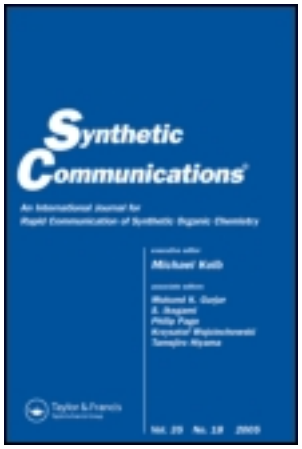

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Environmentally Friendly and Highly Efficient $Co(OAc)_2$-Catalyzed Aerobic Oxidation to Access 2,6-Di-Electron-Donating Group Substituted 4-Hydroxybenzaldehydes

Jian-An Jiang [a] , Jia-Lei Du [a] , Zhong-Nan Zhang [a] , Jiao-Jiao Zhai [a] & Ya-Fei Ji [a]

[a] School of Pharmacy, East China University of Science and Technology , Shanghai , China

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ENVIRONMENTALLY FRIENDLY AND HIGHLY EFFICIENT $Co(OAc)_2$-CATALYZED AEROBIC OXIDATION TO ACCESS 2,6-DI-ELECTRON-DONATING GROUP SUBSTITUTED 4-HYDROXYBENZALDEHYDES

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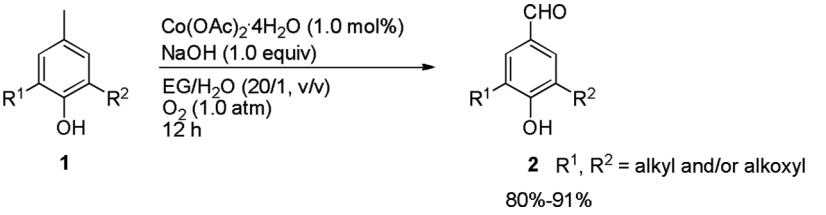
School of Pharmacy, East China University of Science and Technology, Shanghai, China

GRAPHICAL ABSTRACT



Abstract *A highly efficient and green aerobic oxidation has been developed for selectively preparing a series of valuable 2,6-dialkyl-, dialkoxyl-, and alkoxylalkyl-substituted 4-hydroxybenzaldehydes from corresponding 4-cresols in good to excellent yields, using a catalytic system of $Co(OAc)_2 \cdot 4H_2O$ (1.0 mol%)–NaOH (1.0 equiv)–O_2 (1.0 atm) in aqueous ethylene glycol ($EG/H_2O = 20/1$, v/v) at 50°C. Furthermore, a plausible mechanism was proposed for the direct oxyfunctionalization of the aromatic methyl group into the aldehyde group.*

Keywords Aerobic oxidation; $Co(OAc)_2$; ethylene glycol; 4-hydroxybenzaldehydes; oxyfunctionalization

INTRODUCTION

Versatile 4-hydroxybenzaldehydes have been incredibly important organic materials for pharmaceutical, perfume, dye, and agrochemical industries, as well as for fundamental research.[1] For example, 3,5-dimethyl-4-hydroxybenzaldehyde is a significant intermediate for the synthesis of potential cancer chemopreventive agents,[2] nonnucleoside reverse transcriptase inhibitors,[3] and other bioactive compounds.[4] More notably, commercially famous syringaldehyde (3,5-dimethoxy-4-hydroxybenzaldehyde), widely used for the synthesis of the classical antibacterial

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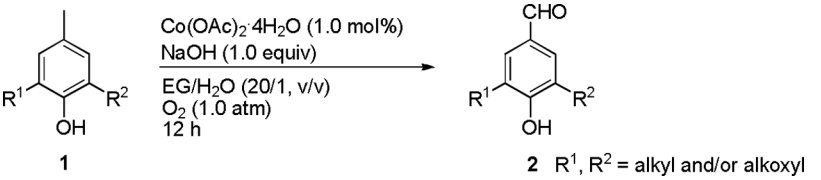
Address correspondence to Ya-Fei Ji, School of Pharmacy, East China University of Science and Technology, Campus P. O. Box 363, 130 Meilong Road, Shanghai 200237, China. E-mail: jyf@ecust.edu.cn

agent Trimethoprim,[5] the antiepileptic drug *N*-isopropyl-3,4,5-trimethoxycinnamide,[6] and many bioactive molecules,[7] was produced on a scale of thousands of tons annually to meet worldwide demands.[8]

Although some strategies, including Reimer–Tiemann reaction,[9] glyoxylic acid method,[10] stoichiometric oxidation by oxidants[11] and electric/electrocatalytic oxidation,[12] have been massively employed for preparing valuable 4-hydroxybenzaldehydes, tedious separation and serious pollution did hinder their widespread application. In this respect, the straightforward catalytic oxidation of the seemingly inert methyl group of 4-cresols into the fascinating aldehyde group becomes the most appealing synthetic approach.[13,14] In past decades, notable achievements in transition-metal-catalyzed oxidation of 2,4,6-trimethylphenol have granted this direct transformation the limelight.[13] As noted, most of the developed catalyst systems for this aerobic oxidation were based on coordination complexes of transition metals, such as cobalt(II)–Schiff base complex,[13a] copper(II)–amine complex,[13b–d] and copper(II)–neocuproine sodium methoxide complex.[13g,h] While effective, needs of ligand/additive and greater oxygen pressure have brought noticeable disadvantages and limitations in view of cost, waste, and safety issues. However, more desired ligand-free catalytic systems have long remained out of reach for the oxidation of 2,4,6-trimethylphenol and its analogs. It was only in 2004 that Li and coworkers reported the first efficient ligand-free, iron-based catalyst, tackling this interesting task with pressured molecular oxygen.[13e,f] Another ligand-free stoichiometric copper-mediated oxidation by hydrogen peroxide was reported in 2008.[13i] Not surprisingly, the development of more green catalytic oxidation has proven to be imperative for sustainable production of the significant 4-hydroxybenzaldehydes.

Herein, we report a highly efficient $Co(OAc)_2 \cdot 4H_2O$ (1.0 mol%)–NaOH (1.0 equiv)–O_2 (1.0 atm) catalytic system that effects aerobic oxidation of 2,6-di-electron-donating group substituted 4-cresols in aqueous ethylene glycol (EG, $EG/H_2O = 20/1$, v/v, Scheme 1). The reactions proceeded in good yields at atmospheric pressure without any ligand/additive and achieved highly chemoselective and regioselective $C(sp^3)$-H oxyfunctionalization, giving valuable 4-hydroxybenzaldehydes without overoxidation to carboxylic acids[14c–e] or quinines.[15] Beyond doubt, it is one of the most important goals in oxidation chemistry to utilize molecular oxygen in an atom-economic and environmentally friendly transformation with water as the only by-product.[16] In addition, general high-boiling-point nonflammable EG can reliably avoid safety issue associated with low-boiling-point organic solvents.[17]

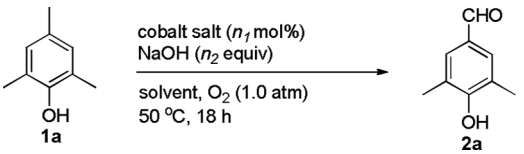


Scheme 1. $Co(OAc)_2$-catalyzed selectively aerobic oxidation of 2,6-disubstituted 4-cresols into valuable 4-hydroxybenzaldehydes.

RESULTS AND DISCUSSION

To identify an efficient catalyst system that meets the criteria of green chemistry, we initially investigated various easily available and less toxic cobalt sources with sodium hydroxide (1.0 equiv) and molecular oxygen (1.0 atm). At first, the influence of different cobalt catalysts on the model oxidation of 2,4,6-trimethylphenol (**1a**) was evaluated in methanol at a mild reaction temperature of 50 °C. We discovered that halogenated cobalt salts $CoCl_2$, $CoBr_2$, and CoF_2 showed some activity toward the oxidation, giving desired product 3,5-dimethyl-4-hydroxybenzaldehyde (**2a**) in poor yields (Table 1, entries 1–3). Then, the slightly improved result was observed by

Table 1. Optimization of the reaction conditions for the aerobic oxidation of **1a** into **2a**[a]



Entry	Co source ($n_1$mol%)	NaOH ($n_2$equiv)	Solvent	Yield (%)[b]
1	$CoCl_2$(5.0)	1.0	MeOH	26
2	$CoBr_2$(5.0)	1.0	MeOH	31
3	CoF_2(5.0)	1.0	MeOH	24
4	Cobalt(II)acetylacetonate (5.0)	1.0	MeOH	45
5	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	MeOH	71
6	Co_3O_4(5.0)	1.0	MeOH	Trace
7	nano-Co_3O_4(5.0)	1.0	MeOH	Trace
8	CoTMPP (5.0)	1.0	MeOH	13
9[c]	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	MeOH	54
10	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	EtOH	69
11	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	*n*-PrOH	65
12	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	*i*-PrOH	63
13	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	EG	85
14	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	THF	0
15	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	CH_3CN	0
16	$Co(OAc)_2 \cdot 4H_2O$ (5.0)	1.0	CH_2Cl_2	0
17	$Co(OAc)_2 \cdot 4H_2O$ (1.0)	1.0	EG	85
18[d]	$Co(OAc)_2 \cdot 4H_2O$ (0.5)	1.0	EG	74
19	$Co(OAc)_2 \cdot 4H_2O$ (1.0)	0.8	EG	68
20	$Co(OAc)_2 \cdot 4H_2O$ (1.0)	0.5	EG	45
21	$Co(OAc)_2 \cdot 4H_2O$ (1.0)	1.5	EG	85
22[e]	$Co(OAc)_2 \cdot 4H_2O$ (1.0)	1.0	EG/H_2O	86
23[f]	**$Co(OAc)_2 \cdot 4H_2O$ (1.0)**	**1.0**	**EG/H_2O**	**88**
24[g]	$Co(OAc)_2 \cdot 4H_2O$ (1.0)	1.0	EG/H_2O	55

[a]Reaction conditions: substrate **1a** (5.0 mmol), cobalt source (n_1 mol%), sodium hydroxide (n_2 equiv), and solvent (5.0 mL), O_2 (1.0 atm), 50 °C for 18 h.
[b]Isolated yield.
[c]Reaction performed at 40 °C.
[d]Reaction time of 24 h.
[e]Reaction time of 16 h, EG/H_2O = 5.0 mL/0.1 mL.
[f]Reaction time of 12 h, EG/H_2O = 5.0 mL/0.25 mL.
[g]Reaction time of 6 h, EG/H_2O = 5.0 mL/0.75 mL.

applying cobalt(II) acetylacetonate (entry 4). To our delight, the oxidation could give **2a** with a promising yield of 71% in the presence of $Co(OAc)_2 \cdot 4H_2O$ (entry 5). However, further screening showed that Co_3O_4, nano-Co_3O_4, and CoTMPP [5,10,15,20-*tetra*(4-methoxyphenyl)-21*H*,23*H*-porphine cobalt(II)] almost were inactive for the transformation (entries 6–8). While lowering the reaction temperature to 40 °C, the reaction provided **2a** in unsatisfactory 54% yield (entry 9). Hence, with effective $Co(OAc)_2 \cdot 4H_2O$, other reaction parameters would be further optimized at 50 °C.

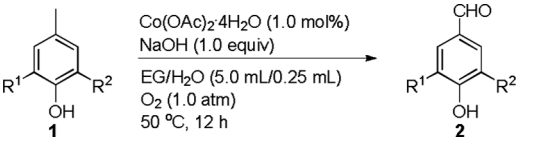
While examining solvents, alcohols were found to be generally effective (entries 10–13), and more polar EG is the best choice to provide the dramatically increased yield of 85% (entry 13). On the other hand, the reactions failed to oxidize **1a** into **2a** in aprotic solvents, clearly proving the indispensable mediation of alcohols to the oxidation (entries 14–16). More pleasingly, variation of catalyst loading indicated that 1.0 mol% $Co(OAc)_2 \cdot 4H_2O$ also efficiently catalyzed the oxidation (entry 17), whereas applying 0.5 mol% $Co(OAc)_2 \cdot 4H_2O$ brought about **2a** in visibly lowered yield, albeit prolonging reaction time to 24 h (entry 18). As surveyed, a decreased amount of sodium hydroxide led to sharply lowered yields (entries 19 and 20), but more sodium hydroxide did not give better outcome (entry 21). Evidently, 1.0 equiv sodium hydroxide was a requisite to efficiently achieving the oxidation with 1.0 mol% $Co(OAc)_2 \cdot 4H_2O$.

Given that water is the only by-product in the oxidation, the influence of water content in EG was also investigated. The results revealed that a small amount of water could facilitate the oxidation, giving greater yields along with reduced reaction time (entries 22 and 23), and the best yield of 88% was achieved for **2a** in aqueous EG ($EG/H_2O = 5.0\,mL/0.25\,mL$, entry 23). However, more water badly impaired the selectivity of this oxidation to result in sharply reduced yield of 55%, though **1a** could be more quickly consumed within 6 h (entry 24). Conclusively, a highly efficient green catalytic system of $Co(OAc)_2 \cdot 4H_2O$ (1.0 mol%)–NaOH (1.0 equiv)–O_2(1.0 atm) in aqueous EG ($EG/H_2O = 20/1$, v/v) at 50 °C has been established as the optimal reaction conditions to fulfil the selectively aerobic oxidation.

With the optimized conditions in hand, a range of 2,6-dialkyl-, dialkoxyl-, and alkoxylalkyl-substituted 4-cresols **1a**–**n** were used to explore the generality of the oxidation. As shown in Table 2, 2,6-dialkyl-4-cresols **1a**–**c** could be oxidized into the corresponding aldehydes **2a**–**c** in good yields of 81–88% (Table 2, entries 1–3). Likewise, for 2,6-dialkoxyl-4-cresols **1d**–**j**, these reactions consistently provided the desired products **2d**–**j** in good to excellent yields of 80%–91% (entries 4–10). As anticipated, the oxidation also enabled 2-alkoxyl-6-alkyl-4-cresols **1k**–**n** to smoothly transform into the aldehydes **2k**–**n** in good yields of 80–83% (entries 11–14). All results undoubtedly demonstrated that this simple $Co(OAc)_2$-catalyzed oxidation could be successfully applied in the efficient conversion of a range of 2,6-di-electron-donating group substituted 4-cresols into the corresponding 4-hydroxybenzaldehydes. It was noteworthy that there was no any formation of salicylaldehydes (with regard to substrates **1a, 1c,** and **1k**–**n**), benzoic acids, or quinones in our reaction system, which exhibited excellent chemoselectivity and regioselectivity.

Further investigations were undertaken to probe the mechanism of the $Co(OAc)_2$-catalyzed oxidation (Scheme 2). The model reactions showed that the feedstock **1** gradually generated the desired **2** via the corresponding ethereal intermediates

Table 2. Generality of **1** for the oxidation[a]



Entry	Substrate	Product	Yield (%)[b]
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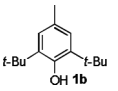
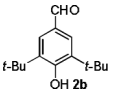
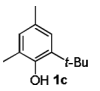
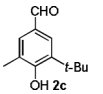
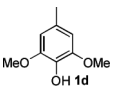
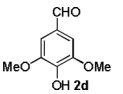
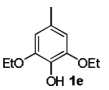
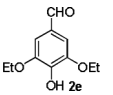
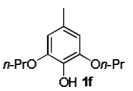
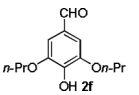
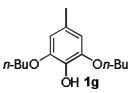
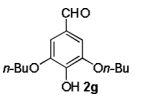
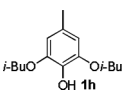
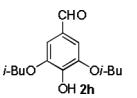
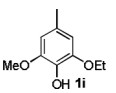
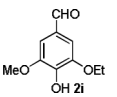
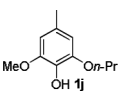
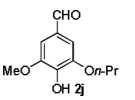
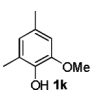
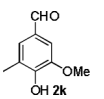
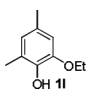
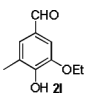
2			81
3			83
4			91
5			83
6			82
7			91
8			81
9			84
10			81
11			83
12			81

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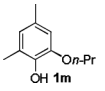
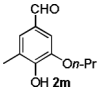
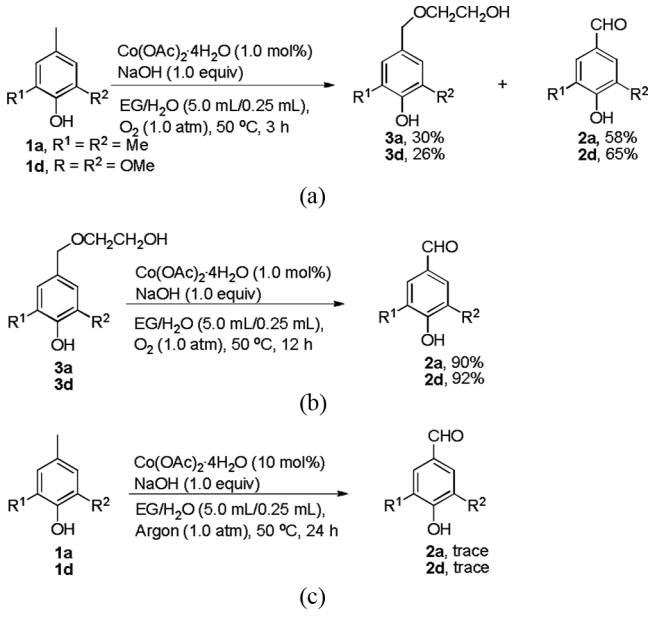
Table 2. Continued

Entry	Substrate	Product	Yield (%)[b]
13			81
14			80

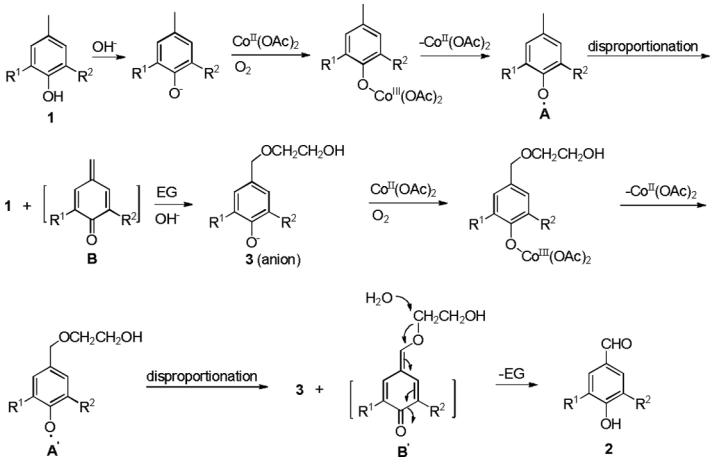
[a]Reaction conditions: substrate **1** (5.0 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.05 mmol, 12 mg), sodium hydroxide (5.0 mmol), EG/H_2O (5.0 mL/0.25 mL), O_2 (1.0 atm), 50 °C for 12 h.
[b]Isolated yield.

3 (Scheme 2a). Indeed, the isolated ethers **3** efficiently underwent the second oxidation into **2** (Scheme 2b). Unlike in previous reports,[13g–i] the acetal intermediates were not detected over our whole scenario. Additionally, under argon atmosphere, the oxidation only gave a trace of the desired products even with 10 mol% $Co(OAc)_2 \cdot 4H_2O$ (Scheme 2c), explicitly instructing molecular oxygen as a terminal oxidant (the experiments see Supplementary Material, available online).

On the basis of these findings, a plausible oxidation mechanism is suggested in Scheme 3. The reaction is initiated by single-electron transfer from phenolic anion of **1** to direct oxidant Co(III) species derived from $Co(OAc)_2$ to generate phenoxy radicals **A**. The radicals **A** are rapidly disproportionated to original **1** and transiently



Scheme 2. Mechanistic investigations.



Scheme 3. Plausible mechanism.

highly reactive *p*-benzoquinone methides **B**,[13g–i,14a,7a,18] to which the nucleophilic additions of EG inevitably lead to ethereal intermediates **3**. In the same fashion, the intermediate anions are converted into transitory **B′**, which give the desired **2** upon fast hydrolysis driven by spontaneous aromatization. In the course of the reaction, molecular oxygen can powerfully activate $Co(OAc)_2$ to regenerate the direct oxidant Co(III) species.

CONCLUSIONS

In summary, we have developed a highly efficient aerobic oxidation of 2,6-dialkyl-, dialkoxyl-, and alkoxylalkyl-substituted 4-cresols into commercially and academically valuable 4-hydroxybenzaldehydes, using simple $Co(OAc)_2 \cdot 4H_2O$ (1.0 mol%)–NaOH (1.0 equiv)–O_2(1.0 atm) catalytic system in aqueous EG (EG/$H_2O = 20/1$, v/v) at 50 °C. This straightforward oxidation protocol has excellent chemoselectivity and regioselectivity but also features green chemistry: atom economy, step economy, inexpensive oxidant, only 1.0 mol% catalyst $Co(OAc)_2 \cdot 4H_2O$, and safe solvent ethylene glycol.

EXPERIMENTAL

All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (TLC, precoated silica-gel plates containing HF_{254}). Reaction products were purified by silica-gel chromatography (200–300 mesh). Melting points were determined using open capillaries and are uncorrected. NMR spectra were determined on Bruker AV400 in $CDCl_3$ with Tetramethylsilane (TMS) as internal standard for ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz), respectively. High-resolution mass spectrometry (HRMS) was carried out on a QSTAR Pulsar I LC/TOF MS mass spectrometer.

Typical Procedure for the $Co(OAc)_2$-Catalyzed Aerobic Oxidation of 1

A mixture of substrate **1** (5.0 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.05 mmol, 12 mg), and NaOH (5.0 mmol, 0.2 g) in EG/H_2O (5.0 mL / 0.25 mL) was stirred with O_2 (1.0 atm) and bubbled at 50 °C for 12 h. Hydrochloric acid (10.0 mL, 2%) and chloroform (10.0 mL) were successively added to the reaction mixture. The chloroform phase was separated, and the aqueous phase was further extracted with chloroform (10.0 mL × 2). The combined organic layer 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, 5/1) to provide the desired products **2**.

3,5-Dimethyl-4-hydroxybenzaldehyde (2a)[11b,14a]

White solid, 0.66 g (88% yield), mp 112–114 °C (lit.[11b] mp 113–114 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.81 (br s, 1H), 7.54 (s, 2H), 5.46 (br s, 1H), 2.31 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 191.5, 158.1 (2C), 131.0, 129.3, 123.7 (2C), 15.8 (2C). HRMS (ESI): m/z [$M + H^+$] calcd. for $C_9H_{11}O_2$ 151.0759; found 151.0750.

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SUPPLEMENTAL MATERIAL

Complete experimental details and ^{1}H NMR, ^{13}C NMR, and HRMS spectra of all products are available online in the Supplemental Material. Supplemental data for this article can be accessed on the publisher's website.

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