



**Vaal University of Technology**

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**Screening of substituted pyrazolone and pyrazole as ligands with  
palladium precursors in the Heck reaction**

By

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## Declaration

I, \_\_\_\_\_ hereby declare that this work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed.....

Date.....

## **Dedication**

To my daughter Emihle Bout and mother Nopumelelo Monakali.

My later grannys Lillian Nokhaya, Monakali, Nowethu, Bawuti,

And grandfather Wenkile Simon, Bawuti.

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## List of abbreviation

Ac	acetate
ACN	acetonitrile
Ar	aryl
$\alpha$	alpha
B	base
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
B.A	butyl acrylate
Bu	butyl
$\beta$	beta
C-C	Carbon-carbon
Conv	conversion
CuCl <sub>2</sub>	copper(II) chloride
Cy	cyclohexyl
°C	degrees Celsius
DAB	1,4-Diazobutadiene
dba	dibenzylacetone
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl

E.A	ethyl acrylate
EDG	electron-donating group
EWG	electron-withdrawing group
ee	Enantiomeric excess
GC	gas chromatography
h	hour(s)
L	ligand
M	Metal
Me	methyl
mol	mole(s)
OTf	triflate (trifluoromethanesulfonate)
OTs	tosylate (p-toluenesulfonate)
o	ortho
o-tol	ortho-tolyl
Pd(OAc) <sub>2</sub>	palladium(II) acetate
Ph	phenyl
Pd(PPh <sub>3</sub> ) <sub>4</sub>	tetrakis(triphenylphosphine)palladium(0)
PPh <sub>3</sub>	Triphenylphosphine
P(o-tol) <sub>3</sub>	tri(o-tolyl)phosphine
Pd(dba) <sub>2</sub>	bis(dibenzylideneacetone)palladium(0)
Pr	propyl



iPr	isopropyl
$\pi$	pi
p	para
TBAB	tetrabutylammonium bromide
Ts	tosylate
TON	turnover number
TOV	turnover value
UV	ultraviolet
X	generic halide/ heteroatom
$\gamma$	gamma

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## Abstract

The arylation and alkenylation of alkenes under the influence of a palladium catalyst, commonly referred to as the Heck reaction, has been extensively exploited by synthetic chemists since its debut in the late 1960's. A traditional Heck coupling is based on an aryl iodide or bromide as the electrophilic partner and a terminal alkene as the nucleophilic partner. Academic and industrial interest in this reaction has increased in recent years, fueled by the development of more active catalyst systems, the discovery of waste-free versions, and the desire to put the vast empirical data on a sound mechanistic basis. In this study, we wish to report the use of commercially available substituted pyrazolones (1-(4-Sulfophenyl)-3-methyl-5-pyrazolone (**L1**), 1-(2,5-Dichloro-4-sulfophenyl)-3-methyl-5-pyrazolone (**L2**) and 5-oxo-1-phenyl-2-pyrazolin-3-carboxylic acid (**L3**)) and pyrazoles ( $\alpha$ -[(2-Ethoxy-2-oxoethoxy)imino]-3-pyrazole acetic acid (**L4**) and 3,5-dimethyl pyrazole (**L5**)) as auxiliary ligands in the Heck coupling reaction. These ligands were used either with PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> to catalyze the Heck reaction of iodobenzene with ethyl acrylate or butyl acrylate. GC-MS was used to monitor the reaction, percentage (%) conversions were determined based on the consumption of iodobenzene.

Different reaction parameters such as ligands, temperature, base, solvent and influence of time were investigated. It was observed that the lower conversion was obtained for ethyl acrylate and conversions above 80% were obtained for butyl acrylate. Ligand effect proved to be very crucial during the Heck coupling reactions of iodobenzene with butyl acrylate and ethyl acrylate. For instance in the absence of ligands with PdCl<sub>2</sub>, the conversions were 29 % and 44 % for butyl acrylate and ethyl acrylate, respectively. When Pd(OAc)<sub>2</sub> was used in the absence of ligands the conversions were 25 % and 36 % for butyl acrylate and ethyl acrylate, respectively. In the study for the effect of temperature, 80 °C was observed as the best temperature since promising conversions were obtained with little or no sign of deactivation of the catalysts. On the other hand, increasing the temperature to 120 °C and above high percent conversions are observed; however deactivation of the catalysts occurs as observed from the precipitation of palladium black at the bottom of the vial. From the results obtained it is clear that pyrazolone and pyrazole ligands/palladium systems are important at very low catalyst loadings and mild temperatures. Based on the employed reaction conditions the influence of base suggested that the organic base

triethylamine was the reagent of choice since better conversions were obtained compared to inorganic bases. The inhomogeneity of the inorganic base proved to be a disadvantage in the reaction of iodobenzene with butyl acrylate at employed reaction conditions. It was also found that parameters such as solvents and time effects were important in the Heck reaction. Polar aprotic solvents proved to be solvents of choice rather than non-polar solvents, from the investigated solvents DMF gave better conversions under the used reaction conditions giving average conversions of 78 % and 75 % for all the ligands in the presence of PdCl<sub>2</sub> and Pd(OAc)<sub>2</sub>, respectively. During the investigation of time effect, it was noteworthy to observe that **L4** had a slow initiation rate, for instance after 0.5 h conversions of 2 % and 10 % were obtained for catalytic systems, PdCl<sub>2</sub> and Pd(OAc)<sub>2</sub> respectively. Also it was observed that under the investigated parameters there was no need to run the reaction for 24 h because after 4 h not much of a difference in conversions was observed. In comparing the influence of these two different auxiliary ligands, pyrazolone based ligands were more efficient than pyrazole based ligands under the investigated parameters. The fully detailed information supporting this has been discussed in Chapter 4.

## CHAPTER 1

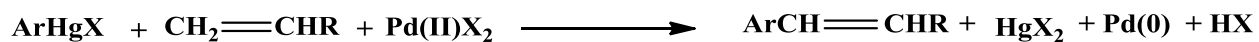
### INTRODUCTION

#### 1.1 Mizoroki-Heck Reaction

The Mizoroki-Heck (MH) reaction, also known as the Heck reaction (Hr) is a powerful and most commonly used method to couple an aryl halide with a terminal olefin [1]. Products such as cinnamate and stilbenes formed from the Heck reaction are of industrial importance, e.g. one of the cinnamate ester derivatives (e.g. stilbenes, cinnamates) is used industrially as UV absorbers, antioxidants in plastic and as intermediates for pharmaceuticals [2]. In 2010, Richard F. Heck and associates were awarded a Nobel prize in chemistry for the discovery and development of this palladium catalysed reaction, leading to the wide recognition of this synthetic method [3]. Ever since its discovery, intensive developments on Heck reaction have occurred, witnessed by large numbers of literature reviews published on the reaction [4]. Nowadays, the Heck reaction is among the most efficient palladium-catalysed transformations for the formation of C-C bonds in organic synthesis [5]. Currently, scientists are faced with the challenge of developing new methodologies to enhance the existing known chemical transformations for academic and industrial purposes [6].

##### 1.1.1 Discovery

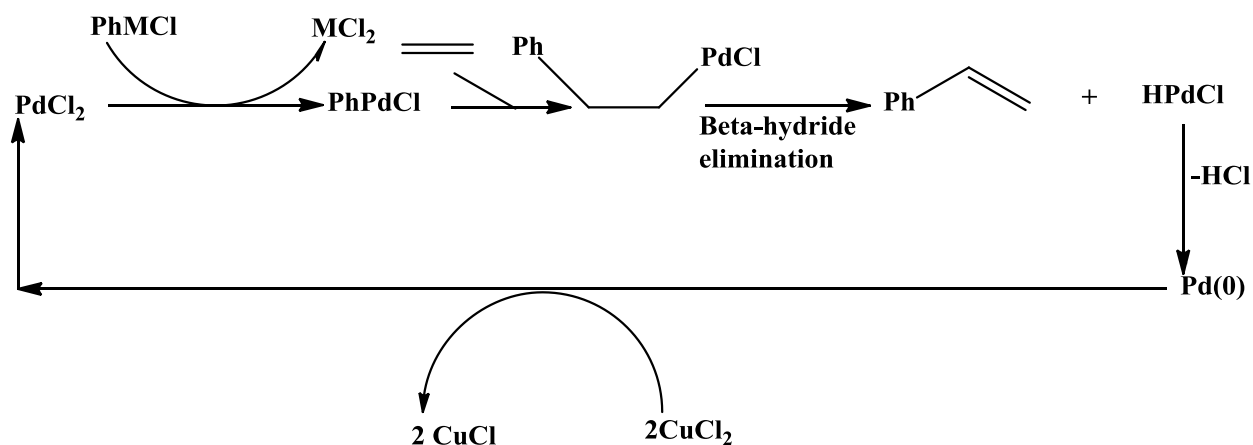
In the late 1960s, Heck [7] reported in a series of papers on the reaction of organometals ( $\text{ArHgX}$ ) containing Hg, Sn, and Pb with alkenes in the presence of one equivalent of a Pd(II) complex ( $\text{PdCl}_2$  or  $\text{Pd(OAc)}_2$ ) leading to substitution of an alkenyl hydrogen with a carbon group of the organometallic reagent, mostly used with organomercury [8] (Scheme 1.1).



**Scheme 1.1:** Stoichiometric Heck reaction

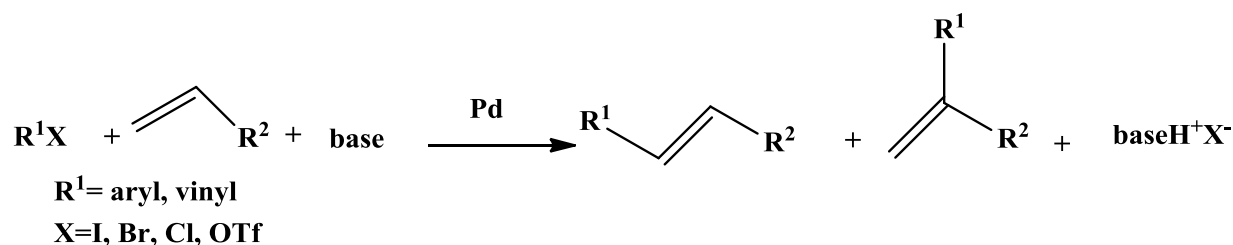


Similar work related to this stoichiometric reaction was reported by Moritani and Fujiwara in 1967; unfortunately both of these stoichiometric reactions were not that interesting from the synthetic point of view [9]. Heck, in one of the papers released in the late 1960s improved the stoichiometric reaction, making it catalytically active by introducing  $\text{CuCl}_2$  as a stoichiometric re-oxidant. The role of  $\text{CuCl}_2$  was to act as a oxidizing agent for  $\text{Pd}(0)$  to  $\text{Pd}(\text{II})$ , thus forming a complete catalytic cycle (Scheme 1.2) [7].



**Scheme 1.2** : Pd(II) catalyzed coupling of aryl chloride and ethylene

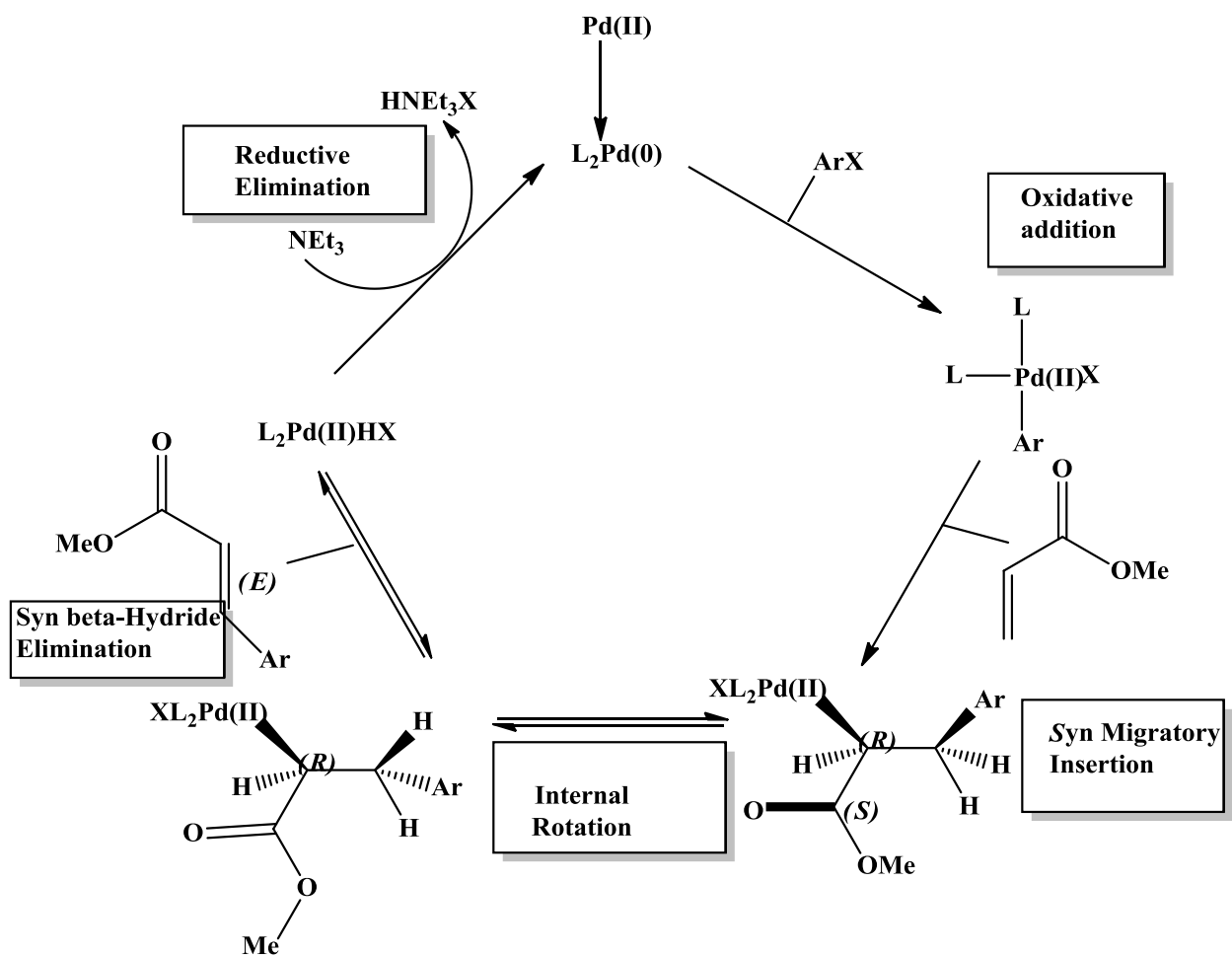
Fitton in 1968 discovered that aryl halide ( $\text{Ar-X}$ ) is able to react with  $\text{Pd}(0)$  to give arylpalladium halides [10]. From these findings Heck was able to notice that if  $\text{Ar-X}$  was to undergo an oxidative addition with  $\text{Pd}(0)$ ; there was no need for stoichiometric metals such as mercury to be used for the formation of arylpalladium halides. Due to this new modification, arylation of an olefin was achieved from the reaction of aryl halide and an olefin in the presence of palladium catalysts. These pioneering studies by Heck opened the way to a new reaction later called the Mizoroki-Heck reaction (Scheme 1.3).



**Scheme 1.3** : Mizoroki-Heck reaction

### 1.1.2 Basic Mechanism

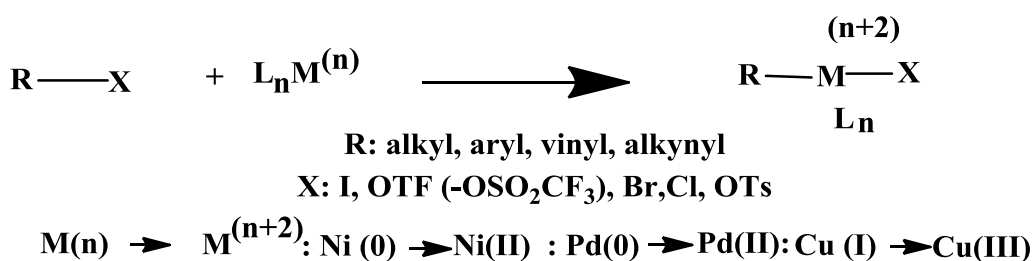
General mechanism of the Heck reaction involves oxidative addition of aryl halide or alkenes to palladium(0), followed by migratory *cis*-insertion of a complexed olefin. Internal rotation of a C-C bond allows a  $\beta$ -hydride elimination step, to generate a new C-C bond before reductive elimination of the product. A base is also required in the reaction media in order to scavenge the HX and regenerate the active Pd(0) catalyst for another catalytic cycle as shown in Scheme 1.4 [11].



Scheme 1.4 : General mechanism of the Heck reaction

### 1.1.2.1 Oxidative addition (First step of catalytic cycle)

One of the important steps in the Heck reaction mechanism is oxidative addition. In this process a low valent palladium(0) or nickel atom inserts into a carbon-heteroatom bond, usually of an aryl halide or sulfonate (Scheme 1.4.1). The formation of carbon-metal bond accompanied by an increase in the oxidation state of the metal by two is known as oxidative addition [12]. This step is the first step of the catalytic cycle.



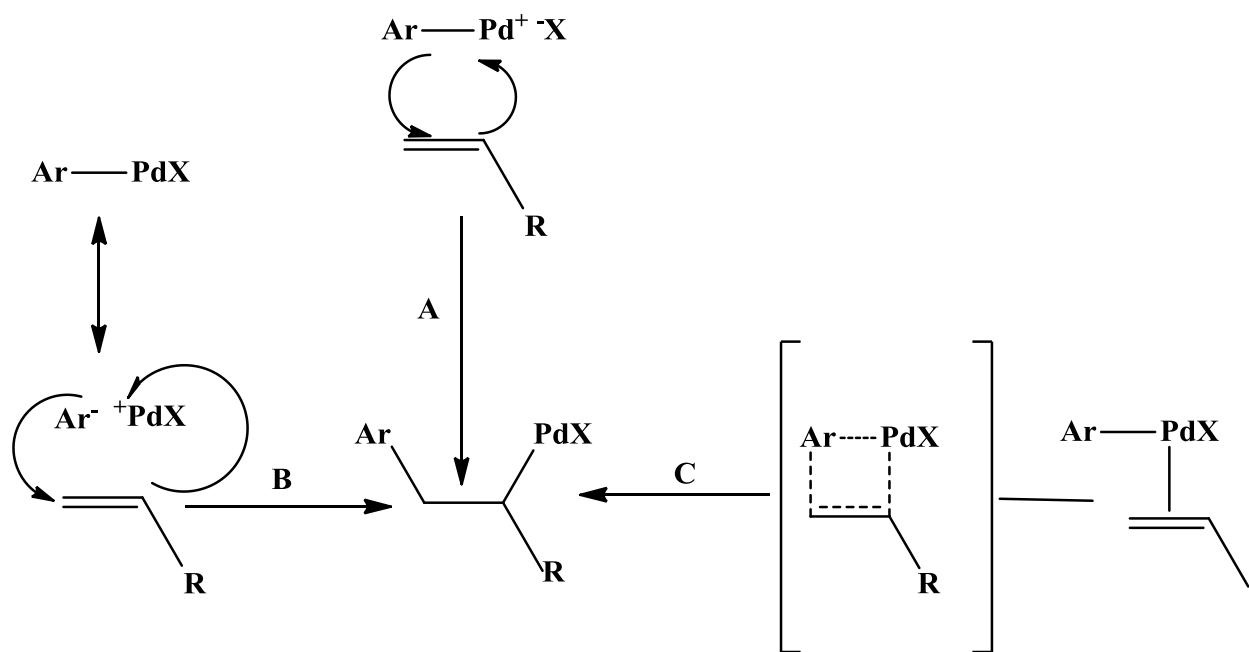
**Scheme 1.4.1:** The general mechanism of oxidative addition

A number of factors such as electron density of the metal determine the capability of the transition metals to undergo oxidative addition. One way to increase the electron density on the metal is by the application of good donor ligands. The more electron rich the metal center, the faster the oxidative addition [13]. The nature of the carbon-heteroatom into which the metal inserts is also important in oxidative addition. In 1971, Fitton and Rick reported the reactivity order of C-I > C-OTf > C-Br >> C-Cl >>> C-F. Aryl and 1-alkenyl halides bearing an electron-withdrawing group (EWG) are more reactive towards oxidative addition than those with electron-donating group (EDG) [5].

### 1.1.2.2 Migratory Insertion

Migratory insertion is the product-forming step of the Heck catalytic cycle, which is the birth of new C-C bond. The understanding of this step is very crucial for the synthetic chemist, since this governs chemo, regio and stereoselectivity of the Heck reaction [14]. Three different pathways in which migratory insertion can occur are shown in the Scheme 1.4.2. Firstly cationic species, for

example  $\text{ArPdX}$  complex, where palladium could be an electrophilic center that undergoes electrophilic addition by dissociation of halide (or triflate) from  $\text{ArPdX}$  giving  $\text{X}^-$  and cationic  $\text{Pd}^{(\text{II})}$  intermediates. The olefin then coordinates to the Pd followed by insertion into the Ar-Pd bond (pathway A). The other possibility is dissociation of a ligand giving the neutral intermediate  $\text{ArPdX}$ , which can be regarded as any Grignard reagent that acts as a carbanion and undergoes nucleophilic addition into the alkene giving the same product as the cationic model (pathway B). It is well known that high reactivity typical Michael donors (such as acrylates, acrylonitrile etc.), are the only supporters of the model (pathway A), which are also highly active in the Heck reaction [15]. Lastly,  $\text{ArPdX}$  and  $\text{Ar-Pd}^+$  intermediates may add to the double bond of alkene in the concerted process (pathway C).



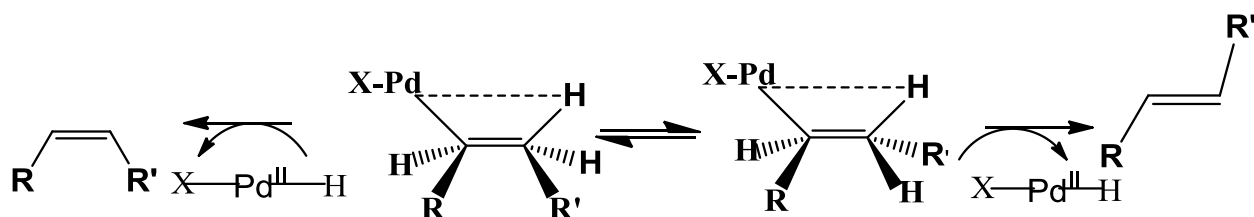
**Scheme 1.4.2** : Suggested mechanisms of migratory insertion

### **1.1.2.3. $\beta$ -Hydride elimination**

In this process, as already suggested by its name, the metal catalyst and hydrogen residing on the carbon atom  $\beta$  to the metal are eliminated from the organic molecule with the concomitant formation of a double bond. Palladium forms a new bond with the hydrogen, and the C-Pd bond

is broken, forming a new  $\pi$ -bond between the  $\alpha$  and  $\beta$  carbon. The newly formed H-Pd(II)-X species can undergo subsequent reductive elimination. In the course of  $\beta$ -elimination the metal has to have a vacant site *cis* to the alkyl substituent, where the hydride can coordinate [16].

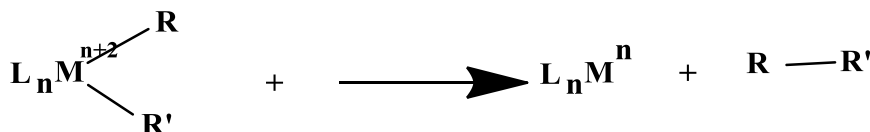
The reaction goes through a near planar transition state, which means that in substrates where such a conformation is disfavored by the organic moiety, the  $\beta$ -hydride elimination might become far too slow for practical applications. If the system has free rotation about the C-C bond as well as two  $\beta$ -hydrides, a mixture of E and Z alkenes can be formed (Scheme 1.4.3). The nature of the metal center might also influence the speed of the  $\beta$ -hydride elimination.



**Scheme 1.4.3:**  $\beta$ -hydride elimination

#### **1.1.2.4 Reductive elimination**

Reductive elimination is an important process that is often the last step in catalytic cycles involving the combination of two organic moieties together by producing a new C-C bond as well as the reformation of the catalytically active species [17]. In this step the oxidation state of the transition metal is usually reduced by two.



**Scheme 1.4.4 :** Reductive Elimination of an R-R' molecule from a mononuclear metal complex.

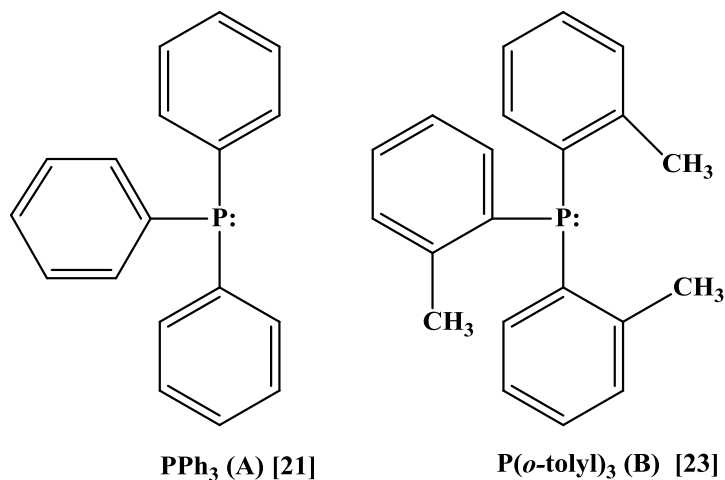
Similarly to oxidative addition, there are many factors that affect the rate of the reductive elimination reaction. In many cases, these factors have the opposite effect on the rate of reductive elimination reactions to the oxidative addition reaction due to the thermodynamic factors. Hence,

those factors that thermodynamically favor oxidative addition opposite to those of reductive elimination reaction. The following series of factors could be considered as the major factors on the reactivity of the metal complexes towards the reductive elimination reaction [18]:

- Reductive elimination in more electron-poor complexes tends to be more favorable than in more electron-rich complexes.
- Reductive elimination in more-hindered complexes tends to be more favorable than in less-hindered complexes.
- Reductive elimination of H ligands is faster than that of R ligands.

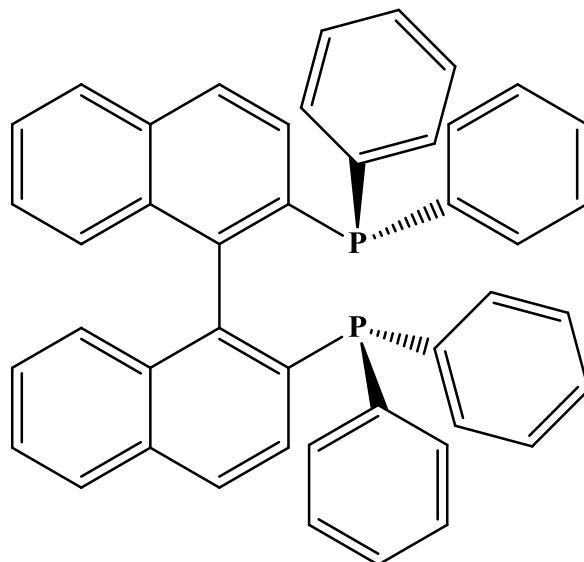
## 1.2 Catalysts used for the Heck reaction

The most widely used transition metal catalysts in the formation of carbon-carbon bonds in the Heck reactions are palladium catalysts (palladium precursors  $\text{PdCl}_2$ ,  $\text{Pd}(\text{OAc})_2$ , etc.), because of the tolerance to functionalities displayed by late transition metal. In the early 1970s, Mizoroki *et al.* reported preliminary results of  $\text{PdCl}_2$  as the catalysts in the arylation of alkenes by an aryl iodide in the presence of potassium acetate [19]. In the following year Heck and Nolley reported a similar reaction but the catalyst this time was  $\text{Pd}(\text{OAc})_2$  with  $n\text{-Bu}_3\text{N}$  as a base. Both of these reactions occurred in the absence of a solvent or in *N*-methylpyrrolidone (NMP) at 100 °C. These researchers proposed a catalytic mechanism for this reaction for the first time [20]. The last contribution by Mizoroki and co-workers was in 1973 [21] when they extended their preliminary research to aryl bromides, most importantly they found that aryl iodide was the most reactive, the order of reactivity is as follows:  $\text{PhI} > \text{PhBr} \gg \text{PhCl}$ . The application of triarylphosphines such as **A** and **B** was found to be slightly beneficial. One of the major drawbacks of these early homogeneous palladium systems was the precipitation of palladium in the form of palladium black, which limits the lifespan of the active species.



Dieck and Heck in 1974 improved the previous findings by introducing  $\text{PPh}_3$  in association with  $\text{Pd}(\text{OAc})_2$  [22]. The reactivity of aryl iodide was found to be more efficient than in the absence of  $\text{PPh}_3$ . More interestingly, the reaction could be extended to aryl bromides at the temperature ranges of 100-135 °C, however aryl chlorides were still unreactive. One of the limitations of the above ligands is that they are poor at promoting oxidative addition of aryl bromides and chlorides.

A much improved catalytic system was discovered by introducing substituted triarylphosphines in combination with  $\text{Pd}(\text{OAc})_2$  *in situ* [23]. Among the phosphines, the tri-*o*-tolylphosphine,  $\text{P}(\text{o-Tol})_3$  was found to be more efficient than  $\text{PPh}_3$  in reactions involving aryl bromides. The interesting property of these ligands is that they are electron rich and sterically demanding. It has been reported that the electron donating ability of phosphines together with their huge size improve catalytic efficiency [23, 24]. The drawback associated with these phosphines is that they have little impact on regio or stereo control to the catalytic reaction. From this limited background it can be mentioned that most palladium precursors can catalyze coupling reactions with or without ligands. But, the presence of ligand stabilizes or partially stabilizes the palladium in its zero valent state, thus enhancing its catalytic ability and preventing the precipitation of palladium in the form of inactive  $\text{Pd}(0)$  clusters, known as palladium black [15].



**BINAP (C) [26]**

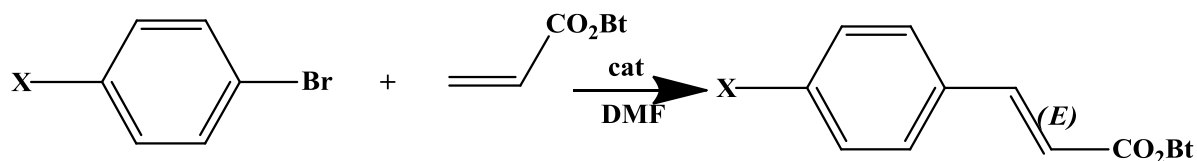
However, it can be concluded that the ligand enhances the metal co-ordination properties. Thus, it determines the catalytic efficiency of the  $\text{Pd}(0)$  complex [25]. Through the exchanging of ligands, a high specificity of the metal center towards the incoming reaction substrate can be tailored. Therefore a careful selection of the ligand can result into highly selective products. Noyori in 1990 found that by applying 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (C) as the phosphine ligand in many catalyzed reactions leads to asymmetric products with good enantioselectivity (*ee*'s) [26]. This led to the development and application of BINAP catalytic system in the Heck reaction, which resulted in a good *ee*'s (96% *R*-BINAP), but yields were low



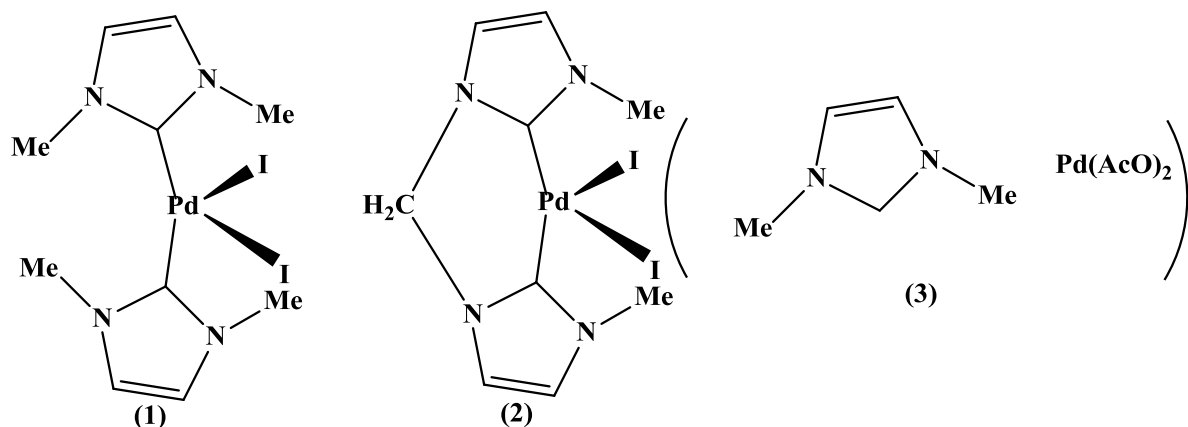
compared to the one of the traditional triarylphosphines ligands [27]. However, the major drawback of the traditional phosphine ligands is that they can be expensive and time consuming to prepare, due to the fact that they need air and a moisture free environment. Also these ligands can be subject to P-C bond degradation at elevated temperatures. In some catalytic processes, deactivation of the catalysts occurs resulting in the use of higher phosphine concentrations [28]. Therefore, in view of practical use, the development of more reactive and stable ligands is of importance for palladium-catalysed Heck reaction. Hence the researchers have been forced into developing alternatively cheaper and relatively stable phosphine-free catalysts systems that can offer comparable properties. On the other hand nitrogen based ligands have been given little attention, whereas currently they are the promising ligands to overcome the drawbacks associated with these phosphines. Nitrogen-based ligands such as the N-heterocyclic carbenes [29], diimines [30] and imines [31] are some of the ligands being currently researched as possible alternatives to phosphines. Some of Pd<sup>0</sup> complexes such as Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd<sub>2</sub>(dba)<sub>3</sub> are commercially available catalysts but they are sensitive to heat, moisture and oxygen [15].

### 1.2.1. Nitrogen-based compounds as catalysts for Heck reaction

The Heck reaction is generally catalyzed by soluble palladium complexes with phosphine ligands. Recently, *N*-heterocyclic carbenes (NHCs) have been shown to have better activity in palladium-catalyzed Heck reaction. These ligands have strong  $\sigma$ -donors with negligible  $\pi$ -accepting ability. Because of these properties they resemble tertiary phosphines as electron donors [32]. In contrast to phosphines, palladium complexes of *N*-heterocyclic carbene ligands are suitable catalyst precursors that are more stable to air, moisture and are more tolerant towards oxidation. The favorable steric and electronic properties exhibited by various nucleophilic carbene ligands make them attractive candidates for mediating the Heck reaction [33].

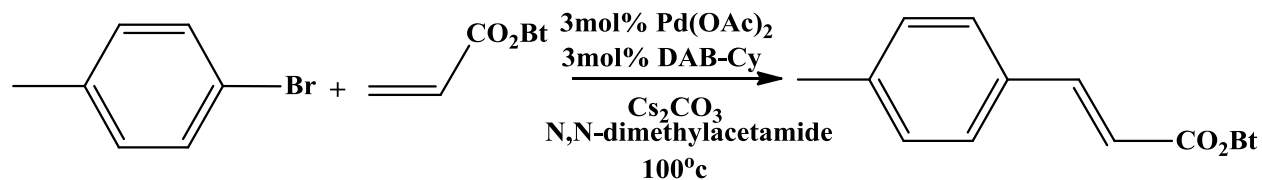


Catalysts =



**Scheme 1.5** : Imidazolylidene complexes used in the Heck reaction.

The first catalytic application of Pd-NHC complexes was reported by Herrmann *et al.* in 1995. This was the start of new palladium systems to be discovered, which later on became well documented. The carbene palladium complexes **1** and **2** can be prepared from Pd(OAc)<sub>2</sub> and then applied in Heck reactions involving the coupling of aryl halides. The results obtained were quite promising in terms of yield and turnover numbers of the catalysts [34]. Moreover, the *in situ* generated complexes of 1,3 dimethylimidazolium iodide ligand/Pd(OAc)<sub>2</sub> (**3**) system were introduced into the reaction and the coupled product was produced in comparable yields to complexes **1** and **2**, thus eliminating the need of preparing palladium complexes (**1** and **2**) beforehand (Scheme 1.5). After those findings by Herrmann *et al.* more research work with different imidazolylidene ligands has been done in the Heck reaction. Nolan *et al.* established catalytic complexes formed *in situ* from sterically demanding imidazolium chlorides salts/palladium precursors systems as the active catalysts in the Heck reaction [35]. Although *N*-heterocyclic carbene ligands have advantages over phosphine ligands, limited structural variation of NHCs ligands are available, due to the fact that most examples are based on imidazole. In addition synthesis of the free carbene often results in low yields in ligand synthesis [36].



**Scheme 1.6** : Influence of DAB-R ligand on the Heck coupling of 4-bromotoluene with *n*-butylacrylate

However, in principle chelating ligands have greater modularity than monodentate *N*-heterocyclic carbenes as the chelate backbone can be adapted to vary the bite angle [37]. In addition, the ease of synthesis and modularity of chelate ligands are an advantage over *N*-heterocyclic carbene ligands. Therefore the development of nitrogen based ligands in which the donor atoms are nitrogen, is another interesting class of chelating ligands. These ligands are currently receiving attention as possible replacements for traditional phosphines. The fascinating property of these compounds stems from their stability to air, moisture and they have been found to be resistant to oxidation. Highly active Heck catalysts of DAB-Cy/Pd (OAc)<sub>2</sub> systems have been reported by Gabriel *et al.* as very effective catalysts for arylation of various olefin with aryl bromides with respect to reaction rate, catalysts loadings and functional group tolerance (Scheme 1.7). More importantly, they further reported the effect of DAB-Cy ligand at very low catalysts loadings and high temperatures. On the other hand Schiff base [N<sup>^</sup>O] and [N<sup>^</sup>N<sup>^</sup>O] chelates provide attractive stabilizing ligands for catalysis due to their ready accessibility and flexibility to modification. These ligands have shown good success in recent years in the stabilization of the early and late transition metal catalysts. Kostas *et al.* [38] and Brayton *et al.* [39] have used Schiff base palladium(II) complexes for Suzuki coupling reactions. However, there are few reports on Schiff based ligands/palladium precursor systems as active catalysts in the cross coupling reactions.

### 1.3 Problem Statement

The Mizoroki-Heck reaction was discovered more than a decade ago [40], and ever since then, it has been identified as one of the powerful fundamental types of the organic processes catalysed by palladium complexes. Generally, researchers often want transition metal catalysts that:

- possess a wide synthetic scope- the ability to process all possible types of substrate;
- are highly selective;
- rely on practicable available reagents,
- can increase the turnover rate, and with long life span
- are easy to recycle

A number of publications and reviews of Mizoroki-Heck reactions have revealed impressive numbers of catalytic systems with efficiency for a very limited group of substrates (such as aryl iodide and active aryl bromides coupling with simple terminal alkenes, such as acrylates or styrene). On the other hand, when the scope of these substrates is expanded these catalytic systems or precatalysts tend to lose their catalytic activity. High selectivity and broadening of the scope to less reactive substrates are achieved by application of ligands which tend to fine tune the properties of palladium metal. Another motivation for application of ligands is attributed to the fact that palladium precursor's catalysts ( $\text{Pd}(\text{OAc})_2$  and  $\text{PdCl}_2$ ) in the Heck coupling reactions are not stable; after some time they form palladium black which deactivates its catalytic activity.

Therefore application of ligands (such as ancillary ligands) as stabilizers has been shown to overcome this challenge. Much work has been done in the past years, for the application of phosphine ligands as the stabilizing material for palladium precursors in the cross-coupling reaction. For a long time, phosphines/Pd complexes were the mostly used catalyst systems for the Heck coupling reaction. As was already discussed, sterically demanding electron-rich phosphines tend to exhibit high activity for different substrates. However, many phosphine complexes have some disadvantages such as chemical sensitivity to moisture, are expensive, and are highly toxic. On the other hand, nitrogen based ligands are chemically stable to moisture, less expensive compared to phosphine ligands, but so far have received comparatively little attention. Therefore,

the development of nitrogen based ligands and their transition metal complexes that can be applied as the catalyst in the Heck coupling reaction are needed.

## **1.4 Aim and Objectives of the Study**

### **1.4.1 Aim of study**

The above introduction makes it clear that nitrogen based ligands offer some benefit to palladium catalysed Heck coupling reactions. From the introduction it was clearly stated that *in situ* homogeneous catalysts do not only reduce the time required for catalyst development, but also eliminates the area of complex preparation beforehand. By doing so, it gives some solutions for the challenge that is faced by chemists, which is to find new methodology that will make the already know chemical transformation simpler, faster, cheaper, and in general, more efficient. Therefore the aim of this study was to use the commercially available pyrazolone and pyrazole based ligands as ancillary ligands with palladium precursors as catalyst systems in the Heck coupling reaction.

### **1.4.2 Objectives of the study**

1. Screening for the suitable alkene bearing electron withdrawing group in the Heck coupling reaction.
2. To investigate the effect of ligands in the Heck coupling reaction.
3. To investigate the effect of temperature in the Heck coupling reaction.
4. To investigate the effect of base in the Heck coupling reaction.
5. To investigate the effect of solvents in the Heck coupling reaction.
6. To investigate the effect of time in the Heck coupling reaction.

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## CHAPTER 2

### Application of nitrogen based ligands in the Heck coupling reaction

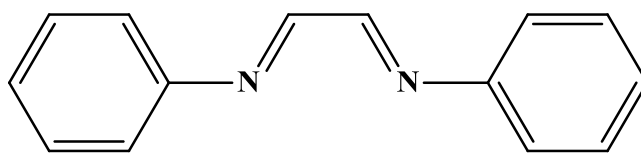
#### 2.1 Introduction.

The developments in the Heck coupling reaction has received tremendous attention of late, its applications have grown exponentially [1]. Its broad scope has ensured recognition as one of the fundamental organic transformations for synthesis. A great advantage of the Heck coupling reaction is that the substrate could be a simple olefin which makes it not be restricted to activated alkenes. Because of this less waste is generated compared to other cross coupling reactions which use a pre-functionalized coupling partner, this reaction is more applied during the synthesis of natural products [2]. Moreover, numerous substrates and ligands have been used several times in the Heck coupling reaction. Concerning the Heck coupling of aryl halides, the most frequently used halogen is the iodine. The reason is that oxidative addition of the C-I bond to palladium occurs much easier than in other halogens such as bromide and chloride. However, although aryl chlorides are much cheaper and more readily available, their application may have some economic implications.

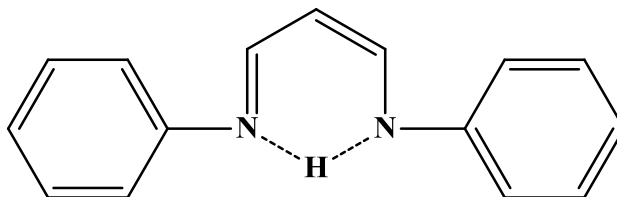
Researchers established that in order to improve the reactivity of aryl chlorides in the Heck coupling reaction, more electron rich palladium complexes are required [3]. That was achieved by the application of ligands that aids the metal properties such as electronic and steric effect, thus enhancing the metal capability to undergo oxidative addition with bromides and chlorides. However, over the past two decades nitrogen based ligands have emerged in the literature as good alternatives for the development of phosphine-free catalysts for the palladium catalyzed reaction. The growing interest in these ligands can be attributed to their low toxicity and stability towards moisture and oxygen. Thus, in recent years, extensive effort has been dedicated to exploring nitrogen-based ligands such as diimines, dipyrindine, hydrazone, imidazole and palladacycles.

### 2.1.1 Diimines as ligands in the Heck coupling reaction

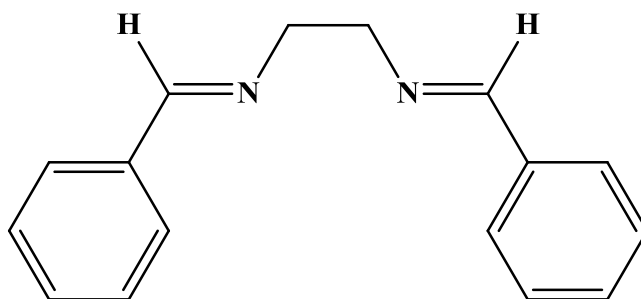
Diimine ligands are neutral, chelating 4-electron donors that are made up of two imine functional groups. There are three types of diimine compounds namely (i)  $\alpha$ -diimines (1,2-diimine), (ii)  $\beta$ -diimines (1,3-diimine) and (iii)  $\gamma$ -diimines (1,4-diimine). The difference between  $\alpha$  or  $\beta$ -diimines and unconjugated diimine compounds lies in the imine C=N bonds forming part of the backbone connecting two imines in the case of  $\alpha$ -or  $\beta$ -diimines. However, in the case of  $\gamma$ -diimines the C=N bond does not form part of the above nitrogen-nitrogen backbone.



**$\alpha$ -diimine ligand [4]**

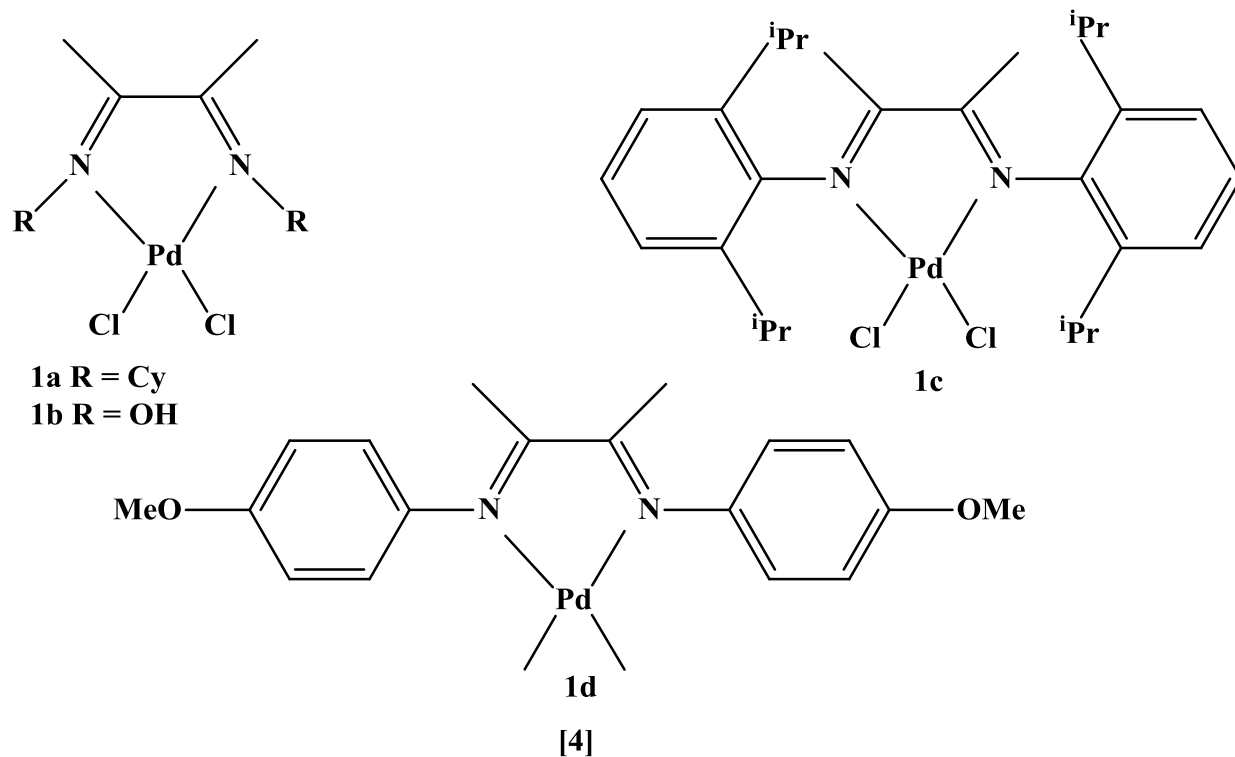


**$\beta$ -diimine ligand [6]**

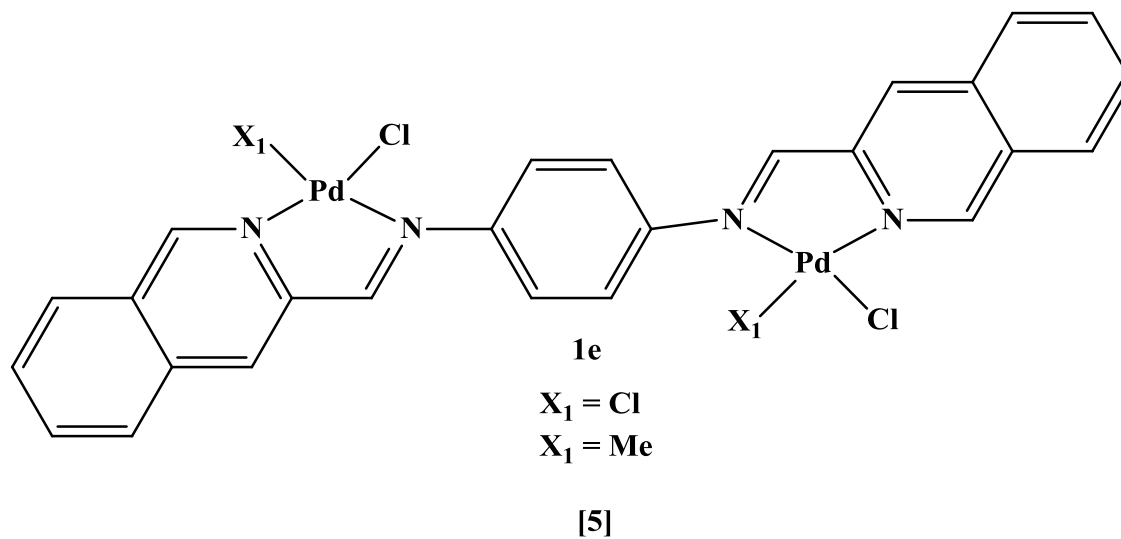


**$\gamma$ -diimine ligand [8]**

These nitrogen donor ligands are useful in coordination with transition-metal forming complexes with good  $\sigma$ -donor and  $\pi$ -acceptor properties, which gives these complexes the ability to be used as catalysts in different organic transformation. Few publications exist in the literature on the application of (diimine)-Pd(II) as pre-catalysts for the Heck coupling reactions.

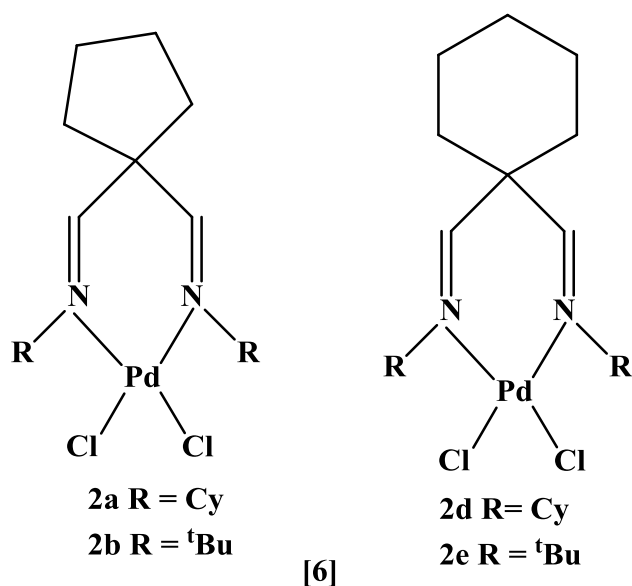


Iyer *et al.* reported the use of ( $\alpha$ -diimine)Pd(II) complexes **1a**, **1b**, **1c** and **1d** in the Heck coupling reaction of bromobenzene and ethyl acrylate [4]. Complex **1a** gave the highest yield (TON of 63) followed by **1b** and **1c** with TONs of 48 and 32, respectively and complex **1d** was the least active giving TON of 16. Addition of Bu<sub>4</sub>NBr gave slightly improved yields. In the case of aryl chloride no activity was observed.

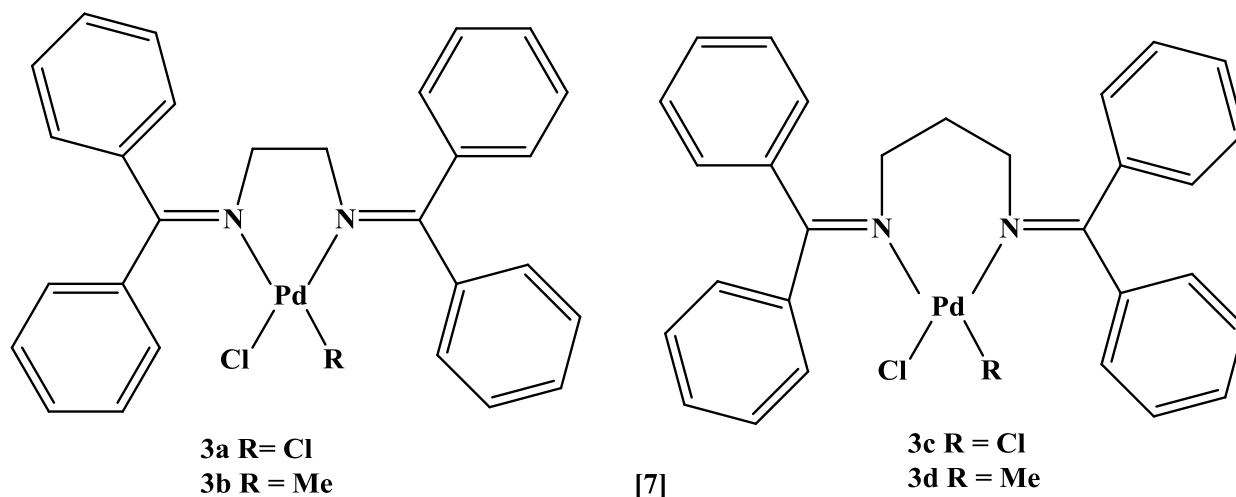


Motswainyana and Onani in 2012 prepared two new phenylene bridged binuclear bis (imino-quinoly) palladium (II) complexes from the reaction of the ligand 1,4-bis (imino-quinoly) benzene, **L1** with either Pd (COD) Cl<sub>2</sub> or Pd (cod) Cl Me [5].

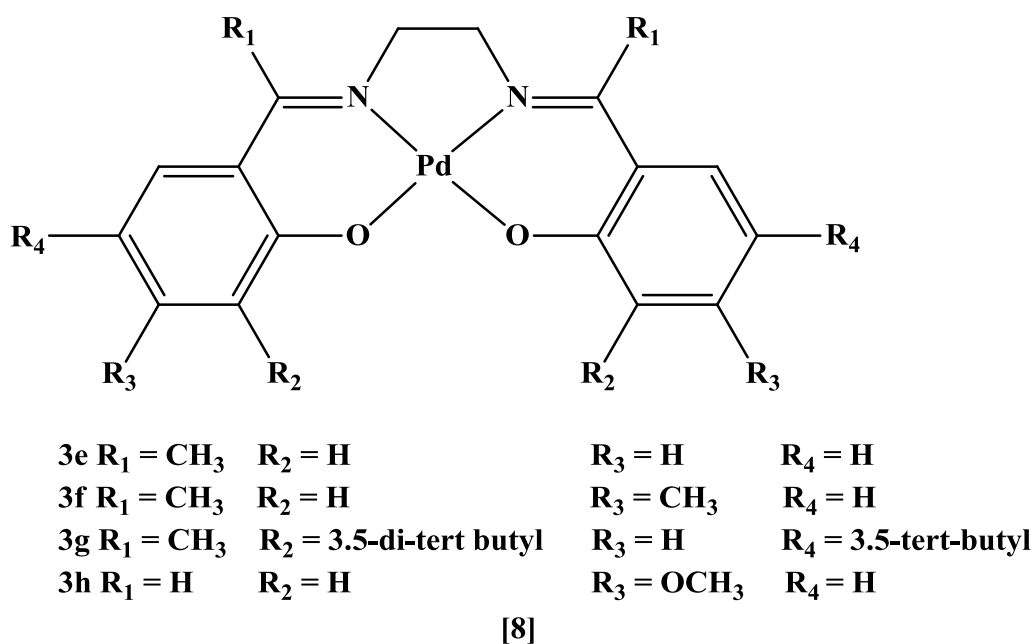
The complexes **1e** showed good activity to catalyze the Heck coupling reactions of iodobenzene with butyl acrylate, giving yields of over 85 %. During the analysis, the Heck product showed the trans-butyl cinnamate as the major coupling product with selectivity ranging from 85 to 88 %. The initial rate was also observed to be significantly higher (over 75 % yield) after only 1 h.



There has been a growing interest into catalytic activity of Pd (II) complexes containing β-diimine ligands. Domin *et al.* in their studies in the Heck coupling reaction of *p*-acetyl bromobenzene with methyl acrylate [6], used complexes with alkyl substituents on the nitrogen atom (**2a-2b** and **2d-2e**) which gave quantitative yields (33 TON). In 2008 Nelana *et al.* claimed to be the first to use the very scarce γ-diimine palladium complexes as precatalysts in the Heck coupling reaction and according to their literature survey, they reported the application of four γ-diimine Pd complexes (**3a-3b** and **3c-3d**) in the Heck coupling of methyl acrylate or butyl acrylate with iodobenzene resulted in a very good conversion to either methyl (2*E*)-3-phenylacrylate or butyl (2*E*)-3-phenylacrylate [7].

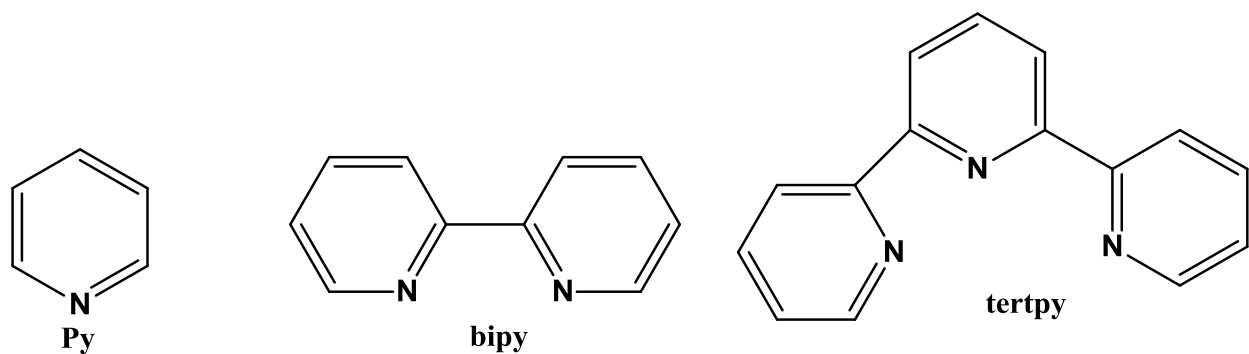


In 2012 Soh and Shamsuddin reported the synthesis for a series of  $\gamma$ -diimine Pd (II) complexes (**2e**, **2f**, **2g** and **2h**), as active pre-catalysts for the Heck cross coupling of bromoacetophenone with methyl acrylate. Activity depended on parameters such as base, solvent, supporting ligands and temperature. For instance in the case complex **3e** when the substitute at position **R<sub>3</sub>** was replaced by a hydrogen, the activity of 58 TON was observed, in the case of **3f** and **3g** a large substituent at position **R<sub>3</sub>** resulted in high activity of 76 and 75 TON, respectively. Lastly complex **3h** with large substituents at position **R<sub>2</sub>** and **R<sub>4</sub>** gave better activity of 100 TON [8].



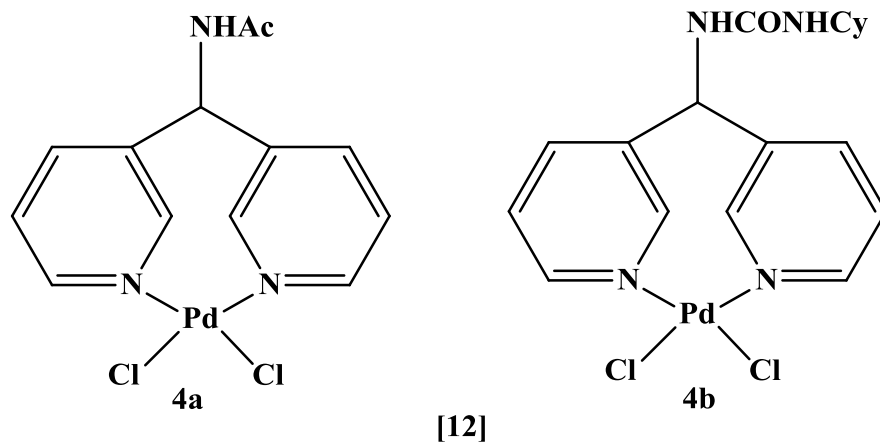
### 2.1.2 Dipyridine ligands in the Heck coupling reaction

Pyridine (py) is a six-membered heterocyclic aromatic ring similar to the benzene ring with one C-H ring set replaced by a nitrogen atom. It's a very flexible organic compound that can undergo both electrophilic and nucleophilic attack. Electrophilic attack is favorable at the nitrogen atom and less favorable at the carbon atom of the py ring. However, nucleophilic attack is possible at the carbon or hydrogen atom of the py ring. The py lone pair reacts with protonic acids to give simple salts, with Lewis acids to form coordination compounds and with transition metals to form complexes. The ligands formed from this organic compound are arguably one of the most important coordinating compounds since they form various complexes with different transition metals. When pys are connected together with different linkers, large different polydentate ligands could be formed [9]. Examples of such ligands formed when two or more pys are connected via a single bond at different positions are 2,2'-bipyridine (bipy), 2,2':6,2''tertpyridine (tertpy) etc.

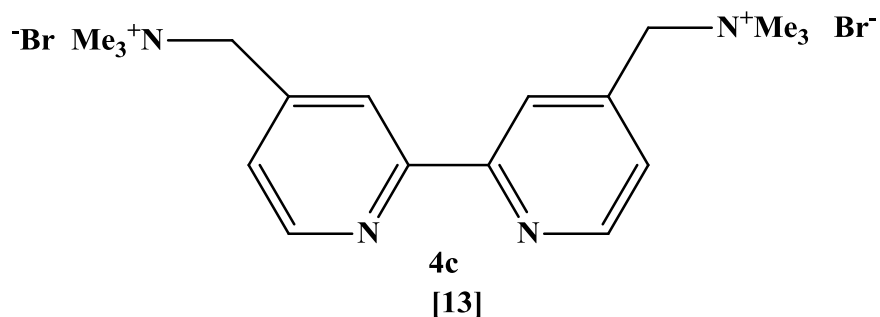


[9]

Due to the following properties these ligands are attractive in coordination chemistry, having  $\pi$  electron deficiency, which makes them to be good  $\pi$  electron acceptors, therefore providing soft sites for metal coordination [10]. However, bipyridine ligands provide stable complexes with palladium compared to amines which tend to coordinate weakly to palladium resulting in low stable complexes. The growing interest in application of chiral py-containing ligands in catalysis was lacking until 1981, when the first report of chiral py-containing ligands for asymmetric catalysis was published [11]. In this literature the study of chiral-py ligands with palladium precursors together with their complexes as precatalysts in the Heck coupling reaction was discussed.



Nejara *et al.* reported palladium-dipyridylmethylamine complexes (**4a**, **4b**) as good catalysts towards the Heck coupling reaction of deactivated aryl iodide and *n*-butyl acrylate at 140 °C in DMF and with Bu<sub>3</sub>N as a base. A catalytic activity of **4a**, and **4b** showed that they have similar efficiencies; TON = 10<sup>5</sup> for both were obtained and TOF = 2.5 and 2x10<sup>5</sup>, respectively [12].

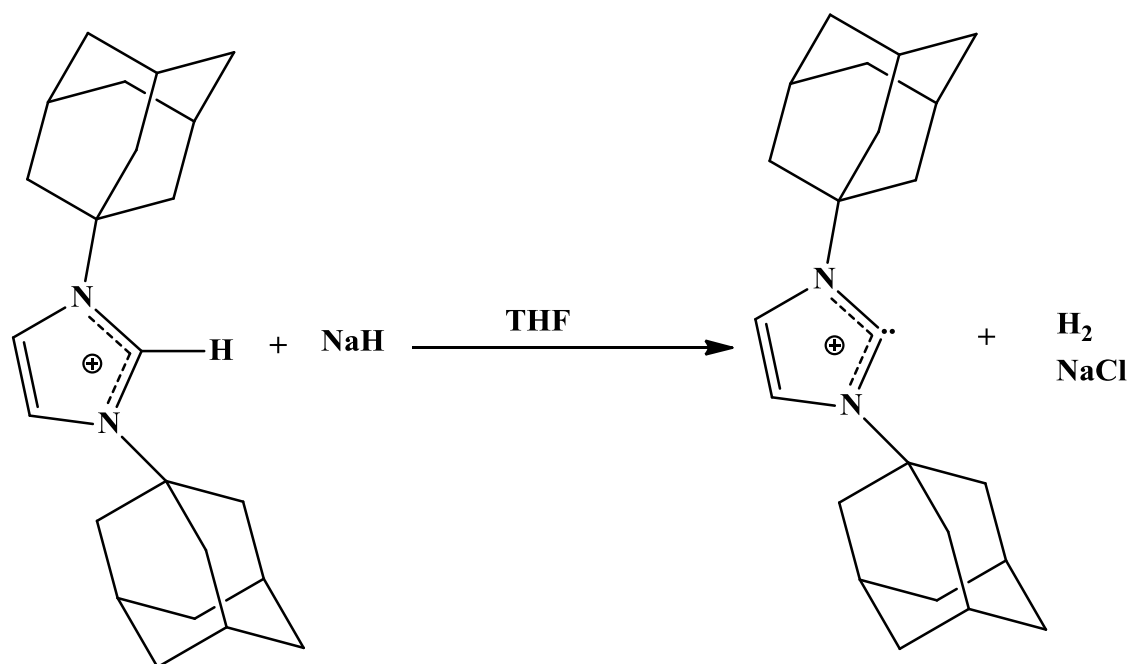


A water-soluble and air-stable Pd(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/cationic 2,2'-bipyridyl system was reported by Huang *et al.* in 2010; they found it to be a highly-efficient and reusable catalyst for the coupling of aryl iodides and alkenes in neat water using Bu<sub>3</sub>N as a base. The reaction was conducted at 140 °C in a sealed tube in air with a catalyst loading as low as 0.0001 mol % for the coupling of activated aryl iodides with butyl and ethyl acrylates, providing the corresponding products in good to excellent yields (48 % and 63 %) with very high turnover numbers (TON = 4800 and 63000), respectively [13]. In the case of styrene, Heck coupling products were obtained in good (38 %) to

high yields (92 %) by using a greater catalyst loading (1 mol %) and TBAB as a phase-transfer agent.

### 2.1.3 N-heterocyclic carbene (NHCs) ligands in the Heck coupling reaction

Carbenes are known as neutral organic species where the carbon atom has six electrons in its valence shell and has a valence of two. In organic chemistry, carbenes are highly reactive electrophilic transient intermediates that are very rarely isolated because of their electron deficiency. In 1991, Arduengo's seminal discovery of a stable N-heterocyclic carbene led to incredible activity and development in coordination chemistry NHCs [14].

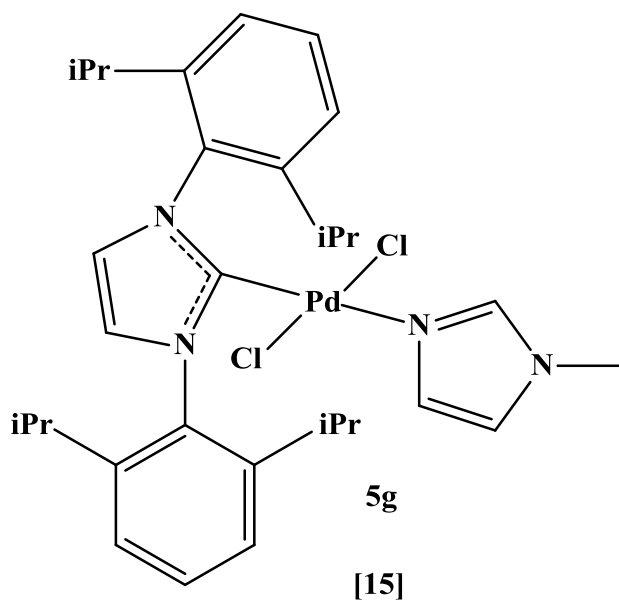


**Scheme 2.1** : The first isolated imidazolylidene carbene prepared by Arduengo *et. al.*

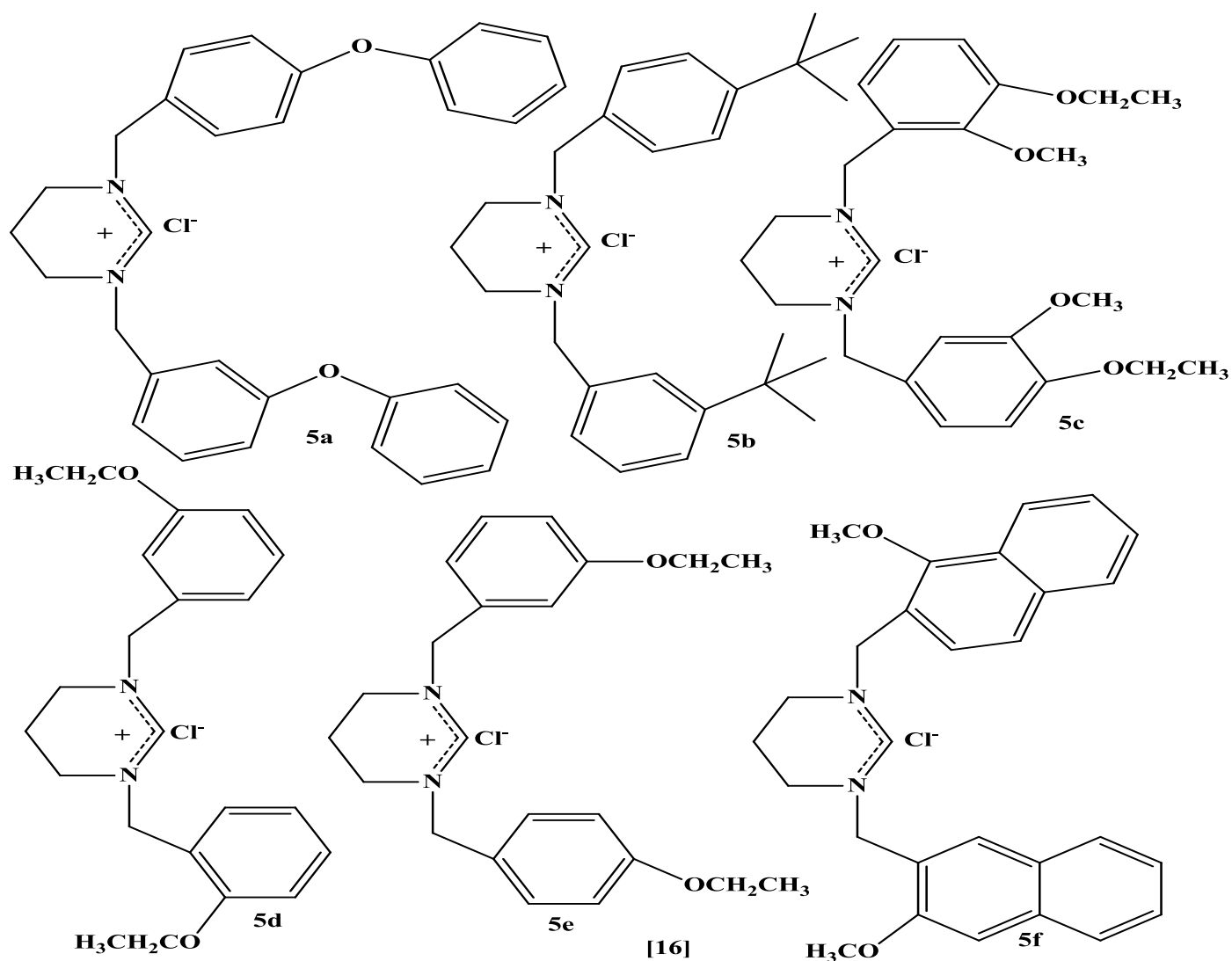
In the past two decades, palladium complexes containing N-heterocyclic carbene (NHC) ligands have received tremendous attention as effective catalysts. The high catalytic activities found in N-heterocyclic carbene-based catalysts have been attributed to the strong  $\sigma$ -donor ability of the carbenes, unique steric properties and enhanced thermal stability of the N-heterocyclic carbene ligands as compared to phosphine ligands. In recent years it has been shown that palladium



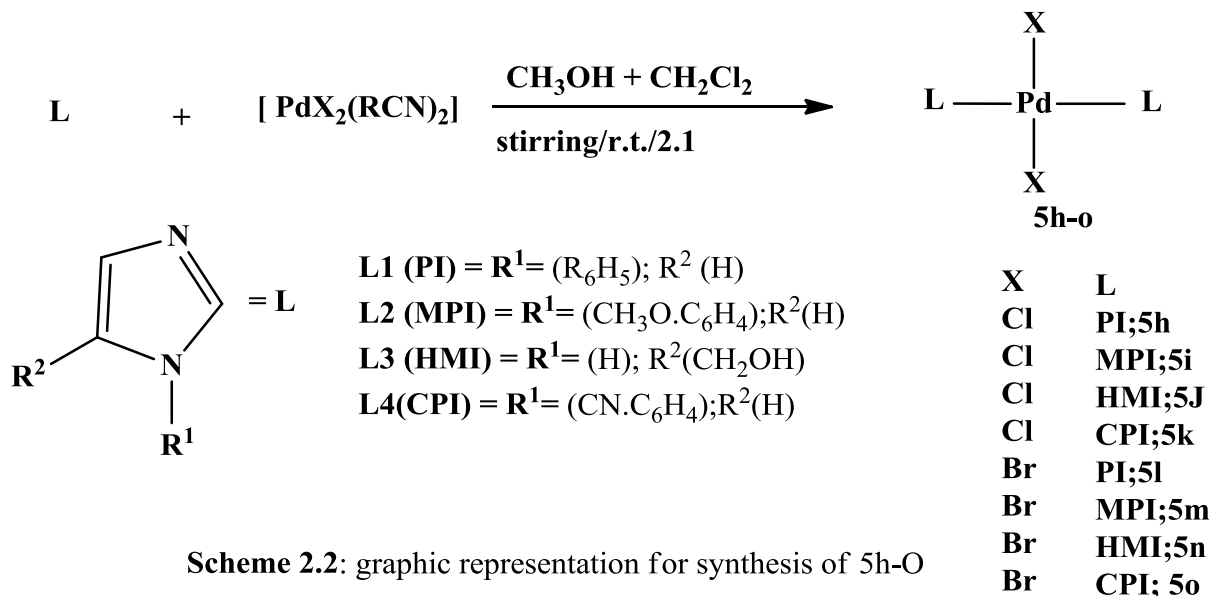
complexes containing NHC ligands are effective catalysts in the Heck coupling reactions for aryl bromides and chlorides



Gao *et al.* reported a well-defined N-heterocyclic carbene-palladium (II)-1-methylimidazole complex **5g** as effective catalysts for the Heck coupling reaction of variety of aryl chlorides with styrene. Both activated and deactivated aryl chlorides were able to give corresponding products in good to excellent yields (94 % to 94 %, respectively) by using tetrabutylammonium bromide (TBAB) as the ionic liquid [15]. In 2010, Yaser *et al.* reported a novel 1,3-dialkyl-3,4,5,6 tetrahydropyrimidinium salt and Pd(OAc)<sub>2</sub> as palladium source. The palladium complexes derived from salts **5a-f** prepared *in situ* showing good catalytic activity in the Heck coupling reaction of 4-bromoacetophenone with styrene in the presence of K<sub>2</sub>CO<sub>3</sub> as base in 3 ml of H<sub>2</sub>O and 3 ml of DMF. Different catalytic activities were observed for salts: **5a** 90 %, **5b** 99 %, **5c** 94 %, **5d** 99 %, **5e** 93 % and **5f** 86 % yields were obtained [16].



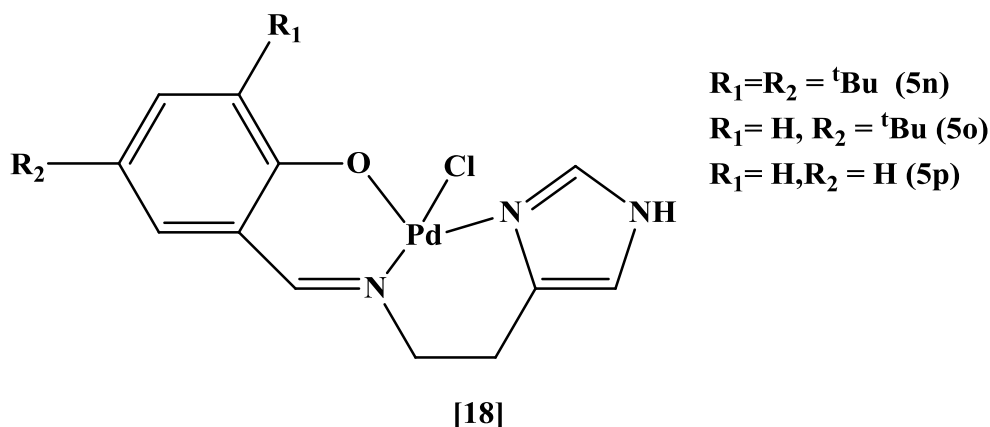
In 2012 Trivedi *et al.* reported a series of new palladium(II) complexes from the general formula  $\text{trans-[PdX}_2\text{L}_2]$  [ X= Cl<sub>2</sub>; Br; L = 1-phenylimidazole (PI), 1-(4-methoxyphenyl)-1H-imidazole (MPI), 4(5)-(hydroxymethyl)-imidazole (HMI), 1-(4-cyanophenyl)-imidazole) (CPI)] as shown in graphic representation in **scheme 2.2**. Complexes **5h-5m** were tested and found to be catalytic active on the Heck coupling reaction of deactivated and activated aryl halides and vinyl compounds in the presence of 0,0001 equivalent Pd catalysts in DMF at 140 °C [17]. Complexes **5h, 5i, 5l** and **5k** exhibited higher catalytic activity than complexes **5j, 5k, 5h,** and **5m**.



**Scheme 2.2:** graphic representation for synthesis of 5h-O

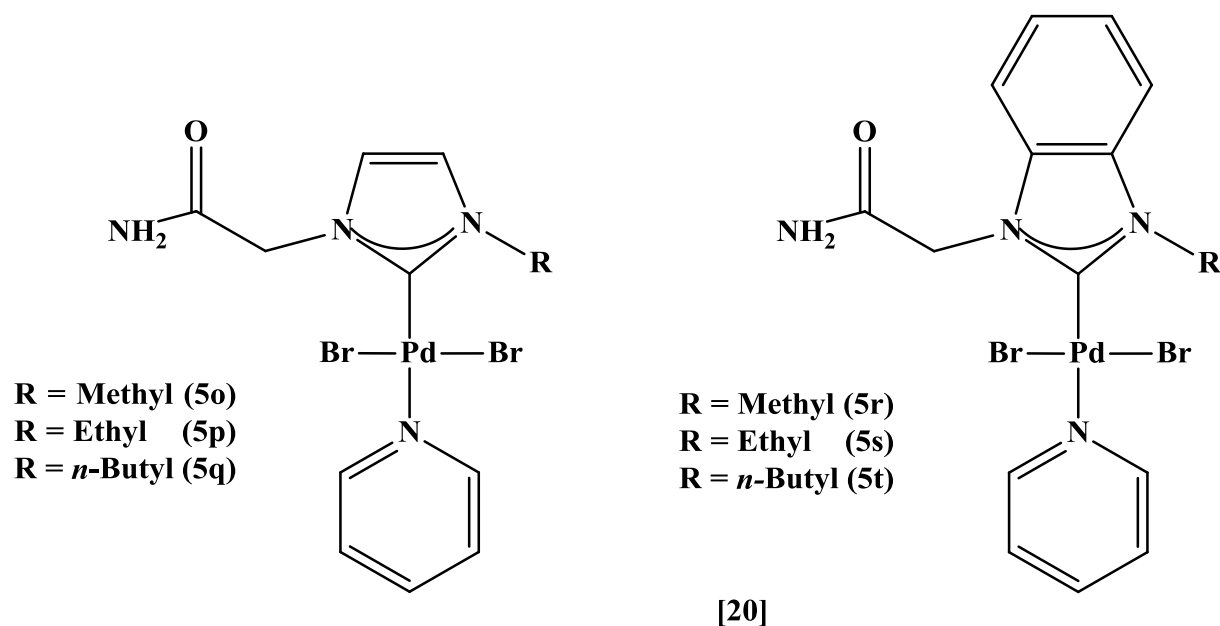
[17]

Darkwa and co-workers reported complexes **5n**, **5o**, **5p**, synthesized from the reaction of 4-tert-butyl-2-2-(2-[1H-imidazole-4-yl]-ethylimino)-methyl-phenol and 2-(2-[H-imidazole-4-yl]-ethylamino)-methyl-phenol ligands reacting with either [Pd(NCMe)<sub>2</sub>Cl<sub>2</sub>] or [Pd(COD)MeCl] affording the pincer palladium complexes [18].



All three complexes (**5n**, **5o** and **5p**) were catalytically active in the Heck coupling reaction of iodobenzene with butyl acrylate. In the presence of triethylamine as a base, conversions of 97 %, 96 %, and 97 %, respectively were obtained. In 2013, series of naphthalenomethyl-substituted imidazolidinium salts were prepared by Aktas *et al.* and they reported that the *in situ* prepared catalytic systems naphthalenomethyl-substituted imidazolidinium salts as precursor, Pd(OAc)<sub>2</sub> as

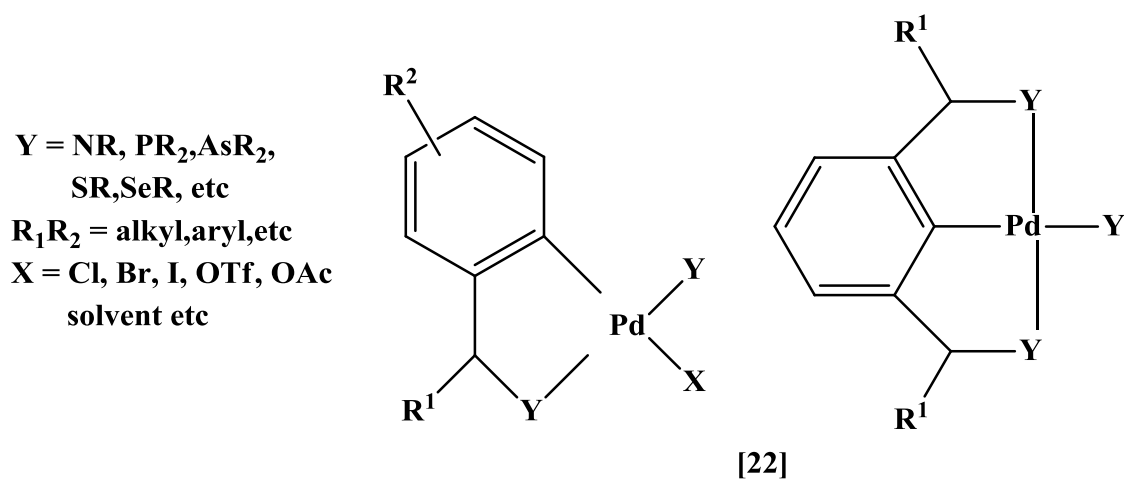
source of palladium and  $K_2CO_3$  as a base, catalyzed quantitatively the Heck coupling and Suzuki Miyaura coupling of aryl halides under mild reaction conditions in aqueous media. For the Heck coupling reaction of various aryl bromides and styrene, catalytic activity of the average 84-99 % yields were obtained [19].



Yang *et al.* reported that in py-enhanced palladium amide-functionalized N-heterocyclic carbene complexes (**5o**, **5p**, **5q**, **5r**, **5s**, and **5t**), as precatalyst in the Heck coupling reaction of aryl chlorides and styrene, all these complexes showed good catalytic activity of 42 %, 48 %, 55 %, 54 %, 68 and 77 % yield [20], respectively. In conclusion benzimidazole-derived complexes showed better catalytic activity than imidazole-based complexes, but when aryl bromide was used all the complexes showed excellent catalytic activity of the average of 99 %.

## 2.2.4 Nitrogen-based palladacycles in the Heck coupling reaction

In general, palladacycles are known as any palladium containing compound containing one palladium-carbon bond intramolecularly stabilized by one or two neutral donor atoms (Y), where the organic moiety act as a C-anionic four electron donor ligands (bidantate) or as a C-anionic six electron donor ligands (tridentate). Structural representation of such compound is shown scheme 3.3.



In 2000 Iyer *et al.* reported the use of complex **6a** in the Heck coupling reaction with TONs of up to 936 and 894 were obtained when aryl bromide was reacted with ethyl acrylate and styrene, respectively. When an activated chloride (*p*-nitrochlorobenzene) was treated with ethyl acrylate, lower activities (TON of 287) were observed [21]. In the case of styrene, higher activities were obtained (TON of 728). In 2001, using complex **6a**, Beletskaya *et al.* conducted the same reaction at different conditions and obtained very low activities of up to 103 TONs [22].



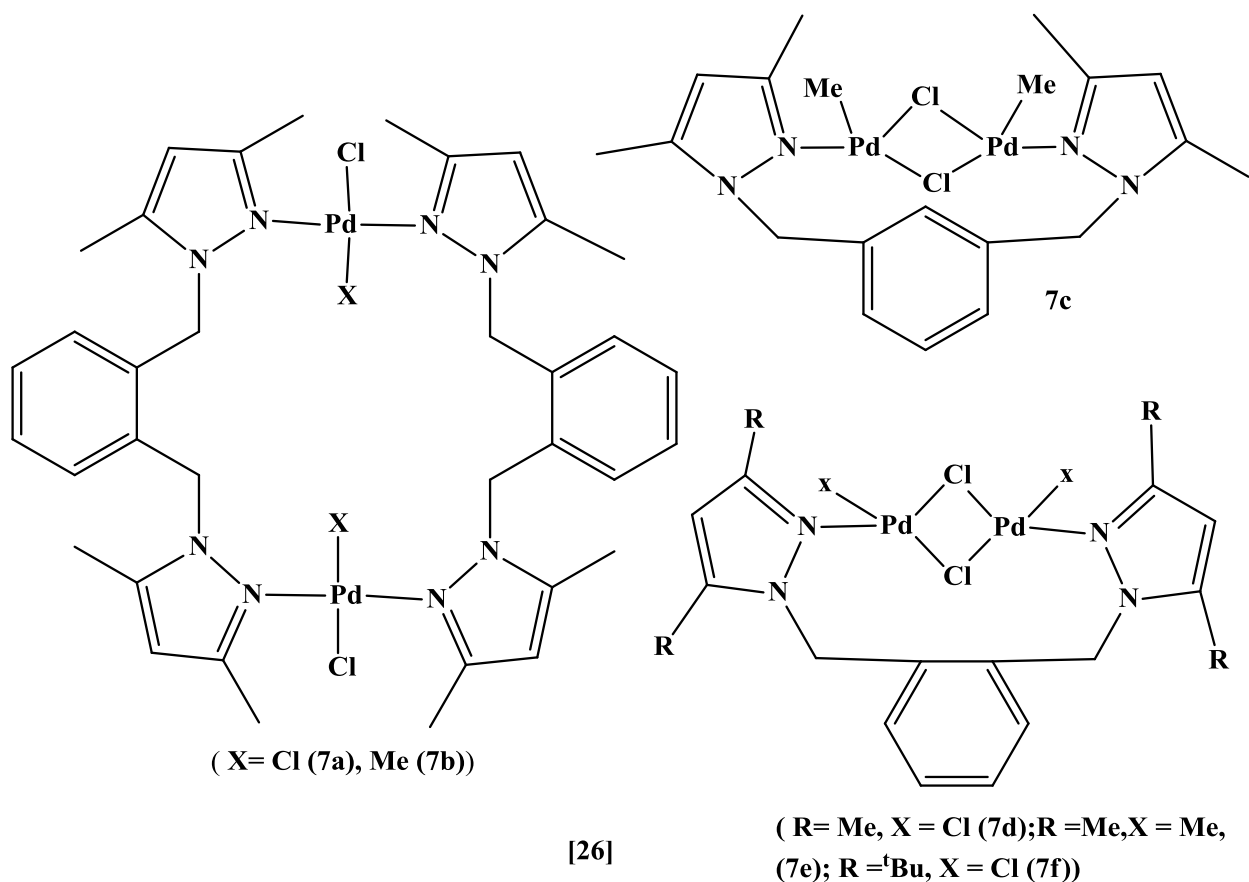
catalytic activity was observed in the case of methyl acrylate and 60 % was obtained in the case of styrene [24].

#### 2.1.4 Pyrazole based ligands in the Heck coupling reaction

The interesting feature of these heterocycles is their  $\pi$ -electron deficiency. This is a most likely identity of bidentate and tridentate nitrogen heterocyclic compounds having 6-membered rings such as 1,10-phenanthroline (phen) and 2,2'-bipyridine (bipy). However, the  $\pi$ -electron excessive five membered nitrogen heterocycle pyrazole, is a poorer  $\pi$ -electron acceptor. In fact, it is a better  $\pi$ -donor and hence acts as a hard donor site [25]. These ligands can bind to metals via N in pyrazole (a), or it can be deprotonated as in (b) which can bind using both nitrogen atoms.

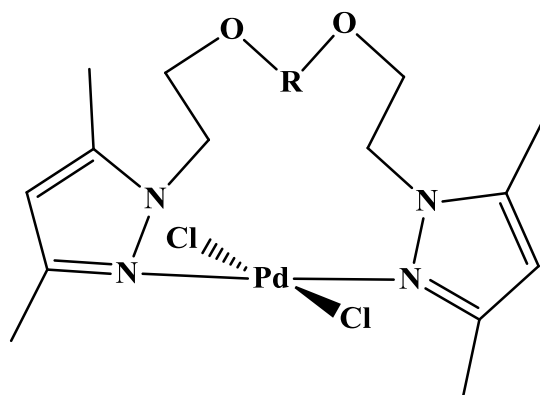


As ligands, they are sensitive towards air and moisture, and their ability to coordinate with various transition metals made them to be interesting ligands. Furthermore, the easy synthesis of various pyrazole ligands is because of its flexibility to allow appropriate choice of substituents on 2-N, 3-C, and 5-C atoms of the pyrazole, hence allowing the opportunity to fine tune both electronic and steric control of the properties of the metal complexes. In the past decade nitrogen donor ligands containing pyrazoles have been used with different palladium precursors to form very active non-phosphine palladium catalysts in the Heck coupling reactions.



Motsoane *et al.* reported poly (pyrazol-1-ylmethyl) benzene ligands reacting with either  $[\text{PdCl}_2(\text{NMe}_2)_2]$  or  $[\text{PdClMe}(\text{COD})]$  to form dinuclear palladium complexes (**7a-h**) [26], which were tested as precatalysts in the Heck coupling reaction of aryl iodide and butyl acrylate at 80 °C for 24 hrs. High catalytic activity ranges from 87.36 to 105 TON were obtained; the lower catalytic activities were obtained for **7c** and **7d** which was 87.36 TON for both, the highest catalytic activity was 98.91 TON for **7a**.

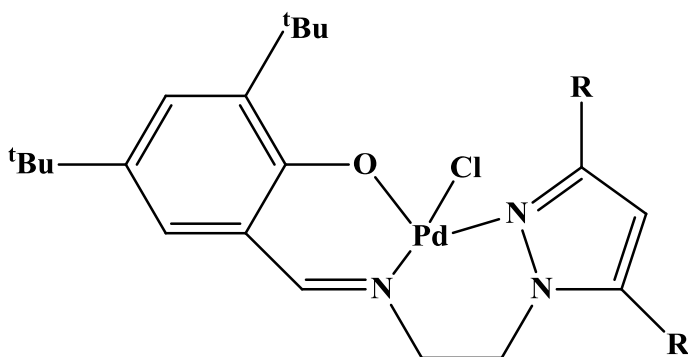




- R = ethyl (7g)**  
**R = *O*-xylyl (7h)**  
**R = *m*-xylyl (7i)**  
**R = *p*-xylyl (7j)**

[27]

In 2010 Guerrero *et al.* reported  $[\text{PdCl}_2(\text{L})]$  complexes (**7g-7j**), where **L** is 3,5-dimethylpyrazolic hybrid ligands *N*-substituted by polyether chains and / or phenyl groups. These complexes have been applied as precatalysts in the Heck coupling reaction between phenyl halides and tert butyl acrylate. All the complexes were efficient to catalyze the Heck olefination and provided good yields under phosphine free conditions even for aryl chlorides. In the case whereby aryl chlorides were used complexes (**7g-7j**) of good catalytic activity of 895,395,372 and 353 TON were obtained and with TOF 17,14,12, and 12, respectively [27].

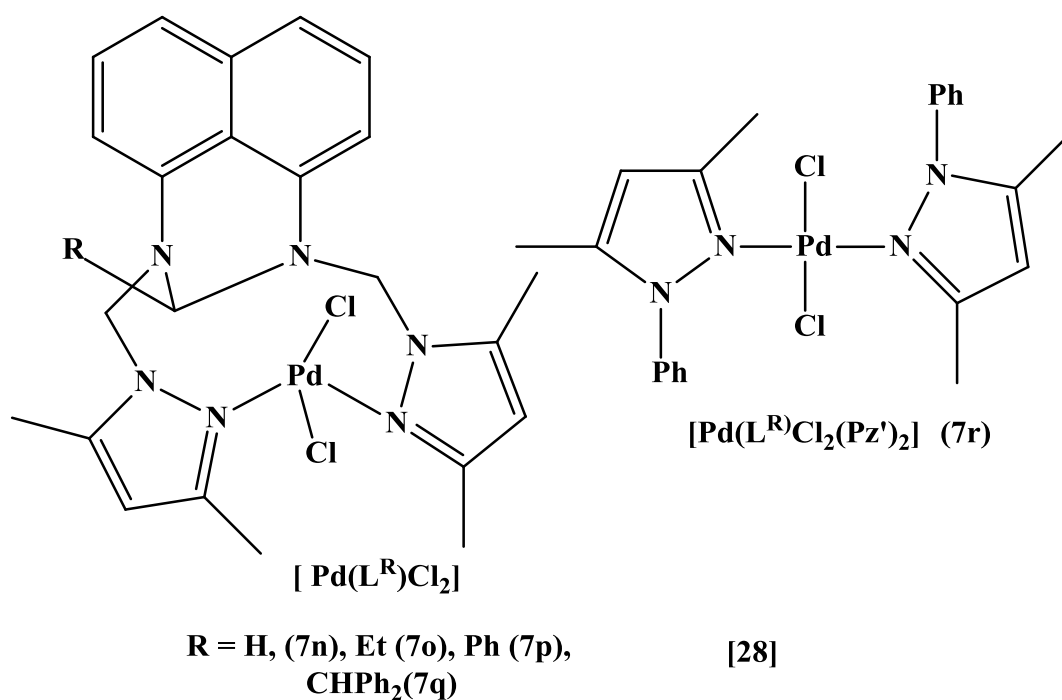


- R = H, X = Cl (7k)**  
**R = Me, X = Cl (7l)**  
**R = Me, X = Me (7m)**

[18]

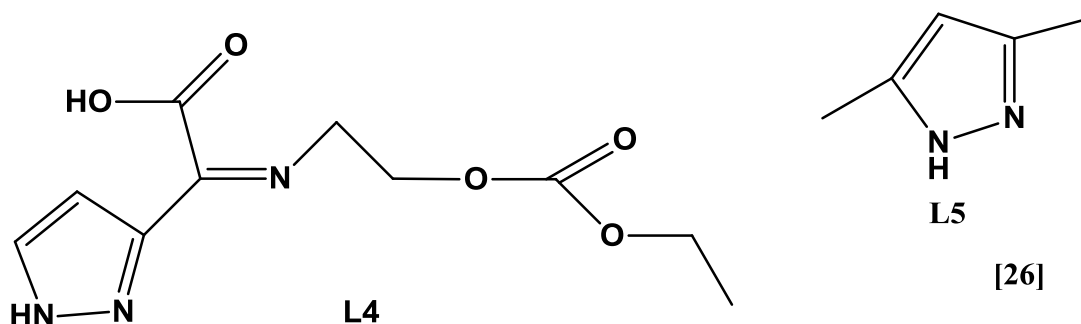
In the same paper reported by Darkwa and co-workers in 2012, complexes **7k**, **7i**, **7m**, were synthesized from the reaction of 2,4 di-tert-butyl-6-[2-pyrazol-yl-ethylimino-methyl]-phenol and 6-[[2-(3,5-dimethyl-pyrazol-1-yl)-ethylimino]-methyl]-phenol with either  $[\text{Pd}(\text{NCMe})_2\text{Cl}_2]$  or  $[\text{Pd}(\text{COD})\text{MeCl}]$  affording the pincer palladium complexes, **7k**, **7i**, **7m** were used as precatalysts

in Heck coupling reaction of butyl acrylate and bromobenzene, giving conversions of 94%, 96%, and 94, respectively [18]. Chou *et al.* reported a new group of mononuclear palladium (II)  $[\text{PdCl}_2(\text{L}^{\text{R}})]$  complexes (**7n-q**) with bidentate trans-chelating pyrazole ligands (R = H, (**7n**), Et (**7o**), Ph (**7p**),  $\text{CHPh}_2$  (**7q**)) and a new mononuclear palladium (II) complex with monodentate trans-chelated pyrazole ligand  $[\text{PdCl}_2(\text{Ph-pz}^{\text{r}})_2]$  (**7r**). Complexes (**7o-r**) were active pre-catalysts for Heck coupling reactions of iodobenzene and *t*-butyl acrylate in MeOH; complex **7q** appeared to be more active with TON 1000 [28]. In the presence of co-catalysts  $[\text{nNBu}_4]\text{Br}$ . However, complex **7r** showed the highest catalytic activity of 97 TON for the Heck coupling reactions of activated bromobenzene and *t*-butyl acrylate.



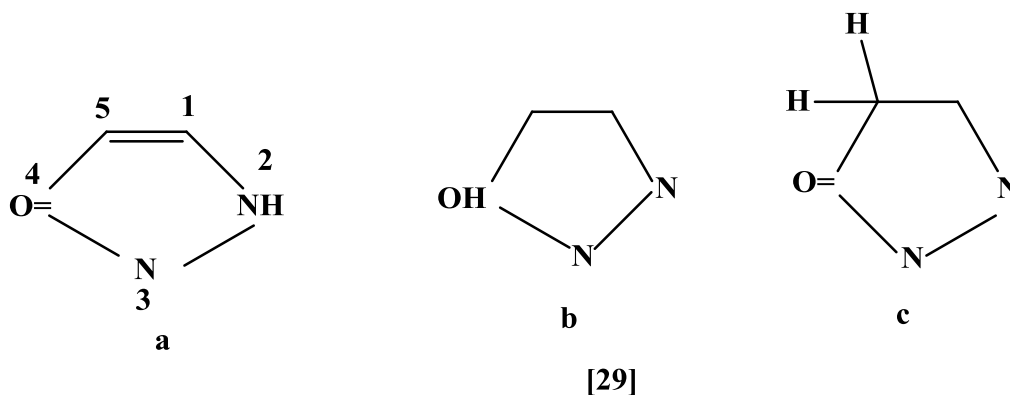
In this work we introduce the following ligands:  $\alpha$ -[(2-Ethoxy-2-oxoethoxy)imino]-3-pyrazole acetic acid (**L4**) and 3,5 dimethyl pyrazole (**L5**) with either  $\text{PdCl}_2$  or  $\text{Pd}(\text{OAc})_2$  catalytic systems in the Heck coupling reactions of iodobenzene with various alkenes at 80 °C. The catalytic activity of these systems is discussed in chapter four. To our best knowledge we are the first

people to use ligand **L4** as ligand in the Heck coupling reaction. In order to compete we used **L5** but in this case we used it as it is, not combined with any other organic compound as a ligand.



#### 2.1.4 Pyrazolone based ligands in Heck coupling reaction

Pyrazolone, a five-membered-ring lactam, is a derivative of pyrazole that has an additional keto (C=O) group. It has a molecular formula of  $C_3H_4N_2O$ . The pyrazolone nucleus has been known to exist in three tautomer structures [29].



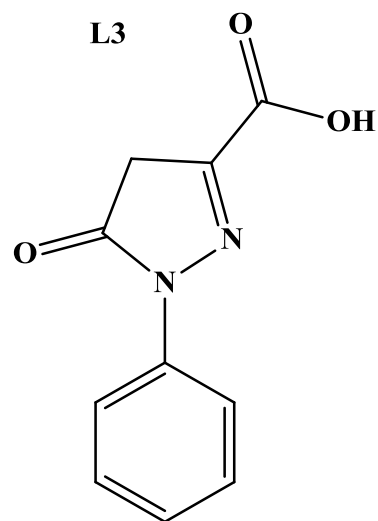
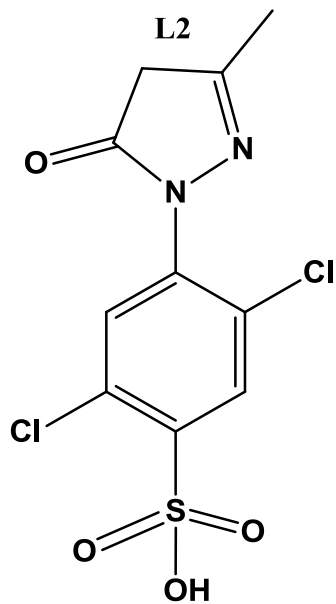
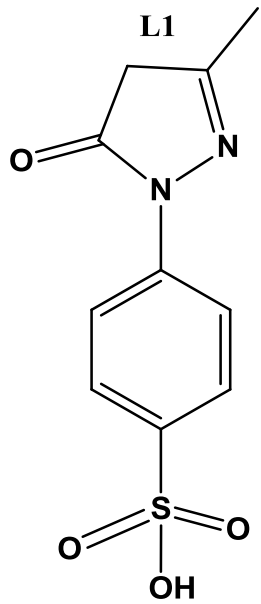
Structure **(a)** exists in several substituted pyrazolones which are mostly known and applied as antipyretic agents. All these ligands are identified by the presence of a phenyl group attached to the nitrogen atom in the 1- position and a methyl group in 3- position. A phenyl group in 1- position and a methyl group in 3- position seem to be important for antipyretic activity. Several 4,4- dimethyl derivatives, as well as pyrazole blue and tartrazine are produced from formula **(b)**,

whereas from structure (c) several pyrazolone dyes have been produced. Ever since, the discovery of pyrazolone was known as non-steroidal anti-inflammatory agent (or drugs), but of late they are known to exhibit antioxidant, anticancer, antibacterial and several other pharmacological actions.

Nevertheless, the application of these compounds in the treatment of human ailments declined drastically after their toxicity towards bone marrow was discovered. However, the application of pyrazolone as drugs has warranted significant attention; wide applications have been discovered for this group of compounds outside the pharmaceutical field. For example, they have been used for solvent extraction of metal ion in both acidic and basic pH [30], for analytical purposes [31], in the preparation of azo colourants [32], as ligands in complexes with catalytic activity [33] and in synthesis of rare earth metal complexes with interesting photophysical properties [34].

In this study the focus is on the application of substituted pyrazolone as auxiliary ligands in forming complex systems with catalytic activity.

We report application of three pyrazolone based ligands which are 1-(4-Sulfophenyl)-3-methyl-5-pyrazolone (**L1**), 1-(2,5-Dichloro-4-sulfophenyl)-3-methyl-5-pyrazolone (**L2**) and 5-oxo-1-phenyl-2-pyrazolin-3-carboxylic acid (**L3**), with either PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> catalytic system in the Heck coupling reaction of iodobenzene with different alkenes (ethyl acrylate, butyl acrylate ) at 80 °C. The results of this work are discussed in chapter four. As far as our literature survey is concerned we are the first to report pyrazolone based ligands in the Heck coupling reaction.



## 2.2 References

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## CHAPTER 3

### Experimental and analytical procedure

#### 3.1 Material

##### 3.1.1 Chemicals and reagents

All reagents were commercially purchased and were used as received. Most of these reagents were bought in their highest grades. The list of reagents, grades, formulas and their supplies are listed in table 3.1.

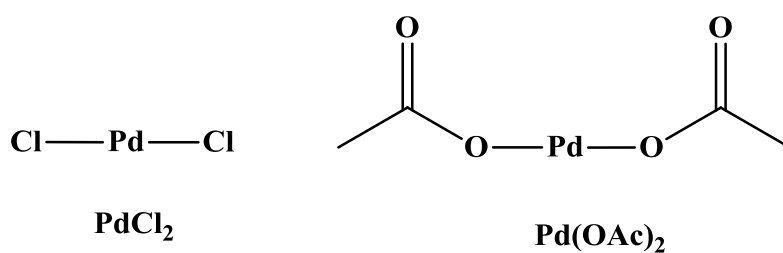
Table 3.1 Chemicals and reagents applied in this work

CHEMICAL	FORMULA	GRADE	SUPPLIER
Butyl acrylate	$C_7H_{12}O_2$	99 %	Merck
Ethyl acrylate	$C_5H_8O_2$	99 %	Merck
Styrene	$C_8H_8$	99 %	Sigma-Aldrich
Triethylamine	$C_6H_{15}N$	98 %	Sigma-Aldrich
Potassium Carbonate	$K_2CO_3$	99 %	Alfa-Aesar
Sodium Carbonate	$Na_2CO_3$	99.5 %	Merck
Cesium Carbonate	$Cs_2CO_3$	99 %	Alfa-Aesar
<i>N,N</i> -dimethylformamide (DMF)	$C_3H_7NO$	Chromasolv Plus for HPLC 99,9 %	Sigma-Aldrich
Dimethylsulfoxide (DMSO)	$C_2H_6SO$	Chromasolv Plus for HPLC 99,9 %	Sigma-Aldrich
Acetonitrile	$C_2H_3N$	99,9 %	Merck
Toluene	$C_7H_{10}$	99,9 %	Merck
Dichloromethane	$CH_2Cl_2$	99,9%	Rochelle Chemicals
Iodobenzene	$C_6H_5I$	Reagent Plus 98 %	Sigma-Aldrich
Acetone	$C_3H_6O$	99,5 %	Rochelle Chemicals

### 3.1.2 Catalysts used

Table 3.2 List for the used pre-catalysts

CHEMICAL	FORMULA	GRADE	SUPPLIER
Palladium(II)chloride	PdCl <sub>2</sub>	99.9 %	Alfa Aesar
Palladium(II) acetate	Pd(OAc) <sub>2</sub>	Reagent grade 98 %	Sigma-Aldrich

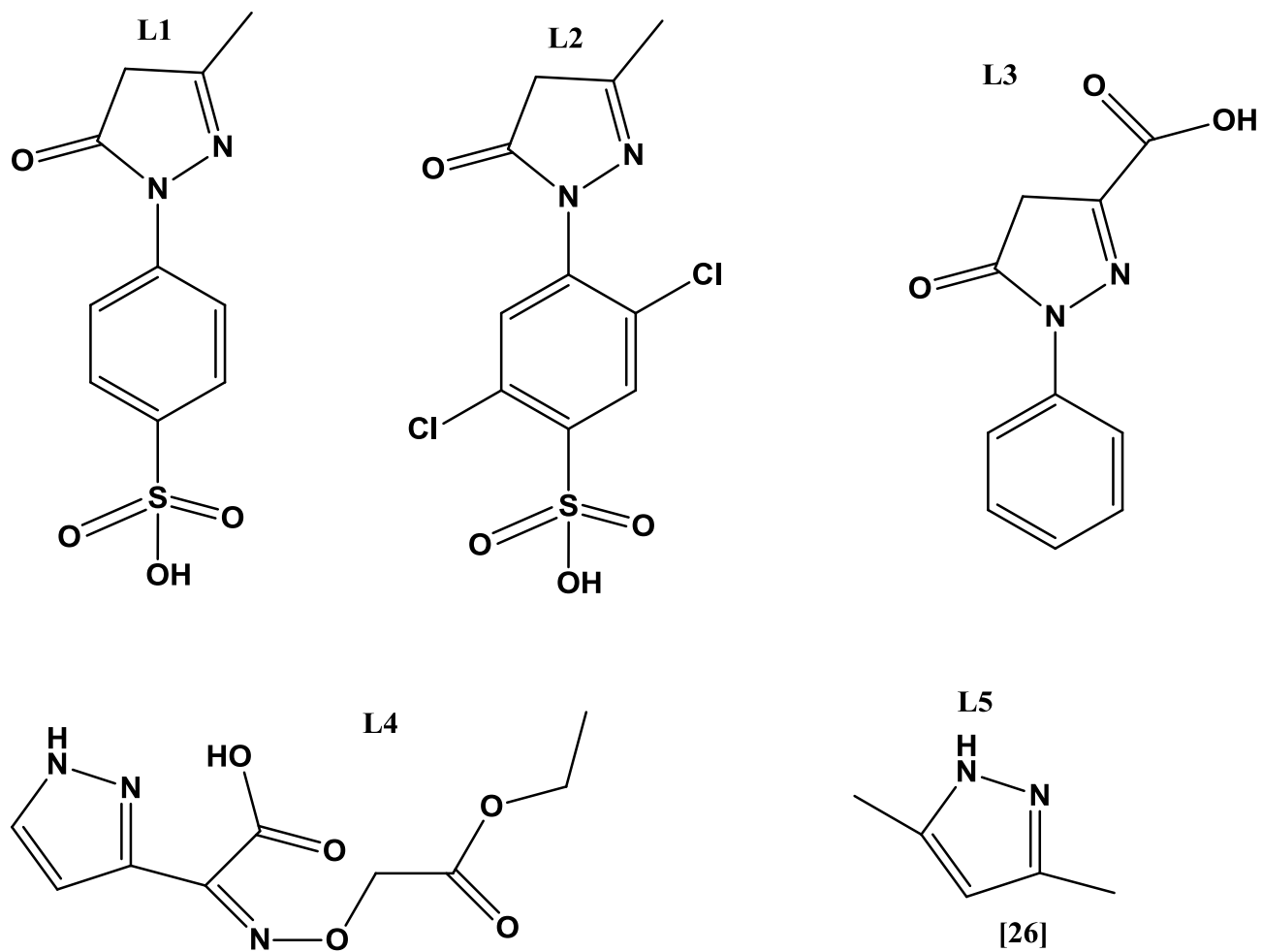


Scheme 3.1 : Structures of the catalysts used in the Heck reaction

### 3.1.3 Ligands used

Table 3.3 List for the ligands used

CHEMICAL	FORMULA	GRADE	SUPPLIER
1-(4-Sulfophenyl)-3-methyl-5-pyrazolone	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub> S	97 %	Sigma-Aldrich
1-(2,5-Dichloro-4-Sulfophenyl)-3-methyl-5-pyrazolone	C <sub>10</sub> H <sub>8</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>4</sub> S	98 %	Sigma-Aldrich
5-Oxo-1-phenyl-2-pyrazolin-3-carboxylic acid	C <sub>10</sub> H <sub>8</sub> N <sub>2</sub> O <sub>3</sub>	98 %	Sigma-Aldrich
α-[(2-Ethoxy-2-oxoethoxy)imino]-3-pyrazole acetic acid	C <sub>9</sub> H <sub>11</sub> N <sub>3</sub> O <sub>5</sub>	97 %, mixture of syn and anti isomer	Sigma-Aldrich
3,5-Dimethyl-pyrazole	C <sub>5</sub> H <sub>8</sub> N <sub>2</sub>	99 % ,synthesis	Merck



**Scheme 3.2:** Structures of the ligands used in the Heck reaction

## 3.2 Methodology

### 3.2.1. Effect of olefins using PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> as source of palladium(0) with pyrazolone and pyrazole as the stabilizing ligands

A 20 ml vial was charged with the aryl iodide (1 mmol), butyl or ethyl acrylate (1,5 mmol), and triethylamine (Et<sub>3</sub>N) (2mmol). To the resultant mixture, the catalyst (PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> (1% mmole) and ligands (**L1-L5**) (1 % mmole) were added. The solution was made up to 10 ml with the *NN*-dimethylformamide (DMF). The mixture was heated in Carousal 12 set at 80 °C for 4 hours under nitrogen gas (N<sub>2</sub>) atmosphere. Initial and final samples were taken and mixed with dichloromethane for GC analysis using an autosample with a 1 ml syringe needle. The percentage conversions were determined based on the consumption of the aryl iodide.

### 3.2.2 Effect of temperatures in Heck coupling reaction

A 20 ml vial was charged with the aryl iodide (1 mmol), butyl or ethyl acrylate (1,5 mmol), triethylamine (Et<sub>3</sub>N) (2 mmol). To the resultant mixture, the catalyst (PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> (1% mmole) and ligands (**L1-L5**) (1 % mmole) were added. The solution was made up to 10 ml with the *N,N*-dimethylformamide (DMF). The mixture was heated in Carousal 12 set at various temperatures for 4 hours under nitrogen gas (N<sub>2</sub>) atmosphere. Initial and final samples were taken and mixed with dichloromethane for GC analysis using an autosample with a 1 ml syringe needle.

### 3.2.3 Effect of the base used in Heck coupling reaction

A 20 ml vial was charged with the aryl iodide (1 mmol), butyl or ethyl acrylate (1,5 mmol), with different bases (2 mmol). To the resultant mixture, the catalyst (PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> (1% mmole) and ligands (**L1-L5**) (1 % mmole) were added. The solution was made up to 10 ml with the *N,N*-dimethylformamide (DMF). The mixture was heated in Carousal 12 set at 80 °C for 3 hours under nitrogen gas (N<sub>2</sub>) atmosphere. Initial and final samples were taken and mixed with dichloromethane for GC analysis using an autosample with a 1 ml syringe needle.

### 3.2.4 Effect of solvents used in the Heck coupling reaction

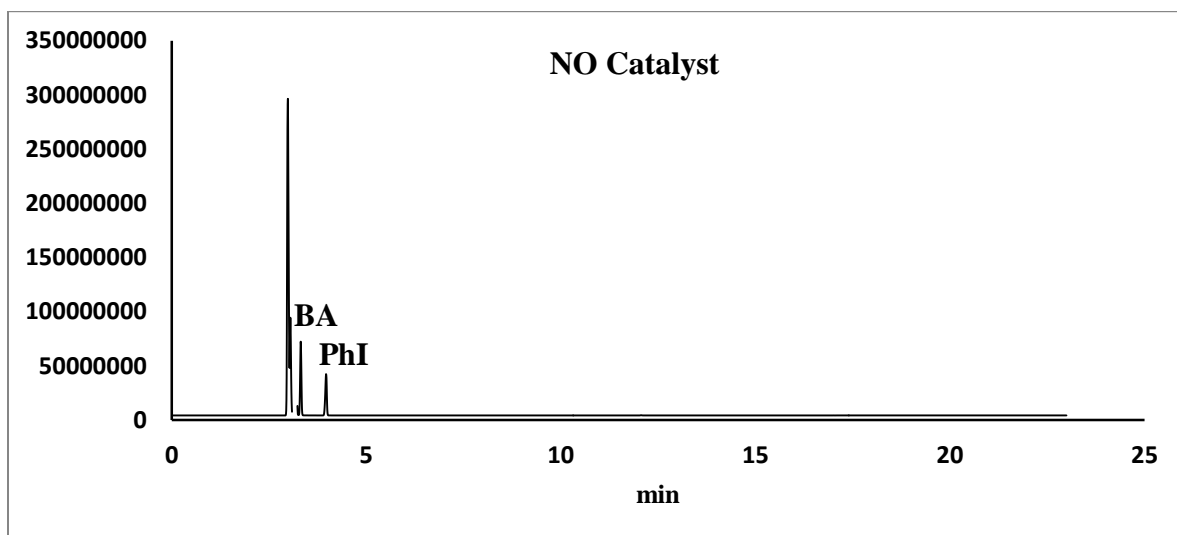
A 20 ml vial was charged with the aryl iodide (1 mmol), butyl or ethyl acrylate (1,5 mmol), triethylamine (Et<sub>3</sub>N) (2 mmol). To the resultant mixture, the catalyst (PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub>) (1% mmole) and ligands (**L1-L5**) (1 % mmole) were added. The solution was made up to 5 ml with various solvents (DMF, DMSO, CH<sub>3</sub>CN and Toluene). The mixture was heated in Carousal 12 set at 80 °C for 3 hours under nitrogen gas (N<sub>2</sub>) atmosphere. Initial and final samples were taken and mixed with dichloromethane for GC analysis using an autosample with a 1 ml syringe needle.

### 3.2.5 Effect of time used in the Heck coupling reaction

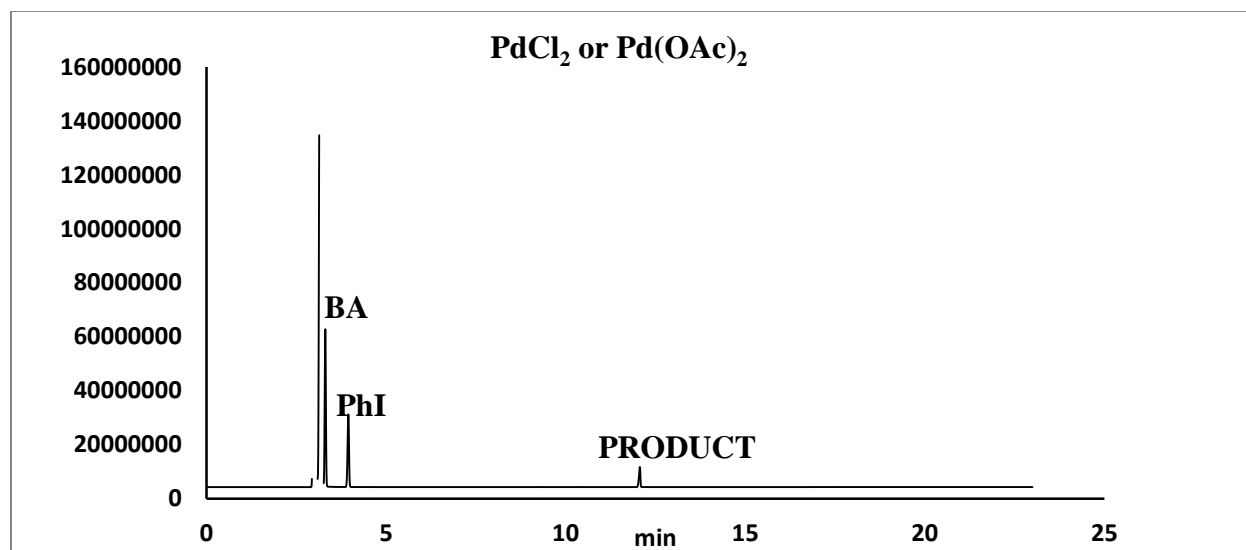
A 20 ml vial was charged with the aryl iodide (1 mmol), butyl or ethyl acrylate (1,5 mmol), triethylamine (Et<sub>3</sub>N) (2 mmol). To the resultant mixture, the catalyst (PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub>) (1 % mmole) and ligands (**L1-L5**) (1 % mmole) were added. The solution was made up to 10 ml with N,N-dimethylformamide (DMF). The mixture was heated in Carousal 12 set at 80 °C for 0,5 h, 1 h, 2 h, 4 h, 8 h and 24h time intervals under nitrogen gas (N<sub>2</sub>) atmosphere. Initial and final samples were taken and mixed with dichloromethane for GC analysis using an autosample with a 1 ml syringe needle.

## 3.3 Analytical instrumentation

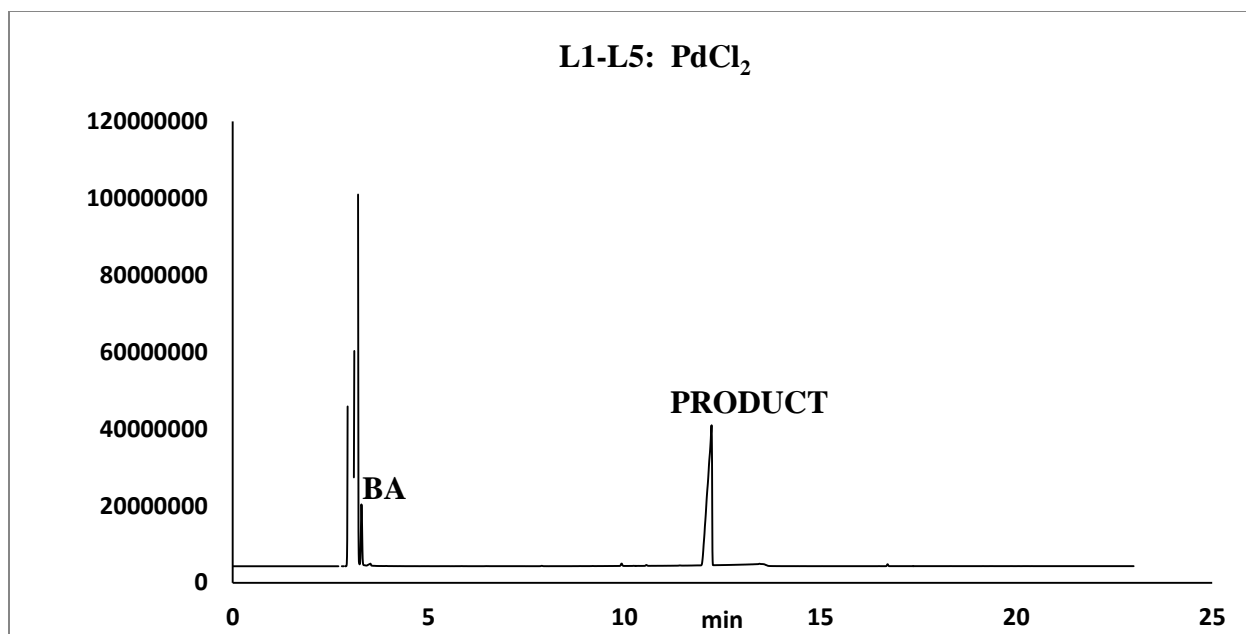
The samples were analyzed by GC/MS ( Clarus 500 gas chromatograph and MS, SQ8S, 30 m, 0.25 mm column with 0.25 mm film thickness) and GC ( Perkin Elmer GC on a 30 m, 0.25 mm capillary column (5 % Dimethylsiloxane, 95 % phenyldimethylsiloxane with a 0.25 mm film thickness and a FID detector). The GC and GC/MS programs applied throughout the analysis were as follows: the column temperature was 40 °C at the beginning of the program and it was heated with a rate of 10 °C / min up to 250 °C, then it was kept at this temperature for 3 min. Throughout the analysis the injector and detector temperatures were kept constant at 280 °C and 300 °C, respectively. The analysis was performed on a split mode with a split ratio of 1/50. A sample of GC chromatogram of a reaction taken at this temperature program is given in Figure 3.1. (a) In absence of the catalyst, (b) In the presence of pre-catalysts, and (c) In the presence of pre-catalyst and ligand.



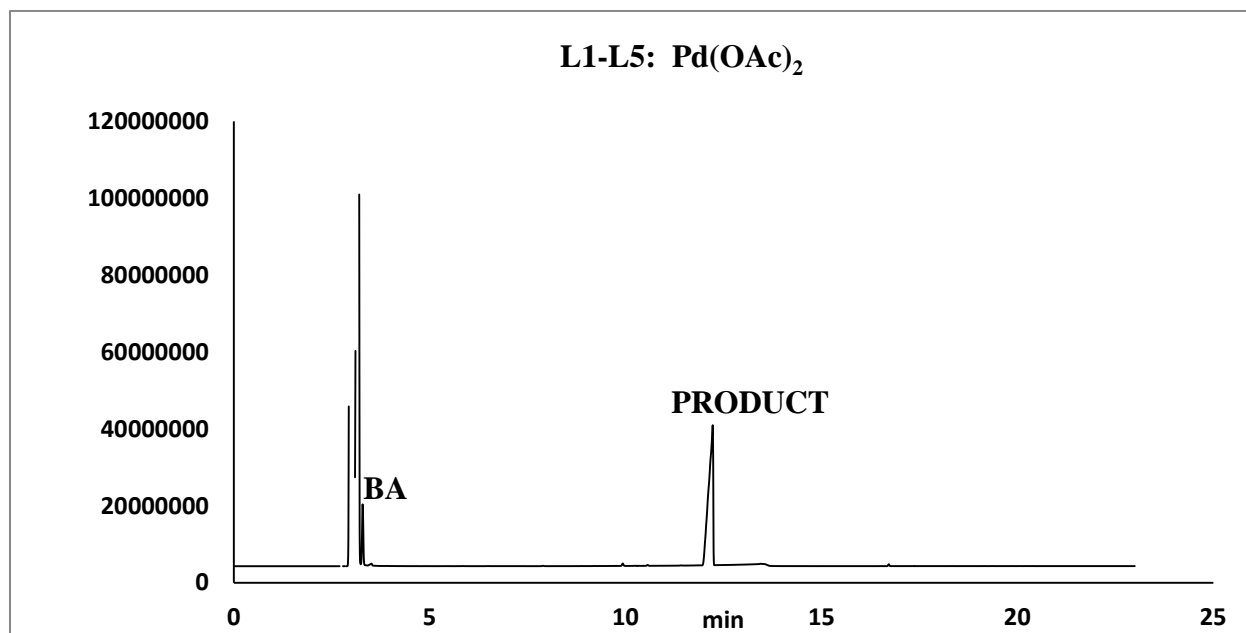
(a) In absence of the catalyst (GC chromatogram)



(b) In the presence of pre-catalysts (GC chromatogram)



(c) In the presence of pre-catalysts PdCl<sub>2</sub> and ligand (**L1-L5**) (GC chromatogram)



(d) In the presence of pre-catalysts Pd(OAc)<sub>2</sub> and ligand (**L1-L5**) (GC chromatogram)



## CHAPTER 4

### Results and discussion

#### 4.1 Effect of olefins

##### 4.1.1. Effect of olefins using PdCl<sub>2</sub> as source of palladium(0) with pyrazolone and pyrazole as the stabilizing ligands

In this study the effect of olefin substrates in the Heck reaction was examined. This was achieved by using different pyrazolone (**L1-L3**) and pyrazole (**L4-L5**) ligands with PdCl<sub>2</sub> (palladium precursor) as catalyst systems in the Heck reaction of iodobenzene (PhI) with different olefins namely ethyl acrylate (EA) and butyl acrylate (BA). Dimethylformamide (DMF) and Triethylamine (Et<sub>3</sub>N) were used as solvent and base respectively at 80 °C under nitrogen gas (**Scheme 4.1**). A molar ratio of ligands to palladium precursor to iodobenzene to olefins of 1:1:1:1.5 was kept constant in every catalytic run. Upon addition of all the substrates, base, **L1-L5** and palladium source to DMF, a homogenous solution was observed. The original colour of the reaction changed after 6 to 8 minutes to yellowish then finally changed to dark red after 30 minutes. For **L4** the first colour change for the reaction took a bit longer than other ligands: roughly 10 to 13 min. In all catalytic experiments, similar changes in colour of the solutions were observed. The percentage (%) conversions were determined based on the consumption iodobenzene, which was monitored by G.C.



In order to determine the efficiency of the mentioned ligands, a comparison was done by considering various catalytic runs, including reactions with ligands present and others independently of ligands. Results are shown at Table 4.1 and 4.4.

**Table 4.1** Heck cross coupling reaction of E.A with Iodobenzene (PdCl<sub>2</sub>)

Entry	Substrate	Ligands	Catalysts	Conversion <sup>b</sup> %
1	Ethyl acrylate		PdCl <sub>2</sub>	44
2	Ethyl acrylate	L <sub>1</sub>	PdCl <sub>2</sub>	57
3	Ethyl acrylate	L <sub>2</sub>	PdCl <sub>2</sub>	68
4	Ethyl acrylate	L <sub>3</sub>	PdCl <sub>2</sub>	55
5	Ethyl acrylate	L <sub>4</sub>	PdCl <sub>2</sub>	78
6	Ethyl acrylate	L <sub>5</sub>	PdCl <sub>2</sub>	61

<sup>a</sup>Reaction conditions: iodobenzene (1 mmole), Alkenes (1.5 mmole), Et<sub>3</sub>N (2 mmole), PdCl<sub>2</sub>/ L<sub>1</sub>-L<sub>5</sub> (0.01 mmole) and DMF (4 ml) at 80 °C, reaction time (3 h). <sup>b</sup>Conversions were determined by GC.

The beneficial ligand effect was proved by running control reactions in the absence of the ligands (Table 4.1-4.2 entry 1), since it is known that naked palladium is capable of catalysing olefins with aryl halides [1]. In the first set of ethyl acrylate with iodobenzene, the presence of pyrazolone ligands improve the % conversion, for example % conversion with the ligand absent was 44 % (Table 4.1 entry 1) which then slightly increased to 57 % and 55 % in the presence of L<sub>1</sub> and L<sub>3</sub>, respectively (Table 4.1, entry 2 and 4). Noteworthy, a high % conversion of 68% was observed in the presence of L<sub>2</sub> (Table 4.1 entry 3). Good activity was also observed when pyrazole ligands were used as PdCl<sub>2</sub> stabilizers. An improvement from 44 % conversion in the absence of ligand up to 61% and 78% were obtained, when L<sub>4</sub> and L<sub>5</sub> were applied as the supporting ligands, respectively (Table 4.1. entry 5 and 6).

The second set of reactions was butyl acrylate with iodobenzene. However, in the case of pyrazolone as supporting ligand significant improvement in iodobenzene conversion to the desired cinnamate product was observed when the olefin was changed to butyl acrylate. It was observed that conversions between 75 % and 82 % were obtained for the three ligands (Table 4.2 entry 2, 3 and 4). Overall, all the ligands performed very well, also in the presence of pyrazole

ligands **L4** and **L5** % conversions of 78 % and 75 % were obtained, respectively (Table 4.2 entry 5 and 6). In the case of butyl acrylate, it is worth noting that the absence of ligands had an effect on the conversion since only 29% was observed for the reaction without the ligand (Table 4.2 entry 1).

**Table 4.2.** Heck cross coupling reaction of B.A (2) with Iodobenzene (PdCl<sub>2</sub>)

Entry	Substrate	Ligands	Catalysts	Conversion <sup>b</sup> %
1	Butyl Acrylate		PdCl <sub>2</sub>	29
2	Butyl Acrylate	<b>L<sub>1</sub></b>	PdCl <sub>2</sub>	83
3	Butyl Acrylate	<b>L<sub>2</sub></b>	PdCl <sub>2</sub>	82
4	Butyl Acrylate	<b>L<sub>3</sub></b>	PdCl <sub>2</sub>	75
5	Butyl Acrylate	<b>L<sub>4</sub></b>	PdCl <sub>2</sub>	78
6	Butyl Acrylate	<b>L<sub>5</sub></b>	PdCl <sub>2</sub>	75

<sup>a</sup>Reaction conditions: iodobenzene (1 mmole), Alkenes (1.5 mmole), Et<sub>3</sub>N (2 mmole), PdCl<sub>2</sub>/**L1-L5** (0.01 mmole) and DMF (4 ml) at 80 °C, reaction time (3 h).

<sup>b</sup>Conversions were determined by GC.

It is not clear why a switch from ethyl acrylate to butyl acrylate produces such a significant change in conversions. In literature, lower substituted alkenes result in higher activity than high substituted alkenes [2]. Similar observations to ours were observed in the studies conducted by Wang *et al.* in 2014 when olefins were changed to methyl acrylate and butyl acrylate. With iodobenzene, lower conversions of 18 % and 27 % respectively were obtained. Also in these studies better conversions were observed when the olefins were butyl acrylate rather than methyl acrylate [2]. In the studies of Shao *et al.* in 2010, an efficient Pd(NH<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/cationic 2, 2'-bipyridyl system as catalyst on the Heck reaction, for the coupling of activated aryl iodide with ethyl and butyl acrylate, corresponding products were observed in good yields with high turnover numbers but better yields were obtained when olefin was changed to butyl acrylate [3]. The contribution for such increase in % conversions when the olefin was changed lower substituted to more substituted could be due to steric and electronic effect possess by the used ligands, which make the catalytic system more favorable for the high substituted alkene than lower substituted one.

#### 4.1.2. Effect of olefins using Pd(OAc)<sub>2</sub> as source of palladium(0) with pyrazolone and pyrazole as the stabilizing ligands

In an effort to select the most effective olefin for the Heck reaction, optimization studies using several pyrazolone (**L1-L3**) and pyrazole (**L4-L5**) ligands as stabilizers of Pd(OAc)<sub>2</sub> were tested on a model reaction (Scheme 4.1). Iodobenzene was reacted with butyl acrylate or ethyl acrylate (1.5 mmole) using a catalytic system of (0.01 mmole) 1:1 molar ratio of ligands to Pd(OAc)<sub>2</sub> precatalysts with (2 mmole) of Et<sub>3</sub>N in 4 ml of DMF. The reaction mixture was stirred at 80 °C for 3h under N<sub>2</sub>. The percentage (%) conversions were determined based on the consumption of iodobenzene, which was monitored by G.C. In order to determine the efficiency of the used ligands, a comparison was done by considering one additional catalytic run without any ligand. Results are shown at Table 4.3 and 4.4.

**Table 4.3** Heck cross coupling reaction of E.A with Iodobenzene (Pd(OAc)<sub>2</sub>)

Entry	Substrate	Ligands	Catalysts	Conversion <sup>b</sup> %
1	Ethyl acrylate		Pd(OAc) <sub>2</sub>	36
2	Ethyl acrylate	<b>L<sub>1</sub></b>	Pd(OAc) <sub>2</sub>	53
3	Ethyl acrylate	<b>L<sub>2</sub></b>	Pd(OAc) <sub>2</sub>	54
4	Ethyl acrylate	<b>L<sub>3</sub></b>	Pd(OAc) <sub>2</sub>	54
5	Ethyl acrylate	<b>L<sub>4</sub></b>	Pd(OAc) <sub>2</sub>	71
6	Ethyl acrylate	<b>L<sub>5</sub></b>	Pd(OAc) <sub>2</sub>	55

<sup>a</sup>Reaction conditions: iodobenzene (1 mmole), Alkenes (1.5 mmole), Et<sub>3</sub>N (2 mmole), Pd(OAc)<sub>2</sub> /**L1-L5** (0.01 mmole) and DMF (4ml) at 80°C, reaction time (3 h).

<sup>b</sup>Conversions were determined by GC.

The first reaction to be carried out was the coupling of ethyl acrylate and iodobenzene. The % conversions are shown at Table 4.3. It was observed that the naked Pd(OAc)<sub>2</sub> was outperformed by the presence of pyrazolone ligands (**L1-L3**), (Table 4.3 entry 2, 3, and 4). In the case of pyrazole ligands (**L4-L5**), (Table 4.3 entry 5 and 6), **L4** was the only exception since it was able to achieve 71% conversions over 55% which were average conversions for the other ligands (Table 4.3 and 2-6). A possible explanation for such a change in conversions is discussed under the effect of the ligands used.

The second set of reactions was the coupling between butyl acrylate and iodobenzene. In overall all the ligands performed very well in relation to naked Pd(OAc)<sub>2</sub>. The pyrazolone ligands. (**L1-L3**) gave conversions of between 76-81 % (Table 4.4 entry 2, 3 and 4) and for pyrazole conversions of between 67-74 % (Table 4.4 entry 4 and 5). Whereas for the naked Pd(OAc)<sub>2</sub> only 23 % conversion was obtained (Table 4.4 entry 1). In general, pyrazolone ligands are more efficient than pyrazole ligands.

**Table 4.4** Heck cross coupling reaction of B.A with Iodobenzene (Pd(OAc)<sub>2</sub>)

Entry	Substrate	Ligands	Catalysts	Conversion <sup>b</sup> %
1	Butyl acrylate		Pd(OAc) <sub>2</sub>	25
2	Butyl acrylate	<b>L<sub>1</sub></b>	Pd(OAc) <sub>2</sub>	76
3	Butyl acrylate	<b>L<sub>2</sub></b>	Pd(OAc) <sub>2</sub>	81
4	Butyl acrylate	<b>L<sub>3</sub></b>	Pd(OAc) <sub>2</sub>	76
5	Butyl acrylate	<b>L<sub>4</sub></b>	Pd(OAc) <sub>2</sub>	74
6	Butyl acrylate	<b>L<sub>5</sub></b>	Pd(OAc) <sub>2</sub>	64

<sup>a</sup>Reaction conditions: iodobenzene (1 mmole), Alkenes (1.5 mmole), Et<sub>3</sub>N (2 mmole), Pd(OAc)<sub>2</sub> /**L1-L5** (0.01 mmole) and DMF (4 ml) at 80°C, reaction time (3 h).

<sup>b</sup>Conversions were determined by GC.

In overall performance for the screening of olefins showed that butyl acrylate was a better olefin than ethyl acrylate. Therefore parameters such as ligands, temperature, base, solvent and time effect were investigated using butyl acrylate as an olefin.

## 4.2 Effect of the ligands used

It is clear from the data in Tables 4.2-4.4 that ligands **L1-L5** were efficient in stabilizing PdCl<sub>2</sub> and Pd(OAc)<sub>2</sub> palladium precursor in the reaction of iodobenzene and butyl acrylate. In the case of PdCl<sub>2</sub> with **L1-L5** conversions in a range of 75% to 83% (Table 4.2 entry 2-5) and for Pd(OAc)<sub>2</sub> with **L1-L5** conversions in a range of 64-81% (Table 4.4 entry 2-5) were obtained. The 29% conversion performance with PdCl<sub>2</sub> (Table 4.2 entry 1) and for Pd(OAc)<sub>2</sub> 25% (Table 4.4 entry 1) conversion were obtained in the absence of ligands.

This strongly supports the idea that higher conversions are a result of ligands used to stabilize the active Pd(0) species. However, in literature Pd(0) has been believed to be the active species which is chemically unstable in the absence of the ligands and results in inactive palladium clusters known as palladium black [4]. There was a clear colour change from original colour (first colour change upon the addition of ligand for **L1**, (Whiter) **L2 and L3** (orange), and **L4 and L5** a clear solution) of the solution to yellow within 10 minutes before tuned to the final colour. This colour change was attributed to the reduction of Pd(II) to Pd(0), **L1-L5** stabilized the Pd(0) species, which then formed an active palladium complex that act as the active catalysts in the reaction. This strongly depends on the ready availability of the coordination site on the ligand. The formation of palladium black is observed if the ligand is not readily accessible to stabilize the Pd(0) clusters that are formed. The formation of inactive palladium species causes the deactivation of the catalysts which results in lower conversion: hence in the absence of ligands, **L1-L5**, lower % conversions were obtained with the formation of palladium black at the bottom of the vials (Table 4.2 and 4.4, entry 1).

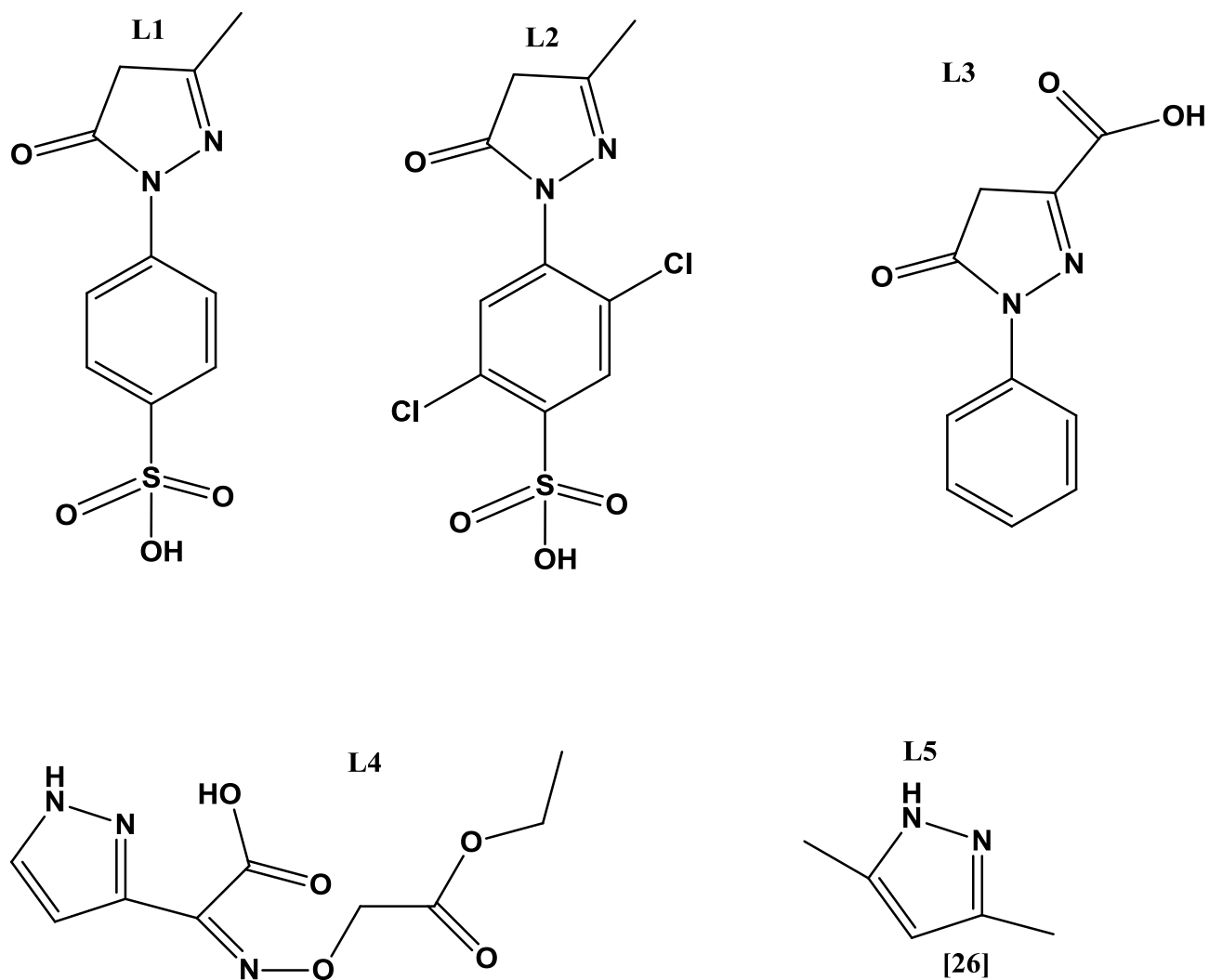
The higher activity in the presence of **L1-L5** could be due to the combinations of electronic and steric effect properties attributed by the applied different ligands. In the studies conducted by Owusu in 2000 high yields were observed when different palladium complexes were used, their explanation for high yields was attributed to a combination of electronic and steric effects contributed by the ligands used in their complexes [5]. Such properties were shown in Nolan's work whereby different nucleophilic carbene ligands were used as suitable ligands for the Heck

coupling reaction. It's a widely known belief that the strong  $\sigma$ -donor ability of the ligands is responsible for high efficiency in promoting the Heck coupling reaction by accelerating Ar-X oxidative addition reaction on a catalytic cycle [6],[7].

The structural diversity of these ligands also attributed to the activity of PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> in the Heck coupling reaction. In general pyrazolone ligands gave better conversions (Tables 4.2 and 4.4 entry 2-4) than pyrazole ligands (Tables 4.2 and 4.4 entry 5-6), with the exception of **L3** which behaves similarly to **L5** and **L6** (Tables 4.2 entry 4-6). In the case of pyrazolones, the structural difference between **L1-L2** are Cl groups (electron withdrawing group) in phenyl ring attached at nitrogen one (N1) of the pyrazolone ring in **L2**. Surprisingly no significant difference in conversions 83 % and 82 % respectively to **L1-L2** occurred, meaning these newly introduced functional groups were not influential under these used reaction conditions. A completely different pyrazolone named **L3** at N1 phenyl ring was introduced with a different substitution of methyl (-CH<sub>3</sub>) group at carbon three (C-3) with carboxylic group (COOH) in the pyrazolone ring, a slight drop in % conversion of 75 % was obtained. A possible explanation could be that **L1** and **L2** resulted in a strong  $\sigma$ -donating ligand compared to **L3**, hence high conversion was obtained. Therefore in the case of **L3**, a more sterically hindered ligand resulted in weaker  $\sigma$ -donation of the ligand, due to the polarizability effect of the carboxylic group attached at C-3, or benzene ring attached at N1 of the pyrazolone, whereas with **L1-L2** the -CH<sub>3</sub> group is the substituent at C-3, and N1 substitution is 1-(4-Sulfohenyl) of the pyrazolone was more favourable.

In the case of pyrazole ligands **L4-L5**, the structural difference between the two is: **L4** at C-3 has a large substituent of  $\alpha$ -[(2-ethoxy-2-oxoethoxy)-imino]-3-acetic acid, whereas **L5** at the same position has the substituent -CH<sub>3</sub> group and also at C-5 has another -CH<sub>3</sub> group which is not present in **L4**. Based on the results obtained in (Table 4.2 entry 4-5) the different substituents at C-3 for **L4-L5** did not have a significant impact on % conversions, hence 78 % and 75 % were obtained, respectively to **L4** and **L5**. From the results in (Table 4.4 entry 4-5) the different substituents at C-3 for **L4** resulted in more strongly electron donating ligands than the two -CH<sub>3</sub> substituent at **L5**. That could be the possible explanation for the obtained conversions of 74 % for **L4** and 65 % for **L5**. In conclusion the role of these ligands in the Heck reaction catalytic cycle was important to the efficiency of the reaction as demonstrated by the results showed in Table 4.2

and 4.4. So far the exact mechanism by which ligands stabilise the active palladium is unknown. However, from the experimental studies it has been clearly shown that the electron and steric effects of these ligands are important in promoting the Heck coupling reaction.



**Scheme 4.1:** Ligands used in Heck coupling



### 4.3 Effect of temperatures in catalytic reaction

In order to investigate the effect of temperature on the Heck reaction, the reaction conditions employed were as follows, iodobenzene (1 mmole), butyl acrylate (1.5 mmole) as substrates, with 4 ml of DMF as solvent, 2 mmole of Et<sub>3</sub>N as a base, PdCl<sub>2</sub> at 1 mmole %, the ligands **L1-L5** at 1 mmole %, under nitrogen, for 3h at 80 °C, 100 °C, 120 °C, 140 °C and 160 °C. Results of this study are listed in Table 2.1. At this particular low catalyst loading (0.01 mmol) it was possible to test the activity and stability of the catalyst system. The catalyst loading is considered to be lowest since most reported catalyst loadings are usually 1 mole% and higher [8]. The motive behind the application of such low catalysts loadings, was noted by De Vries *et al.* that the Heck reaction at low concentrations of Pd(0) in solution will aggregate and deactivate much slower than high concentration [9]. Hence at this low catalyst loading it was efficient to optimize the effect of temperature. From the results it was clearly shown that an increase in temperature leads to increase in % conversions. However, it is well known that temperature has a strong influence in the Heck cross-reaction. From our studies, a significant observation was at 80 °C which is a mild reaction condition compared to 120-160 °C at which most coupling reactions take place [10]-[11]. But at this mild reaction condition, conversions of 70-85 % (Table 4.5, entry 1, 2, 3, 4 and 5) were obtained. In the case of **L1-L3** at this temperature there were no signs of the deactivation of catalysts due to the fact that no palladium black was observed, but for **L4** and **L5** slight signs of deactivation for the catalysts system were observed, since some of the palladium black was deposited in the magnetic stirrer. We also found out that in the case of **L1** and **L2** when the temperature was increased to 120 °C (Table 4.5, entry 7 and 8) there were no significant differences in conversions, but in the case of **L3** a significant increase of ~ 11 % was obtained. The increase in conversion in the case of **L3** could be attributed to the strong influence of temperature in the Heck reaction. At these temperature ranges of 100-120 °C, a slight deactivation of the catalysts was observed, since traces of palladium black were deposited on the magnetic stirrer. However, reaction temperature must be carefully controlled to avoid the formation of palladium black which inhibits the catalytic cycle if the temperature is too high [12]. Thus, when the reaction mixtures were heated at temperatures of 140-160 °C conversion ranges from 85-89 % were obtained (Table 4.5 entry 16-25) but the main challenge was the formation of more palladium black which was pronounced at the bottom of the test tubes. Therefore the signs

of deactivation of catalysts were clearly shown. It is worth mentioning that during this study, the temperature of 80 °C was the better temperature since no signs of deactivation of the catalytic system in the case of **L1-L3** and for **L4-L5** slight signs of deactivation were observed, with better conversions.

**TABLE 4.5** The temperature effect in the Heck reaction of iodobenzene and B.A. (PdCl<sub>2</sub>)

Entry	Temperature °C	Ligands	Catalysts	Conversion <sup>b</sup> %
1	80	L <sub>1</sub>	PdCl <sub>2</sub>	83
2	80	L <sub>2</sub>	PdCl <sub>2</sub>	82
3	80	L <sub>3</sub>	PdCl <sub>2</sub>	75
4	80	L <sub>4</sub>	PdCl <sub>2</sub>	78
5	80	L <sub>5</sub>	PdCl <sub>2</sub>	75
6	100	L <sub>1</sub>	PdCl <sub>2</sub>	84
7	100	L <sub>2</sub>	PdCl <sub>2</sub>	84
8	100	L <sub>3</sub>	PdCl <sub>2</sub>	86
9	100	L <sub>4</sub>	PdCl <sub>2</sub>	81
10	100	L <sub>5</sub>	PdCl <sub>2</sub>	78
11	120	L <sub>1</sub>	PdCl <sub>2</sub>	85
12	120	L <sub>2</sub>	PdCl <sub>2</sub>	85
13	120	L <sub>3</sub>	PdCl <sub>2</sub>	87
14	120	L <sub>4</sub>	PdCl <sub>2</sub>	84
15	120	L <sub>5</sub>	PdCl <sub>2</sub>	78
16	140	L <sub>1</sub>	PdCl <sub>2</sub>	88
17	140	L <sub>2</sub>	PdCl <sub>2</sub>	89
18	140	L <sub>3</sub>	PdCl <sub>2</sub>	89
19	140	L <sub>4</sub>	PdCl <sub>2</sub>	82
20	140	L <sub>5</sub>	PdCl <sub>2</sub>	79
21	160	L <sub>1</sub>	PdCl <sub>2</sub>	87
22	160	L <sub>2</sub>	PdCl <sub>2</sub>	85
23	160	L <sub>3</sub>	PdCl <sub>2</sub>	85

<b>24</b>	160	L <sub>4</sub>	PdCl <sub>2</sub>	88
<b>25</b>	160	L <sub>5</sub>	PdCl <sub>2</sub>	84

<sup>a</sup>Reaction conditions: Iodobenzene (1 mmole), Butyl acrylate (1.5 mmole), Et<sub>3</sub>N (2 mmole), PdCl<sub>2</sub>/**L1-L5** (0.01 mmole) and DMF (4 ml) at various temperatures for 3 h.

<sup>b</sup>Conversions were determined by GC.

To further investigate the effect of temperature, **L1-L5** were used as the supporting ligands for Pd(OAc)<sub>2</sub>. In general Heck coupling reactions are performed between the temperatures of 120-140 °C, since such high temperatures improve the efficiency of the catalytic system. But during this study temperature ranges from 80-160 °C were employed and reaction mixtures were refluxed for 3 hrs under nitrogen atmosphere. The key observations were between 80-120 °C; at these mild reaction conditions some of the reactions showed some slight signs of deactivation of the catalyst system (Table 4.6 entry 1-15). That was attributed by the fact that traces of palladium black were observed in some solutions, more especially at temperatures between 100-120 °C. At higher temperatures of 140-160 °C more palladium black characteristics were observed at the bottom of the reaction mixtures (Table 4.6 entry 16-25).

Another important fact was the relationship between conversion and structures of the catalyst systems. In the case of pyrazolone at 80 °C no significant difference in conversions when **L1** and **L3** was used as the supporting ligand 76 % conversion was obtained for both ligands, but when **L2** was used as the supporting ligand 81 % conversion was obtained (Table 4.6 entry 2). A possible explanation for the higher activity observed with **L2** as the supporting ligand for Pd(OAc)<sub>2</sub> catalyst systems in the Heck reaction could be due to electron-withdrawing groups substituents at **L2**. This phenomenon was already discussed under screening of alkenes and supported with literature. Using pyrazole as the supporting ligand **L4** gave comparable conversion to those achieved by **L1** and **L3** (Table 4.6 entry 1, 3 and 4). However, for **L5** a lower conversion of 64 % was obtained (Table 4.6 entry 5). The reaction at 120 °C showed good conversion ranges from 81-85 % with palladium black formation (Table 4.6 entry 11-15). On the other hand at 80 °C 64-83 % conversion ranges were obtained with slight signs of deactivation of the catalytic system (Table 4.6 entry 1-5), since some of palladium black was observed in the magnetic stirrer bar, unlike with the other temperatures whereby palladium black was observed in the solutions (100-

120 °C) and some as precipitate at the bottom of the test tube (140-160 °C). Therefore parameters such as base, solvent, and time effect were investigated at 80 °C.

**TABLE 4.6** The temperature effect in the Heck reaction of iodobenzene and B.A (PdCl<sub>2</sub>)

Entry	Temperature °C	Ligands	Catalysts	Conversion <sup>b</sup> %
1	80	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	76
2	80	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	81
3	80	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	76
4	80	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	76
5	80	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	64
6	100	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	81
7	100	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	83
8	100	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	79
9	100	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	78
10	100	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	67
11	120	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	83
12	120	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	85
13	120	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	82
14	120	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	81
15	120	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	82
16	140	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	84
17	140	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	86
18	140	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	86
19	140	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	82
20	140	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	83
21	160	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	84
22	160	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	87
23	160	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	90
24	160	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	98
26	160	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	84

<sup>a</sup>Reaction conditions: Iodobenzene (1 mmole), Butyl acrylate (1.5 mmole), Et<sub>3</sub>N (2 mmole),

Pd(OAc)<sub>2</sub>/L1-L5 (0.01 mmole) and DMF (4 ml) at various temperatures for 3 h.  
<sup>b</sup>Conversions were determined by GC.

#### 4.4 Effect of the base used

For further investigation, iodobenzene with butyl acrylate were employed as substrates with various organic and inorganic base with 4 ml of DMF as solvent at 80 °C for 3h with PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> as pre-catalysts with L1-L5 as the supporting ligands results are showed at Tables 4.7 and 4.8 respectively.

**Table 4.7** Effect of base used on the Heck reaction of iodobenzene and B.A (PdCl<sub>2</sub>)

Entry	Base	Ligands	Catalysts	Conversion%
1	Et <sub>3</sub> N	L <sub>1</sub>	PdCl <sub>2</sub>	83
2	Et <sub>3</sub> N	L <sub>2</sub>	PdCl <sub>2</sub>	82
3	Et <sub>3</sub> N	L <sub>3</sub>	PdCl <sub>2</sub>	75
4	Et <sub>3</sub> N	L <sub>4</sub>	PdCl <sub>2</sub>	78
5	Et <sub>3</sub> N	L <sub>5</sub>	PdCl <sub>2</sub>	75
6	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>1</sub>	PdCl <sub>2</sub>	49
7	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>2</sub>	PdCl <sub>2</sub>	34
8	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>3</sub>	PdCl <sub>2</sub>	28
9	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>4</sub>	PdCl <sub>2</sub>	2
10	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>5</sub>	PdCl <sub>2</sub>	10
11	Na <sub>2</sub> CO <sub>3</sub>	L <sub>1</sub>	PdCl <sub>2</sub>	65
12	Na <sub>2</sub> CO <sub>3</sub>	L <sub>2</sub>	PdCl <sub>2</sub>	61
13	Na <sub>2</sub> CO <sub>3</sub>	L <sub>3</sub>	PdCl <sub>2</sub>	66
14	Na <sub>2</sub> CO <sub>3</sub>	L <sub>4</sub>	PdCl <sub>2</sub>	56
15	Na <sub>2</sub> CO <sub>3</sub>	L <sub>5</sub>	PdCl <sub>2</sub>	13
16	K <sub>2</sub> CO <sub>3</sub>	L <sub>1</sub>	PdCl <sub>2</sub>	72
17	K <sub>2</sub> CO <sub>3</sub>	L <sub>2</sub>	PdCl <sub>2</sub>	76
18	K <sub>2</sub> CO <sub>3</sub>	L <sub>3</sub>	PdCl <sub>2</sub>	71

<b>19</b>	K <sub>2</sub> CO <sub>3</sub>	L <sub>4</sub>	PdCl <sub>2</sub>	39
<b>20</b>	K <sub>2</sub> CO <sub>3</sub>	L <sub>5</sub>	PdCl <sub>2</sub>	30

<sup>a</sup>Reaction conditions: iodobenzene (1 mmole), Butyl acrylate (1.5 mmole), Base (2 mmole), PdCl<sub>2</sub>/ **L1-L5** (0.01 mmole) and DMF (4 ml) at 80 °C, reaction time (3 h)

<sup>b</sup>Conversions were determined by GC.

**Table 4.8** Effect of base used on the Heck reaction of iodobenzene and B.A (Pd(OAc)<sub>2</sub>)

<b>Entry</b>	<b>Base</b>	<b>Ligands</b>	<b>Catalysts</b>	<b>Conversion<sup>b</sup></b> %
<b>1</b>	Et <sub>3</sub> N	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	76
<b>2</b>	Et <sub>3</sub> N	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	81
<b>3</b>	Et <sub>3</sub> N	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	76
<b>4</b>	Et <sub>3</sub> N	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	74
<b>5</b>	Et <sub>3</sub> N	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	64
<b>6</b>	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	14
<b>7</b>	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	17
<b>8</b>	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	12
<b>9</b>	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	12
<b>10</b>	Cs <sub>2</sub> CO <sub>3</sub>	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	5
<b>11</b>	Na <sub>2</sub> CO <sub>3</sub>	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	19
<b>12</b>	Na <sub>2</sub> CO <sub>3</sub>	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	26
<b>13</b>	Na <sub>2</sub> CO <sub>3</sub>	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	19
<b>14</b>	Na <sub>2</sub> CO <sub>3</sub>	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	6
<b>15</b>	Na <sub>2</sub> CO <sub>3</sub>	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	15
<b>16</b>	K <sub>2</sub> CO <sub>3</sub>	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	40
<b>17</b>	K <sub>2</sub> CO <sub>3</sub>	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	39
<b>18</b>	K <sub>2</sub> CO <sub>3</sub>	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	79
<b>19</b>	K <sub>2</sub> CO <sub>3</sub>	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	5
<b>20</b>	K <sub>2</sub> CO <sub>3</sub>	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	2

<sup>a</sup>Reaction conditions: iodobenzene (1 mmole), Butyl acrylate (1.5 mmole), Base (2 mmole), Pd(OAc)<sub>2</sub>/**L1-L5** (0.01 mmole) and DMF (4 ml) at 80 °C, reaction time (3 h).

<sup>b</sup>Conversions were determined by GC.

The reaction activity was also influenced by the type of base used in the reaction (Table 4.7). As a model reaction, iodobenzene (1 mmole) was reacted with butyl acrylate (1.5 mmole) using 1 mmole % of PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> with 1 mmole % **L1-L5** catalytic system and 2 mmole of the corresponding base in 5 ml of DMF. Results are showed in Table 4.7 and 4.8.

The presence of base is necessary to bind hydrogen halide formed during the catalytic Heck coupling reaction [13]. Replacing organic base with inorganic bases led to a decrease in % conversions. The order of decrease in activity was as follows: Et<sub>3</sub>N > K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub> > Cs<sub>2</sub>CO<sub>3</sub>. A possible explanation for this could be attributed to the partial inhomogeneity of inorganic base into the organic substrate, reagent and solvent, which lowered the % conversion and requires longer reaction time. In the studies conducted by Huang *et al.* in 2010 they found that inorganic bases were ineffective for coupling of iodobenzene and butyl acrylate, even at a reaction temperature of 140 °C; replacing inorganic base with organic base such as Et<sub>3</sub>N led to formation of trans-cinnamic acid *n*-butyl ester in a 32 % yield [14]. Similar observations as those observed in this study were obtained by Borhade and Waghmode in 2008 whereby using organic bases such as Et<sub>3</sub>N and tributyl amine 100 % conversion was obtained for both bases, and in the case of inorganic bases for K<sub>2</sub>CO<sub>3</sub> 75 %, Na<sub>2</sub>CO<sub>3</sub> 54 %, and Cs<sub>2</sub>CO<sub>3</sub> 34 % conversions were obtained [15].

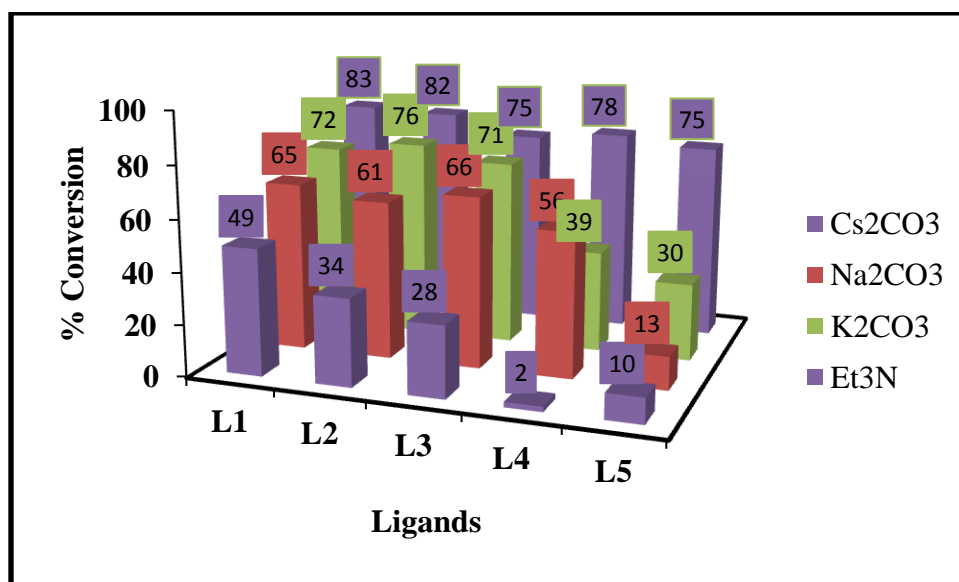


Figure 4.1 PdCl<sub>2</sub> catalytic results using ligands **L1-L5** in four bases

From our investigation for the effect of base, Heck coupling reaction occurred with all the bases irrespective of inorganic or organic base. But based on the results obtained in the Heck catalytic system reactions, the best base examined was Et<sub>3</sub>N ( Table 4.7 entry 1-5), In general pyrazolone ligands **L1-L3** performed better than pyrazole ligands **L4-L5**, with the exception of **L2** which gave comparable conversion with **L4-L5** ( Table 4.7 entry 3, 4 and 5).

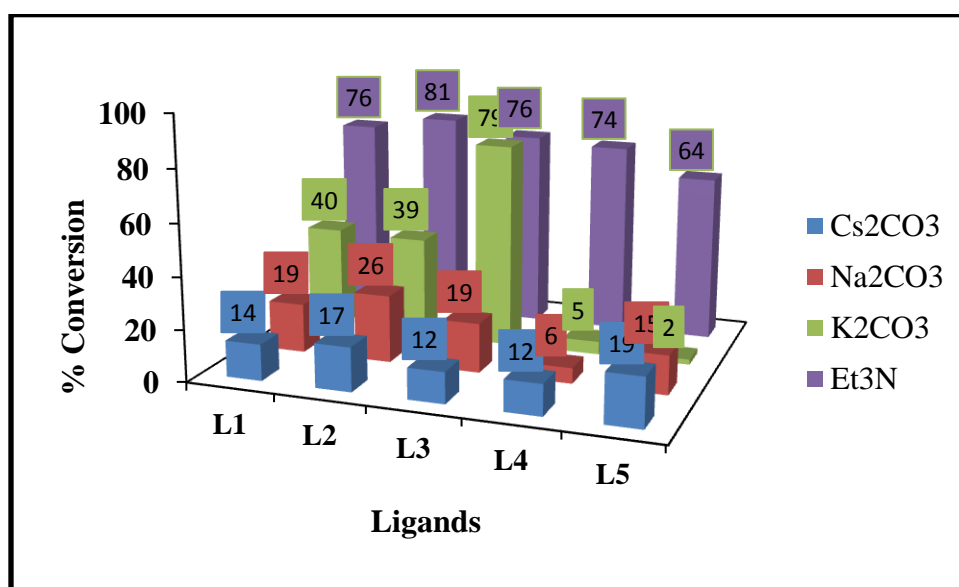


Figure 4.2 Pd(OAc)<sub>2</sub> catalytic results using ligands **L1-L5** in four bases.

When the reaction was performed with Pd(OAc)<sub>2</sub> as palladium precursor it afforded lower % conversions compared to PdCl<sub>2</sub>. In the case of Pd(OAc)<sub>2</sub> with organic base (Et<sub>3</sub>N) better conversions than other inorganic bases (K<sub>2</sub>CO<sub>3</sub>, Na<sub>2</sub>CO<sub>3</sub>, and Cs<sub>2</sub>CO<sub>3</sub>) were obtained, ( Table 4.8 entry 1-20). In the case of Et<sub>3</sub>N slightly lower conversions were obtained (Table 4.8 entry 1-5) for Pd(OAc)<sub>2</sub> than when PdCl<sub>2</sub> was used as palladium precursor (Table 4.8 entry 1-5). In the case of inorganic base poorer conversions were obtained (Table 4.8 entry 6-20) for Pd(OAc)<sub>2</sub> than in the case of PdCl<sub>2</sub> (Table 4.7 entry 6-20). Hence other investigations were conducted with Et<sub>3</sub>N as a base.



#### 4.5 Effect of the solvent used

In order to investigate the influence of different solvents in the Heck coupling reaction, iodobenzene with butyl acrylate were used as substrate with triethylamine as a base with PdCl<sub>2</sub> Pd(OAc)<sub>2</sub> as pre-catalysts supported with ligands **L1-L5** at 80 °C for 3 h under nitrogen atmosphere the results are presented in Tables 4.9-4.10.

**Table 4.9** Effect of solvents on the Heck reaction of iodobenzene and butyl acrylate (PdCl<sub>2</sub>)

Entry	Solvent	Ligands	Catalysts	Conversion <sup>b</sup> %
1	MeCN	L <sub>1</sub>	PdCl <sub>2</sub>	25
2	MeCN	L <sub>2</sub>	PdCl <sub>2</sub>	18
3	MeCN	L <sub>3</sub>	PdCl <sub>2</sub>	41
4	MeCN	L <sub>4</sub>	PdCl <sub>2</sub>	22
5	MeCN	L <sub>5</sub>	PdCl <sub>2</sub>	38
6	DMF	L <sub>1</sub>	PdCl <sub>2</sub>	83
7	DMF	L <sub>2</sub>	PdCl <sub>2</sub>	82
8	DMF	L <sub>3</sub>	PdCl <sub>2</sub>	75
9	DMF	L <sub>4</sub>	PdCl <sub>2</sub>	78
10	DMF	L <sub>5</sub>	PdCl <sub>2</sub>	75
11	DMSO	L <sub>1</sub>	PdCl <sub>2</sub>	41
12	DMSO	L <sub>2</sub>	PdCl <sub>2</sub>	44
13	DMSO	L <sub>3</sub>	PdCl <sub>2</sub>	38
14	DMSO	L <sub>4</sub>	PdCl <sub>2</sub>	36
15	DMSO	L <sub>5</sub>	PdCl <sub>2</sub>	55
16	Toluene	L <sub>1</sub>	PdCl <sub>2</sub>	14
17	Toluene	L <sub>2</sub>	PdCl <sub>2</sub>	19
18	Toluene	L <sub>3</sub>	PdCl <sub>2</sub>	17
19	Toluene	L <sub>4</sub>	PdCl <sub>2</sub>	44
20	Toluene	L <sub>5</sub>	PdCl <sub>2</sub>	6

<sup>a</sup>Reaction conditions: aryl halides (1 mmole), Alkenes (1.5 mmole), Et<sub>3</sub>N (2 mmole),

PdCl<sub>2</sub>/L1-L5 (0.01 mmole) and solvent (4 ml) at 80 °C, reaction time (3 h).

<sup>b</sup>Conversions were determined by GC.

**Table 4.10** Effect of solvents on the Heck reaction of iodobenzene and butyl acrylate Pd(OAc)<sub>2</sub>

Entry	Solvent	Ligands	Catalysts	Conversion <sup>b</sup> %
1	MeCN	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	45
2	MeCN	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	38
3	MeCN	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	50
4	MeCN	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	52
5	MeCN	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	51
6	DMF	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	76
7	DMF	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	87
8	DMF	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	76
9	DMF	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	74
10	DMF	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	64
11	DMSO	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	42
12	DMSO	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	43
13	DMSO	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	54
14	DMSO	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	44
15	DMSO	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	53
16	Toluene	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	7
17	Toluene	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	6
18	Toluene	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	9
19	Toluene	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	36
20	Toluene	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	4

<sup>a</sup>Reaction conditions: aryl halides (1 mmole), Butyl acrylate (1.5 mmole), Et<sub>3</sub>N (2 mmole), Pd(OAc)<sub>2</sub>/L1-L5 (0.01 mmole) and solvent (4 ml) at 80 °C, reaction time (3 h).

<sup>b</sup>Conversions were determined by GC

Widely used solvents such as DMF, DMSO, Toluene, Dioxane, THF, and CH<sub>3</sub>CN had remarkable effects on the coupling reaction. The polar aprotic solvents such as the standard solvent DMF, the more thermostable DMSO, and the relatively low boiling point MeCN and THF, are the most useful [16]. They provide high rates of the reaction due to stabilization of the active palladium species by their weak coordination [17], thus improving its solubility towards organic reagents.

For further investigation we selected the same simple model system, using iodobenzene with butyl acrylate and **L1-L5** / PdCl<sub>2</sub> or Pd(OAc) catalytic systems and Et<sub>3</sub>N as the base. A comparative study was performed between polar aprotic solvents and non-polar solvents, to determine the efficiency of these solvents on the Heck coupling reaction. From the results in (Table 4.9 and 4.10), in the case of PdCl<sub>2</sub> conversions of 70-85 % were obtained for DMF (Table 4.9 entry 6-10), for DMSO 38-45 % (Table 4.9 entry 11-15), for MeCN 18-41 % (Table 4.9 entry 1-5), and toluene 14-20 % (Table 4.9 entry 16-20).

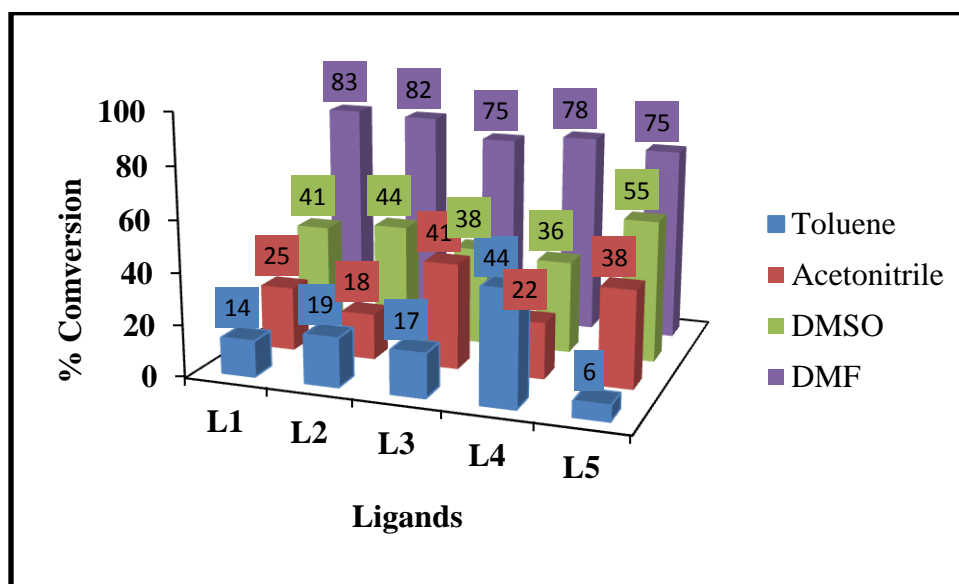


Figure 4.3 PdCl<sub>2</sub> catalytic results using ligands **L1-L5** in four solvents

In the case of Pd(OAc) conversions of 74-87 % were obtained for DMF (Table 4.10 entry 6-10), for DMSO 42-54 % (Table 4.10 entry 11-15), for MeCN 38-52 % (Table 4.10 entry 1-5) and for toluene 7-36 % (Table 4.10 entry 16-20). Similar observations for the effect of solvent were reported by Horniakova *et al.* where they reported the effectiveness of DMF as the solvent for the Heck vinylation of bromoacetophenone with methyl acrylate [18]. Therefore from the results

(Table 4.9 and 4.10), DMF was chosen as the solvent for further studies. As reported in the literature, polar aprotic solvents tend to give the best results for the Heck coupling reaction [19], the reason why polar aprotic solvents turn to work better than other solvents has been already discussed in the last two line of the first paragraph of the previous page.

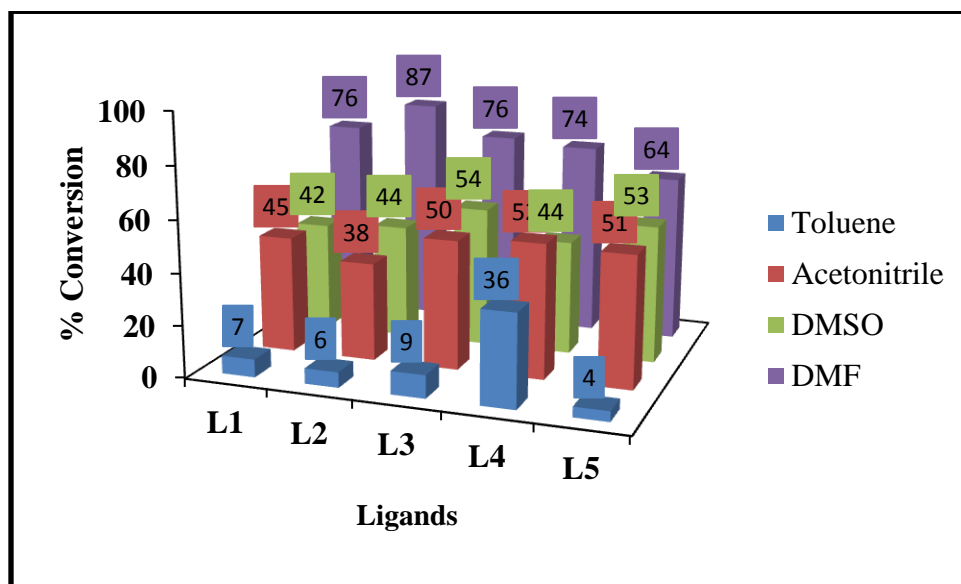


Figure 4.5 Pd(OAc) catalytic results using ligands **L1-L5** in four solvents

#### 4.6 Effect of time

In order to determine the influence of time on the catalytic system using different pyrazolone **L1-L3** and pyrazole ligands **L4-L5** as the stabilizers of PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> (precursors), Heck coupling reaction was performed at different time intervals. To optimize the percentage conversions, from the investigated parameters DMF, Et<sub>3</sub>N at 80 °C was chosen as the reaction conditions.

**Table 4.11** Effect of time on the catalytic activity in Heck coupling reaction (PdCl<sub>2</sub>)

Entry	Time (h.)	Ligands	Catalysts	Conversion <sup>a</sup> %
1.	0.5	L <sub>1</sub>	PdCl <sub>2</sub>	66
2.	0.5	L <sub>2</sub>	PdCl <sub>2</sub>	62
3.	0.5	L <sub>3</sub>	PdCl <sub>2</sub>	70
4.	0.5	L <sub>4</sub>	PdCl <sub>2</sub>	2
5.	0.5	L <sub>5</sub>	PdCl <sub>2</sub>	56
6.	1	L <sub>1</sub>	PdCl <sub>2</sub>	78
7.	1	L <sub>2</sub>	PdCl <sub>2</sub>	68
8.	1	L <sub>3</sub>	PdCl <sub>2</sub>	74
9.	1	L <sub>4</sub>	PdCl <sub>2</sub>	43
10.	1	L <sub>5</sub>	PdCl <sub>2</sub>	69
11.	2	L <sub>1</sub>	PdCl <sub>2</sub>	79
12.	2	L <sub>2</sub>	PdCl <sub>2</sub>	71
13.	2	L <sub>3</sub>	PdCl <sub>2</sub>	75
14.	2	L <sub>4</sub>	PdCl <sub>2</sub>	75
15.	2	L <sub>5</sub>	PdCl <sub>2</sub>	71
16.	4	L <sub>1</sub>	PdCl <sub>2</sub>	82
17.	4	L <sub>2</sub>	PdCl <sub>2</sub>	75
18.	4	L <sub>3</sub>	PdCl <sub>2</sub>	75
19.	4	L <sub>4</sub>	PdCl <sub>2</sub>	80
20.	4	L <sub>5</sub>	PdCl <sub>2</sub>	74

<b>21.</b>	8	L <sub>1</sub>	PdCl <sub>2</sub>	83
<b>22.</b>	8	L <sub>2</sub>	PdCl <sub>2</sub>	81
<b>23.</b>	8	L <sub>3</sub>	PdCl <sub>2</sub>	78
<b>24.</b>	8	L <sub>4</sub>	PdCl <sub>2</sub>	82
<b>25.</b>	8	L <sub>5</sub>	PdCl <sub>2</sub>	78
<b>26.</b>	24	L <sub>1</sub>	PdCl <sub>2</sub>	88
<b>27.</b>	24	L <sub>2</sub>	PdCl <sub>2</sub>	82
<b>28.</b>	24	L <sub>3</sub>	PdCl <sub>2</sub>	85
<b>29.</b>	24	L <sub>4</sub>	PdCl <sub>2</sub>	89
<b>30.</b>	24	L <sub>5</sub>	PdCl <sub>2</sub>	81

<sup>a</sup>Reaction conditions: aryl halides (1 mmole), Alkenes (1.5 mmole), Et<sub>3</sub>N (2 mmole), PdCl<sub>2</sub>/L<sub>1</sub>-L<sub>5</sub> (0.01 mmole) and DMF (4 ml) at 80°C, reaction time (various time).

<sup>b</sup>Conversions were determined by GC.

**Table 4.12** Effect of time on the catalytic activity in Heck coupling reaction (Pd(OAc)<sub>2</sub>)

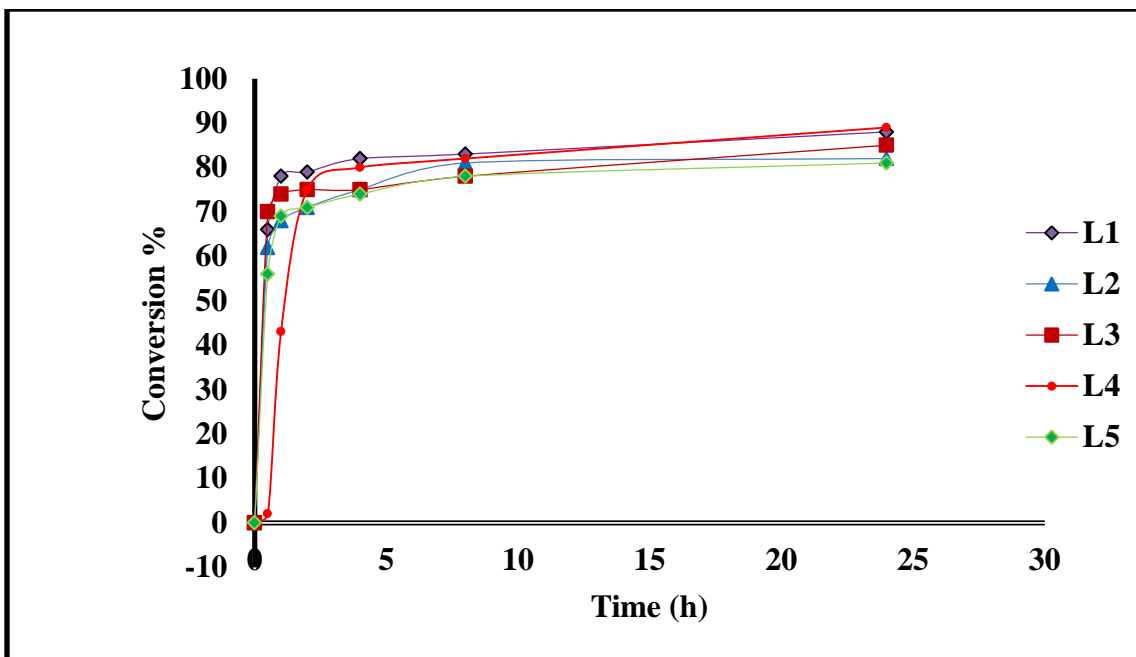
<b>Entry</b>	<b>Time (h.)</b>	<b>Ligands</b>	<b>Catalysts</b>	<b>Conversion<sup>a</sup> %</b>
<b>1.</b>	0.5	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	39
<b>2.</b>	0.5	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	43
<b>3.</b>	0.5	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	45
<b>4.</b>	0.5	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	10
<b>5.</b>	0.5	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	36
<b>6.</b>	1	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	50
<b>7.</b>	1	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	46
<b>8.</b>	1	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	48
<b>9.</b>	1	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	38
<b>10.</b>	1	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	42
<b>11.</b>	2	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	60
<b>12.</b>	2	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	62
<b>13.</b>	2	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	63
<b>14.</b>	2	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	61
<b>15.</b>	2	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	62

<b>16.</b>	4	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	63
<b>17.</b>	4	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	66
<b>18.</b>	4	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	65
<b>19.</b>	4	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	62
<b>20.</b>	4	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	63
<b>21.</b>	8	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	65
<b>22.</b>	8	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	66
<b>23.</b>	8	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	67
<b>24.</b>	8	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	64
<b>25.</b>	8	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	66
<b>26.</b>	24	L <sub>1</sub>	Pd(OAc) <sub>2</sub>	68
<b>27.</b>	24	L <sub>2</sub>	Pd(OAc) <sub>2</sub>	69
<b>28.</b>	24	L <sub>3</sub>	Pd(OAc) <sub>2</sub>	68
<b>29.</b>	24	L <sub>4</sub>	Pd(OAc) <sub>2</sub>	66
<b>30.</b>	24	L <sub>5</sub>	Pd(OAc) <sub>2</sub>	68

<sup>a</sup>Reaction conditions: aryl halides (1 mmole), Alkenes (1.5 mmole), Et<sub>3</sub>N (2 mmole), Pd(OAc)<sub>2</sub>/L1-L5 (0.01 mmole) and DMF (4 ml) at 80°C, reaction time (various time).

<sup>b</sup>Conversions were determined by GC.

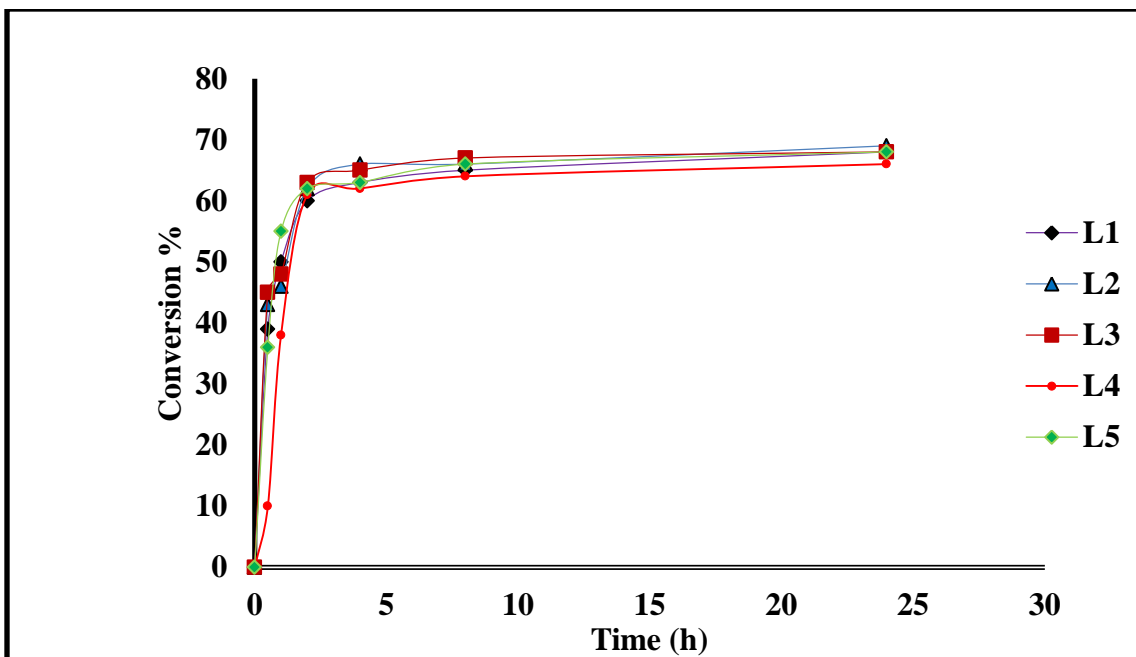
The results for this particular experiment are listed in Tables 4.11 and 4.12. In the case of PdCl<sub>2</sub> as a precursor, all pyrazolone ligands had a significant conversion of 60-70 % within the first 0,5 h of the reaction (Table 4.11 entry 1, 2 and 3). Comparing pyrazolone ligands **L3** showed a faster initiating rate than **L1** and **L2**. In the case of **L1**: conversion of 82 % (Table 4.11 entry 10) after 4h and increase to 88 % (Table 4.11 entry 16) after 24 h. A conversion of 75 % (Table 4.11 entry 11 and 12) was observed in the case of **L2** and **L3** after 4 h and increased to 82 % and 85 % respectively after 24 h (Table 4.11 entry 17, and 18). A clear trend of these results is presented in the plot in Figure 4.5. In the case of pyrazole the initial reaction was slower compared to pyrazolone ligands since at 0.5 h **L4** had 2 % conversion and **L5** 52 % (Table 4.11 entry 4-5). In general **L4** was slightly slower than the **L5** that could be attributed to the steric issues due to the fact that it's a large ligand compared to **L5**. It is noteworthy, between 4 to 24 h high conversions were obtained for **L4** than **L5** (Table 4.11 entry 19-20, 24-25 and 29-30).



**Figure 4.5** Heck coupling reactions varying reaction time using pyrazolone and pyrazole as the supporting ligands of PdCl<sub>2</sub> (**L1-L5**)

In the case of Pd(OAc) as precursor a similar trend as in PdCl<sub>2</sub> was observed: **L4** had a slow initiation as after 0.5 h it obtained a conversion of 10 % ( Table 4.12 entry 4) whereas other ligands showed better initiation averaging above 30 % ( Table 4.12 entry 1, 2, 3 and 5) within 0.5h. This observation indicated that initial rates were faster with pyrazolone than pyrazole based ligands. Although after 2-24h similar conversions were obtained for all five ligands (Table 4.12 entry 11-30).





**Figure 4.6** Heck coupling reactions varying reaction time using pyrazolone and pyrazole as the supporting ligands of Pd(OAc)<sub>2</sub> (L4-L5)

## 4.7 Summary and recommendations

In summary it is clear that palladium precursors such as PdCl<sub>2</sub> and Pd(OAc)<sub>2</sub> were able to catalyze the reaction of iodobenzene and butyl acrylate or ethyl acrylate. The major problem was the rate at which the formation of palladium black occurred. The formation of palladium black resulted in catalytic de-activation of these precatalysts. This characteristic resulted in poor % conversions for the Heck coupling reaction of iodobenzene with both olefins. In the case of PdCl<sub>2</sub> as pre-catalyst, in the presence of butyl and ethyl acrylate as olefins 29 % and 44 % conversions were obtained, respectively. In the case of Pd(OAc)<sub>2</sub> as pre-catalyst, similar observations occurred. In the presence of butyl and ethyl acrylate 25 % and 36 % conversion were obtained, respectively. Noteworthy was that in the presence of naked palladium precursors the general trend occurred, lower substituted alkene resulted in high % conversions and high substituents obtained low % conversion.

In order to improve the catalytic activity of these pre-catalysts, five different ligands (**L1-L5**) were used. From the results it has been shown that the pyrazolone based ligands (**L1-L3**) and pyrazole based ligands (**L4-L5**) are good auxiliary ligands in the catalysis of the Heck coupling reaction of iodobenzene with butyl or ethyl acrylate, since in the presence of ligands conversions ranging from 55 % to 83 % were obtained. Surprisingly, butyl acrylate was more effective than ethyl acrylate. That could be attributed to steric and electronic properties possessed by these auxiliary ligands. Therefore, butyl acrylate was chosen as the best olefin since in the presence of **L1-L5** with PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> average % conversions of 79 % and 74 % were obtained respectively.

The optimization studies of temperature, solvent, base and time effect has an influence on catalytic activity. During the investigation of temperature effect the catalytic system for both palladium precursors with **L1-L5** showed an increase in % conversions as the temperature increases. The major drawback at these high temperature ranges from 120 -160 °C was that better conversions were obtained with the precipitation of palladium as palladium black. Therefore, deactivation of the catalytic system was observed, but 80 °C comparable % conversions were

obtained with no signs of deactivation of the catalytic system, because at this temperature no formation of palladium black was observed.

Furthermore, replacing organic with inorganic bases disfavored the reaction, due to the fact that lower conversions were obtained. The issues of inhomogeneity of the inorganic base proved to be problematic in the Heck coupling reaction of iodobenzene with butyl acrylate, therefore triethylamine was the better base. Also on replacing polar aprotic solvents with non-polar solvents poor % conversions were obtained. DMF was chosen as the best solvent compared to other polar aprotic solvents such as acetonitrile and DMSO, since better conversions were observed in the case of DMF as a solvent.

The influence of time was proven to be an important issue as well, **L4** showed a slower initial rate which resulted in lower % conversion. But after two to three hours similar conversions were obtained as in the case of the ligands used in this study. Noteworthy, in all reactions high conversions were obtained within 4 h, meaning one does not need to run the reaction for 8 to 24 h, because there is no significant improvement in % conversions.

In conclusion, all ligands were shown to be effective catalyst systems with PdCl<sub>2</sub> or Pd(OAc)<sub>2</sub> in the Heck coupling reaction of iodobenzene with butyl acrylate under mild reaction conditions. No sign of deactivation of the catalyst systems was observed for **L1-L3**, but in the case of **L4-L5** slight signs of deactivation of the catalyst system were observed, since deposition of palladium black was observed on the magnetic stirrers. From the optimized reaction conditions PdCl<sub>2</sub> was the better precursor than Pd(OAc)<sub>2</sub> with the employed ligands (**L1-L5**). This catalytic system works better under these reaction conditions, when 1 mmole iodobenzene and 1,5 mmole of butyl acrylate were employed as substrates with 4 ml of DMF as a solvent in the presences of Et<sub>3</sub>N as a base at 80 °C under nitrogen atmosphere for 3h.

For future work, it will be interesting to prepare palladium complexes using **L1-L4** and use them as precatalysts in the palladium catalyzed C-C coupling reactions. Complexes formed from these ligands will give some opportunity to be applied in biphasic homogeneously catalysis, since these ligands are bearing hydrophilic functional groups. The main challenge of homogeneous catalysis is the separation of the catalysts from organic products and organic solvents. A possible solution to this problem is to separate the catalysts and product into two individual and immiscible phases.

Water as the alternative solvent in biphasic reaction medium offers the benefits of allowing simplified recovery and potential recycling of the catalytic species from organic products. Therefore, since the ligands bearing a hydrophilic group during the separation will be held in aqueous phase and organic products will be held in organic phase and by doing so the separation problem will be solved. Also, it would be of interests to determine the Heck mechanism at which these palladium complexes will behave as catalysts.

## 4.8 Reference

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