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# Efficient $Co(OAc)_2$-catalyzed aerobic oxidation of EWG-substituted 4-cresols to access 4-hydroxybenzaldehydes

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ABSTRACT

We reported an efficient ligand-free $Co(OAc)_2{\cdot}4H_2O/NaOH/O_2$/ethylene glycol reaction system that enables selective aerobic oxidation of a wide range of substrates covering 2,6-di-EWG-, 2,3,6-tri-EWG-, 2-EWG-, and 2-EWG-6-EDG-substituted 4-cresols into the corresponding 4-hydroxybenzaldehydes. Based on the experimental investigations and well-defined *p*-benzoquinone methides, a plausible reaction mechanism was proposed. Considering the simplicity of the procedure and importance of the products, the methodology was expected to become a favorable and practical tool in related benzylic $C(sp^3)$–H functionalization chemistry.

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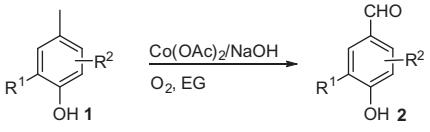
Selective oxidation of 4-cresols into 4-hydroxybenzaldehydes is an important transformation in organic chemistry, since the versatile multifunctional 4-hydroxybenzaldehydes have served as significant chemical feedstocks for pharmaceutical, perfume, dye, and agrochemical industries, as well as other purposes.[1] Although some traditional strategies, like Reimer–Tiemann reaction,[2] glyoxylic acid method,[3] waste-producing oxidation using stoichiometric oxidizing reagents,[4] and electric/electrocatalytic oxidation,[5] have been valid for this kind of aldehyde group formation, tedious separation, serious pollution, sometimes multistep procedures, and harsh reaction conditions did limit their applications. Actually, over recent decades, eco-friendly transition-metal-catalyzed aerobic oxidation of 4-cresols has attracted an intense interest in chemical community in view of their direct benzylic $C(sp^3)$–H oxyfunctionalization, and notable achievements have been acquired.[6–8] However, these precedents are still quite constrained from a practical point of view, due to complex metal-ligand-coordinated catalyst system and possible safety issue associated with the combination of pure $O_2$ and low-boiling flammable solvent.[9] Furthermore, these substrates were strictly confined to 4-cresol[6] and electron-donating group (EDG)-substituted electron-rich 4-cresols.[7,8] By contrast, the aerobic oxidation of 4-cresols bearing the electron-withdrawing group (EWG) has been rarely approached. Therefore, it is necessary, for extending the synthetic scope and utility of the straightforward transformation, to develop a user-friendly and ligand-free transition-metal catalyzed aerobic oxidation. To valorize products and serve practical applications, among the first row of transition metals, inexpensive, lowly toxic, and active cobalt catalyst is highly desirable.

In this context, we attempted to exploit a highly practical $Co(OAc)_2/NaOH/O_2$ reaction system that effects efficient oxygenation of a broad scope of EWG-substituted 4-cresols, including 2,6-di-EWG-, 2,3,6-tri-EWG-, 2-EWG-, and 2-EWG-6-EDG-substituted 4-cresols, into the corresponding 4-hydroxybenzaldehydes (Scheme 1). The ligand-free $Co(OAc)_2$-catalyzed aerobic oxidation enables selective oxyfunctionalization of the benzyl group of EWG-substituted 4-cresols under the mediation of alkaline ethylene glycol (EG). Undoubtedly, it is one of the most important goals in oxidation chemistry that utilization of $O_2$ constitutes a 'green' transformation with water as the only byproduct.[10] In addition, the high-boiling nonflammable EG can effectively avoid latent safety problem.[9]




$R^1$ = EWG; $R^2$ = EWG, H or EDG

**Scheme 1.** $Co(OAc)_2$-catalyzed oxygenation of **1** into **2** in alkaline EG.

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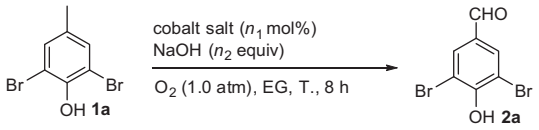
**Table 1**
Selected optimization for the oxygenation of **1a** into **2a**[a]



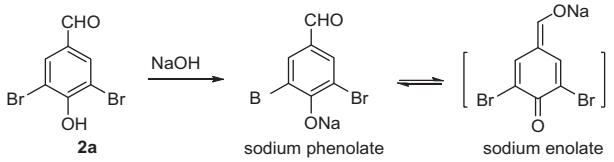

| Entry | Co salt ($n_1$ mol %) | NaOH ($n_2$ equiv) | $T$ (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $CoCl_2$ (3.0) | 1.0 | 50 | Trace |
| 2 | $Co(OAc)_2{\cdot}4H_2O$ (3.0) | 1.0 | 50 | 53 |
| 3 | $Co(OAc)_2{\cdot}4H_2O$ (3.0) | 1.0 | 80 | 76 |
| 4 | $Co(OAc)_2{\cdot}4H_2O$ (3.0) | 0 | 80 | 0 |
| 5 | $Co(OAc)_2{\cdot}4H_2O$ (3.0) | 2.0 | 80 | 90 |
| 6 | $Co(OAc)_2{\cdot}4H_2O$ (3.0) | 3.0 | 80 | 90 |
| 7 | $Co(OAc)_2{\cdot}4H_2O$ (2.0) | 2.0 | 80 | 90 |
| 8 | $Co(OAc)_2{\cdot}4H_2O$ (1.0) | 2.0 | 80 | 90 |
| 9 | $Co(OAc)_2{\cdot}4H_2O$ (0.5) | 2.0 | 80 | 79 |
| 10 | $Co(OAc)_2{\cdot}4H_2O$ (1.0) | 2.0 | 80 | Trace[c] |
| 11 | $Co(OAc)_2{\cdot}4H_2O$ (1.0) | 2.0 | 100 | 90[d] |

[a] Performed with **1a** (1.0 mmol), cobalt salt ($n_1$ mol %), NaOH ($n_2$ equiv), and EG (5 mL), $O_2$ (1.0 atm) for 8 h.
[b] Isolated yield via column chromatography.
[c] Performed under argon atmosphere.
[d] Reaction time of 24 h.

Initially, the model oxidation of 2,6-dibromo-4-cresol (**1a**) into 3,5-dibromo-4-hydroxybenzaldehyde (**2a**) was manipulated in EG with commercially available cobalt salts (3.0 mol %) and NaOH (1.0 equiv) under pure $O_2$ atmosphere (atmospheric pressure, 1.0 atm) for 8 h. Very low yields of the desired **2a** were obtained by employing $CoCl_2$ and other halogenated cobalt salts (Table 1, entry 1, and see Table S1). Then, we turned to commercial organic cobalt salts, the ordinary $Co(OAc)_2{\cdot}4H_2O$ proved to be fruitful giving **2a** in a promising yield of 53% at 50 °C (entry 2). Furthermore, the efficiency of oxidation was remarkably enhanced at an elevated reaction temperature of 80 °C to provide 76% yield (entry 3). On the other hand, no desired product was observed in the absence of NaOH, indicating an essential role of NaOH in initiation of the oxidation (entry 4). Further improved yields were achieved by increasing the amount of NaOH, and 2.0 equiv of NaOH turned out to be adequate to offer the best yield of 90% (entries 5 and 6). More pleasingly, these reactions still worked well to afford **2a** in the excellent yield of 90% when using 2.0 or 1.0 mol % $Co(OAc)_2{\cdot}4H_2O$ (entries 7 and 8, entry 8 as the standard reaction conditions). But, the yield sharply reduced to 79% when the catalyst loading was lowered to 0.5 mol % (entry 9). Besides, only trace of **2a** was observed under anaerobic conditions (entry 10). It was noteworthy that, further screening of solvents showed that the oxidation was generally effective in alcohols, but ineffective in aprotic solvents. These experiments indicated an indispensable mediation of alcohols, and only more polar EG gave the best yield (Table S1).

Impressively, no observable overoxidation product 3,5-di-bromo-4-hydroxybenzoic acid was detected in the oxidation, even elevating reaction temperature and prolonging reaction time (entry 11). We considered that its sodium enolate, derived from the isomerization of sodium phenolate of **2a** via dearomatization-enolization under the alkaline conditions, should account for the highly selective conversion, and synchronously effective protection of the susceptive aldehyde group (Scheme 2).[11]

With the standard reaction conditions in hand, a variety of EWG-substituted hindered 4-cresols **1b–r** were examined to explore the potential scope of the $Co(OAc)_2$-catalyzed oxygenation (Table 2, entries 2–18).[12] Firstly, we were pleased to observe that, similar to the case of entry 1, this simple protocol smoothly oxidized 2,6-dihalogenated 4-cresols **1b** and **1c** into **2b** and **2c** in high yields of 91% and 88%, respectively (entries 2 and 3). Also, *meta*-methyl group-containing 2,6-dibromo-3-methyl-4-cresol




**Scheme 2.** Possible sodium enolate of **2a** under the alkaline conditions.

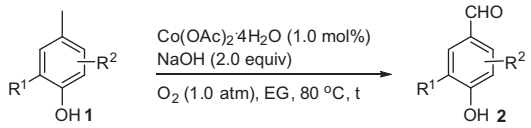
(**1d**) was regioselectively converted into 3,5-dibromo-4-hydroxy-2-methylbenzaldehyde (**2d**) in 86% yield, with the original *meta*-methyl group remaining intact (entry 4). For more electron-deficient 2,3,6-trihalogenated 4-cresols **1e** and **1f**, the desired products **2e** and **2f** were consistently obtained in high yields of 87% and 90%, respectively (entries 5 and 6), under the standard conditions (80 °C, 2.0 equiv of NaOH, 8 h).

As anticipated, in consequence of EDG, the oxidation of 2-EWG-6-EDG-substituted 4-cresols **1g–r** faster proceeded to deliver the corresponding 4-hydroxybenzaldehydes **2g–r** in a short reaction time of 6 h (otherwise consistent conditions: 80 °C, 2.0 equiv of NaOH), with good yields of 82–90% (entries 7–18). Of these, as to more sterically hindered *iso*-butoxy- and *tert*-butyl-substituted 4-cresols **1k** and **1m**, the reactions provided the products **2k** and **2m** with relatively low yields of 83% and 82%, respectively (entries 11 and 13). With respect to the *ortho*-methyl group-containing 2-bromo-6-methyl-4-cresol (**1l**), the oxidation exclusively offered regioselective 4-hydroxybenzaldehydes **2l**, while the original *ortho*-methyl group remained unchanged as well (entry 12).

Next, we focused on the oxygenation of more challenging unhindered 2-EWG-substituted 4-cresols, wherein radical-based coupling side-reactions usually perplexed chemists (entries 19–22).[13] To our delight, with 4.0 equiv of NaOH being employed (otherwise consistent conditions: 80 °C, 8 h), these 2-bromo-, 2-formyl-, and 2-nitro-substituted 4-cresols **1s–v** were successfully converted into the desired 4-hydroxybenzaldehydes **2s–v** in high yields of 87–90%, without obvious coupling side-reactions being observed (entries 19–22). In contrast, the oxidation of the unhindered electron-rich 2-methoxy-4-cresol (**1w**) furnished vanillin (**2w**) with relatively low yields of 53% or 62% in the presence of 4.0 equiv or 6.0 equiv of NaOH (entry 23), under the otherwise consistent conditions (80 °C, 4 h). Therein, the concomitant tar (oligomers), associated with coupling side-reactions, could not be avoided. These facts illustrated that the EWG in unhindered 2-EWG-substituted 4-cresols and the increased amount of NaOH would effectively suppress the undesired couplings. Additionally, 2,6-dimethoxy-4-cresol (**1x**), as a representative of electron-rich hindered 4-cresols, smoothly underwent the oxidation delivering syringaldehyde (**2x**) in a high yield of 91% (entry 24), further demonstrating the practical compatibility of the procedure. As a result of the EDG, complete conversion of readily oxidizable **1w** and **1x** only required a shorter reaction time of 4 h. The results shown in Table 2 indicated an advantage of the oxidation for EWG-substituted 4-cresols: broad scope of substrates including hindered and unhindered 4-cresols. It should be mentioned that **2a** and **2s** are two key intermediates for preparing commercially famous syringaldehyde (**2x**) and vanillin (**2w**), respectively.

Expansive investigations were undertaken to probe the reaction mechanism (Scheme 3). The control experiments showed that the feedstock **1a** gradually produced the desired **2a** via the corresponding ethereal intermediates **3a** (Scheme 3a). Indeed, the isolated ethers **3a** efficiently took part in the further oxidation incurring **2a** (Scheme 3b). Moreover, stoichiometric radical scavenger 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) completely inhibited the reaction, clearly indicating a free radical oxidation process (Scheme 3c). Next, the oxidations of 2-cresol and 4-chloro-2-cresol

**Table 2**
Scope of **1** for $Co(OAc)_2$-catalyzed oxygenation[a]



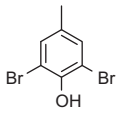
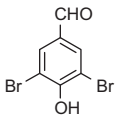
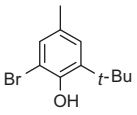
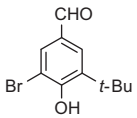
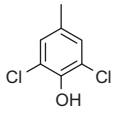
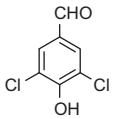
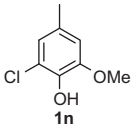
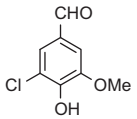
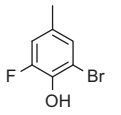
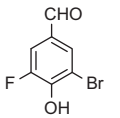
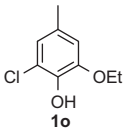
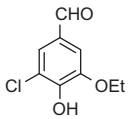
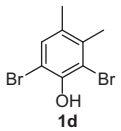
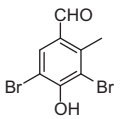
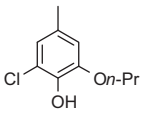
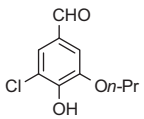
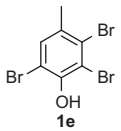
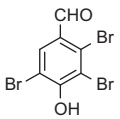
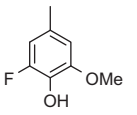
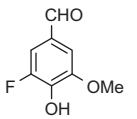
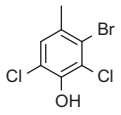
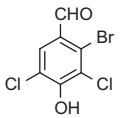
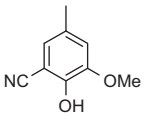
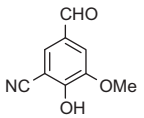
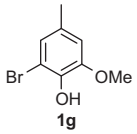
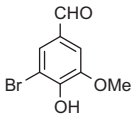
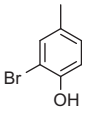
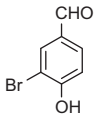
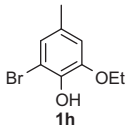
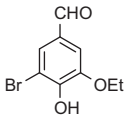
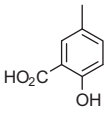
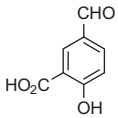
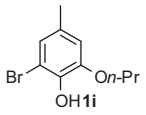
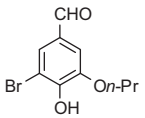
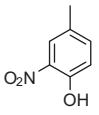
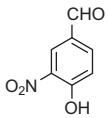
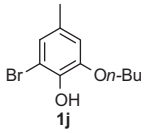
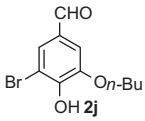
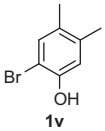
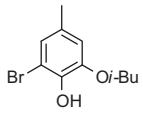
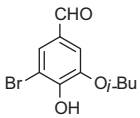
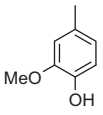
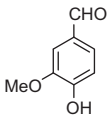
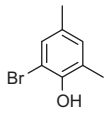
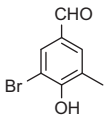
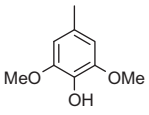
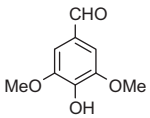
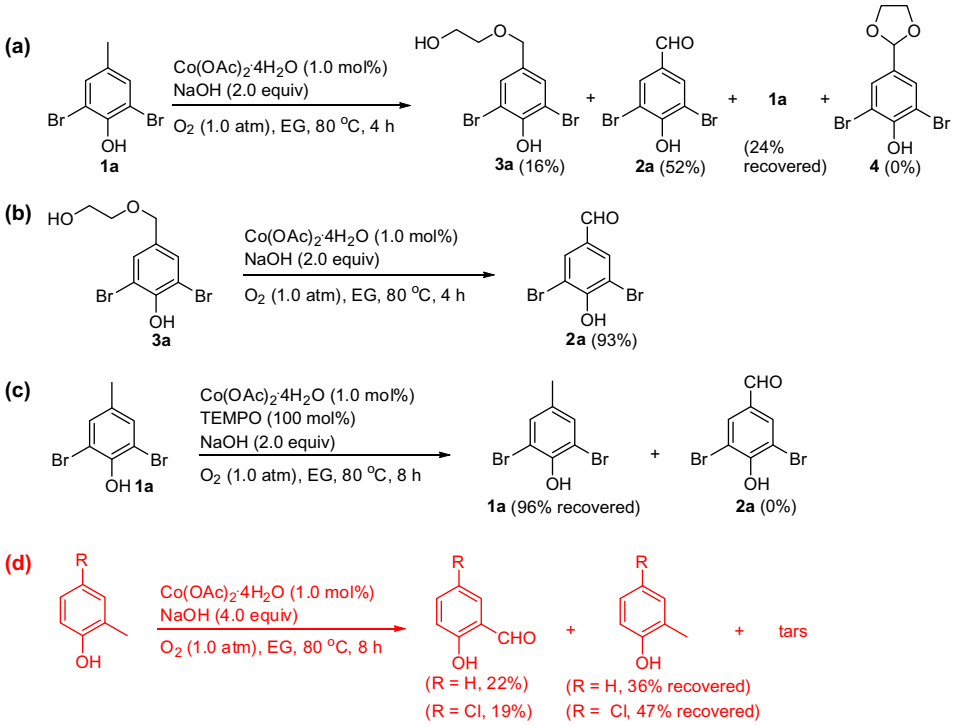

| Entry | Substrate | Product | *t* (h) | Yield[b] (%) | Entry | Substrate | Product | *t* (h) | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  **1a** |  **2a** | 8 | 90 | 13 |  **1m** |  **2m** | 6 | 82 |
| 2 |  **1b** |  **2b** | 8 | 91 | 14 |  **1n** |  **2n** | 6 | 90 |
| 3 |  **1c** |  **2c** | 8 | 88 | 15 |  **1o** |  **2o** | 6 | 89 |
| 4 |  **1d** |  **2d** | 8 | 86 | 16 |  **1p** |  **2p** | 6 | 86 |
| 5 |  **1e** |  **2e** | 8 | 87 | 17 |  **1q** |  **2q** | 6 | 89 |
| 6 |  **1f** |  **2f** | 8 | 90 | 18 |  **1r** |  **2r** | 6 | 86 |
| 7 |  **1g** |  **2g** | 6 | 86 | 19 |  **1s** |  **2s** | 8 | 90[c] |
| 8 |  **1h** |  **2h** | 6 | 87 | 20 |  **1t** |  **2t** | 8 | 89[c] |
| 9 |  **1i** |  **2i** | 6 | 85 | 21 |  **1u** |  **2u** | 8 | 87[c] |
| 10 |  **1j** |  **2j** | 6 | 86 | 22 |  **1v** |  **2v** | 8 | 88[c] |

**Table 2** (*continued*)

| Entry | Substrate | Product | *t* (h) | Yield[b] (%) | Entry | Substrate | Product | *t* (h) | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 11 |  **1k** |  **2k** | 6 | 83 | 23 |  **1w** |  **2w** | 4 | 51[c](62[d]) |
| 12 |  **1l** |  **2l** | 6 | 89 | 24 |  **1x** |  **2x** | 4 | 91 |

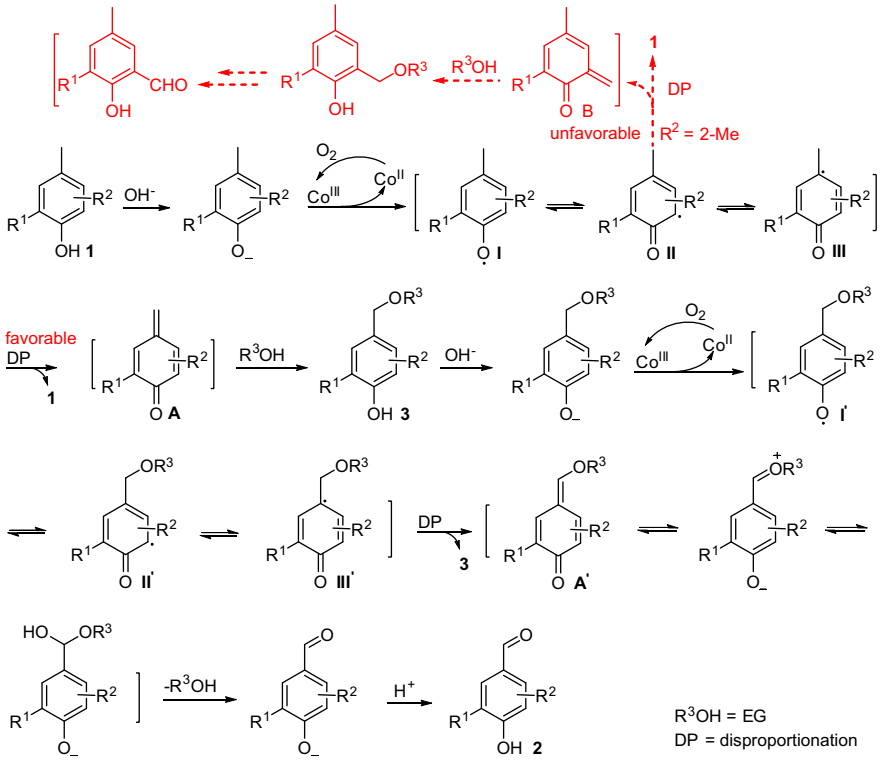
[a] Performed with **1a** (1.0 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.01 mmol), NaOH (2.0 mmol) and EG (5 mL), $O_2$ (1.0 atm) for a specified time (*t*).
[b] Isolated yield via column chromatography.
[c] Performed with NaOH (4.0 mmol).
[d] Performed with NaOH (6.0 mmol).




**Scheme 3.** Mechanistic studies.

gave complex mixtures, including the desired 2-hydroxybenzaldehydes (19% and 22%, respectively), unreacted materials, and undeterminable tars (Scheme 3d). The low yields for 2-hydroxybenzaldehydes unambiguously suggested that the developed $Co(OAc)_2{\cdot}4H_2O/NaOH/O_2$/ethylene glycol reaction system would predominantly oxidize the *para*-methyl group with high selectivity (Table 2, entry 12). Differing from previous reports,[7b–d] in addition, the expected thermodynamically favored EG acetal **4** was not detected over the whole scenario (see Supporting information).

On the basis of the well-defined *p*-benzoquinone methides derived from phenoxy radicals of 4-cresols,[7,8a] all the findings suggested a plausible reaction mechanism for this 4-hydroxyl group-directed remote benzylic $C(sp^3)$–H oxyfunctionalization (Scheme 4). Firstly, the reaction is initiated by single-electron transfer from the phenolate of **1** to the direct oxidant Co(III) species, generated from $Co(OAc)_2{\cdot}4H_2O$ through aeration with $O_2$,[14] to give the phenoxy radical. A favorable disproportionation of the isomeric radical **III** provides the original **1** and highly reactive *p*-benzoquinone methides **A**, and the nucleophilic addition of **A** with EG leads to **3**. Subsequently, the phenolate of **3**, resembling the above-mentioned process, is converted into the transitory enol ether **A′**, which is subjected to a rapid spontaneous aromatization-hydrolysis sequence to attain the desired **2** with releasing EG.[15] It is important to note that, relative to isomeric radical **III**, radical **II** (when $R^2$ = 2-Me) is difficult to undergo a similar disproportionation for generating the corresponding *ortho*-benzoquinone methides **B** to conduct the *ortho*-methyl group oxidation.[7,6h] In essence, the remote hydroxyl group transfers a reactivity to the *para*-methyl group accordingly triggering this gentle oxidation. The whole reaction mechanism includes that: (i) the importance of NaOH facilitating generation of phenoxy radical, protecting the formed aldehyde group via dearomatization-enolization, and suppressing possible coupling side-reactions; (ii) two phenoxy radical processes to form highly reactive *para*-benzoquinone methides;




**Scheme 4.** Plausible mechanism for the oxygenation of **1** into **2**.

(iii) powerful regeneration of redox active catalyst $Co(OAc)_2$ with $O_2$ and efficient mediation of EG.

In summary, an efficient oxygenation of 2,6-di-EWG-, 2,3,6-tri-EWG-, 2-EWG-, and 2-EWG-6-EDG-substituted 4-cresols into synthetically versatile 4-hydroxybenzaldehydes has been developed. The procedure is deservedly compatible with readily oxidizable EDG-substituted 4-cresols. The ligand-free $Co(OAc)_2$-catalyzed aerobic oxidation, characterized by a broad scope of the substrates, high yields with excellent selectivity, mild reaction conditions, and low catalyst loading, unlocks an atom-, step-, and reagent-economical transformation for straightforward C=O bond formation. Further studies on extending this transformation in related benzylic $C(sp^3)$–H functionalization chemistry are currently underway.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.077. These data include MOL files and InChiKeys of the most important compounds described in this article.

## References and notes

1. For selected examples, see: (a) Rao, S. R.; Ravishankar, G. A. *J. Sci. Food Agric.* **2000**, *80*, 289; (b) Lottner, C.; Bart, K.-C.; Bernhardt, G.; Brunner, H. *J. Med. Chem.* **2002**, *45*, 2079; (c) Harini, S. T.; Kumar, H. V.; Rangaswamy, J.; Naik, N. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7588.
2. Komiyama, M.; Hirai, H. *J. Am. Chem. Soc.* **1983**, *105*, 2018.
3. (a) KamLet, J.; Conn, E. U.S. Patent, 2,640,083, 1953.; (b) Zou, B.; Du, D.; Zhou, Y.; He, G.; Mao, H. CN Patent, 101580319A, 2009.
4. (a) Coppinger, G. M.; Campbell, T. W. *J. Am. Chem. Soc.* **1953**, *75*, 734; (b) Goldstein, S. L.; Mcnelis, E. *J. Org. Chem.* **1984**, *49*, 1613; (c) Omura, K. *J. Org. Chem.* **1984**, *49*, 3046.
5. Ohmori, H.; Ueda, C.; Tokuno, Y.; Maeda, H.; Masui, M. *Chem. Pharm. Bull.* **1985**, *33*, 4007.
6. For oxidation of 4-cresol, see: (a) Kim, D. S.; Chang, S. H.; Ahn, W. S. *J. Mol. Catal. A: Chem.* **2002**, *179*, 175; (b) Wang, F.; Yang, G.; Zhang, W.; Wu, W.; Xu, J. *Chem. Commun.* **2003**, 1172; (c) Wang, F.; Yang, G.; Zhang, W.; Wu, W.; Xu, J. *Adv. Synth. Catal.* **2004**, *346*, 633; (d) Rode, C. V.; Sonar, M. V.; Nadgeri, J. M.; Chaudhari, R. V. *Org. Process Res. Dev.* **2004**, *8*, 873; (e) Barton, B.; Logie, C. G.; Schoonees, B. M.; Zeelie, B. *Org. Process Res. Dev.* **2005**, *9*, 62; (f) Mardani, H. R.; Colchoubian, H. *J. Mol. Catal. A: Chem.* **2006**, *159*, 197; (g) Raja, R.; Thomas, J. M.; Greenhill-Hooper, M.; Doukova, V. *Chem. Commun.* **2007**, 1924; (h) She, Y.; Wang, W.; Li, G. *Chin. J. Chem. Eng.* **2012**, *20*, 262.
7. For oxidation of 2,4,6-trimethylphenol, see: (a) Ganeshpure, P. A.; Satish, S. *Tetrahedron Lett.* **1988**, *29*, 6629; (b) Takehira, K.; Shimizu, M.; Watanabe, Y.; Orita, H.; Hayakawa, T. *Tetrahedron Lett.* **1990**, *31*, 2607; (c) Shimizu, M.; Watanabe, Y.; Orita, H.; Hayakawa, T.; Takehira, K. *Tetrahedron Lett.* **1991**, *32*, 2053; (d) Li, K.-T.; Liu, P.-Y. *Appl. Catal. A: Gen.* **2004**, *272*, 167; (e) Li, K.-T.; Liu, P.-Y. *J. Mol. Catal. A: Chem.* **2005**, *241*, 72; (f) Boldron, C.; Gamez, P.; Tooke, D. M.; Spek, A. L.; Reedijk, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3585; (g) Boldron, C.; Özalp-Yaman, S.; Gamez, P.; Tooke, D. M.; Spek, A. L.; Reedijk, J. *Dalton Trans.* **2005**, 3535; (h) Sun, X.; Judeh, Z. M. A.; Ali, B. F.; Alshahateet, S. F. *Catal. Today* **2008**, *131*, 423.
8. For oxidation of other electron-donating group substituted 4-cresols, see: (a) Baik, W.; Lee, H. J.; Jang, J. M.; Koo, S.; Kim, B. H. *J. Org. Chem.* **2000**, *65*, 108; (b) Yoshikuni, T. *J. Mol. Catal. A: Chem.* **2002**, *187*, 143; (c) Tripathi, A. K.; Sama, J. K.; Taneja, S. C. *Indian J. Chem. B* **2010**, *49*, 379; (d) Hu, J.; Hu, Y.; Mao, J.; Yao, J.; Chen, Z.; Li, H. *Green Chem.* **2012**, *14*, 2894.
9. (a) Caron, S.; Dugger, R. W.; Ruggeri, S. G.; Ragan, J. A.; Ripin, D. H. B. *Chem. Rev.* **2006**, *106*, 2943; (b) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
10. Selected reviews on molecular oxygen as oxidant (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329; (b) Piera, J.; Backvall, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 3506; (c) Wu, W.; Jiang, H. *Acc. Chem. Res.* **2012**, *45*, 1736; (d) Parmeggiani, C.; Cardona, F. *Green Chem.* **2012**, *14*, 547.
11. (a) Perrin, C. L.; Engler, R. E. *J. Org. Chem.* **1997**, *62*, 687; (b) Tsunoyama, H.; Sakurai, H.; Negishi, Y.; Tsukuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 9374.
12. Typical procedure for Table 2: a mixture of **1** (1.0 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.01 mmol, 2.5 mg) and NaOH (2.0 mmol or 4.0 mmol) in EG (5 mL) was stirred with $O_2$ (1 atm) being bubbled, under 80 °C for a specified time. Hydrochloric acid (10 mL, 2%) and methyl *tert*-butyl ether (MTBE, 10 mL) were successively added to the reaction mixture at room temperature. The organic layer was separated, and the aqueous phase was further extracted with MTBE

(10 mL × 2). The combined organic phase was dried over anhydrous sodium sulfate and concentrated to give a residue, which was purified by column chromatography on silica gel (eluents: petroleum ether/ethyl acetate, 10/1) to provide the desired products **2**. Representative product **2a** (Table 2, entry 1): white solid, 251.9 mg (90% yield), mp 182–184 °C (lit[16] mp 183 °C); $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 9.80 (br s, 1H), 8.00 (s, 2H), 6.40 (br s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 188.2, 154.4, 133.7 (2C), 131.3, 110.7 (2C); HRMS (ESI): $m/z$ [M−H$^+$] calcd for $C_7H_3Br_2O_2$ 276.8500, found 276.8490.

13. (a) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. *Chem. Soc. Rev.* **2009**, *38*, 3193; (b) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540; (c) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234.
14. (a) Onopchenko, A.; Schultz, J. G. D.; Seekircher, R. *J. Org. Chem.* **1972**, *37*, 1414; (b) Iwahama, T.; Yoshino, Y.; Keitoku, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2000**, *65*, 6502; (c) Baucherel, X.; Gonsalvi, L.; Arends, I. W. C. E.; Ellwood, S.; Sheldon, R. A. *Adv. Synth. Catal.* **2004**, *346*, 286.
15. For hydrolysis of enol ethers, see: (a) Kresge, A. J.; Chen, H. L.; Chiang, Y.; Murrill, E.; Payne, M. A.; Sagatys, D. S. *J. Am. Chem. Soc.* **1971**, *93*, 413; (b) Kresge, A. J.; Chen, H. J. *J. Am. Chem. Soc.* **1972**, *94*, 2818; (c) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228.
16. Kumar, L.; Mahajan, T.; Agarwal, D. D. *Green Chem.* **2011**, *13*, 2187.