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Synthesis of 2-substituted quinones, vitamin K_3, and vitamin K_1 from *p*-cresol. $BF_3{\cdot}OEt_2$-catalyzed methyl migration of 4-*tert*-butyldioxycyclohexadienones

Shun-Ichi Murahashi [a,b,*], Akiko Fujii [a], Yasutaka Inubushi [a], Naruyoshi Komiya [a]

[a] Department of Chemistry, Graduate School of Engineering Science, Osaka University, 1-3, Machikaneyama, Toyonaka, Osaka 560-8531, Japan
[b] Department of Applied Chemistry, Okayama University of Science, 1-1, Ridai-cho, Okayama, Okayama 700-0005, Japan

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ABSTRACT

$BF_3{\cdot}OEt_2$-catalyzed methyl group migration of 4-methyl-4-*tert*-butyldioxycyclohexadienone, which is obtained by ruthenium-catalyzed oxidation of *p*-cresol with *tert*-butyl hydroperoxide, in hexafluoro-2-propanol/toluene gave toluquinone efficiently. The reaction can be applied to the regio-selective short-step syntheses of vitamin K_3 and vitamin K_1 from *p*-cresol.

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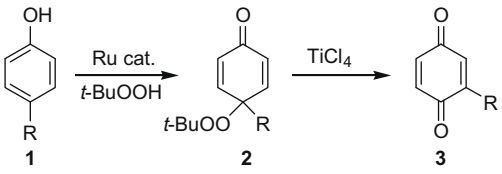
Biomimetic oxidation reaction is of importance in view of its biological and synthetic aspects.[1] Oxidative transformation of phenols is highly useful for organic synthesis; however, oxidation of phenols proceeds non-selectively, giving a variety of side reaction products, derived from radical coupling and over-oxidation.[2] Recently, we discovered that $RuCl_2(PPh_3)_3$-catalyzed oxidation of *p*-substituted phenols with *t*-BuOOH proceeds selectively to give the corresponding *t*-butyldioxycylohexadienones **2**.[3] This oxidation reaction provides a convenient method for direct and selective access to 2-substituted quinones **3** from *p*-substituted phenols **1**.[3]

We report the migratory aptitude of alkyl and aryl groups of *t*-butyldioxycyclohexadienones and the method for selective migration of the most difficult methyl group. Selective synthesis of substituted quinones is of importance in view of organic synthesis and pharmaceutical science.[4] Furthermore, the migration is important for the construction of new carbon–carbon bond via reconstruction of carbon skeletons.[5] Our method is highly useful because the large-scale synthesis can be carried out with ease starting from commercially available phenols.

The ruthenium-catalyzed oxidation of *p*-substituted phenols **1** with *tert*-butyl hydroperoxide gives the corresponding 4-*tert*-butyldioxy-4-substituted cyclohexadienones **2**, selectively. Subsequent alkyl group rearrangement of **1** in the presence of Lewis acids such as $TiCl_4$ gives the corresponding 2-substituted benzoquinones **3** (Eq. 1).



(1)

In order to investigate the scope of this alkyl and aryl group migration, we focused on the migratory aptitude of alkyl and aryl groups. We have found that alkyl group migration of 4-substituted-4-*tert*-butyldioxycyclohexadienone proceeds efficiently in the presence of stoichiometric or even catalytic amount of $BF_3{\cdot}OEt_2$ in HFIP (hexafluoro-2-propanol). As seen in the usual cationic rearrangement, methyl group shows very low migratory aptitude in comparison with other secondary or tertiary alkyl and aryl groups.

The effect of Lewis acids on this reaction was studied for 2-*tert*-butyldioxy-4-cyclohexanones bearing various alkyl groups at the 4-position. As shown in Table 1, the rearrangement reactivity is dependent on the substituent of **2**. When the substituent is a resonance-stabilized group such as phenyl or an electron-donating group such as $PhCH_2$ or *i*-Pr, the migration reaction proceeds efficiently to give **3** upon treatment with $TiCl_4$ (entries 1–3).[3] However, substituents such as CH_3CH_2 and CH_3 show low migratory aptitude (entries 4 and 5). This indicates that the migratory aptitude of the substituent of **2** is in the order Ph > $PhCH_2$ > *i*-Pr ≫ Et > Me in this reaction.

In order to improve the yield of toluquinone (**3e**), various Lewis acids such as $AlCl_3$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ were examined (Table 2); however, none of them promoted the reaction at all (entries 1–4). Although $BF_3{\cdot}OEt_2$-promoted reaction of **2e** did not proceed at all in CH_2Cl_2 (entry 4), the reaction in a fluorinated solvent such as 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) takes place efficiently to give 2-*tert*-butyl-5-methyl-1,4-benzoquinone (**4**) instead of toluquinone (**3e**) (entry 5). Such remarkable solvent effect may be due to the ability of perfluorinated solvent such as HFIP to stabilize cationic intermediates during the migration. When two-component solvent of HFIP/toluene was used, only the product **3e** was obtained in 81% yield, where *t*-Bu group was trapped by toluene to give *p*-*tert*-butyltoluene (entry 6). Furthermore, we found that only catalytic amount of $BF_3{\cdot}OEt_2$ was enough to complete the reaction (entry 7).

* Corresponding author.
E-mail address: mura@chem.es.osaka-u.ac.jp (S.-I. Murahashi).

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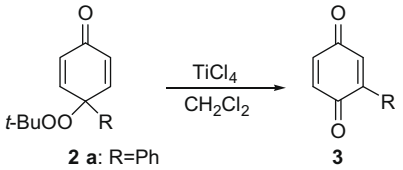
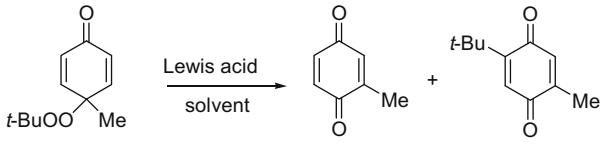
Table 1
$TiCl_4$-promoted rearrangement of *t*-butyldioxy-4-alkylcyclohexadienone (**2**)[a]



Entry	Substrate	Time (h)	Yield[b] (%)
1	**2a**	0.5[c]	93
2	**2b**	0.5[c]	91
3	**2c**	4[d]	86
4	**2d**	1	42[e]
5	**2e**	1	23[e]

[a] A mixture of **2** (1.0 mmol) and $TiCl_4$ (1.2 mmol) in CH_2Cl_2 (4.0 mL)was stirred at room temperature.
[b] Isolated yield.
[c] −78 °C.
[d] −15 °C.
[e] A mixture of unknown compounds was also formed.

Table 2
Lewis acid-promoted rearrangement of *t*-butyldioxy-4-methylcyclohexadienone (**2e**)[a]

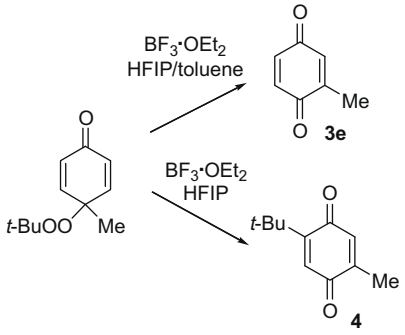


Entry	Lewis acid	Solvent	Time (h)	Yield[c] (%)	
				3e	**4**
1	$TiCl_4$	CH_2Cl_2	1	23[e]	0
2	$AlCl_3$	CH_2Cl_2	24	0[e]	0
3	$SnCl_4$	CH_2Cl_2	24	0[e]	0
4	$BF_3{\cdot}OEt_2$	CH_2Cl_2	24	0[e]	0
5	$BF_3{\cdot}OEt_2$	HFIP	0.5	0	83
6	$BF_3{\cdot}OEt_2$	HFIP/toluene[d]	1	81	0
7[b]	$BF_3{\cdot}OEt_2$	HFIP/toluene[d]	24	84	0

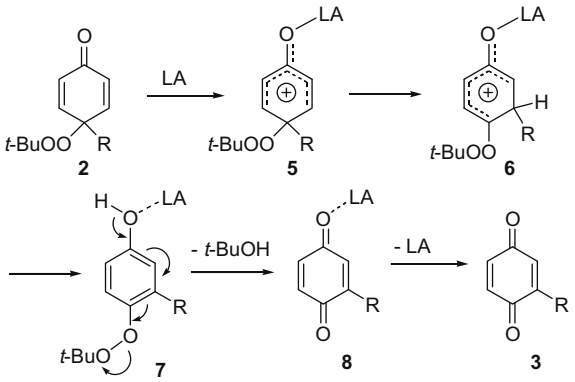
[a] A mixture of **2e** (1.0 mmol) and Lewis acid (1.2 mmol) in a solvent (4.0 mL) was stirred at room temperature.
[b] Catalytic amount (0.12 mmol)of $BF_3{\cdot}OEt_2$ was used.
[c] Isolated yield.
[d] HFIP/toluene = 3:1.
[e] A mixture of unknown compounds was also formed.

The present $BF_3{\cdot}OEt_2$-mediated reaction in HFIP is highly useful for methyl group migration for 4-methyl-4-*tert*-butyldioxycyclohexadienone. By choosing a suitable solvent, two types of products, 5-methyl-2-*tert*-butylbenzoquinone (**4**) and 2-methylbenzoquinone (**3e**), can be obtained selectively (Scheme 1).

The reaction can be rationalized by assuming dienone–phenol rearrangement and subsequent conversion to benzoquinone (Scheme 2). The coordination of the dienone to Lewis acid (LA) would form cationic intermediate **5**. Alkyl group rearrangement (1,2-shift) to give **6** followed by aromatization would result in the formation of **7**. Such mechanisms for dienone–phenol rearrangement are well established for simple dienones.[5a] *p*-Alkyldioxyphenol **7** activated by Lewis acid would be readily converted to **8** by the elimination of *t*-BuOH, which would give benzoquinone **3** and Lewis acid to complete the catalytic cycle. In HFIP solvent, subsequent Friedel–Craft-type reaction of **3** with *t*-BuOH would



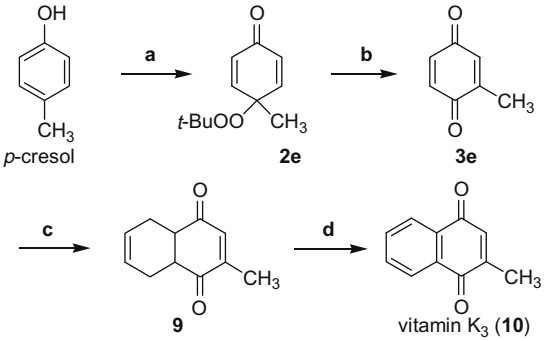
Scheme 1.



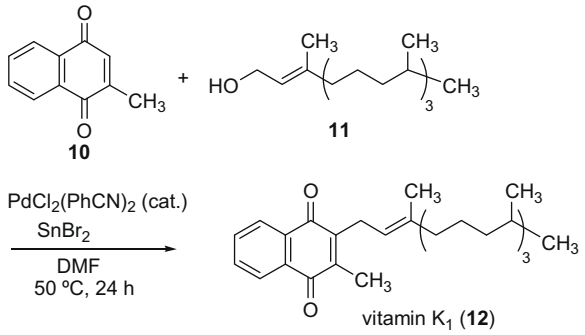
Scheme 2.

take place to give **4**. Actually, we confirmed that $BF_3{\cdot}OEt_2$-promoted alkylation of **3e** with *t*-BuOH gave **4** in 94% yield.

The transformation of *p*-cresol was applied for the synthesis of vitamin K_3,[6] which displays an antihemorrhagic activity and an important starting material for the synthesis of a series of vitamin K as shown in Scheme 3. Thus, the $RuCl_2(PPh_3)_3$-catalyzed oxidation of *p*-cresol with *t*-BuOOH in benzene at room temperature gave 4-*tert*-butyl-4-methylcyclohexadienone (**2e**) in 97% isolated yield. $BF_3{\cdot}OEt_2$-catalyzed reaction of **2e** in HFIP/toluene gave toluquinone **3e** in 84% yield. Diels–Alder reaction of **3e** with 1,3-butadiene in the presence of $Sc(OTf)_3$ catalyst gave **9** (97% yield), which was subsequently dehydrogenated by Pd/C catalyst in acetone to give vitamin K_3 (**10**) in 100% yield. Thus, vitamin K_3 can be obtained by combination of four catalytic reactions in 81% overall yield from *p*-cresol completely without any contamination of



Scheme 3. Reagents and conditions: (a) $RuCl_2(PPh_3)_3$ (1.5 mol%), *t*-BuOOH, C_6H_6, rt, 97%; (b) $BF_3{\cdot}OEt_2$ (10 mol%), HFIP, toluene, rt, 84%; (c) 1,3-butadiene, $Sc(OTf)_3$ (10 mol%), CH_3NO_2, rt, 97%; (d) Pd/C (10 mol%), CH_3COCH_3, reflux, 100%.



Scheme 4.

regio-isomers and others. The preparation of vitamin K_3 has been carried out simply by stoichiometric[7] or catalytic[8] oxidations of 2-methylnaphthalene; however, selective formation without undesired by-product such as 6-methylnaphthoquinone cannot be achieved.[9]

One of the important features of our strategy is the flexibility of the scheme, that is, easy introduction of any substituents at any position, which enables selective synthesis of various vitamin K_3 derivatives with any substituents as shown in Scheme 3.

Vitamin K_3 has been used as an intermediate for the synthesis of vitamin K_1 and K_2.[10] We examined the direct coupling of vitamin K_3 (**10**) and phytol (**11**) to give vitamin K_1 (**12**). Although $BF_3{\cdot}OEt_2$ is not efficient for this purpose, we succeeded in the direct reaction of **10** with **11** using palladium catalyst and tin(II) bromide (Scheme 4).[11] Thus, the reaction of **10** (1.0 mmol) and **11** (2.0 mmol) in the presence of $PdCl_2(PhCN)_2$ (0.1 mmol) and $SnBr_2$ (4.0 mmol) in DMF (3 mL) at 50 °C for 24 h gave **12** in 46% isolated yield.[12] This is the first example for the direct synthesis of vitamin K_1 from the corresponding quinone and allyl alcohol. Further mechanistic study is in progress in our laboratory.

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12. 2,3-Benzo-5-methyl-5-phytylcyclohexane-1,4-dione is also formed in 42% yield as a regioisomer of vitamin K_1. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80–0.88 (m, 12H), 1.03–1.55 (m, 19H), 1.29 (s, 3H), 1.48 (s, 3H), 1.89 (t, J = 7.1 Hz, 2H), 2.28 (dd, J = 14.2 and 7.6 Hz, 1H), 2.46 (dd, J = 14.2 and 7.6 Hz, 1H), 2.84 (d, J = 16.1 Hz, 1H), 3.03 (d, J = 16.1 Hz, 1H), 5.04 (t, J = 7.6 Hz, 1H), 7.68–7.78 (m, 2H), 7.98–8.11 (m, 2H). HRMS (EI) m/z calcd for $C_{31}H_{48}O_2$: 452.3654. Found: 452.3634.