[PdCl$_2$(PPh$_3$)$_2$]–PPh$_3$ catalyzed regiospecific alkoxycarbonylation of α-chlorocyclohexylketone to β-ketoesters

G. Cavinato [a], L. Toniolo [b, *]

[a] *Department of Inorganic Chemistry, University of Padua, Via Loredan 4, 35100 Padua, Italy*
[b] *Department of Chemistry, University of Venice, Calle Larga S. Marta 2137, 30123 Venice, Italy*

Abstract

[PdCl$_2$(PPh$_3$)$_2$]–PPh$_3$, in the presence of NEt$_3$, is moderately active in the ethoxycarbonylation of 2-chlorocyclohexylketone to the β-ketoester (ca. 140 TON in 4 h at 100°C, 100 atm, P/Pd = 2.5, [Pd] = 5×10^{-3} mol l^{-1}, NEt$_3$/substrate = 1.2). The yield increases upon increasing p_{CO}, passes for a maximum when the P/Pd molar ratio is 2.5 and it is approximately of the first order with respect to the concentration of the substrate. A reaction mechanism is proposed, which involves the oxidative addition of the chloride to a Pd(0) species, CO insertion forming a Pd(II) β-ketoacyl complex, nucleophilic attack of ethanol to the carbon atom of the acyl moiety and HCl elimination to regenerate the starting Pd(0) species. When the carbonylation is attempted in the presence of H$_2$O and in the absence of NEt$_3$, in place of the expected carbonylation product, there is hydrogen transfer from the system H$_2$O–CO to the organic substrate with hydrogenolysis of the C–Cl bond. For the hydrodechlorination reaction it is proposed that, after the oxidative addition step to a Pd(0) complex, the Pd–C bond of the alkyl intermediate is protonolyzed by the acid that forms during the course of the reaction and that the Pd(II) complex is then reduced by CO in the presence of H$_2$O. © 1999 Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

A direct and convenient method for the synthesis of carboxylic acids or their derivatives is based on the catalytic carbonylation of olefins, alkanols or organic halides [1,2]. Usually, the carbonylation of olefins is not regioselective, whilst alkanols or halogen derivatives give the desired product in high selectivity.

Recently, we reported that the carbonylation of α,β-ketoolefins is efficiently catalyzed by palladium systems in combination with HCl, to yield γ-ketoacids in 100% regioselectivity [3,4].

The interest for the synthesis of ketoacids, mainly α, β or γ-ketoacids, is due to their use as useful intermediates for the preparation of a large variety of fine chemicals [5,6]. α-Keto-acids can be prepared by double carbonylation

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* Corresponding author. Tel.: +39-41-529-8567/68; Fax: +39-41-529-8517; E-mail: toniolo@unive.it

of organic halides [7]. β-Ketoacids can be prepared by carbonylation of α-halogenoketones [8,9]. γ-Ketoacids can be synthesized, in addition to the procedure reported in Refs. [3,4], also by carbonylation of a ketone–formaldehyde mixture using a Pd/C catalyst in combination with HCl.

The synthesis of β-ketocycloalkylesters has been described in a brief note, starting from a 2-bromocyclohexylketone catalyzed by a [PdCl$_2$(PPh$_3$)$_2$] precursor in the presence of a phase transfer catalyst (PTC), [Et$_3$NCH$_2$C$_6$H$_5$]Cl, and of sodium acetate [10]. At 80°C, under 10 atm of CO, using 0.2 mmol of [PdCl$_2$(PPh$_3$)$_2$], 7.6 mmol of PPh$_3$, 1 mmol of PTC and 15 mmol of fused NaOAc in 40 ml of *t*-BuOH, the yield was 63% after 10 h; at 70°C, after 30 h, it was reported that no reaction occurred.

The easy carbonylation of organic halogenides decreases along the sequence C–I > C–Br > C–Cl ≫ C–F, which correlates with the C–X bond energies. For the palladium catalyzed alkoxycarbonylation the following order of reactivity has been found: allyl > benzyl > phenyl = methyl > vinyl > propyl > ethyl [11], which again correlates with the dissociation energy of the R–X bond. For these reasons there are a few reports on the carbonylation of alkyl derivatives.

Here, we report the regiospecific alkoxycarbonylation of 2-chlorocyclohexylketone to the corresponding β-ketoester using [PdCl$_2$(PPh$_3$)$_2$]–PPh$_3$ as catalyst precursor.

2. Results and discussion

2.1. On the influence of the reaction parameters on the yield and selectivity of the alkoxycarbonylation of 2-chlorocyclohexylketone

The carbonylation of 2-chlorocyclohexylketone occurs in high yield when carried out in the presence of a base, such as NEt$_3$, to the corre-

sponding β-ketoester which occurs with 100% regioselectivity (reaction (1)):

$$\tag{1}$$
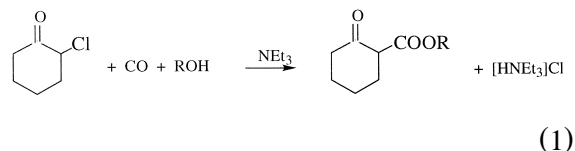
Most of the experiments were carried out using EtOH as a solvent. Typical reaction conditions are: [PdCl$_2$(PPh$_3$)$_2$] 0.05 mmol; PPh$_3$ 0.05–0.1 mmol; 2-chlorocyclohexylketone 10 mmol; NEt$_3$ 12 mmol; p_{CO} 50–100 atm; temperature 60–100°C; reaction volume 10 ml; [Pd] 5 mmol l^{-1}; reaction time 2–4 h. The influence of the following reaction parameters has been studied: concentration of starting substrate; concentration of palladium; P/Pd ratio; p_{CO}; temperature; and reaction time. At 60°C, under the conditions reported in Fig. 1, the yield is just 7%. Note that, using the catalytic system described in Ref. [10], 2-bromocyclohexylketone is not carbonylated at 70°C in 30 h of reaction, even though bromo compounds are known to undergo easier carbonylation than their chloro analogues. The yield is reasonably satisfactory at 100°C. Since under these conditions the precursor does not decompose to palladium metal, most of the experiments where carried out at this temperature.
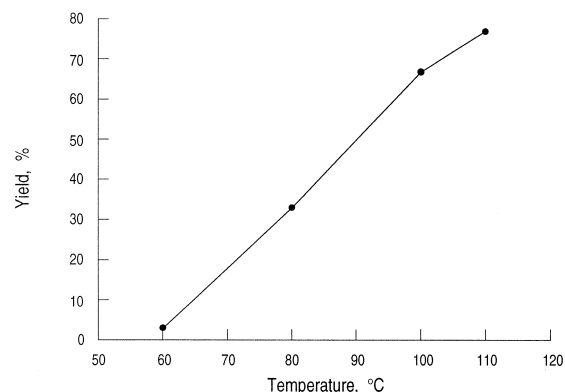

Fig. 1. Run conditions: 2-chlorocyclohexylketone 10 mmol; NEt$_3$ 12 mmol; EtOH 7.1 ml ($V_{tot} = 10$ ml); [PdCl$_2$(PPh$_3$)$_2$] 0.05 mmol; PPh$_3$ 0.025 mmol; p_{CO} 100 atm, at r.t.; reaction time 4 h.

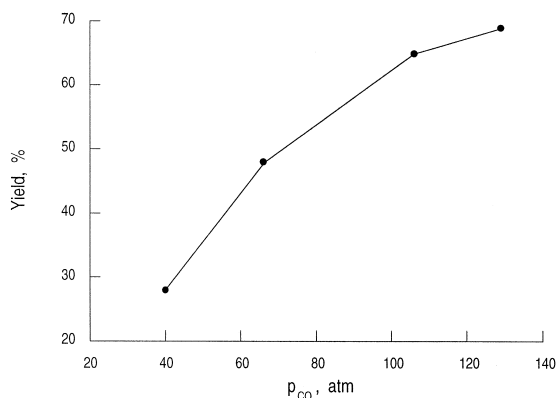Fig. 2. Run conditions: as those reported under Fig. 1, except for the temperature (100°C) and for p_{CO} (at 100°C).

Fig. 4. Run conditions: as those reported under Fig. 1, except for temperature (100°C), [Pd] and Pd/PPh$_3$ = 0.4.

As expected the yield increases upon increasing the pressure of carbon monoxide, as shown in Fig. 2.

The P/Pd ratio has a pronounced effect on the reaction rate. The highest yield is obtained when this ratio is 2.5. Upon increasing this ratio the yield decreases significantly (from 71% to 48% when the ratio is increased from 3/1 to 4/1) (Fig. 3).

The yield increases upon increasing the concentration of palladium (see Fig. 4). Experiments were carried out in the presence of increasing amounts of added PPh$_3$, keeping constant the molar P/Pd ratio at 2.5. Note that the yield is significantly lower when the ratio is 1/4, in agreement with the findings reported in Fig. 3.
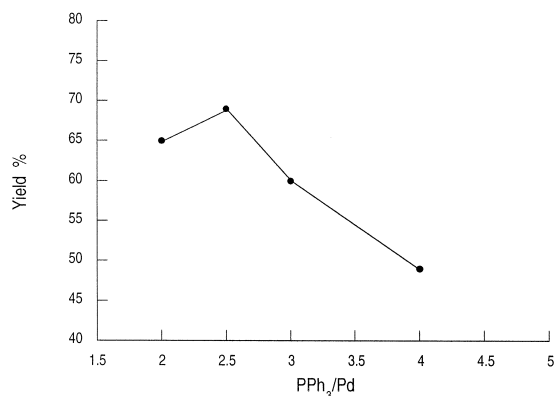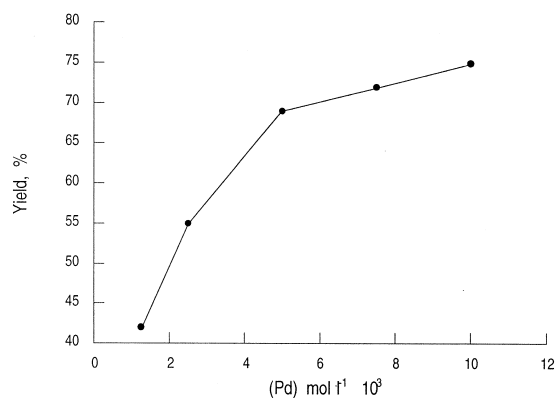
Fig. 5 shows that the yield slightly decreases upon increasing the concentration of the starting substrate, as it varies from 77% to 67% when the concentration increases 3 times. Thus, the reaction rate appears to be almost of first order with respect to the chloride.

Finally, it can be seen (Fig. 6) that the yield increases upon increasing reaction time. The fact that in 2 h the yield is significantly lower suggests that there is an induction period to convert the precursor into an active species that initiates the catalytic cycle.

When reaction (1) is carried out in the absence of NEt$_3$, the yield is much lower. For example, under the conditions reported in Fig. 1, at 100°C, the yield is less than 10%. When

Fig. 3. Run conditions: as those reported under Fig. 1, except for temperature (100°C) and [PPh$_3$].
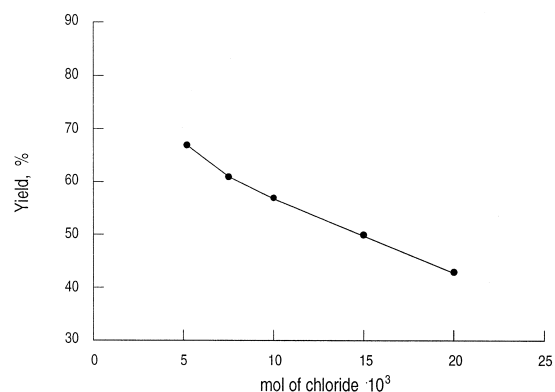

Fig. 5. Run conditions: as those reported under Fig. 1, except for temperature (100°C), reaction time (2 h) and concentration of 2-chlorocyclohexylketone.
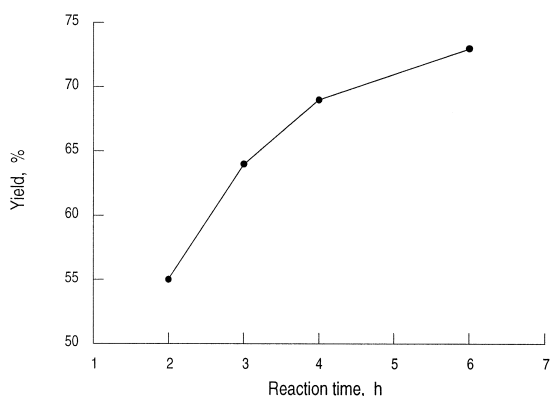
Fig. 6. Run conditions: as those reported under Fig. 1, except for temperature (100°C) and reaction time.

2-chlorocyclohexylketone is treated with CO in the presence of H_2O in place of an alkanol, in the absence of NEt_3, using for example dioxane as a solvent, the reaction takes a quite different pathway: in place of a carbonylation product, the expected β-ketoacid, C–Cl hydrogenolysis occurs as a result of a hydrogen transfer from the system H_2O–CO to the organic substrate:


$$+ CO + H_2O \longrightarrow \qquad + HCl + CO_2 \qquad (2)$$
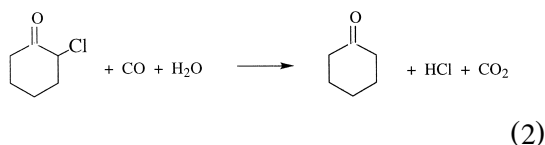
This type of hydrogen transfer reaction has been very recently reported for α-chloro-acetophenone which yields acetophenone using $[PdCl_2(PPh_3)_2]$ or Pd/C as catalysts; the influence of the reaction parameters with a proposed mechanism have been already reported [12].

### 2.2. On the mechanism of the alkoxycarbonylation of 2-chlorocyclohexylketone

The carbonylation of organic halogenides involves the oxidative addition of the halide to a Pd(0) species with formation of a Pd-alkyl intermediate (I), and then usually occurs through two mechanisms [13]:

$$Pd(0) + R–X \rightarrow \underset{(I)}{X–Pd–R} \qquad (3)$$
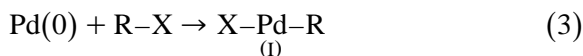
Following one mechanism, the reaction proceeds through the insertion of CO into the Pd–C bond with formation of an acyl intermediate (II). Nucleophilic attack of the alkanol on the C atom of the acyl moiety gives the product and the Pd(0) complex back to the catalytic cycle:

$$X–Pd–R + CO \rightarrow \underset{(II)}{X– Pd –COR} \overset{EtOH}{\underset{B}{\rightarrow}}$$

$$Pd(0) + EtOCOR + B \cdot HX \qquad (4)$$
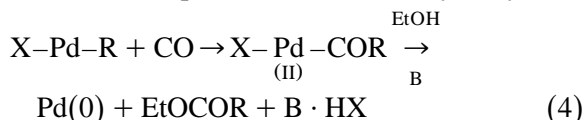
According to the other mechanism, interaction of CO and the alkanol gives rise to carboalkoxy-Pd-alkyl intermediate (III), which, upon reductive elimination of the two ligands, gives the product and the Pd(0) complex to start another catalytic cycle:

$$X–Pd–R + CO + EtOH \underset{-B \cdot HX}{\overset{B}{\rightarrow}} \underset{(III)}{EtOCO–Pd–R}$$

$$\rightarrow EtOCOR + Pd(0) \qquad (5)$$
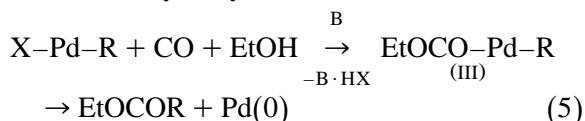
The base favors the formation of the carboalkoxy species (III) because it neutralizes the acid arising from the step forming this species, otherwise this step would be reversed [14].

The Pd(0) complex, such as for example $[Pd(CO)(PPh_3)_3]$ (which has been found in the reaction medium after cooling it once the reaction was carried out), can form through reduction of the precursor by CO in the presence of an extra amount of PPh_3 [15]:

$$[PdCl_2(PPh_3)_2] + 2CO + 2ROH + PPh_3 \overset{B}{\rightarrow}$$

$$[Pd(CO)(PPh_3)_3] + OC(OR)_2 + 2HCl \cdot B \qquad (6)$$
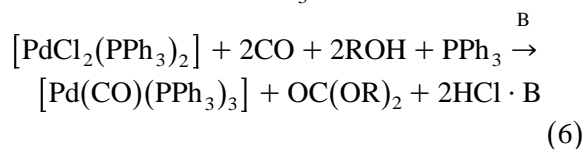
R = H, alkyl.

During the course of the hydroesterification reaction [1], there is concomitant formation of HCl. If the reaction is carried out in the absence of a base the acid would oxidize the Pd(0) complex to $[PdCl_2(PPh_3)_2]$ [16], thus preventing the catalytic cycle to go on.

The fact that reaction (1) is not accompanied by formation of γ-ketoester as side product, suggests that isomerization of the starting chloride to 3-chlorocyclohexylketone, or the isomerization of the 2-palladiumcyclohexylketone in-

termediate (I) to 3-palladiumcyclohexylketone do not occur under the conditions used in the present study. If isomerization would occur, then there would be formation of the γ-ketoester since carbonylation of 3-chlorocyclohexylketone easily occurs in the presence of a [PdCl$_2$-(PPh$_3$)$_2$] catalyst precursor [4].

As already mentioned, when the carbonylation of 2-chlorocyclohexylketone is carried out in the presence of H$_2$O and in the absence of NEt$_3$, in place of the expected carbonylation product, there is hydrogen transfer from the system H$_2$O–CO to the organic substrate with hydrogenolysis of the C–Cl bond (reaction (2)). Under the conditions reported in Section 3, which are close to those employed for the carbonylation reactions, the hydrodechlorination occurs selectively in 60% yield. It is interesting to note that under similar conditions the hydrodechlorination of α-chloroacetophenone is much faster as the same catalytic system is ca. 20 times more active [12].

For the hydrodechlorination reaction we propose that, after the oxidative addition step to a Pd(0) complex, depicted by reaction (3), the Pd–C bond of the alkyl intermediate is protonolyzed by the acid that forms during the course of the reaction (1) when carried out in the absence of the base:

$$Pd(0) + R–Cl \rightarrow \underset{(I)}{Cl–Pd–R} \overset{HCl}{\rightarrow} PdCl_2 + RH$$
(7)
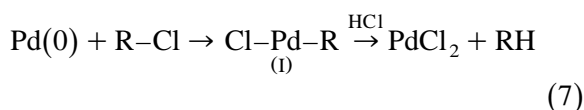
The Pd(II) complex is then reduced by CO in the presence of H$_2$O (reaction (6), R = H) as proposed in [12]:

$$PdCl_2 + CO + H_2O \rightarrow Pd(0) + CO_2 + 2HCl$$
(8)
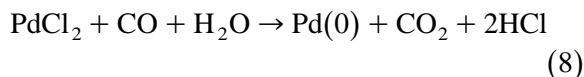
Note that, in the presence of H$_2$O, Pd(II) is reduced to Pd(0) even in the absence of a base, that is in the presence of relatively large amount of HCl that forms during the course of the hydrodechlorination reaction.

3. Experimental

3.1. Materials and reagents

Carbon monoxide, quality N 37, was purchased by S.I.O. Solvents and PPh$_3$ were of commercial grade. α-Chlorocyclohexyketone (Aldrich) was used without further purification. [PdCl$_2$(PPh$_3$)$_2$] [17], [Pd(CO)(PPh$_3$)$_3$] [14] were prepared as reported in the literature.

3.2. Product identification and analysis

Products were identified by NMR on a Bruker 200 AC spectrometer, by IR on a Perkin Elmer model 683 spectrometer, and by MS-GC on a HP 5890-series II instrument equipped with a HP 5971 A detector. Yields were determined by GC on a HP 5890-series II instrument.

3.3. Carbonylation of 2-chlorocyclohexylketone to ethyl β-cyclohexylketocarboxylate catalyzed by [PdCl$_2$(PPh$_3$)$_2$]

In a typical experiment, 10 mmol of 2-chlorocyclohexylketone, 12 mmol of NEt$_3$, 0.05 mmol of [PdCl$_2$(PPh$_3$)$_2$], 0.025 mmol of PPh$_3$ were added 7.1 ml of EtOH in a Pyrex bottle. The bottle was placed into an autoclave which was purged with carbon monoxide at room temperature. The autoclave was then pressurized with 100 atm of the same gas and heated to 100°C. This temperature was maintained for 4 h while stirring. After cooling the reaction medium a solid precipitated. The solid showed (IR) the presence of [Pd(CO)(PPh$_3$)$_3$], [PdCl$_2$(PPh$_3$)$_2$] and [PdCl(COOEt)(PPh$_3$)$_2$]. The solution was analyzed by GC. The yield in ester was 69%.

3.4. Hydrodechlorination of 2-chlrocyclohexylketone to cyclohexanone

For the hydrodechlorination reaction the same procedure as that just reported for the carbony-

lation reaction was followed, but water was added in place of NEt_3. Typically, 10 mmol of the chloro-derivative were dissolved in 7.5 ml of EtOH containing 1 ml of H_2O. To this solution 0.05 mmol of the palladium complex were added together with 0.1 mmol of PPh_3. The mixture was pressurized under 100 atm of CO, heated at 80°C and kept at this temperature for 4 h. After cooling a solid precipitated, whose IR spectrum showed the presence of $[Pd(CO)(PPh_3)_3]$, $[PdCl_2(PPh_3)_2]$ and $[PdCl(COOEt)(PPh_3)_2]$. The solution was analyzed by GC. The hydrodechlorination reaction occurred in 60% yield.

Acknowledgements

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