

# An efficient copper-catalysed aerobic oxybromination of arenes in water†

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An aerobic oxybromination of arenes catalysed by  $\text{Cu}(\text{NO}_3)_2$  was achieved using HBr as a bromine source, molecular oxygen as the oxidant and water as solvent with high selectivity. The catalyst shows not only high chemoselectivity for monobromination, but also a remarkable regioselectivity for *para*-isomers.

Bromoarenes are versatile reagents in synthetic chemistry that are useful in carbon–carbon bond and carbon–hetero atom bond formation *via* Ullmann, Heck, Stille and Suzuki reactions.<sup>1</sup> At the same time, they are also used widely in the manufacture of flame retardants, disinfectants, antibacterial drugs and many other products.<sup>2</sup> Traditional methods for the synthesis of bromoarenes involve aromatic halogenations using various brominating agents such as bromine,<sup>3</sup> NBS,<sup>4</sup> hypobromite,<sup>5</sup> bromate<sup>6</sup> and organic perbromide.<sup>7</sup> Recently, tribromide ionic liquids have been developed as greener and more highly selective brominating agents.<sup>8</sup> However, the Br atom economy is less than 50%.

An alternative solution is oxybromination using bromide anions as a bromine resource. Typically, oxybrominations of aromatic compounds are carried out with a combination of bromide anion and a variety of oxidants.<sup>9</sup> All of these systems require stoichiometric oxidizing agents, which leads to environmental problems due to undesirable by-products.

Compared with that as described above, hydrogen peroxide-based oxybromination is a mild and environmentally friendly system, in which the only byproduct is water.<sup>10</sup> However, the relatively high cost of hydrogen peroxide and its undesirable decomposition during the reaction at elevated temperatures cannot be avoided.

Oxybromination has become more and more atom-economical and environmentally friendly in recent years since  $\text{H}_2\text{O}_2$  was replaced by  $\text{O}_2$ , the most abundant and cheapest oxidant.<sup>11</sup> Several examples of aerobic oxybromination have appeared that all use VOCs (volatile organic compounds) as solvents and metal salts (more than 5 mol%) as catalysts. These cause waste that is hazardous to the environment. Recently, the oxyhalogenation of aromatic compounds was examined in ionic liquids (ILs) to overcome these problems.<sup>12</sup> Apart from their low selectivity, the methods involve the use of stoichiometric amounts of oxidative IL as co-solvent and the applicable scope of aromatic substrates is very narrow.

Herein, we report an aerobic oxybromination using HBr as the bromine source in water with a high selectivity and extensive

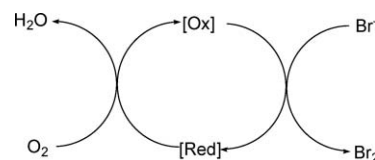
**Table 1** Oxybromination of phenol with HBr catalysed by different metal salts<sup>a</sup>

Entry	Metal salt	Time/h	Conversion <sup>b</sup> (%)
1	$\text{Ni}_2\text{SO}_4$	2	<1
2	$\text{MnSO}_4$	2	<1
3	$\text{Co}(\text{OAc})_2$	2	<1
4	$\text{NaNO}_2$	2	7
5	$\text{FeCl}_2$	2	<1
6	$\text{FeSO}_4$	2	<1
7	$\text{Fe}_2(\text{SO}_4)_3$	2	<1
8	$\text{CuSO}_4$	2	37
9	$\text{Cu}(\text{Ac})_2$	2	50
10	$\text{CuBr}$	2	<1
11	$\text{CuCl}_2$	2	30
12	$\text{CuCl}$	2	<1
13	$\text{Cu}(\text{NO}_3)_2$	2	85
15	$\text{Cr}(\text{NO}_3)_3$	3	100 <sup>c</sup>
16	$\text{KNO}_3$	3	81 <sup>c</sup>
17	$\text{Fe}(\text{NO}_3)_3$	3	21 <sup>c</sup>
18	$\text{Pb}(\text{NO}_3)_2$	3	100 <sup>c</sup>

<sup>a</sup> Aerobic oxybromination conditions were as follows: phenol (5 mmol), HBr (5.5 mmol, 8 mol L<sup>-1</sup> aqueous solution), at 100 °C. <sup>b</sup> Conversion and selectivity were determined by GC. <sup>c</sup> Some by-products were detected besides brominated phenols.

scope of application. Only 1 mol% of  $\text{Cu}(\text{NO}_3)_2$  is used as a catalyst in this research.

Among the reports of aerobic oxybromination, there are some common features of the catalyst (Scheme 1). (1) It can oxidize  $\text{Br}^-$  to  $\text{Br}_2$  and itself turn into a protosalt simultaneously. (2) The protosalt can be oxidized by  $\text{O}_2$  and then repeat the preceding reaction until the  $\text{Br}^-$  is exhausted. Therefore, in our initial study, we tested the activity of various multivalent inorganic metal salts in oxybromination reactions (Table 1). In this experiment, phenol was chosen as the substrate to screen for the best catalyst. Among all of the metal salts tested,  $\text{Cu}^{2+}$  salts, especially  $\text{Cu}(\text{NO}_3)_2$ , showed the best catalytic efficiency, which prompted us to further optimize the reaction conditions.



**Scheme 1** The valence state of catalyst during the oxybromination.

The conditions of oxybromination catalysed by  $\text{Cu}(\text{NO}_3)_2$  are presented in Table 2. The influence of temperature is apparent (Table 2, entries 1–4). Despite the increase of  $\text{Cu}(\text{NO}_3)_2$  significantly accelerating the reaction, it also produces quite a few by-products besides brominated phenols (Table 2, entries 3–6). According to results of our experiments, 1 mol% of catalyst

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**Table 2** Optimization of reaction conditions<sup>a</sup>

Entry	<i>T</i> /°C	Conditions <sup>b</sup>	Time/h	Catalyst (mol%)	Conversion <sup>c</sup> (%)
1	40	1	20	10	<10
2	60	1	20	10	70
3	80	1	4	10	98 <sup>d</sup>
4	Reflux	1	3.5	10	98 <sup>d</sup>
5	80	1	2.5	15	99 <sup>d</sup>
6	80	1	3.5	5	98 <sup>d</sup>
7	80	1	6	1	98
8	80	2	7	1	98
9	80	3	10.5	1	98
10	80	4	8	1	97

<sup>a</sup> Aerobic oxybromination conditions were as follows: phenol (5 mmol), HBr (5.5 mmol, 8 mol L<sup>-1</sup> aqueous solution), at 100 °C. <sup>b</sup> Conditions: 1. O<sub>2</sub> balloon; 2. O<sub>2</sub> pumped into the mixture; 3. air pumped into the mixture with an air compressor; 4. reaction carried out in an open system. <sup>c</sup> Conversion and selectivity were determined by GC. <sup>d</sup> Some by-products were detected besides brominated phenols.

is desirable, which almost completely converts the phenol into bromophenol and avoids the formation of by-products (Table 2, entries 6–10). Compared with pure O<sub>2</sub>, air is much cheaper, more easily available and more desirable.

The optimum reaction conditions (5 mmol of substrate, 5.5 mmol of 8 mol L<sup>-1</sup> aq. HBr and 0.05 mmol of Cu(NO<sub>3</sub>)<sub>2</sub>) were used for the oxybromination of various aromatic compounds (Table 3). From Table 3, we find that the arenes with electron donating groups can be easily brominated in this system (Table 3, entries 1–4, 6 and 7). Phenols with electron withdrawing groups can also be successfully brominated by prolonging the reaction time (Table 3, entry 5). However, electron-deficient arenes did not react with HBr in this system (Table 3, entries 9 and 10). Different from all the methods of aerobic oxybromination previously reported, toluene, a weaker active arene, can be effectively transformed into its monobromide (Table 3, entry 8). All substrates showed good (>93%) *para*-regioselectivities (Table 3, entries 1–3, 7 and 8) and *ortho*-regioselectivities in cases where the *para*-position was occupied (Table 3, entries 4–6). The high chemoselectivity (99%) of this reaction for monobromination products is remarkable. However, it should be emphasized that if the reaction is allowed to progress further, di- and multibrominated products appear. Thus, the reaction

**Table 4** Selectivity in this oxybromination system<sup>a</sup>

Entry	Substrate	Time/h <sup>b</sup>	Selectivity <sup>c</sup>
1	Phenol	9	97 (92)
2	<i>o</i> -Cresol	8	97 (92)
3	<i>m</i> -Cresol	5.5	97 (93)
4	<i>p</i> -Cresol	5	92
5	<i>p</i> -Chlorophenol	21	95
6	Hydroquinone	4	90
7	Anisole	9	98 (97)
8	Toluene	20	98 (93)

<sup>a</sup> Aerobic oxybromination conditions were as follows: aromatic compound (5 mmol), HBr (5.5 mmol, 8 mol L<sup>-1</sup> aqueous solution), Cu(NO<sub>3</sub>)<sub>2</sub> (0.05 mmol), at 80 °C. The reaction was carried out until the substrate was totally exhausted. <sup>b</sup> The reaction time at which the substrate was totally consumed. <sup>c</sup> The selectivity for the monobrominated products (the number in the parentheses are the selectivity for the *para*-bromo products) were determined by GC in comparison with authentic samples.

should be followed by regular GC analysis so as to stop the reaction as soon as the substrate is nearly consumed, in order to avoid further transformations of the monobrominated products.

The conversion of compounds 1–8 increased up to 100% by prolonging the reaction time. However, they showed diverse chemoselectivity and regioselectivity, as presented in Table 4. It is interesting that the compounds that had the *para*-position occupied (Table 4, entries 4–6) show less monoselectivity than those where the *para*-position was unoccupied (Table 4, entries 1–3, 7 and 8). Compared with the other arenes in this study, anisole showed the best regioselectivity (Table 4, entries 1–3, 7 and 8).

A possible mechanism for the copper-catalysed oxybromination is presented in Scheme 2, which can be described as a sequential cascade of double-cycle redox reactions.<sup>13</sup> Cu<sup>2+</sup>/NO<sub>3</sub><sup>-</sup> react with HBr to form Br<sub>2</sub>, while Cu<sup>2+</sup>/NO<sub>3</sub><sup>-</sup> themselves transform to Cu<sup>+</sup>/NO, which can be re-oxidised by oxygen and undergo the next oxidation of HBr. It is worth mentioning that 1 mol% Cu(NO<sub>3</sub>)<sub>2</sub> catalyses the reaction smoothly, different from all of the other aerobic oxybrominations reported.

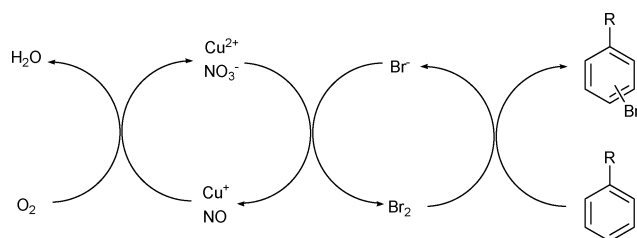
In summary, we have developed a copper-catalysed oxidative bromination of aromatic compounds under mild aerobic conditions. HBr is used as a Br source and only 1% metal catalyst is

**Table 3** The aerobic oxybromination of various arenes<sup>a</sup>

Entry	Substrate	Time/h	Conversion (%) <sup>b</sup>	Product <sup>b</sup> (%)		
				<i>o</i> -	<i>p</i> -	<i>S<sub>m</sub></i> <sup>c</sup>
1	Phenol (1)	8	98	5	94	99
2	<i>o</i> -Cresol (2)	7	97	2	97 (2a)	99(92)
3	<i>m</i> -Cresol (3)	5	97	4	95 (3a)	99(91)
4	<i>p</i> -Cresol (4)	4	92	99 (4a)	—	99(90)
5	<i>p</i> -Chlorophenol (5)	18	94	99 (5a)	—	99(91)
6	Hydroquinone (6)	3	92	99 (6a)	—	99(90)
7	Anisole (7)	8	98	—	99	99(95)
8	Toluene (8)	15	95	5	94	99
9	Chlorobenzene (9)	24	<1	—	—	—
10	Nitrobenzene (10)	24	<1	—	—	—

<sup>a</sup> Aerobic oxybromination conditions were as follows: aromatic compound (5 mmol), HBr (5.5 mmol, 8 mol L<sup>-1</sup> aqueous solution), Cu(NO<sub>3</sub>)<sub>2</sub> (0.05 mmol), air was pumped into the reactor at 80 °C. <sup>b</sup> Conversion and selectivity were determined by GC in comparison with authentic samples.

<sup>c</sup> Selectivity for monobrominated products (the numbers in the parentheses are the isolated yields of the main product).



**Scheme 2** A possible mechanism of the Cu-catalysed oxybromination.

required. This procedure represents an attractive green approach to brominated aromatics for several reasons: (i) it avoids the use and handling of  $\text{Br}_2$ ; (ii) no VOCs (volatile organic compounds) are used as solvents; (iii) the components in the reaction, air–HBr–water, are non-toxic, non-flammable, cheap and readily available. Therefore, this method offers an efficient system for the organic solvent-free oxybromination of aromatics with high atom economy and selectivity.

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