Regioselective bromination of arenes mediated by triphosgene-oxidized bromide

Yingzhou Xu, Dufen Hu, Hui Zheng, David Mei, Zhaobo Gao

PII: S0040-4020(19)30872-5

DOI: https://doi.org/10.1016/j.tet.2019.130539

Reference: TET 130539

To appear in: *Tetrahedron*

Received Date: 14 June 2019

Revised Date: 17 August 2019

Accepted Date: 20 August 2019

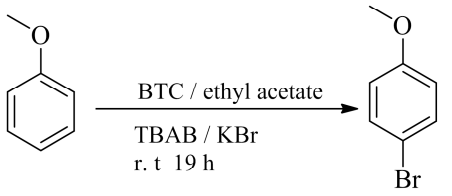
Please cite this article as: Xu Y, Hu D, Zheng H, Mei D, Gao Z, Regioselective bromination of arenes mediated by triphosgene-oxidized bromide, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.130539.

Graphical Abstract

Regioselective bromination of arenes mediated by triphosgene-oxidized bromide

Yingzhou Xu [a], Dufen Hu [a], Hui Zheng [a], David Mei [a], Zhaobo Gao [a*]

[a]Zhejiang Jiuzhou Pharmaceutical Co. Ltd, Waisha Road 99, Taizhou City, 318000, China



Yield:99%

This article first time describes triphosgene (BTC) as an oxidant while the non-toxic and easy-to-handle potassium bromide (KBr) as the source of bromine to the bromination reaction of aromatic substrates. The novel brominating protocol gives excellent para-regioselectivity of the alkoxyl / hydroxyl arenes and high yield, offering good potential of commercial scale applications. The mechanism of “Triphosgene oxidize bromide” was proposed.

Tetrahedron
journal homepage: www.elsevier.com

Regioselective bromination of arenes mediated by triphosgene-oxidized bromide

Yingzhou Xu [a], Dufen Hu [a], Hui Zheng [a], David Mei [a], Zhaobo Gao[a*]

[a]*Zhejiang Jiuzhou Pharmaceutical Co. Ltd, Waisha Road 99, Taizhou City, 318000, China*
Cell: 15858666966 Office: +86-576-8827632
E-mail: zhaobo.gao@jiuzhoupharma.com

ARTICLE INFO

Keywords:
Triphosgene
Oxidizing agent
Potassium bromide
Regioselectivity

ABSTRACT

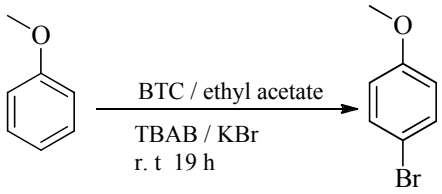
This article first time describes triphosgene (BTC) as an oxidant while the non-toxic and easy-to-handle potassium bromide (KBr) as the source of bromine to the bromination reaction of aromatic substrates. The novel brominating protocol gives excellent para-regioselectivity of the alkoxyl / hydroxyl arenes and high yield, offering good potential of commercial scale applications. The mechanism of "Triphosgene oxidize bromide" was proposed.

1. Introduction

Aryl bromides are high-valued fundamental building blocks in agrochemical, pharmaceutical and material synthesis. With the advancement of transition metal catalysis, the synthetic value of aryl bromides as versatile coupling partners has been well-recognized. Nevertheless, compared to the extensive research on the coupling transformations of aryl bromides, the practical synthesis of this feedstock chemical remains several unexplored. Electrophilic bromination of arenes is one of the fundamental transformations in these constructions of the C–Br bond. Unfortunately, traditional procedures of bromination usually involve the use of elemental bromine under harsh reaction conditions.[1-3] Owing to its toxic nature, the use of elemental bromine is not only troublesome and environmentally hazardous, but also needs cautious control of the addition rate or temperature to avoid undesirable side reactions. The industry applications of transition metal catalyzed coupling reactions have raised an urgent need for more economical and ecological synthesises of aryl bromides.

Therefore, a series of elemental bromine-free protocols have been developed. One alternative method utilizes solid organic ammonium tribromides such as 2,4-diamino-1,3-thiazole hydrotribromide,[4a] Me_4NBr_3,[4b] 1,8-diazabicyclo[5.4.0]undec-7-ene hydrobromide perbromide (DBUHBr$_3$),[4c] Bu_4NBr_3,[4d, 4e] phenyltrimethylammonium tribromide,[4e] 1,2-dipyridiniumditribromide-ethane (DPTBE)[4f] and PyHBr$_3$,[4e, 4g, 4h]. Another method involves in situ generation of bromine via bromic salt oxidation.[5-9] In this regard, it requires these combinations of oxidants and bromides such as H_2O_2-HBr,[5a-5c] t-BuOOH-HBr,[5b, 5c] H_2O_2-V_2O_5-Et_4NBr,[5d] oxone (potassium peroxymonosulfate, $KHSO_5$) / NaBr,[6a] oxone / HBr,[6b] $2KHSO_5$•$KHSO_4$•K_2SO_4, cerium (IV) ammonium nitrate (CAN) / KBr, CAN / LiBr,[7] $NaBrO_3$-NaBr[8] and Selectfluor / KBr[9]. However, the industrial applications were hindered by the inherent explosive nature of the reported oxidants.

Bis(trichloromethyl) carbonate (triphosgene, also known as BTC) was first developed by Eckert as "green phosgene". Attributed to its stable crystalline solid physical properties, BTC is safer and more convenient to handle, transport and store for commercial production purpose, which has been proved to be a useful substitute for phosgene in a variety of synthetic applications (e.g. chloroformylation, chlorination, carboxylation and dehydration reactions). Yet to date, among the numerous reported research on BTC, employing BTC as an oxidizing agent with good performance and excellent properties remains a huge challenge.[10-15]



Yield:99%

Scheme 1. Efficient synthesis routes for 1-bromo-4-methoxybenzene.

To bridge this gap of knowledge, we report herein a new protocol using BTC as an oxidizing agent. BTC is added to the mixture of potassium bromide (KBr) and aromatic substrate in the presence of catalyzed amount of tetrabutylammonium bromide (TBAB) then stir until the end of the reaction (Scheme **1**). The reaction of anisole as the exemplified compound gives almost quantitative yield. With the experimental conditions established, we proceeded to evaluate more aromatic substrates with different functional groups to expand the scope of this method. Furthermore, most of these aromatic substrates are a fragment of some common drugs. Meanwhile, the plausible reaction mechanism of the "Triphosgene oxidize bromide" is proposed. It is noteworthy that the method performed in a regioselective manner, affording mono- and para- brominating products.

2. Results and discussion

To find the best conditions for these reactions, the bromination reaction of anisole **1a** was studied using different ratios of BTC, TBAB and KBr in ethyl acetate at room temperature (Table 1). The best molar ratio of BTC / BTAB / KBr was 1.3:0.5:1.1 (Table 1, entry 6). All compounds of molar equivalent ratios are calculated according to the molar equivalent of anisole. When decreasing KBr from 1.9 to 1.1 (entries 1-6), the product yield has no obvious change. Reducing the amount of BTC results in a decrease of product yield (entries 4, 7, 8, 9, 10, 11, 15). To have the optimal yield, the equivalent of BTC between 1.1 and 1.3 would be the best choice. In addition, even though the reaction time was prolonged, product could not be detected in the system without BTC or TBAB during the reaction process (entries 12 and 15). This shows that BTC and TBAB play critical roles in the reaction. Interestingly, products could be still detected in the system of TBAB with high yields (entries 13 and 14), suggesting that TBAB may serve as a bromine source.

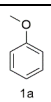
Table 1. Optimization of reaction conditions.

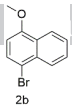
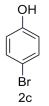
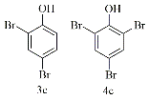
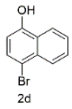
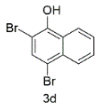
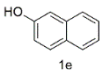
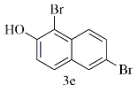
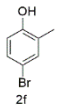
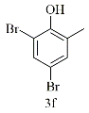
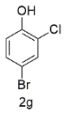
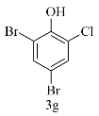
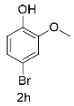
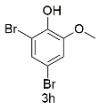
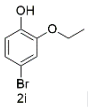
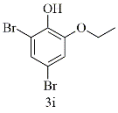
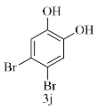
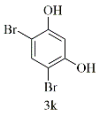
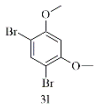
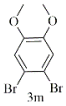
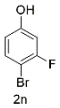
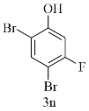
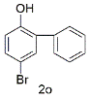
Entry	BTC[a] (equivalent)	TBAB (equivalent)	KBr (equivalent)	Yield[b] (%)
1	1.3	0.10	1.5	93
2	1.3	0.10	1.9	94
3	1.3	0.30	1.5	95
4	1.3	0.50	1.5	100
5	1.3	0.50	1.3	100
6	1.3	0.50	1.1	100
7	1.1	0.50	1.5	98
8	0.90	0.50	1.5	92
9	0.90	0.10	1.1	89
10	0.60	0.10	1.1	86
11	0.30	0.10	1.1	67
12	1.3	0	1.5	0
13	1.3	2.0	0	91
14	1.3	1.1	0	89
15	0	0.10	1.5	0

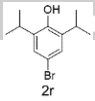
[a] Anisole, TBAB and BTC in the system of ethyl acetate and water at room temperature for 19 h.
[b] Yields refer to HPLC analysis.

Under the optimized reaction conditions (**Table 1**), the substrate scope was further explored (**Table 2**). It is proved that these aromatic substrates **1a-1r** with different alkoxyl or hydroxyl groups, including methoxy groups (**Table 2**, entries 1-2, 8, 12-13, 16), ethoxy group (entry 9), ether (entry 17) and hydroxyl groups (entries 3-7, 10-11, 14-15, 18), all worked well to furnish the para-brominated products **2a-2r** in excellent yields.16 In parallel with anisole **1a** and phenol **1c**, naphthalen-1-ol **1d** and 1-methoxynaphthalene **1b** were para-brominated at 4-position to give products **2a**, **2c**, **2d** and **2b** (entries 1-4). While naphthalen-2-ol **1e** was brominated at ortho-position providing 1-bromonaphthol **2e** in >90% yield (entry 5). Phenol **1f**, **1g**, **1h**, **1i**, **1j**, **1o** bearing a functional group (methyl, chloro, methoxy, ethoxy, hydroxyl, or phenyl group) at the ortho-position could also be brominated, providing expected para-brominated products **2f**, **2g**, **2h**, **2i**, **2j**, **2o** exclusively, as evidenced by the 1H NMR spectroscopic analysis of these crude reaction mixtures, in >80% yield (entries 6-10 and 15). Phenol **1k** and 3-fluorophenol **1n** with the hydroxyl group or fluoro group at meta-position (entries 11 and 14) were also competent substrates in this transformation, and 4-brominated products **2k** and **2n** were afforded in 84% and 85% yields, respectively. 4-Brominated products **2l**, **2m** were efficiently synthesized in excellent yields from 1,3-dimethoxybenzene **1l** and 1,2-dimethoxybenzene **1m** respectively (entries 12 and 13). These reactions with 2-methoxy-1,1'-biphenyl **1p** and (benzyloxy)benzene 1q gave para-position products **2p** and **2q** exclusively (entries 16 and 17). 4-Bromo-2,6-diisopropylphenol **2r** was observed in excellent yield from phenol grafting two isopropyl groups at the ortho-position (entry 18).17 It's worth mentioning that only 4-brominated products **2a**, **2b**, **2p**, **2q** and **2r** were obtained in these crude reaction mixtures, and no di- or tri-brominated products were detected. Few tri-brominated product **4c** was detected by LC-MS analysis of the crude reaction mixtures. In all of the above cases, these ratios of desired brominated products were more than 95% in the obtained products. Based on above result, it is suggested that para-regioselectivity is observed for the bromination of the alkoxyl / hydroxyl arenes and the chemo-selective property may open up more opportunities for long steps of total synthesis,[16, 18] but also have extensive application opportunities in multiple industry fields.

Table 2. Different substrates evaluated in bromination reactions.

Entry	Substrate[a]	BTC (equivalent)	Product	By-product	Isolated yield[b] (%)	Ratio (%)
1	 1a	1.3	 2a	---	99%	**2a** = 100

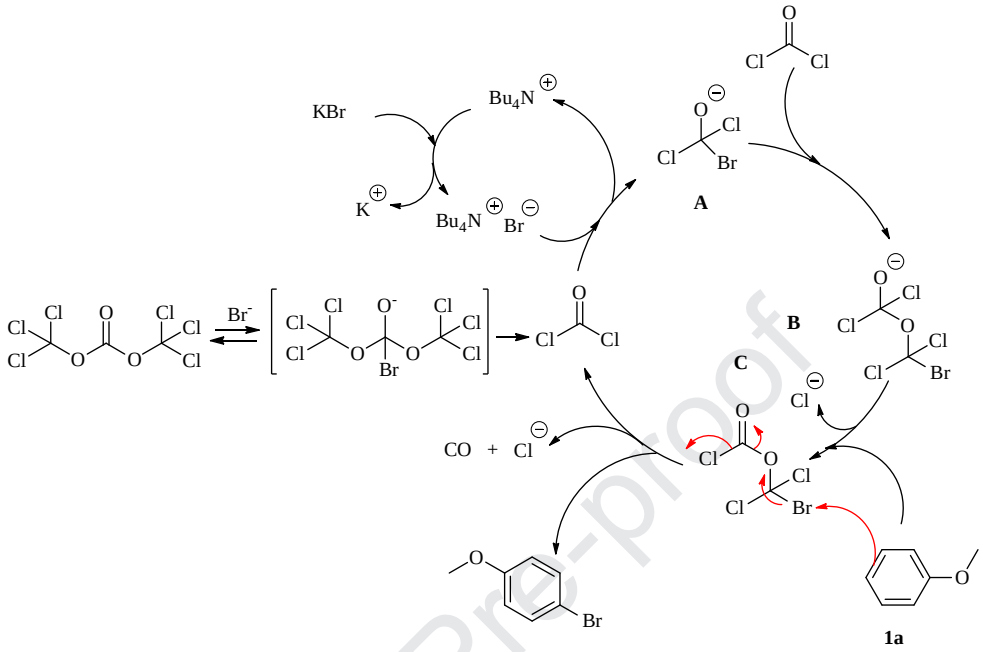
2	 1b	1.3	 2b	---	65%	**2b** = 100
3	 1c	1.3	 2c	 3c 4c	96%	**2c** : **3c** : **4c** = 99.74 : 0.23 : 0.03
4	 1d	1.3	 2d	 3d	89%	**2d** : **3d** = 96.23 : 3.77
5	 1e	1.3	 2e	 3e	94%	**2e** : **3e** = 96.3 : 3.7
6	 1f	1.3	 2f	 3f	98%	**2f** : **3f** = 98.5 : 1.5
7	 1g	1.3	 2g	 3g	92%	**2g** : **3g** = 97 : 3
8	 1h	1.35	 2h	 3h	89%	**2h** : **3h** = 99.88 : 0.12
9	 1i	1.3	 2i	 3i	95%	**2i** : **3i** = 99.74 :0.26
10	 1j	1.0	 2j	 3j	88%	**2j** : **3j** = 96.4 :3.6
11	 1k	1.3	 2k	 3k	84%	**2k** : **3k** = 97.5 : 2.5
12	 1l	1.3	 2l	 3l	96%	**2l** : **3l** = 99.24 : 0.76
13	 1m	1.3	 2m	 3m	94%	**2m** : **3m** = 98.91 : 1.09
14	 1n	1.3	 2n	 3n	85%	**2n** : **3n** = 97.16 : 2.84
15	 1o	1.3	 2o	3o	94%	**2o** : **3o** = 98.3 : 1.7
16	1p	1.3	2p	---	99%	**2p** = 100
17	1q	1.3	2q	---	96%	**2q** = 100

18	 1r	1.3	 2r	---	99%	**2r** = 100

[a] A substrate, TBAB and BTC in the system of ethyl acetate and water at room temperature for 19 h.

[b] Yields refer to HPLC analysis.

The above experimental evidence points out the plausible mechanism outlined in **Scheme 2**.



Scheme 2. Plausible mechanism of the reaction.

The bromide ion, under the reaction condition, is a strong nucleophile that attacks the carbonyl carbon of triphosgene giving diphosgene and phosgene. In turn, diphosgene reacts with bromide ion to give two molecules of phosgene (**Scheme 2**). Owing to the nucleophilicity for bromine ion of TBAB exceeded that of the phosgene, the bromide ion from potassium bromide by the phase transfer catalyst Bu_4N^+ attacking phosgene initially generates intermediate **A**.[19] Due to the instability of the negatively charged body, the intermediate **A** was added at the carbon of phosgene to provide intermediate **B**.[19] Meanwhile, intermediate **B** is converted into a more stable intermediate **C** by extruding a chloride ion. Then compound **1a** and intermediate **C** obtain desired product 1-bromo-4-methoxybenzene by a Friedel-Crafts pathway with releasing a CO, a chloride ion and one equivalent phosgene. The key breakdown pathway of intermediate **C** is shown in arrows. Phosgene / BTC actually acts as an oxidant with the driving force by breakdown of intermediate **C** in the process, which has not previously been reported. Based on above data (**Table 1**, entries 12 and 15), it is demonstrated that product could not be detected in the system without BTC or TBAB. Meanwhile, the existence of CO is proved by the alarm of CO detector. The amount of the releasing CO was detected and shown in **Figure 1**. From **Figure 1**, it could be clearly observed that the amount of CO is increasing with the addition of BTC. In addition, the brilliant mono- and para-regioselectivity indicate that there is a reaction intermediate with much more sterict hindrance than elemental bromine. As far as we know, only intermediate **C** could match well with all the profiles of the theoretical reaction intermediate in view of all the factors.

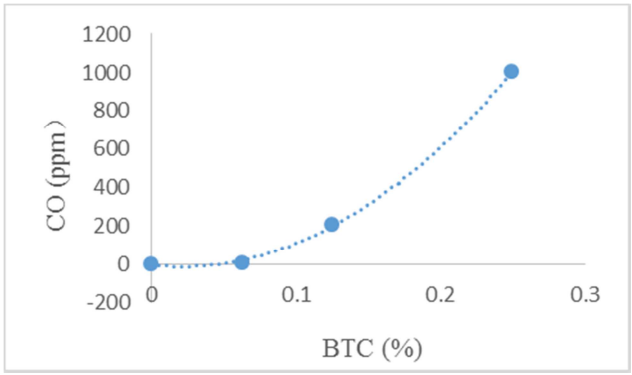


Figure 1. Experiment of the anisole with adding the amount of triphosgene and releasing the amount of carbon monoxide.

3. Experimental section

General methods

Reactions were monitored using Thin Layer Chromatography (TLC) using aluminium-backed Silica-Gel 60 F254 plates. Column chromatography was performed using Silica-Gel 60 (Merck). All chromatography was carried out using a combination of n-hexane and ethyl acetate as an eluent. Preparative TLC was performed using Silica-Gel 60 HF254+366. NMR spectra were recorded using a Bruker and Varian 400 MHz NMR instrument (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz) in $CDCl_3$. All chemical shifts are reported in ppm and *J* values are quoted in Hz.

4. Conclusion

A novel bromination method by BTC / KBr / TBAB was reported, which provided a good potential protocol for

commercial scale applications. BTC acts as an oxidizing agent to convert KBr into a highly regioselective agent with excellent yield. The mechanism of "Triphosgene oxidize bromide" was proposed. We believe that the novel regioselective bromination method will be a promising method for the bromination of aromatic compounds in pharmaceutical chemistry field. Further research of aromatic bromination into alkene substrates is currently ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

These investigations were supported by Zhejiang Jiuzhou Pharmaceutical Co. Ltd.

References and notes

1 Cui, X. M.; Guan, Y. H.; Li, N.; Lv, H.; Fu, L. N.; Guo, K.; Fan, X. H. *Tetrahedron Lett.* **2014**, *55*, 90-93.

2 (a) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335-346; (b) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937-1944; (c) Seevers, R. H.; Counsell, R. E. *Chem. Rev.* **1982**, *82*, 575-590.

3 (a) De la Mare, P. B. Electrophilic Halogenation, Cambridge University Press, Cambridge, UK, **1976**, ch. 5; (b) Taylor, R. Electrophilic Aromatic Substitution, Wiley, Chichester, UK, **1990**.

4 (a) Forlani, L. *Synthesis* **1980**, 487-489; (b) Avramoff, M.; Weiss, J. and Schächter, O. *J. Org. Chem.* **1963**, *28*, 3256; (c) Muathen, H. A. *J. Org. Chem.* **1992**, *57*, 2740-2744; (d) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawophlang, W.; Lakshmiprabha, T. R. and Mandal, G. C. *Tetrahedron Lett.* **1998**, *39*, 8163-8166; (e) Tanaka, K.; Shiraishi, R. and Toda, F. *J. Chem. Soc. Perkin Trans.* **1999**, *1*, 3069-3070; (f) Kavala, V.; Naik, S. and Patel, B. K. *J. Org. Chem.* **2005**, 70, 4267-4271. (g) Toda, F. and Schmeyers, J. *Green Chem.* **2003,** *5*, 701-703; (h) Nakamatsu, S.; Toyota, S.; Jones, W. and Toda, F. *Chem. Commun.* **2005**, 3808-3810.

5 (a) Ho, T. L.; Gupta, B. and Olah, G. A. *Synthesis* **1977**, 676-677; (b) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D.and Bedekar, A. V. *Tetrahedron Lett.* **1998**, *39*, 6349-6350; (c) Barhate, N. B.; Gajare, A. S.; Wakharkar, R. D. and Bedekar, A. V. *Tetrahedron* **1999**, 55, 11127-11142; (d) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T. and Patel, B. K. *Org. Lett.* **2000**, *2*, 247-249.

6 (a) Dieter, R. K.; Nice, L. E. and Velu, S. E. *Tetrahedron Lett.* **1996**, *37*, 2377-2380; (b) Kim, K.-M. and Park, I.-H. *Synthesis* **2004**, 16, 2641-2644.

7 (a) Nair, V.; Panicker, S. B.; Augustine, A.; George, T. G.; Thomas, S. and Vairamani, M. *Tetrahedron* **2001**, *57*, 7417-7422; (b) Roy, S. C.; Guin, C.; Rana, K. K. and Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 6941-6942.

8 Subbarayappa, A.; Ghosh, S.; Patoliya, P. U.; Ramachandraiah, G.; Agrawal, M.; Gandhi, M. R.; Upadhyay, S. C.; Ghosh, P. K. and Ranu, B. C. *Green Chem.* **2008**, *10*, 232-237.

9 Ye, C. and Shreeve, J. M. *J. Org. Chem.* **2004**, *69*, 8561-8563.

10 Saputra, M. A.; Ngo, L. and Kartika, R. *J. Org. Chem*. **2015**, *80*, 8815-8820.

11 Villalpando, A.; Saputra, M. A.; Tugwell, T. H. and Kartika, R. *Chem. Commun.* **2015**, *51*, 15075-15078.

12 Menguy, L.; Drouillat, B.; Couty, F. *Tetrahedron Lett.* **2015**, *56*, 6625-6628.

13 Cleveland, A. H.; Fronczek, F. R. and Kartika, R. *J. Org. Chem.* **2018**, *83*, 3367-3377.

14 Cotarca, L.; Geller, T. and Répási, J. *Org. Process Res. Dev*. **2017**, *21*, 1439-1446.

15 Eckert, H. and Auerweck, J. *Org. Process Res. Dev*. **2010**, *14*, 1501-1505.

16 Ayala, C. E.; Villalpando, A.; Nguyen, A. L.; McCandless, G. T. and Kartika, R. *Org. Lett*. **2012**, *14*, 3676-3679.

17 Mendoza, F.; Ruíz-Guerrero, R.; Hernández-Fuentes, C.; Molina, P.; Norzagaray-Campos, M.; Reguera, E. *Tetrahedron Lett.* **2016**, *57*, 5644-5648.

18 Liang, D. Q.; Li, X. G.; Wang, C. W.; Dong, Q. S.; Wang, B. L.; Wang, H. *Tetrahedron Lett*. **2016**, *57*, 5390-5394.

19 Pasquato, L.; Modena, G.; Cotarca, L.; Delogu, P. and Mantovani, S. *J. Org. Chem.* **2000**, *65*, 8224-8228.

Supplementary Material

Supplementary data (general information, experimental procedures, ^{1}H NMR, ^{13}C NMR and HPLC spectra for **2a-2r**.) associated with this article can be found.

Highlight

1. The novel brominating protocol gives excellent para-regioselectivity of the alkoxyl / hydroxyl arenes and high yield.
2. The triphosgene shows good oxidation properties in the method. And Potassium bromide (KBr) provides a good bromine source in bromination reaction.
3. The method has good industrial application prospect.