

**STUDIES IN CARBONYLATION OF VINYL  
AROMATICS AND ARYL ALCOHOLS USING  
TRANSITION METAL COMPLEX  
CATALYSTS**

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BY

**A. SEAYAD**

AT  
HOMOGENEOUS CATALYSIS DIVISION  
NATIONAL CHEMICAL LABORATORY  
PUNE 411 008  
INDIA

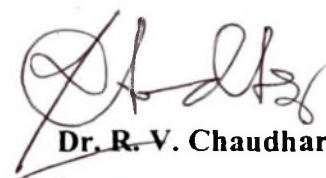
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January, 2000

Pune



**Dr. R. V. Chaudhari**

(Supervisor/Research Guide)



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## Summary and Conclusions

The impact of homogeneous catalysis on the development of new synthetic routes and industrial processes has grown considerably in recent years. A deeper understanding of the structure and reactivity of organometallic complexes<sup>1</sup> has facilitated the growth of this field. The high selectivity, one of the unbeatable advantages of organometallic catalysis, achieved by the fine tuning of electronic and steric factors at the metal centre has helped in minimization of waste production leading to cleaner technologies. Some of the industrially relevant homogeneous catalytic processes are: hydroformylation of olefins to aldehydes in oxo-alcohol synthesis, carbonylation of methanol to acetic acid, carbonylation of propyne to methylmethacrylate, carbonylation of *p*-isobutylphenylethanol to Ibuprofen, copolymerization of ethylene and carbon monoxide to polyketones, L-Dopa by asymmetric hydrogenation, hydrogenation of aromatics to cycloparafins, hydrocyanation of butadiene to adiponitrile, oxidation of *p*-xylene to terephthalic acid, etc.<sup>1,2</sup>

It was the discovery of the Oxo-synthesis by Otto Roelen in 1938, which helped to visualize the potential of organometallic chemistry in industrial processes<sup>1</sup>. This was quickly followed by the carbonylation chemistry developed by Reppe between 1939 and 1945, in which the reactions of carbon monoxide with organic compounds such as acetylenes, olefins, etc., were investigated under the catalytic influence of metal carbonyls such as nickel carbonyls ( $\text{Ni}(\text{CO})_4$ ) to produce the corresponding unsaturated and saturated carboxylic acids respectively.<sup>2,3</sup> Later on, the discovery of stable organophosphine complexes of rhodium and palladium led to milder reaction conditions and to avoid the toxic  $\text{Ni}(\text{CO})_4$ . In recent years, carbonylation processes are also gaining importance for the synthesis of fine chemicals, pharmaceuticals and pharmaceutical intermediates.<sup>4</sup> An important example of application of carbonylation by metal complex catalysts in pharmaceuticals is the synthesis of 2-arylpropionic acids, a class of non-steroidal antiinflammatory agents, like Ibuprofen and Naproxen. A process has been commercialized by Hoechst Celanese Corporation in 1992 at Texas for the production of Ibuprofen by the carbonylation of *p*-isobutylphenylethanol. This is an example of successful commercialization of an environmentally benign catalytic process as an alternative to the classical stoichiometric synthesis.<sup>5</sup> This process uses  $\text{PdCl}_2(\text{PPh}_3)_2$  as the

catalyst precursor in a biphasic medium consisting of methylethyl ketone as the organic phase and 10%  $\text{HCl}_{(\text{aq})}$  as the promoter.<sup>6</sup> The desired high selectivity (>98 %) for Ibuprofen was obtained only at very high pressures (16-35 MPa) of CO. At lower pressures (6.8 MPa), the selectivity to Ibuprofen was reported to be significantly lower (67%). The turnover frequency (TOF) was found to be poor (50–70  $\text{h}^{-1}$ ) even at high pressures (35 MPa). Another alternative route for the synthesis of 2-arylpropionic acids is by the carbonylation of corresponding vinyl aromatic compounds. Because of the practical importance of these reactions, further scope on improvement of the catalyst system for the carbonylation of vinyl aromatics and aryl ethanols is obvious.

Considering the importance of carbonylation of olefins and alcohols in the synthesis of 2-arylpropionic acids, the present study was undertaken with the objective of developing catalyst systems that provide improved catalytic activity and high selectivity towards the branched acid/ester product. It was also the aim of this work to elucidate the mechanism of these reactions and to study their intrinsic kinetics at a molecular level. With these objectives, the following specific problems were chosen for the present work.

1. Hydroesterification of styrene using *in situ* formed  $\text{Pd}(\text{OTs})_2(\text{PPh}_3)_2$  complex catalyst: activity, selectivity and mechanistic studies
2. Kinetics of hydroesterification of styrene using  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{TsOH}$  as the catalyst
3. Carbonylation of 1-aryl ethanols and vinyl aromatics using palladium complex catalyst systems
4. Kinetics of carbonylation of 1-(4-isobutylphenyl)ethanol using  $\text{PdCl}_2(\text{PPh}_3)_2/\text{TsOH}/\text{LiCl}$  as a catalyst

Chapter 1 presents a detailed review of literature on the carbonylation of olefins and alcohols particularly that of vinyl aromatics and aryl alcohols, which produces 2-aryl propionic acids, a class of nonsteroidal anti-inflammatory drugs. Palladium complexes are generally employed as catalysts for these reactions due to their high activity and selectivity. A majority of studies appeared in the literature on this subject mainly focused on improving the catalytic performance and product selectivity or exploring alternative new catalyst systems. These processes, generally required high pressure conditions to achieve the desired product selectivity. As evidenced from the literature, the main



challenge has been in the development of highly active and selective catalyst systems, which work under mild reaction conditions. In order to develop catalyst systems possessing the desired advantages, a knowledge of the kinetics of the reaction as well as the mechanism involved are most essential. However, only limited publications are available, which address these important aspects. A review of the subject and scope of the thesis have been outlined in Chapter 1.

Chapter 2 presents a detailed study on the catalytic activity and selectivity of hydroesterification of styrene using *in situ* formed  $\text{Pd}(\text{OTs})_2(\text{PPh}_3)_2$  from  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{TsOH}$  as the catalyst precursor. This catalyst system provides higher activity compared to the previously reported catalytic systems such as  $\text{PdCl}_2(\text{PPh}_3)_2/\text{HCl}$ ,<sup>7</sup>  $\text{Pd}(\text{dppp})\text{Cl}_2/\text{HCl}$ <sup>8</sup> [10], etc. The reactions were carried out in a high pressure stirred autoclave and in each reaction the absorption of CO was measured as a function of time. The effect of various ligands, promoters, solvents and alcohols on the catalytic activity as well as the selectivity has been studied and the results discussed in this chapter. Regioselectivity to the branched product, methyl-2-phenyl propionate, was found to increase with decrease in basicity of the phosphorous ligands as well as the steric bulk around the palladium center and polarity of the medium. A beneficial effect of hydrogen, TsOH and water on catalytic activity was observed. The promoting effect of TsOH, water and hydrogen was consistent with a hydride mechanism, which was confirmed by isolation of a palladium hydridocarbonyl species under reaction conditions. No palladium carbomethoxy complexes were detected under reaction conditions. The hydride mechanism was further confirmed by isolation of cationic palladium acyl complexes from the reaction mixture and formation of neutral palladium acyl complex  $\text{PdCl}(\text{COCH}_2\text{CH}_2\text{Ph})(\text{PPh}_3)_2$  under reaction conditions. <sup>31</sup>P NMR experiments carried out to investigate the nature of species formed in solution in the presence of CO under reaction conditions also confirmed the formation of Pd–H as well as Pd–alkyl species. Based on these results a catalytic cycle that proceeds through a palladium(II) hydrido carbonyl complex as an active catalytic species (hydride mechanism) is proposed.

Chapter 3 presents a detailed kinetic analysis of the hydroesterification of styrene using Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>/TsOH as the catalyst precursor in methanol as a solvent. All reactions were carried out in a 50 cm<sup>3</sup> autoclave. Absorption of CO as a function of time was recorded and intermediate liquid samples were taken at regular intervals of time and analyzed to get the conversion and product distribution from which the initial rates were calculated. The initial rate data were obtained to study the effect of concentration of styrene, Pd(OAc)<sub>2</sub>, water and partial pressure of CO in a temperature range of 338–358 K. The rate of carbonylation varied linearly with the catalyst and was zero order with respect to styrene concentration in a range of 0.567 to 3.84 kmol/m<sup>3</sup>. An unusual trend of increase in catalytic activity was observed beyond a styrene concentration of 3.84 kmol/m<sup>3</sup>. The rate also increased with increase in the partial pressure of CO initially and was independent beyond 3.4 MPa. Water showed a promoting effect up to a concentration of 9.244x10<sup>-2</sup> kmol/m<sup>3</sup> above which the rate of reaction was found to decrease. Different empirical rate models were considered and the kinetic parameters evaluated. The following rate equation was found to be the best to represent the kinetics of hydroesterification of styrene.

$$R_A = \frac{k_1 C_A (1 + K_B C_B)^2 C_C C_D}{(1 + K_A C_A)(1 + K_D C_D)^2}$$

where R<sub>A</sub> is the initial rate (kmol/m<sup>3</sup>/s), C<sub>A</sub> is the concentration of CO (kmol/m<sup>3</sup>), C<sub>B</sub> is the concentration of styrene (kmol/m<sup>3</sup>), C<sub>C</sub> is the concentration of the catalyst (kmol/m<sup>3</sup>), C<sub>D</sub> is the concentration of water (kmol/m<sup>3</sup>), k<sub>1</sub> (m<sup>6</sup>/kmol<sup>2</sup>/s) is the reaction rate constant and K<sub>A</sub>, K<sub>B</sub>, K<sub>C</sub> are constants (m<sup>3</sup>/kmol). The kinetic parameters were evaluated using an optimization routine and the activation energy was found to be 54.17 kJ/mol.

Chapter 4 presents a detailed study on the carbonylation of 1-ary ethanols and vinyl aromatics using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/TsOH/LiCl as a catalyst system in methyl ethyl ketone as the solvent under homogeneous conditions. This catalyst system provides significantly higher reaction rates (TOF up to 2200 h<sup>-1</sup>) and 2-arylpropionic acid selectivity (>95%) at relatively mild reaction conditions such as 388K and 5.4 MPa CO partial pressure. Vinyl aromatic compounds were found to be more active and selective towards 2-arylpropionic acids compared to their alcohol counter parts. The effect of various parameters such as

catalyst precursors, promoters, solvents, and concentration of water on catalytic activity as well as product distribution for the carbonylation of 1-(4-isobutylphenyl)ethanol (IBPE) was studied in detail. Both concentration of promoters and water was found to have a significant positive effect on catalytic activity and regioselectivity to Ibuprofen. However, at higher amounts of water (>8%), catalytic activity as well as selectivity decreased drastically due to the change of homogeneous nature of the system to biphasic. The reaction was found to proceed through the formation of isobutylstyrene (IBS) and 1-(4-isobutylphenyl)ethyl chloride (IBPCI) as intermediates and IBPCI was confirmed as the active substrate, which undergoes carbonylation. A few  $^{31}\text{P}$  NMR experiments were carried out to investigate the nature of species formed in solution under the reaction conditions. From these studies, it was observed that the Pd(0) species formed after the reduction of the Pd(II) precursor exists mostly as anionic species ligated with  $\text{Cl}^-$  ions under the reaction conditions. The reactivity of these anionic Pd(0) species were verified by the oxidative addition of PhI to form the corresponding alkyl complex as evident from the  $^{31}\text{P}$  NMR experiments. Hence, a catalytic cycle initiated by the oxidative addition of IBPCI to anionic Pd(0) species such as  $\text{Pd}(\text{PPh}_3)_2\text{Cl}^-$  or  $\text{Pd}(\text{CO})(\text{PPh}_3)_2\text{Cl}^-$ , is proposed.

Chapter 5 presents a detailed kinetic analysis of the carbonylation of 1-(4-isobutylphenyl)ethanol using  $\text{PdCl}_2(\text{PPh}_3)_2/\text{PPh}_3/\text{TsOH}/\text{LiCl}$  as the catalyst system for a temperature range of 388–398 K. The carbonylation rate was found to be 0.43, 1, 0.8, 0.7, and 2<sup>nd</sup> order with respect to catalyst, water, CO pressure, concentration of IBPE and promoters (TsOH/LiCl) respectively. The rate data was found to be in kinetic regime and the gas-liquid mass transfer resistance was negligible. The unusual fractional order with respect to catalyst, in spite of kinetic control indicates that the entire precursor is not present in the active form. A reaction pathway which consists of three different steps including the formation of active palladium(0) species, formation of 1-(4-isobutylphenyl)ethyl chloride and carbonylation catalytic cycle has been proposed. A semi-batch reactor model was derived based on a simplified reaction scheme by considering the formation of IBS and IBPCI and the catalytic carbonylation of IBPCI as individual steps. An empirical rate equation based on the experimental trends was used for the carbonylation step. The rate model was found to fit well the concentration-time profiles at all temperatures. The

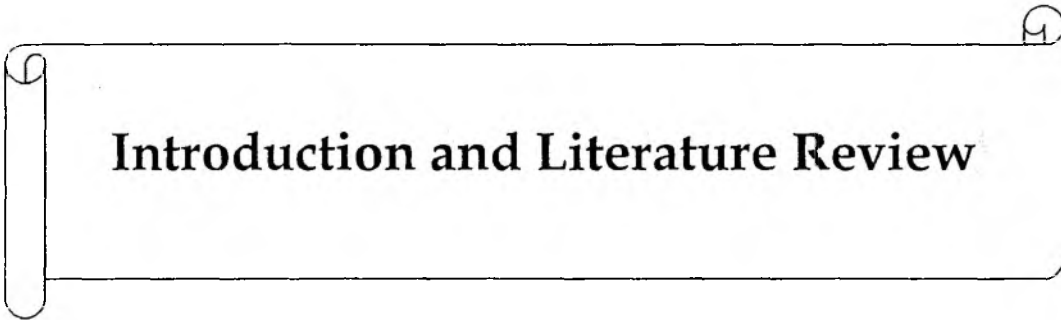
rate parameters were determined and the activation energies corresponding to each rate constants were calculated. An attempt has also been made to develop a dynamic model considering the changes in concentration of all the catalytic species along with reactants and products.

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# Chapter 1



**Introduction and Literature Review**

## 1.1. Introduction

Catalysis plays an important role in the day-to-day life directly or indirectly as exemplified by the manufacture of commodity chemicals, clothing, food, plastics, agrochemicals, pesticides and pharmaceuticals. While the petroleum and petrochemical industry is largely based on catalytic processes, in recent years the small volume specialty and fine chemicals are also preferred to be produced by catalytic routes. Most of the stoichiometric organic reactions, which were practiced in early days by industries for high value products, are also being replaced by catalytic processes due to strict environmental demands. Synthesis by stoichiometric reactions normally produce large amount of waste materials or side products, which need down stream treatments for disposal, unlike that involving catalytic reactions. Hence, catalysis plays a pivotal role in the environmental protection as well as efficient utilization of resources in chemical industry.

Catalysis is generally classified into two types depending on the physical nature of the catalyst employed: as homogeneous, in which the catalyst is soluble in the reaction medium, and heterogeneous in which the catalyst is immiscible with the reaction medium or present as a separate phase. The main advantage of homogeneous metal complex catalysis compared to their heterogeneous counterparts, is their high activity and selectivity under mild reaction conditions. Before the landmark discovery of oxo synthesis by Otto Roelen in 1938, homogeneous catalysis by metal complexes received only occasional mention. The developments in elucidation of structure and reactivity of catalysts as well as catalytic intermediate species followed by understanding of the reaction mechanism paved the way to successful commercialization of many homogeneous catalytic processes. Some of them are hydroformylation of olefins to aldehydes/alcohols, carbonylation of alcohols and olefins to corresponding acids/esters, hydrogenation, oxidation, polymerization, C–C bond coupling, etc.<sup>1</sup>

C<sub>1</sub> chemistry,<sup>2</sup> which involves single carbon compounds as building blocks, became important during the Second World War when the oil crisis occurred. Processes based on C<sub>1</sub> chemistry involve the formation of non-oxygenated compounds such as hydrocarbons, gasoline, etc. by Fischer-Tropsch synthesis, methanol and higher alcohols from synthesis

gas and formation of carbonyl compounds such as carboxylic acids/esters, ketones, aldehydes, etc. Synthesis of carbonyl compounds gained much attention due to a wide spectrum of products, which can be obtained directly or by their derivatization. These include carboxylic acids, esters, anhydrides, acid chlorides, aldehydes, amides, ketones, polyketones, carbamates, isocyanates, amino acids etc. One of the important classes of reactions is the carbonylation involving CO as a C<sub>1</sub> building block.<sup>3</sup> Carbonylation technology has advanced considerably in the last few decades with the development of novel catalysts and ligands as well as better understanding of the reaction mechanism. Several new developments on carbonylation chemistry and technology in recent years have indicated its great potential for new synthetic routes and processes for a wide variety of products (see Section 1.2).

The aim of this thesis is to investigate carbonylation of olefins and alcohols, particularly vinyl aromatics and aryl alcohols to the corresponding carboxylic acids or esters, which has direct relevance to the pharmaceutical and fine chemical industries. The focus of present work would be the development of improved catalytic systems as well as understanding the various catalytic aspects such as catalytic activity, selectivity, reaction mechanism and kinetics. Hence, this chapter presents a brief introduction on the carbonylation of unsaturated compounds and alcohols. Specific importance has been given to the carbonylation of vinyl aromatics and aryl ethanols with respect to catalyst developments, reaction mechanism and kinetics.

## 1.2. Carbonylation

During the last five to six decades, several new reactions involving carbon monoxide have acquired considerable importance.<sup>3</sup> The distinguishing feature of these reactions is that CO inserts into an organic compound in the form of a carbonyl group, thereby leading to the production of new oxygen containing functional groups such as aldehyde, ketone, acid, ester, amide, etc. In the carbonylation chemistry developed by Reppe<sup>4</sup> during 1939 to 1945, reactions of CO with organic compounds such as olefins and acetylenes in the presence of metal carbonyls such as Ni(CO)<sub>4</sub> were involved to form the corresponding carboxylic acids and esters. These were not very attractive for industries from a

commercial point of view due to the very high temperatures (473–573 K) and pressures (10–100 MPa) required. Also these reactions required expensive autoclave equipment and handling of large quantities of toxic, volatile and unstable materials as catalysts. Under such drastic conditions a complex mixture of the products was generally obtained instead of a single major product and required tedious separation. With advances in the knowledge on the nature of active catalytic species involved in these reactions, it was realized that carbonylation reaction could be carried out at significantly higher rates even at lower pressures.<sup>5</sup> Soon after, carbonylation chemistry witnessed spectacular developments, particularly with the work of Wilkinson,<sup>6</sup> Heck<sup>7</sup> and Tsuji,<sup>8</sup> which lead to highly active catalysts based on organophosphine complexes of rhodium and palladium. As a result, many carbonylation reactions can now be carried out at lower temperatures and pressures, even close to atmospheric conditions by using *in situ* generated catalysts from air stable catalyst precursors such as  $\text{PdCl}_2(\text{PPh}_3)_2$  and  $\text{RhCl}(\text{CO})(\text{PPh}_3)_2$ , which are easy to handle and store. Moreover, the scope and understanding of the carbonylation chemistry have grown to such an extent that it can now be well regarded as one of the most useful techniques for synthetic organic chemistry both in industry and research laboratory with a reasonable choice of catalysts. The main functionalities that can be carbonylated to useful products are: unsaturated compounds such as acetylenes, olefins and dienes, alcohols, nitro compounds, amines, organic halides, etc. Important carbonylation processes that were commercialized include production of acetic acid by carbonylation of methanol, acrylic acid by carbonylation of acetylene, propionic acid by carbonylation of ethylene, etc. Some of the examples of industrially relevant carbonylation processes are summarized in Table 1.1.

The important developments on carbonylation of unsaturated compounds such as olefins, alkynes and alcohols are reviewed in the following sections.

### 1.2.1. Carbonylation of unsaturated compounds

A wide variety of carbonyl containing products of practical value are obtained by carbonylation of unsaturated compounds<sup>1,3,9</sup> containing triple, double and conjugated double bonds. The transition metal catalyzed carbonylation of unsaturated compounds



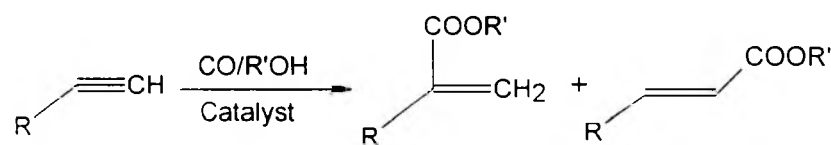
generally involves the participation of acidic hydrogen sources such as water, alcohols, amines, carboxylic acids, thiols, etc., to produce the corresponding derivatives. For these reactions, transition metal complexes of Rh, Co, Ni, Pd and Pt are generally used as catalysts. Carbonylation reactions in the presence of water producing the corresponding carboxylic acids are generally termed as hydroxycarbonylation or hydrocarboxylation. When carbonylation is carried out in the presence of alcohols to produce the corresponding esters, it is generally referred as hydroesterification or alkoxy carbonylation.

**Table 1.1. Industrial processes based on carbonylation**

No.	Process	Catalyst	Company	Reference
		$\text{Co}_2(\text{CO})_8$	BASF	Falbe (1975) <sup>10</sup>
1	Methanol to acetic acid	$[\text{Rh}(\text{CO})_2\text{I}_2]^-$	Monsanto	Roth (1975) <sup>11</sup>
		$\text{IrCl}_3$	BP	Watson (1998) <sup>12</sup>
2	Acetylene to acrylic acid	$\text{NiBr}_2\text{-CuBr}_2$	BASF	Weissermel and Arpe (1993) <sup>13</sup>
3	Ethylene to propionic acid	$\text{Ni}(\text{OCOC}_2\text{H}_5)_2$	BASF	Weissermel and Arpe (1993) <sup>13</sup>
4	Methanol to dimethyl carbonate	$\text{PdCl}_2/\text{CuCl}_2$	Assoreni	Ugo <i>et. al.</i> (1980) <sup>14</sup>
5	Methyl acetate to acetic anhydride	$\text{RhCl}_3$	Eastman	Mayfield (1986) <sup>15</sup>
6	Benzyl chloride to phenylacetic acid	$\text{Na}[\text{Co}(\text{CO})_8]$	Montedison	Cassar <i>et. al.</i> (1969) <sup>16</sup>
7	Butadiene to adipic acid	$\text{HCo}(\text{CO})_4$	BASF	Chem. Week. (1984) <sup>17</sup>
8	Isobutylphenyl ethanol to Ibuprofen	$\text{PdCl}_2(\text{PPh}_3)_2$	Hoechst-Celanese	Armor (1991) <sup>18</sup>
9	Propyne to methyl methacrylate	Pd-pyridyl phosphine	Shell	Schwaar (1994) <sup>19</sup>
10	Co-polymerization of CO with ethylene	$\text{Pd}(\text{OAc})_2/\text{dppp}/\text{TsOH}$	Shell	Ash (1994) <sup>20</sup>

#### 1.2.1.1. Carbonylation of alkynes

Carbonylation of alkynes produces the corresponding unsaturated acids or esters as shown in Scheme 1.1.



R = alkyl or aryl; R' = H or alkyl or aryl

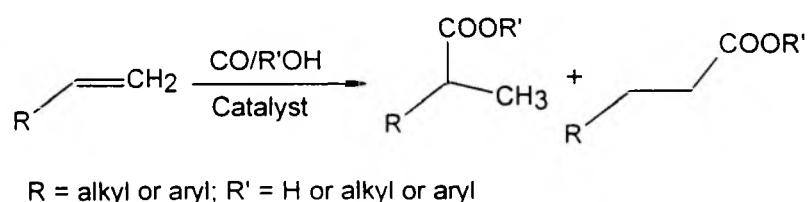
Scheme 1.1. Carbonylation of alkynes

Carbonylation of acetylene, one of the first examples of Reppe carbonylation by metal complexes, gives acrylic acid, which has a worldwide production of more than 338,000 TPA (by all the routes). The catalyst of choice was  $\text{NiBr}_2$  along with copper bromide in THF as a solvent. In this process about 90 % selectivity to acrylic acid was obtained at 4–10 MPa pressure and 453–478 K. This was one of the first large-scale processes to use carbonylation technology. Although, alternative routes to acrylic acid such as propene oxidation are now more competitive, plants based on carbonylation still generate more than 150,000 tons of acrylic acid per annum. Cobalt carbonyl,  $\text{Co}_2(\text{CO})_8$ , was also found to efficiently catalyze the carbonylation of acetylene to acrylic acid at lower pressures. At higher temperatures (>373 K) and pressures (10–20 MPa) an efficient second carbonylation also occurs forming succinic acid in >80% yield.<sup>21</sup> Even though, the carbonylation of acetylene, the simplest alkyne, was efficiently carried out on commercial scale, a similar process for higher alkynes remained underdeveloped mainly because of the problems associated with controlling the regioselectivity.<sup>21</sup> In recent years, attention has been focused on the development of catalysts with modified tertiary phosphines, particularly that of nickel, palladium and platinum.<sup>22</sup> The main goal has been to develop chemo and regioselective carbonylation catalysts for application to higher alkynes for the selective synthesis of certain fine chemicals and pharmaceuticals or their intermediates. Many of these catalysts allow the carbonylation to proceed under milder operating conditions with higher rates compared to those applied in Reppe process. Palladium based catalyst systems such as  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Pd}(\text{OAc})_2/\text{dppf}$ ,<sup>23</sup>  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{dppb}$ ,<sup>24</sup>  $\text{Pd}(\text{dba})_2/4\text{PPh}_3$ <sup>25</sup> have been demonstrated to catalyze the carbonylation of alkynes at lower CO pressures (0.1 to 2 MPa). However, with these catalysts, productivities were inadequate for large-scale industrial application in the production of bulk products such as

methyl methacrylate (MMA). Recently, a highly efficient catalyst for the carbonylation of alkynes was developed by Drent *et. al.*<sup>26</sup> This process uses palladium(II) catalysts along with a ligand containing 2-pyridylphosphine moiety in the presence of acidic promoters having weakly coordinating anions at 6 MPa of CO and 333 K. This catalyst system not only allows the selective and rapid carbonylation of acetylene, but also of higher alkynes. A very high TOF of 40,000 h<sup>-1</sup> with a selectivity of 98.9-99.9 % to MMA was demonstrated for the carbonylation of propyne, thereby allowing a cost-effective single step MMA process<sup>27</sup> on the basis of carbonylation technology. The same catalyst system also gave higher activity for the carbonylation of aryl acetylenes, the branched acid/ester products of which are important intermediates in the production of optically active 2-arylpropionic acids by enantioselective hydrogenation. A TOF of 20,000 h<sup>-1</sup> and 99.9 % selectivity to the branched product methyl-2-phenylpropenoate was reported for the hydroesterification of phenyl acetylene by using Pd(OAc)<sub>2</sub> as the catalyst precursor along with bisphenyl-(6-methyl-2-pyridyl)phosphine as a ligand.<sup>28</sup> Another study on the hydrocarboxylation of phenyl acetylene using a catalyst system Pd(OAc)<sub>2</sub>/2-pyridyl phosphine as a catalyst, reported a TOF of 3,000 h<sup>-1</sup> and >98% selectivity to the branched unsaturated acid, 2-phenylpropenoic acid, at 3 MPa and 323 K.<sup>29</sup> The same report demonstrated carbonylation of 2-(6-methoxy-2-naphthyl)ethyne to 2-(6-methoxy-2-naphthyl)propenoic acid, a Naproxen precursor, at 0.1 MPa even though with very low reaction rate. Pd(OAc)<sub>2</sub> along with 2-pyrimidylphosphines<sup>30</sup> was also reported to give TOFs in the range of 7,000 h<sup>-1</sup> for the carbonylation of alkynes with >97% selectivity to the branched product under similar conditions. Very recently carbonylation of terminal as well as internal acetylenes was reported at very low pressure of CO (0.2 MPa) in the presence of Pd(OAc)<sub>2</sub>/pyridine-2-carboxylic acid/PPh<sub>3</sub> as a catalyst under acidic conditions.<sup>31</sup> It is obvious from these reports that palladium compounds along with phosphines having nitrogen containing heterocycles or nitrogen containing ligands along with phosphines are the most efficient catalysts for the regioselective carbonylation of higher alkynes.

### 1.2.1.2. Carbonylation of olefins

Carbonylation of olefins (Scheme 1.2) is a direct synthetic route for the preparation of a variety of saturated carbonyl compounds such as carboxylic acids, anhydrides, esters, amides, amino acids, etc. The reaction of olefins with carbon monoxide and water or alcohol catalyzed by phosphoric acids, heteropoly acids, boron trifluoride, etc., to produce the corresponding acids or esters (Koch carbonylation) was already well known<sup>32</sup> before the demonstration of the carbonylation process by Reppe.



Scheme 1.2. Carbonylation of olefins

The earlier processes using Koch synthesis required severe conditions (70–90 MPa and 573 K) and metal carbonyls were often regarded as reaction inhibitors.<sup>3</sup> Later on, the developments in transition metal catalyzed carbonylation reactions opened up new catalytic systems for the carbonylation of olefins. These reactions generally produce both the linear as well as the branched carboxylic acids as shown in Scheme 1.2. Metal complexes, which have been employed as catalysts for this reaction include compounds of nickel, cobalt, iron, rhodium, ruthenium, palladium and platinum.<sup>3</sup> In most of the early processes, severe operating conditions, viz. 20–30 MPa and 473–573 K, were required. Higher operating temperature used has the disadvantage of side reactions such as water-gas shift reaction, hydrogenation of unreacted olefins, polymerization, and isomerization as well as formation of aldehydes, alcohols, ketones, etc., and hence further research was focused on the development of catalysts operating at lower temperatures. Pd, Pt, Rh and Ir as catalysts required relatively mild reaction conditions.<sup>3,8,33</sup> A brief review of different catalytic systems used for the carbonylation of olefins is presented in the following sections.

#### 1.2.1.2.1. Different catalytic systems

##### 1.2.1.2.1.1. Nickel catalysts

After Reppe's first catalytic carbonylation of acetylene using nickel carbonyl, the next obvious step was to apply this catalytic system to the carbonylation of olefins. An attempt to prepare propionic acid and its esters by catalytic reaction of ethylene with CO and water or alcohols in the presence of Ni salts or Ni(CO)<sub>4</sub> was an immediate success and NiCl<sub>2</sub> was patented as early as 1943 as a catalyst precursor for the carbonylation of ethylene.<sup>34</sup> For the industrial-scale process, however a halogen-free catalyst system based on Ni(OCOC<sub>2</sub>H<sub>5</sub>)<sub>2</sub> was used.<sup>13,35</sup> Nickel catalysts were used both stoichiometrically as well as catalytically. The catalytic reaction required severe operating conditions (523 K and 20 MPa) compared to the corresponding stoichiometric reaction (423 K and 5 MPa).<sup>36</sup> Carbonylation of higher olefins (C<sub>4</sub>–C<sub>18</sub>) were also reported using Ni(CO)<sub>4</sub> at 523 K and 25 MPa.<sup>37</sup> In the case of carbonylation of internal olefins, predominant formation of branched acid/ester (60–75%) was observed with nickel as a catalyst.<sup>38</sup>

Later developments showed that the presence of acid promoters and phosphine ligands facilitates the Ni(CO)<sub>4</sub> catalyzed carbonylation of olefins even under atmospheric pressures and at ambient temperatures.<sup>39,40</sup> A low pressure carbonylation of ethylene was also reported to be achieved with nickel compounds in the presence of molybdenum, tungsten or chromium and an alkali metal halide promoter.<sup>41</sup> Thus carbonylation of ethylene was reported with NiI<sub>2</sub>, Mo(CO)<sub>6</sub> and LiI as a catalyst system in the presence of added ethyl iodide at 453 K and 5.4 MPa pressure with a rate of 1.75 mol/litre/h. Recently, a halogen free nickel catalyst (nickel propionate) along with ruthenium (ruthenium acetylacetonate) was reported to be effective for ethylene carbonylation under comparatively lower operating conditions (473K and 10 MPa).<sup>42</sup>

##### 1.2.1.2.1.2. Cobalt Catalysts

Cobalt carbonyl Co<sub>2</sub>(CO)<sub>8</sub> is reported as an efficient catalyst for the carbonylation of olefins to carboxylic acids.<sup>43,44</sup> The linear acid/ester product predominated in most cases and the selectivity was shown to increase further by the addition of pyridine as a co-catalyst.<sup>3b</sup> Carbonylation of higher olefins such as 1-octene and dodecene using cobalt

catalysts even with pyridines or alkyl pyridines, as co-catalyst required severe operating conditions (433 K and 16–18 MPa). In the case hydroesterification of 1-octene, maximum conversion and rate were observed with a pyridine to cobalt ratio of 15–35:1. In the absence of pyridine, complete isomerization of 1-octene to internal olefins<sup>45</sup> was reported with only less than 12% yield of ester products.

#### **1.2.1.2.1.3. Rhodium and iridium catalysts**

Rhodium<sup>46</sup> and iridium<sup>47</sup> complexes were reported to catalyze the carbonylation of olefins in presence of iodide promoters and water forming predominantly the branched carboxylic acid. Thus Ir(PPh<sub>3</sub>)<sub>2</sub>(CO)Cl was reported to catalyze the carbonylation of propylene in the presence of aqueous HI in acetic acid as the solvent at 4.8 MPa total pressure (1.3 MPa of CO) and 448 K. Under these conditions butyric acid was produced in 5:1 (*i:n*) ratio with a total selectivity of 99%. Similarly rhodium gave an *i:n* ratio of 1.6:1. A non halide Rh system, Rh(CO)<sub>2</sub>(acac), with Bu<sub>3</sub>P as a ligand was also reported for the carbonylation of ethylene to methyl propionate under 448 K and 4.7 MPa pressure, which gave methyl propionate in 80% selectivity.<sup>48</sup> In a very recent patent<sup>49</sup> by BASF, a halogen free rhodium catalyst together with nitrogen containing heterocycles as a ligand was claimed for the carbonylation of ethylene. A TOF of 200–1280 h<sup>-1</sup> was reported with Rh(acac)(CO)<sub>2</sub> and pyridine at 373 K and 10 MPa with > 95% selectivity to propionic acid.

#### **1.2.1.2.1.4. Ruthenium catalysts**

Only a very little attention has been given to ruthenium as a carbonylation catalyst. In a recent patent<sup>50</sup> assigned to Albermarle Corporation, carbonylation of poly alpha olefins (PAO) was reported with RuCl<sub>3</sub> as a catalyst with aqueous HCl as a promoter in *n*-butanol at 373 K and 13.6 MPa pressure. The TOF was reported to be very low (1.25 h<sup>-1</sup>) with a conversion of 27%.

#### **1.2.1.2.1.5. Palladium and platinum catalysts**

Complexes of palladium and platinum catalyze hydrocarboxylation and hydroesterification of olefins more efficiently than any other metal. In 1959, DuPont

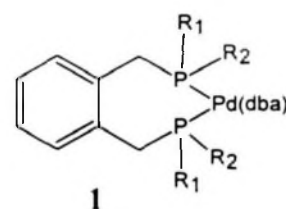
developed a comparatively low temperature process for carbonylation of lower olefins ( $C_2-C_6$ ) using a platinum compound catalyst along with Sn or Ge salts [ $(H_2PtCl_6)-(SnCl_2)$ ] as a catalyst in alcoholic medium.<sup>51</sup> This process required a temperature range of 323–598 K and a pressure range of 30–300 MPa. Following this, during 1970 Kehoe and Schell<sup>52a</sup> reported that the same combination of catalysts with proper choice of solvents such as acetone, methyl isobutyl ketone, etc., can be used for the carbonylation of higher olefins ( $C_2-C_{14}$ ). With this catalyst system, corresponding linear carboxylic acids or esters were produced with high yields (65–85%) under comparably lower CO pressures (20–30 MPa).<sup>52b</sup> A low temperature process, which operated even at 313 K, was reported by Reis and co-workers for the carbonylation of olefins.<sup>53</sup> In this process,  $PdCl_2(PPh_3)_2$  along with 10% HCl in ethanol as a solvent was reported to catalyze the carbonylation of ethylene to ethyl propionate and styrene to ethyl-2-phenyl propionate with 90% and 95% yields respectively at 368 K and 30–70 MPa CO pressure. Tsuji and co-workers also reported independently that the reaction of olefins with CO in an alcoholic solution of HCl in the presence of  $PdCl_2$  leads to esters of saturated and unsaturated acid esters.<sup>54,52</sup> During the late sixties Tsuji published comprehensive reviews dealing with the utilization of palladium catalysts in the carbonylation of olefins.<sup>55</sup> Ligand stabilized palladium(II) complexes such as  $PdCl_2(PPh_3)_2$ ,  $PdCl_2(AsPh_3)$  etc. along with group IVB metal halides such as  $SnCl_2$ ,  $GeCl_2$  and  $PbCl_2$  were also demonstrated to be effective for the carbonylation of  $\alpha$ -olefins providing high selectivity to the linear ester products at mild temperatures (353 K, 30 MPa).<sup>56</sup> In 1973, Fenton<sup>57</sup> reported the hydrocarboxylation of higher  $\alpha$ -olefins such as 1-octene using a catalytic system consisting of  $PdCl_2/2PPh_3$  to produce nonanoic acid at a temperature range of 399–448 K under comparatively lower CO pressures (0.7–5.4 MPa). It was observed that, the *n/iso* ratio was mainly affected by changes in parameters like concentration of  $PPh_3$ , water and CO partial pressure.

In 1983, Alper *et. al.*<sup>58</sup> have reported the carbonylation of terminal aliphatic olefins at room temperature and atmospheric pressure using  $PdCl_2$  as the catalyst in the presence of  $CuCl_2$ , HCl and molecular oxygen. This reaction was particularly selective towards branched isomers for the carbonylation of higher aliphatic olefins. The reaction failed in water as well as in THF containing greater than 5 mol% of water. In this catalyst system, a

lower concentration of HCl was preferred for better activity and a detailed investigation on the effect of different parameters was reported recently, for the hydroesterification of propene.<sup>59</sup>

Another important advancement is the carbonylation under biphasic conditions using water soluble catalysts. The main advantage of this system is the easy separation of catalyst from the products by simple phase separation as well as its recycle. In general *in situ* formed Pd(TPPTS)<sub>3</sub> from a mixture of PdCl<sub>2</sub> and the water soluble ligand TPPTS (triphenylphosphino trisulfonate) was used as the catalyst. The important developments in this field are reviewed in section 1.2.1.2.2.1. Though, the biphasic catalytic system provides separation and recycle advantages, the reaction rates were very low owing to the low solubility of the organic reactants in the aqueous catalytic phase. In order to overcome this limitation, mass transfer agents such as co-solvents, cyclodextrins were used as exemplified in the case of hydrocarboxylation higher  $\alpha$ -olefins such as 1-decene.<sup>60</sup> Another development in the biphasic carbonylation is the use of molten salts such as Et<sub>4</sub>N<sup>+</sup>SnCl<sub>3</sub><sup>-</sup> as a second phase.<sup>61</sup> Under the reaction conditions (358 K and 10 MPa) this system forms a clear homogeneous mixture in ethanol and 1-octene and on cooling, the quaternary salt precipitates thereby facilitating the easy separation.

Though different catalyst systems for carbonylation of olefins were reported including separation advantageous, the main challenge has been in the development of highly active and selective catalyst systems, which work under mild reaction conditions. Recently a highly active palladium(0) complex (1)



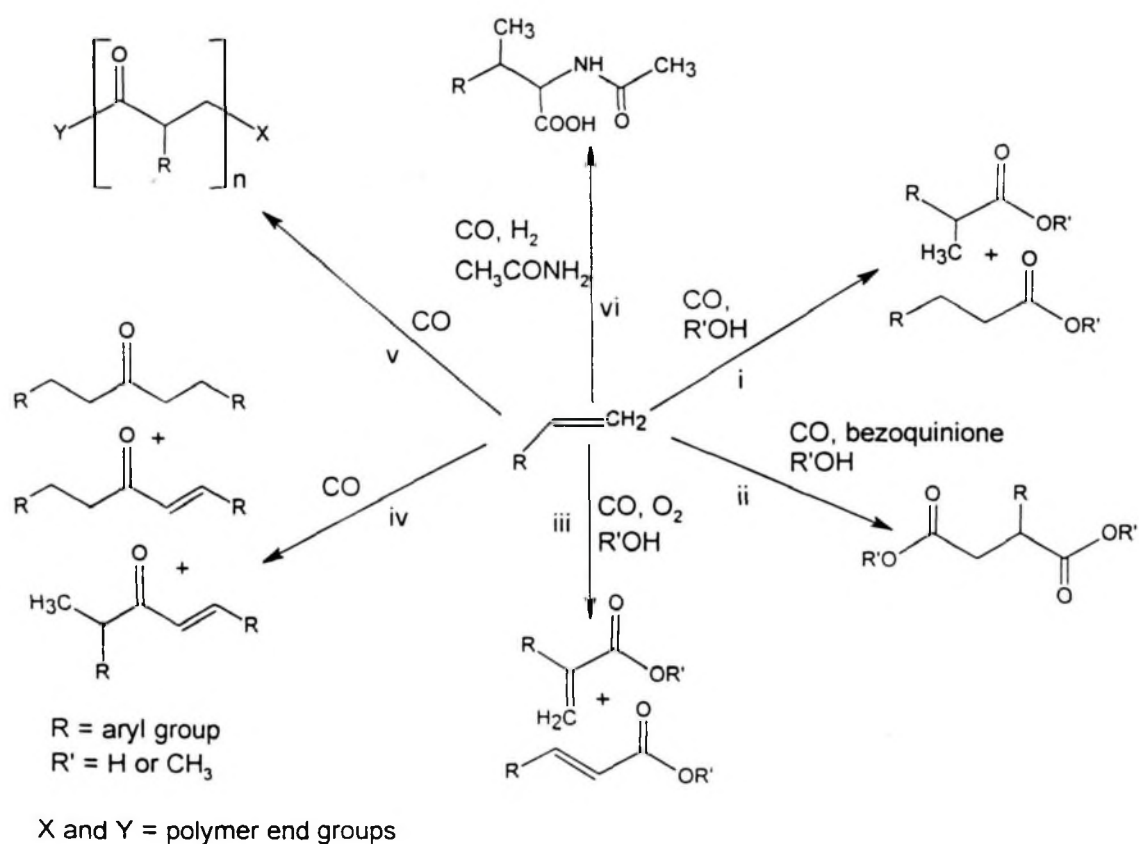
with 1,2-bis(di-*tert*-butylphosphinomethyl)benzene and dibenzylideneacetone as ligands was reported, which gave a TOF of 50,000 h<sup>-1</sup> and a selectivity of 99.98 % to propionic acid for the carbonylation of ethylene under mild conditions of 535 K and 1 MPa total pressure.<sup>62</sup> Palladium catalysts with another bidentate ligand such as 1,3-bis(di-*tert*-butylphosphino)propane<sup>63</sup> also gave a TOF of 15,000 h<sup>-1</sup>, while PPh<sub>3</sub><sup>64</sup> gave only 1800 h<sup>-1</sup> under identical conditions.





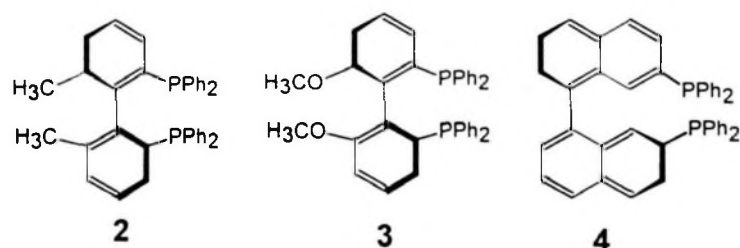
### 1.2.1.2.2. Carbonylation of vinyl aromatics

A variety of carbonyl containing functionalities such as carboxylic acids and esters, ketones and polyketones, amides and amino acids, etc., can be obtained by the carbonylation of styrene and its derivatives by properly selected catalyst systems and reaction conditions as represented below in scheme 1.3. Carbonylation via path **i** produces mono-carboxylic acids and esters and was generally catalysed by palladium complexes. A detailed review on this subject is presented in a later section (Section 1.2.1.2.2.1.). Bisalkoxycarbonylation via path **ii** produces succinates. Palladium catalysts with suitable oxidizing agents were generally used, among them  $\text{PdCl}_2$  and butyl nitrite,<sup>65</sup>  $\text{Pd}(\text{OAc})_2$  and benzoquinone in the presence of molecular oxygen,<sup>66</sup>  $\text{Pd}(\text{acac})_2$  and di-*tert*-butylperoxide,<sup>67</sup> etc. were the important catalytic systems reported.



Scheme 1.3. Carbonylation of vinyl aromatics in the formation different products

Recently, Consiglio and co-workers have reported enantioselective bismethoxycarbonylation of styrene using palladium catalyst and atropisomeric diphosphine ligands such as **2**, **3** and **4**. A maximum of 93% *ee* (*S*) to dimethyl phenylsuccinate was obtained with Pd(acac)<sub>2</sub> as the catalyst and **3**, (2,2'-dimethoxy-6,6'-bis(diphenylphosphino)biphenyl), as a ligand along with TsOH as a promoter at 323 K and 35 MPa pressure in methanol as a solvent.<sup>68</sup> Monoesters like methyl cinnamate and aryl propionates were also formed along with some oligomers. 50 % *ee* to methyl-2-phenylpropionate was also observed under these conditions.



Oxidative carbonylation via path **iii** to produce cinnamic acid derivatives, which have applications in perfumeries, is another industrially important reaction. This process uses a combination of palladium compounds/complexes along with that of Cu or Mn in the presence of molecular oxygen as a catalyst system<sup>69</sup> under 373 K and 3.2 MPa pressure of CO. The main by-products were acetophenone and succinate derivatives. Cationic palladium complexes were generally used for the formation of ketones from olefins and CO (path **iv**). Consiglio and co-workers<sup>70</sup> have reported carbonylation of styrene to form 1,5-diphenylpentan-3-one (SK) and *E*-1,5-diphenylpent-1-en-3-one (*E*-LK) in 5:95 molar ratio with 42% conversion using a bis-solvato complex [(dppp)Pd(MeCN)<sub>2</sub>][BF<sub>4</sub>]<sub>2</sub> in the presence of 16 MPa of an equimolar mixture of CO and H<sub>2</sub> at 350 K in THF. The corresponding dimeric complex such as [(dppp)Pd(μ-OH)<sub>2</sub>Pd(dppp)]X<sub>2</sub>, where X is BF<sub>4</sub><sup>-</sup> or TsO<sup>-</sup>, gave only very low conversions (4.5%) with similar selectivity behaviour. Operating pressure was found to reduce (2 MPa of CO and 0.1 MPa of H<sub>2</sub>) with [(dppp)Pd(OTs)<sub>2</sub>] as a catalyst precursor without much change in activity and selectivity.

Pisano *et. al.*<sup>71</sup> studied the regioselectivity of formation of ketones by the carbonylation of olefins using  $[\text{Pd}(\text{CH}_3\text{CN})_4][\text{BF}_4]_2$  modified with different nitrogen and mono- or bidentate phosphorus ligands under 373 K and 16 MPa of equimolar amount of CO and H<sub>2</sub> in THF. Consiglio and co-workers has also carried out a detailed investigation on various reaction parameters affecting the catalytic activity and selectivity of the carbonylation of olefins to ketones using cationic palladium complexes.<sup>72</sup>

Carbonylation of styrene to form perfectly alternating copolymers<sup>73</sup> of CO and styrene via route **v** is an important class of reaction in the production of poly(1-oxo-2-phenylmethylene), a substitute for polystyrene and has gained much attention in both industry and academic research in recent years.<sup>74</sup> A brief description on the progresses on copolymerization of olefins with CO to form polyketones is presented in section 1.2.1.2.3.

Since a part of the present thesis work is mainly confined to the carbonylation of styrene and substituted styrenes to the corresponding acids/esters, a detailed review of the literature on the carbonylation of styrenes to corresponding acids/esters is given in the following section.

#### **1.2.1.2.2.1. Carbonylation of styrene and its derivatives to carboxylic acids and esters**

Styrene, the simplest vinyl aromatic compound, on carbonylation in the presence of water or alcohol produces both linear and branched carboxylic acids or esters. In general, palladium complexes were used as catalysts and the regioselectivity and catalytic activity were found to vary with the nature of the catalyst precursor, ligands, reaction conditions and the promoters used. Earlier developments were based on  $\text{PdCl}_2(\text{PPh}_3)_2$  as a catalyst precursor along with HCl as the promoter. Selective synthesis of ethyl-2-phenyl propionate (95% yield)<sup>53</sup> was reported with this catalyst system at higher CO pressures of 30–70 MPa and 363 K. The selectivity to *iso*-product decreased when bidentate diphos ligands ( $\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2$ , where *n* is 1–10) were used, instead of triphenylphosphine, under similar reaction conditions.<sup>75</sup> In this case, with increase in alkyl chain length of diphos ligands, the regioselectivity to the linear isomer, ethyl-3-phenyl propionate, increased up to *n* = 4 and decreased with further increase.<sup>76</sup> This observation was explained on the basis of different modes of coordination adopted by the diphos ligands to balance the steric

hindrance.<sup>76</sup> With diphenylphosphinobutane (dppb) as the ligand along with PdCl<sub>2</sub>, the maximum selectivity to ethyl-3-phenyl propionate obtained was 86% with TOF in the range of 10–20 h<sup>-1</sup> and a maximum yield of 38.1%. In another study, more or less exclusive formation of linear isomer was observed for the carbonylation of  $\alpha$ -methyl styrene, using PdCl<sub>2</sub> as a catalyst with two equivalents of (-)-DIOP, (R,R)-2,3-O-isopropylidene-dihydroxy-1,4-bis(diphenylphosphino)butane (**13b**, Section 1.2.1.2.2.1.1) as the ligand at 373 K and 40 MPa pressure in ethanol-benzene mixture as a solvent.<sup>77</sup> But in the case of styrene, selectivity to the linear isomer was only 54% under similar conditions.<sup>77</sup> Noskov *et. al.*<sup>78</sup> have investigated in detail the hydrocarboxylation of styrene using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/PPh<sub>3</sub> as the catalyst system at 2 MPa of pressure and 368–393 K in wet dioxane. With this catalyst system, increased formation of 3-phenylpropionic acid (linear isomer) was reported with increase in temperature. This temperature dependent regioselectivity pattern was explained in terms of the difference in the energy of activation for the formation of linear and branched isomers. In the case of the linear isomer the energy of activation was calculated to be 80 kJ/mol higher than that of the branched isomer. Addition of increased amount of PPh<sub>3</sub> also increased the selectivity of the linear isomer. Furthermore, the use of synthesis gas instead of pure CO<sup>79</sup> and addition of SnCl<sub>2</sub> as promoters were also reported to increase the regioselectivity to the linear isomer.

A majority of the reports after these initial developments were focused mainly on the regioselective synthesis of 2-arylpropionic acids or esters by the regioselective carbonylation of styrene and its derivatives. Many of the substituted 2-aryl propionic acids find applications as anti-inflammatory agents,<sup>80</sup> Ibuprofen, Naproxen, ketoprofen, etc., being the important examples. Alper and co-workers reported that the selectivity towards the branched product increases by using formate esters along with CuCl<sub>2</sub> in the palladium catalyst systems.<sup>81</sup> Up to 93% regioselectivity to the *iso* carboxylic acid was obtained at 373 K and 4.1 MPa pressure for the hydrocarboxylation of 4-methylstyrene<sup>82</sup> with a TOF of 25 h<sup>-1</sup> by using PdCl<sub>2</sub>/CuCl<sub>2</sub>/HCl as the catalyst system. The possible role of CuCl<sub>2</sub> was in the reoxidation of the Pd(0) species to the active Pd(II) species. But, without added oxygen and CuCl<sub>2</sub>, the branched to linear ratio decreased to 2.7 in the case of Pd(PPh<sub>3</sub>)<sub>4</sub> as the catalyst at 423 K and 8.2 MPa. Also, addition of two equivalents of dppb<sup>83</sup> further

decreased the branched to linear ratio to 0.15. Predominant formation of the linear isomer was also reported with Pd(OAc)<sub>2</sub> in the presence of oxalic acid and dppb and PPh<sub>3</sub> as ligands in dimethoxy ethane.<sup>84</sup>

Regioselective formation of methyl esters of 2-arylpropionic acids was reported by Lee and Alper<sup>85</sup> for the hydroesterification of different styrene derivatives using Pd(OAc)<sub>2</sub> immobilized on montmorillonite along with PPh<sub>3</sub> as a ligand at 398 K and low pressures (4 MPa), but with lower rates (20 h<sup>-1</sup>). In this case, acidic promoters were found to be necessary for significant catalytic activity and inorganic acids like HCl was reported to be more effective than organic acids such as *p*-toluenesulphonic acid. Presence of PPh<sub>3</sub> was found to be essential as no carbonylation product was reported without PPh<sub>3</sub>. Diphos ligands were inactive with this system, but were reported to be active with 10% Pd/C as the catalyst in presence of formic acid or oxalic acid as a promoter.<sup>86</sup> With terminal olefins as substrates, predominant formation of linear isomer was reported under these conditions. When Pd(OAc)<sub>2</sub> was used in homogeneous system with phosphinic acid as a ligand and TsOH as an acidic promoter at 403 K and 4 MPa,<sup>87</sup> predominant formation of the linear isomer (35%) compared to that of the branched (7%) was also observed with styrene as the substrate (TOF = 50 h<sup>-1</sup>). However, when PPh<sub>3</sub> was used as the ligand instead of phosphinic acid, regioselective formation of the branched isomer was observed at room temperature and 2 MPa,<sup>88</sup> but with a very low catalytic activity (TOF = 2 h<sup>-1</sup>).

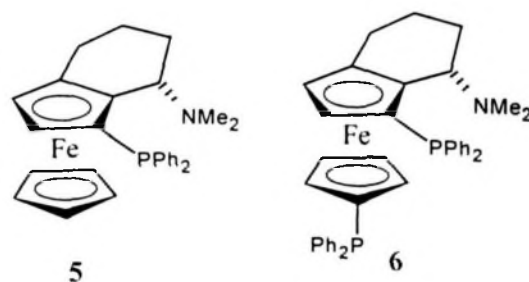
Oi *et. al.* have reported hydroesterification of styrene using a cationic palladium complex [Pd(MeCN)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>](BF<sub>4</sub><sup>-</sup>)<sub>2</sub> at 353 K and 2 MPa of CO.<sup>88</sup> Under these conditions lower selectivity (40%) to the branched isomer was reported with a TOF of 11 h<sup>-1</sup>. Though the selectivity improved at lower temperatures, the activity decreased considerably. A similar trend of lower selectivity to the branched isomer with cationic complexes was also reported by Huh and Alper<sup>89</sup> using [(Cy<sub>3</sub>P)<sub>2</sub>Pd(H)(H<sub>2</sub>O)]<sup>+</sup>BF<sub>4</sub><sup>-</sup> as a catalyst precursor along with added bis(diphenylphosphino) propane in presence of TsOH as a promoter. This system gave a linear to branched ratio of 82:18 under 373 K and 2 MPa pressure with a turnover frequency of 1.68 h<sup>-1</sup>.



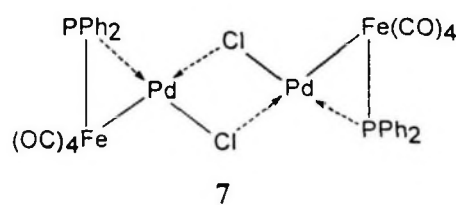
As discussed earlier, one of the industrially important applications of carbonylation of vinyl aromatics is in the production of 2-arylpropionic acids, especially Ibuprofen and Naproxen. Many companies such as Nippon Petrochemical Company Ltd.,<sup>90</sup> Ethyl Corporation,<sup>91</sup> Montedison,<sup>92</sup> etc., have patented their own processes for the production of Ibuprofen from *p*-isobutylstyrene and Naproxen from 2-vinyl-6-methoxynaphthalene. In a process described by Nippon petrochemicals, *p*-isobutylstyrene was carbonylated in a biphasic system consisting of 10% aqueous HCl and toluene as the organic phase in presence of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as a catalyst at 30 MPa of CO and 393 K. Though Ibuprofen was produced in 89% selectivity with 100% conversion, the rate of reaction was found to be very low (TOF = <2 h<sup>-1</sup>).<sup>93</sup> Similarly methyl ester of Ibuprofen was prepared using methanol as the reaction medium at 7 MPa of CO and 363 K with 88.9 % selectivity and a TOF of 100–500 h<sup>-1</sup>. In this system, CuCl<sub>2</sub> was used as a promoter instead of 10% HCl<sub>(aq)</sub>. The use of (+)neomenthyl phosphine with trifluoroacetic acid as the promoter was reported to produce optically active Ibuprofen in 94 % selectivity with 52% *ee* (S) and 95% selectivity to Naproxen with 43% *ee* (S).<sup>92</sup>

In addition to palladium, other metals like platinum, nickel and iron were also been reported as catalysts for the carbonylation of vinyl aromatics. Under atmospheric pressure of CO, carbonylation of styrene with Fe(CO)<sub>5</sub> as a catalyst along with large excess of alkali metal or alkaline-earth metal hydroxides in a solvent mixture of water and isopropanol produced 2-phenylpropionic acid with >96% selectivity at 328 K after four days of reaction.<sup>94</sup> Polymer supported bimetallic catalyst consisting of palladium and nickel<sup>95</sup> along with PPh<sub>3</sub> was also reported to produce 2-aryl propionic acid esters with high selectivity. Thus up to 99% selectivity to methyl-2-phenylpropionate with complete conversion was achieved by using PVP-PdCl<sub>2</sub>-4NiCl<sub>2</sub>-PPh<sub>3</sub> (PVP = poly(*N*-vinyl-2-pyrrolidone)) as a catalyst at 353 K and 2.1 MPa pressure in benzene as a solvent. The rate of the reaction was reported to be very low (TOF = 0.25–0.5 h<sup>-1</sup>). When FeCl<sub>3</sub> or CoCl<sub>2</sub> was used instead of Ni, conversion and selectivity were decreased very much. But when CuCl<sub>2</sub> was used as the second metal, conversion and selectivity were similar to that with Ni as the second metal, but with slightly lower reaction rate.

Ferrocenyl ligands such as ( $S_c,S_m$ )-1-diphenylphosphino- $\alpha$ -*N,N*-dimethylamino-[2,3]tetramethyleneferrocene (5) and ( $S_c,S_m$ )-1,1'-bis(diphenylphosphino)-[2,3]tetramethyleneferrocene (6) were reported to be active in the hydroesterification of styrene when used as a ligand with PdCl<sub>2</sub> as the catalyst.<sup>96</sup> Both the isomeric products were formed in which the linear product predominated in the case of 6 as the ligand and the branched product predominated with 5 as the ligand when an *in situ* prepared PdCl<sub>2</sub>(5) or (PdCl<sub>2</sub>)<sub>3</sub>(6)<sub>2</sub> was used as a catalyst at 383 K and 13 MPa pressure. However, the rates were reported to be very low and 180-450 hours were required to carbonylate 100 mmol of styrene with 0.04 mmol of the catalyst.



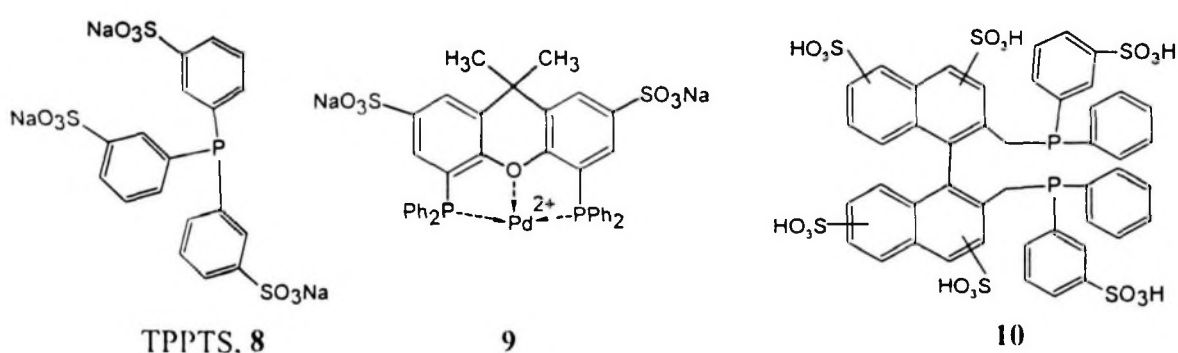
David and Prodsham<sup>97</sup> have reported a mixed metal complex of palladium and iron, 7, in the presence of added AlCl<sub>3</sub> for the carbonylation of styrene at 378 K and 10 MPa pressure. A conversion of 60% in ethanol as a solvent was reported without other details.



Kollar and co-workers<sup>98</sup> have reported that complexes of PdCl<sub>2</sub> with calyx[4]arenes such as 5,11,17,23-tetra-*ter*-butyl-25,26,27,28-tetrakis(2-diphenylphosphinoethoxy)calyx[4]arene and 5,11,17,23-tetra-*ter*-butyl-25,26,27,28-tetrakis(2-diphenylphosphinoethoxy)calyx[4]arene gave equal amount of linear and branched esters for the hydroesterification of styrene at 383 K and 14 MPa pressure. This also has the disadvantages of low activity.

Biphasic catalyst systems consisting of water soluble palladium complexes were also reported in recent years for the hydrocarboxylation of vinyl aromatic compounds. Sheldon and co-workers<sup>99</sup> have reported the hydrocarboxylation of *p*-isobutyl styrene (IBS) using Pd-TPPTS catalyst along with TsOH as a promoter at 338 K and 5 MPa pressure without any added organic solvent. A selectivity of 74% was obtained for the branched

isomer (Ibuprofen), but with lower catalytic activity ( $\text{TOF} = 3 \text{ h}^{-1}$ ), which may be due to the lower solubility of IBS in water. When styrene was used as the substrate, turnover frequencies up to  $49 \text{ h}^{-1}$  was observed at higher styrene/Pd ratios, but the selectivity remained lower (73%). A maximum selectivity of 90% to the branched isomer was obtained with a TPPTS/Pd molar ratio of 4 at 14 MPa and 338 K, but with lower activity ( $5 \text{ h}^{-1}$ ). Monflier and co-workers<sup>100</sup> reported independently the carbonylation of styrene using Pd-TPPTS catalyst in a biphasic system using equal amounts of water and toluene. Very low turnover frequency ( $2 \text{ h}^{-1}$ ) was observed with styrene as the substrate at 373 K and 5 MPa pressure. They established that the catalytic activity was largely dependent on the pH of the solution and maximum initial TOF of  $25 \text{ h}^{-1}$  was obtained at a pH of 1.8. In this case also, the selectivity to the branched product was very low (58%). Higher initial turnovers ( $18\text{--}36 \text{ h}^{-1}$ ) were reported with acids possessing coordinating anions such as HCl, HBr, HI as promoters compared to organic acids with non-coordinating anions such as  $\text{CF}_3\text{COOH}$ ,  $\text{CH}_3\text{SO}_3\text{H}$ , etc. The initial catalytic activity was found to increase approximately five times by using acetonitrile as a cosolvent.<sup>101</sup> The efficient recycle of the aqueous Pd-TPPTS catalyst was also demonstrated without significant loss in activity. However, loss of catalytic activity was reported at higher temperature. In order to eliminate this limitation, alkali metal halide or a protective-colloidal agent like polyvinylalcohol were added to prevent the catalyst decay thereby allowing to maintain higher activities at higher temperatures.<sup>102</sup>

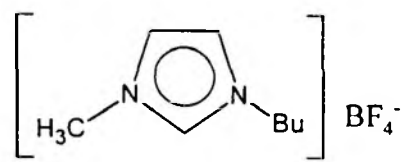


van Leeuwen and co-workers<sup>103</sup> have shown that the palladium complex 9 prepared from water soluble bidendate diphosphine 2,7-bis( $\text{SO}_3\text{Na}$ )-Xantphos was



effective as catalysts for the biphasic carbonylation of olefins in the presence of TsOH as the acidic promoter. Thus styrene was carbonylated with a turnover frequency of  $40 \text{ h}^{-1}$  and an *n/iso* ratio of 65/35 under 343 K and 3 MPa pressure. Another water soluble diphos ligand **10** was reported to be active when  $\text{CuI}_2$  was used along with palladium catalysts.<sup>104</sup> But, the reported TOF was very low ( $0.92 \text{ h}^{-1}$ ) for styrene carboxylation with a total selectivity of 63% to phenylpropionic acid.

In another development, carbonylation of different styrenes was studied in a biphasic system consisting molten ionic salt such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMIT) and isopropanol/cyclohexane as the organic phase by using



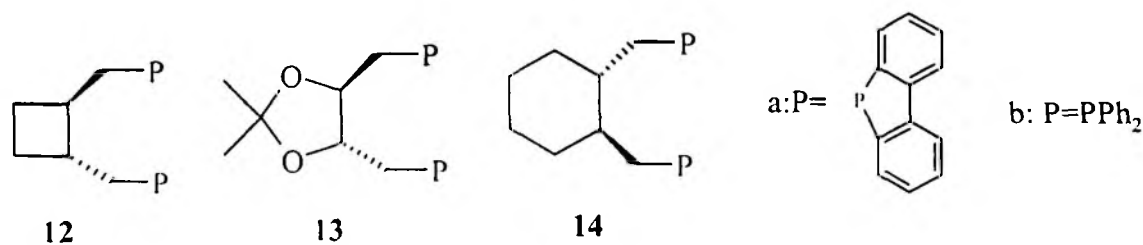
BMIT, **11**

$\text{PdCl}_2(\text{PhCN})_2$  as a catalyst precursor along with (+)neomenthylidiphenylphosphine (NMDP, **21**) as the ligand and TsOH as the promoter.<sup>105</sup> Up to 99.5 % selectivity to 2-phenyl propionate was reported at 1 MPa pressure and 343 K for the hydroesterification of styrene, but with a very low TOF ( $\sim 4 \text{ h}^{-1}$ ). In this system choice of the ligand was critical in deciding the regioselectivity. For example triphenylphosphine instead of NMDP gave only 80 % selectivity to the branched isomer, but can be increased up to 94 % with the increase in pressure to 3 MPa. Hindered phosphines such as tri-*o*-tolylphosphine were completely inactive under this catalyst system.

#### 1.2.1.2.2.1.1. Asymmetric carbonylation

Asymmetric carbonylation of vinyl aromatics is an important synthetic tool for the preparation of chiral 2-arylpropionic acids such as S-Ibuprofen and S-Naproxen. Attempts to carbonylate styrene and its derivatives using palladium salts along with chiral inducing ligands as catalysts were made since early 70's. The first report was published by Botteghi *et. al.*<sup>106</sup> for the hydroesterification of styrene and  $\alpha$ -methyl styrene by using  $\text{PdCl}_2$  as the catalyst and (-)-DIOP as the chiral inducing ligand at room temperature, but at very high pressures (30–35 MPa). Thus (+)(S)-isopropyl-3-phenylbutanoate was obtained in approximately 80% yield (14 % optical purity) and (+)(S)-ethyl hydratropate with 68% yield (2.3 % optical purity) for the hydroesterification of  $\alpha$ -methylstyrene and styrene

respectively. The catalytic activity under these conditions was found to be very low (1.5–3.25 h<sup>-1</sup>). In this system the optical purity was influenced strongly by the alcohol as well as the solvent used. An optical purity of 19.3% was observed with *tert*-butanol, which was further increased in benzene as a solvent for the hydroesterification of  $\alpha$ -methyl styrene at 373 K and 40 MPa pressure. A maximum optical purity of 58.6 % was obtained at a DIOP/Pd ratio of 0.4. Addition of small amount of PPh<sub>3</sub> was found to improve the catalytic activity.<sup>107</sup> Hayashi *et. al.*<sup>108</sup> have studied the asymmetric hydroesterification of  $\alpha$ -methylstyrene using the chiral ligands **12**, **13** and **14** by using Pd(Cl<sub>2</sub>(PhCN)<sub>2</sub>) as the catalyst precursor.

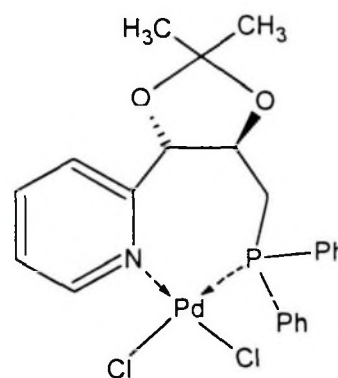


**12a** and **13a** were more effective chiral ligands than **12b** and **13b** and always the S enantiomer of the product was obtained. Maximum optical yield of 44% was observed under 25 MPa of pressure and at 373 K. Very high CO pressures (e.g. 70 MPa) were needed for achieving higher optical yields when **13b** was used. **14a** gave lower optical purity with opposite configuration. In all these cases very low catalytic activity (0.8–3.4 h<sup>-1</sup>) was observed. Deactivation of the catalyst through precipitation of palladium metal was also observed in most of the cases and chloride additives such as LiCl, Bu<sub>4</sub>NCl, etc., were found to prevent the catalyst loss by precipitation of Pd metal as well as to improve the conversion without very much affecting the optical purity. Hydroesterification of styrene to produce esters using PdCl<sub>2</sub>(PhCN)<sub>2</sub>-**13a** system as a catalyst proceeded with higher rates (42 h<sup>-1</sup>) compared to  $\alpha$ -methylstyrene, but only 16 % optical purity was observed.<sup>109</sup>

Most of these earlier reports required high pressure (25-70 MPa) conditions to achieve the desired selectivity. Alper and Hamel<sup>110</sup> reported an efficient catalyst system,

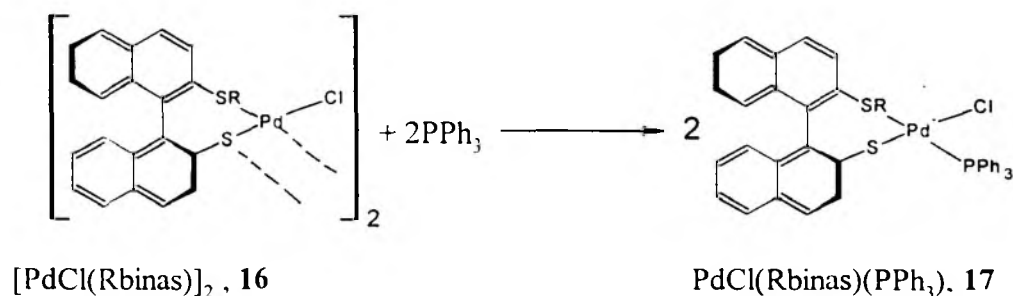
which gave very high enantioselectivities for S-Ibuprofen and S-Naproxen by the hydrocarboxylation of corresponding vinyl aromatic compounds at room temperature and atmospheric pressures. The catalyst system consisted of PdCl<sub>2</sub>, CuCl<sub>2</sub>, HCl and oxygen in the presence of a chiral ligand (R)-(-)- or (S)-(+)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (BNPPA). Up to 84% and 91% optical purities were reported for the carbonylation of *p*-isobutylstyrene and 2-vinyl-6-methoxynaphthalene respectively, but the catalytic activity was very low (~0.39 h<sup>-1</sup>). Under similar conditions, D-menthol gave 94 % yield to ibuprofen, but with a very low optical purity of 2 %. Other chiral ligands such as L-menthol, (R)-1,1'-bi-2-naphthol, D-diethyl tartrate and (S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl were found to be inferior to BNPPA and afforded acids in <10 % optical yield. In another study, Hiyama *et. al.*<sup>111</sup> have reported that the use of 1-menthyldiphenylphosphine (MDPP) allowed the hydroesterification of 2-vinyl-6-methoxynaphthalene to proceed under lower operating conditions of 323 K and 2 MPa pressure with 12 % selectivity to (R)-enantiomer.

Another palladium complex, **15**, with the chiral phosphine PYDIPHOS, (-)-(4S,5R)-4-(2-Pyridyl)-5-(diphenylphosphino)-methyl-2,2-dimethyl-1,3-dioxolane, was reported to give >90% chemoselectivity to ethyl-2-phenyl propionate in the hydroesterification of styrene with an optical purity of 20% for the S isomer.<sup>112</sup> No rate data and details of reaction conditions were available for this system.



(PYDIPHOS)PdCl<sub>2</sub>, **15**

In a very recent report, up to 89 % selectivity to 2-phenylpropionic acid was claimed at 373 K and 3 MPa pressure by using palladium complexes with thiol-thioether atropisomeric ligands such as di-[chloro(2-thiol-2'-(methylthioether)-1,1'-binaphthyl)palladium(II)], [PdCl(Mebinas)]<sub>2</sub>, and di-[chloro(2-thiol-2'-isopropylthioether)-1,1'-binaphthyl)palladium(II)], [PdCl('Prbinas)]<sub>2</sub> in dioxane as a solvent and oxalic acid as a promoter.<sup>113</sup> A maximum TOF of 2.5 h<sup>-1</sup> was reported with [PdCl('Prbinas)]<sub>2</sub> as the catalyst precursor. Addition of small amounts of PPh<sub>3</sub> was found to be necessary for the catalytic activity. It was reported that PPh<sub>3</sub> dissociates the dimer, **16**, to form the monomeric species PdCl(Rbinas)(PPh<sub>3</sub>),



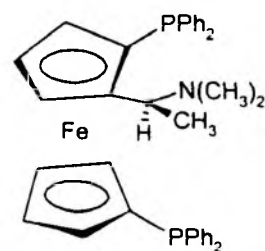
R = Me or <sup>i</sup>Pr

Scheme 4

17. The pre-prepared complex 17 gave higher selectivity (97%) to the branched product, but with lower conversions. No optical purity data was reported for this system.

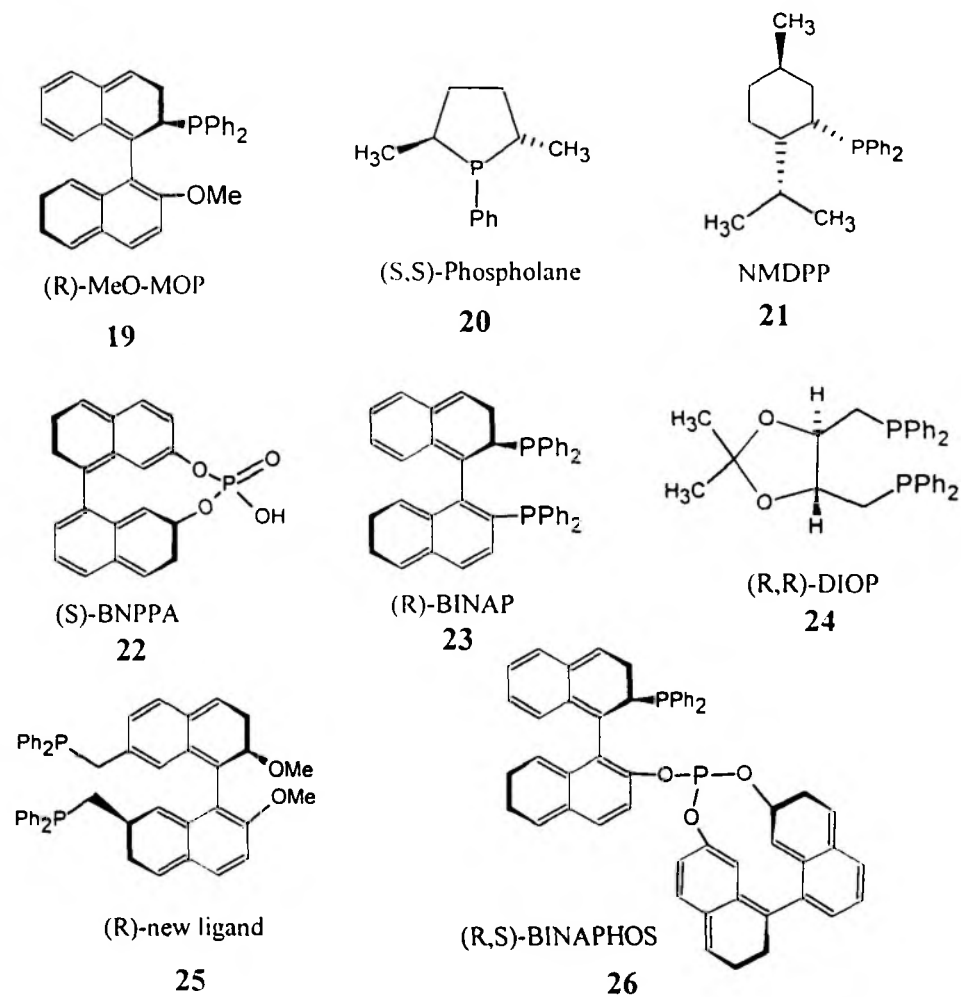
Oi *et. al.*<sup>88</sup> also studied the effects of several chiral phosphines for the asymmetric carbonylation of styrene using Pd(OAc)<sub>2</sub> as a catalyst along with TsOH as a promoter. It was found that a ferrocene containing aminophosphine, (S)-(R)-BPPFA, (S)-1[(R)-1',2-bis(diphenylphosphino)ferrocenyl]ethyl-dimethylamine] provided a high asymmetric induction of 86% *ee* (S) with a selectivity of 44% to the branched ester at room temperature and 2 MPa CO in methanol. An optical yield of 53% to the branched (S) ester of Naproxen was also reported for the carbonylation of 6-methoxy-2-vinylnaphthalene with the same catalyst system.

A heterogeneous palladium system consisting of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> anchored on montmorillonite along with various chiral phosphines (19-26) was also reported to give optically pure 2-aryl propionic acid esters by the hydroesterification of styrene at 4.5 MPa pressure and 393 K in benzene as a solvent.<sup>114</sup> Nearly 100% selectivity to the branched product was observed with mono phosphines (19, 21) as the ligand, but with very poor optical yield (1.5–5.0 % *ee* for S). The configuration was reversed in the case of 19 with 2.4 % *ee*. Both branched and the linear products were formed in almost similar yields with (R)-BINAP and (R,R)-DIOP as the ligands. The new



(S)-(R)-BPPFA, 18

ligand **25** showed a maximum optical purity of 12 % with 100% selectivity to the branched isomer. (R,S)-BINAPHOS, **26**, gave both branched and the linear product (86:14), with an optical purity of 6 %. Recycle of the catalyst showed the same selectivity, but with a lower



activity. Complete precipitation of palladium metal was reported when water was used instead of alcohol as a reaction medium. HCl was found to be the best promoter for this system, while other acidic promoters were found to be inactive.

Table 1.2. Literature on carbonylation of vinyl aromatics to saturated monocarboxylic acids<sup>a</sup>/esters<sup>b</sup>

No.	Catalyst system	Substrate	Reaction conditions			Conv. %	Selectivity, %		Reference
			T, K	P <sub>CO</sub> , MPa	Others		iso	linear	
1.	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> /HCl	styrene	363	30-70	in ethanol	-	65-95 <sup>b</sup>	-	Bittler <i>et. al.</i> (1968) <sup>33</sup>
2.	PdCl <sub>2</sub> /(-)DIOP	styrene, α-methyl styrene	373	28-70	in alcohol-benzene; time, 5-117 h	50-95	-	45-80 <sup>b</sup> (7-14% S)	Boiteghi <i>et. al.</i> (1973) <sup>106</sup> ; Consiglio and Pino (1976) <sup>107b</sup> ; Consiglio (1977) <sup>107a</sup>
3.	PdPPh <sub>2</sub> (CH <sub>2</sub> ) <sub>4</sub> PPh <sub>2</sub> Cl <sub>2</sub>	styrene	373	10-50	in ethanol; 16 h	30-100	9-88 <sup>b</sup>	7-65 <sup>b</sup>	Sugi <i>et. al.</i> (1975) <sup>75</sup>
4.	PdPPh <sub>2</sub> (CH <sub>2</sub> ) <sub>n</sub> PPh <sub>2</sub> Cl <sub>2</sub> n = 1-6, 10	styrene	398	20	in ethanol-benzene; 16h	45-100	12-88 <sup>b</sup>	5-67 <sup>b</sup>	Sugi <i>et. al.</i> (1976) <sup>76</sup>
5.	PdCl <sub>2</sub> +PPh <sub>3</sub> /DIOP/ PPh <sub>2</sub> (neomenthyl)	styrene, α-methyl styrene	373	38-72	in alcohol-benzene	-	1-100 <sup>b</sup>	1-100 <sup>b</sup>	Consiglio and Marchetti (1976) <sup>77</sup>
6.	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> /Ph <sub>2</sub> NNO	2-vinyl-6-methoxy-naphthalene	-	-	in EtOH/BF <sub>3</sub> -Et <sub>2</sub> O	-	69 <sup>b</sup>	-	Takeda <i>et. al.</i> (1977) <sup>115</sup>
7.	PdCl <sub>2</sub> (PhCN) <sub>2</sub> /chiral ligands	α-methyl styrene	373	22-24	in isopropyl alcohol; 17-162 h	27-83	-	74-99 <sup>b</sup> (7-44% S)	Hayashi <i>et. al.</i> (1978) <sup>108</sup> , (1984) <sup>109</sup>

8.	Pd(dba) <sub>2</sub> /(+neomenthylidiphenylphosphine)	styrene; 2-vinyl-6-methoxynaphthalene	293-353	0.1-0.2	in trifluoroacetic acid-methanol; 4h	-	94 <sup>b</sup> (42-52% S)	6 <sup>b</sup>	Cometti and Chiusoli, <sup>92</sup> (1982), (1983) (1984)
9.	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> /SnCl <sub>2</sub>	pentafluorostyrene	373-398	7-12	in methanol-acetone; 24-60 h	9-92	22-79 <sup>b</sup>	21-78 <sup>b</sup>	Fuchikami <i>et. al.</i> (1983) <sup>116</sup>
10.	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> /HCl + m-ClC <sub>6</sub> H <sub>4</sub> C(O)OOH	p-isobutylstyrene	358	2-4	in water-dioxane; 6 h	-	90 <sup>a</sup>	-	Mitsubishi (1984) <sup>117</sup>
11.	Co <sub>2</sub> (CO) <sub>8</sub> /pyridine	styrene	373-423	5	in methanol	40-100	-	25-79 <sup>b</sup>	Zhigao and Zilin (1986) <sup>118</sup>
12.	Pd(II)complex/HCl	p-isobutylstyrene	373	30	in benzene	-	78 <sup>a</sup>	-	Shimizu <i>et. al.</i> <sup>90</sup> (1987) (1992), (1993)
13.	PdCl <sub>2</sub> /HCl/CuCl <sub>2</sub> /O <sub>2</sub>	p-methylstyrene	R.T	0.1	in formate ester-dioxane; 24-95 h	-	90-92 <sup>b</sup>	7 <sup>b</sup>	Mlekuz <i>et. al.</i> (1987) <sup>81</sup>
14.	PdCl <sub>2</sub>	styrene	313	0.1	electrochemical reaction in methanol/LiCl; 16-20 h	75	67 <sup>b</sup>	33 <sup>b</sup>	Wayner and Hartstock (1988) <sup>119</sup>
15.	PdO/HCl/PPPh <sub>3</sub> /ZnO	aryl ethylenes	363	7.5	in methanol	93	98 <sup>b</sup>	2 <sup>b</sup>	Shimizu and Nomura (1988) <sup>120</sup>

16.	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> / SnCl <sub>2</sub>	styrene	368-393	2	in dioxane	Kinetic and mechanistic studies			Noskov <i>et. al.</i> (1989-1997) <sup>78</sup>
17.	Pd(PPh <sub>3</sub> ) <sub>4</sub> or Pd(dba) <sub>2</sub> /dppb	substituted styrenes	423	8.2	in formate ester-toluene; 48-72h	6.6-96 <sup>b</sup>	5-96 <sup>b</sup>	Lin and Alper (1989) <sup>83</sup>	
18.	PdCl <sub>2</sub> /CuCl <sub>2</sub> /HCl/BNPPA	<i>p</i> -isobutyl styrene, 2-vinyl-6-methoxy naphthalene	R.T	0.1	in H <sub>2</sub> O-THF; 18 h	46-89 <sup>a</sup> (55-91% S)	-	Alper and Hamel (1990) <sup>110</sup>	
19.	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	<i>p</i> -isobutylstyrene	393	30	in toluene-10% aq.HCl	100	89 <sup>a</sup>	Shimizu <i>et. al.</i> (1990) <sup>121</sup>	
20.	PdCl <sub>2</sub> (c-C <sub>6</sub> H <sub>11</sub> PPh <sub>2</sub> ) <sub>2</sub>	2-vinyl-6-methoxy naphthalene	373	2-6	in alcohol-Me <sub>2</sub> CO/THF	73-100	1.6-5 <sup>b</sup>	Hiyama <i>et. al.</i> (1991) <sup>111</sup>	
20.	Fe(CO) <sub>5</sub> /OH <sup>-</sup>	styrene	328	0.1	in water/ <i>i</i> -propanol; 96h	>96 <sup>a</sup>	2-3 <sup>a</sup>	Brunet <i>et. al.</i> (1993) <sup>94</sup>	
21.	Pd(OAc) <sub>2</sub> /dppb/PPh <sub>3</sub> /oxalic acid	styrene and substituted styrenes	423	2	in dimethoxy ethane	35-90	78-86 <sup>b</sup>	Ali and Alper (1991) <sup>22b</sup> (1992) <sup>84</sup>	



22.	Pd- C/dppb/PPh <sub>3</sub> /formic acid or oxalic acid	styrene and substituted styrenes	423	0.68-4	in dimethoxy ethane; 24 h	65-80	10-24 <sup>a</sup>	68- 90 <sup>a</sup>	Ali <i>et. al.</i> (1993) <sup>86</sup>
23.	PdCl <sub>2</sub> /CuCl <sub>2</sub> /PPh <sub>3</sub> /HC l	4-isobutyl styrene	323	3.4	in water- THF; 10 h	90-95	96 <sup>a</sup>	-	Wu <sup>91a,b</sup>
24.	PdCl <sub>2</sub> /CuCl <sub>2</sub> /neoment hydridiphenylphosphine/ HCl	4-isobutyl styrene	373	4.8	in water- THF; 10 h	100	100 <sup>a</sup>	-	Wu <sup>91c</sup>
25.	PdCl <sub>2</sub> (PYDIPHOS)	styrene	-	-	in ethanol- benzene	-	> 90 <sup>b</sup> (20% S)	-	Chelucci <i>et. al.</i> (1994) <sup>112</sup>
26.	(C <sub>7</sub> H <sub>7</sub> ) <sub>3</sub> Pd(H)(H <sub>2</sub> O)]BF 4 <sup>-</sup> /dppb/TsOH	styrene and substituted styrenes	373	2	in methanol- THF; 48h	-	12-23 <sup>b</sup>	77 - 88 <sup>b</sup>	Huh and Alper (1994) <sup>89</sup>
27.	Pd(OAc) <sub>2</sub> - Montmorillonite- PPh <sub>3</sub> /HCl	styrene and substituted styrenes	398	4	in methanol- benzene; 24 h	88-100	100 <sup>b</sup>	-	Lee and Alper (1995) <sup>85</sup>
28.	Pd(OAc) <sub>2</sub> /PPh <sub>2</sub> CH <sub>2</sub> C OOH/TsOH	styrene	403	4	in ethanol; 6 h	53	7.6 <sup>b</sup>	38 <sup>b</sup>	Hongying <i>et. al.</i> (1996) <sup>87</sup>
29.	Montmorillonite- diphenylphosphine PdCl <sub>2</sub> /Ligand/HCl	styrene	393	4.5	in methanol- benzene; 24 h	-	50- 100 <sup>b</sup>	2- 50 <sup>b</sup>	Nozaki <i>et. al.</i> (1997) <sup>114</sup>
30.	PdCl <sub>2</sub> /TPPTS/TsOH	styrene and p-isobutyl styrene	338	5-14	in water; 6 h	62-100	56-90 <sup>a</sup>	10 - 33 <sup>a</sup>	Papadagianakis <i>et.</i> <i>al.</i> (1997) <sup>99</sup>

31.	$\text{Pd}(\text{MeCN})_2(\text{PPh}_3)_2$ [(B) $\text{F}_4$ ] <sub>2</sub>	styrene	303– 353	0.5 to 2	in methanol; 4 h	21-94	27–83 <sup>b</sup>	17– 74 <sup>b</sup>	Oi <i>et. al.</i> (1997) <sup>88</sup>
32.	$\text{Pd}(\text{OAc})_2$ / $\text{PPh}_3$ /TsOH or $\text{CF}_3\text{SO}_3\text{H}$	styrene and p-isobutyl styrene	R.T– 323	2	in methanol; 4 h	19-95	75–96 <sup>b</sup>	4–25 <sup>b</sup>	Oi <i>et. al.</i> (1997) <sup>88</sup>
33.	$\text{Pd}(\text{OAc})_2$ / Chiral phosphine/TsOH	styrene, 2- vinyl-6- methoxy naphthalene	R.T	1	in methanol; 20h	17-42	31–44 <sup>b</sup> (10– 86% S)	40– 70	Oi <i>et. al.</i> (1997) <sup>88</sup>
34.	$\text{PdCl}_2$ /TPPTS/HCl, $\text{H}_2\text{SO}_4$ or $\text{CH}_3\text{SO}_3\text{H}$	styrene, 4- methyl styrene and 2,4-dimethyl styrene	373	5	in toluene- water; 6 h	15-98	50–60 <sup>a</sup>	40– 50 <sup>a</sup>	Tilloy <i>et. al.</i> (1997) <sup>100</sup> , Bertoux <i>et. al.</i> (1999) <sup>101</sup> , (1999) <sup>102</sup> ,
35.	[Pd(2,7-bis( $\text{SO}_3\text{Na}$ )- Xanthos)]. $(\text{CH}_3\text{CN})_x(\text{OTs}^-)_2$ / TsOH	styrene	343– 368	3	in water; 3 h	-	35 <sup>a</sup>	65 <sup>a</sup>	Goedheijt <i>et. al.</i> (1998) <sup>103</sup>
36.	$\text{PdCl}_2$ /CuCl <sub>2</sub> /PPH <sub>3</sub> / HCl	4-methyl styrene	373	4	in water- THF; 6 h	29	85 <sup>b</sup>	-	Yoon <i>et. al.</i> (1997) <sup>82</sup>
37.	PVP-PdCl <sub>2</sub> -NiCl <sub>2</sub> - PPh <sub>3</sub>	styrene	353	2	in methanol- benzene; 10- 36 h	79–100	91–99 <sup>b</sup>	1-8 <sup>b</sup>	Wan <i>et. al.</i> (1998) <sup>95</sup>

38.	$\text{PdCl}_2(\text{PhCN})_2$ /p-tert-butyl-calix[4]arene based phosphines and phosphinite	styrene	403	14	in methanol-toluene; 48-140 h	39-70	47-62 <sup>b</sup>	-	Csok <i>et. al.</i> (1998) <sup>98</sup>
39.	$\text{PdCl}_2$ -ferrocene based catalysts	styrene	383	13	in methanol-toluene; 180-450 h	50-100	28 <sup>b</sup>	-	Jedlicka <i>et. al.</i> (1998) <sup>96</sup>
40.	$\text{PdCl}_2(\text{PPh}_3)_2/\text{SnCl}_2$	styrene, $\alpha$ -methyl styrene	403	4	in alcohol-toluene	Mechanistic studies			Benedek <i>et. al.</i> (1999) <sup>122</sup>
41.	$\text{PdCl}(\text{Mebinas})(\text{PPh}_3)$ or $[\text{PdCl}(\text{Mebinas})]_2/\text{nPR}_3/\text{oxalic acid}$	styrene	373	3	in dimethoxy ethane	25-90	74-97 <sup>a</sup>	3-26 <sup>a</sup>	Ruiz <i>et. al.</i> (1999) <sup>113</sup>

#### 1.2.1.2.3. Copolymerization of olefins with CO to form polyketones

Alternating copolymerization of olefin with CO has gained a considerable attention over the last two decades,<sup>123</sup> as the product polyketones produced possess interesting engineering plastic properties. The main attention was focused on aliphatic polyketones because of the low cost and easy availability of the monomers such as ethylene, propylene and CO. The discovery of highly active palladium catalysts for ethylene and CO copolymerization lead this process to a commercial reality.<sup>124</sup>

Free radical copolymerization of ethylene and CO under high pressures (50-150 MPa) was known since late 1940<sup>125</sup> and the metal catalyzed alternating copolymerization of ethylene and CO was first demonstrated by Reppe and Magin in 1951.<sup>126</sup>  $K_2Ni(CN)_2$  was used as the catalyst in water as a solvent, which produced low-melting oligomers along with diethyl ketone and propionic acid. Reports on improved nickel catalysts were followed, which consists of strong acids in solvents such as hexafluoroisopropanol<sup>127</sup> as well as with bidentate anionic phosphorous-oxygen compounds as ligands.<sup>128</sup> Gough at ICI reported the first catalyst based on palladium complex in 1967,<sup>129</sup> but the polymer was produced with relatively lower rate under drastic conditions of 523 K and 200 MPa pressure. The discovery of cationic palladium complexes as effective catalysts under mild conditions by Sen *et. al.*<sup>130</sup> helped to evolve a new technology for polyketones. Bis(triphenylphosphine)palladium tetrafluoroborate was used as the catalyst in aprotic solvents under mild conditions. However, the reaction rate as well as the molecular weight of the polymer formed was very low. A remarkable advancement in catalyst performance was achieved by Shell<sup>131</sup> by the replacement of monodentate phosphine ligand by bidentate phosphine ligands, which lead to high molecular weight polyketones at very high reaction rates (~6000 g/g/h) under economically attractive and mild reaction conditions (358 K and 4.5 MPa). This new cationic palladium catalyst having the combined effect of bidentate ligands and weakly coordinating anions have not only opened the way to efficient and economically attractive production of polyketones but also provided much more stable polymers with catalyst residues measured only in parts per million rather than percentages. The main role of bidentate ligands is in providing *cis* configuration for the growing chain,

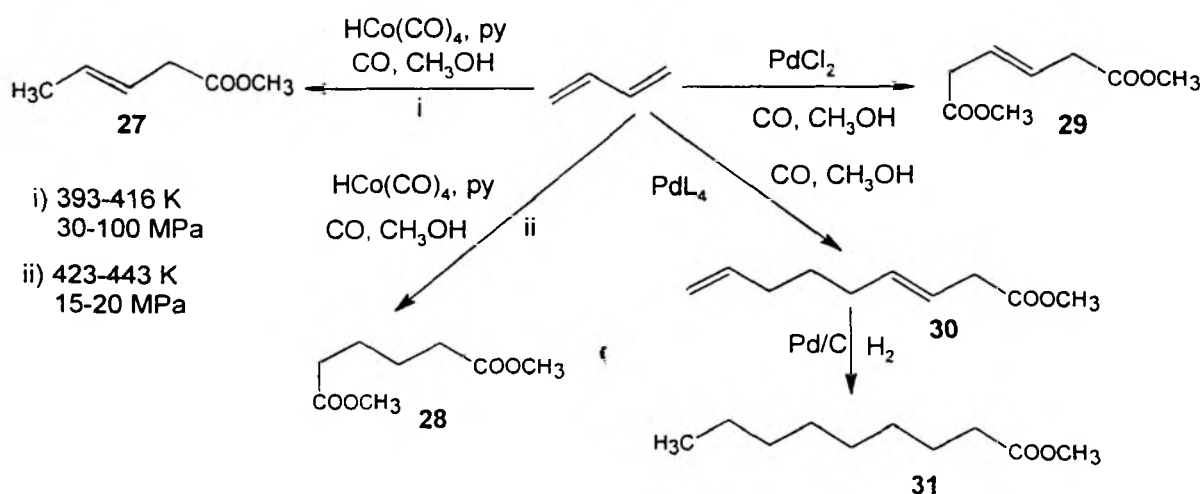
whereas, in the case of monodentate ligands *trans* configuration can predominate, which forms the carboxylic acid/ester easily.<sup>132</sup> Water soluble palladium complexes with sulphonated dppp<sup>133</sup> and 1-10 phenanthroline<sup>133a</sup> derivatives were also reported as efficient catalysts. Recently, kinetics of copolymerization using [(dppp)Pd(H<sub>2</sub>O)(TsOH)]TsOH as the catalyst was reported in which several rate equations were proposed based on different hypothesis on the propagation steps.<sup>134</sup>

Rhodium carbonyls were also reported as catalysts for alternating copolymerization of ethylene and CO in the early 70's,<sup>135</sup> but activity and yield as well as molecular weight was very low. Rhodium phosphine complexes such as HRh(CO)(PPh<sub>3</sub>)<sub>3</sub>, ClRh(CO)(PPh<sub>3</sub>)<sub>2</sub>, etc., were also reported as catalysts.<sup>136</sup>

Recent advancement in polyketone chemistry is its application to higher aliphatic olefins and vinyl aromatics. The copolymerization of styrene with CO was reported to proceed efficiently with palladium complexes of bidentate nitrogen ligands such as 2,2'-bipyridine, 1,10-phenanthroline, etc., and weakly or noncoordinating anions in methanol as a solvent in the presence of an oxidizer.<sup>137</sup> The polymer chain was generated by a net oxidative carbonylation, with quinone as the oxidant, which gets converted to hydroquinone depending on the end groups of the polymer chain. In the absence of oxidants, polymer formation was strongly reduced. The mechanism of these reactions is believed to be initiated by palladium methoxy species and propagation occurs by alternate insertion of styrene into Pd-acyl and CO into Pd-alkyl bonds in a perfect alternating fashion. The main termination mechanism proposed was the  $\beta$ -elimination, which produces a transient palladium hydride and the oxidant reoxidise this to a Pd-methoxy complex before it can decompose to Pd metal. The powerful negative effect of hydrogen on the catalytic activity also gave strong support to the carbomethoxy mechanism. Recently, several publications<sup>138,139</sup> on the mechanism of copolymerisation of olefins with CO have appeared in the literature. Another important finding in the field of copolymerisation of CO and olefins is the formation of polyspiroketal (isomeric with polyketones) under certain operating conditions.<sup>140</sup>

### 1.2.1.3. Carbonylation of dienes

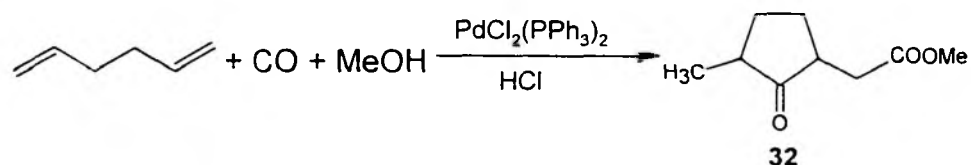
Carbonylation of dienes usually produces a variety of products, and is generally catalyzed by cobalt or palladium complexes. Butadiene, readily available from petroleum source, produces unsaturated monoester **27** and saturated diester **28** with cobalt catalysts or unsaturated diester **29** and dimer carbonylated monoesters **30** with palladium catalysts depending on the reaction conditions used as shown in scheme 1.5.



Scheme 1.5. Carbonylation of butadiene

A halide free palladium complex is generally used to produce 3,8-nonadienoate esters (**30**),<sup>141</sup> hydrogenation of which produces pelargonic acid (**31**). One of the important industrial applications of carbonylation of butadiene is the synthesis of adipic acid commercialized by BASF.<sup>31n,142</sup> This process involves two stages and both utilizes cobalt as a catalyst. In the first stage a fairly high concentration of  $\text{HCo(CO)}_4$  and pyridine is used to ensure rapid carbonylation to give methyl-pent-3-enoate in 90% selectivity. In the second step, the concentration of pyridine has to be kept minimum, since it has an inhibitory effect on the hydroesterification. Dimethyl adipate was obtained in 80% selectivity at slightly higher temperatures compared to the first step (Scheme 1.5).

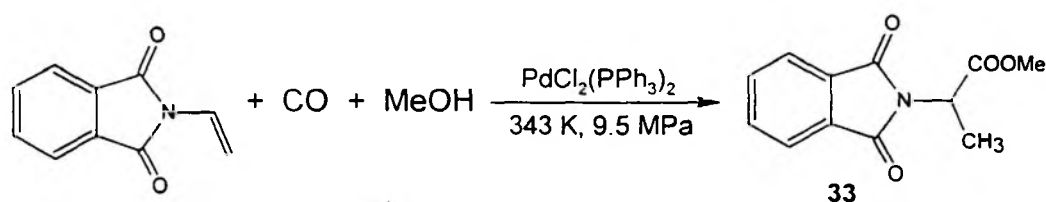
Reactions of nonconjugated dienes such as 1,4-pentadiene and 1,5-pentadiene with CO yield cyclopentanones (**32**),<sup>143</sup> while 1,6-pentadiene gave only traces of ketone.



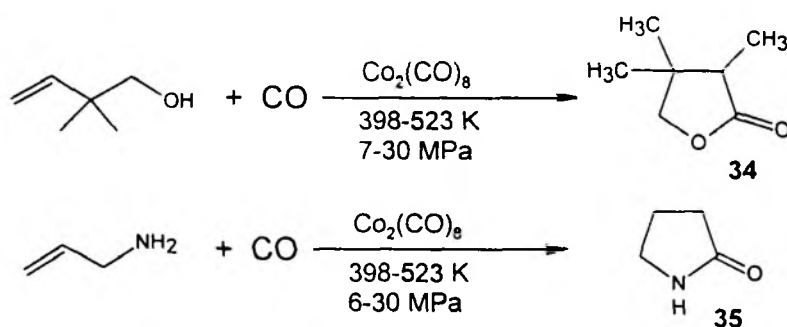
Carbonylation of cycloocta-1,5-diene was reported at 10 MPa pressure and 380 K with a mixed Pd-Fe catalyst **7** as shown in Section 1.2.1.2.2.1.

#### 1.2.1.4. Carbonylation of functionalized olefins

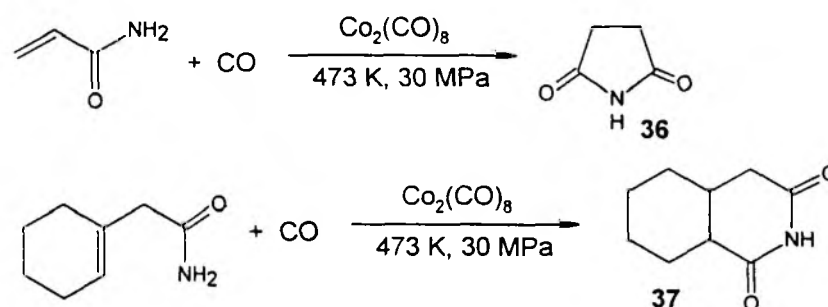
Carbonylation of functionalized olefins produces a variety of products. For example N-vinylphthalimide gave the  $\alpha$ -amino acid derivative, **33**, with 70% yield using  $\text{PdCl}_2(\text{PPh}_3)_2$  as a catalyst.<sup>144</sup>



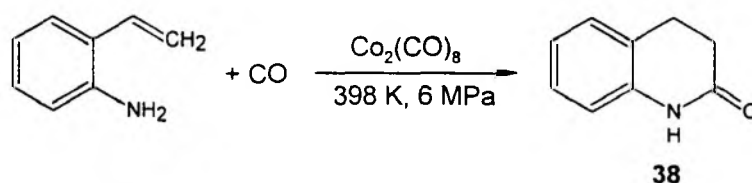
Lactones and lactams are formed when the olefin contains alcohol or amine as a functionality.<sup>145</sup> For example, 2,2-dimethyl-3-butene-1-ol was carbonylated to 2,3,3-trimethyl- $\gamma$ -butyrolactone, **34**, using cobalt or rhodium catalysts.<sup>146</sup> Similarly 2-pyrrolidinone, **35**, was produced from allylamine<sup>147</sup>.



Using  $\text{Co}_2(\text{CO})_8$  as a catalyst at 10–30 MPa and 423–573 K,  $\alpha,\beta$ -unsaturated amides gave five membered imides (**36**) on carbonylation.<sup>148</sup> Similarly  $\beta,\gamma$ -unsaturated amides produced glutarimides (**37**).



This reaction can also be applied to aromatic amines as exemplified by the carbonylation of *o*-aminostyrene to produce **38**<sup>149</sup>.



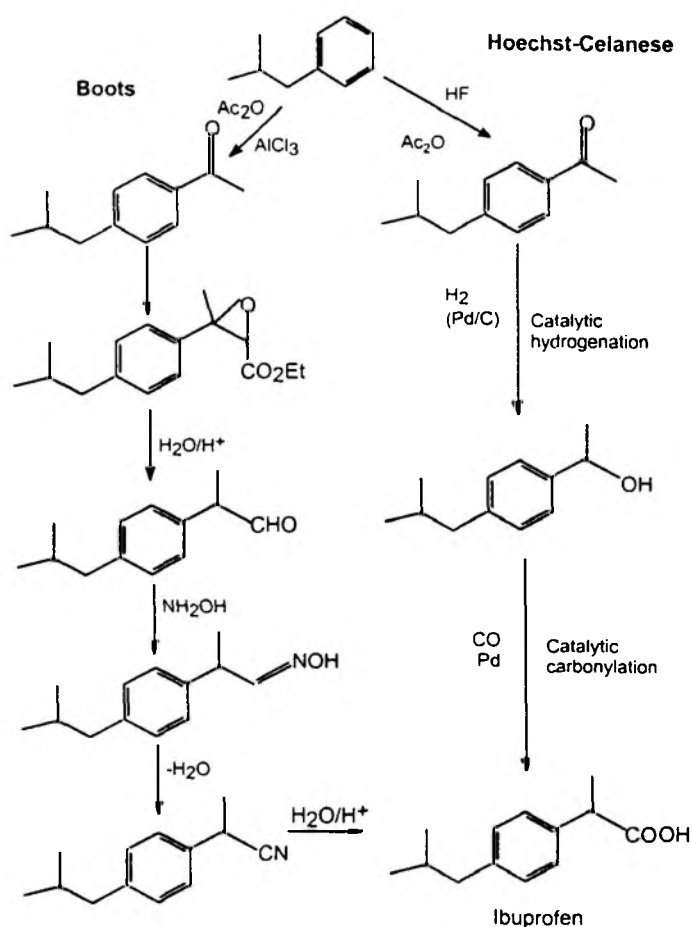
### 1.2.2. Carbonylation of alcohols

Carbonylation of alcohols, and of methanol in particular, perhaps provided the most significant industrial development in homogeneous catalysis. Co, Rh, Ir, Ni, Pd etc., were reported to be active along with iodide promoters and the reaction conditions depend on the metal compound used as the catalyst. Carbonylation of a variety of primary and secondary alcohols was reported and this subject was reviewed several times.<sup>1,2,3,150</sup> Since a part of the present work is mainly confined to the carbonylation of arylethanols to 2-aryl propionic acids, a review of the literature on the carbonylation of aryl ethanols to 2-arylpropionic acids/esters is briefly described in the following section and also is presented in Table 1.3.



### 1.2.2.1. Carbonylation of aryl alcohols

Carbonylation of aryl alcohols, especially 1-arylethanol is of great interest because of its industrial application for the synthesis of 2-arylpropionic acids. This has been first demonstrated by Hoechst Celanese Corporation for the synthesis of Ibuprofen on a commercial scale by carbonylation of 1-(4-isobutylphenyl)ethanol (IBPE). This process is an excellent example of a successful commercialization of an environmentally benign<sup>151</sup> three-step catalytic process (Hoechst Celanese Process) as an



alternative for the six step stoichiometric organic synthetic process (Boots process). In the Boots route, a large amount of waste by-products consisting of inorganic salts are produced, which are difficult to process or dispose. The catalytic process in which carbonylation of IBPE is an important step was commercialized in 1992 by BHC at Texas with a plant capacity of 3,500 TPA.<sup>18</sup> In the carbonylation step  $\text{PdCl}_2(\text{PPh}_3)_2$  or  $\text{PdCl}_2$  in presence of  $\text{PPh}_3$  was used as the catalyst in a biphasic medium consisting methyl ethyl ketone (MEK) as the organic phase and 10% aqueous  $\text{HCl}$  as the promoter at 5–35 MPa pressure and 403 K.<sup>152</sup> High selectivity to Ibuprofen was obtained at high  $\text{CO}$  pressures of 16–35 MPa. Most of the earlier literature on this subject was patented and from the available literature it was observed that the reaction rate ( $45 \text{ h}^{-1}$ ) as well as the selectivity (69 %) to Ibuprofen was very low at moderate reaction conditions of 6.8 MPa and 403

K.<sup>153</sup> Rate was affected only marginally with pressure. Higher reaction rate (TOF = 75–125 h<sup>-1</sup>) was obtained when using an IBPE/Pd ratio of 15,050–30,100 at 10–16 MPa.<sup>154</sup> The aqueous phase can be recycled several times and the catalyst was separated from the reaction mixture by adding a noncoordinating solvent.<sup>155</sup>

Besides palladium, rhodium catalysts such as Rh-halides and [Rh(CO)<sub>2</sub>Cl<sub>2</sub>]<sub>2</sub> along with phosphines and an iodide promoter were also reported for the carbonylation of IBPE. Thus a selectivity of 86 % to Ibuprofen was reported at 3–6 MPa of CO and 0.1–1 MPa of hydrogen and 360–450 K.<sup>156</sup> Nickel compounds were also found to be active along with phosphines and iodide or bromide promoters. With NiI<sub>2</sub>/PPh<sub>3</sub>/MeI as a catalyst, 80–87% selectivity to Ibuprofen was reported at 10 MPa pressure and 443 K.<sup>157</sup> In a recent report, more than 90% selectivity to Ibuprofen was reported at mild reaction conditions of 6.8 MPa pressure and 403 K by using PdCl<sub>2</sub>/PPh<sub>3</sub> as the catalyst along with CuCl<sub>2</sub> and acidic promoters like HCl and H<sub>2</sub>SO<sub>4</sub>,<sup>158</sup> but with low reaction rates (TOF  $\square$  25 h<sup>-1</sup>). Similarly 1-(6-methoxy-2-naphthyl)ethanol was carboxylated to methyl esters of Naproxen under 6 MPa of CO at 373 K in the presence of TsOH instead of inorganic acid promoters.<sup>159</sup> Nearly 100% selectivity was claimed at a TsOH/Pd ratio of 13.1, but the catalytic activity was very low (TOF = 2.1 h<sup>-1</sup>). Very recently, Xie *et. al.*, reported the asymmetric carbonylation of 1-(6-methoxy-2-naphthyl)ethanol to methyl ester of (S) naproxen by using PdCl<sub>2</sub>-CuCl<sub>2</sub> as a catalyst in the presence of 1,4,3,6-dianhydro-2,4-dioxo-2,5-bis(diphenylphosphino)-L-idoitol (DDPPI) as a ligand. In this case a chemical yield of 90% and an optical yield of 81% *ee* was obtained at 373 K and 8 MPa CO pressure in methyl ethyl ketone as a solvent.<sup>160</sup>

Papadogianakis *et. al.*<sup>161</sup> have reported the biphasic carbonylation of IBPE using water soluble Pd(TPPTS)<sub>3</sub> catalyst along with acidic promoters such as TsOH and HCl at 5 MPa pressure and 363 K to produce Ibuprofen in 52–62% selectivity.<sup>162</sup> A maximum selectivity of 82 % was obtained at very high pressures of 10–15 MPa, but with very low catalytic activity (TOF = 2.3–3 h<sup>-1</sup>). A heterogeneous catalyst system consisting supported Pd in the presence of phosphine ligands together with HCl as the promoter was also reported to give Ibuprofen in 23–77 % selectivity at 4 MPa pressure and 398 K.<sup>163</sup> The

selectivity was increased (up to 97%) when silyl ligands were used together with the Pd-montmorillonite catalyst, but the catalytic activity was found to be very low (3–10 h<sup>-1</sup>).

Other patent literature includes that of Mitsubishi petrochemicals<sup>164</sup>, Ferrel International Societe Annonium<sup>165</sup>, Daicel Chemical Industries<sup>166</sup> as summarized in Table 1.3.

### 1.2.3. Carbonylation of 1-aryl halides

The carbonylation of alcohols were generally reported to proceed through the initial formation of corresponding haloderivative as the active substrate, which take part in the carbonylation cycle. Several patents were appeared in the literature for the carbonylation of 1-(4-isobutylphenyl)ethyl chloride (IBPCI), the chloro derivative of IBPE. In the European patent EP 0338852<sup>167</sup> assigned to Hoechst Celanese Corporation, carbonylation of 1-(4-isobutylphenyl)ethyl chloride was reported under conditions similar to that of IBPE. With PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst, a selectivity of 65–74 % to Ibuprofen was obtained at 5.4 MPa of CO and 383–398 K. Similarly, Naproxen was produced with 42–52 % selectivity by the carbonylation of 1-(6-methoxy-2-naphthyl)ethyl chloride. Catalytic activity was found to be in the range of 25–130 h<sup>-1</sup> in both the cases. In another patent<sup>168</sup> assigned to Montedison, a cobalt catalyst was reported for the production of sodium salt of arylpropionic acids at atmospheric pressure and 273–303 K. Under these conditions a selectivity of 57.7 % and 71.9 % for Naproxen and Ibuprofen respectively were reported, but with much lower catalytic activity (TOF = 1–5 h<sup>-1</sup>). Formation of esters of 2-arylpropionic acids were also reported by Ethyl Corporation<sup>169</sup> and Rhone-Poulenc<sup>170</sup> by using a catalyst system similar to Hoechst-Celanese Corporation. Addition of CuCl<sub>2</sub> was reported to increase the branched isomer selectivity to 86–99 %.<sup>171</sup> Baird *et. al.*<sup>172</sup> have described the asymmetric synthesis of 2-arylproionic acids by carbonylation of optically active 1-arylethyl esters using PdCl<sub>2</sub>/PPh<sub>3</sub> at 393 K and 0.68 MPa pressure in the presence of sodium formate. Carbonylation of secondary benzyl halides was also reported in the presence of a base. With Co(CO)<sub>4</sub><sup>-</sup> as catalyst, of 1-aryl halides were carbonylated to 2-aryl propionic acids in the presence of bases such as NaOH, K<sub>2</sub>CO<sub>3</sub> etc.<sup>176</sup> Alcohols were found to be the best solvent for this system because of the high solubility of CO as well as

the bases. Carbonylation of secondary benzyl halides were also reported with complexes of cobalt as catalysts under phase transfer conditions. Thus carbonylation of substituted  $\alpha$ -bromo and  $\alpha$ -chloro phenylethane was reported with  $\text{Co}_2(\text{CO})_8$  as a catalyst in n-butanol/50%aqueous KOH in the presence of PTC such as phenyltrimethylammonium iodide at 308 K and atmospheric pressure.<sup>173</sup> In this case, the 2-arylpropionic acid selectivity was reported to be very low (35-50 %). Rhodium was also found to be active along with titanium and zirconium alkoxides under 348-373 K and atmospheric pressure.<sup>174</sup> Carbonylation of 1-methylbenzyl bromide using  $\text{Pd}(\text{dba})_2$  together with a variety of 2-substituted-3,1,2-oxazaphospholanes in an aq. NaOH/ $\text{CH}_2\text{Cl}_2$  system was reported to produce of 2-phenyl propionic acid with various enantiomeric excesses.<sup>175</sup>

Table 1.3. Literature on carbonylation of 1-arylethanol and 1-aryl halides to 2-aryl propionic acids<sup>a</sup>/esters<sup>b</sup>/salts<sup>c</sup>

No.	Catalyst system	Substrate	Reaction conditions			Conv.	Selectivity, %		Reference
			T, K	P <sub>CO</sub> MPa	Others		iso	linear	
1.	Co(CO) <sub>4</sub>	1-bromo-1-phenylethane	283-293	0.1	in NaOH-ethanol	-	77 <sup>c</sup>	-	Gardano <i>et. al.</i> (1985) <sup>168</sup>
2.	Co(CO) <sub>4</sub>	ArCH(R)X; R=CH <sub>3</sub> or C <sub>6</sub> H <sub>5</sub> ; X=Cl or Br	288-303	0.1	in NaOH-alcohol/PTC	-	20-80 <sup>c</sup>	0-10	Fractalanci <i>et. al.</i> (1985) <sup>176</sup>
3.	Pd(dba) <sub>2</sub> /2-substituted-3, 1,2-oxazaphospholanes (Chiral)	1-methylbenzyl bromide	281	0.1	CH <sub>2</sub> Cl <sub>2</sub> -aq. NaOH	-	10-65 <sup>a</sup>	-	Arzoumanian <i>et. al.</i> (1988) <sup>175</sup>
4.	Rh compound/Iodine compound [e.g. RhI <sub>2</sub> /I <sub>2</sub> ]	IBPE	403-453	3-6	in water-dioxane	-	86	14	Tanaka <i>et. al.</i> , (1988) <sup>156</sup> (1989) <sup>157</sup>
5.	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	IBPE	373-473	3.4-30	in aq. HCl-MEK	90-100	40-100 <sup>a</sup>	10-60 <sup>a</sup>	Elango <i>et. al.</i> (1990) <sup>152</sup> (1988, 1992) <sup>153</sup>
6.	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	IBPE, 1-(6-methoxy-2-naphthyl)ethyl chloride	373-473	3.4-30	in aq. HCl-acetophenone-MEK	99	25-72 <sup>a</sup>	-	Elango (1989) <sup>167</sup>

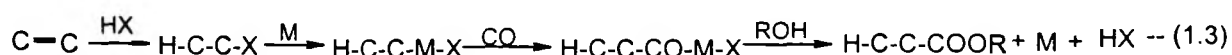
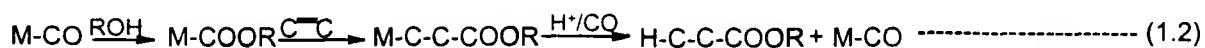
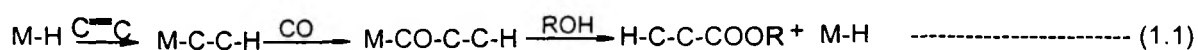
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7.	$\text{PdCl}_2(\text{PPh}_3)_2$	IBPE	373–473	3.4–30	in aq. HCl-MEK	Catalyst recovery studies	Mott <i>et. al.</i> (1990) <sup>155</sup>
8.	Ni compound/Phosphine compound/Iodine compound [e.g. $\text{NiI}_2$ , $\text{PPh}_3/\text{MeI}$ ]	IBPE	443	10	in acetophenone; 2 h	90–99 79–82 <sup>a</sup>	Tanaka and Shima (1990) <sup>157</sup>
9.	$\text{PdCl}_2/\text{PPh}_3$	IBPCI	373–383	5.4	in aq. HCl-MEK	– 82	Stahly <i>et. al.</i> (1991) <sup>169a</sup>
10.	$\text{PdCl}_2(\text{PPh}_3)_2$	IBPE		3.4–30	in aq. HCl-MEK	The presence of ibuprofen in the feed increases the activity	Hendricks and Mott (1992) <sup>153b</sup>
11.	$\text{PdCl}_2/\text{PPh}_3/\text{CF}_3\text{COOH}$	IBPCI	375	5.4	Absolute MeOH/MEK	– 37–50 <sup>b</sup>	Chokalingam (1993) <sup>169c</sup> (1994) <sup>171a</sup>
12.	$\text{Pd}(0)$ or $\text{Pd(II)}$ compound	IBPCI	373–473	1–20	In the presence of $\text{RC}(\text{OR}_1)_3$ , $\text{Ti}(\text{OR}_1)_4$ , $\text{Al}(\text{OR}_1)_3$ MEK; 64 h	– 62 <sup>a</sup>	Manimaran <i>et. al.</i> (1994) <sup>169b</sup>

13.	PdCl <sub>2</sub> /CuCl <sub>2</sub> /PPh <sub>3</sub>	IBPCI	375-388		aq. HCl-MeOH; 8-60 h	-	78-96 <sup>b</sup>	-	Wu (1994) <sup>171b</sup>
14.	PdCl <sub>2</sub> /TPPTS/TsOH	IBPE	363	3	in deaerated water; 20 h	49	62 <sup>a</sup>	38 <sup>a</sup>	Sheldon <i>et. al.</i> (1994) <sup>162</sup> Papadagianakis <i>et. al.</i> (1997) <sup>161</sup>
15.	PdCl <sub>2</sub> /CuCl <sub>2</sub> /PPh <sub>3</sub> /TsOH	1-(6-methoxy-2-naphthyl)ethanol	373	6	in methanol-dioxane; 24 h	96-100	67-100	0-16	Zhou <i>et. al.</i> (1998) <sup>159</sup>
16.	PdCl <sub>2</sub> /CuCl <sub>2</sub> /chiral phosphine (DDPPI)	1-(6-methoxy-2-naphthyl)ethanol	373	8	in MEK; 24-48h	-	90 <sup>b</sup> (S)-81% ee	-	Xie <i>et. al.</i> (1998) <sup>160</sup>
17.	PdCl <sub>2</sub> /PPh <sub>3</sub> /CuCl <sub>2</sub> /H <sub>2</sub> SO <sub>4</sub> /HCl	IBPE	398	5	in 3-pentanone or MEK; 13 h	97-100	66-98 <sup>a</sup>	0-7	Jang <i>et. al.</i> (1999) <sup>158</sup>
18.	Pd-Montmorillonite/PPH <sub>3</sub> /HCl	IBPE	398	4	in 3-pentanone; 13 h	90-99	59-96	1-5	Jang <i>et. al.</i> (1999) <sup>163</sup>

#### 1.2.4. Mechanism of carbonylation of olefins

The different mechanistic pathways proposed for the carbonylation of olefins catalyzed by transition metal complexes are (a) hydride mechanism,<sup>177</sup> which is initiated by the insertion of an olefin into a metal hydride bond and proceeds through the formation of an acyl complex as shown in Eq. 1.1, (b) alkoxy mechanism,<sup>178</sup> which is initiated by the insertion of an olefin into a metal carboalkoxy bond as per Eq. 1.2 and (c) alkylhalide mechanism,<sup>179</sup> which involves oxidative addition of an alkyl halide that may form from the olefin by addition of HX, to a low-valent metal species as per Eq. 1.3.



In the early days, the most popular mechanism of olefin carbonylation has been the one proposed by Heck<sup>180</sup> based on his studies on the nickel carbonyl-catalyzed carboxylation of allyl halides based on the hydride mechanism (Eq. 1.1) involving the hydride species  $\text{HNi}(\text{CO})_2\text{X}$ . An alternative alkyl halide mechanism as per Eq. 1.3 was also proposed for the carbonylation with Ni as a catalyst.<sup>180</sup>

In the case of cobalt catalyzed carbonylation of olefins, both hydride<sup>177a</sup> as well as alkoxy mechanisms<sup>178a</sup> were proposed. The essential features of the hydride mechanism<sup>181</sup> involve the protonation of an olefin by  $[\text{HCo}(\text{CO})_4]$  to yield a carbocation  $\text{CH}_3\text{CH}_2^+$ , which was subsequently attacked by a coordinated carbonyl ligand to yield an acylcobalt species. This acylcobalt species was cleaved via reaction with an alkoxy cobalt intermediate species to form the product and the cobalt hydrido carbonyl species back.<sup>181c</sup> The accelerating effect of pyridine co-catalysts was explained in terms of the enhanced ability to cleave the acyl cobalt species as well as in terms of the formation of pyridine substituted carbonyls which are more active than the  $[\text{HCo}(\text{CO})_4]$ .<sup>182</sup> For many years, the hydride mechanism seemed established for the cobalt systems. Later on, Milstein and co-workers<sup>178a</sup>



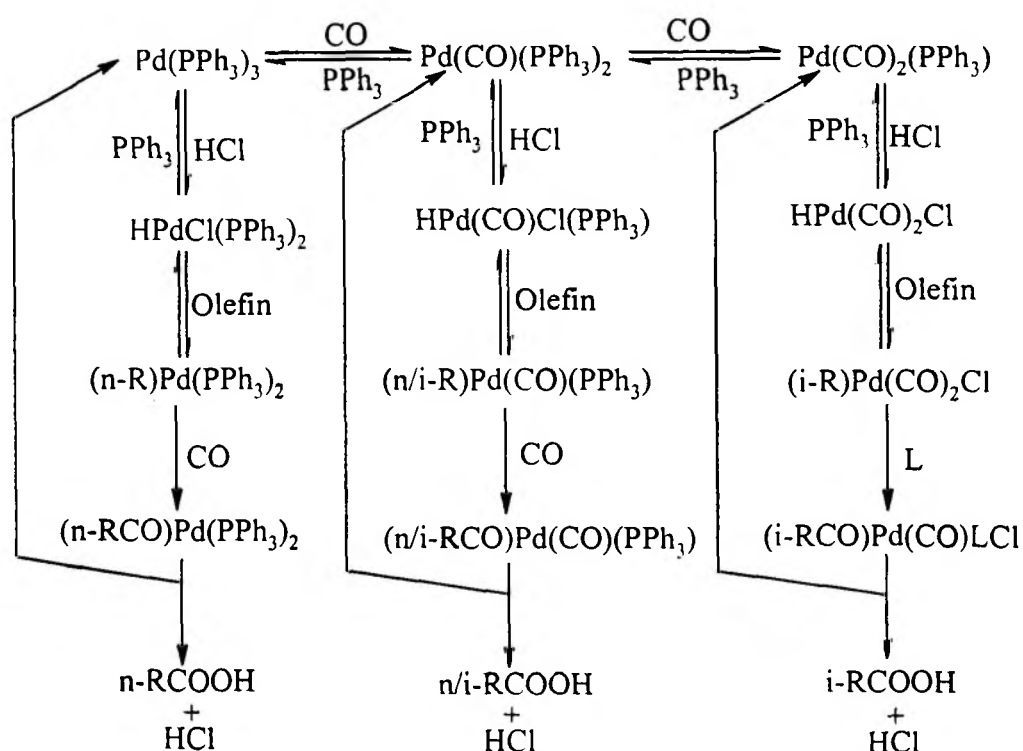
synthesised the cobalt carbomethoxy species such as  $[\text{Co}(\text{COOMe})(\text{CO})_4]$  and  $[\text{Co}(\text{COOMe})(\text{CO})_3\text{PPh}_3]$ . The reaction of these carbomethoxy complexes with butadiene resulted a  $\pi$ -allyl complex  $[\text{Co}(\eta^3\text{-CH}_2\text{CHCHCH}_2(\text{COOMe})(\text{CO})_4)]$  by the addition of Co–COOMe across the olefinic bond, which demonstrated that a carboalkoxy route must also be considered for carbonylation of olefins.

Both alkylhalide and hydride mechanisms were proposed for Rh and Ir catalyzed carbonylation of olefins. Forster *et. al.*<sup>179</sup> carried out kinetic and labeling studies using sensitive radiotracer technique on the carboxylation of ethylene using Rh(I)carbonyl catalyst. It was established that addition of HI with the rhodium iodide catalyst occurs and the reaction proceeds predominantly by the hydride mechanism. They also suggested that a small portion of the propionic acid may also be formed via the alkylhalide (ethyl iodide) mechanism and this mechanism is operative only during the initial portion of the reaction until enough HI is generated so that HI addition can compete with ethyl iodide addition to the Rh(I)carbonyl complex. In another recent study, Christopher *et. al.*<sup>183</sup> have characterized the rhodium hydride species  $[\text{HRh}(\text{CO})_2\text{I}_3][\text{AsPh}_4]$  formed by the reaction of HI with  $[\text{Rh}(\text{CO})_2\text{I}_2][\text{AsPh}_4]$  and its reactivity with ethylene was studied by low temperature NMR spectroscopy. The formation of an acyl species,  $[\text{EtCORh}(\text{CO})_2\text{I}_3][\text{AsPh}_4]$  from a reaction of  $[\text{Rh}(\text{CO})_2\text{I}_2][\text{AsPh}_4]$  with HI and ethylene also gave strong evidence for the hydride mechanism.

In the case of palladium, both hydride as well as alkoxy mechanisms has been proposed. Both the routes have been substantially accepted as a working basis for discussing the palladium-catalyzed carbonylation of olefins. There was no conclusive evidence to exclude either pathway totally and, indeed, it is possible that both routes may be operative under certain conditions. Noskov *et. al.* proposed a hydride mechanism for the hydrocarbonylation of styrene using  $\text{PdCl}_2(\text{PPh}_3)_2$  as a catalyst.<sup>78</sup> In order to explain the hydride mechanism, deuterocarboxylation of styrene in the presence of  $\text{D}_2\text{O}$  instead of  $\text{H}_2\text{O}$  was carried out at 383 K and 2 MPa,<sup>78b</sup> which showed the substitution of terminal protons of the unreacted styrene with deuterium to a significant degree. This has been explained with the help of the reversible insertion of styrene into a Pd–H bond. Hydride



mechanism was again confirmed by the detection of Pd-acyl complex, which is one of the key intermediates in the hydride mechanism, by *in situ* IR studies.<sup>78c</sup> A characteristic absorption at  $1680\text{ cm}^{-1}$  corresponding to  $(\text{PhC}_2\text{H}_4\text{CO})\text{PdCl}(\text{PPh}_3)_2$ , was found to develop as the reaction proceeds. It was shown that under reaction conditions no carbonyl absorptions corresponding to methoxy complexes ( $1600\text{--}1900\text{ cm}^{-1}$ ) were detected. Other carbonyl species detected were Pd(0)-carbonyls such as  $\text{Pd}(\text{CO})(\text{PPh}_3)_2$  and  $\text{Pd}(\text{CO})_2(\text{PPh}_3)_2$ . These carbonyl species were believed to form the active Pd-H species by the oxidative addition of a molecule of HCl. The regioselectivity, a key problem in transition metal catalyzed carbonylation reactions, was explained with the help of three different Pd-H species as the active catalyst initiating different catalytic cycles as shown in Scheme 1.7.



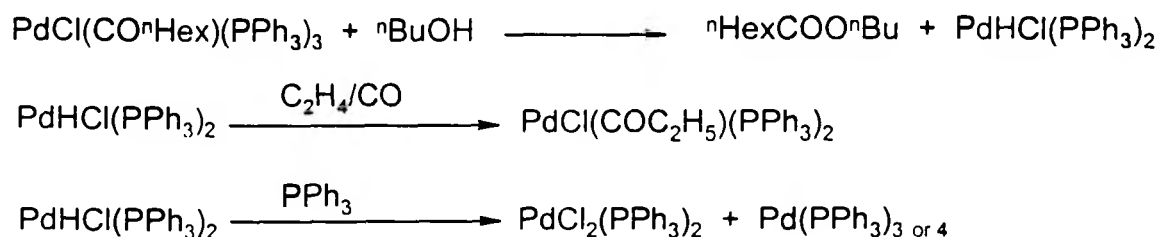
Scheme 7. Mechanism of carbonylation of styrene using  $\text{PdCl}_2(\text{PPh}_3)_2$ , Noskove *et. al.*

It was proposed that the monocarbonyl species,  $\text{Pd}(\text{CO})(\text{PPh}_3)_2$ , produce both the isomers while, exclusive formation of branched and linear products were formed through

the double carbonyl, Pd(CO)<sub>2</sub>(PPh<sub>3</sub>), and the Pd(PPh<sub>3</sub>)<sub>3</sub> species respectively as shown in Scheme 1.7.

With this proposed catalytic cycle the effect of partial pressure of CO and concentration of PPh<sub>3</sub> on the regioselectivity was well explained. In accordance with the <sup>1</sup>H NMR as explained above, the insertion of olefin into the P–H bond leading to the formation of linear coordination is irreversible and only that leading to the branched coordination was reversible under the experimental conditions.<sup>78b</sup> They proposed that the hydrolysis of the acyl intermediates produce the corresponding Pd(0) species rather than the corresponding Pd–H species<sup>78f</sup>.

Cavinato and Toniolo<sup>184</sup> studied the mechanism of carbonylation of linear aliphatic olefins. During the course of their study on hydroesterification reaction of *n*-hexene in ethanol or higher alkanol (at 373 K and 10 MPa) using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst precursor, an acyl complex *trans*-PdCl(CO<sup>*n*</sup>Hex)(PPh<sub>3</sub>)<sub>2</sub> was isolated. But, when the same reaction was carried out in presence of methanol as a solvent, a mixture of carbomethoxy complex *trans*-PdCl(COOMe)(PPh<sub>3</sub>)<sub>2</sub> together with the acyl complex was isolated. The isolated acyl complex, *trans*-PdCl(CO<sup>*n*</sup>Hex)(PPh<sub>3</sub>)<sub>2</sub>, was shown to be reactive towards ethylene in presence of CO, to form butyl-*n*-heptanoate in butanol as a solvent, forming another acyl complex PdCl(COC<sub>2</sub>H<sub>5</sub>)(PPh<sub>3</sub>)<sub>2</sub>. When this reaction was carried out in the absence of CO, the ester was obtained quantitatively and a yellow solid, which was a mixture of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>3 or 4</sub> was isolated.



But when the carbomethoxy complex was treated with *n*-hexene in methanol in the absence of CO, no methyl heptanoate was formed in detectable quantity and the starting

complex was observed quantitatively. Based on these observations, the authors suggest that Pd-methoxy complexes are not active towards insertion of olefin and hence may not be an active species for the carbonylation of olefins and a hydride mechanism has been proposed. Beneficial effects of hydrogen observed in some cases<sup>185</sup> also gave strong support to the hydride mechanism.

Recently Benedek *et. al.*<sup>122</sup> carried out deuteroalkoxycarbonylation of styrene and  $\alpha$ -methyl styrene using  $\text{PdCl}_2(\text{PPh}_3)_2$  and  $\text{PdCl}_2(\text{PPh}_3)_2/\text{SnCl}_2$  as catalysts. Their studies showed that the observed strong influence of structure of the catalyst and substrate on product regioselectivity was due to the different behaviour of the Pd-alkyl intermediates formed in both the cases, which supports the involvement of a hydride mechanism.

### 1.2.5. Kinetics of carbonylation of olefins

Kinetics of carbonylation of olefins was investigated only in a few cases. Noskov and co-workers<sup>186</sup> have reported the kinetics of hydrocarbonylation of styrene using  $\text{PdCl}_2(\text{PPh}_3)_2$  as a catalyst precursor system. As explained above they have studied the mechanism of reaction based on which, kinetic rate models were developed to explain the effect of different parameters on the rates of formation of *iso* as well as linear acid, which determine the regioselectivity. The rate of formation of the linear isomer has only a slight dependency on  $P_{\text{CO}}$  whereas the reaction order for formation of the branched isomer with respect to  $P_{\text{CO}}$  was close to two.<sup>78</sup> Both rates were increased as concentration of water increased to 2 mol/l, above which the rate of formation of the linear isomer became virtually a constant while that of the branched isomer decreased. The following rate equations were proposed for the formation of individual isomers.

$$r_{\text{linear}} = \frac{[\text{H}_2\text{O}][\text{Pd}]_0}{1 + A_1[\text{H}_2\text{O}]^2 P / [\text{HCl}] + A_2[\text{H}_2\text{O}]^2} \times \left[ A_3 + \frac{A_4 P}{1 + A_5 P} \right]$$

$$r_{\text{branched}} = \frac{[\text{H}_2\text{O}]P^2[\text{Pd}]_0}{1 + A_1[\text{H}_2\text{O}]^2 P / [\text{HCl}] + A_2[\text{H}_2\text{O}]^2} \times \left[ \frac{A_4 A_5 P}{1 + A_5 P} + \frac{A_6 [\text{H}_2\text{O}]}{([\text{HCl}] + A_7 [\text{H}_2\text{O}]) (1 + A_8 [\text{H}_2\text{O}])} \right]$$

where  $r_{\text{linear}}$  and  $r_{\text{branched}}$  are the rate of respective reactions,  $A_i$  are the rate constants and equilibrium constants of elementary reactions (as explained in the report),  $[X]$  is the respective concentrations and  $P$  is the apparent pressure of CO. Similar kind of equations were proposed for the influence of styrene, Pd,  $\text{PPh}_3$ <sup>78d</sup> and  $\text{SnCl}_2$ <sup>78e</sup> on the individual reaction rates of both the isomers. Rate of formation of branched isomer decreased to a great extent than that of the linear isomer formation with  $\text{PPh}_3$  concentration, the effect being predominant at higher water concentrations. Both rates depend linearly on catalyst concentration. No other catalytic system has been studied in detail. No mechanistic and kinetic details are available on the hydroesterification of styrene using cationic complexes.

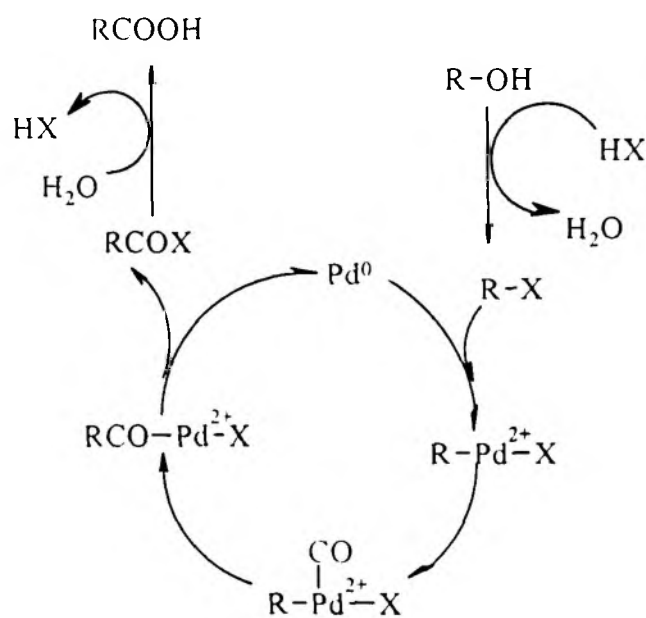
Ercoli *et. al.*<sup>187</sup> have reported the kinetics of carboxylation of cyclohexene using dicobalt octacarbonyl ( $\text{Co}_2(\text{CO})_8$ ) as the catalyst precursor. The rate was found to be proportional to the concentration of water and half power of olefin concentration. At lower pressures (<21 MPa) the rate was directly proportional to the carbon monoxide pressure and decreased proportionately becoming inversely proportional above 34 MPa. Takezaki *et. al.*<sup>188</sup> have also reported a kinetic study on the hydroesterification of cyclohexene using of  $\text{PdCl}_2/\text{PPh}_3$  as a catalyst. A first order dependence with concentration of cyclohexene and zero order dependence with methanol was observed and empirical rate equation was proposed. No other detailed kinetic study was appeared in the literature.

### 1.2.6. Mechanism of carbonylation of alcohols

Carbonylation of methanol to acetic acid is one of the most studied systems for understanding the mechanistic details and the subject has been reviewed extensively.<sup>1,2,3,150</sup> Only limited studies were available for mechanistic details of carbonylation of benzylic alcohols. However, the reaction was proposed to proceed through the corresponding halo derivative (Scheme 1.8) as the active substrate and each of the elementary steps involved in the proposed catalytic cycle was studied separately by different groups and is discussed below.

Stille and co-workers<sup>189</sup> have studied the stereochemical aspects of oxidative addition of  $\alpha$ -methyl benzylbromide to  $\text{Pd}(\text{PPh}_3)_4$ , and  $\text{Pd}(\text{CO})(\text{PPh}_3)_3$  forming a Pd-alkyl

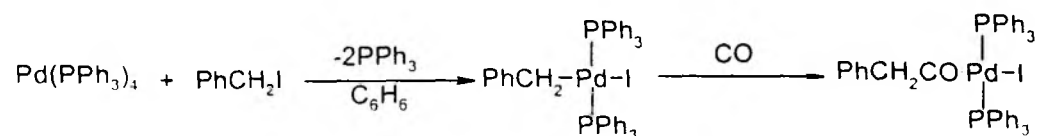
or a Pd-alkylcarbonyl complex respectively. Both were reported to proceed with inversion of configuration, which suggests a  $S_N^2$  displacement of benzylic halide by palladium.<sup>190</sup> It was postulated<sup>191</sup> that oxidative addition proceeds mainly in a low ligated Pd(0) species, which is generated by the dissociation of  $PPh_3$  ligands from the  $Pd(PPh_3)_4$  or  $Pd(CO)(PPh_3)_3$  complexes. The formed Pd-alkylcarbonyl complex forms a Pd-acyl complex through a subsequent intramolecular CO insertion. The Pd-alkyl complex is converted to a Pd-acyl complex in presence of external CO. Migratory insertions step does not involve any change in configuration.<sup>192</sup> These Pd-acyl complexes on reaction with methanol gave the ester with retention of configuration (but with an overall inversion of configuration).  $\alpha$ -phenethyl bromide undergoes oxidative addition to Pd(0) less efficiently compared to benzylbromide.<sup>193</sup> Garrou and Heck<sup>194</sup> also reported the mechanism of carbonylation of benzylic halides using Pd(0) complexes.



Scheme 8. A generalized scheme for the mechanism of palladium catalysed carbonylation of alcohols

Recently, Lin and Yamamoto<sup>195</sup> studied the mechanism of carbonylation of benzyl alcohol to phenyl acetic acid under carbonylation reaction conditions. They proposed a mechanism almost similar to the rhodium-catalyzed carbonylation of methanol to acetic acid. Their model experiments studied separately established that benzyl iodide

could rapidly add to Pd(0) complex to give benzylpalladium species (Eq.1.4) which on subsequent C'O insertion into benzyl-palladium bond forms the phenylacetyl palladium species.



These two steps proceeded very quickly above room temperature and the authors concluded that these could not be the rate determining processes in the actual catalytic cycle. The studies on the reactivity of the phenyl acetyl palladium species with water indicated that the phenyl acetyl complex was resistant to hydrolysis in acidic medium and these species can remain in acidic medium for some time before the reductive elimination of PhCH<sub>2</sub>COI occurs. But under carbonylation conditions the exclusive organopalladium complex containing benzyl moiety detected was a dimeric (phenylacetyl)palladium complex having one phosphine ligand, [Pd(COCH<sub>2</sub>Ph)I(PPh<sub>3</sub>)]<sub>2</sub>, which suggests that either the dimer or a 3-coordinate species formed by dissociation of a PPh<sub>3</sub> from the phenylacetyl palladium species [Pd(COCH<sub>2</sub>Ph)I(PPh<sub>3</sub>)<sub>2</sub>] may be involved as a key intermediate to undergo the reductive elimination of PhCH<sub>2</sub>COI.

### 1.3. Aim and scope of the present work

It is evident from the literature that carbonylation of olefins and aryl alcohols is an industrially important reaction as it provides a clean route for the synthesis of carboxylic acids or esters, particularly the carbonylation of vinyl aromatic compounds and aryl ethanols to 2-aryl propionic acids. While extensive work has been done on the catalytic activity and selectivity of different catalysts, various aspects need further investigations. Challenges are in improving the TON/TOF and selectivity under mild operating conditions to evolve commercially attractive and economically viable catalyst systems. Similarly, the kinetics and mechanism of these reactions has not been well established. Therefore, the following problems were proposed to be investigated for the present thesis.

1. Hydroesterification of styrene using *in situ* formed  $\text{Pd}(\text{OTs})_2(\text{PPh}_3)_2$  complex catalyst: activity, selectivity and mechanistic studies
2. Kinetics of hydroesterification of styrene using  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{TsOH}$  as the catalyst
3. Carbonylation of 1-aryl ethanols and vinyl aromatics using palladium complex catalyst systems
4. Kinetics of carbonylation of 1-(4-isobutylphenyl)ethanol using  $\text{PdCl}_2(\text{PPh}_3)_2/\text{TsOH}/\text{LiCl}$  as a catalyst

This work will not only add to our understanding on the role of different parameters in affecting the catalytic activity and product selectivity, but also provide a basis for a new process for the synthesis of 2-aryl propionic acids.





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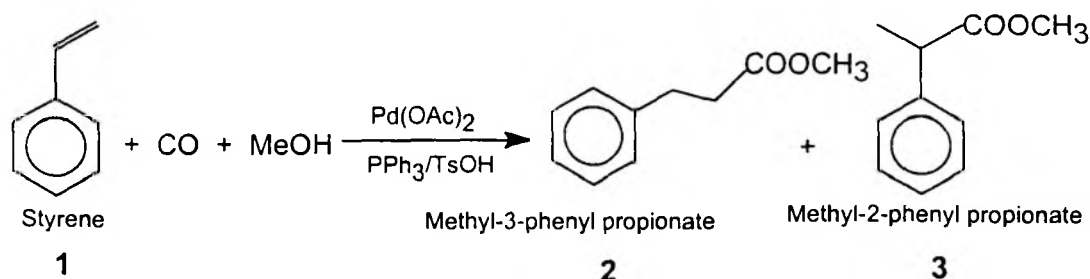
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## Chapter 2

**Hydroesterification of Styrene using *in situ*  
formed Pd(OTs)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> Complex Catalyst:  
Activity, Selectivity and Mechanistic  
Studies**

## 2.1. Introduction

Transition metal catalyzed hydroesterification of vinyl aromatics is gaining importance for the synthesis of industrially valuable products such as 2-phenyl propionic acids/esters, a class of non-steroidal anti-inflammatory agents.<sup>1</sup> A variety of soluble palladium complexes are widely used as catalysts due to their high activity and selectivity.<sup>2</sup> Both branched and linear carboxylic acid esters were formed in these reactions and the regioselectivity was found to dependent strongly on the catalytic system employed and the reaction conditions used.<sup>3</sup> The alkoxycarbonylation of styrene, one of the simplest examples of vinyl aromatics, yields a mixture of 2-phenyl propionate (branched product, 3) and 3-phenyl propionate (linear product, 2), as given below in Scheme 2. 1, using methanol as the alcohol.



Scheme 2.1. Hydroesterification of Styrene

Alkoxycarbonylation (hydroesterification) of styrene with neutral palladium complexes such as PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PdCl<sub>2</sub>(dppp)<sub>2</sub> (dppp = diphenylphosphino propane) was reported to proceed under severe conditions (20–70 MPa of CO and 363–373 K) with very low activity (TOF = 5–20 h<sup>-1</sup>).<sup>4,5</sup> Under these conditions regioselective formation of 3 was observed with monophosphines<sup>4</sup> as ligands and that of 2 was observed with bidentate phosphines (diphos) as ligands.<sup>5</sup> Increased regioselectivity to 3 was reported with Pd(OAc)<sub>2</sub> immobilized on montmorillonite in the presence of HCl as a promoter<sup>6</sup> under mild reaction conditions of 398 K and 4.08 MPa of CO (TOF = 15 to 20 h<sup>-1</sup>). In this case when TsOH was used as the promoter instead of HCl the branched ester product 3 was formed almost regioselectively even though with lower catalytic activity (TOF = 6 h<sup>-1</sup>).

However, increased catalytic activity was reported with a similar homogeneous catalytic system<sup>7</sup> comprising of Pd(OAc)<sub>2</sub> and diphenylphosphinoacetic acid along with *p*-toluenesulphonic acid (TsOH) as the promoter (TOF = 40 h<sup>-1</sup> at 403 K, 4 MPa), with lower selectivity to the branched ester, **3**, (38.7 %). In recent developments, cationic palladium complexes were also found to give good activity and selectivity to the branched ester product under relatively mild reaction conditions. Oi *et. al.*<sup>8</sup> have reported hydroesterification of styrene using a cationic palladium complex, [Pd(PhCN)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>](BF<sub>4</sub>)<sub>2</sub>, with a TOF of 11 h<sup>-1</sup> and a *n/iso* ratio of 1.5. High regioselectivity to the branched ester was also reported under room temperature and 2 MPa pressure using Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>/TsOH as a catalyst system, but with a very low catalytic activity (TOF = 2–4 h<sup>-1</sup>). A detailed review on the carbonylation of vinyl aromatics is presented in chapter 1 (Section 1.2.1.2.2).

In this Chapter, experimental results on hydroesterification of styrene are presented using *in situ* formed Pd(OTs)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, **I**, from a mixture of Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> and TsOH as a catalyst precursor system to address the issues on catalytic activity, selectivity and reaction mechanism. Effect of various parameters such as type of ligand, ligand to metal ratio, anion to catalyst ratio, solvents and the effect of hydrogen at different temperatures on the catalytic activity and product selectivity has been studied. A detailed investigation on the mechanistic aspects was carried out by isolation and characterization of catalytically active intermediates and also by <sup>31</sup>P NMR studies.

## 2.2. Experimental section

### 2.2.1. Materials

Styrene and 4-substituted styrenes, Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>, PPh<sub>3</sub>, P(*p*-tol)<sub>3</sub>, P(*o*-tol)<sub>3</sub>, P(Bu)<sub>3</sub>, P(*p*-ClC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>, P(OPh)<sub>3</sub>, P(MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>, *p*-toluenesulphonic acid monohydrate, methanesulphonic acid, trifluoroacetic acid, triflic acid (all from Aldrich, USA), and CO (Matheson, USA) were used as received without further purification. Methanol (Sd Fine Chemicals, India) was distilled and dried using literature procedures prior to use and a stock solution of methanol having approximately 1500 ppm (analyzed by Karl-Fischer method) of water made using controlled addition of water to the dry methanol. Other solvents and alcohols were also distilled and degassed with argon before use.

### 2.2.2. Analytical methods

Liquid samples were analyzed on a Hewlett Packard 6890 Series GC, controlled by the HP Chemstation software, by using an FFAP megabore column (30 m x 0.53 mm x 0.1  $\mu$ m film thickness, on a poly ethylene glycol stationary phase). IR was obtained using a Shimadzu Hyper IR in DRS (Diffused Reflectance Spectroscopy) mode by mixing samples with KBr as well as in Perkin Elmer Spectrum-2000 in transmission mode using KBr pellets. NMR was obtained from a Bruker- MSL300 and Bruker-AC200 machines. Elemental analysis of the complexes was carried out on a CHNS-O EA1108, Elemental analyzer of Carlo Erba Instruments, Italy, and the ion chromatography on a Waters Ion Chromatograph, Austria, having Waters 432 Conductivity detector, Waters 600S Controller and Waters 626 Pump. The gas phase analysis was carried out in Aimil Nucon GC-5500 by using Poropack-Q (10' x 1/8") column. GCMS was carried out on a Shimadzu QP5000 instrument.

The standard conditions for GC analysis were as follows

Injector (split) temperature	523 K
Flame ionization detector temperature	523 K
Column temperature	373 K–423 K (rate, 30 K/min)
Carrier gas (He) flow	2.5 ml/min
Inlet Pressure (He)	20 psig
Split ratio	1: 100

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

$$\% \text{ Conversion} = \frac{\text{Initial concentration of styrene} - \text{Final concentration of styrene}}{\text{Initial concentration of styrene}} \times 100$$

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

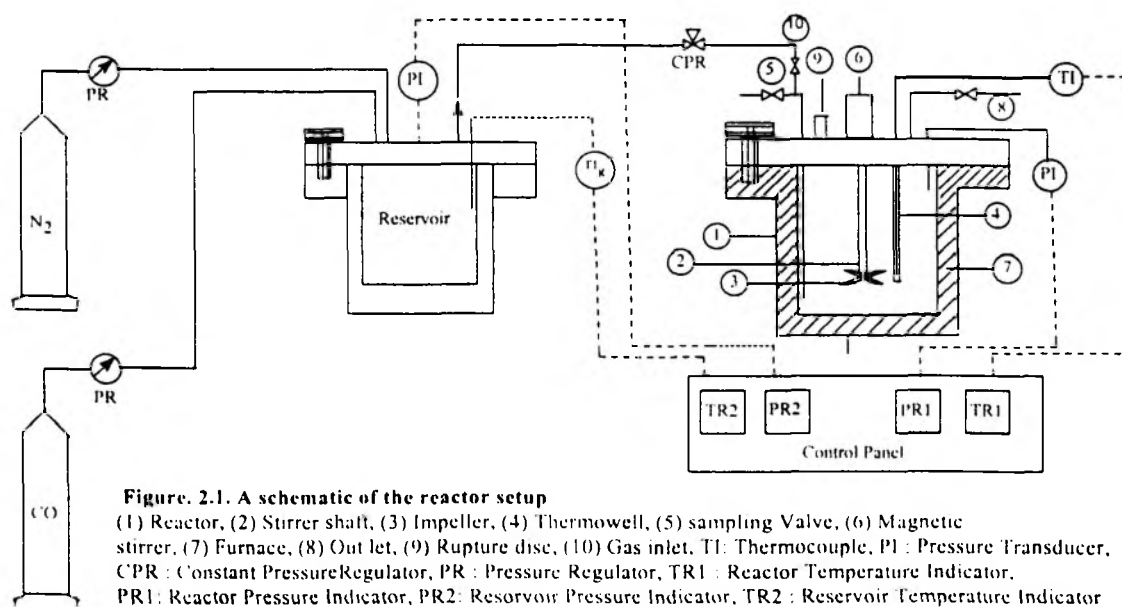
$$\% \text{ Yield} = \frac{\text{No. of moles of product formed}}{\text{No. of moles of styrene charged}} \times 100$$



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

### 2.2.3. General procedure for hydroesterification

All reactions were carried out in a 50 cm<sup>3</sup> Parr Autoclave made of Hastelloy-C-276 having facilities for gas inlet, outlet, intermediate sampling, temperature controlled heating and variable agitation speed (Figure 2.1). As a safety precaution, a rupture disc (gold faced), which can withstand a maximum of 14 MPa pressure, was also attached to the reactor. In a typical experiment, Pd(OAc)<sub>2</sub> (0.06 mmol), PPh<sub>3</sub> (0.24 mmol), TsOH (0.6 mmol) and styrene (14.42 mmol) were dissolved in methanol (23.3 cm<sup>3</sup>) to make the total volume 25 cm<sup>3</sup> and charged into the reactor. The reactor was purged first with nitrogen and subsequently with carbon monoxide from individual reservoirs at room temperature and the contents were heated to 348 K. After attaining the desired temperature, the reactor was pressurised to 3.4 MPa with CO and the reaction was started at 900 rpm. The reaction was carried out at a constant pressure by feeding CO from a reservoir with the help of a constant pressure regulator.



Progress of the reaction was monitored by measuring the change in CO pressure in the reservoir vessel as a function of time. The reaction was carried out for one hour at the end of

which, a small amount of the liquid phase was withdrawn and quantitatively analyzed by GC for reactant and products. The mass balance of CO absorbed and styrene consumed and the products formed was found to agree >97% with the stoichiometry (see Chapter 3).

#### 2.2.4. Preparation of Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>

The literature procedure<sup>9</sup> was followed for the preparation of Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> with a few modifications. Pd(OAc)<sub>2</sub> (0.116 mmol) and PPh<sub>3</sub> (0.235 mmol) were dissolved in toluene with vigorous shaking for 1–3 min. The resulting yellow solution was transferred to another flask and *n*-hexane was added. The precipitated yellow Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> complex was filtered, washed with *n*-hexane and dried under vacuum. Yield: 62%; IR: 1633 cm<sup>-1</sup>, 1350 cm<sup>-1</sup>. Elemental Analysis: Calculated for C<sub>40</sub>H<sub>36</sub>O<sub>4</sub>P<sub>2</sub>Pd: C, 64.13; H, 4.84; P, 8.27, found: C, 64.01; H, 4.9; P, 8.0.

#### 2.2.5. Preparation of Pd(OTs)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, (I)

The complex, Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, was dissolved in toluene and two equivalents of TsOH was added with vigorous shaking in a Schlenk flask under argon atmosphere. Immediate precipitation with *n*-hexane gave a yellowish complex, which was allowed to settle down. The supernatant liquid was decanted and the complex was washed several times with *n*-hexane and finally with small amount of ether and dried under vacuum. Decantation was used because, on filtration majority of the yellow complex, **I** changed to a brownish yellow (sticky mass) even under argon atmosphere. Complex **I** was only moderately stable in air and was found to be stable under inert atmosphere at lower temperatures (~0 °C). IR analysis showed no peaks corresponding to carbonyl vibrations indicating complete replacement of acetate ions by tosylate group. Elemental Analysis: Calculated for C<sub>50</sub>H<sub>44</sub>O<sub>6</sub>P<sub>2</sub>PdS<sub>2</sub>: C, 61.6; H, 4.55; S, 6.58. Found: C, 59.92; H, 5.01; S, 6.37. Complex **I** was also formed when a mixture of Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, and TsOH was used instead of Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the precursor.

#### 2.2.6. Isolation of [HPd(CO)(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup>(TsO<sup>-</sup>), (VI)

A mixture of Pd(OAc)<sub>2</sub> (0.223 mmol), PPh<sub>3</sub> (0.892 mmol), and TsOH (2.23 mmol) was charged to the autoclave, flushed with nitrogen and subsequently with CO, heated to

348 K, charged with 3.4 MPa of CO and stirred for 0.5–1 hour. The reaction mixture was then cooled to room temperature and kept under CO atmosphere for two to six hours. After depressurizing and flushing with argon, the white flakes like complex obtained was transferred to a Schlenk flask under argon atmosphere and the complex was allowed to settle down. The mother liquor was decanted and the complex was washed with degassed methanol and *n*-hexane successively under an atmosphere of argon and dried under vacuum to obtain the complex VI. The complex VI was found to be highly air sensitive and turned reddish brown within a few minutes, on exposure to air and was only moderately stable even under argon atmosphere. IR and NMR were taken immediately. IR(DRS): 2154 (v, Pd-H), 1955.7 (v, Pd-CO),  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ),  $\delta$  -5.90 (s, Pd-H), 2.10 (s, 3H,  $\text{CH}_3$  of TsOH), 7.50–8.10 (m, 35H, Ph of  $\text{PPh}_3$  and  $\text{TsO}^-$ ). NMR spectrum was poorly developed, may be due to the unstable nature of the complex. The complex VI changed to a light yellow complex within a few minutes under argon atmosphere and the IR of the resulted complex showed no Pd-H signal at  $2154 \text{ cm}^{-1}$  (IR) and  $\delta$  -5.9 ppm ( $^1\text{H}$  NMR), while the carbonyl peak at  $1955.7 \text{ cm}^{-1}$  retained. Elemental analysis showed the presence of sulfur and phosphorus in addition to carbon and hydrogen. Further characterization was difficult due to the unstable nature of the complex.

### 2.2.7. Isolation of palladium-acyl complex (XI & XII)

Hydroesterification of styrene (7.2 mmol) was carried out using a mixture of  $\text{Pd}(\text{OAc})_2$  (0.223 mmol),  $\text{PPh}_3$  (0.892 mmol), and TsOH (2.23 mmol) in methanol (moisture content ~500 ppm) at 328 and 3.4 MPa of CO for 1–2 hours. The contents in the reactor were cooled to room temperature and kept for two days under CO atmosphere. The yellow needle shaped air sensitive crystals obtained were transferred to a Schlenk flask under argon atmosphere and isolated as per the procedure given for the isolation of VI (Sec. 2.2.6). IR and NMR of the complex were taken immediately. IR:  $1687 \text{ cm}^{-1}$  (Pd-CO-St),  $^1\text{H}$  NMR ( $\delta$ , ppm,  $\text{CDCl}_3$ ):  $\delta$  1.05 (s,  $\text{CH}_3$ ), 1.60 (Pd-CO- $\text{CH}_2$ - $\underline{\text{CH}_2}$ ), 2.20 (Pd-COCH $_2$ ), 2.30 (s,  $\text{CH}_3$  of  $\text{TsO}^-$ ), 3.60 (Pd-CO-CH), 7.10-7.70 (m, Ph of  $\text{PPh}_3$  and  $\text{TsO}^-$ ), 7.70-8.10 (m, Ph of acyl).

The colour of this complex changed to reddish brown on exposure to air in solid state and also decomposed within a few minutes to palladium metal in solution. The NMR spectrum was poorly developed due to the decomposition of the complex.  $^1\text{H}$  NMR showed that the isolated complex was a mixture of *iso* (XI) and linear (XII) coordinated palladium acyl complex.

### 2.2.8. Preparation of $\text{Pd}(\text{PPh}_3)_4$

Palladium chloride (150 mg) and triphenylphosphine (4–5 equiv) were added to 75  $\text{cm}^3$  of dimethylsulfoxide (dried and degassed) and heated to about 413 K, with stirring, under nitrogen atmosphere. After attaining a clear yellow solution, hydrazine hydrate was added in one portion over a period of 1–2 min with exclusion of air. Nitrogen was evolved in the vigorous ensuing reaction. The reaction flask was then cooled immediately with a water bath (after removing the oil bath) to reduce the temperature of the mixture to about 373 K and then allowing slow cooling. After crystallization overnight, the product was filtered on a glass sinter, washed under nitrogen with ethanol followed by ether and dried under vacuum. Yield = 92%. Elemental Analysis: Calculated for  $\text{C}_{60}\text{H}_{72}\text{P}_4\text{Pd}$ : C, 74.83; H, 5.234; P, 10.727. Found: C, 74.45; H, 5.31; P, 9.97 %.

### 2.2.9. Preparation of palladium acyl complex, $\text{PdCl}(\text{COCH}_2\text{CH}_2\text{Ph})(\text{PPh}_3)_2$ (XIII)

Hydroesterification of styrene (7.2 mmol) was carried out with  $\text{PdCl}_2$  (0.565 mmol),  $\text{PPh}_3$  (2.29 mmol), and  $\text{TsOH}$  (56.5 mmol) in methanol under 348 K and 3.4 MPa of CO for two hours. The contents in the reactor were cooled to room temperature, CO depressurised and the reaction mixture kept in a freezer at about 273 K for two days. The white crystals formed were transferred to a Schlenk flask under argon atmosphere and the complex was isolated as per the procedure given for the isolation of complex VI. IR (DRS, KBr):  $1685.7\text{ cm}^{-1}$  (Pd-CO-St);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$ , ppm 1.60 (t, 2H, Pd-CO-CH<sub>2</sub>-CH<sub>2</sub>), 2.50 (t, 2H, Pd-CO-CH<sub>2</sub>), 7.40–7.70 (m, 30H, Ph of  $\text{PPh}_3$ ), 7.70–7.90 (m, 5H, Ph of acyl ligand);  $^{13}\text{C}$  ( $\text{CDCl}_3$ ):  $\delta$ , ppm 234 (Pd-CO-St), 59.84 (Pd-CO-CH<sub>2</sub>), 32.92 (Pd-CO-CH<sub>2</sub>-CH<sub>2</sub>), 125–141 (Ph of  $\text{PPh}_3$  and acyl ligand);  $^{31}\text{P}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  19.98 s; Elemental Analysis: Calculated for  $\text{C}_{45}\text{H}_{39}\text{ClOP}_2\text{Pd}$ : C, 67.59; H, 4.91; Cl, 4.43; P, 7.74%. Found: C,

66.36; H, 5.07; Cl, 4.10; P, 6.23 %. The difference in calculated and experimental values was due to the presence of small amount of the linear ester product **1** adhered to the complex as evidenced from the  $^1\text{H}$  NMR, IR and GC analysis.

### 2.2.10. $^{31}\text{P}$ NMR experiments

Samples for  $^{31}\text{P}$  NMR experiments were prepared by mixing  $\text{Pd}(\text{OAc})_2$  (0.022 mmol),  $\text{PPh}_3$  (0.088 mmol) and  $\text{TsOH}$  (0.22 mmol) in  $2.5\text{ cm}^3$  of degassed methanol in a 10 mm NMR tube flushed with argon. The spectra were recorded at 121.1 MHz by using 85%  $\text{H}_3\text{PO}_4$  as an external standard and internal  $\text{D}_2\text{O}$  (added in a capillary tube) as the deuterium source. For preparation of samples under CO pressure,  $\text{Pd}(\text{OAc})_2$  (0.112 mmol),  $\text{PPh}_3$  (0.448 mmol) and  $\text{TsOH}$  (1.12 mmol) in  $15\text{ cm}^3$  of degassed methanol were charged to the  $50\text{ cm}^3$  autoclave, flushed with argon followed by CO, heated to 338 K, pressurized to 3.4 MPa with CO and kept under stirring for 30 min. Intermediate samples were directly taken under CO atmosphere to the NMR tube with the help of a sampling device and the spectra recorded as stated above.

## 2.3. Results and discussion

Effect of various parameters such as type of ligand, ligand to metal ratio,  $\text{TsOH}$  to catalyst ratio, solvents, alcohols and the effect of hydrogen at different temperatures on the catalytic activity and product selectivity has been studied and the results are discussed in the respective sections.

### 2.3.1 Effect of catalyst and reaction parameters

#### 2.3.1.1. Catalyst system

The catalyst system used in this work consists of a mixture of  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{TsOH}$ , in the ratio of 1:4:10 unless otherwise stated, from which the active catalytic species was formed *in situ*. This catalyst system showed almost similar activity as that of  $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$  or  $\text{Pd}(\text{OTs})_2(\text{PPh}_3)_2$  (Table 2.1) in the presence of the required amount of  $\text{TsOH}$ . This is because of the immediate formation of  $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$ <sup>10</sup> from  $\text{Pd}(\text{OAc})_2$  and  $\text{PPh}_3$  which, in turn converts to  $\text{Pd}(\text{OTs})_2(\text{PPh}_3)_2$ , **I**, on subsequent reaction with  $\text{TsOH}$  (see experimental).



**Table 2.1.** Effect of catalyst precursors on the hydroesterification of styrene

Run No	Catalyst	Conversion %	Selectivity %, (Yield, %)		<i>n/iso</i> ratio	TOF h <sup>-1</sup>
			<i>iso</i> -ester	<i>n</i> -ester		
1	<sup>a</sup> Pd(OAc) <sub>2</sub>	84.2	39.8 (33.5)	60.2 (50.6)	1.51	203
2	<sup>b</sup> Pd(OAc) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	85.0	40.0 (34.0)	59.8 (50.8)	1.49	205
3	<sup>b,c</sup> Pd(OTs) <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	99.8	40.7 (40.6)	59.2 (59.4)	1.45	248
4	<sup>d</sup> Pd(PPh <sub>3</sub> ) <sub>4</sub>	96.0	38.6 (37.1)	61.3 (58.8)	1.59	234

*Reaction conditions:* styrene, 14.5 mmol; catalyst, 0.06 mmol; TsOH, 0.6 mmol; solvent, methanol; water, 2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa; <sup>a</sup> PPh<sub>3</sub>, 0.24 mmol; <sup>b</sup> PPh<sub>3</sub>, 0.12 mmol; <sup>c</sup> TsOH, 0.48 mmol; <sup>d</sup> no added PPh<sub>3</sub>

All the catalytic precursor systems given in Table 2.1 showed higher reaction rates compared to the neutral precursor PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub><sup>4</sup> as reported in the literature.<sup>4,5</sup> This is due to the fact that charge of the central metal cation of *in situ* formed Pd(OTs)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> is balanced by weakly coordinating anion TsO<sup>-</sup> so that the cation is left with free co-ordination sites able to activate the reactant molecules more effectively compared to the other system, in which the charge of the central metal cation is balanced by strongly coordinating anion such as Cl<sup>-</sup>. A comparison of the catalytic activity and selectivity of different catalytic precursors is given in Table 2.1. Similar selectivity behavior was observed with all the palladium precursors studied with a marginal difference in catalytic activity. Pd(OTs)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and Pd(PPh<sub>3</sub>)<sub>4</sub> gave the highest catalytic activity, however Pd(OAc)<sub>2</sub> was chosen as the catalyst precursor for the present study due to ease of handling.

### 2.3.1.2. Effect of ligands

The effect of different phosphorous ligands was studied and the results are summarized in Table 2.2. The activity was found to increase in the order P(*p*-MeOC<sub>6</sub>H<sub>4</sub>)<sub>3</sub> < P(*p*-ClC<sub>6</sub>H<sub>4</sub>)<sub>3</sub> < P(*p*-tol)<sub>3</sub> < P(*m*-tol)<sub>3</sub> < PPh<sub>3</sub>. No reaction was observed in the case of PCy<sub>3</sub>, PBu<sub>3</sub> and P(OPh)<sub>3</sub> when used as ligands. In the last case,

complete precipitation of the catalyst to palladium metal was observed, unlike the experiments with PCy<sub>3</sub> and PBu<sub>3</sub> in which the solution was light yellow in colour, indicating formation of some stable complexes.

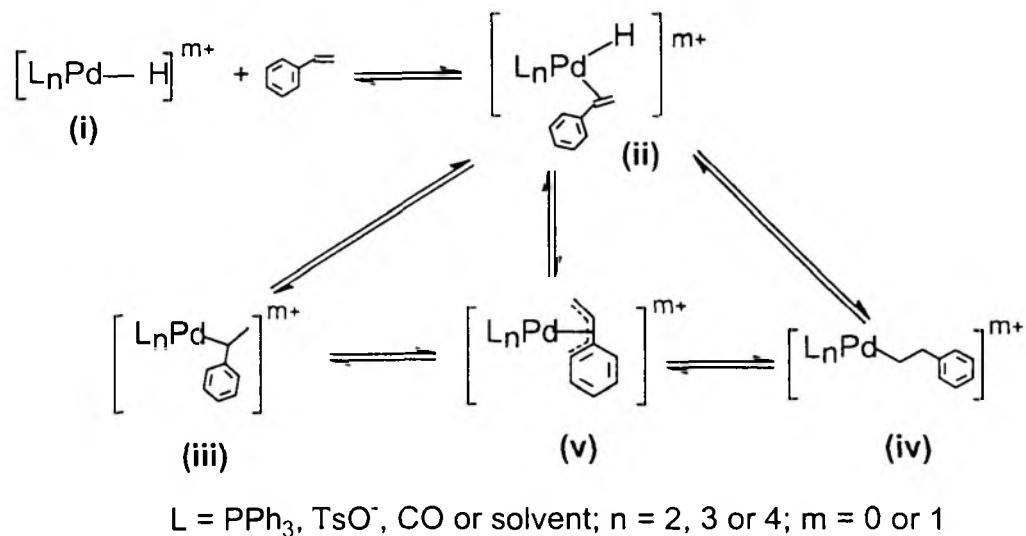
**Table 2.2.** Effect of ligands on the hydroesterification of styrene

Run No	Ligand	Conversion %	Selectivity %, (yield %)		<i>n/iso</i> ratio	TOF h <sup>-1</sup>
			<i>iso</i> -ester	<i>n</i> -ester		
1	PPh <sub>3</sub>	84.2	39.8 (33.4)	60.2 (50.5)	1.51	203
2	P( <i>p</i> -tol) <sub>3</sub>	39.8	25.7 (10.2)	73.6 (29.3)	2.86	83
3	P( <i>m</i> -tol) <sub>3</sub>	39.0	29.0 (11.3)	71.0 (27.7)	2.44	78
4	P( <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	10.6	20.5 (2.2)	79.4 (8.4)	3.86	26
5	P( <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub>	20.5	69.2 (14.1)	30.7 (6.29)	0.44	49

*Reaction conditions:* styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; ligand, 0.24 mmol; TsOH, 0.6 mmol; solvent, methanol; water, 2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

Phosphines having no substituents in the benzene ring (PPh<sub>3</sub>) gave the highest activity (TOF = 203 h<sup>-1</sup>). This may be related to the modified ability of the palladium metal centre to coordinate with styrene and carbon monoxide. For example, with more basic ligands, coordination of styrene may be disfavored, because of nucleophilic characteristic of the vinyl group, while with less basic ligands styrene would bind too strongly. In addition, styrene migration to the coordinated CO (see sec. 2.3.1.9.) can also be affected by the different electronic properties of the ligands. Thus, apparently PPh<sub>3</sub> gave the best compromise with respect to the catalytic activity.

The product selectivity was also affected considerably by the nature of the ligands. *n/iso* ratio was the lowest (*n/iso* = 0.44) with P(*p*-ClC<sub>6</sub>H<sub>4</sub>)<sub>3</sub> and found to increase with increase in basicity of the ligand (see Table 2.2). This indicates that the ligand plays an important role in the regioselectivity-determining step, which is proposed to be the transition from a π-olefin complex **ii** to σ-alkyl complexes **iii** or **iv** as shown in Scheme 2.2.



Scheme 2.2

When the  $\pi$ -complex **ii** changes to the  $\sigma$ -alkyl complex after the insertion of styrene into a Pd-H bond, the styrene moiety can adopt either *iso* (**iii**) or *linear* (**iv**) type coordination depending on the steric as well as electronic factors. The complex **iii** is believed to be in equilibrium with a more stable  $\pi$ -benzylic complex **v**.<sup>11</sup> It is also proposed that **iii** and **iv** can interconvert through **v**, however the equilibrium will be more favorable between **iii** and **v**. Since, the ligands differ only marginally with respect to their influence on steric hindrance, the observed trend in selectivity can be mainly ascribed to the electronic factors. It is interesting to note that using the most basic ligand P(*p*-OMeC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>, or the less basic one, P(*p*-ClC<sub>6</sub>H<sub>4</sub>)<sub>3</sub>, the yield in *n*-ester was not much different (8.4% and 6.29% respectively) while the yield in *iso*-ester was 7 times higher with the less basic ligand (Table 2.2.). This can be due to the fact that electron withdrawing substituents in the phenyl group render the phosphorous atom a poor  $\sigma$ -donor and a good  $\pi$ -acceptor<sup>12</sup>, which decreases the electron density around the palladium center, thereby favoring the formation of **iii** and finally the branched product **2**.

### 2.3.1.3. Effect of PPh<sub>3</sub>/Pd ratio

The ratio of PPh<sub>3</sub>/Pd was also found to affect catalytic activity and product selectivity (Table 2.3). No catalytic activity was observed without phosphorous ligands and complete precipitation of the catalyst to palladium metal resulted under experimental conditions. With a



PPh<sub>3</sub>/Pd ratio of two, substantial precipitation of the active catalyst to Pd metal was observed and no metal precipitation was observed above a ratio of four. The catalytic activity increased up to a PPh<sub>3</sub>/Pd ratio of four, and decreased steadily with further increase. This can be due to the competitive coordination of excess PPh<sub>3</sub> present in the reaction medium to the palladium centre, which reduces the effective activation of reactants.

**Table 2.3.** Effect of PPh<sub>3</sub>/Pd ratio on the hydroesterification of styrene

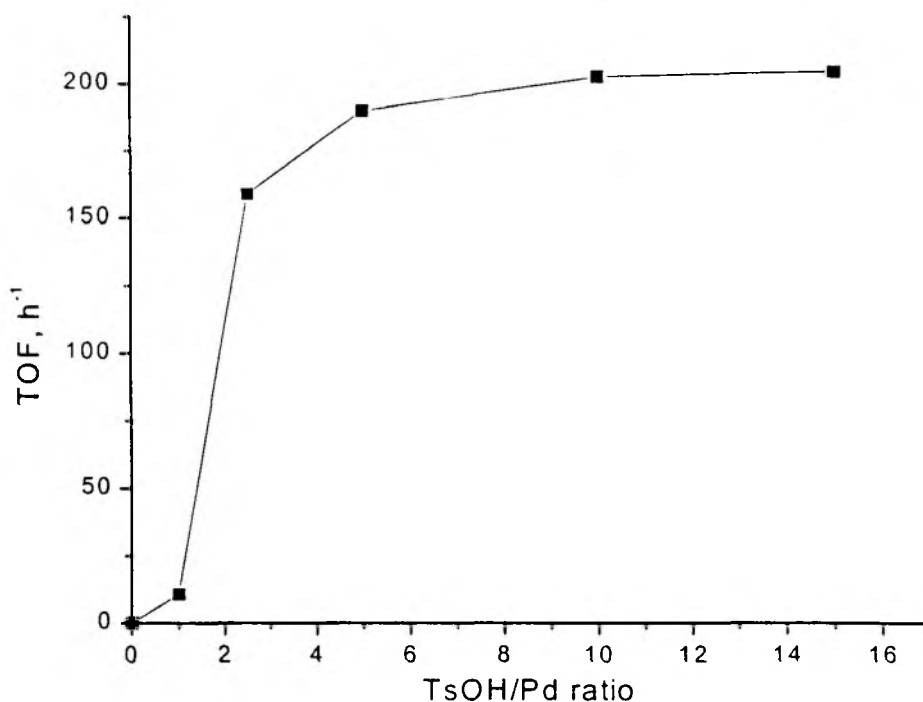
Run No	PPh <sub>3</sub> /Pd ratio	Conversion %	Selectivity %, (yield %)		<i>n/iso</i> ratio	TOF h <sup>-1</sup>
			<i>iso</i> -ester	<i>n</i> -ester		
1	2	81.0	44.0 (35.6)	55.8 (45.2)	1.27	197
2	4	84.2	39.8 (33.5)	60.2 (50.6)	1.51	203
3	6	64.9	37.4 (24.2)	60.6 (39.3)	1.62	153
4	10	55.5	36.5 (20.2)	62.4 (34.6)	1.71	132

*Reaction conditions:* styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol, TsOH, 0.6 mmol; solvent, methanol; water, 2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

A gradual increase in the *n/iso* ratio was observed with increase in PPh<sub>3</sub>/Pd ratio. With increase in the concentration of PPh<sub>3</sub>, it is likely that palladium center can have more than one PPh<sub>3</sub>, which can increase the steric as well as electronic density at the palladium center so that the equilibrium in Scheme 2.2 will be shifted towards iv, resulting in the increased formation of the linear product, 1.

#### 2.3.1.4. Effect of p-toluenesulphonic acid concentration

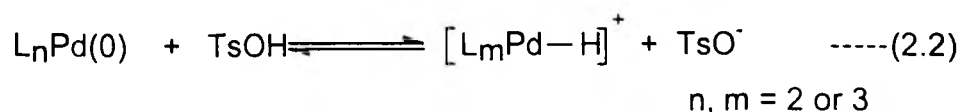
The presence of TsOH was found to be necessary for catalytic activity. In order to find out the optimum concentration of TsOH required, the effect of concentration of TsOH was studied and the variation of catalytic activity with TsOH/Pd ratio is shown in Figure 2.2. The catalytic activity was significantly low (TOF of 11 h<sup>-1</sup>) with one equivalent of TsOH but a sudden jump in TOF (159 h<sup>-1</sup>) was observed as the ratio increased to 2.5, which was in slight excess of the quantity required to form Pd(OTs)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>.



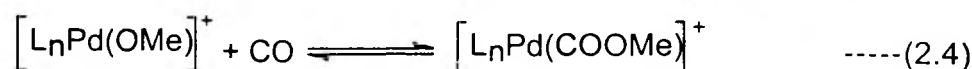
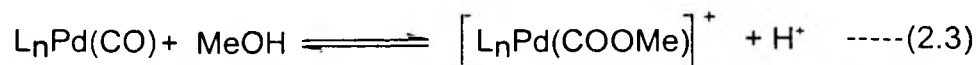
**Figure 2.2.** Effect of concentration of TsOH on the hydroesterification of styrene

*Reaction conditions:* styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol; solvent, methanol; water, 2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

The TOF increased gradually up to a TsOH/Pd ratio of 10 and remained almost constant (TOF = 203 h<sup>-1</sup>) with further increase. This suggests that TsOH is necessary for the initial activation of Pd(OAc)<sub>2</sub> or the formed Pd(OAc)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>. The increased amount of TsOH also plays an important role in the reactivation of any Pd(0) complex that may form during the course of catalysis, in order to regenerate the active Pd-H species:



In addition, at lower concentrations of TsOH and in the presence of excess methanol the palladium precursor can form inactive or less active palladium carbomethoxy<sup>13</sup> complex as per Eq. 2.3 or 2.4. It was found that the selectivity was not influenced by change in TsOH concentration, suggesting that TsO<sup>-</sup> may not be very strongly coordinated to the Pd center.



n = 2 or 3

### 2.3.1.5. Effect of different acidic promoters

The effect of different acidic promoters is given in Table 2.4. The catalytic activity was found to decrease in the order: TsOH > msa > triflic acid > trifluoroacetic acid, which is in the reverse order of the coordination ability of anion. Higher activity was observed with sulphonic acids and higher selectivity to *iso* product was observed in the case of triflic acid. In the presence of anions having higher binding abilities, availability of coordination sites around the central metal atom will be reduced leading to lower catalytic activity.

**Table 2.4.** Effect of different acidic promoters on the hydroesterification of styrene

Sr. No	Acidic promoter	Conversion %	Selectivity %, (yield %)		<i>n/iso</i> ratio	TOF h <sup>-1</sup>
			<i>iso</i> -ester	<i>n</i> -ester		
1	p-toluene sulphonic acid	84.2	39.8 (33.5)	60.2 (50.6)	1.51	203
2	Methane sulphonic acid (msa)	61.6	41.1 (25.3)	58.8 (36.2)	1.43	148
3	Trifluoro methane sulphonic acid (triflic acid)	55.3	43.1 (23.8)	56.8 (31.4)	1.31	133
4	Trifluoro acetic acid	2.8	41.5 (1.1)	58.4 (1.6)	1.40	6.8

Reaction conditions: styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol; acidic promoter, 0.6 mmol; solvent, methanol; water, 2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

Acetic acid<sup>14</sup> and oxalic acid,<sup>15</sup> which were also reported as promoters in hydrocarboxylation reactions, were found to be inactive under the present conditions. No precipitation of Pd metal was observed in these cases, however very faint yellow tinge of the final reaction mixture indicates the formation of some stable Pd complexes.

### 2.3.1.6. Effect of solvents

The effect of solvents was studied using methanol as one of the reactants with a methanol/styrene ratio of 5 and the results are presented in Table 2.5. Catalytic activity was lower in less polar solvents like benzene and toluene. A medium of low polarity favors the association between the complex cation and the counter ion, so that this competes with the reacting molecules for coordination.

**Table 2.5.** Effect of solvents in the hydroesterification of styrene

Run No	Solvent	Conversion %	Selectivity %, (yield %)		<i>n/iso</i> ratio	TOF h <sup>-1</sup>
			<i>iso</i> -ester	<i>n</i> -ester		
1	Benzene	39.75	69.8 (27.7)	30.0 (11.9)	0.429	95
2	Toluene	46.82	65.9 (30.8)	33.3 (15.6)	0.505	112
3	Methyl ethyl ketone	24.83	39.4 (9.7)	60.5 (15.0)	1.53	57
5	Acetone	9.55	30.8 (2.9)	69.1 (6.6)	2.25	23
6	Methanol	84.2	39.8 (33.5)	60.2 (50.6)	1.51	203
7	Styrene	-	63.4	35.2	0.55	411

*Reaction conditions:* styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol; TsOH, 0.6 mmol; methanol, 72.5 mmol; water, 2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

Coordinating solvents such as methyl ethyl ketone and acetone decreased the catalytic activity. This may be due to the fact that these solvents, even if they are known to assist CO migration,<sup>16</sup> may occupy the coordination sites thereby blocking the available coordination sites for reactants. The reactivity pattern can also be affected by the concentration of CO in various solvents depending on the solubility.<sup>17</sup> Despite the lower dielectric constant, catalytic activity was found to be the highest when styrene was used as the solvent (see also Chapter 3, Section 3.3.2.1).

Polarity of the medium also showed a pronounced effect on the product selectivity. The *n/iso* ratio increased with increase in polarity of the medium. Formation of *iso* product **3** was very much enhanced in less polar solvents like benzene and toluene and found to decrease with solvents like methanol having higher polarity. The influence of polarity on product selectivity can also be understood from the examples in which the solvents used were

methyl ethyl ketone (MEK) and acetone. Due to the steric hindrance associated with the coordinating solvents, it is also expected to get a higher *n/iso* ratio with MEK compared to acetone. However, the observed lower *n/iso* ratio for MEK compared to acetone indicates that the polarity of the medium is important in determining the selectivity, though the effect is not very much pronounced.

### 2.3.1.7. Effect of different alcohols

The effect of different alcohols as esterifying agents was studied and the results are presented in Table 2.6. The catalytic activity decreased with increase in the chain length of alkyl group of the alcohol. According to the hydride mechanism, nucleophilic attack of the alcohol to an acyl complex was proposed to be the product forming as well as the rate-limiting step in the hydroesterification reactions of olefins.<sup>18</sup>

**Table 2.6.** Effect of different alcohols on the hydroesterification of styrene

Run No	Alcohol	Conversion %	Selectivity %, (yield, %)		<i>n/iso</i> ratio	TOF h <sup>-1</sup>
			<i>iso</i> -ester	<i>n</i> -ester		
1	Methanol	84.2	39.8 (33.5)	60.2 (50.6)	1.51	203
2	Ethanol	56.2	40.7 (22.8)	59.1 (33.2)	1.47	135
3	<i>n</i> -Propanol	40.7	44.2 (17.9)	55.7 (22.6)	1.25	97.6
4	<i>iso</i> -Propanol	9.4	37.6 (3.5)	62.3 (5.8)	1.65	22.6
5	<i>n</i> -Butanol	11.0	46.5 (5.1)	51.4 (5.6)	1.10	18.9
6	<i>sec</i> -Butanol	3.7	32.3 (1.2)	67.1 (2.4)	2.67	8.7

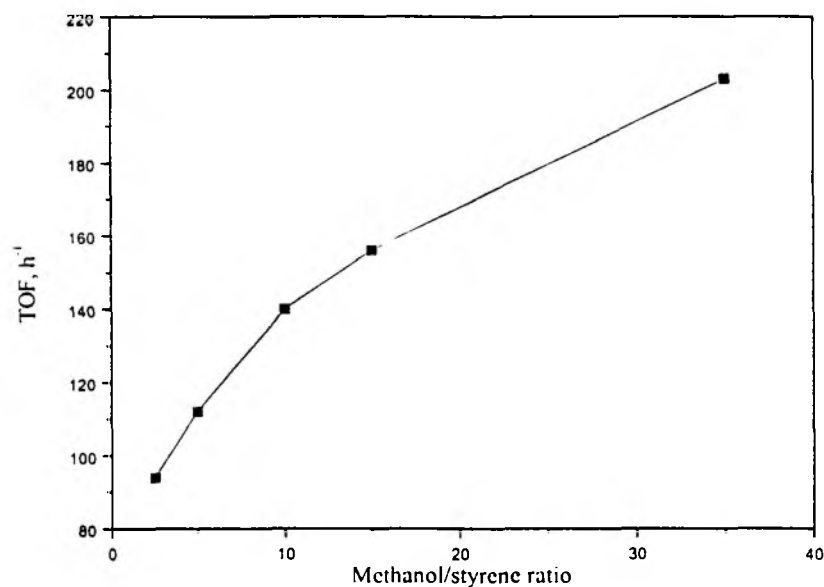
Reaction conditions: styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol; TsOH, 0.6 mmol; water, 2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

The results reported in Table. 2.6 suggest that with increase in carbon chain and increase in the bulkiness of alcohol, the rate of nucleophilic attack decreases and hence a decrease in the overall catalytic activity. This is particularly evident on comparing the results with *n*-propanol and *sec*-propanol and *n*-butanol and *sec*-butanol as solvents. Moreover, the polarity of the medium can also affect the catalytic activity as observed for different solvents in section 2.3.1.6. Methanol, having highest polarity among the alcohols,

gave highest activity. With the exception of *iso*-propanol and *sec*-butanol, the *n/iso* ratio decreased from methanol to *n*-butanol. The decrease in polarity can be one of the reasons for the decreased *n/iso* ratio. In the case of *iso*-propanol and *sec*-butanol the decreased formation of branched product can be attributed to their steric factors.

### 2.3.1.8. Effect of methanol concentration

The effect of methanol concentration was studied in a non-coordinating and less polar solvent such as toluene. As shown in Figure 2.3, at lower methanol concentrations (methanol/styrene = 2.5 to 10), the catalytic activity was found to increase linearly. Above a ratio of 10, the rate of increase in TOF lowered gradually.



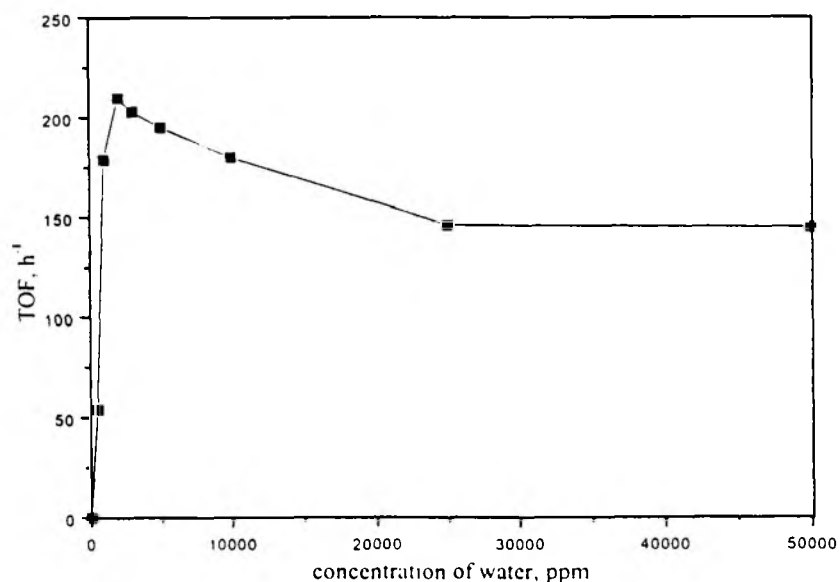
**Figure 2.3.** Effect of methanol concentration on the hydroesterification of styrene  
*Reaction conditions:* styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol; TsOH, 0.6 mmol; solvent, toluene; water, 2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

The linear increase in reaction rate at lower concentration of methanol can be explained on the basis of the nucleophilic attack of methanol as the rate-limiting step. Since, the catalytic activity varies with a fractional order at higher methanol concentration, it is likely that a part of the catalyst precursor is converted to some less active or inactive species or that methanol competes for coordination. This effect can also be a purely kinetic phenomenon.

The selectivity remained almost constant ( $n/iso = 0.52$ ) with increase in methanol concentration up to a methanol to styrene ratio of 10. With further increase in the ratio (10 to 35, pure methanol), a steady increase in  $n/iso$  ratio (0.94 and 1.51 at methanol/styrene ratio of 15 and 36 respectively) was observed. This trend clearly indicates that the product selectivity has a strong dependency on polarity of the medium, unlike in the case of neutral complexes.<sup>18</sup> One interesting result obtained was that when methanol/styrene ratio reduced to 1.44 with excess of styrene, the TOF was found to increase ( $284 \text{ h}^{-1}$ ) and the  $n/iso$  ratio decreased to 0.97. On further decreasing the ratio to 0.8, a dramatic increase in reaction rate (TOF =  $467.5 \text{ h}^{-1}$ ) was observed with a decreased  $n/iso$  ratio (0.52).

### 2.3.1.9. Effect of concentration of water

Water was also found to be one of the essential components for catalytic activity. It was found that the catalytic activity increased (TOF from  $54 \text{ h}^{-1}$  to  $210 \text{ h}^{-1}$ ) with water up to a concentration of 2000 ppm, decreased gradually up to 25000 ppm and then remained almost constant with further increase (Figure 2.4).



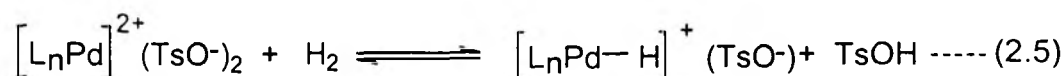
**Figure 2.4.** Effect of concentration of water on the hydroesterification of styrene

*Reaction conditions:* styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol; TsOH, 0.6 mmol; solvent, methanol; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

In dry methanol, the activity was very low (TOF = 54 h<sup>-1</sup>) and the only water available in this case was from TsOH monohydrate and from styrene (total of ~450–550 ppm). At very low concentration of water, effective formation of active catalytic species may be limited. Increase in catalytic activity with water concentration specifies the involvement of water in the formation of active catalytic species, which will be discussed in the mechanistic section below. A gradual decrease in the catalytic activity with further increase in water content implies competition of water with the reactants for co-ordination. This effect was not predominant beyond a concentration of 25000 ppm of water may be due to the weakly coordinating nature of water.<sup>19</sup> A similar trend with water concentration was observed by Vavasori and Toniolo<sup>20</sup> on the productivity of polyketones from ethylene and CO using Pd(OAc)<sub>2</sub>/dppp/TsOH as a catalyst precursor system and a possible role of water-gas shift reaction has been discussed. The product selectivity was also found to vary with concentration of water. In methanol containing very low water content (<500), the *n/iso* ratio was 1.73, which decreased to 1.5 with further increase in water content and remained almost constant up to 2500 ppm. At much higher concentrations of water (>10000 ppm), equal formation of linear and branched products (*n/iso* ≈ 1.1) was observed. This suggests that water also coordinates to the active complex. It is also possible that at higher concentrations of water (above 3000 ppm) the active species can form mono as well as di aqua complexes as reported by Stang *et. al.*<sup>21</sup> for a closely related complex Pd(dppp)(OSO<sub>2</sub>CF<sub>3</sub>)<sub>2</sub>. Replacement of ligands with water molecules in the active complex may help to reduce the steric bulk and electronic repulsion at the metal center, thus enabling co-ordination of styrene in an *iso* fashion and hence decreasing the *n/iso* ratio.

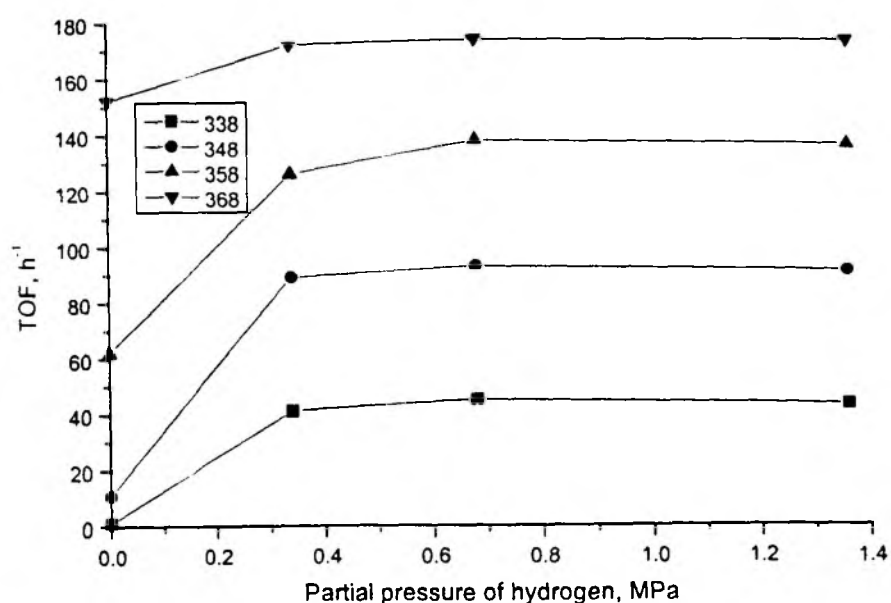
#### 2.3.1.10. Effect of hydrogen

If palladium hydride is the probable active catalytic species in the hydroesterification of olefins,<sup>22</sup> the availability of the hydride source may have a significant effect on the catalytic activity. Hydrogen is such a source which is readily activated by a Pd(II) species as shown in Eq. 2.5.





Only a very small increase in TOF (203 to 224 h<sup>-1</sup>) was observed by the addition of 50 psig of hydrogen in the presence of 10 equivalent of TsOH. However, a dramatic increase (8 fold) in TOF from 11 to 89 h<sup>-1</sup> was observed when 50 psig of hydrogen was added at 348 K and at one equivalent of TsOH (0.06 mmol) concentration as shown in Figure 2.5. Hydrogen effect was also studied at different temperatures to check the consistency of the trends observed. The effect was more pronounced at lower temperatures (below 368 K) and the rate enhancement decreased with increase in temperature. The *n/iso* ratio remained almost unaffected (for a particular temperature) with change in hydrogen partial pressure.



**Figure 2.5.** Effect of hydrogen partial pressure on hydroesterification of styrene

**Reaction conditions:** styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol; TsOH, 0.06 mmol; solvent, methanol; water, 2000 ppm; time, 1 hour; P<sub>CO</sub>, 3.4 MPa

TsOH also can act as a hydride source and in the presence of excess of TsOH, palladium hydride formation will be efficient by suppressing the formation of carbomethoxy species (see Eq. 2.3). At a TsOH/Pd ratio of 1, the effective formation of the active Pd–H species would be limited and addition of hydrogen helps to enhance the formation of active Pd–H according to Eq. 5, thereby increasing the reaction rate. Hence the effect of hydrogen is

more evident only at lower concentrations of the TsOH. This observation suggests a plausible hydride mechanism in the catalytic cycle. This kind of pronounced hydrogen effect was not observed for the hydroesterification of olefins using neutral complexes in methanol,<sup>18</sup> while in *n*-butanol beneficial hydrogen effects were observed. It was proposed that in methanol as a solvent, methoxy mechanism might be predominant, while, the hydride mechanism is preferred in *n*-butanol as a solvent.

### 2.3.1.11. Effect of substituents on styrene.

The hydroesterification of different *para* substituted styrenes was studied and the results are shown in Table 2. 7.

**Table 2.7.** Effect of 4-substituents in styrene

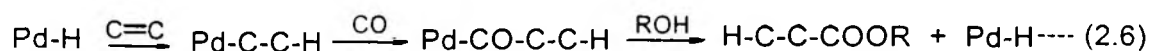
Run No	Substrate	Conversion %	Selectivity %, (yield %)		<i>n/iso</i> ratio	TOF h <sup>-1</sup>
			<i>iso</i> -ester	<i>n</i> -ester		
1	styrene	84.2	39.8 (33.5)	60.2 (50.6)	1.51	203
2	4-methyl styrene	57.1	46.3 (26.4)	53.6 (30.6)	1.15	133
3	4- <i>tert</i> -butyl styrene	36.5	47.4 (17.3)	52.4 (19.1)	1.10	88.2
4	4-chloro styrene	37.5	52.5 (19.6)	47.4 (17.7)	0.90	104
5	4-acetoxy styrene	no reaction and Pd metal precipitation observed				

*Reaction conditions:* styrene, 14.5 mmol; Pd(OAc)<sub>2</sub>, 0.06 mmol; PPh<sub>3</sub>, 0.24 mmol; TsOH, 0.6 mmol; solvent, methanol; water, ~2000 ppm; time, 1 hour; T, 348 K; P<sub>CO</sub>, 3.4 MPa

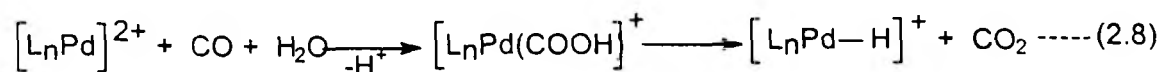
Styrene derivatives either with electron releasing or electron withdrawing substituents at the *para* position, gave lower catalytic activity as well as *n/iso* ratio, compared to styrene. Increased selectivity to the branched product was observed for 4-chloro styrene. In the case of 4-acetoxy styrene, complete precipitation of palladium metal was observed.

### 2.3.2. Reaction mechanism

Palladium catalysed hydroesterification of olefins was proposed to proceed through either a Pd-H<sup>2,3</sup> or Pd-COOR<sup>24</sup> as active catalytic species, which initiates the catalytic cycle.



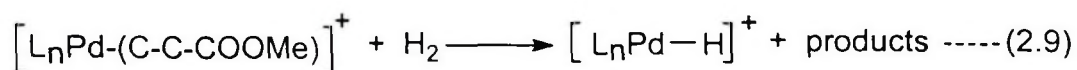
Hydride mechanism (Eq. 2.6) proceeds through the insertion of CO to a Pd-alkyl species formed by the addition of olefin to the Pd-H bond and subsequent nucleophilic attack of ROH on the carbon atom of the acyl ligand producing the product and regenerating the active Pd-H species. Alkoxy mechanism (Eq. 2.7) involves the insertion of olefin into a metal carboalkoxy species, formed by the addition of ROH to initially formed metal carbonyl species. Carbonylation reactions using cationic complexes were also proposed to proceed through both the mechanisms.<sup>25</sup> In principle, both the mechanisms can be operative for the hydroesterification of styrene for the present catalyst system, consisting of Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> and TsOH using methanol as a solvent. However, the enhancement of reaction rate with water, TsOH, and hydrogen suggests that the hydroesterification reaction is more likely to proceed through a hydride mechanism. The beneficial effects of TsOH and hydrogen have been discussed above. Water can increase the concentration of the palladium hydride species through interaction of CO with the formation of a species having Pd-(COOH) moiety, which upon elimination of CO<sub>2</sub> yields a Pd-H species.



GC analysis showed traces of CO<sub>2</sub> and was confirmed by a reaction with excess of catalyst precursor (260 mg of Pd(OAc)<sub>2</sub>), which showed significant amount (0.61% in the gas phase) of CO<sub>2</sub> in the gas phase. Since, water was found to be essential for catalytic activity, it is reasonable to propose that Eq. 2.8 is the major pathway for the formation of active palladium hydride.<sup>26</sup> When the amount of water is not sufficient, formation of the hydride will also be limited causing an overall decrease in the rate of reaction.

In principle, the mechanism as schematised by Eq. 2.7 may also be operative. The beneficial effect of TsOH, may be due to the increase in the rate of cleavage of the Pd-C bond of the Pd-C-C-COOH intermediate in Eq. 2.7 forming the product and the carbomethoxy

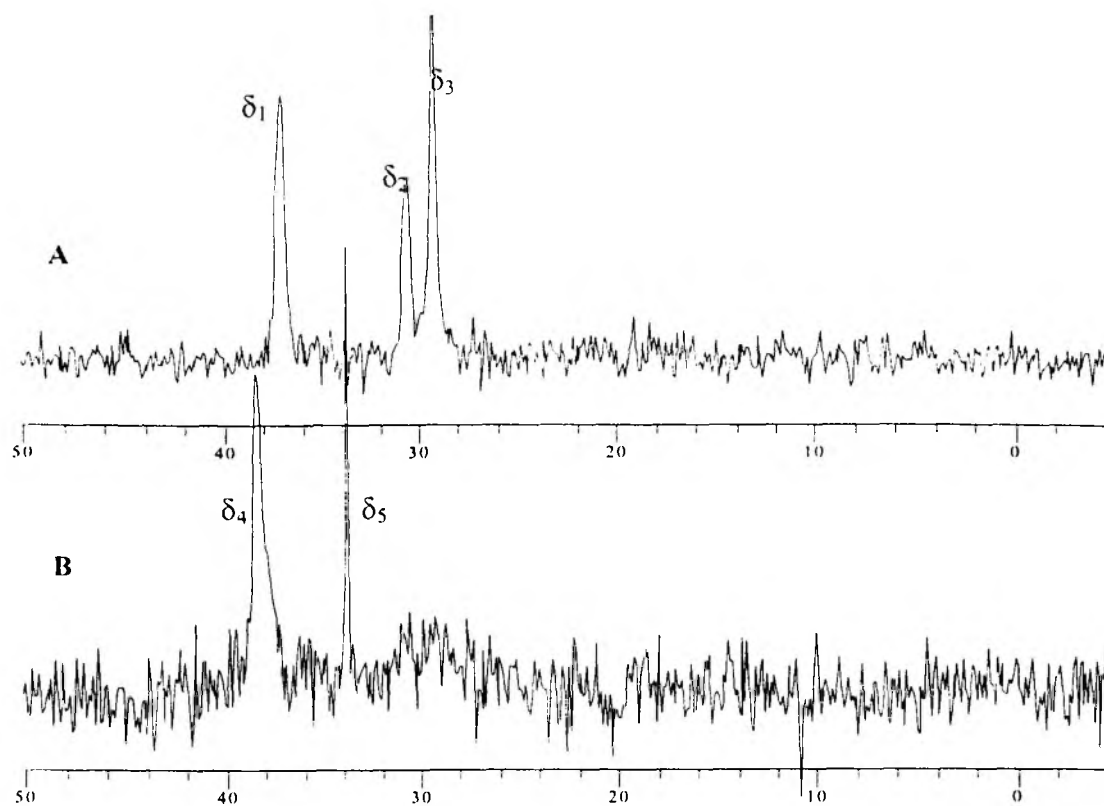
species back. However, this does not explain the beneficial effects of hydrogen and water. For example hydrogen upon activation by the metal cation can split the Pd-C  $\sigma$ -bond of the intermediate **H** giving rise to the product and a Pd-H species as per Eq. 2.9.



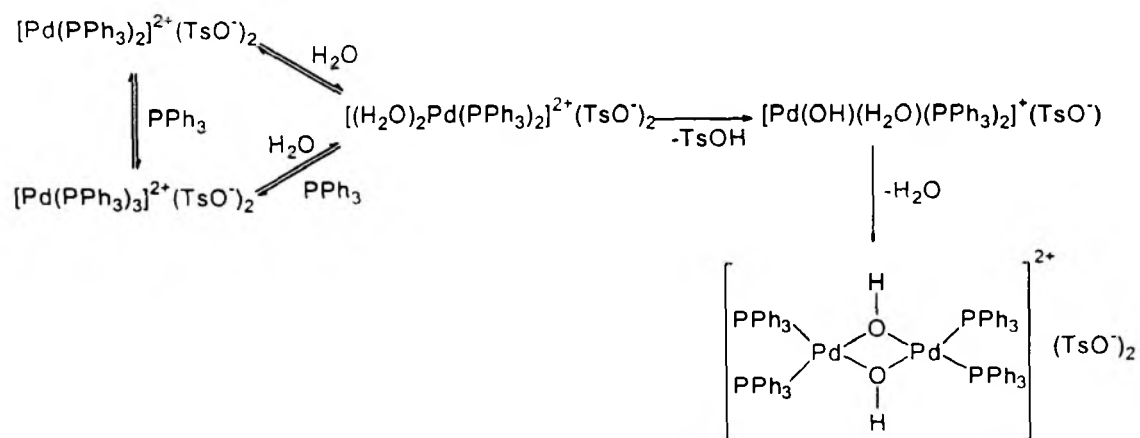
If this is true, the catalysis should proceed further only through the hydride mechanism. In order to further understand the reaction pathway, the nature of active catalytic intermediates formed under reaction conditions was investigated by isolation and characterization and by  $^{31}\text{P}$  NMR experiments, as discussed in following sections.

### 2.3.2.1. Formation active palladium hydride

The *in situ* generated  $\text{Pd}(\text{OTs})_2(\text{PPh}_3)_2$ , **I**, from  $\text{Pd}(\text{OAc})_2/4\text{PPh}_3/10\text{TsOH}$  exists as a cationic species in polar solvents like methanol as evidenced from  $^{31}\text{P}$  NMR analysis. The spectrum (Figure 2.6) showed three signals at 37.06 ( $\delta_1$ ), 30.58 ( $\delta_2$ ) and 29.19 ( $\delta_3$ ) ppm, corresponding to the palladium dicationic complexes  $[\text{Pd}(\text{PPh}_3)_2]^{2+}(\text{TsO}^-)_2$ ,  $[\text{Pd}(\text{H}_2\text{O})_2(\text{PPh}_3)_2]^{2+}(\text{TsO}^-)_2$  and  $[\text{Pd}(\text{PPh}_3)_3]^{2+}(\text{TsO}^-)_2$  respectively according to the values reported in the literature for similar palladium dicationic complexes.<sup>27</sup> This solution showed a different spectrum after keeping for 2–4 hours. Two new signals at 38.35 ( $\delta_4$ ) and 33.8 ( $\delta_5$ ) were developed at the expense of  $\delta_1$ ,  $\delta_2$  and  $\delta_3$  as shown in Figure 2.6. This change in the spectrum could be due to the degradation of these cationic palladium species upon interaction with water present in the solvent. The signal at  $\delta_4$  corresponds to a dicationic species  $[\text{Pd}(\mu\text{-OH})(\text{PPh}_3)_2]^{2+}(\text{TsO}^-)_2$ <sup>28</sup> formed as shown in Scheme 2.3. As mentioned earlier, the isolated  $\text{Pd}(\text{OTs})_2(\text{PPh}_3)_2$  was highly moisture sensitive and changed to a brown sticky mass when exposed to air for 10-15 minutes. The signal at  $\delta_5$  was assigned to triphenylphosphine oxide,  $\text{O}=\text{PPh}_3$ , in consistent with a standard sample in methanol (26.5 ppm in DMF).



**Figure 2.6.**  $^{31}\text{P}$  NMR of a mixture of  $\text{Pd}(\text{OAc})_2/4\text{PPh}_3/10\text{TsOH}$  in methanol, (A) immediately recorded, (B) recorded after 2–4 hours



Scheme 2.3

When the catalyst precursor system ( $\text{Pd}(\text{OAc})_2/4\text{PPh}_3/10\text{TsOH}$ ) was reacted with CO (3.4 MPa) at 348 K for 30 minutes, shining white flakes of a complex were obtained on cooling the reactor contents to room temperature.

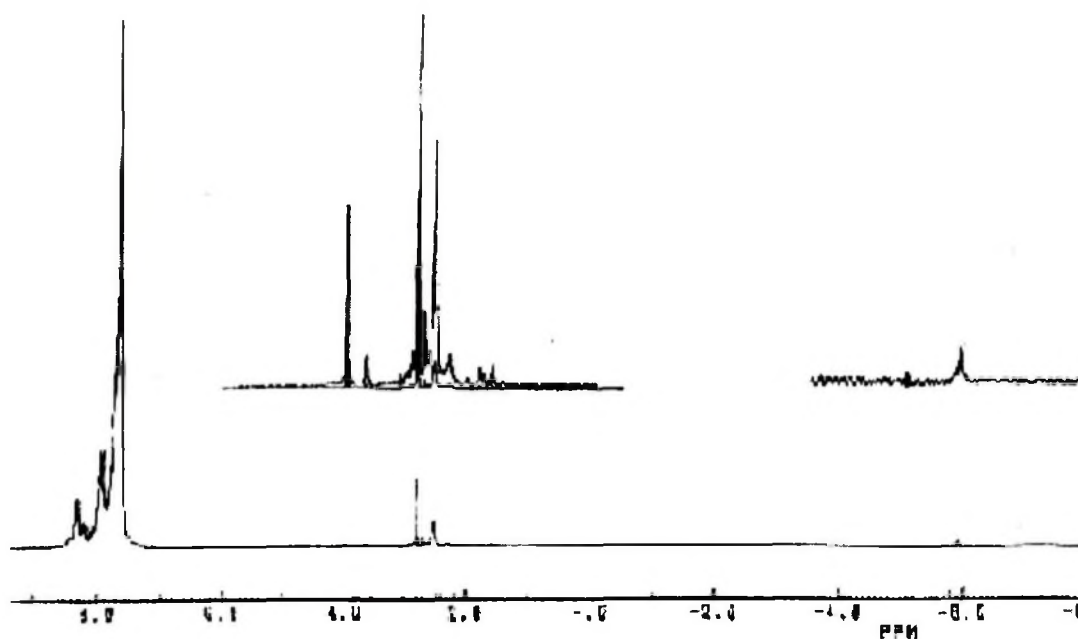


Figure 2.7.  $^1\text{H}$  NMR of the isolated palladium hydride VI

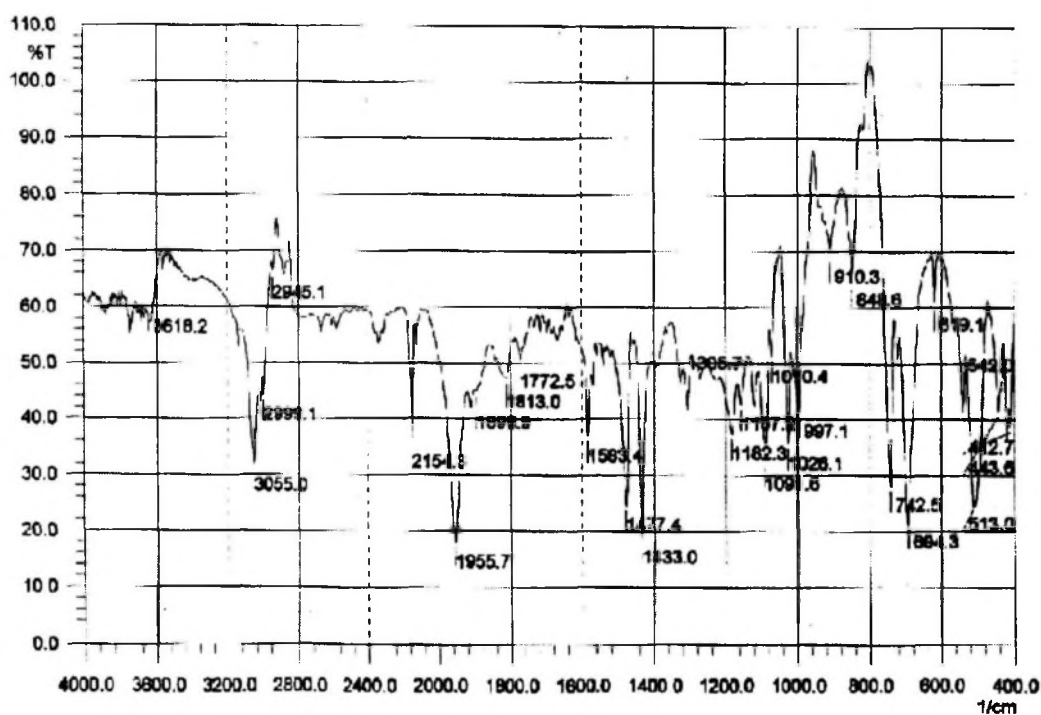


Figure 2.8. FT-IR of the isolated palladium hydride VI

The supernatant solution was light yellow in colour, which changed to black slowly on exposure to air showing precipitation of palladium metal. The white complex was found



to be highly unstable and changed immediately to a light yellow and then to a brown complex and finally to Pd metal.  $^1\text{H}$  NMR (Figure 2.7) and IR (Figure 2.8) of the white complex were taken immediately. IR showed absorption at  $2154\text{ cm}^{-1}$  corresponding to Pd-H<sup>29</sup> in addition to carbonyl absorption at  $1955.7\text{ cm}^{-1}$ .  $^1\text{H}$  NMR showed a weak Pd-H signal at  $-5.9\text{ ppm}$ . This Pd-H signal was found to be different from that observed from a mixture of Pd(PPh<sub>3</sub>)<sub>4</sub> with excess TsOH in CDCl<sub>3</sub>. In the latter case two Pd-H signals at  $-6.7$  and  $-7.3\text{ ppm}$  were observed and can be assigned to [HPd(PPh<sub>3</sub>)<sub>2</sub>S]<sup>+</sup>(TsO<sup>-</sup>) and [HPd(PPh<sub>3</sub>)<sub>3</sub>]<sup>+</sup>(TsO<sup>-</sup>) respectively, where S is a solvent molecule (Appendix-I, Figure A1.1). The *in situ* formation of palladium hydride species from a mixture of Pd(0) complexes with TsOH have been reported earlier.<sup>30</sup> The yellow flakes that formed from the white complex showed only the carbonyl absorption at  $1955.5\text{ cm}^{-1}$  and no signal corresponding to Pd-H was observed in IR (Appendix-I, Figure A1.2) or in  $^1\text{H}$  NMR (Appendix-I, Figure A1.3). Elemental analysis of this complex showed the presence of phosphorous and sulphur. Further characterization was difficult due to its instability even under inert atmosphere and at lower temperature.

From the decomposed solution of the complex in CDCl<sub>3</sub>, transparent faint yellow crystals were obtained in addition to palladium metal. The crystal was identified as PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>.CDCl<sub>3</sub> by X-ray crystallography and may form by the interaction of palladium hydride with the residual HCl present in CDCl<sub>3</sub>. With these evidences, it can be proposed that the isolated complex has a formula [HPd(CO)(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup>(TsO<sup>-</sup>), (VI). Palladium hydrides are generally quite unstable for isolation<sup>31</sup> and have been fully characterized only in few cases.<sup>32</sup> Even though the bridged binuclear palladium hydridocarbonyl species has been well characterized,<sup>33</sup> no mononuclear analogue was isolated and characterized, but has been proposed.<sup>34</sup> Platinum analogue of VI has been reported earlier.<sup>35</sup>

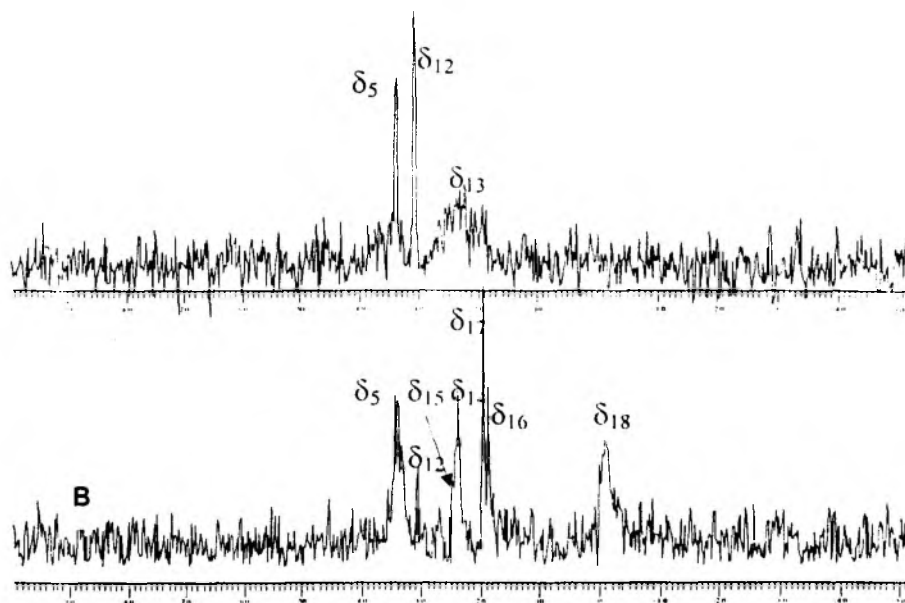
No Pd-methoxy complexes were isolated in the above case in presence of excess TsOH. But, when the same reaction was carried out in the absence of TsOH, yellow microcrystalline complex, which turned slowly to red was obtained on cooling the reactor contents to room temperature. IR (Appendix-I, Figure A1.4) of this complex showed two

characteristic strong carbonyl absorptions at  $1955\text{ cm}^{-1}$  and  $1860\text{ cm}^{-1}$  corresponding to  $\text{Pd}(\text{CO})(\text{PPh}_3)_3$  and  $[\text{Pd}(\text{CO})(\text{PPh}_3)]_n$  respectively.<sup>36</sup>  $^{31}\text{P}$  NMR (Appendix-I, Figure A1.5) of this mixture of complexes showed three signals at 27.43 ( $\delta_6$ ), 22.19 ( $\delta_7$ ) and 20.12 ( $\delta_8$ ) ppm in DMF as a solvent.  $^{31}\text{P}$  NMR spectrum (Appendix-I, Figure A1.6) of the mother liquor (methanol solution) after isolating the above complex showed three weak signals at 19.02 ( $\delta_9$ ), 19.62 ( $\delta_{10}$ ) and 19.92 ( $\delta_{11}$ ) in addition to a sharp signal at  $-4.13$  corresponding to free  $\text{PPh}_3$ . A pale yellow complex was isolated on evaporation of the solvent, IR (Appendix-I, Figure A1.7) of which showed strong carbonyl absorptions at 1671 and  $1654\text{ cm}^{-1}$  and at 1304 and  $1060\text{ cm}^{-1}$  corresponding to  $\text{Pd}(\text{COOMe})(\text{OAc})(\text{PPh}_3)_2$  as well as very weak absorptions at 1630 and  $1010\text{ cm}^{-1}$  corresponding to  $\text{Pd}(\text{COOMe})_2(\text{PPh}_3)_2$ .<sup>37</sup>

When the same reaction was carried out with 2 equivalents of TsOH, pale yellow shining flakes of a complex were obtained, which showed a carbonyl absorption at  $1955\text{ cm}^{-1}$  corresponding to  $\text{Pd}(\text{CO})(\text{PPh}_3)_3$ . Evaporation of the mother liquor gave a yellow complex, which showed strong absorptions (IR) at  $1955\text{ cm}^{-1}$  along with weak carbonyl absorptions at 1751 and  $1625\text{ cm}^{-1}$  (Appendix-I, Figure A1.8). No carbonyl absorption corresponding to carbomethoxy complexes was observed in this case. This suggests that formation of palladium carbomethoxy complexes is quite unlikely in the presence of TsOH. The instability of carbomethoxy species in acidic medium has also been reported earlier.<sup>38</sup>

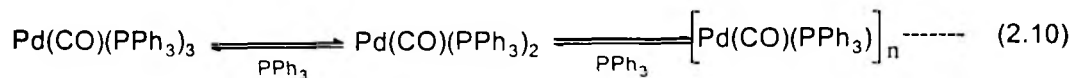
In order to further investigate the nature of species formed in solution in the presence of CO under reaction conditions (348 K and 3.4 MPa of CO), experiments were performed and intermediate liquid samples were taken under CO atmosphere to follow by  $^{31}\text{P}$  NMR analysis. An intermediate sample from the reaction of  $\text{Pd}(\text{OAc})_2/4\text{PPh}_3$  with excess of TsOH (ten equivalents) under 348 K and 3.4 MPa of CO, showed a signal at 30.5 ppm ( $\delta_{12}$ ) and a broad signal between 18–25 ppm ( $\delta_{13}$ ) along with a small signal at  $\delta_5$  (that of  $\text{O}=\text{PPh}_3$ ) as shown in Figure 2.9.



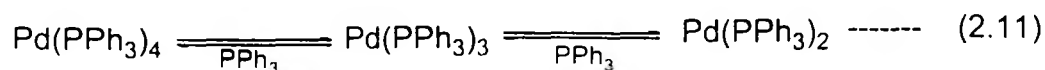


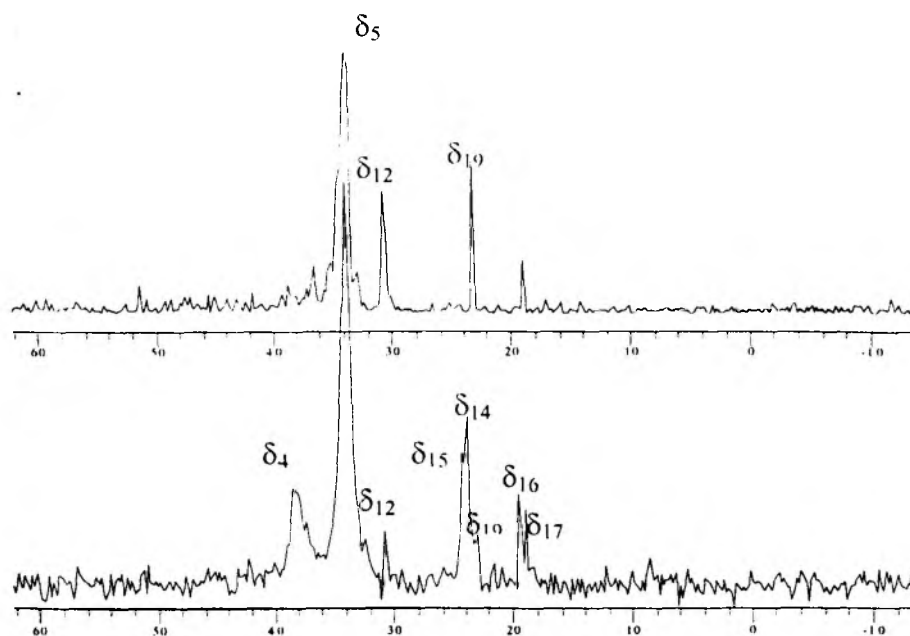
**Figure 2.9.**  $^{31}\text{P}$  NMR of the mother liquor of a reaction of  $\text{Pd}(\text{OAc})_2/4\text{PPh}_3/10\text{TsOH}$  under 3.4 MPa psig at 348 K in methanol. (A) Intermediate sample, (B) Intermediate sample added with styrene.

The broad signal can be assigned to  $\text{Pd}(0)$  carbonyls in fast equilibrium with free  $\text{PPh}_3$  as per Eq. 2.10.



When the spectrum was recorded with immediately added styrene to a fresh intermediate sample of the above reaction, two new signals were found to develop at 23.65 ( $\delta_{14}$ ) and 24.09 ppm ( $\delta_{15}$ ) at the expense of the signal at  $\delta_{12}$  (Figure 2.10). The broad signal at  $\delta_{13}$  disappeared and two new sharp signals at 19.35 ( $\delta_{16}$ ) and 18.72 ( $\delta_{17}$ ) ppm, which can be assigned to  $\text{Pd}(\text{CO})(\text{PPh}_3)_n$ , where  $n=2$  or 3, along with a broad signal from 4 to -4 ppm ( $\delta_{18}$ ) were developed. The new broad signal is due to the fast equilibrium between  $\text{Pd}(0)$ -phosphine complexes and free  $\text{PPh}_3$ <sup>39</sup> as shown in Eq. 2.11.



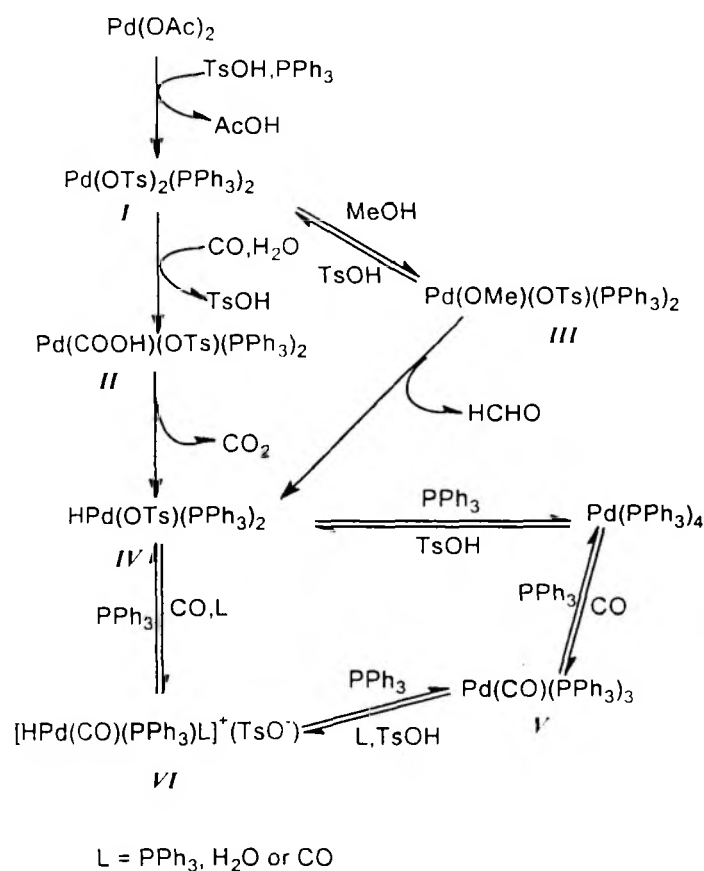


**Figure 2.10.** (A)  $^{31}\text{P}$  NMR of the mother liquor of a reaction of  $\text{Pd}(\text{OAc})_2/4\text{PPh}_3/10\text{TsOH}$  under 3.4 MPa at 348 K after keeping overnight under CO. (B) Spectrum recorded after reaction with styrene

The signals at  $\delta_{14}$  and  $\delta_{15}$ , correspond to Pd-alkyl complexes and can be assigned to the species  $[(n\text{-St})\text{Pd}(\text{CO})(\text{PPh}_3)_2]^+(\text{TsO}^-)$ , (**X**), and  $[(iso\text{-St})\text{Pd}(\text{CO})(\text{PPh}_3)_2]^+(\text{TsO}^-)$ , (**VIII**). These values agree well with those reported for palladium alkyl complexes.<sup>40</sup> Since, these alkyl complexes were formed at the expense of the signal at  $\delta_{12}$ , the complex corresponding to the signal  $\delta_{12}$  can be assigned to the palladium hydride species **VI**. In order to confirm that the signal at 30.5 ppm is the Pd-H species **VI**, a reaction was carried out under similar conditions in which white flakes of Pd-H, **VI** were isolated. The supernatant liquid after keeping overnight under CO showed the signal at  $\delta_{12}$  along with signals at  $\delta_5$ ,  $\delta_{16}$  and  $\delta_{17}$ . A new signal at 23.3 ppm ( $\delta_{19}$ ) was also observed in this case. In this reaction mixture containing the white flakes and the mother liquor, styrene was added and stirred under CO atmosphere at 313 K for 10 minutes. An intermediate sample of this reaction also showed the development of signals at  $\delta_{14}$  and  $\delta_{15}$  at the expense of the signals at  $\delta_{12}$  and  $\delta_{19}$ , in addition to a broad signal at  $\delta_4$  (Figure 2.10). This further confirms that the signal at  $\delta_{12}$  corresponds to the palladium hydride species **VI**. The signal at  $\delta_{19}$  can be



under the present set of conditions. Species **IV** on co-ordination with CO forms the active catalytic intermediate **VI**, which initiates the catalytic cycle.



Scheme 2.5. Formation of the active palladium hydride

As explained before, Pd(0) species were found to be formed under reaction conditions. This suggests that the active Pd–H species is in equilibrium with Pd(0) species such as Pd(PPh<sub>3</sub>)<sub>4</sub> or/and Pd(CO)(PPh<sub>3</sub>)<sub>3</sub> as shown in Scheme 2.4 and 2.5. This fact is also supported by the formation of Pd–H species, on interaction of Pd(PPh<sub>3</sub>)<sub>4</sub> with TsOH as evidenced by the <sup>1</sup>H NMR experiments discussed before. The slight rate enhancement (TOF 230 h<sup>-1</sup>) for hydroesterification reaction with Pd(PPh<sub>3</sub>)<sub>4</sub> also indicates the efficient formation of the active species **VI** from Pd(0) species. The palladium hydride **VI** was also isolated when the catalyst precursor system Pd(PPh<sub>3</sub>)<sub>4</sub>/10TsOH was treated with CO under similar conditions as described earlier.

### 2.3.2.2. Catalytic cycle

Isolation of Pd-H species under reaction conditions and its reactivity towards insertion of styrene forming Pd-alkyl species, as well as for hydroesterification reaction indicate the involvement of hydride mechanism rather than the methoxy mechanism. Another key intermediate in the catalytic cycle, which can prove the involvement of hydride mechanism without ambiguity, is the palladium acyl complex. Generally, nucleophilic attack of methanol to Pd-acyl complexes is regarded as the rate-determining step in the case of carbonylation of olefins proceeding through the Pd-H mechanism.<sup>44</sup> Hence to isolate the palladium acyl species, hydroesterification reaction was carried at lower temperature (328 K) where the reaction rate was very low. From this reaction, an air sensitive yellow crystalline complex was obtained on keeping the reaction mixture under CO pressure for two days.

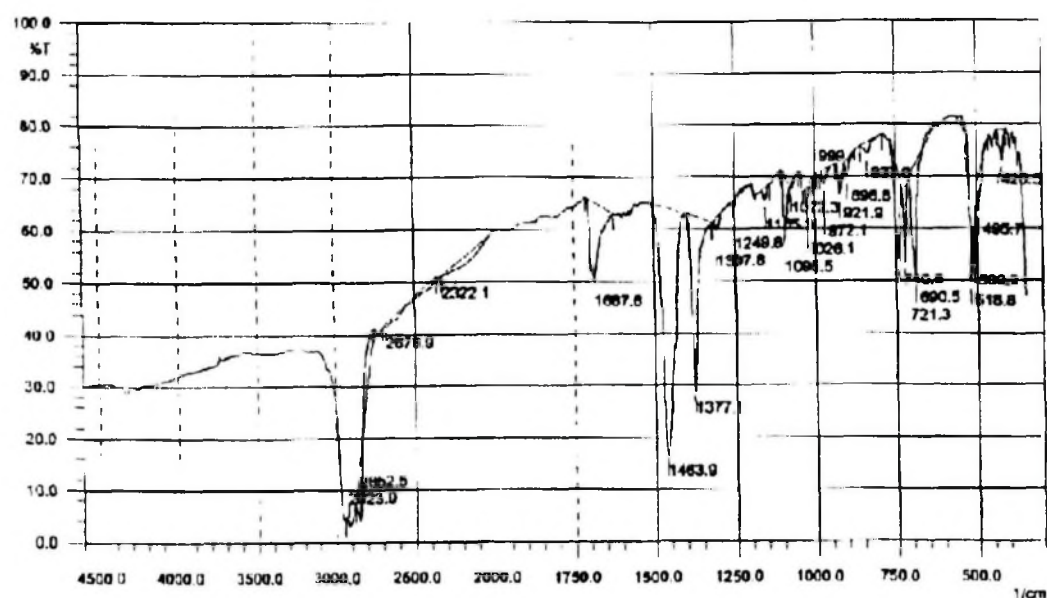
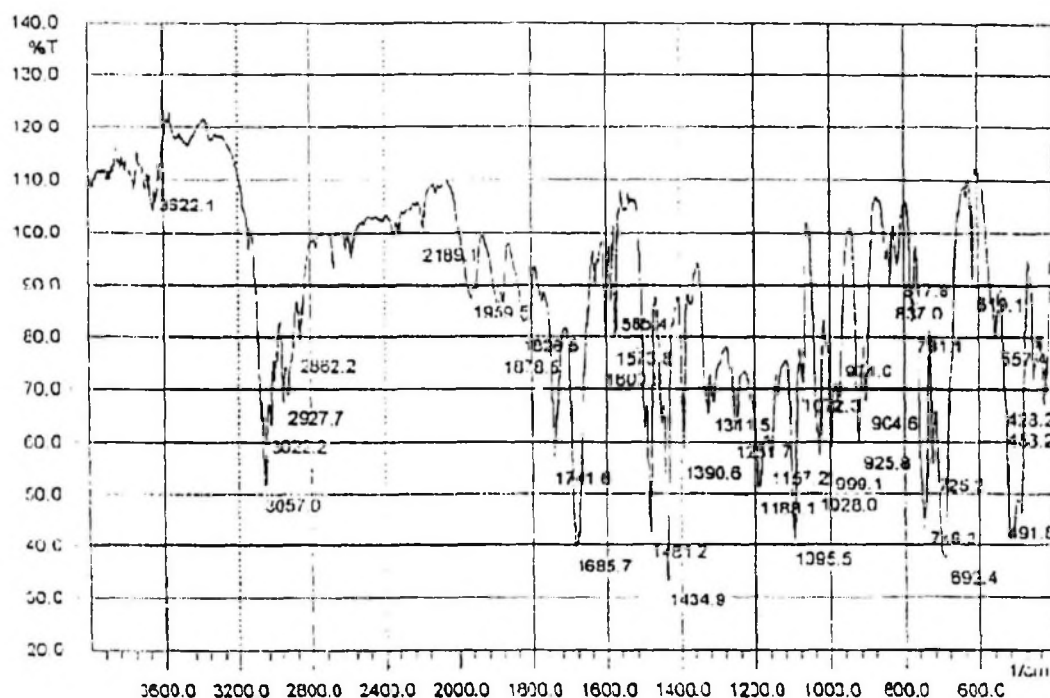


Figure 2.11. IR spectrum of the isolated cationic palladium acyl complex

IR of this complex showed a strong absorption at  $1687\text{cm}^{-1}$ , characteristic frequency of a Pd-acyl complex, and is assigned to Pd-CO-sty species (Figure 2.11).  $^1\text{H}$  NMR (Appendix-I, Figure A1.9) showed that the isolated complex is a mixture of *iso*- and *n*-palladium acyl complexes (XI and XII). The complex was not so stable probably due to the presence of weakly coordinating ligands and immediate decomposition was observed. In order to obtain a more stable acyl complex, hydroesterification reaction was carried out with

$\text{PdCl}_2$  as the catalyst precursor instead of  $\text{Pd}(\text{OAc})_2$  and the formed acyl complex was found to be more stable than the earlier one. This complex showed a strong carbonyl absorption at  $1685\text{ cm}^{-1}$  characteristic of a Pd-acyl group (Figure 2.12).



**Figure 2.12.** IR spectrum of the acyl complex,  $\text{PdCl}(\text{COCH}_2\text{CH}_2\text{Ph})(\text{PPh}_3)_2$  (**XIII**)

The  $^{13}\text{C}$  NMR signal (Figure 2.14) for the acyl CO was observed at 234 ppm, which is 61 ppm down field compared to that of the free ester, **2**.  $^1\text{H}$  NMR (Figure 2.13) showed that the styrene moiety is coordinated in a linear fashion and no *iso*-coordination was detected. A very small amount of the product **1** was detected as an impurity by both IR ( $1741.6\text{ cm}^{-1}$ ) and  $^1\text{H}$  NMR. The observation of only one  $^{31}\text{P}$  NMR (Appendix-1, Figure A1.10) signal (19.99 ppm) indicates that the two phosphine ligands are in the same environment and the complex has a structural formula *trans*- $\text{PdCl}(\text{COCH}_2\text{CH}_2\text{Ph})(\text{PPh}_3)_2$  (**XIII**). Similar types of acyl complexes have been reported to be isolated from the hydrocarbonylation of hexene<sup>45</sup> and propene<sup>46</sup> using  $\text{PdCl}_2(\text{PPh}_3)_2$  as the catalyst precursor. The activity of the isolated Pd-acyl complex, *trans*- $\text{PdCl}(\text{COCH}_2\text{CH}_2\text{Ph})(\text{PPh}_3)_2$ , was checked by shaking the complex with methanol in a Schlenk flask under argon atmosphere.

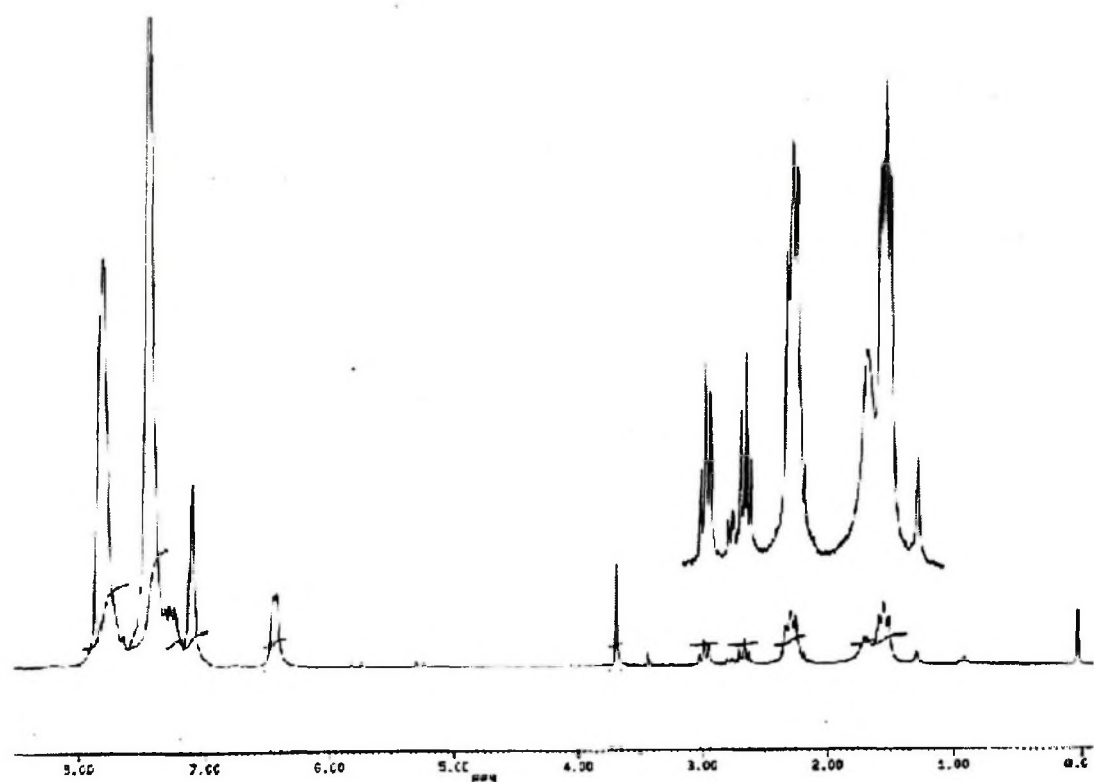


Figure 2.13. <sup>1</sup>H NMR spectrum of the acyl complex, PdCl(COCH<sub>2</sub>CH<sub>2</sub>Ph)(PPh<sub>3</sub>)<sub>2</sub> (XIII)

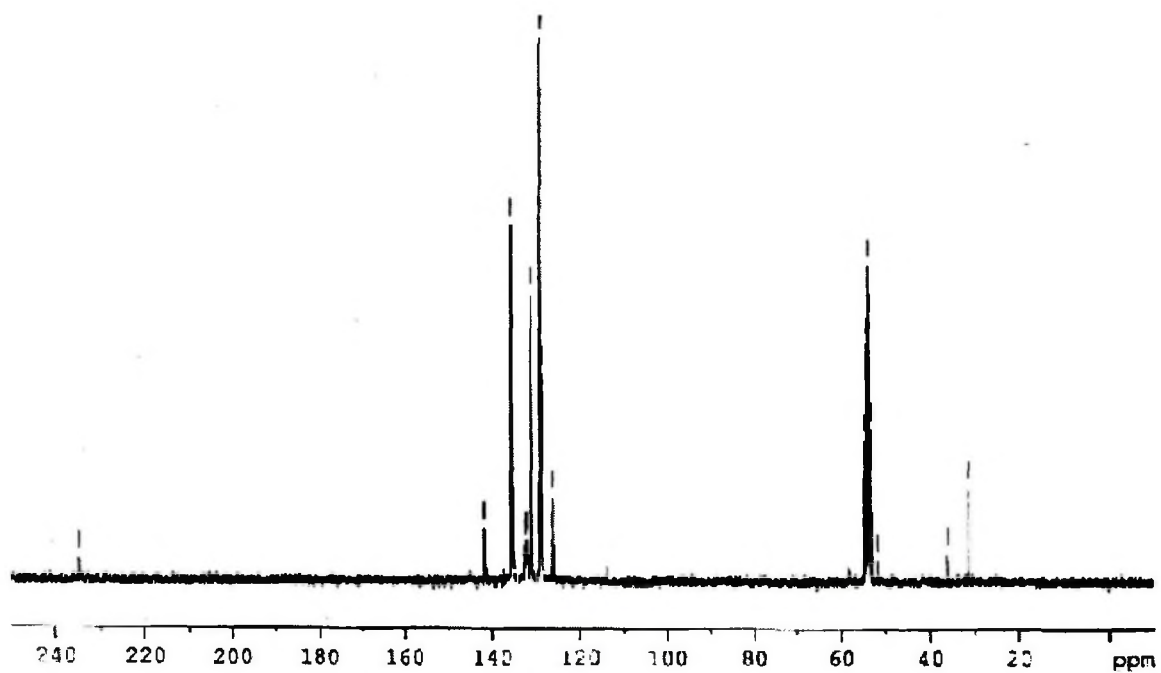
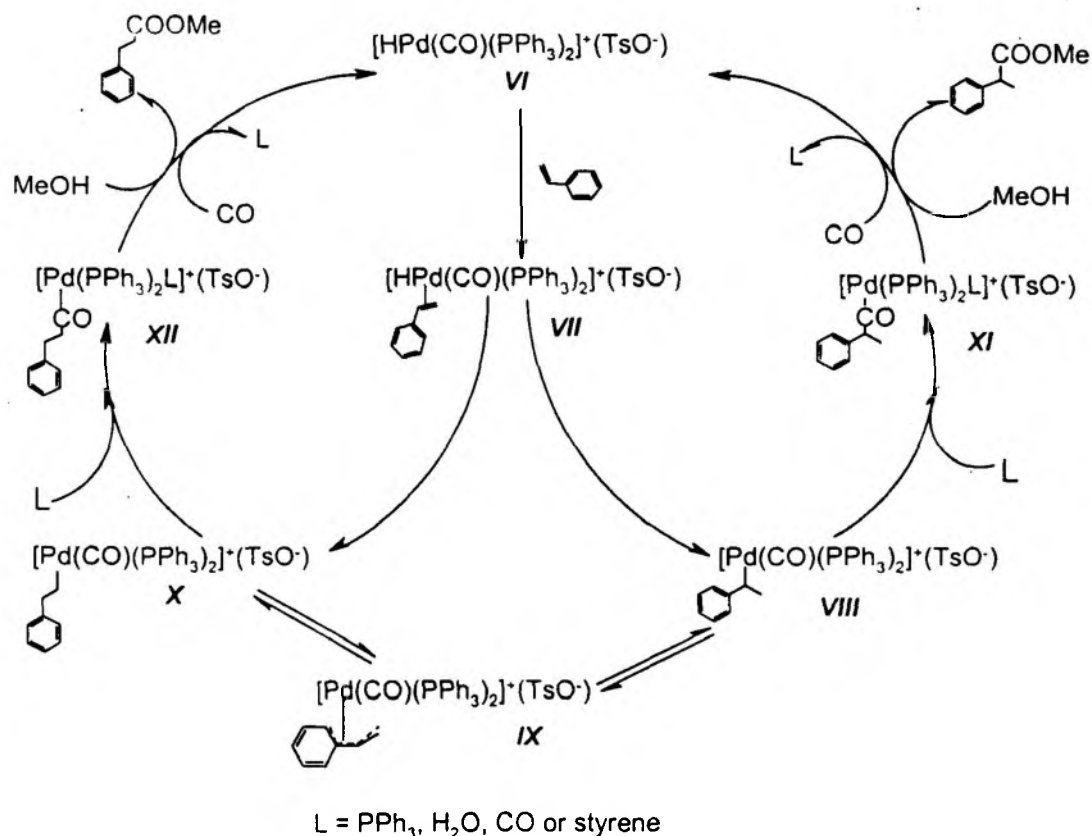


Figure 2.14. <sup>13</sup>C NMR spectrum of Pd-acyl complex, PdCl(COCH<sub>2</sub>CH<sub>2</sub>Ph)(PPh<sub>3</sub>)<sub>2</sub> (XIII)

Formation of **2** was observed (by GC as well as by  $^1\text{H}$  NMR) and the complex changed slowly to reddish brown colour and finally to palladium metal. Formation of **2** as the only product also confirms that the acyl complex is a linear acyl species similar to the species **XII**. A small difference in elemental analysis is due to the presence of impurities and the purification beyond this was difficult because of its unstable nature. The isolation of Pd-H as well as Pd-acyl complexes under reaction conditions confirms the involvement of hydride mechanism for the hydroesterification of styrene using  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{TsOH}$  as the catalyst system. As shown in Scheme 2.6, the catalytic cycle starts with the insertion of styrene into the Pd-H bond<sup>47</sup> of the active palladium hydrido carbonyl species **VI** forming the Pd-alkyl complex (**VIII** or **X**), through **VII** as an intermediate.

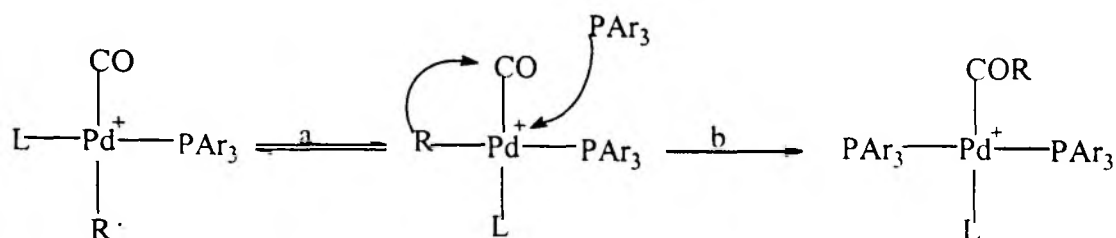


Scheme 2.6. Catalytic cycle

The  $\pi$ -complex **VII** can change to either the complex **VIII** or **X** on insertion into the Pd-H bond depending on steric as well as electronic bulk around the palladium center.



Decreased electronic crowd and steric bulk results in the enhanced formation of **VIII** in which the alkyl group is coordinated in an *iso* fashion. On the other hand formation of **X** is enhanced by increased electronic as well as steric bulk around the palladium centre. The  $\sigma$ -alkyl complexes **VIII** and **X** on migratory insertion form the acyl complexes, **XI** and **XII** respectively. Earlier studies<sup>48</sup> have shown that CO migratory insertion proceeds through intermediates, in which the carbonyl and the alkyl groups are *cis* to each other and the *trans* alkyl complex needs to be converted to the *cis* configuration before migration results (Scheme. 2.7).



Scheme 2.7.

Increase in the coordination ability of the phosphorous ligand (e.g.: PCy<sub>3</sub>, PBu<sub>3</sub>), *trans* to the alkyl group is known to have retarding effect on the rate of migratory insertion.<sup>49</sup> The labile nature of phosphorous ligand, especially that of PPh<sub>3</sub>, helps the migratory insertion by occupying the *trans* position of the migrating alkyl group (step b) and facilitating the easy migration to CO as shown in Scheme 2.7. Electron withdrawing ligands like P(*p*-ClC<sub>6</sub>H<sub>4</sub>)<sub>3</sub> can retard this effect due to low co-ordination ability. If 'L' or 'PAr<sub>3</sub>' is strongly bound to the palladium center, the *cis-trans* isomerization (step a) will not be favored and results in a decreased rate of migratory insertion. Solvents having high co-ordination ability ('L' can be the solvent) have also been reported to retard the migratory insertion and can be one of the reasons for low activity in the case of methyl ethyl ketone and acetone, though the formation of cationic species is enhanced in these solvents.

The formation of product esters from the palladium acyl complex is the final step in the catalytic cycle, which generates the active palladium hydride for further catalysis. Methanol can attack the palladium acyl complex in two ways, i.e., through coordination to the

acyl complex or by the direct nucleophilic attack as explained by Lin and Yamamoto for the hydroesterification of benzylic halides.<sup>50</sup> Though both the modes of attack can be operating in the present system, most plausible one is the direct nucleophilic attack of methanol to the Pd-acyl bond.

## 2.4. Conclusions

Hydroesterification (alkoxycarbonylation) of styrene was investigated in detail using Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>/TsOH as a catalyst precursor system in methanol as a solvent. The presence of TsOH and traces of water was found to be necessary for catalytic activity. The selectivity towards the branched isomer was enhanced by electron withdrawing ligands and lower polarity of the medium. Hydrogen was found to increase the catalytic activity without affecting the product selectivity. The promoting effect of TsOH, water and hydrogen was consistent with a hydride mechanism and was confirmed by isolation of a palladium hydridocarbonyl species under reaction conditions. No palladium carbomethoxy complexes were detected under reaction conditions. The hydride mechanism was further confirmed by isolation of cationic palladium acyl complexes from the reaction mixture and formation of neutral palladium acyl complex PdCl(COCH<sub>2</sub>CH<sub>2</sub>Ph)(PPh<sub>3</sub>)<sub>2</sub> under reaction conditions. <sup>31</sup>P NMR experiments carried out to investigate the nature of species formed in solution in the presence of CO under reaction conditions also confirmed the formation of Pd-H as well as the Pd-alkyl species.

Th. 8320

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## Chapter 3

**Kinetics of Hydroesterification of Styrene  
using Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>/TsOH as the  
Catalyst**

### 3.1. Introduction

A majority of studies appeared in the literature on the carbonylation of vinyl aromatic compounds mainly focused on improving the catalytic performance and product selectivity or exploring alternative new catalyst systems. Generally palladium compounds such as PdCl<sub>2</sub>, Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, Pd(dppb)Cl<sub>2</sub>, etc., were used as catalyst precursors along with acidic promoters like HCl or TsOH as explained in Chapter 1. Use of cationic palladium complexes provided a halogen free catalyst system for the hydroesterification of vinyl aromatics with improved catalytic activity and selectivity at mild reaction conditions compared to that of the neutral complexes. Only a few reports have been published on the kinetics of carbonylation of styrene as evident from Table 1.2 of Chapter 1. Noskov *et. al.*<sup>1</sup> have reported the kinetics of carboxylation of styrene using a neutral palladium complex PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalytic precursor<sup>1,2,3</sup> in dioxane as a solvent. Independent rate equations were developed to explain the influence of concentration of different parameters such as styrene, catalyst, water<sup>2</sup>, SnCl<sub>2</sub><sup>3</sup> and PPh<sub>3</sub><sup>1</sup> as well as partial pressure of CO<sup>2</sup> on the rate of carbonylation. In all these cases rates of formation of both the linear (3-phenyl propionic acid) as well as *iso* (2-phenyl propionic acid) isomers were considered individually and the kinetic parameters evaluated. A brief review of these studies is presented in Chapter 1, Section 1.2.5.

As discussed in the previous chapter, hydroesterification of styrene using *in situ* formed Pd(OTs)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> catalyst from Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> and TsOH provides enhanced catalytic activity as well as selectivity under mild reaction conditions. A detailed investigation on the effect of various parameters affecting the catalytic activity and product selectivity as well as the mechanism has been discussed in Chapter 2. However, a detailed kinetics study is also essential to optimize the reaction conditions as well as to further understand the reaction mechanism. The aim of this work was to study the kinetics of hydroesterification of styrene using Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> and TsOH as a catalyst system. The effect of CO partial pressure, concentration of styrene, Pd(OAc)<sub>2</sub> and water on the rate of hydroesterification reaction has been studied for a temperature range of 338–358 K.



Different empirical rate models were considered and a suitable rate equation proposed, which explains the experimental trends and the kinetic parameters were evaluated.

## 3.2. Experimental Section

Styrene, TsOH (*p*-toluenesulphonic acid monohydrate), PPh<sub>3</sub>, Pd(OAc)<sub>2</sub> (Aldrich, USA) and CO (Matheson, USA) were used as received. Methanol (Sd Fine Chemicals, India) was distilled and degassed before use.

### 3.2.1. Experimental Procedure

All the reactions were carried out in a  $5 \times 10^{-5} \text{ m}^3$  Parr Autoclave made of Hastelloy C-276 having facilities for gas inlet and outlet, rupture disc as a safety measure in case of excessive pressure build up, intermediate sampling, temperature controlled heating and variable agitation speed, details of which are described in Chapter 2, Section 2.2.3. In a typical experiment, required quantities of styrene, Pd(OAc)<sub>2</sub>, PPh<sub>3</sub>, TsOH and methanol were charged into the autoclave and the contents were flushed with nitrogen and subsequently with CO. The autoclave was heated to the desired temperature and after attaining the temperature, the reactor was charged with CO to the required pressure. The reaction was initiated by switching the stirrer on. In order to maintain constant pressure in the reactor, CO was fed through a constant pressure regulator from a reservoir vessel ( $1 \times 10^{-4} \text{ m}^3$ ). The pressure drop in the reservoir vessel was recorded by means of a pressure transducer connected to a strip chart recorder. The consumption of CO as a function of time was recorded in each experiment. For kinetic study, experiments were carried out under different initial conditions and intermediate samples were taken at regular intervals of time during the initial period, in which styrene conversion was less than 10–15%. From the concentration–time profiles in the initial low conversion region, the rate of reaction was calculated. The rates were also evaluated from the CO absorption vs. time plots. In each kinetic run all the liquid samples were analyzed for concentration of reactants and products to verify material balance. Following this procedure, the effect of various parameters on the initial rate of reaction was studied. The reproducibility of experiments was found to be in a range of 95–99 %.

### 3.2.2. Analytical methods

Quantitative analysis of the liquid samples was carried out on a HP-5890 gas chromatograph by using HP-FFAP megabore column (30m x 0.53 mm x 0.1 mm film thickness on polyethylene glycol stationary phase). The standard conditions for analysis were similar to that given in Chapter 2 (Section 2.2.2).

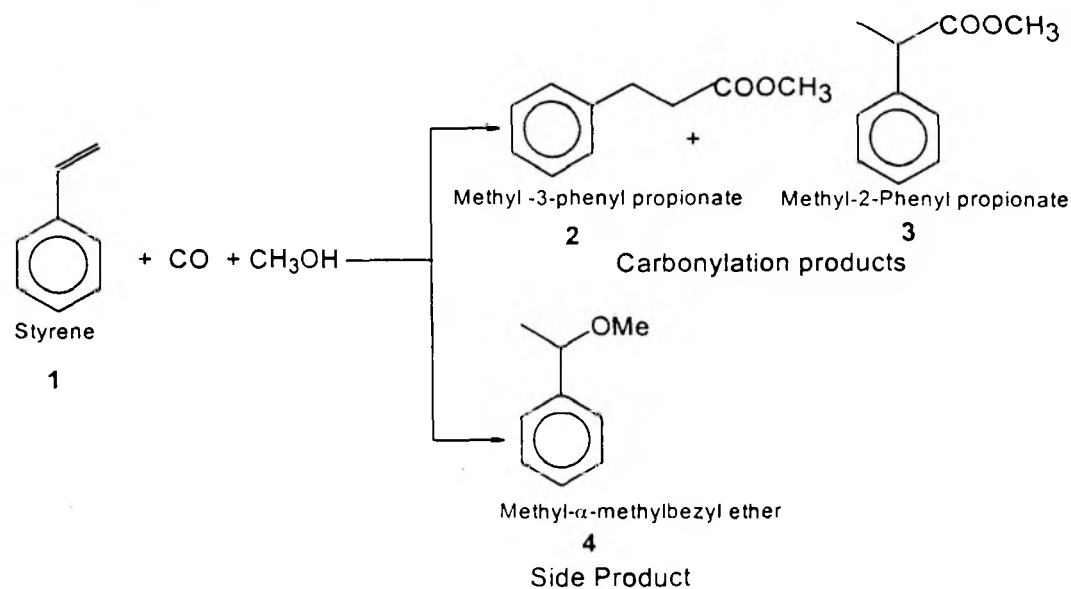
The initial rate of a reaction was calculated as

$$R_A [\text{kmol} \cdot \text{m}^{-3} \cdot \text{s}^{-1}] = \frac{\text{slope of \{concentration of carbonylation products (n + iso)\} [kmol] vs. time [s] plot}}{\text{total reaction volume [m}^3\text{]}}$$

The yield is reported as the concentration of product 2 or 3 formed after one hour of reaction and the overall catalytic activity (TOF) and product selectivity were calculated as described in Chapter 2 (Section 2.2.2).

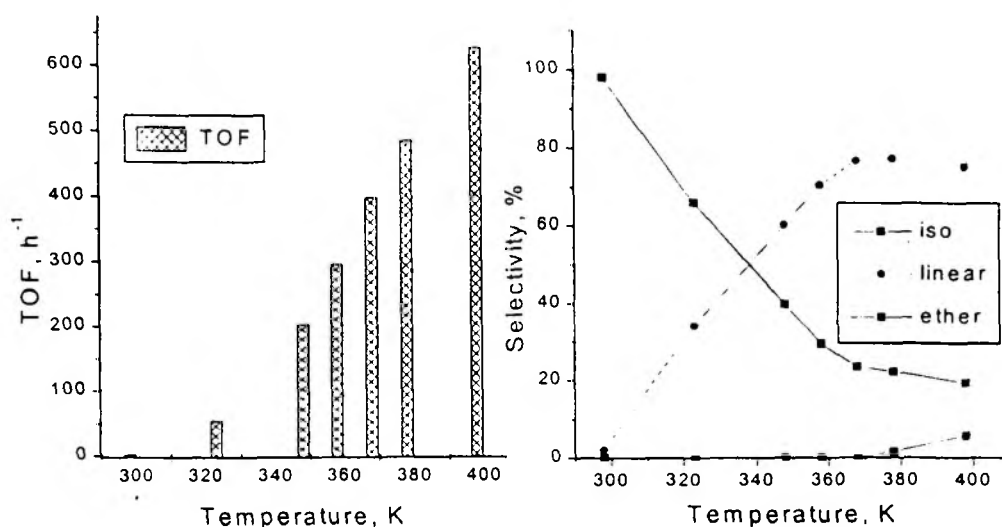
### 3.3. Results and discussion

Some preliminary experiments on the hydroesterification of styrene (Scheme 3. 1) were carried out using Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> and TsOH as the catalyst system in order to select the range of temperature for kinetic study as well as to check the mass transfer effects.



Scheme 3.1. Hydroesterification of styrene

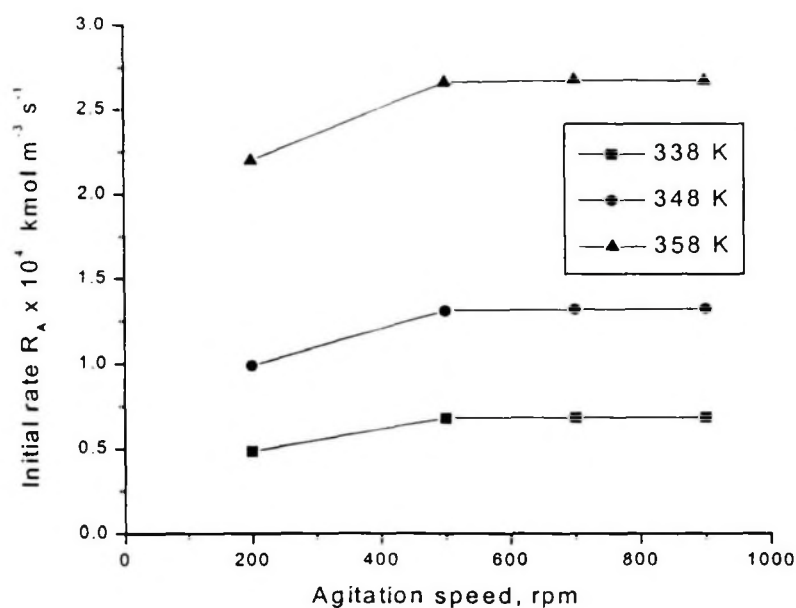
The catalytic activity increased and selectivity towards methyl-2-phenyl propionate (**3**) decreased with increase in temperature (see Figure 3.1). Above a temperature of 378 K, the formation of a byproduct, methyl- $\alpha$ -methylbenzyl ether (**4**) was also observed along with precipitation of palladium metal. At room temperature, even though, the selectivity of **3** was much higher (>98%), the catalytic activity was too low ( $2\text{h}^{-1}$ ). Hence, the most suitable temperature range for the kinetic study was 348 to 368 K.



**Figure 3.1.** Effect of temperature on catalytic activity and product selectivity

Reaction conditions: styrene,  $1.44\text{ kmol/m}^3$ ;  $\text{Pd}(\text{OAc})_2$ ,  $2.4 \times 10^{-3}\text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $9.6 \times 10^{-3}\text{ kmol/m}^3$ ;  $\text{TsOH}$ ,  $2.4 \times 10^{-2}\text{ kmol/m}^3$ ; water,  $4.62 \times 10^{-2}\text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 3.4 MPa

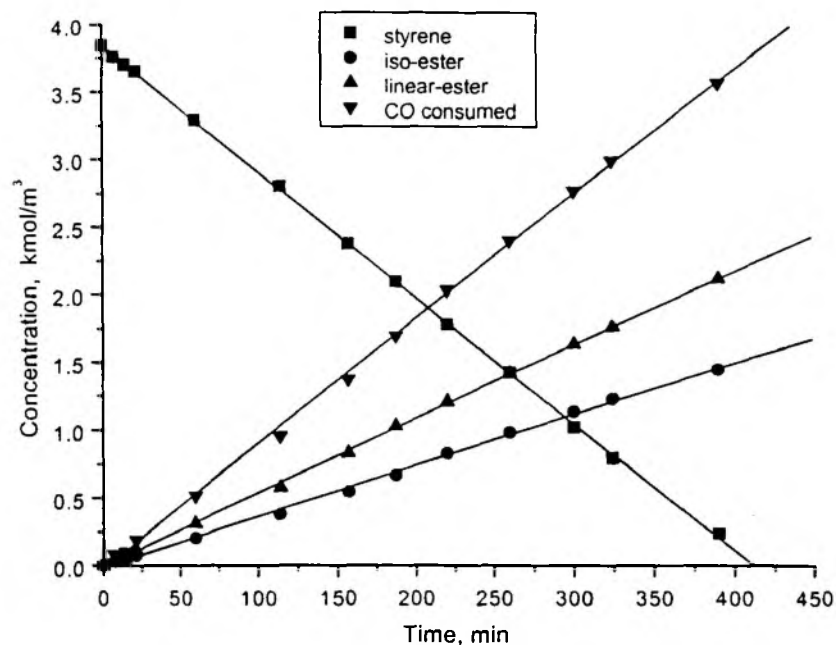
It was also important to ensure that all the experiments for kinetic study were done under kinetic regime, free from gas-liquid mass transfer limitations. In order to ensure that the rate data obtained were in kinetic regime, a few experiments were carried out at different agitation speeds (Figure 3.2). It was observed that, beyond 500 rpm, agitation speed has no effect on the initial rate of reaction at all the temperatures studied, indicating that the gas-liquid mass transfer resistance is unimportant. Hence all experiments for the present study were carried out at 900 rpm.



**Figure 3.2.** Effect of agitation speed on initial rate of reaction

*Reaction conditions:* styrene,  $1.44 \text{ kmol/m}^3$ ;  $\text{Pd}(\text{OAc})_2$ ,  $2.4 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $9.6 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{TsOH}$ ,  $2.4 \times 10^{-2} \text{ kmol/m}^3$ ; water,  $4.62 \times 10^{-2} \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 3.4 MPa

In order to check for the material balance and reproducibility of experiments, a few experiments were also carried out in which, the amount of styrene consumed, products formed as well as CO absorbed were compared for high conversions of styrene. A typical concentration-time profile for the hydroesterification of styrene at a temperature of 348 K is shown in Figure 3.3. The material balance of CO and styrene consumed and the hydroesterification products formed was found to be in the range of 95–99%. Only those experiments, in which the material balance as per the stoichiometry was greater than 96 %, were considered for the initial rate calculations.



**Figure 3.3.** A typical concentration-time profile for the hydroesterification of styrene

*Reaction conditions:* styrene,  $3.846 \text{ kmol/m}^3$ ;  $\text{Pd}(\text{OAc})_2$ ,  $2.4 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $9.6 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{TsOH}$ ,  $2.4 \times 10^{-2} \text{ kmol/m}^3$ ; water,  $4.62 \times 10^{-2} \text{ kmol/m}^3$ ; temperature, 348 K;  $P_{\text{CO}}$ , 3.4 MPa

### 3.3.1. Solubility data

For interpretation of kinetic data, knowledge of concentration of the gaseous reactants in the reaction medium (solubility) is essential. The solubility of CO in methanol, styrene and styrene/methanol mixtures was determined experimentally at 338, 348 and 358 K, using a method described by Purwanto *et. al.*<sup>4</sup> The solubility measurement was conducted in  $6.0 \times 10^{-4} \text{ m}^3$  capacity stirred autoclave supplied by Parr Instrument Company, USA designed for 25 MPa pressure. The equipment was provided with automatic temperature control and a pressure recording system. The temperature of the liquid in the reactor was controlled within  $\pm 1 \text{ K}$ . A pressure transducer having a precession of  $\pm 1 \text{ kPa}$  was used to measure the autoclave pressure.

In a typical experiment for the measurement of solubility of CO, a known volume ( $3 \times 10^{-4} \text{ m}^3$ ) of solvent was introduced into the autoclave and the contents were heated to

the desired temperature after flushing with nitrogen. After the thermal equilibrium was attained, the void space in the reactor was pressurised with CO to the level required. The contents were then stirred for about ten minutes to equilibrate the liquid phase with the solute gas. In general, it required only about 1–3 minutes to saturate the liquid phase. The change in the pressure in the autoclave was recorded as a function of time till it remained constant, indicating saturation of the liquid phase. From the initial and final pressure readings, the solubility was calculated in mole fraction as

$$X_a = \frac{(P_i - P_f)V_g M_s}{RTV_L \rho_s} \quad (3.1)$$

Where  $X_a$  represents the mole fraction of CO in the liquid phase at the partial pressure of the solute gas prevailing at  $P_f$ ,  $P_i$  and  $P_f$  are the initial and final pressure readings in the autoclave,  $V_g$  and  $V_L$  are the volumes of the gas and liquid phases, respectively,  $R$  is the gas constant,  $T$  is the temperature,  $M_s$  is the molecular weight of the solvent and  $\rho_s$  is the molar density of the liquid. The Henry's law constant,  $H_e$  was calculated as

$$H_e = \frac{X_a}{P_f} \quad (3.2)$$

The results are presented as Henry's constant in Table 3.2, which indicate that the increase in styrene concentration in methanol decreases the solubility of CO only marginally (5–7%).

The Henry's constant for carbon monoxide in methanol and styrene were also calculated using the correlation proposed by Reid and Prausnitz (1987)<sup>5</sup> based on the theory of regular solution. The correlation used is:

$$-\ln \chi_A = \ln \left( \frac{f_A^L}{f_A} \right) + \left\{ \frac{2V_A}{V_s} (\delta_s - \delta_A)^2 / RT \right\} \quad (3.3)$$

The use of this Eq. (3.3) requires a knowledge of three parameters of the solute viz: fugacity of hypothetical liquid,  $f_A^L$  (atm), solubility parameter  $\delta$ ,  $(\text{J/m}^3)^{1/2}$  and molar volume  $V_A$ , ( $\text{m}^3/\text{mol}$ ). The fugacity of hypothetical liquid solute ( $f_A^L$ ) depends upon the

critical temperature and critical pressure of the gas and was calculated from a correlation between fugacity and temperature (Eq 3.4), as reported by Yen and Mcketta (1962)<sup>6</sup>

$$f_u^L = P_c \exp \left\{ 7.224 - 5.534 \left( \frac{T_c}{T} \right) - 2.598 \ln \left( \frac{T}{T_c} \right) \right\} \quad (3.4)$$

The regular solution theory also states that the solubility parameters for gas ( $\delta_A$ ) and molar volume of solutes are independent of temperature and was obtained from the work of Prausnitz and Shair (1961)<sup>7</sup> ( $6.4 \times 10^3 \text{ J}^{0.5} \text{ m}^{-1.5}$  for CO). The solubility parameter ( $\delta_s$ ) for methanol and styrene was calculated from the heat of vaporisation as proposed by Hildebrand and Scott (1948).<sup>8</sup>

$$\delta_s = (\Delta H - RT/V_A)^{1/2} \quad (3.5)$$

The solubility values of CO in pure methanol and pure styrene were further used for calculating the solubilities of CO in a mixture of solvents (methanol/styrene) by using the method described by Hildebrand et.al. (1948)<sup>8</sup>, and given by following expression:

$$\left( \ln \chi_A \right)_{mix} = \phi_1 \ln(\chi_{A1}) + \phi_2 \ln(\chi_{A2}) - V_A \beta_{12} \phi_1 \phi_2 \quad (3.6)$$

where  $\beta_{12} = (\delta_{S1} - \delta_{S2})^2 / RT$ ;  $X_{A1}$ ,  $X_{A2}$  are the mole fraction of a gas in pure methanol and styrene,  $\phi_1$ ,  $\phi_2$  and  $\delta_{S1}$  and  $\delta_{S2}$  the volume fraction and the solubility parameters for methanol and styrene respectively.

The results predicted for pure methanol, styrene and methanol–styrene mixtures were found to be in good agreement with the experimental values (within  $\pm 3-4\%$ ) and is shown in Table 2.1. These data were used to calculate the concentration of dissolved CO in the liquid medium for interpretation of kinetic data. The concentration of CO was calculated as  $A^* = P_{CO} \times H_c$ .

**Table 3.1.** Henry's constants of CO in methanol, styrene, and methanol–styrene mixture

CO in	$H_c \times 10^4$ kmol/m <sup>3</sup> /MPa at 338 K		$H_c \times 10^4$ kmol/m <sup>3</sup> /MPa at 348 K		$H_c \times 10^4$ kmol/m <sup>3</sup> /MPa at 358 K	
	Expt.	Predicted	Expt.	Predicted	Expt.	Predicted
Methanol	8.521	8.586	9.004	9.146	9.698	9.728
8% (w/w) styrene in Methanol	7.992	7.949	8.358	8.451	8.924	8.972
20% (w/w) styrene in methanol	7.318	7.399	7.825	7.843	8.311	8.303
25%(w/w) styrene in methanol	7.153	7.267	7.598	7.693	8.141	8.134
50%(w/w) styrene in methanol	7.112	7.136	7.527	7.504	7.892	7.886
70%(w/w) styrene in methanol	7.348	7.476	7.721	7.819	8.127	8.174
80%(w/w) styrene in methanol	7.659	7.766	8.126	8.099	8.452	8.444
styrene	8.412	8.582	8.842	8.896	9.139	9.224

### 3.3.2. Initial rate, catalytic activity and selectivity

The effect of various parameters such as concentration of catalyst, styrene and water as well as partial pressure of CO on the initial rate of hydroesterification of styrene using the catalyst system Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>/TsOH in methanol was studied in the range of conditions given in Table 3.2.

**Table 3.2** Range of conditions for kinetic study

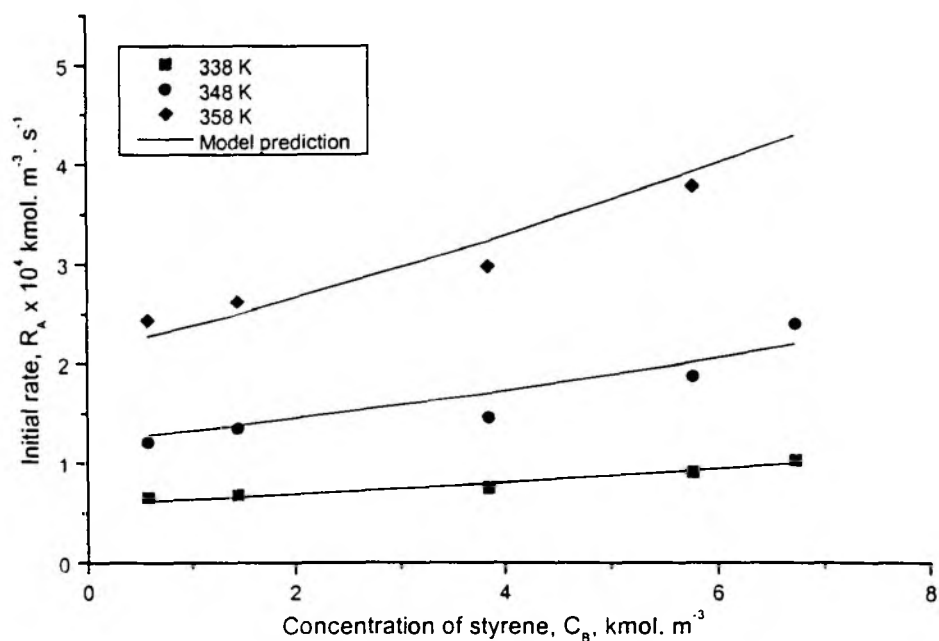
Concentration of Pd(OAc) <sub>2</sub> (kmol/m <sup>3</sup> )	$1.205 \times 10^{-3} - 7.23 \times 10^{-3}$
Concentration of styrene (kmol/m <sup>3</sup> )	0.567 – 6.73
Concentration of water (kmol/m <sup>3</sup> )	$2 \times 10^{-2} - 14 \times 10^{-2}$
Partial pressure of CO (MPa)	0.68 – 4.76
Temperature (K)	338 – 358
Reaction volume (m <sup>3</sup> )	$2.5 \times 10^{-5}$
Agitation speed (rpm)	900



The initial rates were calculated in which the styrene conversion was only 5–15 %. The overall catalytic activity and product selectivity were also calculated after one hour of reaction time and the results are discussed in the following sections.

### 3.3.2.1. Effect of concentration of styrene

The effect of concentration of styrene on the initial rate of hydroesterification of styrene was studied in a range of 0.567 to 6.73 kmol/m<sup>3</sup> at 338, 348 and 358 K and is shown in Figure 3.4. The carbonylation rate was observed to be virtually a constant for an initial styrene concentration within the range of 0.567 to 3.84 kmol/m<sup>3</sup>, beyond which the rate increased considerably.



**Figure 3.4.** Effect of concentration of styrene on initial rate of reaction

*Reaction conditions:*  $Pd(OAc)_2$ ,  $2.41 \times 10^{-3}$  kmol/m<sup>3</sup>;  $PPh_3$ ,  $9.64 \times 10^{-3}$  kmol/m<sup>3</sup>;  $TsOH$ ,  $2.4 \times 10^{-2}$  kmol/m<sup>3</sup>; water,  $4.62 \times 10^{-2}$  kmol/m<sup>3</sup>;  $P_{CO}$ , 3.4 MPa

This trend of increase in reaction rate after a styrene concentration of 3.846 kmol/m<sup>3</sup> was consistent at all the temperatures and the effect was more pronounced at higher temperatures. This kind of increase in reaction rate is interesting and was not obvious from

the previous reports on the hydrocarboxylation of styrene. However, Noskov *et. al.*<sup>9</sup> have reported an enhancement ( $0.58\text{--}0.88 \times 10^{-4} \text{ kmol}\cdot\text{m}^{-3}\cdot\text{s}^{-1}$ ) in the rate of formation of 2-phenyl propionic acid (*iso* product) with concentration of styrene ( $0.325\text{--}1.3 \text{ kmol}/\text{m}^3$ ), while that of 3-phenyl propionic acid was unaffected using  $\text{PdCl}_2(\text{PPh}_3)_2$  as a catalyst. But in the present case, the rate enhancement was observed only after a concentration of  $3.8 \text{ kmol}/\text{m}^3$ . As evidenced from Table 3.3, the yield (yield can be considered as an indirect measure of rate) of both the isomers were found to increase, but that of the *iso* ester (**3**) increased more compared to linear isomer (**2**).

**Table 3.3. Effect of Styrene concentration**

Sr. No	Styrene, $\text{kmol}/\text{m}^3$	Methanol, $\text{kmol}/\text{m}^3$	Selectivity, % (Yield, $\text{kmol}/\text{m}^3$ )		<i>n/iso</i>	TOF, $\text{h}^{-1}$
			<i>iso</i> -ester, <b>3</b>	<i>n</i> -ester, <b>2</b>		
1	0.576	23.01	39.8, (0.192)	60.2, (0.291)	1.53	203
2	1.442	20.49	39.4, (0.188)	60.6, (0.289)	1.62	200
3	1.923	19.12	38.9, (0.187)	59.6, ((0.286)	1.54	201
4	3.846	13.57	39.1, (0.206)	60.6, (0.316)	1.55	220
5	5.769	8.35	50.0, (0.341)	48.3, (0.328)	0.97	284
6	6.730	5.462	63.4, (0.618)	35.2, (0.343)	0.55	411

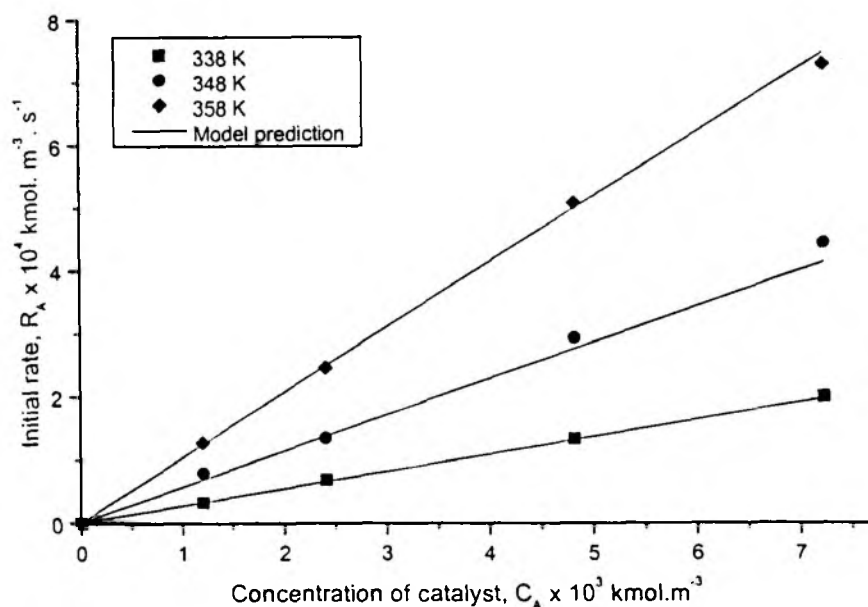
*Reaction conditions:*  $\text{Pd}(\text{OAc})_2$ ,  $2.41 \times 10^{-3} \text{ kmol}/\text{m}^3$ ;  $\text{PPh}_3$ ,  $9.64 \times 10^{-3} \text{ kmol}/\text{m}^3$ ;  $\text{TsOH}$ ,  $2.41 \times 10^{-2} \text{ kmol}/\text{m}^3$ ; temperature, 348 K; water,  $4.62 \times 10^{-2} \text{ kmol}/\text{m}^3$ ;  $P_{\text{CO}}$ , 3.4 MPa; reaction time, 1 hour

The *n/iso* ratio decreased from 1.55 to 0.55 on increasing the concentration of styrene beyond  $3.8 \text{ kmol}/\text{m}^3$ , owing to the difference in the rate of formation of **2** and **3**. The observed change in selectivity pattern can be explained to some extent on the basis of change in polarity of the medium as explained in Chapter 2. At lower styrene concentrations of  $0.576$  to  $3.84 \text{ kmol}/\text{m}^3$ , methanol is in excess (Table 3.3) and the reaction medium will be highly polar (dielectric constant of methanol is 32.63). Under these conditions predominant formation of linear isomer was observed (*n/iso* = 1.55). At higher concentration of styrene

(> 3.8 kmol/m<sup>3</sup>), styrene becomes the solvent and the reaction medium will be less polar (dielectric constant of styrene is 2.4), which leads to the enhanced the formation of branched isomer 3. Though the difference in the rate of formation can be more or less justified, the overall enhancement in the rate of carbonylation needs further explanation. The change in the solubility of CO at higher concentration of styrene is not significant to clarify the increase in the rates and can only be explained on the basis of relative stability or enhanced formation of the active catalytic species in the presence of more amounts of styrene. Further work is necessary to understand the exact role of styrene concentration on the hydroesterification reaction rates.

### 3.3.2.2. Effect of catalyst concentration

The effect of catalyst concentration on initial rate of hydroesterification was studied in a concentration range of  $1.205 \times 10^{-3}$  to  $7.23 \times 10^{-3}$  kmol/m<sup>3</sup>. The initial rate of reaction varied as first order with respect to the catalyst concentration as shown in Figure 3.5.



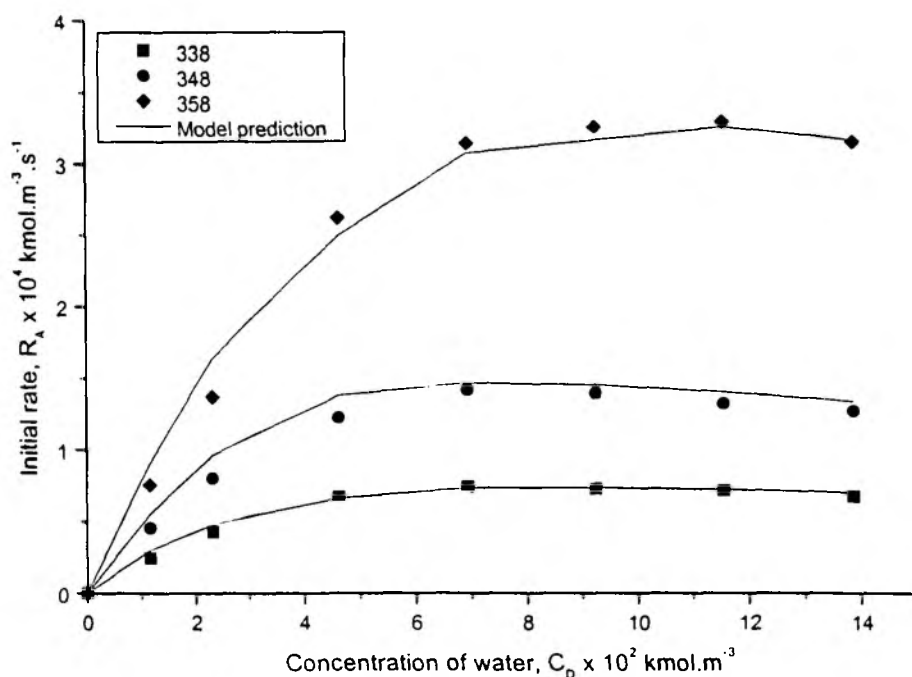
**Figure 3.5.** Effect of catalyst concentration on initial rate of reaction

*Reaction conditions:* styrene, 1.44 kmol/m<sup>3</sup>; PPh<sub>3</sub>/Pd, 4; TsOH,  $2.4 \times 10^{-2}$  kmol/m<sup>3</sup>; water,  $4.62 \times 10^{-2}$  kmol/m<sup>3</sup>; P<sub>CO</sub>, 3.4 MPa

In these experiments, the ratio of Pd/PPh<sub>3</sub> was kept constant at 4. The linear dependency of reaction rate with catalyst concentration also explains kinetic regime for the hydroesterification reaction under the conditions studied. No change in *n/iso* ratio was observed with change in catalyst concentration.

### 3.3.2.3. Effect of concentration of water

The effect of concentration of water on the initial rate of reaction of hydroesterification of styrene was studied for a temperature range of 338-358 K and the results are presented in Figure 3.6. The rate was found to increase with increase in water concentration up to  $9.244 \times 10^{-2} \text{ kmol/m}^3$  and was found to decrease slowly with further increase as also explained in Chapter 2.



**Figure 3.6.** Effect of water concentration on initial rate of reaction

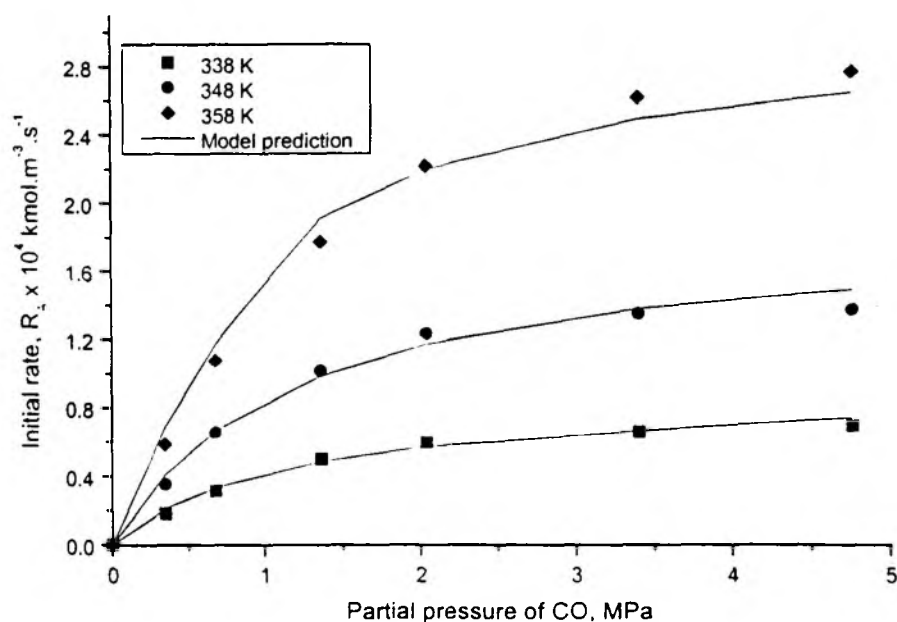
*Reaction conditions:* styrene,  $1.44 \text{ kmol/m}^3$ ; Pd(OAc)<sub>2</sub>,  $2.4 \times 10^{-3} \text{ kmol/m}^3$ ; PPh<sub>3</sub>,  $9.6 \times 10^{-3} \text{ kmol/m}^3$ ; TsOH,  $2.4 \times 10^{-2} \text{ kmol/m}^3$ ; P<sub>CO</sub>, 3.4 MPa

According to the mechanism described in Chapter 2., the role of water is mainly confined to the efficient formation of Pd-H species through a kind of water gas shift reaction

and with the increase in concentration of water, the formation of active catalyst will be more efficient thereby increasing the reaction rate. But higher concentrations of water can retard the reaction rate by its competitive coordination with reacting molecules.<sup>10</sup> Decrease in reaction rate at higher concentration of water can also be due to the small decrease in the solubility of CO with increased concentration of water. However, this aspect has been negligible under the present conditions due to the very small concentration of water used. The variation of *n/iso* with concentration of water is discussed in Chapter 2.

### 3.3.2.4. Effect of partial pressure of CO

The effect of CO partial pressure on the initial rate of hydroesterification of styrene was studied in a range of 0.68 to 4.76 MPa. The initial rate was found to increase with CO partial pressure up to 3.4 MPa and was nearly independent with further increase in pressure and the results are presented in Figure 3.7.



**Figure 3.7.** Effect of CO partial pressure on initial rate of reaction:

*Reaction conditions:* styrene,  $1.44 \text{ kmol/m}^3$ ;  $\text{Pd}(\text{OAc})_2$ ,  $2.41 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $9.64 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{TsOH}$ ,  $2.41 \times 10^{-2} \text{ kmol/m}^3$ ; water,  $4.62 \times 10^{-2} \text{ kmol/m}^3$

The *n/iso* ratio was found to decrease gradually with increase in CO partial pressure from 2.53 to 0.975 (Table 3.4). This is due to the small increase in the rate of formation of the branched isomer compared to that of the linear isomer. This point can be clearly seen from the increased yield (0.065–0.249 kmol/m<sup>3</sup>) of **3** compared to that of **2** (0.165–0.242 kmol/m<sup>3</sup>) after one hour of reaction at 348 K (Table 3.4). A similar trend was also observed by Noskov *et. al.*<sup>2</sup> for hydrocarboxylation of styrene using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst.

**Table 3.4.** Effect of partial pressure of CO

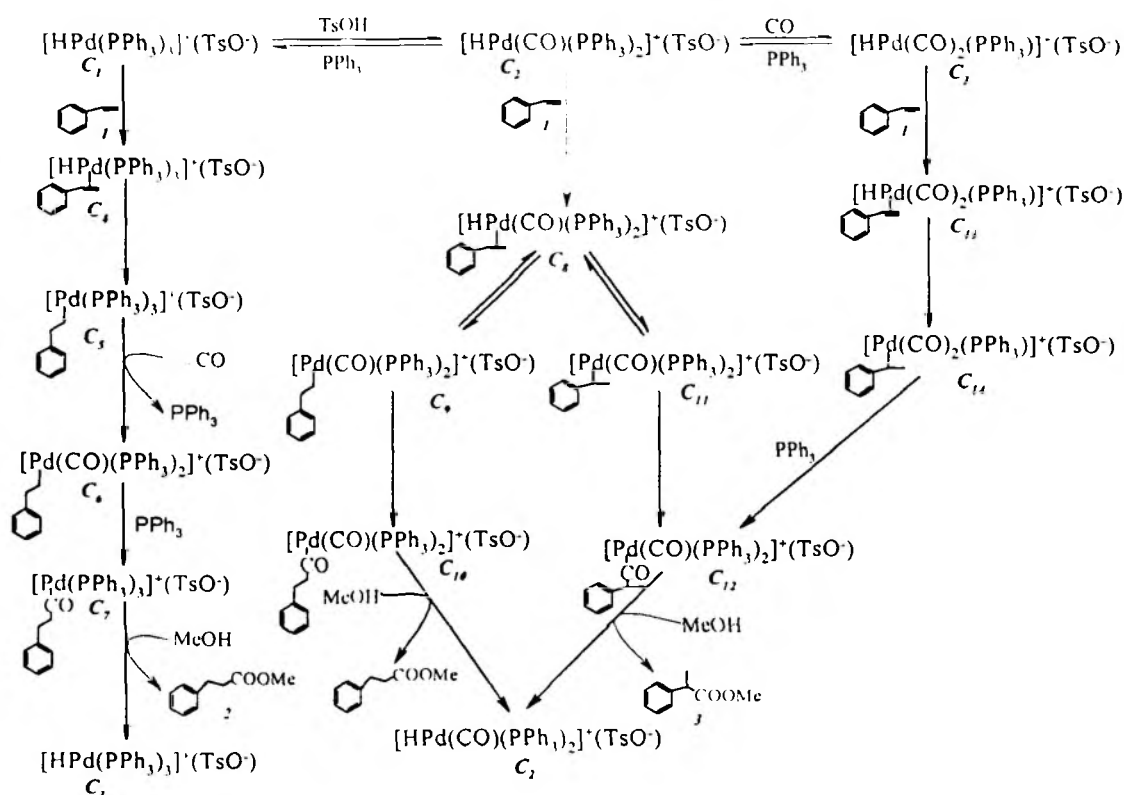
Sr. No	CO Pressure MPa	Selectivity, %, (Yield, kmol/m <sup>3</sup> )		<i>n/iso</i>	TOF h <sup>-1</sup>
		<i>iso</i> -ester, <b>3</b>	<i>n</i> -ester, <b>2</b>		
1	0.68	28.2, (0.065)	71.5, (0.165)	2.53	100
2	1.36	34.3, (0.133)	65.4, (0.254)	1.92	162
3	2.04	37.5, (0.166)	62.5, (0.277)	1.72	183
4	3.40	39.8, (0.194)	60.2, (0.293)	1.51	203
5	4.76	50.0, (0.244)	49.8, (0.243)	1.01	204
6	6.80	50.6, (0.249)	49.3, (0.242)	0.975	205

*Reaction condition:* styrene, 1.44 kmol/m<sup>3</sup>; Pd(OAc)<sub>2</sub>, 2.41x10<sup>-3</sup> kmol/m<sup>3</sup>; PPh<sub>3</sub>, 9.64x10<sup>-3</sup> kmol/m<sup>3</sup>, TsOH, 2.41x10<sup>-2</sup> kmol/m<sup>3</sup>; water, 4.62x10<sup>-2</sup> kmol/m<sup>3</sup>; temperature, 348K

A probable reason for the increased formation of branched product **3** at higher CO partial pressures is the possible formation dicarbonyl Pd species C<sub>3</sub> as one of the active catalytic species. The presence of two carbonyl ligands may decrease the electron density around the Pd center thereby favoring the insertion of styrene in to the Pd–H bond to form a Pd-alkyl species having styrene in *iso* coordination.

At very low partial pressure of CO, it is possible that a certain fraction of the active palladium hydride species formed may not contain any coordinated CO and exists as [HPd(PPh<sub>3</sub>)<sub>3</sub>]<sup>+</sup>(TsO<sup>-</sup>), C<sub>1</sub>, as an active species. Since this species has higher electron density and steric bulk compared to [HPd(CO)(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup>(TsO<sup>-</sup>), C<sub>2</sub>, it is possible that a majority of the linear product is formed from C<sub>1</sub> as an active catalyst. This species may be predominating at

higher concentrations of PPh<sub>3</sub> as well, in which case increased formation of the linear isomer was observed as explained in Chapter 2.



**Scheme 3.5.** Proposed mechanism

With increase in concentrations of CO, the fraction of dicarbonyl hydrido palladium species C<sub>3</sub> can increase. Since the formation of *iso* product 3 was increased with increase in CO partial pressure, it can be proposed that the major fraction of the *iso* product is formed from the dicarbonyl species. Hence, three catalytic cycles may be operating simultaneously with [HPd(PPh<sub>3</sub>)<sub>3</sub>]<sup>+</sup>(TsO<sup>-</sup>), [HPd(CO)(PPh<sub>3</sub>)<sub>2</sub>]<sup>+</sup>(TsO<sup>-</sup>) and [HPd(CO)<sub>2</sub>(PPh<sub>3</sub>)]<sup>+</sup>(TsO<sup>-</sup>), as the active catalyst depending on various reaction conditions. The mono carbonylhydrido palladium species C<sub>2</sub> may catalyse the formation of both the isomers. A catalytic cycle similar to that proposed by Noskov *et. al.*<sup>2</sup> that explains the possible involvement of these species in the formation of *n* and *iso* products is given in Scheme. 3.5. The variation of reaction rate with partial pressure of CO can be due to the varied formation and stability of C<sub>1</sub>, C<sub>2</sub> and C<sub>3</sub>

with change in CO partial pressure. In order to explain this aspect, further investigation of the reaction mechanism using *in situ* techniques under reaction conditions is necessary.

### 3.3.3. Rate equation

The results on the kinetics of hydroesterification of styrene indicate non-linear variation of initial reaction rate with CO, water as well as styrene concentration and linear variation with catalyst concentration. All the experimental trends, except that of concentration of styrene, were in agreement with the elucidated mechanism. An attempt to develop a mechanistic rate model, which explains all the observed trends, was found to be complicated because of the large number of catalytic species involved as well as the lack of knowledge of its relative formation, stability and reactivity under various initial reaction conditions. Also the exact role of styrene in increasing the reaction rate was not clearly understood. Hence, based on the experimental trends, different empirical models were considered and compared as shown in Table 3.5.

**Table 3.5.** Comparison of various rate models for hydroesterification of styrene

No.	Model	T, K	$k_1$	$K_A$	$K_B$	$K_C$	$\phi_{min} \times 10^8$
1.	$R_A = \frac{k_1 C_A (1 + K_B C_B)^2 C_i C_D}{(1 + K_A C_A)(1 + K_B C_B)^2}$	338	19.59	0.0447	12.28	11.21	0.0190
		348	38.34	0.0523	12.10	13.16	0.4637
		358	58.26	0.0650	13.72	7.42	0.8457
2.	$R_1 = \frac{k_1 C_i (1 + K_B C_B) C_i C_D}{(1 + K_i C_i)(1 + K_B C_B)^2}$	338	19.21	0.1037	12.12	11.25	0.0202
		348	41.34	0.1220	11.92	13.73	0.4819
		358	56.15	0.0981	10.89	7.958	2.6113
3.	$R_1 = \frac{k_1 C_i (1 + K_B C_B) C_i C_D}{(1 + K_i C_i)(1 + K_B C_B)^2}$	338	19.10	-0.1146	11.99	12.47	0.3314
		348	32.56	-0.1103	10.07	11.95	1.9852
		358	50.93	-0.1202	11.99	7.23	3.9814



Where,  $R_A$  is the initial reaction rate,  $\text{kmol/m}^3/\text{s}$ ;  $C_A$ , concentration of CO,  $\text{kmol/m}^3$ ;  $C_B$ , concentration of styrene,  $\text{kmol/m}^3$ ;  $C_C$ , concentration of catalyst,  $\text{kmol/m}^3$ ;  $C_D$ , concentration of water,  $\text{kmol/m}^3$ ;  $k_1$ , reaction rate constant,  $\text{m}^6/\text{kmol}^2.\text{s}$  and  $K_A, K_B, K_D$  are constants.

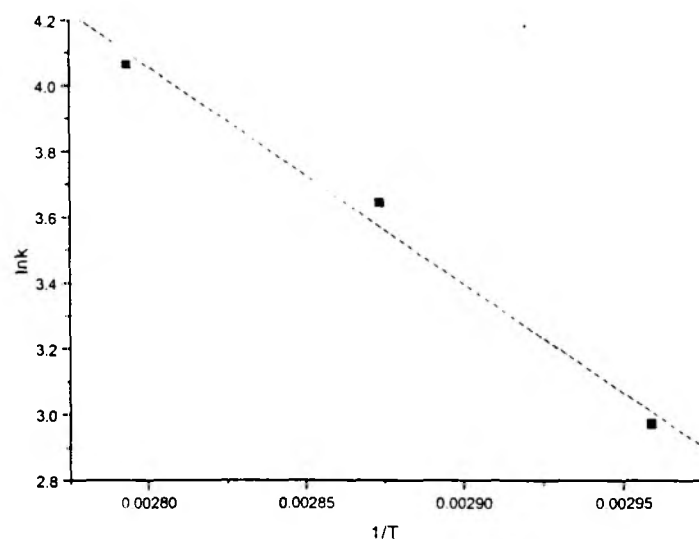
In order to choose a suitable rate equation a non-linear least square regression analysis of these rate models was used to fit the rate data to obtain the best-fit parameters. For this purpose an optimization program based on Marquart's method was used. The model parameters were estimated by minimizing the objective function  $\phi_{\min}$ , defined as:

$$\phi_{\min} = \sum_{i=1}^n (R_{\text{exp}} - R_{\text{pre}})^2 \quad (3.7)$$

where,  $R_{\text{exp}}$  and  $R_{\text{pre}}$  are the observed and predicted rates respectively and  $n$  is the number of data points.

Out of the three models considered, model 3 was rejected because it gave negative values for the constant  $K_A$ . From models 1 and 2, model 1 was chosen as the best to represent the kinetics of hydroesterification of styrene, in view of the lowest  $\phi_{\min}$  values obtained. The error between the predicted and observed rate data was found to be within  $\pm 8\%$  with exception of a few points (see Figure 3.4 to 3.7).

From the temperature dependence of rate parameters (Figure 3.8) the activation energy of the reaction was calculated to be  $54.17 \text{ kJ/mol}$ , which also confirm the conclusion of kinetic regime.



**Figure 3.8.** Temperature dependence of rate constant

### 3.4. Conclusions

Kinetics of the hydroesterification of styrene to methyl-2-phenyl propionate and methyl-3-phenyl propionate has been studied using Pd(OAc)<sub>2</sub>, PPh<sub>3</sub> and TsOH as a catalyst system in methanol. The reaction was found to be first order with respect to catalyst concentration and zero order with styrene up to 3.84 kmol/m<sup>3</sup>. An unusual trend of increase in reaction rate and increased formation of *iso* product was observed with increase in styrene concentration beyond 3.84 kmol/m<sup>3</sup>. Water showed a remarkable promoting effect on the initial rate of hydroesterification of styrene, however, beyond 9.244 × 10<sup>-2</sup> kmol/m<sup>3</sup> the reaction rate decreased. The rate increased with P<sub>CO</sub> up to 3.4 MPa but at higher P<sub>CO</sub> (>3.4 MPa), it was found to be independent of CO partial pressure. A rate equation has been proposed and the kinetic parameters evaluated. The activation energy was found to be 54.17 kJ/mol.

### Nomenclature

- C<sub>A</sub> concentration of CO (kmol/m<sup>3</sup>)
- C<sub>B</sub> concentration of styrene (kmol/m<sup>3</sup>)
- C<sub>C</sub> concentration of catalyst (kmol/m<sup>3</sup>)

$C_D$	concentration of water ( $\text{kmol/m}^3$ )
$f_A$	fugacity of pure gas at atmospheric pressure, MPa
$f_A^l$	fugacity of hypothetical liquid solute at atmospheric pressure, MPa
$H$	Henry's constant, $\text{kmol/m}^3/\text{MPa}$
$k_i$	reaction rate constant
$K_A, K_B, K_D$	Constants
$M_s$	molecular weight of the solvent
$P_i$	initial pressure reading, MPa
$P_f$	final pressure reading, MPa
$R_{\text{exp}}$	observed rate, $\text{kmol/m}^3/\text{s}$
$R_{\text{pre}}$	predicted rate, $\text{kmol/m}^3/\text{s}$
$R$	gas constant, $\text{J/K.mol}$
$R_A$	initial hydroesterification rate ( $\text{kmol/m}^3/\text{s}$ )
$T$	temperature, K
$V_g$	volume of gas phase, $\text{m}^3$
$V_l$	volume of liquid phase, $\text{m}^3$
$X_A$	mole fraction of gas A
$X_{A, \text{mix}}$	mole fraction of gas in the solvent mixture
$X_{A1}$	mole fraction of gas in pure styrene
$X_{A2}$	mole fraction of gas in pure methanol
$X_{A, l}$	mole fraction of the solute gas in the liquid phase
$\delta_A$	solubility parameter for the solute gas, $(\text{J/m}^3)^{1/2}$
$\delta_s$	solubility parameter for the solvent, $(\text{J/m}^3)^{1/2}$
$\phi_{\text{min}}$	parameter defined in Eq. 3.7
$\phi_s$	volume fraction of solvent
$v_A$	molar volume of gas A, $\text{m}^3/\text{mol}$
$\beta_{12}$	$(\delta_{s1} - \delta_{s2})^2/RT$
$\rho_s$	molar density of the liquid, $\text{kmol/m}^3$

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## Chapter 4

**Carbonylation of 1-Aryl ethanols and  
Vinyl aromatics using Palladium Complex  
Catalyst Systems**

## 4.1. Introduction

Carbonylation of 1-aryl ethanols to produce 2-aryl propionic acids, a class of non-steroidal anti-inflammatory drugs, has gained great attention in recent years after the successful commercialization of the Ibuprofen process at Texas by Hoechst Celanese Corporation in 1992.<sup>1</sup> This environmentally benign process employs a three step catalytic route in which carbonylation of 1-(4-isobutylphenyl)ethanol (IBPE) is a key step, instead of the six step non-catalytic process (Chapter 1, Section 1.2.2.1). The conventional stoichiometric organic synthesis required large amounts of non-recyclable auxiliary chemicals thereby producing a huge quantity of waste materials, posing severe environmental threats. The new process, instead, uses completely recyclable catalysts with net effect of 100% atom utilization with completely reduced waste production. In the Hoechst Celanese process,<sup>2</sup> the carbonylation of IBPE was carried out using bis(triphenylphosphino)dichloro palladium(II), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, as the catalyst precursor in a biphasic medium consisting of IBPE in methyl ethyl ketone (MEK) as the organic phase and 10% HCl<sub>(aq)</sub> as the promoter. The desired high selectivity (>95 %) for Ibuprofen was obtained at high pressures of 16–35 MPa, while at lower pressures (6.8 MPa), the selectivity to Ibuprofen was less than 70%. In this reaction, the turnover frequency (TOF) was found to be only 50–150 h<sup>-1</sup> even at high pressures (35 MPa). Recently Sheldon and co-workers have reported<sup>3</sup> carbonylation of IBPE using water-soluble palladium complexes in a biphasic system. This system also has the disadvantages of lower reaction rates (TOF = 2.3 h<sup>-1</sup>) and lower selectivity (72%) under mild reaction conditions. In another study, 95–98% selectivity to ibuprofen was obtained from 4-isobutylstyrene by carboxylation using PdCl<sub>2</sub> along with CuCl<sub>2</sub> but the reaction rates were very low (TOF = 0.5–2 h<sup>-1</sup>).<sup>4</sup> A detailed survey of literature on this subject is given in Chapter 1 (Section 1.2.2.1). In most of the studies on carbonylation of IBPE, two-phase catalyst systems have been employed; either, the catalyst and the substrate were in the organic phase with HCl promoter in the aqueous phase, or the catalyst was in the aqueous phase and the substrate in the organic phase. In all these cases lower reaction rates (TOF = 0.5–60 h<sup>-1</sup>) were

reported at mild reaction conditions and a high selectivity for ibuprofen was achieved only at very high CO pressures (16 –35 MPa).

In this chapter, experimental results on the carbonylation of 1-aryl ethanols and vinyl aromatics are presented using  $\text{PdCl}_2(\text{PPh}_3)_2$  as the catalyst precursor with the aim of developing improved catalytic systems with respect to catalytic activity and 2-arylpropionic acid selectivity under mild reaction conditions. Effect of various parameters such as type of catalyst precursors, promoters, solvents etc. on the catalytic activity and product selectivity has been investigated. A reaction path way and catalytic cycle have also been proposed based on the carbonylation reaction trends and  $^{31}\text{P}$  NMR experiments.

## 4.2. Experimental section

### 4.2.1. Materials

Isobutyl benzene, acetyl chloride,  $\text{AlCl}_3$ , sodium borohydride, methyl ethyl ketone, toluene, N,N-dimethyl formamide, N-methylpyrrolidone, (all from Sd fine chemicals, India), HCl, Dioxane (Ranbaxy, India),  $\text{PdCl}_2$ ,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PPh}_3$ ,  $\text{P}(o\text{-tolyl})_3$ ,  $\text{P}(p\text{-tolyl})_3$ ,  $\text{P}(p\text{-MeOC}_6\text{H}_4)_3$ ,  $\text{P}(p\text{-ClC}_6\text{H}_4)_3$ ,  $\text{P}(p\text{-FC}_6\text{H}_4)_3$ , *trans,trans*-dibenzilideneacetone (dba), cyclooctadiene (COD), benzonitrile, 1-phenylethyl alcohol, styrene, substituted styrenes, aryl ketones (all from Aldrich, USA), methyl-1-(6-methoxynaphthyl)ketone (gift sample) and CO (Matheson, USA, 99.9 % purity) were used as received. All the solvents were freshly distilled using known procedures and degassed by using argon before use.

### 4.2.2. Analytical methods

Liquid samples were analyzed for reactants, intermediates and products on a Hewlett Packard 5890 Series GC, controlled by HP Chemstation software, by using an FFAP capillary column (30 m x 0.32 mm x 0.1  $\mu\text{m}$  film thickness, on a poly ethyleneglycol stationary phase). IR, NMR, GC-MS and elemental analysis were obtained as described in chapter II.

The standard conditions for GC analysis were as follows.

Injector (split) temperature	523 K
Flame ionization detector temperature	523 K
Column temperature	373 K–483 K (rate, 30 K/min)
Carrier gas (He) flow	2.5 cm <sup>3</sup> /min
Inlet Pressure	25 psig–50psig
Split ratio	1: 100

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

$$\text{Total conversion} = \text{Initial concentration of IBPE} - \text{Final concentration of (IBPE + IBS + IBPCI)}$$

$$\% \text{ Conversion} = \frac{\text{Total conversion}}{\text{Initial concentration of IBPE}} \times 100$$

$$\% \text{ Selectivity of Ibuprofen} = \frac{\text{Concentration of Ibuprofen formed}}{\text{Total conversion}} \times 100$$

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

#### 4.2.3. General procedure for carbonylation

The carbonylation reactions were carried out in a Parr Hastelloy C–276 autoclave having capacity of  $5 \times 10^{-5} \text{ m}^3$ . In a typical experiment, known quantities of the substrate, catalyst, ligand, promoters, water and the solvent were charged into the autoclave. The contents were flushed few times with nitrogen followed by carbon monoxide and heated to the desired temperature. After attaining the temperature, the autoclave was pressurized with CO to the required level and the reaction was started by switching on the agitation (1000 rpm). To maintain a constant pressure in the reactor during a batch experiment, CO was fed through a constant-pressure regulator from a reservoir vessel maintained at higher



pressure. The pressure drop in the reservoir vessel was recorded by means of a pressure transducer as a function of time. Intermediate liquid samples were also taken at regular intervals of time. The reaction was continued until the CO absorption was stopped (the reactions which were too slow were stopped after the specified time). After the reaction, the autoclave was cooled to room temperature, CO de-pressurized, flushed with nitrogen and the reaction mixture removed. The analysis of the liquid samples was carried out using GC for product distribution. In the case of biphasic reaction, organic and aqueous layers were separated using a separating funnel. The organic layer was analyzed by GC. The carbonylation products were isolated by evaporation of the solvent and purified further by acid-base extraction. The products were further confirmed by GC-MS, NMR and IR analysis. Spectral data of all the compounds prepared are given in Appendix 2.

#### 4.2.4. Procedure for $^{31}\text{P}$ NMR experiments

Samples for  $^{31}\text{P}$  NMR experiments were prepared by mixing the required amounts of  $\text{PdCl}_2(\text{PPh}_3)_2$ , TsOH and LiCl in  $2.5\text{ cm}^3$  of degassed solvent in a 10 mm NMR tube flushed with argon. The spectra were recorded at 121.1 MHz by using 85%  $\text{H}_3\text{PO}_4$  as an external standard and internal  $\text{D}_2\text{O}$  (added in a capillary tube) as the deuterium source. For preparation of samples under CO pressure,  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.072 mmol),  $\text{PPh}_3$  (0.144 mmol), TsOH (1.8 mmol), LiCl (1.8 mmol) and water ( $0.5\text{--}1\text{ cm}^3$ ) in  $15\text{ cm}^3$  of degassed solvent were charged to the autoclave, flushed with argon followed by CO, heated to 378 K, pressurized to 5.4 MPa with CO and kept under stirring for 10–30 minutes. Intermediate samples were directly taken under CO atmosphere to the NMR tube with the help of a sampling device and the spectra were recorded as stated above.

#### 4.2.5. Preparation of 1-(4-isobutylphenyl)ethanol [IBPE]

IBPE was prepared from isobutyl benzene by a two-step synthesis procedure, which involved acylation of isobutylbenzene to *p*-isobutyl acetophenone and followed by reduction. For the acylation step, isobutylbenzene (67 g) was slowly added under vigorous stirring to a solution of acetyl chloride (58.25 g) and anhydrous  $\text{AlCl}_3$  (100g) in dichloromethane ( $500\text{ cm}^3$ ) at 273–278 K. After 4–5 hours of stirring at 273–278 K, the

reaction was quenched by pouring the reaction mixture into excess of crushed ice. The organic layer was separated from the aqueous layer. The aqueous layer was re-extracted with dichloromethane and the combined organic layer was washed with saturated brine and then with saturated sodium bicarbonate. The washed dichloromethane layer was then dried over anhydrous sodium sulfate, concentrated and distilled under reduced pressure to yield (98%) *p*-isobutyl acetophenone (IBAP).

The reduction of *p*-isobutyl acetophenone was carried out using sodium borohydride. Sodium borohydride (1.4 g) was added to a solution of *p*-isobutyl acetophenone (13 g) in methanol (75 cm<sup>3</sup>) under ice-bath. After one hour of continuous stirring at 273–283 K, the reaction mixture was treated with dilute HCl and extracted with dichloromethane. The dichloromethane layer was washed with brine and then with saturated sodium bicarbonate, dried over anhydrous sodium sulfate, concentrated and distilled under vacuum to yield (98%) pure *p*-isobutyl phenyl ethanol.

#### 4.2.6. Preparation of other 1-aryl ethanols

Other 1-aryl ethanols such as 1-(6-methoxy-2-naphthyl)ethanol, 1-(4-methylphenyl)ethanol, 1-(4-chlorophenyl)ethanol, 1-(4-hydroxyphenyl)ethanol, 1-(4-cyanophenyl)ethanol were prepared by the reduction of corresponding aryl ketones as described above for the preparation of IBPE from IBAP.

#### 4.2.7. Preparation of 1-(4-isobutylphenyl) ethyl chloride [IBPCI]

A solution of IBPE (10<sup>g</sup>) in chloroform (50 cm<sup>3</sup>) was treated with 1.2 equivalents of SOCl<sub>2</sub> under ice bath and kept for stirring at room temperature. After 10 hours, the reaction was quenched by adding the reaction mixture to ice. The aqueous layer was re-extracted with chloroform and the chloroform layer was washed several times with distilled water, dried using anhydrous sodium sulfate, concentrated and distilled under vacuum to yield (93%) pure IBPCI.

#### 4.2.8. Preparation of 4-isobutyl styrene [IBS]

IBS was prepared by the acid catalyzed dehydration of IBPE. *p*-toluene sulphonic acid (0.5 g) was added to a solution of IBPE (10 g) in chloroform (30 cm<sup>3</sup>) and was vigorously stirred at 343-353 K. After 1–2 hours, the reaction mixture was cooled, washed with distilled water several times, dried, concentrated and distilled under vacuum to yield (92 %) pure 4-isobutyl styrene.

#### 4.2.9. Preparation of 1-(6-methoxy-2-naphthyl)ethene

1-(6-methoxy-2-naphthyl)ethene was prepared by the acid catalyzed dehydration of 1-(6-methoxy-2-naphthyl)ethanol as described above for the preparation of IBS from IBPE.

#### 4.2.10. Preparation of PdI<sub>2</sub><sup>5</sup>

To an aqueous HCl solution of PdCl<sub>2</sub> (0.5 g), a saturated solution of KI (3 cm<sup>3</sup>) was added with stirring at room temperature. Instantaneous precipitation of PdI<sub>2</sub> was observed. The dark brown PdI<sub>2</sub> obtained was filtered, washed with distilled water until all the acidic impurities were removed (washings were tested for pH) and was dried under vacuum. Yield = 98%.

#### 4.2.11. Preparation of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub><sup>6</sup>

A solution of PdCl<sub>2</sub> (0.5g) in dilute aqueous hydrochloric acid (50 cm<sup>3</sup>) was slowly added to a stirred warm (333 K) solution of triphenylphosphine (1.85g) in ethanol (200 cm<sup>3</sup>) and was stirred at ~333 K for 3 hrs. The bright yellow complex precipitated was filtered, washed with hot ethanol and dried. The complex was recrystallized from chloroform: yield =97.5 %. Elemental Analysis: Calculated for C<sub>36</sub>H<sub>30</sub>Cl<sub>2</sub>P<sub>2</sub>Pd: C, 61.605; H, 4.308; Cl, 10.102; P, 8.826. Found: C, 61.58; H, 4.31, Cl, 9.82; P, 8.38.

#### 4.2.12. Preparation of PdCl<sub>2</sub>P<sub>2</sub>

The procedure given in section 4.2.11 was followed for the preparation of PdCl<sub>2</sub>P<sub>2</sub>, where P is *p*-tolyl, *o*-tolyl, *p*-chlorophenyl, *p*-fluorophenyl, and *p*-methoxyphenyl. The elemental analysis of the complexes are given in Table 4.1.

#### 4.2.13. Preparation of PdCl<sub>2</sub>(dppb)

The procedure given in section 4.2.11 was followed for the preparation of PdCl<sub>2</sub>(dppb), using 0.1 g of PdCl<sub>2</sub> and 0.43 g of dppb. Yield = 86%. Elemental Analysis: Calculated for C<sub>40</sub>H<sub>38</sub>Cl<sub>2</sub>P<sub>2</sub>Pd: C, 63.383; H, 5.053; Cl, 9.354; P, 8.172. Found: C, 63.29; H, 5.02, Cl, 9.19; P, 7.95.

**Table. 4.1.** Elemental analysis for PdCl<sub>2</sub>P<sub>2</sub>

P, Formula of PdCl <sub>2</sub> P <sub>2</sub>	Yield %	Calculated				Found			
		C	H	Cl	P	C	H	Cl	P
<i>p</i> -tolyl, C <sub>42</sub> H <sub>42</sub> Cl <sub>2</sub> P <sub>2</sub> Pd	97	64.177	5.386	9.020	7.881	64.01	5.37	8.98	7.62
<i>o</i> -tolyl, C <sub>42</sub> H <sub>42</sub> Cl <sub>2</sub> P <sub>2</sub> Pd	76	64.177	5.386	9.020	7.881	63.9	5.40	8.88	7.71
<i>p</i> -chlorophenyl, C <sub>36</sub> H <sub>24</sub> Cl <sub>8</sub> P <sub>2</sub> Pd	90	47.486	2.878	31.14	6.803	47.47	2.87	30.5	6.65
<i>p</i> -fluorophenyl, C <sub>36</sub> H <sub>24</sub> Cl <sub>2</sub> F <sub>6</sub> P <sub>2</sub> Pd	88	53.261	3.228	8.734	7.630	53.21	3.18	8.85	7.43
<i>p</i> -methoxyphenyl C <sub>42</sub> H <sub>42</sub> Cl <sub>2</sub> O <sub>6</sub> P <sub>2</sub> Pd	90	57.193	4.800	8.079	7.023	57.18	4.81	7.92	6.96

#### 4.2.14. Preparation of PdCl<sub>2</sub>(PhCN)<sub>2</sub><sup>6</sup>

A suspension of about 0.5 grams of PdCl<sub>2</sub> in 10 cm<sup>3</sup> of benzonitrile was heated to 353 K for 20–30 minutes to form a red solution. Undissolved materials were removed by filtration of the hot solution. The clear solution obtained was poured into petroleum ether and the precipitated yellow complex formed was filtered, washed with petroleum ether and

dried. Yield = 91%. Elemental Analysis, Calculated for  $C_{14}H_{10}Cl_2N_2Pd$ : C, 43.841; H, 2.628; Cl, 18.487; N, 7.304. Found: C, 43.62; H, 2.61, Cl, 16.87; N, 7.25.

#### 4.2.15. Preparation of $Pd(COD)Cl_2$ <sup>7</sup>

About 0.5 g of  $PdCl_2$  was dissolved in 2 cm<sup>3</sup> of conc. HCl by warming and it was diluted with 50 cm<sup>3</sup> of absolute ethanol. The residue left was filtered and washed with 10 ml of ethanol. To the filtrate 1.5 cm<sup>3</sup> of cyclooctadiene was added with stirring. The yellow precipitate formed was filtered and washed with ether to obtain the complex  $Pd(COD)Cl_2$ . Yield = 88%. Elemental Analysis: Calculated for  $C_8H_{12}Cl_2Pd$ : C, 38.430; H, 4.838; Cl, 14.179. Found: C, 38.41; H, 4.82, Cl, 13.89.

#### 4.2.16. Preparation of $Pd(dba)_2 \cdot CHCl_3$ <sup>8</sup>

$Pd(OAc)_2$  (0.5 g) was added to a solution of *trans,trans*-dibenzylideneacetone (dba) (1.71 g) and sodium acetate (1.1 g) in 80 ml of methanol at 323 K. The temperature was decreased to 313 K, to start the precipitation of a deep violet solid. The mixture was stirred for about four hours at 313 K and then the solid was collected by filtration, washed with water, cold acetone and dried under vacuum. The solid was dissolved in refluxing  $CHCl_3$  (25 ml), the dark red solution was filtered over fine filter paper and the diethylether was added to precipitate  $Pd(dba)_2 \cdot CHCl_3$ . The shining violet coloured complex was filtered, washed with cold diethyl ether and dried under vacuum. Yield = 80 %. Elemental Analysis, Calculated for  $C_{35}H_{29}Cl_3O_2Pd$ : C, 60.542; H, 4.210; Cl, 15.317. Found: C, 60.58; H, 4.20; Cl, 14.9.

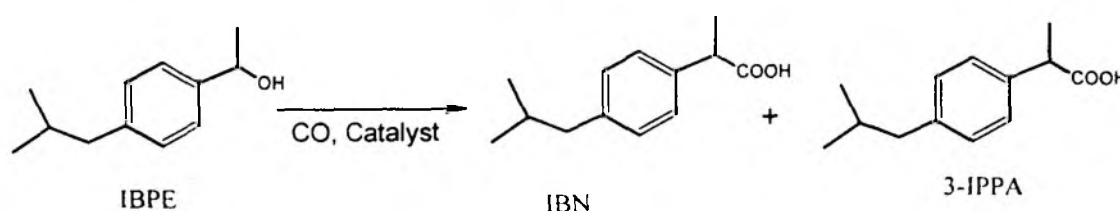
#### 4.2.17. Preparation of $Pd(PPh_3)_4$ <sup>7</sup>

Palladium chloride (0.5 g) and triphenylphosphine (3.7 g) were added to 100 cm<sup>3</sup> of dimethylsulfoxide and heated with stirring to about 413 K under nitrogen. After attaining a clear solution, hydrazine hydrate (0.565 g) was added in one portion over a period of 1–2 min with exclusion of air. Nitrogen was evolved in the vigorous ensuing reaction. The reaction flask was then immediately cooled with water bath to reduce the temperature of the mixture to about 373 K. After crystallization overnight, the product was filtered on a

glass sinter and washed under nitrogen with ethanol, followed by ether and was dried under vacuum. Yield = 92%. Elemental Analysis, Calculated for  $C_8H_{12}Cl_2Pd$ : C, 38.430; H, 4.838; Cl, 14.179. Found: C, 38.41; H, 4.82, Cl, 13.89.

### 4.3. Results and discussion

Carbonylation of IBPE (see Scheme 4.1) produces both branched, 2-(4-isobutylphenyl)propionic acid (Ibuprofen, IBN) and linear, 3-(4-isobutylphenyl)propionic acid (3-IPPA), and the selectivity varies with the reaction conditions used.<sup>2,3</sup>



Scheme 4.1. Carbonylation of IBPE

**Table 4.2.** Carbonylation IBPE under biphasic conditions

Run No.	Catalyst precursor	Ligand	Conversion %	Time, h	Selectivity, %		<i>n/iso</i>	TOF $h^{-1}$
					IBN	3-IPPA		
1	$PdCl_2$	4 $PPh_3$	99.8	10	68	30.6	0.45	50
2	$PdCl_2(PPh_3)_2$	2 $PPh_3$	99	10	66	33.0	0.50	49.2
3	$PdI_2$	4 $PPh_3$	100	4	28	33.1	1.18	77
4	$Pd(COD)Cl_2$	4 $PPh_3$	100	8	57	36.4	0.64	60
5	$Pd(PhCN)_2Cl_2$	4 $PPh_3$	100	6	58	32.8	0.56	76
6	$PdCl_2$	6 $PPh_3$	100	7	64	36.0	0.71	71
7	$PdCl_2$	8 $PPh_3$	99.8	6	47	47.5	1.01	80
8	$PdCl_2$	4 $P(p\text{-tol})_3$	99.9	5	37	54.2	1.5	92
9	$PdCl_2$	4 $P(Bu)_3$	65	10	35	10.2	0.3	14.2

*Reaction conditions:* IBPE, 28.1 mmol; catalyst, 0.056 mmol; 10% HCl, 6 ml; solvent, MEK; T, 408 K;  $P_{CO}$ , 6.2 MPa

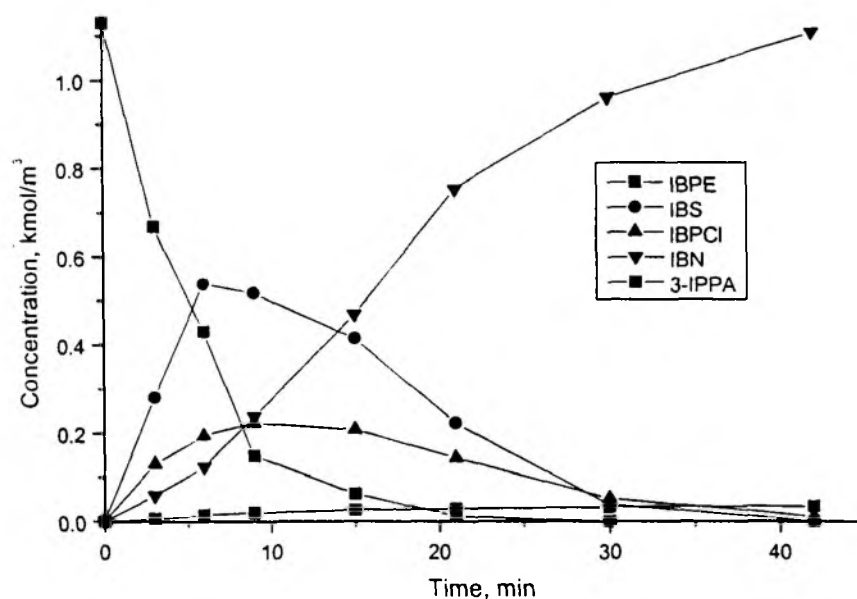
Preliminary investigation on the carbonylation of IBPE was carried out using a biphasic catalytic system with palladium catalysts in the organic phase, methyl ethyl ketone, and 10% HCl<sub>(aq)</sub> as the aqueous phase and the results are summarized in Table 4.2. Catalyst systems PdCl<sub>2</sub>/4PPh<sub>3</sub> and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/2PPh<sub>3</sub> gave similar reaction rates (TOF = 50 h<sup>-1</sup>) and selectivities (*n/iso* = 0.5), as expected. However palladium complexes such as Pd(COD)Cl<sub>2</sub> and Pd(PhCN)<sub>2</sub>Cl<sub>2</sub> gave slightly higher TOFs (60–76 h<sup>-1</sup>) without much affecting the selectivity. Electron releasing ligands like tri-(*p*-tolylphosphine) instead of PPh<sub>3</sub> also gave higher TOFs (92 h<sup>-1</sup>), but selectivity to the branched isomer reduced drastically. Increase in the concentration of PPh<sub>3</sub> also showed similar results and could be due to the stabilization of active Pd(0) species. In all these cases in addition to carbonylation products, small amounts of isobutylstyrene (IBS), isobutylphenyl ethylchloride (IBPCI) and traces of dimerization and trimerization products of IBS were also detected in the final reaction mixture. In the case of PdI<sub>2</sub>, small amount of polymerization product was found to separate out from the final reaction mixture.

As evident from the results presented in Table 4.1, the reaction rate as well as branched carboxylic acid (Ibuprofen) selectivity was much lower in a biphasic catalytic system consisting of the catalyst and substrate in the organic phase with promoters in the aqueous phase. Carbonylation of alcohols promoted by halides has been proposed<sup>9</sup> to proceed through the corresponding halo derivatives formed *in situ* (see Section 1.2.6, Chapter 1) as the active substrate. In case of the biphasic system, formation of the halo derivative (IBPCI in the case of IBPE) may be limited because of the lower concentration of H<sup>+</sup> and Cl<sup>-</sup> in the organic reaction phase. In order to reduce such limitations, the reaction medium was homogenized by appropriate choice of solvent (methyl ethyl ketone) to water ratio. When a homogeneous reaction was carried out (388 K and 5.4 MPa of CO) using concentrated HCl in MEK, 2–3 fold increase in TOF was obtained. But when HCl was replaced with TsOH and LiCl, a dramatic increase in reaction rate (10–20 fold) was achieved under similar conditions. Surprisingly, a remarkable increase in the selectivity to the branched product, Ibuprofen was also observed (>94 %) under the homogeneous conditions. In this case only traces of higher ends were observed in the reaction mixture. A detailed investigation on this catalyst system consisting of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst

precursor and TsOH/LiCl as the promoter in homogeneous medium was carried out and is described in the following sections.

#### 4.3.1. Reaction pathway

The concentration–time profile (Figure 4.1) for the carbonylation of IBPE (5.4 MPa, 388 K) using  $\text{PdCl}_2(\text{PPh}_3)_2/\text{TsOH}/\text{LiCl}$  as a catalyst system, revealed the formation of 4-isobutyl styrene (IBS) and 1-(4-isobutylphenyl)ethyl chloride (IBPCI) as reaction intermediates. It is clear from the concentration-time profile that immediate dehydration of IBPE to IBS occurs under the reaction conditions. It is possible that either the olefin (IBS) or the halide (IBPCI) or both are activated by palladium complexes for carbonylation under the present set of conditions.



**Figure 4.1.** Concentration-time profile for the carbonylation of IBPE

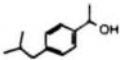
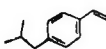
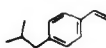
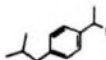
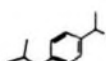
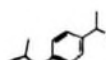
*Reaction conditions:* IBPE, 28.1 mmol;  $\text{PdCl}_2(\text{PPh}_3)_2$ , 0.056 mmol;  $\text{PPh}_3$ , 0.112 mmol; TsOH, 11.2 mmol; LiCl, 11.2 mmol; water, 1.2 cm<sup>3</sup>; solvent, MEK; T, 388 K;  $P_{\text{CO}}$ , 5.4 MPa

In order to clarify this point, carbonylation reaction was carried out using the catalyst precursor  $\text{PdCl}_2(\text{PPh}_3)_2$  in the presence of only the acidic promoter, TsOH. In this



case, only traces of ibuprofen was produced as the carbonylation product after 3–4 hrs of reaction and all the IBPE was transformed to IBS. Hence, it was assumed that a major part of the carbonylation reaction may be proceeding through IBPCl, formed from IBS by the addition of H<sup>+</sup> and Cl<sup>-</sup> ions. To facilitate the formation of IBPCl, LiCl was also added in equivalent amount with TsOH for the carbonylation of IBPE, which resulted in a dramatic enhancement in the carbonylation reaction rate (TOF of 850 h<sup>-1</sup>) with high ibuprofen selectivity (>95%). In order to further confirm the reaction pathway, individual reactions were carried out using IBS and IBPCl as substrates and the results are presented in Table 4.3. No carbonylation product was obtained when IBS was used as the substrate in the presence of only TsOH (11.2 mmol) as the promoter without any added halide promoter, after one hour of reaction. But traces of ibuprofen was obtained after 3–6 hours of reaction.

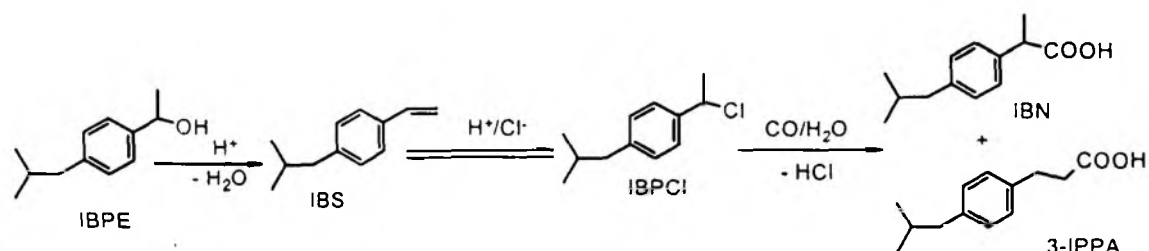
**Table 4.3.** Carbonylation of different substrates to Ibuprofen

Run No.	Substrate	TsOH, mmol	LiCl mmol	Time, h	Conversion %	Selectivity, %		TOF h <sup>-1</sup>
						IBN	3-IPPA	
1		11.2	11.2	0.58	99	96.2	3.7	850
2		11.2	0	6	–	traces	–	–
3		11.2	11.2	0.4	99	97.0	2.8	1240
4		0	0	5	45	96.3	3.1	45
5		0.28	0	3	72	96.8	3	120
6		11.2	11.2	0.41	98.5	97.1	2.8	1220

*Reaction conditions:* substrate, 28.1 mmol; PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 0.056 mmol; water, 1.2 cm<sup>3</sup>; P<sub>(CO)</sub>, 5.4 MPa; T, 388 K; MEK, 19.5 cm<sup>3</sup>



In the presence of both TsOH and LiCl (11.2 mmol) the rate of carbonylation of *p*-isobutylstyrene (IBS) was very much enhanced (TOF of 1240 h<sup>-1</sup>). This clearly indicates that IBPCl is the main active substrate, which undergoes carbonylation. When direct carbonylation of IBPCl was carried out without any added promoter the TOF was too low (45 h<sup>-1</sup>; run 4, Table 4.3). On addition of excess TsOH (11.2 mmol) alone, most of the IBPCl was found to be converted to IBS with apparently no carbonylation reaction. To prevent the formation of IBS, the acidity of the reaction medium was lowered by reducing the TsOH concentration to catalytic amounts (TsOH/Pd = 5), which resulted in more than 70 % conversion of IBPCl to ibuprofen (95.8%), but with a TOF of 120 h<sup>-1</sup> in 3 hours of reaction (run 5, Table 4.3). This shows that under highly acidic conditions, IBPCl undergoes dehydrohalogenation to form IBS, which may not be efficiently activated for carbonylation in the absence of halide promoters under the present conditions. On addition of LiCl in equivalent amount of TsOH (11.2 mmol), the carbonylation reaction proceeded with a TOF of 1220 h<sup>-1</sup> (run 6, Table 4.3). These observations confirm that the active substrate undergoing carbonylation is IBPCl, which is formed from IBPE through IBS as shown in Scheme 4.2.



Scheme 4.2. Reaction pathway for the carbonylation of IBPE

#### 4.3.2. Effect of promoters

As explained above, the acidic as well as the halide promoters have a pronounced effect on the catalytic activity. In order to understand the role of promoters, the effect of different acidic and halide promoters as well as the effect of concentration of TsOH/LiCl on the catalytic activity and product selectivity was studied and the results are presented in Tables 4.4 and 4.5 respectively.

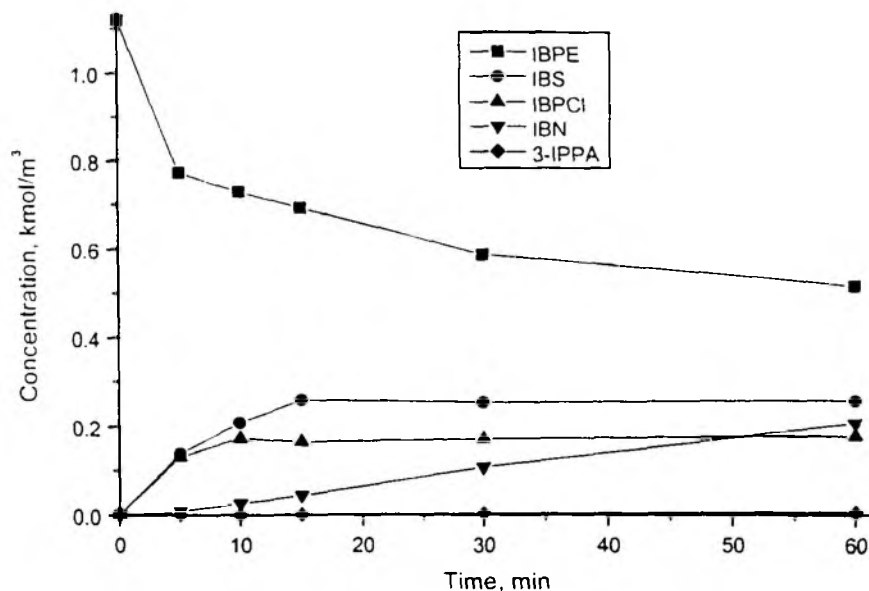
**Table 4.4.** Effect of different promoters on the carbonylation of IBPE

Run No.	Promoter (1:1)		Time, h	Conversion %	Selectivity, %			TOF h <sup>-1</sup>
	Acidic	Halide			IBN	3-IPPA	<i>n/iso</i>	
1.	TsOH	LiCl	1.25	99	96.0	3.9	0.0406	405
2.	MSA	LiCl	2.75	97	92.5	7	0.0757	177
3.		HCl	5.83	95	93.1	2.9	0.0312	90
4.	TsOH	NaCl	2.5	97	97	2.8	0.0289	205
5.	TsOH	KCl	2.15	98	96	3.7	0.0385	228
6.	TsOH	Bu <sub>4</sub> NCl	2.20	98	96.5	3.3	0.0342	223

*Reaction conditions:* IBPE, 28.1 mmol; PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 0.056 mmol; promoter, 5.6 mmol; water, 1.2 cm<sup>3</sup>; P<sub>CO</sub>, 5.4 MPa; T, 388 K; solvent, MEK.

The catalytic activity varied significantly with the nature of counter ions of the acidic as well as halide promoters. In the case of acidic promoters, the catalytic activity decreased in the order TsO<sup>-</sup> > CH<sub>3</sub>SO<sub>3</sub><sup>-</sup> > Cl<sup>-</sup>, which is in a reverse order of coordination ability. In the case of chloride promoters with different cations, the catalytic activity decreased in the order Li<sup>+</sup> > Na<sup>+</sup> ~ K<sup>+</sup> ~ Bu<sub>4</sub>N<sup>+</sup> > H<sup>+</sup>. The combination of TsOH/LiCl was found to be the best with respect to activity and selectivity for carbonylation of IBPE.

An interesting observation was that the homogeneous reaction using concentrated HCl as a promoter instead of TsOH/LiCl gave only lower activity (TOF=90 h<sup>-1</sup>) even though IBPCl was formed in sufficient concentrations (see Figure 4.2).



**Figure 4.2.** Concentration-time profile for the carbonylation of IBPE using HCl promoter  
*Reaction Conditions:* IBPE, 28.1 mmol;  $PdCl_2(PPh_3)_2$ , 0.056 mmol;  $PPh_3$ , 0.112 mmol; HCl, 5.6 mmol; water, 1.2 cm<sup>3</sup>; Solvent, MEK; T, 388 K; Pco, 5.4 MPa

The rate of carbonylation of IBPE was found to increase linearly with concentration of promoters (TsOH/LiCl). Ibuprofen selectivity was found to be almost constant (96%) at higher concentrations of promoters, however, decreased marginally at lower concentrations as given in Table 4.5. This effect on selectivity is noticeable and it can be inferred that promoters may also have a role in the selectivity determining step in addition to activation of the substrate as explained above. It is interesting to note that TOF was very much enhanced and the selectivity decreased to 93% on doubling the concentration of TsOH, keeping that of LiCl as a constant. On the contrary, drastic decrease in TOF and enhanced selectivity was observed on doubling the LiCl concentration instead of TsOH. Considerable amount of palladium metal precipitation was observed at a TsOH to LiCl ratio of 2:1 and precipitation of  $PdCl_2(PPh_3)_2$  was observed at a ratio of 1:2. These results indicate that the nature and concentration of acidic and halide promoters have a significant effect on the catalytic cycle and is discussed on the basis of a proposed mechanism in a

later section. For studying the effect of different parameters, run 2 in Table 4.5 was selected as a standard reaction.

**Table 4.5.** Effect of concentration of TsOH and LiCl on the carbonylation of IBPE

Run No.	Promoter		Time, h	Conversion %	Selectivity, %			TOF h <sup>-1</sup>
	TsOH	LiCl			IBN	3-IPPA	<i>n/iso</i>	
1	11.2	11.2	0.58	99.5	96.2	3.7	0.0384	850
2	5.6	5.6	1.25	99.5	96.0	3.9	0.0406	405
3	2.8	2.8	4.17	95	91.7	8.0	0.0818	100
4	11.6	5.6	0.5	95	93.5	6	0.0642	950
5	5.6	11.2	3.8	96	97.5	2.4	0.0246	125

*Reaction conditions:* IBPE, 28.1 mmol; PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 0.056 mmol; water, 1.2 cm<sup>3</sup>; P<sub>CO</sub>, 5.4 MPa; T, 388 K; MEK, 19.5 cm<sup>3</sup>

#### 4.3.3. Effect of catalyst precursors

In order to understand the electronic and steric influences of ligands on the catalytic activity and selectivity behavior, the effect of various palladium precursors with different phosphine ligands was studied for the carbonylation of IBPE in the presence of TsOH/LiCl promoters under homogeneous conditions and the results are presented in Table 4.6. Highest catalytic activity (405 h<sup>-1</sup>) was observed with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst precursor with a branched selectivity of 96 %. The catalytic activity of Pd complexes with different phosphine ligands varied in the order of (P(*p*-F-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>)<sub>2</sub> < (P(*p*-Cl-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>)<sub>2</sub> < PPh<sub>3</sub> > P(*p*-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>)<sub>2</sub> > (P(*p*-OMe-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub>)<sub>2</sub>, when the ligands are arranged with increasing order of basicity. Highest selectivity (>99.67 %) was observed in the case of palladium complexes with phosphine ligands having electron withdrawing substituents such as tris(*p*-chlorophenyl)phosphine and tris(*p*-fluorophenyl)phosphine as ligands and lower selectivity was observed in the case of electron rich phosphine ligands such as tris(*p*-tolyl)phosphine and tris(*p*-methoxyphenyl)phosphines. These effects can be attributed to the modified properties of the metal center towards activation of the substrates. In the presence of more basic ligands the metal center becomes more nucleophilic<sup>10</sup> facilitating

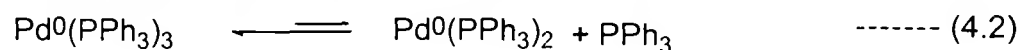
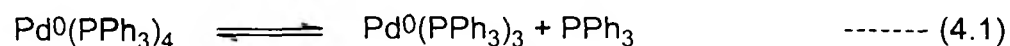
the electrophilic addition of the organic halide. PPh<sub>3</sub>, which is moderately basic and labile, was found to be the best compromise with respect to catalytic activity. In the case of P(*o*-tol-C<sub>6</sub>H<sub>4</sub>)<sub>3</sub> as a ligand, the catalytic activity was very low which may be due to the steric hindrance created at the metal center. Pd(dppb)Cl<sub>2</sub> showed no activity towards carbonylation of IBPE. Unlike the case of biphasic systems (as discussed earlier in Section 4.3), concentration of phosphine ligands did not show any noticeable effect on catalytic activity or selectivity in the range of 2 to 10 (P/Pd).

**Table 4.6.** Effect of different catalyst precursors on the carbonylation of IBPE

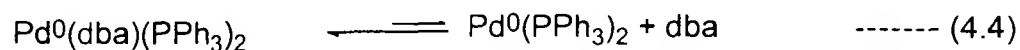
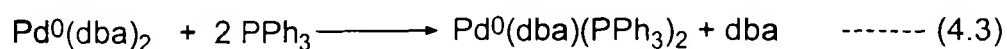
Run No.	Catalyst precursor	Conversion %	Time h	Selectivity, %		<i>n</i> / <i>iso</i>	TOF h <sup>-1</sup>
				IBN	3-IPPA		
1	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	99.5	1.25	96.0	3.9	0.0406	405
2	PdCl <sub>2</sub> (P( <i>p</i> -MeO-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> ) <sub>2</sub>	99	4.0	95.02	4.76	0.05	125
3	PdCl <sub>2</sub> (P( <i>p</i> -Cl-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> ) <sub>2</sub>	98	2.5	99.67	0.25	0.0025	200
4	PdCl <sub>2</sub> (P( <i>p</i> -F-C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> ) <sub>2</sub>	97	2.5	99.81	0.09	0.0009	195
5	PdCl <sub>2</sub> (P( <i>p</i> -tol) <sub>3</sub> ) <sub>2</sub>	99	1.5	94.01	5.89	0.0626	330
6	PdCl <sub>2</sub> (P( <i>o</i> -tol) <sub>3</sub> ) <sub>2</sub>	10	5.0	93.51	6.48	0.07	10
7	Pd(PPh <sub>3</sub> ) <sub>4</sub>	98	1.75	98.29	1.69	0.017	280
8	Pd(dba) <sub>2</sub> .CHCl <sub>3</sub>	98	3.0	98.03	1.93	0.02	160
9	Pd(dppb)Cl <sub>2</sub>	—	5.0	Nil	—	—	—

*Reaction conditions:* IBPE, 28.1 mmol; Pd-complex, 0.056 mmol; TsOH, 5.62 mmol; LiCl, 5.62 mmol, water, 1.2 cm<sup>3</sup>; P<sub>CO</sub>, 5.4 MPa; T, 388 K; MEK, 19.5 cm<sup>3</sup>

Since Pd(0) was proposed as the active catalytic species, the effect of palladium(0) complexes like Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd(dba)<sub>2</sub>.CHCl<sub>3</sub> as catalytic precursors was also studied. Surprisingly in the case of both Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd(dba)<sub>2</sub>.CHCl<sub>3</sub>/4PPh<sub>3</sub> with TsOH/LiCl promoters the catalytic activity was lower compared to that of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>. This may be due to the problems associated with the formation of low ligated active catalytic species Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>2</sub> from the precursor. It is reported that Pd(PPh<sub>3</sub>)<sub>4</sub> exists as Pd(PPh<sub>3</sub>)<sub>3</sub> in solution.<sup>11</sup> The dissociation of one more PPh<sub>3</sub> ligand (Eq. 4.2) is not favored because of the large endergonicity involved, ensuing the formation of only trace levels of the true active catalytic species Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>2</sub> in solution.<sup>11,12</sup>



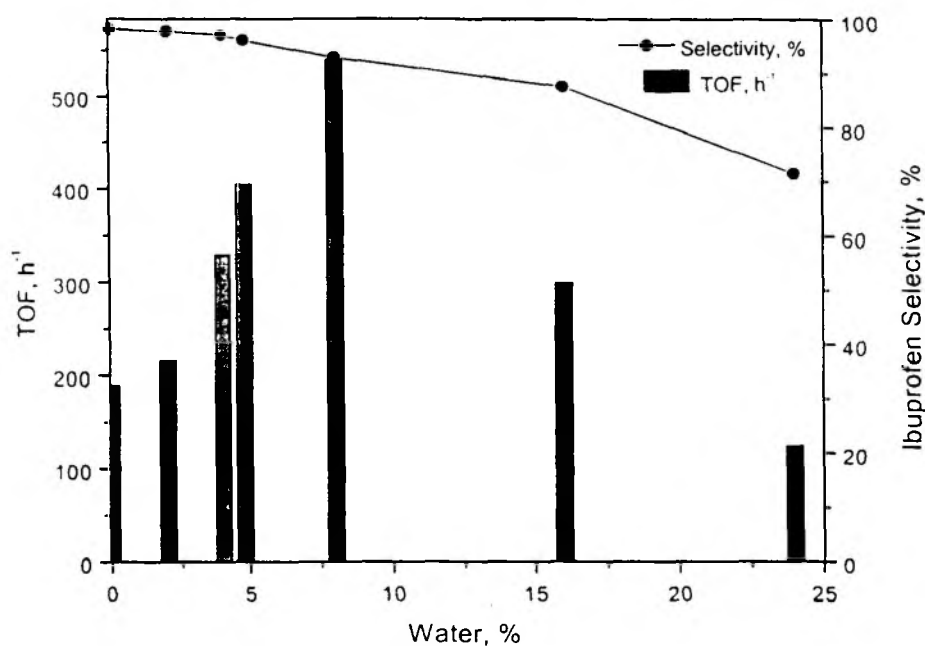
Similarly, the lower catalytic activity of  $\text{Pd}^0(\text{dba})_2$  also emphasizes the negative role or poisoning effect of dba ligand in the initial formation of active catalytic species. It was reported that<sup>13</sup>  $\text{Pd}^0(\text{dba})(\text{PPh}_3)_2$  is the major catalytic species in solution of a mixture of  $\text{Pd}^0(\text{dba})_2$  and  $\text{PPh}_3$  and the concentration of active low-ligated  $\text{Pd}^0(\text{PPh}_3)_2$  is limited due to the very endergonic equilibrium (Eq. 4.4).



However, the *in situ* reduction of  $\text{PdCl}_2(\text{PPh}_3)_2$  forms directly and efficiently the active  $\text{Pd}^0(\text{PPh}_3)_2$ , bypassing totally the two ligand dissociation equilibria,<sup>17</sup> thereby, providing higher reaction rates compared to that of  $\text{Pd}(\text{PPh}_3)_4$  or  $\text{Pd}(\text{dba})_2 \cdot \text{CHCl}_3/4\text{PPh}_3$ .

#### 4.3.4. Effect of concentration of water

Concentration of water has a significant effect on both catalytic activity and selectivity behavior in the carbonylation of IBPE. Catalytic activity increased with concentration of water up to 8 %, beyond which it decreased steadily as shown in Figure 4.3. One of the reasons for the steady decrease in activity is the change of homogeneous nature of the reaction medium to biphasic in which case the concentration of promoters in the organic phase decreases. The increase in catalytic activity at lower range of water concentrations (0–8%) is a noticeable observation. Water is believed to have two important roles in the overall catalytic process. One is the initial formation of active Pd(0) species by a kind of water-gas shift reaction. The second is in the product formation step and regeneration of the active Pd(0) species by reductive elimination. Higher concentration of water may facilitate both these steps thereby increasing the overall catalytic activity under homogeneous conditions.



**Figure 4.3.** Effect of concentration of water on TOF and Selectivity.

*Reaction conditions:* IBPE, 28.1 mmol; PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 0.056 mmol; TsOH, 5.62 mmol; LiCl, 5.62 mmol; P<sub>CO</sub>, 5.4 MPa; T, 388 K; MEK, 19.5 cm<sup>3</sup>

The initial marginal drop in selectivity to the branched acid with increase in concentration of water also indicates probable involvement of water in the catalytic cycle. A sharp decrease in the selectivity beyond a concentration of 8% is probably due to the decreased availability of promoters in the organic phase because of the heterogeneous nature of the system as discussed earlier.

#### 4.3.5. Effect of solvents

The effect of various polar and non-polar solvents on the carbonylation of IBPE was also investigated and the results are presented in the Table 4.7. Among the solvents studied, acetone and methyl ethyl ketone gave the best results. Surprisingly, other polar solvents such as DMF and NMP provided very low reaction rates. In the case of NMP, colloidal Pd formation was observed after the reaction. Dioxane, which is comparatively less polar, also showed lower reaction rates with an initial induction period of 1.5 hrs. One



of the reasons, for the lower reactivity in such solvents may be the lower solubility of CO in reaction medium.<sup>14</sup> Another possibility is the modified stabilization of different active palladium complexes in such solvents. In toluene, the reaction rate was higher than that in DMF and NMP as solvents but less than that with MEK and acetone.

**Table 4.7.** Effect of solvents on the carbonylation of IBPE

Run No.	Solvent	Conversion %	Time h	Selectivity, %		<i>n/iso</i>	TOF h <sup>-1</sup>
				IBN	3-IPPA		
1	MEK	99.5	1.25	96	3.9	0.0406	405
2	Acetone	100	0.8	95.4	4.5	0.0482	620
3	Dioxane	88	3.5	99.6	0.4	0.004	126
4	DMF	40	8	99.8	–	–	25
5	NMP	35	8	99.8	–	–	22
6	Toluene	92	5	92	7.8	0.0847	92

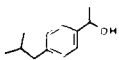

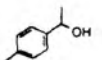
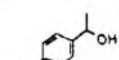
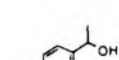
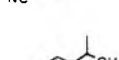

*Reaction conditions:* IBPE, 28.1 mmol; PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 0.056 mmol; TsOH, 5.62 mmol; LiCl, 5.62 mmol, water, 1.2 cm<sup>3</sup>; P<sub>CO</sub>, 5.4 MPa; T, 388 K; solvent, 19.5 cm<sup>3</sup>

#### 4.3.6. Effect of substrates

The carbonylation of different 1-aryl ethanols was studied using the catalyst system PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/TsOH/LiCl and the results are presented in Table 4.8. For comparison of the reactivity of different aryl ethanols, the carbonylation experiments were carried out at higher concentration of TsOH and LiCl (11.2 mmol). *sec*-phenethyl alcohol showed very low reaction rates as compared to IBPE. Other 1-aryl ethanols studied include, phenylethyl alcohols substituted at the 4-position with methyl, chloro, hydroxy and cyano groups. In these cases, the reaction rates were found to vary randomly without any particular trend, but were lower than that of IBPE. In all the cases the selectivity of the branched carboxylic acid predominated (75–95%). Carboxylation of 1-(6-methoxynaphthyl) ethanol was also studied which gave 2-(6-methoxynaphthyl) propionic acid (Naproxen), with high selectivity (97.2 %) with moderate reaction rates (215 h<sup>-1</sup>). The lower reaction rates observed in the case of different 4-substituted 1-aryl ethanols, may be attributed to their

varied ability for dehydration and subsequent addition of  $H^+/Cl^-$ , in addition to the rate of activation of the halide derivatives with Pd complexes.

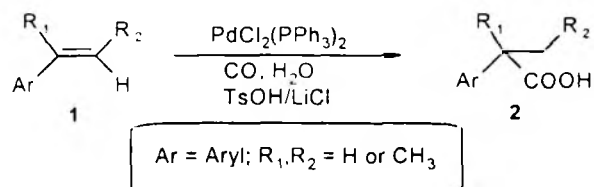
**Table 4.8.** Carbonylation of different 1-aryl ethanols.

Run No.	Substrate	Time, h	Conversion %	Selectivity, %			TOF $h^{-1}$
				<i>iso</i>	<i>n</i>	<i>n/iso</i>	
1		0.58	99	96.2	3.7	0.038	850
2		0.92	90	95.2	4.3	0.045	510
3		3	95	81.9	17.4	0.212	600
4		3	86	75.2	23.1	0.307	300
5		3.33	95	96.2	3.7	0.038	143
6		2.83	97	97.1	2.6	0.027	172
7		2.33	98	97.2	1.6	0.017	215

*Reaction conditions:* IBPE, 28.1 mmol;  $PdCl_2(PPh_3)_2$ , 0.056 mmol;  $TsOH$ , 5.62 mmol;  $LiCl$ , 5.62 mmol, water, 1.2  $cm^3$ ;  $P_{CO}$ , 5.4 MPa;  $T$ , 388 K; MEK, 19.5  $cm^3$

Since carbonylation rate of IBS was found to be higher compared to IBPE (Table 4.3) under identical conditions, carbonylation of different vinyl aromatic compounds (Scheme 4.2) was also studied to investigate the catalytic activity and product selectivity behavior (Table 4.9). In general, significantly higher reaction rates (TOF up to 2250  $h^{-1}$ ) and high regioselectivity (up to 99.8%) to 2-aryl propionic acids was observed. In all the cases, the reaction rates were much higher compared to their alcohol counterparts. The only traces of detected by-product were the isomeric 3-arylpropionic acids. In the case of less hindered terminal olefins, very high reaction rates and selectivity were observed with almost complete conversion. The reaction rate was the highest for styrene. In the case of 4-substituted styrenes, a marginal enhancement in reaction rate was observed for 4-methyl


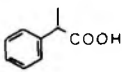
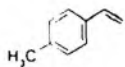
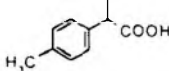
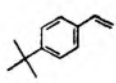
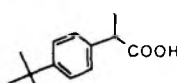
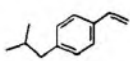
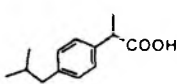
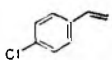
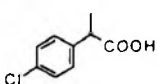
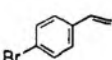
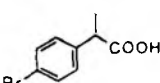

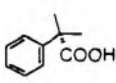
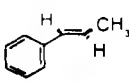
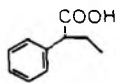
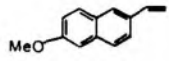
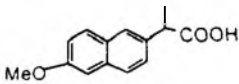
and 4-tertiary butyl styrenes, which have a positive inductive effect compared to 4-chloro and 4-bromostyrenes. But, 4-chloro and 4-bromostyrenes showed very high selectivity for the 2-arylpropionic acids.



**Scheme 4.3.** Carbonylation of vinyl aromatics

With hindered terminal olefins such as  $\alpha$ -methylstyrene, reaction rates were very low, with poor selectivity for 2-methyl-2-phenylpropionic acid product. This may be due to the steric hindrance created at the metal center and isomerisation can easily take place to decrease the strain due to steric bulk at the palladium center. Internal olefins such as  $\beta$ -methylstyrene also showed lower reactivity, but the regioselectivity was comparatively higher compared to  $\alpha$ -methyl styrene.

**Table 4.9** Carbonylation of vinyl aromatics

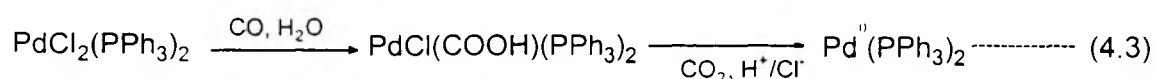
Run No.	Substrate	Time, h	Conversion, %	<i>iso</i> -product	Selectivity, %	TOF, h <sup>-1</sup>
1		0.22	99		99.3	2255
2		0.38	98.7		95	1301
3		0.29	99.2		97.5	1713
4		0.4	99		97	1240
5		0.4	99.6		99.8	1247
6		0.38	98.5		99.7	1298
7		5.5	85		61	77
8		2	90		95.5	225
9		1.17	95		97.5	406

*Reaction conditions:* substrate, 28.1 mmol; PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, 0.056 mmol; TsOH, 11.2 mmol; LiCl, 11.2 mmol, water, 1.2 cm<sup>3</sup>; P<sub>CO</sub>, 5.4 MPa; T, 388 K; MEK, 19.5 cm<sup>3</sup>

#### 4.3.7. Reaction mechanism and catalytic cycle

In the case of halide promoted carbonylation of alcohols, the corresponding organic halide formed *in situ* under reaction conditions is the substrate, which undergoes

carbonylation. The catalytic cycle is believed to be initiated by oxidative addition of the organic halide to an active palladium(0) complex. In most cases, the active Pd(0) complex is generated *in situ* by reduction of the Pd(II) precursor by CO in presence of H<sub>2</sub>O as shown in Eq. 4.3.<sup>15</sup> Analysis of the gas phase after a carbonylation reaction of IBPE, showed formation of CO<sub>2</sub> in catalytic amounts (0.1 to 0.2 %), which supports the formation of Pd(0) species as shown in Eq. 4.3.

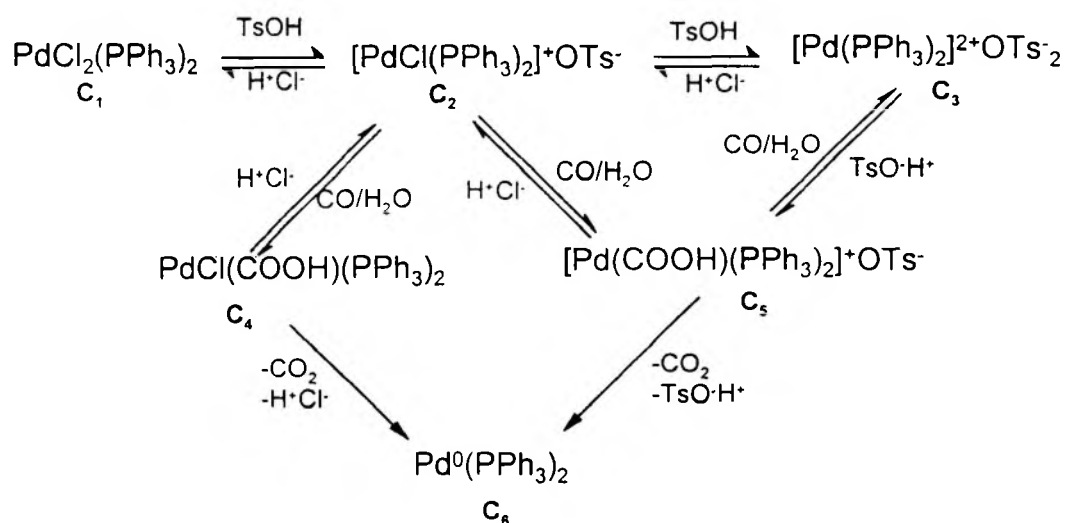


The lower carbonylation rates observed in the case of HCl as a promoter instead of TsOH/LiCl under homogeneous reaction conditions indicate two possibilities, a) the reduction of Pd(II) to active Pd(0) may not be efficient in the case of HCl as the promoter or b) the *in situ* formed Pd(0) complex may be less active in the presence of HCl when compared to that formed in the presence of TsOH and LiCl. An attempt has been made to understand the role of promoters in the mechanism of carbonylation of IBPE using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as the catalyst precursor. As mentioned before (see Table 4.5), the rate of carbonylation reaction was found to increase linearly with the promoter concentration when the ratio of TsOH to LiCl was kept constant at 1:1. However, doubling the concentration of TsOH keeping that of LiCl as a constant resulted in an initial increase in reaction rate, which slowed down very much after 0.25 hours of reaction. In this case significant amount of palladium metal precipitation was observed after the reaction. But when concentration of LiCl was doubled keeping TsOH as a constant, the reaction rate was reduced by more than half of the original value and in this case the catalyst precursor PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was found precipitated after the reaction.

These observations indicate that TsOH helps in the efficient reduction of Pd(II) to Pd(0) species. In the presence of TsO<sup>-</sup> ions, it is possible that the chloride ligands in PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (C<sub>1</sub>) are exchanged with TsO<sup>-</sup> ions forming an equilibrium with the species [Pd(PPh<sub>3</sub>)<sub>2</sub>Cl]<sup>+</sup>(TsO<sup>-</sup>) (C<sub>2</sub>) and [Pd(PPh<sub>3</sub>)<sub>2</sub>]<sup>2+</sup>(TsO<sup>-</sup>)<sub>2</sub> (C<sub>3</sub>) in solution as illustrated in Scheme 4.3. It was known that cationic Pd(II) complexes reduce to Pd(0) species efficiently.<sup>16</sup> In the presence of higher amounts of TsO<sup>-</sup> the equilibrium may shift more

towards  $C_3$ , which is much easily reduced to Pd(0) species. As demonstrated in Chapter 2 (Section 2.3.2.1) dicationic palladium (II) phosphine complexes reduce to form Pd metal even in the presence of small amounts of water. In the presence of more amount of LiCl compared to TsOH, the equilibrium in Scheme 4.4 may shift towards  $C_1$ , thereby resulting in lowering the concentration of active Pd(0) species and hence negatively affecting the net catalytic activity.

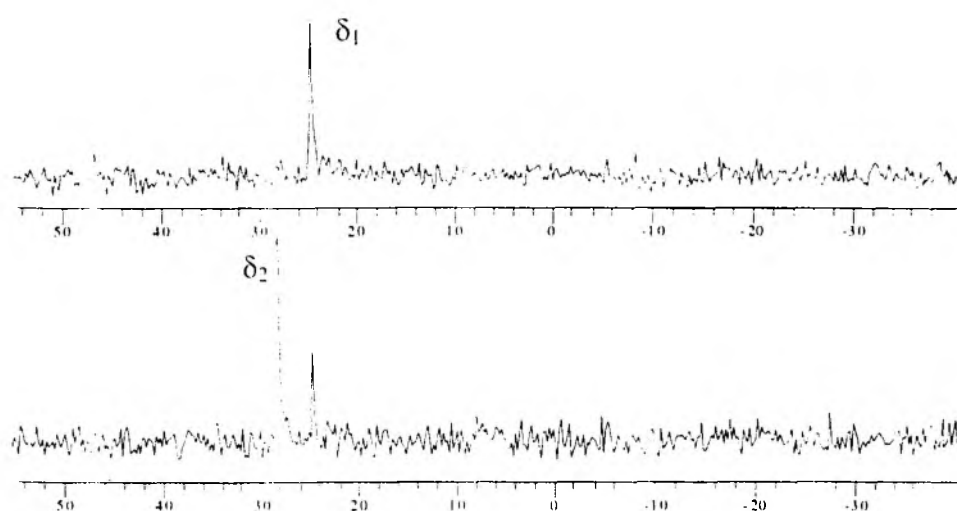
In order to check for the formation of  $C_2$  and  $C_3$ ,  $^{31}\text{P}$  NMR experiments were carried out by adding TsOH to a solution of  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $C_1$ , in DMF (for convenience DMF was used as a solvent instead of MEK, since the  $^{31}\text{P}$  NMR values of most of the species were reported in the literature with DMF as a solvent).



**Scheme 4.4.** Formation of Active Pd(0) complex from Pd(II) precursor

$C_1$  has only poor solubility in DMF at room temperature but dissolved slowly on warming (323 K) and showed a  $^{31}\text{P}$  value of 24.23 ppm ( $\delta_1$ ). Addition of excess of TsOH (25 equivalents) dissolved  $\text{PdCl}_2(\text{PPh}_3)_2$  readily at 323 K which showed a major signal at 28.15 ppm ( $\delta_2$ ) in addition to  $\delta_1$  with a  $\delta_2/\delta_1$  ratio of 3.6. This solution decomposed partly to palladium metal on keeping for 1–3 hours. A comparison of the two spectra is given below in Figure 4.4.

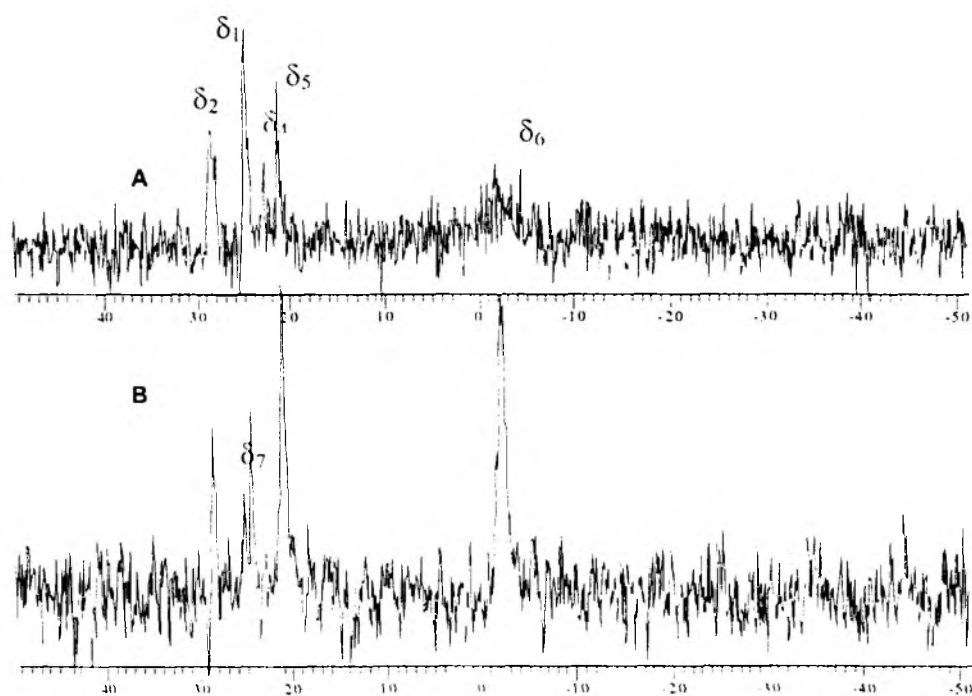
The signal at  $\delta_2$  can be assigned to the monocationic palladium complex  $[\text{PdCl}(\text{PPh}_3)_2]^+\text{TsO}^-$  ( $\text{C}_2$ ) formed by the elimination of a molecule of  $\text{H}^+$  and  $\text{Cl}^-$  ions from  $\text{C}_1$ . No signal corresponding to the dicationic species  $[\text{Pd}(\text{PPh}_3)_2]^{2+}(\text{TsO}^-)_2$ <sup>167</sup> was observed in these cases. Under the present carbonylation reaction conditions, it is possible that both  $\text{C}_2$  as well as  $\text{C}_3$  are responsible for the reduction of  $\text{C}_1$  to the Pd(0) species  $\text{C}_6$  through  $\text{C}_4$  and  $\text{C}_5$  as the intermediates. Complex  $\text{C}_3$  may be more easily reduced than  $\text{C}_2$  and could be the reason for the increased initial reaction rate in the presence of excess TsOH compared to LiCl than with equivalent amount of TsOH and LiCl.



**Figure 4.4.** (A)  $^{31}\text{P}$  NMR spectrum of  $\text{PdCl}_2(\text{PPh}_3)_2$  in DMF, (B) with 25 equivalents of TsOH

The low ligated Pd(0) species,  $\text{C}_6$ , can initiate the catalytic cycle by oxidative addition of the organic halide (IBPCl). If only the reduction of Pd(II) to Pd(0) is the rate limiting step, the catalytic activity should practically be the same in case of both the promoters (HCl and TsOH/LiCl) after an initial induction period during which most of the Pd(II) would have reduced to the active Pd(0) species. On the contrary, the reaction rate in the case of HCl was lower and remained almost the same even after 2 hrs of reaction. Such a difference in the overall catalytic activity in the presence of HCl promoter compared to

TsOH/LiCl suggests that the nature of active Pd(0) species, which initiates the catalytic cycle may be different in both the cases. In order to investigate the nature of Pd(0) species formed in solution under reaction conditions, the reduction of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> was carried out under CO in which the intermediate samples were obtained and analyzed by <sup>31</sup>P NMR and is discussed below. When PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, C<sub>1</sub>, was treated with only TsOH (25 equivalents) under 5.4 MPa of CO at 378 K in DMF as a solvent, the major signal observed was that of C<sub>1</sub> at 24.34 ppm (δ<sub>1</sub>) and a small signal at -5.1 ppm (δ<sub>3</sub>) corresponding to free PPh<sub>3</sub>. No signals corresponding to low ligated Pd<sup>0</sup>(PPh<sub>3</sub>)<sub>2</sub> (C<sub>6</sub>) complexes were obtained. However, lot of palladium metal precipitation was observed after the reaction, which indicates that the Pd(0) species formed were not stable in the presence of excess TsOH alone and may decompose to palladium metal and free PPh<sub>3</sub>.



**Figure 4.5.** <sup>31</sup>P NMR of the intermediate sample on reduction of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> with CO under 378 K and 5.4 MPa pressure in DMF (A) with equivalent amount of TsOH and LiCl and (B) after addition of PhI

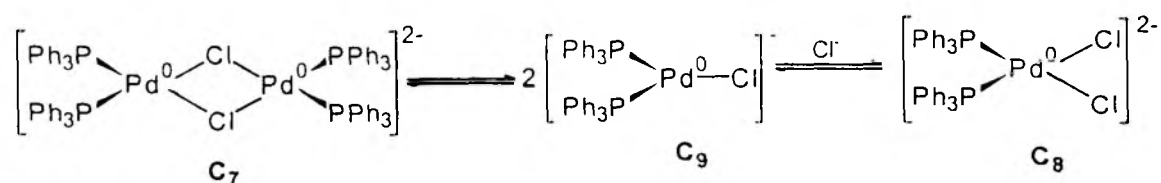
Amatore *et. al.*, also have reported that low ligated Pd(0) species are not stable in the absence of excess phosphines or halides. Hence to prevent decomposition of Pd(0)



species formed, 2 equivalents of  $\text{PPh}_3$  was also added to the following experiments. When the same reaction was repeated with added equivalent amount of  $\text{LiCl}$  and two equivalents of  $\text{PPh}_3$ , two major signals at 24.32 ( $\delta_1$ ) and 28.15 ( $\delta_2$ ) ppm and comparatively smaller signals at 22.83 ( $\delta_4$ ) and 21.28 ppm ( $\delta_5$ ), along with a broad signal at -2.07 ppm (1.31 to -3.84) ( $\delta_6$ ) were observed. In order to check for the formation of any  $\text{Pd}(0)$  species formed,  $\text{PhI}$  was immediately added to this solution. This resulted in the development of a new signal at 25.31 ( $\delta_7$ ) ppm, while the signal at 22.83 ppm ( $\delta_4$ ) disappeared and the broad signal at  $\delta_6$  as well as the signal at  $\delta_5$  were sharpened. The signal at  $\delta_6$  can be assigned to less active  $\text{Pd}(0)$  phosphine complex such as  $\text{Pd}^0(\text{PPh}_3)_3$  as compared to the values reported in the literature.<sup>11,17b</sup> Since the signal at  $\delta_4$  disappeared on the addition of  $\text{PhI}$ , it may also correspond to a  $\text{Pd}(0)$  species and can be assigned to  $\text{Pd}(0)$  species ligated by  $\text{Cl}^-$  ions to form anionic complex such as  $\text{Pd}^0(\text{PPh}_3)_2\text{Cl}_2^{2-}$  in comparison with literature reported values.<sup>12,17</sup> The new signal developed after the addition of  $\text{PhI}$  at  $\delta_7$  correspond to *trans*-aryl  $\text{Pd}(\text{II})$  complexes such as  $\text{PhPdI}(\text{PPh}_3)_2$  or  $\text{PhPdCl}(\text{PPh}_3)_2$  formed by the oxidative addition of  $\text{PhI}$  to the  $\text{Pd}(0)$  species in accordance with the values reported earlier.<sup>18</sup> The signal at  $\delta_5$  was unidentified and may be due to neutral palladium(0) carbonyl species such as  $\text{Pd}(\text{CO})(\text{PPh}_3)_n$ , where  $n = 1$  to 3 as shown in chapter 2. A small amount of palladium metal precipitation was also observed in this sample after keeping for 5–6 hours. It is to be noted that the carbonylation reaction rate in DMF as a solvent was found to be very low (TOF~20-25  $\text{h}^{-1}$ ).

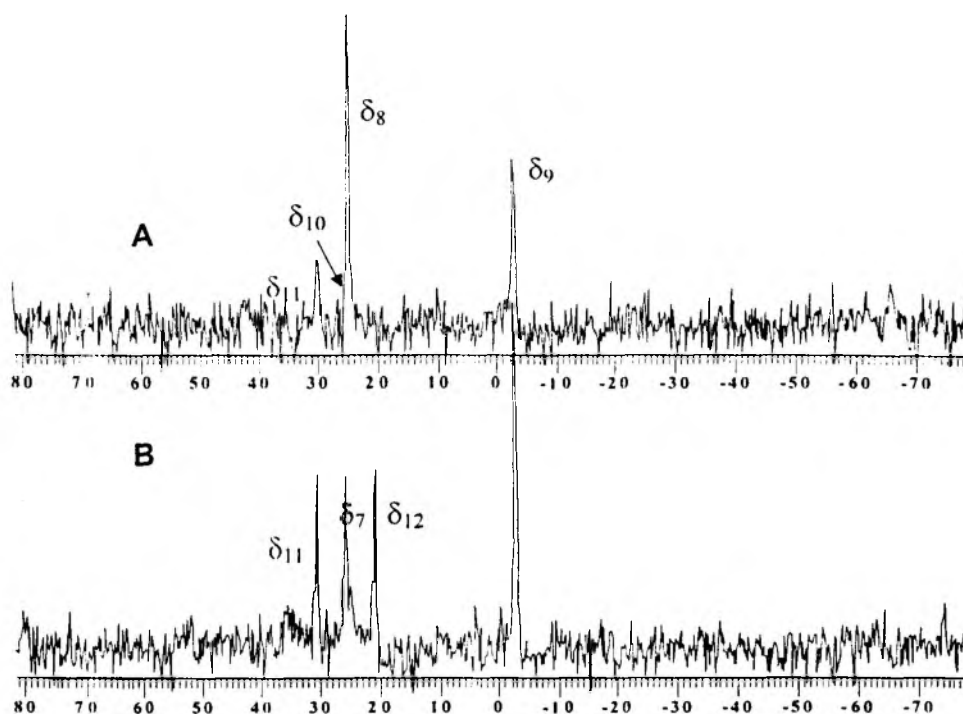
Hence, in order to find out the exact nature of species formed in methyl ethyl ketone as the solvent, the above experiments were also carried out in wet MEK (4–5% water) as the solvent. An intermediate sample from a reaction of  $\text{PdCl}_2(\text{PPh}_3)_2$  with 25 equivalents of  $\text{TsOH}$  and  $\text{LiCl}$  and 2 equivalents of  $\text{PPh}_3$  under 5.4 MPa of  $\text{CO}$  at 378 K, showed strong signals at 24.90 ( $\delta_8$ ) and -2.64 ( $\delta_9$ ) ppm with a relatively weaker signal at 30.33 ( $\delta_{11}$ ) ppm. A weak signal at 25.50 ppm was also observed in this case. When this intermediate sample was reacted with  $\text{PhI}$ , the signal at  $\delta_8$  diminished and new signals at 20.68 ( $\delta_{12}$ ) and 25.71 ( $\delta_7$ ) ppm developed. The signal at  $\delta_7$  correspond to the aryl  $\text{Pd}(\text{II})$  complexes such as  $\text{PhPd}(\text{PPh}_3)_2\text{I}$  or  $\text{PhPd}(\text{PPh}_3)_2\text{Cl}$  formed by the addition of  $\text{PhI}$  to a

Pd(0) complex as discussed before. Since the signal at  $\delta_8$  diminished after the addition of PhI, it can be inferred that  $\delta_8$  corresponds to a Pd(0) species and the most likely species that can be assigned to this signal is a mono anionic Pd(0) species such as  $\text{Pd}^0(\text{PPh}_3)_2\text{Cl}^-$  as reported by Amatore *et. al.* and Negishi *et. al.*<sup>17, 18</sup> Amatore *et. al.* reported that low-ligated Pd(0) species such as  $\text{Pd}^0(\text{PPh}_3)_2$  in the presence of halide ions exists as mono- and di-anionic species, **C**<sub>7</sub> ( $\delta$ , 27.14), **C**<sub>8</sub> ( $\delta$ , 23.15) and **C**<sub>9</sub> ( $\delta$ , 25.22) as shown below in scheme 4.4.<sup>17</sup> The signal at  $\delta_9$  may be assigned to less active  $\text{Pd}^0(\text{PPh}_3)_3$  as described before.

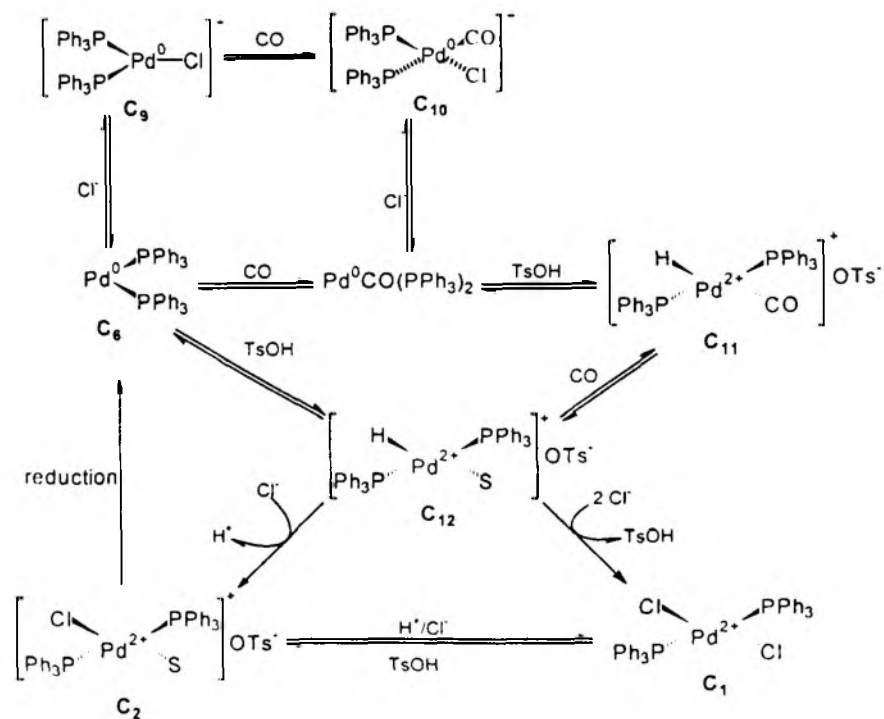


Scheme 4.5

The new signal appeared at  $\delta_{12}$  may correspond to Pd(II) species such as  $\text{PdI}(\text{PPh}_3)_2$  or  $\text{PdI}(\text{PPh}_3)_2^-$  that may be formed by halide exchange reactions.<sup>16</sup> The signal at 30.33 ppm correspond to  $\text{PPh}_3=\text{O}$  in comparison with a standard sample in wet MEK (containing TsOH and LiCl) as a solvent. This signal at  $\delta_{11}$  was almost negligible when the same reaction was carried out in the presence of very small amount of water. This reaction mixture did not show any Pd metal precipitation, but showed slight precipitation of  $\text{PdCl}_2(\text{PPh}_3)_2$  after 6–8 hours. A similar observation was also found with HCl as the promoter in MEK with a comparatively stronger signal at 30.3 ppm

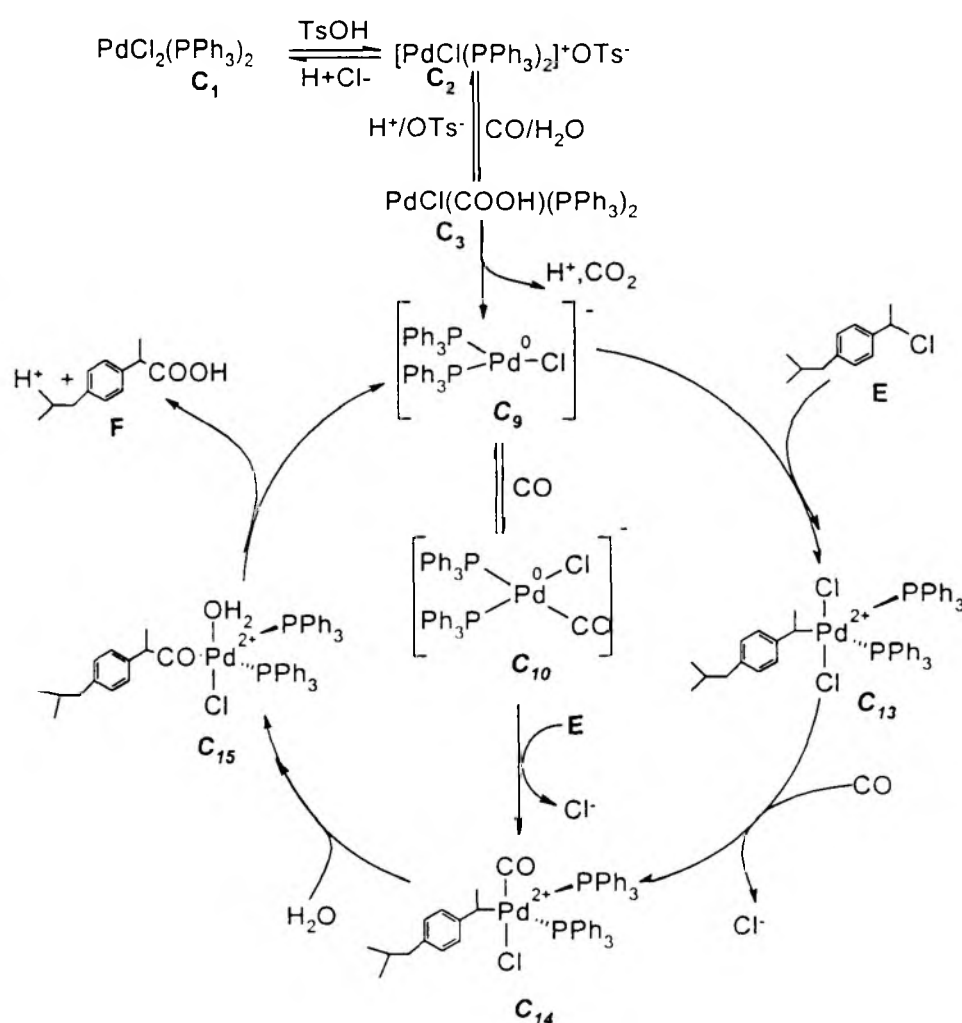


**Figure 4.6.**  $^{31}\text{P}$  NMR of the intermediate sample on reduction of  $\text{PdCl}_2(\text{PPh}_3)_2$  with CO under 378 K and 5.4 MPa pressure in MEK along with two equiv.  $\text{PPh}_3$  (A) with equivalent amount of TsOH and LiCl and (B) after addition of PhI



Scheme 4.6

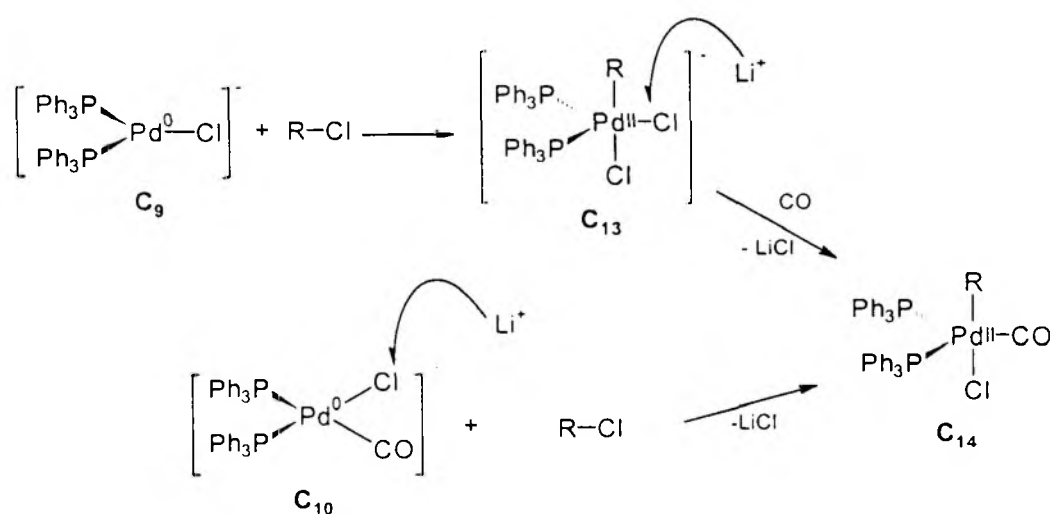
These observations suggests that, under the carbonylation reaction conditions different ionic and neutral palladium complexes may be present in solution as shown in Scheme 4.6. The concentration of each species may vary with the change in reaction conditions. However, in the present system that contains excess  $\text{Cl}^-$  ions the Pd(0) species formed may exist mostly as anionic species, such as  $\text{C}_8$ ,  $\text{C}_9$  and/or  $\text{C}_{10}$  as also indicated by the  $^{31}\text{P}$  NMR experiments discussed above.



Scheme 4.7. Proposed catalytic cycle

High carbonylation rates observed in the presence of  $\text{LiCl}$  compared to  $\text{HCl}$  or any other halides (see Table) also supports the possibility of increased formation of the anionic

palladium species, which may be stabilized as strong ion pairs in the presence of  $\text{Li}^+$  ions in solution.<sup>18</sup> Similar promoting effects of  $\text{Li}^+$  ions on the halide promoted carbonylation of alcohols was reported earlier using Rh and Ni complexes and was also explained on the basis of possible involvement of anionic complexes stabilized by  $\text{Li}^+$  counter ions.<sup>19</sup> Considering all these points, a plausible catalytic cycle that initiates by the oxidative addition of R-Cl to the anionic Pd(0) complexes such as  $\text{C}_9$  and  $\text{C}_{10}$  is proposed as shown in Scheme 4.7. Anionic complexes are highly nucleophilic and the oxidative addition rates are much higher in these cases compared to their neutral counterparts.<sup>12, 20</sup> Presence of  $\text{Li}^+$  ions may also facilitate the abstraction of  $\text{Cl}^-$  ions from the coordination sphere of  $\text{C}_9$  and/or  $\text{C}_{10}$  thereby facilitating the formation of the penta coordinated alkyl species  $\text{C}_{14}$  as shown in scheme 4.8. The intermediate species  $\text{C}_{13}$  may or may not be a true intermediate. It is more likely that oxidative addition of R-Cl to  $\text{C}_9$  and simultaneous absorption of  $\text{Cl}^-$  ligand by  $\text{Li}^+$  occurs to form  $\text{C}_{14}$ . Lower reaction rates obtained with  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Bu}_4\text{N}^+$  as counter ions (see Table 4.4), also support the above argument due to their lower  $\text{Cl}^-$  abstracting power compared to  $\text{Li}^+$ .



Scheme 4.7

The intermediate species  $\text{C}_{14}$ , on migratory insertion of CO to the Pd alkyl bond followed by association of an  $\text{H}_2\text{O}$  molecule at the vacant site created forms the acyl species ( $\text{C}_{15}$ ). The product carboxylic acid can form from the acyl species  $\text{C}_{15}$  through two

different pathways. One, by the reductive elimination of the acid chloride, which subsequently convert to the acid by hydrolysis. Another possibility is by the direct reductive elimination of carboxylic acid regenerating the active anionic Pd<sup>0</sup> species (C<sub>9</sub> or C<sub>10</sub>) as shown in scheme 4.7. The significant positive effect of water (see Section 4.3.4) on the catalytic activity indicates the latter pathway rather than the former. The absence of even trace amounts of acid chloride in the intermediate reaction samples also supports the above proposition.

#### 4.4. Conclusions

The carbonylation of 1-aryl ethanols and vinyl aromatic compounds has been studied using a homogeneous catalyst system consisting of PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/TsOH/LiCl. This catalyst system provides significantly higher reaction rates (TOF up to 2200 h<sup>-1</sup>) and 2-arylpropionic acid selectivity (>95%) at relatively mild reaction conditions such as 388 K and 5.4 MPa CO partial pressure. The reaction proceeds through the formation of IBS and IBPCI as intermediates and IBPCI is confirmed as the active substrate, which undergoes carbonylation. Effect of various parameters such as catalyst precursors, promoters, solvents, substrates and concentration of water on catalytic activity as well as product distribution was studied in detail. Few <sup>31</sup>P NMR experiments were carried out to investigate the nature of species formed in solution under the reaction conditions. Based on the experimental trends and <sup>31</sup>P NMR studies, a catalytic cycle based on anionic palladium(0) species as the active catalytic species is proposed.

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## Chapter 5

**Kinetics of Carbonylation of  
1-(4-isobutylphenyl)ethanol using  
 $\text{PdCl}_2(\text{PPh}_3)_2/\text{TsOH}/\text{LiCl}$  as a Catalyst**

## 5.1. Introduction

Carbonylation of 1-aryl ethanols<sup>1</sup> (e.g. 1-(4-isobutylphenyl)ethanol, IBPE) is gaining importance because of their application in the synthesis of Ibuprofen<sup>2</sup> and other 2-aryl propionic acids,<sup>3</sup> which are important pharmaceuticals.<sup>4</sup> A detailed literature review describing the various processes, catalyst, selectivity behaviour etc. is presented in Chapter 1 (Section 1.2.2.1). Also experimental data on activity and selectivity of some novel palladium catalyst and promoter combinations has been discussed in Chapter 4. From previous reports it is quite evident that Pd complex in combination with acidic as well as halide promoters have been found to be the best catalysts for this system. While, many reports<sup>2,5</sup> have addressed the role of catalyst types, promoters, solvents etc. on the activity selectivity behaviour of this particular reaction (carbonylation of IBPE to Ibuprofen) and aryl propionic acids in general, no published report has discussed the kinetics of this industrially important reaction. A knowledge of the intrinsic kinetics of the reaction and development of a suitable rate equation is important in understanding the reaction mechanism and in practical design of reactors for such processes. Also, it is a case of gas-liquid catalytic reaction in which, in addition to the principal catalytic reaction, other reactions are also involving, which are catalysed by one or more of the promoters. Interpretation of kinetic data and developing rate equations for such multi-step reaction systems is, indeed, challenging. Therefore, the present work was undertaken with the goal of investigating the intrinsic kinetics of carbonylation of IBPE using a homogeneous catalyst system consisting of  $\text{PdCl}_2(\text{PPh}_3)_2/2\text{PPh}_3$  as the catalyst precursor and  $\text{TsOH/LiCl}$  (1:1) as the promoters. Effect of various parameters such as catalyst loading, concentration of IBPE, water and promoters ( $\text{TsOH/LiCl}$ ) and partial pressure of CO on the carbonylation rate as well as the concentration-time profiles was studied to determine the reaction kinetics in a temperature range of 378–398 K.

## 5.2. Experimental section

The carbonylation reactions were carried out in a Parr Hastalloy C-276 autoclave of capacity  $5 \times 10^{-5} \text{ m}^3$ . In a typical reaction, known quantities of the substrate, catalyst, ligand, promoters, water and the solvent were charged to the autoclave. The contents were

flushed few times with nitrogen followed by carbon monoxide and heated to the desired temperature (under low stirring, 10–20 rpm). After attaining the temperature, the autoclave was pressurised with CO to the desired level and the reaction was started by switching on the agitation (1000 rpm). To maintain a constant pressure in the reactor during a batch experiment, CO was fed through a constant-pressure regulator from a reservoir vessel ( $1 \times 10^{-4} \text{ m}^3$ ). Pressure drop in the reservoir vessel was recorded by means of a pressure transducer, as a function of time. Intermediate liquid samples were also taken at regular intervals of time and analysed to obtain the concentration vs. time profile. The analytical details were similar to that described in Chapter 4 (Section 4.2.2).

The rate of carbonylation was calculated as

$$r_A [\text{kmol.m}^{-3}.\text{s}^{-1}] = \frac{\text{slope of \{concentration of carbonylation products (IBN + 3 - IPPA)\} [kmol] vs. time [s] plot}}{\text{total reaction volume [m}^3\text{]}}$$

### 5.3. Results and discussion

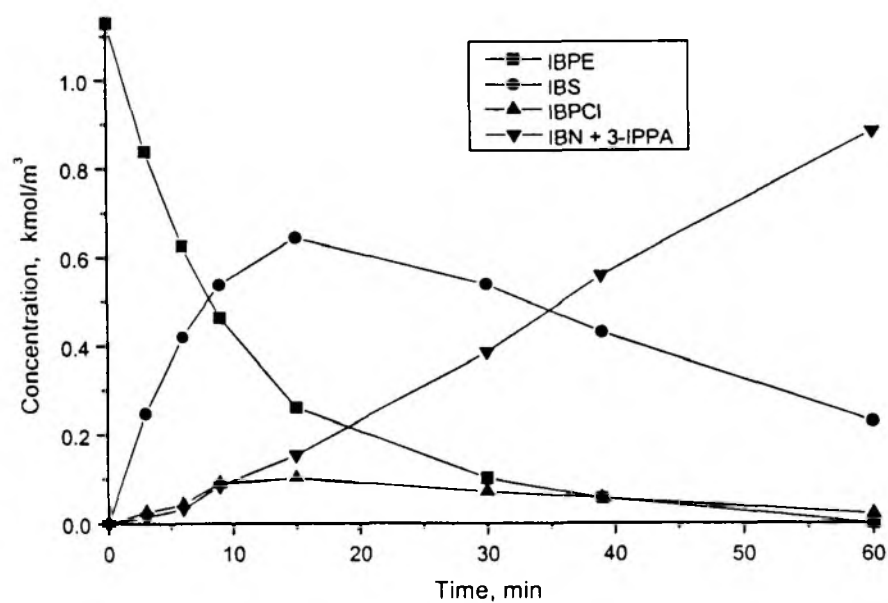
The main objective of this work was (i) to investigate the effect of different reaction and catalyst parameters on the rate of carbonylation of IBPE and analysis of mass transfer effects (ii) to study the intrinsic kinetics of carbonylation of IBPE using a homogeneous palladium catalyst system  $\text{PdCl}_2(\text{PPh}_3)_2/2\text{PPh}_3/\text{TsOH}/\text{LiCl}$  and (iii) to develop rate equations for intrinsic kinetics of the reaction steps involved. For this purpose, several experiments were carried out in a semi-batch mode in which concentration–time data were obtained over a wide range of conditions as given in Table 5.1. The carbonylation rates were evaluated from the rate of formation of total carboxylic acid as described in section 5.2 and also were found to agree with the rates obtained from CO absorption vs. time plots. From Figure 5.1 it may be noticed that after initial few minutes, rate of formation of total carboxylic acid products was nearly constant for most part of the reaction.

In all these experiments, constant CO pressure and isothermal conditions were maintained. A typical concentration–time profile is shown in Figure 5.1. In all the experiments, the material balance of IBPE and CO consumed was consistent (>96%) with

the products (IBS, IBPCI and IBN + IPPA) formed as per the stoichiometry given in Scheme 5.1.

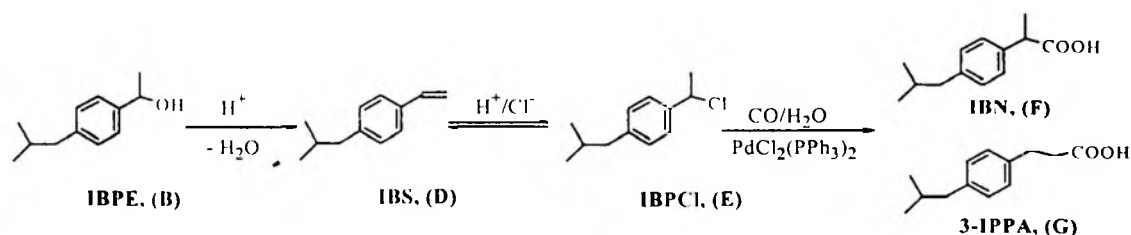
**Table 5.1.** Range of conditions for kinetic study

Catalyst, PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (kmol/m <sup>3</sup> )	$1.121 \times 10^{-3} - 4.482 \times 10^{-3}$
PPh <sub>3</sub> (kmol/m <sup>3</sup> )	$2.242 \times 10^{-3} - 8.964 \times 10^{-3}$
Substrate, IBPE (kmol/m <sup>3</sup> )	0.562 – 2.248
Promoters, TsOH/LiCl (1:1) (kmol/m <sup>3</sup> )	0.224 – 0.896
Partial pressure of CO (MPa)	3.4 – 7.48
Temperature (K)	378 – 398
Volume of liquid phase (m <sup>3</sup> )	$2.5 \times 10^{-5}$
Agitation speed (rpm)	1000

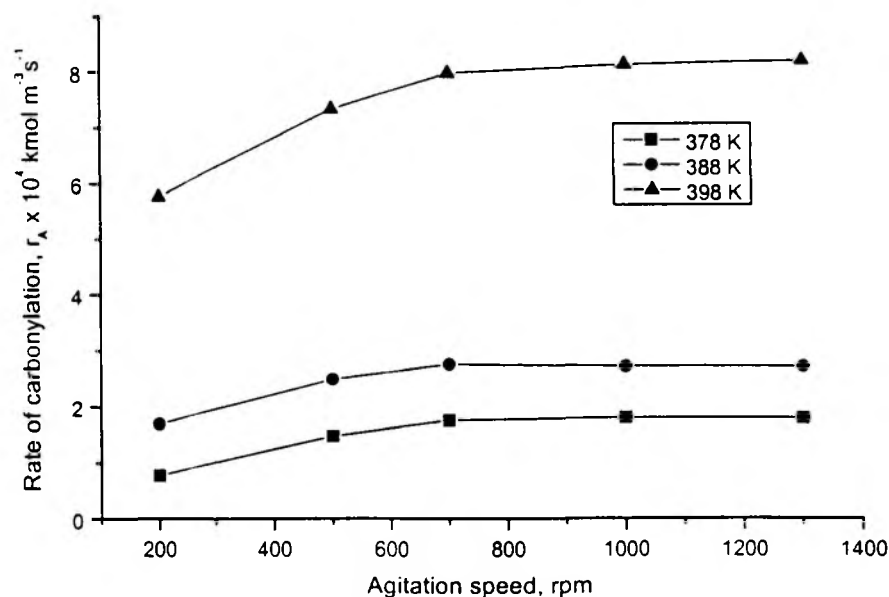


**Figure 5.1.** A typical concentration-time profile for carbonylation of IBPE  
*Reaction conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa; PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ; water =  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$

As also explained in Chapter 4, carbonylation of IBPE proceeds through IBS and IBPCL as the intermediates. IBPE on acid catalysed dehydration forms IBS, which converts to IBPCL by the addition of  $H^+$  and  $Cl^-$  and undergoes carbonylation to form the carboxylic acids 2-(4-isobutylphenyl)propionic acid (IBN) and 3-(4-isobutylphenyl)propionic acid (3-IPPA).



**Scheme 5.1** Reaction scheme for the carbonylation of IBPE

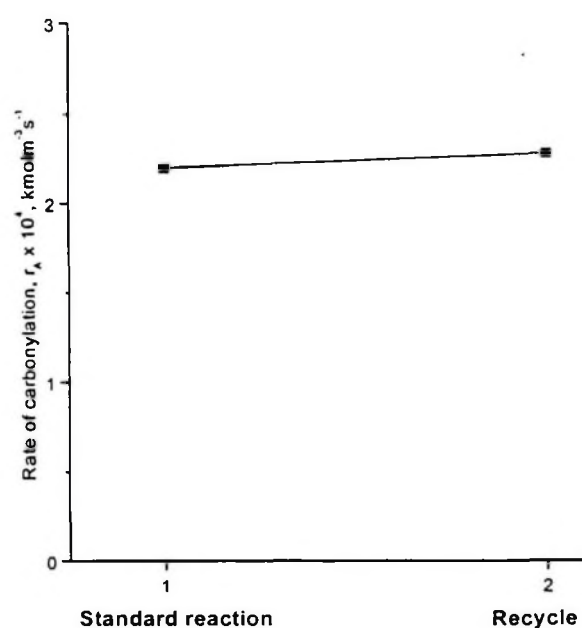


**Figure 5.2.** Effect of agitation speed on rate of carbonylation of IBPE

*Reaction conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl,  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $PdCl_2(PPh_3)_2$ ,  $2.24 \times 10^{-3} \text{ kmol/m}^3$ ;  $PPh_3$ ,  $4.484 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$

Before using the experimental data for evaluation of kinetic parameters, two aspects were examined: (a) significance of mass transfer limitations and (b) constancy of

catalytic activity during an experiment. To assess the importance of mass transfer limitation for the gaseous reactant (gas–liquid mass transfer), the effect of agitation speed on the rate of carbonylation was studied at highest catalyst loading at different temperatures (378, 388 and 398 K). The results shown in Figure 5.2 indicate that beyond 700 rpm, agitation has no influence on the rate of carbonylation and hence we can conclude that gas–liquid mass transfer limitations are not important beyond 700 rpm. All the reactions were carried out at an agitation speed of 1000 rpm.



**Figure 5.3.** Effect of catalyst recycle on the rate of carbonylation of IBPE

*Reaction conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-3} \text{ m}^3$

### 5.3.1. Solubility data

For interpretation of kinetic data, a knowledge of the solubility of CO in MEK–IBPE mixtures was required. The solubility of CO in mixtures of IBPE and MEK containing 4% of water at different concentrations was determined experimentally as per the procedure given in Chapter 3 (Section 3.3.1).

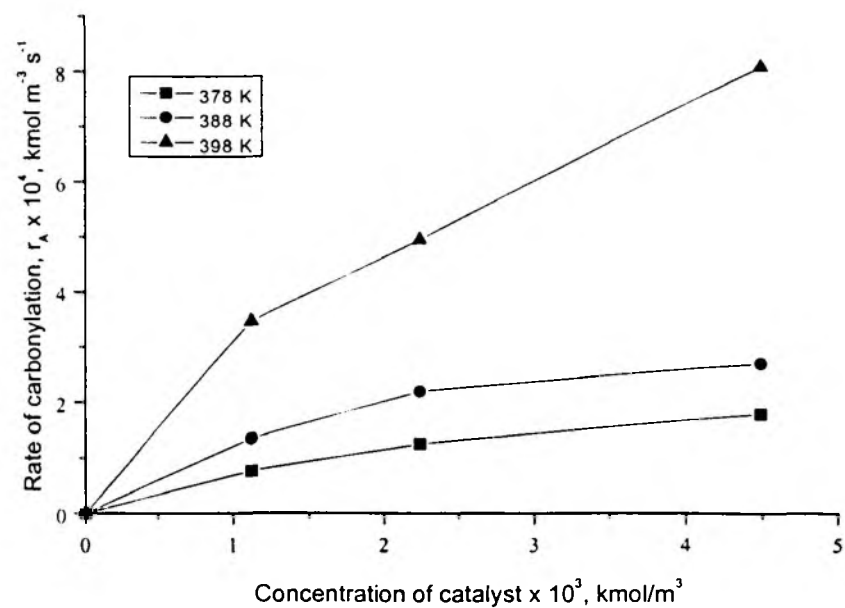
**Table 5.2.** Henry's constants of CO in IBPE and MEK mixture

Mixture of IBPE and MEK (w/w%)	$H_c \times 10^3$ kmol/m <sup>3</sup> /Mpa at 378 K	$H_c \times 10^3$ kmol/m <sup>3</sup> /MPa at 388 K	$H_c \times 10^3$ kmol/m <sup>3</sup> /MPa at 398 K
11% of IBPE	6.131	6.444	6.735
22 % of IBPE	5.579	5.798	6.311
33 % of IBPE	5.051	5.459	5.906

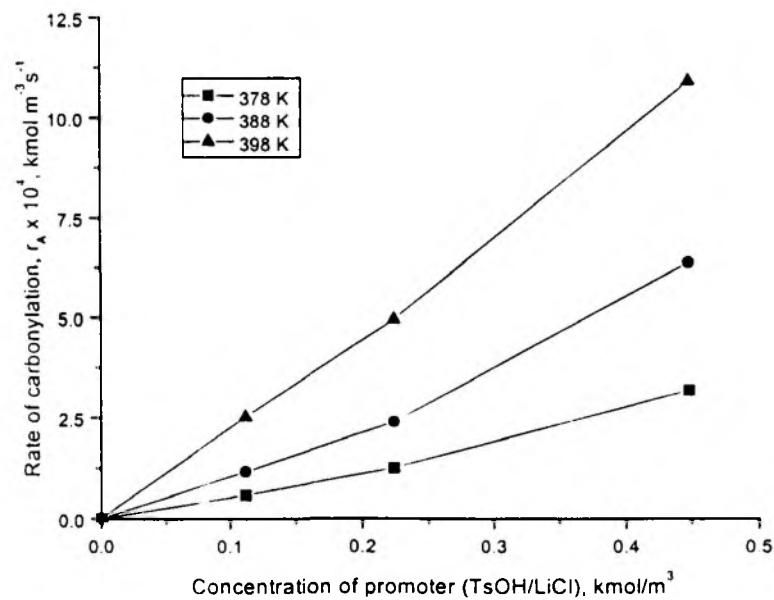
The Henry's constants calculated are given in Table 5.2. It was observed that the solubility of CO in MEK-IBPE mixtures increased with temperature but decreased with increase in concentration of IBPE at all the temperatures studied. The concentration of dissolved CO was calculated as  $A^* = P_{CO} \times H_c$ .

### 5.3.2. Initial rate data

The kinetics of carbonylation of IBPE was studied in a temperature range of 388–398 K. The rate of carbonylation at the very beginning (within 5 min) was found to be very low, which increased steadily and became almost a constant value after 10 minutes and decreased slightly towards the end of the reaction. The lower reaction rate at the initial period of the reaction is because of the inadequate formation of the active carbonylation substrate IBPCl as well as that of the active Pd(0) species. Since, the reaction involves more than one step, the initial rate data may not be very useful in determining the kinetics of the reaction. However, an average rate was calculated for every reaction at 5–25% conversion levels in order to understand the parameter effects on the carbonylation rates and to determine the apparent orders of reaction with respect to each parameter. For this purpose, the data after the initial induction period were used. The rate of carbonylation was found to vary with 0.43<sup>th</sup> order with respect to catalyst concentration as shown in Figure 5.4. This unusual trend of lower reaction order with respect to catalyst concentration in spite of kinetic control indicates that either the catalyst precursor may not be converted entirely to the active form or the active catalyst may be in equilibrium with some less active or inactive palladium species. In such cases only a fraction of the total catalyst charged will be available for catalysis and thus a fractional order may result.



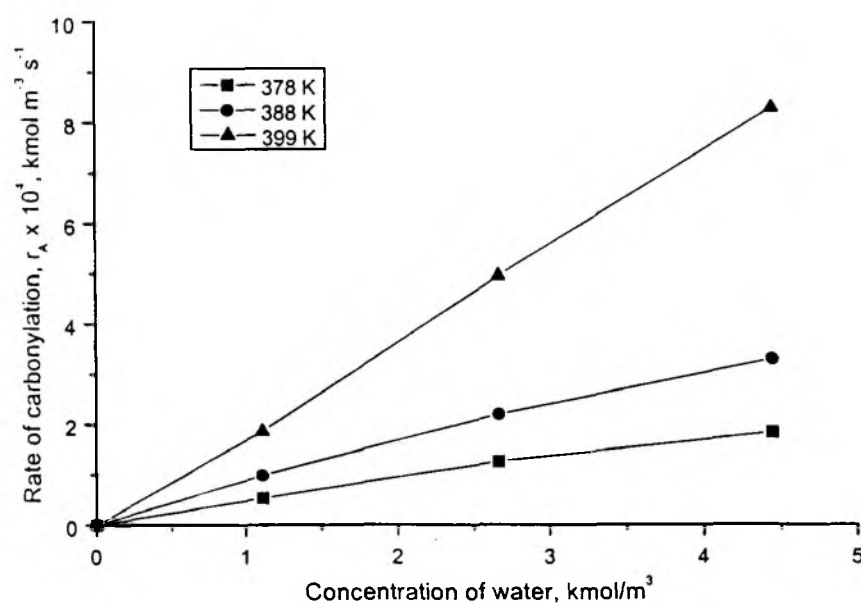
**Figure 5.4.** Effect of concentration of catalyst on the rate of carbonylation of IBPE  
*Reaction conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa; water,  $2.67 \text{ kmol/m}^3$ ;  $PPh_3/Pd$ , 2; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



**Figure 5.5.** Effect of concentration of promoter (TsOH/LiCl) on the rate of carbonylation of IBPE:  
*Reaction conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH:LiCl, 1:1;  $P_{CO}$ , 5.4 MPa;  $PdCl_2(PPh_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $PPh_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$

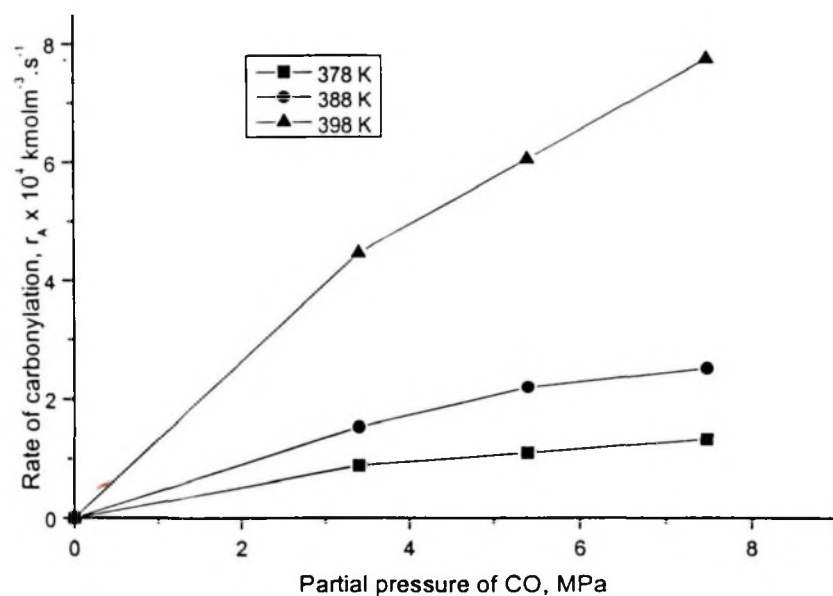


The average rate of carbonylation varied with an order of 2 with concentration of promoters (TsOH/LiCl at 1:1 ratio) and first order with respect to water as shown in Figures 5.5 and 5.6. The second order with respect to promoters may be due to the increased concentration of the active substrate IBPCl accompanied by enhanced rate of formation of the active Pd(0) intermediate as explained in Chapter 4. The linear effect of concentration of water can be due to the enhanced reduction of Pd(II) to Pd(0) through a kind of water gas shift reaction as well as the enhanced formation of product in the final step as explained in Chapter 4. However, more detailed studies will be necessary to understand exact nature of active catalytic species/intermediates.

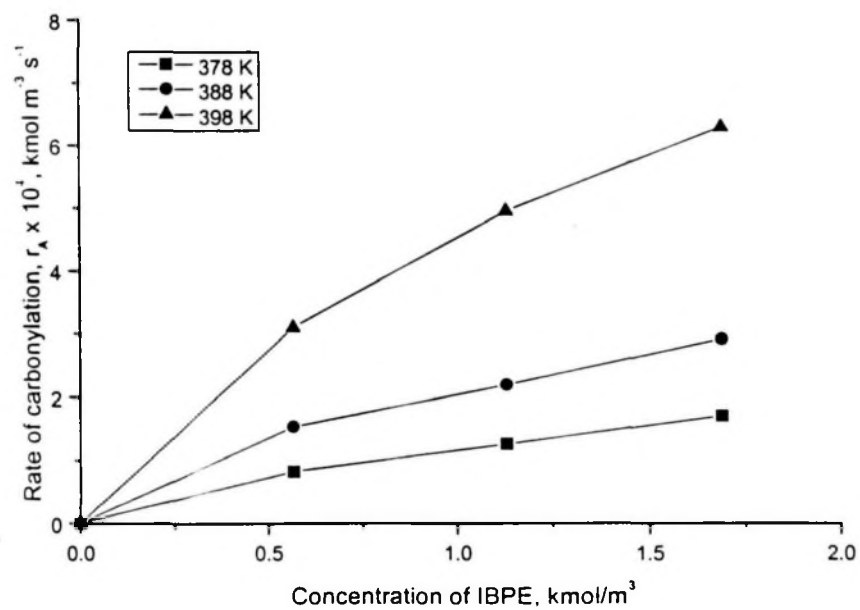


**Figure 5.6.** Effect of concentration of water on the rate of carbonylation of IBPE

*Reaction conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $PdCl_2(PPh_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $PPh_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



**Figure 5.7.** Effect of partial pressure of CO on the rate of carbonylation of IBPE  
*Reaction conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$

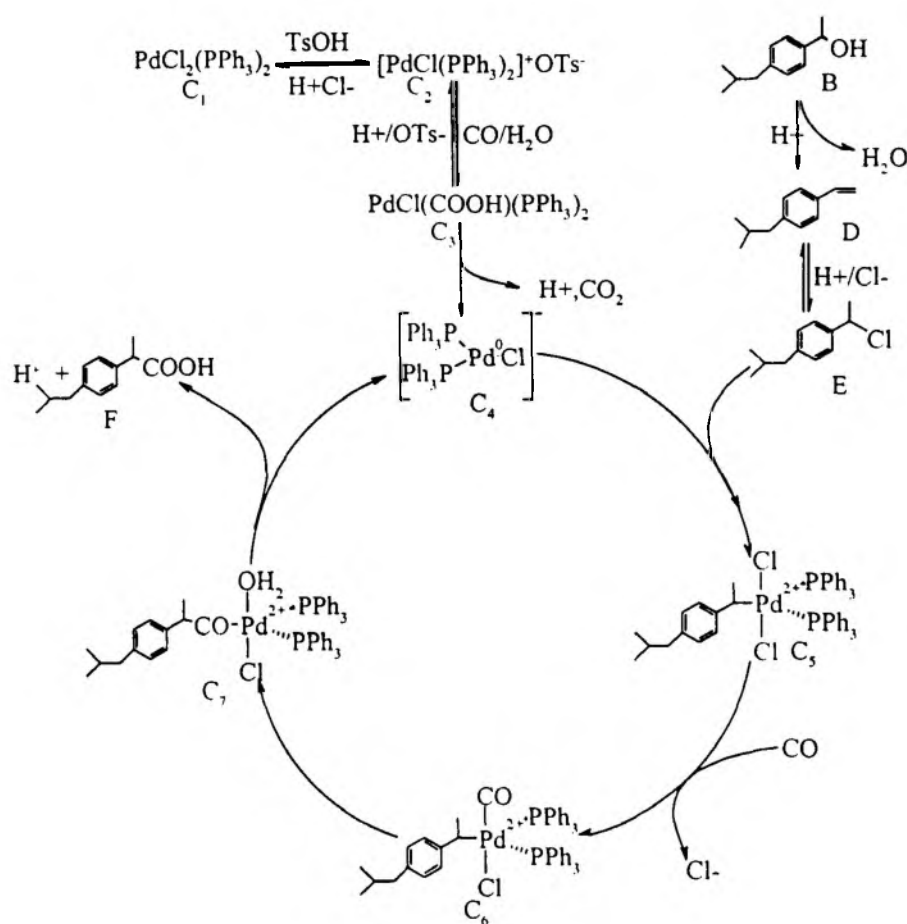


**Figure 5.8.** Effect of concentration of IBPE on the rate of carbonylation of IBPE  
*Reaction conditions:* TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$

The average rate of carbonylation was also found to increase with increase in the concentration of IBPE with an order of 0.7 (Figure 5.7) and partial pressure of CO with an order of 0.8 (Figure 5.8).

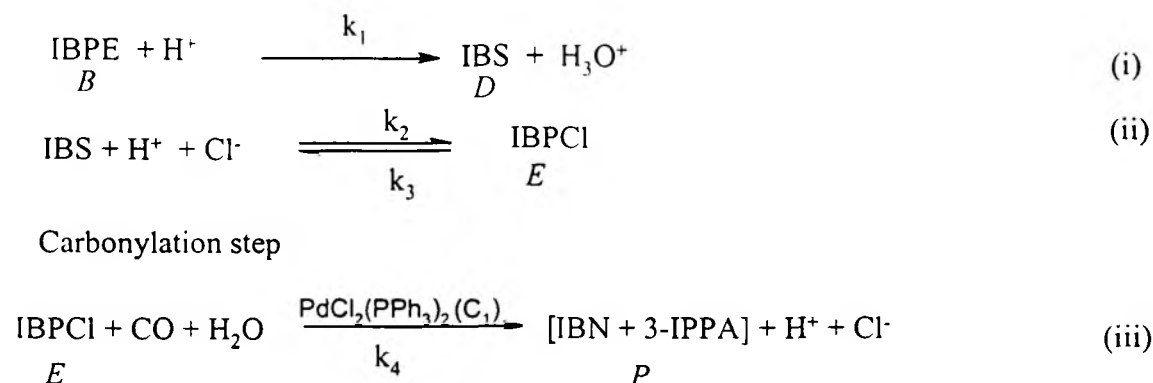
### 5.3.3. Kinetic modeling

As discussed in Chapter 4, carbonylation of IBPE involves three important steps (Scheme 5.2), viz., (i) formation of the active substrate IBPCl (ii) activation of  $\text{PdCl}_2(\text{PPh}_3)_2$  to the active Pd(0) species and (iii) catalytic carbonylation of IBPCl (the main catalytic cycle).



**Scheme 5.2** Proposed mechanistic pathway for carbonylation of IBPE

Due to the involvement of such complex multi-step reactions, in this case, the initial rate data were not very useful for interpretation of kinetics and the rate model developed should predict the integral concentration-time profiles under different sets of conditions. For this purpose, a simplified reaction scheme as shown in Scheme 5.3 was considered.



**Scheme 5.3.** Simplified reaction scheme

For the carbonylation step (overall reaction iii) an empirical rate equation based on observed trends of average rate of carbonylation as given below was considered.

$$r_A = \frac{k_4[E_I][H_2O]A^*C_1^m}{1 + K[E_I]} \quad (5.1)$$

For other steps [i.e reactions (i) and (ii)] the following rate equations were considered.

$$r_i = k_1[B_I][H^+] \quad (5.2)$$

$$r_{ii} = k_2[D_I][H^+][Cl^-] \quad (5.3)$$

$$r_{-ii} = k_3[E_I][H^+] \quad (5.4)$$

The mass balance for reactants and products ion a semi-batch reactor under kinetic regime and isothermal conditions can be represented by the following set of equations.

$$-\frac{dB_I}{dt} = r_i = k_1[B_I][H^+] \quad (5.5)$$

$$\frac{dD_I}{dt} = r_i - r_{ii} + r_{-ii} = k_1[B_I][H^+] - k_2[D_I][H^+][Cl^-] + k_3[E_I][H^+] \quad (5.6)$$

$$\frac{dE_I}{dt} = r_{ii} - r_{-ii} - r_A = k_2[D_I][H^+][Cl^-] - k_3[E_I][H^+] - \frac{k_4[E_I][H_2O]A^*C^m}{1 + K[E_I]} \quad (5.7)$$

$$\frac{dP_I}{dt} = r_A = \frac{k_4[E_I][H_2O]A^*C^m}{1 + K[E_I]} \quad (5.8)$$

With initial conditions

$$\text{At, } t = 0, B = B_0, \text{ and } D_I = E_I = P_I = 0 \quad (5.9)$$

Where,  $r_i$ ,  $r_{ii}$  and  $r_A$  represent reaction rates of steps i, ii and iii respectively,  $r_{-ii}$  is the rate of the reverse reaction in step ii and  $k_1$ ,  $k_2$ ,  $k_3$  and  $k_4$  represent the respective rate constants as shown in Scheme 5.3.  $K$  is a constant,  $m$  is the reaction order with respect to catalyst,  $A^*$ , saturation solubility of CO,  $B_I$ ,  $D_I$ ,  $E_I$  and  $P_I$ , the concentrations of IBPE, IBS, IBPCl and total amount of carbonylated products (IBN+3-IPPA) respectively and  $C_I$  the concentration of catalyst charged.

The differential equations Eq. 5.5 to 5.9 represents variation of concentrations of IBPE, IBS, IBPCl and the total carbonylated product (IBN+3-IPPA) as a function of time. For a given set of initial conditions (Eq. 5.9) and guess values of rate parameters the above set of equations (Eq. 5.5 to 5.8) can be solved to predict the concentration–time behaviour for the carbonylation of IBPE. The guess values were calculated from the approximate values of rates of formation of IBS, IBPCl and total carbonylation products, which were determined from the data in certain region of concentration–time profiles. In order to optimize the rate parameters, a computer program based on Marquart's method<sup>6</sup> (optimization) combined with Runge-Kutta method (for solving differential equations) method was used. The concentration-time profiles were simulated at various conditions

and compared with experimental data. In the optimisation procedure, a parameter  $\phi_{\min}$  defined as follows was minimized.

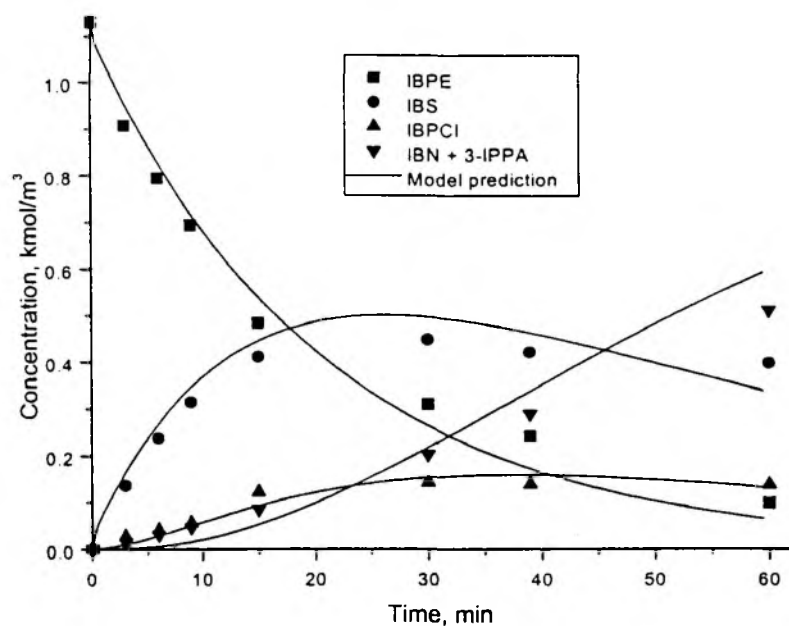
$$\phi_{\min} = \sum_{i=1}^4 \sum_{j=1}^n (Y_{i_{\text{exp}}} - Y_{i_{\text{mod}}})^2 \quad (5.10)$$

where,  $Y_{i_{\text{exp}}}$  is the measured concentration of component  $i$ ,  $Y_{i_{\text{mod}}}$  is the calculated concentration of component  $i$  and  $n$  is the number of data points considered.

Following the above procedure, optimum values of rate parameters were determined and the data are presented in Table 5.3. The  $\phi_{\min}$  values were in a range of  $7 \times 10^{-4}$  to  $8 \times 10^{-5}$ . A comparison of experimental data with model predictions is shown in Figures 5.9 to 5.22 for a few cases, though the predictions agreed over the entire range (Table 5.1) investigated. The experimental and the predicted concentration-time data were found to agree within 5-10% error in exception to few points.

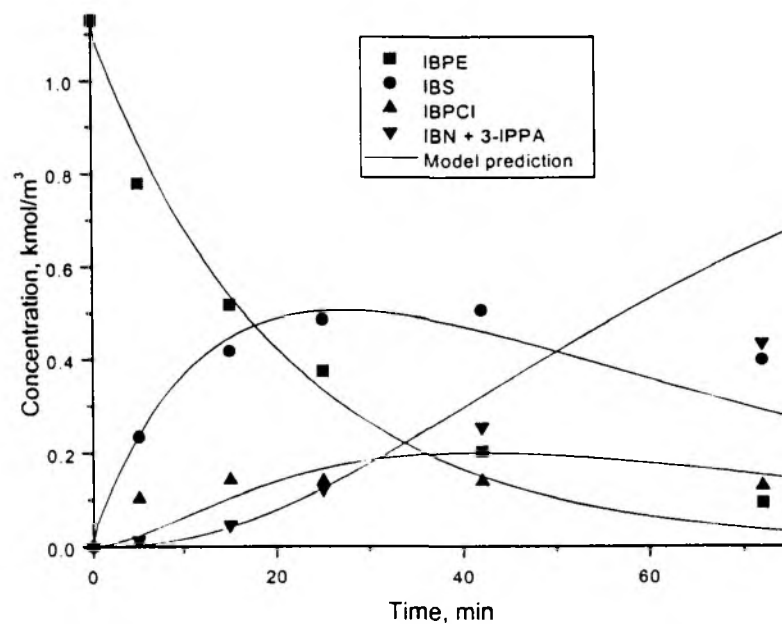
**Table 5.3** Rate parameters evaluated

Temperature K	$k_1 \times 100$ $\text{m}^3/\text{kmols}^{-1}$	$k_2 \times 100$ $(\text{m}^3/\text{kmol})^2\text{s}^{-1}$	$k_3 \times 100$ $\text{m}^3/\text{kmols}^{-1}$	$k_4 \times 100$ $(\text{m}^3/\text{kmol})^{2.43}\text{s}^{-1}$	K $\text{m}^3/\text{kmol}$
378	0.3536	1.2457	0.1927	2.3506	0.5104
388	0.7070	1.3085	0.3816	6.2992	0.5104
398	0.9896	2.7658	0.6840	9.7246	0.5104



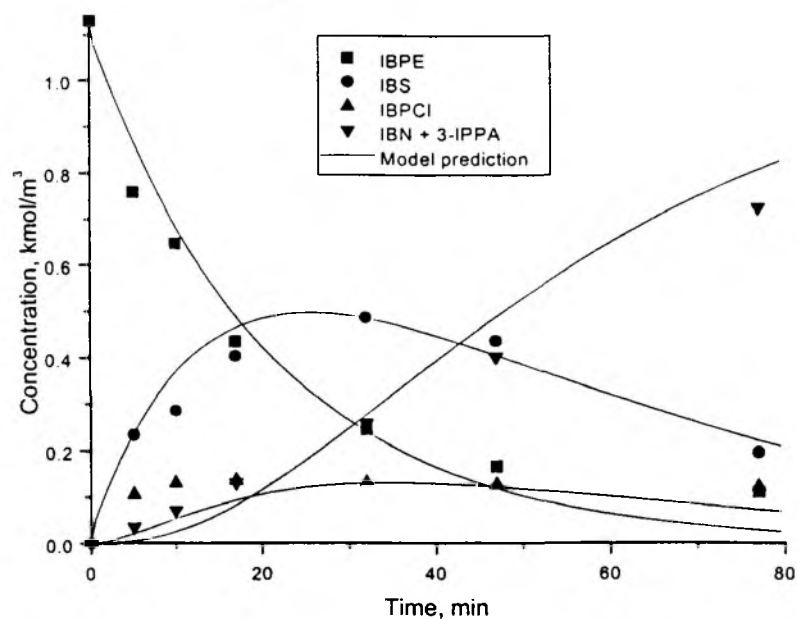
**Figure 5.9.** Standard reaction at 378 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



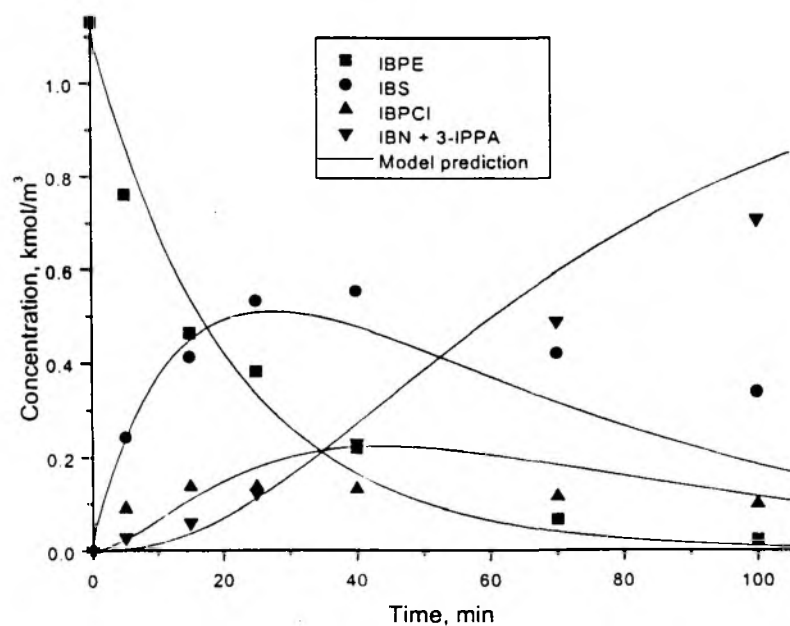
**Figure 5.10.** Effect of concentration of catalyst at 378 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $0.5605 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



**Figure 5.11.** Effect of concentration of catalyst at 378 K

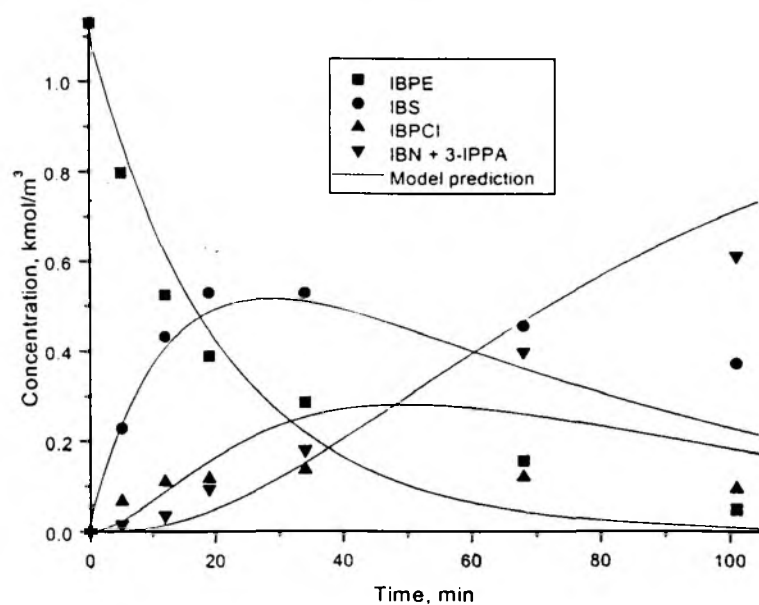
*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $4.484 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



**Figure 5.12.** Effect of partial pressure of CO at 378 K

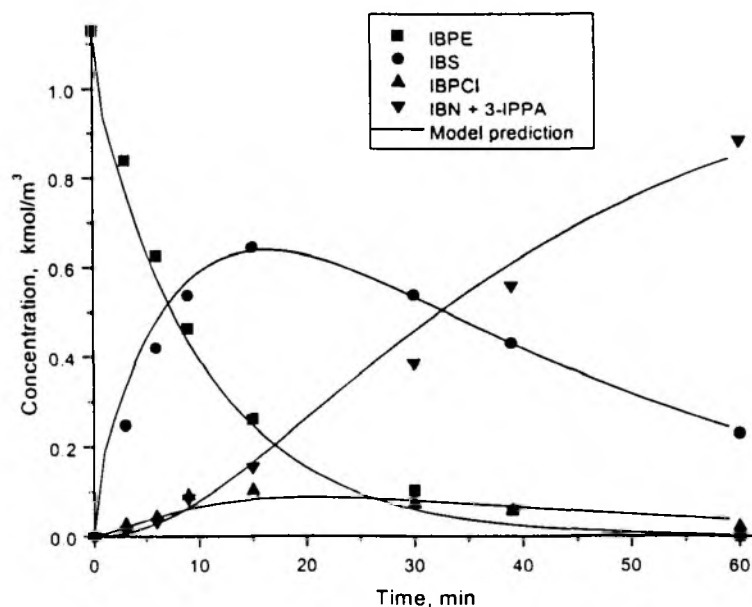
*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 3.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$





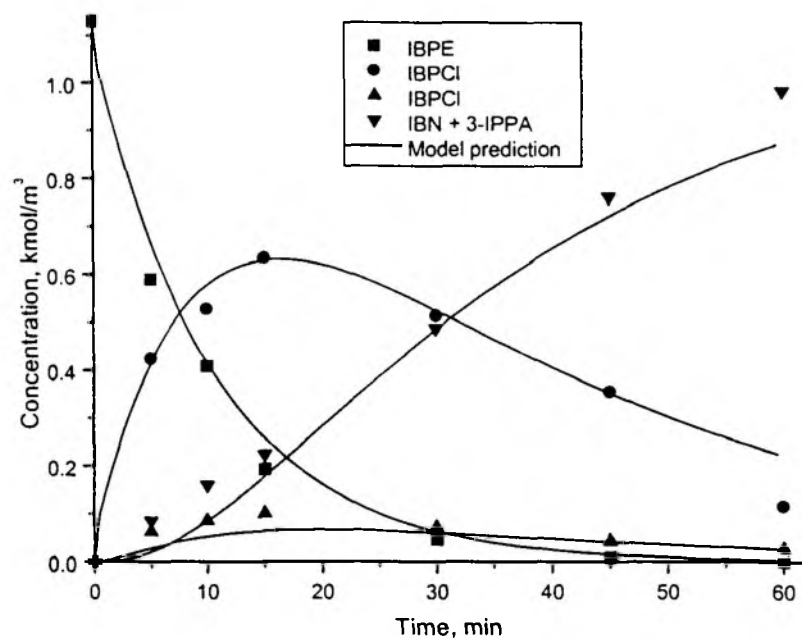
**Figure 5.13.** Effect of concentration of water at 378 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $1.11 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



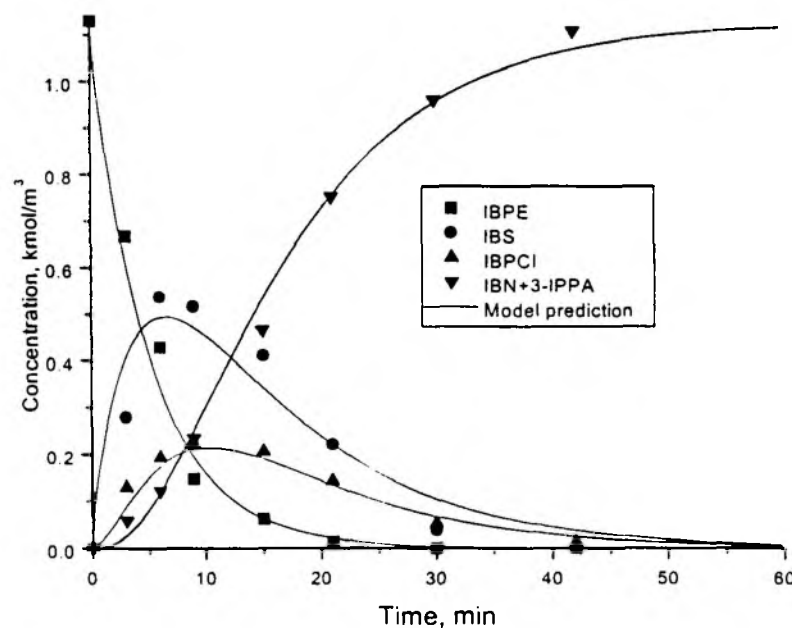
**Figure 5.14.** Standard reaction at 388 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



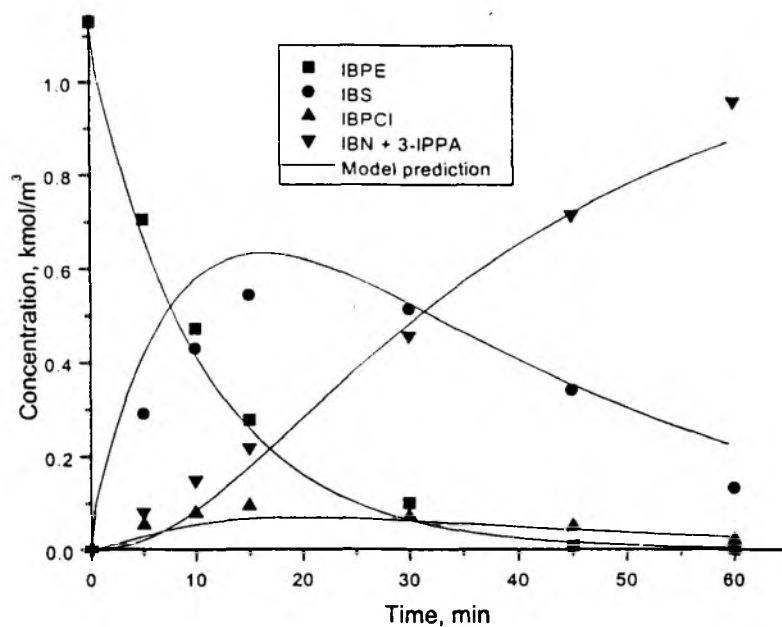
**Figure 5.15.** Effect of partial pressure of CO at 388 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 7.48 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



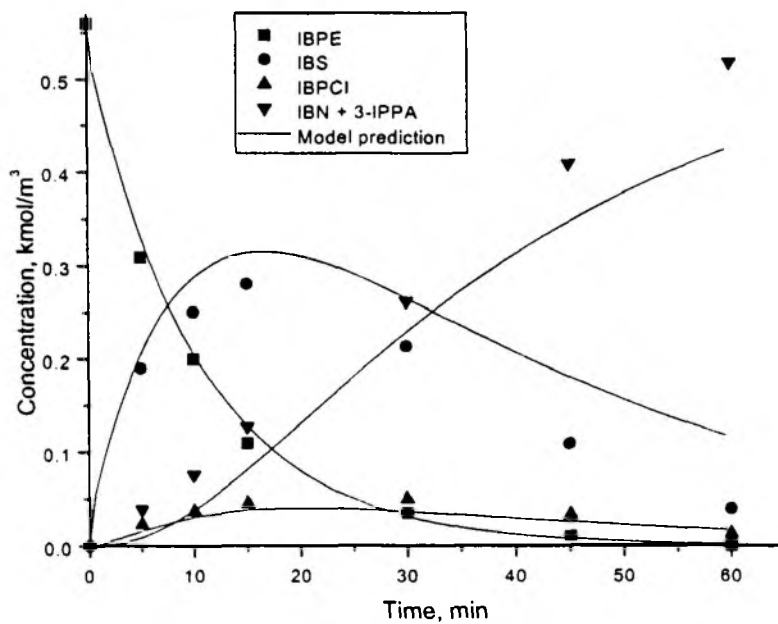
**Figure 5.16.** Effect of concentration of promoters at 388 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.242 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$ ; T, 388 K



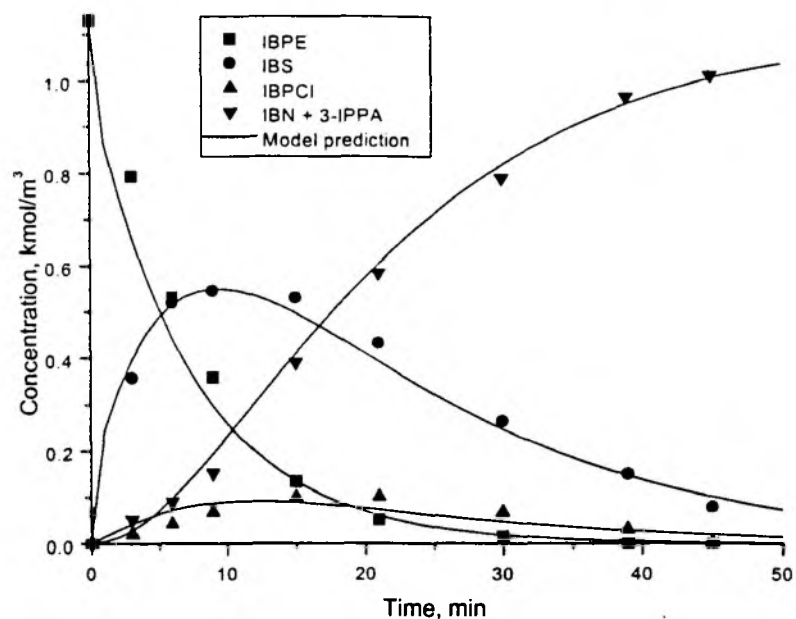
**Figure 5.17.** Effect of concentration of catalyst at 388 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $4.484 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-3} \text{ m}^3$



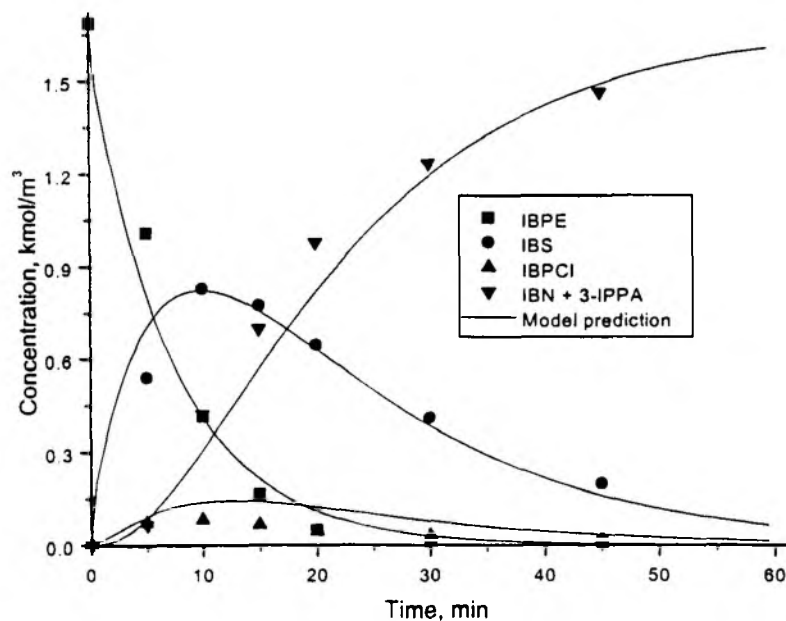
**Figure 5.18.** Effect of concentration of IBPE at 388 K

*Reaction Conditions:* IBPE,  $0.5615 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-3} \text{ m}^3$ ; T, 388 K



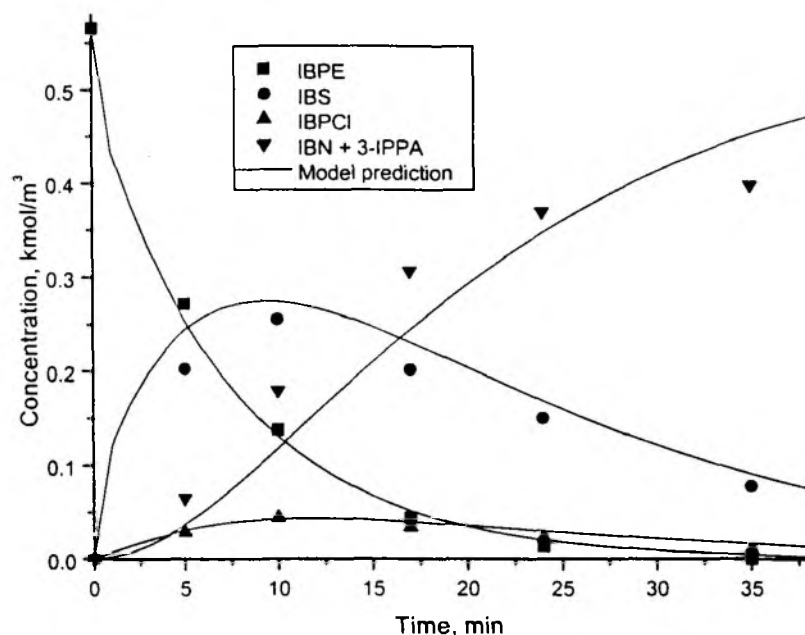
**Figure 5.19.** Standard reaction at 398 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $PdCl_2(PPh_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $PPh_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-3} \text{ m}^3$



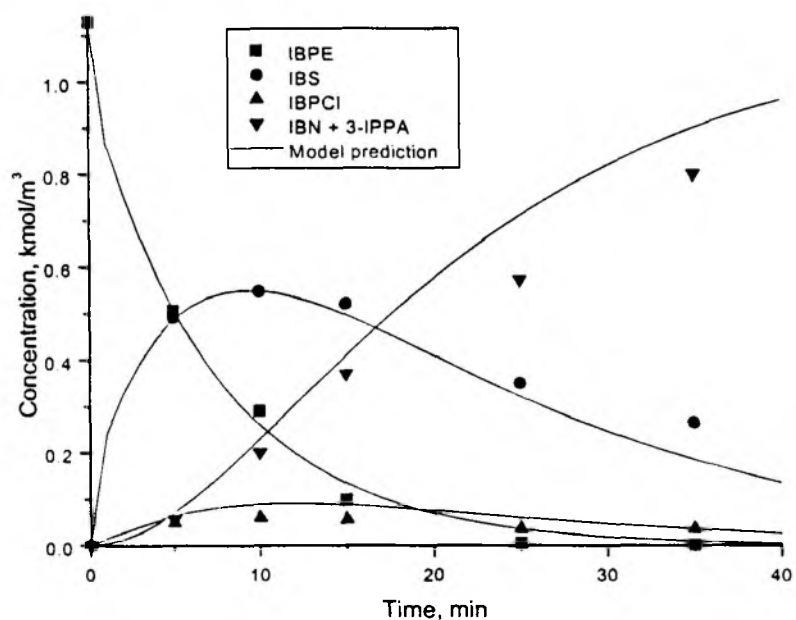
**Figure 5.20.** Effect of concentration of IBPE at 398 K

*Reaction Conditions:* IBPE,  $2.246 \text{ kmol/m}^3$ ; TsOH/LiCl (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $PdCl_2(PPh_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $PPh_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-3} \text{ m}^3$



**Figure 5.21.** Effect of concentration of IBPE at 398 K

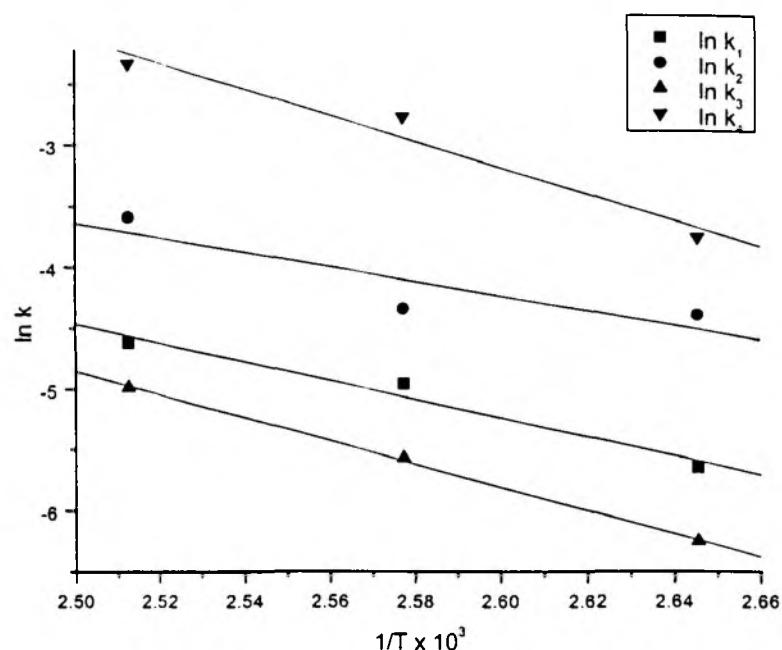
*Reaction Conditions:* IBPE,  $0.5615 \text{ kmol/m}^3$ ;  $\text{TsOH/LiCl}$  (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water =  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$



**Figure 5.22.** Effect of partial pressure of CO at 398 K

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ;  $\text{TsOH/LiCl}$  (1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{\text{CO}}$ , 3.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$

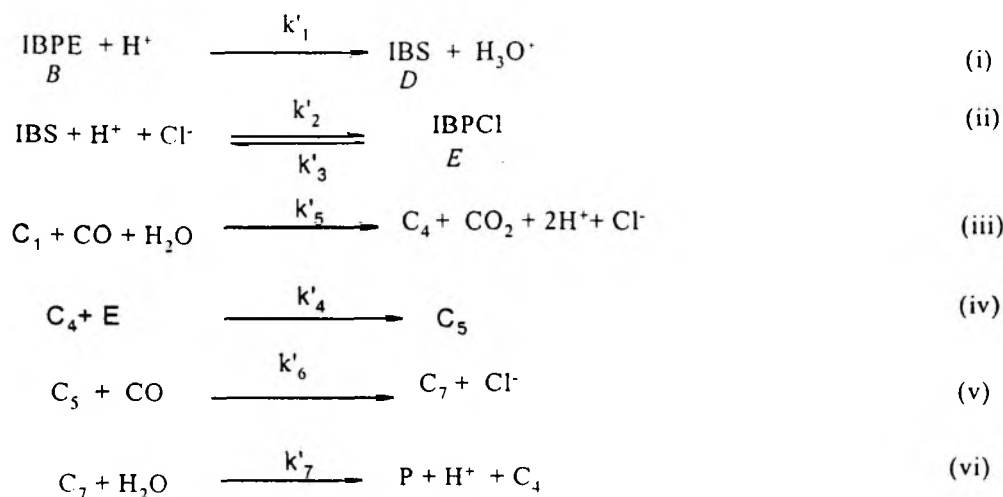
From the temperature dependence of rate constants,  $k_1$ ,  $k_2$ ,  $k_3$  and  $k_4$  (Figure 5.23), the respective activation energies were determined as 64.352, 49.494, 79.279 and 89.081 kJ/mol.



**Figure 5.23.** Temperature dependence of rate parameters

Even though the empirical rate model predicts the concentration-time data well, a more appropriate method would be that considering a molecular level approach. Since, the average rate of carbonylation shows first order dependence with concentration water and strong dependence on CO ( $0.8^{\text{th}}$ ) as well as IBPE ( $0.7^{\text{th}}$ ) concentration and  $0.43^{\text{th}}$  order with respect to catalyst concentration, deriving a rate model assuming any one of the steps as the rate determining step would not explain all the observed trends. In this case, a dynamic analysis incorporating the variation of concentrations of all the catalytic species as well as reaction intermediates with time would be most suitable as it would allow consideration of more than one step as rate limiting. An attempt has been made to interpret the concentration-time data for carbonylation of IBPE using a dynamic approach for one specific case as demonstrated below.

In order to derive the rate equations the following simplified reaction scheme (Scheme 5.4) was considered. This reaction scheme involves all the three principal steps of the reaction such as (a) formation of IBPCl (steps i and ii) (b) formation of the active catalytic species (step iii) and (c) the main catalytic cycle (steps iv to vi).



**Scheme 5.4:** Simplified scheme for the dynamic model

The rate of change of concentration of IBPE, IBS, IBPCl and the carbonylation products as well as the catalytic intermediates (as shown in Scheme 5.4) with time in a semi-batch reactor can be represented as follows.

$$-\frac{dB_I}{dt} = r_1 = k'_1[B_I][H^+] \quad (5.11)$$

$$\frac{dD_I}{dt} = r_1 - r_2 + r_3 = k'_1[B_I][H^+] - k'_2[D_I][H^+][Cl^-] + k'_3[E_I][H^+] \quad (5.12)$$

$$\frac{dE_I}{dt} = r_2 - r_3 - r_4 = k'_2[D_I][H^+][Cl^-] - k'_3[E_I][H^+] - k'_4[E_I][C_4] \quad (5.13)$$

$$-\frac{dC_1}{dt} = r_5 = k'_5[C_1][CO][H_2O] \quad (5.14)$$

$$\frac{dC_4}{dt} = r_5 - r_4 + r_7 = k'_5[C_1][CO][H_2O] - k'_4[E_I][C_4] + k'_7[C_7][H_2O] \quad (5.15)$$

$$\frac{dC_5}{dt} = r_4 - r_6 = k'_4[E_1][C_4] - k'_6[C_5][CO] \quad (5.16)$$

$$\frac{dC_7}{dt} = r_6 - r_7 = k'_6[C_5][CO] - k'_7 C_7[H_2O] \quad (5.17)$$

$$\frac{dP_1}{dt} = r_7 = k'_7 C_7[H_2O] \quad (5.18)$$

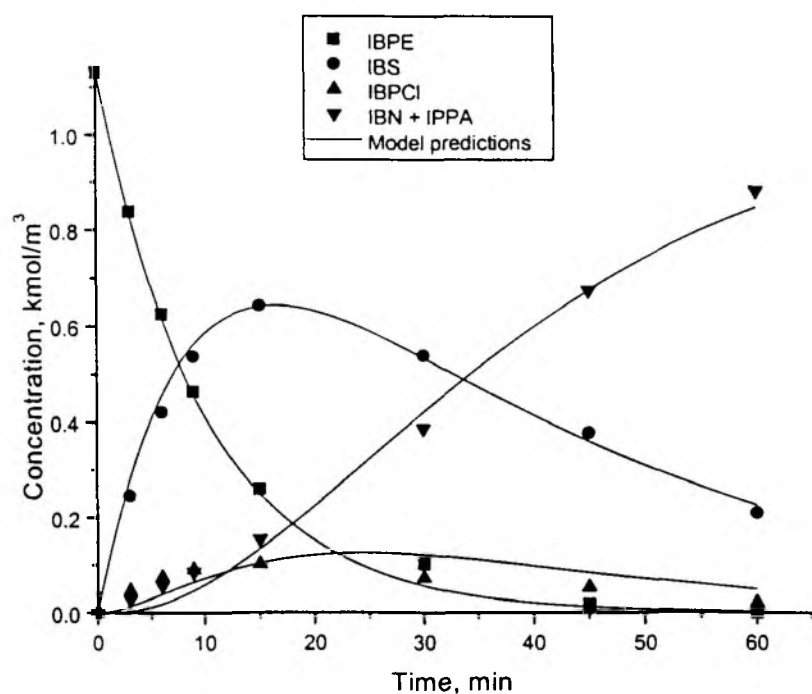
With initial conditions

$$\text{at, } t = 0, B_1 = B_0, D_1 = E_1 = P_1 = 0, C_1 = C_0 \text{ and } C_4 = C_5 = C_7 = 0 \quad (5.19)$$

Where,  $k'_1, k'_2, k'_3, k'_4, k'_5, k'_6$  and  $k'_7$  represent the rate constants for the steps i to vi as shown in Scheme 5.4,  $A^*$ , saturation solubility of CO,  $B_0$  the initial concentration of IBPE,  $B_1, D_1, E_1$  and  $P_1$ , the concentrations of IBPE, IBS, IBPCI and total amount of carbonylated products (IBN+3-IPPA) respectively  $C_0$ , the initial concentration of the catalyst and  $C_1, C_4, C_5$  and  $C_7$  are the concentration of various catalytic species as shown in scheme 5.2 and 5.4.

The differential equations Eq. 5.11 to 5.18 were solved by using the initial conditions (Eq. 5.19) and guess values for the rate parameters using a fourth order Runge-Kutta method. The determined values of rate constants for a set of conditions given in Figure 5.24 are:  $k'_1 = 0.00745, (\text{m}^3/\text{kmol})^2\text{s}^{-1}$ ;  $k'_2 = 0.0125, (\text{m}^3/\text{kmol})^2\text{s}^{-1}$ ;  $k'_3 = 0.0016, \text{m}^3/\text{kmol}\cdot\text{s}^{-1}$ ;  $k'_4 = 1.5939, \text{m}^3/\text{kmol}\cdot\text{s}^{-1}$ ;  $k'_5 = 0.150, (\text{m}^3/\text{kmol})^2\text{s}^{-1}$ ;  $k'_6 = 0.2139, \text{m}^3/\text{kmol}^2\text{s}^{-1}$  and  $k'_7 = 0.952, \text{m}^3/\text{kmol}\cdot\text{s}^{-1}$ . For evaluating the optimised values of the rate parameters considering all the available data, a more rigorous analysis is necessary which would require a much advanced optimisation subroutine. A comparison of the experimental and predicted concentration–time data for a standard experiment using the dynamic model is shown in Figure 5.24.

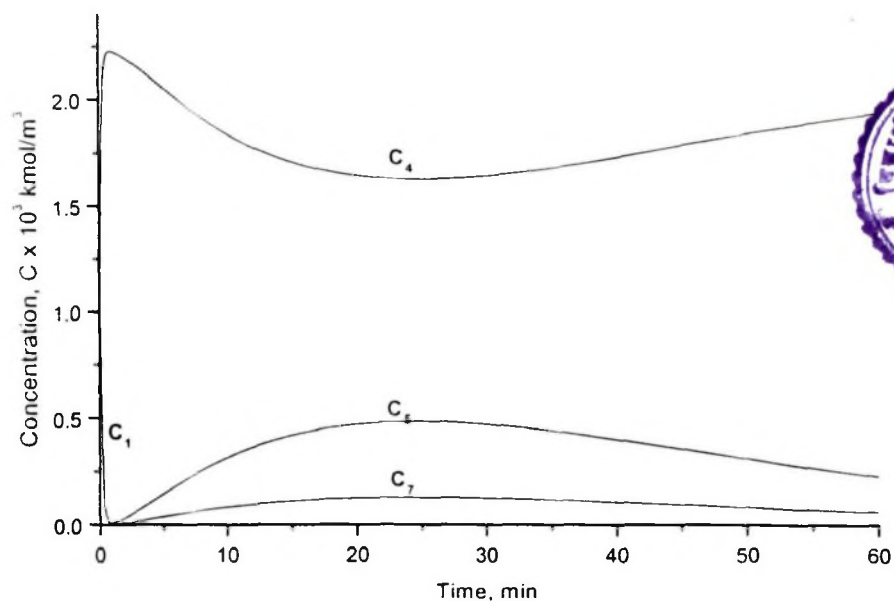




**Figure 5.24.** Comparison of experimental and predicted concentration-time profiles using the dynamic model

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl(1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $PdCl_2(PPh_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $PPh_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; MEK,  $1.95 \times 10^{-5} \text{ m}^3$ ;  $T$ , 388 K

In addition to the prediction of the concentrations of the reaction intermediates, the dynamic model can also be used for the prediction of the change of concentrations of different catalytic intermediates with time as shown in Figure 5.25. The predicted concentration-time profile of the catalytic species using the dynamic model (Figure 5.25) shows that the catalytic species  $C_4$ ,  $C_5$  and  $C_7$  are present in significant amounts at the present set of conditions, which also gives an indication of multiple steps as rate limiting. Considering the complexity involved in the dynamic model, a more rigorous analysis is required which needs a robust numerical/optimisation technique. However, this approach will be more useful in understanding the dynamic changes in the concentration of catalytic species and the kinetics and mechanism in a molecular level.



**Figure 5.25.** Dynamic change in catalytic species concentration with time

*Reaction Conditions:* IBPE,  $1.123 \text{ kmol/m}^3$ ; TsOH/LiCl(1:1),  $0.121 \text{ kmol/m}^3$ ;  $P_{CO}$ , 5.4 MPa;  $\text{PdCl}_2(\text{PPh}_3)_2$ ,  $1.121 \times 10^{-3} \text{ kmol/m}^3$ ;  $\text{PPh}_3$ ,  $2.242 \times 10^{-3} \text{ kmol/m}^3$ ; water,  $2.67 \text{ kmol/m}^3$ ; T, 388 K; MEK,  $1.95 \times 10^{-5} \text{ m}^3$

#### 5.4. Conclusions

Kinetics of Carbonylation of 1-(4-isobutylphenyl)ethanol was studied in a stirred semi-batch reactor using a homogeneous  $\text{PdCl}_2(\text{PPh}_3)_2/\text{TsOH}/\text{LiCl}$  catalyst system for a temperature range of 388–398 K. The carbonylation rate was found to be 0.43, 1, 0.8, 0.7, and 2<sup>nd</sup> order with respect to catalyst, water, CO pressure, concentration of IBPE and promoters (TsOH/LiCl) respectively. The rate data was found to be in kinetic regime and the gas-liquid mass transfer resistance was negligible. The unusual fractional order with respect to catalyst, in spite of kinetic control indicates that the entire precursor is not present in the active form. A reaction pathway, which consists of three different steps including the formation of active palladium(0) species, formation of active carbonylation substrate 1-(4-isobutylphenyl) ethyl chloride and the main carbonylation catalytic cycle has been proposed. A semi-batch reactor model was derived based on a simplified scheme by considering the formation of IBS and IBPCI and the catalytic carbonylation of IBPCI as

individual steps. An empirical rate equation based on the observed experimental trends was used for the carbonylation step. The rate model was found to fit the concentration-time profiles satisfactorily at all temperatures. The rate parameters were determined and the activation energies corresponding to each rate constants were calculated. An attempt has also been made to develop a dynamic model considering the change in concentration of all the catalytic species along with reactants and products.

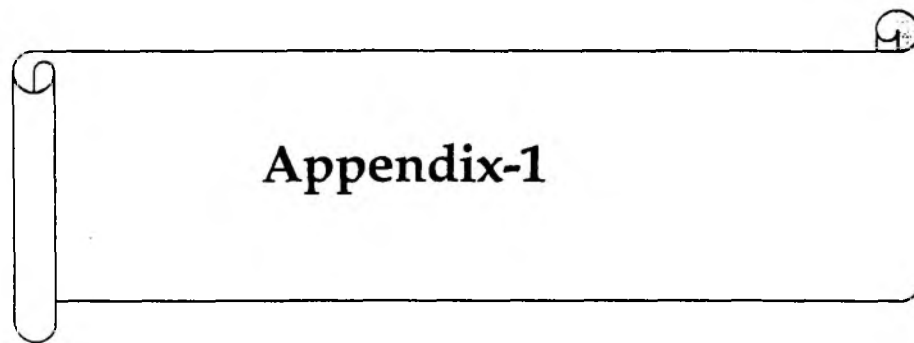
### Nomenclature

$\phi_{min}$	parameter defined in Eq. 5.10
$A^*$	saturation solubility of CO ( $\text{kmol/m}^3$ )
$B_1$	concentration of 1-(4-isobutylphenyl)ethanol ( $\text{kmol/m}^3$ )
$D_1$	concentration of 4-isobutyl styrene ( $\text{kmol/m}^3$ )
$E_1$	concentration of 1-(4-isobutylphenyl)ethyl chloride ( $\text{kmol/m}^3$ )
$B_0$	initial Concentration of 1-(4-isobutylphenyl)ethanol ( $\text{kmol/m}^3$ )
$P_1$	total concentration of carboxylic acid formed (IBN+3-IPPA)( $\text{kmol/m}^3$ )
$C_1$	concentration of catalyst ( $\text{kmol/m}^3$ )
$r_1, r_{ii}, r_{-ii}, r_A$	reaction rates for steps i, ii and iii in the Scheme 5.3
$k_1, k_2, k_3, k_4$	reaction rate constants for steps i, ii and iii in the Scheme 5.3 (units as given in Table 5.3)
$r_1, r_2, r_3, r_4, r_5, r_6, r_7, r_8$	reaction rates for steps i, to vi in the Scheme 5.4
$k'_1, k'_2, k'_3, k'_4,$ $k'_5, k'_6, k'_7$	reaction rates for steps i, to vi in the Scheme 5.4 (units as given in Section 5.3.3)
$K$	a constant
$m$	reaction order with respect to catalyst

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**Appendix-1**

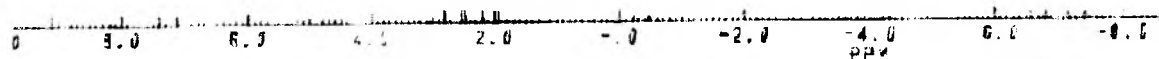


Figure A1.1.  $^1\text{H}$  NMR spectrum of a mixture of  $\text{Pd}(\text{PPh}_3)_4$  and 10 equivalents of TsOH

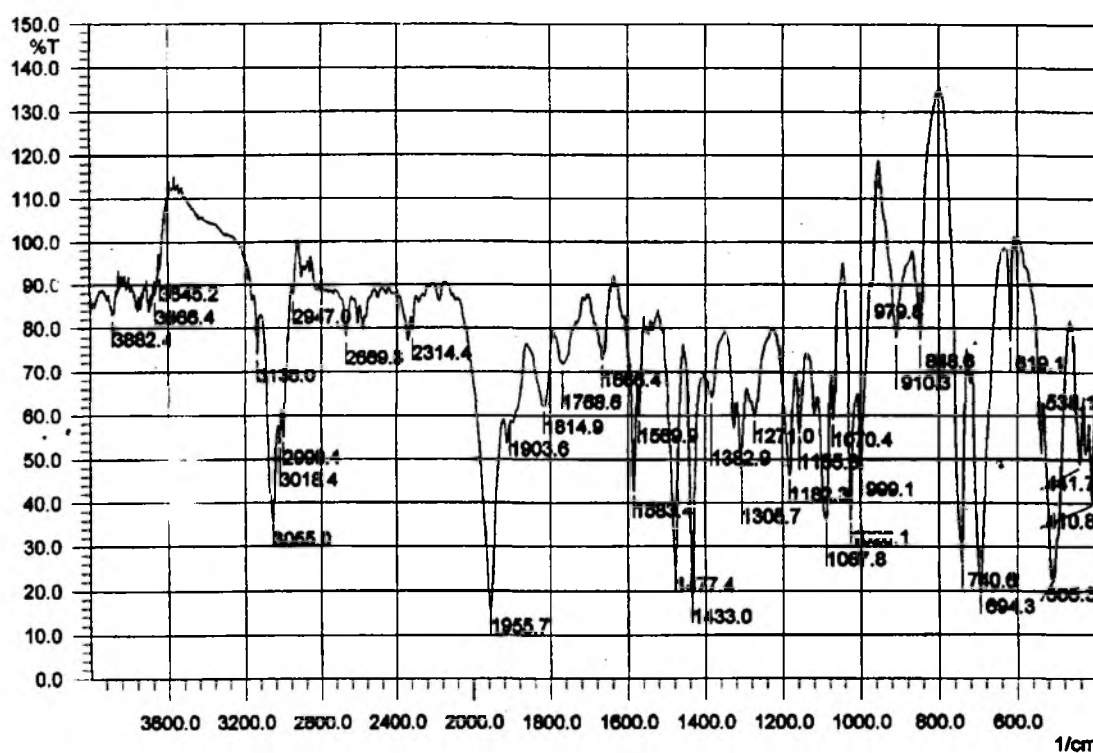


Figure A1.2. IR(DRS) spectrum of the brownish yellow palladium complex obtained from the hydrido carbonyl palladium complex VI.

Figure A1.3.  $^1\text{H}$  NMR spectrum of the yellowish brown complex obtained on decomposition of hydridocarbonyl palladium complex VI

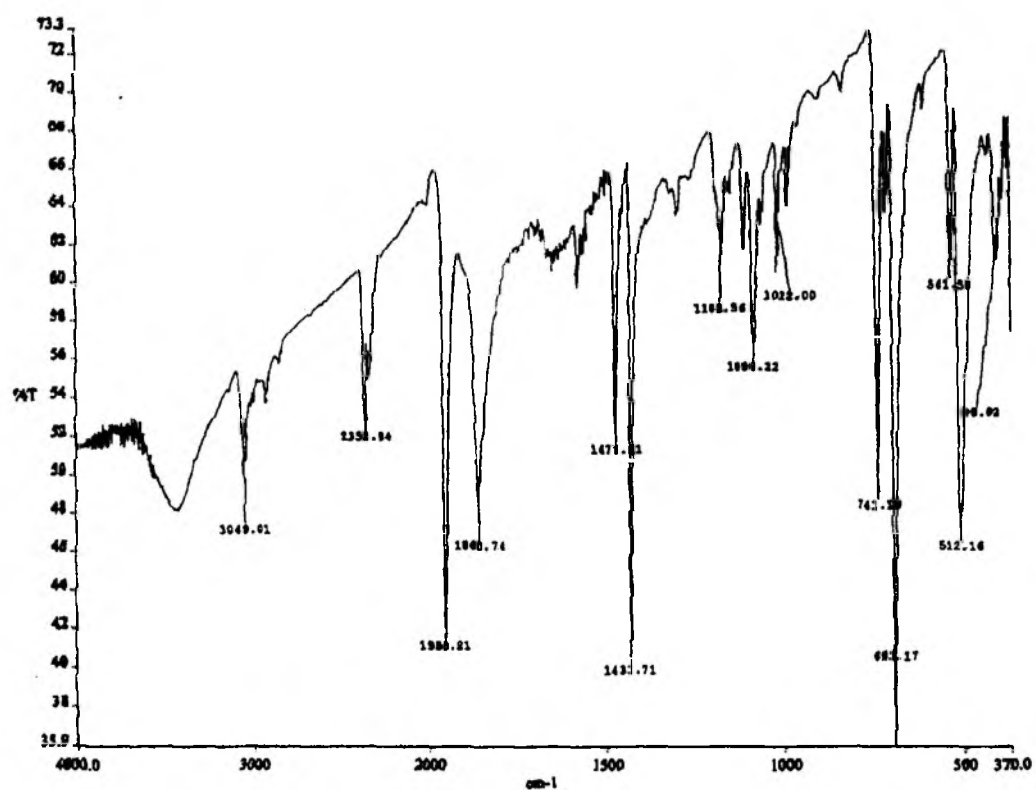
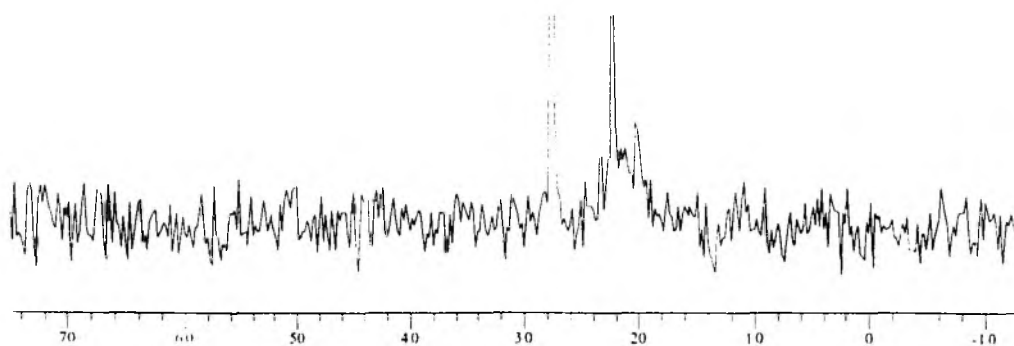
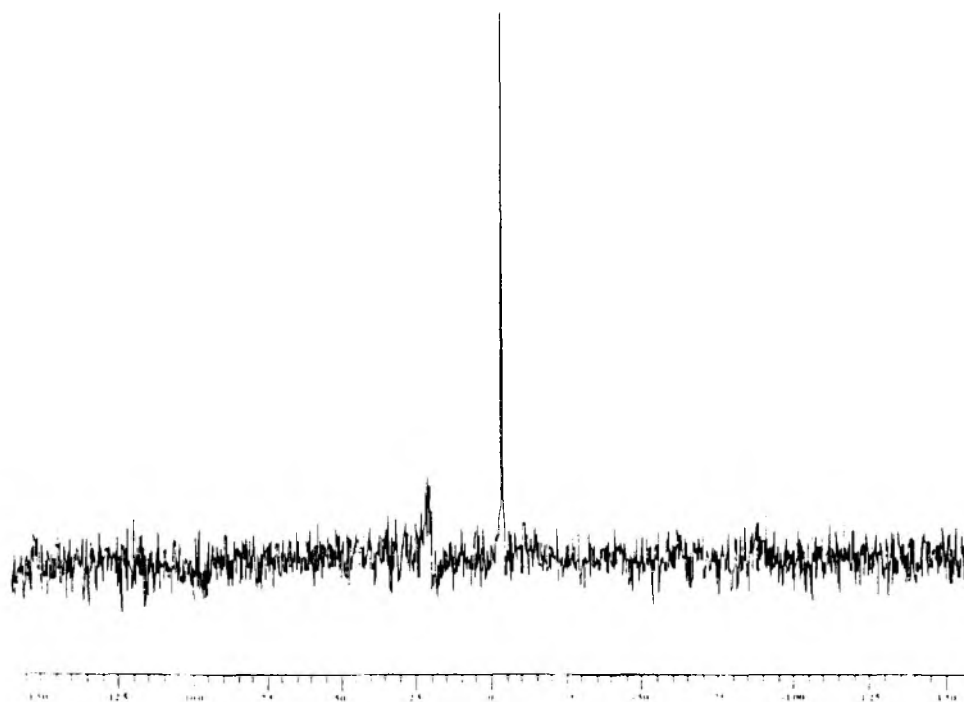


Figure A1.4. IR spectrum of the mixture of Pd-carbonyls obtained



**Figure A1.5.**  $^{31}\text{P}$  NMR spectrum of the isolated mixture of Pd-carbonyl complexes



**Figure A1.6.**  $^{31}\text{P}$  NMR spectrum of a solution of methanol, from which methoxy complexes were isolated



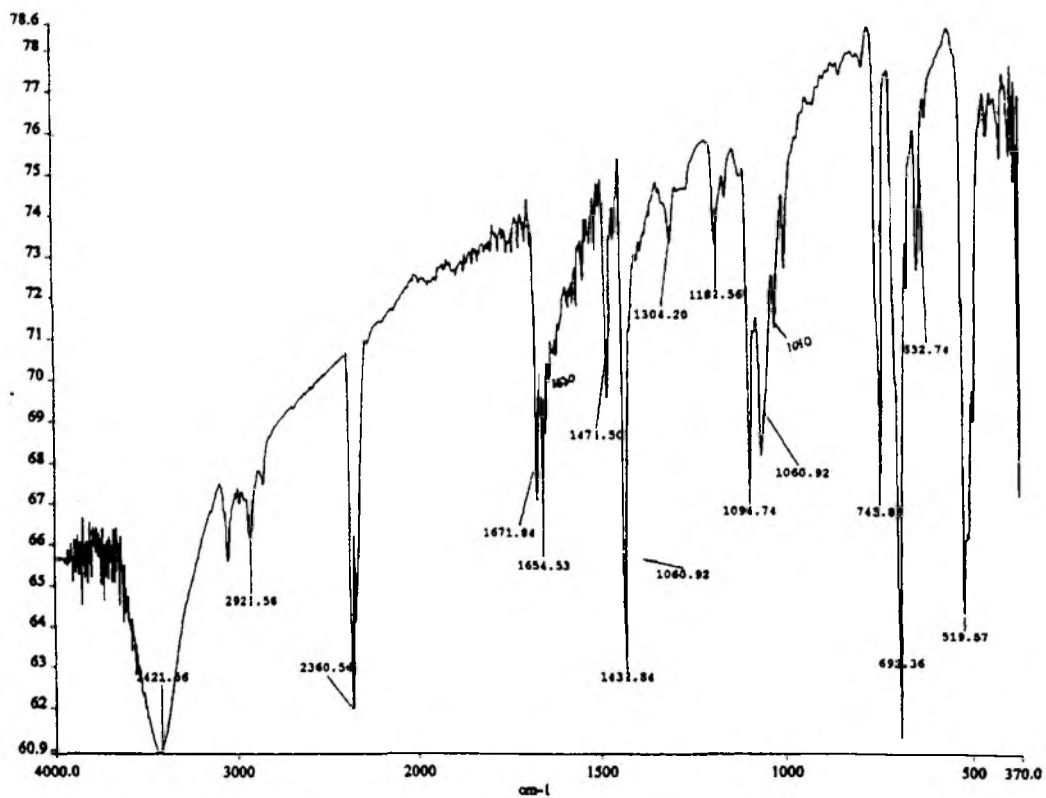


Figure A.7. IR spectrum of the isolated palladium methoxy complex

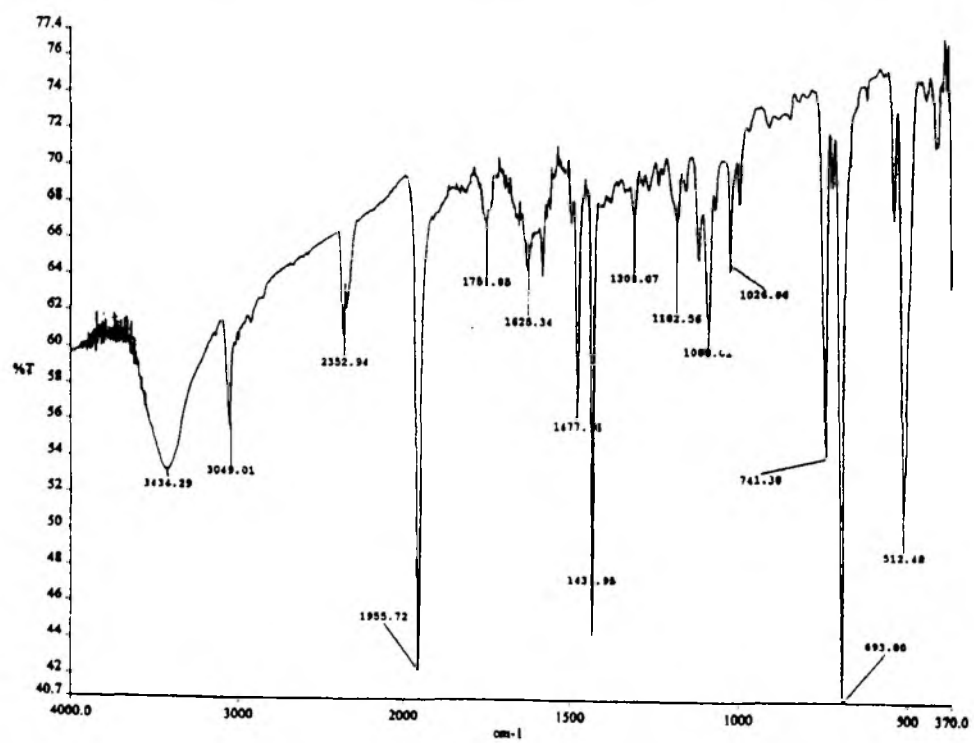


Figure A1.8. IR spectrum of the Yellow complex isolated when the reaction was carried out with 2 equivalents of TsOH

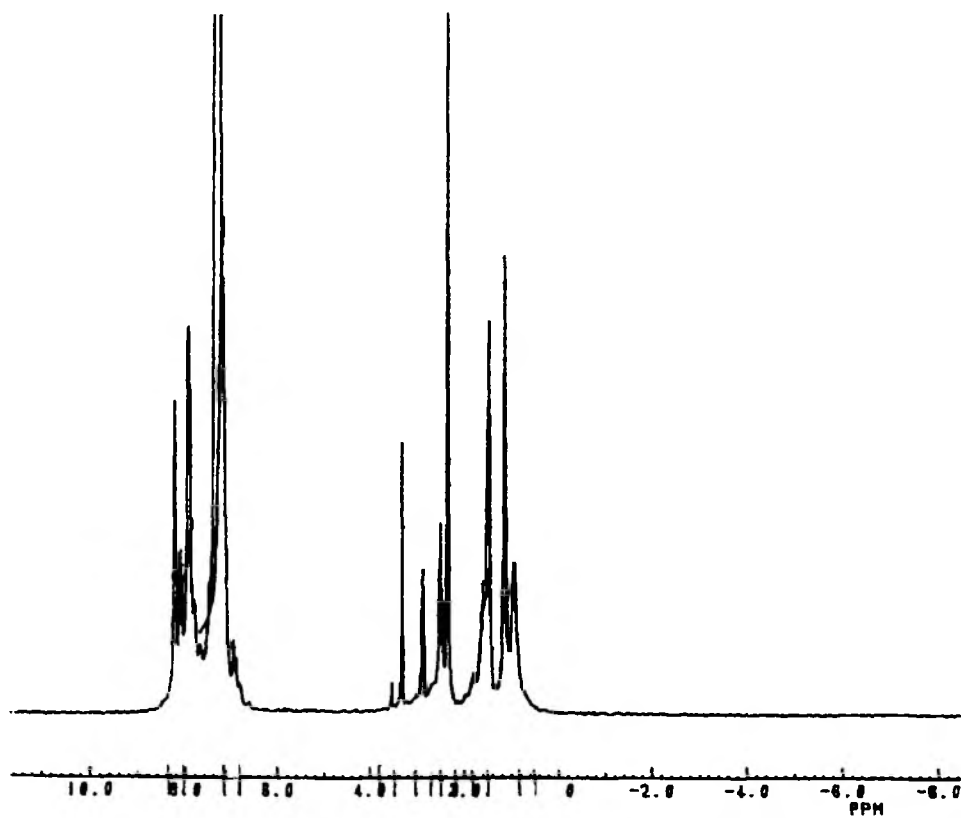


Figure A1.9. <sup>1</sup>H NMR spectrum of the isolated cationic Pd-acyl complex

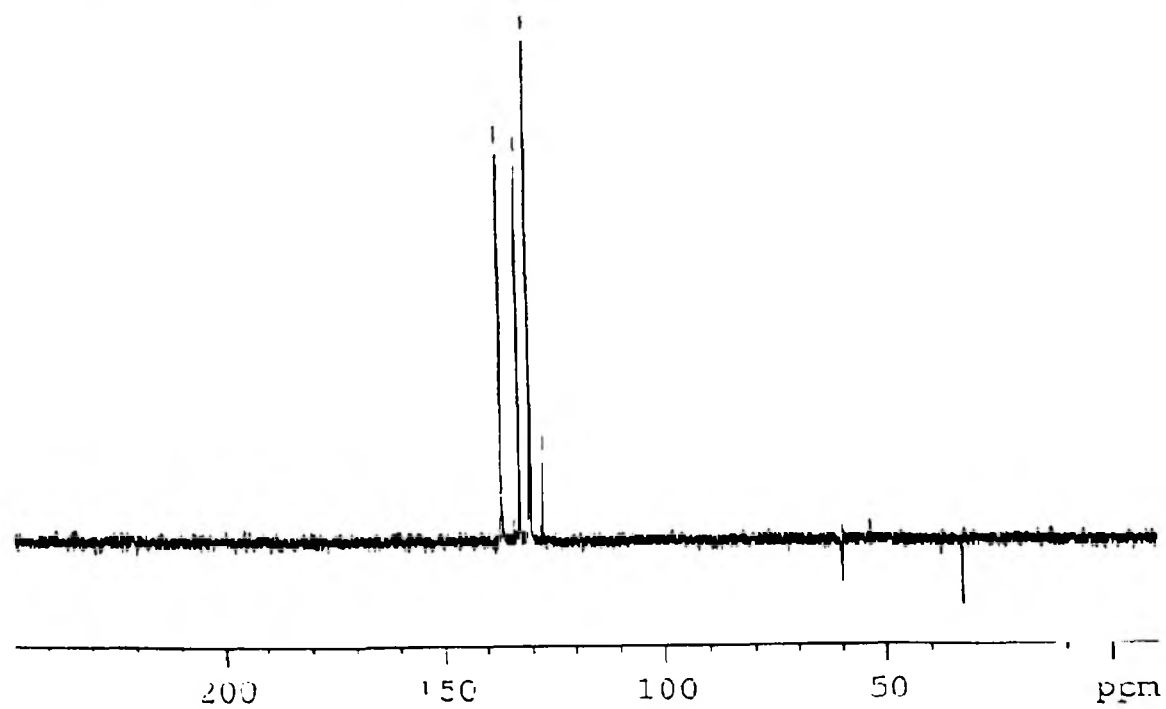


Figure A1.10. <sup>13</sup>C NMR spectrum (DEPT) of the acyl complex, XIII

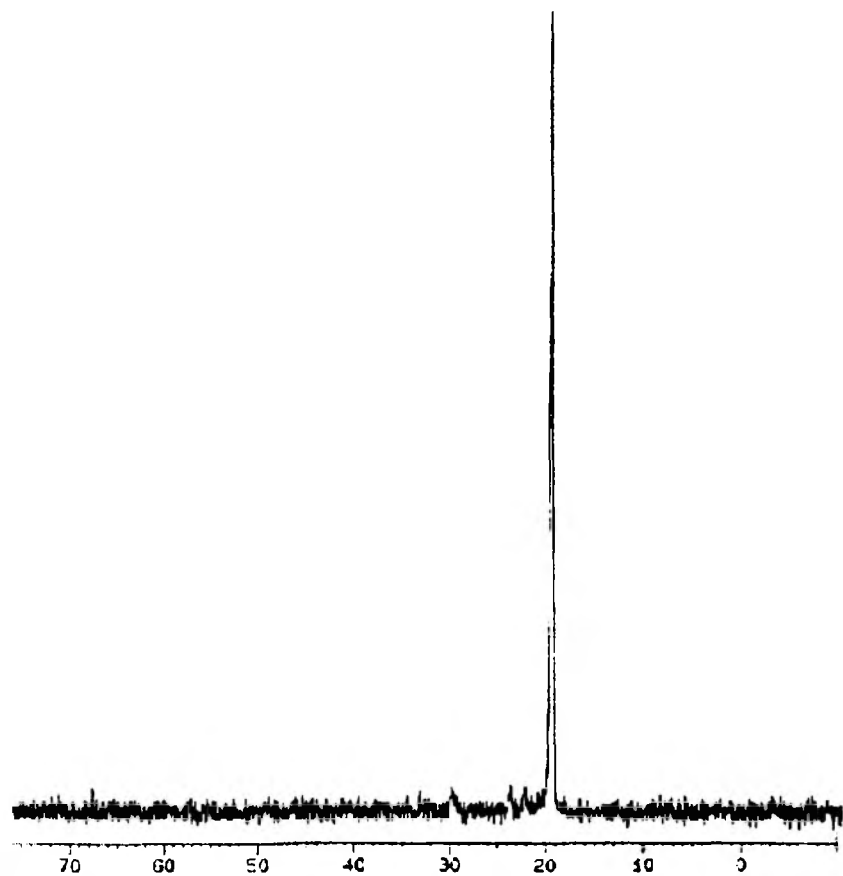
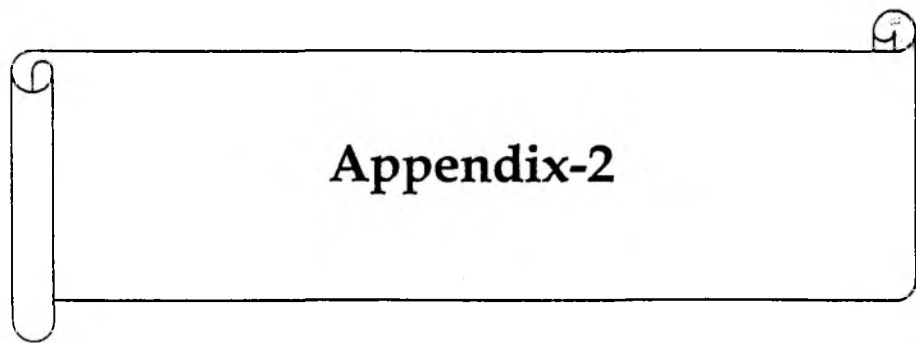
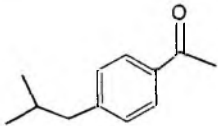
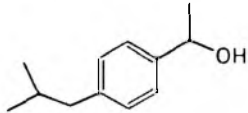
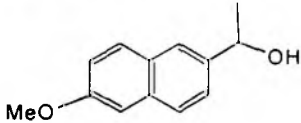
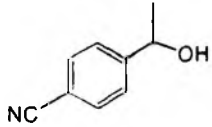
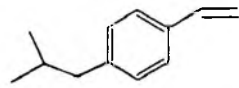
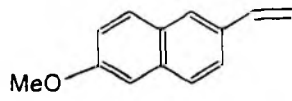
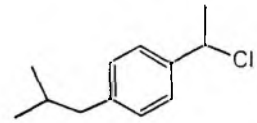
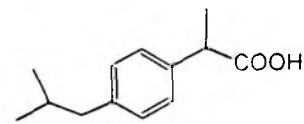
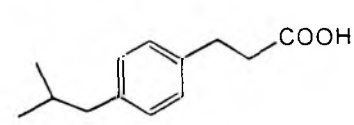
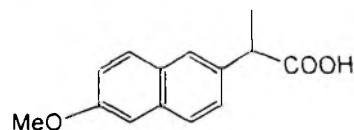


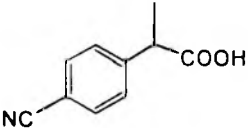
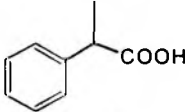
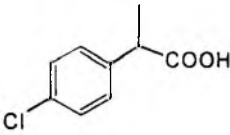
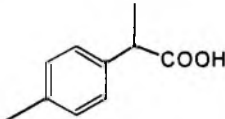
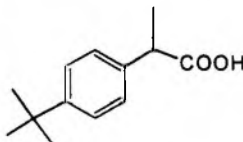
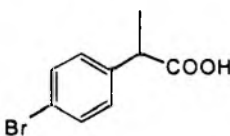
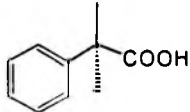
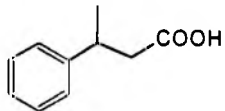
Figure A1.11.  $^{31}\text{P}$  NMR spectrum of the acyl complex XIII



**Appendix-2**

Spectral analysis of the compounds prepared and isolated in Chapter 4

No	Compound	Spectral data (NMR and IR)
1.		$^1\text{H NMR}$ ( $\text{CDCl}_3$ ), 7.86 (d, 2H), 7.22 (d, 2H), 2.53 (s, 3H), 1.88 (m, 1H), 0.89 (d, 6H)
2.		$^1\text{H NMR}$ ( $\text{CDCl}_3$ ), 7.25 (d, 2H), 7.13 (d, 2H), 4.867 (q, 1H), 2.46 (d, 2H), 1.84 (m, 1H), 1.48 (d, 3H), 0.91 (d, 6H)
3.		$^1\text{H NMR}$ ( $\text{CDCl}_3$ ), $\delta$ 7.67-7.05 (m, 6H), 5.045 (q, 1H), 3.932 (s, 1H), 1.598 (d, 3H)
4.		$^1\text{H NMR}$ ( $\text{CDCl}_3$ , $\delta$ ) 7.541 (d, 2H), 7.458 (d, 2H), 4.878 (q, 1H), 3.142 (bs, 1H), 1.441 (d, 3H)
5.		$^1\text{H NMR}$ ( $\text{CDCl}_3$ ), 7.28 (d, 2H), 7.14 (d, 2H), 6.63 (dd, 1H), 5.64 (d, 1H), 5.13 (d, 1H), 2.48 (d, 2H), 1.87 (m, 1H), , 0.93 (d, 6H)
6.		$^1\text{H NMR}$ ( $\text{CDCl}_3$ ), $\delta$ 7.67-7.05 (m, 6H), 6.65 (dd, 1H), 5.67 (d, 1H), 5.16 (d, 1H), 3.865(s, 3H),
7.		$^1\text{H NMR}$ ( $\text{CDCl}_3$ ), 7.28 (d, 2H), 7.14 (d, 2H), 4.88 (q, 1H), 2.48 (d, 2H), 1.87 (m, 1H), 1.51 (d, 3H), 0.93 (d, 6H)
8.		IR ( $\text{CHCl}_3$ ) 3400-2800 (bs), 1705 (s) $\text{cm}^{-1}$ ; $^1\text{H NMR}$ ( $\text{CDCl}_3$ ) $\delta$ 7.3 (d, 2H), 7.125 (d, 2H), 3.75 (q, 1H), 2.5 (d, 3H), 1.85 (m, 1H), 1.515 (d, 2H) 0.945 (d, 6H)
9.		IR ( $\text{CHCl}_3$ ) 3400-2800 (bs), 1705 (s) $\text{cm}^{-1}$ ; $^1\text{H NMR}$ ( $\text{CDCl}_3$ ) $\delta$ 7.3 (d, 2H), 7.125 (d, 2H), 2.905 (t, 2H), 2.646 (t, 2H), 1.85 (m, 1H), 1.515 (d, 2H) 0.945 (d, 6H)
10.		IR ( $\text{CHCl}_3$ ) 3500-3000 (bs), 1710 (s); $^1\text{H NMR}$ ( $\text{CDCl}_3$ ), $\delta$ 7.67-7.05 (m, 6H), 5.075 (q, 1H), 3.865(s, 3H), 1.575 (d, 3H)

11.   $^1\text{H NMR}$  ( $\text{CDCl}_3$ ,  $\delta$ ) 7.609 (d, 2H), 7.504 (d, 2H), 4.962 (q, 1H), 1.497 (d, 3H)
12.  IR (neat) 3500–2500 (bs), 1695 (s)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\delta$ ,  $\text{CDCl}_3$ ): 7.258 (m, 4H), 3.725 (q, 4H), 1.5 (d, 3H)
13.  IR (neat) 3200–2500 (bs), 1695 (bs)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  9.83 (bs, 1H), 7.285 (d, 2H), 7.231 (d, 2H), 3.699 (q, 1H), 1.48 (d, 3H)
14.  IR (neat) 3000–2600 (bs), 1700 (s)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  11.409 (bs, 1H), 7.321 (d, 2H), 7.234 (d, 2H), 3.8 (q, 1H), 2.425 (s, 3H), 1.598 (d, 3H)
15.  IR ( $\text{CHCl}_3$ ) 3100–2600 (bs), 1700(s)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  9.77 (bs, 1H), 7.353 (d, 2H), 7.254 (d, 2H), 3.716 (q, 1H), 1.501 (d, 3H), 1.308 (s, 9H)
16.  IR ( $\text{CHCl}_3$ ) 3300–2600 (bs), 1700(s)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  10.823 (bs, 1H) 7.445 (d, 2H), 7.187 (d, 2H), 3.689 (q, 1H), 1.486 (d, 3H)
17.  IR (neat) 3500–2600 (bs), 1698 (s)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  11.156 (bs, 1H), 7.604–7.278 (m, 5H), 1.706 (s, 6H)
18.  IR (neat) 3500–2600 (bs), 1700 (bs)  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ )  $\delta$  11.245 (bs, 1H), 7.428–7.253 (m, 5H), 3.508 (t, 1H), 2.159 (m, 2H), 0.952 (t, 3H)

### List of Publications based on the present work

1. **Seayad. A.** Kelkar. A. A, and Chaudhari. R. V. Carbonylation of p-Isobutyl Phenylethanol to Ibuprofen Using Palladium Catalyst: Activity and Selectivity Studies, *Studies in Surface Science and Catalysis*, 113 (1998) 883.
2. **Seayad. A.** Kelkar. A. A, Toniolo. L. and Chaudhari. R.V, Kinetics of Carboxylation of Styrene using a Homogenous Pd Complex Catalyst, *Ind. Eng. Chem. Res.*, 37 (1998) 2180.
3. **Seayad. A.,** Kelkar, A. A., Toniolo L. and Chaudhari. R.V., Hydroesterification of Styrene using an *in situ* formed Pd(OTs)<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> Complex Catalyst (Accepted for publication in *J. Mol. Catal. A: Chem.* 1999)
4. **Seayad A.,** Jayasree S., and Chaudhari R. V., An Efficient Catalytic System for the Synthesis of 2-Aryl Propionic Acids by Carbonylation, *Catal. Lett.*, 61 (1999) 99.
5. **Seayad A.,** Jayasree S. and Chaudhari R.V., Carbonylation of vinyl aromatics: Convenient regioselective synthesis of 2-arylpropanoic acids, *Organic Letters*, 1 (1999) 459.
6. **Seayad A.,** Jayasree S., Damodaran K., Chaudhari R.V., and Toniolo L., On the mechanism of hydroesterification of styrene using in situ formed cationic palladium complex. (Accepted for publication in *J. Organomet. Chem.*, 2000)