Studies In Heck Reactions Using Transition Metal Catalysts In Biphasic Medium

BY

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FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

UNDER THE GUIDANCE OF

DR. R. M. DESHPANDE

AT

HOMOGENEOUS CATALYSIS DIVISION
NATIONAL CHEMICAL LABORATORY
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A THESIS
SUBMITTED TO THE
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IN
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Certificate

This is to certify that, the work incorporated in the thesis entitled "**Studies in Heck Reactions Using Transition Metal Catalysts in Biphasic Medium**", submitted by **Mrs. Sangeeta Vijay Jagtap**, for the degree of **Doctor of Philosophy**, was carried out by the candidate under my supervision, in the Homogeneous Catalysis Division, National Chemical Laboratory, Pune – 411008, India. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

May 2007
Pune

Dr. R. M. Deshpande
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Declaration by the candidate

I hereby declare that the thesis entitled **"Studies in Heck Reactions Using Transition Metal Catalysts in Biphasic Medium"**, submitted by me for the degree of **Doctor of Philosophy**, to the University of Pune, is the record of work carried out by me under the guidance of Dr. R. M. Deshpande and has not formed the basis for the award of any degree, Diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning.

I further declare that the material obtained from other sources has been duly acknowledged in this thesis.

May 2007 Sangeeta Vijay Jagtap
Pune (Candidate)

Dedicated to my
Beloved Parents,
Husband and son

For their love and concern,
for sowing in me, the value of education and knowledge,
for their unlimited, unhesitant moral support,
for which I am forever grateful and highly
indebted to them.

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Abstract of the Thesis

Catalysis is of crucial importance for the development of environmentally benign processes. In modern chemistry, approximately 80% of all chemicals are produced with the help of catalysts in one or more process steps. The use of catalysts results in a remarkable acceleration of some reactions and can also influence the selectivity. The catalytic reactions can broadly be divided into two major categories depending on their phase of application. A heterogeneous catalyst is one in which the catalyst phase is different from that of the reactants whereas a homogeneous catalyst is the one in which the catalyst is in the same phase as the reactants and the products. Homogeneous catalysis is generally more selective and operates at milder conditions. However, one of the major problems in homogeneous catalysis is the separation of the catalyst and products, which is often a highly involved task and may also require a regeneration step. It is for this reason that only 20 % of the industrial catalytic reactions involve homogenous catalysis whereas 80 % employ the classical heterogeneous catalysis involving supported metal catalysts. An important approach for overcoming the catalyst product separation issues is the use of biphasic systems wherein the catalyst and reactant/product exist in different phases. This concept has found commercial application in oxo synthesis[1]. Biphasic catalytic reactions using transition metal complexes nowadays is important since they provide unique advantages of homogeneous catalysis along with facilitating easy separation of the catalyst from the products.

The reactions involved in forming carbon-carbon bonds are unquestionably the most important processes in organic chemistry, as they represent key steps in the building of more complex molecules from simple precursors. Among the different methods used to form carbon-carbon bonds, Pd(0)-mediated reactions have been widely used because of their selective and versatile applications[2]. The Pd(0)-catalyzed Heck reaction[3,4] has been called "one of the true power tools of contemporary organic synthesis" because of its versatility and broad tolerance of functional groups[5]. The Heck arylation process, which is considered to be a mild and versatile method for the formation of carbon-carbon bonds, has been extensively investigated in the past. However, though, Heck reaction has been studied in detail there are relatively few reports on Heck reaction in biphasic media. The use of water as reaction medium poses major challenges, as water is a

highly reactive solvent. This calls for development of ligands to provide enhanced catalyst solubility and improved efficiency in water, catalyst-product separation and catalyst recycle. Efforts to develop new, active and selective metal complex catalysts with an industrially feasible separation strategy are most desirable for Heck reaction. Consequently, the objective of this thesis has been to investigate transition metal catalyzed Heck reaction of olefins and aryl halides, with the goal of developing improved catalyst systems with high activity and selectivity for Heck reactions in biphasic media.

With these objectives, the following specific problems were chosen for the present work
(i) Synthesis and characterization of palladium complexes containing chelating nitrogen and phosphorous ligands and their application as catalysts for Heck reaction in biphasic medium (glycol-organic).

(ii) Detailed investigations on the application of $PdCl_2$(bipy) as a catalyst for Heck reaction in two-phase media (glycol-organic) and comparison of its performance with that in a homogeneous medium.

(iii) Investigations of the kinetics of the Heck reaction using $PdCl_2$(bipy) catalyst in glycol-organic biphasic medium, with the objective of developing a suitable rate equation. The kinetics of the Heck reaction in biphasic system was compared with that in a homogeneous medium.

(iv) Investigations on Heck reaction of water-soluble substrates using biphasic system (wherein the catalyst is soluble in the organic phase and the aqueous phase contains the water-soluble substrate and products), in presence of P-C palladacycle catalyst.

(v) Synthesis and characterization of a water-soluble ligand derived from tri-o-tolyl phosphine and its use for synthesis of stable water-soluble Palladium catalyst. Studies on Heck reaction in aqueous-organic biphasic media with detailed investigation on activity and selectivity in a biphasic water-organic system.

The thesis is presented in four chapters, a summary of which is given below:

CHAPTER 1: Literature survey

The Heck reactions, find application in synthesis of pharmaceuticals, fine chemicals, as one of the key step in synthesis route. This chapter presents a detailed literature survey on Heck reactions with the main focus on Heck reactions in biphasic medium.

Transition metals such as palladium, platinum, cobalt, iridium and nickel catalysts are reported to be active catalysts for the Heck reaction, however, among them only Palladium was found to show the maximum activity. Palladium metal is also active for Heck reaction, but works only on reactive substrates. The activity of the catalyst can be enhanced by tailoring of the ligands used for the catalyst to enhance the stability of the catalyst during the course of reaction. Various ligands have been used for Heck reaction. The ligands used for Heck reaction mainly include phosphorous, nitrogen, sulphur and carbene based ligands. Phosphorous-based ligands are the most commonly used. The other ligands are relatively less employed, even though their Palladium complexes are active for Heck reaction. Palladacycle complexes are some of the most active catalysts for the Heck reaction and being more stable relative to Pd-phosphine complex, can be used at higher temperatures. Amongst other complexes, Pd complexes of pincer ligands (P-C-P etc) are also very active for Heck reaction.

From the literature, it can be seen that, the majority of the work carried out till date on the Heck reaction is in mainly using catalysis in the homogeneous medium. Heck reaction using homogeneous catalysts is gaining considerable interest due to the high activity and selectivity observed at milder reaction conditions. However, practical applications of these catalysts have been limited due to difficulties in achieving industrially viable catalyst-product separation. In this context, biphasic catalysis can be used successfully to achieve an efficient separation of catalyst and product. For biphasic systems the reactions are conducted such that the catalyst exists in one phase while reactants and products are present in the other phase. The catalyst-containing phase can thus be easily separated by simple phase separation and recycled for subsequent reactions. The information available using palladium as a catalyst in biphasic medium is scanty. The biphasic catalysis for Heck reaction is mainly carried out using water-soluble ligand such as either TPPTS[6] or a carbohydrate[7] in organic-glycol media. Thus, there is scope in improving Pd-based catalysts in biphasic medium and also investigate the kinetics and mechanism of the Heck reaction in biphasic medium.

CHAPTER 2: Palladium metal complex catalyzed Heck reaction in glycol-organic biphasic media

This chapter deals with the use of Palladium metal complex catalysts for Heck reaction. A number of Pd complexes were synthesized, characterized and the activity of these for Heck reaction of styrene and iodobenzene was assed in organic-glycol media. Amongst all the catalyst screened the $PdCl_2$(bipy)-(bipy: 2,2′-Bipyridine) complex was seen to efficiently catalyze the Heck reaction in a glycol-organic biphasic medium. The catalyst was found to be stable and could be recycled with marginal loss in activity. Although this catalyst is less efficient than P-C Palladacycles[8,9], the $PdCl_2$(bipy) catalyst nevertheless provides an efficient recyclable catalyst in the biphasic system and high cumulative TON's are possible.

The major advantage of the catalyst is that, unlike conventional biphasic systems reported for Heck reactions this catalyst does not employ any water-soluble ligand to achieve biphasic catalysis[5,6], but it employs 2,2'-bipyridine (a organic phase soluble) ligand, which does not have a hydrophilic moiety like that in TPPTS. The catalyst is stable and does not precipitate to Pd metal, as is reportedly the case for other water-soluble catalysts. The chapter is divided into two sections.

Section A: $PdCl_2$(bipy) catalyzed Heck reaction in glycol-organic biphasic media - Activity and selectivity studies

This section presents experimental results on Heck reaction in glycol-organic biphasic media using $PdCl_2$(bipy) as a catalyst with respect to activity, catalyst stability and recycle. This complex is highly active and can catalyze Heck reaction efficiently in glycol-organic biphasic medium and high activity and selectivity were achieved. The two-phase system has been demonstrated for a number of aryl halides, olefins and in the presence of different organic and inorganic bases. The role of different solvent compositions on the activity and selectivity was also assessed.

The activity of aryl iodides were found to be more than bromides, whereas the acrylates were observed to be more reactive than styrene derivatives. In general, it was seen that the aryl halides with a strong electron withdrawing substituents (i.e. more –I or -R effect) showed higher activity whereas those with more electron donating substituents (i.e.

more +I or +R effect) showed poor activity. Olefins with a strong electron donating substituents showed a higher activity whereas those with electron withdrawing substituents showed poor activity. It was observed that, in the homogeneous medium (NMP) the trend of activity for all substrates follows the Hammett correlation. However for biphasic media the correlation was not followed due to solubility limitation of substrates in glycol phase and kinetic effect.

A variety of organic and inorganic bases including aliphatic and aromatic organic bases and monovalent / divalent inorganic bases were screened for their activity in the biphasic system. The acetates were found to have better activity compared to other inorganic bases. With carbonates, a high conversion of iodobenzene was observed, but benzene was the major product formed by a dehalogenation reaction. A similar observation was also made with triethyl amine where dehalogenation was the major reaction. Among organic bases, aliphatic bases like morpholine and piperidine were more active than aromatic bases. The $PdCl_2$(bipy) catalyst was recycled a number of times by simple phase separation with no loss in activity. The catalyst was retained in the glycol phase with practically no leaching of Palladium to the organic phase.

Section B: Kinetic studies of Heck reaction using $PdCl_2$(bipy) catalyst in glycol -organic biphasic media

This section deals with the kinetic studies of Heck reaction. For this study of the effect of concentration of reaction variables on the activity of $PdCl_2$(bipy) catalyst in glycol-organic biphasic media at different temperatures was conducted, with the objective of developing a suitable rate equation.

Following the screening results obtained in Section A, the kinetics of the Heck coupling of styrene with iodobenzene using the $PdCl_2$(bipy) complex was studied over a temperature range of 393-413 K in biphasic [organic (75% n-octane + 25% p-xylene) - glycol] medium. The base used for these reactions was morpholine.

The effects of concentration of the different parameters on the rate of Heck reaction have been studied using a $PdCl_2$(bipy) complex at different temperatures. It was seen that the rate has a complex dependence on the olefin concentration and passes through a maximum, showing typical substrate inhibition kinetics. The rate was found to have a first order dependence on the iodobenzene concentration. At higher iodobenzene concentrations however, a fractional order was observed, tending to a zero order. It was also observed that the rate increases with the base concentration with a first order dependence. With increase in the catalyst concentration the rate showed a partial order dependence.

Numerous semi empirical rate models were discriminated and a rate model of following type (Equation 1) was found to represent the rate data in good agreement. The activation energy was also evaluated and was found to be 72.91 kJ/mol.

$$R = \frac{k \,.\, A \,.\, B \,.\, C \,.\, D}{(1+K_A A)^2 \,(1+K_B B)\,(1+K_C C)} \qquad \text{----------Equation 1}$$

[Where R: Rate of reaction (kmol/m^3.s) ; k: Intrinsic Rate constant ((m^3)^3/$kmol^3$.s)
A: Concentration of olefin (kmol/m^3) ; K_A: Equilibrium constant of olefins (m^3/kmol)
B: Concentration of ArX (kmol/m^3), K_B: Equilibrium constant of ArX (m^3/kmol)
C: Concentration of catalyst (kmol/m^3) ; K_C: Equilibrium constant of catalyst (m^3/kmol)
D: Concentration of Base (kmol/m^3)]

This is the first time that kinetic modeling has been attempted for the Heck reaction in a biphasic medium.

CHAPTER 3: Studies of Heck reaction using $PdCl_2$(bipy) catalyst in NMP solvent

This chapter presents experimental results on $PdCl_2$(bipy) catalyzed Heck reaction in NMP solvent. The major objective of this study was to compare the observations made on the screening and kinetic studies in biphasic media with those under homogeneous conditions. This chapter is divided into two sections.

Section A: $PdCl_2$(bipy) catalyzed Heck reaction in homogeneous medium - Activity, selectivity studies

The feasibility of the Heck reaction using $PdCl_2$(bipy) catalyst in NMP was investigated for a number of aryl halides and olefins in the presence of different organic and inorganic bases. It was found that the reactivity of the substrates in the homogeneous medium was exactly according to Hammett correlation study reported in literature. The activity of the base is highly dependent on the nature of solvent used and the solubility of base in the solvent. Organic bases were in general found to give better activity in organic nonpolar solvents, whereas the inorganic bases showed better activity in polar solvents.

The major difference in the activities observed for different substrates in homogeneous and the biphasic medium was that, in the biphasic medium Hammett correlation was not followed. The bases also were found to behave in a different manner in biphasic medium. This may be due to the solubility limitation of substrates in the catalyst phase.

Section B: Kinetic studies of Heck reaction using $PdCl_2$(bipy) catalyst in homogeneous medium

The effects of concentrations of styrene, iodobenzene, and KOAc on the activity of the Heck reaction in N-Methyl-2-Pyrrolidinone (NMP) solvent was studied using $PdCl_2$(bipy) catalyst over a temperature range of 393-413 K. The rate was found to have a first order dependence on catalyst concentration. A partial positive order dependence was observed for styrene and iodobenzene concentration. At high iodobenzene concentration and at 140^0C a zero order was observed. Partial order dependence was observed with the concentration of base. The results obtained were explained on the basis of the well-accepted mechanism of Heck reaction.

Many semi empirical rate models were discriminated and a rate model of the following type (Equation 2) was found to represent the rate data in good agreement. The activation energy was evaluated and was found to be 98.70 kJ/mol.

$$R = \frac{k \,.\, A \,.\, B \,.\, C \,.\, D}{(1+K_A A)(1+K_B B)(1+K_D D)} \quad \text{----------Equation 2}$$

[Where R: Rate of reaction (kmol/m^3.s) ; k: Intrinsic Rate constant (($m^3)^3$/$kmol^3$.s)
A: Concentration of olefin (kmol/m^3) ; K_A: Equilibrium constant of olefins (m^3/kmol)
B: Concentration of ArX (kmol/m^3), K_B: Equilibrium constant of ArX (m^3/kmol)
C: Concentration of catalyst (kmol/m^3) ; K_D: Equilibrium constant of Base (m^3/kmol)
D: Concentration of Base (kmol/m^3)]

Thus the kinetic behavior of Heck reaction using $PdCl_2$(bipy) catalyst in glycol-organic biphasic media and in NMP solvent was found to be same for the aryl halide concentration, however it was found to be different with respect to styrene, base and catalyst concentration.

CHAPTER 4: Heck reaction using Palladium metal complex catalysts in biphasic aqueous-organic system.

From the literature it was observed that, there are practically no major studies on Heck reaction in biphasic medium using water as one of the phase, as the use of water for catalytic chemistry poses a lot of challenges regarding the solubility of Pd catalysts. All reports till date for Heck reaction using a biphasic medium, makes use of either a nonpolar solvent such as toluene or xylene along with other catalyst phase such as ethylene glycol or or in some other cases water is used along with polar organic solvent like CH_3OH, CH_3CN, DMF, and NMP etc, in an attempt to achieve a homogeneous reaction medium. This chapter deals with the studies on Heck reactions using water as one of the phases in aqueous- organic biphasic media. The chapter is divided into two sections.

Section A: Heck reaction of water-soluble olefinic substrates in biphasic aqueous-organic medium using palladacycle catalyst.

A biphasic (aqueous-organic) system for the Heck reaction of water-soluble olefin (e.g. Sodium acrylate) has been developed. This system employs organic phase soluble catalysts such as $PdCl_2(PPh_3)_{2,}$ $PdCl_2$(DPPE), $PdCl_2$(DPPP), $PdCl_2(Py)_{2,}$ $PdCl_2$(bipy) and Palladacycle catalysts. The Hermann Palladacycle i.e. trans-di(μ-acetato)-bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) was found to give the highest activity for the Heck reaction of sodium acrylate and it could also be recycled conveniently with no loss in the activity. The catalyst system was assessed for the reaction using a variety of bases and aryl halides and found to be active for the synthesis of numerous cinnamic acid derivatives using sodium salt of acrylic acid as the substrate.

The iodoarenes were found to be far more active than the bromoarenes for this system. Sodium hydroxide, carbonate and bicarbonate were found to be excellent bases for this reaction, and were efficient even though present in the second non-catalyst phase. The biphasic system developed has numerous advantages such as efficient sequestration of the halide by dissolved base and prevention of the deactivation of catalyst by excess olefin as the catalyst and olefin are in separate phases. A convenient product separation and efficient catalyst recovery and recycles were achieved. The Palladacycle catalyst was stable toward water, and could be recycled for four times with no loss in the activity.

Section B: Synthesis and characterization of water-soluble Pd-catalyst and its application for Heck reaction in a biphasic aqueous-organic system.

Heck Reaction in an aqueous-organic biphasic medium using a water-soluble catalyst has been established in a biphasic medium, using water and a nonpolar solvent. The Palladium complex of the sulfonated tri-o-tolyl phosphine was synthesized and characterized. The biphasic reaction (organic-water) system has been standardized using this catalyst in such a way, so as to prevent leaching of catalyst or the precipitation of Pd metal. The Heck reaction in the aqueous biphasic system was found feasible for a number of aryl halides and olefins. As is generally observed, aryl iodides were found to be far more active than bromides even in the aqueous-organic medium. Olefins with the substituents possessing –I effect were found to be more active than with +I effect. The organic phase was tailored to achieve an excellent catalyst recycle without loss of catalyst to the organic phase. The catalyst was recycled a number of times maintaining the activity for the Heck coupling of styrene and iodobenzene. Substrates, which were insoluble in water, were made to solubilise in it by using morpholine as a co-solvent. The presence of co-solvent was found to enhance the activity of Heck reaction. The rate of reaction was found to increase with increase in the concentration of co-solvent; which is due to the enhanced solubility of the substrates in the catalyst phase, thereby increasing the rate of the reaction. Morpholine was also observed to work as a base. The reaction system was optimized for the best activity towards the Heck reaction.

Key references

1. Cornils B., Kuntz E., J. Organomet. Chem., 502 (1995) 17.

2. Diederich, F.; Stang, P. J.; Editors *Metal-Catalyzed Cross-Coupling Reactions* 1998.

3. R.F. Heck, Acc. Chem. Res. 12 (1979) 146–151.

4. T. Mizoroki, K. Mori, A. Ozaki, Bull. Chem. Soc. Jpn. 44 (1971) 581.

5. Nicolaou, K. C.; Sorensen, E. J.; Editors *Classics in Total Synthesis* 1996.

6. B. M. Bhanage, F.-G. Zhao, M. Shirai and M. Arai, Tetrahedron Letters 39 (1998) 9509-9512.

7. M. Beller, J. G. E. Krauter and A. Zapf, Angew. Chem. Int. Ed.Engl. 1997, 36, 772.

8. Ohff M.; Ohff A.; Milstein D. (1997). JACS, 119, 11687.

9. Herrmann W.A, Karl Ofele (1994). J. of Organometallic Chemistry, 481, 97.

CHAPTER 1

Literature Survey

1.1 Introduction

Catalysis has always played a vital role in developing new technologies as well as in solving environmental problems. It has been instrumental in the development of new processes and alternative routes for the manufacture of a variety of bulk chemicals, fine chemicals, pharmaceuticals and specialty chemicals. Conventionally, catalysis has been categorized as, homogeneous, in which the catalyst is soluble in the reaction medium along with reactants and products and heterogeneous, in which the catalyst is immiscible with the reaction medium or present in a phase separate from the reactants and products.

1.1.1 Homogeneous catalysis

In recent years, the contribution of homogeneous catalysis to the discovery of new processes/ routes has been remarkable. The unique features of these catalysts are high activity and selectivity at mild operating conditions. Homogeneous catalysis also has been practiced in industry for several years for a number of processes involving carbonylation, hydroformylation, oligomerization, isomerization, polymerization and oxidation[1-5]. A few applications of homogeneous catalysis in industrial processes are given in Table 1.1

The main drawback of homogeneous catalysis is the separation of the catalyst and products, which is often a tedious task involving precipitation of the catalyst by adding non-polar solvents, or high vacuum distillation or extraction of products into a second phase, etc., and hence, while only 20% of the industrial catalytic processes involve homogeneous catalysis, 80% employ heterogeneous catalysts involving supported metal catalysts.

1.1.2 Heterogeneous catalysis

In heterogeneous catalysis, the catalyst is in a different phase from the reactants and products. The main advantage of heterogeneous catalysis is the easy separation of catalyst and products, hence it has been emplyoed in majority of the chemical processes. Heterogeneous catalysis has its own disadvantages like high pressure and temperature requirements for reactions. The higher temperatures, may lead to the deactivation of catalyst; heat transfer is not efficient and may cause hot spots and the reactions are generally guided by principles of surface chemistry.

Table 1.1: Applications of homogeneous catalysis: Industrial processes

Sr.No.	Process	Catalyst	Company
1	Oxidation of ethylene to acetaldehyde	$PdCl_2/CuCl_2$	Wacker-Werke[6]
2	Polymerisation of ethylene to HDPE/LDPE	Ni-complex	Shell[7]
3	Hydrocyanation of butadiene to adipic acid	Ni-complex	Du Pont[8]
4	Hydroformylation of propene to butyraldehyde	Rh/TPPTS	Ruhrchemie-Rhone-Poulenc[9]
5	Carbonylation of ethylene to propionic acid	$Ni(OCOC_2H_5)_2$	BASF[10]
6	Oxidation of p-xylene to terephthalic acid/ester	Co/Mn-salts	Du Pont[11]
7	Oxidative carbonylation of methanol to dimethyl carbonate	$PdCl_2$-$CuCl_2$	Assoreni[12]
8	Hydroformylation of Ethylene oxide to 2-hydroxy propanal	$Co_2(CO)_8$	Shell[13]
9	Hydroformylation of higher olefins to oxo alcohols	$HCo(CO)_3PBu_3$	Shell[14]

Table 1.1: continued…

Sr.No.	Process	Catalyst	Company
10	Carbonylation of methyl acetate to acetic anhydride	Rh/MeI	Halcon[15]
		Rh/MeI	Eastman Chemical[16]
11	Carbonylation of methanol to acetic acid	Rh/ Iodide	Monsanto[17]
		$Co_2(CO)_8$	BASF[18]
		Ir/Iodide	BP chemicals[19]
12	Carbonylation of 1-(4-isobutylphenyl)ethanol To Ibuprofen	$PdCl_2(PPh_3)_2/HCl$	Hoechst-Celanese[20]
13	Carbonylation of benzyl chloride to phenyl acetic acid	$Co_2(CO)_8$	Montedison[21,22]
14	Carbonylation of acetylene to acrylic acid	Ni-salts or carbonyls	BASF[23]
15	Hydroformylation of diacetoxy butene to 1-methyl-4-acetoxy butanal (Vitamin A intermediate)	$HRh(CO)(PPh_3)_3$	Hoffmann-La Roche[24]
		Rh catalyst	BASF[25]

It even requires higher catalyst loading, as all the catalyst is not available for reaction. Thus results in decreasing the TON (Turn Over Number) of the reaction.

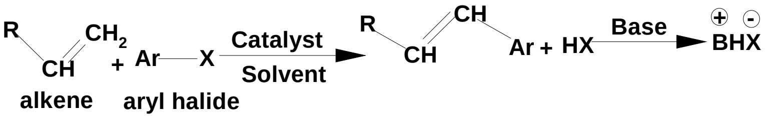
1.1.3 Heterogenization of the catalyst

Since catalyst-product separation is a major problem for the homogeneous reactions, heterogenization of the catalyst is in vogue for the last couple of decades. Various ways have been attempted for heterogenization. The homogeneous metal complex catalysts are heterogenized on to a solid support, by binding on modified silica, polymer and other functionalized supports. The catalysts are also heterogenised into a second immiscible liquid phase as in biphasic catalysts using water, ionic liquids, and perfluorinated solvents etc[26]. Of these biphasic systems, some of the important industrial two-phase processes are, the Shell Higher Olefin Process (SHOP)[27] and the Ruhrchemie/Rhone-Poulenc process for the hydroformylation of propene to butyraldehyde[28]. The other strategies are primarily of academic interest.

In view of growing importance of the heterogenization of catalysts for a number of reactions like hydroformylation, carbonylation, oxidation, hydrogenation, Heck reaction etc, it is essential to investigate the above aspects for important reactions, in greater detail. Since the subject of the present thesis is concerned with investigations on transition metal catalysed Heck reactions in biphasic medium, a detailed literature search was undertaken on this subject. The relevant literature survey on the Heck reaction is therefore summarized and presented in the following sections.

1.2 The Heck Reaction

The palladium-catalyzed C-C coupling between aryl halides or vinyl halides and alkenes in the presence of a base is referred as the "Heck Reaction". The reaction can be described as shown in scheme 1.1



Scheme 1.1: Heck reaction

The arylation or vinylation of alkenes with aryl or vinyl halides was discovered independently by Heck[29] and Mizoroki et.al[30] about 35 years ago and it is nowadays known universally as the Heck reaction.

One of the major drawbacks of the early catalytic systems was the precipitation of palladium black, which limited the lifetime of the active species. It was soon discovered that the addition of phosphines[31] greatly improved the stability of the catalytic system. Later investigations demonstrated that several palladacyclic compounds[32], heterocyclic carbenes[33] etc., also showed improved lifetimes and allowed high activity, to the tune of more than a million, either on their own or with the aid of promoters[34-37]. The palladium-catalyzed Heck reaction is a powerful tool for the construction of aryl- and vinyl-substituted carbon-carbon double bonds[38,39], as it is tolerant to a broad range of functional groups[40-45]. The well-established Heck reaction together with other mechanistically related palladium-catalyzed transformations with arene, alkene, and alkyne derivatives, opens the way to a tremendous variety of elegant and highly convergent routes to structurally complex molecules[46].

1.3 Application of Heck reaction

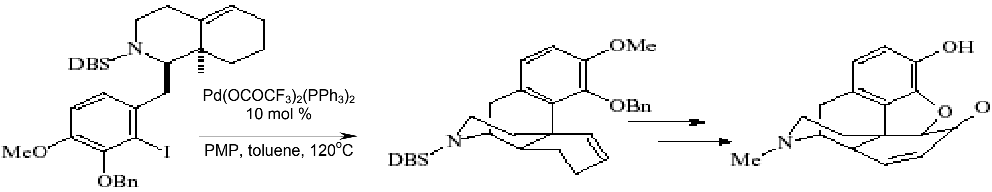
The major advantage of the Heck reaction and its usefulness in synthetic chemistry is due to the following facts

1. The methodology is amenable to a variety of easily available starting materials.
2. The Heck reaction is remarkably tolerant to different functional groups and hence coupling reactions of a variety of functionalized substrateds is possible.
3. Most of the catalysts typically employed are water and air stable.
4. The application can be expanded in organic synthesis.

The Heck reaction finds its application in pharmaceuticals, in fine chemicals, in natural product synthesis and many other industrial processes as one of the key step in its synthetic route.

Heck reaction has been reportedly used for C-C coupling in a number of multistep processes for synthesis of pharmaceutical intermediates e.g. synthesis of potential antiinflammatory agents[47], synthesis of CC-1065/duocarmycin pharmacophore[48], in the development of the antitumor anthracyclines[49], preparation of dopamine analogs[50], preparation of ribozymes and substituted derivatives for treatment of arthritic conditions[51] etc. Heck reaction is also used for the synthesis of P1/P1' modified HIV protease inhibitors[52], and in the preparation of an HIV reverse transcriptase-selective nucleoside chain terminator[53] for the treatment of AIDS. Many reviews describe the pharmaceutical applications of Heck chemistry[54-56].

The last decade has seen an extraordinary growth in the use of stereoselective palladium catalyzed olefination of aryl and vinyl derivatives for complex total synthesis. This has been reviewed in detail by few research groups[57-59]. In most of the cases intramolecular variants offer unprecedented ways to assemble structurally simple precursor molecule to congested polycyclic frameworks; to name few of them, the total synthesis of taxol[60], synthesis of scopadulcic acid B[61], total synthesis of herbertenediol, an isocuparane sesquiterpene isolated from liverworts[62], organic synthesis without protecting group in total synthesis of optically active clavicipitic acid in aqueous media[63], synthesis of novel porphyrins and phthalocyanines[64], DNA-templated synthesis[65], synthesis of an enantiopure thiasteroid by a double Heck reaction[66] and many more. The synthetic potential of intramolecular Heck reaction is elegantly demonstrated by the work of Overman and his group towards the synthesis of morphine as shown in scheme 1.2[67]



Scheme 1.2: Synthesis of morphine

There are many reports which describe the preparation of stilbene and cinnamaldehyde derivatives and some heterocycles via Heck reaction[68-70]. Various polymers for the preparation of LED (light emitting diodes) are also synthesized by using Heck reaction as one of the intermediate step[71-75]. Palladium-catalyzed coupling reactions for industrial fine chemical synthesis have been reviewed in detail by Beller and Zapf[76].

The Heck reaction is also used in the production of fine chemicals. It finds more application in industries when coupled with other reactions[46]. Five commercial products have been identified that are produced on a scale in excess of 1 ton/year as shown in Table 1.2.

Table 1.2: Potential applications of Heck reaction in industrial processes

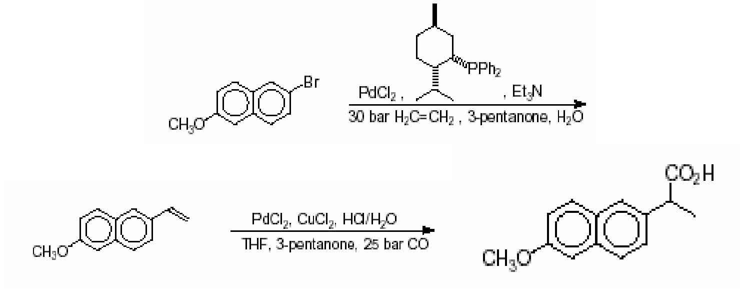
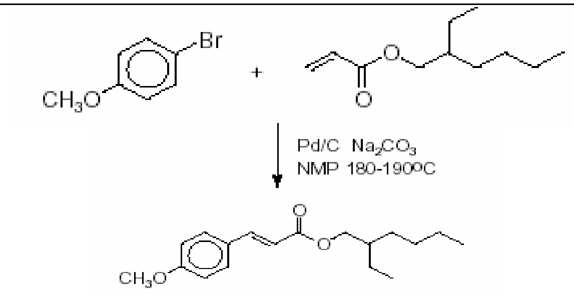
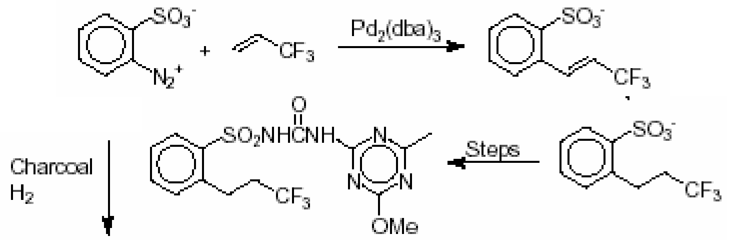
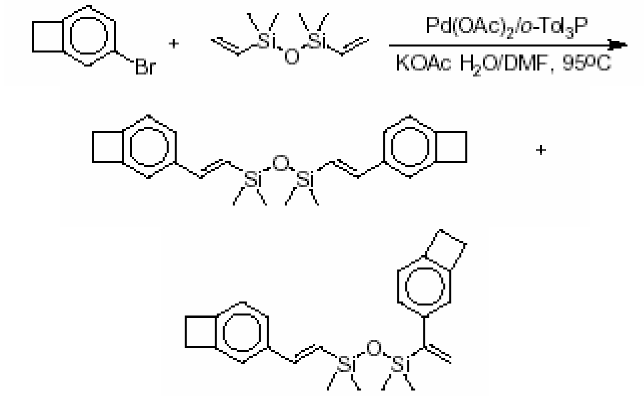
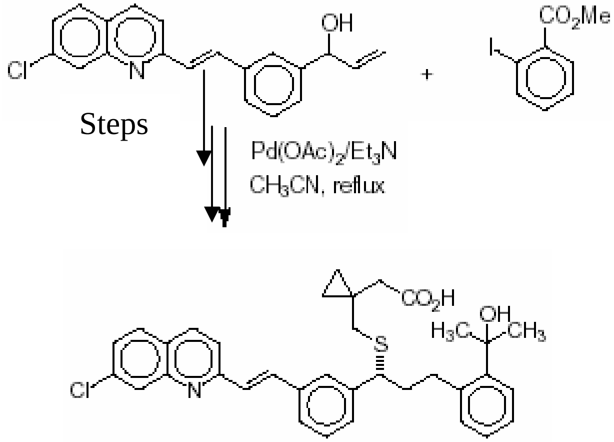
Sr. No.	Name of Compound	Application	Reaction	Company
1	Naproxen	Analgesic		Albemarle[77]
2	2- ethylhexyl *p*-methoxy-cinnamate	UV-B sunscreen agent		Dead Sea[78]
3	Prosulfuron	Herbicide		Ciba-Geigy/ Novartis[79]

Table 1.2: continued…

Sr. No.	Name of Compound	Application	Reaction	Company
4	Cyclotene (benzo cyclobutene-monomers)	for coatings		Dow[80]
5	Singulair	antiasthma agent		Merck's LTD[81]

There are still some hurdles to be overcome before a broader application of Heck reaction can be realized, especially on an industrial scale. As with almost every new application, selectivity problems will have to be unraveled by selection of substrates/ base and fine-tuning of reaction conditions. Expansion of the spectrum of starting materials, especially to the inexpensive chloroarenes and chloroalkenes, remains a desirable goal. In view of a practical industrial application, improvements in catalyst efficiency and catalyst recycling are essential[82].

1.4 Catalysis and chemistry of Heck reaction

Transition metal catalyzed reactions open up new and important synthetic routes that have no analogies in the classical organic chemistry; a striking example of which is the Heck reaction. Heck coupling is carried out in presence of a transition metal in either homogeneous, heterogeneous or in heterogenised media.

1.4.1 Catalysts for Heck reaction

Transition metal catalyzed homogeneous reactions are often preferred for laboratory scale preparations and the majority of mechanistic and parametric studies have been carried out in solution phase. A variety of catalysts are reported for the Heck reaction, where the preferred catalysts are the palladium complexes, often used together with phosphine ligands[83-88]. It is the classical and well-established approach and gives excellent results in a majority of cases. Apart from the traditional Pd(0) phosphine complexes, a good number of improvements and modifications are reported. Pd(II) complex of heterocyclic carbenes[89-91], nitrogen[92-102] or sulfur ligands[103-107] are also reported to be effective catalysts. Jeffrey[108] showed that the addition of tetralkylammonium salts could increase the reactivity and selectivity of the reaction. For an industrial application, the development of “ligand-free” palladium catalytic systems appears particularly interesting[30,109-114]. In Heck reaction the use of zeolites as a support or to encapsulate the metal or the organometallic complexes as a catalyst are also reported[115-118]. Heck reaction using Phase-transfer catalysts are also known[119,120].

1.4.1.1 Different metals used for Heck reaction

Various metals such as Ru[121], Cu[122,123], As[124], Rh[125,126], Ni[127-129], Co[130], Se[131], Ir[132] have been used till date as catalyst for Heck reaction. A Trimetallic nanoparticle such as Au-Ag-Pd has also been reportedly active for Heck reaction[133]. However, most of the work on Heck reaction has been carried out using Palladium metal complexes as catalysts[5,29,30,40,41,134-138]. A Palladium catalyst, in the presence of $Cu(OAc)_2$ as an oxidant has been used to improve the activity of the catalyst in some cases[139]. Bhanage and coworkers[140] have compared the activity, selectivity, stability and recycle performance of various metal-TPPTS complex using Pt, Pd, Rh, Ru, Ni and Co, under identical reaction conditions for Heck reaction and found that Pd is the best transition metal for catalyzing the Heck reaction in comparison to all other metals screened under given reaction conditions.

1.4.1.2 Different ligands used for Heck reaction in homogeneous medium

Various ligands, comprising phosphorous, nitrogen, sulphur or carbene have been used for Heck reaction and a summary of important studies on Pd catalysed Heck reaction with different ligands is presented in Table 1.3.

Amongst phosphorous ligands, Pd(0) phosphine complexes, such as $Pd(PPh_3)_4$ are reported to catalyse the Heck reaction. Kelkar et.al.[141] have carried out vinylation of 4-bromo-4'-hydroxybiphenyl with ethyl acrylate using $Pd(OAc)_2/PPh_3$ catalyst, where ethyl 4-(4'-hydroxyphenyl)cinnamate was formed as the vinylation product, while, 4-hydroxybiphenyl and ethyl cinnamate were formed as side products, attributed to the cleavage of the P-Ph bond of PPh_3 during the reaction. However, even slight modifications in the structure of ligand have found to give appreciable increment in the activity. Palladium(II) complex of Diphosphine ligand (Figure 1.1) as a catalyst precursor has been found to be highly active for the Heck reaction of methyl acrylate and iodobenzene, with a turnover frequency of 11,760 h^{-1} and a turnover no. of 1,176,000[142].

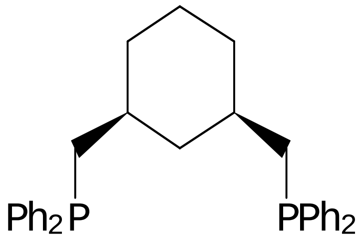


Figure 1.1: Diphosphine ligand

Table 1.3: Ligands/ Complexes used for Pd catalysed Heck reactions

Sr. No.	Type of Ligand / Complex	Reactants	Remark	Reference
Phosphorous based ligand				
1	Diphosphine-palladium(II) complex	Me acrylate, Bu acrylate, or styrene and bromobenzene, iodobenzene or 4-bromo benzaldehyde	TON upto 1,176,000 TOF upto 11,760 h^{-1}	142
2	Herrmann palladacycle $Pd_2(P(o\text{-Tol})_3)_2(\mu\text{-OAc})_2$,	Olefin (mainly acrylates) and bromoarenes	Air and moisture stable complex high TON upto 1,000,000	143
3	Tridentate PCP-ligand	Me acrylate, Bu acrylate, or styrene with aryl iodides and non-activated aryl bromides	Air and moisture stable TON upto 132900 PhCl-do not give good result	144
4	bis(2'-dimethylaminobiphenyl2-yl-*N*,*C*) di-μ-acetatodipalladium, bis(2-acetamidophenyl-*C*,*O*)di-μ-acetatodipalladium, bis[(2-dimethylaminomethyl)phenyl-*C*,*N*]di-μ-acetatodipalladium	Bu acrylate And 4- Me- C_6H_4 Cl	The catalysts are air-stable, and easy to handle Catalysts are also active for Suzuki and Buchwald - Hartwig amination	102
5	Palladacycle catalyst prepared using 2-iodoresorcinol	Bu acrylate And iodobenzene	TON 980 000 TOF 14 000 hr^{-1}	145

Table 1.3: Continued…

Sr. No.	Type of Ligand / Complex	Reactants	Remark	Reference
6	Oxapalladacycle	Bu acrylate, Vinyltributyl stannane With iodobenzene	99% yield of (E)-PhCH:CHCO$_2$Bu	146
7	[PdCl(C$_3$H$_5$)]$_2$-cis,cis,cis-1,2,3,4-tetrakis (diphenylphosphinomethyl)cyclopentane	Wide variety of alkenes vinyl bromides	The high levels of regio and stereo selectivity and the functional group tolerance was observed	147
8	1,4-bis(diisopropyl phosphino) butane (dippb)	Styrenes with derivatives of aryl chlorides	Vinylation of aryl chloride results in good conversions (upto 95%) Reaction is very sensitive to the nature of the chelating ligand since the Monophosphines were found to be ineffective	148
9	Pd$_2$(dba)$_3$.dba/PCy$_3$ (dba=Dibenzylideneacetone)	Cyclohexene and cyclopentene with derivatives of arylbromides	High selectivities for conjugated arylcyclo pentenes was obtained DMSO was used as a co-solvent	149

Table 1.3: Continued…

Sr. No.	Type of Ligand / Complex	Reactants	Remark	Reference
Nitrogen based ligand				
1	di-Me glyoxime, 8-hydroxyquinoline, salen, picolinic acid, DAB	Styrene , ethyl acrylate with derivatives of Aryl iodides, aryl bromides, aryl chlorides	Acetophenone oxime N,N-dimethylbenzyl amine and ferrocenyl oxime palladacycle were better catalysts TON 95,000; TOF 2500 h^{-1}	99
2	Palladacycle derived from chloropalladation of 3-(dimethylamino)-1-phenyl-1-propyne	Iodoarenes and activated bromoarenes with *n*-butylacrylate and styrene	TON up to 85,000 with deactivated bromoarenes and up to 1000 for activated chloroarenes	150
3	Oxime palladacycles	Methyl acrylate with iodobenzene and bromobenzene	Very efficient catalysts for a wide range of C-C coupling reactions. They usually require lower temperatures and shorter reaction times thermally stable complexes not sensitive to air or moisture, easily prepared from very cheap materials	151
4	Dimeric palladacycles complex with chelating N ligands	Bu acrylate p-bromo benzaldehyde	kinetic studies: The role of H_2O in accelerating the initial formation of the active catalyst species is noted	152
5	Amine and oxime palladacycles	Styrene , ethyl acrylate with derivatives of aryl iodides, bromides, and chlorides	TONs of 72, 000 – 1,45,454 TOFs of 1,625 – 20,780 hr^{-1}	153

Table 1.3: Continued…

Sr. No.	Type of Ligand / Complex	Reactants	Remark	Reference
6	N-acetyl-N-pyrid-2-yl-N-(3-methylpyrid-2yl)amine, N-acetyl-N-pyrid-2-yl-N-(6-methylpyrid-2yl)amine, N-acetyl-N-(6methyl-pyrid-2yl)-N-(4-methyl quinolin-2-yl)amine and N-acetyl-N-bis (6-methylpyrid-2-yl)amine	Styrene, ethyl acrylate with iodoarenes bromoarenes and chloroarenes	TON upto 200,000	154
7	*o*-(2-pyridyl)phenyl, *o*-(2-pyridyloxy)phenyl, *o*-(2-pyridylmethyl)phenyl, *o*-(*N*,*N*-dimethylaminomethyl)phenyl, 8-quinolylmethyl	Styrene, Et –acrylate with PhI, PhBr and 4-bromoace tophenone	TON up to 4100000 and TOF up to 530000 hr^{-1}	93
8	trans-bidentate nitrogen ligands, 1,2-bis(2-pyridylethynyl) benzenes	t-Butyl acrylate with derivatives of aryl iodides and aryl bromides	Air-, water-, and heat-stable catalyst TON of 79630 TOF of 1596hr^{-1}	155
9	Di-2-pyridylmethylamine	Bu-acrylate with PhI, PhBr and PhCl	TON of 10^5, TOF 10^4 h^{-1}) for PhI TON of 9300 and 80 for PhBr and PhCl respectively	156
10	Aryl oximes and amines	Ethyl acrylate and styrene with derivatives of iodo, bromo and chlorobenzene	TON upto 91,950 with bromoderivatives whereas less TON (upto 4100) for chloroarenes was obtained	157

Table 1.3: Continued…

Sr. No.	Type of Ligand / Complex	Reactants	Remark	Reference
Sulphur based ligand				
1	Palladacycles mainly derived from the ortho-palladation of benzylic thioethers	Acrylic esters and styrene with aryl iodides, bromides, and chlorides,	Air, water, and highly thermally stable TON 1,850,000	105
2	Salicylaldehyde N(4)-ethylthiosemicarbazone	Aryl bromides with styrene	TONs up to 43,000	158
Carbon based ligand				
1	Carbene-palladium complexes of the imidazole Series	n-Butyl acrylate with derivatives of bromoand chlorobenzene	Advantages are: a) high thermal and hydrolytic durability resulting from exceptionally stable M -C bonds (long shelf-life, stability to oxidation) and b) no need for an excess of the ligand.	33
2	Allylpalladium catalysts	Styrene with aryl halides	Catalyst also active for Suzuki coupling	159

Ohff et.al[144] have developed the air and moisture stable catalysts (Figure 1.2), which consist of Pd(II) species with a tridentate PCP-ligand. No catalyst degradation was observed after heating to 140^{0}C and a TON of 132900 was achieved.

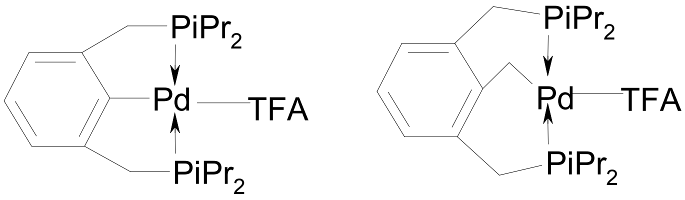


Figure 1.2: Palladium(II) complexes of tridentate PCP-ligand

In recent years, air and moisture stable palladacycles have been synthesized and used for the Heck reaction to achieve high turnover numbers (10^6) and turnover frequencies and also to activate less reactive chlorides[32,160,161]. The re-discovery by Hermann and Beller et.al of the unique catalytic activity of a well known dimeric complex (palladacycle) $Pd_2(P(o\text{-}Tol)_3)_2(\mu\text{-}OAc)_2$ (Figure 1.3), established a milestone in palladium catalysis[162] The complex, which is now often referred to, as Hermann's catalyst (*hc*) is definitely one of the most convenient forms of palladium complexes applied in Heck reactions.

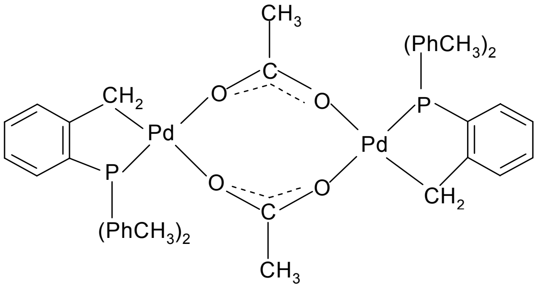


Figure 1.3: Herrmann Palladacycle

Miyazaki et.al.[35], have reported the synthesis of new palladacycle catalyst (Figure 1.4) which showed high catalytic activity with turnover numbers of up to 8,900,000 (mol product per mol Pd) and turnover frequencies of up to 400,000 (mol product per mol Pd per hour) in the coupling of iodobenzene with n-butyl acrylate.

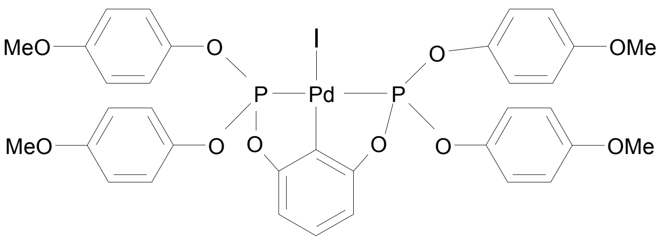


Figure 1.4: Miyazaki Palladacycle

Takenaka and Uozumi[37] have reported the Heck reaction of iodobenzene and methyl acrylate in NMP at 140°C in the presence of 1 mol per billion of the pincer palladium complex (Figure 1.5) to give methyl cinnamate with a TON of 5.2×10^8 and TOF 6500 per second.

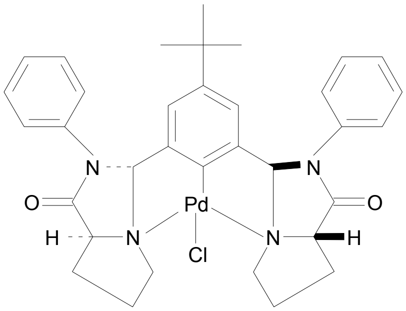


Figure 1.5: Uozumi palladacycle

In addition to tridentate PCP complexes, Pd complexes of a tridentate SCS ligand[163], pincer CNC bis-carbene ligand[164], carbene CCC and CNC Pincer[165], NCN Pincer ligand[166] are also reported for Heck reaction. Advances in phosphine ligands for palladium-catalyzed reactions has been reviewed by Woltermann[167]

Nitrogen based ligands used include mainly, hetrocyclic rings as electron donors, like pyridine, pyrimidine, imidazole rings and/or their combinations. A few examples of nitrogen-based ligands are discussed below.

Reetz and coworkers[168] have observed that the combination of palladium catalysts such as $PdCl_2(MeCN)_2$ and phosphonium halides Ar_4PX (Ar = Ph, 4-MeC_6H_4; X = Cl,Br,I) with the additive N,N-dimethylglycine (DMG) constitute the most active and selective catalyst system for Heck reactions with unreactive aryl halides leading to the product with 98:2 selectivity of trans: cis product at 98% conversion. Tetraarylphosphonium chlorides were found to be the most effective promoters of palladium catalysis in the Heck reaction, with the bromides less effective as promoters and the iodides ineffective. Arylpalladium phosphine complexes, generated in situ from the phosphonium salt and the palladium precursor, were proposed to be the active catalysts.

Tulloch and coworkers[169] have reported the pyridine functionalized N-heterocyclic carbene complexes for the Heck arylation (Figure 1.6, where R = t-Bu, mes, mes = mesityl) with a chelating C-N ligand. The crystal structure of the complex was determined.

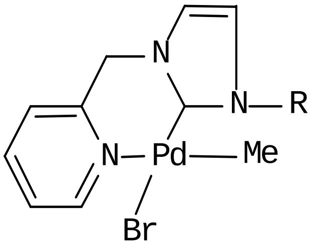


Figure 1.6: Pyridine functionalized N-heterocyclic carbene complex

Kawano et.al[155] have reported Pd(II) catalysts with trans-bidentate pyridine ligands (Figure 1.7), prepared by reaction of palladium(II) salts with the trans-bidentate nitrogen ligand i.e. 1,2-bis(2-pyridylethynyl)benzenes for the Heck olefination of aryl iodides to produce trans-acrylic esters. However the reaction was found to be very sensitive to the nature of the chelating ligand.

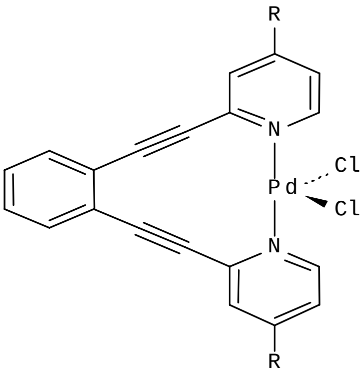
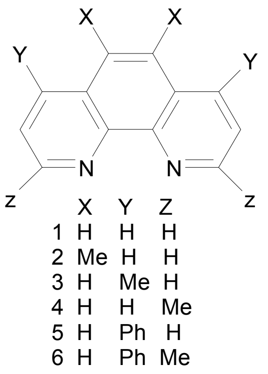


Figure 1.7: Pd(II) catalyst with trans-bidentate pyridine iigand

Cabri et.al[170] have used Pd complex with bidentate nitrogen ligands such as 1,10-Phenanthroline derivatives (Figure 1.8) for Heck type arylation of methyl acrylate and butyl vinyl ether by 1-naphthyl triflate at 80°C in DMF solvent. With this catalyst system a high yield of regioselective controlled product (addition to terminal olefinic carbon only) was obtained. However the same authors have reported that, other ligands such as 2,2'-bioxazoline and 2,2'-dipyridyl showed little or no activity for Heck reaction.



	X	Y	Z
1	H	H	H
2	Me	H	H
3	H	Me	H
4	H	H	Me
5	H	Ph	H
6	H	Ph	Me

Figure 1.8: 1,10-Phenanthroline derivatives

Iyer et.al[99] have reported catalysis by Pd complexes with nitrogen based ligands and have proposed that the nitrogen ligands can be an excellent alternative for the traditional phosphorous ligands in the Pd catalyzed Mizoroki-Heck reaction. They have prepared Pd complexes of di-Me glyoxime, 8-hydroxyquinoline, salen, picolinic acid, DAB ligands (Figure 1.9). Out of which the acetophenone oxime, N,N-dimethylbenzyl amine and ferrocenyl oxime palladacycle gave high yields of the E-cinnamates and E-stilbenes [TON (95,000) and TOF's (2500 h^{-1})]. These complexes were also found to activate aryl chlorides along with aryl iodides, aryl bromides with the help of Lewis acid and $(C_4H_9)_4NI$ as additive.

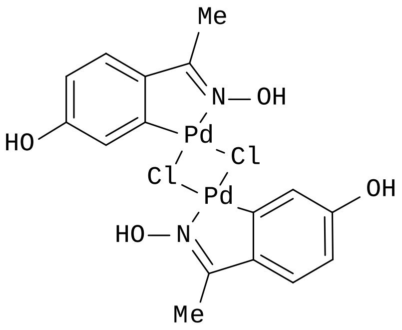


Figure 1.9: oxime-derived palladacycle

Although sulphur containing ligands have been less investigated than other donor atoms, transition metal complexes with these ligands are also found to be active catalysts in Heck reactions. Bayon et.al[171] have reviewed homogeneous catalysts with transition metal complexes containing sulfur ligands, where the use of different types of sulfur ligands and the characteristics of the coordination complexes are described together with the results of the catalytic reactions.

Kovala-Demertzi et.al[158] found that salicylaldehyde N(4)-ethylthiosemicarbazone-palladium complex (Figure 1.10) could catalyse the Heck reaction of aryl bromides with styrene under argon, with turnover nos. of up to 43,000 and with a high selectivity toward trans-stilbenes ranging from 92 to 96%.

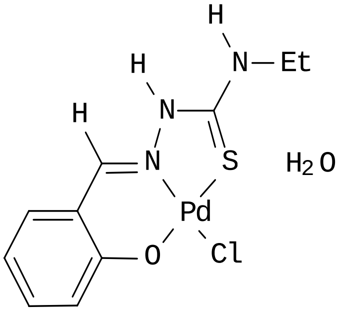


Figure 1.10: Salicylaldehyde N (4)-ethylthiosemicarbazone-palladium complex

Gruber and coworkers[105] have reported sulfur containing palladacycles (Figure 1.11) derived by the ortho palladation of benzylic thioether, as catalyst precursors for the Heck reaction. The reaction can be performed with aryl iodides, bromides, and chlorides, with acrylic esters and styrene, leading to turnover nos. up to 1,850,000.

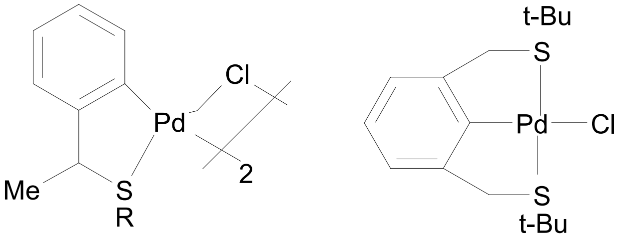


Figure 1.11: sulfur-containing Palladacycles

Apart from Nitrogen and sulphur containing ligands, Pd catalysts of carbon based ligands are also used and are found to catalyse the Heck reaction with appreciable yields

Herrmann and coworkers[33] have used carbene-palladium complex catalyst as shown in Figure 1.12 for the Heck olefination of chloro and bromoarenes. They found that the catalyst possesses the advantages such as: high thermal and hydrolytic stability resulting from the exceptionally stable M-C bonds (long shelf-life, stability to oxidation) and no need for an excess of the ligand.

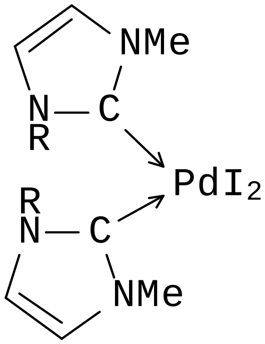


Figure 1.12: Palladium(II) complex of N-heterocyclic carbene

Tinkl and Hafner[159] have reported the use of the allylpalladium catalysts as shown in Figure 1.13 (where L = electron-donating neutral ligand; Z = anionic ligand; D = substituent; p = 0-5) for the Suzuki and Heck coupling in presence of K_2CO_3 using xylene solvent and obtained the product with >95% yield and >99% purity.

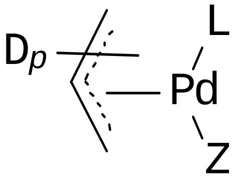


Figure 1.13: Allylpalladium catalysts

Crown ether tagged triarylphosphines, (18-crown-6) $CH_2NHC(O)C_6H_4$-4-PPh_2 and (15-crown-5) $CH_2OC_6H_4$-4-PPh_2 were also synthesized and applied for Heck reactions and their reactivity was evaluated against PPh_3 and polymer-bound PPh_3 catalysts[172].

1.4.1.3 Heck reaction using heterogeneous catalyst

Besides homogeneous catalytic systems, Heck reactions are equally well catalysed by heterogeneous catalysts. The major advantage of these catalysts is the ease of recovery and recycle, which can result in high cumulative TONs. Heterogeneous catalytic systems reported for Heck reactions, which include palladium on carbon[82,173-175], palladium supported metal oxides[176], clays[177] and molecular sieves[116,178,179], are studied in detail. Colloidal catalysts[180,181], soluble palladium clusters and palladium/nickel bimetallic clusters[182], nanoparticles[183] have also been investigated for the Heck reaction. With the more reactive aryl iodides and bromides, no ligands are necessary and hence heterogeneous catalysts like palladium on charcoal are also effective.

1.4.2 Heck reaction using heterogenised homogeneous catalysts

The issues related to the catalyst product separation and catalyst recovery are important and overshadow the application of even the catalysts which give TONs over a millions. A simple strategy to heterogenize the complexes on solid support can lead to very efficient and selective catalysts for the Heck reaction. There are various methods for heterogenization of homogeneous catalysts such as use of modified silica catalysts, polymer-supported catalysts, biphasic catalysis, supported liquid-phase catalysts and catalysis in ionic liquids and perfluorinated solvents. Catalysis in supercritical solvents has also been demonstrated for Heck reaction as described in next section.

1.4.2.1 Techniques used for heterogenization of homogeneous catalysts

1.4.2.1.1 Modified silica catalysts

This type of catalyst is prepared by modifying a support surface in such a way that P- or N-containing groups are linked to it. Hence metal complexes can be bound to the support via N or P containing linking group[184-189]. e.g. Kiviaho et al.[186] studied the vinylation of iodobenzene with methyl acrylate using Pd-based heterogeneous catalysts based on modified silica support. They prepared catalysts of the type SiO_2–X–$(NH)_2$–Pd–L_2 , where L = $P(C_6H_5)_3$ or C_6H_5CN and X = Sn, Al, or Ti. These catalysts were stable and reusable several times without suffering appreciable loss in catalytic activity.

1.4.2.1.2. Polymer-supported catalysts

Various Polymer-Supports such as phosphinated Polystyrene, [poly(styryl)phenanthroline] etc. have been used as supports for the preparation of these catalysts[163,190-196].

A Pd complex anchored to phosphinated polystyrene is reported to be more efficient than Pd/C, $Pd(OAc)_2$, $PdCl_2$, $Pd(OAc)_2/2PPh_3$ or $Pd(PPh_3)_4$ for the Heck reaction[190]

1.4.2.1.3 Supported Liquid-Phase Catalysts (SLPC)

In this variant, the catalyst is dissolved in a high boiling solvent, dispersed as a thin film on a support like silica[197,198]. The reaction takes place by diffusion of reactants into the thin film. This teqchnique cannot be used for liquid phase reactions if the reaction solvent and the supported liquid phase are miscible. To make the applicability more universal, the SLPC have been modified to use either water (SAPC) or glycol (SGPC) or ionic liquids (SILC) as the catalyst phase. There are several reports where SLPC's have been used for Heck reaction[106]. The scematic representation is as shown in Figure 1.14

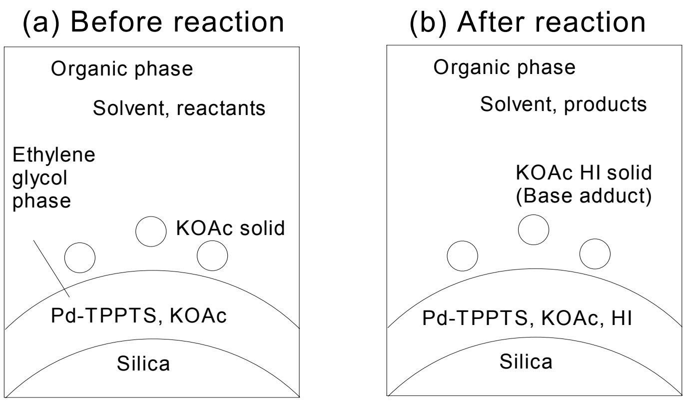


Figure 1.14: Schematic representation of Supported Glycol Phase Catalysts using Pd–TPPTS and an inorganic base -KOAc

1.4.2.1.4 Biphasic catalysis

Biphasic catalysis uses two immiscible liquid phases such that the catalyst exists in one phase while reactants and products are present in the other phase. It is essential that the solubility of the catalyst in the non-catalyst phase is negligible and the reactants and products should have finite solubility in the catalyst phase. Figure 1.15 shows schematic representation of a biphasic system consisting of water and organic liquid. The catalyst-containing phase can easily be separated by simple phase separation and it can be recycled for subsequent reactions. This system provides easy separation and recycling of the catalyst[140,199-203]

Biphasic catalysis is an extremely useful and practical means of solving the catalyst-product separation issues in homogeneous catalysis[28]. Use of Non aqueous Ionic Liquids, fluorous systems, thermophoric conditions and super critical and subcritical fluids are some of the extensions of biphasic catalysis. This strategy can offer the combined advantages of homogeneous and heterogeneous catalysis viz. high reactivity, easy separation of the product from the catalyst and recycle of catalyst by phase separation. Since product is efficiently removed from the reaction zone, any deactivation of the catalyst that may occur by interactions with the reactants or products is avoided leading to longer catalyst life.

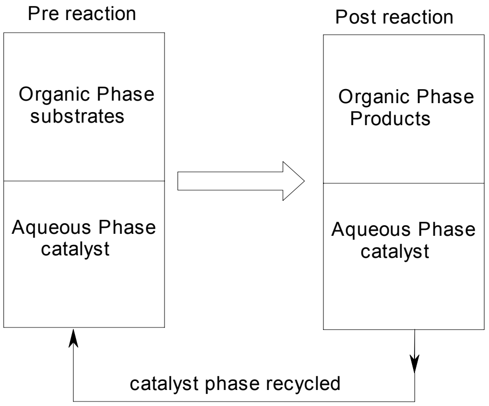


Figure 1.15: Biphasic catalysis

The biphasic media also includes the possibility of the use of water as one of the medium with several advantages like influencing selectivity and catalytic efficiency in addition to its economy and the safety. Since the major objective of this thesis was to develop biphasic catalysis for Heck reaction, the developments of catalysts have been discussed in the further sections, with more emphasis on catalysis in biphasic media.

1.4.2.2 Catalysts used in biphasic catalysis for Heck reaction

Despite all the advancements in the catalyst recovery techniques, most of the approaches are inefficient to prevent loss of catalyst (at ppm level), or prevent deactivation of the catalyst. Novel techniques use exotic materials / supports or approaches, which make them inconvenient for industrial application. The catalysis in biphasic media is one of the most promising approach to address the catalyst product separation issues in Heck chemistry.

Generally one of the phases in biphasic catalysis contains a polar solvent and the other is nonpolar. Catalysts can be designed to be in either of the phase whereas the reactant and product reside in the other phase (Table 1.4). Bhanage and coworkers[140] have reported the activity using various metals in combination with TPPTS [sodium salt of trisulfonated triphenylphosphine] ligand (Figure 1.16) for Heck reaction in a biphasic ethylene glycol and toluene medium. It was found that Pd showed best activity follwed by Ni. Rh was found to be inactive for this system.

Beller et.al.[204] have used carbohydrate-substituted triarylphosphine-ligands (Figure 1.17) for two-phase catalysis in ethylene glycol and xylene for the reaction of aryl bromide with styrene. Similarly Thorpe et.al.[205] have reported synthesis of disulfonated triphenyl phosphine (TPPDS) (Figure 1.18) and its application to biphasic catalysis for Heck reaction of methyl acrylate with iodobenzene. The activity of Pd complex of TPPDS was comparable with TPPTS and TPPMS, and the percentage of leaching was minimum with this ligand (3.5, 2.3 and 1.8ppm for TPPMS, TPPTS and TPPDS respectively).

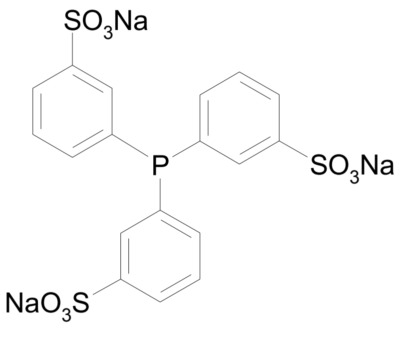
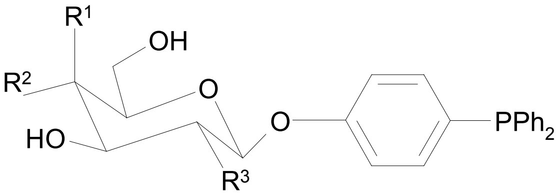


Figure 1.16: TPPTS (trisulfonated triphenylphosphine)



3a R^1=H, R^2=OH, R^3=NHAc
3b R^1=OH, R^2=H, R^3=OH
3c R^1=H, R^2=OH, R^3=OH

Figure 1.17: Carbohydrate substituted triarylphosphines-ligands

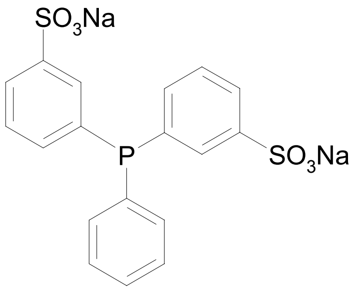


Figure 1.18: TPPDS (Thorpe catalyst)

Table 1.4: Ligands/ Complexes used for Pd catalysed Heck reactions in biphasic medium

Sr. No.	Type of Ligand / Complex	Reactants	Solvent system	Remark	Reference
1	TPPTS (trisodium salt of trisulfonated triphenylphosphine)	Butyl acrylate with iodobenzene	Ethylene glycol + Toluene	Activity, selectivity, stability and recycle performance were compared Pd> Ni > Ru > Co > Pt	140
2	TPPDS (disodium salt of disulfonated triphenylphosphine)	Me Acrylate Iodobenzene	Ethylene glycol + Toluene or xylene	The activity of Pd complex of TPPDS was comparable with TPPTS and TPPMS, and the percentage of leaching was minimum with this ligand	205
3	Carbohydrate substituted Triarylphosphines	Styrene and derivatives of bromobenzene	Ethylene glycol + Toluene	Better yields and higher catalyst activities were obtained than those with TPPTS TON upto 900	204
4	Polar hydrophilic phosphines containing mono- and disaccharide moieties	Styrene with derivatives bromobenezene	Ethylene glycol + xylene	TON upto 9000	206
5	Fluorine substituted triphenylphosphine ligands	Styrene with iodobenzene	Perfluorinated solvent along with organic solvent	The main drawback is the loss of activity of palladium due to the formation of inactive palladium black.	207

Table 1.4: Continued…

Sr. No	Type of Ligand / Complex	Reactants	Solvent system	Remark	Reference
6	Palladacycles with $[RC_6H_3CR':N(R)Pd(\mu\text{-}OAc)]_2$, $[RC_6H_3CHR'S(R)Pd(\mu\text{-}OAc)]_2$, imine p-$[R_{f_8}(CH_2)_3]C_6H_4C[:N(CH_2)_3R_{f_8}](CH_2)_2R_{f_8}$, thioether p-$[R_{f_8}(CH_2)_3]C_6H_4CH[S(CH_2)_3R_{f_8}](CH_2)_2R_{f_8}$	Methyl acrylate with iodobenzene	$CF_3C_6F_{11}$/ toluene or DMF	TON upto 20000 probably the nanoparticles are the active catalysts	208
7	$PdCl_2$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd(dba)_2$, 30% Pd/C, $(PPh_3)2PdCl_2$, and $(dppe)PdCl_2$	Styrene and iodobenzene	Superheated (260°C) and supercritical (400°C) water	Increased hydrogenation and hydrogenolysis, side reactions and lower overall recoveries were observed at the higher temp.	209
8	Phospha-palladacycles	Bromo- and chloro arenas	Non-aq. ionic liqs. (NAILs)	The advantages of homogeneous catalysis like high selectivity and activity of the catalysts as well as the possibility of recycling is possible with this system	210
9	TPPTS	Butyl acrylate with iodobenzene	SGPC (Supported Glycol-Phase Catalysts)	The activity of this catalyst is comparable to the active homogeneous catalysts reported. The catalyst system has advantages that the separation of product from the catalyst is very easy and its recycle efficiency is also very high.	211

Table 1.5: Ligands/ Complexes used for Pd catalysed Heck reactions in aqueous medium

Sr. No.	Type of Ligand / Complex	Reactants	Solvent system	Remark	Reference
1	$Pd(OAc)_2$ / No ligand	Acrylic acid and acrylonitrile with o-, m-, p-iodobenzoic acid and p-iodophenol.	Water	Good activity without ligand in water. simple method for the synthesis of substituted cimnunic acids and cinnamonitriles in high yields.	212
2	TXPTS [tri(4,6-dimethyl-3-sulfonatophenyl) phosphine trisodium salt]	Styrene and sodium acrylate with Derivatives of aryl bromides	CH_3CN / water	Heck couplings of unactivated and deactivated aryl bromides under relatively mild conditions in aqueous solvents have been achieved	213
3	p-hydroxyacetophenone oxime-derived palladacycle	t-butyl acrylate with derivatives of iodobenzene	Water	Mono and diarylation under thermal or microwave conditions TON upto 59000	94
4	Ph_3P, TPPTS, $Pd(dba)_2$ and $Pd(OAc)_2$	Butyl Acrylate with 4-bromo benzonitrile and iodobenzene	$MeOH/H_2O$ $MeCN/H_2O$, DMF/H_2O	A comparative study of some pd-catalysed heck reactions in polar- and aqueous biphasic media. Ligand is essential to a successful reaction when working with bromo substrates in polar or aqueous biphasic media	214
5	$Pd-PPh_3$ in presence of quaternary ammonium salt (QX)	Me acrylate with iodobenzene	Dry CH_3CN and H_2O/CH_3CN	A reactions involving water-insoluble substrates and phosphine ligand can be efficiently realised in water, provided that they are performed in the presence of a combination of an alkali metal carbonate and a quatemary ammonium salt,	215

Table 1.5: Continued….

Sr. No.	Type of Ligand / Complex	Reactants	Solvent system	Remark	Reference
6	$Pd(OAc)_2$ /PPh_3	Ethyl acrylate and different vinylic reagents with aryl iodide bound to a solid support	Water/DMF	Carbon-carbon bonds in high yield under very mild conditions on a solid support. Conversion upto 95% in 4 hrs	216
7	TPPMS (monosodium salt of monosulfonated triphenylphosphine)	Ethylene with derivatives of bromoarenes	H_2O/THF	The yield was poor and a large amount of substrate was recovered unchanged. This was attributed to the solubility of ethylene into water, which is very low	217
8	TPPTS	Intramolecular Heck-type reactions of cyclohexene derivative	H_2O/CH_3CN	By proper choice of the reaction medium, it is thus possible to obtain either the endo or the exo ring closure starting from the same substrate	218
9	Palladium on carbon	Styrene, chlorobenzene and substituted chlorobenzene	Water	PTC enhances the reactivity of chloroarenes Conversions upto 100% were achieved	219

1.4.2.3 Catalysts used in aqueous medium for Heck reaction

The use of aqueous solvents in Heck reaction has been studied to achieve environmentally and technologically safe processes[220]. For use in such aqueous systems, the ligands are modified by incorporating hydrophilic substituents such as sulfonated (e.g. TPPMS[221], TPPTS[140,199]) or carboxylate and ammonium[215] (Figure 1.19). Sulfonated triphenylphosphines are the most commonly used water-soluble ligands, which when complexed with palladium promotes aqueous phase soluble catalysts for reaction in water.

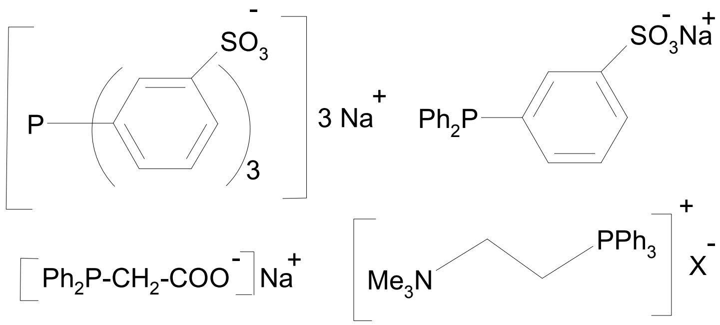


Figure 1.19: commonly used water-soluble ligands

Water-soluble catalytic systems utilizing sulphonated phosphines (TPPTS) have been successfully employed in Heck reaction. In addition TPPMS[221] and TPPDS[205] are known to be active for Heck reaction in water. Also a carbohydrate-substituted moiety is reported to render water solubility for the catalyst[204]. Heck coupling in aqueous media is also reported in the presence of phase transfer catalysts[222]. A summary of important studies on Pd catalysed Heck reaction with different ligands in aqueous medium is presented in Table 1.5.

$Pd(OAc)_2$ catalyzed Heck reactions of aryl halides with acrylic acid or acrylonitrile gave corresponding coupling products in high yields with $NaHCO_3$ or K_2CO_3 as a base in CH_3CN + water[212]. The $Pd(OAc)_2$–TPPTS catalyzed Heck reaction of (*S*)-4-bromotryptophan with 1,1-dimethylallyl alcohol in alkaline aqueous media is reportedly an active system at 130°C, for the synthesis of optically active clavicipitic acid[63] (yield 61%). The functional group in the substrate does not need to be protected in the course of palladium-catalyzed reactions. In presence of organic solvent (dioxane or DMF), the reaction gave a complex mixture. The high dielectric constant of water was thought to be responsible for the higher efficiency in aqueous conditions.

A Pd catalysed Heck coupling reaction for the synthesis of unprotected branched-chain sugar has been reported in DMF-H_2O (5:1) by using $Pd(dba)_2$ and $P(o\text{-}tol)_3$, with high yields (up to 84%)[223]. Water-soluble phosphine ligands containing *m*-guanidinium moieties[224,225] were synthesized and used along with Pd for C-C coupling reactions between p-iodobenzoic acid and (trifluoroacetyl)propargylamine in an aqueous solvent mixture (30-50% CH_3CN/DMF) at 35-50°C, with appreciable activity. Microwave activation appear to be beneficial for Heck-type coupling of simple alkenes in water[226-228]. Bulky phosphine ligands were found to increase the rate of the reaction[229] in such cases.

In addition to palladium catalyst for Heck reactions in water, other transition metals have also been reported active for arylation and vinylation of olefins. Lautens and coworkers[125,230] have studied the arylation of alkene in presence of a rhodium catalyst $[Rh(COD)Cl]_2$, Na_2CO_3 and a surfactant (SDS) in aqueous media. The addition product was found to be strongly affected by the nature of the aryl group.

Amengual et.al.[231] have reported a Li based ligand with Pd catalyst i.e. m- or p-TPPTC (trilithium 3,3',3''- or 4,4',4''-phosphinotriylbenzenecarboxylate), for the reaction of iodobenzene with ethyl acrylate in a 3:1 mixt. of NMP/H_2O giving 100% conversion.

Najera and coworkers[156] have prepared Di-2-pyridylmethylamine - based Palladium complexes (Figure 1.20) for Heck, Suzuki, and Sonogashira reactions in organic and aqueous solvents (NMP / DMF with water) under homogeneous conditions.

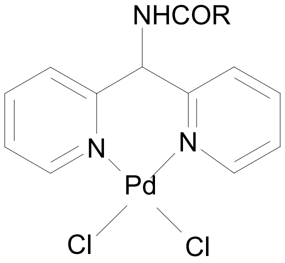


Figure 1.20: Di-2-pyridylmethylamine-based Palladium complex

A TON of 10^5 and TOF of 10^4 was observed for the Heck reaction of iodobenzene with butyl acrylate, whereas for reaction of bromobenzene and chlorobenzene with butyl acrylate, the TONs observed were 9300 and 80 respectively.

Water soluble Pd complexes with TXPTS (tri(4,6-dimethyl-3-sulfonatophenyl)phosphine trisodium salt) (Figure 1.21) ligand have been reported for Heck reaction[213] , but in presence of water and CH_3CN, to form a homogeneous rather than a biphasic aqueous medium

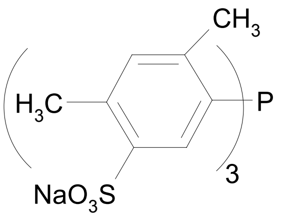


Figure 1.21: Tri (4, 6-dimethyl-3-sulfonatophenyl) phosphine trisodium salt (TXPTS)

Pd Phosphine complexes supported on Amphiphilic resin[232] and Amberlite IRA-400 (basic)[233] have also been used as the catalyst for Heck reaction in water. Palladium catalyzed Heck reactions in aqueous medium has been reviewed in detail in which, the compatibility of water-soluble palladium catalysts has been explained with the conclusion that, the careful selection of reaction conditions, co-solvents and catalysts, is very important for long life catalysts and new selectivities[200,214].

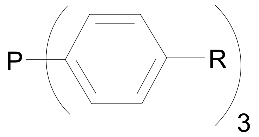
Apart from the above biphasic systems, some other techniques such as use of fluorous systems, Non aqueous Ionic Liquid Solvents, thermophoric system or super critical and subcritical fluids have also been investigated for Heck reaction.

Non aqueous Ionic Liquid Solvents

Non-volatile, room temperature ionic liquids (IL) based on alkylimidazolium and other quaternary ammonium/ pyridinium salts have emerged as valuable, alternative green solvents for catalytic processes over the last few years. Nonaqueous ionic liquid solvents (NAILS) provide a medium that dissolves the palladium catalyst and allows the product and by-products to be easily separated, and so the catalyst and ionic liquid can be recycled. NAILS such as 1-butyl-3-methyl imidazolium or *N*-alkylpyridinium hexafluorophosphate[234], Molten tetrabutyl ammonium bromide[83,210] are reorted to be efficient solvents for Heck reaction. Herrmann and Bohm[210] used phospha-palladacycles, in the medium of several NAILS for Heck reactions. Molten tetrabutyl ammonium bromide was found to be the best solvent. They reported preliminary results with bromoarenes and chloroarenes, indicating that NAILS are a superior reaction medium for the catalytic Heck vinylation of chloroarenes. NAILS have several advantages such as high activity, improved thermal stability, and increased lifetime of the catalyst for Heck reaction, compared with conventional solvents. Development and perspective of ionic liquids in biphasic catalysis has been reviewed in detail[235,236].

Fluorous systems

One of the approaches in the biphasic reaction is based on the use of fluorous biphasic systems (FBS). In this concept, the organometallic catalyst (generally incorporating fluorous moieties) is solubilized in the perfluorinated solvent phase while the reactants remain in the organic phase. The fluorous phase is separated from the reagents and products, either during the process or during the workup. Heck reactions in these media with fluorine substituted triphenylphosphine ligands (Figure 1.22) have been reported[207,237,238]. The main drawback is the loss of activity of palladium due to the formation of inactive palladium black.



1 R=$OCH_2C_7F_{15}$ (%F=58.7)

2 R=C_6F_{13} (%F=60.9)

3 R=$O(CH_2)_2OCH_2CF_2[OCF(CF_3)CF2]_p(OCF_2)_qOCF_3$
p=3.38; Q=0.11
(%F=56.1)

Figure 1.22: Fluorine substituted triphenylphosphine ligands

Thermophoric systems

In this approach, a soluble polymer facilitates catalyst recovery and separation of a catalyst from reaction products. The separation in these systems relies on two ideas.

(i) Many binary and ternary solvent systems exhibit a reversible increase in miscibility with increasing temperature and (ii) a soluble polymer should have a strong phase preference for one phase under biphasic conditions i.e. a liquid/liquid separation process that relies on the ready tunability of polymer solubility to separate and recover ligands, metals, and catalysts in the nonpolar phase of a mixture of polar and nonpolar solvents[220] (Figure 1.23).

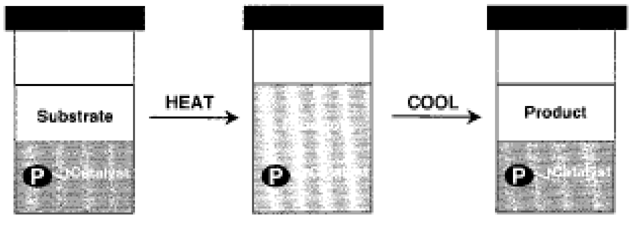


Figure 1.23: Schematic representation of thermophoric catalysis

The authors report the Heck reaction using methyl acrylate with iodobenzene in presence of $CF_3C_6F_{11}$/ toluene or DMF as a solvent system at 140^oC, gave TON upto 20000, which was predicted to be probably due to the formation of the nanoparticles during the reaction.

Supercritical fluids and subcritical fluids

Supercritical fluids have shown promise as media for organic reactions. Supercritical carbon dioxide is considered one of the environmentally friendly solvents. Supercritical CO_2 is a good solvent for organic compounds but a very poor one for organometallic catalysts. Since the solvent properties of supercritical CO_2 are comparable with those of fluorinated solvents, catalyst incorporating fluorine such as palladium trifluoroacetate are used. Catalysis in supercritical solvents with catalyst-separation techniques is one of the promising alternatives for the development of truly ecofriendly processes, as no organic solvent is needed and the solvent–catalyst separation is easy by simple phase separation at ambient pressure[228,239-246].

Besides an academic interest in the fluorous biphasic systems and other biphasic systems, a majority of the studies in biphasic Heck reaction have been conducted with ethylene glycol as the catalyst medium. A few studies have been reported with aqueous systems, however there are practically no reports on a true aqueous phase catalyst for application in biphasic media.

1.4.3 Other components used in Heck reaction

Variety of olefins, aryl halides, transition metal complex catalysts, bases, and solvents have been used to produce the desired products by Heck reaction.

Substrates used for Heck reactions

A wide range of functional groups, both in the alkene and in the halide, are compatible with Heck coupling. It is generally observed that amongst aryl halides iodoarenes reacts faster than bromoarenes, which in turn are faster in their activity than chloroarenes. It is also observed that, if the electron-withdrawing group (-I effect) is attached as a substituent to aryl halide and/or if the electron-donating group (+I effect) is attached as a substituent to olefin then the rate of Heck reaction is enhanced[150]. Hence aryl bromides and aryl iodides, especially those bearing electron-withdrawing substituents are the preferred substrates for the studies. They can be easily activated and very low palladium loadings (<0.0001 mol%) can be used. However, aryl bromides and aryl iodides are relatively expensive, and the heavy halide atom that is lost, results in poor atom efficiency of the process. Alternative halides are cheap aryl chlorides, which unfortunately have a much lower reactivity. Attempts for the activation of aryl chlorides for Heck reactions have been reported[247,248] by designing catalyst system like Pd supported on various oxides, fluorides and activated carbon, incorporated into zeolites etc.

Apart from aryl halide as an arylating agent, other compounds such as aromatic carboxylic anhydrides[249,250] tosylates[251] aroyl chlorides[252] Tetraarylphosphonium halides[253] can also be used for Heck reaction.

The reactivity of the olefinic starting material decreases with the number of substituents on the double bond. Ethylene is therefore the most reactive one but selectivity can be a problem due to further reaction. Monosubstituted alkenes react with ease, whereas higher substituted olefins often give unsatisfactory yields. Depending on the substituents of a monosubstituted olefin, the aryl moiety is attached either to the terminal or the internal carbon and the resulting stereochemistry of the double bond can be either E or Z. As a consequence, many olefins give product mixtures, which are sometimes difficult to separate. Therefore prefered substrates for study are in general the olefins bearing electron-withdrawing groups such as acrylates or acrylonitriles. These olefins mainly give linear products.

Bases used for Heck reactions

Both organic and inorganic bases like Et_3N, Bu_3N, alkali acetates, carbonates, phosphates etc are reported to assist the Heck reaction. The primary function of the base is to neutralize the acid (HX) resulting from the formal exchange of a hydrogen atom with an aryl or vinyl group. Amberlite IRA-400 (basic) ion exchange resin have also been reported to be active for the Heck reaction[254]. Heck reaction under base free condition has also been reported[252]. The preferred bases that are used in majority of investigations are the alkali metal acetates and tri alkyl (ethyl) amine.

Solvents used for Heck reactions

Virtually all solvents have been used for Heck reactions but the most suitable are polar solvents such as acetonitrile, DMF, DMA, and NMP etc having an ability to stabilise palladium complexes (by weak coordination). The search for alternative media is targeted at the development of highly productive, environmentally safe, recyclable techniques, which can be promoted to large-scale applications. In some cases carbon dioxide is used as a solvent for these type of reactions[255].

The Heck reaction without use of solvent are reported with microwave irradiation using potassium fluoride/alumina supported Pd catalyst[256].

Various other techniques used for Heck reactions

Apart from improvement in the catalytic activity, attempts have been made to improve the reaction conditions so as to get improved results. Use of high-pressure conditions[257,258], thermomorphic conditions[103], ultrasound[259] and microwave-promoted reactions[226,260-262] are some of the approaches. Nowadays lot of attention has been paid towards asymmetric Heck reaction, as the importance of stereochemically different substrates have been recognised[263-265]

Heck reaction in combination with Robinson-Type Annulation[266] or catalyzed by Pd/C, in a triphasic-organic/Aliquat 336/aqueous-solvent system[267], or a multi-phase Heck reaction[268], the Double and multiple Heck reactions[269] are few examples which try to enhance the applicability of Heck reaction, in combination with some other reactions or techniques. Computational study of a Heck reaction mechanism catalyzed by palladium species has been reported, where the feasibility of an alternative pathway that involves a Pd^{II}/Pd^{IV} redox system is investigated[270].

1.5 Mechanism of Heck reaction

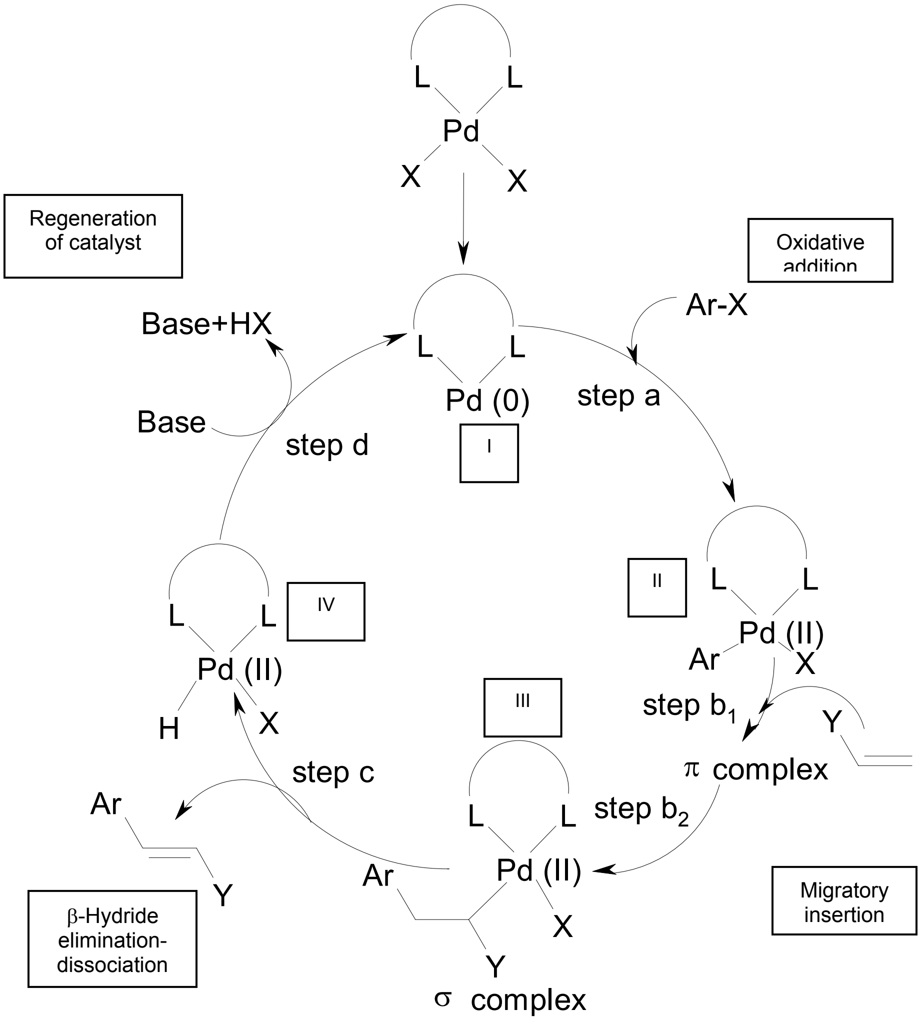
There are many reports in which the mechanism of the Heck reaction has been discussed[271-273]. The generally accepted mechanism is the one reported by Cabri and Candiani[135], which goes through the organometallic intermediates as shown in scheme 1.3. There are two major steps involved in the reaction mechanism, oxidative addition and reductive elimination.

Oxidative addition (Step a)

The oxidative addition (Scheme 1.3, step a) of RX to the palladium(0) complex takes place at a reasonable temperature. The catalytically active species is a 14-electron complex, $L_2Pd(0)$, The oxidative addition (step a) proceeds as a concerted process in which C-X bond rupture is synchronized with the formation of M-C and M-X bonds. This is normally assumed as the rate-determining step.

Coordination-insertion or Migratory insertion (Step b)

This is the step of the Heck cycle, in which a new C-C bond is formed via a π-complex formation. It is this step, which is responsible for regio and stereo discrimination. Theoretical studies on the insertion of olefin indicate that the insertion process requires a coplanar assembly of the metal, olefin, and the hydride. Therefore, the insertion process is stereoselective and occurs in a *syn* manner.



Scheme 1.3: Mechanism of Heck reaction[135]

β-Hydride elimination-dissociation (Step c)

The β-hydride elimination is stereoselective and occurs in a syn manner; its efficiency is related to the dissociation of the olefin from the palladium(II)-hydride complex. The β-hydride elimination is a reversible process, and a slower dissociation of the olefin can determine the formation of several products because of the isomerization of the double bond.

Regeneration of the $L_2Pd(0)$ (Step d).

The presence of a base is necessary in order to transform the Pd (II) complex i.e. $L_2Pd(H)X$ into the active $L_2Pd(O)$ complex and complete the catalytic cycle.

The mechanism given above is formulated based on a Pd^0/Pd^{II} transition. The feasibility of an alternative pathway that involves a Pd^{II}/Pd^{IV} redox system has also been reported[270,274-277], which has also been supporeted by computational studies[270]. However, the most accepted mechanism is the one based on Pd^0/Pd^{II} transition as discussed above.

1.6 Kinetics of Heck reaction

Although the Heck chemistry is now known for more than 35 years, very few studies have been carried out, to understand the kinetic behavior of this reaction[275,278-281], and still fewer kinetic rate models have been proposed[152,272,274,282-284]. In addition a majority of the work carried out till date on the kinetics of this reaction is on the reaction in a homogeneous medium[152,272,274,275,278-287].

Benhaddou et.al[278] reported the homogeneous kinetics of the $PdCl_2$ catalyzed arylation of pent-1-en-3-ol and but-3-en-2-ol. A pseudo-first-order rate constant was reported with aryl iodide concentration. The synergistic effect with a R_3N / NaOAc combination was also observed. These authors proposed no rate equation.

The mechanistic and kinetic studies of Palladium catalytic systems have been reviewed by Amatore and Jutand[275], where the mechanism of elementary steps has been investigated. The review is mainly focused on the role of anions (chloride or acetate ion) on the palladium(II) complexes or the precursors of palladium(0) complexes.

van Strijdonck and co-workers[280] have reported first order kinetics in styrene and zero order in iodobenzene concentration for $Pd(dba)_2$ [dba =dibenzylideneacetone] catalysed Heck reaction (in presence of phosphorus amidite as a additional ligand). A half-order dependence on catalyst concentration was observed, which was attributed to the formation of a dimeric $[PdLArX]_2$ species.

Zhao et.al[284] have investigated the kinetics of Heck vinylation of iodobenzene with Me acrylate using homogeneous $Pd(OAc)_2$/TPP catalyst. The rate was found to have linear dependence on iodobenzene concentration and a partial order with catalyst and Iodide concentrations. The rate passed through a maximum with Et3N (base) concentration. An empirical rate equation (equation1.1) was derived to fit the experimental data.

$$\text{Rate} = \frac{k[\text{PhI}][\text{MeAcr}]^2[\text{Et}_3\text{N}][\text{Cat}]}{(1+K_{Acr}[\text{Acr}]^2)(1+K_{Et3N}[\text{Et}_3\text{N}]^4)(1+K_{Cat}[\text{Cat}])^3(1+K_{TPP}[\text{TPP}])} \qquad [1.1]$$

Rosner et.al.[152] have investigated the kinetics of olefination of p-bromobenzaldehyde with butyl acrylate using a dimeric C-N palladacycle complex under dry conditions. They observed a first-order dependence of the rate on olefin concentration and a zero order dependence on the aryl halide (p-bromobenzaldehyde) concentration. They have proposed the following rate equation (equation1.2).

$$r = \frac{2\,k_1k_2k_3\,[\text{Olefin}][\text{ArX}][\text{Pd}]}{\{k_2k_3\,[\text{ArX}] + k_1(k_2 + k_3\,[\text{Olefin}] + k_1k_2\,[\text{ArX}]) + (k_2k_3\,[\text{ArX}] + k_1(k_{-2} + k_3\,[\text{Olefin}] + k_1k_2\,[\text{Olefin}][\text{ArX}])^2 + 8K_R(k_1(k_{-2} + k_3)[\text{Olefin}])^2[\text{Pd}])^{1/2}} \qquad [1.2]$$

Rosner et.al[283] observed an induction period in the Heck olefination of p-bromobenzaldehyde with Bu acrylate using a dimeric palladacycle complex as a catalyst precursor. They proposed an empirical rate model (equation1.3) to predict the rate data observed.

$$\text{rate} = \frac{V_m\,'[\text{ArX}][\text{olefin}](1-\exp(-k_{diss}\,t))}{(K+[\text{ArX}])} \qquad [1.3]$$

A negative order with respect to olefin has been reported by Amatore et.al[274] for the $Pd(OAc)_2$ / PPh_3 catalyzed vinylation of iodobenzene with styrene and Methyl acrylate in DMF. Following rate equation was proposed by them (equation 1.4).

$$\frac{d[\text{Pd}^0]}{dt} = -\frac{kK_1[\text{PhI}][\text{Pd}^0]}{[\text{L}] + K_1K_2\,[\text{olefin}]} \qquad [1.4]$$

Consorti and coworkers[272] have carried out Heck reaction of iodobenzene with Bu acrylate and Me acrylate using the CN-palladacycle $\{Pd[\kappa^1\text{-}C,\kappa^1\text{-}N\text{-}C{:}(C_6H_5)C(Cl)CH_2NMe2](\mu\text{-}Cl)\}_2$. They report a first order dependence with respect to Pd catalyst and fractional order with respect to iodobenzene and Me acrylate. In this study they have also explained the mechanism of Heck reaction. They have proposed the following rate expression (equation 1.5).

$$-d[PhI]/dt = \frac{k_1k_2k_3[PhI][Acr][Pd]}{k_2k_3[Acr]+k_1k_2[PhI][Acr]+k_1k_3[PhI]} \qquad [1.5]$$

An investigation of the kinetics of the Heck reaction between 4-iodo-anisole and styrene catalyzed by PCP pincer palladium (II) complex {cis-1,3-bis[(di-tert-butylphosphino) methyl]-cyclohexane} palladium (II) iodide has been performed in DMF-d_7 solution by Nilsson and Wendt[282]. A first order dependence, with respect to 4-iodo-anisole and Pd was observed for the coupling reaction. (equation 1.6).

$$rate = K_{obs}[ArX] \; ; K_{obs} = \frac{k_1k_2[Pd][styrene]}{1+k_1[styrene]} \qquad [1.6]$$

Recently Sud et.al.[288] have reported the kinetics of vinylation of 4-bromoacetophenone with *n*-butyl acrylate using Herrmann Palladacycle catalyst, in the presence of sodium acetate as a base and tetrabutylammonium bromide (TBAB) as a promoter in *N*-methyl-2-pyrrolidinone (NMP) solvent. 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. They have proposed the following rate expression (equation 1.7).

$$R = \frac{k\,[ArX][olefin][base][TBAB][catalyst]^{0.5}}{(1+K_B[olefin]^2)(1+K_C[base])(1+K_D[TBAB]^2)} \qquad [1.7]$$

There is only a single report which deals with the effect of various parameters on the rate of Heck reaction using supported liquid (ethylene glycol) phase catalysts (SLPC) comprising Pd-TPPTS (triphenylphosphine trisulfonate sodium salt) complex catalyst[289] for the investigation of the kinetics of iodobenzene and butyl acrylate in the presence of amine. The reaction rate depends on the concentration of Pd-TPPTS complex in the supported ethylene glycol phase. The rate showed first order dependence on iodobenzene and butyl acrylate concentration, whereas with triethylamine (Et_3N) a maximum was observed.

In general it has been observed that the reaction has a positive dependence of the activity on olefin, aryl halide and the base. It can also be seen from the above literature that, the majority of the work on kinetics of Heck reaction carried out till date is in the homogeneous medium and detailed studies on the kinetics of the Heck reaction in biphasic medium are lacking.

1.7 Scope and objectives

It is evident from the literature review presented here that, although, Heck reaction has been studied in detail by many research groups, very few studies have been carried out on Heck reaction in biphasic media. Biphasic catalysis has found numerous industrial applications, however none are in Heck coupling on large scale. It is thus of interest to investigate biphasic Heck reaction in detail.

Biphasic catalytic reactions using water-soluble transition metal complexes are also of importance, since they provide unique advantages of water medium. While, biphasic hydroformylation of olefins using water-soluble rhodium catalysts has been practiced industrially[91] the biphasic Heck reaction of olefins and aryl halide is still at an exploratory stage.

In most of the reports on biphasic Heck reaction, the catalyst employed is a phosphine based complex. Since phosphine free complxes also have stability at high temperatures, development of such catalyst with application in biphasic Heck reaction would be more relevant, in addition to phosphine containing catalysts.

With these objectives, the following specific problems were chosen for the present work

(i) Synthesis and characterization of palladium complexes containing chelating nitrogen and phosphorous ligands and their application as catalysts for Heck reaction in biphasic medium (glycol-organic).

(ii) Detailed investigations on the application of $PdCl_2$(bipy) as a catalyst for Heck reaction in two-phase media (glycol-organic) and comparison of its performance with that in a homogeneous medium.

(iii) Investigations of the kinetics of the Heck reaction using $PdCl_2$(bipy) catalyst in glycol-organic biphasic medium, with the objective of developing a suitable rate equation and comparison of the kinetics with that in homogeneous medium.

(iv) Investigations on Heck reaction of water-soluble substrates using biphasic system (wherein the catalyst is soluble in the organic phase and the aqueous phase contains the water-soluble substrate and products), in presence of P-C palladacycle catalyst.

(v) Synthesis and characterization of a water-soluble ligand derived from tri-o-tolyl phosphine and its use for synthesis of stable water-soluble Palladium catalyst. Studies on Heck reaction in aqueous-organic biphasic media with detailed investigations on activity and selectivity in a biphasic water-organic system using this catalyst.

References

(1) Masters. C Homogeneous Transition-Metal Catalysis,; Chap-man & Hall: London, 1981.

(2) Parshall, G. W. Homogeneous Catalysis; Wiley-Interscience: New York, 1980.

(3) Weisseimel, K.; Arpe, H. J. Industrial Organic Chemistry,2nd ed.; VCH Press: Weinheim, 1993.

(4) Cornils, B.; Herrman, W. A. (Ed.s) Applied Homogeneous Catalysis with Organometallic Compounds, vol 1 and 2; VCH: Weinheim, 1996.

(5) Beller, M.; Riermerier, T. H.; Stark, G. Ed. Mathias Beller, Carsten Bolm, Transition Metals for Organic Synthesis: building blocks and fine chemicals, vol 1 and 2 Wiley VCH: Weinheim, 1998.

(6) Jira, R. Ethylene and its industrial derivatives, Miller S.A. (Ed.), Ernest Benn Ltd., p 650., 1969.

(7) Lutz, E. F. J. Chem. Educ. 1986, 63, 202.

(8) Ludecke, V. D. Encyclopedia of chemical processing and design, Mcketta J.J. and Cunningham W.A. (Eds.), Maedetl and Decker, p. 146., 1976.

(9) Cornils, B.; Kuntz, E. J. Organomet. Chem. 1995, 502 177-186.

(10) Hohenschutz, H.; Franz, D.; Bulow, H.; Dinkhauser, G. (BASF AG), DE 2133349 (1973).

(11) Partenheimer, W. Catalysis Today 1995, 23, 69.

(12) Ugo, R.; Renato, T.; Marcello, M. M.; Plerluigi, R. Ind. Eng. Chem. Prod. Res. Dev. 1980, 19 396.

(13) Powell, J. B.; Slaugh, L. H.; Mullin, S. B.; Thomason, T. B.; Weider, P. R. US 5981808 (1999)

(14) Greene, C. R.; Meeker, R. E. Shell Oil Co. DE-AS 1212953 1967.

(15) Coover, H. W.; Hart, R. C. Chem. Eng. Prog. 1982, 72.

(16) Agreda, V. H.; Pond, D. M.; Zoeller, J. R. CHEMTCH 1992, 172.

(17) Roth, J. F.; Craddock, J. H.; Hershmann, A.; Paulik, F. E. CHEMTCH. 1971, 1, 600.

(18) Hohenschutz, H.; von Kutepow, N.; Himmele, W. Hydrocarbon Process, 45 , 141., 1966.

(19) Watson, D. J. Catalysis of Organic reactions,. Herkes F.E., Heinemann H., (Eds) Marcell Decker Inc. 369, 1998.

(20) Elango, V.; Murphy, M. A.; Mott, G. N.; Zey, E. G.; Smith, B. L.; Moss, G. L. EP 400

892, (1990).

(21) Casssar, L. Chem. Ind. 1985, 67, 256.

(22) Parshall, G. W.; Nugent, W. A. CHEMTCH 1988, 314.

(23) Blumenberg, B. Nahr. Chem. Tech. Lab. 1984, 480.

(24) Fitton, P.; Moffet, H. US 4124619 (1978).

(25) Pommer, H.; Nuerrenbach, A. Pure. Appl. Chem 1975, 43, 527.

(26) Bhanage, B. M.; Arai, M. Catalysis reviews 2001, 43, 315-344

(27) Keim, W. Chem. Ing. Techn. 1984, 56, 850.

(28) Kuntz, E. G. CHEMTECH 1987, 17, 570-575.

(29) Heck, R. F. J.Am.Chem.Soc. 1968, 90, 5518.

(30) Mizoroki, T.; Mori, K.; Ozaki, A. Bull. Chem. Soc. Jpn. 1971, 44, 581.

(31) Dieck, H. A.; Heck, R. F. J. Am. Chem. Soc. 1974, 96, 1133-1136.

(32) Herrmann, W. A.; Brossmer, C.; Reisiger, C. P.; Riermeier, T.-H.; Öfele, K.; Beller, M. Chem. Eur. J. 1997, 3, 1357-1364.

(33) Herrmann, W. A.; Elison, M.; Fisher, J.; Köcher, C.; Artus, G. R. J. Angew. Chem. Int. Ed. Engl. 1995, 34, 2371-2374.

(34) Huang, M.-H.; Liang, L.-C. Organometallics 2004, 23, 2813-2816.

(35) Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. Tetrahedron Lett. 1999, 40, 7379-7383.

(36) Ohff, M.; Ohff, A.; Milstein, D. Chem. Commun. 1999, 357-358.

(37) Takenaka, K.; Uozumi, Y. Adv. Synth. Catal. 2004, 346, 1693 -1696.

(38) Negishi, E. Ed. Handbook of Organopalladium Chemistry for Organic Synthesis; John Wiley & Sons: New York, 2002.

(39) Zapf, A.; Beller, M. Chem. Commun. 2005, 431-440.

(40) de Meijere, A.; Meyer, F. Angew.Chem.,Int.Ed.Engl. 1994, 33, 2379.

(41) Heck, R. F. Palladium Reagents in Organic Synthesis; Academic Press: New York, 1985.

(42) Heck, R. F. Comprehensive Organic Synthesis, vol. 4 (Eds.: B. M. Trost, I. Flemming), p 833 Pergamon Press: Oxford, 1991.

(43) Herrmann, W. A. Applied Homogeneous Catalysis (Eds. B. Cornils, W. A. Herrmann), p 712; VCH: Weinheim, 1996.

(44) Nicolaou, K. C.; Sorensen, E. J. Classics in Total synthesis VCH: Weinheim, 1996.

(45) Tsuji, J. Palladium Reagents and Catalysts - Innovations in Organic Synthesis; Wiley: Chichester, UK, 1995.

(46) de Vries, J. G. Can. J. Chem. 2001, 79, 1086-1092.

(47) Cornec, O.; Joseph, B.; Merour, J.-Y. Tetrahedron Lett. 1995, 36, 8587- 90.

(48) Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H.; J. Chem. Soc., Perkin Trans. 1993, 1, 1941-2

(49) Penco, S. Chim. Ind. 1993, 75, 369-73.

(50) Davies, A. J.; Taylor, R. J. K.; Scopes, D. I.; Wadsworth, A. H. Bioorg. Med. Chem. Lett. 1992, 2, 481-4.

(51) Beigelman, L.; Stinchcomb, D. T.; Jarvis, T.; Draper, K.; Pavco, P.; Mcswiggen, J.; Gustofson, J.; Usman, N.; Wincott, F. et.al PCT Int. Appl. WO 9618736 A2 20 Jun 1996, 306 pp.

(52) Alterman, M.; Sjobom, H.; Safsten, P.; Markgren, P.-O.; Danielson, U. H.; Hamalainen, M.; Lofas, S.; Hulten, J.; Classon, B.; Samuelsson, B.; Hallberg, A. European Journal of Pharmaceutical Sciences 2001, 13, 203-212.

(53) Fraley, A. W.; Chen, D.; Johnson, K.; McLaughlin, L. W. Journal of the American Chemical Society 2003, 125, 616-617

(54) De Vries, J. G.; De Vries, A. H. M.; Tucker, C. E.; Miller, J. A. Innovations in Pharmaceutical Technology 2001, 01, 125-126, 128, 130.

(55) Li, J.; Zheng, L.-M.; King, I.; Doyle, T. W.; Chen, S.-H. Frontiers of Biotechnology & Pharmaceuticals 2000 1, 314-335.

(56) Wu, T.-C.; Ramachandran, V. Innovations in Pharmaceutical Technology 2000 00, 97-101.

(57) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. Angewandte Chemie, International Edition 2005 44, 4442-4489.

(58) Setsune, J.-i. Journal of Porphyrins and Phthalocyanines 2004, 8, 93-102.

(59) Wang, H.-K.; Ohtsu, H.; Itokawa, H. Medicinal and Aromatic Plants--Industrial Profiles 2003, 32, 213-244.

(60) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. Angew. Chem., Int. Ed. Engl. 1995, 34, 1723-6.

(61) Overman, L. E.; Ricca, D. J.; Tran, V. D. J. Am. Chem. Soc. 1993, 115, 2042-4.

(62) Fukuyama, Y.; Kiriyama, Y.; Kodama, M. Tetrahedron Lett. 1996, 37, 1261-4.

(63) Yokoyama, Y.; Hikawa, H.; Mitsuhashi, M.; Uyama, A.; Murakami, Y. Tetrahedron Lett. 1999, 40, 7803.

(64) Sharman, W. M.; Van Lier, J. E. J. Porphyrins Phthalocyanines 2000, 4, 441-453.

(65) Gartner, Z. J.; Kanan, M. W.; Liu, D. R. Angewandte Chemie, International Edition 2002, 41, 1796-1800.

(66) Tietze, L. F.; Luecke, L. P.; Major, F.; Mueller, P. Australian Journal of Chemistry 2004, 57, 635-640

(67) Overman, L. E. Pure Appl. Chem. 1994, 66, 1423.

(68) Dyker, G. Handbook of Organopalladium Chemistry for Organic Synthesis, Volume 1, 1255-1282.

(69) Haerter, R.; Lemke, U.; Radspieler, A. PCT Int. Appl. WO 2005023740 A2 17 Mar 2005, 16 pp.

(70) Ruha, O.; Oswald, T. PCT Int. Appl. WO 2005000777 A2 6 Jan 2005, 35 pp. .

(71) Bao, Z.; Amundson, K. R.; Chen, X. L. U.S. US 6383665 , 2002

(72) Cho, H. N.; Kim, J. K.; Kim, D. Y.; Kim, C. Y.; Song, N. W.; Kim, D. Macromolecules 1999 32, 1476-1481.

(73) Jung, S.-H.; Kim, H. K. J. Lumin. 2000 87-89, 51-55.

(74) Mikroyannidis, J. A. Macromolecules 2002, 35, 9289-9295.

(75) Peng, Z.; Galvin, M. E.; Bao, Z. Polym. Prepr. 1998 39, 103-104

(76) Beller, M.; Zapf, A. Handbook of Organopalladium Chemistry for Organic Synthesis, Volume 1, 1209-1222.

(77) Harrington, P. J.; Lodewijk, E. Org. Process Res. Dev. 1997, 1, 72.

(78) Eisenstadt., A. In Catalysis of organic reactions. Edited by F.E.Herkes. Chemical Industries 75. Chemical Industries, 1998. p.415.

(79) Baumeister, P.; Meyer, W.; Oertle, K.; Seifert, G.; Siegrist, U.; Steiner, H. In Heterogeneous catalysis and fine chemicals IV.Edited by H.U. Blaser, A. Baiker, and R. Prins. Elsevier Science bv., Amsterdam. 1997. p. 37.

(80) DeVries, R. A.; Vosejpka, P. C.; Ash, M. L. In Catalysis oforganic reactions. Edited by F.E. Herkes. Chemical Industries,75, 1998. p. 467.

(81) Higgs, G. Chem. Ind. 1997, 827.

(82) Eisenstadt, A. Catalysis of Organic Reactions (Chem. Ind.)(ed. Herkes, F. E.), vol.75, p. 415; Marcel Dekker Inc: New York, 1998.

(83) Bohm, V. P. W.; Herrmann, W. A. Chem. Eur. J. 2000, 6, 1017.

(84) Kondolff, I.; Doucet, H.; Santelli, M. Tetrahedron Lett. 2003, 44, 8487.

(85) Littke, A. F.; Fu, G. C. J. Am. Chem. Soc. 2001, 123, 6989.

(86) Littke, A. F.; Fu, G. C. Angew. Chem. Int. Ed. 2002, 41 4177.

(87) Valentine, D. H.; Hillhouse, J. H. Synthesis 2003, 2437.

(88) Zapf, A.; Beller, M. Chem. Eur. J. 2001, 7, 2908.

(89) Herrmann, W. A.; ¨Ofele, K.; Preysing, D. v.; Schneider, S. K. J. Organomet. Chem. 2003, 687, 229.

(90) Hillier, A. C.; Nolan, S. P. Platinum Met. Rev. 2002, 46, 50.

(91) Selvakumar, K.; Zapf, A.; Beller, M. Org. Lett. 2002, 4, 3031.

(92) Bedford, R. B.; Cazin, C. S. J.; Hursthouse, M. B.; Light, M. E.; Pike, K. J.; Wimperis, S. J. Organomet. Chem. 2001, 633, 173.

(93) Beletskaya, I. P.; Kashin, A. N.; Karlstedt, N. B.; Mitin, A. V.; Cheprakov, A. V.; Kazankov, G. M. J.of OrganometallicChem 2001, 622, 89-96.

(94) Botella, L.; Najera, C. Tetrahedon Letters 2004, 45, 1833-1836.

(95) Consorti, C. S.; Ebeling, G.; Flores, F. R.; Rominger, F.; Dupont, J. Adv. Synth. Catal. 2004, 346, 617.

(96) Grasa, G. A.; Hillier, A. C.; Nolan, S. P. Org. Lett. 2001, 3, 1077.

(97) Grasa, G. A.; Singh, R.; Stevens, E. D.; Nolan, S. P. J. Organomet. Chem. 2003, 687, 269.

(98) Gupta, A. K.; Song, C. H.; Oh, C. H. Tetrahedron Lett. 2004, 45, 4113.

(99) Iyer, S.; Kulkarni, G. M.; Ramesh, C. Tetrahedron 2004, 60, 2163-2172.

(100) Nowotny, M.; Hanefeld, U.; vanKoningsveld, H.; Maschmeyer, T. Chem. Commun. 2000, 1877.

(101) Park, S. B.; Alper, H. Org. Lett. 2003, 5, 3209.

(102) Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. Angew. chemie Int.Ed. 2002, 41, 3668-3671.

(103) Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. J. Am. Chem. Soc. 2000, 122, 9058-9064.

(104) Gruber, A. S.; Pozebon, D.; Monteiro, A. L.; Dupont, J. Tetrahedron Lett. 2001, 42, 7345.

(105) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. Org. Lett. 2000, 2, 1287-1290.

(106) Thakur, V. V.; Kumar, N. S. C. R.; Sudalai, A. Tetrahedron Lett. 2004, 45, 2915.

(107) Yang, D.; Chen, Y.-C.; Zhu, N.-Y. Org. Lett. 2004, 6, 1577.

(108) Jeffrey, T. Tetrahedron 1996, 52, 10113.

(109) Biffis, A.; Zecca, M.; Basato, M. Eur. J. Inorg. Chem. 2001, 1131.

(110) deVries, A. H. M.; Mulders, J. M. C. A.; Mommers, J. H. M.; Henderickx, H. J. W.; deVries, J. G. Org. Lett. 2003, 5, 3285.

(111) Kohler, K.; Heidenreich, R. G.; Krauter, J. G. E.; Pietsch, J. Chem. Eur. J. 2002, 8, 622.

(112) Reetz, M. T.; Westermann, E. Angew. Chem. Int. Ed. 2000, 39, 165.

(113) Willans, C. E.; Mulders, J. M. C. A.; deVries, J. G.; deVries, A. H. M. J. Organomet. Chem. 2003, 687, 494.

(114) Yao, Q.; Kinney, E. P.; Yang, Z. J. Org. Chem. 2003, 68, 7528.

(115) Djakovitch, L.; Heise, H.; Kohler, K. J. Organomet. Chem. 1999, 584, 16-26.

(116) Djakovitch, L.; Koehler, K. Journal of the American Chemical Society 2001, 123, 5990-5999.

(117) Horniakova, J.; Kubota, Y.; Sugi, Y. Transactions of the Materials Research Society of Japan 2004, 29, 2207-2210.

(118) Mehnert, C. P. Chem. Commun. (Cambridge) 1997, 22, 2215-2216.

(119) Dehmlow, E. V. Aqueous-Phase Organometallic Catalysis (2nd Edition), 272-287.

(120) Jeffery, T.; David Tetrahedron Lett. 1998, 39, 5751-5754.

(121) Na, Y.; Park, S.; Han, S. B.; Han, H.; Ko, S.; Chang, S. Journal of the American Chemical Society 2004, 126, 250-258.

(122) Iyer, S.; Thakur, V. V. J. Mol. Catal. A: Chem. 2000, 157, 275.

(123) Yang, Y. F.; Zhou, R. X.; Zhao, S. F.; Zheng, X. M. Catal. Lett. 2003, 85, 87.

(124) Cai, M. Z.; Zhao, H.; Zhang, R. L. Chinese Chemical Letters 2005, 16, 449-452.

(125) Lautens, M.; Mancuso, J.; Grover, H. Synthesis 2004, 12, 2006-2014.

(126) Pascu, S. I.; Coleman, K. S.; Cowley, A. R.; Green, M. L. H.; Rees, N. H. Journal of Organometallic Chemistry 2005, 690, 1645-1658.

(127) Beller, M.; Andreo, M. G.; Zapf, A.; Karch, R.; Kleinwaechter, I.; Briel, O. Ger. Offen. DE 10062577 A1 11 Jul 2002, 12 pp (German). (Germany).

(128) Bhanage, B. M.; Zhao, F.; Shirai, M.; Arai, M. Catal. Lett. 1998 54, 195-198.

(129) Inamoto, K.; Kuroda, J.-i.; Danjo, T.; Sakamoto, T. Synlett 2005, 10, 1624-1626.

(130) Ikeda, Y.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. Journal of the American Chemical Society 2002, 124, 6514-6515.

(131) Yao, Q.; Kinney, E. P.; Zheng, C. Organic Letters 2004, 6, 2997-2999

(132) Koike, T.; Du, X.; Sanada, T.; Danda, Y.; Mori, A. Angewandte Chemie, International Edition 2003, 42, 89-92.

(133) Tsai, S.-H.; Liu, Y.-H.; Wu, P.-L.; Yeh, C.-S. Journal of Materials Chemistry 2003, 13, 978-980.

(134) Beletskaya, I. P.; Cheprakov, A. V. Chem. Rev. 2000, 100, 3009.

(135) Cabri, W.; Candiani, I. Acc. Chem. Res. 1995, 28, 2-7.

(136) Heck, R. F.; NolleyJr., J. P. J. of organic chemistry 1972, 37, 2320.

(137) Negishi, E.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. Chem. Rev. 1996, 96, 365.

(138) Shibasaki, M.; Boden, C. D. J.; Kejima, A. Tetrahedron 1997, 53, 7371.

(139) Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A.; Nishikata, T.; Hagiwara, N.; Kawata, K.; Okeda, T.; Wang, H. F.; Fugami, K.; Kosugi, M. Organic Letters 2001, 3 3313-3316

(140) Bhanage, B. M.; Zhao, F. G.; Shirai, M.; Arai, M. Tetrahedron Letters 1998, 39, 9509-9512.

(141) Kelkar, A. A.; Hanaoka, T.; Kubota, Y.; Sugi, Y. J. Mol. Catal. 1994 88, L113-L116.

(142) Sjovall, S.; Johansson, M. H.; Andersson, C. European Journal of Inorganic Chemistry 2001, 11, 2907-2912.

(143) Herrmann, W. A.; Bohm, V. P. W.; Reisinger, C.-P. J.Organometallic chem. 1999, 576, 23-41

(144) Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. J. Am. Chem. Soc. 1997, 119, 11687.

(145) Futoshi Miyazaki; Yamaguchi, K.; Shibasaki, M. Tetrahedron Letters 1999, 40, 7379-7383.

(146) Munoz, M. P.; Martin-Matute, B.; Fernandez-Rivas, C.; Cardenas, D. J.; Echavarren, A. M. Adv Syn & Catalysis 2001, 343, 338-342.

(147) Berthiol, F.; Doucet, H.; Santelli, M. Synlet 2003 6, 841-844.

(148) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. Organometallics 1992, 11, 1995 -1996

(149) Hartung, C. G.; Koehler, K.; Beller, M. Organic letters 1999, 1, 709-711.

(150) Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J. Organic letters 2003, 5, 983-986.

(151) Alonso, D. A.; Najera, C.; Pacheco, M. C. Organic letters 2000, 2, 1823-1826.

(152) Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. Journal of the American Chemical Society 2001, 123, 1848-1855.

(153) Iyer, S.; Ramesh, C. Tetrahedon Letters 2000, 41, 8981-8984.

(154) Silberg, J.; Schareina, T.; Kempe, R.; Wurst, K.; Buchmeiser, M. R. Journal of Organometalic Chemistry 2001, 622, 6-18.

(155) Kawano, T.; Shinomaru, T.; Ueda, I. Organic Letters 2002, 4, 2545-2547.

(156) Najera, C.; Gil-Molto, J.; Karlstroem, S.; Falvello, L. R. Organic Letters 2003, 5, 1451-1454.

(157) Iyer, S.; Jayanthi, A. Synlet 2003, 8, 1125-1128.

(158) Kovala-Demertzi, D.; Yadav, P. N.; Demertzis, M. A.; Jasiski, J. P.; Andreadaki, F. J.; Kostas, I. D. Tetrahedron Letters 2004, 45, 2923-2926.

(159) Tinkl, M.; Hafner, A. PCT Int. Appl. WO 9947474 A1 23 Sep 1999, 41pp.

(160) Beller, M.; Riermeier, T. H. Tetrahedron Lett. 1996, 37, 6535.

(161) Hermann, W. A.; Reisinger, C.-P.; Ofele, K.; Brossmer, C.; Beller, M.; Fischer, H. J. Mol. Catal. 1996, 108, 51.

(162) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. Angew. chemie Int.Ed. 1995, 34, 1844-1847.

(163) Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. J. Am. Chem. Soc. 1999, 121, 9531-9538

(164) Peris, E.; Mata, J.; Loch, J. A.; Crabtree, R. H. Chemical Communications (Cambridge) 2001, 2, 201-202.

(165) Gruendemann, S.; Albrecht, M.; Loch, J. A.; Faller, J. W.; Crabtree, R. H. Organometallics 2001, 20, 5485-5488.

(166) Jung Il, G.; Son, S. U.; Park, K. H.; Chung, K.-C.; Lee, J. W.; Chung, Y. K. Organometallics 2003, 22, 4715-4720.

(167) Woltermann, C. J. PharmaChem 2002, 1, 11-14.

(168) Reetz, M. T.; Lohmer, G.; Schwickardi, R. Angew. chemie Int.Ed. 1998, 37, 481-483.

(169) Tulloch, A. A. D.; Danopoulos, A. A.; Cafferkey, S. M.; Kleinhenz, S.; Hursthouse, M. B.; Tooze, R. P. Chem. Commun. (Cambridge) 2000, 14, 1247-1248.

(170) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. Synlett 1992, 11, 871-2.

(171) Bayon, J. C.; Claver, C.; Masdeu-Bulto, A. M. Coord. Chem. Rev. 1999, 193-195 73-145.

(172) Jackson, T.; Routledge, A. Tetrahedron Letters 2003, 44, 1305-1307.

(173) Augustine, R. L.; O’Leary, S. T. J. Mol. Catal. A: Chem. 1992, 72, 229.

(174) Hagiwara, H.; Shimizu, Y.; Hoshi, T.; Suzuki, T.; Ando, M.; Ohkubo, K.; Yokoyama, C. Tetrahedron Letters 2001 42, 4349-4351.

(175) Savoia, D.; Trombini, C.; Umani-Ronchi, A.; Verardo, G. J.Chem. Soc. Chem. Commun. 1981, 541.

(176) Wagner, M.; Köhler, K.; Djakovitch, L.; Weinkauf, S.; Hagen, V.; Muhler, M. Top.Catal. 2000, 13, 319.

(177) Ramachandani, R. K.; Uphade, B. S.; Vinod, M. P.; Wakharkar, R. D.; Chodhary, V. R.; Sudalai, A. Chem. Commun 1997, 2071.

(178) Bennur, D. H.; Ramani, A.; Bal, R.; Chanda, B. M.; Sivasanker, S. Catal. Commun. 2002, 3, 493.

(179) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. J. Am. Chem. Soc. 2002, 124 14127.

(180) Beller, M.; Fischer, H.; Kuehlein, K.; Reisinger, C.-P.; Herrmann, W. A. J. Organomet. Chem. 1996, 520, 257-259.

(181) Li, L.; Shi, J.-l.; Yan, J.-n. Chemical Communications (Cambridge, United Kingdom) 2004, 17, 1990-1991.

(182) Reetz, M. T.; Breinbauer, R.; Wanninger, K. Tetrahedron Lett. 1996, 37, 4499-4502

(183) Toshima, N. Nanoscale Materials, 79-96. Edited by: Liz-Marzan, Luis M.; Kamat, Prashant V. Kluwer Academic Publishers: Norwell, Mass. ISBN: 1-4020-7366-6, 2003.

(184) Alper, H.; Arya, P.; Bourque, C.; Jefferson, G. R.; Manzer, L. E. Can. J. Chem. 2000, 78, 920.

(185) Clark, J. H.; Macquarrie, D. J.; Mubofu, E. B. Green Chem. 2000, 2, 53.

(186) Kiviaho, J.; Hanaoka, T.; Kubota, Y.; Sugi, Y. J. Mol. Catal. A: Chem. 1995, 101, 25.

(187) Macquarrie, D. J.; Fairfield, S. E. J. Mater. Chem. 1997, 7, 2201.

(188) Pan, Y.; Zhang, Z.; Hu, H. J. Mol. Catal. 1990, 62, 297

(189) Wang, Y.; Liu, H. J. Mol. Catal. 1988, 45, 127.

(190) Anderson, C. M.; Korebelass, K.; Awasti, A. K. J. Org. Chem. 1985, 50, 3891.

(191) Hong, L.; Ruckenstein, E. React. Polym. 1992, 16, 181.

(192) Hong, L.; Ruckenstein, E. J. Mol. Catal. 1992, 77, 273.

(193) Schwarz, J.; Bohm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrmann, W. A.; Hieringerand, W.; Raudaschl-Sieber, G. Chem. Eur. J. 2000, 6, 1773.

(194) Zhang, Z.; Hu, H.; Kao, T. React. Polym. 1990, 12, 229.

(195) Zhang, Z.; Pan, Y.; Hu, H.; Kao, T. Synth. Commun. 1990, 20, 3563.

(196) Zhang, Z.; Pan, Y.; Hu, H.; Kao, T. Synthesis 1991, 539.

(197) Arhancet, J. P.; Davis, M. E.; Merola, J. S.; Hanson, B. E. Nature 1989, 339, 454.
(198) Davis, M. E. Chemtech 1992, 498.
(199) Genet, J. P.; Blart, E.; Savignac, M. Synlett 1992, 9, 715-17.
(200) Genet, J. P.; Savignac, M. J. Organomet. Chem. 1999 576, 305-317.
(201) Safi, M.; Sinou, D. Tetrahedron Lett. 1991, 32, 2025
(202) Sengupta, S.; Bhattacharya, S. J. Chem. Soc. Perkin Trans. 1993, 1943.
(203) Zhang, H. C.; Doyle Daves, G. Organometallics 1993, 12, 1499.
(204) Beller, M.; Krauter, J. G. E.; Zapf, A. Angew. Chem. Int. Ed. Engl. 1997, 36, 772-774.
(205) Thorpe, T.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. Tetrahedron Letters 2000, 41, 4503-4505.
(206) Beller, M.; Krauter, J. G. E.; Zapf, A.; Bogdanovic, S. Catalysis today 1999, 48, 279-290.
(207) Moineau, J.; Pozzi, G.; Quici, S.; Sinou, D. Tetrahedron Lett. 1999, 40, 7683-7686.
(208) Rocaboy, C.; Gladysz, J. A. New journal of chemistry 2003, 27, 39-49.
(209) Reardon, P.; Metts, S.; Crittendon, C.; Daugherity, P.; Parsons, E. J. Organometallics 1995, 14, 3810-16.
(210) Herrmann, W. A.; Bohm, V. P. W. J.Organometallic chem 1999, 572, 141-145.
(211) Bhanage, B. M.; Shirai, M.; Arai, M. J.Mol Cat A Chem 1999, 145, 69-74
(212) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. J. Organomet. Chem. 1989, 371, 397-401.
(213) Moore, L. R.; Shaughnessy, K. H. Organic Letters 2004, 6, 225-228.
(214) Bradley, D.; Williams, G.; Lombard, H.; Holzapfel, C. W. Syn Com 2001, 31, 2077-2081.
(215) Jeffery, T. Tetrahedon Letters 1994 35, 3051-3054.
(216) Hiroshige, M.; Hauske, J. R.; Zhou, P. Tetrahedon Letters 1995, 36, 4567-4570
(217) Kiji, J.; Okano, T.; Hasegawa, T. J.Mol Cat A Chem 1995 97, 73-77.
(218) Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genet, J.-P. Tetrahedon Letters 1996, 37, 2003-2006.
(219) Mukhopadhyay, S.; Rothenberg, G.; Joshi, A.; Baidossi, M.; Sasson, Y. Advanced Synthesis & Catalysis 2002 344, 348-354.
(220) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. J. Am. Chem. Soc. 2001, 123, 11105-

11106.

(221) Casalnuovo, A. L.; Calabrese, J. C. J. Am. Chem. Soc. 1990, 112, 4324-4330.

(222) Basnak, I.; Takatori, S.; Walker, R. T. Tetrahedron Lett. 1997, 38, 4869.

(223) Hayashi, M.; Amano, K.; Tsukada, K.; Lamberth, C. J. Chem.Soc., Perkin Trans. 1999, 1, 239.

(224) Hessler, A.; Stelzer, O.; Dibowski, H.; Worm, K.; Schmidtchen, F. P. J. Org. Chem. 1997, 62, 2362.

(225) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. Tetrahedron 2004, 60, 4097.

(226) Bergbreiter, D. E.; Furyk, S. Green Chem. 2004, 6, 280.

(227) Gron, L. U.; Tinsley, A. S. Tetrahedron Lett. 1999, 40, 227.

(228) Zhang, R.; Sato, O.; Zhao, F.; Sato, M.; Ikushima, Y. Chemistry--A European Journal 2004, 10, 1501-1506.

(229) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. J. Org. Chem. 2004, 69, 7919.

(230) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martin-Matute, B. J. Am. Chem. Soc. 2001, 123, 5358.

(231) Amengual, R.; Michelet, V.; Genet, J.-P. Tetrahedron Lett 2002, 43, 5905.

(232) Uozumi, Y.; Kimura, T. Synlett 2002, 12, 2045-2048.

(233) Solabannavar, S. B.; Desai, U. V.; Mane, R. B. Green Chemistry 2002, 4, 347-348.

(234) Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. Org.Lett. 1999, I, 997

(235) Wasserscheid, P. Transition Metals for Organic Synthesis (2nd Edition), Volume 2, 559

(236) Welton, T.; Smith, P. J. Advances in Organometallic Chemistry 2004, 51, 251-284.

(237) Matsubara, H.; Maeda, L.; Ryu, I. Chemistry Letters 2005, 34, 1548-1549.

(238) Richter, B.; De Wolf, A. C. A.; Van Koten, G.; Deelman, B. J. PCT Int. Appl. WO 2000018774 A1 6 Apr 2000, 59 pp. .

(239) Bhanage, B. M.; Fujita, S.-i.; Arai, M. Journal of Organometallic Chemistry 2003 687, 211-218.

(240) Bhanage, B. M.; Ikushima, Y.; Shirai, M.; Arai, M. Tetrahedron Lett. 1999, 40, 6427.

(241) Bhanage, B. M.; Ikushima, Y.; Shirai, M.; Arai, M. Chem. Commun. 1999, 1277.

(242) Cacchi, S.; Farbrizi, G.; Gasparrini, F.; Villain, C. Synlett 1999, 345.

(243) Gron, L. U.; LaCroix, J. E.; Higgins, C. J.; Steelman, K. L.; Tinsley, A. S.

Tetrahedron Letters 2001, 42, 8555-8557.

(244) Kayaki, Y.; Noguchi, Y.; Ikariya Chemical Communications (Cambridge) 2000 22, 2245-2246.

(245) Morita, D. K.; David, S. A.; Tumas, W.; Morita, D. K.; Pesiri, D. R.; Glaze, W. H. Chem. Commun. (Cambridge) 1998, 13, 1397-1398.

(246) Zhang, R.; Zhao, F.; Sato, M.; Ikushima, Y. Chemical Communications (Cambridge, United Kingdom) 2003, 13, 1548-1549.

(247) Littke, A. F.; Fu, G. C. Organic Syntheses 2005, 81, 63-76.

(248) Proeckl, S. S.; Kleist, W.; Koehler, K. Tetrahedron 2005, 61, 9855-9859.

(249) Shmidt, A. F.; Smirnov, V. V. Kinetics and Catalysis (Translation of Kinetika i Kataliz) 2000, 41, 743-744.

(250) Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; De Vries, J. G. Angew. Chem., Int. Ed. 1998 37, 662-664.

(251) Fu, X.; Zhang, S.; Yin, J.; McAllister, T. L.; Jiang, S. A.; Tann, C.-H.; Thiruvengadam, T. K.; Zhang, F. Tetrahedron Letters 2002, 43, 573-576.

(252) Sugihara, T.; Satoh, T.; Miura, M. Tetrahedron Letters 2005, 46, 8269-8271.

(253) Hwang, L. K.; Na, Y.; Lee, J.; Do, Y.; Chang, S. Angewandte Chemie, International Edition 2005, 44, 6166-6169.

(254) Solabannavar, S. B.; Helavi, V. B.; Desai, U. V.; Mane, R. B. Synthetic Communications 2003, 33, 361-365.

(255) Holmes, A. B.; Early, T. R.; Gordon, R. S.; Stamp, L. M.; Shute, R. E.; McConvey, I. F. Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry 2002, 47, 282-283.

(256) Villemin, D.; Caillot, F. Tetrahedron Letters 2001, 42, 639-642.

(257) Hillers, S.; Sartori, S.; Reiser, O. J. Am. Chem. Soc. 1996, 118, 2087-8.

(258) Voigt, K.; Schick, U.; Meyer, F. E.; de Meijere, A. Synlett 1994, 3, 189-90.

(259) Ambulgekar, G. V.; Bhanage, B. M.; Samant, S. D. Tetrahedron Letters 2005, 46, 2483-2485.

(260) Larhed, M.; Moberg, C.; Hallberg, A. Accounts of Chemical Research 2002 35, 717-727.

(261) Wang, J.-X.; Liu, Z.; Hu, Y.; Wei, B.; Bai, L. Journal of Chemical Research, Synopses 2000, 10, 484-485

(262) Xie, X.; Lu, J.; Chen, B.; Han, J.; She, X.; Pan, X. Tetrahedron Letters 2004, 45, 809-811.

(263) Loiseleur, O.; Hayashi, M.; Keenan, M.; Schmees, N.; Pfaltz, A. J. Organomet. Chem. 1999, 576, 16-22.

(264) Shibasaki, M.; Vogl, E. M.; Ohshima, T. Comprehensive Asymmetric Catalysis 2004 Supplement, 1, 73-81.

(265) Tietze, L. F.; Thede, K. Synlett 2000 10, 1470-1472.

(266) Dyker, G.; Grundt, P.; Markwitz, H.; Henkel, G. J. Org. Chem. 1998, 63, 6043-6047

(267) Perosa, A.; Tundo, P.; Selva, M.; Zinovyev, S.; Testa, A. Organic & Biomolecular Chemistry 2004, 2, 2249-2252.

(268) Bader, A.; Arlt, D.; Seng, F. Eur. Pat. Appl. EP 459258 A2 4 Dec 1991, 8 pp. .

(269) Braese, S.; De Meijere, A. Handbook of Organopalladium Chemistry for Organic Synthesis, Volume 1, 1179-1208. .

(270) Sundermann, A.; Uzan, O.; Martin, J. M. L. Chemistry--A European Journal 2001, 7, 1703-1711.

(271) Bergbreiter, D. E.; Osburn, P. L.; Frels, J. D. Advanced Synthesis & Catalysis 2005, 347, 172-184.

(272) Consorti, C. S.; Flores, F. R.; Dupont, J. Journal of the American Chemical Society 2005, 127, 12054-12065

(273) Rothenberg, G.; Cruz, S. C.; Van Strijdonck, G. P. F.; Hoefsloot, H. C. J. Advanced Synthesis & Catalysis 2004, 346, 467-473.

(274) Amatore, C.; Carre, E.; Jutand, A.; Medjour, Y. Organometallics 2002, 21, 4540-4545.

(275) Amatore, C.; Jutand, A. J. Organomet. Chem. 1999, 576, 254-278.

(276) Bohm, V. P. W.; Herrmann, W. A. Chemistry--A European Journal 2001, 7, 4191-4197.

(277) Shaw, B. L. New J. Chem. 1998, 22, 77-79.

(278) Benhaddou, R.; Czernecki, S.; Ville, G.; Zegar, A. Organometallics 1988, 7, 2435-9.

(279) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Beller, M.; Fischer, H. J. Mol. Catal. A 1995, 103, 133.

(280) Van Strijdonck, G. F. P.; Boele, M. D. K.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. Eur. J. Inorg. Chem. 1999, 1073.

(281) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. J. Mol. Catal. A: Chem. 1999, 142,

383-388.

(282) Nilsson, P.; Wendt, O. F. Journal of Organometallic Chemistry. 2005, 690, 4197-4202.

(283) Rosner, T.; Pfaltz, A.; Blackmond, D. G. Journal of the American Chemical Society 2001, 123, 4621-4622.

(284) Zhao, F.-G.; Bhanage, B. M.; Shirai, M.; Arai, M. Stud. Surf. Sci. Catal. 1999, 122, 427-430.

(285) Aggarwal, V. K.; Staubitz, A. C.; Owen, M. Organic Process Research & Development 2006, 10, 64-69.

(286) Blackmond, D. G.; Rosner, T.; Pfaltz, A. Org. Process Res. Dev. 1999 3, 275-280.

(287) Shmidt, A. F.; Smirnov, V. V. Kinetics and Catalysis (Translation of Kinetika i Kataliz) 2001, 42, 800-804.

(288) Sud, A.; Deshpande, R. M.; Chaudhari, R. V. Journal of Molecular Catalysis A: Chemical 2007, 270 144-152.

(289) Fujita, S.-i.; Yoshida, T.; Bhanage, B. M.; Arai, M. Journal of Molecular Catalysis A: Chemical 2002, 188, 37-43.

CHAPTER 2

Palladium Metal Complex Catalyzed Heck Reaction in Glycol-Organic Biphasic Media

2.1 Introduction

The Heck reaction is one of the most useful methods for C-C bond formation[1,2] and has rightly been called “one of the true power tools of contemporary organic synthesis” because of its high selectivity, versatility and broad tolerance of functional groups[3]. However, industrial application of Heck reaction is not widespread[4] because, this reaction too suffers from issues related to catalyst product separation and catalyst recycle[5], as in all homogeneously catalyzed systems. Different approaches have attempted to resolve this problem[6]. One such approach is the use of biphasic catalysis. Use of biphasic solvent system as a means of heterogenisation of catalyst into an immiscible liquid phase is an extremely useful and practical means of overcoming the catalyst-product separation issues in homogeneous catalysis[7]. The separation of product is achieved by mere separation of the two phases with negligible loss of catalyst[6]. The recycle of the catalyst phase for the next reaction hence proves to be a viable alternative over conventional means of catalyst recycle involving thermal or other means.

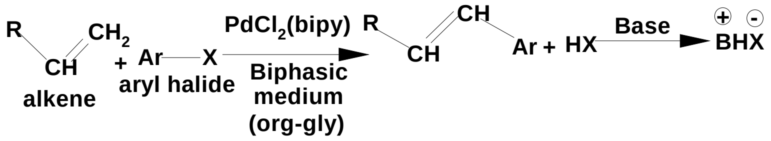
Catalysis employing two-phase media has been commercially exploited for a number of reactions like hydroformylation, dimerisation, hydrogenation, oligomerization etc[7-11]. Of these, the processes using aqueous phase catalysts employ phosphine ligands modified by hydrophilic groups bound to the central metal catalyst[7,12]. The sulfonated phosphines generally used are prone to oxidation, reducing their ability to stabilize the catalysts and hence their utility as ligands, once oxidized. In case of the application of such biphasic media in Palladium catalyzed systems like Heck reactions, the deactivation of the phosphines can lead to insufficient stabilization of the metal. This results in the decomposition of the palladium complex catalyst to the Pd metal. Thus, for application to Heck reactions in biphasic media it is necessary to obtain catalysts with ligands which are stable under reaction conditions.

Heck reactions in aqueous or biphasic media have been reported by a number of groups[13-15]. The primary objective of the studies in aqueous media has been to homogenize the aqueous systems to achieve good conversions. Most of the studies are on water-soluble catalysts like TPPTS, TPPDS etc with solvent mixtures comprising polar solvents like DMF, CH_3CN, and DMAc etc., which are miscible with water. For biphasic systems, most of the studies utilize water-soluble phosphine based catalysts in a glycol – organic biphasic system. Bhanage and coworkers[12] have reported Heck reactions with various metal-TPPTS complexes in a biphasic mode using ethylene glycol-toluene medium. The activity of the Pd complex catalysts for Heck reaction of iodobenzene and butyl acrylate was found to be highly dependent on the ratio of Pd:TPPTS. Due to extensive precipitation of metal, the catalyst could not be recycled at a Pd:TPPTS ratio of less than 1:2. At a Pd: TPPTS, 1:4 no precipitation was observed. Pd complexes incorporating carbohydrate substituted triarylphosphine-ligands have been reported by Beller et.al.[16] for Heck reactions in a xylene – ethylene glycol biphasic medium, at a Pd:phosphine ratio of 1:3. Similarly, Thorpe[17] has reported synthesis of a disulfonated phosphine (TPPDS) and its application to Pd-TPPDS catalyzed Heck reaction of iodobenzene with methyl acrylate, in a toluene – ethylene glycol biphasic medium. In all of these systems, as mentioned earlier, a non-polar organic solvent, either toluene or xylene is used with ethylene glycol as the other phase. In a majority of these systems no detailed investigations on catalyst recycle and recovery have been reported.

One of the major handicaps of the Pd-sulphonated phosphine or any water soluble phosphine is the precipitation of the Pd complex as a metal under the temperature used for the Heck reaction. Though phosphorous containing ligands are likely to provide relatively stable catalysts, development of a phosphine free catalyst for application in a biphasic medium is even more rewarding.

Cabri et.al[18] have reported that Pd complexes of bidentate nitrogen ligand such as 1,10-Phenanthroline derivatives are active for Heck type reactions in homogeneous medium to give 94% product yield. However, surprisingly very little or no activity was observed for Heck reaction using the Pd complexes of 2,2'-bioxazoline and 2,2'-bipyridine ligands. Tsai et.al.[19] have used heterogenized Palladium bipyridyl complex anchored on MCM-41 for Heck reactions as an efficient and recyclable heterogeneous catalyst with a TON up to 10^6 for each reaction. 98% conversion was obtained in 16hrs for the coupling of n-butyl acrylate with p-bromo acetophenone using this catalyst. However, the system required 96 hrs for the n-butyl acrylate and iodobenzene system. The complex is also reportedly active for the Pd (II)-bipyridine catalyzed Suzuki reaction i.e. conjugate addition of arylboronic acid to α,β-unsaturated carbonyl compounds in a homogeneous medium[20].

Despite a report to the contrary[18], our investigations have revealed that $PdCl_2$(bipy) is an excellent and stable catalyst for Heck vinylation. The major advantage of this catalyst is the preferential solubility of the complex in ethylene glycol vis-à-vis non polar organic media like octane, pet ether etc, which makes it a good catalyst for application in biphasic media. This chapter deals with the Heck reaction in a biphasic system using $PdCl_2$(bipy) catalyst, which has been found to be active in an ethylene glycol – organic solvent system.(Equation 2.1).



[2.1]

The major advantage of the proposed catalyst is that biphasic catalysis is achieved by employing a **conventional organic phase soluble ligand- 2,2'-bipyridine** unlike conventional biphasic catalysts reported for biphasic Heck reactions (which employ a catalyst having a hydrophilic moiety like that in TPPTS[12]). The catalyst does not require stringent oxygen free conditions, nor does it precipitate to Pd metal as is observed in other biphasic systems. The catalyst was retained in the glycol phase with practically no leaching to the organic phase. Although this catalyst is less efficient than other reported homogeneous catalysts like P-C Palladacycle[21,22], the $PdCl_2$(bipy) catalyst nonetheless provides an efficient recyclable catalyst in the biphasic system and thus high cumulative TONs are possible. The schematic of the biphasic system employed for reaction is shown in Figure 2.1

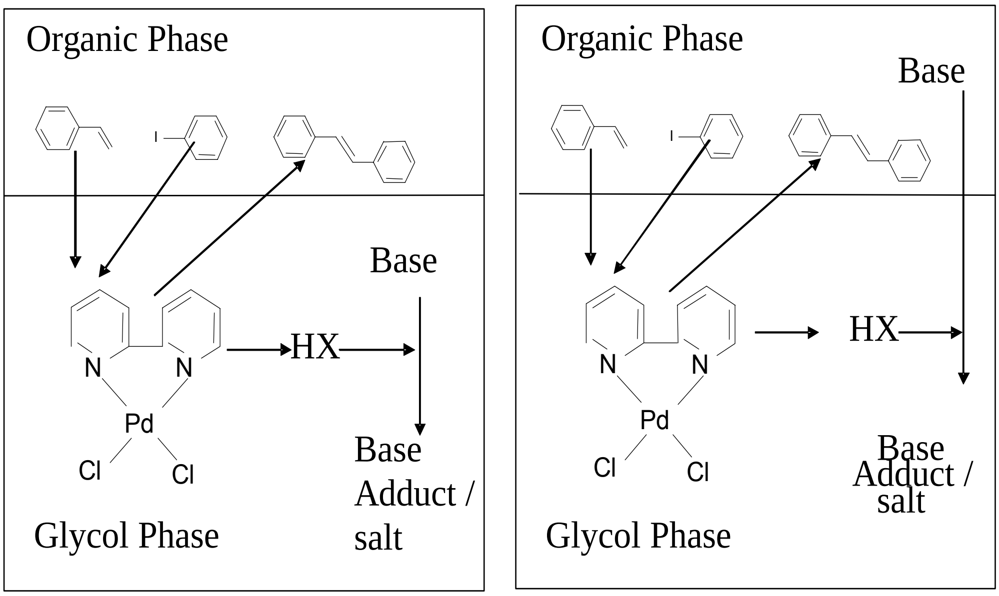


Figure 2.1 Schematic of the biphasic system employed for reaction

The chapter is divided into two sections. Section 2.2 deals with the activity and selectivity studies using $PdCl_2$(bipy) catalyst for Heck reaction in glycol-organic biphasic media and in Section 2.3 the kinetic studies of Heck reaction of styrene and iodobenzene using $PdCl_2$(bipy) catalyst in glycol-organic biphasic media have been discussed.

Section A

2.2: PdCl$_2$(bipy) catalyzed Heck reaction in glycol-organic biphasic media

- Activity and selectivity studies

2.2.1 Introduction

This section presents experimental results on investigation on activity, catalyst stability and recycle of PdCl$_2$(bipy) catalyst (Figure 2.2) for the Heck reaction in a glycol-organic biphasic media. This complex catalyzed the Heck reaction efficiently in glycol-organic biphasic medium and high activity and selectivity were achieved. A proper tailoring of the organic phase ensured that the leaching of the catalyst to the organic phase was negligible. The two-phase system has been demonstrated for the Heck reaction of a number of aryl halides, olefins and in the presence of different organic and inorganic bases. The role of different solvent compositions on the activity and selectivity was also assessed. The catalyst has been recycled for five times without any loss in activity, proving the stability of the catalyst.

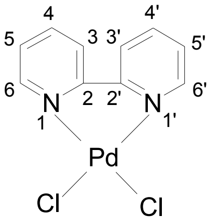


Figure 2.2: PdCl$_2$(bipy) complex

2.2.2. Experimental section

2.2.2.1 Apparatus and chemicals

PdCl$_2$, 2,2'-bipyridine, DPPE [1,2-*bis* (diphenyl phosphino) ethane], DPPPy [Diphenyl phosphino pyridine], tri-o-tolyl phosphine, triphenyl phosphine, olefins and aryl halides used were procured form Aldrich, USA and used without any further treatment. The solvents (n-octane, *p*-xylene, ethylene glycol) and pyridine were obtained from SD Fine Chemicals, India. Bases used were of analytical grade, purchased from Loba Chemicals, India.

Since the temperatures utilized for the reaction were higher than the boiling points of most of the reactants and solvents, the reactions were conducted in a high pressure autoclave of capacity 50 ml manufactured by Ms Amar Engineering, Mumbai and had facilities for withdrawal of liquid and gaseous samples. The temperature was controlled by means of electric heating. The reactor was fitted with a cooling loop for proper control of temperature. The schematic of reactor set-up is shown in Figure 2.3

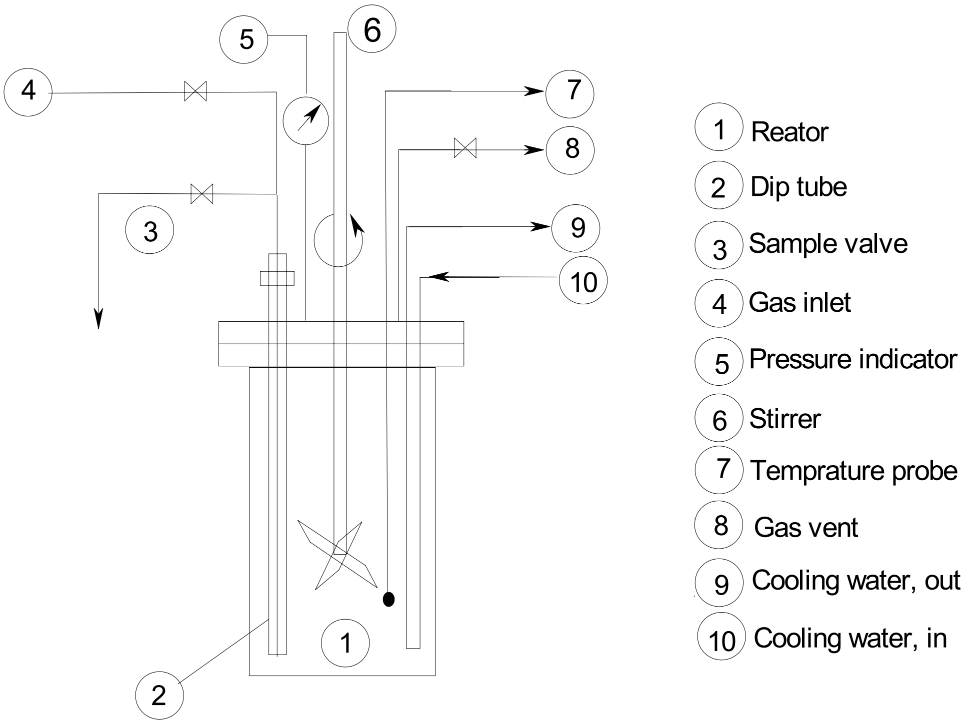


Figure 2.3: Schematic of reactor set-up

2.2.2.2 Synthesis and characterization of complexes

The palladium complexes $PdCl_2$(bipy), $PdCl_2(PPh_3)_2$, $PdCl_2$(DPPE), $PdCl_2(Py)_2$, $PdCl_2$(DPPPy) and the Palladacycle - *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino) benzyl]dipalladium(II) were prepared by standard procedures[23-26] and characterized**.**

2.2.2.2.1 Synthesis of $PdCl_2$(bipy) complex

In a 50 ml round bottom flask containing 10 ml methanol, 0.266g (1.33 mmol) $PdCl_2$ was added followed by 0.234g (1.33 mmol) 2,2'-bipyridine. The mixture was stirred at room temperature for 6 hr. An orange yellow coloured $PdCl_2$(bipy) complex precipitated, was filtered and washed with methanol and then dried under vacuum. Practical yield of the complex was 0.440g (88%). Characterization of the $PdCl_2$(bipy) complex was carried out by IR, NMR and elemental analysis and was found to match with the values reported[27]**.**

Characterization of $PdCl_2$(bipy) complex

2.2.2.2.1.1 Elemental analysis

Elemental analysis of the complexes was carried out on a CHNS-O EA1108, elemental analyzer of Carlo Erba Instruments, Italy. Elemental Analysis was (w/w %): Calculated: C, 36.04; H, 2.40; Cl, 21.32. Found: C, 35.24; H, 2.64, Cl, 20.42.

2.2.2.2.1.2 IR analysis

IR spectra were obtained using a Perkin Elmer Spectrum-2000 in transmission mode using KBr pellets. The IR spectrum of 2,2'-bipyridine and $PdCl_2$(bipy) complex is shown in Figures 2.4 (a, b). In the complex, the coordination of 2,2'-bipyridine ligand was confirmed by the characteristic absorption peak between 1579 to 1415 cm^{-1} for bipyridyl ring, with a blue shift ranging between 1601 to 1448 cm^{-1}. The IR spectra of the complex also showed the shift in vibration peak at 757cm^{-1} to 761cm^{-1} and Pd–N stretching vibrations in the range of 540 to 580 cm^{-1}.

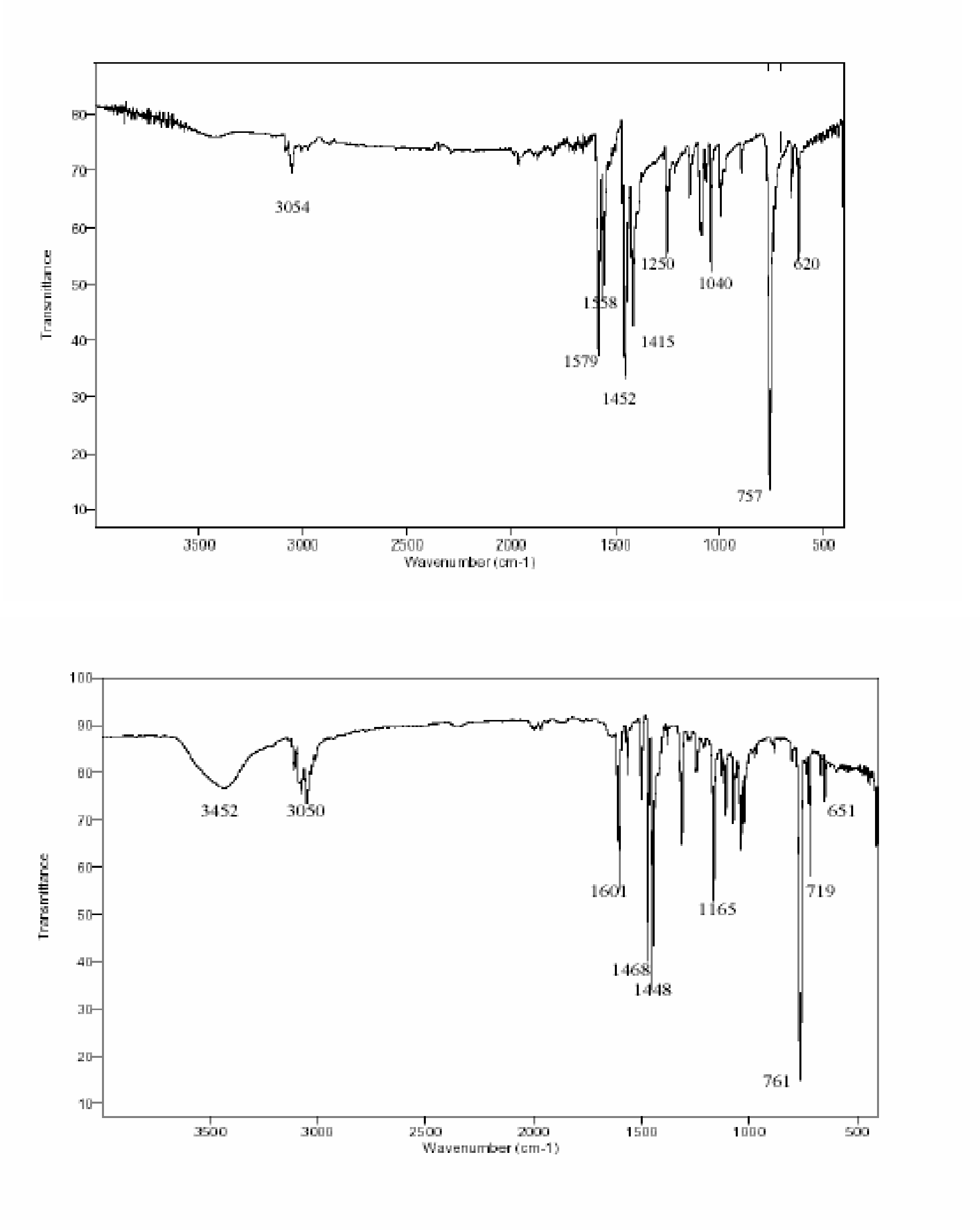


Figure 2.4: IR spectrum of a)2,2'-bipyridine
b)$PdCl_2$(bipy) complex

Far IR spectrum for $PdCl_2$(bipy) complex was also recorded, which showed strong peaks at 479.9, 445.7, 412.7, and 359.3 cm^{-1}, which are typical for Pd–N stretching vibrations. The Pd-Cl stretching vibration occurs at 340 and 347 cm^{-1}.

2.2.2.2.1.3 NMR analysis

NMR spectra were obtained using Brucker-MSL-300 and Brucker-DRX-500 spectrometer. ^1H and ^{13}C NMR spectrum of 2,2'-bipyridine and $PdCl_2$(bipy) complex is shown in Figures 2.5 (a,b) and 2.6 (a,b) respectively.

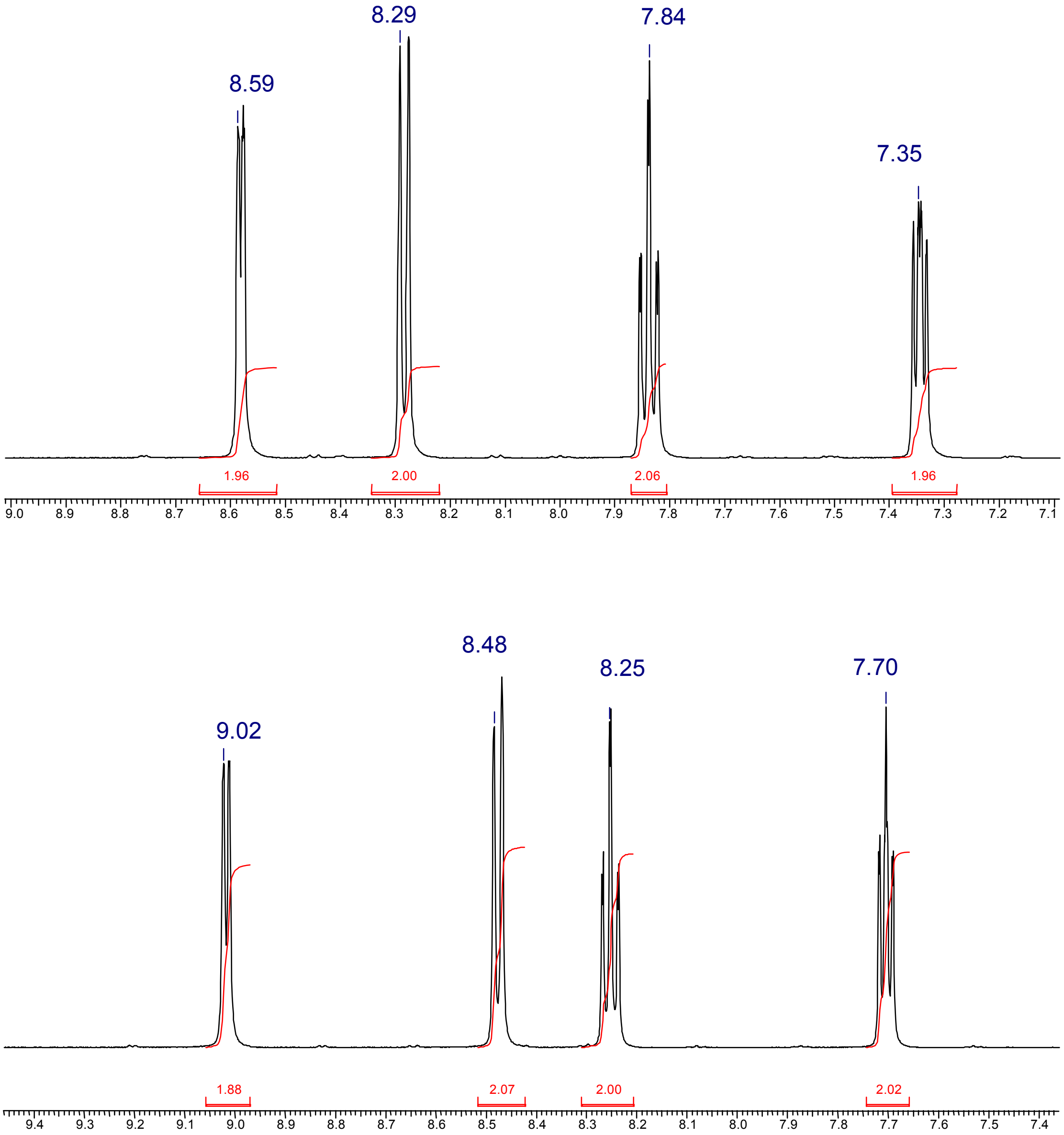


Figure 2.5: Proton NMR spectrum of a) 2,2'-bipyridine

b) $PdCl_2$(bipy) complex

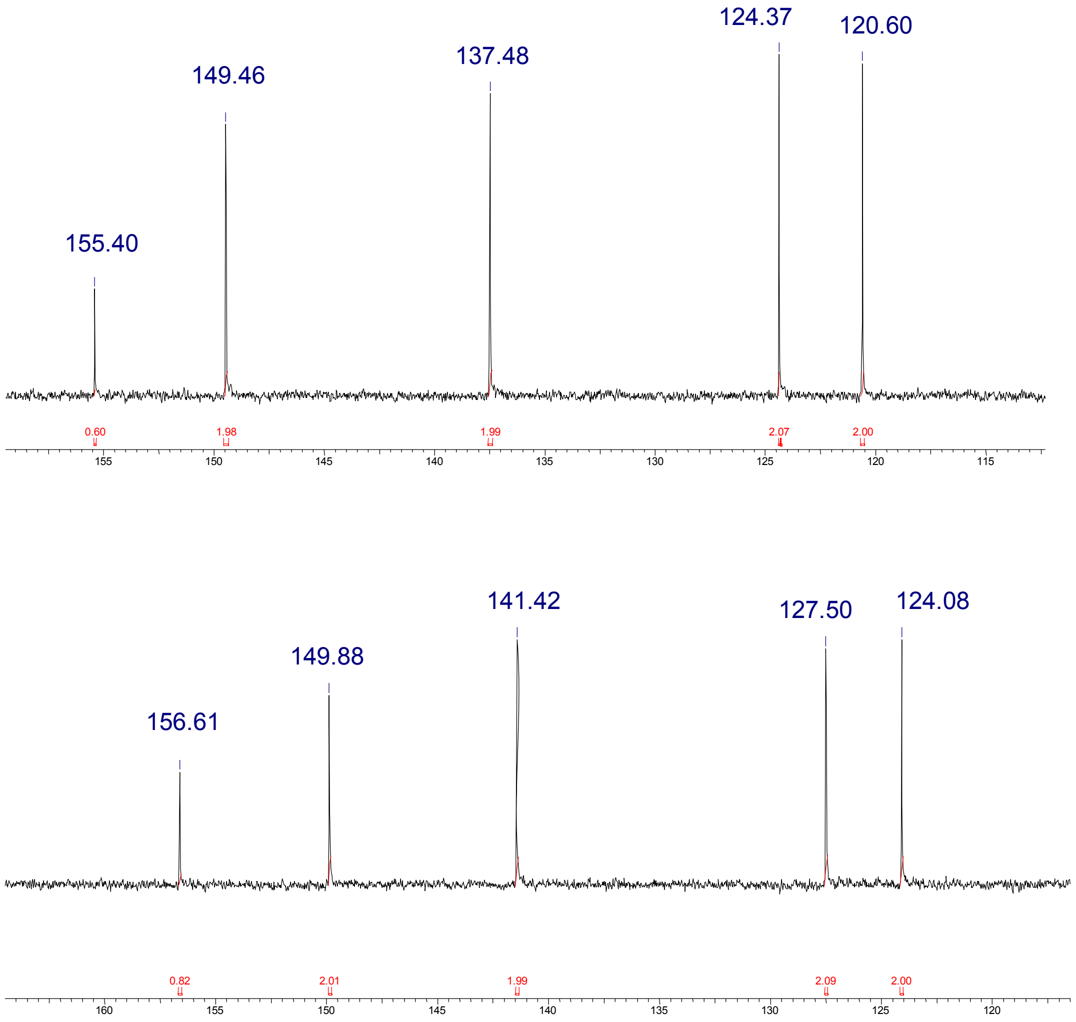


Figure 2.6: Carbon NMR spectrum of a) 2,2'-bipyridine
b) $PdCl_2$(bipy) complex

Proton NMR data for the ligand - 2,2'-bipyridine and the $PdCl_2$(bipy) complex are presented in Table 2.1 (see Figure2.5-(a) and (b) for ^{1}H NMR)

The aromatic protons corresponding to pyridyl rings for the compounds were found between δ= 7 to 9 ppm. From the Table 2.1 it can be seen that there is substantial chemical shift observed when the ligand gets complexed with the Pd metal. The shift is more towards the downfield region to that of the ligand. The chemical shift values of proton NMR of ligand were also compared with the reported values, and were found to be similar. (Reported values of chemical shift for ligand are-7.3ppm, 7.8ppm, 8.4ppm, and 8.6ppm for $H_{5,5'}$, $H_{4,4'}$, $H_{3,3'}$, $H_{6,6'}$ respectively). The multiplicity of the protons remains the same after complexation, whereas the shift in coupling constant (J value) is observed.

Table 2.1: Proton NMR data of $PdCl_2$(bipy) complex

Atom	Ligand (2,2’-bipyridine) δ ppṃ	Catalyst [$PdCl_2$(bipy) complex] δ ppṃ	Shift δ Δ ppṃ
$H_{5,5'}$	7.35 ppm, 2 H, doublet of triplet, (J=1.8,3.6,1.8,3.6,1.8Hz)	7.70ppm, 2 H, doublet of triplet, (J=1.3,5.9,1.3,5.9,1.3Hz)	0.35
$H_{4,4'}$	7.84 ppm, 2 H, doublet of triplet, (J=1.8,5.9,1.8,5.9,1.8Hz)	8.25 ppm, 2 H, doublet of triplet, (J=1.3,6.4,1.3,6.4,1.3Hz)	0.41
$H_{3,3'}$	8.29 ppm, 2 H, d, (J=7.7Hz)	8.48 ppm, 2 H, d, (J=7.7Hz)	0.19
$H_{6,6'}$	8.59 ppm, 2 H, d, (J=3.6Hz)	9.02 ppm, 2 H, d, (J=5.9Hz)	0.43

In the ^{13}C NMR of the $PdCl_2$(bipy) complex, the shift observed is more towards the downfield region to that of the free ligand - 2,2’-bipyridine in the range of 0.4 to 4.0 ppm [Table 2.2 (see Figure 2.6-(a) and (b) for ^{13}C NMR). A plausible assignment of each aromatic carbon is shown in Table 2.2

A shift in the signal position with respect to the free ligand occurs because of the coordination to the metal via two pyridyl nitrogens in the complex.

Table 2.2: Carbon NMR data of $PdCl_2$(bipy) complex

Atom	Ligand (2,2’-bipyridine) δ ppṃ	Catalyst [$PdCl_2$(bipy) complex) δ ppṃ	Shift δ Δ ppṃ
$C_{2,2'}$	155.40	156.61	1.21
$C_{6,6'}$	149.46	149.88	0.42
$C_{4,4'}$	137.48	141.42	3.94
$C_{3,3'}$	124.37	127.50	3.13
$C_{5,5'}$	120.60	124.08	3.48

2.2.2.2.2 Synthesis of $PdCl_2(PPh_3)_2$

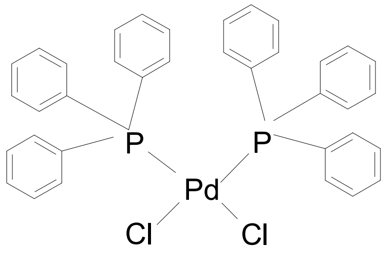


Figure 2.7: $PdCl_2(PPh_3)_2$ complex

A solution of $PdCl_2$ (1 mmol) in dilute 25 ml of aqueous hydrochloric acid was slowly added to a warm stirred solution of PPh_3 (2.1 mmol) in ethanol (20 ml) and was stirred at ~60^{0}C for 2 hrs. The bright yellow complex which precipitated (Figure 2.7), was filtered, washed with hot ethanol and dried in vacuum. The complex was re-crystallized from chloroform to obtain 95% yield of $PdCl_2(PPh_3)_2$ based on $PdCl_2$. Elemental Analysis (w/w %): Calculated: C, 61.61; H, 4.31; Cl, 10.10. Found: C, 60.58; H, 4.36, Cl, 9.82.

2.2.2.2.3 Synthesis of $PdCl_2$(DPPE)

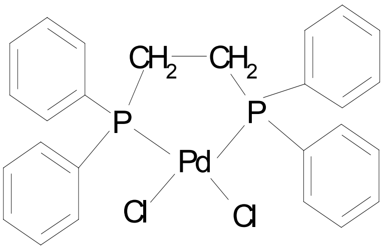


Figure 2.8: $PdCl_2$(DPPE) complex

$PdCl_2$ (1 mmol) and sodium acetate (2 mmol) was taken in 5 ml distilled water and stirred at room temperature till all the $PdCl_2$ was dissolved. To this brown solution, DPPE (1 mmol) was added and the mixture was stirred at ~60^{0}C for 4 hrs. The yellow complex, which precipitated (Figure 2.8), was filtered, washed with distilled water and dried in vacuum. The complex was re-crystallized from chloroform to obtain 96% yield of $PdCl_2$(DPPE) based on $PdCl_2$.

Elemental Analysis (w/w %): Calculated: C, 54.26; H, 4.17; Cl, 12.35. Found: C, 54.15; H, 4.21; Cl, 12.28.

2.2.2.2.4 Synthesis of $PdCl_2(Py)_2$

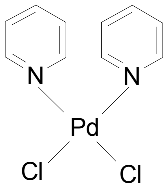


Figure 2.9: $PdCl_2(Py)_2$ complex

A solution of $PdCl_2$ (1 mmol) in dilute 20 ml aqueous hydrochloric acid was slowly added to a stirred warm solution of pyridine (2.2 mmol) in distilled water (100 ml) at ~60^0C for 1 hr. The yellow complex was precipitated (Figure 2.9), filtered, washed with distilled water and dried in vacuum. The complex was re-crystallized from chloroform to obtain 96% yield of $PdCl_2(Py)_2$ based on $PdCl_2$.

Elemental Analysis (w/w %): Calculated: C, 35.82; H, 2.98; N, 8.36; Cl, 21.19. Found: C, 36.01; H, 2.85; N, 8.42; Cl, 21.15.

2.2.2.2.5 Synthesis of $PdCl_2$(DPPPy)

In a 50 ml round bottom flask containing 5 ml ethanol and 1 ml water, 0.040g (2.27 mmol) of $PdCl_2$ and 0.0597g (2.27 mmol) of 2-(Diphenylphosphino) pyridine [DPPPy] were added. One drop of concentrated HCl was added to this mixture.

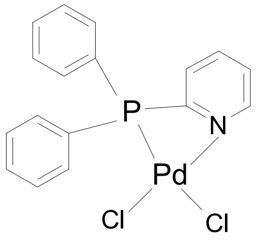


Figure 2.10: $PdCl_2$(DPPPy) complex

The mixture was stirred at room temperature for 3 hrs under inert conditions. A clear dark yellow solution gave a yellow coloured $PdCl_2$(DPPPy) complex (Figure 2.10) after evaporation of solvent. Practical yield of the complex was 0.081g (82%).

Elemental Analysis (w/w %): Calculated: C, 46.34; H, 3.20; Cl, 16.09. Found: C, 44.24; H, 3.34, Cl, 15.42.

2.2.2.2.6 Synthesis of Herrmann Palladacycle

Palladium acetate (4.5 g, 20.0 mmol) was dissolved in 500 ml of toluene. To this reddish brown solution obtained, tri(o-tolyl)phosphine (8.0 g, 26.3 mmol) was added.

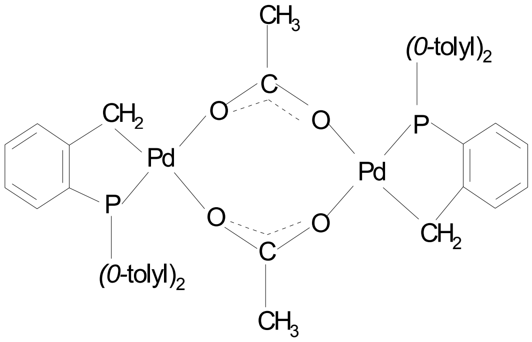


Figure 2.11: Herrmann Palladacycle

The mixture changed colour to bright orange and was heated at 50°C for 3 min and then rapidly cooled to room temperature. About 375 ml of the solvent were removed in vacuum. To this residue 500 ml of hexane was added, which caused the precipitation of the complex. After filtration and drying in vacuum 8.8 g of Herrmann Palladacycle i.e. trans-di(μ-acetato)-bis[o-(di-o-tolylphosphino)benzyl]dipalladium(II) (Figure 2.11) was obtained as a yellow solid [93% yield referred to $Pd(OAc)_2$].

Elemental Analysis (w/w %): Calculated: C, 58.93; H, 4.94; Found: C, 58.89; H, 5.06.

2.2.2.3 General procedure for screening experiments

In a typical experiment, 3.3 mmol of the olefin and 3.0 mmol of aryl halide (ArX) were added to the organic phase (mixture of 75% n-octane and 25% *p*-xylene) to make the volume 15 ml. In another flask, 0.003 mmol of catalyst and 3.0 mmol of base were added to ethylene glycol (15 ml). Both these phases were then mixed thoroughly and the sample was taken for GC analysis. This mixture was then charged into the reactor and the contents were heated to the desired temperature with an agitation of 1000 RPM to ensure thorough mixing in the reactor. The reaction was continued for the desired period (generally 3 hours). The progress of the reaction was monitored by intermediate sampling of the liquid contents in the reactor. A portion of the reaction mixture was repeatedly taken out from the reactor and the two phases were analyzed by using a capillary gas chromatograph with flame ionization detector. The identification of products was done using a GC-MS. From the quantitative analysis, the conversion of the aryl halide, selectivity, Turn Over Number (TON) and turnover frequency (TOF) were calculated by using the following formulae (Equation 2.2-2.5).

$$\text{Conversion (\%)} = \frac{(\text{Initial moles of substrate (ArX)} - \text{Final moles of substrate (ArX)}) \times 100}{\text{Initial moles of substrate (ArX)}} \qquad [2.2]$$

$$\text{Selectivity (\%)} = \frac{\text{moles of product formed} \times 100}{\text{moles of substrate (ArX) consumed}} \qquad [2.3]$$

$$\text{TON} = \frac{\text{moles of product formed}}{\text{moles of catalyst}} \qquad [2.4]$$

$$\text{TOF , hr}^{-1} = \frac{\text{moles of product formed}}{\text{moles of catalyst x time, hr}} \qquad [2.5]$$

2.2.2.4 GC analysis

The liquid samples were analyzed on a GC (Agilent 6850 series II), controlled by the HP Chemstation software, on an HP1 column. GC-MS was carried out on a Agilent 6890N series equipped with 5973N mass selective detector. The standard conditions for GC analysis are given in Table 2.3

Table 2.3: Standard conditions of GC

Column	Capillary column, HP 1, 30 m, film thickness 0.25μm
Oven temperature	Initial temperature – 80°C – 4 min
	Ramp - rate 30°C/min – till 250°C
	Final temperature – 250°C – 7 min
	Post temperature – 280°C –2 min
Injector temperature	250°C
Detector (FID)	Temperature 300°C
	Fuel gas - Hydrogen – 35.0 ml/min
	Oxidant – Air – 320.0 ml/min
Carrier (He)	10 psi

2.2.3 Results and discussion

2.2.3.1 Preliminary reactions

Preliminary experiments were conducted in biphasic (ethylene glycol-p-xylene) medium to compare the activity of various catalysts for the arylation of styrene with iodobenzene. The results are presented in Table 2.4

Table 2.4: Comparison of activity using various catalysts in biphasic medium

Sr. No.	Catalyst	Base	% Conversion of Iodobenzene
1	$PdCl_2$(bipy)	KOAc	83
2		Morpholine	81
3	$PdCl_2(Py)_2$	KOAc	33
4		Morpholine	58
5	$PdCl_2(PPh_3)_2$	KOAc	54
6		Morpholine	72
7	$PdCl_2$(DPPE)	KOAc	43
8		Morpholine	85
9	$PdCl_2$(DPPPy)	Morpholine	96
10	Palladacycle	Morpholine	94

Reaction conditions: Organic phase: styrene (3.3 mmol) + iodobenzene (3.0 mmol) in p-xylene (15 ml); ethylene glycol phase: catalyst (0.003 mmol) + base (3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs).

These reactions were conducted in the presence of an inorganic (KOAc) and also an organic base (morpholine). This was specifically done to understand the role of these bases, with respect to their solubility in the reaction medium.

Palladacycle, $PdCl_2$(DPPE), $PdCl_2$(DPPPy) and to some extent $PdCl_2(PPh_3)_2$ catalyst gave good activity as shown in Table 2.4, however the catalyst was found to be present in the organic phase (p-xylene) at the end of reaction. Hence, these catalysts were inappropriate for the biphasic catalysis as envisaged. $PdCl_2$(DPPPy) complex was partly soluble in the xylene phase and the recycle of the glycol phase gave poor reaction. With $PdCl_2(Py)_2$ catalyst no leaching was observed, however the conversions obtained were poor. The $PdCl_2$(bipy) catalyst was by far the best catalyst which did not leach in to the organic phase. The activity observed for this catalyst is reasonably high with similar conversions for the KOAc as well as morpholine base. Hence all further screening was done using the $PdCl_2$(bipy) catalyst with KOAc as the base.

2.2.3.2 Screening of solvents

In biphasic systems the role of solvent is extremely important. The polarity of the solvent plays a major role in deciding the performance of the catalyst and the solubility of the reactants in the catalyst phase. To develop an efficient biphasic system the two phases have to be tailored such that they are immiscible with each other and the catalyst is soluble in one phase, while the reactants and products are soluble in the second phase. The base used can be soluble in either phase, since the base-HX adduct or quaternary salt formed by the sequestration of the HX is either soluble in the polar phase or is present as a solid, as shown in Figure 2.1.

The use of ethylene glycol phase as a polar phase for solubilization of the catalyst was an obvious choice considering the literature reports on biphasic media for Heck reactions[12,16,17]. In this study the role of mixed organic solvents as the second phase was investigated. The studies were conducted using different compositions of n-octane and *p*-xylene as the organic phase, as this solvent system was found to be immiscible with ethylene glycol. The results are presented in Table 2.5.

Table 2.5: Heck reaction of different combination of solvent (n-octane + p-xylene) with styrene and iodobenzene using $PdCl_2$(bipy) catalyst and KOAc as a base in biphasic medium

Sr. No.	n-octane : p-xylene	% Conversion of iodobenzene	TOF(hr^{-1})
1	100% : 0%	73	227
2	75% : 25%	71	222
3	50% : 50%	67	210
4	25% : 75%	79	253
5	0% : 100%	83	262

Reaction conditions: Organic phase – 15 ml: styrene (3.3 mmol) + iodobenzene (3.0mmol) taken in n-octane + p-xylene (different composition); ethylene glycol phase: catalyst (0.003 mmol) + base (KOAc-3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs). Selectivity >98% for (cis+trans) stilbene

It was observed that the activity was the highest in either pure octane or xylene as solvent. However in case of 100% n-octane, the product, stilbene, precipitated out of the reaction medium as the solubility of stilbene in n-octane is very poor. No leaching of Pd was observed in this case. In case of 100% xylene as the organic phase, although precipitation of the stilbene was not observed, some leaching of the catalyst to the organic phase was observed. Hence, varying proportions of n-octane in p-xylene were studied to optimize the solvent combination.

A solvent composition of 75% n-octane + 25% *p*-xylene (v/v) was found to give good activity (similar to that with pure n-octane), and also ensured no leaching of catalyst to the organic phase. In this solvent mixture the stilbene too was found to be highly soluble. Hence, for all screening studies the biphasic system comprising octane 75%, xylene 25% v/v and ethylene glycol was used.

A typical concentration time profile for the Heck coupling of iodobenzene with styrene in presence of KOAc base in the optimized biphasic solvent system is shown in Figure 2.12. The consumption of iodobenzene and styrene was found to be commensurate with the stilbenes formed.

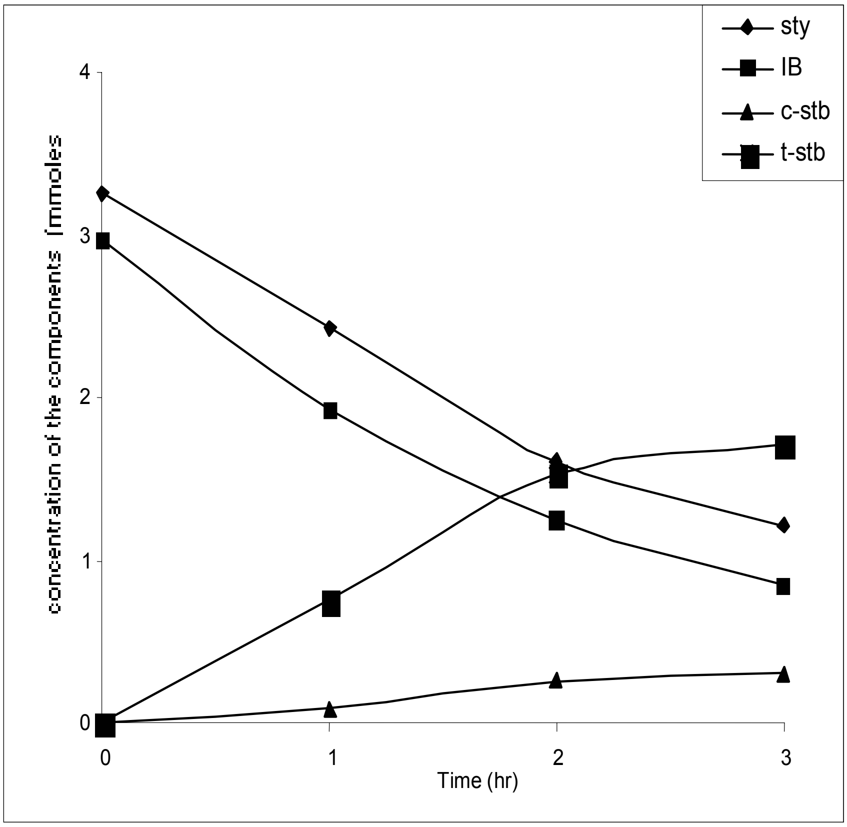


Figure 2.12: Typical concentration profile of Heck reaction in biphasic medium

Reaction conditions: Organic phase – 15 ml: styrene (3.3 mmol) + iodobenzene (3.0mmol) taken in n-octane (75%) + p-xylene (25%); ethylene glycol phase: catalyst (0.003 mmol) + base (KOAc-3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs). Selectivity >98% for (cis + trans) stilbene

2.2.3.3 Screening of base

A detailed screening of bases was conducted using the $PdCl_2$(bipy) catalyst in an organic – glycol biphasic medium for the vinylation of iodobenzene with styrene. A variety of organic and inorganic bases were screened for their activity in biphasic medium, including aliphatic and aromatic organic bases and monovalent / divalent inorganic bases. The results are shown in Table 2.6 and the TONs observed for the different bases are shown graphically in Figure 2.13. As per the reported mechanism, the base helps in the regeneration of the active Pd(0) catalyst complex[28] and for the trapping of H-X generated in the course of the reaction.

Table 2.6: Heck reaction of iodobenzene with styrene with $PdCl_2$(bipy) catalyst using different bases in biphasic medium

Sr. NO.	Bases	% Conversion of iodobenzene	TOF
1	KOAc	71	222
2	NH_4OAc	75	237
3	NaOAc	62	195
4	$Mg(OAc)_2$	78	245
5	$NaHCO_3$	98	213
6	Resin-OAc	17	29
7	Resin-OH	21	47
8	K_2CO_3	92	73
9	Na_2CO_3	100	125
10	Morpholine	60	162
11	Et_3N	92	314
12	NMP	4	10
13	Piperidine	80	258
14	Pyridine	25	73
15	Tribenzylamine	7	36

Reaction conditions: Organic phase – 15 ml: styrene (3.3 mmol) + iodobenzene (3.0mmol) taken in n-octane (75%) + p-xylene (25%); ethylene glycol phase: catalyst (0.003 mmol) + base (KOAc-3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs). Selectivity >98% for (cis + trans) stilbene

Amongst inorganic bases the acetates were found to have better activity compared to others. Sodium, potassium and ammonium acetates gave TONs higher than 500. Even Mg acetate was found to be active for the reaction.

The carbonates of sodium and potassium were also active, and Na_2CO_3 was found to be more active than the K_2CO_3. With carbonates a high conversion of iodobenzene was observed, but, instead of desired product i.e. stilbene, benzene was the major product indicating a dehalogenation in presence of the carbonates. The presence of benzene was confirmed by GC-MS.

The organic bases were also found to be active for the Heck reaction in the biphasic medium. Triethyl amine, morpholine and piperidine gave excellent activity with TONs in the range of 450 to 950. However, although the highest turnover Number (TON) of 943 was obtained for triethyl amine, considerable dehalogenation of iodobenzene was observed. Aliphatic amines were more active than aromatic amines. Morpholine and piperidine showed better activity, as they can form the quaternary ammonium salts easily. As compared to other bases like pyridine, NMP (N-methyl pyrolidinone) and tribenzyl amine, piperidine and triethyl amine showed higher activity, as they are relatively stronger bases.

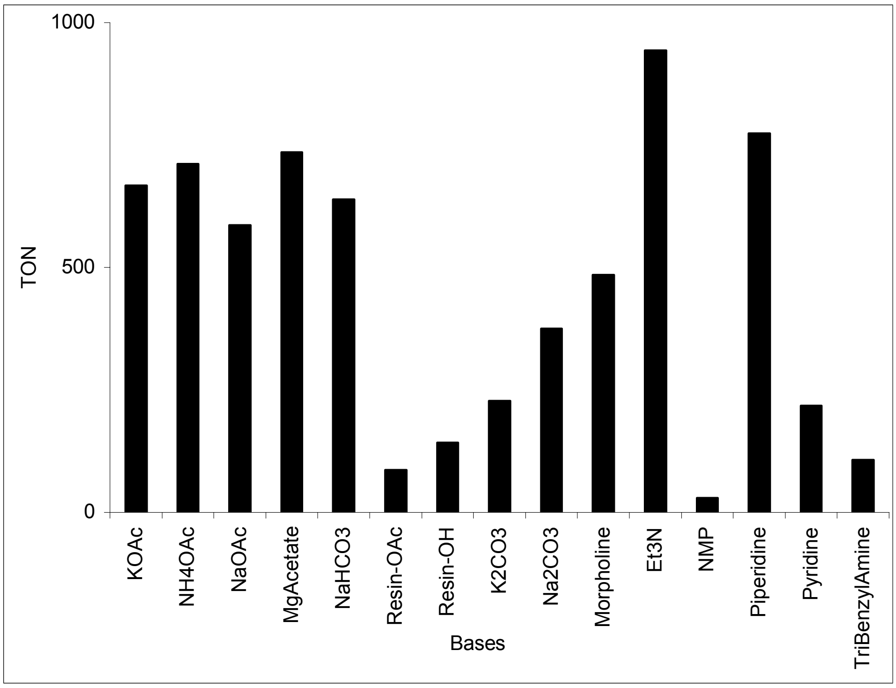


Figure 2.13: TON observed for Heck reaction of iodobenzene and styrene with $PdCl_2$(bipy) catalyst using different bases in biphasic medium

Reaction conditions: Organic phase – 15 ml: styrene (3.3 mmol) + iodobenzene (3.0mmol) taken in n-octane (75%) + p-xylene (25%); ethylene glycol phase: catalyst (0.003 mmol) + base (3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs). Selectivity >98% for (cis + trans) stilbene

Anion exchange resins as bases

The use of anion exchange resins as bases were also investigated. The main objective for these experiments was to see whether use of solid and recyclable bases could be achieved. If successful, the removal of the base-halide adduct would be feasible, ensuring a better catalyst recycle. The anion exchange resin could then be reconverted to the original form by a separate process for further reuse. For this study –OH and –OAc exchanged resins were tested for their activity as bases for the Heck reaction. The quantity of resin used was the molar equivalent of the base concentration used, calculated on the basis of their exchange capacity. The –OH resin was more active compared to the –OAc resin, with the former giving a TON of 142. In comparison a TON of 86 was observed for the –OAc resin. However, although effective as a base for the Heck reaction, the loading required for the ion exchange resin was higher compared to the other bases used.

2.2.3.4 Screening of aryl halide

The activity of $PdCl_2$(bipy) for the Heck coupling in a biphasic n-octane, p-xylene - glycol medium was assessed for the different aryl halides. For this purpose arylation of styrene was investigated in the presence of KOAc as a base. The results are shown in Figure 2.14 as the TON observed for the various ArX. Table 2.7 shows the conversion of aryl halides and the respective TOFs for the different reactions conducted. In all the cases the products were analyzed on GC and identification and confirmation of the product was done by using GC-MS. GC-MS data of the products are presented in Appendix -I.

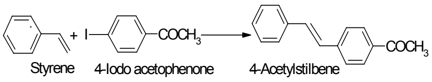
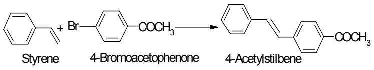
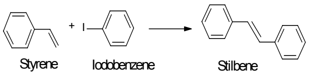
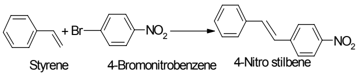
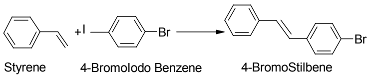
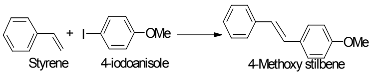
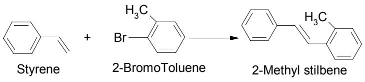
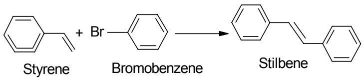
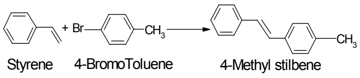
Iodides were found to be more active than bromides amongst aryl halides. It was seen that catalyst showed the highest activity with 4-iodoacetophenone compared to all other compounds studied, with highest conversion of 87% and a TON of 870. With 4-bromotoluene the lowest activity was observed. It is well known that the haloarenes with substituents having a positive inductive effect are less reactive.

For the reaction of 4-bromoiodobenzene only the iodo substituent underwent reaction to produce 4-bromostilbene. Since iodoarenes are reportedly more active than the bromo derivatives[29], this behavior is expected. Also, no further reaction of the 4-bromo stilbene was observed within the reaction period (confirmed by GC-MS).

It was also seen that the aryl halides with strong electron withdrawing substituents showed a very high activity, whereas those with electron donating substituents showed poor activity. This observation is as per the general trends observed for the activities of Pd complex catalyzed Heck reactions.

Although the iodoarenes were far more active than the bromoarenes, the activity of the catalyst observed for the Heck coupling of styrene with different substrates in the biphasic medium was not exactly according to Hammett correlation observed in homogeneous reactions[29]. This is likely to be due to the varying solubilities of the substrates in the glycol phase, where the catalyst is present. The solubility of the reactants was determined and it was found that the activity was comparable to their solubility. The activity observed will be due to the combined effect of the substrate concentration in the glycol (catalyst) phase and the electronic properties of the substrates.

Table 2.7: Heck reaction of different aryl halides with styrene using $PdCl_2$(bipy) catalyst and KOAc as a base in biphasic medium

Sr. No.	Aryl halide	Reaction	% Conversion of Aryl halide	TOF (hr^{-1})
1	4-Iodoacetophenone		87	290
2	4-Bromoacetophenone		87	288
3	Iodobenzene		71	222
4	4-Bromonitrobenzene		70	220
5	4-Bromo-1-iodobenzene		69	218
6	4-Iodoanisole		67	210
7	2-Bromotoluene		21	75
8	Bromobenzene		16	53
9	4-Bromotoluene		12	41

Reaction conditions: Organic phase – 15 ml: styrene (3.3 mmol) + Ar-X (3.0 mmol) taken in n-octane (75%) + p-xylene (25%); ethylene glycol phase: catalyst (0.003mmol) + base (KOAc-3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs). Selectivity >98% for (cis + trans) product.

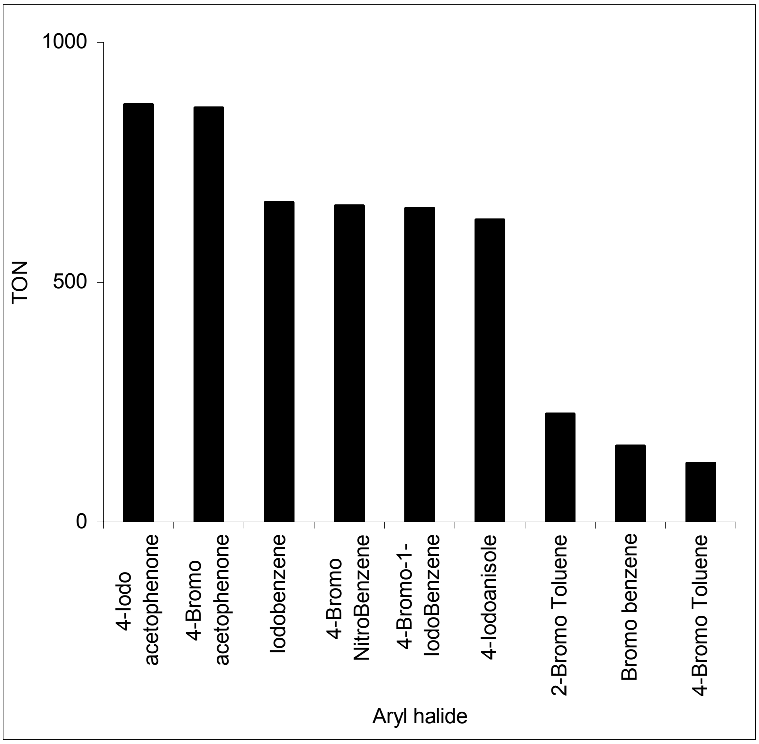


Figure 2.14: TON observed for Heck reaction of various aryl halides with styrene using $PdCl_2$(bipy) catalyst and KOAc as a base in biphasic medium

Reaction conditions: Organic phase – 15 ml: styrene (3.3 mmol) + Ar-X (3.0 mmol) taken in n-octane (75%) + p-xylene (25%); ethylene glycol phase: catalyst (0.003mmol) + base (KOAc-3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs). Selectivity >98% for (cis + trans) product.

2.2.3.5 Screening of olefins

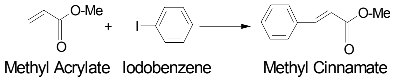
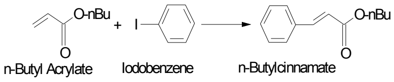
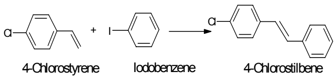
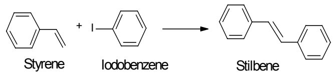
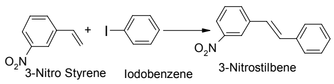
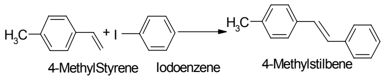
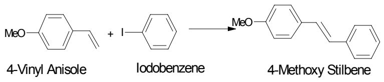
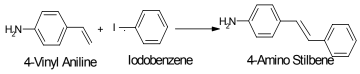
The activity of the $PdCl_2$(bipy) catalyst for the vinylation of iodobenzene with different olefins was studied in the n-octane, p-xylene -glycol biphasic medium in presence of KOAc as the base.. The results are presented in Table 2.8, and the TONs for the different olefins are presented in Figure 2.15. As in the previous experiments, the confirmation of the products formed was done by using GC-MS (see Appendix-I for GC-MS data).

Generally it was seen that the olefins with strong electron withdrawing substituents show poor activity, whereas those with more electron withdrawing substituents show higher activity. This trend is opposite to that observed for aryl halides. The Heck reaction cycle reported suggests an addition of the olefin to the Pd(0) species, to form a π complex. Electron rich olefins will be expected to react faster than those with electron withdrawing substituents.

Acrylates were found to be more reactive than styrene derivatives. The regio selectivity of the product formed in case of acrylates favored 100% trans product, whereas with the styrene derivatives some cis product (<5%) is observed.

In our study, as also observed for the halides, the activity of the catalyst for different substrates in the biphasic medium was not exactly according to Hammett correlation reported for the homogeneously catalyzed Heck reactions. The activity observed in the biphasic medium could thus be due to the combined effect of the solubility of the olefin in the glycol phase and the role played by the various substituents on the olefins.

Table 2.8: Heck reaction of different olefin with iodobenzene using $PdCl_2$(bipy) catalyst and KOAc as a base in biphasic medium

Sr. No.	Olefins used	Reaction	% Conversion of iodobenzene	TOF (hr^{-1})
1	Methyl acrylate		99	329
2	n-Butyl acrylate		98	326
3	4-Chloro styrene		81	263
4	Styrene		71	222
5	3-Nitro styrene		70	219
6	4-Methyl styrene		69	216
7	4-Vinyl anisole		61	194
8	4-Vinyl aniline		49	159

Reaction conditions: Organic phase – 15 ml: olefin (3.3 mmol) + iodobenzene (3.0mmol) taken in n-octane (75%) + p-xylene (25%); ethylene glycol phase: catalyst (0.003 mmol) + base (KOAc-3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs). Selectivity >98% for (cis + trans) product.

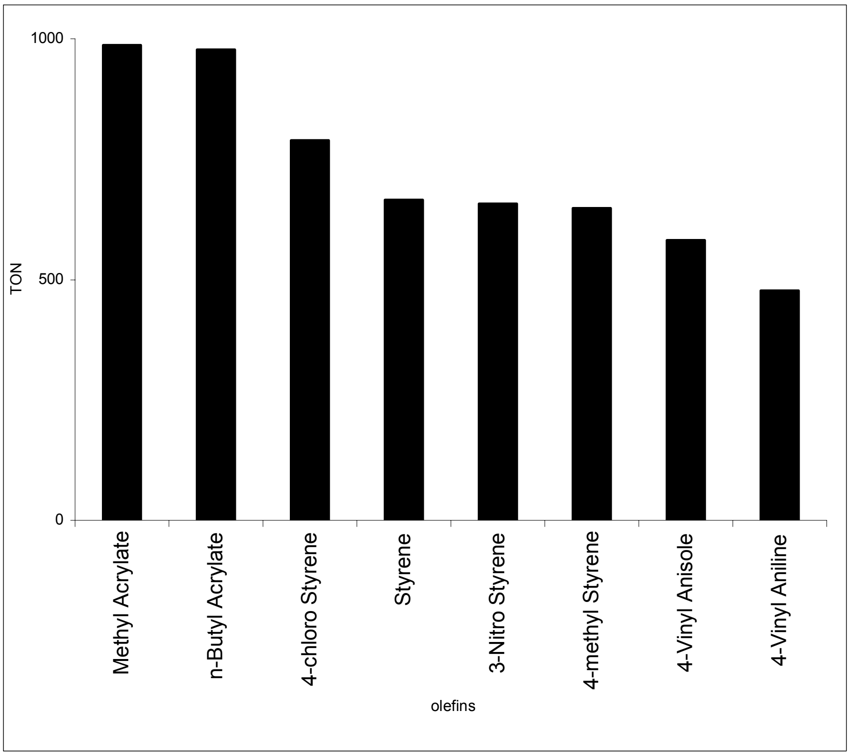


Figure 2.15: TON for Heck reaction of different olefin with iodobenzene using $PdCl_2$(bipy) catalyst and KOAc as a base in biphasic medium

Reaction conditions: Organic phase – 15 ml: Olefin (3.3 mmol) + iodobenzene (3.0mmol) taken in n-octane (75%) + p-xylene (25%); ethylene glycol phase: catalyst (0.003 mmol) + base (KOAc-3.0 mmol) in ethylene glycol (15 ml); 150°C; 1000 RPM (Time: 3hrs). Selectivity >98% for (cis + trans) product.

2.2.3.6 Recycle study for the activity of $PdCl_2$(bipy) catalyst in biphasic medium

A major advantage of the biphasic system is the ease of product separation and recycle of the catalyst. This is achieved by a simple phase separation of two immiscible liquid phases. Since the objective of this study was to develop a biphasic system for an efficient recycle of catalyst, a detailed investigation was done on the recycle of catalyst using KOAc as the base. In the biphasic catalytic system developed, the catalyst and glycol solvent are recycled to the next reaction, after separation of the organic phase. The glycol layer from a Heck reaction in biphasic medium of styrene and iodobenzene using $PdCl_2$(bipy) catalyst in presence of KOAc as a base was separated and recycled a number of times to ascertain the stability and activity of the catalyst and the results are shown in Figure 2.16. The rates as well as the selectivity towards stilbene were found to be unaffected on recycle indicating the reusability of the catalyst. Under the conditions chosen for the study, no side reactions were found to occur and hence, these data represent the overall Heck reaction of styrene with iodobenzene to give stilbene.

As seen in Figure 2.16, the catalyst was recycled for five times and the activity was retained over five recycles with a marginal drop in activity. Neither the precipitation of the catalyst, nor the leaching of palladium to the aqueous phase was observed in the course of the investigations. In this study the base – HX adduct present in the glycol phase was allowed to accumulate for the next recycles. The presence of the adduct was not found to influence the activity of the catalyst. The salt also did not precipitate out of the solution, at the end of 5 recycles.

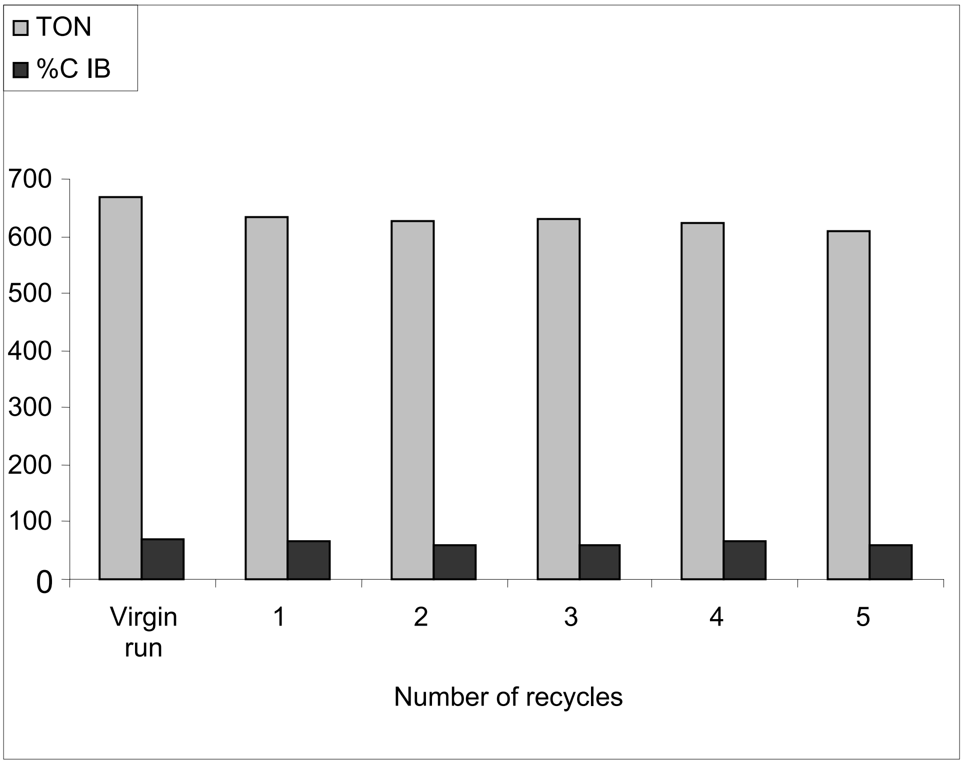


Figure 2.16: Activity of $PdCl_2$(bipy) catalyst on recycle of glycol phase in a glycol-organic biphasic medium for Heck reaction of styrene with iodobenzene and KOAc as a base.

Reaction conditions: Organic phase – 15 ml: styrene (3.3 mmol) + iodobenzene (3.0mmol) taken in n-octane (75%) + p-xylene (25%); ethylene glycol phase: catalyst (0.003 mmol) + base (KOAc-3.0 mmol) in ethylene glycol (15 ml); 150^{o}C; 1000 RPM (Time: 3hrs). Selectivity: (iodobenzene) > 95%.

(For recycle study the ethylene glycol layer is separated and used as it is with the fresh organic layer along with the substrates and the base)

Test of Palladium leaching

The leaching of the catalyst to the organic phase was checked using AAS and the concentration of Pd in the organic phase was negligible (< 1ppm). Moreover a recycle of the organic phase showed no activity for the Heck reaction.

Leaching of palladium was determined as follows: The organic phase was removed and all volatiles were evaporated. The samples were then extracted with aquaregia (3:1 HCl : HNO_3, 0.2 cm^3). Deionised water (5 cm^3) was then added and the samples centrifuged. Analysis was undertaken on a GBC Avanta Ver 1.32 atomic absorption instrument using a series of Pd standards.

2.2.4 Conclusions

Palladium complex consisting of chelating nitrogen ligands i.e. 2,2'-bipyridine has been synthesized and characterized using elemental analysis, IR and NMR spectroscopy. This complex was found to be highly active and catalyzed the Heck reaction efficiently in a glycol-organic biphasic medium and remarkable activity and selectivity were achieved. $PdCl_2$(bipy) complex is found to be active for the Heck reaction in a biphasic glycol-organic solvent system. This catalyst is stable in the glycol phase under reaction conditions with negligible leaching to the organic phase. A major advantage of this catalyst is that, it does not employ water-soluble ligands but employs conventional ligands like bipyridine. This is the first time wherein a biphasic system has been achieved for the Heck reaction, using a Pd complex containing an organic phase soluble bipyridine ligand, instead of a water-soluble ligand, conventionally used. By proper tailoring of the solvent it has been possible to use the complex for application in biphasic medium. The role of different solvent compositions, olefins, aryl halides and bases has been elucidated in the biphasic system. The catalyst was recycled a number of times maintaining the activity.

Section B

2.3: Kinetic studies of Heck reaction using $PdCl_2$(bipy) catalyst in glycol-organic biphasic media

2.3.1 Introduction:

The kinetic study of any reaction is useful in reaction engineering studies and reactor modeling. Kinetics is also necessary for the optimization of reaction conditions. Further, it also provides an understanding of the mechanism of a reaction.

Although the Heck chemistry is now known for more than 35 years, very few studies have been carried out, to understand the kinetic behavior of this reaction[28,30-33], and still fewer rate models have been proposed[34-39]. In addition, a majority of the work carried out till date is on the reaction in homogeneous medium. The detailed kinetics of Heck reaction under different conditions in homogeneous medium has been discussed in Chapter 1 (Section 1.6).

A few studies on the kinetics of Heck reaction have been reported using phosphine containing catalysts (i.e. $PdCl_2$[30], $Pd(OAc)_2TPP$[31], Pd-PCP pincer[39],Hermann Palladacycle[40]), phosphine free (Pd-CN palladacycle[35,36,38] complex) and SLPC[41] catalysts. The general tends observed so far, indicate a positive dependence of the activity on olefin, aryl halide and the base concentration employed. The trend is also found to be dependent on the solvent used. Most of the studies described above are in solvents like NMP, DMF etc, but there is practically no report on such studies in glycol solvent, or in glycol-organic biphasic systems.

This section deals with the results on the investigations on the kinetics of vinylation of iodobenzene with styrene in presence of $PdCl_2$(bipy) catalyst and morpholine as a base in a temperature range of 393 K to 413 K, with the objective of developing a suitable rate equation. An empirical rate model has been proposed to fit the observed data. This is the first time that kinetic modeling has been attempted for the Heck reaction in a biphasic medium.

2.3.2 Experimental section

2.3.2.1 Apparatus and chemicals

$PdCl_2$, 2,2'-bipyridine, styrene and iodobenzene were procured form Aldrich USA and used without any further treatment. The solvents (n-octane, *p*-xylene, ethylene glycol) were obtained from SD fine chemicals, India. Morpholine (Loba chemicals) used was AR grade. The $PdCl_2$(bipy) complex was prepared and characterized as per the procedure given in Section 2.2.2.2.1.

Since the temperatures utilized for the reaction were higher than the boiling points of most of the reactants and the solvents, the reactions were conducted in a high pressure autoclave of 50 ml capacity manufactured by Ms Amar Engineering, Mumbai and had facilities for withdrawal of liquid and gaseous samples. The temperature was controlled by means of electric heater and internal cooling loop. The schematic of reactor set-up shown in Figure 2.3

2.3.2.2 General procedure for kinetic studies of Heck reaction

In a typical experiment, a required amount of the olefin and the aryl halide was added to the organic phase (mixture of 75% n-octane and 25% p-xylene) to make the volume 12 ml. In another flask the catalyst and base were added in the required quantity to ethylene glycol (18 ml). Both these phases were then mixed thoroughly and the sample was taken for GC analysis. This mixture was then charged into the reactor and the contents were heated to the desired temperature under slow stirring. Once the temperature was attained, the reaction was started by increasing the agitation to 1450 RPM to ensure thorough mixing of the two phases in the reactor. The reaction was continued for 1.5 hours. The progress of the reaction was monitored by intermediate sampling of the liquid contents in the reactor. A portion of the reaction mixture was periodically taken out from the reactor and the two phases were analyzed for their contents using a capillary gas chromatograph with flame ionization detector [Agilent 6850 series]. The standard conditions for GC analysis are given in Section 2.2.2.5 and Table 2.3. Formation of stilbene was confirmed on GC by comparison with authentic standards

The kinetic experiments were carried out at three different temperatures for short durations, such that the conversion of liquid phase reactant was less than 20-25% to ensure differential conditions. It was generally observed that in this low conversion range, the rates of Heck reaction were constant. The experiments were found to be reproducible within an error of 4-6%. In each reaction, initial, intermediate and final samples were analyzed, for reactants and products in order to check the material balance. Following this procedure, the effect of catalyst, styrene, iodobenzene and morpholine concentration on the rate of Heck reaction was studied at a temperature of 393, 403 and 413 K.

2.3.3 Results and discussion

2.3.3.1 Preliminary results

The main objective of this work was to investigate the kinetics of Heck reaction in a biphasic medium. It was therefore necessary, to first ensure the material balance and reproducibility of experiments. For this purpose, a few experiments were carried out in which the amount of substrates consumed and the product formed were compared. A typical concentration time profile for a reaction is shown in Figure 2.17.

This pertains to the Heck coupling of styrene and iodobenzene in the presence $PdCl_2$(bipy) catalyst and morpholine as a base at 150°C. In general, it was observed that the material balance of substrates i.e. styrene and iodobenzene consumed was consistent with the amount of total product i.e. stilbene formed. Also, in the range of conditions covered in this work, only trans and cis stilbene were formed, which was confirmed by GC-MS.

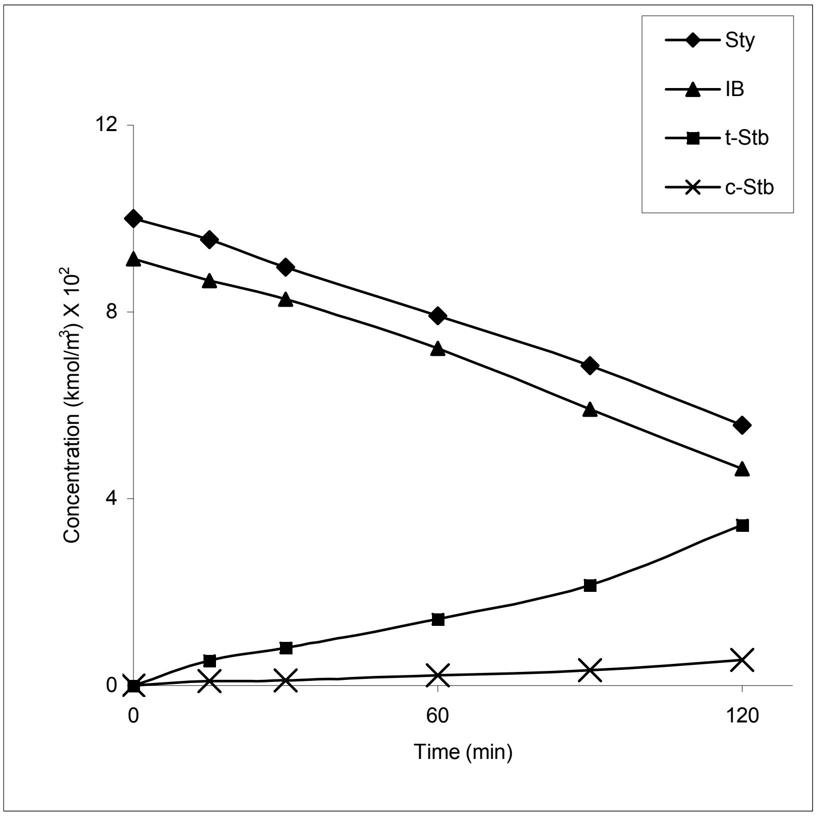


Figure 2.17: Typical concentration profile of Heck reaction in biphasic medium Reaction conditions: concentration of catalyst: 1.0 x 10^{-4}, kmol m^{-3}, concentration of styrene: 1.1 x 10^{-1} kmol m^{-3}, concentration of iodobenzene: 1.0 x 10^{-1} kmol m^{-3}, concentration of morpholine: 1.0 x 10^{-1} kmol m^{-3}. Temperature: 150°C. Reaction volume: organic phase: 12ml, glycol phase: 18ml; glycol phase holdup: 0.6, agitation speed 1450 RPM.

2.3.3.2 Kinetic study

Since the preliminary experiments showed that the catalyst is active for the Heck reaction, further investigations were carried out to understand the influence of different concentrations of styrene, iodobenzene, base and catalyst on the activity of the catalyst, in the temperature range of 120°C-140°C. In each case the amount of stilbene formed, as a function of time was monitored. It was observed that, in the initial period, the rate of reaction was essentially constant. Thus the rates of Heck reaction in biphasic medium were calculated as follows (Equation 2.6)

Rate of Heck reaction,

$$R = \frac{\text{Slope of plot of concentration of stilbene formed}}{\text{(kmol/ m}^3\text{ total volume) v/s Time (s)}} \qquad [2.6]$$

These were essentially initial rates of reaction, observed under differential conditions, as shown in Figure 2.18 for catalyst concentration effect at 140°C (413K).

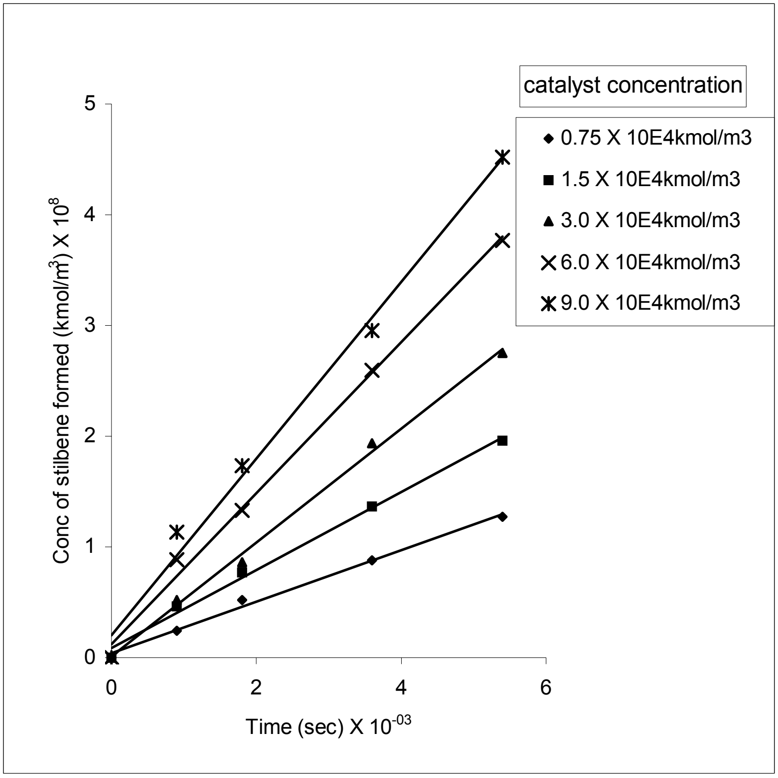


Figure 2.18: Typical concentration v/s time plot for calculation of rate

Reaction conditions: Concentration of styrene: 1.1 x 10^{-1} kmol m^{-3}, concentration of iodobenzene: 1.0 x 10^{-1} kmol m^{-3}, concentration of morpholine: 1.0 x 10^{-1} kmol m^{-3}, Temperature: 413K, Reaction volume: organic phase: 12ml, glycol phase: 18ml; glycol phase holdup: 0.6; Agitation speed 1450 RPM.

The effect of the different parameters on the rate of Heck coupling is discussed below.

2.3.3.2.1 Mass transfer effects in liquid-liquid systems

The Heck reaction in a biphasic glycol –organic (n-octane + p-xylene) medium is a typical case of a liquid-liquid reaction and hence for investigation of intrinsic kinetics of these reactions, it is important to ensure that the rate data obtained are in the kinetic regime. A careful consideration to the significance of mass transfer must be given for kinetic analysis of a complex multiphase reaction involving liquid-liquid system. For a liquid-liquid reaction system, the overall rate would depend on the liquid-liquid mass transfer and the intrinsic kinetics of the reaction in the glycol phase. A few experiments were carried out to investigate the effect of catalyst phase hold up, agitation speed and catalyst concentration on the rate of reaction. These experiments were important to understand the role of mass transfer and ensure that the data obtained were in the kinetic regime.

2.3.3.2.2 Effect of agitation speed

The effect of agitation speed on the rate of Heck reaction in biphasic media was first investigated at the highest temperature of study (413 K) under standard conditions, to check the significance of mass transfer. The results are shown in Figure 2.19.

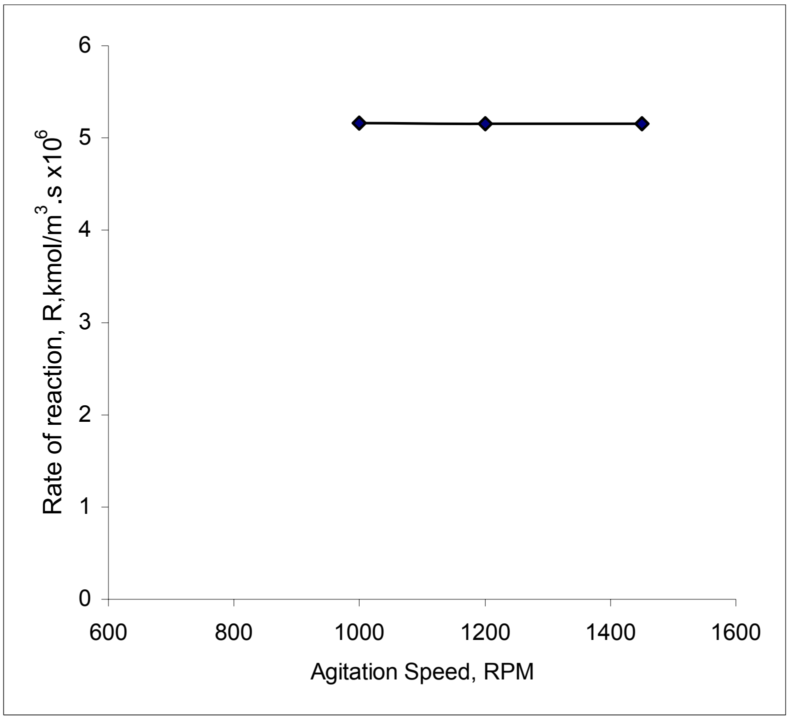


Figure 2.19: Effect of agitation on the rate of Heck reaction in biphasic medium

Reaction conditions: concentration of catalyst: 1.0 x 10^{-4}, kmol m^{-3}, concentration of styrene: 1.1 x 10^{-1}, kmol m^{-3}, concentration of iodobenzene: 1.0 x 10^{-1}, kmol m^{-3}, concentration of morpholine: 1.0 x 10^{-1} kmol m^{-3}, Temperature: 413K Reaction volume: organic phase: 12ml; glycol phase: 18ml; glycol phase holdup: 0.6

It was observed that the rate was independent of agitation beyond 1000 RPM. All reactions were hence conducted at 1450 RPM to ensure that the reaction occurs in the kinetic regime.

2.3.3.2.3 Effect of phase holdup

Figure 2.20 shows the effect of glycol (catalyst) phase hold-up (ε_g) on the initial rate of Heck reaction of styrene and iodobenzene at varying glycol phase holdup. It was observed that the phase inversion takes place at a glycol phase hold up of about 0.5. For glycol phase hold-up less than 0.5, the glycol phase is the dispersed phase, as shown schematically in Figure 2.21(a). In this case, the liquid-liquid interfacial area is determined by glycol phase hold-up (ε_g). For glycol phase hold-up greater than 0.5, the organic phase is the dispersed phase, as shown schematically in Figure 2.21(b). In this case, the liquid-liquid interfacial area will be determined by the organic phase hold-up ($1-\varepsilon_g$).

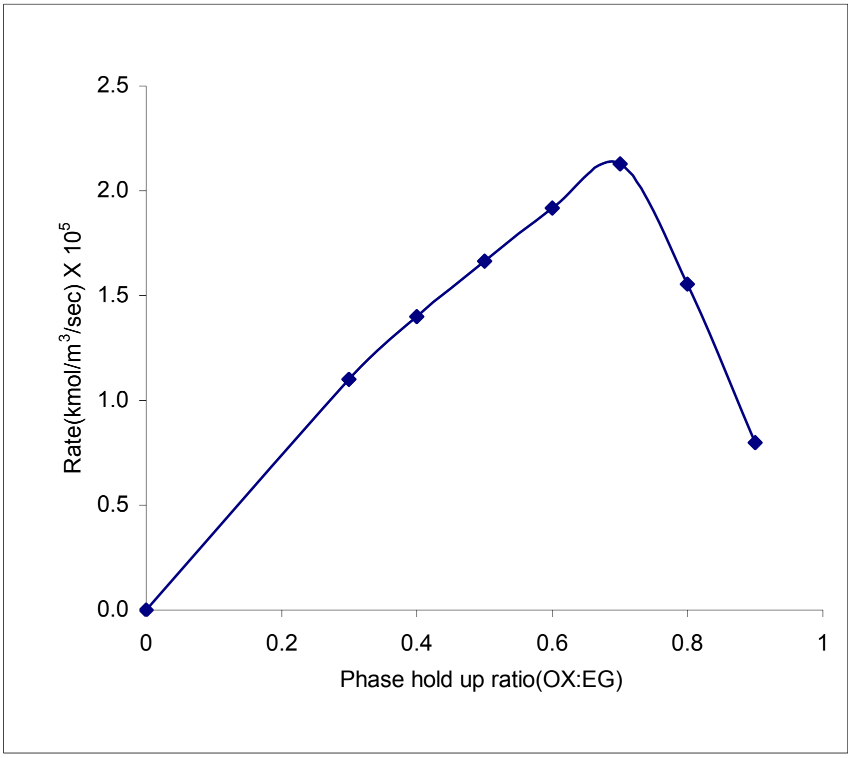
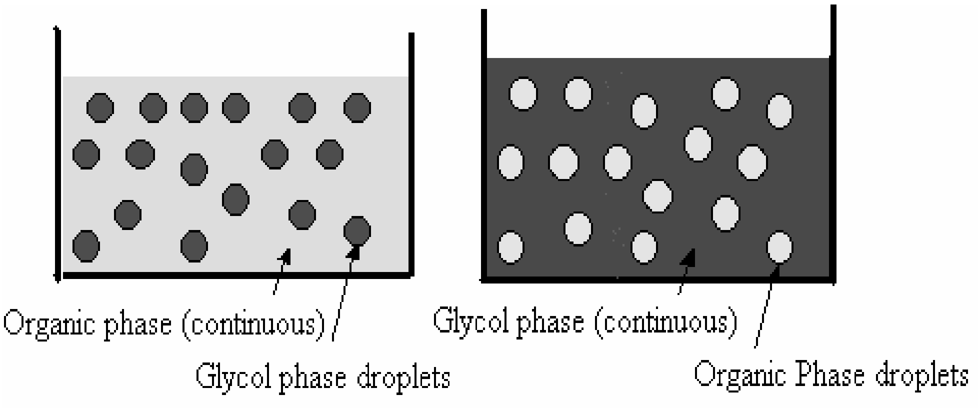


Figure 2.20: Effect of glycol phase holdup on the rate of Heck reaction in biphasic medium

Reaction conditions: concentration of catalyst: 1.0×10^{-4}, kmol m^{-3}, concentration of styrene: 1.1×10^{-1}, kmol m^{-3}, concentration of iodobenzene: 1.0×10^{-1}, kmol m^{-3}, concentration of morpholine: 1.0×10^{-1} kmol m^{-3}, Temperature: 423K. Reaction volume: organic phase + glycol phase = 30ml; Agitation speed 1450 RPM.

Physical description of models



(a) Glycol phase dispersed (0<ε<0.5)

(b) Organic phase dispersed (0.5<ε<1.0)

Figure 2.21: schematic representations of two different physical situations prevailing in the reactor depending upon the phase hold up

As seen from the results in Figure 2.20, the rate was linear up to a ε_g of 0.7. The maximum rate was observed for the glycol phase holdup of 0.7 with respect to ethylene glycol layer, where the ratio of volume of organic layer to the glycol layer was 30:70. The results at glycol phase hold up less than 0.7 indicate kinetic regime. In kinetic regime, the rate per unit volume of the glycol phase is expected to remain constant with increase in glycol phase hold up. However, in the case where the reaction occurs essentially at liquid-liquid interface, it would depend on the liquid-liquid interfacial area, which is governed by both agitation speed and hold up of the dispersed phase. For higher glycol phase hold up the decreasing rate indicates mass transfer limitation. In order to understand this effect requires further studies, however for the kinetic modeling the data below glycol phase hold up of 0.7 were used, wherein kinetic regime prevails. Hence all the kinetic studies were conducted at ε_g=0.6.

Based on above observation the following conditions specified in Table 2.9 were chosen for the kinetics of Heck reaction

Table 2.9: Range of conditions studied for the kinetics of the Heck reaction in biphasic medium

Concentration of catalyst*, kmol/m^3	2.5×10^{-5} to 3.0×10^{-4}
Concentration of styrene*, kmol/m^3	3.6×10^{-2} to 3.3×10^{-1}
Concentration of iodobenzene*, kmol/m^3	3.3×10^{-2} to 3.0×10^{-1}
Concentration of base*, kmol/m^3	3.3×10^{-2} to 3.0×10^{-1}
Temperature, K	393-403 (120°C – 140°C)
Solvents	Organic phase: 75% n-octane + 25% p-xylene Aqueous phase: ethylene glycol
Reaction Volume, cm^3	Organic phase: 12 Glycol phase: 18
Glycol phase holdup	0.6
Agitation speed, RPM	1450
Time, minutes	90

* Concentration based on total volume (30 ml) of reaction mixture (Organic + Glycol)

2.3.3.2.4 Effect of catalyst concentration

The effect of catalyst concentration on the rate of Heck reaction in biphasic media was studied at a styrene concentration: 1.1 x 10^{-1} kmol m^{-3}, iodobenzene concentration: 1.0 x 10^{-1}, kmol m^{-3} and base concentration: 1.0 x 10^{-1} kmol m^{-3}, at a glycol phase holdup of 0.6 in a temperature range of 393-413 K. The results are shown in Figure 2.22.

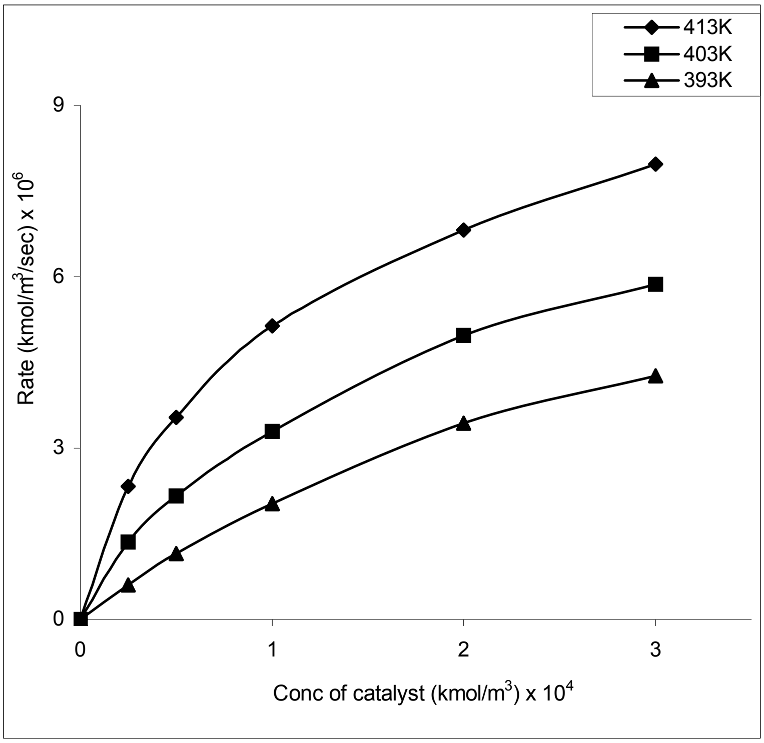


Figure 2.22: Effect of catalyst concentration on the rate of Heck reaction in biphasic medium

Reaction conditions: concentration of styrene: 1.1 x 10^{-1}, kmol m^{-3}, concentration of iodobenzene: 1.0 x 10^{-1}, kmol m^{-3}, concentration of base: 1.0 x 10^{-1}, kmol m^{-3}, Reaction volume: organic phase: 12ml; glycol phase: 18ml; glycol phase holdup: 0.6; Agitation speed 1450 RPM.

It was observed that with increase in the catalyst concentration the rate increased and showed a partial order dependence. The reported mechanism[42] for the Heck reaction in homogeneous media using Pd catalyst is shown in Figure 2.23. The observed trends with respect to catalyst is expected as enhancement in the catalyst concentration increases the concentration of active catalytic species and hence the rate. At higher catalyst loading the rate does not have a first order dependence on catalyst concentration. Similar trends have been reported with Pd catalyst and may be attributed to the formation of dimeric palladium species in equilibrium with the active catalytic species. This can result in a fractional order with respect to catalyst concentration.

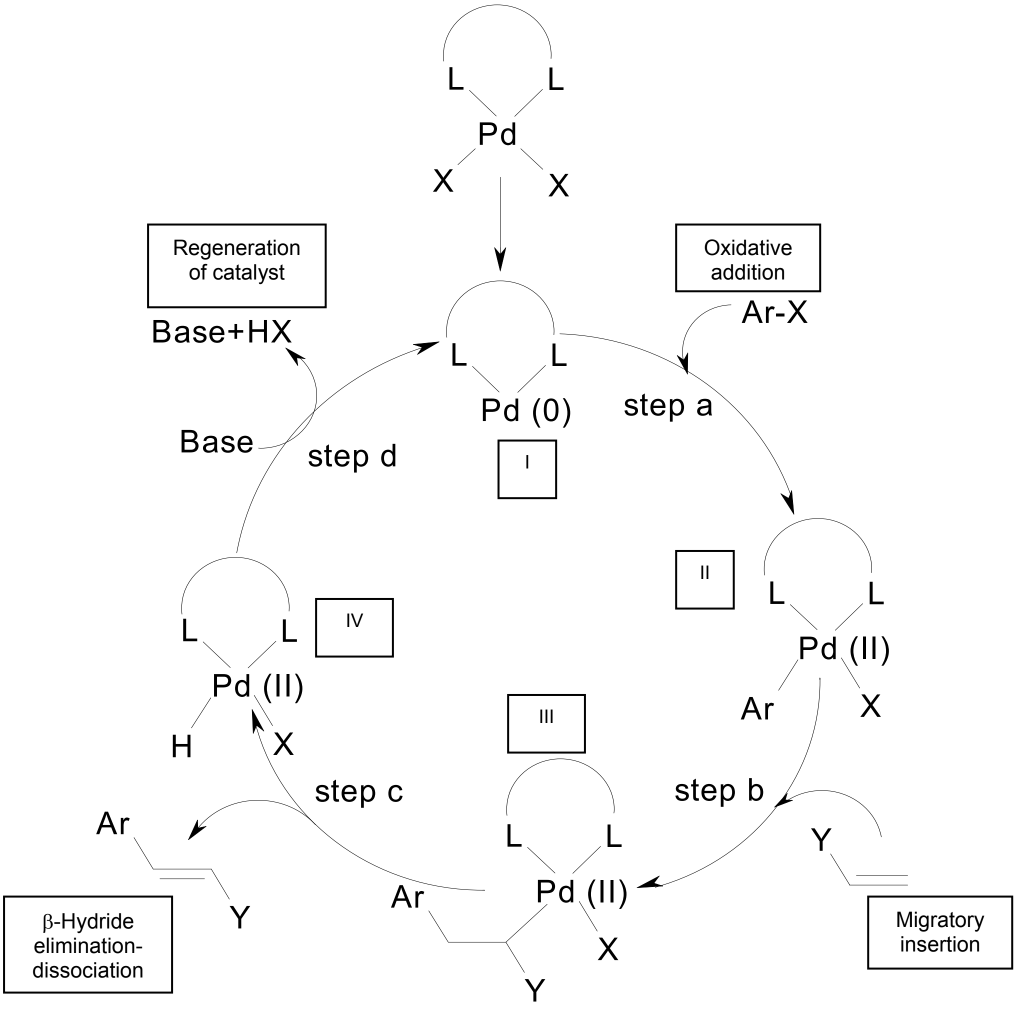


Figure 2.23: Mechanism of Heck reaction

2.3.3.2.5 Effect of iodobenzene concentration

The effect of iodobenzene concentration on the rate of Heck reaction in biphasic media was studied at catalyst concentration: 1.0 x 10^{-4} kmol m^{-3}, styrene concentration: 1.1 x 10^{-1}, kmol m^{-3} and base concentration: 1.0 x 10^{-1} kmol m^{-3}, at a glycol phase holdup of 0.6 in a temperature range of 393-413 K. The results are shown in Figure 2.24. The rate was found to have a first order dependence on the iodobenzene concentration. The oxidative addition of aryl halide (ArX) to the active Pd complex (Step a, Figure 2.23) is the rate-determining step in the Heck reaction and hence with increasing ArX concentration a higher rate was observed. However, at higher concentration of ArX, a partial order is observed. Such an observation is reported in earlier studies on the kinetics in homogeneous medium.

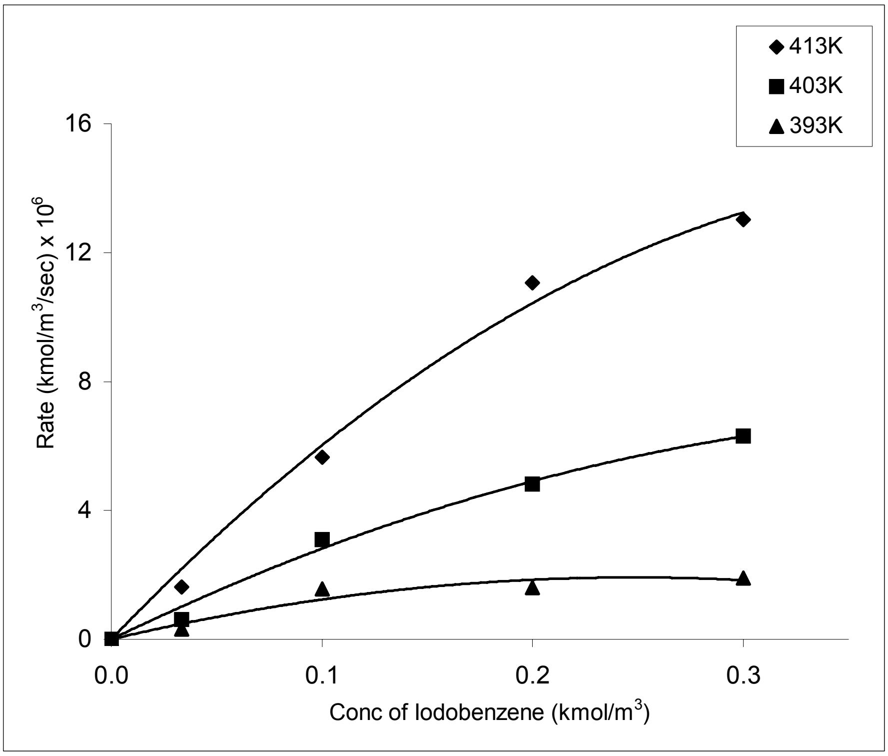


Figure 2.24: Effect of iodobenzene concentration on the rate of Heck reaction in biphasic medium

Reaction conditions: Concentration of catalyst: 1.0 x 10^{-4}, kmol m^{-3}, concentration of styrene: 1.1 x 10^{-1}, kmol m^{-3} concentration of base: 1.0 x 10^{-1}, kmol m^{-3}, Reaction volume: organic phase: 12ml; glycol phase: 18ml; glycol phase holdup: 0.6; Agitation speed 1450 RPM.

2.3.3.2.6 Effect of styrene concentration

The effect of styrene concentration on the rate of Heck reaction in biphasic media was studied at a catalyst concentration: 1.0 x 10^{-4} kmol m^{-3}, iodobenzene concentration: 1.0 x 10^{-1}, kmol m^{-3} and base concentration: 1.0 x 10^{-1} kmol m^{-3}, at a glycol phase holdup of 0.6 in a temperature range of 393-413 K. The results are shown in Figure 2.25. The rate was found to have a complex dependence on the olefin concentration and passed through a maximum, showing typical substrate inhibition kinetics. The first order increase with styrene in the initial stage of concentration is due to an increase in the formation of species III, Figure 2.23, leading to an increase in the rate. At higher concentration of styrene, the formation of the species of the type as $R-CH=CH(PdCl_2L)$[28] is possible, causing a decrease in the concentration of the active catalyst species and thereby the rate (Step b, Figure 2.23).

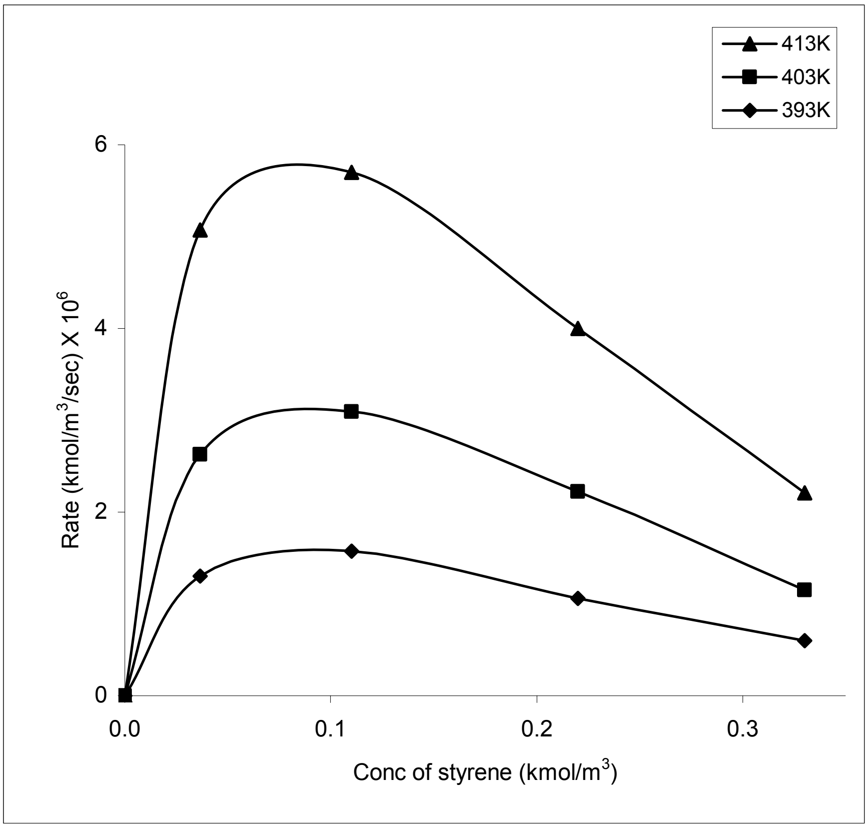


Figure 2.25: Effect of styrene concentration on the rate of Heck reaction in biphasic medium

Reaction conditions: concentration of catalyst: 1.0 x 10^{-4}, kmol m^{-3}, concentration of iodobenzene: 1.0 x 10^{-4}, kmol m^{-3}, concentration of base: 1.0 x 10^{-1}, kmol m^{-3}, Reaction volume: organic phase: 12ml; glycol phase: 18ml; glycol phase holdup: 0.6 Agitation speed 1450 RPM.

2.3.3.2.7 Effect of morpholine (base) concentration

The effect of base concentration on the rate of Heck reaction in biphasic media was studied at catalyst concentration: 1.0 x10^{-4} kmol m^{-3}, styrene concentration: 1.1 x 10^{-1} kmol m^{-3} and iodobenzene concentration: 1.0 x 10^{-1} kmol m^{-3}, at a glycol phase holdup of 0.6 in a temperature range of 393-413 K. The results are shown in Figure 2.26. It was observed that the rate increases with the base concentration with a first order dependence. One of the major roles of the base is the sequestration of the HI formed in the course of the reaction (step d, Figure 2.23). Hence the first order dependence on the base is expected. The base may also play an additional role as a cosolvent or as a ligand to stabilize catalytic species. The observed dependence is probably a cumulative effect of all these phenomena.

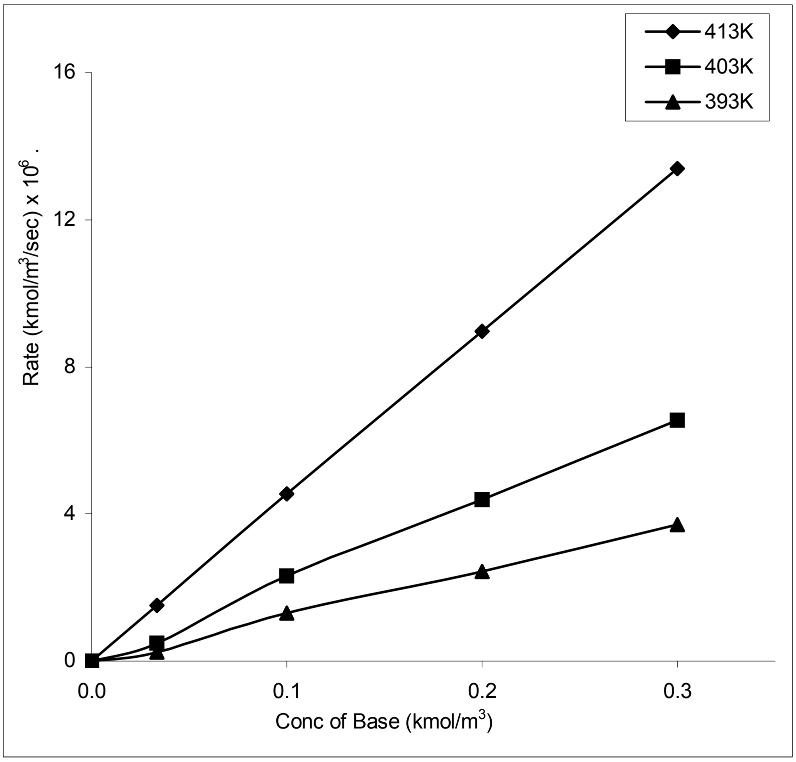


Figure 2.26: Effect of base concentration on the rate of Heck reaction in biphasic medium

Reaction conditions: concentration of catalyst: 1.0 x 10^{-4}, kmol m^{-3}; concentration of styrene: 1.1 x 10^{-1}, kmol m^{-3}; concentration of iodobenzene: 1.0 x 10^{-1}, kmol m^{-3}; Reaction volume: organic phase: 12ml; glycol phase: 18ml; glycol phase holdup: 0.6; Agitation speed 1450 RPM.

2.3.4 Kinetic models

The kinetic modeling of Heck reaction in biphasic media has not been studied extensively. Considering the complexities that have been observed, regarding the variation of rates with different parameters, it is even more important to develop suitable rate model to describe the intrinsic kinetics of the Heck reaction in two-phase media. The rate equations proposed till date (as given in Chapter 1) are all for the Heck reaction in homogeneous medium and may not be adequate to represent the results in a biphasic medium. Also, since the current study involves two immiscible solvents, a careful consideration, to ensure that the data is in kinetic regime, must be given. The results showing rate to be independent of agitation speed and from glycol phase holdup studies indicate that the data obtained are in the kinetic regime. The data was thus further taken up to develop empirical rate equations, based on the observed trends. On the basis of the observed trends, four different forms of rate equations as given in Table 2.10 were evaluated.

Table 2.10: Different empirical rate equations

Model Number	Rate equation
I	$R = \dfrac{k\,.\,A\,.\,B\,.\,C\,.\,D}{(1+K_A A)^2\,(1+K_B B)\,(1+K_C C)}$
II	$R = \dfrac{k\,.\,A\,.\,B\,.\,C\,.\,D}{(1+K_A A^2)\,(1+K_B B)\,(1+K_C C)}$
III	$R = \dfrac{k\,.\,A\,.\,B\,.\,C\,.\,D}{(1+K_A A)^2\,(1+K_B B)}$
IV	$R = \dfrac{k\,.\,A\,.\,B\,.\,C^{0.8}\,.\,D}{(1+K_A A)^2\,(1+K_B B)}$

[Where R: Rate of reaction (kmol/m^3.s); k: Intrinsic rate constant ((m^3)^3/$kmol^3$.s)
A: Concentration of olefin (kmol/m^3); K_A: Equilibrium constant of olefins (m^3/kmol)
B: Concentration of ArX (kmol/m^3); K_B: Equilibrium constant of ArX (m^3/kmol)
C: Concentration of catalyst (kmol/m^3); K_C: Equilibrium constant of catalyst (m^3/kmol)
D: Concentration of base (kmol/m^3)]

The rate parameters k, K_A, K_B and K_C were evaluated at 393, 403 and 413 K by fitting the observed experimental rate data to the different models using nonlinear regression analysis and an optimization routine based on Marquard's method[43]. The values of rate parameters at different temperatures are presented in Table 2.11. The best rate equation was chosen based on the values of Φ_{min}, which is defined as (Equation 2.7)

$$\Phi_{min} = \sum_{i=1}^{n} (R_{exp} - R_{pre})^2 \qquad [2.7]$$

Where R_{exp} is the rate observed experimentally, R_{pre} is the predicted rate using nonlinear regression analysis and n is number of data points.

Besides Φ_{min} the thermodynamic considerations regarding equilibrium constants K_A, K_B and K_C were also relied upon to choose the rate model, best representing the observed kinetic data.

Considering the thermodynamics of any reaction, the values of a kinetic constant should have a positive value (*k,* K_A, K_B or K_C > 0 and Ea > 0). The analysis of model-II and model-III gave negative values of equilibrium constant K_A and K_B respectively at the temperature 413K. Also the magnitude of Φ_{min} for both the models was higher than for other models, suggesting lack of fit of the model-II and model-III. So these were not considered. Comparison of the values of Φ_{min} obtained for model-I and IV shows that model-I fits the observed data with less error and was hence accepted.

$$R = \frac{k\,.\,A\,.\,B\,.\,C\,.\,D}{(1+K_AA)^2\,(1+K_BB)\,(1+K_CC)} \qquad \text{(Model I)}$$

This was found to be in excellent agreement with the predicted rates, as is seen from the plot of $R_{experimental}$ and $R_{predicted}$ (Figure 2.27) for all these temperatures. The model was found to predict the rate data within an error of ±5% (which is within the range of experimental error).

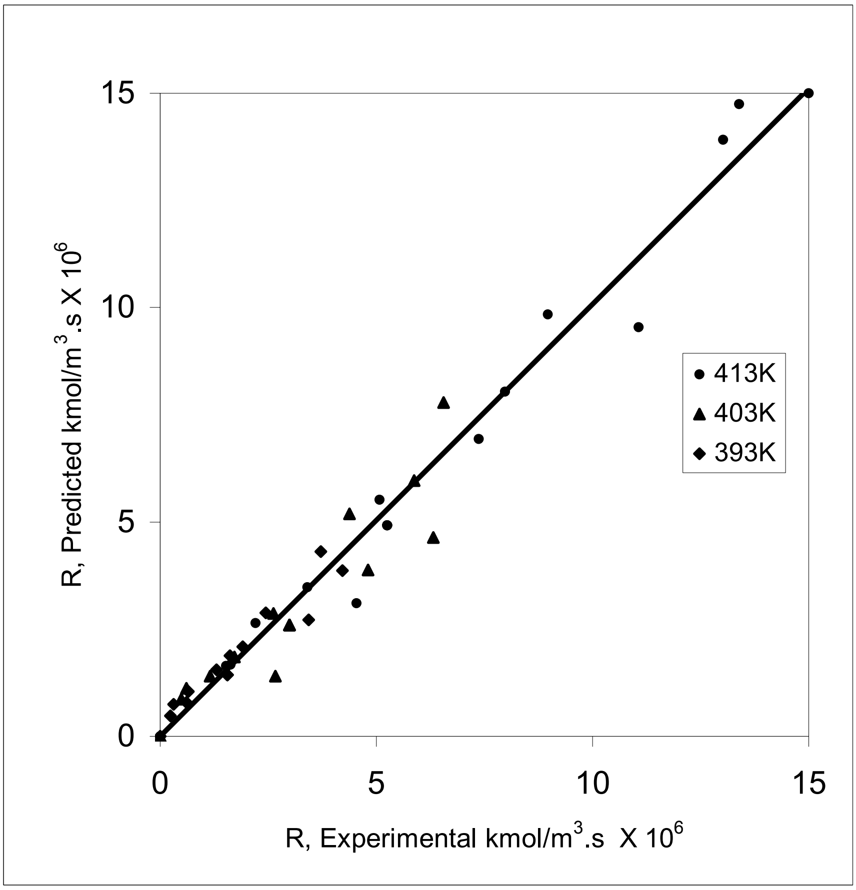


Figure 2.27: Plot of R (predicted) v/s R (experimental) 393K, 403K, 413K

Figure 2.28 - 2.31 show the comparison of experimental and predicted rates for the varying concentration of catalyst, iodobenzene, styrene and base respectively at temperatures of 120^0C-140^0C. The activation energy (E_A)was evaluated from the Arrhenius plot (Figure 2.32) and found to be 72.91 kJ/mol. The constants $K_{A,}$ K_B and K_D were found to be mild function of temperature as seen in Figure 2.33.

Table 2.11: Comparison of different rate models proposed for the Heck reaction in biphasic media.

Model No.	Rate Model	T (K)	k	K_A	K_B	K_C	ϕ_{min}	R^2
I	$R = \frac{k \, . \, A \, . \, B \, . \, C \, . \, D}{(1+K_A A)^2 (1+K_B B)(1+K_C C)}$	393	2.67E+02	1.81E+01	1.15E+01	6.22E+02	1.84E-12	0.9448
		403	4.03E+02	1.90E+01	5.15E+00	1.81E+03	8.64E-12	0.9152
		413	7.83E+02	1.95E+01	3.13E-01	7.17E+03	8.82E-12	0.9753
II	$R = \frac{k \, . \, A \, . \, B \, . \, C \, . \, D}{(1+K_A A^2)(1+K_B B)(1+K_C C)}$	393	1.06E+02	2.41E+02	1.18E+01	6.22E-01	1.17E-12	0.9471
		403	1.19E+02	2.73E+02	7.69E-01	1.58E+03	4.23E-12	0.9431
		413	2.55E+03	-9.49E+01	-4.35E+03	7.26E-01	2.06E-10	0.4405
III	$R = \frac{k \, . \, A \, . \, B \, . \, C \, . \, D}{(1+K_A A)^2 (1+K_B B)}$	393	2.34E+02	1.80E+01	1.15E+01	-	1.29E-12	0.9534
		403	2.20E+02	2.01E+01	3.26E-01	-	5.70E-12	0.9261
		413	4.32E+02	2.28E+01	-5.18E-01	-	3.95E-11	0.8689
IV	$R = \frac{k \, . \, A \, . \, B \, . \, C^{0.8} \, . \, D}{(1+K_A A)^2 (1+K_B B)}$	393	4.23E+01	1.73E+01	1.43E+01	-	2.62E-12	0.8653
		403	3.51E+01	1.88E+01	6.88E-01	-	3.92E-12	0.9454
		413	6.48E+01	1.97E+01	1.23E+00	-	1.91E-11	0.9312

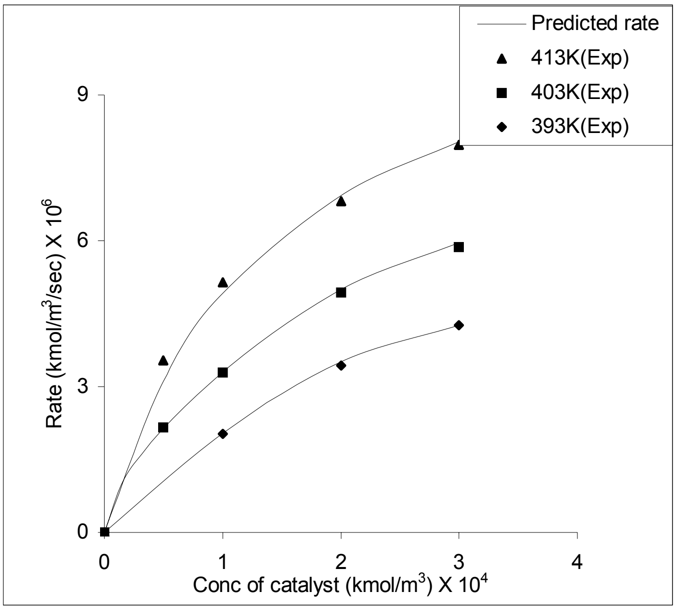


Figure 2.28: Comparison of experimental and predicted rates for effect of catalyst concentration at various temperatures

Reaction conditions: Concentration of styrene: 1.1 x 10^{-1}, kmol m^{-3}; concentration of iodobenzene: 1.0 x 10^{-1}, kmol m^{-3}; concentration of base: 1.0 x 10^{-1}, kmol m^{-3}; glycol phase holdup: 0.6; Agitation speed 1450 RPM.

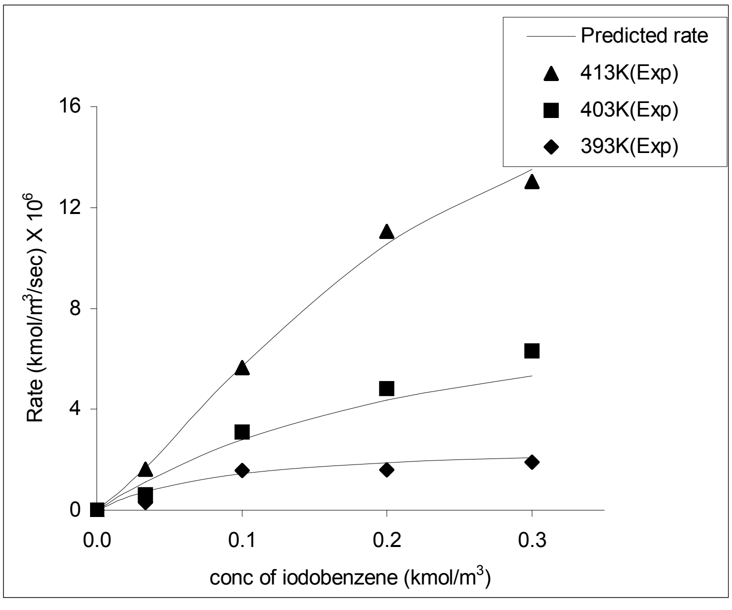


Figure 2.29: Comparison of experimental and predicted rates for effect of iodobenzene concentration at various temperatures

Reaction conditions: concentration of catalyst: 1.0 x 10^{-4}, kmol m^{-3}; concentration of styrene: 1.1 x 10^{-1}, kmol m^{-3}; concentration of base: 1.0 x 10^{-1}, kmol m^{-3}; glycol phase holdup: 0.6; Agitation speed 1450 RPM.

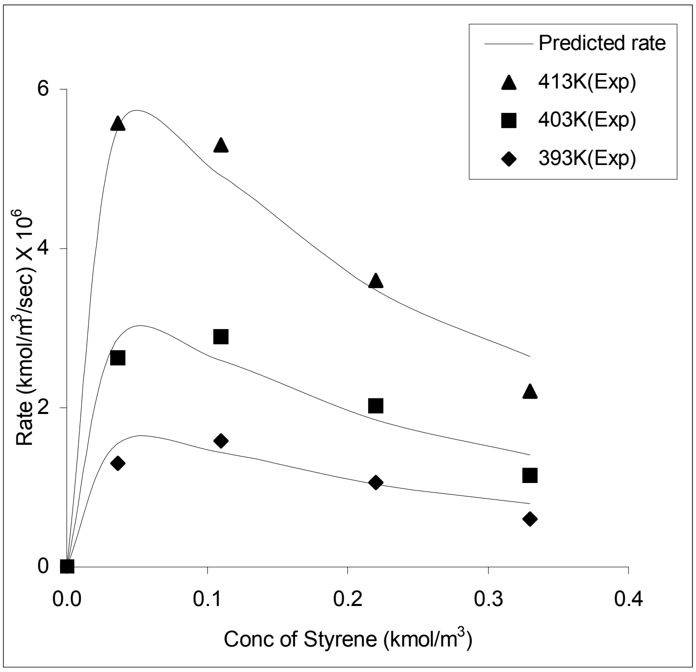


Figure 2.30: Comparison of experimental and predicted rates for effect of styrene concentration at various temperatures

Reaction conditions: concentration of catalyst: 1.0 x 10^{-4}, kmol m^{-3}; concentration of iodobenzene: 1.0 x 10^{-1}, kmol m^{-3}; concentration of base: 1.0 x 10^{-1}, kmol m^{-3}; glycol phase holdup: 0.6; Agitation speed 1450 RPM.

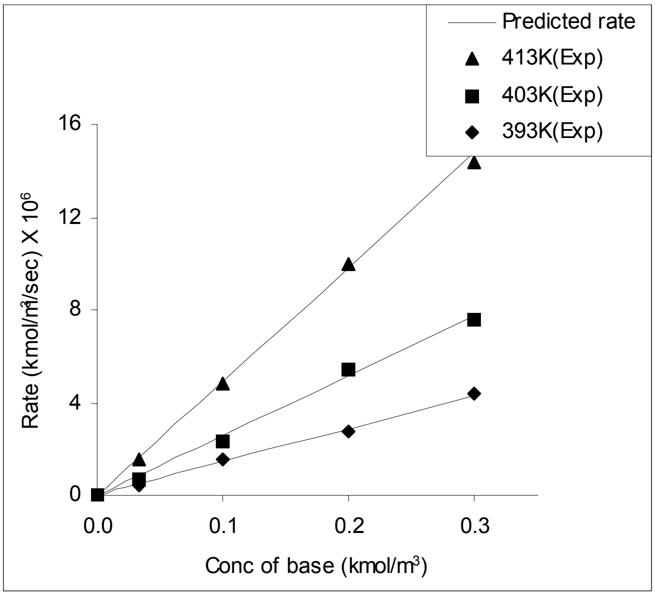


Figure 2.31: Comparison of experimental and predicted rates for effect of base concentration at various temperatures

Reaction conditions: concentration of catalyst: 1.0 x 10^{-4}, kmol m^{-3}; concentration of styrene: 1.1 x 10^{-1}, kmol m^{-3}; concentration of iodobenzene: 1.0 x 10^{-1}, kmol m^{-3}; glycol phase holdup: 0.6; Agitation speed 1450 RPM.

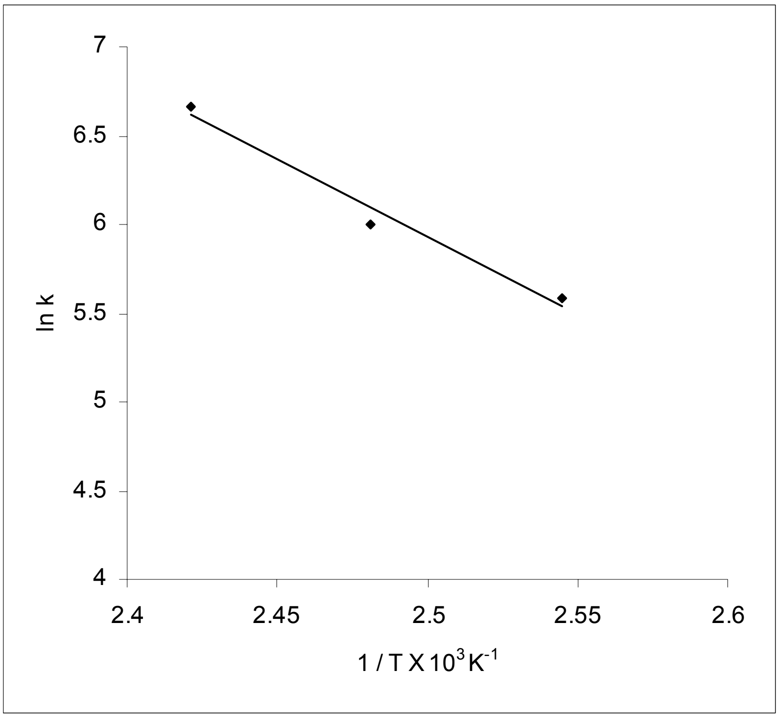


Figure 2.32: Plot of ln k v/s 1/T

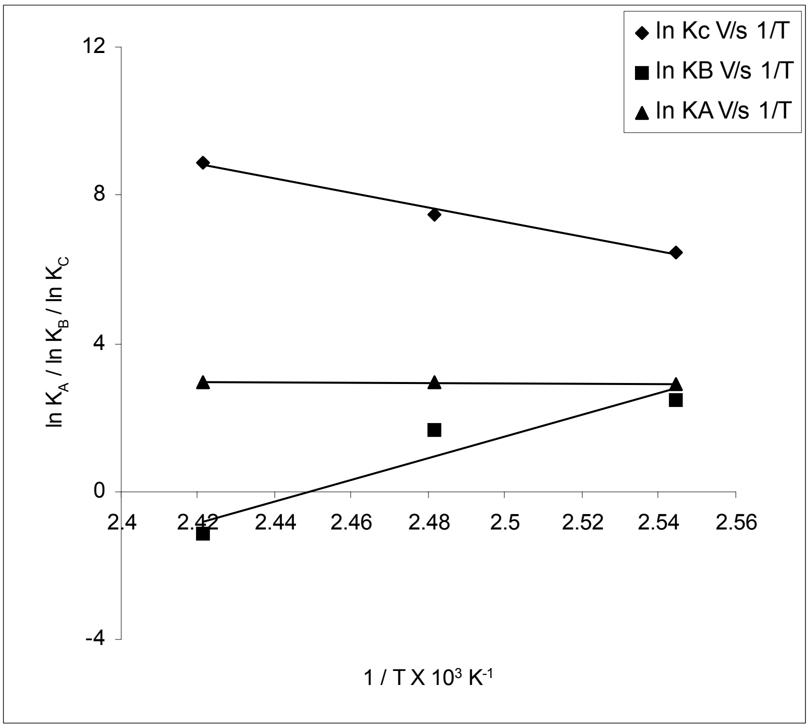


Figure 2.33: Plot of ln K_A, ln K_B, ln K_C v/s 1/T

2.3.5 Conclusions

The kinetics of the $PdCl_2$(bipy) catalyzed Heck reaction of styrene and iodobenzene in a glycol-organic (n-octane + p-xylene) medium has been investigated in a temperature range of 393 K to 413 K in the presence of morpholine as the base. The rate shows a complex dependence on the styrene concentration and passes through a maximum, showing typical substrate inhibition kinetics. The rate was found to have a first order dependence on the iodobenzene as well as catalyst concentration tending to a fractional order at higher concentrations. The rate had a first order dependence on the base concentration. All these observations have been explained on the basis of the known mechanism. Numerous semi empirical rate models were discriminated and a rate model shown below was found to represent the rate data in good agreement.

$$R = \frac{k \cdot A \cdot B \cdot C \cdot D}{(1+K_A A)^2 (1+K_B B)(1+K_C C)}$$

The parameters k, K_A, K_B and K_C were evaluated at all the temperatures. The activation energy was found to be 72.91 kJ/mol. This is the first time that kinetic modeling has been attempted for the Heck reaction in a biphasic medium.

Nomenclature

A : Concentration of olefin ($kmol/m^3$)

B : Concentration of ArX ($kmol/m^3$)

C : Concentration of catalyst ($kmol/m^3$)

D : Concentration of base ($kmol/m^3$)

E_A : Activation energy

k : Intrinsic rate constant ($(m^3)^3/kmol^3.s$)

K_A : Equilibrium constant of olefins ($m^3/kmol$)

K_B : Equilibrium constant of ArX ($m^3/kmol$)

K_C : Equilibrium constant of catalyst ($m^3/kmol$)

R : Rate of reaction ($kmol/m^3.s$);

R^2 : Value of Agreements of points in graph

R_{exp} : Experimentally observed rate

R_{pre} : Predicted rate

ε_g : glycol phase hold-up

References

(1) Negishi, E. Ed. Handbook of Organopalladium Chemistry for Organic Synthesis; John Wiley & Sons: New York, 2002.

(2) Zapf, A.; Beller, M. Chem. Commun. 2005, 431-440.

(3) Nicolaou, K. C.; Sorensen, E. J. Editors Classics in Total Synthesis 1996.

(4) de Vries, J. G. Can. J.Chem. 2001, 79, 1086-1092.

(5) Parshall, G. W. Homogeneous Catalysis; Wiley Interscience: New York, 1980.

(6) Bhanage, B. M.; Arai, M. Catalysis Reviews 2001, 43, 315-344.

(7) Kuntz, E. G. CHEMTECH 1987, 17, 570.

(8) Tokitoh, Y.; Yoshimura, N.; Higashi, T.; Hino, K.; Murasawa, M. EP 436 226, 1991 (Chem. Abstr. 115 (1991) 158508z).

(9) Mercier, G.; Chabardes, P. Pure Appl. Chem. 1994, 66, 1509.

(10) Chauvin, Y.; Einloft, S.; Olivier, H. Catalytic Ind. Eng. Chem. Res. 1995, 34, 1149-1155.

(11) Chauvin, Y.; Gilbert, B.; Guibard, I. J. Chem. Soc., Chem. Commun. 1990, 1715-1716.

(12) Bhanage, B. M.; Zhao, F. G.; Shirai, M.; Arai, M. Tetrahedron Letters. 1998, 39, 9509-9512.

(13) Bradley, D.; Williams, G.; Lombard, H.; Holzapfel, C. W. Synthetic Communications 2001, 31, 2077-2081.

(14) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. Journal of Organometallic Chemistry 1989, 371, 397-401.

(15) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. J. Org. Chem. 2004, 69, 7919-7927.

(16) Beller, M.; Krauter, J. G. E.; Zapf, A. Angew. Chem. Int. Ed. Engl. 1997, 36, 772-774.

(17) Thorpe, T.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. Tetrahedron Letters 2000, 41, 4503-4505.

(18) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. Synlett 1992, 11, 871-2.

(19) Tsai, F.-Y.; Wu, C.-L.; Mou, C.-Y.; Chao, M.-C.; Lin, H.-P.; Liu, S.-T. Tetrahedron Letters 2004, 45, 7503-7506.

(20) Lu, X.; Lin, S. J. Org. Chem. 2005, 70, 9651-9653.

(21) Ohff, M.; Ohff, A.; vanderBoom, M. E.; Milstein, D. J. Am. Chem.Soc 1997, 119, 11687-11688.

(22) Herrmann, W. A.; Ofele, K.; Preysing, D. v.; Schneider, S. K. Journal of Organometallic Chemistry 2003, 687, 229-248.

(23) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. Carbonylation: Direct Synthesis of Carbonyl Compounds; Plenum: New York, 1991.

(24) Escaffre, P.; Thores, A.; Kalck, P. J.Mol. Catal. 1985, 33, 70.

(25) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Ofele, K.; Beller, M. Chem. Eur. J. 1997, 3, 1357.

(26) Komiya, S. -ED. Synthesis of organometallic compounds- A practical Guide ., 1997.

(27) McCormick, B. J.; JaynesJr., E. N.; Kaplan, R. I. Inorg. Synth. 1972, 13, 216.

(28) Amatore, C.; Jutand, A. J.of organometallic chemistry 1999, 576, 254-278.

(29) Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J. Organic Letters 2003, Vol.5, 983-986.

(30) Benhaddou, R.; Czernecki, S.; Ville, G.; Zegar, A. Organometallics 1988, 7, 2435-9.

(31) Zhao, F.; Bhanage, B. M.; Shirai, M.; Arai, M. J. Mol. Catal. A: Chem. 1999, 142, 383-388

(32) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Beller, M.; Fischer, H. J. Mol. Catal. A 1995, 103, 133.

(33) VanStrijdonck, G. F. P.; Boele, M. D. K.; Kamer, P. C. J.; de Vries, J. G.; vanLeeuwen, P. W. N. M. Eur. J. Inorg. Chem. 1999, 1073.

(34) Zhao, F.-G.; Bhanage, B. M.; Shirai, M.; Arai, M. Stud. Surf. Sci. Catal. 1999, 122, 427- 430.

(35) Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. Journal of the American Chemical Society 2001, 123, 1848-1855.

(36) Rosner, T.; Pfaltz, A.; Blackmond, D. G. Journal of the American Chemical Society 2001, 123, 4621-4622

(37) Amatore, C.; Carre, E.; Jutand, A.; Medjour, Y. Organometallics 2002, 21, 4540-4545.

(38) Consorti, C. S.; Flores, F. R.; Dupont, J. Journal of the American Chemical Society 2005, 127, 12054-12065.

(39) Nilsson, P.; Wendt, O. F. Journal of Organometallic Chemistry 2005, 690, 4197-4202.

(40) Sud, A.; Deshpande, R. M.; Chaudhari, R. V. Journal of Molecular Catalysis A: Chemical 2007, 270, 144-152.

(41) Fujita, S.; Yoshida, T.; Bhanage, B. M.; Arai, M. Journal of Molecular Catalysis A: Chemical 2002, 188, 37-43.

(42) Cabri, W.; Candiani, I. Acc. Chem. Res. 1995, 28, 2-7.

(43) Marquardt, D. W. J. Soc. Ind. Appl. Math. 1963, 11, 431.

CHAPTER 3

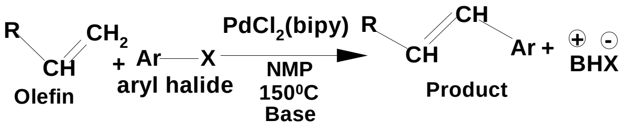
Studies of Heck Reaction Using $PdCl_2$(bipy) Catalyst in NMP Solvent

3.1 Introduction

The use of Pd – phosphine complexes for the Heck reaction has been studied in detail and reported in a majority of studies[1]. Of late, the trend for catalyst development has been towards the synthesis of thermally stable Pd complexes, which can then be used for catalytic reactions at elevated temperatures. The decomposition of phosphine modified Pd catalysts during the Heck reaction is well known, even for the thermally stable palladacycle catalysts[2]. Therefore, the development of stable phosphine-free catalysts tolerant to the reaction temperatures involved would be important. Pd complexes with Nitrogen containing ligands are also reported to be active for the Heck reaction[3,4], however their application to Heck reactions has been relatively less studied[5,6]. There are very few reports on the kinetics of Heck reaction in a homogeneous medium[7,8] in presence of a Pd complex catalyst with nitrogen ligand.

Besides the work presented in the earlier chapter, $PdCl_2$(bipy) was reportedly active when supported on MCM-41 and gave TON as high as 10^5 for the coupling of n-butyl acrylate with p-bromo acetophenone[9], the activity of this catalyst was relatively low for iodobenzene. Surprisingly, the same catalyst was reported to be inactive for Heck reaction[3].

This chapter presents experimental results on $PdCl_2$(bipy) catalyzed Heck reaction in NMP solvent. (Equation 3.1).



[3.1]

The major objective of this study was to compare the results on the screening and kinetic studies in biphasic media (Chapter 2) with those under homogeneous conditions using $PdCl_2$(bipy) catalyst . These studies would elucidate whether the activity observed in biphasic system was the intrinsic activity of the catalyst or whether other issues related to solubility of the substrate in glycol phase were the dominant factor.

The chapter is divided into two sections. Section 3.2 deals with the activity and selectivity studies using $PdCl_2$(bipy) catalyst for Heck reaction in NMP while Section 3.3 discusses the kinetic studies of Heck coupling of styrene and iodobenzene using $PdCl_2$(bipy) catalyst in NMP medium.

Section A

3.2 $PdCl_2$(bipy) catalyzed Heck reaction in homogeneous medium

- Activity, selectivity studies

3.2.1 Introduction

Since the $PdCl_2$(bipy) complex catalyst was active for the Heck coupling in biphasic media, it was of interest to investigate the performance of the catalyst in a polar homogeneous medium like NMP.

3.2.2 Experimental section

3.2.2.1 Materials

$PdCl_2$, 2,2'-bipyridine, the olefins and aryl halides used were procured form Aldrich USA and used without any further treatment. The solvents were obtained from SD Fine Chemicals, India. Bases and TBAB (Tetra butyl ammonium bromide) used were of analytical grade, purchased from Loba Chemicals, India.

The $PdCl_2$(bipy) complex was prepared and characterized as per the procedure given in Chapter 2 (Section 2.2.2.2.1).

3.2.2.2 General procedure for screening experiments of Heck reaction

In a 25ml two necked round bottom flask, 2.2 mmol of olefin, 2 mmol of aryl halide (ArX), 2.0 mmol of base, and 0.002 mmol of catalyst- $PdCl_2$(bipy) were added. TBAB (1% of base) was added as a phase transfer agent every time in case of inorganic bases. Then NMP solvent was added to make the volume to 10 ml. The reaction was carried out for 1 hour at $150^{o}C$ with magnetic stirring. At the end of reaction the reactor was cooled to room temperature and the contents were analyzed on GC for the product formed and substrate reacted. The standard conditions for GC analysis are given in Chapter 2 (Section 2.2.2.4). The identification of products was done using a GC-MS [Agilent 6890N series equipped with 5973N Mass Selective Detector]. From the quantitative analysis, the conversion of the aryl halide, selectivity, TON (Turn Over Number) and turnover frequency (TOF) were calculated by using the formulae given in Chapter 2 (Section 2.2.2.3).

3.2.3. Results and discussion

3.2.3.1 Preliminary reactions and solvent screening studies

The solvents are known to play a very important role in the activity and selectivity of homogeneous catalysts. Hence it was essential to find a suitable solvent for monitoring the activity of $PdCl_2$(bipy) catalyst for Heck coupling reactions. For this purpose a number of solvents were screened for their activity in the coupling of styrene and iodobenzene in the presence of $PdCl_2$(bipy) catalyst with KOAc base and TBAB promoter (1% of KOAc) at a temperature of 150°C. The results are shown in Table 3.1.

Table 3.1: Solvent effect on activity using $PdCl_2$(bipy) catalyst in homogeneous medium

Sr. No.	Solvent	%Conversion iodobenzene	B.P. °C	t-stilbene : c-stilbene
1	NMP	59	202	90:10
2	DMF	46	153	91:09
3	DMSO	36	189	92:08
4	1-Butanol	32	118	87:13
5	Toluene	5	111	100:00
6	n-Octane	3	127	100:00
7	CH_3CN	1	82	100:00
8	MEK	0	80	-

Reaction conditions: styrene (2.2 mmol); iodobenzene (2.0 mmol) taken in solvent (10ml); catalyst (0.002 mmol); base (KOAc-2.0 mmol); TBAB (0.02 mmol) Temperature 150°C; (Time: 1hr); Selectivity of stilbene: 96-100%.

The highest activity was observed in NMP solvent with a TON of 482 in one hour. The reaction was also facilitated in polar solvents like DMF and DMSO where TON's of 369 and 290 were obtained respectively. Other solvents were screened for their activity towards Heck reaction at temperatures equal to their boiling points. Very poor rates were observed in solvents like toluene, n-octane. Surprisingly almost no reaction was observed in MEK or acetonitrile, even though they are relatively polar. This poor activity would be due to the low boiling point of the solvents. It is well known that certain Pd complexes require minimum temperatures for reaction to proceed[10-14]. Since NMP was found to be the best solvent for the reaction, all further studies were conducted in NMP solvent.

3.2.3.2 Screening of base

A detailed screening of bases was conducted using the $PdCl_2$(bipy) catalyst in NMP solvent for the vinylation of iodobenzene with styrene. A variety of organic and inorganic bases (including aliphatic organic bases and monovalent / divalent inorganic bases) were screened for their activity in the given system. Tetra butyl ammonium bromide was added as phase transfer agent (1% of base) in case of inorganic bases. The results are shown in the Table 3.2.

Table 3.2: Base effect on activity using $PdCl_2$(bipy) catalyst in homogeneous medium

Sr. No.	Base	% Conversion of iodobenzene	t-stilbene : c-stilbene
1	TBA+TBAB	68	87:13
2	Et_3N	66	87:13
3	KOAc	59	88:12
4	TBA	56	84:16
5	NaOAc	33	88:12
6	Piperidine	27	90:10
7	$NaHCO_3$	23	89:11
8	Morpholine	20	86:14
9	MgOAc	13	88:12

Reaction conditions: styrene (2.2 mmol) + iodobenzene (2.0 mmol) taken in NMP (10 ml) + catalyst (0.002 mmol) and base; (2.0 mmol) along with TBAB* (0.02 mmol) (*If inorganic bases used); Temperature 150°C; (Time: 1hr); Selectivity of stilbene: 96-100%.

Organic bases were found to give better activity, which is probably influenced by their solubility in the organic solvent. Inorganic bases on the other hand gave relatively lower activity, which increased in the presence of a phase transfer agent like tetra butyl ammonium bromide (TBAB)[15]. Aliphatic bases like Et_3N (tri ethylamine) and TBA (tri butylamine) were found to be more active than piperidine and morpholine. Et_3N and TBA (tertiary amines) have a higher basic character than piperidine and morpholine (secondary amine) and hence show better activity for the Heck coupling. Between Et_3N and TBA, the former is more active probably because it is sterically less hindered compared to TBA. The TON's observed for the different bases are shown in Figure 3.1.

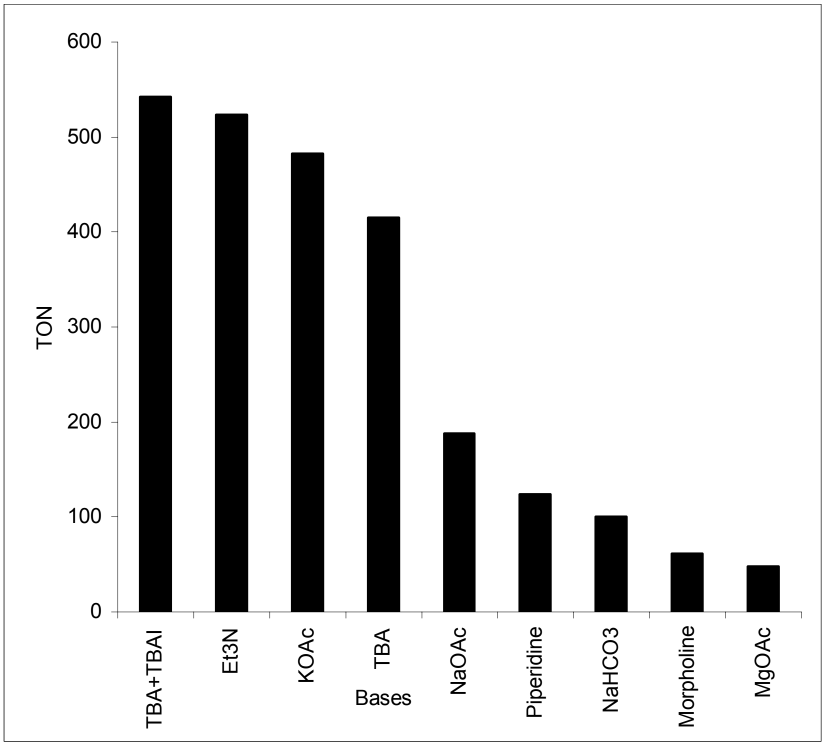


Figure 3.1: TON observed for Heck reaction of iodobenzene and styrene with $PdCl_2$(bipy) catalyst using different bases in homogeneous medium

Reaction conditions: styrene (2.2 mmol) + iodobenzene (2.0 mmol) taken in NMP (10 ml) + catalyst (0.002 mmol) and base; (2.0 mmol) along with TBAB* (0.02 mmol) (*If inorganic bases used); Temperature 150°C; (Time: 1hr); Selectivity of stilbene: 96-100%.

Potassium acetate was found to have better activity compared to other inorganic bases. The role of TBAB does not seem to be restricted to that of a phase transfer catalyst[15], as addition of a quaternary ammonium salt enhances the activity even for organic bases, which are miscible with the reaction solvents (Entry 1 in Table 3.2). The regioselectivity of the product for all the bases – organic and inorganic and regardless of their strength and size - was found to be more or less the same for the iodobenzene and styrene system unlike that reported by Beller and Riermeier[16]. In their study it was observed that, the amine changes the regioselectivity of cyclometallated palladium complexes - catalyzed coupling reaction of aryl bromides with butyl methacrylate at 135-140°C, via coordination to palladium during the catalytic cycle. For styrene and iodobenzene system ~86-90% trans-stilbene was formed with the rest being cis-stilbene

3.2.3.3 Screening of aryl halides

The activity of $PdCl_2$(bipy) was assessed for the coupling of styrene with different aryl halides. The results are presented in Table 3.3. In all the cases the products were analyzed on GC and identification of the product was done by using GC-MS (GC-MS data of the products are presented in Appendix –I).

It was seen that the halides with strong electron withdrawing substituents showed a high activity, whereas those with electron donating substituents showed poor activity. This observation is as per the general trends observed for the activities for Pd complex catalyzed Heck reactions[17]. Only the iodo substituent underwent reaction to produce 4-bromostilbene for the Heck coupling of 4-bromo iodobenzene. Since iodoarenes are reportedly more active than the bromo derivatives, this behavior is expected. Also, no further reaction of the 4-bromo stilbene was observed within the reaction period. This was confirmed by GC-MS, wherein no double Heck reaction product was observed. TON's observed for the different aryl halides are shown in Figure 3.2.

Table 3.3: ArX effect on activity using $PdCl_2$(bipy) catalyst in homogeneous medium

Sr. No.	ArX	% Conversion of Aryl halide	t-stilbene : c-stilbene
1	4-Bromoacetophenone	89	95:5
2	4-Bromo-1- iodobenzene	70	88:12
3	Iodobenzene	59	88:12
4	4-Iodoanisole	58	86:14
5	4-Bromotoluene	54	92:8
6	2-Bromotoluene	45	80:20

Reaction conditions: Styrene (2.2 mmol) + ArX (2.0 mmol) taken in NMP (10 ml) + catalyst (0.002 mmol) and KOAc (2.0 mmol) +TBAB (0.02 mmol); Temperature 150°C; (Time: 1hr); Selectivity of stilbene: 96-100%.

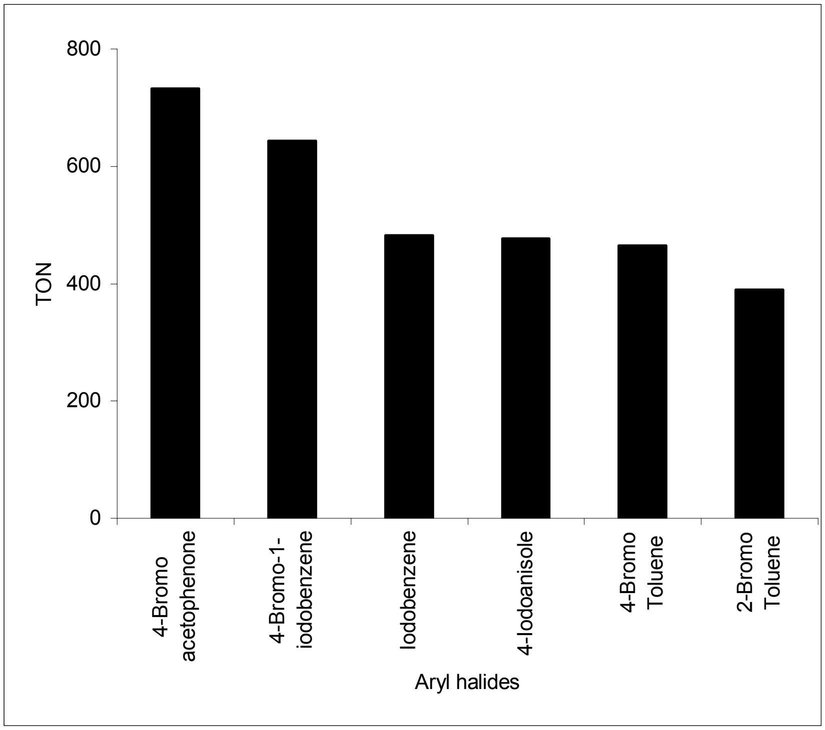


Figure 3.2: TON observed for Heck reaction of various aryl halides with styrene using $PdCl_2$(bipy) catalyst and KOAc as a bases (with TBAB) in homogeneous medium Reaction conditions: styrene (2.2 mmol) + ArX (2.0 mmol) taken in NMP (10 ml) + catalyst (0.002 mmol) and KOAc (2.0 mmol) +TBAB (0.02 mmol); Temperature 150°C; (Time: 1hr); Selectivity of stilbene: 96-100%.

3.2.3.4 Screening of olefins

The results presented in Table 3.4 show the activity of $PdCl_2$(bipy) catalyst for the vinylation of iodobenzene with different olefins. The identification of the product has been done by using GC-MS (GC-MS data of the products are presented in Appendix –I). The TONs observed for the different olefins are shown in Figure 3.3.

It was seen that the olefins with strong electron withdrawing substituents gave poor activity whereas those with electron donating or enriching substituents were more active. This trend is opposite to that observed for the aryl halides. In the reported Heck reaction mechanism, addition of the olefin to the Pd(0) species occurs, to form a π- complex. Electron rich olefins are expected to react faster than those with electron withdrawing substituents for this step, thereby enhancing rates. It can also be seen from Table 3.4 (entry 1, 2, 3) that the regioselectivity of the aliphatic olefins shows 100% trans product, whereas the styrene derivatives show, some cis product formation (~ 8-12%).

Table 3.4: Olefin effect on activity using $PdCl_2$(bipy) catalyst in homogeneous medium

Sr.No.	Olefin	% Conversion of iodobenzene	t-stilbene : c-stilbene
1	Methyl Acrylate	100	100:00
2	Allyl Alcohol	92	100:00
3	n-Butyl Acrylate	84	100:00
4	4-Vinyl Anisole	75	87:13
5	4-Methyl styrene	72	88:12
6	Styrene	59	88:12
7	4-Chloro styrene	48	92:08
8	3-Nitro styrene	40	87:13

Reaction conditions: Olefin(2.2 mmol)+ iodobenzene (2.0 mmol) taken in NMP(10 ml)+ catalyst(0.002 mmol) and KOAc(2.0 mmol)+TBAB(0.02 mmol) ; Temperature 150°C ; (Time:1hr); Selectivity of stilbene: 96-100%.

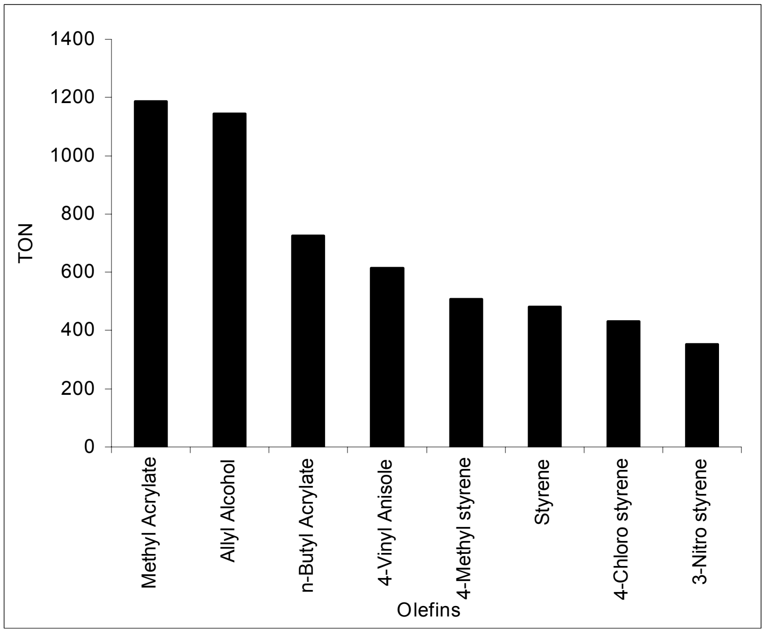


Figure 3.3: TON observed for Heck reaction of different olefin with iodobenzene using $PdCl_2$(bipy) catalyst and KOAc as a bases (with TBAB) in homogeneous medium

Reaction conditions: Olefin(2.2 mmol)+ iodobenzene (2.0 mmol) taken in NMP(10 ml)+ catalyst(0.002 mmol) and KOAc (2.0 mmol)+TBAB (0.02 mmol) ; Temperature 150°C ; (Time:1hr); Selectivity of stilbene: 96-100%.

The results obtained in the screening studies show that, the presence of electron-withdrawing group attached to the aryl halide and an electron donating substituent on an olefin result in higher activity. This is well explained by the mechanism.

3.2.4 Conclusions

$PdCl_2$(bipy) catalyst is found to be an active and stable catalyst for the Heck reaction. This catalyst is stable in polar solvents and does not decompose to metal even at a temperature of 150°C. Detailed investigations on the activity of $PdCl_2$(bipy) catalyst for Heck reaction in homogeneous medium have been conducted. The solvents, olefins, aryl halides and bases have been screened for their activity towards Heck reaction in the homogeneous system. The results show that electron-withdrawing groups attached to the aryl halide and electron donating substituents on olefin enhance the rates. Organic bases were found to be efficient for the reaction whereas inorganic bases showed poor activity due to solubility limitations.

The major difference in the reaction in homogeneous and the biphasic reaction medium was that, the activity of the catalyst for various aryl halides and the olefins in the biphasic medium was not exactly according to Hammett correlation, as observed in homogeneous reactions. This may be due to the solubility limitation of substrates in the glycol phase, containing the catalyst in case of biphasic catalysis.

Section B

3.3 Kinetic studies of Heck reaction using $PdCl_2$(bipy) catalyst in homogeneous medium

3.3.1 Introduction

The kinetics of Heck reaction using Pd complexes has been reported in a few studies[18-23]. In general it has been reported that the activity has a positive dependence on olefin, aryl halide and the base concentration. Although most of the studies have been conducted with $PdCl_2$ or Pd-phosphine complexes, only a few studies on the kinetics exist for the phosphine-free complexes. For the Pd(dba) [dba =dibenzylideneacetone] catalyzed Heck coupling of styrene and iodobenzene, Van Strijdonck et.al.[24] have reported first order kinetics in styrene and zero order in iodobenzene concentration. An empirical rate equation was derived to fit the experimental data. Rosner et.al.[7] have investigated the kinetics of olefination of p-bromobenzaldehyde with butyl acrylate using a dimeric C-N palladacycle complex under dry conditions. They reported a first-order dependence on olefin concentration and a zero order dependence on the aryl halide (p-bromobenz aldehyde) concentration. They also proposed an empirical rate model to predict the rate data observed for the dimeric palladacycles complex with chelating nitrogen ligands[21]. Consorti and coworkers[8] have reported a first order dependence with respect to Pd catalyst and a fractional order with respect to iodobenzene and methyl acrylate for the coupling of aryl halides with butyl acrylate and methyl acrylate using the CN-palladacycle. All these studies are primarily in homogeneous systems. In the previous chapter, for a biphasic medium, the rate was found to have a first order dependence on the iodobenzene as well as catalyst concentration tending to a fractional order at higher concentrations, a first order dependence on the base concentration and a complex dependence on the styrene concentration, which passes through a maximum, showing typical substrate inhibition kinetics, for $PdCl_2$(bipy) catalyzed coupling of styrene with iodobenzene. Since the dependence of the activity on reaction parameters is different from the homogeneous reaction, the kinetics of the coupling of styrene with iodobenzene using $PdCl_2$(bipy) catalyst was investigated in homogeneous medium using NMP as the solvent.

This section deals with study on the effects of concentrations of styrene, iodobenzene, and KOAc in presence of TBAB on the activity of the Heck reaction in N-Methyl-2-Pyrrolidinone (NMP) solvent using $PdCl_2$(bipy) catalyst over a temperature range of 393-413 K. The results obtained were explained on the basis of the well-accepted mechanism of Heck reaction. An empirical rate model has been proposed to fit the observed data, and is found to be in good agreement. The results were also compared with the kinetics of the Heck reaction in biphasic medium (chapter 2, section 2.3)

3.3.2 Experimental section

3.3.2.1 Materials

$PdCl_2$, 2,2'-bipyridine, the olefins and aryl halides used were procured form Aldrich USA and used without any further treatment. The solvents were obtained from SD Fine Chemicals, India. Bases and TBAB (Tetra butyl ammonium bromide) used were of Analytical grade, purchased from Loba Chemicals, India. The $PdCl_2$(bipy) complex was prepared and characterized as per the procedure given in Chapter 2 (Section 2.2.2.2.1).

3.3.2.2 General procedure for kinetic studies

In a 25ml two necked round bottom flask styrene, iodobenzene, potassium acetate, TBAB (1% of base), and catalyst- $PdCl_2$(bipy) were added as per the requisite concentration. N-methyl-2-pyrrolidinone was then added to make volume to 10 ml. The reaction was carried out for 2 hrs at desired temperature (120^oC-140^oC / 393K-413K) with magnetic stirring. The progress of the reaction was monitored by intermediate sampling of the liquid contents in the round bottom flask using GC. The standard conditions for GC analysis are given in Chapter 2 (Section 2.2.2.4).

The kinetic experiments were carried out for a short duration, such that the conversion of liquid phase reactant was less than 20-25% to ensure differential conditions. It was generally observed that in this low conversion range, the rates of Heck reaction were constant. The experiments were found to be reproducible within an error of 2-4%. In each reaction, initial, intermediate and final samples were analyzed, for reactants and products in order to check the material balance. Following this procedure, the effect of catalyst, styrene, iodobenzene and KOAc concentration on the rate of Heck reaction was studied at a temperature of 393, 403 and 413 K.

3.3.3 Results and discussion

3.3.3.1 Preliminary results

There are no studies on the homogeneous Heck reaction using $PdCl_2$(bipy) catalyst and hence it was of interest to investigate the kinetics of Heck reaction using this catalyst. Preliminary experiments were conducted to assess the material balance of the reaction. A typical C-T profile of the Heck coupling of styrene and iodobenzene is shown in Figure

3.4. It was observed that the consumption of the styrene and iodobenzene was commensurate with the amount of stilbene formed. Thus, the rate of consumption of styrene and iodobenzene could be represented by the formation of stilbene.

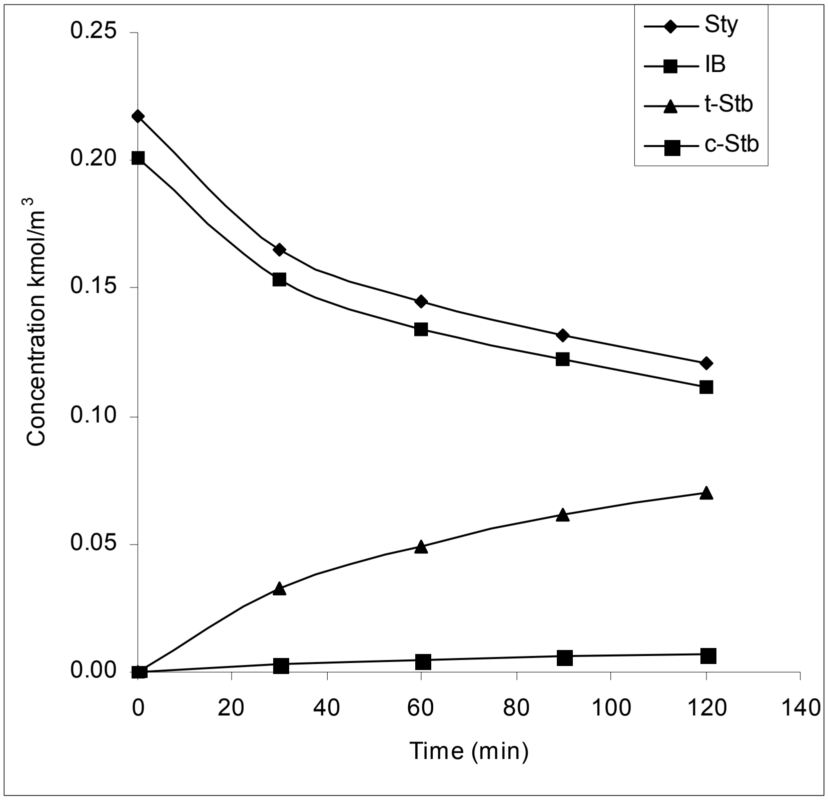


Figure 3.4: Typical concentration profile of Heck reaction in homogeneous medium

Reaction conditions: concentration of styrene: 2.2x10^{-1} kmol/m^3, concentration of iodobenzene: 2.0x10^{-1} kmol/m^3, concentration of base (KOAc): 2.0x10^{-1} kmol/m^3, TBAB: (1%of base), concentration of catalyst [$PdCl_2$(bipy)]: 2.0x10^{-4} kmol/m^3. NMP: 10ml. Temperature 413K.

For the purpose of kinetic study, several experiments were carried out at different concentrations of styrene, iodobenzene, base and catalyst, in the temperature range of 120°C-140°C (393K -413K). In each case the amount of stilbene formed, as a function of time was observed. It was observed that, in the initial period of reaction, the rate of reaction was essentially constant. From these data the rates of Heck reaction were calculated as follows (Equation 3.2)

Rate of Heck reaction,

$$R = \frac{\text{Slope of plot of concentration of stilbene formed}}{(\text{kmol/ m}^3 \text{ total volume) v/s Time (s)}} \qquad [3.2]$$

These were essentially initial rates of reaction, observed under differential conditions as shown in Figure 3.5 for various concentrations of aryl halides at 393K

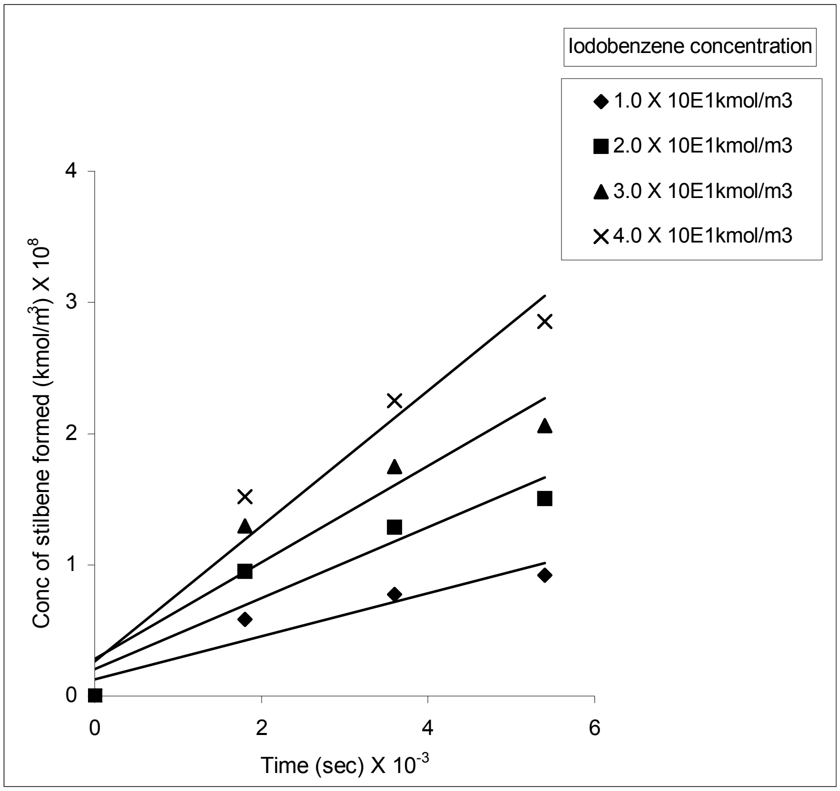


Figure 3.5: Typical concentration of stilbene formed v/s time plot for calculation of rate Reaction conditions: concentration of styrene: 2.2x10^{-1} kmol/m^3, concentration of catalyst: 2.0x10^{-4} kmol/m^3, concentration of KOAc: 2.0x10^{-1} kmol/m^3, TBAB: (1%of base), NMP: 10ml. Temperature 393K

Based on observations of preliminary experiments, the kinetics of Heck reaction was investigated under the range of conditions given in Table 3.5.

Table 3.5: Range of conditions studied for the kinetics of the Heck reaction in NMP medium

Concentration of catalyst, kmol/m^3	1.0 X 10^{-4} to 5.0 X 10^{-4}
Concentration of styrene, kmol/m^3	1.1 X 10^{-1} to 4.4 X 10^{-1}
Concentration of iodobenzene, kmol/m^3	1.0 X 10^{-1} to 4.0 X 10^{-1}
Concentration of base, kmol/m^3	1.0 X 10^{-1} to 4.0 X 10^{-1}
Concentration of tetra butyl ammonium bromide, kmol/m^3	1.0 X 10^{-3} to 4.0 X 10^{-3} (1% of base)
Temperature, K	393-413(120^{o}C–140^{o}C)
Solvent	NMP
Reaction volume, cm^3	10
Time, minutes	120

3.3.3.2 Kinetic study

3.3.3.2.1 Effect of catalyst concentration

The effect of catalyst concentration on the rate of Heck reaction was investigated at an iodobenzene concentration of $2.0\text{x}10^{-1}$ kmol/m^3, styrene concentration of $2.2\text{x}10^{-1}$ kmol/m^3 and KOAc concentration of $2.0\text{x}10^{-1}$kmol/m^3 (with TBAB 1% of KOAc) at temperatures of 393K-413K in NMP. The results are presented in Figure 3.6

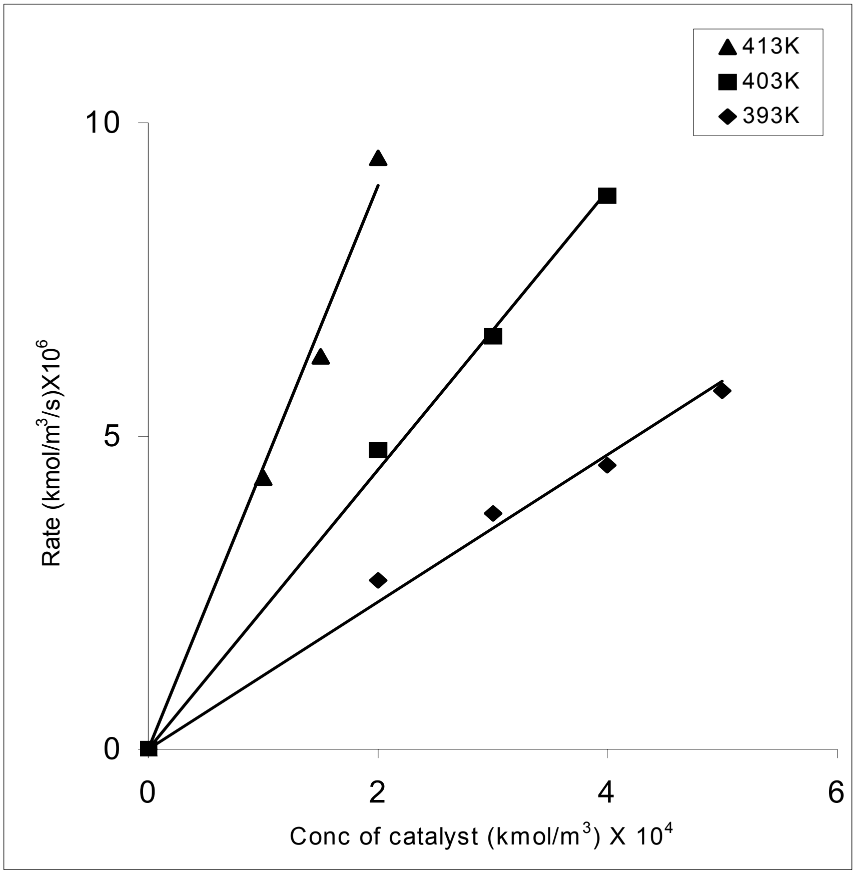


Figure 3.6: Effect of catalyst concentration on the rate of Heck reaction in homogeneous medium

Reaction conditions: concentration of styrene: $2.2\text{x}10^{-1}$ kmol/m^3, concentration of iodobenzene: $2.0\text{x}10^{-1}$ kmol/m^3, concentration of base (KOAc): $2.0\text{x}10^{-1}$ kmol/m^3, TBAB: (1%of base), NMP: 10ml.

The rate was found to have a first order dependence on catalyst concentration. The well-accepted mechanism[25] of Heck reaction has been shown in Figure 3.7. With enhancement of catalyst concentration there is a commensurate increase in the active species. In a large number of Pd catalyzed Heck reactions, a first order tending to a zero order is reported, which is attributed to the formation of inactive dimeric species. It seems that the formation of such dimers does not happen with $PdCl_2$(bipy) catalyst in the range of conditions investigated.

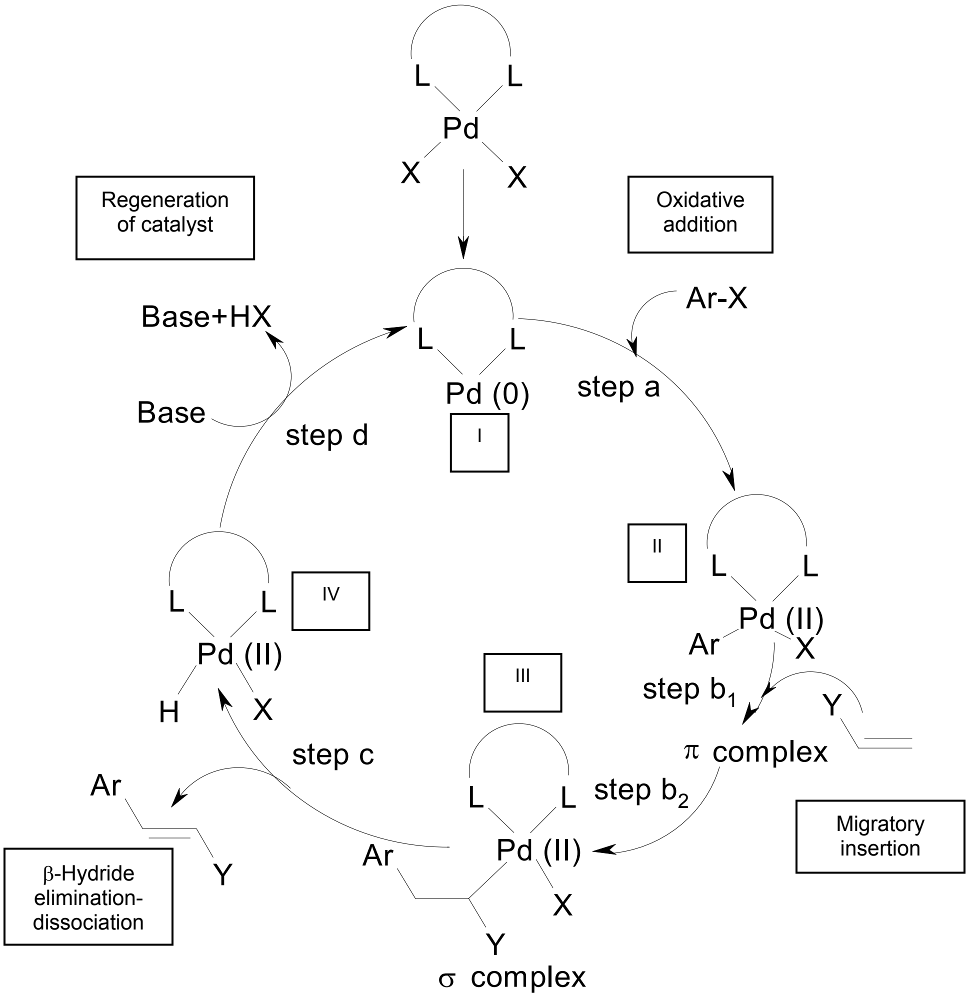


Figure 3.7: Mechanism of Heck reaction

3.3.3.2.2 Effect of iodobenzene concentration

The effect of iodobenzene concentration on activity was investigated at a styrene concentration, of $2.2x10^{-1}$ kmol/m^3, KOAc concentration of $2.0x10^{-1}$ kmol/m^3 (with TBAB 1% of KOAc) and a catalyst concentration of $2.0x10^{-4}$ kmol/m^3 at temperatures of 393K-413K in NMP. The results are presented in Figure 3.8. The rate was found to increase with a first order with respect to iodobenzene concentration at 393K. At higher temperature, a fractional order was observed with iodobenzene concentration. A positive order with respect to iodobenzene is expected from the mechanism as shown in Figure 3.7, step a. An increase in the iodobenzene concentration will enhance the addition of iodobenzene to catalyst species, and hence increase the rate. This step is also reported as the rate-determining step in Heck chemistry.

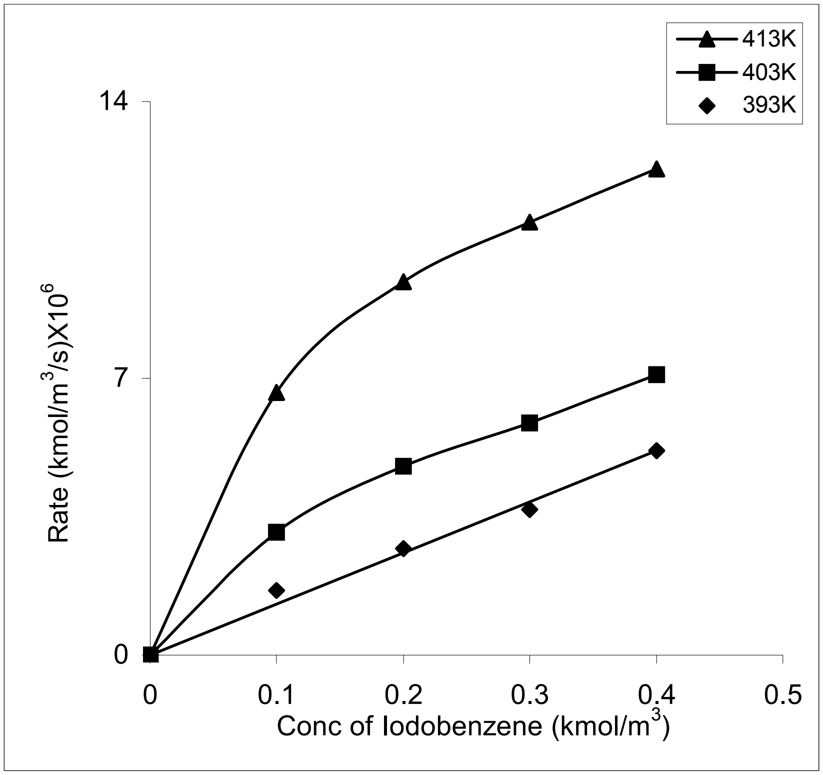


Figure 3.8: Effect of iodobenzene concentration on the rate of Heck reaction in homogeneous medium

Reaction conditions: concentration of styrene: 2.2x10^{-1} kmol/m^3, concentration of base (KOAc): 2.0x10^{-1} kmol/m^3, TBAB: (1%of base), concentration of catalyst [PdCl$_2$(bipy)]: 2.0x10^{-4} kmol/m^3. NMP: 10ml.

3.3.3.2.3 Effect of styrene concentration

The effect of styrene concentration on the activity of PdCl$_2$(bipy) catalyzed coupling reaction was investigated at an iodobenzene concentration of 2.0x10^{-1} kmol/m^3, KOAc concentration of 2.0x10^{-1} kmol/m^3 (with TBAB 1% of KOAc) and a catalyst concentration of 2.0×10^{-4} kmol/m^3 at temperatures of 393K-413K in NMP. The results presented in Figure 3.9 show a fractional order dependence on styrene concentration at all the temperatures studied. Addition of olefin to catalyst complex leads to formation of π-complex (step b_1 in mechanism- Figure 3.7) in an equilibrium reaction followed by σ-complex formation (step b_2 in mechanism- Figure 3.7). This being an equilibrium reaction, at higher olefin concentration a fractional order is observed, particularly at higher temperature.

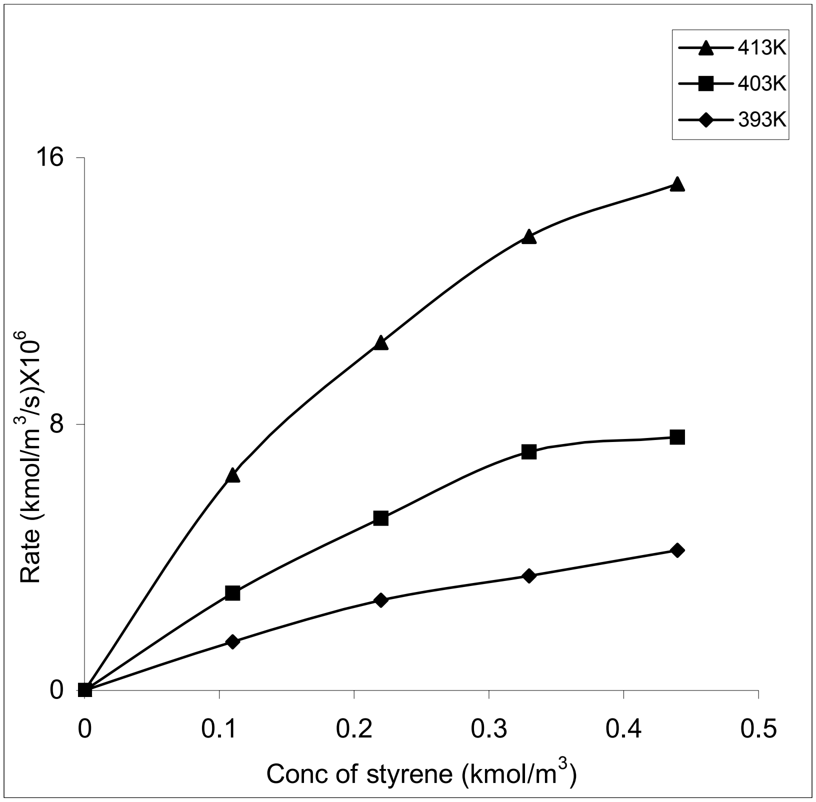


Figure 3.9: Effect of styrene concentration the rate of Heck reaction in homogeneous medium

Reaction conditions: concentration of iodobenzene: 2.0×10^{-1} kmol/m^3, concentration of base (KOAc): 2.0×10^{-1} kmol/m^3, TBAB: (1%of base), concentration of catalyst [$PdCl_2$(bipy)]: 2.0×10^{-4} kmol/m^3. NMP: 10ml.

3.3.3.2.4 Effect of KOAc (base) concentration

The effect of base concentration on activity was investigated at a styrene concentration of 2.2×10^{-1} kmol/m^3, iodobenzene concentration of 2.0×10^{-1} kmol/m^3 and a catalyst concentration of 2.0×10^{-4} kmol/m^3 at temperatures of 393K-413K in NMP. TBAB was added proportional to the base concentration at a 1% w/w concentration with respect to base. The results are presented in Figure 3.10. The rate was found to increase with increase in base concentration in the lower range of potassium acetate concentrations. However, on further increase, zero order dependence was observed. This trend is likely to be observed as the solubility of the base in NMP is limiting and once a saturation is reached, no further rate enhancement is observed. In general, the quaternary ammonium salts added, serves as phase transfer agent to enhance the solubility. At the loading used in our study, the effect is not so pronounced and hence a saturation of the NMP with KOAc is achieved.

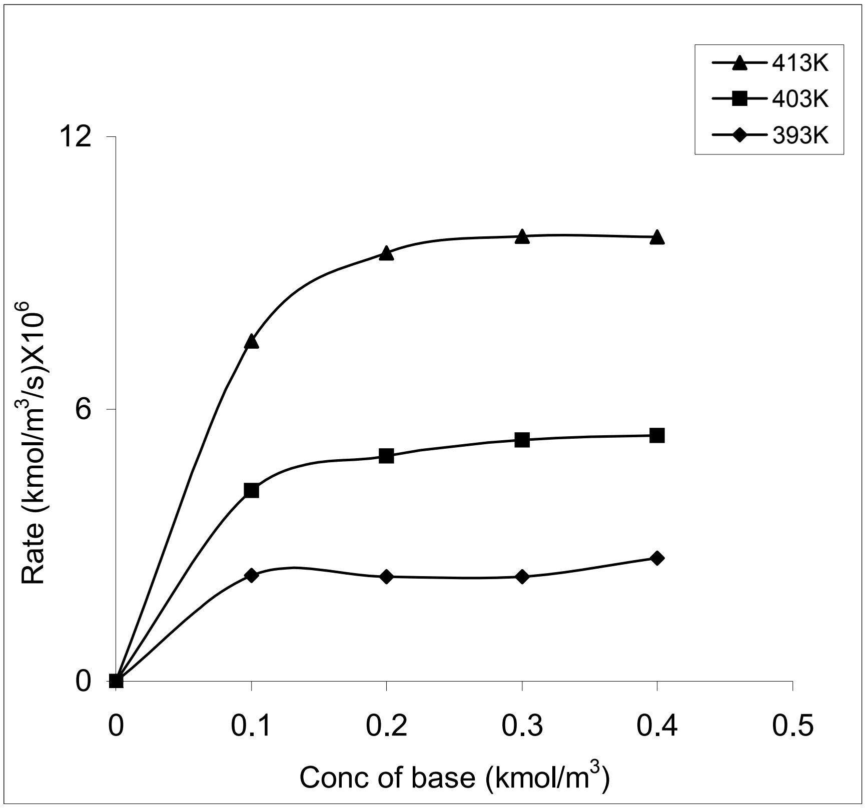


Figure 3.10: Effect of base concentration the rate of Heck reaction in homogeneous medium

Reaction conditions: concentration of styrene: 2.2×10^{-1} kmol/m^3, concentration of iodobenzene: 2.0×10^{-1} kmol/m^3, TBAB: (1% of base), concentration of catalyst [$PdCl_2$(bipy)]: 2.0×10^{-4} kmol/m^3. NMP: 10ml.

3.3.4 Kinetic models

The data was thus further taken to develop empirical rate equations, based on the observed trends. Four different forms of rate equations (Table 3.6) were discriminated and the results are presented in Table 3.7.

Table 3.6: Different empirical rate equations

Model Number	Rate equation
I	$R = \dfrac{k \, . \, A^{0.7} \, . \, B^{0.6} \, . \, C \, . \, D}{(1+K_D D)}$
II	$R = \dfrac{k \, . \, A \, . \, B \, . \, C \, . \, D}{(1+K_D D)}$
III	$R = \dfrac{k \, . \, A \, . \, B \, . \, C \, . \, D}{(1+K_B B)(1+K_D D)}$
IV	$R = \dfrac{k \, . \, A \, . \, B \, . \, C \, . \, D}{(1+K_A A)(1+K_B B)(1+K_D D)}$

[Where R: Rate of reaction (kmol/m^3.s) ; k: Intrinsic Rate constant ((m^3)^3/kmol^3.s)
A: Concentration of olefin (kmol/m^3) ; K_A: Equilibrium constant of olefins (m^3/kmol)
B: Concentration of ArX (kmol/m^3), K_B: Equilibrium constant of ArX (m^3/kmol)
C: Concentration of catalyst (kmol/m^3) ; K_D: Equilibrium constant of base (m^3/kmol)
D: Concentration of base (kmol/m^3)]

The rate parameters k, K_A, K_B and K_D were evaluated at 393, 403 and 413 K by fitting the observed experimental rate data to the different models using nonlinear regression analysis and an optimization routine based on Marquard's method[26]. The values of rate parameters at different temperatures are presented in Table 3.7. The rate equation best fitting the data was chosen based on the values of Φ_{min}, which is defined as (Equation 3.3)

$$\Phi \min = \sum_{i=1}^{n} (R_{exp} - R_{pre})^2 \qquad [3.3]$$

Where R_{exp} is the rate observed experimentally, R_{pre} is the predicted rate using nonlinear regression analysis and n is number of data points.

Table 3.7: Comparison of different rate models proposed for the Heck reaction in homogeneous medium.

Model No.	Rate Model	T,K	*k*	K_A	K_B	K_D	ϕ_{min}	R^2
I	$R = \frac{k \,.\, A^{0.7} \,.\, B^{0.6} \,.\, C \,.\, D}{(1+K_D D)}$	393	9.15E+00	-	-	8.96E+01	2.83E-12	0.9372
		403	1.65E+02	-	-	9.12E+02	2.51E-12	0.9735
		413	9.31E+00	-	-	2.18E+01	7.28E-12	0.9698
II	$R = \frac{k \,.\, A \,.\, B \,.\, C \,.\, D}{(1+K_D D)}$	393	9.37E+02	-	-	3.42E+03	1.41E-12	0.9702
		403	1.55E+03	-	-	3.12E+03	9.56E-12	0.9117
		413	1.72E+01	-	-	1.35E+01	4.18E-11	0.8606
III	$R = \frac{k \,.\, A \,.\, B \,.\, C \,.\, D}{(1+K_B B)(1+K_D D)}$	393	2.05E+01	-	2.62E-04	7.02E+01	1.38E-12	0.9709
		403	8.42E+01	-	2.34E+00	1.05E+01	5.03E-12	0.9412
		413	4.78E+01	-	4.51E+00	1.99E+01	1.29E-11	0.9479
IV	$R = \frac{k \,.\, A \,.\, B \,.\, C \,.\, D}{(1+K_A A)(1+K_B B)(1+K_D D)}$	393	2.07E+01	2.63E-03	1.80E-03	7.06E+01	1.38E-12	0.9709
		403	4.20E+01	6.36E-01	8.52E-02	6.77E+01	8.20E-12	0.9226
		413	8.86E+01	1.31E+00	6.11E+00	2.39E+01	3.68E-12	0.9850

Besides Φ_{min} the thermodynamic considerations regarding equilibrium constants K_A, K_B and K_D also were relied upon to choose the rate model, best representing the observed kinetic data. The analysis of all the models shows absence of negative values for the constants, however in case of model-I and model-II the values of rate constants k are not consistent with temperature and hence they were not considered. Comparison of the values of Φ_{min} obtained for model-III and IV shows that model-IV gives a superior fit and hence is recommended. The model chosen to best represent the kinetics observed is as follows

$$R = \frac{k \, . \, A \, . \, B \, . \, C \, . \, D}{(1+K_A A)(1+K_B B)\,(1+K_D D)} \qquad \text{(model IV)}$$

This model was found to predict the rate data within an error of ± 3% (which is within the range of experimental error). A comparison of the experimental rates with the predicted rates using model IV at three different temperatures i.e. at 393K, 403K and 413K is shown in Figure 3.11, which also indicates a good agreement between experimental and predicted rate.

Figures 3.12-3.15 show the comparison of experimental and predicted rates for the varying concentration of catalyst, iodobenzene, styrene and base respectively at temperatures of 393K-413K. The activation energy (E_A) was evaluated from the Arrhenius plot (Figure 3.16) and found to be 98.70 kJ/mol. The constants $K_{A,}$ K_B and K_D were found to be dependent on temperature as seen in Figure 3.17.

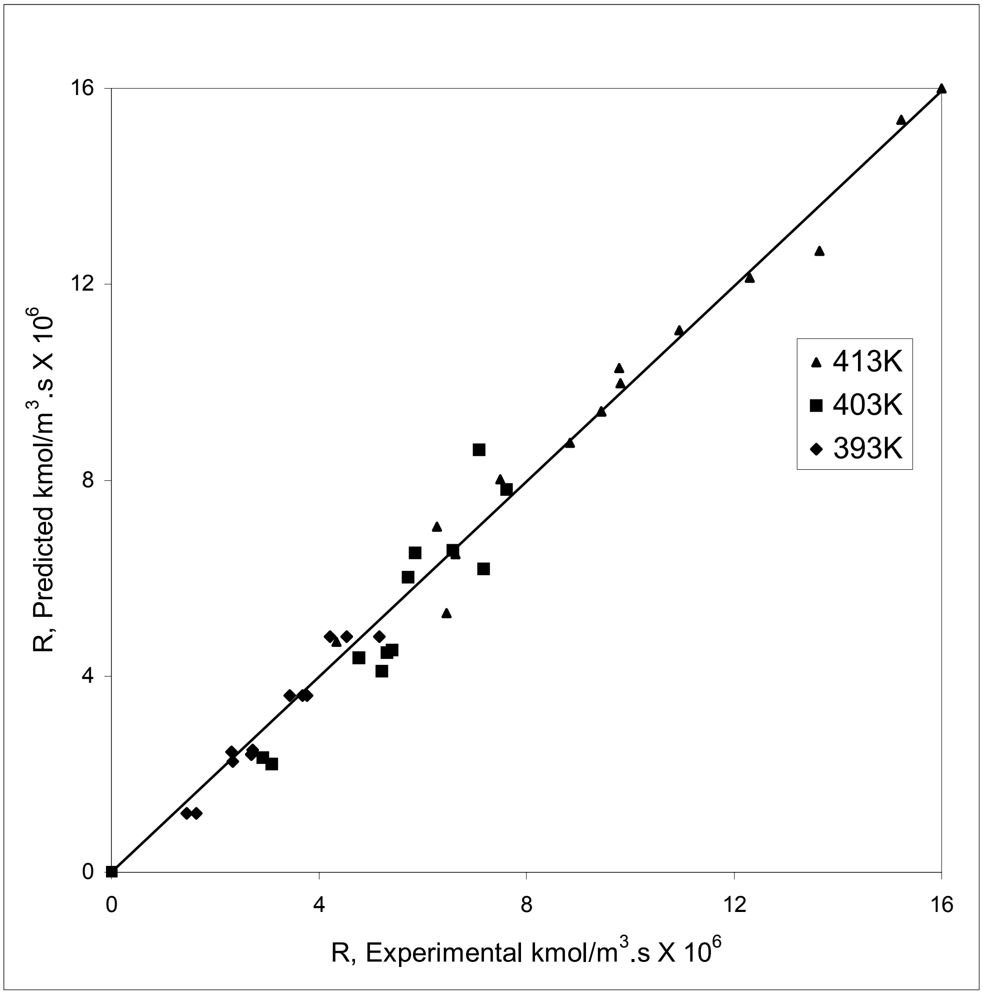


Figure 3.11: Plot of R (predicted) v/s R (experimental) 393K, 403K, and 413K

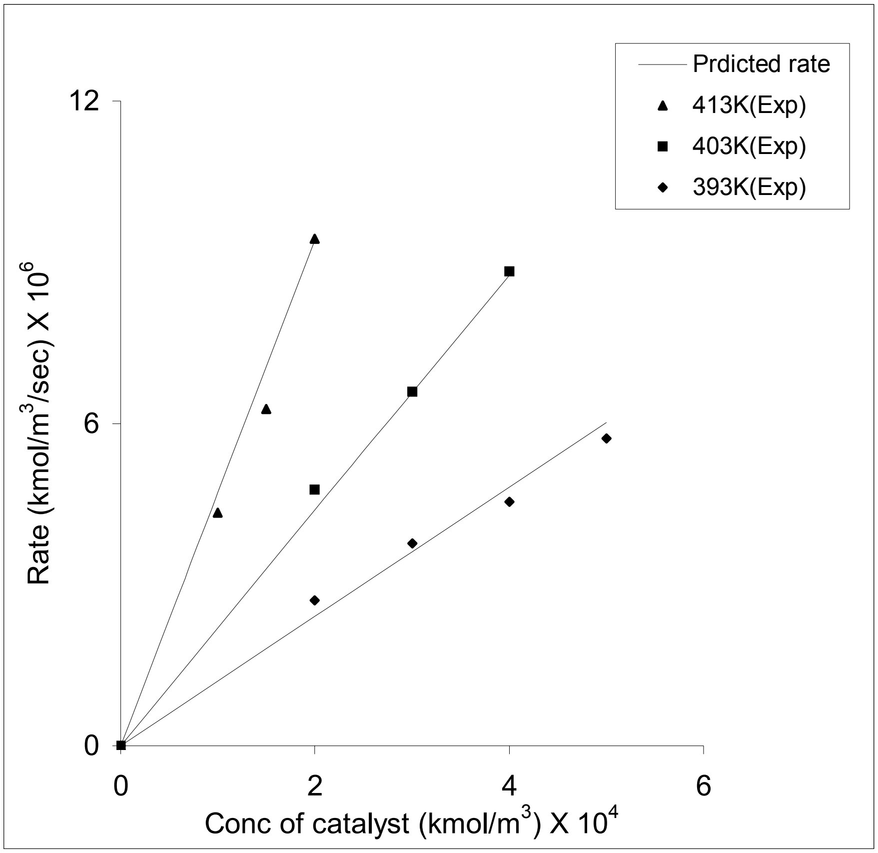


Figure 3.12: Comparison of experimental and predicted rates for effect of catalyst concentration at various temperatures

Reaction conditions: concentration of styrene: $2.2x10^{-1}$ kmol/m^3, concentration of iodobenzene: $2.0x10^{-1}$ kmol/m^3, concentration of KOAc: $2.0x10^{-1}$ kmol/m^3, TBAB: (1%of base), NMP: 10ml.

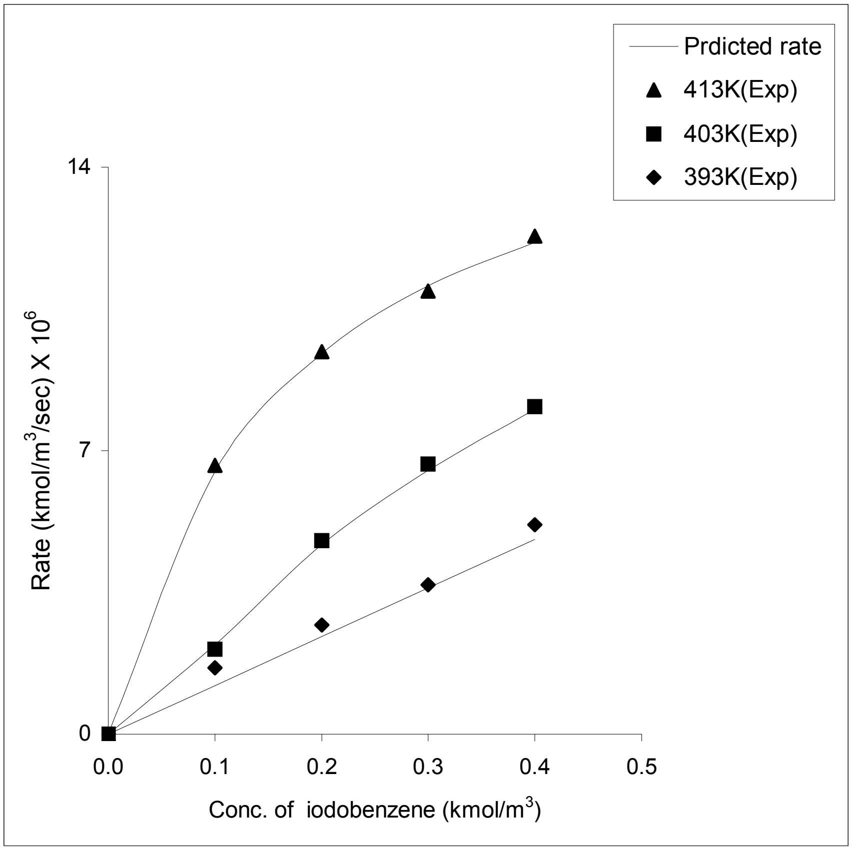


Figure 3.13: Comparison of experimental and predicted rates for effect of iodobenzene concentration at various temperatures

Reaction conditions: concentration of styrene: $2.2\text{x}10^{-1}$ kmol/m^3, concentration of catalyst: $2.0\text{x}10^{-4}$ kmol/m^3, concentration of KOAc: $2.0\text{x}10^{-1}$ kmol/m^3, TBAB: (1%of base), NMP: 10ml.

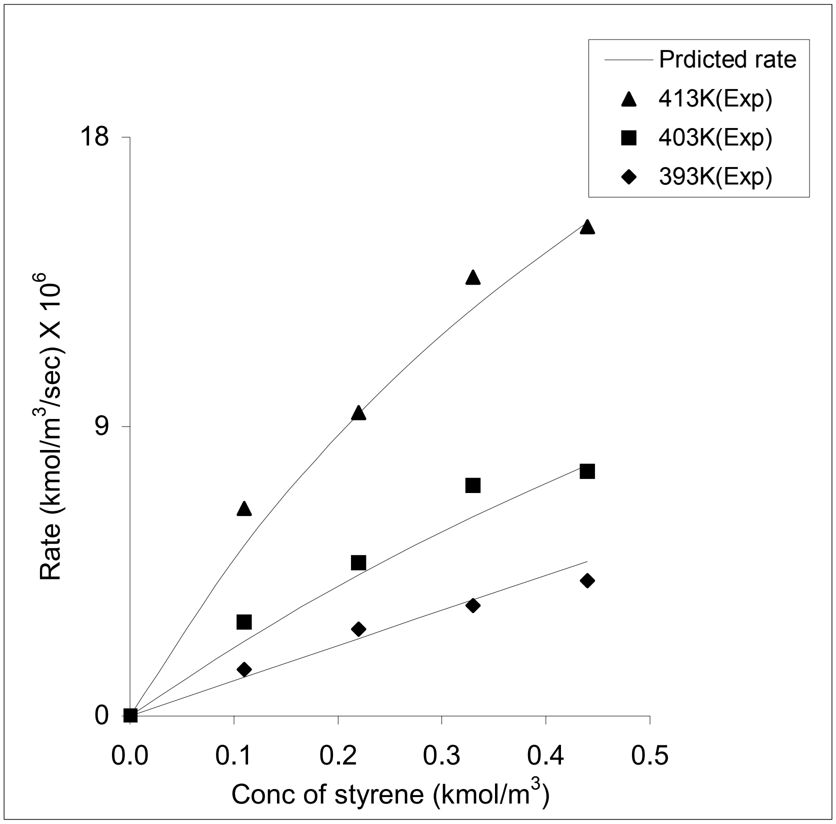


Figure 3.14: Comparison of experimental and predicted rates for effect of styrene concentration at various temperatures

Reaction conditions: concentration of catalyst: 2.2×10^{-4} kmol/m^3, concentration of iodobenzene: 2.0×10^{-1} kmol/m^3, concentration of KOAc: 2.0×10^{-1} kmol/m^3, TBAB: (1%of base), NMP: 10ml.

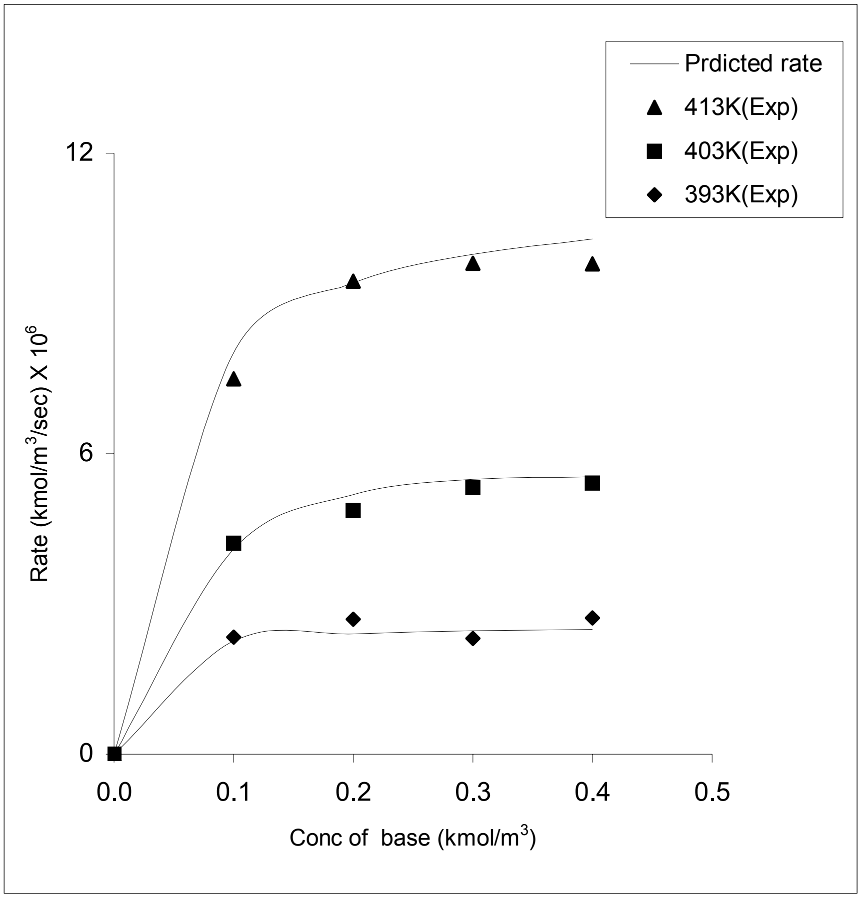


Figure 3.15: Comparison of experimental and predicted rates for effect of base concentration at various temperatures

Reaction conditions: concentration of styrene: $2.2x10^{-1}$ kmol/m^3, concentration of iodobenzene: $2.0x10^{-1}$ kmol/m^3, concentration of catalyst: $2.0x10^{-4}$ kmol/m^3, TBAB: (1%of base), NMP: 10ml.

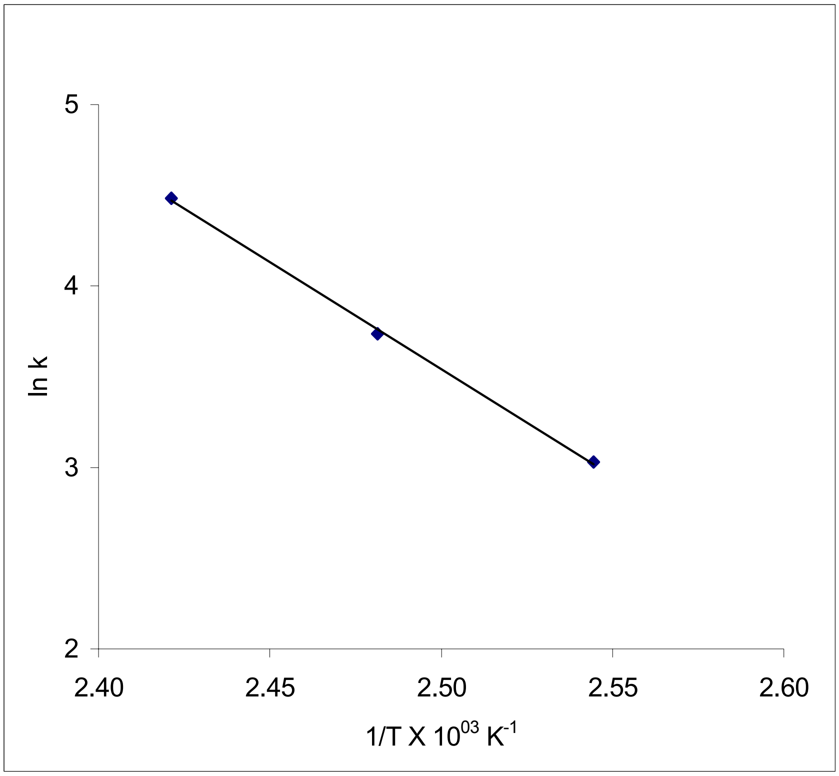


Figure 3.16: Plot of ln k v/s 1/T

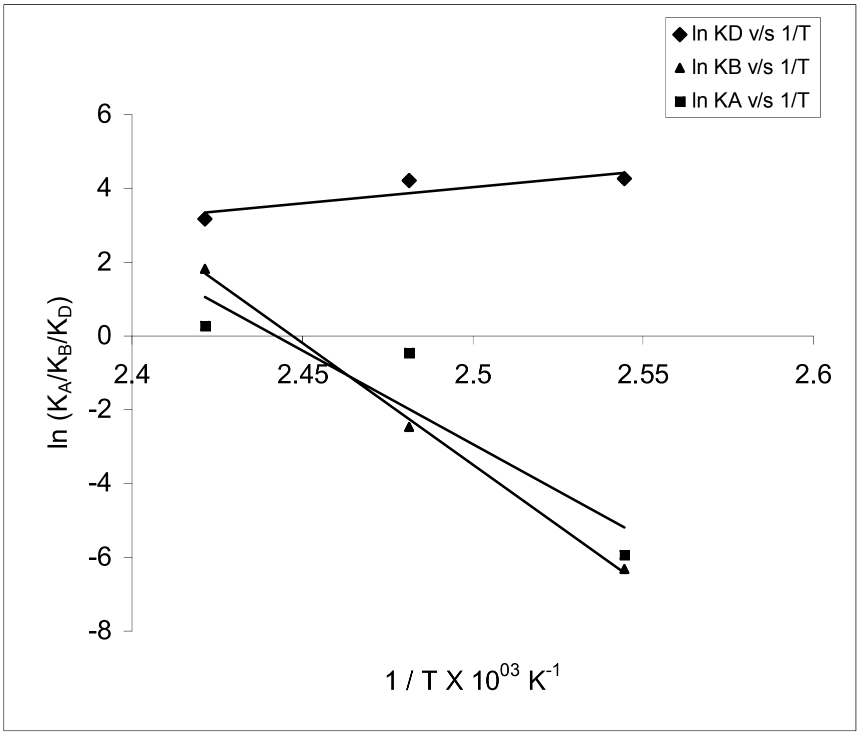


Figure 3.17: Plot of ln K_A, ln K_B, ln K_D v/s 1/T

3.3.5 Comparison of kinetics under homogeneous and biphasic conditions

The rate models developed for the data obtained under varying conditions were different, for the same catalyst. The only common observation was first order tending to zero order with respect to iodobenzene concentration. For the homogeneous system the dependence on all parameters except catalyst concentration was a first order tending to a zero order. In case of biphasic system an inhibition is observed at higher styrene concentrations and with catalyst a 0.8^{th} order was observed. These observations suggest that the rates of individual steps in the mechanism are very much influenced by the solvent.

3.3.6 Conclusions

The kinetics of the coupling reaction of styrene and iodobenzene in presence of KOAc and $PdCl_2$(bipy) catalyst has been investigated in homogeneous medium (NMP solvent). The rate was found to have a first order dependence on catalyst and a partial order dependence on styrene and iodobenzene concentration. Saturation kinetics was observed with varying concentrations of base. The trends were found to be quite close to those observed for the Pd-phosphine catalyzed reaction. Numerous semi empirical rate models were discriminated and a rate model of following type was found to represent the rate data in good agreement.

$$R = \frac{k \, . \, A \, . \, B \, . \, C \, . \, D}{(1+K_A A)\,(1+K_B B)\,(1+K_D D)}$$

The parameters k, K_A, K_B and K_C were evaluated at all the temperatures. The activation energy was also evaluated and was found to be 98.70 kJ/mol.

The kinetic behavior of Heck reaction using $PdCl_2$(bipy) catalyst in glycol-organic biphasic media and in NMP solvent (homogeneous medium) was also compared and difference in the activity with respect to different parameters of the reaction was observed. The kinetic behavior of Heck reaction using $PdCl_2$(bipy) catalyst in glycol-organic biphasic media and in NMP solvent (homogeneous medium) was found to be same for the aryl halide concentration, however it was found to be different with respect to styrene, base and catalyst concentration, which was best represented by a different rate equation.

Nomenclature

A : Concentration of olefin (kmol/m^3)

B : Concentration of ArX (kmol/m^3)

C : Concentration of catalyst (kmol/m^3)

D : Concentration of base (kmol/m^3)

E_A : Activation energy

k : Intrinsic Rate constant ((m^3)^3/kmol^3.s)

K_A : Equilibrium constant of olefins (m^3/kmol)

K_B : Equilibrium constant of ArX (m^3/kmol)

K_D : Equilibrium constant of base (m^3/kmol)

R : Rate of reaction (kmol/m^3.s);

R^2 : Value of Agreements of points in graph

R_{exp} : Experimentally observed rate

R_{pre} : Predicted rate

References

(1) Woltermann, C. J. PharmaChem 2002, 1, 11-14

(2) Beletskaya, I. P.; Cheprakov, A. V. Journal of Organometallic Chemistry 2004, 689, 4055-4082.

(3) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. Synlett 1992, 11, 871-2.

(4) Kawano, T.; Shinomaru, T.; Ueda, I. Organic Letters 2002, Vol. 4, 2545-2547.

(5) Herrmann, W. A.; Elison, M.; Fischer, J.; Koecher, C.; Artus, G. R. J. Angew. Chem., Int. Ed. Engl. 1995, 34, 2371-4

(6) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. Chem. Commun. 2001, 201.

(7) Rosner, T.; Le Bars, J.; Pfaltz, A.; Blackmond, D. G. Journal of the American Chemical Society 2001, 123, 1848-1855.

(8) Consorti, C. S.; Flores, F. R.; Dupont, J. Journal of the American Chemical Society 2005, 127, 12054-12065.

(9) Tsai, F.-Y.; Wu, C.-L.; Mou, C.-Y.; Chao, M.-C.; Lin, H.-P.; Liu, S.-T. Tetrahedron Letters 2004, 45, 7503-7506.

(10) Albisson, D. A.; Bedford, R. B.; Scully, P. N. Tetrahedron Letters 1998, 39, 9793-9796.

(11) Littke, A. F.; Fu, G. C. J. Am. Chem. Soc. 2001, 123, 6989-7000.

(12) Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. Tetrahedron Letters 1999, 40, 7379-7383.

(13) Scrivantia, A.; Bertoldinia, M.; Matteolia, U.; Beghettoa, V.; Antonarolib, S.; Marinib, A.; Crocianib, B. Journal of Molecular Catalysis A: Chemical 2005, 235, 12-16.

(14) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. J. Am. Chem. Soc. 2001, 123, 2677-2678.

(15) Jeffery, T.; Galland, J.-C. Tetrahedron Letters 1994, Vol. 35, 4103-4106.

(16) Beller, M.; Riermeier, T. M. Tetrahedron Lett. 1996, 37, 6535.

(17) Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J. Organic Letters 2003, Vol.5, 983-986.

(18) Amatore, C.; Carre, E.; Jutand, A.; Medjour, Y.; Organometallics 2002, 21, 4540-4545.

(19) Benhaddou, R.; Czernecki, S.; Ville, G.; Zegar, A. Organometallics 1988, 7, 2435-9.

(20) Nilsson, P.; Wendt, O. F. Journal of Organometallic Chemistry 2005, 690, 4197-4202.

(21) Rosner, T.; Pfaltz, A.; Blackmond, D. G. Journal of the American Chemical Society

2001, 123, 4621-4622.

(22) Zhao, F.-G.; Bhanage, B. M.; Shirai, M.; Arai, M. Stud. Surf. Sci. Catal. 1999, 122, 427- 430.

(23) Sud, A.; Deshpande, R. M.; Chaudhari, R. V. Journal of Molecular Catalysis A: Chemical 2007, 270, 144-152.

(24) Van Strijdonck, G. F. P.; Boele, M. D. K.; Kamer, P. C. J.; deVries, J. G.; vanLeeuwen, P. W. N. M. Eur. J. Inorg. Chem. 1999, 1073.

(25) Cabri, W.; Candiani, I. Acc. Chem. Res. 1995, 28, 2-7.

(26) Marquardt, D. W. J. Soc. Ind. Appl. Math. 1963, 11, 431.

CHAPTER 4

Heck Reaction Using Palladium Metal Complex Catalysts in Biphasic Aqueous-Organic System

4.1 Introduction

Catalyst product separation has always been a major issue in process development involving homogeneous catalysts[1,2]. With particular reference to Heck reactions, the multi-component system comprising olefin, aryl halide, vinylated product, base, base-halide adduct, phase transfer agent, catalyst and generally a polar solvent, requires a complex strategy for product separation and catalyst recovery[3] and recycle. Although the extremely active and stable Palladacycle catalysts give very high rates[4,5], conventional strategies of catalyst – product separation still need to be followed, which could lead to catalyst deactivation. There are no details on the recycle of Palladacycle catalyst for Heck reaction in the reported literature. To overcome the issues of catalyst – product separation, the use of biphasic systems has been proposed for Heck reactions[6-10], which involves aqueous or non-aqueous biphasic systems. The non-aqueous biphasic system[6-8] generally uses a polar solvent like ethylene glycol as the catalyst phase and employs a water-soluble catalyst. A number of reports on the application of water-soluble catalysts for Heck reactions[9-11] in homogeneous aqueous organic media have shown the effectiveness of these systems for the coupling reaction of different aryl halides and olefins. The presence of water is also reportedly beneficial for the Heck reaction[11-15]. The solubilization of the base in the reaction medium is enhanced in presence of water leading to improved activity[16-18]. As per the reported mechanism of Heck reaction, water also helps removal of the halide to generate the active catalytic species[19]. However, in a majority of the studies a detailed investigation on the catalyst recycle is not available for Heck reaction in aqueous media.

Catalysis in water offers several advantages for industrial application: easy separation of the product from the catalyst and recycle of catalyst, along with reasonable activity. Water is inexpensive, nontoxic, nonflammable, and readily forms biphasic systems with a variety of organic materials. Therefore, aqueous/organic two-phase catalysis finds wide applications[20]. In spite of these advantages not many studies have been devoted to the palladium-catalyzed reactions of alkenes in aqueous media. This fact seems to stem from a conception that water must be completely excluded from the reaction system, otherwise a Wacker-like reaction occurs[21]. In recent years, investigations were undertaken to use water as the solvent in palladium-catalyzed reactions of alkenes. A few reports have shown that water can be added in the Heck reaction[11-13,15,22]. These studies are concerned with the arylations of acrylic acid, acrylonitrile, or cyclic olefins with iodoarenes.

Considering the advantages of water, two biphasic systems were studied. In the first, the organic soluble catalyst has been used for the coupling of water-soluble olefin i.e. Na acrylate and in the other study, a water-soluble catalyst is employed for the Heck reaction of water immiscible substrates.

The chapter is divided into two sections. Section 4.2 deals with the activity and selectivity studies of Heck reaction of water-soluble olefinic substrates in biphasic aqueous-organic medium using Palladacycle catalyst. In Section 4.3 the synthesis and characterization of water-soluble Pd-catalyst and its application for Heck reaction in a biphasic aqueous-organic system is reported.

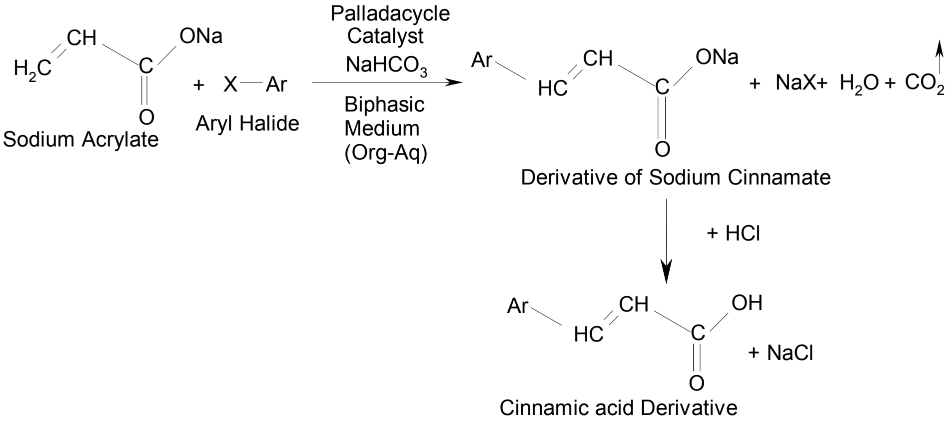
Section A

4.2 Heck reaction of water-soluble olefinic substrates in biphasic aqueous-organic medium using Palladacycle catalyst.

4.2.1 Introduction

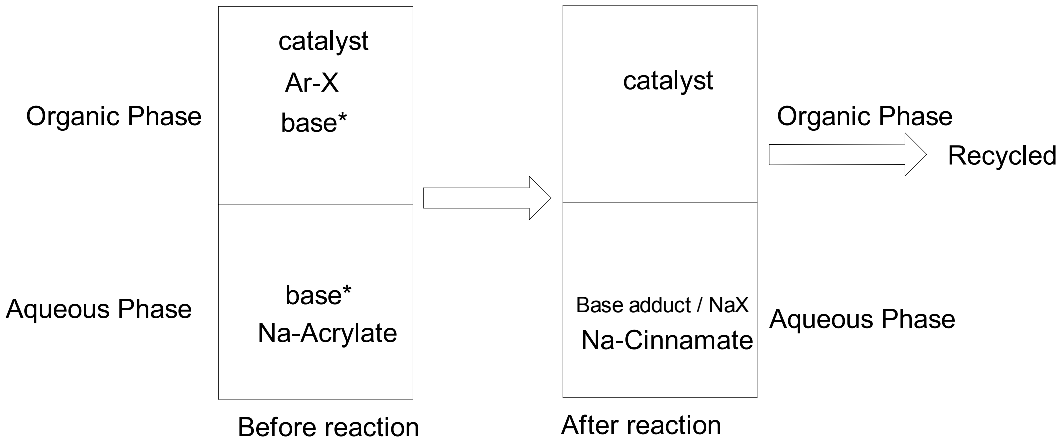
Heck coupling of water-soluble olefins like Na-acrylate are amenable to reactions in aqueous-organic biphasic systems using Pd complex catalysts solubilized in the organic phase. Such a biphasic system offers more advantages over conventional systems with respect to catalyst recycle and product recovery. The presence of water ensures an efficient removal of the halide byproduct, formed in the course of the Heck coupling of Na-acrylate with different aryl halides.

The Heck reaction of acrylic acid salts with aryl halides as shown in Scheme 4.1, results in the synthesis of substituted cinnamic acid derivatives, which have wide ranging applications as UV absorbers, anti-oxidants in plastics, as intermediates for pharmaceuticals[23] and also in medicinal chemistry[24,25].



Scheme 4.1: Heck reaction of acrylic acid salts with aryl halides followed by isolation of product

Since the alkali metal salts of the acrylic acid are water-soluble, a biphasic system can be set up, with the catalyst in the organic phase and the olefin in the aqueous phase as shown in Figure 4.1**.** The use of a biphasic medium for the Heck reaction of the water-soluble Na-acrylate offers distinct advantages specially tuned to the water-soluble products. These are (i) the product formed is a Na-salt of cinnamic acid derivative, which is soluble in water and can be recovered easily (ii) the base/ base-HX adduct or salt formed is also soluble in water and is removed from the catalyst phase and (iii) the organic phase consisting of catalyst and the residual aryl halide can be recycled by mere phase separation.



* base is present in either organic or aqueous phase depending on solubility

Figure 4.1: A schematic of aqueous biphasic system using organic phase soluble catalyst and aqueous phase soluble olefin

This section presents investigations on the Heck coupling of Na acrylate with aryl halides using an aqueous-organic biphasic system in the presence of Palladacycle catalyst. A biphasic [aqueous-organic] system for the Heck reaction of water-soluble olefin has been developed, which employs an organic phase soluble Pd complex catalyst. The catalyst and biphasic solvent system was tested for the coupling reaction of Na-acrylate with different aryl halides and found to be active for the synthesis of cinnamic acid derivatives. The role of organic and inorganic bases on the activity of the catalyst has also been investigated. The stability of the catalyst on recycle has been demonstrated for a few recycles with no loss in the activity.

4.2.2 Experimental section

4.2.2.1 Apparatus and chemicals

$PdCl_2$, $Pd(OAc)_2$, tri-*o*-tolyl phosphine, DPPE, PPh_3, 2,2'bipyridine, sodium acrylate and the aryl halides used were procured from Aldrich USA and used as such. The Pyridine and solvents were obtained from SD Fine Chemicals, India. The bases used (AR grade) were purchased from MS Loba Chemicals, India. The reactions were conducted in a high-pressure autoclave of 50 ml capacity manufactured by MS Amar Engineering, Mumbai.

4.2.2.2 Synthesis of Pd complex catalysts

The palladium complexes of the type $PdCl_2L$, [where L=DPPE, 2, 2'-Bipyridine, $(PPh_3)_2$ and Py_2] and the Palladacycle were prepared by standard procedures[5,26-29]. The details are given in Chapter 2.

4.2.2.3 General procedure for Heck reaction

Aryl halide (3.0 mmol) and catalyst (0.003 mmol) were dissolved in toluene (15ml). Sodium acrylate (3.3 mmol), base (3.0 mmol) and distilled water (15ml) were mixed separately. Both organic and aqueous phases were then added into the autoclave. The reaction was carried out at 150°C with 1450 RPM agitation for a period of 30 minutes. The reaction mixture was cooled, and the aqueous layer was treated with dilute HCl till it was acidic to litmus. The precipitate was filtered, washed with 3 x 5 ml of distilled water, and dried under vacuum. The products obtained were the derivatives of cinnamic acid. Quantitative analysis of the aryl halide consumed was done on GC (Agilent 6850 series II), using a HP-1 capillary column. The standard conditions for GC analysis are given in Chapter 2 (Section 2.2.2.4). The conversion of iodobenzene was monitored along with the isolated yields of cinnamate derivatives.

In the case of products, the isolated yield was observed. The products i.e. cinnamic acid derivatives were isolated from the aqueous solutions by acidification as depicted in scheme 4.1 (Section 4.2.1). The derivatives of cinnamic acid were precipitated and were identified by using GC-MS (Agilent 6890N series equipped with 5973N Mass Selective Detector). From the quantitative analysis, the conversion of the aryl halide, selectivity, TON (Turn Over Number) and turnover frequency (TOF) were calculated by using the formulae given in Chapter 2 (Section 2.2.2.3).

For recycle study, the catalyst phase (organic phase) was separated by simple phase separation and used in the above procedure along with a fresh aqueous phase consisting of substrates and base.

4.2.3 Results and discussion

4.2.3.1 Screening of catalysts

The palladium complexes of the type $PdCl_2L$, [where L=DPPE, 2,2'-Bipy, $(PPh_3)_2$ and Py_2] and the Palladacycle *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl] dipalladium(II) were screened for their activity in the Heck coupling of Na-acrylate with iodobenzene in an aqueous–organic biphasic medium in presence of the base Na_2CO_3. The results are presented in Table 4.1.

Table 4.1: Screening of catalysts for the Heck reaction of sodium acrylate in aqueous-organic biphasic medium

Sr. No.	Catalyst	% Conversion of Iodobenzene	TOF
1	Palladacycle	93	1860
2	$PdCl_2(DPPE)$	65	1298
3	$PdCl_2(PPh_3)_2$	63	1256
4	$PdCl_2(Bipy)$	62	1234
5	$PdCl_2(Py)_2$	33	670

Reaction conditions: organic phase: ArX (3.0 mmol) with catalyst (0.003 mmol) in toluene (15ml); aqueous phase: sodium acrylate (3.3 mmol) and base: Na_2CO_3 (3.0 mmol) in distilled water (15 ml); Temperature: 150^oC; 1450 RPM; Time: 30 min; Selectivity: 96-100%.

When the reaction was conducted in the absence of any ligand with only $PdCl_2$ as a catalyst, $PdCl_2$ was found to precipitate and the activity observed was due to the Pd metal rather than a truly homogeneous catalyst. Of the different Pd-complexes investigated, the highest activity was observed for the Palladacycle complex. The activity of the $PdCl_2$-DPPE complex was almost similar to that observed for $PdCl_2(PPh_3)_2$ complex. Phosphine ligands can stabilize the active catalyst in Heck reactions thus making them more active for the reaction. $PdCl_2(Py)_2$ gave lower activities as compared to the other catalysts. Surprisingly, the $PdCl_2(bipy)$ complex was found to be as active as the phosphine complexes. Bi-dentate ligands are known to stabilize the catalytic complexes and this is probably the reason for the observed rates with the $PdCl_2(bipy)$ catalyst. No precipitation of the Pd metal was observed in any of the reactions with the Pd complex catalysts. No leaching of the metal to the aqueous phase was also observed, as confirmed by the AAS analysis of the aqueous phase. Figure 4.2 shows the conversion of ArX and the TON observed for Heck reaction of various catalysts with sodium acrylate and iodobenzene using Na_2CO_3 as a base in aqueous-organic biphasic medium

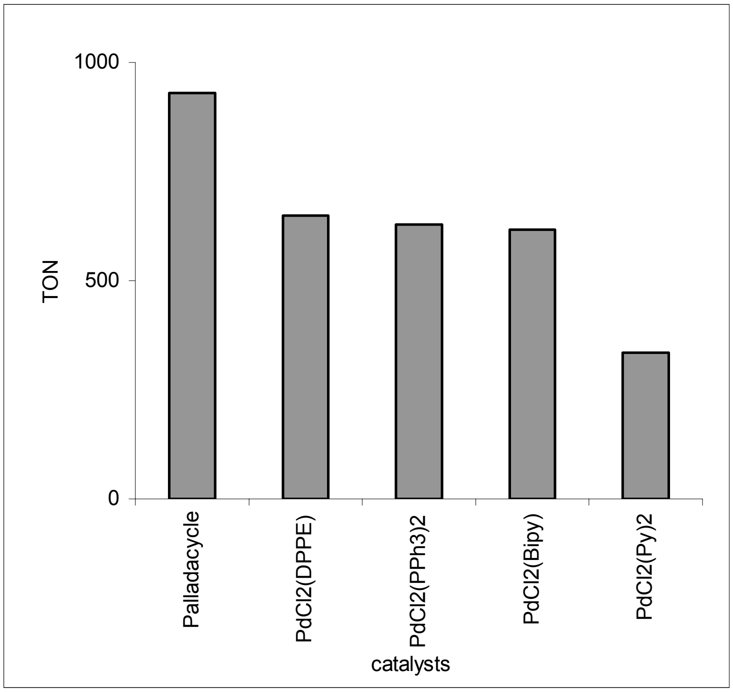


Figure 4.2: TON observed for Heck reaction of various catalysts with sodium acrylate and iodobenzene using Na_2CO_3 as a base in aqueous- organic biphasic medium

Reaction conditions: organic phase: ArX (3.0 mmol) with catalyst (0.003 mmol) in toluene (15 ml); aqueous phase: sodium acrylate (3.3 mmol) and base: Na_2CO_3 (3.0 mmol) in distilled water (15 ml); Temperature: 150°C; 1450 RPM; Time: 30 min; Selectivity: 96-100%. (The regioselectivity of all the product was found to be 100% trans in all the cases)

4.2.3.2 Screening of bases

Since the Hermann's Palladacycle catalyst had the highest activity, a detailed screening of bases was conducted using this catalyst in an aqueous–organic (water–toluene) medium. The results presented in Figure 4.3 show the activities observed for the different inorganic and organic bases screened. The inorganic bases such as carbonate, bicarbonate and hydroxides gave the best activity, as compared to the inorganic acetates and organic amines. This trend is different from that observed in homogeneous catalytic systems, wherein the acetate salts give good activities in polar solvents like NMP, DMF etc, particularly in presence of phase transfer agents like quaternary ammonium halides[30].

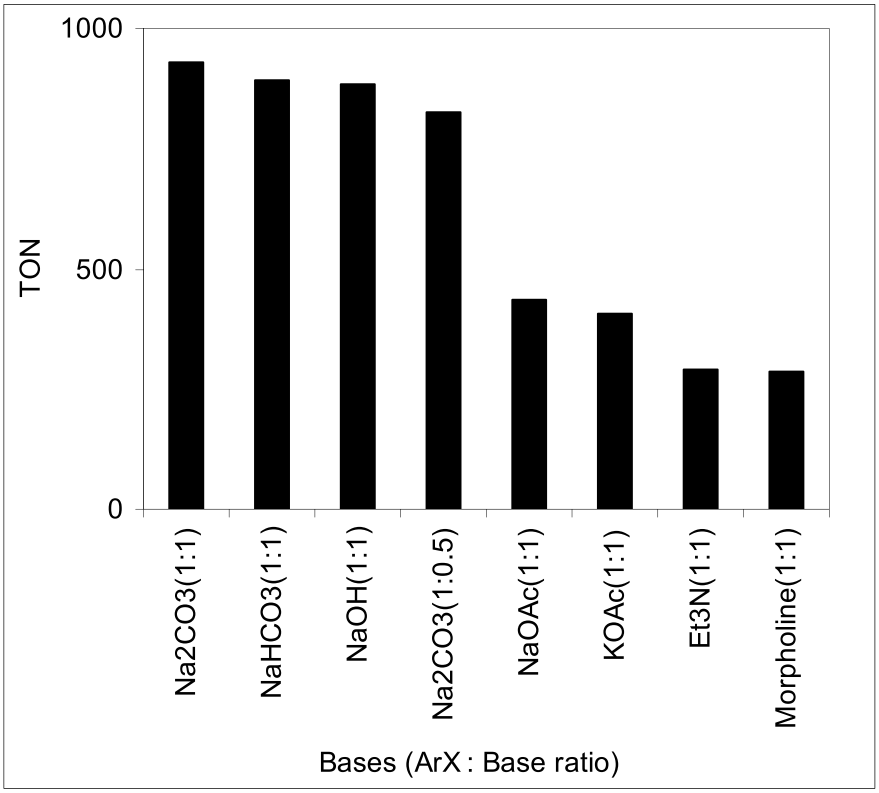


Figure 4.3: Effect of base on activity of Heck reaction using Palladacycle catalyst in aqueous-organic biphasic media

Reaction conditions: organic phase: iodobenzene (3.0 mmol) with Palladacycle catalyst (0.003 mmol) in toluene (15 ml); aqueous phase: sodium acrylate (3.3 mmol) and base (3.0 mmol) in distilled water (15 ml); Temperature: 150°C; 1450 RPM; Time: 30 min; Selectivity: 96-100%.

The acetates are relatively more soluble in polar organic solvents compared to the carbonates, bicarbonates and hydroxides and hence they give better TOFs in such solvents. In aqueous systems, the solubility issues are not so important, as all these bases are water-soluble and hence the activity observed is comparable to the strength of the bases. When the base employed was carbonate or bicarbonate; carbon dioxide, commensurate to the conversion of iodobenzene was generated as seen from the increase in the pressure of reactor during the reaction. The results are tabulated in Table 4.2.

Table 4.2: Screening of various bases for Heck reaction of sodium acrylate and iodobenzene using Palladacycle catalyst in aqueous- organic biphasic medium

Sr. No.	Base	Ratio (IB : Base)	% Conversion of Iodobenzene	TOF (hr^{-1})
1	Na_2CO_3	1:1	93	1860
2	$NaHCO_3$	1:1	84	1784
3	NaOH	1:1	84	1772
4	Na_2CO_3	1:0.5	84	1650
5	NaOAc	1:1	41	868
6	KOAc	1:1	38	812
7	Et_3N	1:1	32	584
8	Morpholine	1:1	26	576

Reaction conditions: organic phase: iodobenzene (3.0 mmol) with Palladacycle catalyst (0.003 mmol) in toluene (15 ml); aqueous phase: sodium acrylate (3.3 mmol) and base (3.0 mmol) in distilled water (15 ml) Temperature: 150°C; 1450 RPM. Time: 30 min.

4.2.3.3 Screening of aryl halides

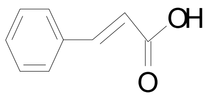
The efficiency of the aqueous-organic biphasic system using Palladacycle catalyst was assessed for the Heck vinylation of a variety of aryl halides, in presence of sodium carbonate as the base. The results are presented in Table 4.3.

The iodoarenes were far more active than the bromoarenes, as expected from the literature reports[31]. The trends observed for the activities of aryl halides are also similar to those reported earlier for Palladacycle catalysts[4,5,30]. Overall, the activity observed for the iodoarenes was lower in the biphasic medium as compared to those observed in homogeneous systems using the Palladacycle catalyst. This is probably due to the poor solubility of the olefin in the catalyst phase, which is limiting. No reaction was observed with chlorobenzene using the biphasic catalysis proposed here.

Table 4.3: Screening of aryl halide for the Heck reaction of sodium acrylate in aqueous-organic biphasic medium

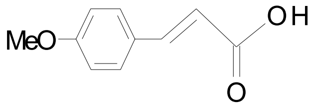
Sr. No.	Aryl halide	Structure of the Isolated product	% Conversion of Aryl halide	TON
1	4-Iodoanisole	**2**	94	939
2	Iodobenzene	**1**	93	930
3	4-Bromotoluene	**3**	1	10
4	Bromobenzene	**1**	1	12
5	Chlorobenzene	-	No reaction	-

Reaction conditions: organic phase: ArX (3.0 mmol) with Palladacycle catalyst (0.003 mmol) in toluene (15 ml); aqueous phase: sodium acrylate (3.3 mmol) and base: Na_2CO_3 (3.0 mmol) in distilled water (15 ml); Temperature: 150°C; 1450 RPM; Time: 30 min; Selectivity: 96-100%. (The regioselectivity of all the product was found to be 100% trans in all the cases)



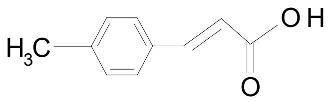
Cinnamic acid

1



4-Methoxy cinnamic acid

2



4-Methyl cinnamic acid

3

4.2.3.4 Recycle study for Palladacycle catalyst in biphasic medium

In the aqueous-organic biphasic system developed in this work, the base employed is soluble in the aqueous phase, along with the base-halide adduct or salt formed. This leaves the catalyst phase free of any base or salt and hence can be recycled with ease. Also, since no thermal processing of any kind is required, the possibility for catalyst deactivation is minimized. The organic phase was separated and recycled to ascertain the stability and activity of the catalyst. As seen in Figure 4.4, the catalyst could be recycled for four times with practically no loss in activity.

The activity was enhanced for the first recycle from a turnover frequency (TOF) of 1784hr^{-1} to a TOF 2105hr^{-1}, and was almost constant for all four recycles. The iodobenzene conversion for the virgin reaction was ~80%, and the residual iodobenzene was recycled along with fresh iodobenzene for the catalyst recycle, which accounts for enhanced TON for recycle. The results on catalyst recycle studies indicate that the catalyst is tolerant to water, and can be recycled with ease. No leaching of the Pd complex to the aqueous phase was observed in the course of the recycle study.

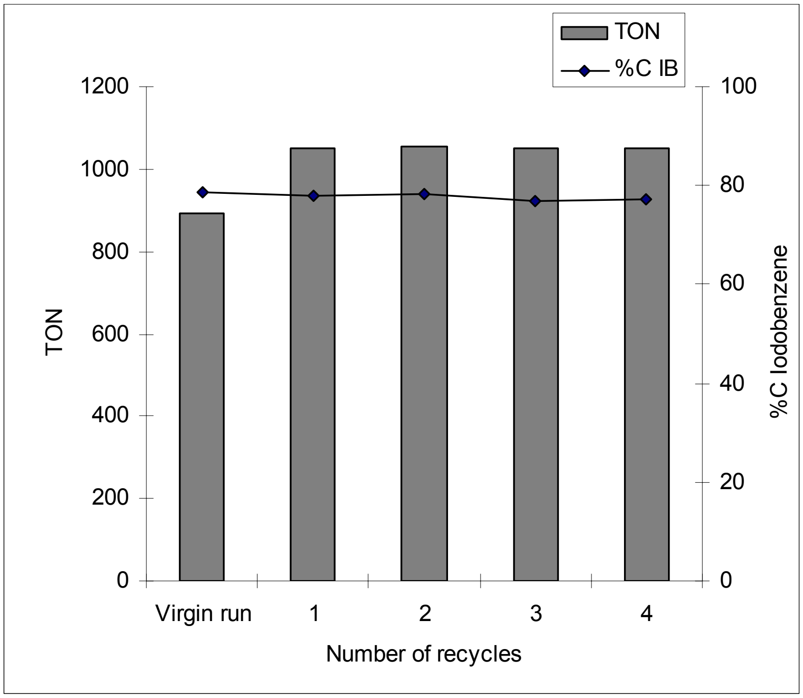


Figure 4.4: Recycle studies using Palladacycle catalyst in aqueous-organic biphasic media

Reaction conditions: organic phase: iodobenzene (3.0 mmol) with Palladacycle (0.003 mmol) or recycled catalyst in toluene (15 ml); aqueous phase: sodium acrylate (3.3 mmol) and base: $NaHCO_3$ (3.0 mmol) in distilled water (15 ml); Temperature: 150°C; 1450 RPM; Time: 30 min; Selectivity: 96-100%.

[For recycle study, the catalyst phase (organic phase) was separated by simple phase separation and used (instead of fresh toluene) in the above procedure and fresh aqueous phase along with substrates and base were added during each recycle along with substrates.]

It is known that Palladacycle complex may degenerate to Pd metal under the reaction conditions used for Heck reaction[32]. However, reports by Herrmann and coworkers indicate that the Palladacycle complex is stable in toluene under reflux even for few days[30,33]. It was hence of interest to see whether any decomposition of the catalyst was observed in the course of the reaction. No precipitation of Pd was observed, even at the end of four recycles. In the biphasic system proposed, the organic phase comprises toluene, Palladacycle catalyst and the aryl halide. The Na- acrylate, product cinnamate and the base/base-HX adduct are present in water. As a result the Palladacycle has minimum exposure to these components. This may be the reason why the Palladacycle is stable under reaction conditions in the biphasic medium used.

Since the objective of this work was to develop a strategy for the product separation and the catalyst recycle, a reaction was conducted till a complete conversion of the iodobenzene was achieved. The concentration time profile for this experiment is shown in Figure 4.5. (Cinnamic acid concentration obtained after acidification)

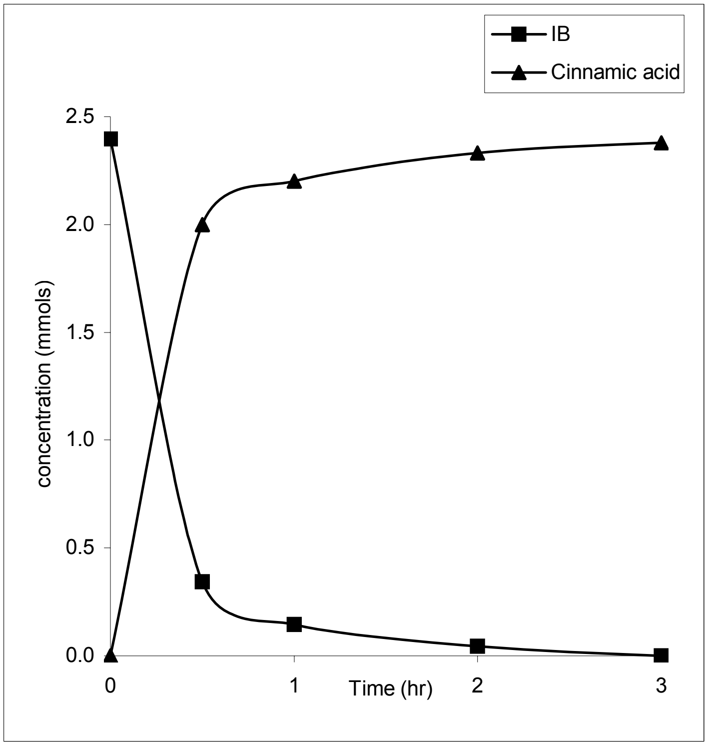


Figure 4.5: Typical concentration profile for Heck reaction in aqueous biphasic medium using Palladacycle catalyst

Reaction conditions: organic phase: iodobenzene (3.0 mmol) with Palladacycle catalyst (0.003 mmol) in toluene (15 ml); aqueous phase: sodium acrylate (3.3 mmol) and base Na_2CO_3 (3.0 mmol) in distilled water (15 ml); Temperature: 150°C; 1450 RPM; Time: 30 min; Selectivity: 96-100%.

At the end of the reaction, analysis of the organic phase showed negligible iodobenzene. The acidification of the aqueous phase gave quantitative formation of cinnamic acid as shown in Figure 4.6.

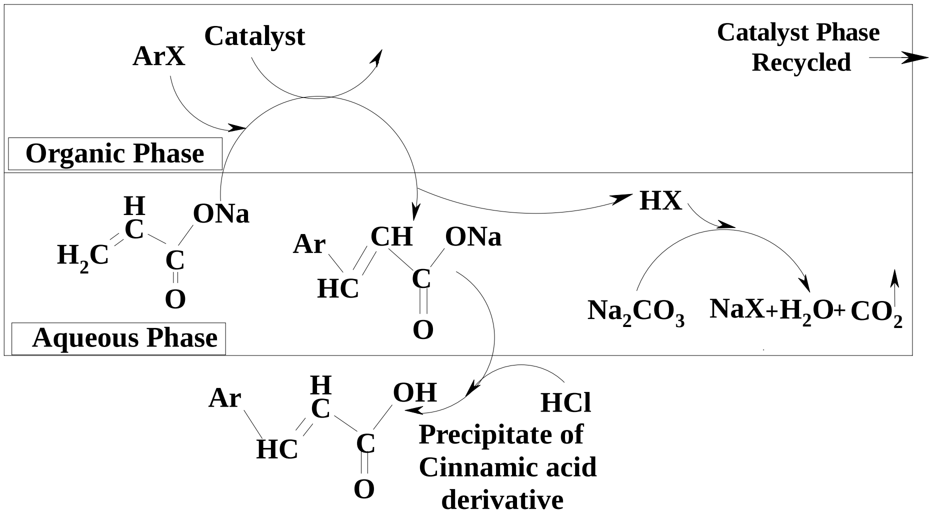


Figure 4.6: Representation of formation of cinnamic acid in aqueous-organic biphasic system using Palladacycle catalyst

From this study it seems to be a feasible strategy to recycle the catalyst after total conversion of the halide. Residual Na-acrylate can also be recovered from the aqueous phase for further recycle. The use of the biphasic medium described above can thus provide an excellent methodology for the recycle of catalyst, separation of product and recycle of unreacted substrates, in the Heck coupling of water-soluble substrates. A high cumulative Turn over number (TON) is achievable with the biphasic medium proposed. (TON up to 5100 has been achieved after 4 recycles in this case)

4.2.4 Conclusions

A biphasic [aqueous-organic] medium is shown to be feasible for the Heck reaction of water-soluble olefin- Na acrylate, with a very efficient catalyst product separation. Sodium hydroxide, carbonate and bicarbonate were found to be excellent bases for this reaction, and were efficient even though retained in the second, non-catalyst phase. The activity observed for the vinylation was highest for iodobenzene followed by bromobenzene. No reaction was observed with chlorobenzene. The Palladacycle catalyst was stable in presence of water, and could be recycled for four times with no loss in the activity. The biphasic system developed has the following advantages viz- (i) efficient catalyst recovery and recycle, (ii) convenient product separation and (iii) efficient sequestration of the halide as base is in a soluble state. Strategies for total conversion of halide followed by an efficient catalyst recycle, isolation of product and a separate stage for recovery of the unreacted Na-acrylate has been outlined.

Section B

4.3 Synthesis and characterization of water-soluble Pd-catalyst and its application for Heck reaction in a biphasic aqueous-organic medium.

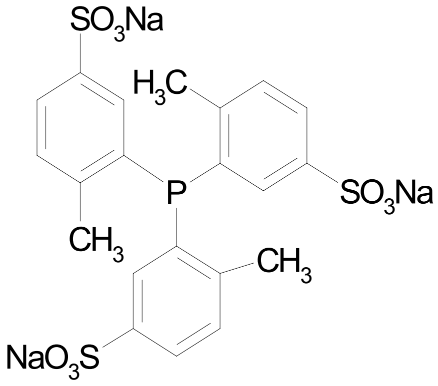
4.3.1 Introduction

Water-soluble catalysts have been employed for the Heck reaction in a number of studies. These studies can broadly be categorized into two types (i) where a non-aqueous biphasic medium is used and (ii) where a homogeneous medium containing water is used, for the Heck reaction. In a majority of the investigations using the biphasic system, water-soluble catalysts are employed in glycol as the catalyst phase along with toluene, xylene or similar organic phase. No water is present in these solvent systems.

There are other reports, which discuss the Heck reaction in water, but they invariably use water-soluble ligands in water along with a polar solvent such as CH_3OH, CH_3CN, DMF, NMP etc. thus making it a homogeneous reaction medium and not a biphasic system. These reports also do not discuss methods for catalyst recycle[9,11,34]. Some studies also suggest that water-soluble catalysts (furan derivatives) used for hydroformylation reaction in toluene-water system, could not be applied to Heck reaction. The solvent mixture of $CH_3CN–H_2O$ as a homogeneous system had to be used instead[35]. $PdCl_2(TPPMS)_2$ catalyzed arylation of ethylene under aqueous conditions[36] has been studied. However, the attempts for an aqueous biphasic system were unsuccessful as a black precipitate of metallic palladium was observed during the reaction. The reduction of a Pd^{2+} species with ethylene in water precedes the coordination of TPPMS, leading to precipitation. A water-soluble palladacycle[37] using TXTPS [tri(4,6-dimethyl-3-sulfonato phenyl)phosphine trisodium] ligand and its application to Heck reaction, is reported in the literature, however, water along with CH_3CN, is used in a homogeneous medium.

The objective of this work was to synthesize stable water-soluble Pd catalyst for Heck reaction in an aqueous biphasic medium. Hence, the water-soluble analog of Herrmann Palladacycle was synthesized and screened for its activity and stability for Heck reaction in water.

In this section we report a water-soluble Palladacycle catalyst prepared by sulphonation of tri *o*-tolyl phosphine (Figure 4.7) and the development of a reaction system using water along with a nonpolar solvent in such a way that the advantages of activity, stability and the biphasic catalysis could be achieved. The Heck reaction in the aqueous biphasic system was demonstrated for a number of aryl halides, olefins and in presence of different concentrations of cosolvent. The catalyst was retained in the water phase with no leaching to the organic phase and was recycled efficiently with no loss in activity.



1

Figure 4.7: TOTPS Ligand

[Trisodium salt of tri-(ortho-tolyl) phosphine tri sulphonate]

The catalyst did not precipitate in water, as reported in earlier studies, using other water soluble catalysts[36]. With this catalyst, the separation of product is achieved by mere separation of the two phases with minimal loss of catalyst.

4.3.2 Experimental section

4.3.2.1 Apparatus and chemicals

The bases (analytical grade) were procured from Loba Chemicals, India. $Pd(OAc)_2$, tri-o-tolyl phosphine (TOTP), the olefins and aryl halides used were from Aldrich, USA and used as such without any further treatment. The n-octane used was obtained from SD Fine Chemicals, India. The solvents- water and n-octane were degassed before use.

Since the temperatures utilized for the reaction were higher than the boiling points of most of the reactants and solvents, the reactions were conducted in a high pressure autoclave of 50 ml capacity manufactured by Ms Amar Engineering, Mumbai and had facilities for withdrawal of liquid and gaseous samples. The heating was controlled by means of electrically heated jacket. The reactor was fitted with a cooling loop for proper control of temperature.

4.3.2.2 Synthesis of TOTPS [Trisodium salt of tri-(ortho-tolyl) phosphine tri sulphonate] [Ligand 1]:

Ligand **1** was prepared by using the sulphonation procedure reported for TPPTS synthesis, by Bhanage et.al.[38]. For this purpose a sulphonation reactor was used. It was a 250ml 3-necked jacketed glass reactor fitted with a high-speed half-moon stirrer and with a provision for monitoring bulk liquid temperature. This reactor was designed so that operations under argon atmosphere were possible. The temperature was controlled by circulation of a constant temperature fluid. The third neck was used for neutralization and quenching of the oleum, also under argon atmosphere.

Sulfuric acid (98%, AR) 20 g, was introduced into the sulphonation reactor. The acid was cooled to 12-15°C, and 1 g of solid tri-o-tolyl phosphine (0.0329 mmol) was introduced at 15°C over the course of 30-45 min, with proper temperature control. A homogeneous yellow-coloured solution of tri-o-tolyl phosphine (TOTP) in sulfuric acid was formed. Then 11.87 g, (6 ml; *d* =1.98 at 35°C) of 65% oleum was introduced into the reactor over a period of 40-45 min, at a temperature of 15°C. The temperature of the reaction mixture was then raised to 22 (±0.5)°C and was maintained for 72 hr. Thereafter, the temperature of the reaction was lowered to -10°C and the reaction was quenched by slow addition of 5 g of cold degassed distilled water. The solution of sulfonated tri-o-tolyl phosphine in sulfuric acid thus obtained was further diluted to approximately 100 ml by addition of cold water (10°C). The diluted solution was neutralized (up to a pH of 7-7.2) with a solution of 50% (w/w) degassed sodium hydroxide, while maintaining the temperature at about 10°C during the entire operation. During the course of neutralization, sodium sulfate precipitated from the solution. This neutralized reaction mixture containing sodium sulfate/TOTPS was concentrated. On addition of methanol to this concentrated solution, the sodium sulfate precipitated. The filtrate was evaporated and then extracted with hot methanol. The methanolic solution was evaporated to dryness to yield the crude TOTPS. The TOTPS was purified by washing with ethanol and characterized using ^{1}H and ^{31}P NMR and elemental analysis and was found to match with the reported values[39,40]. The ^{1}H and ^{31}P spectra are shown in following section (section 4.3.2.4)

Elemental analysis of the complex was carried out on a CHNS-O EA1108, elemental analyzer of Carlo Erba Instruments, Italy. The values obtained are given in Table 4.4, which were found to match with the calculated values.

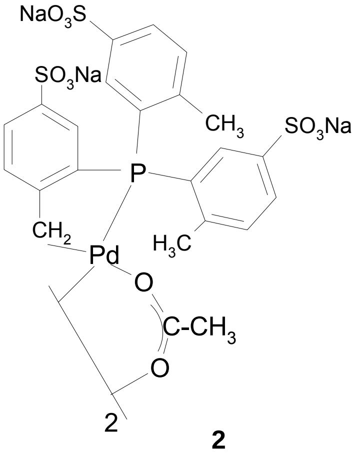
Table 4.4: Elemental analysis of TOTPS complex

Element	Theoretical	Experimental
C	41.32%	39.92%
H	2.97%	2.53%
S	15.76	13.58%

4.3.2.3 Synthesis of Pd complex with TOTPS [Complex 2]:

Complex **2** **(**Figure 4.8) was prepared by using a procedure similar to that reported by Hessler and Stelzer[41].

0.24 mmol (1.0 equivalent, 53.7mg) of $Pd(OAc)_2$ was added under argon to 0.528 mmol (2.2 equivalent, 43.3 mg) of NaOAc and 5.0 ml of degassed distilled water in a round bottom flask, fitted with a reflux condenser. The reaction mixture was stirred for about 20-30 minutes till all $Pd(OAc)_2$ dissolved. 0.24 mmol (1 equivalent, 146.3mg) of ligand **1** was added to the flask under argon.



2

Figure 4.8: Pd(acetate)$_2$-(TOTPS)$_2$ complex

The reaction mixture was then stirred overnight at 50°C. A clear black colour solution of sulfonated Palladacycle catalyst was obtained which was then directly used for the reactions. The ^{31}P-NMR of this solution was found to be different than the ^{31}P-NMR of Ligand **1**, showing coordination of the phosphorous. The ^{31}P-NMR of the Ligand **1** and complex **2** are shown in following section (Section 4.3.2.4)

The complex formed was stable for over a month, as observed from its activity for C-C cross coupling reaction between styrene and iodobenzene, which remained unchanged, during this period.

4.3.2.4 NMR spectra of TOTP, TOTPS and Pd- TOTPS complex

NMR spectra were obtained using a Brucker-MSL-300 and Brucker-DRX-500 machines. ^1H and ^{31}P NMR spectra of TOTP, TOTPS and Pd- TOTPS complex are shown in Figures 4.9 and Figure 4.10 respectively.

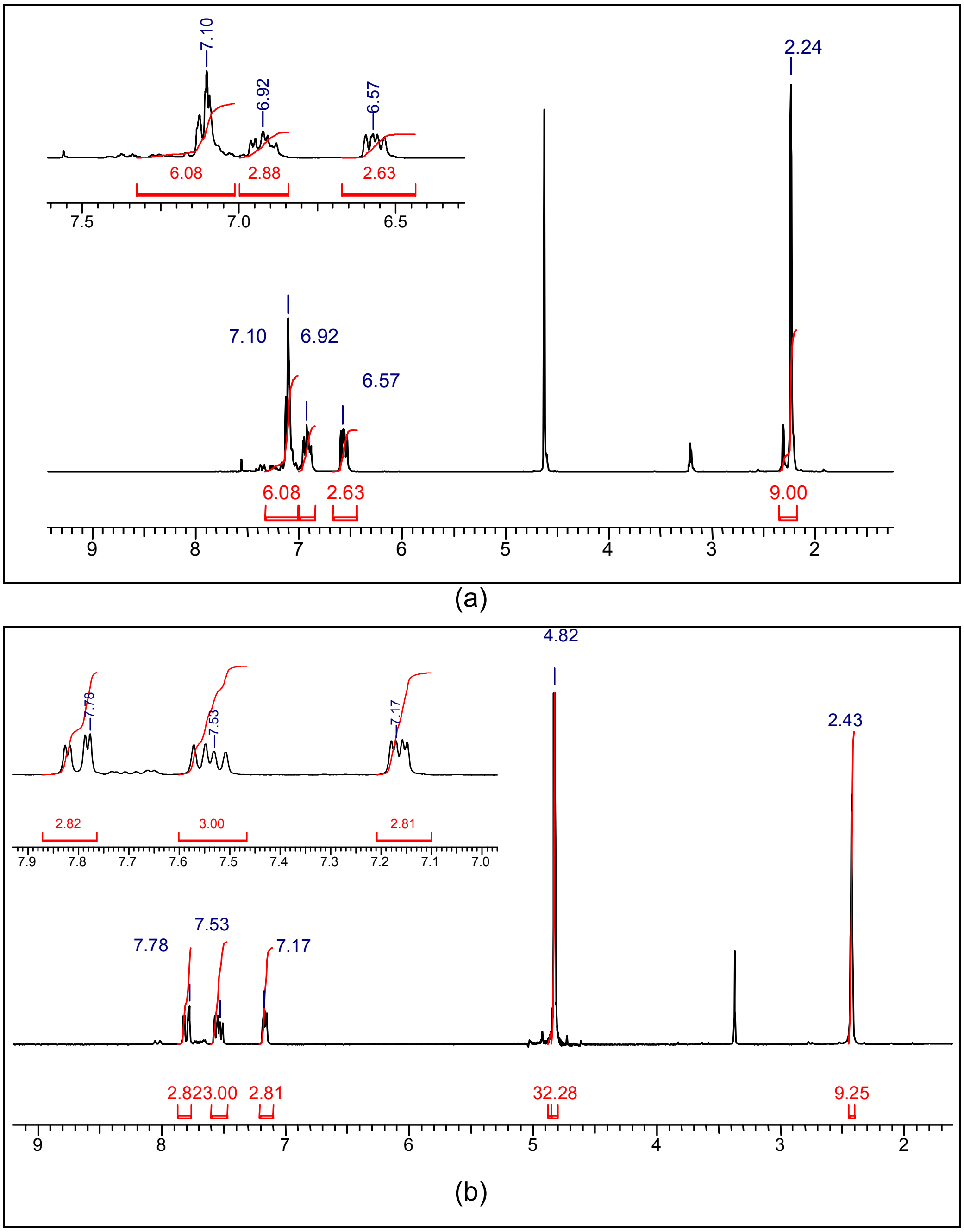


Figure 4.9: ^1H NMR of (a) TOTP

(b) TOTPS

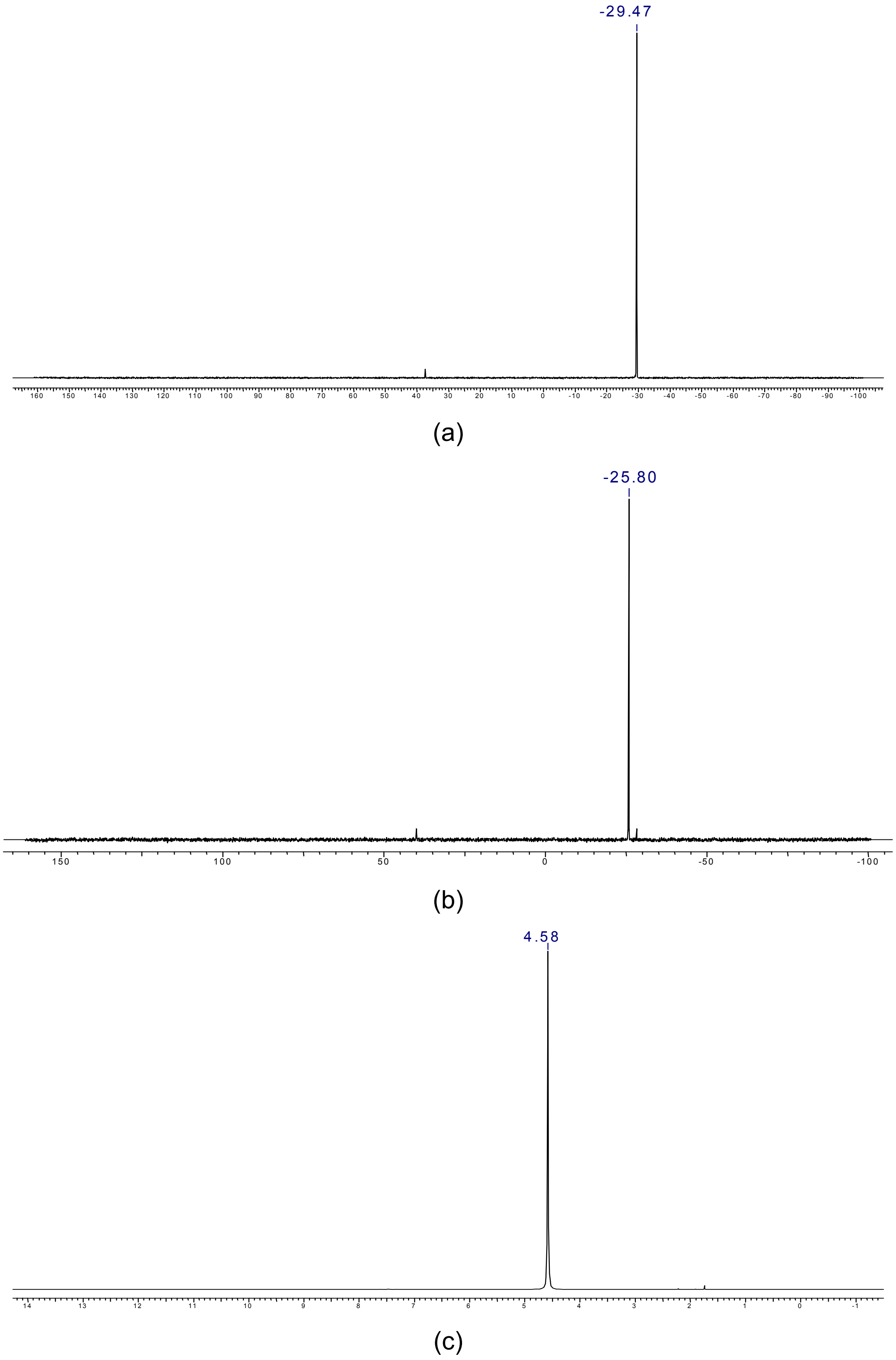


Figure 4.10: ^{31}P NMR of (a) TOTP

(b) TOTPS

(c) Pd-TOTPS

The shift in the δ values (Table 4.5) to the more deshielded region after sulphonation can be observed in the ^1H NMR spectra of TOTP and TOTPS. Even the ^{31}P NMR suggests the formation of sulphonated ligand. This data is also supported by the values observed by Herrmann and coworkers[40] for the sulphonation of TOTP. The Pd-TOTPS also shows the shift in δ values towards downfield after complexation of $Pd(OAc)_2$ with TOTPS, which can be observed by the ^{31}P NMR of the compounds. The ^{31}P NMR signals for TOTP, TOTPS and Pd-TOTPS are -29.47, -25.80, and 4.58 respectively. These NMR data suggest that, the sulphonation of the TOTP ligand has taken place.

Table 4.5: ^1H NMR data of TOTP and TOTPS

Compound	Observed values	Reported values
	δ ppm	δ ppm
TOTP	2.36 (9H) s	2.37 (9H) s
	6.68 (3H) dd	6.71 (3H) dd
	7.05 (3H) dd	7.05 (3H) dd
	7.25 (3H) dd	7.22 (3H) dd
TOTPS	2.43 (9H) s	2.27 (9H) s
	7.17 ((3H) dd	7.17 (3H) dd
	7.53 (3H) dd	7.35 (3H) dd
	7.78 (3H) dd	7.79 (3H) dd

4.3.2.5 General procedure for Heck reaction

Olefin (3.3 mmol) and aryl halide (3.0 mmol) were taken in degassed n- octane (15 ml) in a measuring cylinder. Degassed distilled water (15 ml) along with 0.03 mmol of catalyst, morpholine (10% of aqueous phase inclusive of 3.0 mmol as a base) and 1.0 mmol of NaOAc were taken in another measuring cylinder. Both organic and aqueous layers were mixed together in a mechanically agitated 50 ml autoclave. The reaction was carried out at 150°C with 1450 RPM for 6 hours.

For recycle study, the catalyst phase was separated by simple phase separation and used along with fresh n-octane phase in the above procedure. Fresh base was also added during each recycle along with substrates.

4.3.2.6 Analytical methods

Liquid samples were analyzed on a GC (Agilent 6850 series II), controlled by the HP Chemstation software, on an HP1 column. The analytical methods are the same as that given in Chapter 2 (Section 2.2.2.4). The products were isolated and identified by using GC-MS (Agilent 6890N series equipped with 5973N Mass Selective Detector).

4.3.3 Results and discussion

4.3.3.1 Preliminary reactions

The aqueous biphasic reaction system was standardized using the water soluble catalyst (**Complex 2**) along with n-octane as the organic phase. With this combination of solvents no leaching of the catalyst was observed. However, when toluene was used as a solvent, a significant amount of leaching was observed (~ 5 ppm).

It was observed that preparation of the catalyst in absence of NaOAc led to precipitation of Pd, as the catalyst formed was unstable. The role of NaOAc in the stabilization of the catalyst is well reported[42,43]. Sheldon has suggested that the presence of NaOAc prevents the precipitation of the Pd black. A minimum concentration of 1 mmol was reportedly required for this purpose. The catalyst **2** was prepared with a 1: 2.2 Pd: NaOAc ratio and was stable and did not form metallic Pd. In order to check whether Pd had precipitated in the form of Pd colloidal particles, a UV-Vis spectrum was observed (Figure 4.11). No absorption was seen in the range of 210-230nm, which indicates absence of Pd colloidal particles. This also shows that the reaction occurs due to soluble catalytic complex and not Pd metal.

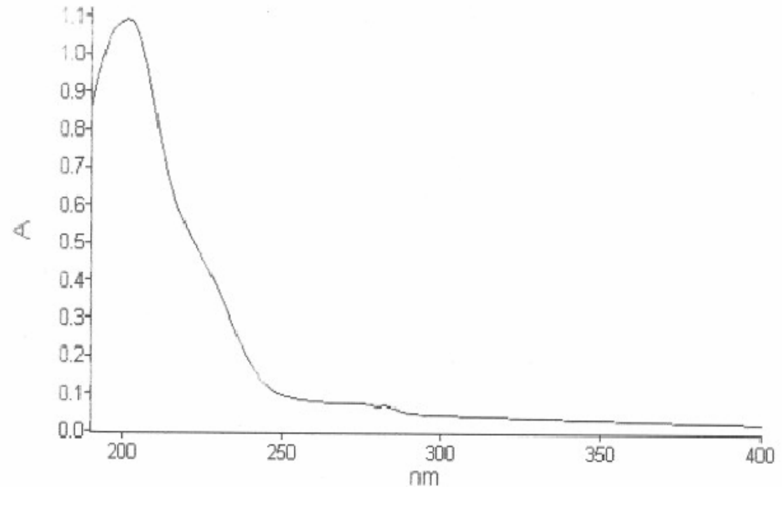


Figure 4.11: UV-Vis spectrum of Complex 2

The reactions were conducted for a period of six hours. For a few experiments intermediate samples were withdrawn, however, under the reaction system employed, a representative sample could not be drawn. In order to ensure that the catalyst had not deactivated a few experiments were conducted under the following conditions for varying time periods (1, 4 and 6 hrs) instead of taking periodic samples.

[Styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed n- octane (15 ml) + degassed distilled water (15ml) along with catalyst (0.03 mmol), cosolvent (morpholine-10% of aqueous phase inclusive of 3.0 mmol as a base) and a stabilizer (NaOAc-1.0 mmol); 150°C; 1450 RPM.]

The results in Table 4.6 and Figure 4.12 show that there is a constant increase in the formation of stilbene and iodobenzene consumption with time. These results confirmed that the catalyst remains active throughout the period. Hence for all the reactions a fixed period of six hours was taken and no intermediate samples were withdrawn. The turn over number (TON) were calculated at the end of 6 hrs reaction (unless otherwise specified)

For the preliminary experiments the consumption of the iodobenzene and styrene and the formation of stilbene were monitored. It was observed that the stilbene formation was commensurate with the reactants consumed. Also under the reaction conditions only Heck coupling products were formed. Hence for all reactions the activity was calculated based on the conversion of ArX during the reaction period (6 hrs).

Table 4.6: Progress of Heck reaction with time using Pd-TOTPS catalyst in the aqueous biphasic system

Sr. No.	Time (hr)	%Conversion of iodobenzene	TON
1	1	21	191
2	4	47	435
3	6	60	555

Reaction conditions: styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed n-octane (15 ml) + degassed distilled water (15 ml) along with catalyst (0.03 mmol) and cosolvent (morpholine- 10% of aqueous phase inclusive of 3.0 mmol as a base) and a stabilizer (NaOAc-1.0 mmol) ; 150°C ; 1450 RPM. For given time. Selectivity of stilbene > 99%.

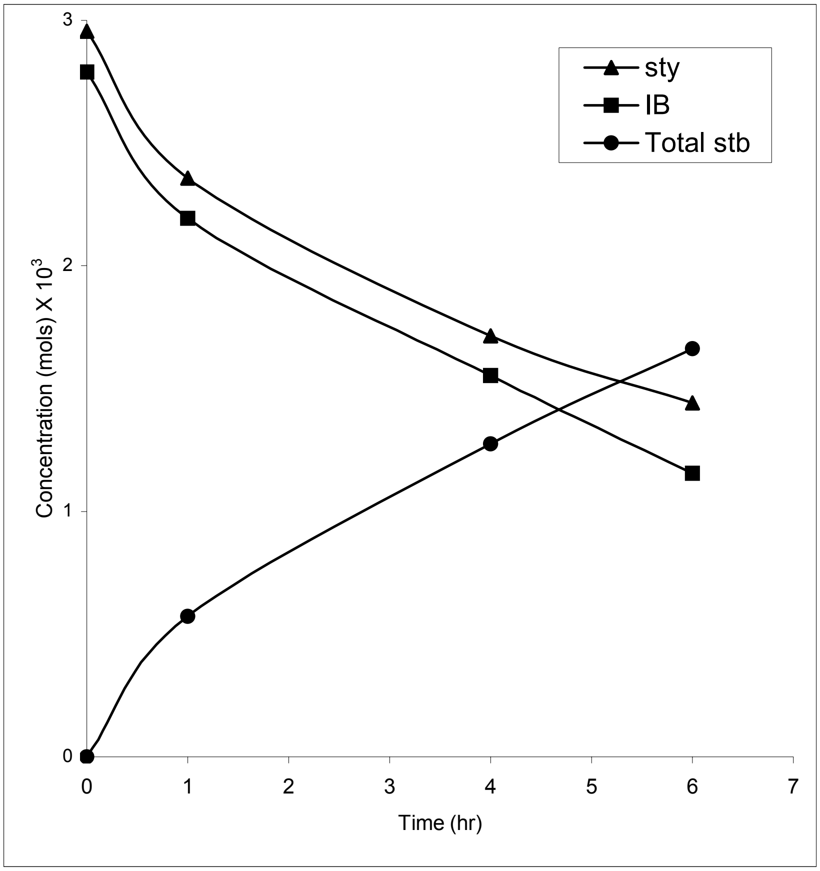


Figure 4.12: Typical concentration v/s time profile for aqueous biphasic reaction Reaction conditions: styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed n-octane (15 ml) + degassed distilled water (15 ml) along with catalyst (0.03 mmol), cosolvent (morpholine- 10% of aqueous phase inclusive of 3.0 mmol as a base) and a stabilizer (NaOAc-1.0 mmol); 150°C ; 1450 RPM. For given time.

4.3.3.2 Role of cosolvent

A typical problem of aqueous phase catalysis is the poor solubility of the substrates, viz styrene and stilbene in the aqueous phase. Initially the reaction was conducted in the simple biphasic medium using NaOAc as the base. NaOAc was already present in the catalyst phase as a stabilizing agent. In this case after 6 hours reaction, there was practically no reaction. Since application of co-solvents to enhance the activity is well known in aqueous biphasic hydroformylation reaction[44], a similar strategy was employed for improving the rates of reaction for Heck coupling reactions.

For this study co-solvents like morpholine, NMP and 1,4 dioxane (at a 10% v/v aqueous phase concentration) were used in presence of NaOAc (already present as a stabilizer).

60% conversion of iodobenzene was observed, when morpholine was used as a cosolvent.

Although the solubility of the substrates is enhanced in presence of NMP / 1,4 dioxane cosolvent, no reaction was observed. This is probably due to the inability of NaOAc to function as a base in aqueous conditions.

Since morpholine was also capable of functioning as a base and cosolvent, an experiment was conducted with only stoichiometric equivalent morpholine (as base) in the reaction medium along with the NaOAc (Pd: NaOAc 1: 2.2). A 20% conversion of iodobenzene was observed after 6 hours. This experiment confirmed that the morpholine could have a dual function in aqueous biphasic Heck reactions. Analysis of morpholine in the reaction system showed a conversion of morpholine equivalent to the consumption of the aryl halide.

The feasibility of using NMP / 1,4 dioxane as a cosolvent was studied in presence of morpholine as a base but in absence of NaOAc. In both these cases Pd metal precipitated.

The above diagnostic experiments confirmed that

(i) NaOAc was essential to ensure the stability of the Pd complex, and prevent precipitation. The role of NaOAc was not as a base.

(ii) Morpholine was functioning both as a base and cosolvent.

(iii) Enhancement in the rate was substantial with morpholine as a cosolvent.

From these results the final composition of the aqueous biphasic system was chosen as follows.

Aqueous phase : water + NaOAc + catalyst
Organic phase : n-octane + ArX + olefin
Cosolvent : morpholine
Base : morpholine

Further, detailed studies on the role of morpholine as a cosolvent were conducted. The reactions were taken with varying amounts of morpholine and the conversion of iodobenzene was monitored. The results are presented in Table 4.7 and Figure 4.13.

Table 4.7: Heck reaction of olefin with iodobenzene in aqueous biphasic medium using various concentrations cosolvent

Sr. No.	% Morpholine (w.r.t. aqueous phase)			%Conversion of Iodobenzene	TON	TOF (hr^{-1})
	Total	as base	as cosolvent			
1	0	0	0	0	0	0
2	2	2	0	20	215	36
3	6	2	4	39	354	59
4	10	2	8	60	555	92
5	14	2	12	80	694	116
6	18	2	16	87	738	123

Reaction conditions : styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed n-octane (15 ml) + degassed distilled water (15 ml) along with catalyst (0.03 mmol), morpholine (cosolvent and base) and a 1.0 mmol of NaOAc as a stabilizer; 150°C; 1450 RPM. (Time: 6hrs). Selectivity of stilbene > 99%.

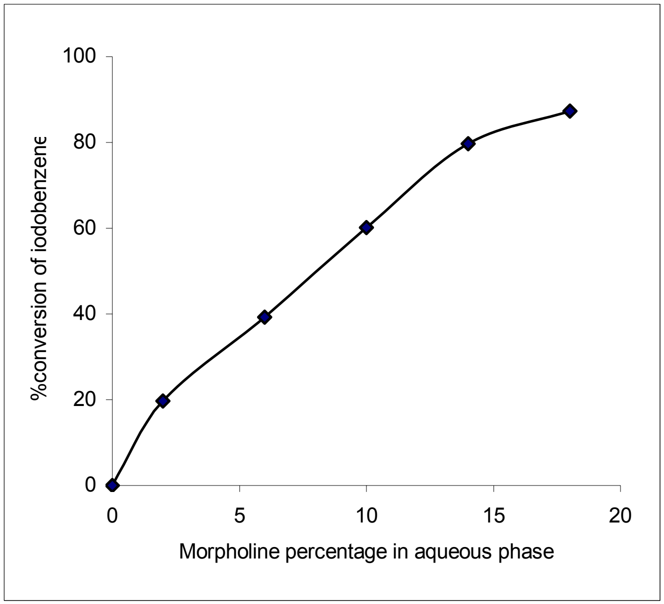


Figure 4.13: %Conversion of iodobenzene v/s morpholine percentage in aqueous phase Reaction conditions : styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed n-octane (15 ml) + degassed distilled water (15ml) along with catalyst (0.03 mmol), morpholine (cosolvent and base) and a 1.0 mmol of NaOAc as a stabilizer; 150°C; 1450 RPM. (Time:6hrs). Selectivity of stilbene > 99%.

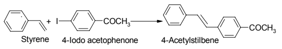
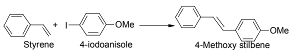
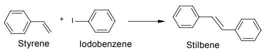
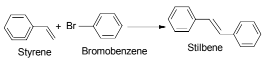
As seen from Table 4.7, as the percentage of morpholine as a cosolvent in the aqueous phase increases, the rate of reaction increases. Since morpholine in this case acts as a base as well as a cosolvent, the concentration of morpholine was varied in such a way that a minimum of 2% morpholine concentration (which corresponds to the mole equivalent of the substrates) is present as a base for all reactions and the remaining as a cosolvent. No reaction was observed in absence of morpholine, which is due to the absence of any base.

As seen in Figure 4.13, up to 14% loading of the morpholine cosolvent in the aqueous phase, a linear dependence was observed, beyond which no major rate enhancement was seen. Thus for all further screening studies 10% morpholine as a cosolvent + base was utilized. Under these conditions analysis of the organic phase showed no leaching and recycle of the organic phase also showed no activity, indicating that the reaction was a true aqueous phase reaction.

4.3.3.3 Screening of aryl halide

The catalyst was assessed for its activity for the Heck reaction of various aryl halides and the results are given in the Table 4.8. In all the cases the products were analyzed on GC and identification and confirmation of the product was done by using GC-MS. (GC-MS data of the products are presented in Appendix –I).

Table 4.8: Heck reaction of aryl halides with styrene in aqueous biphasic medium

Sr. No.	Aryl halide	Reaction	%Conversion of ArX	TON
1	4-Iodoacetophenone		100	875
2	p-Iodoanisole		72	663
3	Iodobenzene		60	555
4	Bromobenzene		2	5

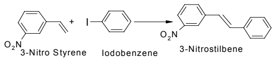
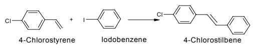
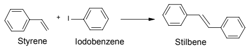
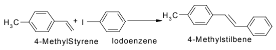
Reaction conditions: styrene (3.3 mmol), ArX (3.0 mmol) taken in degassed n- octane (15 ml) + degassed distilled water (15ml) along with catalyst (0.03 mmol) and cosolvent (morpholine- 10% of aqueous phase inclusive of 3.0 mmol as a base) and a stabilizer (NaOAc-1.0 mmol); 150^{o}C; 1450 RPM. (Time: 6hrs) Selectivity of product > 99%.

It was seen from Table 4.8 that the 4-iodoacetophenone gives faster rates than 4-iodoanisole and iodobenzene proving that the halides with substituents having a more –I effect i.e. a strong electron withdrawing character, show high activity towards the vinylation. (It is well known that electron-withdrawing substituents on the aryl halide enhance the rate of oxidative addition of the substrate to the Pd atom[31]). Bromobenzene gave very poor activity due to the inherent low reactivity of the bromo-substrate under the reaction conditions.

4.3.3.4 Screening of olefins

The activity of Pd-TOTPS complex catalyst was assessed for the Heck vinylation of iodobenzene in aqueous biphasic reaction. Various olefins were screened for their activity. The results are presented in Table 4.9. The confirmation of the product formed was done by using GC-MS.

Table 4.9: Heck reaction of olefin with iodobenzene in aqueous biphasic medium

Sr. No.	Olefin	Reaction	% Conversion of ArX	TON
1	3-Nitro styrene		86	1008
2	4-chloro styrene		68	737
3	Styrene		60	555
4	4-methyl styrene		53	544

Reaction conditions: olefin (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed n-octane (15 ml) + degassed distilled water (15ml) along with catalyst (0.03 mmol) and cosolvent (morpholine- 10% of aqueous phase inclusive of 3.0 mmol as a base) and a stabilizer (NaOAc-1.0 mmol); 150°C; 1450 RPM. (Time: 6hrs). Selectivity of product > 99%.

Among olefins, 3-nitrostyrene was seen to be more reactive than 4-chlorostyrene, styrene and 4-methyl styrene. This was a surprising behavior, as generally presence of electron withdrawing groups attached to the aromatic ring reduces the activity of the aryl halide compared to electron donating groups. This observation could be due to the variation in solubility for the biphasic reaction. The reactivity of acrylates could not be assessed, as the acrylates were found to react with morpholine and form an addition product as a result of which the Heck coupling reaction could not occur. The formation of the addition product was confirmed by GC-MS [Appendix-I (16)].

4.3.3.5 Recycle study for the activity of Pd- TOTPS catalyst in aqueous biphasic medium

The primary objective of developing an aqueous phase catalyst for the Heck reaction was to facilitate catalyst recycle and recovery. The Pd-TOTPS catalyst was recycled for two times and the results are shown in Figure 4.14. The catalyst gave consistent activity on recycle, with good conversion of iodobenzene and with appreciable TON values. No leaching of the catalyst to the organic phase was observed during the recycle study as confirmed by Pd analysis of organic phase.

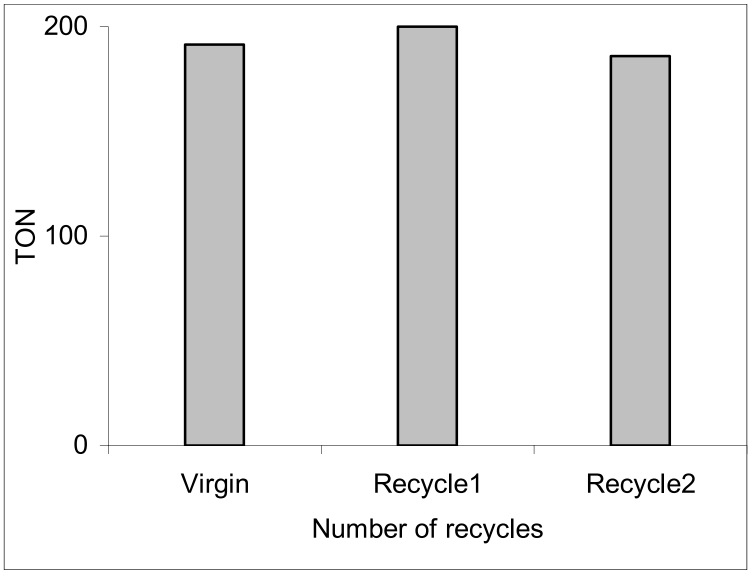


Figure 4.14: Activity of Pd-TOTPS catalyst on recycle of aqueous phase in an aqueous-organic biphasic medium for Heck reaction of styrene with iodobenzene.

Reaction conditions: styrene (3.3 mmol), iodobenzene (3.0 mmol) taken in degassed n-octane (15 ml) + degassed distilled water (15 ml) along with catalyst (0.03 mmol or recycled) and cosolvent (morpholine- 10% of aqueous phase inclusive of 3.0 mmol as a base) and a stabilizer (NaOAc-1.0 mmol); 150^{o}C; 1450 RPM. (Time: 1hr). Selectivity of stilbene > 99%.

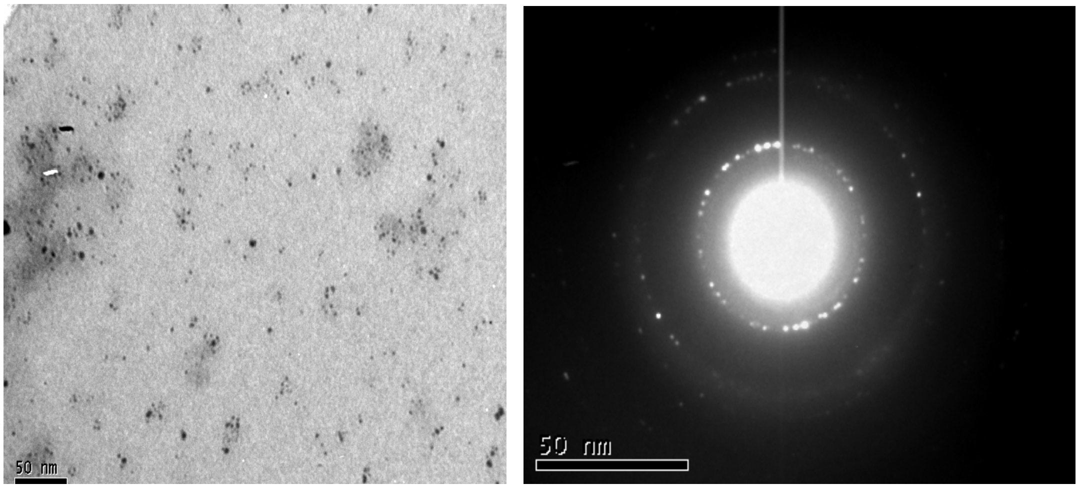
There are reports, which indicate that the Heck reaction is catalyzed by Pd complex in homogeneous state and also by Pd metal[45]. In systems where water is a component in the solvent (either homogeneous or biphasic), one of the major issues reported has been the precipitation of the Pd metal[36]. Since the Pd-TOTPS catalyst system was observed to be stable and recyclable under reaction conditions, it was of interest to confirm the homogeneous nature of the complex.

A UV spectrograph of the aqueous solution of catalyst is shown in Figure 4.11. It can be seen that there is no peak in the range of 210-230nm, which is characteristic of Pd nanoparticles. However a slight shoulder is observed at 230 nm. This could be due to a small concentration of Pd nanoparticles.

A TEM Study of the catalyst was done before and after the reaction as shown in Figure 4.15 and 4.16 respectively.

The TEM of the catalyst solution, before reaction, shows presence of widely scattered Pd particles, in low concentration. After reaction, the TEM shows absence of any Pd particles, which suggests that the reaction is indeed catalyzed by homogeneous aqueous phase soluble complex. The Pd nanoparticles although very small in number - redissolve under reaction conditions. Such a phenomenon has been reported earlier[45].

The above studies suggest that the Pd-TOTPS complex catalyst is stable in water, but very slowly it can form Pd nanoparticles. A TEM of the catalyst solution after a period of one month showed a similar TEM micrograph with particle size of ~10 nm. The UV spectrum also did not show any absorption in the region 210 – 230 nm except a similar shoulder with weak intensity.



(a) Nanoparticles of Pd-TOTPS complex (b) Diffraction pattern

Figure 4.15: TEM of catalyst before reaction

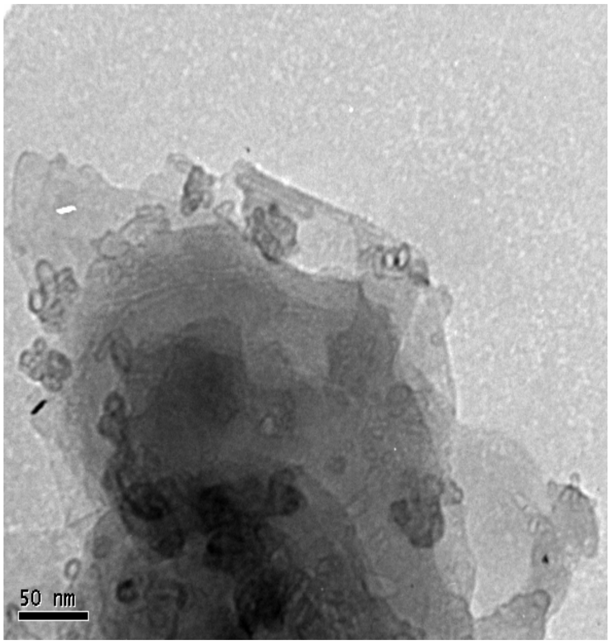


Figure 4.16: TEM of catalyst after reaction

4.3.4 Conclusions

Pd-TOTPS complex catalyst has been synthesized and is stable in aqueous medium. This catalyst is found to be active for the Heck reaction, in presence of morpholine cosolvent. The reaction conditions have been standardized in such a way that there was no leaching to the organic phase. The catalyst is stable in water and could be recycled for two times with no loss in the activity. The role of cosolvent concentration, olefins and aryl halides has been elucidated in the aqueous biphasic system. A slight degradation of the complex to Pd metal nanoparticles has been observed, however, TEM analysis shows that the reaction is catalyzed by a homogeneous aqueous phase catalyst. This is one of the few studies so far, wherein aqueous biphasic catalyst has been demonstrated for Heck reaction.

References

(1) Kuntz, E. G. Chemtech **1987**, 17, 570.

(2) Parshall, G. W. Homogeneous Catalysis; Wiley Interscience: New York, 1980.

(3) Bhanage, B. M.; Arai, M. Catalysis Reviews **2001**, 43, 315- 344.

(4) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. Angew. Chem. Int. Ed. Engl. **1995**, 34, 1844.

(5) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Ofele, K.; Beller, M. Chem. Eur. J. **1997**, 3, 1357.

(6) Beller, M.; Krauter, J. G. E.; Zapf, A. Angew. Chem. Int. Ed. Engl. **1997**, 36, 772-774.

(7) Bhanage, B. M.; Zhao, F. G.; Shirai, M.; Arai, M. Tetrahedron Letters **1998**, 39, 9509-9512

(8) Thorpe, T.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. Tetrahedron Letters **2000**, 41, 4503-4505.

(9) DeVasher, R. B.; Moore, L. R.; Shaughnessy, K. H. J. Org. Chem. **2004**, 69, 7919-7927.

(10) Bradley, D.; Williams, G.; Lombard, H.; Holzapfel, C. W. Synthetic Communications **2001**, 31, 2077-2081.

(11) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. Journal of Organometallic Chemistry **1989**, 371, 397-401.

(12) Casalnuovo, A. C.; Calabrese, J. C. J. Am. Chem. Soc. **1990**, 112, 4324.

(13) Genet, J. P.; Blart, E.; Savignac, M. Synlett. **1992**, 715.

(14) Genet, J. P.; Savignac, M. J. Organomet. Chem. **1999**, 576, 305.

(15) Jeffery, T. Tetrahedron Lett. **1994**, 35, 3051.

(16) Arrad, O.; Sasson, Y. J. Am. Chem. Soc. **1988**, 110, 185-189.

(17) Dehmlow, E. V.; Dehmlow, S. S. Phase Transfer Catalysis, 3rd ed.; VCH: Weinheim, New York, 1993.

(18) Eisenstadt, A. F. E. Herkes Ed., Catalysis of Organic Reactions, p. 415; Marcel Dekker: New York, 1998.

(19) Beletskaya, I. P.; Cheprakov, A. V. Chem. Rev. **2000**, 100, 3009-3066.

(20) Herrmann, W. A.; Kohlpaintner, C. W. Angew. Chem. Int. Ed. Engl. **1993**, 32, 1524.

(21) Translated from de:Wacker-Verfahren

(22) Zhang, H. C.; Daves, G. D. Organometallics **1993**, 12, 1499.

(23) Garbe, D.; Gerhartz, W.; Yamamoto, J. S.; Campbell, I. T.; Pfefferkorn, R.; Rounsville, J. F. (Eds.) Ullmann's Encyclopaedia of Industrial Chemistry, vol. A7,

pp. 99; VCH: Weinheim, 1992.

(24) Adisakwattana, S.; Sookkongwaree, K.; Roengsumran, S.; Petsom, A.; Ngamrojnavanich, N.; Chavasiri, W.; Deesamer, S.; Yibchok-anun, S. Bioorg Med Chem Lett. **2004**, 14, 2893-6.

(25) Natella, F.; Nardini, M.; Felice, M. D.; Scaccini, C. J. Agric. Food Chem. **1999**, 47, 1453̃-1459.

(26) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. Carbonylation: Direct Synthesis of Carbonyl Compounds; Plenum: New York, 1991.

(27) Escaffre, P.; Thores, A.; Kalck, P. J.Mol. Catal. **1985**, 33, 70.

(28) Komiya, S. -ED. Synthesis of organometallic compounds- A practical Guide , 1997.

(29) McCormick, B. J.; JaynesJr., E. N.; Kaplan, R. I. Inorg. Synth. **1972**, 13, 216.

(30) Herrmann, W. A.; Bohm, V. P. W.; Reisinger, C.-P. J. Organomet. Chem. **1999**, 576, 23-41.

(31) Consorti, C. S.; Zanini, M. L.; Leal, S.; Ebeling, G.; Dupont, J. Organic Letters **2003**, 5, 983-986.

(32) Beletskaya, I. P.; Cheprakov, A. V. Journal of Organometallic Chemistry **2004**, 689, 4055-4082.

(33) Herrmann, W. A.; O¨fele, K.; Preysing, D. v.; Schneider, S. K. Journal of Organometallic Chemistry **2003**, 687, 229-248.

(34) Bumagin, N. A.; Andryuchova, N. P.; Beletskaya, I. P. Izv. Akad. Nauk SSSR, Ser. Khim. **1988**, 6, 1449-50.

(35) Eymery, F.; Burattin, P.; Mathey, F.; Savignac, P. Eur.J.Org. Chem. **2000**, 2425-2431.

(36) Kiji, J.; Okano, T.; Hasegawa, T. Journal of Molecular Catalysis A: Chemical **1995**, 97, 73-77

(37) Moore, L. R.; Shaughnessy, K. H. Organic Letters **2004**, Vol. 6, 225-228.

(38) Bhanage, B. M.; Divekar, S. S.; Deshpande, R. M.; Chaudhari, R. V. Org. Proc. Res.Dev. **2000**4, 342-345.

(39) Gulyas, H.; Szollosy, r.; Hansonc, B. E.; Bakosd, J. Tetrahedron Letters **2002**, 43, 2543-2546.

(40) Herrmann, W. A.; Albanese, G. P.; Manetsberger, R. B.; Lappe, P.; Bahrmann, H. Angew. Chmi. Int Ed. Engl. **1995**, 34, 811-813.

(41) Hessler, A.; Stelzer, O. J. Org. Chem. **1997**, 62, 2362-2369

(42) Brink, G.-J. t.; Arends, I. W. C. E.; Papadogianakis, G.; Sheldon, R. A. Chem. Commun. **1998**, 2359-2360.

(43) Brink, G.-J. t.; Arends, I. W. C. E.; Sheldon, R. A. Science **2000**, Vol. 287, 1636 - 1639.

(44) Deshpande, R. M.; Purwanto;; Delmas, H.; Chaudhari, R. V. IndECR **1996**, 35, 3927.

(45) Consorti, C. S.; Flores, F. R.; Dupont, J. Journal of the American Chemical Society **2005**, 127, 12054-12065.

Future scope of the Heck reaction in biphasic media

The major focus of the future industrial processes will be on developing new catalytic systems that will be energy saving, environment friendly and allow optimal use of raw materials. There are still some hurdles to be overcome before a broader application of Heck reaction can be realized, especially on an industrial scale. Hence, further challenges are seen in the improvement of the catalysts in terms of their performance (especially lifetimes) in biphasic medium for the Heck reaction. Regarding the commercialization of the Heck reaction, the expensive Iodo and bromo starting compounds will govern the process economy – another reason to improve the efficiency of Heck coupling reactions of chloroaromatics.

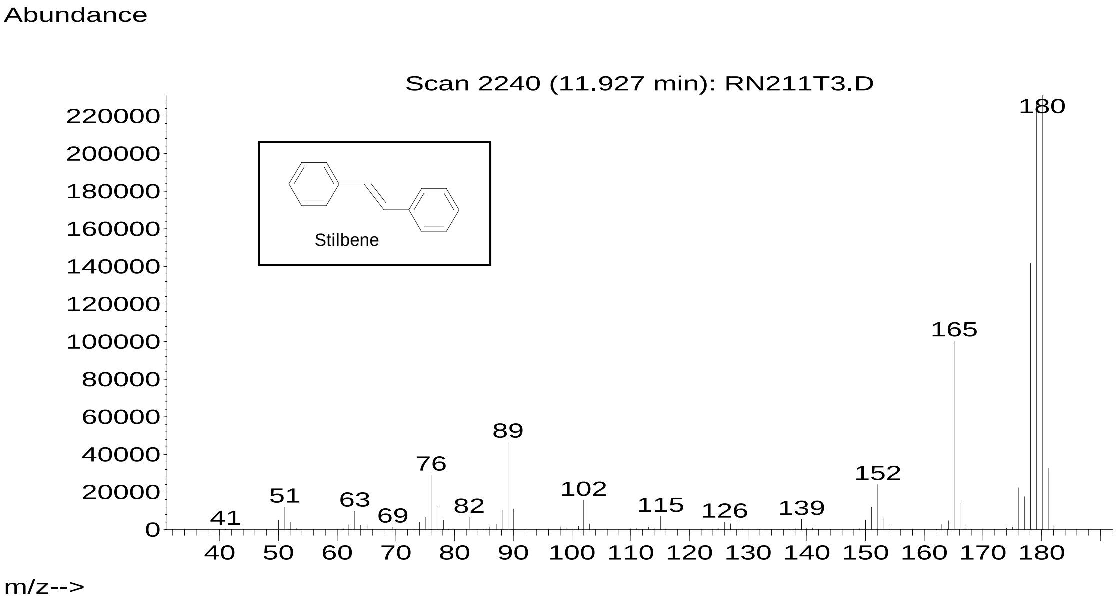
Biphasic systems have proved to be one of the most convenient method for most of the reaction processes, provided proper choice of the catalyst, ligand and solvent etc are maintained.

In the present thesis, the Heck reaction in biphasic medium has mainly been discussed. $PdCl_2$(bipy) catalyst was found to work efficiently in the biphasic medium, however the reaction system can further be modified for commercial purpose. The comparison of the kinetics in homogeneous and in biphasic system can definitely be useful for the future developments in Heck reaction on large scale.

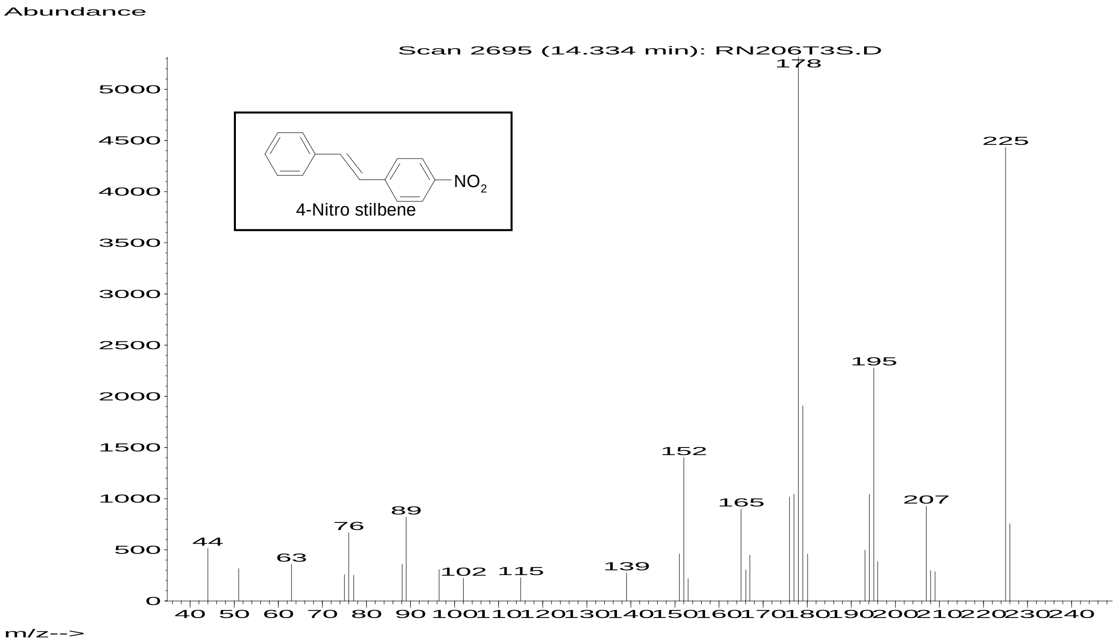
Ligand TOTPS also has proved its efficiency in biphasic system, especially with water as one of the phase. The feasibility of the Palladium complex of TOTPS has been demonstrated in this thesis for the Heck reaction in aqueous biphasic system. Further modifications of this ligand such as heterogenisation, ossification etc can improve its performance. The aqueous biphasic system can also be further tailored for application to synthesis of industrially important products.

APPENDIX-I

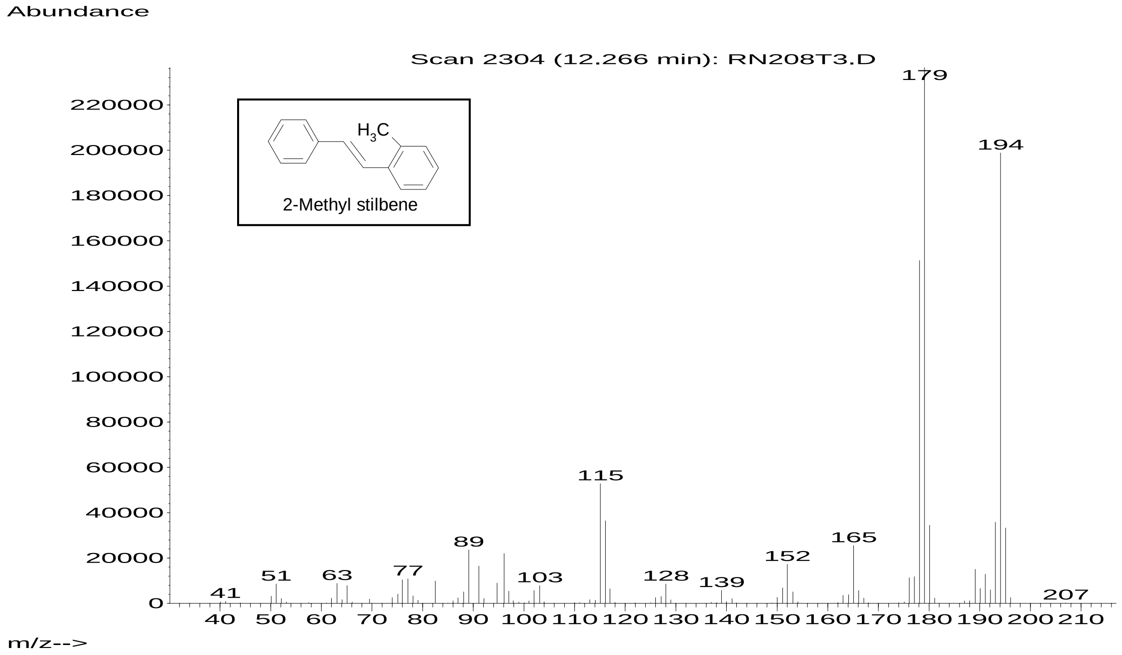
Confirmation of the product formed by Heck reaction by GCMS



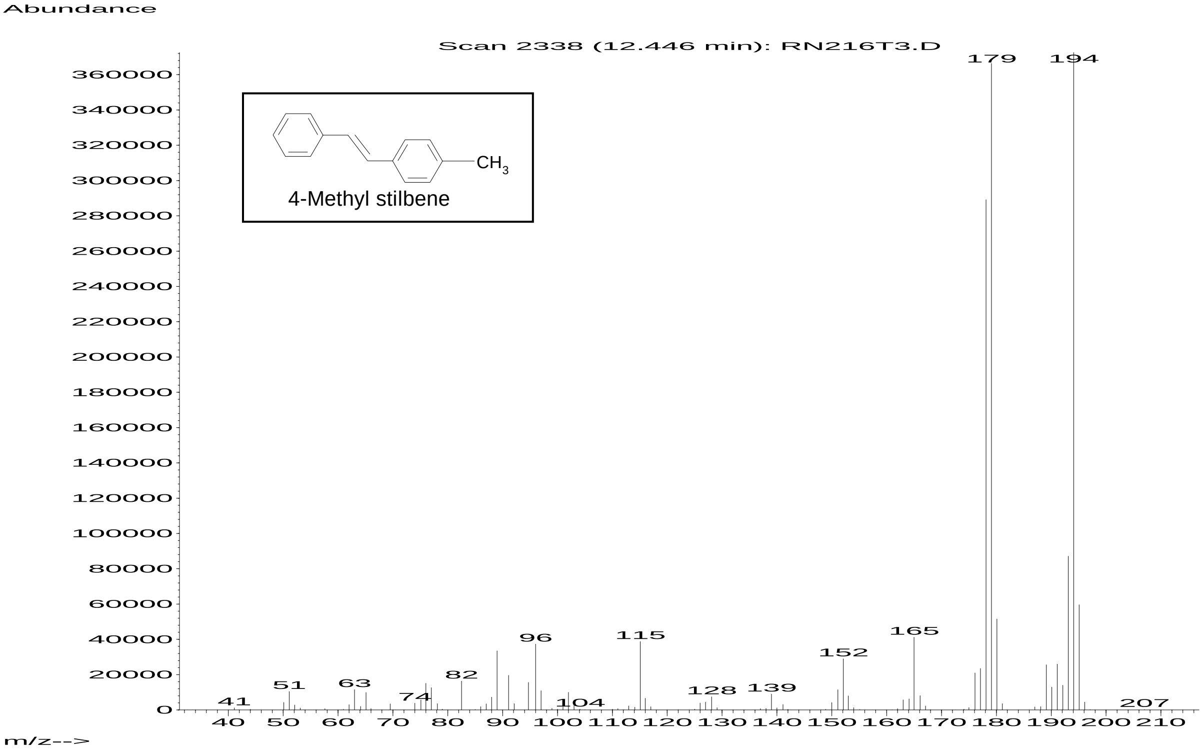
(1) Stilbene



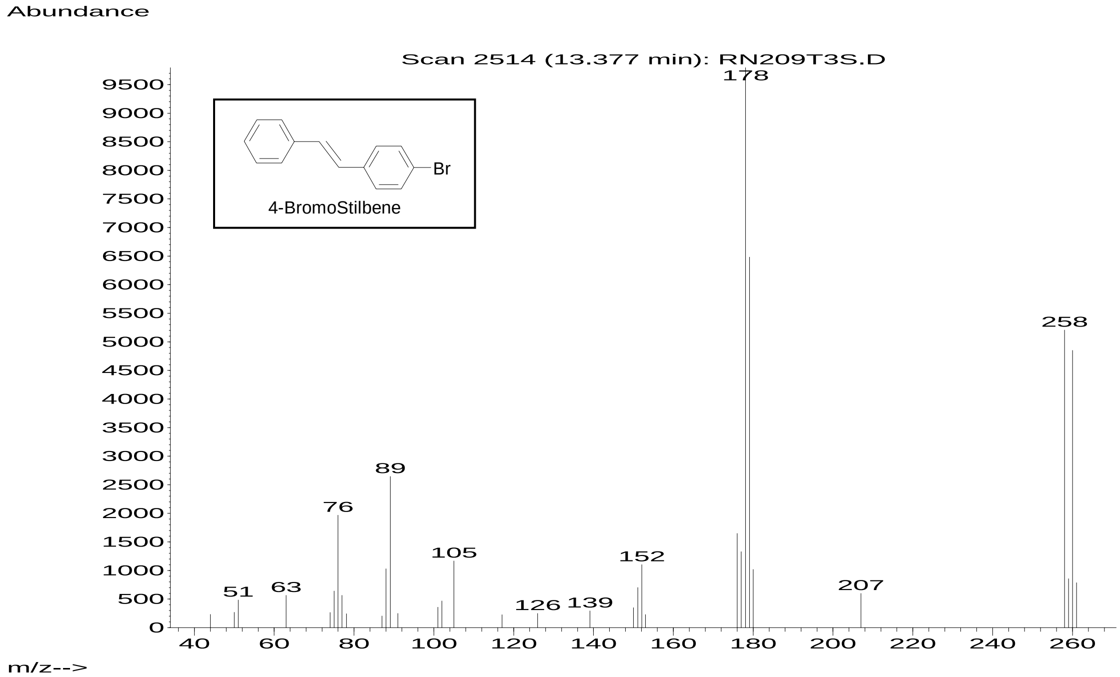
(2) 4-Nitro stilbene



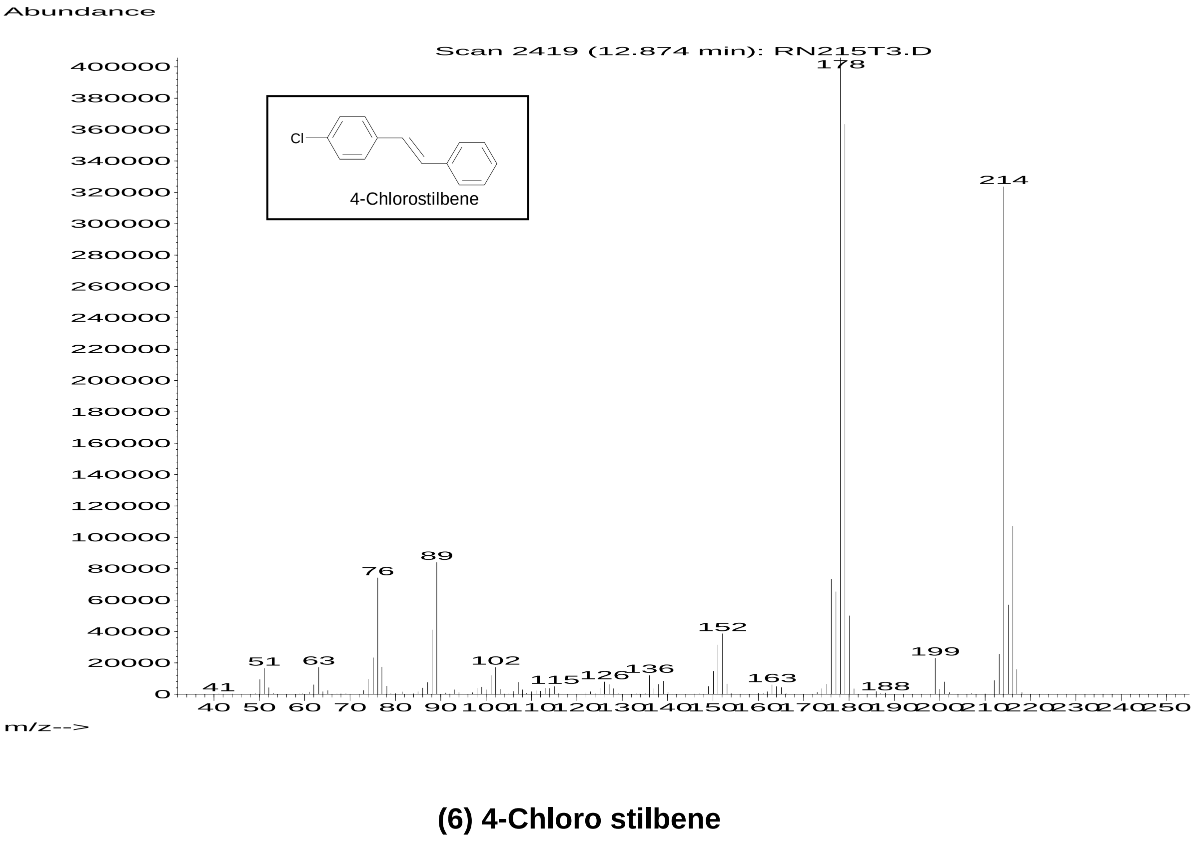
(3) 2-Methyl stilbene



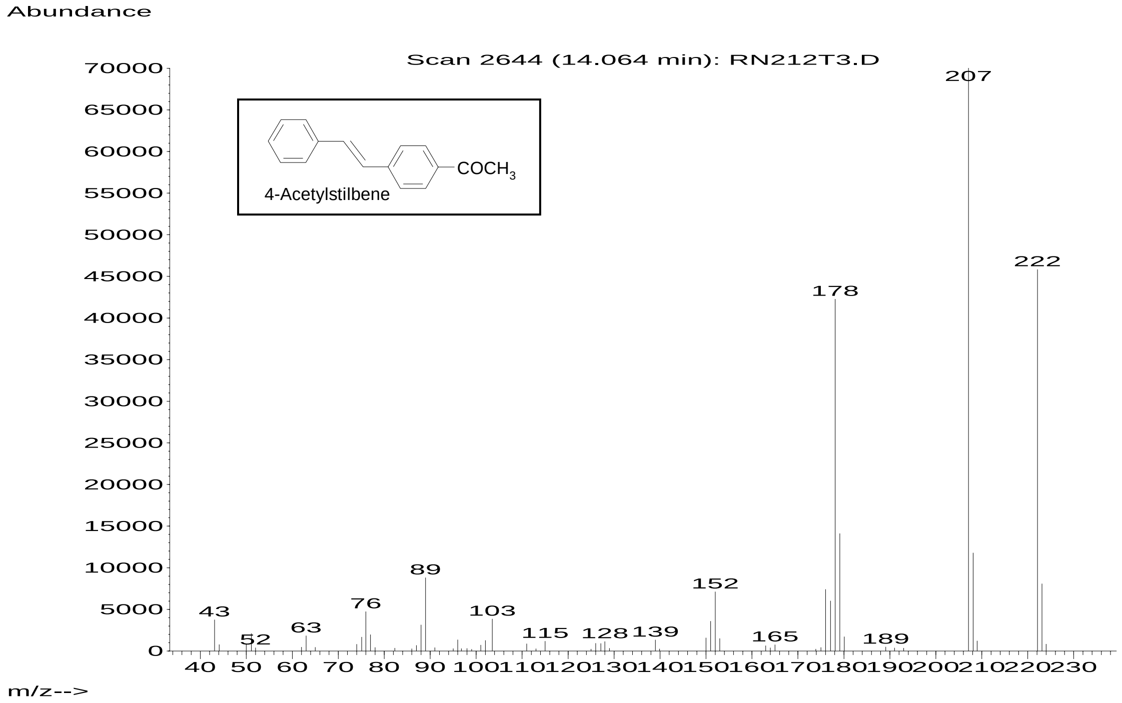
(4) 4-Methyl stilbene



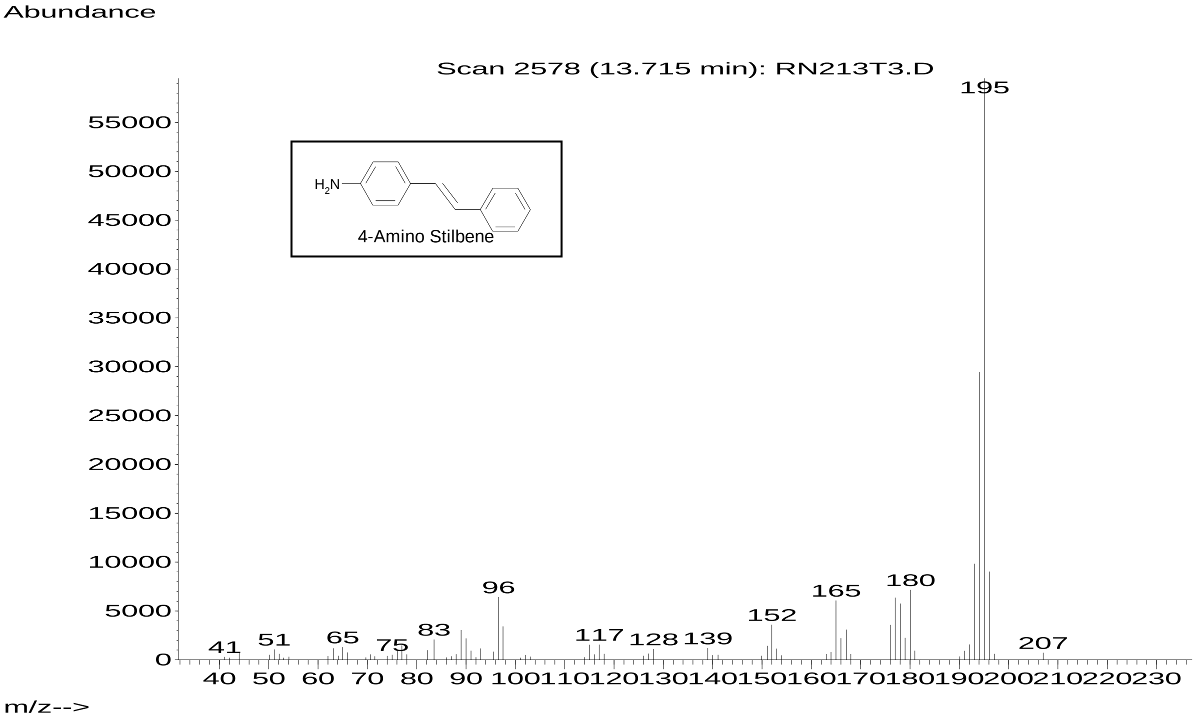
(5) 4-Bromo stilbene



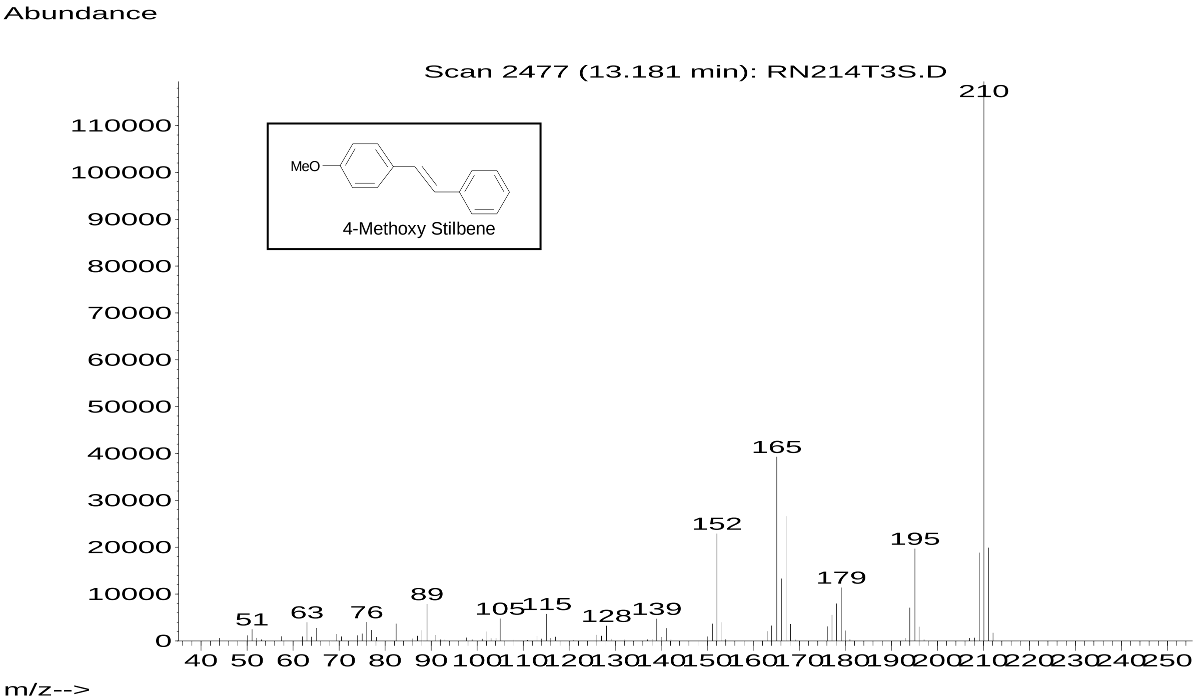
(6) 4-Chloro stilbene



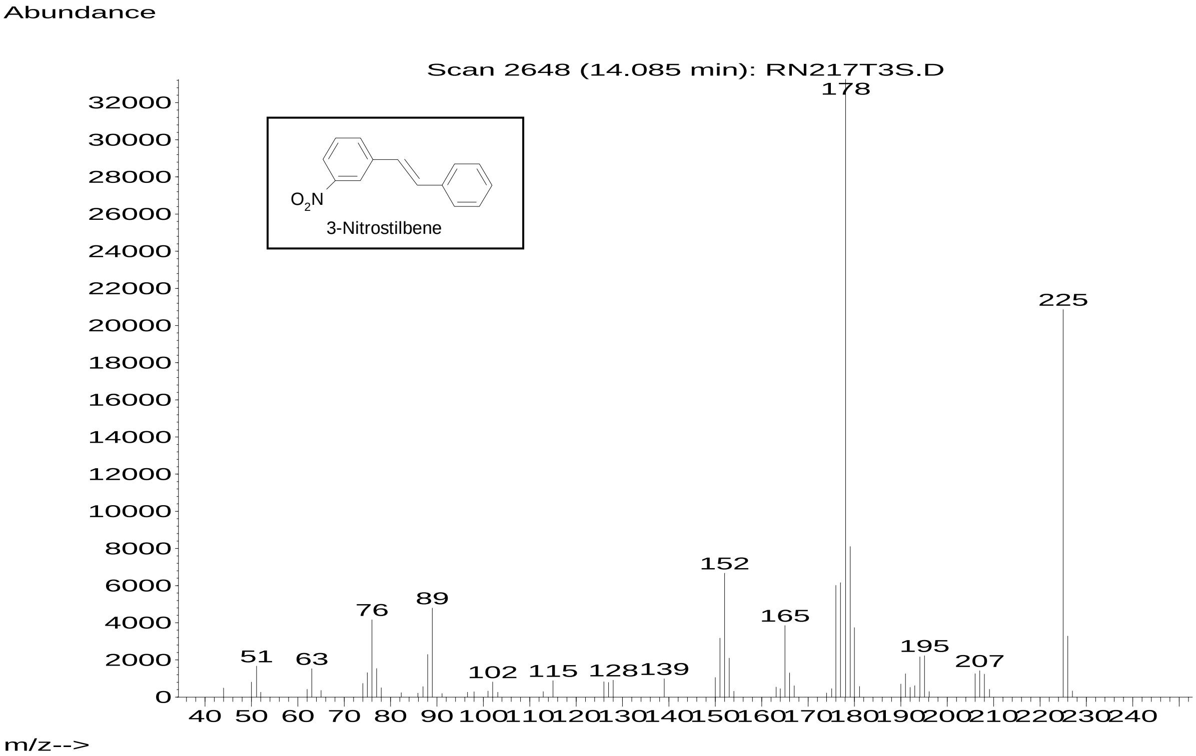
(7) 4-Acetyl stilbene



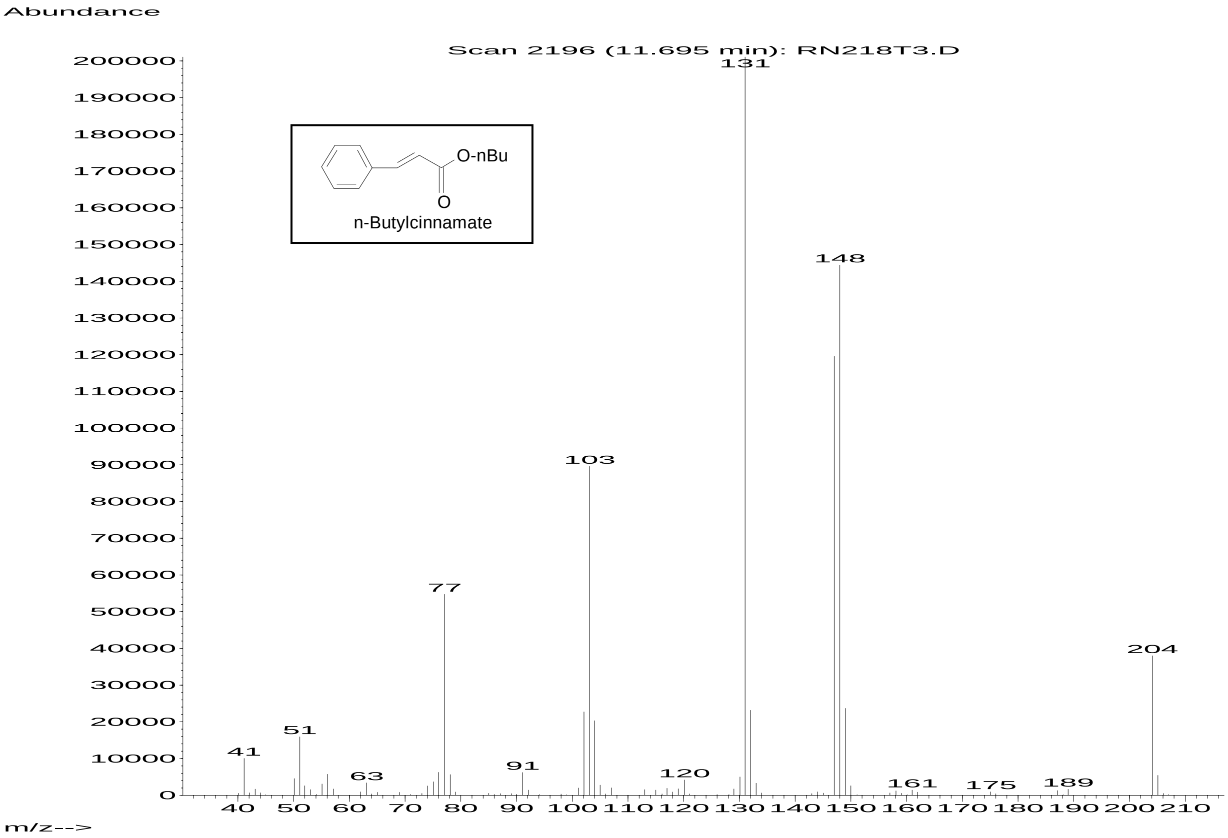
(8) 4-Amino stilbene



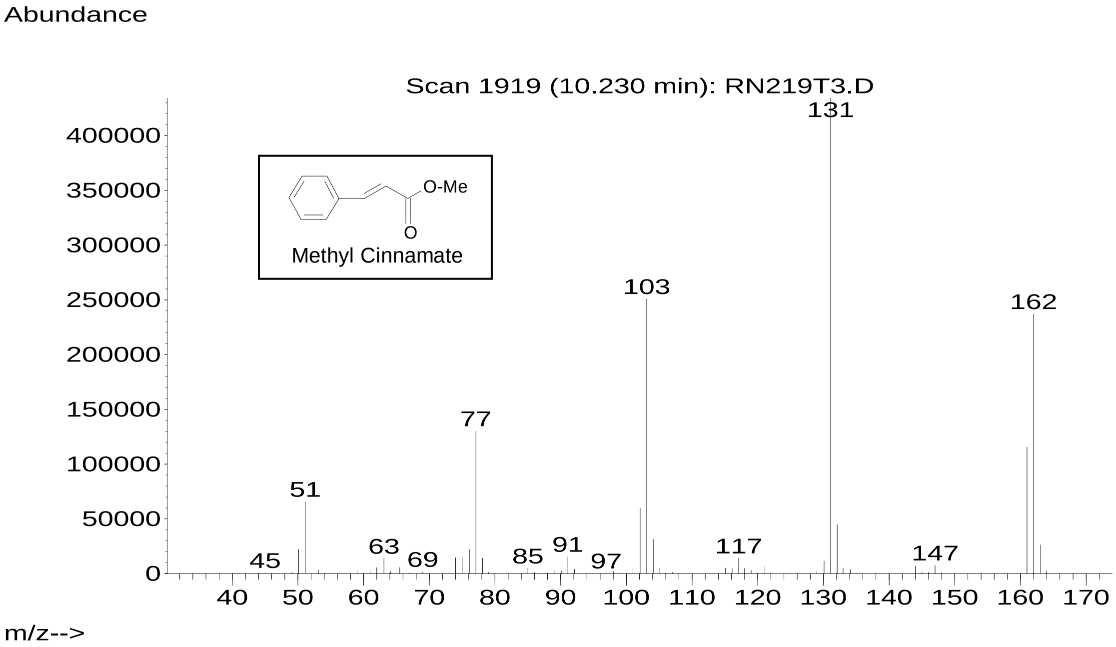
(9) 4-Methoxy stilbene



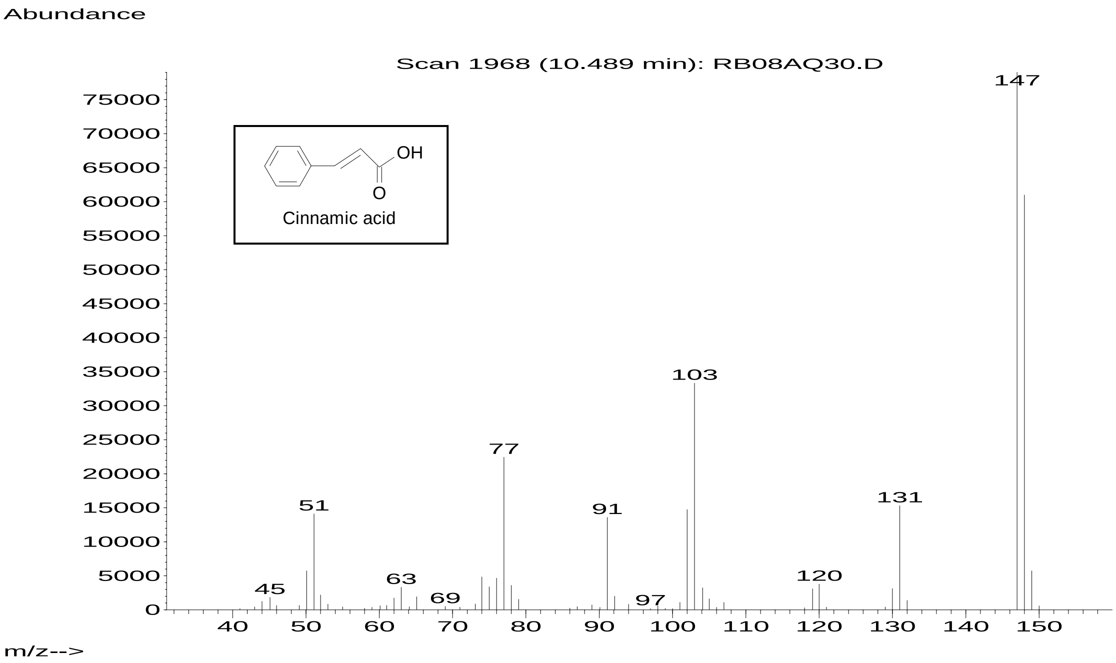
(10) 3-Nitro stilbene



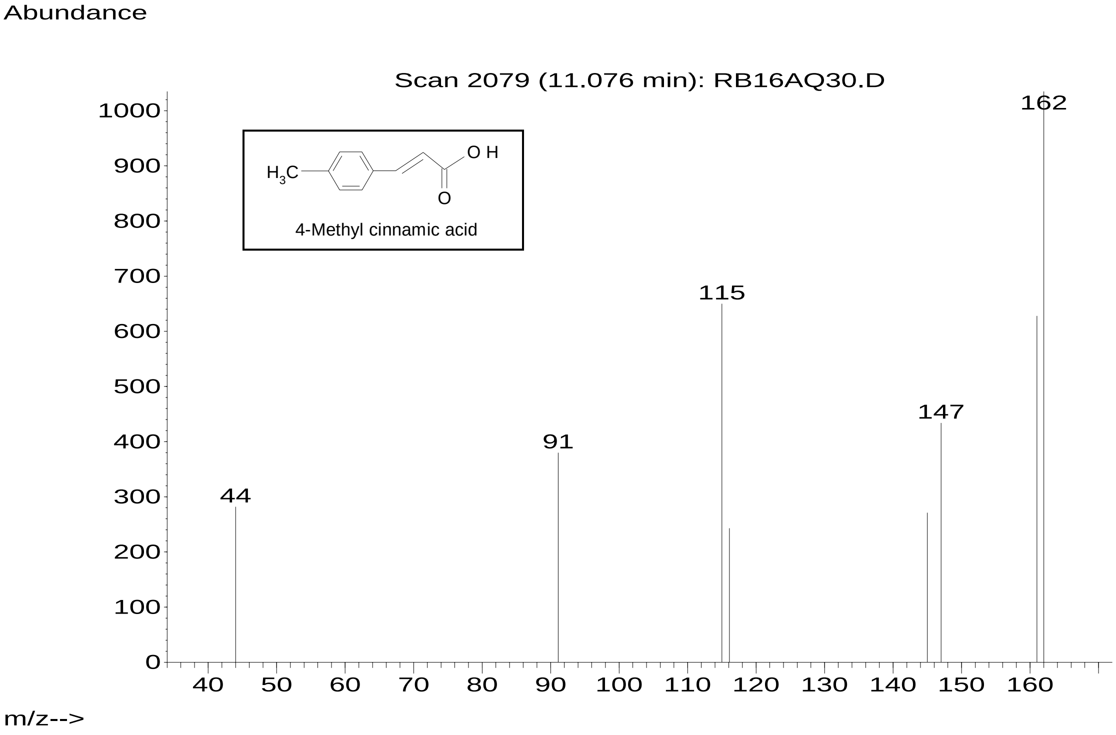
(11) n-Butyl cinnamate



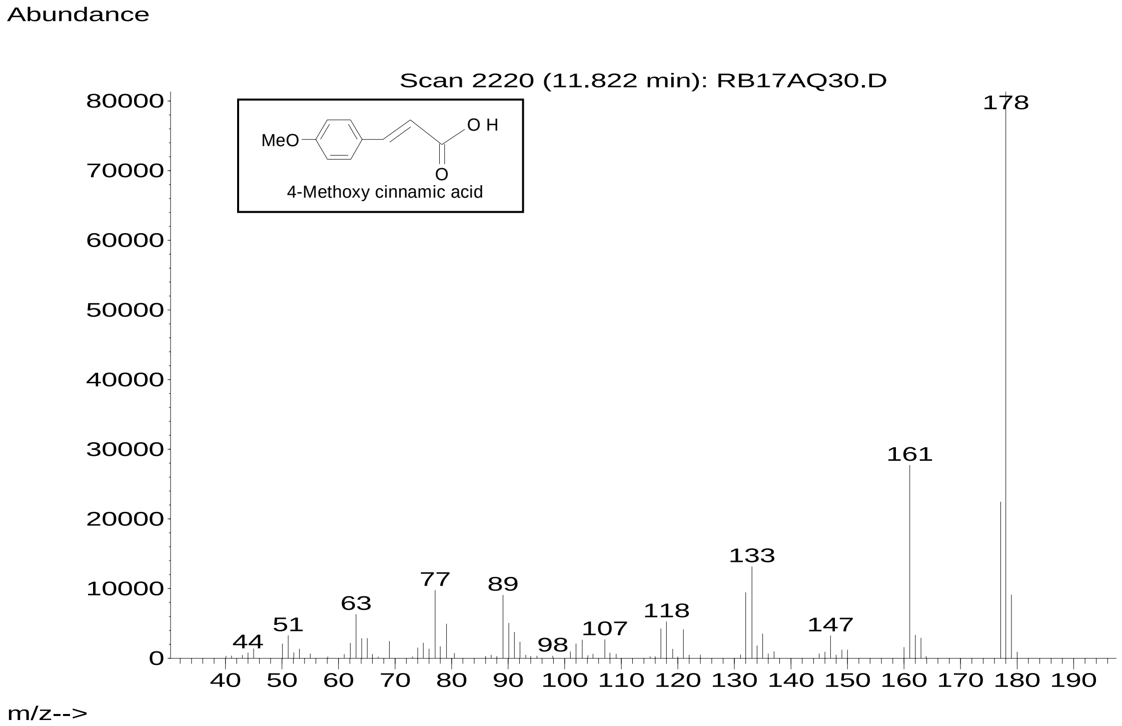
(12) Methyl cinnamate



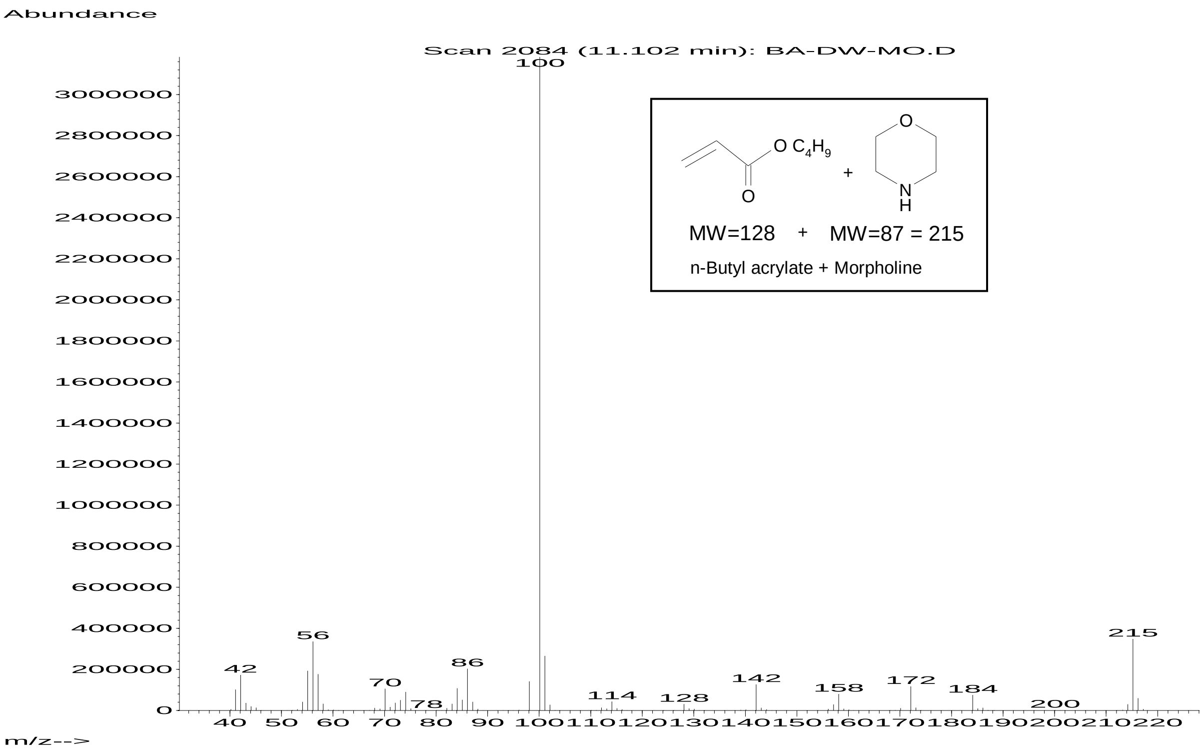
(13) Cinnamic acid



(14) 4-Methyl cinnamic acid



(15) 4-Methoxy cinnamic acid



(16) n-Butyl acrylate + Morpholine

APPENDIX II

List of abbreviations

%C	:	% Conversion
AAS	:	Atomic absorption spectroscopy
B.P.	:	Boiling Point
bipy	:	2,2’-Bipyridine
Conc.	:	Concentration
c-Stb	:	cis Stilbene
C-T	:	Concentration-time
DMF	:	N,N-Dimethylformamide
DMSO	:	N,N-Dimethylsulfoxide
DPPE	:	1,2-*bis* (diphenyl phosphino) ethane
DPPPy	:	Diphenyl phosphine pyridine
e.g.	:	For example
EG	:	Ethylene Glycol
GC	:	Gas Chromatography
i. e.	:	That is
IB	:	Iodobenzene
IR	:	Infra Red Spectroscopy
MEK	:	Methyl ethyl ketone
n-	:	Normal
NMP	:	N-methyl-2-pyrrolidinone
NMR	:	Nuclear Magnetic Resonance Spectroscopy
OX	:	Mixture of 75% n-octane + 25%p-xylene
Py	:	Pyridine
RPM	:	Rotation per minute
Stb	:	Stilbene
Sty	:	Styrene
T	:	Temperature (K)
TBA	:	Tributyl amine
TBAB	:	Tributyl ammonium bromide
TBzA	:	Tribenzyl Amine
TEM	:	Transmission Electron Microscopy

TOF	:	Turn Over Frequency
TON	:	Turn Over Number
TOTP	:	tri-o-tolyl phosphine
TOTPS	:	Trisodium salt of tri-(ortho-tolyl) phosphine tri sulphonate
TPP	:	Tri Phenyl Phosphine
t-Stb	:	trans Stilbene
UV-Vis	:	Ultraviolet-Visible
V	:	Volume
viz.	:	Namely
w.r.t.	:	With respect to

List of Publication / Conference / symposium

Accepted paper

1. $PdCl_2$(bipyridine) complex - an efficient catalyst for Heck reaction in glycol-organic biphasic medium.

S.V. Jagtap and R. M. Deshpande

Catalysis Today

Presentations at Conference / Symposium

1. $PdCl_2$(bipyridine) complex - an efficient catalyst for Heck Reaction in glycol-organic biphasic medium.
S.V. Jagtap and R. M. Deshpande
Presented a paper in the 4th Asia -Pacific Congress on Catalysis (APCAT 4) during 6 to 8 December 2006 held at Nanyang Technological University, Singapore,

2. Kinetics of Heck reaction in biphasic medium.
S. V. Jagtap and R. M. Deshpande
Poster Presentation at the 6th International Symposium on Catalysis in Multiphase Reactors (CAMURE-6) & 5th International Symposium on Multifunctional Reactors (ISMR-5), during January 14-17, 2007 held at National Chemical Laboratory, Pune, India.

3. $PdCl_2$(bipy) complex - an efficient catalyst for Heck Reaction in Homogeneous medium.
S.V. Jagtap and R. M. Deshpande
Poster Presentation at the 9th National symposium in Chemistry sponsored by Chemical Research Symposium in Chemistry (CRSI) and Department of Chemistry, University of Delhi during February 01to 04, 2007 held at Department of Chemistry, University of Delhi, Delhi.

Manuscripts Communicated

1. Kinetics of Heck reaction using $PdCl_2$(bipy) complex in glycol-organic biphasic medium.

S. V. Jagtap and R. M. Deshpande – Industrial Engineering Chemical Research.

2. Heck reaction using $PdCl_2$(bipy) complex catalyst in homogeneous medium.

Sangeeta V. Jagtap and Raj M. Deshpande – Journal of Molecular Catalysis.

Manuscripts under preparation

1. Heck reaction in an aqueous -organic biphasic medium using water-soluble catalyst.

S.V. Jagtap and R. M. Deshpande

2. Cinnamic acid derivatives via Heck reaction in a biphasic catalytic system.

. **S. V. Jagtap** and R. M. Deshpande