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Dehydroxyalkylative Halogenation of C(aryl)-C Bonds of Aryl Alcohols

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S5Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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We herein report Cu mediated side-directed dehydroxyalkylative halogenation of aryl alcohols. C(aryl)-C bonds of aryl alcohols were effectively cleaved, affording corresponding aryl chlorides, bromides and iodides in excellent yields. Aryl alcohols could serve as both aromatic electrophilic and radical synthetic equivalents during the reaction.

C-C(OH) bonds constitute the major linkages of lignin which is the only naturally renewable aromatic resource.¹ In the context of developing future biorefineries, the development of effective ways to cleave and functionalize C-C(OH) bonds is of crucial importance to produce high-value chemical products from lignin, but very challenging.² In this regard, previous work primarily focused on activation and functionalization of C(alkyl)-C(OH) in alcohols,³ lignin model compounds⁴ or native lignin.⁵ In recent years, the selective activation and functionalization of C(aryl)-C(OH) bonds is gaining increasing attention from both academic and industrial points of views.

To overcome this issue, transition-metal catalyzed selective cleavage of the C(alkyl)-C(OH) bonds of primary aryl alcohols was achieved by dehydroxymethylation. In these processes, various cheap alcohols could be effectively utilized, but limited in functionalization of terminal C(alkyl)-C(OH) bonds and producing one carbon shorter products.⁶ On the other hand, β -elimination of metallized substrates is a desired strategy for C(aryl)-C(OH) bond cleavage. Tertiary alcohols⁷ and directing groups functionalized secondary alcohols were employed as substrates.^{7a, 8} Therefore, developing a versatile method for

selective cleavage and functionalization of C(aryl)-C bond of alcohols is very desired, but remains an unsolved problem.

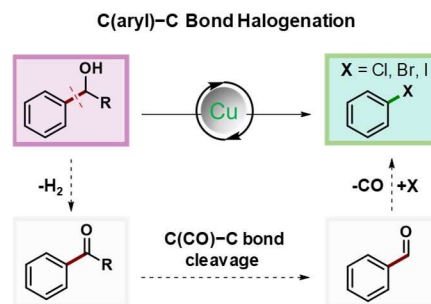


Figure 1. This work: dehydroxyalkylative halogenation of aryl alcohols mediated by aldehyde intermediate.

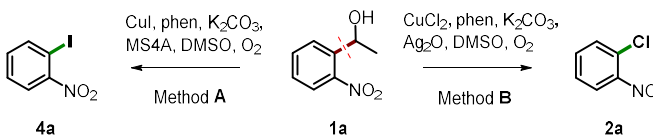
Aryl halides are not only widely used as building blocks in organic synthesis, but also as starting materials for the generation of a diverse range of products in chemical industry.⁹ The established methods are hindered by the generation of multi-halogenated by-products, and the requirement of fossil resource derived pre-functionalized feedstocks which are expensive and not easily available.¹⁰ Therefore, chemical conversion of abundant aryl alcohols into aryl halides by side-directed C(aryl)-C bond activation has attracted our attention. Since lignin is essentially a kind of polymeric aryl alcohol and features abundant C(aryl)-C(OH) bonds in their linkages, the development of such transformation routes is potentially inspiring with regards to lignin valorization. Herein, we report a strategy for aerobic dehydroxyalkylative halogenation of aryl alcohols. Using environmentally benign molecular oxygen as the oxidant and Cu-based catalysts, a diverse range of aryl alcohols are selectively converted into aryl chlorides, bromides and iodides in excellent yields (Fig. 1). Mechanism study demonstrated that the transformation proceeds via oxidative cleavage of C(OH)-C bonds to afford aldehyde intermediates followed by decarbonylative halogenation.

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Optimization of reaction conditions


Entry	Variation from Method A	Yield	Entry	Variation from Method B	Yield
1	Method A	91%	10	Method B	87%
2	Decrease to 100% CuI	61%	12	Decrease to 50% CuCl ₂	38%
3	Increase to 250% phen	55%	13	Decrease to 75% phen	59%
4	Decrease to 400% K ₂ CO ₃	69%	14	Decrease to 250% K ₂ CO ₃	83%
5	Na ₂ CO ₃ instead of K ₂ CO ₃	64%	15	Cs ₂ CO ₃ instead of K ₂ CO ₃	82%
6	Cs ₂ CO ₃ instead of K ₂ CO ₃	33%	16	Ag ₂ CO ₃ instead of Ag ₂ O	86%
7	DMF instead of DMSO	0%	17	AgCl instead of Ag ₂ O	57%
8	Toluene instead of DMSO	2%	18	DMF instead of DMSO	6%
9	100 mg MS4A	66%	19	Toluene instead of DMSO	0%

Reaction conditions: Experiments were performed on 0.2 mmol scale unless otherwise noted. Yield was determined by gas chromatography (GC). Method **A** for bromination and iodation: 125% CuBr/CuBr₂ for bromination and 125% CuI for iodation, 125% 1,10-phenanthroline (phen), 500% K₂CO₃, 200 mg molecular sieve 4A (MS4A), 2 mL DMSO, 0.5 MPa O₂, 140 °C, 18 h. Method **B** for chlorination: 75% CuCl₂, 50% Ag₂O, 125% phen, 500% K₂CO₃, 2 mL DMSO, 0.5 MPa O₂, 140 °C, 18 h.

Initially, we investigated various combinations of different amounts of CuI, bases and solvents using 1-(2-nitrophenyl)ethanol (Table 1, Table S1, **1a**) as the model substrate for the iodation reaction. Under optimized condition, the yield of corresponding aryl iodide product (**4a**) reached 91% yield using method **A** (entry 1, for details, please refer to the caption of Table 1). Other bases such as Na₂CO₃ and Cs₂CO₃ led to decreased yield of **4a** (entries 5 and 6). The reaction could not proceed in DMF or toluene (entries 7 and 8). By replacing CuI with Cu bromide (i.e., CuBr or CuBr₂), the corresponding aryl bromide (**3a**) was generated with yield up to 72% (Table S2). It is noteworthy that the other reaction conditions for bromination and iodation were the same. By adding Ag₂O co-catalyst into the reaction system as electron-transfer mediators for chlorination,¹¹ the corresponding aryl chloride (**2a**) was generated with 87% yield (Method **B**). Excess amount of K₂CO₃ did not significantly affect the yield of **2a** (entry 14). Other bases such as Cs₂CO₃ showed similar performances with K₂CO₃ (entry 15). Other Ag salts such as Ag₂CO₃ could also promote the chlorination reaction (entry 16). In this regard, Ag₂O was selected for further investigation due to its higher stability and lower price. Notably, the chlorination reaction was also suppressed in DMF and toluene. During the oxidative reaction, H₂O is inevitably generated in situ. MS4A could play an important role as water absorbent for iodination reaction, but

did not significantly affect the chlorination reaction. Details of optimization of reaction conditions of iodation, bromination and chlorination are shown in supplementary information (Table S1-3).

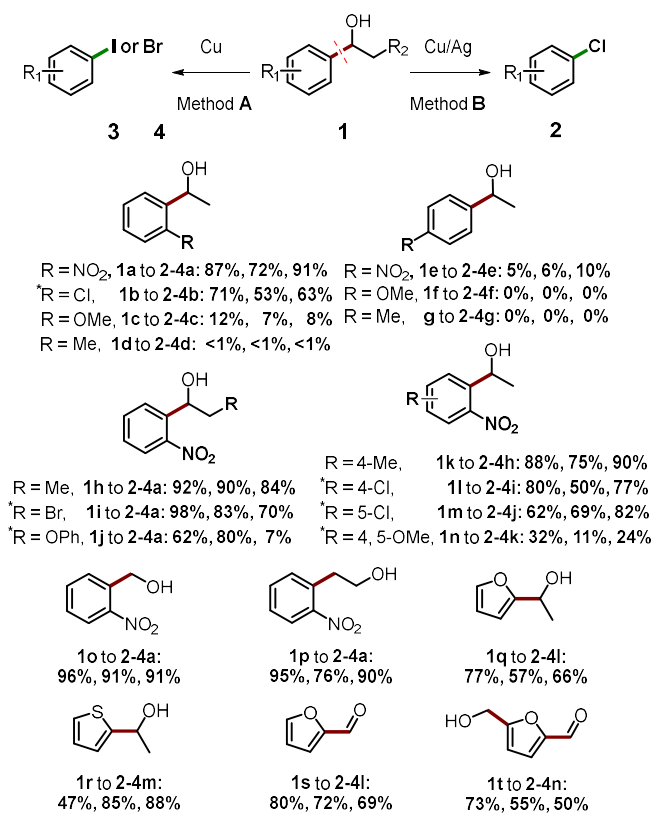


Figure 2. Substrates scope of dehydroxyalkylative halogenation of aryl alcohols. Reaction conditions were the same as Table 1 if not specified. *Reaction time was 36 h. Me: methyl-; OMe: methoxy-; OPh: phenoxy-.

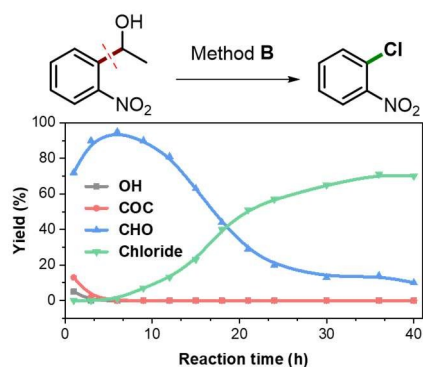
Using the optimized methods **A** and **B**, we further investigated the substrate scope of the dehydroxyalkylative halogenation reactions including chlorination, bromination and iodization (Figure 2). Aromatic secondary and primary alkyl alcohols (**1a-1b**, **1h-1n**, **1o-1p**) were effectively converted into corresponding halides in excellent yields (76–96%). A wide variety of 1-phenylethanol derivatives with substituent groups on the methyl group (**1h-j**) or the aromatic ring (**1k-n**) were tested to investigate the substituent effect. Overall, ortho-functionalized aryl alcohol substrates, especially those with electron-withdrawing groups (**1a-b**, **1h-p**), were successfully transformed into corresponding chlorides, bromides and iodides. Dehydroxyalkylative halogenation of heteroaryl alcohol substrates including biomass-derived furan and thiophene compounds (**1q-1t**) were also achieved with good yields (47–88%). In this case, poly-halogenated by-products were generated and led to relatively lower yield of corresponding halides. On the contrary, the oxidative conversion of aryl alcohol substrates containing electron-donating groups (**1c**, **1n**) are not satisfactory and the yields of targeted compounds were ranging from 7 to 32%.

In order to get some evidences to study the reaction mechanism, we subsequently employed ketone, aldehyde and acid derivatives of 1-(2-nitrophenyl)ethanol as possible intermediates and subjected them into each dehydroxyalkylation reactions using methods **A-B** (Fig. 3a, Fig. S1). In comparison with the alcohol substrate, ketone and aldehyde substrates were transformed into corresponding halide products in similar yields (~90%). On the contrary, the acid substrate showed very poor reactivity (yield: <10%). Hence, we deduce that the dehydroxyalkylative halogenation reactions proceed *via* dehydrogenation of alcohol, C(CO)-C bond activation of ketone intermediate followed by decarbonylative halogenation of aldehyde (Fig. S2). The decarbonylative halogenation of aldehydes to halides has not been reported.

a. Possible intermediates used as substrates.

	Substrates			
	OH	COC	CHO	COOH
Iodide	91%	89%	84%	7%
Chloride	87%	82%	85%	5%

b. Out-situ experiments by GC.



c. Radical inhibition experiments.

		Yield
	Blank	84%
	BHT	3%
	TEMPO	0%
	Blank	85%
	BHT	80%
	TEMPO	85%

Figure 3. Mechanism study. (a) Yields of corresponding products when possible intermediates including ketone (COC), aldehyde (CHO) and acid (COOH) derivatives of 1-(2-nitrophenyl)ethanol were subjected into the dehydroxyalkylative chlorination and iodization reactions (methods **A-B**). Products are labeled as chloride and iodide in the vertical column. (b) Out-situ kinetic study about the evolution of intermediates of representative dehydroxyalkylative chlorination reactions. (c) Radical inhibition experiments of decarbonylative chlorination and iodization.

Temporal evolution of chlorination reaction further confirmed our hypothesis (Fig. 3b). Alcohol substrates and momentary ketone intermediates were consumed quickly and completely at the early stage. The yield of products gradually increased with the depleting of aldehyde intermediate. Notably, the slow rate of disappearance of aldehyde intermediate indicates that decarbonylative chlorination is the rate-determining step (Fig. 3b).

In the presence of suitable oxidants, acyl radicals could be generated from aldehydes for coupling reactions.¹² We further conducted radical inhibition experiments to investigate the intermediacy of aryl radicals under optimized halogenation conditions (Fig. 3c). 2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO) radical scavengers suppressed the decarbonylative iodization reaction, but did not affect the decarbonylative chlorination reaction. These results indicated that decarbonylative iodization reaction proceeds via radical pathway.

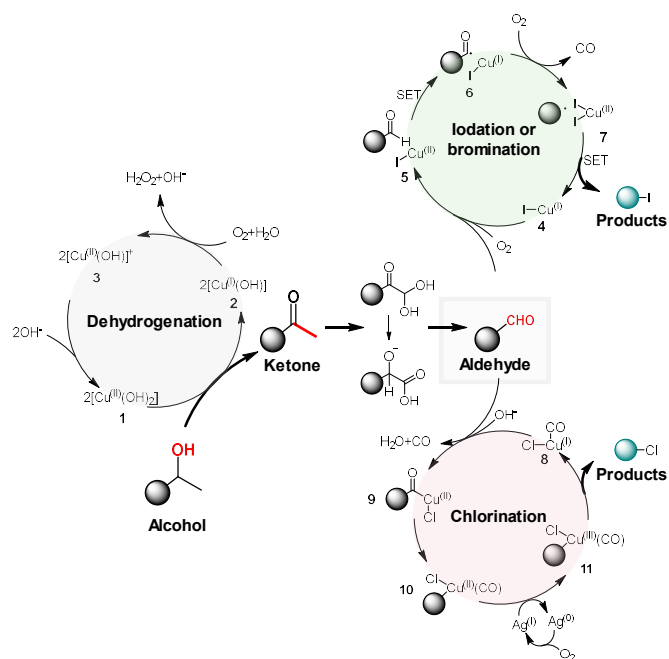


Figure 4. Proposed mechanism of the Cu-mediated dehydroxyalkylative halogenation of aryl alcohols.

Based on the above-mentioned experimental results and previous reports about aerobic Cu catalyzed organic reactions, we proposed a plausible mechanism for the dehydroxyalkylative halogenation of aryl alcohols (Fig. 4). In general, the reaction starts from dehydrogenation of aryl alcohol substrate to ketone intermediates. Then the cleavage of C(CO)-C bonds of ketone intermediate leads to the formation of aldehyde intermediate which further undergoes decarbonylative halogenation. For detailed discussions of the proposed mechanism, please refer to the Supporting Information.

Overall, the substrate scope of the developed dehydroxyalkylative halogenation reaction is primarily limited to ortho electron-withdrawing substituted aryl alcohols at this stage, and aldehyde products were mainly generated from non-ortho-substituted substrates (Figure S4). This ortho-substituent effect has also been observed in other decarboxylative reactions reported previously.^{10a, 13} On one hand, ortho-substituted substrates are inherently less stable in comparison to their meta- and para-substituted substrates. On the other hand, the presence of an ortho-electron-withdrawing substituent group could potentially stabilize the transition state. These two electronic effects could cooperatively reduce the activation barriers and promote decarboxylative halogenation reaction.¹⁴ In addition, the possible transformation pathway of primary alcohol substrates (**1p**) is given in Fig. S5.^{4b, 5}

In summary, we discovered that aryl halides could be synthesized by dehydroxyalkylative halogenation of C(aryl)-C bond of aryl alcohols, using oxygen as the oxidant and Cu halides as both catalyst and halide source. Aryl alcohols served as aromatic electrophilic or radical synthetic equivalents in the reaction, and were efficiently converted into aryl halides (chlorides, bromides and iodides) in excellent yields. The reaction proceeds via dehydrogenation of alcohol substrate, C(CO)-C bonds cleavage of ketone, and decarboxylative halogenation of aldehyde intermediate. Since C(aryl)-C(OH) bonds represent the most predominant motifs in the linkages of lignin, we believe that this new method to synthesize aryl halides will inspire explorations for the activation and functionalization of C(aryl)-C bonds and has promising potential for valorization of lignin to produce high-value products, and further research is currently ongoing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors thank the National Natural Science Foundation of China (21972146, 21733011), Beijing Municipal Science & Technology Commission (Z181100004218004), National Key Research and Development Program of China (2017YFA0403103), and the Chinese Academy of Sciences (QYZDY-SSW-SLH013).

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