

Ligand-free Pd-catalyzed oxidation of styrenes at room temperature

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Abstract: A convenient protocol for the oxidation of a styrene to the corresponding methyl ketone was developed. Without the requirement of an extra additive or ligand, this method allows Wacker-type oxidation to proceed efficiently at room temperature in the presence of a commercially available palladium trifluoroacetate catalyst and inexpensive aqueous *tert*-butyl peroxide. This transformation is highly functional group tolerant. Furthermore, aliphatic alkenes, di-substituted alkenes and internal alkenes could also be converted into the corresponding ketones.

Keywords: Pd-catalyzed; ligand-free; Wacker oxidation; styrene; ketone

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The development of an effective procedure for oxidizing a readily available terminal alkene to a ketone is very important in organic synthesis, agrochemicals and pharmaceuticals^[1-3]. One of the landmark achievements is using a palladium/copper catalyst system which is known as Wacker-Tsuji oxidation^[4-5]. However, the reaction rate and selectivity need to be improved in many cases^[6-8]. Consequently, a great many methods have been developed for the oxidation of an alkene to the corresponding ketone. Efforts have been focused on the identification of new catalyst systems that enable efficient catalytic turnover of the palladium catalyst without needing a copper salt as a co-catalyst^[9-11]. The systems of palladium catalyst combined with benzoquinone/ $\text{NaNO}_2/\text{HClO}_4$ and metal macrocycle/quinone have been reported for the oxidation of olefins to ketones^[12-13]. The uses of other oxidants such as potassium bromate^[14], chromium trioxide^[15] and benzoquinone^[16], iron(III) sulphate^[17] and hypervalent iodine^[18], have also been developed. Oxygen is an attractive oxidant from an economic point of view, and a

number of methods for the oxidation of terminal olefins have been developed^[19-21]. However, the methods are not effective for the oxidation of styrenes to their corresponding acetophenones in many cases. In addition, most of the methods required relatively harsh conditions.

We were attracted to the use of the peroxides as the terminal oxidant in our aim to develop a new catalytic system for Wacker-type oxidation of an alkene under relatively mild conditions. In this regard, hydrogen peroxide has been examined and found to be a sustainable oxidant for Wacker-type reactions^[22-24]. Especially for the Pd-catalyzed oxidation of styrenes, reports have been shown that ionic liquids^[25] and phase transfer catalysts^[26] could improve the performance of Pd(II)/ H_2O_2 system for the oxidation of styrenes. The group of Muldoon studied the effect of a ligand in the reaction and found that a 2-(2-pyridyl)benzoxazole (PBO) ligated palladium catalyst allowed a variety of alkenes to transform efficiently into their corresponding methyl ketones under Pd(II)/ H_2O_2 conditions (Fig.

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1(a))^[27]. On the other hand, Sigman and co-workers used *tert*-butyl peroxide (TBHP) under Pd and Ag co-catalysts system for the oxidation of styrenes (Fig. 1(b)). In their protocol, the presence of 2,6-diisopropylphenyl ligand was necessary to achieve the desired product^[28]. The group also found that a quinoline-2-oxazoline (Quinox) modulated Pd catalyst could also efficiently transform aliphatic olefins to ketones^[29]. The absence of the ligands led to considerable levels of oxidative cleavage, which resulted in low yields^[30]. Although a few ligand-free methods for the oxidation of styrenes have been reported, an elevated reaction temperature was required to afford the satisfied yields^[31].

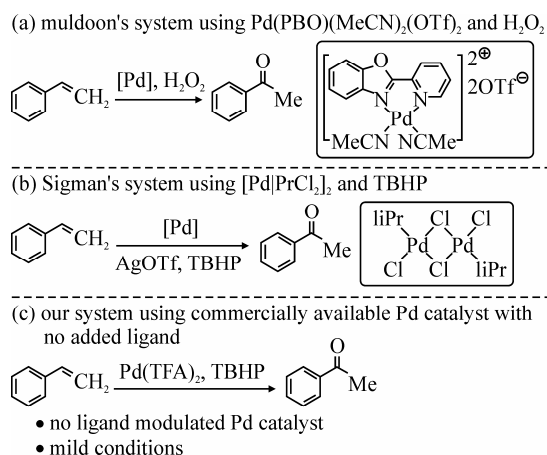


Fig. 1 Ligand modulated catalyst for oxidation of styrene

Herein, we report a method for the oxidation of a styrene by the use of commercially available palladium trifluoroacetate (Pd(TFA)₂) catalyst and TBHP oxidant at room temperature. This protocol is simple and convenient, and can be performed under air without the requirement of any extra additive or ligand. A variety of substituted alkenes have been examined and found to be oxidized to the corresponding ketones in good yields.

1 Experiment

1.1 General information

All chemicals used in this work were purchased from commercial sources and used without further purification. Column chromatography was generally performed on silica gel (300-400 mesh) and reactions

were monitored by thin-layer chromatography (TLC) using UV light to visualize the course of the reactions. ¹H NMR spectras recorded at 400 MHz are referenced to the residual solvent peak at 7.26 ppm (CDCl₃). ¹³C NMR spectras recorded at 126 MHz are referenced to the residual solvent peak at 77.0 ppm (CDCl₃).

1.2 General procedure

A tube was added Pd(TFA)₂ (0.025 mmol), alkenes (0.500 mmol), *tert*-butyl peroxide (70% solution in H₂O, 0.750 mmol) and dichloroethane (DCE) (1.0 mL). The reaction mixture was stirred at the indicated temperature for 12 h. After this time, the reaction mixture was filtered and quenched with saturated Na₂SO₃ solution (consumption of residual TBHP), extracted with ethyl acetate. The combined organic layer was dried over with Na₂SO₄ and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford the corresponding product.

2 Results and discussion

As a starting point, the oxidation of styrene (**1a**) catalyzed by palladium acetate Pd(OAc)₂ (2 mol%) in the presence of Na₂S₂O₈ (1.0 equiv) as an oxidant in MeCN at 50 °C for 12 h was studied. Fortunately, 7% of the methyl ketone (**2a**) was obtained (Table 1, entry 1). TBHP was found to be the most efficient oxidant among those that were tested, giving the desired product in 25% yield (Table 1, entry 4). We then carried out the solvent screen and found that DCE was the most suitable (Table 1, entries 5-7). Increasing the loading of catalyst to 5 mol% gave a slightly higher yield compared with that using 2 mol% of Pd(OAc)₂. However, no improvement was achieved by increasing the catalyst loading further (Table 1, entries 8 and 9). Interestingly, the reaction also proceeded well at room temperature, affording the desired product in 53% yield (Table 1, entry 10). TFA has previously been found to aid the oxidation of olefins, however^[32], no improvement in the yield was observed by adding an extra equivalent of TFA in this case (Table

Table 1 Optimization of oxidation of styrene^[1]

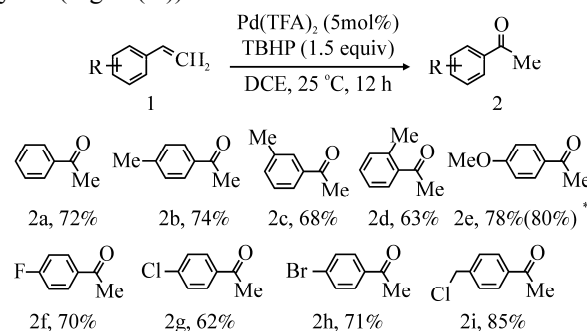
$\text{1a} \xrightarrow[\text{solvent, } T(^{\circ}\text{C})]{\text{catalyst, oxidant}} \text{2a}$					
Entry	Cat/(mol%)	Oxidant	Solvent	$T/^{\circ}\text{C}$	Yield/%
1	$\text{Pd}(\text{OAc})_2$ (2)	$\text{Na}_2\text{S}_2\text{O}_8$	MeCN	50	7
2	$\text{Pd}(\text{OAc})_2$ (2)	$(\text{NH}_4)_2\text{S}_2\text{O}_8$	MeCN	50	NR
3	$\text{Pd}(\text{OAc})_2$ (2)	H_2O_2	MeCN	50	10
4	$\text{Pd}(\text{OAc})_2$ (2)	TBHP	MeCN	50	25
5	$\text{Pd}(\text{OAc})_2$ (2)	TBHP	H_2O	50	15
6	$\text{Pd}(\text{OAc})_2$ (2)	TBHP	DMSO	50	7
7	$\text{Pd}(\text{OAc})_2$ (2)	TBHP	DCE	50	35
8	$\text{Pd}(\text{OAc})_2$ (5)	TBHP	DCE	50	46
9	$\text{Pd}(\text{OAc})_2$ (10)	TBHP	DCE	50	48
10	$\text{Pd}(\text{OAc})_2$ (5)	TBHP	DCE	25	53
11	$\text{Pd}(\text{OAc})_2$ (5)	TBHP	DCE	25	55 ^[2]
12	$\text{Pd}(\text{OAc})_2$ (5)	TBHP	DCE	25	47 ^[3]
13	$\text{Pd}(\text{TFA})_2$ (5)	TBHP	DCE	25	75
14	PdCl_2 (5)	TBHP	DCE	25	52

Note: (1) Yields are of pure isolated products, the reactions were performed by using 0.5 mmol of **1a**, 1.5 equiv of oxidants in 1 mL of solvent for 12 h; (2) An equivalent of TFA was added in the reaction; (3) An equivalent NaOAc was added in the reaction.

1, entry 11). The addition of NaOAc slightly decreased the yield to 47% (Table 1, entry 12). Finally, we found that the use of $\text{Pd}(\text{TFA})_2$ as a catalyst allowed the oxidation to proceed efficiently, giving the methyl ketone product in 75% yield (Table 1, entry 13). Importantly, only small amount of benzaldehyde was obtained under these conditions.

With suitable conditions, we turned our attention to the scope of the substrates. Gratifyingly, this oxidative process was very general (Fig. 2), with both electron-donating and -withdrawing groups being tolerated well (for example, *p*-OMe (Fig. 2 (2e)) and *p*-F (Fig. 2 (2f)) were obtained in 78% and 70% isolated yield, respectively). The methyl group at different positions were tested and all were found to be compatible (Fig. 2 (2b-2d)). Satisfyingly, the reaction conditions were compatible with Cl and Br without the observation of any homocoupling products (Fig. 2 (2g) and (2h)), providing a convenient handle for further functionalization. The chloromethyl group is an important motif in organic synthesis, and it was found that the substrate,

1-(chloromethyl)-4-vinylbenzene, could be oxidized efficiently to the corresponding methyl ketone in 85% yield (Fig. 2 (2i)).

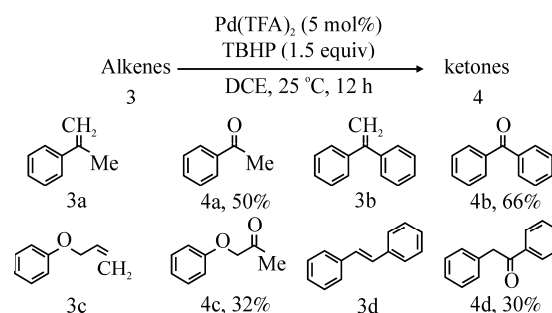


*: The reactions were performed by using 10 mmol (1.34 g) of 1-methoxy-4-vinylbenzene; #: Yields are of pure isolated products.

Fig. 2 Scope of the oxidation of styrene derivatives[#]

This methodology is easily scalable. Applying our standard conditions, without any modification to the oxidation of 4-methoxystyrene (10 mmol, 1.34 g) in the presence of $\text{Pd}(\text{TFA})_2$ catalyst and TBHP oxidant, afforded the corresponding methyl ketone in 80% isolated yield (Fig. 2 (2e)).

To extend the application of this method, some other types of alkenes were also tested. Interestingly, the di-substituted terminal alkenes could also be oxidized to the ketones at 50 °C (Fig. 3 (4a) and (4b)). This transformation may undergo epoxidation, re-arrangement, oxidation and decarboxylation sequence^[33]. The aliphatic alkene was examined and found to be a suitable substrate under the oxidizing conditions (Fig. 3 (3c)), giving the corresponding product in an acceptable 32% yield at 50 °C (Fig. 3 (4c)). Finally, the internal alkene 1,2-diphenylethene **3d** was treated with the same conditions, giving 1,2-diphenylethan-1-one in 30% yield (Fig. 3 (4d)).

**Fig. 3 Scope of the oxidation of alkenes^{*}**

*: Yields are of pure isolated products.

3 Conclusions

We report a readily available Pd(TFA)₂ catalyzed oxidation of an alkene to a methyl ketone without adding an extra ligand or additive. This protocol allows a variety of styrenes bearing both electron-withdrawing and electron-donating groups to undergo oxidation to the corresponding methyl ketones at room temperature under air. In addition, a couple of selected aliphatic alkenes, di-substituted alkenes and internal alkenes could also undergo this oxidative process, affording the corresponding ketones.

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室温下无配体体系钯催化苯乙烯氧化反应研究

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摘要: 报道了一种操作简单且有效的钯金属催化苯乙烯及其衍生物转化为苯乙酮类化合物的方法。研究表明, 该反应在温室下, 使用商业化的三氟乙酸钯催化剂以及廉价的过氧叔丁醇水溶液即可实现 Wacker 氧化, 且无需额外配体稳定或活化催化剂。该方法具有高官能团兼容性, 且末端脂肪烯烃、双取代末端烯烃以及中间体均可在该条件下转化为相应的酮。

关键词: 钯催化; 无配体; Wacker 氧化; 苯乙烯; 酮

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