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Practical Ligand-Free Copper-Catalysed Short-Chain Alkoxylation of Unactivated Aryl Bromides

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An efficient and practical short-chain alkoxylation of unactivated aryl bromides has been developed with special attention focussed on the applicability of the reaction. Sodium alkoxide is used as the nucleophile, and the corresponding alcohol as the solvent. The reaction requires neither precious metals nor organic ligands. It uses a catalytic system consisting of copper(I) bromide as a catalyst, the corresponding alkyl formate as a noncontaminating cocatalyst, and lithium chloride as an additive. A wide range of substrates and test cases highlight the synthetic utility of the approach. Considering the commercial accessibility and affordability of the feedstocks, this protocol shows promise as a new alternative for the sustainable preparation of aryl alkyl ethers.

Introduction

It is well known that aryl alkyl ethers are important structures that are often found in pharmaceuticals, agrochemicals, and fine organic chemicals (Figure 1).[1] For instance, ethyl vanillin, which has an aryl ethyl ether framework, is a value-added analogue of vanillin, and is one of the most famous flavouring agents in the food industry.[2] In addition, the aryl butyl ether derivative pramoxine has served clinically as a classic local anaesthetic agent for decades as a result of its high anaesthetic potency and low toxicity.[1a] Furthermore, the convenient *O*-dealkylation of aryl alkyl ethers represents a useful approach to phenols.[3]

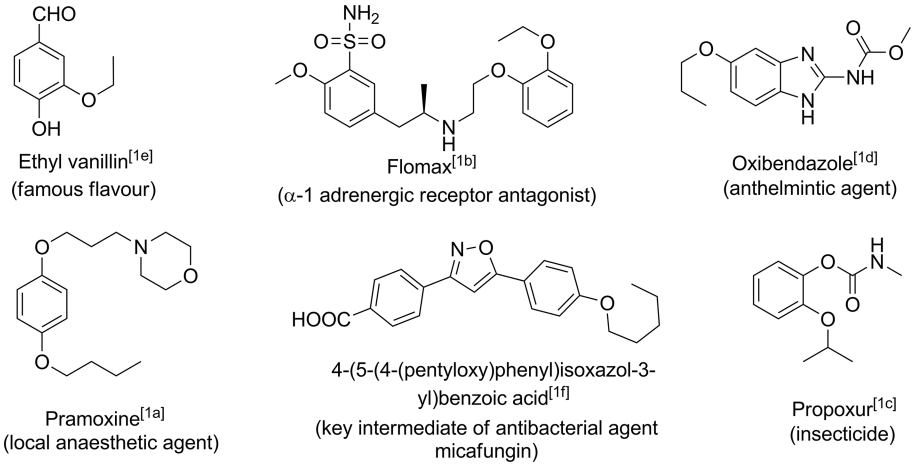

Figure 1. Selected important compounds containing aryl alkyl ether motifs.

Unlike activated aryl halides bearing strongly electron-withdrawing groups like NO_2, CN, CF_3, etc. which react by an aromatic S_NAr mechanism,[4] unactivated electron-rich aryl substrates require a transition-metal catalyst to undergo nucleophilic coupling reactions. Although the palladium-catalysed C–O coupling of unactivated aryl halides has been quite successful,[5] some inherent limitations such

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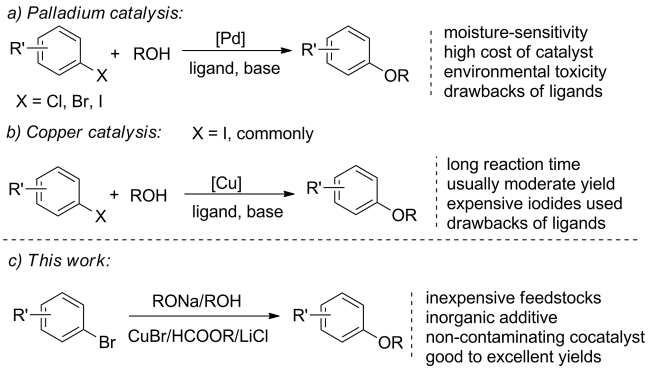
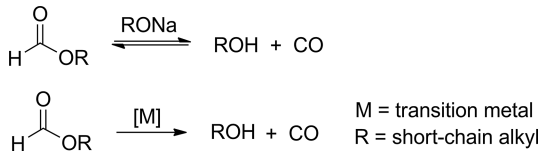
as moisture sensitivity, the cost of palladium, the tedious synthesis of the ligands, the environmental toxicity of phosphine ligands,[6] and the possibility of a competing β-H elimination side-reaction,[7] might restrict its synthetic applicability (Scheme 1, a).



Scheme 1. Transition-metal-catalysed alkoxylation of aryl halides.

In contrast, copper-catalysed Ullmann-type C–O bond formation has been an attractive alternative by virtue of the relatively low toxicity and cost of the catalyst, as well as a decreased amount of β-H elimination.[8] For these reasons, considerable efforts have been devoted to the development of copper-catalysed C–O coupling methods for the construction of aryl alkyl ethers. Generally, these catalytic systems have required ligands for the transformations to be effective.[9] Drawbacks associated with the use of ligands include issues of cost, separation, and pollution. Furthermore, from a practical perspective, the use of aryl iodides as reaction substrates and copper iodide as catalyst would still make an alkoxylation reaction uneconomical compared to the more cost-effective aryl bromide and copper bromide (Scheme 1, b). Therefore, it would be highly desirable to develop a ligand-free copper-catalysed alkoxylation reaction of unactivated aryl bromides.

Until now, ligand-free copper-catalysed alkoxylation strategies have remained scarce for unactivated aryl halides, due to the low catalytic activity and instability of copper(I) ions in the absence of organic ligands.[10] Recently, we disclosed a ligand-free method, catalysed by copper(I) chloride/methyl formate, for the methoxylation of unactivated aryl bromides to give anisoles in nearly quantitative yields.[11] As part of our ongoing research into the exploration of practical methods for C_{sp2}–OR_{alkyl} formation, in this paper we report a ligand-free copper-catalysed method for the short-chain alkoxylation of unactivated aryl bromides. The protocol uses nonprecious copper(I) bromide as a catalyst, the matching alkyl formate as a cocatalyst, inorganic lithium chloride as an additive, the corresponding sodium alkoxide as the nucleophile, and the corresponding alcohol as the solvent (Scheme 1, c). The presence of the sodium alkoxide, which can function both as a strong base and an active nucleophile, could enhance the etherification process under the ligand-free conditions. The alkyl formate plays a cocatalytic role by undergoing a nucleophilic addition with the alkoxide anion in the catalytic cycle.[11] Moreover, it enables the clean recovery of the alcohol solvent after completion of the reaction, due to its decarbonylative decomposition into alcohol and CO in the presence of sodium alkoxide and transition metal in the open system (Scheme 2).[12]

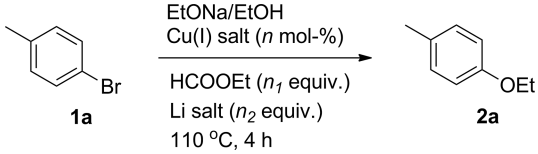


Scheme 2. Decarbonylative decomposition of alkyl formates.

Results and Discussion

Given the fact that copper(I) ion can quickly be reduced into elemental copper in ethanolic sodium ethoxide, and thus lose its catalytic activity,[13] we chose ethoxylation as a model reaction to optimize the reaction conditions. The model reaction with substrate 4-bromotoluene (**1a**) was conducted in a Teflon®-lined sealed tube at 110 °C for 4 h, in the presence of copper(I) salt (15 mol-%) as the catalyst, and ethyl formate (1.0 equiv.) as the cocatalyst (Table 1). Initially, we observed that the reaction gave only a 39% conversion (by GC–MS analysis) in the absence of a lithium salt (Table 1, entry 1). The low yield is probably due to the reduction of copper(I) ion (Scheme 3).[13] Hence, it was crucial to find an additive that could suppress the reductive

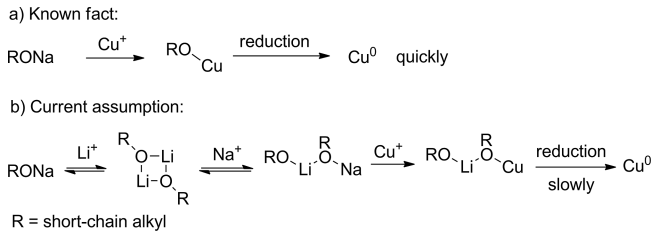
Table 1. Optimization of the reaction conditions.[a]



Entry	Cu^I salt (n mol-%)	HCOOEt [n_1 equiv.]	Li salt (n_2 equiv.)	Conversion [%]/ selectivity [%][b]
1	CuBr (15)	1.0	0	39/100
2	CuBr (15)	1.0	$(COO)_2Li_2$ (1.0)	84/100
3	CuBr (15)	1.0	HCOOLi (1.0)	94/100
4	CuBr (15)	1.0	PhCOOLi (1.0)	96/100
5	CuBr (15)	1.0	LiBr (1.0)	96/100
6	CuBr (15)	1.0	AcOLi (1.0)	100/100
7	CuBr (15)	1.0	LiCl (1.0)	100/100
8	CuBr (15)	1.0	LiCl (0.7)	95/100
9	CuBr (0)	1.0	LiCl (1.0)	0/0
10	CuBr (15)	0	LiCl (1.0)	0/0
11	CuCl (15)	1.0	LiCl (1.0)	40/100
12[c]	CuBr (15)	NMP	0	0/0
13[d]	CuBr (15)	1.0	LiCl (1.0)	0/0
14[e]	CuBr (15)	1.0	LiCl (1.0)	100/100

[a] Reaction conditions: **1a** (3.0 mmol), EtONa [6.0 mmol, freshly prepared from Na (6.0 mmol) and EtOH (6 mL)], Cu^I salt (n mol-%), HCOOEt (n_1 equiv.), and Li salt (n_2 equiv.) in a Teflon®-lined sealed tube at 110 °C for 4 h. [b] Conversion [%] and selectivity [%] determined by GC–MS using the area normalization method in the total ionization chromatogram. [c] Reaction with 1-methyl-2-pyrrolidinone (NMP; 6 mL) instead of HCOOEt in a flask. [d] **1a** replaced by 4-chlorotoluene. [e] **1a** replaced by 4-iodotoluene.

capacity of alkoxide anion. Inspired by previous elegant work,[14,15] we realized that the single-shell lithium ion has a unique affinity for oxygen,[14] and probably forms a dimeric oxygen–lithium complex to decrease the reductive capacity of the alkoxide anion (Scheme 3).[15]



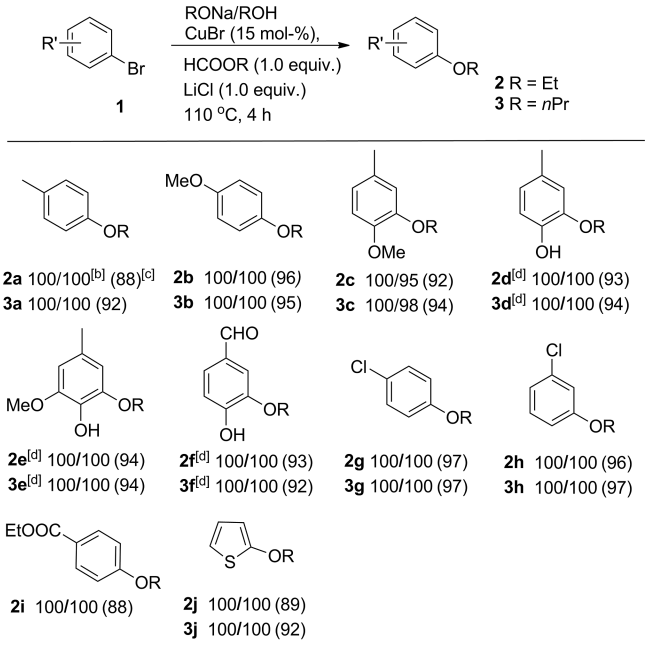
Scheme 3. Reduction of Cu^{I} ion by sodium alkoxide in the absence or presence of a lithium salt.

To our delight, the screening of lithium salts revealed that lithium oxalate had a beneficial effect on the reaction, giving 84% conversion (Table 1, entry 2). The ethoxylation reaction of **1a** proceeded even more effectively when lithium formate, lithium benzoate, or lithium bromide was used as the additive, delivering the desired product (i.e., **2a**) with 94–96% conversion and excellent selectivity (Table 1, entries 3–5). Lithium acetate and lithium chloride were equally effective, and gave the highest efficiency (Table 1, entries 6 and 7). We chose to use inorganic lithium chloride as the additive due to its nontoxicity, low cost, and ready recoverability.[16] Lowering the loading of lithium chloride (0.7 equiv.) resulted in a visible loss of efficiency (95% conversion; Table 1, entry 8).

Next, the catalyst and cocatalyst were evaluated in the presence of lithium chloride. We found that copper(I) bromide and ethyl formate were equally important for the reaction. In the absence of either of these, no product was detected (Table 1, entries 9 and 10). On the other hand, the conversion of **1a** decreased sharply to 40% when copper(I) bromide was replaced with copper(I) chloride (Table 1, entry 11). When 1-methyl-2-pyrrolidinone (NMP) was used as an aprotic cosolvent instead of ethyl formate and lithium chloride,[13] none of the desired product was produced, and the rapid generation of elemental copper was observed (Table 1, entry 12). Moreover, 4-chlorotoluene did not deliver any of the product (Table 1, entry 13), whereas its more reactive counterpart 4-iodotoluene underwent ethoxylation as effectively as **1a** with full conversion and exclusive selectivity (Table 1, entry 14). On the basis of these results, the standard reaction conditions (Table 1, entry 7) were established to probe the generality of the alkoxylation process.

Ethoxylation and propoxylation were evaluated first, and the results are shown in Table 2. In general, substrates containing electron-donating (**1a**–**1e**) and weakly electron-withdrawing (**1g**–**1i**) substitutents were cleanly transformed into the corresponding aryl ethers in excellent yields, using ethyl formate or propyl formate as the matching cocatalyst. The vast majority of the aryl bromides delivered the desired products with full conversion and exclusive selectivity. A range of functionalities including methyl, methoxy, hydroxy, chloro, formyl, ethoxycarbonyl, and thiophenyl groups were well tolerated.

Table 2. Substrate scope of the ethoxylation and propoxylation reactions.[a]



[a] Reaction conditions: **1** (3.0 mmol), RONa [6.0 mmol, freshly prepared from Na (6.0 mmol) and ROH (6 mL)], CuBr (0.45 mmol), HCOOR (1.0 equiv.), LiCl (1.0 equiv.) in a Teflon®-lined sealed tube at 110 °C for 4 h. [b] Conversion [%] and selectivity [%] were determined by GC–MS using the area normalization method in the total ionization chromatogram. [c] Isolated yields [%]; **2a**, **3a**, **2j**, and **3j** as volatile products had lower yields. [d] The substrate with a phenolic hydroxyl group needed an additional 1.0 equiv. of RONa.

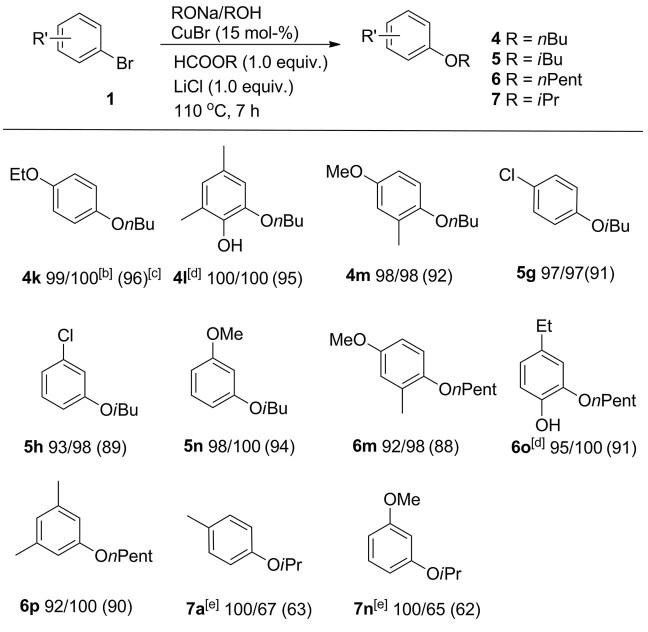
We found that a trace amount of dehalogenated by-product was formed in the cases of the aryl bromides containing an *ortho*-methoxy group (95 and 98% selectivity for **2c** and **3c**, respectively, see Supporting Information).[17] In contrast, the dehalogenation was not observed in *ortho*-hydroxy-substituted substrates (full conversion and exclusive selectivity for **2d**–**2f** and **3d**–**3f**). We presume that coordination between the phenolate anion and the active copper species removes the possibility of dehalogenation in these cases. This protection effect resulting from the presence of the formyl and hydroxy groups is proposed based on the previously described dearomatization–enolization of 4-hydroxybenzaldehydes in the synthesis of vanillin analogues (**2f** and **3f**).[11]

For substrate **1i**, the ethoxylation gave a slightly lower yield of 88% of the product (i.e., **2i**), mainly due to the lower stability of the ethoxycarbonyl group. The electron-rich heterocyclic 2-bromothiophene (**1j**) was also amenable to this protocol, delivering the target products (i.e., **2j** and **3j**) with full conversion and exclusive selectivity.

Next, we examined further short-chain sodium alkoxides as reaction partners (Table 3). Butoxylation, isobutoxylation, and pentyloxylation reactions were conducted with a

prolonged reaction time of 7 h, but under otherwise identical conditions. Gratifyingly, the butoxylation reactions of *para*-bromophenetole (**1k**) and *ortho*-bromophenol (**1l**) proceeded smoothly to give the products (i.e., **4k** and **4l**) in >95% yields. The butoxylation of *ortho*-methyl-substituted bromoarene **1m** also gave **4m** in good yield, but a trace amount of dehalogenated by-product was observed (98% conversion/98% selectivity). Although the sterically more demanding isobutoxylation reactions suffered somewhat with slightly lower conversions of 93–98% (**1g**, **1h**, and **1n**) and marginal dehalogenations (**1g** and **1h**), the reactions still gave the isobutyl ethers in >89% yields (**5g**, **5h**, and **5n**). In the pentyloxylation reactions, substrates **1m**, **1o**, and **1p** were effectively converted into products **6m**, **6o**, and **6p** with excellent yields of 88–91%. Meanwhile, some dehalogenation was seen in the reaction to give **6m**.

Table 3. Further substrate scope of the alkoxylation reactions.[a]

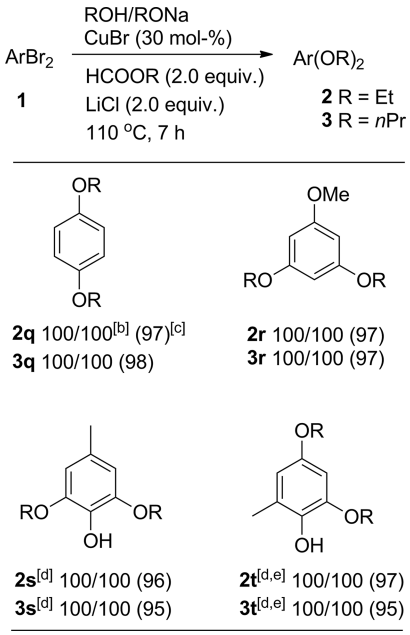


[a] Reaction conditions: **1** (3.0 mmol), RONa [6.0 mmol, freshly prepared from Na (6.0 mmol) and ROH (6 mL)], CuBr (0.45 mmol), HCOOR (1.0 equiv.), LiCl (1.0 equiv.) in a Teflon®-lined sealed tube at 110 °C for 7 h. [b] Conversion [%] and selectivity [%] determined by GC–MS using the area normalization method in the total ionization chromatogram. [c] Isolated yield [%]. [d] The substrate with a phenolic hydroxyl group needed an additional 1.0 equiv. of RONa. [e] For a reaction time of 12 h.

Although the isopropoxylation reactions of **1a** and **1n** proceeded with full conversions, they gave only moderate yields (**7a** and **7n**, see Supporting Information) as a result of severe dehalogenation. This is in contrast with the results of the linear propoxylation reaction.[9e,9f] We speculate that the bulky secondary alkoxide anion, which has a poor affinity for the copper(I) ion,[9f] requires a longer reaction time to complete the desired alkoxylation. However, during these slower reactions, the copper reacts competitively with the unreacted bromoarenes to give an arylcopper species that then leads to the formation of the dehalogenated arenes.[13]

The method can also be used with unactivated dibromoarenes (Table 4). Most of the substrates underwent diethoxylation and dipropoxylation with full conversion and exclusive selectivity (**2q**–**2s**, **3q**–**3s**). A prolonged reaction time of 10 h was required for dibromoarene **1t**, which then gave an almost quantitative yield. This approach to polyalkoxylation clearly has the potential for further development.

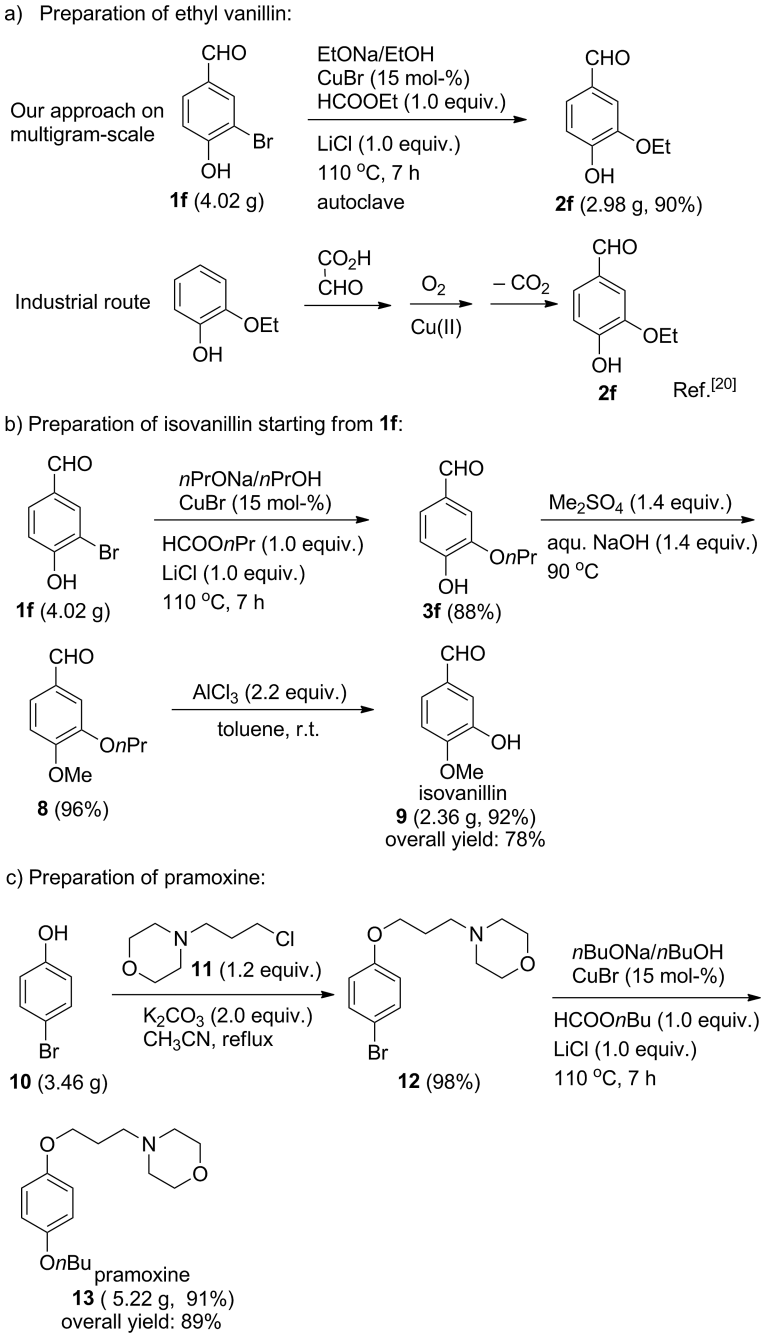
Table 4. Dialkoxylation.[a]



[a] Reaction conditions: **1** (2.0 mmol), RONa [8.0 mmol, freshly prepared from Na (8.0 mmol) and ROH (8 mL)], CuBr (0.6 mmol), HCOOR (2.0 equiv.), LiCl (2.0 equiv.) in a Teflon®-lined sealed tube at 110 °C for 7 h. [b] Conversion [%] and selectivity [%] determined by GC–MS using the area normalization method in the total ionization chromatogram. [c] Isolated yield [%]. [d] The substrate with a phenolic hydroxyl group needed an additional 1.0 equiv. of RONa. [e] For a reaction time of 10 h.

There is a trend to replace vanillin in the flavouring and food industries by ethyl vanillin (**2f**; 3-ethoxy-4-hydroxybenzaldehyde) because of its superior properties.[2a] To demonstrate the synthetic utility of the protocol, the preparation of **2f** was carried out on a multigram scale (Scheme 4, a). Pleasingly, **1f** was smoothly converted into ethyl vanillin (**2f**) in 90% yield, with the clean and quantitative recovery of ethanol. Compared with the industrial route (Scheme 4, a),[18] the new method introduces a promising alternative for the synthesis of **2f** on the basis of the efficient preparation of **1f**.[11]

The synthetic utility of this alkoxylation approach was further demonstrated through the multigram-scale preparations of the common organic intermediate isovanillin (**9**; Scheme 4, b)[19] and the classic anaesthetic agent pramoxine (**13**; Scheme 4, c).[1a] Notably, the new route to **9** delivered an overall yield of 78% through a facile three-step sequence of propoxylation, methylation, and depropylation.[20] Similarly, the new approach to pramoxine staring from inexpen-

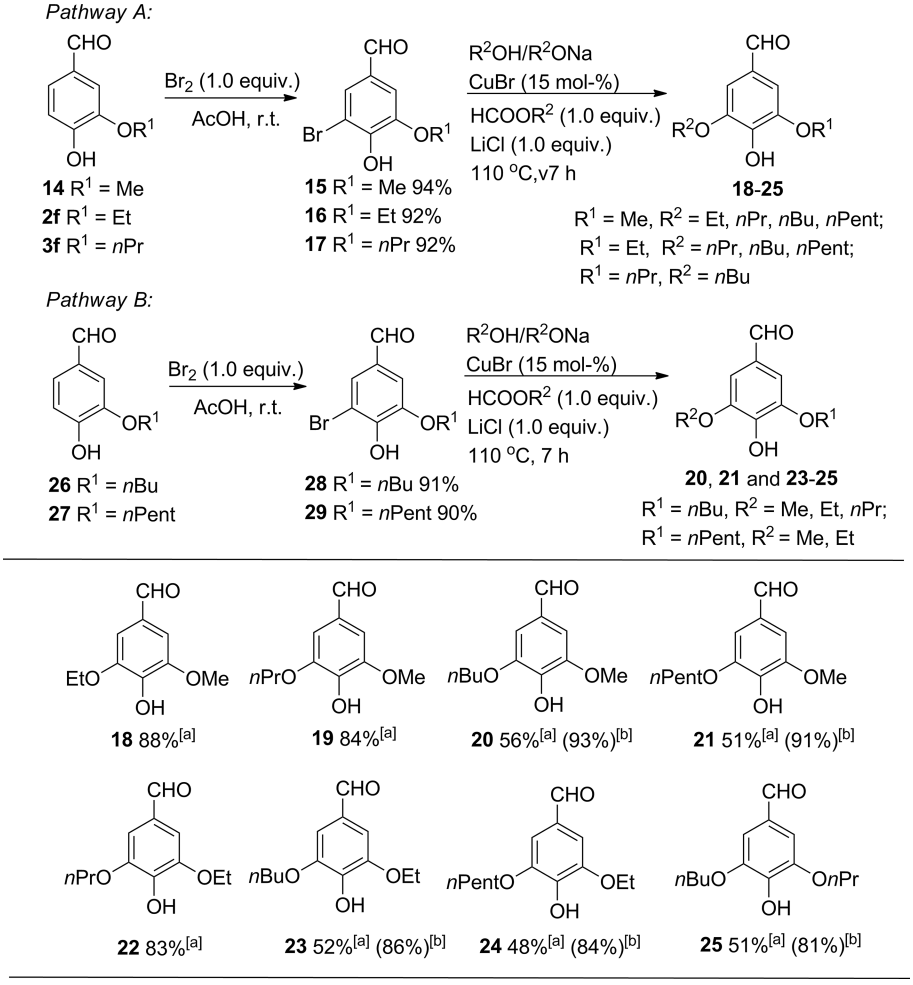


Scheme 4. Applications of the alkoxylation protocol in the synthesis of high-value compounds on a multigram scale.

sive 4-bromophenol (**10**) was successfully implemented to give an overall yield of 89% in a high-yielding two-step sequence of condensation and butoxylation.

In addition, our alkoxylation protocol gave convenient access to 3,5-di-*hetero*-alkoxy-4-hydroxybenzaldehydes (unsymmetrical syringaldehydes; Table 5). Syringaldehyde, a synthetically useful feedstock with the skeleton of natural gallic acid, is a versatile building block in the pharmaceutical industry and for drug discovery.[21] Therefore, a strategy that would allow the preparation of unsymmetrical syringaldehydes would be highly valuable for drug discovery. As shown in Table 5, substrates **14**, **2f**, **3f**, **26**, and **27** underwent bromination followed by alkoxylation to achieve a collection of unsymmetrical syringaldehydes. Using a short-before-long approach (pathway A), the butoxylation and pentoxylation steps gave lower yields of 48–56% for products **20**, **21**, and **23**–**25**. In contrast, the long-before-short approach (pathway B) gave these products with improved yields of >81% in the last alkoxylation steps (see Supporting Information). These results also proved that the ethoxylation and propoxylation processes are more robust than butoxylation and pentoxylation.

Table 5. Synthesis of unsymmetrical syringaldehydes.



[a] Isolated yield of the alkoxylation step by pathway A. [b] Isolated yield of the methoxylation or alkoxylation step by pathway B (see Supporting Information).

Conclusion

In summary, we have developed a ligand-free copper(I)-bromide-catalysed short-chain alkoxylation process for unactivated aryl bromides. The sodium alkoxide is used as the nucleophile, the corresponding alkyl formate as a cocatalyst, and the corresponding alcohol as the solvent. A lithium chloride additive enables the reaction, which would otherwise be difficult under ligand-free conditions, to proceed efficiently to give various alkoxylated products in high yields, with easy quantitative recovery of the alcohol solvent. The method is very practical for the preparation of high-value aryl alkyl ethers. We anticipate that the approach developed here will become a useful tool for organic synthesis.

Experimental Section

General Methods: Unless otherwise indicated, reagents were obtained from commercial sources, and were used as received without further purification. Reactions were carried out in a Teflon®-lined stainless steel sealed tube or autoclave. Solvents were dried only with 4 Å molecular sieves. Reaction products were purified by column chromatography on silica gel (300–400 mesh). Melting points were determined using an open capillaries. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were determined with a Bruker AV400 instrument in $CDCl_3$ or [D_6]DMSO, with tetramethylsilane as internal standard. HRMS spectra were measured with a QSTAR Pulsar I LC/TOF MS mass spectrometer or a Micromass GCTTM gas chromatograph/mass spectrometer. GC–MS measurements were carried out with an Agilent 6890–5973N gas chromatograph/mass spectrometer.

General Procedure for the Alkoxylation of Aryl Bromides: (see Tables 2 and 3) A Teflon®-lined sealed tube (25 mL) was loaded with a solution of RONa in ROH [freshly prepared from metallic Na (0.14 g, 6.0 mmol) and ROH (6 mL)], LiCl (0.13 g, 3.0 mmol), aryl bromide (3.0 mmol), CuBr (0.06 g, 0.45 mmol), and HCOOR (3.0 mmol). The mixture was stirred in the sealed tube for 15 min, and then it was heated at 110 °C for the time stated. After the reaction was complete, the mixture was stirred open to the air for 0.5 h at room temperature. Then the mixture was concentrated in vacuo to recover the ROH solvent and give a residue. MTBE (10 mL) and dilute hydrochloric acid (1.0 M; 10 mL) were added to the residue. The organic phase was separated, and the aqueous phase was extracted with MTBE (3× 10 mL). The combined or-

ganic layers were dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product was evaluated by GC–MS to measure the conversion and selectivity. Lastly, purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) gave the desired product.

1-Ethoxy-4-methylbenzene (2a): Colourless oil, the best result: (conversion/selectivity: 100/100%), 0.36 g (88%, volatile product). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, J = 8.0 Hz, 2 H), 6.79 (d, J = 8.0 Hz, 2 H), 3.99 (q, J = 7.2 Hz, 2 H), 2.28 (s, 3 H), 1.39 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 129.9 (2 C), 129.7, 114.4 (2 C), 63.4, 20.5, 14.9 ppm. HRMS (EI): calcd. for $C_9H_{12}O$ $[M]^+$ 136.0888; found 136.0887.

1-Methyl-4-propoxybenzene (3a): Colourless oil (conversion/selectivity: 100/100%), 0.41 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, J = 8.4 Hz, 2 H), 6.80 (d, J = 8.4 Hz, 2 H), 3.89 (t, J = 7.2 Hz, 2 H), 2.28 (s, 3 H), 1.79 (sext, J = 7.2 Hz, 2 H), 1.03 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 129.9 (2 C), 129.7, 114.4 (2 C), 69.6, 22.7, 20.5, 10.6 ppm. HRMS (EI): calcd. for $C_{10}H_{14}O$ $[M]^+$ 150.1045; found 150.1046.

1-Ethoxy-4-methoxybenzene (2b): Colourless oil (conversion/selectivity: 100/100%), 0.44 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 4 H), 3.98 (q, J = 7.2 Hz, 2 H), 3.77 (s, 3 H), 1.39 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7, 153.1, 115.4 (2 C), 114.6 (2 C), 64.0, 55.7, 15.0 ppm. HRMS (ESI): calcd. for $C_9H_{13}O_2$ $[M + H]^+$ 153.0916; found 153.0924.

1-Methoxy-4-propoxybenzene (3b): Colourless oil (conversion/selectivity: 100/100%), 0.47 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 4 H), 3.87 (t, J = 7.2 Hz, 2 H), 3.77 (s, 3 H), 1.78 (sext, J = 7.2 Hz, 2 H), 1.03 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7, 153.3, 115.4 (2 C), 114.6 (2 C), 70.2, 55.7, 22.7, 10.6 ppm. HRMS (EI): calcd. for $C_{10}H_{14}O_2$ $[M]^+$ 166.0994; found 166.0995.

2-Ethoxy-1-methoxy-4-methylbenzene (2c): Yellowish oil (conversion/selectivity: 100%/95%), 0.46 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, J = 7.6 Hz, 1 H), 6.71 (s, 1 H), 6.70 (s, 1 H), 4.09 (q, J = 6.8 Hz, 2 H), 3.84 (s, 3 H), 2.29 (s, 3 H), 1.46 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.0, 147.1, 130.3, 120.8, 113.9, 111.5, 64.2, 56.0, 21.0, 14.9 ppm. HRMS (ESI): calcd. for $C_{10}H_{15}O_2$ $[M + H]^+$ 167.1072; found 167.1076.

1-Methoxy-4-methyl-2-propoxybenzene (3c): Yellowish oil (conversion/selectivity: 100%/98%), 0.51 g (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, J = 8.0 Hz, 1 H), 6.71 (s, 1 H), 6.69 (s, 1 H), 3.96 (t, J = 7.2 Hz, 2 H), 3.84 (s, 3 H), 2.29 (s, 3 H), 1.87 (sext, J = 7.2 Hz, 2 H), 1.04 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 147.3, 130.4, 120.9, 114.2, 111.9, 70.4, 56.1, 22.6, 21.0, 10.5 ppm. HRMS (ESI): calcd. for $C_{11}H_{17}O_2$ $[M + H]^+$ 181.1229; found 181.1231.

2-Ethoxy-4-methylphenol (2d): Yellowish oil (conversion/selectivity: 100/100%), 0.42 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (d, J = 7.6 Hz, 1 H), 6.68 (s, 1 H), 6.66 (s, 1 H), 5.56 (br. s, 1 H), 4.10 (q, J = 6.8 Hz, 2 H), 2.29 (s, 3 H), 1.45 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 143.5, 129.5, 121.5, 114.1, 112.7, 64.4, 21.1, 15.0 ppm. HRMS (ESI): $[M + Na^+]$ calcd. for $C_9H_{12}O_2Na$ 175.0735; found 175.0762.

4-Methyl-2-propoxyphenol (3d): Yellowish oil (conversion/selectivity: 100/100%), 0.47 g (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (d, J = 7.6 Hz, 1 H), 6.68 (s, 1 H), 6.65 (s, 1 H), 5.52 (br. s, 1 H), 3.99 (t, J = 7.2 Hz, 2 H), 2.28 (s, 3 H), 1.84 (sext, J = 7.2 Hz, 2 H), 1.05 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 143.6, 129.4, 114.1, 112.7, 70.4, 22.7, 21.1, 10.5 ppm. HRMS (ESI): $[M + Na^+]$ calcd. for $C_{10}H_{14}O_2Na$ 189.0891; found 189.0888.

2-Ethoxy-6-methoxy-4-methylphenol (2e): Yellowish oil (conversion/selectivity: 100/100%), 0.51 g (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (s, 2 H), 5.37 (br. s, 1 H), 4.09 (q, J = 6.8 Hz, 2 H), 3.87 (s, 3 H), 2.28 (s, 3 H), 1.43 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 146.1, 132.7, 128.7, 106.7, 105.7, 64.7, 56.2, 21.6, 15.0 ppm. HRMS (ESI): calcd. for $C_{10}H_{15}O_3$ $[M + H]^+$ 183.1021; found 183.1023.

2-Methoxy-4-methyl-6-propoxyphenol (3e): Yellowish oil (conversion/selectivity: 100/100%), 0.55 g (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (s, 2 H), 5.35 (br. s, 1 H), 3.98 (t, J = 7.2 Hz, 2 H), 3.87 (s, 3 H), 2.28 (s, 3 H), 1.84 (sext, J = 7.2 Hz, 2 H), 1.04 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 146.2, 132.7, 128.6, 106.7, 105.7, 70.8, 56.2, 22.6, 21.5, 10.5 ppm. HRMS (ESI): calcd. for $C_{11}H_{17}O_3$ $[M + H]^+$ 197.1178; found 197.1187.

Ethyl Vanillin (2f): Yellowish solid (conversion/selectivity: 100/100%), 0.46 g (93%), m.p. 76–78 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 7.41 (d, J = 2.0 Hz, 1 H), 7.39 (s, 1 H), 7.03 (d, J = 8.4 Hz, 1 H), 6.35 (br. s, 1 H), 4.19 (q, J = 7.2 Hz, 2 H), 1.47 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 151.8, 146.4, 129.8, 127.3, 114.3, 109.6, 64.8, 14.7 ppm. HRMS (EI): calcd. for $C_9H_{10}O_3$ $[M]^+$ 166.0630; found 166.0631.

4-Hydroxy-3-propoxybenzaldehyde (3f): Yellowish solid (conversion/selectivity: 100/100%), 0.50 g (92%), m.p. 82–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.82 (s, 1 H), 7.42 (d, J = 2.0 Hz, 1 H), 7.40 (s, 1 H), 7.04 (d, J = 8.4 Hz, 1 H), 6.24 (br. s, 1 H), 4.09 (t, J = 7.2 Hz, 2 H), 1.87 (sext, J = 7.2 Hz, 2 H), 1.06 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 151.8, 146.5, 129.8, 127.3, 114.3, 109.6, 70.7, 22.4, 10.4 ppm. HRMS (EI): calcd. for $C_{10}H_{12}O_3$ $[M]^+$ 180.0786; found 180.0787.

1-Chloro-4-ethoxybenzene (2g): Colourless oil (conversion/selectivity: 100/100%), 0.45 g (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 4.00 (q, J = 6.8 Hz, 2 H), 1.40 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.6, 129.3 (2 C), 125.3, 115.7 (2 C), 63.7, 14.8 ppm. HRMS (EI): calcd. for C_8H_9ClO $[M]^+$ 156.0342; found 156.0343.

1-Chloro-4-propoxybenzene (3g): Colourless oil (conversion/selectivity: 100/100%), 0.49 g (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 3.88 (t, J = 7.2 Hz, 2 H), 1.80 (sext, J = 7.2 Hz, 2 H), 1.03 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 134.8, 130.2, 120.6, 114.9, 113.1, 69.7, 22.5, 10.5 ppm. HRMS (EI): calcd. for $C_9H_{11}ClO$ $[M]^+$ 170.0498; found 170.0500.

1-Chloro-3-ethoxybenzene (2h): Colourless oil (conversion/selectivity: 100/100%), 0.45 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, J = 8.4 Hz, 1 H), 6.91 (d, J = 8.4 Hz, 1 H), 6.88 (t, J = 2.4 Hz, 1 H), 6.77 (dd, J = 8.4, J = 2.4 Hz, 1 H), 4.00 (q, J = 6.8 Hz, 2 H), 1.40 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 134.8, 130.2, 120.7, 114.8, 113.1, 63.7, 14.7 ppm. HRMS (EI): calcd. for C_8H_9ClO $[M]^+$ 156.0342; found 156.0344.

1-Chloro-3-propoxybenzene (3h): Colourless oil (conversion/selectivity: 100/100%), 0.49 g (97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (t, J = 8.0 Hz, 1 H), 6.92 (d, J = 2.0 Hz, 1 H), 6.90 (t, J = 2.0 Hz, 1 H), 6.79 (dd, J = 8.0, J = 2.0 Hz, 1 H), 3.90 (t, J = 7.5 Hz, 2 H), 1.80 (sext, J = 7.5 Hz, 2 H), 1.04 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 134.8, 130.2, 120.6, 114.8, 113.1, 69.7, 22.5, 10.5 ppm. HRMS (EI): calcd. for $C_9H_{11}ClO$ $[M]^+$ 170.0498; found 170.0499.

Ethyl 4-Ethoxybenzoate (2i): Colourless oil (conversion/selectivity: 100/100%), 0.51 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 4.34 (q, J = 7.2 Hz, 2 H), 4.08 (q, J = 7.2 Hz, 2 H), 1.43 (t, J = 7.2 Hz, 3 H), 1.37 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 162.7, 131.5 (2 C), 122.7, 113.9 (2 C), 63.6, 60.6, 14.7, 14.4 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}O_3$ $[M + H]^+$ 195.1021; found 195.1025.

2-Ethoxythiophene (2j): Colourless oil (conversion/selectivity: 100/100%), 0.34 g (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (dd, J = 5.6, J = 3.6 Hz, 1 H), 6.54 (dd, J = 5.6, J = 1.2 Hz, 1 H), 6.21 (dd, J = 3.6, J = 1.2 Hz, 1 H), 4.10 (q, J = 6.8 Hz, 2 H), 1.42 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 124.7, 111.8, 104.7, 69.5, 14.8 ppm. HRMS (EI): calcd. for C_6H_8OS $[M]^+$ 128.0296; found 128.0297.

2-Propoxythiophene (3j): Colourless oil (conversion/selectivity: 100/100%), 0.39 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.71 (dd, J = 5.6, J = 3.6 Hz, 1 H), 6.53 (dd, J = 5.6, J = 1.2 Hz, 1 H), 6.20 (dd, J = 3.6, J = 1.2 Hz, 1 H), 3.99 (t, J = 7.2 Hz, 2 H), 1.81 (sext, J = 7.2 Hz, 2 H), 1.03 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 124.7, 111.7, 104.5, 75.4, 22.6, 10.4 ppm. HRMS (EI): calcd. for $C_7H_{10}OS$ $[M]^+$ 142.0452; found 142.0454.

1-Butoxy-4-ethoxybenzene (4k): Yellowish oil (conversion/selectivity: 99/100%), 0.56 g (96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 4 H), 3.98 (q, J = 6.8 Hz, 2 H), 3.91 (t, J = 6.4 Hz, 2 H), 1.74 (quint, J = 6.4 Hz, 2 H), 1.48 (sext, J = 7.2 Hz, 2 H), 1.39 (t, J = 6.8 Hz, 3 H), 0.97 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 153.0, 115.4 (4 C), 68.3, 64.0, 31.5, 19.3, 15.0, 13.9 ppm. HRMS (EI): calcd. for $C_{12}H_{18}O_2$ $[M]^+$ 194.1307; found 194.1309.

2-Butoxy-4,6-dimethylphenol (4l): Yellow oil (conversion/selectivity: 100/100%), 0.55 g (95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.55 (s, 1 H), 6.53 (s, 1 H), 5.57 (br. s, 1 H), 4.01 (t, J = 6.5 Hz, 2 H), 2.25 (s, 3 H), 2.22 (s, 3 H), 1.79 (quint, J = 6.5 Hz, 2 H), 1.49 (sext, J = 7.5 Hz, 2 H), 0.99 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4, 141.6, 128.4, 126.4, 23.3, 110.0, 68.6, 31.4, 21.0, 19.3, 15.4, 13.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{19}O_2$ $[M + H]^+$ 195.1385; found 195.1390.

1-Butoxy-4-methoxy-2-methylbenzene (4m): Yellow oil (conversion/selectivity: 98%/98%), 0.53 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, J = 9.2 Hz, 1 H), 6.74 (s, 1 H), 6.67 (d, J = 9.2 Hz, 1 H), 3.92 (t, J = 6.4 Hz, 2 H), 3.76 (s, 3 H), 2.23 (s, 3 H), 1.77 (quint, J = 6.4 Hz, 2 H), 1.62 (sext, J = 7.6 Hz, 2 H), 0.99 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7, 140.5, 136.3, 128.9, 126.7, 115.1, 67.0, 62.9, 28.0, 21.0, 15.9, 13.3 ppm. HRMS (ESI): calcd. for $C_{12}H_{19}O_2$ $[M + H]^+$ 195.1385; found 195.1395.

1-Chloro-4-isobutoxybenzene (5g): Colourless oil (conversion/selectivity: 97%/97%), 0.50 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, J = 8.8 Hz, 2 H), 6.82 (d, J = 8.8 Hz, 2 H), 3.68 (d, J = 6.8 Hz, 2 H), 2.12–2.02 (m, 1 H), 1.02 (d, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 132.8, 130.2, 129.2, 125.2, 115.8, 74.7, 28.3, 19.2 (2 C) ppm. HRMS (EI): calcd. for $C_{10}H_{13}ClO$ $[M]^+$ 184.0655; found 184.0657.

1-Chloro-3-isobutoxybenzene (5h): Colourless oil (conversion/selectivity: 93%/98%), 0.49 g (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, J = 8.4 Hz, 1 H), 6.91 (s, 1 H), 6.90 (d, J = 2.4 Hz, 1 H), 6.78 (dd, J = 8.4, J = 2.4 Hz, 1 H), 3.70 (d, J = 6.8 Hz, 2 H), 2.12–2.03 (m, 1 H), 1.02 (d, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 134.8, 130.1, 120.6, 114.9, 113.1, 74.6, 28.2, 19.2 (2 C) ppm. HRMS (EI): calcd. for $C_{10}H_{13}ClO$ $[M]^+$ 184.0655; found 184.0657.

1-Isobutoxy-3-methoxybenzene (5n): Colourless oil (conversion/selectivity: 98/100%), 0.51 g (94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, J = 8.4 Hz, 1 H), 6.50 (dt, J = 8.4, J = 2.4 Hz, 2 H), 6.47 (t, J = 2.4 Hz, 1 H), 3.79 (s, 3 H), 3.70 (d, J = 6.8 Hz, 2 H), 2.13–2.03 (m, 1 H), 1.02 (d, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 160.6, 129.8, 106.7, 106.1, 100.9, 74.4, 55.2, 28.3, 19.3 (2 C) ppm. HRMS (ESI): calcd. for $C_{11}H_{17}O_2$ $[M + H]^+$ 181.1229; found 181.1224.

4-Methoxy-2-methyl-1-(pentyloxy)benzene (6m): Yellow oil (conversion/selectivity: 92/98%), 0.55 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75–6.73 (m, 2 H), 6.66 (dd, J = 8.8, J = 3.2 Hz, 1 H), 3.90 (t, J = 6.8 Hz, 2 H), 3.76 (s, 3 H), 2.22 (s, 3 H), 1.78 (quint, J = 6.8 Hz, 2 H), 1.49–1.34 (m, 4 H), 0.93 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 151.6, 128.2, 116.9, 112.3, 110.8, 68.8, 55.6, 29.3, 28.4, 22.5, 16.4, 14.1 ppm. HRMS (EI): calcd. for $C_{13}H_{20}O_2$ $[M]^+$ 208.1463; found 208.1464.

4-Ethyl-2-(pentyloxy)phenol (6o): Yellow oil (conversion/selectivity: 95/100%), 0.57 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, J = 8.4 Hz, 1 H), 6.69 (s, 1 H), 6.68 (d, J = 8.4 Hz, 1 H), 5.50 (br. s, 1 H), 4.03 (t, J = 6.8 Hz, 2 H), 2.57 (q, J = 7.2 Hz, 2 H), 1.82 (quint, J = 6.8 Hz, 2 H), 1.48–1.36 (m, 4 H), 1.21 (t, J = 6.8 Hz, 3 H), 0.94 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 143.7, 136.2, 120.1, 114.1, 111.4, 68.8, 29.0, 28.6, 28.2, 22.5, 16.0, 14.0 ppm. HRMS (EI): calcd. for $C_{13}H_{20}O_2$ $[M]^+$ 208.1463; found 208.1462.

1,3-Methyl-5-(pentyloxy)benzene (6p): Yellowish oil (conversion/selectivity: 92/100%), 0.52 g (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (s, 1 H), 6.54 (s, 2 H), 3.92 (t, J = 6.8 Hz, 2 H), 2.29 (s, 6 H), 1.77 (quint, J = 6.8 Hz, 2 H), 1.47–1.35 (m, 4 H), 0.93 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 131.4 (2 C), 126.6, 111.1 (2 C), 68.2, 29.1, 28.4, 22.5, 20.4 (2 C), 14.1 ppm. HRMS (EI): calcd. for $C_{13}H_{20}O$ $[M]^+$ 192.1514; found 192.1516.

1-Isopropoxy-4-methylbenzene (7a): Colourless oil (conversion/selectivity: 100%/67%), 0.28 g (63%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, J = 7.6 Hz, 2 H), 6.83 (d, J = 7.6 Hz, 2 H), 4.53 (heptet, d, J = 5.2 Hz, 1 H), 2.31 (s, 3 H), 1.35 (d, J = 5.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 129.9 (2 C), 129.8, 115.9 (2 C), 70.0, 22.1 (2 C), 20.5 ppm. HRMS (EI): calcd. for $C_{10}H_{14}O$ $[M]^+$ 150.1045; found 150.1044.

1-Isopropoxy-3-methoxybenzene (7n): Colourless oil (conversion/selectivity: 100%/65%), 0.31 g (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, J = 8.0 Hz, 1 H), 6.50 (d, J = 8.0 Hz, 2 H), 6.47 (s, 1 H), 6.53 (heptet, d, J = 6.0 Hz, 1 H), 3.79 (s, 3 H), 1.35 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 159.2, 129.8, 107.9, 106.1, 102.3, 69.8, 55.2, 22.1 (2 C) ppm. HRMS (EI): calcd. for $C_{10}H_{14}O_2$ $[M]^+$ 166.0994; found 166.0995.

General Procedure for the Dialkoxylation: (Table 4): A Teflon®-lined sealed tube (25 mL) was loaded with a solution of RONa in ROH [freshly prepared from metallic Na (0.18 g, 8.0 mmol) and ROH (8 mL)], LiCl (0.17 g, 4.0 mmol), aryl bromide (2.0 mmol), CuBr (0.09 g, 0.6 mmol), and HCOOR (4.0 mmol). The mixture was stirred in the sealed tube for 15 min, and then it was heated at 110 °C for 7 h. After the reaction was complete, the mixture was stirred open to the air for 0.5 h at room temperature, and then it was concentrated in vacuo to recover the ROH solvent and give a residue. MTBE (10 mL) and dilute hydrochloric acid (1.0 M; 10 mL) were added to the residue. The organic phase was separated, and the aqueous phase was extracted with MTBE (3× 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product, which was evalu-

ated by GC–MS to measure the conversion and selectivity. Lastly, purification of the crude product by column chromatography on silica gel (petroleum ether/ethyl acetate, 20:1) gave the desired product.

1,4-Diethoxybenzene (2q): White solid (conversion/selectivity: 100/100%), 0.32 g (97%), m.p. 71–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 4 H), 3.98 (q, J = 6.8 Hz, 4 H), 1.39 (t, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0 (2 C), 115.4 (4 C), 64.0 (2 C), 15.0 (2 C) ppm. HRMS (EI): calcd. for $C_{10}H_{14}O_2$ $[M]^+$ 166.0994; found 166.0996.

1,4-Dipropoxybenzene (3q): Yellow oil (conversion/selectivity: 100/100%), 0.38 g (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 4 H), 3.87 (t, J = 6.8 Hz, 4 H), 1.78 (sext, J = 6.8 Hz, 4 H), 1.02 (t, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2 (2 C), 115.4 (4 C), 70.2 (2 C), 22.7 (2 C), 10.5 (2 C) ppm. HRMS (EI): calcd. for $C_{12}H_{18}O_2$ $[M]^+$ 194.1307; found 194.1309.

1,3-Diethoxy-5-methoxybenzene (2r): Colourless oil (conversion/selectivity: 100/100%), 0.38 g (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (s, 3 H), 3.99 (q, J = 6.8 Hz, 4 H), 3.76 (s, 3 H), 1.39 (t, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 160.8 (2 C), 93.8, 93.3 (2 C), 63.5 (2 C), 55.3, 14.8 (2 C) ppm. HRMS (EI): calcd. for $C_{11}H_{16}O_3$ $[M]^+$ 196.1099; found 196.1101.

1-Methoxy-3,5-dipropoxybenzene (3r): Colourless oil (conversion/selectivity: 100/100%), 0.43 g (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (s, 3 H), 3.88 (t, J = 7.2 Hz, 4 H), 3.76 (s, 3 H), 1.79 (sext, J = 7.2 Hz, 4 H), 1.02 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 161.0 (2 C), 93.9, 93.3 (2 C), 69.5 (2 C), 55.3, 22.6 (2 C), 10.5 (2 C) ppm. HRMS (EI): calcd. for $C_{13}H_{20}O_3$ $[M]^+$ 224.1412; found 224.1415.

2,6-Diethoxy-4-methylphenol (2s): White solid (conversion/selectivity: 100/100%), 0.38 g (96%), m.p. 81–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.37 (s, 2 H), 5.38 (br. s, 1 H), 4.09 (q, J = 6.8 Hz, 4 H), 2.27 (s, 3 H), 1.43 (t, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1 (2 C), 133.0, 128.5, 106.8 (2 C), 64.7 (2 C), 21.5, 15.0 (2 C) ppm. HRMS (EI): calcd. for $C_{11}H_{16}O_3$ $[M]^+$ 196.1099; found 196.1100.

4-Methyl-2,6-dipropoxyphenol (3s): White solid (conversion/selectivity: 100/100%), 0.42 g (95%), m.p. 57–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.38 (s, 2 H), 5.35 (br. s, 1 H), 3.98 (t, J = 7.2 Hz, 4 H), 2.26 (s, 3 H), 1.84 (sext, J = 7.2 Hz, 4 H), 1.03 (t, J = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3 (2 C), 133.1, 128.5, 106.9 (2 C), 70.8 (2 C), 22.7 (2 C), 21.5, 10.5 (2 C) ppm. HRMS (EI): calcd. for $C_{13}H_{20}O_3$ $[M]^+$ 224.1412; found 224.1414.

2,4-Diethoxy-6-methylphenol (2t): White solid (conversion/selectivity: 100/100%), 0.38 g (97%), m.p. 66–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, J = 2.8 Hz, 1 H), 6.27 (d, J = 2.8 Hz, 1 H), 5.32 (br. s, 1 H), 4.06 (q, J = 6.8 Hz, 2 H), 3.95 (q, J = 6.8 Hz, 2 H), 2.23 (s, 3 H), 1.43 (t, J = 6.8 Hz, 3 H), 1.38 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 145.8, 138.0, 123.6, 107.4, 98.2, 64.5, 64.0, 15.8, 15.0, 14.9 ppm. HRMS (EI): calcd. for $C_{11}H_{16}O_3$ $[M]^+$ 196.1099; found 196.1100.

2-Methyl-4,6-dipropoxyphenol (3t): Yellow oil (conversion/selectivity: 100/100%), 0.43 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.35 (d, J = 2.8 Hz, 1 H), 6.28 (d, J = 2.8 Hz, 1 H), 5.31 (br. s, 1 H), 3.96 (t, J = 6.8 Hz, 2 H), 3.84 (t, J = 6.8 Hz, 2 H), 2.23 (s, 3 H), 1.87–1.73 (m, 4 H), 1.04 (t, J = 6.8 Hz, 3 H), 1.02 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 145.9, 138.0, 123.6, 107.4, 98.2, 70.5, 70.2, 22.7, 22.6, 15.8, 10.6, 10.5 ppm. HRMS (EI): calcd. for $C_{13}H_{20}O_3$ $[M]^+$ 224.1412; found 224.1414.

Procedure for the Preparation of Isovanillin (9) on a Multigram Scale

4-Hydroxy-3-propoxybenzaldehyde (3f): A Teflon®-lined autoclave (100 mL) was loaded with a solution of *n*PrONa in *n*-propanol [freshly prepared from *n*PrOH (40 mL) and metallic Na (1.38 g, 60 mmol)], LiCl (0.85 g, 20 mmol), 3-bromo-4-hydroxybenzaldehyde (**1f**; 4.02 g, 20 mmol), CuBr (0.43 g, 3.0 mmol), and HCOO*n*Pr (1.94 mL, 0.91 g/mL, 20 mmol). The mixture was stirred in the autoclave for 15 min, and then it was heated at 110 °C for 7 h. After the reaction was complete, the mixture was stirred open to the air for 0.5 h at room temperature, and then it was concentrated in vacuo to recover the *n*PrOH solvent and give a residue. MTBE (60 mL) and dilute hydrochloric acid (1.0 M; 60 mL) were added to the residue. The organic phase was separated, and the aqueous phase was extracted with MTBE (3 × 30 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give **3f** (3.16 g, 88%) as a yellowish solid.

4-Methoxy-3-propoxybenzaldehyde (8): A four-necked flask was loaded with the above product **3f** (3.16 g, 17.6 mmol) and water (10 mL) under a nitrogen atmosphere, then the mixture was heated to 90 °C. Dimethyl sulfate (2.33 mL, 1.332 g/mL, 24.6 mmol) and aqueous sodium hydroxide solution (5 M; 4.92 mL) were added dropwise to the mixture over 40 min. Subsequently, the mixture was stirred for a further 2 h at 90 °C. After the reaction was complete, MTBE (20 mL) was added to the mixture. The organic phase was separated, and the aqueous phase was extracted with MTBE (3 × 15 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 10:1) to give **8** (3.28 g, 96%) as a white solid, m.p. 46–47 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (s, 1 H), 7.44 (dd, J = 8.0, J = 1.6 Hz, 1 H), 7.40 (d, J = 1.6 Hz, 1 H), 6.97 (d, J = 8.0 Hz, 1 H), 4.04 (t, J = 7.2 Hz, 2 H), 3.95 (s, 3 H), 1.89 (sext, J = 7.2 Hz, 2 H), 1.05 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 154.8, 149.1, 130.1, 126.6, 110.6, 110.3, 70.5, 56.2, 22.3, 10.4 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}O_3$ $[M + H]^+$ 195.1021; found 195.1019.

Isovanillin (9): A three-necked flask was loaded with toluene (15 mL), the above product **8** (3.28 g, 16.9 mmol), and anhydrous $AlCl_3$ (4.96 g, 37.2 mmol). The solution was stirred at room temperature for 8 h, and then it was quenched with saturated aqueous ammonium chloride (15 mL). The organic phase was separated, and the aqueous phase was extracted with toluene (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give **9** (2.36 g, 92%) as a white solid, m.p. 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.85 (s, 1 H), 7.44 (s, 1 H), 7.42 (d, J = 1.6 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 1 H), 5.75 (br. s, 1 H), 3.99 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.2, 151.9, 146.2, 130.6, 124.7, 114.1, 110.2, 56.2 ppm. HRMS (ESI): calcd. for $C_8H_9O_3$ $[M + H]^+$ 153.0552; found 153.0549.

Preparation of Pramoxine (13) on a Multigram Scale

4-[3-(4-Bromophenoxy)propyl]morpholine (12): A three-necked flask was loaded with 4-bromophenol (**10**; 3.46 g, 20 mmol), 4-(3-chloropropyl)morpholine (**11**; 3.93 g, 24 mmol), K_2CO_3 (5.53 g, 40 mmol), and CH_3CN (15 mL). The solution was stirred under reflux for 2 h. After the reaction was complete, the mixture was concentrated in vacuo. MTBE (30 mL) and brine (30 mL) were added to the residue. The organic phase was separated, and the

aqueous phase was extracted with MTBE (3× 15 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give **12** (5.88 g, 98%) as a white solid, m.p. 56–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.8 Hz, 2 H), 6.77 (d, J = 8.8 Hz, 2 H), 3.99 (t, J = 6.4 Hz, 2 H), 3.73 (br. s, 4 H), 2.52–2.48 (m, 6 H), 1.96 (quint, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 132.2 (2 C), 116.3 (2 C), 112.7, 67.0 (2 C), 66.3, 55.5, 53.8 (2 C), 26.4 ppm. HRMS (EI): calcd. for $C_{13}H_{18}NBrO_2$ $[M]^+$ 299.0521; found 299.0525.

Pramoxine (13): A Teflon®-lined autoclave (100 mL) was loaded with a solution of *n*BuONa in *n*BuOH [freshly prepared from *n*BuOH (40 mL) and metallic Na (0.90 g, 39.2 mmol)], LiCl (0.83 g, 19.6 mmol), the above product **12** (5.88 g, 19.6 mmol), CuBr (0.42 g, 2.94 mmol), and HCOO*n*Bu (2.2 mL, 0.91 g/mL, 19.6 mmol). The mixture was stirred in the autoclave for 15 min, and then it was heated at 110 °C for 7 h. After the reaction was complete, the mixture was stirred open to air for 0.5 h at room temperature, and then it was concentrated in vacuo to recover the *n*BuOH solvent and give a residue. MTBE (40 mL) and brine (40 mL) were added to the residue. The organic phase was separated, and the aqueous phase was extracted with MTBE (3× 20 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give **13** (5.22 g, 91%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 4 H), 3.97 (t, J = 6.4 Hz, 2 H), 3.90 (t, J = 6.4 Hz, 2 H), 3.73 (br. s, 4 H), 2.55–2.48 (m, 6 H), 1.96 (quint, J = 6.4 Hz, 2 H), 1.74 (quint, J = 6.4 Hz, 2 H), 1.48 (sext, J = 7.2 Hz, 2 H), 0.96 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 153.0, 115.4 (4 C), 68.3, 67.0 (2 C), 66.7, 55.6, 53.7 (2 C), 31.5, 26.5, 19.3, 13.9 ppm. HRMS (EI): calcd. for $C_{17}H_{27}NO_3$ $[M]^+$ 293.1991; found 293.1995.

Synthesis of the Unsymmetrical Syringaldehydes

Bromination Procedure of Pathway A: A three-necked flask was loaded with 3-alkoxy-4-hydroxybenzaldhyde (3.0 mmol) and CH_3COOH (5 mL). A solution of bromine (0.15 mL, 3.119 g/mL, 3.0 mmol) in CH_3COOH (3 mL) was then added dropwise over 2 h at room temperature. The mixture was then stirred for a further 5 h. Ice water (10 mL) was added to the solution, which led to the formation of a precipitate. The precipitate was washed with water until neutral pH, and then it was dried in vacuo at 50 °C to give the desired crude product, which was directly used in the next step.

3-Bromo-4-hydroxy-5-methoxybenzaldehyde (15): Yellow solid, 0.65 g (94%), m.p. 164–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 7.64 (d, J = 1.6 Hz, 1 H), 7.37 (d, J = 1.6 Hz, 1 H), 6.49 (br. s, 1 H), 3.99 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7, 148.9, 147.7, 130.1, 130.0, 108.2, 108.0, 56.7 ppm. HRMS (EI): calcd. for $C_8H_6BrO_3$ $[M - H]^-$ 228.9500; found 228.9491.

3-Bromo-5-ethoxy-4-hydroxybenzaldehyde (16): Yellow solid, 0.68 g (92%), m.p. 142–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 7.63 (d, J = 1.6 Hz, 1 H), 7.34 (d, J = 1.6 Hz, 1 H), 6.53 (br. s, 1 H), 4.22 (q, J = 7.2 Hz, 2 H), 1.50 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 149.0, 146.9, 130.0 (2 C), 108.7, 108.1, 65.4, 14.7 ppm. HRMS (EI): calcd. for $C_9H_8BrO_3$ $[M - H]^-$ 242.9657; found 242.9652.

3-Bromo-4-hydroxy-5-propoxybenzaldehyde (17): Yellow solid, 0.71 g (92%), m.p. 136–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 7.62 (d, J = 1.6 Hz, 1 H), 7.34 (d, J = 1.6 Hz, 1 H), 6.59 (br. s, 1 H), 4.10 (t, J = 7.2 Hz, 2 H), 1.88 (sext, J = 7.2 Hz, 2 H), 1.06 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 149.1, 147.0, 130.0 (2 C), 108.8, 108.1, 71.3, 22.3, 10.4 ppm. HRMS (EI): calcd. for $C_{10}H_{10}BrO_3$ $[M - H]^-$ 256.9813; found 256.9811.

Alkoxylation Procedure of Pathway A: A Teflon®-lined sealed tube (25 mL) was loaded with a solution of R^2ONa in the corresponding alcohol [freshly prepared from metallic Na (0.14 g, 6.0 mmol) and R^2OH (6 mL)], LiCl (0.08 g, 2.0 mmol), 3-bromo-5-alkoxy-4-hydroxybenzaldehyde (2.0 mmol), CuBr (0.04 g, 0.3 mmol), and $HCOOR^2$ (2.0 mmol). The mixture was stirred in the sealed tube for 15 min, and then it was heated at 110 °C for 7 h. After the reaction was complete, the mixture was stirred open to the air for 0.5 h at room temperature, and then it was concentrated in vacuo to recover the R^2OH solvent and give a residue. MTBE (10 mL) and dilute hydrochloric acid (1.0 M; 10 mL) were added to the residue. The organic phase was separated, and the aqueous phase was extracted with MTBE (3× 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give the desired product.

3-Ethoxy-4-hydroxy-5-methoxybenzaldehyde (18): White solid, 0.34 g (88%), m.p. 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1 H), 7.14 (d, J = 1.6 Hz, 1 H), 7.13 (d, J = 1.6 Hz, 1 H), 6.09 (br. s, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 3.97 (s, 3 H), 1.49 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 147.4, 146.5, 141.0, 128.3, 107.6, 106.6, 65.1, 56.4, 14.8 ppm. HRMS (EI): calcd. for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0814; found 197.0804.

4-Hydroxy-3-methoxy-5-propoxybenzaldehyde (19): White solid, 0.35 g (84%), m.p. 84–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1 H), 7.13 (s, 2 H), 6.06 (br. s, 1 H), 4.09 (t, J = 7.2 Hz, 2 H), 3.97 (s, 3 H), 1.88 (sext, J = 7.2 Hz, 2 H), 1.06 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 146.4, 145.6, 140.0, 127.3, 106.6, 105.6, 70.0, 55.4, 21.4, 9.4 ppm. HRMS (EI): calcd. for $C_{11}H_{15}O_4$ $[M + H]^+$ 211.0970; found 211.0962.

3-Butoxy-4-hydroxy-5-methoxybenzaldehyde (20): White solid, 0.25 g (56%), m.p. 56–58 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 7.14 (s, 2 H), 6.05 (br. s, 1 H), 4.13 (t, J = 6.8 Hz, 2 H), 3.97 (s, 3 H), 1.84 (quint, J = 7.2 Hz, 2 H), 1.51 (sext, J = 7.2 Hz, 2 H), 0.99 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 147.4, 146.7, 141.0, 128.3, 107.6, 106.7, 69.3, 56.4, 31.1, 19.2, 13.8 ppm. HRMS (EI): calcd. for $C_{12}H_{16}O_4$ $[M]^+$ 224.1049; found 224.1052.

4-Hydroxy-3-methoxy-5-(pentyloxy)benzaldehyde (21): White solid, 0.24 g (51%), m.p. 54–56 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.80 (s, 1 H), 7.13 (s, 2 H), 6.08 (br. s, 1 H), 4.11 (t, J = 6.8 Hz, 2 H), 3.96 (s, 3 H), 1.86 (quint, J = 6.8 Hz, 2 H), 1.49–1.35 (m, 4 H), 0.93 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 147.4, 146.7, 141.1, 128.3, 107.6, 106.7, 69.6, 56.4, 28.8, 28.0, 22.4, 14.0 ppm. HRMS (EI): calcd. for $C_{13}H_{18}O_4$ $[M]^+$ 238.1205; found 238.1208.

3-Ethoxy-4-hydroxy-5-propoxybenzaldehyde (22): White solid, 0.37 g (83%), m.p. 93–94 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 7.12 (s, 2 H), 6.07 (br. s, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.08 (t, J = 6.8 Hz, 2 H), 1.88 (sext, J = 7.2 Hz, 2 H), 1.48 (t, J = 6.8 Hz, 3 H), 1.06 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 146.8, 146.6, 141.4, 128.3, 107.7 (2 C), 71.1, 65.1, 22.5, 14.8, 10.4 ppm. HRMS (EI): calcd. for $C_{12}H_{16}O_4$ $[M]^+$ 224.1049; found 224.1050.

3-Butoxy-5-ethoxy-4-hydroxybenzaldehyde (23): White solid, 0.25 g (52%), m.p. 115–117 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 7.12 (s, 2 H), 6.06 (br. s, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.12 (t, J = 6.8 Hz, 2 H), 1.84 (quint, J = 6.8 Hz, 2 H), 1.55–1.47 (m, 5 H), 0.99 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 146.8, 146.6, 141.3, 128.3, 107.7, 107.6, 69.3, 65.0, 31.1, 19.2, 14.8, 13.8 ppm. HRMS (EI): calcd. for $C_{13}H_{18}O_4$ $[M]^+$ 238.1205; found 238.1204.

3-Ethoxy-4-hydroxy-5-(pentyloxy)benzaldehyde (24): White solid, 0.24 g (48%), m.p. 99–100 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 7.12 (s, 2 H), 6.07 (br. s, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.11 (t, J = 6.8 Hz, 2 H), 1.86 (quint, J = 6.8 Hz, 2 H), 1.48 (t, J = 7.2 Hz, 3 H), 1.45–1.35 (m, 4 H), 0.93 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.8, 146.8, 146.6, 141.3, 128.3, 107.7, 107.6, 69.6, 65.1, 28.8, 28.1, 22.4, 14.8, 14.0 ppm. HRMS (EI): calcd. for $C_{14}H_{20}O_4$ $[M]^+$ 252.1362; found 252.1361.

3-Butoxy-4-hydroxy-5-propoxybenzaldehyde (25): White solid, 0.26 g (51%), m.p. 49–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 7.12 (s, 2 H), 6.04 (br. s, 1 H), 4.12 (t, J = 7.2 Hz, 2 H), 4.08 (t, J = 7.2 Hz, 2 H), 1.93–1.81 (m, 4 H), 1.51 (sext, J = 7.2 Hz, 2 H), 1.06 (t, J = 7.2 Hz, 3 H), 0.99 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 146.8, 146.7, 141.4, 128.2, 107.8, 107.7, 71.0, 69.3, 31.1, 22.4, 19.1, 13.8, 10.4 ppm. HRMS (EI): calcd. for $C_{14}H_{20}O_4$ $[M]^+$ 252.1362; found 252.1364.

Bromination Procedure of Pathway B: This procedure was the same as the bromination procedure of pathway A.

3-Bromo-5-butoxy-4-hydroxybenzaldehyde (28): Yellow solid, 0.74 g (91%), m.p. 109–110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 7.62 (d, J = 1.6 Hz, 1 H), 7.34 (d, J = 1.6 Hz, 1 H), 6.50 (br. s, 1 H), 4.15 (t, J = 6.8 Hz, 2 H), 1.84 (quint, J = 6.8 Hz, 2 H), 1.50 (sext, J = 7.2 Hz, 2 H), 1.0 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.8, 149.0, 147.0, 130.0, 129.9, 108.7, 108.0, 69.9, 30.9, 19.1, 13.8 ppm. HRMS (EI): calcd. for $C_{11}H_{12}BrO_3$ $[M - H]^-$ 270.9970; found 270.9966.

3-Bromo-4-hydroxy-5-(pentyloxy)benzaldehyde (29): Yellow solid, 0.77 g (90%), m.p. 88–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.78 (s, 1 H), 7.62 (d, J = 1.6 Hz, 1 H), 7.34 (d, J = 1.6 Hz, 1 H), 6.51 (br. s, 1 H), 4.14 (t, J = 6.8 Hz, 2 H), 1.86 (quint, J = 6.8 Hz, 2 H), 1.48–1.37 (m, 4 H), 0.94 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.7, 149.0, 147.0, 130.0, 129.9, 108.7, 108.0, 69.8, 28.6, 28.0, 22.4, 14.0 ppm. HRMS (EI): calcd. for $C_{12}H_{15}BrO_3$ $[M]^+$ 286.0205; found 286.0208.

Methoxylation Procedure of Pathway B: A Teflon®-lined sealed tube (25 mL) was loaded with methanolic MeONa [freshly prepared from metallic Na (0.14 g, 6.0 mmol) and MeOH (6 mL)], 5-alkoxy-3-bromo-4-hydroxybenzaldhyde (2.0 mmol), CuCl (0.008 g, 0.08 mmol), and HCOOMe (0.05 mL, 0.98 g/mL, 0.8 mmol). The mixture was stirred in the sealed tube for 15 min, and then it was heated at 110 °C for 4 h. After the reaction was complete, the mixture was stirred open to the air for 0.5 h at room temperature, and then it was concentrated in vacuo to recover the MeOH solvent and give a residue. MTBE (10 mL) and dilute hydrochloric acid (1.0 M; 10 mL) were added to the residue. The organic phase was separated, and the aqueous phase was extracted with MTBE (3 × 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$, and then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 8:1) to give the desired product.

3-Butoxy-4-hydroxy-5-methoxybenzaldehyde (20): Prepared by methoxylation of **28**, white solid, 0.42 g (93%), m.p. 56–58 °C; the characterization data is given above.

4-Hydroxy-3-methoxy-5-(pentyloxy)benzaldehyde (21): Prepared by methoxylation of **29**, white solid, 0.43 g (91%), m.p. 54–56 °C; the characterization data is given above.

Alkoxylation Procedure of Pathway B: This procedure was the same as the alkoxylation procedure of pathway A.

3-Butoxy-5-ethoxy-4-hydroxybenzaldehyde (23): Prepared by ethoxylation of **28**, white solid, 0.41 g (86%), m.p. 115–117 °C; the characterization data is given above.

3-Ethoxy-4-hydroxy-5-(pentyloxy)benzaldehyde (24): Prepared by ethoxylation of **29**, white solid, 0.42 g (84%), m.p. 99–100 °C; the characterization data is given above.

3-Butoxy-4-hydroxy-5-propoxybenzaldehyde (25): Prepared by propoxylation of **29**, white solid, 0.41 g (81%), m.p. 49–50 °C; the characterization data is given above.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR, GC–MS, and HRMS spectra of the products.

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