Copper-Catalyzed Oxidative Coupling of 2,4,6-Trimethylphenol with Oxygen

Kenichi Oyaizu, Kei Saito, and Eishun Tsuchida*
*Advanced Research Institute for Science and Engineering, Department of Polymer Chemistry, Waseda University,
Tokyo 169-8555*

2,4,6-Trimethylphenol was oxidized with oxygen in the presence of (1,4,7-tribenzyl-1,4,7-triazacyclononane)copper(II) chloride as a catalyst to produce exclusively a coupled product stilbenequinone, without the formation of oxygenated products.

The outcome of the copper-catalyzed oxidation of 2,4,6-trimethylphenol with oxygen has been dominated by oxygenated products such as 4-hydroxy-3,5-dimethylbenzaldehyde, 2,6-dimethyl-*p*-benzoquinone, and 4-alkoxy-2,6-dimethylphenols.[1,2] This reaction, effectively catalyzed by copper(II) chlorides coupled with diethylamine, hydroxylamine, or oximes, has attracted much attention not only as a convenient synthetic method for *p*-hydroxybenzaldehyde that is an important intermediate in the industrial synthesis of dyes, polymers, pharmaceutical and agrochemicals, but also as the relevant model for the biosynthesis of vitamin E.[3] Another important oxidation chemistry of phenols is the coupling of *o*- and/or *p*-unsubstituted phenols to give diphenoquinones and phenylene oxide polymers.[4–7] On the other hand, the oxidative coupling of 2,4,6-trialkylated phenols at the benzylic carbon is less frequent, and has so far required a large amount of strong oxidants in the absence of oxygen. For example, the oxidation of 2,6-di-*tert*-butyl-4-methylphenol with iodine gives a mixture of 1,2-bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)ethane and 3,3',5,5'-tetra-*tert*-butylstilbene-4,4'-quinone,[8] and 2,4,6-trimethylphenol is oxidized by silver carbonate into stilbenequinone,[9] though the product is not well characterized. Herein we report our successful attempts to use oxygen as an oxidant for the oxidative coupling of 2,4,6-trimethylphenol. Combination of X-ray crystallographic and spectroscopic methods revealed that the product is solely the corresponding stilbenequinone **4**.

Recently, it was shown that the oxidative polymerization of 2,6-difluorophenol with oxygen is accomplished using copper complexes with 1,4,7-trialkyl-1,4,7-triazacyclononane ligands as catalysts.[10] The strong oxidizing power of the complex demonstrated by the reaction led us to examine the oxidation of 2,4,6-trimethylphenol. The overall oxidation from trimethylphenol to stilbenequinone is a 3-electron, 3-proton transfer process. Under argon, upon the addition of a CH_2Cl_2 solution of 3 equiv of (1,4,7-tribenzyl-1,4,7-triazacyclononane)copper(II) chloride ([(tacn)CuCl$_2$]) to a solution of 2,4,6-trimethylphenol in CH_2Cl_2 containing 3 equiv of triethylamine at −5 °C, the greenish yellow solution slowly turned to a transitory brown color indicative of the formation of the corresponding copper(I) and phenoxyl radical (Scheme 1),[8] which changed to dark red upon standing overnight. Layering the solution with diethyl ether afforded dark red crystals of the product in 90% yield. The ^{1}H and ^{13}C NMR spectra of the crystallized product[11] revealed a coupled quinoid structure having only two nonequivalent methyl groups, which corresponded to those of the centrosym-
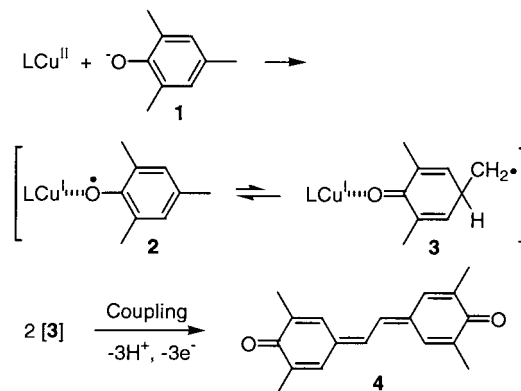
Scheme 1.

metric stilbenequinone coupled at the *o*- or *p*-position. X-ray analysis[12] revealed the *p*-coupled structure having the crystallographic center of symmetry located at the center of the molecule (Figure 1). The product, 3,3',5,5'-tetramethylstilbene-4,4'-quinone, is a fully oxidized dimer. The partially oxidized struc-
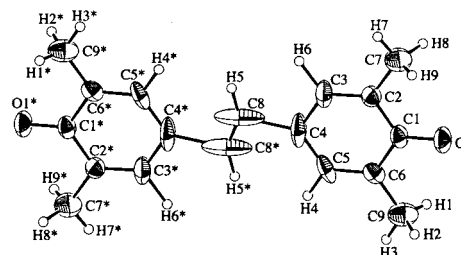

Figure 1. ORTEP view (30% probability ellipsoids) of **4**. Selected bond length (Å) and angles (deg): C(1)-O(1), 1.235(5); C(4)-C(8), 1.69(2); C(8)-C(8)*, 1.07(2); O(1)-C(1)-C(2), 121.0(5); C(3)-C(4)-C(8), 109.7(7); C(4)-C(8)-C(8)*, 99.8(1).

tures such as 1,2-bis(3,5-dimethyl-4-hydroxyphenyl)ethane and *trans*-1,2-bis(3,5-dimethyl-4-hydroxyphenyl)ethylene are excluded by the planar framework of the molecule and the short C–O distance which is close to the typical bond length of a carbonyl group. The short C(8)–C(8)* bond length corresponds to the partial double bond in stilbenequinone. After the reaction, a reasonable amount of the copper(I) complex (Figure 2) was isolated.[13] It should be noted that the partially oxidized dimers are not produced even when only 0.3 equiv of [(tacn)CuCl$_2$] is reacted with 2,4,6-trimethylphenol under argon; **4** is obtained as the sole product in 10% yield, and unreacted trimethylphenol is recovered from the solution. The absence of the partially oxidized by-products supports the fact that they are more easily oxidized by the copper(II) complex.[8] On the contrary, **4** is obtained in 100% yield when the same reaction is carried out in the presence of oxygen, indicating that the catalytic oxidation with oxygen is accomplished. The amount of oxygen uptake with respect
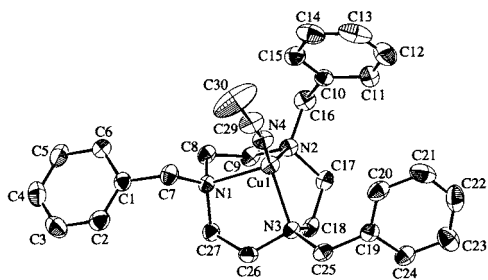
Figure 2. ORTEP view (30% probability ellipsoids) of [(tacn)Cu(CF$_3$SO$_3$)-(CH$_3$CN)]. Selected bond length (Å) and angles (deg): Cu(1)-N(1), 2.189(4); Cu(1)-N(2), 2.122(7); Cu(1)-N(3), 2.126(4); Cu(1)-N(4), 1.849(6); N(1)-Cu(1)-N(2), 84.6(2); N(1)-Cu(1)-N(3), 86.0(2); N(1)-Cu(1)-N(4), 112.3(2); N(2)-Cu(1)-N(3), 86.2(2); N(2)-Cu(1)-N(4), 140.5(2); N(3)-Cu(1)-N(4), 128.7(2).

to the yield of **4** (150 mol%) was in accordance with the 4e⁻ reduction of oxygen.[14]

The question arises as to the origin of the contrast with the precedented oxygenation of 2,4,6-trimethylphenol at the *p*-methyl group that takes place when the conventional copper(II) complexes are used as the catalyst (Scheme 2).[1,2] Recently,

Scheme 2.
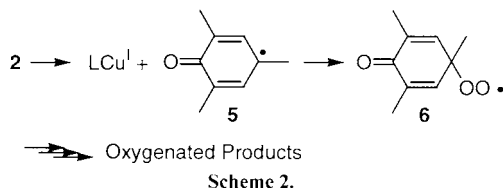
Kobayashi et al. reported that a phenoxyl radical-copper(I) intermediate is generated instead of the free phenoxyl radical during the oxidative polymerization of phenol catalyzed by (1,4,7-triisopropyl-1,4,7-triazacyclononane)copper(II) chloride.[15,16] In addition, it was shown that a phenoxocopper(II) complex isolated from the reaction of 4-fluorophenol and a copper(II) complex with a bulky ligand could be equibrated with a copper(I) phenoxyl complex in solution due to the resonance.[17] Thus, the resulting phenoxyl radical could stay in the coordination sphere of copper(I).[18] A similar reaction has been reported for the oxidation of catechol to give a copper(I) semiquinone complex.[19] By analogy to these reactions, it is postulated that the phenoxyl radical is bound to copper(I) (Scheme 1). Although the isolation of the copper(I) phenoxyl complex **2** is unsuccessful, it seems reasonable to suppose that the coupling reaction prevails due to the lower reactivity of **2** toward oxygen (Scheme 1) than that of the free radical **5** (Scheme 2). This is partly corroborated by a control experiment using (1,4,7-triazacyclononane)copper(II) chloride as a catalyst, which should less strongly binds phenolate:[20] concurrent side reactions give a significant amount of the oxygenated products. The control of phenoxyl coupling by the coordination of a copper complex is reminiscent of the regioselective oxidative polymerization of 2,6-unsubstituted phenol.[15,16] The high selectivity for the coupling of **2** should allow kinetic and energetic studies, which is the topic of our continuous research.

References and Notes

1. M. Shimizu, Y. Watanabe, H. Orita, T. Hayakawa, and K. Takehira, *Bull. Chem. Soc. Jpn.*, **66**, 251 (1993).
2. M. Shimizu, Y. Watanabe, H. Orita, T. Hayakawa, and K. Takehira, *Tetrahedron Lett.*, **32**, 2053 (1991).
3. K. Takehira, M. Shimizu, Y. Watanabe, H. Orita, and T. Hayakawa, *J. Chem. Soc., Chem. Commun.*, **1989**, 1705.
4. A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Am. Chem. Soc.*, **81**, 6335 (1959).
5. A. S. Hay, *J. Polym. Sci., A*, **36**, 506 (1988).
6. E. Tsuchida, H. Nishide, and T. Maekawa, *J. Macromol. Sci., Chem.*, **A21**, 1081 (1984).
7. D. G. Hewitt, *J. Chem. Soc., C*, **1971**, 2967.
8. K. Omura, *J. Org. Chem.*, **49**, 3046 (1984).
9. V. Balogh, M. Fétizon, and M. Golfier, *J. Org. Chem.*, **36**, 1339 (1971).
10. K. Oyaizu, K. Saito, and E. Tsuchida, *Macromolecules*, **33**, 5766 (2000).
11. Spectroscopic data for **4**: ^{1}H NMR (500 MHz, CDCl$_3$, TMS, ppm) δ: 2.09 (methyl, 6H, s), 2.13 (methyl, 6H, s), 7.05 (phenyl, 2H, s), 7.23 (phenyl, 2H, s), 7.55 (methide, 2H, s); ^{13}C NMR (500 MHz, CDCl$_3$, TMS, ppm) δ: 16.45 and 17.04 (methyl C), 128.1, 133.1, 136.4, 137.5, 138.0, 138.4 and 187.3 (quinone methide C); IR (KBr, cm^{-1}) v_{max}: 2948, 2915 (CH$_3$), 1637 (C=O), 1595, 1502, 1435, 1370, 1323, 1233, 1177, 1027, 941, 907, 781, 610, 456.
12. Crystal data for **4**: C$_{18}$H$_{18}$O$_2$, MW = 266.34, monoclinic, space group $P2_1$/c (#14), a = 4.340(3), b = 12.252(4), c = 13.670(4) Å, β = 91.56(6)°, V = 726.6(6) Å^3, D_{calc} = 1.217 g cm^{-3}, Z = 2, μ (Mo Kα) = 0.78 cm^{-1}, 1977 reflections measured, 1758 unique (R_{int} = 0.028), 586 observations (I > 3.00σ(I)), 128 variables, final $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.073$, $R_w = (\Sigma w(|F_o| - |F_c|)^2/(\Sigma wF_o^2))^{1/2} = 0.045$.
13. Another curious feature is the first isolation and crystal structure determination of a copper(I) complex bearing tacn ligand, which has been difficult because of its high reactivity toward O$_2$. Single crystals were grown by carefully layering the solution with acetonitrile containing tetrabutylammonium triflate strictly in the absence of oxygen. Crystal data for [(tacn)Cu(CF$_3$SO$_3$)·(CH$_3$CN)]: C$_{30}$H$_{36}$CuF$_3$N$_4$O$_3$S, MW = 653.24, orthorhombic, space group *P*bca (#61), a = 19.17(6), b = 20.03(6)), c = 16.14(8) Å, V = 6198(35) Å^3, D_{calc} = 1.400 g cm^{-3}, Z = 8, μ (Mo Kα) = 8.27 cm^{-1}, 7756 reflections measured, 7754 unique (R_{int} = 0.373), 4114 observations (I > 3.00σ(I)), 520 variables, final $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.064$, $R_w = (\Sigma w(|F_o| - |F_c|)^2/(\Sigma wF_o^2))^{1/2} = 0.049$.
14. In the presence of phenols, the copper(I) complex (Figure 2) reduced O$_2$ into H$_2$O without the formation of partially reduced oxygen species.
15. H. Higashimura, K. Fujisawa, Y. Moro-oka, M. Kubota, A. Shiga, A. Terahara, H. Uyama, and S. Kobayashi, *J. Am. Chem. Soc.*, **120**, 8529 (1998).
16. H. Higashimura, M. Kubota, A. Shiga, K. Fujisawa, Y. Moro-oka, H. Uyama, and S. Kobayashi, *Macromolecules*, **33**, 1986 (2000).
17. K. Fujisawa, Y. Iwata, N. Kitajima, H. Higashimura, M. Kubota, Y. Miyashita, Y. Yamada, K. Okamoto, and Y. Moro-oka, *Chem. Lett.*, **1999**, 739.
18. F. Harrod, *Can. J. Chem.*, **47**, 637 (1969).
19. M. Berreau, S. Mahapatra, J. A. Halfen, R. P. Houser, V. G. Young, Jr., and W. B. Tolman, *Angew. Chem., Int. Ed.*, **38**, 207 (1999).
20. P. Chaudhuri and K. Wieghardt, *Prog. Inorg. Chem.*, **35**, 329 (1988).