A ligand-free, powerful, and practical method for methoxylation of unactivated aryl bromides by use of the CuCl/HCOOMe/MeONa/MeOH system

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Abstract A ligand-free, powerful, and practical method for mono and polymethoxylation of unactivated aryl bromides has been developed; CuCl was used as catalyst, HCOOMe as cocatalyst, and methanolic MeONa as both nucleophile and solvent. This eco-friendly procedure is characterized by operational simplicity, inexpensive substrates (unactivated mono to polybromoarenes), full conversion, and direct recovery of pure MeOH.

Keywords Cu-catalysis · Unactivated aryl bromides · Methoxylation · Aryl methyl ethers · Recovery of pure MeOH

Introduction

Over the past century, Cu-catalyzed methoxylation of unactivated aryl halides with no strong electron-withdrawing groups, for example NO₂, CN, and CF₃, on the aromatic ring, a classical Ullmann-type C–O coupling reaction, has been widely used to prepare aryl methyl ethers [1]. The reaction has many practical applications in the preparation of pharmaceuticals, agrochemicals, fragrances, dyes, polymers,

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and other fine chemicals [2–13]. Typical polymethoxylated arenes include the classical antibacterial agent trimethoprim [14], the vasodilator agent buffomedil [15], and the agricultural antifungal agent metrafenone [16] (Fig. 1). Aryl methyl ethers are also precursors of phenols [17] and these electron-rich aromatic ethers are also particularly useful for Friedel–Crafts-type reactions [18], *ortho* metalations [19], and electrophilic aromatic substitution [20].

Traditionally, ligand-free, Cu-catalyzed methoxylation of unactivated aryl halides has been conducted with MeONa as nucleophile, Cu(I) salt as catalyst, and aprotic polar amides, e.g. *N*,*N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidinone (NMP), or hexamethylphosphorus triamide (HMPT), as solvents. However, unsatisfactory efficacy [1–6], troublesome work up [21], and hazards to reproductive health [22] associated with these solvents do not meet the demands of eco-awareness and cost-consciousness. Also, in the presence of MeONa, decomposition of the amides unavoidably complicates the reaction work up. In recent decades, to overcome these problems, substantial efforts have been made to improve methoxylation [5, 6, 23–31]; these have mainly involved use of amides [5], esters [6], carbon dioxide [23], or pyridine [24] as cocatalysts to achieve the transformation. Other Cu(I)-catalyzed methoxylations with complex ligands also work well [25–31], but disadvantages associated with ligand chemistry—cost, separation, and pollution issues—are inevitably encountered in large-scale production (Scheme 1).

From environmental and economic perspectives, a practical method for methoxylation of unactivated aryl halides should have crucial sustainable features:

- 1. use of aryl bromides as substrates, rather than aryl chlorides, which are poorly reactive under ligand-free conditions, or expensive and excessively active aryl iodides;
- 2. methanolic MeONa as both nucleophile and solvent;
- 3. inexpensive CuCl as catalyst rather than expensive CuI or noble metal salts;
- 4. avoidance of unpractical cocatalysts or ligands; and
- 5. full conversion and excellent yield.

As part of our work on sustainable and green processes for preparing organic intermediates and fine chemicals [32–35], we have reported a highly efficient monomethoxylation using CuCl as catalyst, HCOOMe as cocatalyst, and methanolic MeONa as both methoxylating reagent and solvent with several unactivated monobromoarenes [36]. This powerful methoxylation was performed in a closed



Fig. 1 Selected important compounds bearing polymethoxylated arene moieties

Traditional methoxylation:



Scheme 1 Cu(I)-catalyzed methoxylation of unactivated aryl halides

autoclave to completely avoid loss of low-boiling HCOOMe, in contrast with the open system used by Capdevielle et al. [6]. Nevertheless, further study of a more broadly applicable procedure to improve the transformation is highly desired. In this context, we report herein extensive experiments conducted to study this facile and sustainable methoxylation reaction further, using a wide range of substrates from mono to polybromoarenes, and scale-up investigations with decagrams and even on an industrial scale (Scheme 1).

Results and discussion

First, the model methoxylation of bromobenzene in a Teflon-lined autoclave at 115 °C for 2 h was investigated to optimize the CuCl/HCOOMe catalyst system (Table 1). When 8 mmol% CuCl and 50 mmol% HCOOMe were used, the reaction provided anisole (1) quantitatively, with full conversion and 100 % GC yield (entry 1). When 35 mmol% HCOOMe was used, conversion noticeably reduced to 90 % (entry 3). In comparison, 40 mmol% HCOOMe proved optimum for the methoxylation (entry 2). Further study of the effect of catalyst loading showed that 4 mol% CuCl was adequate for full conversion (entries 4–6). Thus, the optimized catalyst system CuCl (4.0 mmol%)/HCOOMe (40 mmol%) was established to achieve complete methoxylation (entry 5). It was noteworthy that all the methoxylations

	^{Br} 115 °C, autoclave, 2 h		1	
Entry	CuCl $(n_1 \text{ mmol}\%)$	HCOOMe (n ₂ mmol%)	Substrate/product/ byproduct ratio ^b	
1	8.0	50	0/100/0	
2	8.0	40	0/100/0	
3	8.0	35	10/90/0	
4	5.0	40	0/100/0	
5	4.0	40	0/100/0	
6	3.0	40	7/93/0	
7	None	40	98/2/0	
8	4.0	None	92/8/0	
9	4.0	$40^{\rm c}$	16/84/0	
10	4.0	40^{d}	2/98/0	
11 ^e	4.0	40	100/0/0	
12 ^f	4.0	40	0/89/11	
13 ^g	4.0	40	96/4/0	

MeONa (2.0 equiv)/MeOH

CuCl (n1 mmol%)/HCOOMe (n2 mmol%)

Table 1 Optimization of the CuCl/HCOOMe system^a

Bold signifies the standard conditions

^a Reaction conditions: PhBr (10.0 mmol), MeOH (10 mL), MeONa (20.0 mmol), CuCl (n₁ mmol%), HCOOMe ($n_2 \text{ mmol}\%$) in autoclave

^b Substrate/product/byproduct ratio determined by GC-MS, by use of the area-normalization method with total ion current chromatography of the volatile products

^c HCOOMe replaced by *N*,*N*-diethylformamide

^d HCOOMe replaced by MeCOOEt

^e PhBr replaced by PhCl

 $^{\rm f}$ PhBr replaced by PhI to give 89 % of the desired 1 and 11 % of the byproduct methyl benzoate (1')

^g The ethoxylation reaction performed with HCOOEt as cocatalyst in ethanolic EtONa

consistently supplied 1 as the sole product, indicating the absence of side-reactions in the transformation of bromobenzene (entries 1-6). In essence, both CuCl and HCOOMe were crucial for the methoxylation, and the absence of either led to unsuccessful conversion (entries 7 and 8). Compared with reported cocatalyst amides [5] and esters [6], indeed, HCOOMe resulted the most excellent outcome among DMF [36], MeCOOMe [36], N,N-diethylformamide (entry 9), and MeCOOEt (entry 10). Treatment of poorly reactive chlorobenzene provided no product (entry 11) whereas methoxylation of highly reactive iodobenzene proceeded smoothly with full conversion, but with a noticeable amount (11 %) of the methoxycarbonylation byproduct methyl benzoate (1'; entry 12). Furthermore, when a control ethoxylation of bromobenzene was performed with the corresponding HCOOEt as cocatalyst and ethanolic sodium ethoxide as both nucleophile and solvent, the method gave only a trace amount of the phenetole with extremely low conversion (entry 13), presumably because the ethoxide anion is a stronger reducing agent than the copper(I) ion [6]. As pointed out in Ref. [36], the methoxylation procedure has the remarkable features of green chemistry, wherein pure MeOH (colorless, purity >99 %, water content <0.12 %) can be recovered after completion of the reaction. In the presence of MeONa, HCOOMe was completely degraded into pure MeOH and carbon monoxide via decarbonylation in the open system [37, 38]. Although unstable carbonyl Cu(I) species are possibly formed [39], no negative effects have been observed.

Using the optimized monomethoxylation conditions, we then investigated the substrate scope of the reaction of unactivated aryl bromides (Table 2). In general, the method achieved perfect methoxylation of all monobromoarenes, irrespective of whether electron-donating or weak electron-withdrawing substituent(s) were present on the substrates (1–15). Accordingly, most of the products were obtained with full conversion and in excellent yields (1–7, 10–15; an additional one equivalent of MeONa was required for 6 and 7). Even when the substrates had three or more

Table 2 Substrate scope of the methoxylation^a



^a Reaction condition: ArBr_n (10.0 mmol), MeOH (10 mL), MeONa (10.0(1 + n) mmol), CuCl ((3(n - 1) + 4) mmol%), HCOOMe ((20(n - 1) + 40) mmol%) in autoclave

^b Substrate/product/byproduct ratio determined by GC–MS using area normalization method in the total ionization chromatography

- ^c Isolated yield (%; 1, 2, 3, 14, 15 as the volatile products)
- ^d The substrate with phenolic hydroxyl group needing additional one equivalent of MeONa
- ^e For a reaction time of 7 h

electron-donating groups, the procedure afforded full conversion and more than 93 % yield (7–9). For *ortho*, *ortho*-dimethyl, or *ortho*-methoxy-*ortho*-methyl-substituted substrates, steric effects were observed and resulted in dehalogenation [40] (product/byproduct ratio 95/5 for 8 and 9). However, when sterically hindered *ortho*-monosubstituted bromoarenes 10 and 11 with isopropyl and phenyl groups, respectively, were subjected to the methoxylation, reaction occurred without dehalogenation affording the desired products in more than 95 % yield, after a prolonged reaction time of 7 h. With the electron-rich five-membered heterocyclic compounds 2-bromothiophene and 3-bromothiophene the method also furnished the desired products with full conversion, because of their stability under the alkaline conditions (14 and 15) [41].

More challenging polymethoxylation of unactivated polybromoarenes (ArBr_n, n = 2, 3) was also investigated. The reaction system was further optimized by using (1 + n) equiv MeONa, (3(n - 1) + 4) mmol% CuCl, and (20(n - 1) + 40)mmol% HCOOMe for polymethoxylation (16-22). For example, 3 equiv MeONa, (3 + 4) mmol% CuCl, and (20 + 40) mmol% HCOOMe were used for dimethoxylation of dibromoarenes (16-20; an additional one equiv MeONa was required for 16–19). The method exclusively provided all the dimethoxylation products with full conversion and satisfactory yields (16-20). Moreover, the results of trimethoxylation clearly revealed that the method was sufficiently powerful to accomplish full transformation with sole products 21 and 22. It should be noticed that dehalogenation was not detected for the ortho-hydroxy-ortho-methyl substituted substrate (22), in comparison with 8 and 9. We speculate that coordination between the phenolate anion and the active Cu(III) species suppressed debromination. Unusually, the seemingly labile aldehyde and hydroxyl groups of 4-hydroxybenzaldehydes did not need additional protection (19). We therefore concluded the structure of the sodium enolate was responsible for protecting the original aldehyde and hydroxyl groups via a dearomatization-enolization process (Scheme 2) [36].

The practical utility of the approach was revealed by the preparation of syringaldehyde (**19**) [42, 43], a highly commercially valuable intermediate crucial in the synthesis of the classical antibacterial agent trimethoprim, and of 1,3,5-trimethoxybenzene (**21**) [44, 45], a common pharmaceutical intermediate. Scale-up experiments revealed that **19** and **21** could be prepared on the decagram scale without significantly altered reaction efficiency (Scheme 3a, b). It is worthy of note that major advantages of the methoxylation method are that HCOOMe has both excellent co-catalytic performance and promotes non-contaminating decarbonylative decomposition to achieve a completely clean transformation.



Scheme 2 Isomerization of 4-hydroxybenzaldehydes under alkaline conditions



Scheme 3 Practical applications on decagram and industrial scales

Finally, the procedure was successfully used for commercial manufacture of 3,4,5-trimethoxybenzaldehyde, an intermediate in the synthesis of trimethoprim [43], on an industrial scale, with recovery of pure MeOH in the plant (Scheme 3c) [46]. Treatment of the recovered pure MeOH with sodium metal could be used for direct production of methanolic MeONa in the plant to achieve economy of recycling. The reaction has no significant risk of scale sensitivity, and long-term process robustness was observed in large-scale production [47].

On the basis of previous investigations [4, 6], a modified mechanism is proposed for this HCOOMe co-catalyzed reaction (Scheme 4). Crucially, HCOOMe acting as reactive cocatalyst furnishes the methoxylated intermediate II [48, 49], which combines with the cuprate-like intermediate I, resulting in the key tetrahedral intermediate III. Next, oxidative addition of the aryl bromide to the Cu^I center generates a new Cu(III) species IV [50, 51], furnishing intermediate V. Reductive elimination then effectively releases the desired product and regenerates the Cu(I) species III. In addition, with *ortho,ortho*-disubstituted aryl bromides (Table 2, 8 and 9), steric effects result in possible dehalogenation during the reductive elimination.

Conclusions

In summary, we have developed ligand-free, powerful, and practical CuCl/ HCOOMe-catalyzed methoxylation of unactivated aryl bromides to aryl methyl ethers. The eco-friendly method enables simple operation, and is applicable to a



Scheme 4 Modified mechanism

wide range of inexpensive substrates from unactivated mono to polybromoarenes with direct recovery of pure MeOH. Its practicability on an industrial-scale plant has been confirmed. We expect the new methoxylation reaction to have more extensive applications in chemistry.

Experimental

Unless otherwise indicated, all reagents were obtained from commercial sources and were used as received without further purification. All reactions were performed in a Teflon-lined autoclave. All solvents were only dried over 4 Å molecular sieves. Reaction products were purified by silica gel column chromatography with petroleum ether–ethyl acetate as mobile phase. Melting points were determined by use of open capillaries and are uncorrected. ¹H and ¹³C NMR spectra were acquired with a Bruker AV400, at 400 and 100 MHz, respectively, in CDCl₃, with TMS as internal standard. HRMS was performed with a QSTAR Pulsar I LC/TOF MS mass spectrometer or Micromass GCTTM gas chromatograph–mass spectrometer. GC–MS was also performed with an Agilent 7890A gas chromatograph–mass spectrometer.

Typical procedure for synthesis of 1 (Table 1)

A Teflon-lined autoclave (25 mL) was charged with MeONa (1.08 g, 20.0 mmol), MeOH (10 mL), CuCl (40 mg, 0.40 mmol), HCOOMe (0.25 mL, 0.97 g/mL, 4.0 mmol), and monohaloarene (10.0 mmol) then heated to 115 °C, with stirring, for 2 h. After completion of the reaction, the reactor was cooled to room temperature. The mixture was stirred for 0.5 h in the open, then concentrated to recover pure MeOH. Diethyl ether (15 mL) and dilute hydrochloric acid (1.6 M, 15 mL) were added to the residue. The mixture separated into two layers, and the aqueous phase was extracted with diethyl ether (15 mL × 3). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to give a residue which was purified by column chromatography on silica gel (mobile phase: petroleum ether–ethyl acetate 15:1) to furnish 1 (conversion and selectivity were determined by GC–MS analysis). The purity of the recovered MeOH was measured as more than 99 % by GC, and the water content of the recovered MeOH was measured as less than 0.12 % by use of the Karl Fischer method.

Anisole (1)

Colorless oil, substrate/product/byproduct ratio: 0/100/0, 0.87 g (80 %, as the volatile product); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.31 (t, J = 7.6 Hz, 2H), 6.99–6.91 (m, 3H), 3.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 159.5, 129.4 (2C), 120.6, 113.8 (2C), 55.0; HRMS (EI): m/z [M⁺] calcd. for C₇H₈O: 108.0575; found: 108.0576.

Methyl benzoate (1')

Colorless oil, 0.12 g (9 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 8.04 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.2$ Hz, 2H), 7.56 (dt, $J_1 = 7.6$ Hz, $J_2 = 1.2$ Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 3.92 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 165.9, 133.0, 130.1, 129.9 (2C), 128.6 (2C), 51.5; HRMS (EI): m/z [M⁺] calcd. for C₈H₈O₂: 136.0524; found: 136.0526.

1-Methoxy-2-methylbenzene (2)

Colorless oil, substrate/product/byproduct ratio: 0/100/0, 1.01 g (83 %, as the volatile product); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.22 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.90 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 3.86 (s, 3H), 2.27 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 157.7, 130.6, 126.8, 126.6, 120.3, 109.9, 55.2, 16.3; HRMS (EI): m/z [M⁺] calcd. for C₈H₁₀O: 122.0732; found: 122.0733.

1-Methoxy-4-methylbenzene (3)

Colorless oil, substrate/product/byproduct ratio: 0/100/0, 1.03 g (84 %, as the volatile product); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.10 (d, J = 8.4 Hz, 2H),

6.82 (d, J = 8.4 Hz, 2H), 3.80 (s, 3H), 2.30 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 157.5, 129.9 (2C), 129.8, 113.7 (2C), 55.3, 20.5; HRMS (EI): m/z [M⁺] calcd. for C₈H₁₀O: 122.0732; found: 122.0729.

7-Methoxy-3,4-dihydro-2H-benzo[b]1,4-dioxepine (4)

Colorless oil, substrate/product/byproduct ratio: 0/100/0, 1.75 g (97 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.91 (d, J = 8.8 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.48 (dd, J = 8.8, 2.4 Hz, 1H), 4.18 (t, J = 5.6 Hz, 2H), 4.12 (t, J = 5.6 Hz, 2H), 3.74 (s, 3H), 2.16 (quint, J = 5.6 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 155.6, 152.0, 145.3, 121.9, 108.7, 106.8, 70.85, 70.78, 55.6, 32.3; HRMS (ESI): *m*/ *z* [M + H⁺] calcd. for C₁₀H₁₃O₃: 181.0865; found: 181.0872.

1,2-Dimethoxy-4-methylbenzene (5)

Pale yellow solid, substrate/product/byproduct ratio: 0/100/0, 1.51 g (99 %), m.p. 18–20 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.70–6.79 (m, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 2.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 148.8, 146.9, 130.4, 120.8, 112.5, 111.3, 55.9, 55.7, 21.0; HRMS (ESI): *m/z* [M + Na⁺] calcd. for C₉H₁₂O₂Na: 175.0735; found: 175.0721.

4-Ethyl-2-methoxyphenol (6)

Pale yellow oil, substrate/product/byproduct ratio: 0/100/0, 1.49 g (98 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.84 (d, J = 8.0 Hz, 1H), 6.71 (s, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.45 (br s, 1H), 3.89 (s, 3H), 2.59 (quart, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 146.4, 143.5, 136.3, 120.3, 114.2, 110.5, 55.9, 28.6, 16.0; HRMS (ESI): m/z [M + H⁺] calcd. for C₉H₁₃O₂: 153.0916; found: 153.0924.

2-Methoxy-4-methyl-6-propoxyphenol (7)

Pale yellow oil, substrate/product/byproduct ratio: 0/100/0, 1.92 g (98 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.38 (s, 2H), 5.35 (s, 1H), 3.98 (t, J = 7.0 Hz, 2H), 3.87 (s, 3H), 2.28 (s, 3H), 1.84 (sext, J = 7.0 Hz, 2H), 1.03 (t, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 146.9, 146.2, 132.7, 128.6, 106.7, 105.7, 70.8, 56.2, 22.6, 21.5, 10.5; HRMS (ESI): m/z [M + H⁺] calcd. for C₁₁H₁₇O₃: 197.1178; found: 197.1187.

2-Methoxy-1,3,5-trimethylbenzene (8)

Colorless oil, substrate/product/byproduct ratio: 0/95/5, 1.40 g (93 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.83 (s, 2H), 3.70 (s, 3H), 2.26 (s, 6H), 2.25 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 154.8, 133.1, 130.5 (2C), 129.4 (2C), 59.7, 20.7, 16.0 (2C); HRMS (ESI): *m*/*z* [M + H⁺] calcd. for C₁₀H₁₅O: 151.1123; found: 151.1122.

1,2,3,4,5-Pentamethoxy-6-methylbenzene (9)

Pale yellow solid, substrate/product/byproduct ratio: 0/95/5, 2.25 g (93 %), m.p. 28–32 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 3.91 (s, 3H), 3.87 (s, 6H), 3.79 (s, 6H), 2.13 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 147.5 (2C), 145.1, 143.1 (2C), 120.1, 61.3, 61.1 (2C), 60.6 (2C), 8.8; HRMS (ESI): *m*/*z* [M + H⁺] calcd. for C₁₂H₁₉O₅: 243.1232; found: 243.1236.

1-Isopropyl-2-methoxybenzene (10)

Colorless oil, substrate/product/byproduct ratio: 0/100/0, 1.43 g (95 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.22 (d, J = 7.6 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.94 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.34 (m, 1H), 1.22 (d, J = 7.2 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 156.8, 137.0, 126.6, 126.0, 120.6, 110.3, 55.3, 26.7, 22.7 (2C); HRMS (EI): m/z [M ⁺] calcd. for C₁₀H₁₄O: 150.1045; found: 150.1046.

2-Methyl-1,1'-biphenyl (11)

Yellow oil, substrate/product/byproduct ratio: 0/100/0, 1.78 g (97 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.53 (d, J = 7.2 Hz, 2H), 7.41 (t, J = 7.2 Hz, 2H), 7.33 (m, 3H), 7.04 (t, J = 8.0 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 156.5, 138.6, 130.9, 130.7, 129.6 (2C), 128.7, 128.0 (2C), 126.9, 120.9, 111.2, 55.6; HRMS (EI): m/z [M ⁺] calcd. for C₁₃H₁₂O: 184.0888; found: 184.0889.

Methyl 4-methoxybenzoate (12)

Yellow solid, substrate/product/byproduct ratio: 0/100/0, 1.63 g (98 %), m.p. 41–43 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.99 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 3.88 (s, 3H), 3.86 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 166.8, 163.3, 131.5 (2C), 122.6, 113.6 (2C), 55.3, 51.8; HRMS (ESI): *m*/ *z* [M + H⁺] calcd. for C₉H₁₁O₃: 167.0708; found: 167.0709.

1-Chloro-4-methoxybenzene (13)

Pale yellow oil, substrate/product/byproduct ratio: 0/100/0, 1.38 g (97 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.24 (dt, J = 8.8, 3.6 Hz, 2H), 6.83 (dt, J = 8.8, 3.6 Hz, 2H), 3.79 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 158.2, 129.3 (2C), 125.5, 115.2 (2C), 55.4; HRMS (EI): m/z [M⁺] calcd. for C₇H₇OCI: 142.0185; found: 142.0184.

2-Methoxythiophene (14)

Colorless oil, substrate/product/byproduct ratio: 0/100/0, 0.91 g (80 %, as the volatile product); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.72 (dd, J = 5.6, 3.2 Hz,

1H), 6.54 (d, J = 5.6 Hz, 1H), 6.20 (d, J = 3.2 Hz, 1H), 3.89 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 166.7, 124.8, 111.7, 103.7, 60.4; HRMS (EI): m/z [M⁺] calcd. for C₅H₆OS: 114.0139; found: 114.0129.

3-Methoxythiophene (15)

Colorless oil, substrate/product/byproduct ratio: 0/100/0, 0.89 g (78 %, as the volatile product); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.18 (dd, J = 5.2, 2.4 Hz, 1H), 6.75 (d, J = 5.2 Hz, 1H), 6.25 (d, J = 2.4 Hz, 1H), 3.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 158.7, 124.7, 119.2, 96.6, 57.3; HRMS (EI): m/z [M⁺] calcd. for C₅H₆OS: 114.0139; found: 114.0138.

2,4-Dimethoxy-6-methylphenol (16)

White solid, substrate/product/byproduct ratio: 0/100/0, 1.65 g (98 %), m.p. 102–104 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.36 (d, J = 2.4 Hz, 1H), 6.29 (d, J = 2.4 Hz, 1H), 5.30 (s, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 2.25 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 152.7, 146.7, 137.8, 123.8, 106.6, 96.8, 56.0, 55.7, 15.8; HRMS (EI): m/z [M⁺] calcd. for C₉H₁₂O₃: 168.0786; found: 168.0787.

2,6-Dimethoxy-4-methylphenol (17)

Pale yellow solid, substrate/product/byproduct ratio: 0/100/0, 1.65 g (98 %), m.p. 38–40 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.39 (s, 2H), 5.37 (s, 1H), 3.86 (s, 6H), 2.29 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 146.9 (2C), 132.4, 128.7, 105.6 (2C), 56.2 (2C), 21.6; HRMS (ESI): m/z [M + H⁺] calcd. for C₉H₁₃O₃: 169.0865; found: 169.0879.

4-(tert-Butyl)-2,6-dimethoxyphenol (18)

Yellow oil, substrate/product/byproduct ratio: 0/100/0, 2.08 g (99 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.60 (s, 2H), 5.37 (br s, 1H), 3.90 (s, 6H), 1.31 (s, 9H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 146.5 (2C), 142.5, 132.6, 102.4 (2C), 56.3 (2C), 34.7, 31.6 (3C); HRMS (ESI): *m*/*z* [M + H⁺] calcd. for C₁₂H₁₉O₃: 211.1334; found: 211.1332.

4-Hydroxy-3,5-dimethoxybenzaldehyde (19)

Pale yellow solid, substrate/product/byproduct ratio: 0/100/0, 1.79 g (98 %), m.p. 110–112 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 9.82 (s, 1H), 7.15 (s, 2H), 6.10 (s, 1H), 3.97 (s, 6H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 190.8, 147.4 (2C), 140.9, 128.3, 106.7 (2C), 56.5 (2C); HRMS (ESI): m/z [M + H⁺] calcd. for C₉H₁₁O₄: 183.0657; found: 183.0635.

1,2,4-Trimethoxybenzene (20)

Colorless oil, substrate/product/byproduct ratio: 0/100/0, 1.65 g (98 %); ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.78 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 2.8 Hz, 1H), 6.39 (dd, J = 8.8, 2.8 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 154.2, 149.8, 143.4, 111.9, 102.9, 100.3, 56.4, 55.7, 55.6; HRMS (ESI): m/z [M + H⁺] calcd. for C₉H₁₃O₃: 169.0865; found: 169.0885.

1,3,5-Trimethoxybenzene (21)

White solid, substrate/product/byproduct ratio: 0/100/0, 1.65 g (98 %), m.p. 42–44 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.09 (s, 3H), 3.77 (s, 9H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 161.6 (3C), 92.9 (3C), 55.2 (3C); HRMS (ESI): m/z [M + H⁺] calcd. for C₉H₁₃O₃: 169.0865; found: 169.0850.

2,4,6-Trimethoxy-3-methylphenol (22)

Pale yellow solid, substrate/product/byproduct ratio: 0/100/0, 1.94 g (98 %), m.p. 47–50 °C; ¹H NMR (400 MHz, CDCl₃), δ (ppm): 6.31 (s, 1H), 5.15 (br s, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 2.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 150.8, 146.1, 145.1, 132.9, 112.5, 93.0, 60.5, 56.5, 56.4, 8.5; HRMS (ESI): m/z [M + H⁺] calcd. for C₁₀H₁₅O₄: 199.0970; found: 199.0949.

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