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A Journal of
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Accepted Article

Title: Regioselective Oxidative Chlorination of Arenols Using NaCl and Oxone

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801063

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801063

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10.1002/ejoc.201801063

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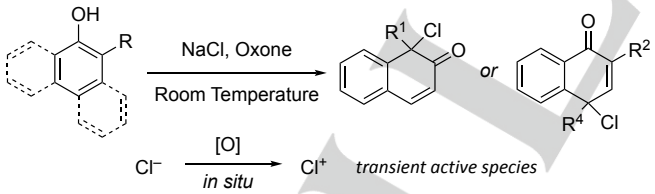
Regioselective Oxidative Chlorination of Arenols Using NaCl and Oxone

Muhammet Uyanik,[a] Naoto Sahara,[a] and Kazuaki Ishihara*[a]

Abstract: We developed a practical and environmentally benign method for the chlorinative dearomatization of arenols using transient electrophilic chlorinating species generated *in situ* from inexpensive sodium chloride and Oxone as a Cl source and oxidant, respectively, under mild conditions. Moreover, the regioselective chlorination or chlorinative dearomatization of 1-naphthols was also achieved by changing the reaction conditions.

Introduction

The dearomatization of arenols has emerged as a promising tool for the synthesis of various natural products and biologically active compounds.[1] Planar achiral substrates can be transformed into chiral three-dimensional structures through an sp^2-to-sp^3 change in geometry on one of the sp^2-hybridized carbon centers. Several different compounds can be generated depending on the nature of the reagents used.[1] In this context, the halogenative, especially the chlorinative, dearomatization of arenols has been developed using electrophilic halogenating reagents.[2] In 1883, Benedikt and Schmidt first reported the chlorinative dearomatization of polychlorinated phenols using toxic chlorine gas.[3] Since the 1950s, various electrophilic chlorinating systems including isocyanuric chloride, *N*-chlorosuccinimide (NCS), SO_2Cl_2, *t*BuOCl, NaOCl, $SbCl_5$, SbF_5-CH_2Cl_2 and hypervalent iodine compounds have been developed for the chlorinative dearomatization of phenols.[4] Recently, the enantioselective chlorinative dearomatization of naphthols has also been developed using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH).[5] The development of an efficient method for the chlorinative dearomatization of arenols using less-toxic and inexpensive chlorinating reagents is still needed.

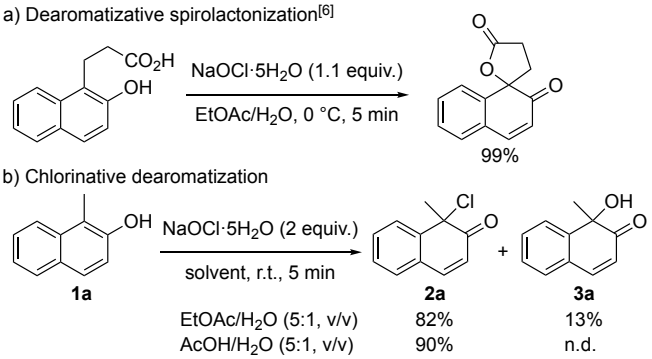


Scheme 1. Chlorinative dearomatization of naphthols using NaCl and Oxone.

Here, we report a practical and environmentally benign protocol for the chlorinative dearomatization of naphthols and phenols with transient chlorinating species generated *in situ* from inexpensive sodium chloride and Oxone as a Cl source and oxidant, respectively, under mild conditions (Scheme 1). Moreover, the regioselective chlorination or chlorinative dearomatization of 1-naphthols was achieved depending on the use of different reaction conditions.

Results and Discussion

Recently, we reported a dearomatizative spirolactonization of phenols tethered to a carboxylic acid moiety at the *ortho*-position using sodium hypochlorite pentahydrate ($NaOCl·5H_2O$) as an oxidant (Scheme 2a).[6] Compared to conventional aqueous NaOCl solution (ca. 10 wt%, pH ~13), this solid oxidant offers several advantages, including higher chlorine content (ca. 42%), lower pH upon dissolution (pH ~11) and high stability at lower temperatures.[7] We envisioned that $NaOCl·5H_2O$ could be applied as a chlorinating agent to the chlorinative dearomatization of arenols in the absence of an intramolecular nucleophilic moiety at an appropriate position (Scheme 2b). Indeed, the rapid reaction of 1-methyl-2-naphthol (**1a**) with $NaOCl·5H_2O$ (2 equiv.) in a mixed solvent of ethyl acetate and water at room temperature afforded 1-chloro-1-methylnaphthalen-2(1*H*)-one (**2a**) in 82% yield. However, undesired *ortho*-quinol **3a**[8] was also obtained in 13% yield as a side product. The reaction of **2a** under identical conditions did not afford **3a** and most of the **2a** was recovered, which revealed that **3a** might be obtained from the direct oxidation of **1a**.[9] A brief screening of conditions revealed that the generation of **3a** could be suppressed under acidic conditions in aqueous acetic acid.[9]



Scheme 2. Oxidative dearomatization of 2-naphthols with $NaOCl·5H_2O$.

We next focused on the *in situ* generation of electrophilic chlorinating species from chloride (-1) under oxidative conditions[10] for the chlorinative dearomatization of **1a** (Table 1). First, conventional oxidants (2 equiv.) were investigated under similar conditions (i.e., $EtOAc/H_2O$ at room temperature) in the presence of 2 equivalents of sodium chloride (entries 1–5). Almost no reaction occurred with the use of hydrogen peroxide or alkyl hydroperoxides (*tert*-butyl hydroperoxide (TBHP) and

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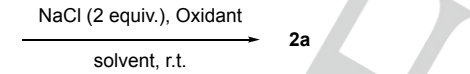
cumene hydroperoxide (CHP)) (entries 1–3). On the other hand, the reaction with *meta*-chloroperbenzoic acid (*m*CPBA) as an oxidant afforded a complex mixture of unidentified products (entry 4). To our delight, the chlorinative dearomatization of **1a** proceeded efficiently with 1 equivalent of Oxone (as 2 equiv. of oxidant, $KHSO_5$), an inexpensive triple inorganic salt ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$). Notably, undesired quinol **3a** was not detected under these acidic conditions (pH of the aqueous phase ~1.6)[9] and **2a** was obtained in 90% yield as a single product (entry 5). A brief screening of organic solvents (entries 6–8) revealed that the reaction rate was slightly increased in a mixed *tert*-butyl methyl ether/water solvent, and **2a** was obtained in 92% isolated yield (entry 8). Notably, the use of water as a co-solvent under these biphasic conditions was crucial to dissolve Oxone and control the selective oxidative reaction, since **1a** was almost recovered in the absence of water (entry 9).

Chlorine (Cl_2) or hypochlorous acid (HOCl) might be generated *in situ* as an active electrophilic chlorinating species from NaCl and Oxone under acidic conditions.[10,11] Interestingly, the reaction was completed within 5 minutes, as in the stoichiometric reaction with $NaOCl \cdot 5H_2O$ (see Scheme 2), when NaCl was pre-mixed with Oxone for 1 h to generate active chlorinating species before the addition of **1a** (Table 1, entry 10 versus entry 5). This result suggested that the transient active species was generated *in situ* slowly and consumed rapidly, and therefore the concentration of the highly reactive chlorinating species could be minimized to induce high chemoselectivity compared to stoichiometric chlorinating reagents such as NaOCl (*vide infra*).

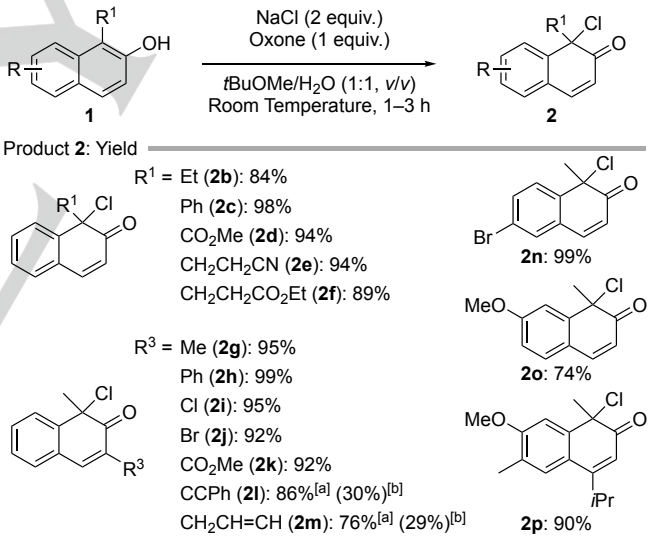
Table 1. Investigation of Chlorinative Dearomatization of **1a** with NaCl.



Entry	Oxidant (equiv)	Solvent	Time [h]	**2a**, Yield [%][a]
1	30% H_2O_2 (2)	EtOAc/H_2O[c]	12	<5 (>95)
2	TBHP (2)	EtOAc/H_2O[c]	12	<5 (>95)
3	CHP (2)	EtOAc/H_2O[c]	12	<5 (>95)
4	*m*CPBA (2)	EtOAc/H_2O[c]	12	<5 (<5)
5	Oxone (1)	EtOAc/H_2O[c]	1.5	90 (<5)
6	Oxone (1)	CH_3CN/H_2O[c]	4	91 (<5)
7	Oxone (1)	Toluene/H_2O[c]	1.5	90 (<5)
8	Oxone (1)	*t*BuOMe/H_2O[c]	1	92[d] (<5)
9	Oxone (1)	*t*BuOMe	12	<5 (>90)
10[b]	Oxone (1)	EtOAc/H_2O[c]	0.08	92 (<5)

[a] Determined by ^{1}H NMR analysis. Yields of recovered **1a** are shown in parentheses. [b] NaCl and Oxone were pre-mixed for 1 h before the addition of **1a**. [c] Organic solvent/H_2O (1:1, *v*/*v*). [d] Isolated yield. TBHP, *tert*-butyl hydroperoxide; CHP, cumene hydroperoxide, n.d., not detected.

A series of 1-substituted 2-naphthols **1** bearing electron-donating or -withdrawing groups were examined for the oxidative chlorinative dearomatization using NaCl and Oxone under optimized conditions (Scheme 3). In most cases, the corresponding **2** were obtained in high to excellent yields as sole products. Several functional groups such as alkoxycarbonyl (**2d**, **2f** an **2k**), cyano (**2e**), bromo (**2j** and **2n**), alkynyl (**2l**), alkenyl (**2m**) and methoxy (**2o** and **2p**) groups were tolerated under these mild conditions. Notably, a chemoselective chlorinative dearomatization of **1p** afforded **2p**, a Cl-analogue of the natural product lacinilene C methyl ether,[8,12] in high yield. However, several unidentified byproducts were also obtained from the reactions of 2-naphthols **1l** and **1m** bearing alkynyl and alkenyl groups, respectively. Chemoselective chlorination of these challenging substrates could be achieved under slightly modified conditions that maintained a low concentration of the transient chlorinating species. Considering the over-chlorination or undesired chlorination at multiple bonds of these substrates,[9] a cleaner reaction proceeded by lowering the amount of NaCl (2 to 1 equiv.) used for these reactions, and the corresponding **2** were obtained in good yields. In sharp contrast, the reactions of these naphthols using $NaOCl \cdot 5H_2O$ afforded complex mixtures of products and desired **2l** and **2m** were obtained in only low yields (Scheme 3).

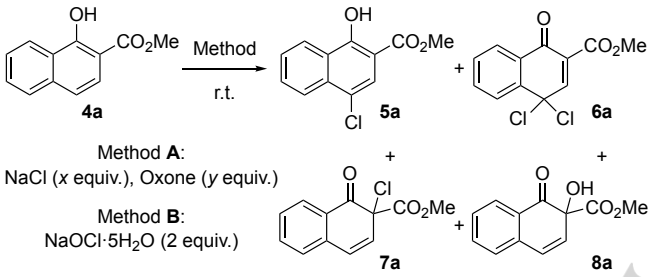


Scheme 3. Oxidative chlorinative dearomatization of 2-naphthols **1** with NaCl and Oxone. [a] NaCl (1 equiv.) was used. [b] Reactions were performed under stoichiometric conditions with $NaOCl \cdot 5H_2O$ in AcOH as in Scheme 2.

Next, we examined the chlorination of 1-naphthol **4a** (Table 2). The reaction of **4a** using NaCl and Oxone (Method A) under conditions similar to those for 2-naphthols afforded the *para*-chlorinated product **5a** and dearomatized *para*-dichloro product **6a** as major products, which were produced via chlorination at the most nucleophilic 4-position of **4a** (entry 1). *ortho*-Chlorinative dearomatized product **7a** was a minor component, and, as in 2-naphthols, *ortho*-quinol **8a** was not detected under these acidic conditions. A *para*-selective reaction proceeded exclusively in an ethyl acetate/water mixed solvent (entry 2). To

our delight, both **5a** and **6a** could be obtained selectively in high yield by controlling the amount of reagents used (entries 3 and 4). We next examined $NaOCl·5H_2O$ as a chlorinating agent for the same reaction (Method B). Similarly, only *para*-chlorinated products **5a** and **6a** were obtained under acidic conditions using 2 equivalents of $KHSO_4$ as an additive (pH of the aqueous phase ~3.4)[9] or aqueous acetic acid as a solvent (entries 5 and 6). On the other hand, *ortho*-chlorinative dearomatized product **7a** was obtained in 62% isolated yield as a major product under basic conditions (pH of the aqueous phase ~10.1[9]) in an ethyl acetate/water mixed solvent (entry 7). As expected, *ortho*-quinol **8a**[8] was also obtained under these basic conditions. Notably, slightly higher chemo- and regioselectivities were obtained with $NaOCl·5H_2O$ compared to conventional 10% aqueous NaOCl (entry 7 versus entry 8).

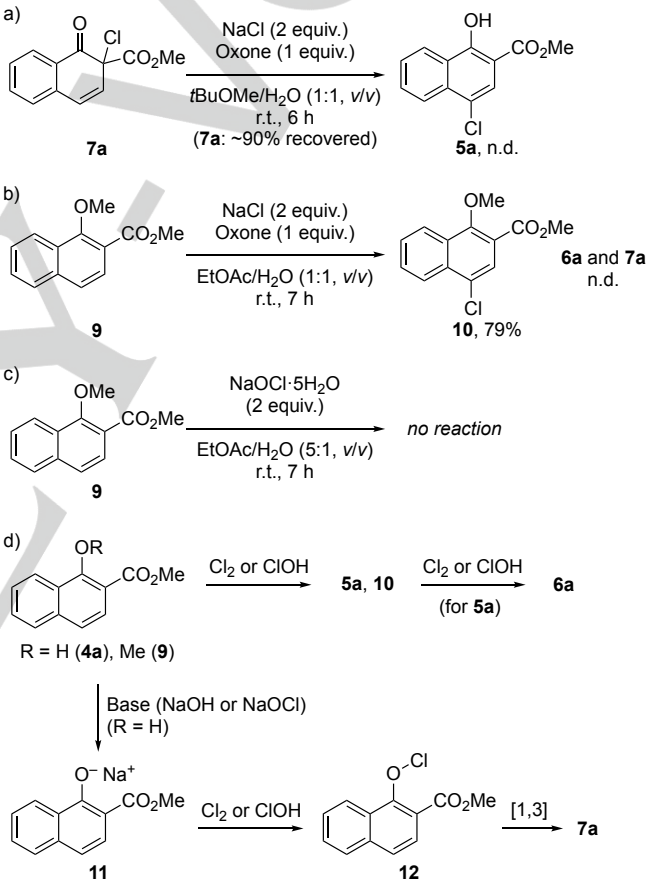
Table 2. Regio- and Chemoselective Chlorination of 1-Naphthol **4a**.



Entry	Method **A** (*x*, *y*) or **B**	Solvent	Time [h]	Yield [%][a] 5a	6a	7a	8a
1	**A** (2, 1)	*t*BuOMe/H_2O[d]	3	51	24	13	n.d.
2	**A** (2, 1)	EtOAc/H_2O[d]	3	45	43	<5	n.d.
3	**A** (1, 1)	EtOAc/H_2O[d]	4	85[f]	<5	<5	n.d.
4	**A** (3, 1.5)	EtOAc/H_2O[d]	2	<5	87[f]	<5	n.d.
5	**B**	AcOH/H_2O[e]	0.5	62	25	<5	n.d.
6	**B**[b]	EtOAc/H_2O[e]	0.5	67	29	<5	n.d.
7	**B**	EtOAc/H_2O[e]	3	<5	10	62[f]	10
8	**B**[c]	EtOAc/H_2O[e]	3	10	15	58	12

[a] Determined by ^{1}H NMR analysis. [b] $KHSO_4$ (2 equiv.) was added as an additive. [c] NaOCl (10% aq.) was used instead of $NaOCl·5H_2O$. [d] Organic solvent/H_2O (1:1, *v*/*v*). [e] Organic solvent/H_2O (5:1, *v*/*v*). [f] Isolated yield.

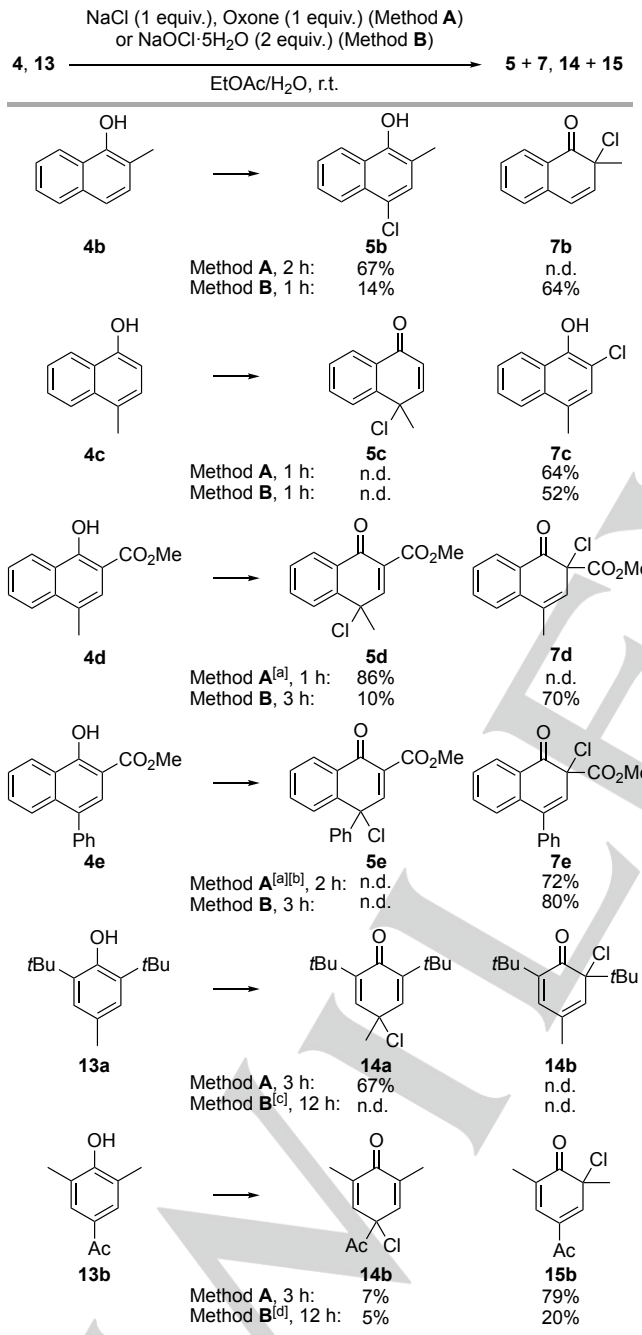
To understand the *ortho*-/*para*-selectivity observed for the chlorination of 1-naphthol **4a**, several control experiments were conducted. First, no isomerization was observed from isolated *ortho*-product **7a** to *para*-product **5a** under our acidic conditions (Scheme 4a).[4e,13] Moreover, the reaction of the methyl ether **9** under acidic conditions using NaCl and Oxone afforded the corresponding *para*-chlorinated product **10** selectively in 79% yield (Scheme 4b). Notably, a lower reaction rate was observed for **9** under identical conditions compared to **4a**, and dearomatized product **6a** was not observed even in the presence of 2 equivalents of NaCl (for comparison, see: Table 2, entry 2). This might be due to lower local nucleophilicity at the *para*-position of methyl ethers **9** or **10** compared to 1-naphthols **4a** or **5a**.[14] In sharp contrast, no reaction occurred and **9** was recovered under basic conditions using $NaOCl·5H_2O$ (Scheme 4c). These results suggested that the *para*-chlorinated products **5a** or **10** might be generated via electrophilic aromatic substitution with *in situ*-generated electrophilic chlorinating species at the most nucleophilic *para*-position of **4a** or **9** under acidic conditions (Scheme 4d).[15] Similarly, subsequent chlorinative dearomatization of **5a** would also proceed at the 4-position to give **6a** in the presence of excess Cl source. On the other hand, 1-naphthoxide **11** would be generated first under basic conditions and react with the chlorinating agent to afford naphthyl hypochlorite **12** followed by a 1,3-shift to give *ortho*-chlorinated product **5a** (Scheme 4d).[15]



Scheme 4. Control experiments for the regioselective chlorination of **4a**.

In contrast to the chlorination of 2-naphthols, which proceeded exclusively at the 1-position under acidic or basic conditions, the regioselectivity of the reaction of 1-naphthols and phenols depended on the reaction conditions and/or steric and electronic effects of the substituents at the *ortho*- and *para*-positions. A series of 1-naphthols **4** and phenols **13** were examined under acidic and basic conditions using NaCl/Oxone (Method A) or $NaOCl·5H_2O$ (Method B), respectively (Scheme 5).[16] 2-Methyl-1-naphthol **4b** afforded the *para*-chlorinated product **5b** or *ortho*-chlorinated product **7b** selectively under

acidic or basic conditions, respectively. Similarly, **4d** bearing ester and methyl substituents at the *ortho*- and *para*-positions, respectively, afforded the corresponding **5d** and **7d** selectively depending on the conditions used. On the other hand, since the electrophilic aromatic substitution reaction proceeded at less-hindered 2-postions of 4-methyl-1-naphthol (**4c**) and **4e**, a 4-phenyl analogue of **4d**, only *ortho*-chlorinated products **7c** and **7e** were obtained selectively under both acidic and basic conditions.



Scheme 5. Regioselective chlorination of 1-naphthols **4** and phenols **13**. Isolated yields are shown. [a] NaCl (2 equiv.) was used. [b] A *t*BuOMe/H_2O mixed solvent was used. [c] A messy reaction mixture was obtained. [d] **13b** was recovered in 50% yield.

On the other hand, the chlorinative dearomatization of phenols **13a** and **13b** under acidic conditions using NaCl and Oxone proceeded efficiently at the most nucleophilic and less-hindered *para*- or *ortho*-positions to afford the corresponding *para*- (**14a**) or *ortho*-product (**15b**), respectively, in good yields. In sharp contrast, the reaction of **13a** using NaOCl·5H_2O under basic or acidic[9] conditions gave a complex mixture of many unidentified products, whereas a sluggish reaction of **14a** afforded the both *ortho*- and *para*-products **14b** and **15b** in low yield. These results demonstrated again the utility of the transient generation of chlorinating species instead of stoichiometric reagents to induce high chemoselectivity.

Conclusions

A practical and efficient chlorinative dearomatization of arenols was developed using transient chlorinating species generated *in situ* from inexpensive sodium chloride and Oxone as a Cl source and oxidant, respectively. Chemoselective chlorination could be achieved under these mild conditions that maintained a low concentration of the transient chlorinating species. Moreover, regioselective chlorination or chlorinative dearomatization of 1-naphthols was also achieved depending on the use of different reaction conditions.

Acknowledgements

Financial support for this project was partially provided by JSPS.KAKENHI (15H05755, 15H05484, 18H01973), and the Program for Leading Graduate Schools: IGER Program in Green Natural Sciences (MEXT). We are grateful to the Kaneka Corporation for providing NaOCl·5H_2O.

Keywords: chlorination • dearomatization • oxidation • phenol • chemoselective • regioselective

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[16] The reaction of 1-naphthol using NaCl/Oxone afforded both *ortho*- and *para*-chlorinated products in similar yield. The use of $NaOCl{\cdot}5H_2O$ gave *ortho*-chlorinated and 2,4-dichlorinated products. On the other hand, unfortunately, the reactions of 1,1'-bi-2-naphthol and 5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-naphthol using both methods gave a complex reaction mixture. See Supporting Information for details.

10.1002/ejoc.201801063

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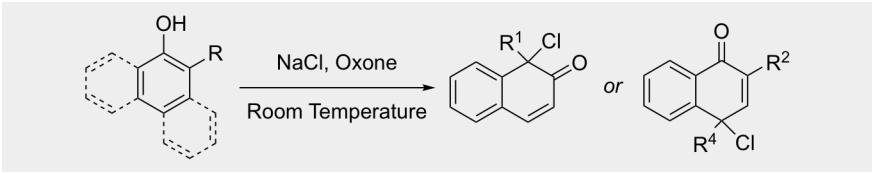

A practical and efficient chlorination of naphthols and phenols was developed using transient chlorinating species generated *in situ* from inexpensive sodium chloride and Oxone as a Cl source and oxidant, respectively, under mild conditions.

Chlorinative Dearomatization*

*Muhammet Uyanik, Naoto Sahara, Kazuaki Ishihara**

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Regioselective Oxidative Chlorination of Arenols Using NaCl and Oxone