Synthesis of γ-ketocycloalkanecarboxylic acid esters by region-specific alkoxy carbonylation of α,β-ketocycloolefins catalyzed by palladium

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Abstract

$PdCl_2(PPh_3)_2$, in combination with HCl, is highly active in the alkoxycarbonylation of α,β-ketocycloolefins to 3-oxocycloalkanecarboxylic acid esters. The reaction is region specific. The catalytic system is stabilized by addition of PPh_3, which depresses the activity but prevents decomposition to inactive palladium metal. Typical reaction conditions are: Pd/P/cyclohexenone/HCl $= 1/2-4/200-600/50-100$; [Pd] $= 0.1-1 \cdot 10^{-2}$ mol l^{-1}; $P_{CO} = 100$ atm; temperature 100°C; solvent dioxane, THF, or benzene. With 2-cyclohexen-1-one the effect of the following variables on the yield has been examined: temperature, pressure of carbon monoxide, concentration of cyclohexenone, ethanol, catalyst, Pd/P ratio, cyclohexenone/HCl ratio, reaction time, and solvent. As expected the yield increases with increasing reaction time, pressure of carbon monoxide, concentration of catalyst at constant Pd/P ratio, and temperature. The yield passes through a maximum when increasing the concentration of HCl and EtOH, after which the yield decreases because the catalyst decomposes to palladium metal. The yield is almost insensitive to the polarity of solvents such as dioxane, THF, or benzene, but it rather depends on the bulkyness of the alkanol as the reaction rate decreases in the order: MeOH > EtOH > n-PrOH > n-BuOH > s-PrOH.

The proposed reaction mechanism proceeds through the following steps. (i) The starting Pd^{II} precursor is reduced to a Pd^0 complex which gives oxidative addition of HCl with formation of a Pd-hydride species; (ii) cyclohexenone inserts into a Pd–H bond giving a β-ketocyclohexyl-Pd intermediate; (iii) this inserts CO with formation of the corresponding carbonyl derivative; (iv) alcoholysis of this intermediate yields the final product with regeneration of the hydride. The reaction is region specific because of the keto group which directs the anti-Markownikoff addition of Pd–H to the conjugated C=C double bond.

1. Introduction

Catalytic carbonylation of organic substrates continues to be extensively studied because it is an efficient direct method which finds many new applications for the synthesis of many classes of useful carbonyl compounds [1]. Thus for example, esters can be obtained by addition of carbon monoxide and an alkanol to an alkene. The carbonylation of functionalized olefins is an attractive way to synthesize di- or poly-functional derivatives.

Recently, we have reported the synthesis of levulinic acid, a γ-keto acid of much interest as an intermediate of many fine chemicals [2]; it is formed by highly region-specific carbonylation of methyl vinyl ketone, a conjugated keto-α-olefin catalyzed by a Pd-HCl system, which is highly

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active only when the acid is present in amounts comparable to the substrate [3]. Pd^0 or Pd^{II} complexes can be conveniently employed as catalyst precursors. They decompose to palladium metal. Pd/C is also highly active. When catalysis is carried out in the presence of an alkanol such as methanol or ethanol, the corresponding esters are obtained. Under the reaction conditions the starting α,β-ketoolefin reacts with the alkanol or with the acid with formation of the corresponding β-ketoether or β-ketochloride. These substrates can also be carbonylated. They give levulinic acid practically in the same yield as that obtainable starting from the ketoolefin. It is believed that the reaction is highly region selective because the keto group directs the anti-Markownikoff addition of HCl to the conjugated C=C double bond yielding a β-ketochloride RCOCH$_2$CH$_2$Cl which adds to nucleophilic low valent palladium with formation of a catalytic intermediate having a (Pd-CH$_2$CH$_2$COR) moiety which, upon CO insertion and nucleophilic attack of the alkanol to the resulting ketoacyl intermediate, yields the product.

More recently, it has been reported that a PdCl$_2$(PPh$_3$)$_2$ precursor in combination with SnCl$_2$ as cocatalyst is active in the alkoxycarbonylation of monoterpenes to C$_{11}$ esters. Carbonylation involves a terminal C=C double bond. Internal olefins conjugated with a keto group, such as pulegone, give the keto acid that arises from the carbonylation of the terminal olefin that forms upon isomerization of the starting substrate. Carvone, a derivative of an allylic olefin substituted with a cyclohexenone group where the keto and the olefin double bonds are conjugated, is carbonylated only at the allylic double bond [4].

To our knowledge the carbonylation of conjugated ketoolefins having an internal C=C double bond that cannot isomerize to a terminal C=C double bond has not yet been reported. The carbonylation of conjugated cycloakenones, by analogy with the carbonylation of methyl vinyl ketone, can be a convenient direct method for the region-specific synthesis of 3-oxocycloalkanecarboxylic acids, a useful precursor of several pharmacologically active compounds [5]. Available methods

for the synthesis of these acids are based on multistage reactions [6–9].

Hereafter, we present and discuss the results on the synthesis of these acids via region-specific carbonylation of 2-cycloalken-1-ones catalyzed by a homogeneous palladium system.

2. Experimental

2.1. Materials

Carbon monoxide was purchased from S.I.O. Solvents and 2-cyclohexen-1-one were of commercial grade. Pd(CO)(PPh$_3$)$_3$, PdCl$_2$(PPh$_3$)$_2$, Pd(PPh$_3$)$_4$ were prepared as reported in the literature [11,23,24].

2.2. Product identification and analysis

Reaction products and yields were determined by GC, using a Hewlett-Packard gas chromatograph, model 5830 equipped with a Hewlett-Packard terminal model 18850. Analysis was performed on a 6 ft OV 17 column. Products were identified by IR, using a Perkin-Elmer spectrometer model 683 and by NMR, on a Varian FT 80 A instrument, and by GC MS on a Carlo Erba QMD 1000 instrument.

2.3. Catalytic hydroesterification of 2-cyclohexen-1-one to 3-oxocyclohexane carboxylic acid esters

The reactions were carried out in a stainless steel autoclave of ca. 70 ml. The catalyst, reagent and solvent were contained in a Pyrex bottle placed in the autoclave. A magnetic stirrer was provided to stir the reaction medium.

In a typical experiment, 10 mmol of the ketoolefin, 1.5 ml of EtOH containing 2 mmol of dry HCl, 7.5 ml of dioxane, together with PdCl$_2$(PPh$_3$)$_2$ (35 mg, 0.05 mmol), and PPh$_3$ (13 mg, 0.05 mmol) were pressurized with 100 atm of carbon monoxide at room temperature, after purging the autoclave with the same gas. The auto-

clave was placed in a heated oil bath. The working temperature, typically 100°C, was reached in ca. 10 min and maintained throughout the experiment (2 h). The autoclave was then cooled in an ice bath and slowly depressurized. The reaction solution was analyzed by GC.

When the catalytic reaction is carried out using a larger amount of catalyst (0.2 mmol of the palladium complex and 0.5 mmol of PPh_3) in the absence of HCl, the precursor is recovered, after the reaction is over and after cooling the autoclave at room temperature, as a yellow–orange microcrystalline powder, whose IR spectrum showed a band at 1860 cm^{-1} for a bridging ν_{CO} and a band at 360 cm^{-1} for ν_{Pd-Cl} of the starting complex.

When the catalytic reaction is carried out employing $Pd(CO)(PPh_3)_3$ as catalyst precursor in combination with PPh_3 and HCl, the catalytic activity is practically the same as that observed when employing the $PdCl_2(PPh_3)_2$ precursor under the same conditions.

3. Results and discussion

3.1. On the catalytic carbonylation

The palladium catalyzed region-specific synthesis of esters of 3-oxocycloalkanecarboxylic acids is schematized by reaction (1):

$$\text{(reaction scheme)} \quad + \text{ROH} \longrightarrow \text{COOR}$$
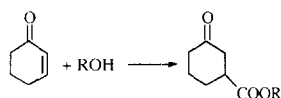
(1)

When $PdCl_2(PPh_3)_2$ is employed as catalyst precursor in the presence of PPh_3, which stabilizes the system against decomposition to inactive palladium metal, the yield of the γ-keto acid is rather low. For example, at 100°C under 100 atm of carbon monoxide in dioxane as solvent (EtOH/dioxane = 1/5, v/v) the yield, after 2 hours, is only 4% when employing the catalyst and the substrate in ratio Pd/P/cyclohexenone = 1/6/200, [Pd] = 0.5·10^{-2} mol l^{-1}. When using a much larger amount of catalyst (Pd/P/cyclohexen-
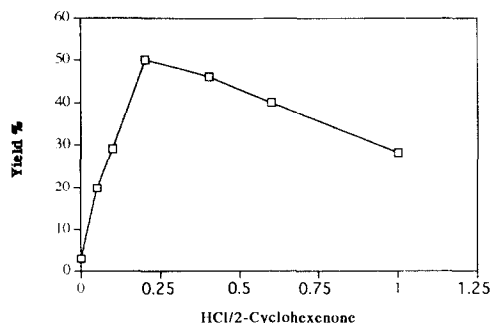

Fig. 1. Run conditions: cyclohexenone, 10 mmol; dioxane, 7.5 ml; EtOH, 1.5 ml; $PdCl_2(PPh_3)_2$, 0.05 mmol; P_{CO} = 100 atm; temperature, 100°C; reaction time, 2 h.

one = 1/4/50) the yield is 83% after 15 hours. In this case the precursor is recovered after cooling the reaction medium at room temperature as a yellow–orange microcrystalline solid whose i.r. spectrum in nujol mull shows bands centered at 1860 cm^{-1} for bridging ν_{CO} carbonyl phosphine clusters of Pd^0 [10,11].

When the catalyst is employed in combination with HCl, typically HCl/cyclohexenone = 2–5/10, a much higher activity is observed. The catalytic activity passes through a maximum when the ratio HCl/cyclohexenone is ca. 0.2. At lower concentration of HCl the catalyst partially decomposes to palladium metal. For the carbonylation of methyl vinyl ketone the yield regularly increases upon increasing the ratio HCl/ketoolefin even up to 3/1. The trend shown in Fig. 1 suggests also that HCl competes with other reacting molecules for the activation on the metal. Moreover, it should be underlined that, as found
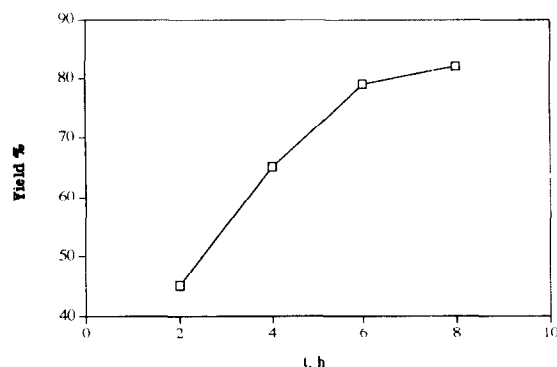

Fig. 2. Run conditions: cyclohexenone, 10 mmol; dioxane, 8 ml; EtOH, 1 ml; HCl, 4 mmol; $PdCl_2(PPh_3)_2$, 0.1 mmol; P_{CO} = 100 atm; temperature, 100°C.
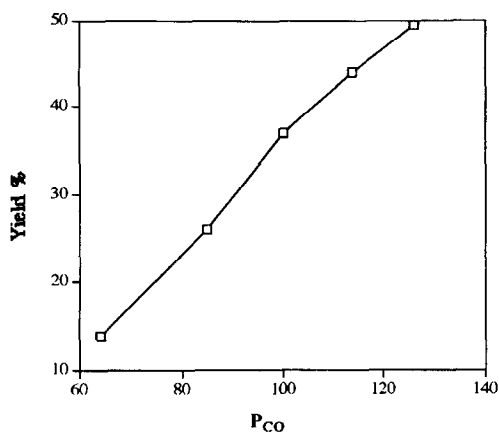
Fig. 3. Run conditions: cyclohexenone, 10 mmol; dioxane, 7.5 ml; EtOH, 1.5 ml; HCl, 2 mmol; $PdCl_2(PPh_3)_2$, 0.05 mmol; PPh_3, 0.05 mmol; temperature, 100°C; reaction time, 2 h.
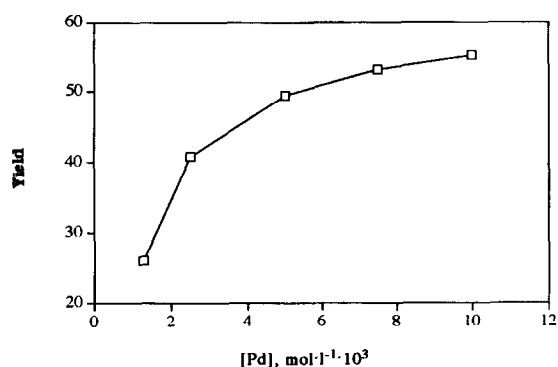
Fig. 4. Run conditions: cyclohexenone, 10 mmol; dioxane, 7.5 ml; EtOH, 1.5 ml; HCl, 2 mmol; Pd/P = 1/3; P_{CO}, 100 atm; temperature, 100°C; reaction time, 2 h.
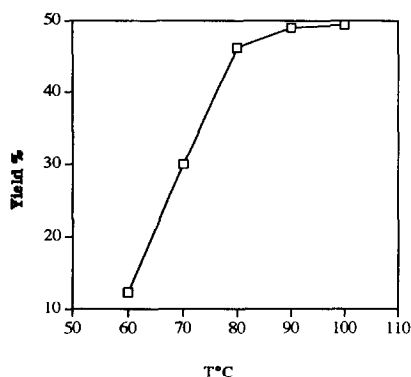
Fig. 5. Run conditions: cyclohexenone, 10 mmol; dioxane, 7.5 ml; EtOH, 1.5 ml; HCl, 2 mmol; $PdCl_2(PPh_3)_2$, 0.05 mmol; P_{CO}, 100 atm; reaction time, 2 h.

for the carbonylation of α,β-keto terminal olefins, reaction (1) is highly region specific, the other possible isomer, 2-oxocyclohexanecarboxylic acid ester, being formed in trace amounts.

The effect of the following other variables on the yield has been examined: temperature, pressure of carbon monoxide, concentration of cyclohexenone, ethanol, catalyst, Pd/P ratio, reaction time, and the solvent. Most of the experiments were carried out at a constant ratio HCl/cyclohexenone = 0.2 because of the trend shown in Fig. 1. As expected the yield increases with increasing reaction time, pressure of carbon monoxide, concentration of catalyst at constant Pd/P ratio, and the temperature, as shown in Figs. 2–5, respectively. Above 100°C extensive decomposition of the catalyst precursor occurs so that most of the results here reported refer to carbonylations carried out at 100°C.

As already mentioned, in the absence of added PPh_3 the catalyst precursor decomposes to palladium metal which is inactive, which is at variance with what found for the carbonylation of terminal olefins conjugated to a keto group [3]. However, the catalytic activity decreases significantly with increasing concentration of PPh_3 (Fig. 6). This fact indicates that this ligand competes with the other reacting molecules for coordination to the metal center. The reaction rate is practically of the first order with respect to cyclohexenone as shown in Fig. 7.

The yield increases with increasing concentration of EtOH up to EtOH/solvent = 0.4 (Fig. 8) as found for the carbonylation of methyl vinyl ketone [3]. When the reaction is carried out in the presence of a higher concentration of EtOH
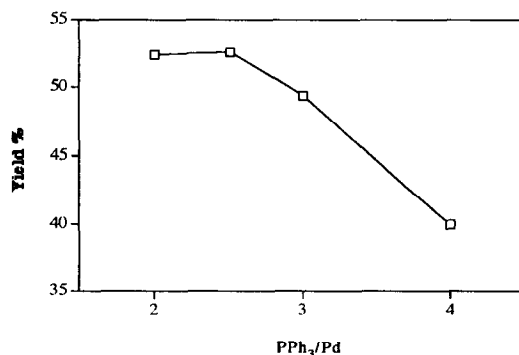
Fig. 6. Run conditions: cyclohexenone, 10 mmol; dioxane, 7.5 ml; EtOH, 1.5 ml; HCl, 2 mmol; $PdCl_2(PPh_3)_2$, 0.05 mmol; P_{CO}, 100 atm; temperature, 100°C; reaction time, 2 h.
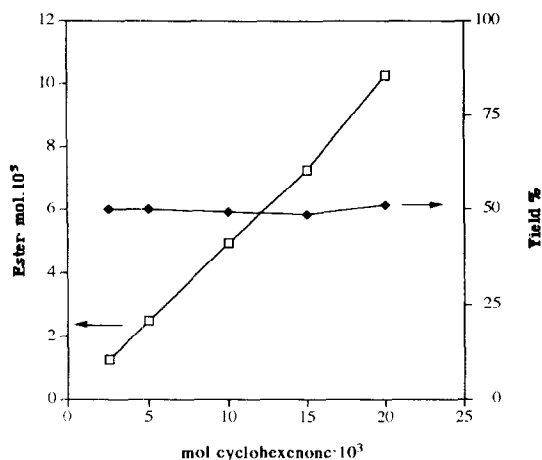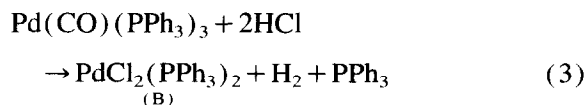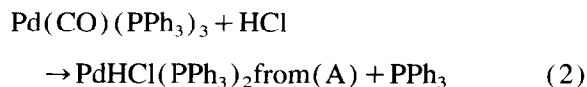
Fig. 7. Run conditions: dioxane + cyclohexenone, 8.5 ml; EtOH, 1.5 ml; HCl, 2 mmol; PdCl$_2$(PPh$_3$)$_2$, 0.05 mmol; PPh$_3$, 0.05 mmol; P_{CO}, 100 atm; temperature, 100°C; reaction time, 2 h.

(EtOH/solvent > 0.4), decomposition of the catalyst precursor to palladium metal occurs and the yield decreases. An analogous result was found in the carbonylation of cyclohexene in MeOH catalyzed by PdCl$_2$(PPh$_3$)$_2$, in the absence of HCl. In pure MeOH decomposition to the metal occurs and the yield is much lower than when the carbonylation is carried out in a solution containing 20 vol.-% of MeOH in benzene [12].

3.2. On the catalytic cycle

The proposed catalytic cycle occurs through the steps (4–7). Under carbonylation conditions the precursor of Pd^{II} decomposes to Pd^0 complexes. In addition to the carbonyl–phosphine clusters of Pd^0 isolated when the carbonylation is carried out in the absence of HCl, there might be formation of Pd(CO)(PPh$_3$)$_3$ [11,12]. It has been reported that this complex reacts with stoichiometric amounts of HCl to give the hydride–chloride of Pd^{II} (A), whilst with an excess of the acid it gives a dichloride of Pd^{II} (B) [13], probably after hydrogen evolution [14]:

$$Pd(CO)(PPh_3)_3 + HCl$$

$$\rightarrow PdHCl(PPh_3)_2 \text{from(A)} + PPh_3 \qquad (2)$$

$$Pd(CO)(PPh_3)_3 + 2HCl$$

$$\rightarrow \underset{(B)}{PdCl_2(PPh_3)_2} + H_2 + PPh_3 \qquad (3)$$

Hydride (A) may be in equilibrium with CO, Cl$^-$, cyclohexenone to give hydride–palladium (C), where L can be any of these ligands, in addition to PPh$_3$, and where n satisfies the coordination number of Pd^{II}:

$$\underset{(A)}{\text{CO,Cl}^-, \text{ketoolefin}} \rightarrow \underset{(C)}{PdHL_n} \qquad (4)$$
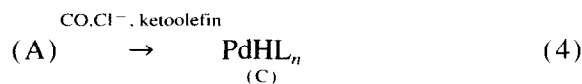
A coordinated ketoolefin adds the Pd–H bond of hydride (C) with formation of a ketocyclohexyl-palladium intermediate (D), which inserts CO to give a ketocyclohexylcarbonyl-palladium intermediate (E):

$$(C) \rightarrow \underset{(D)}{Pd(\text{ketocyclohexyl})L_n} \qquad (5)$$

$$(D) \rightarrow \underset{(E)}{Pd(\text{COketocyclohexyl})L_n} \qquad (6)$$
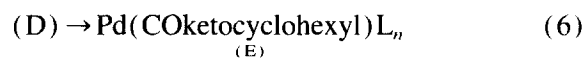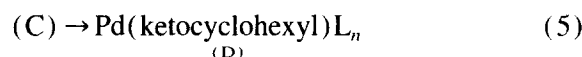
The alkanol causes nucleophilic attack to the carbon atom of the carbonyl-palladium species (E) to yield the product γ-ketoester with concomitant regeneration of hydride (C):

$$(E) + ROH \rightarrow (C) + \gamma - \text{ketoester} \qquad (7)$$
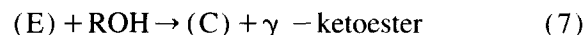
It has been found that the yield depends on the bulkyness of the alkanol as the reaction rate decreases in the order: MeOH > EtOH > n-PrOH > n-BuOH > s-PrOH (Table 1). This suggests that the slow step of the catalytic cycle is reaction (7). It is interesting to observe that also
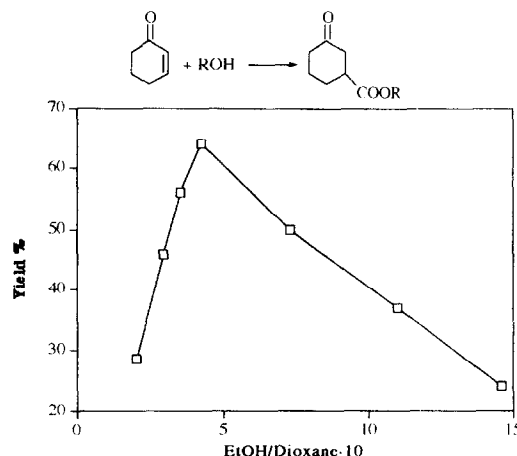

Fig. 8. Run conditions: dioxane + EtOH, 9 ml; cyclohexenone, 10 mmol; HCl, 4 mmol; PdCl$_2$(PPh$_3$)$_2$, 0.05 mmol; P_{CO}, 100 atm; temperature, 100°C; reaction time, 2 h.

Table 1
Effect of the alkanol and of the solvent on the carbonylation of cyclohexenone

Run	Alkanol	Solvent	Yield, %
1	MeOH	Dioxane	62
2	EtOH	Dioxane	50
3	n-PrOH	Dioxane	39
4	n-BuOH	Dioxane	36
5	iso-PrOH	Dioxane	15
6	EtOH	THF	58
7	EtOH	Benzene	54

Run conditions: solvent + alkanol, 9 ml; cyclohexenone, 10 mmol; alkanol, 26 ml; HCl, 2 mmol; $PdCl_2(PPh_3)_2$, 0.05 mmol; PPh_3, 0.05 mmol; P_{CO}, 100 atm; temperature, 100°C; reaction time, 2 h.

for the reactions of $PdCl(COMe)(PPh_3)_2$ with MeOH or EtOH it has been found that the rate of nucleophilic attack decreases when the bulk of the alkanol is increased [15] and that the rate of hydroesterification of α-olefins catalyzed by a $PdCl_2(PPh_3)_2$–$SnCl_2$ system is also higher for primary alcohols than for secondary ones, even though MeOH or n-hexyl alcohol give the same reaction rate [16]. The yield is almost insensitive to the polarity of solvents (such as dioxane, THF, or benzene (Table 1)).

Even though it has been reported that cyclohexenone does not add HCl at room temperature in chloroform [17], we have found that, under the explored catalytic reaction conditions, i.e. typically 60–100°C, cyclohexenone adds HCl and ROH to give the corresponding β-ketocyclohexyl chloride or β-ketocyclohexyl ether, respectively, which becomes less abundant when protracting the reaction time, in which case a higher yield in the γ-ketoester is obtained. This fact suggests that either the ketochloride is consumed because it is in equilibrium with cyclohexenone which is the only substrate that undergoes carbonylation or that also the β-ketochloride is carbonylated to the product. In this case the proposed intermediate (D) could form upon oxidative addition of the β-ketocyclohexyl chloride. As a matter of fact, the oxidative addition of halogen derivatives to Pd^0 complexes is a well established reaction which plays an important role in the carbonylation of such substrates [18–22].

As already mentioned reaction (1) is region specific, as the other possible isomer, the corresponding β-ketoester, forms in trace amounts. This can be due to the possibility that the keto group directs the anti-Markownikoff addition to the conjugated C=C double bond of hydride (C) with formation of intermediate (D) or of HCl with formation of a β-ketochloride which eventually could insert nucleophilic palladium to give intermediate (D). As proposed in the case of the carbonylation of methyl vinyl ketone, it seems that the reaction is region specific mainly because of the conjugation of the two double bonds, rather than due to any peculiar ability of the catalytic system.

Thus, it appears that the carbonylation of cyclohexenone has several features in common with the carbonylation of methyl vinyl ketone, the main difference being that the former is catalyzed by a homogeneous Pd^0–Pd^{II} system, while the latter is catalyzed by Pd metal, which is inactive in the carbonylation of cyclohexenone. Probably, the two reactions occur via two different mechanisms. In the former case intermediate (D) would form via insertion into a Pd–H bond, while in the latter it would form via oxidative addition of the β-ketochloride $CH_3COCH_2CH_2Cl$ to the metal.

Acknowledgements

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