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Cu-Catalyzed Halogenation of Diaryliodonium Salts Containing Ortho-sidearm

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Abstract

A simple and efficient halogenation pathway has been delivered with various diaryliodonium salts, containing an ortho alcoholic sidearm, and CuCl or CuBr to produce chloroarenes and bromoarenes in para position only without any ortho aromatic isomer. The reaction conditions include temperature (60 oC), solvent (DMF) and reaction time (2 hours) were optimized in order to obtain high yields of products. All products were isolated and characterized via 1H-NMR and 13C-NMR. With further investigation, these methods could be the main entrance to prepare herbicides, insecticides and bactericides containing haloarenes in their structures.

Keywords: Diaryliodonium Compounds, Cuprous Halide, Halogenation, Haloarenes.

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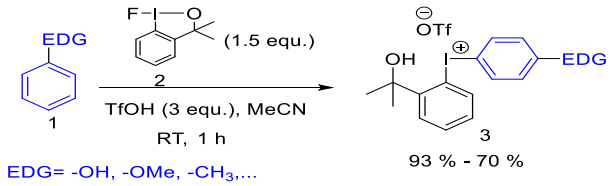
Introduction

Hypervalent iodine (III) compounds are of considerable attention in organic chemistry due to their selectivity, reactivity and mild reaction conditions (Papis, et al., 2023). Diaryliodonium salts compounds are considered the best example of hypervalent iodine. The application of diaryliodonium salts have been reported in several studies due to the electron-deficient nature and their high selectivity and reactivity allowing many reactions to happen in moderate conditions without using additional amounts of reagents (Singhal, et al., 2023). Generally, they considered a variable arylating agents with set of nucleophiles, like, heteroarenes (Wang, et al., 2021), electron-rich arenes (Kuriyama, et al., 2020) and carbonyls (Phipps, et al., 2008).

For many years, Ar-X have been a great interest because their serve as precursors for the synthesis of organometallic compounds (Sotomayor, et al., 2003) as well as for nucleophilic substitution reactions with aromatic ring contains a strong electron-withdrawing group (Rohrbach, et al., 2019). As soon as the cross coupling reaction appeared (Mirza-Aghayan, et al., 2023), the value of Ar-X have extremely expanded. Consequently, they can be considered the fundamental components of organic synthesis. Furthermore, they are widely used as herbicides, insecticides, bactericides and fungicides.

The traditional method (Sandmeyer reaction) (Akhtarl, et al., 2022) for the synthetic halo-arenes include the production of a halide from an amine group via the formation of diazonium salt. For instance, the reaction of arenediazonium salt in the presence of CuX, needs an excessive amount of CuX at 65°C in concentrated acid (Siméon, et al., 2009).

Recently, we reported a new pathway for the fluorination of a new class of diaryliodonuim salts with ortho-sidearm using KF as a fluorinating reagent to produce Ar-F (Abudken, et al., 2020). In keeping with our continuing interest in improving the use of the unsymmetrical diaryliodonium salts and inspiring by Jian's report (Lia, et al., 2013), we reported an efficient and simple method for preparation of Ar-Cl and Ar-Br with copper halide using diaryliodonium salts prepared previously (Scheme 1) (Abudken, et al., 2020). In comparison with the previous studies (Lia, et al., 2013, and Jiang, 2023) lower temperature and high yield was obtained.



Scheme 1: Preparation of Diaryliodonium Salts 3

Materials and Methods

Materials

All chemical, reagents and solvents were used in this work was provided from Sigma-Aldrich and used without any purifications.

Methods

General Halogenation Procedure of Asymmetrical Diaryliodonium Salts with CuX (Table 2).

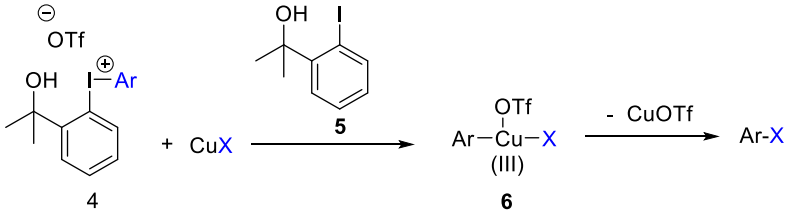
Diaryliodonium salt (1.0 mmol), CuX (1.5 mmol) and DMF 20 mL was placed in a Schlenk flask. The reactant was stirred vigorously for 2 hours under 60 °C. The crude product was cooled to 25 °C, and stirred with water (10 mL) for 10 min. The reaction mixture was extracted with 20 mL of ethyl acetate (20 mL x 3). The organic layers were combined, washed with 50 mL of water, separated via separating funnel and dried over $MgSO_4$. After that, it was concentrated in rotary evaporator to afford the impure product. This crude was purified via silica gel column, using petroleum ether 40-60 °C and ethyl acetate 1:9 as solvents, to produce pure products which was analyzed by ^1H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$). (Lia, et al., 2013)

Results and Discussion

The first investigation was concentrated on the reaction of diaryliodonium salt **1a** with KCl and KBr. However, no result was obtained with these reagents (entry **1**, 2, Table **1**). The first sign of product *p*-bromoanisole **3a** was

detected using CuBr in MeCN at RT for 24 h (entry **3**, Table **1**). The same reaction conditions were applied using different solvents, including DMF, DMSO, DCM and THF (entry **4-7**). DMF was found to be the best solvent in terms of yield (45 %) and the reaction rate to produce *p*-bromoanisole **3a** under the same conditions as seen in entry **4**. The yield of **3a** was changed from 45 % to 85 % when the temperature was increased to 60°C after 2 hours (entry **8**). Raising the temperature of the reaction to 80°C in entry **9**, leads to reduce the desired product to 72 %. Moreover, reducing the reaction time to 1 hour gave only 65 % of **3a** (entry **10**). Further investigation with $CuBr_2$ was also tested under the same conditions (entry **11**), nevertheless, the yield was dropped to 62 %. The effects of changing the counter-anion from triflate (OTf^-) to tetrafluoroborate (BF_4^-) and tosylate (OTs^-) were carried out under the optimised conditions, however, lower yield of **3a** was obtained (entry **12, 13**). It has been observed that the reactivity of anions of these salts were different because of the distinct nucleophilicities and solubility. The chlorination of diaryliodonium salt **1a** was also tested using cuprous chloride as chlorination reagent. 83 % yield was generated in the same conditions as in entry **8** (entry **14**).

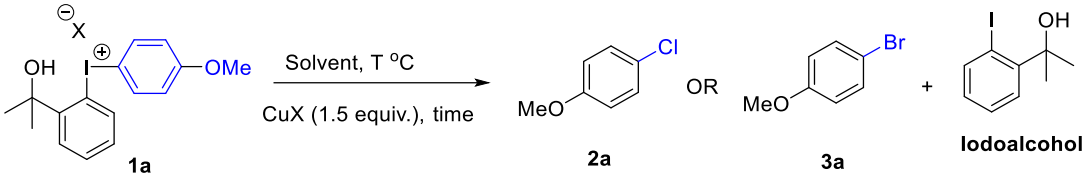
After optimization of the reaction conditions, we examined the scope of diaryliodonium salts, containing an activated aromatic ring, with both CuCl and CuBr in DMF at 60 ºC for 2 hours. The halogenation results are shown in **Table 2**. The asymmetrical salts were prepared previously from the reaction of fluoroiodine **2** and activated arenes (**Scheme 1**). It can be noted that high yields were obtained with *para* and *meta*-substituted salts (entry **1-4**, Table **2**). In contrast, good to moderate yields were produced with *ortho*-substituted salts. This might be due to "*ortho* effect" as Sanford reported (Sanford, et al., 2013).



Scheme 2: Proposed Mechanism for the Halogenations with CuX

The reasonable mechanism of the aromatic compounds is shown in (Scheme **2**). Firstly, the oxidative addition of CuX with asymmetrical diaryliodonium salts **4** took place to generate Cu-complex **6** by removing iodoalcohol **5**. Elimination of -CuOTf from intermediate **6** afforded Ar-x.

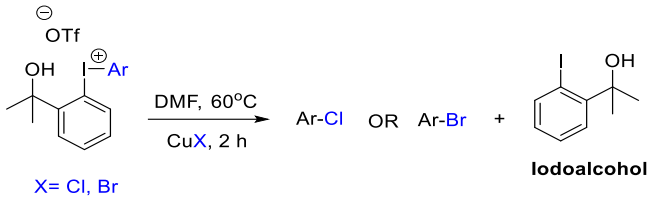
Table 1: Optimization of Halogenation Conditions

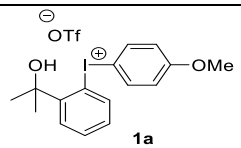
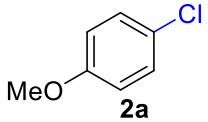
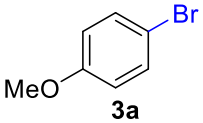
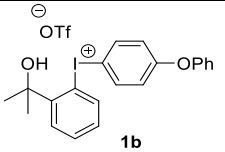
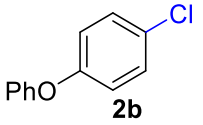
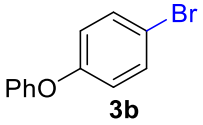
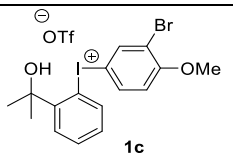
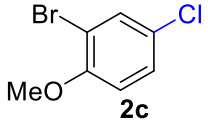
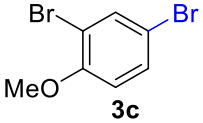
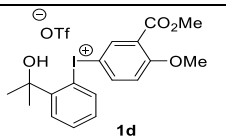
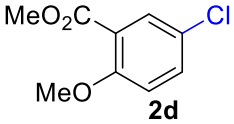
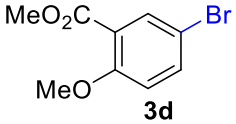
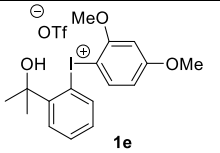
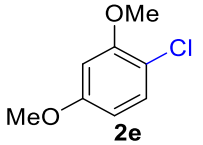
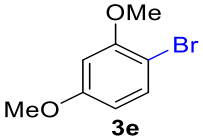
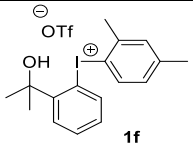
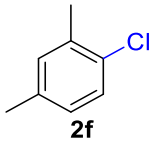
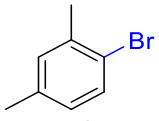
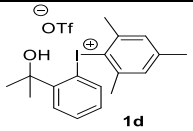
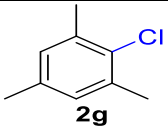
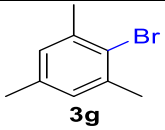


Entry	Halide resource	X	solvent	T (ºC)	Time (h)	Isolated Yield (%)
1	KBr	OTf	MeCN	25	24	-
2	KCl	OTf	MeCN	25	24	-
3	CuBr	OTf	MeCN	25	24	30
4	CuBr	OTf	DMF	25	24	45
5	CuBr	OTf	DMSO	25	24	22
6	CuBr	OTf	DCM	25	24	13
7	CuBr	OTf	THF	25	24	20
8	CuBr	OTf	DMF	60	2	85
9	CuBr	OTf	DMF	80	2	72
10	CuBr	OTf	DMF	60	1	65
11	$CuBr_2$	OTf	DMF	60	2	62
12	CuBr	OTs	DMF	60	2	60
13	CuBr	BF_4	DMF	60	2	59
14	CuCl	OTf	DMF	60	2	83
15	$CuCl_2$	OTf	DMF	60	2	67

Substrate **1a** (1 mmol) and CuCl (1.5 mmol) were mixed in DMF (2 mL), then heating to 60 ºC for 2 hours.

Table 2: Substrate Scope of the Halogenation with CuX



Entry	Substrate	Ar-Cl	Yield (%)	Ar-Br	Yield (%)
1	 **1a**	 **2a**	83	 **3a**	85
2	 **1b**	 **2b**	88	 **3b**	87
3	 **1c**	 **2c**	85	 **3c**	89
4	 **1d**	 **2d**	77	 **3d**	74
5	 **1e**	 **2e**	68	 **3e**	70
6	 **1f**	 **2f**	68	 **3f**	65
7	 **1d**	 **2g**	54	 **3g**	58

Characterisation Data of Isolated Products

1-Chloroanisole **(2a) (**Lia, et al., 2013**).**

Yield: 118 mg (83 %) ^{1}H NMR: = 7.29 (m, 2H,Ar-*H*), 7.01 (m, 2H, Ar-*H*), 3.35 (s, 3H,-OC*H*$_3$). ^{13}C NMR= 159.2, 131.4, 127.2, 116.5, 55.5.

1-Bromoanisole **(3a) (**Lia, et al., 2013**).**

Yield: 160 mg (85 %) ^{1}H NMR: = 7.13 (m, 2H,Ar-*H*), 7.0 (m, 2H,Ar-*H*), 3.49 (s, 3H,-OC*H*$_3$). ^{13}C NMR= 158.9, 128.7, 123.4, 114.5, 56.0.

4-Chloro-diphenylether **(2b) (**Swapna, et al., 2011**)**

Yield: 180 mg (88 %) ^{1}H NMR = 7.32 (m, 4H,Ar-*H*), 7.08 (m, 1H,Ar-*H*), 7.0 (m, 4H,Ar-*H*).^{13}C NMR= 156.9, 156.1, 129.8, 129.7, 128.1, 123.6, 120.1, 119.0.

4-Bromo-diphenylether **(3b) (**Swapna, et al., 2011**)**

Yield: 217 mg (87 %) ^{1}H NMR = 7.41 (d,1H,Ar-*H*), 7.26 (m, 3H,Ar-*H*), 7.07 (m, 2H,Ar-*H*), 7.01 (d, 2H,Ar-*H*), 6.88 (d, 1H,Ar-*H*) .^{13}C NMR= 156.5, 155.8, 133.1, 129.9, 123.7, 120.3, 119.0, 115.5.

2-Bromo-4-chloroanisole **(2c) (**Maibunkaew, et al., 2014**)**

Yield: 188 mg (85 %) ^{1}H NMR = 7.49 (d,1H,Ar-*H*), 7.32 (s, 1H,Ar-*H*), 6.79 (d, 1H, Ar-*H*), 3.87 (s, 3H,-OC*H*$_3$).^{13}C NMR= 154.4, 132.6, 130.5, 127.6, 123.6, 113.3, 56.3.

2,4-Dibromoanisole **(3c) (**Hamamoto, et al., 2011**)**

Yield: 186 mg (70 %) ^{1}H NMR = 7.65 (d,1H,Ar-*H*), 7.37 (s, 1H,Ar-*H*), 6.78 (d, 1H, Ar-*H*), 3.87 (s, 3H,-OC*H*$_3$). ^{13}C NMR= 155.3, 135.6, 131.5, 131.4, 113.0, 112.4, 56.4.

Methyl 5-chloro-2-methoxybenzoate (**2d**) **(**Voskressensky, et al., 2016**)**

Yield: 154 mg (77 %) ^{1}H NMR = 7.74 (s, 1H,Ar-*H*), 7.40 (d, 1H,Ar-*H*), 6.90 (d, 1H, Ar-*H*), 3.92 (s, 3H,-OC*H*$_3$ in -COOCH$_3$), 3.90 (s, 3H,-OC*H*$_3$ on phenyl ring). ^{13}C NMR= 165.4, 157.6, 133.1, 131.3, 125.2, 113.7, 113.5, 56.3, 55.1.

Methyl 5-Bromo-2-methoxybenzoate (**3d**) **(**Voskressensky, et al., 2016**)**

Yield: 181 mg (74 %) ^{1}H NMR = 7.64 (s, 1H,Ar-*H*), 7.35 (d, 1H,Ar-*H*), 7.01 (d, 1H, Ar-*H*), 3.87 (s, 3H,-OC*H*$_3$ in -COOCH$_3$), 3.91 (s, 3H,-OC*H*$_3$ on phenyl ring). ^{13}C NMR= 165.8, 158.2, 136.4, 132.6, 123.7, 114.6, 113.1, 57.0, 55.4.

1-Chloro-2,4-dimethoxybenzene (**2e**) **(**Yang, et al., 2009**)**

Yield: 117 mg (68 %) ^{1}H NMR = 7.24 (d, 1H,Ar-*H*), 6.60 (d, 1H,Ar-*H*), 6.43 (s, 3H, Ar-*H*), 3.89 (s, 3H,-OC*H*$_3$), 3.86 (s, 3H,-OC*H*$_3$). ^{13}C NMR= 159.8, 155.6, 130.1, 129.9, 113.7, 107.3, 101.2, 56.3, 55.1.

1-Bromo-2,4-dimethoxybenzene **(3e) (**Yang, et al., 2009**)**

Yield: 152 mg (70 %) ^{1}H NMR = 7.38 (d, 1H,Ar-*H*), 6.50 (d, 1H,Ar-*H*), 6.48 (s, 1H, Ar-*H*), 3.87 (s, 3H,-OC*H*$_3$), 3.85 (s, 3H,-OC*H*$_3$). ^{13}C NMR= 160.1, 157.0, 132.1, 129.9, 109.7, 104.7, 101.1, 56.3, 55.2.

1-Chloro-2,4-dimethylbenzene **(2f) (**Kandepi, et al., 2012**)**

Yield: 95 mg (68 %). ^{1}H NMR = 7.27 (d, 1H, Ar-*H*), 7.04 (s, 1H, Ar-*H*), 7.0 (d, 1H, Ar-*H*), 2.33 (s, 3H,-C*H*$_3$), 2.26 (s, 3H,-C*H*$_3$). ^{13}C NMR= 136.8, 135.4, 133.0, 131.7, 128.1, 126.9, 22.2, 21.2.

1-Bromo-2,4-dimethylbenzene **(3f) (**Kandepi, et al., 2012**)**

Yield: 120 mg (65 %). ^{1}H NMR = 7.39 (d, 1H, Ar-*H*), 7.12 (s, 1H, Ar-*H*), 7.01 (d, 1H, Ar-*H*), 2.36 (s, 3H,-C*H*$_3$), 2.25 (s, 3H,-C*H*$_3$). ^{13}C NMR= 137.8, 135.9, 133.8, 130.5, 127.1, 124.9, 23.4, 22.1.

2-Chloromesitylene **(2g)**

Yield: 84 mg (54 %). The NMR spectrum **2g** matched that of the original sample (Sigma - Aldrich) ^{1}H NMR = 6.95 (s, 2H,Ar-*H*), 2.36 (s, 6H,-C*H*$_3$), 2.29 (s, 3H,-C*H*$_3$). ^{13}C NMR= 137.0, 135.4, 132.8, 127.8, 22.2, 21.6.

2-Bromomesitylene **(3g) (**Pan, et al., 2011**)**

Yield: 115 mg (58 %). ^{1}H NMR = 6.85 (s, 2H,Ar-*H*), 2.43 (s, 6H,-C*H*$_3$), 2.38 (s, 3H, -C*H*$_3$).^{13}C NMR= 138.2, 135.6, 131.8, 125.6, 23.7, 22.1.

Conclusion

In summary, this work describes an efficient and convenient halogenation reaction with diaryliodonium salts and commercially available CuCl and CuBr in DMF at 60 ºC for 2 hours to produce chloroarenes and bromoarenes in a high to moderate yields (88 % - 54 %). The halogen was introduced in para position only. During the optimization the reaction conditions, different solvents (MeCN, DMF, DMSO, DCM and THF), temperature, reaction time (1-24 h) as well as the effect of counter-anion (OTS^-, OTf^-, BF_4^-) were investigated. It is important to point out that the iodoalcohol, which was produce from the halogenation reaction, can be isolated and used to prepare fluoroiodine **2**

compound (Abudken, et al., 2020). Synthesis pesticides containing haloarene in para position such as DDD, DDT and DDE (Novak and Kovac, 2011) are currently underway using our protocol.

References

Abudken, A.M., Hope, E.G., Singh, K., & Stuart, A.M. (2020). Fluorinations of unsymmetrical diaryliodonium salts containing ortho-sidearms; influence of sidearm on selectivity. *Organic & Biomolecular Chemistry*, *18*(31), 6140-6146.

Akhtar, R., Zahoor, A.F., Rasool, N., Ahmad, M., & Ali, K.G. (2022). Recent trends in the chemistry of Sandmeyer reaction: a review. *Molecular Diversity*, *26*(3), 1837-1873.

Hamamoto, H., Hattori, S., Takemaru, K., & Miki, Y. (2011). Hypervalent iodine (III)-LiX combination in fluoroalcohol solvent for aromatic halogenation of electron-rich arenecarboxylic acids. *Synlett*, *2011*(11), 1563-1566.

Ichiishi, N., Canty, A.J., Yates, B.F., & Sanford, M.S. (2013). Cu-catalyzed fluorination of diaryliodonium salts with KF. *Organic letters*, *15*(19), 5134-5137.

Jiang, H., Liu, M., Ye, Z., Song, Z., Wu, Y., & Zhang, F. (2023). Metal-free meta-halogenation of cyclic diaryliodonium salts via aryne intermediates. *Organic Chemistry Frontiers*, *10*(15), 3856-3860.

Kandepi, V.K.M., & Narender, N. (2012). Ecofriendly oxidative nuclear halogenation of aromatic compounds using potassium and ammonium halides. *Synthesis*, *44*(01), 15-26.

Kuriyama, M., Hanazawa, N., Abe, Y., Katagiri, K., Ono, S., Yamamoto, K., & Onomura, O. (2020). N-and O-arylation of pyridin-2-ones with diaryliodonium salts: base-dependent orthogonal selectivity under metal-free conditions. *Chemical Science*, *11*(31), 8295-8300.

Li, J., Liu, L., Ding, D., & Sun, J.T. (2013). Halogen exchange via a halogenation of diaryliodonium salts with cuprous halide. *Letters in Organic Chemistry*, *10*(8), 541-548.

Novak, I., & Kovač, B. (2011). Electronic structure of pesticides: 1. Organochlorine insecticides. *Journal of Electron Spectroscopy and Related Phenomena*, *184*(8-10), 421-426.

Maibunkaew, T., Thongsornkleeb, C., Tummatorn, J., Bunrit, A., & Ruchirawat, S. (2014). Practical and metal-free electrophilic aromatic halogenation by interhalogen compounds generated in situ from N-halosuccinimide and catalytic TMSCl. *Synlett*, *25*(12), 1769-1775.

Mirza-Aghayan, M., Moieni, A. S., & Boukherroub, R. (2023). Graphene loaded with metal nanoparticles/complexes catalyzed cross-coupling reactions: A review. *Journal of Organometallic Chemistry, 995,* 122737.

Pan, J., Wang, X., Zhang, Y., & Buchwald, S.L. (2011). An improved palladium-catalyzed conversion of aryl and vinyl triflates to bromides and chlorides. *Organic letters*, *13*(18), 4974-4976.

Papis, M., Foschi, F., Colombo, S., Beccalli, E.M., Loro, C., & Broggini, G. (2023). Copper-Catalyzed/Hypervalent Iodine-Mediated Functionalization of Unactivated Compounds. *Catalysts*, *13*(9), 1-71.

Phipps, R.J., Grimster, N.P., & Gaunt, M.J. (2008). Cu (II)-catalyzed direct and site-selective arylation of indoles under mild conditions. *Journal of the American Chemical Society*, *130*(26), 8172-8174.

Rohrbach, S., Smith, A.J., Pang, J.H., Poole, D.L., Tuttle, T., Chiba, S., & Murphy, J.A. (2019). Concerted nucleophilic aromatic substitution reactions. *Angewandte Chemie International Edition*, *58*(46), 16368-16388.

Siméon, F.G., Wendahl, M.T., & Pike, V.W. (2009). Efficient and regioselective halogenations of 2-amino-1, 3-thiazoles with copper salts. *The Journal of organic chemistry*, *74*(6), 2578-2580.

Singhal, R., Choudhary, S. P., Malik, B., & Pilania, M. (2023). Cyclic diaryliodonium salts: applications and overview. *Organic & Biomolecular Chemistry, 21(21),* 4358-4378.

Sotomayor, N., & Lete, E. (2003). Aryl and heteroaryllithium compounds by metal-halogen exchange. Synthesis of carbocyclic and heterocyclic systems. *Current Organic Chemistry*, *7*(3), 275-300.

Swapna, K., Murthy, S.N., Jyothi, M.T., & Nageswar, Y.V.D. (2011). Recyclable heterogeneous copper oxide on alumina catalyzed coupling of phenols and alcohols with aryl halides under ligand-free conditions. *Organic & Biomolecular Chemistry*, *9*(17), 5978-5988.

Voskressensky, L.G., Golantsov, N.E., & Maharramov, A.M. (2016). Recent advances in bromination of aromatic and heteroaromatic compounds. *Synthesis*, *48*(05), 615-643.

Wang, D., Li, Q., Li, M., Du, Z., & Fu, Y. (2021). Recent progress in arylation reactions with diaryliodonium salts. *Current Organic Chemistry*, *25*(11), 1298-1320.

Yang, L., Lu, Z., & Stahl, S.S. (2009). Regioselective copper-catalyzed chlorination and bromination of arenes with O 2 as the oxidant. *Chemical communications*, (42), 6460-6462.