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Communication

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Copper-Catalyzed Hydroxylation of (Hetero)aryl Halides under Mild Conditions

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Supporting Information Placeholder

ABSTRACT: The combination of $Cu(acac)_2$ and *N*,*N*'-bis(4-hydroxyl-2,6-dimethylphenyl)oxalamide (BHMPO) provides a powerful catalytic system for hydroxylation of (hetero)aryl halides. A wide range of (hetero)aryl chlorides bearing either electron-donating or electron-withdrawing groups proceeded well at 130 °C, delivering the corresponding phenols and hydroxylated heteroarenes in good to excellent yields. When more reactive (hetero)aryl bromides and iodides were employed, the hydroxylation reactions completed at relatively low temperatures (80 °C and 60 °C, respectively) at low catalytic loadings (0.5 mol % Cu).

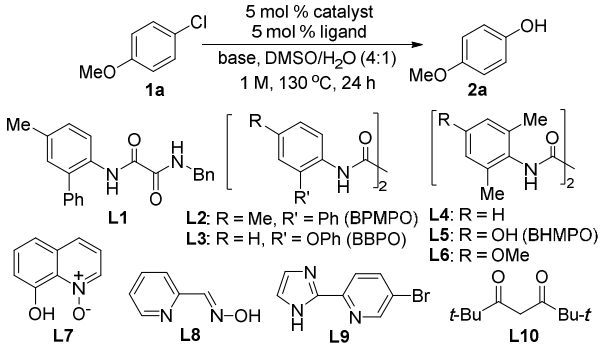
Phenols, hydroxylated heteroarenes and their derivatives are important structural constituents of numerous pharmaceuticals, agrochemicals, polymers and natural products.[1] The development of efficient synthetic methodologies that allow the assembly of phenols and hydroxylated heteroarenes from readily available starting materials under mild reaction conditions has attracted continuing interest. Among the existing methods of constructing phenols and hydroxylated heteroarenes,[2-7] the hydroxylation of (hetero)aryl halides has been recognized over years as one of the most valuable approaches. This is because (hetero)aryl halides are readily available in great abundance and variety, and the hydroxylation can allow access phenols and hydroxylated heteroarenes in a diverse and economical manner.[3] Other advantages of using (hetero)aryl halides as the precursors of phenols and hydroxylated heteroarenes include free of protecting groups, employment of stable arene feedstocks, and free-maneuver of the regioselectivity by introducing another functional group on the aromatic ring. Consequently, significant attention has been directed to the development of new catalytic systems for hydroxylation of (hetero)aryl halides during the past decade.[4,5] In this context, Buchwald, Beller and other groups discovered that, under the assistance of some sterically hindered phosphines, the Pd-catalyzed hydroxylation of (hetero)aryl halides could proceed under mild conditions.[4] Their substrates include less reactive aryl chlorides and in some cases the reaction proceeded at room temperature.[4e,4h] However, the cost issue of both Pd precursors and phosphine ligands limited their synthetic applications, particularly for large scale production. Alternatively, although a number of bidentate ligands were found to be effective for promoting Cu-catalyzed hydroxylation of aryl iodides and bromides,[5] relatively high catalytic loadings (5-10 mol % copper salts, 10-300 mol % ligands) and harsh reaction conditions (100-140 °C) are often needed to ensure satisfactory conversions. The most striking limitation is the poor applicability of inexpensive aryl chlorides as the substrates, because none of the existing copper catalysts[5e-5h] were capable of providing phenols in good yields unless electron-poor aryl chlorides were employed. Thus, it is highly desirable to develop more sophisticated ligands to enhance the efficiency and substrate scope of Cu-catalyzed hydroxylation of (hetero)aryl halides.

Recently, we discovered that a series of N,N'-disubstituted oxalamides are extremely effective ligands for promoting Cu-catalyzed coupling reactions of aryl chlorides and nucleophiles,[8] leading to the formation of aryl amines and diaryl ethers under relatively mild conditions. Further studies revealed that *N*,*N*'-bis(4-hydroxy-2,6-dimethylphenyl)-oxalamide (BHMPO), easily prepared from commerically available 4-hydroxy-2,6-dimethylaniline[9] and oxalyl chloride, is a very efficient ligand for Cu-catalyzed hydroxylation of (hetero)aryl halides. The ligand not only allows the hydroxylation of (hetero)aryl chlorides to complete at 130 °C, but also enables the hydroxylation of (hetero)aryl bromides and iodides to proceed smoothly at 60-80 °C even at low catalytic loadings. Herein, we wish to disclose our results.

As demonstrated in Table 1, we commenced our hydroxylation study by reacting 4-chloroanisole with lithium hydroxide in a mixture of DMSO and water. Initially, we tried N-aryl-N'-alkyl substituted oxalamide **L1**, a ligand that worked well for CuI-catalyzed diaryl ether formation.[8c] It was found that at 130 °C, hydroxylation occurred with a very limited conversion (entry 1). We then moved our attention to **L2** and **L3** that had excellent performance in CuI-catalyzed coupling of aryl chlorides with ammonia,[8b] but found that they did not give any conversions (entries 2 and 3). A slight improvement of yield was observed in case of 2,6-dimethylaniline derived amide **L4** as the ligand (entry 4). Further exploration revealed that its hydroxyl-analogue **L5** gave a much better conversion (entry 5). Since **L6**, a methoxy-analogue of **L4** still gave a poor yield (entry 6), we believed that the free hydroxyl group in **L5** played an essential role for its high efficiency. An obvious explanation is that the corresponding phenolic salts are more soluble in the present reaction media and therefore facilate the coupling reaction. Using **L5** as a ligand, we examined various

copper salts and found that $Cu(acac)_2$ gave the best result (entries 7-10). In this case, 4-methoxyphenol **2a** was obtained in 85% isolated yield. Among various bases examined, lithium hydroxide was the most superior one and incomplete conversions were observed when NaOH or KOH was used (entries 11 and 12), presumably because the ligand is not stable in the presence of stronger bases at 130 °C. Some known ligands that could catalyze the hydroxylation of aryl iodides and bromides were also tested under similar reaction conditions. It was found that only **L9**[5k] gave a poor conversion, while no formation of the desired product was observed with 8-hydroxyquinolin-*N*-oxide **L7**,[5g] oxime **L8**,[5e] and 2,2,6,6-tetramethyl-3,5-heptanedione **L10**[5a] as the ligands. These results indicated that **L5** is the choice of ligand for Cu-catalyzed hydroxylation of aryl chlorides. It is notable that using mixed DMSO and H_2O as the reaction media is essential for the reaction. Large amount of water is needed to inhibit the coupling of resultant phenols with aryl chlorides, while DMSO can enhance the solvability of reactants and intermediates. Replacing DMSO by DMAc and NMP decreased the conversions (see SI).

Table 1. Cu-catalyzed hydroxylation of 4-chloroanisole in the presence of different ligands and bases.[a]

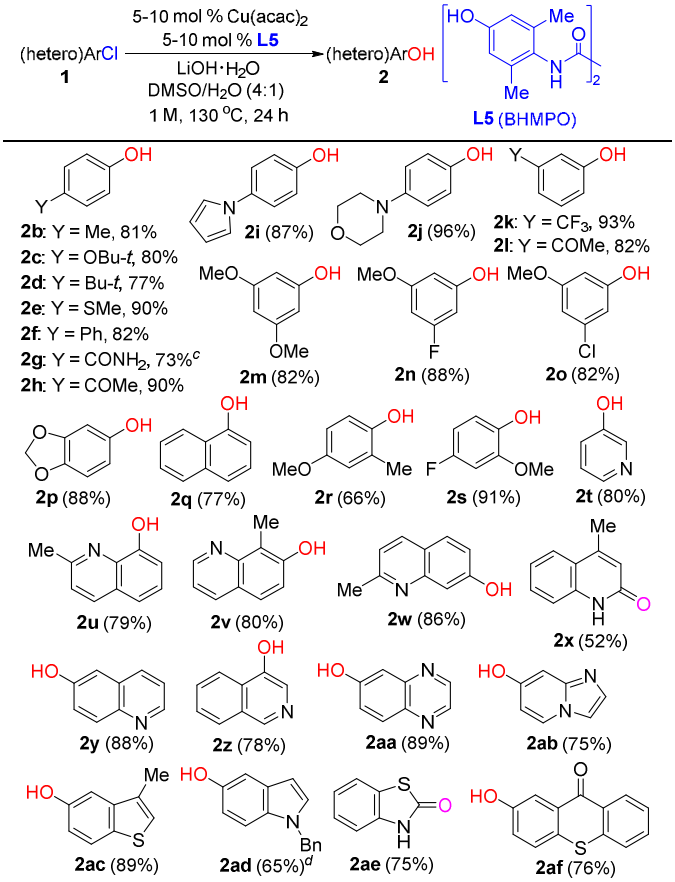


Entry	Catalyst	Ligand	Base	Yield (%)[b]
1	CuI	**L1**	$LiOH·H_2O$	2
2	CuI	**L2**	$LiOH·H_2O$	0
3	CuI	**L3**	$LiOH·H_2O$	0
4	CuI	**L4**	$LiOH·H_2O$	14
5	CuI	**L5**	$LiOH·H_2O$	75
6	CuI	**L6**	$LiOH·H_2O$	20
7	Cu_2O	**L5**	$LiOH·H_2O$	71
8[c]	CuCl	**L5**	$LiOH·H_2O$	79
9	$Cu(acac)_2$	**L5**	$LiOH·H_2O$	87 (85)[c]
10	$CuCl_2$	**L5**	$LiOH·H_2O$	82
11	$Cu(acac)_2$	**L5**	NaOH	44
12	$Cu(acac)_2$	**L5**	KOH	26
13	$Cu(acac)_2$	**L7**	$LiOH·H_2O$	0
14	$Cu(acac)_2$	**L8**	$LiOH·H_2O$	0
15	$Cu(acac)_2$	**L9**	$LiOH·H_2O$	14
16	$Cu(acac)_2$	**L10**	$LiOH·H_2O$	0

[a]General conditions: **1a** (2 mmol), catalyst (0.1 mmol), ligand (0.1 mmol), base (4.2 mmol), DMSO (1.6 mL), water, (0.4 mL), 130 °C, 24 h. [b]The yield was determined by ^1H NMR analysis of crude products using 1,3,5-trimethoxybenzene as the internal standard. [c]Isolated yield.

The established optimal conditions were then examined by varying (hetero)aryl chlorides and the results are summarized in Table 2. For *para*-substituted aryl chlorides, both electron-rich and electron-deficient substrates worked well, providing phenols **2b-2h** in 73-90% yields. In case of 4-chlorobenzonitrile, the coupling reaction was accompanied with the hydration of its cyano-moiety to afford amide **2g**. Hydroxylation of two substrates containing a heterocycle at the *para*-position proceeded smoothly, leading to the formation of phenols **2i** and **2j** in excellent yields. The *meta*-substituted aryl chlorides bearing either electron-donating or withdrawing groups were all applicable, giving the mono-substituted phenols **2k**, **2l**, and the disubstituted phenols **2m-2p** with yields ranging from 82% to 93%. Interestingly, mono-hydroxylation could be achieved when 3,5-dichloroanisole was used. The chloride moiety in product **2o** could be further manipulated via other coupling reactions. The hydroxylation reaction of 1-chloronaphthane (**2q**) was found to be relatively sluggish, presumably because of its steric hindrance. The similar problem was also seen in case of 3-methyl-4-chloroanisole as the substrate. The desired hydroxylation product **2r** was obtained in only 66% yield owing to incomplete conversion under the present conditions. However, an excellent yield was obtained when less sterically hindered 2-chloro-4-fluoroanisole (**2s**) was utilized.

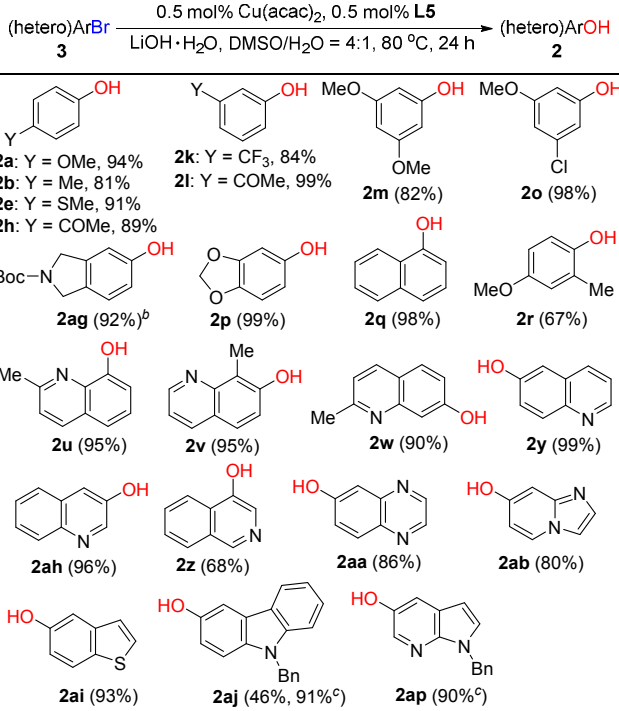
Table 2. Cu-catalyzed hydroxylation of (hetero)aryl chlorides.[a,b]



[a]General conditions: **1** (2 mmol), $Cu(acac)_2$ (0.1 mmol), **L5** (0.1 mmol), $LiOH•H_2O$ (4.2 mmol), DMSO (1.6 mL), H_2O (0.4 mL), 130 °C, 24 h. [b]Isolated yield. [c]4-Chlorobenzonitrile as the substrate. [d]0.2 mmol of $Cu(acac)_2$ and **L5** were used.

We next explored hydroxylation of heteroaryl chlorides because these transformations should be more interesting in medicinal chemistry. To our delight, a wide range of (hetero)aryl chlorides are compatible with these conditions, delivering the corresponding hydroxylated heteroarenes in good yields. These heteroarenes include pyridine (**2t**), quinoline (**2u-2y**), isoquinoline (**2z**), quinoxaline (**2aa**), imidazopyridine (**2ab**), benzothiaphene (**2ac**), indole (**2ad**), as well as benzothiazole (**2ae**). When 2-chloro-4-methylquinoline was employed, the product existed as the lactam form and the yield was only moderate because partial hydroxylation of the lactam **2x** took place. Similarly, hydroxylation of 2-chlorobenzothiazole produced benzothiazolone **2ae** in 75% yield. In case of a indole-embodied substrate (**2ad**), the coupling reaction became rather slow, and an increasing catalytic loading was required to ensure a satisfactory conversion. Additionally, tricyclic phenol **2af** could be prepared by hydroxylation of the corresponding chloride.

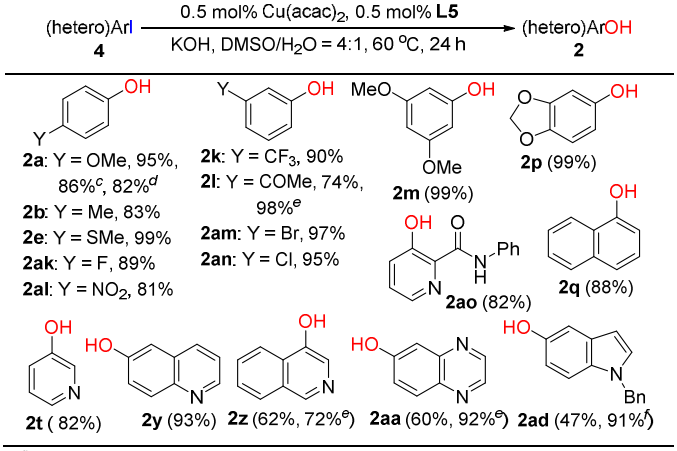
Table 3. Cu-catalyzed hydroxylation of (hetero)aryl bromides.[a]



[a]General conditions: **3** (4 mmol), $Cu(acac)_2$ (0.02 mmol), **L5** (0.02 mmol), $LiOH•H_2O$ (8.4 mmol), DMSO (1.6 mL), water, (0.4 mL), 80 °C, 24 h, isolated yield. [b]The reaction was carried out on a 20 mmol scale. [c]The reaction was carried out at 100 °C with 2 mol% catalyst and ligand.

In view of the above encouraging results, we thought that it was necessary to check if BHMPO (**L5**) is a superior ligand for promoting Cu-catalyzed hydroxylation of (hetero)aryl bromides and iodides. As demonstrated in Table 3, we were pleased to observe that the combination of $Cu(acac)_2$ and **L5** could make a variety of (hetero)aryl bromides hydroxylize at 80 °C, even at rather low catalytic loading (0.5 mol %). When 3-chloro-5-bromoanisole was applied, the hydroxylation took place selectively at the bromide part to provide **2o** in 98% yield. The reaction could be easily scaled up, as illustrated by production of 4.36 g of **2ag** via hydroxylation of the corresponding bromide (20 mmol). Hydroxylation of 3-methyl-4-bromoanisole gave **2r** in a relatively low yield, indicating that the steric hindrance of aryl bromides was still a limiting issue for this reaction. In case of heteroaryl bromides as the substrates, good to excellent yields were observed for hydroxylated quinoline (**2u-2w**, **2y**, **2ah**), isoquinoline (**2z**), quinoxaline (**2aa**), imidazopyridine (**2ab**) and benzothiophene (**2ai**). However, under the same conditions *N*-benzyl-5-bromocarbozole gave a moderate conversion. The problem could be solved by increasing catalytic loadings to 2 mol % and reaction temperatures to 100 °C. In this case **2aj** were produced in 91% yields. Similarly, pyrrolopyridine **2ap** was obtained from the corresponding bromide, which is a key intermediate for assembling Abbvie's antitumor drug Venclexta®.[10] Noteworthy is that the similar compound was previously synthesized via stepwise borylation and oxidation from protected 5-bromo-1*H*-pyrrolo-[2,3-*b*]pyridine.

Table 4. Cu-catalyzed hydroxylation of (hetero)aryl iodides.[a,b]

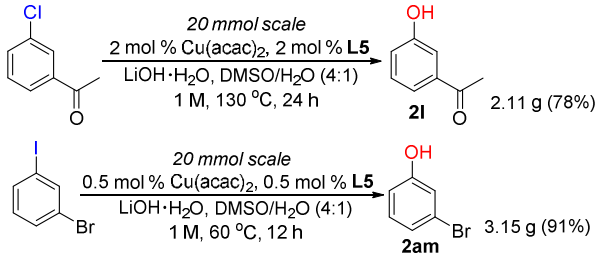


[a]General conditions: **4** (4 mmol), $Cu(acac)_2$ (0.02 mmol), **L5** (0.02 mmol), KOH (12 mmol), DMSO (1.0 mL), water (mL), 60 °C, 24 h. [b]Isolated yield. [c]80 °C, 12 h. [d]40 °C, 24 h. [e]$LiOH·H_2O$ as the base. [f]80 °C, 24 h.

When more reactive (hetero)aryl iodides were used as the substrates, the working temperature could be further decreased to 60 °C and KOH was found to be a slightly better base than LiOH (Table 4). This is probably due to stronger ability of KOH for the deprotonation of the ligand **L5**. Under these conditions, the hydroxylation of 4-iodoanisole **1a** completed after 24 h to afford **2a** in 95% yield. If this reaction was carried out at 80 °C, a complete conversion was found after 12 h. Interestingly, the hydroxylation of **1a** took place even at 40 °C, albeit with 85% conversion after 24 h. This mild condition should be of benefit for hydrolyzing some substrates with base-sensitive functional groups. When bromo- and chloro-containing aryl iodides were employed, excellent chemoselectivity was achieved (**2am** and **2an**). For electron-deficient substrates (for **2l**, **2z** and **2aa**), relatively low yields were observed initially, presumably because some side reactions occurred under strong basic conditions. Changing base to relatively mild LiOH gave improved results. Similar to the corresponding heteroaryl chloride and bromide, the indole-embodied substrate (**2ad**) was less reactive, and a higher reaction temperature was needed to ensure an excellent yield.

It is notable that the catalytic loadings could be further reduced and the reaction time could be even shorten in a scaled-

up experiment. For example, the hydroxylation of 1-(3-chlorophenyl)-ethanone on a 20 mmol scale completed in 24 h by using only 2 mol % catalyst and ligand (Scheme 1), while a complete conversion was observed in 12 h when the hydroxylation of 3-bromo-1-iodobenzene was run on a 20 mmol scale. These additional advantages make the present method more attractive for large-volume production of phenols.



Scheme 1. Scaling up the hydroxylation reaction

In conclusion, we have demonstrated that *N*,*N*'-bis(4-hydroxy-2,6-dimethylphenyl)oxalamide (BHMPO) is a superior ligand for promoting Cu-catalyzed hydroxylation of (hetero)aryl halides, which not only enables the hydroxylation of various (hetero)aryl chlorides, but also allows the much more facile formation of phenols and hydroxylated heteroarenes from (hetero)aryl bromides and iodides comparing to previous methods. The hydroxylation features a broad substrate scope, the low costs of both catalyst and ligand, as well as mild reaction conditions, which should be applicable in organic synthesis.

ASSOCIATED CONTENT

Supporting Information.
Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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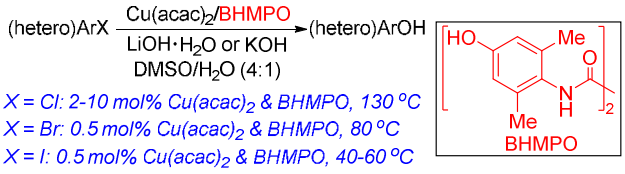
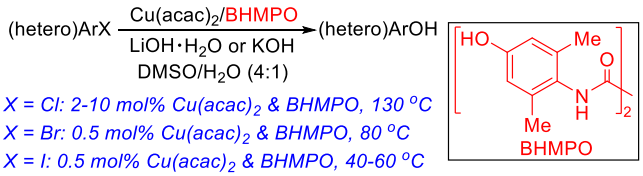

(hetero)ArX
Cu(acac)2/BHMPO
LiOH·H2O or KOH
DMSO/H2O (4:1)
(hetero)ArOH
X = Cl: 2-10 mol% Cu(acac)2 & BHMPO, 130 °C
X = Br: 0.5 mol% Cu(acac)2 & BHMPO, 80 °C
X = I: 0.5 mol% Cu(acac)2 & BHMPO, 40-60 °C
HO
Me
O
N
H
Me
-2
BHMPO

TOC


(hetero)ArX
Cu(acac)2/BHMPO
LiOH·H2O or KOH
DMSO/H2O (4:1)
(hetero)ArOH
X = Cl: 2-10 mol% Cu(acac)2 & BHMPO, 130 °C
X = Br: 0.5 mol% Cu(acac)2 & BHMPO, 80 °C
X = I: 0.5 mol% Cu(acac)2 & BHMPO, 40-60 °C
HO
Me
O
N
H
Me
2
BHMPO

TOC