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Site-selective Oxidative Dearomatization of Phenols and Naphthols into *ortho*-Quinols or Epoxy *ortho*-Quinols using Oxone as the Source of Dimethyldioxirane

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Abstract. A novel reactivity of dimethyldioxirane, generated *in situ* from Oxone and acetone, with substituted phenols and naphthols is reported. This methodology allowed the synthesis of *ortho*-quinols or epoxy *ortho*-quinols from a site-selective oxidative dearomatization process, with good yields under very mild conditions. A short total synthesis of natural product lacinilene C methyl ether is also described using this process as the key step.

Keywords: Oxidative dearomatization; dimethyldioxirane; Oxone; *ortho*-quinols; epoxy *ortho*-quinols

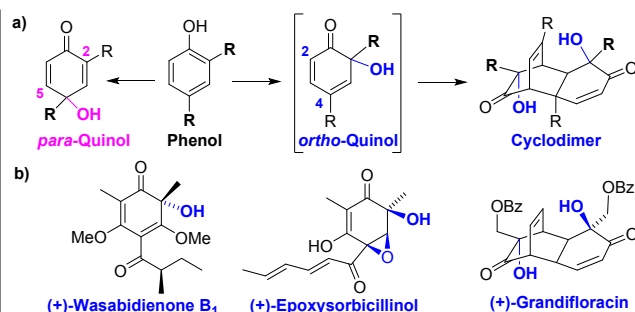


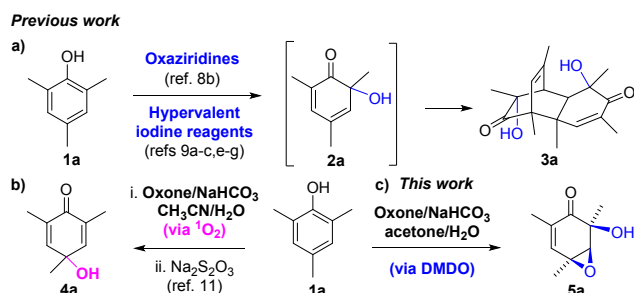
Figure 1. a) *para*-Quinols and *ortho*-quinols / cyclodimers from the oxidative dearomatization of phenols. b) Examples of natural *ortho*-quinol, epoxy *ortho*-quinol and cyclodimer.

The oxidative dearomatization of phenols is a unique and versatile strategy for obtaining synthetically useful compounds such as *para*- and *ortho*-quinols (Figure 1a).¹ The structure of cyclohexa-2,5- or 2,4-dienone of these derivatives allows further functionalization on different positions of the ring in a very regioselective manner opening access to several complex natural products and biologically active compounds.² It is evident that the chemistry of *para*-quinols is more abundant than that of *ortho*-quinols which are less stable, undergoing Diels-Alder dimerizations, rendering the corresponding cyclodimers (Figure 1a).^{1,2} Nevertheless, *ortho*-quinols have the advantage over *para*-quinols that they are inherently chiral bearing a stereogenic center at C-6. Moreover, *ortho*-quinols and their [4+2] cyclodimers also constitute the main structural elements of many natural products (Figure 1b) such as wasabidienone B₁,³ epoxysorbicillinol⁴ and grandifloracin.⁵

The transformation of phenols and naphthols into the corresponding *ortho*-quinol derivatives has been investigated by using (oxo)- or (peroxo)metal species,⁶ selenium compounds,⁷ oxaziridines,⁸ and hypervalent iodine compounds.⁹ Nevertheless, new and environmentally friendly strategies for their site-selective synthesis under mild conditions still represents a synthetic challenge.¹⁰

If we consider the oxidative dearomatization of phenol **1a** with oxaziridines^{8b} or hypervalent iodine reagents^{9a-c,g} (Scheme 1a), only the cyclodimer **3a** was obtained. When the reaction of **1a** is performed with Oxone/NaHCO₃/CH₃CN, as source of singlet oxygen (¹O₂), followed by reduction with Na₂S₂O₃, the *para*-quinol **4a** was formed (Scheme 1b).¹¹ In this work (Scheme 1c), we report that **1a**, in the presence of Oxone/NaHCO₃/acetone, as source of dimethyldioxirane (DMDO), provides the epoxy *ortho*-quinol **5a** resulting after epoxidation of the initially formed *ortho*-quinol **2a**. The scope and usefulness of the methodology is demonstrated with the site-selective oxidative dearomatization of several 2,4,6-trisubstituted phenols, 2-substituted 1-naphthols and 1-substituted-2-naphthols, including the total synthesis of the natural product lacinilene C methyl ether.

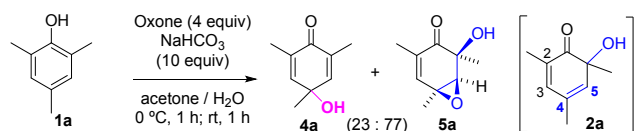
Oxone, a very cheap commercially available triple salt (2KHSO₅·KHSO₄·K₂SO₄), is nowadays a popular reagent for different oxidations¹² and very commonly used for the generation of dioxiranes,¹³ non-metal ecofriendly electrophilic oxygen transfer agents which are the reagents of choice for most epoxidation reactions due to its substrate-induced selectivity, specificity, and reactivity under mild conditions.¹⁴



Scheme 1. Oxidative dearomatizations of 2,4,6-trimethylphenol (**1a**): a) Previous synthesis of cyclodimer **3a** using oxaziridines or hypervalent iodine reagents. b) Previous synthesis of *para*-quinol **4a** using Oxone in CH₃CN. c) This work: synthesis of epoxy *ortho*-quinol **5a** using Oxone in acetone.

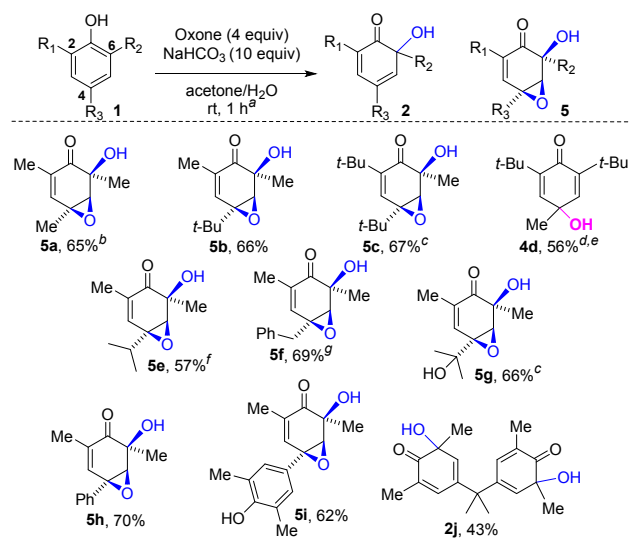
Although several reactions of mono- or di-substituted phenols with DMDO have been reported, all of them provided complex mixtures of oxidized compounds, mainly quinones, in low to moderate yields.¹⁵ A previous study with differently substituted phenols showed us that the best results in terms of selectivity and isolated yields were obtained with 2,4,6-trisubstituted phenols. For this reason, we chose phenol **1a** as the model to optimize the experimental conditions to perform the oxidative dearomatization process (see SI).

Thus (Scheme 2), after slow addition (1 hour)^{16,17} of an aqueous solution of Oxone (4 equiv) into a solution of phenol **1a** and 10 equiv of NaHCO₃ in acetone/water at 0 °C followed by stirring 1 hour at rt, a 23:77 mixture of *para*-quinol **4a** and epoxy *ortho*-quinol **5a** was formed. After chromatographic separation, it was possible to isolate a 20% yield of *para*-quinol **4a**, arising from the oxidative dearomatization of phenol **1a** at the *para* position and a 65% yield of epoxy *ortho*-quinol **5a**,¹⁸ probably resulting from the epoxidation of the initially formed *ortho*-quinol **2a**. This epoxidation was completely regio- (only the C4-C5 double bond of **2a** reacted) and diastereoselective (only the epoxyde *cis* to the OH group was formed).¹⁹ This high selectivity was probably directed by the allylic hydroxy group present in the *ortho*-quinol intermediate **2a**.²⁰ It was not possible to isolate neither the *ortho*-quinol **2a** nor the cyclodimer **3a** even in the presence of less equivalents of reagents, thus indicating that, under our conditions, the epoxidation of the initially formed *ortho*-quinol **2a** was faster than the common cyclodimerization process.



Scheme 2. Site-selective oxidative dearomatization of 2,4,6-trimethylphenol (**1a**) with Oxone in acetone.

In order to evaluate the scope of this oxidative dearomatization, several 2,4,6-trisubstituted phenols **1** were utilized as starting materials (Scheme 3).

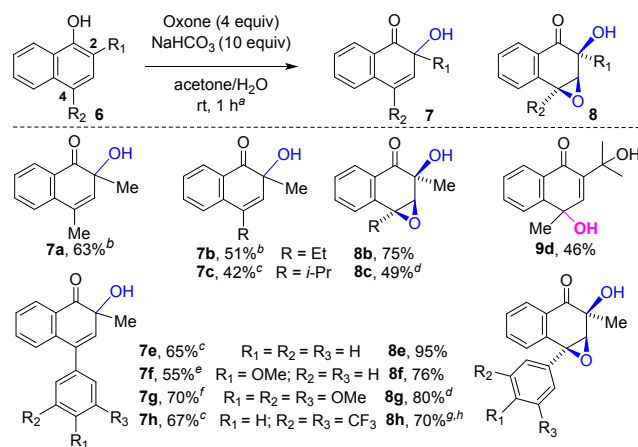


Scheme 3. Scope of the oxidative dearomatization of 2,4,6-trisubstituted phenols (**1**) with Oxone in acetone. ^aIsolated yields. ^bOxone addition at 0 °C and stirring 1 hour at rt. ^c6 equiv of Oxone, 15 equiv of NaHCO₃. ^d8 equiv of Oxone, 20 equiv of NaHCO₃. ^e77% conversion. ^fFrom a 82:18 mixture of **5e** and *p*-quinol **4e**. ^gFrom a 80:20 mixture of **5f** and *p*-quinol **4f**.

When phenol **1b**, bearing a *tert*-butyl group at the *para* position, was submitted to the oxidative dearomatization conditions shown in Scheme 3, the corresponding epoxy *ortho*-quinol **5b** was exclusively obtained in 66% yield. In the case of phenol **1c**, with two *tert*-butyl groups at the *ortho* and *para* positions, a higher excess of reagents was necessary to consume the phenol furnishing only epoxy *ortho*-quinol **5c** in 67% yield. The reaction of phenol **1d**, with two bulky *tert*-butyl groups at the *ortho* positions, needed 8 equiv of Oxone and 20 equiv of NaHCO₃ for a 77% conversion giving the *para*-quinol **4d** (56% isolated yield). In the case of other phenols **1e-g**, bearing alkyl substituents with different steric hindrance at the *para* positions, the epoxy *ortho*-quinols were obtained as majors (**5e**, 57%; **5f**, 69%), with a little amount of the corresponding *p*-quinols, or as the sole compound (**5g**, 66% yield). When the oxidative dearomatization was performed with the *para*-phenyl substituted phenol **1h**, the epoxy *ortho*-quinol **5h** was exclusively formed in 70% yield (Scheme 3). In the case of *bis*-phenol **1i** only the formation of epoxy *ortho*-quinol **5i** was observed (62% yield) after oxidative dearomatization and epoxidation of one of the phenol rings of **1i**, even in the presence of excess of reagents. Finally, the reaction of *bis*-phenol **1j** afforded only *bis* *ortho*-quinol **2j** (43% isolated yield), as an equimolecular mixture of diastereoisomers, after oxidative dearomatization of the two phenol rings without observing any epoxidation even in the presence of excess of reagents.

This strategy of oxidation was also successfully employed for the hydroxylative dearomatization of 1-naphthols (Scheme 4). Initially, the reaction of 2-substituted derivatives without substitution at C-4 gave mixtures of epoxy *ortho*-quinols and naphthoquinones. For this reason, several 2-4-

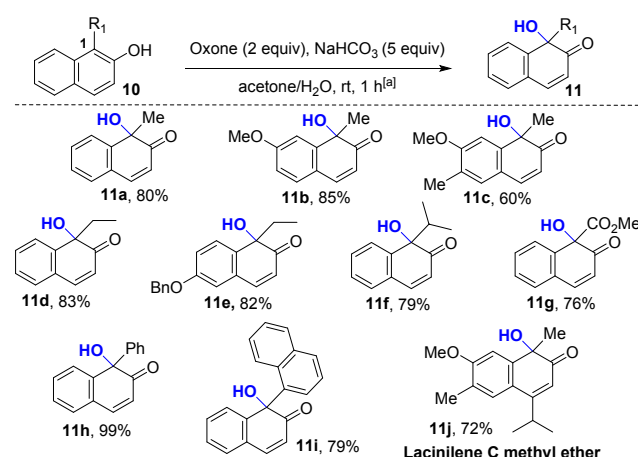
disubstituted-1-naphthols were prepared and submitted to the conditions shown in Scheme 4. Thus, the oxidative dearomatization of 2,4-dimethyl-1-naphthol (**6a**) afforded exclusively *ortho*-quinol **7a**²¹ in 63% isolated yield. This result was noteworthy evidencing that in these naphtholic systems the *ortho* position was much more reactive than the *para* position because we could not detect the corresponding *para*-quinol (observed in the case of some phenol derivatives, see Scheme 3). In this particular case, we could not detect the corresponding epoxy *ortho*-quinol, even in the presence of a higher excess of reagents.



In the case of other naphthols **6b-c** with ethyl or *iso*-propyl groups at the *para* positions, the epoxy *ortho*-quinols could be obtained as the unique compounds, under our standard conditions (**8b**, 75% yield), or using excess of reagents (**8c**, 49% yield). The corresponding *ortho*-quinols **7b** (51% yield) and **7c** (42% yield) could be isolated using less amount of reagents. When the reaction was performed on naphthol **8d**, bearing a bulky dimethylcarbinol at C-2, the *ortho*-oxidation was completely suppressed and the *para*-quinol **9d** was obtained, as the unique compound, in 46% isolated yield (Scheme 4). In the case of the reaction of 4-aryl substituted naphthols **6e-h**, under the standard conditions or excess of reagents (Scheme 4), the epoxy *ortho*-quinols **8e-h** were exclusively obtained (70–95% yields) whereas using less amount of reagents *ortho*-quinols **7e-h** could be isolated in 55–70% yields.

Finally, our oxidative dearomatization method was also applied to several 1-substituted-2-naphthols **10** affording exclusively the corresponding *ortho*-quinols in good to excellent isolated yields (Scheme 5). Thus, the reaction of 1-methyl-2-naphthol **10a** with 2 equiv

of Oxone and 5 equiv of NaHCO₃ in acetone gave rise to *ortho*-quinol **11a** in 80% isolated yield.



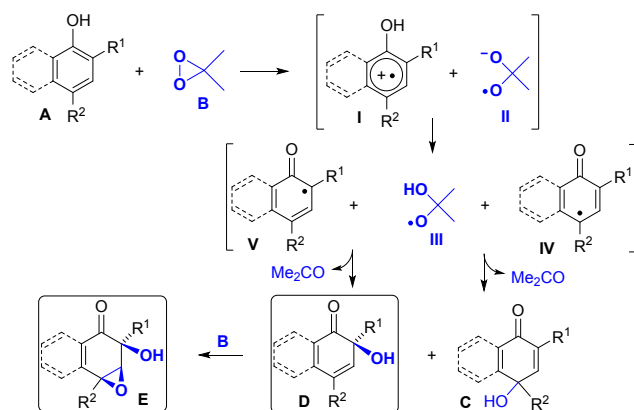
Scheme 5. Scope of the oxidative dearomatization of 1-substituted-2-naphthols (**10**) with Oxone in acetone. ^aIsolated yields.

Other 2-naphthols **10b-f**, with methyl, ethyl or *iso*-propyl groups at C-1, behaved in a similar way to give *ortho*-quinols **11b-f** in 60–85% yields. Moreover, the reaction of 2-naphthols **10g-i**, with an ester or aryl groups at C-1, also furnished *ortho*-quinols **11g-i** with good to excellent yields (76–99%). Finally, in order to demonstrate the usefulness of our methodology, the antibacterial natural product lacinilene C methyl ether **11j**^{22,23} could be synthesized by oxidative dearomatization of 2-naphthol **10j**, in 72% yield. The total synthesis was accomplished in only 8 steps from commercially available 7-methoxy-2-naphthol (see SI) and to the best of our knowledge is the shortest up to date.

To get insight into the possible mechanism and to demonstrate that DMDO was the oxidizing agent involved, we performed two oxidations using an acetone solution of isolated DMDO.²⁴ Thus, the reactions of naphthol **10a** and *ortho*-quinol **7e** with isolated DMDO, after 1h at rt, furnished *ortho*-quinol **11a** (98% yield) and epoxy *ortho*-quinol **8e** (86% yield), respectively. Though in most dioxirane oxidations a somewhat concerted oxenoid insertion has been suggested to explain the possible mechanism, some studies on the DMDO oxidation of phenols and 1,4-hydroquinones also suggested electron transfer mechanisms.^{15a,b} Taking into account these precedents and our own results, we propose the mechanism depicted in Scheme 6.

Initially, the process would be triggered by a one-electron transfer between the phenol or naphthol **A** and DMDO (**B**) to afford phenoxyl cation-radical **I** and anion-radical **II**. Next, the proton transfer from **I** to **II** would result in radical **III** and C-centered phenoxyl radicals **IV** (*para* position) and **V** (*ortho* position). Finally, the reaction of radicals **III** and **IV** with concomitant loss of acetone would afford *para*-quinols **C** whereas **III** and **V** would furnish *ortho*-quinols **D** or

epoxy *ortho*-quinols **E**, after selective epoxidation of **D** with more DMDO. The oxidative dearomatization at the *para* position (evolution of radical **IV**) is the only when R^1 is a bulky substituent (*t*-Bu or dimethylcarbinol) which stabilizes radical **V**. On the other hand, when R^1 is a Me group, the *ortho* oxidation (evolution of radical **V**) is the major pathway when R^2 is a Me, *i*-Pr or Bn group and unique when R^2 is a *t*-Bu, dimethylcarbinol or aryl substituents, which strongly stabilize radical **V**. Finally, in the case of substituted 1-naphthols, the *ortho* selectivity is enhanced with respect to substituted phenols probably due to the greater stabilization of radical **IV** by the presence of the additional aromatic ring leading to the unique evolution through radical **V**.



Scheme 6. Mechanistic proposal.

In summary, we have developed a quite general highly site-selective oxidative dearomatization of substituted phenols and naphthols from an ecofriendly procedure which uses, as the final oxidant, dimethyldioxirane generated *in situ* with Oxone/ NaHCO_3 /acetone. Depending on the starting material, the corresponding *ortho*-quinols, including natural product lacinilene C methyl ether, or epoxy *ortho*-quinols could be obtained in good yields (up to 99%) under very mild conditions.

Experimental Section

General remarks.

Melting points were obtained in open capillary tubes and are uncorrected. ^1H - and ^{13}C -NMR spectra were recorded in CDCl_3 at 300 and 75 MHz, respectively. All reactions were monitored by thin layer chromatography that was performed on pre-coated sheets of silica gel 60, and flash column chromatography was done with silica gel 60 (230-400 mesh) of Merck. Eluting solvents are indicated in the text. The apparatus for inert atmosphere experiments was dried by flaming in a stream of dry nitrogen. The use of water Type I (ultrapure Milli-Q water), with a resistivity >18 ($\mu\Omega\cdot\text{cm}$), was specified. CH_2Cl_2 , THF and CH_3CN were dried over 4Å molecular sieves. All other reagent quality solvents were used without purification.

Method A: General procedure for the oxidative dearomatization at room temperature.

NaHCO_3 and the corresponding phenol or naphthol derivative were dissolved in acetone (0.1 M) and Milli-Q water (0.1 M). A solution of Oxone in Milli-Q water was added dropwise to the mixture at rt for 1 h, using a syringe pump (see SI). The crude mixture was extracted with DCM (x3), dried over MgSO_4 and concentrated. The residue was purified by flash chromatography (the specific conditions are indicated in each case) to give the desired product.

(1*R**,2*S**,6*R**)-6-(*tert*-Butyl)-2-hydroxy-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**5b**)

Following Method A, epoxy *ortho*-quinol **5b** (30.3 mg, 0.14 mmol, 66% yield) was obtained as a colorless oil from 4-(*tert*-butyl)-2,6-dimethylphenol (**1b**) (40.0 mg, 0.22 mmol), NaHCO_3 (184.8 mg, 2.20 mmol) and a solution of Oxone (275.9 mg, 0.90 mmol) in Milli-Q water (4.4 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1). ^1H NMR δ 6.98–6.94 (m, 1H), 3.67 (d, J = 0.8 Hz, 1H), 3.66 (s, 1H), 1.89 (d, J = 1.5 Hz, 3H), 1.30 (s, 3H), 1.04 (s, 9H). ^{13}C NMR δ 199.9, 141.8, 136.6, 74.6, 62.7, 59.4, 32.1, 25.5, 25.0, 16.1. HRMS (ESI): calculated for $\text{C}_{12}\text{H}_{18}\text{O}_3\text{Na}$ ($[\text{M}+\text{Na}]^+$) 233.1148, found 233.1146.

2-Hydroxy-2,4-dimethylnaphthalen-1(2*H*)-one (**7a**)

Following Method A, *ortho*-quinol **7a** (13.7 mg, 0.07 mmol, 63% yield) was obtained, as a white solid, from 2,4-dimethylnaphthalen-1-ol (**6a**) (19.8 mg, 0.11 mmol), NaHCO_3 (48.7 mg, 0.58 mmol) and a solution of Oxone (71.3 mg, 0.23 mmol) in Milli-Q water (2.3 mL). The crude mixture was purified by flash chromatography column (heptane/EtOAc : 9/1). Mp: 104.0–105.0 $^\circ\text{C}$. ^1H NMR δ : 7.73 (dd, J = 7.6, 1.1 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 7.46 (td, J = 7.5, 1.3 Hz, 1H), 7.36 (td, J = 7.6, 1.4 Hz, 1H), 6.13 (d, J = 1.0 Hz, 1H), 3.73 (s, 1H), 2.38 (d, J = 1.2 Hz, 3H), 1.54 (s, 3H). ^{13}C δ : 204.5, 154.0, 145.0, 130.6, 129.7, 127.7, 125.7, 125.6, 122.0, 77.0, 33.5, 20.6. HRMS (ESI): calculated for $\text{C}_{12}\text{H}_{12}\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$) 211.0735, found 211.0728.

1-Hydroxy-1-phenylnaphthalen-2(1*H*)-one (**11h**)

Following Method A, *ortho*-quinol **11h** (21.0 mg, 0.09 mmol, 99% yield) was obtained, as a white solid, from 1-phenylnaphthalen-2-ol (**10h**) (19.9 mg, 0.10 mmol), NaHCO_3 (42.0 mg, 0.50 mmol) and a solution of Oxone (55.8 mg, 0.20 mmol) in Milli-Q water (0.9 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc 9/1). Mp: 115.2–115.8 $^\circ\text{C}$. ^1H NMR δ : 7.65–7.61 (m, 3H), 7.48–7.46 (m, 2H), 7.46–7.41 (m, 5H), 7.40–7.35 (m, 6H), 7.24 (s, 15H), 6.15 (d, J = 9.9 Hz, 3H), 4.63 (s, 3H). ^{13}C NMR δ : 202.5, 146.4, 143.6, 141.3, 131.0, 129.7, 129.3, 128.7, 128.5, 128.3, 127.8, 125.7, 123.0, 80.4. HRMS (ESI): calculated for $\text{C}_{16}\text{H}_{12}\text{O}_2\text{Na}$ ($[\text{M}+\text{Na}]^+$) 259.0729, found 259.0720.

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