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Copper-catalyzed aromatic C–H bond halogenation with lithium halides under aerobic conditions†

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A concise and practical Cu-catalyzed protocol for the preparation of chloro- and bromoarenes via C-H bond activation has been developed. The advantages of this strategy are the employment of cheap $Cu(NO_3)_2\cdot 3H_2O$, LiX and O_2 , and its compatibility with both electron-donating and electron-withdrawing substituents on aryl rings.

Aryl halides are a valuable class of synthetic materials that have broad synthetic applications, for example, as coupling partners in transition-metal-catalyzed cross-coupling reactions,¹ as well as important structural motifs in many natural products and manufactured drugs.² The majority of the synthetic efforts for making halogenated arenes have focused on electrophilic aromatic substitution using different types of halogenating reagents (wherein dangerous Cl₂ or Br₂ is often utilized)³ and *ortho*-lithiation followed by a halogen quench.⁴ Designing alternative and atom-economical methods for preparing aryl halides remains a challenge in organic synthesis.

Over the past decades, transition-metal-catalyzed C–H bond functionalization has attracted considerable attention and has gradually become a modern and benign tool in organic synthesis.⁵ Compared to the fast development of carbon–carbon bond forming reactions *via* C–H bond activation, employment of this strategy to construct carbon–halogen bonds is not well explored.⁶ Recently, palladium-catalyzed C–H bond halogenation was achieved under the assistance of directing groups.⁶ A significant advance in this area was reported by Kakiuchi and coworkers who demonstrated a Pd-catalyzed chlorination and bromination of chelation-assisted aromatic C–H bonds with simple halogenating reagents, *aqueous HCl and HBr*, by means of electrochemical oxidation.⁷ Inspired by this work, we envisioned that halogenation of aryl C-H bonds could be achieved in the presence of a copper catalyst combined with cheap and nontoxic lithium halide. Copper is one of the most inexpensive metals; however, less attention has been paid to copper-catalyzed C-H bond halogenation.8 To the best of our knowledge, several pioneering and elegant examples of copper-catalyzed ortho-selective halogenation have been reported by Yu,⁹ Gusevskaya,^{10,17a} Stahl¹¹ and others.¹² Unfortunately, these methods are limited by the scope of electronrich substrates^{10,11,17a} or by employing toxic halogen sources such as Cl₂CHCHCl₂ (which is also used as a solvent in Yu's system).9 As part of our ongoing research, we continue to investigate Cu-catalyzed C-H bond functionalization. In 2011, we reported that Cu-catalyzed sp² C–H halogenation by using CrO₃ as an oxidant and Ac₂O as an additive.¹³ Low reactivity and poor regioselectivity of these reactions in this oxidative system were observed. Therefore, a general and simple copper catalytic system with cheap LiX(X = Cl, Br) as the halogen source and oxygen as a green oxidant is highly desired for the construction of valuable and versatile C-Cl and C-Br bonds via C-H bond activation. Herein, we wish to demonstrate our recent results on the aromatic C-H bond halogenation catalyzed by cheap $Cu(NO_3)_2 \cdot 3H_2O$ in the presence of LiX and O_2 .

Due to the advantage of the Cu-O₂ system, initially, we envisioned a reaction of 2-phenylpyridine 1a with LiCl by using 20 mol% Cu(NO₃)₂·3H₂O in an O₂ atmosphere and acetic acid as the solvent; to our delight, a 70% yield of the desired chlorinated product 3a was obtained (along with a trace amount of product 2a) (Table 1, entry 1). After screening a series of copper catalysts, we found that most copper salts, such as $Cu(OAc)_2$, $CuSO_4$, $Cu(OH)_2$, $Cu(ClO_4)_2 \cdot H_2O$, $Cu(acac)_2$, CuS·H₂O, CuO(nano), Cu₂O, CuOAc, CuCN and CuSCN, gave slightly decreased yields relative to Cu(NO₃)₂·3H₂O (Table 1, entries 5-11 and 13-16). In contrast, $CuCl_2$ and $Cu(OTf)_2$ showed very poor activity for this transformation (Table 1, entries 12 and 17). Notably, running reactions in the absence of a copper catalyst or under a nitrogen atmosphere showed that no chlorinated products were observed, indicating that both oxygen and copper catalysts are critical for chlorination

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 Table 1
 Optimization of reaction conditions^a



^{*a*} Reaction conditions: 2-phenylpyridine (0.3 mmol), Cu catalyst (20 mol%, 0.06 mmol), LiCl (3 equiv., 0.9 mmol), HOAc (2 mL), O_2 (1 atm), 150 °C. ^{*b*} Isolated yield: both monochlorinated product **2a** and dichlorinated product **3a** can be isolated separately. ^{*c*} Without any copper salts. ^{*d*} Under air. ^{*e*} Under a N₂ atmosphere.

(Table 1, entries 2 and 4). Next, we tried to perform the reaction under air, and found that the corresponding chlorinated products with low yields were obtained (Table 1, entry 3). In addition, solvent screening (AcOH, CH₃CN, toluene, Ac₂O) revealed AcOH to be the most effective. Hence, the optimal conditions involve Cu(NO₃)₂·3H₂O (20 mol%) and LiCl (3 equiv.) in O₂ and HOAc at 150 °C.

To evaluate the generality of the $Cu(NO_3)_2 \cdot 3H_2O - O_2$ system, we next applied this procedure to a variety of commercially available or readily synthesized14 arenes bearing nitrogen atoms as directing groups (Table 2). A series of functional groups at the para-position on the aryl rings, including fluoro (1b), chloro (1c), trifluoromethyl (1d), methyl (1e), tert-butyl (1f) and methoxyl (1g), proceeded very well in this system and provided the corresponding dichlorinated products in good to acceptable yields with trace amounts of monochlorinated products. It is noteworthy that exclusive ortho-regioselectivity was observed as compared to our previous report with CrO₃ as an oxidant,13 indicating that environment-friendly molecular oxygen as an oxidant greatly improved the efficient methodologies for the synthesis of aryl halides and made this transformation more practical. Gratifyingly, monochlorination of this reaction was achieved by a steric effect. As expected, substrates bearing ortho- and meta-methyl groups on the phenyl ring produced monochlorinated products 2j (55% yield) and 2h (58% yield). When the pyridine ring contains the 3-methyl substituent, monoselectivity becomes a single pathway to give

Table 2 Copper-catalyzed chlorination of aromatic C–H bonds with oxygen as the terminal oxidant^{a,b}



^{*a*} Conditions: substrate 1 (0.3 mmol), Cu(NO₃)₂·3H₂O (20 mol%, 0.06 mmol), LiCl (3 equiv., 0.9 mmol), HOAc (2 mL), O₂ (1 atm), 150 °C. ^{*b*} Isolated yield.

the corresponding product **2k** in 57% yield. In addition to this substrate, both electron-donating and electron-withdrawing groups on the phenyl side, such as *p*-methyl, *p*-tert-butyl, *p*-methoxy, *m*-methoxy, *p*-F and *p*-CF₃, were well-tolerated, affording mono-chlorinated products **2l–2q** in 52–72% yields. Although these reaction conditions were optimized for the pyridine-directed C–H bond chlorination, substrates bearing a pyrimidine-directing group efficiently underwent chlorination to produce the corresponding products in good yield. Benzo[*h*]quinoline under the standard conditions resulted in the 10-chlorobenzo[*h*]quinoline **2w** as a single product in 78% yield. By using quinoline as the

directing group, substrate **1x** afforded monochlorinated product **2x** with diminished efficiency (27% yield).



To gain an insight into the mechanism of a chlorination reaction, we investigated the isotope effect by using substrate **1aa** bearing deuterate atom at the 2-position of the phenyl ring. When **1aa** was subjected to the standard chlorination conditions, no obvious intramolecular isotope effect was observed (eqn (1)). This experiment revealed that the C-H bond activation is not the turnover limiting step. Next, we added radical inhibitors, such as 2,6-di-*tert*-butyl-4-methylphenol (BHT, 20 mol%) and 1,4-dinitrobenzene (20 mol%), into reactions. The results showed that both radical inhibitors have no evidently suppressing effect on these reactions (eqn (2) and (3)). Thus, these two experiments ruled out the possibility of a radical pathway.^{12,15}

On the basis of the seminal reports on Cu(m) intermediates in the field of the copper-mediated aromatic C–H bond activation by Stahl¹⁵ and others,¹⁶ a plausible mechanism is outlined in Scheme 1. Firstly, the coordination of a nitrogen atom in substrate **1a** to the copper center, followed by *ortho*-C–H bond activation, would form the cyclometalated Cu(n) intermediate **6**. Disproportionation of Cu(n) species takes place to afford the Cu(m) intermediate 7 and Cu(n) species. Lastly, the reductive elimination of Cu(m) intermediate 7 can provide the corresponding chlorinated product **2a** and Cu(n) species, which would then be oxidized by O_2 under acidic conditions to



Scheme 1 Proposed reaction pathway.

regenerate the Cu(n) species. Nevertheless, we cannot completely exclude a single electron transfer (SET) pathway proposed by Yu.⁹

For bromination, LiBr was used as a brominating reagent in place of LiCl. It was found that the Cu(NO₃)₂·3H₂O-O₂ system is still the best condition (Table 3). Meanwhile, it is observed that a red-brown gas was generated upon heating, implicating the possible formation of bromine during this process. In order to test this hypothesis, next, we ran two control reactions in the presence of Br₂ (2 equiv.): one experiment with the addition of 20 mol% Cu(NO₃)₂·3H₂O afforded the desired products (eqn (4)); in sharp contrast to this experiment, no reaction occurred in the absence of $Cu(NO_3)_2 \cdot 3H_2O$ (eqn (5)). These experiments reveal that a copper catalyst is necessary for C-H halogenation of substrate 1a and the generation of molecular bromine in situ is a likely step.^{11,17} Although the actual mechanism of a bromination reaction is not clear at this moment, it can be suggested that electrophilic bromination is likely to operate in this transformation, as proposed by Stahl.¹¹ Five substrates bearing electron-donating and electron-withdrawing groups showed Cu-catalyzed bromination with slightly less reactivity than a chlorination reaction (displayed in Table 3).

 Table 3
 Copper-catalyzed bromination of 2-arylpyridines with LiBr as a brominating reagent^a



^{*a*} Conditions: substrate 1 (0.3 mmol), Cu(NO₃)₂·3H₂O (20 mol%, 0.06 mmol), LiCl (3 equiv., 0.9 mmol), HOAc (2 mL), O₂ (1 atm), 150 °C. ^{*b*} The yields of 4 and 5 were isolated separately by column.

Particularly notably, Cu-catalyzed halogenation of an aromatic C–H bond is not limited to lithium halide as the halogenating reagents. The representative results presented here are realized by using cheaper chlorinating sources in place of LiCl. It is observed that the chlorination of 2-phenylpyridine with NaCl provides the desired product in 65% yield, slightly less than that of LiCl (eqn (6)). Other chloride salts, such as CaCl₂ and KCl, are efficient chlorinating reagents as well. Accordingly, these results further expand the generality and application of Cu-catalyzed halogenation transformation.

$$\begin{array}{c} & & Cl \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$$

Conclusions

We have demonstrated a concise and practical Cu-catalyzed protocol for the preparation of chloro- and bromoarenes *via* C-H bond activation. The use of readily available and inexpensive Cu(NO₃)₂·3H₂O as a catalyst, LiX (X = Cl, Br) as a halogenating reagent and O₂ as the terminal oxidant is the significant advantage for this transformation. Moreover, the halogenating source can be extended to cheaper sodium halide. Further investigation of a catalytic C–H halogenation mechanism is currently in progress in our lab.

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