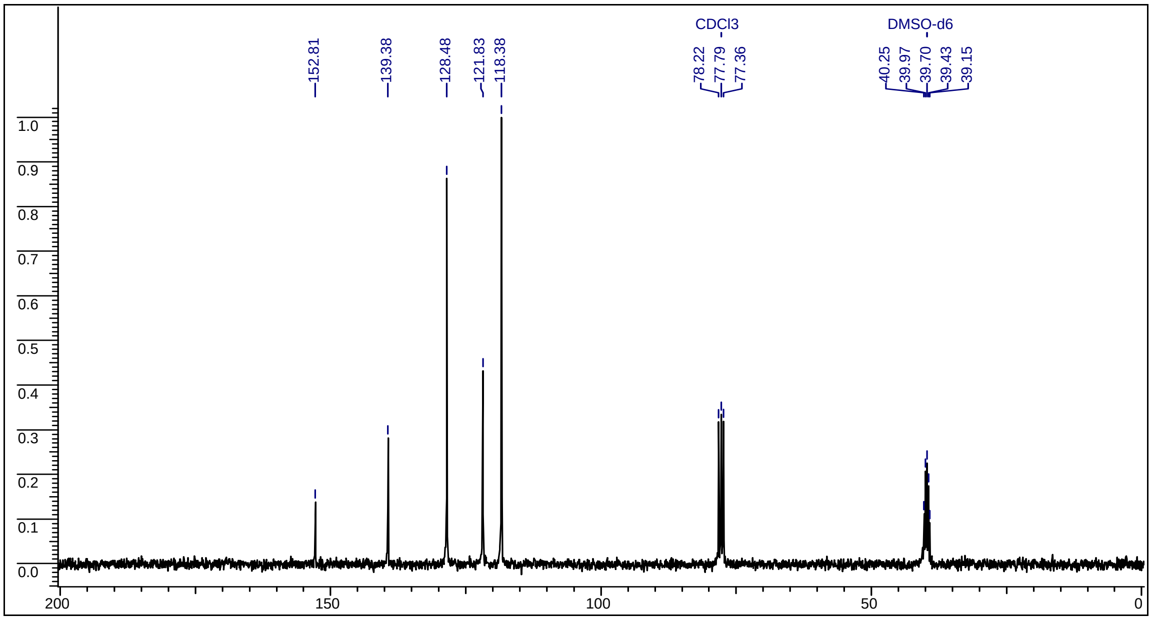
SPECTRA



^{1}H NMR of 1,3-diphenylurea in DMSO-d_6



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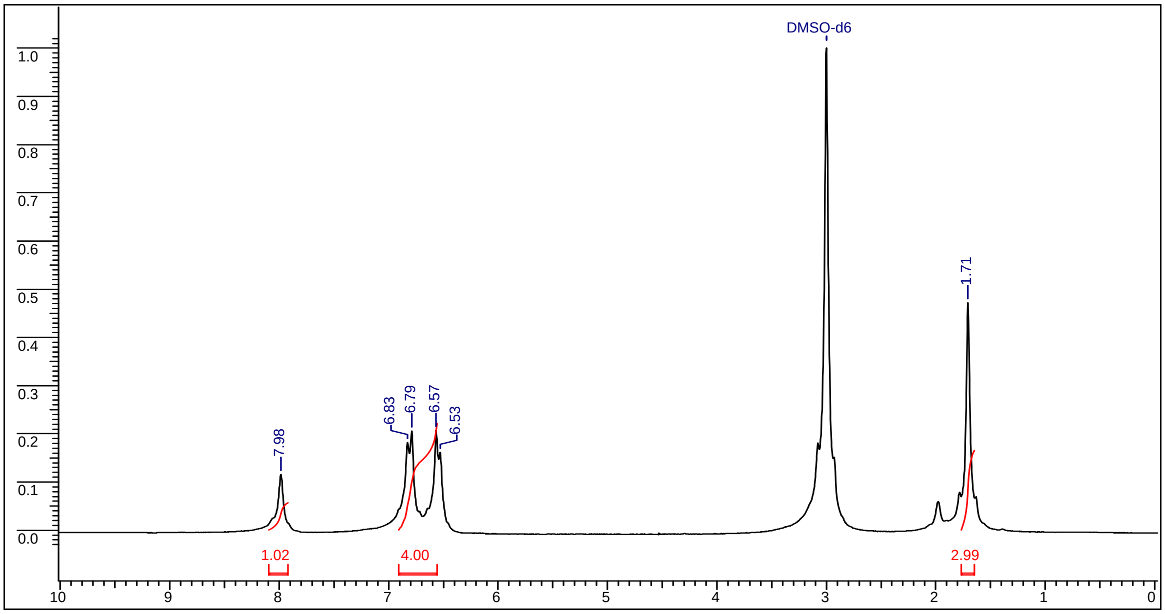

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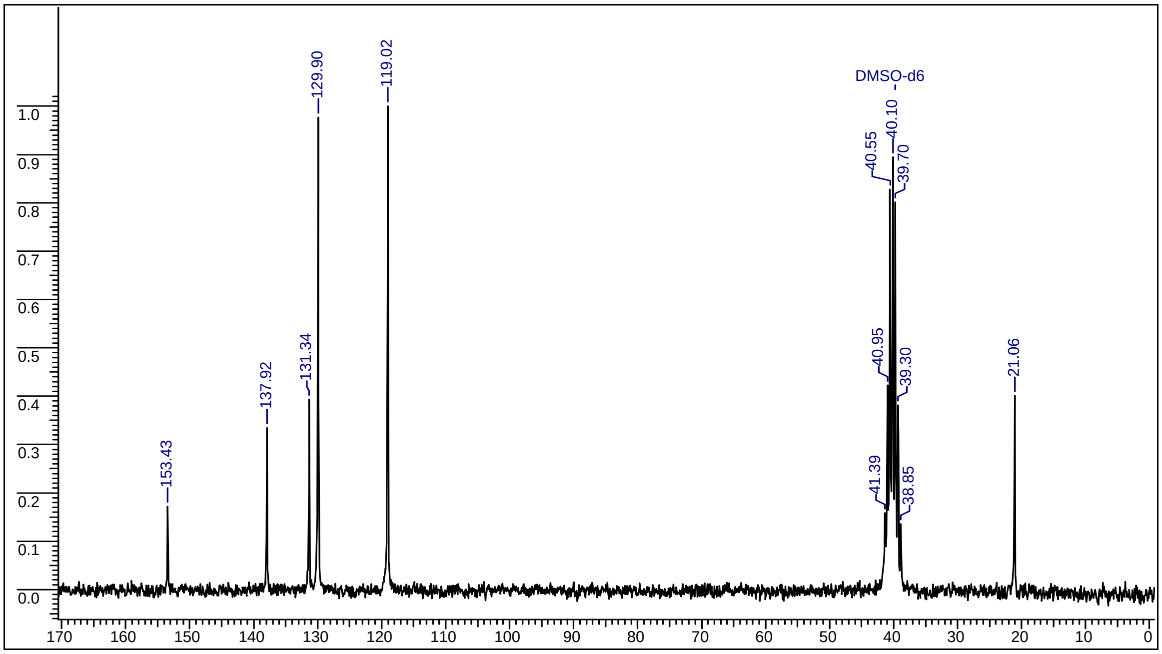

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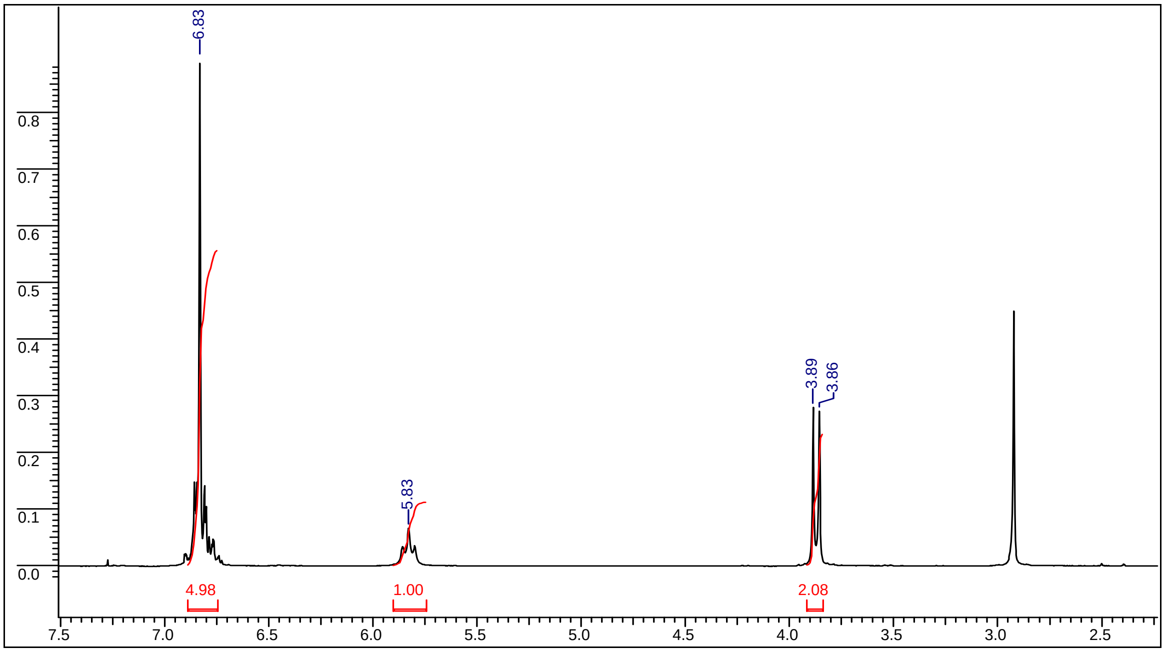

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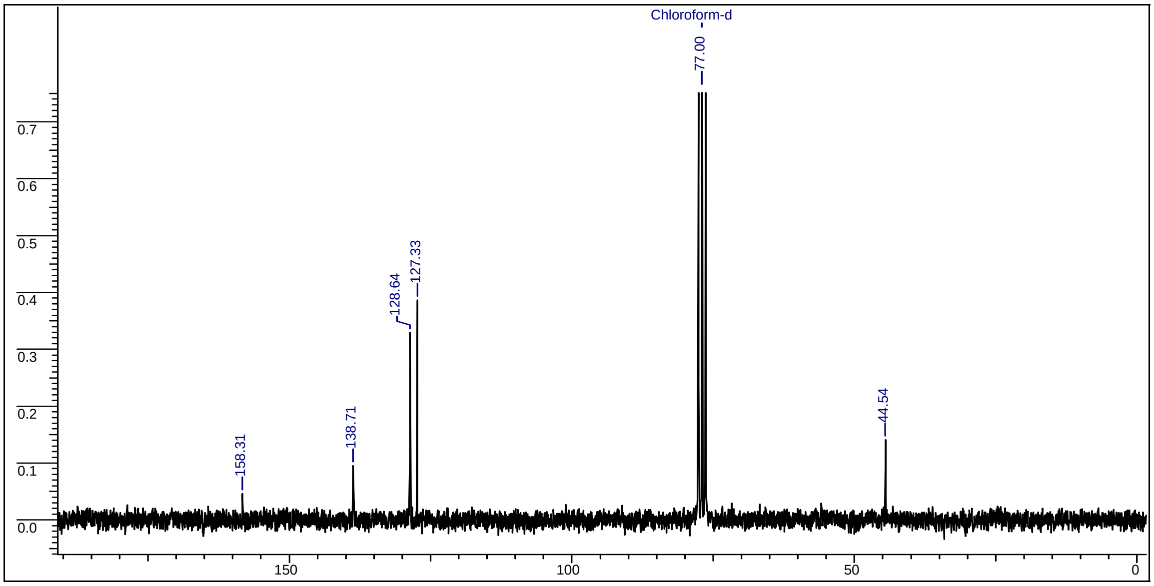
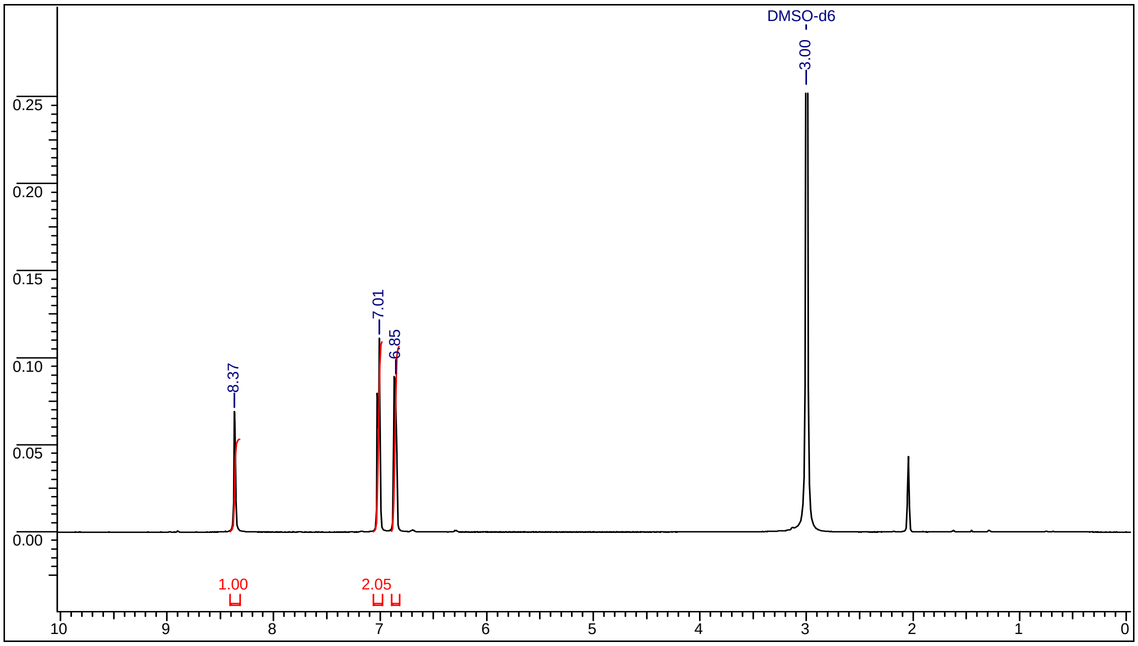
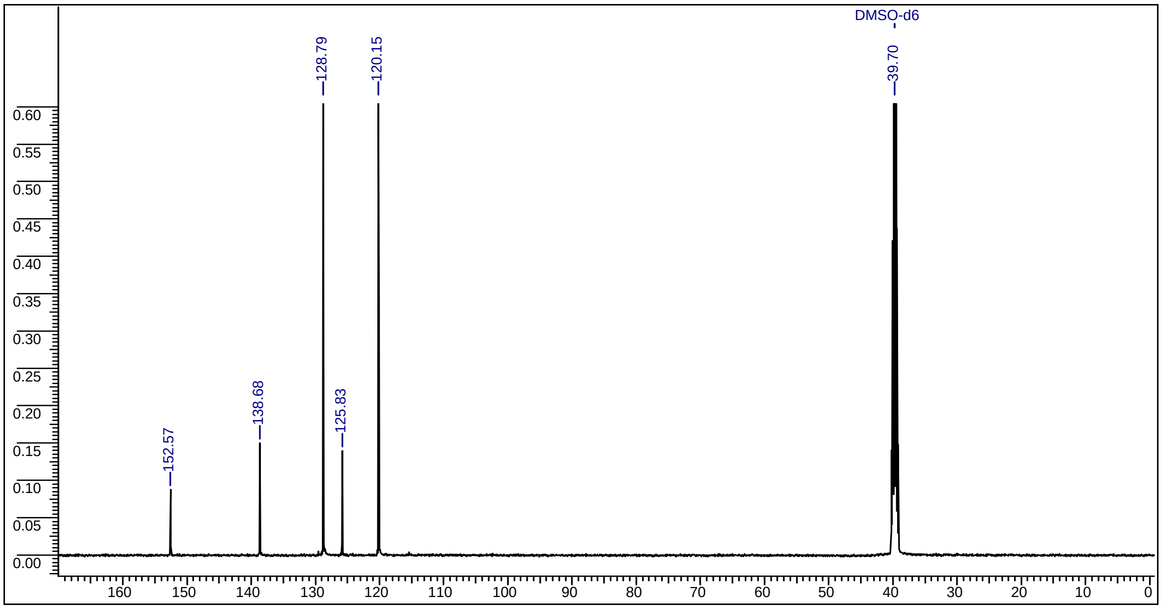


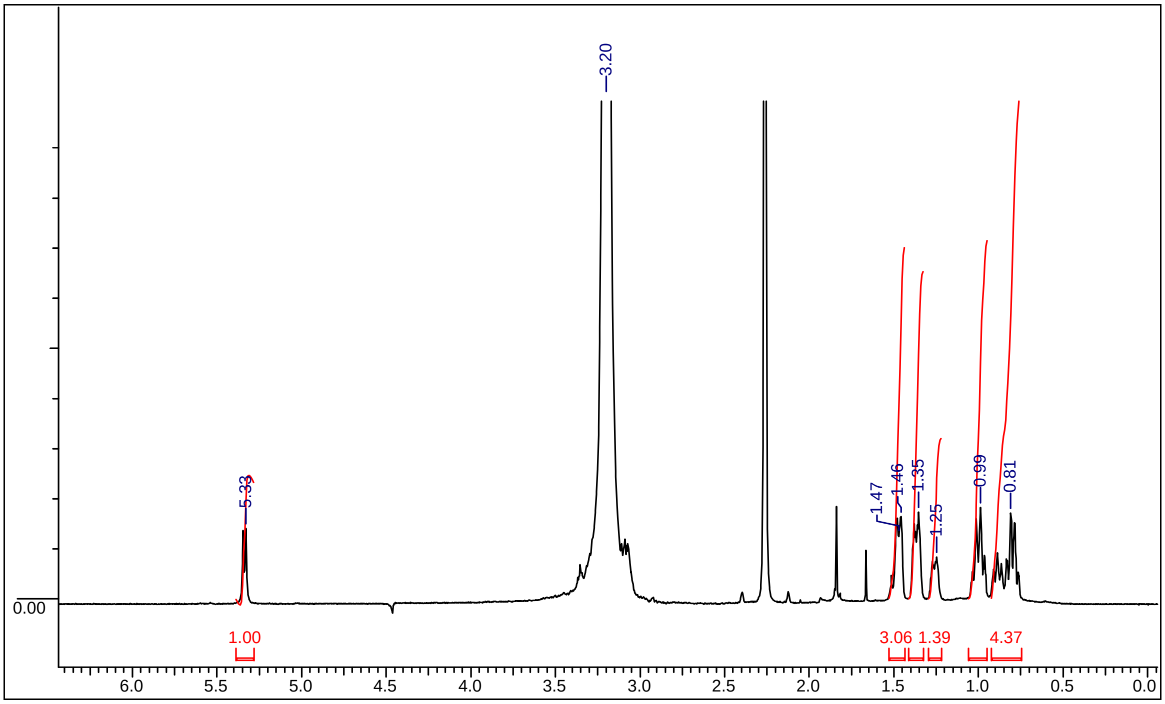
^{13}C NMR of 1,3-dibenzylurea in $CDCl_3$



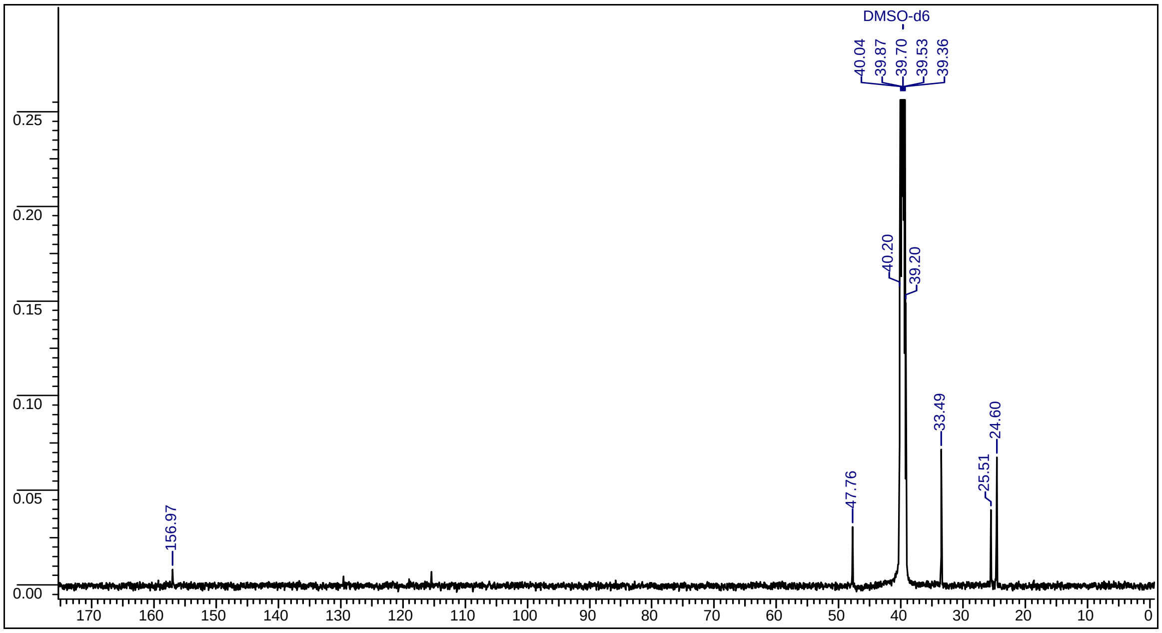
^{1}H NMR of 1,3-bis(4-chlorophenyl)urea in DMSO-d_6



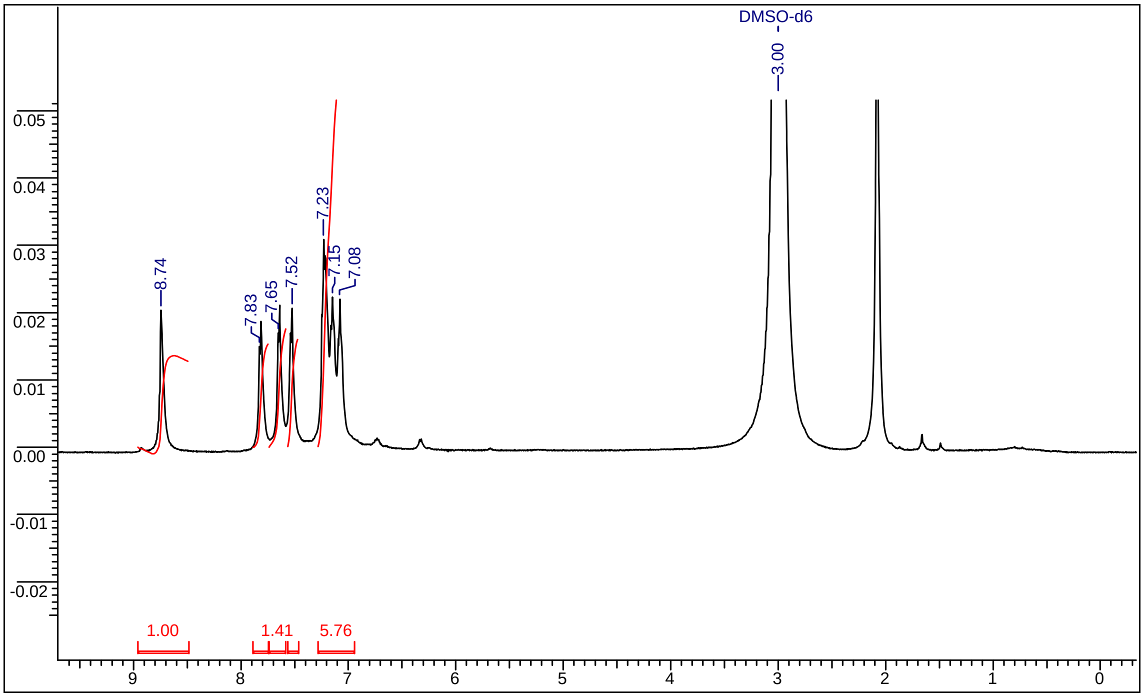
^{13}C NMR of 1,3-bis(4-chlorophenyl)urea in DMSO-d_6



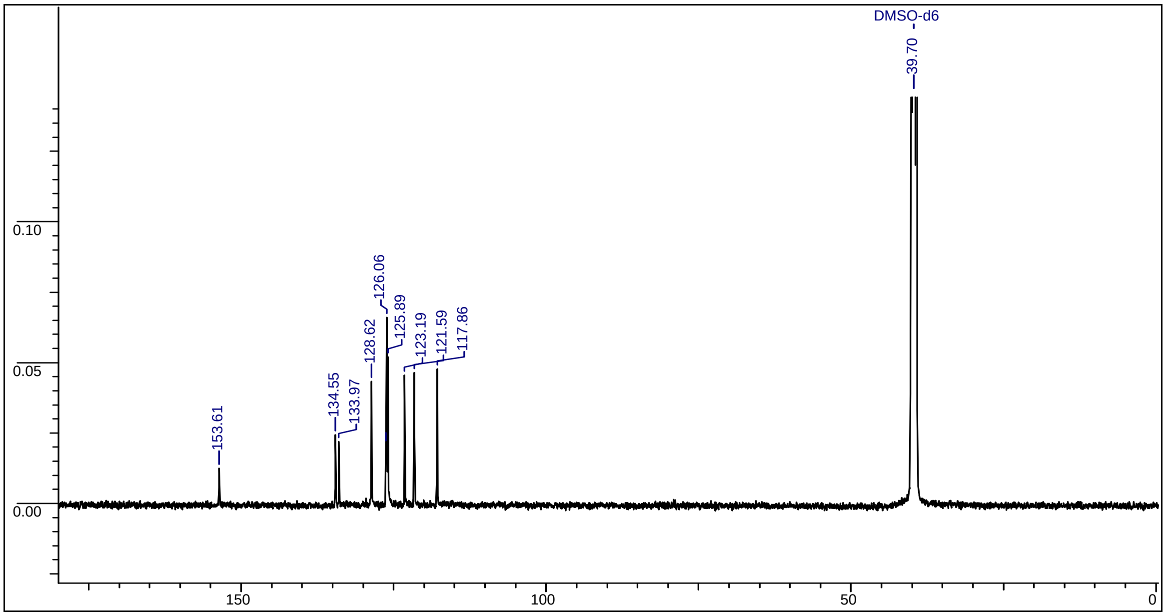
^{1}H NMR of 1,3-dicyclohexylurea in DMSO-d_6



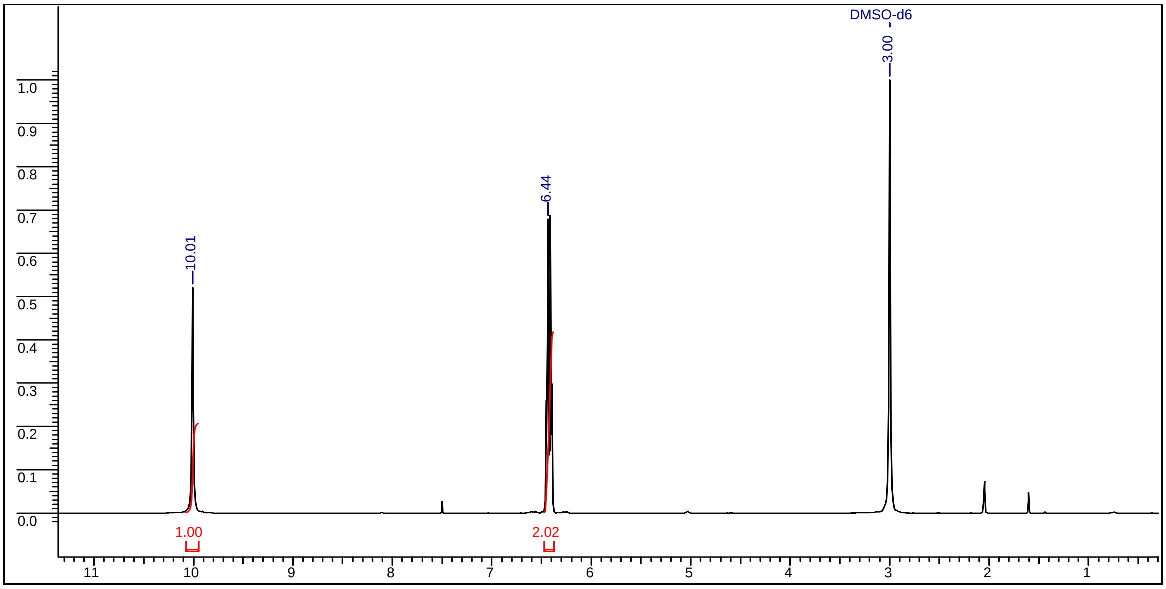
^{13}C NMR of 1,3-dicyclohexylurea in DMSO-d_6



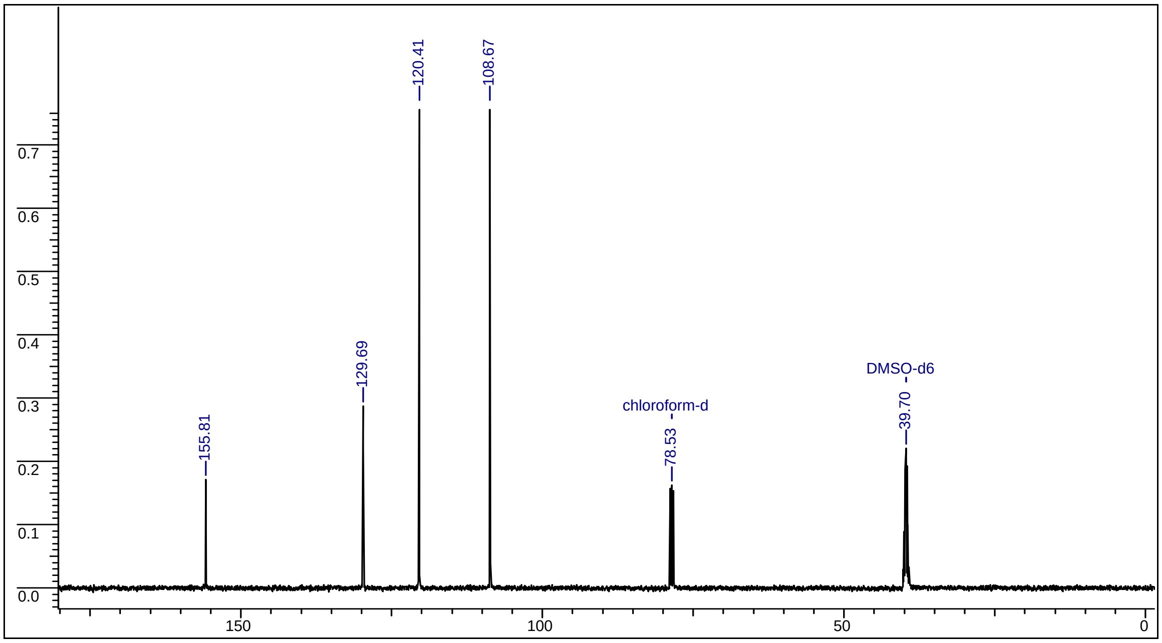
^{1}H NMR of 1,3-dinaphthylurea in DMSO-d_6



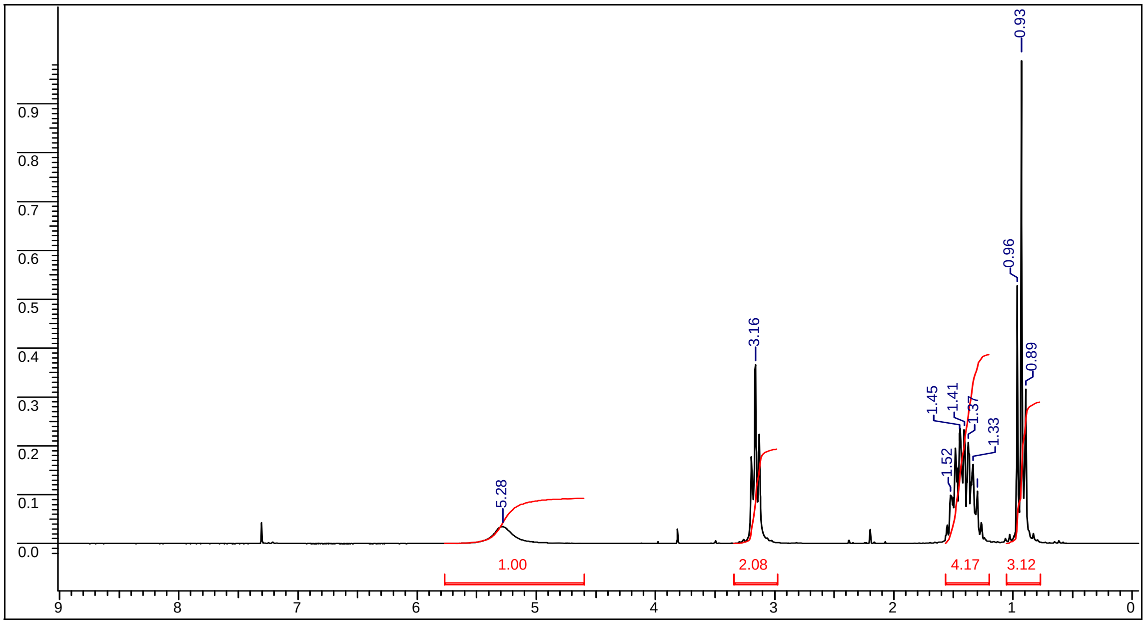
^{13}C NMR of 1,3-dinaphthylurea in DMSO-d_6



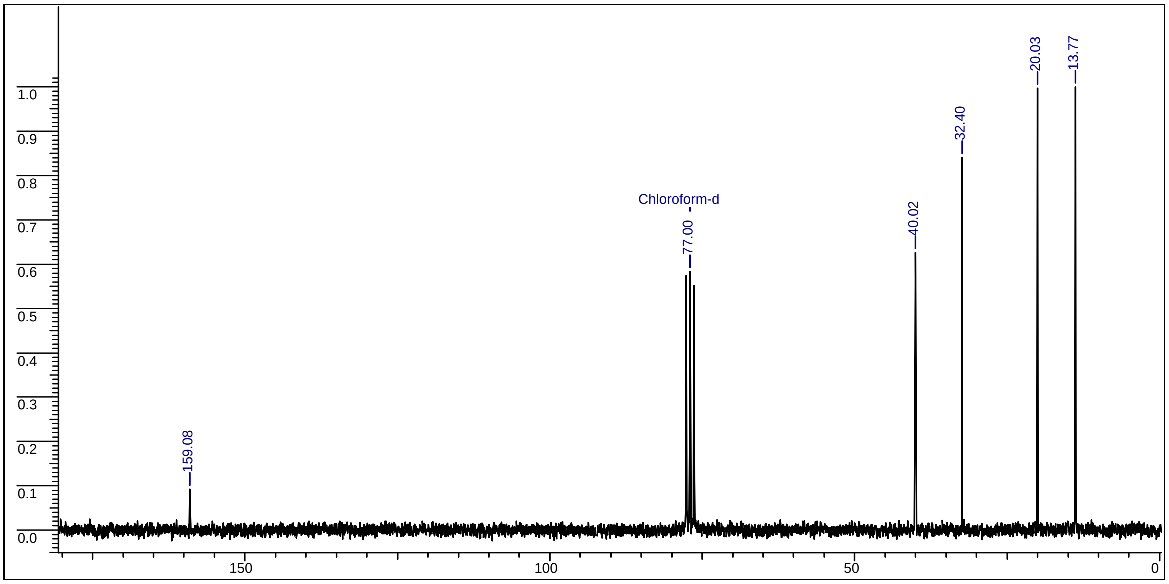
^1H NMR of 1H-benzo[d]imidazol-2(3H)-one (*o*-phenylene urea) in DMSO-d_6



^{13}C NMR of 1H-benzo[d]imidazol-2(3H)-one (*o*-phenylene urea) in DMSO-d_6



^{1}H NMR of 1,3-dibutylurea in $CDCl_3$



^{13}C NMR of 1,3-dibutylurea in $CDCl_3$

Chapter 3

Lead Oxide Catalyzed Methoxycarbonylation of Amines with Dimethylcarbonate

This chapter describes a detailed study of methoxycarbonylation of amines for selective synthesis of carbamates using red lead (Pb_3O_4) catalyst. A few reported catalysts as well as lead compounds have been screened to take a comparative account of their catalytic activities. The different parametric studies on the activity and selectivity for the reaction have been performed for the proper understanding and optimization of the catalyst. From the results of variations in reaction conditions and parameters, a rate model has been proposed. The validity of the rate model has been crosschecked with experimental data; and the activation energy for aniline methoxycarbonylation has been evaluated based on Arrhenius plot. Possible mechanism for the formation of carbamate have been proposed, and catalyst pretreatment study coupled with IR spectroscopic investigations of the catalyst has been carried out in an attempt to shed light on the reaction mechanism. Several carbamates have been synthesized with Pb_3O_4 catalyst, and isolated and characterized by conventional spectroscopic methods for product identification.

3.1. INTRODUCTION

Carbamates are very useful intermediates in organic synthesis and find several applications in many areas of chemistry like agrochemicals, pharmaceuticals, dyestuffs, linkers in combinatorial synthesis, etc.[1],[2] They are used as protecting agents, especially in peptide synthesis.[3] Carbamates have also gained immense significance in the combinatorial synthesis[4],[5] in the preparation of small chiral molecule libraries of pharmacological importance, which has contributed to the understanding of structure and folding, biological function, and therapeutic potential of biological macromolecules like polypeptides. Dicarbamates or diurethanes too, are compounds of great interest from an industrial viewpoint as, upon thermolysis, they afford diisocyanates, which are widely employed as precursors of polymeric materials.[6] Some important diisocyanates which can be obtained from their corresponding dicarbamates include 4,4'-methylenediphenyl diisocyanate (MDI), 2,4-toluene diisocyanate (TDI) and isophorone diisocyanate (IPDI), which are most commonly used diisocyanates in polyurethane industry.

The conventional synthetic route for carbamate involves reaction of phosgene with aromatic amines.[7] However, this route has serious drawbacks, owing to acute toxicity of phosgene. It is a colourless gas, is 3.4 times heavier than air and may travel along the ground. Also, despite being a molecule of high reactivity, it has thermal stability up to 300°C. Phosgene is an extremely reactive chemical. It has the potential to cause adverse effects in humans, the primary target organ being the respiratory system. Acute severe phosgene exposure primarily causes respiratory disease (pulmonary oedema) and may result in death. Besides the health hazard, phosgene also poses some serious operational problems, for example, it generates stoichiometric amounts of HCl during the reaction. Also, the reaction is highly exothermic and requires elaborate cooling arrangements, adding up to the process cost. Additionally, in case of synthesis of diisocyanates, the phosgenation gives lower selectivities.

Several alternative phosgene-free synthetic routes to diurethanes are currently explored, which are based on very different synthetic approaches, such as: (a) the oxidative carbonylation of amine in the presence of alcohols[8] (b) the reductive carbonylation of nitroaromatics[9] (c) the reaction of amines with CO_2 in the presence of alkylating agents[10] (d) the reaction of diamines with urea and alcohols or phenols, at high temperature (>473 K)[11] (e) alcoholysis of substituted urea[12] (f) the transfunctionalization of substituted ureas with organic carbonates[13] the methoxycarbonylation of amines by organic carbonates or aminolysis of organic carbonates[14] (Scheme 3.1)

$$\mathrm{RR'NH} + \mathrm{R''OC(O)OR''} \longrightarrow \mathrm{RR'NHC(O)OR''} + \mathrm{R''OH}$$

R, R'= H, alkyl, aryl; R''= alkyl, aryl

Scheme 3.1. Synthesis of carbamates *via* amine methoxycarbonylation

This synthesis method has been in great attention since DMC has been synthesized from phosgene and methanol. In 1983, however, a non-phosgene process for preparing DMC from methanol, carbon monoxide, and oxygen in liquid phase was developed.[15]

Several catalyst systems have been successfully attempted for amine alkoxycarbonylation using organic carbonates, a larger part being investigated on methoxycarbonylation using DMC. For example, Porta et al. reported the reaction of diethyl carbonate with 1-propylamine gave the corresponding carbamates in the presence of metal compounds such as $AlCl_3$,[16] Lissel et al. reported that aniline can be methoxycarbonylated with dimethyl carbonate in the presence of K_2CO_3, and 18-crown-6.[17]

Some of them involve Lead salts and oxides,[18] zinc salts,[19] Ytterbium triflates,[20] etc. Aresta et al. have reported excellent catalytic activity of organophosphorous Brönsted acids in the aminolysis of diphenylcarbonate by DMA and TDA, to yield mono- and dicarbamates in high yields.[21]

T. Baba et al.[19] have thoroughly investigated the catalytic activity of zinc acetate in the methoxycarbonylation of diamines, which yield mono- and dicarbamates at 453 K. In this study, they have found that substrate to catalyst ratios in the range of 25 are required to get satisfactory yields. Also, the formation of mono and dicarbamates with zinc acetate catalyst depends largely on the reaction temperature, with monocarbamate being the dominant product upto 413 K, and the dicarbamate above this temperature. Sima et al. have reported the application of various ionic liquids as catalysts for the synthesis of carbamates by alcoxycarbonylation of amines.[22] Several patents have been disclosed for the synthesis of carbamates from dialkyl carbonates and amines including aniline.

It has been observed that, with most of the catalyst systems discussed above, an induction period is observed. In the case of zinc acetate or lead acetate as catalyst systems, the induction period vanished upon pretreating the catalyst with either DMC or methanol, suggesting that the catalyst is modified by DMC or methanol, to achieve a catalytically active species. Interestingly, pre-treatment with the amine had no effect on the induction period.

The state of the art on amine methoxycarbonylation shows exploration of several catalyst systems. However, lead compounds are by far the most effective as catalysts. Despite this, the literature reports lack a systematic study for a lead catalyzed system in terms of kinetics and mechanism. With the increasing scope of the use of DMC for carbonylation of organic functionalities to replace the conventional potentially hazardous reagents, it becomes important to understand the kinetics and mechanistic aspects of such a system, which selectively yield the industrially important carbamate products.

3.2. EXPERIMENTAL SECTION

3.2.1. MATERIALS

Aniline, substituted anilines and cyclohexylamine were purchased from Merck Chemicals, India Ltd. Dimethyl carbonate was purchased from Spectrochem Chemicals, India. Lead oxides and salts; and zinc acetate were purchased from SD Fine Chemicals, India. The solvents acetone, methanol, ethanol, chloroform and ethyl acetate were purchased from Spectrochem Chemicals, India, and were distilled prior to use. The deuterated solvents $CDCl_3$ and acetone-d_6 were purchased from Aldrich Chemicals, USA.

3.2.2. EXPERIMENTAL SET-UP

The reactions were carried out in a 50 ml Parr autoclave, made of Hastelloy B and equipped with a magnetic stirrer along with a tachometer (to measure the RPM) and arrangements for internal cooling, thermowell, a rupture disc, a liquid sampling valve and a transducer. The autoclave was provided with a furnace for controlled heating. The sensors for autoclave temperature, furnace temperature, pressure, and tachometer were connected to a PID controller (Watlow) with a digital display unit. Figure 3.1 shows the Parr autoclave system used for the methoxycarbonylation reactions.

Figure 3.1. Parr Autoclave and Watlow PID controller

3.2.3. TYPICAL EXPERIMENTAL PROCEDURE FOR METHOXYCARBONYLATION OF AMINES

Measured quantities of amine and DMC were charged into the autoclave. Initial sample was taken for GC analysis and quantification of aniline. Weighed quantity of the lead catalyst was then charged to the autoclave. The autoclave was then sealed and flushed thrice with nitrogen (100 psig). The autoclave contents were then stirred at 100 RPM, and the heating was started. As the temperature approached the desired value, the agitation was increased to 600 RPM, as the reaction started. Intermittent samples were drawn from the autoclave using a cooling sampler, and the samples were filtered through Whatman filter paper (No. 1) and the filtrate was analyzed by G.C. and H.P.L.C. for the quantification of amine and the methyl carbamate, respectively. The reaction was carried out for a fixed time, and then the autoclave was cooled to room temperature.

3.2.4. TYPICAL EXPERIMENTAL PROCEDURE FOR KINETIC STUDIES

A procedure similar as above was followed for the kinetic experiments. For particular sets of experiments in case of the catalyst concentration variation effect data (initial rate data and concentration-time profile data), stock solutions of aniline in DMC were used to avoid the weighing errors.

3.2.5. CATALYST RECYCLE EXPERIMENT PROCEDURE

The virgin experiment was carried out with the same procedure as explained in 3.2.3. At the end of this experiment, the autoclave was allowed to cool to 303K, the agitation was stopped, and the autoclave was allowed to stand for 10-15 minutes, in order for the catalyst to settle completely. The autoclave was then opened and the liquid reaction mixture was carefully siphoned off using a pipette and analysed by GC and HPLC. About 10 ml of DMC was poured into the autoclave and the solid catalyst settled at the bottom was washed with it. The autoclave was again kept standing for some and the catalyst was allowed to settle. The DMC was then siphoned off. This kind of washing was carried out for three times. After this, the catalyst settled at the bottom was allowed to dry at room temperature. For the first recycle experiment, the autoclave containing the catalyst was charged with fresh aniline and DMC and the experiment was carried out in the same fashion as that of the typical methoxycarbonylation experiment. The same procedure was repeated for further recycles.

3.2.6. EXPERIMENTAL PROCEDURE FOR CATALYST PRETREATMENT INVESTIGATION

The catalyst pre-treatment experiments were carried out with individual reactions, i.e., aniline and DMC in the 50 ml Parr autoclave. For investigation of DMC pre-treatment effect, the weighed quantity of catalyst (Pb_3O_4) was taken into the autoclave along with DMC; the charge of the components was taken the same as that of the typical aniline methoxycarbonylation experiment. The autoclave was then sealed, purged with nitrogen, and then the autoclave contents were stirred at 10 Hz at room temperature for 2 hours. After this, the autoclave was allowed to stand for 10 minutes, and DMC was siphoned off. The catalyst at the bottom was washed thrice with DMC in the same fashion as explained in section 3.2.5. The dry catalyst was named as C-1. Similar catalyst pre-treatment experiments were taken with DMC at 423 K and 433 K, and the catalysts obtained from these reactions were termed C-3 and C-5 respectively.

The aniline pre-treatment effect was carried out with the same procedure as that for DMC pre-treatment effect above, at three different temperatures- room temperature, 423 K and 433 K. The catalysts obtained from these experiments were termed C-2, C-4 and C-6 respectively, and used for pre-treatment effect experiment, wherein the autoclave containing this pre-treated catalyst was charged with the standard charge of aniline and DMC, and the typical aniline methoxycarbonylation reaction was carried out as explained in section 3.2.3 above, but for 20 minutes only, to check for the elimination of induction period. (Refer to Table 3.4)

The IR spectra of fresh and pre-treated catalysts (C-1 to C-6) were recorded and compared.

3.2.7. REACTION WORK-UP AND ISOLATION OF CARBAMATES

At the end of a methoxycarbonylation reaction, the reaction mixture was filtered though Whatman paper no. 1 to remove the lead catalyst. The filtered reaction mixture was concentrated on a rotavap, and subjected to column chromatography. The solvent system suitable for column chromatography was found out from thin layer chromatographic analysis using various solvent combinations. In case of isolation of MPC, 1%EtOAc-$CHCl_3$ was found to be the suitable solvent combination. The fraction showing a single spot on TLC was concentrated on rotavap to get the fluffy white solid of carbamate. For isolation of the some of the carbamates, the DMC was removed on rotavap, to get crystalline powder, which was washed with cold hexane several times to remove the coloured impurities, and then recrystallised from chloroform or ethanol.

3.3. ANALYTICAL METHODS

IR spectra of the catalysts and urea products were obtained using a Perkin Elmer Spectrum-2000 in transmission mode using KBr pellets. NMR was obtained from a Brucker-AV-200 and Brucker-MSL-300 machines. Elemental analyses of the ureas were carried out on a CHNS-O EA1108, Elemental analyzer of Carlo Erba Instruments, Italy.

For quantification of amines, liquid samples were analyzed on a Hewlett Packard 6890 Series GC equipped with an auto sampler and controlled by HP Chemstation software, and using a Restek 66567 capillary column (30 m × 320 μm × 0.25 μm film thickness, on a 5% phenyl methyl siloxane stationary phase). The conditions used for the gas chromatographic analysis were as described in Table 3.1.

Table 3.1. Standard conditions for GC analysis

Parameter	**Conditions**
Injector (split) temperature	523 K
Flame ionization detector (FID) temperature	573 K
Column temperature (HP-5 capillary column)	313 K–563 K (programmed)
Inlet Pressure (He)	20 psig
Carrier gas (He) flow rate	2 ml/min
Split ratio	25:1

The quantification of methyl-*N*-phenyl carbamate (MPC) was done by HPLC analysis of liquid samples on an Agilent Series 1100 High Performance Liquid Chromatograph using a Symmtery Shield^{TM} RP$_8$ (Waters) RP-18 column (250 mm × 0.5 mm ID × 0.21 μ film thickness) using a Quaternary LC Pump. The detector used was a UV-DAD and the monitoring wavelength used in typical analysis was 254 nm. The injection volume and flush volume used in the method were 20 μl and 700 μl using methanol-water as the mobile phase under gradient conditions. A gradient program was used for the analysis, as detailed in Table 3.2.

Table 3.2. Mobile phase gradient programme for HPLC analysis

Ramp	Time, min	Hold Time, min	Methanol (%)	Water (%)	Flow rate (ml/min)
1	0.00	0.00	40	60	1
2	5.00	5.00	40	60	1
3	10.00	5.00	50	50	1
4	12.00	02.00	60	40	1
5	15.00	03.00	60	40	1
6	20.00	05.00	80	20	1
7	25.00	05.00	90	10	1
8	30.00	05.00	100	0	1
9	35.00	05.00	100	0	1
10	40.00	05.00	80	20	1
11	42.00	02.00	60	40	1
12	45.00	03.00	40	60	1
13	50.00	05.00	40	60	1

GC-MS was carried out on Agilent 6890 instrument employing earlier standardized GC method. The standard conditions for GC analysis are given in Table 3.1, while those for HPLC analysis are given in Table 3.2. The fresh and recovered catalysts were characterized by powder XRD on a PanAnalytical XRD instrument controlled by software (XPert HighScore Plus), to check the crystallinity of the catalyst after the reaction.

The conversion, selectivity, yields and turn over numbers (TON) were calculated as follows

$$\%\,\text{Conversion} = \frac{(\text{initial moles of aniline - final moles of aniline})}{(\text{initial moles of aniline})} \times 100$$

$$\%\,\text{Selectivity} = \frac{\text{moles of MPC formed}}{\text{converted moles of aniline}} \times 100$$

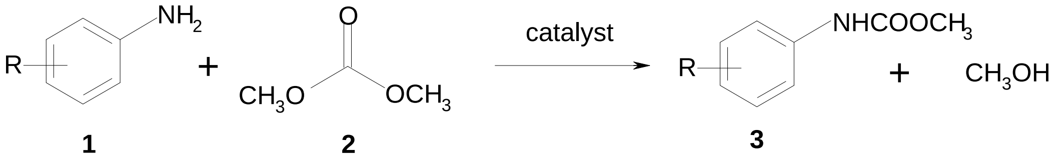
$$\%\,\text{Yield} = \frac{\%\,\text{conversion} \times \%\,\text{selectivity}}{100}$$

$$\mathrm{TON} = \frac{\text{moles of MPC formed}}{\text{moles of } \mathrm{Pb_3O_4} \text{ charged}}$$

$$\mathrm{TOF} = \frac{\mathrm{TON}}{\mathrm{Time}}, \mathrm{h}^{-1}$$

3.4. RESULTS AND DISCUSSION

The aim of the present work was to investigate the catalytic activity of lead compounds towards methoxycarbonylation of amines **1** with dimethylcarbonate **2**, for the selective synthesis of a carbamate **3**. (Scheme 3.2) with regard to the kinetics and mechanism. For this purpose, the catalytic activity of lead compounds was first of all compared, and then the kinetic and mechanistic investigation was carried out using the selected lead catalyst, with aniline as the model substrate and dimethyl carbonate as the methoxycarbonylation agent as well as the solvent. The reactivity of different amines towards methoxycarbonylation using the model catalyst also was investigated, and the carbamates products formed in the reaction were isolated and characterized by conventional spectroscopic methods.



Scheme 3.2. General scheme for the catalytic synthesis of carbamates

3.4.1. PRELIMINARY CATALYST SCREENING

Several lead compounds and a few zinc compounds were screened to assess the catalytic activity for the methoxycarbonylation of aniline using DMC. The results are shown in Table 3.3 below. The comparison of catalytic activities of the screened catalysts is better observed in Figure 3.2, where Pb_3O_4 clearly appears as the most active catalyst in terms of turnover frequency. It should be noted however, that, almost all the catalysts gave good selectivity to MPC. Also, the lead compounds are evidently better catalysts compared to zinc acetate catalyst.

Table 3.3. Screening of catalysts for aniline methoxycarbonylation to MPC

Sr.	Catalyst	Aniline conversion, %	MPC selectivity, %	MPC yield, %	TOF, $^{h-1}$
1	PbO	44.2	96.3	42.6	17.4
2	$Pb(OAc)_2$	42.1	90.1	37.9	22.6
3	Pb_3O_4	57.8	97.0	56.1	70.5
4	$PbCO_3$	39.5	95.7	37.8	53.8
5	$Pb(OAc)_2.3H_2O$	42.6	87.9	37.5	26.1
6	$Zn(OAc)_2.2H_2O$	29.1	89.8	26.2	10.5

Reaction Conditions: Aniline 0.222 kmol/m^3, Catalyst 1.8×10^{-3} kmol/m^3, DMC up to total volume 1.75 × 10^{-5} m^3, Temperature 433 K, Agitation 10 Hz, Reaction time 60 min

Selection of catalyst

It was observed from the results obtained as above that, the lead compounds gave good catalytic activity for the methoxycarbonylation of aniline using DMC.

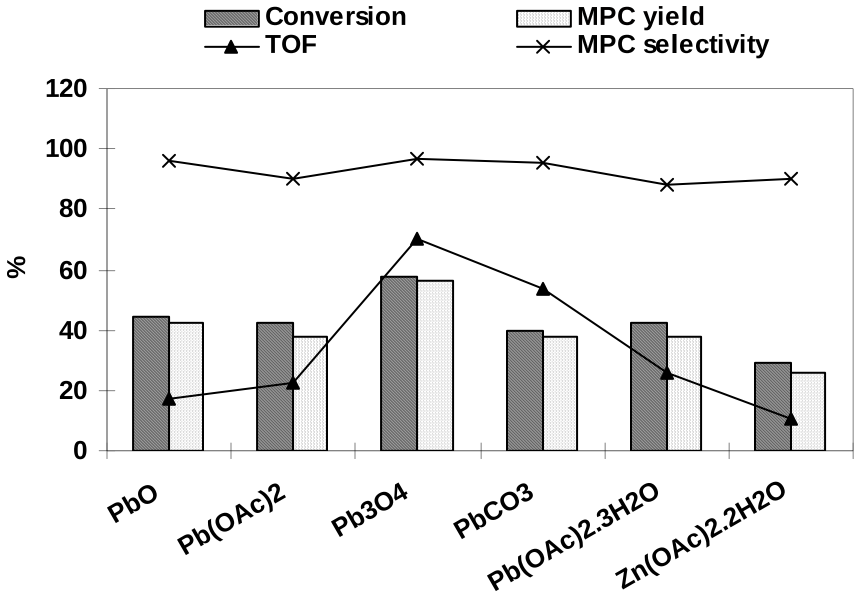


Figure 3.2. Comparative catalytic activities for aniline methoxycarbonylation

Reaction Conditions: Aniline 0.222 kmol/m^3, Catalyst 1.8×10^{-3} kmol/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433 K, Agitation 10 Hz, Reaction time 60 min

Although there was marginal difference in the catalytic efficiency of lead compounds, the comparatively better Pb_3O_4 was chosen as catalyst for further exploration of this reaction.

3.4.2. STANDARD CONCENTRATION-TIME (C-T) PROFILE AND MASS BALANCE

Standard C-T profile for aniline methoxycarbonylation of aniline in DMC solvent was obtained using analysis of reaction samples drawn at various time intervals. A cooling condenser was used for sampling to avoid possible loss of volatile components by evaporation. The liquid samples of the reactions were analyzed by GC and HPLC for the quantification of aniline and MPC, respectively, based on standard calibration curves. It was found that MPC was formed in all the reactions with high selectivity and the C-T profile drawn showed excellent agreement between aniline consumption and MPC yield, as observed from figure 3.3.

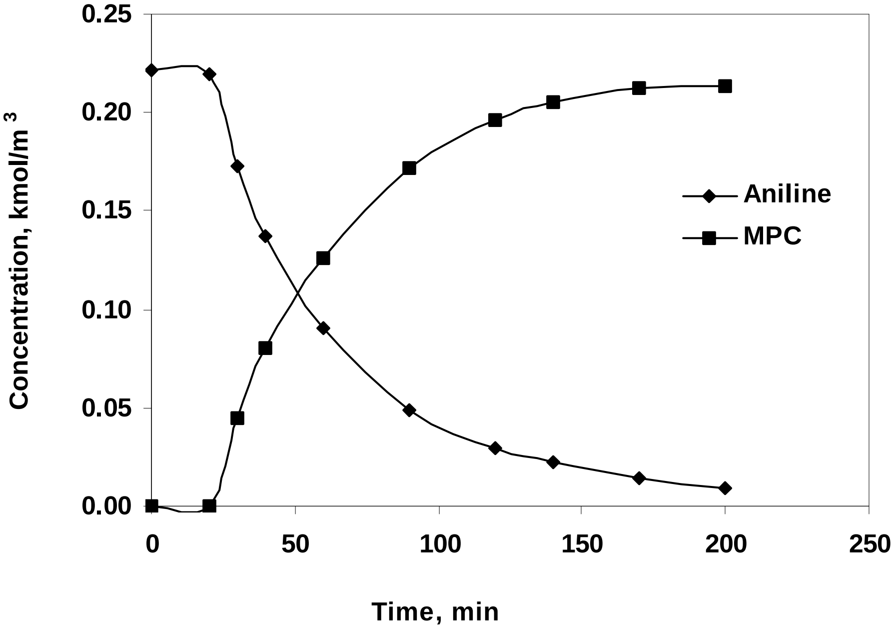


Figure 3.3. Concentration-time profile for Pb_3O_4 catalysed methoxycarbonylation of aniline in DMC.

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433 K, Agitation 10 Hz, Time 200 min.

3.4.3. INDUCTION PERIOD

From the concentration-time profile for the methoxycarbonylation of aniline, it was evident that the there was an induction period of approximately 20 minutes in the reaction, under the experimental conditions investigated. A similar induction period has been reported by Ono et al.[18] in the lead nitrate catalyzed methoxycarbonylation of aniline with DMC. The authors have studied the effect of catalyst pre-treatment on the induction, wherein; the catalyst has been pre-treated with methanol and DMC, which resulted in the elimination of induction period. This essentially shows that the lead catalyst is first modified with dimethyl carbonate, which is then attacked by the nucleophilic amine, resulting in the elimination of carbamate.

It was further necessary to study the effect of various reaction parameters on the reactant-product concentration profiles as well as on the induction period. At all the ranges of variations in reaction parameters, induction period was essentially observed, although the amount of time decreased at higher values of certain screened parameters.

3.4.3.1. Effect of Pb_3O_4 Concentration on Induction Period

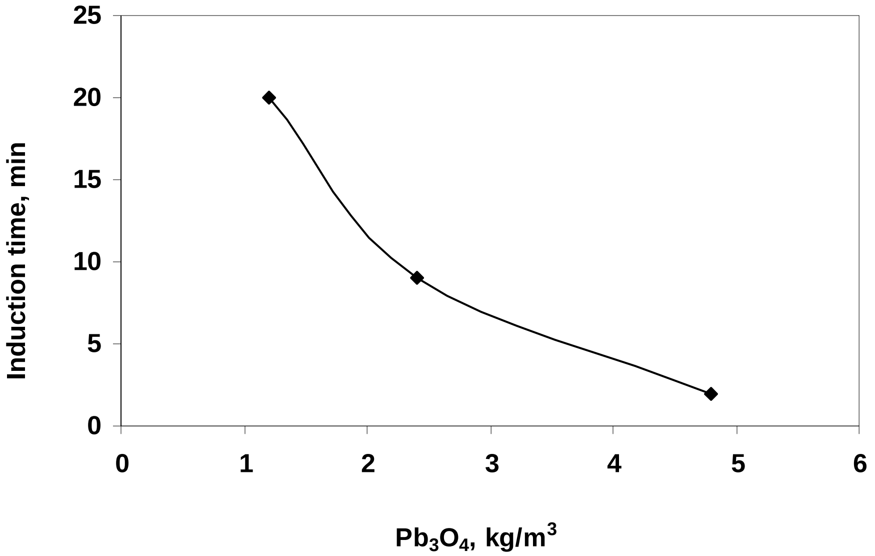


Figure 3.4. Effect of catalyst (Pb_3O_4) concentration on induction period

Reaction conditions: Aniline 0.222 kmol/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433 K, Agitation 10 Hz, Time 200 min.

The induction period was found to be inversely proportional to the catalyst concentration. The effect was studied in the range of 1.2 - 4.8 kg/m^3 concentration of Pb_3O_4. However, the decrease was not linear.

3.4.3.2. Effect of Aniline Concentration on Induction Period

The effect of substrate concentration variation on the induction period was studied between 0.11– 0.429 kmol/m^3 concentration range of aniline. There was no pronounced effect of aniline concentration variation on the induction period. A plot of molar ratio of aniline to Pb_3O_4 versus induction period is shown in Figure 3.5, to elucidate the effect of aniline concentration on the reaction.

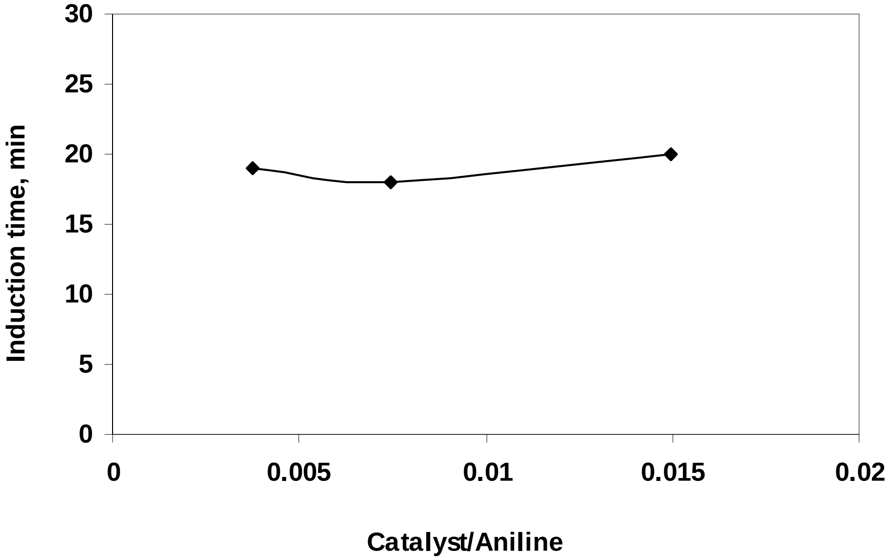


Figure 3.5. Effect of aniline concentration on induction period

Reaction conditions: Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433 K, Agitation 10 Hz, Time 200 min.

3.4.3.3. EFFECT OF REACTION TEMPERATURE ON INDUCTION PERIOD

The effect of temperature variation on the induction period was studied between 423-443 K. The induction period decreased with increasing temperature. A plot of 1/T versus log of time is shown in figure 3.6.

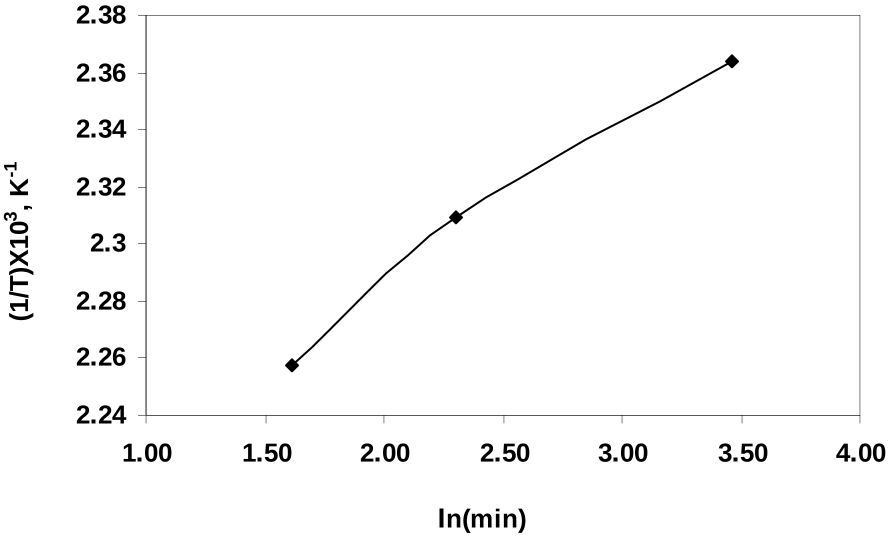


Figure 3.6. Effect of reaction temperature on induction period

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, Time 200 min.

This probably indicates that the active metal complex or species in formed more efficiently at higher temperatures, thereby causing the induction period to decrease.

3.4.4. INHIBITION OF REACTION PROGRESS BY PRODUCTS

It is reported in the literature that the alcohol generated in the reaction in stoichiometric quantities adversely affects the reaction rates in the methoxycarbonylation of amines for the synthesis of carbamates.[23] Therefore, to understand the true kinetics of the system, it was necessary to study the effect of products on the overall rate of reaction.

3.4.4.1. Effect of Methyl-N-Phenyl Carbamate

In the literature available on catalytic methoxycarbonylation of amines for synthesis of carbamates, there is no report on inhibition of the reaction due to the presence of carbamate in the reaction. Nevertheless, it was important for understanding the true kinetics of the reaction to ensure that there was no inhibition of reaction due to the formation of the product in the course of reaction. Therefore, a model reaction was taken for methoxycarbonylation of aniline with doping of MPC into the reaction at the beginning, and a C-T profile was compared with the standard profile (Figure 3.7). For this purpose, the maximum amount of carbamate that could form in the reaction with maximum loading of aniline in the range of study was calculated, and charged into a model reaction. It was observed that, the presence of carbamate in the reaction did not impart any negative effect on the reaction rate.

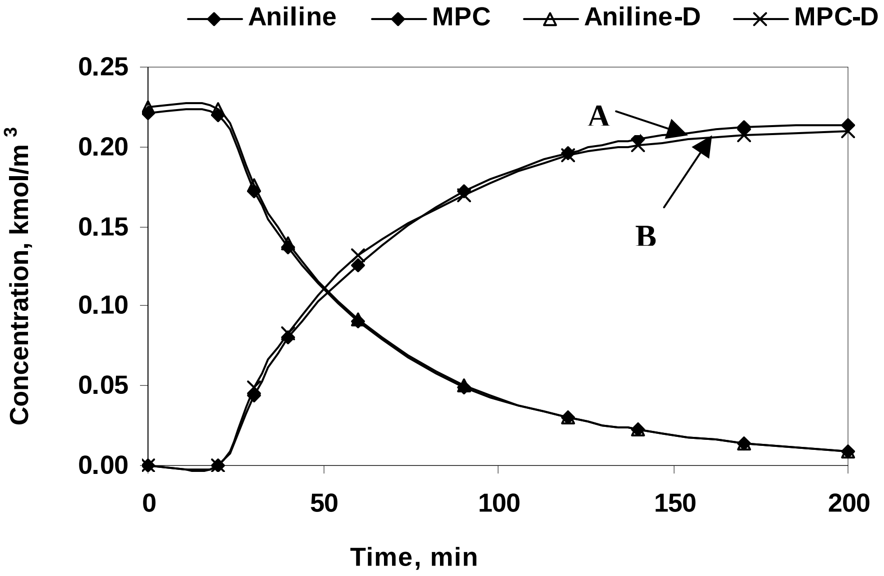


Figure 3.7. Comparison of C-T profiles in a) a typical aniline methoxycarbonylation experiment with b) MPC doped aniline methoxycarbonylation experiment**

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433 K, Agitation 10 Hz, Time 200 min, D- MPC 0.21 kmol/m^3 charged in the reaction, **- Concentration of MPC calculated by substraction of doped MPC at each data point.

3.4.4.2. Effect of Methanol Concentration

A few experiments were carried out under the standard set of conditions, along with methanol in various percentages (wt % of total reaction mixture). It was found that, at the concentrations lower than 10 % methanol there was no considerable negative effect on the rate of aniline conversion. As can be seen from Figure 3.8, there is drastic adverse effect of methanol beyond 10% (w/w), and there is no apparent conversion of aniline at 60% methanol (%w/w). Under the standard set of reaction conditions in the present study, the weight percentage of methanol, which is formed in the reaction, cannot exceed 1.35 %. Therefore, no inhibition due to the formed methanol could occur under the studied reaction conditions.

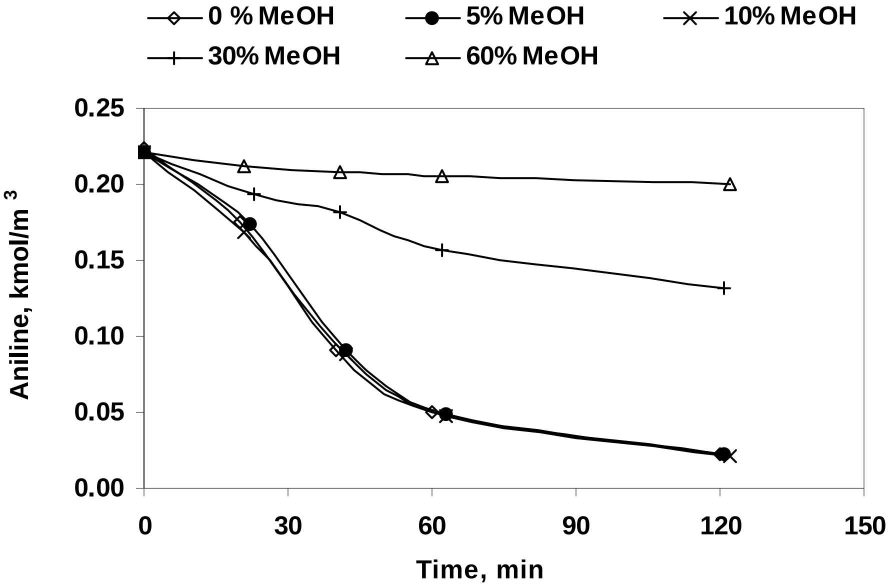


Figure 3.8. Inhibitory effect of methanol on methoxycarbonylation of aniline
Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, (DMC+methanol) up to total volume 1.75×10^{-5} m^3, Temperature 433 K, Agitation 10 Hz.
(Note: Induction period has been excluded while plotting the concentration-time profile for aniline in this study.)

3.4.5. CATALYST RECYCLE

A few reactions were carried out to assess the recycle activity of the catalyst under optimized conditions, using aniline as the substrate. The results are shown in the Figure 3.9. As it can be seen, there was no loss in the activity of the catalyst. Rather, Fu et al.[18] have proposed in the PbO catalyzed aniline methoxycarbonylation, that, the catalyst sites are modified during the course of this reaction, and this actually causes an elimination of induction period upon recycle. This particular aspect of modification of the solid catalyst and formation of a modified species has been carried out in the section on mechanistic studies separately.

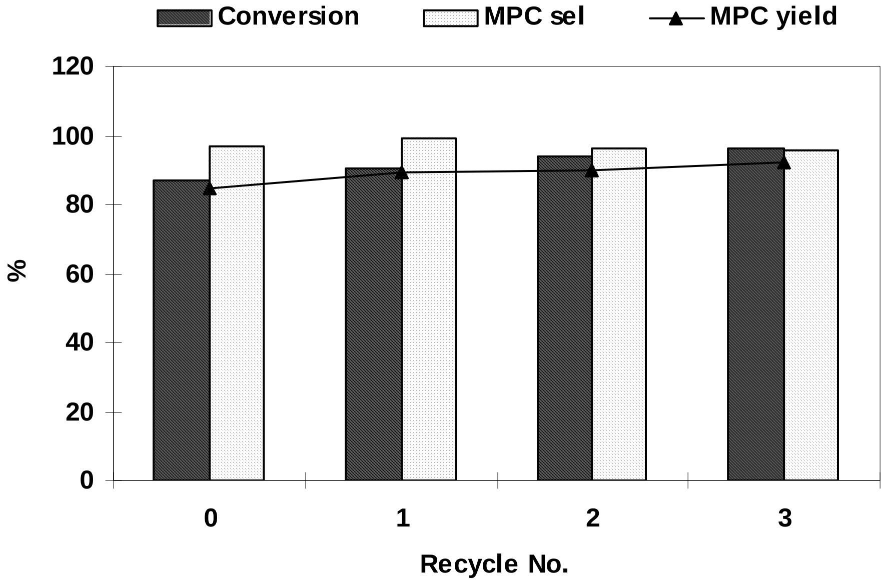


Figure 3.9. Catalyst recycle study

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433 K, Agitation 10 Hz, time 120 min.

3.4.6. EFFECT OF CATALYST PRE-TREATMENT

The catalyst pre-treatment effect was studied considering the two substrates, aniline as well as DMC. To check the catalyst pre-treatment effect, the recovered catalysts were used for carrying out fresh reaction for a short duration, to check the effect on induction period.

3.4.6.1. Effect of catalyst pre-treatment with aniline

The catalyst Pb_3O_4 and aniline were stirred in the autoclave at room temperature, 423 K and 433 K for 2 hours. The catalysts thus pre-treated with aniline at room temperature, 423 K and 433 K temperatures were washed several times with DMC and termed as C-2, C-4 and C-6 respectively. It was observed that at 423 K and 433 K temperatures, the catalyst turned slightly darker, while the excess aniline showed purple colour. The liquid phase was checked for aniline consumption, and it was found that the aniline was being consumed, and the conversion rate was proportional to contact time. The catalysts; C-2, C-4 and C-6, were then used for the induction period experiment (Table 3.4).

The possibility of the lead catalyst forming some soluble species upon reaction with aniline, and dissolving in the liquid (aniline) phase was also considered. Therefore, the recovered liquid from the aniline pre-treatment reaction at 433K was filtered through Whatman paper 1, and concentrated on rotavap to remove the DMC. The concentrated purple coloured liquid was termed RC-2, and used as such for the pre-treatment effect reaction. It was observed that there was no elimination of induction period with any of the aniline-pre-treated catalysts or with RC-2.

Aromatic amines are known to form coupling products at higher temperatures in presence of metals. The purple coloured liquid formed in the reaction could be aniline black, which is a common product in metal mediated conversion of aniline at high temperatures.

3.4.6.2. Effect of catalyst pre-treatment with dimethyl carbonate

The catalyst pre-treatment effect study with DMC was carried out in a similar fashion as that of aniline pre-treatment. The pre-treatment reactions were carried out at room temperature, 423 K and 433 K for 2 hrs each; and the recovered catalysts were dried and termed as C-1, C-3 and C-5 respectively.

Table 3.4. Catalyst pre-treatment effect

Sr	Catalyst	Pretreatment with	Pretreatment conditions	Aniline conversion, %*
1	C-1	DMC	R.T., 2 hrs	Nil
2	C-2	Aniline	R.T., 2 hrs	Nil
3	C-3	DMC	433K, 2 hrs	trace
4	C-4	Aniline	423K, 2 hrs	Nil
5	C-5	DMC	433K, 2 hrs	60.1
6	C-6	Aniline	433K, 2 hrs	Nil
7	RC-2	Aniline	433K, 2 hrs	Nil
8	C-7	Reaction recovered catalyst	-	59.2

Reaction Conditions: Aniline 0.222 kmol/m^3, Catalysts (pre-treated): 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, * Reaction time 20 min

The liquid phase recovered from DMC pre-treatment run at 433 K was concentrated to check the presence of any high boiler, which could indicate the formation of a soluble complex of lead. However, no formation of any solid or high-boiler liquid could be observed upon concentration of the supernatant liquid. The dried catalysts were then used for the induction period experiments, which were carried out for 20 minutes each. The results are presented in Table 3.4. It was observed that, the induction period disappeared after the pre-treatment at 433K (entry 5), indicating modification of the solid catalyst only at the temperature beyond 433K. These catalysts were then investigated by IR spectroscopy for understanding the nature of modification of Pb_3O_4 (see section 3.4.9).

3.4.7. SCREENING OF AMINE SUBSTRATES

Various amines were screened for the Pb_3O_4 catalysed methoxycarbonylation by DMC. It was found that aliphatic amines gave excellent yields of the carbamates, while the yields varied vastly in case of aromatic amines. The carbamates were identified by GC-MS analyses, and also by IR, NMR and elemental analyses. The carbamates were isolated from reaction mixtures by column chromatography or solvent extraction. The results obtained in the amine screening study is given in the Table 3.5.

In the substrate screening experiments, it was found that the aromatic amines having better basicity were better substrates. Analogously, the amine conversions and carbamate yields increased with increasing *p*Ka values of the amine substrates. For example, in the Table 3.5, it can be observed that, 4-toluidine (entry 2, *p*Ka 5.07) is a better substrate than 4-nitroaniline (entry 8, *p*Ka 0.98) or anthranilic acid (entry 11, *p*Ka 2.04). This is in agreement with the proposed reaction mechanism, where the efficiency of the neucleophilic attack of the amine on the DMC carbocation depends on the neucleophilicity of the NH_2 group. Moderately or strongly activating substituents on the aromatic ring are expected to give better amine conversions (entries 2-7) and product yields, while deactivating substituents on the ring should make the amines (entries 8-11) comparatively less active substrates. This is exactly what is observed from the table 3.5.

Table 3.5. Screening of amines for Pb_3O_4 catalysed methoxycarbonylation using DMC

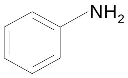
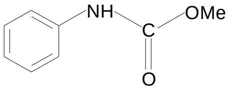
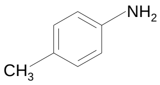
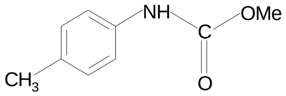
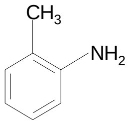
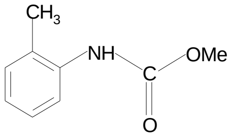
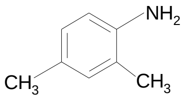
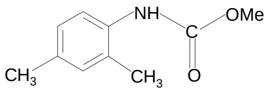
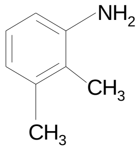
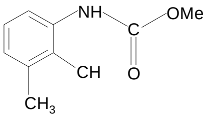
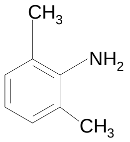
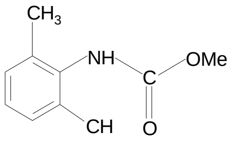
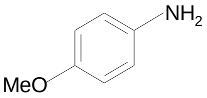
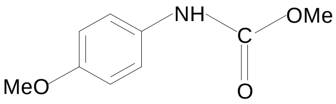
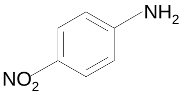
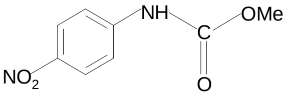
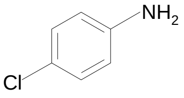
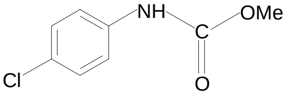
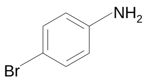
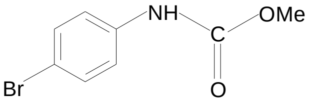
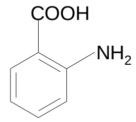
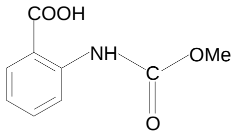
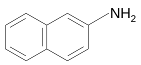
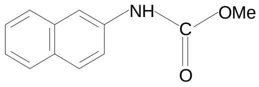
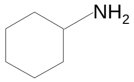
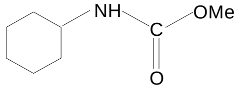
Sr	Amine	pKa	Carbamate	Amine conversion, %	Carbamate yield, %
1		4.64		95.7	91.84
2		5.07		95.05	92.41
3		4.38		88.70	83.08
4		-		97.05	91.81
5		-		95.81	92.33
6		-		95.28	93.28
7		5.29		86.98	84.37
8		0.98		35.11	34.23
9		3.81		83.22	79.85

Table 3.5. Screening of amines for Pb_3O_4 catalysed methoxycarbonylation using DMC (cont'd)

Sr	**Amine**	**pKa**	**Carbamate**	**Amine conversion,**	**Carbamate yield, %**
10		3.91		81.8	80.17
11[a]		2.04		2.5	0
12		3.92		84.4	80.65
13[b]		9.82		86.44	-

Note:

a- There was no or very low conversion of the amine

b- Many peaks observed on GC, indicating formation of several byproducts.

Reaction Conditions: Amine 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433 K, 10 Hz, Reaction time 120 min

The isolated carbamates were characterized by spectroscopic methods as well as elemental analysis. The melting points of solid products were recorded. The results are given in the Table 3.6.

Table 3.6. Characterization of isolated carbamate products

Sr.	Carbamate	Molecular formula	M. P., °C	IR $\nu_{(C=O)}$, cm^{-1}	Microanalysis		
					Element	Calc, %	Obtained, %
1	Methyl N- phenyl carbamate	$C_8H_9NO_2$	51-53	1708	C	63.05	65.44
					H	5.71	5.96
					N	8.98	9.27
2	Methyl N-(2-methyl phenyl) carbamate	$C_9H_{11}NO_2$	41-42	1690	C	65.81	65.44
					H	6.51	6.49
					N	9.66	8.48
3	Methyl N-(4-methoxy phenyl) carbamate	$C_9H_{11}N_1O_3$	41-43	1732	C	59.42	59.66
					H	6.017	6.12
					N	7.42	7.73
4	Methyl N-(4-methylphenyl) carbamate	$C_9H_{11}N_1O_2$	51-53	1719	C	65.07	65.44
					H	6.50	6.71
					N	8.16	8.48
5	Methyl N-(4-chlorophenyl) carbamate	$C_8H_8N_1O_2Cl$	61-63	1700	C	51.77	51.39
					H	4.34	4.11
					N	7.55	7.39
					Cl	19.10	19.08
6	Methyl N-napthyl carbamate	$C_{12}H_{11}N_1O_2$	87-90	1698	C	71.72	71.63
					H	5.83	5.51
					N	8.20	6.96
7	Methyl N-(4-bromo) carbamate	$C_8H_8N_1O_2Br$	61-62	1731	C	41.77	41.97
					H	3.51	3.15
					N	6.09	5.35
					Br	34.73	34.66
8	Methyl N-(2,4-xylidene) carbamate	$C_{10}H_{13}N_1O_2$	39-42	1697	C	66.86	67.02
					H	7.00	7.31
					N	7.17	7.82
9	Methyl N-(2,3-xylidene) carbamate	$C_{10}H_{13}N_1O_2$	43-44	1701	C	66.9	67.02
					H	7.06	7.31
					N	7.20	7.82

3.4.8. KINETIC STUDY

3.4.8.1. PRELIMINARY EXPERIMENTS

A few preliminary experiments were carried out to optimise the reaction conditions and parameters for the kinetic studies. It was necessary to ensure that the experimental data was in kinetic regime.

Beyond a substrate concentration of 8.88 kmol/m^3, it was found that white crystalline product precipitated out of the reaction mixture, which would add complications in developing a proper methodology for liquid phase analysis of the samples. All these experiments were carried out for a fixed reaction time of 15 minutes, in order to assess properly the effect of the variations on the rate of aniline conversion. It is important to note that, the data points recorded in the kinetic studies are exclusive of induction period.

3.4.8.2. EFFECT OF CATALYST (Pb_3O_4) CONCENTRATION

The catalyst concentration effect on methoxycarbonylation of aniline was studied in the range of 0.065 to 7.3 kg/m^3 of Pb_3O_4. The conversion of aniline was found to be directly proportional to the concentration of Pb_3O_4 up to 2.39kg/m^3.

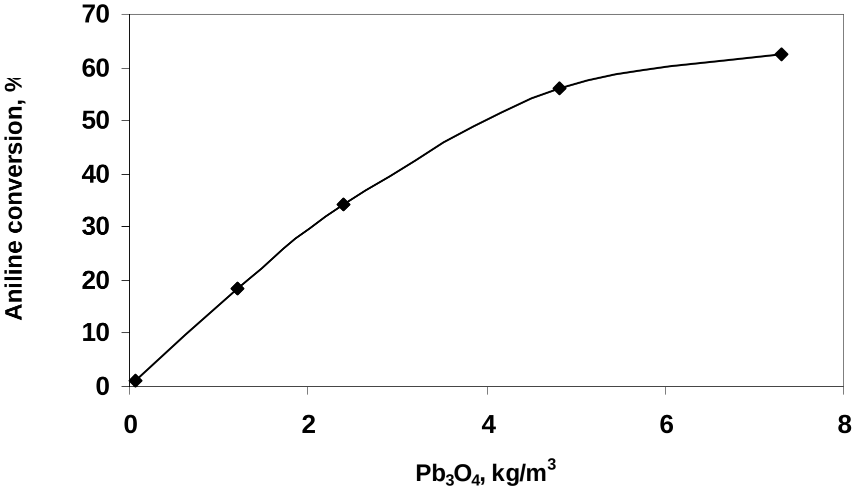


Figure 3.10. Effect of catalyst concentration on aniline conversion

Reaction conditions: Aniline 0.222 kmol/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433K, Agitation 10 Hz, Time 200 min.

3.4.8.3. EFFECT OF TEMPERATURE

The effect of temperature was studied in the range of 403 K to 443 K. The results can be observed from the Figure 3.11. The aniline conversion increased linearly with increase in reaction temperature. Further investigations were done at a temperature of 423 K.

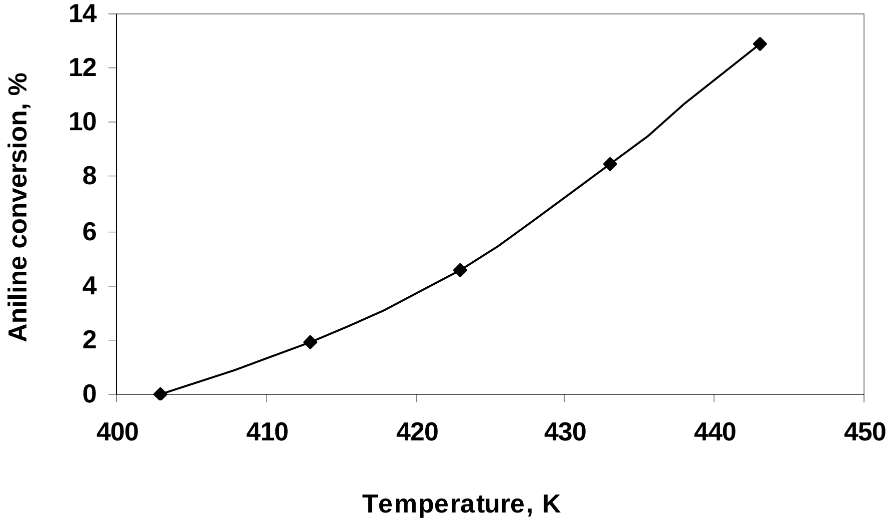


Figure 3.11. Effect of temperature on aniline conversion

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, Time 200 min.

3.4.8.4. EVALUATION OF KINETIC REGIME

3.4.8.4.1. Effect of agitation speed

For the kinetic study, it is essential that the reaction should operate in kinetic regime and not under the conditions where mass transfer is controlling. For that purpose, the effect of agitation speed on the rate of reaction rate was studied, and the results are presented in Figure 3.12. The rate was found to be independent of agitation speed beyond 6.66 Hz, clearly indicating that the reaction is in kinetic regime. Therefore, all the reactions for the kinetic studies of methoxycarbonylation of amines using Pb_3O_4 carried out at an agitation speed of 10Hz to ensure that the reaction occurred in kinetic regime.

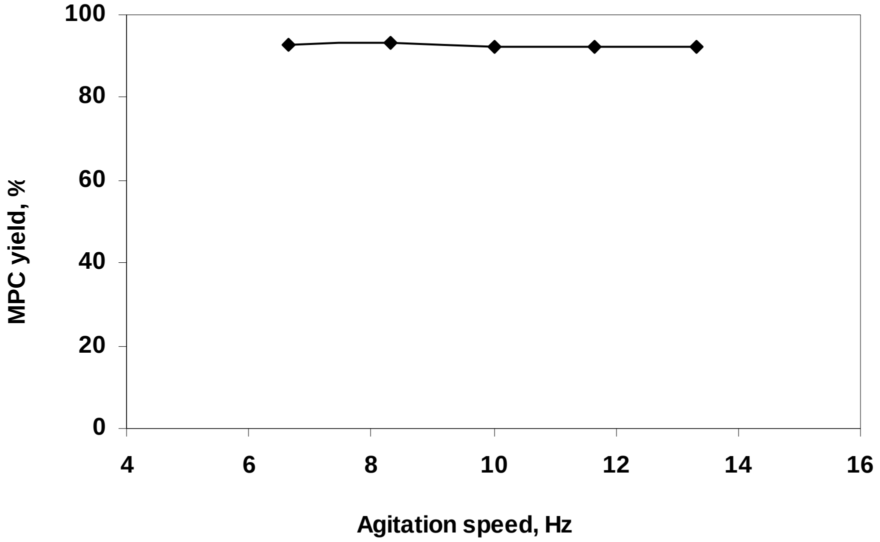


Figure 3.12. Effect of agitation speed on aniline methoxycarbonylation

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Temperature 433 K.

Zweitering (1958) has proposed a correlation to predict the minimum speed of agitation required to keep the solid particle in complete suspension. The correlation is

$$Nm = \frac{B_2 d_p^{0.2} \mu_L^{0.1} g^{0.45} (\rho_P - \rho_L)^{0.45} w^{0.13}}{\rho_L^{0.55} d_1^{0.85}} \qquad 3.1$$

Where,

N_m = minimum speed of agitation required for complete suspension of the catalyst in the reaction medium (Hz);

$$B_2 = \text{constant} = 2\left(\frac{d_T}{d_1}\right)^{1.33} \qquad 3.2$$

Using the above correlation, it was found that the minimum agitation speed required for the highest catalyst loading (4.81 kg/m^3) was 5.53 Hz (331.5 R.P.M.). The study for effect of agitation speed on MPC yield also showed no effect of agitation in the studied range. Hence, all the heterogeneous reactions were carried out at 10 Hz (600 R.P.M.).

3.4.8.4.2. Mass Transfer Effects

The analysis of overall rate of reaction for solid-liquid catalytic reactions is given by Ramchandran et al. The basic steps involved in L-S catalytic reaction of methoxycarbonylation of aniline are-

1. The diffusion of aniline and DMC onto the external surface of the catalyst and into the pores.
2. Adsorption of one or both the reactants onto the active sites of the catalyst.
3. The chemical reaction of aniline and DMC on the surface of the catalyst OR between the surface adsorbed species (reactant) and the other reactant in the liquid phase
4. Desorption of the products (MPC and methanol) from the surface of the catalyst.
5. Diffusion of the products out of the pores of the catalyst and into the liquid phase.

The following criteria described by Ramchandran and Chaudhari were used to check the significance of mass transfer effects.

3.4.8.4.3. Liquid-Solid mass transfer

The liquid-solid mass transfer resistance can be considered unimportant if a factor α_{ls} (the enhancement factor) defined in equation 3.3 is less than 0.1.

$$\alpha_{ls} = \left[\frac{R_i}{k_S a_P C_i *} \right] < 0.1 \qquad 3.3$$

Where, k_s is the liquid to solid mass transfer coefficient (s^{-1}), 0.019 s^{-1} and a_p is the interfacial area of the particles per unit volume of the liquid phase (m^2/m^3) defined by equation 3.4

$$a_p = \frac{6w}{\rho_p d_p} \qquad 3.4$$

Where, w is the catalyst mass per unit volume of the reactor (kg/m^3), 1.2 kg/m^3

ρ_p is the density of the catalyst particle (kg/m^3) = 9100 kg/m^3

d_p is the particle diameter (m). = 0.00005 m

Substituting for all the required values (w = 1.2 kg/m^3), average particle diameter of lead oxide catalyst = 50 μ

k_s, the liquid to solid mass transfer coefficient, can be calculated based on the Equation proposed by Sano and coworkers[24] (equation 3.5)

$$\frac{k_S d_P}{DF_c} = 2 + 0.4\left[\frac{e(d_p)^4(\rho_l)^3}{(\mu_l)^3}\right]^{0.25}\left[\frac{\mu}{\rho_l D}\right]^{0.33} \qquad 3.5$$

Where, d_p is particle diameter (m). D is the molecular diffusivity (m^2/s), F_c is the shape factor assumed to be unity for spherical particles, ρ_l is the density of the liquid (kg/m^3), μ_l is the viscosity of the liquid (P or kg/m.s) and e is the energy supplied to the liquid per unit mass (m^2/s). Prasher and Wills[25] give the following equation for calculation of e (equation 3.6)

$$e = \frac{P}{\rho_L V_L} = \frac{8N^3 d_1^{\,5} \psi}{d_T L} \qquad 3.6$$

Where, P is Power consumption for agitation (kg/m^2/s^3),

ρ_L is density of liquid phase (kg/m^3),

V_L is the total volume (m^3),

N is the speed of agitation (s^{-1}),

d is diameter of impeller (m),

Ψ is the correction factor (this correction factor is reported to be non-significant for low catalyst loadings and for catalysts with low densities).

L is the total height of the liquid (m)

Based on the equation 3.5, the value of ks was calculated as 1.90×10^{-2} ms^{-1} at 600 rpm. The value of overall mass transfer coefficient, $k_s a_p$ (required in equation 3.5) was calculated as 1.168 s^{-1}.

The initial rate data were thus analyzed to check the significance of liquid-solid mass transfer effects under the conditions used to study the kinetics. In these criteria α, which are defined as the ratios of the observed rates to the maximum rates of liquid-solid mass transfer. It was found that the rate data obtained for methoxycarbonylation of aniline with lead oxide catalyst were in the kinetic regime, under the given set of conditions and can be reliably used to evaluate the intrinsic kinetic parameters. The results are also consistent with the negligible effect of agitation shown in Figure 3.12.

3.4.8.5. INITIAL RATE DATA

The kinetics of methoxycarbonylation of aniline using lead oxide as catalyst was investigated in the range of conditions as shown in the Table 3.7 as per the procedure described earlier.

Table 3.7. The range of operating conditions used in kinetic study

Parameter	**Range**
Substrate; Aniline, $kmol/m^3$	0.11-0.43
Catalyst; Pb_3O_4, kg/m^3	1.21-4.81
Total volume	1.75×10^{-5} m^3
Agitation speed, Hz	6.66-13.33
Temperature, K	403-443
Reaction time	120 min

The initial rates of methoxycarbonylation were calculated from the plot of aniline conversion as a function of time. Under the conditions chosen for kinetic study, no side reactions were found to occur and hence these data will be representative of the overall methoxycarbonylation of aniline to the MPC. An induction was observed as described in previous section. Hence for the calculation of the rate, the data was corrected for the induction period. These were essentially initial rates of the reaction, observed under differential conditions. The results showing the dependence of the rates on the different parameters and a kinetic model based on these data are discussed in the following section.

3.4.8.5.1. Effect of catalyst concentration (Pb_3O_4)

The effect of variation in the concentration of Pb_3O_4 was carried out in the range of 1.21 to 4.81 kg/m^3 concentration at different temperatures (Table 3.8). The initial rates obtained in the study were calculated and plotted against the range of variation.

Table 3.8. Effect of catalyst concentration on initial rate

Sr.	Pb_3O_4 Concentration, kg/m^3	Initial rate, kmol/m^3/min		
		423K	433K	443K
1	0	0	0	0
2	1.21	0.0024	0.0048	0.0086
3	2.39	0.0038	0.0088	0.0126
4	4.81	0.0088	0.012	0.0144

3.4.8.5.2. Effect of aniline concentration

The effect of variation in the concentration of aniline was carried out in the range of 0.11 to 0.43 kmol/m^3 of aniline concentration at three different temperatures(Table 3.9). The initial rates obtained in the study were calculated and plotted against the range of variation.

Table 3.9. Effect of aniline concentration on initial rate

Sr	Aniline concentration, kmol/m^3	Initial rate, kmol/m^3/min		
		423K	433K	443K
1	0	0	0	0
2	0.11	0.0009	0.0014	0.0029
3	0.22	0.003	0.0048	0.0126
4	0.43	0.0107	0.0158	0.0215

The increase in catalyst concentration and aniline concentration showed increasing reaction rates at the studied temperature range of 423-443 K, as shown in the Table 3.8 and 3.9 respectively. It was further necessary to check the effect of catalyst concentration on the reaction rate up to complete conversion of aniline. Therefore, individual reactions were carried out for fixed time intervals, similar to the C-T profile experiments. Complete C-T profiles were thus obtained for catalyst concentration as well as aniline concentration variation.

3.4.8.6. EFFECT OF PARAMETRIC VARIATIONS ON THE C-T PROFILE

3.4.8.6.1. Effect of variation in catalyst (Pb_3O_4) concentration

Similar experiments as in case of substrate concentration variation study were carried out in the range of 423, 433 and 443 K, to study the effect of variation in catalyst-Pb_3O_4 concentration on the complete reaction profile. The effects observed are given below in terms of graphical representation. The rate of aniline consumption increases with increase in the concentration of Pb_3O_4, as can be seen from Figure 3.15.

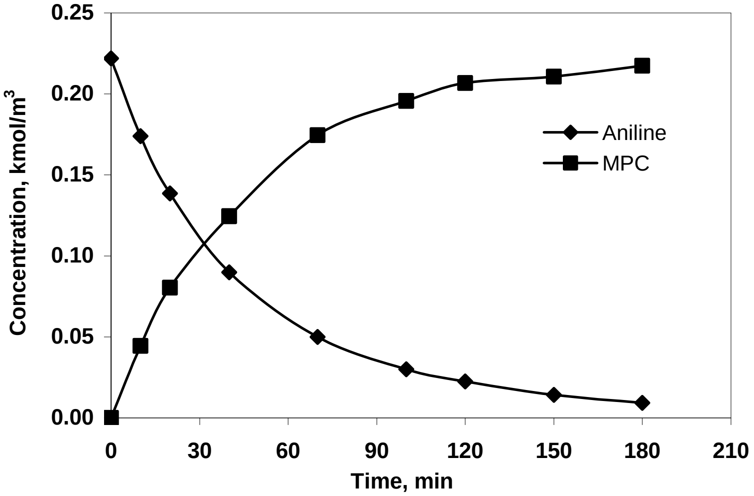


Figure 3.13. Typical C-T profile for aniline methoxycarbonylation at the catalyst loading of 1.21 kg/m^3.

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4, 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, time 180min.

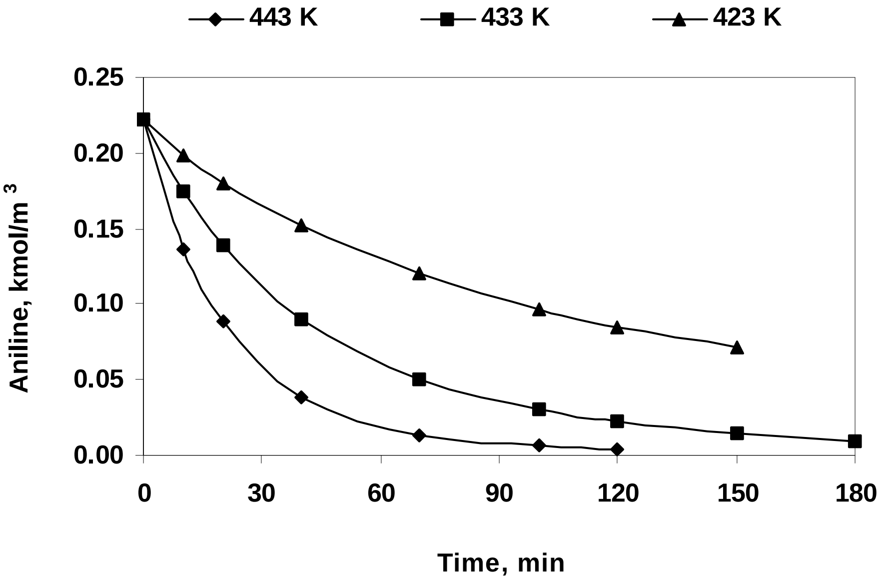


Figure 3.14. The aniline consumption profile at model catalyst loading of 1.21 kg/m^3 at different temperatures.

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4, 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, time 180min.

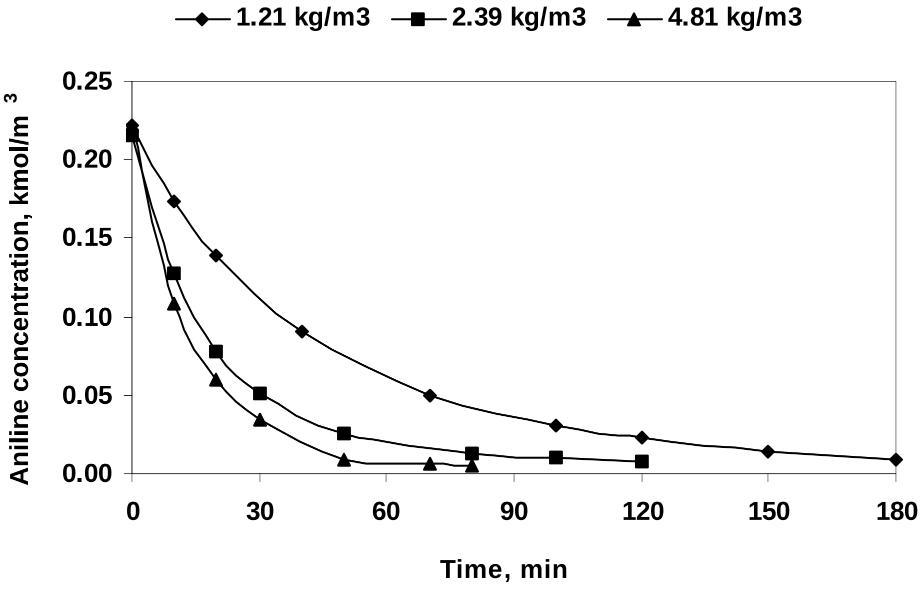


Figure 3.15. The aniline consumption profile at 433K with different catalyst loadings.

Reaction conditions: Aniline 0.222 kmol/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, time 180min.

3.4.8.6.2. Effect of variation in substrate (aniline) concentration

Experiments were carried out in the range of 0.11 to 0.429 kmol/m^3 of aniline concentration; at the temperatures of 423, 433 and 443 K, to study the effect of variation in aniline concentration on the complete reaction profile.

The aniline consumption profile at the model aniline concentration of 0.222 kmol /m^3 at different temperatures is shown in Figure 3.16. Figure 3.17 shows the aniline consumption profile at various aniline concentrations, i.e. 0.11, 0.222 and 0.429 kmol/m^3, at the temperature of 433 K.

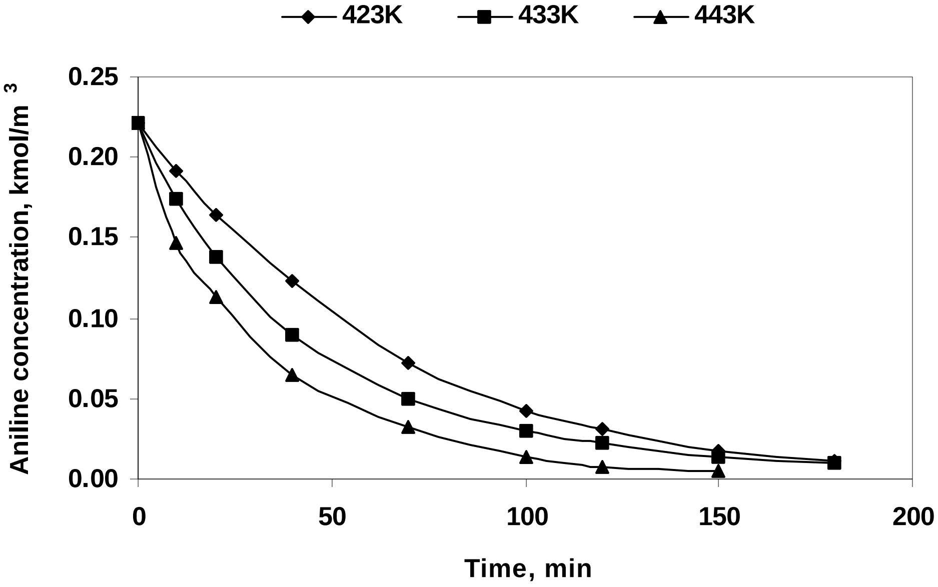


Figure 3.16. The aniline consumption profile at the model aniline concentration of 0.222 kmol /m^3 at different temperatures.

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4, 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, time 180min.

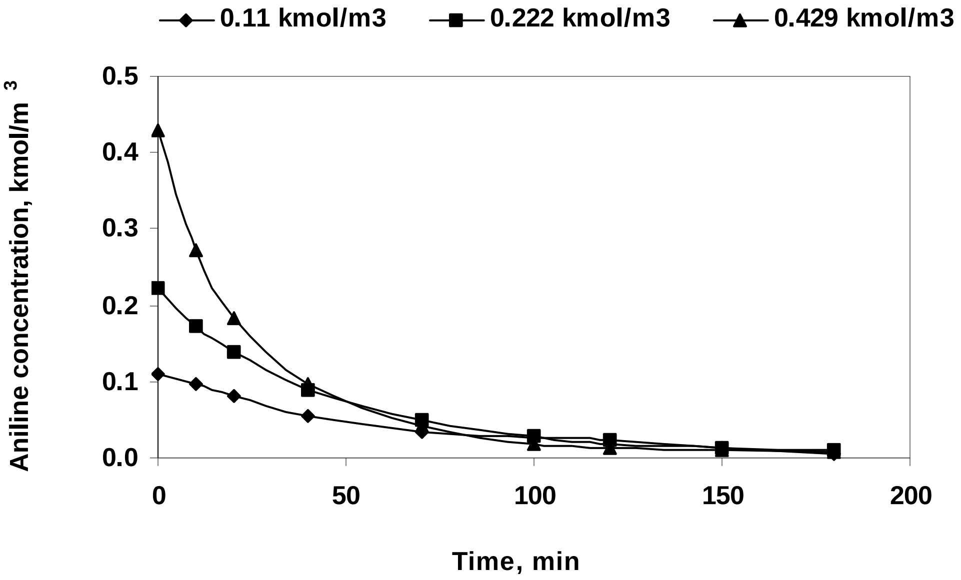


Figure 3.17. The aniline consumption profile at various aniline concentrations at 433 K. **Reaction conditions:** Pb_3O_4, 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, time 180min.

It is evident from the Figure 3.17 that the initial rate of aniline consumption increases with increase in aniline concentration.

3.4.8.7. KINETIC MODEL

The concentration-time data in the kinetic regime at different temperatures (423-443 K) were fitted to several forms of equations, which are purely imperical models. It was found that the reaction was first order with respect to catalyst and substrate. The list of other equations considered along with the best parameters obtained is presented in Table 3.10. In order to select a suitable rate equation, a non-linear least squares regression analysis was used for each rate equation to obtain the best-fit values for the parameters. For this purpose, an optimisation program based on Marquardt's method was used. The objective function was chosen as follows-

$$F = \sum_{j-1}^{N} [R_{Ai}' - R_{Ai}]_j^2 \qquad 3.7$$

Where, F is the objective function to be minimized (ϕ_{min}) representing the sum of squares of difference between the observed and the predicted rates, N is the number of experimental data points and R_{Ai} and R_{Ai}' represent the experimental and predicted rates respectively.

Table 3.10. Comparison of models for aniline methoxycarbonylation at different temperatures

Model	Equation	Temperature, K	k	K	Φ min
M_1	$r = \frac{wkA}{(1+KA)^2}$	423	5.41E-02	5.90E+02	5.93E-09
		433	1.03E-01	6.62E+02	4.33E-09
		443	2.05E-01	7.68E+02	2.73E-08
M_2	$r = \frac{wkA}{(1+KA)}$	423	9.67E-04	1.03E+02	4.43E-07
		433	1.07E-01	5.83E+03	2.45E-05
		443	2.70E-02	7.78E+02	4.69E-06
M_3	$r = \frac{wkA}{(1+KA^2)}$	423	9.84E-02	3.05E+02	4.29E-01
		433	1.83E-02	1.64E+02	1.36E-03
		443	1.35E-02	3.74E+02	1.37E-03
M_4	$r = \frac{wkA}{(1+KA)^4}$	423	1.11E-01	2.82E+02	1.74E-05
		433	1.89E+00	8.70E+02	1.96E-04
		443	5.28E+00	8.64E+02	1.85E-04
M_5	$r = \frac{wkA}{(1+KA)^3}$	423	2.23E-01	9.66E+01	9.60E-05
		433	2.97E+01	2.46E+02	1.06E-02
		443	3.91E-02	4.93E+01	1.99E-02

The minimum absolute squared-error objective function (Φ_{min}) was selected as the basis for the discrimination of the models. The values of rate parameters and Φ_{min} are represented in the Table 3.10. It is evident from this table, that in case of model 2, the value of Φ_{min} is higher than model 1. In models 3 and 4, the increases in k value are not consistent with the observed rate dependence. Also, the Φ_{min} values are higher. Similarly, in model 5, the k value increases for first two temps, but it decreases in the third temp, which is not thermodynamically. Therefore, the model 1 was found to be the best among the five models proposed for representing the kinetics of methoxycarbonylation of aniline using Pb_3O_4 as catalyst.

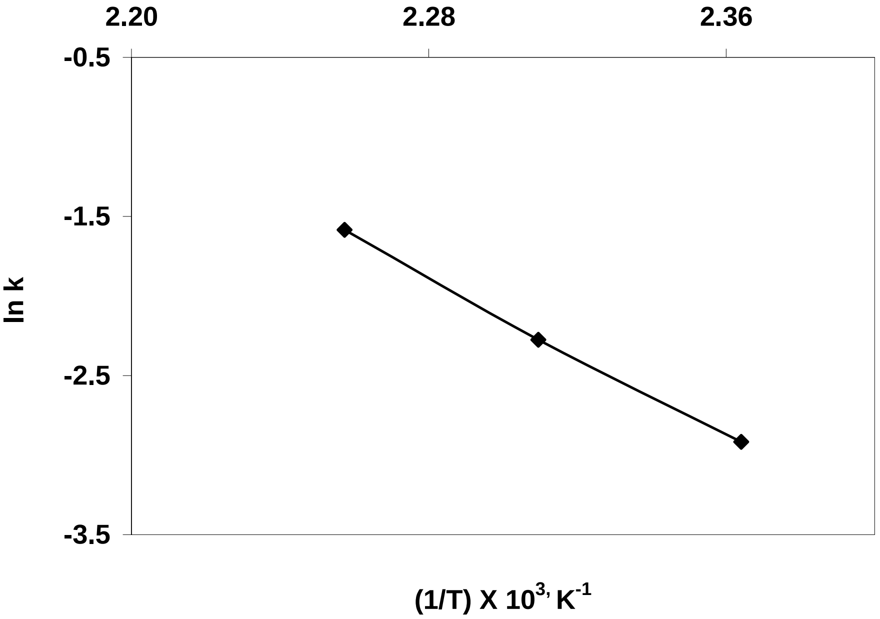


Figure 3.18. Temperature dependence of rate constant *k*

The temperature dependence of the reaction was studied, as shown by the Arrhenius plot in Figure 3.18. The activation energy for model 1 for methoxycarbonylation of aniline using Pb_3O_4 catalyst was found to be 94.0 kJ/mol. According to this model, the methoxycarbonylation of aniline followed a 1st order with respect to aniline; which later becomes independent of aniline concentration, 1st order with respect to catalyst, and 0th order with respect to DMC. Figures 3.19(A) , 3.19(B) and 3.19(C) show a comparison of experimental and predicted profiles for aniline and MPC at three different temperatures. It can be observed that there is good agreement between the experimental results and predictions under the studied range of experimental conditions.

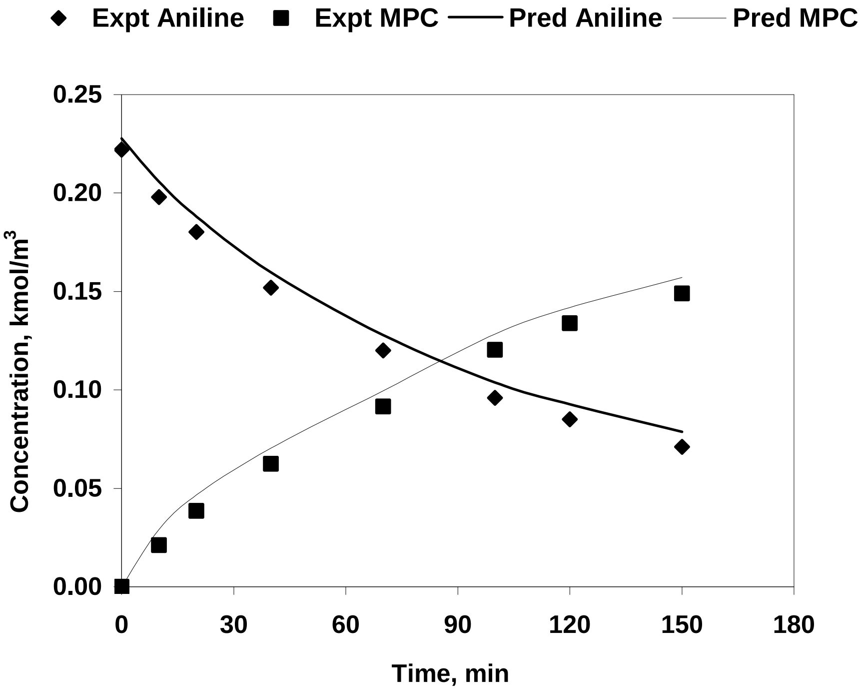


Figure 3.19 (A) Validation of proposed rate model (Model 1) at 423 K

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4, 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, time 180min.

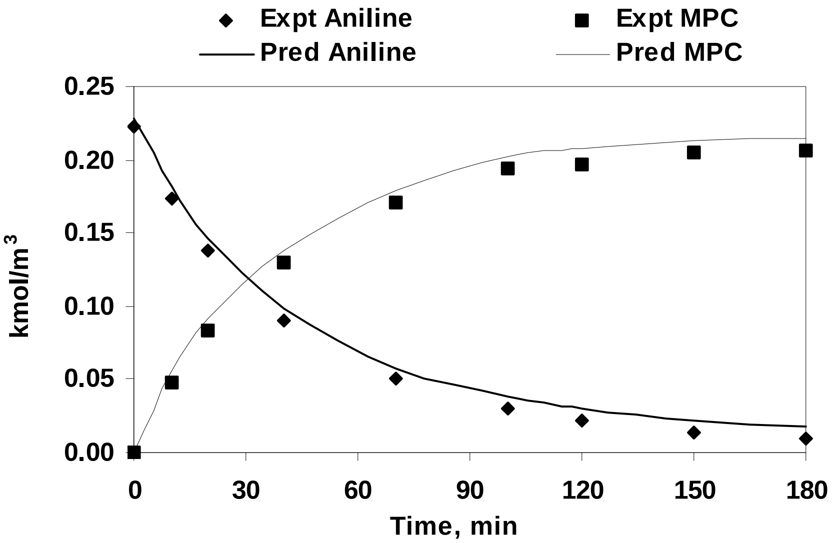


Figure 3.19 (B) Validation of proposed rate model (Model 1) at 433 K

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4, 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, time 180min.

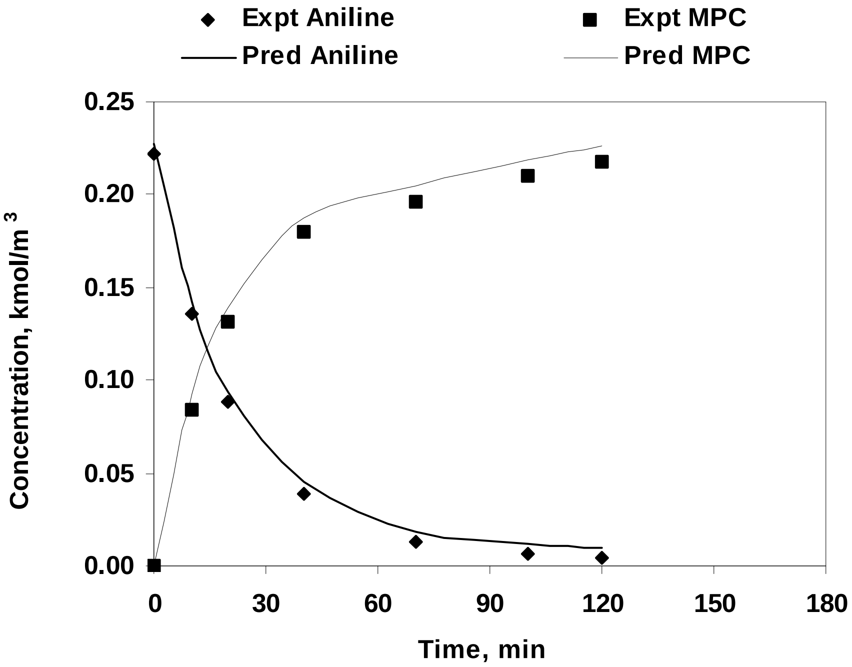


Figure 3.19 (C) Validation of proposed rate model (Model 1) at 443 K

Reaction conditions: Aniline 0.222 kmol/m^3, Pb_3O_4, 1.21 kg/m^3, DMC up to total volume 1.75×10^{-5} m^3, Agitation 10 Hz, time 180min.

3.4.8.8. BATCH REACTOR MODEL

In order to verify the applicability of the kinetic model under integral conditions, experimental data on the liquid phase concentration of aniline and MPC as a function of time were also obtained. For the present case, the following assumptions were made in deriving the batch reactor model.

1. The L-S mass transfer effects were assumed to be negligible.
2. The temp remains constant throughout the reaction.
3. The total volume is considered to remain constant.

The variation in the concentrations of aniline and MPC can be represented by following mass balance equations-

$$-\frac{dC_A}{dt}=\frac{w*k_1A}{(1+K_2A)} \qquad 3.8$$

$$\frac{dC_B}{dt} = \frac{w*k_1A}{(1+K_2A)} \qquad 3.9$$

Where,

w= concentration of catalyst

It was found that the initial conditions are-

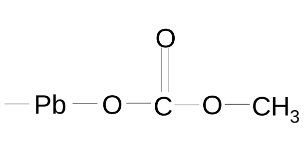
Time T=0, A=A_i, B=0

The equations 3.8 and 3.9 were solved numerically by Runge-Kutta 4th order to obtain the concentrations of aniline and MPC as a function of time. For this purpose, the intrinsic rate parameters determined from initial rate data were used. The comparison of experimental and predicted results for some cases are presented in Figure 3.19, which show excellent agreement between the experimental and predicted data.

3.4.9. REACTION MECHANISM

For the metal-catalysed synthesis of alkyl carbamates, starting from an amine and an organic carbonate, two plausible mechanistic approaches can be envisaged-

1. Activation of the organic carbonate with the metal catalyst, followed by the nucleophilic attack of amine on the carbocation of the carbonate-lead adduct, or
2. The activation of amine with lead catalyst, followed by the nucleophilic attack of this adduct on the carbocation of organic carbonate.

Fu and Ono[16] have proposed a mechanism for the methoxycarbonylation in the PbO catalysed methoxycarbonylation of aniline, wherein, the activation of DMC with lead to form a  $-\mathrm{Pb}-\mathrm{O}-\overset{\overset{\displaystyle \mathrm{O}}{\|}}{\mathrm{C}}-\mathrm{O}-\mathrm{CH_3}$ type of species is shown, which eventually is attacked by the basic amine, to form carbamate. The form of lead that initiates the catalytic cycle is described as the surface Pb-OH groups, which are modified by DMC. The latter is a versatile moiety, which has two carbon centres at which the amine nucleophile may react- the *carbonyl* group and the *methyl* group.

When a nucleophile attacks at carbonyl carbon of DMC (Mech-I), the cleavage of acyl-oxygen bond results in a methoxycarbonyl product. When a necleophile attacks at the methyl carbon of DMC (Mech-II), the methylation product is produced by the alkyl-oxygen bond cleavage (Figure 3.20)

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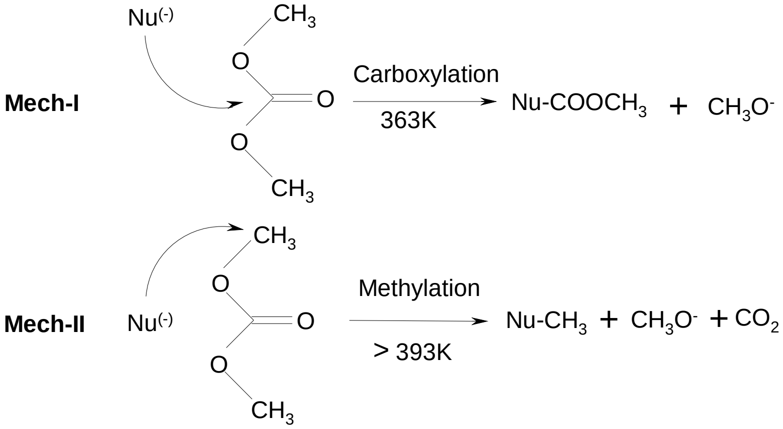
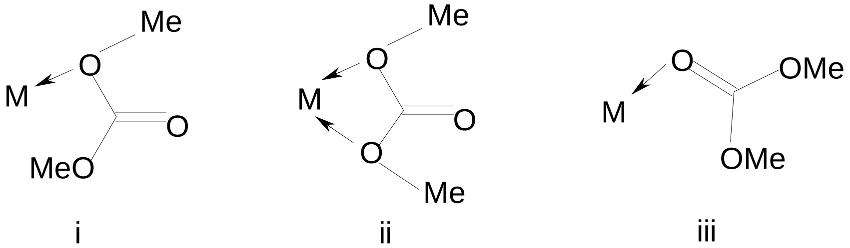


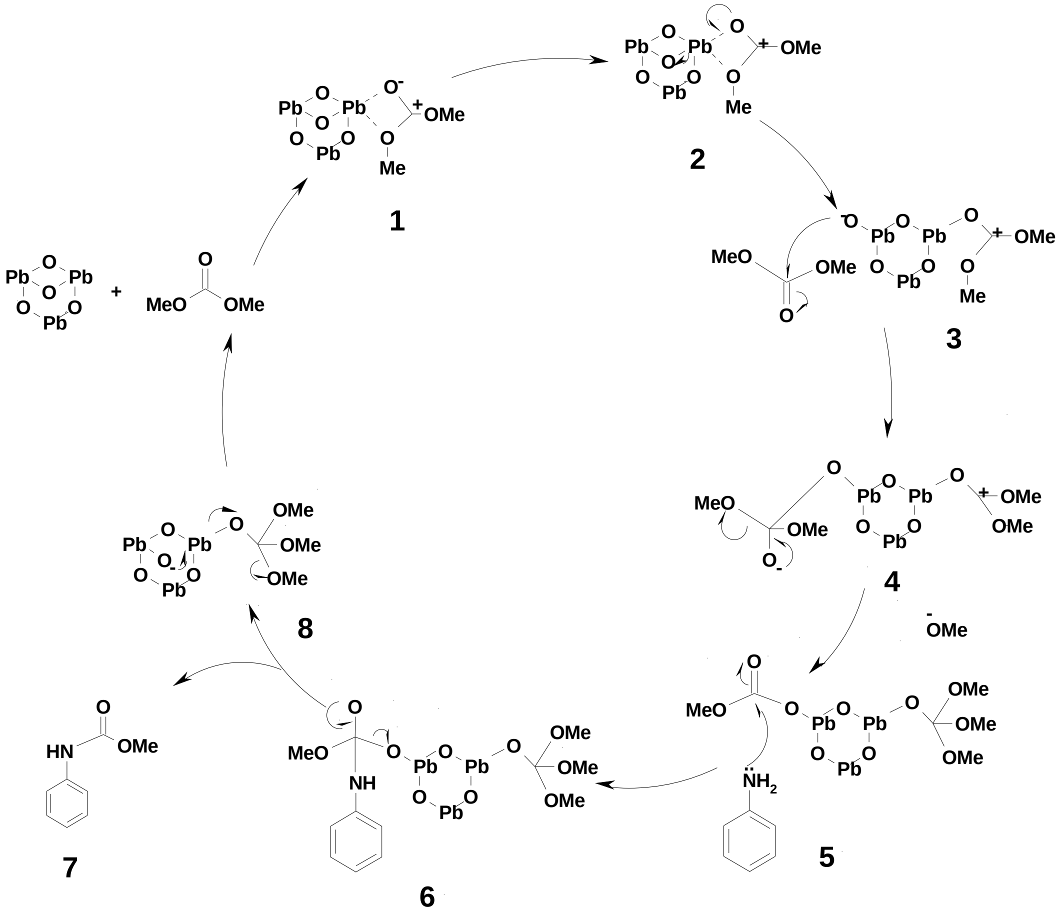
Figure 3.20. Reactivity of DMC towards nucleophilic attack

The product selectivity in these reactions is often tailored by the use of catalyst and the reaction temperature. The coordination of DMC to a metal is possible *via* three ways as shown in Scheme 3.3.



Scheme 3.3. Possible ways of coordination of DMC with the metal center

Distaso et al.[26] have carried out the IR studies for finding out the mode of coordination, according to which, the coordination via the carbonyl oxygen is evident. Though the carboxylation reaction of amines with CO_2 cannot be compared to that with organic carbonates in terms of mechanism, we find some analogy in the sequence of steps in the two reactions. According to Srivastava et al.,[27] in the zeolite-catalysed carboxylation of aniline, the CO_2 first binds with the metal, followed by the oxidative addition of amine to the metal to yield carbamate. Baba et al. have proposed a similar mechanism for Zn catalysed methoxycarbonylation of amines.[17] Based on this approach, a mechanism for Pb_3O_4 catalysed methoxycarbonylation of aniline has been proposed. The schematic representation of the proposed mechanism is shown in Scheme 3.4.

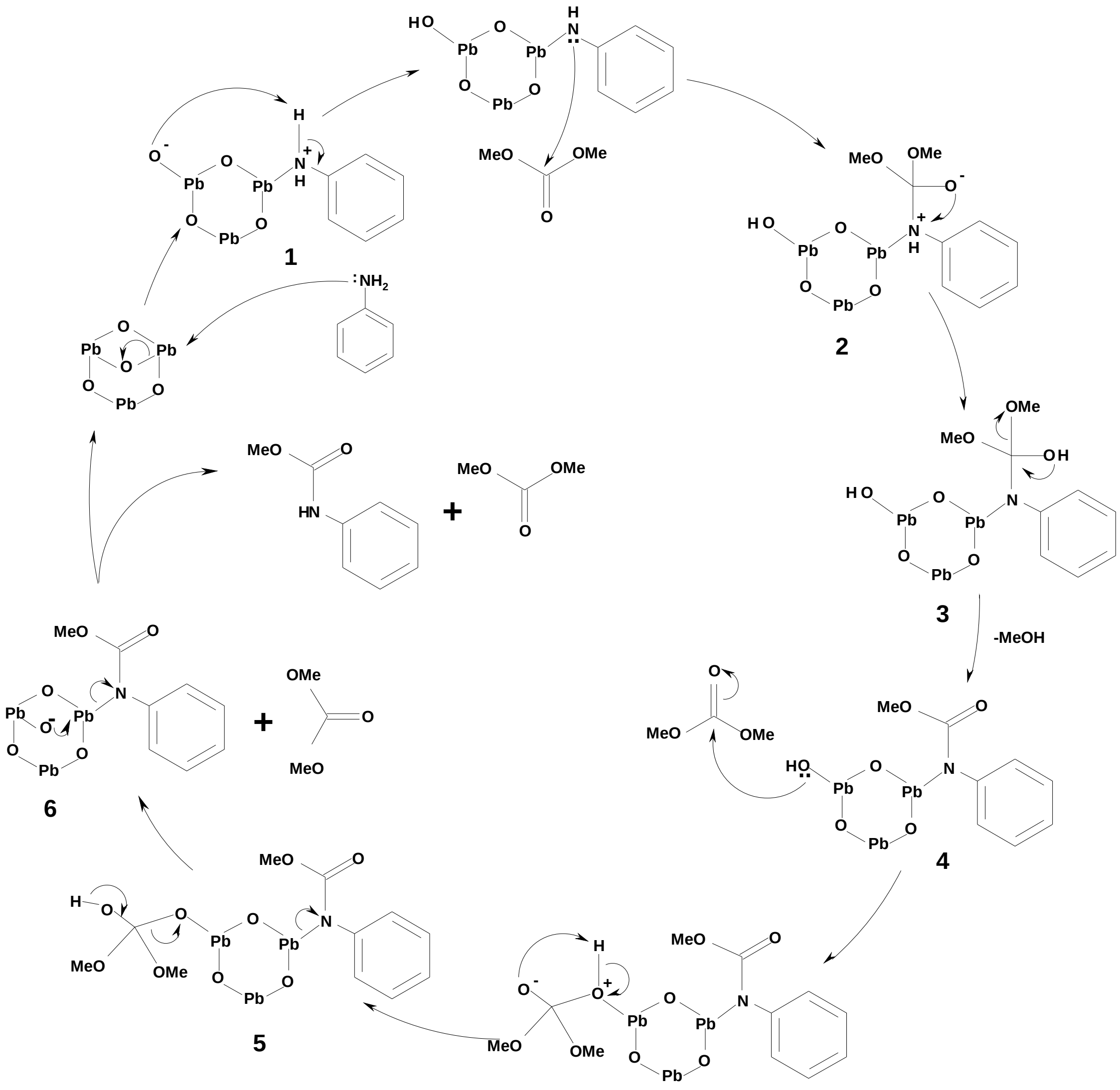


Scheme 3.4. Plausible mechanism (I) for Pb_3O_4 catalysed methoxycarbonylation of aniline

According to another approach, the activation of amine takes place first by coordination with the metal, followed by the attack of this adduct onto dimethylcarbonate. Fu-Kui Xiao et al.[28] have done IR investigations on the DMC mediated zinc acetate catalysed methoxycarbonylation of 1,5-naphthalenediamine (NDA). According to this study, the pre-treatment effect of DMC on zinc acetate in the temperature range of 403-453 K showed no modification of the latter, as evident from the unchanged IR patterns of the catalysts, whereas, the pre-treatment study for zinc acetate catalyst with NDA showed disappearance of the characteristic values and appearance of new bands at 3116 and 901 cm^{-1}, and also a shift in the ν_a and ν_s of COO^- group, indicating formation of a complex of the amine with zinc, at temperatures beyond 403 K. This study showed that two molecules of NDA could coordinate with one molecule of zinc acetate. The authors have concluded from the study that the activation of amine first takes place with the catalyst, which then acts as the suitable nucleophilic agent, and attacks DMC, to yield the carbamate. A similar mechanism could be proposed for the Pb_3O_4 catalysed methoxycarbonylation of aniline with DMC, which is shown in Scheme 3.5.

To find out the behavior of the catalyst and sequence of steps in the mechanism, a few reactions on the pre-treatment effect were carried out. In this study, the catalyst Pb_3O_4 was pre-treated with DMC and aniline independently at different temperatures, and these catalysts were then tested for the model aniline methoxycarbonylation reaction, to check if the induction period disappeared. It was observed that, at room temperature, there was no activation of either aniline or DMC with Pb_3O_4. Reactions taken at temperatures beyond 423 K with DMC showed that the colour of catalyst changed, and also the induction period disappeared when the solid catalyst recovered form this DMC pre-treatment experiment was used.

IR spectra were recorded for fresh and pre-treated Pb_3O_4 catalysts (C-1 to C-6) as well as for the catalyst recovered from a typical aniline methoxycarbonylation experiment (C-7) (Section 3.4.6.2; Table 3.4). The IR spectra can be seen in Figures 3.21 (a), (b) and (c).



Scheme 3.5. Plausible mechanism (II) for Pb_3O_4 catalysed methoxycarbonylation of aniline considering modification of the catalyst by aniline as the initiation of catalytic cycle

The Pb-O stretching frequency in the cyclic structure of Pb_3O_4, as can be observed from Figure 3.21 (a) is at 531 cm^{-1}. This frequency, in case of PbO is 465 and 505.[29] Figure 3.21 (b) shows the IR spectrum of the DMC pre-treated catalyst (C-5). It is evident that, there is modification in the structure of the catalyst. A similar spectrum (Figure 3.21 (c)) of aniline pre-treated catalyst (C-5) shows no difference from that of

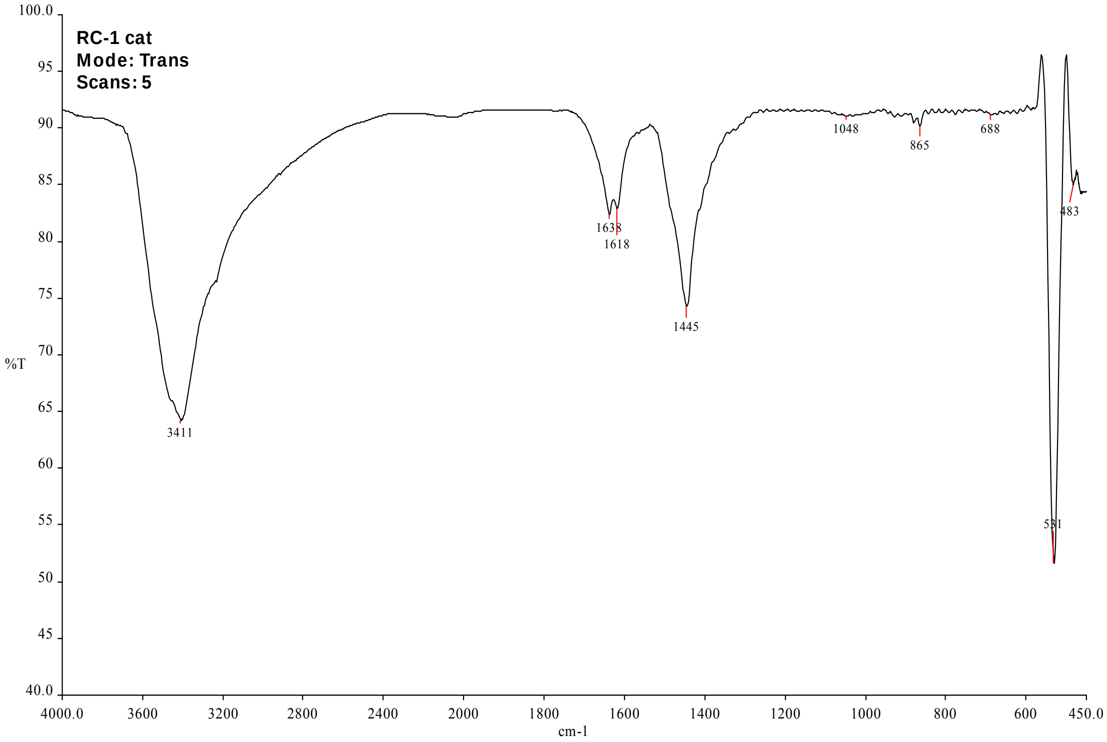


Figure 3.21 (a) IR spectrum of Fresh Pb_3O_4 catalyst

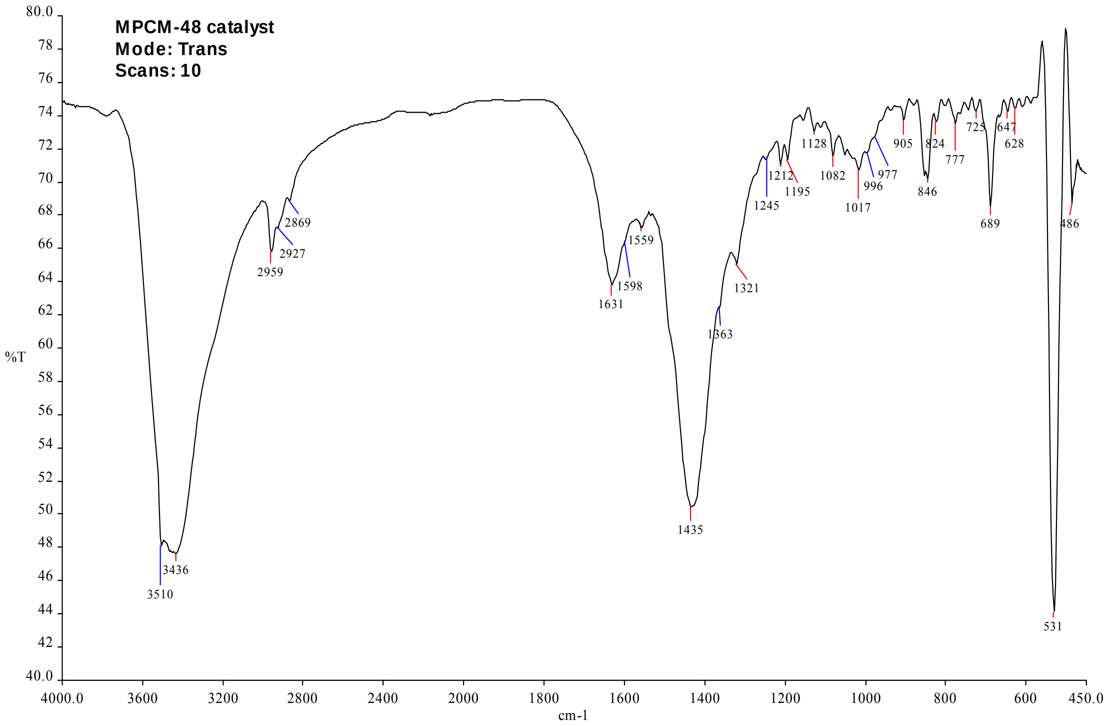


Figure 3.21 (b) IR spectrum of catalyst C-5

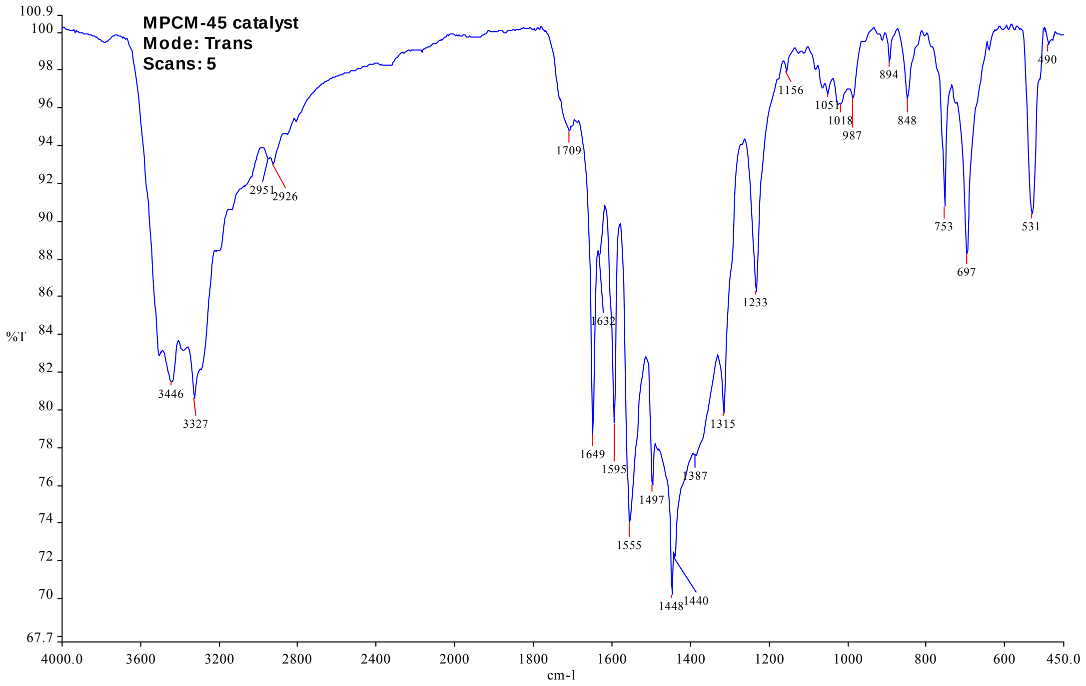


Figure 3.21 (c) IR spectrum of catalyst C-7.

unused Pb_3O_4, which is in complete agreement with the experimental evidence, where the aniline pre-treated catalyst does not eliminate the induction period. The elimination of induction period due to DMC pre-treatment is obviously due to the formation of an active catalyst complex. If the IR spectra of catalysts C-5 and C-7 are compared, many similarities can be observed. The modified Pb complex is speculated to have the structure as shown in Figure 3.19(B). The coordination of DMC through the carbonyl oxygen (Mode iii, Scheme 3.3) is obvious from the disappearance of $\nu_{(C=O)}$ at 1780 cm^{-1}. The C-O stretching frequency in the DMC-Pb complex probably shifts to 1321 cm^{-1}. The red shift is much higher compared to the coordination of DMC with other catalysts like $Sc(OTf)_3$ or other such reported metal catalysts. The higher shift can be assigned to the high electronegativity of Pb compared to Sc (Table 3.11.)[30]

Table 3.11. A comparative account of Pauling electronegativities of some metals

Sr.	Metal	Pauling Electronegativity
1	Pb	2.33
2	Sc	1.36
3	Zn	1.65
4	Sn	1.96

The bands at 1631 and 1632 cm^{-1} in the spectra of C-5 and C-7 respectively, may be assigned to the uncoordinated carbonyl frequency $\nu_{(C=O)}$.

The observations are consistent with those of Sc(OTf)$_3$ catalyzed methoxycarbonylation of amines, wherein, Distaso et al.[26] have demonstrated that the pre-treatment of the scandium triflate catalyst with dimethyl carbonate causes a coordination of DMC via the carbonyl oxygen to metal (Sc). Similarly in the present study, the shift to red ($\Delta\nu_{(C=O)}<0$) allows us to exclude coordination modes (a) or (b) in Scheme 3.22.

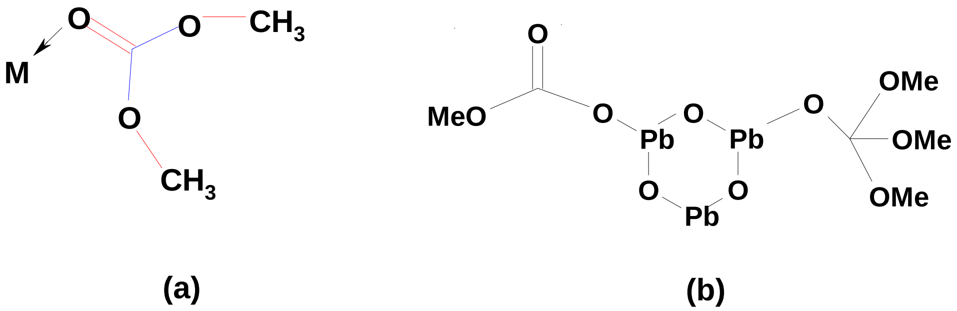


Figure 3.22. (a) Shifts in IR frequencies due to coordination of DMC with metal (b) Possible adduct formed due to pre-treatment of Pb$_3$O$_4$ with DMC.

3.5. CONCLUSION

A detailed investigation of Pb_3O_4 catalysed methoxycarbonylation of aniline at various reaction parameters was carried out. It was found that, red lead is an excellent catalyst for selective synthesis of methyl N-aryl carbamates by methoxycarbonylation of aromatic amines with dimethyl carbonate. The standard concentration-time profile for the model reaction system established excellent agreement between the consumed amine and formed carbamate. A characteristic induction period for the reaction was observed in the reaction. The effect of variations in the reaction parameters on the induction period was studied. For the sake of convenience, the induction period was eliminated from the concentration-time profiles, and kinetic analysis of the reaction system was carried out.

For the kinetic studies, various effects like substrate concentration, catalyst concentration and operational parameters like temperature and agitation frequency was studied. Based on the data obtained from this experimental study, a rate equation was proposed.

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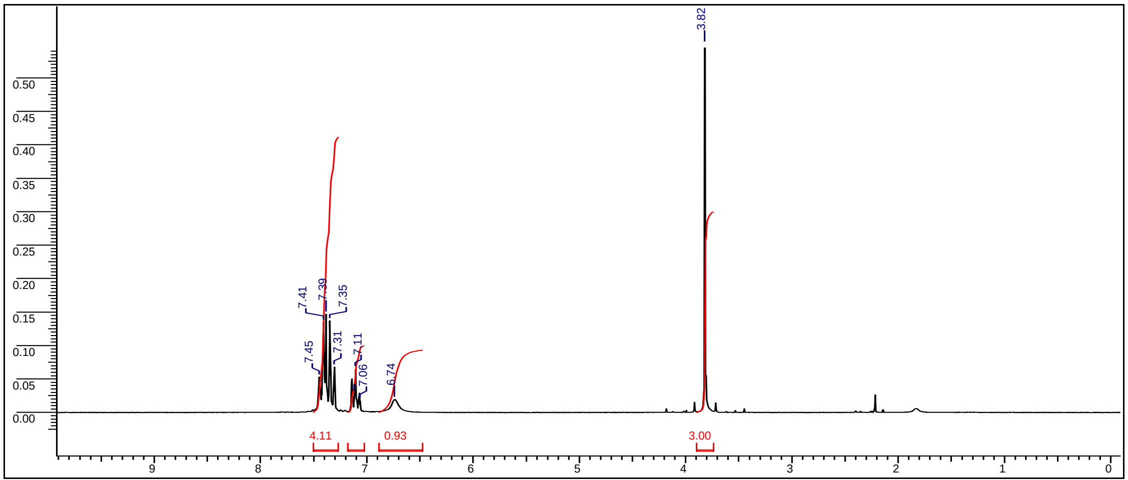
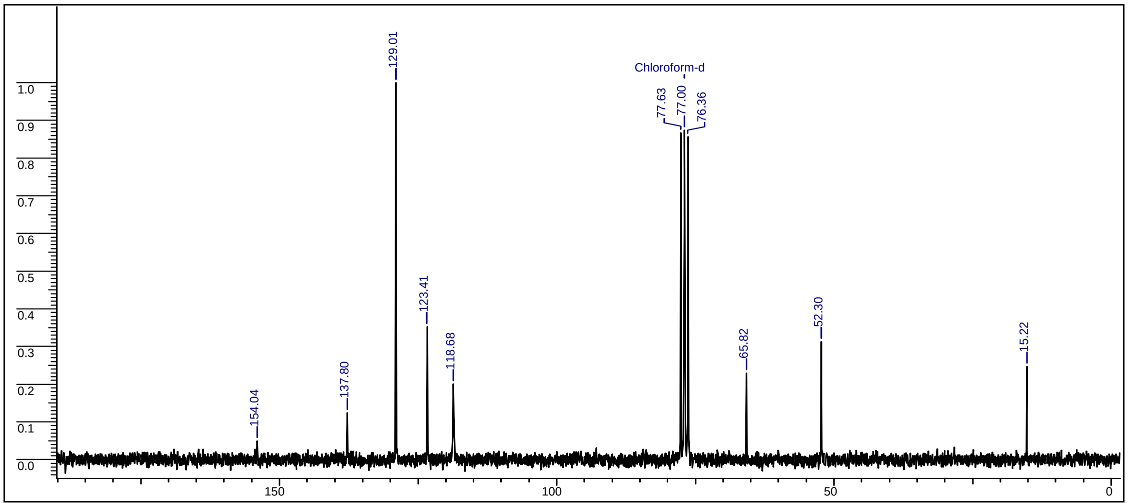
SPECTRA



^{1}H NMR of Methyl N-phenyl Carbamate in $CDCl_3$



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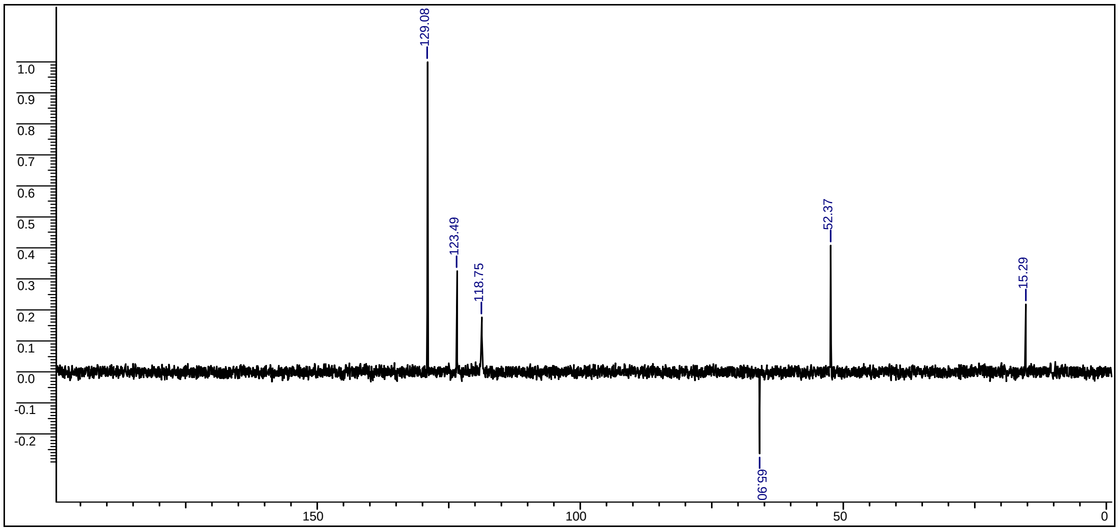

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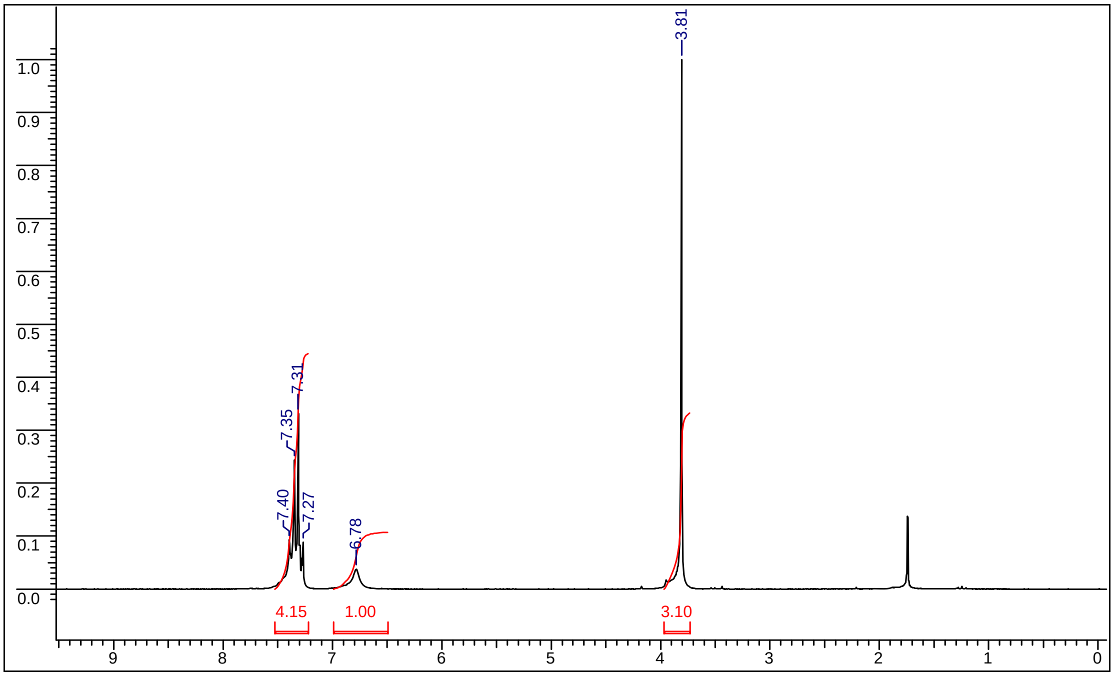

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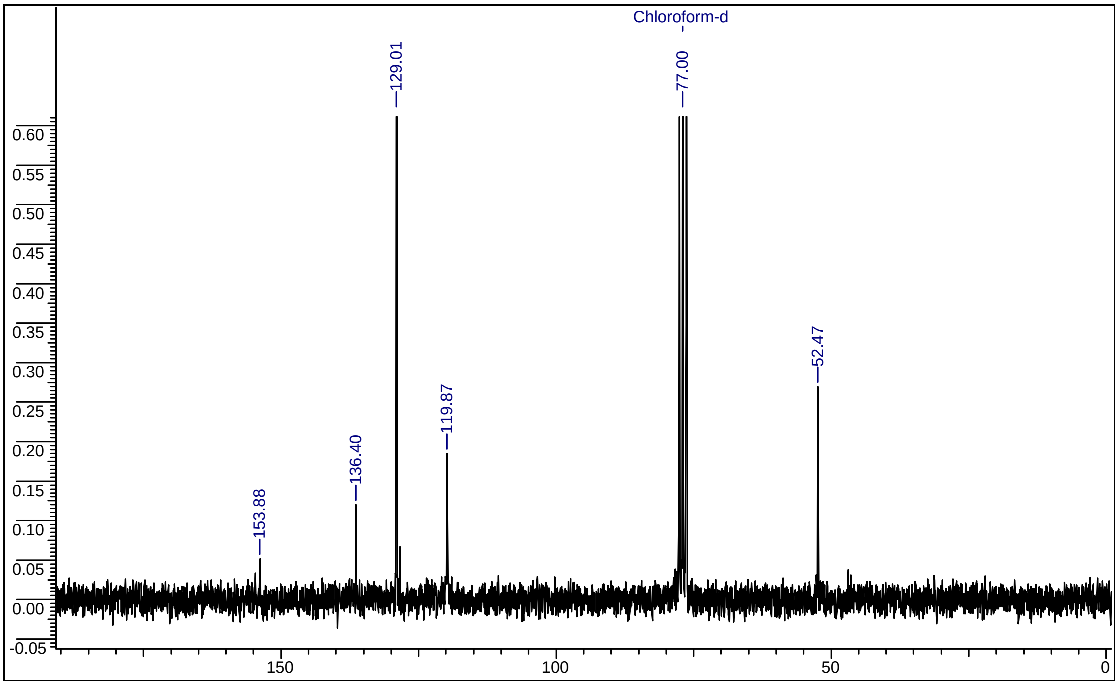

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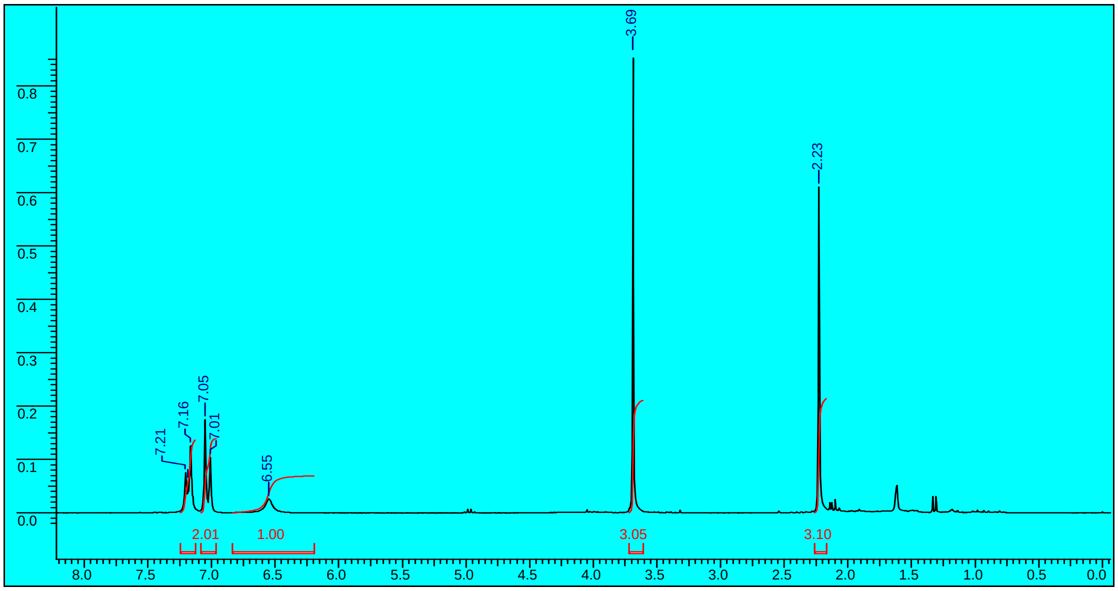

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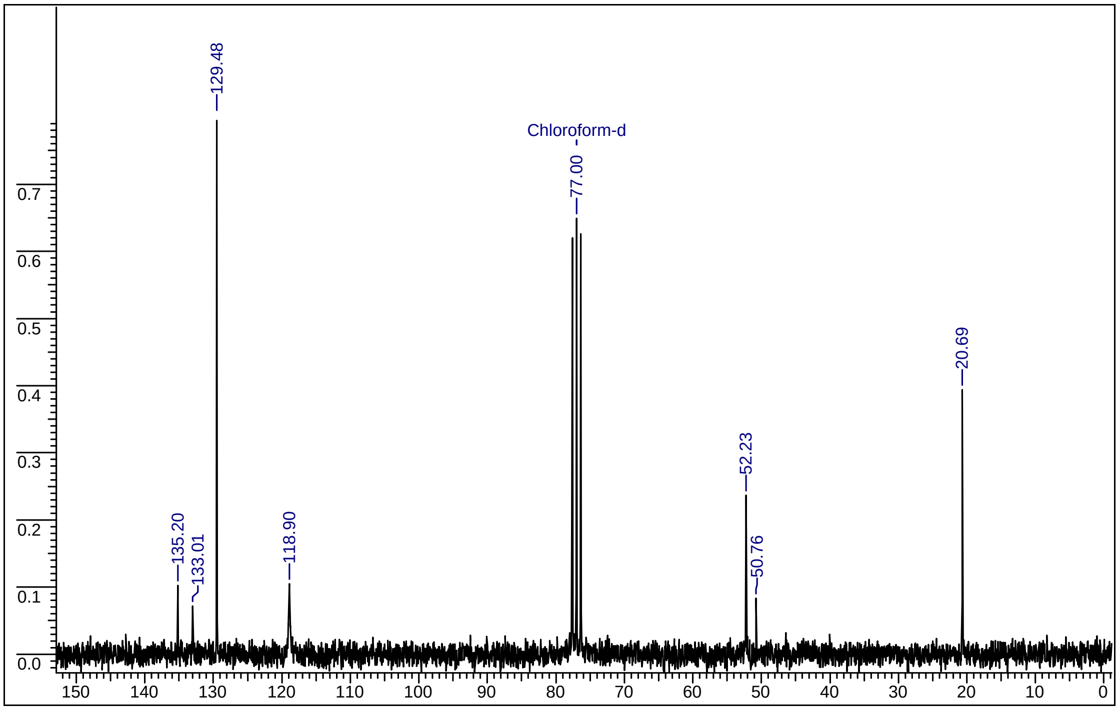

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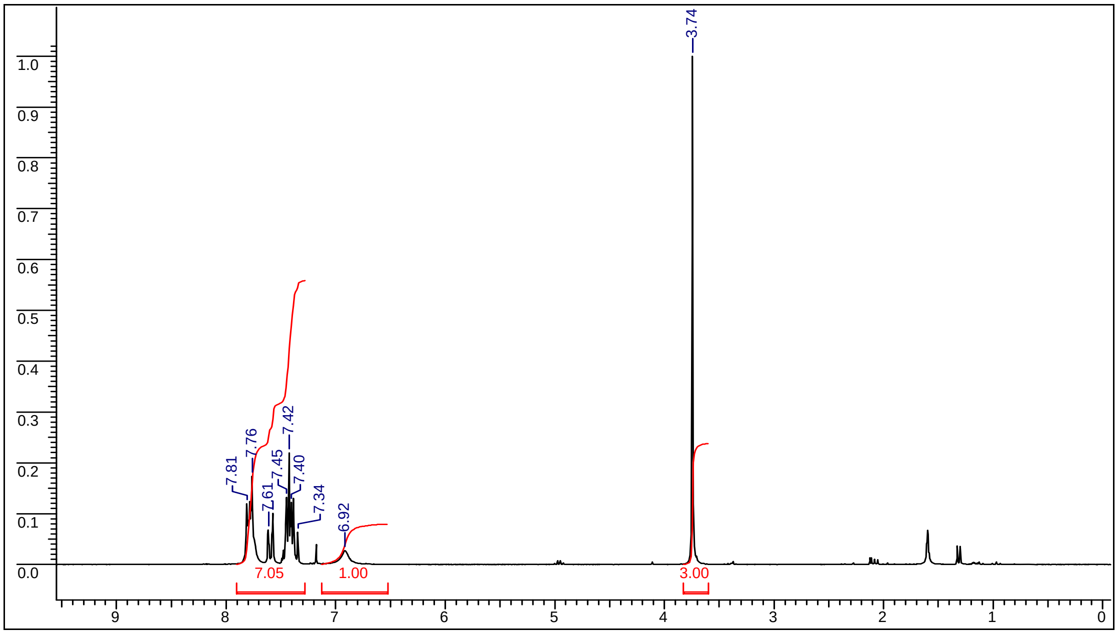

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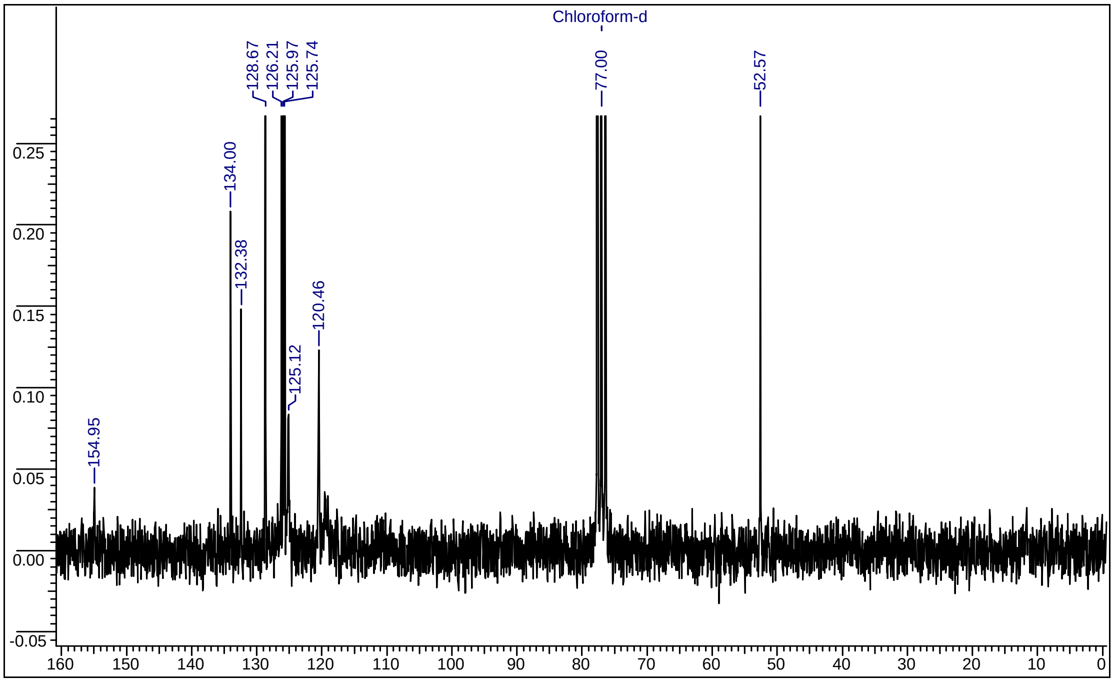

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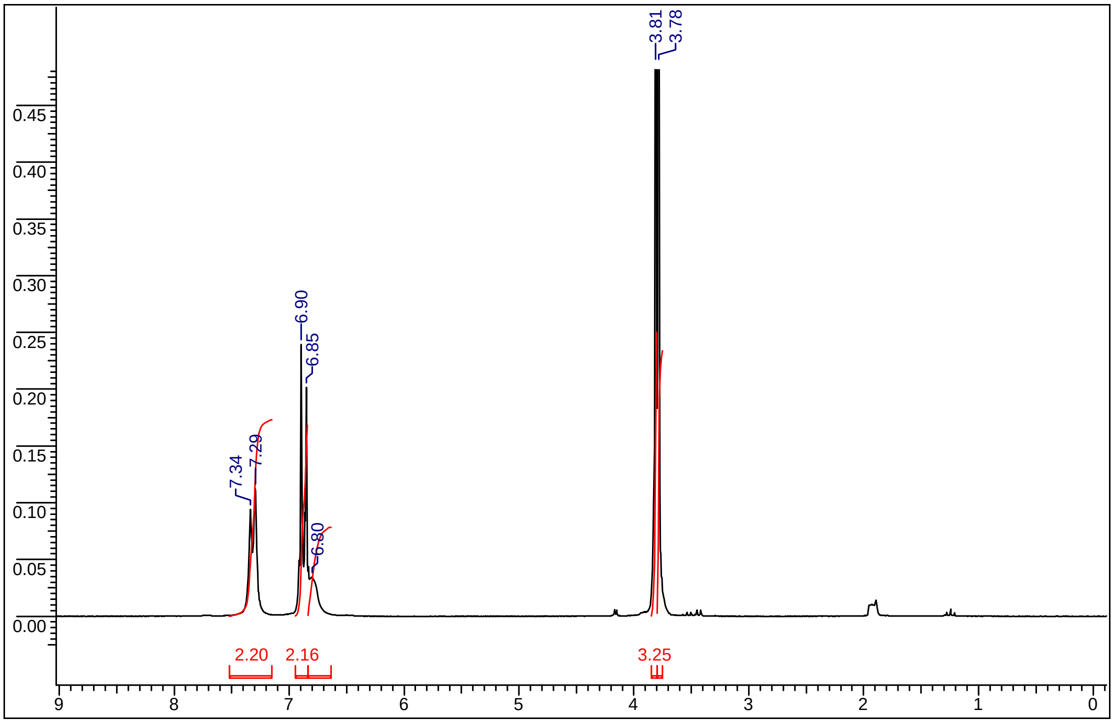

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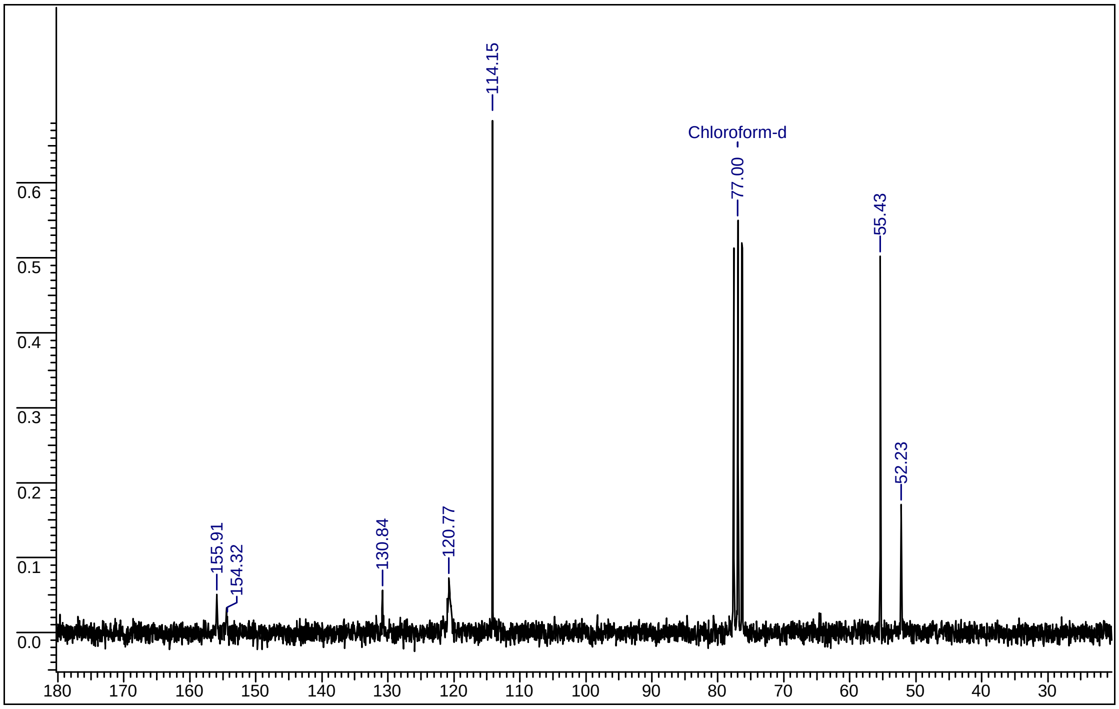

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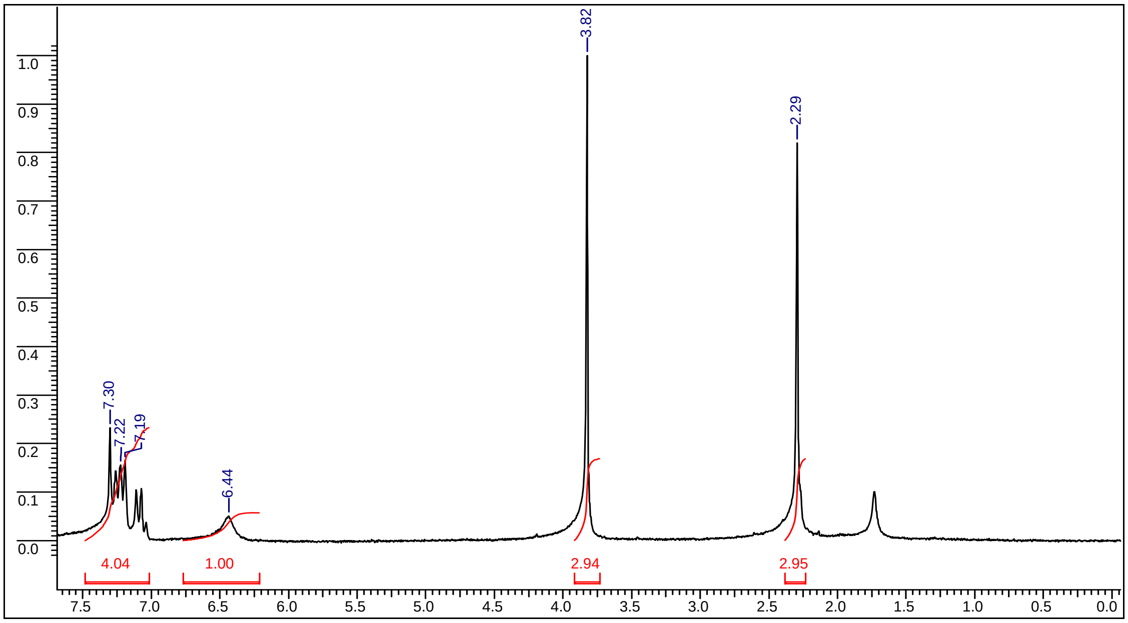

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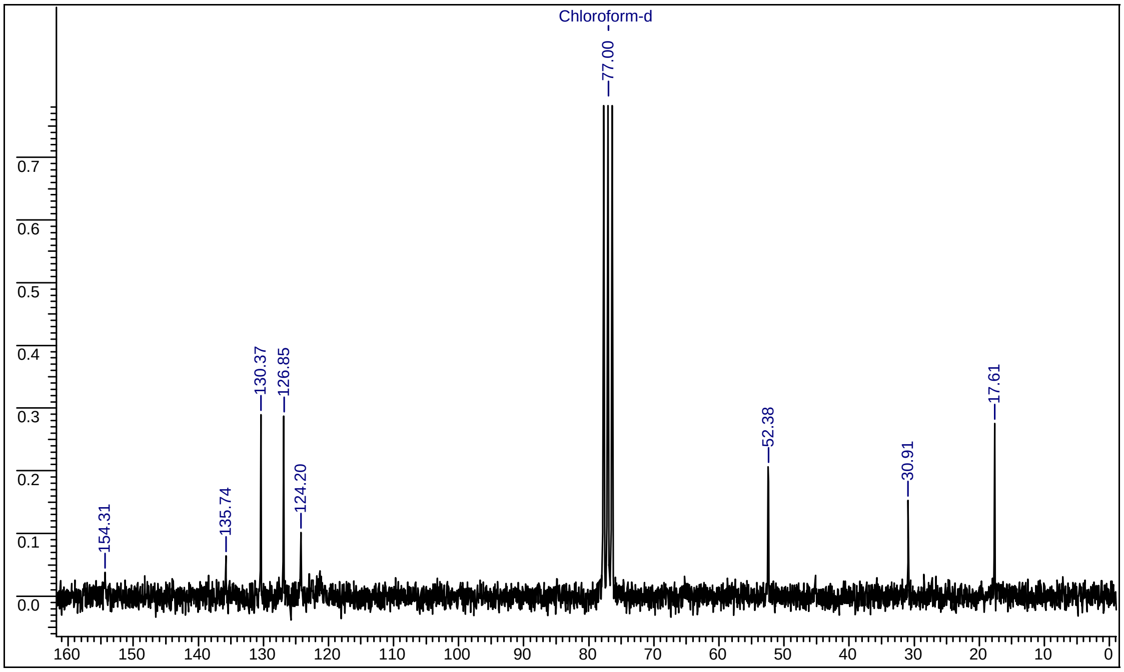

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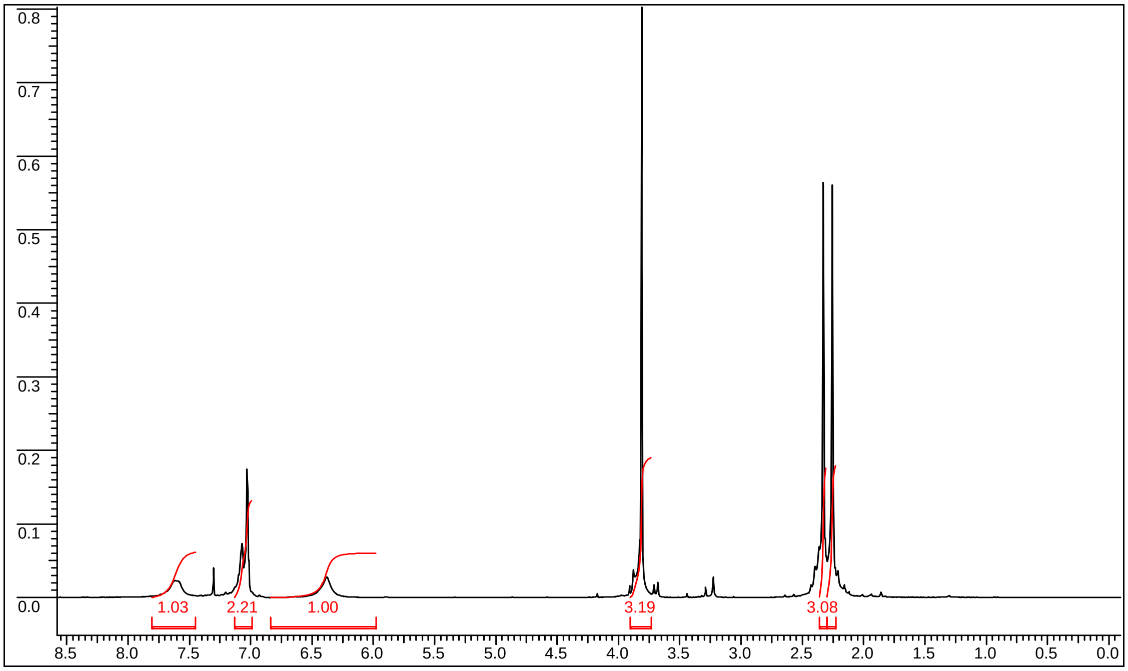

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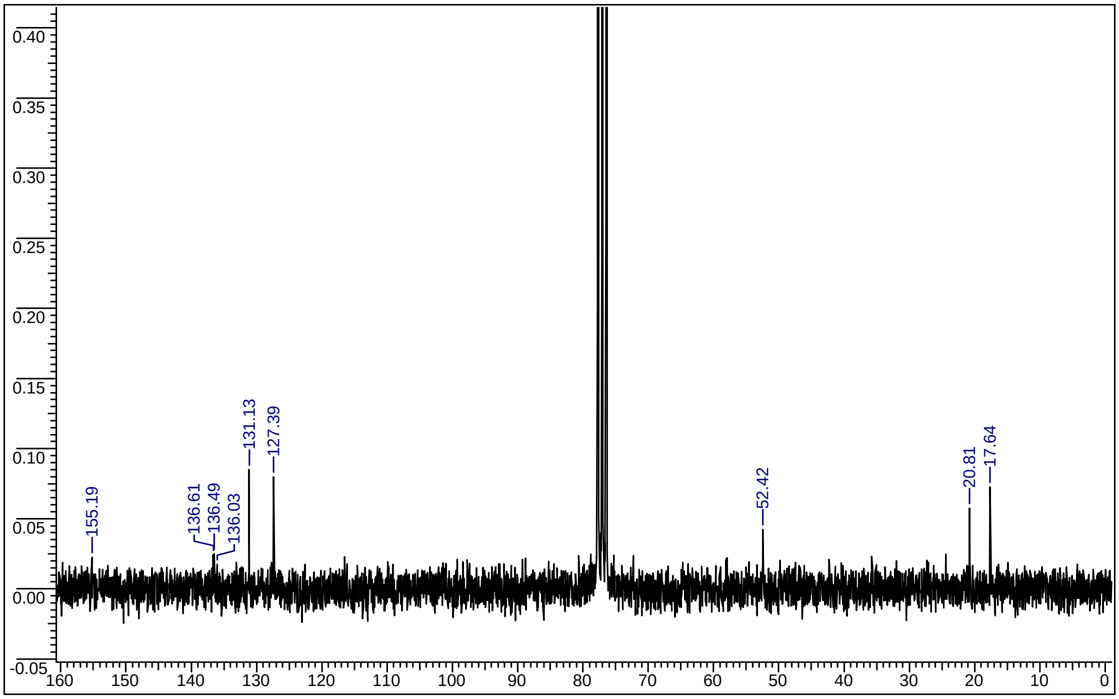

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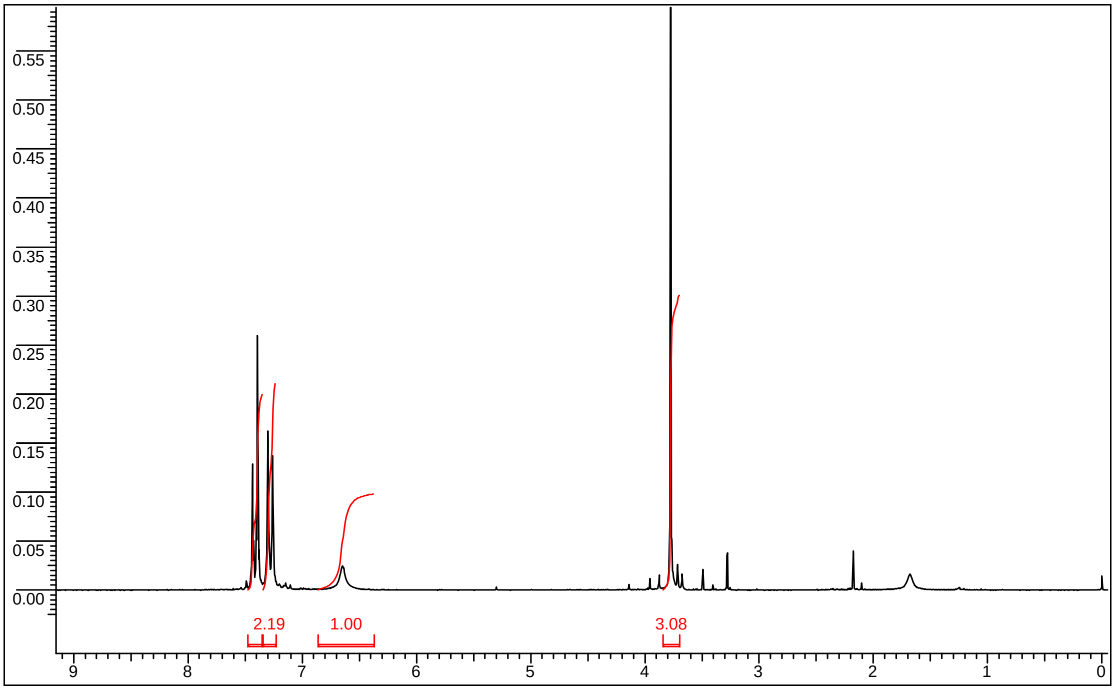

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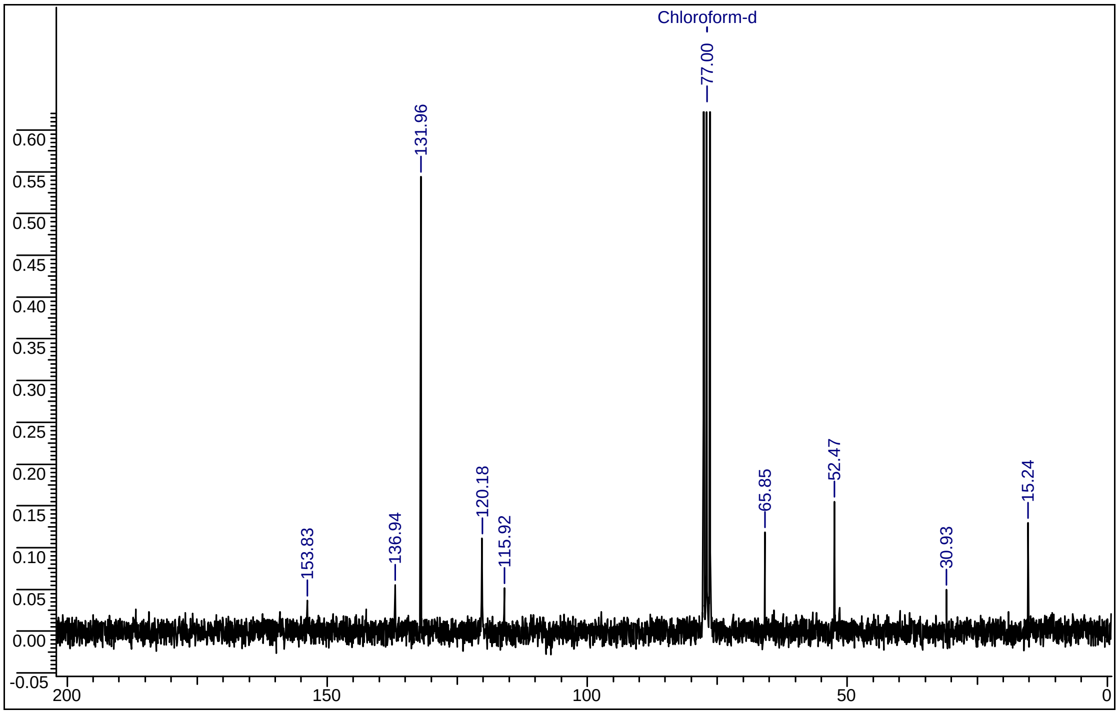

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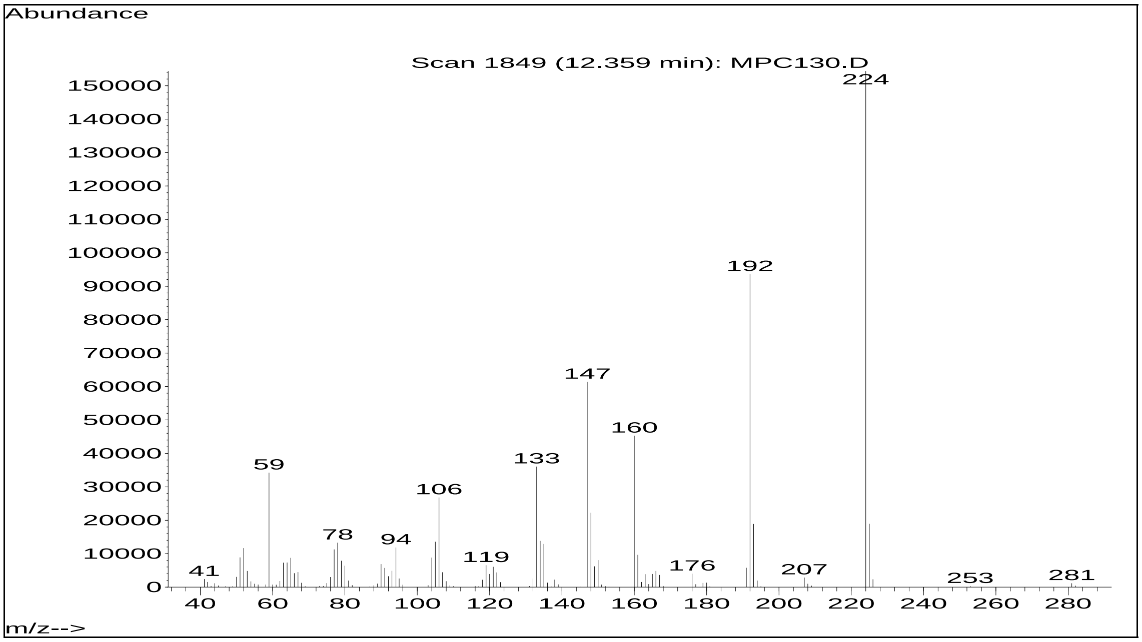
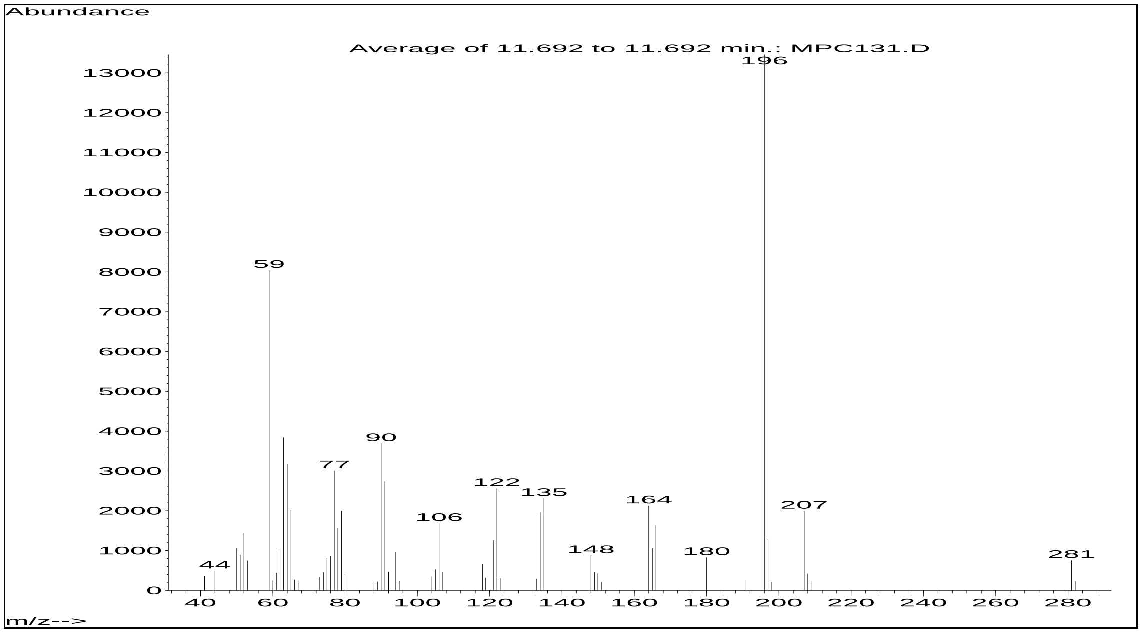


GC-MS Spectrum of Dimethyl 1,3-Phenylenedicarbamate [Bis(methyl(1,3-phenylene)-dicarbamate)]



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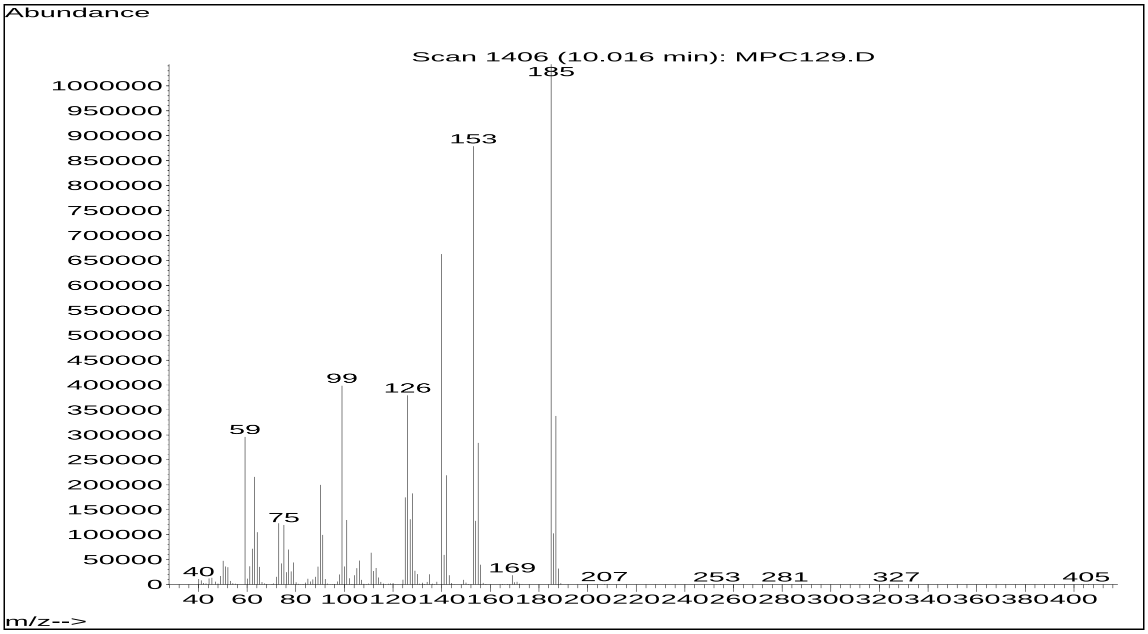

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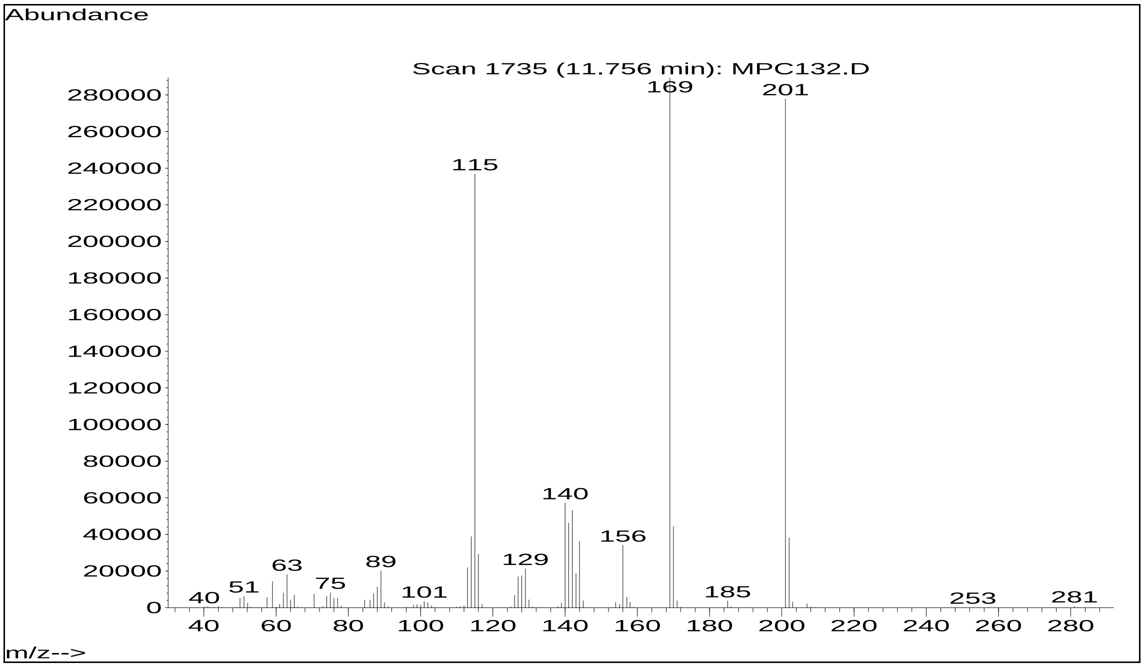

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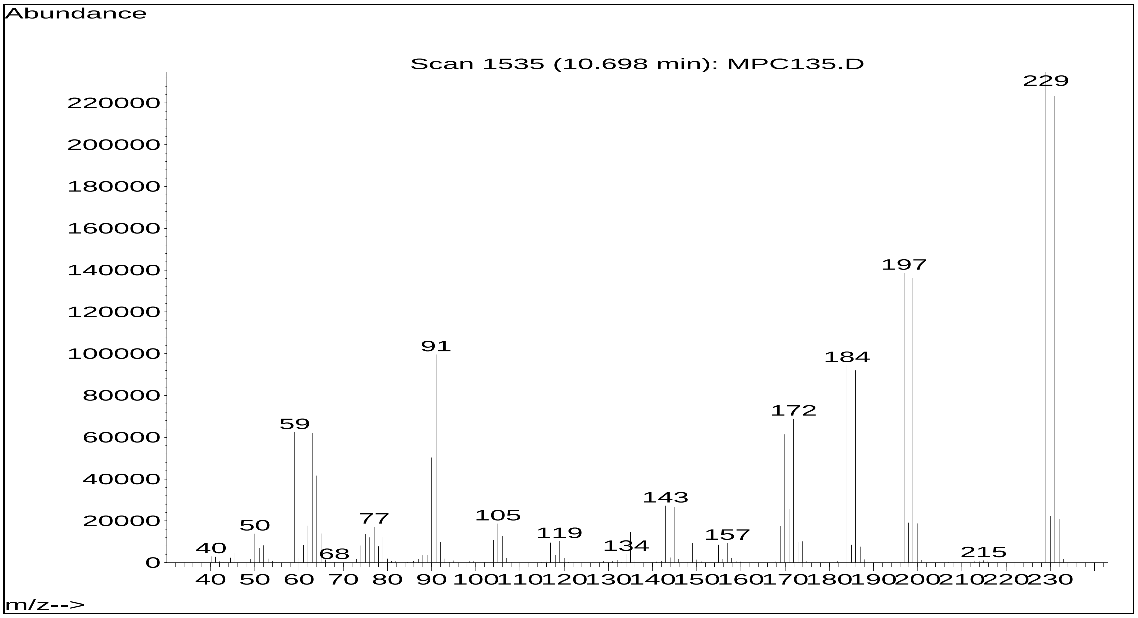

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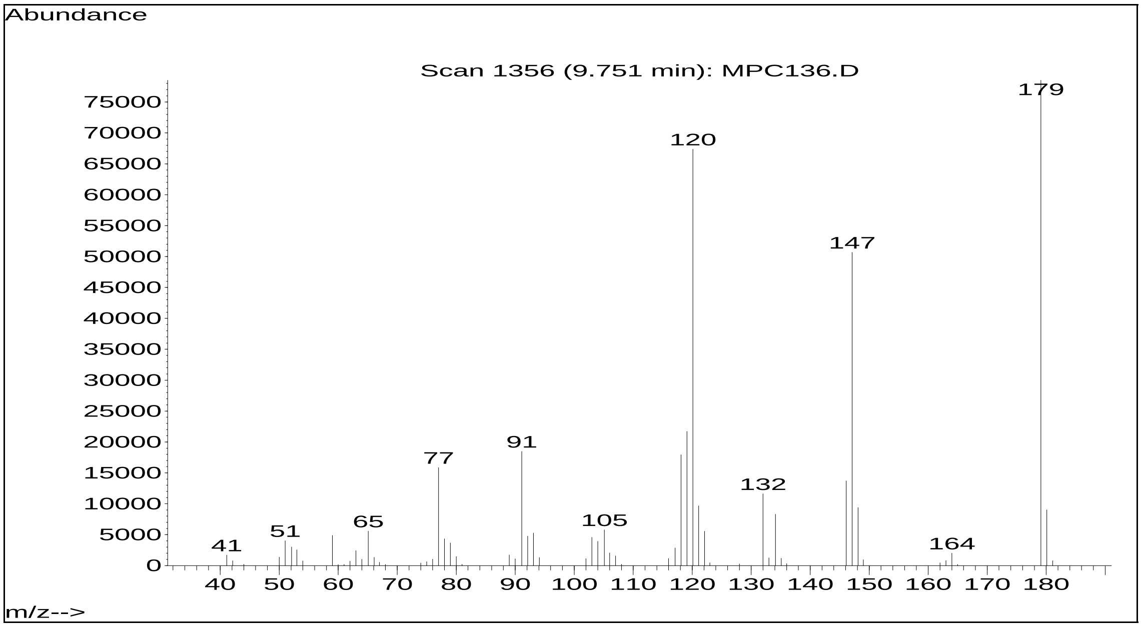

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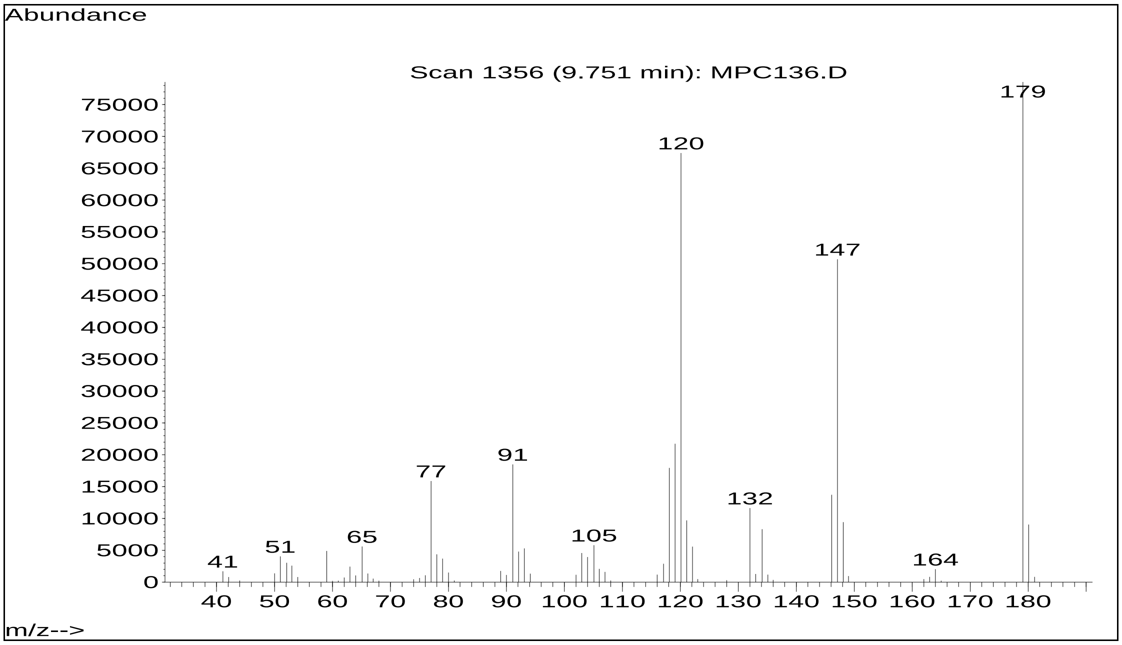

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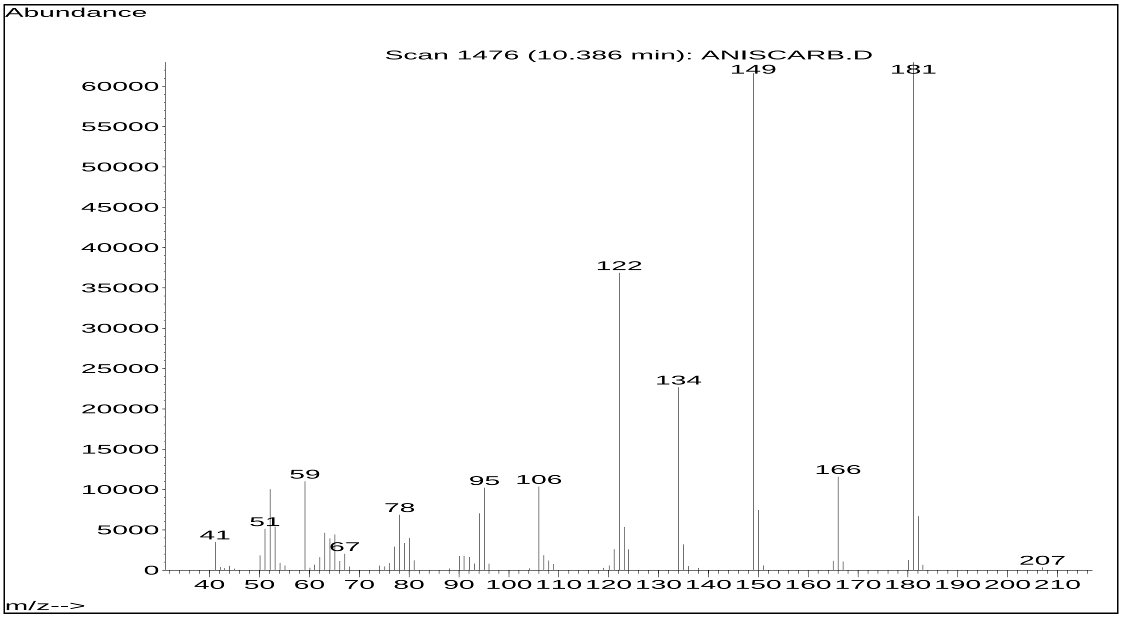
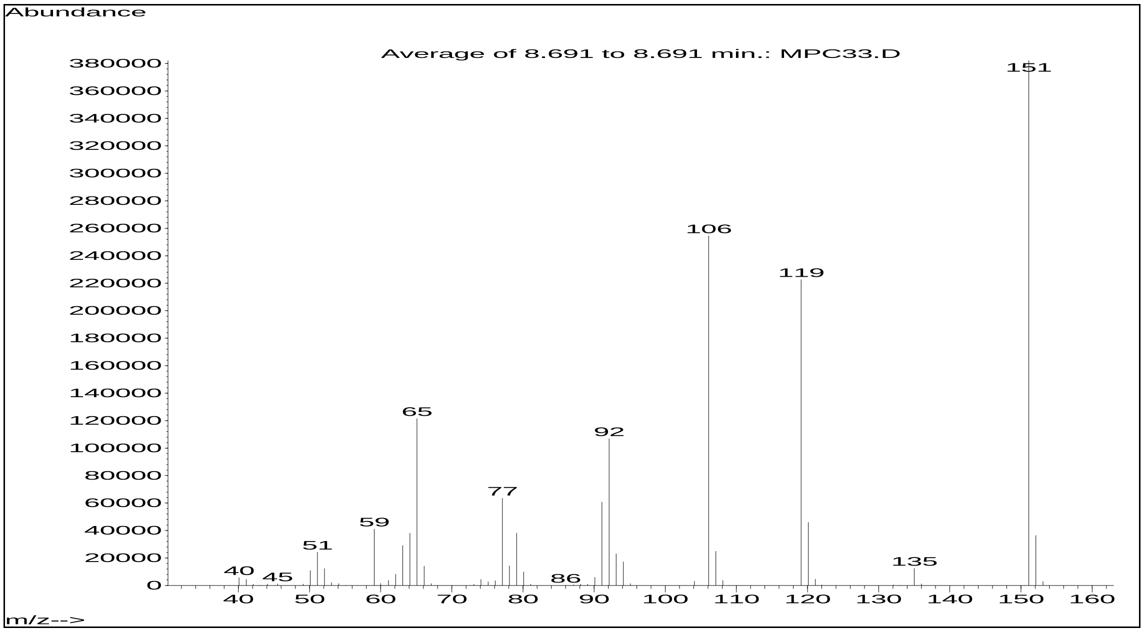
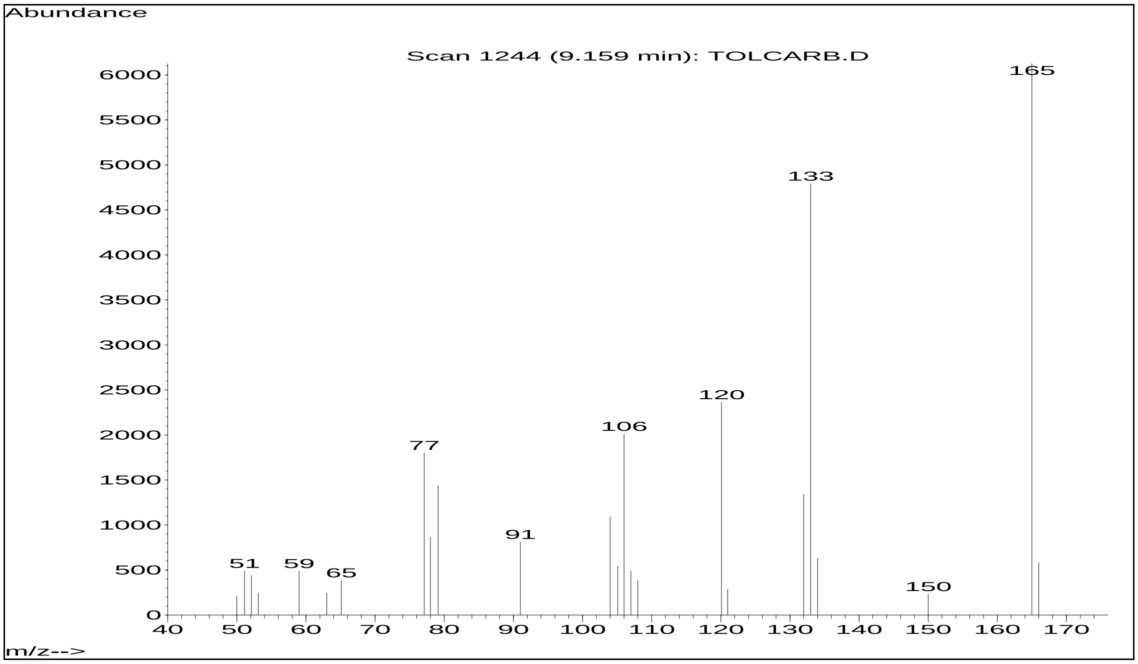


GC-MS Spectrum of Methyl 4-methoxyphenylcarbamate



GC-MS Spectrum of Methyl N-Phenylcarbamate



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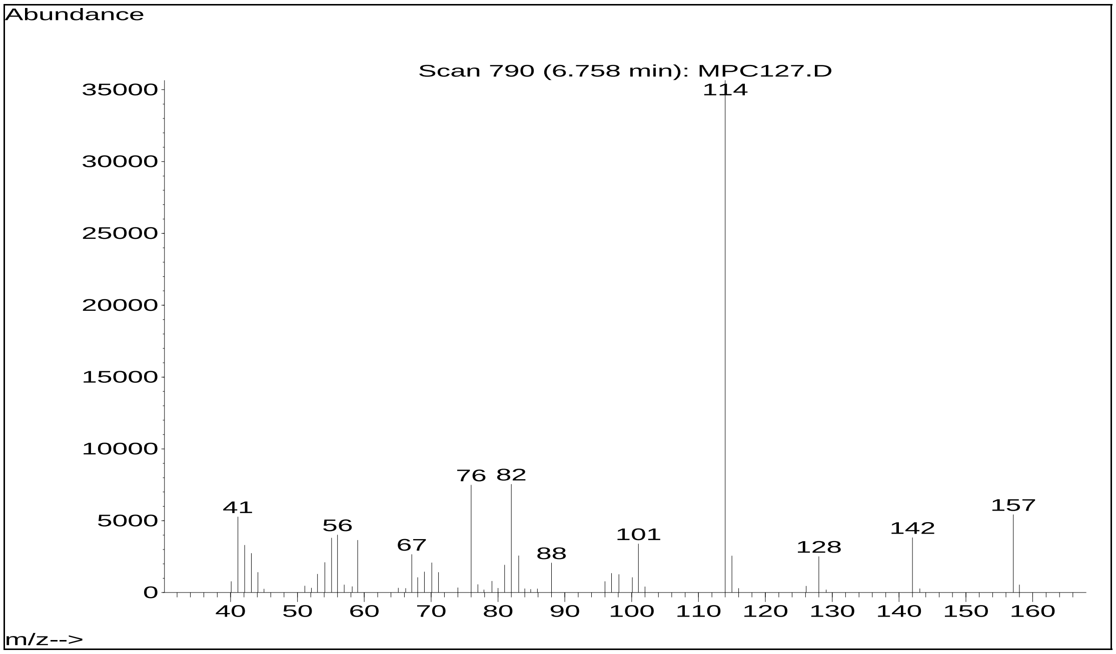
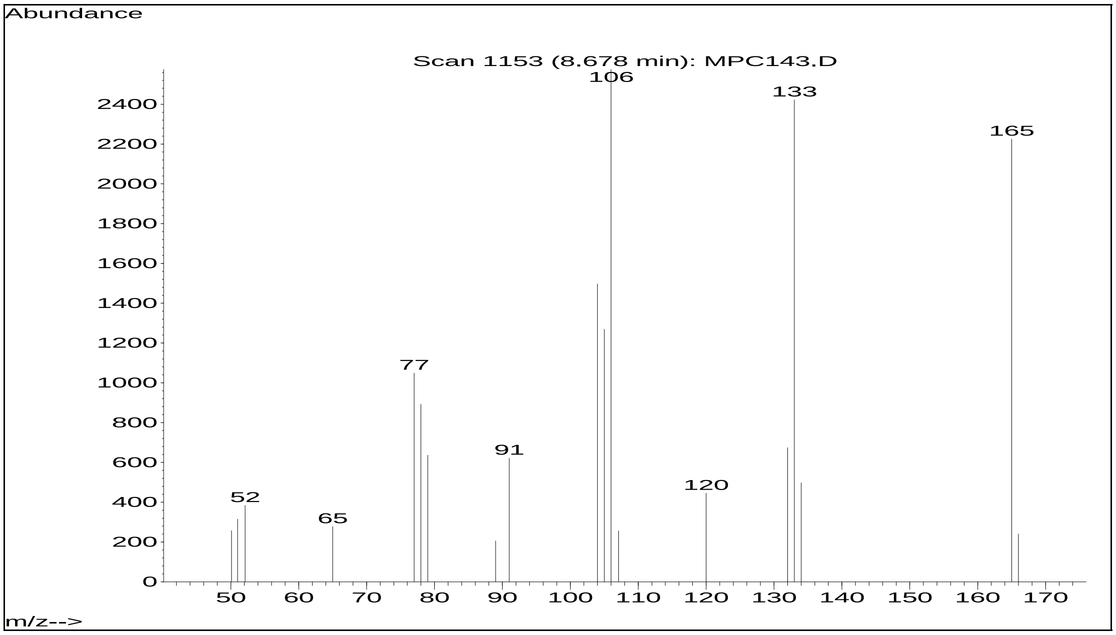


GC-MS Spectrum of Methyl N-(cyclohexyl)carbamate



GC-MS Spectrum of Methyl N-(2-methylphenyl)carbamate

Chapter 4

Oxidative Carbonylation of Amines for the Synthesis of Disubstituted Ureas Catalysed by Pd Nanoparticles Immobilized on Amine-functionalized Zeolite

This chapter describes the synthesis and characterization of novel heterogenized palladium nanoparticles and their catalytic application for the oxidative carbonylation of amines for synthesis of disubstituted ureas.

4.1. INTRODUCTION

Research in catalysis is a key factor for the development of starting chemicals, fine chemicals and drugs from raw materials. During the twentieth century, chemists have made considerable achievements in heterogeneous catalysis, whereas homogeneous catalysis progressed after the second world war (hydroformylation) and especially since the early 1970s (hydrogenation).[1] Although heterogeneous catalysis benefits from easy removal of catalyst materials and possible use of high temperatures, it suffers from certain drawbacks, some of which include lack of chemo or regioselectivity, low metal dispersion in the medium resulting in considerably lower catalytic activity in terms of turnover frequencies of the catalyst; and. lack of the understanding of the mechanistic aspects that are indispensable for parameter improvements. Homogeneous catalysts, by the virtue of ligands, are very efficient and selective. Also, being molecular catalysts, a very high dispersion is achieved, resulting in a much higher catalytic activity compared to their heterogeneous counterparts. However, the homogeneous catalysts suffer from the difficulty of recovery of the catalyst from the reaction media. Green catalysis aspects now obviously require that environmentally friendly (for instance phosphine-free) catalysts be designed for easy removal from the reaction media and recycling many times with very high efficiency.

These demanding conditions bring a new research impetus for catalyst development at the interface between homogeneous and heterogeneous catalysis, gathering the sophisticated fulfilment of all the constraints that were far from being fully taken into account by the pioneers and even the specialists in each catalytic discipline in the former decades. Yet the considerable knowledge gained from the past research in homogeneous, heterogeneous, supported and biphasic catalysis, including also studies in non-classical conditions (solvent-free, aqueous, use of ionic liquids, fluorine chemistry, microemulsions, micelles, reverse micelles, vesicles, surfactants, aerogels, polymers or dendrimers), should now help establish the desired optimized catalytic systems.

In this context, the use of transition - metal nanoparticles (NPs) in catalysis[2] is crucial as they mimic metal surface activation and catalysis at the nanoscale and thereby bring selectivity and efficiency to heterogeneous catalysis. Transition-metal NPs are clusters containing from a few tens to several thousand metal atoms, stabilized by ligands, surfactants, polymers or dendrimers protecting their surfaces. Their sizes vary between the order of one nanometer to several tens or hundreds of nanometers, but the most active in catalysis are only a few nanometers in diameter, i.e. they contain a few tens to a few hundred atoms only.[3]

Transition metal nanoparticles have been tested successfully as catalysts in several important catalytic reactions in the recent history, including the Rh-nanocluster catalyzed hydroformylation of 1-decene,[4] carbonylation of methanol to acetic acid using Rh nanoparticles,[5] and C-C coupling reactions catalyzed by Ru nanoparticles,[6] and these catalysts have shown great promise in terms of catalytic activity. However, leaching of metal in the reaction medium is a serious concern. Immobilization of nanoparticle catalysts has been attempted by several means. Mesoporous structures would seem to be ideal for forming a scaffold in which three-dimensional dispersions of metal nanoparticles could be supported. For these reasons, the application of metal nanoparticles deposited on such porous materials has increased recently.[7] Amine groups are known to bind very well with Pd nanoparticles. This property has been utilized by Mandal et al.[8] for the immobilization of palladium on an amine-functionalized zeolite. The authors have investigated the catalytic activity of these nano-particles in the C-C coupling reactions with remarkable enhancement in the turnover frequencies (TOF). In this chapter, the efficacy of such palladium nanoparticles immobilized on amine-functionalized zeolites has been evaluated for the oxidative carbonylation of amines for the selective synthesis of disubstituted ureas. The structural, morphological and chemical properties of the catalyst are studied in detail by various characterization tools like UV spectroscopy, powder XRD, TGA, TEM, XPS etc.

4.2. EXPERIMENTAL

4.2.1. Materials

3-aminopropyltrimethoxysilane (APTS), palladium nitrate dihydrate [$Pd(NO_3)_2$]. $2H_2O$, sodium borohydride ($NaBH_4$), sodium iodide were obtained from Aldrich Chemicals and used as received. Aniline, substituted anilines and aliphatic amines, ethyl iodide, and the solvents, all GR grade, were purchased from Merck Chemicals India Ltd. 5% Pd/C was purchased from Arora Matthey, India. Solvents were freshly distilled before use. Amines were freshly distilled or recrystallized prior to use. Carbon monoxide (99.99%) and oxygen (99.90%) were purchased from Matheson Gas Company, U.S.A. Water used for the synthesis of water-soluble complexes and for oxidative carbonylation reactions was double distilled through a glass water-distillation unit and deionised using a Mili-Q membrane filter.

4.2.2. SYNTHESIS OF THE IMMOBILIZED PALLADIUM NANOPARTICLE CATALYST

The synthesis of supported Pd nanoparticles was carried out in a two-step procedure-

(i) Synthesis of Na-Y zeolite and functionalization of the zeolite surface by amine groups (APTS-Y) and,

(ii) Synthesis of palladium nanoparticles in aqueous medium and immobilization of the same on the surface of the amine-functionalized Na-Y zeolite.

(i) Synthesis and functionalization of Na-Y zeolite by APTS grafting (APTS-Y)

The zeolite Na-Y has been synthesized according to the procedure described by Mukhopadhyay et al.[9] In a typical synthesis, seed crystals were made separately by stirring the aqueous solution containing Na_2SiO_3 (95 mmol, 28% SiO_2 and 8.4% Na_2O), $NaAlO_2$ (9.76 mmol, 43% Al_2O_3 and 39% Na_2O) and NaOH (70 mmol) for 1 h and allowed to stand for 18 h. The seed solution followed by $NaAlO_2$ (34.2 mmol), NaOH (92.5 mmol), $Al_2(SO_4)_3.16H_2O$ (6.02 mmol) and 35 ml of water were added into an aqueous solution of Na_2SiO_3 (355 mmol) under constant stirring conditions for 2 h. The final molar gel composition of the zeolite Na-Y was 25.0 SiO_2/4.9 Al_2O_3/27.0 Na_2O/552 H_2O. The gel was aged for 12 h at 373 K, cooled to ambient temperature, filtered and washed several times with distilled water.

For amine functionalization of Na-Y zeolite, 5.73 mmol APTS was added slowly into a slurry containing 1 gm calcined Na-Y in anhydrous dichloromethane at room temperature and atmospheric pressure. The slurry was allowed to stir for 16 h. The white solid was filtered and washed repeatedly with dichloromethane. The white amine functionalized cake (APTS-Y) was dried in vacuum and used for further application.

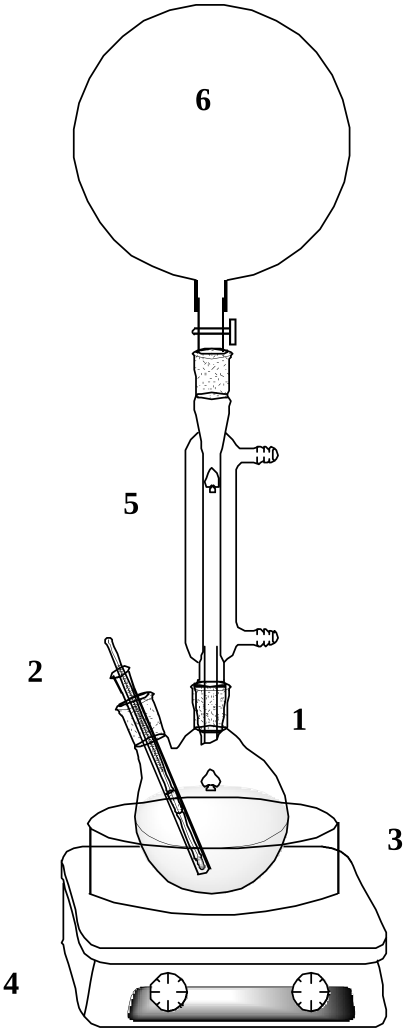
(ii) Synthesis of palladium nanoparticles and immobilization on the surface of the amine-functionalized Na-Y zeolite

In a typical experiment, 100 ml of a 10^{-4} M concentrated aqueous solution of palladium nitrate ($Pd(NO_3)_2.2H_2O$) was reduced by 0.01 gm of sodium borohydride ($NaBH_4$) at room temperature to yield a blackish-brown colored solution, which indicates the formation of Pd nanoparticles. This colloidal palladium solution was used for immobilization on amine-functionalized Na-Y zeolite. 0.02 g of APTS-Y was added into the Pd colloidal solution and stirred for 12 h at room temperature. The solid was allowed to settle, filtered and washed several times with hot water to remove nitrate ions. The mass loading of the zeolite particles by palladium nanoparticles was estimated by inductively coupled plasma (ICP) measurements to be 3.6 wt % for palladium. The immobilized palladium nanoparticle catalysts thus formed is henceforth termed as **[Pd]-APTS-Y** catalyst.

4.2.3. TYPICAL EXPERIMENTAL PROCEDURE FOR OXIDATIVE CARBONYLATION OF AMINES

4.2.3.1. Experimental set-up and typical oxidative carbonylation procedure

The reactions were carried out in a two-necked round-bottomed flask of 10 ml capacity. The set-up used for conducting the experiments is shown in Figure 4.1. In a typical experiment, weighed amounts of amine, solvent, sodium iodide and the catalyst were charged into the dried flask along with a magnetic needle. The stirring was done using a magnetic stirrer with digital indicator. A reflux condenser was fitted on the flask, on which a two-way glass cock along with a bladder filled with a mixture of CO and O_2 ($CO:O_2 = 8:1$). The contents were flushed few times with nitrogen followed by the $CO+O_2$ mixture. The reaction was started by dipping the flask into a preheated oil bath maintained at the desired temperature, and by starting the stirring at the desired agitation speed. The temperature in the oil bath was carefully maintained constant with the help of a heating coil connected through a rheostat. The reaction was continued for the specified period of time. After the reaction, the flask and its contents were cooled to room temperature and the reaction mixture was filtered through a Whatman filter paper no. 1, and analyzed by G. C. and H.P.L.C. for the quantification of aniline and DPU respectively. The gas mixture in the bladder was vented off in a hood kept under continuous vacuum.



1- Round-bottomed reaction flask; 2- Thermometer through thermowell; 3- Oil bath with coil connected to a rheostat; 4- Magnetic stirrer with digital RPM control; 5- double-walled condenser; 6- Bladder containing CO+O_2 mixture

Figure 4.1. Experimental set-up for oxidative carbonylation of amines using [Pd]-APTS-Y catalyst

4.2.3.2. Procedure for catalyst recycle experiments

The procedure for evaluating the reusability of the [Pd]-APTS-Y catalyst was similar to that in section 4.2.3.1 except for a few changes, which are explained as follows-

(i) The iodide promoter NaI was not charged as a solid compound in these experiments. A NaI stock solution was prepared in DMF and aliquots were taken for each recycle, making up the remaining volume with DMF. Aniline was freshly charged in all reactions.

(ii) After each experiment, the reaction mixture was allowed to settle for 2 hours, the supernatant reaction mixture was siphoned off, and the catalyst at the bottom was washed several times with methanol, followed by diethyl ether, and vacuum dried, to which the fresh reaction components, i. e. aniline, NaI aliquot in DMF and make-up DMF were charged. Each reaction was taken for 4 hours.

4.2.4. ANALYTICAL METHODS

4.2.4.1. CHRACTERIZATION OF CATALYSTS AND CATALYST PRECURSORS

UV-visible (UV-vis) spectroscopic studies were performed on a Shimadzu dual beam spectrometer (model UV- 1601 PC) operated at a resolution of 1 nm. UV-vis spectra of the palladium nanoparticles immobilized on APTS modified Na-Y zeolite (**[Pd]-APTS-Y**) were recorded after sonication of the sample in water.

TGA profiles of carefully weighed quantities of powders of APTS modified Na-Y zeolite and **[Pd]-APTS-Y** were recorded on a Seiko Instruments model TG/DTA 32 instrument at a heating rate of 10^{o}C/min.

Transmission electron microscopy (TEM) measurements were performed on a JEOL model 1200EX instrument operated at an accelerating voltage of 120 kV. Samples of **APTS-Y** and **[Pd]-APTS-Y** before and after different reactions were made on carbon-coated grids after dispersing the powders in isopropyl alcohol for transmission electron microscopy (TEM) measurements. These films were allowed to dry for 1 minute following which the extra solution was removed using a blotting paper.

Powder X-ray diffraction (XRD) measurements were performed on a Philips PW 1830 instrument consisting of a rotating anode generator with a copper target (Cu Kα radiation, λ=1.5418Å) operating at 40 kV and a current of 30 mA. The XRD patterns of the parent Na-Y zeolite, **APTS-Y** and **[Pd]-APTS-Y** samples were recorded in the range 5º - 85º at a scan rate of 1º per minute.

X-ray Photoemission Spectroscopy (XPS) measurements of **[Pd]-APTS-Y** samples were carried out on a VG MicroTech ESCA 3000 instrument at a pressure $<1x10^{-9}$ Torr. The general scan and the C1s and Pd 3d core level spectra were recorded with un-monochromatized Mg Kα radiation (photon energy, *h*ν = 1253.6 eV) at pass energy of 50 eV and electron takes off angle (angle between electron emission direction and surface plane) of 60º. The overall resolution was 1 eV for the XPS measurements. The core level spectra were background corrected using the Shirley algorithm28 and the chemically distinct species were resolved using a non-linear least squares fitting procedure. The core level binding energies (BE) were aligned with the adventitious carbon binding energy of 285 eV.

The metal content of the catalysts was determined using a Perkin Elmer Plasma 1000 ICP-OES spectrometer. The liquid and catalyst samples after the oxidative carbonylation experiments were also analyzed for metal content to examine the extent of leaching of the metals during reactions.

IR spectra of the products were recorded using Bio-rad FTS 175C machine in transmission mode using KBr pellets. The elemental analyses were done on a CHNS-O EA 1108, Elemental analyzer of Carlo-Erba Insrtuments, Italy. Pd metal analysis was done using AAS.

4.2.4.2. CHARACTERIZATION OF REACTANTS AND PRODUCTS

The liquid samples were analyzed for amine quantification by gas chromatographic analysis of the organic phase at the end of the reaction. The analysis was done on a Hewlett Packard 6890 Series Gas Chromatograph using an HP-5 (Crosslinked 5% phenyl methyl siloxane stationary phase) column and FID, and controlled by HP Chemstation Software. The separation and quantification of *N,N'*-diphenylurea (DPU) was done on HPLC, using a Waters RP-8 column, UV detector and acetonitrile-water as a mobile phase. All the products reported in this work were isolated by column chromatography and characterized by NMR, FTIR and elemental analysis. The quantification of all the components was done using calibration curves prepared based on synthetic standards The conversion, selectivity, yields and turn over numbers (TON) were calculated as follows

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

$$\%\text{Selectivity} = \frac{(2 \times \text{moles of DPU formed})}{\text{Converted moles of aniline}} \times 100$$

$$\%\text{Yield} = \frac{\%\ \text{Conversion} \times \%\ \text{Selectivity}}{100}$$

$$\text{TON} = \frac{\text{moles of DPU formed}}{\text{moles of catalyst charged}}$$

$$\text{TOF} = \frac{\text{moles of DPU formed}}{\text{moles of catalyst charged} \times \text{time in hours}},\ \text{h}^{-1}$$

The identification of products isolated from the oxycarbonylation experiments was done using elemental analysis, IR and NMR. The elemental analyses were done on a CHNS-O EA 1108, Elemental analyzer of Carlo-Erba Insrtuments, Italy.

4.3. RESULTS AND DISCUSSION

The transition metal nanoparticles immobilized on functionalized Na-Y zeolite have been reported as active catalysts for hydrogenation and Heck reactions.[8] Also, their advantage over supported catalysts in terms of activity and reusability has been established. The stabilization of Pd nano-particles has been achieved in the present catalyst system by binding the nanoparticles strongly using amine groups.

For a particular catalytic reaction, not only the activity of the heterogeneous catalyst, but also its reusability and the processing required to regenerate the catalyst in its original state in terms of dispersion, morphology and oxidation state are important aspects. In this regard, it was important to characterize the nano-catalyst before and after its application for a particular catalytic reaction, i.e. oxidative carbonylation reaction in this case. Accordingly, the synthesis, characterization and performance of Pd nanocatalyst **[Pd]-APTS-Y** for fresh and recycle experiments is presented in this part.

4.3.1. CHARACTERIZATION

Figure 4.2 shows UV-vis spectra recorded for **[Pd]-APTS-Y** after dispersion in water. The broad absorption band from **[Pd]-APTS-Y** can be clearly seen at approximately 258 nm, which arises due to excitation of surface plasmon vibrations in palladium nanoparticles.[10] This clearly indicates the formation of nanosized palladium particles on the amine-functionalized zeolite.

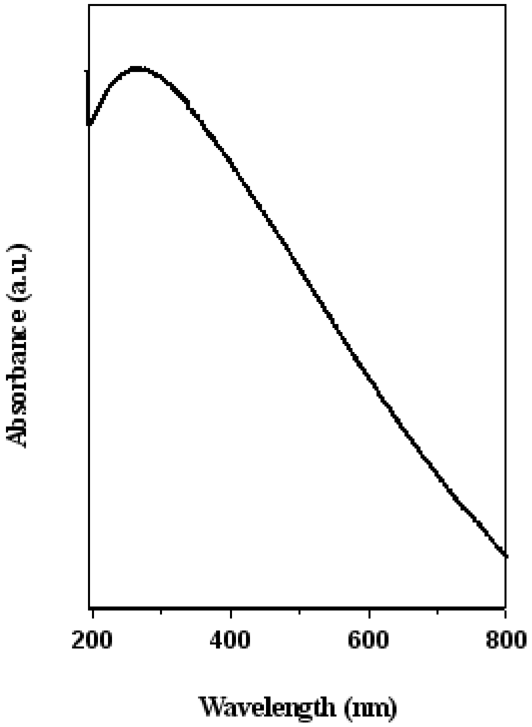


Figure 4.2. UV-vis spectra recorded for **[Pd]-APTS-Y** after dispersion in water

The thermogravimetric analyses of immobilized transition metal nanoparticles are very important, especially if functionalized mesoporous materials like the amine functionalized NaY zeolite is used as the support. These analyses give important information regarding the strength (thermal sustainability) and nature of the interaction between the amine and the palladium nanoparticle surface. Figure 4.3 shows a plot of the TGA data recorded from a carefully weighed quantity of the amine-functionalized Na-Y zeolite powder (curve 1), after immobilization of palladium nanoparticles on the amine-functionalized zeolite (curve 2).

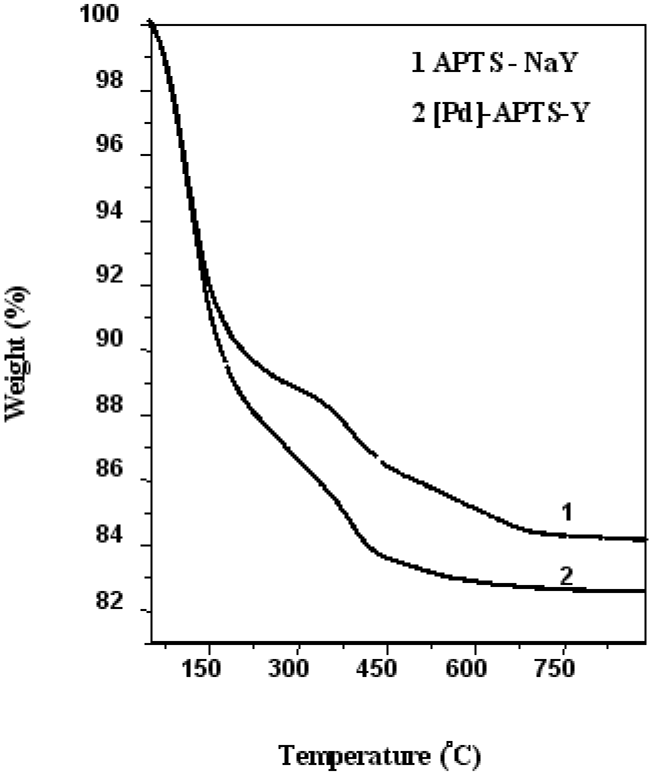


Figure 4.3. TGA data recorded for APTS functionalized Na-Y zeolite powder (curve 1), and for **[Pd]-APTS-Y** (curve 2).

Two monotonic weight losses of 7% and 8% are observed in the temperature interval of 50-142°C and 145-725°C respectively for APTS modified zeolite. The weight loss in the temperature interval of 50-142°C is attributed to desorption of water molecules present in the amine functionalized Na-Y zeolite powder, while the weight loss in the temperature interval 145-725°C is due to desorption of surface-bound APTS molecules from the surface of the Na-Y zeolite (curve 1). A careful comparison between the curves 1 and 2 shows that the nature of the two curves is similar; however, the percentage (%) of weight loss is more in case of **[Pd]-APTS-Y** (curve 2) compared to amine functionalized zeolite (curve 1). In curve 2, the weight loss is 7% upto 142°C due to desorption of water molecules present in the zeolites, whereas in the temperature interval of 145-725°C the weight loss is approximately 10% for **[Pd]-APTS-Y**. In the temperature interval of 145-725°C the 2% higher weight loss for **[Pd]-APTS-Y** was observed compared the weight loss in the same range for the APTS modified zeolite. When desorption of surface bound APTS molecules occurs from the surface of Na-Y zeolites, the palladium atoms are also desorbed with the APTS molecules and a higher percentage of weight loss is attributed to desorption of palladium nanoparticles bound on the Na-Y zeolite surface through binding with the amine group of the APTS molecules. From the TGA data, it is clearly seen that strength of the interaction between amine group of the APTS molecule and palladium nanoparticles are strong enough, at least up to 145°C (desorption of surface bound APTS molecules starts at about 145°C). Therefore **[Pd]-APTS-Y** catalyst is stable in our experimental conditions (maximum 80°C). From the above discussion it can be concluded the platinum and palladium nanoparticles are bound on the zeolite through binding with the amine group of the APTS molecules only.

Figure 4.4A shows the XRD patterns recorded in the 2θ range 5°-30° from the Na-Y zeolite before amine functionalization (curve 1), after amine-functionalization of the Na-Y zeolite powder (curve 2), after immobilization of palladium nanoparticles on the amine-functionalized zeolite (curve 3 for **[Pd]-APTS-Y**). After amine functionalization and binding of palladium nanoparticles to the underlying zeolite template, there are no significant changes in the peak positions and peak width of the Bragg reflections arising from the zeolite. This indicates that if amorphisation occurs during the modification of the surface of Na-Y zeolite with APTS molecules and immobilization of Pd nanoparticles, the percentage of amorphisation is extremely small. Kaleta et al.[11] have reported that encapsulation of hetero polyanions in channels of Si-MCM-41 lead to a loss in crystalinity of the mesoporous template. The XRD results in Figure 4.4A thus show that the palladium nanoparticles are bound to the surface of the zeolite particles and are not trapped within the pores of the zeolite.

Figure 4.4 B shows the XRD patterns recorded in the 2θ range 35º-85º for **[Pd]-APTS-Y**. The positions of the Bragg reflections correspond very well with those reported in the literature for face centered cubic (fcc) Pd.[12] The broadening of the Bragg reflections from palladium bound to the amine-functionalized Na-Y zeolite template clearly indicates that the particles are nanocrystalline.

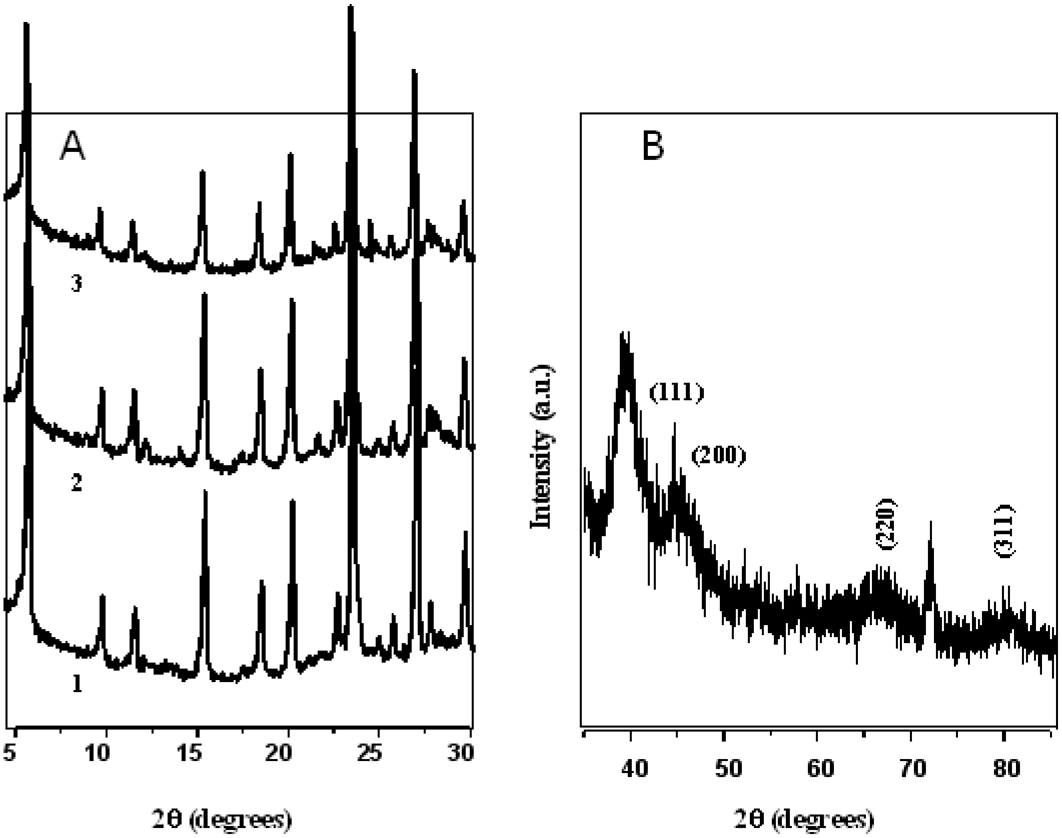


Figure 4.4. (A) XRD patterns recorded from the samples of Na-Y zeolite (curve 1), amine-functionalized Na-Y zeolite (curve 2) and **[Pd]-APTS-Y** (curve 3) in the 2θ range 5°-30° (B) XRD pattern recorded from the samples **[Pd]-APTS-Y** in the 2θ range 35°-85°.

The nano-size of the immobilized Pd is substantiated by TEM measurements. To examine the immobilization of palladium nanoparticles on the amine-functionalized Na-Y zeolite, TEM measurements of the samples were carried out at different stages. Figure 4.5 shows representative TEM micrographs of the as-prepared amine-functionalized zeolite particles (A), after immobilization of palladium nanoparticles on the amine-functionalized Na-Y zeolite (unused **[Pd]-APTS-Y**) (B); and the [Pd]-APTS-Y catalyst recovered at the end of the first (C) and the fifth (D) recycle. In Figure 4.4A, it is clearly seen that the surface of the amine-functionalized Na-Y zeolite is clean and smooth, whereas after immobilization of Pd nanoparticles on the zeolite, the surface is covered by the Pd nanoparticles (4.4B). Figure 4.5B also clearly indicates that the Pd nanoparticles are bound to the zeolite surface at fairly high concentration.

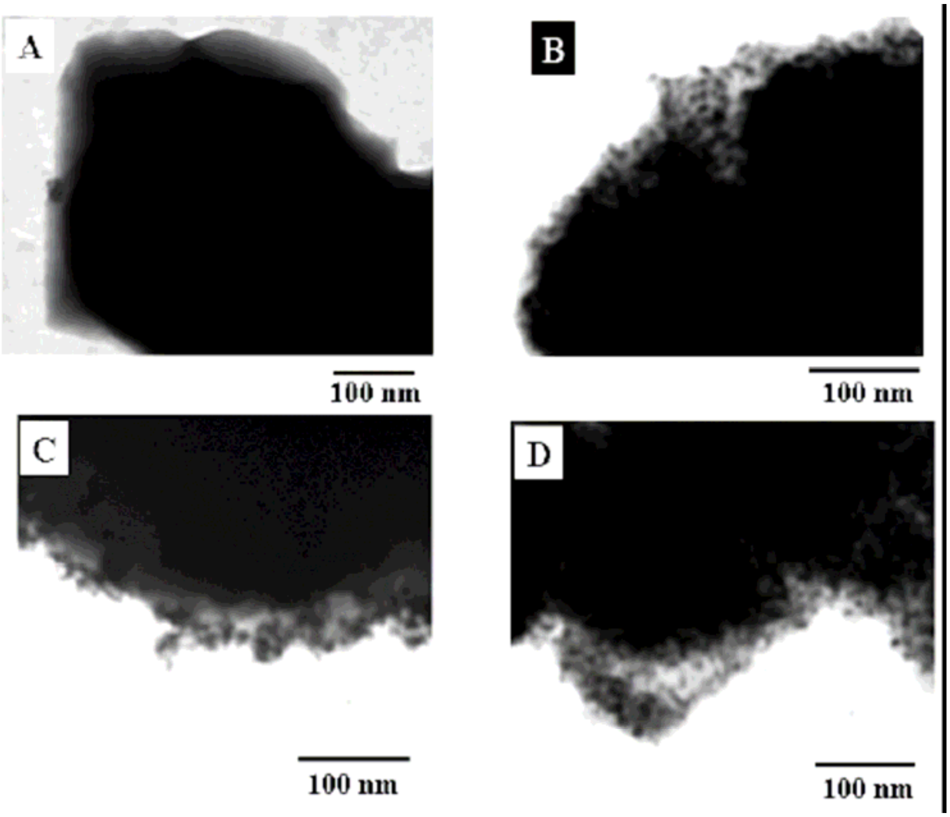
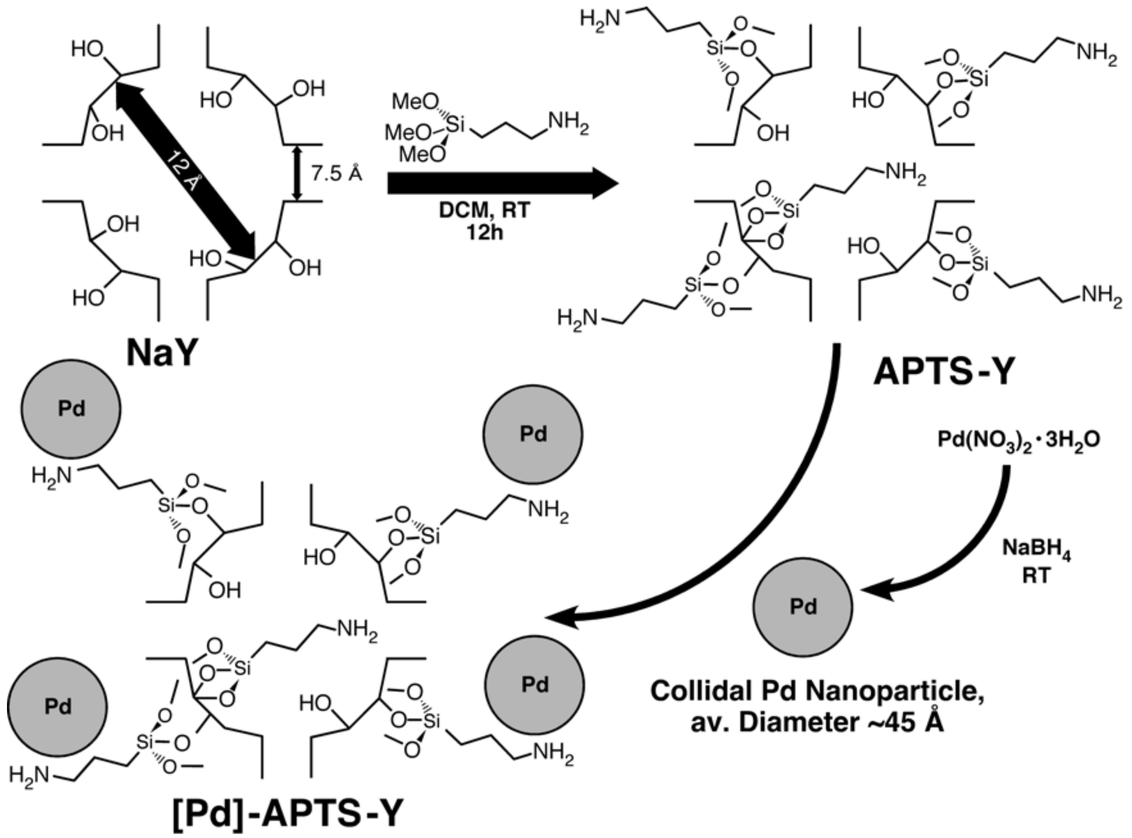


Figure 4.5 (A) - (D): Representative TEM images of amine-functionalized zeolite, **[Pd]-APTS-Y** before reaction and **[Pd]-APTS-Y** after reaction respectively on a carbon-coated TEM grid.

TEM images of the fresh and used catalysts indeed showed that the palladium nanoparticles supported on amine-functionalized zeolite remain unchanged at the end of the reactions. XPS analyses support these observations.

Additionally, the immobilization of the nano-particles is only on the exterior of the zeolite. The XRD, TGA and TEM measurements support this statement. The details of the particle size of the zeolite and that of the palladium nanoparticle also support this hypothesis. This can be explained as follows. Zeolite Y has a large supercage of 12 Å connected to four channels of 7.4 Å each. If it is assumed that APTS molecule can bind to the silanol groups inside the channels, the tethered moiety ($(\text{-O})_3SiCH_2CH_2CH_2NH_2$) will have a length of 6.065 Å (using Mercury 1.1.2 software, Cambridge Crystallographic Data Center). However, a bare palladium nanoparticle possesses an average particle size in the range of 4-5 nm, which are far bigger than the channels of the zeolite Y. Therefore, though the amine functionalities of APTS molecules are present inside the supercages, those are not accessible to the bare Pd nanoparticles. From this discussion, it is understood that the Pd nanoparticles are bound to the surface of the zeolite and not inside the cages (Scheme 4.1).



Scheme 4.1. Schematic representation of selective outer-cage synthesis of **[Pd]-APTS-Y** nanocomposites

A chemical analysis of the **[Pd]-APTS-Y** samples was also performed using XPS and the metal core level spectra obtained (Pd 3d) are shown in Figure 4.6. Curve A in the figure is for the fresh, unused [Pd]-APTS-Y; while curve B is for the catalyst recovered from the recycle study, washed with methanol, followed by ether, and then dried. The general scan spectra of the above samples showed the presence of C 1s, N 1s and Pd 3d core levels with no evidence of impurities. Also, the recovered and fresh catalysts do not show considerable shift in the B.E. values for Pd 3d levels, indicating that the catalyst is recovered in its original chemical form after the oxidative carbonylation reaction. In Figure 4.6, the Pd 3d level (curve A) shows the presence of two chemically distinct spin-orbit pairs centered at 335.4 (curve 1) and 340.6 eV (curve 2) BE. As in the case of Pd nanoparticles, the low BE component corresponds to fully reduced Pd nanoparticles while the high BE peak is due to unreduced Pd^{2+} ions on the surface of the metal core.[13] Therefore, Pd(II) species are present in minor quantities along with the Pd(0) species in the **[Pd]-APTS-Y** nanocomposites.

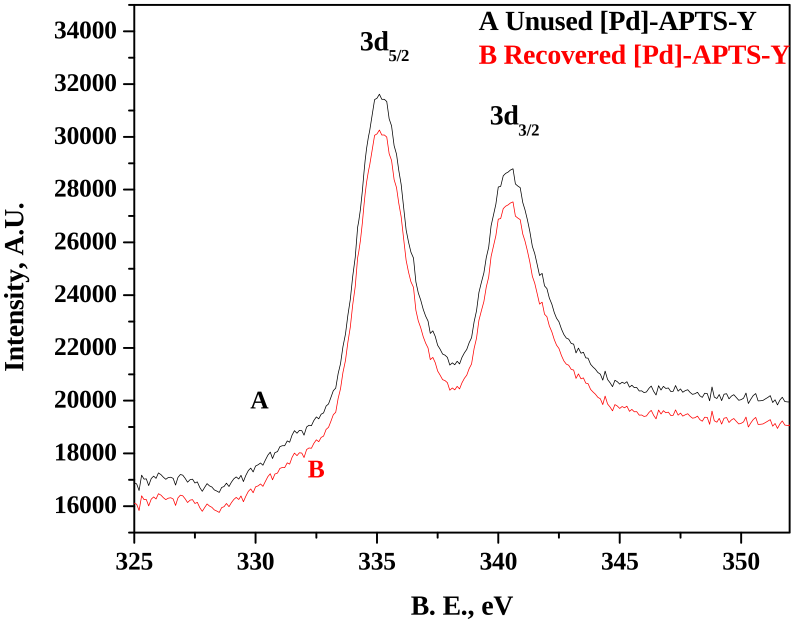


Figure 4.6. Pd 3d core level spectra recorded for (A) the fresh (unused) **[Pd]-APTS-Y** and (B) **[Pd]-APTS-Y** recovered after oxidative carbonylation reaction.

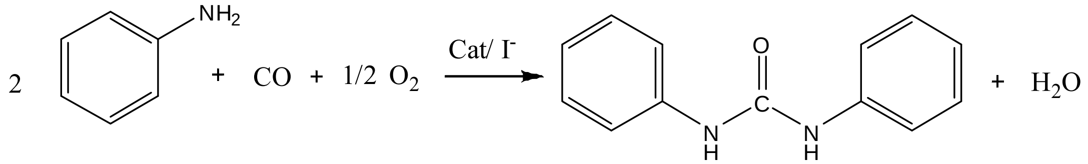
4.3.2. Oxidative carbonylation Using [Pd]-APTS-Y catalyst

4.3.2.1. Model Reaction and Concentration-time profile

Oxidative carbonylation reactions using the immobilized Pd nanoparticle catalysts, i.e. [Pd]-APTS-Y was carried out with aniline as the model substrate, and NaI as the iodide promoter; with DMF as the solvent. The concentration of aniline taken for the reaction was such that the *N,N'*-diphenyl urea (DPU) formed from the aniline should have complete solubility in the solvent.

The oxidative carbonylation of amines is known to yield several byproducts like formamides, azo compounds, etc. depending on the catalyst system used and reaction conditions used. Therefore, it was essential to establish component balance for the reaction for various conversion levels of aniline. A series of experiments were carried out for different durations, and the reaction conditions and parameters were maintained identical in all the experiments except the reaction time. The component balance for all these experiments were checked by analyzing the amount of aniline consumed in all the samples and the amount of DPU formed in the respective samples.

The stoichiometry of the reaction for oxidative carbonylation of aniline is shown in Scheme 4.2. For every 2 moles of aniline consumed, one mole of DPU is formed. The component balance for all the C-T profile experiments was evaluated considering this stoichiometry.



Scheme 4.2. Oxidative carbonylation of aniline with [Pd]-APTS-Y catalyst

It was found that the component balance was satisfactory in all the cases. A plot of reaction time versus the consumption of aniline and formation of DPU is shown in Figure 4.7. The selectivity of DPU based on the aniline consumed was found to be more than 99% in all the experiments.

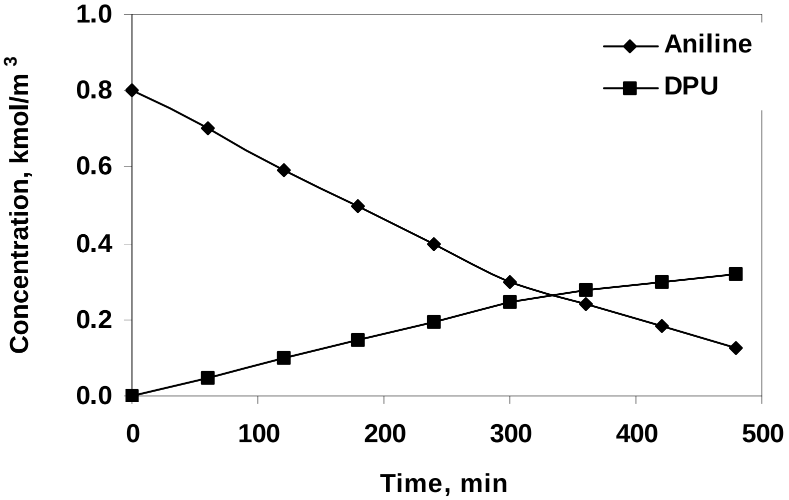


Figure 4.7. Concentration-time profile for aniline oxidative carbonylation with Pd-APTS-Y catalyst

Reaction conditions: Aniline 0.80 kmol/m^3; [Pd]-APTS-Y 1.854 kg/m^3; NaI 0.001237 kmol/m^3; Temp, 333K; CO:O$_2$ 8:1; Agitation 16.6 Hz; Solvent, DMF, 5.6×10^{-6} m^3

4.3.2.2. Effect of agitation speed

[Pd]-APTS-Y catalysed oxidative carbonylation of amines is a G-L-S (Gas-Liquid-Solid), it was essential to confirm that there were no mass transfer limitations in the reaction; so that the effect of other reaction conditions and parameters could be properly evaluated. The agitation speed of the magnetic stirrer could be adjusted with the help of the digital control. The effect of agitation speed was studied in the range of 10 to 25 Hz, under standard conditions. All the reactions were carried out up to partial conversions of aniline, for a fixed amount of time, i.e. 60 minutes. It was observed that there was no effect of agitation speed in the range studied (Figure 4.8). Further studies were, therefore carried out at 16.66 Hz.

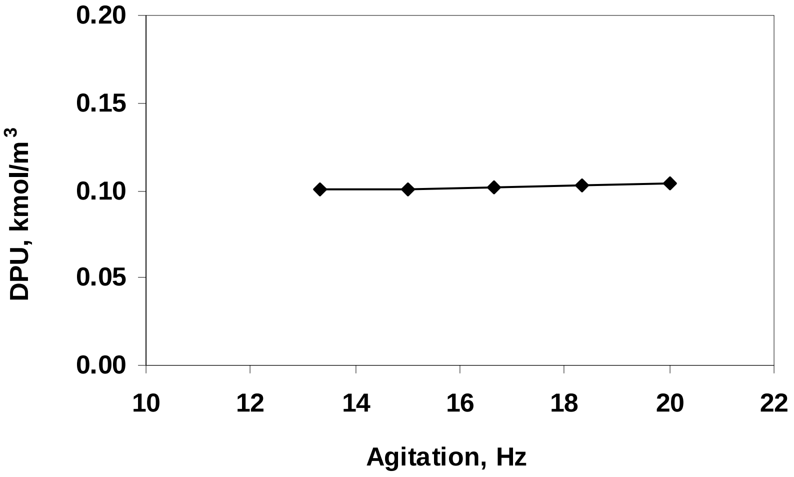


Figure 4.8. Effect of agitation speed

Reaction conditions: Aniline 0.7867 kmol/m^3; [Pd]-APTS-Y 1.854 kg/m^3; NaI 0.001237 kmol/m^3; Temp, 333 K; CO:O$_2$ 8:1; Solvent, DMF, 5.6×10^{-6} m^3, Time, 120 min

4.3.2.3. Effect of temperature

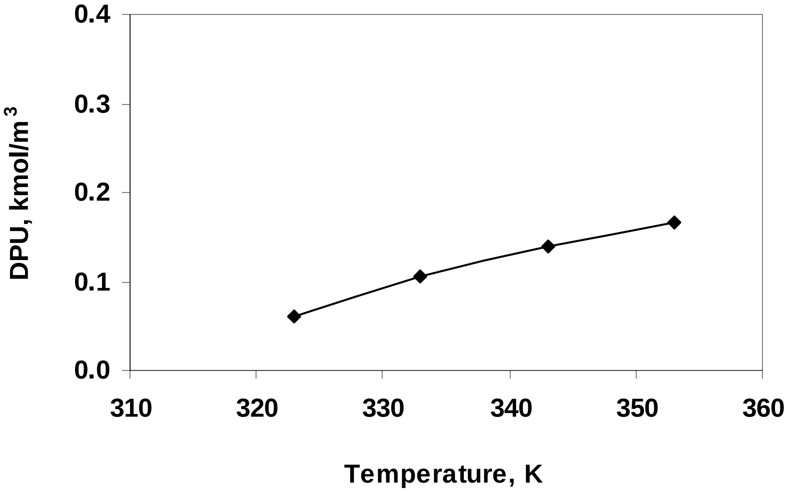


Figure 4.9. Effect of temperature on [Pd]-APTS-Y catalyzed amine oxycarbonylation

Reaction conditions: Aniline 0.824 kmol/m^3; Pd-APTS-Y 1.854 kg/m^3; NaI 0.001237 kmol/m^3; CO:O$_2$ 8:1; Agitation 16.6 Hz; Solvent, DMF, 5.6×10^{-6} m^3, Time, 120 min.

The effect of reaction temperature was studied in the range of 323 to 353 K, and the results can be seen in Figure 4.9. The formation of the product at different temperatures was monitored, keeping the other reaction conditions and parameters same. The formation of diphenyl urea was found to increase linearly with temperature, up to 353 K. The activation energy was calculated from the Arrhenius plot (shown in Figure 4.10) as 29.7 kJ/mol for oxidative carbonylation of aniline with [Pd]-APTS-Y.

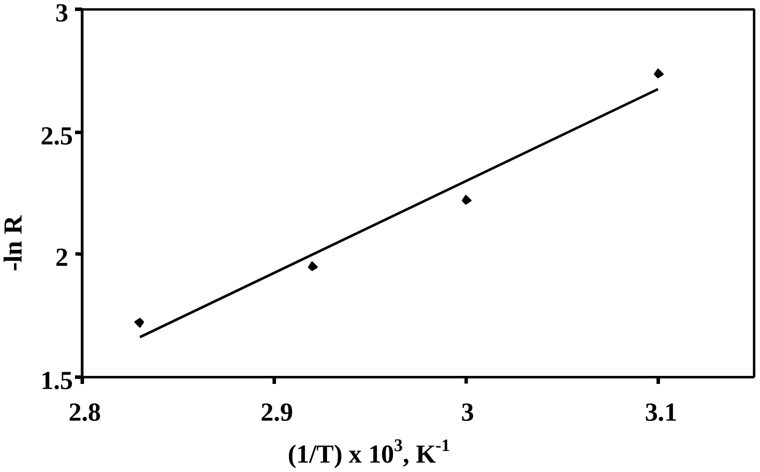


Figure 4.10. Temperature dependence of [Pd]-APTS-Y catalyzed aniline oxycarbonylation

4.3.2.4. Effect of solvents

Oxidative carbonylation of aniline in the presence of [Pd]-APTS-Y catalyst and NaI promoter was studied in different solvent systems and the results are shown in Figure 4.11. The selectivity for DPU was almost constant (~98%) for all the solvents whereas conversion (and consequently the yield also) varied depending upon the solvent used. A decrease in conversion was directly related to the polarity of the solvents used. The Burdick & Jackson solvents are arranged in order of increasing polarity index, a relative measure of the degree of interaction of the solvent with various polar test solutes. According to this report, the solvents screened in this study can be arranged in a decreasing order of their polarity indices as follows- DMF (6.4), methanol (5.1), ethanol

(5.2), methyl ethyl ketone (4.7) and THF (4.0) Figure 4.11 shows the activity of the catalyst which follows a pattern of decreasing activity with decreasing polarity index. This observation shows that the active catalytic species or complexes formed during the catalytic cycle are probably having some definite polarity, and the stabilization of these species is favored by the polarity of the reaction medium.[14] Since the best catalytic activity with [Pd]-APTS-Y was obtained using DMF as the solvent, it was used as a solvent for further studies.

It is important to note here that the selectivity to DPU remained unchanged and the *N*-phenyl carbamates were not identified as products with solvents like methanol or ethanol. This is attributed to the lower temperature (333 K) in our present study. Kanagasabapathy et al.[15] have studied the effect of temperature on oxidative carbonylation using alcohols as solvents. The authors have reported that the non-catalytic reaction between the substituted urea and alcohols to yield the corresponding carbamates are significant only at or above 378 K. The results obtained in the solvent screening study are in agreement with these findings.

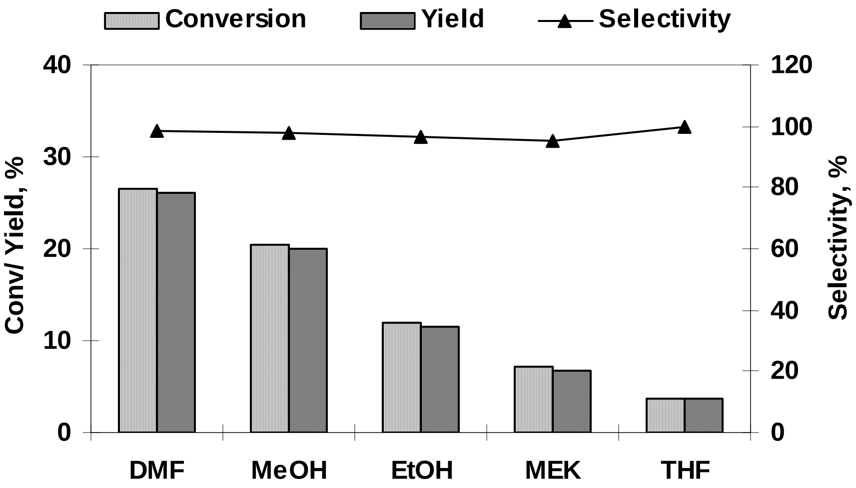


Figure 4.11. Effect of solvents on [Pd]-APTS-Y catalyzed oxidative carbonylation of aniline.

Reaction conditions: Aniline 0.824 kmol/m^3; [Pd]-APTS-Y 1.854 kg/m^3; NaI 0.001237 kmol/m^3; CO:O_2 8:1; Agitation 16.6 Hz; Solvent, 5.6×10^{-6} m^3, Time, 120 min

4.3.2.5. Effect of iodide concentration

The effect of iodide concentration on the reaction was studied in the NaI concentration range of 0.0033 to 0.0333 mmol; or at the various Pd:iodide molar ratios between 1 to 6. The effect is shown in Figures 4.12 A and B.

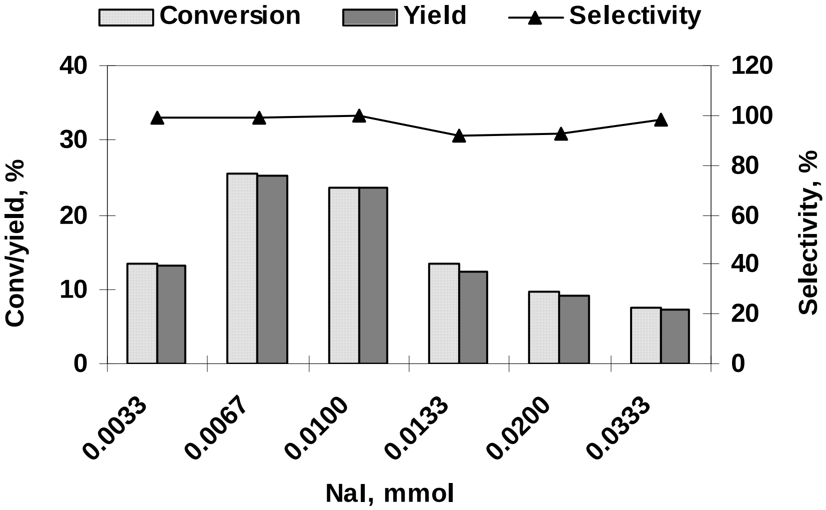


Figure 4.12 (a). Effect of iodide concentration on oxidative carbonylation

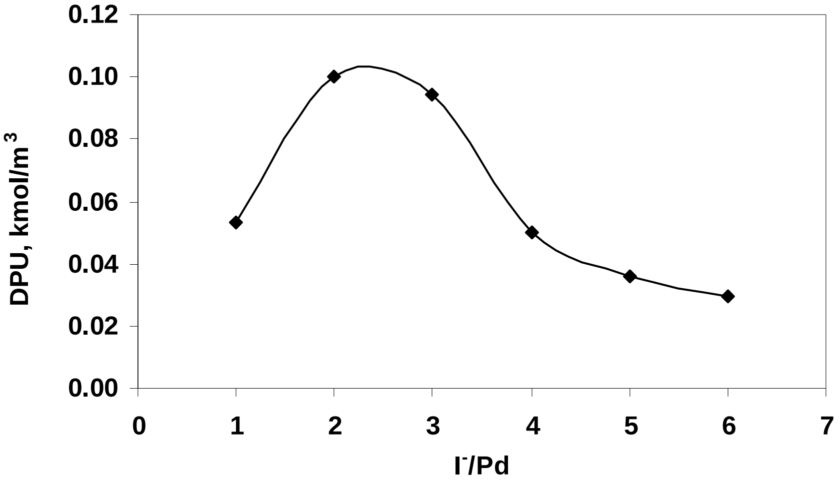


Figure 4.12 (b). Effect of iodide:Pd ratio on the rate of formation of DPU

Reaction conditions: Aniline, ~0.80 kmol/m^3; [Pd]-APTS-Y 1.854 kg/m^3; CO:O$_2$, 8:1 (50 psig); Agitation 16.6 Hz; Solvent, DMF, 5.6×10^{-6} m^3, Time, 120 min

It can be observed that lower or higher concentrations of iodide do not affect the selectivity of the reaction towards the disubstituted urea, but the rate of reaction is altered. The appearance of a maxima in Figure 4.12B indicates inhibitory effect of iodide on the desired reaction. The optimum iodide:Pd is found to be ~2, which is more than the value observed earlier by Gupte et al.[16]

4.3.2.6. Catalyst recycle experiments

In order to check the stability of the immobilized Pd nanoparticles under the oxidative carbonylation reaction conditions, the catalyst was recycled five times. It may be noted that NaI was replenished in the recycle experiment. It was observed that conversion of aniline and selectivity of DPU remained unchanged during all the runs. The results of recycle runs are shown in Figure 4.13. The ICP-OES analysis of the liquid phase samples after each recycle runs showed that there was no traceable Pd metal present in the supernatant liquid. This proves the stability of [Pd]-APTS-Y as a catalyst.

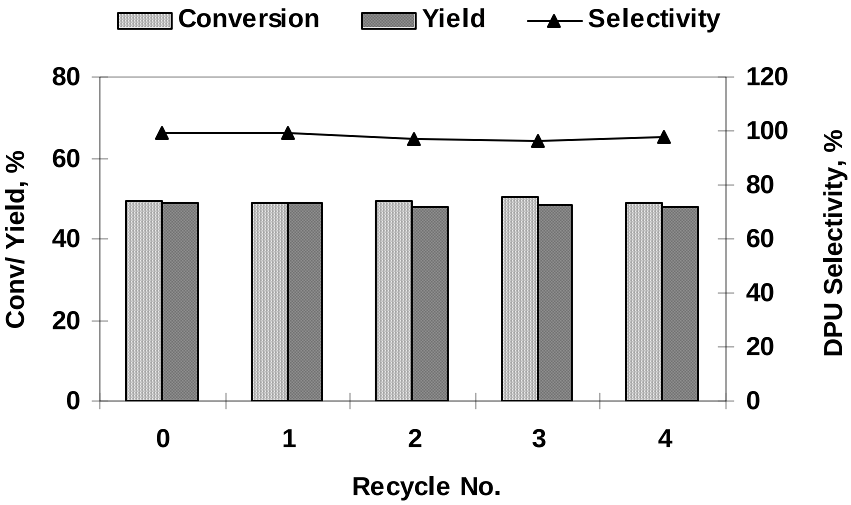


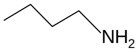
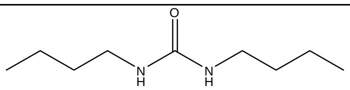
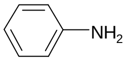
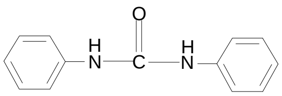
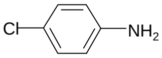
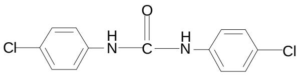
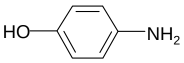
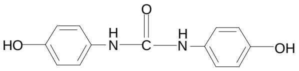
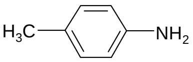
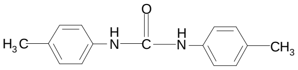
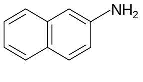
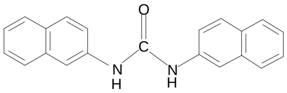
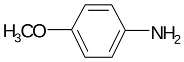
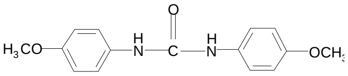
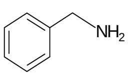
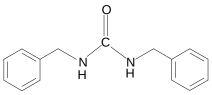
Figure 4.13. Recycle studies of [Pd]-APTS-Y catalyst for oxidative carbonylation of aniline

Reaction conditions: Aniline: 0.82 kmol/m^3; [Pd]-APTS-Y: 1.854 kg/m^3; NaI 1.24×10^{-3} kmol/m^3; $P_{(CO:O2)}$: 50 psig; Temp.: 333 K; solvent: DMF; time: 4 h

4.3.2.7. Effect of substrate

Catalytic activity of the [Pd]-APTS-Y catalyst was tested for conversion of several amines to the corresponding ureas in the presence of NaI as a promoter and dimethyl formamide (DMF) as a solvent at 333 K. The results on conversion, selectivity, yield and turnover frequencies (TOF) for different amines are presented in Table 4.1. All the products were separated and characterized by NMR, FTIR and elemental analysis.

Table 4.1. Results on oxidative carbonylation of amines using [Pd]-APTS-Y- NaI Catalyst System

Sr.	Amine	Urea	Amine conv., %	Urea sel., %	Yield, %	TOF, h^{-1}
1			93.4	91.6	85.6	148.9
2			98.5	96.4	95.0	157.5
3			68.7	96.8	66.5	109.6
4			55.3	93.2	51.5	88.2
5			95.9	98.0	94.0	152.9
6			91.1	92.1	83.9	145.3
7			78.3	93.0	72.8	124.9
8			91.8	91.8	84.3	146.4

Reaction conditions: Amine 0.80 kmol/m^3; [Pd]-APTS-Y 1.854 kg/m^3; NaI 1.24 ×10^{-3} kmol/m^3; Temperature 333 K; $P_{(CO:O2)}$: 50 psig; Solvent: DMF, time: 8 h

Therefore, the yields reported in Table 4.1 are isolated yields of the reactions. It is evident from the table that the immobilized Pd nano-catalyst showed good conversion

(55-98%) and selectivity (>90%) to the urea derivatives for all the amines and suitable for a wide range of amines with or without functional groups in ortho- or para- positions.

Table 4.2. IR and elemental analysis of substituted urea products

Sr.	**Disubstituted urea**	**Molecular formula**	**IR $\nu_{(C=O)}$, cm^{-1}**	**Microanalysis, %**		
				Ele.	**Calc.**	**Obtained**
1	1,3-Diphenyl urea	$C_{13}H_{12}N_2O$	1649	C H N	73.56 5.70 13.20	73.47 5.73 12.99
2	1,3-di-*p*-tolylurea	$C_{15}H_{16}N_2O$	1640	C H N	74.97 6.71 11.66	74.18 6.70 11.77
3	1,3-bis (4-methoxyphenyl)urea	$C_{15}H_{16}N_2O_3$	1634	C H N	66.17 5.88 10.29	66.28 5.93 10.31
4	1,3-di (naphthalen-2-yl)urea	$C_{21}H_{16}N_2O$	1632	C H N	80.77 5.13 8.97	80.98 5.22 8.94
5	1,3-dibutylurea	$C_9H_{20}N_2O$	1623	C H N	62.79 11.63 16.28	62.77 11.41 16.32
6	1,3-dibenzylurea	$C_{15}H_{16}N_2O$	1627	C H N	74.97 6.71 11.66	74.90 6.54 11.73
7	1,3-bis (4-chlorophenyl)urea	$C_{13}H_{10}Cl_2N_2O$	1633	C H N Cl	55.54 3.59 9.96 25.22	55.49 3.32 10.01 25.38

The influence of different *p*-substituents on conversion is shown in entry 3-5 and 7. The conversion level improved from electron withdrawing (deactivating) groups such as chloride (entry 3; 68.7%) to methoxy (better activating group; entry 7; 78.3%) to methyl (good activating group; entry 5; 95.9%) as the *p*-substituents. The carbamate products isolated from the amine screening study were analyzed by various techniques, and the results are summarized in Table 4.2.

4.4. CONCLUSIONS

In this chapter, the synthesis of highly dispersed Pd nanoparticles stabilized by immobilizing them on an amine functionalized zeolite support; and its application for the oxidative carbonylation of amines is demonstrated. The catalyst provides highly active, recyclable heterogeneous catalysts for the oxidative carbonylation of amines for the selective synthesis of disubstituted ureas. Detailed spectroscopic characterization of the catalyst has been undertaken to understand the exact nature of the nanocomposites; and the important observations of these studies are listed below.

- UV-visible spectra confirm the formation of Pd metal nanoparticles
- TGA analysis confirms that [Pd]-APTS-Y nanocomposites are stable till 145ºC, and also that Pd nanoparticles are bound to the zeolite surface through the amine functionality of APTS molecule.
- Powder XRD data indicates that the zeolite structure remains unchanged during the surface grafting by APTS molecules and metal immobilization. The formation of face centered cubic Pd nanoparticles on the outer surface of Na-Y zeolite is also interpreted by the XRD data.
- The TEM measurements support the observations of XRD analysis, and also show that palladium nanoparticles are highly dispersed on the APTS-Y zeolite, and in a very high concentration. This indicates that the technique used in the present study for immobilization of Pd nanoparticles can make the loading of palladium very high on the support, while still keeping the nano form intact; unlike the state of the art methodologies, which can generate very low nanoparticulate Pd loadings on the support.
- Different oxidation states of Pd present in [Pd]-APTS-Y nanocomposites are confirmed by XPS studies.

With regard to the catalytic activity [Pd]-APTS-Y for amine oxycarbonylation, following conclusions can be drawn based on the studies performed in this chapter.

- The synthesized platinum and palladium nanoparticles show very good catalytic activity for the oxidative carbonylation of amines. More importantly, the stability of these catalysts in these reactions was found to be good, and the catalyst could be recycled conveniently for at least five times without appreciable loss in the catalytic activity.
- The catalyst is capable of yielding disubstituted ureas from a range of amines.
- The TGA profile of the catalyst shows that the catalyst has potential to be exploited for higher reaction temperatures, which means that the present reaction if taken in a suitable alcohol medium can lead to the selective synthesis of desired carbamates, since the substituted ureas are known to alcoholyze at higher temperatures non-catalytically.

The high activity of the catalyst can be attributed to the nano size of the metal particles, whereas the large grain size of the zeolite takes care of easy separation of the catalyst from the liquid phase after reaction. The methodology reported here for the synthesis of supported nano catalysts has great potential for synthesis of heterogeneous catalysts useful for practical applications.

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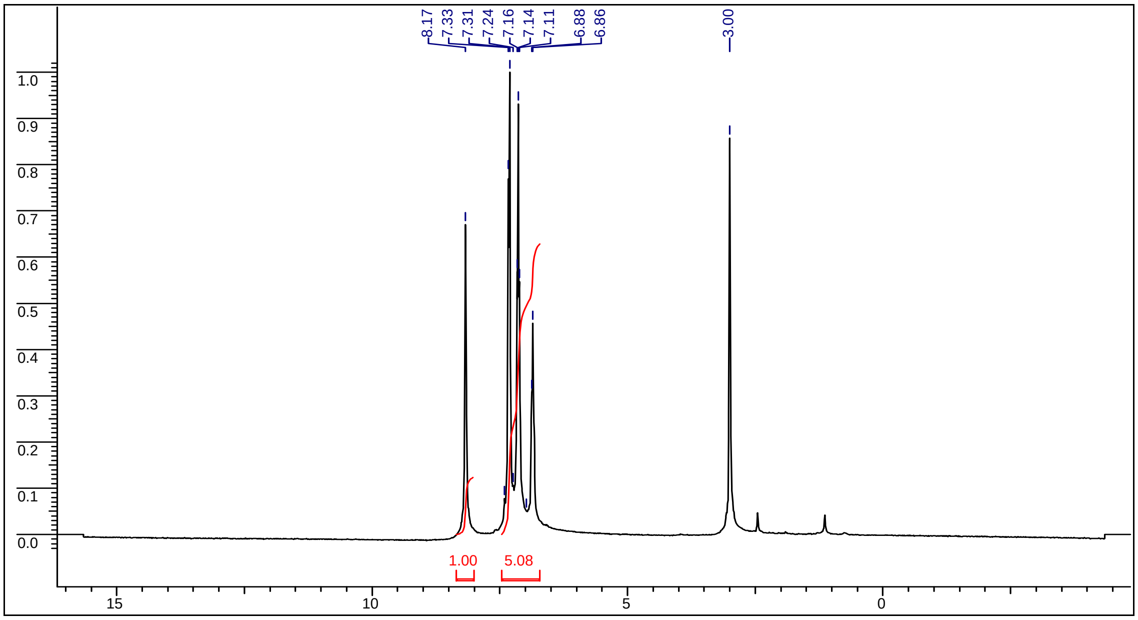
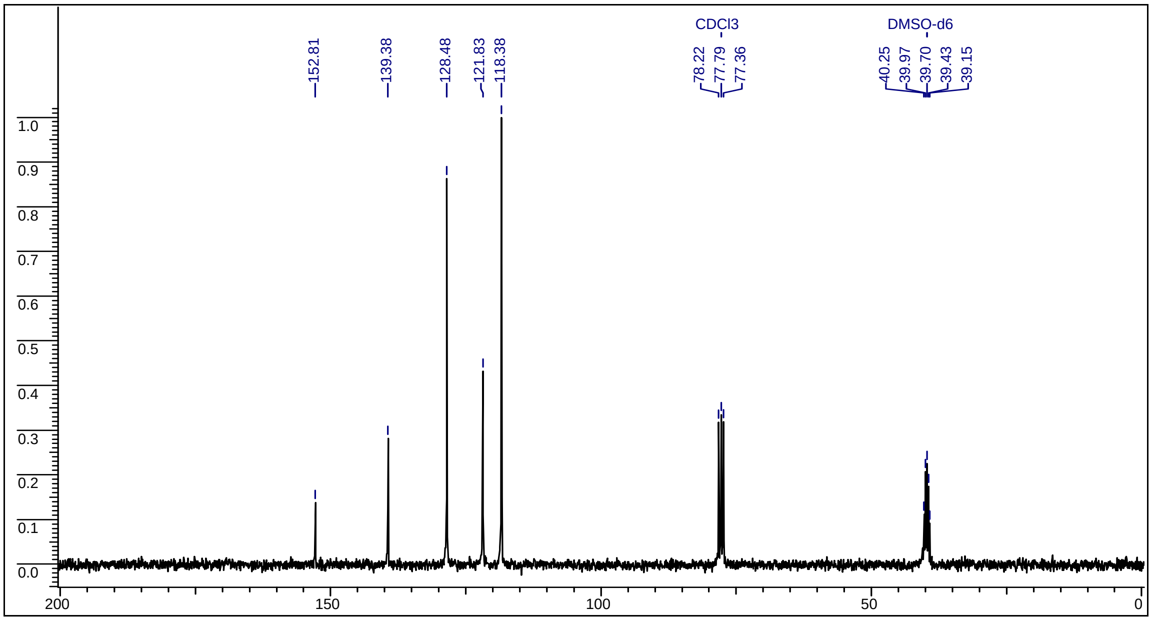
SPECTRA



^{1}H NMR of 1,3-diphenylurea in DMSO-d_6



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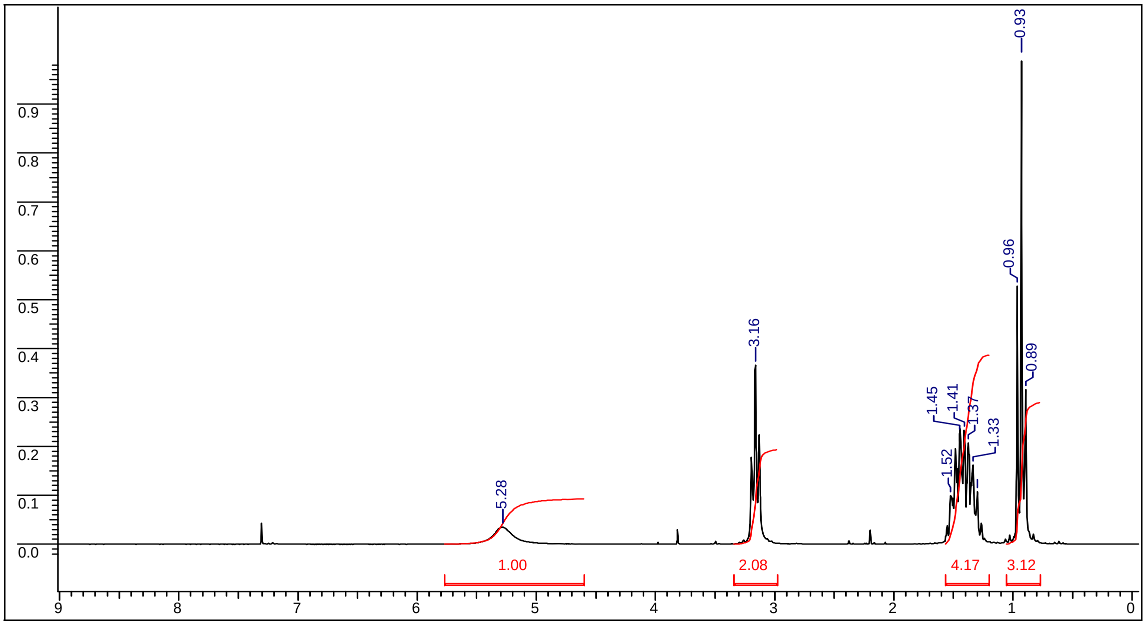

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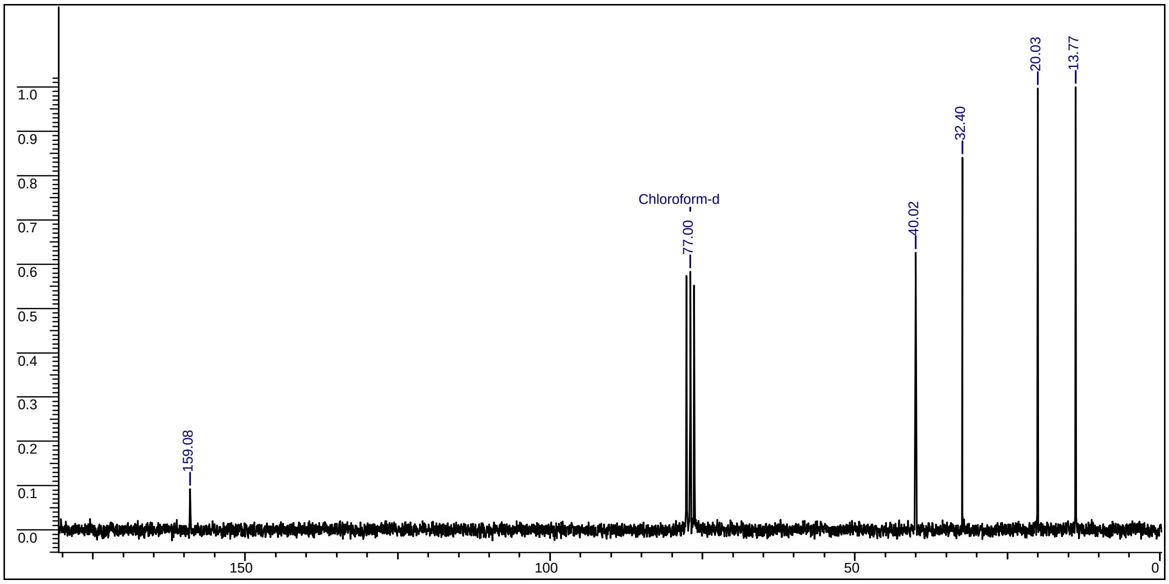

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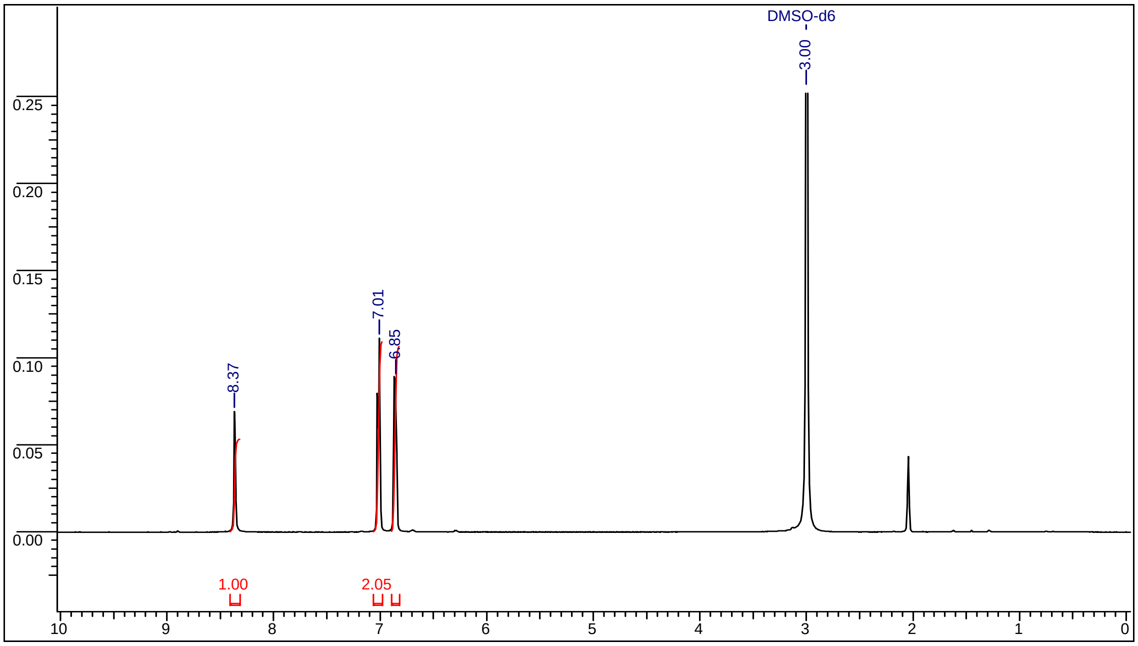

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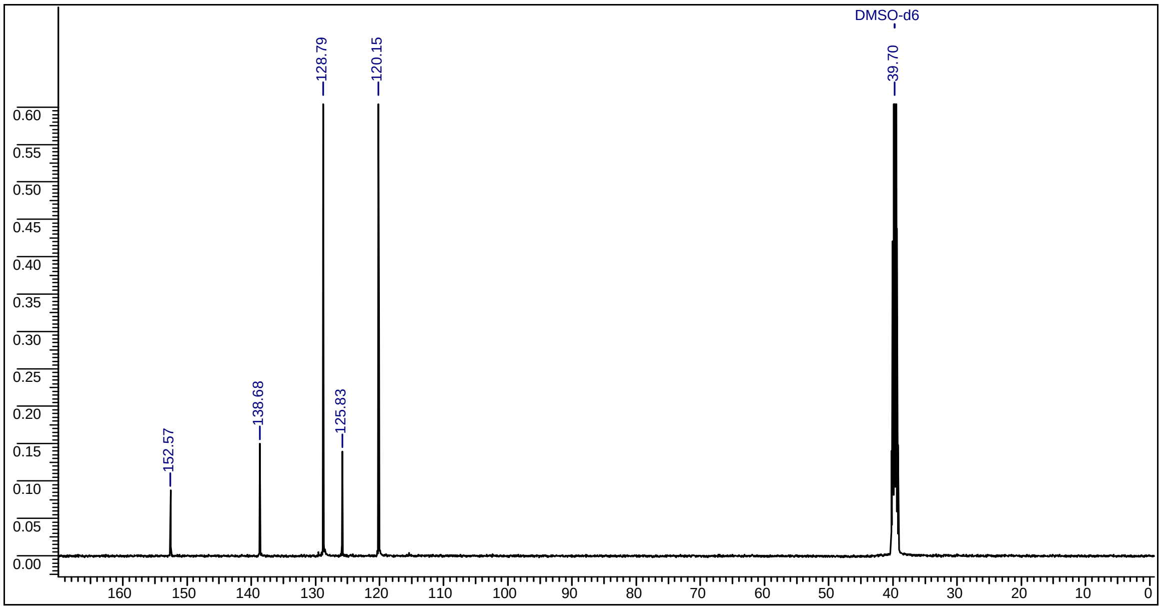

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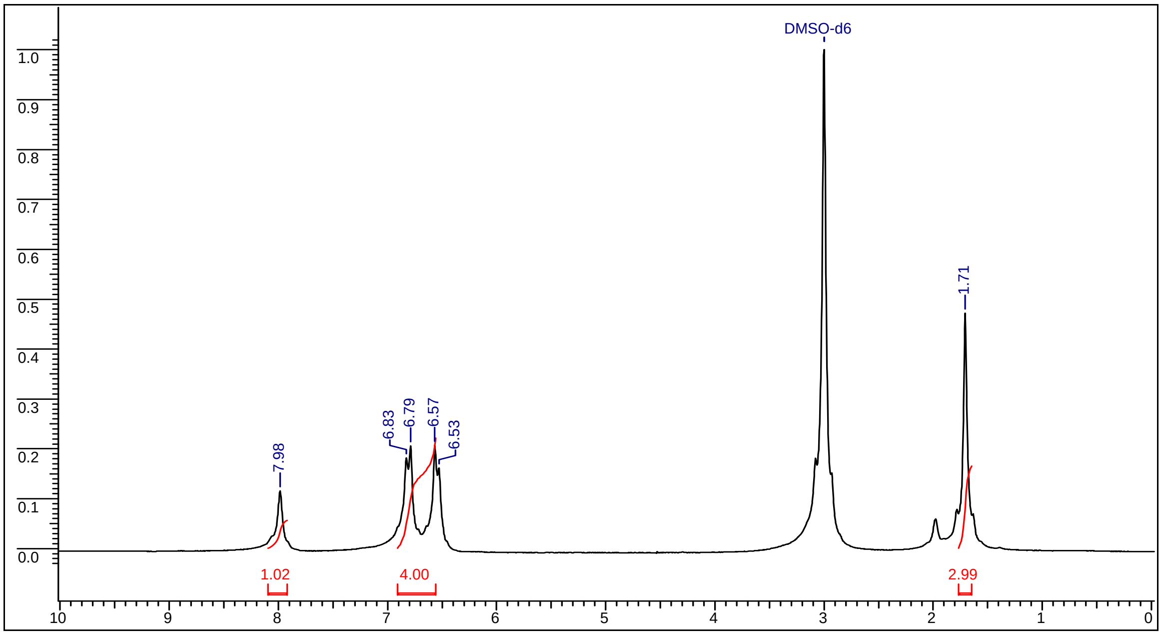

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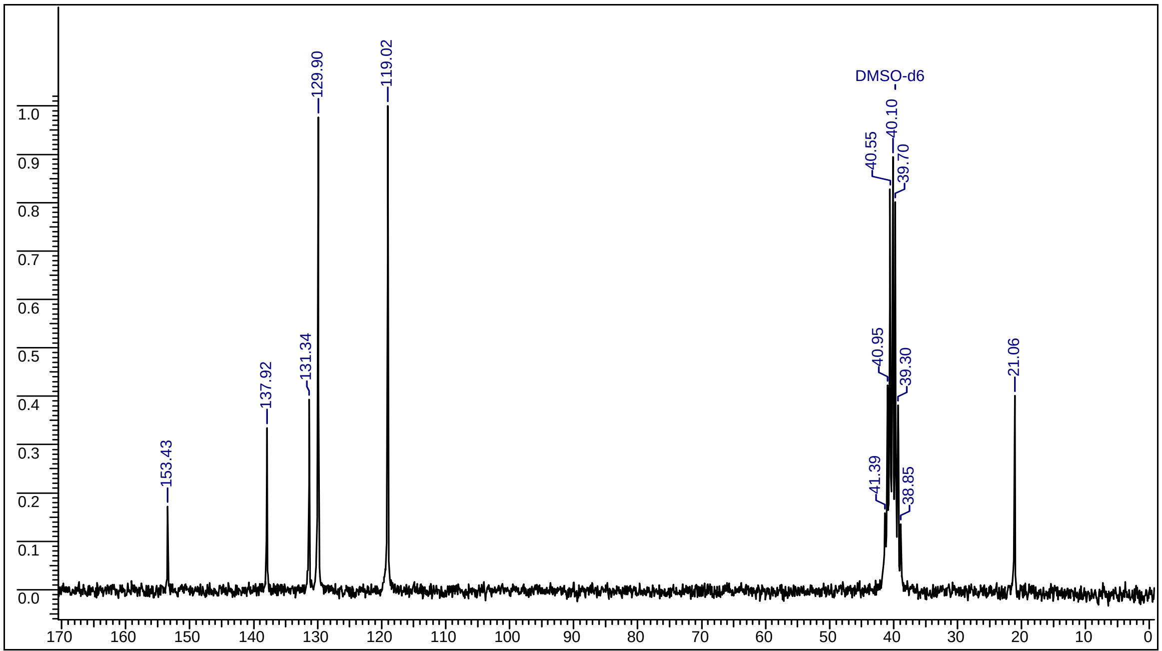

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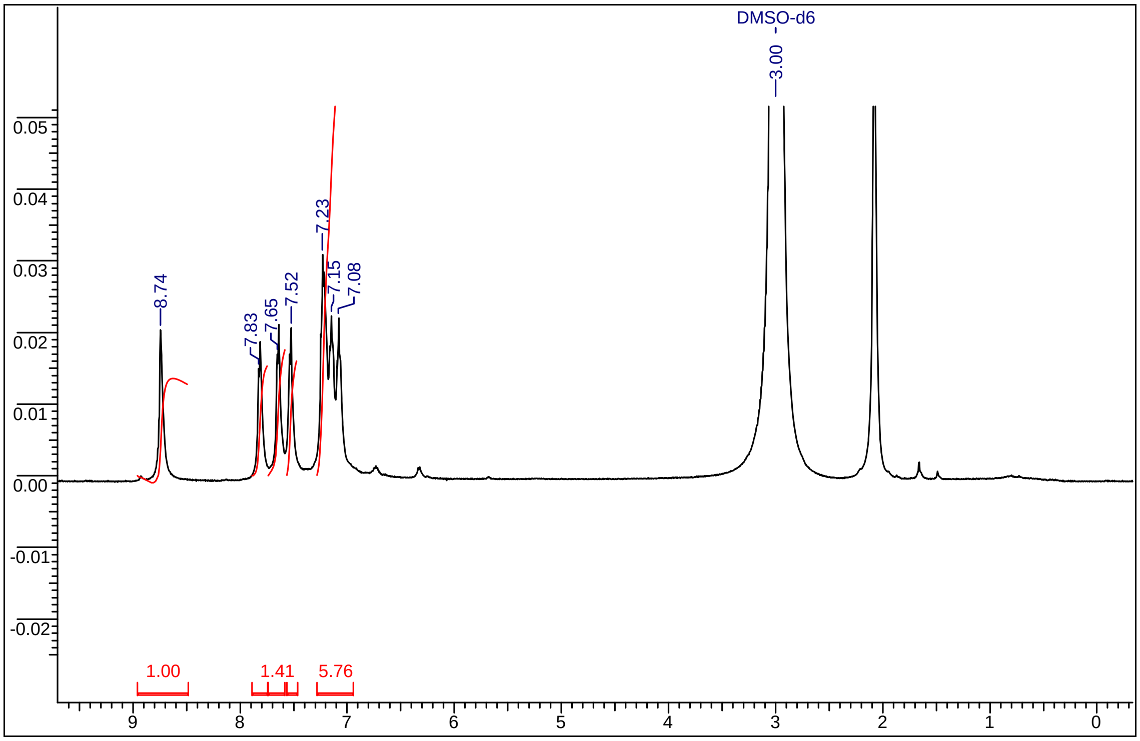

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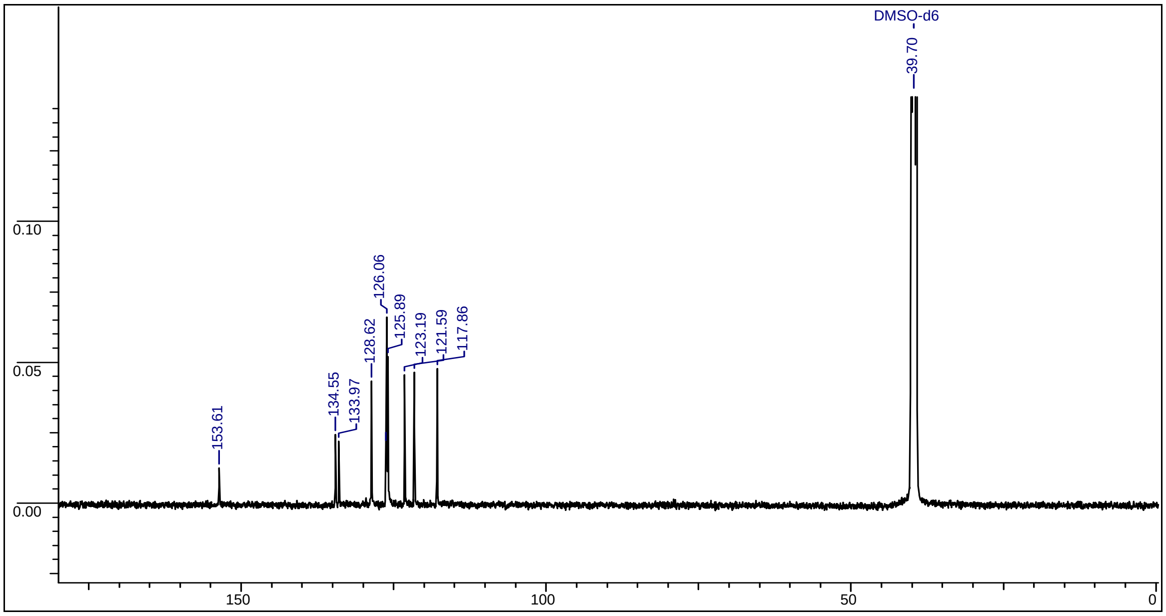

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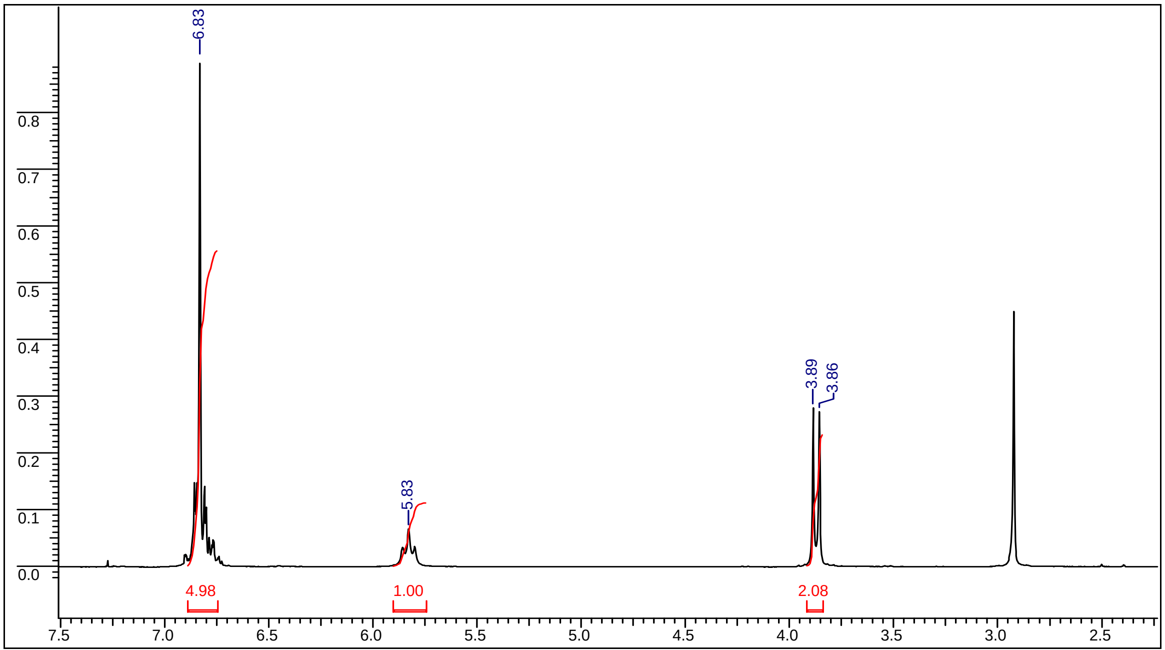

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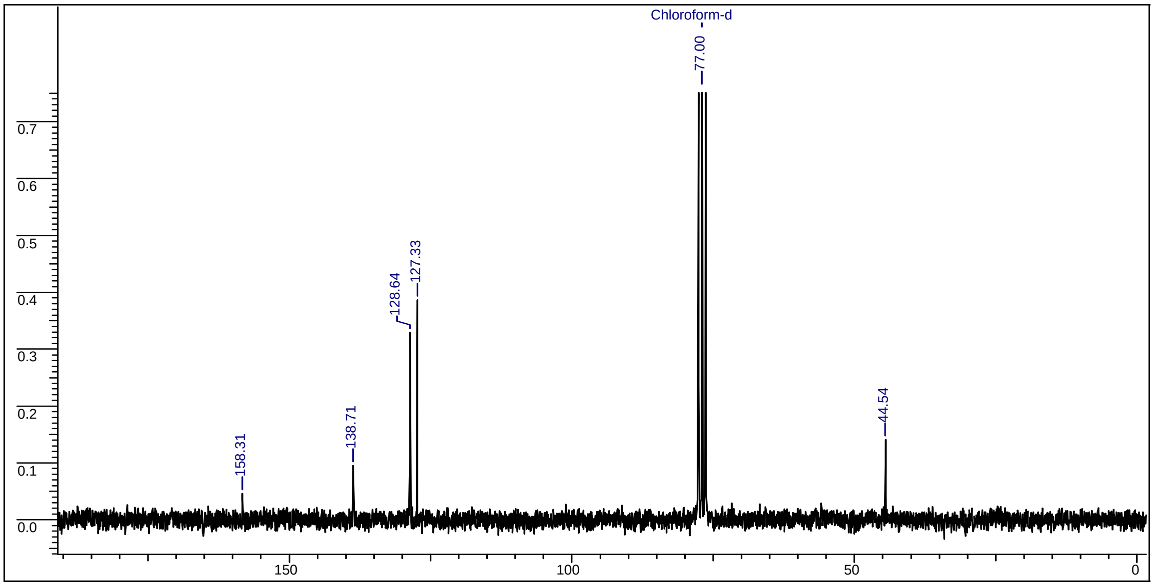

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