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Facile *p*-toluenesulfonic acid-promoted *para*-selective monobromination and chlorination of phenol and analogues

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ABSTRACT

para-Regioselective bromination of phenol and analogues, promoted by *p*-toluenesulfonic acid, is achieved in high to excellent yields at room temperature with *N*-bromosuccinimide. Chlorination with *N*-chlorosuccinimide and catalysed by *p*-toluenesulfonic acid also gives *para*-chlorinated phenol analogues in good yields at room temperature.

1. Introduction

Bromophenols serve as an important and useful synthetic intermediates in a variety of palladium-catalysed and copper(I)-assisted reactions, such as the Heck, Stille and the Ullmann reactions.[1,2] They are also important constituents of various naturally occurring biologically active compounds, especially those of the marine sponge metabolites.[3] Due to the high electrophilic reactivity of phenol and the highly reactive bromonium ion, phenol ring bromination faces many challenges that include polybromination, and the difficulties in monobromination and regioselectivity controls.[4]

Numerous electrophilic *ortho*- and *para*-bromination methods exist for phenol. Reagents for *ortho*-bromination of phenols include *N*-bromodialkylamine/*N*,*N*-dibromoalkylamine,[5a] *N*-bromosuccinimide in the presence of primary/secondary aliphatic amines[5b] and 1,3-dibromo-5,5-dimethylhydantoin.[5c] Examples of the reagents or methodologies for *para*-bromination of phenol include tetraalkylammonium tribromide,[6a] halodimethylsulfonium halides,[6b] dioxygen catalyzed oxobromination,[6c] hexamethylenetetramine tribromide,[6d] 4,4-dibromo-3-methylpyrazol-5-one,[6e] V_2O_5/H_2O_2,[6f] KBr and oxone/H_2O_2 over zeolites,[6g] Br_2 and heteropoly acid cesium salt/cetyltrimethylammonium bromide,[6h] Br_2/tetrabutylammonium peroxydisulfate,[6i] *N*-methylpyrolidin-2-one hydrotribromide,[6j] KBr/benzyltriphenylphosphonium peroxymonosulfate,[6k] dixoxane dibromide,[6l] β-cyclodextrin,[6m] $ZrBr_4$/diazene[6n] and 1-butyl-3-methylpyridinium tribromide.[6o]

These methods, however, employ either expensive catalysts, or not-readily available brominating agents, or corrosive substances, such as HBr, or harsh reaction conditions. On the other hand, a readily available and relatively inexpensive brominating agent for phenols is *N*-bromosuccinimide (NBS). The catalysts for many of the reported methods for phenol *para*-bromination with NBS, which include SiO_2,[7a] HZSM-5,[7b] $HBF_4.Et_2O$,[7c] TBAB,[7d] SO_3H-functionalised silica[7e] and ammonium acetate,[7f] are potentially expensive or difficult to employ. Hence, a simple, inexpensive and mild methodology with excellent regioselectivity for phenol *para*-bromination is still desirable.

Previously, we reported a facile and highly regioselective methodology for iodination of phenol and analogues using a simple combination of *N*-iodosuccinimide (NIS) and *p*-toluenesulfonic acid (*p*TsOH). The combination of *p*TsOH and NIS, previously demonstrated in the iodination of polyalkylbenzenes,[8a] and recently in the syntheses of 3-iodo and 3-halo-5-iodo analogues of *N*-acetyl-L-tyrosine,[8b] was found to give high *para*-regioselective monoiodination of phenol and analogues in excellent yields at room temperature.[9] As a part of our continuing effort to complete the methodology for regioselective monohalogenation of phenol and analogues and also towards the eventual syntheses of mixed halogenated phenols, our investigation, which initially paid attention to the investigation of regioselective monoiodination, has now turned to bromination, and also chlorination. We therefore wish to report our findings on *para*-selective monobromination of phenol and analogues using a facile combination of NBS and *p*TsOH. To complete the series and to provide a comparison to bromination, monochlorination investigation of phenol and analogues using the same combination of reagents, but with *N*-chlorosuccinimide (NCS) instead of NBS, is also reported herein.

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2. Results and discussions

2.1. Bromination

The optimisation of the bromination reaction was conducted with phenol. With three available positions for electrophilic bromination, one at the *para* and the other two at the *ortho* positions, phenol poses a regioselective challenge.

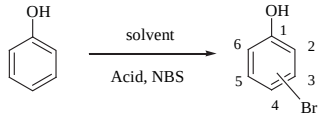
With one equiv of *p*TsOH, added prior to the NBS addition, phenol (**1**) was converted with mediocre yields to 4-bromophenol (**1a**) at room temperature in 1,4-dioxane, methanol and chloroform (Table 1, entries 1, 2 and 4). In water the yield of **1a** was low and 2,4,6-tribromophenol, absent in other solvents, was found admixed in the reaction with yields of 20–25% (Table 1, entry 3). However, in acetonitrile stirring at room temperature for 16 h, **1a** was afforded with 95% selectivity (Table 1, entry 5). The same reaction, but with only 2 h of stirring, still gave a 95% yield of **1a** and the same yields for 2-bromophenol and 2,4-dibromophenol (Table 1, entry 7). Lowering the temperature to 0 °C did not enhance the yield of **1a**. On the contrary, the reaction at ice-bath temperature gave only an 80% yield of **1a**, an incomplete reaction and an increased yield of 2-bromophenol. In the absence of *p*TsOH, the reaction in acetonitrile produced a mixture of **1a** (32%), 2,4-dibromophenol (8%) and 2,4,6-tribromophenol (60%). Substituting *p*TsOH with other types of acids such as H_2SO_4, HCl, H_3PO_4 and CH_3CO_2H did not enhance the *para*-selectivity or the yields of **1a**. With CH_3CO_2H as the promoting acid, the reaction gave a low yield of **1a** (44%) and an increase of 2,4-dibromophenol (11%) and 2,4,6-tribromophenol (16%), (Table 1, entry 13). With 1 equiv of HCl, the reaction fared better by showing an improved yield of **1a** and an absence of 2,4,6-tribromophenol.

However, the selectivity of this reaction is poor due to the presence of 2-bromophenol (10%) and 2,4-dibromophenol (10%) in the reaction mixture (Table 1, entry 11). Among the acid candidates, H_2SO_4 comes close to emulating the success of *p*TsOH as a *para*-selective promoter. In the reaction mixture containing 1 equiv of H_2SO_4, the yield of **1a** reached 88%, while the starting material and other side products (11%) account for the remaining 12% (Table 1, entry 10).

The optimisation of *p*TsOH in the reaction mixture showed that 0.5 equiv of *p*TsOH afforded none of the unwanted 2,4-dibromophenol and at the same time gave a 95% yield of **1a** (Table 1, entry 16). Other sulfonic acids, such as methanesulfonic acid, 3-pyridinesulfonic acid and 4-chlorobenzenesulfonic acid were tested for their effectiveness in promoting *para*-selectivity. With methanesulfonic acid, **1a** was obtained in 93% yield, while 4-chlorobenzenesulfonic acid gave a 91% yield of **1a** and an increase of 2,4-dibromophenol (Table 1, entries 17 and 19). Compared to the two previously-mentioned sulfonic acids, 3-pyridinesulfonic acid fared worse in the production of **1a** and also in the suppression of the undesired 2,4-dibromophenol (Table 1, entry 18). Compared to sulfuric acid, which gave a higher yield of **1a** and less of 2,4-dibromophenol, 3-pyridinesulfonic acid performed poorly in the regioselectivity category. Nevertheless compared to the mineral acids used in the study, the sulfonic acids, except 3-pyridinesulfonic acid, gave excellent *para*-regioselectivity and yields of **1a**. *p*TsOH is the best among the sulfonic acids. Based on our findings, a correlation between the pK_a values of the acids and *para*-regioselectivity is not evident. The mechanistic reason for such regioselective promotion by the sulfonic acids is not clear and requires further study.

Various *ortho*, *meta* and *para*-substituted phenol substrates were investigated. For *ortho*-substituted phenols (compounds **2**–**5**), bromination with NBS in room temperature acetonitrile without *p*TsOH gave poor yields and selectivities of the desired products **2a**–**5a** (Table 2, entries 1a–4a). Bromination of 2-chlorophenol (**3**) without *p*TsOH gave a high yield of the undesired dibrominated product, 4,6-dibromophenol (40%). However, with *p*TsOH (added to the reaction mixture prior to the NBS addition), bromination of **2**–**5** afforded high to excellent *para*-selective brominated products. Thus, bromination of **2** with *p*TsOH gave **2a** in 95% yield and 100% selectivity (Table 2, entry 1b). The same bromination reaction sequence converted **3** to the *para*-brominated product, **3a**, in 93% yield (Table 2, entry 2b). Bromination of phenol analogues containing electron-withdrawing *ortho*-substituted acetyl and methyl ester groups, compounds **4** and **5**, affords the

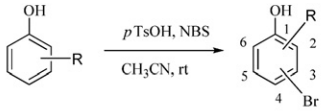
Table 1
Optimisation of conversion of **1** to 4-bromophenol (**1a**)



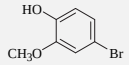
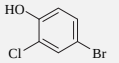
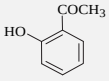
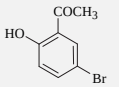
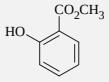
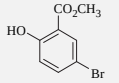
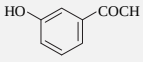
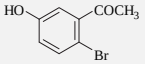
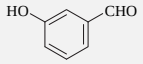
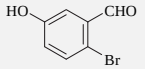
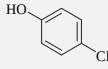
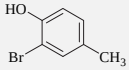
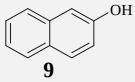
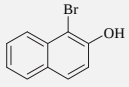
Entry	Acid[a] (equiv)	Solvent	Temp	Time (h)	Product composition[a] (%)					
					S	2	**4**	2,4	2,6	2,4,6
1	*p*TsOH	1,4-Dioxane	rt	16	11	25	62	2	0	0
2	*p*TsOH	CH_3OH	rt	16	0	7	69	24	0	0
3	*p*TsOH	H_2O	rt	16	20	10	37	8	0	25
4	*p*TsOH	$CHCl_3$	rt	16	0	21	67	12	0	0
5	*p*TsOH	CH_3CN	rt	16	0	3	95	2	0	0
6	None	CH_3CN	rt	16	0	0	32	8	0	60
7	*p*TsOH	CH_3CN	rt	2	0	3	95	2	0	0
8	*p*TsOH	CH_3CN	0 °C	2	12	8	80	0	0	0
9	*p*TsOH	CH_3CN[b]	rt	2	20	10	68	2	0	0
10	H_2SO_4	CH_3CN	rt	16	1	9	88	1	0	1
11	HCl	CH_3CN	rt	16	3	10	77	10	0	0
12	H_3PO_4	CH_3CN	rt	16	0	9	80	11	0	0
13	CH_3CO_2H	CH_3CN	rt	16	12	13	44	11	4	16
14	*p*TsOH (0.1)	CH_3CN	rt	16	18	5	77	0	0	0
15	*p*TsOH (0.3)	CH_3CN	rt	16	12	8	80	0	0	0
16	*p*TsOH (0.5)	CH_3CN	rt	16	1	4	95	0	0	0
17	CH_3SO_3H (0.5)	CH_3CN	rt	2	1	5	93	1	0	0
18	3-PyrSO_3H (0.5)	CH_3CN	rt	2	0	4	82	14	0	0
19	4-$ClC_6H_4SO_3H$ (0.5)	CH_3CN	rt	2	0	2	91	7	0	0

[a] The products were characterized by GC–MS, ^1H and ^{13}C NMR. One equiv of acid was used, unless stated otherwise. The numbers in the product composition denote the positions of bromination relative to the OH (numbered one) of the phenol and S refers to the substrate.
[b] *p*TsOH (1 equiv) was added with a 15 min delay to the stirred solution (10 mL) containing the substrate and NBS.

Table 2
Bromination of phenol analogues



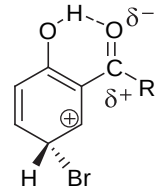
R = 3,4-C_4H_4, 2-OCH_3, 2-$COCH_3$, 2-CO_2CH_3, 2-Cl, 3-$COCH_3$, 3-CHO, 4-CH_3

Entry	Substrate	Solvent	Product composition[a] (%)								Product	Isolated (%)
			S	2	4	6	2,4	2,6	4,6	2,4,6		
1a		CH_3CN[b]	50	3 (C3)	42	5	—	—	0	—		82
1b		CH_3CN	5	0 (C3)	95	0	—	—	0	—		
1c	**2**	CH_3CN[c]	4	11 (C3)	85	0	—	—	0	—	**2a**	
2a		CH_3CN[b]	31	—	24	5	—	—	40	—		81
2b		CH_3CN	3	—	93	4	—	—	0	—		
2c	**3**	CH_3CN[c]	17	—	52	6	—	—	25	—	**3a**	
3a		CH_3CN[b]	80	—	17	2	—	—	1	—		50
3b		CH_3CN	18	—	78	4	—	—	0	—		
3c	**4**	CH_3CN[c]	51	—	46	3	—	—	0	—	**4a**	
4a		CH_3CN[b]	90	—	10	0	—	—	0	—		72
4b		CH_3CN[d]	3	—	82	12	—	—	3	—		
4c	**5**	CH_3CN[c]	85	—	15	0	—	—	0	—	**5a**	
5a		CH_3CN[b]	50	0	32	0	0	0	2	16		45
5b		CH_3CN	2	0	54	31	0	0	13	0		
5c	**6**	CH_3CN[c]	37	0	34	11	0	0	5	13	**6a**	
6a		CH_3CN[b]	34	0	30	2	0	0	10	24		51
6b		CH_3CN	6	0	54	31	0	0	9	0		
6c	**7**	CH_3CN[c]	27	0	37	25	0	0	7	4	**7a**	
7a		CH_3CN[b]	26	73	—	—	—	1	—	—		88
7b		CH_3CN	10	90	—	—	—	0	—	—		
7c	**8**	CH_3CN[c]	12	84	—	—	—	4	—	—	**8a**	
8a		CH_3CN[b]	2	98	—	—	—	—	—	—		91
8b		CH_3CN	0	100	—	—	—	—	—	—		
8c	**9**	CH_3CN[c]	1	96	—	—	3 (1,3)	—	—	—	**9a**	

[a] Reaction conditions: *p*TsOH (0.5 equiv) was added to the stirred solution (10 mL) containing the substrate (0.5 mmol), maintained at room temperature. After 5 min, 1 equiv of NBS was added to the mixture and stirred for 2 h. The major products were characterized by GC–MS, ^1H and ^{13}C NMR. The numbers in the product composition denote the positions of bromination relative to the OH (numbered 1) of the phenol and S refers to the substrate.
[b] Without *p*TsOH.
[c] *p*TsOH (0.5 equiv) was added with a 15 min delay to the stirred solution (10 mL) containing the substrate and NBS.
[d] The reaction was stirred at room temperature for 16 h.

para-brominated products, **4a** and **5a**, in yields of 78% and 82%, respectively (Table 2, entries 3b and 4b). Unlike the bromination of **3**, which has only 3% of the substrate remaining after 2 h, bromination of **4** in the same time period still has 18% of the substrate unreacted. Bromination of **5**, after a 2-h reaction period, furnished only 12% of **5a**, but in a 16 h reaction its yield rose to 82%.

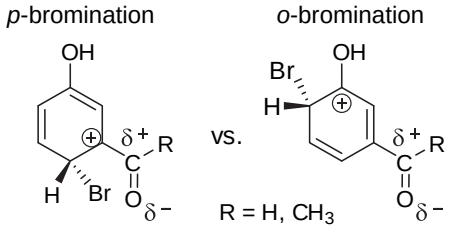
Among compounds **3**–**5**, which are all *ortho*-substituted phenols, the yields of **4a** and **5a** are lower than that of **3a**. In the case of **3**, the stability of the sigma complex cation is affected only by the inductive effect (electronegativity) of the chlorine atom. On the other hand, the enhanced positive character of the *o*-carbonyl moiety, caused by the hydrogen bonding of the phenol OH, is capable of additional destabilisation of the sigma complex (Scheme 1). Likewise, the electronic effect of the substituents appears to affect C-4 bromination of 3-acetylphenol (**6**) and 3-formylphenol (**7**). Thus, using the same sequential additions of *p*TsOH and NBS as used in the productions of **2a**–**5a**, bromination of **6** afforded **6a** in 54% yield. Admixed in the product mixture were *o*-bromination product, 4-bromo-3-hydroxyacetophenone (31%) and 2,4-dibromo-5-hydroxyacetophenone (13%). With **7** as the substrate, the bromination reaction produced **7a** in 54% yield, and admixed in the reaction products were also *o*-bromination product, 4-bromo-3-hydroxybenzaldehyde (31%)



R = H, CH_3

Scheme 1.

and 2,4-dibromo-5-hydroxybenzadehyde (9%). The electronic influence on the sigma complex stability, as argued for **4** and **5**, also appears to be at work in the monobromination reactions of **6** and **7**. In the case of **6** and **7** *para*-brominations, the effect is more fully felt due



Scheme 2.

to the location of a sigma complex cation at the C-3 carbon, the same carbon with the electron-withdrawing carbonyl moiety (Scheme 2).

The steric factor of the acetyl and the formyl groups at C-3 positions is potentially another possibility for the cause of the decline of **6a** and **7a** yields. However, in a *p*TsOH-catalysed bromination of *m*-cresol (possessing similar steric hindrance as those of **6** and **7**), the *para*-brominated product, 4-bromo-3-methylphenol, was obtained in a high 86% yield. Such finding lends support to the electronic effect explanation as being the main contributing factor in *meta*-substituted phenol bromination, and discounts the steric argument.

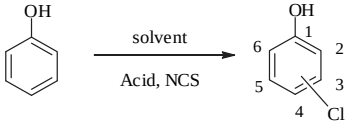
An example of a *para*-substituted phenol is 4-methylphenol (**8**), which upon bromination gave 2-bromo-4-methylphenol (**8a**) in 90% yield and 100% selectivity (Table 2, entry 7b). Unlike phenol, which has two different competing sites (*o*, *p*) for the bromonium ion, bromination of **8** proceeds as a monobromination process despite the existence of two equal competing sites that could have led to dibromination of the substrate. This finding demonstrates the effectiveness of *p*TsOH and NBS combination in affecting monobromination.

The effectiveness of monobromination is further demonstrated in the reaction of 2-naphthol, which in the presence of *p*TsOH and NBS in room temperature acetonitrile gave only 1-bromo-2-naphthol and in 100% yield (Table 2, entry 8b).

2.2. Chlorination

A logical extension of the bromination study is the application of the combination of *p*TsOH and *N*-halosuccinimide to the chlorination of phenol and its analogues.[10] As with the bromination of phenol and analogues, the optimum solvent for *para*-selective chlorination of phenol is still acetonitrile (Table 3, entry 7). With 1 equiv of *p*TsOH in room temperature acetonitrile and stirring for 16 h, the selectivity of 4-chlorophenol (**1b**) from **1** is 81% (69% yield). In a 2-h reaction the selectivity and yields of **1b** did not alter significantly and **1b** was afforded in 68% yield and 80% selectivity (Table 3, entry 9). Without *p*TsOH, the 2-h reaction gave no products (Table 3, entry 8). Two equivalents of *p*TsOH after 2 h of stirring afforded the highest conversion of **1** (90%) and a 73% yield of **1b** (Table 3, entry 14). Various other acids were investigated for their effects on phenol chlorination *para*-selectivity. Unlike bromination, H_2SO_4, HCl and H_3PO_4 showed modest *para*-selectivity towards **1b**. The selectivities ranged from 75 to 78% (Table 3, entries 17–19). Although showing a modest 72% selectivity for **1b**, acetic acid as a *para*-selective promoter performed poorly as an activator of NCS. A poor conversion to **1b** (18%) was observed after a 2-h reaction (Table 3, entry 20). Other sulfonic acids were compared for their ability to promote *para*-selective chlorination. In room temperature acetonitrile containing 2 equiv of methanesulfonic acid, chlorination of **1** with NCS afforded **1b** in 63% yield and 76% selectivity (Table 3, entry 21). With 2 equiv of

Table 3
Optimisation of conversion of **1** to 4-chlorophenol (**1b**)



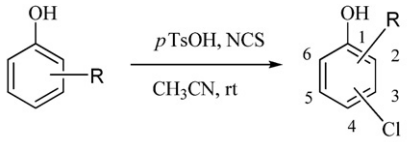
Entry	Acid (equiv)	Solvent	Temp	Time (h)	Product composition[a] (%)					
					S	2	**4**	2,4	2,6	2,4,6
1	*p*TsOH	1,4-Dioxane	rt	16	10	35	54	1	0	0
2	*p*TsOH	THF	rt	16	13	31	56	0	0	0
3	*p*TsOH	EtOAc	rt	16	23	25	52	0	0	0
4	*p*TsOH	$CHCl_3$	rt	16	11	38	51	0	0	0
5	*p*TsOH	CH_3OH	rt	16	14	32	54	0	0	0
6	*p*TsOH	Acetone	rt	16	100	0	0	0	0	0
7	*p*TsOH	CH_3CN	rt	16	15	16	69	0	0	0
8	None	CH_3CN	rt	2	100	0	0	0	0	0
9	*p*TsOH	CH_3CN	rt	2	15	17	68	0	0	0
10	*p*TsOH	CH_3CN[b]	rt	16	23	18	59	0	0	0
11	*p*TsOH	CH_3CN	0 °C	2	19	16	65	0	0	0
12	*p*TsOH (0.5)	CH_3CN	rt	2	13	18	69	0	0	0
13	*p*TsOH (1.5)	CH_3CN	rt	2	10	18	72	0	0	0
14	*p*TsOH (2.0)	CH_3CN	rt	2	10	17	73	0	0	0
15	*p*TsOH (2.5)	CH_3CN	rt	2	11	19	70	0	0	0
16	*p*TsOH (3.0)	CH_3CN	rt	2	13	19	68	0	0	0
17	H_2SO_4 (2.0)	CH_3CN	rt	2	18	20	62	0	0	0
18	HCl (2.0)	CH_3CN	rt	2	16	21	63	0	0	0
19	H_3PO_4 (2.0)	CH_3CN	rt	2	23	17	60	0	0	0
20	CH_3CO_2H (2.0)	CH_3CN	rt	2	82	5	13	0	0	0
21	CH_3SO_3H (2.0)	CH_3CN	rt	2	17	20	63	0	0	0
22	3-$PyrSO_3H$ (2.0)	CH_3CN	rt	2	22	19	59	0	0	0
23	4-$ClC_6H_4SO_3H$ (2.0)	CH_3CN	rt	2	19	20	61	0	0	0

[a] The major products were characterized by GC–MS, ^1H and ^{13}C NMR. One equiv of acid used, unless stated otherwise. The numbers in the product composition denote the positions of chlorination relative to the OH (numbered one) of the phenol and S refers to the substrate.
[b] *p*TsOH (1 equiv) was added with a 15 min delay to the stirred solution (10 mL) containing the substrate and NCS.

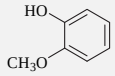
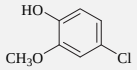
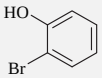
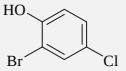
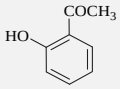
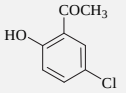
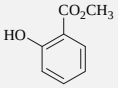
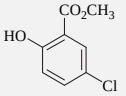
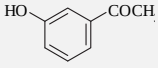
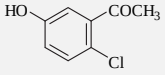
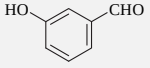
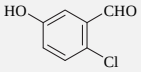
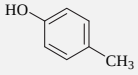
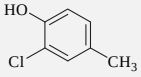
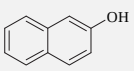
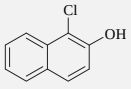
4-chlorobenzenesulfonic acid, **1b** was obtained in 61% yield and 75% selectivity (Table 3, entry 23). 3-Pyridinesulfonic acid gave **1b** in 59% yield and 76% selectivity (Table 3, entry 22).

Various phenol analogues containing different types of substituents at the *ortho*, *meta* and *para* positions were investigated. In the control reactions, which were conducted in acetonitrile without *p*TsOH and stirring for 2 h, none of the substrates, except for **6**—albeit with a paltry 3% yield of **6b**, gave any products (Table 4, entries 1a–8a). In the two types of reactions, one with the initial addition of *p*TsOH and the other with the addition of *p*TsOH after NCS, the yields of the *para*-chlorinated products and their selectivities were almost identical (Table 4, entries 1b–8b and 1c–8c). The significant difference between the two reaction conditions was the chlorination of **8**. In the normal addition sequence of the reagents—*p*TsOH before NCS—chlorination of **8** furnished **8b** in 86% yield and 100% selectivity (Table 4, entry 7b). In the reverse sequence, **8b** was obtained in 56% yield, but still with 100% selectivity (Table 4, entry 7c). The almost identical outcome of the reactions of both sequences is not surprising in lieu of the findings of the control reactions that showed no chlorination in the absence of *p*TsOH. Furthermore the previous study of polyalkylbenzenes chlorination via NCS also showed that NCS activation, and hence

Table 4
Chlorination of phenol analogues



R = 3,4-C_4H_4, 2-OCH_3, 2-$COCH_3$, 2-CO_2CH_3, 2-Br, 3-$COCH_3$, 3-CHO, 4-CH_3

Entry	Substrate	Solvent	Product composition[a] (%)								Product	Isolated[d] (%)
			S	2	4	6	2,4	2,6	4,6	2,4,6		
1a		CH_3CN[b]	100	—	0	0	—	—	0	—		44
1b		CH_3CN	14	3 (C3)	69	14	—	—	0	—		
1c		CH_3CN[c]	19	4 (C3)	62	15	—	—	0	—	**2b**	
	2											
2a		CH_3CN[b]	100	—	0	0	—	—	0	—		42
2b		CH_3CN	12	—	78	10	—	—	0	—		
2c		CH_3CN[c]	21	—	69	10	—	—	0	—	**10b**	
	10											
3a		CH_3CN[b]	100	—	0	0	—	—	0	—		49
3b		CH_3CN	17	—	78	5	—	—	0	—		
3c		CH_3CN[c]	14	—	82	4	—	—	0	—	**4b**	
	4											
4a		CH_3CN[b]	100	—	0	0	—	—	0	—		57
4b		CH_3CN	22	—	75	3	—	—	0	—		
4c		CH_3CN[c]	21	—	77	2	—	—	0	—	**5b**	
	5											
5a		CH_3CN[b]	95	0	3	2	0	0	0	0		33
5b		CH_3CN	23	7	41	29	0	0	0	0		
5c		CH_3CN[c]	27	7	41	25	0	0	0	0	**6b**	
	6											
6a		CH_3CN[b]	100	0	0	0	0	0	0	0		42
6b		CH_3CN	27	0	52	20	0	0	1	0		
6c		CH_3CN[c]	28	0	51	20	0	0	1	0	**7b**	
	7											
7a		CH_3CN[b]	100	0	—	—	—	0	—	—		40
7b		CH_3CN	14	86	—	—	—	0	—	—		
7c		CH_3CN[c]	44	56	—	—	—	0	—	—	**8b**	
	8											
8a		CH_3CN[b]	100	0	—	—	—	—	—	—		70
8b		CH_3CN	21	79 (C1)	—	—	—	—	—	—		
8c		CH_3CN[c]	22	78 (C1)	—	—	—	—	—	—	**9b**	
	9											

[a] Reaction conditions: *p*TsOH (2 equiv) was added to the stirred solution (10 mL) containing the substrate (0.5 mmol), maintained at room temperature. After 5 min, 1 equiv of NCS was added to the mixture and stirred for 2 h. The major products were characterized by GC–MS, ^1H and ^{13}C NMR. The numbers in the product composition denote the positions of chlorination relative to the OH (numbered one) of the phenol and S refers to the substrate.

[b] Without *p*TsOH.

[c] *p*TsOH (2 equiv) was added with a 15 min delay to the stirred solution (10 mL) containing the substrate and NCS.

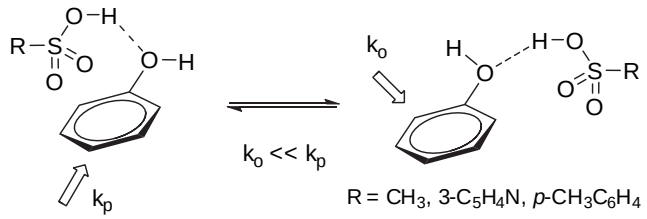
[d] Due to the high volatility of compounds **2b**, **4b**, **5b**, **8b** and **10b**, their isolated yields are lower after solvent evaporation.

the commencement of the reaction, is indispensably dependent on *p*TsOH.[8a] The same study also showed that a high ratio of *p*TsOH to NCS is necessary for an effective and high yielding reaction.

2.3. *para*-Selectivity: the roles of *p*TsOH and acetonitrile

The findings reported herein suggest that the action of *p*TsOH is perhaps more than just a phenoxide suppressant.[9] Evidence suggest *p*TsOH has dual roles, one as the suppressor of the phenoxide and the other as an *ortho* hindering group.

The suppression of the phenoxide is caused by the H^+ of *p*TsOH and thereby making the phenol form to be the actual substrate of the aromatic bromination reaction. Based on such an argument, the bromination reaction and as well as chlorination should display typical *ortho*/*para* product ratio. Yet, the high selectivity of **1a** and together with the lack of competing *ortho*-products in acetonitrile suggests that the lone phenoxide suppression argument is insufficient. For example, an aqueous solution of *p*TsOH, which should have the phenol form as the substrate, gave a poor selectivity of **1a** and admixed among the products were the undesired 2-bromophenol and 2,4-dibromophenol (Table 1, entry 3). But the same reaction with *p*TsOH in acetonitrile affords excellent selectivity of **1a** (Table 1, entries 5 and 7). In acetonitrile the acid dissociation of *p*TsOH is probably incomplete or absent. Therefore, in order to exert its effect on the phenoxide suppression, *p*TsOH is believed to exist as an integral unit. In order to suppress the phenoxide, a hydrogen bond is believed to exist between the acidic hydrogen of *p*TsOH and the phenol OH group. Due to the 'close' proximity of the sulfonic acid to the phenol ring, the



Scheme 3.

ortho position is effectively hindered (or blocked) to any approaching reagents such as *N*-halosuccinimides. These halonium-donating species are themselves large groups that could impose additional steric hindrance to the *ortho* site (Scheme 3).

While other sulfonic acids exert similar effects on the *para*-selective monobromination of phenol (94% and 91% for methanesulfonic acid and 4-chlorobenzenesulfonic acid, respectively), 3-pyridinesulfonic acid shows a lower selectivity to **1a** (82%). In this case, the lone pair on the pyridine nitrogen is believed to interfere with the hydrogen bonding of the sulfonic groups and the phenol OH by hydrogen bonding itself with the OH of the phenol. This effectively causes the whole sulfonic moiety to be further removed from the *ortho* site. For methanesulfonic acid and 4-chlorobenzenesulfonic acid, their effect on *para*-selectivity is similar to that of *p*TsOH (95% selectivity). The aryl and the alkyl groups of these sulfonic acids appear to have little impact on the selectivity. This is also observed with the smaller H_2SO_4, which is still capable of exerting an effective selectivity (89%) when compared to the other sulfonic acids.

Unlike bromination, which does not require *p*TsOH for NBS activation as shown by its control reactions, chlorination of phenol analogues is indispensably dependent on *p*TsOH for the NCS activation. In order to overcome the low activity of NCS as a chloronium-donating agent, *p*TsOH is vital for NCS activation. However, such activation, while enabling NCS to be more reactive, causes the activated NCS to be too reactive for the phenol system. Hence, a reduction in the *para*-selectivity of chlorination is observed throughout. Interestingly, in a comparative study of the relative reactivities of these halonium-donating systems (monitored by GC–MS), chlorination of **1** was completed in only 10 min while bromination and iodination of the same substrate took 1 h and 14 h, respectively.

3. Conclusion

High to excellent yields of *para*-brominated phenol and analogues were obtained in room temperature acetonitrile with sequential addition of *p*TsOH and NBS. *para*-Selective monobromination of phenol and analogues—although less effective at ice-bath temperature—were promoted by a combination of acetonitrile and *p*TsOH, which for the latter is believed to act as a hindering group at the *ortho* position. The highest yields of *para*-brominated phenol analogues were obtained with *ortho*-substituted phenol, and good to moderate yields were found with *meta*-substituted phenols. In the case of *para*-substituted phenol, excellent yields with high output of monobromination were obtained. For chlorination, acetonitrile also gave high *para*-selective monochlorination of phenol and analogues. In chlorination, *p*TsOH, although not as commanding as in bromination, is nevertheless effective in promoting *para*-selectivity. The sequence of *p*TsOH and NCS addition is as critical as in the bromination. The *para*-selectivity for chlorination is high. Good yields were obtained with *ortho* and *para*-substituted phenols. The yields of chlorination with *meta*-substituted phenols were moderate but were still above the 50% mark. Monochlorination was dominant in all reactions. Side products arising out of dichlorination were less of a problem with chlorination, and hence, despite the lower yields compared to bromination, chlorination by this methodology is still effective for the synthesis of *para*-selective monohalogenated phenol and analogues.

4. Experimental

4.1. Materials

Phenol and analogues were obtained from Aldrich and used without further purification. All solvents used in the reactions are of AR grade and were obtained from LabScan Co. Ltd. (Thailand). *N*-Bromosuccinimide and *N*-chlorosuccinimide were from Aldrich Chemical Co. *p*-Toluenesulfonic acid monohydrate was from Fluka and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer in $CDCl_3$ using TMS as an internal standard. The product composition and relative yields were carried out on a gas chromatograph-mass spectrometer (Agilent 6890 GC system and Agilent 5973 Mass Selective Detector) using HP-1 capillary column (0.32 mm×24.9 m×0.17 μm). IR spectra were recorded on a Perkin–Elmer Spectrum 100 FT-IR Spectrometer. Separations of products were carried out on a centrifugal thin-layer chromatography (Harrison Research, USA) using a plate coated with 2 mm of silica gel $60GF_{254}$. Microanalyses of **6a** and **6b** were performed by the Department of Chemistry, Mahidol University.

4.2. General procedure for bromination and chlorination of phenol analogues

Reaction conditions: *p*TsOH (bromination: 0.25 mmol (47.6 mg), chlorination: 1.0 mmol (190.4 mg)) was added to the stirred solution (10 mL) containing the substrate (0.5 mmol), maintained at room temperature. After 5 min, NBS (89.1 mg, 0.5 mmol) or NCS (66.8 mg, 0.5 mmol) was added to the mixture and the mixture was stirred for 2 h. The reaction was quenched by 20 mL of 10% $Na_2S_2O_3$ and extracted with 60 mL of diethyl ether. The organic solution was washed with 20 mL of 10% $Na_2S_2O_3$ solution twice, and then followed by 15 mL of water

twice. The ether solution was then dried over anhydrous Na_2SO_4. The product composition was determined by GC–MS. The major product of each reaction was isolated by silica gel chromatography (10–20% CH_2Cl_2/hexanes). The products reported herein, except for compounds **6a** and **6b**, are known compounds and were characterized by GC–MS, ^1H and ^{13}C NMR. The spectroscopic data of the known compounds are in agreement with those reported in the literature.

*4.2.1. 4-Bromophenol (**1a**)*[11]. Colourless liquid; yield: 87% (0.075 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (2H, d, *J* 8 Hz, Hs at C-3 and C-5), 6.72 (2H d, *J* 8 Hz, Hs at C-2 and C-6), 5.54 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 132.5, 117.2, 112.7; GC–MS (EI), *m*/*z* (rel int.): 172 (100, M^+), 174 (98, $(M+2)^+$); IR (neat): 3339 cm^{-1}.

*4.2.2. 4-Bromo-2-methoxyphenol (**2a**)*[12]. Colourless liquid; yield: 82% (0.083 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.01 (1H, dd, *J* 8, 2 Hz, H at C-5), 6.98 (1H, d, *J* 2 Hz, H at C-3), 6.82 (1H, d, *J* 8 Hz, H at C-6), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.3, 144.9, 124.2, 115.8, 114.2, 111.6, 56.2; GC–MS (EI), *m*/*z* (rel int.): 202 (100, M^+), 204 (98, $(M+2)^+$); IR (neat): 3538 cm^{-1}.

*4.2.3. 4-Bromo-2-chlorophenol (**3a**)*[6m]. White solid; yield: 81% (0.084 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (1H, d, *J* 2 Hz, H at C-3), 7.28 (1H, dd, *J* 9, 2 Hz, H at C-5), 6.90 (1H, d, *J* 9 Hz, H at C-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.7, 131.4, 125.0, 120.8, 117.7, 112.3; GC–MS (EI), *m*/*z* (rel int.): 206 (77, M^+), 208 (100, $(M+2)^+$), 210 (24, $(M+4)^+$); IR (neat): 3531 cm^{-1}.

*4.2.4. 2-Acetyl-4-bromophenol (**4a**)*[13]. White solid; yield: 50% (0.054 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.84 (1H, d, *J* 2 Hz, H at C-3), 7.55 (1H, dd, *J* 9, 2 Hz, H at C-5), 6.90 (1H, d, *J* 9 Hz, H at C-6), 2.63 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 161.3, 139.1, 132.9, 125.0, 120.5, 110.4, 26.7; GC–MS (EI), *m*/*z* (rel int.): 214 (55, M^+), 216 (54, $(M+2)^+$); IR (neat): 3616, 1647 cm^{-1}.

*4.2.5. Methyl 5-bromo-2-hydroxybenzoate (**5a**)*[14]. Colourless liquid; yield: 72% (0.083 g). ^1H NMR (300 MHz, $CDCl_3$): δ 10.69 (1H, s, O*H*), 7.94 (1H, d, *J* 2 Hz, H at C-6), 7.52 (1H, dd, *J* 9, 2 Hz, H at C-4), 6.88 (1H, d, *J* 9 Hz, H at C-3), 3.96 (3H, s, CO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 160.6, 140.9, 138.4, 119.5, 113.8, 110.8, 52.6; GC–MS (EI), *m*/*z* (rel int.): 230 (38, M^+), 232 (37, $(M+2)^+$); IR (neat): 3437, 1681 cm^{-1}.

*4.2.6. 3-Acetyl-4-bromophenol (**6a**).* White solid; yield: 45% (0.048 g). Mp (ether/pet. ether) 76–77 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (1H, d, *J* 9 Hz, H at C-5), 6.96 (1H, d, *J* 3 Hz, H at C-2), 6.82 (1H, dd, *J* 9, 3 Hz, H at C-6), 2.64 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.7, 155.4, 142.0, 134.9, 119.6, 116.0, 108.9, 30.4; GC–MS (EI), *m*/*z* (rel int.): 214 (42, M^+), 216 (44, $(M+2)^+$); IR (neat): 3499, 1694 cm^{-1}; Anal. Calcd for $C_8H_7BrO_2$: C, 44.68; H, 3.28. Found: C, 44.86; H, 2.99.

*4.2.7. 2-Bromo-5-hydroxybenzaldehyde (**7a**)*[15]. White solid; yield: 51% (0.051 g). ^1H NMR (300 MHz, $CDCl_3$): δ 10.29 (1H, s, C*H*O), 7.51 (1H, d, *J* 9 Hz, H at C-3), 7.45 (1H, d, *J* 3 Hz, H at C-6), 7.03 (1H, dd, *J* 9, 3 Hz, H at C-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.5, 155.8, 134.9, 123.6, 117.6, 115.7, 114.7; GC–MS (EI), *m*/*z* (rel int.): 200 (89, M^+), 202 (88, $(M+2)^+$); IR (neat): 3502, 1695 cm^{-1}.

*4.2.8. 2-Bromo-4-methylphenol (**8a**)*[16]. Colourless liquid; yield: 88% (0.082 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (1H, d, *J* 1 Hz, H at C-3), 7.00 (1H, dd, *J* 8, 1 Hz, H at C-5), 6.90 (1H, d, *J* 8 Hz, H at C-6), 5.39 (1H, br s, O*H*), 2.26 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.0, 132.1, 131.4, 129.8, 115.8, 109.8, 20.2; GC–MS (EI), *m*/*z* (rel int.): (100, M^+), (98, $(M+2)^+$); IR (neat): 3513 cm^{-1}.

*4.2.9. 1-Bromo-2-naphthol (**9a**)*[17]. White solid; yield: 91% (0.101 g). ^1H NMR (300 MHz, $CDCl_3$): δ 8.01 (1H, d, *J* 9 Hz, H at C-9), 7.75 (1H, d, *J* 9 Hz, H at C-6), 7.71 (1H, d, *J* 9 Hz, H at C-4), 7.55 (1H, m, H at C-8), 7.37 (1H, m, H at C-7), 7.25 (1H, d, *J* 9 Hz, H at C-3), 5.93 (1H, s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.6, 132.3, 129.7, 129.3, 128.2, 127.8, 125.3, 124.1, 117.1, 106.1; GC–MS (EI), *m*/*z* (rel int.): 222 (100, M^+), 224 (97, $(M+2)^+$); IR (neat): 3507 cm^{-1}.

*4.2.10. 4-Chlorophenol (**1b**)*[18]. Colourless liquid; yield: 73% (0.031 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.15 (2H, d, *J* 9 Hz, Hs at C-3 and C-5), 6.74 (2H, d, *J* 9 Hz, Hs at C-2 and C-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 129.6, 125.7, 116.8; GC–MS (EI), *m*/*z* (rel int.): 128 (100, M^+), 130 (34, $(M+2)^+$); IR (neat): 3368 cm^{-1}.

*4.2.11. 4-Chloro-2-methoxyphenol (**2b**)*[18a]. Colourless liquid; yield: 44% (0.035 g). ^1H NMR (300 MHz, $CDCl_3$): δ 6.84 (3H, s, Hs at C-3, C-5 and C-6), 5.55 (1H, s, O*H*), 3.87 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.0, 144.3, 124.6, 121.1, 115.2, 111.4, 56.1; GC–MS (EI), *m*/*z* (rel int.): 158 (97, M^+), 160 (32, $(M+2)^+$); IR (neat): 3539 cm^{-1}.

*4.2.12. 2-Bromo-4-chlorophenol (**10b**)*[6m]. Colourless liquid; yield: 42% (0.043 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (1H, d, *J* 2 Hz, H at C-3), 7.19 (1H, dd, *J* 9, 2 Hz, H at C-5), 6.95 (1H, d, *J* 9 Hz, H at C-6); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.2, 131.4, 129.2, 121.8, 116.9, 110.4; GC–MS (EI), *m*/*z* (rel int.): 206 (78, M^+), 208 (100, $(M+2)^+$), 210 (24, $(M+4)^+$); IR (neat): 3504 cm^{-1}.

*4.2.13. 2-Acetyl-4-chloro-phenol (**4b**).* White solid; yield: 49% (0.042 g). ^1H NMR (300 MHz, $CDCl_3$): δ 12.14 (1H, s, O*H*), 7.69 (1H, d, *J* 2 Hz, H at C-3), 7.41 (1H, dd, *J* 9, 2 Hz, H at C-5), 6.94 (1H, d, *J* 9 Hz, H at C-6), 2.62 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.6, 160.9, 136.3, 129.9, 123.6, 120.3, 120.1, 26.7; GC–MS (EI), *m*/*z* (rel int.): 170 (48, M^+), 172 (15, $(M+2)^+$); IR (neat): 3467, 1648 cm^{-1}.

*4.2.14. Methyl 5-chloro-2-hydroxybenzoate (**5b**)*[19]. White solid; yield: 57% (0.053 g). ^1H NMR (300 MHz, $CDCl_3$): δ 10.67 (1H, s, O*H*), 7.79 (1H, d, *J* 2 Hz, H at C-6), 7.39 (1H, dd, *J* 9, 2 Hz, H at C-4), 6.92 (1H, dd, *J* 9, 0.9 Hz, H at C-3), 3.95 (3H, s, CO_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 160.2, 135.7, 129.2, 123.9, 119.2, 113.3, 52.6; GC–MS (EI), *m*/*z* (rel int.): 186 (41, M^+), 188 (14, $(M+2)^+$); IR (neat): 3436, 1678 cm^{-1}.

*4.2.15. 3-Acetyl-4-chlorophenol (**6b**).* White solid; yield: 33% (0.028 g). Mp (ether/pet. ether) 79–81 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (1H, d, *J* 9 Hz, H at C-6), 7.07 (1H, d, *J* 3 Hz, H at C-2), 6.91 (1H, dd, *J* 9, 3 Hz, H at C-5), 2.66 (3H, s, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.3, 154.8, 139.5, 131.8, 122.6, 119.7, 116.1, 30.8; GC–MS (EI), *m*/*z* (rel int.): 170 (44, M^+), 172 (14, $(M+2)^+$); IR (neat): 3401, 1688 cm^{-1}; Anal. Calcd for $C_8H_7ClO_2$: C, 56.32; H, 4.14. Found: C, 56.80; H, 4.14.

*4.2.16. 2-Chloro-5-hydroxybenzaldehyde (**7b**).* White solid; yield: 42% (0.033 g). ^1H NMR (300 MHz, $CDCl_3$): δ 10.41 (1H, s, C*H*O), 7.41 (1H, d, *J* 3 Hz, H at C-6), 7.34 (1H, d, *J* 9 Hz, H at C-3), 7.07 (1H, dd, *J* 9, 3 Hz, H at C-4), 5.97 (1H, br s, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.0, 154.9, 133.0, 131.8, 125.0, 123.0, 115.0; GC–MS (EI), *m*/*z* (rel int.): 156 (84, M^+), 158 (28, $(M+2)^+$); IR (neat): 3435, 1664 cm^{-1}.

*4.2.17. 2-Chloro-4-methylphenol (**8b**).* Colourless liquid; yield: 40% (0.028 g). ^1H NMR (300 MHz, $CDCl_3$): δ 7.03 (1H, s, H at C-3), 6.86 (2H, s, Hs at C-5 and C-6), 2.17 (3H, s, CH_3); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 149.1, 131.1, 129.4, 129.0, 119.7, 116.2, 20.3; GC–MS (EI), *m*/*z* (rel int.): 142 (58, M^+), 144 (19, $(M+2)^+$); IR (neat): 3544 cm^{-1}.

*4.2.18. 1-Chloro-2-naphthol (**9b**)*[20]. White solid; yield: 70% (0.063 g). ^1H NMR (300 MHz, $CDCl_3$): δ 8.06 (1H, d, *J* 9 Hz, H at C-9), 7.79 (1H, d, *J* 8 Hz, H at C-6), 7.71 (1H, d, *J* 9 Hz, H at C-4), 7.57 (1H, dt, *J* 7, 1 Hz, H at C-8), 7.40 (1H, dt, *J* 7, 1 Hz, H at C-7), 7.26 (1H, d, *J* 9 Hz, H at C-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.4, 131.1, 129.5, 128.4, 128.2, 127.6, 124.1, 122.8, 117.2, 113.3; GC–MS (EI), *m*/*z* (rel int.): 178 (100, M^+), 180 (33, $(M+2)^+$); IR (neat): 3530 cm^{-1}.

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References and notes

1. (a) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, NY, 1990; (b) Georgiades, S. N.; Clardy, J. *Org. Lett.* **2006**, *8*, 4251–4254; (c) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944.
2. (a) Heck, R. F. *Org. React.* **1982**, *27*, 345–390; (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524; (c) Suzuki, A.; Miyaura, N. *Chem. Rev.* **1995**, *95*, 2457–2483; (d) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460.
3. Fusetani, N.; Matsunaga, S. *Chem. Rev.* **1993**, *93*, 1793–1806.
4. Fuson, R. C. *Reactions of Organic Compounds*; Wiley: New York, NY, 1962; 98–10258–65; Braendin, H. P.; McBee, E. T. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley: New York, NY, 1964; Vol. III, Chapter 46; Norman, R. O. C.; Taylor, R. *Electrophilic Substitution in Benzenoid Compounds*; Elsevier: New York, NY, 1965; pp 130–132; de la Mare, P. B. D. *Electrophilic Halogenation*; Cambridge University: Cambridge, UK, 1976; Brittain, J. M.; de la Mare, P. B. D. Supplement D, pt. 1 In *The Chemistry of Functional Groups*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, NY, 1983; pp 522–532.
5. (a) Schmitz, E.; Pagenkopft, I. *J. Prakt. Chem.* **1985**, *6*, 998–1006; (b) Eguchi, H.; Tokumoto, K.; Shuyama, H. *Toso Kenkyu Hokoku* **1993**, *37*, 109–116; (c) Alam, A.; Takaguchi, Y.; Tsuboi, S` *Okayama Daigaku Kankyo Rikogakubu Kekyu Hokoku* **2005**, *10*, 105–109.
6. (a) Berthelot, J.; Guette, C.; Ouchefoune, M.; Desbene, P. L.; Basselier, J. J. *J.Chem. Res., Synop.* **1986**, *10*, 381; Smith, K.; James, D. M.; Matthews, I.; Bye, M. R. *J. Chem. Soc.* **1992**, *15*, 1877–1878; (b) Olah, G. A.; Ohannesian, L.; Arvanaghi, M.; Donald, P.; Katherine, B. *Synthesis* **1986**, *10*, 868–870; (c) Neumann, R.; Assael, I. *Chem. Commun.* **1988**, *19*, 1285–1287; Menini, L.; Parreira, L. A.; Gusevskaya, E. V. *Tetrahedron Lett.* **2007**, *48*, 6401–6404; (d) Bisarya, S. C.; Rao, R. D. *Synth. Commun.* **1993**, *23*, 779–788; (e) Mashraqui, S. H.; Mudaliar, C. D.; Hariharasubrahmanian, H. *Tetrahedron Lett.* **1997**, *38*, 4865–4868; (f) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, *2*, 247–249; (g) Narender, N.; Srinivasu, P.; Ramakrishna Prasad, M.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2002**, *32*, 2313–2318; Narender, N.; Krishna Mohan, K. V. V.; Vinod Reddy, R.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *J. Mol. Catal. A: Chem.* **2003**, *192*, 73–77; (h) Firouzabadi, H.; Iranpoor, N.; Amani, K. *J. Mol. Catal. A: Chem.* **2003**, *195*, 289–294; (i) Park, M. Y.; Yang, S. G.; Jadhav, V.; Kim, Y. H. *Tetrahedron Lett.* **2004**, *45*, 4887–4890; (j) Singhal, S.; Jain, S. L.; Sain, B. *J. Mol. Catal. A: Chem.* **2006**, *258*, 198–202; (k) Adibi, H.; Hajipour, A. R.; Hashemi, M. *Tetrahedron Lett.* **2007**, *48*, 1255–1259; (l) Chaudhuri, S. K.; Roy, S.; Saha, M.; Bhar, S. *Synth. Commun.* **2007**, *37*, 579–583; (m) Suresh, P.; Annalakshmi, S.; Pitchumani, K. *Tetrahedron* **2007**, *63*, 4959–4967; (n) Stropnik, T.; Bombek, S.; Kocevar, M.; Polanc, S. *Tetrahedron Lett.* **2008**, *49*, 1729–1733; (o) Borikar, S. P.; Daniel, T.; Paul, V. *Tetrahedron Lett.* **2009**, *50*, 1007–1009.
7. (a) Konishi, H.; Aritomi, K.; Okano, T.; Kijii, J. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 591–593; (b) Paul, V.; Sudalai, A.; Daniel, T.; Srinivasan, K. V. *Tetrahedron Lett.* **1994**, *35*, 7055–7056; (c) Oberhauser, T. *J. Org. Chem.* **1997**, *62*, 4504–4506; (d) Ganguly, N. C.; De, P.; Dutta, S. *Synthesis* **2005**, 1103–1105; (e) Das, B.; Venkateswarlu, K.; Krishnaiah, M.; Holla, H. *Tetrahedron Lett.* **2006**, *47*, 8693–8697; (f) Reddy, K. R. *J. Mol. Catal. A: Chem.* **2007**, *267*, 30–33.
8. (a) Bovonsombat, P.; Angara, G. J.; McNelis, E. *Synlett* **1992**, 131–132; Bovonsombat, P.; McNelis, E. *Synthesis* **1993**, 237–241; (b) Bovonsombat, P.; Khanthapura, P.; Krause, M. M.; Leykajarakul, J. *Tetrahedron Lett.* **2008**, *49*, 7008–7011.
9. Bovonsombat, P.; Leykajarakul, J.; Khan, C.; Pla-on, K.; Krause, M. M.; Khanthapura, P.; Ali, R.; Doowa, N. *Tetrahedron Lett.* **2009**, *50*, 2664–2667.
10. Previous examples of *para*-chlorination of phenol and analogues see, using *N*-chloroamines: Lindsay Smith, J. R.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1529–1536; Lindsay Smith, J. R.; McKeer, L. C.; Taylor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1537–1543; Minisci, F.; Vismara, E.; Fontana, F.; Platone, E.; Faraci, G. *J. Chem. Soc., Perkin Trans. 2* **1989**, 123–126; Using *N*-chlorodimethylsulfonium chloride: Olah, G. A.; Ohannesian, L.; Arvanaghi, M. *Synthesis* **1986**, 868–870; Using KCl and Oxone®: Narender, N.; Srinivasu, P.; Kulkarni, S. J.; Raghavan, K. V. *Synth. Commun.* **2002**, *32*, 279–286.
11. Magano, J.; Chen, M.; Clark, J.; Nussbaumer, T. *J. Org. Chem.* **2006**, *71*, 7103–7105.
12. Fujikawa, N.; Ohta, T.; Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron* **2006**, *62*, 594–604.
13. (a) Davies, S.; Mobbs, B.; Goodwin, C. *J. Chem. Soc., Perkin Trans. 1* **1987**, *12*, 2597–2604; (b) Hansel, P. *Magn. Reson. Chem.* **2005**, *31*, 23–37.
14. Zhao, J.; Larock, R. *J. Org. Chem.* **2007**, *72*, 583–588.
15. Tietze, L.; Vock, C.; Krimmelnbein, I.; Nacke, L. *Synthesis* **2009**, *12*, 2040–2060.
16. Sorgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589–592.
17. (a) Wawrzyniak, P.; Heinicke, J. *Tetrahedron Lett.* **2006**, *47*, 8921–8924; (b) Mying, Y.; Pasha, M. *J. Chem. Res.* **2004**, *11*, 732–734.
18. (a) Menini, L.; Gusevskaya, E. *Appl. Catal., A* **2006**, *309*, 122–128; (b) Ludowska, E.; Plenkiewicz, J. *Tetrahedron: Asymmetry* **2007**, *18*, 1202–1209; (c) Tlili, A.; Xia, N.; Monnier, F.; Tailerfer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8725–8728.
19. Snider, B.; Patricia, J. *J. Org. Chem.* **1989**, *54*, 38–46.
20. Takazawa, Y.; Munakata, T.; Iwasa, Y.; Suzuki, T.; Mitsuhashi, T. *J. Org. Chem.* **1985**, *50*, 4383–4386.