

## Ruthenium-Catalyzed Oxidation of Phenols with Alkyl Hydroperoxides. A Novel, Facile Route to 2-Substituted Quinones

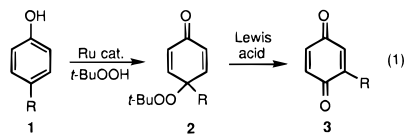
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Oxidative transformation of phenols is of importance in view of its biological<sup>1</sup> and synthetic aspects.<sup>2</sup> However, the oxidation of phenols generally lacks selectivity because of coupling reactions caused by phenoxy radicals,<sup>3</sup> and hence a novel practical method for oxidation of phenols still waits to be explored. During the course of our systematic study on the simulation of the enzymatic function of cytochrome P-450 with low valent ruthenium complex catalysts,<sup>4</sup> we have found a biomimetic method for selective oxidation of phenols.

The ruthenium-catalyzed oxidation of phenols **1** with *tert*-butyl hydroperoxide gives the corresponding (*tert*-butyldioxy)cyclohexadienones **2**, which are versatile synthetic intermediates. As a typical example, the present oxidation provides a novel and convenient method for direct access to 2-substituted quinones **3** from phenols by Lewis acid promoted migration reactions of **2** (eq 1).



Generally, metal-catalyzed oxidation of phenols with peroxides proceeds nonselectively, giving a variety of side products such as radical coupling products<sup>3</sup> and overoxidation products.<sup>5</sup> Selective oxidation of phenols is limited to those bearing substituents at their 2- and 6-positions.<sup>6</sup> The representative results of the oxidation of phenols with *t*-BuOOH are summarized in Table 1. Various phenols bearing para substituents can be converted into the corresponding *tert*-butyldioxy dienones selectively.

The catalytic activity of various metal complexes was examined for the oxidation of *p*-cresol (**1a**) with *t*-BuOOH. RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> has proved to be the most effective catalyst for the selective formation of 4-(*tert*-butyldioxy)-4-methyl-2,5-cyclohexadienone (**2a**). Other ruthenium catalysts such as RuCl<sub>3</sub>·*n*H<sub>2</sub>O gave satisfactory results. A typical experimental procedure is as follows. To a solution of **1a** (0.652 g, 6.0 mmol)

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**Table 1.** Ruthenium-Catalyzed Oxidation of Phenols with *t*-BuOOH<sup>a</sup>

entry	phenol	product <sup>b</sup>	yield, <sup>c</sup> %
1			85 <sup>d</sup>
2			86 <sup>d</sup>
3			78
4			91 <sup>d</sup>
5			82
6			87
7			77
8			91
9			71
10			68 <sup>d</sup>
11	<b>4</b>	<b>5</b>	85 <sup>d</sup>
12	<b>7</b>	<b>8</b>	89 <sup>d</sup>

<sup>a</sup> The reaction was carried out as described in the text. <sup>b</sup> The structure of the product was determined on the basis of the IR, NMR, and mass spectra and analytical data. <sup>c</sup> Isolated yield. <sup>d</sup> Benzene was used as a solvent.

and RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (0.173 g, 0.18 mmol) in ethyl acetate (6.0 mL) was added a 3.30 M solution of *t*-BuOOH in dry benzene (7.3 mL, 24.0 mmol) dropwise with stirring at room temperature over a period of 2 h. After stirring for an additional 3 h, removal of excess *t*-BuOOH upon treatment with a solution of sodium bisulfite, followed by short column chromatography (Florisil), gave the peroxide **2a** (1.01 g, 85%).

The oxidation can be rationalized by assuming hydrogen abstraction from phenol by the oxoruthenium intermediate<sup>4</sup> derived from RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> and *t*-BuOOH, to afford a phenoxy radical–Ru<sup>III</sup>(OH) intermediate. Electron transfer from the phenoxy radical to ruthenium gives a cationic intermediate, which undergoes nucleophilic reaction with the second molecule of *t*-BuOOH, to give *tert*-butyldioxy product **2**, water, and the ruthenium(II) complex to complete the catalytic cycle. Selective formation of **2** is due to fast single electron transfer<sup>7</sup> to ruthenium from the phenoxy radical, to form the cationic intermediate before radical couplings can occur.

4-(*tert*-Butyldioxy)cyclohexadienones **2** thus obtained are versatile synthetic intermediates. As an example, we want to show a novel, convenient method for TiCl<sub>4</sub>-promoted transformation of **2** to 2-substituted quinones **3**. Quinones are an important class of compounds in view of their wide spectrum of biological activities<sup>8</sup> and usefulness as synthetic intermediates;<sup>9</sup> however, synthetic reactions of substituted quinones are limited to few cases.<sup>10–15</sup>

A typical procedure for the synthesis of quinones is as follows. To a solution of TiCl<sub>4</sub> (0.6 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) was added a solution of **2a** (0.119 g, 0.5 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) dropwise with stirring over a period of 30

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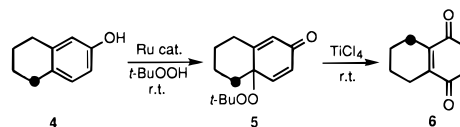
**Table 2.** TiCl<sub>4</sub>-Promoted Transformation of *tert*-Butyldioxy dienones to 2-Substituted Quinones<sup>a</sup>

entry	peroxide	conditions	quinone	yield, <sup>b</sup> %
1		25°C, 1 h		82
2		-15°C, 4 h		86
3		-78°C, 0.5 h		93
4		-78°C, 0.5 h		91
5		0°C, 1 h		93
6		-78°C, 0.5 h		93

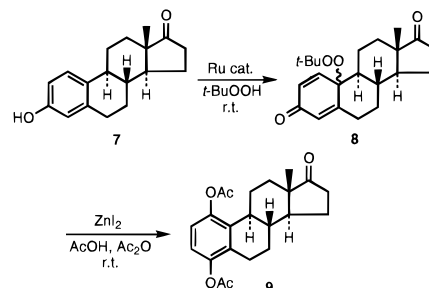
<sup>a</sup> The reaction was carried out as described in the text. <sup>b</sup> Isolated yield.

min at -78 °C. After the mixture was stirred for an additional 1 h at room temperature, usual workup followed by chromatography on silica gel (hexane:EtOAc = 10:1) gave 2-methyl-*p*-benzoquinone (**3a**) in 82% yield. Representative results are summarized in Table 2. The TiCl<sub>4</sub>-promoted reactions of 4-phenyl- and 4-benzyl-(*tert*-butyldioxy) dienones were complete within 0.5 h at -78 °C (entries 3 and 4), while those possessing 4-methyl- and 4-isopropyl substituents occurred at 25 and -15 °C (entries 1 and 2). The migratory aptitude of the substituents of **2** is in the order Ph ≈ PhCH<sub>2</sub> > *i*-Pr > Me >> CH<sub>2</sub>CO<sub>2</sub>Me. Importantly, disubstituted quinones can be obtained selectively (entries 5 and 6). The reaction of peroxide **5**, derived from bicyclic phenol **4** (85%), gave bicyclic quinone

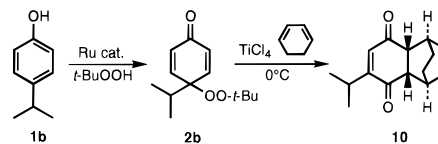
**6** (99%), where the carbon at the 4-position of the cyclohexadienone ring migrates to the 2-position.



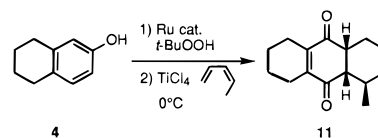
It is noteworthy that the treatment of a diastereomeric mixture of the peroxide **8** (56:44), which was derived from the oxidation of the estrone **7** (89%), with ZnI<sub>2</sub> in a mixture of acetic anhydride and acetic acid gave the diacetate **9** in 55% yield.



An additional application of the transformation of phenols is illustrated by sequential migration-Diels-Alder reactions. Thus, the treatment of **2b**, derived from **1b**, with TiCl<sub>4</sub> in the presence of cyclohexadiene gave bicyclic compound **10** (78%) selectively.



Similar one-pot reaction of *tert*-butyldioxy dienone **5** in the presence of *cis*-1,3-pentadiene gave *cis*-fused octahydroanthraquinone **11** (73%). It can clearly be seen that the two-step synthesis of **11** from **4** shows great promise for further synthetic applications.



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**Supporting Information Available:** IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectral data for products of ruthenium-catalyzed oxidation of phenols and TiCl<sub>4</sub>-induced migration reactions of peroxides (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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