

Efficient Method for the Preparation of Aromatic Bromides and Iodides by Ferrocenium Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate-Catalyzed Halogenation with Bromine and Iodine Monochloride

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Direct iodination and bromination of various aromatic compounds with 1.1–2.0 molar amounts of iodine monochloride (ICl) and 1.1–3.0 molar amounts of bromine proceeded smoothly to afford the corresponding aromatic iodides and bromides, respectively, in good to excellent yields by using 0.05 molar amount of ferrocenium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate, $Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (**1**), in the presence of ZnO. Iodination of toluene in the coexistence of 0.5 molar amount of DDQ also proceeded to give iodotoluenes in high yield.

Aromatic halides are widely used in organic synthesis as reagents that form a new carbon-carbon or carbon-heteroatom bond on aromatic rings by substitution of their halogen atoms. For instance, Grignard reagents,[1] prepared from aromatic halides and magnesium, react with electrophiles such as aldehydes or ketones to form the substituted aromatic compounds. Also, Ullmann reaction[2] is employed for the coupling of two aromatic halides in the presence of copper to give either symmetrical or unsymmetrical biaryls. Furthermore, aromatic halides are frequently used in palladium-catalyzed coupling reactions such as Heck,[3] Stille[4] and Suzuki reactions.[5] Because these aromatic iodides and bromides are more reactive than the corresponding chlorides, they are often used in the above reactions.

Aromatic iodinations known to date are roughly classified into the following three methods: (1) iodination by Sandmeyer reaction,[6] (2) iodination of metalated aromatics,[7] and (3) direct iodination of aromatics.[8] Concerning preparation of aromatic iodides, iodination of aromatic diazonium salts with iodide ion or iodo radical is commonly employed (Sandmeyer reaction). Although this method generally gives the desired aromatic iodides in satisfactory yields, it involves several steps and various side reactions such as replacement of diazo group by hydrogen, along with the formation of azo compounds and biaryls. Iodination of metalated aromatics is also an important method: for example, thallium derivatives, useful metalated aromatics, are smoothly converted to aromatic iodides on treatment with KI or NaI. This method, however, needs a stoichiometric amount of toxic thallium salt. In order to improve these problems, several methods for the direct iodination of aromatics are developed. Namely, (i) the use of strong Lewis acids such as CF_3COOAg,[9] $AgNO_2$[10] and $AlCl_3$–$CuCl_2$[11] increase electrophilic abilities of I_2 by the coordination of Lewis acids; (ii) the use of mixed anhydrides of hypoiodite[12] such as CF_3COOI, and CH_3COOI; and (iii) oxidation of I_2 by using strong oxidizing agents such as HIO_3/H_2SO_4,[13] $SbCl_5$,[14] metal ions (Ce(IV),[15] Cu (II)[16]), CH_3CO_3H,[17] $C_6H_5I(OCOCF_3)_2$,[18] and $NO^+BF_4^-O_2$[19] to generate active iodonium ion (I^+).

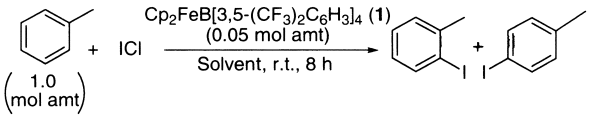
Aromatic brominations are also classified into the following three methods: (1) bromination by the combined use of Br_2 and metal salts such as HgO,[20] $AlBr_3$,[21] FeI_2,[22] and $CuBr_2$:[23] these aromatic brominations are usually carried out under acidic conditions using excess amounts of metal salts; (2) bromination of metalated aromatics involving a metalation reaction aided by silicon,[24] tin,[25] thallium(Ⅲ) trifluoroacetate,[26] or germanium(Ⅲ)[27] and subsequent conversion of these metalated aromatics into aromatic bromides with Br_2; (3) the use of active brominating reagents such as trifluoroacetyl hypobromite,[9b] BrF,[28] 1,3-dibromo-5,5-dimethylhydantoin,[29] DBU–HBr_3,[30] ^{t}BuBrNH,[31] Me_4NBr_3,[32] NBS-DMF,[33] NBS–H_2SO_4,[34] and HBr–DMSO.[35]

In these iodination and bromination methods, however, the same problems are being carried over since they have to use stoichiometric amounts of activating reagents under drastic conditions. Here, a more efficient halogenation method was sought in which conditions were milder and molecular halogens were activated by a catalytic amount of Lewis acid. It was reported from our laboratory that a catalytic amount of a borate compound such as $TrB(C_6F_5)_4$ or $LiB(C_6F_5)_4$ worked effectively as a Lewis acid in catalytic glycosylation,[36] aldol,[37] and Friedel–Crafts benzylation[38] reactions. These results prompted us to develop a convenient method for the direct halogenation of aromatics by using Lewis acids having $B(C_6F_5)_4$ or $B[3,5\text{-}(CF_3)_2C_6H_3]_4$ anion, which is one of the most weakly-coordinating anions[39] and whose salt is soluble even in nonpolar organic solvents. In the present paper, we would like to report detailed results on the direct iodination and bromination of several aromatics using a catalytic amount of $Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (**1**) in the presence of ZnO.

Results and Discussion

Synthesis of Aromatic Halides by Using a Catalytic

Table 1. Effect of Solvents and Amounts of ICl on the Direct Iodination of Toluene



Entry	Solvent	ICl/mol amt	*o*/*p*[a]	Yield/%[a]
1	$CHCl_3$	1.0	46/54	22
2	CCl_4	1.0	40/60	16
3	$ClCH_2CH_2Cl$	1.0	46/54	32
4	CH_3CN	1.0	—	trace
5	THF	1.0	—	N.R.
6	CH_2Cl_2	1.0	47/53	33
7	CH_2Cl_2	2.0	49/51	66
8	CH_2Cl_2	3.0	48/52	40

a) Determined by GC-analysis.

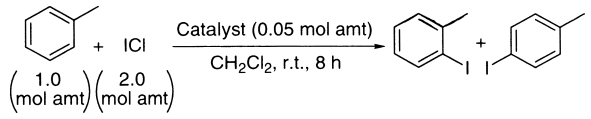
Amount of $Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4$ In the first place, catalytic iodination of toluene with iodine monochloride (ICl)[40] was tried as a model reaction by using 0.05 molar amount of $Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (**1**); effects of solvents and amounts of ICl were examined (Table 1).

The ferrocenium ion was thought to interact with an electron at the outer sphere,[41] and it was expected that the ferrocenium salt **1** would work as a mild Lewis acid in the present iodination of aromatics. Recently, Molins et al. reported on the preparation of **1**.[42] They described that this ferrocenium salt was purified easily by recrystallization, which was stored in air for at least one month. By taking these characteristic properties into consideration, **1** was at first chosen as a catalyst.

When the catalytic iodination of toluene was carried out by using one equivalent of ICl in nonpolar and polar solvents in the presence of 0.05 molar amount of **1**, iodotoluene was obtained in low yields (0–33%) in all cases (Table 1, Entries 1–6). Among the solvents examined, the use of dichloromethane and 1,2-dichloroethane gave better results (Table 1, Entry 3 and 6). Polar solvents such as acetonitrile and THF were not suitable for the iodination of aromatics, probably due to the deactivation of the catalyst **1** by coordinating those polar solvents to the ferrocenium ion. The amount of ICl influenced greatly the catalytic iodination reaction, i.e. the yield of iodotoluene was improved up to 66% yield by increasing the amount of ICl from one to two molar amounts, while the yield of iodotoluene decreased to 40% when three molar amounts of ICl were used (Table 1, Entries 6–8).

Next, effects of several metal borate salts were examined. A result similar to that of non-catalyzed iodination with ICl was observed when the iodination of toluene was tried in CH_2Cl_2 by using 2 molar amounts of ICl and 0.05 molar amounts of $LiB(C_6F_5)_4$ (**2**) which was reported to be an effective catalyst in Friedel-Crafts benzylation[38] (Table 2, Entry 1 and 2). $LiB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (**3**) also showed a little effect, and then $Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (**1**) was found to be a better catalyst. On the other hand, the desired product was not obtained at all when I_2 was used in the **1**-catalyzed iodination, as I_2 was far less reactive than ICl (Table 2, Entry 5).

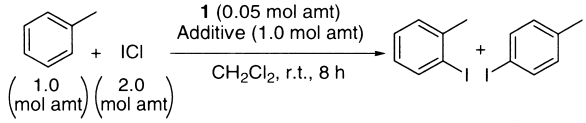
Table 2. Effect of Catalyst on the Direct Iodination of Toluene



Entry	Catalyst	*o*/*p*[a]	Yield/%[a]
1	none	49/51	48
2	$LiB(C_6F_5)_4$ (**2**)	44/56	50
3	$LiB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (**3**)	49/51	59
4	$Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (**1**)	49/51	66
5[b]	**1**	—	N.R.[c]

a) Determined by GC-analysis. b) I_2 (2.0 mol amt) was used. c) No reaction.

Table 3. Effect of the Additive on the Iodination of Toluene



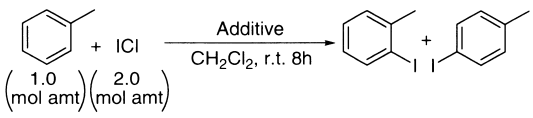
Entry	Additive	*o*/*p*[a]	Yield/%[a]
1	none	49/51	66
2	ZnO	47/53	68
3	MgO	49/51	62
4	Et_3N	47/53	11
5	Pyridine	—	N.R.
6	DDQ (0.5)	47/53	82[b]

a) Determined by GC-analysis.
b) Chlorotoluene was detected in 13% yield (*o*/*p* = 67/33) by GC-analysis.

Next, the effects of several additives, especially several bases to scavenge HCl, were examined, since it was reported that HCl which formed during the iodination reacted with ICl to form a less reactive iodinating reagent, $HICl_2$ (Table 3).[43] Contrary to our expectation, addition of bases or other HCl scavengers did not improve the yields of iodotoluene while the addition of DDQ improved the yields of iodotoluenes up to 82% (Table 3, Entry 6).[44]

As shown in Table 4, DDQ itself did not catalyze the iodination of toluene; results were almost the same to those obtained by the iodination using ICl alone (Table 4, Entry 1 and 2). When the iodination of toluene was carried out in a large scale

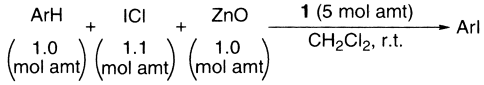
Table 4. Effect of DDQ and ZnO

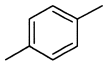
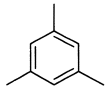
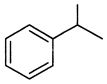
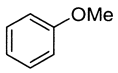
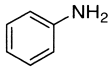
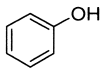


Entry	Additive (eq)	*o*/*p*[a]	Yield/%[a]
1	none	49/51	48
2	DDQ (0.5 eq)	49/51	50
3	ZnO (1.0 eq)	49/51	51

a) Determined by GC-analysis.

Table 5. Aromatic Iodination with ICl Using a Catalytic Amount of $Cp_2FeB[3,5\text{-}C_6H_3(CF_3)_2]_4$



Entry	ArH	Time/h	*o*/*p*[a]	Yield/%[a]
1		8	47/53 (47/53)	68[b] (82)[b,e,f]
2		2	3-/4-iodo-*o*-xylene 79/21	83
3		3	4-iodo-*m*-xylene	91 (62)[e]
4		3	—	70[d] (56)[d,e]
5		3	—	93
6		8	19/81[d]	82[d]
7		3	11/89 (1/99)	95 (70)[e]
8		3	5/95 (1/99)	88[c] (54)[e]
9		3	16/84[d]	89[c]

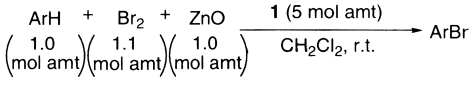
a) Determined by GC-analysis. b) ICl (2.0 mol amt) was used. c) Isolated yield. d) Determined by ^{1}H NMR spectra. e) DDQ (0.5 mol amt) was used instead of using ZnO (1.0 mol amt). f) Chlorotoluene was obtained in 13% yield (*o*/*p* = 64/33).

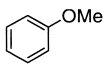
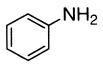
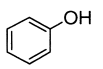
by using toluene (10 mmol), **1**, and DDQ, the desired iodotoluene was isolated by distillation in 84% yield, indicating that the present reaction is applicable to the practical preparation of iodinated aromatic compounds.

Even when the direct iodination of several aromatic compounds was carried out in the presence of DDQ and **1**, the yields of iodinated products were not so high as in the case of toluene (Table 5, Entries 1, 3–4, and 7–8). On the other hand, it was found that various aromatic compounds were readily iodinated with 1.1 molar amounts of ICl at room temperature to afford the desired iodinated compounds in high yields in the presence of ZnO (Table 5). It may be probably due to the trapping of undesirable HCl with ZnO and the smooth turnover of the catalyst **1**. Concerning regioselectivities of the present iodination reaction, good ortho/para ratios were observed in the cases of anisole, phenol, and aniline, as was reported in the previous preliminary communication (Table 5, Entries 7–9).[45]

Finally, the above mentioned catalyst system, **1** and ZnO, was applied to the direct bromination of aromatic compounds (Table 6).

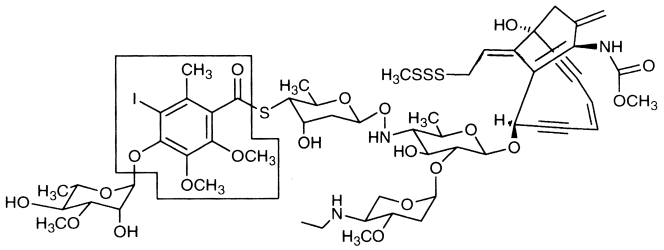
Table 6. Aromatic Bromination with Br_2 Using a Catalytic Amount of $Cp_2Feb[3,5\text{-}C_6H_3(CF_3)_2]_4$



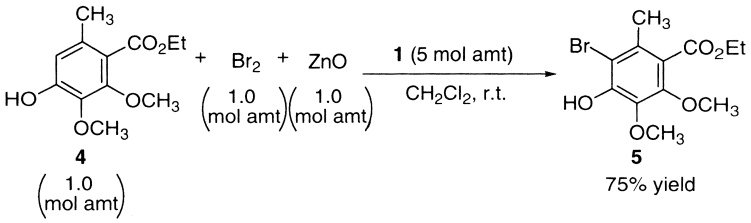
Entry	ArH	Conc./M	Time/h	*o*/*p*[a]	Yield/%[a]
1[b]		5	7	—	81
2[b]		0.25	8	34/66	86
3		0.25	1	3-/4-bromo-*o*-xylene 24/76	95
4		0.25	1.5	2-/4-bromo-*m*-xylene	93
5		0.25	1.5	—	99
6		0.25	3.5	—	84
7		0.25	8	12/88	86[d]
8		0.25	3	4-bromo-anisole > 99	83
9[g]		0.25	1	3/97	40[f]
10		0.25	2.5	18/92[d]	84[f]
11[c,e]		5	4	13/87	79
12[c,e]		5	3	Dibromo-benzene 17/83	94
13[c,e]		5	4	24/76	83
14		0.25	3	1-Bromo-naphthalene	91

a) Determined by GC-analysis. b) Br_2 (2.0 mol amt) was used. c) Br_2 (3.0 mol amt) was used. d) Determined by ^{1}H NMR spectra. e) Reaction temperature was reflux. f) Isolated yield. g) Br_2 (1.5 mol amt) was used.

The desired aromatic bromides were obtained in good to high yields, as listed in Table 6. It was noted that deactivated aromatics such as chlorobenzene and iodobenzene were also brominated directly in 79 and 83% yields, respectively (Table 6, Entry 11 and 13). Interestingly, dibromobenzene was obtained in 94% yield (Table 6, Entry 12) when 3.0 molar amounts of bromine were used in the bromination of benzene, suggesting that mono- or dibromobenzene was selectively obtained by changing the amount of bromine (Table 6, Entry 1 and 12). However, bromination of aniline gave monobrominated aniline in a low yield (40%), since di- and tribrominated



Calichemicin $\gamma^{I}_{1\alpha}$



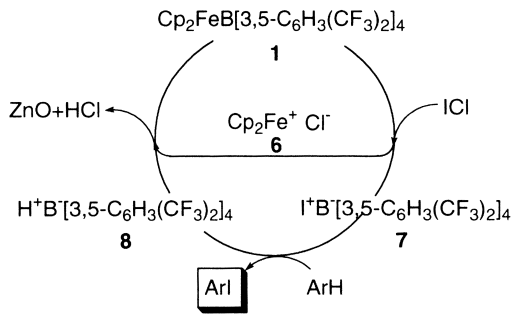
Scheme 1. Syntheses of Aromatic Constituents of the Calichemicin $\gamma^{I}_{1\alpha}$ Derivative.

aniline were also formed as major products (Table 6, Entry 9).

Moreover, the catalyst system was applied to direct bromination of ethyl ester of Calichemicin $\gamma^{I}_{1\alpha}$ fragment (**4**) whose mother body Calichemicin $\gamma^{I}_{1\alpha}$ is one of new classes of naturally occurring compounds with potent biological activities.[46] The desired bromide **5** was obtained in 75% yield indicating that the present reaction is applicable to the preparation of compounds having many functional groups in the same molecule (Scheme 1).

The present direct iodination would proceed via a reactive intermediate, I^+ ion, which in turn forms a σ-complex in a transition state, as proposed by Galli et al.[47] Concerning the catalytic cycle of the present direct iodination reaction, it is assumed that the catalyst **1** would react with ICl to generate an intermediate containing active iodo cation **7**. This intermediate then reacts with aromatic compounds to give the desired iodinated aromatic compounds along with **8**, which in turn reacts with **6** to regenerate the catalyst **1** along with the capture of HCl with ZnO (Scheme 2). It was assumed that DDQ would effectively work to prevent unfavourable radical iodination of toluene forming benzyliodide, although the role of DDQ has not yet been made clear.

In conclusion, iodination or bromination of aromatic compounds with 1.1–2.0 molar amounts of ICl or 1.1–3.0 molar amounts of bromine were effectively promoted by a catalytic amount of **1** in the coexistence of ZnO. Also, iodination of toluene proceeded in high yield in the coexistence of DDQ. Results shown here demonstrate that **1** has served as a mild Lewis acid catalyst in the direct iodination and bromination of aromatic compounds.



Scheme 2. The Catalytic cycle.

Experimental

All melting points were determined by a Yanagimoto micro melting point apparatus and are not corrected. IR spectra were recorded by a Hobita FT-300 infrared spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM LA-300 spectrometer, and tetramethylsilane (TMS) served as internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM LA-300 spectrometer, and TMS served as internal standard. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. All reactions were carried out under argon atmosphere in dried glassware.

Dichloromethane, chloroform, 1,2-dichloroethane, and acetonitrile were distilled from P_2O_5 and then from CaH_2, and dried over MS4A. Other distilled solvents were purchased from Kokusan Chemical Co., Inc., and were used without further purification. Anisole, benzene, toluene, xylene, mesitylene, cumene, aniline, phenol, chlorobenzene, iodobenzene, naphthalene were distilled or recrystallized before use. I_2 was purchased from Kokusan Chemical Co., Inc. and was used without further purification. ICl (1.0 M CH_2Cl_2 solution) (1 M = 1 mol dm^{-3}) was purchased from Aldrich Chemical Company, Inc. DDQ was purified by recrystallization from benzene. MgO, and ZnO were purchased from Kanto Chemical Co., Inc. and were used without further purification. Lithium tetrakis(pentafluorophenyl)borate (**2**)·$(C_2H_5)_2O$ (1/1.9–2.3) addition compound was purchased from Tokyo Kasei Kogyo Co., Ltd. and was dried under 13.3 Pa at 30 °C for 5 h before use.

Ferrocenium Tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (1). The borate **1** was prepared according to the procedure of Molins and Manríquez.[42] A mixture of ferrocenium tetrafluoroborate (1.10 g, 4.04 mmol) dissolved in dichloromethane (123 mL) was added to sodium tetrekis[3,5-bis(trifluoromethyl)phenyl]borate (3.43 g, 4.04 mmol)[39a] and the mixture was heated under re-

flux for 0.5 h. The solvent was removed in vacuum and the product was extracted with diethyl ether. The diethyl ether was concentrated in vacuum to ca. 20 mL. Pentane (140 mL) was added and the blue precipitate which formed was collected by filtration, washed with pentane and then dried in vacuum. The solid was recrystallized with pentane-dichloromethane (1:1) to give **1** as blue crystals (86% yield). IR (KBr) 1126, 1280, 1357 cm^{-1}.

Lithium Tetrekis[3,5-bis(trifluoromethyl)phenyl]borate (3). The borate **3** was prepared according to the procedure of Yoshimura.[39a] IR (KBr) 1087–1172, 1288, 1365 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.61 (br, 2H), 7.69 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 117.64, 119.90, 122.60, 125.31, 134.00; ^{19}F NMR (DMSO-d_6) δ 14.18.

Typical Experimental Procedure for the Catalytic Iodination of Aromatic Compounds with $Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (1) and ICl: Synthesis of Iodotoluene with ICl and ZnO (Table 3, Entry 2). A solution of ICl in dichloromethane (1.0 M, 2.29 mL) was added to a mixture of **1** (5.73×10^{-2} mmol) and ZnO (1.15 mmol) in dichloromethane (2.30 mL) at room temperature. After stirring for 30 min, toluene (122 μL, 1.15 mmol) was added and the reaction mixture was stirred for 8 h at room temperature. Adding saturated aqueous sodium sulfite quenched the reaction, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The yield and the isomeric ratio of iodotoluene was determined by GC-analysis of the resulting residue (68%, *o*/*p* = 47/53).

Synthesis of Iodotoluene with ICl and DDQ (Table 3, Entry 6). To a mixture of **1** (0.05×10^{-1} mmol) and DDQ (0.55 mmol) in dichloromethane (2.20 mL), a solution of ICl in dichloromethane (1.0 M, 2.21 mL) was added at room temperature. After stirring for 30 min, toluene (118 μL, 1.11 mmol) was added and the reaction mixture was stirred for 8 h at room temperature. The usual workup procedure gave a crude product containing 82% of iodotoluenes (*o*/*p* = 47/53) and 13% of chlorotoluenes (*o*/*p* = 67/33).

Synthesis of Iodotoluene in a Large Scale (10 mmol) with ICl and DDQ. To a mixture of **1** (0.50 g, 5.00×10^{-1} mmol) and DDQ (1.14 g, 5.00 mmol) in dichloromethane (20 mL), a solution of ICl in dichloromethane (1.0 M, 20.0 mL) was added at room temperature. After stirring for 30 min, toluene (1.06 mL, 10.0 mmol) was added and the reaction mixture was stirred for 8 h at room temperature. Adding saturated aqueous sodium sulphite quenched the reaction, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was distilled under reduced pressure and gave iodotoluenes (1.91 g, 84%, *o*/*p* = 53/47).

Typical Experimental Procedure for the Catalytic Bromination of Aromatic Compounds with $Cp_2FeB[3,5\text{-}(CF_3)_2C_6H_3]_4$ (1) and Bromine: Synthesis of Bromobenzene with Br_2 and ZnO (Table 6, Entry 1). To a mixture of **1** (4.81×10^{-2} mmol) and ZnO (0.96 mmol) in dichloromethane (0.20 mL), Br_2 (1.93 mmol) was added at room temperature. After stirring for 30 min, benzene (86 μL, 0.96 mmol) was added and the reaction mixture was stirred for 7 h at room temperature. After the workup procedure described above, the yield and the isomeric ratio of bromobenzene were determined by GC-analysis of the resulting residue (81%).

Synthesis of Bromochlorobenzene (Table 6, Entry 11). To a mixture of **1** (5.11×10^{-2} mmol) and ZnO (1.02 mmol) in dichloromethane (0.20 mL), Br_2 (3.07 mmol) was added at room temperature. After stirring for 30 min, chlorobenzene (104 μL, 1.02 mmol) was added and the reaction mixture was stirred for 4 h at reflux. After the workup procedure described above, the yield and the isomeric ratio of bromochlorobenzene were determined by GC-analysis of the resulting residue (79%, *o*/*p* = 13/87).

Synthesis of Dibromobenzene (Table 6, Entry 12). To a mixture of **1** (5.76×10^{-2} mmol) and ZnO (1.15 mmol) in dichloromethane (0.20 mL), Br_2 (3.45 mmol) was added at room temperature. After stirring for 30 min, benzene (103 μL, 1.15 mmol) was added and the reaction mixture was refluxed for 3 h. After the workup procedure described above, the yield and the isomeric ratio of dibromobenzene were determined by GC-analysis of the resulting residue (94%, *o*/*p* = 17/83).

Synthesis of Bromoiodobenzene (Table 6, Entry 13). To a mixture of **1** (4.77×10^{-2} mmol) and ZnO (0.96 mmol) in dichloromethane (0.20 mL), Br_2 (2.87 mmol) was added at room temperature. After stirring for 30 min, iodobenzene (107 μL, 0.96 mmol) was added and the reaction mixture was refluxed for 4 h. After the workup procedure described above, the yield and the isomeric ratio of bromoiodobenzene were determined by GC-analysis of the resulting residue (83%, *o*/*p* = 24/76).

The products listed in Table 5, Entry 9, Table 6, Entry 9 and 10 were isolated and characterized by ^1H NMR. The yields of the products in Table 5, Entry 4 and 6, Table 6, Entry 7 were determined by ^1H NMR spectra using triphenylmethane as an internal standard. All of other products were characterized by comparing GC retention times with those of authentic samples, and their yields and isomer ratios were determined by GC analyses (SHIMADZU CAPILLARY COLUMN HiCap Series CBP10-M25-0.25).

2-Iodophenol. IR (neat) 748, 1458, 3479 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.30 (s, 1H), 6.67 (ddd, 1H, *J* = 8.1, 8.1, 1.5 Hz), 7.00 (dd, 1H, *J* = 8.1, 1.5 Hz), 7.24 (ddd, 1H, *J* = 8.1, 8.1, 1.5 Hz), 7.65 (dd, 1H, *J* = 8.1, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 85.74, 115.13, 122.42, 130.20, 138.20, 138.24, 154.73.

4-Iodophenol. mp 91–99 °C; IR (KBr) 602, 1481, 3378 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.12 (broad s, 1H), 6.64 (d, 2H, *J* = 8.8 Hz), 7.50 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 82.72, 117.76, 138.42, 155.23.

2-Bromophenol. IR (neat) 656, 1342, 3525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.64 (s, 1H), 6.78 (ddd, 1H, *J* = 8.1, 8.1, 1.5 Hz), 7.01 (dd, 1H, *J* = 8.1, 1.5 Hz), 7.19 (ddd, 1H, *J* = 8.1, 8.1, 1.5 Hz), 7.43 (dd, 1H, *J* = 8.1, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 110.17, 116.11, 121.76, 129.10, 131.99, 152.14.

4-Bromophenol. mp 64–66 °C; IR (KBr) 647, 1342, 3347 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.13 (s, 1H), 6.71 (d, 2H, *J* = 9.0 Hz), 7.33 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 112.93, 117.16, 132.46, 154.41.

2-Bromoaniline. mp 29 °C; IR (KBr) 663, 3186 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.74 (broad s, 2H), 6.60 (m, 1H), 6.71 (dd, 1H, *J* = 1.5, 8.1 Hz), 7.09 (m, 1H), 7.40 (dd, 1H, *J* = 1.5, 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ = 109.24, 115.69, 119.34, 128.27, 132.50, 144.00.

4-Bromoaniline. mp 61 °C; IR (KBr) 602, 3379 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (broad s, 2H), 6.54 (m, 2H), 7.23 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$) δ 110.10, 116.63, 131.90, 145.34.

Ethyl 5-Bromo-4-hydroxy-2,3-dimethoxy-6-methylbenzoate (5). IR (neat) 416, 1712, 2838 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (t, 3H, *J* = 7.2 Hz), 2.32 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 4.38 (q, 2H, *J* = 7.2 Hz), 6.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.28, 19.77, 61.08, 61.45, 61.53, 107.15, 122.34, 130.84, 137.99, 148.04, 148.94, 165.22, 167.17; HRMS (FAB) Found: 319.0179.

Calcd for $C_{12}H_{16}O_5Br$ $[M]^+$: 319.0181.

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