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Article

Sustainable Aerobic Bromination with Controllable Chemoselectivity

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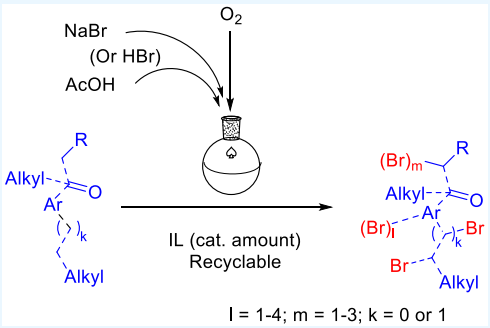
ABSTRACT: The formation of C−Br(s) is one of the most fundamental reactions in organic synthesis. Oxidative bromination is a "green" way to achieve it. Aerobic bromination has drawn great interest in the past decades, while the poor substrate scope and selectivity, low efficiency, and the use of metal catalyst still confine its application. In this article, we establish a transition-metal-free aerobic bromination promoted by ionic liquid in a catalytic amount with controllable chemoselectivity toward numbers of C−Br(s) formed, and both NaBr/AcOH and HBr(aq) could be used as the bromine source. This methodology shows high efficiency and has a broad substrate scope for various kinds of C−H(s). We also validate this system by the gram-scale (one-pot) synthesis of functional molecules and direct recycle of the catalyst. The possible radical pathway of this catalysis is also presented with evidence.



INTRODUCTION

Organic compounds with C−Br(s) are important building blocks/intermediates in synthesis;[1] many (multi)bromo-substituted hydrocarbons are also used directly as functional agents, such as pharmaceuticals, flame retardants, herbicides, etc.[2] (Figure 1). The most simple and traditional synthesis of these compounds is C−H(s) bromination with bromine molecules.[3] However, the poor selectivity and hard-handling of liquid bromine limit its application. Over the past decades, many organic ammonium tribromides (OATBs) have emerged to increase the monochemoselectivity,[4] while the atom economy of Br is still low (less than 33%).

One possible solution to increase the atom efficiency of bromine atom is using agents directly with "Br^+" (e.g., NBS). Several examples are reported and applied in industry by using these agents,[3a,5] whereas the whole atom economy is still unsatisfied due to the high whole molecule weight of these agents, according to principles of green chemistry,[6] since other parts rather than Br in these reagents convert to byproducts/waste (e.g., NBS to succinimide). The other alternative with better whole atom efficiency is oxidative bromination, which uses the bromine anion as a bromine source and oxidants to generate active "Br^+" for the substitution of existing H in hydrocarbons (Scheme 1). Among all oxidants used,[7] molecular oxygen (air) is the most cheap and available one.[7a] Research on aerobic oxidative bromination has exploded in the last two decades, with the aim to develop a "greener" (metal-free, VOC-free, catalyst-recyclable, etc.) methodology,[7a,8,9] while other important aspects of organic synthesis, such as substrate scope, selectivity, efficiency, etc., were ignored to a certain extent.

Liang's group first reported transition-metal-free oxidative bromination with oxygen as oxidants.[9e] The substrate scope is only confined to phenyl ethers, methylarenes, or acetophenone derivatives, and hazardous VOCs (CH_3CN) are used as solvent. About a decade ago, we first reported solvent-free aerobic bromination (Scheme 2a),[9a] and 1 mol % of transition metal salt is used as catalyst. Ren et al. released a reusable IL-catalyzed bromination of phenyl esters. Although IL used in this report can be reused, liquid bromine is used as a Br source, and more than stoichiometric IL is used as both catalyst and solvent (Scheme 2b).[9b] Not long ago, we first reported ionic liquid (IL) promoted aerobic bromination in only a catalytic amount.[9c,d] The main drawback of this method is that the IL catalyst can be reused only by adding nitric acid after workup (Scheme 2c), let alone the low efficiency and poor substrate scope. All of the reported aerobic brominations[7a,8,9] have several common drawbacks: (1) The chemoselectivity (mono/di/multibromination)[10] is not controlled. Substrates can only convert to monobrominated product, while common reagents other than aerobic bromination (e. g., Br_2, NBS) can control the number of C−Br(s) formed, which can possibly be

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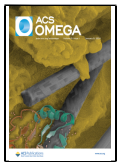


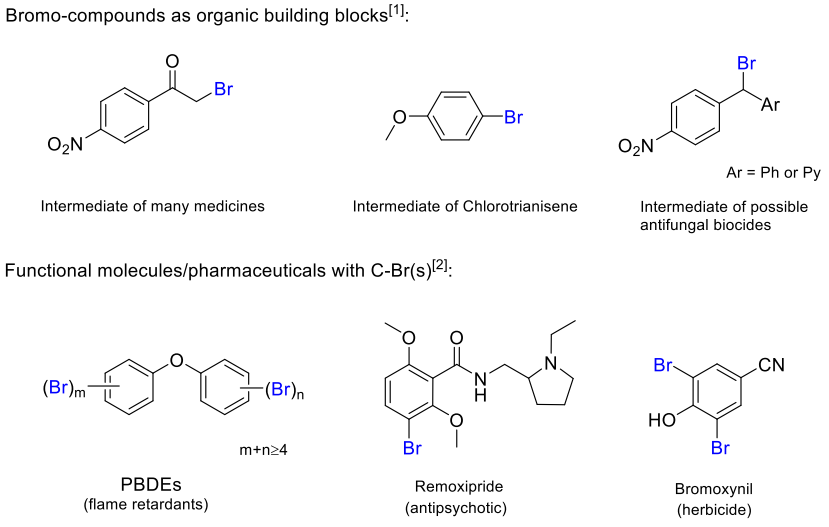
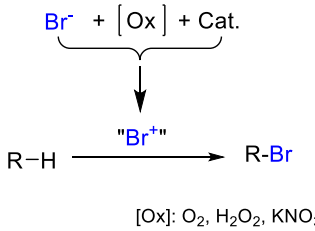


Figure 1. Examples of functional molecules and intermediates with C−Br(s).

Scheme 1. Pathway of Oxidative Bromination



attributed to the poor efficiency of the catalyst in aerobic halogenation, especially the metal-free ones. (2) The substrate scope is only confined to the phenylic position of active aromatic compounds (arenes with EDGs) or the α-position of benzophenone derivatives. (3) The catalyst (used in a catalytic amount) cannot be directly recycled. Thus, the aim of exploring effective aerobic bromination with high efficiency and broad substrate scope is of great significance, especially when considering sustainability and practicability for controllable multibromination.

In this work, we present an efficient (compared to all existing aerobic halogenations) aerobic bromination system for various kinds of C−H(s) bonds; many examples can proceed at room temperature. Besides, other advantages of this methodology consist of its high sustainability and controllable chemoselectivity.

RESULTS AND DISCUSSION

Selection of Ionic Liquid Catalyst. Initially, according to our previous reports,[9c,d] we chose pyridinium as the anion and substituted *N*-H with *N*-alkyl, aiming to make the IL more amphipathic and stable. Thus, we synthesized *N*-butyl, *N*-heptanyl, and *N*-dodecanylpyridinium nitrate ([C_4Py]-NO_3\[C_7Py]NO_3\[C_{12}Py]NO_3, their structures are shown in Figure S1 in Supporting Information (SI)) and used anisol as the model substrate. For these ILs, there is only a slight difference in catalytic activity in anisol bromination (Table 1, entries 1−3, and Table S1 in SI for details). *N*-Butylpyridinium nitrate ([C_4Py]NO_3) is the most practical among these three, when considering raw material cost[11] and molecular weight (atom efficiency).[6] The reaction with 5 mol % of [C_4Py]NO_3 as the catalyst shows good efficiency, and it takes only 2 h at

Scheme 2. Featured Examples of VOC-Free Aerobic Oxidative Bromination

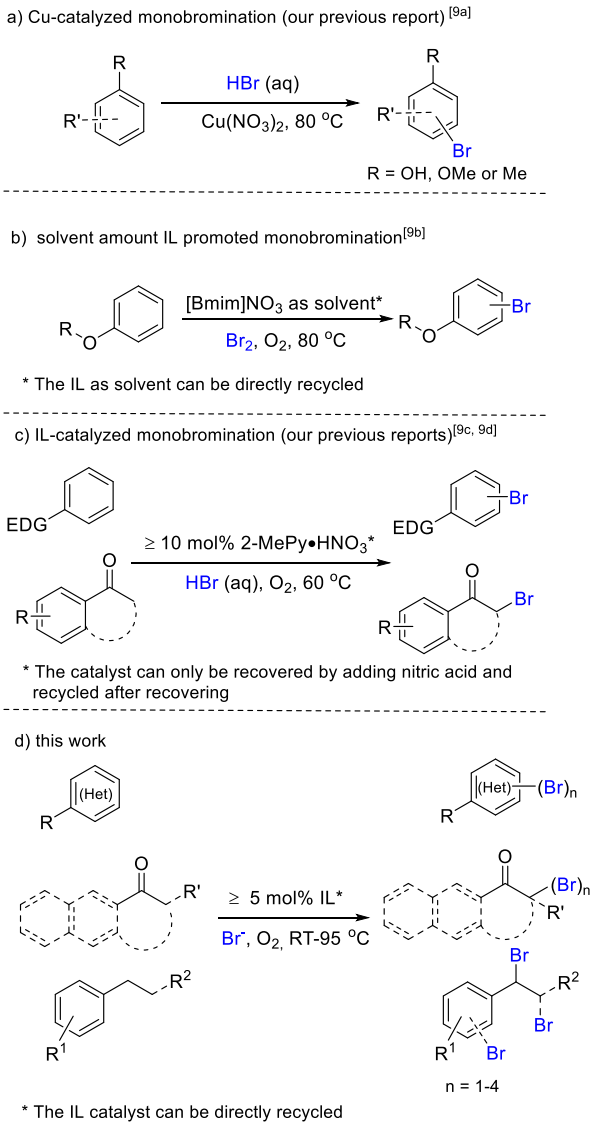


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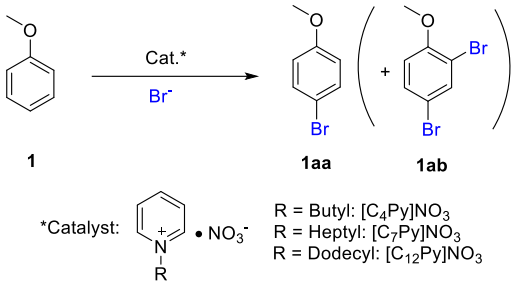
Table 1. Screen of the Catalyst and Comparison with Previous Metal and VOC-Free Reports[a]



try	Catalyst	Cat. amount	Time	Conversion[b]	ref.
1	$[C_4Py]NO_3$	1 mmol %	18 h	99%	/
2	$[C_7Py]NO_3$	1 mmol %	16 h	99%	/
3	$[C_{12}Py]NO_3$	1 mmol %	16 h	99%	/
4	$[C_4Py]NO_3$	5 mmol %	2 h	100% (99)	/
5[c]	$[C_4Py]NO_3$	5 mmol %	6 h	99% (98)	/
6[d]	2-MePy·NO_3	10 mmol %	48 h	99% (97)	9c
7[e]	$[Bmim]NO_3$	solvent	24 h	99% (70)	9b
8[f]	$[C_4Py]NO_3$	5 mol %	5 h	99% (98)	/

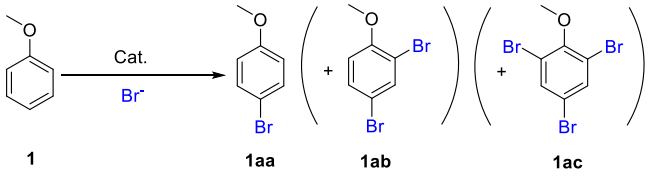
[a]Reaction conditions: 2 mmol anisol (**1**), 1.1 equiv of HBr (48% aq). Reaction takes place at RT with O_2 balloon equipped. [b]Determined by GC. Numbers in the parentheses are isolated yields. [c]Air was used as an oxidant instead of an O_2 balloon. [d]5 mmol of **1** reacts with 5.5 mmol of HBr with air as oxidant. [e]0.5 mmol of **1** reacts with 0.5 mmol of HBr at 80 °C with air as oxidant. [f]1.2 equiv NaBr and 7 mL ofAcOH are used instead of hydrobromic acid.

RT to complete the bromination in this condition (Table 1, entry 4). We also compared this catalyst to previous reports of aerobic bromination,[8,9] and it seems $[C_4Py]NO_3$ is much more effective, especially when compared to the metal and VOC free ones (Table 1, entries 5−7).[9] Besides, this methodology could also be applied with NaBr and acetic acid (AcOH, Table 1, entry 8 and Table S1 in the SI), which all edible (NaBr as an ingredient of sea salt and AcOH as an ingredient of vinegar). Although the NaBr/AcOH system requires longer reaction time, the conversion is comparable to HBr bromination (entry 8, Table 1). Inspired by the high activity of $[C_4Py]NO_3$ for catalyzing aerobic bromination, we planned to obtain di- and multibromo products by simply change the Br^- ratio and reaction conditions after optimization of monobromination (details of the screen of the catalyst and bromine source are presented in Table S1 in SI).

Reaction Condition Optimization. Through optimization (Table 2 and Table S2 in SI for details), the condition for monobromination is ascertained (Table 2, Entry 4), and as discussed above, we also tried to get di- and tribromo anisols by multiplying Br^- usage and increasing catalyst loading/reaction temperature. The results confirm our conception that the chemoselectivity of this aerobic bromination can be controlled simply by changing the amount of reagents and reaction temperature under mild conditions (Table 2, Entries 6 and 7; details of optimization for di- and tribromination are presented in Table S3 in SI). Besides, the NaBr/AcOH system was also optimized, and the yields are similar to those of the HBr system (Table 2, Entries 8−10; details of the optimization are presented in Table S4 in SI).

Substrate Scope Extension for Aromatic Bromination. Substrate scope extension is then performed. HBr (method A) or NaBr/AcOH (method B) is used as the bromine source. As shown in Scheme 3, various bromoarenes can be synthesized with $[C_4Py]NO_3$ catalysis. Two specialties which distinguish this methodology from other aerobic brominations should be noted: (1) di- (**1ab**, **1eb**), tri- (**1ac**, **1ec**), and multi- (**1ed**) bromination could also proceed smoothly with high yields, making the method chemoselective; (2) aromatic substrates with an EWG group can also be brominated in moderate yields (**1j**, **1k**). Also, like other reports,[8,9] monobromo phenyl products with strong (**1aa**, **1b**, **1ea**, **1g**) and weak EDG (**1c**, **1da** + **1db**, **1f**) are all obtained in high efficiency. Bromoarene, other than phenyl derivatives (**1h**), could also be synthesized in very high yield, as well as bromo-heteroarene (**1i**).

Table 2. Summary of Optimization and Further Exploration for $[C_4Py]NO_3$-Catalyzed Bromination[a]



Entry	Catalyst amount	Br^- (equiv)	Temperature	Time	Conversion[b]	Selectivity[b]
1	3 mol %	1.1	RT	8 h	100%	98%[c](97)
2	1 mol %	1.05	RT	24 h	100%	99%[c](99)
3	3 mol %	1.05	RT	10 h	100%	99%[c](99)
4	5 mol %	1.05	RT	3 h	100%	99%[c](99)
5	5 mol %	1.02	RT	12 h	92%	99%[c]
6	10 mol %	2.3	60 °C	8 h	100%	93%[d](86)
7	20 mol %	3.2	90 °C	40 h	100%	87%[e](77)
8[f]	5 mol %	1.15	RT	5 h	100%	99%[c](99)
9[f]	10 mol %	2.3	60 °C	12 h	100%	95%[d](90)
10[f]	20 mol %	3.5	90 °C	50 h	94%	90%[e] (72)

[a]Reaction conditions: 2 mmol of anisol, catalyst, HBr (48% aq). Reaction takes place with O_2-balloon equipped. [b]Conversion (for the substrate with one less Br) and selectivity are determined by GC with comparison to the NIST2017 Mass Spectral Library by GC-MS. Numbers in the parentheses are isolated yields. [c]Selectivity for **1aa**. [d]Selectivity for **1ab**. [e]Selectivity for **1ac**. [f]NaBr and AcOH (8, 15, or 20 mL) are used as a bromine source.

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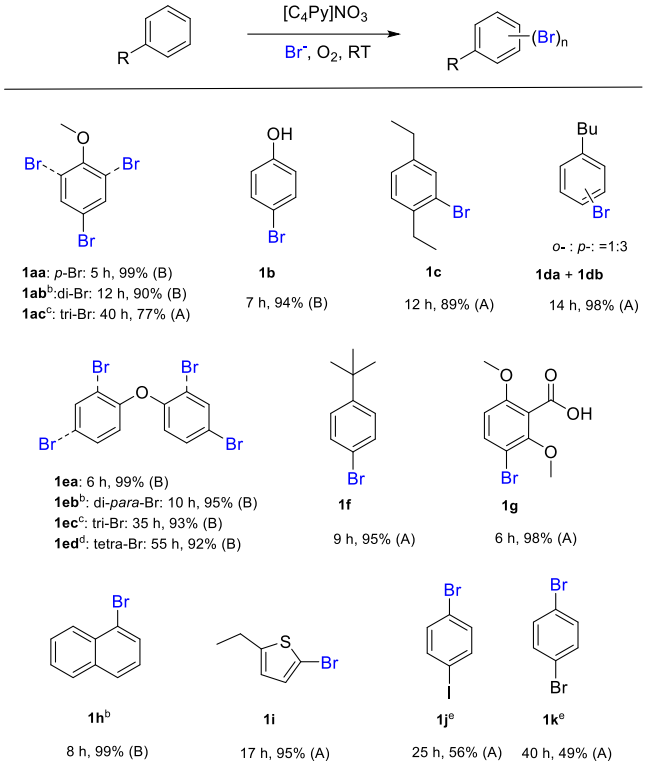
Scheme 3. Aromatic Bromination in the O_2/$[C_4Py]NO_3$/HBr System[a]

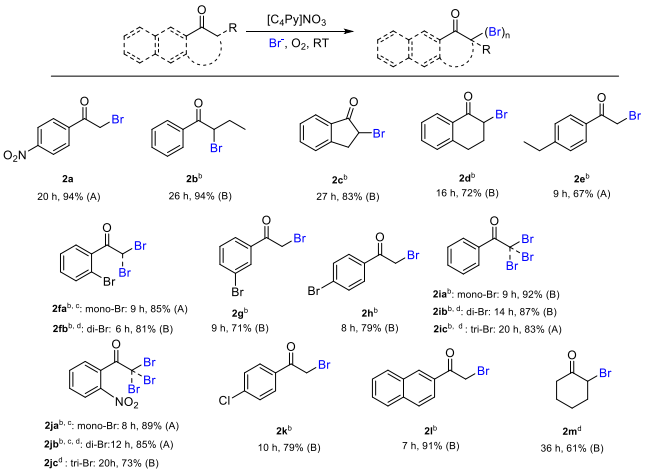


[a]Reaction conditions: substrate (2 mmol), catalyst (0.1 mmol), O_2 balloon, RT. Method A: HBr (48% aq): 2.1 mmol for monobromination, 4.6 mmol for dibromination, 6.4 mmol for tribromination. Method B: 2.3 mmol NaBr and 8 mL of AcOH for monobromination, 4.6 mmol of NaBr and 15 mL of AcOH for dibromination, 7 mmol of NaBr and 15 mL of AcOH for tribromination, and 9 mmol of NaBr and 20 mL of AcOH for tetrabromination. Letter in the parentheses following isolated yield signifies which Br source (A/B) is used. [b]Reaction was carried out at 60 °C with 0.2 mmol of catalyst. [c]Reaction was carried out at 90 °C with 0.4 mmol of catalyst. [d]Reaction was carried out at 95 °C with 0.6 mmol of catalyst. [e]Reaction was carried out at 95 °C with 2.0 mmol of catalyst and 2.8 mmol of HBr.

Substrate Scope Extension for Ketonic Bromination. Next, due to the similarity of electrophilic aromatic bromination and ketonic α-bromination, several ketones were chosen to expand the substrate scope (Scheme 4). The tested ketones could all be brominated in excellent yields (**2a**−**2l**). Like previous aromatic scope extension (Scheme 3), we also successfully controlled the chemoselectivity by simply changing the amount of reagents and temperature (**2fb**; **2ib**, **2ic**; **2jb**, **2jc**), and aliphatic monoketone is comparatively inert. Its metal-free aerobic bromination has not yet been reported, while in our system, cyclohexanone could be aerobically brominated with good efficiency (**2m**).

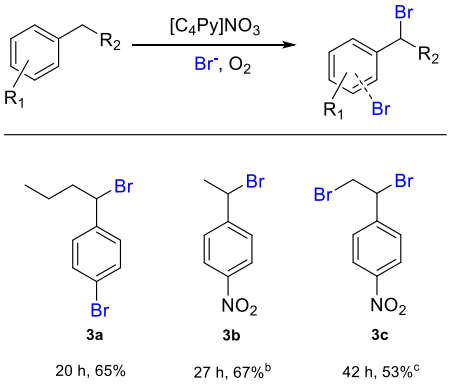
Attempt of Aerobic Benzylic Bromination. When butylbenzene was used as the substrate in our dibromination trials, a major product other than 2,4-dibromo butylbenzene was detected. The second bromine atom goes to the benzylic position instead of the aromatic position in the phenyl ring (Scheme 5, **3a**). Based on this, another benzene derivative was tested; the result shows this method could be applied to benzylic bromination (Scheme 5, **3b**), which is rarely reported in aerobic halogenation. To our surprise, the second bromine goes to β-carbon instead of di-α-bromination when more than 2 equiv of Br^- was used for *p*-nitro ethylbenzene.

Scheme 4. α-Ketonic Bromination in the O_2/$[C_4Py]NO_3$/HBr System[a]



[a]Reaction conditions: substrate (2 mmol), catalyst (0.1 mmol), O_2 balloon, RT. Method A: HBr: 2.1 mmol for monobromination, 4.6 mmol for dibromination, 6.5 mmol for tribromination. Method B: 2.3 mmol of NaBr and 8 mL of AcOH for monobromination, 4.6 mmol of NaBr and 15 mL of AcOH for dibromination, and 7 mmol of NaBr and 15 mL of AcOH for tribromination. Letter in the parentheses following isolated yield signifies which Br source (A/B) is used. [b]Reaction was carried out at 50 °C with 0.2 mmol of catalyst. [c]HBr(aq) was added dropwise (one drop per 30 min). [d]Reaction was carried out at 95 °C.

Scheme 5. Benzylic/Alkyl Bromination in the O_2/$[C_4Py]NO_3$ System[a]



[a]Reaction conditions: substrate (2 mmol), catalyst (0.4 mmol), HBr (4.2 mmol, 48% aq), stirred at 60 °C in an oil bath with an O_2 balloon. [b]HBr (2.5 mmol) is used. [c]4.5 mmol HBr is used, and the reaction is stirred at 80 °C.

Catalyst Recycling in Gram-Scale Application. In substrate scope extension, many bromo products are important intermediates (**1g**, **2a**)[12] in pharmaceutical synthesis or could directly function as useful molecules (**1ed**),[13] which encouraged us to try large-scale application of this methodology.

To test the sustainability and practicability of this methodology, the recyclability of IL in catalytic amounts is conducted at the gram-scale. *p*-Nitro α-bromo acetophenone—the intermediate of chloramphenicol[1a,12a]—is chosen as the testing template. As shown in Table 3, the catalyst can be reused

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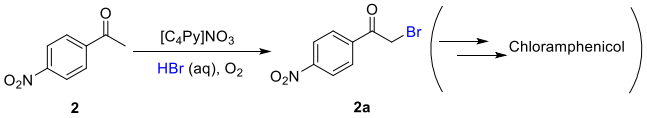
Table 3. Recycle of IL Catalyst at the Gram Scale[a]



2 2a

Entry	Recycle time	T (°C)	HBr (equiv)	Yield[b] (%)	Time (h)
1	0	40	1.2	95	32
2	1[c]	50	1.5	95	38
3	2	50	1.5	93	45
4	3	50	1.5	91	55
5	4	50	1.5	91	62

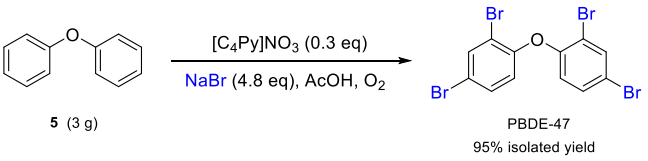
[a]10 mmol of **2**, HBr (40% aq), 0.25 equiv of $[C_4Py]NO_3$, stirred with an O_2 balloon. [b]Isolated yield. [c]Both HPLC and TLC show no significant change of IL catalyst.

directly at least 4 times in the gram scale without a significant loss of activity. The regaining of activity is only possible by simple extraction from the reaction mixture with water/EtOAc (in the aqueous layer); product **2a** is simply isolated by recrystallization from the organic layer without chromatography (see detailed procedures in the SI). This result is different from our previously reported IL, which needs to regenerate catalyst by adding nitric acid after each run.[9c,d] We then used an internal standard method to monitor the decomposition of $[C_4Py]NO_3$ in aerobic bromination of **2** (Figure S3 in SI), and it shows that after 20 h of reaction only about 10% and 30% of the catalyst decays at RT and 90 °C, respectively (Figure S3 in SI).

Gram-Scale One-Pot Pharmaceutical Application. Next, we tried to validate the methodology in the pharmaceutical synthesis. With the result of obtaining the Remoxipride intermediate[12b−d] (Scheme 3, **1g**), we tried to synthesize this antipsychotic (in racemic form) in one pot and in the gram scale. As shown in Scheme 6, 2 g of 2,6-dimethoxyphenyl-benzoic acid (**3**) was used as the substrate and monobrominated in the $HBr/O_2/[C_4Py]NO_3$ system. Without the isolation of intermediate **1g**, $SOCl_2$ was added, followed by (1-ethylpyrrolidin-2-yl) methanamine (**4**). After full exhaustion of **1g**, racemic Remoxipride (**4a**) was obtained in very good yield without column chromatography (Scheme 6, and detailed simple isolation procedures in SI).

Gram-Scale Multibromination for Synthesizing Other Useful Molecules. As one advantage of this methodology, aerobic multibromination is tested in the gram scale. PBDEs (polybrominated diphenyl ethers) were aimed to be synthesized in this aerobic way. PBDEs are one of the most commonly used fire retardants,[1,13] of which PBDE-47 is one common ingredient. PBDEs are usually produced by the coupling of freshly synthesized iodonium salts with bromophenols in two steps since direct multibromination of diphenyl ether requires harsh conditions with bromine molecules and Lewis acid.[13] Is synthesis by aerobic oxidative bromination has not yet been reported. In our preliminary substrate extension (Scheme 3, **1ed**), it can be successfully synthesized in the $NaBr/AcOH/O_2/[C_4Py]NO_3$ system, which promote us to try gram-scale application. As shown in Scheme 7, 3 g of diphenyl ether (**5**) can be aerobically multibrominated in very high yield. Again, only chromatography-free procedures (extraction and crystallization) were used during product isolation and purification, indicating that this system is possibly practical for large-scale production (Scheme 7 and detailed simple isolation procedures in SI).

Scheme 7. $[C_4Py]NO_3$-Catalyzed Aerobic Bromination to Synthesize PBDE



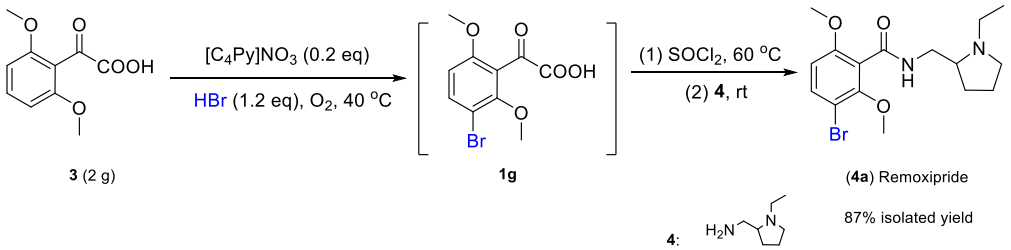
5 (3 g) PBDE-47 95% isolated yield

Competition Experiment. As presented above, this aerobic oxidative system can be applied to aromatic, kenonic, α-, and benzylic bromination. Thus, the competition bromination among C−Hs of these three kinds with HBr as the bromine source proceeds (Scheme S2 in SI), and as expected, the ease of bromo substitution of H of phenyl with EDG > ketonic α → benzylic, whether the reaction takes place at RT or higher temperature.

Preliminary Investigation of Possible Mechanisms. To initially prove the key role of catalyst, a homogeneous system with AcOH/NaBr/Anisol was set with 5 mol % of $[C_4Py]NO_3$ added or not. The conversion with $[C_4Py]NO_3$ goes to 100% with time lengthened, while without $[C_4Py]NO_3$, the reaction conversion is only trace even after days in a 100 °C oil bath, which is the same when $[C_4Py]Br$ is used as a catalyst. These results confirm the catalytic activity of NO_3^-. Also, with the consideration of previous reports,[9] it seems that butyl pyridinium could stabilize NO_3^-, thus making the catalyst directly recyclable.[9c]

Next, due to the radical property of decomposed intermediates of NO_3^- (NO and NO_2), we assume that radical intermediate(s) plays a key role in the pathway, especially for the benzylic bromination product. Thus, we designed several parallel experiments with different amounts of radical scavenger/promoter using butylbenzene as a substrate for comparison. As shown in Figure S4 in the SI, when more radical scavenger BHT (2,6-di-*tert*-butyl-4-methylphenol) is added, the catalysis is retarded; this is more prominent at lower temperature. In contrast, bromination proceeds better if a

Scheme 6. One-Pot Synthesis of Remoxipride with $[C_4Py]NO_3$-Catalyzed Aerobic Bromination



3 (2 g) 1g (4a) Remoxipride 87% isolated yield 4:

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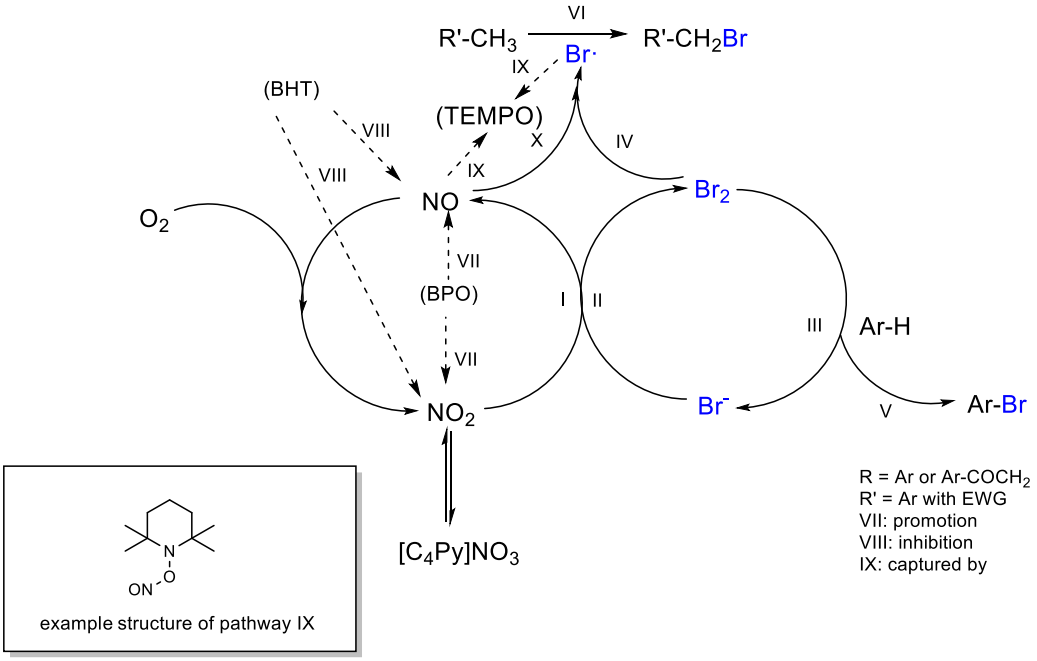
Scheme 8. Possible Mechanism in This Bromination System



radical promoter (benzoyl peroxide, BPO) is added, and the degree (speed) of reaction retardation/promotion is positively correlated to the amount of radical scavenger/promoter added. These results suggest that the reaction possibly goes through a radical pathway, while we did not see the ratio of phenyl/benzyl bromo product change within all conditions we tested. The reaction efficiency is not affected by natural light or in dark conditions. All the above indicate that the homolysis of Br_2 may possibly be catalyzed by radical(s) like NO or NO_2.[15]

We also tried another radical additive, TEMPO, and captured intermediates characterized by GC-MS (structures captured and their spectra are listed in SI, and an example is shown in Scheme 8), which indicates the existence of NO and Br radicals during reaction. As expected, with the deactivation of radical intermediates (such as NO) by TEMPO, the reaction was retarded obviously.

With the previous results and related reports,[9,14] we speculate the entire pathway of this IL-catalyzed aerobic bromination as Scheme 8. The radical scavenger/promoter can both affect the survival and activity of NO_2 and NO, which are commonly known as radicals.[15] They are critical for catalyzing aerobic oxidation of Br^- to Br_2 (steps I and II). These radical intermediates not only can catalyze the oxidative formation of Br_2 (steps I and II) by O_2 but also may participate in the homolysis of Br_2 to generate the Br• radical (steps IV and X), before step VI happens (radical bromination). Other pathways are normal, such as Br_2-electrophilic bromination of arenes to regenerate Br^- (steps III and V). Although many reports give a possible mechanism for nitrate-catalyzed aerobic bromination, they seldom mentioned the detailed radical pathway.[9,14] All additives used above (BPO, BHT, and TEMPO) could influence these radical pathways (steps VII, VIII, and IX, Figure S4 in SI), and some radical intermediates were captured by TEMPO (step IX; see SI for more captured structures). These explorations and explanations could possibly enlighten the future development of regioselective (e.g., aromatic/benzylic position) aerobic bromination.

CONCLUSIONS

In summary, a sustainable and efficient aerobic bromination has been developed; different kinds of C−H(s) can be transformed to C−Br(s) in mild conditions with controllable chemoselectivity. Several peculiarities of this metal-free methodology might be emphasized: (1) chemoselectivity of mono/di/multiaerobic bromination can be controlled simply by changing the amount of Br^- and reaction temperature; (2) excellent substrate scope is achieved, and several types of brominations other than aromatic halogenations are performed successfully, such as benzylic/alkyl bromination and (aliphatic) ketonic α-bromination; (3) phenyl substrates with EWG can also be brominated in moderate yields; (4) only a catalytic amount of metal-free IL is used, and it can be directly reused by simple workup in the gram-scale; (5) both hydrobromic acid (VOC and solvent-free) And NaBr/AcOH (all exist in ordinary condiment) could be used as the bromine source. Besides, the practicability of this methodology is also validated by several examples of (one-pot) synthesis of intermediates for pharmaceuticals and other functional molecules in the gram scale. We also tried some controlled comparison experiments and captured intermediates to preliminarily explore the possible mechanism, which might be through a radical pathway. Several related projects are currently studied in our group, e.g., establishing regioselective aerobic halogenation, screening more efficient/cheap ILs, applying this method to other kinds of halogenations (such as bromination of alkenes, chlorination, and iodination), investigating more detailed mechanisms, etc.

EXPERIMENTAL SECTION

General Procedure of Aerobic Bromination. Substrate, ionic liquid catalyst, and bromine source (hydrobromic acid or NaBr/AcOH) were mixed at room temperature in a flask with condenser. The system was sealed and equipped with an O_2 balloon. The mixture was stirred at a certain temperature for several hours (monitored by TLC or GC). After the reaction

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was completed, all VOCs were removed under reduced pressure, and then water and EtOAc were added to the mixture with stirring at room temperature. The workup (recrystallization or column chromatography) of the organic layer was then to give the brominated product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c05954.

Detailed optimization, experimental procedures, and characterization of intermediates and products, etc. (PDF)

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Notes

The authors declare no competing financial interest.

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