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### Letter

# Selective Oxidation of Styrene Derivatives to Ketones over Palladium(0)/Carbon with Hydrogen Peroxide as the Sole Oxidant

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recyclable catalyst, green oxidant

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**Abstract**  $Pd^0/C$  catalyst exhibited excellent catalytic activity in the Wacker oxidation of styrene derivatives to corresponding ketones with hydrogen peroxide as a clean oxidant. Compared with the conventional Wacker system, the newly developed method offers a cost-efficient and environmentally friendly option without the use of a copper salt as a cocatalyst.

**Key words** Wacker oxidation, palladium catalysis, heterogeneous catalysis, hydrogen peroxide, styrenes, ketones

Since the groundbreaking research of Smidt et al. in the 1950s, Pd(II) has been widely applied as catalyst for the oxidization of olefins to give methyl ketones, useful for the manufacture of fine chemicals, agrochemicals, and organic intermediates.<sup>1</sup> In particular, the Tsuji-Wacker oxidation is a well-known method for the efficient oxidation of more complex substrates that generally employs PdCl<sub>2</sub>, CuCl, and O<sub>2</sub> in a DMF-H<sub>2</sub>O solvent system (Figure 1, A).<sup>2</sup> However, there are still many problems with this method, including difficulties in catalyst recovery, the formation of chlorinated byproducts, and the dimerization of double bonds. Most importantly, contamination by copper ions during this process has been recognized as a considerable limitation of the reaction. To replace the copper co-catalyst, some researchers have used new catalysts, such as palladium complexes,<sup>3</sup> or new solvents, such as ionic liquids<sup>4</sup> or ethylene carbonate.<sup>5</sup> Also, several new oxidation systems, such as iron(III) sulfate,<sup>6</sup> nitrous oxide,<sup>7</sup> 1,4-benzoquinone,<sup>8</sup>  $CrO_3$ ,<sup>9</sup> Sc(OTf)<sub>3</sub>,<sup>10</sup> hypervalent iodine,<sup>11</sup> or ambient-pressure oxygen,<sup>12</sup> have been reported. Undoubtedly, many of these modifications are important contributions and offer copper-free Wacker-type oxidations, but there is still a need to explore simple, cost-effective, and environmentally friendly options.

In terms of green chemistry, hydrogen peroxide has gained importance as an oxidant in many reactions.<sup>13</sup> A low concentration of aqueous hydrogen peroxide is an ideal oxidant for the Wacker oxidation, because it is flexible, cheap, and safe.<sup>4,14</sup> In 1980, Roussel and Mimoun developed a new oxidation system consisting of  $H_2O_2$  with palladium acetate (Figure 1, B).<sup>15</sup> A limitation of this method is that it is not effective for styrene derivatives. More recently, Cao and coworkers used 1 mol% of a Pd(II) catalyst prepared from a 2-(2-pyridyl)benzoxazole ligand and AgOTf to realize the transformation of styrene derivatives into ketones (Figure 1, C).<sup>16</sup> Therefore, with these challenges, it is of great interest



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to discover a convenient catalytic coupling with hydrogen peroxide as the oxidant to form a reactive intermediate that will efficiently execute the Wacker oxidation of styrenes.

In 2013, a new route was developed by Kulkarni and coworkers, who employed Pd<sup>0</sup>/C and KBrO<sub>3</sub> to realize the Wacker oxidation of styrenes (Figure 1, D).<sup>17</sup> By using this heterogeneous recyclable catalyst, the Wacker oxidation becomes simple and inexpensive to perform. Inspired by Kulkarni's work, we recently explored a new copper-free method using Pd<sup>0</sup>/C, with H<sub>2</sub>O<sub>2</sub> as a green oxidant.

Styrene derivatives were used as model compounds, because they are valuable but challenging substrates.<sup>4,18</sup> In our initial experiment, styrene was treated with 5 wt% Pd<sup>0</sup>/C (5 mol%) and 30 wt%  $H_2O_2$  (6 equiv) in the presence of 70 wt%  $H_2SO_4$  (0.4 equiv) as co-catalyst in MeCN (5 mL) at room temperature to give a 71% yield of acetophenone (Table 1, entry 1). Raising the temperature to 45 or 65 °C improved the yield of acetophenone, whereas a higher temperature led to a reduction in the yield as a result of the decomposition of the hydrogen peroxide (entries 2–4). A temperature of 65 °C was selected in subsequent experiments as being more conducive to the synthesis of the corresponding ketones.

Table 1	l Optimizatio	on of the Rea	action Conc	litions <sup>a</sup>			
$\begin{array}{c} \begin{array}{c} \begin{array}{c} Pd \text{ catalyst} \\ \hline \\ H_2O_2, \text{ acid, solvent} \end{array} \end{array} \begin{array}{c} \begin{array}{c} O \\ \hline \\ \end{array}$							
Entry	Catalyst	H <sub>2</sub> SO <sub>4</sub> (equiv)	H <sub>2</sub> O <sub>2</sub> (equiv)	Temp (°C)	Time (h)	Yield <sup>ь</sup> (%)	
1	Pdº/C	0.4	6	r.t.	24	71	
2	Pdº/C	0.4	6	45	12	94	
3	Pdº/C	0.4	6	65	8	90	
4	Pdº/C	0.4	6	75	8	63 <sup>c</sup>	
5	Pdº/C	0.2	6	65	8	93	
6	Pdº/C	0.05	6	65	8	76	
7	Pdº/C	-	6	65	8	trace	
8	Pdº/C	0.2	12	65	8	92	
9	Pdº/C	0.2	3	65	8	83	
10	Pdº/C	$\operatorname{acid}^{\operatorname{d}}$	6	65	8	<57	
11 <sup>e</sup>	Pdº/C	0.2	6	65	8	<42	
12	PdCl <sub>2</sub>	0.2	6	65	8	68	
13	$Pd(OAc)_2$	0.2	6	65	8	73	

 $^a$  Reaction conditions: styrene (1 mmol), catalyst (5 mol%),  $H_2O_2$  (30 wt%), acid (70 wt%), MeCN (5 mL).

<sup>b</sup> Determined by GC with an external standard.

<sup>c</sup> 24% of benzaldehyde was obtained.

 $^{\rm d}$  With HCl, HNO<sub>3</sub>,  $\dot{\rm H}_3 PO_4$ , HCO<sub>2</sub>H, AcOH, or oxalic acid as the acid (70 wt%, 0.2 equiv).

 $^{\rm e}$  With EtOH, MeOH, EtOAc, THF, 1,4-dioxane, or ethylene carbonate as the solvent (5 mL).

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On further optimizing and reducing the amount of H<sub>2</sub>SO<sub>4</sub> to 0.2 mmol, the yield of acetophenone reached 93% (Table 1, entry 5). In the absence of sulfuric acid, only trace amounts of the product were obtained (entry 7). The use of six equivalents of hydrogen peroxide resulted in the best yield of 93% (entry 5); increasing the amount of hydrogen peroxide to 12 equivalents had little effect on the reaction (entry 8), whereas decreasing the amount of hydrogen peroxide to three equivalents gave a lower yield of acetophenone (entry 9). Although Kolb et al.<sup>19a</sup> and Horowitz<sup>19b</sup> have demonstrated that inorganic acids can enhance the rate of olefin oxidation, we found that other acids, such as hydrochloric acid, nitric acid, phosphoric acid, formic acid, acetic acid, or oxalic acid, gave lower yields of the product (entry 10). Moreover, screening showed that other solvents also gave inferior results (entry 11), which implies that acetonitrile has as an important role in this reaction. To examine the effects of replacing Pd<sup>0</sup>/C with other palladium catalysts, we tested palladium(II) chloride (entry 12) and palladium(II) acetate (entry 13); neither of these catalysts showed a better catalytic effect than Pd<sup>0</sup>/C, possibly because of the larger surface area of Pd<sup>0</sup>/C. In summary, the optimal conditions for the reaction are Pd<sup>0</sup>/C (5 mol%), sulfuric acid (0.2 equiv), and hydrogen peroxide (6 equiv) in acetonitrile (5 mL) at 65 °C.

Following the optimization study, we selected various substrates for further research (Table 2). To our delight, the substrates tested gave good to excellent yields of the corresponding ketones, and no epoxide was detected in any case. The presence of a substituent in the 2-position reduced the yield (Table 2, entry 3). Styrenes with electron-donating substituents in the *para*-position were easily transformed into the corresponding methyl ketones. Electron-withdrawing substituents led to lower yields, but a fluoro substituent had a different effect than other electron-withdrawing substituents (entries 4–13).

We then used hex-1-ene as a substrate to explore the oxidation of aliphatic olefins under the optimized conditions (Table 2, entry 14). Unsurprisingly, hex-1-ene was also oxidized to the corresponding methyl ketone in good yield and with complete Markovnikov selectivity. Similarly, the conditions were applied to *trans*-stilbene, and gave the corresponding ketone in 65% yield (entry 15). To further explore the gram-scale application of this selective oxidation method, the reaction of styrene on a 9.6 mmol scale was examined. In this experiment, the desired product was separated in an excellent yield of 90% (entry 16).

At the end of reaction, the Pd<sup>0</sup>/C was readily separated from the mixtures by using a centrifuge and thoroughly washed with acetonitrile for reuse in a subsequent run under the same conditions. After the Pd<sup>0</sup>/C had been reused five times, its catalytic activity showed a slow decrease (Table 3, entries 1–5).We then conducted a filtration test, and the result confirmed that traces of Pd species had leached

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 Table 2
 Substrate Scope of the Wacker Oxidation Reaction<sup>a</sup>

→ P <sup>2</sup>	Pd <sup>0</sup> /C (5 wt%, 0.05 mmol) H <sub>2</sub> SO <sub>4</sub> (70 wt%, 0.2 mmol)	о Д <sub>В<sup>2</sup></sub>
R <sup>1</sup>	H <sub>2</sub> O <sub>2</sub> (30 wt%, 6 mmol) MeCN (5 mL)	R <sup>1</sup>
	$R^1$ = aryl or alkyl, $R^2$ = H or phe	nyl

Entry	R <sup>1</sup>	R <sup>1</sup>	Time (h)	Yield <sup>b</sup> (%)
1	4-CIC <sub>6</sub> H <sub>4</sub>	Н	12	82
2	3-CIC <sub>6</sub> H <sub>4</sub>	Н	12	73
3°	$2-CIC_6H_4$	Н	12	62
4	$4-BrC_6H_4$	Н	12	69
5	$4-FC_6H_4$	Н	8	90
6	$4-MeC_6H_4$	Н	8	95
7	4-MeOC <sub>6</sub> H <sub>4</sub>	Н	8	89
8	4-CICH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Н	8	80
9	4-t-BuC <sub>6</sub> H <sub>4</sub>	Н	8	88
10 <sup>c</sup>	$4-O_2NC_6H_4$	Н	12	63
11	$4-EtC_6H_4$	Н	8	86
12	4-i-PrC <sub>6</sub> H <sub>4</sub>	Н	8	85
13	2,4-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	Н	8	82
14	n-Bu	Н	8	71
15 <sup>c</sup>	Ph	Ph	12	65
16 <sup>d</sup>	Ph	Н	8	90

 $^a$  Reaction conditions: olefin (1 mmol), 5 wt% Pd^0/C (0.05 mmol), 30 wt%  $H_2O_2$  (6 mmol), 70 wt%  $H_2SO_4$  (0.2 mmol), MeCN (5 mL), 65 °C.  $^b$  Isolated yield.

° 75 °C.

 $^{\rm d}$  Styrene (9.6 mmol, 1.0 g), 5 wt% Pd<sup>0</sup>/C (5 mol%), 30 wt% H<sub>2</sub>O<sub>2</sub> (6 equiv), 70 wt% H<sub>2</sub>SO<sub>4</sub> (0.2 equiv), MeCN (48 mL), 65 °C.

from the catalyst (Table 3, entry 6). This process presents a better recyclability of the catalyst which conforms to the green chemistry principles.

Table 3	<b>3</b> Reusability of the Catalyst in the Reaction <sup>a</sup>						
	Pd <sup>0</sup> /C (5 wt% H <sub>2</sub> SO <sub>4</sub> (70 wt <sup>2</sup> ) H <sub>2</sub> O <sub>2</sub> (30 wt <sup>2</sup> ) MeCN	0.05 mmol) %, 0.2 mmol) %, 6 mmol) (5 mL)					
Entry	Time (h)	Yield <sup>b</sup> (%)					
1	8	91					
2	8	86					
3	8	85					
4	12	83					
5	12	78					
6 <sup>c</sup>	8	31					

 $^a$  Reaction conditions: styrene (1 mmol), Pd^/C (5 wt%, 0.05 mmol), H\_2O\_2 (30 wt%, 6 mmol), H\_2SO\_4 (70 wt%, 0.2 mmol), MeCN (5 mL), 65  $^\circ$ C.

<sup>b</sup> Calculated by GC with an external standard.

<sup>c</sup> The Pd<sup>0</sup>/C catalyst was filtered off after 2 h.



On the basis of earlier reports,<sup>4b,15,20</sup> we propose a plausible catalytic mechanism for the Pd<sup>0</sup>/C catalyzed transformation of olefins with  $H_2O_2$  as the oxidant (Scheme 1). Palladium hydroperoxide species are probably formed by the addition of  $H_2SO_4$  and  $H_2O_2$  (Scheme 1, step 1). These species transfer oxygen to the olefin through a pseudocyclic hydroperoxypalladation process of the coordinated olefin, eventually giving the corresponding ketone and hydroxypalladium species (steps 2 and 3). In the presence of a large excess  $H_2O_2$ , this hydroxypalladium species is converted back into the palladium hydroperoxidic species, completing the catalytic cycle (step 4). On the other hand, in the presence of a low amount of  $H_2O_2$ , the hydroxypalladium species might effect hydroxypalladation of the olefin, eventually affording the ketone and Pd<sup>0</sup> (step 5).



Scheme 1 Plausible mechanism for the reaction

In conclusion, we have successfully developed a green, economical, and efficient catalyst system for the Wacker oxidation of styrene derivatives.<sup>21</sup> The palladium catalyst could be easily recovered by using a centrifuge and reused at least five times without great loss of activity. We believe that Pd<sup>0</sup>/C, as a recyclable catalyst, has considerable potential in Wacker oxidations with hydrogen peroxide as a green oxidant. Finally, the newly developed system smoothly transforms styrene derivatives and several other olefins into the corresponding ketones in high yields, which might provide a practical method for the synthesis of ketones. Efforts to expand the scope of the reaction are ongoing, and will be reported in due course.

## **Supporting Information**

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588656.

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- (21) Wacker Oxidation of Olefins; General Procedure
  - 5 wt% Pd<sup>0</sup>/C (0.05 mmol) and 70 wt% H<sub>2</sub>SO<sub>4</sub> (0.2 mmol) were added to a solution of the appropriate styrene (1 mmol) in MeCN (5 mL), and the mixture was stirred for about 15 min at r.t. Then, 30 wt% H<sub>2</sub>O<sub>2</sub> (6 mmol) was added dropwise, and the mixture was heated at 65 °C until the reaction was complete (TLC). The Pd<sup>0</sup>/C was removed by centrifugation and the remaining mixture was partitioned between H<sub>2</sub>O and EtOAc. The layers were separated, and the organic layer was washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography.

#### Acetophenone (Table 2, Entry 16)

Light-yellow liquid; yield: 1.03 g (90%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.96 (d, *J* = 7.1 Hz, 2 H), 7.57 (t, *J* = 7.3 Hz, 1 H), 7.47 (t, *J* = 7.4 Hz, 2 H), 2.61 (s, 3 H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  = 198.1, 136.9, 133.0, 128.4, 128.2, 26.5.