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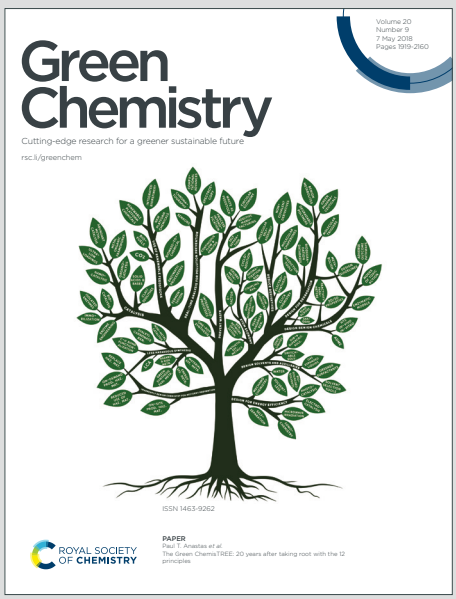

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COMMUNICATION

Visible-Light-Promoted Oxidative Halogenation of (Hetero)Arenes

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Organic halides are critical building blocks, which participate in various cross-coupling reactions. Furthermore, they widely exist as natural products and artificial molecules in drug with important physiological activities. Although halogenation has been well studied, to the best of our knowledge, studies focus on sensitive systems (e.g. aryl amines) have not been reported. Herein, we describe a compatible oxidative halogenation of (hetero)arenes with air as oxidant and halide ions as halide sources under ambient conditions (visible light, air, aqueous system, room temperature, and normal pressure). Moreover, this protocol is practically feasible to gram-scale synthesis, which shows potential for industrial application.

Aryl halides, especially bromo- and iodoarenes, are classes of significant compounds due to their irreplaceable roles in transition-metal-catalyzed cross-coupling reactions,[1] which serve as both starting materials and the precursors of organometallic reagents, such as organolithium[2] and Grignard reagents.[3] Beyond synthesis applications, they are widespread in nature as well. More than 1700 bromo- and iodoarenes have been isolated,[4] which inspire their prevalence in medicinal studies. Until now, there are more than 60 bromo- and iodoarenes approved as clinic drugs,[4] such as antianxiety drug Bomazepam,[5] BRAF/MEK inhibitors Binimetinib,[6] antineoplastic drug Vandetanib,[7] treatment of respiratory disease drug Bromhexine,[8] MEK inhibitor drug Trametinib,[9] and cholecystography Iopanoic acid[10] as shown in Figure 1. Furthermore, among the most popular prefunctionalization in the process of drug synthesis, bromination and iodination have occupied 46%, according to Schneider group's statistics.[11]

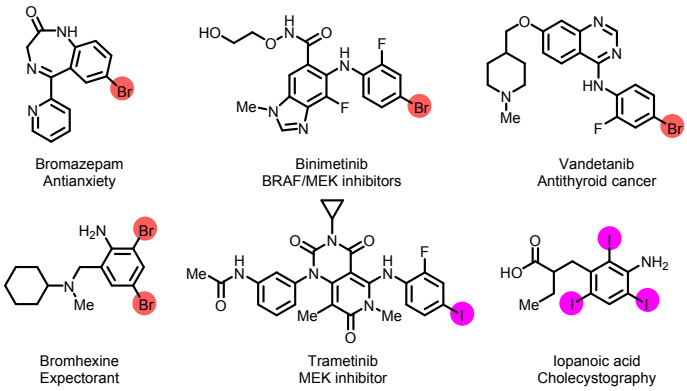

Figure 1. Representative halide-containing drugs.

Conventionally, aromatic halides are prepared through electrophilic aromatic substitution with molecular halogens (Cl_2, Br_2, and I_2).[12] However, they suffer from limitations of hazardous and corrosive conditions, poor tolerance and regioselectivity, as well as over-halogenations (Figure 2A, Method 1). Subsequently, various mild and easily-handled halogenating reagents, represented by NXS (X = Br and I) prepared from molecular halogen were developed under transition-metal-catalyzed conditions,[13] albeit with lower atom-efficiency (Figure 2A, Method 2). Alternatively, electrophilic halide X^+ (X = Br and I) can be generated from halide ions[14] with stoichiometric amounts of strong oxidants, however, functional groups sensitive to oxidative conditions are not well tolerated (Figure 2A, Method 3). Therefore, it is of great demand for developing green oxygenation method for synthetic aryl halides.

Recently, halogenation[15] of arenes has been achieved *via* visible-light photocatalysis[16]. The first selective bromination of electron-rich aromatics with oxygen gas was reported by Fukuzumi group in 2011,[17] with 9-mesityl-10-methylacridinium perchlorate (Acr^+–Mes) as photocatalyst and aqueous HBr as Br source (Figure 2B), which prefer electron strong donor (poly)methoxy-substituted arenes. König group[15d] established an excellent photocatalytic

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bromination method utilizing protonated sodium anthraquinone sulfonate (SAS)

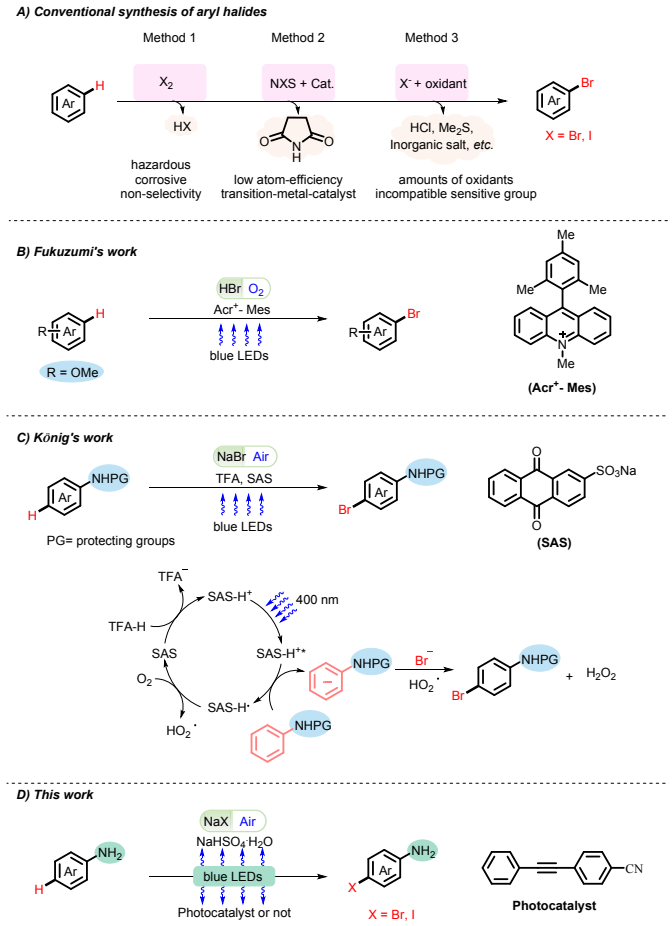


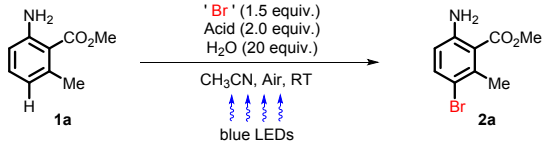
Figure 2. Construction of aryl halides.

as an oxidizing photocatalyst (E_{ox} = 1.8-2.3 V), in which long-lived triplet state SAS-H^{+}* under visible light irradiation conditions was critical for oxidizing arenes (Figure 2C). Despite with a broader functional group compatibility, until now, halogenation of unprotected primary arylamine has never been realized since of paradoxical challenges: 1) aromatic amines are susceptible to oxidation; 2) acids conditions are incompatible with amines with ammonium salts generation.

Inspiring from photocatalysis[18] in our group, we tried to establish mild ambient conditions for the bromination and iodization with great compatiblity, in which strategy accomplished the electron transfer between oxygen and halide anions *via* substrate as both catalyst and reactant controlling releasing rate of active halogen. Herein we describe the oxyhalogenation under inorganic halide sources, air, water, visible-light, room temperature, and normal pressure for primary arylamine and (hetero)arenes (Figure 2D).

We commenced our studies with methyl 2-amino-6-methylbenzoate **1a**，an intermediate[19] of 4-hydroxyphenylpyruvate dioxygenase inhibitors which with broad-spectrum weed control as well as excellent crop selectivity **,** as the model substrate with source of bromine, acid and water. Initially, different bromine anions were

Table 1: Conditions optimization[a]



Entry	' Br ' Source	Acid	Yield (%)[b]
1	LiBr	$NaHSO_4{\cdot}H_2O$	58
2	**NaBr**	**$NaHSO_4{\cdot}H_2O$**	**89 (85)[c]**
3	KBr	$NaHSO_4{\cdot}H_2O$	83
4	NH_4Br	$NaHSO_4{\cdot}H_2O$	42
5	TBAB	$NaHSO_4{\cdot}H_2O$	85
6	NaBr	$KHSO_4$	77
7	NaBr	AcOH	Trace
8	NaBr	H_3PO_4	36
9	NaBr	CSA	66
10	NaBr	H_2SO_4	74
11[d]	NaBr	$NaHSO_4{\cdot}H_2O$	76
12[e]	NaBr	$NaHSO_4{\cdot}H_2O$	63

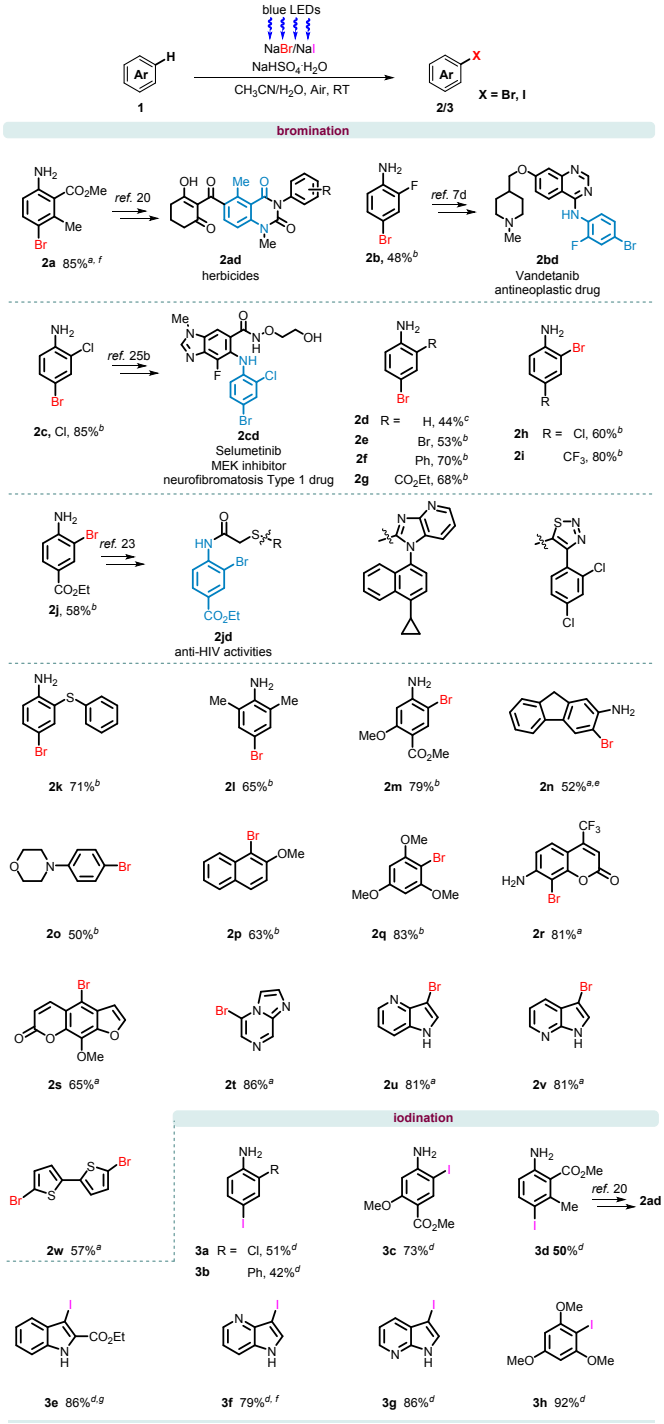
[a]The reaction condictions: **1a** (0.2 mmol), H_2O (4.0 mmol), NaBr (0.3 mmol), $NaHSO_4{\cdot}H_2O$ (0.4 mmol), CH_3CN (2.0 mL), room temperature, air, 2*3 W blue LEDs, 15 h. [b]NMR yields with CH_2Br_2 as internal standard. [c] isolated yields. [d]c = 0.05 M, 0.1 mmol scale. [e] c = 0.3 M, 0.3 mmol scale, 36 h.

tested, such as LiBr, NaBr, KBr, NH_4Br, and TBAB. Desired product **2a** were detected with good to excellent yields (Table 1, entries 1-5), and NaBr is the best (Table 1, entry 2). When $KHSO_4$ was used instead of $NaHSO_4.H_2O$, the desired product **2a** can be obtained in 77% yield (Table 1, entry 6). However, other Brønsted acids failed to perform better (Table 1, entries 7-10). The desired product **2a** was obtained in 76% yield when the concentration of the system decreased to 0.05 M (Table 1, entry 11), while yield dropped sharply when increased to 0.3 M (Table 1, entry 12). Thus, the reaction with 0.1 M at room temperature under blue LEDs irradiation was found to be the optimal conditions. Moreover, control experiment displays that no desired product **2a** was detected in the absence of acid, light, or air (Table S1).

With the optimized conditions in hand, we investigated the related compatibility of halogenation based on anilines and heteroarenes, as shown in Table 2. In general, anilines with different substituents can be well compatible. Originally, the product **2a** can be obtained from polysubstituted aniline **1a** with 85% yield, which used to serve as a pivotal intermediate for synthesis of triketone herbicides **2ad**.[19] Aniline and *ortho*- or *para*-substituted aromatic amines with transformable halogens and different electron-deficient were tested with moderate to good yields (**2b**-**2j**). It is note worthy that they are the key skelecton of pharmacoactive molecules, such as

antineoplastic drug Vandetanib **2bd**,[7] treating respiratory disease drug Bromhexine[8] (Figure 1). Among them, **2c** can be used as the starting material for the synthesis of MEK inhibitor Selumetinib **2cd**[20], which was granted orphan drug status by European medicines agency (EMA) for the treatment of neurofibromatosis type 1 (NF1) in 2018. Moreover, **2j** as an intermediates for synthesis of anti-HIV activities molecules **2jd**. [21] In addition, the oxidatively sensitive phenylthioaniline is also tolerated (**2k**). Other polysubstituted anilines (**2l** and **2m**), even within condensed aromatic systems (**2n**) can also be well transformed. In addition, tertiary aryl amine (**2o**) and other electron-rich aromatics (**2p** and **2q**) also experienced efficient bromination. More importantly, late-stage modification of natrual products, such as Coumarin **151** (**2r**) and Xanthotoxin (**2s**), delieverd desired products in good yields. Beyond arylamines, transformations with heterocyclics,[22] such as midazo[1,2-*a*]pyrazine and unprotected azaindole, presented successful results as well (**2t**-**2v**). Meanwhile, 5,5'-dibromo-2,2'-bithiophene (**2w**), an important intermediate of organic optoelectronic materials,[23] was successfully constructed under standard conditions with dual bromination. Subsequently, related iodination was also studied with sodium iodide instead of sodium bromide. Generally, substituted anilines and heteroaromatic amines can be well transformed (**3a**-**3d**). **3d** can be used in the synthesis of triketone herbicides.[19] Furthermore, unprotected ethyl 1*H*-indole-2-carboxylate and 4 or 7- *N*-hetero indole could afford the related products (**3e**-**3g**) in excellent yields. And 1,3,5-trimethoxybenzene came into being corresponding iodinated product in excellent yields (**3h**). Futhermore, gram-scale reaction demonstrated the possibility of industrial synthesis, accomplished with **2a** (74%, 1.793 g) and **3f** (63%, 1.538 g) yields, as shown figure 3.

Table 2: Aryl halides synthesis[a]



Conditions: [a]**1** (0.2 mmol, 1.0 equiv.), H_2O (4.0 mmol, 20 equiv.), $NaHSO_4 \cdot H_2O$ (0.4 mmol, 2.0 equiv.), NaBr (0.3 mmol, 1.5 equiv.), CH_3CN (2.0 mL), room temperature, air, 2*3 W blue LEDs; [b]with 4-(phenylethynyl)benzonitrile (0.04 mmol, 20 mol%); [c]with 2-(phenylethynyl)thiophene (0.04 mmol, 20 mol%); [d]NaI (0.6 mmol, 3.0 equiv.) instead of NaBr; [e]acetone as solvent; [f]10 mmol scale; [g]NH_4I instead of NaI; yields of the isolated products are given.

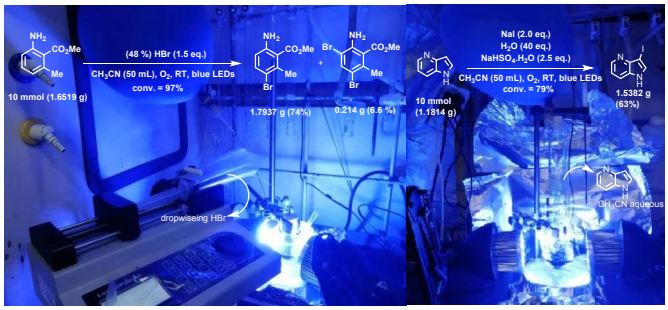


Figure 3. Gram-scale reactions.

Further mechanistic studies were carried out to figure out the intrinsic mechanism of this transformation. First, according to ultraviolet-visible absorption spectrums, aniline instead of other species was found to be photosensitizer, absorbing light energy and providing energy for the subsequent electron transfer (SI, Section III-1). Then, fluorescent quenching experiments disclosed NaBr can quench the active aryl amine efficiently (SI, Section III-2). Radical trapping experiment with 1,1-diphenylethylene suggested the existence of bromo radical through the detection of trapping product **4** by GCMS, which further proved the electron-transferring process between bromide anion and photosensor (SI, Section III-3). Subsequently, active oxygen species were explored. Electron

paramagnetic resonance (EPR) study with 5,5-dimethyl-1-pyrroline-1-oxide (DMPO) did not show apparent radical signals, indicating neither superoxide radicals ($O_2^{-\bullet}$) nor hydroxyl radicals (HO•) were crucial species (SI, Section III-4). Simultaneously, the above results were further corroborated by experiments with various active oxygen species inhibitors, such as singlet oxygen ($^1O_2$) inhibitors (NaN_3, 1,3-diphenylisobenzofuran), superoxide radical ($O_2^{-\bullet}$) inhibitors (1,3-diphenylisobenzofuran), and hydroxy radical (HO•) inhibitor (^{t}BuOH) (SI, Section III-5). Finally, another important active oxygen species—hydrogen peroxide (0.0109 mmol) was found in standard system *via* quantitative iodometric experiments (SI, Section III-6) , which might be helpful to oxidize bromo anion to radical

According to the above results, a postulated reaction mechanism is displayed in Figure 4. Initially, arylamine were excited to generate an excited state (**SM***) under blue light. Then, electron transfer between **SM*** and halogen anion formed aromatic amine radical anion (**SM**$^{-\bullet}$) and halogen radical. The oxidation of **SM**$^{-\bullet}$ by air assisted by a proton, generating active oxidant hydrogen peroxide and regenerated ground-state arylamine (**SM**). Then, X_2 might be generated from halide radical, followed by subsequent electrophilic aromatic substitution ($E_{Ar}S$) between X_2 and **SM** producing **P**. Controlled release and oxidization helped to prompt the regioselectivity.

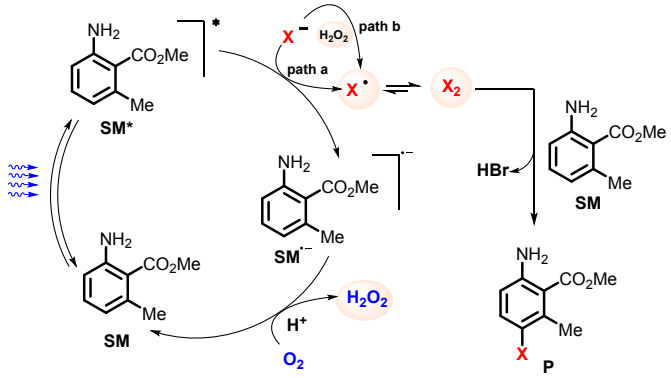


Figure 4 Proposed mechanism.

Conclusions

In summary, an easily-handled method for constructing (hetero)arenes bromide and iodide have been developed at room temprature and normal pressure under blue light, employing abundant halide anions in water as halide source, air as oxidant. This strategy provided green methodology for constructing important phamaceutical intermediates and modifing valuable molecules. Gram-scale reactions proved its practicability. Further explorations of industrial applications *via* this protocol are underway in our laboratory.

General Procedure

In a 25 mL Schlenk tube, **1** (0.2 mmol, 1.0 equiv.), NaBr (0.3 mmol, 1.5 equiv.), $NaHSO_4.H_2O$ (0.4 mmol, 3.5 equiv.), H_2O (72.0 mg, 20.0 equiv.) were added into CH_3CN (2.0 mL), and the reaction mixture was stirred at room temperature irradiated with 2*3 W blue LEDs, which is opened to air. After the reaction completed, the reaction mixture was neutralized with saturated sodium bicarbonate and extracted with dichloromethane for three times. Then, organic layers were combined, dried over sodium sulfate and filtration. After evaporation of solvent, the residue was purified by column chromatography (PE/EA) to give the corresponding products **2** or **3**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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