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Oxidation of ketone by palladium(II). α-Hydroxyketone synthesis catalyzed by a bimetallic palladium(II) complex

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Abstract

A bimetallic palladium(II) complex containing a triketone ligand and a bridging dinitrogen ligand oxidizes ketones in aqueous THF to α-hydroxyketone by a direct air oxidation. While the normal synthesis of α-hydroxyketones involves a series of reactions, this synthesis performs the transformation in one step in a catalytic air oxidation. This synthesis does not involve an olefin and is almost unprecedented in transition metal catalysis. Its main virtue is its simplicity and actually it is an enolization reaction. Methanesulfonic acid is used to accelerate the enolization of ketones. The reaction is carried out in the presence of $CuCl_2$ and/or dioxygen only. In particular, it is found that the hydroxyketone formation does not require the presence of $CuCl_2$. Matrix assisted laser desorption ionization (MALDI) and time-of-flight mass spectrometry (TOFMS) are used to record the mass spectra of α-hydroxyketones products. α-Cyano-4-hydroxycinnamic acid (CHCA) matrix promoted the molecular ion detection when 180 pmol of α-hydroxyketones is introduced into the TOFMS.

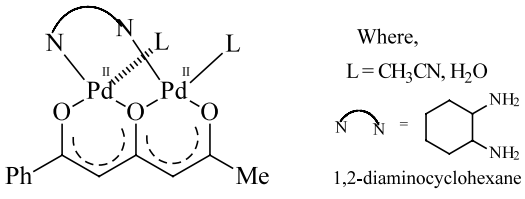
Keywords: Palladium(II); Catalysis; Hydroxyketone

1. Introduction

The oxidation of carbonyl compounds by metal species is a well-known and widely studied reaction [1–3]. Many of these apparently proceed by oxidation of the enol tautomer. Thus, the oxidation of ketones by the two-electron oxidants, Hg(II), Tl(III) and Mn(VII), were postulated to involve the enol isomer [4]. Some one-electron oxidants such as Mn(III) [5] and tris(1,10-phenanthroline) complexes of Fe(III) and Ru(III) [6] also attack the enol isomer. Recently, palladium(II) chloride has been used in the catalytic carbonylation of ketones [7].

A number of important compounds that show interesting pharmacological properties possess α-hydroxycarbonyl groupings, which are common structural features of many natural products. Furthermore, α-hydroxycarbonyl groupings are useful chiral building units in the preparation of biologically active compounds. The isomerization of α-hydroxycarbonyl compounds is of crucial importance in metabolism [8].

The importance of α-hydroxyketones mentioned above brought us to investigate and describe the catalytic oxidation of ketones using achiral bimetallic catalyst **A**, while the asymmetric version reactions are now under processing [9].



bimetallic catalyst, **A**

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2. Experimental

2.1. Materials

All solvents used were analytical grade reagents. Tetrakis(acetonitrile)palladium (II) tetrafluoroborate {[$Pd(MeCN)_4$](BF_4)$_2$} was purchased from Strem Chemicals. 1,2-Diaminocyclohexane (DACH) and all starting materials for the triketone ligand and all ketones were obtained from Aldrich Chemical Co. The triketone ligand, 1-phenyl-1,3,5-hexanetione (PHT) was prepared as before [10]. Diacetonitrile-1-phenyl-1,3,5-hexanetrione-μ-1,2-diaminocyclohexanedipalladium(II) tetrafluoroborate {[$Pd_2(MeCN)_2$(PHT)(DACH)](BF_4)$_2$} was synthesized by a similar procedure described for the chiral analogue [10] and characterized by ^{1}H- and ^{13}C-NMR.

2.2. Instrumentation

All ^{1}H- and ^{13}C-NMR spectra were recorded on a 400 MHz Varian VXR 400 spectrometer using $CDCl_3$. Chemical shifts for ^{1}H and ^{13}C are relative to $(CH_3)_4Si$. Measurements were performed at ambient probe temperature using 5 mm o.d. sample tubes. GLC analyses were carried out on a GOW-MAC gas chromatograph (Model 350). IR spectra were recorded on an ATI Mattson Genesis series FTIR spectrometer. Molecular weight spectra were acquired using a modified Wiley–McLaren design 'time-of-flight mass spectrometry' (TOFMS) (model D850, R. M. Jordan Co., Grass Valley, CA) in the linear mode. A nitrogen laser (337 nm, 5 mW peak laser power, 3 ns pulse width, and a $\sim$400 μm^2 spot size) was used to induce desorption (model VSL-337ND, Laser Science, Newton, MA). Samples preparation for MS were conducted as described before [11].

2.3. General procedure for the catalytic oxidation of ketones

In a typical experiment a 250-ml two-necked cone shaped flask, with indented sides to increase the efficiency of stirring, was equipped with a magnetic stirring bar, subseal septum and vacuum adapter. The flask was charged with 15 ml of H_2O, 15 ml of THF, 2.00 g (14.9 mmol) of $CuCl_2$, 0.70 g (7.3 mmol) of CH_3SO_3H, and 0.10 mmol of catalyst. The flask was then placed in a constant-temperature bath at 25 °C and connected to the gas uptake system [10,12]. The system was evacuated for 10 min on the vacuum line with the stirrer running. The stirring was stopped and the system pressurized to 1 atm. with dioxygen. Then 8 mmol of ketone was added to the reaction mixture by syringe. The mercury in the gas buret and the leveling bulb were equalized, and a reading was taken. The stirrer was turned on to start the reaction. The pressure was kept constant at 1 atm. by continuously leveling the mercury in the gas buret and bulb. Gas uptake readings were taken at regular intervals. The reaction was allowed to run until the reaction mixture was at least 0.25 M in total oxidation product. The oxidation product was separated from the reaction mixture by continuous extraction with ether over night. The ether was dried over anhydrous $MgSO_4$ and removed by distillation. Analysis of the product was carried out by GLC, MS, FTIR, and ^{1}H- and ^{13}C-NMR. In every reaction, 8–15% of the starting material was recovered. The percent yields based on the amount of dioxygen uptake for all runs.

2.3.1. Hydroxylation of cyclohexanone

Oxidation of cyclohexanone by the procedure described above afforded only one product in a 90% yield. GLC and ^{1}H- and ^{13}C-NMR identified the product as 2-hydroxy cyclohexanone. $m/z = 114.139$. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.66$–2.10 (m, 6H), 2.30–2.40 (m, 2H), 2.75–2.82 (m, OH), 4.35 (ddd, 1H, $J = 1.10$, 5.08, 8.65 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 22.9$, 27.1, 37.4, 39.3, 62.8, 203.0 ppm. FTIR (neat): 3146, 2969, 1790, 1716, 1383, 1097 cm^{-1}.

2.3.2. Hydroxylation of 2-methylcyclohexanone

This oxidation afforded two products in relative yields of 86 and 14%, respectively, and in a chemical yield 85%. ^{1}H- and ^{13}C-NMR identified the products as 6-methyl-2-hydroxycyclohexanone, and 2-methylcyclohex-2-en-1-one, respectively. Spectral data of the products were as follows. 6-methyl-2-hydroxycyclohexanone: $m/z = 128.165$. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (d, 3H, $J = 6.8$ Hz), 1.55 (d, OH), 1.71–1.79 (m, 2H), 1.93–2.07 (m, 1H), 2.10–2.19 (m, 1H), 2.20–2.30 (m, 2H), 2.56 (dd, 1H, $J = 5.08$, 8.65 Hz), 4.22 (t, 1H, $J = 7.38$ Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta =$ 21.7, 28.1, 33.9, 34.3, 44.9, 60.4, 204.1 ppm. FTIR (neat): 3150, 2973, 1796, 1717, 1383, 1097 cm^{-1}. 2-methyl cyclohex-2-en-1-one: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.86$ (s, 3H), 1.97 (m, 2H), 2.43 (q, 2H, $J = 5.70$ Hz), 2.52 (t, 1H, $J = 7.0$ Hz), 5.93 (t, 1H, $J =$ 4.76 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 23.0$, 24.4, 38.9, 44.9, 116.3, 151.5, 194.4 ppm.

2.3.3. Hydroxylation of cyclopentanone

Hydroxylation of cyclopentanone gave 2-hydroxycyclopentanone in a 92% yield. $m/z = 100.113$. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.66$ (br.s, OH), 1.90–2.30 (m, 6H), 4.10 (t, 1H, $J = 7.35$ Hz) ppm. ^{13}C–NMR (100 MHz, $CDCl_3$): $\delta = 19.3$, 33.5, 35.1, 58.3, 210.8 ppm. FTIR (neat): 3153, 2970, 1790, 1721, 1386, 1089 cm^{-1}.

2.3.4. Hydroxylation of 2-butanone

Hydroxylation of 2-butanone gave 3-hydroxy-2-butanone, and 1-hydroxy-2-butanone in relative yields of 78%, and 22%, respectively, and in a chemical yield 94%. Spectral data for 3-hydroxy-2-butanone: $m/z = 88.105$. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.60$ (d, 3H, $J = 6.8$ Hz), 2.32 (s, 3H), 3.73 (s, OH), 4.30 (q, 1H, $J = 6.2$ Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 20.2$, 25.8, 59.1, and 187.8 ppm. FTIR (neat): 3150, 2973, 1796, 1717, 1383, 1097 cm^{-1}. Data for 1-hydroxy-2-butanone: $m/z = 88.103$. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.10$ (t, 3H), 2.15 (br.s, OH), 2.63 (q, 2H), and 4.07 (s, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 8.4$, 32.6, 61.4, and 195.6 ppm.

2.3.5. Hydroxylation of 3-pentanone

Oxidation of 3-pentanone afforded only one product in a 91% yield. GLC and ^{1}H- and ^{13}C-NMR identified the product as 2-hydroxy-3-pentanone. $m/z = 102.130$. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 1.08$ (t, 3H, $J = 7.20$ Hz), 1.57 (d, 3H, $J = 6.2$ Hz), 2.38 (d, OH), 2.61 (dq, 1H), 2.75 (dq, 1H), 4.34 (q, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 8.0$, 20.4, 31.7, 58.4, 206.0 ppm. FTIR (neat): 3154, 2972, 1793, 1719, 1383, 1095 cm^{-1}.

2.3.6. Hydroxylation of 2-hexanone

Hydroxylation of 2-hexanone gave two products in relative yields of 88 and 12%, respectively, and in a chemical yield 88%. ^{1}H- and ^{13}C-NMR identified the products as 3-hydroxy-2-hexanone, and 1-hydroxy-2-hexanone, respectively. Spectral data for 3-hydroxy-2-hexanone: $m/z = 116.155$. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (t, 3H, $J = 7.40$ Hz), 1.35–1.56 (m, 2H), 1.75–1.96 (m, 2H), 2.10 (br.s, OH), 2.29 (s, 3H), 4.14 (dd, 1H, $J = 5.59$, 8.52 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 13.4$, 19.3, 25.8, 35.8, 64.0, 203.4 ppm. FTIR (neat): 3158, 2980, 1788, 1720, 1383, 1096 cm^{-1}. Data for 1-hydroxy-2-hexanone: ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta =$ 0.95 (t, 3H, $J = 7.40$ Hz), 1.32–1.54 (m, 2H), 1.75–1.92 (m, 2H), 2.14 (br.s, OH), 2.52 (t, 2H, $J = 7.30$ Hz), 4.10 (s, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 14.0$, 22.3, 28.4, 39.4, 71.4, 194.6 ppm.

2.3.7. Hydroxylation of 4-heptanone

Hydroxylation of 4-heptanone afforded only one product in a 93% yield. A pure sample was isolated by preparative GC and identified as 3-hydroxy-4-heptanone. $m/z = 130.180$. ^{1}H-NMR (400 MHz, $CDCl_3$): $\delta =$ 0.91 (t, 3H, $J = 7.40$ Hz), 1.00 (t, 3H, $J = 7.35$ Hz), 1.63 (m, 2H), 1.80 – 2.05 (m, 2H), 2.15 (br.s, OH), 2.61 (t, 2H, $J = 7.29$ Hz), 4.12 (dd, 1H, $J = 5.60$, 8.12 Hz) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): $\delta = 10.6$, 13.6, 17.1, 27.2, 40.6, 65.2, 205.4 ppm. FTIR (neat): 3151, 2974, 1794, 1716, 1383, 1096 cm^{-1}.

2.4. Control experiments

To confirm that the bimetallic catalyst is the actual catalyst, two control experiments were carried out. First, the oxidation of cyclohexanone was attempted using all reactants except the bimetallic catalyst. The results have shown that there was no oxygen uptake and no hydroxyketone product was detected by GLC. Second, the reaction was done until the usual amounts of product were accumulated. The catalyst was isolated from the reaction mixture as the bromide compound. It was proved to be the bimetallic catalyst by ^{1}H- and ^{13}C-NMR analysis. A third experiment was carried out using dioxygen instead of $CuCl_2$. The result indicated the formation of hydroyketone in a high yield and the catalyst is recovered. This control experiment indicated that oxidation is an air oxidation and does not require the presence of $CuCl_2$.

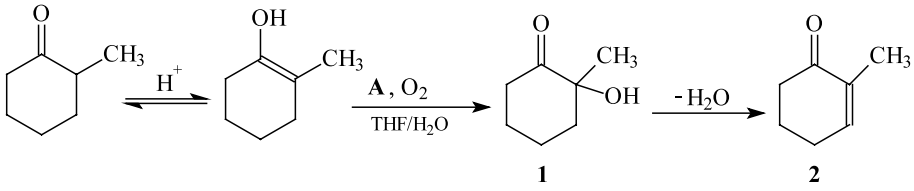
Table 1
Catalytic hydroxylation of ketones in aqueous THF by dipalladium catalyst in the presence of $CuCl_2$

Run	Ketone	Products (relative yields) [a]	Yield (%) [b]
1	Cyclohexanone	2-Hydroxycyclohexanone	90
2	2-Methylcyclohexanone	6-Methyl-2-hydroxycyclohexanone (86%), 2-methylcyclohex-2-en-1-one (14%)	85
3	Cyclopentanone	2-Hydroxycyclopentanone	92
4	2-Butanone	3-Hydroxy-2-butanone (78%), 1-hydroxy-2-butanone (22%)	94
5	3-Pentanone	2-Hydroxy-3-pentanone	91
6	2-Hexanone	3-Hydroxy-2-hexanone (88%), 1-hydroxy-2-hexanone (12%)	88
7	4-Heptanone	3-Hydroxy-4-heptanone	93

All runs contain 0.08–0.1 mmol of dipalladium catalyst in 30 ml of solvent and are 0.5 M in $CuCl_2$ and 0.2 M in CH_3SO_3H. Temperature: 25 °C. The solvent was a H_2O–THF mixture.

[a] The relative yields were determined by GLC analysis.

[b] The yield was determined based on O_2 uptake using gas burets and assuming O_2 is a four-electron oxidant. Turnovers were in the range 180–200.

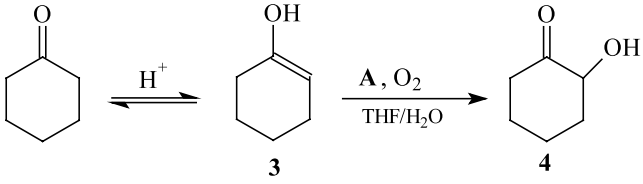


Scheme 1.

3. Results and discussion

Previous studies on the oxidation of internal olefins under the chlorohydrin conditions have shown, in addition to the ketones produced by the Wacker oxidation, that hydroxyketones were also obtained [10]. This result encourages us to investigate complementary reactions using ketones as substrates instead of internal olefins.

The characterizations of the α-hydroxyketones products were achieved by using spectroscopic techniques such as ^{1}H-, ^{13}C-NMR, FTIR and MS (see Section 2). The α-hydroxyketones products, namely 2-hydroxycyclohexanone, 6-methyl-2-hydroxycyclohexanone, 2-hydroxycyclopentanone, 3-hydroxy-2-butanone, 2-hydroxy-3-pentanone and 3-hydroxy-2-hexanone products all prepared in ~85–92% yield. The products distribution and the percentage yields are summarized in Table 1. On the other hand, the other minor products, namely 2-methylcyclohex-2-en-1-one (**2**, Scheme 1), 1-hydroxy-2-butanone, and 1-hydroxy-2-hexanone, are produced in low yields (Table 1). The route for the formation of 2-methylcyclohex-2-en-1-one (**2**) is shown in Scheme 1 and most likely due to the elimination of water from the α-hydroxyketone (**1**). Previously, a similar result was obtained by the same mechanism in a study of carbonylation of ketones catalyzed by palladium(II) chloride [7].

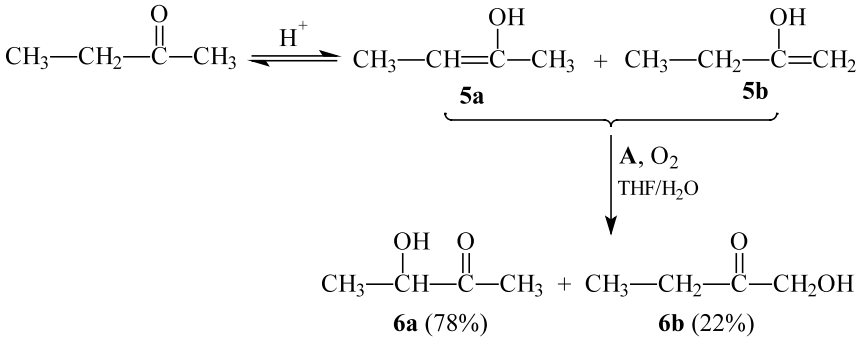


Scheme 2.

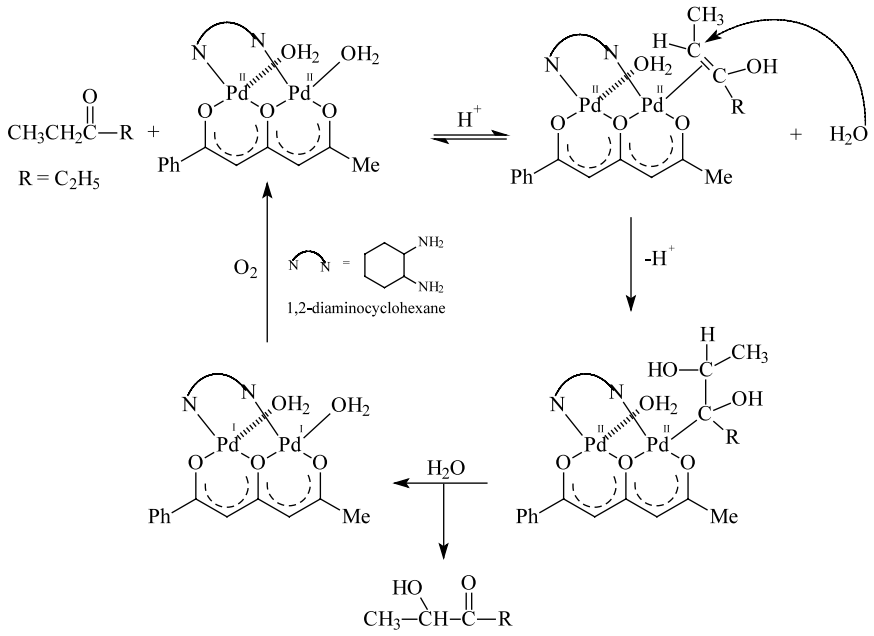
The symmetrical ketones namely, cyclohexanone, cyclopentanone, 3-pentanone, and 4-heptanone afford only one product (**4**, Scheme 2) (Table 1) which results from one expected enol form (**3**, Scheme 2). Scheme 2 represents the reaction using cyclohexanone as a substrate.

Whereas the unsymmetrical ketones namely, 2-methylcyclohexanone, 2-butanone, and 2-hexanone gave two products (Table 1) resulted from the two possible enols (**5a**, **5b**) forms as indicated in Scheme 3. Scheme 3 illustrates the reaction using 2-butanone as a substrate. Compound **6a** is found to be the major product rather than compound **6b**. This result may be explained by the formation of the most stable enol form (**5a**). Since the reaction is an enolization, it would be expected to be acid catalyzed. Methanesulfonic acid was used in all reactions to accelerate the enolization of ketone. The oxidation becomes faster and gave almost quantitative yields.

The hydroxylation of ketones by dipalladium(II) is a new method used to prepare α-hydroxyketones. Since the normal synthesis of chiral α-hydroxyketones involves a series of reactions [13,14]. The present synthesis performs the transformation in one step in a catalytic air oxidation. However, the asymmetric syntheses of α-hydroxyketones by using chiral bimetallic catalyst are underway [9]. In particular, the formation of α-hydroxyketone does not require the presence of $CuCl_2$. The reaction of ketone was run with a bimetallic catalyst A in chloride-free media using dioxygen as a reoxidant and gave the desired α-hydroxyketones in high yield.



Scheme 3.



Scheme 4.

The bimetallic complex, **A**, is analogous to the catalysts previously employed for the asymmetric chlohydrin synthesis [10]. Of course in the chlorohydrin synthesis, the chelating bimetallic ligand was chiral. As shown in Scheme 4 using 3-pentanone oxidation as an example, the reason for this air oxidation capability is that Pd(I) dimer, rather than Pd(0), is the reduced species. This Pd(I) dimer is readily oxidized back to the Pd(II) dimer before Pd(0) can form. Similar results were observed in previous reported studies [15].

In conclusion, we have developed a novel hydroxylation of ketones since it does not involve an olefin and is almost unique in transition metal catalysis.

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