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Copper(II)-Catalyzed Aromatization Followed by Bromination of Cyclohexenones Leading to Phenols and Bromophenols

Hung-Chun Tong,[a] K. Rajender Reddy,*[b] and Shiuh-Tzung Liu*[a]

Keywords: Aromatization / Copper / Bromination / Homogenous catalysis / Oxidation / Aromatic substitution

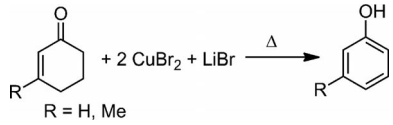
Conversion of substituted cyclohexenones into the corresponding phenols can be achieved using copper acetate as the catalyst in the presence of LiBr and CF_3COOH under oxygen. With the use of excess LiBr, electrophilic aromatic bromination afforded the corresponding bromophenol under similar catalytic conditions.

Introduction

Phenols are an important class of compounds with many uses; these include, but are not limited to, pharmaceuticals, herbicides, electronic materials, and polymeric materials. Industrial-scale production of phenols involves the partial oxidation of cumene followed by rearrangement chemistry.[1] Electrophilic aromatic substitution provides a useful way to introduce substituents on the ring. However, the strong directing effect of the hydroxy group limits this particular approach. Other traditional synthetic approaches leading to substituted phenols are also available, but drawbacks such as multi-step procedures, isomeric products, limitations of substrate scope and severe reaction conditions restrict the application of these methods.[1,2] Many complementary approaches leading to substituted phenols make use of transition-metal catalysts for cross-coupling and C–H functionalization chemistries.[3,4]

Recently, catalytic dehydrogenation of carbocyclic compounds such as cyclohexanones and cyclohexenones to generate substituted phenol derivatives has received much attention because of a broad substrate scope.[5–7] Stahl and co-workers reported that various cyclohexanones/cyclohexenones can be converted into phenols by Pd-catalysed dehydrogenation under oxygen.[5] Instead of dehydrogenation, Moriuchi et al. reported a vanadium-catalysed oxidative aromatization of 2-cyclohexenones leading to phenol products with Bu_4NBr or concentrated HBr as promoters.[8]

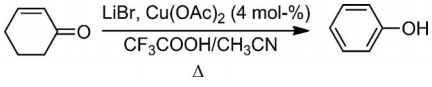
Despite these synthetic advances, there remains a strong need for efficient, easy-to-carry-out, and catalytic methods for converting cyclohexenones to phenols, particularly those bearing various substituents. It has been disclosed by Bondon et al. that treatment of cyclohexenone with $CuBr_2$ and LiBr gave the corresponding phenol in good yields (Scheme 1).[9] However, this method calls for the use of stoichiometric amounts of copper salt thereby rendering the approach non-catalytic. Inspired by this work, we set out to study this reaction under catalytic conditions and also to expand the reaction scope. Since copper salts are excellent metal catalysts for aerobic oxidative halogenations,[10] we report here our investigation into the Cu^{II}-catalysed aromatization of cyclohexenone by bromination/elimination followed by bromination leading to bromophenols in the presence of LiBr.



Scheme 1. Aromatization of cyclohexenones to phenols.

Results and Discussion

Initially, oxidative aromatization of 2-cyclohexenone catalysed by various copper complexes in the presence of LiBr under atmospheric pressure of O_2 at 80 °C was examined to identify ideal catalytic conditions (Scheme 2); results are



Scheme 2. Conversion of cyclohexenone into phenol catalysed by Cu^{II}.

[a] Department of Chemistry, National Taiwan University
1, Sec. 4, Roosevelt Road, Taipei, Taiwan 106
E-mail: stliu@ntu.edu.tw
[b] Inorganic and Physical Chemistry Division, CSIR – Indian Institute of Chemical Technology,
Tarnaka, Hyderabad 500607, India
E-mail: rajender@iict.res.in
http://www.ch.ntu.edu.tw/

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Table 1. Aromatization of 2-cyclohexenone leading to phenol catalyzed by various copper salts.[a]

Entry	Copper salt	Ligand[b]	Yield[c] [%]
1	–	–	–
2	$CuBr_2$	–	73
3	CuBr	–	58
4	CuI	–	39
5	$Cu(OAc)_2$	–	91
6	CuBr	2,2′-bipyridine	39
7	$Cu(OAc)_2$	2,2′-bipyridine	51
8	CuBr	$Me_2N(CH_2)_2NMe_2$	73
9	$Cu(OAc)_2$	$Me_2N(CH_2)_2NMe_2$	77
10	$Cu(OAc)_2$	2-aminopyridine	23
11[d]	$Cu(OAc)_2$		trace
12[e]	$Cu(OAc)_2$		57

[a] Reaction conditions: 2-cyclohexenone (0.6 mmol), LiBr (0.3 mmol) and copper salt (0.024 mmol) in CF_3COOH/CH_3CN (0.4 mL/0.8 mL) at 80 °C under O_2 (1 atm) for 10 h. [b] 0.024 mmol. [c] Yield of phenol based on NMR integration. [d] Reaction performed under nitrogen. [e] Reaction performed in air.

summarized in Table 1. It was noticed that the reaction did not proceed without the copper catalyst, indicating the necessity of metal ions (Table 1, Entry 1). Screening revealed that a number of copper ions did catalyse the reaction, although it was the use of $Cu(OAc)_2$ that enabled optimum production of phenol (Table 1, Entry 5). On the other hand, reactions using ligands such as tetramethylethylenediamine or bipyridine did not proceed well (Table 1, Entries 6–9). Additionally, only trace amounts of product could be obtained when carrying out the reaction under nitrogen (Table 1, Entry 11).

Table 2. Optimal reaction conditions for catalysis.[a]

Entry	Solvent (mL)	Bromide (mmol)	Yield[b] [%] Phenol	Yield[b] [%] *p*-BrC_6H_4OH
1	CH_3CN (1.2)	LiBr (0.3)	0	0
2	CH_3CN (0.8) CF_3COOH (0.4)	LiBr (0.3)	91	trace
3	CH_3CN (0.8) CF_3COOH (0.4)	KBr (0.3)	53	0
4	CH_3CN (0.8) CF_3COOH (0.4)	$MgBr_2$ (0.3)	50	9%
5	CH_3CN (0.4) CF_3COOH (0.8)	LiBr (0.3)	40	0
6	CH_3CN (0.8) CH_3COOH (0.4)	KBr (0.3)	0	0
7	THF (0.8) CF_3COOH (0.4)	LiBr (0.3)	68	trace
8	THF (0.8) CF_3CO_2H (0.4)	LiBr (1.8)	45	12%
9	CH_3CN (0.8) Et_3N (0.4)	LiBr (0.3)	0	0
10	CH_3CN (0.8) CF_3CO_2H (0.4)	LiBr (1.8)	6	90%
11	CH_3CN (0.8) CF_3COOH (0.4)	LiI (0.3)	–[c]	
12	CH_3CN (0.8) CF_3COOH (0.4)	LiCl (0.3)	NR[d]	

[a] Reaction conditions: 2-cyclohexenone (0.6 mmol), LiBr and $Cu(OAc)_2$ (0.024 mmol) in solvent at 80 °C under O_2 (1 atm) for 10 h. [b] Based on NMR integration. [c] No desired product. [d] No reaction.

Further efforts were then focused on optimizing the reaction conditions with a particular emphasis on solvent and salt effects. We found that $Cu(OAc)_2$ played a crucial role in the presence of trifluoroacetic acid but not acetic acid (Table 2, Entries 2 vs. 6). Moreover, the amount of acid employed had a dramatic impact on the production of the desired product (Table 2, Entry 5), suggesting that the acid strength can influence the catalytic reaction. When the reaction was carried out under basic or neutral conditions (Table 2, Entries 1 and 9), cyclohexenone was recovered quantitatively indicating complete failure of the reaction to proceed. Notably, the effects of various bromide salts on the phenol yields were investigated with lithium affording the best outcome (Table 2, Entries 2–4). It was noticed that this catalytic reaction provided *p*-bromophenol exclusively upon use of 300 mol-% LiBr with all other conditions similar to those previously identified as ideal with respect to other variables (Table 2, Entry 10). Presumably, this brominated product results from electrophilic aromatic substitution under Cu-catalyzed conditions.[11] A significant feature of this chemistry is that bromination of phenol can be controlled by manipulation of the reaction conditions. The application of larger amounts of LiBr in this catalytic transformation assists in further bromination of the aromatic ring.

Subsequently, the generality of the reaction with other cyclohexenes under the optimized conditions was explored (Table 3). We were pleased to find that various substituted cyclohexenones reacted smoothly to give the desired phenols or bromophenols in good to excellent yields. With the use of 300 mol-% LiBr, 3,5-diphenylcyclohexenone (**1**) was converted into the corresponding bromophenol in 65% yield (Table 3, Entry 1), whereas phenol **1b** was obtained in 64% yield when using less LiBr and a higher loading of $Cu(OAc)_2$ (20 mol-%). The catalytic oxidative aromatization was also effectively performed on a series of 3,4,5-trisubstituted cyclohexenes to yield the corresponding phenols (Table 3, Entries 3–12). Again, non-brominated phenols can be obtained in good yields when using 50 mol-% LiBr. The typical conditions for aromatization followed by bromination of **2**–**5** did not afford any selective monohalogenation product. However, dibrominated phenols **2a**–**5a** were obtained in excellent yields when 400 mol-% LiBr was used. Compound **7**, containing a thiophenyl substituent, underwent aromatization smoothly to give **7b** in 79% yield (Table 3, Entry 11). It was noticed that electrophilic bromination does not take place on the thiophene ring. Under similar catalytic conditions, treatment of carvone with 300 mol-% LiBr gave 4-bromo-5-isopropyl-2-methylphenol (**10a**) in 97% yield. Apparently, the double bond of the propenyl group in **10** was isomerized during the aromatization. Both 3-ethoxycyclohexenone (**11**) and cyclohexane-1,3-dione (**12**) were converted into tribromoresorcinol (**11a**) in excellent yields. (Table 3, Entries 16 and 17). In addition, 1,4-cyclohexanedione was converted into bromo-1,4-benzenediol (**13a**) in 88% yield (Table 3, Entry 18).

It should be noted that this catalytic system could be successfully applied to a gram-scale reaction for the aroma-

Table 3. Aromatization of substituted 2-cyclohexenones.[a]

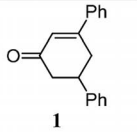
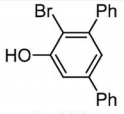
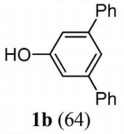
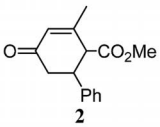
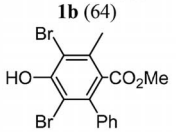
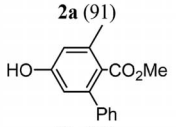
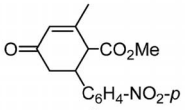
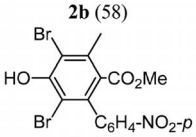
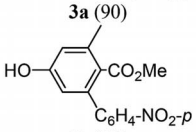
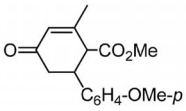
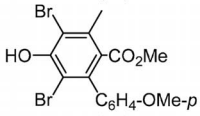
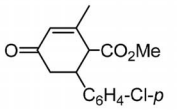
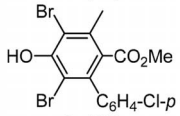
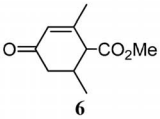
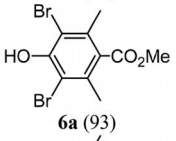
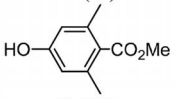
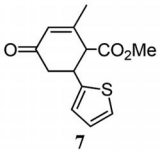
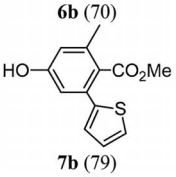
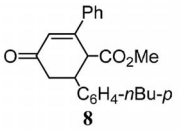
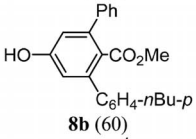
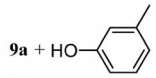
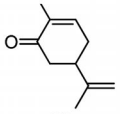
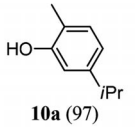
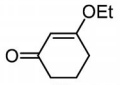
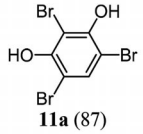
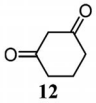
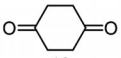
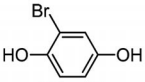
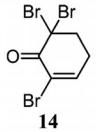
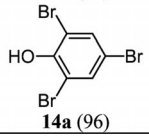
Entry	Substrate	LiBr [mol-%]	Product (yield [%])
1	 **1**	300	 **1a** (65)
2	**1**	50	 **1b** (64)
3	 **2**	400	 **2a** (91)
4	**2**	50	 **2b** (58)
5	 **3**	400	 **3a** (90)
6	**3**	50	 **3b** (68)
7	 **4**	400	 **4a** (94)
8[c]	 **5**	400	 **5a** (97)
9	 **6**	400	 **6a** (93)
10	**6**	50	 **6b** (70)
11	 **7**	100	 **7b** (79)
12	 **8**	50	 **8b** (60)
13	 **9**	300	 **9a** (91)

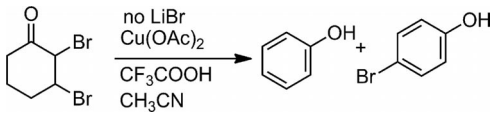
Table 3. *(Continued)*

Entry	Substrate	LiBr [mol-%]	Product (yield [%])
14	**9**	50	**9a** +  (45) **9b** (46)
15[c]	 **10**	300	 **10a** (97)
16	 **11**	400	 **11a** (87)
17	 **12**	400	**11a** (89)
18	 **13**	100	 **13a** (88)
19[c]	 **14**	300	 **14a** (96)

[a] Reaction conditions: 2-cyclohexenone (0.6 mmol), LiBr and copper salt (0.024 mmol) in CF_3COOH/CH_3CN (0.4 mL/0.8 mL) at 80 °C under O_2 (1 atm) for 10 h. [b] Isolated yields. [c] Reaction performed on gram-scale.

tization and halogenation of carvone to afford **10a**. Thus, a mixture of carvone (1 g), 4 mol-% $Cu(OAc)_2$ and 300 mol-% of LiBr in CF_3COOH (2 g)/CH_3CN (4 g) was heated at 80 °C under O_2 (1 atm) overnight; compound **10a** was isolated almost quantitatively.

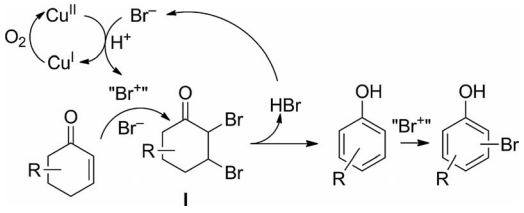
This aromatization methodology was found to not apply to cyclohexanone. Under the typical reaction conditions, only trace amounts of cyclohexanone were converted into α-bromocyclohexanone, not the phenol molecule. On the other hand, copper-catalysed aromatization of 2,3-dibromocyclohexanone was achieved without additional bromide ion (Scheme 3). In this reaction, *p*-bromophenol was obtained as a side product (25%). Apparently, the bromide from the elimination step acts as the bromide source for halogenation of the aromatic ring. When carrying out this reaction in the absence of Cu^{II} ions, the elimination step proceeded very slowly, suggesting that copper ions might also play some role in the aromatization.



Scheme 3. Aromatization of 2,3-dibromocyclohexanone.

A plausible pathway for this aromatization is shown in Scheme 4. Under acidic conditions, the bromide ion is oxid-

ized to "Br^+", which acts as an electrophile for bromination of the alkenyl group leading to **I**,[10] which then undergoes elimination of HBr followed by tautomerization to yield the phenol product. Meanwhile, the reduced Cu^I species is re-oxidized by O_2 to generate Cu^{II}. Subsequently, the electrophilic aromatic bromination might take place under the reaction conditions leading to bromophenols.



Scheme 4. Possible reaction pathway for the aromatization.

Conclusions

A protocol has been developed for the aromatization of cyclohexenones in the presence of LiBr by a Cu^{II}-catalysed aerobic bromination followed by elimination under acidic conditions. The advantages of this method are (i) the general applicability to various cyclohexenes leading to high product yields, (ii) copper acetate as catalyst, and (iii) mild reaction conditions. Furthermore, the corresponding bromophenols can be readily obtained when using large amounts of bromide sources. This catalytic system can be applied to gram-scale reactions making it an attractive and useful methodology for organic synthesis.

Experimental Section

General: All catalytic reactions were carried out in a sealed high-pressure tube. Chemicals were purchased from the suppliers and used without further purification, unless otherwise noted. All compounds were characterized by ^1H, ^{13}C NMR and mass spectra. NMR spectra were recorded in $CDCl_3$ or [D_6]acetone. Chemical shifts are given in ppm relative to Me_4Si for ^1H and ^{13}C. Compounds **1**[12a] and **2**–**6**[12b] were prepared according to reported procedures. Compounds **9**–**12** were obtained from commercial sources, and used without further purification.

Preparation of Compound 7: Piperidine (2 mmol, 40 mol-%) was added to a solution of 2-thiophenecarbaldehyde (5 mmol) and methyl acetoacetate (10 mmol) in EtOH (8 mL). The resulting mixture was stirred at 80 °C for 6 h. The reaction mixture was then quenched with aqueous NH_4Cl solution, extracted with diethyl ether, and washed with water/brine. The organic layer was dried with anhydrous $MgSO_4$. The solution was concentrated by rotary evaporation, and the residue was chromatographed on silica gel (mixture of EtOAc/hexane) to give product **7** as a yellow liquid. ^1H NMR (400 MHz, $CDCl_3$; diastereomers): δ = 7.16–7.105 (m, 1 H), 6.91–6.78 (m, 2 H), 6.00 (m, 1 H, olefinic H), 3.98–3.78 (m, 1 H), 3.65 (s, 2 H, OCH_3), 3.52–3.25 (m, 1 H), 3.49 (s, 1 H, OCH_3), 2.85–2.57 (m, 2 H), 1.97 (m, , 3 H, olefinic CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.55, 196.21, 171.21, 169.85, 155.48, 155.22, 144.62, 143.42, 128.50, 128.39, 126.72, 124.59, 124.27, 124.15, 124.04, 54.70, 53.62, 52.33, 52.18, 42.70, 38.88, 38.76, 37.88, 23.16, 22.82 ppm. HRMS-ESI (TOF): calcd. for $C_{13}H_{15}O_3S$ $[M + H]^+$ 251.0742, found 251.0735. $C_{13}H_{14}O_3S$ (250.31): calcd. C 62.38, H 5.64; found C 62.11, H 5.38.

Preparation of Compound 8: The procedure was similar to that used to generate **7**. Viscous yellow liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.0 Hz, 2 H), 7.37–7.26 (m, 5 H), 7.21 (d, J = 8.0 Hz, 2 H), 6.50 (d, J = 2.4 Hz, 1 H, olefinic H), 3.46 (m, 1 H), 3.07 (m, 1 H), 2.92 (m, 1 H), 2.74 (m, 2 H), 2.63 (t, J = 7.6 Hz, 2 H), 1.62 (m, 2 H), 1.38 (m, 2 H), 0.93 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.22, 158.61, 145.57, 143.27, 135.47, 128.83, 128.76, 126.99, 126.74, 126.09, 124.27, 43.90, 40.96, 36.15, 35.34, 33.29, 22.25, 13.84 ppm. HRMS-ESI (TOF): calcd. for $C_{22}H_{25}O$ $[M + H]^+$ 305.1905, found 305.1906. $C_{22}H_{24}O$ (304.43): calcd. C 86.80, H 7.95; found C 86.48, H 7.63.

General Procedure for the Catalysis: A mixture of substrate (0.6 mmol), $Cu(OAc)_2$ (2.4×10^{-2} mmol), LiBr in a solution of CF_3COOH (0.4 mL) and CH_3CN (0.8 mL) was loaded in a 15 mL reaction tube. The reaction vessel was flushed with O_2 and the mixture heated to 80 °C for a period of time. After cooling to room temp., the reaction mixture was poured into a saturated NaCl solution, extracted with CH_2Cl_2 and dried with anhydrous $MgSO_4$. After removal of the solvents, the residue was chromatographed on silica gel. All products were characterized by spectroscopic methods and analysis. All characterization data are summarized in the Supporting Information.

2-Bromo-3,5-biphenylphenol (1a):[13] Yield 126.8 mg (65%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2 H), 7.44–7.39 (m, 7 H), 7.36–7.35 (m, 1 H), 7.27 (d, J = 2.0 Hz, 1 H), 7.14 (d, J = 2.0 Hz, 1 H), 5.85 (br., 1 H, OH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.76, 143.47, 141.62, 140.81, 139.57, 129.16, 128.96, 128.80, 128.30, 128.04, 127.81, 127.78, 126.94, 121.83, 113.10, 110.21 ppm. ESI-HRMS (TOF): calcd. for $C_{18}H_{12}{}^{79}Br(^{81}Br)O$ $[M - H]^-$ 323.0072 (325.0051), found 323.0071 (325.0035).

3,5-Biphenylphenol (1b): Yield 96 mg (64%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, J = 7.6, 1.2 Hz, 4 H), 7.44–7.32 (m, 7 H), 7.02 (d, J = 1.2 Hz, 2 H), 5.11 (br., 1 H, OH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 156.13, 143.31, 140.68, 128.69, 127.52, 127.11, 118.86, 112.97 ppm. ESI-HRMS (TOF): calcd. for $C_{18}H_{13}O$ $[M - H]^-$ 245.0966, found 245.0972. $C_{18}H_{14}O$ (246.31): calcd. C 87.78, H 5.73; found C 87.48, H 5.37.

Methyl 3,5-Dibromo-4-hydroxy-2-methyl-6-phenylbenzoate (2a): Yield 218.4 mg (91%), white solid, m.p. 142–143 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.23 (m, 5 H), 5.01 (br., 1 H, OH), 3.44 (s, 3 H, OCH_3), 2.42 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 168.36, 150.32, 140.15, 138.47, 135.18, 129.09, 129.02, 128.22, 128.01, 112.29, 109.25, 52.13, 20.78 ppm. ESI-HRMS (TOF): calcd. for $C_{15}H_{11}{}^{79}Br_2O_3$ $[M - H]^-$ 396.9075, found 396.9080. $C_{15}H_{12}Br_2O_3$ (400.07): calcd. C 45.03, H 3.02; found C 44.86, H 2.87.

Methyl 4-Hydroxy-2-methyl-6-phenylbenzoate (2b): Yield 84.3 mg (58%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.25 (m, 5 H), 6.61 (s, 2 H), 6.09 (br., 1 H, OH), 3.49 (s, 3 H, OCH_3), 2.31 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.64, 156.43, 142.59, 140.80, 138.15, 128.15, 127.85, 127.30, 125.31, 115.96, 114.18, 51.73, 19.87 ppm. ESI-HRMS (TOF): calcd. for $C_{15}H_{13}O_3$ $[M - H]^-$ 241.0865, found 241.0868. $C_{15}H_{14}O_3$ (242.27): calcd. C 74.36, H 5.82; found C 74.01, H 5.48.

Methyl 3,5-Dibromo-4-hydroxy-2-methyl-6-(*p*-nitrophenyl)benzoate (3a): Yield 240.3 mg (90%), light yellow solid, m.p. 150–151 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, J = 8.4 Hz, 2 H), 7.45 (d, J = 8.4 Hz, 2 H), 5.09 (br., 1 H, OH), 3.49 (s, 3 H, OCH_3), 2.43 (s,

3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.68, 150.64, 147.66, 145.10, 138.01, 135.90, 130.42, 128.98, 123.31, 113.54, 108.19, 52.35, 20.91 ppm. ESI-HRMS (TOF): calcd. for $C_{15}H_{10}{}^{79}Br_2NO_5$ $[M - H]^-$ 441.8926, found 441.8929. $C_{15}H_{11}Br_2NO_5$ (445.06): calcd. C 40.48, H 2.49; found C 40.17, H 2.05.

Methyl 3,5-Dibromo-4-hydroxy-2-methyl-6-(*p*-nitrophenyl)benzoate (3b):[14] Yield 117.2 mg (68%). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.8 Hz, 2 H), 7.45 (d, J = 8.8 Hz, 2 H), 6.72 (d, J = 2.0 Hz, 1 H), 6.62 (d, J = 2.0 Hz, 1 H), 5.43 (br., 1 H, OH), 3.52 (s, 3 H, OCH_3), 2.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.36, 156.33, 147.61, 147.12, 140.46, 139.16, 128.85, 127.57, 123.42, 117.14, 113.99, 51.81, 20.03 ppm. ESI-HRMS (TOF): calcd. for $C_{15}H_{12}NO_5$ $[M - H]^-$ 286.0715, found 286.0713.

Methyl 3,5-Dibromo-4-hydroxy-6-(*p*-methoxyphenyl)-2-methylbenzoate (4a): Yield 242.6 mg (94%), yellow solid, m.p. 126–127 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.12 (d, J = 8.8 Hz, 2 H), 6.89 (d, J = 8.8 Hz, 2 H), 3.83 (br., 1 H, OH), 3.80 (s, 3 H, OCH_3), 3.44 (s, 3 H, OCH_3), 2.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 168.36, 159.26, 150.13, 139.70, 134.85, 130.63, 130.25, 129.24, 113.32, 111.95, 109.68, 55.13, 52.08, 20.63 ppm. ESI-HRMS (TOF): calcd. for $C_{16}H_{13}{}^{79}Br_2O_4$ $[M - H]^-$ 426.9181, found 426.9184. $C_{16}H_{14}Br_2O_4$ (430.09): calcd. C 44.68, H 3.28; found C 44.45, H 2.97.

Methyl 3,5-Dibromo-6-(*p*-chlorophenyl)-4-hydroxy-2-methylbenzoate (5a): Yield 258.1 mg (97%), m.p. 130–131 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, J = 8.4 Hz, 2 H), 7.14 (d, J = 8.4 Hz, 2 H), 3.94 (br., 1 H, OH), 3.44 (s, 3 H, OCH_3), 2.35 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 168.02, 150.31, 138.79, 136.74, 135.24, 134.25, 130.47, 128.82, 128.24, 112.60, 108.97, 52.17, 20.71 ppm. ESI-HRMS (TOF): calcd. for $C_{15}H_{10}{}^{79}Br_2{}^{35}ClO_3$ $[M - H]^-$, 430.8685, found 430.8686. $C_{15}H_{11}Br_2ClO_3$ (434.51): calcd. C 41.46, H 2.55; found C 41.09, H 2.22.

Methyl 3,5-Dibromo-4-hydroxy-2,6-dimethylbenzoate (6a): Yield 188.6 mg (93%), white solid, m.p. 140–141 °C: ^1H NMR (400 MHz, $CDCl_3$): δ = 6.20 (br., 1 H, OH), 3.92 (s, 3 H, OCH_3), 2.33 (s, 6 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 169.18, 150.01, 134.55, 128.66, 110.41, 52.51, 20.72 ppm. ESI-HRMS (TOF): calcd. for $C_{10}H_9{}^{79}Br_2O_3$ $[M - H]^-$ 334.8918, found 334.8922. $C_{10}H_{10}Br_2O_3$ (338.00): calcd. C 35.54, H 2.98; found C 35.35, H 2.78.

Methyl 4-Hydroxy-2,6-dimethylbenzoate (6b):[15] Yield 75.7 mg (70%). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.45 (s, 2 H, ArH), 5.37 (br., 1 H, OH), 3.84 (s, 3 H, OCH_3), 2.24 (s, 6 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.41, 156.23, 137.92, 125.99, 114.76, 114.47, 51.69, 20.06 ppm. ESI-HRMS (TOF): calcd. for $C_{10}H_{11}O_3$ $[M - H]^-$ 179.0708, found 179.0708.

Methyl 4-Hydroxy-2-methyl-6-(thiophen-2-yl)benzoate (7b): Yield 117.7 mg (79%), white solid, m.p. 113–114 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.23 (m, 1 H), 6.97–6.96 (m, 2 H), 6.71 (d, J = 2.4 Hz, 1 H), 6.57 (d, J = 2.4 Hz, 1 H), 6.17 (br., 1 H, OH), 3.67 (s, 3 H, OCH_3), 2.25 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 170.94, 156.30, 141.64, 137.79, 134.12, 127.31, 125.79, 125.76, 125.54, 116.48, 114.38, 52.22, 19.67 ppm. ESI-HRMS (TOF): calcd. for $C_{13}H_{11}O_3S$ $[M - H]^-$ 247.0429, found 247.0428. $C_{13}H_{12}O_3S$ (248.30): calcd. C 62.88, H 4.87; found C 62.56, H 4.59.

3-(*p*-Butylphenyl)-5-phenylphenol (8b): Yield 108.9 mg (60%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 6.8 Hz, 2 H), 7.52 (d, J = 8.4 Hz, 2 H), 7.44–7.34 (m, 4 H), 7.25 (d, J = 8.4 Hz, 2 H), 7.02 (m, 2 H), 5.17 (br., 1 H, OH), 2.66 (t, J = 7.6 Hz, 2 H), 1.73 (m, 2 H), 1.43 (m, 2 H), 0.96 (t, J = 7.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 156.07, 143.24, 142.41, 140.77, 137.97, 128.78, 128.68, 127.47, 127.12, 126.94, 118.72, 112.82, 112.72, 35.22, 33.53, 22.32, 13.88 ppm. ESI-HRMS (TOF): calcd. for $C_{22}H_{21}O$ $[M - H]^-$ 301.1592, found 301.1595. $C_{22}H_{22}O$ (302.42): calcd. C 87.38, H 7.33; found C 87.02, H 7.11.

4-Bromo-3-methylphenol (9a):[16] Yield 108.9 mg (97%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 8.6 Hz, 1 H, Ar-H), 6.71 (d, J = 2.9 Hz, 1 H, Ar-H), 6.54 (dd, J = 2.9, 8.6 Hz, 1 H, Ar-H), 5.13 (br., 1 H, OH), 2.31 (s, 3 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 154.47, 139.13, 132.99, 117.75, 115.46, 114.44, 22.87 ppm. ESI-HRMS (TOF): calcd. for $C_7H_6{}^{79}BrO$ $[M - H]^-$ 184.9608; found 184.9603.

4-Bromo-5-isopropyl-2-methylphenol (10a):[17] Yield 133.3 mg (97%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (s, 1 H, Ar-H), 6.68 (s, 1 H, Ar-H), 4.89 (br., 1 H, OH), 3.30 (m, J = 6.9 Hz, 1 H, CH), 2.17 (s, 3 H, CH_3), 1.18 (d, J = 6.9 Hz, 6 H, CH_3) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 153.18, 146.01, 134.33, 123.23, 114.19, 113.16, 32.49, 22.72, 15.01 ppm. ESI-HRMS (TOF): calcd. for $C_{10}H_{12}{}^{79}BrO$ $[M - H]^-$ 227.0077, found 227.0074.

2,4,6-Tribromobenzene-1,3-diol (11a):[18] Yield 181 mg (87%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1 H, ArH), 5.89 (s, 2 H, OH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 149.70, 132.90, 100.29, 98.20 ppm. ESI-HRMS (TOF): calcd. for $C_6H_2{}^{79}Br_3O$ $[M - H]^-$ 326.7661, found 326.7656.

2-Bromobenzene-1,4-diol (13a):[19] Yield 99.8 mg (88%). ^1H NMR (400 MHz, [D_6]acetone): δ = 6.65 (dd, J = 8, 3 Hz, 1 H), 6.80 (d, J = 8 Hz, 1 H), 6. 90 (d, J = 3 Hz, 1 H), 8.5 (br., 2 H, OH) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 151.28, 147.11, 119.2, 117.33, 116.3, 110.5 ppm.

2,4,6-Tribromophenol (14a):[20] Yield 176.6 mg (89%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (s, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 148.87, 134.14, 112.59, 110.32 ppm. ESI-HRMS (TOF): calcd. for $C_6H_3{}^{79}Br_3O$ $[M - H]^-$ 327.7734, found 327.7729.

Gram-Scale Preparation of 10a: A mixture of **10** (1.0 g, 6.67 mmol), $Cu(OAc)_2$ (48 mg, 0.26 mmol) and LiBr (1.74 g, 20 mmol) in a solution of CF_3COOH (2 g) and CH_3CN (4 g) was heated at 80 °C under O_2 (1 atm) overnight, The reaction mixture was poured into a saturated NaCl solution (10 mL), extracted with CH_2Cl_2 (2 × 20 mL) and dried with $MgSO_4$. After removal of the solvents, the residue was passed through a short silica gel column. Compound **10a** was obtained upon concentration (0.98 g, 97%).

Supporting Information (see footnote on the first page of this article): NMR spectra of the obtained compounds.

Acknowledgments

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