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Palladium-catalyzed Oxidation of Benzyl Ketones to Synthesis of α-Acetoxy Ketones Using Molecular Oxygen

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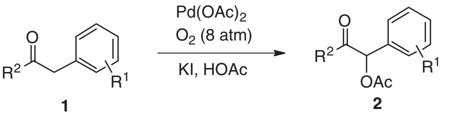
An efficient procedure for the preparation of α-acetoxy ketone derivatives by palladium-catalyzed oxidation reactions employing molecular oxygen as the sole oxidant has been reported. A variety of benzyl ketones were used to investigate the scope of the reactions.

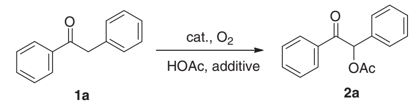
Oxidation reactions are central components of organic chemistry. Over the past decades, transition-metal-catalyzed oxidation reactions have been important tools for constructing carbon–carbon and carbon–heteroatom bonds, and hence are the focus of intense synthetic attention.[1] Among them, palladium-catalyzed oxidation reactions have emerged as one of the most powerful roles in organic synthesis since the development of the Wacker reaction in the late 1950s.[2] However, a great amount of oxidants such as PIDA, IBX, DDQ, BQ, Oxone, and other noble metals have been needed for the oxidation process which are problematic for the cost and environmental impact. Oxygen is regarded as an ideal oxidant due to its inexpensive and environmentally benign nature. Therefore, palladium-catalyzed aerobic oxidation has been one of the hot topics in organic synthetic chemistry.[3]

α-Acetoxy ketones are important sources for α-hydroxy ketones which are highly desirable building blocks for fine chemistry and pharmaceuticals. Several approaches have been developed for the preparation of α-acetoxy ketones, such as the oxidation of terminal alkynes in the presence of hypervalent iodine compounds,[4] gold-catalyzed hydration of propargyl acetates,[5] iodobenzene-catalyzed oxidation of α-methylene ketones,[6] oxidative coupling reactions of carbonyl compounds with carboxylic acids,[7] lead tetraacetate oxidation of trimethylsilyl enol ethers or ketones,[8] the oxidation of ketones with manganese acetate,[9] the [Cu(acac)$_2$]-catalyzed insertion reaction of α-diazo ketones,[10] the anodic oxidation of enol acetates,[11] and some other methods.[12] However, some of them present significant limitations, such as expensive raw materials and oxidants, low yields, and environmental problems. Therefore, the continuous development of new reactions with safe and environmentally friendly systems remains challenging. Herein, we report an efficient oxidation of benzyl ketones to α-acetoxy ketones catalyzed by palladium with O$_2$ as the sole oxidant (Scheme 1).[13]



Scheme 1. Palladium-catalyzed synthesis of α-acetoxy ketones with O$_2$ as the oxidant.

Table 1. Optimization of reaction conditions[a]



Entry	Cat.	Additive	Yield/%[b]
1			n.r.[c]
2	FeCl$_3$		n.p.[d]
3	AgNO$_3$		n.p.
4	Cu(OAc)$_2$		10
5	PdCl$_2$		27
6	Pd(OAc)$_2$		46
7	Pd(OAc)$_2$	I$_2$	30
8	Pd(OAc)$_2$	ZnCl$_2$	45
9	Pd(OAc)$_2$	KI	85 (78)
10	[Pd(dba)$_2$]	KI	trace
11	[Pd(PPh$_3$)$_4$]	KI	trace
12[e]	Pd(OAc)$_2$	KI	23
13[f]	Pd(OAc)$_2$	KI	trace
14[g]	Pd(OAc)$_2$	KI	trace

[a]Reactions were performed with **1a** (1 mmol), pressure of O$_2$ (8 atm), catalyst (5 mol %), and additive (1 equiv) in 2 mL of acetic acid at 120 °C for 10 h. [b]Determined by GC. Isolated yield is in parentheses. [c]No reaction. [d]No product. [e]60 °C. [f]Reacted in pressure of O$_2$ (1 atm). [g]Reacted in pressure of O$_2$ (12 atm).

As a starting point for the development of transition-metal methodology, we chose 1,2-diphenylethanone (**1a**) under 8 atm of O$_2$ in acetic acid as the model reaction to study the oxidation conditions. As summarized in Table 1, the reaction did not proceed without catalyst (Table 1, Entry 1). Several different commonly used metal salts were tested as the catalyst to conduct this reaction, iron salt and silver salt were inactive for the transformation (Table 1, Entries 2 and 3). To our delight, we found that palladium salts and copper salts could smoothly promote the transformation and palladium acetate was the most efficient catalyst (Table 1, Entries 4–6). Inspired by this finding, different additives were then tried, and we were pleased to find that KI could improve the isolated yield (Table 1, Entries 7–9). Further investigation on other palladium catalysts in the new conditions led to inefficient results (Table 1, Entries 10 and 11). Lower temperature disfavored the reaction (Table 1, Entry 12). The pressure of oxygen is essential to the transformation. For example, 1 atm of oxygen gave low conversion even with a prolonged time and higher pressure mainly produced the side product of benzoic acid (Table 1, Entries 13 and 14). After some attempts, we considered that the optimized reaction conditions

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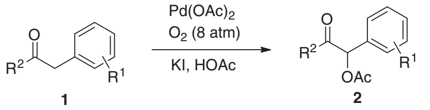
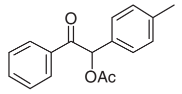
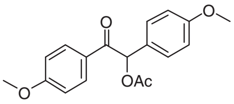
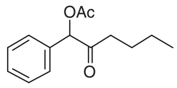
Table 2. Palladium-catalyzed oxidation of benzyl ketones for synthesis of α-acetoxy ketones[a]




2b 86%


2c 79%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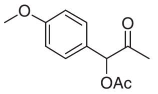
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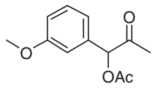
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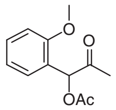
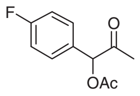
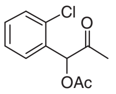
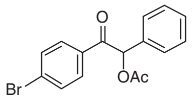
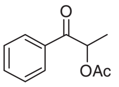

2g 60%


2h 69%


2i 70%

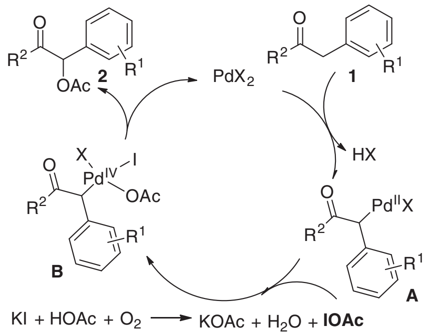

2j 83%


2k 32%

[a]The reactions were carried out with **1** (1 mmol), pressure of O_2 (8 atm), $Pd(OAc)_2$ (5 mol %), and KI (1 equiv) in 2 mL of acetic acid at 120 °C for 10 h.

are as follows: **1a** (1 mmol), KI (1 equiv), O_2 (8 atm) with acetic acid (2 mL) and $Pd(OAc)_2$ (5 mol %) at 120 °C for 10 h (Table 1, Entry 9).

With the optimized conditions in hand (Table 1, Entry 9), we next turned our attention to the scope of this palladium-catalyzed oxidation reaction. As showed in Table 2, different ketones with either electron-donating or electron-withdrawing groups attached to the benzene rings were applicable for such an oxidation reaction, the corresponding α-acetoxy ketone products could be obtained in moderate to good yields. It seemed that both the aromatic and the aliphatic groups attached to the carbonyl group had no obvious impact on the transformation (**2b**–**2j**). Substitution at the 2-position of the aromatic ring slightly lowered the yields (**2e**–**2g**). It should be pointed out that carbon–halogen bonds were well tolerated and the products containing halogen were afforded smoothly. Especially the aryl bromides and chlorides could be further functionalized (**2i** and **2j**). Phenyl ketone (**1k**) was also tried under the standard conditions, however, poor yield was obtained, which proved that the high activity of the benzyl position plays important role for such a reaction (**2k**). This reaction was not applicable to allyl ketones for the double bonds were also oxidized.



Scheme 2. Possible oxidation mechanism.

Although the reaction mechanism has not been clarified in detail yet, a plausible Pd^{II}–Pd^{IV} mechanism is proposed[13h] in Scheme 2. First, the Pd^{II} catalyst as the electrophilic reagent undergoes electrophilic substitution at the benzyl position to afford intermediate **A**.[14] Next, the organopalladium intermediate **A** is oxidized to a Pd^{IV} intermediate **B** by IOAc generated in situ by reacting KI, HOAc with oxygen.[13e] Finally, elimination results in the formation of α-acetoxy ketone product and Pd^{II}.

In summary, we have developed an environmentally benign and expedient procedure for the synthesis of α-acetoxy ketones by palladium catalysis with O_2 as sole oxidant.[15] The results also indicated that the oxidation reaction tolerated a variety of functional groups.[16] Further synthetic applications and studies of the mechanism of the oxidation reaction are in progress.

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15 Typical experimental procedure: the reactions were carried out in a HF-15 autoclave. Benzyl ketone (1 mmol), KI (1 mmol), $Pd(OAc)_2$ (5 mol %), and acetic acid (2 mL) were added into a 15-mL autoclave in sequence. O_2 was pumped into the autoclave with a cooling pump to reach the desired pressure, then the autoclave was heated with an oil bath under magnetic stirring at 110 °C for 10 h. After the reaction was finished, the autoclave was allowed to cool to room temperature and O_2 was vented. Water (10 mL) was added and the solution was extracted with ethyl acetate (3 × 8 mL), the combined extract was dried with anhydrous $MgSO_4$. Solvent was removed, and the residue was separated by column chromatography to give the pure sample.

16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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