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# A highly efficient approach to vanillin starting from 4-cresol†

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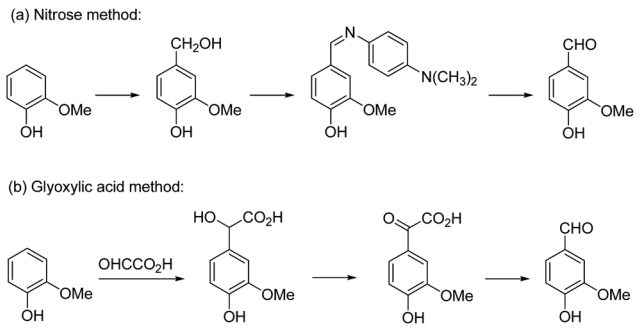
A highly efficient approach to the famous flavor and fragrance compound vanillin has been developed starting from 4-cresol with the attention focused on improving the sustainability of all the reactions. The approach involves a three-step sequence of the quasi-quantitative selective clean oxybromination of 4-cresol, the high-yield selective aerobic oxidation of 2-bromo-4-cresol, and the quantitative methoxylation of 3-bromo-4-hydroxybenzaldehyde with the recovery of pure methanol. Herein, the pivotal oxidation and methoxylation reactions are logically investigated and developed into two concise methodologies. As a green alternative, the approach holds significant value for the sustainable manufacturing of vanillin.

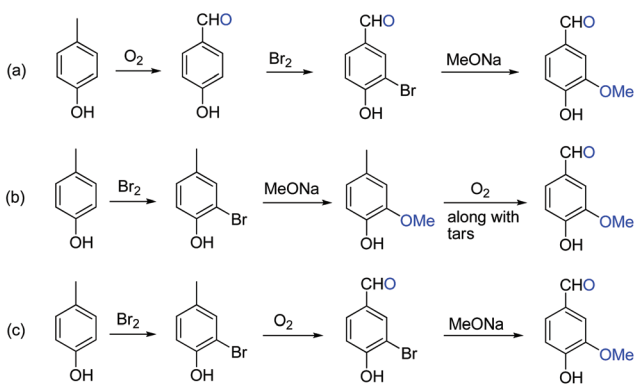
## Introduction

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is a most famous flavor and fragrance compound, and remains the global leader in the flavoring and perfumery industries.[1] It is also an important chemical feedstock for the production of innumerable active pharmaceutical ingredients and fine chemicals. Nowadays, more than 16 000 tons of vanillin is chemically produced annually, mainly from the intermediate guaiacol *via* the nitrose method (Scheme 1a) and the glyoxylic acid method (Scheme 1b), [2,3] and only a rather small amount of the remainder originates from vanilla pods.[2] In the face of the worldwide growing demand for vanillin, the high production cost, tedious reaction steps (including the preparation of guaiacol), cumbrous separations and vast amount of wastewater have brought about heavy burdens for its mass manufacture.[1–3] For the sake of economical interests and ecological considerations, academia and industry have been devoted to developing a sustainable approach to vanillin over recent decades.[4]

As an innovative alternative strategy (Scheme 2), vanillin can be synthesized starting from the less-expensive 4-cresol, combinatorially *via* a three-step sequence of oxidation–bromination–methoxylation (Scheme 2a), bromination–methoxylation–oxidation (Scheme 2b)[4b] or bromination–oxidation–methoxylation (Scheme 2c).[4d] The theoretical zero-carbon emission, the recyclable bromine element, and the molecular oxygen as a green oxidant[7] apparently make Scheme 2 highly desirable for the production of vanillin on a commercial scale.




**Scheme 1** Traditional production of vanillin from guaiacol.




**Scheme 2** Synthesis of vanillin starting from 4-cresol.

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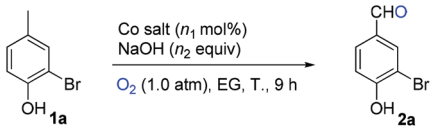
Comparing with the traditional methods (Scheme 1), the relevant straightforward benzylic C($sp^3$)–H oxyfunctionalization of 4-cresols is an ideal and eco-friendly approach to 4-hydroxybenzaldehydes from the viewpoints of atom-, step- and reagent-economy.[4–6] However, these oxidations, of 4-cresol and 2-methoxy-4-cresol for example, are constrained by the use of impractical metal–ligand-coordinated catalysts,[6b–f] high oxygen pressure,[5,6b] as well as the potential safety issues associated with the combination of pure $O_2$ and low-boiling point flammable methanol.[8] In addition, inseparable tars (oligomers), generated from the free radical-based coupling side-reactions, usually cause difficulties for chemists. Recently, Li and co-workers reported a Co-[Salen-Py][$PF_6$]$_2$-catalyzed oxidation of 2-methoxy-4-cresol to vanillin with ethylene glycol (EG) and water as solvents to overcome the cumbersome tar problem,[9] but it is extremely difficult to implement this oxidation on a commercial scale because of the complexity of the catalyst.

Very recently, we have developed a ligand- and additive-free Cu(OAc)$_2$-catalyzed and EG-mediated atmospheric oxidation of 2,6-di-electron-donating group (EDG) substituted hindered 4-cresols to the corresponding 4-hydroxybenzaldehydes.[10] However, for the unhindered 4-cresols (Scheme 2), the direct benzylic C($sp^3$)–H oxyfunctionalization remains an outstanding challenge. It was found that low conversion and undesired coupling reactions inevitably emerged in the Cu-catalyzed oxidations of 4-cresol and 2-methoxy-4-cresol.[10,11] In contrast, a better selectivity with fewer tars was found for the oxidation of the electron-withdrawing group (EWG)-containing 2-bromo-4-cresol.[10] We reasonably speculated that 2-bromo-4-cresol possibly promises an improved conversion with a high selectivity under suitable oxidation conditions (Scheme 2c). In this work, based on a selective oxybromination of 4-cresol to 2-bromo-4-cresol, we described a practical and high-yield ligand-free Co(OAc)$_2$-catalyzed aerobic oxidation of 2-bromo-4-cresol to 3-bromo-4-hydroxybenzaldehyde under the alkaline conditions and mediation of non-flammable EG. The quantitative methoxylation of the intermediate 3-bromo-4-hydroxybenzaldehyde was subsequently developed, ultimately realizing a green and concise three-step sequence to synthesize vanillin (Scheme 2c).

## Results and discussion

Firstly, considering the high catalytic activity of cobalt, commercially available cobalt salts, acting as inexpensive and low toxic catalysts, were surveyed to explore an efficient, practical and straightforward oxidation of 2-bromo-4-cresol (**1a**) to 3-bromo-4-hydroxybenzaldehyde (**2a**). When undecorated $CoCl_2$ or other halogenated cobalt salts (3.0 mol%) were employed, only traces of the desired **2a** were obtained with pure $O_2$ (1.0 atm) under the mediation of NaOH (2.0 equiv.) and EG (Table 1, entry 1, and see ESI† for details). Next, we turned to organic cobalt salts, and Co(OAc)$_2$·4$H_2O$ proved to be effective to give **2a** with a promising yield of 53% at 50 °C (entry 2). Furthermore, an elevated reaction temperature of 80 °C remarkably enhanced the yield to 76% (entry 3). It was found that

**Table 1** Selected optimizations for the reaction conditions (see ESI for details)[a]




| Entry | Co salt ($n_1$) | NaOH ($n_2$) | $T$ (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $CoCl_2$ (3.0) | 2.0 | 50 | Trace |
| 2 | Co(OAc)$_2$·4$H_2O$ (3.0) | 2.0 | 50 | 53 |
| 3 | Co(OAc)$_2$·4$H_2O$ (3.0) | 2.0 | 80 | 76 |
| 4 | Co(OAc)$_2$·4$H_2O$ (3.0) | 0 | 80 | 0 |
| 5 | Co(OAc)$_2$·4$H_2O$ (3.0) | 3.0 | 80 | 84 |
| 6 | Co(OAc)$_2$·4$H_2O$ (3.0) | 4.0 | 80 | 90 |
| 7 | Co(OAc)$_2$·4$H_2O$ (2.0) | 4.0 | 80 | 90 |
| 8 | Co(OAc)$_2$·4$H_2O$ (1.0) | **4.0** | **80** | 90 |
| 9 | Co(OAc)$_2$·4$H_2O$ (1.0) | 4.5 | 80 | 90 |
| 10 | Co(OAc)$_2$·4$H_2O$ (0.5) | 4.0 | 80 | 79 |
| 11 | Co(OAc)$_2$·4$H_2O$ (1.0) | 4.0 | 80 | Trace[c] |

[a] Reaction conditions: **1a** (5.0 mmol), Co salt ($n_1$ mol%), NaOH ($n_2$ equiv.), EG (10 mL), $O_2$ (1.0 atm), 9 h. [b] Isolated yield. [c] Performed under argon atmosphere.

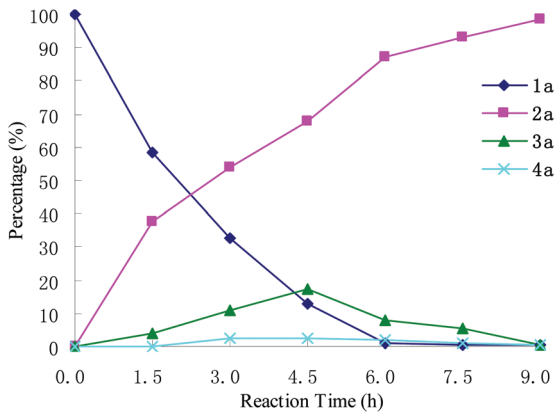
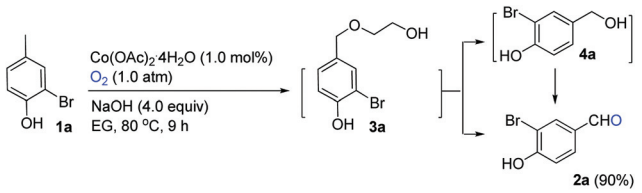



**Fig. 1** Time-dependence curves for the oxidation of **1a** to **2a** (percentages as their respective ratios from the total ionization chromatography area normalization method). Reaction conditions: **1a** (5.0 mmol), Co(OAc)$_2$·4$H_2O$ (12.5 mg, 0.05 mmol), NaOH (0.80 g, 20 mmol), EG (10 mL) and $O_2$ (1.0 atm) at 80 °C (see ESI† for details).

NaOH was essential to trigger the oxidation. Meanwhile, the dimer[10] and tars resulting from coupling side-reactions were undetected under the alkaline conditions (entries 4–6),[5] and 4.0 equiv. of NaOH turned out to be sufficient to afford the highest yield of 90% (entry 6). More pleasingly, the same yield was maintained when using 2.0 or 1.0 mol% Co(OAc)$_2$·4$H_2O$ (entries 7 and 8, entry 8 with optimal reaction conditions). However, the product yield did not increase further when using 4.5 equiv. of NaOH (entry 9). On the other hand, the yield sharply reduced to 79% with a lower catalyst loading of 0.5 mol% (entry 10). In addition, only a trace amount of **2a** was observed under the anaerobic conditions (entry 11).

Apart from the desired product **2a**, the ether **3a** and the alcohol **4a** as two intermediates were also detected during the oxidation by GC-MS analysis (Fig. 1 and Scheme 3). A higher

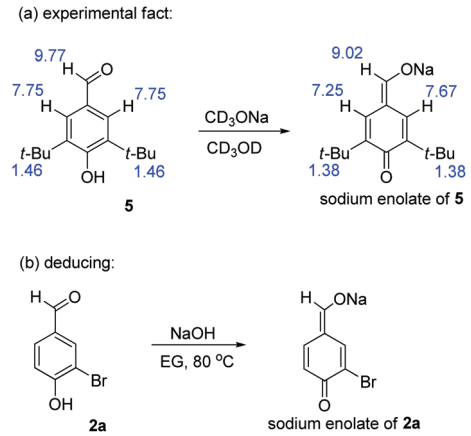



Scheme 3 Oxidation process of **1a**.

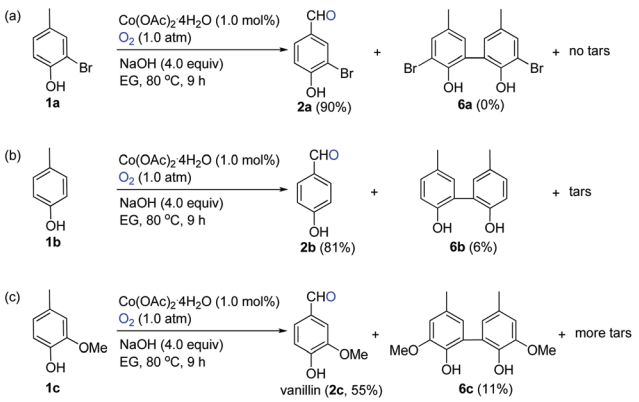
selectivity to **3a** than to **4a** suggests that **3a** should be the intermediate formed first, whereas **4a** should be its inferior derivative. Indeed, the control experiments clearly showed that the isolated **3a** efficiently underwent this oxidation providing **2a** along with the generation of **4a**. In contrast, the alcohol **4a** was cleanly oxidized to **2a** without any **3a** being observed in the process. Significantly, the oxidation proceeded smoothly in methanol *via* a similar reaction process with the intermediates 2-bromo-4-(methoxymethyl)phenol (**3a′**) and 2-bromo-4-(hydroxymethyl)-phenol (**4a**) being detected. However, a comparatively long reaction time of 60 h was required for completion of the methanol-mediated oxidation of **1a**, only affording **2a** in a 71% yield (see ESI† for details). The distinct contributions arising from the EG and the methanol are attributed to their polarity differences.[10]

The oxidation system of $Co(OAc)_2{\cdot}4H_2O/NaOH/O_2$ was impressive for selectively transforming **1a** to 4-hydroxy-benzaldehyde **2a** without the overoxidation product 3-bromo-4-hydroxybenzoic acid being formed,[5] even when elevating the reaction temperature to 100 °C or prolonging the reaction time to 60 h in methanol (see ESI† for details). Although the resonance between 4-hydroxybenzaldehydes and enolates is seemingly a reasonable protection for the susceptive aldehyde group,[10] we still wondered why **2a** was not further oxidized to the corresponding 4-hydroxybenzoic acid under these harsh alkaline conditions. It was considered that the sodium phenolate of **2a** possibly isomerized into its sodium enolate *via* dearomatization–enolization, accordingly protecting the original labile aldehyde group. On the one hand, $^1H$ NMR analysis showed that **2a** routinely formed its thermodynamically stable sodium phenolate instead of the preconceived sodium enolate in $CD_3ONa/CD_3OD$ under the test conditions. On the other hand, the fact of capturing the sodium enolate of the sterically hindered 4-hydroxybenzaldehyde **5** lent support to **2a** isomerizing into its sodium enolate under the reaction conditions as depicted in Scheme 4 (see ESI† for details). Also, a SciFinder search revealed that 2,6-di-*tert*-butyl-4-(methoxymethylene)-cyclohexa-2,5-dienone (the methyl enol ether of **5**) was a solely documented example, derived from the dearomatization–enolization–methylation of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde due to the highly sterically hindered structure.[12]

With the oxidation reaction conditions in hand, we next compared the oxidations of 2-bromo-4-cresol (**1a**), 4-cresol (**1b**) and 2-methoxy-4-cresol (**1c**), in order to evaluate the aforementioned approaches (Scheme 2). As displayed in Scheme 5, compared to **1a**, the unsubstituted and electron-neutral 4-cresol **1b**




Scheme 4 Isomerization of **2a** into its sodium enolate under the reaction conditions.

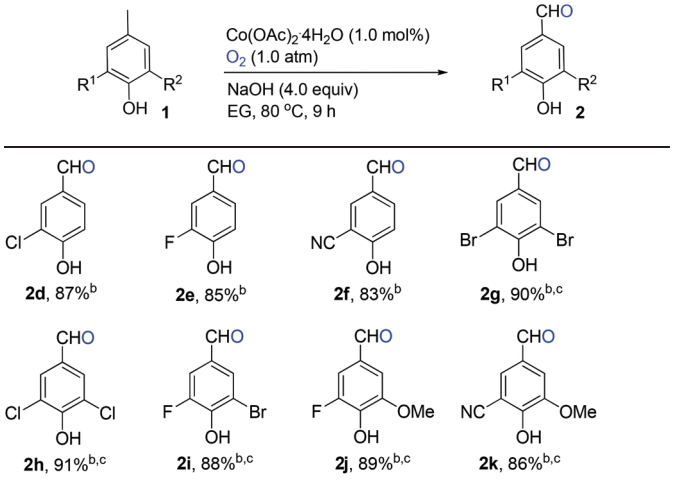



Scheme 5 Oxidations of **1a**, **1b** and **1c** under the standard conditions. Reaction performed with **1** (5.0 mmol), $Co(OAc)_2{\cdot}4H_2O$ (12.5 mg, 0.05 mmol), NaOH (0.80 g, 20 mmol), EG (10 mL) and $O_2$ (1.0 atm) at 80 °C for 9 h (see ESI† for details).

delivered the desired 4-hydroxybenzaldehyde (**2b**) in a relatively low yield of 81%, along with the dimer **6b** (6% yield) and undeterminable tars derived from undesired couplings. In sharp contrast, 2-EDG-substituted 4-cresol **1c** suffered from more severe coupling side-reactions only providing the desired oxidation product (vanillin) with a 55% yield, as well as the dimer **6c** (11%) and the concomitant tars. The facts indicated that the bromine atom as an EWG could inherently suppress potential coupling side-reactions under the strong alkaline conditions, accordingly guaranteeing a high selectivity to **2a** (Scheme 5a). On the basis of the pivotal oxidation reactions, the sequence of bromination–oxidation–methoxylation (Scheme 2c) should be the most likely to efficiently access vanillin from 4-cresol.

Another defining attribute of the undecorated $Co(OAc)_2$-catalyzed oxidation protocol is its validity to transform a series of EWG-substituted 4-cresols to the corresponding 4-hydroxybenzaldehydes. As shown in Table 2, the oxidation of various 2-EWG-substituted 4-cresols worked well with this protocol. Firstly, we were pleased to observe that, this simple protocol

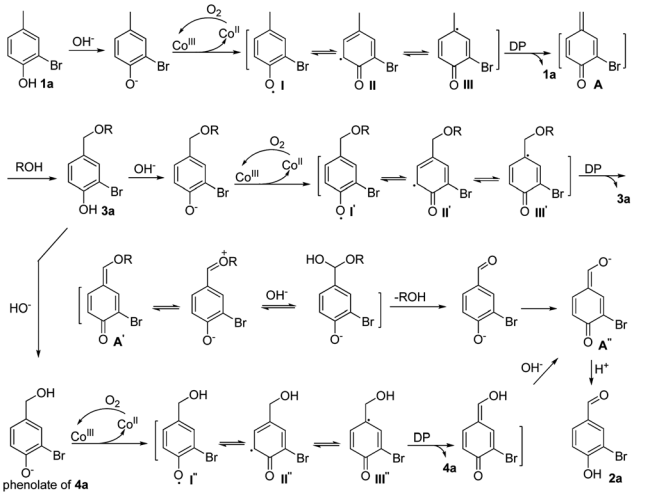
Table 2 $Co(OAc)_2$-catalyzed oxidation of **1**[a]




[a] Reaction conditions: **1** (5.0 mmol), $Co(OAc)_2·4H_2O$ (12.5 mg, 0.05 mmol), NaOH (0.80 g, 20.0 mmol), EG (10 mL) and $O_2$ (1.0 atm) at 80 °C for 9 h. [b] Isolated yield *via* column chromatography. [c] Performed with NaOH (0.40 g, 10.0 mmol).

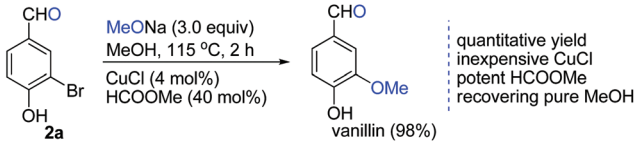
smoothly provided 3-EWG-substituted 4-hydroxybenzaldehydes **2d–f** in high yields of 83–87% from the corresponding unhindered 2-EWG-substituted 4-cresols. Furthermore, as for the hindered 2,6-di-EWG- or 2-EWG-6-EDG-substituted 4-cresols, all the desired products **2g–k** were efficiently obtained with high yields of 86–91%. In the current case of the hindered 4-cresols, only 2.0 equiv. of NaOH was needed to render the high yields (**2g–k**). Significantly, this alkaline $Co(OAc)_2$-catalyzed oxidation of the EWG-containing 4-cresols is an important complementary protocol to the previous $Cu(OAc)_2$-catalyzed oxidation of the sterically hindered electron-rich 4-cresols.[10]

At the moment, based on the above findings and the previously reported Baik-Ji-type reaction mechanism beginning with a phenoxy radical,[6a,10] a similar mechanism was proposed to rationalize the alkaline $Co(OAc)_2$-catalyzed oxidation (Scheme 6). In the first phase, the reaction is initiated by single-electron transfer from the phenolate of **1a** to the direct oxidant Co(III) species, derived from $Co(OAc)_2·4H_2O$ through oxygenation,[13] to give the phenoxy radical. The isomeric radical **III** is disproportionated to the original **1a** and the highly reactive *p*-benzoquinone methide **A**, and the nucleophilic addition of **A** with EG results in the ether **3a** (Scheme 3). Similarly, in the second phase, the phenolate of **3a** is converted to the enol ether **A′**, which is subjected to a rapidly spontaneous aromatization followed by the release of EG to attain the desired **2a**.[14] Of course, the sodium enolate of **2a** (**A″**) should effectively protect the original aldehyde group under the strong alkaline conditions. In addition, a high concentration of NaOH will split the firstly formed intermediate **3a** releasing the phenolate of **4a** (Scheme 3), which is further oxidized to **2a** *via* the same fashion. In the process, NaOH holds three crucial roles: (i) facilitating phenoxy radical formation *via* phenolate anion; (ii) inhibiting free radical-based coupling side-reactions; (iii) protecting *in situ* the formed aldehyde group *via* dearomatization–enolization.




Scheme 6 A plausible mechanism for the typical oxidation of **1a** (ROH = EG, DP = disproportionation).

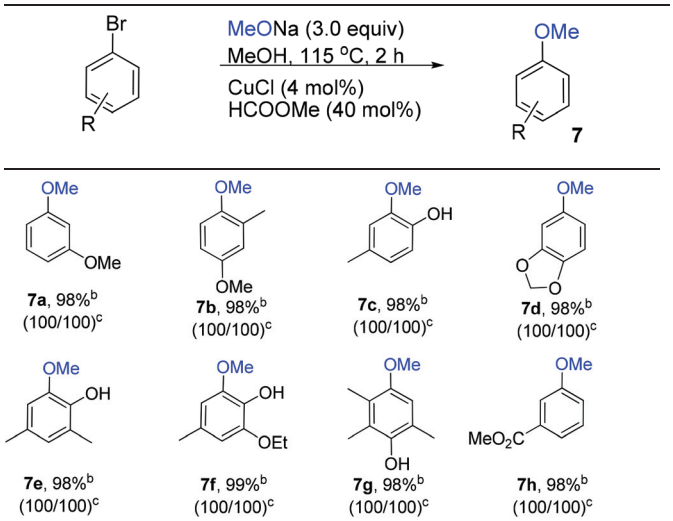
Having established the efficient oxidation of **1a** to **2a**, we had to make an effort with the methoxylation of **2a** into vanillin. Traditionally, a practical methoxylation of unactivated aryl bromides (no strong EWG such as $NO_2$, CN, $CF_3$, *etc.* on the aromatic ring) with MeONa requires a copper(I) salt as a catalyst, assisted by aprotic polar amides like dimethylformamide, *N*-methyl-2-pyrrolidinone or hexamethylphosphorous triamide, as solvents or co-catalysts.[15] As a result, the unsatisfactory efficacy, troublesome workup[16] and reproductive health hazards[17] associated with these solvents make them unsuitable due to current eco-awareness. Also, the contaminating decomposition of these amides unavoidably takes place in the presence of MeONa. For this reason, an eco-friendly and powerful protocol has been developed to implement a quantitative methoxylation (98% yield). The reaction was carried out in a Teflon-lined autoclave at 115 °C for 2 h, with the most inexpensive copper(I) salt CuCl (4.0 mol%) as a catalyst and the decomposable HCOOMe (40 mol%) as a co-catalyst, as well as methanolic MeONa (3.0 equiv.) as both a nucleophile and solvent (Scheme 7). Compared to an open system,[18] the closed reaction system played two vital roles for guaranteeing the quantitative methoxylation: (i) avoiding the loss of low boiling point HCOOMe; and (ii) elevating the reaction temperature to 115 °C. In particular, due to the fully uncontaminated decomposition of HCOOMe into MeOH and carbon monoxide




Scheme 7 Methoxylation of **2a** into vanillin.

**Table 3** CuCl/HCOOMe-catalyzed methoxylation of aryl bromides[a]



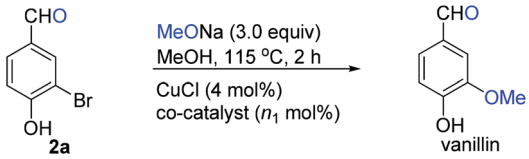

[a] Reaction conditions: aryl bromides (4.0 mmol), MeOH (5 mL), MeONa (0.65 g, 12 mmol), CuCl (15.8 mg, 0.16 mmol) and HCOOMe (0.10 mL, $d$ = 0.97 g mL$^{-1}$, 1.6 mmol) at 115 °C for 2 h. [b] Isolated yield *via* column chromatography. [c] Conv. (%)/Sele. (%) determined by GC-MS from the total ionization chromatography area normalization method (see ESI for details).

in the presence of MeONa, pure MeOH (colourless, purity >99%, water content <0.12%) was directly recovered after the completion of the reaction under the open system.[18]

To further unravel the efficiency and applicability of the CuCl/HCOOMe–MeONa/MeOH system, a variety of unactivated aryl bromides were evaluated for a classic Ullmann-type C–O coupling reaction (Table 3). Most pleasingly, the protocol could consistently realize a perfect methoxylation of EDG-substituted aryl bromides to access the corresponding anisoles **7a–g** in quantitative yields. Likewise, for weak EWG-substituted aryl bromides, the methoxylation protocol quantitatively achieved the desired anisoles **7h**. A conversion of 100% and a selectivity of 100% were detected by GC-MS analysis in all the cases excluding the common dehalogenation side-reaction (see ESI† for details).[19] The excellent efficiency and direct recovery of pure MeOH highlighted the potential of this protocol in practical applications.

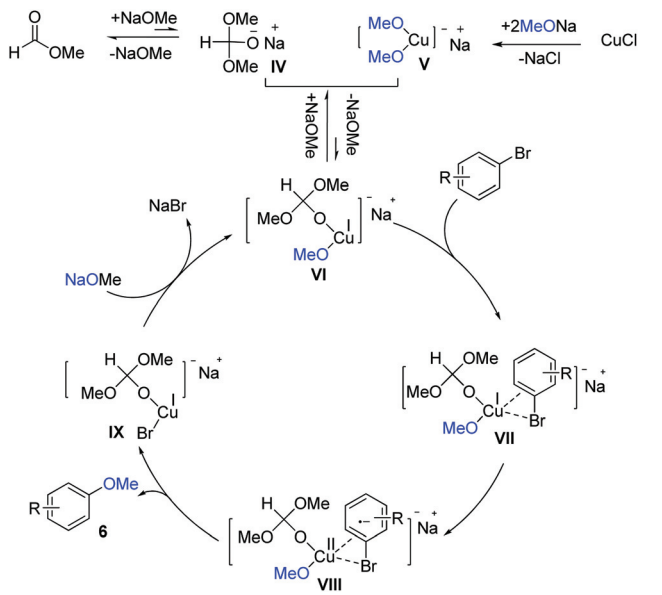
The control experiments on the methoxylation of **2a** demonstrably suggested that, relative to MeCOOMe and DMF, HCOOMe was the most powerful co-catalyst (Table 4). According to earlier reports,[18,20] a modified mechanism was proposed for the CuCl/HCOOMe-catalyzed methoxylation (Scheme 8). Comparing with acetates or amides,[18b] the formate HCOOMe possesses a higher reactivity firstly bringing about the tetrahedral intermediate **IV** under alkaline conditions. Then **IV** and a cuprate-like intermediate **V**[20a] are incorporated into a direct contributing intermediate **VI**, of which the aryl bromide coordinating with the copper-center gives a complex **VII**. Eventually, the copper(II) intermediate **VIII**, which is formed by transferring electron density from the copper(I) atom to the aryl moiety, decomposes into the product and the

**Table 4** CuCl-catalyzed methoxylation of **2a** with different co-catalysts[a]




| Entry | Co-catalyst | $n_1$ mol% | Conv./Sele.[b] (%) | Yield[c] (%) |
|---|---|---|---|---|
| 1 | HCOOMe | 40 | 100/100 | 98 |
| 2 | MeCOOMe | 40 | 95/100 | 91 |
| 3 | DMF | 40 | 94/100 | 89 |

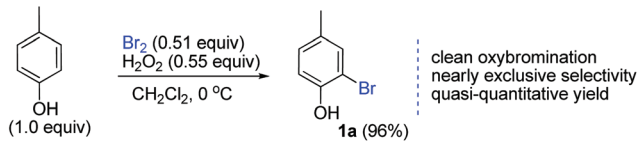
[a] Reaction conditions: **2a** (4.0 mmol), MeOH (5 mL), MeONa (0.65 g, 12 mmol), CuCl (15.8 mg, 0.16 mmol) and co-catalyst ($n_1$ mol%) at 115 °C for 2 h. [b] Determined by GC-MS from the total ionization chromatography area normalization method (see ESI for details). [c] Isolated yield *via* column chromatography.




**Scheme 8** Possible mechanism for CuCl/HCOOMe-catalyzed methoxylation.

copper(I) species **IX** *via* a synergistic reductive elimination process. Subsequently, the key intermediate **VI** is regenerated *via* an anion metathesis of **IX** and MeONa. Also, it was reasonably presumed that, similar to the sodium enolate of **2a** (Scheme 4), the sodium enolate of vanillin should occur under the working conditions, accordingly protecting its original aldehyde group.

Finally, our efforts focused on developing a clean and selective bromination protocol for the synthesis of the intermediate 2-bromo-4-cresol (**1a**) from 4-cresol. As an alternative for traditional bromination, oxybromination has attracted considerable attention and remarkable advances have been acquired.[21] Experiments have shown that common chlorinated light alkanes, such as 1,2-dichloroethane, carbon tetrachloride, chloroform, and dichloromethane, are able to conduct oxy-




Scheme 9 Hydrogen peroxide-based oxybromination of 4-cresol.



bromination with high selectivity.[21b,c] Choosing the lower toxic $CH_2Cl_2$ as a solvent here,[22] we successfully carried out a mild and highly selective oxybromination of 4-cresol with 0.51 equiv. $Br_2$ and 0.55 equiv. $H_2O_2$ as the brominating agents (Scheme 9). To the solution of 4-cresol (10 mmol), $H_2O_2$ (30%, 5.5 mmol) and $CH_2Cl_2$ (10 mL),[22] a solution of bromine (5.1 mmol) and $CH_2Cl_2$ (5 mL) were slowly added at 0 °C for 4 h through a syringe pump. The resulting mixture was stirred for another 4 h so as to provide the desired ortho-monobromination product **1a** in a quasi-quantitative yield (96%) with a near exclusive selectivity (only 0.9% dibromination product, see ESI†). With the excellent bromine atom-economy, the extra recovery of HBr and its environmental impact were excluded. In comparison, the oxybromination of 4-hydroxybenzaldehyde (**2b**) was of a lower selectivity giving the desired monobromination product **2a** in a reduced yield of 73% (13% dibromination product, see ESI†). Obviously, the perfect oxybromination of 4-cresol again demonstrated that Scheme 2c is feasible for preparing vanillin. We achieved this approach to vanillin with a highly efficient three-step sequence of oxybromination–oxidation–methoxylation using common chemicals 4-cresol, $Br_2$ and $H_2O_2$ as the starting feedstocks (Scheme 2c).

## Conclusions

In conclusion, we have developed an efficient and practical approach to the famous flavor and fragrance compound vanillin from 4-cresol *via* a three-step sequence of quasi-quantitative selective clean oxybromination, high-yield selective aerobic oxidation and quantitative methoxylation with recovery of pure methanol. Given the simplicity and sustainability of the reaction steps, as well as the commercial importance of the product, the approach could unlock a promising application prospect in the manufacturing of vanillin.

## Experimental section

### General information

All reactions were carried out in oven-dried glassware and monitored by thin layer chromatography (TLC, pre-coated silica gel plates containing $HF_{254}$). Reaction products were purified *via* column chromatography on silica gel (300–400 mesh). Melting points were determined using open capillaries and were uncorrected. NMR spectra were determined on a Bruker AV400 in $CDCl_3$ or DMSO-$d_6$, with TMS as the internal standard for $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz), respectively. HRMS were carried out on a QSTAR Pulsar I LC/TOF MS mass spectrometer or a Micromass GCTTM gas chromatograph-mass spectrometer. GC-MS were carried out on an Agilent 6890-5973N gas chromatograph-mass spectrometer.

### General procedure for oxybromination of 4-cresol into 1a

A three-necked flask was charged with 4-cresol (1.08 g, 10 mmol), $CH_2Cl_2$ (10 mL)[22] and $H_2O_2$ (30%, 0.58 mL, $d$ = 1.11 g mL$^{-1}$, 5.5 mmol), and then the solution was cooled to 0 °C. At this temperature, to the solution was slowly added a solution of bromine (0.26 mL, $d$ = 3.12 g mL$^{-1}$, 5.1 mmol) and $CH_2Cl_2$ (5 mL) over 4 h through a syringe pump. Afterwards, the mixture was stirred for another 4 h. Aqueous $NaHSO_3$ (10 mL, 2%) was added to the mixture at 0 °C, and the reaction solution was allowed to stir for 1 h at room temperature. Furthermore, the solution was partitioned into two layers, and the aqueous phase was extracted with $CH_2Cl_2$ (5 mL × 3). Finally, the combined organic layers were dried over anhydrous $Na_2SO_4$, and concentrated to give a crude oil, which was purified *via* column chromatography on silica gel (eluent: petroleum ether–ethyl acetate 20 : 1) to provide the desired product **1a** (chromatographic purification can provide a more credible yield). Yellow oil, 1.80 g (96%); $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 7.28 (br d, $J$ = 1.6 Hz, 1H), 7.02 (br d, $J$ = 8.0, 1H), 6.92 (br d, $J$ = 8.0 Hz, 1H), 5.40 (br s, 1H), 2.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 150.0, 132.1, 131.4, 129.8, 115.8, 109.8, 20.2; HRMS (EI): $m/z$ [$M^+$] calcd for $C_7H_7OBr$ 185.9680, found 185.9682.

### General procedure for the oxidation of 1a into 2a

A three-necked flask was charged with EG (10 mL), **1a** (0.94 g, 5.0 mmol), $Co(OAc)_2{\cdot}4H_2O$ (12.5 mg, 0.05 mmol) and solid NaOH (0.80 g, 20 mmol), and then the solution was heated to 80 °C. The molecular oxygen was continuously supplied to the reaction through a top tube inlet for 9 h. Hydrochloric acid (10 mL, 10%) and methyl *tert*-butyl ether (MTBE, 15 mL) were successively added to the reaction mixture at room temperature. The MTBE phase was separated, and the aqueous phase was further extracted with MTBE (15 mL × 2). The combined organic layers were dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* to give a residue, which was purified *via* column chromatography on silica gel (eluent: petroleum ether–ethyl acetate 20 : 1) to provide the desired product **2a** (chromatographic purification can provide a more credible yield). Pale yellow solid, 0.90 g (90%), m.p. 130–132 °C (lit.[10] m.p. 130–132 °C); $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 9.83 (br s, 1H), 8.04 (br s, 1H), 7.77 (br d, $J$ = 8.4 Hz, 1H), 7.15 (br d, $J$ = 8.4 Hz, 1H), 6.43 (br s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 192.7, 151.8, 132.9, 130.3, 128.1, 127.5, 127.4; HRMS (EI): $m/z$ [$M^+$] calcd for $C_7H_5O_2Br$ 199.9473, found 199.9474.

### General procedure for the methoxylation of 2a into vanillin

The Teflon-lined autoclave (25 mL) was charged with **2a** (0.80 g, 4.0 mmol), MeOH (5 mL), MeONa (0.65 g, 12 mmol), CuCl (15.8 mg, 0.16 mmol) and HCOOMe (0.10 mL, $d$ = 0.97 g mL$^{-1}$, 1.6 mmol). The autoclave was heated to 115 °C, and stirred for 2 h. After the completion of the reaction, the reactor

was cooled to room temperature. The reaction mixture was stirred for 0.5 h in an open system, and then concentrated to recover pure MeOH. To the residue was added MTBE (5 mL) and diluted hydrochloric acid (1.0 M, 8 mL) to adjust the pH to 2.0–3.0. Furthermore, the solution was partitioned into two layers, and the aqueous phase was extracted with MTBE (5 mL × 3). The combined organic layers were dried over anhydrous $Na_2SO_4$, and concentrated *in vacuo* to give a solid, which was purified *via* column chromatography on silica gel (eluent: petroleum ether–ethyl acetate 15 : 1) to provide the desired vanillin. White solid, 0.59 g (98%), m.p. 82–83 °C (lit.[3a] m.p. 80–81 °C); $^1$H NMR (400 MHz, $CDCl_3$, ppm): $\delta$ 9.82 (br s, 1H), 7.43–7.41 (m, 2H), 7.04 (br d, $J$ = 8.8 Hz, 1H), 6.30 (br s, 1H), 3.96 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, ppm): $\delta$ 191.1, 151.8, 147.2, 129.8, 127.6, 114.5, 108.9, 56.1; HRMS (ESI): $m/z$ [M − H$^+$] calcd for $C_8H_7O_3$ 151.0395, found 151.0400. Generally, the purity of the recovered MeOH was more than 99% as measured by GC, and the water content was less than 0.12% as measured by the Karl Fischer method.

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## Notes and references

1 (*a*) S. R. Rao and G. A. Ravishankar, *J. Sci. Food Agric.*, 2000, **80**, 289; (*b*) M. J. W. Dignum, J. Kerler and R. Verpoorte, *Food Rev. Int.*, 2001, **17**, 119.

2 E. H. Hansen, B. L. Møller, G. R. Kock, C. M. Bunner, C. Kristensen, O. R. Jensen, F. T. Okkels, C. E. Olsen, M. S. Motawia and J. Hansen, *Appl. Environ. Microbiol.*, 2009, **75**, 2765.

3 (*a*) J. Kamlet and E. Conn, *US Pat*, 2640083, 1953; (*b*) H.-R. Bjorsvik, L. Liguori and F. Minisci, *Org. Process Res. Dev.*, 2000, **4**, 534.

4 (*a*) R. H. H. van den Heuvel, M. W. Fraaije, C. Laane and W. J. H. van Berkel, *J. Agric. Food Chem.*, 2001, **49**, 2954; (*b*) L.-Q. Tan, L.-L. Xia, H.-F. Mao and C.-Z. Zhang, *CN Pat*, 1401622A, 2003; (*c*) R. H. H. van den Heuvel, W. A. M. van den Berg, S. Rovida and W. J. H. van Berkel, *J. Biol. Chem.*, 2004, **279**, 33492; (*d*) The route (Scheme 2c) disclosed by our group: Y.-F. Ji, H. Wan, J.-L. Zhang, Y.-F. Chen, W.-H. Jin and Y. Wang, *CN Pat*, 101774897A, 2010.

5 For oxidation of 4-cresol mediated by NaOH, see: (*a*) F. Wang, G. Yang, W. Zhang, W. Wu and J. Xu, *Chem. Commun.*, 2003, 1172; (*b*) F. Wang, G. Yang, W. Zhang, W. Wu and J. Xu, *Adv. Synth. Catal.*, 2004, **346**, 633; (*c*) C. V. Rode, M. V. Sonar, J. M. Nadgeri and R. V. Chaudhari, *Org. Process Res. Dev.*, 2004, **8**, 873.

6 Selected examples for the oxidation of electron-donating group-containing 4-cresols, see: (*a*) W. Baik, H. J. Lee, J. M. Jang, S. Koo and B. H. Kim, *J. Org. Chem.*, 2000, **65**, 108; (*b*) T. Yoshikuni, *J. Mol. Catal. A: Chem.*, 2002, **187**, 143; (*c*) C. Boldron, P. Gamez, D. M. Tooke, A. L. Spek and J. Reedijk, *Angew. Chem., Int. Ed.*, 2005, **44**, 3585; (*d*) C. Boldron, S. Özalp-Yaman, P. Gamez, D. M. Tooke, A. L. Spek and J. Reedijk, *Dalton Trans.*, 2005, 3535; (*e*) X. Sun, Z. M. A. Judeh, B. F. Ali and S. F. Alshahateet, *Catal. Today*, 2008, **131**, 423; (*f*) A. K. Tripathi, J. K. Sama and S. C. Taneja, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2010, **49**, 379.

7 Selected reviews on molecular oxygen as oxidant, see: (*a*) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329; (*b*) J. Piera and J. E. Backvall, *Angew. Chem., Int. Ed.*, 2008, **47**, 3506; (*c*) W. Wu and H. Jiang, *Acc. Chem. Res.*, 2012, **45**, 1736; (*d*) C. Parmeggiani and F. Cardona, *Green Chem.*, 2012, **14**, 547.

8 (*a*) S. Caron, R. W. Dugger, S. G. Ruggeri, J. A. Ragan and D. H. B. Ripin, *Chem. Rev.*, 2006, **106**, 2943; (*b*) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks and T. Y. Zhang, *Green Chem.*, 2007, **9**, 411.

9 J. Hu, Y. Hu, J. Mao, J. Yao, Z. Chen and H. Li, *Green Chem.*, 2012, **14**, 2894.

10 J.-A. Jiang, C. Chen, J.-G. Huang, H.-W. Liu, S. Cao and Y.-F. Ji, *Green Chem.*, 2014, **16**, 1248.

11 (*a*) M. C. Kozlowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev.*, 2009, **38**, 3193; (*b*) J. A. Ashenhurst, *Chem. Soc. Rev.*, 2010, **39**, 540; (*c*) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234.

12 M. Inagaki, N. Haga, M. Kobayashi, N. Ohta, S. Kamata and T. Tsuri, *J. Org. Chem.*, 2002, **67**, 125.

13 (*a*) A. Onopchenko, J. G. D. Schultz and R. Seekircher, *J. Org. Chem.*, 1972, **37**, 1414; (*b*) T. Iwahama, Y. Yoshino, T. Keitoku, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2000, **65**, 6502; (*c*) X. Baucherel, L. Gonsalvi, I. W. C. E. Arends, S. Ellwood and R. A. Sheldon, *Adv. Synth. Catal.*, 2004, **346**, 286.

14 For hydrolysis of enol ethers, see: (*a*) A. J. Kresge, H. L. Chen, Y. Chiang, E. Murrill, M. A. Payne and D. S. Sagatys, *J. Am. Chem. Soc.*, 1971, **93**, 413; (*b*) A. J. Kresge and H. J. Chen, *J. Am. Chem. Soc.*, 1972, **94**, 2818; (*c*) A. J. Kresge, D. S. Sagatys and H. L. Chen, *J. Am. Chem. Soc.*, 1977, **99**, 7228.

15 J. Lindley, *Tetrahedron*, 1984, **40**, 1433.

16 (*a*) K. E. Torraca, X.-H. Huang, C. A. Parrish and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 10770; (*b*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131.

17 W. J. Moorman, H. W. Ahlers, R. E. Chapin, G. P. Daston, P. M. D. Foster, R. J. Kavlock, J. S. Schnorr, T. M. Morawetz and S. M. Schrader, *Reprod. Toxicol.*, 2000, **14**, 293.

18 (*a*) J.-F. Carpentier, Y. Castanet, J. Brocard, A. Mortreux and F. Petit, *Tetrahedron Lett.*, 1991, **32**, 4705; (*b*) P. Capdevielle and M. Maumy, *Tetrahedron Lett.*, 1993, **34**, 1007.

19 (*a*) D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, 1956, **21**, 516; (*b*) J.-K. Huang, Y. Chen, J. Chan, M. L. Ronk, R. D. Larsen and M. M. Faul, *Synlett*, 2011, **22**, 1419.

20 (*a*) H. L. Aalten, G. V. Koten, D. M. Grove, T. Kuilman, O. G. Piekstra, L. A. Hulshof and R. A. Sheldon, *Tetrahedron*, 1989, **45**, 5565; (*b*) J.-F. Marcoux, S. Doye and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 10539.

21 (*a*) U. Bora, G. Bose, M. Chaudhuri, S. Dhar, R. Gopinath, A. Khan and B. Patel, *Org. Lett.*, 2000, **2**, 247; (*b*) R. Mestres and J. Palenzuela, *Green Chem.*, 2002, **4**, 314; (*c*) S. Adimurthy, G. Ramachandraiah, A. V. Bedekar, S. Ghosh, B. C. Ranu and P. K. Ghosh, *Green Chem.*, 2006, **8**, 916; (*d*) B. Ganchegui and W. Leitner, *Green Chem.*, 2007, **9**, 26.

22 Relative to $CHCl_3$ and $CCl_4$, $CH_2Cl_2$ as a harmfullness halogenated solvent has been frequently used, see: (*a*) M. H. A. Janssen, J. F. Chesa Castellana, H. Jackman, P. J. Dunn and R. A. Sheldon, *Green Chem.*, 2011, **13**, 905; (*b*) D. D. Do Pham, G. F. Kelso, Y. Yang and M. T. W. Hearn, *Green Chem.*, 2012, **14**, 1189; (*c*) J. Bensemhoun and S. Condon, *Green Chem.*, 2012, **14**, 2595; (*d*) R. Turgis, I. Billault, S. Acherar, J. Auge and M.-C. Scherrmann, *Green Chem.*, 2013, **15**, 1016.

 