Methoxycarbonylation of higher olefins catalysed by (pyrazolyl-ethyl)-pyridine palladium(II) complexes

by

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Submitted in fulfilment of the requirement for the degree of

Master of Science

in

Chemistry

in the

College of Agriculture, Engineering and Science

at the

University of KwaZulu-Natal

Supervisor: Prof. Stephen O. Ojwach

DECLARATION

I declare that the thesis titled ‘Methoxycarbonylation of higher olefins catalysed by (pyrazolyl-ethyl)-pyridine palladium(II) complexes’ is my authentic work. The content of this work has not been submitted for the award of any degree or examination at any university, all authors of data and any other information are assigned as references.

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DECLARATION 2: CONFERENCE PRESENTATIONS

1. Siyabonga Zulu, DST-NRF Centre of Excellence in Catalysis c*change (CoE): Centre for Catalysis Research Conferences (2016 & 2017). (Ukhahlamba Drakensburg, KwaZulu-Natal, Nov. 2016; Pilanesberg, North West, Nov. 2017). Oral presentation. Methoxycarbonylation of higher olefins catalyzed by (pyrazolyl-ethyl)-pyridine palladium(II) complexes.
2. Siyabonga Zulu and Steven Ojwach, Catalysis South Africa Conference (2016 & 2017) (CATSA) (Ukhahlamba Drakensburg, KwaZulu-Natal, Nov. 2016; Pilanesberg, North West, Nov. 2017). Poster presentation. Methoxycarbonylation of higher olefins catalyzed by (pyrazolyl-ethyl)-pyridine palladium(II) complexes.

DEDICATIONS

To

My family and friends

ACKNOWLEDGEMENTS

I thank God, for with Him, nothing is impossible. I am also grateful to my supervisor Professor Stephen Ojwach, not only for giving me this opportunity to work in this project but for his guidance, perseverance and dedication in his craft which encouraged me to always work hard. The value of his critique and patience with me were second to none. I also very much appreciate him for giving me an opportunity to attend prestigious conferences. I also thank Dr. M.G. Alam for his valuable assistance in this work with regards to synthesis of the compounds. I would like to acknowledge Dr. Akerman for single crystal X-ray data collection and structural refinement of the compounds. I would like to express my gratitude towards NRF and DST Centre for Excellence (c*change) for their financial support. The undertaking of this study would be inconceivable without them. I am grateful to the School of Chemistry and Physics at the University of KwaZulu Natal, Pietermaritzburg Campus, for providing resources to make the completion of this research work possible. I am also grateful to my family and friends for their untiring emotional support.

ABSTRACT

Methoxycarbonylation belongs to the family of carbonylation reactions that are efficiently catalysed by homogeneous palladium catalysts to give ester products. To date, achieving cost effect, stable and selective catalysts still remains a major challenge in ligand design and catalyst development. Reactions of 2-[1-(3,5-dimethylpyrazol-1-yl)ethyl]pyridine **(L1)** and 2-[1-(3,5-diphenylpyrazol-1-yl)ethyl]pyridine **(L2)** with the [Pd(COD)Cl_2] or [Pd(COD)MeCl] produced novel palladium(II) complexes [Pd(**L1**)ClMe] (**C1**), [Pd(**L1**)Cl_2] (**C2**), [Pd(**L2**)ClMe] (**C3**), and [Pd(**L2**)Cl_2] (**C4**) in low to satisfactory yields. The characterization of these compounds involved ^{1}H- and ^{13}C-NMR spectroscopy, infrared spectroscopy, elemental analysis (for compounds), mass spectrometry, and single crystal X-ray crystallography of compounds **L2, C1**, **C2** and **C4**. The solid state structures of all the complexes were mononuclear and showed ligands **L1** and **L2** binding in bidentate coordination modes. Catalytic investigations of the palladium(II) complexes **C1-C4** indicated that all the complexes gave active catalysts in the methoxycarbonylation of olefins. Catalyst **C2** containing two auxiliary coordinating chloride ligands and methyl substituents on the ligand structure was the most active in the methoxycarbonylation reaction. Reactions using HCl, an acid promoter produced the highest activity while *p*-TsOH gave no catalytic activity. Furthermore, changing the phosphine used from non-chelating to chelating resulted in decreased catalytic activities. Changes in catalyst concentration, temperature, pressure, solvent, time and substrate also influenced the regioselectivity and catalytic activities.

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ABBREVIATIONS

MP	methyl propionate
COD	clycloоctadiene
ESI-MS	electron spray ionisation mass spectrometry
L	ligand
NMR	nuclear magnetic resonance
py	pyridine
pz	pyrazole
GC-MS	gas chromatography mass spectrometry
TOF	turn over frequency
FT-IR	fourier transform infrared
dppe	1,2-bis(diphenylphosphino)ethane
MSA	methanesulfonic acid
NSAID’s	nonsteroidal anti-inflammatory drugs
NMR	nuclear magnetic resonance
m/z	mass to charge ratio

CHAPTER 1

Synthesis, reactions, and applications of olefins and their role in the transition metal-catalysed methoxycarbonylation reaction

1. General introduction

Olefins, the name derived from the property of these compounds to form oily liquids, are a class of chemicals with the chemical formula C_nH_{2n} containing at least one C=C double bond.[1-4] They are building blocks for a wide variety of products such as plastics, rubber and solvents. Their usefulness in these applications is largely influenced by the location of the double bond within their structure (internal or terminal).[2] Furthermore, since olefins can be either linear or branched, this influences their physical and chemical properties, and eventual application.[5]

At first, chlorination/dehydrochlorination of linear paraffins and thermal cracking of waxes were the main pathways to linear α-olefins and linear internal olefins synthesis.[6] Industrially, higher olefins, C_8-C_{20}, can be obtained through the oligomerization of alkene monomers such as ethylene and mono-substituted ethylenes (alpha olefins);[7] also Fischer Tropsch synthesis,[8] cross-metathesis[9] and thermal cracking of petroleum.[6-9] It is their high reactivity that makes them good substrates for catalytic reactions such as oligomerization, polymerization, hydrogenation and carbonylation. As a result, they have a wide range of uses in catalysis, particularly homogeneous catalysis in the production of industrial and domestic products.[2]

1.1. Synthesis of α-olefins

1.1.1. Ethylene oligomerization

Ethylene oligomerisation is one of the main synthetic routes towards the production of α-olefins by means of Shell Higher Olefin Process (SHOP).[10] Terminal alkenes of C_4-C_{20} (α-

olefins) are employed in the production of co-monomers in the ethylene/α-olefin copolymerization.[11] Industrial processes that employed ethylene oligomerisation reactions include the Shell Higher Olefin Process (SHOP), Chevron Corp. processes, Albemarle, and the Idemitsu process.[12-17]

1.1.2. Fischer-Tropsch synthesis

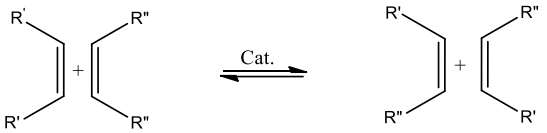
The Fischer-Tropsch reactions uses carbon monoxide in a heterogeneous hydrogenation to give aliphatic chains of different lengths (C_2 to $C_{10\,000}$) which generally terminate as paraffin, olefins, primary alcohols and aldehydes.[18] The main products are linear paraffins and α-olefins which can further be diverted to other refining processes such as alkylation and etherification. However, the identity of products produced depends on the catalyst and reaction conditions employed. It is accepted that a higher yield of α-olefins is obtained at elevated pressures and Fe-, Ni-, Co- and Ru- based catalyst can be used.[19] Sasol South Africa produces olefins *via* the Fischer-Tropsch synthesis (FTS). In this route, the alkali promoted iron-based catalysts are generally used due to their high activity and selectivity towards olefins production.[20]

1.1.3. Metathesis of olefins

Metathesis, which is a Greek word for transposition, involves the exchange of ions in a solution containing two ion pairs in order to produce the most stable ion pair (Equation 1).[21]

Equation 1: $A^+B^- + C^+D^- \rightleftharpoons A^+D^- + C^+B^-$

Similarly, an exchange between two carbenes of an olefin (if they are different) can take place to yield another recombination leading to the two symmetrical olefins (Scheme 1.1).



Scheme 1.1: An illustration of olefin recombination to produce two symmetrical olefins

This reaction uses Schrock[22] and Grubbs[23] catalysts (Figure 1.1), which facilitates a transformation in an alkene double bond resulting to its cleavage and formation. Schrock catalyzed reaction uses a molybdenum catalyst {Figure 1.1**(A)**} which possesses greater reactivity than the first generation Grubbs catalyst {Figure 1.1**(B)**} particularly with sterically demanding and electron deficient olefins. However, this catalyst has been less commonly used since the development of the second generation Grubbs catalyst {(Figure 1.1**(C)**}. The Grubbs catalysts are ruthenium-based complexes (Figure 1.1) which gives them good functional group compatibility. Furthermore, the second generation Grubbs catalysts which possesses N-heterocyclic carbene ligands (NHC) are more reactive and maintain high functional group tolerance, air and moisture stability.

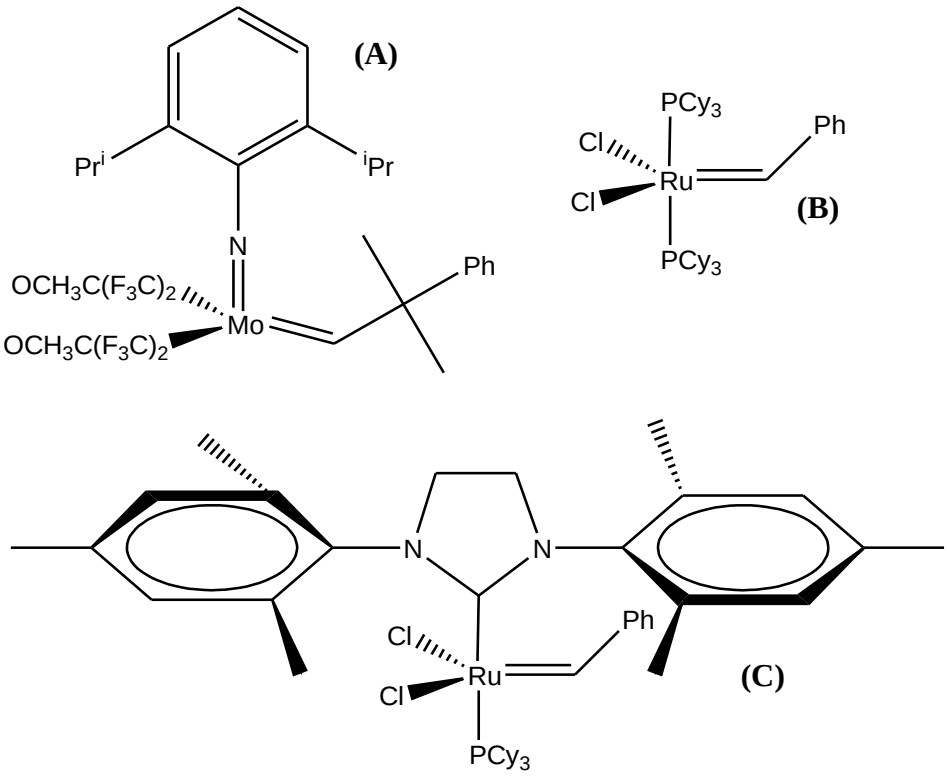


Figure 1.1: Schrock and Grubbs well defined catalysts used in the metathesis reaction[22-23]

1.1.4. Thermal Cracking

Thermal cracking of individual or mixed saturated hydrocarbons (long chain alkanes) is a well-known petrochemical process that can produce olefins, and depending on the hydrocarbon feed used, ethylene. [24] To obtain linear α-olefins, linear alkanes, waxes, must be used. Products such as C_{3-} to C_{5-}, C_4- and C_{5-} dienes, and C_{6-} to C_{8-}aromatics can be obtained depending on the molecular mass of the feed material (Figure 1.2).[25]

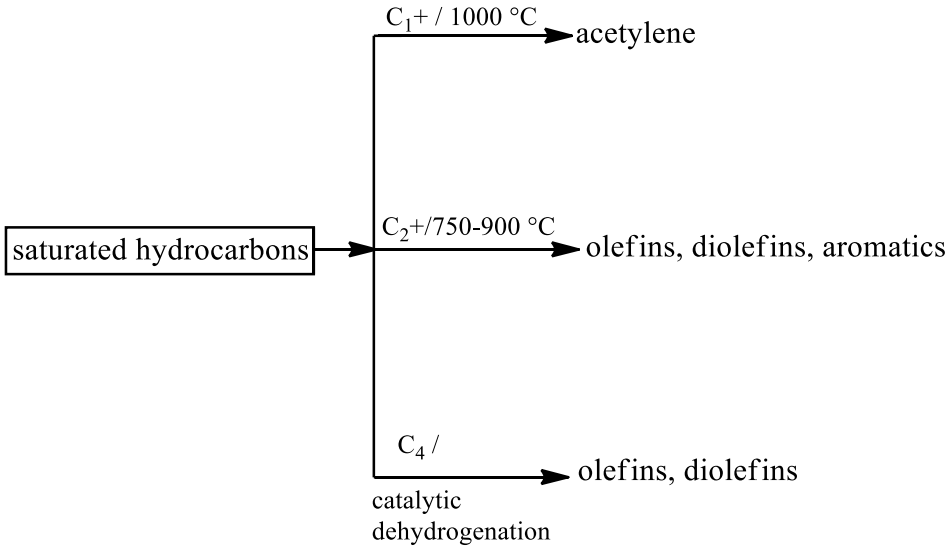


Figure 1.2: Pyrolysis and catalytic dehydrogenation of saturated hydrocarbons to give olefins[24]

1.2. Significance and applications of olefins

Since their first commercial production in 1964, α-olefins have attracted major interest due to their usefulness and attractive prices.[26-27] Due to high supply and demand of these products, the annual growth during 2012–2018 (Figure 1.3) is expected to rise by just over 3% annually through 2018.[28]

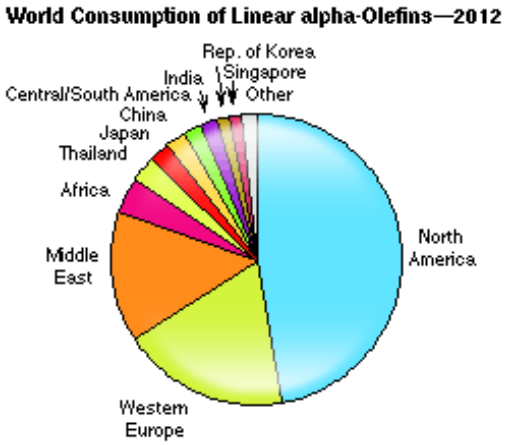


Figure 1.3: A chart showing world consumption of linear α-olefins in 2012. Adapted from Lappin *et al*. [28]

Sasol Olefins and Surfactants under Sasol Limited, a renowned global supplier of alcohols with a total capacity in excess of 600 000 metric tonnes per annum, has recently increased their oxo-alcohol production by 65 000 metric tonnes per annum. This was facilitated by the optimization of the olefin and paraffin streams to provide increased raw material for alcohol production.[29]

One of the largest uses of higher α-olefins is the production of polyethylene (as co-monomers), for the production of oxo alcohols which are mainly used in detergents ($>C_{11}$) and plasticizers ($<C_{11}$) synthesis; and for the production of polyalphaolefins which are used in the synthesis of synthetic lubricants base stock.[30] This oxo process has been used since 1971 by Monsato (from C_6 –C_{10} olefins) and Exxon (from C_7-C_{11} olefins) since 1983.[31-34] As a result, linear α-olefins are valuable commodity chemicals (Figure 1.4).

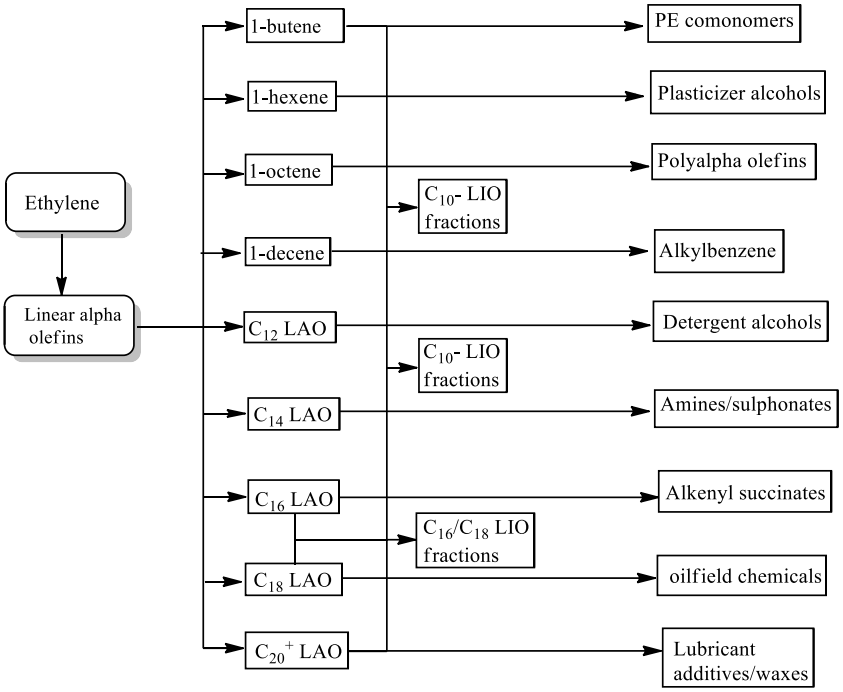
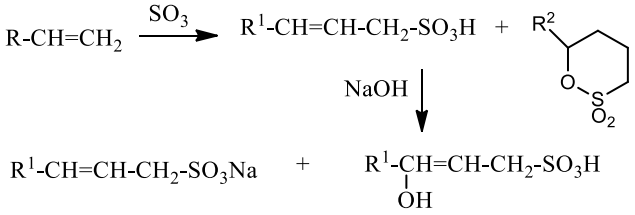


Figure 1.4: An illustration showing linear alpha olefins and their industrial applications.[34]

In addition to the aforementioned applications, olefins are used in the synthesis of linear alkylbenzenesulfonates (LABS) and α-alkenesulfonates (both also used in detergent production) through direct sulfonation of C_{14}-C_{18} α-olefins (Scheme 1.2).[35]



Scheme 1.2: Reaction mechanism towards the production of α-alkenesulfonates (AOS)

They are used in the synthesis of bromoalkanes and derived products such as thiols and in the production of copolymers where 1-butene, 1-hexene and 1-octene are used as comonomers in the production of high density polyethylene (HDPE) and low density polyethylene (LLDPE).[36]

The addition of α-olefins significantly modifies the density and other properties of the polymer. The reaction between α-olefins and peracid produces epoxides, they can also be converted into secondary monoalkylsulfates which are used in surfactants and detergents.[37-38]

Moreover, α-olefins and their compositions are utilized in the production of alkyl-aryl sulfonate surfactants which then aids during the process of waxy crude oil production.[39-40] In this oil recovery method, there is significance in the quality of the surfactant that only a narrow fraction of the alpha-olefins are used to make the surfactant (Figure 1.5). Currently, the alpha-olefin market is predominantly driven by the need of C_{10} and lower fractions since they are used in the production of plastics such as polyethylene and/or polypropylene.[41]

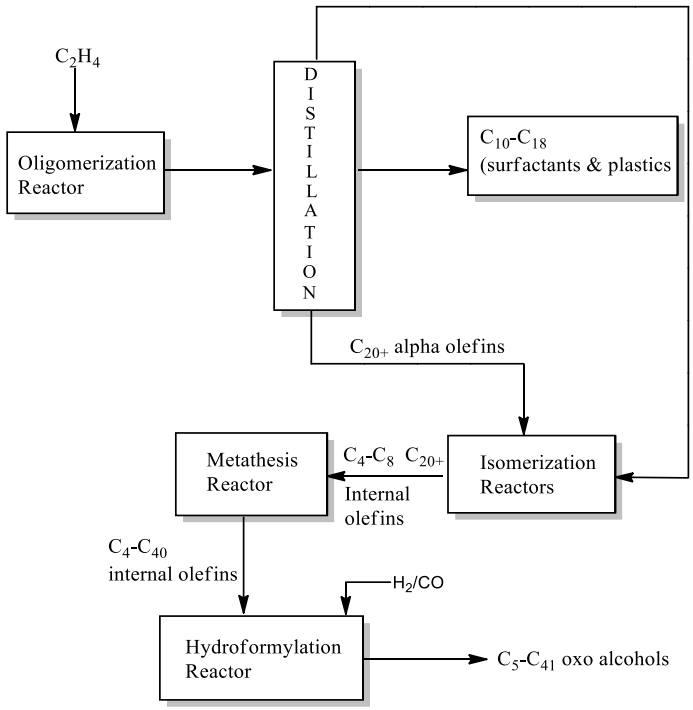


Figure 1.5: An illustration showing Sasol production and various uses of olefins[41]

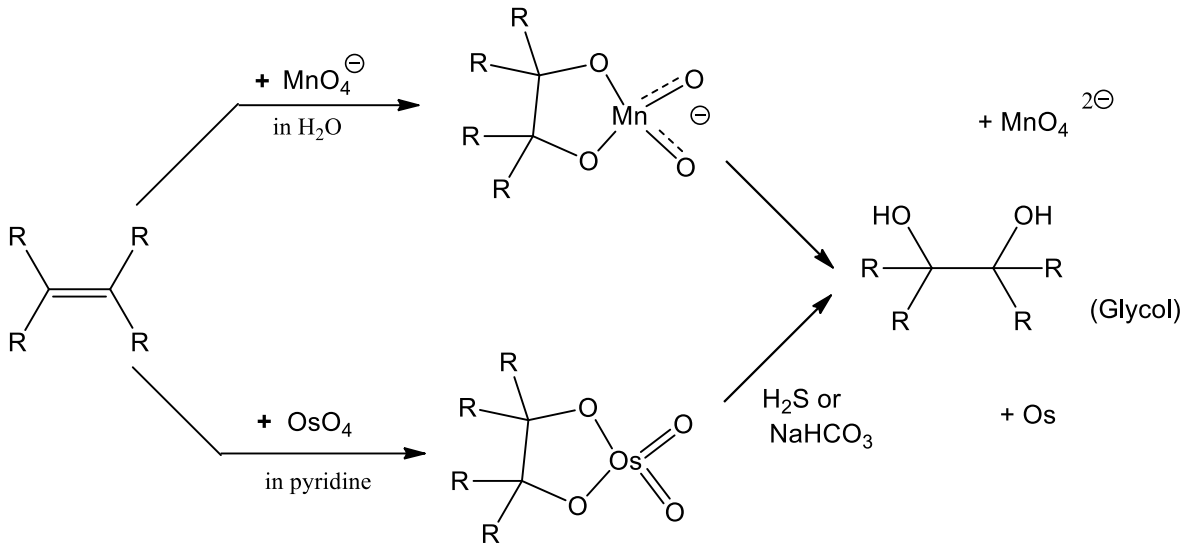
Therefore, the use of C_{10} bottoms i.e., C_{12} and lower fractions in this process is considerable. In fact, taking the entire C_{10} bottoms would eliminate many costly fractionation steps, thus further lowering the cost of the alpha-olefin feedstock for the surfactant.[42]

1.3. Reactions of higher olefins

1.3.1. Oxidation of olefins

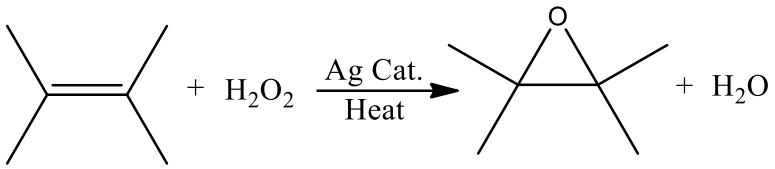
One of the most well-known olefin transformation reaction is Wacker oxidation where ethylene is transformed to acetyldehyde (ethanal) in the presence of palladium(II) chloride and copper(II) chloride as catalysts.[43] This was an important reaction as acetalydehyde can be used as an intermediate towards the synthesis of important compounds such as acetic acid, n-butyl alcohol, ethyl acetate, and other important compounds.

Glycols, ketones, epoxides and aldehydes are some of the derivatives that can be obtained through the oxidation of olefins.[44]This is an industrially important reaction as the aforementioned products have various uses in both fine and heavy/bulk chemical industry. For instance, olefins are oxidized to glycols (Scheme 1.3). Triethyl glycol is used as a solvent, in plasticizers and in gas dehydration, subsequently, ethylene glycol is used in polyesters production.[45] This well-known process produces methyl ketones from the oxidation of terminal olefins, on an industrial scale (e.g. acetophenone).[46-47] It uses a Pd (II) catalyst and stoichiometric amount of $CuCl_2$ co-catalyst under aerobic conditions, but has been modified and applied to achieve oxidation of various olefins to acetaldehydes.[48]



Scheme 1.3: An illustration of a transition metal catalysed oxidation of olefins to glycols[48]

Epoxidation of higher olefin substrates can also be carried out in the presence of oxygen and silver catalyst (Ag /Al_2O_3).[49-50]An epoxide is formed through hydroxylation of olefins with hydrogen peroxide in glacial acetic acid. The product then can subsequently react with water in an acidic medium to form a glycol (Scheme 1.4).[51]



Scheme 1.4: Mechanism for catalytic epoxidation of olefins using hydrogen peroxide

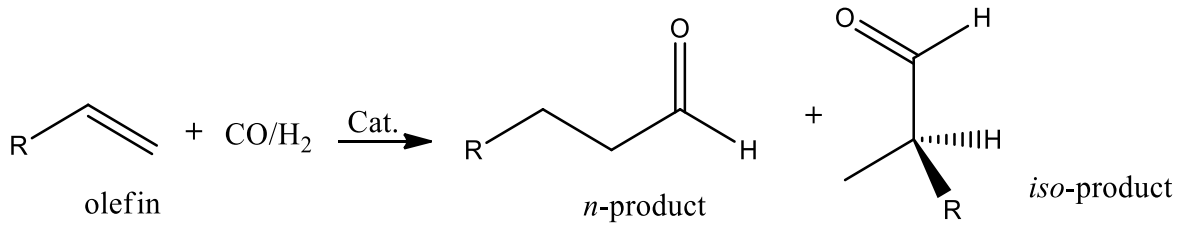
1.3.2. Reactions of olefins with carbon monoxide

Reactions of olefins with carbon monoxide (carbonylation), namely, hydroformylation and methoxycarbonylation are significant due to the high industrial value of the products formed. These techniques present a relatively straight forward path to aldehydes, alcohols, esters and carboxylic acids.[52] Hydroformylation reaction which uses carbon monoxide and hydrogen through addition reaction in the presence of the catalyst yields aldehydes and alcohols.[53] This

carbonylation reaction has been an essential part of homogeneous catalysis since the discovery of "oxo synthesis" by Otto Roelen in 1938.[54] Methoxycarbonylation reaction, also, a straight forward route from olefins to carboxylic esters uses carbon monoxide and methanol has been explored extensively with aim to optimise reaction conditions for possible commercial application.

1.3.2.1. Hydroformylation

This is an atom efficient process for the production of aldehydes where more than 10 million tons of oxo products are industrially produced by hydroformylation each year.[55-56]

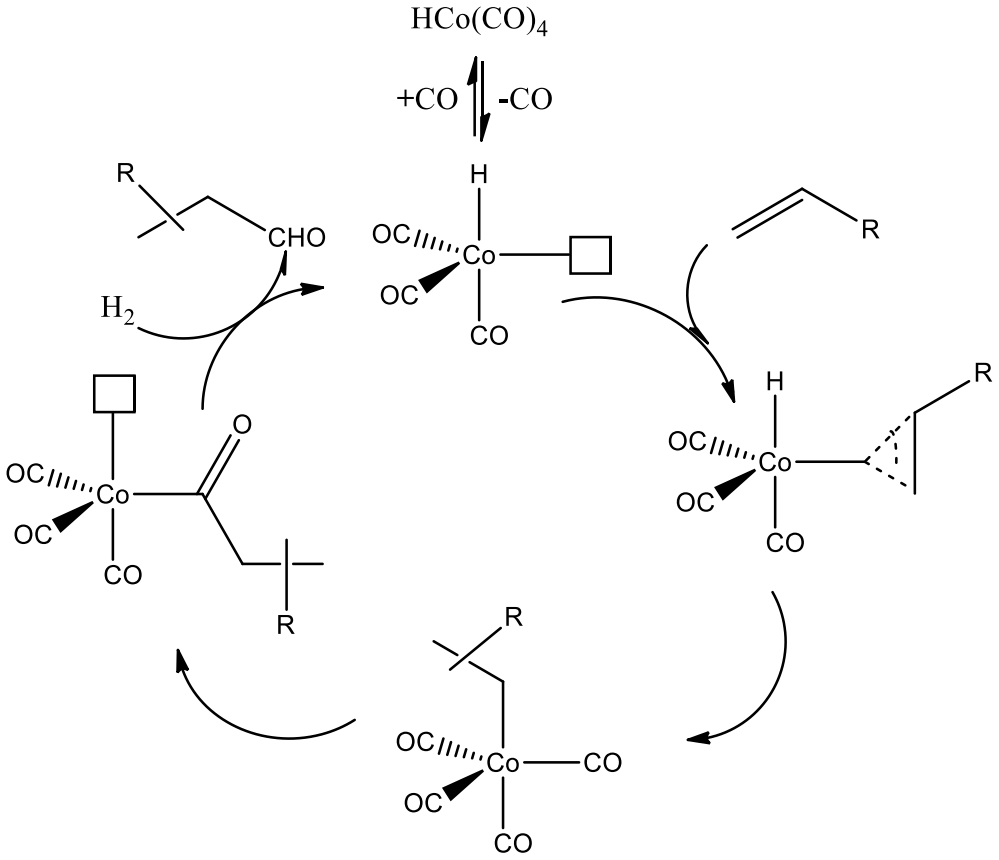


Scheme 1.5: An illustration for catalysed hydroformylation reaction of olefins to aldehydes[57]

As exhibited in Scheme 1.5, formylation can take place at the internal or terminal carbon atom which allows for the opportunity of obtaining linear (*n*) and branched (*iso*) products. However, isomerization of the double bond can take place leading to considerable hydroformylation of the internal olefins. This bodes well with the high demand of the branched aldehydes bearing a stereogenic center in the pharmaceutical industry although linear products can also be used as intermediates in the production of bulk chemicals.[58]

Cobalt-based complexes were the first catalysts used in the hydroformylation process as depicted in Scheme 1.6. However, the rhodium-based catalytic systems have been adopted due

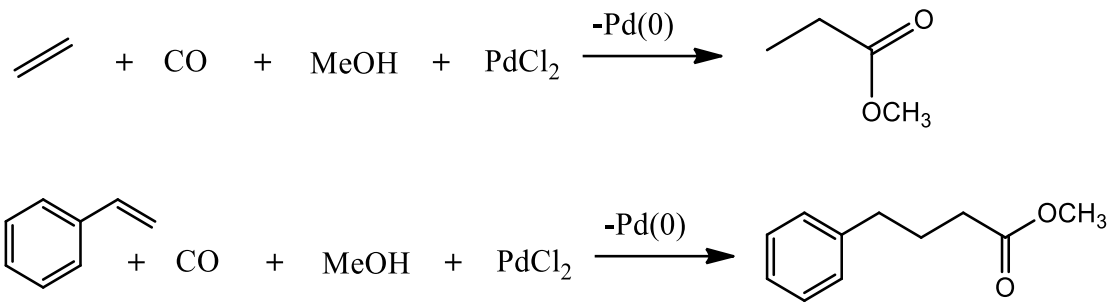
to their better catalytic activity and selectivity to hydroformylate longer chain olefins and internal olefins. [59]



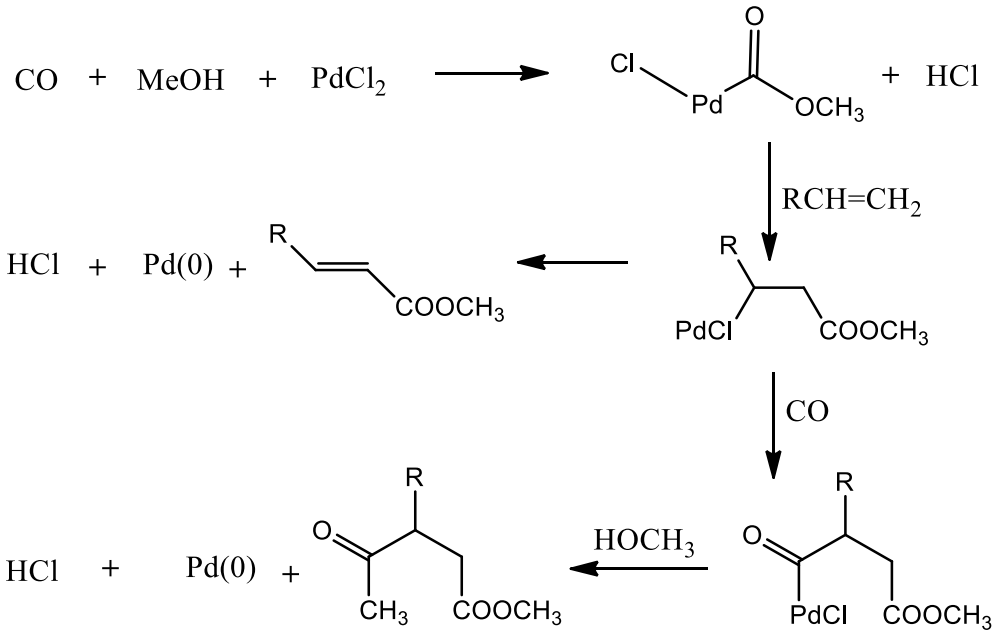
Scheme 1.6: Heck-Breslow mechanism for the cobalt-catalyzed hydroformylation reaction[60]

1.3.2.2. Methoxycarbonylation

Methoxycarbonylation is a one step process towards ester synthesis.[61-62]In this reaction, carbon monoxide and the alcohol (methanol) are added to an olefin's double bond to yield an ester. This process can be achieved in various ways. Oxidative methoxycarbonylation can take place where a stoichiometric amount of a palladium(II) salt, usually, $PdCl_2$, and methanol are used to transform an olefin into an ester (Scheme 1.7).[63] The use of a suitable oxidant such as benzoquinone allows this reaction to be catalytic with regards to palladium (Scheme 1.8). As a result, diesters can be obtained from this reaction through further CO insertion.[64]



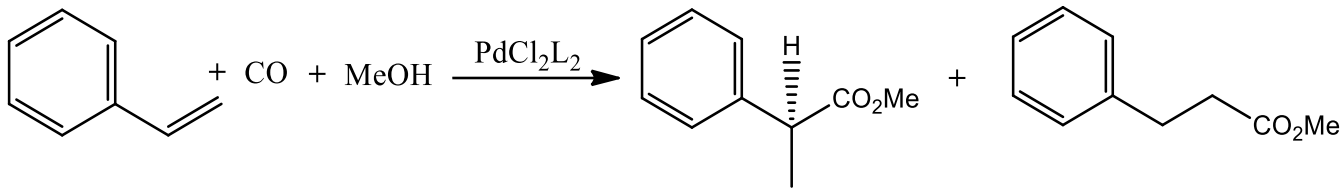
Scheme 1.7: Stoichiometric oxidative methoxycarbonylation of olefins[63]



Scheme 1.8: Catalytic oxidative carbonylation showing the methoxycarbonylpalladium species succeeded by olefin carbopalladative addition[64]

In another route that does not use an oxidant, the methoxycarbonylation (hydroxymethoxycarbonylation) takes place in the presence of methanol and palladium(II) catalyst (Scheme 1.9).[65] In this pathway, it is suggested that the catalytic cycle is discontinued by protolysis which leads to the formation of diesters and unsaturated esters but also involves methoxycarbonylpalladium species involved in oxidative carbonylation. Diesters and

unsaturated esters are formed due to the competing β-hydride elimination and carbonylation of the organopalladium intermediate.



L = Phosphine, nitrogen donor

Scheme 1.9: Mechanism for the palladium (II) catalyzed methoxycarbonylation of olefins[65]

1.4. Significance of methoxycarbonylation: products and applications

Palladium-catalyzed methoxycarbonylation reaction (Reppe carbonylation), a one-step synthesis route to esters is a well-known catalytic approach to carbon-carbon bond formation. Esters are used as precursors for non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen in the pharmaceutical industry (Figure 1.6).[66-70]

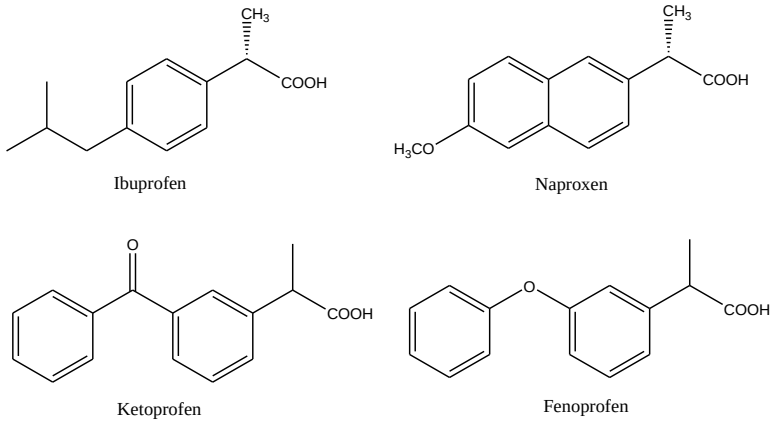


Figure 1.6: Commercial non-steroidal anti-inflammatory agents (NSAID's) that can be obtained through methoxycarbonylation[66-70]

Most importantly, the aliphatic ester products produced through the methoxycarbonylation of olefins can be used in detergent and surfactant production, as constituent for perfumes, essential oils, food flavourings, cosmetics, solvents, as monomers for diverse bulk polymers, and are envisaged as promising prospects for fuel supplements.[71] For these reasons, this process is significant in terms of value addition to establishments such as Sasol. The methoxycarbonylation of ethene to yield methyl propionate is especially interesting due to the importance of methyl propionates (MP) as an intermediate in the production of methyl methacrylate (MMA).[72] MMA is a monomer for the production of poly-methylmethacrylate (PMMA) which is a highly demanded transparent thermoplastic with many useful applications. PMMA is used as a lightweight or shatter-resistant alternative to glass, as a casting resin, in inks and coatings areas such as in architecture and construction, electronics and energy, automotive, sanitary and transportation.[73]

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CHAPTER 2

Literature review of palladium (II) complexes as catalysts in olefin methoxycarbonylation

2.1. General background

Methoxycarbonylation ("Reppe carbonylation") of olefins, has received much attention in homogeneous catalysis as it offers a relatively straight forward route to the synthesis of esters.[1] As a result, it has been of industrial interest for about five decades; as recorded in, including but not limited to, patents.[2-4] It is well known that the regioselectivity of the products is controlled by the ligands bound to a transition metal centre and the reaction conditions. Metal complexes containing bidentate diphosphine ligands have been frequently used as catalysts for this reaction, but generally produces low regio- and enantioselectivity to the branched product.[5-6]

However, since the invention of the Lucite process, for the production of methyl methacrylate, the palladium-based catalysts have been extensively studied for the alkoxycarbonylation reactions.[7] The use of cobalt and ruthenium-based catalysts have been reported,[8-11] however, the most common and successful palladium-based catalytic system used possesses mono- and bidentate aromatic phosphines.[12-13] When these catalysts are employed under optimal reaction conditions, high catalytic activity and regioselectivity towards the branched or linear products can be achieved.

Palladium(II)-based catalysts (such as in PdX_2L_2) have been commonly used as catalysts in the methoxycarbonylation of including, but not limited to, ethylene, cyclohexene, 1-hexene, 1-octene, styrene, 1-nonene and 1-decene.[14] Methoxycarbonylation of ethylene can be achieved efficiently under mild reaction conditions using palladium–phosphine complex catalysts,

which generally produce high catalytic activity and product selectivity.[15-16] However, obtaining desirable chemoselective and regioselective control of the methoxycarbonylation products for most substrates is still challenging. This is attributed to that these catalysts can become inactive due to the decomposition of palladium to palladium black. For this reason, the factors influencing the catalytic activity and selectivity of the catalysts including reaction parameters, the catalyst precursors and coordinated ligands plays a huge role in the interphase between catalyst design and homogeneous catalysis.

2.2. Role of an acid promoter

One of the crucial parameters employed in this reaction is the use of an acid promoter as it determines the type of the counterion coordinated to the palladium metal centre. A strong Brønsted acid with a pKa of 4 or above is needed to promote the reaction and preserve catalytic activity by enabling protonation of inactive Pd(0) species into active Pd-H species.[17] This is caused by that the methoxycarbonylation catalytic cycle follows a hydride mechanism[18] where the protic promoters function as hydride source in the formation of catalytically active Pd-H species and therefore commence the reaction.[19] As a result, it is generally accepted that the optimum acid promoters are strong acids that coordinate weakly to the palladium metal centre. Furthermore, the reaction rates are found to improve at higher acid loadings, which indicates that the role of an acid does not end in the formation of the Pd-H species but also in the final step where methanolysis occurs.[20-21]

However, these acids are strong and may therefore cause the starting product to undergo transesterification when using monodentate phosphines.[22-23]Other complications in utilizing these acid promoters include the manipulation and corrosion of reaction equipment especially

if added in significant amount. [24]They can also protonate the ligand and subsequently affect the catalyst stability and reaction rates and thus it is imperative that its amount be carefully controlled.[24-25] In an effort to avoid these aforementioned disadvantages, recently, the ionic liquids in liquid-liquid diphase have been used since they can be easily designed to have auxiliary reactivity of similar character to that of Brønsted acids. [26-27] Furthermore, in a study by Williams *et al.*,[28] Lewis acids such as $Al(OTf)_3$ in the methoxycarbonylation reaction of styrene and 1-pentene may be used instead Brønsted acids to form the anticipated ester products in high yields while producing higher reaction rates.

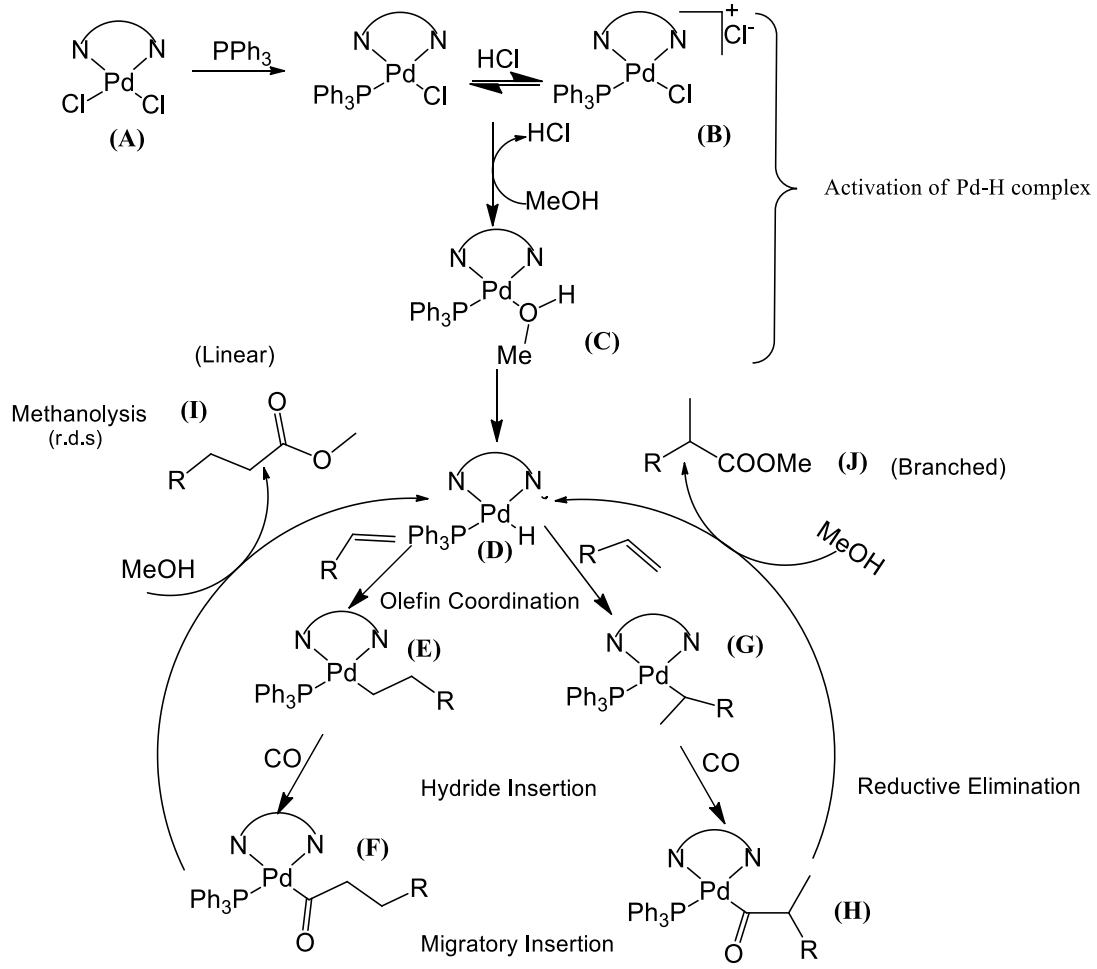
In addition to the significance of the coordinated counterion on the catalytic activity of the catalyst in the presence of a particular promoter, the olefinic substrate being transformed in the reaction is also important to consider. The catalytic activity can be influenced by the identity of the Brønsted acid (a cocatalyst) and substrate used in that this order for the methoxycarbonylation of styrene is obtained: *p*-toulene sulfonic acid > methane sulfonic acid > trifluoro methanesulfonic acid> trifluoro acetic acid > hydrochloric acid.[29] This trend is not observed for most substrates such as ethene and propene, because methoxycarbonylation of these substrates requires fairly high catalyst loading.[30]

In addition to the role played by an acid promoter, numerous previous studies have established that the regioselectivity of the methoxycarbonylation products is strongly dependent on the ligands bound to a transition metal centre. They function as stabilizers of the active palladium species and thus their steric and electronic properties have a significant effect on the reaction. As a result, the activity, selectivity and stability of the palladium catalysts for methoxycarbonylation relies largely on the coordinated ligands. In a study by Drent *et al.*, [31] it

was indicated that changing the ligand from PPh_3 to $Ph_2P(2\text{-py})$ led to increased reaction rates in the transformation of propyne and an increase in regioselectivity to branched products from 89% to 99%.

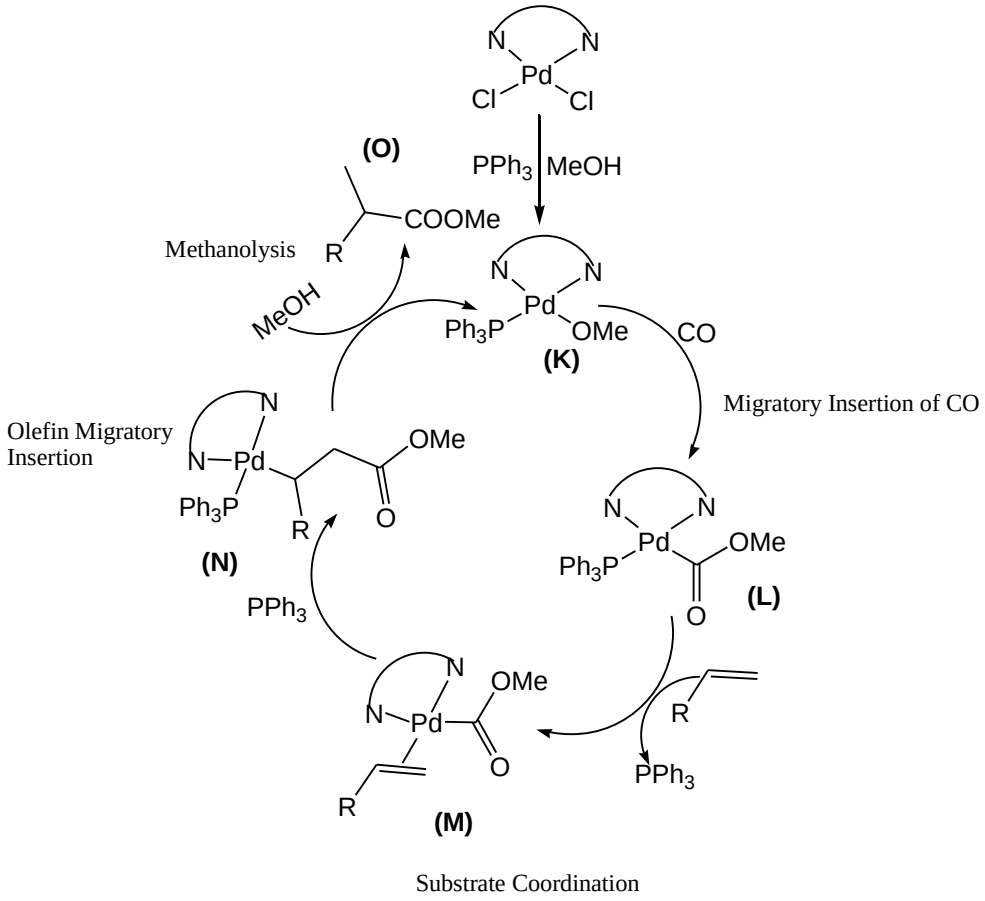
2.3. Mechanism of palladium (II) catalyzed methoxycarbonylation reaction

The palladium catalyzed methoxycarbonylation reaction is reported to follow either the methoxycarbonyl or hydride cycle/mechanisms.[32] However, the hydride cycle has been the widely accepted pathway for methoxycarbonylation reactions as applied to ethylene since all the intermediates in this cycle can be correctly identified through spectroscopy.[33] The hydride cycle (Scheme 2.1) begins with the addition of PPh_3 as a stabilizer and HCl (acid promoter) to the catalyst **A** giving a cationic species **B** which is then reduced with methanol to give **C**. Then coordination of the substrate to **D**, followed by insertion into the Pd-H bond then leads to the formation of Pd-alkyl complex (reversible by β-elimination) which is converted into an acyl complex (**F, H)** by migratory insertion of CO. Olefin insertion into a Pd-acyl bond (**D**) is accepted to be a crucial step in the palladium-catalyzed methoxycarbonylation since this gives significant contribution to the stability of the intermediate **E**. Subsequently, the nucleophilic attack of methanol on the acyl carbonyl leads to the formation of **I** (linear ester) or **J** (branched ester) depending on the reaction conditions and the regeneration of the catalyst.



Scheme 2.1: Hydride cycle for the palladium-catalyzed methoxycarbonylation reactions[32-33]

In the methoxycarbonyl cycle, Scheme 2.2, the cycle begins with the insertion of CO into the Pd-OMe bond of **K** to yield **L**. This is then followed by the coordination and insertion of the olefin into the metal-carbonyl bond. Then methanolysis occurs which lead to the formation of **O**, an ester product. Similar cyclic process is accepted for the generation of the linear product.



Scheme 2.2: Methoxycarbonyl cycle for the palladium-catalyzed methoxycarbonylation reactions[32-33]

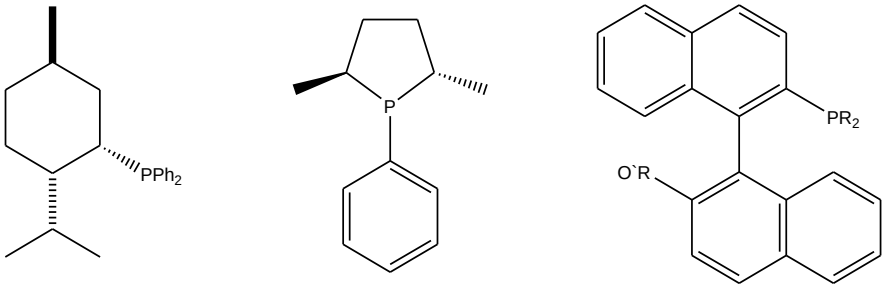
2.4. Palladium(II) catalysts in methoxycarbonylation reaction

2.4.1. Palladium(II) catalysts bearing phosphine donor ligands

Transition metal complexes supported by phosphine-based ligands, lean on the ability of the phosphine ligands to act as both π-acid and σ-base hence capable of stabilising the metal complexes in low oxidation states. These catalysts have been extensively used in homogeneous catalysis.[34-38] However, what makes them more desirable with regards to catalysis is that they can be fine-tuned to include pendant groups on the phosphorus atom thus introducing differing steric and electronic properties. The most common catalytic system involves palladium(II) and mono- and bidentate aromatic phosphines. Palladium complexes comprising of monodentate

phosphine ligands have been of interest for the methoxycarbonylation reactions since they yield high reactivity and regioselectivity to the branched ester. However, they also give low product enantioselectivity.[35-38]

The monophosphine-based palladium(II) catalytic system has also been used in the asymmetric methoxycarbonylation of styrene to obtain 2-arylproprionic acids, a vital class of nonsteroidal anti-inflammatory drugs. [39] Furthermore, the methoxycarbonylation of other substrates such as norbonene has been reported. [40] Generally, monophosphines are highly regioselective, but give low enantiomeric excess (Figure 2.1).[39] However, in a study by Zhou *et al.*,[41] an optimum yield of >99.3% for the branched isomer was obtained in the methoxycarbonylation of styrene using similar monodentate phosphines palladium(II) complexes.



Cometti *et al.*[42]
ee = 52%
b/l = 94/6

Nozaki *et al.*[43]
ee = 2.4%
b/l = 98/2

Kawashima *et al.*[44]
ee = 53%
b/l = 100/-

Figure 2.1: Monodentate phosphines previously used in asymmetric methoxycarbonylation[42-44]

Zuniga and co-workers[45] used *trans*-[η^5-$C_5H_4PPh_2$)$Re(CO)_3$]$PdCl_2$(NCMe), a monophosphine ligand-based palladium complex in the methoxycarbonylation of vinylarenes (Figure 2.2). They reported that the catalytic system *trans*-[η^5-$C_5H_4PPh_2$)$Re(CO)_3$]$PdCl_2$(NCMe) in the presence of HCl and methanol gave >99% catalytic activity, as well as high regioselectivity towards the branched esters (94%).

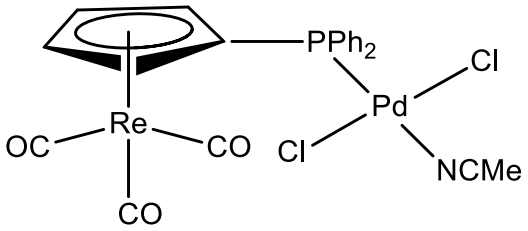


Figure 2.2: Organometallic phosphine ligand-based palladium(II) complex used by Zuniga *et al.*, in the methoxycarbonylation of vinylarenes.[45]

Munõz *et al.*,[46] found that under mild conditions, their chiral monodentate phosphine catalytic system produces generally low activity but also favored the formation of branched products. Zolezzi *et al.*,[47] employed palladium complexes containing naphthylphosphine ligands as a catalysts in the methoxycarbonylation reaction of various olefins (Figure 2.3). This catalytic system showed high activity (93%) and selectivity (100%) in the methoxycarbonylation of styrene after only 6 h with the TOF value of 62 h^{-1}.

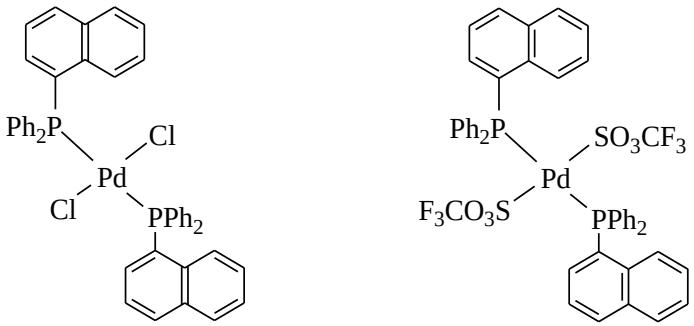


Figure 2.3: palladium(II) complexes containing naphthylphosphine ligands used by Zolezzi *et al.* in the methoxycarbonylation various olefins[47]

Although the phosphine-based catalytic system is regioselective towards the branched products, in contrast to the behaviour of the monodentate ligands which favour the formation of the branched products, catalytic systems bearing bidentate ligands generally lead to a greater amount of linear products.[48] This is evident in the studies conducted by Guiu *et al.*,[49] and Ooka *et al.*,[50] where they obtained regioselectivity up to 92% in favour of branched ester using

bidentate diphosphine ligands. Furthermore, in a study conducted by Frew *et al.*, [51] the methoxycarbonylation of styrene was reported to yield 2% activity when the neutral phosphine-based palladium(II) complexes such as [($PdCl_2$)(dppp)] was employed. However, when the less bulky phosphine-containing catalysts were used, under the same reaction conditions, an improvement in the percentage conversion (87%) and regioselectivity (67%) towards the formation of the branched products was observed (Figure 2.4).

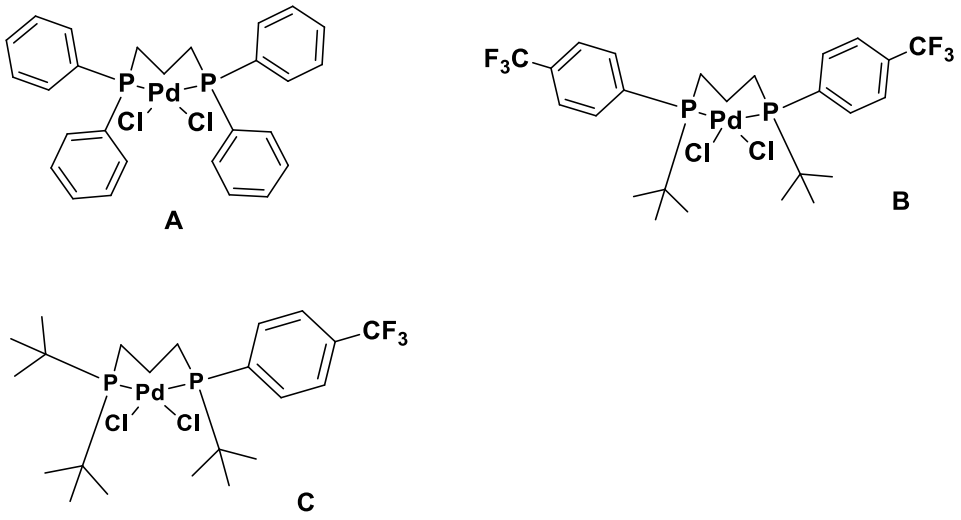


Figure 2.4: Bidentate phosphine (P^P) palladium(II) complexes used in the methoxycarbonylation of styrene by Frew *et al.*[51]

Despite their low regio- and enantioselectivity, catalysts containing bidentate diphosphine ligands have been more frequently used for this reaction and other successful examples have been reported. For instance, Bianchini *et al.*,[52] found palladium(II) complexes [Pd(H_2O)$_2$(dppf)](OTs)$_2$] and [Pd(H_2O)$_2$-(dppomf)](OTs)$_2$] to be effective catalysts for the methoxycarbonylation of ethene (Figure 2.5).

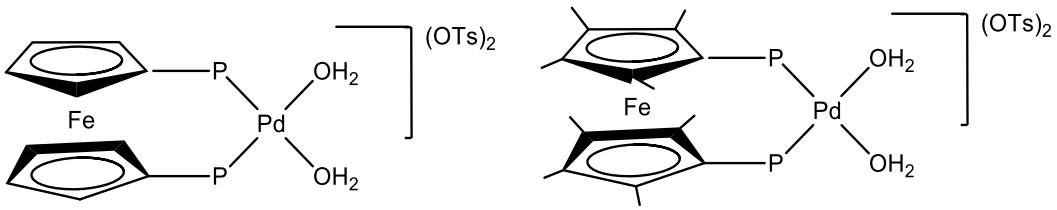
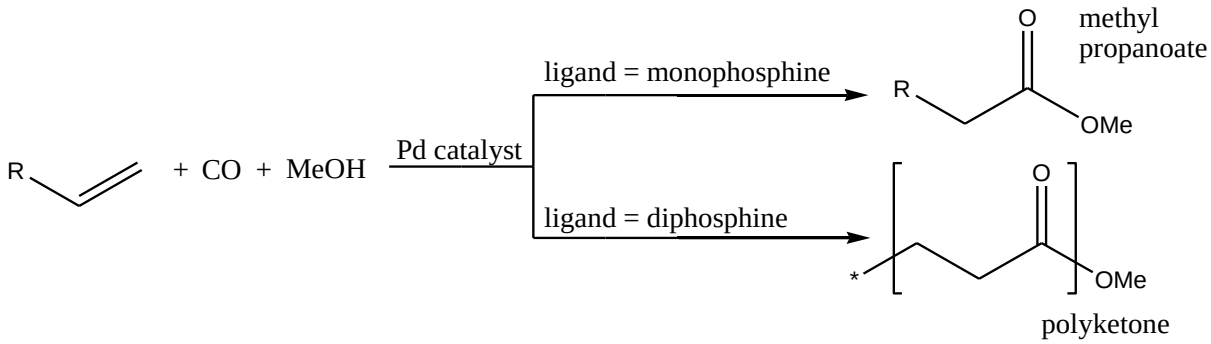


Figure 2.5: The square-planar bis(aquo) palladium(II) complexes $[Pd(H_2O)_2(dppf)](OTs)_2$ and $[Pd(H_2O)_2$-(dppomf)$](OTs)_2$ employed by Bianchini *et al.*[52] in the methoxycarbonylation of ethene

In this study, they found that the dppf-based catalyst produces numerous low molecular weight oxygenates, ranging from methyl propanoate to alternating oligoketones, while the dppomf catalyst produced only methyl propanoate.[52] In a similar study by Drent *et al.*, [53] it was established that the monodentate phopshines favor methoxycarbonylation of ethene to methyl propanoate, while bidentate phosphines allows for the formation of polyketones. This is not a surprising result since it is accepted that the selectivity of the methoxycarbonylation process exhibits a drastic dependence on the ligand nature. Monophosphine systems favour the formation of a methyl ester while diphosphines give the polyketone (Scheme 2.3).[54]



Scheme 2.3: Possible products from phosphine-donor palladium(II)-catalyzed methoxycarbonylation of olefins

Considering the proposed mechanism (see section 2.3), this difference between monophosphines and diphosphines can be explained by considering the possibility of a *cis-trans* isomeration equilibrium of the formed acyl species. This may occur in the medium when

monophosphines are used. As a result, the *trans* acylpalladium intermediate can progress to the corresponding ester by methanolysis to give methyl propanoate. However, this *cis-trans* isomerisation is forbidden in the case of diphosphines such as dppp.[54] The decoordination of a molecule of carbon monoxide frees a coordination site where a new molecule of an olefin can be inserted into the acylpalladium complex. By successive insertion of carbon monoxide and ethylene the chain grows generating the polyketone.

Evidently, fine–tuning the ligand is essential in regulating the performance of methoxycarbonylation reactions, chelating diphosphine ligand possessing metallocenic fragments, similar to those used by Bianchini *et al*., has been previously studied in several carbon-carbon and carbon-nitrogen bond forming reactions.[52-55] The success of the formed complexes in catalysis is largely due to their unique flexibility that allows one to build up molecular structures with different sandwiched metals and substituents either on the cyclopentadienyl ligands (Cp) or on the phosphorus atoms. This is demonstrated in the study by Zuniga *et al*., [55]where palladium complexes with ferrocene derivatives were used in the methoxycarbonylation of styrene (Figure 2.6).

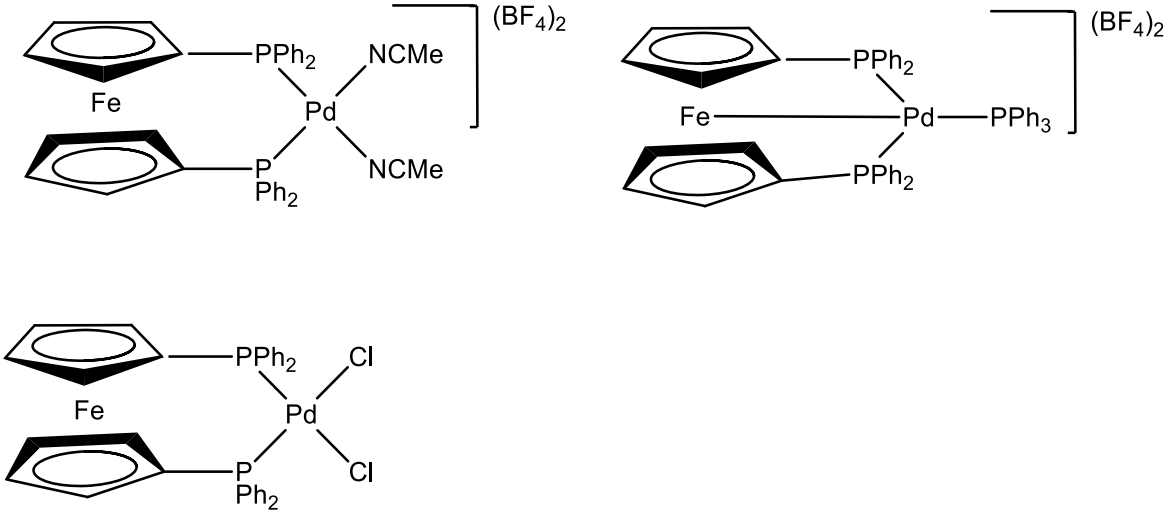


Figure 2.6: Palladium(II) complexes bearing phosphine and ferrocene ligands employed in the methoxycarbonylation of styrene by Zuniga *et al.*[55]

In this study, high catalytic activities and regioselectivity of up to 100% towards the branched product were reported. This was obtained after 24h reaction time using a Pd/Subtrate ratio of 1:400. Bianchini *et al.*,[56] used paladium(II) complexes (Figure 2.7) with 1,1-bis(diphenylphosphino)ferrocene(dppf),1,1bis(diphenylphosphino)octamethylferrocene(dppomf),1,1-bis(diphenylphosphino)ruthenocene (dppr) and 1,1-bis(diphenylphosphino)osmocene (dppo) in the methoxycarbonylation of styrene. Regioselectivity of up to 85% towards the linear isomer methyl-3-phenylpropanoate ester was achieved.

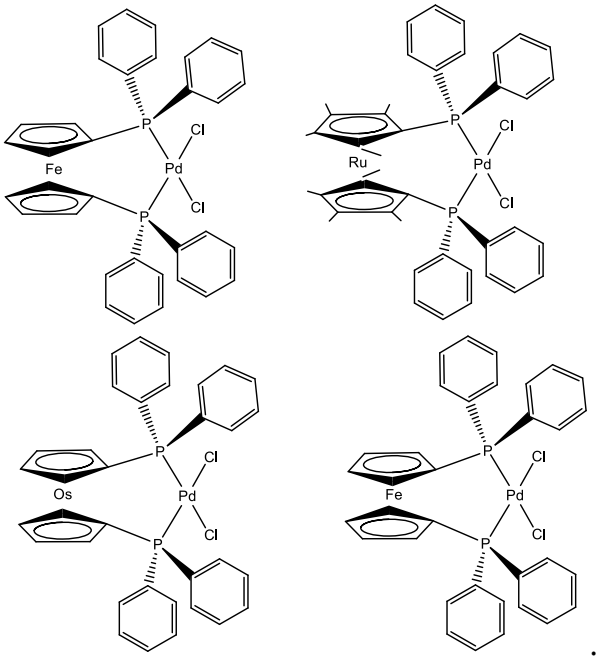


Figure 2.7: Diphosphine palladium(II) complexes bearing diphosphine ligands used by Bianchini *et al*. in the methoxycarbonylation of styrene.[56]

In another related study by Gusev *et al.,*[57] employed the similar palladium (II) complexes with 1,1-bis(diphenylphosphino) octamethylferrocene (dppomf) and 1,1-bis(diphenylphosphino) osmocene (dppo) for the methoxycarbonylation of olefins. They reported that both precursors are catalytically active and regioselective towards linear esters. This was attributed to the steric demands of phosphine ligands thus favouring the formation of linear products through the

promotion of 2,1-insertion followed by CO insertion into a Pd-styryl bond and termination by methanolysis.

In a study by Clegg *et al*., [58] several complexes bearing phosphine ligands with oxygen donor co-ligand/auxiliary ligands were reported and used in the methoxycarbonylation of ethene to methyl-propanoate (Figure 2.8). In this study, high catalytic activities were reported even when the reaction conditions such as solvent, acid promoter and the coordinated auxiliary ligand were altered. These catalysts also achieved activity of >99% and exhibited stability over time (TOF= 6.7 over 3 h reaction time). Evidence for the involvement of a Pd–H species in the catalytic methoxycarbonylation of ethene to methyl propaonate was reported.

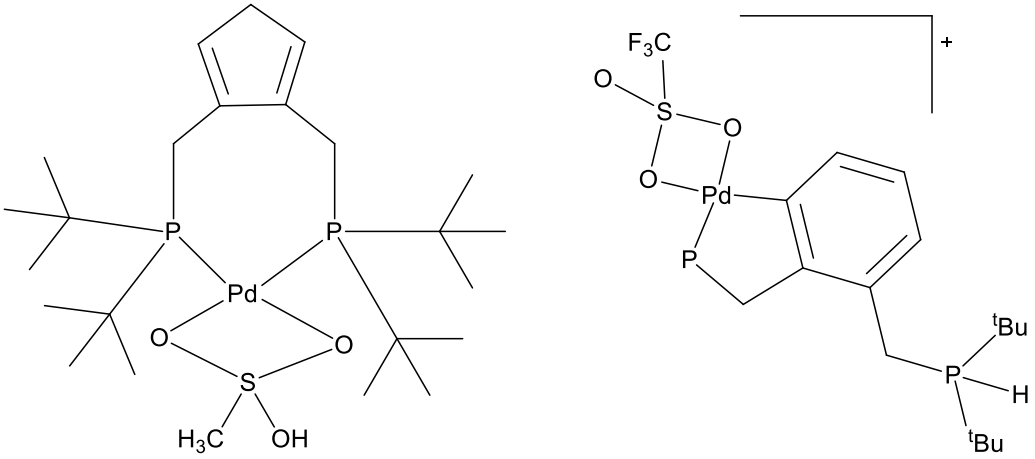


Figure 2.8: P^P-donor palladium(II) catalysts employed by Clegg *et al.* in the methoxycarbonylation of ethene.[58]

2.4.2. Mixed phosphine- and nitrogen–donor (P^N) palladium(II) catalysts

Heterobidentate P^N-donor ligands represent an important class of ligands that have been applied in various catalytic transformations, but they have been scarcely used in metal catalyzed carbonylation reaction.[59] However, some methoxycarbonylation studies have applied these P,N-donor heterobidentate ligands in various olefin transformations catalyzed by

palladium(II) complexes. In a study by Aguirre *et al.*, [60] the methoxycarbonylation of styrene was achieved with nearly complete chemoselectivity (99%) and regioselectivity (97%) to branched esters (Figure 2.9). Methoxycarbonylation of cyclohexene and 1-hexene also showed catalytic activity of 99% with the TOF of 67 h^{-1} after 6 h of reaction time.

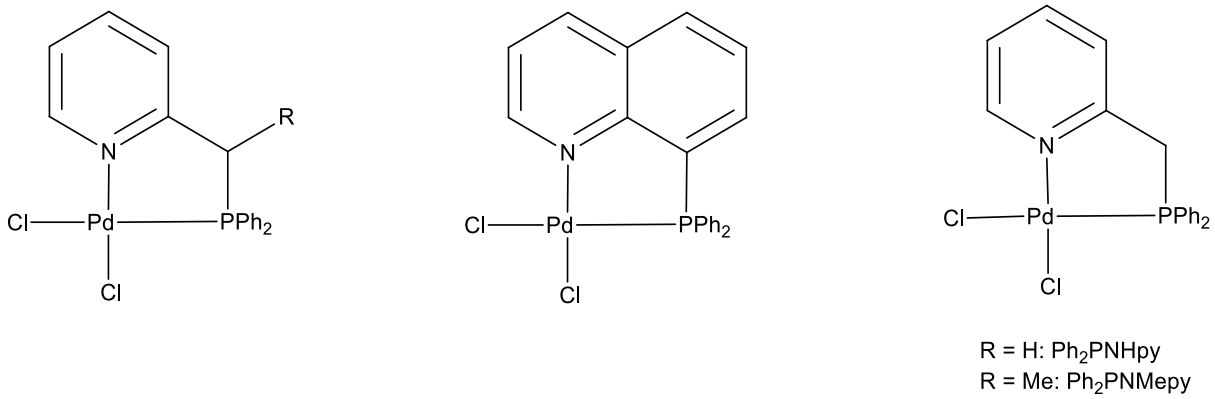


Figure 2.9: P^N-donor palladium catalysts employed by Aguirre *et al.* in the methoxycarbonylation of olefins.[60]

In a study by Abarca *et al.*, [61] palladium complexes of the type $[Pd(L)Cl(PPh_3)]Cl$ (L=2-diphenylphosphinoamino)pyrimidine, or 2-diphenylphosphinoaniline) were used in the methoxycarbonylation of styrene (Figure 2.10). Using these catalysts, 99% conversion and 97% regioselectivity towards branched esters was obtained. Typically, the P^N system involving bidentate phosphine-nitrogen backbone and give catalytic activity and regioselectivities towards linear alkoxycarbonylation products of >99% and >92% respectively.[62-65] This is attributed to the presence of the diphosphines which generate high catalytic activities (See Section 2.4.1).

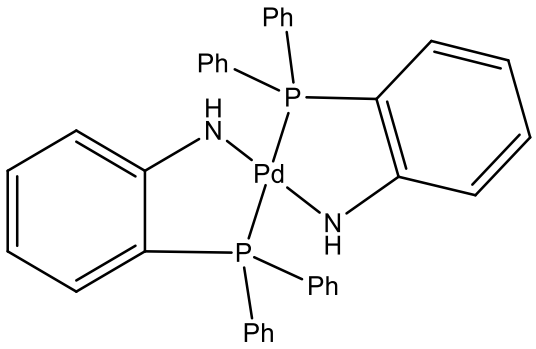


Figure 2.10: P^N-donor palladium catalyst employed by Abarca *et al.* in the methoxycarbonylation of styrene.[61]

2.4.3. Nitrogen- and oxygen donor (N^N and N^O) palladium(II) catalytic systems

Another well-known ligand system used to prepare palladium (II) complexes as catalysts is based on the N^N bidentates. In a study conducted by Tshabalala *et al.,* [66] complexes bearing bidentate nitrogen ligands (Figure 2.11) were used as catalysts in the methoxycarbonylation of styrene, 1-hexene, 1-octene, 1-nonene and 1-decene substrates. Their best result came from the methoxycarbonylation of styrene where 88% conversion and 82% regioselectivity towards linear products was obtained (TOF=7.1).

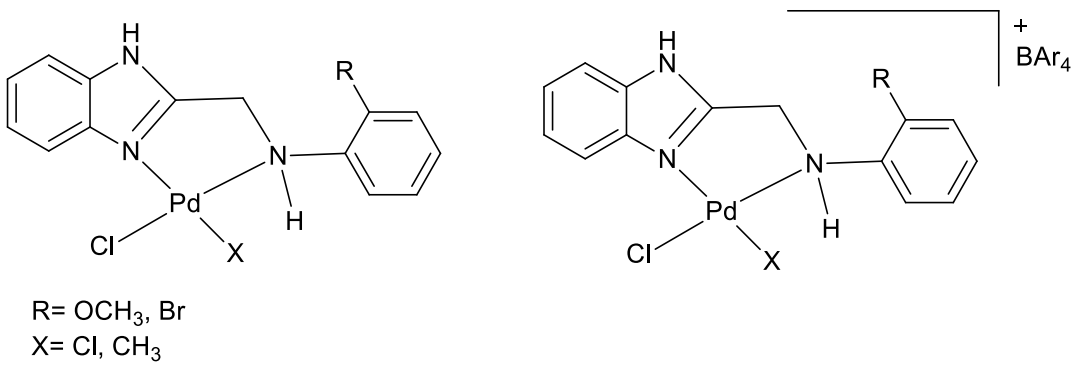


Figure 2.11: N^N-donor palladium catalyst employed by Tshabalala *et al.* in the methoxycarbonylation of higher olefins.[66]

In a previously mentioned study by Zuniga *et al.*,[45] a bidentate nitrogen-nitrogen palladium(II) complex was also used as a catalyst in the methoxycarbonylation of styrene (Figure 2.12). This catalyst was found to produce regioselectivity of 91% in favour of the branched ester with the percentage conversion at 17%. Low catalytic activity was attributed to the instability of the catalyst under the employed reaction conditions and weak π-retrodonation in the metal-nitrogen bond since inactive metallic palladium was found in the system during the catalysis.

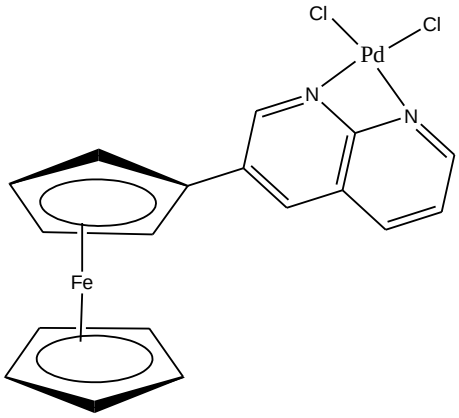


Figure 2.12.: N^N-donor palladium catalyst employed by Zuniga *et al.* in the methoxycarbonylation of styrene[45]

In a study by Smrecki *et al.*, [67] metal complexes bearing N-arylalkyl derivatives were used in the methoxycarbonylation of iodobenzene (Figure 2.13). A maximum conversion of 85% was achieved after 2 h of reaction time and the catalyst showed stability over time (TOF=7.9). The factors influencing the catalytic activity, stability and selectivity of the catalysts including their precursors plays a huge role in the interphase between ligand design and homogeneous catalysis. To date, balancing the activity and stability of transition metal catalysts remains a major challenge in ligand design and catalyst development for any given catalytic

transformation. As a result of, not many previously reported palladium(II) catalysts have been applied commercially.

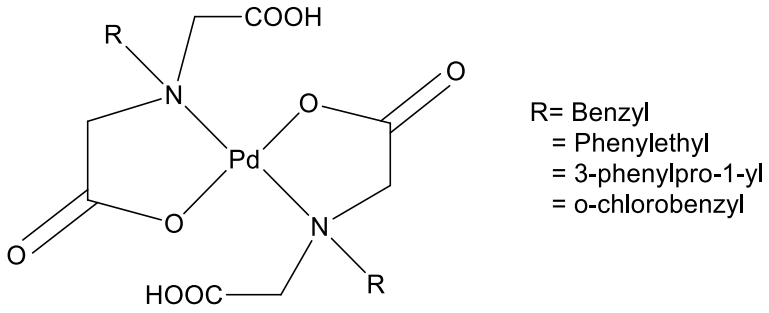
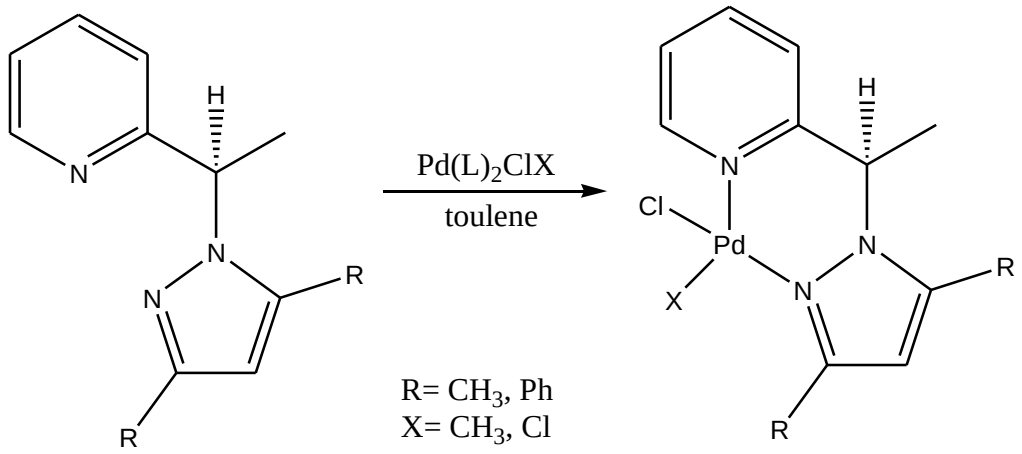


Figure 2.13: N^O-donor palladium catalyst employed by Smrecki *et al.* in the methoxycarbonylation of iodobenzene[67]

Based on this literature review, the current work is aimed at producing catalytically active and stable catalysts. This will be achieved through the use of catalytically active and stable palladium(II) (pyrazolyl-ethyl)-pyridine complexes as catalysts in the methoxycarbonylation of olefins (Scheme 2.4).



Scheme 2.4: Proposed route for the synthesis of palladium(II) (pyrazolyl-ethyl)-pyridine catalysts

2.5. Statement of the problem

The factors influencing the catalytic activity, stability and selectivity of the catalysts including their precursors plays a huge role in the interphase between ligand design and homogeneous catalysis. To date, balancing the activity and stability of transition metal catalysts remains a major challenge in ligand design and catalyst development for this given catalytic transformation. As a result, not many previously reported palladium(II) catalysts have been applied commercially, due to lack of combined catalytic activity, stability and selectivity.

2.6. Rationale and justification of the study

Methoxycarbonylation reaction produces intermediate of industrial and academia importance and there is a need for a more stable and active catalyst. The implementation of the palladium(II) complexes supported by nitrogen donor ligands as catalysts in the methoxycarbonylation of olefins is expected to reduce costs of the catalysts comparable to the cost of phosphine based palladium(II) complexes. The use of nitrogen donor ligands on the palladium(II) metal centre is expected to improve the stability and activity of the catalysts. In this project, the aim is to develop active palladium(II) catalysts that are cheaper and stable in the methoxycarbonylation of olefins. The design and development of these catalysts is expected to allow them to exhibit high catalytic activities and be used as suitable alternatives to the well-established phosphine-based palladium(II) catalysts.

2.7. Aims and objectives of the study

In this the project, the main focus was on the activity and selectivity of palladium(II) catalysts based on (pyrazolyl-ethyl)-pyridine ligands on the methoxycarbonylation of higher olefins.

Thus, the project aimed at designing versatile palladium catalysts of nitrogen donor ligands towards methoxycarbonylation of higher olefins with the specific objectives formulated as follows:

Specific objectives:

1. To synthesize (pyrazolyl-ethyl)-pyridine ligands and their corresponding palladium(II) complexes.

2. Investigate the synthesized palladium complexes as catalysts in the methoxycarbonylation reaction of higher olefins to understand the effects of complex structure on the methoxycarbonylation reactions.

3. To optimize the catalytic conditions in the methoxycarbonylation reaction of higher olefins to achieve better activity and selectivity.

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CHAPTER 3

Palladium(II) complexes of (pyrazolyl-ethyl)-pyridine ligands: Synthesis and Molecular Structures

3.1. Introduction

Methoxycarbonylation of olefins is usually catalysed by homogeneous palladium(II) complexes. Despite some success achieved in recent years, various methoxycarbonylation reactions are still far from industrial applications.[1]Therefore, identifying and fine-tuning the parameters that influence the activity and selectivity of the metal catalysts used in methoxycarbonylation reactions still constitute a major challenge. Most of the palladium(II) catalysts used in this reaction are based on phosphine, where diphosphines have been employed extensively.[2] To date, there is an emergence of the use of nitrogen donor palladium(II) complexes.[3-5] Nitrogen donor compounds such as pyrazole form bonds with the majority of metals and thus act as stabilizing ligands in palladium oxidation reactions.[6-13] This result to stabilization of Pd(II) and Pd(0) oxidation states during the catalytic cycle. As a result, the nitrogen-based catalysts have been reported to be stable in the presence of carbonyl compounds such as carbon monoxide.[14-19]

Nitrogen-based ligands such as (pyrazol-1-ylmethyl)benzene compounds which were initially documented in 1995 by Hartshorn and Steel[20-21] were reported to have different coordination modes. Thus far, very few reports of the use of these compounds have been used with palladium salts.[22]In an attempt to extend the use of these nitrogen-based ligands to other catalytic systems, we have explored the design and synthesis of the palladium(II) complexes bearing (pyrazolyl-ethyl)-pyridine ligands in the methoxycarbonylation of higher olefins. Therefore, in this chapter, we report on the synthesis of these complexes using 2-[1-(3,5-dimethylpyrazol-1-

yl)ethyl]pyridine (**L1**) and 2-[1-(3,5-diphenylpyrazol-1-yl)ethyl]pyridine (**L2**) were utilized to give four palladium complexes, [PdCl(**L1**)Me] (**C1**), [$PdCl_2$(**L1**)] (**C2**), [PdCl(**L2**)Me] (**C3**), and [$PdCl_2$ (**L2**)] (**C4**).

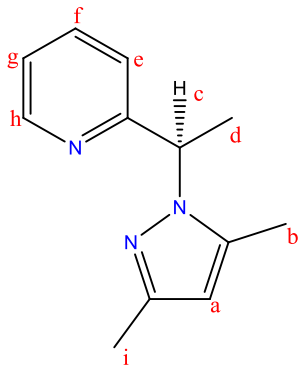
3.2. Experimental

3.2.1. Materials, general methods and instrumentation

All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. The solvents used i.e. absolute ethanol (≥96%), diethylether (≥99%), dichloromethane (≥99.8%) and toulene (≥99.8%) were of analytical grade and were dried over sodium, distilled prior to use, and distilled and dried over P_2O_5 respectively. Reagents, 3,5-dimethylpyrazole (99% purity), 1,5-cyclooctadiene (≥99%), 1,3-diphenyl-1,3-propanedione (98%), tetrabutylammonium bromide (≥99%), sodium hydroxide (≥98%), sodium borohydride (≥99%), 2-acetylpyridine (≥99%), palladium(II) chloride (≥99%) and thionyl chloride (≥99%) were obtained from Sigma Aldrich and used as received. Compound 2-(1-chloroethyl)-pyridine was synthesized by reducing 2-acetylpyridine using $NaBH_4$ and reacting the formed alcohol with $SOCl_2$. The palladium(II) metal precursors, [Pd(COD)Cl_2] and [Pd(COD)MeCl)] were prepared according to literature procedures.[23] NMR spectra were recorded on a Bruker Ultrashield 400 instrument (^{1}H NMR 400 and 500 MHz, ^{13}C {^{1}H} NMR 100 MHz) in DMSO-d_6 and $CDCl_3$ solutions at room temperature. Chemical shifts are reported in δ (ppm) and referenced to the residual $CHCl_3$ in $CDCl_3$. Coupling constants are measured in Hertz (Hz). Elemental analyses were performed using CHNS-O Flash 2000 Thermoscientific analyser. Mass spectra were recorded on an LC Premier micro-mass spectrometer while infrared spectra were obtained using Spectrum 100 FT-IR spectrometer at the University of KwaZulu-Natal.

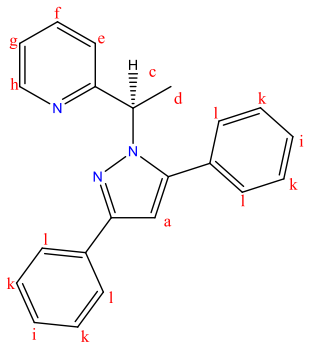
3.2.2. Synthesis of (pyrazolyl-ethyl)-pyridine ligands

3.2.2.1. 2-[1-(3,5-dimethylpyrazol-1-yl)ethyl]pyridine **(L1)**



To a solution of 2-(1-chloroethyl)-pyridine (2.02 g, 14.30 mmol) and 3,5-dimethylpyrazole (1.37 g, 14.30 mmol) in toluene (40 mL) was added, 40% aqueous NaOH (10 mL) and 40% aqueous tetrabutylammonium bromide (5-6 drops) were added. The mixture was then refluxed for 5 days. The organic layer was separated from the aqueous layer then washed with deionised water, dried over anhydrous Na_2SO_4, filtered and evaporated in *vacuo* to give a yellow liquid. This crude product obtained was purified by column chromatography, using a mixture of CH_2Cl_2:hexane (4:1) as eluent, to afford analytically pure compound **L1** as a solid. Yield: 0.57 g (52%). ^{1}HNMR ($CDC1_3$,δ, ppm): 2.30 (s, 3H, H_b); 2.40 (s, 3H, H_i); 1.56 (d, 3H, $^3J_{HH}$ =8.2, H_d); 4.98 (q, 1H, $^3J_{HH}$ =6.1, H_c); 5.87 (s, 1H, H_a); 7.29 (dd, 1H, $^3J_{HH}$ =7.7, H_g); 7.18 (d, 1H,$^3J_{HH}$ =7.8, H_e); 7.75 (td,1H, $^3J_{HH}$ =7.8, H_f); 8.58 (d, 1H, $^3J_{HH}$ =8.0, H_h). ^{13}C NMR ($CDC1_3$, δ, ppm): 13.71 (3-pz-CH_3), 14.05 (5-pz-CH_3), 20.19 (CH_3), 59.17 (2-py-CH), 105.64 (4-pz-CH), 120.25 (5-py-CH), 122.13 (3-py-CH), 137.07 (4-py-CH), 139.49 (2-pz-C), 147.50 (6-py-CH), 148.77 (4-pz-C), 162.10 (2-pz-C). MS (ESI): *m/z* (%) =201.27 (M^+, 100%). FT-IR: $\nu_{C=N(pz)}$ = 2287 cm^{-1}, $\nu_{C=N(py)}$ = 1980 cm^{-1}.

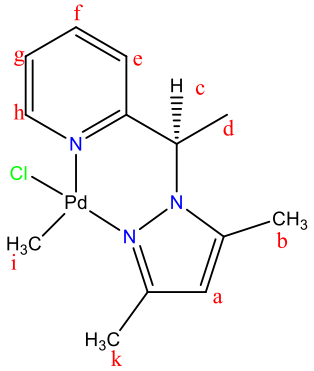
3.2.2.2. 2-[1-(3,5-diphenylpyrazol-1-yl)ethyl]pyridine **(L2)**



The synthesis of **L2** followed the same method as described for **L1** using 2-(1-chloroethyl)-pyridine (2.02 g, 14.30 mmol), 3,5-diphenylpyrazole (3.14 g, 14.30 mmol) was added to give a light orange liquid **L2**. Yield: 0.55 g (58%).^{1}H NMR (CDC1$_3$, δ, ppm): 2.05 (d, 3H, $^{3}J_{HH}$= 8.8, H$_d$); 5.75 (q, 1H, $^{3}J_{HH}$= 6.6, H$_c$); 6.70 (s, 1H, H$_a$); 7.57 (d, 1H, $^{3}J_{HH}$= 7.9, H$_h$); 7.94 (td, 1H, $^{3}J_{HH}$= 7.8, H$_f$); 7.33 (dd, 1H, $^{3}J_{HH}$= 7.4, H$_g$), 7.47 (d, 1H, $^{3}J_{HH}$= 7.4, H$_e$), 7.41 (m, 4H, H$_l$), 7.44 (m, 4H, H$_k$), 7.39 (m, 2H, H$_i$). ^{13}C-NMR (CDC1$_3$, δ, ppm): 21.04 (CH$_3$), 59.72 (CH), 100.12 (4-pz-C), 103.63 (5-py-C), 120.83 (3-py-C), 122.14, 125.64 (2-ph-C), 125.71 (6-ph-C), 127.62 (2-ph-C), 128.25 (6-ph-C), 128.60 (3-ph-C), 128.65 (5-ph-C), 128.70 (3-ph-C), 128.90 (5-ph-C), 128.96 (1-ph-C), 130.57 (1-ph-C), 133.79 (2-pz-C) , 136.96 (3-py-C), 145.69 (5-pz-C), 148.82 (2-pz-C), 150.79 (4-pz-C), 162.10 (2-py-C). MS (ESI): *m/z* (%) = 348.17 ([M+Na]$^{+}$, 100%). FT-IR: $\nu_{C=N(pz)}$ = 1975 cm^{-1}, $\nu_{C=N(py)}$ = 1605 cm^{-1}.

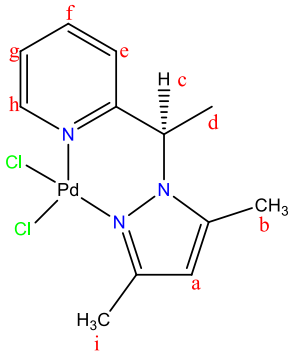
3.2.3. Synthesis of palladium(II) complexes C1-C4

3.2.3.1. *Synthesis of [{2-(3,5-dimethylpyrazol-1-yl)ethylpyridine}PdClMe]* **(C1)**



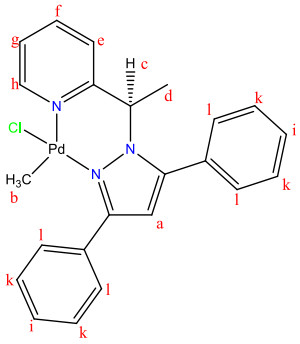
To a solution of Pd(COD)MeCl (0.10 g, 4.96 mmol) in diethylether (15 mL) was added a solution of **L1** (0.132 g, 4.96 mmol) in diethyl ether (10 mL) to form a light yellow precipitate. The resultant mixture was stirred for 24 h and filtered to give a light yellow solid, which was recrystallized from a mixture of CH_2Cl_2:hexane (2:1) to give single crystals suitable for X-ray analysis. Yield: 0.65 g (58%).^{1}HNMR ($CDC1_3$, δ, ppm): 0.95 (s,3H, H_i), 2.34 (s, 3H, H_b); 2.68 (s,3H, H_k); 1.94 (d, 3H, $^3J_{HH}$ =8.9, H_d); 5.67 (q, 1H, $^3J_{HH}$= 6.7, H_c); 6.92 (s, 1H, H_a); 7.29 (d, 1H, $^3J_{HH}$= 7.8, H_e); 7.32 (dd, 1H, $^3J_{HH}$=7.8, H_g); 7.79 (td, 1H, $^3J_{HH}$ = 7.9, H_f); 8.52 (d, 1H, $^3J_{HH}$= 8.0, H_h). ^{13}C-NMR ($CDC1_3$, δ, ppm): δ 11.87 (3-pz-CH_3), 15.11 (6-pz-CH_3), 22.96 (Pd-CH_3), 25.17 (CH_3), 58.66 (CH), 107.40 (4-pz-C), 122.82 (5-py-C), 124.68 (3-py-C), 138.35 (4-py-C), 140.16 (2-pz-C), 151.20 (6-py-C), 152.18 (5-pz-C), 155.57 (2-py-C). MS (ESI): *m/z* (%) = 308.05 ([M+Na]$^+$, 100%). FT-IR: $\nu_{C=N(pz)}$ = 2162 cm^{-1}, $\nu_{C=N(py)}$ = 1980 cm^{-1}. Anal. Calcd for $C_{13}H_{18}ClN_3$: C, 43.59; H, 5.07; Cl, 9.90; N, 11.73. Found: C, 42.76; H, 2.28; N, 10.44.

3.2.3.2. Synthesis of [{2-(3,5-dimethylpyrazol-1-yl)ethylpyridine}$PdCl_2$] **(C2)**



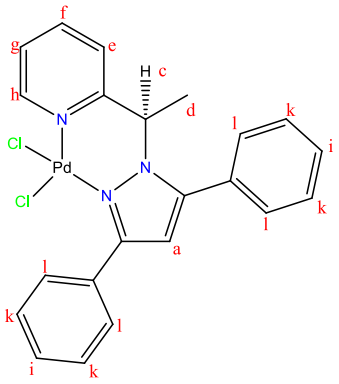
To a solution of [Pd (COD)Cl_2] (0.10 g, 4.96 mmol) in dichloromethane (10 mL) was added a solution of **L1** (0.13 g, 4.96 mmol) in dichloromethane (10 ml) and the resultant clear orange solution was stirred for 24 h. After the reaction period, the solution was then concentrated, followed by the addition of hexane (10 mL) and the mixture was kept at -4 °C to afford yellow single crystals suitable for X-ray analysis. Yield: 0.55 g (48%). ^{1}H NMR (DMSO, δ, ppm): 2.45 (3H, s, H_i); 2.44 (3H, s, H_b); 2.94 (d, 3H, $^{3}J_{HH}$ = 8.75, H_d); 6.17 (q, 1H, $^{3}J_{HH}$= 7.90, H_c); 5.51 (s, H, H_a); 8.88 (d, 1H, $^{3}J_{HH}$= 7.94, H_h); 8.12 (td, 1H, $^{3}J_{HH}$=7.74, H_f); 7.61 (dd, 1H, $^{3}J_{HH}$ = 7.4, H_g); 7.92 (d, 1H, $^{3}J_{HH}$= 7.48, H_e). ^{13}C NMR (DMSO, δ, ppm): 11.65 (2-pz-CH_3), 15.24 (4-pz-CH_3), 23.19 (CH_3), 58.21 (CH), 108.21 (3-pz-C), 125.82 (5-py-C), 126.09 (3-py-C), 141.56 (4-py-C), 143.33 (2-pz-C), 152.07 (6-py-C), 154.16 (4-pz-C), 156.06 (2-py-C). MS (ESI): *m/z* (%) = 401.98 ([M+Na]$^{+}$, 100%). FT-IR: $\nu_{C=N(pz)}$ = 2164 cm^{-1}, $\nu_{C=N(py)}$ = 2112 cm^{-1}. Anal. Calcd for $C_{12}H_{15}Cl_2N_3Pd$: C, 38.07; H, 3.99; N, 11.10. Found: C, 37.55; H, 2.97; N, 10.57.

3.2.3.3. Synthesis of [{2-(3,5-diphenylpyrazol-1-yl)ethylpyridine}PdClMe] **(C3)**



Complex **C3** was prepared following the procedure described for **C1** using [Pd(COD)MeCl] (0.10 g, 4.96 mmol) and **L2** (0.14 g, 4.96 mmol) to give a yellow solution. Slow diffusion of hexane into a CH_2Cl_2 solution (2:1) gave single crystals suitable for X-ray analysis. Yield: 0.18 g (53%).^{1}H-NMR ($CDC1_3$,δ, ppm): 2.99 (d, 3H, $^3J_{HH}$ = 8.8, H_d); 2.20 (s, 3H, H_b); 5.77 (q, 1H, $^3J_{HH}$ = 6.6, H_c); 6.54 (s, 1H, H_a), 7.46 (dd, 1H, $^3J_{HH}$= 7.8, H_g), 7.13 (d, 1H, $^3J_{HH}$= 7.7, H_e), 7.79 (td, 1H, $^3J_{HH}$= 7.7, H_f), 9.25 (d, 1H, $^3J_{HH}$= 7.6, H_h), 8.27 (m, 4H,H_k), 7.77 (m, 4H, H_l), 7.46 (m, 2H, H_i). ^{13}C NMR ($CDC1_3$, δ, ppm): 13.73 (Pd-CH_3), 23.19 (CH_3), 59.73 (CH), 107.53 (3-pz-C), 122.85 (5-py-C), 124.90 (3-py-C), 128.22 (2-ph-C), 128.42 (2-ph-C), 128.73 (6-ph-C), 128.86 (6-ph-C), 129.07 (3-ph-C), 129.12 (3-ph-C), 129.30 (5-ph-C), 129.38 (5-ph-C), 129.64 (4-ph-C), 130.09 (4-ph-C), 134.14 (1-ph-C), 134.23(1-ph-C), 135.10 (4-py-C), 146.15 (6-py-C), 155.15 (4-pz-C), 156.26 (2-py-C). MS (ESI): *m/z* (%) =483 (M^+, 100%). FT-IR: $\nu_{C=N(pz)}$ = 2162 cm^{-1}, $\nu_{C=N(py)}$ = 1606 cm^{-1}. Anal. Calcd for $C_{23}H_{22}ClN_3Pd$: C, 57.28; H, 4.60; N, 8.71. Found: C, 56.55; H, 3.43; N, 7.80.

3.2.3.4. Synthesis of [{2-(3,5-Diphenylpyrazol-1-yl)ethylpyridine}PdCl$_2$] **(C4)**

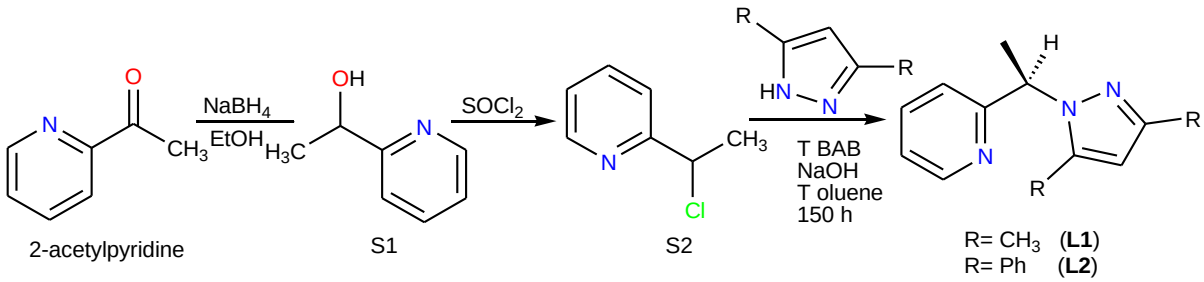


Complex **C4** was prepared following the procedure described for **C2** using [Pd(COD)Cl$_2$] (0.10 g, 4.96 mmol) and **L2** (0.14 g, 4.96 mmol). The solution was then concentrated to about 10 mL before adding, hexane (10 mL) at -4 °C to give orange single crystals suitable for X-ray analysis. Yield: 0.15 g (44%).^{1}H NMR (DMSO, δ, ppm): 3.29 (d, 3H, $^3J_{HH}$ =8.6, H$_d$); 5.73 (q, 1H, $^3J_{HH}$ = 6.4, H$_c$); 6.56 (s, H, H$_a$), 7.43 (dd, 1H, $^3J_{HH}$ = 7.8, H$_g$), 7.64 (td, 1H, $^3J_{HH}$ = 7.7, H$_f$), 9.35 (d, H, $^3J_{HH}$ = 7.6, H$_h$), 7.27 (d, 1H, $^3J_{HH}$ = 7.6, H$_e$), 7.48 (m, 2H, H$_i$), 7.62 (m, 4H, H$_k$), 8.27 (m, 4H, H$_l$). ^{13}C NMR (DMSO, δ, ppm): 20.17 (CH$_3$), 52.19 (CH), 108.11(3-pz-C), 124.14 (5-py-C), 125.65 (3-py-C), 127.56 (2-ph-C), 128. 30 (2-ph-C), 128.41(6-ph-C), 128.59 (6-ph-C), 130.61 (1-ph-C), 130.87 (1-ph-C), 134.01(4-py-C), 144.92 (2-pz-C), 146.92 (6-py-C), 154.79 (4-pz-C), 155.28 (2-py-C). MS (ESI): *m/z* (%) =503 (M$^+$, 100%). FT-IR: $\nu_{C=N(pz)}$ = 2164 cm^{-1}, $\nu_{C=N(py)}$ = 1605 cm^{-1}. Anal. Calcd for $C_{22}H_{19}Cl_2N_3Pd$: C, 52.56; H, 3.81; N, 8.36. Found: C, 52.10; H, 2.99; N, 6.89.

3.3. Results and discussion

3.3.1. Synthesis and characterization of (pyrazolyl-2-ethyl)pyridine ligands and their palladium(II) complexes

The reduction of 2-acetylpyridine using $NaBH_4$ as the reducing agent produced the alcohol intermediate (**S1**) which then subsequently gave 2-(1-chloroethyl)-pyridine (**S2**) through reactions with thionyl-chloride (Scheme 3.1). The reactions of 2-(1-chloroethyl)-pyridine with equal stoichiometric quantities of 3,5-dimethylpyrazole and 3,5-diphenylpyrazole generated ligands **L1** and **L2**, respectively.



Scheme 3.1: The synthetic route of the (pyrazolyl-ethyl)-pyridine ligands **L1** and **L2**

Purifications of **L1** and **L2** by column chromatography using a hexane:diethyl ether (3:2) mixture gave the analytically pure compounds in low to satisfactory yields (44–58%). Characterization of the ligands involved using ^{1}H NMR (Figure 3.2), ^{13}C NMR, FT-IR, mass spectrometry and single X-ray crystallography.

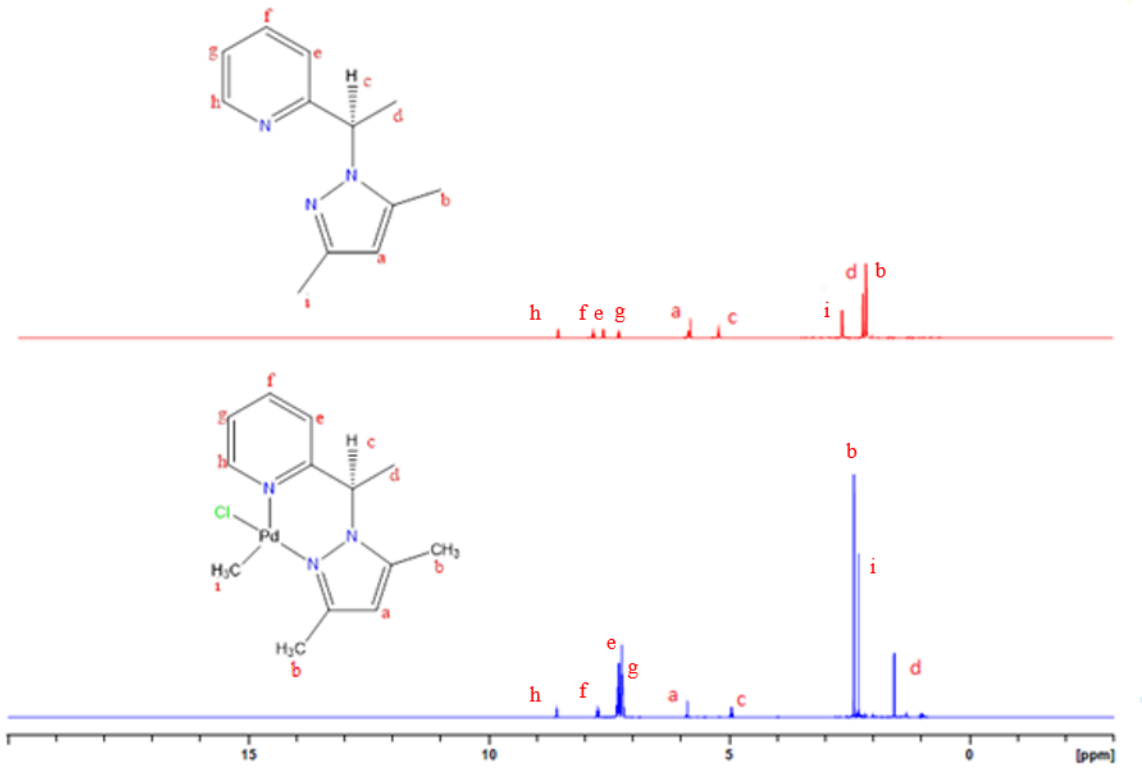


Figure 3.1: ^{1}H NMR spectrum of ligand **L1** and complex **C1** showing expected signature peaks for signals labelled a, c and d.

For example, **L1** exhibited two characteristic up-field singlet signals at 2.30 ppm and 2.40 ppm for the two methyl groups of the pyrazolyl moiety. A quartet peak at 4.95 ppm was assigned to the methylene proton, and the doublet peak at 1.56 ppm belonged to the methyl group of the methylene linker. The corresponding complex **C2** showed downfield shift of the singlet signal arising from CH_3 (d) from 1.56 ppm to 2.44 ppm. This trend was observed for all the complexes and their corresponding ligands. ^{13}C NMR of the synthesized compounds gave the expected number of signals. Electron spray positive and negative ion mass spectrometry data were also collected for compounds **L1** and **L2** to establish their composition. The positive ion mass spectra of these compounds showed the molecular ion peaks of the cations along with various other peaks corresponding to molecular fragments. ESI-MS of ligand **L1** (Figure 3.2) showed a base peak [M^+] at *m/z* =202 corresponding to the molecular mass of the compound.

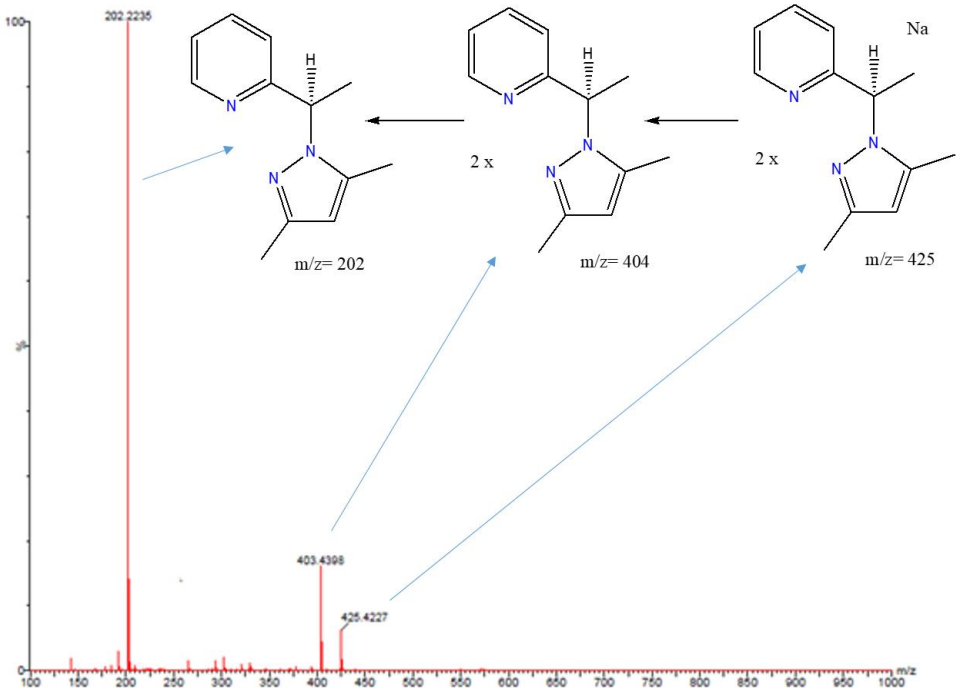
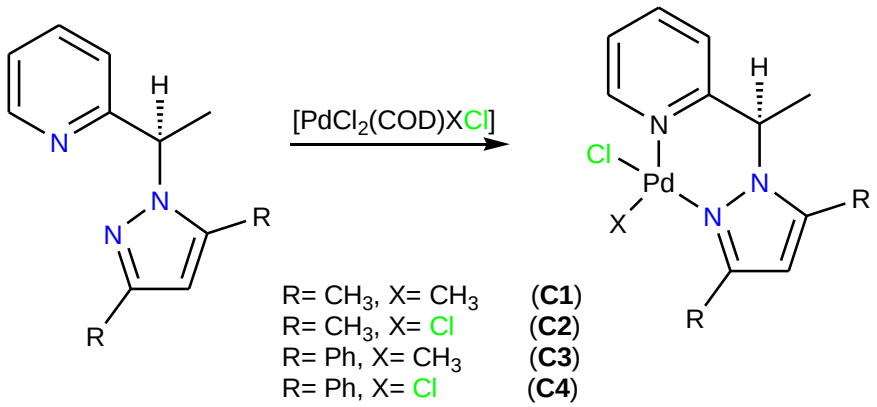


Figure 3.2: ESI-MS of ligand **L1** showing an [M^+] peak at m/z=202 amu with the peaks at m/z= 404 amu and m/z= 425 amu corresponding to two [M^+] and [M^+-Na] fragmentations.

Subsequent reactions of compounds **L1** and **L2** with metal salts [Pd(COD)Cl_2] or [Pd(COD)ClMe] produced the corresponding neutral complexes **C1-C4** in low to good yields of 44-84% (Scheme 3.2).



Scheme 3.2: The synthetic route to 2-(pyrazolyl-ethyl)-pyridine palladium(II) complexes **(C1-C4)**.

All the complexes were also characterized using ^{1}H NMR, ^{13}C NMR, FT-IR, mass spectroscopy, elemental analysis, and single crystal X-ray crystallography. Elemental analyses indicated that the complexes formed were monometallic and possessed one ligand unit per metal ion, in agreement with the proposed structures for all complexes (Scheme 3.2). Mass spectrometry data were also collected for compounds **C1**-**C4** to elucidate the structures and molecular mass (Figure 3.3).

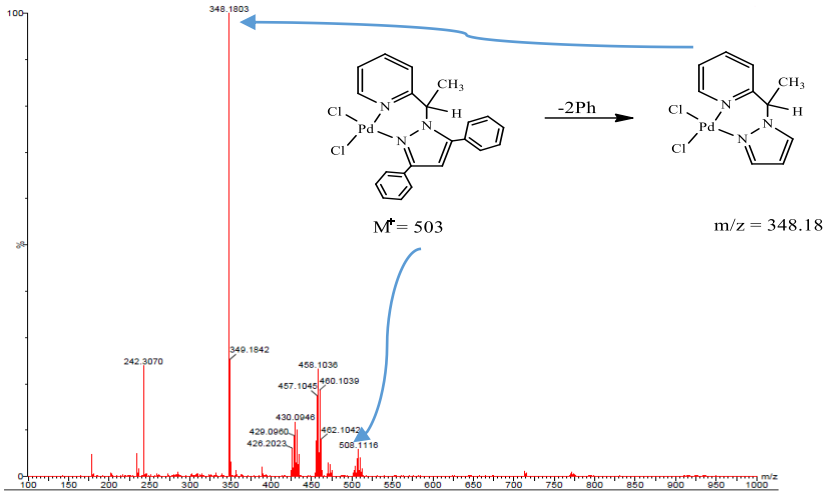


Figure 3.3: ESI-MS of [{2-(3,5-diphenylpyrazol-1-yl)ethylpyridine}PdClMe] complex **C4**

Mass spectrum of complex **C4** showed fragmentation pattern consistent with the loss of the two phenyl groups at m/z= 348 (base peak). The signal at m/z= 503 amu corresponds to the molecular mass of the complex (Figure 3.3). Similar trends were observed for the other complexes **C1**, **C2** and **C4**. Infrared spectroscopy (IR) was used for the analysis of both the ligands and complexes. By comparing the spectra of ligand **L2** with that of the corresponding metal complex **C4**, the formation of the metal complexes could be established (Figure 3.4).

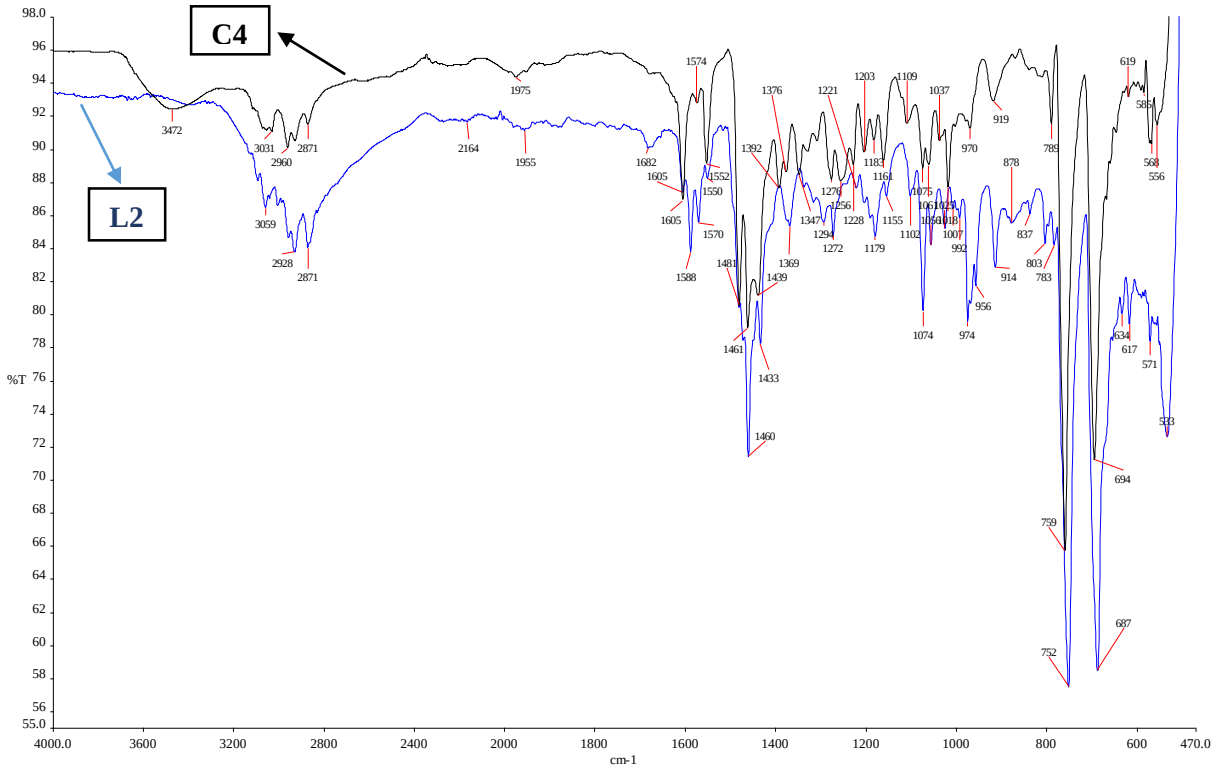


Figure 3.4: FT-IR spectrum of ligand (**L2**) and complex (**C4**) showing peaks indicating the formation of the metal complex

IR spectral data contained in Table 3.4 is consistent with the expected C=N(py,pz) frequencies in both ligands and complexes. C=N frequencies of the pyridine and pyrazolyl moieties of **L1** were observed at 2287 cm^{-1} and 1980 cm^{-1}, respectively while the C=N(py) frequencies of the corresponding **C1** were at 2162 and 1980 cm (Table 3.1). Similar spectra were observed for other palladium(II) complexes.[21-2]

Table 3.1: Pyridine and pyrazolyl C=N frequencies observed for ligands **L1** and **L2** and complexes **C1-C4**

Compound	**Pyrazolyl C=N (cm^{-1})**	**Pyridine C=N (cm^{-1})**
L1	2287	1980
L2	1975	1605
C1	2162	1980
C2	2164	2112
C3	2162	1606
C4	2164	1605

3.3.2. Solid state structures of L2 and palladium complexes C1, C2 and C4

To verify the proposed coordination modes of the (pyrazolyl-2-ethyl)-pyridine ligands **L1** and **L2**, solid state structures of complexes **C1**, **C2** and **C4** were determined. Single crystals suitable for X-ray crystallographic analyses were obtained by slow evaporation from their corresponding solutions of CH_2Cl_2-hexane for **C1** and **C4**, and hexane for **C2**). A summary of crystallographic data and structure refinement parameters for these complexes is represented in Table 3.2, while Table 3.3 contains selected bond lengths (Å) and angles **(°)**. Molecular structures of **L2, C1, C2** and **C4** are shown in Figures 3.5-3.8 respectively

Table 3.2: Crystal data and structural refinement parameters for **L2**, **C1, C2** and **C4**

	L2	**C1**	**C2**	**C4**
Empirical formula	C_{22} H_{19} N_3	C_{13} H_{18} Cl N_3 Pd	C_{12} H_{15} Cl_2 N_3 Pd	C_{22} H_{19} Cl_2 N_3 Pd
Formula weight	325.40	358.18	378.57	502.73
Temperature (K)	296(2)	100(2)	100(2)	100(2)
λ (Å)	0.71073	0.71073	0.71073	0.71073
Crystal system, space group	Monoclinic, P-2_1/n	Orthorhombic, $P2_12_12_1$	Triclinic, P-1	Triclinic, P-1
Unit cell dimensions	a = 8.348 Å α = 90° b= 13.852 Å β=103° c=15.587Å γ= 90°	a = 7.274 Å α = 90° b= 12.404 Å β= 90° c=15.2783 Å γ= 90°	a = 8.185 Å α = 71° b= 8.562 Å β= 87° c=11.245Å γ= 69°	a = 10.736 Å α = 115° b= 10.936 Å β= 97° c=12.390 Å γ= 104°
Volume ($Å^3$)	1754.5	1378.5	695.8	1233.4
Z	4	4	2	2
Crystal size (mm^3)	0.46 x 0.25 x 0.11	0.22 x 0.09 x 0.06	0.42 x 0.08 x 0.04	0.70 x 0.31 x 0.15
Index ranges	-10<=h<=10, -17<=k<=14, -19<=l<=19	-7<=h<=8, -15<=k<=15, -18<=l<=18	-10<=h<=10, -10<=k<=10, -13<=l<=13	-13<=h<=13, -13<=k<=13, -15<=l<=15
Absorption coefficient (mm^{-1})	0.074	1.718	1.702	0.979
Theta range for data collection	1.99 to 25.99°	2.115 to 26.090°	1.918 to 26.023°	1.878 to 26.121°
Reflections collected	14543	18238	22403	30530
Independent reflections	3414 [R(int) = 0.0214]	2708 [R(int) = 0.0285]	2701 [R(int) = 0.0239]	4845 [R(int) = 0.0225]
Data/restraints/parameters	3414 / 0 /227	2708 / 6 /167	2701/ 0 /166	4845/ 0 /254
Goodness-of-fit on F^2	1.367	1.113	1.044	0.561
Final R indices [I>2σ(I)]	R1 = 0.0386, wR2 = 0.1527	R1 = 0.0371, wR2 = 0.1045	R1 = 0.0138, wR2 = 0.0339	R1 = 0.0197, wR2 = 0.0551
R indices (all data)	R_1 = 0.0426, wR_2 = 0.1607	R_1 = 0.0374, wR_2 = 0.1048	R_1 = 0.0143, wR_2 =0.0342	R_1=0.0203, wR_2 =0.0559
Largest diff. peak and hole ($e.Å^{-3}$)	0.259 and -0.200	0.656 and -2.221	0.410 and -0.375	0.858 and -0.874

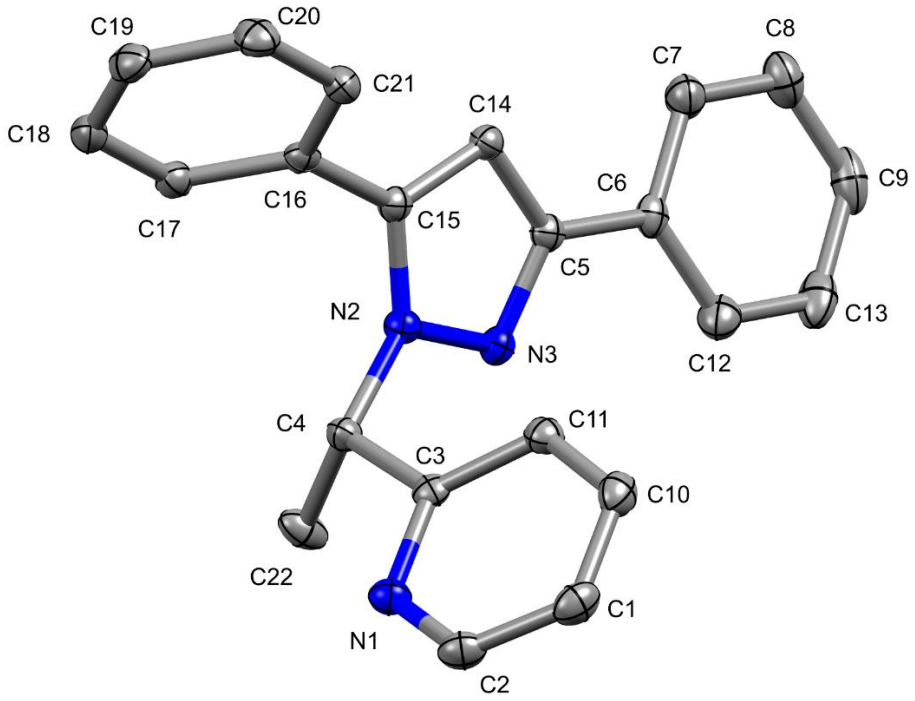


Figure 3.5: Molecular structure of **L2** shown with 50% probability ellipsoids (H atoms omitted for clarity)

Ligands **L1** and **L2** bind in a bidentate coordination mode with the remaining coordination sites occupied by either Cl or CH_3 ligands. In the solid state structure of **L2** (Figure 3.5), the aromatic rings show considerable distortion caused by the steric demands and flexibility of the CH_2 linker. This was expected since the steric properties of these units and most crystal structures of benzene derivatives are generally not flat compounds.[25-26] Coordination of **L1** and **L2** to the palladium metal centre gave complexes exhibiting different Pd–N(py) bond lengths. For example, complexes bearing methyl groups on pyrazolyl moeity, **C1** and **C2**, the Pd-N(py) bond distances are at 2.067(16) Å and 2.028(16), respectively (Table 3.3). However, the Pd-N(py) bond length in **C1** is about 0.04 Å longer than that of **C2** and **C4**. This indicates that there were minimal changes in electronic effects exerted by methyl and phenyl groups and changes of these groups had more influence on steric demands than electronic effects.

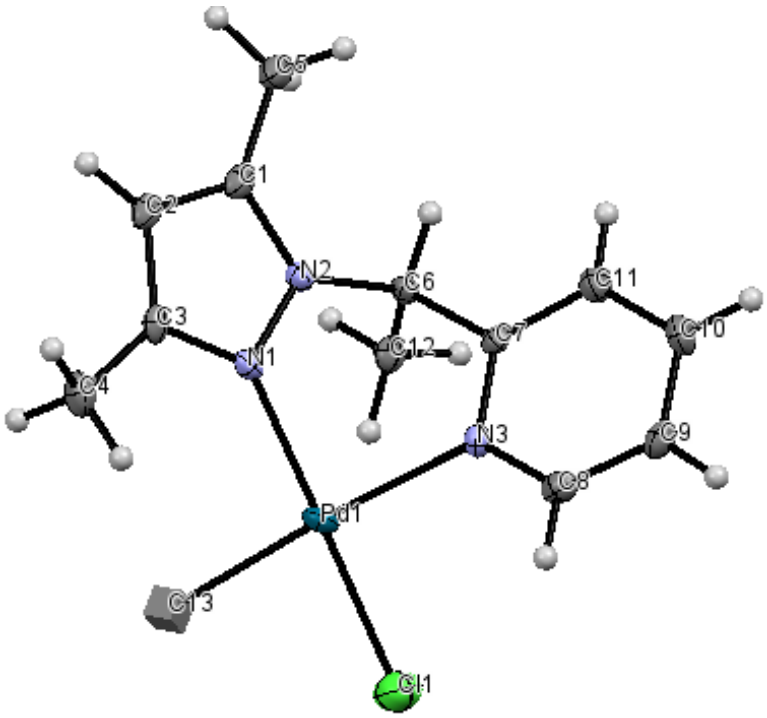


Figure 3.6: Molecular structure of **C1** shown with 50% probability ellipsoids (H atoms omitted for clarity).

The distortion of the pyrazole ring was more notable in the ligand structure than in the metal complex structure, where they adopt a boat conformation resulting into deviations in bond lengths and angles. The Pd–N(pz) bond length of complex **C1** was found to be 2.130(3) Å, 2.022(15) Å for **C2** and 2.036(16) Å for **C4**, respectively. There is a trend showing a general increase in Pd–N(pz) bond length in the complexes bearing methyl substituents in the pyrazolyl ring. These observations were attributed to the steric demands of the ligands caused by the presence of the alkyl groups. The distortion caused by the substituents on the pyrazolyl moeity was more prominent in complexes bearing phenyl substituent (**C4**) than methyl substituent (**C1** and **C2**). For instance, complex **C4**, containing a bulkier phenyl group in its molecular structure exhibited greater steric demands therefore causing the elongation of the Pd–N(pz) bond length.[25-27] The Pd–Cl distances in complexes **C1**, **C2** (Figure 3.6) and **C4** were found to be 2.272(2) Å, 2.296(11) Å and 2.296(11) Å, respectively.

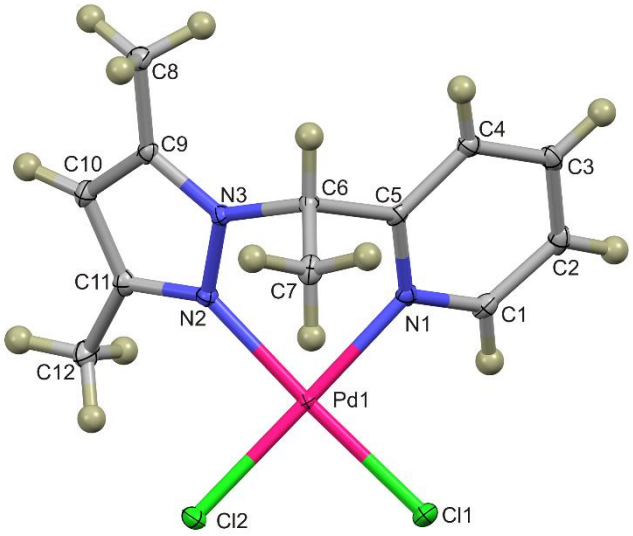


Figure 3.7: Molecular structure diagram of **C2** shown with 50% probability ellipsoids (H atoms omitted for clarity).

The difference of ~0.02 Å can also be attributed to the presence of the methyl group located directly opposite the Pd-N(pz) bond causing the bond elongation because of *trans* effect. These bond distance values were found to be consistent with those previously reported.[28]As expected, because of their covalent bonding character, the Pd-C13 bond length of 2.141(3) Å for complex **C1** was found to be shorter than the abovementioned corresponding Cl. The bond angle of complex **C1** for N(py)-Pd(1)-Cl(1) at 179.4(1) was found to be higher than that of N(pz)-Pd(1)-C13 at 175.6(1). This difference is attributed to the aforementioned *trans* effect and steric restrictions arising from the bidenticity of the ligand with the pyrazole being bulkier than the pyridine moiety. The corresponding bonds in complex **C2** (Figure 3.7) were found to be 177.5(4)° for N(py)-Pd(1)-Cl(1) and 174.6(4)° for N(pz)-Pd(1)-Cl(2). This deviation from the model value of 180° was comparable in both complexes, with the difference between N(py)-Pd-Cl and N(pz)-Pd-Cl greater than 2.5. This is attributed to the steric demands exerted by the

bulkier pyrazolyl moiety causing the N(pz)-Pd-Cl angle to be more acute than the N(py)-Pd-Cl. However, as expected, the corresponding bond angles for complex **C4** were higher. The N(pz)-Pd-Cl bond angle was found to be 174.5(4)° while that of N(py)-Pd-Cl was 178.2(4)°.

Table 3.3: Selected bond lengths and angles for palladium(II) complexes **C1**, **C2** and **C4**

Bond lengths (Å)		**Angles (°)**	
C1			
Pd(1)-N(1)	2.067(3)	N(1)-Pd(1)-Cl(1)	179.4(1)
Pd(1)-N(3)	2.130(3)	N(3)-Pd(1)-C13	175.6(1)
Pd(1)-C13	2.141(3)	N(1)-Pd(1)-N(3)	87.5(1)
Pd(1)-Cl(1)	2.272(2)	N(1)-Pd(1)-C13	96.4(1)
C2			
Pd(1)-N(1)	2.028(16)	N(2)-Pd(1)-Cl(1)	177.5(4)
Pd(1)-N(2)	2.022(15)	N(1)-Pd(1)-Cl(2)	174.5(4)
Pd(1)-Cl(1)	2.290(10)	N(2)-Pd(1)-N(1)	87.2(7)
Pd(1)-Cl(2)	2.296(11)	N(2)-Pd(1)-Cl(2)	96.2(6)
C4			
Pd(1)-N(1)	2.023(16)	N(2)-Pd(1)-Cl(1)	174.6(4)
Pd(1)-N(2)	2.036(16)	N(1)-Pd(1)-Cl(2)	178.2(4)
Pd(1)-Cl(1)	2.284(10)	N(1)-Pd(1)-N(2)	86.3(6)
Pd(1)-Cl(2)	2.296(11)	N(2)-Pd(1)-Cl(2)	92.6(5)

In terms of geometry, the bond angle of complex **C1** for N(py)-Pd(1)-Cl(1) at 179.4(1) was found to be higher than that of N(pz)-Pd(1)-C13 at 175.6(1). This difference is attributed to the steric restrictions arising from the bidenticity of the ligand. The corresponding bonds in complex **C2** (Figure 3.7) were found to be 177.5(4)° for N(py)-Pd(1)-Cl(1) and 174.6(4)° for N(pz)-Pd(1)-Cl(2). This deviation from the model value of 180° was comparable in both complexes, with the difference between N(py)-Pd-Cl and N(pz)-Pd-Cl greater than 2.5. This is

attributed to the steric demands exerted by the bulkier pyrazolyl moiety causing the N(pz)-Pd-Cl angle to be more acute than the N(py)-Pd-Cl. As expected, the corresponding bond angles for complex **C4** were higher (Figure 3.8).

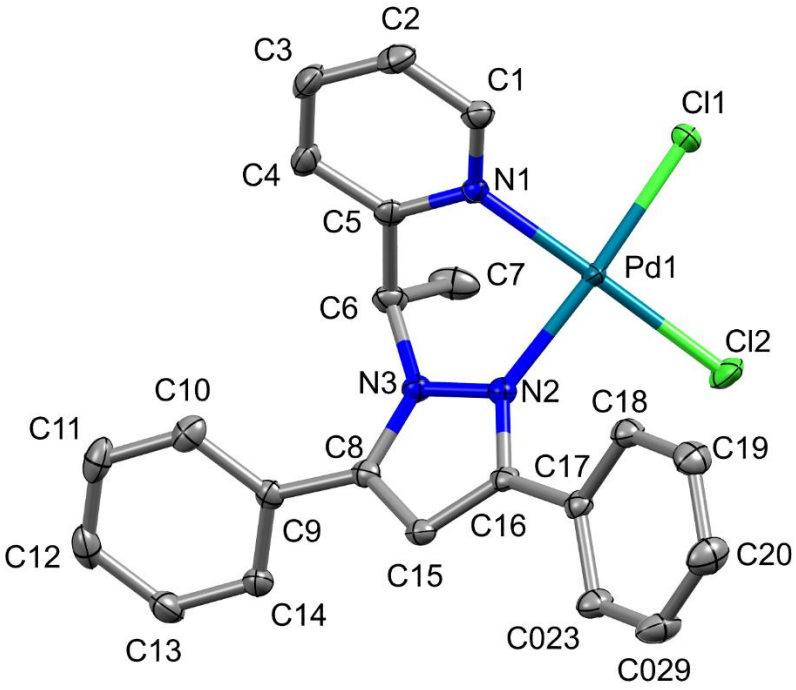


Figure 3.8: Molecular structure diagram of **C4** shown with 50% probability ellipsoids (H atoms omitted for clarity).

3.4. Conclusions

Synthesis of (pyrazolyl-ethyl)-pyridine ligands **L1** and **L2** was successful. These compounds were fully characterized by spectroscopic techniques and elemental analyses. Reactions of these compounds with the palladium salts [PdClMe(COD)] or [$PdCl_2$(COD)] gave four coordinate mononuclear complexes (**C1-C4**) in satisfactory to good yields. The solid state structural characterization of the complexes indicated that these complexes possesses **L1** and **L2** coordinated in an N(pz)^N(py) bidentate coordination mode. All the complexes exhibited

distorted square planar geometry with all the structures showing dependence on steric and electronic factors.

3.5. References

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Chapter 4

Methoxycarbonylation of olefins catalyzed by (pyrazolyl-ethyl)pyridine palladium(II) complexes.

4.1. Introduction

The palladium(II) based complexes, as indicated in the literature review in Chapter 2, are the best performing catalysts in the methoxycarbonylation of olefins. Various palladium complexes have been reported to produce high activity and selectivity for methoxycarbonylation of ethene[1], hexene[2] or styrene[3] under moderate reaction conditions. High regioselectivity of greater than 90% towards branched isomers could be obtained in moderate temperatures and low partial pressures of carbon monoxide.[4-5] Complexes such as $[PdCl_2(PPh_3)_2]$, in the presence of HCl as a promotor, have been used in the methoxycarbonylation of olefins.[6-7]

Ligands coordinated to the palladium metal centres of the methoxycarbonylation catalysts do not only stabilize the catalysts but control the selectivity and activity.[8] For instance, monodentate phosphines favour methoxycarbonylation of ethene while bidentate phosphines do not.[9] Furthermore, introducing different groups around the phosphines influences the steric and electronic effects.[10] This has been recently reported in studies done by Abarca *et al.*[11] and Aguirre *et al*.[12] where $[Pd(L)Cl(PPh_3)]Cl$ (L=2-diphenylphosphinoamino)pyrimidine, or 2-diphenylphosphinoaniline) and $[PdCl(Ph_2PNHpy\text{-}k2\ P,N)(PPh_3)]Cl$, respectively, were employed. The acid promoter employed also influences the catalytic activity and selectivity. For instance Rosales *et al.,* [13] employed PdL_2X_2 catalysts in the methoxycarbonylation of 1-hexene, cyclohexene and styrene using *p*-TsOH. In the presence of *p*-TsOH, the order of

individual activities was found to be 1-hexene>styrene>cyclohexene and was regioselective towards the linear product.

Furthermore, the type of acid used, whether Bronsted acid (*p*-TsOH) or Lewis acid $Al(OTf)_3$ influences both the reaction rate and selectivity with Lewis acids generally giving better catalytic effect.[13-15] This is attributed to their promotion of Pd-H formation and the role they play in the final methanolysis step.[16] In this Chapter, experimental results on the catalytic evaluation of the palladium(II) complexes synthesized in Chapter 3 (Figure 4.1) in the methoxycarbonylation of higher olefins are discussed. The effects of catalyst structure, identity of substrate, reaction conditions, acid promoter and phosphine derivative have been systematically studied and are herein reported.

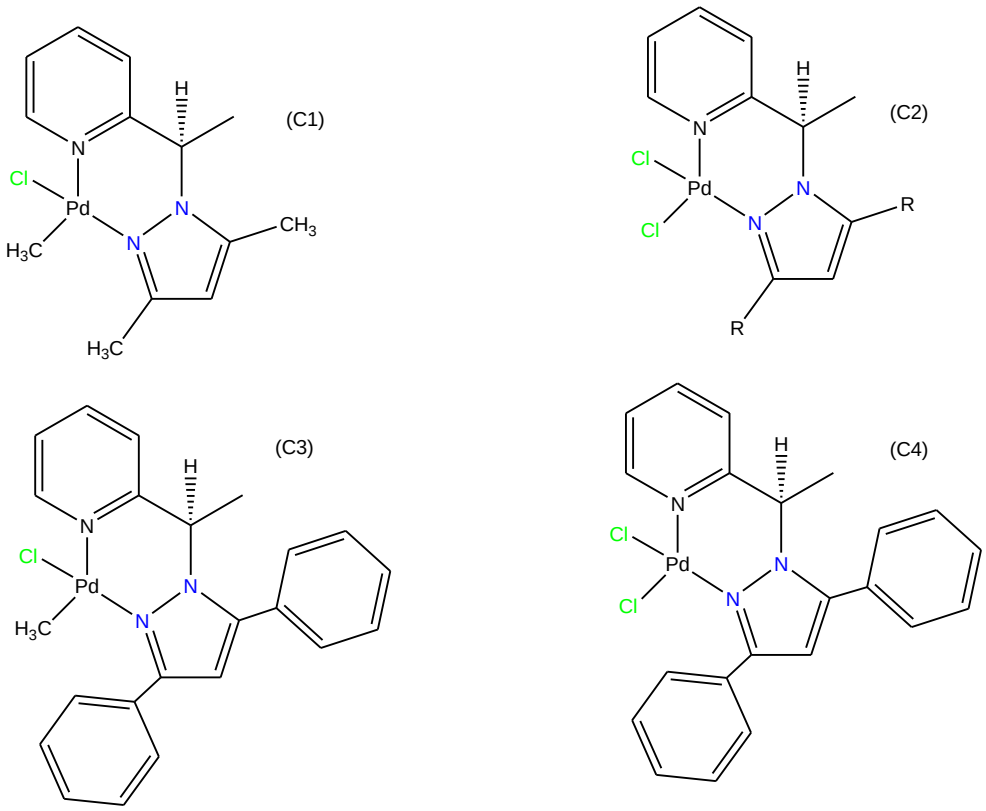


Figure 4.1: Palladium(II) complexes used for the methoxycarbonylation reactions.

4.2. Experimental

4.2.1. Materials and instrumentation

Catalytic methoxycarbonylation of olefins were performed in a stainless steel autoclave equipped with a temperature control unit and a sampling valve. Olefins, C_6–C_{10}, hydrochloric acid (HCl) (ACS reagent, 32%), para-toulenesulfonic acid (*p*-TsOH) (ACS reagent ≤ 99%), sulfuric acid (H_2SO_4) (≤ 99.99%), and PPh_3 (≤ 99%) were obtained from Sigma Aldrich and used as they were. Toluene and methanol were purchased from Merck chemicals and dried prior to use. Toulene was distilled and dried over P_2O_5 while methanol was distilled and stored in molecular sieves. The palladium(II) complexes used were prepared in chapter 3. GC-MS analyses were run under the following standard chromatography conditions: -25 m CPSil 19 capillary column, 1.2 mm film thickness, Helium carrier column gas 5 psi, injector temperature 250 ˚C, oven program 50 ˚C for 4 minutes rising to 200 ˚C at 20 ˚C/min and holding at 200 ˚C.

4.2.2. General procedure for methoxycarbonylation reactions

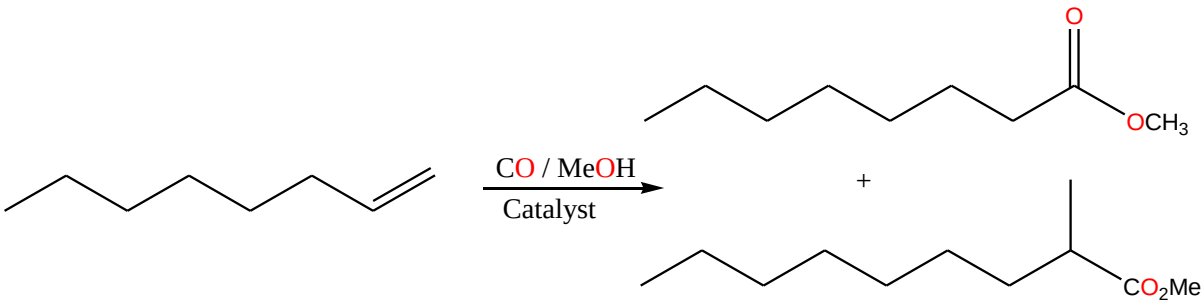
The catalytic methoxycarbonylation reactions were performed in a high pressure Parr reactor equipped with temperature control unit and a sample valve. In a typical experiment, **C2** (24.12 mg, 0.06 mmol), PPh_3 (33.42 mg, 0.13 mmol), HCl (0.02 mL, 0.64 mmol) and 1-octene (2.00 mL, 12.74 mmol) were dissolved in a mixture of methanol (50 mL) and toluene (50 mL). The reactor was evacuated and the catalytic solution was introduced to the reactor *via* a cannula. The reactor was purged three times with CO, and then set at the required pressure, heated to the desired temperature and the reaction stirred at 500 rpm. At the end of the reaction time, the reaction was cooled, excess CO was vented off and the samples drawn for GC analysis to determine the percentage conversion of the alkene substrate to esters. A typical sample was prepared by passing it through a microfilter into a GC vial. GC-MS analyses were run under

the following standard chromatography conditions: -25 m CPSil 19 capillary column, 1.2 mm film thickness, Helium carrier column gas 5 psi, injector temperature 250 ˚C, oven program 50 ˚C for 4 minutes rising to 200 ˚C at 20 ˚C/ min and holding at 200 ˚C. The identities of the ester products were assigned using standard authentic samples and mass spectral data.

4.3. Results and discussion

4.3.1. Catalytic screening of palladium(II) complexes in methoxycarbonylation reactions

The preliminary screening of all palladium complexes for methoxycarbonylation of olefins were carried out using 1-octene as substrate (Scheme 4.1). The catalytic reactions were performed at 90 °C with 60 bar of CO pressure, and a [Pd]:PPh_3:HCl:1-octene ratio of 1:2:10:200 in methanol-toluene solvent mixture. Under these conditions, catalytic activity and regioselectivity towards linear products of up to 91% and 59% respectively, were obtained.



Scheme 4.1: An illustration of major products obtained in the methoxycarbonylation of 1-octene

The products from the methoxycarbonylation were characterized by gas chromatography and GC–MS. The assignment of the branched and linear esters was done using standard authentic samples. Figures 4.2 and 4.3 represent a typical GC and GC–MS trace for 1-octene reaction,

respectively. From Figure 4.2, a base peak at m/z = 158 was observed corresponding to both methyl nonanoate (linear product) and methyl-2-methyloctanoate (branched product).

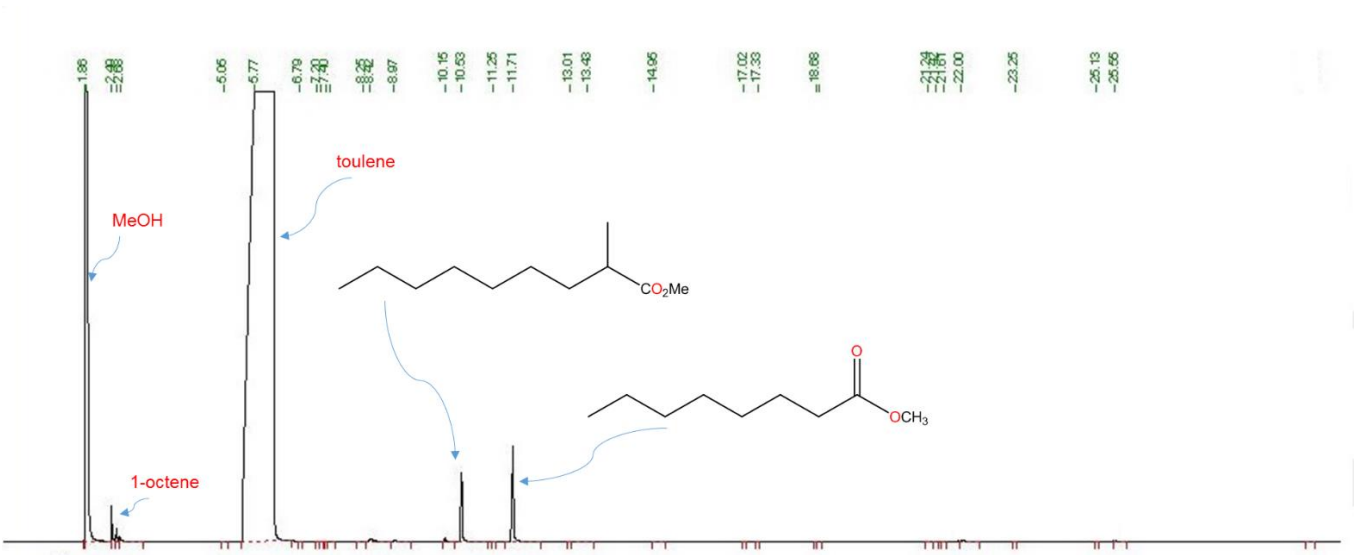
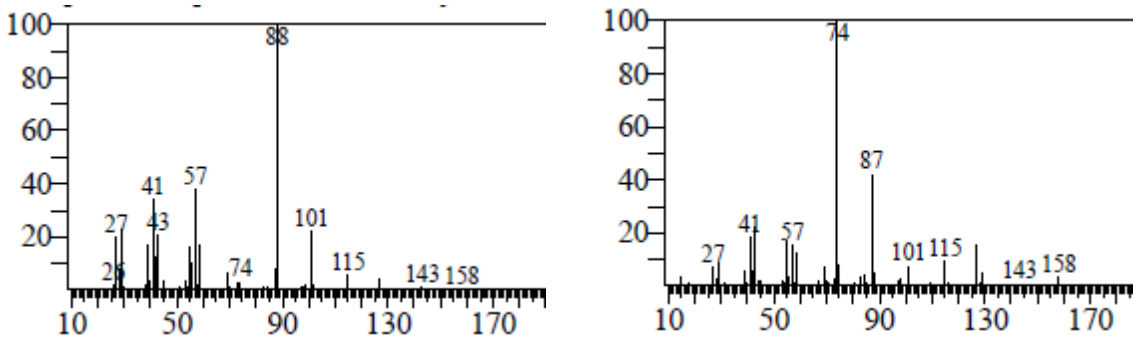


Figure 4.2: GC spectra of methoxycarbonylation product obtained from 1-octene using complex **C2** (0.06 mmol), solvent: toluene (50 mL) and methanol (50 mL); Pd/1-octene ratio, 200:1, Pd/ HCl ratio; 1:10; Pressure (CO) = 60 bar; temperature; 90 °C; time 24 h.



B L

Figure 4.3: GC-MS spectrum for the branched (B) (methyl-2-methyloctanoate) and linear products (L) (methyl nonanoate). m/z- 115; showing different fragmentation patterns.

4.3.2. Effect of palladium(II) catalyst structure on methoxycarbonylation of 1-octene

All the complexes (**C1-C4**) showed good chemoselectivity towards the formation of ester products. The effect of ligand substituent in the pyrazole ring was observed, to an extent, to influence the catalytic activity. For example, complexes **C1** and **C2** bearing methyl substituent on the pyrazolyl ring were slightly more active (Table 4.1), than the corresponding complexes **C3** and **C4**, containing the phenyl substituent. This is attributed to the electron donating ability of the phenyl group through inductive effects and hyperconjugation and thus making the metal center more electron rich than that in **C1** and **C2**. This accounts for better catalytic activity with regards to **C1** and **C2** because of their better electron deficient metal centres.[12-17]

Table 4.1: Preliminary methoxycarbonylation of 1-octene (24 h) using catalysts **C1-C4**[a]

Entry	**Catalyst**	**Conv. (%)**	**l/b (%)**[b]	**TOF (h^{-1})**
1	**C1**	86	58/42	6.9
2	**C2**	91	59/41	7.3
3	**C3**	82	51/49	5.8
4	**C4**	84	55/45	6.6

[a]T=90 °C; solvent= 50 ml toluene and 50 ml methanol; 1-octene/Pd = 1/200, Pd/Acid = 1:10; Pd/PPh_3= 1/2. Pressure (CO) = 60 bar; time= 24 h; molar ratio between linear and branched product determined by GC-FID analysis[b]

Furthermore, steric demands exerted by the alkyl groups on the pyrazolyl moiety, which are more prominent in the presence of the phenyl group than CH_3 resulting into an ease in olefin coordination for complexes **C1** and **C2** than in complexes **C3** and **C4**. Another factor that affected the catalytic activity was the Pd-Cl/Me bond on the complex structure.

Complex **C2** and **C4** containing Pd-Cl bond showed higher catalytic activity (Table 4.1, entry 2 and 4) compared to **C1** and **C3** bearing Pd-Me bonds (Table 4.1, entry 1 and 3). This could

be attributed to the ease of CO coordination and insertion into Pd-Cl bond since Cl is a good leaving group, consistent with the previously reported work by Kumlah and Darkwa.[18]

The results indicated that the complex structure did not significantly affect the regioselectivity of the esters. From Table 4.1, it is evident that, all complexes gave lower percentages of the branched esters (41%-49%), showing marginal regioselectivity towards linear esters. Complex **C2,** because of its better catalytic activity**,** was chosen for further catalytic investigations on changing reaction conditions.

4.3.3. Effect of phosphine derivatives and acid promoters on methoxycarbonylation reactions

An acid promoter is an important parameter to examine in the methoxycarbonylation reactions, since it plays a crucial role in the stabilization of the active palladium(II) species by limiting decomposition of palladium(II) to Pd(0).[13-20] Methoxycarbonylation reactions using **C2** were thus performed using different acid promoters to investigate their effect on catalytic activity (Table 4.2, entries 1-6). When HCl was used as an acid promoter (Table 4.1-4.4), high catalytic activity was observed. On the other hand, employing sulfuric acid as the acid promoter (Table 4.2, entry 2) lead to lower catalytic activity (70%).This signifies a particular function of the anion and not the quantity of free acid on the product yield. The catalytic activity of these acid promoters can be related to the proposed hydride mechanism where protic promoters serve as hydride source for the formation of a catalytically active Pd-H and initiate thus the reaction.[21] As a result, the best promoters are strong acids with weak coordinating ability.[22-25] H_2SO_4 is a strong acid and thus would lead to rapid formation of the palladium hydride species.

The identity of the acid promoter also influenced product regioselectivity. In the presence of HCl, high regioselectivity towards the linear ester was obtained while high regioselectivity towards the branched ester was obtained with H_2SO_4 (Table 4.2). No catalytic activity was observed with the use of strong organic acids such *p*-TsOH and MSA which could be attributed to their weak coordinating ability and thus unable to stabilize active palladium species during alcoholysis (Table 4.2, entries 3-4). This possibly led to the formation of the by-products during methanolysis due to rapid alkylation leading to unstable palladium species and subsequent metal plating; an observation that has been reported in similar previous studies.[22-25]

Table 4.2: The effect of varying an acid promotor in the methoxycarbonylation of 1-octene[a]

Entry	**Acid/Phosphine derivative**	**Conv. (%)**	**l/b (%)[b]**
1	HCl	91	59/41
2	H_2SO_4	70	51/49
3	*p*-TsOH	-	-
4	[d]MSA	-	-
5	$EtAlCl_2$	72	19/81
6	$AlMe_3$	80	56/44
7	PPh_3	91	59/41
8	[e]DPPe	16	33/67
9	[f]$P(Cy)_3$	37	36/64
10	ethyldiphenylphosphine	79	40/60
11	$P(OMe)_3$	56	18/82

[a]T=90 °C; solvent= 50 ml toluene and 50 ml methanol; 1-octene/Pd = 1/200, Pd/Acid = 1:10; Pd/PR_3 = 1:2; Pressure (CO)= 60 bar; time= 24 h; molar ratio between linear and branched product determined by GC-FID analysis[b]. [d]Methanesulfonic acid, [e]1,2-bis(diphenylphosphino)ethane, [f]tricyclohexylphosphine.

The efficacy of Lewis acids; $EtAlCl_2$ and $AlMe_3$ was also investigated (Table 4.2, entries 5-6). The catalytic activity of **C2** was significantly enhanced by increased Lewis acidity of the respective promoter. For example, the most acidic $AlMe_3$ was the most active with 91% conversion, while the least basic between these two acids, $EtAlCl_2$, gave the least activity of 72%. The difference in regioselectivity in the presence of Lewis acids is more significant than the selectivity obtained with Brønsted-acids. Lewis Acids showed marked differences in regioselectivity. $EtAlCl_2$ (Table 4.2, entry 5) was regioselective towards branched esters (81%) while $AlMe_3$ (Table 4.2, entry 6) gave 44%. This difference could be largely attributed to $EtAlCl_2$ being more active and as a result it will be more selective towards the branched ester. The selectivity towards the branched ester may be related to better catalytic activity which would lead to more isomers being formed, in this case, there is more 2,1-insertion of the substrate leading to more branched esters.

Complex **C2** was then used in the methoxycarbonylation reactions involving different phosphine derivatives (Table 4.2, entries 7-11). Reactions without PPh_3 showed complete decomposition of the palladium complexes to palladium black, with no catalytic activity. However, addition of PPh_3 derivative to the palladium complexes resulted in higher catalytic activities (Table 4.2, entry 7). From previous reports, [26-27] it is believed that the PPh_3 group improves the stability of the active species by limiting decomposition to Pd(0) [11]. Indeed, extensive decomposition of the complexes to Pd(0) black was observed in reactions performed without PPh_3. However, when reactions were carried out in the presence of added PPh_3, all complexes showed good catalytic activity and no formation of palladium black.

A comparison of different chelating and non-chelating phosphines under the same reaction conditions shows that non-chelating phosphines gave improved activities compared to chelating phosphines (Table 4.2, entries 7-11). This suggests that there is inability of the non-chelating phosphine such as $P(Cy)_3$ (Table 4.2, entry 9) to stabilize the palladium catalyst resulting to decomposition to palladium black. This was in agreement with the obtained palladium black sediments in the reaction mixture. As a result, a decrease in catalytic activity from 91% to 37% (Table 4.2, entry 7 and 8).

There was also 75% decrease in catalytic activity resulting from changing the non-chelating phosphine (PPh3) to DPPe, a chelating phosphine (Table 4.2, entries 7 and 8). This could be attributed to the competition for the vacant coordination site on the palladium metal between the chelating phosphine and the olefin substrate.[28] High regioselectivity towards branched esters was also obtained with the use of $P(OMe)_3$ than DPPe (82% and 67%, respectively). This could be associated with the steric hindrance which is high on the chelating DPPe ligand than in $P(OMe)_3$ resulting into more 1,2-insertions thus producing more linear esters; while there would be more 2,1-insertion with the use of $P(OMe)_3$ giving more branched products.[28] In related experiments,[29-30] regioselectivities of 45–86% and 21-34% towards branched esters in the absence and presence of phosphine were reported.

4.3.4. Effect of varying reaction conditions in methoxycarbonylation reactions

The effect of varying pressure, temperature, time and was also investigated. Carbon monoxide pressure substantially influenced the catalytic activity since at higher pressures, the catalytic activity increased, while lower pressures resulted to lower catalytic activity (Table 4.3, entries

1, 4 and 5). For example, an increase in CO pressure from 40 to 60 bar resulted to a substantial increase in percentage conversion from 48% to 93%. This result can be attributed to the faster insertion of CO at higher pressures which would result into higher catalyst induced conversion of substrate to the products. Considering the CO pressure/reaction time relation, it is possible to conclude that over 60 bar the conversion increases significantly as time goes on, but after 24 h the methoxycarbonylation of 1-octene shows >90% conversion (Table 4.3, entries 1, 7-9). However, there was no appreciable change in product regioselectivity with change in CO pressure.

We did not observe any effect on the catalytic activity of **C2** with change in reaction temperature as was evident in comparable conversions of 89% and 91% at 60 °C and 90 °C, respectively (Table 4.3, entries 2 and 6). No significant decomposition and changes in regioselectivity was observed as a result of this change in temperature. This indicates good stability of the catalysts since comparable catalytic conversions were observed at these temperatures. These observations are comparable with those found by Tshabalala *et al*.[30] where conversions of 85% and 86% at 60 ℃ and 90 ℃ respectively, were obtained.

Table 4.3: Effect of varying pressure, temperature, time and concentration on the methoxycarbonylation of 1-octene using **C2**[a]

Entry	**P_{CO} (bar)**	**T (°C)**	**Time (h)**	**[Pd]: [substrate]**	**Conversion (%)**	**l/b (%)[b]**	**TOF (h^{-1})**
1	60	90	24	1/100	93	60/40	6.9
2	60	90	24	1/200	91	58/42	6.6
3	60	90	24	1/400	55	82/18	7.7
4	40	90	24	1/200	48	55/45	4.1
5	50	90	24	1/200	77	57/43	5.1
6	60	60	24	1/200	89	59/41	6.1
7	60	90	12	1/200	46	74/16	6.7
8	60	90	32	1/200	94	55/45	7.2
9	60	90	36	1/200	99	51/49	7.8

[a]T=90 °C; solvent= 50 ml toluene and 50 ml methanol; 1-octene/Pd = 1/200, Pd/Acid = 1:10; Pd/PPh_3 = 1:2; Pressure (CO)= 60 bar; time= 24 h; molar ratio between linear and branched product determined by GC-FID analysis[b].

The effect of changing catalyst concentration at fixed substrate concentration was also investigated (Table 4.3, entries 1-3). Increasing the substrate/catalyst ratio from 200 to 100, gave higher catalytic activity (93%), while when the substrate/catalyst ratio was lowered to 400, lower catalytic activity (55%) was obtained (Table 4.3, entries 1-3). These results indicate that the conversion of the reaction increases when the concentration of substrate/catalyst increases, probably because of an increased production of Pd-H active species. Similar observations to these in corresponding studies by Zolezzi *et al.*[32] and Vavasori *et al.*[33] have

been reported. Increasing catalyst concentration from 100 to 400 also improved regioselectivity towards the branched products from 18% to 40%. This observation has been reported in previous studies, and is attributed to the high catalyst loading resulting to higher conversion of substrates to products and thus isomerization reactions.[34]

Investigations on the effect of varying the reaction time on catalytic activity of **C2** found that the catalytic activity improves as reaction time increases (Table 4.3, entries 6-9). After reaction time of 12 h, catalytic conversion of 46% was achieved, while a percentage conversion of 99 was obtained after 36 h of reaction time. TOF values ranged from 6.1 h^{-1} to 7.8 h^{-1} after 36 h of reaction time. The catalyst stability under the studied reaction conditions thus did not show significant deterioration over change in time. Changing reaction time also influenced the regioselectivity as increasing reaction time from 12 h to 36 h gave high regioselectivity towards the branched ester from 16% to 49% (Table 4.3, entries 7-9).

Changes in solvent system used influenced both the catalytic activity and regioselectivity. The toluene/MeOH and the chlorobenzene/methanol solvent systems were found to be the most effective with the achieved percentage conversions of 91% and 87%, respectively (Table 4.4, entry 1 and 3). This is attributed to the high polarity of these solvents compared to non-polar cyclohexane (19%), indicating high affinity of the catalysts with the polar solvents and therefore resulting to higher catalytic activities. However, the use of more polar solvents, dimethylsulfoxide significantly decreased activity (67%; Table 4.4, entry 4). A change in solvent system did not significantly influence the regioselectivity to either branch or linear esters.

Table 4.4: The effect of varying a solvent on percentage conversion and regioselectivity on methoxycarbonylation of 1-octene using catalyst **C2**[a]

Entry	**Solvent system**	**Conv. (%)**	**l/b (%)**[b]
1	toluene/ MeOH	91%	59/41
2	cyclohexane/methanol	19	55/45
3	chlorobenzene/methanol	87	54/36
4	dimethyl sulfoxide	67	60/40

[a]T=90°C; 1-octene/Pd=1/200, Pd/Acid=1:10; Pd/PPh_3=1:2; Pressure (CO)=60 bar, time=24 h; molar ratio between linear and branched product determined by GC-FID analysis[b].

4.3.5. Effect of changing olefinic substrate on methoxycarbonylation using catalyst C2

Further investigations on the effect of olefins such as; styrene, 1-octene, 1-nonene and 1-decene on the methoxycarbonylation reactions using complex **C2** are presented in Figure 4.4. The results indicated that the catalytic activity was significantly influenced by the nature of the substrate. When 1-hexene was used, higher catalytic activity of up to 93% was achieved. This was much higher than the conversion of 78% recorded for 1-decene (Figure 4.4). It is therefore apparent that despite generally good catalytic activity with all olefins studied, increasing the chain length of the substrate, that is, from 1-hexene to 1-decene resulted in lower catalytic activities. This could be attributed to the increased steric hindrance.[35] The identity of the substrate, to an extent influenced the regioselectivity of the products as 41% of the branched ester was obtained for 1-hexene while 48% branched esters were obtained using 1-decene as the substrate. This could be attributed to the high probability of higher alkenes to form high number of possible isomers.[36]

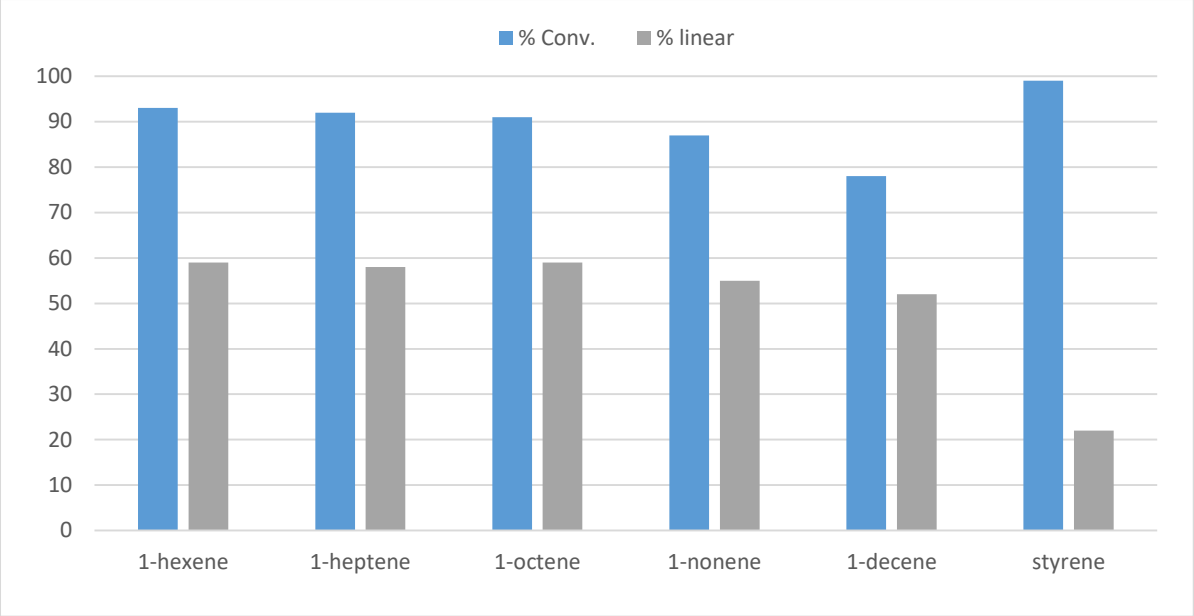


Figure 4.4: Graphical presentation on the effect of olefin substrate on percentage conversion and regio-selectivity towards linear esters using catalyst **C2.**

4.4. Conclusion

In conclusion, we have evaluated the methoxycarbonylation of higher linear 1-alkenes employing neutral palladium(II) complexes. These synthesized complexes showed good catalytic activities. Methoxycarbonylation reactions gave linear esters as major products; whilst with styrene as the olefin substrate there was high selectivity was to the branched ester product. The electronic and steric factors affected the catalytic behaviour of the catalysts. Complexes bearing electron donating methyl groups were found to be more catalytically active than those bearing phenyl groups. Employing a strongly coordinating HCl as an acid promoter gave higher catalytic activity compared to the weakly-coordinating acids *p*-TsOH and H_2SO_4. The use of non-chelating phosphines rather than chelating phosphines resulted to improved catalytic activities. High reaction pressures, temperatures and catalyst concentration resulted into higher catalytic activities. Reactivity and selectivity of the catalysts were also influenced

by the chain length of the substrates. Increasing the olefin chain length resulted in lower catalytic activities and high regioselectivity towards the branched esters.

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Chapter 5

Overall conclusions and potential further developments

5.1. Overall conclusions

In summary, this work, focused on the design, synthesis and employment of 2-(pyrazolyl-ethyl)-pyridine palladium(II) complexes as potential methoxycarbonylation catalysts. Characterization of these synthesized included the use of ^{1}H and ^{13}C NMR, elemental analysis, and single crystal X-ray crystallography. The solid state structures of **C1, C2** and **C4** showed the bidentate coordination mode of 2-(pyrazolyl-ethyl)-pyridine to the palladium(II) central atom. Palladium complexes possessing less bulky electron donating groups were more active and stable compared to those complexes bearing bulky electron donating groups. The presence, and increase of the stabilizer, PPh_3, resulted in higher catalytic activities and higher regioselectivity towards the linear esters. No catalytic activity was observed in the absence of PPh_3. The use of less harsh, weakly coordinating anions, gave lower (H_2SO_4) or no (*p*-TsOH) catalytic activity. Amongst the acid promoters employed, the use of HCl which is a strongly coordinating anion resulted in higher percentage conversions of olefins to esters. Reaction parameters such as pressure, temperature, catalyst concentration and time were also investigated. High pressure resulted in high catalytic activity. Changes in temperature did not influence big changes in activity while an increase in catalysts concentration, chain length and reaction time resulted in high percentage conversion and better regioselectivity towards the branched ester. Overall, the catalytic performance of synthesized palladium(II) complexes in methoxycarbonylation of olefins was largely influenced by the catalytic structure, acidic medium, reaction conditions and the olefinic substrate used. All complexes exhibited complete selectivity to ester formation.

5.2. Potential further developments

The catalytic investigations reported here indicated that the 2-(pyrazolyl-ethyl)-pyridine complexes are highly active in the methoxycarbonylation of olefins. These catalysts are more regioselective towards the linear esters. However, the branched esters are of more industrial importance since they are applied in the manufacturing of non-steroidal anti-inflammatory drugs such as aspirin, ketoprofen, ibuprofen and naproxen. These could be obtained through the use of palladium complexes containing a less sterically hindered metal center (non-bulky ligands) or employing catalysts based on bidentate phosphines. Alternatively, methoxycarbonylation of internal olefins as reported by previous studies to result to branched esters as products. From the work reported here, further manipulations could be done to investigate the effect on catalytic activity on changing the catalytic backbone from N^N to N^P/N^O (Figure 5.1).

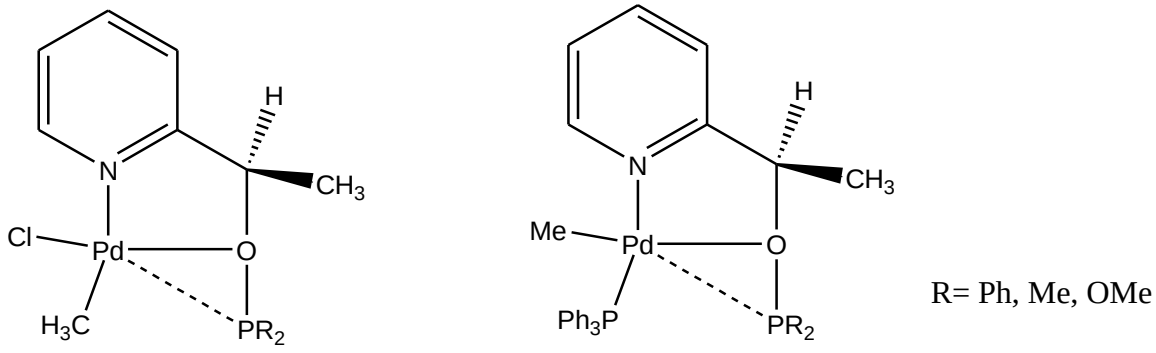

Figure 5.1: palladium(II) complexes bearing N^P/N^O ligands proposed for the methoxycarbonylation of olefins

Comparsion of the catalytic performance of these two catalytic systems in the methoxycarbonylation of olefins, including internal olefins would be necessary. The effects of

changing the acidic medium, for instance employing different Lewis acids such as methane sulfonic acid (MSA) could also be explored. In addition, efforts to separate the enantiomers and compare the catalytic activities synthesized from the chiral ligands could give more insight on the characteristics of these compounds. A major challenge with homogeneous catalysts is catalysts recovery and obtaining pure products due to difficulty in separation of products from the reaction mixture. As a result, heterogenizing the catalysts would allow catalysts recycling since the products and catalyst would be in two immiscible, separate phases. This would also possibly allow for the enhancement of TOF and possibly catalytic conversion as well as selective regioselectivity; considering the higher surface areas of supports like zeolites, carbon nanotubes and electrospun fibres.