Selective aromatic chlorination of activated arenes with sodium chlorite, (salen)manganese(III) complex, and alumina in dichloromethane

Masao Hirano, Shigetaka Yakabe, Hiroyuki Monobe, and Takashi Morimoto

Abstract: The reaction of alkyl phenyl ethers with sodium chlorite in dichloromethane in the presence of a (salen)manganese(III) complex and alumina preloaded with a small amount of water afforded monochlorination products with unusually high *para* selectivities under mild conditions. The $NaClO_2$-based biphasic system can also be successfully used for the regioselective monochlorination of substituted anisoles and polymethoxybenzenes.

Key words: aromatic chlorination, alkyl aryl ethers, sodium chlorite, (salen)manganese(III) complex, alumina.

Résumé : La réaction des phénoxyalcanes avec le chlorite de sodium, dans le dichlorométhane et en présence d'un complexe (salen)manganèse(III) et d'alumine à laquelle on a préalablement ajouté une faible quantité d'eau, conduit, dans des conditions douces, à des produits de monochloration avec des sélectivités élevées en faveur des produits *para*. On peut aussi utiliser avec succès le système biphasique basé sur le $NaClO_2$ pour effectuer la monochloration régiosélective d'anisoles et de polyméthoxybenzènes substitués.

Mots clés : chloration aromatique, oxydes d'alkyles et d'aryles, chlorite de sodium, complexe (salen)manganèse(III), alumine.

[Traduit par la rédaction]

Introduction

Sodium chlorite **1** has enjoyed an important position in pulp and carbohydrate chemistry (1) because of its mild oxidative property. As an organic synthetic reagent, **1** has been utilized for the selective oxidation of formyl groups to the carboxylic acids in aqueous acidic media (eq. [1]) in the presence of what is generally termed a "chlorine scavenger" such as sulfamic acid (2, 3), resorcinol (2, 4), DMSO (5, 6), hydrogen peroxide (5, 7), or 2-methylbut-2-ene (8) for scavenging HClO and unpleasant ClO_2 (eqs. [1] and [2]). However, there has been no synthetically useful reaction using **1** other than for the aldehyde-to-carboxylic acid oxidations. Indeed, aromatic hydrocarbons or alcohols, upon treatment with **1** in strongly acidic media, undergo competitive chlorination and oxidation, affording only complex mixtures of products (9). In addition, the conventional reactions (1–10) were conducted under aqueous or semiaqueous conditions owing to the negligible solubility of **1** in organic solvents, and therefore its synthetic utility in a water-free medium has so far remained unexplored.

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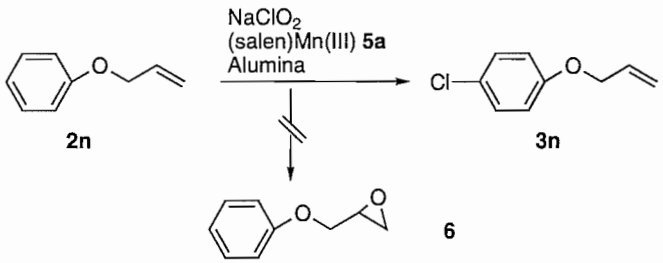
Scheme 1.

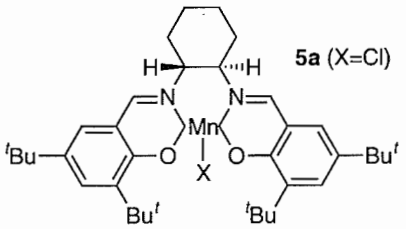


[1] $R\text{-}CHO + ClO_2^- \rightarrow R\text{-}COO^- + HOCl$

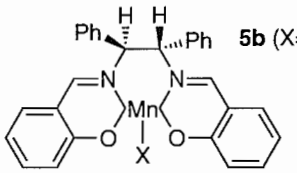
[2] $HOCl + 2\ ClO_2^- \rightarrow ClO_2 + Cl^- + OH^-$

In connection with one of our ongoing projects, we recently needed a simple procedure for the transformation of functionalized alkenes, such as allyl phenyl ether **2n**, into the corresponding epoxide **6** (Scheme 1). Attempted reaction of **2n** with a combination of **1**, chromatographic alumina, and a (salen)manganese(III) complex **5a** (11), a recently developed catalyst for the epoxidation of alkenes (12), in dichloromethane failed to yield the desired product **6**,[2] but resulted in the formation of monochlorinated ether **3n** in good yield (see

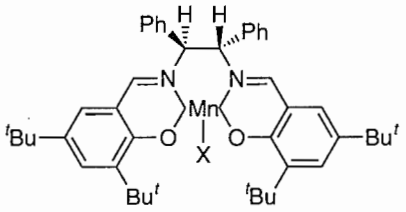
[2] Oxidation of sulfides with a reagent combination of sodium chlorite, **5a**, and alumina in dichloromethane under comparable conditions to those employed in the present chlorination led to the formation of chiral sulfoxides, albeit with moderate to low ee's (13).



5a (X=Cl)



5b (X=OAc)



5c (X=OAc)

also entry 25 in Table 2). Intrigued by the unexpected and facile incorporation of a chlorine atom into the aromatic moiety, our attention was drawn to the chlorination since this procedure is expected to provide a mild and convenient aromatic chlorination method (for preliminary results, see ref. 14). In this article, we would like to report a new nuclear monochlorination of activated arenes under heterogeneous conditions.[3]

Experimental

Instruments

^{1}H NMR spectra were measured with a JEOL JNM-FX200 or JNM-FX500 spectrometer for solutions in deuteriochloroform using TMS as an internal standard. Analytical GC was carried out on a Shimazdu GC-4BM or GC-14B instrument, equipped with a flame ionization detector through a 2 m × 6 mm diam. glass column packed with 5% PEG-20M on Chromosorb WAW-DMCS and interfaced with a Shimazdu Chromatopac C-R6A integrator, with temperature programming. Mass spectra were determined on a JEOL model SX-102A mass spectrometer, which was coupled with a Hewlett Packard model GC5890 Series II GC apparatus via a heated capillary column. Atomic absorption analyses were carried out on a Hitachi model 170–30 instrument.

Starting materials

Dichloromethane was rigorously dried, distilled, and stored over molecular sieves. Sodium chlorite was purchased from Kanto Chemical Co., Ltd. (Japan). Anisole **2a**, phenetole **2b**, butyl phenyl ether **2e**, allyl phenyl ether **2n**, benzyl phenyl ether **2o**, substituted anisoles **6a–d**, xylenes, mesitylene, and di- and tri-methoxybenzenes **10a–d** and **12a,b**, respectively, are commercial chemicals and the reagents can be used without further purification. Cycloalkyl phenyl ethers, **2l** and **2m**, were prepared by heating a mixture of phenol, potassium hydroxide, and cycloalkyl chlorides in DMSO (16). Other alkyl phenyl ethers **2c**, **2d**, and **2f–k** were synthesized by the reactions of sodium phenoxide with alkyl bromides in ethanol (17). The purities of all substrates were checked by GC prior to use; *p*- and *o*-chloroanisole **3a** and **4a**, respectively, and mesityl chloride **9** were commercially available as reference compounds. *Moist* alumina was prepared by adding deionized water (0.2 g) to oven-dried (500°C, 6 h) chromatographic neutral alumina (ICN BIOMEDICALS: Alumina N, Super I; 1 g) in portions, followed by vigorous shaking of the mixture for a few minutes after every addition until a free-flowing powder was obtained, 1 g of which was immediately used for the chlorination. Optically active (salen)manganese(III) complexes **5a** (11), **5b** (18), and **5c** (18) were synthesized according to standard methods. Commercial inorganic cobalt and manganese salts (vide infra) were finely ground prior to use.

Chlorination procedures

The following procedure for anisole **2a** is representative. A 30 mL, round-bottom, two-necked flask, equipped with a 1.5 cm long Teflon-coated stirrer bar, a 25 cm long condenser, and a glass gas-inlet tubing connected to an argon-filled balloon, was arranged in order to perform the reaction under dry conditions by linking the top of the condenser to a liquid paraffin trap via a flexible silicone rubber tubing. In the flask were placed **2a** (1.5 mmol), freshly prepared *moist* alumina (1 g), the catalyst **5a** (1 mol% with respect to **2a**), and dichloromethane (10 mL) in that order, and the resultant dark mixture was stirred for a few minutes. Sodium chlorite **1** (2.85 mmol; [**1**]/[**2a**] = 1.9) was added in one portion with magnetic stirring and the flask was then deaerated by passing a gentle stream of dry argon through the system. The reaction was carried out by vigorously stirring the heterogeneous mixture; care should be taken in continuing efficient stirring during the reaction to ensure smooth chlorination and to attain reproducible results. After a given time (agitation periods after addition of **1** are indicated in Tables 1–3), the whole mixture was transferred onto a sintered glass funnel, and the insoluble residues were thoroughly washed with portions of dry ether (in toto ca. 100 mL). The combined clear filtrate was condensed on a rotary evaporator under reduced pressure to leave an oil contaminated with a catalyst residue. Chromatography on a silica gel column (Merck Silica Gel 60, hexane – ethyl acetate) afforded a mixture of monochloroanisoles in 97% yield based on starting **2a**.

[3] For recent developments in supported reagent chemistry, see the books listed in ref. 15.

The recovery of anisole and the yield of *para*- and *ortho*-chloroanisole **3a** and **4a** were determined by GC using biphenyl as an internal standard. Reuse of **5a** was found to be impractical because of the tedious recovery of the catalyst in such low concentration from a mixture of spent reagents and products, and of some skeleton destruction of **5a** during the chlorination.

The other mono-, di-, and tri-alkoxybenzenes were similarly subjected to the chlorination with a **1**–**5a** – *moist* alumina system, followed by common work-up and chromatographic separation, to yield the indicated products, which were characterized by NMR and MS spectroscopies.

3b: δ ($CDCl_3$), ^{1}H NMR: 1.40 (t, 3H), 4.95 (q, 2H), 6.70 (d, 2H), 7.15 (d, 2H); *m/e*: 158 (M+2, 32.2% of M^+), 156 (M^+).

3c: δ ($CDCl_3$), ^{1}H NMR: 1.03 (t, 3H), 1.74–1.85 (m, 2H), 3.88 (t, 2H), 6.81 (d, 2H), 7.21 (d, 2H); *m/e*: 172 (M+2, 34.2% of M^+), 170 (M^+).

3d: δ ($CDCl_3$), ^{1}H NMR: 1.31 (d, 6H), 4.89–5.03 (m, 1H), 6.80 (d, 2H), 7.21 (d, 2H); *m/e*: 172 (M+2, 32.2% of M^+), 170 (M^+).

3e: δ ($CDCl_3$), ^{1}H NMR: 0.97 (*t*, 3H), 1.39–1.56 (m, 2H), 1.71–1.83 (m, 2H), 3.92 (t, 2H), 6.81 (d, 2H), 7.21 (d, 2H); *m/e*: 186 (M+2, 34.0% of M^+), 184 (M^+).

3f: δ ($CDCl_3$), ^{1}H NMR: 0.96 (t, 3H), 1.27 (d, 3H), 1.59–1.77 (m, 2H), 4.19–4.28 (m, 1H), 6.81 (d, 2H), 7.21 (d, 2H); *m/e*: 186 (M+2, 33.0% of M^+), 184 (M^+).

3g: δ ($CDCl_3$), ^{1}H NMR: 1.01 (d, 6H), 2.00–2.13 (m, 1H), 3.67 (d, 2H), 6.81 (d, 2H), 7.20 (d, 2H); *m/e*: 186 (M+2, 31.3% of M^+), 184 (M^+).

3h: δ ($CDCl_3$), ^{1}H NMR: 1.33 (s, 9H), 6.92 (d, 2H), 7.22 (d, 2H); *m/e*: 186 (M+2, 29.7% of M^+), 184 (M^+).

3i: δ ($CDCl_3$), ^{1}H NMR: 0.92 (t, 3H), 1.32–1.47 (m, 4H), 1.70–1.84 (m, 2H), 3.90 (t, 2H), 6.80 (d, 2H), 7.21 (d, 2H); *m/e*: 200 (M+2, 33.2% of M^+), 198 (M^+).

3j: δ ($CDCl_3$), ^{1}H NMR: 0.90 (t, 3H), 1.28–1.69 (m, 6H), 1.70–1.83 (m, 2H), 3.91 (t, 2H), 6.81 (d, 2H), 7.21 (d, 2H); *m/e*: 214 (M+2, 32.6% of M^+), 212 (M^+).

3k: δ ($CDCl_3$), ^{1}H NMR: 0.89 (t, 3H), 1.29–1.52 (m, 10H), 1.67–1.85 (m, 2H), 3.90 (t, 2H), 6.81 (d, 2H), 7.20 (d, 2H); *m/e*: 242 (M+2, 33.0% of M^+), 240 (M^+).

3l: δ ($CDCl_3$), ^{1}H NMR: 1.58–1.84 (m, 8H), 4.65–4.77 (m, 1H), 6.79 (d, 2H), 7.20 (d, 2H); *m/e*: 198 (M+2, 32.3% of M^+), 196 (M^+).

3m: δ ($CDCl_3$), ^{1}H NMR: 1.17–2.17 (m, 10H), 4.12–4.24 (m, 1H), 6.81 (d, 2H), 7.21 (d, 2H); *m/e*: 212 (M+2, 33.0% of M^+), 210 (M^+).

3n: δ ($CDCl_3$), ^{1}H NMR: 4.50 (d, 2H), 5.25–5.45 (q, 2H), 5.93–6.12 (m, 1H), 6.83 (d, 2H), 7.21 (d, 2H); ^{13}C NMR: 69.1, 116.0, 117.8, 125.7, 129.3, 132.9, 157.2; *m/e*: 170 (M+2, 34.8% of M^+), 168 (M^+).

3o: δ ($CDCl_3$), ^{1}H NMR: 5.02 (s, 2H), 6.90 (d, 2H), 7.22 (d, 2H), 7.33–7.41 (m, 5H); ^{13}C NMR: 70.3, 116.9, 125.8, 127.4, 128.0, 128.6, 129.3, 136.6, 157.3; *m/e*: 220 (M+2, 33.1% of M^+), 218 (M^+).

7a: δ ($CDCl_3$), ^{1}H NMR: 2.18 (s, 3H), 3.80 (s, 3H), 6.73 (d, 1H), 7.08 (s, 1H), 7.10 (d, 1H); ^{13}C NMR: 16.1, 55.5, 110.9, 124.9, 126.3, 128.5, 130.3, 156.3; *m/e*: 158 (M+2, 31.8% of M^+), 156 (M^+).

7b: δ ($CDCl_3$), ^{1}H NMR: 2.33 (s, 3H), 3.75 (s, 3H), 6.65 (d, 1H), 6.75 (s, 1H), 7.20 (d, 1H); ^{13}C NMR: 20.2, 55.4, 112.5, 116.4, 125.8, 129.5, 136.9, 158.1; *m/e*: 158 (M+2, 32.8% of M^+), 156 (M^+).

7c: δ ($CDCl_3$), ^{1}H NMR: 2.17 (s, 3H), 2.31 (s, 3H), 3.78 (s, 3H), 6.63 (d, 1H), 7.14 (d, 1H); ^{13}C NMR: 12.5, 16.7, 55.7, 108.8, 126.2, 126.3, 126.9, 135.2, 156.1; *m/e*: 172 (M+2, 31.9% of M^+), 170 (M^+).

7d: δ ($CDCl_3$), ^{1}H NMR: 2.24 (s, 6H), 3.68 (s, 3H), 6.98 (s, 2H); ^{13}C NMR: 15.9, 59.7, 128.4, 128.4, 132.5, 155.6; *m/e*: 172 (M+2, 32.2% of M^+), 170 (M^+).

9: δ ($CDCl_3$), ^{1}H NMR: 2.24 (s, 3H), 2.33 (s, 6H), 6.88 (s, 2H); ^{13}C NMR: 20.6, 20.6, 129.2, 131.6, 135.5, 135.8; *m/e*: 156 (M+2, 32.0% of M^+), 154 (M^+).

11a: δ ($CDCl_3$), ^{1}H NMR: 3.86 (s, 3H), 3.88 (s, 3H), 6.75–6.91 (m, 3H); ^{13}C NMR: 56.0, 56.1, 112.0, 112.1,120.3, 125.7, 149.6, 149.6; *m/e*: 174 (M+2, 32.4% of M^+), 172 (M^+).

11b: δ ($CDCl_3$), ^{1}H NMR: 3.78 (s, 3H), 3.86 (*s*, 3H), 6.40 (s, 1H), 6.47 (d, 1H), 7.23 (d, 1H); ^{13}C NMR: 55.5, 56.0, 100.0, 105.2, 114.2, 130.1, 155.7, 159.5; *m/e*: 174 (M+2, 34.6% of M^+), 172 (M^+).

11c: δ ($CDCl_3$), ^{1}H NMR: 3.78 (s, 3H), 3.85 (s, 3H), 6.75 (d, 1H), 6.85 (d, 1H), 6.95 (s, 1H); ^{13}C NMR: 55.9, 56.8, 112.9, 113.3, 116.2, 123.0, 149.4, 153.9; *m/e*: 174 (M+2, 32.9% of M^+), 172 (M^+).

11d: δ ($CDCl_3$), ^{1}H NMR: 2.16 (s, 3H), 3.79 (s, 6H), 6.55 (d, 1H), 7.13 (d, 1H); ^{13}C NMR: 55.8, 60.3, 60.3, 106.8, 119.6, 121.9, 126.8, 154.7, 157.5; *m/e*: 188 (M+2, 31.0% of M^+), 186 (M^+).

13a: δ ($CDCl_3$), ^{1}H NMR: 3.84 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 6.62 (d, 1H), 7.05 (d, 1H); ^{13}C NMR: 56.2, 61.1, 61.1, 107.8, 107.9, 123.9, 143.6,150.0, 152.7; *m/e*: 204 (M+2, 34.1% of M^+), 202 (M^+).

13b: δ ($CDCl_3$), ^{1}H NMR: 3.80 (s, 3H), 3.89 (s, 6H), 6.18 (s, 2H); ^{13}C NMR: 55.6, 56.3, 91.8, 156.7, 159.5; *m/e*: 204 (M+2, 33.3% of M^+), 202 (M^+).

Results and discussion

Chlorination of anisole

The current chlorination can be readily carried out only by efficiently stirring a heterogeneous mixture of an aromatic ether, catalyst **5a**, **1**, chromatographic alumina, and an aprotic solvent. Independent experiments were first made to estimate reaction parameters such as solvents, temperature, and water content of the alumina using anisole **2a** as the test substrate in order to optimize reaction conditions. When **2a** was treated with **1** without metal catalyst in the absence and presence of commercial or oven-dried or water-loaded alumina in dichloromethane, no reaction took place, **2a** being recovered essentially unchanged (**2a** recovery 98% by GC on every run). In the presence of oven-dried alumina or when no alumina was added, no reaction occurred even though catalyst **5a** was added. On the other hand, when **2a** was treated with a $NaClO_2$–**5a** system in the presence of the optimally water-loaded alumina (*moist* alumina; water content 17% by weight) in dichloromethane at ambient temperature it was completely consumed within 30 min, affording a mixture of *p*-chloroanisole **3a** (92.6%) and *o*-chloroanisole **4a** (4.5%) in quasi quantitative yield (Scheme 2, R = Me; total 97%) with high selectivity to the *para* isomer (*para*/*ortho* ratio, 41 after statistical correction), but no *meta*-chloroanisole. Consequently, the catalyst **5a** and *moist* alumina are essential for chlorination to occur under mild conditions.

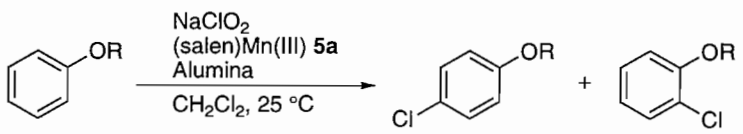
The choice of solvent was found to be another important

Table 1. Aromatic chlorination of anisole in various solvents.[a]

Entry no.	Solvent	Distribution (%)[b] PhOMe	*p*-ClC_6H_4OMe	*o*-ClC_6H_4OMe
1[c]	Dichloromethane	0	93	4.5
2	Chloroform	98	0	0
3	Tetrachloromethane	94	0	0
4	1,2-Dichloroethane	99	0	0
5	Acetone	98	0	0
6	Acetonitrile	97	0	0
7	1,4-Dioxane	98	0	0
8	Ethanol	98	0	0
9	Ether	98	0	0
10	Ethyl acetate	99	0	0
11	Hexane	99	0	0
12	Tetrahydrofuran	98	0	0

[a]Reaction conditions: 25°C; 2 h; anisole, 1.5 mmol; $NaClO_2$, 3 mmol; (salen)Mn(III) catalyst **5a**, 0.015 mmol; solvent, 10 mL, *moist* alumina, 1 g.
[b]Determined by GC using biphenyl as an internal standard.
[c]30 min.

Scheme 2.



2 **3** **4**

a R = Me **e** R = *n*-Bu **i** R = *n*-Pentyl **m** R = *c*-Hexyl
b R = Et **f** R = *s*-Bu **j** R = *n*-Hexyl **n** R = Allyl
c R = *n*-Pr **g** R = i-Bu **k** R = *n*-Octyl **o** R = $PhCH_2$
d R = *i*-Pr **h** R = *t*-Bu **l** R = *c*-Pentyl

factor: of common solvents examined, only dichloromethane favored the chlorination whereas no chlorination occurred in the other solvents during extended periords of time (Table 1). In contrast to the remarkable solvent effect, the chlorination exhibited little temperature dependence — control experiments conducted in the range of 0–30°C revealed that there was no significant change in the yield of monochloroanisoles or the *para* selectivity with a change of the temperature. Another comparative study using related (salen)manganese(III) complexes **5a**, **5b**, and **5c** showed that, although there is no significant difference in the activity of the catalysts and the *para* selectivity, the reaction using **5a** gave monochloroanisoles in slightly superior yield to those with use of **5b** and **5c** (97, 91, and 91%, respectively). In addition, **5a** can be synthesized by a simpler method (11) than those used for the preparation of **5b** and **5c** (18). Consequently, the subsequent chlorinations were carried out by using **5a** as the catalyst, in dichloromethane in the presence of *moist* alumina.

Although it is known that some heterogeneous reactions are affected by the presence of water (19, 20), the remarkable sensitivity of the current reaction towards the water content of the alumina and towards the solvent was unexpected and unusual. Sodium chlorite is insoluble in dichloromethane, no reaction occurred in the absence of alumina, and atomic absorption analyses of the reaction solvent showed no detectable amount of manganese species. These observations suggest that the chlorination presumably occurs on the alumina surface and that the solvent – alumina surface interface plays a decisive role in the present reaction. There might be a fine balance between keeping the right amount of water on the alumina surface to help break up the sodium chlorite lattice[4] and moderate solvent polarity to enable the chlorination to take place under mild conditions. It should be noted that no evidence was found for the formation of 2,4-dichlorinated or poly-chlorinated product(s), or for demethylation (22) or rearrangement to phenolic compound in the experiments described above.

Chlorination of aromatic monoethers

Applicability of the $NaClO_2$–**5a** – *moist* alumina system to a series of simple alkyl phenyl ethers **2b–o** was then tested (Scheme 2) and the results are collected in Table 2. Although it is known that some heterogeneous chlorinations have been considerably affected by a slight structual change in the substrates (23), there is apparently no serious dependence of the reactivity of the ethers on the shape and size of the alkyl moiety in the current reactions. For example, comparative studies

[4] A similar explanation has been given for the acceleration of reactions with the use of solid reagents by a small amount of water: see ref. 21.

Scheme 3.

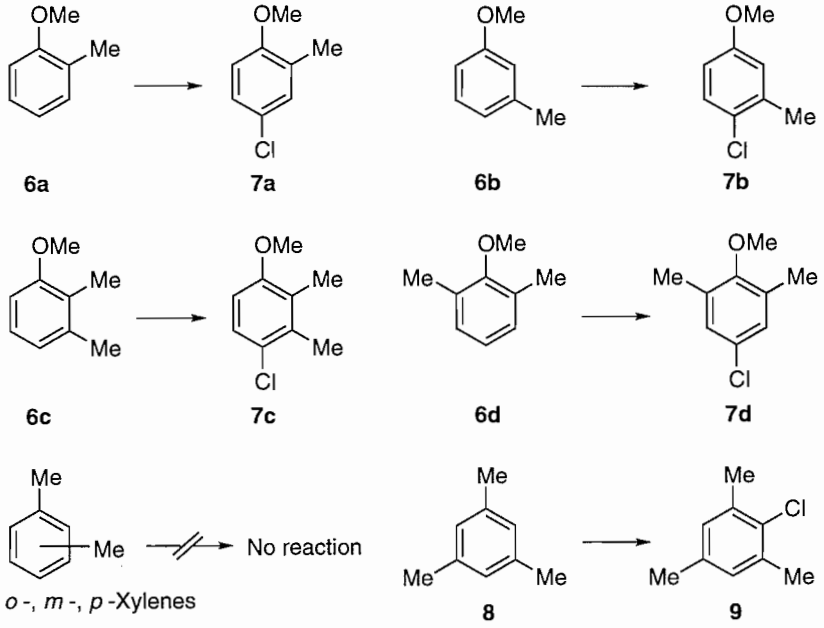


Table 2. Aromatic monochlorination of alkyl pheny ethers **2**.[a]

Entry no.	Ether	$NaClO_2$ (mmol)	Time (min)	Product	Yield (%)[b]
1[c]	**2a**	2.85	30	**3a**+**4a** (95:5)[d]	97
13[c]	**2b**	2.85	30	**3b**	Quant.
14[c]	**2c**	2.7	30	**3c**	96
15	**2d**	2.7	30	**3d**	96
16[c]	**2e**	2.85	30	**3e**	97
17	**2f**	2.85	30	**3f**	96
18	**2g**	2.85	30	**3g**	98
19	**2h**	2.7	30	**3h**	93
20[c]	**2i**	3.0	40	**3i**	94
21[c]	**2j**	2.7	30	**3j**	Quant.
22[c]	**2k**	3.0	30	**3k**	Quant.
23	**2l**	2.7	30	**3l**	93
24	**2m**	3.0	50	**3m**	91
25	**2n**	3.0	45	**3n**	56 (60)[e]
26	**2o**	3.0	60	**3o**	97

[a]Reaction conditions: 25°C; **2**, 1.5 mmol; *moist* alumina, 1 g; (salen)Mn(III) catalyst **5a**, 0.015 mmol (1 mol% with respect to **2**); CH_2Cl_2, 10 mL.
[b]Isolated yield of *para*-chlorinated ether **3** (plus **4a** in the case of **2a**) based on the starting **2**.
[c]Reference 14.
[d]Product ratio, **3a**:**4a**, determined by GC using biphenyl as an internal standard.
[e]GC yield (internal standard: biphenyl); number in parentheses is the yield of **3n** based on consumed **2n**.

using ethers having C_3- (**2c–d**) and C_4-alkyl groups (**2e–h**) clearly indicated that the reactivity of the ethers is little influenced by steric bulk around the ether linkage. Interestingly, the reactions of **2b–o** led to exclusive *para*-chlorination, giving **3b–o** in excellent to quantitative yields. The side chain of **2n** is assumed to be highly susceptible to chlorination, but it gave **3n** in good yield (60% based on **2n** consumed).

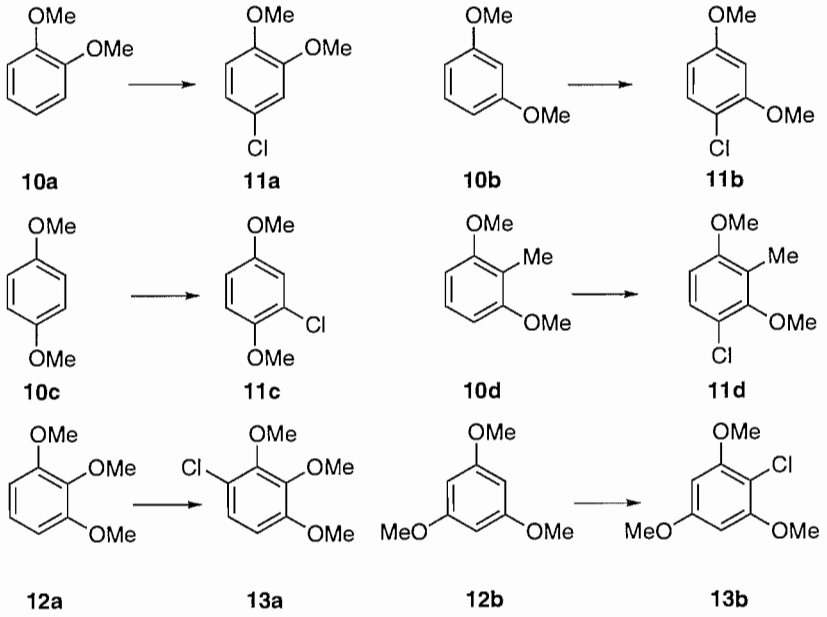
Table 3. Selective monochlorination of various activated arenes.[a]

Entry no.	Ether	$NaClO_2$ (mmol)	Time (min)	Product	Yield (%)[b]
27	**6a**	3.3	30	**7a**	83
28	**6b**	2.4	30	**7b**	87
29	**6c**	2.7	50	**7c**	85
30	**6d**	3.9	35	**7d**	92
31	**8**	3.5	70	**9**	81 (85)
32	**10a**	3.0	30	**11a**	89 (93)
33	**10b**	2.4	40	**11b**	82 (86)
34	**10c**	3.6	30	**11c**	84 (92)
35	**10d**	2.2	55	**11d**	94
36	**12a**	2.4	50	**13a**	89
37	**12b**	2.6	40	**13b**	84 (87)

[a]Reaction conditions: 20°C; substrate, 1.5 mmol; *moist* alumina, 1 g; (salen)Mn(III) catalyst **5a**, 0.015 mmol (1 mol% with respect to **2**); CH_2Cl_2, 10 mL.
[b]Based on the starting ether (numbers in parentheses are yields based on consumed substrates).

Encouraged by the unusually high *para* selectivity in the chlorination of simple monoether substrates **2a–o**, chlorination of methyl- and dimethyl-substituted anisoles **6a,b** and **6c,d**, respectively, with a **1**–**5a** – *moist* alumina system was also investigated. As shown in Scheme 3, the chlorination occurred selectively at positions *para* to the MeO groups, producing monochlorination products **7a–d** in excellent yields (entries 27–30 in Table 3). In sharp contrast to the facile chlorination of **6a** and **6b**, xylenes resisted chlorination, leading to the recovery of unchanged substrates even after prolonged reactions (120 min; substrate recovery 97–99%). This might suggest that activation by the two methyl groups is not adequate for the nuclei to undergo chlorination, since mesitylene **8** afforded mesityl chloride **9** in fairly good yield (Entry 31).

Scheme 4.



Chlorination of di- and tri-methoxybenzenes

The reactions of a series of di- and tri-methoxybenzenes, **10** and **12**, were carried out in order to examine the regiospecificity in the chlorination of the polyether substrates (Scheme 4). Chlorinations of 1,2- and 1,3-dimethoxybenzene **10a** and **10b** occurred at the position *para* to the MeO group, affording **11a** and **11b**, respectively. 1,4-Dimethoxybenzene **10c** has no substitutable hydrogen at the position *para* to each MeO group, but it was readily chlorinated to give **11c** in excellent yield. The usefulness of the present procedure for the monochlorination of triether substrates, **12a** and **12b**, is also apparent.

Aromatic chlorination has been an important reaction in organic chemistry (for reviews, see ref. 24) and many interesting methods have been developed employing molecular chlorine, sulfuryl chloride, hypochlorite and its esters, metal chlorides, N-chloro compounds, etc. as chlorinating agents (24–34). So far as we are aware, both the yield and the selectivity of the chlorination product resulting from solid–solution biphasic systems (23, 28–31) are, in general, superior to those from simple solution-phase counterparts. For example, chlorination of aralkyl ethers (**2a–c**, **2e**, and **2i**) by alumina-supported $CuCl_2$ reagent ([$CuCl_2$]/[**2**], ca. 5 (mole ratio); 100°C, 2–3 h) gives excellent yields and *para* selectivity (30). Our chlorination compared favorably with this procedure in terms of the generally *higher* yield, much *milder* conditions (< 25°C), *shorter* reaction periods, and use of *smaller* amounts of the *cheaper* chlorinating reagent ([$NaClO_2$]/[**2**] $\leq$ 2). In addition, the chlorination of a wide variety of substrates can be performed readily and efficiently, and the regioselectivities are impressive. These advantages, together, may make the new system an attractive alternative to conventional chlorination methodologies.

The current alumina-promoted chlorination formally amounts to a simple chlorine transfer to arenes. This study had a preparative rather than a mechanistic purpose and, in addition, convincing evidence to permit a physicochemical interpretation of the reaction has not been yet provided, since there is uncertainty with regard to the catalysis of **5a** and the active species wherein the chlorite itself and (or) its degradation product(s) might be involved. The following observations and comparisons with related literature data, however, might show interesting aspects of the chlorination.[5] Since chlorine itself is very reactive and small in size, the recent development in selective chlorinations owes its success either to the use of bulky chlorinating agents (27, 32) or shape-selective catalysts such as cyclodextrin (25), zeolites (27, 28), or, as noted above, to the reaction performance under biphasic conditions (23, 27–31), all of which are based on the sterically (or dimensionally) controlled access of chlorinating agents to the reactive, electron-rich position(s) of aromatic nuclei. For the present chlorination, it might be expected that chlorine transfer from a bulky **5a**–chlorine complex to arenes is responsible for the high regioselectivity. However, this should be unlikely, since simple inorganic metal salts, e.g., $CoSO_4$, $Co(NO_3)_2$, $CoCl_2$, $CoBr_2$, $MnSO_4$, $MnCl_2$, $Mn(OAc)_2$, $KMnO_4$, $NaMnO_4$, can be used in place of **5a** for the chlorination of **2a** and there has been no significant change in the **3a/4a** ratios and the yields of chloroanisoles; typically, **3a/4a** = 95:5 and 94:6 with use of $CoSO_4$ and $MnSO_4$, respectively (total yields of **3a** plus **4a** were 94 and 95%, respectively). Thus **5a** is considered to serve as a catalytic activator of **1** or to be involved in the degradation process of **1** en route to the generation of the active chlorine species. In addition, the chlorination of simple aromatic ethers occurred selectively or exclusively at positions *para* to the alkoxy groups (entries 1 and 13–26). It is noteworthy that, in the case of methyl- (entries 27, 28, and 35) and dimethyl-substituted anisoles (entries 29 and 30), positions *para* to the MeO groups are chlorinated, but not those *para* to the Me substituent(s), indicating clearly that chlorine displaces hydrogens attached to the more nucleophilic carbon atoms on the benzene rings (ref. 24*d*, Chap. 2; ref. 24*e*, p. 513; 33, 34). Together, these results undoubtedly support the view that electronic effects are a decisive factor in controlling the

[5] Valuable suggestions from one of the referees regarding the observed regioselectivities are gratefully acknowledged.

regioselectivy of the current chlorination, in which the alumina might contribute not only to facilitating the reaction, but to enhancing the regioselectivity of the product (23*a*, 30). Smooth reactions of **6b**,**c**, **8**, **10b–d**, and **12a**,**b** may account for the lesser influence of steric factors. Finally, even if some interaction between electron-rich ether oxygen (34) and the alumina surface is present, it seems unimportant in determining the reactivity of an ether and the regioselectivity of the chlorination product, since **2h**, for example, was readily chlorinated to afford exclusively **3h** (entry 19).

Conclusion

We have demonstrated here that the $NaClO_2$-based biphasic system serves as an efficient electrophilic chlorine source that is capable of regiospecifically chlorinating the electron-rich position on the benzene ring of a variety of aromatic ethers under mild and neutral conditions.

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References

1. T.P. Nevell. Methods Carbohydr. Chem. **3**, 182 (1963).
2. B.O. Lindgren and T. Nilsson. Acta Chem. Scand. **27**, 888 (1973).
3. J.A. Moore and E.M. Partain III. Org. Prep. Proced. Int. **17**, 203 (1985); L. Colombo, C. Gennari, M. Santandrea, E. Narisano, and C. Scolastico. J. Chem. Soc. Perkin Trans. 1, 136 (1980); F. M. Hauser and S. R. Ellenberger. Synthesis, 723 (1987).
4. G.S. Arora, H. Shirahama, and T. Matsumoto. Chem. Ind. (London), 318 (1983).
5. E. Dalcanale and F. Montanari. J. Org. Chem. **51**, 567 (1986).
6. J.P. Bayle, F. Perez, and J. Courtieu. Bull. Soc. Chim. Fr. **127**, 565 (1990).
7. M. Floor, L.P.M. Hofsteede, W.P.T. Groenland, L.A.Th. Verhaar, A.P.G. Kieboom, and H. van Bekkum. Recl. Trav. Chim. Pays-Bas, **108**, 384 (1989).
8. B.S. Bal, W.E. Childers, Jr., and H.W. Pinnick. Tetrahedron, **37**, 2091 (1981); G.A. Kraus and B. Roth. J. Org. Chem. **45**, 4825 (1980); G.A. Kraus and M.J. Taschner. J. Org. Chem. **45**, 1175 (1980); D.S. Matteson and E.C. Beedle. Tetrahedron Lett. **28**, 4499 (1987); L.R. Hills and R.C. Ronald. J. Org. Chem. **50**, 470 (1985).
9. K. Paluch, J. Otto, and R. Starski. Rocz. Chem. **48**, 1453 (1974) (Chem. Abstr. **82**, 111821 (1975)); K. Paluch and J. Jogielski. Zesz. Nauk Politech. Szczecin., Chem., 113 (1972) (Chem. Abstr. **80**, 59772 (1974)); J. Otto and K. Paluch. Rocz. Chem. **47**, 967 (1973) (Chem. Abstr. **79**, 136679 (1973)); Rocz. Chem. **46**, 1551 (1972) (Chem. Abstr. **78**, 57909 (1973)).
10. B.R. Babu and K.K. Balasubramaniam. Org. Prep. Proced. Int. **26**, 123 (1994); E.A. Harrison, Jr., K. C. Rice, and M. E. Rogers. J. Heterocycl. Chem. **14**, 909 (1977).
11. L. Deng and E.N. Jacobsen. J. Org. Chem. **57**, 4320 (1992).
12. K. Srinivasan, P. Michaud, and J.K. Kochi. J. Am. Chem. Soc. **108**, 2309 (1986); E.N. Jacobsen, W. Zhang, A.R. Muci, and J.R. Ecker. J. Am. Chem. Soc. **113**, 7063 (1991); T. Katsuki. J. Mol. Catal. A: Chem. **113**, 87 (1996).
13. M. Hirano, S. Yakabe, J.H. Clark, H. Kudo, and T. Morimoto. Synth. Commun. **26**, 1875 (1996).
14. M. Hirano, S. Yakabe, H. Monobe, J.H. Clark, and T. Morimoto. Synth. Commun. **27**, 3749 (1997).
15. J.H. Clark, A.P. Kybett, and D.J. Macquarrie. Supported reagents. Preparation, analysis, and applications, VCH, New York. 1992; J.H. Clark. Catalysis of organic reactions by supported inorganic reagents. VCH, New York. 1994; K. Smith (*Editor*). Solid supports and catalysts in organic synthesis. Ellis Horwood, Chichester. 1992; P. Laszlo (*Editor*). Preparative chemistry using supported reagents. Academic Press, San Diego. 1987; M. Balogh and P. Laszlo. Organic chemistry using clays. Springer-Verlag, Berlin. 1993; K. Smith, C.V. Fry, and M. Tzimas. *In* Chemistry of waste minimization. *Edited by* J.H. Clark. Chapman and Hall, London. 1995. Chap. 4.
16. M. Siskin, G. Brons, A.R. Katritzky, and R. Murugan. Energy Fuels, **4**, 482 (1990).
17. R.A. Smith. J. Am. Chem. Soc. **55**, 3718 (1933).
18. R. Irie, Y. Noda, Y. Ito, N. Matsumoto, and T. Katsuki. Tetrahedron: Asymmetry, **2**, 481 (1991).
19. T. Nishiguchi and F. Asano. J. Org. Chem. **54**, 1531 (1989); M. Kodomari, H. Satoh, and S. Yoshitomi. Bull. Chem. Soc. Jpn. **61**, 4149 (1988); S. Yasui, M. Fujii, K. Nakamura, and A. Ohno. Bull. Chem. Soc. Jpn. **60**, 963 (1987); M.O. Brimeyer, A. Mehrota, S. Quici, A. Nigam, and S.L. Regen. J. Org. Chem. **45**, 4254 (1980); F.M. Menger and C. Lee. J. Org. Chem. **44**, 3446 (1979); E. Keinan and Y. Mazur. J. Org. Chem. **43**, 1020 (1978); M. Hojo and R. Masuda. Synth. Commun. **5**, 169 (1975); Tetrahedron Lett., 613 (1976); B.B. Jarvis and M.M. Evans. J. Org. Chem. **39**, 643 (1974).
20. M. Onaka, K. Sugita, and Y. Izumi. J. Org. Chem. **54**, 1116 (1989); T. Ando, T. Kawate, J. Yamawaki, and T. Hanafusa. Chem. Lett. 935 (1982).
21. L.A. Carpino and A.C. Sau. J. Chem. Soc. Chem. Commun. 514 (1979); M. Tanaka and M. Koyanagi. Synthesis, 973 (1981).
22. M. Tiecco. Synthesis, 749 (1988).
23. (*a*) M. Kodomari, S. Takahashi, H. Watanabe, and S. Yoshitomi. Nippon Kagaku Kaishi, 1753 (1987) (Chem. Abstr. **109**, 37557 (1988)); (*b*) I. Tanimoto, K. Kushioka, T. Kitagawa, and K. Maruyama. Bull. Chem. Soc. Jpn. **52**, 3586 (1979).
24. (*a*) D.E. Pearson and C.A. Buehler. Synthesis, 455 (1971); (*b*) H. Heavy. *In* Comprehensive organic chemistry. Vol. 1. *Edited by* D.H.R. Barton and W.D. Ollis. Pergamon Press, Oxford. 1979. p. 291; (*c*) E.B. Merkushev. Synthesis, 923 (1988); (*d*) R. Taylor. Electrophilic aromatic substitution. John Wiley & Sons, Chichester. 1990. p. 363; (*e*) J. March. Advanced organic chemistry. Reactions, mechanisms, and structure. 4th ed. John Wiley & Sons, New York. 1992. p. 531.
25. R. Breslow and P. Campbell. J. Am. Chem. Soc. **91**, 3085 (1969); Bioorg. Chem. **1**, 140 (1971); Tetrahedron Lett. 1645 (1976).
26. H.A. Muathen. Tetrahedron Lett. **52**, 8863 (1996); F. Bellesia, F. Ghelfi, U.M. Pagnoni, and A. Pinetti. J. Chem. Res. (S), 284 (1991); G.A. Olah, L. Ohanneslan, and M. Arvanaghi. Synthesis, 868 (1986); I. Tanimoto, K. Kushioka, T. Kitagawa, and K. Maruyama. Bull. Chem. Soc. Jpn. **52**, 3586 (1979); J.G. Lee, H.T. Cha, U.C. Yoon, Y.S. Suh, K.C. Kim, and I.S. Park. Bull. Korean Chem. Soc. **12**, 4 (1991).
27. W.D. Watson. J. Org. Chem. **50**, 2145 (1985); R. Rathore, S.H. Loyd, and J.K. Kochi. J. Am. Chem. Soc. **116**, 8414 (1994).
28. K. Smith and M. Butters. Tetrahedron Lett. **29**, 1319 (1988).
29. K. Smith, M. Butters, and B. Nay. Synthesis, 1157 (1985); L. Delaude and P. Laszlo. J. Org. Chem. **55**, 5260 (1990).

30. M. Kodomari, S. Takahashi, and S. Yoshitomi. Chem. Lett. 1901 (1987).
31. L. Delaude, P. Laszlo, and K. Smith. Acc. Chem. Res. **26**, 607 (1993); L. Delaude and P. Laszlo. Catal. Lett. **5**, 35 (1990); M. Kodomari, H. Satoh, and S. Yoshitomi. J. Org. Chem. **53**, 2093 (1988).
32. J.R. Lindsay Smith, L.C. McKeer, and J.M. Taylor. J. Chem. Soc. Perkin Trans. 2, 1533 (1987); 385 (1988); 1529 (1989); 1537 (1989).
33. G. Castelfranchi and G. Borra. Ann. Chim. (Rome), **43**, 293 (1953).
34. Y. Ogata, M. Kimura, and Y. Kondo. J. Chem. Soc. Perkin Trans. 2, 451 (1984).