

Carbonylation of 1-arylethanols using homogeneous Pd complex catalysts

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Abstract

Carbonylation of 1-arylethanols has been studied using homogeneous palladium complex catalysts in the presence of TsOH and LiCl as promoters. Effect of various parameters, such as promoters, catalyst precursors, solvents, various substrates and concentration of water on the catalytic activity as well as the product selectivity was studied. ^{31}P NMR experiments were carried out to investigate the nature of active palladium species formed in solution under the reaction conditions. Based on the experimental trends and ^{31}P NMR studies, a catalytic cycle based on an anionic palladium(0) species as the active catalytic species is proposed. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Carbonylation; 1-Arylethanols; 1-(4-Isobutylphenyl)ethanol; Ibuprofen; Homogeneous catalysis; Palladium; 2-Arylpropionic acid; Catalytic cycle

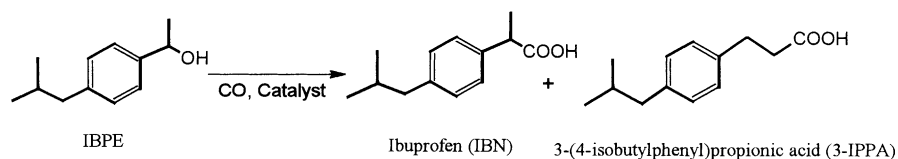
1. Introduction

Carbonylation of 1-arylethanols is a reaction of considerable industrial importance, since it provides an environmentally benign route for the synthesis of 2-arylpropionic acids, a class of non-steroidal anti-inflammatory agents [1,2]. This has been first demonstrated by Hoechst Celanese Corporation [3] for the synthesis of Ibuprofen on a commercial scale by the carbonylation of 1-(4-isobutylphenyl)ethanol (IBPE) (Scheme 1).

In this process, the desired high selectivity (>98%) for Ibuprofen was achieved at high CO pressures (16–34 MPa) using $\text{PdCl}_2(\text{PPh}_3)_2$ or $\text{PdCl}_2\text{-4PPh}_3$ as

a catalyst precursor in a biphasic medium consisting of methyl ethyl ketone (MEK) as the organic phase and 10% aqueous HCl as the promoter at 403 K [3]. At moderate CO pressures (~ 6.8 MPa) the Ibuprofen selectivity was reported to be below 70% [4], which was improved up to 98% by the use of CuCl_2 as a cocatalyst [5]. Low catalytic activities (turnover frequency, $\text{TOF} = 10\text{--}175\text{ h}^{-1}$) were observed in all these cases besides the tedious separation of the catalyst from products, which involves precipitation of the complex by adding non-polar solvents [6]. In order to make the catalyst recovery more facile, biphasic catalyst systems consisting of water-soluble palladium-TPPTS complexes were used, in which case also very low reaction rates ($\text{TOF} = 2.3\text{--}18\text{ h}^{-1}$) were reported [7,8]. Regiospecific carbonylation of 1-(6-methoxynaphthyl)ethanol to methyl ester of Naproxen was also reported recently by using

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Scheme 1. Carbonylation of 1-(4-isobutylphenyl)ethanol.

$\text{PdCl}_2\text{-PPh}_3\text{-CuCl}_2\text{-TsOH}$ as a catalyst system under homogeneous conditions at 6 MPa of CO and 373 K, but with significantly lower catalytic activity ($\text{TOF} = 2 \text{ h}^{-1}$) [9]. Thus, it has been a challenge to accomplish a highly active catalytic system for the regioselective synthesis of 2-arylpropionic acids that works under mild reaction conditions.

Our preliminary studies on the carbonylation of IBPE using Pd(II) complexes showed that the catalytic activity as well as Ibuprofen selectivity can be significantly enhanced by using a combination of TsOH and LiCl as promoters under homogeneous conditions at relatively lower CO pressures [10,11]. For instance, Ibuprofen selectivities >95% and high reaction rates (TOF up to 1200 h^{-1}) were achieved for the carbonylation of IBPE using $\text{PdCl}_2(\text{PPh}_3)_2/\text{TsOH}/\text{LiCl}$ as the catalyst system in MEK as a solvent under 5.4 MPa of CO pressure and 388 K [10]. Supported Pd metal catalysts along with excess phosphine ligands and TsOH/LiCl promoters also gave very high regioselectivity (up to 99.5%) and high TOF (up to 3375 h^{-1}) for the carbonylation of 1-arylethanol to 2-arylpropionic acids under similar conditions [12]. In this case, though the catalyst was efficiently recycled achieving high TON (>55,000), a significant part of the reaction was found to be homogeneously catalyzed and the enhanced catalytic activity and selectivity was due to the combination of Pd with PPh_3 and TsOH/LiCl promoters. In this paper a detailed investigation on the effect of various parameters, such as type of promoters, catalyst precursors, solvents, substrates and concentration of water on the catalytic activity and product selectivity is reported in order to address the catalytic activity-selectivity pattern and reaction mechanism for the carbonylation of 1-arylethanol using $\text{PdCl}_2(\text{PPh}_3)_2/\text{TsOH}/\text{LiCl}$ as the catalyst system and IBPE as a model substrate under homogeneous conditions.

2. Experimental

2.1. General

The procedure for preparing IBPE is described elsewhere [10]. The 1-arylethanol substrates, 1-(6-methoxy-2-naphthyl)ethanol, 1-(4-methylphenyl)ethanol, 1-(4-chlorophenyl)ethanol and 1-(4-cyanophenyl)ethanol were prepared by sodiumborohydride reduction of the corresponding aryl ketones. The complexes PdCl_2R_2 [13], $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3$ [14] and $\text{Pd}(\text{PPh}_3)_4$ [15] were prepared following literature procedures. *p*-toluenesulfonic acid monohydrate, methanesulfonic acid (Aldrich, USA), HCl, halide salts (Sd. Finechem, India) and CO (Matheson, USA, 99.9% purity) were used as received. All the solvents were freshly distilled using known procedures and degassed by argon before use.

2.2. Carbonylation procedure

The reactions were carried out in a 50 ml Parr Autoclave made of Hastelloy C-276 having facilities for gas inlet and outlet, rupture disc as a safety measure in case of excessive pressure build up, intermediate sampling, temperature controlled heating and variable agitation speed [16]. In a typical carbonylation reaction, known quantities of the substrate, catalyst, promoters, water and the solvent were charged to the autoclave. The contents were flushed few times with nitrogen followed by carbon monoxide and heated to the desired temperature (under low stirring, 10–20 rpm). After attaining the temperature, the autoclave was pressurized with CO to the desired level and the reaction was started by agitation (1000 rpm). To maintain a constant pressure in the reactor, CO was fed through a constant-pressure regulator from a reservoir vessel (100 ml). Pressure drop in the

reservoir vessel was recorded by means of a pressure transducer, as a function of time. Intermediate liquid samples were also taken at regular intervals of time and were subjected to analysis to determine the conversion and selectivity at a given time from which TOF and selectivities were calculated. The analysis of the liquid samples was carried out using a gas chromatograph (HP 5890) using a HP-FFAP capillary column. The products were further characterized by NMR and IR analysis. The conversion, TOF and selectivity were calculated as follows.

$$\begin{aligned} \text{Net conversion} &= \text{Initial concentration of IBPE} \\ &\quad - \text{Final concentration of (IBPE} \\ &\quad + \text{IBS} + \text{IBPCI)} \\ \% \text{ Conversion} &= \frac{\text{Net conversion}}{\text{Initial concentration of IBPE}} \times 100 \end{aligned}$$

$$\begin{aligned} \% \text{ Selectivity of the product} \\ &= \frac{\text{Concentration of the product formed}}{\text{Net conversion}} \times 100 \end{aligned}$$

$$\begin{aligned} \text{Turnover frequency (TOF, h}^{-1}\text{)} \\ &= \frac{\text{No. of moles of carbonylation products formed}}{\text{No. moles of catalyst} \times \text{time (h)}} \end{aligned}$$

2.3. ^{31}P NMR experiments

Samples for ^{31}P NMR experiments were prepared by mixing the required amounts of $\text{PdCl}_2(\text{PPh}_3)_2$, TsOH and LiCl in 2.5 cm^3 of degassed solvent in a 10 mm NMR tube flushed with argon. The spectra were recorded at 121.1 MHz by using 85% H_3PO_4 as an external standard and internal D_2O (added in a capillary tube) as the deuterium source. For the preparation of samples under CO pressure, $\text{PdCl}_2(\text{PPh}_3)_2$ (0.072 mmol), PPh_3 (0.144 mmol), TsOH (1.8 mmol), LiCl (1.8 mmol) and water ($0.5\text{--}1 \text{ cm}^3$) in 15 cm^3 of degassed solvent (MEK or DMF) were charged to the autoclave, flushed with argon followed by CO, heated to 378 K, pressurized to 5.4 MPa with CO and kept under stirring for 10–30 min. Intermediate samples were directly taken under CO atmosphere to the NMR tube with the help of a sampling device and the spectra were recorded immediately as discussed above.

3. Results and discussion

3.1. Catalyst system

The catalytic system used in this work is a mixture of $\text{PdCl}_2(\text{PPh}_3)_2/\text{TsOH}/\text{LiCl}$, in the ratio of 1:100:100 unless otherwise stated, from which the active catalyst species is formed in situ.

3.1.1. Role of promoters

As explained in our previous communication [10], carbonylation of IBPE in the presence of acidic and halide promoters proceeds through the formation of 4-isobutylstyrene (IBS) and 1-(4-isobutylphenyl)ethyl chloride (IBPCI) as intermediates. IBPE on acid catalyzed dehydration forms IBS that on addition of H^+ and Cl^- ions forms IBPCI and undergoes carbonylation to form the carboxylic acids 2-(4-isobutylphenyl)propionic acid (IBN) and 3-(4-isobutylphenyl)propionic acid (3-IPPA). Hence, it is expected that the nature and concentration of promoters have a pronounced effect on the catalytic activity. In order to further understand the role of promoters, the effect of concentrations of TsOH and LiCl as well as the effect of different acidic and halide promoters on the catalytic activity and product selectivity were investigated. A study on the effect of the ratio of TsOH to LiCl on catalytic activity and selectivity (Table 1) showed that the initial TOF increased to 950 h^{-1} with a marginal decrease in Ibuprofen selectivity when TsOH: LiCl ratio was changed to 2:1 (Run no. 2, Table 1) from 1:1 (TOF = 405 h^{-1} , Run no. 1, Table 1). In this case, significant amount of Pd metal precipitation was observed after the reaction. On the contrary, a drastic decrease in catalytic activity (TOF = 125 h^{-1}) and enhanced Ibuprofen selectivity (97.5%) was observed at a TsOH: LiCl ratio of 1:2 (Run no. 3, Table 1) along with precipitation of the catalyst precursor $\text{PdCl}_2(\text{PPh}_3)_2$ during the course of reaction. Thus, the optimum catalytic activity and stability was achieved with a TsOH to LiCl ratio of 1:1 and hence all further reactions were carried out at a TsOH to LiCl ratio of 1:1. The catalytic activity increased linearly and Ibuprofen selectivity improved marginally with increase in concentrations of TsOH and LiCl at a ratio of 1:1 (Table 1).

The catalytic activity was found to vary significantly with the nature of counter ions of the acidic as well as halide promoters. In the case of acidic promoters,

Table 1
Effect of concentration of TsOH and LiCl on the carbonylation of IBPE^a

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

^a Reaction conditions: IBPE, 28.1 mmol; PdCl₂(PPh₃)₂, 0.056 mmol; water, 1.2 cm³; P_{CO}, 5.4 MPa; T, 388 K; MEK, 19.5 cm³.

Table 2
Role of promoters on the carbonylation of IBPE^a

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

^a Reaction conditions: IBPE, 28.1 mmol; PdCl₂(PPh₃)₂, 0.056 mmol; promoter, 5.6 mmol; water, 1.2 cm³; P_{CO}, 5.4 MPa; T, 388 K; solvent, MEK.

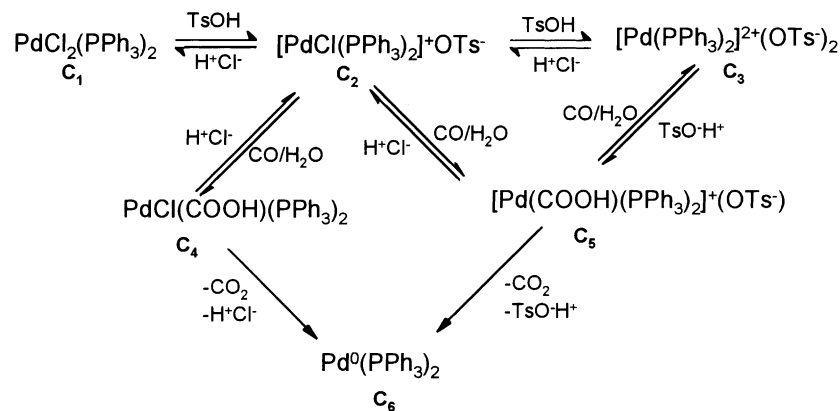
the catalytic activity decreased in the order TsO⁻ > CH₃SO₃⁻ > Cl⁻, which is in a reverse order of coordination ability. In the case of chloride promoters with different cations, the catalytic activity decreased in the order Li⁺ > Na⁺ ~ K⁺ ~ Bu₄N⁺ > H⁺. It is to be noted that in the case of HCl as the promoter significantly lower catalytic activity (TOF = 90 h⁻¹, Run no. 3, Table 2) was attained in spite of the formation of sufficient amounts of IBPCI,¹ which is the active carbonylation substrate [10].

Thus the strong influence of the promoters TsOH and LiCl on catalytic activity is noteworthy, which suggests the role of promoters in the catalytic cycle in addition to the formation of active carbonylation substrate IBPCI. It is possible that TsOH facilitate the efficient reduction of the stable Pd(II) precursor to the active Pd(0) species, which activate IBPCI by oxidative addition. In the presence of excess TsO⁻ ions, the chloride ligands of PdCl₂(PPh₃)₂ (C₁) can

be exchanged with TsO⁻ ions forming an equilibrium of cationic species [Pd(PPh₃)₂Cl]⁺(TsO⁻) (C₂) and [Pd(PPh₃)₂]²⁺(TsO⁻)₂ (C₃) in solution as illustrated in Scheme 2. Cationic Pd(II) complexes easily reduce to Pd(0) species [17,18]. In the presence of higher amounts of TsO⁻ the equilibrium may shift more towards C₃, which is much easily reduced to Pd(0) species than that of C₂. Dicationic palladium (II) phosphine complexes are known to reduce to Pd metal even in the presence of small amounts of water [19]. On the other hand, presence of more amount of LiCl than TsOH, the equilibrium in Scheme 2 may shift towards C₁ thereby retarding the effective formation of the active Pd(0) species and hence negatively affecting the net catalytic activity.

In order to check for the formation of C₂ and C₃, ³¹P NMR experiments were carried out by adding TsOH to a solution of PdCl₂(PPh₃)₂, C₁, in DMF. C₁ has only low solubility in DMF at room temperature but dissolved slowly on warming (323 K) and showed a ³¹P NMR signal at 24.23 ppm (δ₁). In the presence of excess of TsOH (25 equivalents), PdCl₂(PPh₃)₂

¹ As indicated by the analysis of intermediate liquid samples by GC.



Scheme 2. Formation of active Pd(0) complex from Pd(II) precursor.

dissolved readily at 323 K showing a major signal at 28.15 ppm (δ_2) in addition to δ_1 with a δ_2/δ_1 ratio of 3.6. This solution decomposed partly to palladium metal on keeping for 1–3 h. A comparison of the two spectra is given in Fig. 1. The signal at δ_2 can be assigned to the monocationic palladium complex $[\text{PdCl}(\text{PPh}_3)_2]^+\text{TsO}^-$ (C_2) formed from C_1 as shown in Scheme 2. No ^{31}P NMR signals corresponding to the dicationic species $[\text{Pd}(\text{PPh}_3)_2]^{2+}(\text{TsO}^-)_2$ [17–19] was observed in this case, however, can be formed in the presence of excess of TsOH under reaction conditions. The low ligated Pd(0) species, C_6 , formed by

the reduction of Pd(II) precursor in the presence of CO and water can initiate the catalytic cycle by oxidative addition of the organic halide (IBPCl).

3.1.2. Activity of various catalyst precursors

In order to understand the electronic and steric influences of ligands on the catalytic activity and selectivity behavior, the effect of various palladium precursors with different phosphine ligands was studied for the carbonylation of IBPE in the presence of TsOH/LiCl promoters under homogeneous conditions (Table 3). The highest catalytic activity

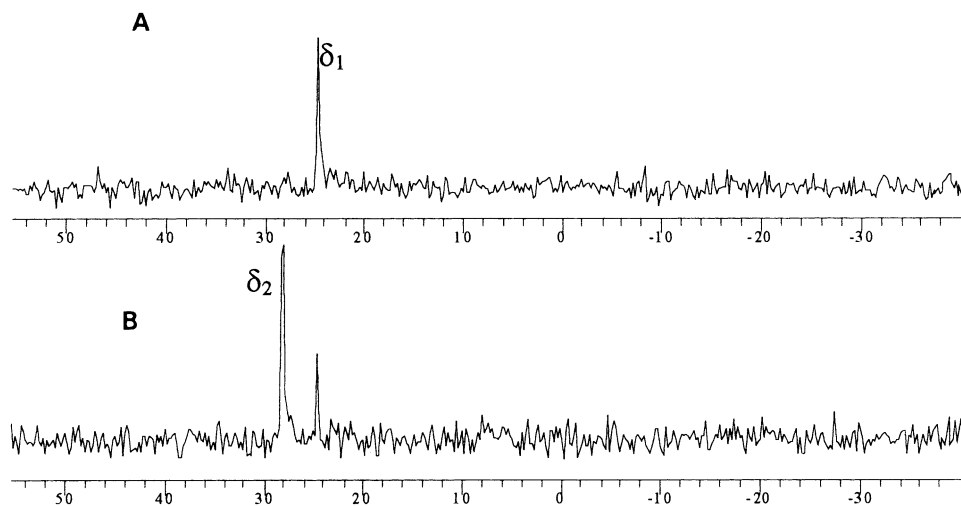
Fig. 1. (A) ^{31}P NMR spectrum of $\text{PdCl}_2(\text{PPh}_3)_2$ in DMF; (B) with 25 equivalents of TsOH.

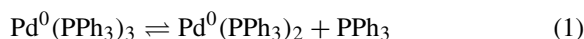
Table 3
Effect of different catalyst precursors on the carbonylation of IBPE^a

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

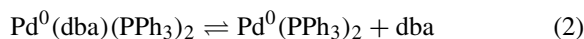
^a Reaction conditions: IBPE, 28.1 mmol; Pd-complex, 0.056 mmol; TsOH, 5.6 mmol; LiCl, 5.6 mmol, water, 1.2 cm³; P_{CO}, 5.4 MPa; T, 388 K; MEK, 19.5 cm³.

(TOF = 405 h⁻¹) was observed with triphenylphosphine as the ligand and the catalytic activity of Pd complexes with different phosphine ligands varied in the order of P(*p*-F-C₆H₄)₃ < P(*p*-Cl-C₆H₄)₃ < PPh₃ > P(*p*-CH₃-C₆H₄)₃ > P(*p*-OMe-C₆H₄)₃, when the ligands were arranged with increasing order of basicity. These effects can be attributed to the modified properties of the metal center towards activation of the substrates. In the presence of more basic ligands the metal center becomes more nucleophilic facilitating the electrophilic addition of the organic halide [20,21]. But CO insertion is more favored in the case of less basic weakly coordinating ligands compared to more basic strongly coordinating ligands [22]. Thus, PPh₃ that is moderately basic and labile, was found to be the best compromise with respect to catalytic activity. In the case of P(*o*-tol)₃ as a ligand, the catalytic activity was very low (TOF = 10 h⁻¹, Run no. 6, Table 3), which may be due to the steric hindrance created at the metal center. Pd(dppb)Cl₂ showed no activity towards carbonylation of IBPE under the present reaction conditions. Highest selectivity (>99.67%) was observed in the case of palladium complexes with phosphine ligands having electron withdrawing substituents, such as tris(*p*-chlorophenyl)phosphine and tris(*p*-fluorophenyl)phosphine as ligands and lower selectivity was observed in the case of electron rich phosphine ligands, such as tris(*p*-tolyl)phosphine and tris(*p*-methoxyphenyl)phosphines (Table 3) as also observed earlier in the case of hydroesterification of styrene [23].

Since Pd(0) species are the most plausible active catalytic species for this reaction, the effect of palladium(0) complexes like Pd(PPh₃)₄ (Run no. 7, Table 3) and Pd₂(dba)₃·CHCl₃ (Run no. 8, Table 3) as catalytic precursors was also studied. In the case of both Pd(PPh₃)₄ and Pd(dba)₂·CHCl₃/4PPh₃ with TsOH/LiCl promoters the catalytic activity was lower compared to that of PdCl₂(PPh₃)₂. This can be due to the insufficient formation of the true active catalytic low ligated species Pd⁰(PPh₃)₂ in solution from the precursor because of the unfavorable dissociation of PPh₃ ligand from Pd⁰(PPh₃)₃. (Eq. (1)) [24–27]



Similarly, the lower catalytic activity of Pd₂⁰(dba)₃·CHCl₃ also emphasizes the negative role or poisoning effect of dba ligand in the initial formation of active catalytic species. It is known that Pd⁰(dba)(PPh₃)₂ is the major catalytic species in solution of a mixture of Pd⁰(dba)₂ and PPh₃ and the concentration of active low-ligated Pd⁰(PPh₃)₂ is limited due the very endergonic equilibrium (Eq. (2)) [28–30].



However, the in situ reduction of PdCl₂(PPh₃)₂ forms directly and efficiently the active Pd⁰(PPh₃)₂ [28–30], thereby, providing higher reaction rates compared to that of Pd(PPh₃)₄ or Pd₂(dba)₃·CHCl₃/4PPh₃.

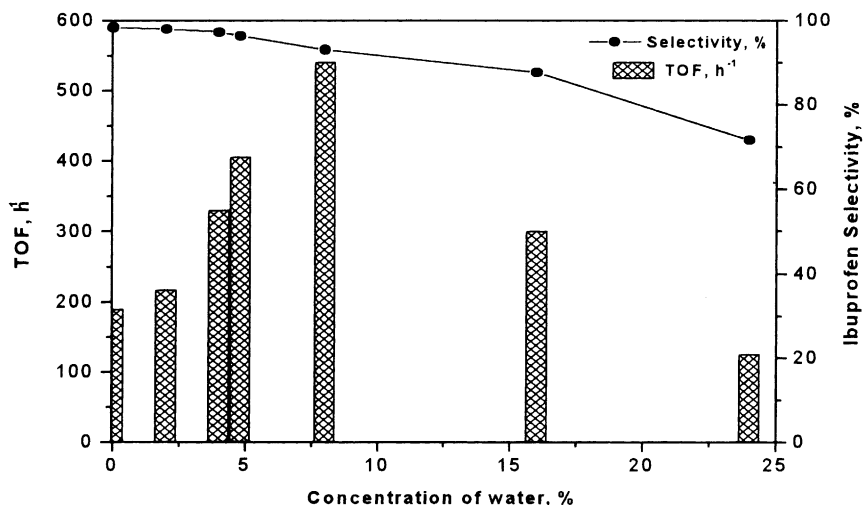


Fig. 2. Effect of concentration of water on TOF and selectivity. Reaction conditions: IBPE, 28.1 mmol; PdCl₂(PPh₃)₂, 0.056 mmol; TsOH, 5.62 mmol; LiCl, 5.62 mmol; P_{CO}, 5.4 MPa; T, 388 K; MEK, 19.5 cm³.

3.1.3. Effect of water

Concentration of water has a significant effect on both catalytic activity and selectivity behaviour in the carbonylation of IBPE. Catalytic activity increased with concentration of water up to 8%, beyond which it decreased steadily (Fig. 2).

The main reason for the steady decrease in activity and selectivity beyond a concentration of 8% of water is the change of homogeneous nature of the reaction medium to biphasic in which case the concentration of promoters in the organic phase decreases. However, the increase in catalytic activity within lower concentrations (0–8%) is notable (Fig. 2). Water is believed to have two important roles in the overall catalytic process. One is the initial formation of active

Pd(0) species by a kind of water-gas shift reaction [31–35]. The second is in the product formation step and regeneration of the active Pd(0) species from the Pd-acyl species by coordination and subsequent reductive elimination or by direct nucleophilic attack. Higher concentration of water may facilitate these steps thereby, increasing the overall catalytic activity under homogeneous conditions.

3.1.4. Effect of solvents

The effect of various polar and non-polar solvents on the carbonylation of IBPE was investigated and the results are presented in the Table 4. Among the solvents studied, the highest catalytic activity was achieved in the presence of acetone (TOF = 620 h⁻¹,

Table 4
Effect of solvents on the carbonylation of IBPE^a

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

^a Reaction conditions: IBPE, 28.1 mmol; PdCl₂(PPh₃)₂, 0.056 mmol; TsOH, 5.6 mmol; LiCl, 5.6 mmol, water, 1.2 cm³; P_{CO}, 5.4 MPa; T, 388 K; solvent, 19.5 cm³.

Run no. 1, Table 4) and MEK (TOF = 405 h⁻¹, Run no. 2, Table 4). Surprisingly, other polar solvents such as DMF (TOF = 25 h⁻¹, Run no. 4, Table 4) and NMP (TOF = 22 h⁻¹, Run no. 5, Table 4) provided significantly lower catalytic activities. In the case of NMP, colloidal Pd formation was observed after the reaction. Dioxane, which is comparatively less polar, also showed lower catalytic activity (TOF = 126 h⁻¹, Run no. 3, Table 4) with an initial induction period of 1.5 h. In toluene (TOF = 92 h⁻¹, Run no. 6, Table 4), the catalytic activity was higher than that in DMF and NMP but was less than that in MEK and acetone. A possible reason for the lower catalytic activity in such solvents may be the lower solubility of CO [36].

3.1.5. Carbonylation of various 1-arylethanol

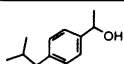

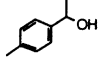
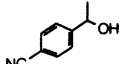
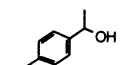
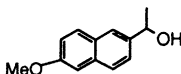
The carbonylation of various 1-arylethanol substrates was studied using the catalyst system PdCl₂(PPh₃)₂/TsOH/LiCl (Table 5). For comparison of the reactivity of different arylethanol, the carbonylation experiments were carried out at higher concentration of TsOH and LiCl (11.2 mmol). In general, good catalytic activities (TOF in the range of 140–850 h⁻¹) and high regioselectivity (80–97%) to 2-aryl propionic

acids were observed. The major byproduct was the isomeric 3-arylpropionic acid. The *sec*-phenethyl alcohol showed lower catalytic activity as compared to IBPE. In the case of 4-substituted (4-methyl, 4-chloro, and 4-cyano) *sec*-phenethylalcohols, the catalytic activity varied randomly without any particular trend, but was lower than that of IBPE. Carbonylation of 1-(6-methoxynaphthyl)ethanol gave 2-(6-methoxynaphthyl) propionic acid (Naproxen), with high selectivity (97.2%) with moderate reaction rates (215 h⁻¹). The lower catalytic activity observed in the case of different 1-arylethanol, may be due to their varied activities for dehydration and subsequent addition of H⁺/Cl⁻, in addition to the varied rate of activation of the halide derivatives by Pd(0) complexes.

3.2. Reaction mechanism

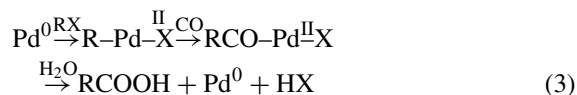
In the case of halide promoted carbonylation of alcohols, the major active carbonylation substrate is the corresponding organic halide formed in situ under reaction conditions as also confirmed for the present case [10]. The catalytic cycle can be initiated by

Table 5
Carbonylation of different 1-aryl ethanol^a

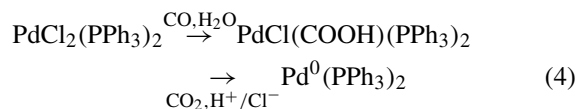
Run no.	Substrate	Time (h)	Conversion (%)	Selectivity (%)		<i>n</i> / <i>iso</i>	TOF (h ⁻¹)
				<i>iso</i>	<i>n</i>		
1		0.58	99	96.2	3.7	0.038	850
2		0.92	90	95.2	4.3	0.045	510
3		3	95	81.9	17.4	0.212	600
4		3.33	95	96.2	3.7	0.038	143
5		2.83	97	97.1	2.6	0.027	172
6		2.33	98	97.2	1.6	0.017	215

^a Reaction conditions: IBPE, 28.1 mmol; PdCl₂(PPh₃)₂, 0.056 mmol; TsOH, 11.2 mmol; LiCl, 11.2 mmol, water, 1.2 cm³; P_{CO}, 5.4 MPa; T, 388 K; MEK, 19.5 cm³.

oxidative addition of the organic halide to an active palladium (0) complex forming a Pd(II) alkyl complex [20,21] which undergoes further CO insertion and reductive elimination steps to form the product acids (Eq. (3)).

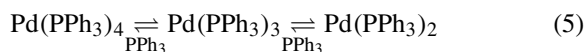


The active Pd(0) species may be generated in situ under reaction conditions by the reduction of the Pd(II) precursor by CO in presence of H₂O as shown in Eq. (4) [17,18].



In the present case, analysis of the gas phase after carbonylation of IBPE, showed formation of CO₂ in catalytic amounts (0.1–0.2%), suggesting the formation of Pd(0) species as shown in Eq. (4). The positive effect of concentration of water as well as TsOH on the catalytic activity also supports this proposal. In order to investigate the nature of Pd(0) species formed in solution under the reaction conditions, the reduction of PdCl₂(PPh₃)₂ was carried out under CO and the intermediate samples were analyzed by ³¹P NMR spectroscopy. When PdCl₂(PPh₃)₂, C₁, was treated with only TsOH (25 equivalents) under 5.4 MPa of CO at 378 K in DMF as a solvent, the major signal observed was that of C₁ at 24.34 ppm (δ₁) and a small signal at –5.1 ppm (δ₃) corresponding to free PPh₃. No signals corresponding to the low ligated Pd⁰(PPh₃)₂ (C₆) or Pd⁰(PPh₃)₃ complexes were observed in this sample [24,37]. However, a significant amount of palladium metal precipitation was observed after the reaction, which indicates that the Pd(0) species formed were not stable in the presence of excess TsOH alone and may decompose to palladium metal and free PPh₃. It is known that low ligated Pd(0) species are stable only in the presence of excess phosphines or halides [37]. Hence to prevent decomposition of Pd(0) species formed, two equivalents of PPh₃ was also added in all further experiments. When the above reaction was repeated with added equivalent amounts of LiCl and TsOH and two equivalents of PPh₃, two major signals at 24.32 (δ₁) and 28.15 ppm (δ₂) and comparatively

smaller signals at 22.83 (δ₄) and 21.28 ppm (δ₅), along with a broad signal at –2.07 ppm (1.31 to –3.84) (δ₆) were observed. In order to check for the formation of any Pd(0) species formed, this solution was reacted with PhI immediately which resulted in the development of a new ³¹P NMR signal at 25.31 ppm (δ₇), while the signal at 22.83 ppm (δ₄) disappeared and the broad signal at δ₆ as well as the signal at δ₅ were sharpened (Fig. 3). The signal at δ₆ can be assigned to the less active Pd(0) phosphine species Pd⁰(PPh₃)₃ in equilibrium (Eq. (5)) with free phosphine in accordance with the values reported in the literature [24,37].



Since the signal at δ₄ disappeared on addition of PhI, it may also correspond to a Pd(0) species and was assigned to an anionic Pd(0) species ligated with Cl[–] ions; Pd⁰(PPh₃)₂Cl₂^{2–}, in comparison with literature reported values [24,37]. The new signal developed after the addition of PhI at δ₇ correspond to *trans*-aryl Pd(II) complexes such as PhPdI(PPh₃)₂ or PhPdCl(PPh₃)₂ formed by the oxidative addition of PhI to the Pd(0) species [38,39]. The signal at δ₅ may be due to neutral palladium(0) carbonyl species, such as Pd(CO)(PPh₃)_n, where n = 1 to 3 [19]. A small amount of palladium metal precipitation was also observed in this sample after keeping for 5–6 h.

Since the catalytic activity for carbonylation reaction was found to be lower in DMF as a solvent, the above ³¹P NMR experiments were also carried out in wet MEK (4–5% water) as the solvent to understand the nature of active species formed. An intermediate sample from a reaction of PdCl₂(PPh₃)₂ with 25 equivalents of TsOH and LiCl and 2 equivalents of PPh₃ under 5.4 MPa of CO at 378 K, showed strong signals at 24.90 (δ₈) and –2.64 (δ₉) ppm with a relatively weaker signal at 30.33 (δ₁₁) ppm. A weak signal at 25.50 ppm was also observed in this case. When this intermediate sample was reacted with PhI, the signal at δ₈ diminished and new signals at 20.68 (δ₁₂) and 25.71 ppm (δ₇) developed (Fig. 4). The signal at δ₇ correspond to the aryl Pd(II) complexes such as PhPd(PPh₃)₂I or PhPd(PPh₃)₂Cl formed by the addition of PhI to a Pd(0) complex as discussed before [38,39]. Since the signal at δ₈ diminished after reaction with PhI, it was assigned to a Pd(0) species and can be a mono anionic Pd(0) species, such as

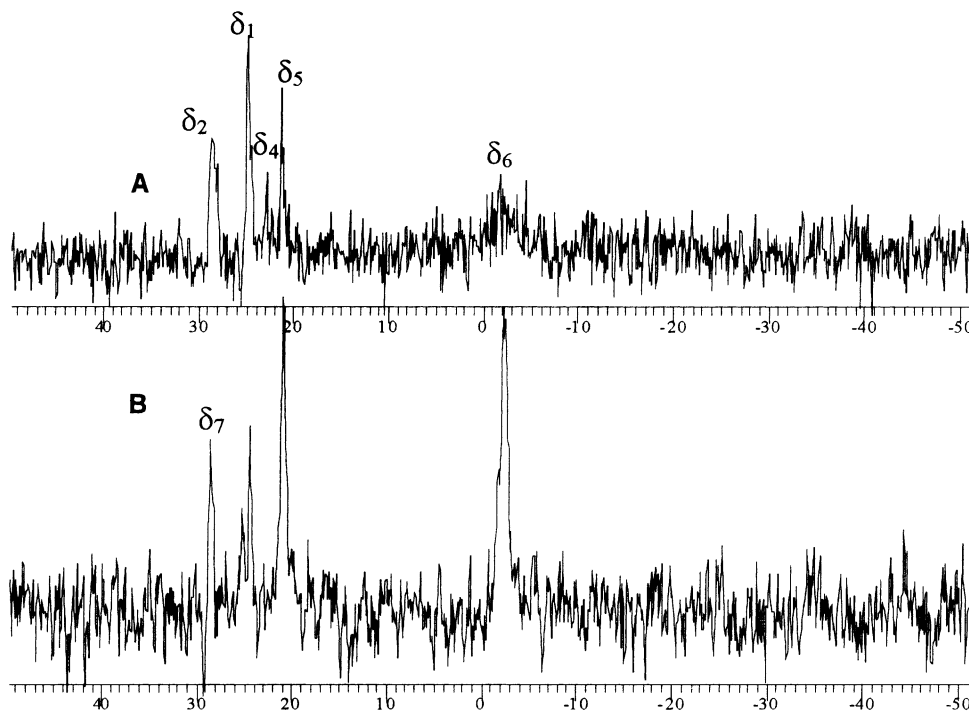


Fig. 3. ^{31}P NMR of the intermediate sample on reduction of $\text{PdCl}_2(\text{PPh}_3)_2$ with CO under 378 K and 5.4 MPa pressure in DMF: (A) with equivalent amount of TsOH and LiCl and (B) after addition of PhI.

$\text{Pd}^0(\text{PPh}_3)_2\text{Cl}^-$ in comparison with literature values [37–39]. The signal at δ_9 was assigned to the less active $\text{Pd}^0(\text{PPh}_3)_3$ species. The new signal appeared at δ_{12} may correspond to Pd(II) species, such as $\text{PdCl}(\text{PPh}_3)_2$ or $\text{PdI}(\text{PPh}_3)_2^+$ that may be formed by halide exchange reactions [17,18]. The signal at 30.33 ppm correspond to $\text{PPh}_3 = \text{O}$ in comparison with a standard sample in wet MEK containing small amounts of TsOH and LiCl. This reaction mixture did not show any Pd metal precipitation, but showed slight precipitation of $\text{PdCl}_2(\text{PPh}_3)_2$ after 6–8 h.

These observations suggest that, under the carbonylation reaction conditions different ionic and neutral palladium complexes may be present in solution as shown in Scheme 3, the concentration of which will vary with the change in reaction conditions. In the presence of excess Cl^- ions the Pd(0) species formed is most likely to exist as anionic species, such as C_8 , C_9 and/or C_{10} in solution as indicated by the ^{31}P NMR experiments discussed above.

High carbonylation rates observed in the presence of LiCl compared to HCl or other halide sources

(Table 2) also supports the possibility of increased formation of the anionic palladium species, which can be stabilized as strong ion pairs in the presence of Li^+ ions in solution [38,39]. Similar promoting effects of Li^+ ions on the halide promoted carbonylation of alcohols was reported earlier using Rh and Ni complexes and was also explained on the basis of possible involvement of anionic complexes stabilized by Li^+ counter ions [40–42]. Considering all these points, a plausible catalytic cycle that initiates by the oxidative addition of IBPCL to the anionic Pd(0) complexes such as C_9 and C_{10} is proposed as illustrated in Scheme 4.

Anionic complexes are highly nucleophilic and their oxidative addition rates are much higher than that of corresponding neutral complexes [24,43–45]. Presence of Li^+ ions may also facilitate the efficient abstraction of Cl^- ions from the coordination sphere of C_9 and/or C_{10} thereby facilitating the formation of the penta-coordinated alkyl species C_{14} as shown in Scheme 5. It is likely that oxidative addition of R–Cl to C_9 and simultaneous absorption of Cl^- ligand by Li^+ occurs to form C_{14} . Lower reaction rates ob-

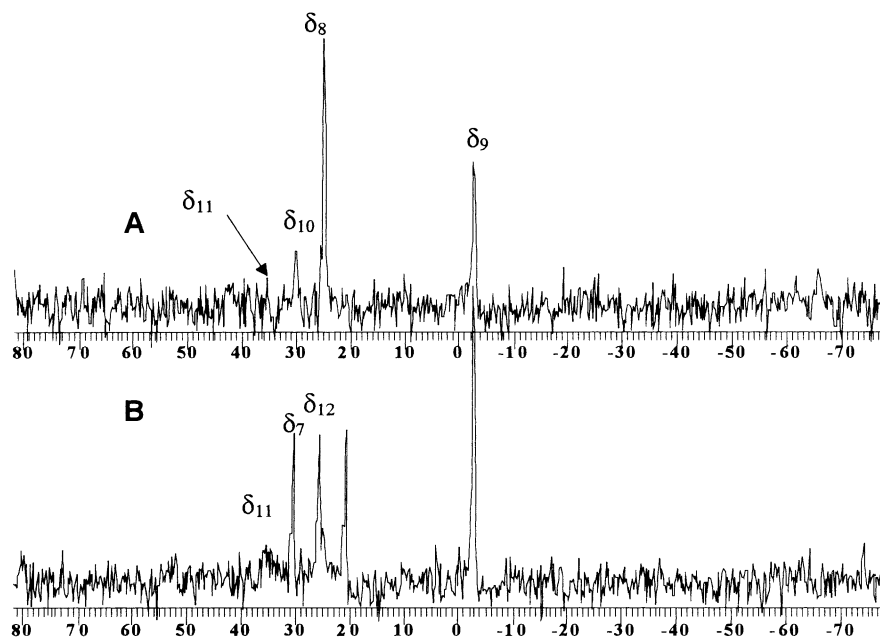
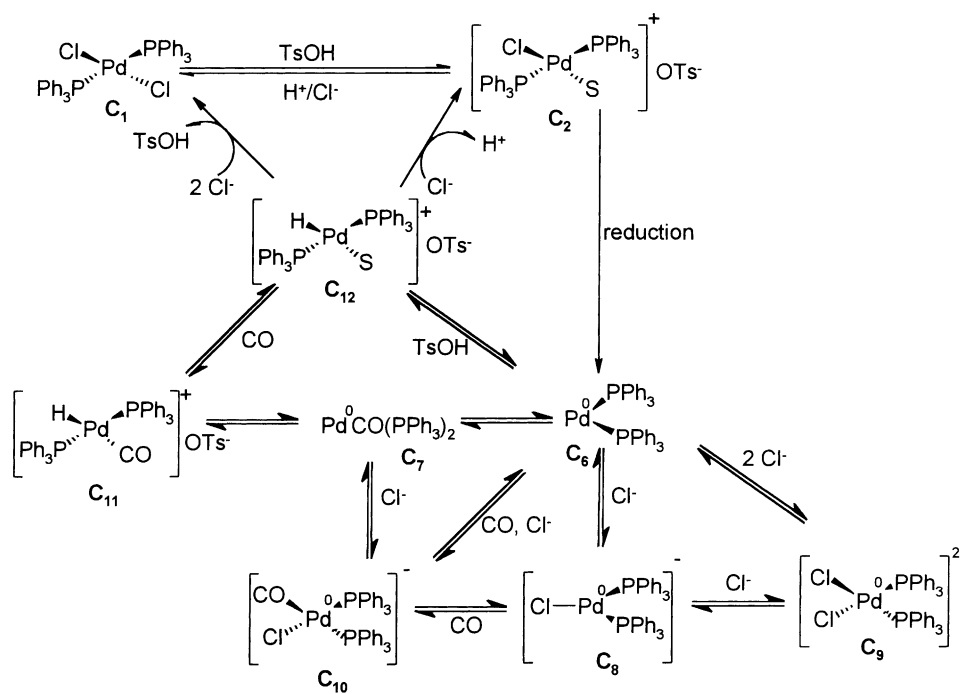
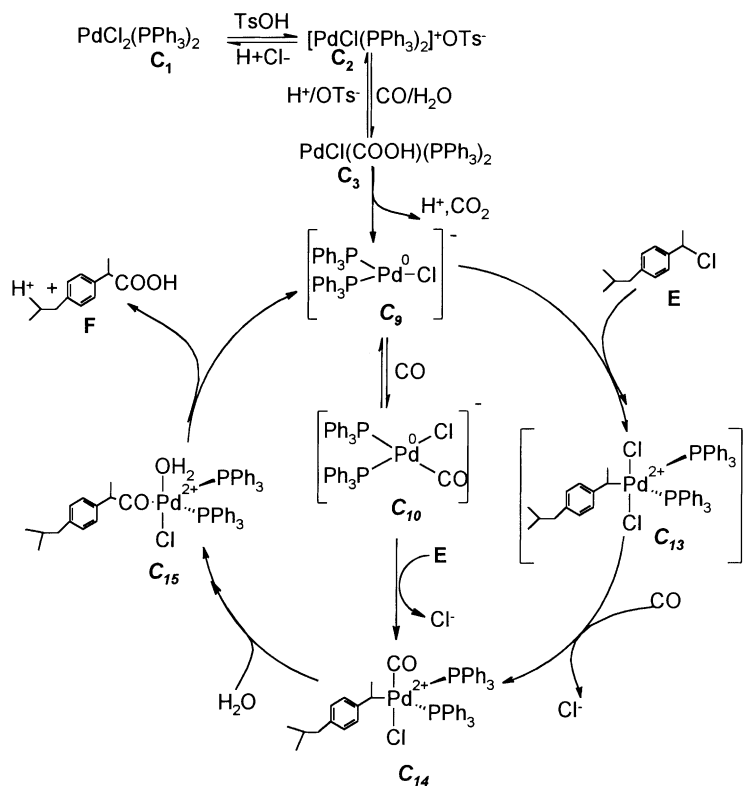


Fig. 4. ^{31}P NMR of the intermediate sample on reduction of $\text{PdCl}_2(\text{PPh}_3)_2$ with CO under 378 K and 5.4 MPa pressure in MEK along with two equivalents of PPh_3 : (A) with equivalent amount of TsOH and LiCl and (B) after addition of PhI.



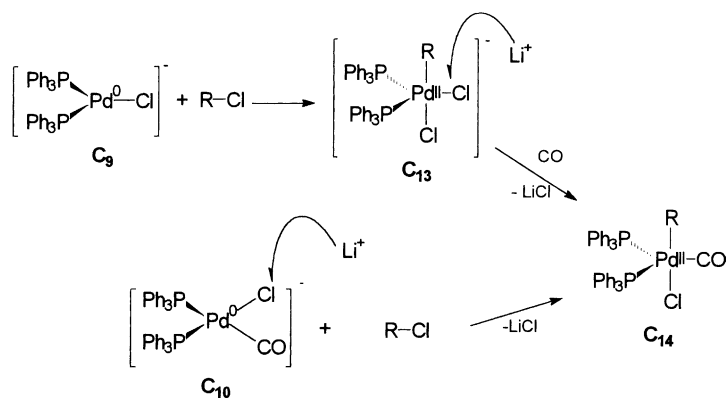
Scheme 3. Different possible catalytic species under reaction conditions.



Scheme 4. Proposed catalytic cycle.

tained with Na^+ , K^+ and Bu_4N^+ (compared to Li^+) as counter ions, also support the above argument due to their lower Cl^- abstracting power compared to Li^+ [24,37].

The intermediate species **C₁₄**, on migratory insertion of CO to the Pd alkyl bond followed by association of a H_2O molecule at the vacant site created forms the acyl species (**C₁₅**). The product carboxylic acid can

Scheme 5. Abstraction of Cl^- ligand by Li^+ .

form from the acyl species C_{15} through two different pathways. One, by the reductive elimination of the acid chloride, which subsequently converts to the acid by hydrolysis or by the direct reductive elimination of carboxylic acid regenerating the active anionic Pd^0 species (C_9 or C_{10}) as shown in Scheme 4. The significant positive effect of water on the catalytic activity indicates the latter pathway rather than the former. The absence of even trace amounts of acid chloride in the intermediate reaction samples also supports the above proposition.

4. Conclusions

Carbonylation of arylethanols to 2-arylpropionic acids has been studied using palladium phosphine complexes under homogeneous conditions. A combination of $PdCl_2(PPh_3)_2$ as the catalyst and TsOH and LiCl at a ratio of 1:1 gave significantly higher catalytic activity and >95% 2-arylpropionic acid selectivity at relatively mild reaction conditions, such as 388 K and 5.4 MPa CO partial pressure. The effect of various parameters such as catalyst precursors, promoters, solvents, substrates and concentration of water on catalytic activity as well as product distribution for the carbonylation of 1-(4-isobutylphenyl)ethanol (IBPE) was studied in detail. Both concentration of promoters and water was found to have a significant positive effect on catalytic activity and regioselectivity to Ibuprofen. However, at higher amounts of water (>8%), catalytic activity as well as selectivity decreased drastically due to the change of homogeneous nature of the system to biphasic. ^{31}P NMR experiments carried out to investigate the nature of species formed in solution under the reaction conditions indicated that the $Pd(0)$ species formed after the reduction of the $Pd(II)$ precursor exists mostly as anionic species ligated with Cl^- ions. Based on these observations and experimental trends a catalytic cycle initiated by the oxidative addition of IBPE to anionic $Pd(0)$ species, such as $Pd(PPh_3)_2Cl^-$ or $Pd(CO)(PPh_3)_2Cl^-$, is proposed.

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