EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: New in situ Formed I(III)-Based Reagent for the Electrophilic ortho-Chlorination of Phenols and Phenol-Ethers: the Use of PIFA-AlCl3 System

Authors: César R. Solorio-Alvarado, Pradip D. Nahide, Velayudham Ramadoss, Kevin A. Juárez-Ornelas, Yuvraj Satkar, Rafael Ortiz-Alvarado, Juan M. J. Cervera-Villanueva, Ángel J. Alonoso-Castro, Juan R. Zapata-Morales, Alan J. Ruiz Padilla, and Martha A Deveze-Álvarez

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701399

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701399

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201701399

WILEY-VCH

New *in situ* Formed I(III)-Based Reagent for the Electrophilic *ortho*-Chlorination of Phenols and Phenol-Ethers: the Use of PIFA-$AlCl_3$ System

Pradip D. Nahide,[a]& Velayudham Ramadoss,[a]& Kevin A. Juárez-Ornelas,[a] Yuvraj Satkar,[a] Rafel Ortiz-Alvarado,[a] Juan M. J. Cervera-Villanueva,[a] Ángel J. Alonso-Castro,[a] Juan R. Zapata-Morales,[a] Marco A. Ramírez-Morales,[a] Alan J. Ruiz-Padilla,[a] Martha A. Deveze-Álvarez,[a] and César R. Solorio-Alvarado*[a]

Abstract: A new and *in situ* formed reagent generated by mixing PIFA/$AlCl_3$ was introduced in the organic synthesis for the direct and highly regioselective *ortho*-chlorination of phenols and phenol-ethers. An efficient electrophilic chlorination for these electron rich arenes as well as the starting scope of the reaction are described herein. An easy, practical and open flask reaction allowed us to introduce a chlorine atom, which is a highly important functional group in organic synthesis. The reproducibility of our method has been demonstrated in gram-scale by carrying out the reaction in 6-bromo-2-naphthol. This halogenation reaction also proceeds in excellent conditions by first preparing the iodine(III)-based chlorinating reagent. Our new chlorinating reagent can be stored at least for two weeks at 4 ºC without losing its reactivity.

Introduction

Chlorinated compounds are ubiquitous in nature. We can find them in naturally occurring compounds,[1] agrochemicals,[2] synthetic intermediates,[3] and materials science[4] among others. Specifically, chlorophenols are a relevant class of substrates, they are very important in the industrial and pharmacological area[5] (**Figure 1**).

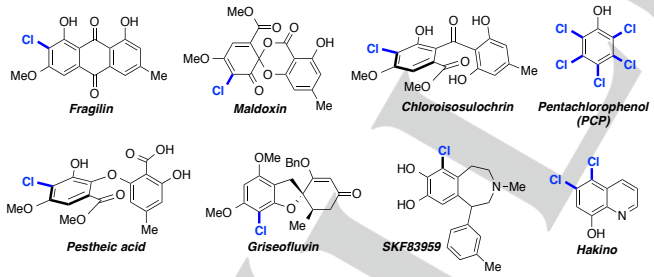


Figure 1. Relevance of chlorophenol core.

The synthesis of aryl chlorides has been widely described. In big scale, the industrial chlorination uses chlorine gas, however, it is hazardous and special attention is required.[6] In the academic organic synthesis-laboratory, some chlorination procedures for aryls including phenols and its derivatives are available. A broadly described protocol implies the use of *N*-chlorosuccinimide in DMF,[7] CCl_4[8] or HCl-H_2O[9] (**Scheme 1A**). However, due to the relative low electrophilicity at chlorine-atom, a reagent-activation is commonly necessary by using Lewis bases (Ph_3PS),[10] strong Brönsted acids (TfOH),[11] metallic Lewis acids ($ZrCl_4$,[12] Ru(III),[13] $Pd(OAc)_2$,[14] $PdCl_2$ or $CuCl_2$,[15] CuX_2-$Pd(OAc)_2$[16]), non-metallic Lewis acids (TMS-Cl[17]) or oxidants (CAN,[18] CAN-HCl[19]) in order to have an electrophilic enough chlorine atom to be attacked by the arene. On the other hand significant efforts have been placed to develop more mild and reactive chlorination reagents such as trichloroisocyanuric acid (TCICA), 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), 2,2,6,6-tetramethylpiperidine (TMPH) /SO_2Cl_2,[20] Zeolites[21] and nanocrystalline Ceria[22] (**Scheme 1B**).

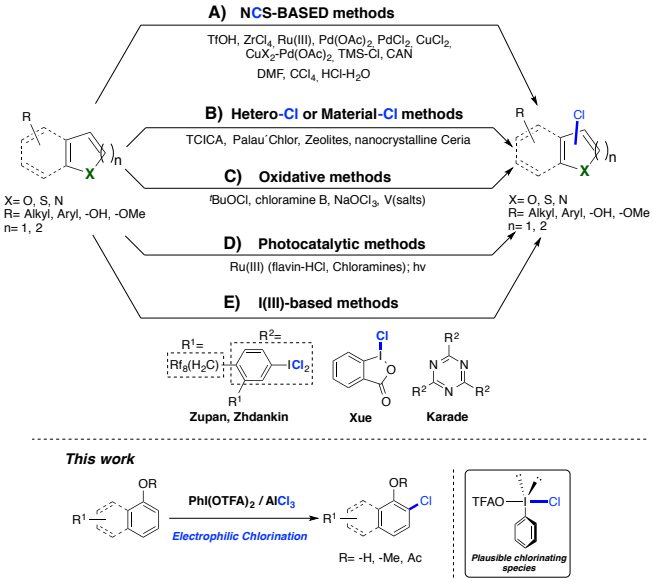
Recently Baran *et al* described an elegant and broad method for heteroarenes-chlorination. This approach uses the guanidine-base reagent (Palau´Chlor®).[23] On the other hand are worth to mention the strong-oxidative chlorinating methods, which use ^{t}BuOCl,[24] Chloramine B, [25] $NaOCl_3$/HCl/AcOH[26] or divanadium salts (with H_2O_2[27] or Selectfluor®[28]) (**Scheme 1C**). The arene chlorination by photocatalysis with flavin hydrochloride,[29] or chloramines in presence of Ru(III) complexes[30] are also valuable alternatives (**Scheme 1D**). Finally, the chlorination of arenes including phenols and phenol-ethers by using hypervalent iodine (III)-based reagents were initially described by Zupan and Zhdankin.[31] Also Karade[32] and Xue[33] described a chlorination of some arenes by using iodine (III)-based reagents (**Scheme 1E**).

Even though a vast amount of chlorinating procedures for arenes are available, all of them show relevant disadvantages. For example the reagent activation or preparation, costly acquisition, or polymerization. In regards to the iodine (III)-based chlorinating methods, the low solubility is an important drawback.

Herein we described the first iodine (III)-based chlorinating reagent generated *in situ* by the easy mix of bis[(trifluoroacetoxy)iodobenzene] (PIFA) and $AlCl_3$. The reagent is totally soluble in the organic reaction solvent and is used in the same reaction flask. The use of inexpensive reagents and the fast *in situ* reagent-formation are the main advantages of our procedure over those previously described (**Scheme 1**). We apply this protocol to the direct chlorination of some phenols and phenol-ethers, which are described below.

[a] Universidad de Guanajuato, Cerro de la Venada S/N, 36040, Guanajuato, Gto., México. Departamento de Química, División de Ciencias Naturales y Exactas, Campus Guanajuato.
E-mail: csolorio@ugto.mx
& These two authors contributed equally.

Supporting information for this article is given via a link at the end of the document.

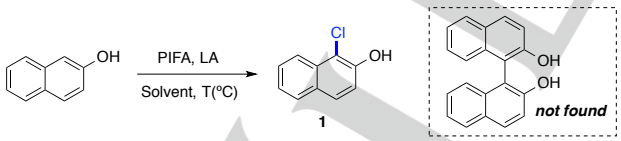


Scheme 1. Different chlorinating methods for arenes.

Results and Discussion

The total synthesis of dimeric naturally occurring compounds is one of the research interests in our group. We are currently carrying out the synthesis of some these alkaloids. While searching for a new route to dimeric natural products via the dimerization of naphthol using PIFA and a Lewis acid, we surprisingly observed selective halogenation at the alpha position rather than dimerization with $AlCl_3$. In such a way that the development of the present chlorinating method was the result of a Lewis acid screening, looking for a new ligand-activation procedure[34] in the PIFA-mediated oxidative dimerization of phenols[35] (**Table 1**).

Table 1. Ligand screening and optimization in the PIFA-$AlCl_3$ mediated chlorination of 2-naphthol.



Entry	LA (Equiv)	Solvent	T (ºC)	Time (h)	Yield %
1	$BF_3{\cdot}Et_2O$ (1.0)	DCM	-78	2	n. r.
2	$BF_3{\cdot}Et_2O$ (1.0)	DCM	23	1	c. m.
3	$GaCl_3$ (1.0)	DCM	23	0.5	dec.
4	$AlCl_3$ (1.0)	DCM	23	3	60[a]
5	$AlCl_3$ (2.0)	DCM	23	2	63[a]
6	$AlCl_3$ (1.0)	CH_3Cl	23	3	30[b]
7	$AlCl_3$ (1.5)	$CHCl_3$	23	2.5	40[b]
8	$AlCl_3$ (2.0)	$CHCl_3$	23	2.5	41[b]
9	$AlCl_3$ (1.0)	MeCN	23	2	22[b,c]
10	$AlCl_3$ (1.5)	MeCN	23	2	51[b,d]
11	$AlCl_3$ (2.4)	MeCN	23	2	63[b,e]

All the reactions were carried out by using 1 equiv of PIFA. The reported yields are the average of two runs. [a] Very complicated chromatography purification; [b] Isolated yield; [c] 60% of starting material recovered; [d] 35% of starting material recovered; [d] 1.2 equiv of PIFA were used. LA = Lews acid; n.r.= no reaction was observed; c.m.= complex reaction mixture; dec.= decomposition of starting material.

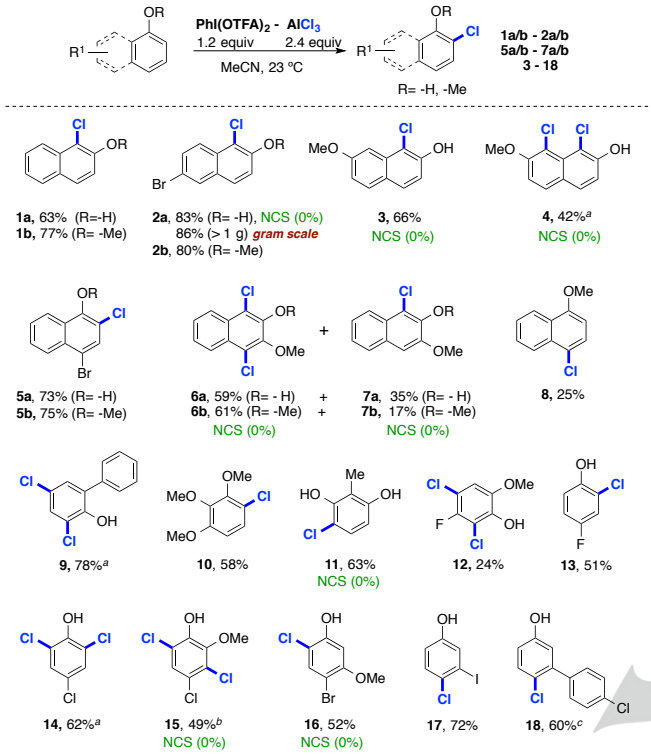
After carrying out some reactions and testing different Lewis acids, we could not find the desired 2-naphthol dimer. Instead, we found **1** as the product of the chlorination reaction at the α-position (**Table 1**). The starting screening by using $BF_3{\cdot}Et_2O$ gave a complex mixture or the reaction did not proceed (Entries 1 and 2). The use of $GaCl_3$ only showed the decomposition of the starting material (Entry 3). Surprisingly, by using $AlCl_3$ at 23 ºC, we observed the formation of 1-chloro-2-naphthol **1** in a good 60% as the main product (Entry 4). The formation of the corresponding dimer was not observed.

At this point, we rationalized that the only source of chlorine atoms comes from the Lewis acid ($AlCl_3$). Thus, this necessarily implicates the oxidation of Cl^- by the iodine (III) reagent to give an electrophilic "Cl^+" equivalent. Subsequently, the 2-naphthol reacted and led to **1**. To the best of our knowledge, this is the first report that describes and supports the oxidation of chlorine atoms in $AlCl_3$ by an iodine (III) reagent. With this hypothesis, we focused our attention to develop a new procedure for direct chlorination of phenols by using this non-described PIFA-$AlCl_3$ system.

The next step consisted in testing two equivalents of $AlCl_3$ to increase the amount of chlorine atoms. We found a shorter reaction time along with a slightly increased yield (Entry 5). Nevertheless, a complex mixture of reaction was observed in this solvent (dichloromethane). The use of chloroform for screening different $AlCl_3$ equivalents produced moderate yields (30-41%) at 23 ºC in 2.5-3 h (Entries 6-8). Finally, the screening of 1, 1.5 and 2.4 equivalents of $AlCl_3$ in acetonitrile (Entries 9-11), gave the best yield (63%). Thus, the optimized conditions were 2.4 equivalents of $AlCl_3$ at 23 ºC in only 2 hours of reaction (Entry 11). Additionally, this reaction works at room temperature, in short reaction times (2-3 h) and open flask conditions.

With this new reagent for the chlorination of 2-naphthol and with its optimized conditions, we proceed to test the scope of the protocol over different phenols. We also decided to test the procedure in some phenol-ethers (**Scheme 2**).

Scheme 2. Scope for the chlorination of phenols, naphthols and naphthol-ethers by using the PIFA-$AlCl_3$ system.



The reactions were carried out by using 1.2 equiv of PIFA and 2.4 equiv of $AlCl_3$. [a] 1.8 equiv of PIFA and 3.6 equiv of $AlCl_3$ were used to get a single compound since an *o/p* mixture was observed under the optimized conditions. [b] 2.4 equiv of PIFA and 4.8 equiv of $AlCl_3$ were used to get a single compound since an *o/p* mixture was observed under the optimized conditions. [c] The *ortho*-regioisomer was obtained in 25% (see SI for full details). The new formed carbon-chlorine bond formed is highlighted in blue color.

Some naphthols and phenols containing either electron-donating or electron-withdrawing groups were tested. The 2-napthol, as well as its methyl-ether, were regioselectively chlorinated in *ortho* position in excellent 63% and 77% yields, respectively (**1a-b**). The electronegativity of the bromine atom in the naphthol nucleus did not affect the reaction. We found a 83% and 73% of yield (**2a**, **5a**, respectively) for the chlorination of 6-bromo-2-naphthol and 4-bromo-1-naphthol. In fact, the gram-scale reaction proceeded in good 86% for **2a**. Its corresponding methyl-ethers also proceed in 80% and 75% of yield (**2b**, **5b**). On the other side, the electron-rich 7-methoxy-2-naphthol gave a good 66% yield for the monochlorinated (**3**) or 42% for bichlorinated (**4**) products.[36] An additional example on 3-methoxy-2-naphthol as starting material gave a separable mixture of mono and bichlorinated naphthols **6a** (59%) and **7a** (35%), in that order. The methyl-ether analogues **6b** (61%) and **7b** (17%) were also obtained and separated without any problem by column chromatography. Some attempts to control the mono- or bichlorination processes led to complex reaction mixtures. For completing the series of naphthols, 1-methoxynaphthalene was chlorinated in a modest 25% of yield at *para* position respect to the methoxy group.

Regarding to the phenol derivatives, those containing electron-donating groups like phenyl (**9**), methoxy (**10**) or methyl (**11**) were *ortho*-chlorinated from good to excellent yields (58%-78%). The presence of any halogen in the phenol core was well tolerated by our procedure. Thus, 5-fluoro-2-methoxyphenol and 4-fluorophenol were chlorinated in 24% and 51% of yield (**12** and **13**, respectively). The chlorophenols **14** and **15**[37] were also obtained in 62% and 49% starting from 4-chlorophenol and 5-chloro-2-methoxyphenol respectively. The 4-bromo-3-methoxyphenol gave rise to bromophenol **16** in moderate 52%. Finally, the 3-iodophenol and 3-(4-chlorphenyl)phenol were chlorinated in excellent 72% and 60%, yielding **17**[38] and **18** at *para* position respect to the hydroxyl group.

The examples **8**, **17** and **18** were exceptions to the general *ortho*-chlorination reaction observed for this series. All of the reactions were completed under very mild conditions of temperature (23 ºC), in short periods of time and in open flask.

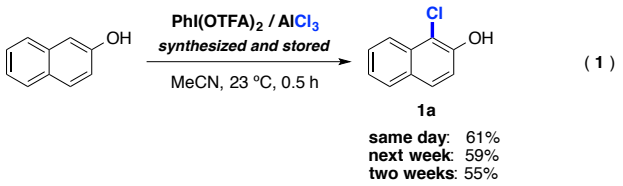
Thereby, the *ortho*-chlorination is a remarkable aspect in our method that we discuss as follows. The naphthols **1a/b, 2a/b, 5a/b** to **7a/b** were obtained as regioselective *ortho*-chlorinated compounds, which match with those previously described.[39] Compound **9** shows a coupling of *J*=2.5 Hz at 7.22 and 7.24 ppm, consistent with *meta* coupling at the benzene ring which contains the chlorine atoms. Therefore, this suggessts an *ortho*-chlorinated structure as shown in **Scheme 2**. The compounds **10** and **11** have a *J*= 8.5 Hz at 7.06 and 6.62 ppm, which implies an *ortho* coupling as well as the chlorination for both arenes. Aromatic compounds **12** to **16** showed mono- or bichlorination from 24% to 62% of yield. In a general way, all of these examples were chlorinated in *ortho* and *ortho, para* positions respect to the hydroxyl group.

In order to support the *ortho-selectivity* in our protocol is important to mention that: 1) compound **9** showed a mixture of *ortho* and *para* regioisomers in 3:1[40] (see SI for full details). The *para* product was observed as the minor regioisomer. Then, an additional optimization was carried out to get a single bichlorinated product (**Scheme 2**); 2) the bis-*ortho*-substituted naphthols with the hydroxyl group in the middle of both substituents ***did not react*** even when heating at 80 ºC for 12 h (see **Scheme 3**). The former observation alludes to an initial ***ortho-chlorination*** instead to the known *para* reactivity, which fully supports the *ortho*-regioselectivity observed in our protocol. However, compounds **17** and **18** were exceptions to the aforementioned regioselectivity.

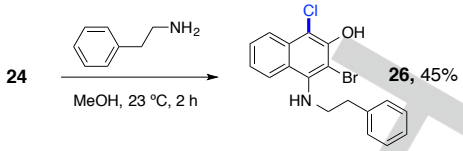
A broad set of experiments in synergy with theoretical calculations is necessary to generalize our protocol and find out a detailed mechanism of reaction, which fully explain the *ortho*/*para* ratios. At this point, the series of examples herein described demonstrated a reaction with initial *ortho*-selectivity.

One notable aspect in our work is the remarkable reactivity of our *in situ* formed reagent. It was effective in the chlorination of some naphthols and phenols randomly chose like **2a**, **3**, **4**, **6b**, **7b**, **11**, **15** and **16** for which NCS totally failed. This observation broadly supports the advantage of our procedure over those NCS-based methodologies.

Also, we found that after storing our chlorinating reagent by two weeks at 4 ºC,[41] it essentially did not lose its reactivity (**Ec 1**).



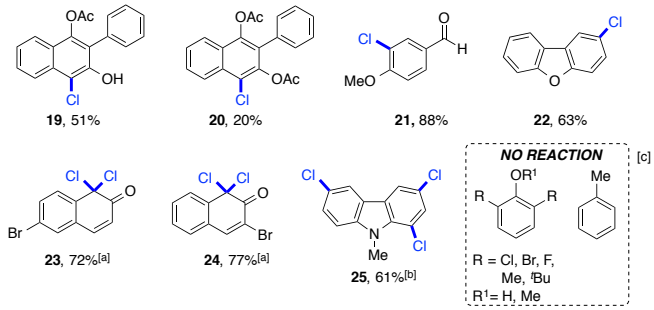
(1)



(2)

On the other hand, for testing additional functional group-tolerance and limitations in our protocol, we set up some more elaborated phenols and a heterocycle (**Scheme 3**).

Scheme 3. Scope and limitations in the arene chlorination by using the PIFA-$AlCl_3$ system.



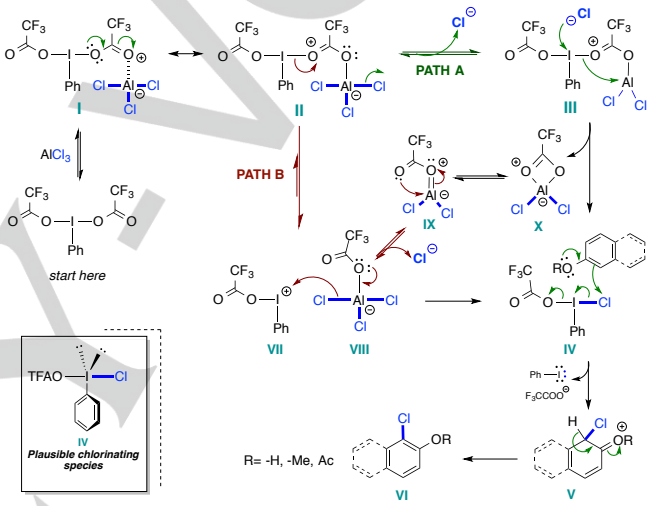
The reactions were carried out by using 1.2 equiv of PIFA and 2.4 equiv of $AlCl_3$. [a] 2.4 equiv of PIFA and 4.8 equiv of $AlCl_3$ were used. [b] 4 equiv of PIFA and 6 equiv of $AlCl_3$ were used; the tetra chlorinated derivative was obtained in 13% (see SI for full details). [c] The chlorination reaction did not proceed neither at 23 ºC nor 80 ºC for 12 h. The new carbon-chlorine bond formed is highlighted in blue color.

The 3-hydroxy-2-phenylnaphthalen-1-yl acetate was regioselectively *ortho*-chlorinated to the hydroxy group to give **19** in moderated 51% yield (**Scheme 3**). The analogue biacetylated 1,3-naphthodiol was also *ortho*-chlorinated respect to the 3-acetoxy group yielding **20** in 20%. These examples expand the scope of our procedure at the hydroxyl group of naphthol by including the acetyl functionality. An arene containing formyl group like *p*-anisaldehyde was also chlorinated giving an excellent 88% of yield to get **21**. The dibenzofuran was chlorinated in *para* position to the oxygen to obtain **22** in 63%. Even though this example is out of the observed regioselectivity for our developed procedure, it can be applied in principle to *O*-heterocyclic systems. On the other hand, looking for conditions toward bichlorination of 6-bromo-2-naphthol and 3-bromo-2-napthol, we found a very attractive chlorinative dearomatization, which yields *gem*-chlorohydronaphthalenes. This reaction proceeds in excellent yields of 72% for **23** and 77% for **24**. Finally the scope at *N*-heterocycles was demonstrated by the trichlorination of the *N*-methylcarbazole, giving rise to **25** in 61% of yield.

According to the literature,[42] compounds such as **23** and **24** are starting materials in the synthesis of highly substituted anilines. Thus, in order to test the application of the synthesized compounds by our procedure, we decide to use **24** in the synthesis of a highly functionalized aniline **26** (**Ec 2**).

Thereby aniline **24** was successfully synthesized in 45% of yield and in only two hours of reaction.

Finally, according to the experimental observations we rationalize a plausible chlorinating species like **IV** to explain the **C-Cl** bond formation in the chlorination reaction. Thus, we propose the following mechanism of reaction (**Scheme 4**).



Scheme 4. Mechanistic proposal for the *ortho*-chlorination reaction observed in our developed method.

PIFA coordinates to $AlCl_3$ to get **I**, which is in resonance with **II**. Two possible pathways are envisioned. The pathway A implies the release of a chloride anion giving rise to **III**. Thus the released chloride attacks to the electrophilic iodine center to produce aluminate **X** and the intermediate **IV**. This is in fact, the plausible reagent, proposed as the *in situ* formed chlorinating species. Afterwards, the naphthol carries out a regioselective *ortho* attack to the chlorine atom producing the intermediate **V**. Finally, the loss of a proton aromatizes the arene and yields the *ortho*-chlorinated phenol. On the other hand, pathway B starts with dissociation of **II** giving rise to **VII** and **VIII**. This is in equilibrium with **IX** by chloride anion loose which attacks to **VII** producing the proposed chlorinating species **IV**. The rest of the mechanism proceeds as previously described by generation of intermediate **V** and final phenol **VI**.

Conclusions

In summary, we have developed a new procedure for the *ortho*-selective chlorination of phenols and phenol-ethers. Our protocol takes place under very mild conditions, short reaction times, in good to excellent yields and in open flask. The method scope includes the methyl and acetyl groups at the oxygen of the phenol and was applied to the chlorination of the dibenzofuran and *N*-methylcarbazole. This novel protocol has an I(III)-based reagent which is formed *in situ* and contains the chlorine atom attached to the hypervalent iodine center. Our theoretical calculations support the formation of the structure **IV** (**scheme 3**) as the plausible chlorinating species. Finally, to the best of our knowledge, this is the first method that oxidizes the chlorine atoms coming from $AlCl_3$ and they are used as an electrophilic source of chlorine in the chlorination of phenols. All of the previous features described in our protocol represent an important advantage over the rest of chlorination procedures that have been previously described.

Experimental Section

***General procedure for chlorination**:* A 25 ml dry round bottom flask was charged with PIFA (1.2 equiv) and dry acetonitrile [0.33 *M*] at 25 ºC. Afterwards, $AlCl_3$ (2.4 equiv) was suspended and the mixture was stirred for 10 min. A yellowish precipitate appears and then the corresponding phenol derivative (1 equiv) was added to the mixture. The reaction allows proceeding for 2-12 h following the advance until fully starting material consumption judging by TLC. The reaction mixture was extracted with EtOAc (3x10 mL) and the water (10 mL). The organic extracts were collected, dried over anhydrous sodium sulfate, filtered, and concentrated in *vacuo* to remove solvent. The product was purified by column chromatography on silica gel (100-200 mesh) with EtOAc/hexane system.

1-chloronaphthalen-2-ol (**1a**). The following compound was obtained according to the general procedure for chlorination by using 2-napthtol in 63% yield as a colourless liquid. IR (cm^{-1}): 3496, 3393, 3061, 2962, 1625, 1600, 1468, 1195, 1150,809, 746. ^1H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.9 Hz, 1H), 7.59 (t, *J* = 8.8 Hz ,1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.27 (s, 1H), 5.90 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.3, 131.0, 129.4, 128.4, 128.1, 127.5, 124.1, 122.7, 117.2, 113.3. HRMS (ESI+) calcd. for $C_{10}H_7ClO$ [M+H]: 179.0185, found 179.0111. The spectroscopic data match with those previously described. [43]

1-chloro-2-methoxynaphthalene (**1b**). The following compound was obtained according to the general procedure for chlorination by using 2-methoxynaphtalene in 77% yield as with solid. m.p. 47- 49 ºC, IR (cm^{-1}): 3051, 2975, 1625, 1504, 1269, 1067, 801. ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.5 Hz, 1H), 7.80 (t, *J* = 7.0 Hz, 2H), 7.58 (t, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 8.0 Hz 1H), 7.32 (d, *J* = 9.0 Hz, 1H,) 4.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.5, 131.8, 129.5, 128.0, 127.9, 127.4, 124.3, 123.4, 116.9, 113.7, 57.0. HRMS (ESI+) calcd. for $C_{11}H_9ClO_2$ [M+H]: 193.0342, found 193.0424. The spectroscopic data match with those previously described. [44]

6-bromo-1-chloronaphthalen-2-ol (**2a**)**.** The following compound was obtained according to the general procedure for chlorination by using 6-Bromo-2-napthol in 83% yield as a withe solid. m.p. 84-86 °C. IR (KBr, cm^{-1}) 3423, 1621, 1567, 1589, 1498, 1464, 1404, 1381, 1353, 1338, 1198, 1183, 1148, 1132, 1066, 1000, 938, 897, 805, 556, 514. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 9.9 Hz, 2H), 7.51 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 1H), 5.84 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.7, 130.9, 130.5, 130.2, 129.7, 127.6, 124.7, 118.5, 118.1, 113.6. HRMS (ESI-): calcd. for $C_{10}H_5BrCl_2O$ [M-H]: 255.9291, found 254.1203. **Gram scale reaction.** This scalable reaction was carried out by using PIFA (2.45 g, 1.2 euqiv), $AlCl_3$ (1.52 g, 2.4 equiv) and 6-Bromo-2-napthol (1.06 g, 1 equiv). The reaction was completed in 3 h and purified by column chromatography to yield 1.05 g of **2a** (86%). The spectroscopic data match with those previously described. [45]

6-bromo-1-chloro-2-methoxynaphthalene (**2b**). The following compound was obtained according to the general procedure for chlorination by using 2-bromo-6-methoxynaphthalene in 80% yield as white solid. m.p. 76-78°C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 9.1 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.55 (dd, *J* = 9.1, 1.9 Hz, 1H), 7.25 (d, *J* = 9.1 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.0, 130.9, 130.6, 130.6, 130.0, 127.1, 125.5, 118.3, 117.3, 114.8, 57.1. The spectroscopic data match with those previously described. [46]

1-chloro-7-methoxynaphthalen-2-ol (**3**). The following compound was obtained according to the general procedure for chlorination by using 7-methoxy-2-napthol in 66% yield as a withe solid. m.p. 68-70 °C. IR (KBr, cm^{-1}) 3391, 2934, 1517, 1623, 1427, 1443, 1400, 1280, 1249, 1123, 1188, 1023, 1007, 837, 803, 603, 548, 523. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.8 Hz, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.33 (s, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 5.90 (s, 1H), 3.97 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.4, 150.0, 132.6, 130.0, 128.2, 124.8, 116.7, 114.6, 112.6, 101.7, 55.5. The spectroscopic data match with those previously described. [47]

1,8-dichloro-7-methoxynaphthalen-2-ol (**4**). The following compound was obtained according to the general procedure for chlorination by using 7-methoxy-2-napthol in 42% yield as a dark red solid. m.p. 84-86°C. IR (KBr, cm^{-1}): 3474, 1618, 1514, 1462, 1438, 1358, 1325, 1285, 1246, 1222, 1138, 1093, 963, 894, 830, 794, 761, 729, 553, 529, 453. ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, *J* = 9.0 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 2H), 6.44 (s, 1H), 4.01 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.3, 152.2, 129.6, 129.2, 128.9, 126.6, 115.5, 111.5, 111.4, 57.1. The spectroscopic data match with those previously described. [48]

4-bromo-2-chloronaphthalen-1-ol (**5a**). The following compound was obtained according to the general procedure for chlorination by using 4-bromo-1-naphtol in 73% yield as withe solid. m.p. 90-92 ºC. IR (KBr cm^{-1}): 3360, 2923, 1716, 1518, 851,753. ^1H NMR (500 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.2, 7.8 Hz, 1H), 8.17 (dd, *J* = 8.5, 8.2 Hz, 1H), 7.71-7.51 (m, 3H), 6.0 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 128.9, 128.0, 127.7, 127.0, 126.9, 126.8, 125.5, 124.4, 122.5, 122.5. HRMS (ESI+) calcd. for $C_{10}H_6BrClO$ [M+H]: 256.9108, found 256.5110. The spectroscopic data match with those previously described. [49]

4-bromo-2-chloro-1-methoxynaphthalene (**5b**). The following compound was obtained according to the general procedure for chlorination by using 4-bromo-1-methoxynaphtalene in 75% yield as a colourless solid. m.p. 53- 56 ºC. IR (KBr cm^{-1}): 2917, 2849, 1578, 1449, 1365, 1247, 1211, 979, 691. ^1H NMR (500 MHz, $CDCl_3$): δ 8.17 (m, 2H), 7.78 (s, 1H), 7.62(m, 2H), 4.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 151.7, 131.8, 130.7, 129.7, 127.5, 127.7, 127.5, 122.9, 122.4, 117.7, 61.5. HRMS (ESI+) calcd. for $C_{11}H_8BrClO$ [M+K]: 310.5380, found 310.1464.

1,4-dichloro-3-methoxynaphthalen-2-ol (**6a**). The following compound was obtained according to the general procedure for chlorination by using 3-methoxy-2-napthol in 59% yield as withe solid. m.p. 128-130 ºC. ^1H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz,

2H), 7.58 (dd, *J* = 10.7, 0.9 Hz, 1H), 7.51 (dd, *J* = 10.7, 0.9 Hz, 1H), 6.29 (s, 1H), 4.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.8, 144.2, 128.6, 127.3, 126.3, 125.6, 124.2, 123.2, 122.3, 113.1, 61.4. HRMS (ESI-) calcd. for $C_{11}H_8Cl_2O_2$ [M-H]: 240.9901, found 240.9703.

1,4-dichloro-2,3-dimethoxynaphthalene (**6b**).The following compound was obtained according to the general procedure for chlorination by using 2,3-dimethoxynaphtalene in 61% yield as a colourless solid. m.p. 48-50 ºC. IR (KBr cm^{-1}): 3051, 2975, 1625, 1504, 1269, 1067, 801. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* = 4.4 Hz, 2H), 7.59 (d, *J* = 4.4 Hz, 2H), 4.03 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.2, 128.7, 126.9, 124.4, 123.2, 61.3. HRMS (ESI+) calcd. for $C_{12}H_{10}Cl_2O_2$ [M+H]: 257.0058, found 257.0151. The spectroscopic data match with those previously described. [50]

1-chloro-3-methoxynaphthalen-2-ol (**7a**). The following compound was obtained according to the general procedure for chlorination by using 3-methoxy-2-naphtol in 35% yield as a colourless solid. m.p. 62-64 ºC. IR (KBr cm^{-1}): 3415, 2920, 1633, 1462, 1017, 820. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.47 (dd, *J* = 13.7,1.2 Hz, 1H), 7.40 (dd, *J* = 12.2, 1.1 Hz, 1H), 7.09 (s, 1H), 6.24 (s, 1H), 4.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.1, 142.1, 128.6, 126.9, 126.8, 125.2, 124.7, 122.9, 113.5, 104.8, 56.1. HRMS (ESI+) calcd. for $C_{11}H_9ClO_2$ [M+H]: 209.0291, found 209.0383.

1-chloro-2,3-dimethoxynaphthalene (**7b**). The following compound was obtained according to the general procedure for chlorination by using 2,3-dimethoxynaphtalene in 17% yield as a yellowish liquid. IR (KBr cm^{-1}): 3068, 2941, 1588, 1456, 1396, 1244, 994, 746. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 4.0 Hz, 1H), 7.72 (d, *J* = 6.7 Hz, 1H), 7.47 (d, *J* = 4.6 Hz, 2H), 7.13 (s, 1H), 4.0 (s, 3H), 3.98 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.4, 145.8, 131.1, 126.7, 126.6, 126.1, 124.8, 124.3, 124.0, 106.0, 60.9, 55.9. HRMS (ESI+) calcd. for $C_{12}H_{11}ClO_2$ [M+H]: 223.0448, found 223.0544.

1-chloro-4-methoxynaphthalene (**8**). The following compound was obtained according to the general procedure for chlorination by using 1-methoxynaphtalene in 25% yield as slightly yellow oil. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.4 Hz, 2H), 8.20 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.2 Hz, 2H), 4.00 (s, 6H). ^{13}C RMN (126 MHz, $CDCl_3$): δ 154.8, 131.4, 127.6, 126.8, 126.1, 125.9, 124.4, 123.4, 122.6, 104.0, 55.8. The spectroscopic data match with those previously described. [51]

3,5-dichloro-[1,1'-biphenyl]-2-ol (**9**). The following compound was obtained according to the general procedure for chlorination by using [1,1'-biphenyl]-2-ol, 1.8 equiv of PIFA and 3.6 equiv of $AlCl_3$ in 78% yield as white solid. m.p. 38-40 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.0 Hz, 2H), 7.46 (dd, *J* = 10.1, 4.7 Hz, 2H), 7.40 (t, *J* = 6.7 Hz, 1H), 7.34 (d, *J* = 2.5 Hz, 1H), 7.22 (d, *J* = 2.5 Hz, 1H), 5.66 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.4, 136.0, 130.8, 129.3, 129.1, 128.8, 128.2, 127.8, 125.5, 121.3. HRMS (ESI-) calcd. for $C_{12}H_7Cl_2O$ [M-H]: 236.9879, found 236.9629.

1-chloro-2,3,4-trimethoxybenzene (**10**). The following compound was obtained according to the general procedure for chlorination by using 1,2,3-trimethoxybenzene in 58% yield as colourless liquid. IR (KBr cm^{-1}): 2942, 2836, 1594, 1476, 1253, 1000, 777. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.8 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.7, 150.0, 143.6, 123.9, 119.9, 107.8, 61.12, 61.11, 56.2. HRMS (ESI+) calcd. for $C_9H_{11}ClO_3$ [M+H]: 203.0397, found 203.0488. The spectroscopic data match with those previously described. [52]

4-chloro-2-methylbenzene-1,3-diol (**11**). The following compound was obtained according to the general procedure for chlorination by using 2-methylbenzene-1,3-diol in 63% yield as withe solid. m.p. 34-36 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.01 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 8.7 Hz, 1H), 5.66 (s, 1H), 5.31 (s, 1H), 2.19 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.6, 150.0, 125.5, 112.0, 111.6, 108.0, 8.8.

2,5-dichloro-3-fluoro-6-methoxyphenol (**12**). The following compound was obtained according to the general procedure for chlorination by using 3-fluoro-6-methoxyphenol in 24% yield as colourless liquid. IR (KBr cm^{-1}): 3510. 3031, 2943, 1597, 1482, 1397, 1269, 1050, 833, 853. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H), 5.93 (s, 1H), 3.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.6, 142.1, 123.7, 123.6, 119.8, 110.7, 56.6. HRMS (ESI+) calcd. for $C_7H_5Cl_2FO_2$ [M+]: 209.9651, found 209.9085

2-chloro-4-fluoro-phenol (**13**). The following compound was obtained according to the general procedure for chlorination by using 4-fluoro-phenol in 51% yield as a with solid. m.p. 51-53° C. IR (KBr, cm^{-1}): 3515, 3062, 1600, 1495, 1410, 1321, 1259, 1203, 1070, 906, 861, 829, 783, 588. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (dd, *J* = 7.9, 2.9 Hz, 1H), 6.97 (dd, *J* = 9.0, 5.1 Hz, 1H), 6.91 (ddd, *J* = 9.0, 7.9, 2.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.4 (d, *J* = 241.7 Hz), 148.0 (d, *J* = 2.8 Hz), 119.9 (d, *J* = 10.9 Hz), 116.7 (d, *J* = 8.4 Hz), 116.0 (d, *J* = 26.4 Hz), 115.4 (d, *J* = 22.9 Hz). The spectroscopic data match with those previously described.[53]

2,4,6-trichlorophenol (**14**). This compound was synthesized according to the general procedure for chlorination by using 4-chloro-phenol, 1.8 equiv of PIFA and 3.6 equiv of $AlCl_3$ in 62% yield as a withe solid. m.p. 69-71 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (s, 2H), 5.80 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): 121.7, 125.5, 128.2, 147.0. The spectroscopic data match with those previously described.[54]

2,3,4-trichloro-6-methoxyphenol (**15**). The following compound was obtained according to the general procedure for chlorination by using 4-chloro-6-methoxyphenol 2.4 equiv of PIFA and 4.6 equiv of $AlCl_3$ in 49% yield as a brownish solid. m.p. 30-32 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H), 5.92 (s, 1H), 3.92 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.7, 142.1, 123.7, 123.6, 119.7, 110.7, 56.6. The spectroscopic data match with those previously described.[55]

4-bromo-2-chloro-5-methoxyphenol (**16**). The following compound was obtained according to the general procedure for chlorination by using 4-bromo-5-methoxyphenol in 52% yield as a brownish solid. m.p. 41-43 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (s, 1H), 6.62 (s, 1H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.9, 151.6, 131.9, 111.4, 102.0, 100.4, 56.5.

2-Chloro 3-iodophenol (17). This compound was synthesized according to the general procedure for chlorination by using 3-iodophenol in 72% yield as white solid. m.p. 78-80 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (d, *J* = 2.8 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.5, 130.1, 129.6, 127.0, 117.0, 98.0. The spectroscopic data match with those previously described.[56]

4-chloro-3-(4-chlorophenyl)phenol (18). This compound was synthesized according to the general procedure for chlorination by using 3-(4-chlorophenyl)phenol in 60% yield as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 6.79 (s, 1H), 6.78 (d, *J* = 9.0 Hz, 2H), 4.96 (bs, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.5, 140.6, 137.7, 134.0, 131.2, 130.9, 128.5, 124.1, 118.2, 116.1.

4-chloro-3-hydroxy-2-phenylnaphthalen-1-yl acetate (**19**). The following compound was obtained according to the general procedure for chlorination by using 3-hydroxy-2-phenylnaphthalen-1-yl acetate in 51% yield as slightly yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.1, 147.5, 143.9, 132.3, 130.8, 130.1, 128.6, 128.5, 128.3, 125.1, 123.6, 123.3, 123.2, 122.1, 112.1, 20.47. HRMS (ESI+) calcd. for $C_{18}H_{14}ClO_3$ [M+H]: 311.0480, found 311.0553.

4-chloro-2-phenylnaphtalene-1,3-diyl acetate (**20**). The following compound was obtained according to the general procedure for chlorination by using 2-phenylnaphtalene-1,3-diyl acetate in 20% yield as pale yellow oil. ^{1}H RMN (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.5 Hz, 2H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.67 (t, *J* = 7.1 Hz, 2H), 7.59 (t, *J* = 7.1 Hz, 2H), 7.45 – 7.37 (m, 6H), 7.32 (d, *J* = 8.2 Hz, 4H), 2.07 (s, 6H), 2.03 (s, 6H). ^{13}C RMN (126 MHz, $CDCl_3$): δ 168.7, 168.2, 143.81, 143.3, 132.6, 130.9, 130.0, 129.9, 128.3, 128.2, 127.4, 126.5, 124.9, 122.3, 122.2, 115.5, 29.9, 20.4. HRMS (ESI+) calcd. for $C_{20}H_{16}ClO_4$ [M+H]: 355.0737, found 355.0726.

3-chloro-4-methoxybenzaldehyde (**21**) The following compound was obtained according to the general procedure for chlorination by using 4-methoxybenzaldehyde in 88% yield as faint yellow solid. m.p. 42-44 °C. IR (KBr, cm^{-1}) 1697, 1597, 1568, 1504, 1315, 1276, 1256, 1199, 1059, 1013, 894, 818, 714, 687, 638, 616. 556. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.78 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 4.00 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.8, 160.0, 131.4, 130.6 130.5, 123.9, 111.8, 56.6. The spectroscopic data match with those previously described.[57]

2-chlorodibenzo[*b, d*]furan (**22**). The following compound was obtained according to the general procedure for chlorination by using dibenzofuran in 63% yield as withe solid. m.p. 99-101 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 – 7.89 (m, 4H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.51 – 7.47 (m, 4H), 7.41 (dd, *J* = 8.3, 1.7 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.9, 154.6, 128.4, 128.1, 128.0, 127.30, 123.2, 120.1, 120.6, 113.1, 112.8, 112.0. The spectroscopic data match with those previously described.[58]

6-bromo-1,1-dichloronaphthalen-2(1*H*)-one (**23**). The following compound was obtained according to the general procedure for chlorination by using 6-Bromo-2-napthol in 72% yield as orange solid. m.p. 40-42 °C. IR (KBr, cm^{-1}) 1688, 1582, 1553, 1481, 1308, 1281, 1236, 1198, 1080, 926, 890, 792, 790, 693, 646, 563. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.48 (s, 1H), 7.36 (d, *J* = 9.8 Hz, 1H), 6.39 (d, *J* = 9.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 185.3, 143.3, 139.5, 134.1, 132.1, 131.2, 128.7, 124.9, 124.0, 79.9. HRMS (ESI-): calcd. for $C_{10}H_5BrCl_2O$ [M-H]: 288.8823, found 288.2923.

3-bromo-1,1-dichloronaphthalen-2(1*H*)-one (**24**). The following compound was obtained according to the general procedure for chlorination by using 6-Bromo-2-napthol in 72% yield as orange solid. m.p. 46-48 °C. IR (KBr, cm^{-1}) 1705, 1604, 1562, 1343, 1227, 1147, 955, 923, 826, 813, 759, 746, 681, 656, 621. 580. 530. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 7.56 (d, *J* = 14.3 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 180.5, 146.1, 140.1, 131.6, 131.1, 129.7, 129.2, 127.1, 118.4, 80.6. HRMS (ESI-): calcd. for $C_{10}H_6BrClO$ [M-H]: 288.8823, found 288.2921.

1,3,6-trichloro-9-methyl-9*H*-carbazole (**25**). The following compound was obtained according to the general procedure for chlorination by using *N*-methylcarbazole, 4 equiv of PIFA and 6 equiv of $AlCl_3$ in 61% yield as white solid. m.p. 136-138 ºC. IR (KBr, cm^{-1}) 2921, 1315, 1448, 1279, 1077, 844, 791, 697. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.87 (s, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.41 (s, 1H), 7.33 (d, *J* = 8.7 Hz, 1H), 4.19 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7, 135.3, 127.8, 127.4, 125.64, 125.60, 124.7, 122.7, 120.2, 118.9, 116.8, 110.3, 32.3. The spectroscopic data match with those previously described.[59]

1,3,6,8-tetrachloro-9-methyl-9*H*-carbazole (**25a**). IR (KBr, cm^{-1}) 2922, 1556, 1453, 1264, 1043, 835, 715. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.42 (s, 1H), 4.49 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.8, 129.0, 125.7, 125.6, 118.7, 117.6, 35.1. The spectroscopic data match with those previously described.[60]

3-bromo-1-chloro-4-(phenethylamino)naphthalen-2-ol (**26**). A 25 ml dry round bottom flask was charged with compound **23** (1.0 equiv), phenylethylamine (1.2 equiv) and dissolved in methanol [0.3 *M*]. The reaction was stirred by 2 h. Then reaction mixture was evaporated and purified by chromatography column by using ethylacetate/hexane to yield **24** in 45% yield as grey solid. m.p. 66-68°C. IR (KBr, cm^{-1}) 3496, 2926, 1578, 1496, 1453, 1387, 1344, 1217, 1145, 1105, 1029, 942, 813, 755, 699. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.1 Hz, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.31 (d, *J* = 7.1 Hz, 2H), 7.28 -7.22 (m, 3H), 6.16 (s, 1H), 3.51 (t, *J* = 6.9 Hz, 2H), 2.98 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.0, 144.3, 139.0, 130.7, 128.9, 128.7, 128.0, 126.6, 124.6, 124.2, 124.0, 123.5, 108.3, 105.3, 51.9, 37.4.

Acknowledgements

A We gratefully thank to CONACyT (CB-2013/220836), FOMIX (CONACyT-CONCyTEG GTO-2012-C03-194610) and University of Guanajuato through project 962/2016 for financial support. We acknowledge the facilities from the DCNyE, Chemistry Department, the National Laboratory UG-CONACyT (LACAPFEM) in Guanajuato University for full characterization. We thank to CONACyT for the fellowship to P. D. Nahide, V. Ramadoss, Y. Satkar and K. Juárez. We especially thank to A.D. Galván and I.J Arroyo for preliminary experimentation..

Keywords: Electrophilic chlorination of phenols • PIFA/$AlCl_3$ system • Iodine (III) reagents • New chlorinating reagent • Chlorophenols

[1] a) Rønnest, M. H.; Raab, M. S.; Anderhub, S.; Boesen, S.; Kr krämer, A.; Larsen, T. O.; Clausen, M. H. *J. Med. Chem.* **2012**, *55*, 652-660. b) Boger, D. L. *Med. Res. Rev.* **2001**, *21*, 356-381. c) Liu, L.; Liu, S.; Jiang, L.; Chen, X.; Guo, L.; Che, Y. *Org. Lett.* **2008**, *10*, 1397-1400. d) Liu, L.; Li, Y.; Liu, S.; Zheng, Z.; Chen, X.; Zhang, H.; Guo, L.; Che, Y. *Org. Lett.* **2009**, *11*, 2836-2839. e) Liu, L.; Bruhn, T.; Guo, L.; Götz, D. C. G.; Brun, R.; Stich, A.; Che, Y.; Bringmann, G. *Chem. Eur. J.* **2011**, *17*, 2604-2613. f) Liu, L. *Mycology* **2011**, *2*, 37-45.

[2] a) Krieger, R. Hayes' Handbook of Pesticide Toxicology, Vol. 1; Elsevier: London, **1991**. b) Latch, D. E.; Packer, J. L.; Stender, B. L.; VanOverbeke, J.; Arnold, W. A.; McNeill, K. *Environ. Toxicol. Chem.* **2005**, *24*, 517-525.

[3] La Regina, G.; D'Auria, F. D.; Tafi, A.; Piscitelli, F.; Olla, S.; Caporuscio, F.; Nencioni, L.; Cirilli, R.; La Torre, F.; Rodrigues De Melo, N.; Kelly, S. L.; Lamb, D. C.; Artico, M.; Botta, M.; Palamara, A. T.; Silvestri, R. *J. Med. Chem.* **2008**, *51*, 3841-3855.

[4] Tang, M. L.; Bao, Z. *Chem. Mater.* **2011**, *23*, 446-455.

[5] Regina, G. L.; D´Auria, F. D.; Tafi, A.; Piscitelli, F.; Olla, S.; Caporuscio, F.; Nencioni, L.; Cirilli, R.; La Torre, F.; De Melo, N. R.; Kelly, S. L.;

Lamb, D. C.; Artico, M.; Botta, M.; Palamara, A. T.; Silvestri, R. *J. Med. Chem.* **2008**, *51*, 3841-3855.

[6] a) Jaeger, D. A.; Clennan, M. W.; Leyden, D. E.; Murthy, R. S. S. *Tetrahedron Lett.* **1987**, *28*, 4805-4808. b) Watson, W. D. *J. Org. Chem.* **1985**, *50*, 2145-2148. c) De Kimpe, N.; De Bucyk, L.; Verhé, R.; Wychuyse, F.; Schamp, N. *Syn. Comm.* **1979**, *9*, 575-582.

[7] Radhakrishnmurti, P. S.; Sahu, S. N. *I.J.C-B* **1978**, *16B(1)*, 81-82.

[8] Gruter, G. J. M.; Akkerman, O. S.; Bickelhaupt, F. *J. Org. Chem.* **1994**, *59*, 4473-4481.

[9] Sharma, S. K. *Res. J. Chem. Sci.* **2015**, *5*, 54-73.

[10] Maddox, S. M.; Nalbandian, C. J.; Smith, D. E.; Gustafson, J. L. *Org. Lett.* **2015**, *17*, 1042-1045.

[11] Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 4440-4444.

[12] Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, *18*, 2837-2842.

[13] Yu, Q.; Hu, L.; Wang, Y.; Zheng, S.; Huang, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15284-15288.

[14] a) Zhang, P.; Hong, L.; Li, G.; Wang, R. *Adv. Synth. Catal.* **2015**, *357*, 345-349. b) Sarkar, D.; Melkonyan, F. S.; Gulevich, A. V.; Gevorgyan, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 10800-10804. c) Huang, C.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Adv. Synth. Catal.* **2011**, *353*, 1285-1305.

[15] Jafarpour, F.; Hazrati, H.; Zarei, S.; Izadidana, S. *Synthesis* **2014**, *46*, 1224-1228.

[16] Santra, S. K.; Banerjee, A.; Mohanta, P. R.; Patel, B. K. *J. Org. Chem.* **2016**, *81*, 6066-6074.

[17] Mainbunkaew, T.; Thongsornkleeb, C.; Tummatorn, J.; Bunrit, A.; Ruchirawat, S. *Synlett* **2014**, *25*, 1769-1775.

[18] Bose, A.; Mal, P. *Tetrahedron Letters* **2014**, *55*, 2154-2156.

[19] Tale, N. P.; Shelke, A. V.; Karade, N. N. *Synth. Commun.* **2012**, *42*, 2959-2965.

[20] Chlorinating procedures involving reagents which contain N-Cl bond: a) for TCICA: Mendonca, G. F.; de Mattos, M. C. S. *Curr. Org. Synth.* 2013, 10, 820-836. b) for DCDMH, this protocol describes a highly *ortho*-chlorination of anilines: Xion, X.; Yeung, Y-Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 16101-16105. c) for TMP-Cl formed by using TMPH/SO_2Cl_2, this protocol describes a regioselective *ortho*-chlorination of phenols: Saper, N. I.; Snider, B. B. *J. Org. Chem.* **2014**, *79*, 809-813.

[21] a) Boltz, M.; Losch, P.; Louis, B.; Rioland, G.; Tzanis, G.; Daou, T. J. *RSC Adv.* **2014**, *4*, 27242-27249. b) Mendonca, G. F.; Bastos, A. R.; Boltz, M.; Louisb, B.; Paleb, P.; Estevesa, P. M.; Mattos, M. C. S. *Appl. Catal. A: Gen.* **2013**, *460-461*, 46-51.

[22] Leyva-Pérez, A.; Cómbita-Merchán, D.; Cabrero-Antonino, J. R.; Al-Resayes, S. I.; Corma, A. *ACS Catal.* **2013**, *3*, 250-258.

[23] Rodriguez, R. A.; Chung-Mao, P.; Yabe, Y.; Kawamata, Y.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 6908-6911.

[24] Binhua, L.; Xiaomin, C.; Chaozhong, L. *Chin. J. Chem.* **2011**, *29*, 2809-2812.

[25] Lu, Z.; Li, Q.; Tang, M.; Jiang, P.; Zheng, H.; Yang, X. *Chem. Commun.* **2015**, *51*, 14852-14855.

[36] Moon, B. S.; Choi, H. Y.; Koh, H. Y.; Chi, D. Y. *Bull. Korean Chem. Soc.* **2011**, 32, 472-476.

[27] Mizuno, N.; Kamata, K.; Yamaguchi, K. *Catal. Today*. **2012**, *185*, 157-161.

[28] Shi. L.; Zhang, D.; Lin, R.; Zhang, C.; Li, X.; Jiao, N. *Tetrahedron Letters* **2014**, *55*, 2243-2245.

[29] Hering, T.; Mühldorf, B.; Wolf, R.; König, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 5342-5345.

[30] Hering, T.; König, B. *Tetrahedron* **2016**, *72*, 7821-7825.

[31] a) Šket, B.; Zupan, M.; Zupet, P. *Tetrahedron* **1984**, *40*, 1603-1606. b) Chen, J. M.; Zeng, X. M.; Middleton, K.; Zhdankin, V. V. *Tetrahedron Lett.* **2011**, *52*, 1952-1955.

[32] Thorat, P. B.; Bhong, B. Y.; Karade, N. N. *Synlett* **2013**, *24*, 2061-2066.

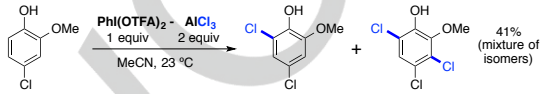
[33] a) Wang, M.; Zhang, Y.; Wang, T.; Wang, C.; Xue, D.; Xiao, J. *Org. Lett.* **2016**, *18*, 1976-1979. b) A relevant I(III) –bsed reagent for ethoxychlorination was recentrly identified by ESI: Nocquet-Thibault, S.; Minard, C.; Retailleau, P.; Cariou, K.; Dodd, R. H. *Tetrahedron*, **2014**, *70*, 6769-6775.

[34] Dohi, T.; Morimoto, K.; Murayama, A.; Kita, Y. *Org. Lett.* **2006**, *8*, 2007-2010.

[35] a) Dohi, T.; Minamitsuji, Y.; Murayama, A.; Hirose, S.; Kita, T. *Org. Lett.* **2008**, *10*, 3559-3562. b) Dohi, T.; Ito, M.; Itani, I.; Yamaoka, N.; Morimoto, K.; Fujioka, H.; Kita, I. *Org. Lett.* **2011**, *13*, 6208-6211. c) Morimoto, K.; Yamaoka, N.; Ogawa, C.; Nakae, T.; Fujioka, H.; Dohi, T.; Kita, Y. *Org. Lett.* **2010**, *12*, 3804-3807.

[36] Several attempts to optimize reaction to get better yields for mono- or bichlorination gave only complex reaction mixtures.

[37] This reaction was optimized to get the bichlorinated product. Standard conditions gave a regioisomeric mixture.



[38] Maddox, S. M.; Dinh, A. D.; Armenta, F.; Um, J.; Gustafson, J. L. *Org. Lett.*, **2016**, *18*, 5476-5479.

[39] References that described the spectroscopic data of synthesized chlorinated naphthols. For **1a** and **1b**: Ohkubo, Kei. *Chem. Asian J.,* **2016**, *11,* 996-999. For **5a:** Stevens, C. L.; Beereboom, John J.; Rutherford, Jr.; Kenneth G. *J. Am. chem. Soc.*, **1955**, *77*, 4590-4593. For **5b**: Lorz, E.; Baltzly, R. *J. Am. Chem. Soc.,* **1951**, *73,* 93-95. For **6b**: Bell, F.; Buck, K. R. *J. Chem Soc.,* **1963**, 4626-4633.

[40] The *ortho*/*para* regioselectivity found is much lower compared with those described by professor Gustafson in reference 56.

[41] The synthesis of our regent consists on the easy mix of PIFA-$AlCl_3$ in 1.2 : 2.4 ratio in MeCN followed by solvent evaporation after 30 minutes. Based upon **scheme 4**, we considered for stoichiometry calculations, that the weight of the obtained solid is a mixture of **IV** and **X**. The purification of reagent **IV** has not been successfully carried out.

[42] Brittain, J. M.; Calvert, D. J.; de la Mare, P. B. D.; Jones, T. C.; Newman, P. A.; Waters, J. M. *J. Chem. Soc. Perkin Trans II.,* **1983**, 247-253.

[43] Ginsberg, D. *J. Am. Chem. Soc.* **1951**, 73, 2723-2725.

[44] Franzen, H.; Stauble, G. *Journal fuer Praktische Chemie*, **1922**, *103*, 352-390.

[45] Matsunaga, N.; Ojida, A.; Tanaka, T.; Hara, T.; Yamaoka M.; Kusaka, M.; Tasaka, A.; Kaku, T. *Bioorg. Med. Chem.* **2011**, *19*, 1751-1770.

[46] Rana, S.; Bag S.; Patra, T.; Maiti, D. *Adv. Synth. Catal.* **2014**, *356*, 2453-2458.

[47] Mariano A. E.; Mendieta**,** P**.** B**.;** Hu**,** Q**.;** Engel**,** M**.;** Hartmann**,** W. R**.** *J. Med. Chem*. **2013**, *56*, 6101-6107.

[48] Guy, A.; Lemaire, M.; Guetté J. P. *Tetrahedron*, **1982**, *38*, 2347-2354.

[49] Stevens, C. L.; Beereboom, J. J. Jr.; Rutherford, K. G. *J. Am. Chem. Soc.*, **1955**, *77*, 4590-4593.

[50] Bell, F.; Buck, K. R. *J. Chem. Soc.*, **1963**, 4626-4633.

[51] Orazi, V. O. O.; Salellas, J. F.; Fondovila, M. E.; Corral, R. A.; Mercere, N. M. I.; Alvarez, E. C. *Anales de la Asociacion Quimica Argentina*, **1952**, *40*, 61-73.

[52] Friedman, D.; Ginsburg, D. *J. Org. Chem.,* **1958**, *23*, 16-17.

[53] Finger, G.C.; Reed, Frank H.; Tehon, Leo R. *Illinois State Geol. Survey Circ.* **1955**, *199*, 1-15.

[54] Castroviejo, M. P.; Fernandez, Y.; Fananas, F.J.; Sanz R. *J. Org. Chem.* **2005**, *70*, 6548-6551.

[55] Wallis, A. F. A.; Smith, Terrence J.; Wearne, R. H. *International Symposium on Wood and Pulping Chemistry, 8th, Helsinki, June 6-9*, **1995**, *3*, 377-382.

[56] Andrew, D.; Felipe, A.; Joann U.; Gustafson J. L.; Madox, S. *Org. Lett.* **2016**, *18*, 5476-5479.

[57] Julien, P.; Duwald, R.; Hilali, E. M. E.; Duchene, A.; Thibonneta J.; Ngi, I. S. *Adv. Synth Catal*. **2013**, *355*, 2936- 294.

[58] Oita, K.; Johnson, R. G.; Gilman, H. *J. Org. Chem.*, **1955**, *20*, 657-67.

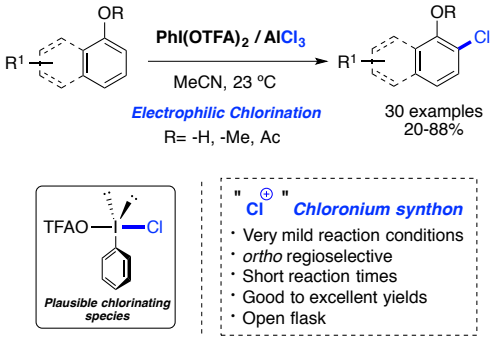
[59] Mishra, A. K.; Nagarajaiah, H.; Moorthy, J. N. *Eur. J. Org. Chem.* **2015**, 2733-2738.
[60] Bonesi, S. M.; Erra-Balsells, R. *J. Heterocycl. Chem.* **1997**, *34(3)*, 891-900.

10.1002/ejoc.201701399

WILEY-VCH

COMMUNICATION

Chlorination of Arenes



New Iodine (III) reactions*

*Pradip D. Nahide, Velayudham Ramados, Kevin A. Juárez Ornelas, Yuvraj Satkar, Rafel Ortiz Alvarado, Juan M. J. Cervera-Villanueva, Ángel J. Alonso-Castro, Juan R. Zapata-Morales, Marco A. Ramírez-Morales, Alan J. Ruiz-Padilla, Martha A. Deveze-Álvarez and César R. Solorio-Alvarado**

Page No. – Page No.

New *in situ* Formed I(III)-Based Reagent for the Electrophilic *ortho*-Chlorination of Phenols and Phenol-Ethers: The use of PIFA/$AlCl_3$ System

* Electrophilic chlorination of phenols • PIFA/$AlCl_3$ system • Iodine (III) reagents • New chlorinating reagent • Chlorophenols