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Copper-promoted oxidative mono- and di-bromination of 8-aminoquinoline amides with HBr and DMSO†

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An efficient and convenient method for oxidative mono- and di-bromination of 8-aminoquinoline amides is presented, utilizing hydrogen bromide (HBr) as the brominating reagent and dimethyl sulfoxide (DMSO) as a mild oxidant. Copper salts act as Lewis acid catalysts, facilitating the bromination process. The formation of C5-monobrominated products is promoted by copper sulfate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$), whereas the generation of C5, C7-dibrominated products necessitates the participation of copper nitrate ($\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$). A wide range of substrates bearing diverse functional groups undergo smooth transformation, resulting in brominated products with good to excellent yields.

Introduction

Brominated aromatics are one of the most important types of building blocks and are ubiquitous in natural products, pharmaceutically important molecules, pesticides, and flame retardants.¹ Meanwhile, due to the emergence of transition metal-catalysed cross-coupling reactions, aryl bromides are frequently employed as synthetic intermediates in the construction of carbon–carbon and carbon–heteroatom bonds.² Therefore, bromination of arenes and heteroarenes is still an important transformation in modern organic synthesis. Currently, the most commonly used bromination approach is electrophilic aromatic substitution using molecular bromine as the reagent. Nevertheless, molecular bromine is in fact extremely toxic and corrosive, posing significant handling challenges. Furthermore, its use often necessitates harsh conditions, leading to the generation of hazardous waste and undesirable polybrominated byproducts. In this context, many improved brominating reagents have been developed by bonding Br to C, N, or O atoms. However, low atom economy and high cost have limited their application.³ Given the considerations of green chemistry, atom economy, operational simplicity and selectivity, continuous investigations for the development of new brominating reagents and bromination methodologies are of great importance.

Oxidative bromination, which is inspired by the enzyme-catalysed halogenation in nature, has become a powerful tool

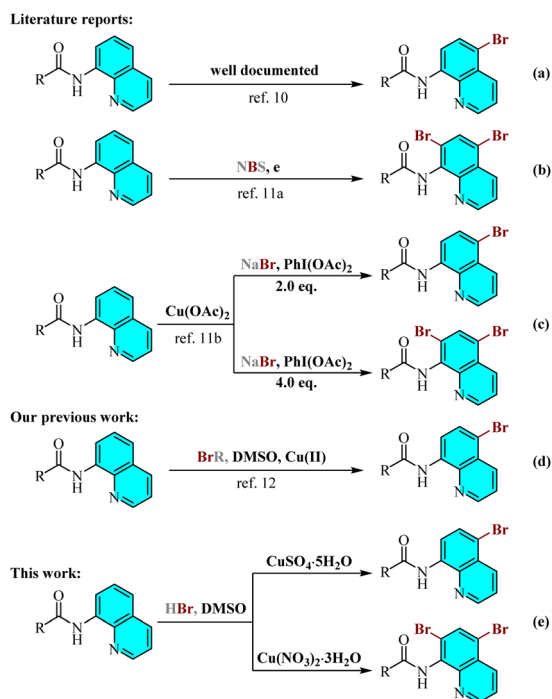
for the synthesis of bromo-containing molecules in recent years.⁴ With the assistance of various oxidants, such as molecular oxygen, hydrogen peroxide, persulfates, peracids, hypervalent iodine, selectfluor, metal-based oxidants, and others, a variety of less hazardous brominating reagents have been successfully used for the electrophilic as well as radical bromination of arenes. Among these brominating reagents, hydrogen bromide (HBr) has been proven to be a better one due to its low cost, ready availability, low toxicity, high atom economy, ease of handling, and reducibility.⁵ Moreover, hydrogen bromide is also a by-product of the Br_2 -based bromination and can be re-oxidized by stoichiometric amounts of oxidants, thereby achieving a significantly high atomic economy. Dimethyl sulfoxide (DMSO), an extremely important polar aprotic solvent both in lab and industrial settings, has been extensively employed as a reagent, catalyst, and more importantly, as an oxidant in organic synthesis.⁶ Therefore, the combination of hydrogen bromide and dimethyl sulfoxide has been widely used as an efficient brominating system for the bromination of many kinds of organic molecules.⁷

Quinoline derivatives have received continuous attention due to their widespread presence in natural products, significant biological and pharmaceutical activities, and important usage in material science.⁸ Given the significance of quinolines, considerable effort has been dedicated to the development of effective synthesis methodologies.⁹ Among them, the bromination of 8-aminoquinoline at the C5 position has received considerable attention. A number of transition metal-catalysed and metal-free bromination reactions of 8-aminoquinolines have been well documented over the past few years (Scheme 1a).¹⁰ However, compared with numerous C5 bromination reactions, only a few reports in the literature have described the dibromination reaction at the C5 and C7 positions. Xie and co-

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Scheme 1 Methods for mono- and di-bromination of 8-aminoquinolines.

workers reported an electrochemically oxidative dibromination of 8-aminoquinoline amides at the C5 and C7 positions using NBS as the halogen source (Scheme 1b).^{11a} Zhang's group developed a copper-catalysed mono- and di-bromination of 8-aminoquinoline amides by tuning the amount of NaBr/PhI(OAc)₂ (Scheme 1c).^{11b} Despite notable progress in the bromination of quinolines, the continued reliance on toxic and expensive oxidants or brominating reagents makes these reactions not only uneconomical but also suffering from low atom economy.

Recently, we have developed a copper-promoted C5-selective monobromination reaction of 8-aminoquinoline amides, employing both activated and unactivated alkyl bromides as the brominating agents, with DMSO serving as the solvent (Scheme 1d).¹² As a continuation of our efforts to explore practical and eco-friendly halogenation reaction, we now report a copper-promoted mono- and di-bromination of 8-aminoquinoline amides, employing readily available HBr/DMSO as the brominating system (Scheme 1e).

Results and discussion

We began our investigation into the regioselective bromination of 8-aminoquinoline amides with an evaluation of a range of reaction conditions employing *N*-(quinolin-8-yl)benzamide (**1a**) as the model substrate (Table 1). Initially, **1a** was treated with 40% aqueous HBr (2.5 equiv.) in the presence of CuSO₄·5H₂O (20 mol%) in DMSO (1.0 mL) at 100 °C for 12 h. To our delight, the C5-brominated product **2a** was obtained in 73% yield and the dibrominated product **3a** was not observed (Table 1, entry 1).

According to Yoshida's and Jiao's report,¹³ the bromide cation, which is generated *in situ* from DMSO and HBr, would coordinate with excess DMSO to form Br⁺(DMSO)_{*n*}, thereby dramatically reducing the electrophilic bromination reactivity. Therefore, a series of organic solvents such as acetonitrile (MeCN), ethyl acetate (EA), tetrahydrofuran (THF), 1,2-dichloroethane (DCE), and *N,N*-dimethylformamide (DMF) were screened with 0.5 mL of DMSO as the mild oxidant (Table 1, entries 2–6). MeCN was proved to be the best solvent for this reaction, achieving a yield of 93% (Table 1, entry 2), which suggests that the polarity of the solvent benefits the yield of **2a**. However, when DMF was used as the solvent, only 34% of **2a** was obtained (Table 1, entry 6), indicating that alkaline solvent inhibits the progress of the reaction. Subsequently, the bromination reaction was examined with a range of catalysts, including Cu(OAc)₂·H₂O, CuCl₂·2H₂O, CuBr₂, CuCl, and CuBr (Table 1, entries 7–11), and the results indicated that these copper-based catalysts exhibit comparable catalytic efficiency. Based on preliminary results, the effects of reagent dosage, temperature, and reaction time on the C5 bromination reaction were investigated, and the results are listed in entries 12–19. The desired product **2a** was obtained in 83% yield upon reducing the catalyst loading to 10 mol% (Table 1, entry 12). Notably, the bromination reaction still proceeds satisfactorily in the absence of CuSO₄·5H₂O, affording **2a** with 77% yield (Table 1, entry 13). These results suggest that copper catalyst promotes the bromination and an electrophilic substitution pathway may be involved. The quantity of HBr can be reduced to 2.0 equivalents without affecting the yield, while using 1.5 equivalents of HBr, the yield can also reach up to 90% (Table 1, entries 14–15). A volume of 0.2 mL of DMSO is sufficient for the reaction, and a further reduction in the quantity of DMSO leads to a significant decrease in the yield of **2a** (Table 1, entries 16–17). The yield decreased to 69% when the temperature was reduced from 100 °C to 80 °C (Table 1, entry 18). Finally, the C5-bromination reaction could be finished within 6 hours (Table 1, entry 19).

Interestingly, during the screening of copper catalysts for the bromination reactions, it was observed that the use of Cu(NO₃)₂·3H₂O resulted in the formation of C5, C7-dibrominated product **3a** in a yield of 45%, as well as C5-monobrominated compound **2a** in a yield of 31%, under the similar reaction conditions to those described in entry 19 (Table 1, entry 20). Through the judicious modulation of the concentrations of DMSO and HBr, it was observed that an augmentation in the concentration of DMSO was conducive to the formation of dibrominated products (Table 1, entries 21–23). Conversely, a solitary increase in the HBr concentration resulted in the predominance of monobrominated products (Table 1, entry 24). The optimal molar volume ratio of HBr to DMSO was determined to be 1 : 2 (Table 1, entry 22). When both HBr and DMSO were increased simultaneously at this optimal ratio, the dibrominated product could be obtained with a yield of 90% (Table 1, entries 25–26). Finally, when alternative copper catalysts were employed or no catalyst was incorporated, only C5-monobrominated product was formed (Table 1, entries 27–30). Consequently, a facile copper-promoted mono- and di-

Table 1 Optimization of the copper-promoted bromination reaction^a

Reaction scheme: 1a (8-aminoquinoline amide) reacts with HBr and DMSO in the presence of a catalyst and solvent to yield 2a (8-bromo-8-aminoquinoline amide) and 3a (8,8-dibromo-8-aminoquinoline amide).

Entry	Catalyst	HBr (eq.)	DMSO (mL)	Solvent	Yield ^b (%) 2a/3a
1	CuSO ₄ ·5H ₂ O	2.5	—	DMSO	73/NR
2	CuSO ₄ ·5H ₂ O	2.5	0.5	MeCN	93/NR
3	CuSO ₄ ·5H ₂ O	2.5	0.5	EA	76/NR
4	CuSO ₄ ·5H ₂ O	2.5	0.5	THF	58/NR
5	CuSO ₄ ·5H ₂ O	2.5	0.5	DCE	11/NR
6	CuSO ₄ ·5H ₂ O	2.5	0.5	DMF	34/NR
7	Cu(OAc) ₂ ·H ₂ O	2.5	0.5	MeCN	89/NR
8	CuCl ₂ ·2H ₂ O	2.5	0.5	MeCN	83/NR
9	CuBr ₂	2.5	0.5	MeCN	87/NR
10	CuCl	2.5	0.5	MeCN	80/NR
11	CuBr	2.5	0.5	MeCN	79/NR
12 ^c	CuSO ₄ ·5H ₂ O	2.5	0.5	MeCN	83/NR
13	—	2.5	0.5	MeCN	77/NR
14	CuSO ₄ ·5H ₂ O	2.0	0.5	MeCN	93/NR
15	CuSO ₄ ·5H ₂ O	1.5	0.5	MeCN	90/NR
16	CuSO ₄ ·5H ₂ O	2.0	0.2	MeCN	93/NR
17	CuSO ₄ ·5H ₂ O	2.0	0.1	MeCN	82/NR
18 ^d	CuSO ₄ ·5H ₂ O	2.0	0.2	MeCN	69/NR
19 ^e	CuSO₄·5H₂O	2.0	0.2	MeCN	93(90)/NR
20 ^e	Cu(NO ₃) ₂ ·3H ₂ O	2.0	0.2	MeCN	31/45
21 ^e	Cu(NO ₃) ₂ ·3H ₂ O	2.0	0.6	MeCN	28/52
22 ^e	Cu(NO ₃) ₂ ·3H ₂ O	2.0	0.8	MeCN	23/57
23 ^e	Cu(NO ₃) ₂ ·3H ₂ O	2.0	1.0	MeCN	23/58
24 ^e	Cu(NO ₃) ₂ ·3H ₂ O	3.0	0.2	MeCN	74/15
25 ^e	Cu(NO ₃) ₂ ·3H ₂ O	3.0	1.2	MeCN	12/79
26 ^e	Cu(NO₃)₂·3H₂O	4.0	1.6	MeCN	NR/90(86)
27 ^e	Cu(CO ₂ CF ₃) ₂ ·xH ₂ O	4.0	1.6	MeCN	82/NR
28 ^e	Cu(OTf) ₂	4.0	1.6	MeCN	73/NR
29 ^e	CuSO ₄ ·5H ₂ O	4.0	1.6	MeCN	84/NR
30 ^e	—	4.0	1.6	MeCN	73/NR

^a Reaction conditions: **1a** (0.2 mmol, 1.0 eq.), HBr, DMSO, catalyst (20 mol%), solvent (1.0 mL), stirred under air at 100 °C for 12 h. ^b ¹H NMR yield with dibromomethane as the internal standard, isolated yield in parentheses. ^c Catalyst loading is 10 mol%. ^d Stirred at 80 °C. ^e 6 hours.

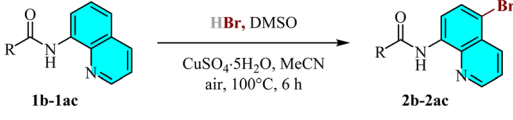
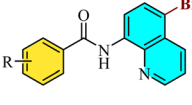
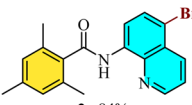
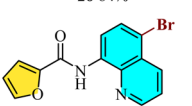
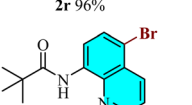
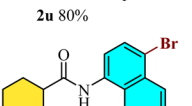
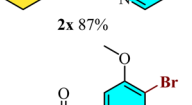
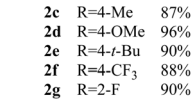
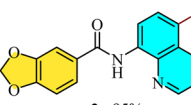
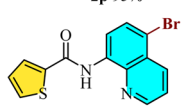
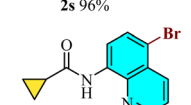
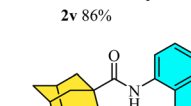
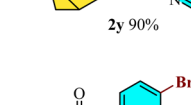
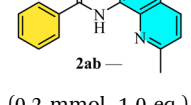
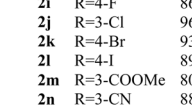
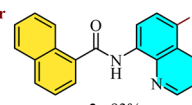
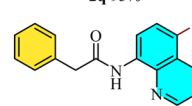
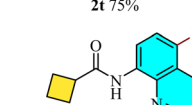
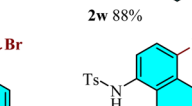
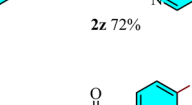
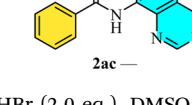
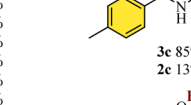
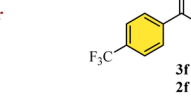
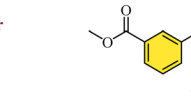
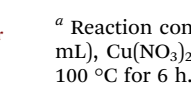
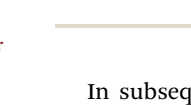
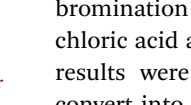
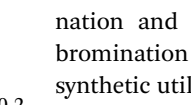
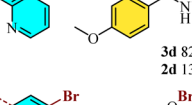
bromination of 8-aminoquinoline amides with HBr and DMSO was established.

Having secured the optimal reaction conditions for mono- and di-bromination of 8-aminoquinoline amides with HBr and DMSO, as detailed in Table 1, entries 19 and 26, we subsequently explored into the substrate scopes and limitations of our devised catalytic system across a diverse range of 8-aminoquinoline amides. As illustrated in Table 2, it was gratifying to observe that the majority of monobromination reactions of substrates with aryl, alkyl, and heterocyclic moieties proceeded smoothly under standard conditions, yielding the corresponding products in good to excellent yields, ranging from 72% to 97%. A variety of functionalized benzamides, including those with simple groups on the phenyl ring such as methyl (**1b–1c**), methoxy (**1d**), *tert*-butyl (**1e**), and trifluoromethyl (**1f**), were well tolerated, affording products with yields of 87–97%. In recent years, a significant proportion of currently available pharmaceuticals, as well as those undergoing clinical trials, contain halogen atoms, which have been demonstrated to exert

a pronounced influence on the bioactivity and physicochemical properties of small molecules.¹⁴ It is worthy of note that halogen atoms (F, Cl, Br and I) exhibited excellent compatibility with the bromination reaction (**1g–1l**). Furthermore, despite the presence of HBr, the ester (**1m**) and cyano (**1n**) groups remained intact during the reaction, ensuring their successful retention in the products.

Meanwhile, the reaction also proceeded smoothly with multisubstituted benzamides as substrates, delivering the desired products in yields ranging from good to excellent (**1o–1p**). Encouragingly, amides bearing fused aryl (**1q**) and heteroaryl (**1r–1s**) groups furnished the C5-brominated products in yields of 93–96%, with no detectable side products substituting on the naphthalene, furan, or thiophene rings. Additionally, this protocol was compatible with aliphatic amides (**1t–1y**), including small rings under considerable ring stress, which endured the reaction entirely (**1v–1w**). The protocol was also successfully extended to sulphonamide derivatives, yielding the target product in 72% yield (**1z**). Finally, substituted 8-

Table 2 Substrate scope for the monobromination reaction^a

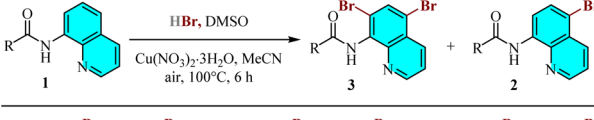
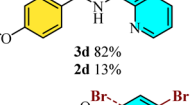
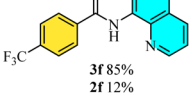
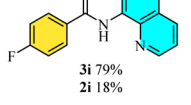
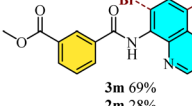
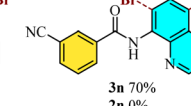
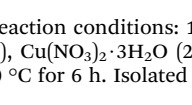
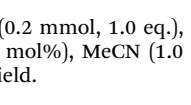
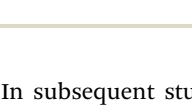
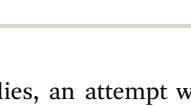
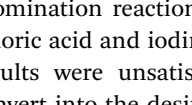
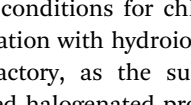
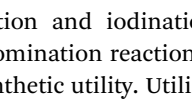
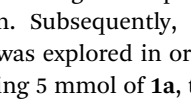
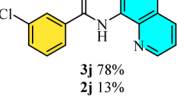
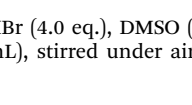
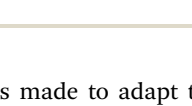
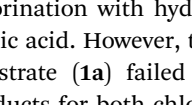
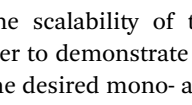
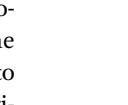
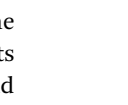
		
1b-1ac		2b-2ac
	2b R=2-Me 97%	2h R=3-F 91%
	2c R=4-Me 87%	2i R=4-F 86%
	2d R=4-OMe 96%	2j R=3-Cl 96%
	2e R=4- <i>t</i> -Bu 90%	2k R=4-Br 93%
	2f R=4-CF ₃ 88%	2l R=4-I 89%
	2g R=2-F 90%	2m R=3-COOMe 80%
	2h R=3-F 91%	2n R=3-CN 88%
	2i R=4-F 86%	
	2j R=3-Cl 96%	
	2k R=4-Br 93%	
	2l R=4-I 89%	
	2m R=3-COOMe 80%	
	2n R=3-CN 88%	
	2o 84%	
	2p 95%	
	2q 93%	
	2r 96%	
	2s 96%	
	2t 75%	
	2u 80%	
	2v 86%	
	2w 88%	
	2x 87%	
	2y 90%	
	2z 72%	
	2aa 95%	
	2ab —	
	2ac —	

^a Reaction conditions: **1** (0.2 mmol, 1.0 eq.), HBr (2.0 eq.), DMSO (0.2 mL), CuSO₄·5H₂O (20 mol%), MeCN (1.0 mL), stirred under air at 100 °C for 6 h. Isolated yield.

aminoquinoline amides (**1aa–1ab**) and other heterocycle (**1ac**) substrates were tested. However, it was found that only methoxy-substituted compound (**1aa**) underwent monobromination with 95% yield. Neither the methyl-substituted compound (**1ab**) nor the heterocyclic substrate (**1ac**) yielded the corresponding brominated products.

Next, the substrate scope of the dibromination reaction was further investigated. As shown in Table 3, the reaction exhibited excellent functional group tolerance, transforming benzamides with both electron-donating and electron-withdrawing groups into the corresponding dibrominated products in yields ranging from moderate to good. Specifically, benzamides with methyl (**1c**), methoxy (**1d**), *tert*-butyl (**1e**), trifluoromethyl (**1f**), fluorine (**1i**), chlorine (**1j**), ester (**1m**), and cyano (**1n**) groups on their benzene rings underwent smooth reactions, predominantly forming the desired dibrominated products in good yields. Unfortunately, due to the absence of aromatic conjugation in the reactant structure, the aliphatic amide yielded exclusively the monobrominated product under the optimal conditions (**1x**).

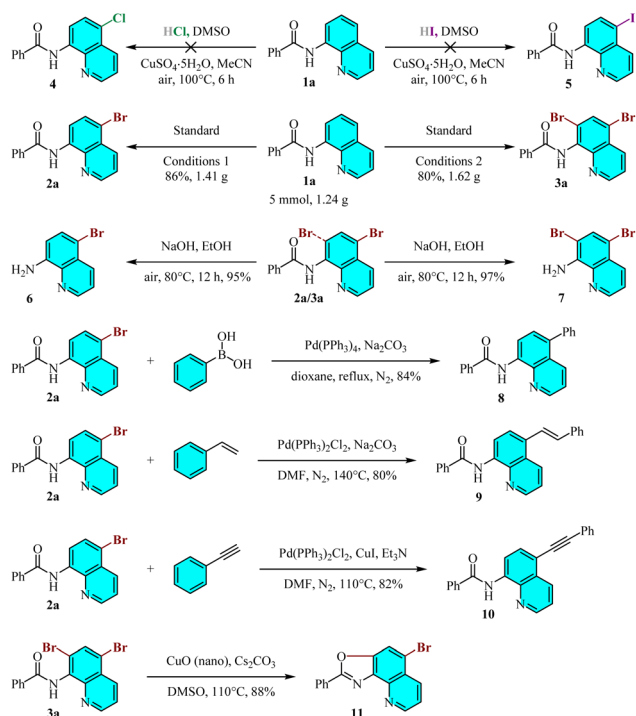
Table 3 Substrate scope for the dibromination reaction^a

		
1		3 + 2
	3c 85%	
	3e 13%	
	3g 80%	
	3i 85%	
	3k 12%	
	3m 69%	
	3o 28%	
	3q 88%	
	3s 79%	
	3u 78%	
	3w 0%	
	3y 0%	
	3aa 0%	
	3ac 0%	

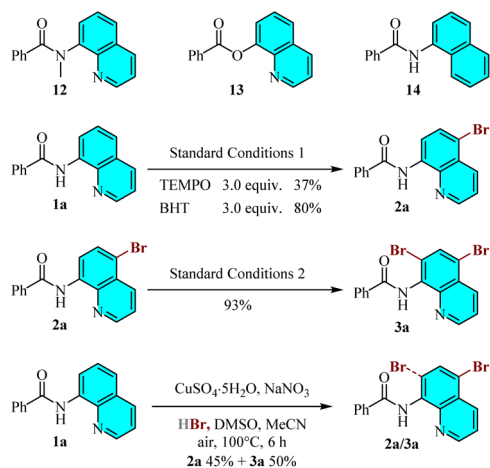
^a Reaction conditions: **1** (0.2 mmol, 1.0 eq.), HBr (4.0 eq.), DMSO (1.6 mL), Cu(NO₃)₂·3H₂O (20 mol%), MeCN (1.0 mL), stirred under air at 100 °C for 6 h. Isolated yield.

In subsequent studies, an attempt was made to adapt the bromination reaction conditions for chlorination with hydrochloric acid and iodination with hydroiodic acid. However, the results were unsatisfactory, as the substrate (**1a**) failed to convert into the desired halogenated products for both chlorination and iodination. Subsequently, the scalability of the bromination reaction was explored in order to demonstrate its synthetic utility. Utilising 5 mmol of **1a**, the desired mono- and di-substituted brominated products were isolated in 86% and 80% yield, respectively. Moreover, the bromo amide could be readily hydrolysed under basic conditions to yield bromine-substituted 8-aminoquinolines. Finally, Suzuki coupling,^{10d} Heck reaction,¹⁵ and Sonogashira reaction^{10b} from **2a** enabled the synthesis of C5-functionalized 8-aminoquinoline amides. In addition, the azoloquinoline derivative **11** can be prepared from **3a** according to literature procedures (Scheme 2).^{11b}

In order to gain more insight into the reaction mechanism, a series of control experiments were carried out (Scheme 3). Under the standard reaction conditions, quinolinamide analogs **12** and **13**, along with naphthylamide **14**, did not result in the formation of brominated products. While the precise rationale remains to be elucidated, this observation underscores the importance of the free NH group in amides and the presence of nitrogen on the quinoline scaffold. Subsequently, radical inhibition experiments were conducted to exclude the possibility of a radical mechanism. When radical scavengers, such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) or BHT (butylated hydroxytoluene), were added to the reaction mixture under optimal conditions, the desired product **2a** was still obtained, albeit in reduced yields of 37% and 80% respectively, suggesting that a radical pathway is not the primary mechanism. Furthermore, when the monobrominated product **2a** was subjected to the standard dibromination conditions as the starting material,



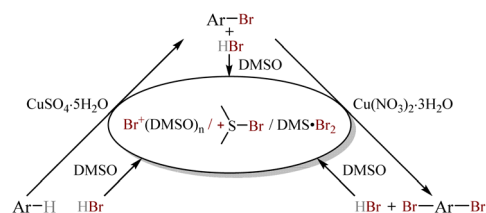
Scheme 2 Gram-scale application and synthetic utility.



Scheme 3 Mechanistic studies.

the desired compound **3a** could be isolated in 93% yield. Finally, the dibromination product **3a** was obtained in 50% yield accompanied by the monobromination product **2a** in 45% yield when $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and 0.2 mmol NaNO_3 were used instead of $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ under the standard conditions 2. This experimental results show the effect of anions in the copper catalyst on the catalytic capacity.

In consideration of the experimental findings and previous reports,¹⁶ we propose that an aromatic electrophilic substitution mechanism is involved in the bromination process. As illustrated in Scheme 4, HBr is oxidized by the mild oxidant DMSO, potentially producing $\text{Br}^+(\text{DMSO})_n$, bromodimethylsulfonium,



Scheme 4 Proposed mechanism.

or $\text{DMS} \cdot \text{Br}_2$. Subsequently, the bromide reagents react with the 8-aminoquinoline substrates to form the monobrominated products, which are accompanied by the generation of HBr that is recycled for further oxidation by DMSO. With the assistance of the more effective $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ catalyst, the monobrominated products undergo further bromination to yield the dibrominated products. It is speculated that copper catalysts may facilitate the formation of the electrophilic Br^+ reagent during the bromination step, and the anionic species present in these catalysts have a significant influence on the selectivity. However, further studies are needed to elucidate the detailed mechanism.

Experimental

General procedure for the monobromination reaction

A 35 mL sealed tube equipped with a stir bar was charged with 8-amidequinolines (**1**, 0.2 mmol, 1.0 equiv.), $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (0.04 mmol, 20 mol%), HBr (0.4 mmol, 2.0 equiv.), DMSO (0.2 mL), and MeCN (1.0 mL). The tube was sealed with a Teflon cap under air, then the mixture was stirred at 100 °C for 6 h. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated sodium bicarbonate and brine successively. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified on preparative thin layer chromatography (PTLC) to afford the desired product **2**.

General procedure for the dibromination reaction

A 35 mL sealed tube equipped with a stir bar was charged with 8-amidequinolines (**1**, 0.2 mmol, 1.0 equiv.), $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (0.04 mmol, 20 mol%), HBr (0.8 mmol, 4.0 equiv.), DMSO (1.6 mL), and MeCN (1.0 mL). The tube was sealed with a Teflon cap under air, then the mixture was stirred at 100 °C for 6 h. After completion, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with saturated sodium bicarbonate and brine successively. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified on preparative thin layer chromatography (PTLC) to afford the desired product **3** and the incidental mono-substituted product **2**.

Conclusions

In conclusion, a straightforward, convenient, and environmentally benign method for synthesizing C5-brominated and

C5, C7-dibrominated 8-aminoquinoline amides *via* a copper-promoted, regioselective oxidative bromination process employing HBr and DMSO has been devised. This transformation boasts high efficiency, exhibits broad functional group tolerance, and delivers the desired products in yields ranging from good to excellent.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Changdong Shao: conceptualization, methodology, resources, project administration, writing – original draft, funding acquisition. Jingyi Liu: investigation, data curation. Yanan Shen: investigation, data curation. Li Li: investigation, data curation. Chen Ma: investigation, data curation. Zhengsong Hu: resources, data curation. Yuhe Kan: resources, data curation. Ping Chen: resources, data curation. Tingting Zhang: validation, supervision, writing – review & editing, funding acquisition.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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