

## Direct hydroxylation of substituted benzenes to phenols with air and CO using molybdovanadophosphates as a key catalyst

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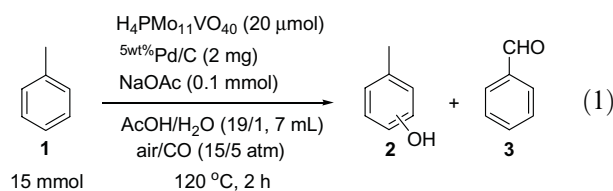
**Abstract**—A direct synthetic method of cresols from toluene by hydroxylation with air using CO as a reducing agent was developed. The reaction of toluene with air (15 atm) and CO (5 atm) in the presence of catalytic amounts of  $\text{H}_4\text{PMo}_{11}\text{VO}_{40}\cdot 31\text{H}_2\text{O}$  and Pd/C in aqueous acetic acid at 120 °C for 2 h afforded a mixture of *o*-, *m*-, and *p*-cresols in 9.9% yield at 83% selectivity. Cresols were obtained in 19% yield by recharging air and CO under these conditions. A variety of substituted benzenes were hydroxylated by this method to give the corresponding phenol derivatives in higher selectivity.

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Cresols, which are used as basic raw materials for the synthesis of herbicides and insecticides, are manufactured by several methods to a large extent in the chemical industry worldwide.<sup>1</sup> The synthetic methods employed differ from each other in respect to the three isomer cresols. For instance, *m*- and *p*-cresols are produced in analogy to the Hock process from *m*- and *p*-isopropyltoluenes, respectively.<sup>2</sup> On the other hand, *o*-cresol is produced by methylation of phenol with methanol in the gas or liquid phase, although the reaction is accompanied by the formation of xylenols whose amounts are considerably dependent on the reaction conditions.<sup>2</sup> Although there have been several attempts for the direct synthesis of cresols from toluene by treating with  $\text{N}_2\text{O}^3$  or  $\text{H}_2\text{O}_2$ ,<sup>4</sup> a limited number of methods have appeared for the hydroxylation of toluene using molecular oxygen.<sup>5</sup> Recently, Burton and Kozhevnikov reported that the oxidation of benzene or toluene with oxygen (5–10 atm) by  $\text{Pd}(\text{OAc})_2\text{-H}_5\text{PMo}_{10}\text{V}_2\text{O}_{40}$  system leads mainly to oxidative coupling (biphenyl and terphenyl or bitolyl) and ring hydroxylation (phenol or cresol).<sup>6</sup> In a previous paper, we have shown the hydroxylation of benzene to phenol with air and CO using molybdovanadophosphoric acids ( $\text{H}_{3+n}\text{PMo}_{12-n}\text{V}_n\text{O}_{40}\cdot x\text{H}_2\text{O}$ ;  $n = 1\text{--}4$ ) without any co-catalysts.<sup>7</sup> This

strategy was found to be extended to the cresol synthesis from toluene by adding a very small amount of Pd/C to  $\text{H}_{3+n}\text{PMo}_{12-n}\text{V}_n\text{O}_{40}\cdot x\text{H}_2\text{O}$  ( $n = 1\text{--}4$ ) catalysts. In this letter, we would like to report the direct synthesis of cresols from toluene with air using CO as a reducing agent under the influence of  $\text{H}_4\text{PMo}_{11}\text{VO}_{40}\cdot 31\text{H}_2\text{O}$  ( $\text{HPMo}_{11}\text{V}$ )<sup>8</sup> and a very small amount of Pd/C.

Previously, we found that the Heck-type coupling of toluene with acrylates by  $\text{Pd}(\text{OAc})_2$  using  $\text{O}_2$  and  $\text{H}_{3+n}\text{PMo}_{12-n}\text{V}_n\text{O}_{40}\cdot x\text{H}_2\text{O}$  as a reoxidation system of the resulting Pd(0) affords a small amount of cresols as by-products.<sup>9</sup> Thus, we examined direct hydroxylation of toluene (**1**) into cresol (**2**) with  $\text{O}_2$  under various conditions and found an efficient catalytic system consisting of  $\text{HPMo}_{11}\text{V}$  and Pd/C for conversion of **1** into **2** (Eq. 1).



**Keywords:** Hydroxylation; Benzene; Phenol; Heteropoly acid.

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**Table 1.** Hydroxylation of **1** to **2** by HPMo<sub>11</sub>V combined with Pd/C under various conditions<sup>a</sup>

Run	Temperature (°C)	Conv. (%)	Yield (%) <sup>b</sup>	
			<b>2</b>	<b>3</b>
1	120	12	9.9 (53:18:29) [83]	1.3
2 <sup>c</sup>	120	3.6	1.5 (50:19:31) [42]	1.5
3 <sup>d</sup>	120		No reaction	
4 <sup>e</sup>	120	2.3	1.6 [70]	
5 <sup>f</sup>	120	11	6.2 (57:7:36) [56]	1.5
6 <sup>g</sup>	120	13	9.4 (54:20:26) [72]	1.1
7 <sup>h</sup>	120	11	8.8 (52:18:30) [80]	1.3
8 <sup>i</sup>	120		No reaction	
9 <sup>j</sup>	120		No reaction	
10	130	13	9.7 (53:19:28) [75]	1.2
11	150	15	9.8 (54:20:26) [65]	1.3
12	100	10	8.8 (51:21:28) [88]	1.1

<sup>a</sup> **1** (15 mmol) was reacted in the presence of H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub>·31H<sub>2</sub>O (20 μmol), 5% Pd/C (2 mg), and AcONa (0.1 mmol) under air (15 atm) and CO (5 atm) in AcOH/H<sub>2</sub>O (19/1, 7 mL) at 120 °C for 2 h.

<sup>b</sup> Numbers in parenthesis and blanket show the ratio of *o*-, *m*-, *p*-cresol and the selectivity of **1** to **2**, respectively.

<sup>c</sup> In the absence of Pd/C.

<sup>d</sup> In the absence of H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub>·31H<sub>2</sub>O.

<sup>e</sup> In the absence of H<sub>2</sub>O.

<sup>f</sup> In the absence of AcONa.

<sup>g</sup> Air/CO (15/7 atm).

<sup>h</sup> Air/CO (15/1 atm).

<sup>i</sup> In the absence of CO.

<sup>j</sup> H<sub>2</sub> (5 atm) was placed instead of CO.

In order to confirm optimal reaction conditions, **1** was reacted under various reaction conditions and representative results are shown in Table 1. The reaction of **1** under air (15 atm) and CO (5 atm) by HPMo<sub>11</sub>V in the presence of a very small amount of 5% Pd/C in a mixed solvent (7 mL) of acetic acid and water (19:1) at 120 °C for 2 h afforded **2** (*o*-**2**:*m*-**2**:*p*-**2** = 53:18:29) in 9.9% yield at higher selectivity (83% selectivity) and a small amount of benzaldehyde (**3**) (1.3%) at 12% conversion of **1** (run 1). The reaction indicated the *ortho* and *para* orientation and the ratio of *o*-**2** to *p*-**2** was roughly 2, which is statistically satisfactory. The result seems to be the first successful direct synthesis of **2** from **1** with air and CO, which can be applied to industrial chemistry. The reaction of **1** by HPMo<sub>11</sub>V alone led to **2** in low yield, but no reaction was induced by Pd/C in the absence of HPMo<sub>11</sub>V (runs 2 and 3). It was found that water is an essential component to activate the HPMo<sub>11</sub>V catalyst, since the reaction was markedly retarded in anhydrous acetic acid (run 4). The reaction in the absence of NaOAc resulted in a decrease of the selectivity of **1** to **2** (56%) (run 5). The reaction was influenced by the partial pressure of air and CO. For instance, under air (15 atm) and CO (7 atm), the selectivity of **2** was slightly lowered than that of CO (5 atm) (run 6). Under low CO pressure (1 atm), the yield of **2** was slightly decreased (run 7). However, when CO was removed from the reaction system, no reaction was induced at all (run 8). No reaction took place when H<sub>2</sub> was used in place of CO as the reducing agent (run 9). The reaction at 100, 130, and 150 °C was not considerably different from that at 120 °C (runs 10–12).

**Table 2.** Hydroxylation of **1** to **2** by various heteropoly acids combined with 5 wt % Pd/C<sup>a</sup>

Run	Catalyst	Conv. of <b>1</b> (%)	Yield (%)	
			<b>2</b>	<b>3</b>
1	H <sub>4</sub> PMo <sub>11</sub> VO <sub>40</sub> ·31H <sub>2</sub> O	12	9.9 (53:18:29) [83]	1.3
2	H <sub>3</sub> PMo <sub>10</sub> V <sub>2</sub> O <sub>40</sub> ·25H <sub>2</sub> O	8.6	6.9 (49:22:29) [42]	1.4
3	H <sub>6</sub> PMo <sub>9</sub> V <sub>3</sub> O <sub>40</sub> ·20H <sub>2</sub> O	9.9	7.1 (52:20:28) [72]	1.0
4	H <sub>7</sub> PMo <sub>8</sub> V <sub>4</sub> O <sub>40</sub> ·25H <sub>2</sub> O	7.3	6.2 (53:19:28) [85]	0.9
5	H <sub>3</sub> PMo <sub>12</sub> O <sub>40</sub> ·23H <sub>2</sub> O		No Reaction	
6	H <sub>5</sub> PW <sub>10</sub> V <sub>2</sub> O <sub>40</sub> ·21H <sub>2</sub> O	4.0	3.2 (53:19:28) [80]	0.6
7	VO(acac) <sub>2</sub>	0.4	0.2 (38:23:38) [50]	0.1
8	NaVO <sub>3</sub>	0.9	0.6 (51:20:29) [67]	0.3

<sup>a</sup> The reaction was run under the same conditions as Run 1 in Table 1.

Table 2 shows the hydroxylation of **1** under air/CO (15/5 atm) catalyzed by several heteropoly acids or vanadium compounds combined with 5% Pd/C under the same conditions as run 1 in Table 1.

The hydroxylation of **1** to **2** was found to be also promoted by H<sub>3+n</sub>PMo<sub>12-n</sub>V<sub>n</sub>O<sub>40</sub>·xH<sub>2</sub>O (*n* = 2–4)<sup>8</sup> to give a mixture of *o*-, *m*-, and *p*-**2** in the yields of 6.2–9.9%, but H<sub>3</sub>PMo<sub>12</sub>O<sub>40</sub>·23H<sub>2</sub>O lacking the vanadium atom did not catalyze the hydroxylation of **1** at all. The catalytic activity of H<sub>5</sub>PW<sub>10</sub>V<sub>2</sub>O<sub>40</sub>·21H<sub>2</sub>O was low compared with that of the corresponding molybdenum compound, H<sub>5</sub>PMo<sub>10</sub>V<sub>2</sub>O<sub>40</sub>·25H<sub>2</sub>O. Almost no reaction was induced by simple vanadium compounds like VO(acac)<sub>2</sub> and NaVO<sub>3</sub>. On the basis of these results, the real active vanadium species promoting the hydroxylation of **1** is thought to be a certain vanadium species in molybdovanodophosphoric acids.

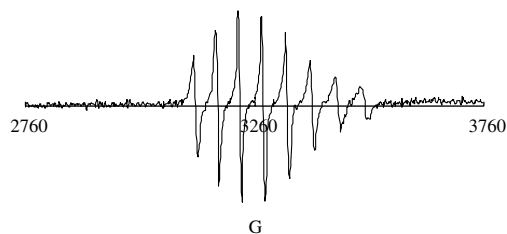
To obtain information on the role of a Pd species in the present hydroxylation, it may be interesting to compare the reaction of CO with air by HPMo<sub>11</sub>V in the presence of Pd/C with that in the absence of Pd/C under the same conditions as the hydroxylation (Table 3).

The oxidation of CO with air was most smoothly promoted by HPMo<sub>11</sub>V combined with Pd/C to form 5 mmol of CO<sub>2</sub>, while the reaction afforded only 1.6 mmol of CO<sub>2</sub> by HPMo<sub>11</sub>V (runs 1 and 2). Similarly, the formation of CO<sub>2</sub> by Pd/C alone was also low (run 3). It is difficult to ascertain the role of the Pd/C in the present reaction at the present stage. However, it does not seem that the Pd/C promotes directly the present reaction as the key catalyst, since the hydroxylation **1** to **2** was induced to some extent by HPMo<sub>11</sub>V alone but not by Pd/C as shown in runs 2 and 3 in Table 1. In addition, we showed that the hydroxylation of benzene to phenol was efficiently catalyzed by molybdova-

**Table 3.** Generation of CO<sub>2</sub> from CO and air by several conditions<sup>a</sup>

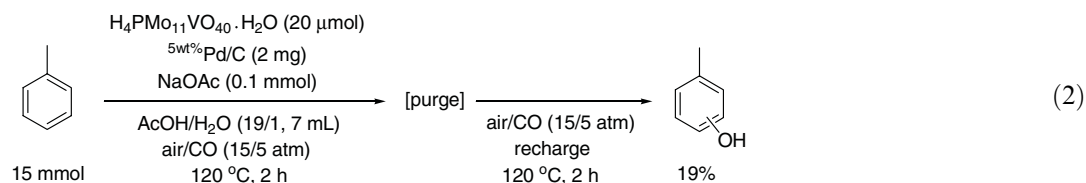
Run	Catalyst	CO <sub>2</sub> (mmol)
1	HPMo <sub>11</sub> V–Pd/C	5.0
2	HPMo <sub>11</sub> V	1.6
3	Pd/C	2.0

<sup>a</sup> The reaction was run without **1** under the same conditions as run 1 in Table 1.



**Figure 1.** ESR spectrum of  $\text{HPMo}_{11}\text{V}$  upon treatment with air/CO (15/5 atm) in aq acetic acid at 90 °C.

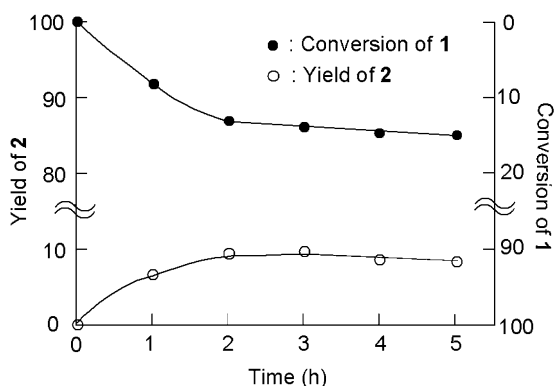
nadophosphoric acids alone under similar conditions.<sup>7</sup> The Pd/C seems to assist the reduction of  $\text{HPMo}_{11}\text{V}$  with CO generating  $\text{V}^{4+}$ , which is considered as the real active species for the hydroxylation of **1** to **2**. Indeed, the hydroxylation of **1** was not promoted by  $\text{HPMo}_{11}\text{V}$  even



in the presence of Pd/C by the use of  $\text{H}_2$  in place of CO as a reducing agent, since hydrogen is not suited for the generation of  $\text{V}^{4+}$  by the reduction of  $\text{HPMo}_{11}\text{V}$  under these conditions. In fact, a hyperfine structure based on  $\text{V}^{4+}$  ( $g = 1.944$ )<sup>10</sup> was clearly observed upon treatment of  $\text{HPMo}_{11}\text{V}$  with air/CO (15 atm/5 atm) in acetic acid containing water at 90 °C (Fig. 1), but only a very weak signal of  $\text{V}^{4+}$  was observed by treating it by air/ $\text{H}_2$  (15 atm/5 atm).

These results may indicate that the real active species, which promotes the hydroxylation of **1** is  $\text{V}^{4+}$  ions in molybdovanadophosphoric acids rather than a Pd species.

Figure 2 shows the time-dependence curves for the reaction of **1** to **2** under the same conditions as run 1 in Table 1.



**Figure 2.** Time-dependence curves for the reaction of **1** to **2**.

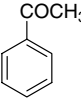
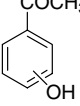
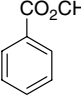
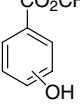
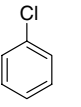
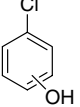
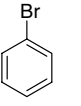
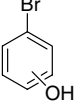

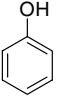
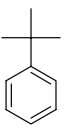
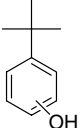
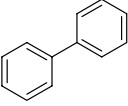
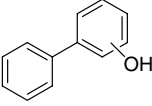
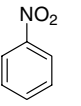
It was found that the reaction of **1** terminated in about 2 h. In order to know the reason for the termination at the early stage of the reaction, after the reaction for 2 h the mixed gases were once purged from an autoclave, and air (15 atm) and CO (5 atm) were recharged. Then the reaction was carried out for an additional 2 h under the same conditions as the first run. The hydroxylation of **1** was smoothly restarted to give **2** in a yield of 19%, which corresponds to about 2 times that of the first run (Eq. 2). This indicates that both catalysts,  $\text{HPMo}_{11}\text{V}$  and Pd/C, were not deactivated, but the ratio of air to CO, which was first charged may be deviated from that suited for the hydroxylation of **1** by evolving  $\text{CO}_2$  with the progress of the hydroxylation. Unfortunately, it was difficult to improve the yield of **2** by further recharge of air and CO. Further studies are now in progress.

On the basis of these results, the hydroxylation of a variety of substituted benzenes was examined by recharging air (15 atm) and CO (5 atm) under the same conditions as Eq. 2. These results are summarized in Table 4. The hydroxylation of the various substituted benzenes was successfully achieved to give the corresponding phenols in higher selectivity (Table 4).

Acetophenone and methyl benzoate were also hydroxylated under these conditions to give the corresponding phenol derivatives in higher selectivity (runs 1 and 2). It is interesting to note that the hydroxylation of chlorobenzene indicates highly *ortho* and *para* orientation to afford *o*- and *p*-chlorophenol in a ratio of 45:55 in 88% selectivity at 25% conversion (run 3). In the hydroxylation of bromobenzene, almost the same results were obtained as that of chlorobenzene except for the formation of a small amount of *meta* isomer (run 4). The hydroxylation of benzene by this method afforded phenol in 24% yield at 32% conversion (run 5). For *tert*-butylbenzene, *p*-*tert*-butylphenol was obtained in preference to *o*-*tert*-butylphenol in contrast to the hydroxylation of **1**, which leads mainly to *ortho* isomer, catechol, than *para* isomer, hydroquinone (run 6). Biphenyl was also hydroxylated to form the corresponding *o*- and *p*-phenylphenol as major products (run 7). However, nitrobenzene was difficult to be hydroxylated by this method (run 8).

In conclusion, we have successfully achieved the direct hydroxylation of benzenes to phenols with air and CO, which can be extended to large scale synthesis as an efficient alternative method.

**Table 4.** Hydroxylation of various substituted benzenes<sup>a</sup>

Run	Substrate	Conv. (%)	Product	Yield (%) (o:m:p)
1		36		27 [75] (49:31:20)
2		34		29 [85] (40:37:23)
3		25		22 [88] (45:0:55)
4		24		21 [88] (43:3:54)
5		32		24 [75]
6		33		23 [70] (25:0:75)
7		38		29 [76] (44:8:48)
8			No reaction	

<sup>a</sup> The reaction was run under the same conditions as that in Eq. 2.

**Experimental. General procedure for the oxidation of toluene (1):** The reaction was carried out using a Teflon autoclave. To a solution of H<sub>4</sub>PMo<sub>11</sub>VO<sub>40</sub>·31H<sub>2</sub>O (20 μmol), 5% Pd/C (2 mg), and AcONa (0.1 mmol) in AcOH (9 mL) and water (1 mL) was added **1** (15 mmol). Then, air (15 atm) and CO (5 atm) were charged and the mixture was reacted under stirring at 120 °C for 2 h.

After the reaction, the GC and GC–MS analyses were performed. The conversions and yields of products were estimated from the peak areas based on the internal standard technique using GC.

Reaction by recharged procedure of air and CO: After the reaction for 2 h, the residual gases were purged and air (15 atm) and CO (5 atm) were recharged and reacted under the same conditions for an additional 2 h.

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