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LETTERS

## Palladium(II) catalyzed carbonylation of ketones

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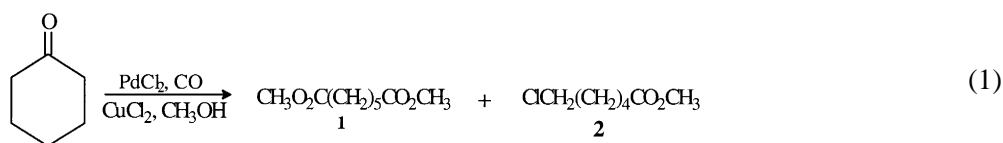
### Abstract

Cyclic ketones react with PdCl<sub>2</sub> in methanol under a CO atmosphere to give mainly diesters by a ring cleavage reaction along with some chloro-substituted monoester. <sup>13</sup>C labeling experiments indicate the major product is formed by a mechanism involving Pd(II)-CO<sub>2</sub>CH<sub>3</sub> insertion across the double bond of the enol form of the ketone. Pd(II) elimination and acid-catalyzed ring cleavage form a second methyl ester group. © 2000 Elsevier Science Ltd. All rights reserved.

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The palladium(II)-catalyzed oxidation of olefins is one of the most synthetically useful transition metal catalyzed reactions. One class of such reactions is the carbonylation reaction to give diesters or lactones.<sup>1–4</sup> In comparison, examples of the use of ketones in palladium(II) catalysis as substrates are quite rare. They include telomerizations of butadiene<sup>5</sup> catalyzed by Pd(0) and the dehydration of cyclohexanone.<sup>6</sup> An extension of the utilization of ketones as substrates in palladium(II) catalytic chemistry would be a valuable addition to this chemistry. This communication will describe the catalytic carbonylation of ketones.

The reaction of several ketones with CO in methanol containing catalytic amounts of palladium(II) chloride and CuCl<sub>2</sub> as reoxidant produced a mixture of diesters and terminally chloride substituted α-esters. Eq. (1) illustrates the reaction using cyclohexanone as substrate. The major product is the diester **1** with smaller amounts of the chlorinated product **2**. Table 1 summarizes the results for several ketones.



2-Methylcyclohexanone gave products analogous to those obtained from carbonylation of cyclohexanone and the methyl group allows determination of the position of a <sup>13</sup>C label. In order to test possible

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Table 1  
Catalytic carbonylation of ketones in methanol by palladium(II) chloride in the presence of CuCl<sub>2</sub><sup>a</sup>

Ketone	Products (Relative Yields)	Yield
Cyclopentanone	Dimethyl adipate (85%) Methyl 5-chloropentanoate (15%)	73%
Cyclohexanone	Dimethyl pimelate (87%) Methyl 6-chlorohexanoate (13%)	78%
Cycloheptanone	Dimethyl subarate (90%) Methyl 7-chloroheptanoate (10%)	83%
2-Methylcyclopentanone	Dimethyl 2-methyladipate (88%) Methyl 5-chlorohexanoate (12%)	78%
2-Methylcyclohexanone	Dimethyl 2-methylpimelate (90%) Methyl 6-chloroheptanoate (10%)	78%

<sup>a</sup>Reaction mixtures contained 0.6 mmol PdCl<sub>2</sub>, 5 mmol ketone and 15 mmol CuCl<sub>2</sub> in 15 mL methanol. The CO pressure was approximately 2 atm.

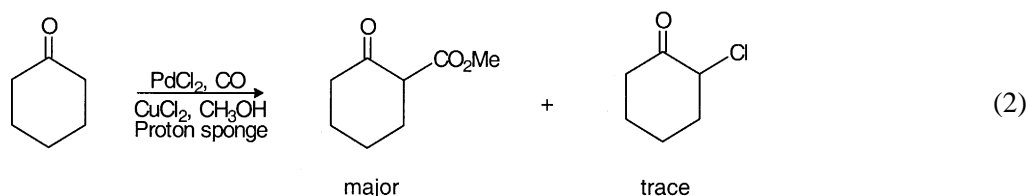
mechanisms, 2-methylcyclohexanone was carbonylated in the presence of <sup>13</sup>CO in one experiment. Analysis of the two products by <sup>1</sup>H and <sup>13</sup>C NMR showed that the diester product contains only one labeled carbon, while the chloro compound has no labeled carbon.

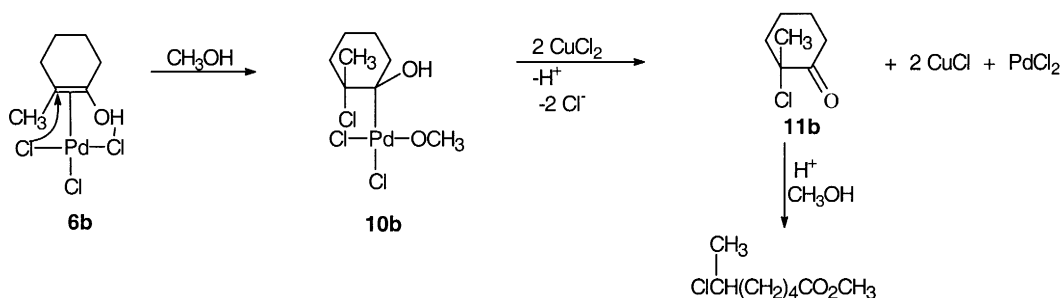
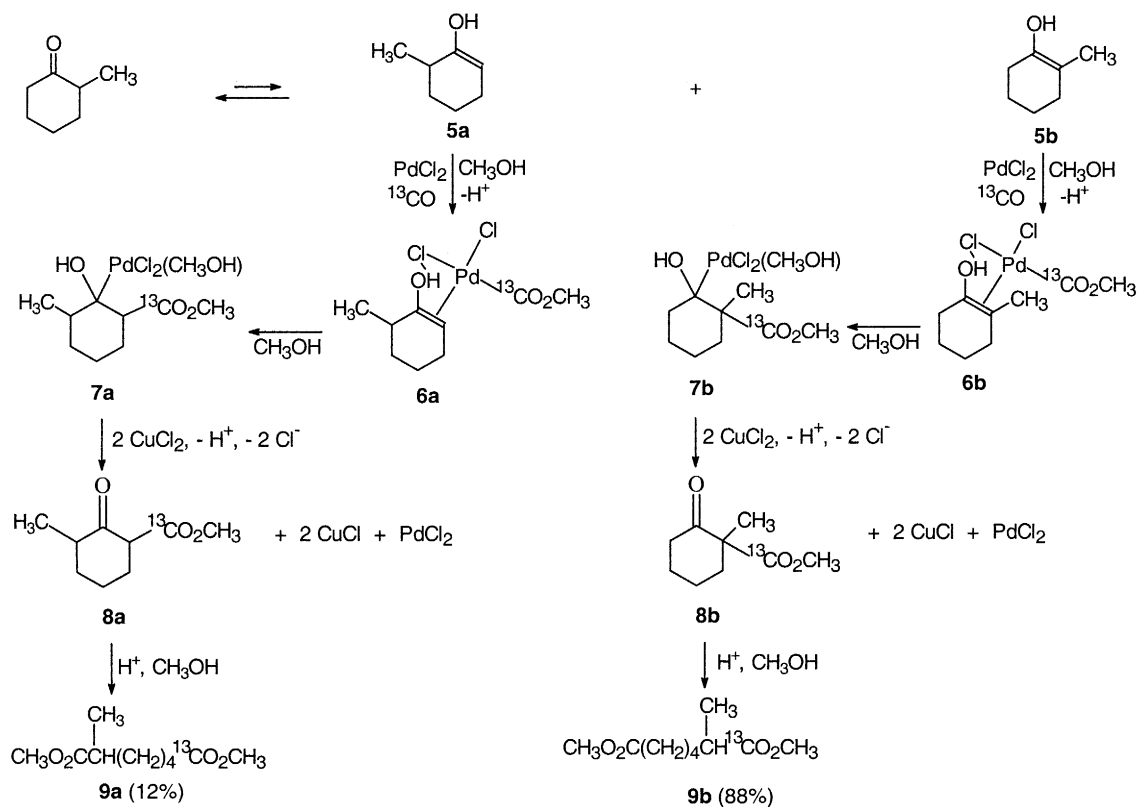
This result requires that one of the methyl ester groups in the diester product arises from the ketone function. The initial enolization gives the species **5a** and **5b** (Scheme 1). The complexes, **6a** and **6b**, insert the carboxymethyl group to give **7a** and **7b** which decompose to give **8a** and **8b**. The final products, **9a** and **9b**, arise from ring cleavage of **8a** and **8b** catalyzed by acid formed during the course of the reaction. Most of the products arose from the **5b** route. As expected from this mechanism the straight chain ketone, 2-decanone, gives methyl nonanoate and methyl acetate.

The route for the chlorine containing product, shown in Scheme 2, is analogous to the diester route shown in Scheme 1. However chloride, rather than carboxymethyl, adds to **5b** gives the intermediate **10b** that decomposes in the same fashion as **7b** in Scheme 1. The addition to **5a** would eventually give methyl-6-chloro-2-methylhexanoate. This product was not observed.

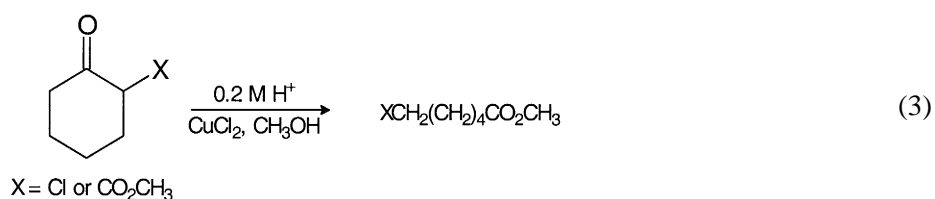
Several control experiments were run to test Schemes 1 and 2. Firstly, the reaction with non-labeled CO was run in the presence of all reactants except PdCl<sub>2</sub>. No reaction occurred proving that the reaction was Pd(II) catalyzed.

Secondly, cyclohexanone was reacted under the usual reaction conditions in the presence of proton sponge to remove any acid present. As shown in Eq. (2), the major product was 2-carbomethoxycyclohexanone, with traces of 2-chlorocyclohexanone. Thus, the ring cleavage must be acid catalyzed.





Finally, the methyl 2-oxocyclohexanone recovered from the above experiment and a commercial sample of 2-chlorocyclohexanone were reacted with 0.2 M HCl in methanol containing 0.7 M CuCl<sub>2</sub>. As shown in Eq. (3), the only products observed in both experiments were the ring cleavage products, methyl-6-chlorohexanoate and dimethyl adipate, respectively. Thus, **11b** and **8a** or **8b** will undergo ring cleavage under the reaction conditions.



*General procedure for the PdCl<sub>2</sub>-catalyzed carbomethoxylation of ketones.* A 100 mL, two-necked flask was equipped with magnetic stirring bar, septum and balloon, CuCl<sub>2</sub> (15.0 mmol, 2.0 g), PdCl<sub>2</sub> (0.1 g) and methanol (15 mL). The air in the flask was replaced by CO by evacuating on an aspirator and then pressuring with CO through a needle. Then 5 mmol of ketone was injected and the CO pressure was raised to about 2 atm. The reaction mixture was stirred at room temperature for 4 days. After removing the solvent under reduced pressure the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, washed with diluted NaHCO<sub>3</sub> (20 mL) and dried over MgSO<sub>4</sub>. CH<sub>2</sub>Cl<sub>2</sub> was removed under reduced pressure, the residue was purified by either preparative GLC or column chromatography (hexane/AcOEt=8/2). In every reaction 15–20% of the starting material was recovered. The percent yields based on ketone were obtained by GLC analysis in the presence of an internal standard.

In summary, this report describes a novel carbonylation of ketones that generally occurs with carbon–carbon bond cleavage to give diesters. A side reaction is the formation of terminally chlorine substituted acid esters.

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