STUDIES IN HYDROCARBOXYLATION OF STYRENE AND DERIVATIVES USING PALLADIUM COMPLEX CATALYSTS

BY

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ABSTRACT

Carbonylation of aryl olefins and alcohols using homogeneous Pd catalysts has gained considerable interest due to their important applications in the synthesis the non-steroidal anti-inflammatory drugs consisting of 2-arylpropionic acids (e.g. Ibuprofen®, Naproxen®). In this work, different homogeneous palladium catalysts were compared for their performances in the hydrocarboxylation of styrene to identify the best performing catalyst system using Pd(pyca)(PPh_3)(OTs) as a precursor, which shows above 99% regio-selectivity to 2-phenylpropionic acid as well as high activity. Therefore, this work mainly investigated the kinetics of hydrocarboxylation of styrene using Pd(pyca)(PPh_3)(OTs)/PPh_3/TsOH/LiCl catalyst system. Particularly, parametric study was carried out to understand the effects of different reaction parameters on the rate of hydrocarboxylation in a batch reactor as well as the concentration-time profiles. For interpretation of the reaction kinetics, a molecular level description of the reaction mechanism (catalytic cycle) was proposed to explain the unique observation of induction period at lower pressures of CO. The experimental concentration-time data for styrene, water and acid products were used to simulate the intrinsic rate parameters using an optimization program. The proposed reaction mechanism based on a Pd-hydride complex as an intermediate active species well explains the experimental data at different temperatures. The approach of micro-kinetic modeling does not require assumption of a rate determining step and provides good description of the complex trends with respect to reaction and catalyst parameters over a wide range of conditions. The approach is also useful to discriminate different reaction mechanisms and obtain intrinsic kinetic parameters for design and scale-up of reactors.

DEDICATED TO

My Family

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CHAPTER 1

PROJECT BACKGROUND AND LITERATURE REVIEW

1-1 Introduction

Catalysis is the process in which the rate of a chemical reaction is either increased or decreased by means of a chemical substance called “catalyst”. Research in catalysis is a major field in applied science involving various multidisciplinary areas of chemistry, including organometallic chemistry, material science, spectroscopic and surface characterization and chemical engineering. Today, catalysis plays an important role in the growth of modern chemical industry, since it provides atom-effective and environmentally benign routes for the manufacture of various commodity chemicals, pharmaceuticals, specialties, etc. Developing catalytic reactions to replace stoichiometric processes is one of the important principles of green chemistry, facilitating waste minimization, maximizing atom economy and minimizing energy consumption. Indeed, catalysis has revolutionized chemical industry over the past hundred years by fundamentally transforming the processes for manufacture of chemicals. Soluble metal salts were used commercially as catalysts for reactions of acetylene as early as 1910, which led to the well−known Reppe Chemistry.[1] Rapid development of catalysis was further stimulated by the impetus for new process technologies for the production of many new materials between 1940 and 1960. During this period, the Nobel prizes winners, Fischer, Wilkinson, Ziegler, and Natta made their outstanding contributions by providing the basis for homogeneous catalysis based on their fundamental research. Today, dozens of major industrial catalyzed processes are operating in practice based on their fundamental discoveries.[1] With increasingly stringent environmental regulations today, development of new catalytic processes has gained more and more attention for achieving sustainable development of modern chemical industries.

Catalytic actions are generally classified into two types defined based on the physical nature of catalyst used: homogeneous and heterogeneous. Homogeneous catalysts essentially represent those catalysts which are soluble in the reaction medium. In contrast, in heterogeneous catalysis, the catalyst is present as a separate phase either in a solid state or as an immiscible liquid phase. The two families of catalysts have their unique features, advantages and disadvantages. Homogeneous catalysts in general have high activity and selectivity under relatively mild reaction conditions, with commercial applications in processes like carbonylation, hydroformylation, hydrogenation, isomerization, polymerization and oxidation.[1-3] On the other hand, heterogeneous catalysts are easy to use in practice due to convenient separation from the products and effective recycle of catalysts. Heterogeneous catalysis is widely employed in industrial processes, but development of these catalysts involves challenges in achieving activity, selectivity and longer life of the catalysts. Since the success of homogeneous catalyzed hydroformylation process for the industrial synthesis of aldehydes/alcohols (oxo alcohols) from alkenes and CO/H_2 based on the work of Otto Roelen in 1938, homogeneous catalysis by organometallic complexes gained significant interest for application to many industrial processes. Selected examples of applications of homogeneous catalysis in industry are shown in Table 1-1.

Table 1-1. Industrial applications of homogeneous catalysis

No.	Process	Catalyst	Company
1	Oxidation of ethylene to acetaldehyde	$PdCl_2/CuCl_2$	Wacker and Hoechst[4]
2	Oxidation of p-xylene to terephthalic acid/ester	Co/Mn-salts	Imhausen[5,6]
3	Polymerization of ethylene to HDPE/LDPE	Ni-complex	Shell[7]
4	Asymmetric hydrogenation of acetamido cinnamic acid	$[Rh(diene)(solvent)]^+$ /DIPAMP	Monsanto[8]
		$NaCo(CO)_4$	BASF[9]
		$HCo(CO)_3PBu_3$	Shell[10]
5	Hydrocyanation of butadiene to adipic acid	Ni-complex	Du Pont[11]
6	Hydroformylation of propene to butyraldehyde	$HRh(CO)(PPh_3)_3$	Union Carbide[12]
		Rh/TPPTs	Ruhrchemie Rhone-Poulenc[13]
7	Carbonylation of methanol to acetic acid	CoI_2	BASF[14]
		Rh/MeI	Monsanto[14]
		$IrCl_3$	BP[15]
8	Oxidative carbonylation of methanol to Dimethyl carbonate	$PdCl_2$-$CuCl_2$	Assoreni[16]

Several significant trends in the development of homogeneous catalysis have emerged since 1970s and continue to date.[17] An important trend is to develop new cleaner and cheaper feedstocks and “hybrid catalysts” combining the practical advantages of homogeneous and heterogeneous catalysis to respond to the demand of the chemical industry for greener and more economical processes. Further enhancement in selectivity of homogeneous catalysis to meet the increasing competition in pharmaceutical and fine chemical industries is another important trend. The virtue of homogeneous catalysis with respect to high selectivity to certain organic compounds and especially the optically active compounds makes it particularly attractive for pharmaceutical as well as fine chemical industries, because most new products consisting of drugs, insecticides and food additives are expected to be the optically active isomers.[18] One important example is the selective synthesis of the *l* isomer of 3,4-dihydroxyphenylalanine which is the active component in the treatment of Parkinson's disease. The synthesis process was firstly commercialized by Monsanto in which the *l*-dopa is produced through hydrogenation of a prochiral olefin using a soluble rhodium catalyst with a chiral phosphine ligand.[19]

Among various catalytic reactions, transition metal catalyzed carbonylation reactions have gained considerable attention because of numerous industrially important products produced directly from CO. Carbonylation reactions involve the insertion of carbon monoxide to form different carbonyl compounds such as carboxylic acids/esters, ketones, aldehydes, etc. Carbonylation of olefins, alkynes, alcohols and other unsaturated substrates provides environmentally benign and atom-economic routes for the synthesis of various chemicals with applications as bulk chemicals or pharmaceutical and fine chemicals.[20,21] In the last few decades, considerable work has been done on the development of novel catalysts, kinetics and mechanism and fundamental aspects of isolation and characterization of catalytic species. While a large number of catalysts and reactions have been investigated, only a few of them are highly-selective and understood mechanistically. The aim of this thesis is to investigate Pd catalyzed hydrocarboxylation of styrene and derivatives, and develop intrinsic kinetic models to describe the overall rate and selectivity behavior of the homogeneous catalysts. The relevant literatures on the subject and scope of this thesis are presented in the following sections.

1-2 Carbonylation Reactions

Carbonylation is a class of catalytic reaction involving the insertion of CO in C-O, C-N, C-Cl or C-H bonds in substrates consisting of olefins, alcohols, amines, and halides to form various carbonyl compounds (aldehydes, carboxylic acids, amides, etc). These transformations are catalyzed by transition metal such as Rh, Pd, Co or Ir complexes coordinated with different ligands and provide a fundamental basis for developing environmentally friendly routes for the synthesis of numerous commercially important chemical products.

The carbon-carbon bond-forming reactions were discovered several decades ago and became the foundations of modern synthetic organic chemistry. The CO based reactions still attract myriad of attention from the organic chemists because of the versatile functionalities of the carbonyl group.[22] In carbonylation reactions, transition metal complex catalysts are used to activate carbon monoxide and facilitate further reactions with various organic compounds. Since the carbonyl group has inherent reactivity enabling both nucleophilic attack at carbon and electrophilic attack at oxygen, and polarity effect on neighboring atoms or functional groups in the presence of catalysts[20], it can be directly introduced into different sites in an organic molecule leading to good yields and high selectivity to end products.

The first well-developed catalytic carbonylation reaction was discovered eighty years ago by Otto Roelen during investigations of the mechanism of cobalt catalyzed Fischer-Tropsch synthesis of hydrocarbons from carbon monoxide and hydrogen.[23,24] In his research, he observed that the addition of ethene to the usual syngas mixture led to the formation of propanal in high yield (see Eq. 1-1).

$$H_2C = CH_2 + CO + H_2 \xrightarrow{HCo(CO)_4} CH_3CH_2CHO \qquad \text{Eq.1-1}$$

The work of Reppe and co-workers at IG Farben quickly followed Roelen's discovery and extended it to catalytic synthesis of many types of organic carbonyl compounds from unsaturated hydrocarbons.[25] These researchers developed an effective nickel carbonyl catalyst $Ni(CO)_4$ carbonylation of acetylene to acrylic acid as shown in Eq.1-2.

$$HC\equiv CH + CO + H_2O \xrightarrow{Ni(CO)_4} H_2C=CHCOOH \qquad \text{Eq. 1-2}$$

In the following twenty five years, the initial discoveries of Roelen and Reppe still remained the essential foundations of the carbonylation chemistry with diverse applications to industrial products.[26] However, most of the carbonylation reactions still require high temperature (373 ~ 573 K) and pressure (10 ~ 100 MPa). The use of severe conditions and in some cases corrosive promoters or co-catalysts often required expensive reaction equipment, and handling of toxic, volatile and unstable catalysts [$Ni(CO)_4$, $Fe(CO)_5$, $HCo(Co)_4$, etc.]. The generation of byproducts and toxic wastes requiring tedious removal from major products also posed serious difficulties in their applications. In recent years, outstanding advances in developing stable but highly active catalysts have been achieved based on the work of Wilkinson, Heck, and Tsuji on organophosphine complexes of rhodium and palladium.[27-29] In addition, the application of new techniques such as phase transfer catalysis to existing catalytic systems based on cobalt or iron also gained significant developments.[30,31] Based on these advances, numerous carbonylation processes were developed under mild conditions (below 373 K and close to atmospheric pressure) using only traces of non-volatile, air-stable catalyst precursors such as $PdCl_2(PPh_3)_2$ or $RhCl(CO)(PPh_3)_2$ which are *in situ* converted to the corresponding active species. To date, the understanding of carbonylation chemistry has developed to a significant level that makes it one of the generally useful techniques of synthetic organic chemistry. Table 1-2 shows the applications of different types of carbonylation reactions in industrial processes.

Table 1-2. Industrial applications of carbonylation reactions

No.	Process	Catalyst	Company
1	Carbonylation of methanol to acetic acid	CoI_2 Rh/MeI $IrCl_3$	BASF[14] Monsanto[14] BP[15]
2	Carbonylation of methyl acetate to acetic anhydride	Rh/MeI	Eastman Chemical[32]
3	Carbonylation of ethylene to propionic acid	$Ni(OCOC_2H_5)_2$	BASF[33]
4	Carbonylation of acetylene to acrylic acid	Ni-salts/carbonyls	BASF[34]
5	Carbonylation of benzyl chloride to phenyl acetic acid	$Co_2(CO)_8$	Montedison[35,36]
6	Carbonylation of 1-(4-isobutyl phenyl)ethanol to Ibuprofen	$PdCl_2(PPh_3)_2/HCl$	Hoechst-Celanese[37]
7	Oxidative carbonylation of methanol to dimethyl carbonate	$PdCl_2$-$CuCl_2$	Assoreni[38]
8	Carbonylation of propyne to MMA	$Pd(OAc)_2$/2-$PyPPh_2$	Shell[39]
9	Oxidative carbonylation of phenol to diphenyl carbonate	Pd^{II} ammonium salt /co-catalysts	GE[40]
10	Carbonylation of butadiene to adipic acid	$Co_2(CO)_8$/ Pyridine	BASF[41]

Although carbonylation chemistry has significantly advanced over the last few decades, its full potential in synthetic chemistry and chemical industry has not yet been realized. Many new perspectives of carbonylation chemistry are emerging specially using palladium-based catalyst systems, expanding the scope to new substrates and products, developing heterogeneous catalysts, and studying the fundamental catalytic reaction mechanism. In the following sections, the syntheses of carboxylic acids especially 2-

arylpropionic acids via carbonylation of olefins or alcohols are reviewed, which is relevant to the specific topic and test reaction chosen for this thesis.

1-2-1 Carbonylation of Olefins

Carbonylation of olefins leads to a myriad of saturated and unsaturated carbonyl compounds such as carboxylic acids/esters, unsaturated carboxylic acids/esters, diacids/diesters, amides, amino acids, ketones, poly ketones and anhydrides. Figure 1-1 shows the examples of syntheses of different carbonyl compounds through various carbonylation reactions. Depending on the types of substrates and products, the olefin carbonylation reactions can be classified as hydrocarboxylation/hydroesterification, dicarboxylation, amidocarbonylation, oxidative carbonylation, copolymerization, etc.

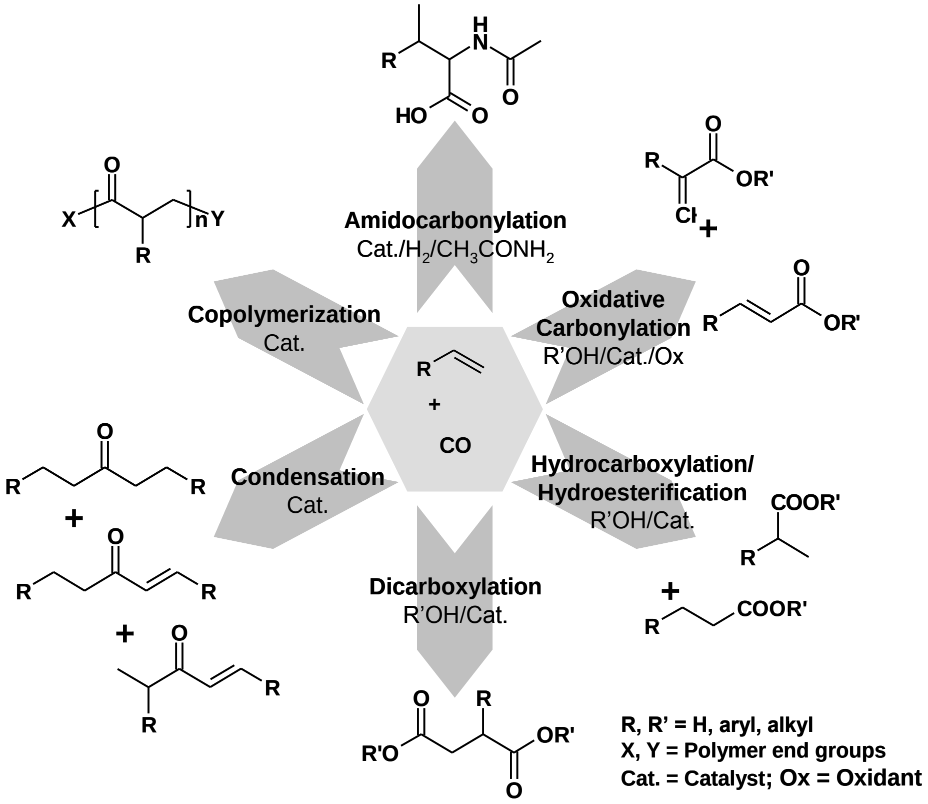


Fig. 1-1. Carbonylation of olefins[42]

The important developments in carbonylation reactions have been facilitated by the advances in transition metal catalysis. Since the early development of Co and Ni catalysts by Roelen and Reppe respectively, several efforts have been made to improve the catalytic activity and selectivity of Ni, Co, Pd, Pt, Rh, Ir catalysts in carbonylation of olefins.[42] Pd complex catalysts were found to be very effective for a variety of carbonylation reactions, and hence, palladium-catalyzed hydrocarboxylation of aryl olefins is highlighted in the following sections.

1-2-1-1 Transition Metal Catalysts for Carbonylation of Olefins

After initial discovery of Reppe using nickel carbonyl catalyzed carbonylation of acetylene for synthesis of acrylic acid, several Ni-complex catalytic systems have been developed to broaden the application of nickel catalysts to carbonylation of olefins.[43-50] As early as 1943, a catalyst using $NiCl_2$ as a catalyst precursor was patented for carbonylation of ethylene to propionic acids and its esters.[51] With the requirement of industrial application, a halogen-free nickel catalyst was developed using *in situ* formed $Ni(OCOC_2H_5)_2$ as a precursor for hydrocarboxylation of ethylene.[33, 52] However, this Ni-catalytic system had a major drawback of severe operating conditions (high temperature 543K~593K, and high pressure 20 ~ 24 MPa). Carbonylation of both alpha-olefins and internal olefins using an unpromoted nickel catalyst was also reported to give 43% ~ 70% yield to branched acids products at 573 K and 41 MPa.[43,44, 45-50] In 1971, the nickel complexes of the type $NiX_2(PPh_3)_2$ (where X represents a halide) were reported for hydrocarboxylation of propylene giving a total yield of 76.1% to both butyric and isobutyric acids with n/i ratio of 1:1 under 0.2 ~ 2.5 MPa of CO pressure.[53] In recent years, several other nickel catalyst systems were also reported to perform at relatively mild conditions.[54-55]

Cobalt carbonyl, $Co_2(CO)_8$, has been reported as catalyst for carbonylation of olefins to carboxylic acids/esters.[56, 57] In fact, most commercial carbonylation processes until 1970s used cobalt carbonyl catalysts.[58] The cobalt carbonyl precursors along with pyridine as a co-catalyst led to linear acid/ester isomers as the main products, and the selectivity was observed to increase with addition of pyridine. However, using the cobalt carbonyl/pyridine catalytic system, severe reaction conditions (433 K and 16~18 MPa) were required in the carbonylation of higher olefins such as 1-octene and 1-dodecene to obtain the desired activity and selectivity.

Since nickel and cobalt based catalysts showed poor performance under mild conditions, and they are also sources of toxic wastes, later research in the field of olefin carbonylation was focused on investigations of noble metals such as Pd, Pt, Rh, Ru and Ir as catalysts. Among these, a few reports addressed the use of Rh, Ru, Ir as catalysts in carbonylation of olefins. In 1971, Iridium[59] and Rhodium[60] complexes along with iodide promoters were patented as catalysts for carbonylation of propylene. Ir complex $Ir(PPh_3)_2(CO)Cl$ with aqueous HI in acetic acid gave 99% butyric acids with i:n ratio of 5:1 at 1.3 MPa CO pressure (4.8 MPa total pressure) and 448 K. Similarly, Rh complex gave an i:n ratio of 1.6:1. Later, a non halide Rh complex, Rh (acac) $(CO)_2$, in the presence of Bu_3P as a ligand, was reported to give 80% selectivity to methyl propionate at 4.7 MPa and 448K in carbonylation of ethylene.[61,62] In 1999, BASF patented a halogen free Rh catalyst system using $Rh(acac)(CO)_2$ as a catalyst precursor with nitrogen-containing heterocycle as a ligand for carbonylation of ethylene, which showed high activity (TOF= 200 ~ 1280 h^{-1}) as well as selectivity (> 95%) to propionic acid at 373 K and 10 MPa.[63] A very recent report described an immobilized rhodium catalyst [Rh(cod)(4-picoline)$_2$](PF$_6$)/P(4-VP) to catalyze conversion of C_6-C_8 olefins in naphtha, to 91% selectivity of the carbonylation products at 383K and 2.2 MPa.[64] Ruthenium catalysts received very little attention for their application in olefin carbonylation reactions. K. Asenaratne et al. have reported a $RuCl_3$/aqueous HCl system in n-butanol solvent for carbonylation of poly alpha olefins at 373 K and 13.6 MPa.[65] However, the reaction showed very low catalytic activity. A platinum halide salt together with an alcohol-soluble Sn or Ge salt was patented by Du Pont as early as 1959 to catalyze carbonylation of lower olefins (C_2 – C_6) at below 623 K.[66]

The demand for developing catalysts with higher activity and selectivity at mild operating conditions finally led to the development of palladium based catalysts.[67] Initial reports described $PdCl_2(PPh_3)_2$ catalyzed synthesis of esters by olefin carbonylation in alcoholic medium.[68] Independent discoveries were reported by Tsuji et al. to show that $PdCl_2$ in an alcoholic solution of HCl catalyzes formation of saturated or unsaturated esters via carbonylation of corresponding olefins at 353 K and 10 MPa.[69-72] Later, Reis and co-workers also reported carbonylation of ethylene and styrene with $PdCl_2(PPh_3)_2$ catalyst with 10% HCl in ethanol with 90% and 95% yields of ethyl propionate and ethyl-2-phenyl propionate respectively at 368 K and 30 ~ 70 MPa.[67] In 1973, Fenton reported hydrocarboxylation of higher alpha-olefins using $PdCl_2/PPh_3$ catalyst at 399 ~ 448 K and low CO pressure of 0.7 ~ 5.4 MPa.[73] Alper et al. reported a bi-metallic catalyst consisting of $PdCl_2$-$CuCl_2$ with aqueous HCl and molecular oxygen for carbonylation of alpha-olefins to branched isomers at room temperature and atmospheric pressure.[74] In 1992, Elali and Alper reported a catalyst system $Pd(OAc)_2$/dppb/PPh_3 in presence of formic acid for hydrocarboxylation of mono- or disubstituted olefins to yield 45 ~ 98% carboxylic acids.[75, 76] Xu et al. reported their study on a Pd (I) carbonyl cation ($[c\text{-}Pd_2(\mu\text{-}CO)_2]^{2+}$) / 96% H_2SO_4 system for carbonylation of alpha- and cyclo- olefins to tert-carboxylic acids in high yield at room temperature and atmospheric pressure.[77]

In the last ten years, a number of new palladium catalyst systems with specific ligands, promoters and solvents have been reported for their performances in hydrocarboxylation of styrene and derivatives. These developments are presented in the next section.

1-2-1-2 Hydrocarboxylation and Hydroesterification of Styrene and Derivatives

Palladium catalyzed hydrocarboxylation or hydroesterification of aryl-substituted olefins to both linear and branched acid/ester isomers have attracted considerable attention. The catalytic reactions provide environmentally benign and atom-effective alternative routes for synthesizing industrially important chemicals, especially the branched isomers, 2-arylpropionic acids/2-arylpropionates, which have significant applications as a class of nonsteriodal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, ketoprofen, etc. The most important commercial example is the Hoechst Celanese Process[37] for ibuprofen production using palladium catalyzed carbonylation of 1-(4-isobutylphenyl) ethanol (IBPE). It is important to note that even though the initial substrate is an alcohol, the reaction proceeds through hydrocarboxylation of isobutyl styrene formed as an intermediate. The catalytic hydrocarboxylation route has condensed the conventional multistep production of ibuprofen to three steps, and significantly reduced the toxic wastes and byproducts. Thus the Hoechst Celanese Process is a significant technological advance compared to the stoichiometric Boots Process[78] for the production of ibuprofen with high atom efficiency and environmental compatibility. Figure 1-2 briefly shows the two industrial processes. Boots Process has six steps to produce ibuprofen, and each step is stoichiometric synthesis which generates large amount of wastes or byproducts. In contrast, the Hoechst Celanese Process has only three steps including two catalytic syntheses: hydrogenation of *p*-isobutylacetophenone to IBPE and hydrocarboxylation of IBPE to ibuprofen. In the hydrocarboxylation step, $PdCl_2(PPh_3)_2$/10% aqueous HCl catalyst system was used.

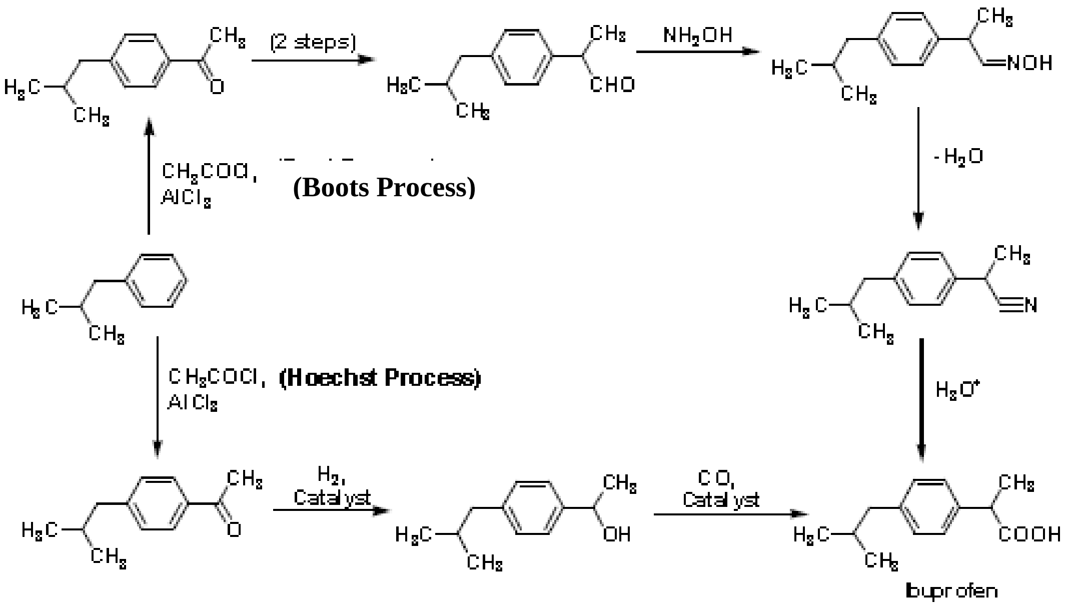


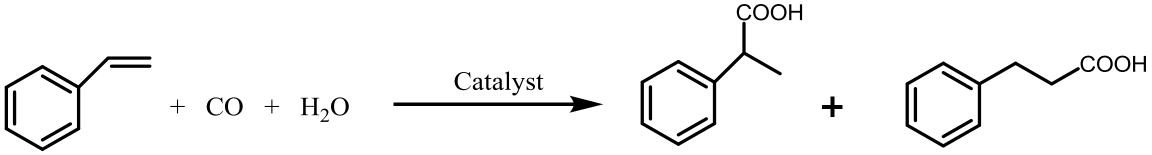
Fig. 1-2. Boots and Hoechst-Celanese processes for synthesis of ibuprofen

The Hoechst Celanese process successfully achieved above 95% regio-selectivity to ibuprofen at CO pressure of 16 ~ 35 MPa. However, there are some limitations of this process in that the high selectivity can be obtained only at high pressure. At lower pressure of 6.8 MPa, only less than 70% regio-selectivity can be achieved and the catalyst system showed lower activity (TOF=50~70 h^{-1}) even at higher pressure of 35 MPa.[78]

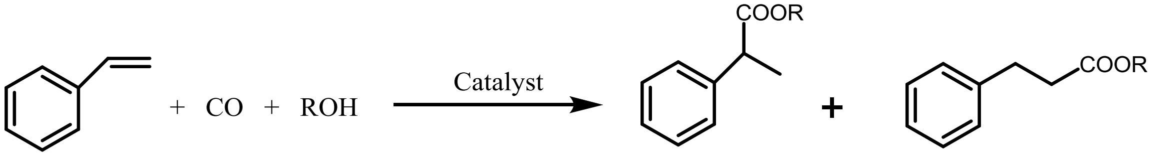
While the carbonylation route is generally applicable, it has not been commercialized for the production of other important NSAIDs such as naproxen.

Numerous efforts have been made to develop more advanced catalysts by modifying ligands, promoters and reaction media to achieve more effective hydrocarboxylation or hydroesterification of aryl olefins to synthesize 2-ayrlpropionic acids/esters. Among the various aryl-substituted olefins, styrene is the simplest substrate with which most studies on metal catalyzed aryl olefin carbonylation were initiated. This subsection mainly presents important developments in the last ten years in hydrocarboxylation and hydroesterification of styrene and derivatives (Table 1-3).

Hydrocarboxylation of styrene

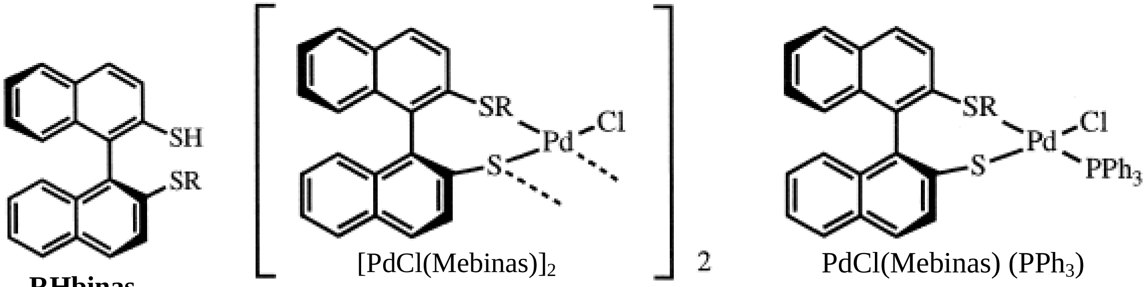


Hydroesterification of styrene



Scheme 1-1. Hydrocarboxylation and hydroesterification of styrene

Scheme 1-1 presents hydrocarboxylation and hydroesterification of styrene to the desired branched products, 2-phenylpropionic acid and 2-phenylpropionate (ester). In 1999, Ruiz et al. reported thiol-thioether atropisomeric ligated palladium catalysts in the presence of triphenylphosphine and oxalic acid showing up to 97% regio-selectivity to 2-phenylpropionic acid at 373 K and 3.0 MPa CO pressure.[79] These researchers prepared the *S, S'*-heterotopic atropisomeric ligands (RHbinas) which have a thioether and a thiol group as sulfur containing arms. The ligands were reacted with $PdCl_2(PhCN)_2$ to form the new structured catalyst complexes (Figure 1-3).



RHbinas
R=Me or ^{i}Pr

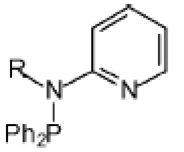
[PdCl(Mebinas)]$_2$
or
[PdCl(^{i}Prbinas)]$_2$

PdCl(Mebinas) (PPh_3)
or
PdCl(^{i}Prbinas)(PPh_3)

Fig. 1-3. Molecular structure of RHbinas and their ligated Pd catalysts

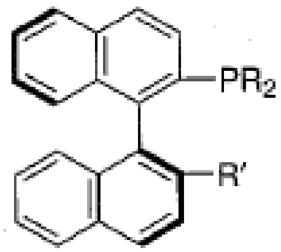
In the same year, Brugat et al. synthesized mononuclear $[PdCl(SC_2H_4PPh_2)PPh_3]$ and binuclear $[Pd_2Cl_2(\mu\text{-}SC_3H_6PPh_2)_2]$ catalysts and applied them in hydroesterification of styrene. Both complexes could perform at mild conditions (T=353K, Pco=3.0MPa) in the absence of any promoter to yield relatively high selectivity to methyl 2-phenylpropionate, but showed very low activity (TOF=0.3 ~ 1.0 h^{-1}).[81] In 2000, Seayad et al. reported a highly effective catalyst system using $Pd(pyca)(PPh_3)(OTs)$ complex as a precursor, TsOH and LiCl (molar ratio of 1:1) as promoters for hydrocarboxylation of different substrates.[83] Above 99% regio-selectivity to 2-phenylpropionic acids along with high TOF in range of 800 h^{-1}~2600 h^{-1} was obtained in hydrocarboxylation of styrene at 388 K and 5.4 MPa CO pressure. The same regio-selectivity to ibuprofen along with high TOF of 1313 h^{-1} was also obtained in hydrocarboxylation of 4-isobutyl styrene at the same moderate conditions. Recently, Aguirre et al. reported high regio-selective palladium complexes bearing *P, N*-donor ligands.[97] The palladium complex $PdCl_2(Ph_2PNHpy)$ with

TsOH and PPh_3 was found to give 97% regio-selectivity to methyl-2-phenylpropionate at 348K and 5.0 MPa.



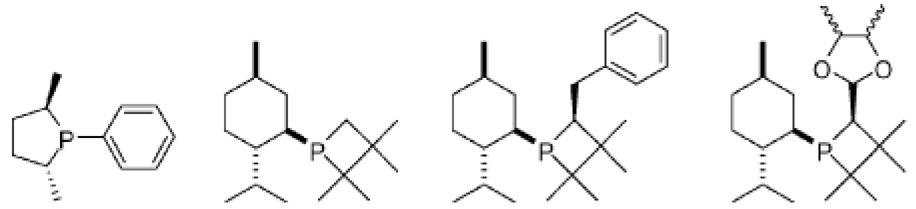
R=H: Ph_2PNHpy
R=Me: $Ph_2PNMepy$

Developing bulky ligands with specific steric structures is an important direction to achieve highly selective, especially the enantio-selectively catalytic synthesis. It will be another focus for hydrocarboxylation and hydroesterification of aryl olefins, since most useful anti-inflammatory agents have chiral structure. In 2004, Nozaki et al. reported their observation about dialkymonoaryl- and monoalkyldiarylphosphines for palladium catalyzed hydroesterification of aryl olefins.[90] In their study, menthyldiphenylphosphine (MDPP) and neomenthyldiphenylphosphine (NMDPP) as ligands were found to favor the regio-selectivity to branched ester methyl-2-phenylpropionate (100%) in $PdCl_2$ catalyzed hydroesterification of styrene at 323 K and 2.0 MPa CO pressure. More importantly, the researchers successfully prepared asymmetric ligands as shown below to achieve enantioselective syntheses of methyl-2-phenylpriopionate (up to 51% ee) and (*S*)-naproxen methyl ester (up to 53% ee).



R= *c*-C_6H_{11}, *c*-C_5H_9 or *i*-Pr;
R'=OMe, O^iPr, OBn, NMe_2, OTMS or O^iBu

In 2007, based on their preliminary research on chiral ligands for asymmetric hydroesterification of styrene, [102] Claver et al. reported their important observations about using chiral monodentate phosphetanes and phospholane ligands to achieve asymmetric Pd-catalyzed hydroesterification of styrene derivatives.[98] The chiral ligands used in their study are shown in Figure 1-4. The synthesized new palladium complexes $PdCl_2(L)_2$ (L=ligang 1, 2, 3 or 4 in Fig. 1-5) showed above 95% regio-selectivity to the branched ester and up to 29% ee value for *R* chiral product in hydroesterification of styrene at 343 ~ 363 K and CO pressure of 3.5 MPa. Moreover, these researchers further investigated the hydroesterification of other styrene derivatives such as 4-methoxystyrene, 4-methylstyrene, 4-florostyrene and 2-vinylnaphthalene using $PdCl_2$(**2**)$_2$ (**2**=chiral ligand **2 P(S)** in Fig. 1-4). Above 92% regio-selectivity to branched esters was observed, wherein, 50% ee value for *S* product was obtained in hydroesterification of 4-methoxystyrene.



1 (*S,S*)　**2** P(*S*)　**3** P(*R*)C(*S*)　**4a** P(*R*)C(*R*)(*R,R*)
4b P(*R*)C(*R*)(*S,S*)

Fig. 1-4. Chiral mono-phosphine ligands[98]

With the demand for easy organic product–catalyst separation and effective recyclability of catalysts, many researchers dedicated to explore heterogeneous catalysts for carbonylation of styrene and derivatives. A number of heterogeneous palladium catalyst systems have been developed via modification of ligands, immobilization technology, and employment of ionic solvent for the catalytic reactions. In 2000, a water-soluble palladium catalyst for hydrocarboxylation of aryl olefins was reported by

Jayasree et al.[85] They modified a palladium complex Pd(pyca)(PPh_3)(OTs) by replacing the ligand PPh_3 with a water soluble tris(m-sulfophenyl)phosphine trisodium salt (TPPTS). In the presence of coordinated TPPTS, the palladium catalyst could perform under biphasic conditions. Above 92% regio-selectivity to the branched acids along with good activity (TOF=147~550 h^{-1}) were observed for the biphasic hydrocarboxylation of aryl olefins. Recycle experiments showed good reusability of the biphasic palladium catalyst at lower temperatures of 373 ~ 378 K. Xia et al. reported their study on polymer-supported palladium-copper/nickel bimetallic catalyst systems for hydroesterification of aryl olefins and alcohols.[86] They presented a PVP-$PdCl_2$-$CuCl_2$ catalyst which showed high regio-selectivity (83% ~ 100%) to the branched esters in presence of PPh_3 at mild conditions (T=353K, Pco= 2.5MPa). Ooka et al. published their important study on palladium catalyst promoted by polymeric sulfonic acids for hydroesterification of styrene.[93] Using the Pd/polymeric CH_3SO_3H/DTBPMP catalyst system, the hydroesterification of styrene could even be carried out at room temperature and nearly atmospheric pressure to give up to 89% regio-selectivity to the branched ester. Good activity and selectivity were maintained after three recycles.

In 2002, Chaudhari's group[87] reported new anchored palladium complex in highly ordered mesoporous silica MCM-41 and MCM-48 synthesized following the method previously presented by Shephard et al.[103] The anchored catalysts along with PPh_3/TsOH/LiCl showed above 99% regio-selectivity to 2-aryl propionic acids with high activity (TOF=260 ~ 470 h^{-1}) in hydrocarboxylation of aryl olefins (styrene, 4-methylstyrene, 4-*t*-butylstyrene) at 388 K and 3.1 MPa CO pressure. The high activity and selectivity of these anchored catalysts remained even after three recycles, and the structure of the catalytic complex was also found to be intact. Both observations proved good stability of these anchored palladium catalysts. More recently, Sarkar and Chaudhari reported a new immobilization technology, ossification[94] (Figure 1-5), to synthesize heterogeneous palladium catalysts for hydrocarboxylation of olefins and alcohols. The complex Pd(pyca)(PPh_3)(OTs) was modified to water-soluble Pd(pyca)(TPPTS) complex which has -SO_3H group. Then the aqueous-soluble complex was added to a solution of Ba^{2+} or Sr^{2+} to form the so-called ossified catalysts. The ossified-Pd(pyca)(TPPTS) showed above 99.2% regio-selectivity to 2-ayrlpropionic acids as well as high activity (TOF = 180 ~190 h^{-1}) for hydrocarboxylation of aryl olefins at mild conditions. High activity and selectivity of the ossified catalysts remained no variation even after four recycles.

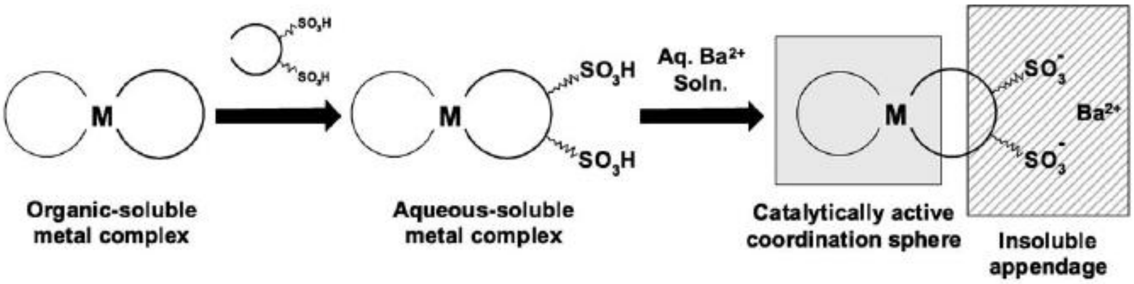


Fig. 1-5. Ossification methodology[94]

Developing biphasic reaction medium is another way to achieve heterogeneously metal-catalyzed synthesis. Several groups have reported different biphasic media for carbonylation of styrene.[91,92]

1-2-2 Carbonylation of Aryl Alcohols

Carbonylation of aryl alcohols provides another route for synthesis of 2-arylpropionic acids. As mentioned in the beginning of section 1-2-1-2, the commercial ibuprofen process (Hoechst Celanese Process) applied the palladium catalyzed carbonylation of 1-(4-isobutylpenyl) ethanol (IBPE) to achieve effective synthesis of ibuprofen.[37] The important developments on palladium catalysts for carbonylation of aryl alcohols are summarized in Table 1-4. Seayad et al. reported a $PdCl_2PPh_3/PPh_3/TsOH/LiCl$ system for carbonylation of aryl alcohols.[104,105] In carbonylation of *p*-IBPE, the catalyst system showed 96.2% regio-selectivity to ibuprofen along with high activity (TOF=850 h^{-1}) at 388 K and 5.4 MPa. They also observed 82% selectivity to naproxen and TOF of 600 h^{-1} in carbonylation of 6-methoxy-2-naphthyl ethanol using the same catalyst system. Good performing $Pd(pyca)(PPh_3)(OTs)/TsOH/LiCl$ system for hydrocarboxylation of aryl olefins also showed high regio-selectivity (99%) as well as activity (TOF=804 h^{-1}) in carbonylation of *p*-IBPE at moderate conditions (T=388 K, Pco=5.4 MPa).[83]

Most study focus on develop heterogeneous palladium catalysts for the carbonylation of aryl alcohols. Jayasree et al. reported a series supported palladium catalysts (Pd/C, Pd/*r*-alumina, etc) for carbonylation of *p*-IBPE to obtain above 99% regio-selectivity as well as very high activity (TOF=550 ~ 3400 h^{-1}).[106] The drawback of these supported catalysts is their poor stability. High leaching (37% for Pd/C case) occurred after reaction. In 2000, Park et al. reviewed their work on preparing heterogeneous catalysts for carbonylation of aryl alcohols.[107] They has found a catalyst $(C_6H_5CN)_2PdCl_2$ anchored on montmorillonite showed high selectivity to ibuprofen (92.3%) and naproxen (83.3%) in the presence of ligand $(C_2H_5O)_3Si(CH_2)_3NH_2$ and HCl under mild conditions. In carbonylation of *p*-IBPE, all the immobilized $Pd(pyca)(PPh_3)(OTs)$ catalysts reported by Chaudhari's group showed outstanding performance.[87, 94, 99] Above 97% regio-selectivity to ibuprofen was obtained in presence of appropriate promoters at mild conditions (T=388K, Pco=3.1~5.4MPa). Moreover, all the immobilized catalysts showed good stability in the reaction.

Table 1-3. Palladium-catalyzed carbonylation of styrene and derivatives

Sl. No.	Catalyst precusor	Substrates	Ligand	Promoter	Solvent	Reaction conditions			Conversion (%)	Selective			TOF (h^{-1})	Ref
						T (K)	Pco(MPa)	t (h)		iso (%)	linear(%)	i/n		
1	[PdCl(Mebinas)]$_2$	styrene	Mebinas	oxalic acid; PPh_3	DME	373	3.0	24	90	89	11	8.1	-	N. Ruiz et al. (1999)[79]
2	PdCl(Mebinas)(PPh_3)	styrene	Mebinas;PPh_3	oxalic acid; PPh_3	DME	373	3.0	24	25	96	4	24.0	-	
3	[PdCl(Prbinas)]$_2$	styrene	Prbinas	oxalic acid; PPh_3	DME	373	3.0	24	92	74	26	2.8	-	
4	PdCl(Prbinas)(PPh_3)	styrene	Prbinas	oxalic acid; PPh_3	DME	373	3.0	24	69	97	3	32.3	-	
5	$PdCl_2(PPh_3)_2$	styrene	PPh_3	$BF_3P{\cdot}OEt_2$	MeOH	363	5.0	18	98(90% yield to ester)	46	54	0.9	-	M.C. Bonnet et al. (1999)[80]
		Isobutyl styrene (IBS)	PPh_3	$BF_3P{\cdot}OEt_2$	MeOH	363	5.0	18	97(70% yield to ester)	74	26	2.8	-	
7	$PdCl(SC_2H_4PPh_2)PPh_3$ =[PdCl(dppet)PPh_3]	styrene	dppet; PPh_3	-	MeOH; 1,2-CH_2Cl_2	333	3.0	-	29	84	16	5.3	0.4	N. Brugat et al. (1999)[81]
8	$Pd_2Cl_2(\mu\text{-}SC_3H_6PPh_2)_2$ =[Pd_2Cl_2(dpppt-P,μ-S)$_2$	styrene	dpppt-P,μ-S	-	MeOH; 1,2-CH_2Cl_2	353	3.0	-	7	84	16	5.3	0.3	
9	$Pd(OAc)_2$	styrene	PPh3	TsOH	MeOH	338-388			84.2	39.8	60.2	0.7	203	A. Seayad et al. (2000)[82]
10	Pd(pyca)(PPh_3)(OTs)	styrene	-	TsOH; LiCl	-	388	5.4	0.18	97	99	1	99.0	2600	S. Jayasree et al. (2000)[83]
		4-isobutyl styrene	-	TsOH; LiCl	-	388	5.4	0.35	95	99	1	99.0	1313	
11	$PdCl_2(PhCN)_2$	styrene	PPh_3	$H_2C_2O_4$	DME	373	3.0	20	98	95	5	19.0	-	I. del R'ıo et al. (2000)[84]
			PPh2(o-Tol)	$H_2C_2O_4$	DME	373	3.0	20	76	100	0	-	-	
			$P(p\text{-}C_6H_4OMe)_3$	$H_2C_2O_4$	DME	373	3.0	20	79	98	2	49.0	-	
12	Pd(pyca)(TPPS)(OTs)	styrene	pyca; TPPS	TsOH; LiCl	Toluene	388	5.4	1.5	93	90.7	8.7	10.4	282	S. Jayasree et al.(2000)[85]
		IBS	pyca; TPPS	TsOH; LiCl	Toluene	388	5.4	5	81	98	1.5	65.3	147	
		6(-methoxy-2-vinyl) naphthalene	pyca; TPPS	TsOH; LiCl	Toluene	388	5.4	12	45.5	93	6.5	14.3	10	
13	PVP-$PdCl_2$-$CuCl_2$/MeOH	styrene	PPh_3	TsOH	MEK	353	2.5	10	100	93.4	1.6	58.4	-	Y.Y. Li et al. (2001)[86]

Table 1-3. Palladium-catalyzed carbonylation of styrene and derivatives (continued)

14	Pd-pyca-MCM-41	Styrene	PPh_3	TsOH; LiCl	MEK	388	3.1	12	98.1	99.3	0.7	141.9	463	K. Mukhopadhyay et al. (2002)[87]
		4-methylstyrene	PPh_3	TsOH; LiCl	MEK	388	3.1	12	97.8	98.6	1.4	70.4	406	
		4-tBu-styrene	PPh_3	TsOH; LiCl	MEK	388	3.1	12	93.4	99.3	0.7	141.9	286	
15	Pd-pyca-MCM-48	Styrene	PPh_3	TsOH; LiCl	MEK	388	3.1	12	98.4	99	1	99.0	417	
		4-methylstyrene	PPh_3	TsOH; LiCl	MEK	388	3.1	12	98.1	99.1	0.9	110.1	367	
		4-tBu-styrene	PPh_3	TsOH; LiCl	MEK	388	3.1	12	95.1	99.2	0.8	124.0	262	
16	[Pd(OTs)(dppo)](OTs)	styrene	-	TsOH	not mentioned	353	5.5	3	-	30	70	0.4	63	O.V. Gusev, et al. (2003)[88]
17	PVP-$PdCl_2$-$NiCl_2$/H_2O	styrene	PPh_3	TPPTS	MEK	373	4.0	6	100	63	36	1.8	-	F.W. Li et al. (2003)[89]
18	$PdCl_2$	styrene	MDPP	-	MeOH-acetone	323	2.0	24	95	100	-	-	-	Y. Kawashima et al., (2004)[90]
			NMDPP	-	MeOH-acetone	323	2.0	24	96	100	-	-	-	
			$(c\text{-}C_6H_{11})_2PPh$			323	4.0	50	86	98	2	49.0	-	
19	$PdCl_2(PPh_3)_2$	styrene	PPh_3	HCl	TBAB-heptane	383	7.0	7	97.8	66.1	24.6	2.7	-	A.L. Lapidus et al. (2004)[91]
20	$PdCl_2(PPh_3)_2$	styrene/EtOH	PPh_3	-	[BMIM][BF_4]	373	10.0	24	59	48	11	4.4	-	G. Rangits et al. (2005)[92]
		styrene/BzOH	PPh_3	-	[BMIM][BF_4]	373	10.0	24	93	93	0	-	-	
		styrene/EtOH	PPh_3	-	[BMIM][PF_6]	373	10.0	24	100	9	91	0.1	-	
21	$Pd(OAc)_2$	styrene	DTBPMB	polymeric CH_3SO_3H	MeOH	R.T	0.6	17	100	89	11	8.1	-	H. Ooka et al. (2005)[93]
22	$Pd_2(dba)_3$	styrene	DTBPMB	polymeric CH_3SO_3H	MeOH	R.T	0.6	18	97	86	11	7.8	-	
23	Barium ossified Pd(pyca)(TPPTS)	styrene	PPh_3	TsOH; LiCl	MEK	388	5.4	6	96	99.9	-	-	194	B. R. Sarkar et al. (2006)[94]
		4-methylstyrene	PPh_3	TsOH; LiCl	MEK	388	5.4	6	94	99.8	0.1	998.0	184	
		4-tBu-styrene	PPh_3	TsOH; LiCl	MEK	388	5.4	6	92	99.2	0.7	141.7	183	
24	$PdCl_2(PhCN)_2$	styrene	TPPTS	TsOH	water	338	10.0	1.5	99	-	-	9.1	-	A. Ionescu et al. (2006)[95]

Table 1-3. Palladium-catalyzed carbonylation of styrene and derivatives (continued)

25	diphosphine-Pd(II)	styrene	diphosphine(3)	HCl	Toluene and MeOH	373	7.0	1	99.4 (98.3% yield to ester)	74	26	2.8	-	E. Guiu et al. (2006)[96]
26	$PdCl_2(Ph_2PNHpy)$	styrene	Ph_2PNHpy (P-,N-donor)	TsOH; PPh_3	Toluene	348	5.0	6	99	97	3	32.3	67	P. A. Aguirre et al. (2007)[97]
27	$[PdCl(PPh_3)(Ph_2PNHpy)]Cl$	styrene	Ph_2PNHpy (P-,N-donor)	TsOH	DCE	348	5.0	20	98	90	10	9.0	-	
28	$[PdCl_2(1)_2]$ (Pd-phospholane complex)	styrene	five-membered ring phospholane	HCl	THF : MeOH (1:1)	363	5.0	24	97(95% yield to ester)	96	4	24.0	-	B. K. Muñoz et al. (2007)[98]
29	bis-phosphetane complex $[PdCl_2(2)_2]$ (Pd-phosphetane complex)	styrene	bis-phosphetane	TsOH	Toluene:MeOH (1:1)	343	3.5	24	97(99% yield to ester)	95	5	19.0	-	
		4-methoxy-styrene	bis-phosphetane	TsOH	THF : MeOH (1:1)	333	3.5	24	71(21% yield to ester)	94	6	15.7	-	
		4-methylstyrene	bis-phosphetane	TsOH	THF : MeOH (1:1)	333	3.5	24	33(58% yield to ester)	92	8	11.5	-	
		4-florine styrene	bis-phosphetane	TsOH	THF : MeOH (1:1)	333	3.5	24	11(75% yield to ester)	96	4	24.0	-	
		2-vinylnaphthalene	bis-phosphetane	TsOH	THF : MeOH (1:1)	333	3.5	24	36(84% yield to ester)	93	7	13.3	-	
30	$[PdCl_2(3)_2]$(Pd-phosphetane complex)	styrene	bis-phosphetane	TsOH	THF : MeOH (1:1)	343	3.5	24	92(99% yield to ester)	99	1	99.0	-	
31	bis-phosphetane complex $[PdCl_2(4)_2]$(Pd-phosphetane complex)	styrene	bis-phosphetane	TsOH	THF : MeOH (1:1)	343	3.5	24	26(94% yield to ester)	97	3	32.3	-	
32	Pd-pyca-PTA-Y	styrene	PPh_3	LiCl	MEK	388	5.4	12	98.1	99.26	0.73	136.0	279	B.R. Sarkar, et al. (2007)[99]
		4-methylstyrene	PPh_3	LiCl				12	96.6	99.11	0.87	113.9	275	
		4-*t*Bu-styrene	PPh_3	LiCl				13	94.1	99.3	0.7	141.9	247	
33	racemic Pd–bidentate phosphine complex	styrene	para-substituted ligand	LiCl	butanone	393	5.0	16	86	-	-	30.8	-	J. Frew et al. (2008)[100]
34	$Pd(FeNN)Cl_2$	styrene	PPh_3	TsOH	methanol	348	5.0	24	17.1	91.4	8.6	10.6	-	C. Zúñiga et ak, (2009)[101]
35	$Pd(dppf)Cl_2$	styrene	PPh_3	TsOH	methanol	348	5.0	24	98.8	21.9	78.1	0.3	-	
36	$[Pd(dppf)(MeCN)_2](BF_4)_2$	styrene	PPh_3	TsOH	methanol	348	5.0	24	99.7	33.7	66.3	0.5	-	
37	$[Pd(dppf)(PPh_3)](BF_4)_2$	styrene	PPh_3	TsOH	methanol	348	5.0	24	97.8	31.6	68.4	0.5	-	

Table 1-4. Palladium-catalyzed carbonylation of aryl alcohols

Sl. No.	Catalyst precusor	Substrates	Ligand	Promoter	Solvent	Reaction conditions			Conversion (%)	Selective			TOF (h^{-1})	Ref
						T (K)	Pco(MPa)	t (h)		iso (%)	linear(%)	i/n		
1	$PdCl_2(PPh_3)_2$	p-IBPE	PPh_3	TsOH; LiCl	MEK	388	5.4	0.58	99	96.2	3.7	26	850	A. Seayad et al. (1999)[104]
		1-Phenyl ethanol	PPh_3	TsOH; LiCl	MEK	388	5.4	0.92	90	95.2	4.3	22.1	510	A. Seayad et al. (2001)[105]
		α-(6-methoxy-2-naphthyl)ethanol	PPh_3	TsOH; LiCl	MEK	388	5.4	2.33	95	81.9	17.4	4.7	600	
2	$PdCl_2(PPh_3)_2$	1-Phenyl ethanol	PPh_3	$HBF_4{\cdot}OEt_2$	CH_2Cl_2	363	5.0	6	99 (64% yield to ester)	21	79	0.3	-	M.C. Bonnet et al. (1999)[80]
3	Pd/C	p-IBPE	PPh_3	TsOH; LiCl	MEK	388	5.4	4.2	96	99.2	0.8	124.0	3375	S. Jayasree, et al. (1999)[108]
4	Pd/γ-alumina	p-IBPE	PPh_3	TsOH; LiCl	MEK	388	5.4	5.5	90	99	1	99.0	2285	
5	Pd/H-ZSM-5	p-IBPE	PPh_3	TsOH; LiCl	MEK	388	5.4	24	90	99.2	0.8	124.0	550	
6	Pt/C	p-IBPE	PPh_3	TsOH; LiCl	MEK	388	5.4	5.5	92	99.5	0.5	199.0	2475	
7	$(C_6H_5CN)_2PdCl_2$ /montmorillonite	p-IBPE	$(C_2H_5O)_3Si(CH_2)_3NH_2$	HCl	3-pentanone	398	5	13	98.1	92.3	0	infinite	-	E.D. Park et al. (2000)[107]
		α-(6-methoxy-2-naphthyl)ethanol	$(C_2H_5O)_3Si(CH_2)_3NH_2$	HCl	1,4-dioxane	373	5	-	100	83.4	-	-	-	
8	$Pd(pyca)(PPh_3)(OTs)$	p-IBPE	-	TsOH; LiCl	MEK	388	5.4	-	99	99	1	99.0	804	S. Jayasree et al. (2000)[83]
9	PVP-$PdCl_2$-$CuCl_2$/MeOH	1-Phenyl ethanol	PPh_3	TsOH	MEK	373	4.0	20	98.5	4.7	0	-	-	Y.Y. Li et al. (2001)[86]
		α-(6-methoxy-2-naphthyl)ethanol	PPh_3	TsOH	MEK	373	6.0	32	96.4	86.9	4.8	18.1	-	
10	Pd-pyca-MCM-41	p-IBPE	PPh_3	TsOH; LiCl	MEK	388	3.1	12	95.6	97.5	2.5	39.0	450	K. Mukhopadhyay et al. (2002)[87]
11	Pd-pyca-MCM-48	p-IBPE	PPh_3	TsOH; LiCl	MEK	388	3.1	11	95	97.9	2	49.0	439	
12	PVP-$PdCl_2$-$NiCl_2$/H_2O	p-IBPE	PPh_3	TPPTS	MEK	373	4.0	6	100	61	38	1.6	-	F.-W. Li et al. (2003)[89]

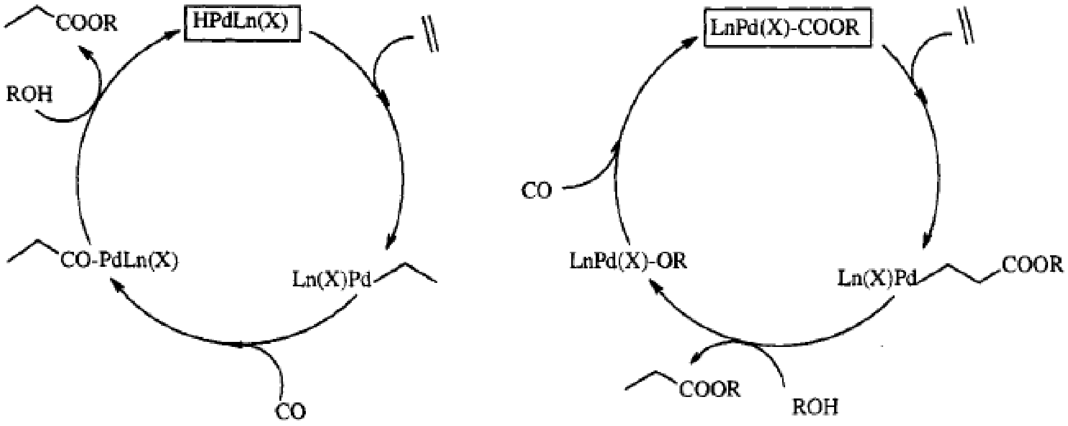
Table 1-4. Palladium-catalyzed carbonylation of aryl alcohols (continued)

13	$Pd(OAc)_2$	1-Phenyl ethanol	-	TBAB;$TsOH{\cdot}H_2O$		383	5.0	2	81.2	-	-	1.1	-	A. Lapidus et al. (2006)[108]
	$Pd(OAc)_2$		-	[BMIM]Br		383	5.0	2	86.3	-	-	0.4	-	
	$Pd(OAc)_2$		-	[BMIM]Cl		383	5.0	2	4.3	-	-	0.3	-	
14	$PdCl_2(PPh_3)_2$	1-Phenyl ethanol	PPh_3	TBAC		383	5.0	2	100	-	-	89.5	-	
15	$PdCl_2(PhCN)_2$	1-Phenyl ethanol	PhCN	TBAB		383	5.0	2	84.5	-	-	2.2	-	
16	Barium ossified Pd(pyca)(TPPTS)	*p*-IBPE	PPh_3	TsOH; LiCl	MEK	388	5.4	11	93	99.8	0.1	998.0	96	B. R. Sarkar et al. (2006)[94]
17	Pd-pyca-PTA-Y	*p*-IBPE	PPh_3	LiCl	MEK	388	5.4	13	95.1	98.1	1.9	51.6	0.25	B. R. Sarkar et al. (2007)[99]

1-3 Mechanism of Olefin/Alcohol Carbonylation

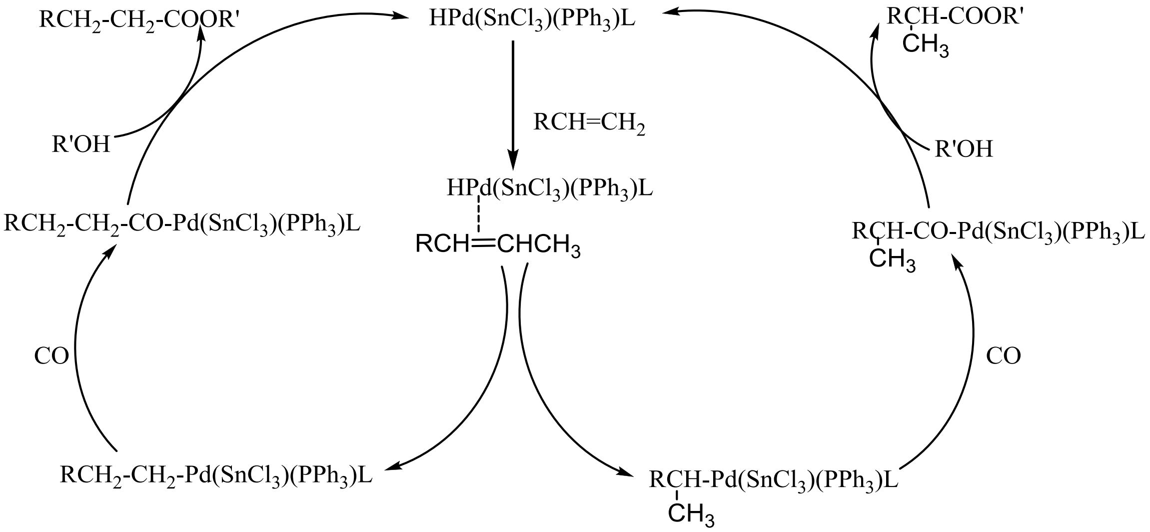
The good performance of palladium-based catalyst systems for carbonylation of olefins and alcohols under mild reaction conditions attracted considerable interest in exploring the catalytic reaction mechanism. This section briefly reviews the important studies on the mechanism of Pd-catalyzed olefin/alcohol carbonylation reactions.

The hydroesterification reaction has been extensively studied and two mechanisms have been suggested (Scheme 1-2) .[109-113] One explains that the catalytic cycle is initiated by a hydrido-metal complex. In this mechanism, the olefin insertion into a Pd-H bond has been considered followed by the migratory insertion of CO into an alkyl-metal bond to form an acyl-metal complex. With further alcoholysis of the acyl-metal species, the ester is formed and the Pd hydride complex is regenerated. Another mechanism considers that the catalytic cycle is initiated with an alkoxycarbonyl-metal complex. The olefin inserts into a Pd-carbon bond followed by alcoholysis to produce the ester and the alkoxymetal species. The alkoxycarbonylmetal complex is regenerated by the insertion of CO into the alkoxylmetal species.



Scheme 1-2. Mechanisms proposed for the hydroesterification of olefins[114]

Both the mechanisms have been generally accepted as the basis for palladium-catalyzed carbonylation of olefins. Knifton[110] has proposed a hydride mechanism for hydroesterification of olefins using a $PdCl_2(PPh_3)_2/SnCl_2$ catalyst system, which is supported by study on isolation of a hydrido palladium complex $HPd(PPh_3)_2(SnCl_3)$ from a stoichiometric reaction of $PdCl_2(PPh_3)_2$ with $SnCl_2 \cdot 2H_2O$ in benzene-ethanol solvent under CO atmosphere.



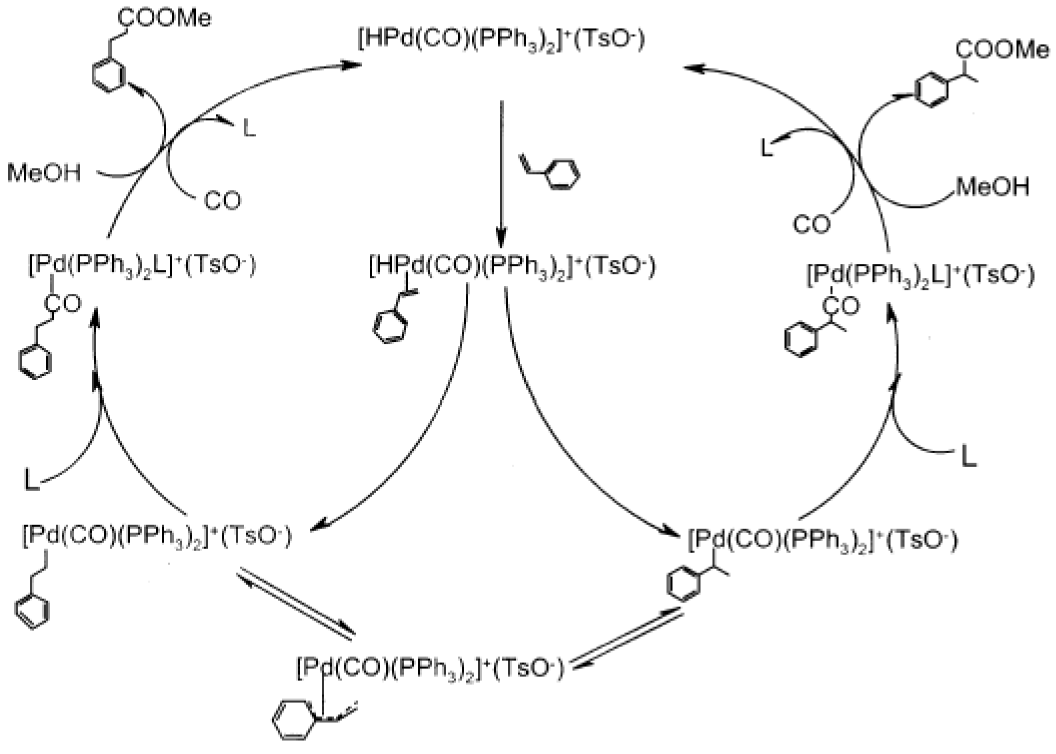
L=$SnCl_3^-$, PPh_3, CO or Cl^-

Scheme 1-3. Proposed mechanism for carbonylation of alpha-olefin using $PdCl_2(PPh_3)_2/SnCl_2$ catalyst system[110]

Noskov et al. have carried out detailed studies on the mechanism and kinetics of hydrocarboxylation of olefins using $PdCl_2(PPh_3)_2$ as a catalyst precursor.[115] A hydride mechanism was proposed for the hydrocarboxylation of styrene using $PdCl_2(PPh_3)_2$ in wet-dioxane as a solvent. The hydride mechanism was confirmed by the *in situ* IR study by detection of Pd-acyl complex which is one of the key intermediates in the proposed hydride route.[115c]

Using ^1H and ^{31}P NMR, Sheldon and co-workers have observed a water soluble Pd-H species in the form of $[HPd(TPPTS)_3]^+$ from a mixture of $Pd(OAc)_2$ and TPPTS in aqueous triflouroacetic acid.[116] They studied the reaction of the aqueous Pd-H complex with ethene and CO, and have identified the Pd-alkyl and Pd-acyl intermediates which were supposed to be the crucial complexes formed in the hydride route. Hence, these observations provide strong evidences for the hydride mechanism for the biphasic hydrocarboxylation of olefins under acidic conditions.

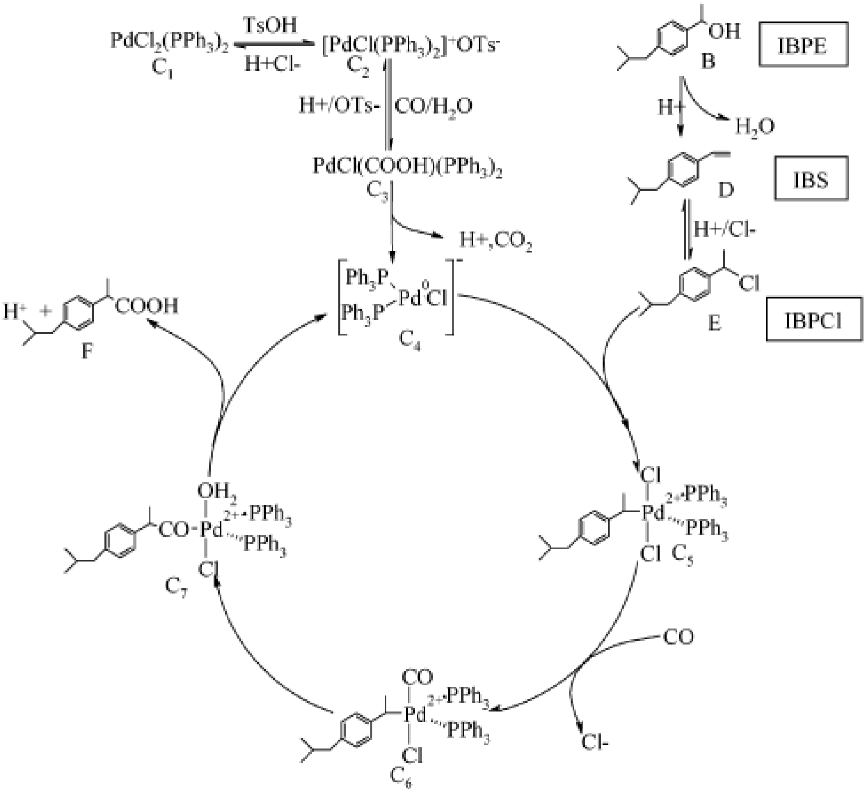
Seayad et al. have reported their detailed investigation on the mechanism and kinetics of hydroesterification of styrene using an *in situ* formed cationic palladium complex $Pd(OTs)_2(PPh_3)_2$ from $Pd(OAc)_2$, PPh_3 and TsOH in methanol as a solvent.[117] The authors proposed a mechanism (Scheme 1-4) through a cationic hydrido palladium complex $[HPd(CO)(PPh_3)_2]^+(TsO^-)$ which has been successfully isolated and identified. The formation of Pd-H species was also confirmed by ^1H NMR characterization. The results of ^{31}P NMR analyses also supported the formation of Pd-alkyl complexes of the type $[(n\text{-Styrene})Pd(CO)(PPh_3)_2]^+(TsO)^-$ and $[(iso\text{-Styrene})Pd(CO)(PPh_3)_2]^+(TsO)^-$ which were essential intermediates following the hydride mechanism. Moreover, the authors found drastic increase of TOF under 0.34 MPa hydrogen,[118] also indicating the Pd-H mechanism.



L = PPh_3, H_2O, CO or styrene

Scheme 1-4. Proposed mechanism for hydroesterification of styrene using $Pd(OAc)_2$/$4PPh_3$/10TsOH catalyst system in methanol[117]

Seayad et al. have also carried out a detailed study on the kinetics and mechanism of carbonylation of *p*-IBPE using an effective $PdCl_2(PPh_3)_2$/TsOH/LiCl catalyst system.[119, 120] The authors proposed a mechanism in which an anionic Pd^0 complex $[Pd^0(PPh^3)^2Cl]^-$ was postulated to act as the active intermediate that initiates the catalytic cycles (Scheme 1-5). As shown in Scheme 1-5, in the presence of TsOH and LiCl, the active substrate involved in the main carbonylation is IBPCl which is formed from reductive elimination of initial IBPE to IBS, thereby oxidative addition of IBS to IBPCl. It is well known that the organic halide substrates are activated by their oxidative addition to a low-valent metal complex,[121] Pd^0 complex in the case of palladium.[122,123] The presence of weakly coordinating TsO^- favors the formation of Pd^0 from the Pd^{II} catalyst precursor through a water-gas shift reaction. Besides, the presence of halide anion Cl^- leads to the low ligated Pd^0 species in the form of an anionic Pd species as $[Pd^0(PPh^3)^2Cl]^-$.[124, 125]



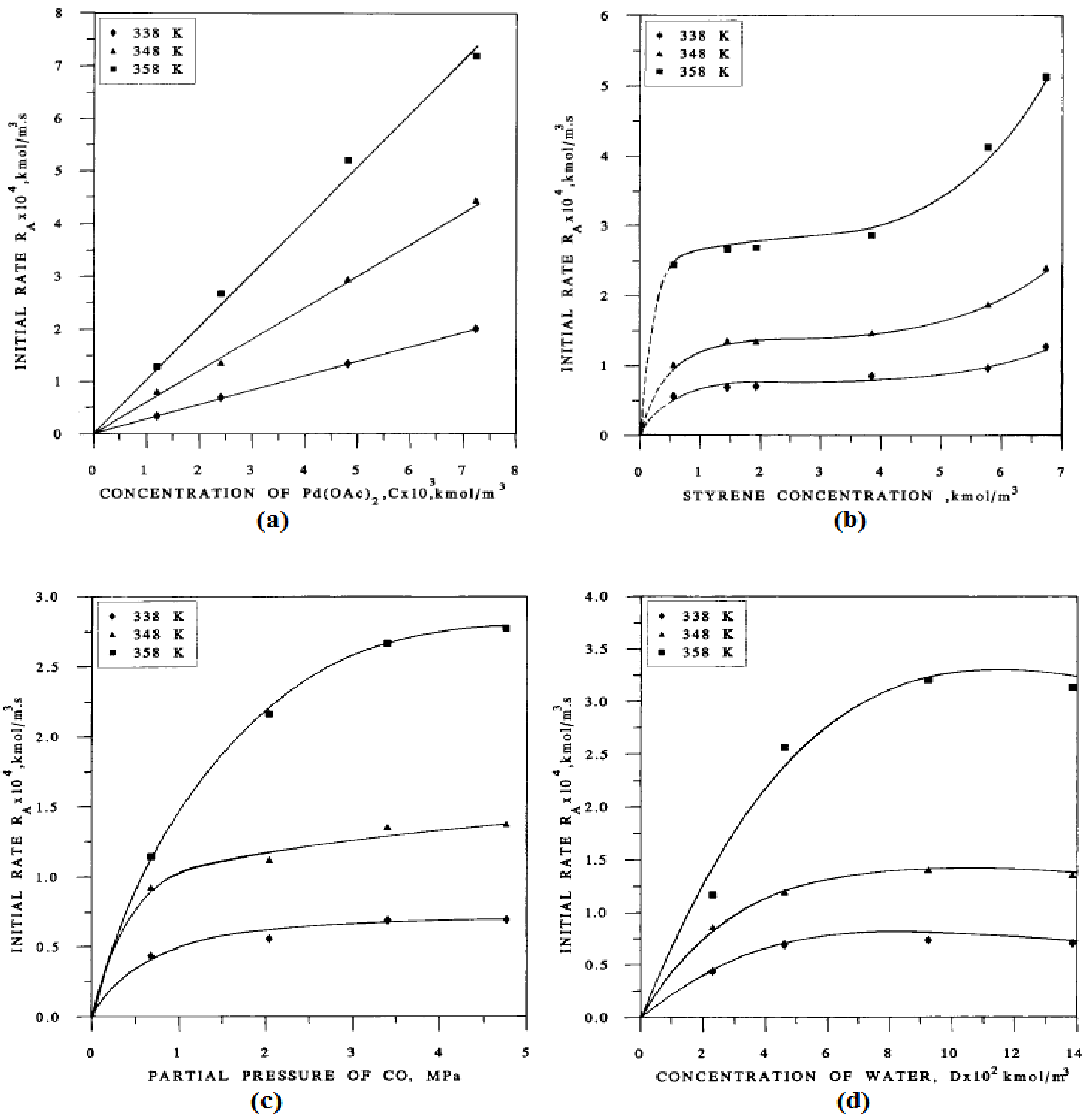
Scheme 1-5. Proposed mechanism for carbonylation of IBPE using $PdCl_2(PPh_3)_2$/TsOH/LiCl as catalyst system[120]

1-4 Kinetic Modeling for Homogeneous Carbonylation of Aryl Olefins and Alcohols

Kinetic modeling of catalytic reactions is one of the important aspects investigated in order to understand the rate behavior of catalytic reactions as well as reaction mechanism. Study on intrinsic reaction kinetics and development of rate equations are most essential for optimal reactor design.[126] Since homogeneous catalysis provides highly effective routes for the synthesis of several fine chemicals and pharmaceuticals, development of kinetic models for homogeneously catalytic reactions is especially essential for their practical applications. Today, only limited information is available on the subject of kinetic modeling for homogenous catalysis.[1, 127-131] In this section, the procedure for carrying our kinetic modeling is presented through several specific examples.

In the kinetic modeling, the first step is to explore the reaction pathways and catalytic reaction mechanism. As presented in Section 1-3, the mechanism of the homogenous carbonylation reactions is generally complex since the catalytic cycle always consists of several stoichiometric reactions. In the presence of co-catalysts or promoters, more steps will be associated with the catalytic cycle making the mechanism more complicate. Consider the complexities, the kinetics of the catalytic reactions are often described by non-linear rate equations. These equations could be empirical developed from the experimental observations of effects of catalyst, substrate, CO pressure, etc. The rate equations could also be derived based on a proposed mechanism.

Chaudhari's group has carried out a number of studies on the kinetic modeling of catalytic reactions. In 1998, the group reported their kinetic study for methoxycarbonylation of styrene using a $Pd(OAc)_2/PPh_3/TsOH$ catalyst system.[132] A series of experiments were carried out to investigate the effects of catalyst, styrene, water, partial pressure of CO and temperature on the initial rate (Figure 1-6).



(a) (b)

(c) (d)

Fig. 1-6. Effects of catalyst, styrene, water concentration on the initial rate of reaction[132]

Based on the results, the authors proposed a non-linear overall rate equation involving all the reaction parameters (Eq. 1-3).

$$R_A = \frac{k_1 P_{co}(1+k_B B)^2 CD}{(1+k_{CO}P_{co})(1+k_D D)^2} \qquad \text{Eq. 1-3}$$

Where R_A is the initial reaction rate, kmol/m^3/s; B, the concentration of styrene, kmol/m^3, C, the concentration of catalyst, kmol/m^3; D, the concentration of water, kmol/m^3; k_1, a reaction rate constant, (m^3/kmol)^2/s; k_{co}, k_B, k_D, the respective equilibrium constants. By solving the rate equation with the experimental data, the kinetic constants at different temperature were evaluated. Besides, the activation energy was also calculated from the Arrhenius plots for temperature-dependent rate constants. The error between the predicted and observed rates was less than 8% indicating goodness of fit. The satisfactory match of predicted values with experimental data also confirmed the empirical rate equation.

Several years later, Chaudhari's group reported extensive kinetic modeling of carbonylation of *p*-IBPE using a homogeneous $PdCl_2(PPh_3)_2$/TsOH/LiCl catalyst system.[121] They also investigated the effects of all reaction parameters on the average rate of carbonylation. Here, the average rate was taken instead of initial rate for further kinetic determination. Because the reaction was found to involve multiple steps, initial rate might not precisely reflect the reaction kinetics. The results of these effects are shown in Figure 1-7. Then, the average rate equation was proposed based on the observed trends (Equation 1-7).

They also proposed a mechanism for the whole catalytic reaction which has been demonstrated in Section 1-3. For kinetic modeling, the whole reactions were simplified to three steps (Eq 1-4, 1-5 and 1-6) which can interpret the kinetics of the various reactions.

$$\underset{\text{B}}{\text{IBPE}} + H^+ \xrightarrow{k_1} \underset{\text{D}}{\text{IBS}} + H_3O^+ \qquad \text{Eq. 1-4}$$

$$\underset{\text{D}}{\text{IBS}} + H^+ + Cl^- \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{\text{E}}{\text{IBPCl}} \qquad \text{Eq. 1-5}$$

$$\mathrm{IBPCl} + \mathrm{CO} + \mathrm{H_2O} \xrightarrow[k_3]{\mathrm{PdCl_2(PPh_3)_2}\ (\mathrm{C})} \underset{P_1 + P_2 = P}{[\mathrm{IBN} + \text{3-IPPA}]} + \mathrm{H^+} + \mathrm{Cl^-} \qquad \text{Eq. 1-6}$$

$$r_A = \frac{k_3[E][H_2O]AC^m}{1+K[E]} \qquad \text{Eq.1-7}$$

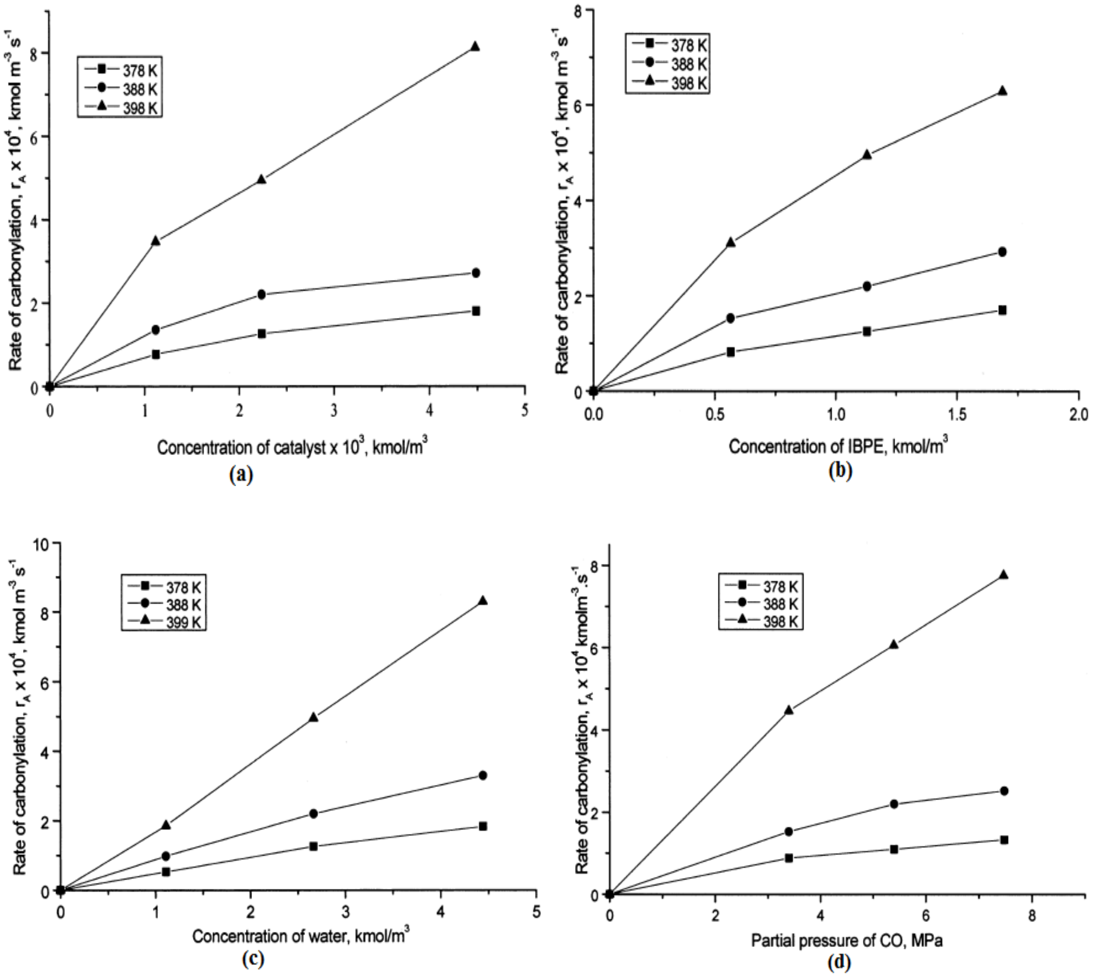


Fig. 1-7. Effects of catalyst, IBPE, water concentration, and partial pressure of CO[120]

The rate equations for substrate IBPE (B), intermediate substrate IBS (D), active substrate IBPCl (E), product IBN + 3-IPPA (P) were derived based on the reaction steps and the empirical rate equation for the main carbonylation reaction. The rate equations were then solved by a fourth-order Runge-Kutta method with given guess values of the rate constants and initial conditions. An optimization program using Marquart's method was developed to optimize the rate constants for different temperature by minimizing the deviations between the simulations and experimental data.

1-5 Scope and Objectives

It is well-known from the literature reviews that transition metal catalyzed carbonylation of olefins and alcohols are industrially important reactions which provide greener and more efficient routes for the synthesis of carboxylic acids or esters. The study on these catalytic reactions has gained considerable attention. The challenge is in evolving commercially attractive catalyst systems which can achieve high activity as well as selectivity under mild operating conditions. Also, to develop heterogeneous catalysts to approach convenient catalyst-product separation is another important aspect. Besides, kinetic study is necessary to understand the reaction mechanism and for further optimal design of reactor. In this context, the objectives of this work are as follows

- Investigation of different Pd catalyst systems for hydrocarboxylation of styrene and derivatives to identify the best performing catalyst system.
- Detailed kinetic modeling for hydrocarboxylation of styrene and derivatives using the best performing catalyst system including the following steps.
    1) Investigation for the effects of different reaction parameter such as catalyst loading, substrate concentration, water concentration, partial pressure of CO, etc.
    2) Proposal of reaction mechanism based on the parametric study.
    3) Development and calculation of rate equations.
    4) Optimization of the rate constants to obtain good match of simulated results with experimental data.

References

1. G. W. Parshall, *Homogeneous Catalysis*, Wiley-Interscience, New York (1980).
2. B. Cornills, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds,* Weinheim: Wiley-VCH, vol 1, 2 and 3 (2002).
3. K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, Weinheim [Cambridge]: Wiley-VCH (2003).
4. K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, Weinheim [Cambridge]: Wiley-VCH (2003) p. 167.
5. K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, Weinheim [Cambridge]: Wiley-VCH (2003) p. 395-397.
6. J. Scheirs and T. E. Long (Eds.), *Modern Polyesters: Chemistry and Technology of Polyesters and Copolyesters*, John Wiley & Sons, Ltd (2003).
7. E.F. Lutz, *J. Chem. Educ*., 63 (1986) 202.
8. W. A. Knowles, *Acc. Chem. Res*., 16 (1983) 106.
9. BASF AG, *Hydrocarbon Process*, 11 (1977) 135, and 172.
10. T.H. Johnson, (Shell Oil Co.), US 4584411 (1985).
11. V. V. Ludecke, *Encylcopedia of Chemical Processing and Design*, J. J. Mcketta and W. A. Cunningham (Eds.), Maedetl and Decker, (1976) p.146.
12. D. Astruc, *Organometallic Chemistry and Catalysis*, Springer-Verlag, Berlin Heidelberg (2007) p.433.
13. B. Cornils. *Org. Proc. Res. Dev.* **2** (1998), p. 121.
14. K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, Weinheim [Cambridge]: Wiley-VCH (2003) p.177-179.
15. D. J. Watson, *Catalysis of Organic Reactions*, E. F. Herkes, H. Heinemann (Eds.), Marcell Decker Inc. (1998) p. 369.
16. R. Ugo, T. Renato, M. M. Marcello, R. Plerluigi, *Ind. Eng. Chem. Prod. Res. Dev.*, 19 (1980) 396.
17. F. Basolo and R. L. Burwell (Eds.), *Catalysi, Progress in Research*, Plenum Press, 1973.
18. P. L. Mills, R. V. Chaudhari, *Catal. Today*, 37 (1997) 367.
19. *Chem. Week*, 71 (Nov. 20, 1974); *Ind. Res.*, 23 (Oct. 1974).
20. H. M. Colquhoun, D. J. Thompson, M. V. Twigg, *Carbonylation-Direct Synthesis of Carbonyl Compounds*, Plenum Press New York (1991).
21. J. Falbe (Ed.), *New Synthesis with Carbon Monoxide*, Springer-Verlag, Berlin (1980).
22. S. Warren, *Chemistry of the Carbonyl Group*, Wiley, London (1974).
23. O. roelen (to Rührchemie AG), German Patent No. 849548 (1938).
24. W. A. Herrmann, *J. Organomet. Chem.*, 383 (1990) 21.
25. W. Reppe (IG Farbers) German Patent No. 855110 (1939).
26. C. W. Bird, *Chem. Rev.*, 62 (1962) 283.
27. J. A. Osborn, J. F. Young, and G. Wilkinson, *J. Chem. Soc., Chem. Commun.*, 17 (1965).
28. R. F. Heck, *Palladium Reagents in Organic Synthesis*, Academic Press, New York (1985).
29. J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer-Verlag, Berlin

(1980).

30. H. Alper and H. des Abbayes, *J. Organomet. Chem.*, 134 (1977) C11.
31. L. Cassar and M. Foà, *J. Organomet. Chem.*, 134 (1977) C15.
32. V. H. Agreda, D. M. Pond, J. R. Séller, *CHEMTCH*, (1992) 172.
33. H. Hohenschutz, D. Fanz, H. Bulow, G. Dinkhauser (BASF AG), DE 2133349 (1973).
34. B. Blumenberg, *Nahr. Chem. Tech. Lab.*, (1984) 480.
35. L. Casssar, *Chem. Ind.,* 67 (1985) 256.
36. G. W. Parshall, W. A. Nugent, *CHEMTCH*, (1988) 314.
37. V. Elango, M. A. Murphy, G. N. Mott, E. G. Zey, B. L. Smith, G. L. Moss, EP 400892 (1990).
38. R. Ugo, T. Renato, M. M. Marcello, R. Plerluigi, *Ind. Eng. Chem. Prod. Res. Dev.*, 19 (1980) 396.
39. R. H. Schwaar, Methacrylic acid and esters, Report No. 11D, SRI International (1994).
40. J. E. Hallgren, R. O. Mathews, *J. Organomet. Chem.*, 175 (1979) 135.
41. W. Bertleff, *Ullmann's Encycl. Ind. Chem.*, 5th Ed., VCH, Weinheim (1986).
42. B.R. Sarkar and R.V. Chaudhari, *Catalysis Surveys from Asia*, 9 (2005) 193.
43. D. R. Levering and A. F. Glasebrook, *J. Org. Chem.*, 23 (1958) 1836.
44. J. E. Germain, *Catalytic Conversions of Hydrocarbons*, Academic Press, New York (1969) 278.
45. G. P. Chiusoli and S. Merzoni, *Chimica E L'Industria*, 51 (1969) 612.
46. C. W. Bird, R. C. Cookson, J. Hudec and U. Williams, *J. Chem, Soc.*, 94 (1968) 6927.
47. B. Fell and J. M. Tetteroo, *Angew. Chem.*, 77 (1965) 813.
48. G. P. Chiusoli and G. Cometti, *J. Chem. Soc. Chem. Comm.*, 18 (1972) 1015.
49. G. P. Chiusoli, G. Commetti, and S. Merzoni, *Org. Chem. Syn.*, 1 (1972) 439.
50. G. P. Chiusoli, *Acc. Chem. Res.*, 6 (1973) 422.
51. W. Reppe, H. Kroper, (BASF) DE 862748, DE 863194 (1952).
52. K. Weissermel, H. J. Arpe, *Industrial Organic Chemistry*, Weinheim [Cambridge]: Wiley-VCH (2003) p.141-142
53. Kunichika, S., Sakakibara, Y., Okamoto, T., and Takagi, K., *Bull. Inst. Chem. Res., Kyoto Univ.*, 49 (1971) 122.
54. N. Rizkalla, US 4540811 (1985).
55. F. Loppert, A. Hohn, M. Schafer, L. Hupfer, (BASF) US 5705683 (1998).
56. P. Hofmann, K. Kosswing and W. Schaefer, *Ind. Eng. Chem. Prod. Res. Dev.*, 19 (1980) 330.
57. R. Eroli, DAS 1092015 (1956), Montecatini.
58. J. Falbe, *Carbon Monoxide in Organic Synthesis*, Springer-Verlag (1970).
59. J. H. Craddock, A. Hershman, F. E. Paulik, J. F. Roth, US 3579551 (1971).
60. J. H. Craddock, A. Hershman, F. E. Paulik, J. F. Roth, US 3579552 (1971).
61. D. E. Morris, G. V. Johnson, *Sympos. Rh. Homogen. Catal.*, Veszprem, Hungary (1978).
62. M. Kilner, N. J. Winter, *J. Mol. Catal. A: Chem.*, 112 (1996) 327.
63. M. Schafer, A. Hohn, F. Lippert, (BASF) US 5866716 (1999).
64. A. J. Pardey, J. D. Suárez, G. Gastón, M. C. Ortega, C. Longo, and S. A. Moya,

Catal. Lett., 126 (2008) 112.

65. K. P. A. Senaratne, K. C. Lilje, (Albemarle Corp.) US 5322633 (1994).
66. E. L. Jenner and R. V. Lindsey, jr., (Du Pont) US 2876254 (1959).
67. K. Bittler, N. V. Kutepow, D. Neubauer, and H. Reis, *Angew. Chem. Internal. Edit.*, 7 (1968) 329.
68. N. V. Kutepow, K. Bittler, and d. Neubauer, (BASF) German 1221224 (1963); German 1227023 and 1229089, both patents are supplements to German Pat. 1221224, BASF.
69. J. Tsuji, M. Morikawa, and J. Kiji, *Tetrahedron Letters*, 1963, 1437.
70. J. Tsuji, M. Morikawa, and J. Kiji, *Tetrahedron Letters*, 1963, 1811.
71. J. Tsuji, J. Kiji, S. Imamura, and M. Morikawa, *J. Amer. Chem. Soc.*, 86 (1964) 4350.
72. J. Tsuji, S. Imamura, and J. Kiji, *J. Amer. Chem. Soc.*, 86 (1964) 4491.
73. D. M. Fenton, *J. Org. Chem.*, 38 (1973) 3192.
74. H. Alper, J. B. Woell, B. Depeyroux, and D. J. H. Smith, *J. Chem. Soc. Chem. Commun.*, (1983) 1270.
75. B. Elali and H. Alper, *J. Mol. Catal.*, 77 (1992) 7.
76. B. Elali and H. Alper, *J. Mol. Catal.*, 80 (1993) 377.
77. Q. Xu, Y. Souma, J. Umezawa, M. Tanaka, and H. Naktani, *J. Org. Chem.*, 64 (1999) 6306.
78. J. S. Nicholson and S. S. Adams, (Boot) US 3385886 (1968).
79. N. Ruiz, I. del Río, J. L. Jiménez, C. Claver, J. Forniés-Cámer, C. C. J. Cardin, and S. Gladiali, *J. Mol. Catal. A: Chem*, 143 (1999) 171.
80. M. C. Bonnet, A. L. Monteiro, and I. Tkatchenko, *J. Mol. Catal. A: Chem*, 143 (1999) 131.
81. N. Brugat, A. Polo, A. Álvarez-Larena, J. F. Piniella, and J. Real, *Inorg. Chem.*, 38 (1999) 4829.
82. A. Seayad, A. A. Kelkar, L. Toniolo, and R. V. Chaudhari, *J. Mol. Catal. A: Chem.*, 151 (2000) 47.
83. S. Jayasree, A. Seayad, and R. V. Chaudhari, *Org. Lett.*, 2 (2000) 203.
84. I. del Río, N. Ruiz, C. Claver, L. A. van der Veen, and P. W. N. M. van Leeuwen, *J. Mol. Catal. A: Chem.*, 161 (2000) 39.
85. S. Jayasree, A. Seayad and R. V. Chaudhari, *Chem. Commun.*, (2000) 1239.
86. Y. Y. Li and C. G. Xia, *Appl. Catal. A*, 210 (2001) 257
87. K. Mukhopadhyay, B. R. Sarkar and R. V. Chaudhari, *J. Am. Chem. Soc.*, 124 (2002) 9692.
88. O. V. Gusev, A. M. Kalsin, P. V. Petrovskii, K. A. Lyssenko, Y. F. Oprunenko, C. Bianchini, A. Meli, and W. Oberhauser, *Organometallic*, 22 (2003) 913.
89. F. W. Li, L. W. Xu and C. G. Xia, *Appl. Catal. A*, 253 (2003) 509.
90. Y. Kawashima, K. Okano, K. Nozaki and T. Hiyama, *Bull. Chem. Soc. Jpn.*, 77 (2004) 347.
91. A. L. Lapidus, O. L. Eliseev, N. N. Stepin and T. N. Bondarenkon, *Russ. Chem. Bull., Int. Ed.*, 53 (2004) 2564.
92. G. Rangits and L. Kollár, *J. Mol. Catal. A*, 242 (2005) 156.
93. H. Ooka, T. Inoue, S. Itsuno and M. Tanaka, *Chem. Commun.*, (2005) 1173.
94. B. R. Sarkar, R. V. Chaudhari, *J. Catal.*, 242 (2006) 231.

95. A. Ionescu, G. Laurenczy and O. F. Wendt, *Dalton Trans.*, (2006) 3934.
96. E. Guiu, M. Caporali, B. Muñoz, C. Müller, M. Lutz, A. L. Spek, C. Claver, and P. W. M. van Leeuwen, *Organometallic*, 25 (2006) 3102.
97. P. A. Aguirre, C. A. Lagos, S. A. Moya, C. Zúñiga, C. Vera-Oyarce, E. Sola, G. Peris, and J. C. Bayón, *Dalton Trans.*, (2007) 5419.
98. B. K. Muñoz, C. Godard, A. Marinetti, A. Ruiz, J. Benet-Buchholz and C. Claver, *Dalton Trans.*, (2007) 5524.
99. B. R. Sarkar, K. Mukhopadhyay and R. V. Chaudhari, *Catal. Commun.*, 8 (2007) 1386.
100. J. J. R. Frew, M. L. Clarke, U. Mayer, H. V. Rensburg and R. P. Tooze, *Dalton Trans.*, (2008) 1976.
101. C. Zúñiga, S. A. Moya and P. Aguirre, *Catal. Lett.*, 130 (2009) 373.
102. B. K. Muñoz, A. Marinetti, A. Ruiz, S. Castillón and C. Claver, *Inorg. Chem. Commun.*, 8 (2005) 1113.
103. D. S. Shephard, W. Zhou, T. Maschmeyer, J. M. Matters, L. Caroline, C. L. Roper, S. Parsons, B. F. G. Johnson, and M. J. Duer, *Angew. Chem., Int. Ed.*, 37 (1998) 2719.
104. A. Seayad, S. Jayasree and R. V. Chaudhari, *Catal. Lett.*, 61 (1999) 99.
105. A. Seayad, S. Jayasree and R. V. Chaudhari, *J. Mol. Catal. A*, 172 (2001) 151.
106. S. Jayasree, A. Seayad and R. V. Chaudhari, *Chem. Commun.*, (1999) 1067.
107. E. D. Park, K. H. Lee and J. S. Lee, *Catalysis Today*, 63 (2000) 147.
108. A. Lapidus, O. Eliseev, T. Bondarenko and N. Stepin, *J. Mol. Catal. A*, 252 (2006) 245
109. R. F. Heck, *J. Am. Chem. Soc.*, 94 (1972) 2712.
110. J. Knifton, *J. Org. Chem.*, 41 (1976) 2885.
111. G. Cavinato and L. Toniolo, *J. Organomet, Chem.*, 398 (1990) 187.
112. D. Milstein, *Acc. Chem. Res.*, 21 (1988) 428.
113. M. Kawana, S. Nakamura, E. Watanabe and H. Urata, *J. Organomet. Chem.*, 542 (1997) 185.
114. I. del Río, C. Claver and P. van Leeuwen, *Eur. J. Inorg. Chem.*, (2001) 2719.
115. (a) Yu. G. Noskov, M. I. Terekhova and E. S. Petrov, *Kineticka. Kataliz.*, 30 (1989) 234. (b) Yu. G. Noskov, M. I. Terekhova and E. S. Petrov, *Kineticka. Kataliz.*, 32 (1991) 331. (c) Yu. G. Noskov, M. I. Terekhova and E. S. Petrov, *Kinetics and Katalysis*, 34 (1993) 898. (d) Yu. G. Noskov and E. S. Petrov, *Kinetics and Katalysis*, 35 (1994) 672. (e) Yu. G. Noskov and E. S. Petrov, *Kinetics and Katalysis*, 38 (1997) 520. (f) Yu. G. Noskov and E. S. Petrov, *Kinetics and Katalysis*, 34 (1993) 902.
116. G. Vespui, I. I. Moiseev, A. R. Sheldon, *J. Organomet. Chem.*, 586 (1999) 196.
117. A. Seayad, S. Jayasree, K. Damodaran, L. Toniolo and R. V. Chaudhari, *J. Organomet. Chem.*, 601 (2000) 100.
118. A. Seayad, A. A. Kelkar, L. Toniolo and R. V. Chaudhari, *J. Mol. Catal. A*, 151 (2000) 47.
119. A. Seayad, S. Jayasree and R. V. Chaudhari, *Catal. Lett.*, 61 (1999) 99.
120. A. Seayad, J. Seayad, P. L. Mills and R. V. Chaudhari, *Ind. Eng. Chem. Res.*, 42 (2003) 2496.
121. J. P. Collman and L. S. Hgedus, *Principles and Applications of Organotransition*

Metal Chemistry, Kelly, A., Ed., University Science Books: CA (1980).

122. K. S. Y. Lau, P. K. Wong and J. K. Stille, *J. Am. Chem. Soc.*, 98 (1976) 5832.
123. J. K. Stille and K. S. Y. Lau, *Acc. Chem. Res.*, 10 (1977) 434.
124. E. I. Negishi, T. Takahashi and K. Akiyoshi, *J. Chem. Soc., Chem. Commun.*, (1986) 1338.
125. C. Amatore, M. Azzabi and A. Jutand, *J. Am. Chem. Soc.*, 113 (1991) 8375.
126. R. V. Chaudhari, A. Seayad, S. Jayasree, *Catalysis Today*, 66 (2001) 371.
127. B. R. James, *Homogeneous Hydrogenation*, Wiley, NY (1973).
128. J. M. Smith, *Chemical Engineering Kinetics*, McGraw-Hill, NY (1981).
129. E. Santacesaria, *Catal. Today*, 52 (1999) 113.
130. J. K. Kochi, *Organometallic Mechanisms and Catalysis*, Academic Press, NY (1978).
131. C. Master, *Homogenous Transition-Metal Catalysis*, Chapman & Hall, London (1981).
132. A. Seayad, A. A. Kelkar and R. V. Chaudhari, *Ind. Eng. Chem. Res.*, 37 (1998) 2180.

CHAPTER 2

HYDROCARBOXYLATION OF STYRENE USING PALLADIUM COMPLEX CATALYST: ACTIVITY AND SELECTIVITY STUDIES

2-1 Introduction

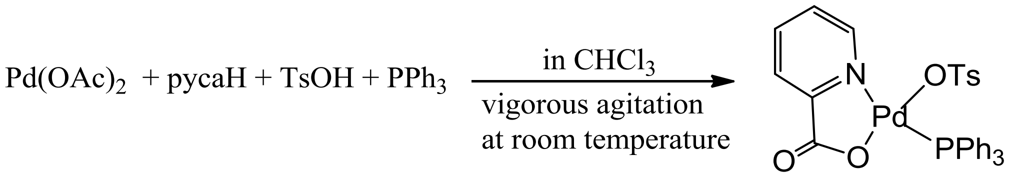
The review of literature presented in Chapter 1 indicates that Pd catalysts are among the best candidates for hydrocarboxylation of olefins considering both overall efficiency and economic utilization. In recent years, a number of Pd complex catalysts with different promoters and ligands have been reported to show high activity as well as selectivity for carbonylation of styrene and derivatives, and aryl alcohols for the synthesis of 2-arylpropionic acids/esters under mild reaction conditions. Some of these catalyst systems show high regioselectivity (> 90%) to the branched isomers under low partial pressures of carbon monoxide (2.5-5.0MPa) and moderate temperatures (348-388K).[1-9] Ooka et al. [10] even reported that $Pd(OAc)_2$ and $Pd_2(dba)_3$ catalysts as precursors with polymeric CH_3SO_3H as an acidic promoter in DTBPMB solvent can perform at room temperature and 0.6 MPa partial pressure of carbon monoxide yielding 86-89% of the branched phenyl propionate product. Del R´ıo et al. [3] reported a $PdCl_2(PhCN)_2$/ PPh_2(o-Tol)/ $H_2C_2O_4$ catalyst in DME solvent giving 100% selectivity to the branched product in carbonylation of styrene. Among the various catalyst systems, palladium acetate and palladium chloride are the most common commercial homogeneous catalyst precursors which also show desirable activity and selectivity for carbonylation reactions in the presence of appropriate ligands and promoters. A lab synthesized homogeneous catalyst, Pd(pyca)(PPh_3)(OTs), has been reported [4] to give high activity (TOF=800 ~ 2600 h^{-1}) as well as regio-selectivity (>99%) to 2-arylpropionic acids with TsOH and LiCl as promoters. It is also demonstrated that this Pd(pyca)(PPh_3)(OTs) complex is an ideal homogeneous catalytic precursor for synthesis of a heterogeneous catalyst for carbonylation of aryl olefins and alcohols, which facilitates catalyst-product separation and hence has a broader potential in many applications.[11]

In this chapter, experimental results on the catalytic performance of three different homogeneous catalysts, $Pd(OAc)_2$, $PdCl_2$, and Pd(pyca)(PPh_3)(OTs) are discussed with respect to their activity and regio-selectivity in hydrocarboxylation of styrene. From the previous studies, it was observed that the roles of these catalyst precursors, ligands and promoters in activity and selectivity of hydrocarboxylation reactions are not well understood. Considering the importance of this class of reactions in the synthesis of pharmaceutically active products like Ibuprofen® and Naproxen®, it is thought important to undertake a systematic study on the performance of these catalysts. Such a study will also be valuable in understanding the catalytic reaction mechanism in carbonylation reactions and propose catalytic cycle consistent with the effects of promoters and catalyst precursors. The details of experimental methods used and results of catalyst performance are discussed in the following sections.

2-2 Experimental

2-2-1 Materials

The catalyst precursors, $PdCl_2$, $Pd(OAc)_2$ and $PdCl_2(PPh_3)_3$ were ordered from Alfa Aesar. The complex catalyst, Pd(pyca)(PPh_3)(OTs) was synthesized following a route[12] shown in Scheme 2-1.



Pd(pyca)(PPh$_3$)(OTs)

Scheme 2-1. Synthesis of Pd(pyca)(PPh$_3$)(OTs) complex catalyst

In synthesis of Pd(pyca)(PPh$_3$)(OTs), desired amount of Pd(OAc)$_2$, pyridine-2-carboxylic acid, TsOH and PPh$_3$ in the molar ratio of 1:1:2:2 were added to the least amount of chloroform. The solution was vigorously stirred for a few minutes until all the solid chemicals were completely dissolved and the solution turned yellow. Then, the product was isolated as a yellow oily mass by addition of sufficient *n*-hexane. The product was washed several times with *n*-hexane and then by diethyl ether and kept under vacuum in a desiccator to obtain a yellow fluffy solid, which is the Pd(pyca)(PPh$_3$)(OTs) complex. For further characterization, the synthesized catalyst was purified through re-precipitation from chloroform several times.

The other homogeneous palladium catalysts, dppbPd(II), dppfPd(II)acetone, dppp Pd(II)acetone, Pd(BINAP)Br$_2$, dcppPdCl$_2$, (XANTPHOS)PdCl$_2$ were supplied by Johnson Matthey Company.

2-2-2 Characterization of Pd(pyca)(PPh$_3$)(OTs) Catalyst

The synthesized Pd(pyca) complex was characterized by FT-IR, NMR(^{1}H,^{31}P) and elemental analyses. Figure 2-1 shows the FT-IR spectrum for the KBr sample pellet of Pd(pyca)(PPh$_3$)(OTs).

In the catalyst complex containing an anionic chelating N-O ligand, the coordination of pyca ligand was confirmed by the characteristic carbonyl absorption peak at 1668 cm^{-1} with a shift of 50 cm^{-1} as compared to the free ligand (1718 cm^{-1}). The IR spectrum also showed the $O=C-O^{-}_{s}$ stretching vibration at 1335 cm^{-1}, and Pd-N stretching vibration[13] at 569 cm^{-1}. The absorption peaks for C=N and C=C in the hetero-cyclic ring of the chelating ligand appeared at 1601 cm^{-1} and 1583 cm^{-1}, respectively. In addition, the absence of broad absorption peak of free carboxylic acid (-COOH) group in the free ligand at 3000 cm^{-1} indicated the loss of the proton due to the coordination of this group in the synthesized catalyst complex. Table 2-1 lists selected IR spectroscopic data of the absorption peaks of essential functional groups in Pd(pyca)(PPh$_3$)(OTs) complex.

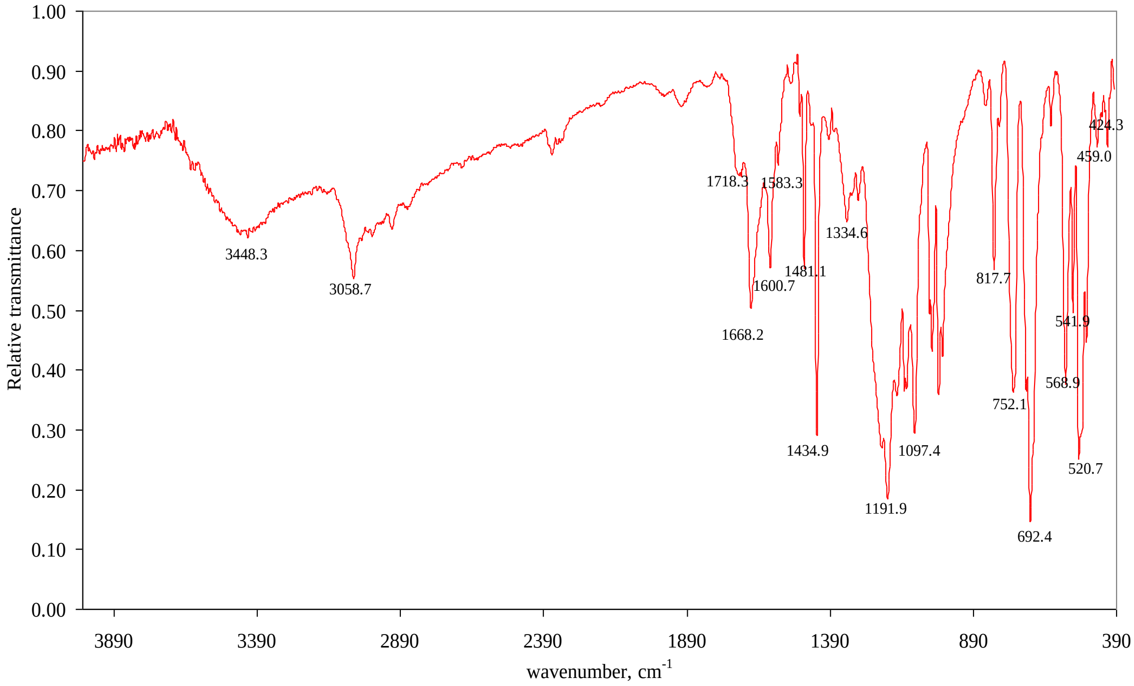


Fig. 2-1. FT-IR spectrum of Pd(pyca)(PPh$_3$)(OTs) complex

Table 2-1. IR spectroscopic data for Pd(pyca)(PPh$_3$)(OTs) complex

ν_{as} C=O cm^{-1}	ν_{s} O=C-O cm^{-1}	ν C=N cm^{-1}	ν C=C cm^{-1}	ν Pd-N cm^{-1}
1668	1335	1601	1583	569

^{1}H and ^{31}P NMR analysis was carried out in a Bruker DRX-400 NMR (400MHz) for the Pd(pyca)(PPh$_3$)(OTs) sample in chloroform-D. The NMR spectra are shown in Figure 2-2, and the analytical data are listed in Table 2-2. In the ^{1}H NMR spectrum, the aromatic protons corresponding to phenyl and pyridyl rings in the complex were observed between δ = 7 to 8 ppm. The tosyl CH$_3$ protons in TsO$^-$ ligand were shown at δ =2.28 ppm.

The PPh$_3$ coordinating ligand in the complex was confirmed by ^{31}P NMR analysis. In stead of a single signal, the ^{31}P NMR spectrum of Pd(pyca) complex showed two unequal signals. The strong signal was at δ =34.31 ppm, and the weak one was at δ =35.99 ppm. This analytical result might be due to the existence of *cis* (P *cis* N) and *trans* (P *trans* to N) isomers in the CDCl$_3$ liquid sample, which also indicated the coordination of PPh$_3$ to the metal center.

Dry solid sample of Pd(pyca)(PPh$_3$)(OTs) was sent to Columbia Analytical Service for elemental analysis of C, H, N, S in the complex. The analytical data were compared with the calculated data for the complex with molecular formula $C_{31}H_{26}NO_5PPdS$ (Table 2-3). The analytical results were found to be in satisfactory agreement with the calculated data for the formula of Pd(pyca)(PPh$_3$)(OTs) complex.

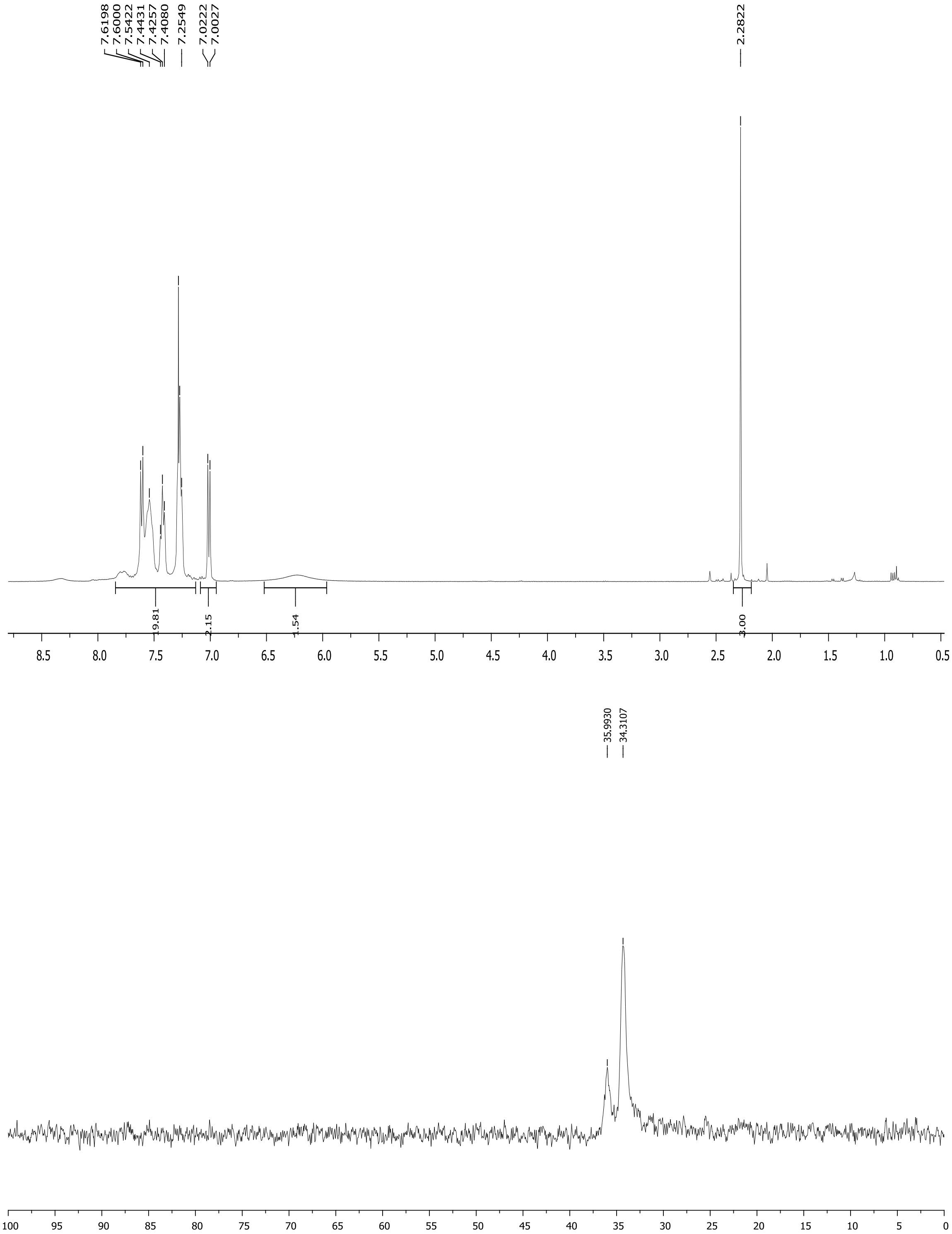


Fig. 2-2. ^{1}H and ^{31}P NMR spectra of Pd(pyca)(PPh$_3$)(OTs) complex

Table 2-2. ^1H and ^{31}P NMR data for Pd(pyca)(PPh_3)(OTs) complex*

NMR Type	^1H, $CDCl_3$ δ , ppm	^{31}P, $CDCl_3$ δ , ppm
Atom	2.28 s (tosyl CH_3, 3H); 7-8 (aromatic H, 23H)	34.31 s; 35.99 w

* s is strong, w is weak.

Table 2-3. Elemental analyses for Pd(pyca)(PPh_3)(OTs) complex

$C_{31}H_{26}NO_5PPdS$	Elemental content	C, wt%	H, wt%	N, wt%	S, wt%
	Theoretical	55.18	4.23	1.91	4.38
	Analytical	55.47	4.49	1.07	4.39

2-2-3 Hydrocarboxylation Experiments

The hydrocarboxylation experiments for catalyst performance tests were carried out in a 100 mL high pressure (up to 3000 psi), high temperature (573K) Parr autoclave reactor. The batch reactor was equipped with a heating arrangement, overhead stirrer, thermo well, pressure gauge as well as a pressure transducer, gas inlet, gas outlet, sampling valve and a rupture disc. The schematic of the 100 mL Parr reactor set-up is shown in Figure 2-3.

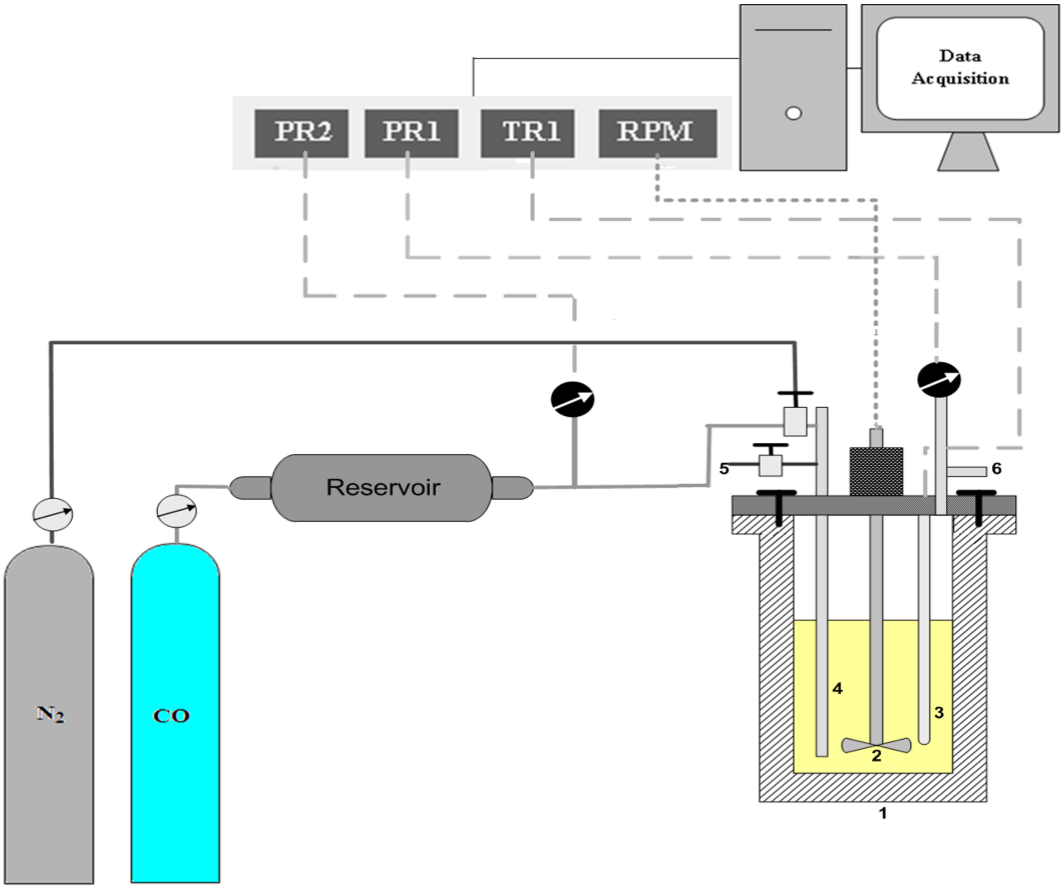


Fig. 2-3. Schematic of 100 mL Parr reactor set-up 1. Reactor; 2. stirrer shaft with impeller; 3. thermal well; 4. sampling and gas inlet tube; 5. sampling valve; 6. gas vent; PR1. reactor pressure indicator; TR1. reactor temperature indicator; PR2. reservoir pressure indicator.

In order to achieve easier and safer control of inlet gas and supply of CO as the reaction progressed, the autoclave was connected to a 150 mL CO gas reservoir. A constant pressure regulator was equipped between the autoclave and reservoir to control the required pressure inside the reactor. In these experiments, carbon monoxide was fed to reservoir from gas cylinder up to pressure such that even after the completion of reaction, the pressure in the reservoir was higher than that in the reactor. The real time data of temperature, reservoir pressure, reactor pressure and agitation speed were monitored and recorded by a Labview software. In a typical carbonylation reaction, the standard operation procedure was as follows:

1) Desired quantities of styrene, catalyst precursor, promoters were dissolved in MEK and charged into the autoclave, and the contents were flushed with N_2 followed by CO for 2 to 3 times.
2) Autoclave was heated to a desired temperature under very low stirring (50 rpm).
3) When the desired temperature was reached, the autoclave was pressurized with CO quickly to the required pressure. Then, the reaction was initiated by starting agitation up to 900 rpm.
4) During the reaction, CO was fed through a constant-pressure regulator from a reservoir vessel to maintain a constant desired pressure in the autoclave. The pressure drop in the reservoir was then monitored and recorded in the Labview. The pressure drop in reservoir gives the CO consumption as a function of time, while keeping the pressure in reactor constant.
5) Samples were withdrawn at different times and analyzed by GC (Column: DB-FFAP 30m×0.32mm×0.25µm) to determine the changes in concentrations of reactants and products.
6) These experimentally measured concentration-time profiles at constant CO pressures were used to evaluate the material balance and the activity as well as regio-selectivity for each catalytic system and experiment.

For the analysis of the liquid samples, the GC column was installed to an automatic Agilent GC analytical instrument, equipped with an autosampler. In order to set the appropriate analytical conditions, a mixture of styrene, 2-phenylpropionic acid and 3-

phenylpropionic acid was injected into the column for standardization and calibration of the system. The conditions set are shown in Table 2-4. The standard samples of solution of substrate and products in reaction solvent with different concentration were prepared and analyzed for calibration. Finally, the correlation between the peak area of each compound and its corresponding concentration was obtained for further quantitative analysis.

In catalyst performance tests for hydrocarboxylation of styrene, three Pd catalyst precursors, $Pd(OAc)_2$, $PdCl_2$, and synthesized $Pd(pyca)(PPh_3)(OTs)$ complex, were initially investigated for their performance (activity and regio-selectivity) with addition of different promoters. In addition, some Pd catalysts from Johnson Matthey Company were also investigated. Table 2-5 shows the standard reaction conditions for each hydrocarboxylation reaction.

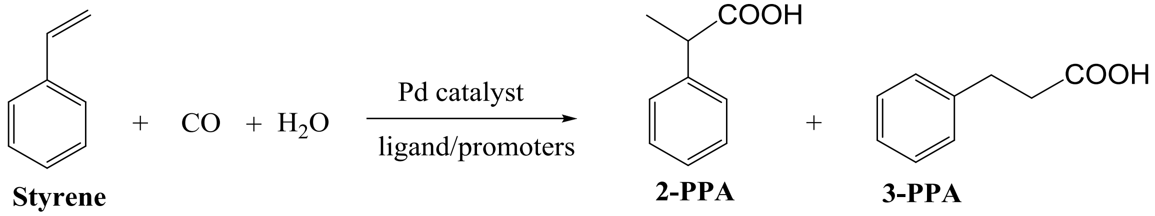
Table 2-4. Analytical conditions of DB-FFAP GC column for styrene, 2-PPA and 3-PPA

Injector (split) temperature	250 °C
Inlet pressure	9.1436 psi
Total inlet flow	105 ml/min
Septum purge flow	3 ml/min
Split ratio	50:1
Carrier gas (He) flow	2 ml/min
Initial oven temperature	40 °C
Ramp 1 condition	20 °C/min to 100 °C
Ramp 2 condition	30 °C/min to 200 °C
Ramp 3 condition	10 °C/min to 240 °C
Total run time	16.333 min

Table 2-5. Standard reaction conditions for hydrocarboxylation of styrene using different homogeneous Pd catalysts

Reaction parameter	Condition
Pd catalyst precursor	2.4 mol/m^3
Pd/PPh$_3$ (molar ratio)	1:4
Pd:TsOH:LiCl (molar ratio)	1:10:10
Styrene	30.5 mmol
Water	1.3 ml
Pco	6.0 MPa
Temperature	388 K
Solvent	MEK
Total volume	50 ml
Agitation speed	1000 rpm
Reaction time	3 h

The hydrocarboxylation reaction is shown in Scheme 2-2.



Scheme 2-2. Hydrocarboxylation of styrene

In order to evaluate the activity of each catalyst system, turnover number (TON) and turnover frequency (TOF) were defined and calculated as follows. The conversion, regio-selectivity and i/n ratio were also calculated. The real time for complete reaction with styrene conversion > 99 % was taken for TOF calculation. For catalytic systems with low activity which can not achieve complete styrene conversion in the reaction time, the total reaction time was used for the TOF calculation.

$$TON = \frac{Number\ of\ moles\ of\ styrene\ converted}{Number\ of\ moles\ of\ catalyst}, kmol/kmol$$

$$TOF, h^{-1} = \frac{Number\ of\ moles\ of\ styrene\ converted}{Number\ of\ moles\ of\ catalyst \times time}, kmol/(kmol \cdot h)$$

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

$$selectivity, \% = \frac{Number\ of\ moles\ of\ the\ product\ formed\ (kmol)}{Number\ of\ moles\ of\ styrene\ converted\ (kmol)} \times 100, \%$$

$$i/n\ ratio = \frac{Number\ of\ moles\ of\ the\ branched\ product\ formed}{Number\ of\ moles\ of\ the\ linear\ product\ formed}$$

2-3 Results and Discussion

In the catalyst performance tests, $Pd(OAc)_2$ and $PdCl_2$, and their complexes, $Pd(OAc)_2(PPh_3)_2$, $PdCl_2(PPh_3)_2$ were investigated for hydrocarboxylation of styrene as a first step. The results for $Pd(OAc)_2$ and $Pd(OAc)_2(PPh_3)_2$ as catalyst precursors are shown in Table 2-6. The reaction conditions for each catalytic reaction are presented in Table 2-5. Comparing catalyst systems 1 and 2, it was found that the catalytic activity (TOF from 20 h^{-1} to 246 h^{-1}) as well as regio-selectivity to the desired 2-phenylpropionic acid (selectivity to 2-PPA from 31% to 89%, and i/n ratio from 0.42 to 22.25) was significantly improved with the addition of lithium chloride as a promoter. When the concentration of LiCl was reduced to half (system 5) of that in system 2, both activity and selectivity were clearly decreased. These observations indicate the important role of LiCl in the rate limiting steps that govern the activity and regioselectivity. However, the results from system 12 without the acidic promoter TsOH, also showed negligible activity even in the presence of LiCl. The limited styrene consumed was almost totally converted to the branched isomer, 2-PPA. This observation is plausible due to the generation of active catalyst species was favored in the presence of acidic promoter under the reaction conditions.[14]

Table 2-6. Performance of catalytic systems using $Pd(OAc)_2$ or $Pd(OAc)_2(PPh_3)_2$ as a precursor

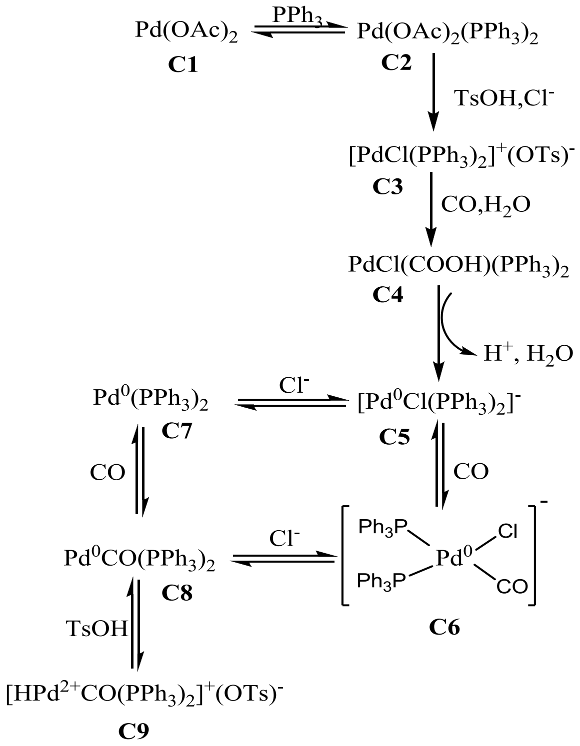
Item	Catalyst system	Conversion (%)	Selectivity			TON	TOF (h^{-1})
			2-PPA (%)	3-PPA (%)	i/n		
1	$Pd(OAc)_2/PPh_3/TsOH$	24.97	31	74	0.4	60.4	20.1
2	$Pd(OAc)_2/PPh_3/TsOH/LiCl$	99.80	89	4	22.2	246.4	246.4
3	$Pd(OAc)_2/PPh_3/TsOH/LiCl^a$	99.85	94	8	11.8	253.2	126.6
4	$Pd(OAc)_2/PPh_3/TsOH/LiCl^b$	80.20	71	14	5.1	197.6	65.9
5	$Pd(OAc)_2/PPh_3/TsOH/LiCl^c$	98.17	96	12	8.0	267.9	160.7
6	$Pd(OAc)_2(PPh_3)_2/TsOH/LiCl$	85.75	99	1	99.0	237.3	79.1
7	$Pd(OAc)_2$/Pyridine-2-carboxylic acid/$TsOH^d$	0.00	0	0	-	0.0	0.0
8	$Pd(OAc)_2$/Pyridine-2-carboxylic acid/$PPh_3/TsOH^d$	21.78	37	82	0.4	55.8	18.6
9	$Pd(OAc)_2/PPh_3/TsOH/NaCl^e$	99.20	83	19	4.4	242.7	161.8
10	$Pd(OAc)_2/PPh_3/TsOH/Na(OAc)^f$	3.67	2.1	4.4	0.5	-	-
11	$Pd(OAc)_2/PPh_3/TsOH/Li(OAc)^g$	10.01	0.1	1.4	0.1	-	-
12	$Pd(OAc)_2/PPh_3/LiCl$	1.26	82.7	0.0	-	-	-

[a] molar ratio of Pd to TsOH and LiCl equaled to 1:5:5; [b] molar ratio of Pd to TsOH and LiCl equaled to 1:2:2; [c] molar ratio of Pd to TsOH and LiCl equaled to 1:10:5; [d] pyridine-2-carbonylic acid was used instead of PPh_3; [e] NaCl was used as promoter instead of LiCl; [f] Na(OAc) was used as promoter instead of LiCl; [g] Li(OAc) was used as promoter instead of LiCl.

The results also suggest that the regio-selectivity-determining step (olefin activation) is significantly favored by LiCl rather than TsOH. When the concentrations of TsOH and LiCl were decreased simultaneously in the same ratio as shown in catalytic system 3 and 4, TOF as well as selectivity steadily decreased. In another words, both TsOH and LiCl played important roles in the formation of active species for generation of 2-phenylpionic acid (2-PPA) as an end product.

In system 7 and 8, pyridine-2-carboxylic acid (pycaH) was used as a free ligand. There was no reaction in the absence of triphenylphosphine (system 7). System 8 with the addition of triphenylphosphine gave comparable TOF as well as selectivity to that obtained in system 1. Both the results showed that the pycaH cannot facilitate the formation of an effective catalyst complex from $Pd(OAc)_2$ for the hydrocarboxylation reaction. In order to understand the role of the LiCl, some other alkali promoters were investigated for the hydrocarboxylation reaction. Using NaCl as the alkali promoter, relatively good activity (TOF=162 h^{-1}) as well as regio-selectivity (83%) was obtained. But the performance was not as good as the catalytic system 2 with LiCl as a promoter. Using sodium acetate or lithium acetate as a promoter, the reactivity was not improved but even inhibited with a drastic decrease in the regio-selectivity. These observations indicated the influence of the promoters on reactivity was based on the halide ion.

Seayad et al. have proposed a mechanism of hydroesterification of styrene using $Pd(OAc)_2$ as a precursor and TsOH as a promoter in methanol solution.[14] They proposed a hydride mechanism based on previous work on the similar reactions[15, 16] and confirmed through successful isolation of a palladium hydridocarbonyl species. Several years later, a mechanism for carbonylation of 1-(4-Isobutylphenyl) ethanol (IBPE) using a homogeneous $PdCl_2(PPh_3)_2$/TsOH/LiCl catalyst system in MEK solution was also proposed.[17] An anionic Pd(0) species containing coordinated Cl^- was suggested as a likely active species in the catalytic cycle in the presence of TsOH and LiCl. According to some of the observations for hydrocarboxylation of styrene using $Pd(OAc)_2/PPh_3$/TsOH/LiCl as catalyst precursors, and the review for the information of similar reaction systems, the possible catalyst species formed in hydrocarboxylation reaction are shown in Scheme 2-3.

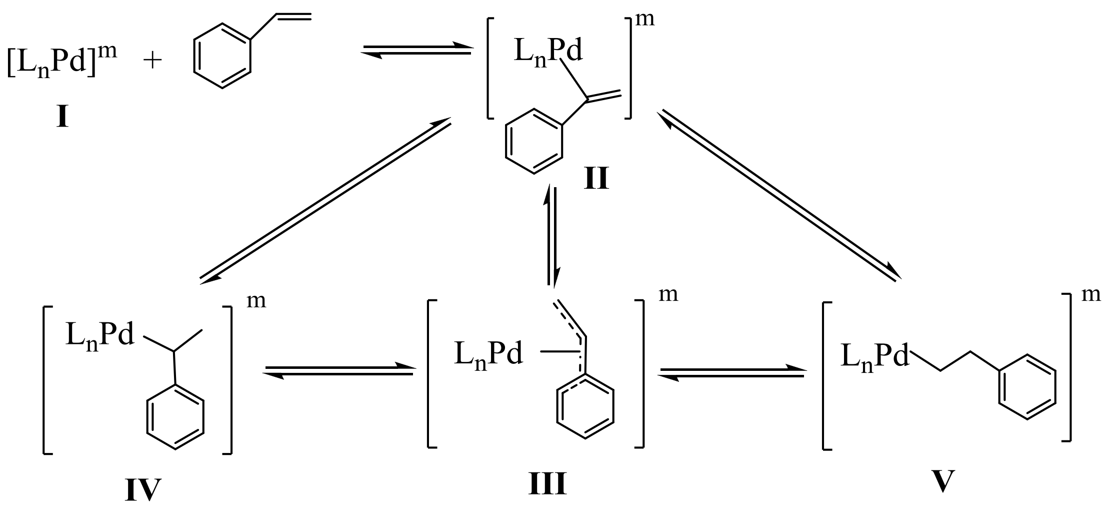


Scheme 2-3. Possible catalyst species in reaction system

When starting from $Pd(OAc)_2$, a $Pd(OAc)_2(PPh_3)_2$ (C2) complex could be formed *in situ.*[14] Then, the weak coordinated anionic ion OAc^- is replaced by much stronger OTs^- and Cl^- to form $[PdCl(PPh_3)_2]^+(OTs)^-$ (C3). The coordination of CO and water molecule to the palladium center followed by reductive elimination is likely to give an anionic species, $[Pd(0)Cl(PPh_3)_2]^-$ (C5), generated along with a palladium hydride species (C9). With further addition of CO, the species $[Cl(CO)Pd(0)(PPh_3)_2]^-$ (C6) is formed. This proposal for the active species could explain experimental observations on the effects of TsOH and LiCl on catalytic activity. The presence of TsOH and Cl^- from LiCl significantly improved the formation of the anionic active catalyst species. In absence of LiCl, a palladium hydride (C9) might be formed,[14] but the catalyst activity was ten times lower than that in presence of LiCl, further indicating that the reaction is not likely to go through the hydride intermediate species. Very low activity without TsOH indicates a unique role of the acidic promoter in the formation of active species. It is plausible that the formation of species C3 is a necessary step for the formation of C4 thereby the formation of active species C5.

The observation about the important effects of alkali halide promoter, especially the anionic halide ion, on the regio-selectivity of the catalyst system can be explained by the regioselectivity-determining step, which is proposed to be the transition from a π-olefin complex (II) to σ-alkyl complexes (IV or V) as shown in Scheme 2-4. After coordination of styrene to the active Pd(0) center, a relatively stable π-benzylic complex (III) is believed to be formed.[18,19] Complex III could be in equilibrium with IV and V. Because the active catalyst species C6 is ligated with electron withdrawing Cl which decreases the electron density around the palladium center, the formation of complex IV and finally the branched isomer product is favored. On the other hand, the much lower regio-selectivity observed for catalyst systems 10 and 11 using alkali acetate as a promoter also supports the proposed regioselectivity-determining step, since acetate ion has very weak electron withdrawing ability than Cl^-.

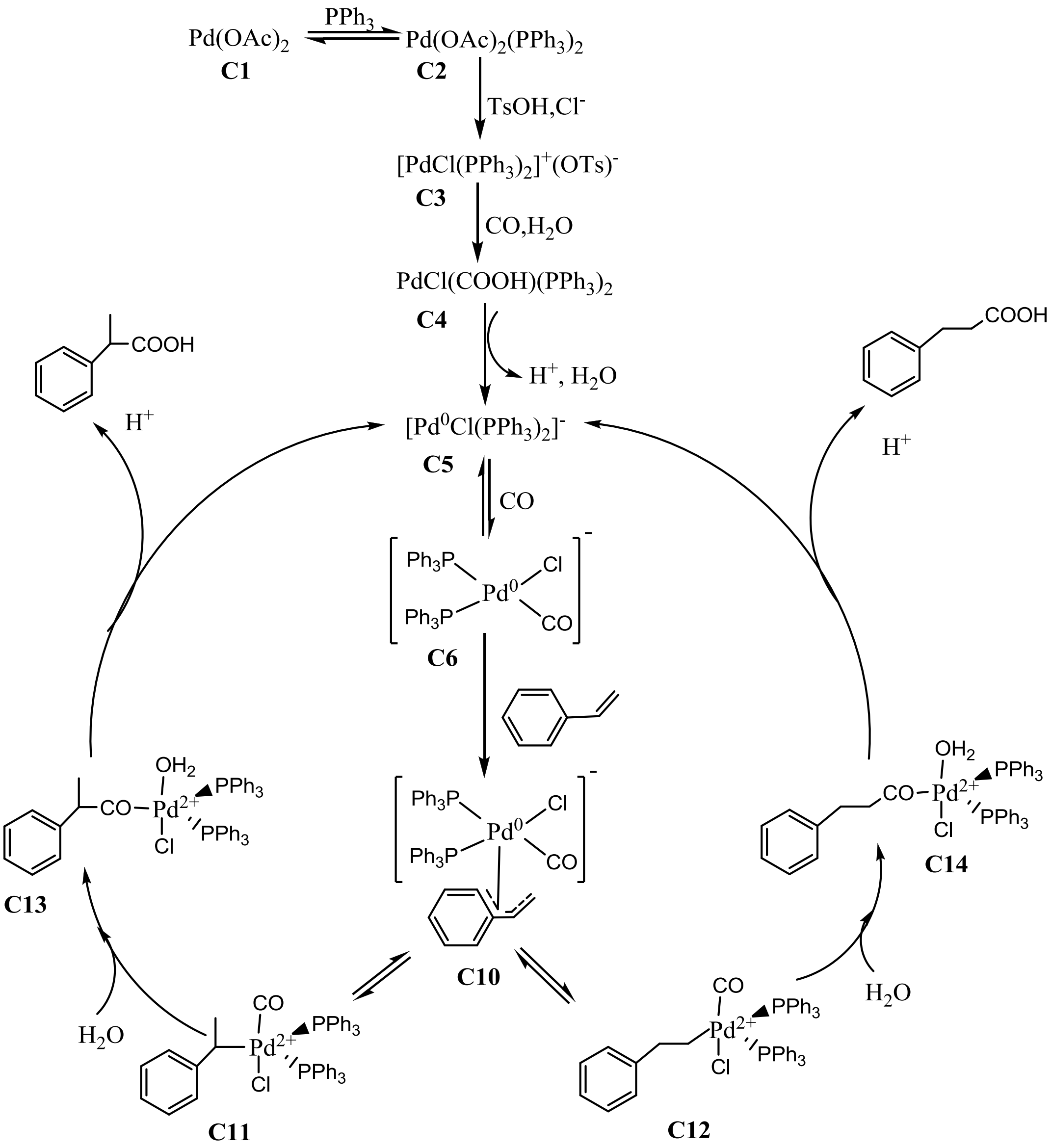
The promoting effect of the cationic alkali ion, Li^+ or Na^+, is believed to be due to their strongly stabilizing ability to the anionic catalyst species.[20,21] Possible explanation about the similar promoting effects of Li^+ on halide promoted carbonylation of alcohols using Rh and Ni complexes has been reported earlier on the basis of proposed involvement of anionic complexes stabilized by Li^+ counter ion.[22-24] The lower activity with Na^+ comparing to Li^+ is due to its weaker power for abstracting Cl^-.



L=PPh$_3$, TsO$^-$, CO or H$_2$O; n=3, or 4; m=-1 or 0

Scheme 2-4. Possible formation route for styrene coordinated catalyst intermediates

Based on all these considerations, a possible reaction mechanism is proposed as shown in Scheme 2-5. Actually, more vigorous work including catalyst species isolation, characterization or kinetic study is required to further understand the reaction mechanism and the roles of different catalyst components. At this moment, the macroscopic effects of promoters have been investigated and the proposed mechanism can reasonably explain the experimental observations very well, also consistent with the work by other researchers on the similar reaction systems.



Scheme 2-5. Proposed catalytic cycle for hydrocarboxylation of styrene using $Pd(OAc)_2/PPh_3/TsOH/LiCl$ as catalyst system[14,17]

Experimental results for hydrocarboxylation of styrene using $PdCl_2$ or $PdCl_2(PPh_3)_2$ as a catalyst precursor are presented in Table 2-7. The reaction conditions are similar to that in Table 2-5. In experiments using $PdCl_2/PPh_3/TsOH$ as a catalyst system, 98.84% conversion of styrene was obtained in 2.5 h. But the regio-selectivity to 2-PPA was only 61%, and the catalytic activity was also lower (TOF=98.9 h^{-1}) compared

]

to that observed for catalyst system 2 (TOF=246.6 h^{-1}). More importantly, the addition of LiCl in system 2 drastically enhanced the regio-selectivity up to about 100% along with achievement of 99.54% conversion in 1 h, indicating the important promoting effect of LiCl on the activity and regio-selectivity-determining step in the hydrocarboxylation reaction.

Table 2-7. Performance of catalytic systems using $PdCl_2$ or $PdCl_2(PPh_3)_2$ as a precursor

Item	Catalyst system	Conversion (%)	Selectivity			TON	TOF (h^{-1})
			2-PPA (%)	3-PPA (%)	i/n		
1	$PdCl_2/PPh_3$/TsOH	98.84	61	31	2.0	247.1	98.9
2	$PdCl_2/PPh_3$/TsOH/LiCl	99.54	105	3	35.0	246.6	246.6
3	$PdCl_2(PPh_3)_2$/TsOH/LiCl	98.63	96	2	48.0	267.8	321.3
4	$PdCl_2(PPh_3)_2/PPh_3$/TsOH /LiCl[a]	99.41	100	4	25.0	256.4	307.7
5	$PdCl_2$/pycaH/TsOH/LiCl	0.19	84	0	-	0.5	0.02
6	$PdCl_2/PPh_3$/pycaH/TsOH /LiCl[b]	99.74	98	3	32.7	282.2	282.2

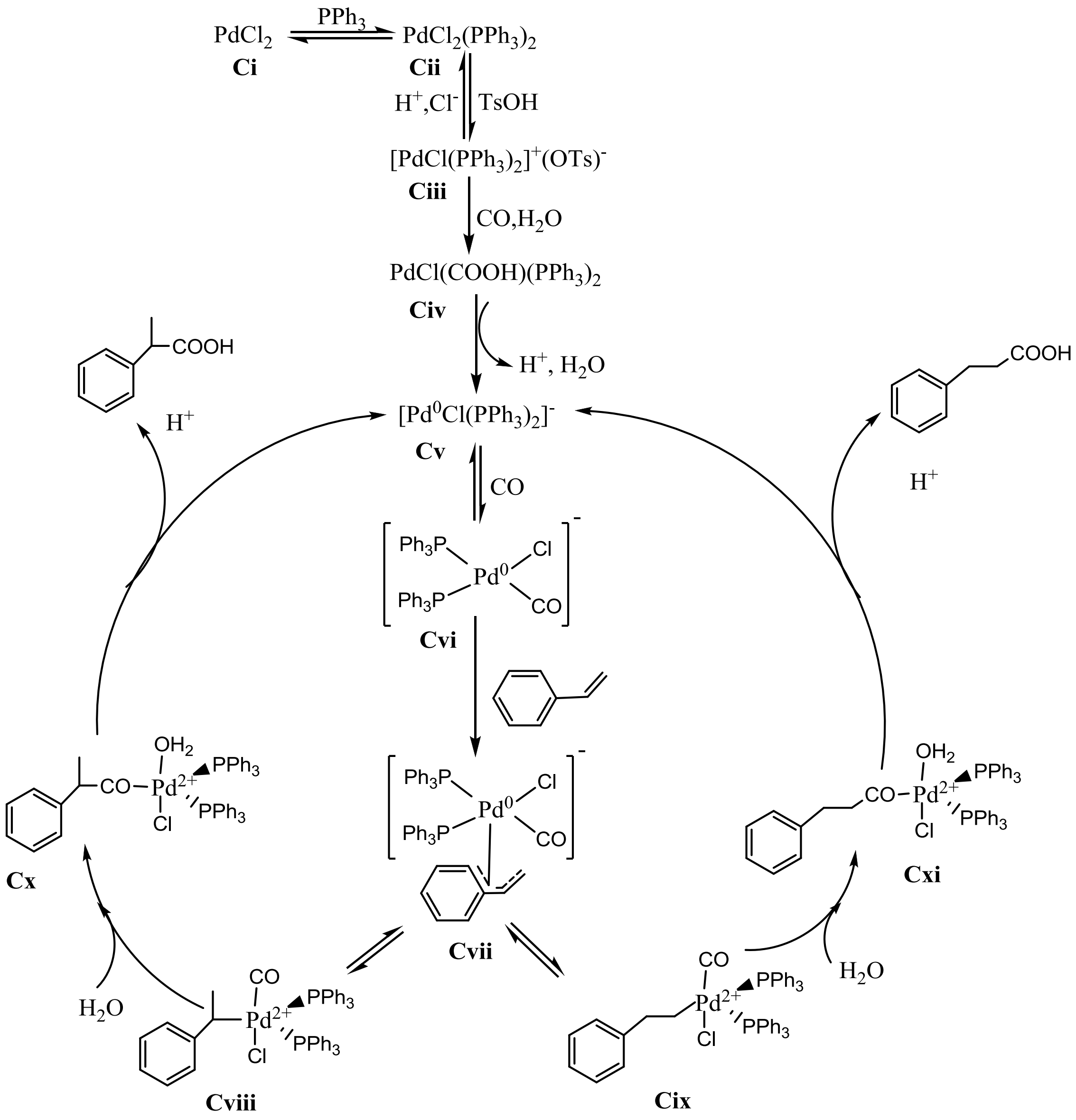
a. Molar ratio of $PdCl_2(PPh_3)_2$ to PPh_3 =1:2

b. Molar ratio of $PdCl_2:PPh_3$:pycaH = 1:4:4

Since it is considered that a palladium chloride complex, $PdCl_2(PPh_3)_2$, can be formed *in situ* by coordination of a free ligand PPh_3 to $PdCl_2$, two catalyst systems 3 and 4 using $PdCl_2(PPh_3)_2$ as a precursor were also tested for their performance and the performance compared to that for system 2. As shown in Table 2-7, the catalyst complex showed better but still comparable activity and regio-selectivity with respect to $PdCl_2$ under the same reaction conditions. Possible reason for this marginal enhancement is the rapid formation of active species from $PdCl_2(PPh_3)_2$ since its *in situ* formation is eliminated. Another reason may be that there is no or less excess free ligand in systems 3 and 4. The excess free ligand may hinder formation of active species or direct to generate other inactive palladium species. This inhibition effect of the free ligand also explains why system 4 with addition of twice equivalent amount of the free ligand showed a slight decrease of TOF and i/n ratio compared to system 3 without PPh_3.

Catalyst system 5 using pycaH as a ligand instead of PPh_3 did not show any activity for the hydrocarboxylation reaction. However, with the addition of molar equivalent amount of PPh_3, catalyst system 6 showed very similar activity and regio-selectivity as that shown by system 2. These observations indicated the negligible coordination effect of pycaH as a ligand.

The reaction mechanism for $PdCl_2/PPh_3/TsOH/LiCl$ catalyst system is proposed as shown in Scheme 2-6.[17] Similar to the $Pd(OAc)_2/PPh_3/TsOH/LiCl$ system, the catalytic cycle is also initiated by an anionic Pd(0) complex (Cv). The presence of TsOH and LiCl is necessary for the formation of the active anionic palladium intermediate. Also, LiCl plays a significant role in the regioselectivity-determining step for the formation of 2-phenylpropionic acid.



Scheme 2-6. Proposed catalytic cycle for hydrocarboxylation of styrene using $PdCl_2/PPh_3/TsOH/LiCl$ catalyst system

Performance of the synthesized $Pd(pyca)(PPh_3)(OTs)$ complex in hydrocarboxylation of styrene was investigated with different promoters as shown in Table 2-8. In the absence of LiCl, system 1 showed very low activity. The addition of LiCl significantly improved the activity of catalyst system 2 and achieved very high regio-selectivity (~100%). With the addition of excess PPh_3, slight decrease in TOF and regio-selectivity was observed. The reaction mechanism will be discussed in Chapter 3 along with the interpretation of kinetic data.

Table 2-8. Performance of catalytic systems using Pd(pyca)(PPh_3)(OTs) as a precursor

Item	Catalyst System	Conversion (%)	Selectivity			TON	TOF (h^{-1})
			2-PPA (%)	3-PPA (%)	i/n		
1	Pd(pyca)(PPh_3)(OTs)/ TsOH	5.85	61	10	6.1	14.8	4.9
2	Pd(pyca)(PPh_3)(OTs)/ TsOH/LiCl	100	101	1	101.0	250.2	250.2
3	Pd(pyca)(PPh_3)(OTs)/ PPh_3/TsOH/LiCl	95.01	95	3	31.7	231.5	231.5

The performance of other homogeneous catalyst systems using diphosphine or bulky ligand ligated catalyst supplied by Johnson Matthey as a precursor, TsOH and LiCl as promoters was also investigated and compared with previously studied catalyst systems. The experimental results for all the similar catalyst systems in the presence of same promoting agents are presented in Table 2-9, and a comparison of selected systems is shown in Figure 2-4. The comparison showed that the Pd(pyca)(PPh_3)(OTs)/TsOH/LiCl gave the best regio-selectivity along with high activity for hydrocarboxylation of styrene under the same reaction conditions. Actually, this catalyst system is also the best one among all the known catalyst systems for this kind of catalytic reaction reported to date.

Diphosphine ligated palladium catalysts, dppb Pd(II), dppf Pd(II)acetone, dppp Pd(II)acetone and dcpp $PdCl_2$ showed much lower activity and regio-selectivity even in the presence of TsOH and LiCl. The lower regio-selectivity may be due to the nature of the diphosphine ligand coordinated to the palladium center. As reported in previous literature, regio-selectivity in the alkoxycarbonylation of alkenes has essential dependence on the nature of the phosphorous ligands. Pd/monophosphine complexes favor the formation of branched isomers, whereas Pd/diphosphine systems favors the formation of linear isomers.[25,26] (XANTPHOS)$PdCl_2$ /TsOH/LiCl catalyst system showed good activity but lowest regio-selectivity (32%) for the branched product. This observation can be explained by the steric hindrance of the bulky ligand coordinated to palladium center which disfavors the formation of branched isomer.

Table 2-9. Performance of different homogeneous Pd catalyst precursors and TsOH/LiCl as promoters

Catalyst System		Conversion (%)	Selectivity			TON	TOF (h^{-1})	Time (h)
			2-PPA (%)	3-PPA (%)	i/n			
a	$PdCl_2/PPh_3$/TsOH	98.84	61	31	2.0	247.1	98.85	2.5
	$PdCl_2/PPh_3$/TsOH/LiCl	99.54	105	3	35.0	246.6	246.6	1.0
	$Pd(OAc)_2/PPh_3$/TsOH	24.97	31	74	0.4	60.4	20.1	3.0
	$Pd(OAc)_2/PPh_3$/TsOH/LiCl	99.8	89	4	22.2	246.4	246.4	1.0
b	Pd(pyca)(PPh_3)(OTs)/TsOH	5.85	61	10	6.1	14.8	4.9	3.0
	Pd(pyca)(PPh_3)(OTs)/TsOH/ LiCl	100	101	1	101.0	250.2	250.2	1.0
	Pd(pyca)(PPh_3)(OTs)/PPh_3/TsOH/LiCl	95.01	95	3	31.7	231.5	231.5	1.0
c	dppb Pd(II)/TsOH/LiCl	0.9	90	28	3.2	0.2	0.1	3.0
	dppf Pd(II)acetone/TsOH/LiCl	59.68	15	31	0.5	165.8	52.4	3.0
	dppp Pd(II)acetone/TsOH/LiCl	-	0	0	-	0.0	0.0	3.0
	(S-BINAP)$PdBr_2$ /TsOH/LiCl	10.73	6	2	3.0	10.6	3.8	3.0
	dcpp $PdCl_2$ /TsOH/LiCl	0	-	-	-	0.0	0.0	2.6
	(XANTPHOS)$PdCl_2$ /TsOH/LiCl	95.54	32	47	0.7	209.7	209.7	1.0

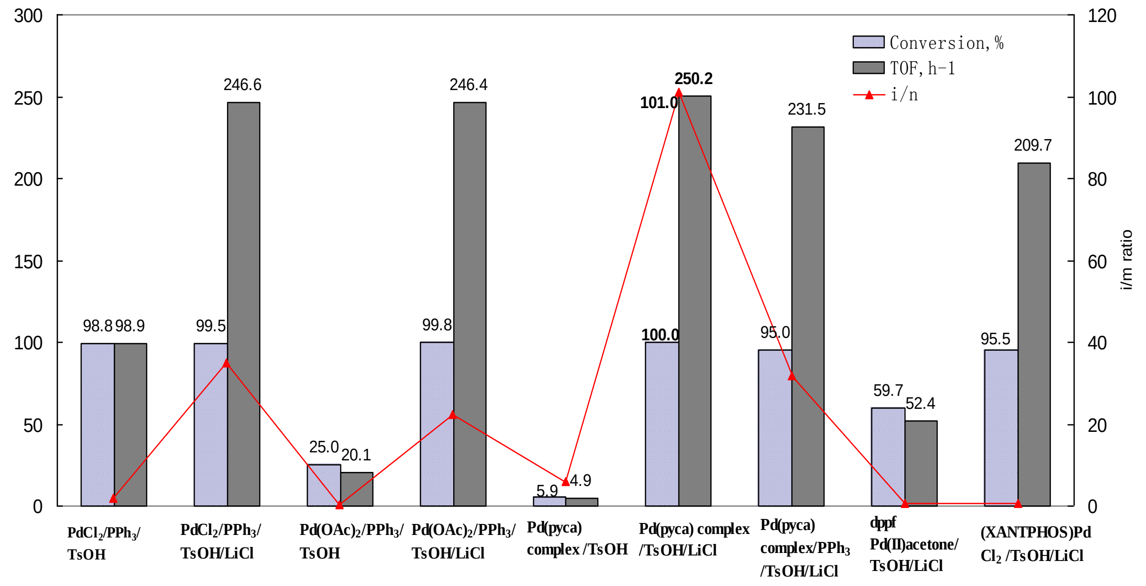


Fig. 2-4. Performance comparison of different homogeneous catalyst systems

2-4 Heterogeneous Pd Complex Catalysts

Most of the pharmaceutical products are thermally unstable and consist of non-volatile organic compounds, hence they are difficult to be separated by conventional means like distillation. This demands an efficient catalyst-product separation technology, particularly when expensive homogeneous catalysts are used in their production. A possible solution to this problem is developing heterogeneous catalysts by immobilizing the active homogeneous catalysts to form supported catalysts or the so-called biphasic catalysts based on the principles of phase differentiation.[27,28] Immobilization of the homogeneous catalysts on inert organic materials (polymers) or inorganic supports (silica, alumina oxide, NaY zeolite, etc) can be achieved using anchoring, tethering or encapsulation techniques.[29] In this work, two heterogeneous Pd complex catalysts, Fiber Cat 1032 (Johnson Matthey) and tethered Pd(pyca)(PPh_3)(OTs)-PTA-Y were investigated to evaluate their performance in hydrocarboxylation of styrene. Using a similar tethering technique[30], $Pd(OAc)_2(PPh_3)_2$ and $PdCl_2(PPh_3)_2$ were also heterogenized. However, these two complexes were found difficult to be tethered to the phosphotungstic acid functionalized zeolite NaY, because of their limited solubilities. Thus, only the results of two catalysts, namely, Fiber Cat 1032 (JMC supplied) and tethered $Pd(pyca)(PPh_3)(OTs)$ will be discussed here.

The Fiber catalyst 1032 supplied by Johnson Matthey Company was tested for carbonylation styrene with TsOH and LiCl (TsOH:LiCl=1:1) as promoters. At relatively mild conditions (T=388K, Pco=6.0MPa), 65.7% conversion of styrene was achieved in 3 h with a regio-selectivity (to 2-PPA) of 77% and i/n ratio of 5.9. The average turnover frequency was only 58.3 h^{-1}. During the reaction, it was found that there was no CO consumption in the initial twenty minutes showing an induction period, but gradually the rate increased thereafter. The color of the fiber catalyst was bright yellow after the reaction with no black palladium precipitation, indicating the stability of the fiber catalyst during the hydrocarboxylation reaction. Although, the activity as well as selectivity of this fiber catalyst was not good compared to that of the homogeneous Pd complex catalysts, it showed good stability and recyclability. However, further work is needed to verify the potential of this fiber catalyst for its application in hydrocarboxylation of styrene.

Tethered $Pd(pyca)(PPh_3)(OTs)$ catalyst was prepared following the literature procedure. [30, 31] There were two main steps in the preparation: 1) Functionalization of zeolite material NaY by attaching phosphotungstic acid (PTA) to zeolite surface; 2) Tethering $Pd(pyca)(PPh_3)(OTs)$ complex to functionalized NaY (PTA-Y) through grafting the complex molecule to soluble PTA through some ionic interactions. The performance of this tethered catalyst in the presence of PPh_3, TsOH and LiCl was investigated in hydrocarboxylation of styrene. The results of conversion, TOF and selectivity at different times are presented in Table 2-10. The concentration-time profiles for each component in the reaction were determined as shown in Figure 2-5. Nearly complete conversion of styrene with 95% regio-selectivity to 2-PPA was observed using this tethered catalyst along with promoters, which is comparable to that shown by the homogeneous analogues. However, the average TOF was only 18 h^{-1} which is about one tenth of that shown by the homogeneous catalyst system. Even though the tethered catalyst showed lower activity, it has potential to be further developed since it has good stability in carbonylation reactions and can also work without addition of any acidic promoter.[30]

Table 2-10. Results of hydrocarboxylation of styrene using Pd(pyca)(PPh_3)(OTs)-PTA-Y/ PPh_3/TsOH/LiCl catalyst

Catalyst system	Conversion (%)	Styrene consumption (mmol)	CO consumption (mmol)	Selectivity			TOF (h^{-1})	Time (h)
				2-PPA (%)	3-PPA (%)	i/n		
Pd(pyca)-PTA-Y /PPh_3/TsOH/LiCl=0.7 :4:10:10	41.30	7.19	6.30	98	1	98.0	29.0	3.0
	61.81	10.76	10.51	99	1	99.0	26.0	5.0
	78.48	13.66	12.61	100	2	50.0	23.6	7.0
	88.18	15.04	15.13	95	3	31.7	20.6	9.0
	94.77	16.49	16.81	97	3	32.3	18.2	11.0

The work on heterogeneous catalysts for hydrocarboxylation is still very preliminary. Considering the increasing importance of the heterogeneous catalysts in achieving greener and more economic synthesis of 2-arylpropionic acids through carbonylation of aryl olefins, there is real potential for developing new immobilized palladium catalysts. This will also be one of the focuses of my future work on the project.

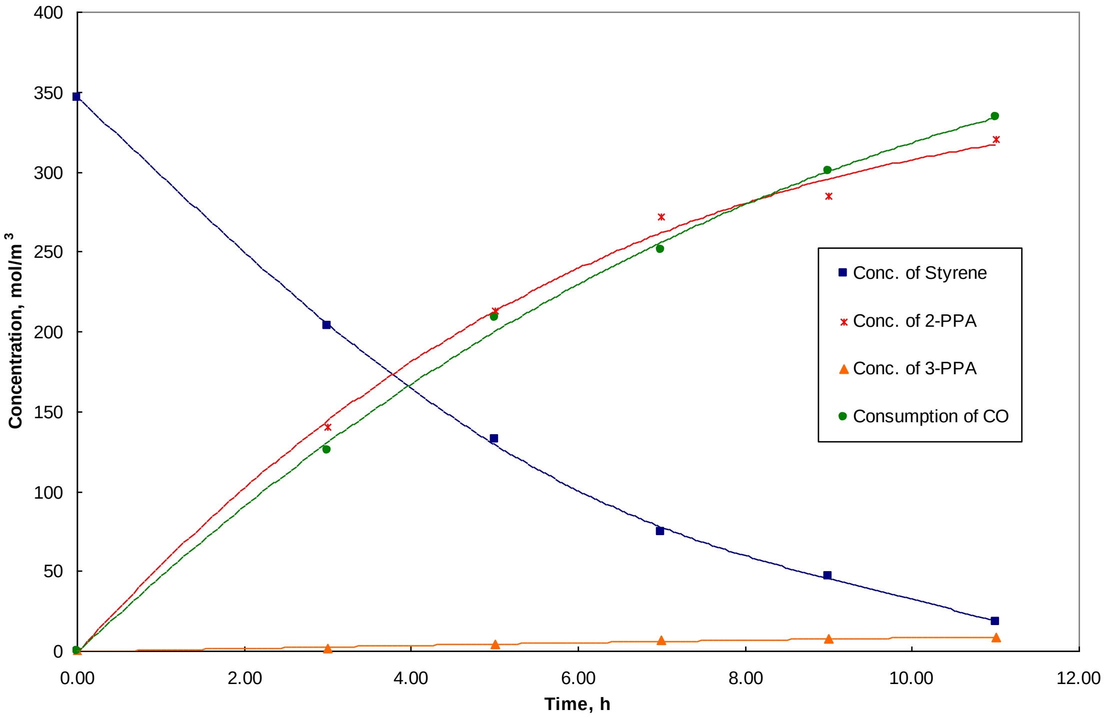


Figure 2-5. Concentration-time profiles for hydrocarboxylation of styrene using Pd(pyca)(PPh_3)(OTs)-PTA-Y/ PPh_3/TsOH/LiCl catalyst system

2-5 Conclusions

Performance (activity and regio-selectivity) of different homogeneous catalyst systems in hydrocarboxylation of styrene has been studied. It has been found that the presence of TsOH and LiCl promoted the performance of the catalyst system using Pd(OAc)$_2$, PdCl$_2$ or Pd(pyca)(PPh_3)(OTs) as precursor. The regio-selectivity to 2-phenylpropionic acids was significantly increased with the addition of LiCl. The possible reaction mechanism of hydrocarboxylation of styrene using Pd(OAc)$_2$/PPh_3/TsOH/LiCl or PdCl$_2$/PPh_3/TsOH/LiCl catalyst system has been proposed.

Among all the catalyst systems, Pd(pyca)(PPh_3)(OTs) along with TsOH and LiCl as promoters showed the best regio-selectivity along with desirable high activity for the hydrocarboxylation of styrene. It is worthy to note that this complex has been also reported to be a very desirable homogeneous precursor candidate for synthesis of heterogeneous catalysts.[30,32,33] The immobilized catalyst precursor showed very good stability in hydrocarboxylation of aryl olefins, indicating the good recyclability of these heterogeneous catalysts. Consider the potential for industrial application of the desired homogeneous catalyst system, it is important to study the reaction kinetics to understand the reaction mechanism and develop appropriate rate equations. The work on kinetic study for hydrocarboxylation of styrene using Pd(pyca)(PPh$_3$)(OTs)/PPh$_3$/TsOH/LiCl will be illustrated in details in Chapter 3.

References

1. Nuria Ruiz, Inmaculada del R´ıo, Jose´ Luis Jime ́nez, Carmen Claver, Jorge Fornie ́s-C ́amer, Christine C.J. Cardin, Serafino Gladiali, *Journal of Molecular Catalysis A*: *Chemical*, 143 (1999),171–180.
2. A. Seayad, S. Jayasree, and R.V. Chaudhari, *Catalysis Letters* 61 (1999) 99–103.
3. Inmaculada del R´ıo, Nuria Ruiz, Carmen Claver,Lars A. van der Veen, Piet W.N.M. van Leeuwen, *Journal of Molecular Catalysis A*: *Chemical* 161 (2000) 39–48.
4. S. Jayasree, A. Seayad, and R.V. Chaudhari, *Org. Letters.,* 2 (2000) 203-206.
5. E.D. Park, K. H. Lee, J. S. Lee, *Catalysis Today* 63 (2000) 147–157.
6. A. Seayad, S. Jayasree, and R.V. Chaudhari, *Journal of Molecular Catalysis A: Chemical*, 172 (2001) 151–164.
7. Y.Y. Li, C.G. Xia., *Applied Catalysis A: General*, 210 (2001) 257–262.
8. S. Jayasree, A. Seayad, and R.V. Chaudhari, *Journal of Molecular Catalysis A: Chemical,* 181 (2002) 221–235.
9. G. Rangits, L. Koll′ar, *Journal of Molecular Catalysis A: Chemical* 246 (2006) 59–64.
10. H. Ooka, T. Inoue, S. Itsuno, and M. Tanaka, *Chem.Commun.* (2005) 1173-1175.
11. K. Mukhopadhyay, B. R. Sarkar, and R. V. Chaudhari, *J. Am. Chem. Soc.,* 124 (2002) 9693.
12. R.V. Chaudhari, S. Majeed, A. Seayad, US006093847A (2000).
13. K. Nakamoto, *Infrared Spectra of Inorganic and Coordinated Compounds,* Wiley Interscience, New York, 1970, pp 152.
14. A. Seayad, A. A. Kelkar, and R. V. Chaudhari, *Ind. Eng. Chem. Res.*, 37 (1998) 2180-2187.
15. J. F. Knifton, *J. Org. Chem.* 41 (1976) 793.
16. M. Sperrle, G. Consiglio, *Chem. Ber.*, 130 (1997) 1557.
17. A. M. Seayad, J. Seayad, P. L. Mills, and R. V. Chaudahri, *Ind. Eng. Chem. Res.*, 42 (2003) 2496-2506.
18. Y. Becker, J. K. Stille, *J. Am. Chem. Soc.*, 100 (1978) 845.

19. J.S. Roberts, K. J. Klabunde, S. P. Nolan, *Organometallics*, 17 (1998) 534.
20. I. Ei. Negishi, T. Takahashi, K. Akiyoshi, *J. Chem, Soc. Chem. Commun.*, (1986) 1338.
21. C. Amatore, M. Azzabi, A. Jutand, *J. Organomet. Chem.*, 363 (1989) C41.
22. B. L. Smith, G. P. Torrence, M. A. Murphy, A. Aguilo, *J. Mol. Catal.*, 39 (1987) 115.
23. A. A., Kelkar, R. S. Ubale, R. V. Chaudhari, *J. Catal.*, 136 (1992) 605.
24. R. S. Ubale, A. A. Kelka, R. V. Chaudhari, *J. Mol. Catal.* 118 (1997) 9.
25. G. Gonsiglio, M. Marchetti, *Chimia*, 30(1976), 26-27.
26. G. Consiglio, S. C. A. Nefkens, C. Pisano, F. Wenzinger, *Helv. Chim. Acta*, 74 (1991) 323-325.
27. W. A. Herrmann, B. Cornils, *Angew. Chem. Intl. Ed.*, 36 (1997) 1048.
28. D. J. Cole-Hanilton, *Science*, 299 (2003) 1702.
29. B. Cornils, W. A. Herrmann (Eds.), *Applied Homogeneous Catalysis with Organometallic Compounds*, vols. 1-3, 2nd ed., Wiley-VCH, Weinheim, 2004.
30. B. R. Sarkar, K. Mukhopadhyay, R. V. Chaudhari, *Catal. Commun.*, 8 (2007) 1386.
31. K. Mukhopadhyay, A. B. Mandale, R. V. Chaudhari, *Chem. Mater.*, 15 (2003) 1766.
32. K. Mukahopadhyay, B. R. Sarkar, R. V. Chaudhari, *J. Am. Chem. Soc.*, 124 (2002) 9692.
33. B. R. Sarkar, R. V. Chaudhari, *Journal of Catalysis*, 242 (2006) 231.

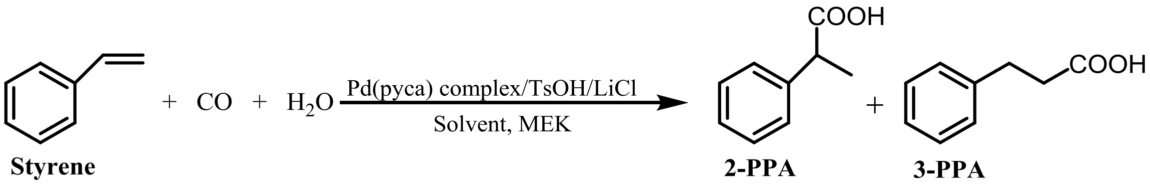
CHAPTER 3

KINETIC MODELING OF HYDROCARBOXYLATION OF STYRENE USING PALLADIUM COMPLEX CATALYST

3-1 Introduction

Palladium-catalyzed carbonylation of vinyl aromatics provides atom-effective and eco-friendly routes for the synthesis of industrially important pharmaceutical products such as 2-arylpropionic acids/esters, a class of non-steroidal anti-inflammatory drugs (NSAIDs).[1-3] The hydrocarboxylation reaction has gained considerable interest as one of the best examples of the role of catalysis in developing greener routes replacing stoichiometric organic syntheis.[4,5] A typical example is the commercial Hoechst-Celanese process for the manufacture of Ibuprofen® which involves carbonylation of 1-(4-isobutylphenyl) ethanol $PdCl_2(PPh_3)_2$ catalyst as a key step.[6] In this process, high regio-selectivity to Ibuprofen® (> 95%) can be obtained only at high pressure (16 ~ 35 MPa) of CO in the presence of the aqueous HCl as a promoter. However, the selectivity reduces to 67% with a low TOF (50 ~ 70 h^{-1}) at lower pressure of 6 ~ 7 MPa. In Chapter 1, a literature review on this subject has been presented specifically using palladium based catalysts for the hydrocarboxylation of styrene and derivatives. Most studies reported to date were focused on improving the catalytic performance (activity and selectivity), exploring novel catalyst systems, or developing heterogeneous catalysts from the design and synthesis perspective. Only limited reports have been published on the kinetics of hydrocarboxylation of styrene and derivatives. Knowledge of the intrinsic kinetics of the catalytic reaction and development of suitable rate equations are essential for understanding the mechanism and also the optimal design of reactors.[7]

As demonstrated in Chapter 2, the Pd(pyca)(PPh_3)(OTs)/TsOH/LiCl catalyst system showed the best performance in hydrocarboxylation of styrene (Scheme 3-1). This catalyst system has shown high activity (TOF= 1313 ~ 2600 h^{-1}) as well as regio-selectivity (99%) to the 2-arylpropionic acids in hydrocarboxylation of aryl olefins.[8] However, no report on the kinetics of carbonylation of olefins using this best performing catalyst system has been published so far. Interpretation of intrinsic kinetics and developing rate equations for the complex multi-step reaction systems is a real challenge. In this chapter, the detailed kinetic study for hydrocarboxylation of styrene using the Pd(pyca)(PPh_3)(OTs)/TsOH/LiCl catalyst system is presented, in which, investigation of effects of reaction parameters, determination of solubility, proposal of a mechanism, and micro-kinetic modeling is illustrated extensively. The stoichiometric reaction is given below:



Scheme 3-1. Hydrocarboxylation of styrene using Pd(pyca)(PPh_3)(OTs)/TsOH/LiCl

It is shown that the micro-kinetic model based on a catalytic reaction mechanism explains all the parametric effects and particularly the induction period observed under certain conditions. The model predictions were compared with experimental data obtained at different sets of initial conditions to demonstrate that the model is applicable over a wide range of conditions. Intrinsic kinetic parameters have been determined at different temperatures.

3-2 Experimental

3-2-1 Reactor Set-up and Procedure

For the kinetic study, it is necessary to carry out a series of experiments to understand the effects of the reaction parameters such as catalyst, styrene, and water concentrations, partial pressure of carbon monoxide, concentration of promoters and temperature. In these experiments, generally concentration-time profiles for different initial sets of parameters were measured. These data were used to identify all the major and minor product, material balance analysis and analysis of rate behavior with respect to different parameters, and determination of intrinsic kinetic parameters. These parametric experiments were carried out in a 300 ml Parr autoclave made of Hastalloy C-276 MOC, connected to a Cal controller (Figure 3-1) to achieve precise temperature control (setpoint ±1 °C) during the reaction.

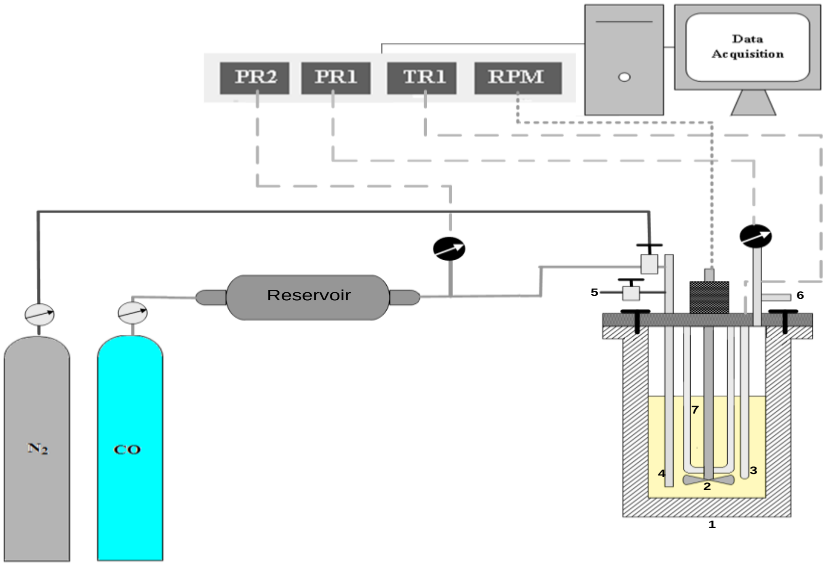


Fig. 3-1. Schematic of 300 mL Parr batch reactor set-up 1. Reactor; 2. stirrer shaft with impeller; 3. thermal well; 4. sampling and gas inlet tube; 5. sampling valve; 6. gas vent; 7. cooling coil; PR1. reactor pressure indicator; TR1. reactor temperature indicator; PR2. reservoir pressure indicator.

As shown in Figure 3-1, the reactor setup is very similar to that for catalyst performance test shown in Chapter 2 (Figure 2-3). The only difference is the 300 ml autoclave was also equipped with a cooling coil, and connected with a Cal controller. When the temperature inside the autoclave exceeds the setpoint, the controller will automatically switch on to cooling water to enable control of temperature at the setpoint.

The experimental procedure for carbonylation experiments was the same as discussed in 2-3-1. More liquid samples were taken during the initial period (beginning 10 min) of reaction to calculate the initial reaction rates and turnover frequency (TOF). The ranges of reaction conditions for each parameter are shown in Table 3-1. In these experiments, only one parameter was varied to investigate the effect by keeping other conditions unchanged. The agitation speed was set to > 900 rpm to eliminate the gas to liquid mass transfer resistance for CO dissolution in the liquid phase.

Table 3-1. Ranges of reaction conditions in parametric study

Reaction parameter	**Condition**
Pd catalyst precursor	0.32 ~ 1.26 mol/m^3
PPh_3	1.2 ~ 4.7 mol/m^3
TsOH:LiCl (molar ratio)=1:1	0 ~ 24.0 mol/m^3
Styrene	145.46 ~ 1163.71 mol/m^3
Water	694.4 ~ 5555.6 mol/m^3
Pco	1.5 ~ 7.5 MPa
Temperature	368 ~ 388 K
Solvent	MEK
Total volume	1.2 x 10^{-4} m^3
Agitation speed	900 rpm
Reaction time	2 h

3-2-2 Experimental Results

The concentrations of styrene and products at different times were determined by quantitative GC analysis. The consumption of carbon monoxide at different times was also observed from the pressure drop in the reservoir vessel. The calculation method for the CO consumption is shown below in Equation 3-1.

$$\text{Consumption of CO, mol} = \frac{\text{Pressure drop in reservoir, Pa} \times \text{Dead volume of reservoir, m}^3}{R\text{, J/K/mol} \times \text{Temperature in reservoir, K}} \quad \text{Eq. 3-1}$$

Where, *R* is the gas constant which equals to 8.314 J/K/mol. The total conversion of styrene and the formation of phenylpropionic acids were found to be consistent with the total consumption of carbon monoxide and the overall stoichiometry. The typical concentration-time profiles for the liquid components, styrene and acids obtained at standard reaction conditions are shown in Figure 3-2. It was found that styrene was predominantly converted (~99%) to the desired 2-phenylpropionic acid (2-PPA) using the Pd(pyca)(PPh$_3$)(OTs)/PPh$_3$/TsOH/LiCl catalyst system at mild reaction conditions (388K and 6 MPa).

In order to understand the effect of each parameter, initial rate of the hydrocarboxylation reaction was determined by Equation 3-2.

Initial Reaction Rate [mol/m^3/min] = Slope of {concentration of styrene [mol/m^3]

versus time [min] plot} at t=0 Eq. 3-2

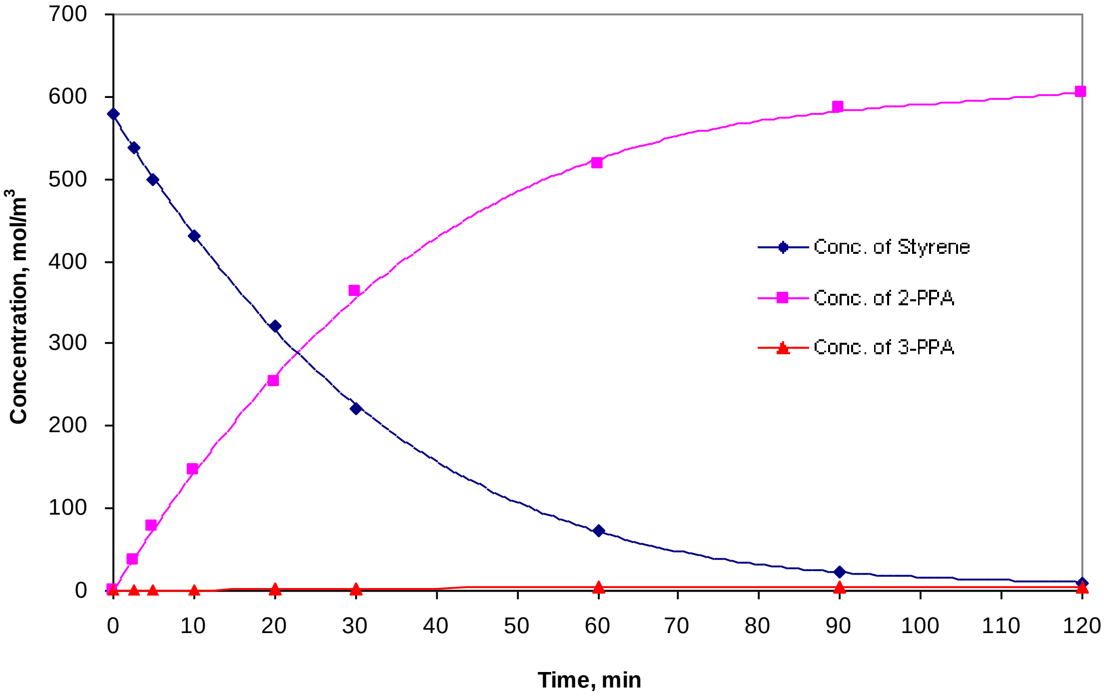


Fig. 3-2. Concentration-time profiles for hydrocarboxylation of styrene using Pd(pyca)(PPh$_3$)(OTs)/PPh$_3$/TsOH/LiCl catalyst system
Reaction conditions: catalyst Pd(pyca)(PPh$_3$)(OTs), 0.64 mol/m^3; Pd:PPh$_3$, 1:4; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water,1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; temperature, 388 K.

3-2-2-1 Effect of Catalyst Concentration

The effect of the concentration of catalyst precursor [Pd(pyca)(PPh_3)(OTs)] on the activity of the catalytic system was investigated at different concentrations of PPh_3. Figure 3-3 shows the effect of catalyst concentration at different PPh_3 concentrations at 388 K. It was found that, the initial reaction rate increased with the increase in catalyst concentration, but an induction period was found at the lower catalyst concentrations as shown in Figure 3-4. At the beginning of reaction (~ 10 min), the rate was quite low, indicating that the rate of formation of active catalyst species was very low at lower catalyst concentrations. It was also found that higher concentration of PPh_3 disfavored the reaction rate. This observation was further confirmed by the experimental results shown in 3-2-2-2 about the effect of concentration of PPh_3. The regio-selectivity showed no changes (~ 99%) at different catalyst concentrations.

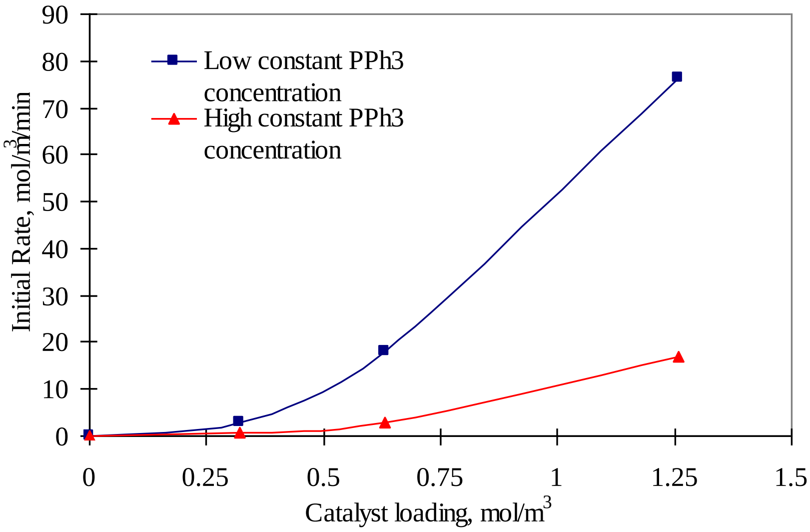


Fig. 3-3. Effect of concentration of catalyst precursor on the initial rate of hydrocarboxylation of styrene. Reaction condition: PPh_3(low), 2.34 mol/m^3, PPh_3(high), 9.31 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; temperature, 388K.

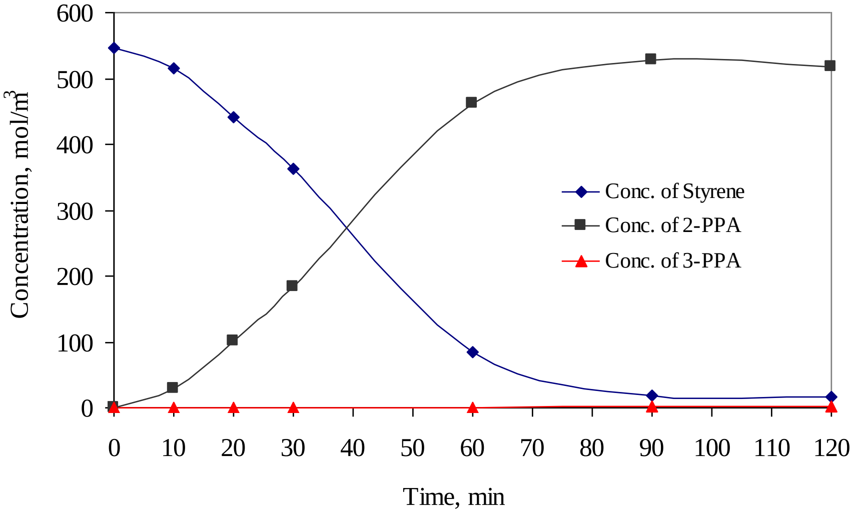


Fig. 3-4. Concentration-time profiles for hydrocarboxylation of styrene at low catalyst concentration. Reaction condition: catalyst precursor, 0.32 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; temperature, 388K.

3-2-2-2 Effect of PPh_3 Concentration

During the investigations on effect of catalyst concentration, it was found that the concentration of PPh_3 also affected the reaction rate significantly. In order to further understand the influence of PPh_3, separate experiments were carried out at constant catalyst concentration. As shown in Figure 3-5, the initial reaction rate gradually decreased with the increase in PPh_3 concentration but no change in regio-selectivity to 2-PPA was observed. The free PPh_3 may compete with the reactant molecules for co-ordination, causing decrease in the activity.[9]

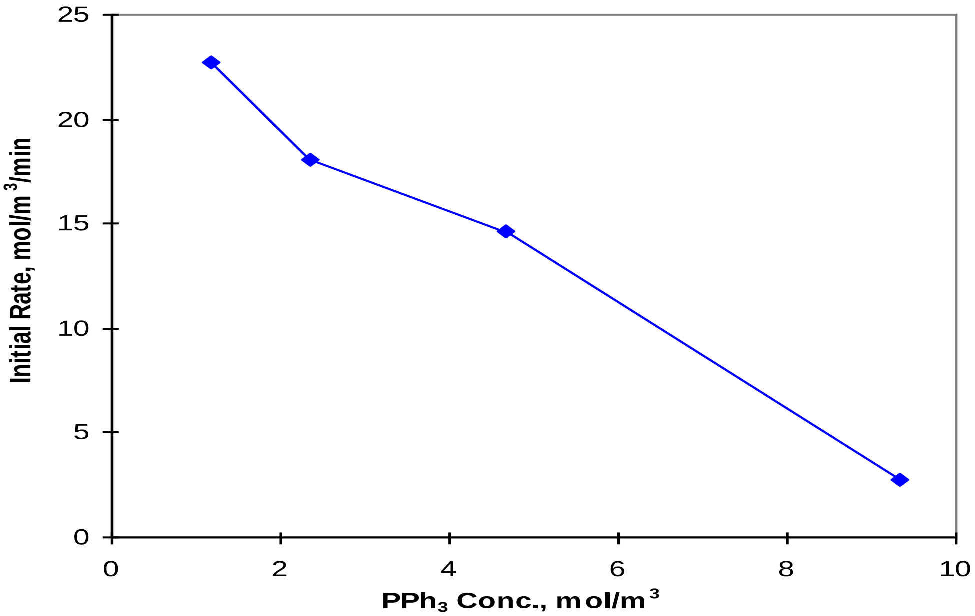


Fig. 3-5. Effect of PPh_3 concentration on the initial rate of hydrocarboxylation of styrene. Reaction conditions: catalyst precursor, 0.64 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; temperature, 388K.

3-2-2-3 Effect of Promoters

As important components in the multicomponent catalytic system for hydrocarboxylation, the promoters TsOH and LiCl lead to significant enhancement of the catalytic activity as well as regio-selectivity. Therefore, investigation of the effects of these promoters on initial rate becomes important to understand their specific roles in the catalytic reaction. The initial rate was found to increase with the concentration of TsOH (Fig. 3-6) almost linearly. In the absence of TsOH, very low activity (TOF=52.7 h^{-1}) was observed, indicating the positive influence of TsOH in the formation of active catalyst intermediates. However, the regio-selectivity showed no variation in the absence of TsOH.

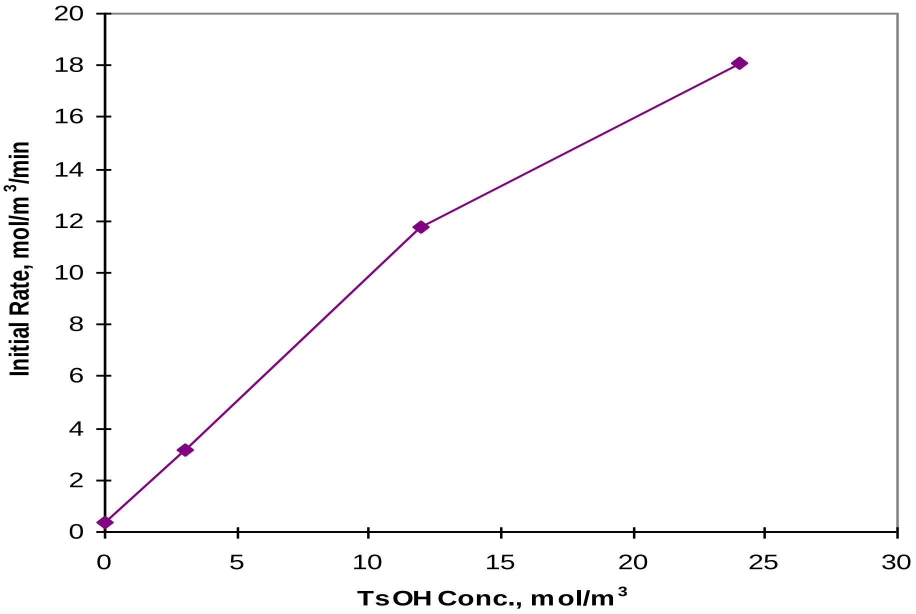


Fig. 3-6. Effect of TsOH concentration on the initial rate of hydrocarboxylation of styrene. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; LiCl, 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; temperature, 388K.

The initial rate was also found to increase with increase in the concentration of LiCl up to 12 mol/m^3. When the concentration of LiCl was increased to 24 mol/m^3, the initial reaction rate decreased. The observations indicate that LiCl favors the reaction step for the formation of active catalyst species up to a certain extent, but too much excess of LiCl may hinder the reaction rate by favoring the formation of some inactive species. The regio-selectivity was found to decrease with a decrease in the concentration of LiCl (i/n ratio from 100 to 1.1). In the absence of LiCl, 2-PPA was no longer the predominant product indicating the essential role of LiCl in the regioselectivity-determining step.

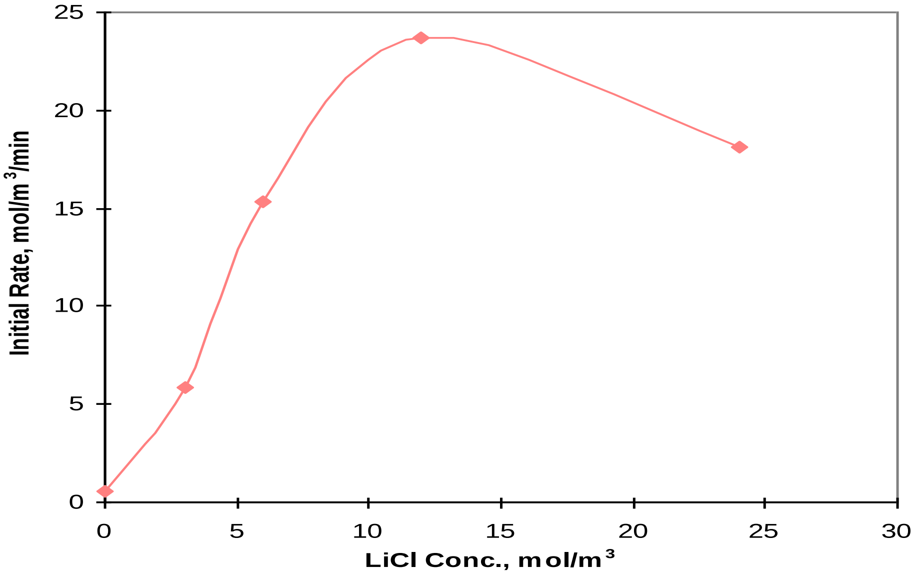


Fig. 3-7. Effect of LiCl concentration on the initial rate of hydrocarboxylation of styrene. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH, 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; temperature, 388K.

3-2-2-4 Effect of Styrene Concentration

The effect of concentration of styrene on the initial reaction rate was observed to gradually increase with increase in styrene concentration (Figure 3-8). No induction period was observed even at the lowest styrene concentration, suggesting that the increase in substrate concentration favors the addition of olefin molecule to a possibly formed Pd-H active catalytic complex to form the intermediate, Pd-alkyl complex. No obvious variation of regio-selectivity was observed at different styrene concentration.

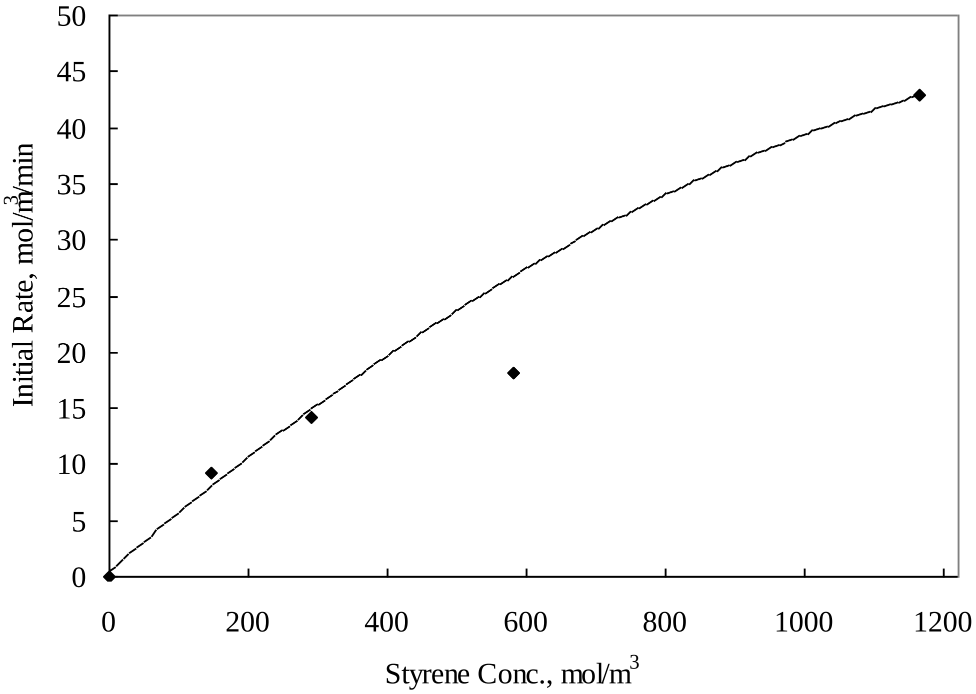


Fig. 3-8. Effect of styrene concentration on the initial rate of hydrocarboxylation of styrene. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; temperature, 388K.

3-2-2-5 Effect of Water Concentration

Since water is also a reactant in the hydrocarboxylation of styrene, the effect of initial water concentration on the reaction rate was investigated. It was found that the initial reaction rate increased with water concentration up to 2.78×10^3 mol/m^3 beyond which the reaction rate decreased with increase in water concentration. This is due to the obvious phase change of the reaction system from homogeneous to a two phase system. The presence of aqueous phase will dissolve most of the acidic promoter TsOH and LiCl, thereby limiting the availability of the promoters in the organic phase to promote essential catalyst species. In addition, the solubility of carbon monoxide also significantly decreases in the biphasic medium, which will also reduce the reaction rate.

Under homogeneous conditions, no change of regio-selectivity (i/n=100) was found. However, in the biphasic medium, the regio-selectivity decreased (i/n=14), which could be due to limited availability of LiCl in the reaction phase.

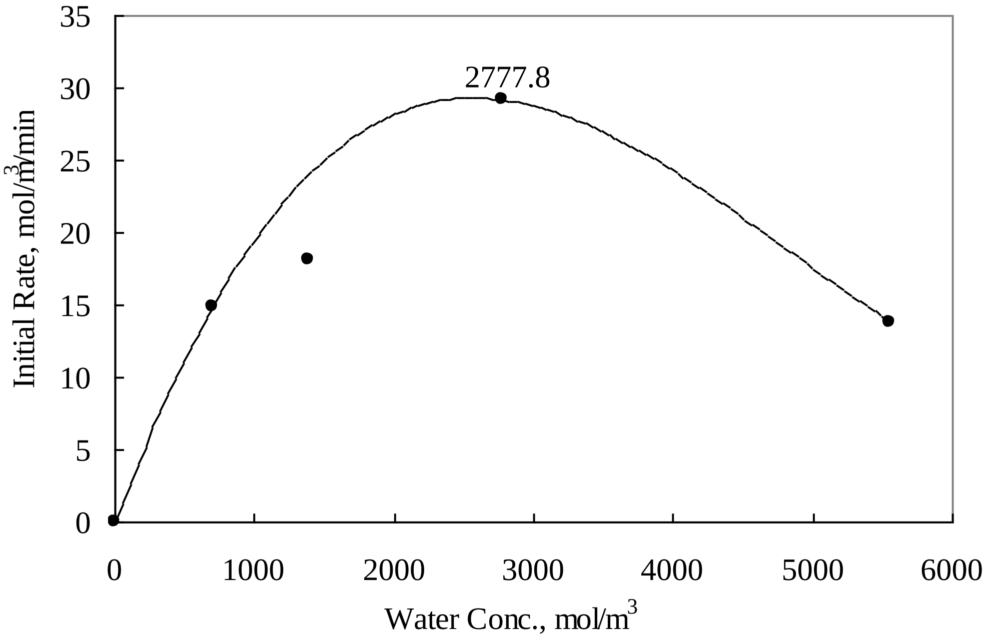


Fig. 3-9. Effect of water concentration on the initial rate of hydrocarboxylation of styrene. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; temperature, 388K.

3-2-2-6 Effect of Partial Pressure of Carbon Monoxide

The effect of partial pressure of carbon monoxide on the initial reaction rate was investigated. The results (Figure 3-10) showed an interesting trend in which induction period was observed to be strongly pressure dependent. As a result, the initial rate was very low at lower CO pressures of 1.5 ~ 4.5 MPa (Figure 3-11) at the beginning of reaction. However, after the induction region, the reaction rate was found to be quite

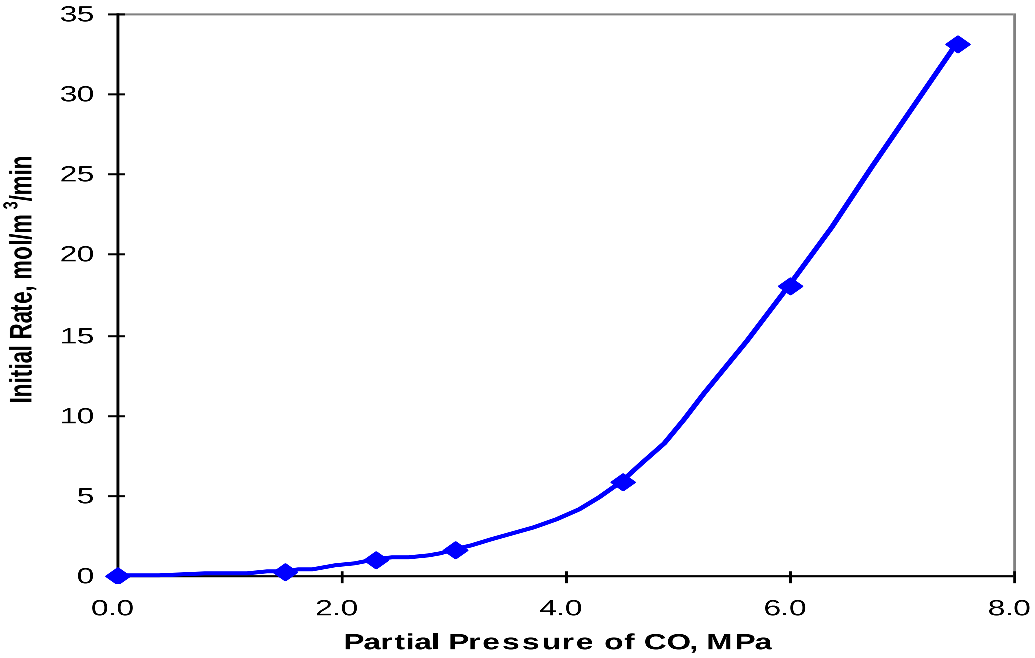


Fig. 3-10. Effect of CO pressure on the initial rate of hydrocarboxylation of styrene. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; temperature, 388K.

comparable at different CO pressures until complete consumption of the substrate was achieved. These observations show the important role of carbon monoxide in the formation of the active catalytic species. Lower regio-selectivity (i/n=30~50) was also found at lower CO pressures (1.5 MPa~3.0 MPa).

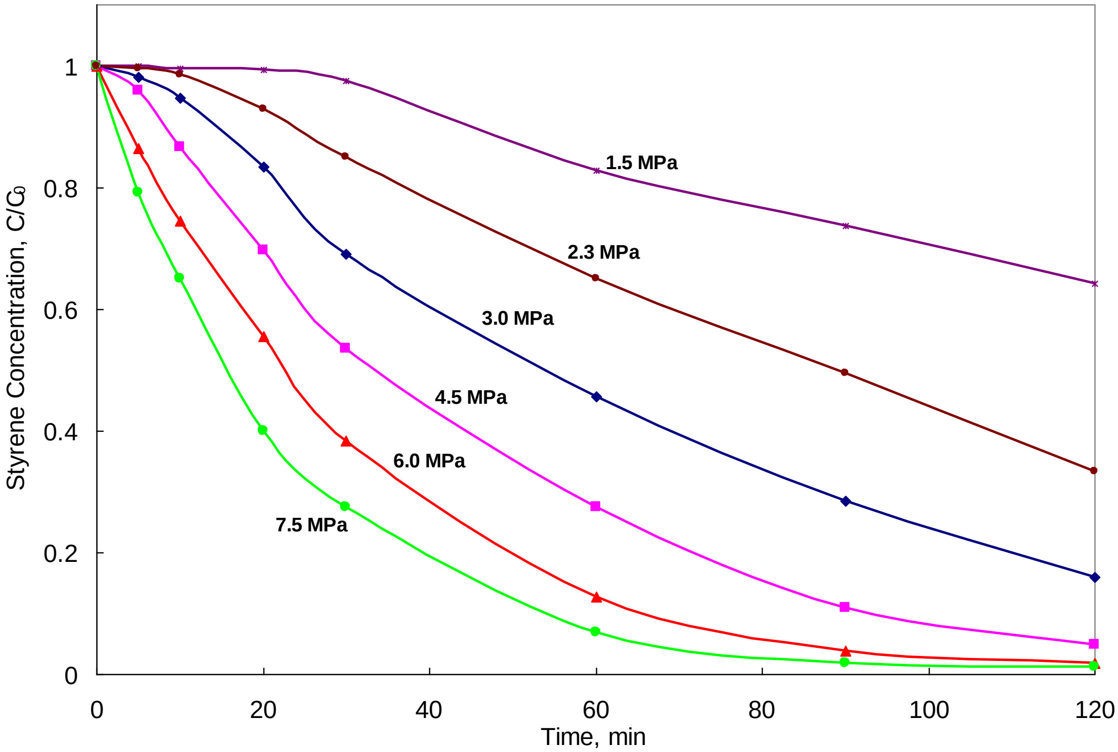


Fig. 3-11. Concentration-time profiles for styrene under different CO pressure. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; temperature, 388K.

3-2-2-7 Effect of Temperature

Temperature is always considered as an important factor which influences the activity of catalyst and the reaction energy barriers of individual reaction steps. In this study, the effect of temperature was investigated at different concentrations of catalyst, styrene, water, and CO pressure (Figure 3-12, 3-13, 3-14, 3-15). It was found that higher temperature favored the reaction rate as expected. Moreover, the similar trends on the effects of concentrations of catalyst, styrene and water and CO pressure were also observed at different temperatures, indicating a similar reaction pathway.

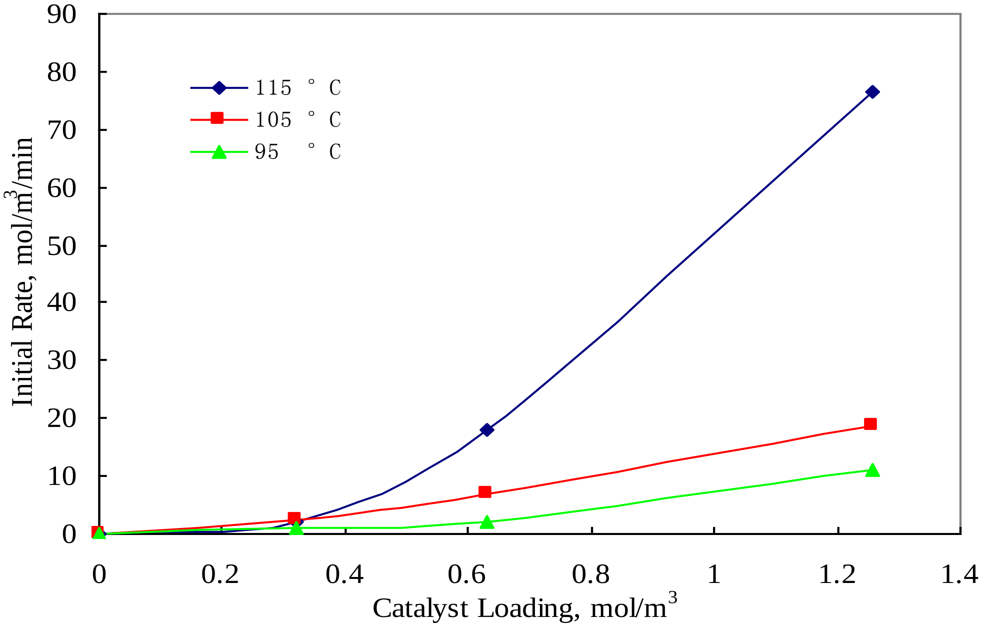


Fig. 3-12. Effect of temperature at different catalyst loadings. Reaction condition: PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa.

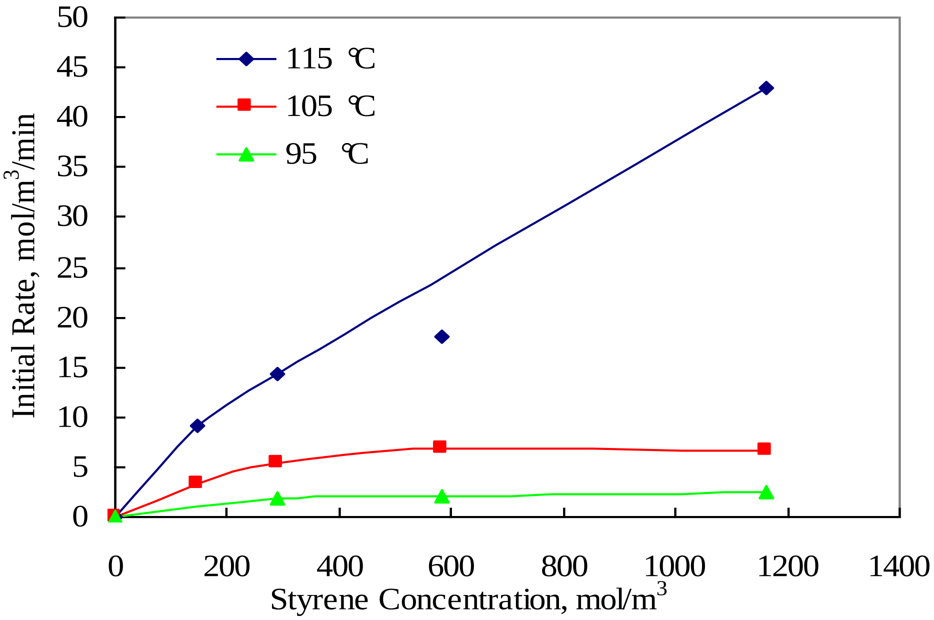


Fig. 3-13. Effect of temperature at different styrene concentrations. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa.

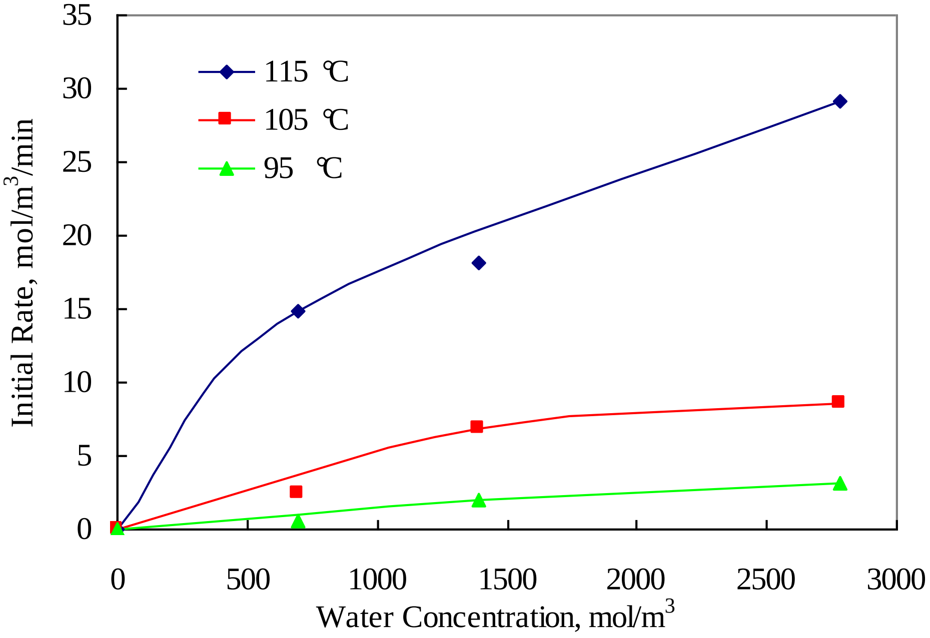


Fig. 3-14. Effect of temperature at different water concentrations. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa.

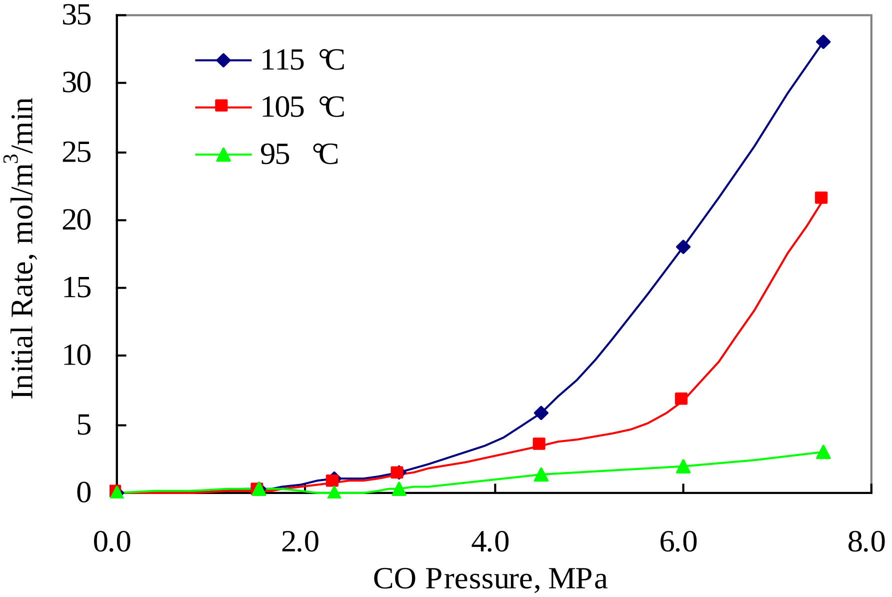


Fig. 3-15. Effect of temperature under different CO pressure. Reaction condition: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3;

styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3.

3-3 Solubility of Carbon Monoxide in the Reaction Medium

In order to interpret the kinetic data, it is necessary to know the CO solubility in the liquid reaction medium. Both theoretical calculations and experimental measurements were carried out to obtain the CO solubility, which are presented in the following subsections.

3-3-1 Theoretical Calculations for CO Solubility

The theoretical calculation was attempted to obtain CO solubility at first. For calculating the CO solubility in MEK, styrene and their binary mixtures, a correlation (Eq. 3-3) proposed by Prausnitz and Shair was used.[10] The semi-empirical correlation, applicable for the solubility of gases in pure, nonpolar solvents at atmospheric pressure based on the theory of regular solutions, can be expressed as:

$$-\ln x_A = \ln(f_A^L / f_A) + \varphi_S^2 V_A^L (\delta_S - \delta_A)^2 / RT \qquad \text{Eq. 3-3}$$

where x_A represents the mole fraction of the dissolved gas phase solute in the solvent at 1 atm pressure, f_A^L and f_A are the fugacity of hypothetical liquid of gas solute and fugacity of pure gas solute at atmospheric pressure respectively, φ_S is the volume fraction of the solvent which is assumed to be unity because volume of gas solute in the liquid can be neglected, V_A^L is the molar volume of hypothetical liquid of gas solute, δ_S, δ_A are solubility parameters for solvent and gas solute, respectively.

In order to calculate f_A^L, the following correlation (Eq. 3-4) proposed by Yen et al. was applied,[11] where $P_{c,A}$ and $T_{c,A}$ are the critical pressure and critical temperature of the gas solute, respectively.

$$f_A^L = P_{c,A} \exp[7.224 - 5.534(T_{c,A}/T) - 2.598 \ln(T/T_{c,A})] \qquad \text{Eq. 3-4}$$

The fugacity of pure CO gas f_A (1 atm) at different temperatures can be calculated by the following correlation.[12]

$$\ln(\frac{f}{P}) = \left(\ln\frac{f}{P}\right)^{(0)} + \omega\left(\ln\frac{f}{P}\right)^{(1)} \qquad \text{Eq. 3-5}$$

Where $\left(\ln\frac{f}{P}\right)^{(0)}$, $\left(\ln\frac{f}{P}\right)^{(1)}$ can be obtained from Lee-Kesler Fugacity-Pressure ratio table listed in the literature.[12] Volume fraction of the solvent φ_S is considered as unity because the solubility of CO in the solvent is very low. V_A^L, δ_A are considered as constants with change in temperature, the values of which can be found in the published paper.[11]

The solubility parameter is the key parameter which can be calculated by:

$$\delta_S = [(\Delta H_v - RT)/V_s]^{1/2} \qquad \text{Eq. 3-6}^{13}$$

where ΔH_v represents the heat of vaporization and *Vs* is the molar volume of the solvent. Two methods (Eq. 3-7, 3-8)[14] for calculating ΔH_v for different solvents at different temperature were compared, where ω represents the acentric factor of CO, T_r the reduced temperature of CO, $T_{r,T}$ is reduced temperature when real temperature is *T*, $T_{r,T}$ is reduced temperature at boiling point.

$$\Delta H_v = RT_c[7.08(1-T_r)^{0.354} + 10.95\omega(1-T_r)^{0.456}],\ 0.6 < T_r \le 1.0 \qquad \text{Eq. 3-7}$$

$$\Delta H_{v,T} = \Delta H_{v,b}(\frac{1-T_{r,T}}{1-T_{r,b}})^n,\ n = 0.375\, or\, 0.38 \qquad \text{Eq. 3-8}$$

The difference between the calculated values is less than 5%. In the further calculation of solubility, Eq. 3-7 was applied. The molar volume of different solvents, *Vs* was calculated from Peng-Robinson equation of state.[15] Based on the calculated data for all the parameters shown above, Henry's constants, *H,* at different temperatures were calculated by the following equations.

$$C_A = x_A / V_S \qquad \text{Eq. 3-9}$$

$$H = C_A / P,\ P = 0.101325MPa \qquad \text{Eq. 3-10}$$

Table 3-2 shows the calculated solubility of carbon monoxide in different pure solvents at different temperatures.

Table 3-2. Calculated solubility of carbon monoxide in methanol, water, styrene and MEK

T, K	*H, kmol/m^3/Mpa*			
	MeOH	Water	Styrene	MEK
298	1.45×10^{-3}	1.51×10^{-10}	2.72×10^{-2}	3.41×10^{-2}
338	6.66×10^{-3}	1.16×10^{-8}	4.17×10^{-2}	5.66×10^{-2}
348	9.32×10^{-3}	3.09×10^{-8}	4.59×10^{-2}	6.32×10^{-2}
358	12.86×10^{-3}	7.84×10^{-8}	5.04×10^{-2}	7.03×10^{-2}
388	31.38×10^{-3}	1.02×10^{-6}	6.56×10^{-2}	9.44×10^{-2}
398	41.12×10^{-3}	2.25×10^{-6}	7.10×10^{-2}	10.28×10^{-2}
448	66.48×10^{-3}	7.52×10^{-5}	10.05×10^{-2}	14.46×10^{-2}

Examination of the published data for CO solubility in different solvents (methanol, water, toluene, etc),[16-18] shows that Henry's constant of CO in methanol is in the range of 8×10^{-2} to 10.8×10^{-2} *kmol/m*^{3}*/Mpa* when temperature varies between 293K to 448K; CO in water, between 7×10^{-3} to 9×10^{-3} *kmol/m*^{3}*/Mpa* when temperature varies from 298K to 448K. For CO in other organic solvents like toluene, 1-octene, the solubility is of the order of 10^{-2} *kmol/m*^{3}*/Mpa*. The calculated data in Table 3-2 for MEK and Styrene are reasonable compared to these reported data. However, the data for MeOH and water are not reliable. The possible reason is the correlation for calculating x_A has some limitations: it is for the solubility of gases in pure, nonpolar solvents at 1 atm. Water and methanol cannot be approximated as non-polar solvents. To use these correlations, it is required to correct the solubility parameter of the solvents. In order to further calculate the CO solubility in MEK-styrene mixtures, the following correlation (Eq. 3-11)[19] was used.

$$(\ln x_A)_{mix} = \varphi_1 \ln x_{A1} + \varphi_1 \ln x_{A2} - V_A^L \beta_{12} \varphi_1 \varphi_2 \qquad \text{Eq. 3-11}$$

where φ_1, φ_2 represent the volume fraction of solvent 1 and 2, respectively, and

$$\varphi_i = x_i V_i / (\sum x_i V_i) \qquad \text{Eq. 3-12}$$

x_{A1}, x_{A2} are the molar fractions of gas in solvent 1 and 2, respectively. β_{12} can be calculated by

$$\beta_{12} = (\delta_{S1} - \delta_{S2})^2 / (RT) \qquad \text{Eq. 3-13}$$

where δ_{S1}, δ_{S2} represent the solubility parameters of solvents 1 and 2, respectively.

Finally, the CO solubility in MEK, styrene and mixtures with different concentration were obtained as shown in Table 3-3. Based on these calculations, it was found that the CO solubility decreased with the increase in styrene concentration in MEK, but increased with temperature.

Table 3-3. Calculated CO solubility in MEK, styrene and mixtures

Solvent	Henry's Constant ×10^2, $kmol/m^3/Mpa$				
	338 K	348 K	358 K	388 K	398 K
MEK	5.656	6.323	7.029	9.439	10.281
1.92% w/w Styrene in MEK	5.630	6.293	6.995	9.389	10.226
3.84% w/w Styrene in MEK	5.604	6.262	6.960	9.338	10.169
7.65% w/w Styrene in MEK	5.551	6.200	6.888	9.234	10.056
15.3% w/w Styrene in MEK	5.445	6.077	6.746	9.029	9.828
Styrene	4.172	4.593	5.038	6.558	7.096

3-3-2 Experimental Measurement for CO Solubility

The theoretical calculation for CO solubility in the MEK-styrene binary medium is less reliable due to the limitation of the methods only for non-polar solvents. In order to obtain more reliable CO solubility for the kinetic study, experimental measurement was carried out. The measurement of CO solubility in water, MEK, styrene and mixtures was carried out in the 300 ml autoclave with precise temperature control (setpoint ±1 °C) following the reported procedure[20] with some modifications. In a typical experiment, a known volume of the solvent was introduced into the autoclave and the contents were heated to a desired temperature. After the desired temperature was reached, the void space in the autoclave was carefully flushed with carbon monoxide and pressurized to the level required (not exceed 200 psi). The contents were then stirred for about 10 min to equilibrate the liquid phase with CO gas. After stirring, the contents were kept still for another 5 min to attain stable saturation of the CO gas in the solvent. The change in the pressure in the autoclave was recorded on-line as a function of time until it remained constant. From the initial and final pressure readings, the CO solubility was calculated as:

$$C_A = (P_i - P_f)V_g / RTV_L \qquad \text{Eq. 3-14}$$

where C_A represents the CO concentration in the solvent at partial pressure of 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 in the autoclave. Therefore, the Henry's constant was calculated as:

$$H = C_A / P_f \qquad \text{Eq. 3-15}$$

Table 3-4 shows the measured CO solubility in different solvents at various temperatures.

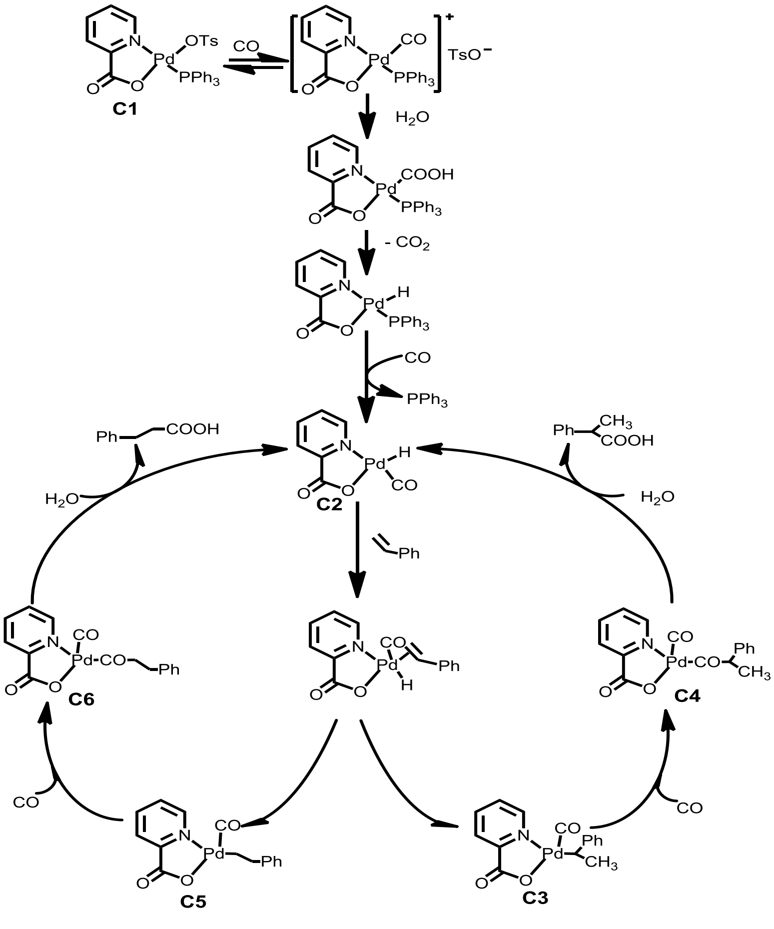
It was observed that the CO solubility decreased with styrene concentration as well as temperature.

Table 3-4. Measured CO solubility in water, MEK, styrene and MEK-styrene-water mixture

Solvent	Henry's Constant ×10^2,kmol/m^3/MPa									
	294K	308K	318K	328K	338K	348K	358K	368K	378K	388K
Water	0.785	0.782	0.778	0.764	0.762	0.684	0.683	0.681	0.678	0.661
MEK	7.759	7.477	7.294	7.110	6.798	6.795	6.791	6.792	6.788	6.778
3.84% w/w Styrene in MEK	7.268	7.251	6.804	6.473	6.366	6.139	6.121	5.792	5.584	5.376
7.65% w/w Styrene in MEK	6.334	6.334	6.333	6.295	6.050	5.777	5.577	5.608	5.485	5.362
15.3% w/w Styrene in MEK	5.889	5.877	5.867	5.784	5.507	5.402	5.236	5.208	5.098	4.988
Styrene	4.696	4.643	4.604	4.438	4.273	4.215	4.175	4.072	3.979	3.886

3-4 Reaction Mechanism

As discussed in Chapter 1, the hydrocarboxylation of styrene using Pd(pyca)(PPh_3)(OTs)/PPh_3/TsOH/LiCl catalyst system in MEK medium, the catalytic cycle most likely follows the Pd-H mechanism.[21] Similar to the analogous hydroesterification reaction,[22] the hydrocarboxylation of styrene is assumed to follow the steps below: 1) the formation of Pd-H complex involving the PdCOOH fragment which is highly unstable and rapidly degrades to palladium hydride and carbon dioxide[23,24]; 2) the insertion of olefin into the Pd-H bond; 3) the migratory insertion of CO into an alkyl-metal bond to produce an acyl-metal complex; and 4) the hydrolysis of the acyl-metal species to regenerate the Pd-H complex and yield the carboxylic acids. Based on Seayad's work[25] on hydroesterification of styrene using the same catalyst system and the investigations about the effects of catalyst concentration, concentration of styrene and water, and partial pressure of carbon monoxide, the plausible reaction mechanism has been proposed as shown in Scheme 3-2.



Scheme 3-2. Proposed reaction mechanism of hydrocarboxylation of styrene using Pd(pyca)(PPh_3)(OTs)/PPh_3/TsOH/LiCl catalyst system

In the mechanism, the effects of free ligand PPh_3, and promoters TsOH and LiCl are not taken into account since they were kept constants for kinetic study. Through addition of CO and water, elimination of CO_2, further addition of CO, the catalyst precursor **C1** converts to the active hydrido-palladium complex **C2**. The irreversible formation process of **C2** is considered as the induction step in the whole reaction mechanism. Once the Pd-H complex is formed, the main hydrocarboxylation is initiated and continues following the catalytic cycles to generate the acid products.

More detailed studies are needed to further establish this reaction mechanism through characterization of the essential intermediates **C2-C6** or micro-kinetic modeling of the experimental data at different reaction conditions. In the next section, a batch reactor model based on the catalytic cycle is presented along with details of evaluation of optimized rate parameters. In the catalytic cycle, no specific step has been assumed as a rate-determining step allowing the evaluation of rate parameters for the elementary reactions between various intermediate catalytic species.

3-5 Kinetic Modeling for Hydrocarboxylation of Styrene Using Pd(pyca)(PPh₃)(OTs)/PPh₃/TsOH/LiCl Catalyst System

Based on the reaction mechanism presented above, the reaction pathways for the predominant product 2-PPA can be simplified to the following four steps:

$$\mathbf{C1} + \mathrm{A} + \mathrm{E} \xrightarrow{k_1} \mathbf{C2} \qquad (1)$$

$$\mathbf{C2} + \mathrm{B} \xrightarrow{k_2} \mathbf{C3} \qquad (2)$$

$$\mathbf{C3} + \mathrm{A} \xrightarrow{k_3} \mathbf{C4} \qquad (3)$$

$$\mathbf{C4} + \mathrm{E} \xrightarrow{k_4} \mathbf{C2} + \mathrm{P} \qquad (4)$$

A: CO
B: Styrene
E: H_2O
P: 2-PPA

The reaction rate for each step can be expressed as:

$$r_1 = k_1 \mathrm{C1}(\mathrm{A})^{\mathrm{m}}(\mathrm{E}) \qquad \text{Eq. 3-16}$$

$$r_2 = k_2 \mathrm{C2}(\mathrm{B}) \qquad \text{Eq. 3-17}$$

$$r_3 = k_3\mathrm{C3(A)^n} \qquad \text{Eq. 3-18}$$

$$r_4 = k_4\mathrm{C4(E)} \qquad \text{Eq. 3-19}$$

where m=2, and n=1 since carbon monoxide has significant effect on the induction period of the reaction. The rate equations for change in concentrations of styrene, water, 2-PPA, and the catalyst species (**C1-C4**) can be described as shown below. The initial conditions are also presented. For solving these ODEs, it is necessary to know the guess values of rate constants in each reaction step. From the concentration-time profiles, the reasonable guess values for all the four rate constants can be calculated. Combined with the initial conditions and guessed rate constants, the ODEs can be solved by a subroutine using the fourth-order Runge-Kutta algorithm.

Rate Equations

$$-\frac{d\mathbf{C1}}{d\mathrm{t}} = r_1 = k_1\mathbf{C1}(\mathrm{A})^{\mathrm{m}}(\mathrm{E}) \qquad \text{Eq. 3-20}$$

$$-\frac{d\mathbf{C2}}{d\mathrm{t}} = -r_1 + r_2 - r_4 = -k_1\mathbf{C1}(\mathrm{A})^{\mathrm{m}}(\mathrm{E}) + k_2\mathbf{C2}(\mathrm{B}) - k_4\mathbf{C4}(\mathrm{E}) \qquad \text{Eq. 3-21}$$

$$-\frac{d\mathbf{C3}}{d\mathrm{t}} = -r_2 + r_3 = -k_2\mathbf{C2}(\mathrm{B}) + k_3\mathbf{C3}(\mathrm{A})^{\mathrm{n}} \qquad \text{Eq. 3-22}$$

$$-\frac{d\mathbf{C4}}{d\mathrm{t}} = -r_3 + r_4 = -k_3\mathbf{C3}(\mathrm{A})^{\mathrm{n}} + k_4\mathbf{C4}(\mathrm{E}) \qquad \text{Eq. 3-23}$$

$$-\frac{d\mathrm{B}}{d\mathrm{t}} = r_2 = k_2\mathbf{C2}(\mathrm{B}) \qquad \text{Eq. 3-24}$$

$$-\frac{d\mathrm{E}}{d\mathrm{t}} = r_1 + r_4 = k_1\mathbf{C1}(\mathrm{A})^{\mathrm{m}}(\mathrm{E}) + k_4\mathbf{C4}(\mathrm{E}) \qquad \text{Eq. 3-25}$$

$$-\frac{d\mathrm{P}}{d\mathrm{t}} = -r_4 = k_4\mathbf{C4}(\mathrm{E}) \qquad \text{Eq. 3-26}$$

$$\mathrm{m} = 2, \mathrm{n} = 1$$

where A, B, E, P represent the concentrations of CO, styrene, water, 2-PPA in liquid phase, mol/m^3; **C1**, **C2**, **C3**, **C4** represent the concentrations of the four catalyst species in liquid phase, mol/m^3.

Initial Conditions

$$B = B_0, E = E_0, P = 0$$

$$\mathbf{C1} = C_0, \mathbf{C2} = \mathbf{C3} = \mathbf{C4} = 0$$

where B_0, E_0 and C_0 represent the initial concentrations of styrene, water, and catalyst, respectively.

In order to optimize the rate constants to approach the real values, an optimization program using the Levenberg-Marquardt algorithm was coupled with the ODE solver. In this method, the optimal rate constants were achieved through minimizing the deviation between the simulated results and the experimental data (Eq. 3-27) at measured times during each cycle of iteration. Finally, the minimized deviation was converged at 1.49×10^{-8} which is above the machine precision.

$$\phi = \sum_{i=1}^{N} \sum_{j=1}^{M} (Y_{ij,\exp} - Y_{ij,\mathrm{mod}})^2 \qquad \text{Eq. 3-27}$$

Table 3-5. Simulated rate constants at different temperatures

T, K	$k_1 \times 10^{10}$, (m^3/mol)^3/min	$k_2 \times 10^2$, m^3/mol/min	$k_3 \times 10^2$, m^3/mol/min	$k_4 \times 10^2$, m^3/mol/min
368	6.416	5.372	3.131	1.800
378	8.482	10.047	7.806	4.141
388	9.145	13.815	24.252	7.392

The optimized values of rate constants are shown in Table 3-5. The constant k_1 is much less than the other three, indicating that the induction period appears in the first reaction step. Each rate constant increases with temperature, showing consistency with the Arrhenius law. The activation energies for the single reaction steps 2, 3 and 4 calculated from the rate constants at different temperatures are shown in Table 3-6.

Table 3-6. Calculated activation energies for reaction 2, 3 and 4

Ea_2, kJ/mol	Ea_3, kJ/mol	Ea_4, kJ/mol
56.21	121.37	83.96

The comparison of simulated concentration-time profiles with the experimental data at different reaction conditions are shown in the following figures (Fig.3-16 ~ Fig.3-34).

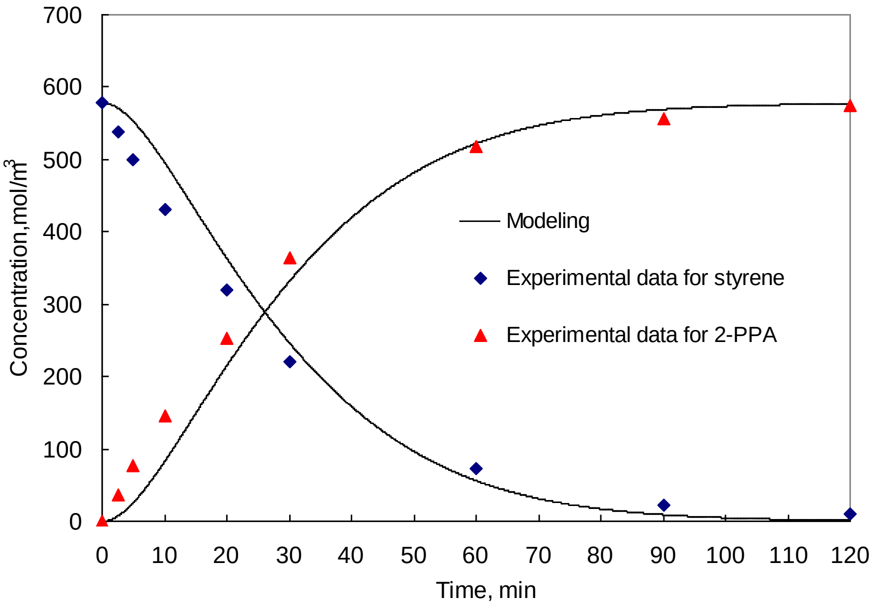


Fig. 3-16. Standard reaction at 388 K Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 388 K; reaction time, 2 h.

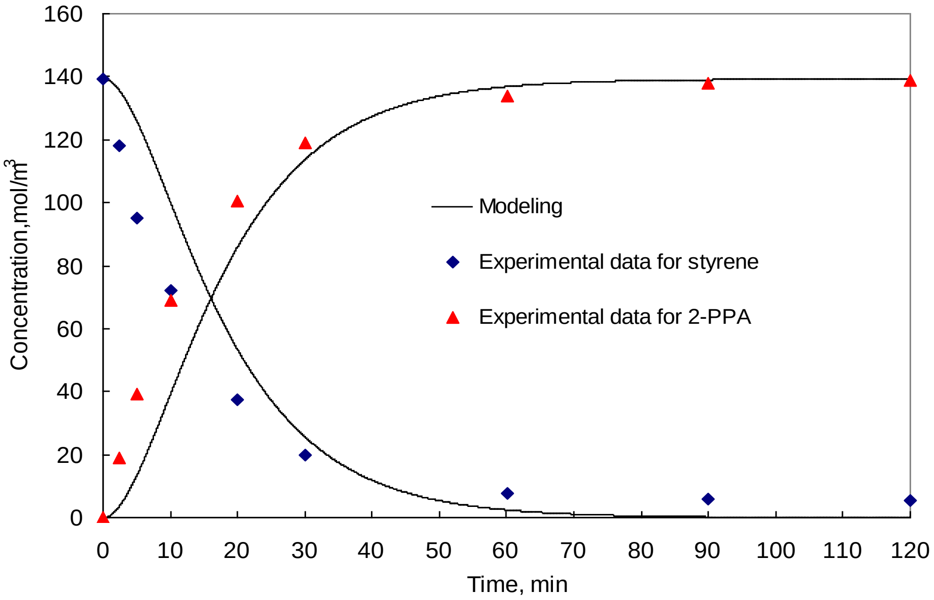


Fig. 3-17. Effect of styrene concentration at 388 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 145.46mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 388 K; reaction time, 2 h.

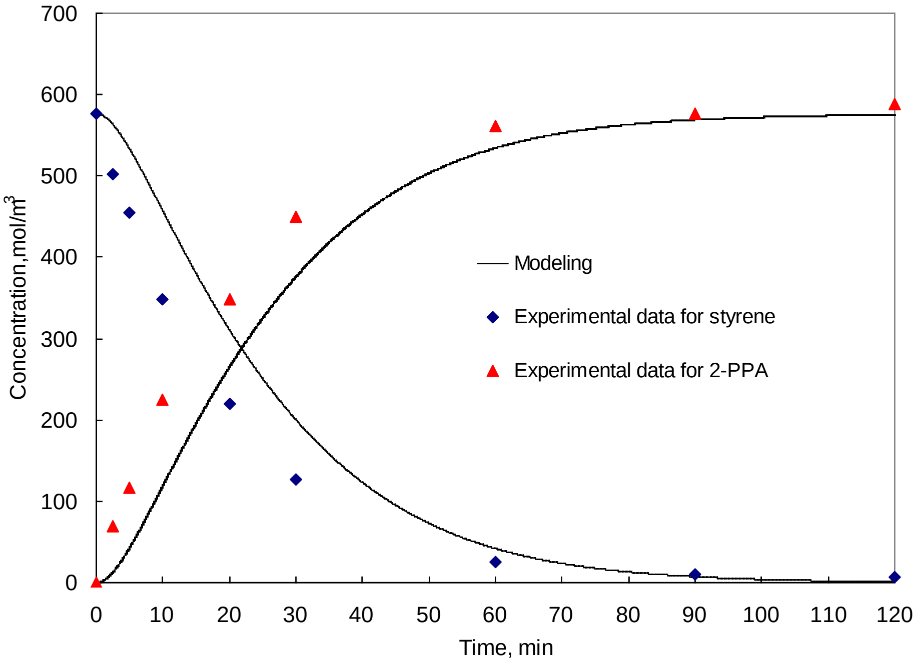


Fig. 3-18. Effect of water concentration at 388 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 2777.78 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 388 K; reaction time, 2 h.

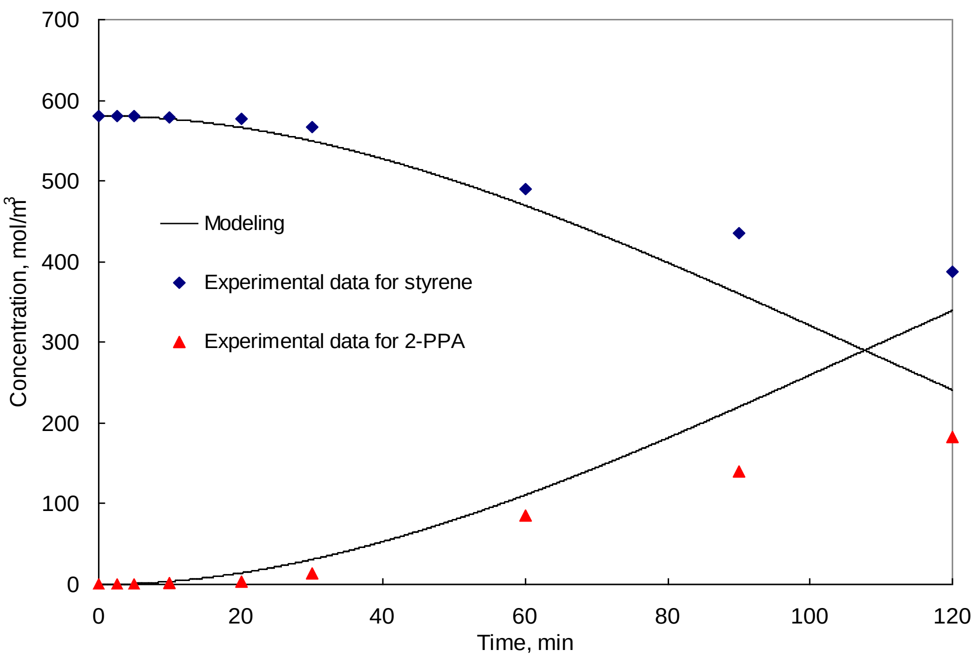


Fig. 3-19. Effect of CO pressure at 388 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 1.5 MPa; T, 388 K; reaction time, 2 h.

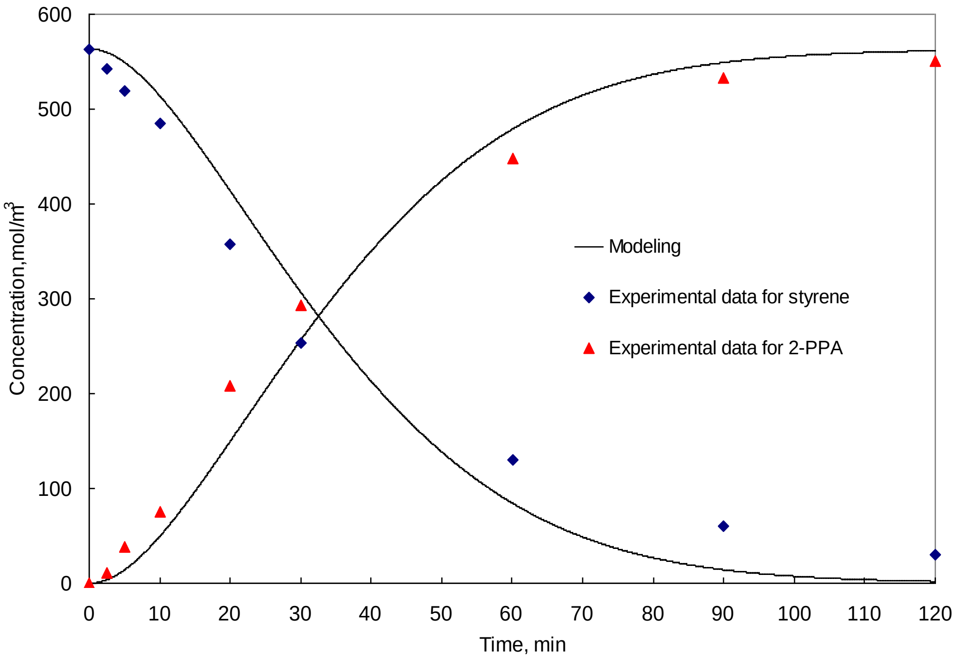


Fig. 3-20. Effect of CO pressure at 388 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 4.5 MPa; T, 388 K; reaction time, 2 h.

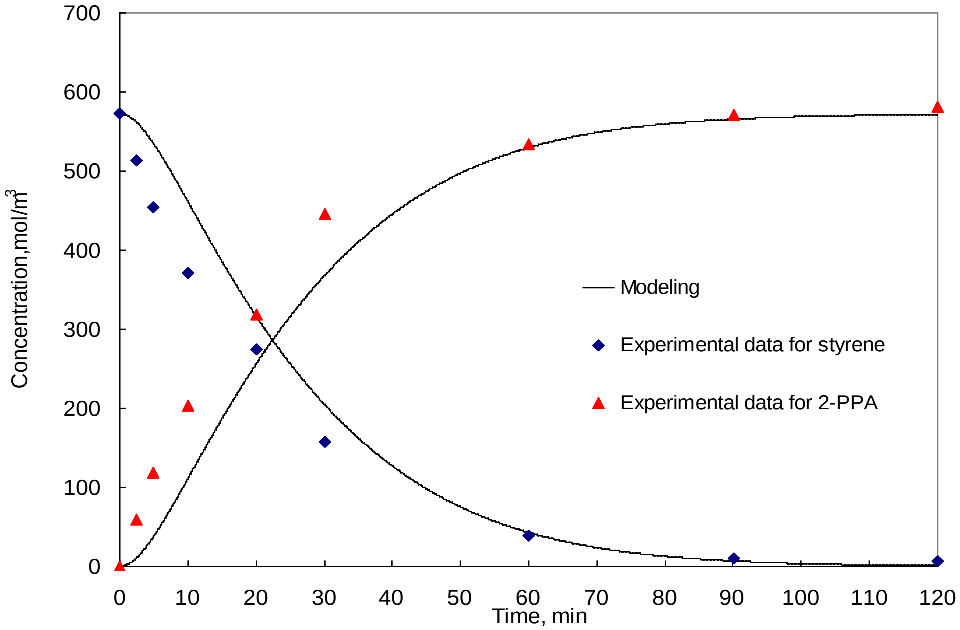


Fig. 3-21. Effect of CO pressure at 388 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 7.5 MPa; T, 388 K; reaction time, 2 h.

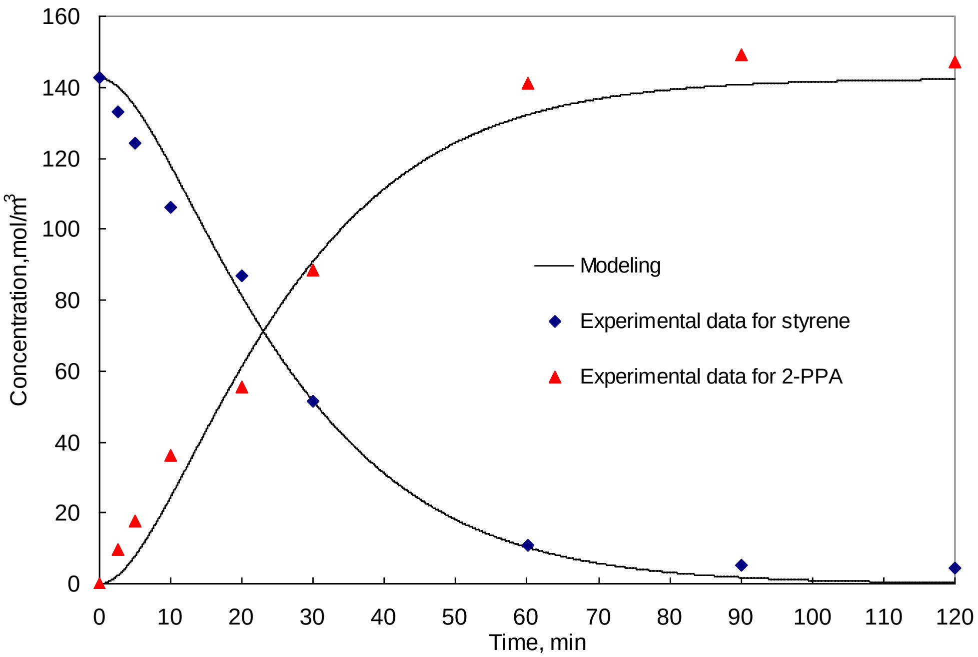


Fig. 3-22. Effect of styrene concentration at 378 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 145.46 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 378 K; reaction time, 2 h.

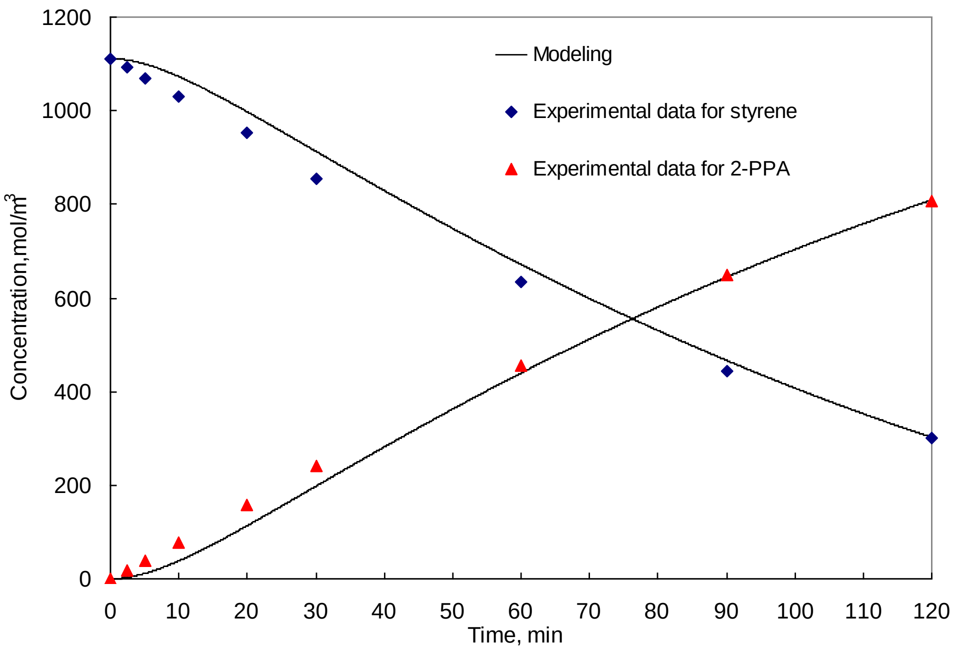


Fig. 3-23. Effect of styrene concentration at 378 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 1163.71mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 378 K; reaction time, 2 h.

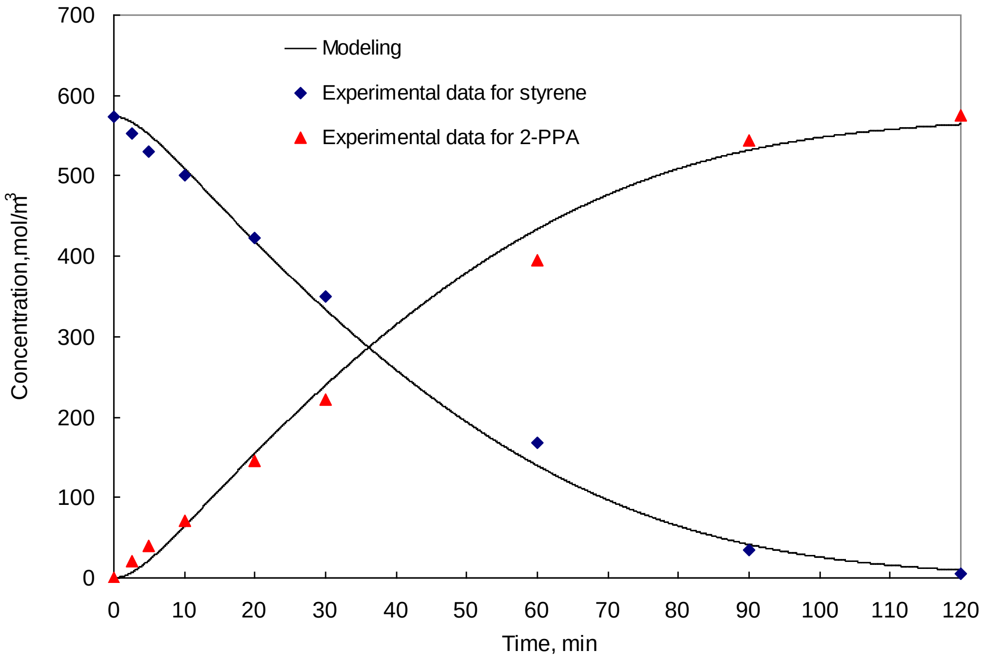


Fig. 3-24. Effect of water concentration at 378 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 2777.78 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 378 K; reaction time, 2 h.

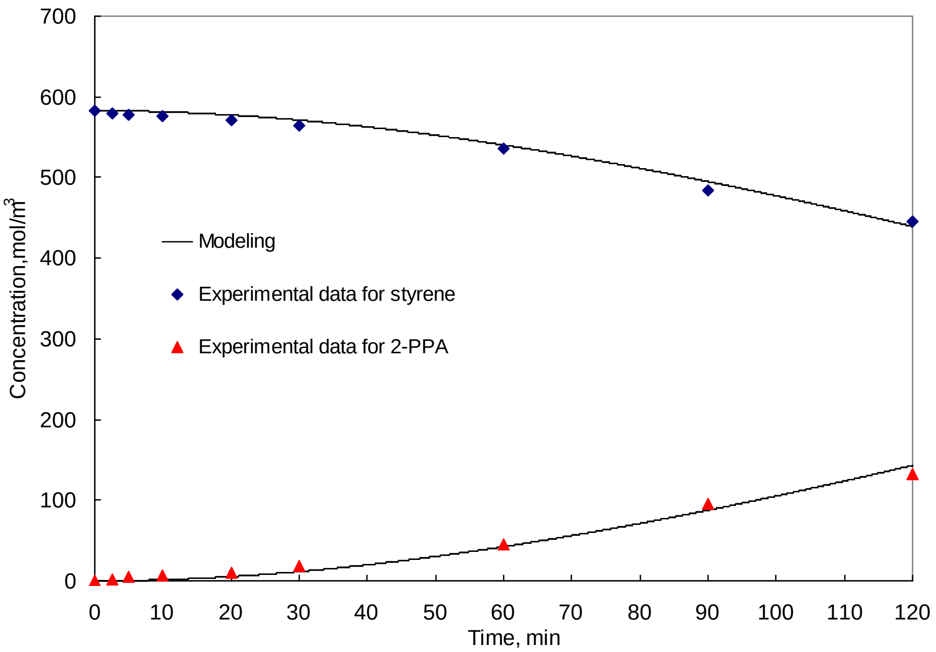


Fig. 3-25. Effect of CO pressure at 378 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 1.5 MPa; T, 378 K; reaction time, 2 h.

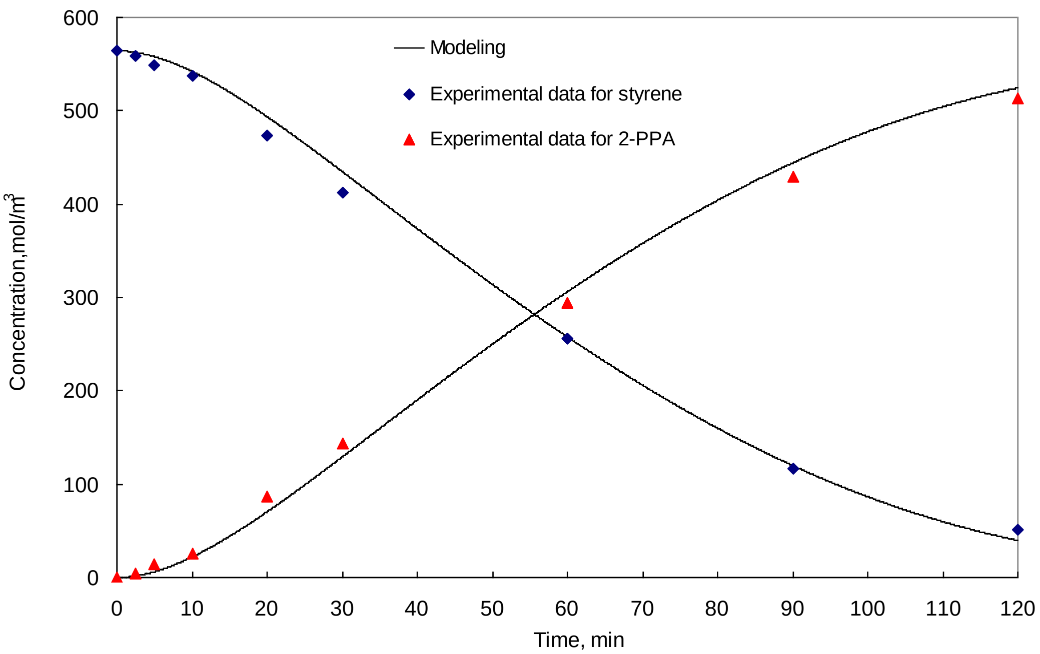


Fig. 3-26. Effect of CO pressure at 378 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 4.5 MPa; T, 378 K; reaction time, 2 h.

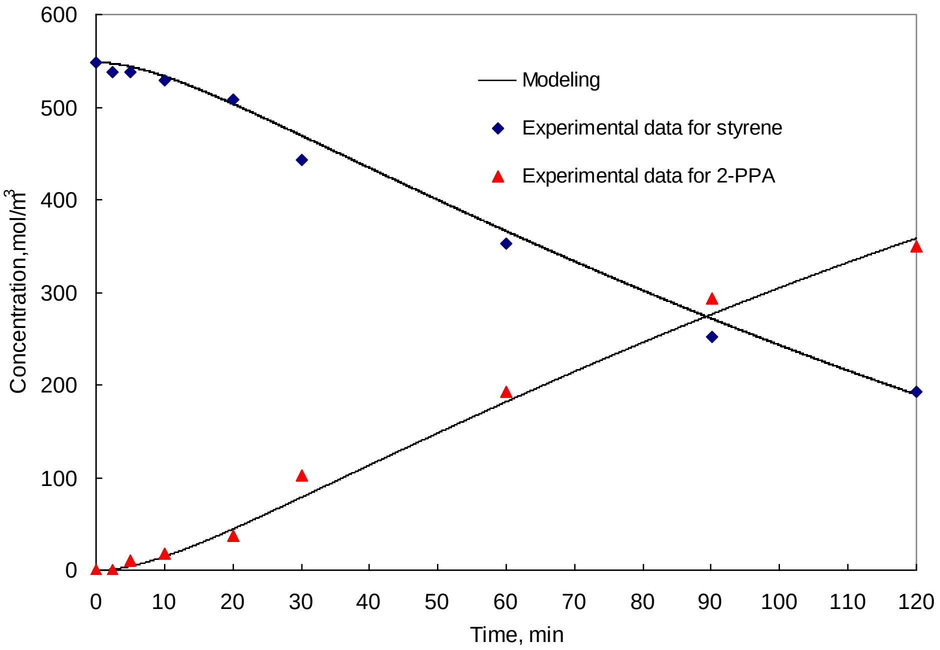


Fig. 3-27. Standard reaction at 368 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 368 K; reaction time, 2 h.

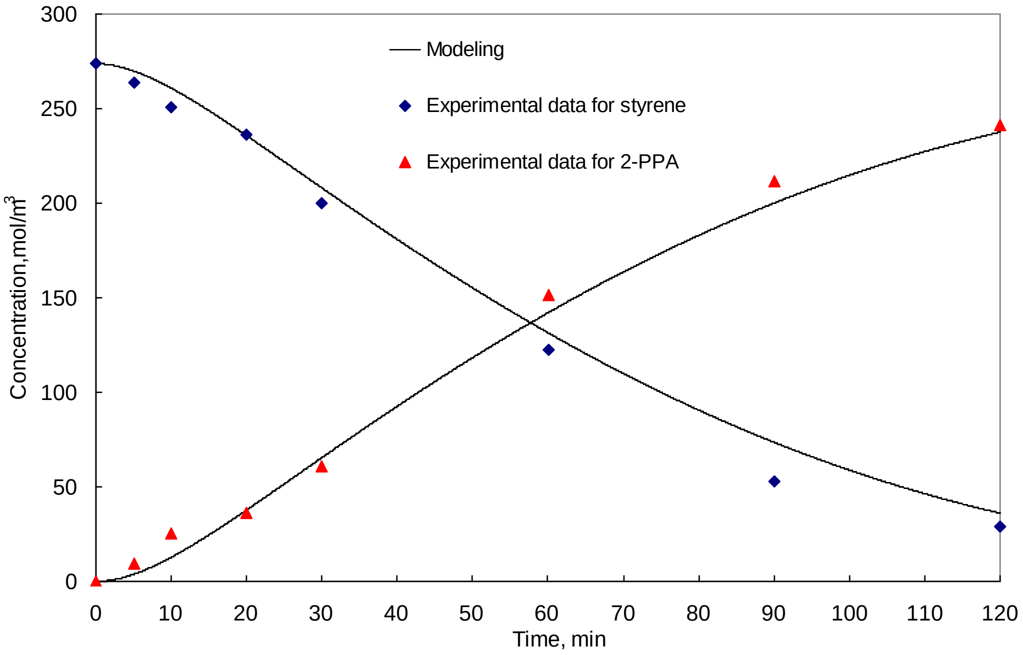


Fig. 3-28. Effect of styrene concentration at 368 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 287.34 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 368 K; reaction time, 2 h.

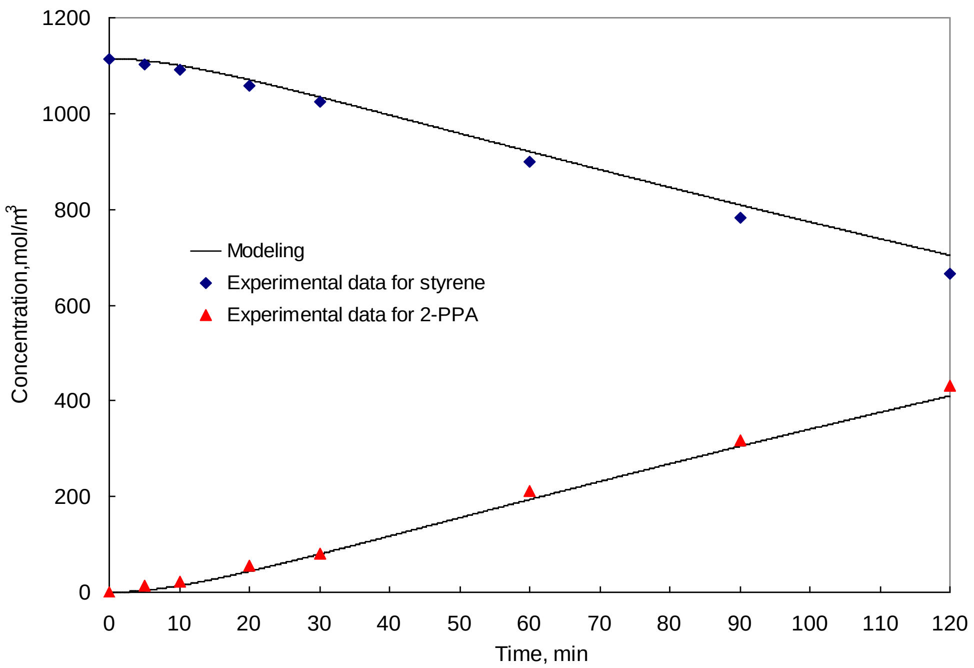


Fig. 3-29. Effect of styrene concentration at 368 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 1163.71mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 368 K; reaction time, 2 h.

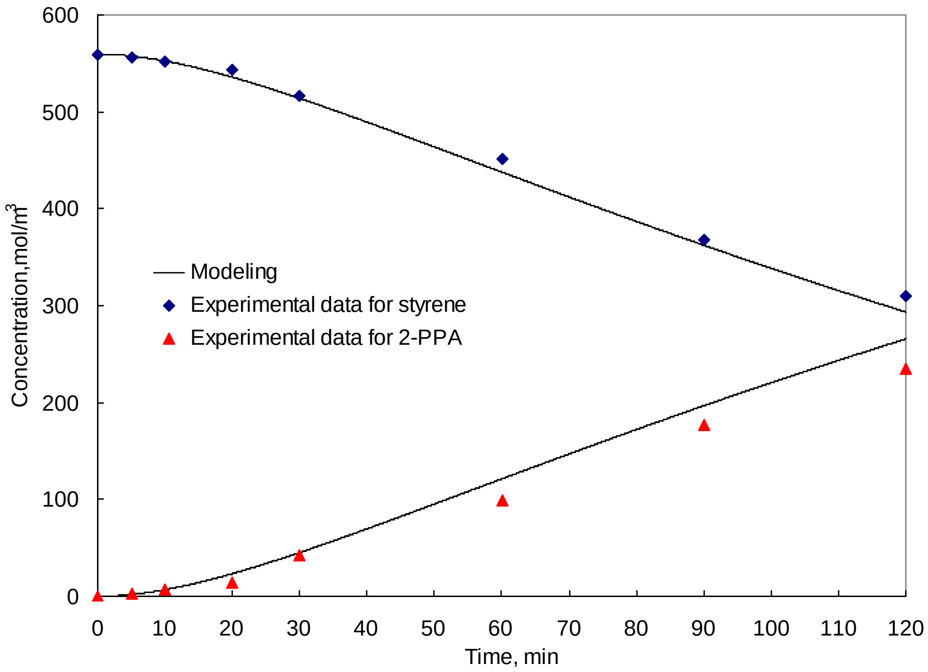


Fig. 3-30. Effect of water concentration at 368 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 694.44mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 368 K; reaction time, 2 h.

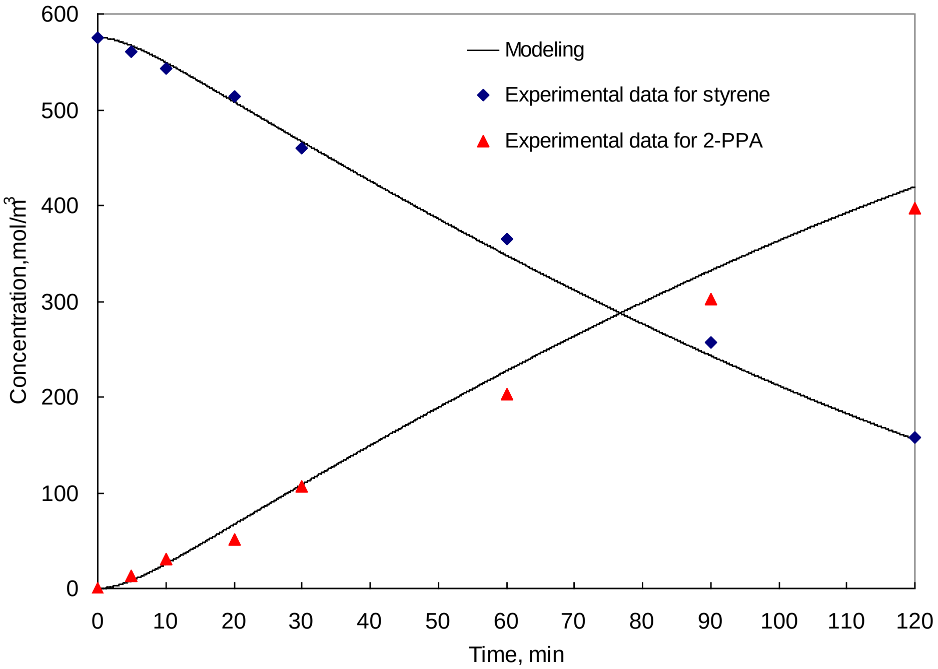


Fig. 3-31. Effect of water concentration at 368 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 2777.78mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 368 K; reaction time, 2 h.

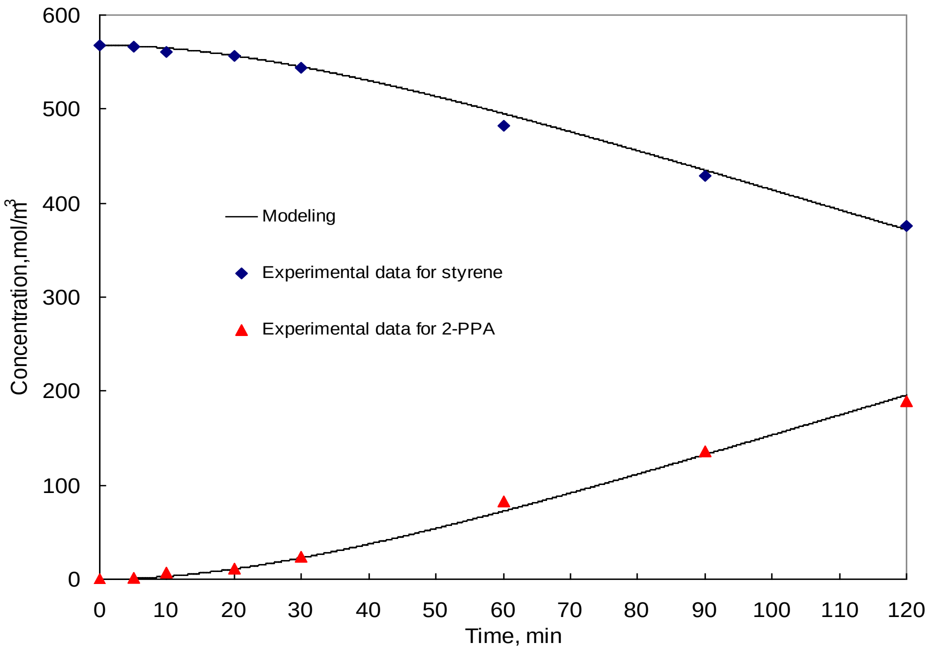


Fig. 3-32. Effect of CO pressure at 368 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 3.0 MPa; T, 368 K; reaction time, 2 h.

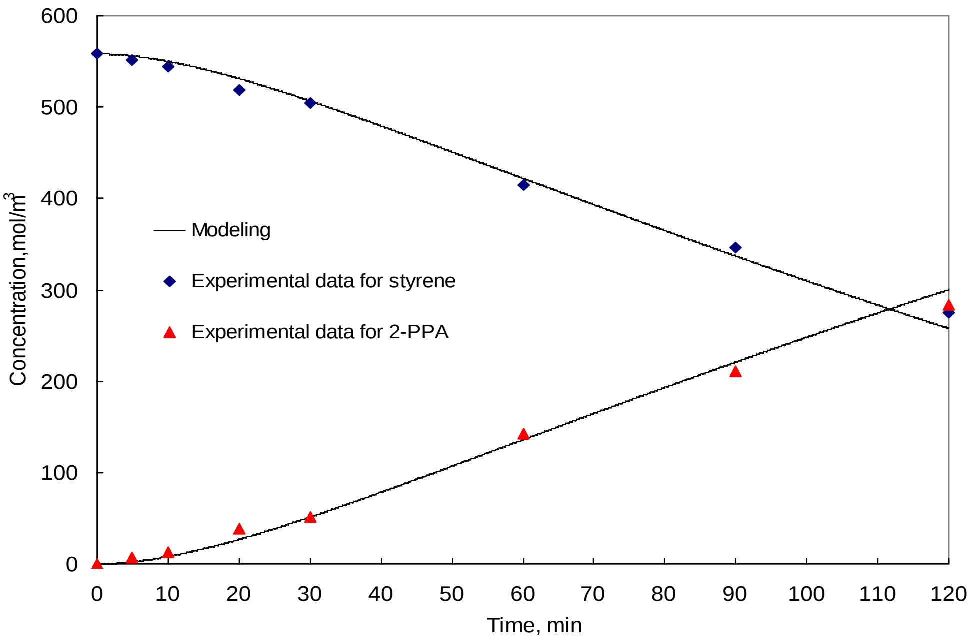


Fig. 3-33. Effect of CO pressure at 368 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 4.5 MPa; T, 368 K; reaction time, 2 h.

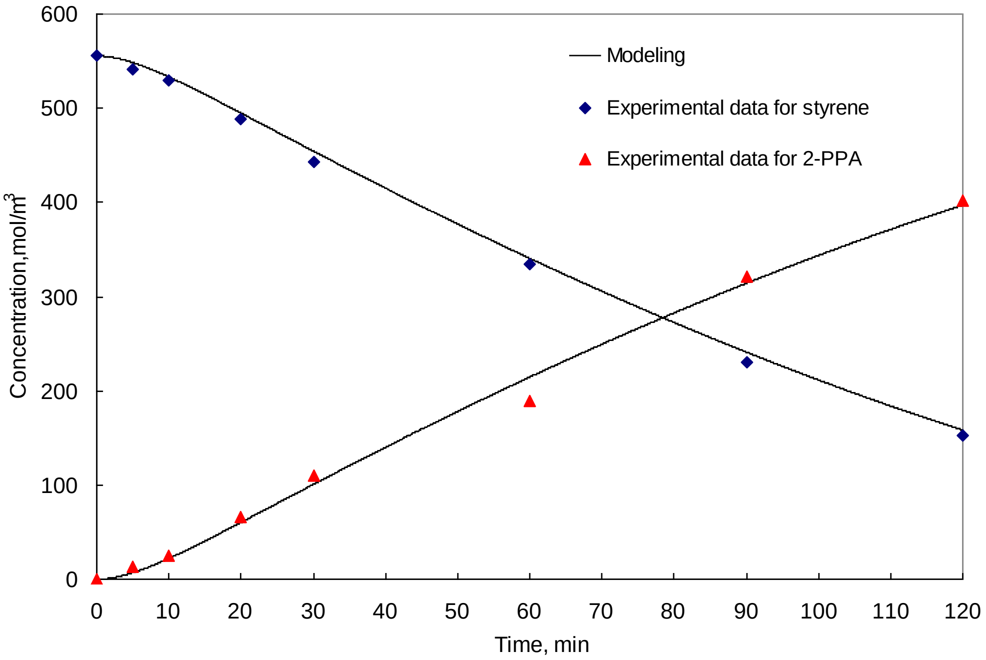


Fig. 3-34. Effect of CO pressure at 368 K. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh$_3$, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 7.5 MPa; T, 368 K; reaction time, 2 h.

The excellent match between the experimental and predicted results at widely different conditions indicates that the reaction mechanism represents the hydrocarboxylation of styrene. The parity plots shown in Figure 3-35 and 3-36 clearly indicate the goodness of fit of the experimental data with model prediction. The proposed model also allows prediction of the concentrations of all the four catalyst species. As shown in the typical concentration-time profiles for the catalyst species in Figure 3-37, catalyst precursor C1 converts to the other three species C2-C4 during the reaction. In the end of the reaction, only the active Pd-H complex C2 exists in the system and has stable concentration which may achieve continuous reaction.

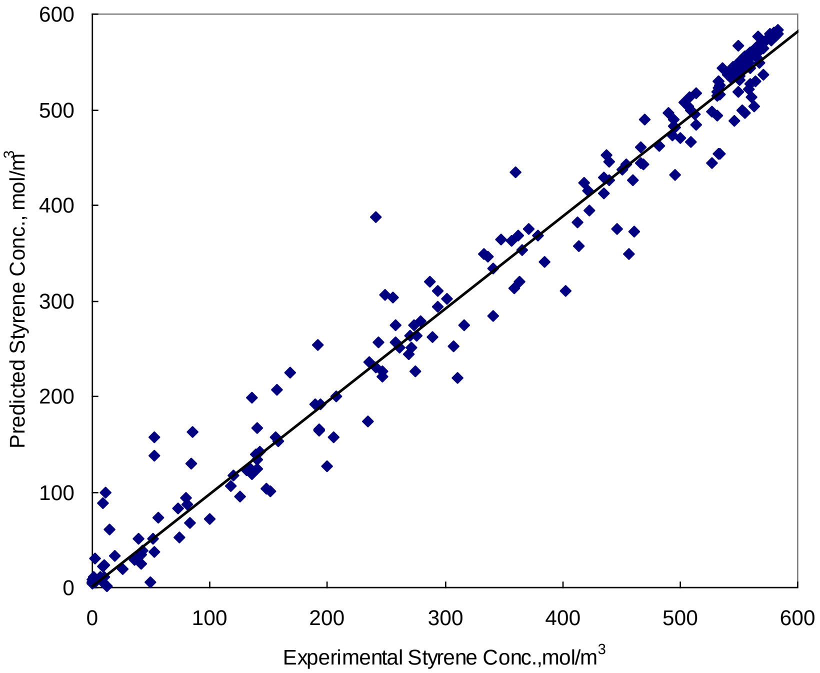


Fig. 3-35. Comparison of modeling predicted concentration of styrene with experimental data.

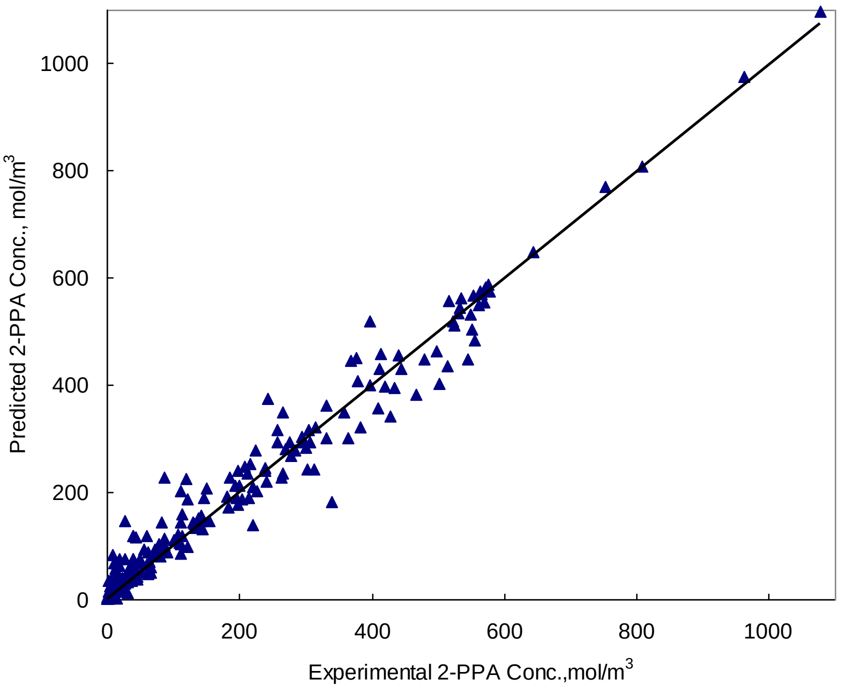


Fig. 3-36. Comparison of modeling predicted concentration of 2-PPA with experimental data.

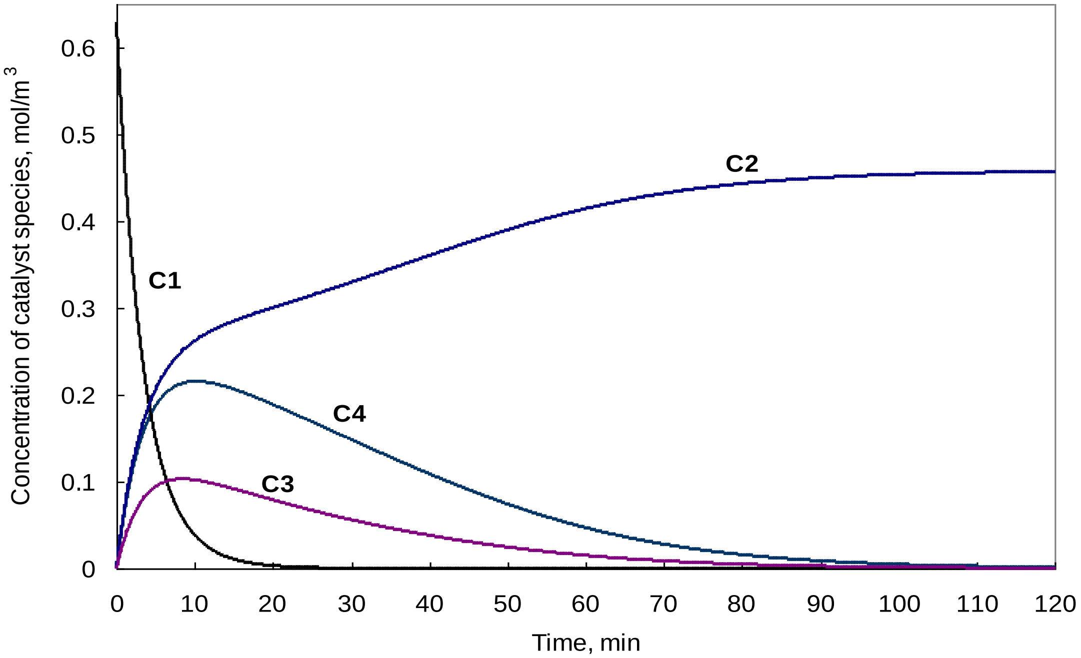


Fig. 3-37. Typical simulated concentration-time profiles of catalyst species. Reaction conditions: catalyst precursor, 0.64 mol/m^3; PPh_3, 2.34 mol/m^3; TsOH:LiCl (1:1), 24 mol/m^3; styrene, 581.85 mol/m^3; water, 1388.89 mol/m^3; solvent, MEK; total volume, 1.2×10^{-4} m^3; Pco, 6.0 MPa; T, 388 K; reaction time, 2 h.

3-6 Conclusions

A detailed kinetic study for hydrocarboxylation of styrene using Pd(pyca)(PPh_3)(OTs)/PPh_3/TsOH/LiCl catalyst system has been carried out. Effects of all the reaction parameters, including catalyst, styrene and water concentration, CO pressure, ligand and promoters concentrations were investigated. It is shown that a catalytic cycle based on Pd-H mechanism represents the kinetic data including the induction period observed under certain conditions (e.g. lower CO pressure and catalyst precursor concentration). It is further demonstrated that the complex rate behavior is well represented using the approach of micro-kinetic modeling in which no single step is assumed as a rate controlling step. Although, further work would be necessary to support the nature of active species, the present work and the approach of kinetic modeling is a significant step towards understanding the reaction mechanism using kinetic modeling as one of the tools. Besides, the present work provides the first kinetic study for hydrocarboxylation of styrene using the most active Pd-Pyca catalyst system.

References

1. J. Falbe (Ed.), *New Synthesis with Carbon Monoxide*, Springer-Verlag, Berlin (1980).
2. M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem. Int. Ed.*, 43 (2004) 3368.
3. G. Kiss, *Chem. Rev.*, 101 (2001) 3435.
4. B. Cornills, W. A. Herrmann, *Applied Homogeneous Catalysis with Organometallic Compounds*, Weinheim: Wiley-VCH, vol 1, 2 and 3 (2002).
5. R. A. Sheldon, *Chem, Ind.*, (1992) 903.
6. V. Elango, K. G. Davenport, M. A. Murphy, G. N. Mott, E. G. Zey, B. L. Smith, G. L. Moss, G. Mott, *Eur. Appl.* EP 400892 (1990).
7. A. Seayad, J. Seayad, P. L. Mills and R. V. Chaudhari, *Ind. Eng. Chem. Res.*, 42 (2003) 2496.
8. S. Jayasree, A. Seayad and R. V. Chaudhari, *Chem, Commun.*, (1999) 1067.
9. A. Seayad, A. A. Kelkar, L. Toniolo and R. V. Chaudhari, *J. Mol. Catal. A: Chem.*, 151 (2000) 47.
10. J. M. Prausnitz and F. H. Shair, *AIChE J.*, 7 (1961) 682.
11. L. C. Yen and J. J. Mcketta, *AIChE J.*, 8 (1962) 501.
12. R.C. Reid, J. M. Prausnitz and B. E. Poling, *The properties of Gases and Liquids*,

McGraw-Hill, (1987) p103.
13. J. H. Hildebrand, R. L. Scott, *Solubility of Electrolytes and Non-electrolytes, Am. Chem. Soc.*, 424 (1948) 9.
14. R.C. Reid, J. M. Prausnitz and B. E. Poling, *The properties of Gases and Liquids*, McGraw-Hill, (1987) p220, p228.
15. D. Y. Peng and D. B. Robinson, *Ind. Eng. Chem. Fundam.*, 15 (1976) 59.
16. Subodh B. Dake and R. V. Chaudhari, *J. Chem. Eng. Data*, 30 (1985) 400.
17. P. Lühring and A. Schumpe, *J. Chem. Eng. Data*, 34 (1989) 250.
18. U. J. Jáuregui-Haza, E. J. Pardillo-Fontdevila, A. M. Wilhelm and H. Delmas, *Latin American Applied Research*, 34 (2004) 71.
19. J. H. Hildebrand, J. M. Prausnitz and R. L. Scott, *Regular and Related Solutions*, Van Nostrend-Relnhold: New York (1970).
20. Purwanto, R. M. Deshpande, R. V. Chaudhari and H. Delmas, *J. Chem. Eng. Data*, 41 (1996) 1414.
21. I del Río, C. Claver and P. W. N. M. van Leeuwen, *Eur, J. Inorg. Chem.*, (2001) 2719.
22. G. Cavinato and L. Toniolo, *J. Organomet. Chem.*, 398 (1990) 187.
23. T. Yoshida, Y. Ueda and S. Otsuka, *J. Am. Chem. Soc*., 100 (1978) 3941.
24. E. Drent, *Pure. Appl. Chem.*, 62 (1990) 661.
25. J. Seayad, *Studies on carbonylation of olefins, alkynes and alcohols using homogeneous and heterogeneous catalysts*, (2000) 133-143