STUDIES ON ARYLATION AND CARBONYLATION REACTIONS USING PALLADIUM COMPLEX CATALYSTS

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BY

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CERTIFICATE

This is to certify that the work incorporated in the thesis, "**Studies on Arylation and Carbonylation Reactions using Palladium Complex Catalysts**" submitted by Mr. A. Shashi Bairagi, for the degree of Doctor of Philosophy, was carried out by the candidate under my supervision at Chemical Engineering and Process Development Division, National Chemical Laboratory, Pune 411008, India. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

Dr. Raghunath V. Chaudhari

(Research Supervisor)

Declaration

I hereby declare that the thesis entitled "**Studies on Arylation and Carbonylation Reactions using Palladium Complex Catalysts**", 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. R. V. Chaudhari. 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: (A. Shashi Bairagi)

Place:

Dedicated to my Family

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Abstract of Thesis

Catalytic chemistry has made pioneering contribution to the synthesis of a wide variety of products which include materials, energy application, food products, pharmaceuticals and many more having a direct impact on the quality of human life. Many chemical transformations and discoveries in chemistry are based on use of catalytic materials, which are not consumed but facilitate a particular transformation very often with a desired selectivity to specific products. The subject of catalysis, its industrial applications and several scientific and engineering aspects have been extensively reviewed in monographs by Cornils and Herrmann[1] and Gates et al[2]. The types of catalysts used are classified as homogeneous and heterogeneous depending on the form (solid state or soluble) that they are used. While heterogeneous catalysis have been widely used in industrial processes, homogeneous catalysts consisting of transition metal complexes have their own place as they catalyze some unique reactions like oxidation, carbonylation, hydroformylation, oligomerization, polymerization, hydrocyanation etc. Some of the important examples of homogeneous catalytic reactions are carbonylation of methanol to acetic acid, low pressure hydroformylation process for oxo-alcohols, synthesis of L-dopa by asymmetric catalysis, hydrocyanation of butadiene to adiponitrile, oxidation of *p*-xylene to terephthalic acid etc. The potential of designing new ligands and catalytic complexes is believed to be highly significant and hence, further research in this area is considered rewarding. Development of environmentally benign and economically viable catalytic routes for synthesis of useful products is of prime importance.

In this context reactions involving Heck arylation[3] and carbonylation[4] are also considered important. While the Heck arylation is a unique environmentally benign and atom efficient route for synthesis of olefin derivatives by C-C coupling reaction, carbonylation; provides another interesting reaction for the synthesis of carboxylic acid derivatives.

The aim of this thesis is to investigate the synthesis of new catalysts for Heck arylation and Carbonylation reactions as well as study their catalytic performance and reaction mechanism with an ultimate goal to develop clean catalytic pathways for value added industrial products. Specific problems chosen for studies in this thesis are:

- Synthesis, characterization of new NC palladacycles and screening of these palladacycles in the arylation of ethylene to achieve high activity, selectivity for the industrially important substrates
- Kinetic modeling of arylation of *n*-butylacrylate with 3-bromo-benzophenone using NC palladacycle catalyst
- Hydroesterification of 2-vinyl-6-methoxynaphthalene with palladium complexes containing chelating nitrogen ligands

This study is relevant particularly to develop an improved catalytic route for α-arylpropanoic acids such as Ketoprofen, Fenoprofen, Ibuprofen, Naproxen, Indoprofen etc. as anti inflammatory drugs. It is well known that these products are conventionally manufactured by stoichiometric organic reactions involving toxic and corrosive chemicals such as HF, NaCN, $COCl_2$, $AlCl_3$ etc. Though for Ibuprofen a three step catalytic route involving acylation, hydrogenation and carbonylation is already in commercial practice,[5] it involves the use of corrosive reagents such as HF, $AlCl_3$ in one of the steps (acylation). In addition, the carbonylation step requires severe conditions (P_{CO} = 16 MPa) to achieve the desired high regio-selectivity. The problem chosen for this thesis involves a sequential Heck and Carbonylation reactions having potential to eliminate such problems for the synthesis of α-arylpropanoic acids. In order to achieve this goal detailed investigations on the role of catalysts, ligands, solvents, and promoters in the performance of the catalyst for both Heck arylation and carbonylation steps is most essential. The complexity of reaction mechanism in these, provide a challenge in understanding scientific issues on kinetics and reaction mechanism. The thesis proposed will be presented in four different chapters a summary of which is given below:

Chapter 1 presents, a detailed review of the literature on the types of catalyst used, role of promoters, co-catalysts, solvents, kinetics and mechanism of Heck arylation of olefins and hydroesterification of aryl olefins is presented. Heck reaction is well known for several decades for synthesis of C-C coupling products. However, Heck arylation of gaseous olefins like ethylene has not been extensively studied. There are very few reports on the arylation of ethylene. Some studies on the arylation of ethylene with aryl halides[6] as substrates and other pseudohalides[7] (acid chlorides, diazonium

salts, and triflates), have been reported using $Pd(OAc)_2$ as the catalytic system. These involve use of high catalyst loading (~ 0.05 mol%) and are not so efficient in terms of turnover frequencies (<15 h^{-1}). Specifically, the arylation of ethylene to produce 2-vinyl-6-methoxynaphthalene using Herrmann palladacycle[8] (*trans*-Di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium) and $PdCl_2$/ NMDP[9] (neomenthyldiphenylphosphine) catalysts have been reported with TOFs of 85 h^{-1} and 444 h^{-1} respectively. The performance of the colloids $[Pd(CH_3CN)_2Cl_2].6Ph_4PCl$ has also been described for these reactions (TOF=75h^{-1}).[10] The drawbacks of these catalyst systems are higher operating temperature (~413K) & catalyst loading (~0.05 mol %) to obtain good activity and desired selectivity (for Herrmann palladacycle), and use of expensive ligand (NMDP, considering the industrial perspective). Therefore, further improvement in the catalyst performance enhanced TOFs, selectivity and stability, working under milder reaction conditions, is highly desirable.

A review of literature on transition metal catalyzed carbonylation of aryl-olefins to 2-arylpropanoic acids and esters has also been presented in details to understand the activity, selectivity behavior and the scope of development. The literature reports extensive studies on the hydroesterification of styrene as a model substrate. Palladium complexes containing chelating N-N, N-O ligands are shown to be most promising catalysts for the carbonylation reaction. For example, Jayasree et al[11] have described $Pd(pyca)(PPh_3)(OTs)$ complex system using TsOH & LiCl promoters, for the carbonylation reactions of a variety of olefins and alcohols. This catalyst system showed breakthrough advancement (TOF ~2600 h^{-1} for hydroxycarbonylation of styrene) in low pressure catalytic carbonylation (P_{CO}~5.4 MPa, 388K) reactions. However, there are only a few reports on the hydroesterification 2-vinyl-6-methoxynaphthalene (VMN) – the intermediate to naproxen. The catalytic systems reported for the hydroesterification of VMN include $PdCl_2(MDPP)_2$[12] (MDPP=menthyldiphenylphosphine); $PdCl_2$/different dicycloalkylphosphinobinaphthalene;[13] and silica-supported chitosan-palladium complex (CS-$PdCl_2$/ SiO_2),[14] which showed very low turnover frequencies (< 10 h^{-1}). Use of cationic Pd-complex, $Pd(OAc)_2$/ BPPFA/ *p*-toluenesulfonic acid[15] gave very poor conversions (~13%). Thus, hydroesterification of 2-vinyl-6-methoxynaphthalene (VMN)

needs improved catalysts with respect to activity, selectivity and stability. Based on the complete review, the following observations were noted,

- Limited literature on arylation of ethylene opens a possibility of exploring new catalytic system
- Applicability of Heck reactions to different substrates.
- Carbonylation of 2-vinyl-6-methoxynaphthalene needs to be investigated with new catalyst systems to enhance reaction rates, turnovers and selectivity.

Chapter 2 presents synthesis, characterization and catalytic activity of new NC palladacycles in the arylation of ethylene. Such use of NC palladacycles in the arylation of ethylene is described for the first time. The palladacycles with NC coordination were designed from readily available and inexpensive ligands. The various NC ligands used include 2-phenylpyridine, 2-phenylquinoline, 8-methylquinoline, N,N-dimethylbenzylamine and benzophenoneoxime. The NC palladacycle complexes were prepared in two steps. The first step involves the reaction of palladium salts (or palladating agent, $Pd(OAc)_2$ or Li_2PdCl_4) and the ligands to form a dinuclear molecule with acetate or halide bridged NC palladacycle.[16] In the second step, the obtained palladacycle is treated with triphenylphosphine ligand and *p*-toluenesulfonic acid to get the appropriate mononuclear palladacycle. Attempts to prepare the palladacycle in single step i.e. by mixing the palladium salts and the respective ligands resulted in the precipitation of palladium black. The structures of these palladacycles were determined by single crystal X-ray molecular structure analysis and by other spectroscopic techniques like NMR, IR, X-ray photoelectron spectroscopy and elemental analysis. These palladacycles are not sensitive to air or moisture and can be stored indefinitely under ambient conditions.

The catalytic activities of these palladacycles were tested in the arylation of ethylene with industrially important substrates such as 2-bromo-6-methoxynaphthalene (BMN), 3-bromobenzophenone (BBP) and 4-bromo-isobutylbenzene. These Palladacycles with NC coordination showed TOF > 4000 h^{-1}. The reaction showed a high selectivity towards 2-vinyl-6-methoxynaphthalene (>97%), and the selectivity towards the dehalogenated product was <2%. The effect of reaction parameters such as substrate concentration, catalyst loading, ethylene pressure and base was studied

in detail. Thus, the new NC palladacycle catalysts demonstrated significantly higher activity and chemo-selectivity for the Heck arylation of ethylene and found to be the most promising candidates for a green catalytic route of 2-aryl olefins.

Chapter 3 presents the kinetics of arylation of *n*-butylacrylate (BA) with 3-bromobenzophenone (BBP) using the complex Pd(ppy)(PPh_3)(OTs). This kinetic study was undertaken in order to develop a deeper understanding into the Heck reactions and with the aim to provide inputs to optimize the reaction conditions. The experiments were carried out in a 50 ml two necked stirred glass reactor equipped with a condenser and a magnetic stirrer. A few preliminary experiments were carried out to ensure material balance of reactants/ products and to select a suitable solvent and a base for the kinetic study. In all the experiments C-T profiles were obtained by intermittent time-sampling of the reaction mixture. The initial rates were calculated from the observed data on the consumption of 3-bromo-benzophenone as a function of time. The rate was found to be first order with respect to Catalyst, first order tending to zero order with respect to n-butylacrylate and NaOAc concentration. The rates passed through maxima with variation of BBP concentrations. Various empirical models were considered to explain the observed trends. The rates predicted by model were found to be in good agreement with the observed experimental data.

Chapter 4 presents hydroesterification of 2-vinyl-6-methoxynaphthalene (VMN) using palladium complexes containing chelating nitrogen ligands (pyridine-2-carboxylate, 2-acetylpyridine, 2-pyridine-carboxaldehyde, bipyridine). The hydroesterification reaction was performed in a 50 ml Parr autoclave made of Hastealloy-C-276 under 40 atmospheres of CO. Among the complexes screened, a palladium complex containing 2-acetylpyridine as the ligand was found to be superior to other Pd catalysts with different ligands. Both acid and halide promoters were necessary to induce the hydroesterification effectively. As an acid promoter benzenesulfonic acid was found to be more effective compared to *p*- toluenesulfonic acid. It was observed that this reaction also forms different side products such as ether and other oligomeric/ polymerized products. Special attention towards reducing unwanted side reaction such as the ether formation and the characterization of the

oligomeric/ polymerization product was also given. The polymerization occurs because of the high reactivity of the starting material 2-vinyl-6-methoxynaphthalene under the reaction conditions. The problem of polymerization persists even after using *t*-buytlcatechol as the polymerization inhibitor. The reaction shows 70% formation of the ester, and the rest is converted to the polymerized product. The turnover frequency using the complex $Pd(acpy)(PPh_3)(OTs)_2$ (acpy = 2-acetylpyridine) is 42 h^{-1}, this is the highest in the literature for the hydroesterification of VMN. With the optimized reaction conditions the effect of various parameters such as solvents, CO pressure, and alcohols, olefins on the catalytic activity as well as the selectivity was studied and detailed results are presented in Chapter 4.

In summary, the problems studied in this thesis are relevant to the development of environmentally benign routes for the synthesis of important drugs consisting of aryl propanoic acids. The NC Palladacycle catalysts proposed are the first reports and their catalytic performance in Heck arylation is an important advancement. Further work in this direction would be necessary to develop the complete catalytic processes, mainly to address important issues like catalyst-product separation and reaction mechanism.

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Chapter 1

Introduction

and

Literature Survey

1.1. Introduction

Catalysis has played an important role in the development of chemical industry during the last century. The applications of catalytic processes have been in diverse fields, which include petrochemicals, agrochemicals, pharmaceuticals, polymers, fine and specialty chemicals. Particularly, the applications in the development of environmentally benign processes and innovations in the pharmaceutical products have been highly significant. The catalytic materials used are generally classified as homogeneous or heterogeneous catalysts. While most of the industrial processes employ heterogeneous catalysts, the homogeneous catalysis by soluble metal complexes have some unique features in providing high activity and selectivity under mild operating conditions. Development of environmentally benign and economically viable catalytic routes for synthesis of useful products is of prime importance. Conventional stoichiometric synthetic routes used in pharmaceuticals have several drawbacks, such as generation of waste products consisting of inorganic salts, and use of toxic and corrosive reagents or raw materials with significant safety issues. In recent years, increasingly stringent environmental regulations and societal awareness of safety aspects, coupled with increasing competition have led to innovations in new catalytic processes. For example, catalytic reactions involving hydrogenation, oxidation, carbonylation, hydroformylation, epoxidation, and amination are extensively used in defining novel synthetic routes with significant economic advantages for pharmaceutical products. In order to enhance the catalytic activity, selectivity, stability of the catalysts and to improve environmental compatibility of these processes, many new concepts have been developed. Some examples of these concepts include tandem synthesis (to combine number of reaction steps using multicomponent catalysts), design of novel ligands and metal complexes (including chiral complexes for asymmetric catalysis), and heterogenization of homogeneous catalysts (encapsulation, biphasic catalysis etc.). The applications of homogeneous catalysis in industry have been previously described in several reviews.[1] The important factors responsible for driving new developments are (i) the possibility of environmentally benign synthetic routes at milder operating conditions with high activity and selectivity, (ii) a wide variety of reactions, such as carbonylation, hydroformylation, amination, epoxidation, hydrogenation, C-C coupling reactions and oxidation with homogeneous catalysis provide alternative processes that could have a competitive advantage over the

conventional stoichiometric or non-selective catalytic methods, (iii) synthesis of biologically active molecules with high enantioselectivity by asymmetric catalysis, and (iv) promising developments in heterogenization of these catalysts to facilitate catalyst-product separation.

α-Arylpropanoic acids have emerged as an important class of non-steroidal anti-inflammatory agents during the past three decades. Structures of few important nonsteroidal antiinflammatories are presented in Figure 1.1.

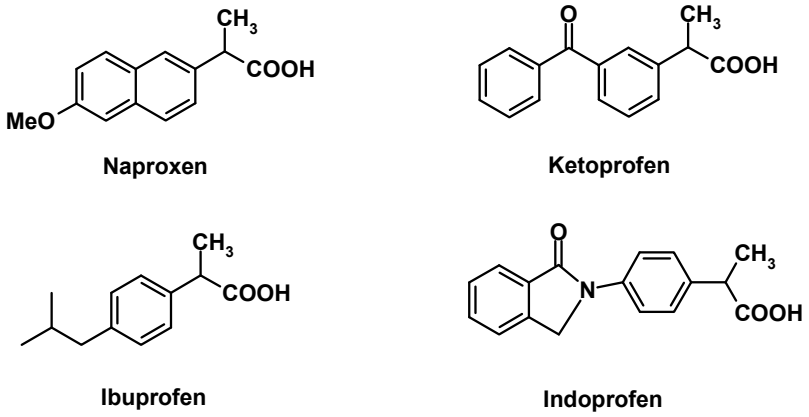
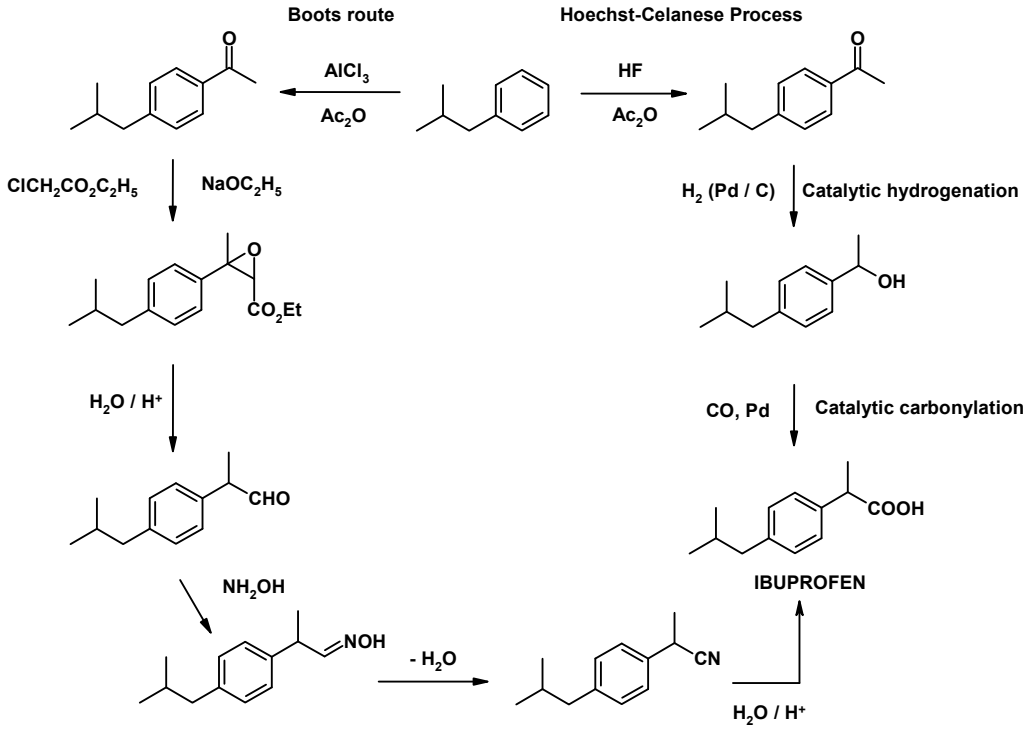


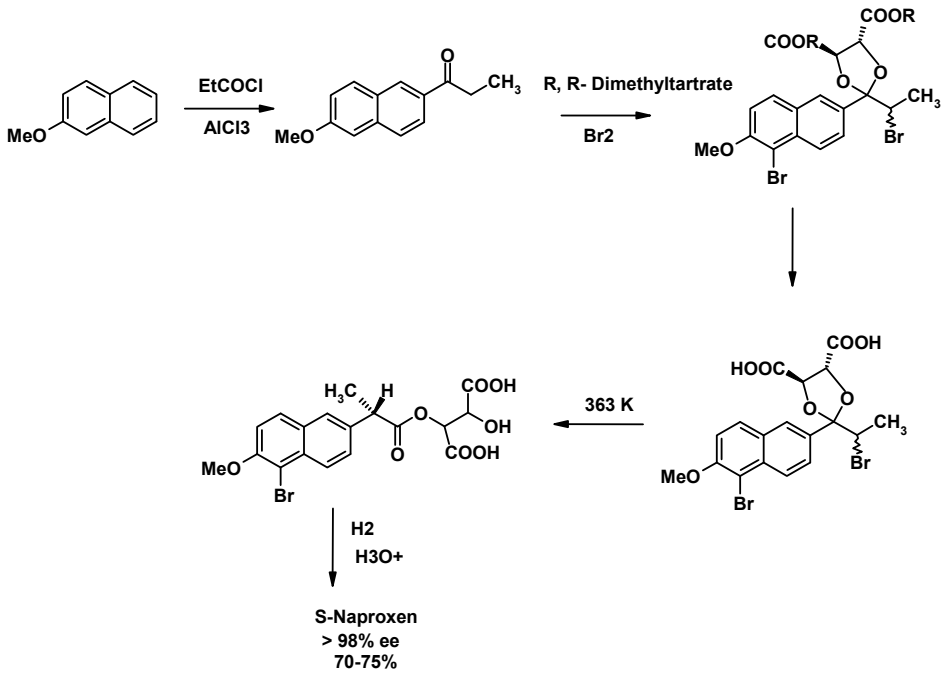
Figure1.1. Nonsteroidal Antiinflammatories

The synthesis of Ibuprofen by the conventional Boots route involves a six-step process wherein stoichiometric amounts of aluminium chloride, ethylchloroacetate etc. are used in different steps leading to formation of large amount of inorganic salts (13 kg/ kg of product) as by-products, with only 50% overall yield of the desired product. In a subsequent development, a new Hoechst-Celanese process[2] involving only three catalytic steps (Scheme 1.1) has replaced the conventional route giving more than 95% regioselectivity to ibuprofen with no waste products, but their catalyst system [$PdCl_2(PPh_3)_2$/ aq.HCl] requires high-pressure conditions (> 16MPa) to achieve the regioselectivity.

The synthesis of Naproxen by Zambon process is shown in Scheme 1.2.[3] The Zambon process involves the Friedel-Crafts acylation which generates aluminium hydroxide wastes. The other step involves ketalization (with (R,R)-dimethyl tartrate), bromination and ester hydrolysis. During the bromination the 1-position of 2-methoxy-6-propionylnaphthalene is also labile in the bromination, thus it requires further



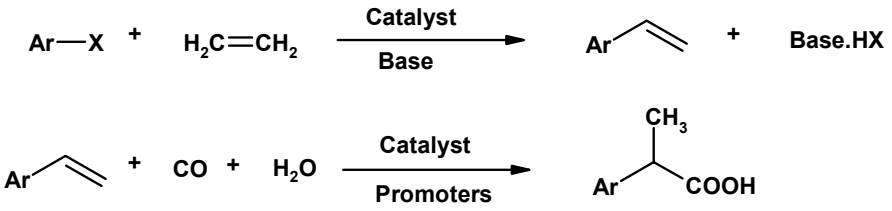
Scheme 1.1. Synthesis of Ibuprofen by Boots Route and Hoechst-Celanese Process



Scheme 1.2. The Zambon Process for Naproxen

debromination in the synthesis. There are also concerns regarding the mechanics of tartaric acid recycle. All these steps make the process too complicated.

One of emerging alternative process for the production of α-Arylpropanoic acids is based on the Heck reaction of arylhalides with ethylene, followed by carbonylation. Herrmann et al have described the arylation of ethylene with 2-bromo-6-methoxynaphthalene.[84] Allen et al have also described the arylation of ethylene and carbonylation route for the synthesis of Naproxen and Ketoprofen.[85]



Scheme1.3. Synthesis of α-Arylpropanoic acids

In this context, reactions such as Heck arylation and carbonylation are considered important. While the Heck reaction is a unique environmentally benign and atom efficient route for synthesis of olefin derivatives by C-C coupling reaction, carbonylation provides another interesting route for the synthesis of carboxylic acid derivatives. The aim of this thesis was to investigate the important class of catalytic reactions, namely the Heck reaction (arylation of ethylene) and carbonylation reaction for the synthesis of α-Arylpropanoic acids (Scheme1.3), class of non-steroidal anti-inflammatory drugs (Ibuprofen, Naproxen, Ketoprofen etc Figure1.1) having a substantial market size.

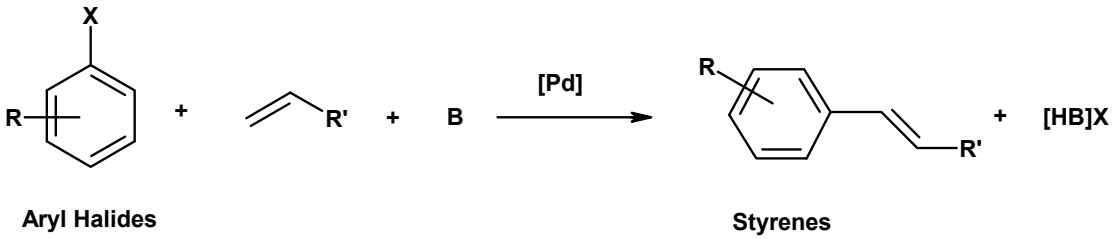
Thus, the problem chosen for this thesis involves studies on a sequential Heck and Carbonylation reactions having potential to eliminate such problems for the synthesis of α-arylpropanoic acids. In order to achieve this goal, detailed investigations including role of catalysts, ligands, solvents, and promoters in the performance of the catalyst for both Heck arylation and carbonylation steps are targeted.

For the Heck reaction it was proposed to investigate the arylation of ethylene with industrially important substrates (2-bromo-6-methoxynaphthalene, 3-bromo-benzophenone and 4-bromo-isobutylbenzene) to produce vinylaromatics using new palladacycles of different types. The detailed study of the kinetics of arylation of butylacrylate using homogeneous palladacycles has also been explored. Finally the

carbonylation of the Heck product (specifically the naproxen precursor) is carried out with palladium complexes containing chelating nitrogen ligands. The following sections present, the background of the subject, a review of Heck and carbonylation literature and specific research problems chosen along with the scope and objectives of this thesis.

1.2. Introduction to the Heck Reaction

The palladium-catalyzed arylation of an alkene with an organic halide was independently reported by Mizoroki[14] and Heck[15] in the early 1970s. The classical reaction involves bond formation between two sp^2 carbon centers by an overall substitution of a C-H bond of an alkene by R from the RX substrate (where R = aryl or vinyl; X = halide) under basic conditions. Heck has carried out extensive research work on this reaction and hence the reaction is known as the Heck reaction (Scheme 1.4). A traditional Heck coupling was based on an aryl iodide or bromide as the electrophilic partner and a terminal alkene as a nucleophilic partner.



Scheme1.4. Heck Coupling Reaction

Since its discovery, the methodology was found to be highly versatile and applicable to a wide range of aryl and vinyl species, where X = Cl, Br, I, OTf, OTs, N_2^+. A diverse range of olefins have also been found to undergo the Heck reaction readily. In order that the catalytic cycle continue, regeneration of the active complex is effected by the addition of a base to remove HX from the inactive complex.

The Heck reaction has received increasing attention both from the academic community as well as from producers of fine chemicals for the past few years. Recent potential applications in fine chemical production include Prosulfuron,[4] an agrochemical by Novartis, the sunscreen agent octyl *p*-methoxy-cinnamate, monomers for coatings from Dow, Albemarle's Naproxen and the anti-asthma agent Singulair from Merck. [5,6]

Some of the potential processes involving the Heck reactions are summarized in the Table 1.1.

The reaction is remarkably selective, and almost any functional group (cyano, carbomethoxy, carboxy, aldehyde, nitro, dimethylamino, hydroxyl, amino, acetamido, acetoxy, and polynuclear aromatic groups) can be present in the organic halide or the olefin. The aryl group prefers the less substituted carbon of the double bond regardless of the substituents present in either reactant. The percent of substitution at each of the double bond carbons on palladium-catalyzed reaction with bromobenzene at 373 K is shown for several olefins in the Figure 1.2.[7] The stereochemistry of the Heck product delivered is usually a *trans* disubstituted alkene. The stereochemistry of the reaction seems best explained as the result of a *syn* addition of the organopalladium compound followed by a *syn* elimination of the palladium hydride (Figure 1.3).[8] The *trans* isomer is also formed by an isomerization of the thermodynamically less stable *cis* isomer.

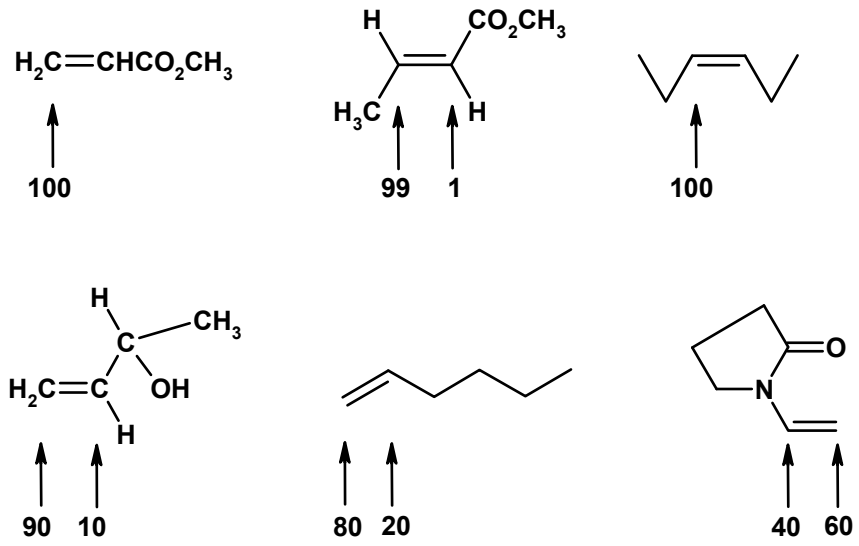


Figure1.2. Orientation of Addition of Bromobenzene to Various Olefins

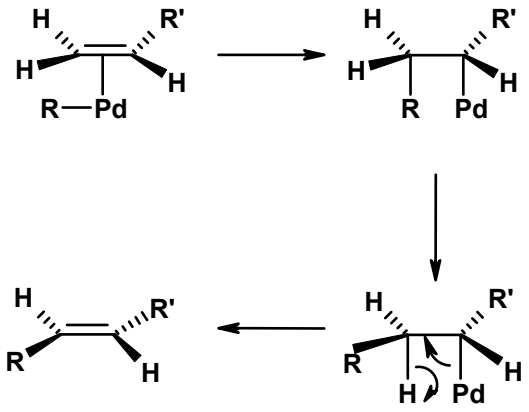
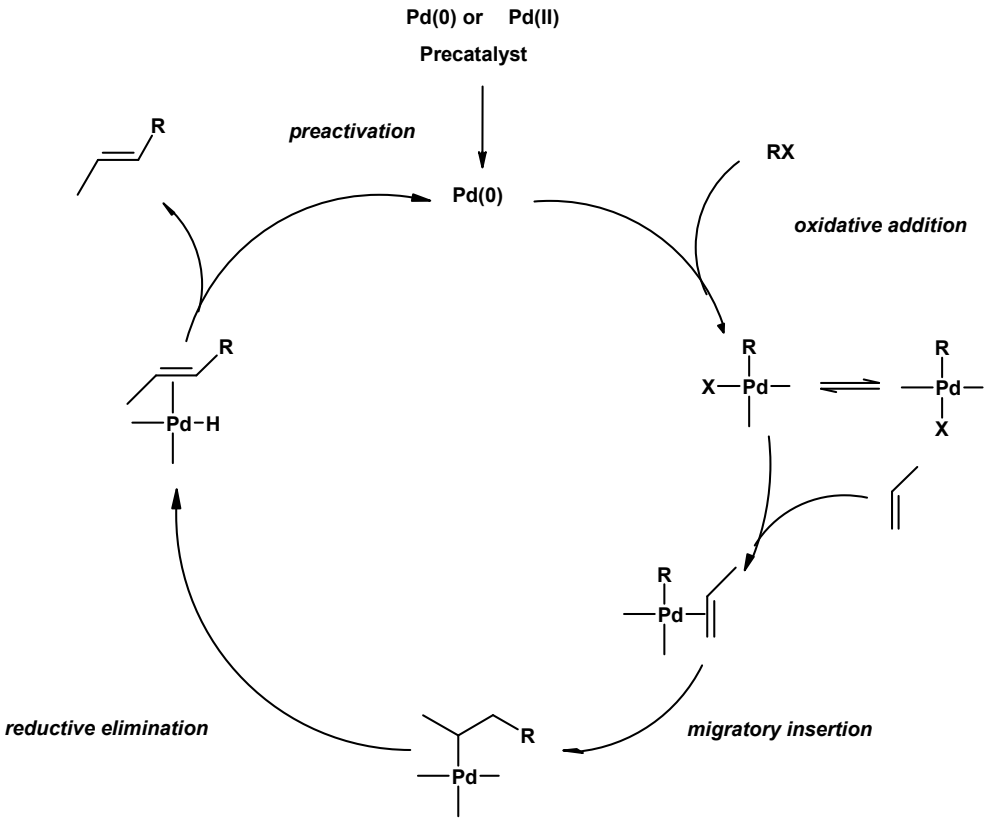


Figure1.3. Mechanism Showing the Formation of Trans Product

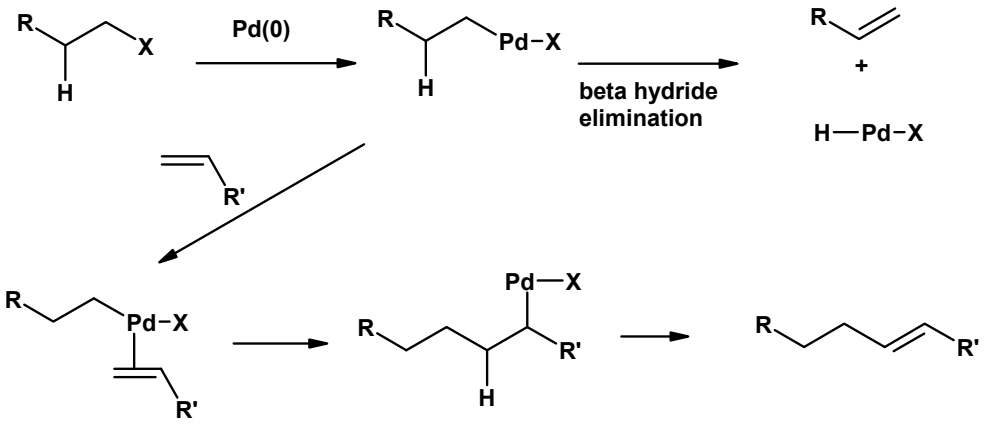
The mechanism for the Heck reaction has traditionally been presented as illustrated in Scheme 1.5.[9] The entry of palladium into the catalytic cycle includes the reduction of Pd(II) complexes to Pd(0) and the generation of active species through multiple ligand exchange equilibria. The oxidative addition proceeds as a concerted process in which C-X bond rupture is more or less perfectly synchronized with the formation of M-C and M-X bonds. Oxidative addition of RX occurs to generate a *cis*-$RPdXL_2$ species, which consequently isomerises to the thermodynamically more stable *trans* configuration. The oxidative addition depends on the strength of C-X and M-X bonds. The order of the reactivity of halides are I > Br > Cl (the experimentally found bond dissociation energies for phenyl halides (D_{Ph-X}) are 126, 96, 81, and 65, kcal/mol at 298K for X= F, Cl, Br, I respectively). The migratory insertion is the product-forming step of the Heck cycle, in which a new C-C bond is formed. The reaction of the product of oxidative addition with olefin requires that palladium gets rid of one of the strongly bonded ligands to free a coordination site for alkene.[9] The alkene inserts into the Pd-R bond, resulting in the formation of an unstable σ-bond. Rotation about the C-C bond and β-hydride elimination produces the substituted alkene, which is then eliminated from the system. Active PdL_2 complex is regenerated by the interaction of base to remove HX from the inactive $HPdXL_2$ complex to continue the catalytic cycle.



Scheme 1.5. Traditional Mechanism of the Heck Reaction

1.2.1. Limitations of Heck Reaction

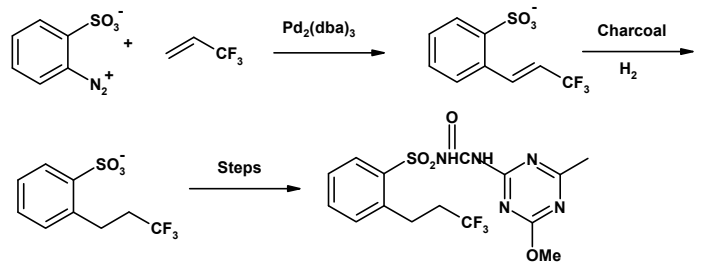
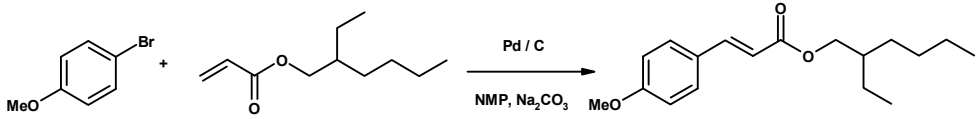
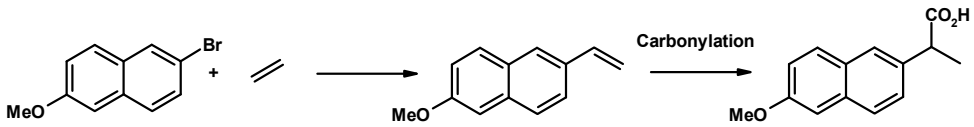
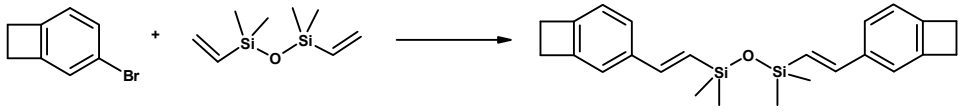
The major limitation of the Heck reaction is that the organic halides, which are employed, must not contain β -hydrogen to the halide atom as the substrate. The alkylpalladiums formed from such halides normally undergo β-hydride elimination more rapidly than insertion of alkenes. The product delivered is not the Heck product, Scheme 1.6.

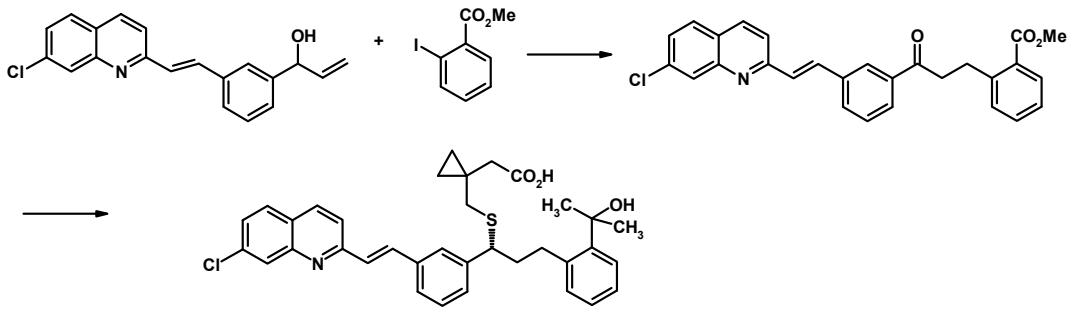
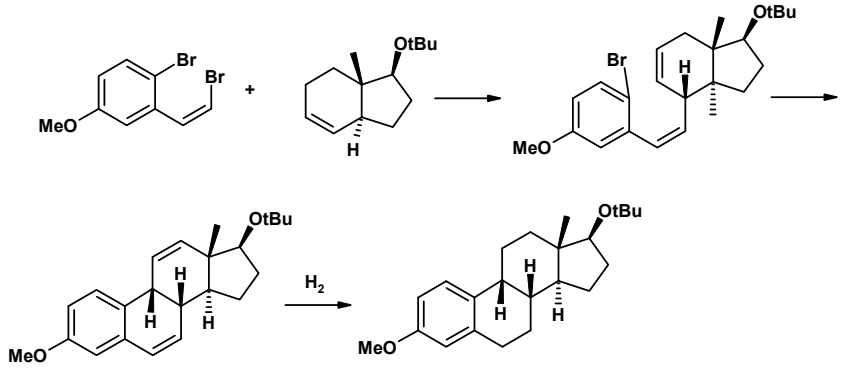


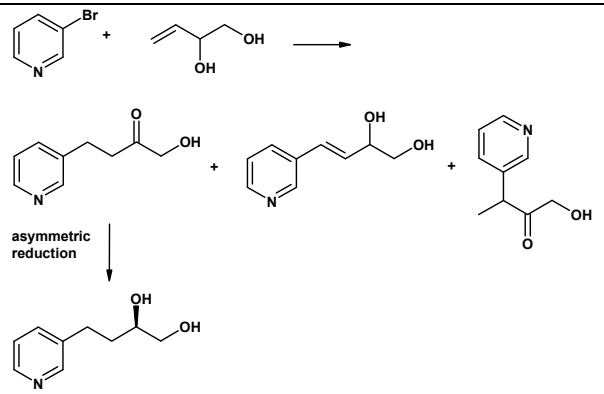
Scheme 1.6. Aryl halides Having *β*-Hydrogen do not Deliver the Heck Product

The utilization of chloro- and fluoroarenes has not been generally successful since these compounds demonstrate considerably lower reactivities than do their iodo and bromo counterparts. No example of Heck reactions which use aryl or alkenyl fluorides as substrates has been documented to date, while traditionally, chlorides require harsh conditions.

Table1.1. Potential Applications of Heck Reaction in the Production of Fine Chemicals

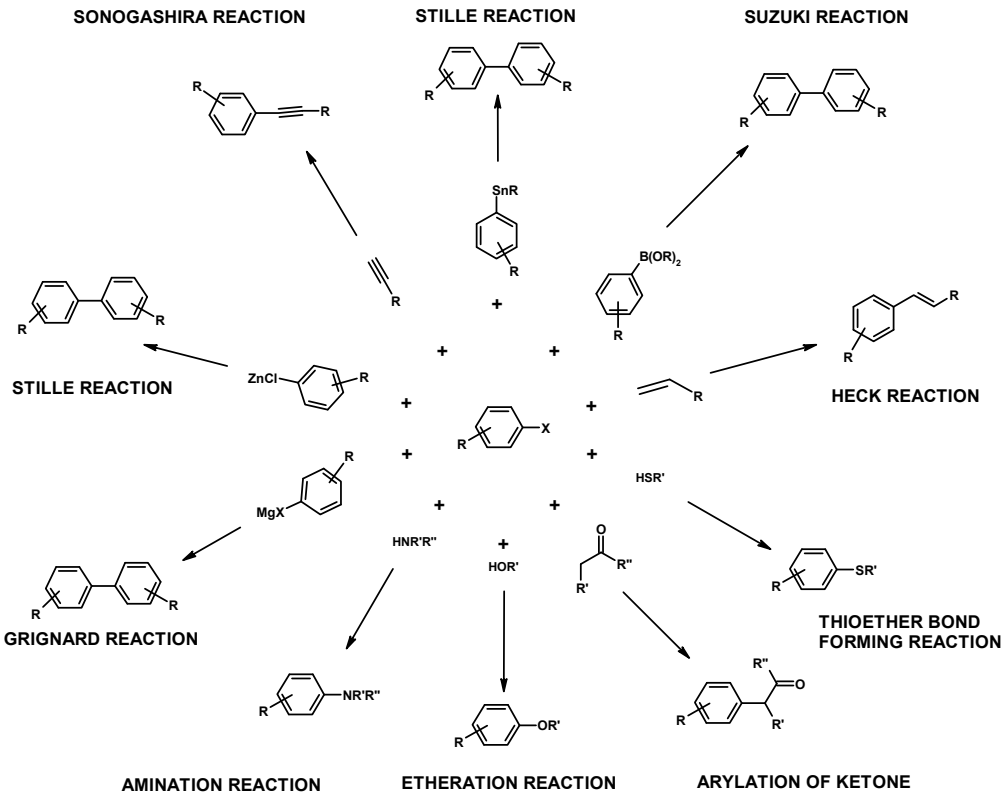
Name of the Product	Key Reaction	Catalyst for Heck Reaction	Reference
Herbicide Prosulfuron		$Pd_2(dba)_3$	4
Sunscreen agent		Pd / C	6
Naproxen		$PdCl_2$ / NMDP (neomenthyldiphenylphosphine)	5
Monomers for coatings of electronic components		$Pd(OAc)_2$ / *o*-Tol_3P	5

Name of the Product	Key Reaction	Catalyst for Heck Reaction	Reference
Antiasthama agent		$Pd(OAc)_2$	6
Steroids		Trans-di(*μ*-acetato)-bis[o-(di-o-tolylphosphino)benzyl]dipalladium (II)	Tietze et al[10]

Name of the Product	Key Reaction	Catalyst for Heck Reaction	Reference
1-hydroxy-4-(3-pyridyl)butan-2-one, an intermediate in a candidate drug, Pyridine diol		$Pd(OAc)_2$ / *o*-Tol_3P	Ainge et al[11]

1.3. Palladium Catalyzed Heck Reactions

Palladium complexes occupy a special place and have been used as active and selective catalysts for many years, and used in reactions of many substrates providing new useful synthetic organic products. Among those processes, palladium catalyzed reactions with aryl halides are of particular importance (Scheme 1.7).



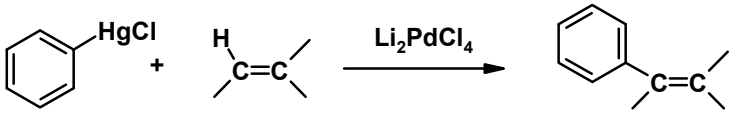
Scheme. 1.7. Palladium Catalyzed Coupling Reactions of aryl-X Derivatives

Heck reaction has been extensively investigated using palladium catalysts and found to be the best catalyst for this reaction. A detailed discussion on the Heck reaction using palladium complexes is presented in the following sections.

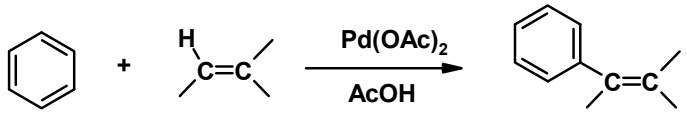
1.3.1. Heck Reaction with Aromatic Bromides and Iodides

Generally, aryl bromides, iodides, and activated alkenes are employed as the cross-coupling reactants, and a variety of efficient palladium catalysts have been

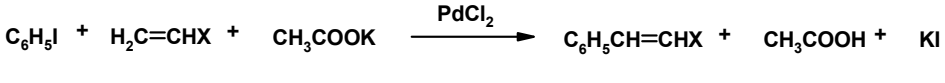
developed. In early sixties Heck[12] described the arylation reactions of olefins with arylating agents such as arylmercuric halides in the presence of group VIII metal salts, and showed that palladium salts are the most useful, but the major difficulties were the problem of obtaining organomercury compounds and there was the problem of working with thick slurries of salts. The reactions were performed at room temperature and the yield of the reaction was found to be in the range of 15 – 85% for the various substrates studied.



To overcome the above difficulty Fujiwara et al[13] demonstrated that direct arylation of olefins with aromatic compounds could be obtained in the presence of acetic acid under reflux conditions, however stoichiometric amount of $Pd(OAc)_2$ was required for the Heck transformation, which makes the process costly. Mixtures of trans and cis isomers were obtained and the reaction gives 10 % to ca. 90 % yield of the arylated products.

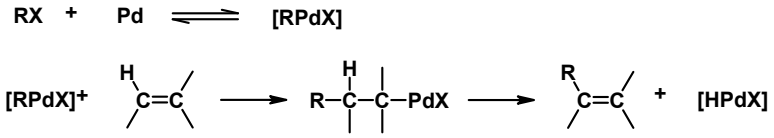


Later Mizoroki et al[14] demonstrated when base such as potassium acetate was used in the arylation of olefin with iodobenzene the reaction could be conducted using catalytic amount of $PdCl_2$ in methanol at 393 K. The base captures the hydrohalide liberated in the reaction and also generates the catalytically active palladium species. The reaction can be represented as follows



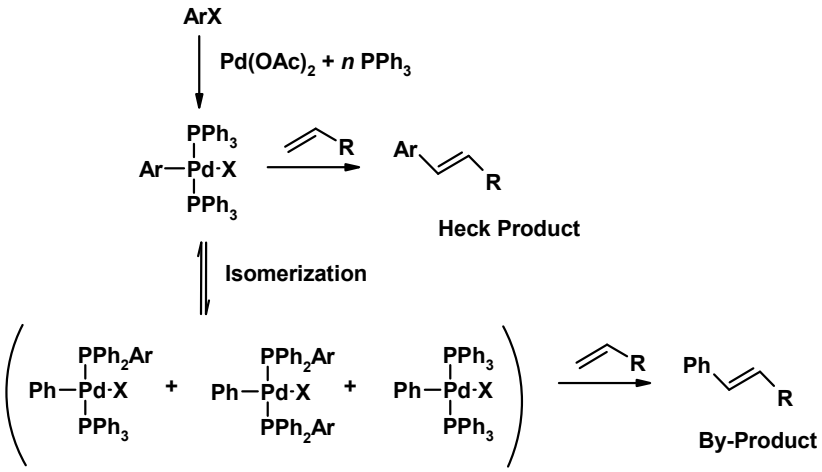
(X = H, C_6H_5, CH_3, $COOCH_3$)

Heck et al[15] similarly reported the reaction of various iodides and olefinic compounds using $Pd(OAc)_2$ as the catalytic system in the presence of tri-*n*-butylamine as the base, these reactions could be carried out under steam bath conditions than were used by Mizoroki[14] (393 K). Bromo halides reacted sluggishly. A mechanism of the reaction was also proposed, in which the first step is the oxidative addition between palladium metal (formed by an *in situ* reduction of the palladium acetate initially added by olefin) and organic halides producing very reactive organopalladium (II) halides. These organopalladium halides undergo an addition reaction with the olefin, and the adduct decomposes by eliminating a hydridopalladium halide, forming the substituted olefinic compound.



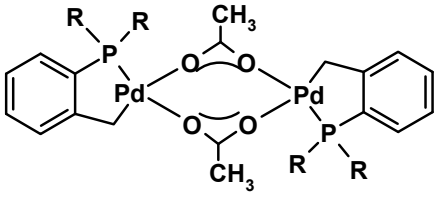
The initial reports by Mizoroki and Heck used simple palladium salts $Pd(OAc)_2$ or $PdCl_2$ as the catalysts in the absence of any ligand, and showed good activity only for reactive substrates such as iodo compounds which are often difficultly obtainable. Later Heck et al[16] demonstrated that bromocompounds could be activated in the presence of the $Pd(OAc)_2$ / PPh_3 catalyst system (PPh_3 facilitates oxidative addition of bromocompounds to palladium complex). Triphenylphosphine was the first ligand reported for the Heck reaction. A variety of aryl bromides were found to react, and in general electron-withdrawing substituents increased the reactivity of the bromides. Later Heck demonstrated that bromides with electron-donating substituents such as hydroxyl and amino groups can also be used but with the catalyst system comprising of $Pd(OAc)_2$ and tri-*o*-tolylphosphine (for the reaction of 4-bromophenol and methylacrylate using $Pd(OAc)_2$/ PPh_3 the yield of the reaction was 3%, however with the catalyst system $Pd(OAc)_2$/ $(o\text{-}tol)_3P$ the yield increased to 98%).[17]

Triarylphosphine ligand was used to increase the lifetime of the catalyst above 393 K, however, this often leads to competitive degradation of the palladium catalyst and the formation of unwanted by-products through thermally activated P-C bond cleavage of a coordinated phosphine ligand.[18]



In most of the work carried out by Heck, solvent was not used and a high catalyst loading of 1 – 2 mol% (based on halide) was used, limiting the turnover numbers attained to a maximum of 100. Spencer demonstrated that the reaction could be carried out at very low catalyst loadings (0.01 mol%) with suitable strongly polar solvent and carboxylate anion as a base. For example the reaction of 4-bromobenzaldehyde and acrylonitrile using N,N-Dimethylformamide as a solvent and sodium acetate as a base in the presence of $Pd(OAc)_2[P(o\text{-}Tol)_3]_2$ catalyst a high turnover number (8800) was obtained.[19] The reactions thus carried out by Spencer with $P(o\text{-}Tol)_3$ ligand provided a benchmark for further reactions. After this study, the aim of all further development in phosphine assisted catalyst for these type of reactions was to obtain highly active catalysts, which could give improved TON and TOF at low catalyst concentrations and also activate aryl chlorides to undergo Heck reaction. Since $P(o\text{-}Tol)_3$ turned out to be a good ligand for Heck reaction, it was imperative that the use of preformed complex of palladium with this ligand be tested for Heck reaction. The use of such complex was reported by Herrmann[20] for the first time and this set a precedence for a new class of catalysts – palladacycle to be synthesized and utilized for Heck reactions. Herrmann et al[20] described the complex derived from treatment of $Pd(OAc)_2$ with tris(*o*-tolyl)phosphine in toluene to afford the cyclometalation product. The dinuclear molecule has two acetate bridges which brings the two metal centers to within 311.5 pm, a nonbonding distance. This palladacycle is thermally stable molecule and is not sensitive to air. This palladacycle can be used as a catalyst without addition of any extra phosphine, the turnover numbers for the reaction of 4-bromobenzaldehyde

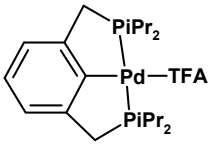
and *n*-butylacrylate using this palladacycle as a catalyst reached values of 2,00,000, and the turnover frequency was found to be 16,666 h^{-1} (0.0005 mol% catalyst, 408 K, >99 % yield). This catalyst was also found to be active for chloroarenes e.g., in the Heck coupling of 4-chlorobenzaldehyde with n-butylacrylate, 80% butyl (E)-4-formylcinnamate was obtained with a TON of 600-800. However the addition of quaternary salts such as tetrabutylammonium bromide (TBAB) is required for the stabilization of the catalyst (0.05 mol% catalyst, 403 K, TBAB 10 mol%) while using chlorides as the substrate.

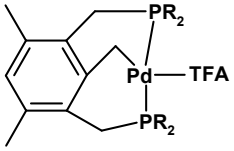


R = *o*-tolyl

Herrmann Palladacycle

Manuela et al[21] described complex derived by the treatment of $Pd(TFA)_2$ (TFA=$OCOCF_3$) with the corresponding diphosphines in THF at 353 K.



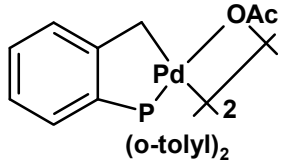
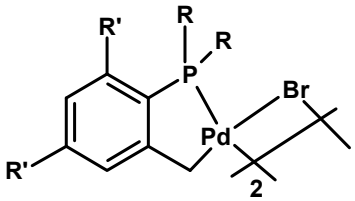


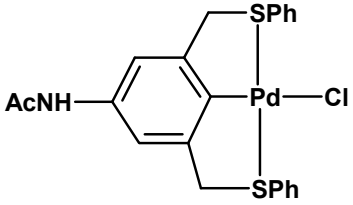
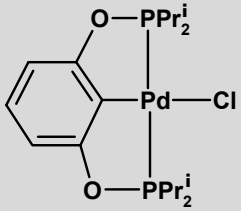
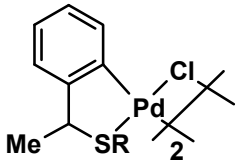
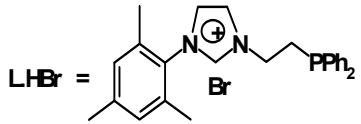
R = i-Pr, t-Bu

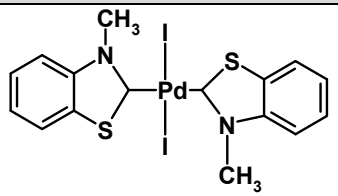
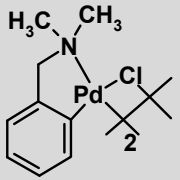
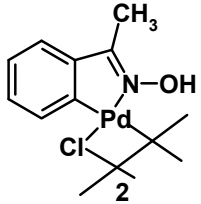
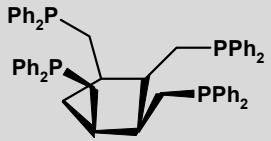
The complex showed high activity in the catalytic arylation of olefins with aryl iodides and bromides. Because of the stabilizing tridentate PCP ligand, the complexes are thermally stable and the reactions could be carried in air with no change in efficiencies or yield. During catalysis, the formation of palladium black is minimal and ligand exchange of TFA takes place with the corresponding halide. A high turnover number of 1,32,900 is reported for the reaction of bromobenzene and methylacrylate (0.0007 mol% catalyst, 413 K, 93% yield).

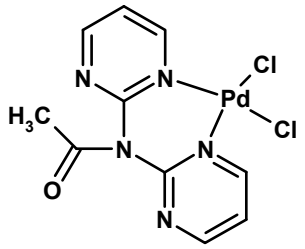
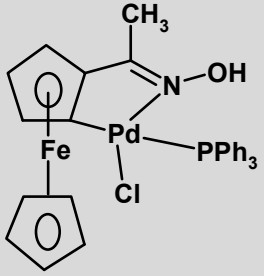
The characteristic features of palladacycle are that (a) they are thermally very stable molecules, with decomposition temperatures above 523 K, (b) the catalyst become active at temperatures above 353 K and the formation of palladium black, which is a feature of many Heck reactions, occurs rarely and in trace amounts, (c) the complications associated with P-C bond cleavage can also be circumvented, as the generation of scrambled by-products does not occur until reaction temperatures exceed 438 K and (d) the catalysts are extremely active and are ideal candidates for the transformations of challenging substrates such as aryl chlorides. Since then numerous palladacycles particularly those with nitrogen, phosphorous, sulfur and oxygen containing donor ligands and various other active catalyst were practiced for the Heck coupling reactions. A brief review of the literature is presented in the Table 1.2.

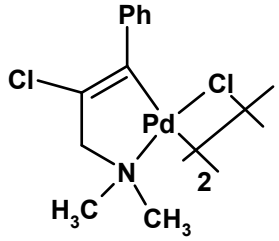
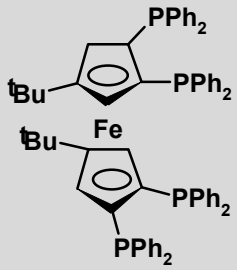
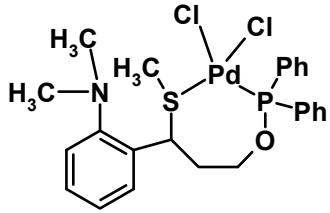
Table 1.2. Literature Report for the Heck coupling Reactions

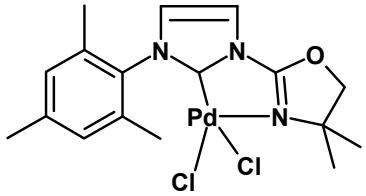
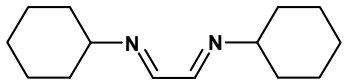
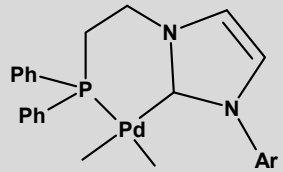
S.No	Aromatic Halide	Olefin	Catalyst	Conditions, others	Yield %	Reference
1	4-bromoflorobenzene	Butylmethacrylate	 (0.1 mol%)	DMAc, 408-413 K, 4h, NaOAc TON=650	27	Beller et al[22]
2	4-bromoacetophenone	n-butylacrylate	$Pd_{colloid}[N(C_8H_{17})_4]Cl$ (0.05 mol%)	DMAc, 413 K, 5min, NaOAc TOF= 24,000h^{-1}	97	Beller et al[23]
3	4-bromobenzaldehyde	n-butylacrylate	 **R = mesityl** **R' = CH_3** (0.01 mol%)	DMAc, 413 K, 2h, NaOAc TON= 10000	99	Beller et al[24]
4	Bromobenzene	n-butylacrylate	$[Pd(CH_3CN)_2Cl_2].6Ph_4PCl$ (0.01 mol%)	NMP, 403 K, NaOAc TON = 9800	97	Reetz et al[25]
5	4-bromoanisole	Styrene	$Pd(OAc)_2$/ P(O-2,4-$^tBu_2C_6H_3)_3$	DMAc, 413-433 K, Na_2CO_3 TON= 31,000	31	Beller et al[26]
6	Bromobenzene	Styrene	$PdCl_2(PhCN)_2$/ N-N-dimethyl glycine (0.01 mol%)	NMP, 403 K, NaOAc	93	Reetz et al[27]

S.No	Aromatic Halide	Olefin	Catalyst	Conditions, others	Yield %	Reference
7	Iodobenzene	Methylacrylate	 (0.1 mol%)	NMP, 383 K, NaOAc or Et_3N	92	Bergbreiter et al[28]
8	Iodobenzene	Styrene	 ($7x10^{-4}$ mol%)	DMF, Na_2CO_3 5h TON= 1,41,430	99	Jensen et al[29]
9	Iodobenzene	Methylacrylate		DMAc, 413 K, Et_3N, 1h TON= 47,000	94	Dupont et al[30]
10	4-bromo-N,N-dimethylaniline	*n*-butylacrylate	$Pd_2(dba)_3$ / P(*t*-Bu)$_3$	Dioxane, r.t. Cy_2NMe	97	Fu et al[31]
11	4-bromotoluene	*n*-butylacrylate	$Pd(dba)_2$/ L.HBr  (0.5 mol%)	DMAc, 393 K, Cs_2CO_3, 4h	96	Nolan et al[32]

S.No	Aromatic Halide	Olefin	Catalyst	Conditions, others	Yield %	Reference
12	Bromobenzene	3-hydroxy-2-methylenealkanoates	 (2 mol%)	TBAB, Sodium fromate, Na_2CO_3 403 K, 20 h	77	Calo et al[33]
13	4-iodoanisole	Ethylacrylate	 (0.001 mol%)	NMP, K_2CO_3, 423 K, 8 h TON = 89,540	88	Iyer et al[34]
14	Iodobenzene	Methylacrylate		DMF, TEA, 383 K, 2h, TON = 9,800	98	Najera et al[35]
15	2-methylbromobenzene	n-butylacrylate	$[Pd(C_3H_5)Cl]_2$ /  (0.01 mol%)	DMF, K_2CO_3, 403 K, 20h, TON = 7,800	78	Santelli et al[36]

S.No	Aromatic Halide	Olefin	Catalyst	Conditions, others	Yield %	Reference
16	Bromobenzene	Styrene	 (0.006-0.03 mol%)	DMAc, Bu_3N, 423 K, TON = 88,600	96	Buchmeiser et al[37]
17	4-iodoanisole	Ethylacrylate		NMP, NaOAc, 423 K, TON = 14,000	84	Iyer et al[38]
18	Iodobenzene	*n*-butylacrylate	$PdCl_2(SEt_2)_2$ / $N(^nBu)_4Br$ (0.002 mol%)	DMAc, NaOAc, 393 K, TON = 50,000	100	Dupont et al[39]

S.No	Aromatic Halide	Olefin	Catalyst	Conditions, others	Yield %	Reference
19	4-bromo-acetophenone	*n*-butylacrylate		DMAc, NaOAc, 423 K, 24 h, TON = 1,00,000	97	Dupont et al[40]
20	4-bromobenzaldehyde	*n*-butylvinylether	$[PdCl(\eta^3\text{-}C_3H_5)]_2$ / 	DMF, K_2CO_3, 403 K,	100	Hierso et al[41]
21	4-bromoanisole	Styrene		DMF, NaOAc, 403 K, 24 h, TON = 133	13	Kostas et al[42]

S.No	Aromatic Halide	Olefin	Catalyst	Conditions, others	Yield %	Reference
22	4-bromoacetophenone	Styrene	 (0.2 mol%)	DMAc, K_3PO_4, 408 K, 2h	97	Gade et al[43]
23	Bromobenzene	Ethylacrylate	$Pd(OAc)_2$	Poly(ethyleneglycol), Et_3N, 353 K, 8h	97	Chandrasekhar et al[44]
24	4-bromotoluene	n-butylacrylate	$Pd(OAc)_2$ / 	DMAc, Cs_2CO_3, n-Bu_4NBr, 3h, 373 K	95	Nolan et al[45]
25	4-bromoacetophenone	Methylacrylate	 **Ar = 2,6-Pr^i_2-C_6H_3**	NMP, Et_3N, 393 K, 6h TON = 184	92	Andreas et al[46]

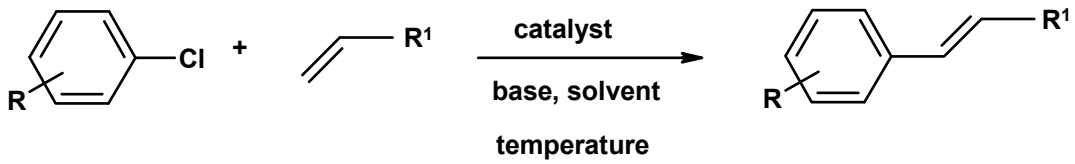
1.3.2. Heck Reaction with Aromatic Chlorides

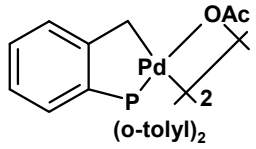
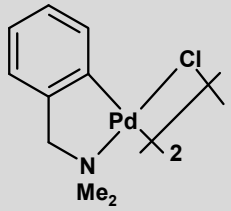
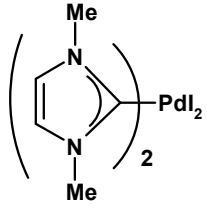
Aryl chlorides are cheaper and more easily available than bromides and iodides, but less reactive. The low reactivity of chlorides is attributed to the strength of the C-Cl bond, which leads to reluctance by aryl chlorides to oxidatively add to Pdº centers, which is the critical initial step in palladium-catalyzed coupling reactions. Most of the cited literature (Table 1.3) deals with the activated aryl chlorides or the activated alkenes in order to achieve satisfactory yields. The earliest examples of Heck reactions of activated nonheteroaryl chlorides were described by Spencer,[47] who established that $Pd(OAc)_2$/ PPh_3 catalyzes coupling of electron-deficient aryl chlorides with electron-deficient alkenes at 423 K in poor to modest yield. Herrmann et al.[48] were the first to demonstrate that palladacycles can catalyze Heck coupling of activated aryl chlorides, to obtain high conversions, nBu$_4$NBr was employed as a co-catalyst. Subsequently, both nitrogen-[49] and sulfur-[50] containing palladacycles have also been shown to be reasonably efficient catalysts for heck reactions of activated aryl chlorides. Herrmann et al. pioneered not only the use of palladacycles, but also of palladium carbenes as catalysts for heck couplings of activated aryl chlorides.[51] Additional palladium-carbene adducts have been shown to be active, however only electron-poor chlorides are suitable substrates, and elevated temperatures are required (Table 1.3., entries 4 - 6).[52] Beller and Zapf have established that Pd/ phosphite mixtures catalyze Heck couplings of activated aryl chlorides; both trialkyl- and triarylphosphites are effective.[53] Li et al. have demonstrated that Pd(II) complexes that bear phosphinous acid ligands are useful for the heck reaction of an electron-poor aryl chloride (palladium complexes possessing phosphinous acid ligands generate catalytically active electron-rich anionic species and such anionic complexes can be incorporated into catalytic oxidative addition and reductive elimination processes for cross-coupling reactions of aryl halides by facilitating the rate-limiting oxidative addition of unactivated aryl chlorides to palladium complexes).[54] A wide-ranging study of palladium-catalyzed Heck couplings of activated aryl chlorides in the presence of a variety of phosphorous ligands has been also described by Zapf and Beller.[55] Dupont and co-workers have reported that the phosphane-free catalyst system $[PdCl_2(SEt_2)_2]$/ nBu$_4$NBr, is effective for reactions of activated aryl chlorides.[56] Davison et al have reported that reaction of electron neutral chlorobenzene with styrene proceeds in modest yield in the presence of bidentate 1,2-

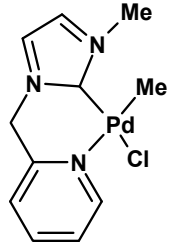
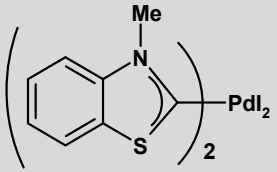
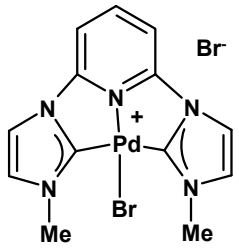
bis(diphenylphosphanyl)ethane (dppe).[57] Milstein and co-workers observed that use of a bulky, electron-rich, chelating phosphane ligand (1,4-bis(diisopropylphosphanyl)butane;dippb) furnishes a palladium catalyst that can efficiently couple electron-poor and electron-rich chlorides. Other bulky, electron-rich chelating phosphanes, such as dippp and dippe, as well as monodentate phosphanes such as P(*i*Pr)$_3$, provide essentially inactive catalysts (the reaction of chlorobenzene and styrene using Pd(OAc)$_2$ and dippb yielded 84% of heck product and the conversion was 85%).[58] Heck reactions of unactivated aryl chlorides with styrene can be performed in the presence of Pd/ dippp under reducing, nonbasic conditions to generate cis-stilbenes. Coupling of electron-rich 4-chloroanisole proceeds in a respectable yield of 49%, although dehalogenation is a significant side reaction.[59] An important contribution in the development of Heck chemistry of unactivated aryl chlorides was described by Reetz et al in 1998. In this study, they noted that simple Pd(II) complexes such as [PdCl$_2$(MeCN)$_2$] and Pd(OAc)$_2$ exhibit high activities in Heck couplings of electron-neutral aryl chlorides with styrene in the presence of tetraphenylphosphonium salts. The addition of N,N-dimethylglycine (DMG) improves the regioselectivity of the reaction (85% yield without DMG, in presence of DMG the yield is 97%). Turnover numbers in the range of 130 to 950 can be obtained for chlorobenzene and 4-chlorobenzaldehyde, respectively.[60] The most versatile method that has been reported to date for Heck couplings of unactivated aryl chlorides employs Pd/ P(*t*Bu)$_3$ as the catalyst. In 1999, Littke and Fu reported a first-generation system based on this combination. In the presence of Cs_2CO_3, this catalyst couples both electron-rich and hindered aryl chlorides with styrene and methyl acrylate. The reaction temperature was (373-393 K) was lower than for other catalysts that had been described at that time.[61] A significant improvement in the scope and the mildness of this catalyst system was realized by replacing Cs_2CO_3 with Cy_2NMe.[62] Heck couplings of activated aryl chlorides can be accomplished at room temperature with this new catalyst system. Importantly, the scope of the reaction with respect to the olefin partner was considerably widened. A range of monosubstituted and disubstituted olefins are arylated with high E/ Z stereoselectivity; essentially all previous studies of Heck couplings of aryl chlorides had focused exclusively on styrene and acrylic acid derivatives, which are particularly reactive coupling partners. The catalyst is effective for electron-rich, hindered, and heteroaryl aryl chlorides. In addition, a high turnover

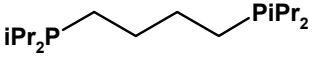
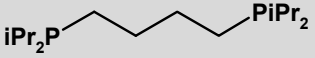
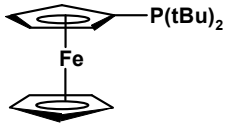
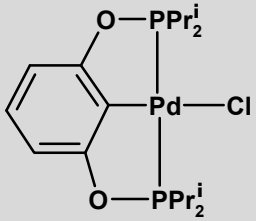
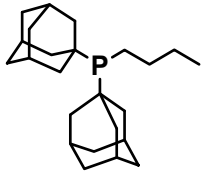
number (~300) can be achieved in the relatively challenging coupling of chlorobenzene with methyl methacrylate. Commercially available [Pd{P(*t*Bu)$_3$}$_2$], sometimes in combination with [Pd$_2$(dba)$_3$], can be employed for many of these reactions. The unusually high reactivity of Pd/ P(tBu)$_3$ in Heck reactions of aryl chlorides was discovered independently by Hartwig and co-workers through a fluorescence-based assay in which over 40 phosphane ligands were screened for activity. Only two, P(tBu)$_3$ and di(tert-butyl)phosphanylferrocene, were effective for Heck couplings of unactivated aryl chlorides.[63] Jensen and co-workers have determined that a phosphate PCP-pincer complex, is an effective catalyst for Heck reaction of a range of aryl chlorides, including hindered and electron-rich substrates. A disadvantage of this system is that a very high temperature (453 K, 24 h) or a prolonged reaction time (393 K, 5 days) is required.[64] Beller and co-workers have established that di(1-adamantyl)-*n*-butylphosphane is a highly effective ligand for Heck couplings of unactivated aryl chlorides, although hindered aryl chlorides furnish modest yields.[65] An array of bulky, electron-rich dialkylaryl- and trialkylphosphanes were screened for the palladium-catalyzed coupling of 4-chlorotoluene and styrene, and it was determined that di(1-adamantyl)-n-butylphosphane and P(*t*Bu)$_3$ afford the highest yields and turnover numbers.

Table 1.3. Literature Report on Heck Reaction Using Aromatic Chlorides as the Substrate



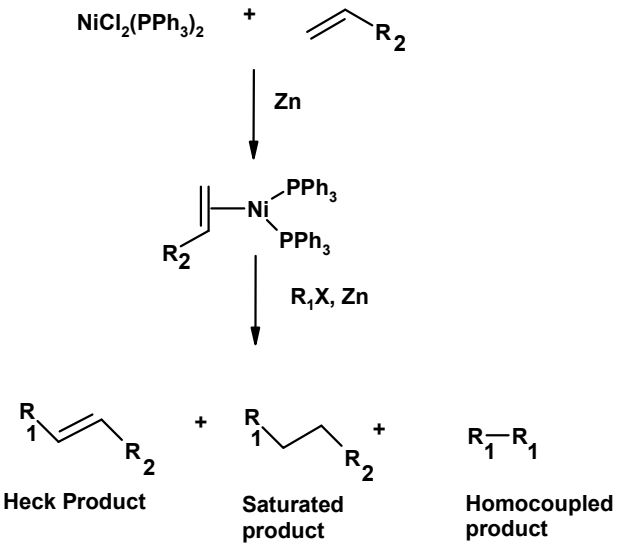
S. No.	R	R^1	Catalyst	Conditions	Yield	Reference
1	4-CHO, CN, COMe	Ph, CO_2nBu		NaOAc, DMA, 403 K	32-81	Herrmann et al[48]
2	4-NO_2	Ph, CO_2Et		K_2CO_3, NMP, 423 K	51-71	Iyer et al[49]
3	4-CHO, NO_2	CO_2nBu		NaOAc, DMA, nBu$_4$NBr,403 K	99	Herrmann et al[51]

S. No.	R	R^1	Catalyst	Conditions	Yield	Reference
4	4-CHO	CO_2nBu		NaOAc, DMA, nPr$_4$NBr, 393 K	75	Cavell et al[52a]
5	4-NO_2	CO_2nBu		$NaHCO_3$, nBu$_4$NBr, 403 K	95	Lopez et al[52b]
6	4-CHO	Ph		NaOAc, DMA, reflux	75	Crabtree et al[52c]
7	4-CF_3, 3-CF_3	Ph, $CONMe_2$	$Pd(OAc)_2$/ $P(OR)_3$ R = 2,4-(tBu)$_2$C$_6$H$_3$ or Et	Na_2CO_3, DMA, 403 K	15-89	Beller et al[53]
8	4-COMe	CO_2tBu	[$PdCl_2${P(tBu)$_2$OH}$_2$]	NaOAc, DMF, 408 K	66	Li et al[54]
9	4-COMe	Ph	$Pd(OAc)_2$/ P(nBu)$_3$	Na_2CO_3, DMA, 433 K	85	Zapf et al[55]
10	H	Ph	$Pd(OAc)_2$/ dppe	NaOAc, DMF, H_2O, 403 K	53	Davison et al[66]

S. No.	R	R^1	Catalyst	Conditions	Yield	Reference
11	4-NO_2, CHO, H, CH_3	Ph	$Pd(OAc)_2$/ 	NaOAc, DMF, 423 K	55-95	Milstein et al[58]
12	4-COMe, H, OMe, 3-OMe	Ph	$Pd(OAc)_2$/ 	Zn, DMF, 413 K	49-88	Milstein et al[59]
13	4-CHO, H	Ph	$[PdCl_2(MeCN)_2]$/ PPh_4Cl	NaOAc, NMP, 423 K	96-98	Reetz et al[60]
14	4-COMe, H, OMe, 2-Me	Ph, CO_2Me	$[Pd_2(dba)_3]$/ P(*t*Bu)$_3$]	Cs_2CO_3, dioxane, 393 K	70-84	Littke et al[61]
15	4-CO_2Me, Me, OMe	CO_2nBu	$[Pd_2(dba)_3]$/ P(*t*Bu)$_3$] or 	NaOAc, DMF, 383 K	48-97	Hartwig et al[63]
16	4-CHO, COMe, H, OMe, 2-Me	Ph		CsOAc, dioxane, 393 K	81-99	Jensen et al[64]
17	4-H, Me, OMe, 2-Me	Ph, $CO_2C_8H_{17}$	$Pd(dba)_2$/ 	K_3PO_4, dioxane, 393 K	33-98	Beller et al[65]

1.4 Other Metals in Heck Reaction

Nickel: Nickel is the close member of palladium among the group 10 triad and seems to be an appealing candidate for possible replacement of expensive palladium catalysts in the Heck reaction. However, there are certain drawbacks for e.g., $NiCl_2(PPh_3)_2$ complex showed arylation is possible but required stoichiometric amounts of a reductant such as Zn to ensure catalytic effect, which means that Ni(0) species are not effectively regenerated by the mechanism common to palladium-catalyzed Heck reaction through deprotonation of hydride complex by base.[67] The yield of the Heck product was low and also the formation of saturated and homocoupled by-products was observed.



R_1 = aryl, R_2 = electron withdrawing group, X = I, Br, Cl

A catalytic system comprising of $NiCl_2(PPh_3)_2$/ zinc/ pyridine was also found to be active for the activated and deactivated aryl bromides, but when acrylates were used there was a predominant formation of the saturated product.[68] Sugi et al developed zinc free system such as $NiCl_2.H_2O$/ PPh_3, however good conversion of 89% was achieved at higher temperatures of 433 K.[69] Bozell and Vogt showed that Nickel in the presence of palladium i.e. Pd/ Ni ($NiBr_2$/NaI/Pd_2dba_3/$P(o\text{-}Tol)_3$) protocol could be used

for the Heck reaction with aryl chlorides. The chlorides were converted to iodides in situ by the addition of sodium iodide, which then performed the Heck reaction.[70]

Platinum: The third member of the nickel triad is the Pt, which was also found to be able to participate in Heck chemistry. Platinum complex $Pt(COD)Cl_2$ with two equivalent of triphenylphosphine catalyzes the arylation of simple olefin by aryl iodides at 403 K. [71] Platinum is an expensive catalyst and gave low turnovers and inferior selectivity (5-10% reductive dehalogenation product formed) makes this catalyst hardly worthy for study. [71]

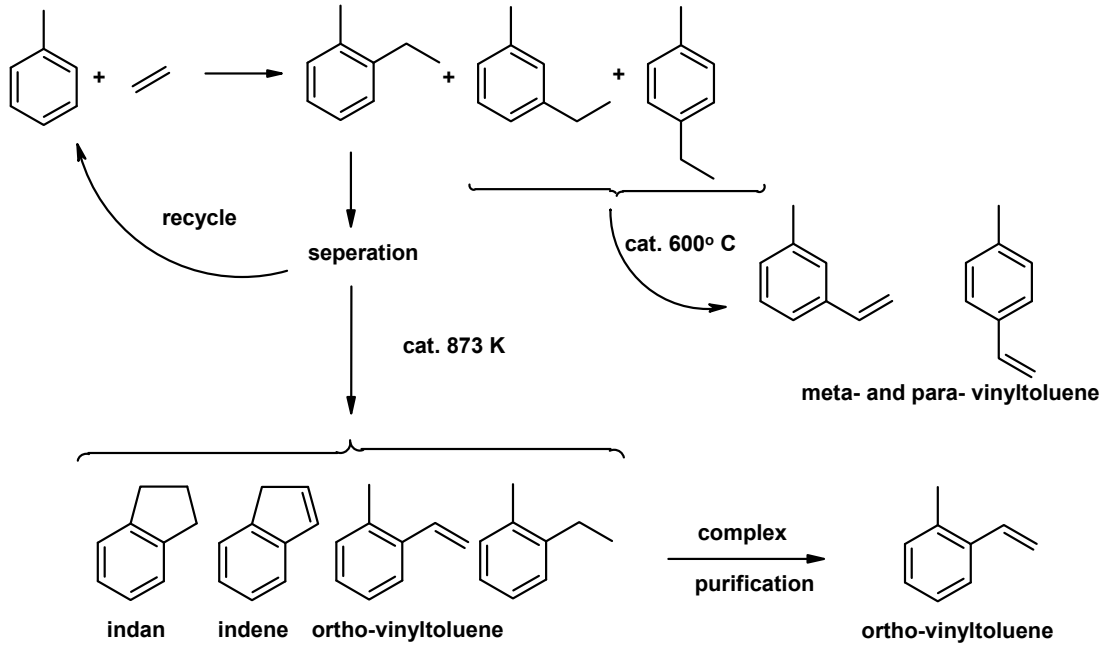
Cobalt, Rhodium and Iridium: The complexes $CoCl(PPh_3)_3$, $RhCl(PPh_3)_3$, $IrCl(CO)(PPh_3)_2$, required harsh conditions (5mol% catalyst, 423 K and 24h) to give high yields of arylation products in reactions of aryl iodides with methylacrylate or styrene.[72]

Copper: Cuprous salts either in catalytic or equimolar amounts in the absence of any extra ligands were shown to enable the arylation of olefins.[73] These systems have a poor catalytic efficiency; also the mechanism of arylation is unknown which hampers further progress of this potentially interesting method.

1.5. Arylation of Ethylene

Ethylene is the smallest of alkenes and is an extremely important building block in the petrochemical industry (some major types of reactions include, polymerization, oxidation, alkylation, etc). There are only few reports available on the arylation of ethylene (Table 1.4). The arylation of ethylene produces aryl olefins, which have great industrial importance as fine chemicals, UV absorbers, starting materials for polymers and intermediates for active compounds. Palladium catalyzed Heck arylation of ethylene offers an easy and general entry to substituted styrenes and replaces classical Friedel-Crafts chemistry and other classical organic chemistry sufficed for the production of most aromatic compounds and forms the basis for environmentally friendly production processes.[74] For example, historically *o*-vinyltoluene has been prepared by separating the *o*-ethyltoluene obtained during the alkylation of toluene with ethylene, followed by steam cracking of ethylbenzene.[75] This process to vinyltoluenes

is not very selective and generates large quantities of indan and indene during the cracking of o-ethyltoluene Scheme 1.8. These impurities are extremely difficult to separate on an industrial scale even with extensive distillation. On the other hand, the palladium catalyzed arylation of ethylene with bromotoluene affords *o*-vinyltoluene directly.[75]

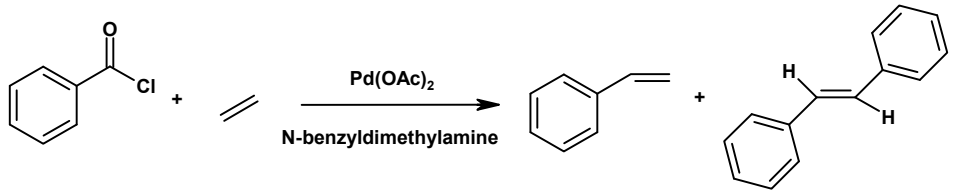


Scheme 1.8. Early Commercial Route to Vinyltoluene

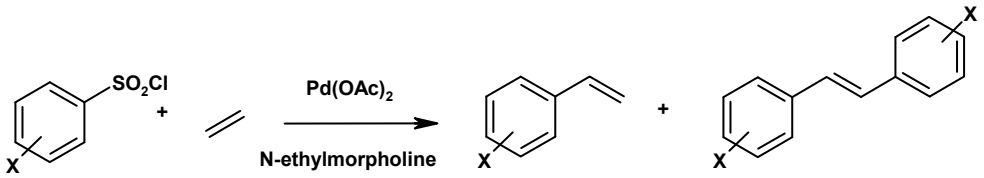
Both aryl halides as well as pseudo halides have been used as the substrate for the arylation reactions. Simple palladium salts such as $Pd(OAc)_2$ or $PdCl_2$ with or without the ligands have been used as the catalyst for Heck reaction. Earliest example of arylation of ethylene dates back to 1970s when Mizoroki et al[76] described the arylation using iodobenzene and catalytic amount of $PdCl_2$ with potassium acetate as the base. The yield of the reaction was 74% and the reaction was carried out at 393 K for a period of 3 h. The characteristic feature of this reaction was that reaction was effectively catalyzed without accompanying polymerization of the corresponding styrene derivative formed, as long as the amount of base added is greater than that of iodobenzene used. Heck et al[77] introduced the generality of the reaction by studying the reaction employing a variety of aryl bromides. Styrene derivatives with methyl, nitro, acetamide, amino, formyl, and carboxyl substituents were prepared and the yield

of the products ranged from 45 to 86%. The catalytic system comprised of $Pd(OAc)_2$ and tri-*o*-tolylphosphine in the ratio of 1:2, and reactions were carried out at 398 K and at ethylene pressure 0.689-1.37 MPa. Activity of these catalysts was found to be low (turnover frequency < 50 h^{-1}) and high catalyst loading (1 mol% of palladium salt based on halide) was essential for good activity.

Pseudo halides such as aroyl chlorides, arylsulphonylchlorides, diazonium salts have also been used as the substrates in the arylation of ethylene, e.g. Alwyn spencer[78] showed that the arylation of ethylene with pseudo halides such as aroyl chlorides, catalyzed by $Pd(OAc)_2$, leads to styrene and stilbene derivatives as shown in the scheme. The ratio of styrene to stilbene was found to dependent on ethylene pressure. At atmospheric pressure more of stilbene was formed while at 1.01 MPa the styrene formation was formed as the major product.

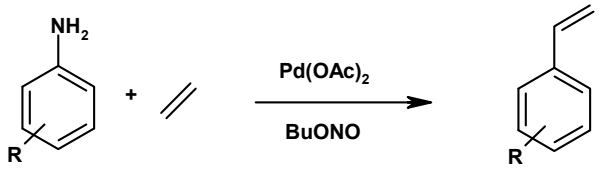


Kasahara et al[79] described the palladium-catalyzed arylation with arylsulphonylchlorides to give styrene and stilbene derivative at atmospheric pressure. The reaction required temperature of 423 K and a reaction time of 8 h to achieve a conversion of 60%, the reaction showed the formation of styrene and stilbene derivatives. Bases such as N-ethylmorpholine and N-benzyldimethylamine were used in these reactions.

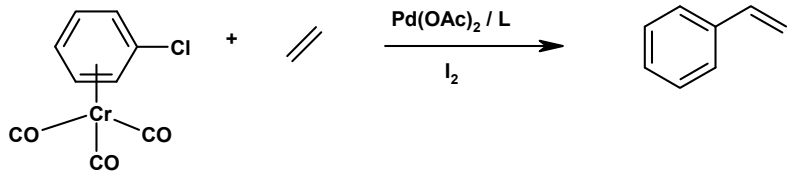


In yet another example Beller et al[80] have shown the palladium catalyzed arylation of ethylene with anilines via diazonium intermediate. The tandem diazotization-Heck reaction proceeds best with tert-butyl nitrite as diazotization reagent in a mixture of acetic acid and organic solvents. This method is the first example that describes high chemoselectivity to styrenes under low pressure of ethylene (atmospheric pressure).

Unlike other examples as described above this reaction proceeds in the absence of a base, the yields of the Heck product was in the range of 60-70 %.

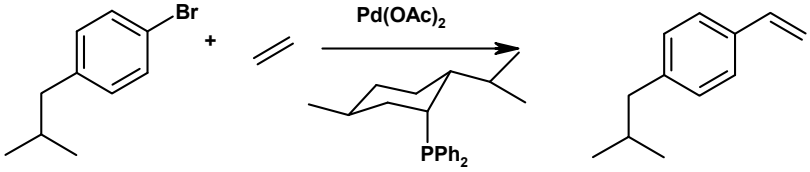


Kiji et al[81] have shown the palladium-catalyzed arylation of ethylene under aqueous or aqueous-organic solvent two-phase condions using $PdCl_2L_2$ [L = sodium *m*-(diphenylphosphino)benzenesulfonate $(C_6H_5)_2P(m\text{-}C_6H_4SO_3Na)$(tppms) or triphenylphosphine]. Three combinations were investigated out in two-phase system under basic conditions (a) both catalyst and haloarene are water-soluble and present in the aqueous phase, (b) catalyst is water-soluble and haloarene is water-insoluble, and (c) catalyst is water-insoluble and haloarene is water-soluble. Both water soluble and water insoluble bromoarenes possessing electron withdrawing groups react with ethylene to give the styrenes in good yields with water-soluble catalyst $PdCl_2(tppms)_2$. The same authors have described the arylation of ethylene using the substrate (chlorobenzene)$Cr(CO)_3$ complexes as shown in the scheme below.[82] After the reaction, the chromium complexes were oxidized with iodine and the resulting Cr-free products were analyzed by gas chromatography.

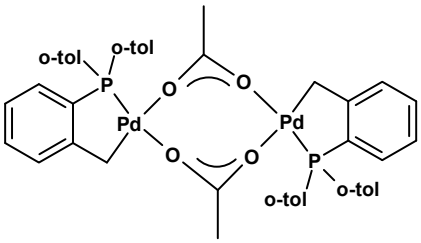


At lower ethylene pressures (0.2 MPa) the side products such as stilbene, biphenyl and benzophenone were formed. $Cr(CO)_3$ moiety serves as a source of CO in the self-coupling of coordinated chlorobenzene leading to benzophenone. However at higher ethylene pressure (4.05 MPa) the side reactions were suppressed and the yield for the styrene increased.

There are only few patents on the arylation of ethylene with industrially important substrates such as 4-bromo-isobutylbenzene, 3-bromo-benzophenone and 2-bromo-6-methoxynaphthalene, which are the precursors for the synthesis of anti-inflammatory drugs such as Ibuprofen, Ketoprofen and Naproxen respectively. Tse-Chong Wu et al[83] described the arylation of ethylene with 4-Bromoisobutylbenzene with catalytic system comprising $Pd(OAc)_2$ and NMDP (neomenthyldiphenylphosphine). These reactions were studied in the temperature range of 353-393 K, and ethylene pressure of 1.93-3.58 MPa using acetonitrile as a solvent and triethylamine as the base. The results obtained have been expressed as area percent based on GC analysis, formation of 4,4'-Diisobutylstilbene in trace quantities was also reported. Several other ligands like $P(o\text{-}tol)_3$, $P(cyclohexyl)_3$ and PPh_3 were studied, but better results were conferred using NMDP as a ligand. One example involving 2-bromo-6-methoxynaphthalene is also described using the above catalyst system, the reaction was carried out at 353 – 358 K for 5 h, the yield of the reaction was 96%.



Herrmann et al[84] have described the use of palladacycle, trans-di(μ-acetato-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) for the arylation of ethylene with 2-bromo-6-methoxynaphthalene. The reaction was performed at 413 K and 2 MPa of ethylene pressure. More than 96 % conversion was achieved in 10-16 h and the yield of the reaction was 89 % (TOF = 85 h^{-1}). The structure of the palladacycle is shown below.



Allen et al[85] have described the arylation with *m*-bromobenzophenone and 2-bromo-6-methoxynaphthalene (BMN) using the catalytic system comprising of $PdCl_2$ and NMDP. For the reaction with 2-bromo-6-methoxynaphthalene the reaction was carried out at ethylene pressure of 2.93-3.1 MPa at 368 K for a period of 4-6 h, the

reaction gave > 95 % BMN conversion and the yield of the product was 85-95% (TOF: 444 h^{-1}). There is only one example on the arylation of *m*-bromobenzophenone and the detailed work is not carried out. The performance of the colloids $[Pd(CH_3CN)_2Cl_2].6Ph_4PCl$ as described by Reetz et al [86] have also been described for this reaction (TOF = 75 h^{-1}).The Table 1.4 summarizes the reaction conditions and catalytic system that has been used for various substrates by various authors in the literature.

Table 1.4. Literature Reports on Arylation of Ethylene

S. No.	Substrate	Catalytic system	Reaction Conditions				References
			T, K	$P_{Ethylene}$, MPa	Time, h	Others	
1	Iodobenzene	$PdCl_2$ (1 mol%)	393	0.79	3	CH_3COOK,CH_3OH, Yield = 74%	Mizoroki et al[76]
2	Substituted Bromides	$Pd(OAc)_2$/ P(*o*-tol)$_3$ (1:2 mol%)	398	0.82-1.37	2-66	$(C_2H_5)_3N$, CH_3CN Yield = 45-86%	Heck et al[77]
3	*m*-Bromobenzoic acid	$PdCl_2(tppms)_2$ (6 mol%)	373	4.82	4	$(C_2H_5)_3N$, H_2O/THF, Yield = 82%	Jitsuo et al[81]
4	2-Bromo-6-methoxynaphthalene	Herrmann palladacycle (0.05 mol%)	413	1.93	10-16	CH_3COONa, N,N-dimethylacetamide Yield = 89%	Hermann et al[84]
5	2-Bromo-6-methoxynaphthalene	$PdCl_2$/NMDP (neomenthyldiphenyl phosphine) (0.05 mol%)	368	2.93-3.1	4-6	$(C_2H_5)_3N$, Diethylketone, H_2O Yield = 85-95%	Allen et al[85]
6	*m*-Bromobenzophenone	$PdCl_2$/NMDP (0.05 mol%)	368	2.96	7-8	$(C_2H_5)_3N$, Diethylketone	Allen et al[85]
7	Benzoyl chloride	$Pd(OAc)_2$ (1 mol%)	373	0.96	4	N-benzyldimethylamine, Toluene, Yield = 45%	Spencer et al[78]
8	Arylsulphonyl chlorides	$Pd(OAc)_2$ (2 Mol%)	423	0.101	8	Cymine, N-ethylmorpholine Yield = 50-60%	Kasahara et al[79]
9	Aniline	$Pd(OAc)_2$ (5 mol%)	303	0.101	18	BuONO, CH_3CO_2H, CH_2Cl_2, Yield = 60-70%	Beller et al[80]
10	2-Bromo-6-methoxynaphthalene	$[Pd(CH_3CN)_2Cl_2]$.6Ph$_4$PCl (0.05 mlo%)	413	1.99	24	N,N-dimethylacetamide	Reetz et al[86]

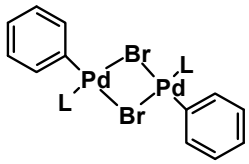
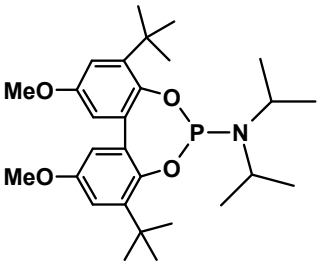
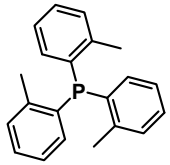
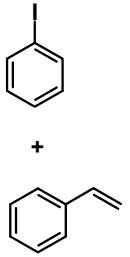
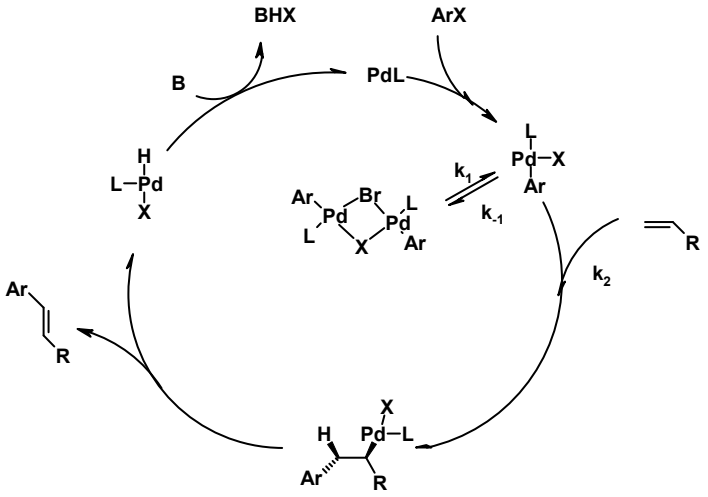
1.6. Kinetics of Heck Reactions

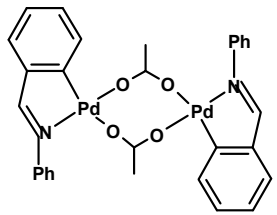
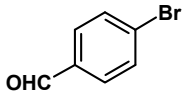
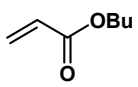
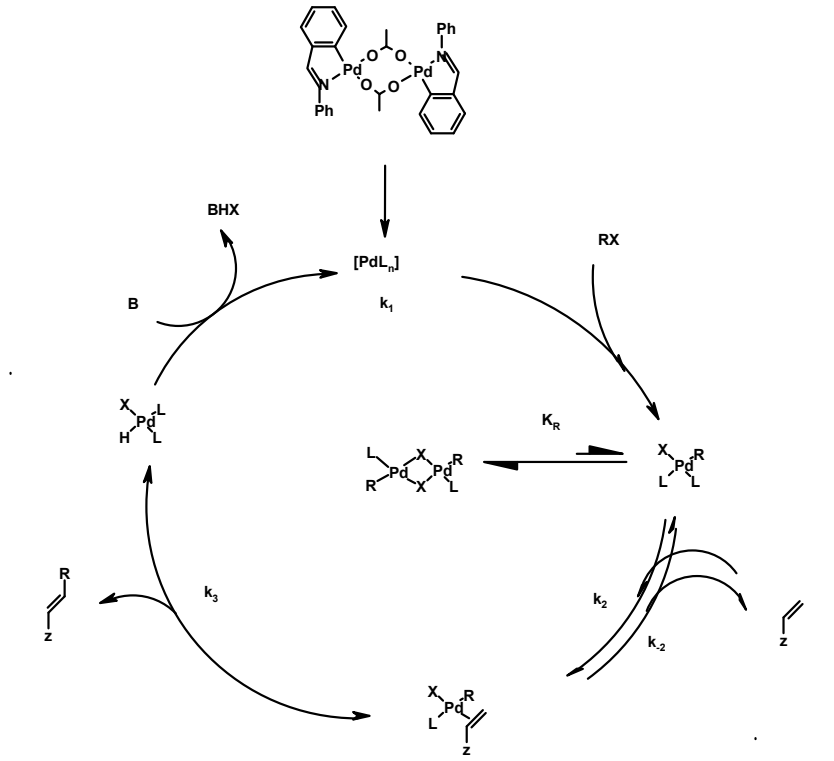
Chemical reaction kinetics is a key aspect of research and development in chemical industries, and academic institutes. Reaction kinetics translates the chemical processes into a mathematical rate expression that can be used to translate laboratory and pilot scale data into the design of a commercial scale unit. The rate or kinetic expression tells how the reaction rate varies with process conditions such as temperature, pressure, compositions and the concentration of the catalytic sites. Though voluminous work has been carried out in the Heck chemistry, for example developing new ligands and catalysts only few kinetic studies have been carried out. A summary of kinetic studies in homogeneously catalyzed Heck reaction is presented in the Table 1.5. The table reveals that different catalytic systems have been employed for the kinetic studies ranging from simple palladium salts, dimeric palladium complexes to pincer palladium complexes. Zhao et al[87] have studied the kinetics of the Heck reaction of iodobenzene with methylacrylate using $Pd(OAc)_2$/ PPh_3 as the catalyst and found that the rate of the reaction has a fractional order dependence on the $Pd(OAc)_2$ concentration, first order with respect to iodobenzene concentration, and a first order tending to zero with respect to methyl acrylate concentration. With respect to triethylamine concentration they have observed that the rate passes through a maximum with increasing triethylamine concentration. Van Leeuwen and co-workers[88] reported kinetic studies of iodobenzene and styrene using bulky monodentate phosphorus ligands, which showed the reaction to be first order with respect to styrene, zero order with respect to iodobenzene concentration, and half-order dependence on catalyst concentration. Since the rate is independent of the concentration of iodobenzene, the oxidative addition is not the rate limiting step in these systems. The rate-limiting step in this system is either alkene complexation or the migratory insertion. Blackmond et al[89] studied the kinetics of Heck reaction of *p*-bromobenzaldehyde and *n*-butylacrylate using a NC palladacycle, this reaction exhibits an induction period before a maximum in rate is reached at ca. 15% conversion of the aryl halide. They have reported a fractional order dependence of the rate on the catalyst concentration, first-order dependence on the concentration of olefin, and zero order on halide concentration. The kinetic model predicts that the rate-limiting step in this reaction is the initial binding of the olefin to form the π-complex. Blackmond et al[90] have reported

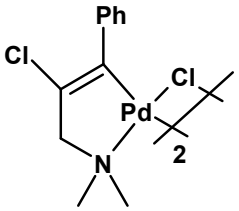
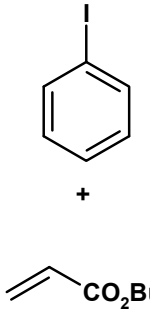
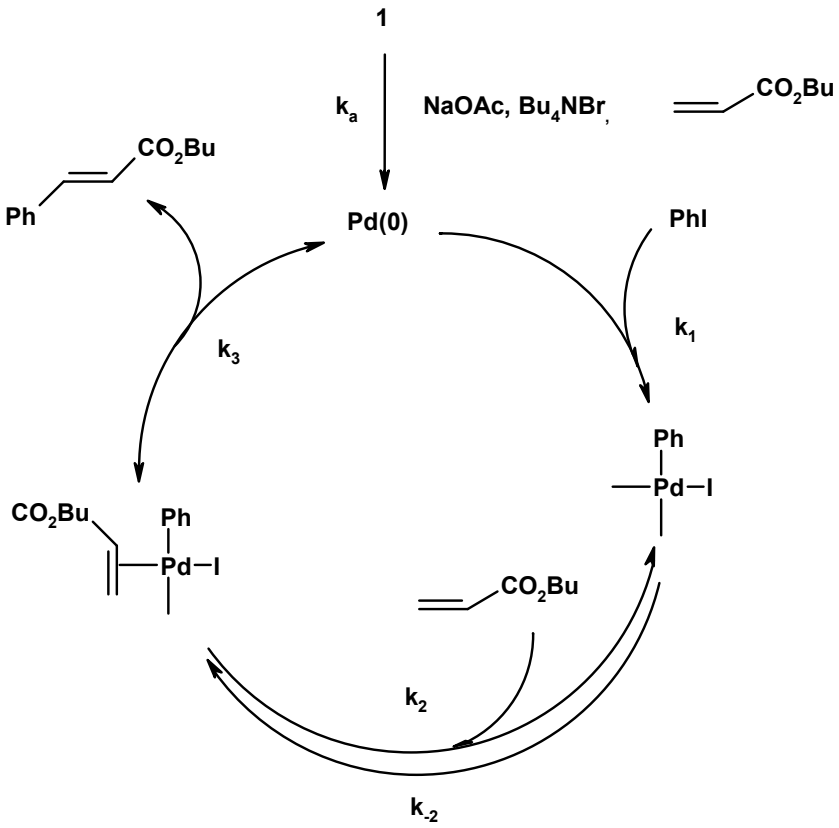
the same reaction (Heck reaction of *p*-bromobenzaldehyde and *n*-butylacrylate) under dry conditions. The rate showed the first order dependence on aromatic halide and olefin, and time dependence of catalyst concentration (concentration of active catalyst species increases as the reaction proceeds). Dupont et al[91] have reported the Heck kinetics of iodobenzene and *n*-butylacrylate using NC palladacycle as a catalyst precursor. They found first order dependence of reaction rate with respect to palladacycle concentration and a zero order dependence on NaOAc and Bu_4NBr concentrations. Saturation kinetics was found for both iodobenzene and n-butylacrylate substrates. Wendt et al[92] reported the kinetic studies of 4-iodoanisole and styrene using palladacycle complex having an aliphatic backbone, i.e., $PC_{sp3}P$ pincer complex (Table 1.5). Chaudhari et al[93] have described the kinetics of vinylation of 4-bromoacetophenone with *n*-butylacrylate using Herrmann palladacycle catalyst recently. The rate was found to be first order with respect to 4-Bromoacetophenone, fractional order with the catalyst, and first order tending to zero order with NaOAc concentration. The rates passed through a maximum with variation of TBAB and *n*-butyl acrylate concentrations.

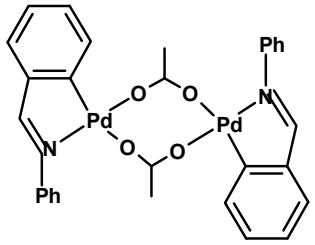
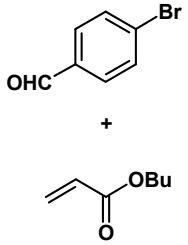
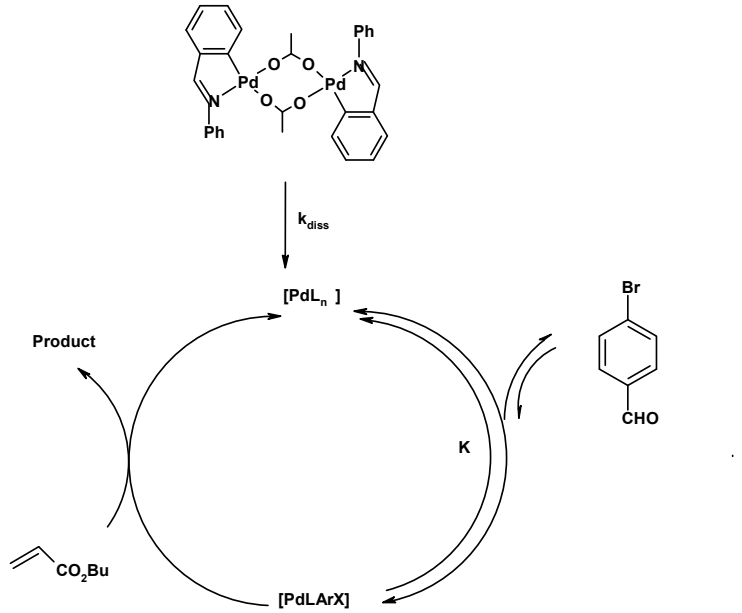
It can be seen from the above literature that, the majority of the work on kinetics of Heck reaction was carried out using dimeric palladacycle as the catalyst. There are no reports on the detailed kinetics of Heck reaction using monomeric palladacycle as catalyst precursor.

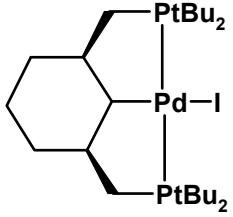
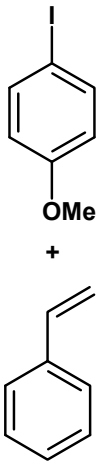
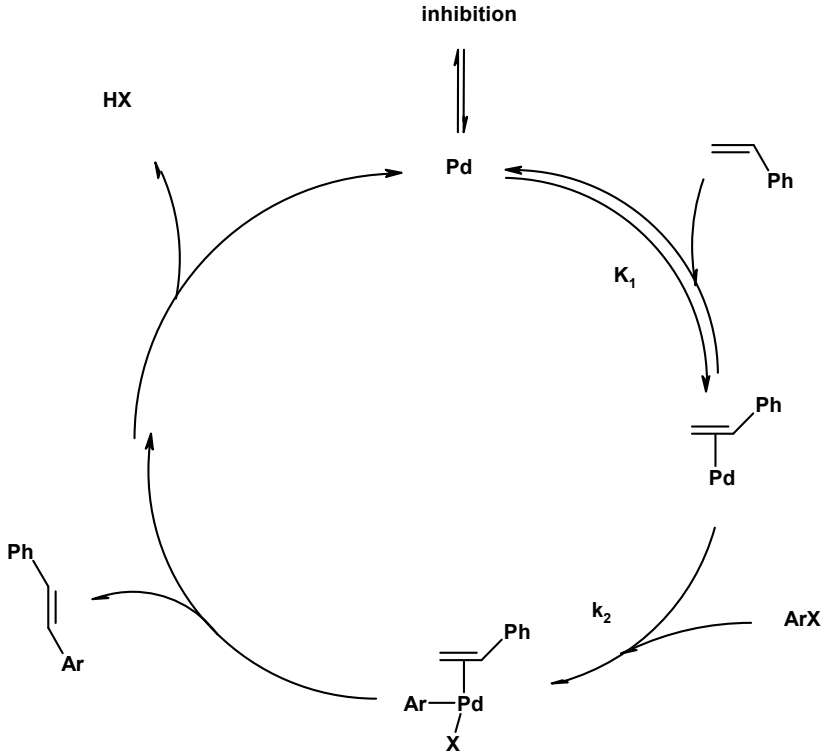
Table 1.5. Rate Equations and the Catalytic Cycle

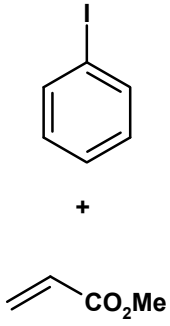
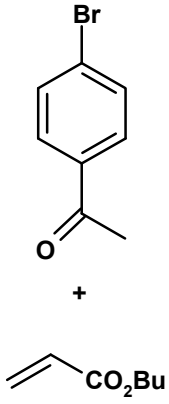
Catalyst	Reaction Scheme	Catalytic cycle	Others	Reference
 L =  Or 		 Rate = $k_2K^{1/2}$[alkene][Pd]$^{1/2}$ K = k_1/k_{-1}	338 K, CH_3CN, Et_3N, monitored by GC	Van Leeuwen et al[88]

Catalyst	Reaction Scheme	Catalytic cycle	Others	Reference
	 +  Halide = 1 Olefin = 2	 $r = \frac{2k_1k_2k_3[1][2][Pd]}{\{k_2k_3[2]+k_1(k_2+k_3[1]+k_1k_2[2])+(k_2k_3[2]+k1(k_{-2}+k_3[1][2])^2+8KR(k1(k-2+k3)[1]2[Pd])\frac{1}{2}}$	Reaction calorimeter DMAc KOAc 413 K	Blackmond et al[89]

Catalyst	Reaction Scheme	Catalytic cycle	Others	Reference
 **1**		 $r = \frac{k_1 k_2 k_3 [PhI][Acr][Pd]}{k_2 k_3 [Acr] + k_1 k_2 [PhI][Acr] + k_1 k_3 [PhI]}$	Time resolved IR using ATR probe DMA TBAB NaOAc 353 K	Dupont et al[91]

Catalyst	Reaction Scheme	Catalytic cycle	Others	Reference
	 Halide = 1 Olefin = 2	 $r = \frac{V_m'[1][2](1-\exp(-(k_{diss}t))}{(K+[1])}$	Reaction calorimeter DMAc NaOAc 413 K	Blackmond et al[90]

Catalyst	Reaction Scheme	Catalytic cycle	Others	Reference
		 $r = k_{obs}[ArX]$ $k_{obs} = \frac{K_1 k_2 [pd][styrene]}{1 + K_1[styrene]}$	DMF-d7 solution A.J. Young NMR-tube 1H NMR spectroscopy, Et3N 433 K (olefin is activated before the aryl halide)	Wendt et al[92]

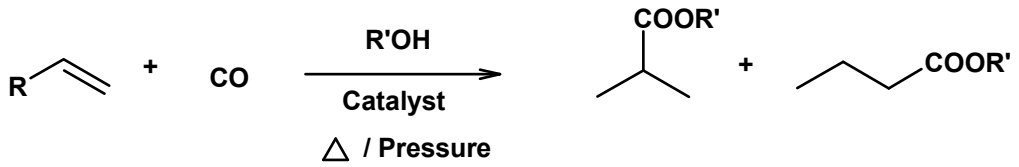
Catalyst	Reaction Scheme	Catalytic cycle	Reference
$Pd(OAc)_2$/ PPh_3		$r = \frac{k[PhI][olefin]^2[Me_3N][catalyst]}{(1+K_1[olefin]^2)(1+K_2[Me_3N]^4)(1+K_3[catalyst])^3(1+K_4[PPh_3])}$	Zhao et al[88]
Herrmann palladacycle		$r = \frac{k[BAP][BA][NaOAc][TBAB][catalyst]^{0.5}}{(1+K_{BA}[BA]^2)(1+K_{NaOAc}[NaOAc])(1+K_{TBAB}[TBAB]^2)}$	Chaudhari et al[93]

1.7. Carbonylation

In this reaction, a CO moiety is inserted into an organic substrate, forming a carbonyl compound such as aldehyde, ketone, acid, amide, lactone, anhydride etc. Various functionalities that can be carbonylated include acetylenes, mono- and di-olefins, alcohols, nitrocompounds, amines, organic halides, etc. for both aliphatic and aromatic analogs.

1.7.1. Carbonylation of Olefins

The hydroesterification (hydroalkoxycarbonylation) of olefins is one of the most important and oldest applications of transition metal complex catalyzed carbonylation reactions. A schematic representation of the reaction using a terminal olefin is illustrated in the Scheme 1.9. When R' is H, the reaction gives the arylpropanoic acid and the reaction is known as hydrocarboxylation.



R = Aryl, Alkyl, H

R' = Alkyl, H

Scheme1.9. Carbonylation of Olefins

A number of patents and publications, which have appeared on this subject, reveal that drastic conditions were often required to effect this transformation. Initial catalysts involved $Ni(CO)_4$ and $Co_2(CO)_8$ as a carbonylation catalyst which required high temperature and pressure.[94] In the later years other catalysts based on Pt, Pd, Rh were found to be more attractive because of their better performance under milder reaction conditions (Table 1.6.).[95]

Table 1.6. Comparison of Hydrocarboxylation of Olefin Using Different Catalyst Systems [Beller and Tafesh][96]

Catalyst	$Ni(CO)_4$	$Co_2(CO)_8$	PdX_2L_2	$PtX_2L_2 + SnX_2$	RhX_3
Temperature (K)	473-593	423-473	343-393	353-373	373-403
Pressure (MPa)	13-20	15-30	0.1-15	0.1-20	0.1-10

Most of these catalysts generally give mixtures of straight chain and branched chain acids/ esters. Hence, in these reactions chemo as well as regioselectivity of carboxylic acids/ esters formed is an important issue. In, general, hydrocarboxylation of α-olefins using Ni catalysts provide enhanced selectivity to the branched carboxylic acid (60—70 %), but catalysts based on Co are selective for the linear carboxylic acids. For example, the hydrocarboxylation of isomers of undecene using Co-pyridine catalyst yielded dodecanoic acid with approximately 80% selectivity.[97] However, in the case of Co and Ni, further control of carboxylic acid selectivity was difficult because of the higher operating temperature (523-593 K) that led to side reactions such as hydrogenations, oligomerization and isomerization of olefins. Since palladium, rhodium and platinum catalysts were active under relatively milder reaction conditions, they offered superior chemo and regioselectivities. For example, $PdCl_2$[98] and $PdCl_2(PPh_3)_2$[99] alongwith 10% HCl in ethanol as a solvent was reported to catalyze the carbonylation of ethylene to ethylpropionate and styrene to ethyl-2-phenyl propionate with 90% and 95% yields respectively at 368K and 30-70 MPa CO pressure. When bidentate phosphine ligands ($Ph_2P(CH_2)_nPPh_2$, n is 1-10) were used, instead of triphenylphosphine, under similar reaction conditions, the selectivity pattern was reversed attaining high regioselectivity to the liner carboxylic ester.[100] Monophosphine and Arsine ligands stabilized palladium and platinum complexes in the presence of group IV B metal halides ($SnCl_2$, $GeCl_2$, $PbCl_2$ etc.) as promoters and produced upto 98% selectivity to linear isomeric product for the hydroesterification of α-olefins.[101] $PdCl_2(PPh_3)_2$ and $PtCl_2(AsPh_3)_2$ were used here as catalysts under reaction conditions of 353 K and 30 MPa pressure. These observations indicate that the activity as well as the selectivity (both chemo- and regioselectivity) varies with the reaction parameters (temperature, pressure etc.) and catalyst properties (transition metal involved, stereo-electronic environments of ligands used, promoters, co-catalysts etc.) for the

carbonylation of olefins. Palladium complexes were found to be the best catalysts for the hydrocarboxylation and the hydroesterification of the olefins compared to other metals.

The hydroesterification of styrene derivatives produces valuable intermediates for perfumes and pharmaceuticals. For example, the production of 2-arylpropanoic acids, which constitute an important class of non-steroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen), is a scientifically interesting and potentially useful pursuit. Many companies such as Nippon Petrochemical Company Ltd.,[102] Ethyl Corporation,[103] Montedison,[104] etc., have patented their own processes for the production of Ibuprofen from *p*-isobutylstyrene and Naproxen from 2-vinyl-6-methoxynaphthalene. In a process described by Nippon petrochemicals, *p*-iosbutylstyrene was carbonylated in a biphasic system consisting of 10% aqueous HCl and toluene as the organic phase in the presence of $PdCl_2(PPh_3)_2$ as a catalyst at 30 MPa of CO and 393 K. Though Ibuprofen was produced in 89% selectivity with 100% conversion, the rate of the reaction was found to be very low (TOF = < 2 h^{-1}).[105] Similarly methyl ester of Ibuprofen was prepared using methanol as the reaction medium at 7 MPa of CO and 363 K with 88.9% selectivity and a TOF of 100-500 h^{-1}. In this system, $CuCl_2$ was used as a promoter instead of 10% HCl(aq).

The literature reports extensive studies on the hydroesterification of styrene as a model substrate. The results of the literature reports are documented in the Table 1.8. Lee et al[106] desribed the hydroesterification of 4-methylstyrene using the catalytic system $PdCl_2$-$CuCl_2$-PPh_3 in a non-polar solvent. Almost complete conversion in 2 h, and 97% selectivity to the desired branched acid were achieved. Each catalytic component and solvent had its specific role and optimal reaction conditions were defined. Both PPh_3 and $CuCl_2$ were required for the regiospecific hydroesterification of 4-methylstyrene. One of the role of PPh_3 is to stabilize molecular palladium species and to prevent the formation of inactive metal particles. $CuCl_2$ is the promoter which reoxidizes Pd(0) to active Pd(II) in palladium redox catalysis. Acidity of the reaction mixture has to be avoided and alcohol concentration should be minimized in order to prevent the formation of ether. HCl as a promoter was not found to be beneficial in this system. Yoon et al[107] reported the hydrocarboxylation and hydroesterification of 4-

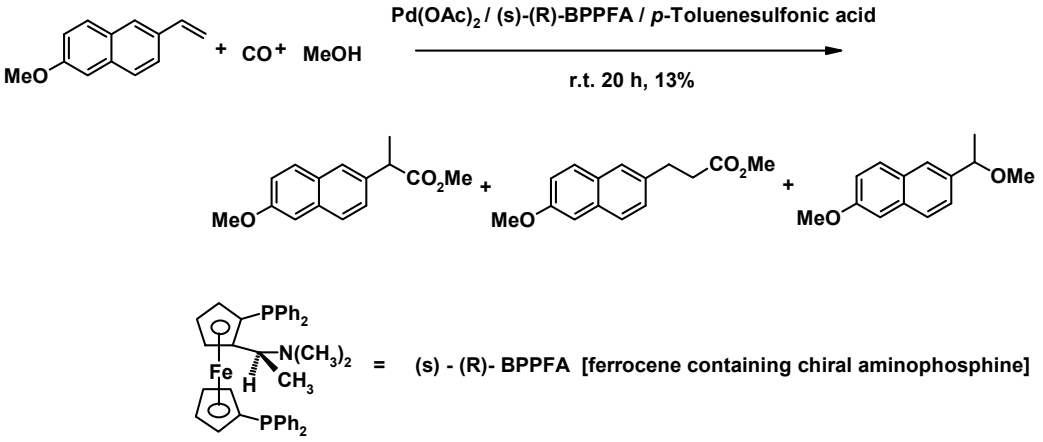
methylstyrene at 373 K and 4.1 MPa pressure using $PdCl_2$/ $CuCl_2$/ HCl catalyst system in the presence of PPh_3 as a ligand, which gave high regioselectivity (93%) to the branched aryl propionic acid/ ester with a TOF in the range of 25 h^{-1}. Cationic palladium complexes were found to be active for the hydroesterification of olefins under mild conditions. For example cationic palladium complexes such as $[Pd(MeCN)_2(PPh_3)_3](BF_4)_2$[108] and $[(Cy_3P)_2Pd(H)(H_2O)]^+BF_4^-$[109] were shown to be active for the hydroesterification of styrene to methyl-3- and methyl-2-phenyl propionates in excellent yields. Another cationic palladium complex $Pd(OTs)_2(PPh_3)_2$ formed in situ from a mixture of $Pd(OAc)_2$/ PPh_3 and TsOH is highly active for the hydroesterification of styrene. The high activity of such cationic complexes is attributed to the availability of vacant coordination sites capable of easy activation of reactants under mild operating conditions. High regioselectivity up to 96% to methyl-2-phenyl propionate was achieved at room temperature and 2 MPa, but with a very low catalytic activity (TOF = 2 h^{-1}). Seayad et al[110] have published detailed study on the hydroesterification of styrene using the above catalyst. High activities (TOF = 411 h^{-1}) were reported at higher concentration of styrene (6.73 kmol/m^3) at 348 K and 3.4 MPa. It has been shown that the regioselectivity towards methyl-2-phenyl propionate increases with decrease in the basicity of phosphine ligands as well as steric bulk around the palladium centre and polarity of the reaction medium. Seayad et al[111] reported a catalyst system consisting of $PdCl_2(PPh_3)_2$ along with promoters like TsOH and LiCl which was highly active for the carbonylation of vinyl aromatics to 2-arylpropionic acids. This catalyst system offered high turnovers (TOF up to 2255 h^{-1}) and branched acid selectivities up to 99.8% at 388 K and 5.4 MPa. Jayasree et al[112] investigated a class of novel cationic palladium complexes containing hemi-labile N-O, and N-N chelating ligands for the carbonylation reactions. Of the various complexes investigated, the $Pd(pyca)(PPh_3)(OTs)$ complex (pyca = pyridine-2-carboxylate) showed excellent activity and > 99.8 % selectivity to the desired branched carboxylic acid isomer in the presence of TsOH and LiCl promoters, under milder reaction conditions for the carbonylation of different alkenes. TOF's of 2600 h^{-1} and ~ 1300 h^{-1} were obtained for styrene and *p*-isobutylstyrene carbonylation respectively, which set new benchmark for homogeneous carbonylation of olefins. Jayasree et al described a novel water-soluble catalyst system for the hydrocarboxylation of olefins, producing excellent activity and selectivity.[113] The novel biphasic catalyst system consisted of Pd(pyca)(TPPTS)(OTs)

with LiCl and TsOH as promoters (TPPTS = triphenylphosphine trisulphonate, sodium salt). The aqueous soluble complex was prepared by simple partition technique of the exchange of the PPh_3 ligand with TPPTS, which actually brings the complex to the aqueous phase. Styrene was considered as the model substrate and catalyst system showed good catalytic activity (TOF ~ 281 h^{-1}, for styrene), and selectivity (~91% branched product) patterns.

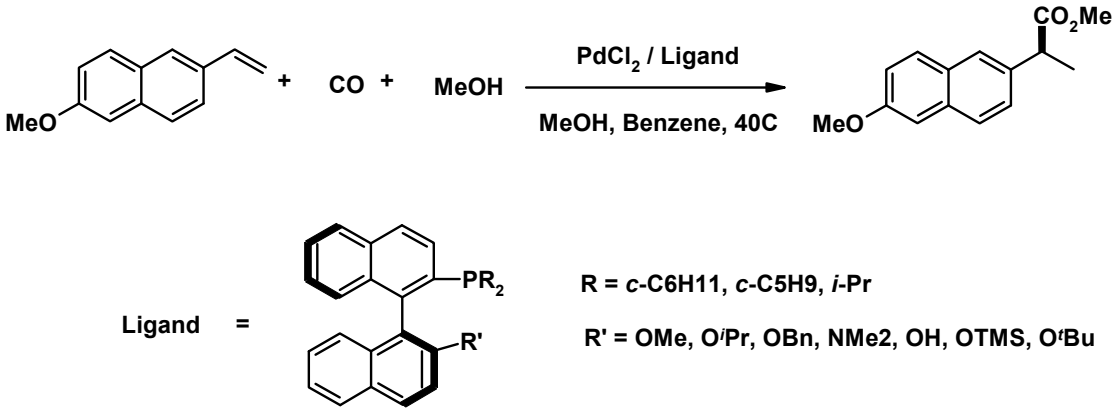
There are only a few reports on the hydroesterification of 2-vinyl-6-methoxynaphthalene (VMN) – which is an intermediate for the synthesis of naproxen. From the comparison of styrene and VMN in the carbonylation reaction it was noted that VMN as a substrate exhibited lower activity than styrene as a substrate.[111] The catalytic systems described in the literature (Table 1.7) for hydroesterification of VMN can be divided into two categories, one involving asymmetric catalysis and the other uses achiral catalysis. Among the asymmetric catalysis the chiral ligands used are as follows (i) ferrocene-containing chiral aminophosphine, (S)-(R)-BPPFA (ii) NMDP (neomenthydiphenylphosphine) (iii) dicycloalkylphosphinobinaphthalene derivatives. Achiral catalysis involves the use of catalyst such as $PdCl_2(L)_2$; L= PPh_3, $MePPh_2$, $EtPPh_2$, $P(c\text{-}C_6H_{11})_3$, ($c\text{-}C_6H_{11}PPh_2$). In chiral reaction the main aim of authors was to achieve higher regioselectivity to iso ester and look for enantioselectivity using new chiral ligands.

Takeda et al[114] described the hydroesterification of VMN using the complex $PdCl_2(PPh_3)_2$ and $BF_3\text{-}Et_2O$ in ethanol. Ph_2NNO (N-nitrosodiphenylamine) was used as a polymerization inhibitor. The yield of the reaction was 69% (ethyl-α-(6-methoxy-2-naphthyl)-propionate). Cometti and Chiusoli[104] reported catalyst system $Pd(dba)_2$/ + Neomenthyldiphenylphosphine achieving greater than 95% regioselectivity towards the branched isomer (methyl 2-(6-methoxy-2-naphthyl)-propinoate) with an enantiomeric excess of 43.8%. Hiyama et al[115] described several palladium complexes for the hydroesterification of VMN which includes, $PdCl_2(MDPP)_2$ (MDPP=menthyldiphenylphosphine), $PdCl_2(PPh_3)_2$, $PdCl_2(MePPh_2)_2$, $PdCl_2(c\text{-}C_6H_{11}PPh_2)_2$, $PdCl_2(PEt_3)_2$. Among these the palladium complex derived from the ligand $c\text{-}C_6H_{11}PPh_2$ was found to give good yields of the branched isomer; at 6.07 MPa of CO, temperature of 373 K and a reaction time of 20 h the yield of 86% was obtained. But when $PdCl_2(MDPP)_2$ was used the reaction could be carried out at milder reaction

conditions at 1.01 MPa of CO and temperature of 323 K for a period of 41 h, the yield of the reaction was 88%. Inoue et al[116] described a catalyst system comprising of $Pd(OAc)_2$ / *p*-toluenesulfonic acid, (S)-(R)- BPPFA (ferrocene-containing chiral aminophosphine) which gave very poor conversion (~13%) at room temperature over a reaction time of 20 h.



Hiyama et al[117] have also described the catalyst system $PdCl_2$/ Dicyclohexyl-phosphinobinaphthyl derivatives for the VMN hydroesterification at 313 K and 3.0 MPa of CO. The yields were in the range of 15-99% and enantiomeric excess 28-53%.



Xia et al[118] have described a heterogeneous catalyst system comprising of a silica-supported chitosan (CS) palladium complex CS-$PdCl_2$-$NiCl_2$/ SiO_2.

Most of the literature reported for the hydroesterification of VMN was carried out using asymmetric ligands which showed difficulty in obtaining both high regio- and enantioselectivities. There are only three reports (Table 1.7) on the Hydroesterification of VMN using achiral system. And the achiral catalytic system reported showed low turnover frequencies (< 10 h^{-1}). Thus there is need to develop a catalyst system which shows high activity, selectivity and stability in the hydroesterification of VMN.

Table 1.7. Literature Report on Hydroesterification of VMN

No.	Catalyst System	Reaction conditions			Conv %	Reference
		T, K	P_{co}, MPa	Miscellany		
Chiral Catalytic Systems						
1	$Pd(dba)_2$/ NMDP	323	0.1-0.2	CF_3COOH, CH_3OH, 4h,ee = 43.8%	-	104b
2	$Pd(OAc)_2$/ (S)-(R)-BPPFA	300	2.02	*p*-TsOH, CH_3OH, 20h, 53% (S)-ester	13	116
3	$PdCl_2$/ Dicyclohexylphosphinobinaphthyl derivatives	313	3	CH_3OH,C_6H_6, 24-144h, yields=20-100% ee=20-53%		117
Achiral Catalytic Systems						
4	$PdCl_2(PPh_3)_2$	353	8.33	BF_3-Et_2O, EtOH,Ph_2NNO Yield = 69%	-	114
5	$PdCl_2(c\text{-}C_6H_{11}PPh_2)_2$	373	2-6	ROH-Me_2CO/ THF,iso ester=64-95%	73-100	115
6	CS-$PdCl_2$-$NiCl_2$/ SiO_2/ PPh_3	373	4	HCl, CH_3OH, dioxane, 10 h, Conv.=96%, iso ester=95%	96	118

Table 1.8. Literature Report on Carbonylation of Olefins to Esters

No.	Catalyst system	Substrate	Reaction conditions			Conv. %	Selectivity, %		Reference
			T, K	P_{CO}, MPa	Miscellany		Iso	n	
1.	$PdCl_2(PPh_3)_2$/HCl	Styrene	363	30–70	EtOH	–	65-95	-	Bittler et al[119]
2.	$PdPh_2(CH_2)_4PPh_2]Cl_2$	Styrene	373	10–50	EtOH; 16 h	30–100	9–88	7–65	Sugi et al[120]
3.	$Pd[PPh_2(CH_2)_nPPh_2]Cl_2$ n = 1-6, 10	Styrene	398	20	EtOH-C_6H_6; 16h	45–100	12–88	5–67	Sugi et al[121]
4.	$PdCl_2$+PPh_3/DIOP/ PPh_2(neomenthyl)	Styrene, α-methyl styrene	373	38–72	ROH-C_6H_6	–	1–100	1–100	Consiglio & Marchetti[122]
5.	$PdCl_2(PPh_3)_2/SnCl_2$	Pentafluoro styrene	373–398	7–12	MeOH-Me_2CO; 24–60 h	9–92	22–79	21–78	Fuchikami et al[123]
6.	$Co_2(CO)_8$/pyridine	Styrene	373–423	5	MeOH	40-100	–	25-79	Zhigao & Zilin[124]
7.	$PdCl_2/HCl/CuCl_2/O_2$	*p*-Methyl styrene	RT	0.1	Dioxane; 24-95 h	–	90–92	7	Mlekuz et al[125]
8.	$PdCl_2$	Styrene	313	0.1	MeOH/LiCl; 16-20 h	75	67	33	Wayner & Hartstock[126]
9.	PdO/HCl/PPh_3/ZnO	Arylethylenes	363	7.5	MeOH	93	98	2	Shimizu and Nomura[127]

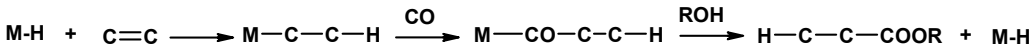
No.	Catalyst system	Substrate	Reaction conditions			Conv. %	Selectivity, %		Reference
			T, K	P_{CO}, MPa	Miscellany		Iso	n	
10.	$Pd(PPh_3)_4$ or $Pd(dba)_2$/dppb	Substituted styrenes	423	8.2	48-72 h		6.6-96	5-96	Lin and Alper[128]
11.	$PdCl_2(PPh_3)_2$/ $SnCl_2$	Styrene	368-393	2	Dioxane	Kinetic and mechanistic studies			Noskov et al[129]
12.	$(Cy_3P)Pd(H)(H_2O)]BF_4^-$ /dppb/TsOH	Substituted styrenes	373	2	MeOH -THF; 48h	–	12-23	77–88	Huh & Alper[130]
13.	$Pd(OAc)_2$-Montmorillonite-PPh_3/HCl	Substituted styrenes	398	4	MeOH-C_6H_6; 24 h	88–100	100	–	Lee & Alper[131]
14.	$Pd(OAc)_2$/PPh_2CH_2COOH /TsOH	Styrene	403	4	EtOH; 6 h	53	7.6	38	Hongying et al[132]
15.	Montmorillonite-diphenylphosphine $PdCl_2$/Ligand/HCl	Styrene	393	4.5	MeOH-C_6H_6; 24 h		50–100	2–50	Nozaki et al[133]
16.	$Pd(MeCN)_2(PPh_3)_2](BF_4)_2$	Styrene	303–353	0.5 to 2	MeOH; 4 h	21-94	27–83	17–74	Oi et al[134]
17.	$Pd(OAc)_2$/ PPh_3/TsOH or CF_3SO_3H	Styrene & *p*-IBS	RT–323	2	MeOH; 4 h	19–95	75–96	4–25	Oi et al[134]
18.	PVP-$PdCl_2$-$NiCl_2$-PPh_3	Styrene	353	2	MeOH – C_6H_6; 10-36 h	79–100	91–99	1-8	Wan et al[135]
19.	$PdCl_2(PhCN)_2$ /p-tert-butyl-calix[4]arene based phosphines/ phosphinite	Styrene	403	14	MeOH-toluene; 48-140 h	39–70	47–62	–	Csok et al[136]
20.	$PdCl_2$-ferrocene based catalysts	Styrene	383	13	MeOH-toluene; 180-450 h	50–100	28	–	Jedlicka et al[137]

No.	Catalyst system	Substrate	T, K	P_{CO}, MPa	Miscellany	Type of study	Reference
21.	$PdCl_2(PPh_3)_2/SnCl_2$	Styrene, α-methyl styrene	403	4	ROH-toluene	Mechanistic studies	Benedek et al[138]
23.	$Pd(OAc)_2/PPh_3$/TsOH	Styrene	348	3.4	MeOH	Kinetic studies	Seayad et al[110b]
24.	$Pd(OAc)_2/PPh_3$/TsOH	Styrene	348	3.4	MeOH	Mechanistic studies	Seayad et al[139]

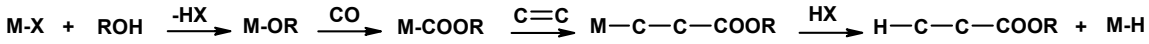
1.7.2. Mechanistic Considerations

The mechanism of hydroesterification and hydrocarboxylation of olefins catalyzed by transition metal complexes has been extensively studied and two kind of mechanisms have been proposed viz., one involving hydridometal and acyl metal intermediate followed by solvolysis (M-H addition)[140] and the other involving (alkoxycarbonyl)- or hydroxycarbonyl)metal and [β-(alkoxycarbonyl)alkyl]- or [β-(hydroxycarbonyl)alkyl]metal intermediates followed by acid cleavage of the palladium-alkyl bond (M-COOR addition).[141]

M-H addition



M-COOR addition



Both the routes have been generally accepted as basis for palladium-catalyzed carbonylation of olefins. There was no conclusive evidence to exclude either pathway totally and, indeed, it is possible that both routes may be operative, apparently depending on the reaction conditions, particularly added acids or bases, the transition metals and substrates.

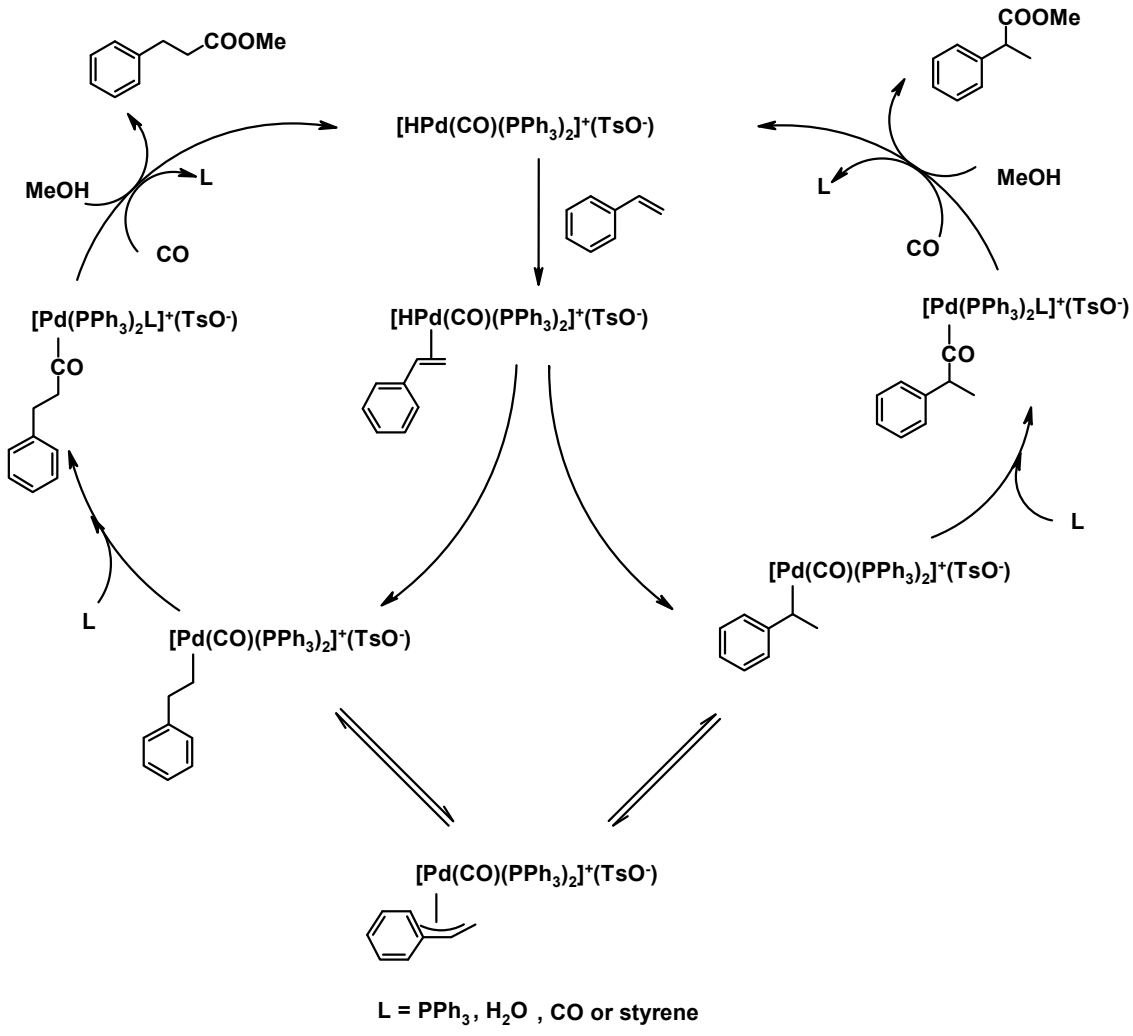
Knifton[101a] proposed a hydride mechanism for the hydrocarboxylation of olefins using $PdCl_2(PPh_3)_2$/ $SnCl_2$ catalyst system, which is supported by the isolation of a hydrido palladium complex $HPd(PPh_3)_2(SnCl_3)$ from a stoichiometric reaction of $PdCl_2(PPh_3)_2$ with $SnCl_2.2H_2O$ in benzene-ethanol as solvent under CO and was proposed to be the active catalytic intermediate initiating the catalytic cycle.

Noskov et al have carried out a detailed investigation on the kinetics and mechanism of hydrocarboxylation of olefins using $PdCl_2(PPh_3)_2$ as a catalyst precursor. The authors

proposed a hydride mechanism for the hydrocarbonylation of styrene using $PdCl_2(PPh_3)_2$ as a catalyst in wet-dioxane as a solvent.[129] In order to explain the hydride mechanism, deutrocarboxylation of styrene in the presence of D_2O instead of H_2O was carried out at 383 K and 2 MPa,[129b] which showed substitution of terminal protons of the unreacted styrene with deuterium to a significant degree. This has been explained with the help of the reversible insertion of styrene into a Pd-H bond. Hydride mechanism was confirmed by the detection of Pd-acyl complex, which is one of the key intermediates in the hydride mechanism, by *in situ* IR studies.[129c] A characteristic absorption at 1680 cm^{-1} corresponding to $(PhC_2H_4CO)PdCl(PPh_3)_2$, was found to develop as the reaction proceeds. It was shown that under reaction conditions no carbonyl absorptions corresponding to methoxy complexes (1600-1900 cm^{-1}) were detected. Other carbonyl species detected were Pd(0)-carbonyls such as $Pd(CO)(PPh_3)_2$ and $Pd(CO)_2(PPh_3)_2$. These carbonyl species were believed to form the active Pd-H species by the oxidative addition of a molecule of HCl. The regioselectivity, a key problem in transition metal catalyzed carbonylation reactions, was explained with the help of three different Pd-H species as the active catalyst initiating different catalytic cycles. With this proposed catalytic cycle the effect of partial pressure of CO and concentration of PPh_3 on the regioselectivity was well explained. In accordance with the ^1H NMR as explained above, the insertion of olefin into the Pd-H bond leading to the formation of linear coordination is irreversible and only that leading to the branched coordination was reversible under the experimental conditions.[129b] They proposed that the hydrolysis of the acyl intermediates produce the corresponding Pd(0) species rather than the corresponding Pd-H species.[129f] It was proposed that the monocarbonyl species, $Pd(CO)(PPh_3)_2$, produce both the isomers while, exclusive formation of branched and linear products were formed through the double carbonyl, $Pd(CO)_2(PPh_3)$, and the $Pd(PPh_3)_3$ species respectively.

Seayad et al[139] have reported a detailed investigation on the hydroesterification of styrene using an *in situ* formed cationic palladium complex $Pd(OTs)_2(PPh_3)_2$ from $Pd(OAc)_2$, PPh_3 and TsOH in methanol. The authors have isolated a cationic hydrido palladium complex of the type $[HPd(CO)(PPh_3)_2]^+(TsO^-)$ by the reaction of the catalyst precursor system $Pd(OAc)_2$/ $4PPh_3$/ 10TsOH with CO (3.4 MPa) at 348 K. No Pd-methoxy complexes were isolated in the presence of excess TsOH, but were isolated

from reactions in the absence of TsOH. The formation of Pd-H species was also confirmed by ^{31}P NMR experiments in which, the ^{31}P NMR analysis of intermediate samples of the above reaction before and after adding styrene were made, which indicated the formation of Pd-alkyl complexes of the type$[(n\text{-St})Pd(CO)(PPh_3)_2]^+(TsO^-)$ and $[(iso\text{-St})Pd(CO)(PPh_3)_2]^+(TsO^-)$ on addition of styrene. Further, an acyl complex of the type trans-$PdCl(COCH_2CH_2Ph)(PPh_3)_2$ was isolated from the hydroesterification reaction of styrene using $PdCl_2$/ $4PPh_3$/ 10TsOH as the catalyst system at lower reaction temperature. Based on these observations a catalytic cycle was proposed which proceeds through the hydride mechanism initiated by the cationic hydridocarbonylpalladium(II) complex.



1.8. Summary of the Literature Surveyed

The following observations emerged from literature review

- ✓ Though palladium, platinum, nickel, cobalt, and rhodium complexes have been shown to be active catalysts for Heck and carbonylation reactions, most of the research focuses on palladium catalysts.
- ✓ Presently research on Heck reaction is devoted to design catalysts that have higher activity and stability and thus can give very high TON. Research in this direction has led to the development of palladacycle catalysts, which have turned out to be one of the most active catalysts employed for Heck reaction of bromo and chloroarenes in terms of TON and TOF.
- ✓ There is a scarcity in the literature on arylation of ethylene with industrially important substrates such as BMN, BBP and BIBB. Also there are no reports on the arylation of ethylene using NC palladacycles as catalysts.
- ✓ There are very few kinetic studies with homogeneous catalyst complexes. Kinetic studies using dimeric palladacycle complex is reported but there are no reports using monomeric palladacycle complexes.
- ✓ There are very few reports on the hydroesterification of VMN and needs improved catalysts with respect to activity, selectivity and stability. Also there are no studies using palladium complexes containing chelating nitrogen ligands for the hydroesterification of VMN.

1.9. Scope and Objectives

It is evident from the literature review presented that Heck arylation of ethylene followed by carbonylation provide cleaner routes for the synthesis of carboxylic acids or esters. While extensive work has been done on the catalytic activity and selectivity of differernt catalysts, various aspects need further investigations. Challenges are in improving the TON/ TOF and selectivity under mild operating conditions to evolve commercially attractive and economically viable catalyst system. Consequently, the main objective of the present work was to develop improved homogeneous catalyst system for Heck arylation and Carbonylation reaction to 2-aryl propionic acids/ esters which are important in fine chemical and pharmaceutical industries. The complexity of

reaction mechanism in these reactions, provide a challenge in understanding scientific issues on kinetics and reaction mechanism. With these objectives, the following specific problems were chosen for the present work.

- Synthesis, characterization of new NC palladacycles and their catalytic performance in the arylation of ethylene
- Kinetic modeling of arylation of *n*-butylacrylate with 3-bromo-benzophenone using NC palladacycle catalyst
- Hydroesterification of 2-vinyl-6-methoxynaphthalene with palladium complexes containing chelating nitrogen ligands

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Chapter 2

Synthesis and Characterization of New NC Palladacycles and their Catalytic Performance in the Heck Arylation of Ethylene

2.1. Introduction

Palladium compounds containing at least one metal-carbon bond intramolecularly stabilized by at least one donor atom, termed as cyclopalladated compounds or palladacycles, are one of the most popular class of organopalladium derivatives as novel catalysts for a variety of reactions.[1] The general structures of such complexes are shown in Figure 2.1.

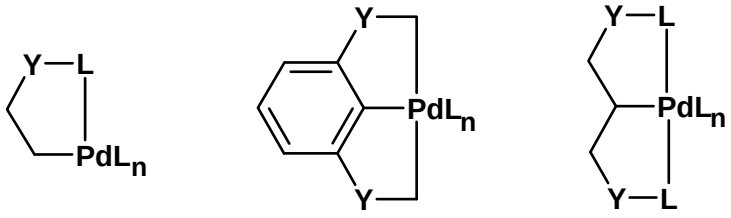
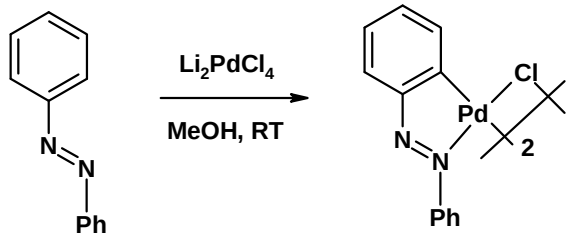


Figure 2.1. Generalized Palladacyclic Structures

L = donor, Y = linker group

The metallated carbon is usually an aromatic sp^2 carbon and less commonly sp^3 carbon or a sp^2 vinylic carbon. Palladacycle complexes such as (Scheme 2.1) were initially isolated and characterized from the cyclopalladation of azobenzene derivatives in the middle of 1960s.[2] Since then, numerous cyclopalladated[1] compounds have been synthesized and used as homogeneous catalysts for applications in organic synthesis. There are many types of palladacycles, particularly those with nitrogen[3], phosphourous[4], sulphur[5] and oxygen[6] containing donor ligands.

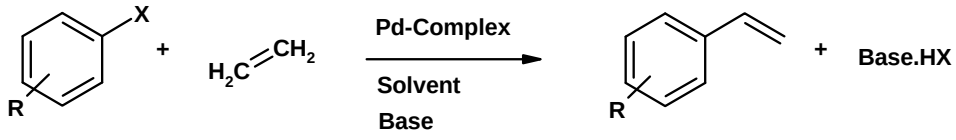


Scheme 2.1 Formation of Palladacycle with Azobenzene

A plethora of cyclopalladated compounds have been successfully used in the C-C coupling[7] reactions. The tide of palladacycles for Heck reaction began in 1995 by a pioneering work by Herrmann et al[8], who discovered that a well-known complex (*trans*-Di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II)), readily formed by heating $Pd(OAc)_2$ with $(o\text{-tol})_3P$, shows an outstanding catalytic activity, far surpassing

the activity of classical $Pd(OAc)_2$/ $(o\text{-tol})_3P$ catalytic system. This complex is most extensively studied and used in different types of Pd-catalyzed Heck reactions[9]. They are not sensitive to air or moisture and can be stored indefinitely. They are thermally stable molecules which is the main reason for exhibiting higher activity.

The palladium catalyzed coupling reaction of organic halides with olefins allows a one step synthesis of aromatic olefins, which is of considerable importance in fine organics, specialty monomers, pharmaceuticals, UV absorbers and precursors of active compounds. The arylation of ethylene with substrates such as 2-bromo-6-methoxynaphthalene, 3-bromo-benzophenone and 4-bromo-isobutylbenzene produces vinyl aromatics which are key intermediates for the synthesis of anti-inflammatory drugs such as Naproxen, Ketoprofen, and Ibuprofen respectively. Major emphasis of the work during recent times has been on the development of catalysts that are more stable compared to the classical palladium (0) phosphine complexes. Typical examples are palladacycles, which remain active at higher temperatures (373 to 413 K) leading to higher reaction rates and thus allow lower catalyst loadings and high turnover number (~2,00,000). From the literature reports (see Chapter 1, Table 1.4), it was observed that though enormous reports are available for Heck reactions there are very few reports available on the arylation of ethylene, particularly for the important substrates having potential applications in the synthesis of important drugs such as Ibuprofen, Naproxen etc. The arylation of ethylene is described by the following generalized stoichiometry:



X = I, Br, Cl

R = electronwithdrawing/ donating group

The catalytic system proposed previously for the arylation of ethylene with 2-bromo-6-methoxynaphthalene (BMN) includes the Herrmann palladacycle and $PdCl_2$/ NMDP (neomenthyldiphenylphosphine). However the activity of these catalysts was found to be very low (TOF: 85 h^{-1} and 444 h^{-1} respectively). The performance of the

colloids $[Pd(CH_3CN)_2Cl_2].6Ph_4PCl$[10] has also been described for these reactions (TOF: 75 h^{-1}). For the arylation of ethylene with 3-bromobenzophenone, $PdCl_2$/ NMDP catalyst showed a TOF of 229 h^{-1} (Table 2.1, No. 3). The arylation of ethylene with 4-bromoisobutylbenzene was also carried using $PdCl_2$/ NMDP catalyst, but the results are based on area percent in GC analysis, do not provide quantitative details of yields (Table 2.1, No. 4). Table 2.1 describes the reaction conditions for the arylation reactions using various catalyst systems studied previously for industrially important substrates.

Table 2.1. Literature on Arylation of Ethylene With Important Substrates

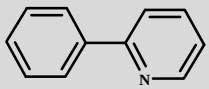
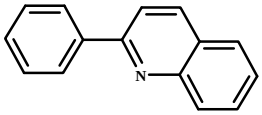
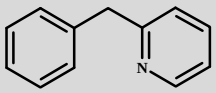
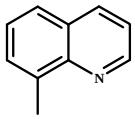
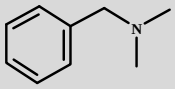
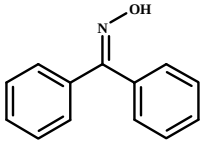
No.	Substrate	Catalyst	Reaction Conditions			Reference/ (TOF, h^{-1})
			T, K	$P_{C_2H_4}$ MPa	Others	
1	BMN	Herrmann Palladacycle	413	1.93	N, N-Dimethyl-acetamide, NaOAC, time: 10-16 h, Conv.: 95%,Yield: 89%	11 (85)
2	BMN	$PdCl_2$/ NMDP	368	2.93-3.1	Diethylketone Triethylamine H_2O, time: 4-6 h Conv.: 95%, Yield: 85-95%	12 (444)
3	BBP	$PdCl_2$/ NMDP	368	2.75-3.1	Diethylketone Triethylamine time: 8 h Yield: 93%	13 (229)
4	BIBB	$Pd(OAc)_2$/ NMDP	398	1.93	Acetonitrile, Triethylamine time: 2 h	14

2-Bromo-6-methoxynaphthalene (BMN), 3-Bromobenzophenone (BBP), 4-bromo-isobutylbenzene (BIBB)

The drawbacks of these catalyst systems are higher operating temperature (413 K) & catalyst loading (~0.05 mol %) to obtain good activity and desired selectivity (for Herrmann palladacycle, Table 2.1), and use of expensive ligand (NMDP, considering the industrial perspective). Therefore, further improvement in the catalyst

performance to enhance TOFs, selectivity (under milder reaction conditions) and stability is highly desirable. Palladacycle complexes are stable at higher temperatures,[8] however, catalytic activity was found to be very low for the Heck arylation of ethylene.[11] The objective of this study was to establish the potential of nitrogen containing palladacycles as catalysts in the arylation of ethylene, partly since phosphorous and sulphur ligands are generally much more expensive than the corresponding nitrogen ligands. Also, there are no previous reports on arylation of ethylene using NC Palladacycle catalysts. In the present work new NC palladacycle complexes were prepared using cheaper and easily available ligands such as 2-phenylpyridine, 2-phenylquinoline, 2-benzylpyridine, 8-methylquinoline, N,N-dimethylbenzylamine and benzophenoneoxime (Table 2.2). The Palladacycle complexes were characterized in detail and their usefulness as catalysts in Heck arylation of ethylene have been demonstrated.

Table 2.2. Aromatic Ligands Used for the Synthesis of NC Palladacycle Complexes

Ligand	Structure	Abbreviation
2-Phenylpyridine		ppy
2-Phenylquinoline		pquin
2-Benzylpyridine		Bnpy
8-methylquinoline		mquin
N,N-dimethylbenzylamine		dim
Benzophenoneoxime		bpoxime

2.2. Experimental Section

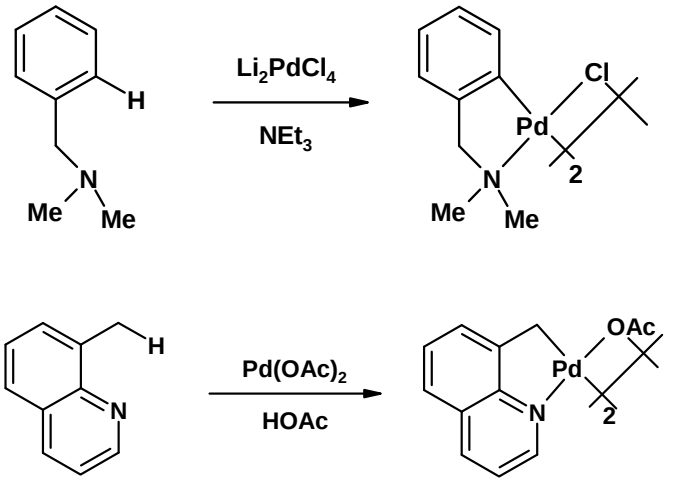
2.2.1. Methods for Preparation of Palladacycles

The synthesis of palladacycle complexes is facile and it is possible to modulate their electronic and steric properties simply by changing (i) the size of the metallacyclic ring (3-10 member), (ii) the nature of the metallated carbon atom (aliphatic, aromatic, vinylic, etc.), (iii) the type of donor group (N-, P-, S-, O- containing group, etc.) and its substituent (alkyl, aryl, etc.), or (iv) the nature of the ligands (halide, triflate, or solvent, e.g. THF, H_2O). These factors determine whether the complex is dimeric, monomeric, neutral, or cationic.

There are several methods available for the synthesis of palladacycles (C – H activation, oxidative addition, transmetalation, or nucleophilic addition onto unsaturated bond), a brief discussion of which is presented below.[1]

2.2.1.1 C – H Bond Activation

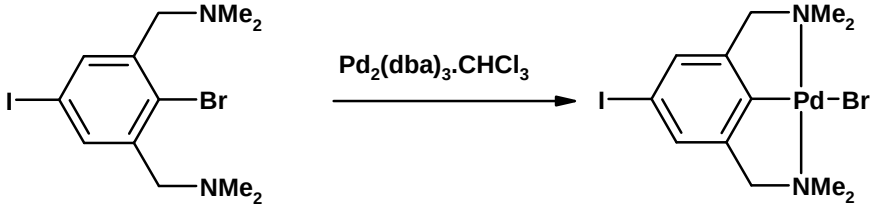
Palladation of C–H bonds is the most simple and direct method for the construction of palladacycles, also termed orthopalladation. Common palladation agents include tetrachloropalladated salts or palladium acetate. Cyclopalladation of aromatic derivatives is generally considered to occur by a simple electrophilic aromatic substitution pathway. Cyclopalladation via C – H bond activation is shown in the Scheme 2.2.



Scheme 2.2. Examples of Cyclopalladation via C – H Bond Activation using Different Palladating agents[15]

2.2.1.2 Oxidative Addition

The oxidative addition of aryl halides and, to a lesser extent, alkyl halides, containing a two-electron donor group, is useful method for the generation of various palladacycles that cannot usually be obtained by direct C – H bond activation procedures. The palladium starting material used are $Pd(dba)_2$ or $Pd_2(dba)_3$ or $Pd(PPh_3)_4$. Scheme 2.3. shows the palladacycle formed by oxidative addition.[16] The major drawback of the oxidative addition methodology is the accessibility of the halo starting material, which in many cases is prepared by a multistep procedure.

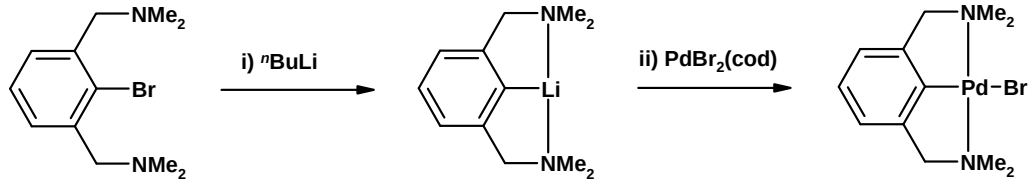


Scheme 2.3. Palladacycle Formation via Oxidative Addition

Solid $[Pd_2(dba)_3.CHCl_3]$ was added to a solution of $IC_6H_2(CH_2NMe_2)_2$-3,5-Br-4 in toluene at 193 K. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure to form the palladacycle.

2.2.1.3 Transmetallation

The transmetalation reaction is an interesting and often-used methodology for the generation of palladacycles. In most cases the transmetalating agents are organolithium or organomercurial reagents (Scheme 2.4). The organolithium reagents can be prepared directly by the selective lithiation of the ligand or by Li/ halogen exchange, which is usually quantitative.

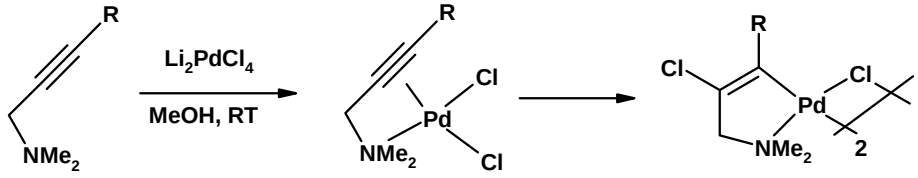


Scheme 2.4. Palladacycle Formation via a Transmetalation Reaction[17]

A solution of $Li(C_6H_3(CH_2NMe_2)_2)$ was prepared by adding drop wise the aryl halide as a solution in diethyl ether to stirred suspension of excess lithium shavings in diethyl ether and refluxed. The solution of the lithium compound was slowly added to $PdBr_2(cod)$ at 273 K. the mixture was stirred and the product was collected by filtration.

2.2.1.4 Nucleophilic Addition onto Unsaturated Bond

The reaction proceeds through coordination of both the donor group and C = C bond to the electrophilic Pd (II) center followed by nucleophilic addition to the unsaturated carbon, leading to more stable palladacyclic ring (Scheme 2.5.).



Scheme 2.5. Palladacycle preparation by Chloropalladation of Acetylenes[18]

The Palladacycles described here in this chapter are prepared by C – H bond activation method.

2.2.2 Instrumentation

^1H NMR spectra were obtained on a Bruker AC-200 Spectrometer in $CDCl_3$ at room temperature. ^{31}P NMR spectra were obtained on a Bruker AC-200 or MSL-300 spectrometer in $CDCl_3$ at room temperature. The peak positions are reported with positive shifts in ppm downfield of TMS as calculated from the residual solvent peaks or downfield of external H_3PO_4. FT-IR spectra were recorded on the Bio-Rad Spectrophotometer. The analysis of reactants and products was carried out by a gas chromatographic method using a capillary column packed with 5% phenyl methyl siloxane. For this purpose, HP 6890 gas chromatograph was used. GC-MS analysis was carried out on an Agilent GC machine of 6890N series equipped with 5973 N Mass Selective Detector.

2.2.3 Materials

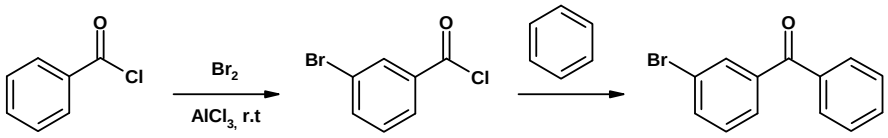
2-Phenylpyridine, 2-Phenylquinoline, 8-Methylquinoline, 2-Benzylpyridine, N – N-dimethylbenzylamine, triphenyl phosphine (PPh_3), *o*-tolylphosphine ($P(o\text{-tol})_3$),

Palladium acetate $Pd(OAc)_2$, Palladium dichloride ($PdCl_2$), *p*-toluenesulphonic acid monohydrate ($TsOH.H_2O$) were obtained from Aldrich Chemicals, USA and were used as obtained. 2-Bromo-6-methoxynaphthalene (BMN), $AlCl_3$, $PhNO_2$, Br_2, Benzoyl chloride, Isobutylbenzene, N-methyl-2-pyrollidone (NMP), N-N-dimethylacetamide (DMAc), N-N-dimethylformamide (DMF), acetonitrile, Diethylketone, Sodium acetate, Potassium acetate, Sodium carbonate, Potassium carbonate, Calcium oxide, Sodium orthophosphate hydrate, Cesium carbonate, Dicyclohexylamine, Diisopropylamine, Triethylamine were procured either from Merck or SD fine chemicals ltd.

2.2.4 Syntheses

2.2.4.1 Synthesis of *m*-Bromobenzophenone

The synthetic procedure followed was similar to that described in the literature.[13] *m*-Bromobenzophenone was prepared from benzoyl chloride by a two-step procedure, which involved bromination of benzoyl chloride to *m*-bromobenzoyl chloride followed by aromatic condensation with benzene to give *m*-bromobenzophenone. For the bromination step, benzoyl chloride (8g) was added drop wise under vigorous stirring to a mixture of bromine (12.5g) and anhydrous $AlCl_3$ (10 g) at room temperature in a glass reactor. After stirring for 2-3 h, nitrobenzene (5g) was added and excess Br_2 was removed by bubbling nitrogen through the reaction mixture at 328-333 K.



Aromatic condensation was carried out by adding benzene (9 g) drop wise at 328 K and stirred the mixture for 2-3 h. The reaction mixture was poured onto crushed ice and stirred for 1 h. Toluene was added and the aqueous phase was removed. Toluene/H_2O was removed under reduced pressure and nitrobenzene was distilled off. To the cooled reaction mixture *n*-hexane was added and filtered to give an off-white solid mp= 345-347 K.

2.2.4.2 Synthesis of *p*-isobutyl bromobenzene

The synthesis of *p*-isobutyl bromobenzene was carried out using the procedure described in literature.[19] To a solution of isobutyl benzene in liquid sulfur dioxide, under

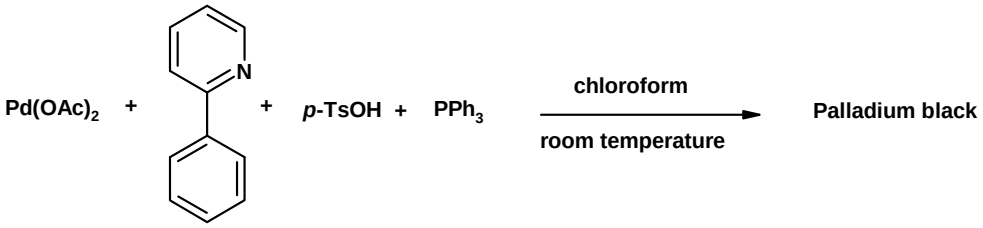
a nitrogen atmosphere, liquid bromine was added at 241 K (228 K bath). The mixture was kept at about 240 K for an hour then treated with water and allowed to warm to room temperature, during this time sulfur dioxide and byproduct hydrogen bromide were evaporated. The resultant organic phase was separated from the small aqueous phase. The aqueous phase was diluted with water and extracted with methylene chloride. The methylene chloride extract was combined with the original organic phase and washed with 20% sodium hydroxide solution and then twice with half-saturated sodium chloride solution. The organic solution was dried over anhydrous calcium chloride, and then concentrated under vacuum to give light yellow-colored oil.

2.2.4.3 Synthesis of Herrmann Palladacycle

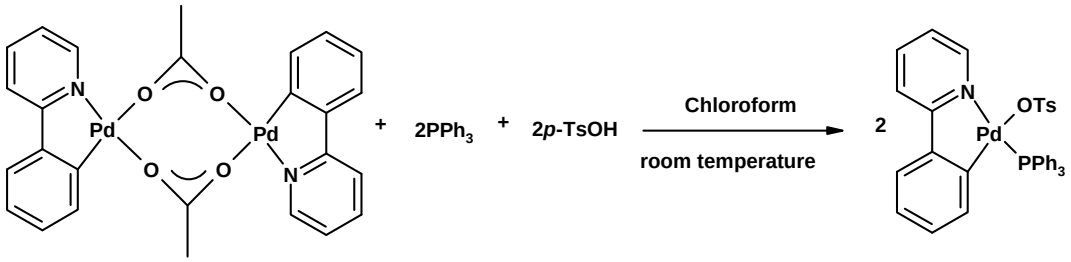
The palladacycle was synthesized according to the procedure described by Herrmann[11]. In a typical procedure $Pd(OAc)_2$ was dissolved in toluene and stirred until the solution became homogeneous (brown color). Tris(*o*-tolyl)phosphine was added to this solution and heated at 323 K for 3 min, the solution turns to light orange. The resultant solution was concentrated and the precipitation was effected by the addition of *n*-hexane. The precipitate was dissolved in dichloromethane and re-precipitated back by the addition of *n*-hexane.

2.2.4.4 Synthesis of NC Palladacycles

The synthesis of NC palladacycles was carried out in two steps. Attempts to prepare the palladacycle in a single step i.e. the addition of the palladium salts and the ligands resulted in the precipitation of palladium black. For example, the addition of $Pd(OAc)_2$, Triphenylphosphine and *p*-toluenesulfonic acid resulted in the formation of palladium black.

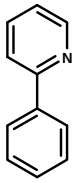
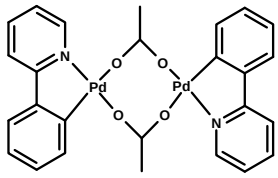


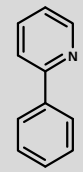
On the other hand the treatment of the dimeric Palladacycle ([{Pd(μ-OAc)(κ^2-N,C-$C_{11}H_8N$)}$_2$]) with the respective ligands gave the desired palladacycle in quantitative yields.

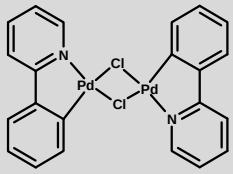


Therefore, all the complexes were prepared in two steps. A number of nitrogen-based ligands 2-phenylpyridine, 2-phenylquinoline, 8-Methylquinoline, N,N-dimethylbenzylamine, 2-benzylpyridine, and benzophenone oxime were chosen and dimeric palladacycles were prepared according to the procedures described in the literature (Table 2.3). Accordingly, these palladacycles were prepared by the reaction of palladium salts ($Pd(OAc)_2$ or Li_2PdCl_4) with the ligands to form dinuclear molecules with acetate or halide bridged NC palladacycle. These are listed in the Table 2.3. Thus, seven different palladacycles with different steric and electronic properties were prepared. The complexes [{Pd(μ-OAc)(κ^2-N,C-$C_{11}H_8N$)}$_2$], [{Pd(μ-OAc)(κ^2-N,C-$C_{15}H_{10}N$)}$_2$], were prepared according to the procedure described by Hiraki et al[20] and ppy and pquin were taken for the respective complexes instead of Bnpy. The complex [{Pd(μ-OAc)(κ^2-N,C-$C_{10}H_8N$)}$_2$] was prepared according to the procedure described by Herrmann et al,[8] the ligand 8-methylquinoline was used for the preparation of the complex.

Table 2.3. Synthesis of Dimeric Palladacycles

Ligand	Dimeric Palladacycle	Reaction Conditions/ reference
	 [{Pd(μ-OAc)(κ^2-N,C-$C_{11}H_8N$)}$_2$]	Hiraki et al[20] Reflux $Pd(OAc)_2$ (1.31 mmol) and ppy (1.31 mmol) in glacial acetic acid for 3-4 h. Cool it and add distilled water. Filter the ppt, wash with water and dry. Yield 88%.

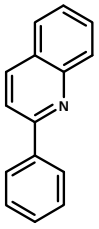


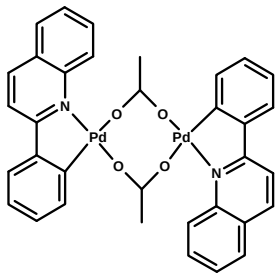


[{Pd(μ-Cl)(κ^2-N,C-$C_{11}H_8N$)}$_2$]

Kasahara[21]

Dissolve $PdCl_2$ (1.69 mmol) and LiCl (3.373 mmol) in methanol. Add ppy (1.69 mmol) and stir at room temperature for 7-8 h. Filter the ppt, wash with MeOH and dry. Yield 84%.

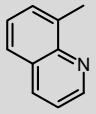


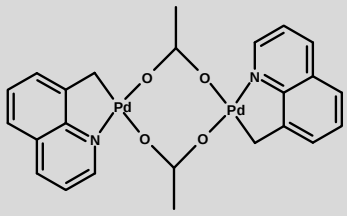


[{Pd(μ-OAc)(κ^2-N,C-$C_{15}H_{10}N$)}$_2$]

Hiraki et al[20]

$Pd(OAc)_2$ (0.432 mmol) and pquin (0.44 mmol) were dissolved in glacial acetic acid and refluxed for 3-4 h. Cooled the contents and distilled water added. Filtered the ppt, washed with water and dried. Yield 80%.

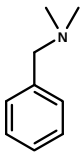


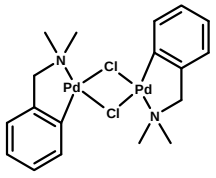


[{Pd(μ-OAc)(κ^2-N,C-$C_{10}H_8N$)}$_2$]

Herrmann et al[8]

Refluxed a solution of $Pd(OAc)_2$ (0.89 mmol) and mquin (1.06 mmol) in toluene for 2-3 h. Cooled it and *n*-hexane added. Filtered the ppt. and dried. Yield 95%.

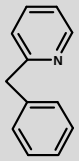
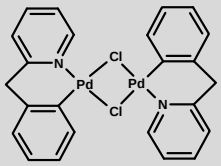
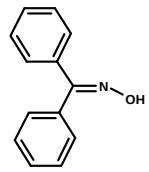
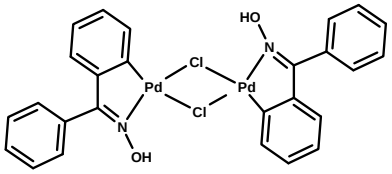




[{Pd(μ-Cl)(κ^2-N,C-$C_9H_{12}N$)}$_2$]

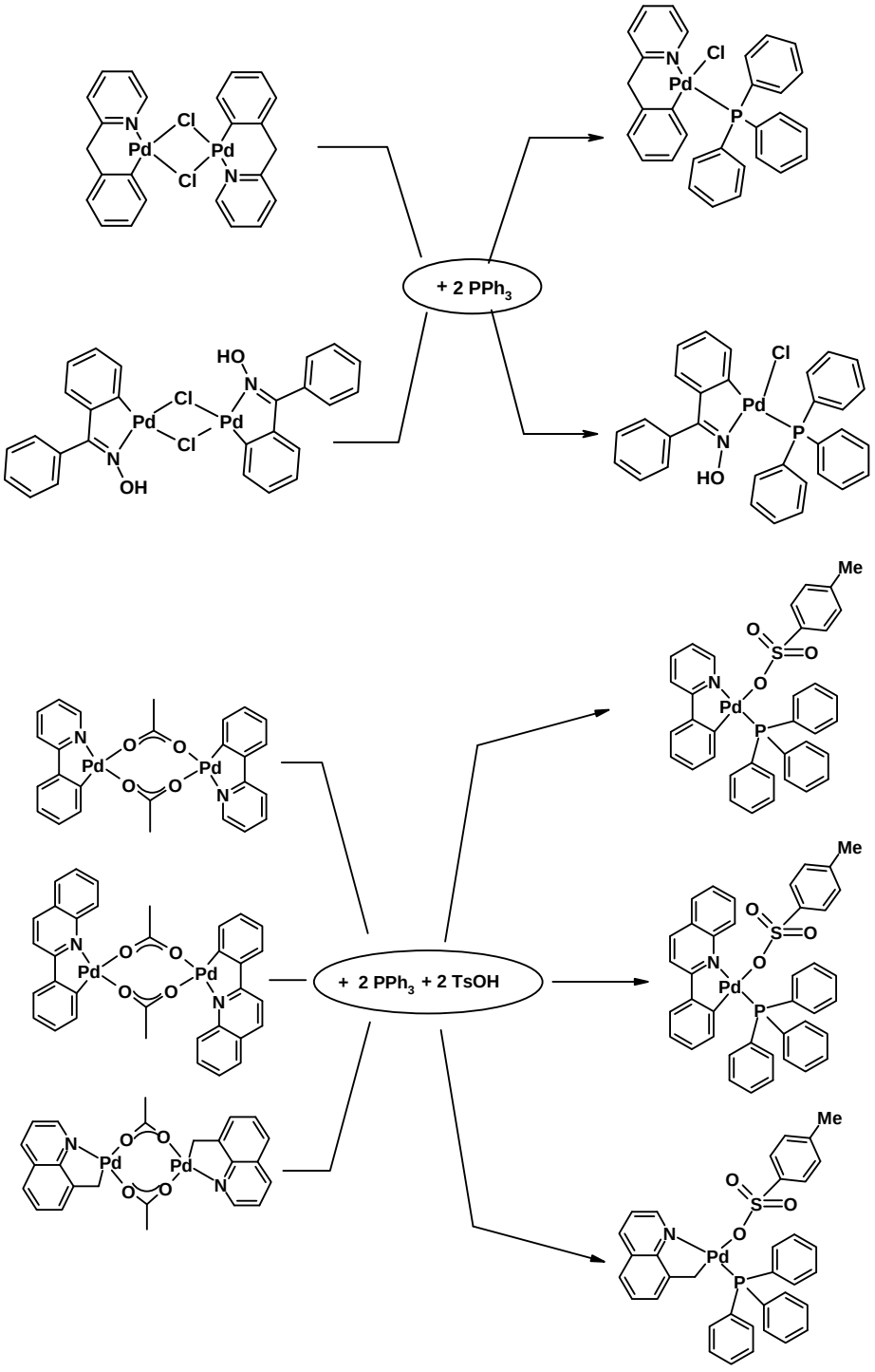
Cope and Friedrich[22]

To a solution of $PdCl_2$ (2.82 mmol) and LiCl (5.61 mmol) in methanol. dim (5.45 mmol) was added and stirred the mixture at room temperature for a period of 7-8 h. Filtered the ppt, washed with MeOH and dried. Yield 92%.

	 [{Pd(μ-Cl)(κ^2-N,C-$C_{12}H_{10}N$)}$_2$]	Hiraki et al[20] Refluxed a solution of $Pd(OAc)_2$ (2.22 mmol) and Bnpy (2.22 mmol) in glacial acetic acid for 3-4 h. Cooled it and added distilled water. Filtered the ppt, washed with water and dried. Yield 87%. The ppt (0.15 mmol) and LiCl (0.59 mmol) in acetone were stirred as a suspension at room temperature for 2 days. Filtered the precipitate and washed with 1:1 methanol and water. Yield 77%.
	 [{Pd(μ-OAc)(κ^2-N,C-$C_{13}H_{10}NO$)}$_2$]	Nakagawa et al[23] Dissolve $PdCl_2$ (1.69 mmol) and LiCl (3.37 mmol) in methanol. Add bpoxime (5.45 mmol) and stir at room temperature for 2 days. Filter the ppt, to the filterate add water to ppt yellow material. Dry it and wash thoroughly with *n*-hexane. Yield 90%.

2.2.4.5 Synthesis of Monomeric Palladacycles

The synthesis of monomeric palladacycles was effected by the treatment of dimeric palladacycles (Section 2.2.4.4) with the appropriate ligands to obtain the desired palladacycle, Scheme 2.6. The palladium dimer reacted quite rapidly. The monomeric palladacycle complexes obtained were stable at room temperature and can be crystallized with appropriate solvents. These complexes can be stored as such without any precautions (the NMR spectrum does not show any variations even after keeping the catalyst at room temperature for 2 – 3 months).



Scheme 2.6. Schematic for the Synthesis of NC palladacycles

2.2.4.5.1 Pd(ppy)(PPh_3)(OTs) Complex

The palladium dimer [{Pd(μ-OAc)(κ^2-N,C-$C_{11}H_8N$)}$_2$] (0.2g, 0.313mmol) was dissolved in chloroform resulting in a homogeneous solution. To this solution triphenylphosphine (0.1806 g, 0.688 mmol) was added followed by the con-comitant addition of *p*-toluenesulfonic acid monohydrate (0.131 g, 0.688 mmol) to give a pale-yellow colored solution, which was stirred at room temperature for 15 min. The mixture was immediately filtered through a plug of celite with chloroform rinses. *n*-Hexane was added to effect the precipitation of the product. The product was collected by filtration and recrystallized from chloroform/ hexane to afford yellow crystals (0.399 g, 92% yield) suitable for X-ray analysis.

2.2.4.5.2 Pd(quin)(PPh_3)(OTs) Complex

Similar procedure as described in the Section 2.2.4.5.1 was used for the synthesis of Pd(quin)(PPh_3)(OTs) using the palladacycle [{Pd(μ-OAc)(κ^2-N,C-$C_{15}H_{10}N$)}$_2$] (0.1g, 0.135 mmol) as a precursor. To the chloroform solution of dimer, triphenylphosphine (0.078 g, 0.297 mmol) was added followed by the addition of *p*-toluenesulfonic acid monohydrate (0.056 g, 0.297 mmol) to give a pale-yellow colored solution, which was stirred at room temperature for 15 min. The mixture was immediately filtered through a plug of celite with chloroform rinses. *n*-Hexane was added to effect precipitation of the product. The product was collected by filtration and recrystallized from dichloromethane/ hexane to afford yellow crystals (0.191 g, 95% yield) suitable for X-ray analysis.

2.2.4.5.3 Pd(mquin)(PPh_3)(OTs) Complex

Similar procedure as described in the Section 2.2.4.5.1 was used for the synthesis of Pd(mquin)(PPh_3)(OTs) using the palladacycle [{Pd(μ-OAc)(κ^2-N,C-$C_{10}H_8N$)}$_2$] (0.261g, 0.424 mmol). To the chloroform solution of dimer, triphenylphosphine (0.244 g, 0.9304 mmol) was added followed by the addition of *p*-toluenesulfonic acid monohydrate (0.177 g, 0.9304 mmol) to give a pale-yellow colored solution, which was stirred at room temperature for 15 min. The mixture was immediately filtered through a plug of celite with chloroform rinses. *n*-Hexane was added to effect precipitation of the product. The product was collected by filtration and

recrystallized from chloroform/ hexane to afford yellow crystals (0.517 g, 90% yield), suitable for X-ray analysis.

2.2.4.5.4 Pd(ppy)(PPh_3)(Cl) Complex

Pd(ppy)(PPh_3)(Cl) was prepared according to a procedure reported by Edward et al.[24] To a suspension of [{Pd(μ-Cl)(κ^2-N,C-$C_{11}H_8N$)}$_2$] (0.1g, 0.1689 mmol) in chloroform, triphenylphosphine (0.097 g, 0.369 mmol) was added to give a pale-yellow colored solution, which was stirred at room temperature for 15 min. The mixture was immediately filtered through a plug of celite with chloroform rinses. *n*-Hexane was added to effect precipitation of the product. The product was collected by filtration and recrystallized from chloroform/ hexane to give as yellow crystals (0.162 g, 86% yield), suitable for X-ray analysis.

2.2.4.5.5 Pd(Bnpy)(PPh_3)(Cl) Complex

Similar procedure as described in the Section 2.2.4.5.4 was used for the synthesis of Pd(Bnpy)(PPh_3)(Cl) using the palladacycle [{Pd(μ-Cl)(κ^2-N,C-$C_{12}H_{10}N$)}$_2$] (0.0711g, 0.114 mmol). To the chloroform solution of dimer, triphenylphosphine (0.066 g, 0.251mmol) was added to give a pale-yellow colored solution, which was stirred at room temperature for 15 min. The mixture was immediately filtered through a plug of celite with chloroform rinses. *n*-Hexane was added to effect precipitation of the product. The product was collected by filtration and recrystallized from chloroform/ hexane to give as yellow crystals (0.120 g, 92% yield), suitable for X-ray analysis.

2.2.4.5.6 Pd(dim)(PPh_3)(Cl) Complex

Pd(dim)(PPh_3)(Cl) was prepared according to a procedure reported by Bedford et al.[25] To a solution of palladacycle [{Pd(μ-Cl)(κ^2-N,C-$C_9H_{12}N$)}$_2$] (0.214g, 0.387 mmol) in chloroform, triphenylphosphine (0.223 g, 0.85 mmol) was added to give a pale-yellow colored solution, which was stirred at room temperature for 15 min. The mixture was immediately filtered through a plug of celite with chloroform rinses. *n*-Hexane was added to effect precipitation of the product. The product was collected by filtration and recrystallized from chloroform/ hexane to give as yellow crystals (85% yield), suitable for X-ray analysis.

2.2.4.5.7 Pd(bpoxime)(PPh_3)(Cl) Complex

Pd(bpoxime)(PPh_3)(Cl) was prepared according to a procedure reported by Nakagawa et al.[23] To a solution of palladacycle [{Pd(μ-OAc)(κ^2-N,C-$C_{13}H_{10}NO$)}$_2$] (0.1g, 0.147 mmol) in chloroform, triphenylphosphine (0.085 g, 0.324 mmol) was added to give a pale-yellow colored solution, which was stirred at room temperature for 15 min. The mixture was immediately filtered through a plug of celite with chloroform rinses. *n*-Hexane was added to effect precipitation of the product. The product was collected by filtration and recrystallized from chloroform/ hexane to give as yellow crystals (89% yield), suitable for X-ray analysis.

The structures of these seven palladacycles are shown in the Figure 2.2.

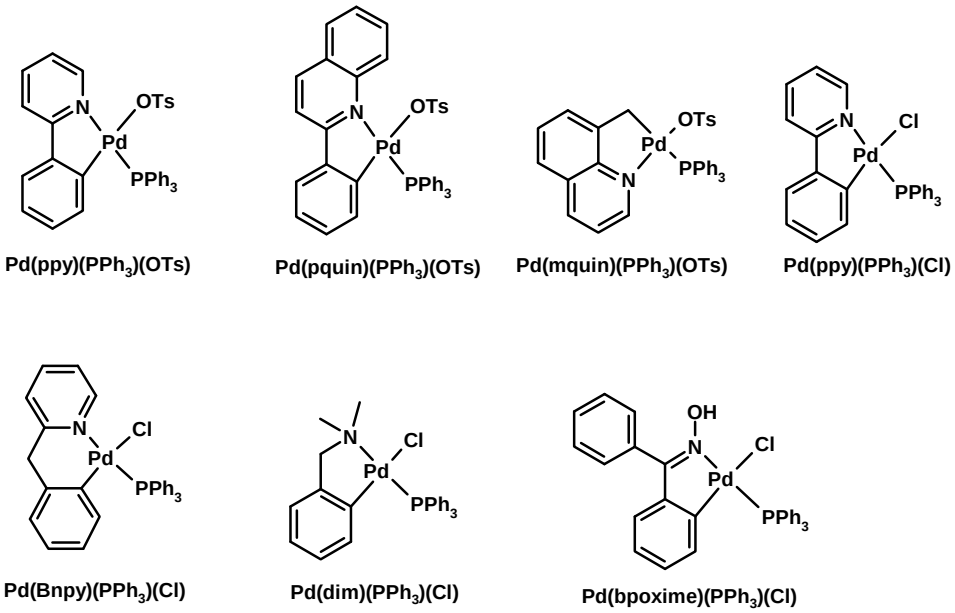


Figure 2.2. Structures of the NC Palladacycle Complexes Prepared

The palladacycles Pd(ppy)(PPh_3)(Cl), Pd(dim)(PPh_3)(Cl) and Pd(bpoxime)(PPh_3)(Cl) are the known ones, these palladacycles could be successfully reproduced and were confirmed by the elemental analysis (found to be in agreement with the formulation) and also by single crystal X-ray diffraction studies (the structures of these complexes are shown in the Section 2.3.1).

2.2.5 Procedure for the Arylation of Ethylene

The Heck reaction was carried out in a 50 cm^3 Parr Autoclave made of Hastelloy-C-276. In a typical Heck reaction, a mixture of BMN (10.54 mmol), Base (15.8 mmol), solvent (NMP-25 ml) and NC palladacycle complex (0.0014 mmol) was prepared to make the total volume 25 cm^3 and charged into the reactor. The reactor was purged with nitrogen to remove the traces of air inside the reactor at room temperature and the contents were heated to the desired temperature. After attaining the temperature, the reactor was pressurized to 1.99 MPa of ethylene and the reaction was initiated by setting the agitation speed at 1000 rpm. The progress of the reaction was monitored by taking aliquot samples at regular intervals of time and analyzed by GC immediately. After the reaction was stopped, the reactor was cooled to room temperature and ethylene gas was vented off.

(Precaution: Special care should be taken while sampling the reaction mixtures; inorganic salts can block the sampling tube).

2.2.6 Analytical and Characterization Methods

The liquid samples of the arylation reactions were analyzed by gas chromatography using Hewlett-Packard 6890 series GC instrument controlled by the HP Chemstation software and equipped with an auto sampler unit, by using an HP-1 capillary column of length 30 m, 320μm diameter, 0.25μm stationary phase film thickness (methyl siloxane as stationary phase, helium gas as mobile phase) and a flame ionization detector. The quantitative analysis was carried out by constructing calibration-table in the range of concentrations studied. The % conversion, % selectivities, TON and TOF (h^{-1}) were calculated using the formulae given below. The standard GC conditions for the analysis of products of different reactions are given in Table 2.4. Complete mass balance of the liquid phase components was thus evaluated from the quantitative GC analysis, except in few cases.

Table 2.4. Standard Conditions for GC Analysis

Injector Temperature (K)	523		
Flame Ionization Detection Temp (K)	523		
Inlet Flow Total (He)	20 ml/min		
Split Ratio for Injector	100:1		
Oven Temperature	Rate (K/min)	Temp (K)	Hold Time (min)
		423	0.5
	35	443	6
	40	523	3
	45	543	5
Column Pressure	13.50 psi		

$$\%\ Conversion = \frac{\left(Initial\ Concentration\ of\ substrate - Final\ Concentration\ of\ substrate\right)}{Initial\ Concentration\ of\ substrate} \times 100$$

$$\%Selectivity = \frac{No.\ of\ moles\ of\ arylated\ product\ formed}{No.\ of\ moles\ of\ substrate\ converted} \times 100$$

$$TON = \frac{No.\ of\ moles\ of\ arylated\ product\ formed}{No.\ of\ moles\ of\ catalyst\ used}$$

$$TOF, h^{-1} = \frac{No.\ of\ moles\ of\ arylated\ product\ formed}{No.\ of\ moles\ of\ catalyst\ used \times time\ in\ hours}$$

2.3 Characterization of the Palladacycles

The complexes synthesized were characterized by means of spectral techniques which include ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, elemental analysis, IR, XPS, single crystal X-ray diffraction that indicates the formation of complexes. The

monomeric NC palladacycles *viz*. Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) and Pd(mquin)(PPh_3)(OTs) bearing monophosphine and sulphanato ligands and Pd(Bnpy)(PPh_3)(Cl) have been synthesized for the first time. The complex Pd(bpoxime)(PPh_3)(Cl) is known from previous work[23] and its synthetic procedures are reported in the literature but lacks the characterization details, therefore its characterization details are also included in this section. The monomeric palladacycle complexes bearing monophosphine and chloride ligand [(Pd(ppy)(PPh_3)(Cl), Pd(dim)(PPh_3)(Cl)] are already known, however the crystal structure for the complex Pd(ppy)(PPh_3)Cl is not reported. The crystal structure for the complex Pd(dim)(PPh_3)Cl has been reported earlier[25] as $C_{27.35}H_{27}Cl_{1.30}NO_{0.25}PPd$ with solvent of crystallization. However, in the present work crystals of the complex were obtained without any solvent in crystal lattice. Thus the complex was found to crystallize as $C_{27}H_{27}ClNPPd$.

The elemental analysis data for complexes were found to be in agreement with the given formulation and are presented in Table 2.5.

Table 2.5. Elemental Analysis for Complexes

Complex (Molecular wt.)	Theoretical (%)				Experimental (%)			
	C	H	N	S	C	H	N	S
Pd(ppy)(PPh_3)(OTs) $C_{36}H_{30}NO_3PPdS$ (694.04)	62.29	4.32	2.01	4.61	62.07	4.27	2.14	4.14
Pd(pquin)(PPh_3)(OTs) $C_{40}H_{32}NO_3PPdS.CH_2Cl_2$ (829.02)	59.4	4.13	1.69	3.85	59.07	4.27	1.44	3.44
Pd(mquin)(PPh_3)(OTs) $C_{35}H_{30}NO_3PPdS$ (682.03)	61.6	4.4	2.05	4.69	61.21	4.37	2.37	4.35
Complex (Molecular wt.)	Theoretical (%)				Experimental (%)			
	C	H	N	Cl	C	H	N	Cl
Pd(ppy)(PPh_3)(Cl) $C_{29}H_{23}NPClPd$ (557.87)	62.38	4.15	2.51	6.35	61.99	4.12	2.51	6.97
Pd(bpoxime)(PPh_3)(Cl) $C_{31}H_{25}ClNOPPd$ (600.34)	62.0	4.16	2.33	5.91	62.04	4.07	2.34	6.13
Pd(benz)(PPh_3)(Cl) $C_{30}H_{25}NPClPd$ (571.87)	62.95	4.40	2.45	6.19	62.14	4.29	2.41	6.56
Pd(dim)(PPh_3)(Cl) $C_{27}H_{27}ClNPPd$ (538.32)	60.24	5.06	2.60	6.59	59.99	5.48	2.61	6.58

^{1}H-NMR

NMR data for the complexes are presented in the Table 2.6. and their respective ^{1}H-NMR spectra are given in the Figures 2.4 – 2.8. All the complexes synthesized have aromatic protons as the major contribution, for the complexes with tosyl group the CH_3 protons can be distinguished easily. The aromatic protons corresponding to phenyl and NC ligands for the complexes were found between δ 6.39-9.68 ppm. The tosyl CH_3 protons were observed between δ 2.14-2.30 ppm. The presence of TsO^- group was also confirmed by the ^{13}C NMR in which the tosyl CH_3 appeared between δ 21.10-21.24 ppm. Bedford et al[25] have reported that the proton on the carbon ortho to the palladated carbon appears at the low field in the range 6.18-6.44 ppm. However, the characteristic peak associated with the said proton was not seen because of the overlap of the other phenyl ring protons in this region. The complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) & Pd(Bnpy)(PPh_3)(Cl) have proton ortho to the nitrogen atom which appears at the low field at δ 9.14, 9.68 & 9.25 ppm respectively. Whereas 2-phenylquinoline do not show peak in this region due to the absence of the ortho proton to the nitrogen. The respective methyl group for the complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) & Pd(mquin)(PPh_3)(OTs) from the sulphanato group in the ^{1}H NMR spectra appears as singlet at δ 2.3, 2.14 & 2.24 ppm. The methylene protons for the complex Pd(mquin)(PPh_3)(OTs) appears as doublet at δ 2.93-2.95 ppm. The complex Pd(pquin)(PPh_3)(OTs) has a methylene chloride as the solvent of crystallization which appears as singlet at δ 5.29 ppm. The complex Pd(Bnpy)(PPh_3)(Cl) shows a peak at 1.59 ppm, this is due to the water molecules present in the complex. The complex has water molecule because one of the steps of the synthesis involves water as one of the solvent. The complex Pd(Bnpy)(PPh_3)(Cl) is a six membered cyclopalladated complex, a model is shown in the Figure 2.3 which indicates that the six-membered ring has a boat form (from single crystal X-ray analysis).

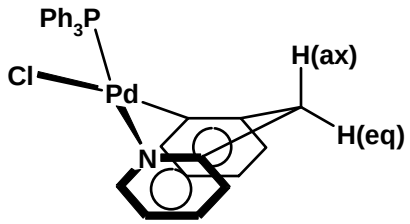


Figure 2.3. Boat Form of the Six Membered Palladacycle Ring

The protons of the methylene group in the 2-benzylpyridine moiety in the complex appear as two different doublets at δ 3.91 and 4.85 ppm for the H_{ax} and H_{eq} respectively at room temperature (the equatorial (eq) proton is de-shielded relative to the axial (ax) proton).

Table 2.6. ^{1}H NMR Values of the Palladium Complexes

Complex	Tosyl CH_3	Aromatic	Remarks
Pd(ppy)(PPh_3)(OTs)	2.30	(6.46-7.81) & 9.14	
Pd(pquin)(PPh_3)(OTs).CH_2Cl_2	2.14	6.47-8.59	CH_2 (5.29)
Pd(mquin)(PPh_3)(OTs)	2.24	6.84-8.29& 9.68	CH_2 d(2.93-2.95)
Pd(bpoxime)(PPh_3)(OTs)	-	6.39-7.81&	OH (10.73)
Pd(Bnpy)(PPh_3)(Cl)	-	6.25-7.62 & 9.25	CH_2 d(3.91-3.98) & d(4.85-4.92)

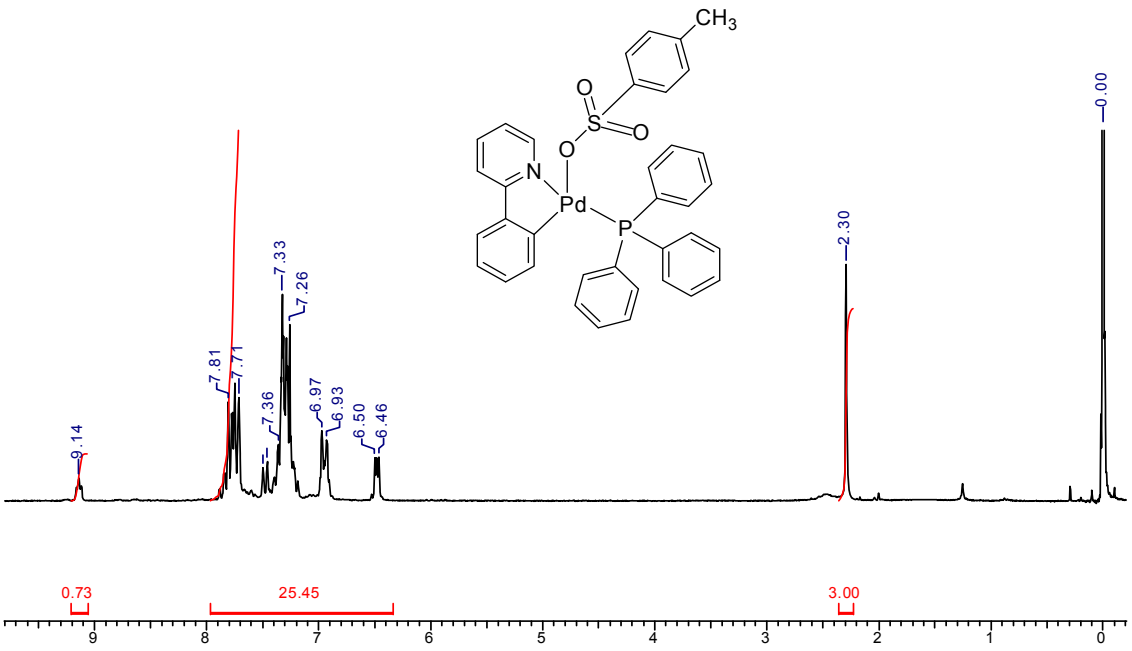


Figure 2.4. ^{1}H-NMR Spectrum of the Complex Pd(ppy)(PPh_3)(OTs)

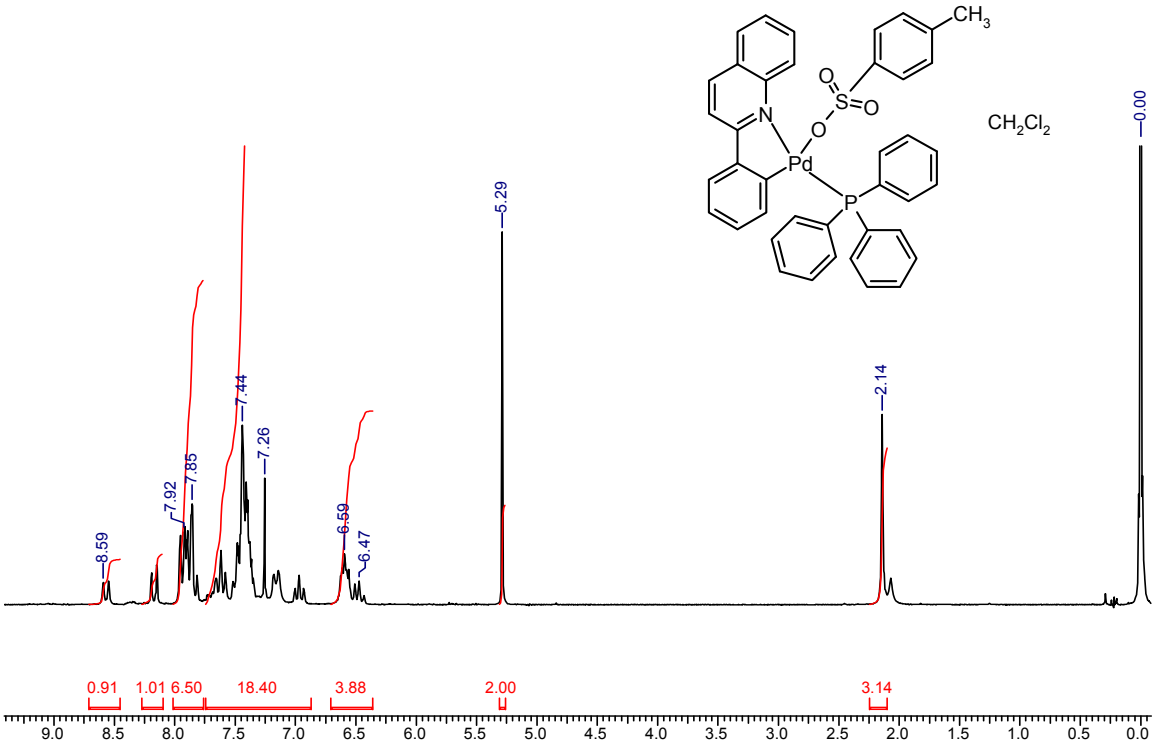


Figure 2.5. ^{1}H-NMR Spectrum of the Complex Pd(pquin)(PPh_3)(OTs)

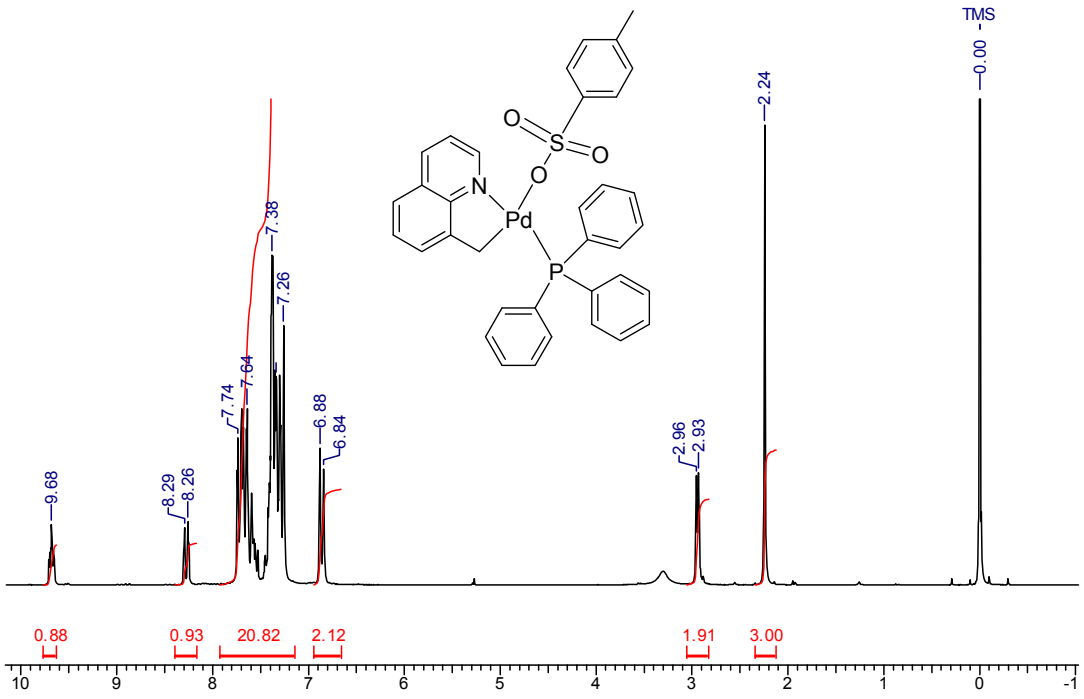


Figure 2.6. ^{1}H-NMR Spectrum of the Complex Pd(mquin)(PPh_3)(OTs)

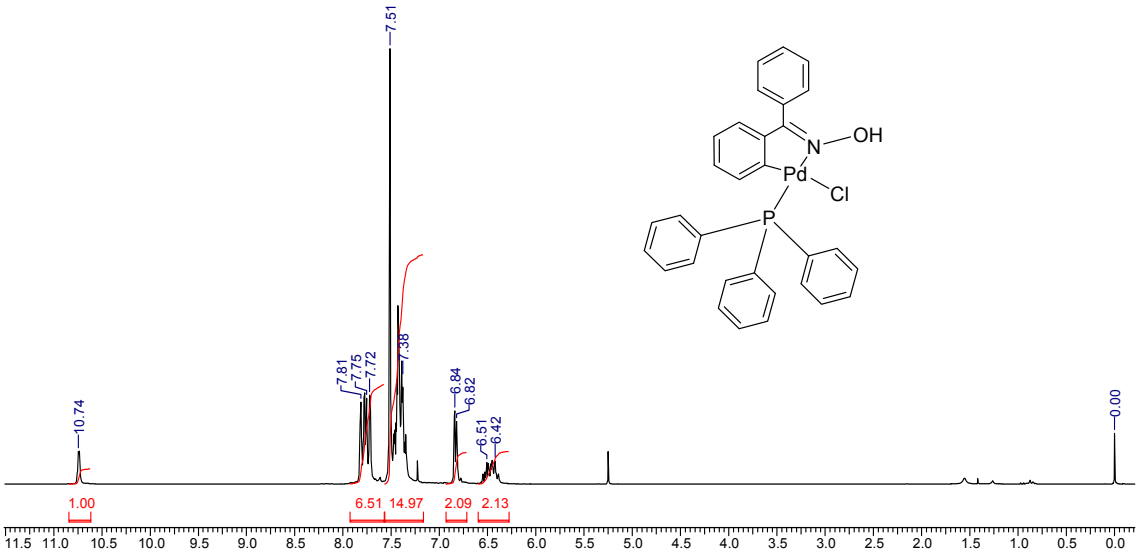


Figure 2.7. ^{1}H-NMR Spectrum of the Complex Pd(bpoxime)(PPh_3)(OTs)

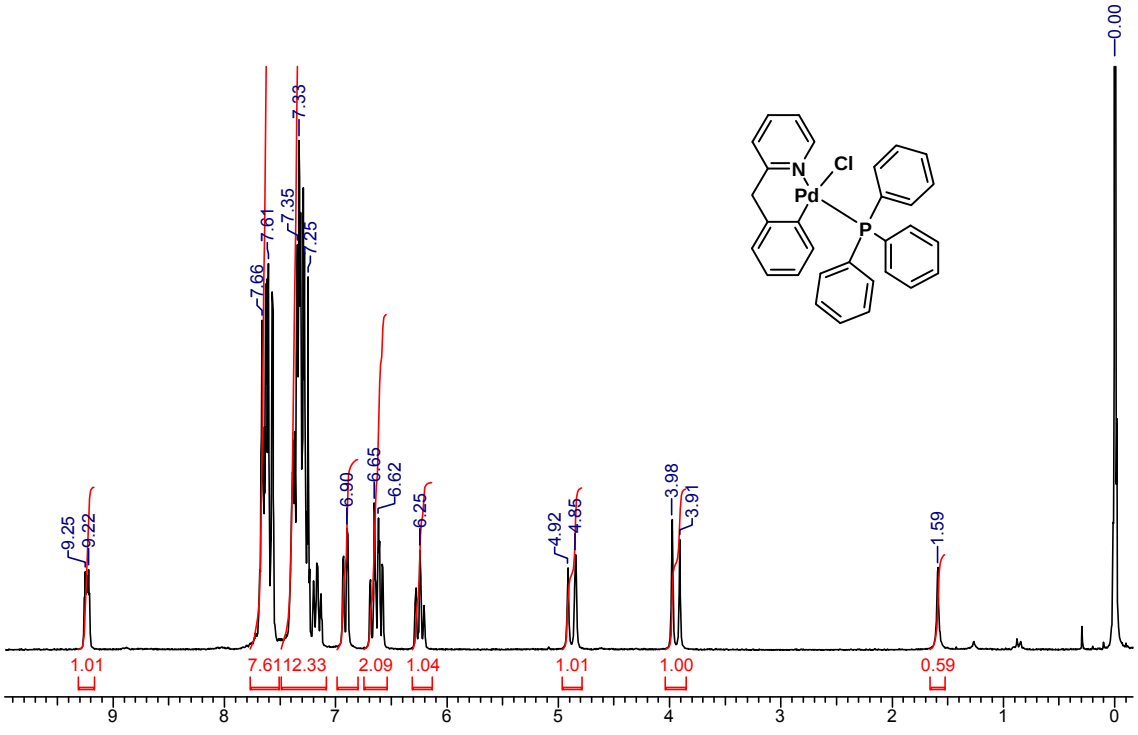


Figure 2.8. ^{1}H-NMR Spectrum of the Complex Pd(Bnpy)(PPh_3)(Cl)

^{31}P-NMR

The ^{31}P NMR spectra of the complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) & Pd(mquin)(PPh_3)(OTs) show peaks at δ 39.9, 41.98 & 32.42 ppm, respectively (Table 2.7). These complexes have similar PPh_3 and OTs motifs and differ in their type of NC coordination ligands. When an extra aromatic ring as in the case of 2-phenylquinoline compared to 2-phenylpyridine is present, a downfield shift in the ^{31}P NMR spectra from δ at 39.9 to 41.98 ppm takes place. In the case of Pd(ppy)(PPh_3)(OTs) and Pd(pquin)(PPh_3)(OTs) the metallated carbon is a sp^2 centre. Whereas the metallated carbon is sp^3 carbon for Pd(mquin)(PPh_3)(OTs). There is upfield shift in ^{31}P NMR for Pd(mquin)(PPh_3)(OTs) as compared to Pd(ppy)(PPh_3)(OTs) and Pd(pquin)(PPh_3)(OTs). This can be attributed to the increased electron density at the palladium centre by methylene protons thereby showing ^{31}P signals at high field. This is also seen in the complex Pd(Bnpy)(PPh_3)(Cl) where the metallated carbon is the sp^3 carbon. The formation of single peak in the ^{31}P NMR indicates the formation

one isomer, further single crystal structure determination confirmed the trans isomer i.e. the phosphorous is trans to the N-donor. The respective ^{31}P spectrums of the complexes are shown in Appendix (II).

Table 2.7. ^{31}P NMR Values of the Palladium Complexes

Complex	Metallated carbon	^{31}P NMR values
Pd(ppy)(PPh_3)(OTs)	sp^2	39.92
Pd(quin)(PPh_3)(OTs)	sp^2	41.98
Pd(mquin)(PPh_3)(OTs)	sp^3	32.42
Pd(bpoxime)(PPh_3)(Cl)	sp^2	42.12
Pd(Bnpy)(PPh_3)(Cl)	sp^3	34.14

^{13}C-NMR

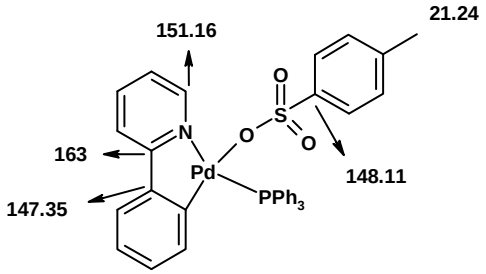
The complexes contain carbon atoms, and majority of them are from aromatic rings (NC ligands, triphenylphosphine, sulphanato group). Some of the characteristic ^{13}C NMR values are shown in the Figure 2.9. ^{13}C NMR of the complexes show that the methyl group for the complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs), and Pd(mquin)(PPh_3)(OTs) appear at δ 21.24, 21.10, and 21.16 ppm respectively. The methylene protons in the case of Pd(mquin)(PPh_3)(OTs) and Pd(Bnpy)(PPh_3)(Cl) appear at δ 28.48 & 50.26 ppm respectively. The values obtained for the complexes are presented in the Table 2.8.

Table 2.8. ^{13}C Values of the Palladium Complexes

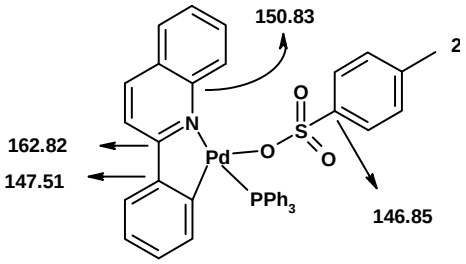
Complex	13 C Values
Pd(ppy)(PPh_3)(OTs)	21.24, 118.04, 122.47, 123.98, 124.83, 126.24, 128.25 (d, J = 11.51 Hz), 128.76 (d, J=5.76 Hz), 128.93, 130.48, 130.68, 131.98, 134.78 (d, J = 11.51 Hz), 135.51 (d, J = 11.52 Hz), 139.2, 139.59, 141.58, 147.35, 148.11, 151.16, 163.10 DEPT 13 C NMR shows the disappearance of the peaks at 128.93, 130.09, 130.48, 139.59, 147.35, 148.11, 163.10
Pd(pquin)(PPh_3)(OTs)	21.10, 53.40, 116.22, 124.75, 125.69, 125.78, 126.57, 126.93, 127.36, 127.7, 128.29 (d, J = 10.98 Hz), 129.47, 130.34, 130.48, 130.81 (d, J = 2.56 Hz), 135.67 (d, J = 12.08 Hz), 138.74, 139.51, 141.14, 146.85, 147.52 (d, J = 1.83 Hz),

	150.83, 162.85 (d, J = 3.66 Hz) DEPT 13 C NMR shows the disappearance of the peaks at 125.67, 129.47, 130.48, 138.74, 141.14, 146.85, 147.51, 150.83, 162.82
Pd(mquin)(PPh_3)(OTs)	21.16, 28.44, 122.07 (d, J = 3.66 Hz), 124.13, 126, 127.4, 128.05, 128.19 (d, J = 4.39 Hz), 128.45, 128.83, 129.62, 130.55 (d, J = 2.56 Hz), 134.47 (d, J = 12.07 Hz), 137.92, 139.34, 141.57, 146.85, 150.53 (d, J = 2.93 Hz), 151.47, 154.53 DEPT 13 C NMR shows the disappearance of the peaks at 128.83, 129.62, 139.34, 141.57, 146.85, 150.50
Pd(bpoxime)(PPh_3)(Cl)	124.24, 128.15, 128.23, 128.37, 128.76, 129.37, 129.74, 129.87, 130.75, 131.03 (d, J = 12.08 Hz), 135.21 (d, J = 12.08 Hz), 137.80 (d, J = 10.61 Hz), 144.75, 153.35, 166.01 DEPT 13 C NMR shows the disappearance of the peaks at 129.37, 129.74, 130.75, 144.75, 153.35, 166.01
Pd(Bnpy)(PPh_3)(Cl)	50.26, 121.81, 123.29, 125.16, 125.75, 127.95 (d, J = 9.59 Hz), 130.21, 131.20, 131.61, 134.91 (d, J = 11.52 Hz), 138.13, 138.34, 153.18, 159.21 DEPT 13 C NMR shows the disappearance of the peaks at 131.20, 131.61, 138.13, 159.21

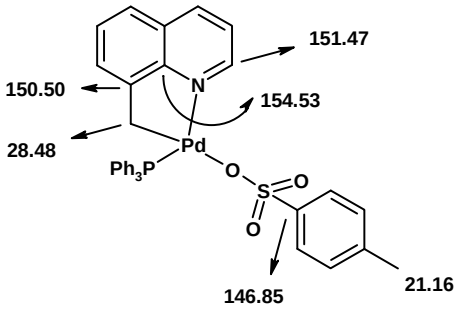
Some of the characteristic ^{13}C values of the complexes are presented in the Figure 2.9.



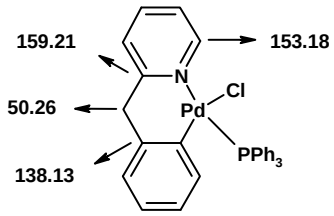
Pd(ppy)(PPh_3)(OTs)



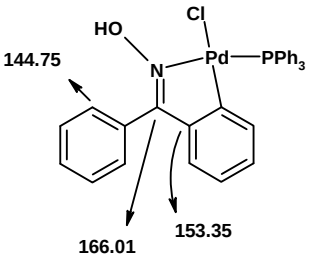
Pd(pquin)(PPh_3)(OTs)



Pd(mquin)(PPh_3)(OTs)



Pd(Bnpy)(PPh_3)(Cl)



Pd(bpoxime)(PPh_3)(Cl)

Figure 2.9. Characteristic ^{13}C values of the Complexes

IR analysis of the complexes

The selected IR spectroscopic data for the complexes are presented in Table 2.9. The complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) and Pd(mquin)(PPh_3)(OTs) have sulphanato groups; typically sulfonic acids show the asymmetric (higher frequency) and symmetric S=O stretching frequency in the range (1350-1342) and (1165-1150) respectively. In the complexes these stretching frequencies were observed peaks in the range of 1216-1260 cm^{-1} which can be attributed to the asymmetric S=O stretching frequencies. The IR spectrums for the complexes are shown in the Figures 2.10 - 2.14. The O-H stretch for

Pd(bpoxime)(PPh_3)Cl appears as the strong peak at 3059 cm^{-1}. The C=N stretching vibrations appear in the range 1689 - 1471 cm^{-1}.

Table 2.9. IR Data for the NC palladacycles

Complex	$\nu_{O=S=O}$ (sym) cm^{-1}	$\nu_{O=S=O}$ (assym) cm^{-1}	Others cm^{-1}
Pd(ppy)(PPh_3)(OTs)	1150	1255	
Pd(pquin)(PPh_3)(OTs)	1152	1260	
Pd(mquin)(PPh_3)(OTs)	1154	1216	CH_2 (C-H, 2925)
Pd(bpoxime)(PPh_3)Cl	-	-	O-H (3059)
Pd(Bnpy)(PPh_3)Cl	-	-	CH_2 (C-H, 3047)

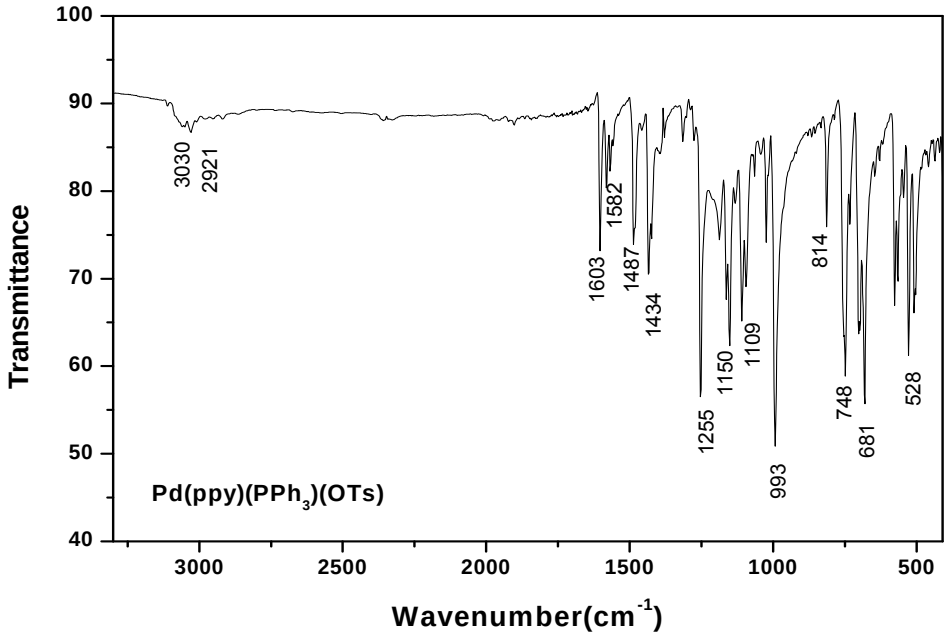


Figure 2.10. IR Spectrum of the Complex Pd(ppy)(PPh_3)(OTs)

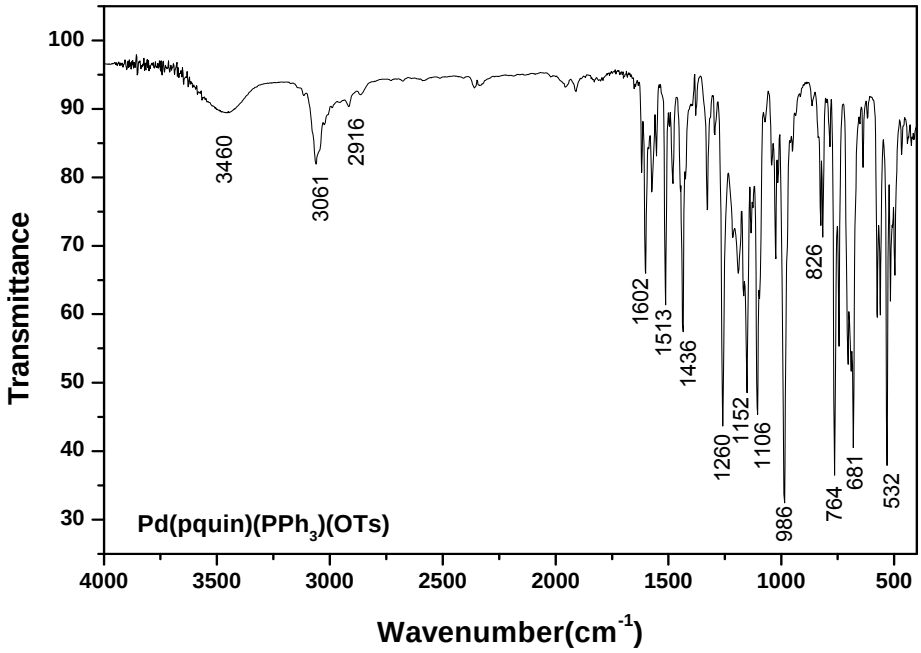


Figure 2.11. IR Spectrum of the Complex Pd(pquin)(PPh_3)(OTs)

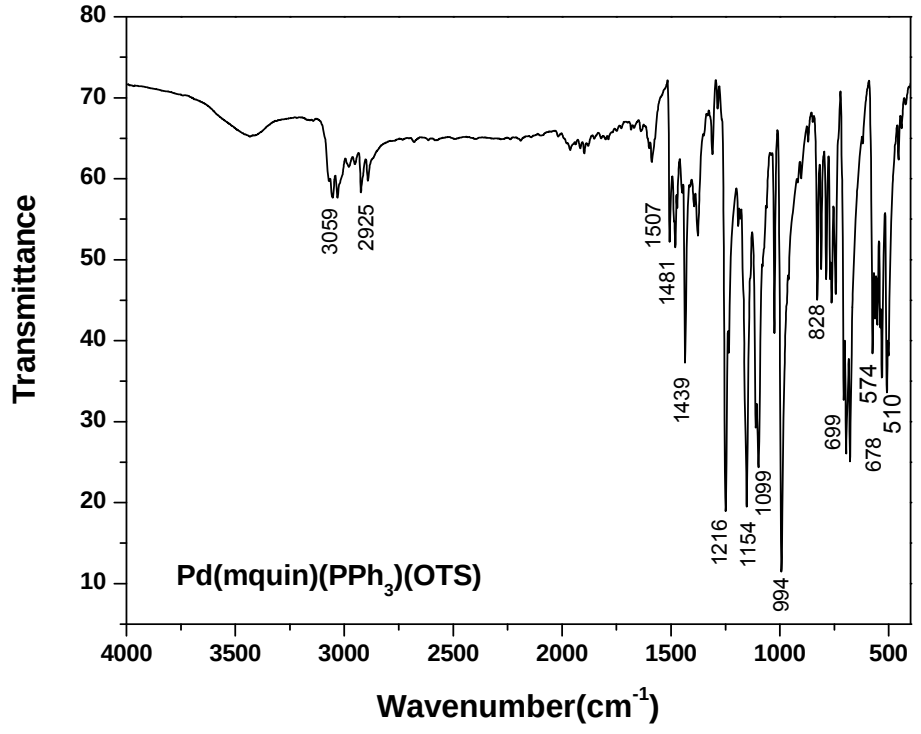


Figure 2.12. IR Spectrum of the Complex Pd(mquin)(PPh_3)(OTs)

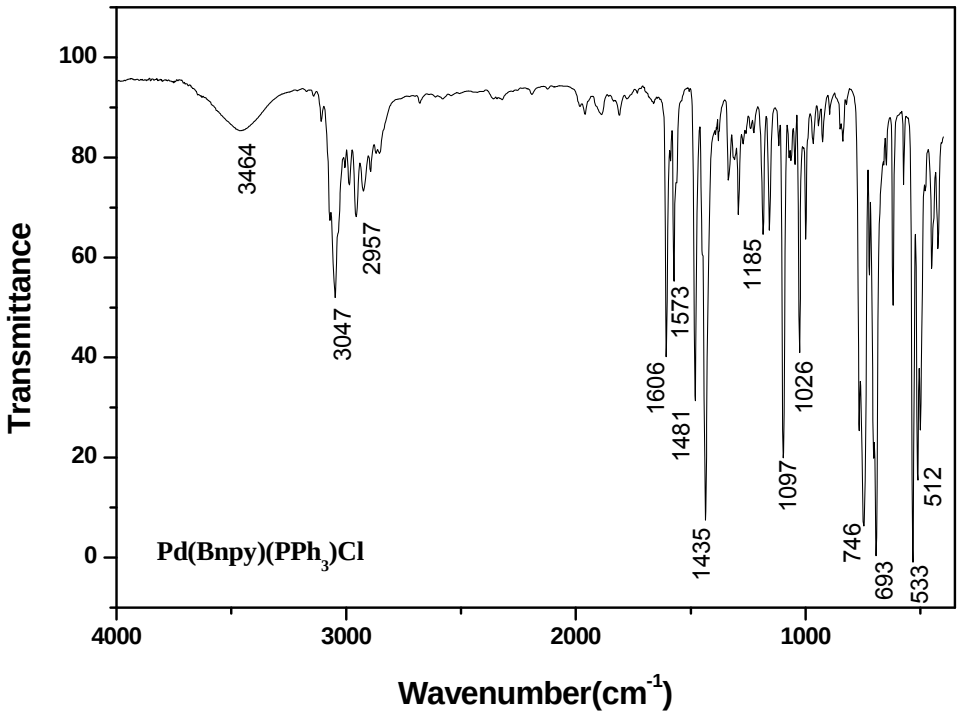


Figure 2.13. IR Spectrum of the Complex Pd(Bnpy)(PPh_3)(Cl)

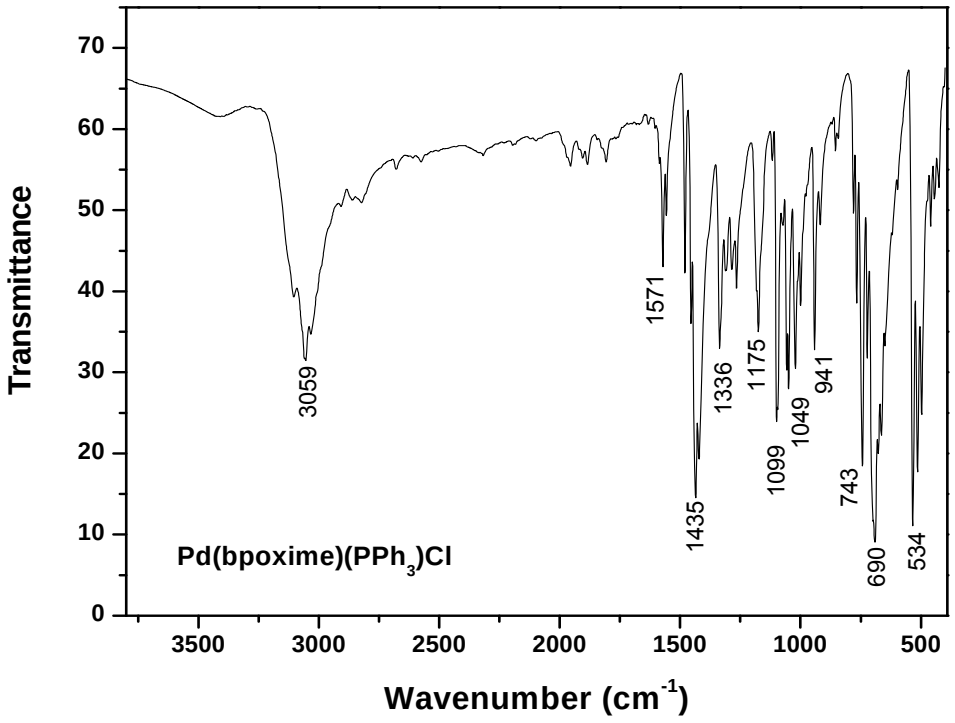
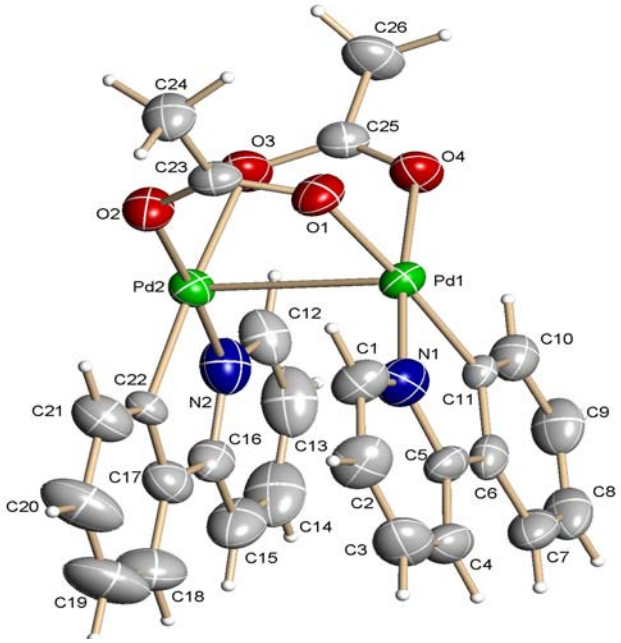


Figure 2.14. IR Spectrum of the Complex Pd(bpoxime)(PPh_3)(Cl)

2.3.1 Molecular Structures of NC Palladacycle Complexes

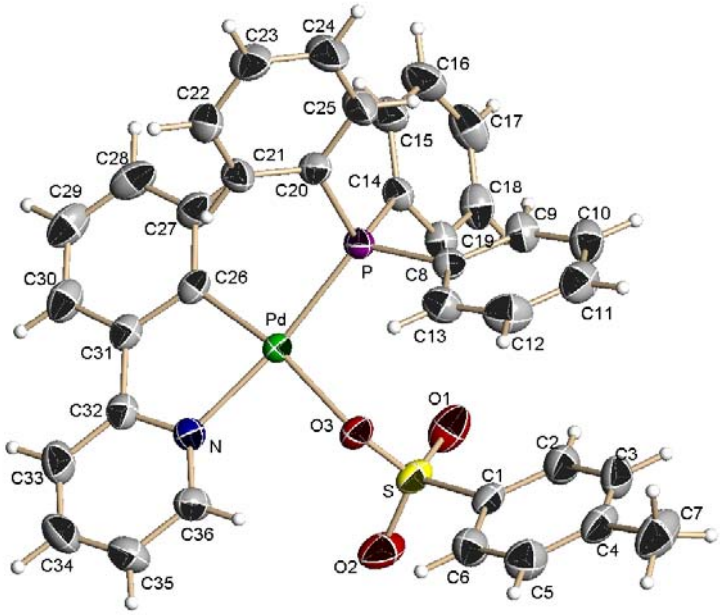
From X-ray crystallographic data it was observed that the palladacyclic complexes adopt distorted square-planar geometries at the palladium atom and the phosphorous atom is in trans position to the donor N atom. The angle P-Pd-N varies from 168.94 to 177.92°. The Pd-N bond lengths for Pd(pquin)(PPh_3)(OTs) and Pd(dim)(PPh_3)Cl are longer compared to the rest of the compounds. When the bulkiness of the ligand is more as in complex Pd(pquin)(PPh_3)(OTs) with respect to Pd(ppy)(PPh_3)(OTs), there is an increase in the P-Pd-O bond angle and a decrease in the N-Pd-O bond angle. Compound Pd(dim)(PPh_3)Cl is known and is reported as $C_{27.35}H_{27}Cl_{1.30}NO_{0.25}PPd$ (triclinic space group), now the compound is reported as $C_{27}H_{27}ClNPPd$ crystallizing in the orthorhombic system. The structure is very similar with essentially identical Pd-C, Pd-P and Pd-N bond lengths, however in the present case the Pd-Cl bond is longer compared to the previous system. The crystallographic data for the palladium complexes are summarized in Appendix I. For the complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) and Pd(mquin)(PPh_3)(OTs) having similar PPh_3, OTs motifs differing in the NC coordination, the respective C-Pd-N bond angles (Å) are as follows: 81.25 ° , 80.95 ° and 83.53 °.

Figure 2.15. Crystal Structure of the Complex $[Pd_2(ppy)_2(OAc)_2]$



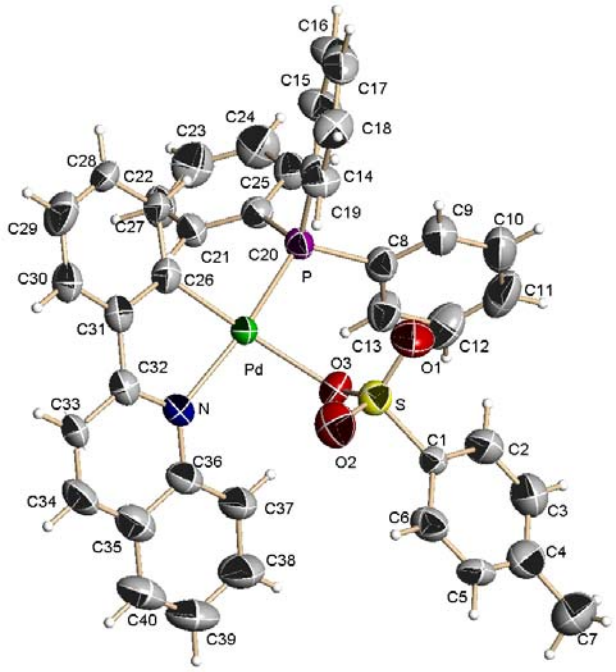
(C_{26} H_{22} N_2 O_4 Pd_2): M = 639.26, Crystal approximate size 0.17 x 0.05 x 0.04 mm, multiscan data acquisition. Total scans = 3, total frames = 1558, exposure / frame = 20.0 sec / frame, θ range = 2.39 to 25.00 º, completeness to θ of 25.0 º is 100.0%. Monoclinic, space group , $P2_1/n$, a = 9.7201 (6), b = 19.2330 (11), c = 12.8938 (7) Å, β = 101.691(1)º, V = 2360.4(2)$Å^3$, Z = 4, D_c = 1.799mg m^{-3}, μ (MoK_α) = 1.559 mm^{-1}, 14540 reflections measured, 4155 unique [I>2σ(I)], R value 0.0306, wR2 = 0.0788.

Figure 2.16. Crystal Structure of the Complex [Pd(ppy)(PPh_3)(OTs)]



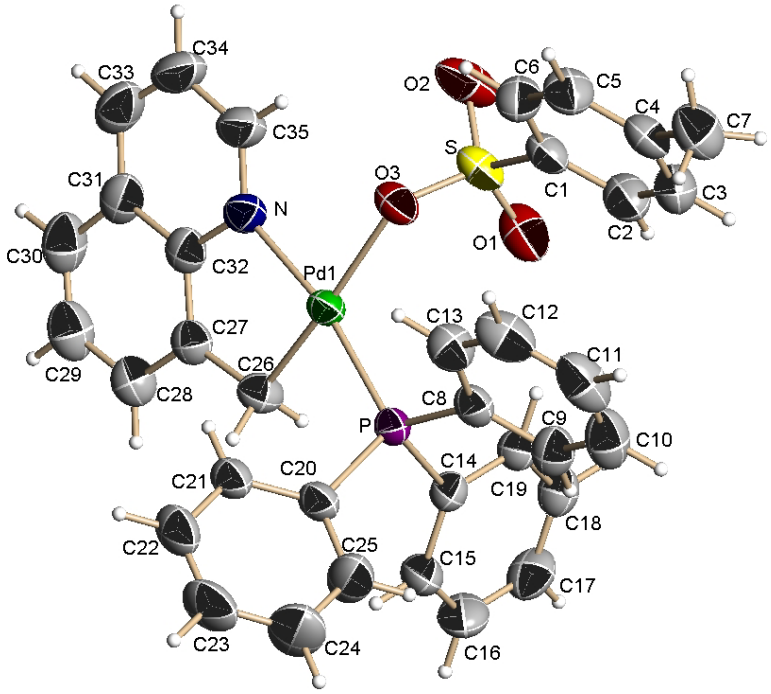
(C_{36} H_{30} N O_3 P Pd S): M = 694.04, Crystal of aproximate size 0.42 x 0.17 x 0.10 mm, multiscan data acquisition. Total scans = 5, total frames = 3030, exposure / frame = 15.0 sec / frame, θ range = 2.06 to 25.00 º, completeness to θ of 25.0 º is 100.0 %. monoclinic, space group $P2_1$ / n, a 10.7329(4), b = 16.7366(7), c = 17.2684(7) Å, β = 101.608(1)º, V = 3038.5(2) $Å^3$, Z = 4, D_c = 1.517mg m^{-3}, μ (MoK_α) = 0.770 mm^{-1}, 31910 reflections measured, 5356 unique [I>2σ(I)], R value 0.0320, wR2 = 0.0803.

Figure 2.17. Crystal Structure of the Complex [Pd(pquin)(PPh_3)(OTs)]



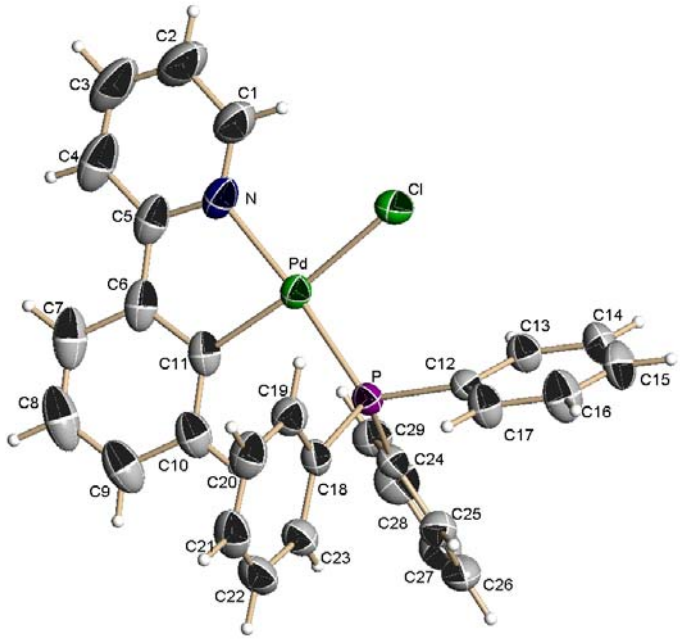
$[C_{40}H_{32}NO_3PPdS.(CH_2Cl_2)]$: M = 829.02, Crystal of approximate size 0.43 x 0.39 x 0.24 mm, multiscan data acquisition. Total scans = 4, total frames = 2404, exposure / frame = 5.0 sec / frame, θ range = 2.00 to 25.00 º, completeness to θ of 25.0 º is 99.9 %. monoclinic, space group $P2_1$ / c, a = 10.6960 (5), b = 16.8380 (8), c = 22.2180 (9) Å, β = 113.500(1) º, V = 3669.6(3) A^3 , Z = 4, D_c = 1.501 mg m^{-3}, μ (MoK_α) = 0.792 mm^{-1}, 34092 reflections measured, 6462 unique [I>2σ(I)], R value 0.0340, wR2 = 0.0897. The palladium complex crystallizes along with a disordered dichloro methane molecule as a solvent of crystallization.

Figure 2.18. Crystal Structure of the Complex [Pd(mquin)(PPh_3)(OTs)]



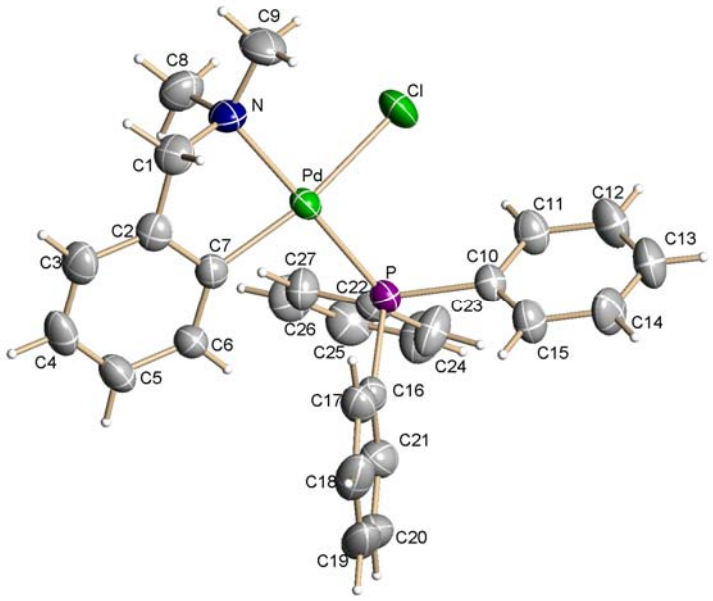
(C_{35} H_{30} N O_3 P Pd S): M = 682.03, Crystal approximate size 0.38 x 0.24 x 0.17 mm, hemisphere data acquisition. Total scans = 3, total frames = 1271, exposure / frame = 10.0 sec / frame, θ range = 2.14 to 25.00 º, completeness to θ of 25.0 º is 99.7 %. Monoclinic, space group , $P2_1/n$, a = 10.6375 (4), b = 15.9797 (6), c = 18.0061 (7) Å, β = 95.578 (1)º, V = 3046.3(2) $Å^3$, Z = 4, D_c = 1.487 mg m^{-3}, μ (MoK_α) = 0.767 mm^{-1}, 15185 reflections measured, 5351 unique [I>2σ(I)], R value 0.0255, wR2 = 0.0635.

Figure 2.19. Crystal Structure of the Complex [Pd(ppy)(PPh_3)(Cl)]



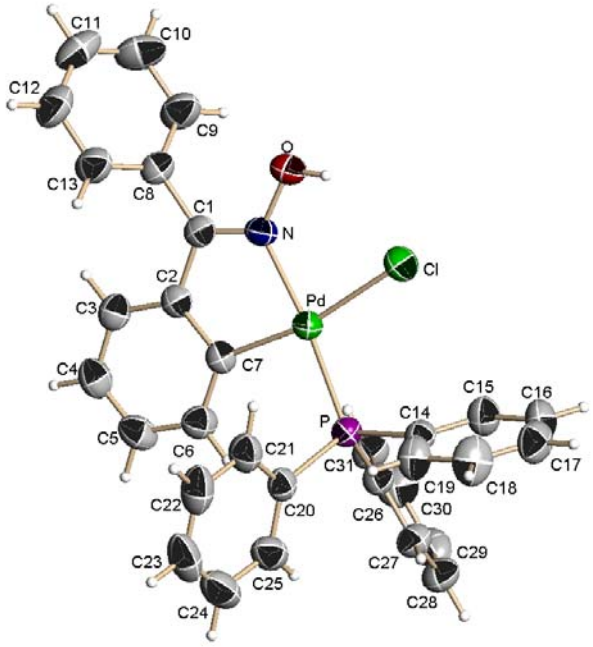
(C_{29} H_{23} Cl N P Pd): M = 558.30, crystal, approximate size 0.50 x 0.47 x 0.33 mm, multiscan data acquisition. Total scans = 4, total frames = 2424, exposure / frame = 5.0 sec / frame, θ range = 2.14 to 25.00 °, completeness to θ of 25.0 ° is 99.8 %. Triclinic, space group , P-1, a = 9.9575 (4), b = 10.3204 (4), c = 13.5965 (5) Å, α = 78.847 (1), β = 70.540 (1), γ = 67.960 (1)º, V = 1217.41 (8) $Å^3$, Z = 2, D_c = 1.523 mg m^{-3}, μ (MoK_α) = 0.955 mm^{-1}, 11836 reflections measured, 4280 unique [$I>2\sigma(I)$], R value 0.0214, wR2 = 0.0600.

Figure 2.20. Crystal Structure of the Complex [Pd(dim)(PPh_3)(Cl)]



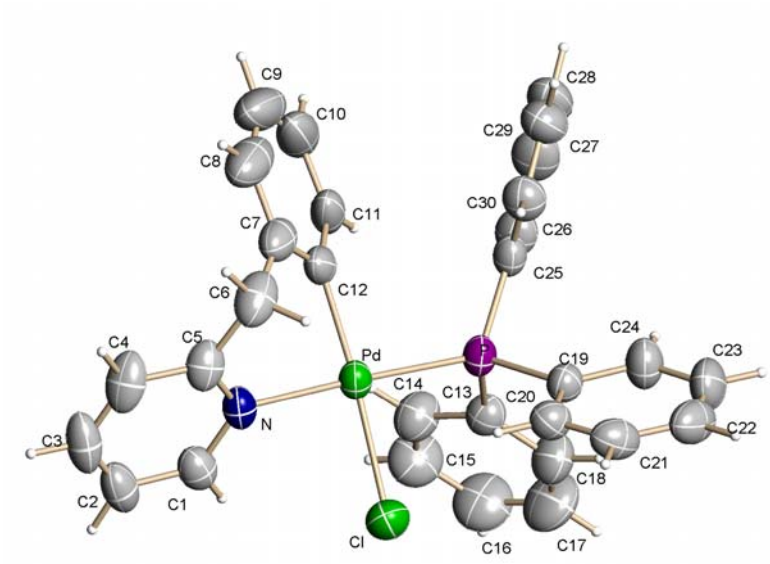
(C_{29} H_{23} Cl N P Pd): M = 558.30, Crystal approximate size 0.09 x 0.07 x 0.06 mm, multiscan data acquisition. Total scans = 5, total frames = 2610, exposure / frame = 20.0 sec / frame, θ range = 2.40 to 25.00 º, completeness to θ of 25.0 º is 100%. Orthorhombic, space group, $Pna2_1$, a = 28.5444 (15), b = 8.0494 (4), c = 10.5384 (6) Å, V = 2421.4 (2) $Å^3$, Z = 4, D_c = 1.477 mg m^{-3}, μ (MoK_α) = 0.957 mm^{-1}, 23702 reflections measured, 4264 unique [$I>2\sigma(I)$], R value 0.0375, wR2 = 0.0835

Figure 2.21. Crystal Structure of the Complex [Pd(bpoxime)(PPh_3)(Cl)]



(C_{31} H_{25} Cl N O P Pd): *M* = 600.34, Crystal dimensions 0.13 x 0.09 x 0.05 mm, multirun data acquisition. Total scans = 4, total frames = 2424, exposure / frame = 20.0 sec / frame, θ range = 2.02 to 25.0º, completeness to θ of 25.0 º is 99.8 %, triclinic, space group P-1, *a* = 9.8861(6) , *b* = 10.5028(6), *c* = 14.0789(8) Å, α = 75.252(1), β = 74.277(1), γ = 79.892(1)º, *V* = 1351.84(14) $Å^3$, *Z* = 2, D_c = 1.475 mg m^{-3}, μ (Mo K_α) = 0.869 mm^{-1}, 13248 reflections measured, 4759 unique [I>2σ(I)], R value 0.0278, wR2 = 0.0655

Figure 2.22. Crystal Structure of the Complex [Pd(Bnpy)(PPh_3)(Cl)]



(C_{30} H_{35} Cl N O_5 P Pd): M = 662.41, Crystal of aproximate size 0.36 x 0.16 x 0.13 mm, Quadrant data acquisition. Total scans = 4, total frames = 2424, exposure / frame = 20.0 sec / frame, θ range = 1.37 to 25.00 º, completeness to θ of 25.0 º is 100.0 %. Trigonal, space group R-3, a = 29.1847(8), b = 29.1847(8), c = 18.4122(8) Å, V = 13581.5(8) $Å^3$, Z = 18, D_c = 1.458 g /cc, μ (MoK_α) = 0.795 mm^{-1}, 44312 reflections measured, 5320 unique [I>2σ(I)], R value 0.0296, wR2 = 0.0845

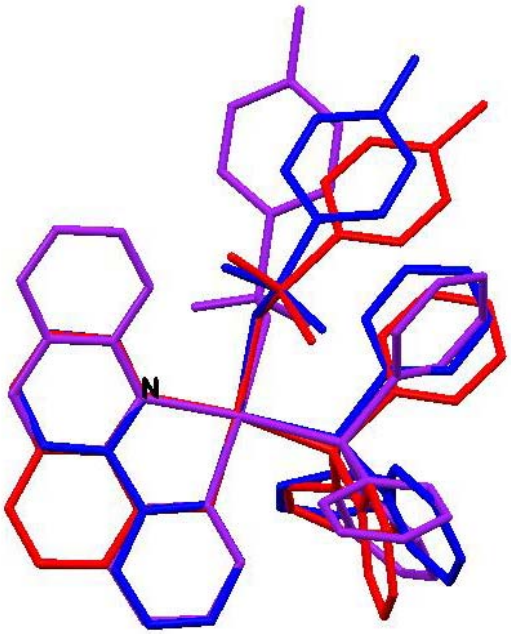


Figure 2.23. Spatial Orientation of Pd complexes after Superimposing NC Coordinating Ligand

Red–Pd(mquin)(PPh_3)(OTs),Blue– Pd(ppy)(PPh_3)(OTs), Violet – Pd(pquin)(PPh_3)(OTs)

For the complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) and Pd(mquin)(PPh_3)(OTs), PPh_3 and OTs ligands are common and ligands forming NC palladacycles are different. In order to check the spatial orientation, NC coordination was fixed and the structures were superimposed (Figure 2.23). From the figure it can be clearly seen that the orientation of OTs and PPh_3 ligand changes significantly. The crystal packing structures of the complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) and Pd(mquin)(PPh_3)(OTs) are shown in the Figures 2.24 – 2.26 respectively. The packing of the molecules in the unit cell is shown in the Figure 2.27. The packing diagram shows that the molecules are closely packed in Pd(mquin)(PPh_3)(OTs) followed by less close packing in Pd(ppy)(PPh_3)(OTS) and least in Pd(pquin)(PPh_3)(OTs). The structure analysis clearly indicates that the spatial orientation as well as packing of crystals in lattice is affected by the ligands around the palladium.

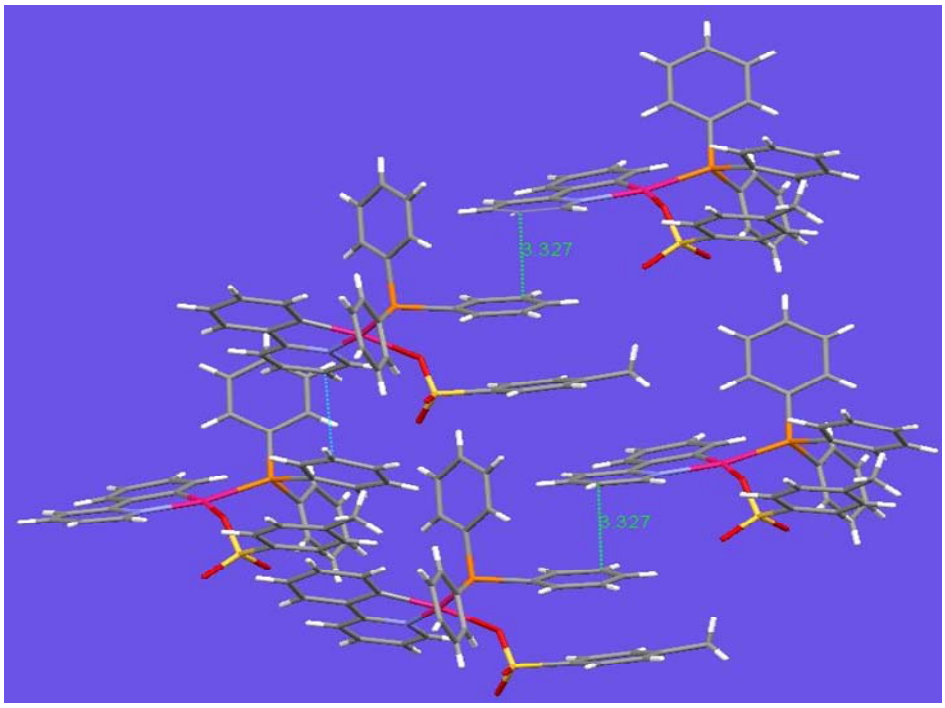


Figure 2.24.Crystal Packing Diagram for Pd(ppy)(PPh_3)(OTs)

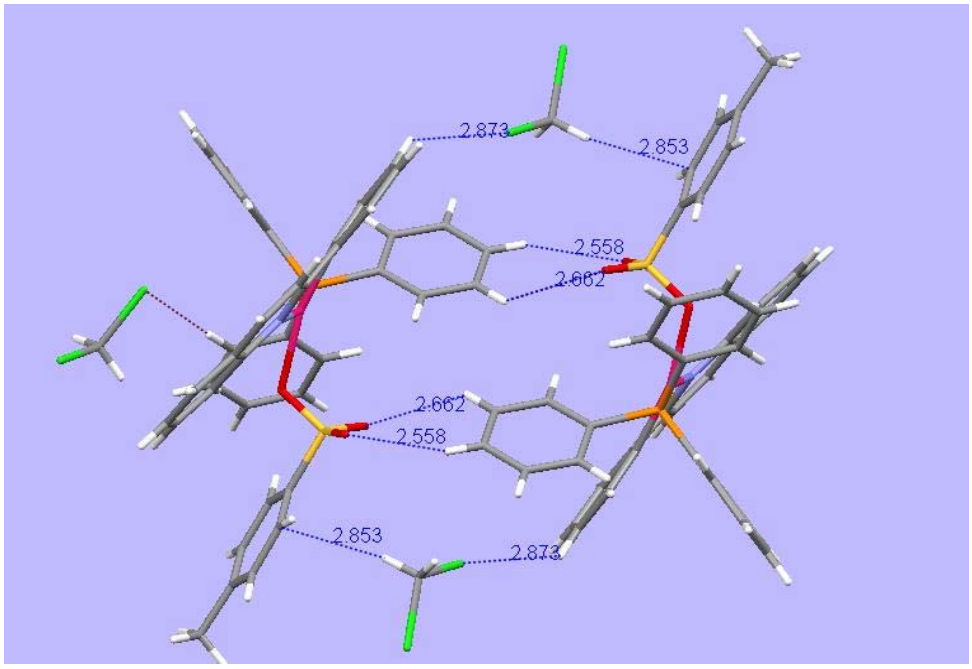


Figure 2.25.Crystal Packing Diagram for Pd(pquin)(PPh_3)(OTs)

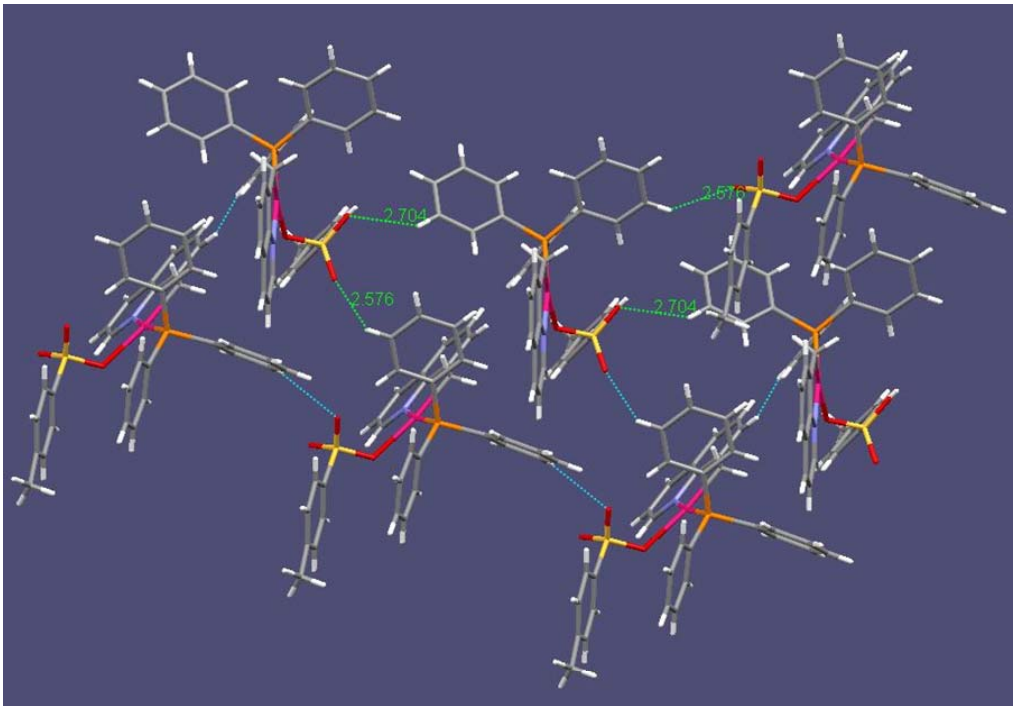
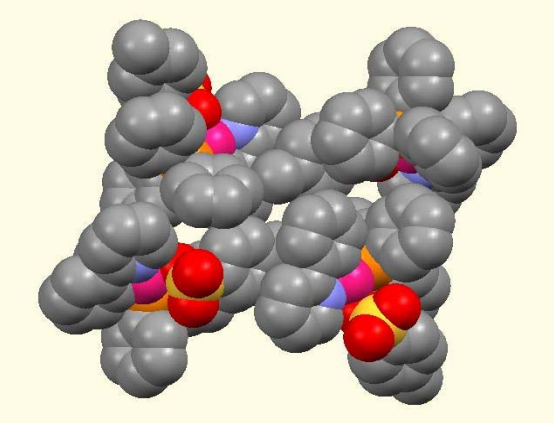
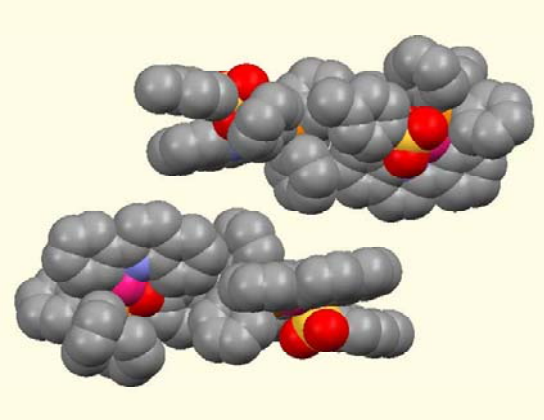


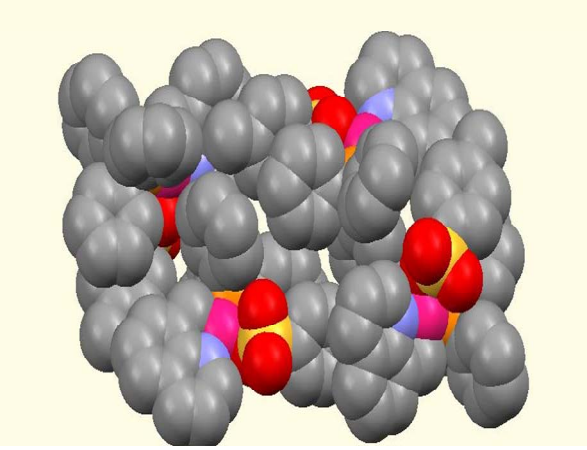
Figure 2.26.Crystal Packing Diagram for Pd(mquin)(PPh_3)(OTs)



Pd(ppy)(PPh_3)(OTs)



Pd(pquin)(PPh_3)(OTs)

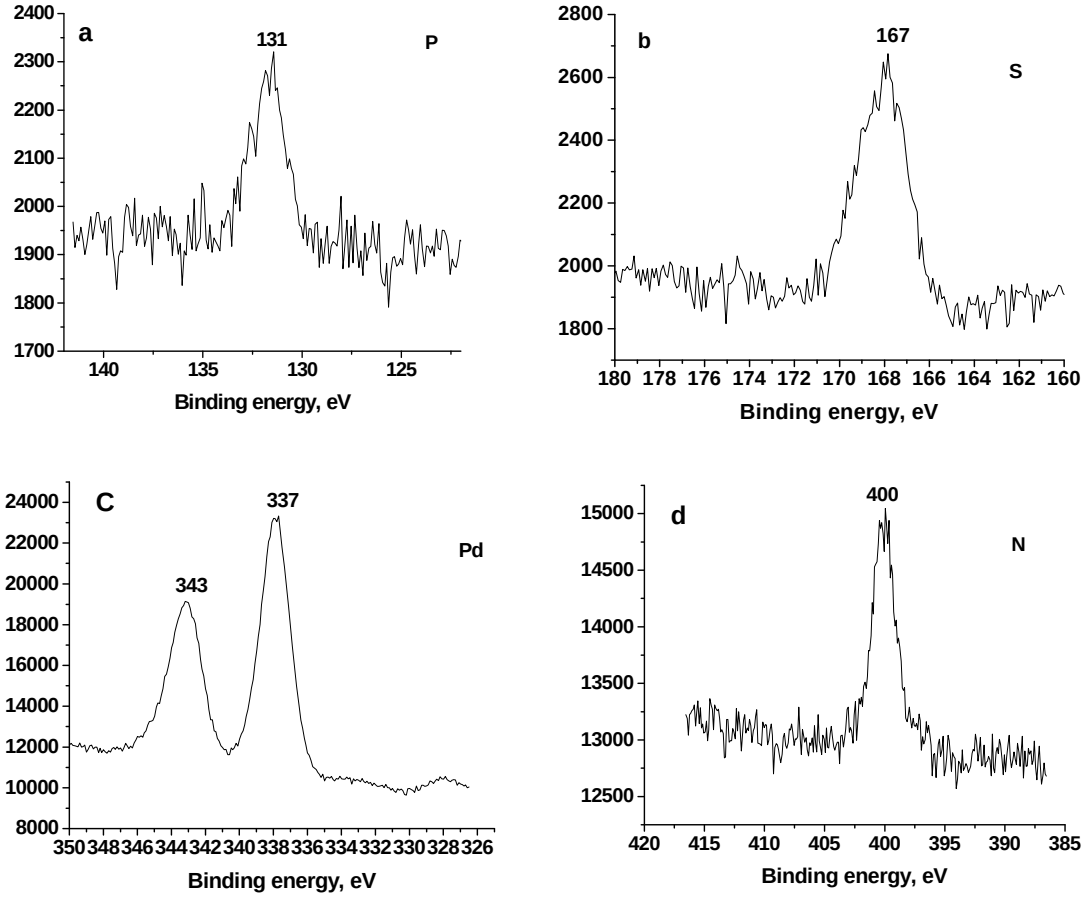


Pd(mquin)(PPh_3)(OTs)

Figure 2.27. Packing of Molecules in Unit Cell

2.3.2 X-ray Photoelectron Spectroscopy (XPS)

The peaks in the spectra are typically identified as the different elements present in the complex (Palladium, Nitrogen, Sulphur, Chlorine, Carbon, Phosphorous and Oxygen) and the binding energies were used to assign the oxidation states of the respective elements. All the values were corrected to the standard carbon 1s peak arising out of the adventitious carbon at 285 eV. The data of the complex namely Pd(ppy)(PPh_3)(OTs), Pd(quin)(PPh_3)(OTs), Pd(mquin)(PPh_3)(OTs), Pd(benz)(PPh_3)(Cl), Pd(bpoxime)(PPh_3)(Cl) are presented in the Table 2.10. The XPS spectra for various elements present in the complex Pd(ppy)(PPh_3)(OTs) are shown in the Figure 2.28.



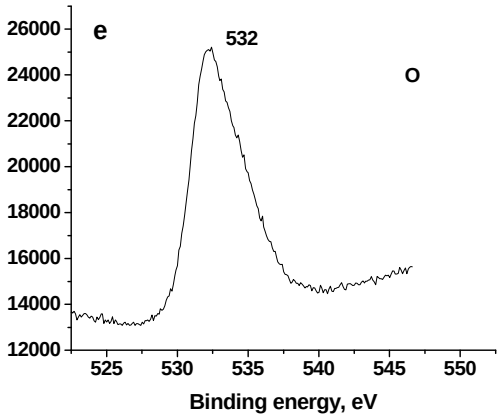


Figure 2.28. X-ray Photoelectron Spectra (XPS) of Pd(ppy)(PPh_3)(OTs) (a) P $2p_{3/2}$ (b) S $1s_{1/2}$ (c) Pd^{2+} (3 $d_{5/2}$ & 3 $d_{3/2}$) (d) N $1s_{1/2}$ (e) O $1s_{1/2}$

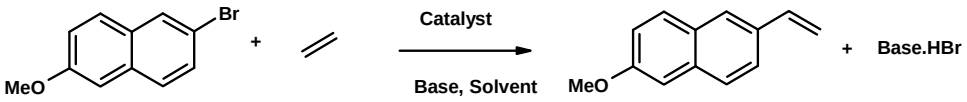
Table 2.10. XPS Values for Different Elements Present in Palladium Complexes

Elements / Comlpex	Pd 3 $d_{5/2}$; 3 $d_{3/2}$	N $1s_{1/2}$	S $1s_{1/2}$	P $2p_{3/2}$	O $1s_{1/2}$
Pd(ppy)(PPh_3)(OTS)	337; 343	400	167	131	532
Pd(pquin)(PPh_3)(OTS)	337.8; 342.8	399.5	167.9	131.6	531.2
Pd(mquin)(PPh_3)(OTS)	337.6; 342.8	399.6	168	131.8	530.3
	Pd 3 $d_{5/2}$; 3 $d_{3/2}$	N $1s_{1/2}$	Cl $2p_{3/2}$	P $2p_{3/2}$	
Pd(Bnpy)(PPh_3)(Cl)	342.6; 337.5	399.6	197.2	134.3	
Pd(bpoxime)(PPh_3)(Cl)	342.3; 337.4	399.5	196.7	134.5	

2.4. Catalytic Reactions for the Arylation of Ethylene

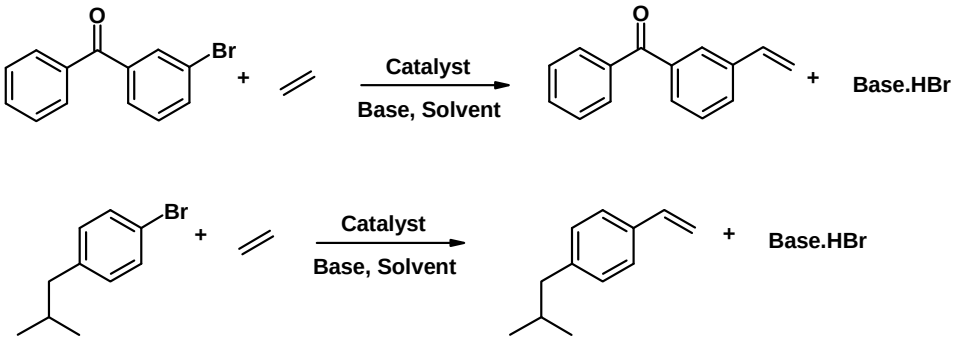
Substrate BMN was chosen for the preliminary experiments on arylation reactions, as it was easily available. Other substrates *m*-bromobenzophenone and 4-bromoisobutylbenzene were not available and hence synthesized (Section 2.2.4.1 and 2.2.4.2). The schematic of the arylation of ethylene with BMN is shown (Scheme 2.7.), which gives 2-vinyl-6-methoxynaphthalene as the major product, which is an intermediate for the synthesis of Naproxen. Effect of various reaction conditions such as solvents, bases, temperature, substrate and catalyst concentration and ethylene

partial pressure on activity and selectivity was investigated using various NC palladacycle complexes. The results are presented in the following section.



Scheme 2.7. Arylation of Ethylene with BMN

Further arylation reactions were also carried out with the substrates *m*-bromobenzophenone and *p*-isobutyl-bromobenzene that give vinyl aromatics (Scheme 2.8) which are the precursors for the synthesis of anti-inflammatory drugs Ketoprofen and Ibuprofen respectively.

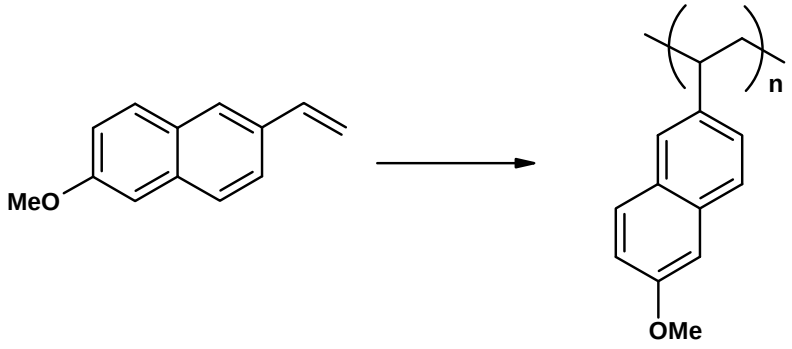


Scheme 2.8. Arylation of Ethylene with BBP and BIBB

2.4.1 Preliminary Investigations on Arylation of Ethylene with BMN

The preliminary experiments were carried out using Pd(ppy)(PPh_3)(OTs) complex as a catalyst on arylation of ethylene to establish the material balance, product distribution and benchmark the performance for comparison with other catalysts. Reactions were carried out using BMN (10.5 mmol) in N-methyl-2-pyrrolidone (NMP) solvent under the following reaction conditions: BMN = 10.5 mmol, Cat = 0.05 mol%, NMP = 23 ml, NaOAc = 15.75 mmol, T = 413 K, ethylene pressure = 1.99 MPa. The progress of the reaction was monitored by taking the intermittent reaction samples at different times to determine the changes in concentrations of the reactant BMN and products formed. It was found that more than 96% of BMN was converted to the product 2-vinyl-6-methoxynaphthalene in a very short time (< 10

minutes). Thus the reaction was completed in a much shorter time compared to those described previously in patented literature.[11] An important observation made was that the product VMN was a highly reactive compound and tends to polymerizes at higher temperatures > 393 K (Scheme 2.9.). It has also been reported that the compound VMN has the tendency to polymerize.[26] The polymer product is not detected by GC and an indirect proof of its formation was seen in the decreased area percent of VMN with time in samples withdrawn by GC analysis and lack of material balance. Mass balance of > 98% was observed for the first 15 minutes afterwards the product degrades and the mass balance was found to 85% after a period of 1 h. The next section describes the effect of temperature on the arylation of ethylene with BMN.



Scheme 2.9. Polymerization of VMN

The workup of the reaction was carried out as follows: after completion of the reaction (1.5 h) the reaction mixture was filtered to remove the solid base (NaOAc) and NaBr (during the reaction conditions the base was insoluble in NMP as seen in the samples withdrawn). To the filtrate 5% HCl was added, the product is precipitated from the mother liquor, the solution is held at room temperature during the HCl addition. The precipitated solid is washed with methanol and dried under high vacuum at room temperature. The appendix I shows the NMR spectrum and the GC-MS results of the product VMN.

2.4.1.1 Effect of Temperature

The effect of temperature on activity and selectivity was investigated in a temperature range of 363 – 413 K. The reactions were carried at a catalyst loading of 0.0137 (~ 0.014) mol% and the results are shown in the Figure 2.29. The figure clearly

reflects that at a temperature of 393 K the rate of arylation is very fast as compared to other temperatures. However for temperatures above 393 K the product VMN degrades and the selectivity towards the Heck product VMN decreases. The reaction lacks the material balance above the temperature of 393 K. For the reaction temperature of 413 K the material balance after a period of one hour was found to be 80%. The reaction at 383 K showed perfect mass balance with > 99% conversion for the reactant consumed and the product formed. Based on this observation further reactions were done at this temperature. The reaction showed a high selectivity towards VMN (> 97%) and the dehalogenated product Methoxynaphthalene (MN) was also observed (< 2%) during the reaction.

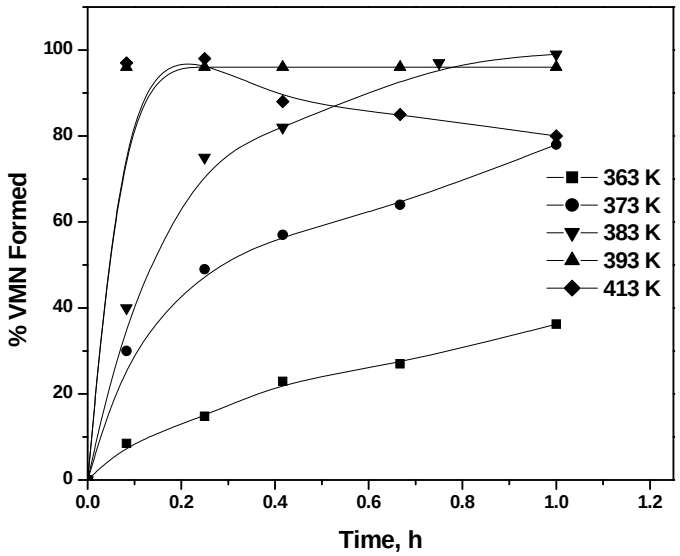


Figure 2.29. Plots of Percent VMN Formed Against Time for the Arylation of Ethylene with BMN at Various Temperatures.

Reaction Conditions: BMN,10.54 mmol; [Pd(ppy)(PPh$_3$)(OTs)], 1.4 x 10^{-3} mmol; NaOAc, (15.81 mmol); P$_{Ethylene}$, 1.99 MPa; Solvent (NMP ~ 23 ml); Time, 1 h

2.4.1.2. Effect of Catalyst Loading

The activity of the catalyst increased with increase in catalyst concentration in a range of 0.16 x 10^{-3} – 4 x 10^{-3} mmol. With further increase in catalyst concentration no change in the catalytic activity was observed. The observed trend was confirmed by repeating few reactions at high catalyst loading. Lower catalyst loadings can be used for obtaining high turnover numbers, however when lower catalyst loadings are used, there was the problem of reproducibility of the results. Using such a small amount of

catalyst, it is likely that even traces impurities in the solvent or reagents affects the TON. For all the experiments catalyst solution was prepared, the complex was dissolved in NMP and the respective amount was taken for the reactions. The stock solution of palladacycle was utilized for the arylation reactions and its activity was retained even after standing at room temperature for few days. In order to avoid catalyst contamination the reactor was rinsed with aqua regia prior to use, and dried thoroughly. The catalyst loading of 0.014 mol% gave high TOFs of 4629 h^{-1} and gave reproducible results, this loading was taken as benchmark for further experiments.

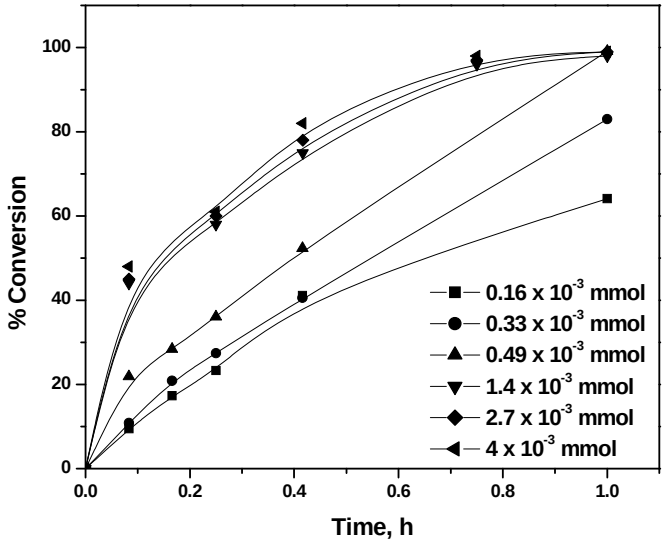


Figure 2.30. Plots of Percent VMN Formed Against Time for the Arylation of Ethylene with BMN at Various Catalyst Loadings.

Reaction Conditions: BMN, 10.54 mmol; NaOAc, 15.81 mmol; $P_{Ethylene}$, 1.99 MPa; Solvent (NMP ~ 23 ml); T , 383 K; Catalyst, [Pd(ppy)(PPh_3)(OTs)]; Time, 1h

2.4.1.3. Effect of Solvent

Since most of the chemical reactions require the solution phase, the solvent plays a crucial role on the overall rate and activity/ selectivity of the catalyst systems, either on a laboratory or industrial scale. Few solvents (N-methyl-2-pyrollidone, N,N-dimethylformamide, N,N-dimethylacetamide, Diethylketone and Acetonitrile) were screened to find the best solvent system for this reaction and the results are presented in the Table 2.11. N-methyl-2-pyrrollidone (NMP) was found to be the most suitable solvent for this reaction among the solvents screened. Using acetonitrile as a solvent

no conversion was observed indicating that acetonitrile perhaps acts as a ligand and coordinates with the palladium thus deactivating the catalytic species. Applying diethylketone as a solvent gave poor conversions. The polar aprotic solvents viz. N,N-dimethylformamide and N,N-dimethylacetamide also yield good conversions for the reaction. Since the Heck reaction mainly involves ionic components, and the exclusion of an acid in each catalytic step, polar aprotic solvents are the most desirable. Further experiments were conducted with NMP, as a solvent. As NMP is a polar solvent it can also facilitate the solubility of NaOAc, thus making the reaction more homogeneous and hence the higher activity.

Table 2.11. Effect of the Solvent in the Arylation of Ethylene with BMN

entry	Solvent	Conv(%)	Time, h	TOF h^{-1}
1	N-methyl-2-pyrollidone	98	1.5	4629
2	N,N-dimethylformamide	80	1.5	4102
3	N,N-dimethylacetamide	90	1.5	4325
4	Diethylketone	17	1.5	870
6	Acetonitrile	-	2	-

Reaction Conditions: BMN, (10.54 mmol); NaOAc, 15.81 mmol; T , 383 K; $P_{Ethylene}$,1.99 MPa; Solvent ~23 ml; [Pd(ppy)(PPh_3)(OTs)] ,1.4 x 10^{-3} mmol

2.4.1.4. Effect of Base

The choice of a base can have a crucial effect on the rate and product distribution of Heck reactions. The role of the base is to regenerate the active palladium complex by capturing the acid HBr and to complete the catalytic cycle. A number of organic and inorganic bases were tested in the arylation reactions, and the results indeed showed a strong dependence of the catalytic activity on the base used. The results are summarized in the Table 2.12. The selectivity towards the formation of Heck product VMN was not affected with the changes in the bases, the reaction formed only the single product with > 98% selectivity. The use of organic bases gave low conversions (entry 8-10) as compared to inorganic salts. Organic bases such as triethylamine can act as ligands[27] and they are strongly bound to Pd thereby making the catalytically active centre less accessible for the activation of the arylbromides, hence a lower activity was observed with these bases. The use of calcium oxide and

sodium carbonate as a base gave a lower conversion of 35%. The comparison of sodium carbonate and potassium carbonate showed that the activity with potassium salts is higher, this may be attributed to better ionization of the potassium bases in the organic solvents as compared to sodium bases. Sodium and potassium acetate which are also less expensive and nonflammable were found to be the best base systems for these reactions.

Table 2.12. Effect of Different Bases in the Arylation of Ethylene with BMN

entry	Base	Conv (%)	Time, h	TOF h^{-1}
1	Sodium acetate	98	1.5	4629
2	Sodium carbonate	35	1.5	1391
3	Calcium oxide	35	1.5	1408
4	Sodium orthophosphate hydrate	84	1.5	3413
5	Cesium carbonate	70	1.5	3695
6	Potassium acetate	97	1.5	4272
7	Potassium carbonate	77	1.5	3326
8	Dicyclohexylamine	60	1.5	3087
9	Diisopropylamine	68	1.5	3316
10	Triethylamine	38	1.5	1711

Reaction Conditions: BMN,10.54 mmol; Base,15.81 mmol; T, 383 K; $P_{Ethylene}$, 1.99 MPa; Solvent (NMP ~23 ml); [Pd(ppy)(PPh_3)(OTs)], 1.4 x 10^{-3} mmol,

2.4.1.5. Screening of the NC Palladacycle Complexes as Catalysts in Arylation of Ethylene with BMN

The results for the arylation reaction using the synthesized palladacycles are summarized in Table 2.13. and progress of the reactions with time in Figure 2.31. In all the reactions, a complete conversion of BMN with a high selectivity of > 98% selectivity towards VMN was observed in 1.5 h duration for all the complexes investigated. It may

be noted that the difference in activity is marginal. However, at 0.75 h, the catalytic activity was found to be different for the various complexes investigated. According to these results the catalytic activity of the complexes varied in decreasing order as follows: Pd(ppy)(PPh_3)Cl > Pd(bpoxime)(PPh_3)Cl > Pd(pquin)(PPh_3)(OTs) > Pd(ppy)(PPh_3)(OTs) = Pd(Bnpy)(PPh_3)Cl > Pd(dim)(PPh_3)Cl > Pd(mquin)(PPh_3)(OTs).

Complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) and Pd(mquin)(PPh_3)(OTs) have different NC ligands, while other ligands viz. PPh_3 and OTs are common. As discussed earlier (Section 2.3.1) the X-ray structure analysis demonstrates that the bite angle N-Pd-C decreases in the order Pd(mquin)(PPh_3)(OTs) - 83.53° > Pd(ppy)(PPh_3)(OTs) – 81.25° > Pd(pquin)(PPh_3)(OTs) – 80.95°, and the catalytic activity on the contrary increased in the order Pd(mquin)(PPh_3)(OTs) < Pd(ppy)(PPh_3)(OTs) < Pd(pquin)(PPh_3)(OTs). Also crystal packing and orientation of OTs and PPh_3 is different in the complexes Pd(ppy)(PPh_3)(OTs), Pd(pquin)(PPh_3)(OTs) and Pd(mquin)(PPh_3)(OTs). It is likely that various geometrical and electronic factors may be responsible for the observed trends in catalytic activity for Heck arylation reaction.

Whereas for the complexes containing the chloride ligands, the order of reactivity decreased as: Pd(ppy)(PPh_3)Cl > Pd(bpoxime)(PPh_3)Cl > Pd(Bnpy)(PPh_3)Cl > Pd(dim)(PPh_3)Cl. The complex Pd(ppy)(PPh_3)Cl is a five membered palladacycle and Pd(Bnpy)(PPh_3)Cl is a six membered palladacycle and the result (Table 2.13) show that the five membered palladacycle is more active than the six membered palladacycle. Looking at the bite angles N-Pd-C for these complexes show that Pd(Bnpy)(PPh_3)Cl – 86.56° > Pd(ppy)(PPh_3)Cl – 80.90° whereas the activity shows a reverse trend (Five membered palladacycle is a planar ring whereas the six membered palladacycle has boat form from single crystal X-ray diffraction studies).

These results suggest that simple NC Palladacycle complexes show excellent performance for arylation reactions with high turnover frequencies (TOF>4000 h^{-1}). The reaction requires less catalyst, lower temperature, and the palladacycles were prepared from inexpensive ligands. All the seven NC palladacycle are the potential candidates for the arylation reactions.

Table 2.13. Arylation of Ethylene with BMN Using Different NC Palladacycles

Palladacycle	Catalyst (mol%)	Conversion (%)	TOF h^{-1}
Pd(ppy)(PPh_3)(OTs)	0.014	98	4629
Pd(pquin)(PPh_3)(OTs)	0.014	93	4457
Pd(mquin)(PPh_3)(OTs)	0.014	97	4634
Pd(ppy)(PPh_3)Cl	0.014	98	4636
Pd(dim)(PPh_3)Cl	0.014	93	4628
Pd(bpoxime)(PPh_3)Cl	0.014	96	4729
Pd(Bnpy)(PPh_3)Cl	0.014	96	4700

Reaction Conditions: BMN, 10.54 mmol; NaOAc, 15.81 mmol; T ,383 K; $P_{Ethylene}$ = 1.99 MPa; Time ,1.5 h; Solvent (NMP ~23 ml)

The catalytic performance of the catalyst is also shown in the Figure 2.31.

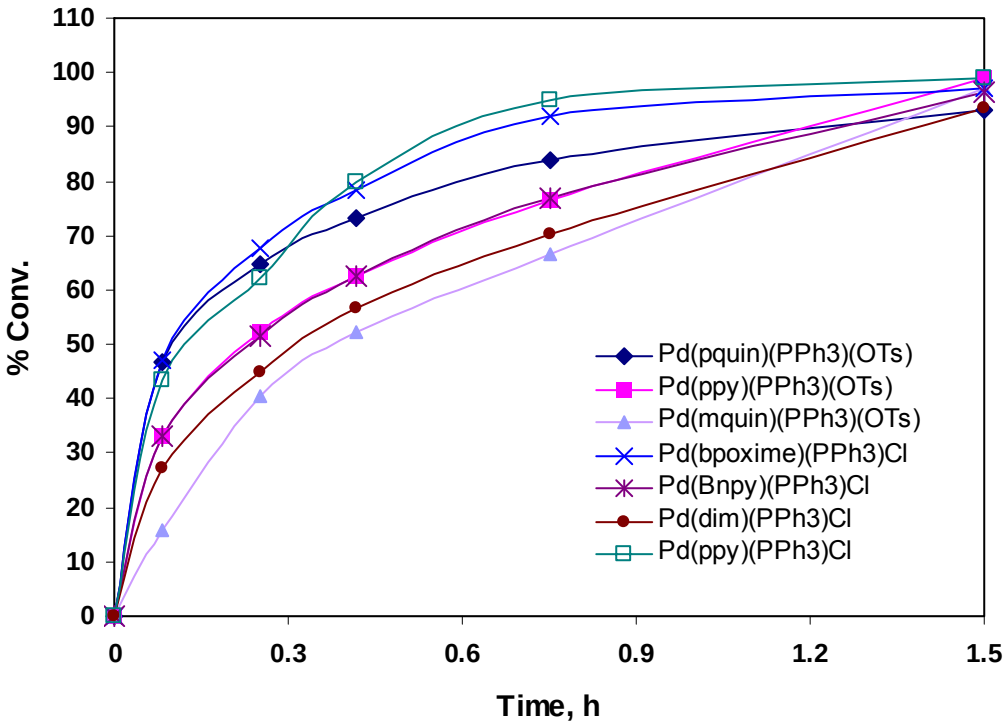


Figure 2.31. Conversion of VMN vs. Time for Various Palladium Complexes

2.4.1.6. Comparison of NC Palladacycle with Herrmann Palladacycle

Since Herrmann Palladacycle is the well known catalyst for the Heck reaction the activity of NC palladacycle catalyst was compared with Herrmann palladacycle under standardized reaction conditions, the result of which are shown in the Figure 2.32 as the concentration-time plot.

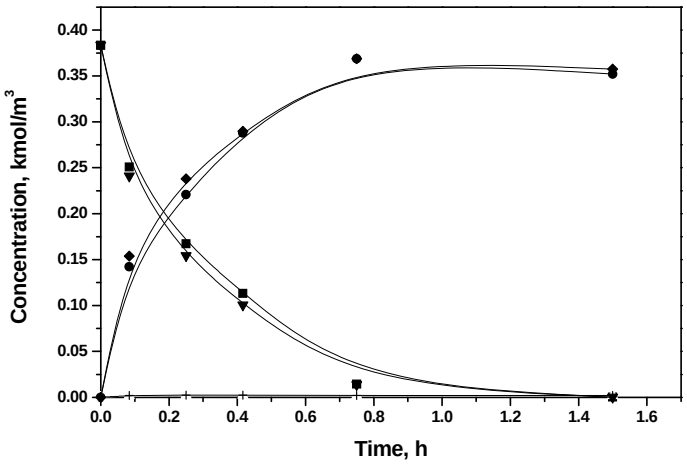
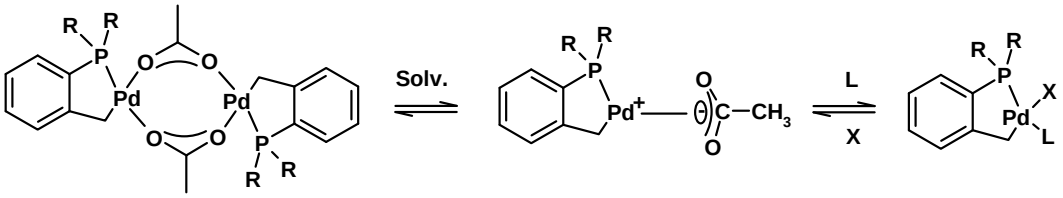


Figure 2.32. Concentration vs. reaction time for the Arylation of Ethylene with BMN using the complex [Pd(κ^2-N,C-$C_{11}H_8N$)(PPh_3)(OTs)] (2) and *trans*-Di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium (*hc palladacycle*).

Reaction Conditions: BMN, 10.54 mmol; Catalyst, 1.44x 10^{-3} mmol; NaOAc, 15.81 mmol; $P_{Ethylene}$, 1.99 MPa; Solvent (NMP ~ 23 ml); Time, 1.5 h

It is clearly seen that both the catalysts follow the same reaction pathway. The concentration-time profile shows the perfect mass balance between the reactant (BMN) consumed and the product (VMN) formed. The Herrmann palladacycle is a dimer molecule whereas the NC palladacycle is a monomeric palladacycle complex. The Herrmann palladacycle which is a dinuclear molecule exists as monomer/ dimer equilibria in solution, because of the weakly bound acetate ligands enter into monomer complex in which the solvent molecules are involved. Thus the dimer behaves as the monomeric cyclopalladated complex.[8] There is no observation of the induction period for these reactions, the reaction starts rapidly after the ethylene gas is filled.



R = *o*-tolyl, L = NMP, DMF; X = Br

2.4.1.7. Parametric Variation for the arylation of ethylene with BMN at 363 K

Having chosen NMP as the solvent and NaOAc as a base for this reaction a few parametric variations were studied at 363 K to understand the activity and selectivity pattern of the reaction. At a temperature of 363 K the reaction is slow and helps to understand details of the reaction more precisely.

Table 2.14 Effect of BMN Concentration and Ethylene Pressure in Arylation at 363 K

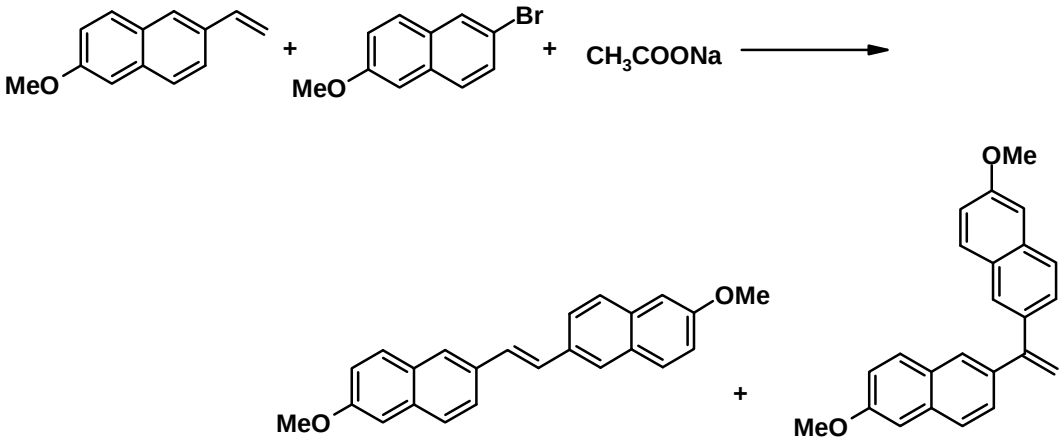
entry	BMN, mmol	Conv, %	Ethylene pressure (MPa)	Time, h	VMN selectivity	TON	TOF, h^{-1}
1	21.09	35	1.99	1	98	770	770
2	10.54	75	1.99	1	98	944	944
3	5.27	95	1.99	1	98	566	566
4	2.63	95	1.99	1	98	282	282
5	10.54	100	0.24	2	73	1014	507
6	10.54	100	0.48	2	85	1136	568
7	10.54	74	1.03	2	90	958	479

Reaction Conditions: [Pd(ppy)(PPh_3)(OTs)] ,7.2 x 10^{-3} mmol; NaOAc,15.81 mmol; Solvent (NMP ~ 23 ml).

The results in Table 2.14 demonstrate that when the reaction is carried out at lower ethylene pressure, the selectivity towards the desired product VMN is low (73%). However, increasing the ethylene pressure leads to an increase of the selectivity towards VMN to 98%. Such behavior has also been observed[28] in the arylation of

ethylene with 2-bromo-toluene as substrate (the formation of *trans*-1,2-bis(*ortho*-tolyl) ethylene and *gem*-1,1'-bis(*ortho*-tolyl)ethylene at lower ethylene pressure).

At lower ethylene pressure other products were obtained which could not be detected by GC for the arylation reaction, thus the reason for the low selectivity (73%) at ethylene pressure (0.24 MPa). Side reactions such as bisarylations arylations can take place in the reaction, which is shown in Scheme 2.10 assuming the formation of by-products as described by De Vries.[28] No attempt was made to isolate the side products. However, no side reaction takes place at an ethylene pressure of 290 psi. The TOF increases from 282 h^{-1} to 944 h^{-1} for BMN concentrations in the range 2.63 to 10.54 mmol, but with a further increase of BMN to 21.09 mmol the TOF decreases to 770 h^{-1}.

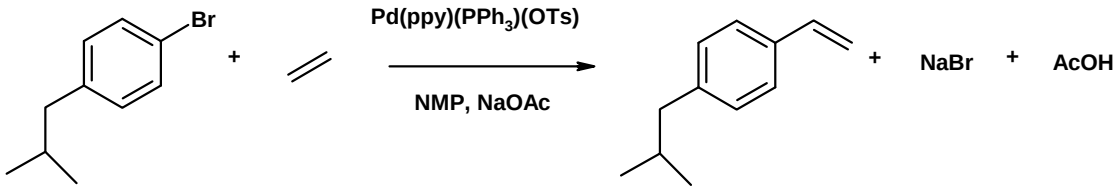


Scheme 2.10. Side product in the Arylation of Ethylene with BMN (bisarylation)

Conclusions: The arylation of ethylene with BMN was carried out using various NC palladacycles. From the experiments carried it was observed that when the reaction was carried at 383 K, there is a perfect material balance between the reactant (BMN) consumed and the product (VMN) formed. The use of NMP as the solvent and NaOAc as the base exhibited the highest activity. The reaction showed a high turnover frequency (> 4000 h^{-1}). At lower ethylene pressure side products are formed in the reaction, however at a ethylene pressure of 1.99 MPa, there is exclusive formation of the Heck product VMN. All the NC palladacycles prepared exhibited high catalytic activity in the arylation of ethylene.

2.4.2. Arylation of Ethylene with 4-Bromoisobutylbenzene

Arylation of ethylene with 4-bromo-iosbutylbenzene gives 4-vinyl-isobutylbenzene; the precursor for the Ibuprofen synthesis (Scheme 2.11.). For this purpose the reaction was carried out using the monomeric Pd(ppy)(PPh_3)(OTs) palladacycle as a catalyst. It may be noted that 4-vinyl-isobutylbenzene is a highly reactive compound and has the tendency to polymerize under the reaction conditions. Also the substituted isobutyl group is electron donating in nature which increases the electron density at the C-Br bond thereby strengthening the bond and requires higher thermal energy to activate in the palladium catalysis. A preliminary investigation using the similar conditions as described for the arylation of ethylene with BMN gave very low conversions (~35%). However with the reaction temperature of 398 K, the conversion was good (95%) and the selectivity towards the Heck product was 75%. The concentration-time profile of the reaction is shown in the Figure 2.33.



Scheme 2.11. Arylation of Ethylene with BIBB

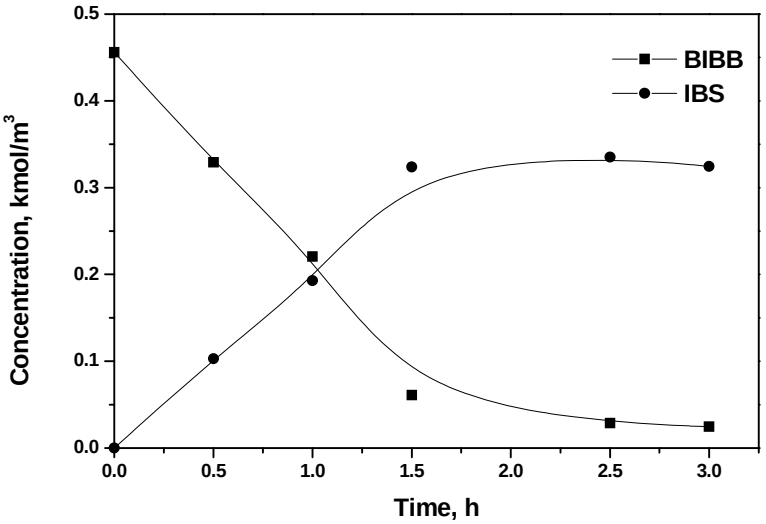


Figure 2.33. Concentration-Time Profile for the Arylation of Ethylene with BIBB

Reaction Conditions: BIBB, 10.54 mmol; NaOAc, 15.81 mmol; Solvent (NMP ~23 ml), [Pd(ppy)(PPh_3)(OTs)], 0.001 mmol; T , 398 K; $P_{Ethylene}$ = 1.99 MPa; Time, 3h

Reaction conditions were varied to obtain the high selectivity towards the Heck product, the results are presented in the Table 2.15. All the reactions were performed without using any polymer inhibitor. At lower temperature of 383 K and catalyst loading of 0.004 mmol the selectivity towards IBS was 97.5% but the conversion was lower (58%). When the temperature was increased to 393 K using the same catalyst loading, the conversion increased to 90% but the selectivity decreased to 85%. With increase in the ethylene pressure from 1.99 – 3.1 MPa the conversion increased but there was no change in the selectivity of the Heck product (entry 3 & 5).It is observed that reaction with BIBB is very sensitive towards the polymer formation (indicated with decreased selectivity towards the IBS). It was found that the p-isobutylbenzene is a difficult substrate for the arylation of ethylene. The detailed work has also not been reported in the literature, patent[14] express the results based on GC area precent, but the proper material balance of the reaction has not been shown for this reaction. The reactions catalyzed by Pd(ppy)(PPh_3)(OTs) showed high turnover frequencies.

Table 2.15. Arylation of Ethylene with BIBB

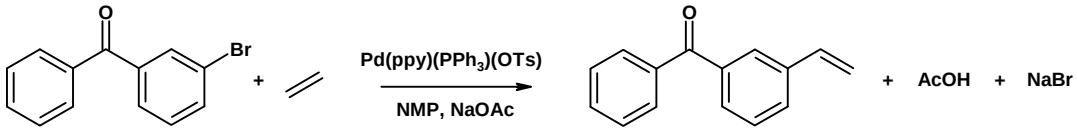
entry	Catalyst mmol	Time, h	Temp K	$P_{Ethylene}$ MPa	Conv.%	Selectivity IBS %	TOF, h^{-1}
1	0.004	3	383	1.99	58	97.5	496
2	0.004	3	393	1.99	90	85	671
3	0.008	2.5	383	1.99	49	85	219
4	0.008	3	393	1.99	95	73	304
5	0.008	3	383	3.1	90	86	339
6	0.001	3	398	1.99	95	75	2503

Reaction Conditions:BIBB, 10.54 mmol; NaOAc,15.81 mmol; Solvent (NMP ~23 ml); Catalyst, [Pd(ppy)(PPh_3)(OTs)]

2.4.3. Arylation of Ethylene with 3-bromo-benzophenone

The reaction of arylation of ethylene with 3-bromo-benzophenone was also undertaken as this gives the 3-vinyl-benzophenone (VBP) (Scheme 2.12) the precursor for the synthesis of the anti-inflammatory drug Ketoprofen. This reaction was carried using the palladium complex Pd(ppy)(PPh_3)(OTs). In contrast to reactions carried out with BIBB as a substrate, 3-BBP showed a perfect mass balance between the amounts of reactant consumed versus the product formed (indicating no polymer formation

during reaction). A typical concentration-time profile for the reaction is shown in the Figure 2.34. The reaction showed high selectivity towards VBP (>98%).The dehalogenated product benzophenone was also observed in the reaction but the selectivity was very low (<1%). The pure product VBP is an oily liquid product, when left as such in the flask at room temperature turns to solid mass. Hence the substrate VBP after purification has to be stored at lower temperatures in inert atmosphere and using polymerization inhibitor.



Scheme 2.12. Arylation of Ethylene with BBP

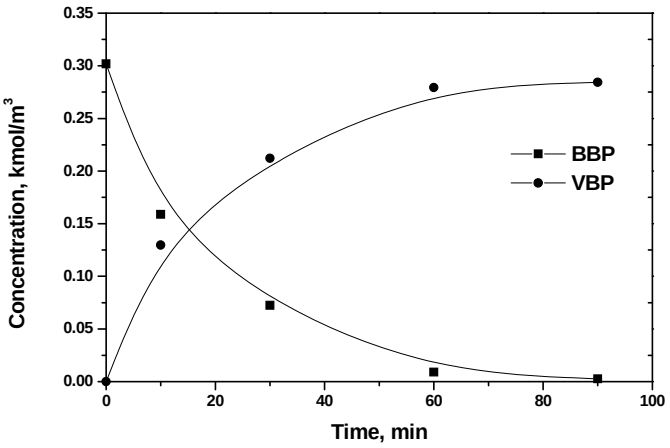


Figure 2.34. Concentration-Time Profile for the Arylation of Ethylene with BBP

Reaction Conditions:BBP, 7.63mmol; Pd(ppy)(PPh$_3$)(OTs), 0.1 x 10^{-3} mmol; NaOAc,11.44 mmol; T ,383 K; P$_{Ethylene}$, 1.99 MPa; Time , 1.5 h; Solvent (NMP ~23 ml)

The effect of few parameters on the activity and selectivity was carried out and the details are presented below:

2.4.3.1 Effect of Temperature

The effect of temperature was investigated on the arylation of ethylene with BBP and the results are presented in the Figure 2.35. At 393 K the reaction was very fast giving complete conversion in 60 min. As compared to BMN and BIBB the substrate BBP readily undergoes the Heck arylation reaction. This can be attributed to the electron

withdrawing group at the meta position in BBP as compared to electron donating substituents in BMN and BIBB. Based on the observations the decreasing order of reactivity towards the arylation of ethylene with the substrates can be arranged as: BBP > BMN > BIBB, and their respective TOFs h^{-1} are as follows 4842 > 4629 > 2692. The temperature of 383 K was chosen as the benchmark and the effect of various reaction conditions were studied.

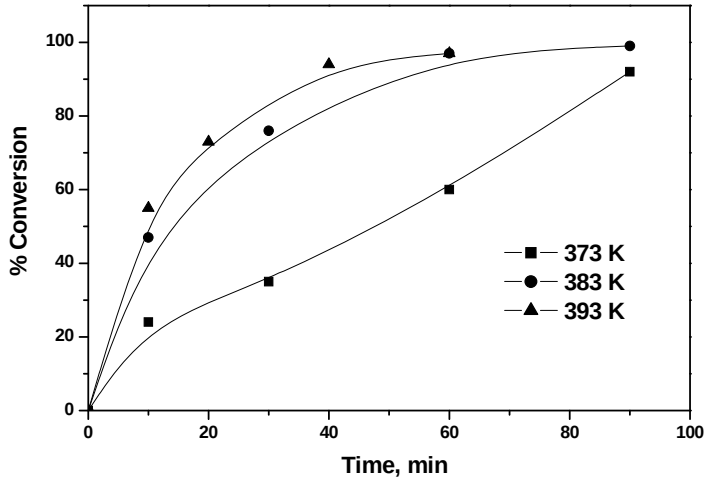


Figure 2.35. Plots of Conversion Against Time for the Arylation of Ethylene with BBP at Various Temperatures

Reaction Conditions:BBP, 7.63mmol; Pd(ppy)(PPh$_3$)(OTs), 0.1 x 10^{-3} mmol; NaOAc,11.44 mmol; $P_{Ethylene}$, 1.99 MPa; Time , 1.5 h; Solvent (NMP ~23 ml)

2.4.3.2 Effect of Catalyst Loading

The effect of catalyst loading was investigated at three different concentration and the results are presented in the Table 2.16.

Table 2.16. Effect of Catalyst Concentration on the Arylation of Ethylene with BBP

entry	Cat, mmol	Time, h	Conv %	TON	TOF, h^{-1}
1	0.0007	1	95	9528	9528
2	0.0014	1	97	4842	4842
3	0.0028	0.5	98	2232	4464

Reaction Conditions: BBP,7.63 mmol; NaOAc,11.44 mmol; Solvent (NMP ~23 ml), 383 K; Catalyst, Pd(ppy)(PPh$_3$)(OTs); $P_{Ethylene}$, 1.99 MPa

The result shows that high activity can be obtained at lower catalyst concentration, but at lower concentration of catalyst (< 0.0007 mmol), the results are not reproducible, it is likely that even traces of impurities in the solvent or reagents affects the TON. The result show that for the catalyst concentration studied, with increase in the catalyst concentration the TOF decreases for the reaction.

2.4.3.3 Effect of Ethylene Pressure

The effect of ethylene pressure was investigated at three different pressures viz at 0.68, 1.99 and 3.44 MPa.

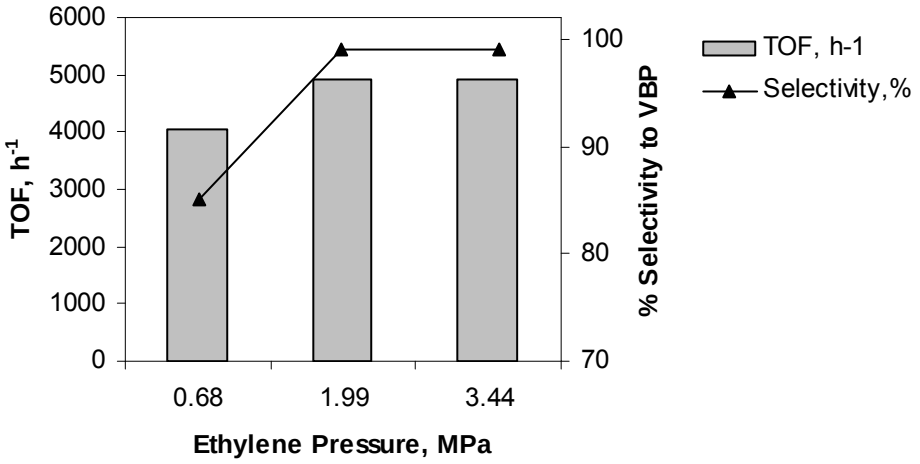


Figure 2.36. Effect of Ethylene Pressure in the Arylation with BBP

Reaction Conditions: BBP, 7.63 mmol; NaOAc, 11.44 mmol; T, 383 K; Pd(ppy)(PPh$_3$)(OTs),0.0014 mmol; Solvent (NMP ~23 ml); Time, 1h

At lower ethylene pressure the selectivity towards the VBP is 85%, the low selectivity can be attributed to the side reaction such as bisarylation taking place. However at pressures greater than 290psi the selectivity towards the Heck product is high (98%).

2.5 Conclusions

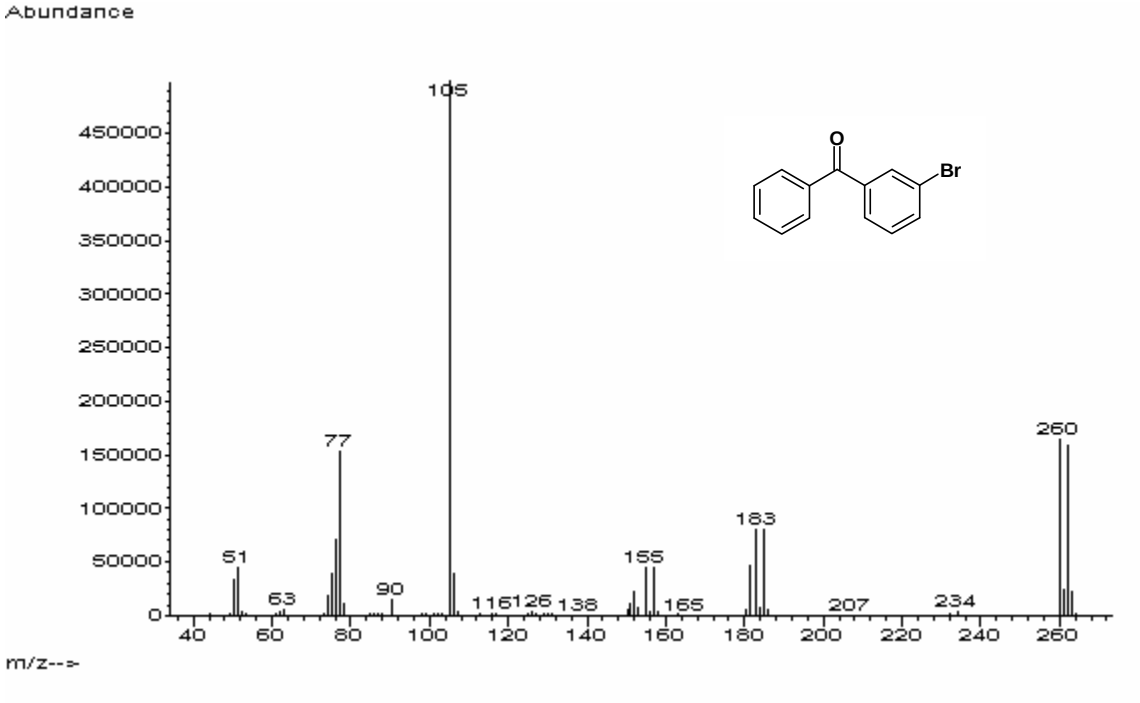
New NC palladacycles were synthesized for the first time, as well as their catalytic activity in the Heck arylation of ethylene has been described for the first time. The palladium complexes were characterized using IR, NMR, XPS and single crystal X-ray diffraction techniques. These complexes are highly active catalysts for heck arylation of

ethylene with substrates such as BMN, BBP and BIBB. Except with the substrate BIBB remarkable activity and selectivity were achieved. N-methyl-2-pyrrolidone was found to be the best solvent for the reaction. Inorganic bases such as NaOAC and KOAc which are non-inflammable and less expensive were found to be best bases for the system and showed good activity. The NC palladacycle complexes described can be excellent alternatives for the catalyst system such as $PdCl_2$/ NMDP, which uses a costly ligand. The complexes were prepared from less expensive and readily available NC ligands. The reaction requires less catalyst, and lower temperature, and these catalysts showed a high turnover frequency of > 4000 h^{-1} and this is the highest in the literature for such systems.

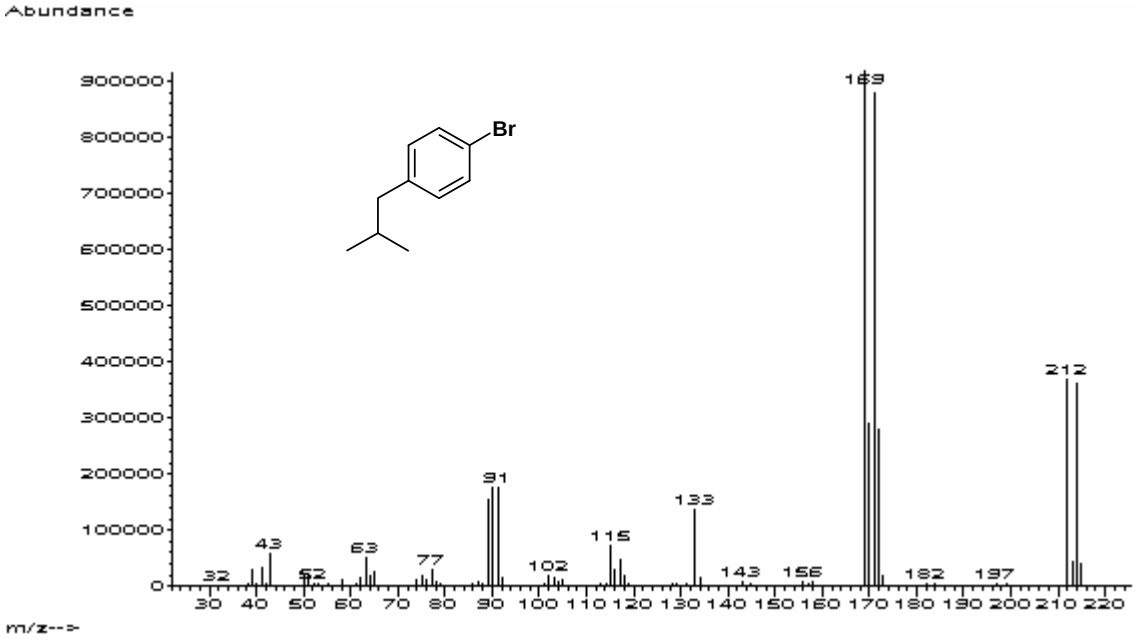
Appendix I

GC-MS

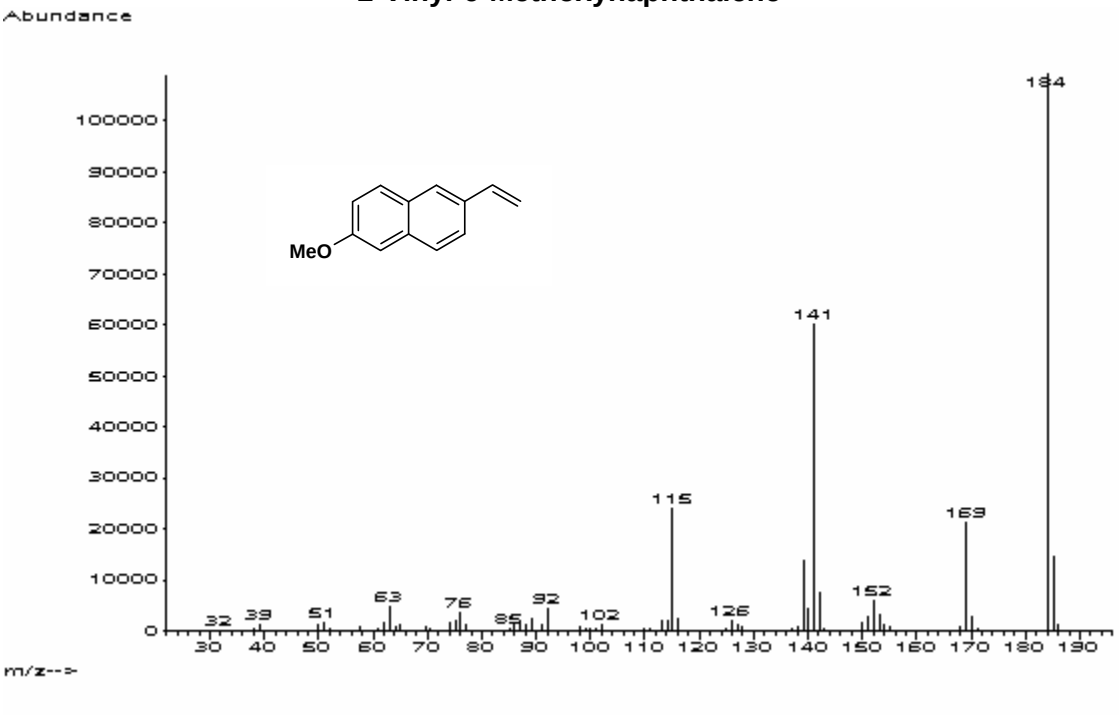
3-Bromo-benzophenone



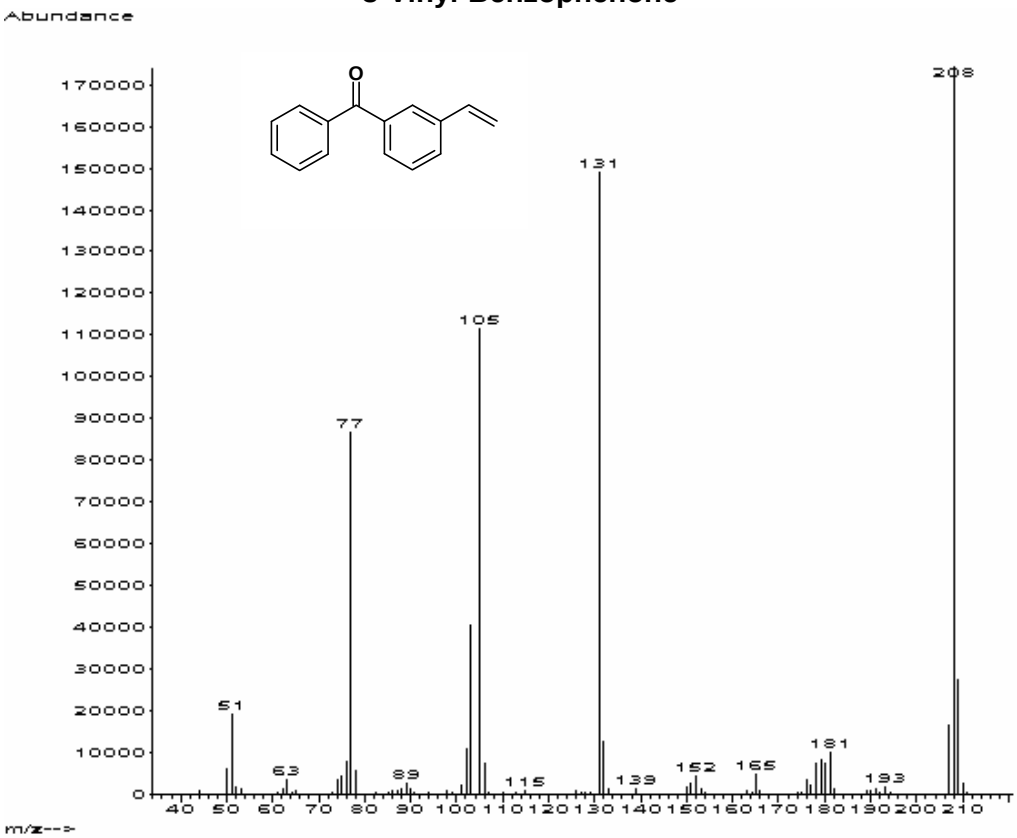
4-Bromo-isobutylbenzene



2-Vinyl-6-Methoxynaphthalene

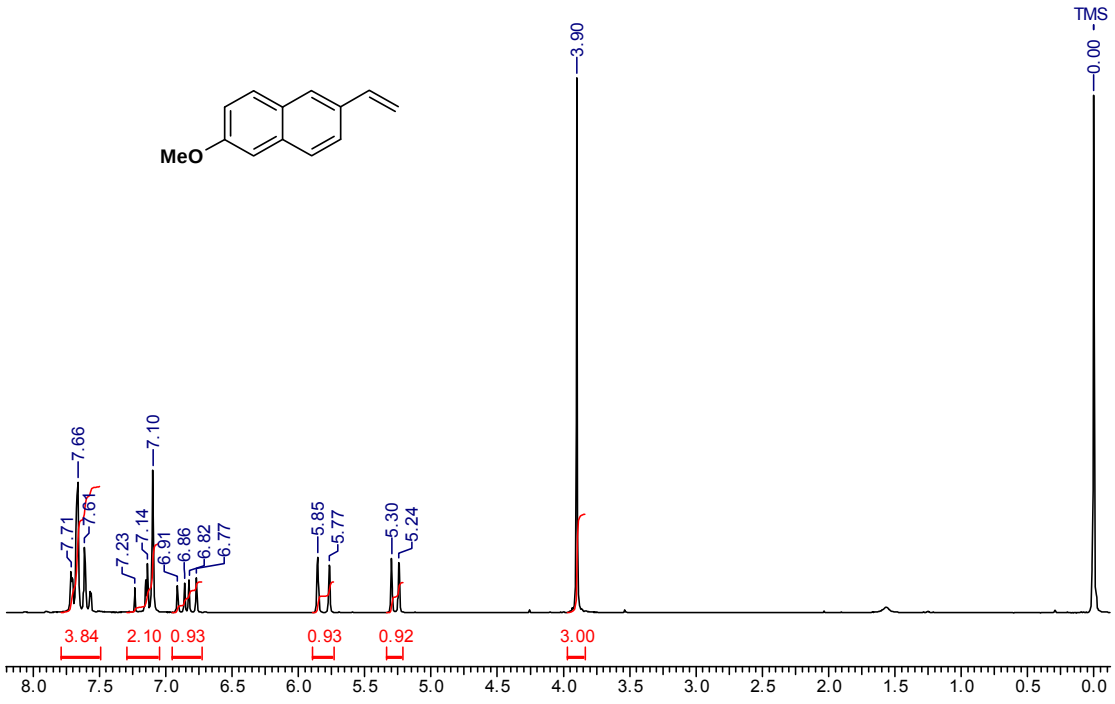


3-Vinyl-Benzophenone

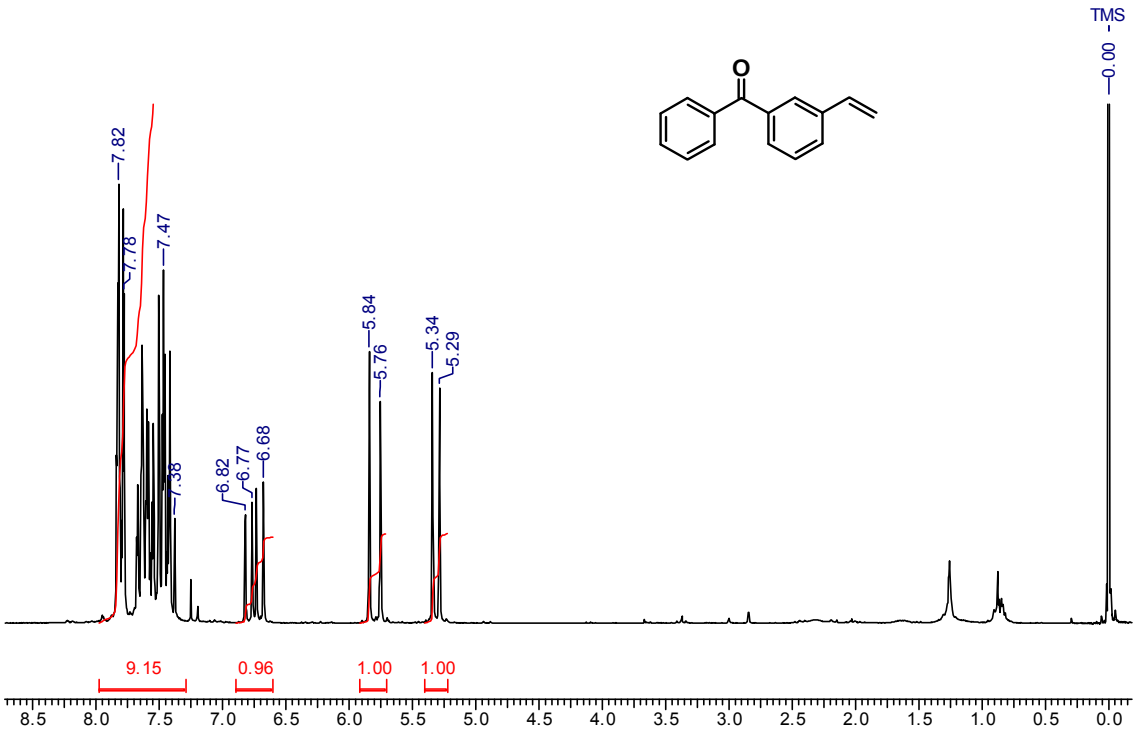


Proton NMR of substrates

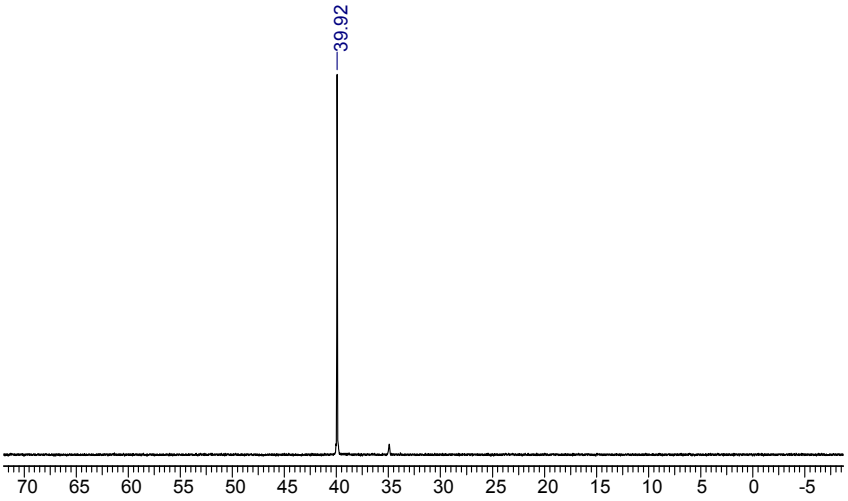
^{1}H NMR of VMN



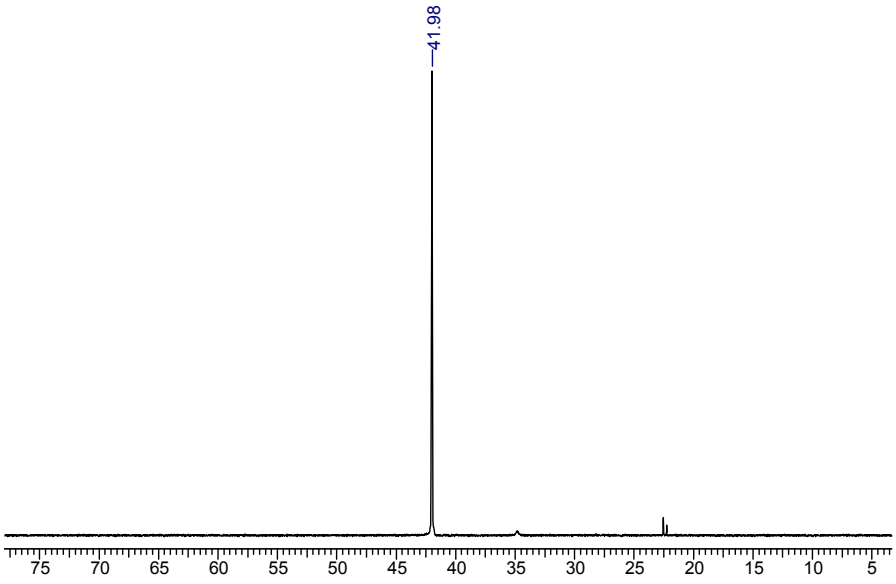
^{1}H NMR of VBP



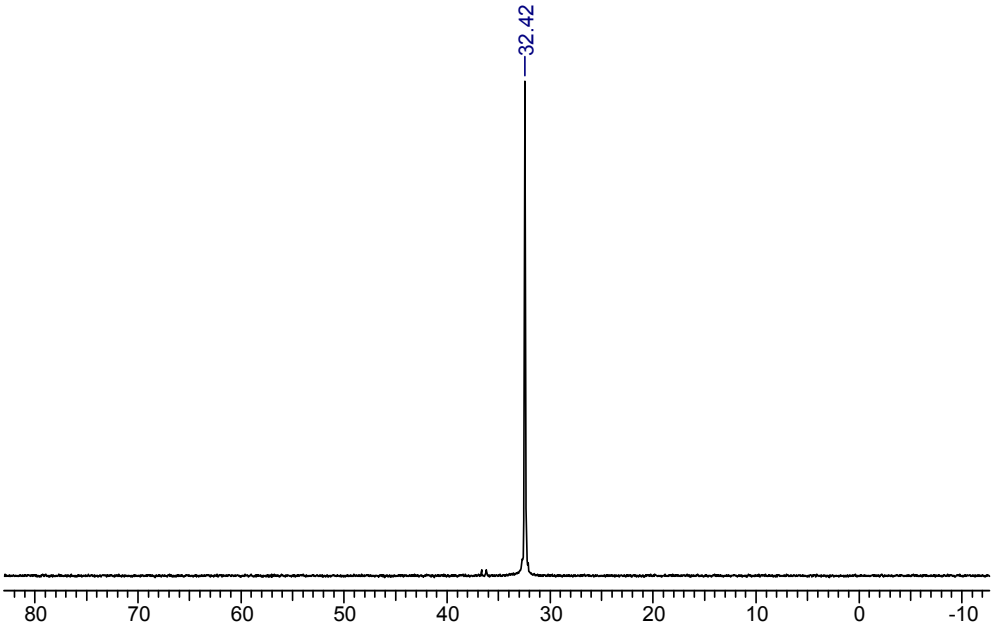
^{31}P NMR of the Pd-complexes



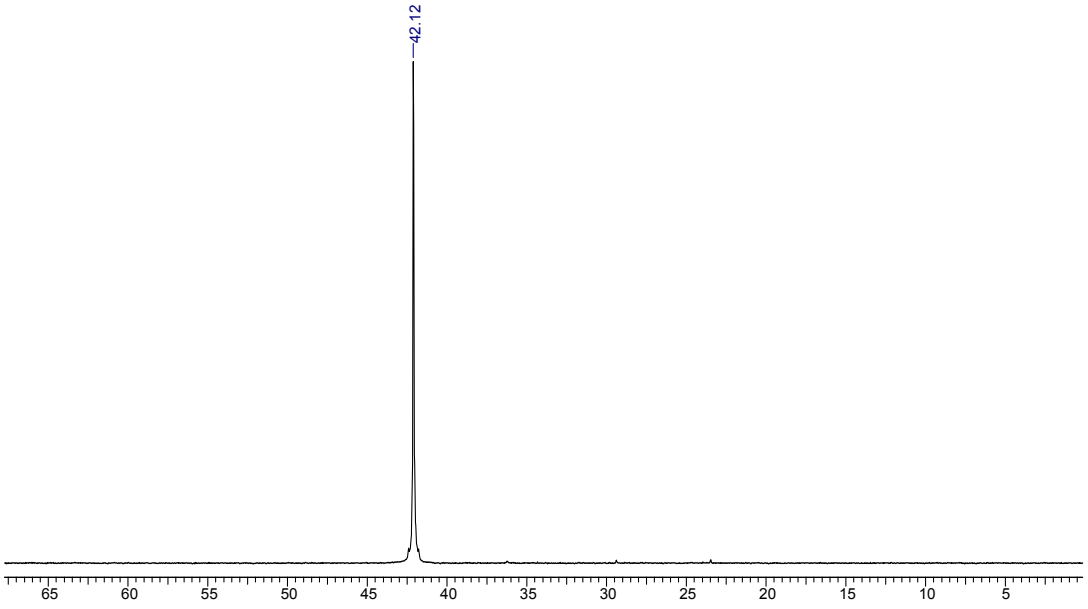
Pd(ppy)(PPh_3)(OTs)



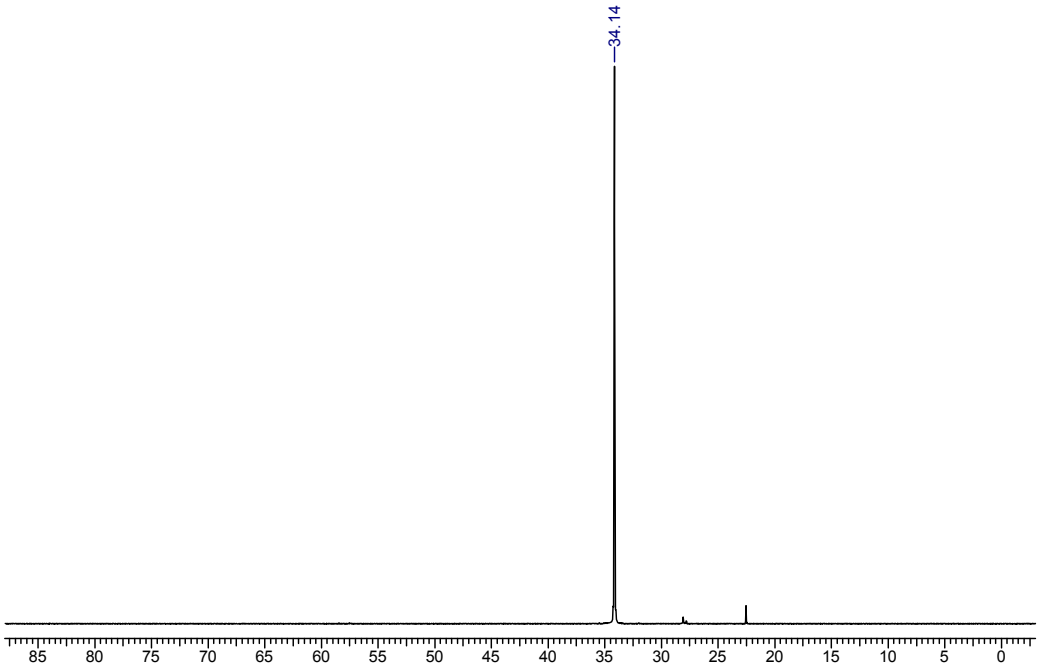
Pd(pquin)(PPh_3)(OTs)



Pd(mquin)(PPh_3)(OTs)



Pd(bpoxime)(PPh_3)(Cl)



Pd(Bnpy)(PPh_3)(Cl)

Bond Length and Bond Angles of the Complexes

Bond length [Å] for Pd(ppy)(PPh_3)(OTs)

Pd-C(26)	1.985(3)
Pd-N	2.085(2)
Pd-O(3)	2.1351(19)
Pd-P	2.2758(7)
P-C(14)	1.829(3)
P-C(8)	1.830(3)
P-C(20)	1.830(3)
S-O(1)	1.437(3)
S-O(2)	1.439(3)
S-O(3)	1.479(2)
S-C(1)	1.764(3)
N-C(36)	1.339(4)
N-C(32)	1.346(4)
C(1)-C(2)	1.369(4)
C(1)-C(6)	1.374(5)
C(2)-C(3)	1.371(5)
C(2)-H(2)	0.93
C(3)-C(4)	1.375(5)
C(3)-H(3)	0.93
C(4)-C(5)	1.381(5)
C(4)-C(7)	1.503(5)
C(5)-C(6)	1.377(5)
C(5)-H(5)	0.93
C(6)-H(6)	0.93
C(7)-H(7A)	0.96
C(7)-H(7B)	0.96
C(7)-H(7C)	0.96
C(8)-C(13)	1.382(4)
C(8)-C(9)	1.385(4)
C(9)-C(10)	1.381(4)
C(9)-H(9)	0.93
C(10)-C(11)	1.361(5)
C(10)-H(10)	0.93
C(11)-C(12)	1.358(5)
C(11)-H(11)	0.93
C(12)-C(13)	1.393(5)
C(12)-H(12)	0.93
C(13)-H(13)	0.93
C(14)-C(15)	1.381(4)
C(14)-C(19)	1.385(4)
C(15)-C(16)	1.389(5)
C(15)-H(15)	0.93
C(16)-C(17)	1.377(5)
C(16)-H(16)	0.93
C(17)-C(18)	1.367(5)
C(17)-H(17)	0.93
C(18)-C(19)	1.384(4)
C(18)-H(18)	0.93
C(19)-H(19)	0.93
C(20)-C(21)	1.378(4)
C(20)-C(25)	1.385(4)

C(21)-C(22)	1.381(4)
C(21)-H(21)	0.93
C(22)-C(23)	1.362(5)
C(22)-H(22)	0.93
C(23)-C(24)	1.367(5)
C(23)-H(23)	0.93
C(24)-C(25)	1.383(5)
C(24)-H(24)	0.93
C(25)-H(25)	0.93
C(26)-C(27)	1.387(4)
C(26)-C(31)	1.412(4)
C(27)-C(28)	1.386(5)
C(27)-H(27)	0.93
C(28)-C(29)	1.365(5)
C(28)-H(28)	0.93
C(29)-C(30)	1.360(5)
C(29)-H(29)	0.93
C(30)-C(31)	1.391(4)
C(30)-H(30)	0.93
C(31)-C(32)	1.462(4)
C(32)-C(33)	1.383(4)
C(33)-C(34)	1.361(5)
C(33)-H(33)	0.93
C(34)-C(35)	1.360(5)
C(34)-H(34)	0.93
C(35)-C(36)	1.373(5)
C(35)-H(35)	0.93
C(36)-H(36)	0.93

Bond Angles [deg] for Pd(ppy)(PPh_3)(OTs)

C(26)-Pd-N	81.25(11)
C(26)-Pd-O	(3)169.07(10)
N-Pd-O(3)	89.10(8)
C(26)-Pd-P	95.50(9)
N-Pd-P	169.74(7)
O(3)-Pd-P	94.87(6)
C(14)-P-C(8)	102.24(13)
C(14)-P-C(20)	107.67(13)
C(8)-P-C(20)	99.18(13)
C(14)-P-Pd	116.79(9)
C(8)-P-Pd	116.06(10)
C(20)-P-Pd	112.95(9)
O(1)-S-O(2)	115.36(18)
O(1)-S-O(3)	111.84(13)
O(2)-S-O(3)	111.43(15)
O(1)-S-C(1)	107.88(16)
O(2)-S-C(1)	107.51(14)
O(3)-S-C(1)	101.76(13)
C(36)-N-C(32)	119.5(3)
C(36)-N-Pd	125.8(2)
C(32)-N-Pd	114.42(19)
S-O(3)-Pd	122.59(12)
C(2)-C(1)-C(6)	119.5(3)
C(2)-C(1)-S	121.1(3)
C(6)-C(1)-S	119.3(2)

C(1)-C(2)-C(3)	120.4(3)
C(1)-C(2)-H(2)	119.8
C(3)-C(2)-H(2)	119.8
C(2)-C(3)-C(4)	121.2(3)
C(2)-C(3)-H(3)	119.4
C(4)-C(3)-H(3)	119.4
C(3)-C(4)-C(5)	118.0(3)
C(3)-C(4)-C(7)	121.2(4)
C(5)-C(4)-C(7)	120.9(4)
C(6)-C(5)-C(4)	121.1(4)
C(6)-C(5)-H(5)	119.4
C(4)-C(5)-H(5)	119.4
C(1)-C(6)-C(5)	119.8(3)
C(1)-C(6)-H(6)	120.1
C(5)-C(6)-H(6)	120.1
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(13)-C(8)-C(9)	118.0(3)
C(13)-C(8)-P	118.5(2)
C(9)-C(8)-P	123.0(2)
C(10)-C(9)-C(8)	121.0(3)
C(10)-C(9)-H(9)	119.5
C(8)-C(9)-H(9)	119.5
C(11)-C(10)-C(9)	120.5(3)
C(11)-C(10)-H(10)	119.8
C(9)-C(10)-H(10)	119.8
C(12)-C(11)-C(10)	119.4(3)
C(12)-C(11)-H(11)	120.3
C(10)-C(11)-H(11)	120.3
C(11)-C(12)-C(13)	121.0(3)
C(11)-C(12)-H(12)	119.5
C(13)-C(12)-H(12)	119.5
C(8)-C(13)-C(12)	120.0(3)
C(8)-C(13)-H(13)	120
C(12)-C(13)-H(13)	120
C(15)-C(14)-C(19)	119.8(3)
C(15)-C(14)-P	124.0(2)
C(19)-C(14)-P	116.2(2)
C(14)-C(15)-C(16)	119.8(3)
C(14)-C(15)-H(15)	120.1
C(16)-C(15)-H(15)	120.1
C(17)-C(16)-C(15)	120.1(4)
C(17)-C(16)-H(16)	120
C(15)-C(16)-H(16)	120
C(18)-C(17)-C(16)	120.0(3)
C(18)-C(17)-H(17)	120
C(16)-C(17)-H(17)	120
C(17)-C(18)-C(19)	120.6(3)
C(17)-C(18)-H(18)	119.7
C(19)-C(18)-H(18)	119.7
C(18)-C(19)-C(14)	119.7(3)
C(18)-C(19)-H(19)	120.1

C(14)-C(19)-H(19)	120.1
C(21)-C(20)-C(25)	118.2(3)
C(21)-C(20)-P	120.5(2)
C(25)-C(20)-P	121.1(2)
C(20)-C(21)-C(22)	120.9(3)
C(20)-C(21)-H(21)	119.5
C(22)-C(21)-H(21)	119.5
C(23)-C(22)-C(21)	120.1(3)
C(23)-C(22)-H(22)	119.9
C(21)-C(22)-H(22)	119.9
C(22)-C(23)-C(24)	120.1(3)
C(22)-C(23)-H(23)	120
C(24)-C(23)-H(23)	120
C(23)-C(24)-C(25)	120.1(3)
C(23)-C(24)-H(24)	120
C(25)-C(24)-H(24)	120
C(24)-C(25)-C(20)	120.6(3)
C(24)-C(25)-H(25)	119.7
C(20)-C(25)-H(25)	119.7
C(27)-C(26)-C(31)	116.8(3)
C(27)-C(26)-Pd	129.9(2)
C(31)-C(26)-Pd	113.1(2)
C(28)-C(27)-C(26)	121.0(3)
C(28)-C(27)-H(27)	119.5
C(26)-C(27)-H(27)	119.5
C(29)-C(28)-C(27)	121.2(3)
C(29)-C(28)-H(28)	119.4
C(27)-C(28)-H(28)	119.4

C(30)-C(29)-C(28)	119.4(3)
C(30)-C(29)-H(29)	120.3
C(28)-C(29)-H(29)	120.3
C(29)-C(30)-C(31)	120.7(3)
C(29)-C(30)-H(30)	119.6
C(31)-C(30)-H(30)	119.6
C(30)-C(31)-C(26)	120.8(3)
C(30)-C(31)-C(32)	122.0(3)
C(26)-C(31)-C(32)	117.2(2)
N-C(32)-C(33)	119.9(3)
N-C(32)-C(31)	113.7(2)
C(33)-C(32)-C(31)	126.4(3)
C(34)-C(33)-C(32)	120.3(3)
C(34)-C(33)-H(33)	119.8
C(32)-C(33)-H(33)	119.8
C(35)-C(34)-C(33)	119.2(3)
C(35)-C(34)-H(34)	120.4
C(33)-C(34)-H(34)	120.4
C(34)-C(35)-C(36)	119.3(3)
C(34)-C(35)-H(35)	120.4
C(36)-C(35)-H(35)	120.4
N-C(36)-C(35)	121.7(3)
N-C(36)-H(36)	119.2
C(35)-C(36)-H(36)	119.2

Pd bond length[Å] for Pd(pquin)(PPh_3)(OTs)

Pd-C(26)	1.987(3)
Pd-N	2.143(2)
Pd-O(3)	2.167(2)
Pd-P	2.2749(7)
P-C(14)	1.823(3)
P-C(8)	1.831(3)
P-C(20)	1.835(3)
S-O(1)	1.438(2)
S-O(2)	1.440(2)
S-O(3)	1.483(2)
S-C(1)	1.770(3)
N-C(32)	1.327(4)
N-C(36)	1.383(4)
C(1)-C(6)	1.383(4)
C(1)-C(2)	1.387(4)
C(2)-C(3)	1.370(5)
C(2)-H(2)	0.93
C(3)-C(4)	1.384(5)
C(3)-H(3)	0.93
C(4)-C(5)	1.375(5)
C(4)-C(7)	1.512(5)
C(5)-C(6)	1.379(5)
C(5)-H(5)	0.93
C(6)-H(6)	0.93
C(7)-H(7A)	0.96
C(7)-H(7B)	0.96
C(7)-H(7C)	0.96
C(8)-C(9)	1.380(4)
C(8)-C(13)	1.390(5)
C(9)-C(10)	1.383(5)
C(9)-H(9)	0.93
C(10)-C(11)	1.371(5)
C(10)-H(10)	0.93
C(11)-C(12)	1.375(5)
C(11)-H(11)	0.93
C(12)-C(13)	1.379(5)
C(12)-H(12)	0.93
C(13)-H(13)	0.93
C(14)-C(19)	1.383(4)
C(14)-C(15)	1.386(4)
C(15)-C(16)	1.374(5)
C(15)-H(15)	0.93
C(16)-C(17)	1.377(5)
C(16)-H(16)	0.93
C(17)-C(18)	1.378(5)
C(17)-H(17)	0.93
C(18)-C(19)	1.379(5)
C(18)-H(18)	0.93
C(19)-H(19)	0.93
C(20)-C(21)	1.382(4)
C(20)-C(25)	1.391(4)
C(21)-C(22)	1.382(5)
C(21)-H(21)	0.93
C(22)-C(23)	1.373(5)

C(22)-H(22)	0.93
C(23)-C(24)	1.381(5)
C(23)-H(23)	0.93
C(24)-C(25)	1.375(5)
C(24)-H(24)	0.93
C(25)-H(25)	0.93
C(26)-C(27)	1.388(4)
C(26)-C(31)	1.416(4)
C(27)-C(28)	1.386(4)
C(27)-H(27)	0.93
C(28)-C(29)	1.374(5)
C(28)-H(28)	0.93
C(29)-C(30)	1.370(5)
C(29)-H(29)	0.93
C(30)-C(31)	1.392(4)
C(30)-H(30)	0.93
C(31)-C(32)	1.471(4)
C(32)-C(33)	1.413(4)
C(33)-C(34)	1.343(5)
C(33)-H(33)	0.93
C(34)-C(35)	1.401(5)
C(34)-H(34)	0.93
C(35)-C(36)	1.412(4)
C(35)-C(40)	1.424(5)
C(36)-C(37)	1.407(5)
C(37)-C(38)	1.370(5)
C(37)-H(37)	0.93
C(38)-C(39)	1.399(6)
C(38)-H(38)	0.93
C(39)-C(40)	1.335(6)
C(39)-H(39)	0.93
C(40)-H(40)	0.93
C(41)-Cl(1)	1.623(7)
C(41)-Cl(2)	1.842(9)
C(41)-H(411)	0.97
C(41)-H(412)	0.97

Pd bond angles [deg] for Pd(pquin)(PPh_3)(OTs)

C(26)-Pd-N	80.95(11)
C(26)-Pd-O(3)	166.42(10)
N-Pd-O(3)	97.94(9)
C(26)-Pd-P	94.95(9)
N-Pd-P	168.94(7)
O(3)-Pd-P	88.44(6)
C(14)-P-C(8)	104.27(13)
C(14)-P-C(20)	106.65(13)
C(8)-P-C(20)	100.35(13)
C(14)-P-Pd	116.02(9)
C(8)-P-Pd	115.11(10)
C(20)-P-Pd	112.85(9)
O(1)-S-O(2)	114.92(15)
O(1)-S-O(3)	111.72(15)
O(2)-S-O(3)	112.18(14)
O(1)-S-C(1)	107.06(14)

O(2)-S-C(1)	107.02(15)
O(3)-S-C(1)	102.98(12)
S-O(3)-Pd	117.51(11)
C(32)-N-C(36)	118.9(2)
C(32)-N-Pd	112.46(19)
C(36)-N-Pd	128.6(2)
C(6)-C(1)-C(2)	119.0(3)
C(6)-C(1)-S	120.6(2)
C(2)-C(1)-S	120.5(2)
C(3)-C(2)-C(1)	120.1(3)
C(3)-C(2)-H(2)	120
C(1)-C(2)-H(2)	120
C(2)-C(3)-C(4)	121.6(3)
C(2)-C(3)-H(3)	119.2
C(4)-C(3)-H(3)	119.2
C(5)-C(4)-C(3)	117.8(3)
C(5)-C(4)-C(7)	120.9(3)
C(3)-C(4)-C(7)	121.3(3)
C(4)-C(5)-C(6)	121.6(3)
C(4)-C(5)-H(5)	119.2
C(6)-C(5)-H(5)	119.2
C(5)-C(6)-C(1)	120.0(3)
C(5)-C(6)-H(6)	120
C(1)-C(6)-H(6)	120
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(9)-C(8)-C(13)	119.1(3)
C(9)-C(8)-P	122.9(2)
C(13)-C(8)-P	117.9(2)
C(8)-C(9)-C(10)	120.2(3)
C(8)-C(9)-H(9)	119.9
C(10)-C(9)-H(9)	119.9
C(11)-C(10)-C(9)	120.3(3)
C(11)-C(10)-H(10)	119.8
C(9)-C(10)-H(10)	119.8
C(10)-C(11)-C(12)	119.9(3)
C(10)-C(11)-H(11)	120.1
C(12)-C(11)-H(11)	120.1
C(11)-C(12)-C(13)	120.2(4)
C(11)-C(12)-H(12)	119.9
C(13)-C(12)-H(12)	119.9
C(12)-C(13)-C(8)	120.2(3)
C(12)-C(13)-H(13)	119.9
C(8)-C(13)-H(13)	119.9
C(19)-C(14)-C(15)	118.5(3)
C(19)-C(14)-P	117.8(2)
C(15)-C(14)-P	123.7(2)
C(16)-C(15)-C(14)	120.7(3)
C(16)-C(15)-H(15)	119.7
C(14)-C(15)-H(15)	119.7
C(15)-C(16)-C(17)	120.5(3)
C(15)-C(16)-H(16)	119.8

C(17)-C(16)-H(16)	119.8
C(16)-C(17)-C(18)	119.4(3)
C(16)-C(17)-H(17)	120.3
C(18)-C(17)-H(17)	120.3
C(17)-C(18)-C(19)	120.2(3)
C(17)-C(18)-H(18)	119.9
C(19)-C(18)-H(18)	119.9
C(18)-C(19)-C(14)	120.7(3)
C(18)-C(19)-H(19)	119.6
C(14)-C(19)-H(19)	119.6
C(21)-C(20)-C(25)	118.3(3)
C(21)-C(20)-P	120.5(2)
C(25)-C(20)-P	121.1(2)
C(22)-C(21)-C(20)	120.7(3)
C(22)-C(21)-H(21)	119.7
C(20)-C(21)-H(21)	119.7
C(23)-C(22)-C(21)	120.3(3)
C(23)-C(22)-H(22)	119.8
C(21)-C(22)-H(22)	119.8
C(22)-C(23)-C(24)	119.7(3)
C(22)-C(23)-H(23)	120.1
C(24)-C(23)-H(23)	120.1
C(25)-C(24)-C(23)	119.9(3)
C(25)-C(24)-H(24)	120
C(23)-C(24)-H(24)	120
C(24)-C(25)-C(20)	121.0(3)
C(24)-C(25)-H(25)	119.5
C(20)-C(25)-H(25)	119.5

C(27)-C(26)-C(31)	117.2(3)
C(27)-C(26)-Pd	129.7(2)
C(31)-C(26)-Pd	112.4(2)
C(28)-C(27)-C(26)	121.1(3)
C(28)-C(27)-H(27)	119.4
C(26)-C(27)-H(27)	119.4
C(29)-C(28)-C(27)	120.9(3)
C(29)-C(28)-H(28)	119.5
C(27)-C(28)-H(28)	119.5
C(30)-C(29)-C(28)	119.6(3)
C(30)-C(29)-H(29)	120.2
C(28)-C(29)-H(29)	120.2
C(29)-C(30)-C(31)	120.4(3)
C(29)-C(30)-H(30)	119.8
C(31)-C(30)-H(30)	119.8
C(30)-C(31)-C(26)	120.8(3)
C(30)-C(31)-C(32)	122.0(3)
C(26)-C(31)-C(32)	117.2(3)
N-C(32)-C(33)	122.1(3)
N-C(32)-C(31)	115.1(2)
C(33)-C(32)-C(31)	122.7(3)
C(34)-C(33)-C(32)	119.9(3)
C(34)-C(33)-H(33)	120.1
C(32)-C(33)-H(33)	120.1
C(33)-C(34)-C(35)	119.8(3)
C(33)-C(34)-H(34)	120.1
C(35)-C(34)-H(34)	120.1
C(34)-C(35)-C(36)	118.7(3)

C(34)-C(35)-C(40)	122.2(3)
C(36)-C(35)-C(40)	119.1(4)
N-C(36)-C(37)	120.6(3)
N-C(36)-C(35)	120.6(3)
C(37)-C(36)-C(35)	118.8(3)
C(38)-C(37)-C(36)	119.9(4)
C(38)-C(37)-H(37)	120.1
C(36)-C(37)-H(37)	120.1
C(37)-C(38)-C(39)	121.2(4)
C(37)-C(38)-H(38)	119.4
C(39)-C(38)-H(38)	119.4
C(40)-C(39)-C(38)	120.3(4)
C(40)-C(39)-H(39)	119.9
C(38)-C(39)-H(39)	119.9
C(39)-C(40)-C(35)	120.8(4)
C(39)-C(40)-H(40)	119.6
C(35)-C(40)-H(40)	119.6
Cl(1)-C(41)-Cl(2)	111.7(4)
Cl(1)-C(41)-H(411)	109.3
Cl(2)-C(41)-H(411)	109.3
Cl(1)-C(41)-H(412)	109.3
Cl(2)-C(41)-H(412)	109.3
H(411)-C(41)-H(412)	107.9

Pd bond lengths [Å] of Pd(mquin)(PPh_3)(OTs)

Pd(1)-C(26)	2.025(2)
Pd(1)-N	2.0836(18)
Pd(1)-O(3)	2.1702(15)
Pd(1)-P	2.2403(6)
P-C(14)	1.819(2)
P-C(20)	1.821(2)
P-C(8)	1.823(2)
S-O(2)	1.440(2)
S-O(1)	1.4442(19)
S-O(3)	1.4805(16)
S-C(1)	1.769(2)
C(15)-C(14)	1.385(3)
C(15)-C(16)	1.386(4)
C(15)-H(15)	0.93
C(23)-C(22)	1.360(4)
C(23)-C(24)	1.381(4)
C(23)-H(23)	0.93
N-C(35)	1.320(3)
N-C(32)	1.377(3)
C(14)-C(19)	1.395(3)
C(2)-C(1)	1.377(3)
C(2)-C(3)	1.387(4)
C(2)-H(2)	0.93
C(20)-C(21)	1.383(3)
C(20)-C(25)	1.383(3)
C(26)-C(27)	1.500(3)

C(26)-H(26A)	0.97
C(26)-H(26B)	0.97
C(19)-C(18)	1.378(3)
C(19)-H(19)	0.93
C(8)-C(9)	1.383(3)
C(8)-C(13)	1.387(3)
C(27)-C(28)	1.372(3)
C(27)-C(32)	1.404(3)
C(32)-C(31)	1.415(3)
C(1)-C(6)	1.386(3)
C(18)-C(17)	1.373(4)
C(18)-H(18)	0.93
C(31)-C(33)	1.403(4)
C(31)-C(30)	1.419(4)
C(28)-C(29)	1.405(4)
C(28)-H(28)	0.93
C(5)-C(6)	1.375(4)
C(5)-C(4)	1.381(4)
C(5)-H(5)	0.93
C(13)-C(12)	1.381(4)
C(13)-H(13)	0.93
C(4)-C(3)	1.380(4)
C(4)-C(7)	1.504(4)
C(17)-C(16)	1.371(4)
C(17)-H(17)	0.93
C(35)-C(34)	1.402(4)
C(35)-H(35)	0.93
C(3)-H(3)	0.93

C(6)-H(6)	0.93
C(30)-C(29)	1.339(4)
C(30)-H(30)	0.93
C(9)-C(10)	1.384(4)
C(9)-H(9)	0.93
C(33)-C(34)	1.360(4)
C(33)-H(33)	0.93
C(29)-H(29)	0.93
C(11)-C(10)	1.362(4)
C(11)-C(12)	1.373(4)
C(11)-H(11)	0.93
C(34)-H(34)	0.93
C(10)-H(10)	0.93
C(12)-H(12)	0.93
C(7)-H(7A)	0.96
C(7)-H(7B)	0.96
C(7)-H(7C)	0.96
C(16)-H(16)	0.93
C(25)-C(24)	1.377(4)
C(25)-H(25)	0.93
C(21)-C(22)	1.388(3)
C(21)-H(21)	0.93
C(22)-H(22)	0.93
C(24)-H(24)	0.93

Pd bond angles [deg] for Pd(mquin)(PPh_3)(OTs)

C(26)-Pd(1)-N	83.53(8)
C(26)-Pd(1)-O(3)	171.64(8)
N-Pd(1)-O(3)	90.16(7)
C(26)-Pd(1)-P	87.16(7)
N-Pd(1)-P	169.30(5)
O(3)-Pd(1)-P	99.59(5)
C(14)-P-C(20)	107.27(10)
C(14)-P-C(8)	105.86(10)
C(20)-P-C(8)	99.71(10)
C(14)-P-Pd(1)	111.23(8)
C(20)-P-Pd(1)	114.75(8)
C(8)-P-Pd(1)	116.92(8)
O(2)-S-O(1)	115.22(13)
O(2)-S-O(3)	110.91(12)
O(1)-S-O(3)	111.75(10)
O(2)-S-C(1)	107.83(11)
O(1)-S-C(1)	106.81(12)
O(3)-S-C(1)	103.48(10)
C(14)-C(15)-C(16)	119.9(2)
C(14)-C(15)-H(15)	120.1
C(16)-C(15)-H(15)	120.1
C(22)-C(23)-C(24)	120.1(2)
C(22)-C(23)-H(23)	119.9
C(24)-C(23)-H(23)	119.9
S-O(3)-Pd(1)	119.84(9)
C(35)-N-C(32)	119.0(2)
C(35)-N-Pd(1)	128.41(18)
C(32)-N-Pd(1)	112.49(14)
C(15)-C(14)-C(19)	119.0(2)
C(15)-C(14)-P	123.93(18)
C(19)-C(14)-P	116.68(16)
C(1)-C(2)-C(3)	119.7(2)
C(1)-C(2)-H(2)	120.2
C(3)-C(2)-H(2)	120.2
C(21)-C(20)-C(25)	118.4(2)
C(21)-C(20)-P	120.38(17)
C(25)-C(20)-P	120.88(18)
C(27)-C(26)-Pd(1)	108.82(15)
C(27)-C(26)-H(26A)	109.9
Pd(1)-C(26)-H(26A)	109.9
C(27)-C(26)-H(26B)	109.9
Pd(1)-C(26)-H(26B)	109.9
H(26A)-C(26)-H(26B)	108.3
C(18)-C(19)-C(14)	120.2(2)
C(18)-C(19)-H(19)	119.9
C(14)-C(19)-H(19)	119.9
C(9)-C(8)-C(13)	118.7(2)
C(9)-C(8)-P	123.63(19)
C(13)-C(8)-P	117.39(18)
C(28)-C(27)-C(32)	118.0(2)
C(28)-C(27)-C(26)	123.6(2)
C(32)-C(27)-C(26)	118.4(2)
N-C(32)-C(27)	116.7(2)
N-C(32)-C(31)	121.8(2)

C(27)-C(32)-C(31)	121.5(2)
C(2)-C(1)-C(6)	119.5(2)
C(2)-C(1)-S	120.82(19)
C(6)-C(1)-S	119.63(19)
C(17)-C(18)-C(19)	120.3(2)
C(17)-C(18)-H(18)	119.8
C(19)-C(18)-H(18)	119.8
C(33)-C(31)-C(32)	117.1(3)
C(33)-C(31)-C(30)	125.5(3)
C(32)-C(31)-C(30)	117.4(3)
C(27)-C(28)-C(29)	121.2(3)
C(27)-C(28)-H(28)	119.4
C(29)-C(28)-H(28)	119.4
C(6)-C(5)-C(4)	121.8(2)
C(6)-C(5)-H(5)	119.1
C(4)-C(5)-H(5)	119.1
C(12)-C(13)-C(8)	120.3(3)
C(12)-C(13)-H(13)	119.8
C(8)-C(13)-H(13)	119.8
C(3)-C(4)-C(5)	117.6(2)
C(3)-C(4)-C(7)	121.1(3)
C(5)-C(4)-C(7)	121.2(3)
C(16)-C(17)-C(18)	120.0(2)
C(16)-C(17)-H(17)	120
C(18)-C(17)-H(17)	120
N-C(35)-C(34)	122.0(3)
N-C(35)-H(35)	119
C(34)-C(35)-H(35)	119

C(4)-C(3)-C(2)	121.6(3)
C(4)-C(3)-H(3)	119.2
C(2)-C(3)-H(3)	119.2
C(5)-C(6)-C(1)	119.8(2)
C(5)-C(6)-H(6)	120.1
C(1)-C(6)-H(6)	120.1
C(29)-C(30)-C(31)	120.8(3)
C(29)-C(30)-H(30)	119.6
C(31)-C(30)-H(30)	119.6
C(8)-C(9)-C(10)	120.4(3)
C(8)-C(9)-H(9)	119.8
C(10)-C(9)-H(9)	119.8
C(34)-C(33)-C(31)	120.2(3)
C(34)-C(33)-H(33)	119.9
C(31)-C(33)-H(33)	119.9
C(30)-C(29)-C(28)	120.9(3)
C(30)-C(29)-H(29)	119.5
C(28)-C(29)-H(29)	119.5
C(10)-C(11)-C(12)	120.0(3)
C(10)-C(11)-H(11)	120
C(12)-C(11)-H(11)	120
C(33)-C(34)-C(35)	119.9(3)
C(33)-C(34)-H(34)	120.1
C(35)-C(34)-H(34)	120.1
C(11)-C(10)-C(9)	120.4(3)
C(11)-C(10)-H(10)	119.8
C(9)-C(10)-H(10)	119.8
C(11)-C(12)-C(13)	120.3(3)

C(11)-C(12)-H(12)	119.9
C(13)-C(12)-H(12)	119.9
C(4)-C(7)-H(7A)	109.5
C(4)-C(7)-H(7B)	109.5
H(7A)-C(7)-H(7B)	109.5
C(4)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(17)-C(16)-C(15)	120.6(2)
C(17)-C(16)-H(16)	119.7
C(15)-C(16)-H(16)	119.7
C(24)-C(25)-C(20)	120.9(3)
C(24)-C(25)-H(25)	119.6
C(20)-C(25)-H(25)	119.6
C(20)-C(21)-C(22)	120.7(2)
C(20)-C(21)-H(21)	119.7
C(22)-C(21)-H(21)	119.7
C(23)-C(22)-C(21)	120.1(2)
C(23)-C(22)-H(22)	120
C(21)-C(22)-H(22)	120
C(25)-C(24)-C(23)	119.9(3)
C(25)-C(24)-H(24)	120.1
C(23)-C(24)-H(24)	120.1

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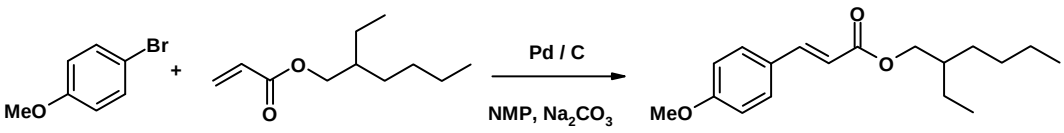
Chapter 3

Kinetic Modeling of Arylation of n-Butylacrylate with 3-Bromobenzophenone using NC Palladacycle Catalyst

3.1 Introduction

The reactions involving the use of acrylate as an olefin source are very important, as the products are industrially useful cinnamates. The cinnamates obtained are used as UV absorbers, antioxidants, and as intermediates in perfumery, pharmaceutical, and dye industry. For example octyl *p*-methoxy-cinnamate[1] is a sunscreen agent obtained by the reaction as shown in Scheme 3.1.



Scheme 3.1. Heck Reaction of *p*-bromoanisole and 2-ethylhexylacrylate

The coupling of olefin with aryl halide can be accomplished by a plethora of palladium catalyst precursors under various reaction conditions as discussed in Chapter 1. Among these catalytic processes, palladacycles including CP, CN, CS, PCP, SCS, NCN, are one of the most investigated classes of catalyst precursors, in particular due to their facile synthesis, thermal stability, and possibility to modulate their steric and electronic properties. The mechanism of this reaction using palladacycle catalysts is often discussed, two mechanisms were reported for the Heck reaction one following Pd(II)/ Pd(IV) mechanism and the other with Pd(0)/ Pd(II) mechanism.[2] It is now accepted (based on inhibition tests using Hg, Dibenzo[a,e]cyclooctatetraene, PVPy)[6b,15] that in most of the cases, the catalytically active species involved in these reactions are based on Pd (0) and that the reaction proceeds through a Pd (0)/ Pd (II) catalytic cycle, whatever the nature of the catalyst precursor.[3] Significant progress has been made in the development of catalytic systems for Heck catalysis over the last 30 years; it is surprising that few detailed kinetic studies (see Chapter 1) have been carried out for these important reactions. As evident from the literature review in Chapter 1, the majority of the kinetic studies (Table 1.5) have been done using the dimeric palladacycles as catalysts. In most cases, the kinetics was investigated at only one temperature. The substrates such as Iodobenzene & styrene, *p*-bromobenzaldehyde & *n*-butylacrylate, Iodoanisole & Styrene and *p*-bromoacetophenoe & *n*-butylacrylate have been used as the coupling partners for the kinetic studies using dimeric palladacycles. There are no reports on the kinetics using

the monomeric palladacycle as the catalyst precursor. The reactions carried with dimeric palladacycles showed that in the solution it turns to monomeric complexes and also exhibited the induction periods, indicating the formation of catalytically active species during the reactions. It is therefore necessary to understand the role of the monomeric palladacycles in the Heck reactions. In homogeneous catalytic systems, the reactions are extremely sensitive to the temperature and hence detailed kinetic studies at different temperatures are necessary to understand the rate behavior as well as the mechanism of the reaction.

In this chapter, experimental results on kinetics of arylation of *n*-butylacrylate (BA = butylacrylate) with 3-bromo-benzophenone using a monomeric palladacycle complex Pd(ppy)(PPh_3)(OTs) catalyst have been presented. The effect of concentration of the substrates, base, and catalyst was studied at three different temperatures (413 – 433 K). Based on these data, rate equations have been proposed and possible reaction pathway discussed. The results have also been discussed in the light of mechanistic work carried out for the Heck reaction of BMN and *n*-BA.

3.2 Experimental Section

3.2.1 Chemicals

3-bromo-benzophenone (BBP) and 4-bromo-isobutylbenzene were synthesized according to the procedures described in the Chapter 2. 2-bromo-6-methoxynaphthalene was procured from SD fine chemicals, 4-bromo-anisole, 9-bromophenanthrene, 4-bromo-benzaldehyde, 4-bromo-nitrobenzene, 4-bromo-benzonitrile were procured from spectrochem chemicals. Bases KOAc, NaOAc, Na_2CO_3, K_2CO_3 and the solvents NMP, DMF, DMAc were procured from SRL. 2-phenylpyridine, $Pd(OAc)_2$, Triphenyl phosphine, *p*-toluene-sulphonic acid were procured from Sigma Aldrich.

3.2.2 Preparation of the Complex Pd(ppy)(PPh_3)(OTs) : This complex was prepared as described in the Chapter 2, Section 2.2.4.5.1.

3.2.3 Preparation of the Substrate 3-bromobenzophenone: The substrate was prepared according to the procedure described in Chapter 2, Section 2.2.4.1.

3.2.4 Reaction Methodology – Heck Coupling

Heck coupling reactions were carried out in a 50 ml two necked stirred glass reactor equipped with a condenser and a magnetic stirrer. The other neck was sealed with a septum as a provision for intermediate sampling. In a typical reaction, the requisite amounts of reactants (aryl halide, *n*-butylacrylate, solvent, base, catalyst) were charged in a glass reactor. The glass apparatus containing the above chemicals along with the magnetic stirrer was placed on a preheated oil bath to the desired temperature; the temperature of the oil bath was maintained with electronic controlling devices. The contents were stirred using magnetic needle and, intermediate samples were withdrawn at regular intervals of time with the help of syringe by ceasing the stirring temporarily. The reactions were carried out for a fixed time duration.

For kinetic studies, slightly different approach was followed in which, the requisite amounts of reagents were charged to the reactor except the catalyst and placed on the preheated oil bath. After the contents in the reactor attained the desired temperature (usually 10-15 min), the stock solution of the catalyst was injected via a syringe and the reaction started by the switching the stirrer on. All of the experiments were performed under nitrogen atmosphere.

(Note: The glass reactor when placed in the preheated oil at the reaction temperature, the contents of glass reactor usually take some time to attain the reaction temperature. The duration of the time depends on the temperature. The time to equilibrate was found to be 12-15 minutes for 413 K, 10 minutes for 423 K and 8 minutes for 433 K, after which the catalyst was added. These times were calculated by carrying independent experiments by placing a thermocouple inside the glass reactor and calculating the time required to attain the required temperature. These experiments were performed to ensure that the temperature is constant during the kinetic studies.)

3.2.5 Analytical Methods

The liquid samples of the arylation reactions were analyzed by gas chromatography using Agilent 6890 series GC instrument controlled by the HP Chemstation software and equipped with an auto sampler unit, by using an HP-1 capillary column of length 30 m, 320μm diameter, 0.25μm stationary phase film thickness (methyl siloxane as stationary phase, helium gas as mobile phase) and a

flame ionization detector. The quantitative analysis was carried out by constructing calibration-table in the range of concentrations studied. The % conversion, % selectivities, and TOF(h^{-1}) were calculated using the formulae given below. The standard GC conditions for the analysis of products of different reactions are given in Table 3.1. Complete mass balance of the liquid phase components was thus obtained from the quantitative GC analysis. For the identification of the products in Heck coupling reactions GC-MS was primarily used. An Agilent 6890 GC instrument attached with Agilent 5973 N Mass Selective Detector was used for the GC-MS analyses using a method similar to that in the GC analysis.

Table 3.1 Operation Parameters of the Method for GC analysis

Injector Temperature	523 K		
Flame Ionization Detection Temp	523 K		
Inlet Flow Total (He)	20 ml/min		
Split Ratio for Injector	100:1		
Oven Temperature	Rate (K/min)	Temp (K)	Hold Time (min)
		423	0.5
	35	443	6
	40	523	3
	45	543	5
Column Pressure	13.50 psi		

Based on the results of the gas chromatography, the conversion, selectivity and turnover frequency were calculated as follows,

$$\%\ Conversion = \frac{\left(Initial\ Concentration\ of\ \ Substrate - Final\ Concentration\ of\ \ Substrate\right)}{Initial\ Concentration\ of\ \ Substrate} \times 100$$

$$\%Selectivity = \frac{No.\ of\ \ moles\ of\ \ arylation\ \ product\ \ formed}{No.\ of\ \ moles\ of\ \ substrate\ converted} \times 100$$

$$TOF, h^{-1} = \frac{No.\ of\ moles\ of\ arylation\ product\ formed}{No.\ of\ moles\ of\ catalyst\ used \times time\ in\ hours}$$

The calculations of conversion etc. were done using the quantitative analysis of aryl halide (substrate) by GC, since the aryl halide is the limiting component while *n*-butylacrylate is present in excess in the reaction.

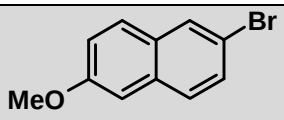
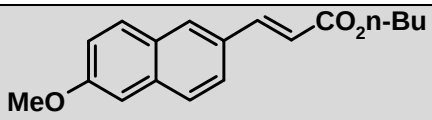
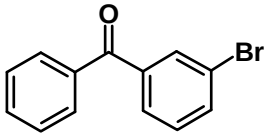
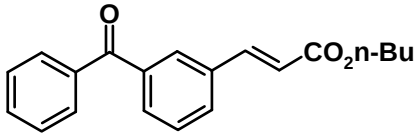
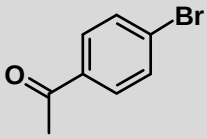
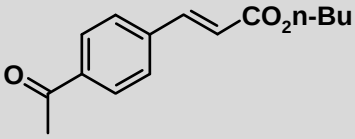
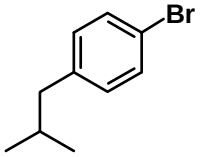
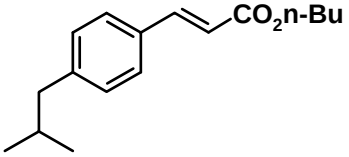
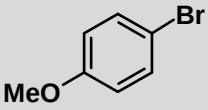
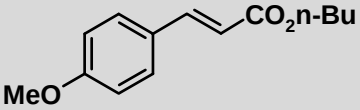
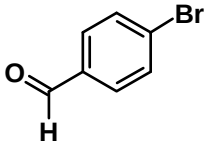
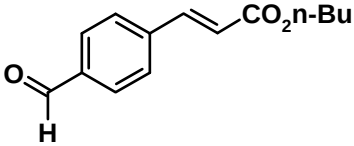
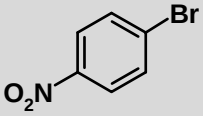
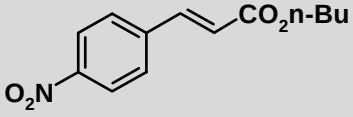
3.3 Results and Discussions

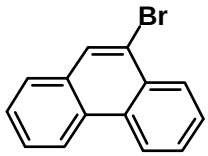
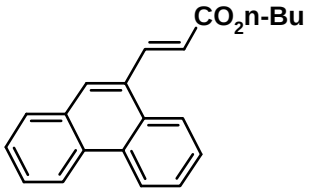
3.3.1 The Pd(ppy)(PPh_3)(OTs) Catalyzed Reaction of n-BA with Aromatic halides

In order to extend the scope of the reaction using the complex Pd(ppy)(PPh_3)(OTs), a spectrum of aryl bromides bearing electron-donating or electron-withdrawing groups were subjected to Heck catalysis using *n*-butylacrylate as the olefin partner. The arylation was performed to test the catalytic activity of the NC palladacycle and the results obtained are shown in the Table 3.2. These reactions were performed at a temperature of 423 K, NMP was used as a solvent and 0.04 mol% of the catalyst in presence of NaOAc as the base. As compared to reactions with ethylene performed in parr reactor (pressurized systems), these reactions required higher temperatures of > 403 K for attaining good activity. The Heck C-C coupling products obtained were identified by GC and GC-MS (Appendix II). The reaction was found to be stereoselective giving selectively the E-isomer, and there was no indication of any other regio- or stereoisomer. The vinylic substitution mainly occurs at the least hindered terminal position of the olefin.[4] The products obtained in these reactions are exclusively the E-isomers (the factors controlling the stereochemistry of palladium-catalyzed arylations have been discussed elsewhere[5]). Studies showed that the reaction is strongly dependent on the substituents present in the aryl group, electron withdrawing groups favouring the reaction and vice-versa. Turnover frequencies (h^{-1}) of 625, 1666 and 1225 respectively were achieved with Pd(ppy)(PPh_3)(OTs) catalyst for substrates such as 4-bromoacetophenone, 4-bromobenzaldehyde, 3-bromobenzophenone. With the deactivated aryl bromides such as 4-bromoanisole higher temperature of 433 K is required to achieve conversions of 85% (TOF 531 h^{-1}) in 4 h. Similarly 4-bromoisobutylbenzene required the temperature of 433K to obtain 100% conversion in 3 h. The results show that vinylic substitution reaction is compatible with a number of functional groups cyano, carboxy, aldehyde, nitro, and

polynuclear aromatic groups (9-phenanthryl) under reaction conditions. These groups may be ortho, meta, or para to the reacting bromo substituent. One example with 3-bromobenzophenone is shown, which afford smooth and selective transformation to the product. Quantitative coupling of 3-bromo-benzophenone and butylacrylate was achieved after only 2 h.

Table 3.2 Heck Coupling Reactions Catalyzed by Pd(ppy)(PPh_3)(OTs)

No	aryl bromide	product	Time, h	Conv. %	TOF, h^{-1}
1			3	95	791
2			2	98	1225
3			4	100	625
4*			3	100	833
5*			4	85	531
6			1.5	100	1666
7			1.5	100	1666

8			1.5	100	1666

Reaction Conditions: Aryl Halide, 3.43 mmol; BA, 5.1 mmol; NaOAc, 5.1 mmol; Pd(ppy)(PPh$_3$)(OTs), (0.04 mol%); Solvent (NMP), total volume (25 ml);T, 423 K, ******* *Reaction was carried out at 433 K*

In summary, the results presented here illustrate that NC palladacycle is an effective catalyst system for the C-C coupling reaction of *n*-butylacrylate with aromatic bromides for the synthesis of (*E*)-butylcinnamates. From the experiments performed, m-bromo-benzophenone and n-butylacrylate were selected as the coupling partners for the kinetic studies using the monomeric palladacycle Pd(ppy)(PPh$_3$)(OTs).

3.3.2 Preliminary Experiments for the Kinetic Study of Arylation of *n*-butylacrylate with 3-bromobenzophenone

Few experiments were carried out to find a suitable solvent and base for the reaction system. The results are discussed in the following sections. From the learning of results in Chapter 2 and other literature reports, polar aprotic solvents have been found to be suitable for the Heck reactions. The solvents viz DMF, NMP and DMAc were selected for the studies. The choice of the base is important while working with acrylates; bases such as NaOH, KOH decompose the *n*-butylacrylate to give n-butanol and acrylic acid and don't give the desired Heck products. Theses bases are also believed to dehalogenate the Ar-Br compounds to give Ar-H product. Hence, the popular bases viz Na_2CO_3, K_2CO_3, NaOAc, KOAc commonly employed in the Heck reactions were used for the present studies.

3.3.2.1 Effect of Solvent on the Arylation of *n*-BA with BBP

Solvents play a critical role in making the reaction homogeneous and allowing the molecular interactions to be more efficient. Since Heck reaction mainly involves ionic components, involves the exclusion of acid (Figure 3.2), so polar aprotic solvents are the candidates of choice. The effect of different polar solvents viz DMF, NMP and DMAc on the reaction rate has been studied and the results are summarized in Table

3.3. The activity of catalyst was found to be higher in NMP as compared to DMAc and DMF. The best solvent for the reaction was found to be NMP and hence further studies were carried out using this solvent. One of the roles of the polar solvents is to solubilize the base (inorganic salts) to make the reaction homogeneous, which will facilitate the faster regeneration of the active catalytic species by abstraction of HBr in the catalytic cycle.

Table 3.3 Effect of Solvent in the Reaction of BBP and *n*-BA

entry	Solvent	Time, h	Conversion	TOF, h^{-1}
1	DMF	2.5	85	850
2	DMAc	2	90	1125
3	NMP	2	98	1225

Reaction Conditions: BBP, 3.43 mmol; BA, 5.1 mmol; NaOAc, 5.1 mmol; Pd(ppy)(PPh_3)(OTs) (0.04 mol%), Solvent, total volume (25 ml); T, 423 K

3.3.2.2 Effect of Different Bases

The choice of base can have a crucial effect on the rate and product distribution of Heck reactions. The results of the reactions carried with inorganic bases are shown in the Table 3.4. Though potassium acetate gave good conversion, it was not considered for the kinetic study because of its hygroscopic nature. NaOAc was taken as the base for the kinetic studies.

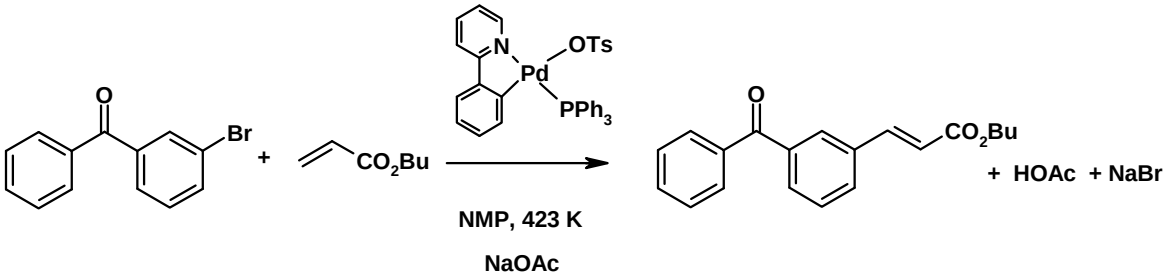
Table 3.4 Effect of Inorganic Bases on the Reaction of BBP and *n*-BA

entry	Base	Time	Conversion	TOF, h^{-1}
1	NaOAc	2	98	1225
2	KOAc	2	100	1250
3	Na_2CO_3	2	60	750
4	K_2CO_3	2	80	1000

Reaction Conditions: BBP, 3.43 mmol; BA, 5.1 mmol; Base, 5.1 mmol; Pd(ppy)(PPh_3)(OTs) (0.04 mol%); Solvent (NMP), total volume (25 ml); T, 423 K

A typical concentration-time profile for the reaction of BBP and *n*-BA (Scheme 3.2) using NMP as the solvent and NaOAc as the base is presented in the Figure 3.1, which

clearly shows a perfect mass balance between the amount of reactant BBP consumed and the product cinnamate formed.



Scheme 3.2. Heck Reaction of BBP and n-BA catalyzed by Pd(ppy)(PPh_3)(OTs)

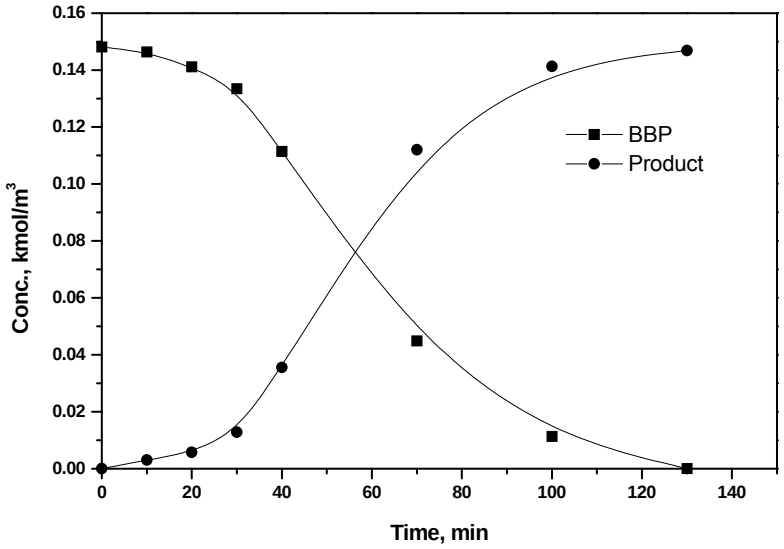


Figure 3.1. **Concentration-time profiles in Arylation of BA with BBP**

Reaction Conditions: BBP, 3.43 mmol; BA, 5.1 mmol; NaOAc, 5.1 mmol; Pd(ppy)(PPh_3)(OTs) (0.04 mol%);Solvent (NMP), total volume (25 ml); T,423 K; Time, 2.1 h

3.3.3 Kinetic Analysis

The kinetics of arylation of *n*-BA with 3-bromo-benzophenone with NC palladacycle Pd(ppy)(PPh_3)(OTs) in the presence of NaOAc as a base using NMP as a solvent was studied. For this study, several experiments were carried out in the range of conditions shown in Table 3.5. The progress of the reaction was monitored by analysis of concentrations of reactants/ products as a function of time after the induction time. The results revealed that the reaction exhibits an induction period. It is likely that during this time the actual catalytic species are generated from NC

palladacycle precursor (Pd(ppy)(PPh_3)(OTs)). The active species can consist of highly active form of low-ligated Pd(0) species stabilized by anions (acetate or halides) or solvent molecules. It may be noted that previous reports using dimeric palladacycle complexes also displayed induction period.[6] As per these reports the dimer is converted to Pd(0) species and hence induction period is observed. In the case of Pd(ppy)(PPh_3)(OTs) the complex is present in Pd(II) state and needs to be converted to Pd(0). This will involve the removal of PPh_3 and OTs ligands to form active species. Hence induction period is observed. The exact mechanism of the formation of active catalytic species is not known. The reduction of Pd(II) to Pd(0) can be accomplished by either acetate ions (NaOAc) or olefin (*n*-butylacrylate) under reaction conditions. There is no information about the exact nature of the Pd species involved during the catalytic cycle. Ligand L could be a solvent molecule, ligands derived from palladacycle.

The initial rates were calculated from the observed data on the consumption of 3-bromo-benophenone as a function of time after the induction period. The amount of BBP consumed per unit volume was plotted against time, for an initial period of 10-15 minutes after the induction period, and the slope was measured as the rate of arylation. The initial rate of arylation is defined as the number of moles of BBP consumed per unit time, per unit volume of the reactants.

$$r = \frac{no.of\ moles of\ BBP consumed}{time \times volume of\ the reactant}$$

The dependence of rate on the various parameters was investigated at three different temperatures. The results showing the dependence of rates on different parameters and kinetic modeling are discussed below.

Table 3.5 Range of Parameters for Kinetic Studies

Parameters	***Units***	***Range***
Catalyst	(kmol m^{-3})	4.32 x 10^{-5} to 1.74x10^{-4}
3-bromo-benzophenone	(kmol m^{-3})	0.07-0.3
n-butyl acrylate	(kmol m^{-3})	0.11-0.45
NaOAc	(kmol m^{-3})	0.11-0.45
Temperature	(K)	413-433
Volume of liquid phase, NMP	m^3	2.5 x 10^{-5}

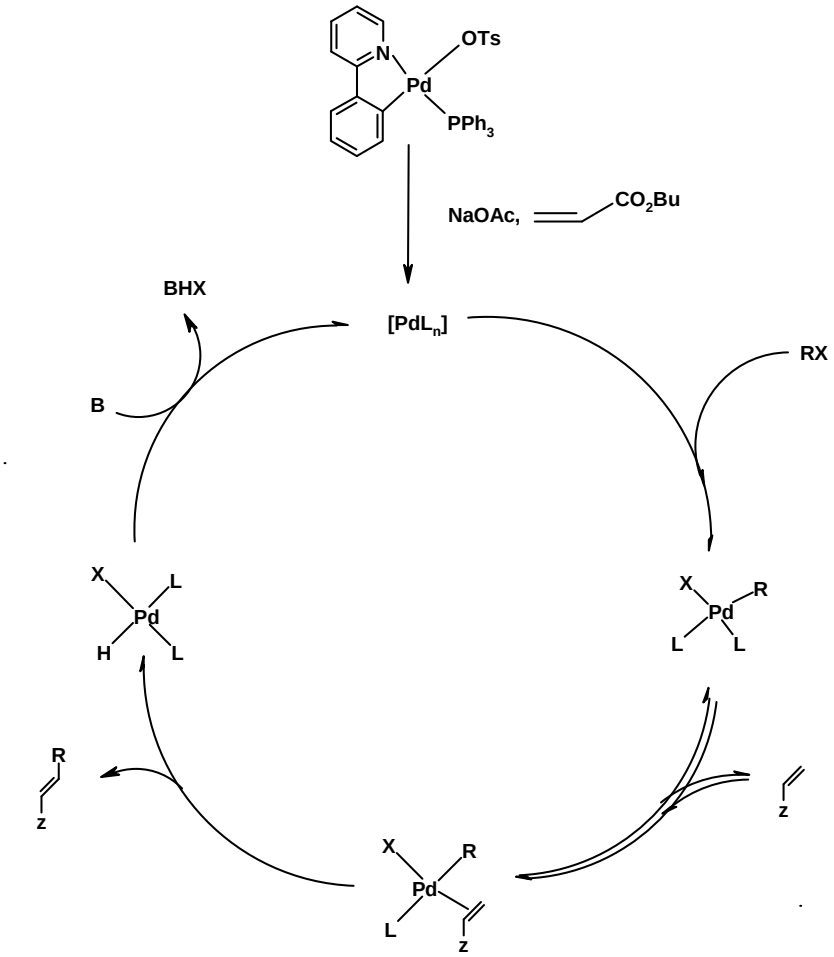


Figure 3.2. Heck Catalytic Cycle

3.3.3.1 Effect of Catalyst Concentration on the Rate of Reaction

Effect of catalyst loading was studied at three different temperatures in the range of 413-433 K, which is shown in Figure 3.3. Increase in the amount of catalyst in the reaction system increased the rate of reaction, indicating dependence on palladium concentration in the range investigated. The increase in rate can be attributed to the increased concentration of catalytically active species. A first-order-rate dependence on catalyst concentration was observed. The proposed Heck catalytic cycle (Figure 3.2) is initiated by oxidative addition of bromobenzophenone, followed by the coordination of the olefin to the oxidative addition product.[7] The other steps are olefin insertion, reductive elimination and the dissociation of the Heck product. Dupont et al[6b] have also shown that the first-order dependence of reaction rate on NC palladacycle

(palladacycle is converted to catalytically active Pd (0) species) for the reaction of iodobenzene and *n*-butylacrylate.

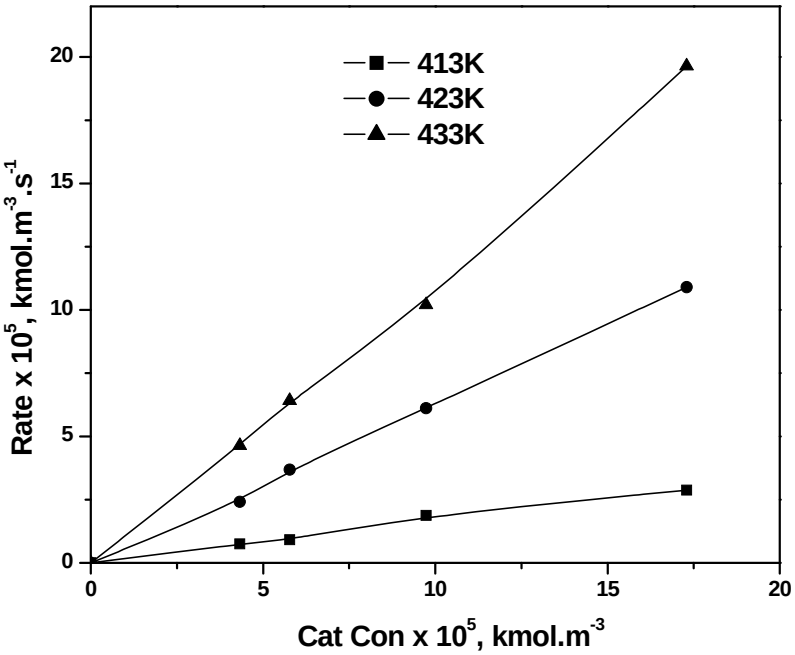


Figure 3.3 Effect of Catalyst Concentration on the Reaction Rates

Reaction Conditions: BBP, 0.137 kmol/m^3; BA, 0.203 koml/m^3; NaOAc, 0.203 koml/m^3; Pd(ppy)(PPh$_3$)(OTs), Solvent (NMP), total volume (25 ml)

3.3.3.2 Effect of BBP Concentration on the Rate of the Reaction

The effect of 3-bromo-benzophenone concentration variation on the rate of reaction was studied at constant *n*-BA, NC palladacycle, NaOAc concentrations of 0.07, 0.15, 0.22, and 0.3 kmol/m^3, respectively in a temperature range of 413 – 433 K. The results are shown in Figure 3.5. An unusual observation was noted, that with increase in the BBP concentration the rate passes through a maximum showing a substrate inhibition. This is the first time such an observation has been made for the Heck reaction of 3-bromo-benzophenone and *n*-butylacrylate using the catalyst Pd(ppy)(PPh$_3$)(OTs). In previous literature report[8] rates were found to increase with increase in the aryl bromide concentration. Addition of ArBr moiety to the palladium species is explained as the rate determining step and any increase in the concentration of the Ar-Br increases the oxidative addition step and hence first order dependence is expected. Zhao et al[10] also have described the first order dependence on iodobenzene

concentration. Blackmond et al[6a] described the zero order dependence on halide (4-bromo-benzaldehyde) concentration. Dupont et al also have reported saturation kinetics in iodobenzene.

In the present case the rate increases at lower concentration of BBP, but as the substrate concentration is further increased the rate decreases. As per the accepted mechanism (Figure 3.2) the first step is the oxidative addition of aryl halide to the palladium (0) complex. At high BBP concentration, the concentration of RPdX increases. As per literature reports[6b] the association equilibrium involving olefin coordination to palladium is a highly unfavorable step and hence a slow reaction. It is quite likely that at higher concentration of RPdX (Figure 3.4), part of the RPdX undergoes dehalogenation to give Pd (PdX_2, PdX^{3-}, PdX_4^{2-}, and $Pd_2X_6^{2-}$)[9,6b] species which are inactive for the Heck reaction. These species are slowly converted back to catalytically active species. It may be noted that the formation of benzophenone (dehalogenated product) was observed at higher concentration of BBP. Thus the observed drop in initial rate of reaction at higher BBP concentration can be explained on the basis of the conversion of RPdX species to inactive species. The possible deactivation steps as proposed by Shmidt et al[9] and Dupont et al[6b] are presented in Figure 3.4

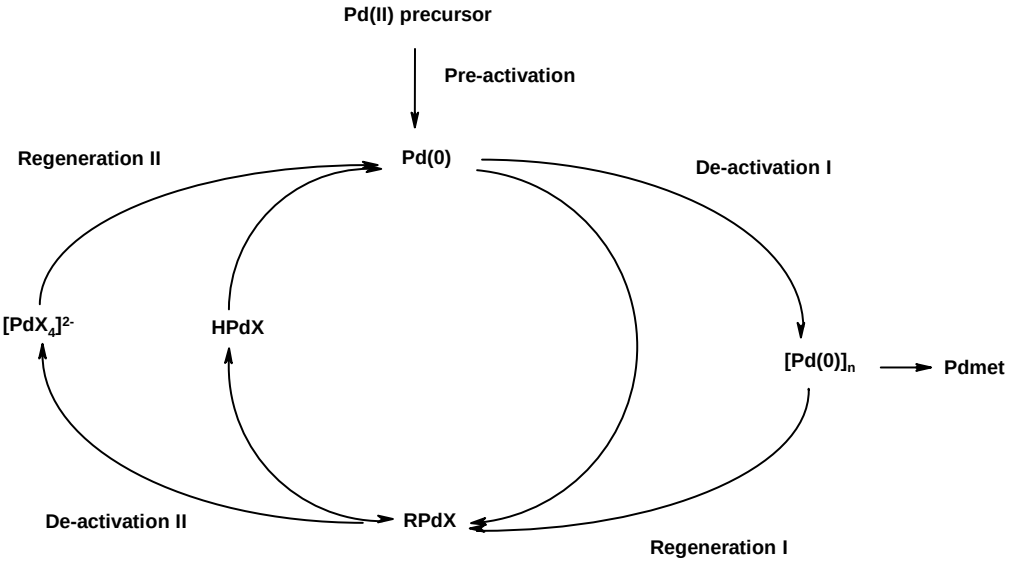


Figure 3.4 Possible Deactivation/ Regeneration of the Pd species involved in the Heck Catalytic Process

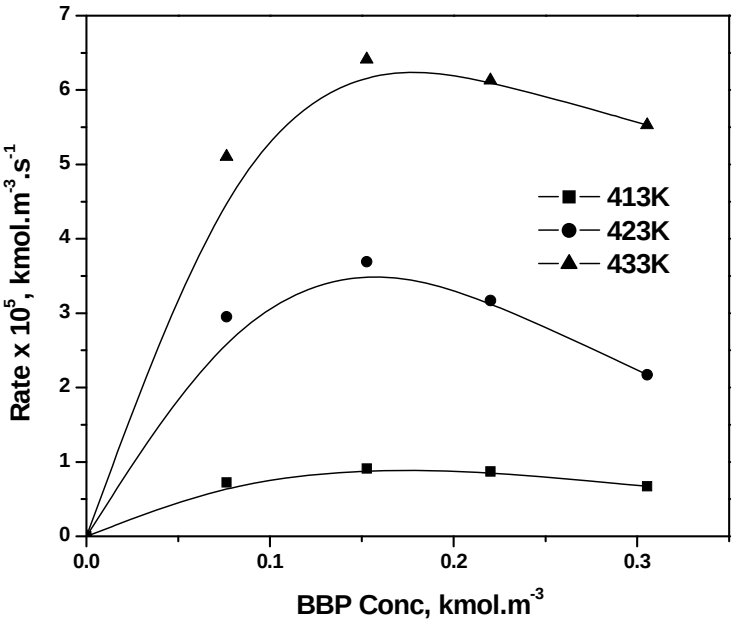


Figure 3.5. Effect of BBP Concentration on the Reaction Rates

Reaction Conditions: n- BA, 0.203 koml/m^3; NaOAc, 0.203 koml/m^3; Pd(ppy)(PPh_3)(OTs), 5.76 x 10^{-5} kmol/m^3; Solvent (NMP), total volume (25 ml)

3.3.3.3 Effect of *n*-butylacrylate Concentration on the Rate of the Reaction

The reaction showed a first order tending to zero order dependence of rate on the olefin concentration (Figure 3.6). It has been reported[6b] that the coordination of olefin to the palladium is a highly unfavorable step and there is equilibrium involving olefin coordination to palladium as shown in the Figure 3.2. Zhao et al[10] have reported a first order tending to zero order dependence of rates on the olefin concentration. Blackmond[6a] and co-workers also have reported a first order dependence on the olefin concentration for the reaction of *p*-bromobenzaldehyde with *n*-butylacrylate using NC palladacycle catalyst. Du-pont and coworkers[6b] report a saturation kinetics with respect to *n*-BA concentration for the reaction of *n*-BA with iodobenzene.

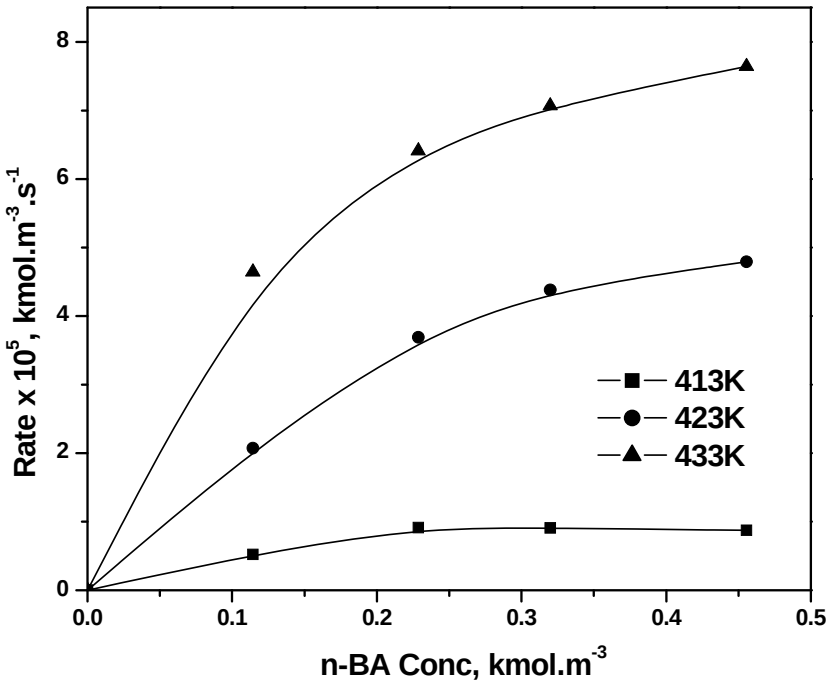


Figure 3.6 Effect *n*-BA Concentration on the Reaction Rates

Reaction Conditions: BBP, 0.137 kmol/m^3; NaOAc, 0.203 kmol/m^3; Pd(ppy)(PPh$_3$)(OTs), 5.76 x 10^{-5} kmol/m^3; Solvent (NMP), total volume (25 ml)

3.3.3.4 Effect of Sodium acetate Concentration on the Rate of the Reaction

The effect of base concentration on the arylation of BA with BBP was studied at constant BBP, BA, NC palladacycle concentrations of 0.11, 0.22, 0.32 and 0.45 kmol/m^3, respectively, in a temperature range of 413-433 K. In these studies the reaction rate was found to be independent of base concentration (Figure 3.7). This observation indicates that the participation of base occurs after the rate-limiting step in the reaction. The role of the base is to neutralize the acid HBr liberated in the reaction to complete the catalytic cycle. Dupont and co-workers[6b] also have shown a zero order dependence on base concentration. Zhao et al[10] have reported the rate passing through a maximum as the concentration of the base (triethylamine) is increased.

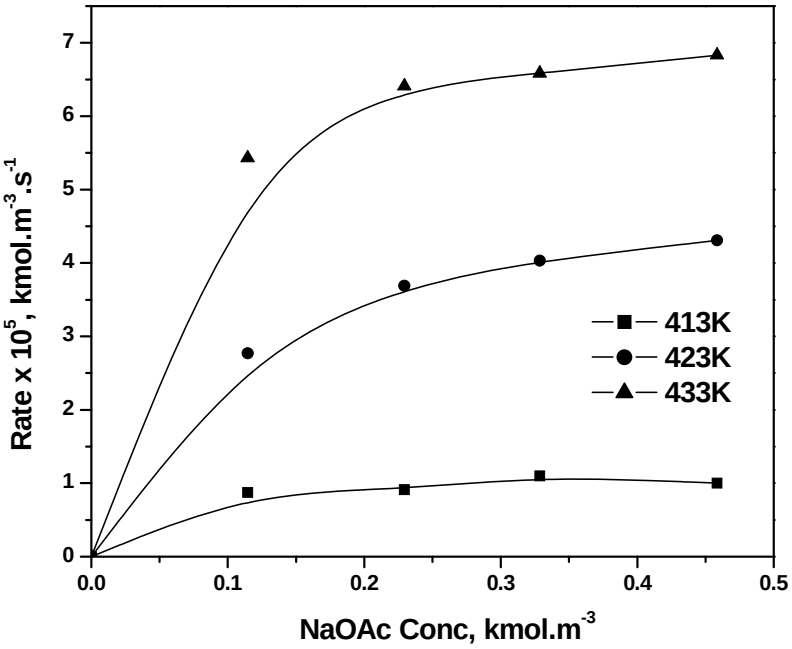


Figure 3.7 Effect of NaOAc Concentration Variation on the Reaction Rates

Reaction Conditions: BBP, 0.137 kmol/m^3; n-BA, 0.203 kmol/m^3; Pd(ppy)(PPh$_3$)(OTs), 5.76 x 10^{-5} kmol/m^3; Solvent (NMP), total volume (25 ml)

3.3.4 Rate Model

The kinetic data was used to develop a rate equation for the Heck reaction of 3-bromobenzophenone and *n*-butylacrylate. Based on the observed trends, a variety of empirical models were examined, and the best model was selected based on the criterion of the least average error between predicted and experimental rates (ϕ_{min}) which is defined as

$$\phi_{\min} = \sum_{i=1}^{n} (R_{EXP} - R_{PRE})^2$$

Where R_{EXP} is the observed rate of the reaction and R_{PRE} is the rate predicted by the respective models.

3.3.5 Estimation of Kinetic Parameters and Model Discrimination

The rate parameters k_1, K_2, K_3, K_4 were evaluated at 413 K, 423 K and 433 K by fitting the experimental rate data with equations (I)-(V) using non-linear regression

analysis and an optimization routine based on the Marquardts method.[11] The values of the rate parameters at different temperatures are presented in the Table 3.6.

$$r = \frac{k_1 ABCD}{(1+K_2B)^2(1+K_3C)\ (1+K_4D)} \quad \textbf{(I)}$$

$$r = \frac{k_1 ABCD}{(1+K_2B)\ (1+K_3C)^2(1+K_4D)^2} \quad \textbf{(II)}$$

$$r = \frac{k_1 ABCD}{(1+K_2B)(1+K_3C)^2(1+K_4D)} \quad \textbf{(III)}$$

$$r = \frac{k_1 ABCD}{(1+K_2B)\ (1+K_3C)\ (1+K_4D)} \quad \textbf{(IV)}$$

$$r = \frac{k_1 ABCD}{(1+K_2B)^3(1+K_3C)^3(1+K_4D)^3} \quad \textbf{(V)}$$

Where

r = rate of reaction, expressed in kmol/(m^{3}s); A = concentration of NC palladacycle (kmol/m^3); B = concentration of *m*-bromobenzophenone (kmol/m^3); C = concentration of *n*-butylacrylate (kmol/m^3); D = concentration of NaOAc (kmol/m^3); k_1 = rate constant

K_2, K_3, K_4 are equilibrium constants

Table 3.6 Values of Kinetic Parameters at Different Temperatures

Rate Model	Temp. (K)	k_1	K_2	K_3	K_4	ϕ_{min}
(**I**)	413	258.60	26.80	58.50	384.90	7.12E-13
	423	546.80	8.20	45.00	50.10	5.43E-13
	433	792.67	6.68	8.56	19.00	3.10E-13
(**II**)	413	2679.53	86.60	3.08	3.18	4.39E-10
	423	22351.97	602.48	1.09	1.84	2.78E-10
	433	10755.19	85.09	1.86	2.88	2.94E-10
(**III**)	413	7833.12	94.37	3.08	31.14	4.39E-10
	423	12499.08	240.50	1.07	7.90	2.72E-10
	433	23046.46	77.99	1.83	24.03	2.57E-10
(**IV**)	413	1211.80	52.85	-174.47	-78.61	4.60E-10
	423	1852.00	88.91	-246.54	-137.40	9.36E-10
	433	7058.00	54.28	-466.47	-235.45	9.37E-10
(**V**)	413	598.92	3.68	1.71	1.66	4.22E-10
	423	1030.22	4.18	0.70	1.07	7.94E-11
	433	2042.99	3.01	1.07	1.51	1.23E-10

The discrimination of rate models was done based on the thermodynamic criteria, activation energy and the ϕ_{min} values. The rate models II and III were rejected based on the thermodynamic criteria of inconsistency of temperature dependence of equilibrium constant and range of activation energy values. Model IV had rate parameters less than zero (or –ve) and hence was rejected. In the remaining two models I and V, the model V was discriminated based on the higher ϕ_{min} values than model I. Model (IV) was rejected as it gave negative value of the rate constant. Model (II)-(V) gave high value of ϕ_{min}. The model (I) thus turned out to be superior amongst all the models considered.

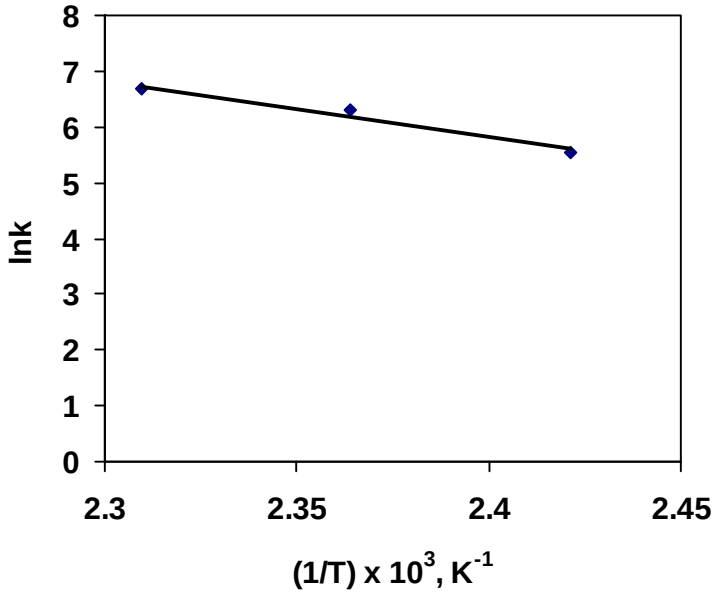


Figure 3.8. Temperature Dependence of Rate Constant (*k*) (Arrhenius plot)

The Arrhenius plot showing the effect of temperature on the rate parameters is shown in Figure 3.8 from which the activation energy was evaluated as 84.7 kJ/mol.

A comparison of the experimental rates with the rates predicted by model I are shown in Figure 3.9, which shows a reasonably good fit of the experimental data. The average deviation in the predicted and observed rates was found to be in the range of ± 2 %.

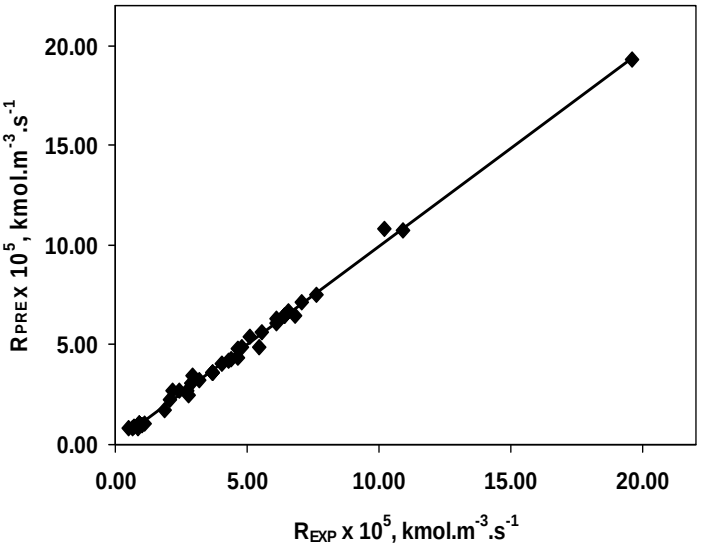


Figure 3.9 Comparison of Experimental Rates and Rates Predicted using model (I)

3.3.6 Conclusions

The detailed kinetics of arylation of *n*-butylacrylate with 3-bromo-benzophenone was studied using monomeric NC palladacycle as catalyst, in NMP as solvent and NaOAc as the base. The effect of different parameters *viz.,* concentrations of the substrates, catalyst and base on the rate of the reaction was investigated in the temperature range of 413-433 K. Substrate inhibition kinetics with respect to BMN was observed for the first time. The rate data were fitted to various empirical rate models. The following rate equation was found to predict the rates in good agreement with experimental values:

$$r = \frac{k_1 ABCD}{(1+K_2 B)^2 (1+K_3 C)\ (1+K_4 D)}$$

3.4 Preliminary Mechanistic Investigations in the Arylations of n-Butylacrylate with BMN using Pd(ppy)(PPh_3)(OTs)

As presented earlier It was observed that induction period is exhibited by monomeric palladacycle Pd(ppy)(PPh_3)(OTs) used as a catalyst precursor, similar to that for dimeric palladacycle. During the induction period the catalytically active Pd species are generated, and the exact nature of the species involved is not understood. Also for the first time substrate inhibition was observed which is very rare. In order to understand the mechanistic features ^{31}P-NMR, ESI-MS and poisioning experiments were carried out and the results are presented in the following sections.

3.4.1 ^{31}P-NMR Experiments

Since the complex contains phosphorous element, ^{31}P-NMR experiments were performed to find different types of Pd containing phosphorous species appearing during the reaction. The reaction conditions are described in the Table 3.7. NMR measurements were carried out at 300 K on a 9.4 Tesla Bruker Avance 400 Pulse Fourier Transform Spectrometer equipped with a 5 mm Triple Resonance Inverse Probehead. Reaction samples were dissolved in a mixture of NMP/$CDCl_3$ (v:v = 3:1). The spectra have been acquired with Proton Composite Pulse Decoupling (CPD). The ^{31}P frequency is 161.975 MHz. Referencing has been done by the substitutive Method. i.e. H_3PO_4 85% is measured in an extra sample tube at the same field as the respective

sample, and the so obtained spectrometer reference frequency has been put into the spectra of the actual samples. Stoichiometric reactions (Table 3.7) for the ^{31}P-NMR experiments were carried in round-bottomed flask in nitrogen atmosphere, to understand the role of each reagent on the palladium complex Pd(ppy)(PPh_3)(OTs) and their probable association with the complex. The complex Pd(ppy)(PPh_3)(OTs) dissolved in NMP at room temperature shows the peak value at δ = 43.52 ppm. Whereas the complex Pd(ppy)(PPh_3)(OTs) in $CDCl_3$ shows peak at δ = 42.69 ppm (In Chapter 1, the value for this complex is δ = 39.92 ppm; the variation is because of different $CDCl_3$ and nmr instrument used for these reactions). All the stoichiometric nmr experiments performed as described in Table 3.7, showed that a new peak has appeared in the region δ 26.18 – 27.73 ppm (the small variations in chemical shift value can be due to the minor changes in the concentration of the species with respect to other experiments). These reactions showed formation of single peak in this region for all the nmr experiments carried. The stacked plots of all the phosphorous nmr reactions performed are shown in the Figure 3.10. The peaks around δ 43 ppm are due to the residual unreacted complex remained in the reaction mixture. Since ^{31}P-NMR do not give the exact structure of the complex formed in the reaction mixture, ESI-MS experiments were performed. ESI-MS gives the mass of each component present in the reaction mixture from which probable species formed in the reaction mixture can be deduced. To confirm the peak identity ESI-MS experiments were performed and the details are presented in the Section 3.4.2.

Table 3.7. Results of the ^{31}P-NMR Experiments

Entry	Reaction	Reaction Conditions Temp = 378 K, time = 0.5 h	Chemical shifts δ ppm
1*	Cat + $CHCl_3$	Cat = 0.028 mmol NMP = 5 ml	42.69
2*	Cat + NMP	Cat = 0.05 mmol NMP = 5 ml	43.52
3	Cat + NMP	Cat = 0.05 mmol NMP = 5 ml	26.81
4	Cat + BMN + NMP	Cat = 0.05 mmol BMN = 0.06 mmol NMP = 5 ml	26.7 23.7
5	Cat + BA + NMP	Cat = 0.07 mmol BA = 0.29 mmol NMP = 5 ml	27.73 43.62
6	Cat + BMN + BA + NMP	Cat = 0.07 mmol BMN = 0.09 mmol BA = 0.13 mol NMP = 5 ml	26.18 43.46
7	Cat + NaOAc + NMP	Cat = 0.07 mmol NaOAc =0.01 mmol NMP = 5 ml	26.64
8	Cat + BMN + NaOAc + NMP	Cat = 0.07 mmol BMN = 0.08 mmol NaOAc = 0.108 mmol NMP = 5 ml	26.22
9	Cat + BA + NaOAc + NMP	Cat = 0.0721 mmol BA = 0.1008 mmol NaOAc = 0.108 mmol NMP = 5 ml	26.43
10	Cat + BMN + BA + NaOAc	Cat = 0.05 mmol BMN = 2.109 mmol BA = 1.597 mmol NaOAc = 1.59 mmol NMP = 5 ml	26.86

* the complex was dissolved at room temperature;

Cat = $Pd(ppy)(PPh_3)(OTs)$

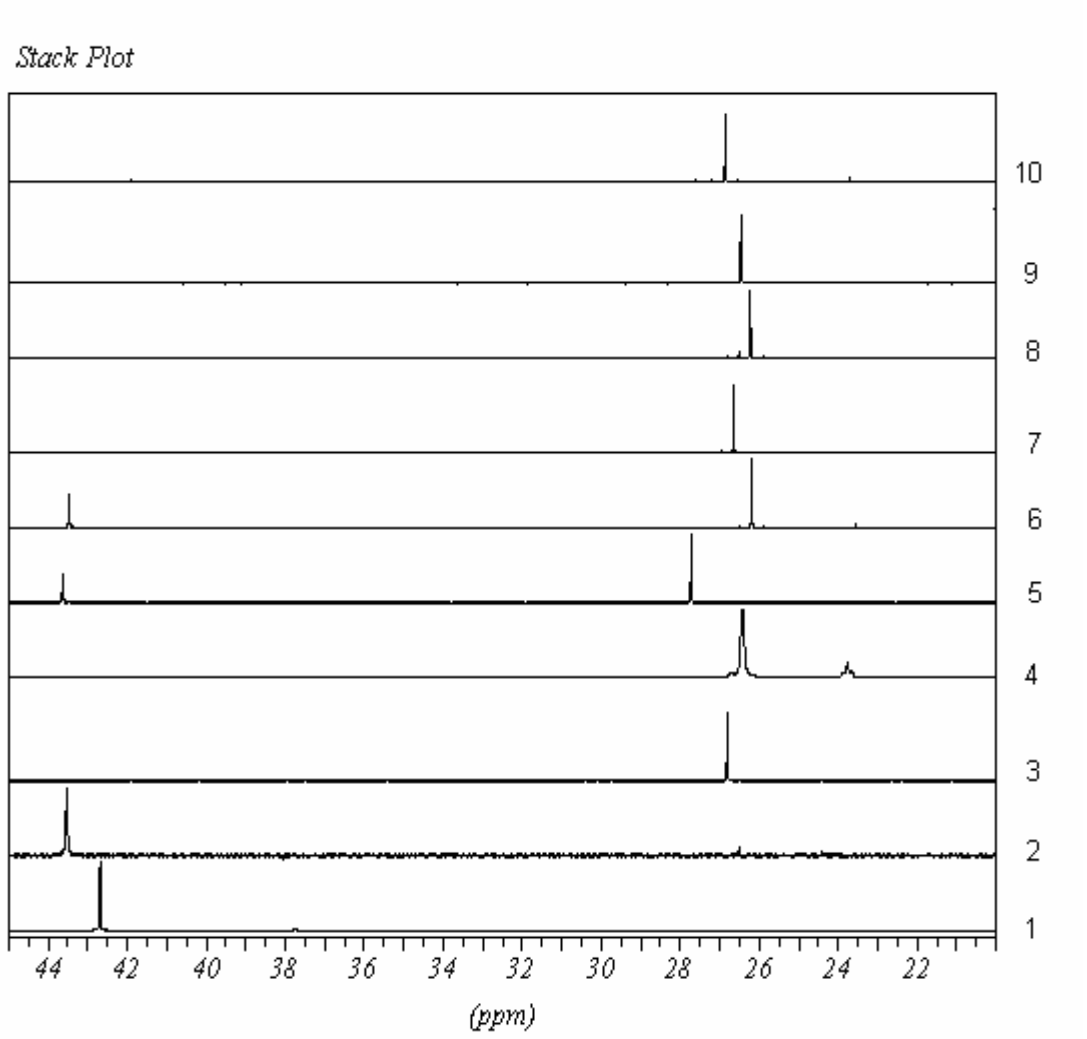
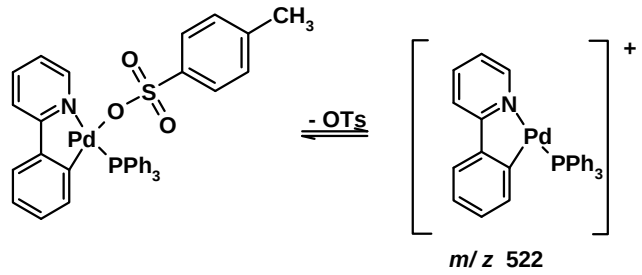


Figure 3.10 Stacked Plots of ^{31}P-NMR Results

3.4.2 ESI-MS Experiments

Electrospray ionization mass spectrometry[12] is a soft ionization technique which has become increasingly popular as a mechanistic tool for studying short lived reactive intermediates involved in organometallic catalytic reactions.[13] The gentleness by which ions are formed in ESI-MS is an important feature for its application in organometallic chemistry. In addition, ESI-MS also permits working directly from dilute solutions. This is a major advantage in studies of catalytic species that exist only under these conditions. ESI-MS has been used recently for the screening of palladium catalysts and for the determination of the mechanism of the Heck reaction with arene diazonium salts.[13] Peaks due to species containing palladium are easily detected by the

characteristic isotope distribution of the metal [^{102}Pd(1.02%), ^{104}Pd(11.14%), ^{105}Pd(22.33%), ^{106}Pd(27.33%), ^{108}Pd(26.46%), ^{110} Pd(11.72%)]. In ESI-MS only ionic compounds can be detected [cations in the ESI(+) mode and the anions in the ESI(-) mode].[14] The specific goal was to direct detection by mass spectrometry of the intermediates within reaction mixture in order to learn about the catalytic role of the palladium complex. The peaks which resulted for the various reactions are summarized in the Table 3.8. The complex Pd(ppy)(PPh_3)(OTs) dissolved in NMP at room temperature showed the mass of 522, which can be attributed to the formation of Pd(ppy)(PPh_3)$^+$ as shown in the Scheme 3.3. The ESI-MS shows the peak arising of species of mass 522, shown in the Figure 3.11. The cationic complex is detected by MS as an isotopomeric cluster of singly charged ions centered at m/ z 522 (for ^{106}Pd), and with an isotopic pattern $C_{29}H_{23}NPPd$.



Scheme 3.3. ESI-MS of the Complex Pd(ppy)(PPh_3)(OTs)

Though the ESI studies shows the mass spectrum of the complex dissolved in NMP at room temperature, but for other reactions performed at reaction temperature of 383 K, did not show any palladium species. Figure 3.12 shows the ESI-MS of the reaction mixture containing palladium, BMN, BA and NaOAc, which do not show the formation of Pd species. The reasons for this can not be ascertained, but further detailed work is required for the understanding. The peaks obtained at m/ z of 300.57 and 579.27 can be assigned for [PPh_3O-Na]$^+$ and [2PPh_3O-Na]$^+$ respectively. The other peak arising at m/ z 857 was also not from the palladium complex. The sodium ions are observed because of the traces of cations present in the methanol solvent used for injection to ESI. Thus experiments show that triphenylphosphine from the complex is converted to triphenyloxide under the reaction conditions. Thus, the peak arising in phosphorous nmr experiments can be assigned because of the PPh_3=O.

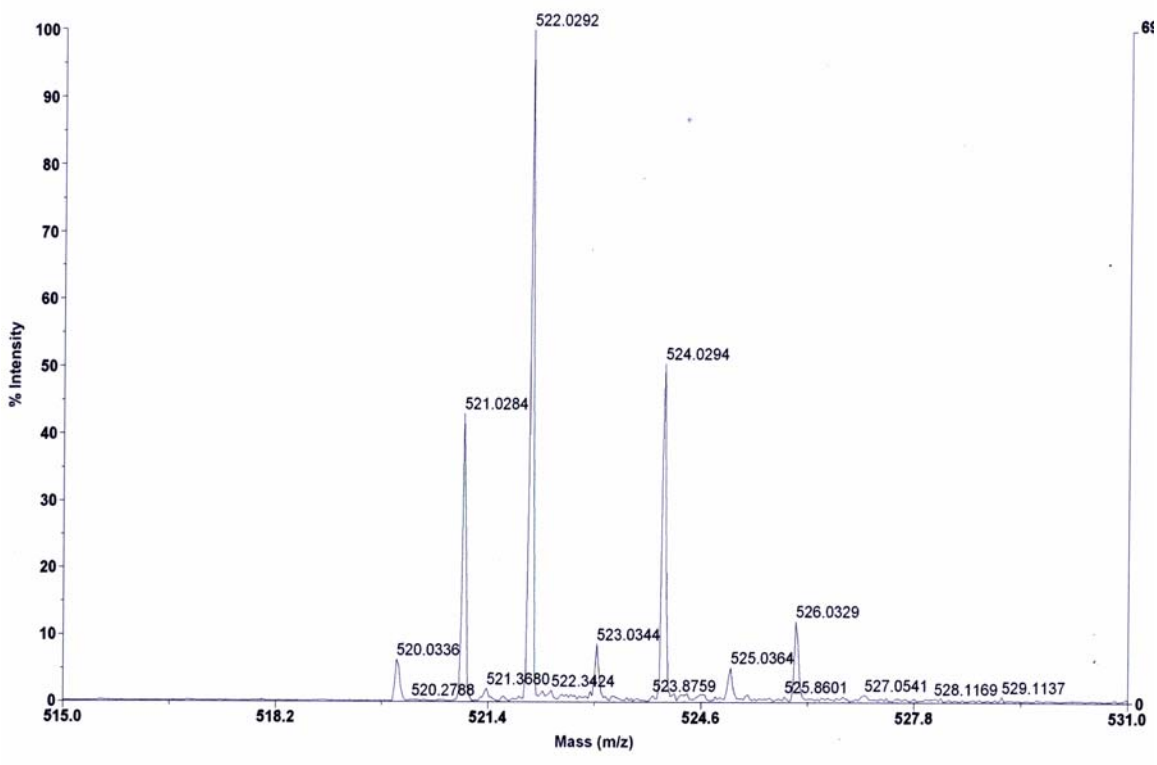


Fig. 3.11 ESI(+) -MS of the Palladacycle Pd(ppy)(PPh_3)(OTs)

Table 3.8. Results of ESI-MS Studies

Entry	Reaction	Detected Species
1	Cat + NMP (room temperature)	m/z 522
2	Cat + NMP	m/z 279 m/z 301 m/z 579 m/z 339
3	Cat + BMN + BA + NaOAc	m/z 857 m/z 579 m/z 301
4	Cat + BMN + NaOAc + NMP	m/z 857 m/z 579 m/z 301

Reaction temperature 378 K, Cat = Pd(ppy)(PPh_3)(OTs)

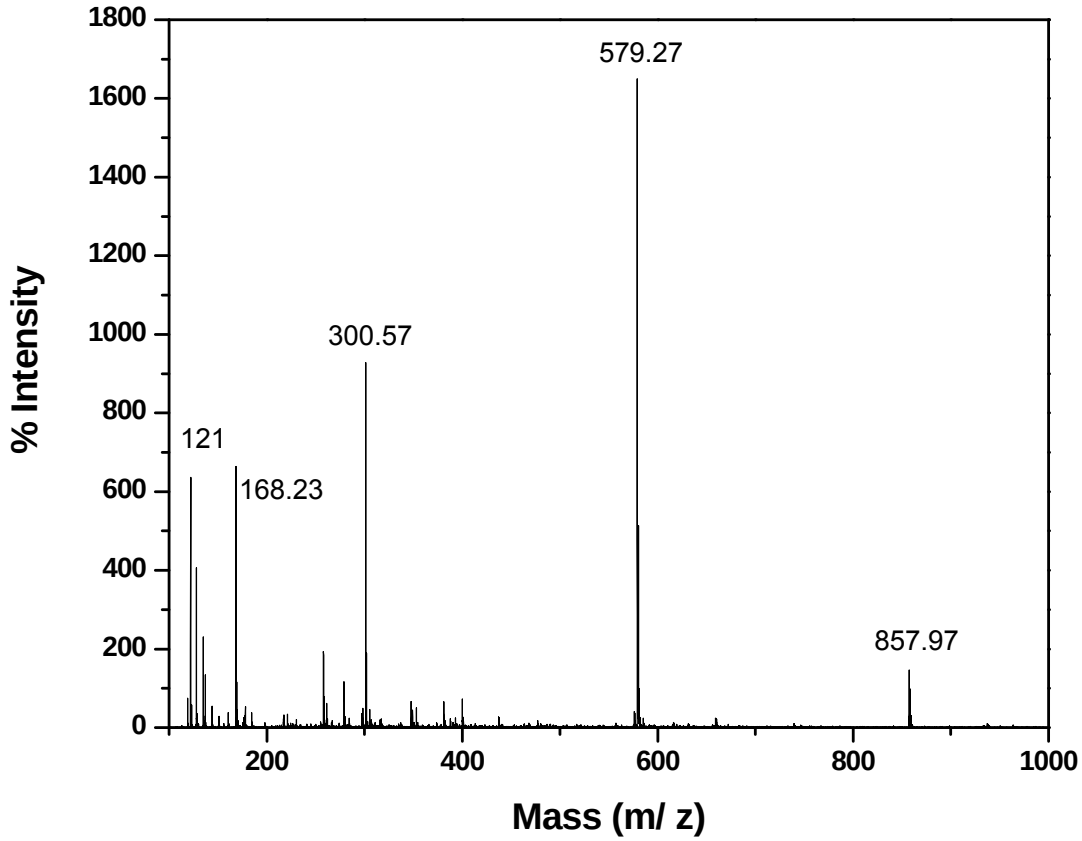


Fig.3.12 ESI-MS of the Reaction Mixture

3.4.3 Poisoning Studies

Literature reports that the palladacycles have a tendency to form soluble palladium(0) colloids or nanoparticles, with less reactive substrates such as aryl bromides or chlorides at high temperatures. To find whether the reaction is because of the palladium nanoparticles, a poisoning experiment was carried out. For the poisoning test, 300 equiv of polyvinylpyridine was added to the catalytic reactions. It has been demonstrated that highly cross-linked poly(vinylpyridine) traps soluble Pd species by coordinating to the metal centre and removing it from solution.[15] The results show (Figure 3.13) that with the use of PVPy the reaction was not occurring (<3 % conversion). This suggests that Pd(ppy)(PPh_3)(OTS) decomposes under the catalytic reactions.

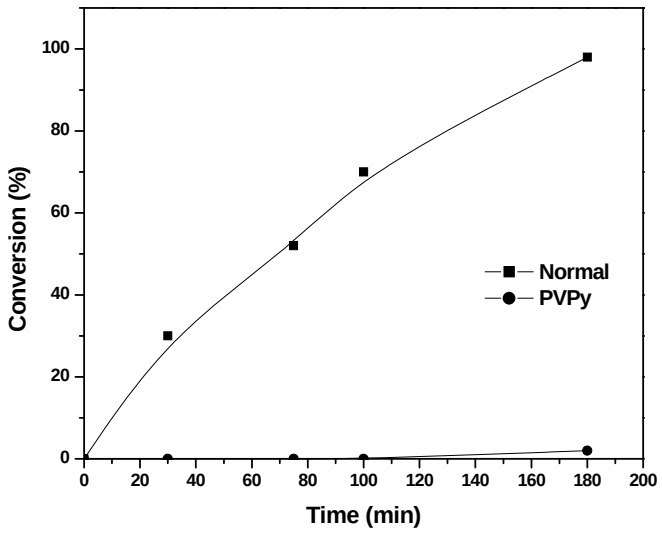


Figure 3.13. Results of Normal Reactions and Using PVPy

Reaction Conditions: BMN, 10.54 mmol; BA, 15.81 mmol; NaOAc, 15.81 mmol; Pd(ppy)(PPh$_3$)(OTs) (0.04 mol%), Solvent (NMP), total volume (25 ml); for poisoning experiment PVPy=1.5 g of M.W. 60,000; T, 423 K

A reaction was also carried out using celite material (50 mg) in the reaction mixture (without PVPy), after the completion of the reaction, the mixture was filtered and washed with methanol. The grey solid obtained (palladium deposited on celite) was subjected to TEM analysis, the TEM image is shown in the Figure 3.14.

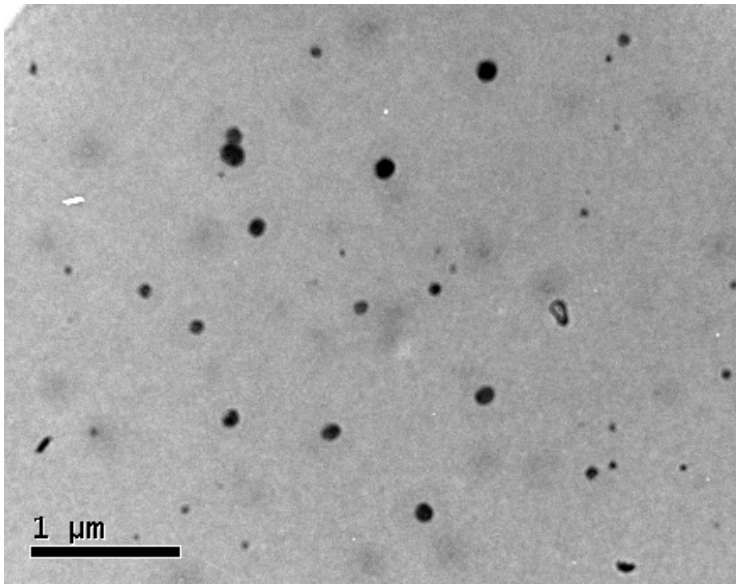


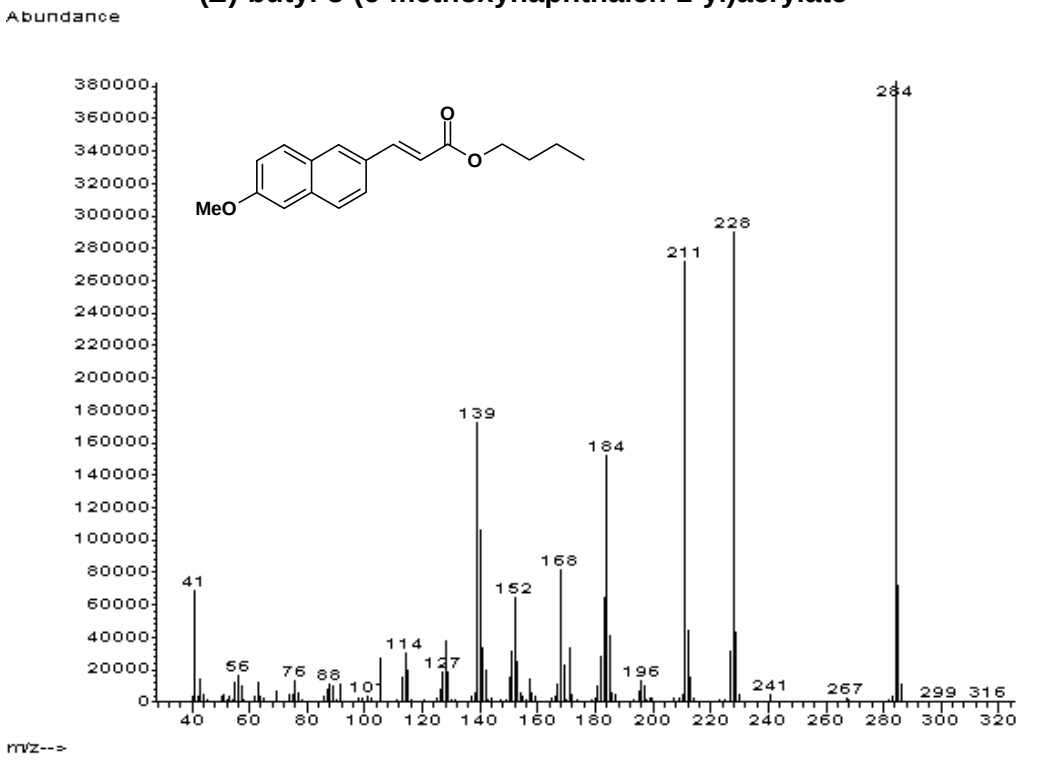
Figure 3.14. TEM Picture of Palladium Deposited on Silica from Heck Reaction

3.4.4 Conclusions:

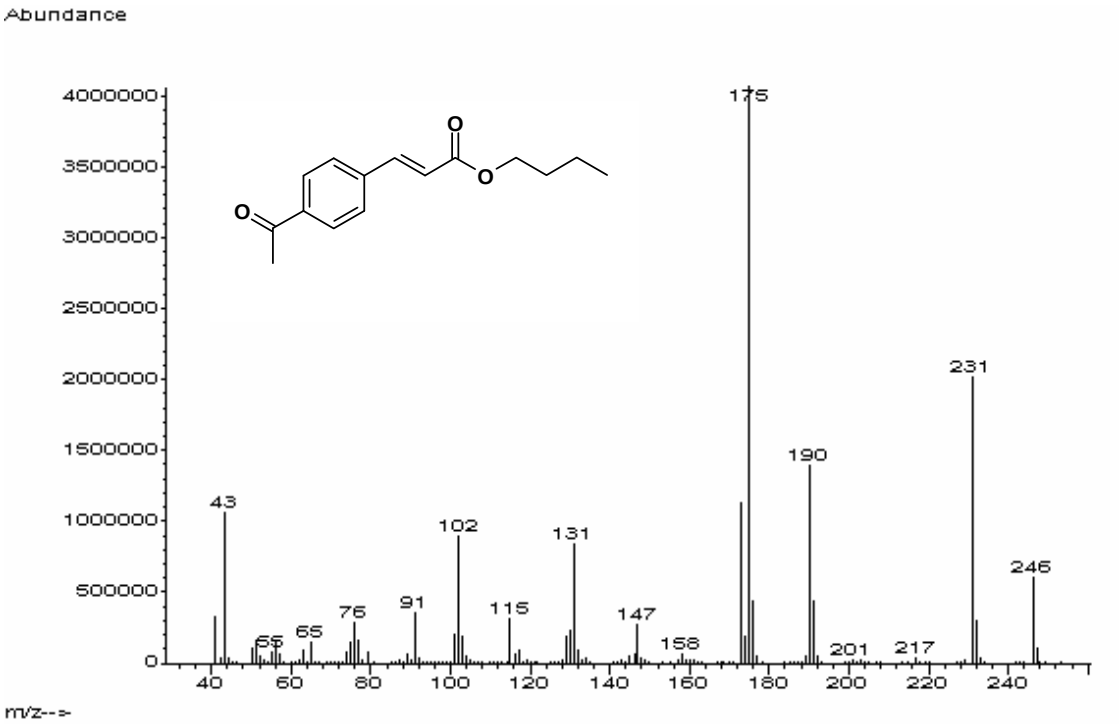
The ^{31}P-NMR and ESI-MS studies have shown that under the reaction conditions the triphenylphosphine moiety of the complex is detached from the palladium and is converted to triphenylphosphineoxide. Also from ESI-MS studies it can be noted that OTs ligand can be easily detached from the complex at room temperature. However at room temperature PPh_3 is attached to Pd. The poisoning experiments have shown the involvement of palladium nanoparticles in the Heck reaction. Thus the catalytic cycle contains a Pd(0) intermediate, as PVPy quenched essentially all activity. At the end of the reaction the catalytically active Pd(0) complexes present in the reaction, are unstable in solution and aggregate to form palladium metal, which is shown in TEM micrograph. Thus the palladium complex Pd(ppy)(PPh_3)(OTs) used as a catalyst precursor is stable in reaction mixture at room temperature (indicated by NMR and ESI-MS studies). Complex looses OTs^- ligand easily at room temperature, however PPh_3 is intact under the reaction conditions (as indicated by ESI-MS investigations). Pd complex looses OTs^- and PPh_3 ligands under reaction conditions to form the active catalytic species. Work carried out is preliminary in nature and detailed investigations are necessary to understand the nature of catalytically active species involved.

Appendix II

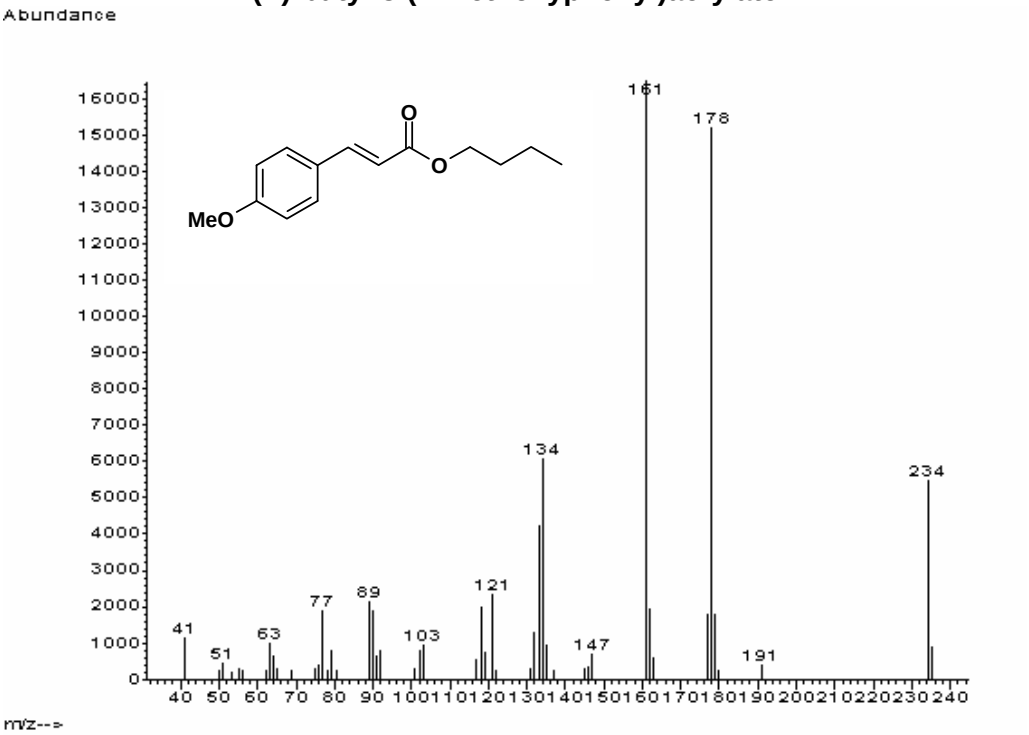
(*E*)-butyl-3-(6-methoxynaphthalen-2-yl)acrylate



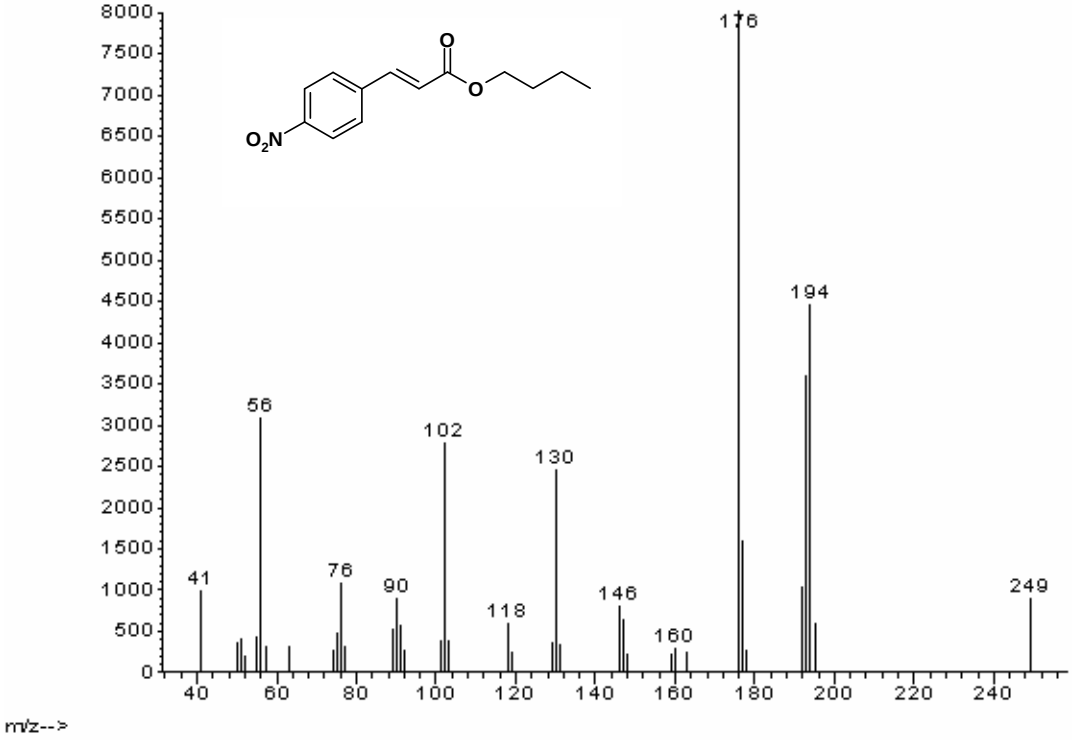
(*E*)-butyl-3-(4-acetylphenyl)acrylate



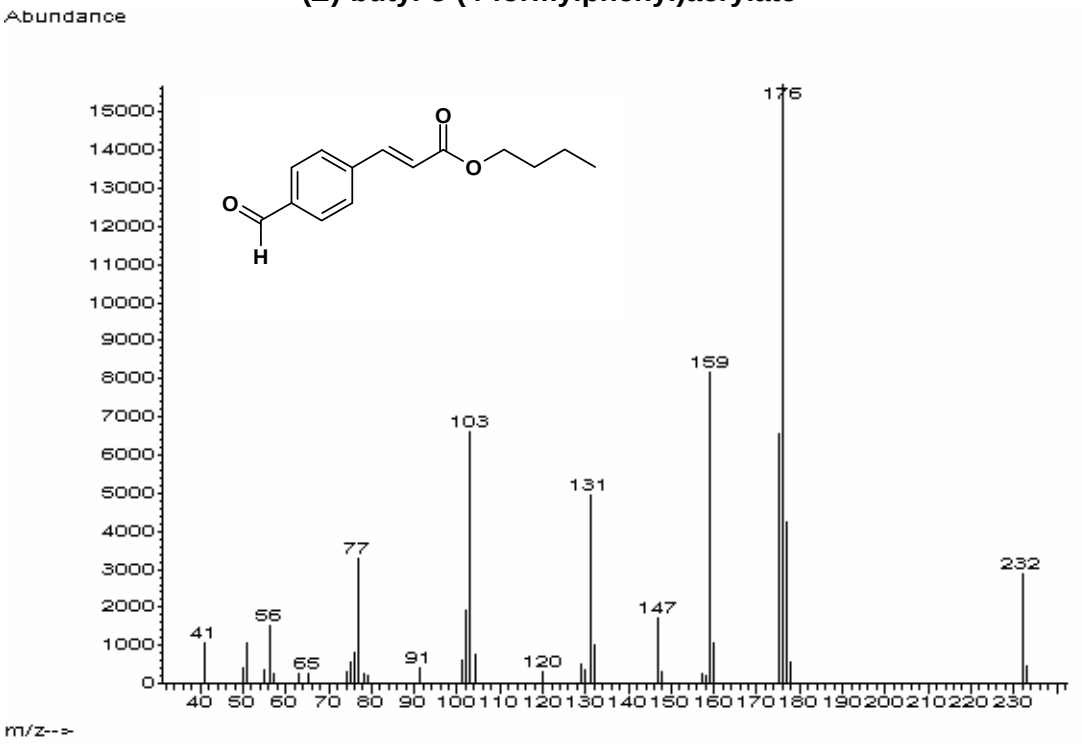
(*E*)-butyl-3-(4-methoxyphenyl)acrylate



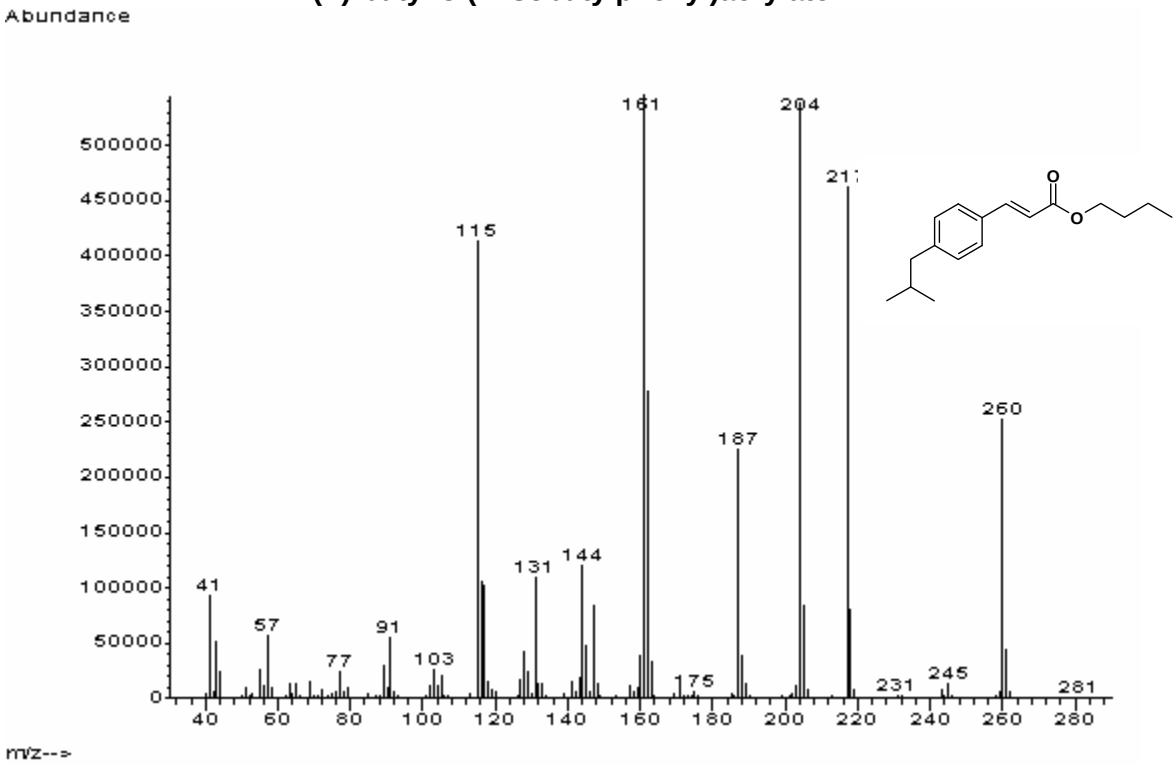
(*E*)-butyl-3-(4-nitrophenyl)acrylate



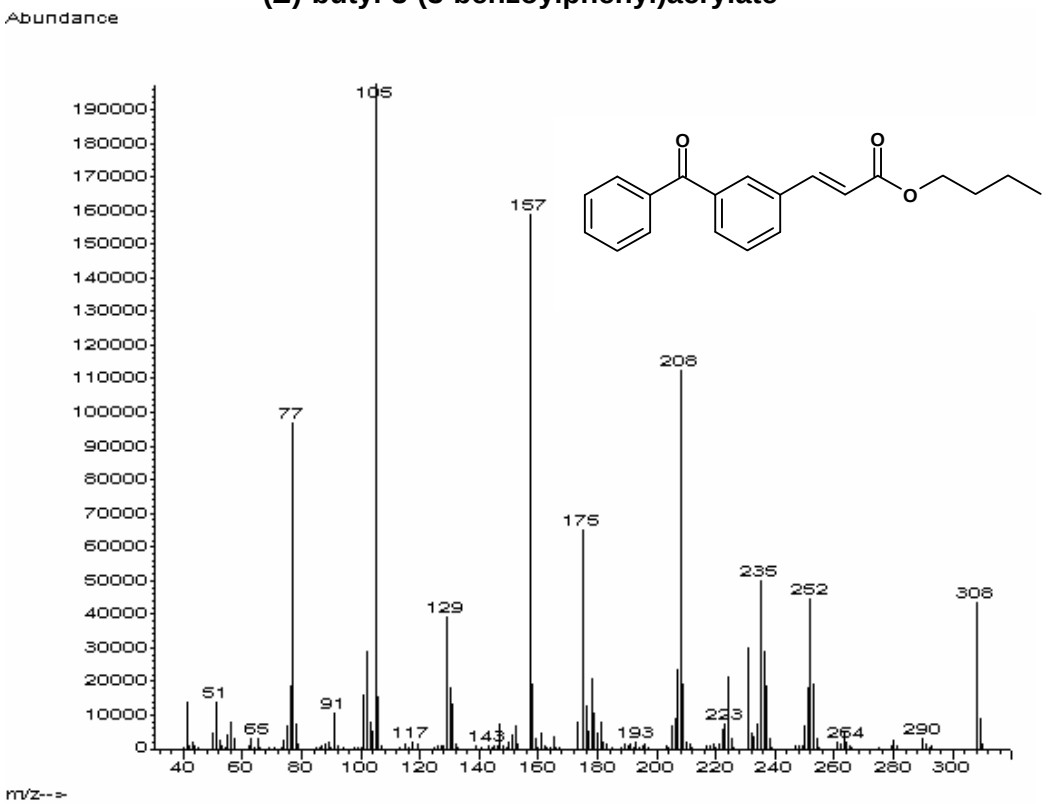
(*E*)-butyl-3-(4-formylphenyl)acrylate



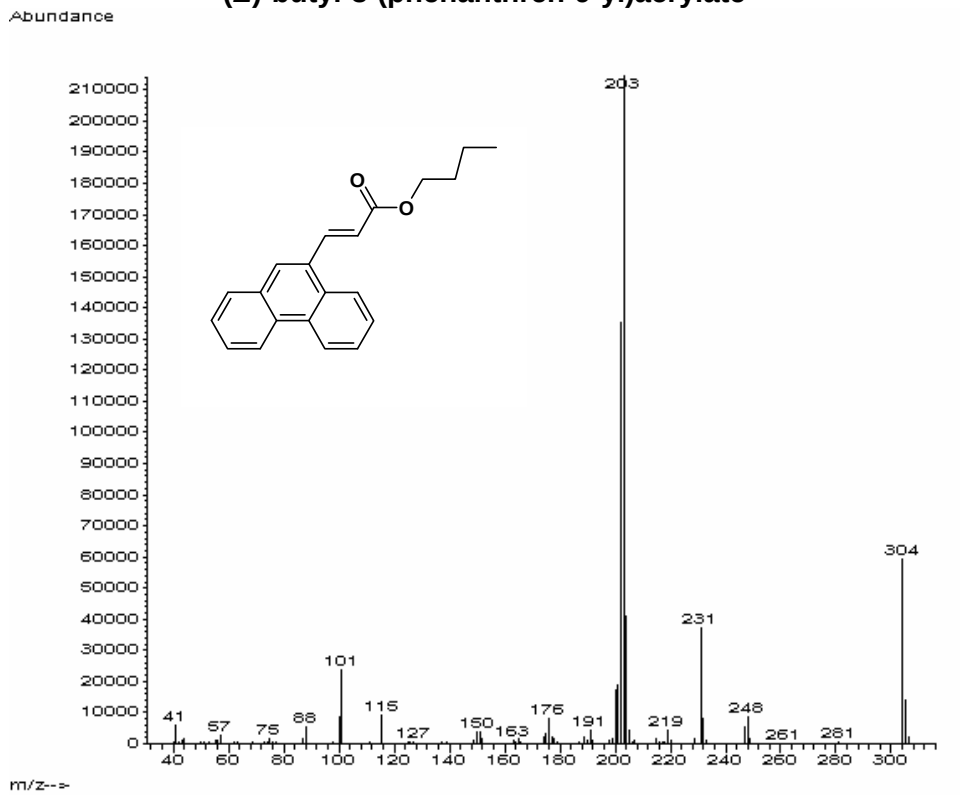
(*E*)-butyl-3-(4-isobutylphenyl)acrylate



(*E*)-butyl-3-(3-benzoylphenyl)acrylate



(*E*)-butyl-3-(phenanthren-9-yl)acrylate



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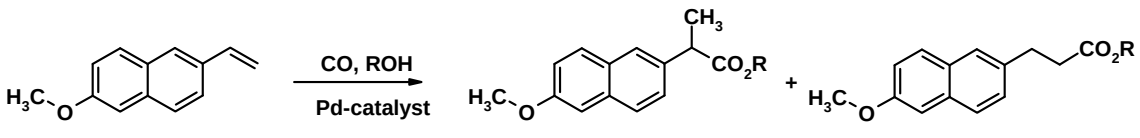
Chapter 4

Hydroesterification of
2-vinyl-6-methoxynaphthalene
with Palladium Complexes
Containing Chelating Nitrogen Ligands

4.1 Introduction

Transition metal catalyzed carbonylation of organic substrates is gaining considerable attention due to its potential in synthesis of a wide variety of complex organic molecules with high atom efficiency. Carbon monoxide can be directly introduced into unsaturated substrates consisting of olefins, alcohols and amines to produce organic molecules such as aldehydes, ketones, esters, amides, and other carbonyl containing functionalities. Although, many transition metals are effective catalysts for the carbonylation reactions, palladium complexes are the most widely employed for the carbonylation of aromatic olefins.[1] Palladium catalyzed carbonylation of styrene derivatives in the presence of alcohols (hydroesterification) affords 2-arylpropanoic esters, which are precursors for the most important class of non-steroidal anti-inflammatory agents such as ibuprofen, naproxen and ketopforen. The catalytic hydroesterification of vinyl aromatics with CO and an alcohol usually affords a mixture of normal and branched acid esters and it is often of interest to achieve high regioselectivity for most practical applications. By a proper choice of the ligand, the reaction can be directed to selectively synthesize a desired isomer product. It is therefore important to understand the factors influencing the rates and selectivity behavior of these carbonylation reactions.

In Chapter 2, investigations on arylation of ethylene with substrates such as 2-bromo-6-methoxynaphthalene, 3-bromobenzopheone and 4-bromoisobutylbenzene have been presented. The products of these arylation reactions are: 2-vinyl-6-methoxynaphthalene, 3-vinylbenzophenone and 4-isobutylstyrene, which are the precursors for the synthesis of Naproxen, Ketoprofen and Ibuprofen respectively. In this chapter, a detailed study on hydroesterification of 2-vinyl-6-methoxynaphthalene to the esters of Naproxen (Scheme 4.1) has been presented. The stoichiometric reaction is:



Scheme 4.1. Hydroesterification Reaction for the Synthesis of Naproxen Ester

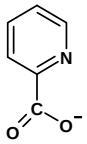
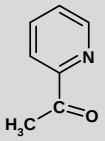
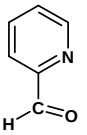
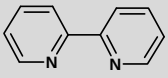
In the previous works, hydroesterification of styrene as the substrate has been investigated using palladium salts or classical palladium complexes such as $PdCl_2(PPh_3)_2$ with promoters as catalysts as reviewed in the Chapter 1 (Section 1.7.1, Table 1.8). Palladium complexes containing chelating nitrogen ligands as catalysts have shown most promising results in carbonylation reaction of olefins and alcohols. For example Jayasree et al[2] have described $Pd(pyca)(PPh_3)(OTs)$ catalyzed carbonylation reactions for a variety of olefins and alcohols, showing a breakthrough advancement in the low pressure catalytic carbonylation. The $Pd(pyca)(PPh_3)(OTs)$ complex showed a TOF of 150 h^{-1} in the hydroesterification of styrene at P_{CO}~5.4 MPa and 388 K. All the relevant studies on hydroesterification of styrene and derivatives are summarized in Chapter 1 (Table 1.8). However, there are only a few reports on the hydroesterification of practically important substrates such as 2-vinyl-6-methoxynaphthalene (VMN) – the intermediate to naproxen (Scheme 4.1). The catalytic systems described in the literature for hydroesterification of VMN (Chapter 1, Table 1.7) can be divided into two categories one involving asymmetric catalysis and the other achiral catalysis. Among the asymetric catalysis the chiral ligands used are as follows (i) ferrocene-containing chiral aminophosphine, (S)-(R)-BPPFA (ii) NMDP (neomenthydiphenylphosphine) (iii) dicycloalkylphosphinobinaphthalene; the structures of the ligands are shown in Chapter 1 (Section 1.7.1). Achiral catalysis involves the use of catalyst such as $PdCl_2(L)_2$; L= PPh_3, $MePPh_2$, $EtPPh_2$, $P(c\text{-}C_6H_{11})_3$, (c-$C_6H_{11}PPh_2$).

The drawbacks of asymmetric catalysis has been the difficulty in obtaining simultaneously both high regio- and enantioselectivities. The use of catalyst system $Pd(OAc)_2$/ (S)-(R)-BPPFA[3] gave very low conversion of 13% at room temperature with very long reaction times of (20 h). The catalytic systems $PdCl_2$/ dicycloalkylphosphinobinaphthalene[4] showed a yield of 21% in 24 h, the enantioselectivity of the product obtained was 53% (313 K, 3.0 MPa CO). With the catalytic system $Pd(dba)_2$/ NMDP[5] enantioselectivity of 43.8% was achieved at 323 K and 0.1 MPa of CO over a period of 4 h.

The achiral catalytic systems $PdCl_2(L)_2$[6] showed complete conversions within a reaction time of 20-40 h at 373 K and 4-7 MPa of CO. The complexes showed very poor turnover frequency (TOF) of < 10 h^{-1}.

Thus, hydroesterification of 2-vinyl-6-methoxynaphthalene (VMN) needs improved catalysts with respect to activity, selectivity and stability. In general, palladium-catalyzed hydroesterification requires various promoters in order to achieve the desired activity, selectivity and stability of the catalyst.[2] There are very few reports on hydroesterification of VMN and the role of various promoters is not well understood. In this part of the thesis, the hydroesterification of VMN was carried out using palladium complex having hemi-labile chelating ligand such as *pyca* [pyridine-2-carboxylic acid], *acpy* [2-acetylpyridine], *pycald* [pyridine-2-carboxaldehyde], and *bipy* [2,2'-bipyridine] as catalysts. The effect of reaction parameters such as solvents, CO pressure, and alcohols, olefins on the catalytic activity as well as the selectivity was studied the results of which are presented in this Chapter.

Table 4.1. Nitrogen Ligands Used in the Present Work

Ligand	Structure	Abbreviation	Mode of coordination
Pyridine-2-carboxylate		pyca	N-O$^-$
2-acetylpyridine		acpy	N-O
Pyridine-2-carboxaldehye		pycald	N-O
2,2'-bipyridine		bipy	N-N

4.2. Experimental

4.2.1. Materials

$Pd(OAc)_2$, 2-acetylpyridine, pyridine-2-carboxylic acid, 2,2'-bipyridine, pyridine-2-caboxaldehyde, Triphenylphosphine, *p*-toluenesulfonic acid, benzenesulfonic acid, methanesulfonic acid, trifloromethanesulfonic acid, trifloroacetic acid, lithium chloride,

methanol, 4-tert-butylcatechol and CO (Matheson, USA) were used as received without further purification. Solvents and alcohols were of analytical grade either from Merck or S.D. fine chemicals and were used as received. 6-Methoxy-2-naphthylethene, 3-vinylbenzophenone and 4-isobutylstyrene was prepared by the Heck arylation of ethylene with 2-bromo-6-methoxynaphthalene using the NC palladacycle catalyst as described in the Chapter 2 (Section 2.4).

4.2.2. Preparation of $Pd(pyca)(PPh_3)(OTs).H_2O$

The complex was prepared following the procedure as described earlier.[2] In a typical procedure $Pd(OAc)_2$ (0.89 mmol), pyridine-2-carboxylic acid , *p*-toluenesulfonic acid (1.78 mmol) and triphenylphosphine (1.78 mmol) in chloroform were vigorously stirred or shaken until all the components were completely homogeneous. The product was isolated as a yellow oil by addition of hexane. The oily product was washed several times with *n*-hexane and was kept under vacuum to obtain a yellow solid (Yield = 94%). Anal. Calcd for $C_{31}H_{26}NO_5PPd.SH_2O$: C, 54.76; H, 4.15; N, 2.06; S, 4.71. Found: C, 55.18; H, 4.23; N, 1.91; S, 4.38

The complexes $Pd(acpy)(PPh_3)(OTs)_2.2H_2O$, $Pd(pycald)(PPh_3)(OTs)_2.2H_2O$ and $Pd(bipy)(PPh_3)(OTs)_2.3H_2O$ were synthesized by a procedure described previously.[7] The typical procedures are as follows:

4.2.3.Preparation of $Pd(acpy)(PPh_3)(OTs)_2.2H_2O$

$Pd(OAc)_2$ (0.89 mmol), 2-acetylpyridine (0.89 mmol) , *p*-toluenesulfonic acid (1.78 mmol) and triphenylphosphine (1.78 mmol) in chloroform were vigorously stirred or shaken until all the components were completely homogeneous. The product was isolated as a yellow oil by addition of *n*-hexane. The oily product was washed several times with n-hexane and was kept under vacuum to obtain a yellow solid (yield = 89%). Anal. Calcd for $C_{31}H_{26}NO_5PPd.SH_2O$: C, 53.95; H, 4.64; N, 1.61; S, 7.38. Found: C, 54.39; H, 4.93; N, 1.01; S, 7.08

4.2.4. Preparation of $Pd(pycald)(PPh_3)(OTs)_2.2H_2O$

$Pd(OAc)_2$ (0.89 mmol), pyridine-2-carboxaldehyde (0.89 mmol), *p*-toluenesulfonic acid (1.78 mmol) and triphenylphosphine (1.78 mmol) in chloroform were vigorously stirred or shaken until all the components were completely homogeneous. The product was isolated as a yellow oil by addition of hexane. The oily product was washed several times with *n*-hexane and was kept under vacuum to obtain a yellow solid (Yield = 92%). Anal. Calcd for $C_{31}H_{26}NO_5PPd.SH_2O$: C, 53.43; H, 4.48; N, 1.64; S, 7.51. Found: C,55.32; H, 4.68; N, 1.22; S, 6.78

4.2.5. Preparation of $Pd(bipy)(PPh_3)(OTs)_2.3H_2O$

$Pd(OAc)_2$ (0.89 mmol), 2-2'-bipyridine (0.89 mmol) , *p*-toluenesulfonic acid (1.78 mmol) and triphenylphosphine (1.78 mmol) in chloroform were vigorously stirred or shaken until all the components were completely homogeneous. The product was isolated as a yellow oil by addition of hexane. The oily product was washed several times with *n*-hexane and was kept under vacuum to obtain a yellow solid (Yield =85%). Anal. Calcd for $C_{31}H_{26}NO_5PPd.SH_2O$: C, 54.76; H, 4.70; N, 3.04; S, 6.96. Found: 55.28; H, 4.53; N, 2.65; S, 6.56

The structures of the complexes synthesized is shown in the Figure 4.1.

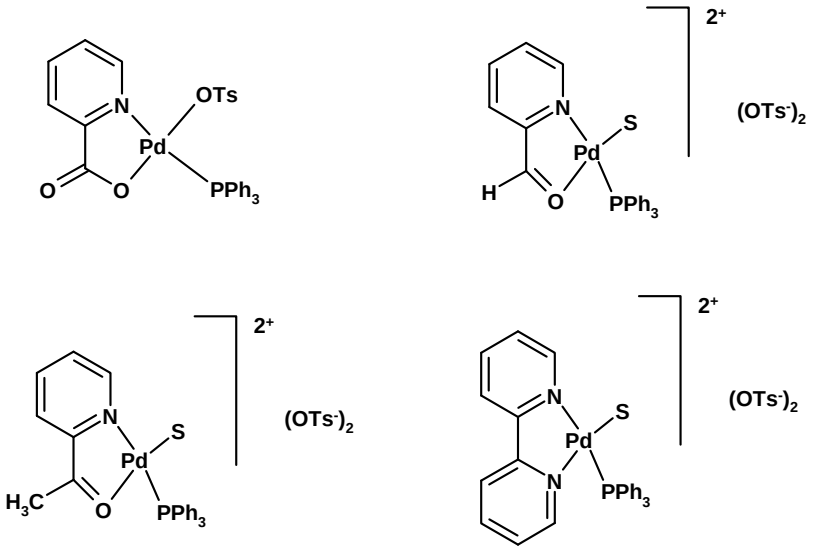


Figure 4.1. Structures of the Complexes

4.3. Experimental Procedure for Hydroesterification

All carbonylation♦ reactions were carried out in a 50 ml Parr Autoclave made of Hastelloy-C-276 and having facilities for gas inlet, outlet, liquid sampling, temperature controlled heating and variable agitation speed (Figure 4.2). As a safety precaution, a rupture disc (gold faced), which can withstand a maximum of 14 MPa pressure, was also attached to the reactor.

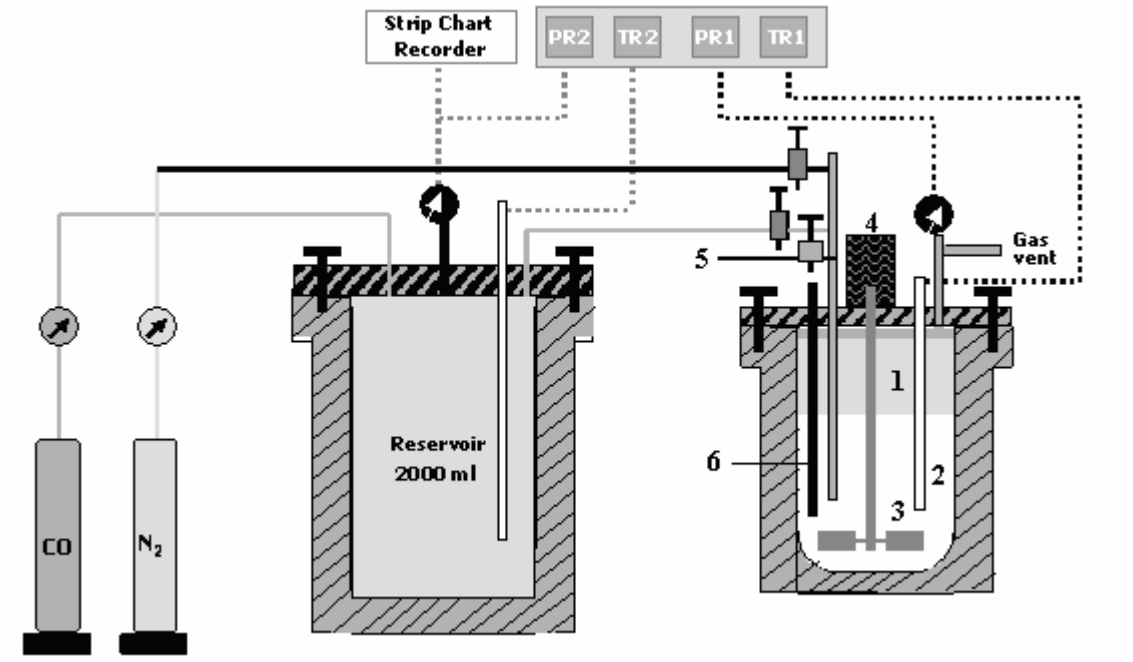
In a typical experiment, required amounts of the catalyst, substrate, promoters were dissolved in a solvent to make the total volume 25 ml and charged into the reactor. The reactor was purged first with nitrogen and subsequently with carbon monoxide from individual reservoirs at room temperature and the contents were heated to the required temperature. After attaining the temperature, the reactor was pressurized with CO to a desired value and the reaction was started by setting the agitation speed to 1000 rpm. The reaction was carried out at a constant pressure by feeding CO from a reservoir with the help of a constant pressure regulator. Progress of the reaction was monitored by measuring the change in CO pressure in the reservoir vessel as a function of time and also by intermediate sampling. The reaction was carried out for a specified time at the end of which, a small amount of the liquid phase was withdrawn and quantitatively analyzed by GC for reactants and products.

4.4. Analytical Methods

Elemental analysis of the complexes was carried out on a CHNS-O EA1108, Elemental analyzer of Carlo Erba Instruments, Italy. Liquid samples were analyzed on a Agilent 6890 Series GC, controlled by the HP Chemstation software, by using an HP-I capillary column of length 30 m, 320μm diameter, 0.25μm stationary phase film thickness (methyl siloxane as stationary phase, helium gas as mobile phase) and a flame ionization detector. Products were identified by comparison with standard samples (calibration data obtained from authentic samples of VMN, product esters and ether at four different concentrations). The standard conditions for GC analysis are given in Table 4.2. GC-MS analyses of the samples were performed using Agilent 5973 N Mass Selective Detector attachment. Molecular weight of the polymer (obtained as a by-product) was determined by GPC in chloroform as an eluent having six Ultra

♦ CO is poisonous hence safe and expert handling during experiments required

Styragel columns (50 to 10^5 Å porosities) and UV-100 and RI-150 detectors. Molecular weight (M_n) and polydispersities (M_w/M_n) were determined using a calibration curve obtained by polystyrene standards from PSS Germany.



1: Reactor; 2: Thermo well; 3: stirrer shaft with impeller; 4: magnetic stirrer; 5: liquid sampling valve; 6: internal cooling tube; TR1: Reactor temperature indicator; PR1: Reactor pressure indicator; TR2: Reservoir temperature indicator; PR2: Reservoir pressure indicator; N2: Nitrogen cylinder; CO: Carbon monoxide cylinder

Figure 4.2. A Schematic of the Reactor Setup

The conversion, selectivity and turnover frequency (TOF) were calculated as follows

$$\%\ Conversion = \frac{\left(Initial\ Concentration\ of\ substrate - Final\ Concentration\ of\ substrate\right)}{Initial\ Concentration\ of\ substrate} \times 100$$

$$\%\ Selectivity = \frac{No.\ of\ moles\ of\ carbonylation\ product\ formed}{No.\ of\ moles\ of\ substrate\ converted} \times 100$$

$$TON = \frac{No.\ of\ moles\ of\ carbonylation\ product\ formed}{No.\ of\ moles\ of\ catalyst\ used}$$

$$TOF, h^{-1} = \frac{No.\ of\ \ moles\ of\ \ carbonylation\ \ product\ \ formed}{No.\ of\ \ moles\ of\ \ catalyst\ used \times time\ in\ hours}$$

Table 4.2.Standard Conditions for GC Analysis

Injector Temperature	523 K		
Flame Ionization Detection Temp	523 K		
Inlet Flow Total (He)	20 ml/min		
Split Ratio for Injector	100:1		
Oven Temperature	Rate (K/min)	Temp (K)	Hold Time (min)
		423	0.5
	35	443	6
	40	523	3
	45	543	5
Column Pressure	13.50 psi		

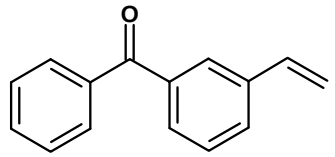
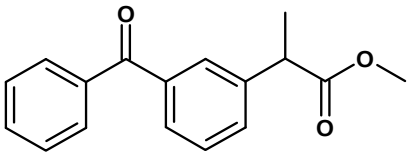
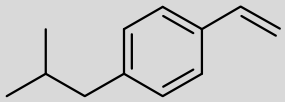
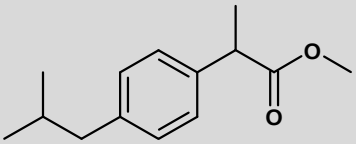
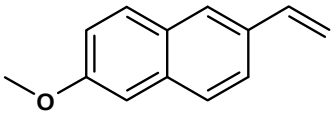
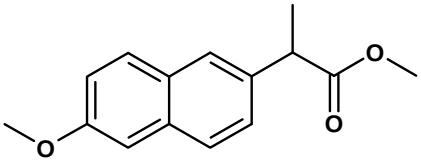
4.5. Results and Discussions

4.5.1. Hydroesterification of Important Substrates

Hydroesterification of few important substrates *viz.* 3-vinylbenzophenone (VBP, precursor for ketoprofen), 4-isobutyl styrene (IBS, precursor for ibuprofen), 2-vinyl-6-methoxynaphthalene (VMN, precursor for Naproxen) was carried out using Pd(pyca)(PPh_3)(OTs) as the catalyst precursor (Table 4.3). The reactions were performed in the presence 4-tert-butylcatechol as polymer inhibitor because the styrene derivatives (VBP, IBS, VMN) have the tendency to polymerize during reaction conditions. Products formed during hydroesterification were confirmed by GC-MS analysis, which indicated that desired products has formed for all the reactions. However since authentic samples of esters were not available, quantitative analysis was not carried out for these reactions. Hence results on the conversion of starting material are presented in Table 4.3, while details of product identification by GC-MS are presented in Appendix III.

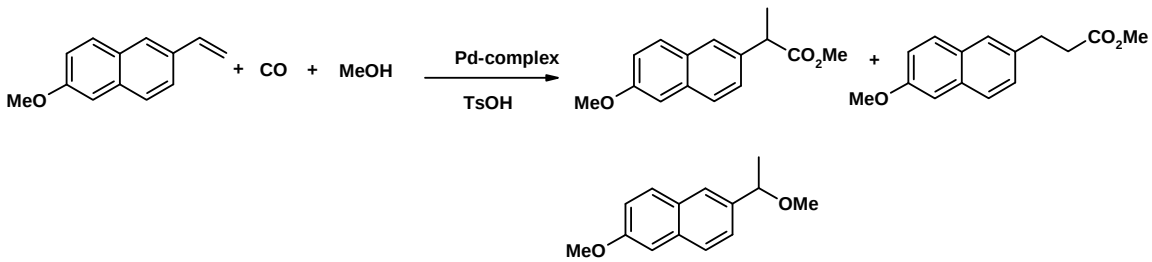
The substrate VMN was chosen for detailed investigation to present work on conceptual route for Naproxen synthesis from BMN. Detailed results on the Heck arylation of ethylene with BMN to VMN have been presented in Chapter 2. Methyl ester of Naproxen was prepared by esterification of authentic sample of Naproxen and was used for preparing calibration curve for quantitative analysis. A detailed investigation on the effect of various reaction conditions on the activity and selectivity was carried out and the results are presented below.

Table.4.3. Results of Hydroesterification of VBP, IBS and VMN

Substrate	Product	Conversion %
		80
		75
		74

Reaction Conditions: Substrate, 4.89 mmol; Pd(pyca)(PPh$_3$)(OTs),0.035 mmol; TsOH,0.35 mmol ; LiCl, 0.35 mmol; P_{CO} 4.1 MPa; T,348 K ; MeOH, 2ml ; Methyl ethyl ketone, 23 ml; 4-tert-Butylcatechol, 0.03 mmol; Time, 3h

The stoichiometric reaction of hydroesterification of VMN is shown Scheme 4.2. This reaction also forms other side products such as ether (2-methoxy-6-(1-methoxyethyl)naphthalene) and polymer which are discussed in the following sections.



Scheme 4.2. Hydroesterification of 2-vinyl-6-methoxynaphthalene

The GC-MS analysis showed the formation of methyl ester of Naproxen (methyl 2-(6-methoxy-2-naphthyl)propanoate) and its linear isomer (methyl 3-(6-methoxy-2-naphthyl)propanoate), and by-product ether (2-methoxy-6-(1-methoxyethyl)naphthalene, the products of a simple etherification reaction between the starting olefin VMN and alcohol). But the concentration-time profile for the hydroesterification reaction shown in the Figure 4.3, indicates that the material balance (75 % accounted) of these products formed is not complete when compared with the reactant consumed.

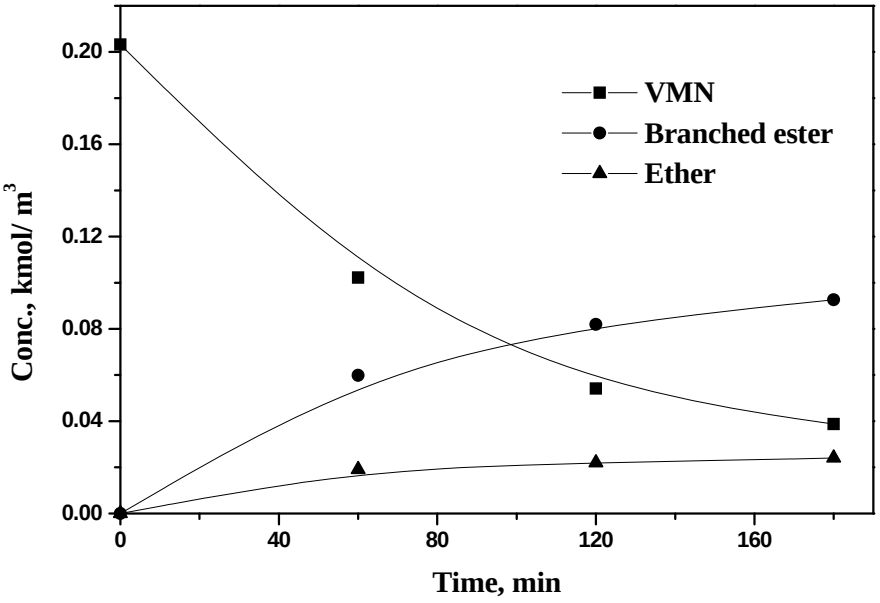


Figure 4.3. Concentration vs. Time profile for the hydroesterification of VMN

Reaction Conditions: VMN,4.89 mmol ; Pd(pyca)(PPh_3)(OTs),0.035 mmol ; TsOH,0.35 mmol ;LiCl, 0.35 mmol; P_{CO} 4.1 MPa, ; T,348 K ; MeOH, 2ml ; Methyl ethyl ketone, 23 ml; 4-tert-Butylcatechol, 0.03 mmol

The deviation in mass balance clearly indicates formation of other products during the reaction conditions that could not be identified by GC (previous literature results for this reaction do not show any concentration-time profile[8]). VMN is not stable compound and is known to undergo polymerization.[9] To quantify the deviation in mass balance; the reaction mixture was taken and the solvent was removed using rotavap. The residue obtained was washed thoroughly with methanol (the Pd-complex, promoters, ester product and ether are easily soluble in methanol). The residue was further given soxhlet treatment in methanol for 8 hrs and dried under vaccum. The resultant material

was analyzed by ^{1}H-NMR, ^{13}C-NMR (in $CDCl_3$ solvent), IR and GPC. The NMR spectrum of the material (Figure 4.7) showed broad signals for aromatic and methoxy protons and gave the clue for the possible formation of a polymeric material. This assumption was based on broad aromatic signals exhibited by the polymer poly(4-chloromethylstyrene).[10] For further understandings, the material was subjected to GPC analysis for the molecular weight determination. Measurements were carried out in chloroform at room temperature. The GPC analysis showed a single peak (Figure 4.4) and the weight average molecular weight was found to be 29027. The GPC result indicated that the polymerization has taken place that can be attributed to the high reactivity of the starting material under the reaction conditions.

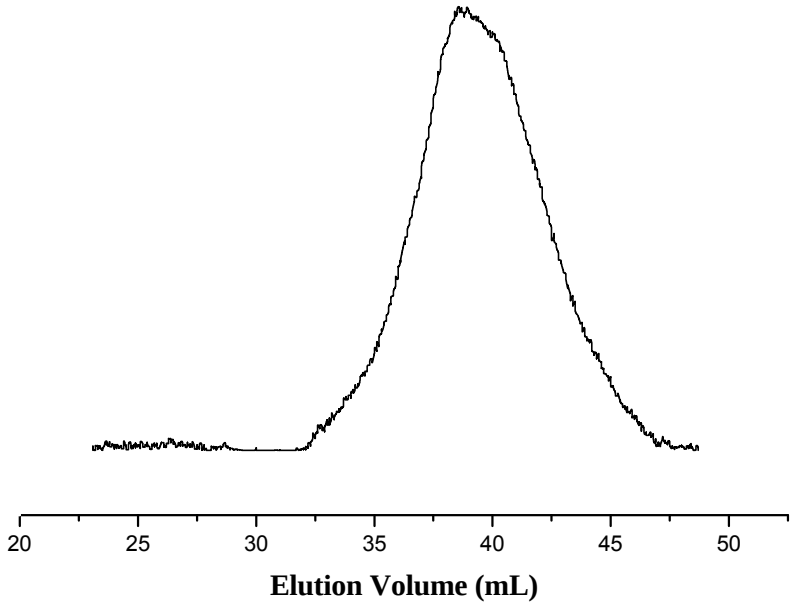


Figure 4.4. A Typical GPC Chart of poly(VMN)

M_n = 12360 (M_n = number average molecular weight)

M_w = 29027 (M_w = weight average molecular weight)

PDI = 2.347 (PDI is polydispersity index)

PDI = M_w / M_n

On comparing the NMR spectrums (Figure 4.6 & Figure 4.7) of pure VMN and poly(VMN) revealed the changes in the structure of the molecule. The VMN shows

doublet at 5.24, another doublet at 5.77 and quartet at 6.77 (δ ppm) for the olefinic protons of VMN. These characteristic protons for VMN disappeared and new broad peaks appeared for the poly(VMN) at δ 1.48 and at δ 1.87 ppm. The aromatic protons also appeared as broad signals in ^{1}HNMR for the poly(VMN). The evidence for linear structure was given by the comparison of integral ratio between methoxy group and aromatic group in ^{1}HNMR (Figure 4.7). The integral ratio is 1:2, which indicated that the obtained poly(VMN) is linear without any cross-linking.

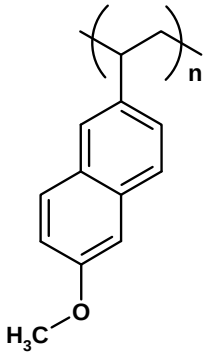


Figure 4.5. Structure of poly-VMN

The ^{13}CNMR (Figure 4.8) showed the peak values at δ ppm (29.67 (CH_2), 40.34 (-CH-), 55.13 (-OCH_3), 105.59, 118.20, 126.40, 128.76, 132.85, 140.04, 156.93), the ^{13}C-DEPT (Figure 4.9) showed disappearance of peaks at (132.85, 140.04, 156.93) and the peak at δ 29.67 ppm corresponds to methylene (-CH_2-) unit. The ^{13}C-NMR clearly shows that it does not contain any resonance peaks arising due to C=O functionality indicating that the polymer product is not a result of carbonylation reaction but a side reaction of olefinic substrate.

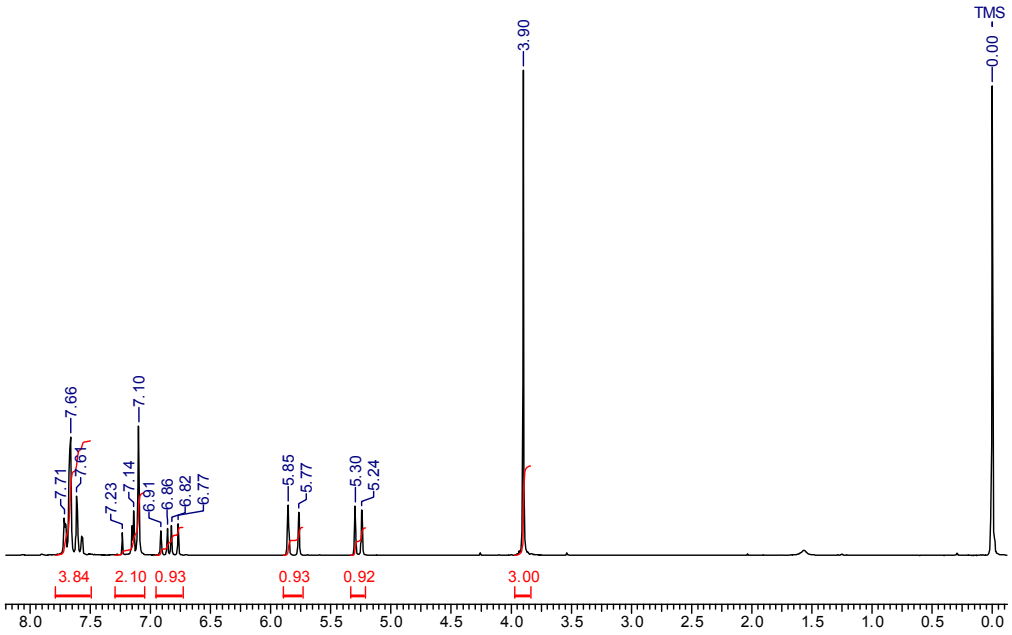


Figure 4.6. ^{1}HNMR of 2-vinyl-6-methoxynaphthalene

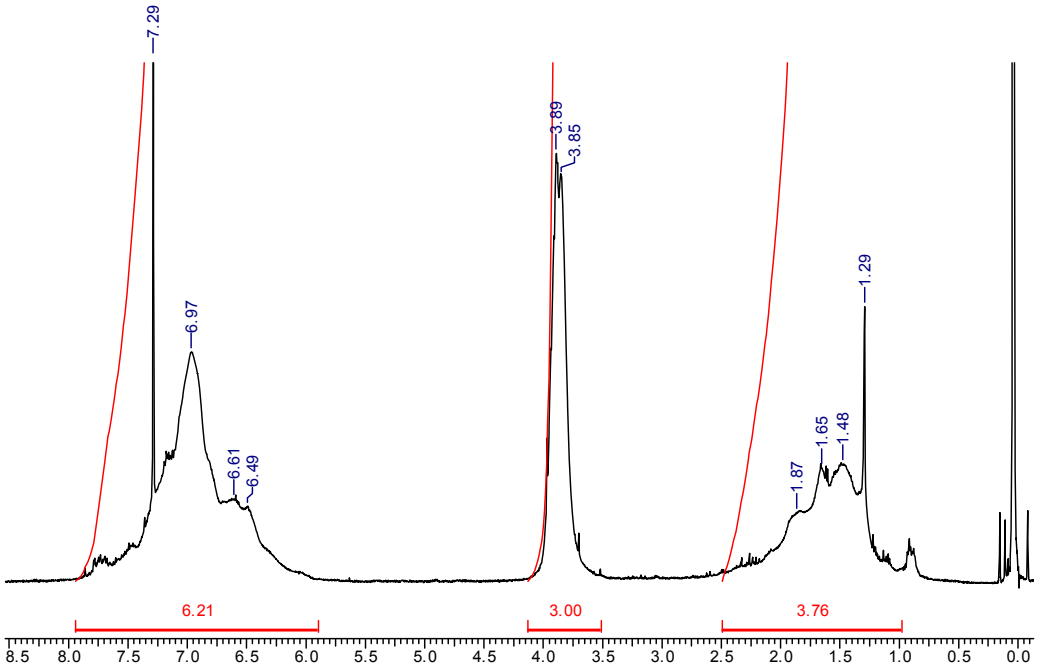


Figure 4.7. ^{1}H NMR (500 MHz) Spectrum of poly(VMN) (M_n = 12360, M_w / M_n = 2.347)

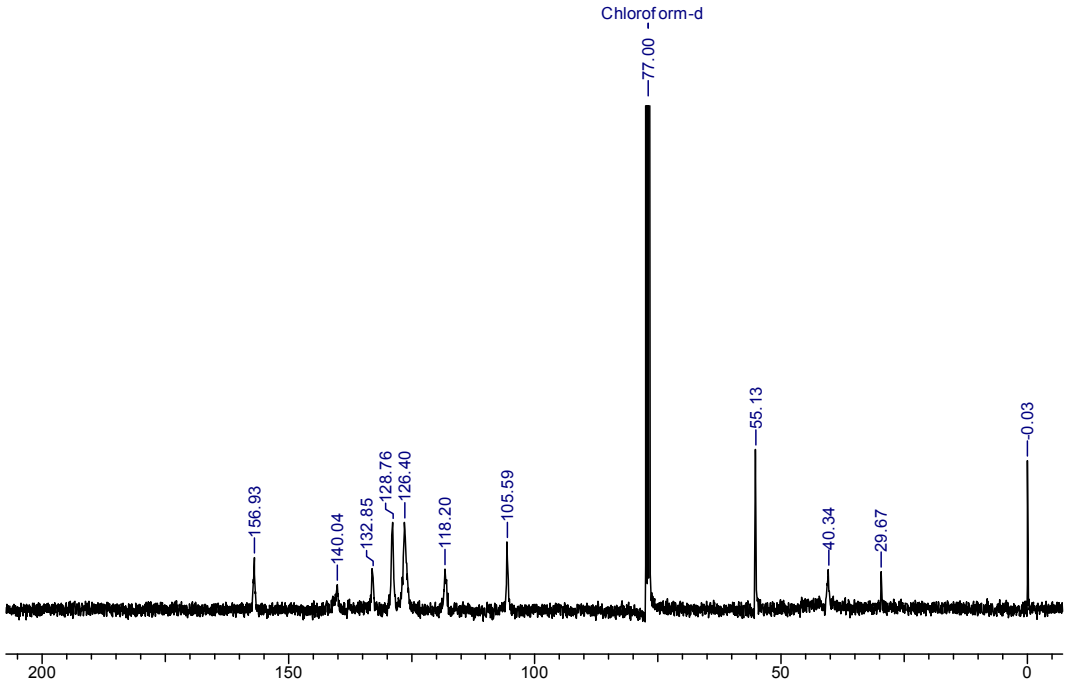


Figure 4.8. ^{13}C NMR (500 MHz) Spectrum of poly(VMN)

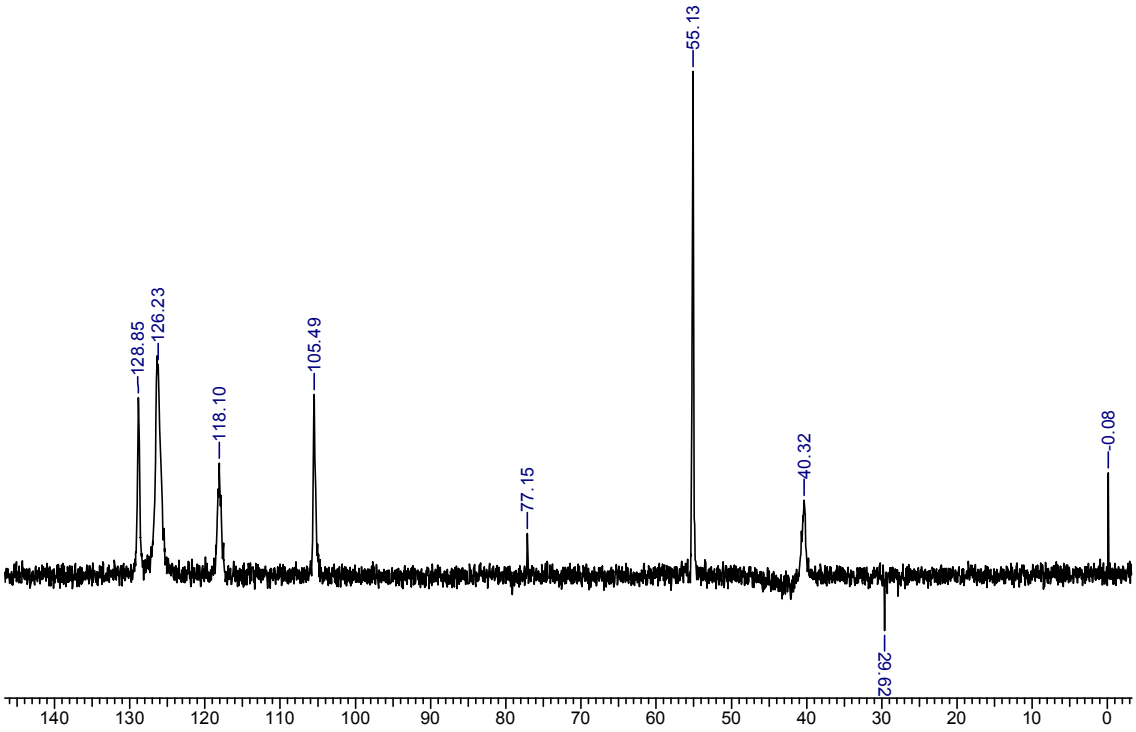


Figure 4.9. ^{13}C DEPT NMR (500 MHz) Spectrum of poly(VMN)

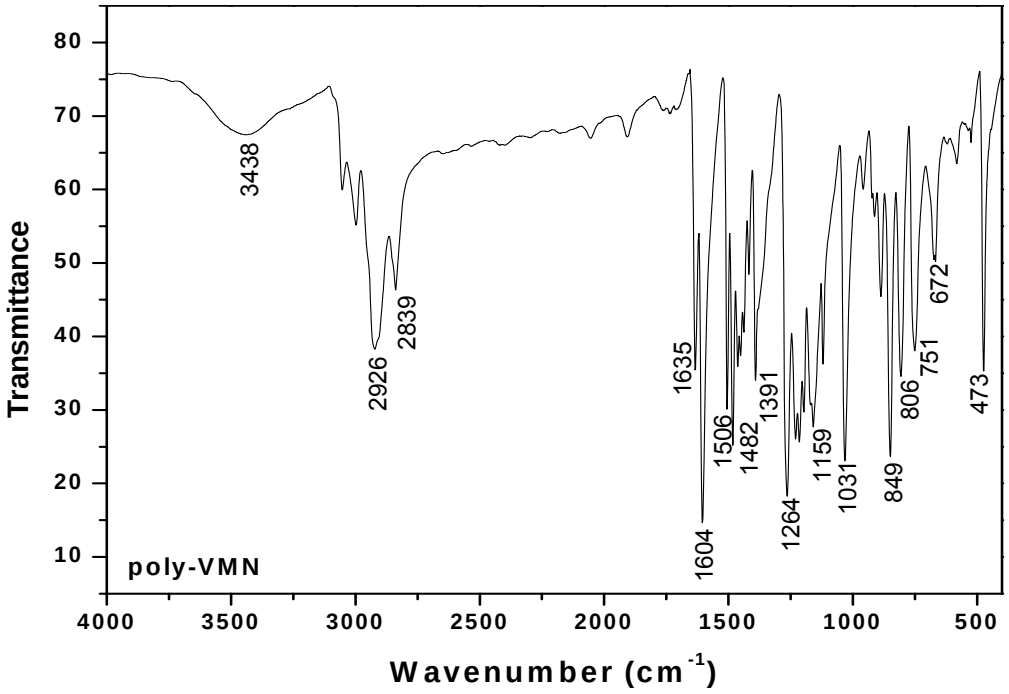
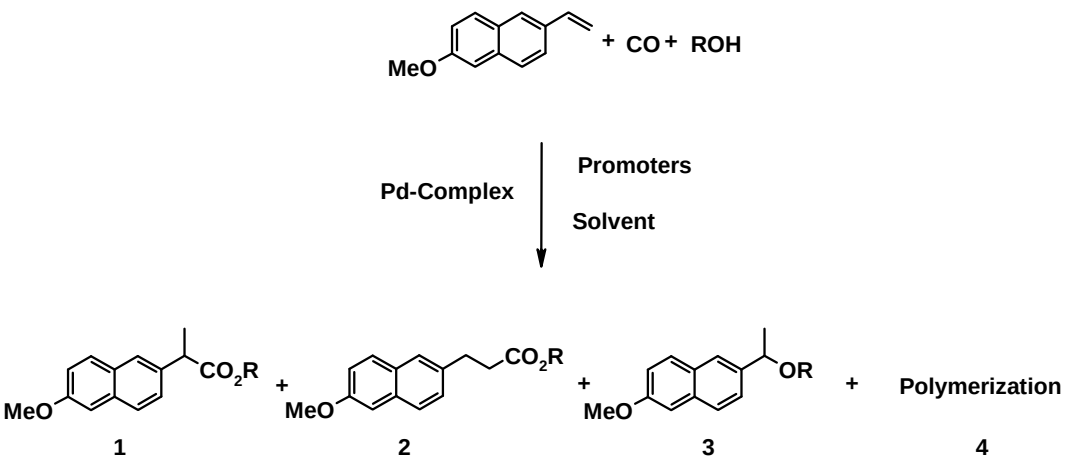


Figure 4.10. IR Spectrum of poly(VMN)

The IR spectra of the poly(VMN) is shown in the Figure 4.10. The IR spectra revealed the absence of C=O stretching vibrations, the peaks arising at 1635, 1604, 1506 cm^{-1} can be due to the C=C ring stretch. The aromatic C-H stretch shows peak at 3438 cm^{-1} and the methyl C-H stretch appears at 2926, 2839 cm^{-1}.

Thus four different products are formed during the hydroesterification of VMN (Scheme 4.3). The formation of polymer persists and could not be eliminated using t-butylcatechol as the polymerization inhibitor. Thus there is loss of selectivity because of the polymerization. All the results mentioned in this work are as per the GC analysis and the amount of deviation in the mass balance is assigned for the polymerized product.



Scheme 4.3. Different Products Formed in the Hydroesterification of VMN

4.5.2 Screening of Various Palladium Complexes

The results of hydroesterification using different catalyst system are presented in the Table 4.4. In all the reactions performed using different palladium complexes the formation of the polymer as well as ether products was observed. Relatively higher conversion and selectivity was exhibited by the complex $Pd(acpy)(PPh_3)(OTs)_2$. The complex with 2-acetylpyridine as a ligand showed better activity compared to that with 2-pyridine carboxylate ligand. One reason can be the cationic nature of $Pd(acpy)(PPh_3)(OTs)_2$ than the complex $Pd(pyca)(PPh_3)(OTs)$. The cationic comlpexes have shown high activity in the hydroesterification of styrene.[11] The high activity of such cationic complexes can be attributed to the availability of vacant coordination sites capable of easy activation of reactants. The cationic complexes $Pd(pycald)(PPh_3)(OTs)_2$ and $Pd(bpy)(PPh_3)(OTs)_2$ showed lower activity with conversions of 69 & 63% respectively in the hydroesterification of VMN. Taking $Pd(acpy)(PPh_3)(OTs)_2$ as the benchmark catalyst, the effect of various reaction parameters was studied in the hydroesterification to obtain the optimum reaction conditions, and to reduce the undesirable side reactions.

Table 4.4. Results of Hydroesterification with Different Catalyst Systems

entry	Catalyst precursor	Conv. %	Time, h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	$Pd(pyca)(PPh_3)(OTs)$	74	3	63	0.51	10.8	25	21
2	$Pd(pycald)(PPh_3)(OTs)_2$	69	3	54.4	0.25	15.2	30	17
3	$Pd(acpy)(PPh_3)(OTs)_2$	84	3	63.5	0.6	10.8	25	24
4	$Pd(bpy)(PPh_3)(OTs)_2$	63	3	53.6	0.51	18.7	27	15

Reaction Conditions: VMN,4.89 mmol ; Pd-complex,0.035 mmol ; TsOH, 0.35 mmol ;LiCl,0.35 mmol ; P_{CO}, 4.1 MPa; T,348 K ; MeOH,2 ml ; Methyl ethyl ketone, 23 ml;4-tert-Butylcatechol, 0.03 mmol

4.6 Parametric Effects

4.6.1 Effect of Acid and Halide Promoter

Based on the earlier results on the carbonylation of styrene,[2] reactions with VMN were carried carried out using $Pd(acpy)(PPh_3)(OTs)_2$ as catalyst precursor, TsOH as acid promoter and LiCl as the halide promoter (Table 4.5). From the results (Table 4.5) it can be clearly seen that both the promoters are necessary for good catalytic activity. With only TsOH as a promoter, conversion was very low (19 %) with significant formation of ether (41.7 %) and polymer (20 %) as by-products and 31.4% selectivity to desired branched ester. Formation of ether and polymer as by-products is expected based on literature reports. This also indicates that polymerization as well as etherification are dominant compared to hydroesterification reaction. With LiCl as the only promoter conversion was very low (17 %) with very high (90.4 %) selectivity to desired branched ester and no polymer formation. However, formation of ether (9.5 %) as a by-product in the absence of acid promoter probably indicates that Pd catalysts may be involved in this reaction. With the use of both the promoters, conversion increased significantly (84 %) in 3 h reaction time with 63.5 % selectivity to desired branched ester. However, in this case polymer (20 %) as well as ether (10.8 %) formation in good quantities was observed. Thus the results of VMN hydroesterification convey that both acid and halide promoters are required to enhance the catalytic activity.

Table 4.5. Results of Effect of Promoter on the Hydroesterification Reaction

No	Promoter	Conv., %	Time h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	TsOH	19	3	31.4	6.7	41.7	20	2
2	LiCl	17	3	90.4	-	9.5	-	7
3	TsOH + LICl	84	3	63.5	0.6	10.8	25	24

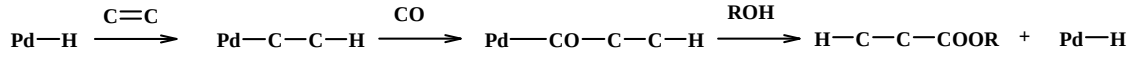
Reaction Conditions: VMN,4.89 mmol ;Pd(acpy)(PPh_3)$(OTs)_2$,0.035 mmol ; TsOH,0.35 mmol ;LiCl, 0.35 mmol; P_{CO} 4.1 MPa, ; T,348 K ; MeOH, 2ml ; Methyl ethyl ketone, 23 ml; 4-tert-Butylcatechol, 0.03 mmol

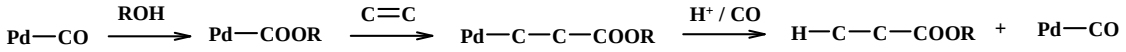
In contrast for styrene hydroesterification reported in the literature, [11] good activity was observed without any halide promoter, VMN substrate on the other hand does require the halide ion as the promoter. With styrene as a substrate, no ether and polymer formation was observed whereas VMN is prone to form the ether as well as polymerization. One more difference is that the with styrene as a substrate hydroesterification leads to the *n*-ester (methyl-3-phenyl propionate) as well as *iso*-ester (methyl-2-phenyl propionate) in substantial amounts compared to VMN hydroesterification which forms *iso*-ester (methyl 2-(6-methoxy-2-naphthyl)propanoate) as the major product. The differences are summarized in the Table 4.6. These results imply that the structure of the reactants can change the activity as well as selectivity for the hydroesterification reaction.

Table 4.6. The Differences in the Chemical Reactivity for Styrene and VMN in Hydroesterification Reactions

Chemical reaction	**Styrene (literature reports)[11]**	**2-vinyl-6-methoxynaphthalene (present work)**
Ether formation	No	Yes (10 %)
Polymer formation	No	Yes (20%)
n-ester	Substantial amounts (60 %)	Minor amount (5 %)
iso-ester	Substantial amounts (40 %)	Major product (65 %)

In the hydroesterification of styrene as described by Jayasree et al[7] promoters such as TsOH, LiCl etc. were used along with palladium complex Pd(pyca)(PPh_3)(OTs) as the catalytic system. In the presence of only TsOH promoter and palladium complex the reaction showed the selectivity of 37% towards the iso ester (methyl-2-phenylpropionate) and 63% towards linear ester (methyl-3-phenylpropionate). When the TsOH was replaced with LiCl, the selectivity of branched ester increased to 61.5 % (from 37%), whereas the linear ester decresed to 38.4% (from 63%). The simultaneous presence of both TsOH and LiCl showed the iso ester selectivity of 64% and linear selectivity of 36%. Comparison of the literature reports on styrene[7] and present results show that in both cases use of LiCl as a promoter gave higher selectivity to iso ester. In case of VMN iso ester is preferred and even with acid promoter (TsOH) iso ester is obtained in good quantity. Use of both the promoters results in good selectivity to branched ester. Thus, the presence of chloride ions was found to enhance the selectivity of the iso product, Jayasree et al[7] have explained the observed difference in the selectivity with and without LiCl based on the possible involvement of different types of palladium complexes as the active species in each case. In the presence of TsOH, the active species can be palladium hydride as shown in the Scheme 4.4. In the presence of LiCl, it is possible that majority of the Pd-H species formed are easily converted to the corresponding chloro derivatives by displacement with strongly coordinating Cl^- ions. Such instability of Pd-H complexes in the presence of halide ions was reported earlier.[12] Consequently, the catalytic cycle operating with hydridopalladium complex as the active species may decrease considerably or may be even arrested. In such cases, palladium carbomethoxy complexes can be the major active species.





Scheme 4.4. Two kind of Mechanisms for the Hydroesterification Reaction

In the hydroesterification of VMN it is likely that carbomethoxy complexes are the major active catalytic species, as the simultaneous presence of both LiCl and TsOH showed a selectivity of 63.52% towards the Naproxen ester. The hydride mechanism can not

be overruled completely without detailed investigations. Also the system has complications of significant ether and polymer formation.

4.6.2 Screening of Acid Promoters

Since the hydroesterification reaction required the combination of both the acid and halide promoter, different promoters were tested along with $Pd(acpy)(PPh_3)(OTs)_2$ for good activity and selectivity for the reaction. For this purpose the halide promoter LiCl was fixed and the acid promoters were varied. The results using different acidic promoters for the hydroesterification are presented in Table 4.7. Good conversions of 96% were obtained with benzenesulfonic acid as compared to the *p*-toluene sulfonic acid (84%) (*p*-toluenesulfonic acid is considered as one of the important promoter in the carbonylation reactions[2]). Though the conversions with benzenesulfonic acid was higher (96%) there was not much difference in the selectivity with different promoters. Other sulfonic acids viz. Methanesulfonic acid, trifloromethanesulfonic acid also gave good conversions (80-88 % conversion).

Table 4.7. Influence of Acid Promoter on Reaction Performance

No	Promoter	Conv %	Time, h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	*p*-toluenesulfonic acid	84	3	63.5	0.6	10.8	25	24
2	Methanesulfonic acid	88	3	57.3	0.52	7	35	23
3	Benzenesulfonic acid	96	3	63	0.5	5.9	30	28
4	Trifloromethanesulfonic acid	80	3	54.7	0.71	9.5	35	20
5	Trifloroacetic acid	72	3	68.6	1.4	1.7	28	23

Reaction Conditions: VMN,4.89 mmol ;$Pd(acpy)(PPh_3)(OTs)_2$,0.035 mmol ; Acid Promoter,0.35 mmol , ;LiCl,0.35 mmol ; P_{CO}, 4.1 MPa; T,348 K ; MeOH,2 ml ; Methyl ethyl ketone, 23 ml; 4-tert-Butylcatechol, 0.03 mmol

The order of reactivity of the acid promoters in the hydroesterification of VMN was observed as: Benzenesulfonic acid > Methanesulfonic acid > *p*-toluenesulfonic acid > Trifloromethanesulfonic acid > Trifloroacetic acid. Further work was carried using benzenesulfonic acid as the promoter.

4.6.3 Effect of Different Halide Promoters

Having found benzenesulfonic as the promoter of choice, different halide promoters were screened for hydroesterification of VMN and the results are presented in the Table 4.8. Quarternary ammonium salts such as Bu_4NBr and Bu_4NI favored the formation of ether (2-methoxy-6-(1-methoxyethyl)naphthalene) and gave poor conversion (24-55 %). Quarternary ammonium salts are phase transfer catalysts and their applications in the etherification reactions have been demonstrated (for other substrates) previously.[13] Excellent conversions of 96% and selectivity of 63% were observed using LiCl as the promoter. The use of NaCl was also found suitable for this reaction and the reaction is slow as compared to LiCl. Halide ions also play a major role on the carbonylation reaction. Branched esters were favored with strongly coordinated Cl^-, however while the weakly bound one such as Br^- and I^- used favored the linear ester as well as the ether formation. Further work was carried out using LiCl as the promoter.

Table 4.8. Influence of Halide Promoter on Reaction Performance

No	Promoter	Conv. %	Time h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	LiCl	96	3	63	0.5	5.9	30	28
2	Bu_4NBr	58	3	45.7	2.9	24.3	27	12
3	Bu_4NI	29	3	19.6	5.6	54.7	20	2
4	NaCl	72	3	68.8	2.25	3.7	25	23

Reaction Conditions: VMN,4.89 mmol ; Pd(acpy)(PPh_3)($OTs)_2$,0.035 mmol ; Benzene sulfonic acid,0.35 mmol; Halide promoter, 0.35 mmol ; P_{CO}, 4.1 MPa; T,348 K ; MeOH,2 ml ; Methyl ethyl ketone, 23 ml; 4-tert-Butylcatechol, 0.03 mmol

4.6.4 Effect of Benzenesulfonic acid:LiCl ratio

The perfect combination of benzenesulfonic acid to lithium chloride is of considerable importance to tune the reaction to the desired product (excess of the acid promoter can lead to the undesired side reactions such as formation of ether and polymerization). Effect of benzenesulfonic acid : LiCl ratio on hydroesterification of VMN was investigated and the results are presented in Table 4.9. It was found that

with excess of acid promoter, entry 2 the ether formation was marginally reduced (<3%); and observed results can be explained as shown in Scheme 4.5. Thus increase in the selectivity towards the branched ester was observed. The conversion of 95% was obtained in 3 h. With excess of lithium chloride, entry 4 the conversion of 96% could be achieved in a shorter time of 2 h. Excess chloride ions can serve as ligand of an active palladium complex, which leads to high activity. The catalyst precursors containing chloride as the anion have shown good conversions in the hydrocarboxylation of styrene.[14,15] There was no large difference in the selectivity pattern for the reaction. An optimal ratio of the promoters as shown in the entry 4 was found to be ideal (H^+ : Cl^- = 0.35 : 0.7) and further reaction parameters were studied.

Table 4.9.Effect of Promoters in the Hydroesterification of 2-vinyl-6-methoxynaphthalene

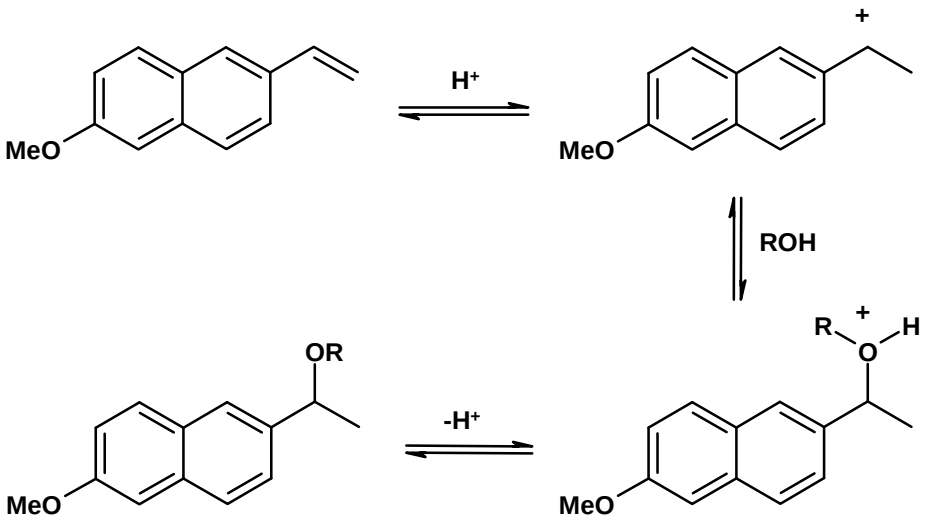
No	H^+ : Cl^- ratio	Conv., %	Time h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	0.175 : 0.35	89	3	59.54	1.09	4.29	35	24
2	0.7 : 0.35	95	3	71.7	0.9	2.1	25	31
3	0.35 : 0.35	96	3	63	0.5	5.9	30	28
4	0.35 :0.7	96	2	63	0.9	5.9	30	42
5	0.35 :0.175	82	3	68.4	2.9	3.6	25	26

Reaction Conditions: VMN,4.89 mmol ; Pd(acpy)(PPh$_3$)(OTs)$_2$,0.035 mmol ; P_{CO}, 4.1 MPa; T,348 K ; MeOH,2 ml ; Methyl ethyl ketone, 23 ml; 4-tert-Butylcatechol, 0.03 mmol ; H^+ = Benzenesulfonic acid, Cl^-= LiCl

4.6.5 Effect of Different Alcohols

Various alcohols were screened for the hydroesterification of VMN and the results are presented in the Table 4.10. Methanol was found to be the alcohol of choice in hydroesterification because of its high polarity and low bulkiness. With increase in the carbon length of the alcohol (decreasing the polarity of alcohol), the selectivity towards the branched ester decreased and ether formation increased. The substantial ether formation observed with 2-vinyl-6-methoxynaphthalene could be explained by the resonance effect of the electron-donating methoxy group that stabilizes carbocation

intermediate, Scheme 4.5.[16] The carbocation then reacts with the alcohol giving ether. Use of sterically hindered *t*-buytlalcohol gave lower conversion of 16%. On increasing the carbon length of alcohol from methanol to *n*-Butanol the selectivity of 1 decreased from 63 to 47.6 %, whereas the selectivity to ether increased from 5.9 to 21 %.



Scheme 4.5. The Formation of Ether by the Acid-Catalyzed Reaction of VMN and Alcohols

Table 4.10.Effect of Alcohols in the Hydroesterification of 2-vinyl-6-methoxynaphthalene

No	Alcohol	Conv., %	Time h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	Methanol	96	2	63	0.9	5.9	30	42
2	Ethanol	96	2	60.2	2.8	6.9	30	40
3	*n*-Propanol	91	2	55	2.1	12.6	30	34
4	*n*-Butanol	97	2	47.6	1.1	21	30	32
5	*t*-butylalcohol	16	2	-	-	-	-	-

Reaction Conditions: VMN,4.89 mmol ; Pd(acpy)(PPh_3)($OTs)_2$,0.035 mmol ; Benzene sulfonic acid,0.35 mmol ;LiCl, 0.7 mmol ; P_{CO}, 4.1 MPa; T,348 K ; Alcohol,2 ml ; Methyl ethyl ketone, 23 ml; 4-tert-Butylcatechol, 0.03 mmol

4.6.6 Effect of Different Solvents

The hydroesterification was investigated using a variety of organic solvents and the results are presented in Table 4.11. The reaction was faster in solvents like toluene and methylethylketone, the use of basic solvents like N,N-dimethylformamide strongly disfavored the hydroesterification reaction. Toluene as a solvent gave substantial amounts of ether. The differences in selectivity upon changing the solvent are difficult to rationalize at this point. Using methanol as the solvent, the activity was lower (65% conversion) the reaction afforded both the linear (10.4%) and branched ester (10.4%), and predominantly forms the ether product. The substrate VMN is insoluble in methanol as well as acetone at room temperature. Good activity (96 % conversion) and selectivity (63%) was observed using 2-butanone as the solvent. Previous report on the hydroesterification of styrene[11] showed methanol as the best solvent system, however hydroesterification of VMN using methanol afforded poor conversion (65%) with low selectivity towards the desired product.

Table 4.11.Effect of Solvents in the Hydroesterification of 2-vinyl-6-methoxynaphthalene

No	Solvent	Conv., %	Time h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	Toluene	98	2	62.9	1.12	20.24	15	43.9
2	Methyl ethyl ketone	96	2	63	0.9	5.9	30	42
3	Acetone	84	2	58.2	1.3	5.2	35	40.6
4	Methanol	65	2	10.4	10.4	54	25	7.2
5	N,N-dimethylformamide	No rxn.	2	-	-	-	-	-

Reaction Conditions: VMN,4.89 mmol ; Pd(acpy)(PPh_3)($OTs)_2$,0.035 mmol ; Benzene sulfonic acid,0.35 mmol; LiCl, 0.7 mmol ; P_{CO}, 4.1 MPa; T,348 K ; MeOH, 2 ml ; Solvent, 23 ml; 4-tert-Butylcatechol, 0.03 mmol

4.6.7 Effect of Reaction Temperature

The hydroesterification was studied in a temperature range of 328 to 368 K, and the results are presented in the Table 4.12. At 328 K there was exclusive formation of the branched ester (88% vs 60-65% at other temperatures) and without forming any polymer, but the conversion was 50%. For the temperature in a range of 338 to 358 K, the conversion increased but there was no significant difference in the selectivity pattern for the products obtained. However, further increase in the temperature above 358 K, caused the decrease in activity, indicating the lower stability of the catalytically active species at higher temperatures. The temperature of 338 K was chosen and further studies were carried out.

Table 4.12. Effect of Reaction Temperature in the Hydroesterification of 2-vinyl-6-methoxynaphthalene

No	Temp, K	Conv., %	Time h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	328	50	3	88	-	12	-	20
2	338	90	2	67.8	0.7	7.1	25	42
3	348	96	2	63	0.9	5.9	30	42
4	358	98	2	62.1	1	6.6	30	42
5	368	70	2	58.4	2.2	14.1	25	28

Reaction Conditions: VMN,4.89 mmol ; Pd(acpy)(PPh_3)($OTs)_2$,0.035 mmol ; Benzene sulfonic acid,0.35 mmol ;LiCl, 0.7 mmol ; P_{CO}, 4.1 MPa; MeOH,2 ml ; MEK, 23 ml; 4-tert-Butylcatechol, 0.03 mmol

4.6.8 Effect of Amount of Methanol

Since ether formation was the undesirable side reaction, the judicious use of methanol can decrease the ether formation. The results on the effect of amount of methanol on the hydroesterification reaction are presented in the Table 4.13. It was seen that with decrease in the amount of methanol the formation of ether was reduced (7.1 to 0.4 %) and thus there was increase in the selectivity of the branched ester (67.8-87.5%). The rate of the carbonylation reaction also decreases with decrease in

the methanol amount as is evident from the Table 4.13. that the reaction takes longer time for the completion (entry 4 & 5).

Table 4.13. Effect of Amount of Methanol at 338 K

No	Methanol, ml	Conv., %	Time h	Selectivity, %				TOF h^{-1}
				1	2	3	4	
1	2	98	2	67.8	0.7	7.1	25	30
2	1	95	3	71.8	0.3	2.7	25	31
3	0.8	95	3.5	72	0.75	2.2	25	27
4	0.5	80	3.5	78	0.72	1.0	20	25
5	0.25	70	3.5	87.5	-	0.4	12	24

Reaction Conditions: VMN,4.89 mmol ; Pd(acpy)(PPh_3)$(OTs)_2$,0.035 mmol ; Benzene sulfonic acid,0.35 mmol ; LiCl, 0.7 mmol ; P_{CO}, 4.1 MPa; MEK, 23 ml; 4-tert-Butylcatechol, 0.03 mmol

4.6.9 Effect of Catalyst Loading and Carbon monoxide Pressure

Effect of catalyst loading and carbon monoxide pressure was studied at a temperature of 338 K and 0.5 ml of methanol, selectivity towards the linear ester and ether are low under these reaction conditions. When the catalyst loading was doubled keeping the reaction conditions constant, the conversion increased however the polymerization formation was not reduced. The concentration time-profile of these reactions are showed in Figure 4.11 & Figure 4.12. (NPN is the methyl ester of naproxen).

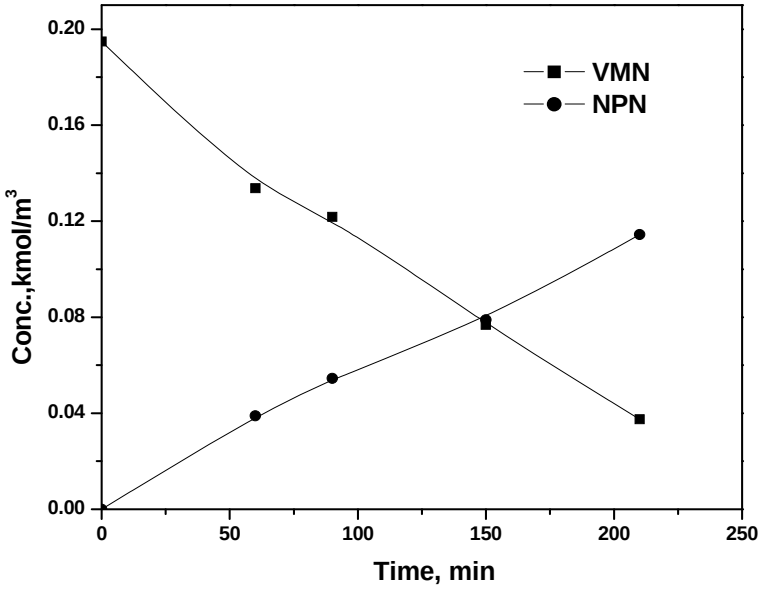


Figure 4.11.Concentration Time Profile for Pd(acpy)(PPh_3)$(OTs)_2$ Loading of 0.035 mmol and 4.1 MPa CO

Reaction Conditions: VMN,4.89 mmol ; Benzene sulfonic acid,0.35 mmol; LiCl, 0.7 mmol ; MEK, 23 ml; 4-tert-Butylcatechol, 0.03 mmol; T, 338 K

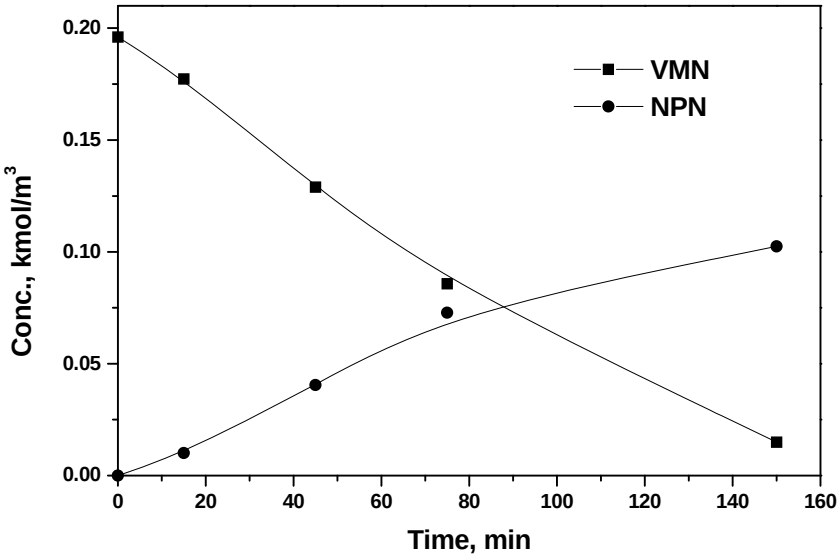


Figure 4.12. Concentration Time Profile for Pd(acpy)(PPh_3)$(OTs)_2$ Loading of 0.07 mmol and 4.1 MPa CO

Reaction Conditions: VMN,4.89 mmol ; Benzene sulfonic acid,0.35 mmol; LiCl, 0.7 mmol ; MEK, 23 ml; 4-tert-Butylcatechol, 0.03 mmol; T, 338 K

When the carbonmonoxide pressure was increased from 4.1 MPa to 5.5 MPa, so as to increase rate of carbonylation and minimize the polymerization, however significant polymer formation was observed. The concentration-time profile for the reaction carried at 5.5 MPa is shown in the Figure 4.13.

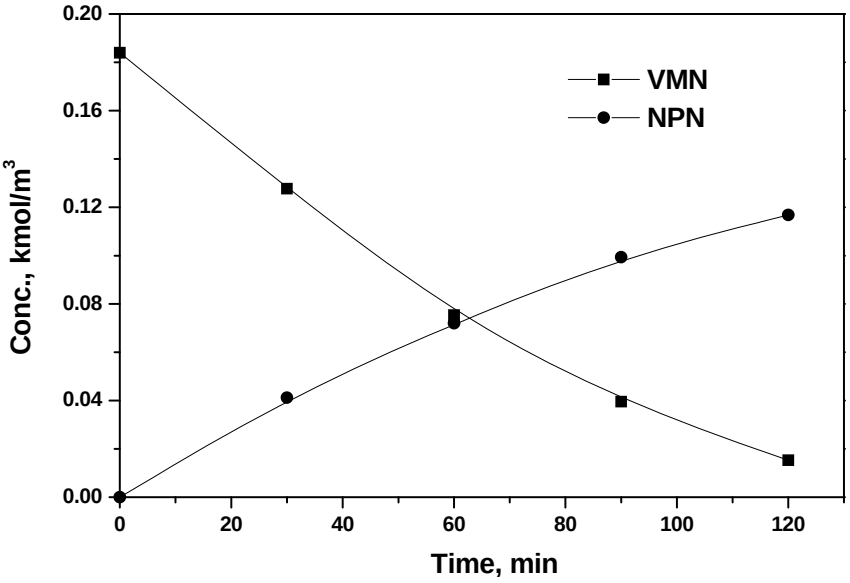


Figure 4.13. Concentration Time Profile for Pd(acpy)(PPh_3)$(OTs)_2$ Loading of 0.07 mmol and 5.5 MPa CO

Reaction Conditions: VMN,4.89 mmol ; Benzene sulfonic acid,0.35 mmol; LiCl, 0.7 mmol ; MEK, 23 ml; 4-tert-Butylcatechol, 0.03 mmol; T, 338 K

The above reactions were performed by charging the reactor with the requisite amount of reagents and flushing the reactor with nitrogen to remove the traces of air inside the reactor. The reactor was heated by placing it on an heating mantle. After acquiring the desired temperature the CO gas was filled and reaction started at agitation of 1000 rpm. In this process the reactant VMN which is having an electron-donating methoxy group is exposed under the reaction conditions of benzenesulfonic acid and lithium chloride till the reaction temperature is attained. There are chances that proton can serve as the initiator for the polymerisation. So, in one experiment the CO gas was filled initially and pressurized with desired pressure and heated to required temperature and the reaction was monitored by withdrawing samples at regular intervals of time and

analysing by gas-chromatography immediately. The results (Fig. 4.14) showed the reactant conversion of 96% and the selectivity of the desired branched ester is 67%.

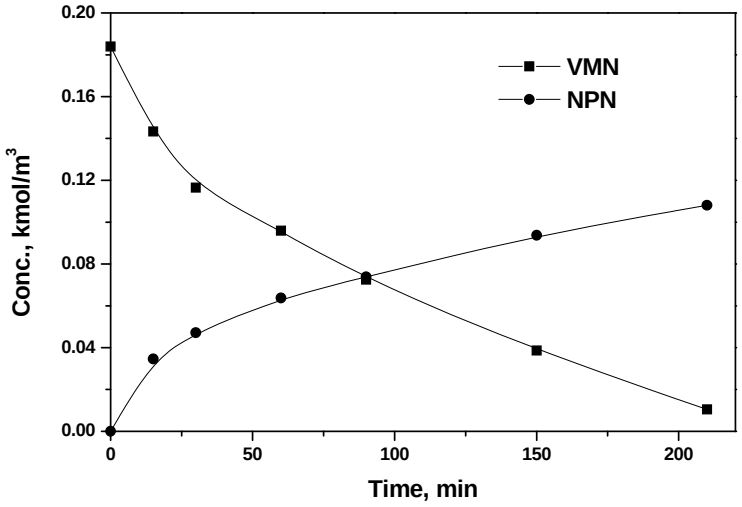


Figure 4.14. Concentration Time Profile for Pd(acpy)(PPh_3)($OTs)_2$ Loading of 0.07 mmol and 4.1 MPa CO, the Gas was Filled at Room Temperature

Reaction Conditions: VMN,4.89 mmol ; Benzene sulfonic acid,0.35 mmol; LiCl, 0.7 mmol ; MEK, 23 ml; 4-tert-Butylcatechol, 0.03 mmol; T, 338 K

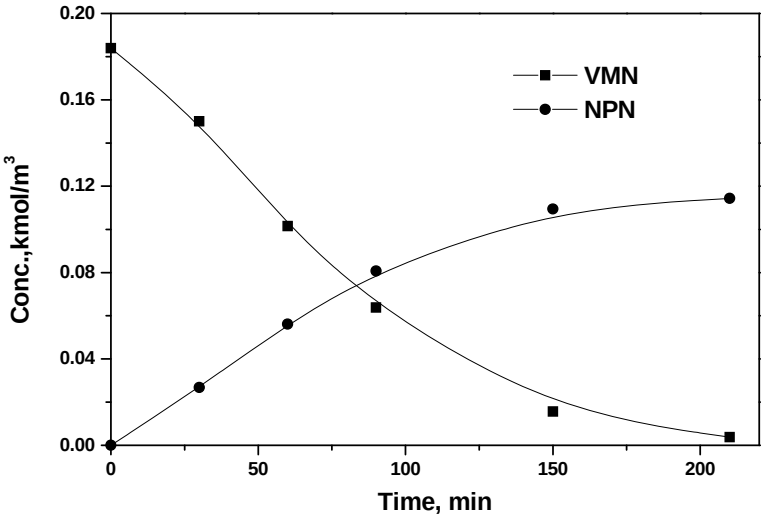


Figure 4.15. Concentration Time Profile for Pd(acpy)(PPh_3)($OTs)_2$ Loading of 0.035 mmol and 5.5 MPa CO

Reaction Conditions: VMN,4.89 mmol ; Benzene sulfonic acid,0.35 mmol; LiCl, 0.7 mmol ; MEK, 23 ml; 4-tert-Butylcatechol, 0.03 mmol; T, 338 K

Table 4.14. Effect of Catalyst Loading and Pressure on the Hydroesterification

Catalyst	Press	Conv	Methanol	Time	Selectivity				TOF
mmol	MPa	%	ml	h	1	2	3	4	h^{-1}
0.035	4.1	80	0.5	3.5	78	0.7	1	20	25
0.07	4.1	92	0.5	2.5	62	1	2	35	17.3
0.07	5.5	92	0.5	2	67	1	2	30	23.4
0.07[a]	4.1	94	0.8	3.5	67	1	2	30	13.3
0.035	5.5	97	0.8	3.5	67	1	2	30	26

Reaction Conditions: VMN,4.89 mmol ; Benzene sulfonic acid, 0.35 mmol; LiCl, 0.7 mmol ; MEK, 23 ml; T, 338 K; 4-tert-Butylcatechol, 0.03 mmol; Catalyst, Pd(acpy)(PPh_3)($OTs)_2$; [a] CO was filled at room temperature and reaction started

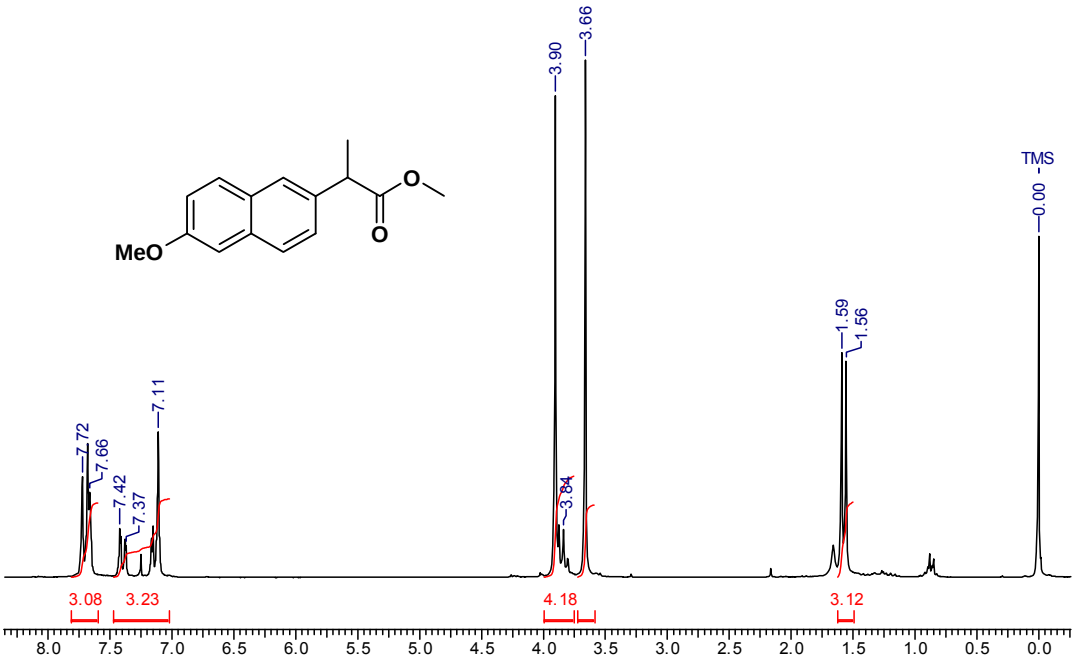
The results of the reaction are also presented in Table 4.14. Thus under these reaction conditions the formation of polymerization could not be suppressed.

4.7. Conclusions

Hydroesterification of VMN has been investigated using palladium complexes containing different nitrogen ligands. Presence of acid and halide promoters was necessary for high catalytic activity and good selectivity to branched ester. Best results were obtained using benzenesulphonic acid and LiCl as promoters. Effect of various reaction conditions on the activity and selectivity was investigated and it was observed that ether and polymer formed as by-products under all reaction conditions. Ether formation was suppressed with decrease in methanol concentration. Polymer formed was characterized by GPC and NMR analysis. Various alcohols were screened and with *t*-butanol as a reactant product formation was not observed. Selectivity to branched ester was found to decrease with increase in chain length of the carbon for alcohols screened. Temperature was found to have significant effect on the reaction and polymer formation was not observed at 328 K with 88% selectivity to iso ester. Selectivity to iso ester decreased with increase in temperature of the reaction. This is the first report on the use of palladium complexes containing nitrogen ligands for hydroesterification of VMN.

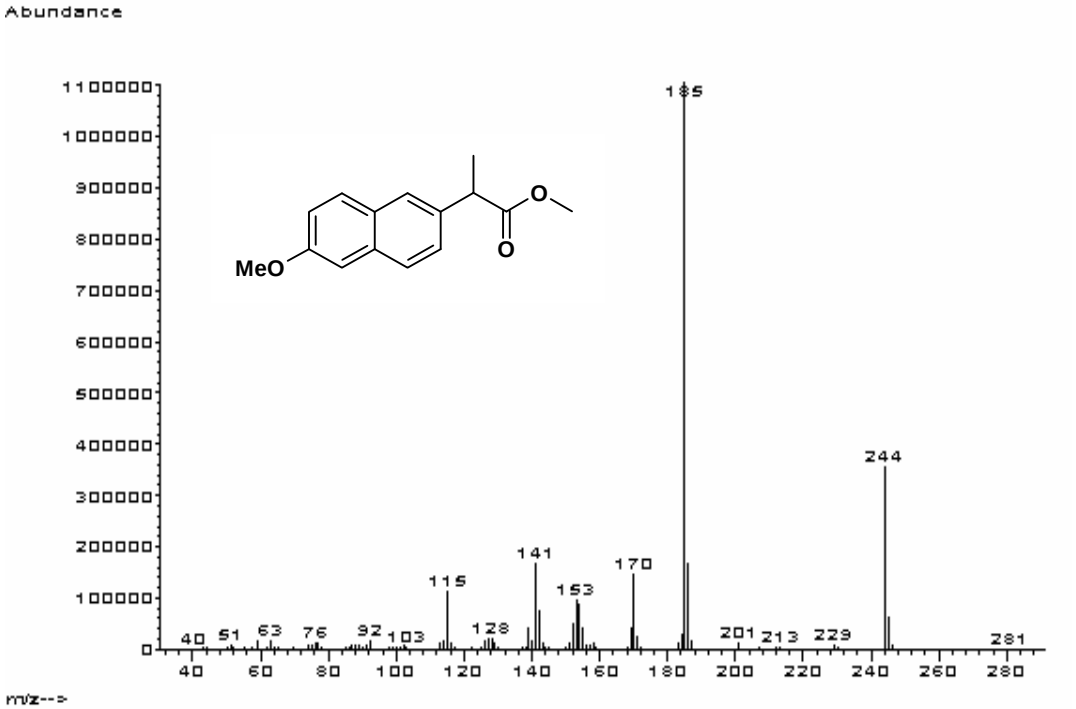
Appendix III

^{1}H NMR of methyl-2-(6-methoxy-2-naphthyl)propanoate

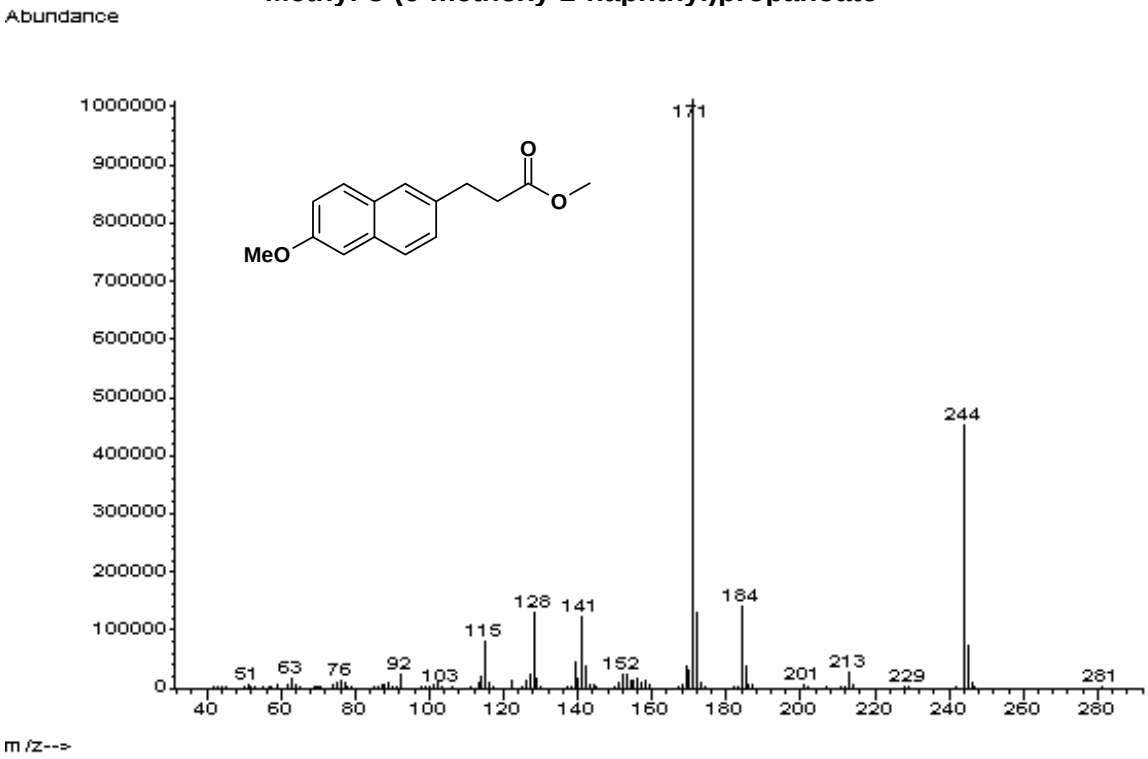


GC-MS

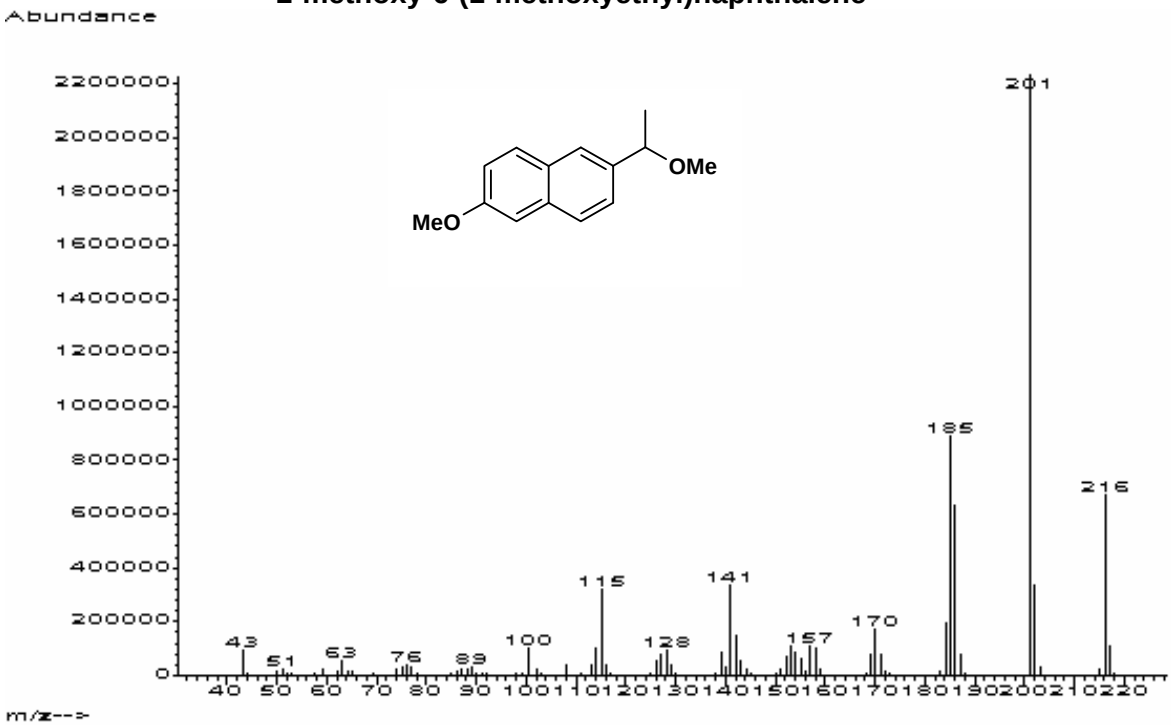
Methyl-2-(6-methoxy-2-naphthyl)propanoate



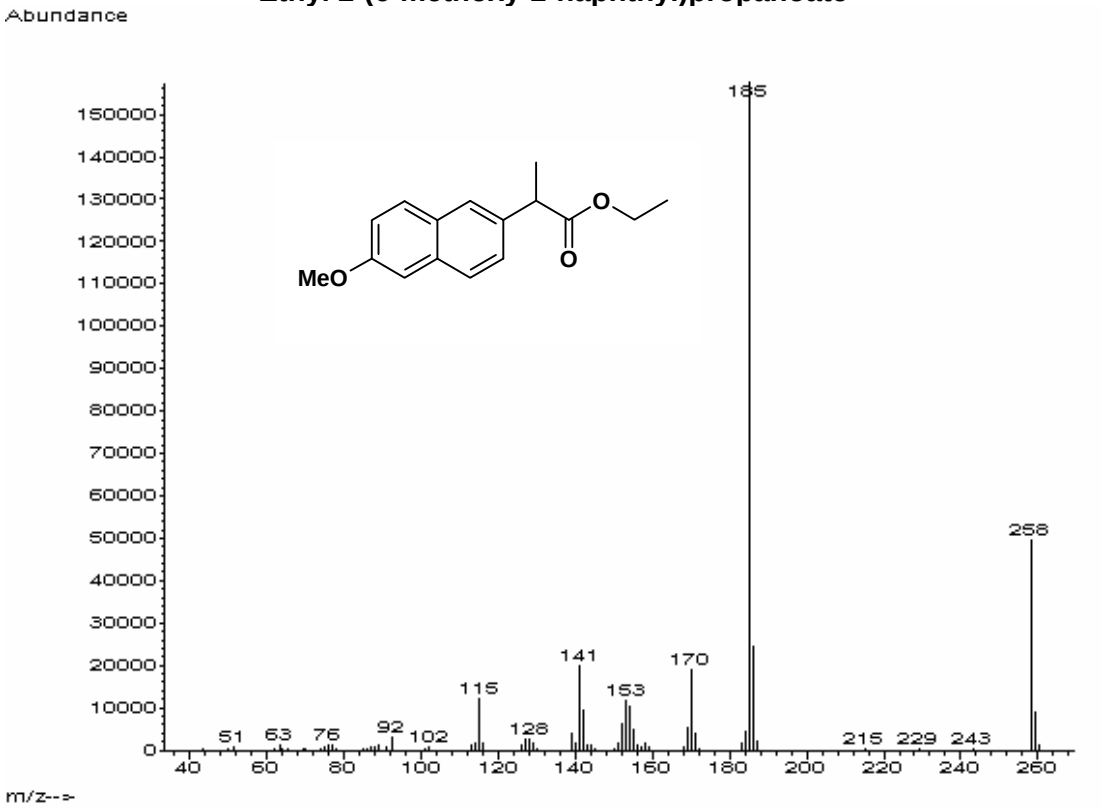
Methyl-3-(6-methoxy-2-naphthyl)propanoate



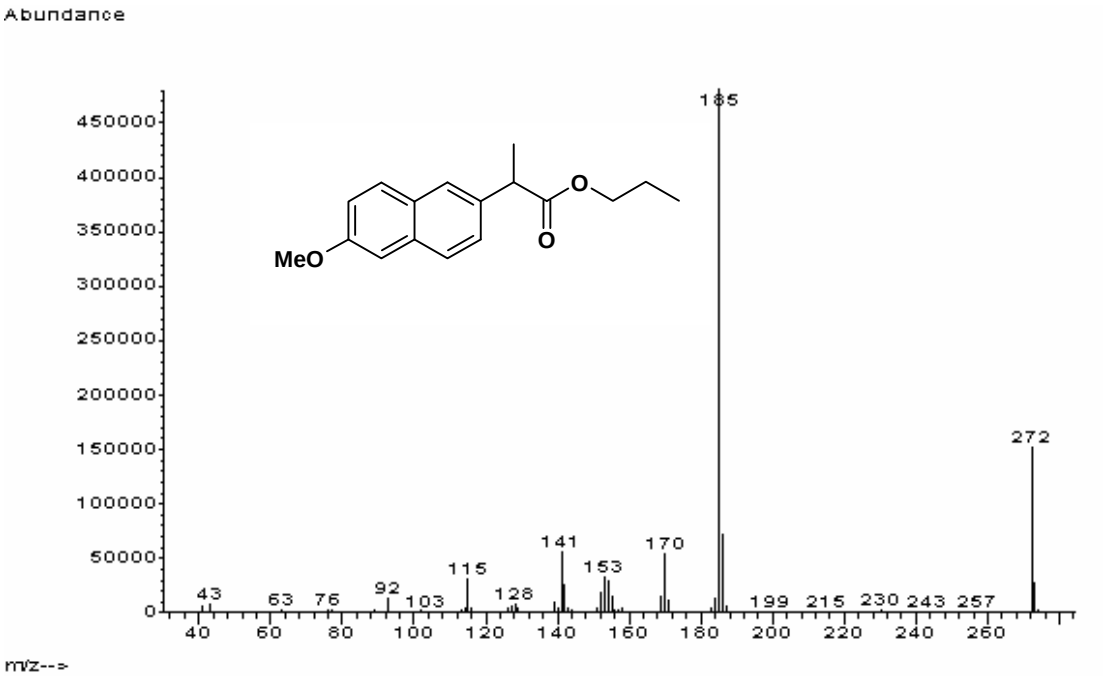
2-methoxy-6-(1-methoxyethyl)naphthalene



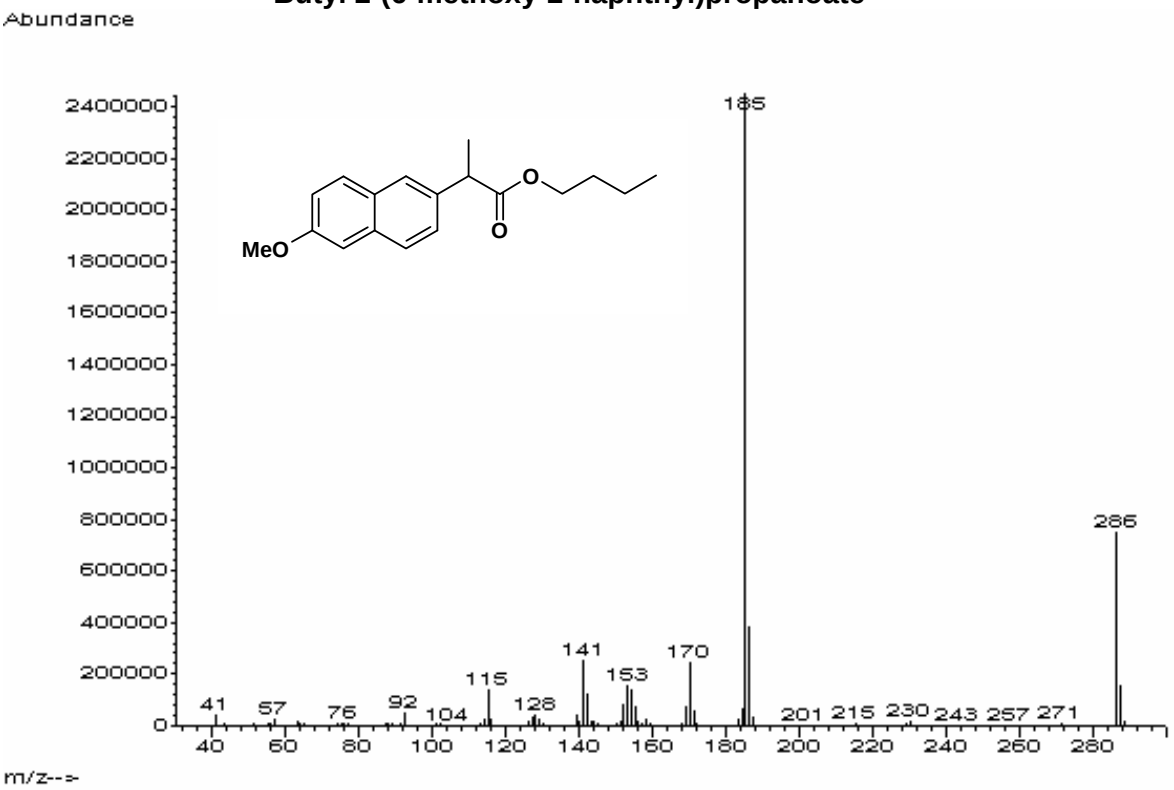
Ethyl 2-(6-methoxy-2-naphthyl)propanoate



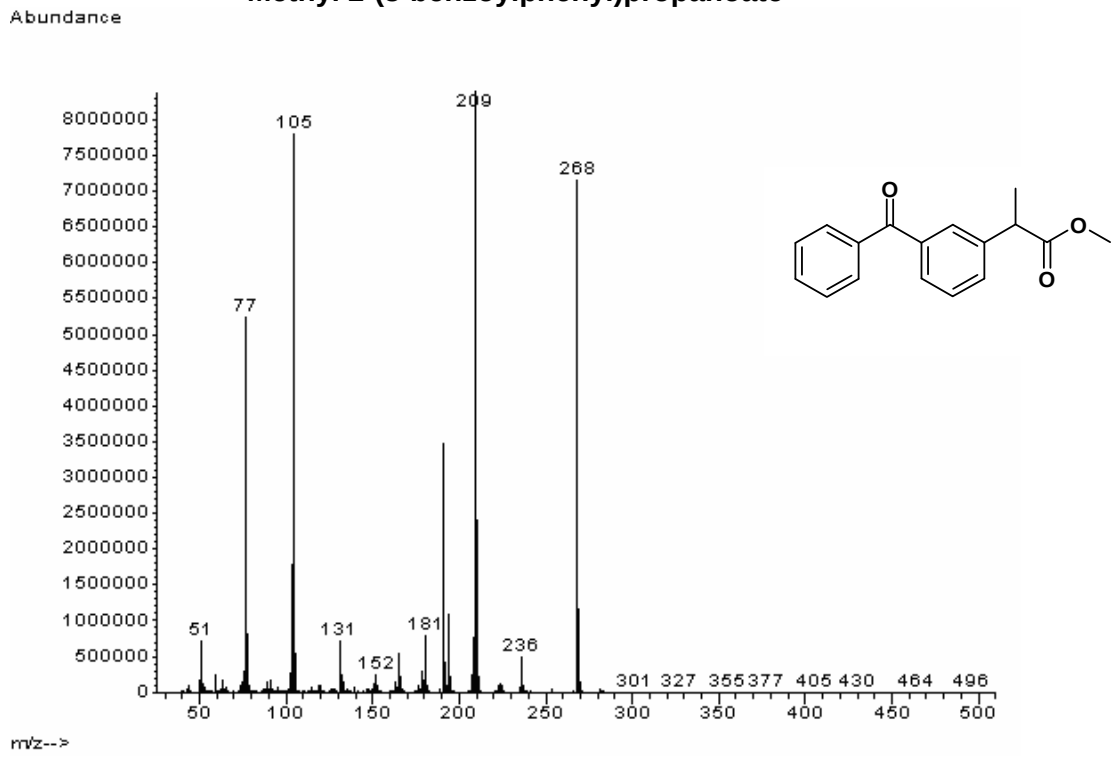
Propyl 2-(6-methoxy-2-naphthyl)propanoate



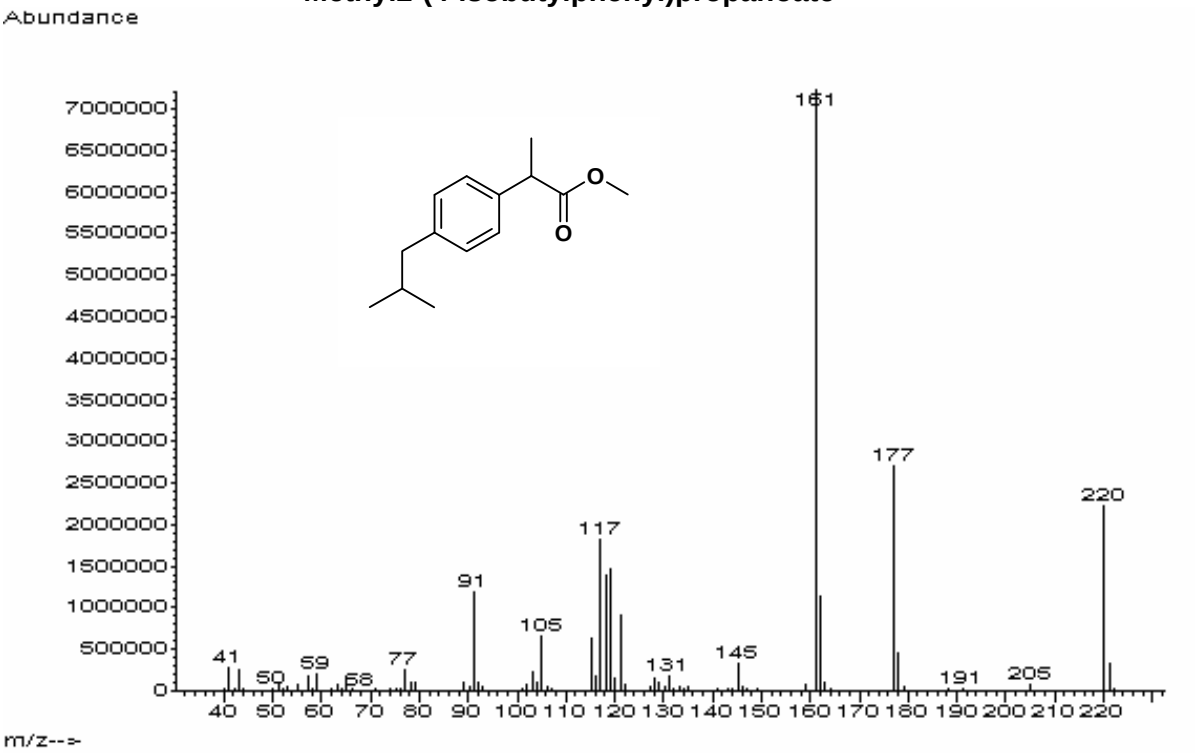
Butyl 2-(6-methoxy-2-naphthyl)propanoate



Methyl 2-(3-benzoylphenyl)propanoate



Methyl2-(4-isobutylphenyl)propanoate



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