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Autoxidation of Phenols Catalyzed by Copper(II)–Ethylenediamine Complexes: The Reaction Mechanism

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The mechanism of the autoxidation of phenols with molecular oxygen catalyzed by Cu(II)–ethylenediamine complexes is elucidated. The kinetics are of first order in both [phenol] and [complex] and of one-half order in [O_2]. Those results imply the formation of a oxygen-bridged complex in the course of the reaction. The C–C coupling of two phenoxy radicals is facilitated within the coordination sphere of Cu(II) and affords the primary oxidation products, i. e., 2,2′-biphenyldiols. The bulkiness of substituents determines the type of the secondary products and either benzofuran or dioxepin is produced. Taking into account the results of oxidation of 2,2′-biphenyldiols, the mechanism of the production of benzofuran and dioxepin is also clarified. In the Cu(II) complex with sterically crowded biphenyldiolate, the oxidation activity of Cu(II) has been enhanced and the coordinating biphenyldiolate is immediately oxidized to benzofuran. On the contrary, the biphenyldiolate–Cu(II) complex with square-planar geometry could not produce benzofuran. After the complex is forced into the active tetrahedral configuration by the access of phenoxy radical–Cu(II) complex, the biphenyldiolate is oxidized to biphenyloxy radical and suffers C–O coupling with the phenoxy radical to afford dioxepin.

In the autoxidation of phenols with molecular oxygen in the presence of copper–amine complexes, the complexes are known to play an important role not only in the initiation of the reaction, but in the determination of the coupling pattern.[1-3]

We found that chelate complexes of diamine with Cu(II) were more active than the monoamine complexes and the catalytic activity of the complexes, i. e., the oxidation activity of Cu(II), was affected by the type of alkyl groups on *N,N′*-dialkylethylenediamine. The most active Cu(II) complexes have alkyl branching on the carbon attached to nitrogen and therefore are forced into a tetrahedral configuration.[4,5]

In this paper, we have investigated kinetically the initial stage of the oxidation of phenols to obtain a empirical rate expression. Moreover, taking account of the data concerning the products described previously, we elucidate a mechanism of the autoxidation of phenols catalyzed by Cu(II)–ethylenediamine complexes.

Results and Discussion

(I) Kinetic Studies. The kinetics were studied in the presence of *N,N′*-di-*tert*-butyl-, *N,N′*-diisopropyl-, and *N,N′*-diethyl-substituted ethylenediamine–Cu(II) complexes, respectively. The 2:1 complex of diamine with Cu(II) was the only active catalyst species in the reaction.[4] 2,4-Di-*tert*-butylphenol (1) was oxidized under a set of standard conditions (see Experimental Section) and minor deviations from these conditions, if any, are specified. The initial rate of the reaction ([products] min^{-1}) was determined. As a typical example, the results of the oxidation of 1 in the presence of *N,N′*-diisopropylethylenediamine–Cu(II) complex are shown below. Table I indicates that the initial rate (v) increased linearly with the concentration of the complex. From plots of log v against log [Cu(II)–diamine complex], the dependence on [Cu(II)–diamine complex] is of the first order. The dependence on 2,4-di-*tert*-butylphenol concentration is shown in Table II and is also of the first order. In Table III, the change in the initial rate (v) with partial pressure of oxygen is shown. The kinetic plots indicated that the dependence on [O_2] is of one-half order, as the partial pressure of oxygen is proportional to the oxygen concentration (Figure 1). The type of alkyl groups of *N,N′*-dialkylethylenediamine did not affect the kinetic results, and therefore Cu(II)–ethylenediamine complexes participate in autoxidation of

Table I. Dependence of Initial Rate on Complex Concentration[a]

[complex], mol m^{-3} [b]	[product 5], mol m^{-3} min^{-1} [c]
0.243	0.30
0.485	0.55
0.97	1.10
1.94	2.00
3.88	4.10

[a] 4.85×10^{-4} mol of 2,4-di-*tert*-butylphenol in 10 mL of methanol. P_{O_2} 1 atm. [b] 2:1 complex of diamine with Cu(II). [c] Analysis by GLC.

Table II. Dependence of Initial Rate on 2,4-Di-*tert*-butylphenol (1) Concentration[a]

[phenol 1], mol m^{-3}	[product 5], mol m^{-3} min^{-1} [b]
2.43	0.057
4.85	0.115
12.1	0.270
24.3	0.530
48.5	1.10
97	2.20
146	3.16
194	4.48
388	8.50

[a] 9.7×10^{-6} mol of $CuCl_2$ and 1.94×10^{-5} mol of diamine in 10 mL of methanol. P_{O_2} 1 atm. [b] Analysis by GLC.

Table III. Dependence of Initial Rate on Partial Pressure of Oxygen[a]

P_{O_2}, atm[b]	[product 5], mol m^{-3} min^{-1} [c]
0.125	0.36
0.25	0.58
0.50	0.84
1.00	1.20

[a] 9.7×10^{-6} mol of $CuCl_2$, 1.94×10^{-5} mol of diamine, and 4.85×10^{-4} mol of 2,4-di-*tert*-butylphenol in 10 mL of methanol. [b] Oxygen mixed with nitrogen. [c] Analysis by GLC.

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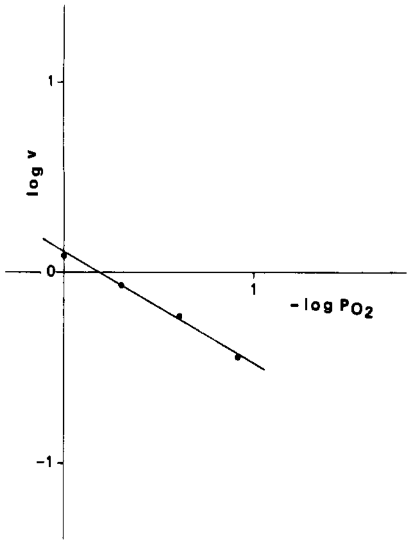
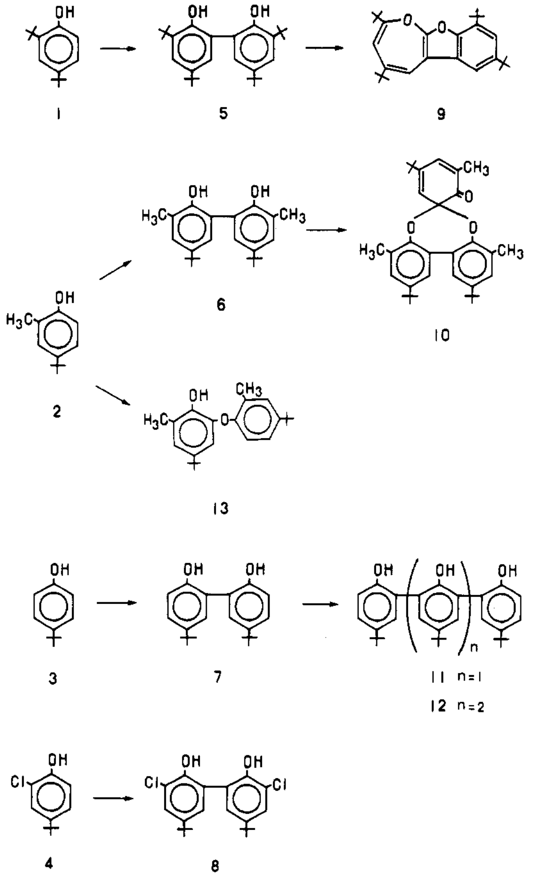


Figure 1. Kinetic plot.

Scheme I



phenols by the same mechanism. Conclusively, the following empirical rate expression was deduced.

$$v = k[\text{Cu(II)–diamine complex}]^1 \times [\text{2,4-di-}tert\text{-butylphenol}]^1[O_2]^{1/2}$$

Scheme II

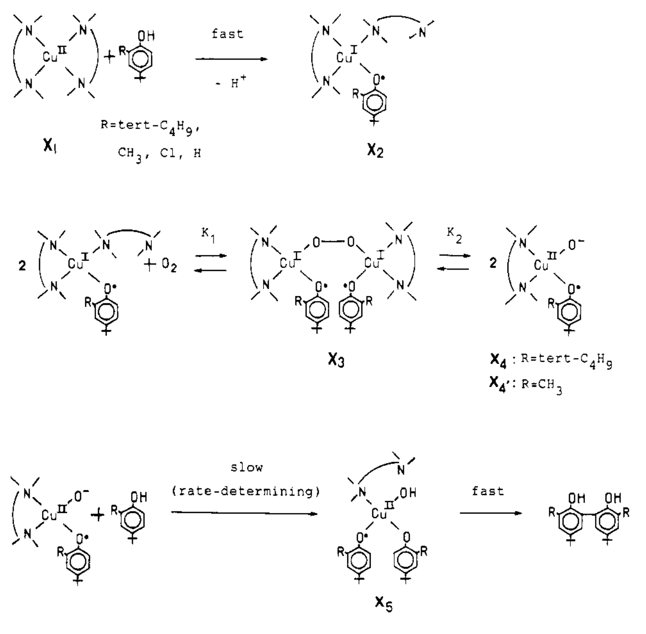


Table IV. Oxidation of Phenol 1 or Biphenyldiol 5

	1^a		5^b
min	5^c	9^c	9^c
3	25	13	61
10	15	52	94
17	6	75	98
24	3	85	99

[a] 2.43×10^{-4} mol of phenol in 10 mL of methanol. [b] 1.22×10^{-4} mol of biphenyldiol in 10 mL of methanol. [c] % yields of products based on starting material.

(II) Mechanism of the Production of Biphenyldiols. The oxidation of 2,4-di-*tert*-butylphenol (1) gave only 3,3′,5,5′-tetra-*tert*-butyl-2,2′-dihydroxybiphenyl (5) and its oxidation product 2,4,7,9-tetra-*tert*-butyloxepino[2,3-*b*]benzofuran (9). Diphenyl ether and the products found in the oxidation involving the 2- and/or 4-positions of 1, e.g., 2,4-di-*tert*-butyl-4-hydroxy-5,6-epoxy-2-cyclohexenone[6] or 3,5-di-*tert*-butyl-1,2-benzoquinone,[7,8] were not detected. Likewise, 4-*tert*-butyl-2-methylphenol (2), 4-*tert*-butylphenol (3), and 4-*tert*-butyl-2-chlorophenol (4) gave the substituted biphenyldiols: 5,5′-di-*tert*-butyl-2,2′-dihydroxy-3,3′-dimethylbiphenyl (6), 5,5′-di-*tert*-butyl-2,2′-dihydroxybiphenyl (7), and 5,5′-di-*tert*-butyl-3,3′-dichloro-2,2′-dihydroxybiphenyl (8). Biphenyldiols 6 and 7 were subsequently oxidized to 2,5′,10-tri-*tert*-butyl-3′,4,8-trimethyldibenzo[*d*,*f*][1,3]dioxepin-6-spirocyclohexa-3′,5′-dien-2′-one (10) and terphenyltriol (11) and quarterphenyltetrol (12), respectively (Scheme I). Under our conditions, biphenyldiols were the principal primary oxidation products, but 4′,5-di-*tert*-butyl-2-hydroxy-2′,3-dimethyldiphenyl ether (13) was exceptionally formed in the oxidation of 2 (discussed in a later section). A sequence of the production of biphenyldiols most consistent with the kinetic data is represented in Scheme II.

(1) The Key Intermediate. In Scheme II, the complex (X_5) is considered to be a key intermediate. It has been shown that the most active complexes are forced into a tetrahedral configuration by two molecules of the sterically crowded ethylenediamine around Cu(II) and undergo a facile electron transfer.[4] As the complex (X_5) is sterically crowded, the phenolate anion in the complex (X_5) is immediately oxidized to phenoxy radical. The principal C–C coupling reaction of two phenoxy radicals is facilitated by their coordination to the same Cu(II) and the coupling took place between the uncrowded positions. The formation of biphenyldiolate within the coordination sphere of Cu(II) is certified by the process in which dioxepin 10 was pro-

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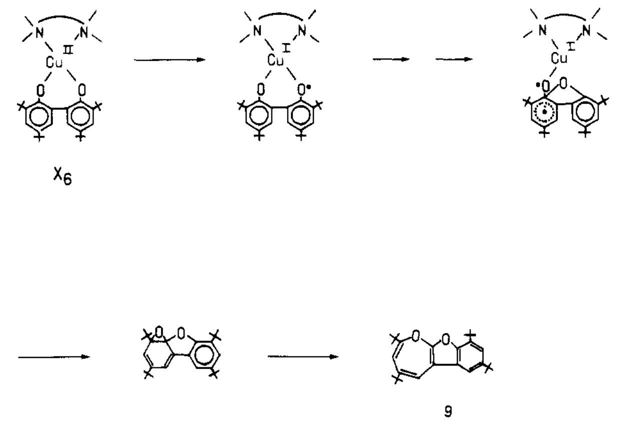
Scheme III



duced (discussed in a later section).

(2) The Rate-Determining Step. Assuming that the complex (X_4) is in a steady state and that the process in which the complex (X_4) coordinates with a phenolate anion is the rate-determining step, the foregoing empirical rate expression based on the kinetic studies is interpreted as follows,

$$v = k'[\text{complex }(X_4)][\text{phenol}] \quad (1)$$

$$K_1 = [\text{complex }(X_3)]/[\text{complex }(X_2)]^2[O_2]$$

$$K_2 = [\text{complex }(X_4)]^2/[\text{complex }(X_3)]$$

$$K_1K_2 = K_3 = [\text{complex }(X_4)]^2/[\text{complex }(X_2)]^2[O_2]$$

$$[\text{complex }(X_4)] = K_3{}^{1/2}[\text{complex }(X_2)][O_2]^{1/2} \quad (2)$$

$$[\text{complex }(X_2)] \doteqdot [\text{Cu(II)–diamine complex }(X_1)]_{\text{initial}} \quad (3)^9$$

from (1), (2), and (3)

$$v = k[\text{Cu(II)–diamine complex }(X_1)]^1[\text{phenol}]^1[O_2]^{1/2} \quad (4)$$

We assume that, preceding the rate-determining step, an equilibrium between the complexes (X_2), (X_3), and (X_4) has occurred. Since copper species are labile in their oxidation states,[10] Cu(I)–complex (X_2) would quickly attain equilibrium with Cu(II)–complex (X_4). The intermediate oxygen-bridged complex (X_3) may be rather unstable, but kinetic studies require formation of the complex (X_3) by the simultaneous reaction of two Cu(I)–complex (X_2) with one molecule of oxygen. The rate expression (eq 4) derived by those assumptions satisfies the empirical reaction kinetics.

(3) The Formation of C–O Coupled Product. In the reaction of phenol **2**, C–O coupled product, i. e., diphenyl ether **13**, was produced as a byproduct (Scheme I). The C–O coupling of phenoxy radicals occurred intermolecularly between two complexes ($X_{4'}$). Since the unpaired electron is delocalized toward the aromatic carbon atom, the C–O coupling would be inherent in the present phenol oxidation. However, the C–O coupled products were not afforded from less reactive **3** and **4** in the quantity sufficient to be detected and phenol **1**, in spite of its high reactivity, cannot produce a cross-coupled product, because the oxygen atom with the unpaired electron is hindered from coupling by the neighboring bulky *tert*-butyl.

Table V. Oxidation of Phenol 2[a]

min	2[b]	products[c]		
		6	10	13
0	48.5	0	0	0
5	36.0	2.84	1.59	0.85
15	28.0	2.26	4.62	1.17
25	23.1	1.40	6.72	1.22
35	20.1	0.92	7.92	1.26

[a] Standard conditions. [b] Recovery of substrate in mol × 10^5. [c] Yields of products in mol × 10^5.

Table VI. Oxidation of Biphenyldiol 6[a]

min	6[b]	10[c]
0	24.3	0
5	24.2	0.19
15	23.9	0.40
25	23.4	0.48
35	23.1	0.55

[a] Standard conditions. [b] Recovery of substrate in mol × 10^5. [c] Yields of product in mol × 10^5.

Table VII. Oxidation of Phenol 2 and Biphenyldiol 6[a]

min	2[b]	6[b]	10[c]
0	16.2	16.2	0
5	14.7	15.4	0.91
15	12.3	14.4	2.38
25	10.9	13.2	4.02
35	8.9	12.1	5.33

[a] Solvent: 10 mL of methanol. [b] Recovery of substrates in mol × 10^5. [c] Yields of product in mol × 10^5.

(III) Mechanism of the Production of Benzofuran 9 and Dioxepin 10. The primary products, **5** and **6**, were subsequently oxidized to give **9** and **10**, respectively. In order to elucidate the mechanism, biphenyldiol **5** or **6** was oxidized in place of phenol and the results are discussed together with those obtained in the oxidation of phenol **1** or **2**.

(1) Benzofuran 9. The percent yields of the oxidation products of **1** for each reaction time are shown in Table IV together with those of **5**. In the oxidation of **1**, the yield of **5** reached the maximum after the first 3 min and then decreased rapidly, while that of **9** increased with the reaction time. This implies that benzofuran **9** is produced from **1** via biphenyldiol **5**. Actually, in the early stage of the reaction, oxidation of **5** gave **9** in higher yield than was obtained by the oxidation of phenol **1**. The mechanism of the production of **9** via copper–complex of **5** (X_6) is represented in Scheme III.

(2) Dioxepin 10. In the oxidation of phenol **2**, the yield of biphenyldiol **6** reached a maximum within 5 min and then gradually decreased, while that of **10** increased with the reaction time (Table V). On the other hand, biphenyldiol **6**, used in place of **2**, was essentially unreactive (Table VI). These results suggested that the complex involving the phenoxy radical ($X_{4'}$) is indispensable for the production of **10** and that the dioxepin **10** is produced by cross-coupling of phenoxy and biphenyloxy radicals. Consequently, we conducted an experiment using both **2** and **6** as substrates. The total molar quantity of both substrates (Table VII) was equivalent to that of **2** (Table V). The yields of **10** for each reaction time are shown in Table VII together with the recovery of substrates. The larger decrease of **2** than **6** in competitive reaction indicates that phenol **2** is coordinated to Cu(II)–ethylenediamine complex (X_1) more easily than biphenyldiol **6** and quickly oxidized to a coordinated phenoxy radical, which is then led to the biphenyldiolate–Cu(II) complex and subse-

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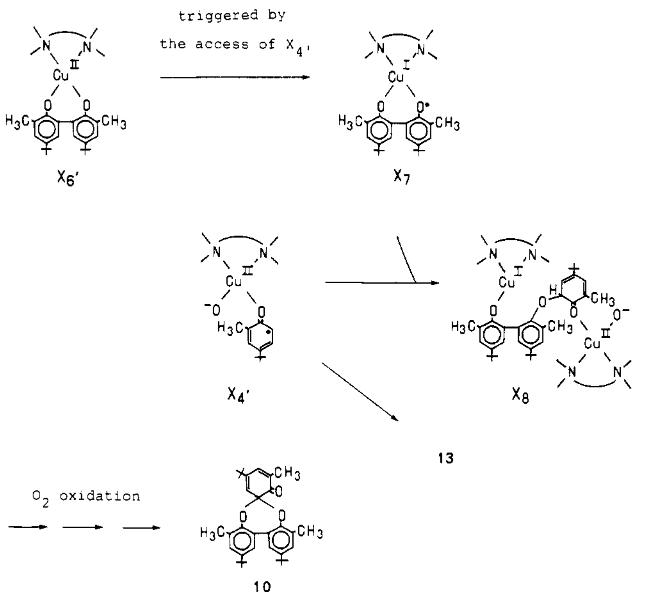
[9] In the presence of a large excess of phenol, the Cu(II)–diamine complex (X_1) which exists in the catalytic amount reacts quickly with phenol and is converted into complex X_2. The concentration of complex X_2 is approximately equal to that of initial complex X_1.

[10] Bacon, R. G. R.; Hill, H. A. O. *Chem. Soc. Rev.* **1965**, *19*, 95.

Scheme IV



quently dioxepin **10**. The decrease of **6** reveals that biphenyldiol **6** is also incorporated into dioxepin **10**. However, the yields of **10** were always lower than those observed in the independent oxidation of **2** (Table V and VII). This implied that the biphenyloxy radical–Cu(I) complex (X_7) necessary for the reaction was less effectively produced from biphenyldiol. The complex (X_7) is formed mainly from phenol **2** via biphenyldiolate–Cu(II) complex ($X_{6'}$), which is produced efficiently by the coupling of the phenoxyls within the coordination sphere of Cu(II), and reacts with phenoxy radical complex ($X_{4'}$) to give a higher yield of **10**. The C–O coupling was observed also in the formation of diphenyl ether **13** and already discussed in detail. The mechanism of the production of **10** is summarized in Scheme IV.

(3) The Rate-Determining Step in the Production of Benzofuran 9 and Dioxepin 10. We have already pointed out that the process in which the phenoxy radical complex (X_4) coordinates with a phenolate anion is rate determining in the production of **5** from **1**. The same process seems to be the rate-determining one also in the production of **9** from **1**, because the biphenyldiol **5**, used in place of **1**, was rapidly converted to **9** and gave a better yield for the same reaction period. The rate-determining step in the production of **10** from phenol **2** seems to be the same. As can be seen from Table V, the yield of **6** passed through a maximum after 5 min of oxidation and decreased gradually, while that of **10** increased in substantial quantity with reaction time. Undoubtedly the biphenyldiolate in complex ($X_{6'}$) is quickly incorporated into **10** and the rate-determining step is not present in this process.

(4) The Factors Involving Selective Production of Benzofuran and Dioxepin. We can discuss the selective production of benzofuran or dioxepin on the basis of the effect of the steric configuration of Cu(II) on its oxidation activity.[4] As the biphenyldiolate produced in the oxidation of phenol **1** has bulky *tert*-butyls in the 3- and 3′-positions, its coordination to Cu(II) causes steric crowding around copper(II). The configuration of complex (X_6) becomes tetrahedral, and Cu(II) is activated enough to oxidize the biphenyldiolate to benzofuran. C–O coupling could not take place with phenol **1** because the oxygen atom is hindered from coupling by the bulky, neighboring *tert*-butyl. Consequently, phenol **1** did not afford either diphenyl ether or dioxepin. On the contrary, a square-planar geometry for the copper–biphenyldiolate complex ($X_{6'}$) resulting from phenol **2** is not disturbed by small methyls in the 3- and 3′-positions and the biphenyldiolate was not oxidized to benzofuran. Probably, the complex ($X_{6'}$) will be forced into tetrahedral configuration by the access of phenoxy radical–Cu(II) complex ($X_{4'}$) and oxidized to biphenyloxy radical complex (X_7), which then suffers C–O coupling with phenoxy radical complex ($X_{4'}$) to give the final product, i.e., dioxepin **10**, via complex X_8.

Experimental Section

GLC analyses were carried out on a JEOL Model JGC-20K equipped with 3% Apiezone L grease on a Celite 545 NAW column. HPLC analyses were performed on a Shimadzu Model LC-3A liquid chromatograph with Zorbax ODS column with methanol. The temperature of the thermostat used for kinetics was controlled (±0.15 °C) by using a Komatsu-Yamato Coolnics CTR-220.

Materials. Anhydrous copper(II) chloride was prepared by heating the dihydrate in an oven at 100 °C for 20 h. *N*,*N*′-diisopropyl- and *N*,*N*′-di-*tert*-butylethylenediamine,[11] 4-*tert*-butyl-2-methylphenol (**2**),[12] 3,3′,5,5′-tetra-*tert*-butyl-2,2′-dihydroxybiphenyl (**5**),[13] and 5,5′-di-*tert*-butyl-2,2′-dihydroxy-3,3′-dimethylbiphenyl (**6**)[14] were prepared by literature procedures, and diamines were distilled before use. Oxygen, nitrogen, and a mixture of these gases were obtained in bombs from Seitetsu Kogyo Co.

Standard Conditions. 2-Substituted-4-*tert*-butylphenol (4.85×10^{-4} mol), anhydrous copper(II) chloride (9.7×10^{-6} mol), and the ethylenediamine (1.94×10^{-5} mol) were dissolved in methanol, and the volume was increased to 10 mL. Oxygen was bubbled through the mixture at atmospheric pressure and 25 °C for an indicated time. In some of the kinetic studies, nitrogen–oxygen mixtures were bubbled.

Kinetic Measurements. 2,4-Di-*tert*-butylphenol (**1**) was oxidized under standard conditions for 11 min. The initial rate of the reaction ([products] min^{-1}) was determined by GLC.

Oxidation of Phenol 1 or Biphenyldiol 5. Phenol **1** (2.43×10^{-4} mol) or biphenyldiol **5** (1.22×10^{-4} mol) was oxidized in the presence of *N*,*N*′-di-*tert*-butylethylenediamine–Cu(II) complex under standard conditions for 24 min. The yields of the products **5** and **9** were determined by HPLC at suitable intervals.

Oxidation of Phenol 2 and/or Biphenyldiol 6. Phenol **2** (4.85×10^{-4} mol), biphenyldiol **6** (2.43×10^{-4} mol), or both **2** (1.62×10^{-4} mol) and **6** (1.62×10^{-4} mol) were oxidized in the presence of *N*,*N*′-di-*tert*-butylethylenediamine–Cu(II) complex under standard conditions for 35 min. The yields of the products **6**, **10**, and **13** and recovery of the substrates **2** and **6** were determined by HPLC at suitable intervals.

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Registry No. **2**, 98-27-1; **3**, 98-54-4; **4**, 98-28-2; **5**, 6390-69-8; **6**, 32750-14-4; **7**, 22385-96-2; **8**, 87586-51-4; **9**, 65355-46-6; **10**, 15175-44-7; **11**, 62224-34-4; **12**, 87586-49-0; **13**, 37971-56-5; $CuCl_2 \cdot 2H_2O$, 10125-13-0; 2,4-di-*tert*-butylphenol, 96-76-4.

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