January, 1993] © *1993 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, ***66***, *251—257(1993)* 251

The Oxidation of 2,4,6-Trimethylphenol with Molecular Oxygen Catalyzed by a Copper(II)-Oxime or Copper(II)-Amine System[1)]

Masao Shimizu,* Yoshihito Watanabe, Hideo Orita, Takashi Hayakawa, and Katsuomi Takehira*
National Chemical Laboratory for Industry, Tsukuba Research Center, Tsukuba, Ibaraki 305

(Received July 23, 1992)

2,4,6-Trimethylphenol (**1a**) was selectively oxidized to 3,5-dimethyl-4-hydroxybenzaldehyde (**2a**) by molecular oxygen in the presence of a copper(II) chloride-oxime or copper(II) chloride-amine catalyst in alcohol at ambient temperature. When an acid was present in the catalyst system, the formation of both 2,6-dimethyl-*p*-benzoquinone (**3**) and a formaldehyde dialkyl acetal was accelerated. It is likely that **2a** is produced by way of the formation of a quinonemethide intermediate, followed by a repeated 1,6-addition of alcohol on the intermediate to form a 4-(alkoxymethyl)-2,6-dimethylphenol (**5a**), and then 3,5-dimethyl-4-hydroxybenzaldehyde dialkyl acetal, which would be hydrolyzed to **2a**. When the reaction time was shortened, **5a** was isolated in good yield. Oxidations of the other *p*-methyl-substituted phenols were also examined using the present oxidation system.

p-Hydroxybenzaldehydes are important intermediates in the industrial synthesis of a wide variety of special chemicals, such as pharmaceutical chemicals, flavor and fragrance chemicals, dyes, polymers, and agrochemicals; several processes for *p*-hydroxybenzaldehyde synthesis have so far been developed.[2)] Although the *p*-hydroxybenzaldehydes can be synthesized by a Reimer-Tiemann reaction of chloroform with phenol,[3)] or a condensation of phenol with formaldehyde[4)] or glyoxylic acid,[5)] a direct conversion of *p*-methyl-substituted phenols to *p*-hydroxybenzaldehydes is attractive and several methods have been proposed:[2)] chlorination followed by hydrolysis, stoichiometric oxidation with inorganic oxidants, electric/electrocatalytic oxidations, and catalytic oxygen transfer with some oxygen donors. The most promising method seems to be catalytic oxidation with molecular oxygen; several attempts have been made to realize it: *p*-cresols are oxidized with molecular oxygen to the corresponding *p*-hydroxybenzaldehydes in the presence of a catalytic amount of cobalt(II) Schiff base complexes[6)] or cobalt(II) chloride.[5)] However, yields of the *p*-hydroxybenzaldehydes in oxidation assisted by Schiff base complexes were low (at most 48%), and a long reaction time and strongly basic conditions were required in oxidation assisted by cobalt(II) chloride. We herein describe a novel and effective oxidation of 2,4,6-trimethylphenol to the corresponding *p*-hydroxybenzaldehyde with molecular oxygen assisted by a copper(II)-amine catalyst.

Results and Discussion

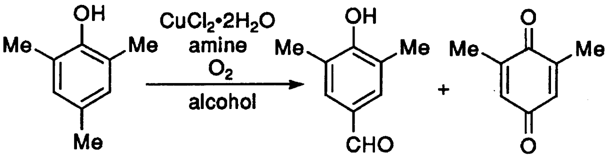
In preceding papers[7)] we reported that the oxidation of 2,3,6-trimethylphenol to trimethyl-*p*-benzoquinone with molecular oxygen was effectively catalyzed by copper(II) chloride coupled with amines, hydroxylamines, or oximes. In this oxidation the other *p*-unsubstituted phenol, such as 2,6-dimethylphenol, was also oxidized to the corresponding *p*-benzoquinone in good yield. We have now applied this system to the oxidation of *p*-substituted phenols, i.e., 2,4,6-trimethylphenol (**1a**).

Effect of the Various Additives. The results of the oxidation of **1a** with molecular oxygen catalyzed by several copper(II)-additive systems are shown in Table 1. A typical oxidation result is illustrated as follows: **1a** (2 mmol) was stirred with copper(II) chloride dihydrate (0.2 mmol) and diethylamine (0.2 mmol) in 1-hexanol (2 ml) at 60°C for 4 h under an oxygen atmosphere (114.7 kPa); 3,5-dimethyl-4-hydroxybenzaldehyde (**2a**) was obtained in 77.7% yield, along with 2,6-dimethyl-*p*-benzoquinone (**3**, 3.7% yield) (Run 3) (Scheme 1). The products were identified by comparing the IR and NMR spectra with those of authentic samples. Copper(II) chloride alone (Run 1) and coupled with lithium chloride (Run 2) showed low activity, and **2a** was obtained in 2.7% and 3.5% yield, respec-

Table 1. Oxidation of **1a** with a $CuCl_2 \cdot 2H_2O$-Additive/O_2 System [a)]

Run No.	Additive	Rate[b)] mmol h^{-1}	Time min	Conv. %	Yield/% 2a	3
1	—	0.144	300	40.0	2.7	2.7
2	LiCl	0.155	300	45.6	3.5	1.8
3	Et_2NH	0.815	240	97.6	77.7	3.7
4	$Et_2NH \cdot HCl$	0.497	300	95.0	44.5	4.2
5	$Me_2C{=}NOH$	2.92	54	98.7	85.6	6.1
6	$Me_2C{=}NOH+HCl$[c)]	1.70	120	93.6	52.1	21.9
7	$NH_2OH \cdot HCl$	3.40	54	94.5	47.9	27.4
8	$NH_2OH \cdot 0.5H_2SO_4$	2.81	54	96.5	61.6	15.9

a) **1a**, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.2 mmol; additive, 0.2 mmol; 1-hexanol, 2 ml; reaction temperature, 60°C; oxygen pressure, 114.7 kPa. b) Maximum rate of oxygen consumption. c) Hydrochloric acid (0.2 mmol, 36% aqueous solution) was added.



1a **2a** **3**

Scheme 1.

tively. The effect of the addition of lithium chloride was not so clear as that observed in the oxidation of 2,3,6-trimethylphenol.[7)] The use of diethylamine alone as an additive (Run 3) resulted in a large increase in activity, while diethylamine hydrochloride (Run 4) caused a substantial decrease in activity. Similarly, the addition of hydrochloric acid into a catalyst system of copper(II) coupled with acetone oxime, which showed a very high activity in this oxidation (Run 5), caused clear decreases in both the selectivity to **2a** and the reaction rate (Run 6). Thus, the presence of acid was not favorable for the selective oxidation of 2,4,6-trimethylphenol (**1a**) to the *p*-hydroxybenzaldehyde (**2a**), but rather accelerated the formation of *p*-benzoquinone (**3**), together with bis(hexyloxy)methane (**4**) (Run 6).

In the oxidation of 2,3,5-trimethylphenol to trimethyl-*p*-benzoquinone with a catalyst system of copper(II) chloride coupled with acetone oxime, the addition of an acid, such as hydrochloric or sulfuric, largely enhanced the activity of the catalyst.[7)] When hydroxylamine hydrochloride or sulfate was used as the additive (Runs 7 and 8) in the present oxidation, although a very high rate of oxygen consumption was observed, the aldehyde **2a** was obtained in lower yield than when an amine or oxime alone was employed as additive. In these cases the presence of an acid also accelerated the formation of **3**. It is thus likely that the acid in the present catalyst system accelerates *p*-benzoquinone formation by way of oxygen incorporation onto the aromatic ring.

Effects of the Ratio of Additives to the Copper(II) Catalyst. The effects of the amount of amines or acetone oxime as additives are shown in Table 2. Secondary amines, such as diethylamine or dipropylamine, were more preferable than tertiary amines, such as triethylamine, for producing **2a**. When diethylamine was employed as an additive (Runs 3, 9, and 10), the oxygen consumption rate increased with an increasing amount of diethylamine added. Interestingly, the yield of **2a** showed a maximum value at an equimolar amount of diethylamine to the catalyst (Run 3); it then rapidly decreased upon a further addition of diethylamine (Run 10). A further increase in the diethylamine vs. copper(II) ratio resulted in no production of **2a**, even though the rate of oxygen consumption still increased. The use of an excess amount of the amine to copper(II) caused the formation of a reddish-brown precipitate in the reaction solution (Run 10), suggesting the occurrence of an oxidative polymerization of the phenol. Similar phenomena, i.e., an unfavorable effect due to an excess amount of the amine to the copper(II), were also observed when other amines, such as dipropylamine and triethylamine, were employed (Runs 11—14).

Table 2. Oxidation of **1a** with a $CuCl_2 \cdot 2H_2O$-Additive/O_2 System [a)]

Run No.	Additive (mmol)	Rate[b)] mmol h^{-1}	Time min	Conv. %	Yield/% 2a	3a
9	$Et_2NH(0.1)$	0.498	300	98.2	71.0	2.1
3	$Et_2NH(0.2)$	0.815	240	97.6	77.7	3.7
10	$Et_2NH(0.3)$	1.92	120	98.2	—	1.4
11	$n\text{-}Pr_2NH(0.2)$	1.03	180	96.4	75.0	5.4
12	$n\text{-}Pr_2NH(0.4)$	3.14	120	100	2.7	—
13	$Et_3N(0.2)$	1.73	212	95.1	42.1	3.7
14	$Et_3N(0.4)$	1.94	180	100	15.7	—
15	$Me_2C{=}NOH(0.2)$	2.92	54	98.7	85.6	6.1
16	$Me_2C{=}NOH(0.4)$	3.75	45	97.5	91.7	5.0
17	$Me_2C{=}NOH(0.6)$	4.46	37	100	89.9	6.5

a) **1a**, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.2 mmol; 1-hexanol, 2 ml; reaction temperature, 60°C; oxygen pressure, 114.7 kPa.
b) Maximum rate of oxygen consumption.

The UV-vis absorption spectra of a copper(II) chloride-diethylamine system in ethanol are shown in Fig. 1. Upon the addition of diethylamine to a solution of copper(II) chloride in ethanol, a clear change was observed in the spectra: An absorption maximum was observed at 290 nm with $CuCl_2 \cdot 2H_2O$ alone, and shifted toward lower wavelengths, i.e., 265, 260, and 250 nm at molar ratios of diethylamine to copper(II) chloride of 0.5, 1.0, and 2.0, respectively. When the molar ratio exceeded a value of 2.0, the absorption maximum still kept a constant wavelength at 250 nm, and a new absorption maximum appeared at 370 nm. A further increase in the molar ratio caused the precipitation of a purple solid material in the solution during the UV-vis absorption measurement. It is likely that the precipitate was $CuCl_2(Et_2NH)_2$, which was also obtained by the addition of an excess amount of diethylamine to the solution of copper(II) chloride in ethanol. When copper(II) chloride dihydrate is dissolved in ethanol, hydrating water molecules can be replaced by ethanol to

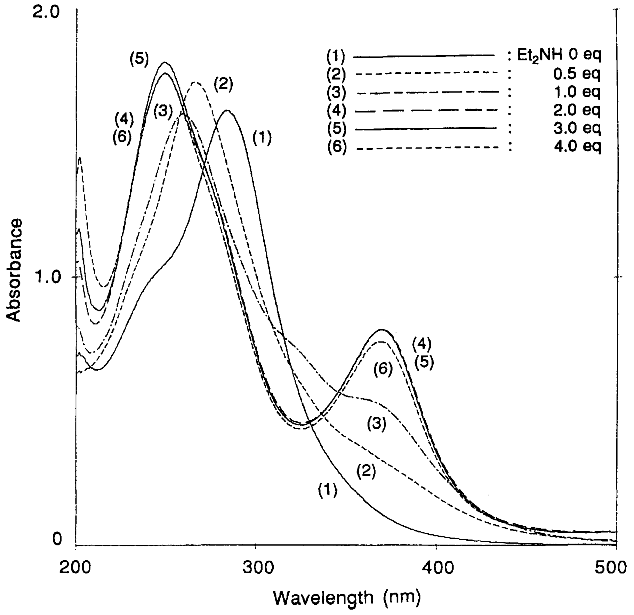


Fig. 1. UV-vis spectra of $CuCl_2 \cdot 2H_2O$-diethylamine in ethanol. $CuCl_2 \cdot 2H_2O$, 0.5 mmol dm^{-3}; 25°C.

give $CuCl_2(EtOH)_2$. The spectral changes mentioned above suggest that a ligand exchange between ethanol and diethylamine on the copper(II) complexes occurs upon the addition of diethylamine, and that the reaction reaches an equilibrium state depending on the amine/copper(II) molar ratio when increasing the molar ratio up to 2.0. Finally, $Cu(II)(Et_2NH)_2Cl_2$ can form at molar ratios above 2.0. In view point of the catalytic activity, however, an active catalyst may require a non-coordinated site as well as amine coordination on the copper(II) complexes. It is therefore likely that $Cu(II)(Et_2NH)(EtOH)Cl_2$ is the active species in the present oxidation of **1a** to **2a**, since ethanol is a weak ligand, and can easily be liberated from the complex to give a non-coordinated site on it.

When the molar ratio of acetone oxime to copper(II) chloride was increased, the rate of oxygen consumption simply increased, and both the high yield and high selectivity of **2a** were still retained, even at high molar ratios above 2.0 (Runs 15—17). The likely acetone oxime works as an additive in a different way from the case of the amines: Acetone oxime can be hydrolyzed into acetone and hydroxylamine; the latter can work as effective additive, as was previously reported regarding the case of 2,3,6-trimethylphenol oxidation.[7] In these oxidations the presence of an acid also caused a great decrease in the yield of **2a**.

Solvent Effect. The oxidations of **2a** were carried out in several kinds of alcohols by using a catalyst system of copper(II) chloride coupled with acetone oxime; the results are shown in Table 3. Primary alcohols as solvent generally afforded both a high oxidation rate and a good yield of **2a**, even though alcohols having a short alkyl chain (methanol and ethanol) gave some exceptional results (Runs 18 and 19). However, secondary and tertiary alcohols showed only a low oxidation rate. These results were perfectly different from those observed in copper(II) chloride catalyzed 2,3,6-trimethylphenol oxidation;[7] rather highly substituted alcohols, such as *t*-butyl alcohol, afforded both a high oxidation rate and a good yield of trimethyl-*p*-benzoquinone, compared to primary alcohols. The facts that methanol and ethanol retarded the oxidation (Runs 18 and 19) might be due to their stronger coordination ability to copper(II) than 1-propanol and 1-butanol (Runs 20 and 21). The difference in the solvent effect observed above, between **1a** to **2a** and 2,3,6-trimethylphenol to trimethyl-*p*-benzoquinone oxidations, clearly suggests that the reaction mechanisms differ from each other in both cases. A high reaction temperature was clearly favorable for **2a** production: An increase of 20°C in the reaction temperature caused an increase in the oxidation rate, greater than two times as high as the original value (Runs 21 and 22, 25 and 26). Similar tendencies were also observed when amines were employed as an additive. The use of acetonitrile as a solvent resulted in the precipitation of a reddish-brown solid material which might be formed by an oxidative polymerization of the phenol.

Reaction Mechanism. The time course of the oxidation of **1a** with molecular oxygen catalyzed by the copper(II) chloride-acetone oxime system in 1-hexanol was followed by analyzing the reaction products (Fig. 2). 2,6-Dimethyl-4-(hexyloxymethyl)phenol (**5aa**) appeared and increased in its amount, reaching a maximum value at the initial stage of the oxidation, then decreased and was finally replaced by **2a** during oxidation. 2,6-Dimethyl-*p*-benzoquinone (**3**) and bis(hexyloxy)methane (**4**) were detected, and increased even in small quantities during the entire reaction time. When isolated **5aa** was treated under the oxidation conditions in 1-hexanol, **2a** was obtained in 53% yield. Most likely, (alkoxymethyl)phenol **5a** is an intermediate in the oxidation of phenol **1** to aldehyde **2** with molecular oxygen

Table 3. Solvent Effect on the Oxidation of **1a** with a $CuCl_2 \cdot 2H_2O$-Acetone Oxime/O_2 System [a)]

Run No.	Solvent	Temp °C	Rate[b)] mmol h^{-1}	Time min	Conv. %	Yield/% 2a	3a
18	MeOH	40	0.102	300	43.6	8.1	—
19	EtOH	40	0.695	300	97.3	55.4	3.1
20	*n*-PrOH	40	0.965	248	100	78.4	4.3
21	*n*-BuOH	40	1.24	195	100	77.2	3.5
22	*n*-BuOH	60	2.60	86	100	81.7	3.3
23	*t*-BuOH	40	0.196	300	40.3	21.9	—
24	*t*-BuOH	60	0.212	300	62.3	42.2	—
25	*n*-$C_6H_{13}OH$	40	0.955	195	97.6	73.0	2.7
26	*n*-$C_6H_{13}OH$	60	1.82	120	100	82.5	2.9
27	*i*-BuOH	60	2.77	86	100	83.0	5.8

a) **1a**, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.1 mmol; $Me_2C{=}NOH$, 0.2 mmol; solvent, 2 ml; oxygen pressure, 114.7 kPa.
b) Maximum rate of oxygen consumption.

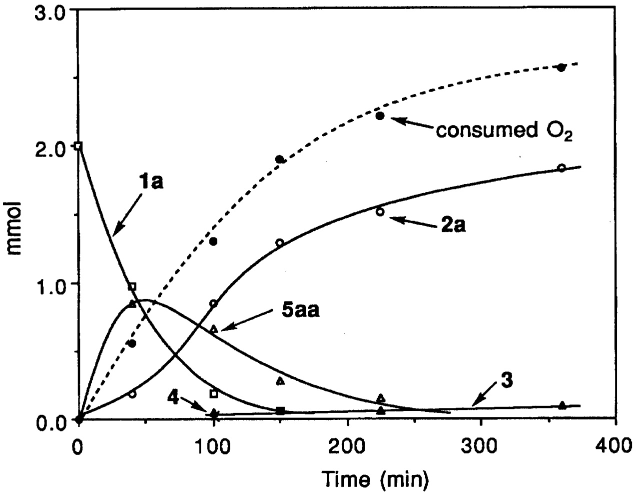


Fig. 2. Time course of **1a** oxidation with a copper(II) chloride-acetone oxime catalyst. **1a**, 2 mmol; $CuCl_2 \cdot 2H_2O$, 0.1 mmol; acetone oxime, 0.2 mmol; 1-hexanol, 2 ml; oxygen pressure, 114.7 kPa; 40°C.

being catalyzed by using the copper(II) chloride-acetone oxime system. When **1a** was oxidized in the presence of an acid, i.e., with the copper(II) chloride-hydroxylamine hydrochloride catalyst in 1-hexanol, **5a** was not produced and the amounts of both **3** and **4** substantially increased along with a decrease in the yield of **2a**.

A plausible mechanism for the oxidation of **1a** is shown in Scheme 2. Phenol **1a** is converted to a phenoxyl radical, which tautomerizes to a 2,5-cyclohexadien-4-one radical **6** by way of a one-electron transfer to copper(II); thus-formed copper(I) ion activates molecular oxygen. The radical species **6** reacts with the activated oxygen species to produce **7**. When an acid is absent in the oxidation system, **7** would be initially converted to a quinonemethide intermediate (**8**), as reported in the literature;[8] **5a** was then formed by a 1,6-addition of alcohol to the quinonemethide intermediate. These steps can be repeated once more upon **5a** to form an acetal (**9**) which would be easily hydrolyzed to **2a**. A small part of **9** is oxidatively decomposed to **3** and **4**. When an acid is present in the oxidation solution, **7** would be protonated to its hydroperoxide, which is then converted to the *p*-benzoquinone **3**. Thus, the presence of an acid is favorable for the *p*-benzoquinone formation in the present **1a** oxidation, as was previously reported concerning the oxidation of 2,3,6-trimethylphenol.[7]

Synthesis of 4-(Alkoxymethyl)phenols. Although there are many synthetic methods of substituted phenols,[9] 4-(alkoxymethyl)-2,6-dimethylphenols have been synthesized by only a few methods.[10] As shown in Fig. 2, the yield of **5aa** reached a maximum value when the amount of oxygen consumed reached almost half the equivalent of the starting phenol. Thus, a synthesis of 4-(alkoxymethyl)phenols was attempted by interrupting the oxidation while monitoring the oxygen consumption. As shown in Table 4, 4-(alkoxymethyl)-2,6-dimethylphenols were synthesized in various alcohols together with a small amount of 3,5-dimethyl-4-hydroxybenzaldehyde **2a**. The oxidation in primary alcohols (Runs 28, 29, 30, 32, 34, and 35) produced **5a** in better yields than those in secondary and tertiary alcohols; secondary and tertiary alcohols afforded a relatively high selectivity to **2a** (Runs 31, 33, 35, and 39). When oxidation was carried out in methanol (Run 28), it took a long reaction time to consume enough oxygen and to complete the oxidation of **1a** to 2,6-dimethyl-4-(methoxymethyl)phenol. The oxidation of **1a** for a long reaction time resulted in a perfect conversion of **5a** to **2a** (Runs 35 and 36). When 2-butanone oxime (Run 37) and diethylamine (Run 38) were employed in 1-hexanol instead of acetone oxime, **5a** were also obtained in relatively low yield. Thus, the synthesis of various 4-(alkoxymethyl)-2,6-dimethylphenols was achieved in good yields starting from **1a**.

Table 4. Oxidation of **1a** with a $CuCl_2\cdot 2H_2O$-Acetone Oxime/O_2 System [a]

Run No.	Alcohol	Time min	Conv. %	Yield/% 5a(Product)	2a
28	Methanol	360	79	64(**5ab**)	4
29	Ethanol	99	73	59(**5ac**)	4
30	1-Propanol	65	76	60(**5ad**)	6
31	2-Propanol	44	74	45(**5ae**)	21
32	1-Butanol	65	73	55(**5af**)	6
33	*t*-Butyl alcohol	420	76	12(**5ag**)	10
34	1-Pentanol	68	89	61(**5ah**)	24
35	1-Hexanol	67	90	63(**5aa**)	14
36	1-Hexanol	360	100	0	87
37	1-Hexanol[b]	42	95	55(**5aa**)	23
38	1-Hexanol[c]	90	89	51(**5aa**)	13
39	Cyclohexanol	300	62	51(**5ai**)	10

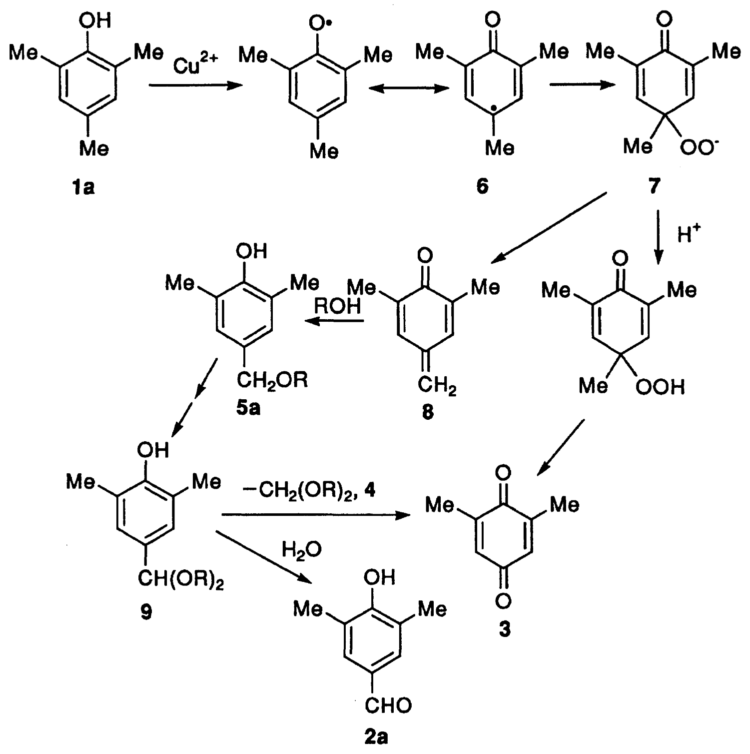
a) **1a**, 2 mmol; $CuCl_2\cdot 2H_2O$, 0.2 mmol; acetone oxime, 0.2 mmol; alcohol, 2 ml; 40°C; oxygen pressure, 114.7 kPa. b) 2-Butanone oxime was used instead of acetone oxime. c) Diethylamine was used instead of acetone oxime.

Oxidations of the other Substituted Phenols. The other 2,4,6-trisubstituted phenols were oxidized with molecular oxygen by using the copper(II) chloride-acetone oxime catalyst in alcohol; the results are shown in Table 5 (Scheme 3). 2-*t*-Butyl-4,6-dimethylphenol (**1b**) was oxidized in ethanol to afford 2-*t*-butyl-4-(ethoxymethyl)-6-methylphenol (**5bc**), along with the corresponding *p*-hydroxybenzaldehyde (**2b**) (Run 40). On the other hand, although 2,6-di-*t*-butyl-4-methylphenol (**1c**) was completely consumed, it afforded neither the 4-(alkoxymethyl)phenol (**5c**) nor the 4-hydroxybenzaldehyde (**2c**) in ethanol (Run 41). When the amount of ethanol was increased to 5 ml, **1c** gave 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (**2c**) in low yield (Run 42). Furthermore, decreasing the amount of catalyst ($CuCl_2\cdot 2H_2O$: 0.01 mmol, acetone oxime: 0.1 mmol) caused the formation of 2,6-di-*t*-butyl-4-(ethoxymethyl)phenol (**5cb**) as the main product in 61% yield (Run 43); the use of 1-hexanol also afforded 2,6-di-*t*-butyl-4-(hexyloxymethyl)phenol (Run 44). However, in the case of 2,4-disubstituted phenols (**1d**, **e**), no 4-(alkoxymethyl)phenols were obtained (Runs 46 and 47): 2-*t*-Butyl-4-methylphenol (**1d**) gave a dimer which is coupled at the ortho position of each phenol ring.[11]

Conclusion. The oxidation of 2,4,6-trimethylphenol with molecular oxygen catalyzed by the copper(II) chloride-acetone oxime system selectively occurred on the *p*-methyl group to yield 3,5-dimethyl-4-hydroxybenzaldehyde in high yield. The aldehyde can be formed by way of a quinonemethide intermediate, followed by the formation of 4-(alkoxymethyl)-2,6-dimethylphenol; the latter can also be isolated in good yield by interrupting the oxidation.

Experimental

The melting points were determined on a Yanagimoto micro-melting apparatus. ^1H NMR spectra were obtained with a Hitachi R-40 High-Resolution NMR Spectrometer (90

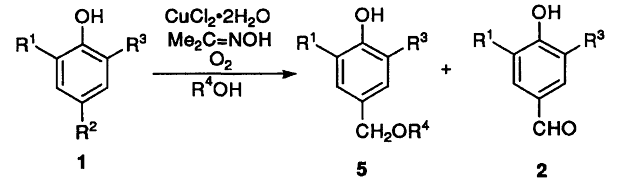


Scheme 2.

Table 5. Oxidation of *p*-Substituted Phenols with a $CuCl_2 \cdot 2H_2O$-Acetone Oxime/O_2 System [a)]

Run No.	Phenol	R^4	$CuCl_2 \cdot 2H_2O$ mmol	$Me_2C{=}NOH$ mmol	Alcohol ml	Time min	Conv. %	Yield/%(Product) 5	2
40	**1b**	Et	0.2	0.2	2	85	83	49(**5bc**)	5(**2b**)
41	**1c**	Et	0.2	0.2	2	30	100	—	—
42	**1c**	Et	0.2	0.2	5	300	98	—	10(**2c**)
43	**1c**	Et	0.01	0.1	5	300	87	61(**5cc**)	5(**2c**)
44	**1c**	Me	0.01	0.1	5	300	45	25(**5cb**)	—
45	**1c**	1-Hexyl	0.01	0.1	5	300	81	19(**5ca**)	5(**2c**)
46	**1d**	Et	0.2	0.2	2	155	62[b)]	—	—
47	**1e**	Et	0.2	0.2	2	160	72	—	—

a) Phenol, 2 mmol; 40°C; oxygen pressure, 114.7 kPa. b) A dimer[11)] was obtained in 13% yield.



1

	R^1	R^2	R^3
b	*t*-Bu	Me	Me
c	*t*-Bu	Me	*t*-Bu
d	*t*-Bu	Me	H
e	Me	Me	H

5

	R^1	R^3	R^4
bc	*t*-Bu	Me	Et
ca	*t*-Bu	*t*-Bu	C_6H_{13}
cb	*t*-Bu	*t*-Bu	Me
cc	*t*-Bu	*t*-Bu	Et

2

	R^1	R^3
b	*t*-Bu	Me
c	*t*-Bu	*t*-Bu

Scheme 3.

MHz) with tetramethylsilane used as an internal standard. IR spectra were recorded on a JASCO FT/IR-7000 Fourier Transfer Infrared Spectrometer. UV-vis spectra were obtained with a Shimadzu UV-265 Spectrophotometer. Gas chromatographic analyses were performed on a Shimadzu GC-R1A gas chromatograph fitted with a Thermon 3000 column.

General Procedure for the Oxidation of Phenols. The oxidations were carried out using a gas-sealed system. A phenol (2 mmol), copper(II) chloride dihydrate (0.2 mmol), and an additive (0.2 mmol) were put into a 10 ml glass reactor equipped with a magnetic stirrer, a gas inlet, and a manometer. A solvent (2 ml) was added to the mixture and the reaction was started with vigorous stirring under an oxygen atmosphere (114.7 kPa) at 60°C. The amount of consumed oxygen was measured by a gas burette. The yields of the products were determined by a GLC method.

Preparation of $CuCl_2(Et_2NH)_2$. To a solution of copper(II) chloride dihydrate (0.5 mmol) in ethanol(5 ml) was added diethylamine (2.0 mmol) in ethanol (5 ml). After the mixture was stirred at room temperature for 2 h, a precipitated crystalline was collected and recrystallized from benzene. Mp 130—132°C (lit,[12)] 140°C); IR (KBr) 3236, 2972, 1468, 1390, 1075, 1035, 850, 814, 455 cm^{-1}. Found: C, 33.77; H, 7.86; N, 9.73%. Calcd for $C_8H_{22}Cl_2CuN_2$: C, 34.23; H, 7.90; N, 9.98%.

Synthesis of 5a with a $\mathrm{CuCl_2\cdot 2H_2O}$-Acetone Oxime/$\mathrm{O_2}$ Oxidation System. The oxidations were carried out using a gas-sealed system. A phenol (2 mmol), copper(II) chloride dihydrate (0.2 mmol), and acetone oxime (2 mmol) were put into a 10 ml glass reactor equipped with a magnetic stirrer, a gas inlet, and a manometer. A solvent (2 ml) was added to the mixture and the reaction was started with vigorous stirring under an oxygen atmosphere (114.7 kPa) at 40°C. The amount of oxygen consumed was measured by a gas burette. The reaction was stopped at the time when 1 mmol of oxygen was consumed. Products were chromatographed on silica gel with a dichloromethane or benzene-ethyl acetate (1 : 10) mixture as an eluent. The yields of the products were determined by isolation.

2,6-Dimethyl-4-(hexyloxymethyl)phenol (5aa). Bp 185 °C/133 Pa; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.7—0.9 (m, 3H), 1.2—1.8 (m, 8H), 2.17 (s, 6H), 3.43 (t, 2H, J=7 Hz), 4.33 (s, 2H), 4.84 (s, 1H), 6.91 (s, 2H); IR (neat) 3398, 2932, 1491, 1201, 1151, 1087, 870 cm^{-1}. Found: C, 76.12; H, 10.27%. Calcd for $\mathrm{C_{15}H_{24}O_2}$: C, 76.22; H, 10.24%.

2,6-Dimethyl-4-(methoxymethyl)phenol (5ab). Mp 52—54°C (lit,[10d] 52—53°C); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=2.14 (s, 6H), 3.31 (s, 3H), 4.28 (s, 2H), 5.46 (s, 1H), 6.89 (s, 2H); IR (KBr) 3286, 2918, 1493, 1388, 1228, 1158, 1075, 944, 899, 870 cm^{-1}.

4-(Ethoxymethyl)-2,6-dimethylphenol (5ac). Mp 30—32°C (lit,[10a] 36—37°C); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.21 (t, 3H, J=7 Hz), 2.17 (s, 6H), 3.49 (q, 2H, J=7 Hz), 4.33 (s, 2H), 4.38 (s, 1H), 6.92 (s, 2H); IR ($\mathrm{CHCl_3}$) 3612, 3010, 1491, 1199, 1152, 1093 cm^{-1}.

2,6-Dimethyl-4-(propoxymethyl)phenol (5ad). Bp 115°C/133 Pa; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.90 (t, 3H, J=7 Hz), 1.60 (hex, 2H, J=7 Hz), 2.16 (s, 6H), 2.39 (t, 2H, J=7 Hz), 4.32 (s, 2H), 4.99 (s, 1H), 6.90 (s, 2H); IR (neat) 3388, 2966, 1491, 1203, 1152, 1079, 868 cm^{-1}. Found: C, 74.14; H, 9.48%. Calcd for $\mathrm{C_{12}H_{18}O_2}$: C, 74.19; H, 9.34%.

2,6-Dimethyl-4-(isopropoxymethyl)phenol (5ae). Bp 120°C/133 Pa; mp 37—38°C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.20 (d, 6H, J=7 Hz), 2.26 (s, 6H), 3.67 (sept, 1H, J=7 Hz), 4.33 (s, 2H), 4.98 (s, 1H), 6.90 (s, 2H); IR (KBr) 3312, 2974, 1491, 1332, 1218, 1125, 1040 cm^{-1}. Found: C, 74.35; H, 9.51%. Calcd for $\mathrm{C_{12}H_{18}O_2}$: C, 74.19; H, 9.34%.

4-(Butoxymethyl)-2,6-dimethylphenol (5af). Bp 127°C/133 Pa; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.89 (t, 3H, J=7 Hz), 1.1—1.8 (m, 4H), 2.17 (s, 6H), 3.43 (t, 2H, J=7 Hz), 4.33 (s, 2H), 4.99 (s, 1H), 6.90 (s, 2H); IR (neat) 3408, 2962, 1491, 1201, 1152, 1083, 868 cm^{-1}. Found: C: 74.68, H: 9.63%. Calcd for $\mathrm{C_{13}H_{20}O_2}$: C, 74.96; H, 9.68%.

4-(*t*-Butoxymethyl)-2,6-dimethylphenol (5ag). Bp 130°C/133 Pa; Mp 85—87°C; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.27 (s, 9H), 2.14 (s, 6H), 4.26 (s, 2H), 4.90 (s, 1H), 6.87 (s, 2H); IR (KBr) 3286, 2974, 1491, 1365, 1191, 1050, 1006, 859 cm^{-1}. Found: C, 74.87; H, 9.75%. Calcd for $\mathrm{C_{13}H_{20}O_2}$: C, 74.96; H, 9.68%.

2,6-Dimethyl-4-(pentyloxymethyl)phenol (5ah). Bp 151 °C/133 Pa; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.88 (t, 3H, J=7 Hz), 1.2—1.7 (m, 6H), 2.15 (s, 6H), 3.43 (t, 2H, J=7 Hz), 4.33 (s, 2H), 5.07 (s, 1H), 6.90 (s, 2H); IR (neat) 3412, 2936, 1491, 1203, 1152, 1087, 866 cm^{-1}. Found: C, 75.36; H, 10.16%. Calcd for $\mathrm{C_{14}H_{22}O_2}$: C, 75.63; H, 9.98%.

4-(Cyclohexyloxymethyl)-2,6-dimethylphenol (5ai). Mp 54—55°C (from hexane); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.0—2.1 (m, 10H), 2.14 (s, 6H), 3.2—3.4 (m, 1H), 4.35 (s, 2H), 5.02 (s, 1H). 6.88 (s, 2H); IR (KBr) 3308, 2932, 1491, 1220, 1154, 1069, 868 cm^{-1}. Found: C, 76.84; H, 9.51%. Calcd for $\mathrm{C_{15}H_{22}O_2}$: C, 76.88; H, 9.47%.

2-*t*-Butyl-4-(ethoxymethyl)-2-methylphenol (5bc). Mp 62°C (from pentane); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.22 (t, 3H, J=7 Hz), 1.39 (s, 9H), 2.20 (s, 3H), 3.51 (q, 2H, J=7 Hz), 4.37 (s, 2H), 4.81 (s, 1H), 7.00 (s, 1H), 7.10 (s, 1H); IR (KBr) 3390, 2954, 1483, 1350, 1180, 1079, 864 cm^{-1}. Found: C, 75.73; H, 10.12%. Calcd for $\mathrm{C_{14}H_{22}O_2}$: C, 75.63; H, 9.98%.

3-*t*-Butyl-4-hydroxy-5-methylbenzaldehyde (2b). Mp 150—151°C (from hexane); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.42 (s, 9H), 2.31 (s, 3H), 5.73 (s, 1H), 7.57 (s, 1H), 7.71 (s, 1H), 9.83 (s, 1H); IR (KBr) 3234, 2960, 1669, 1576, 1305, 1263, 1176, 923 cm^{-1}. Found: C, 74.85; H, 8.48%. Calcd for $\mathrm{C_{12}H_{16}O_2}$: C, 74.96; H, 8.39%.

3,5-Di-*t*-butyl-4-hydroxybenzaldehyde (2c). Mp 189—190°C (from ethyl acetate) (lit,[13] 185—187°C); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.46 (s, 18H), 5.84 (s, 1H), 7.74 (s, 2H), 9.89 (s, 1H).

2,6-Di-*t*-butyl-4-(hexyloxymethyl)phenol (5ca). Bp 190°C/133 Pa; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=0.8—1.5 (m, 11H), 1.40 (s, 18H), 3.45 (t, 2H, J=7 Hz), 4.36 (s, 2H), 5.10 (s, 1H), 7.10 (s, 2H); IR (neat) 3648, 2960, 1437, 1363, 1236, 1158, 1100, 876 cm^{-1}. Found: C, 78.68; H, 11.41%. Calcd for $\mathrm{C_{21}H_{36}O_2}$: C, 78.69; H, 11.32%.

3,5-Di-*t*-butyl-4-(methoxymethyl)phenol (5cb). Bp 136°C/133 Pa; mp 98—99.5°C (lit,[14] 99.5°C); ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.45 (s, 18H), 3.36 (s, 3H), 4.32 (s, 2H), 5.15 (s, 1H), 7.12 (s, 2H); IR (KBr) 3548, 2958, 1435, 1379, 1238, 1098, 973, 872 cm^{-1}.

2,6-Di-*t*-butyl-4-(ethoxymethyl)phenol (5cc). Bp 143°C/133 Pa; ^{1}H NMR ($\mathrm{CDCl_3}$) δ=1.22 (t, 3H, J=7 Hz), 1.41 (s, 18H), 3.54 (q, 2H, J=7 Hz), 4.36 (s, 2H), 5.13 (s, 1H), 7.14 (s, 2H); IR (neat) 3648, 2962, 1437, 1236, 1098, 868 cm^{-1}. Found: C, 76.87; H, 10.68%. Calcd for $\mathrm{C_{17}H_{28}O_2}$: C, 77.22; H, 10.67%.

References

1) Preliminary communications: K. Takehira, M. Shimizu, Y. Watanabe, H. Orita, and T. Hayakawa, *Tetrahedron Lett.*, **31**, 2607 (1990); M. Shimizu, Y. Watanabe, H. Orita, T. Hayakawa, and K. Takehira, *Tetrahedron Lett.*, **32**, 2053 (1991).

2) R. A. Sheldon and N. de Heij, "The Role of Oxygen in Chemistry and Biochemistry," in "Studies in Organic Chemistry," ed by W. Ando and Y. Moro-oka, Elsevier, Amsterdam (1988), Vol. 33, p. 243.

3) A. Schouteeten and Y. Christidis, Eur. Patent Appl. 0019531 (1980); *Chem. Abstr.*, **94**, 191933e (1981); A. Schouteeten, Y. Christidis, and J. C. Vallejos, Eur. Patent Appl., 0047693 (1982); *Chem. Abstr.*, **96**, 217481z (1982).

4) M. Komiyama and H. Hirai, *J. Am. Chem. Soc.*, **105**, 2018 (1983), and references cited therein.

5) K. Nishizawa, K. Hamada, and T. Aratani, Eur. Patent Appl. 0012939 (1979); *Chem. Abstr.*, **94**, 46967q (1981).

6) T. Shimizu, A. Nishinaga, and T. Matsuura, "Preprint of the 12th Oxidation Symposium," Synth. Org. Chem. Soc. Jpn., Tokyo, 1978, p. 74.

7) K. Takehira, M. Shimizu, Y. Watanabe, H. Orita, and T. Hayakawa, *Tetrahedron Lett.*, **30**, 6691; K. Takehira, M. Shimizu, Y. Watanabe, H. Orita, and T. Hayakawa, *J. Chem. Soc., Chem. Commun.*, **1989**, 1705; M. Shimizu, Y. Watanabe, H. Orita, T. Hayakawa, and K. Takehira, *Bull. Chem. Soc. Jpn.*, **65**, 1522 (1992).

8) H. -D. Becker, *J. Org. Chem.*, **30**, 982 (1965); C. M. Orlando, Jr., *J. Org. Chem.*, **33**, 2516 (1968).

9) For example: M. Iwahara, Jpn. Patent 88-239243 (1988); *Chem. Abstr.*, **111**, 96817f (1989), for synthesis of (alkoxymethyl)phenols.

10) a) E. Adler, G. Andersson, and E. Edman, *Acta Chem. Scand., Ser. B*, **29**, 909 (1975); b) K. Omura, *J. Org. Chem.*, **49**, 3046 (1984); c) M. Bouquet, A. Guy, M. Lemaire, and J. -P. Guetté, *Acad. Sci. C. R. Seances, Paris, Ser. 2*, **299**, 1389 (1984); d) S. L. Goldstein and E. McNelis, *J. Org. Chem.*, **49**, 1613 (1984).

11) W. W. Kaeding, *J. Org. Chem.*, **28**, 1063 (1963); D. R. Armstrong, C. Cameron, D. C. Nonhebel, and P. G. Perkins, *J. Chem. Soc., Perkin Trans. 2*, **1983**, 589; M. Shimizu, H. Orita, T. Hayakawa, Y. Watanabe, and K. Takehira, *Bull. Chem. Soc. Jpn.*, **64**, 2583 (1991).

12) S. Prasad and P. D. Sharma, *J. Proc. Inst. Chem. (India)*, **30**, 254 (1958); *Chem. Abstr.*, **53**, 11086e (1959).

13) T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **74**, 1469 (1952).

14) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1435 (1957).
