



# Copper and L-sodium ascorbate catalyzed hydroxylation and aryloxylation of aryl halides

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## ABSTRACT

CuSO<sub>4</sub>·5H<sub>2</sub>O and NaAsc catalyzed hydroxylation and C–O/C–S cross-coupling reactions of aryl halides with phenols or 4-methylbenzenethiol were described. A wide range of substrates and test cases highlight the synthetic utility of the approach. A series of phenols, diaryl ethers, alkylaryl ethers, and diaryl thioethers were synthesized in high yield.

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## 1. Introduction

Phenols, diaryl ethers, alkylaryl ethers, and diaryl thioethers are served as versatile synthetic intermediates playing an important role in the chemical processes, pharmaceutical, and materials industries.<sup>1</sup> The C–O/C–S bond forming reaction has recently gained increased attention.<sup>2</sup> Traditionally, copper-catalyzed Ullmann C–O/C–S cross coupling has been extensively used for the formation of phenols and ethers due to its low cost and less toxicity. However, the harsh reaction conditions such as higher temperatures (>125–220 °C), stronger bases, lots of copper, longer reaction time, which limited in the general use of this reaction, especially on a large scale.<sup>3</sup>

At the end of the 20th century, pioneering research by a few groups led to investigations on the use of ligands in metal-catalyzed cross-coupling reactions, allowing for much milder conditions.<sup>4</sup> Since 2001, the studies and the potential attractiveness of copper has led to a spectacular resurgence of interest in catalyzed Ullmann–Goldberg couplings. Many research groups have thus developed new copper/ligand systems to improve the variety and efficiency of the coupling reactions. However, with a lot of literatures about synthesis of phenols<sup>5</sup> and ethers,<sup>6</sup> the catalysts have been mostly limited to copper(I). Ligands, mostly

bidentate ligands such as phenanthrolines, bipyridines, β-diketones, β-diamines, and amino acids, have been frequently used nowadays for this type of chemistry. Very recently, the efficient Cu-catalyzed direct hydroxylation of aryl halides has been reported which was under mild conditions (120 °C) with Cu(OAc)<sub>2</sub> and a green ligand D-glucose.<sup>7</sup> In addition, when arylboronic acids were used as the substrates to obtain phenols, copper(II) salts<sup>8</sup> could also be an efficient catalysts. Lately, Liu<sup>9</sup> has reported the synthesis of ethers through copper(II)-catalyzed C–O/C–S cross-coupling reaction, which was limited to use aliphatic diols and aryl halides. A large number of experiments have shown that the key of these reactions are copper(I) species.<sup>10</sup> Other alternative methods such as metal catalysis (Cu nanoparticles,<sup>11</sup> FeCl<sub>3</sub>,<sup>12</sup> NiL<sub>n</sub>,<sup>13</sup> Rh(OAc)<sub>4</sub>,<sup>16</sup> etc.), direct oxygenation of benzene<sup>14</sup> and microwave-assisted without catalyst<sup>15</sup> have been also reported for the synthesis of phenols and ethers.

Recently, our group has reported the synthesis of N-function-alized 1,2,3-triazoles with 3,4-dihydropyrimidinone via the click reaction catalyzed by copper(I) which generated in situ from copper(II)/L-sodium ascorbate (NaAsc).<sup>17</sup> What's more, the copper(II)/NaAsc catalyzed amination of aryl halides with aqueous ammonia and amides have also been achieved in our group.<sup>18</sup> Herein, we explored the possibility of application of the CuSO<sub>4</sub>·5H<sub>2</sub>O/NaAsc-catalyst systems for the C–O/C–S cross-coupling of aryl halides delivering phenols and ethers. Compared to copper(I), the CuSO<sub>4</sub>·5H<sub>2</sub>O/NaAsc catalyst systems are cheaper, stable and the

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reaction can be carried out in a homogeneous system promoting the overall efficiency of a given synthesis.

## 2. Result and discussion

Initially, we examined the effects of ligands on the hydroxylation of iodobenzene **1a** as a model substrate to optimize the reaction conditions (Table 1). We were pleased to find that the hydroxylation successfully performed in the presence of  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  and NaAsc (**L1**) to afford phenol **2a** in a yield of 86% (Table 1, entry 1). We then test other ligands, however, only a trace amount of **2a** was detected in the presence of ligands **L2–L4** (Table 1, entry 2). None of ligands **L5–L7** was effective for this reaction to give phenol (Table 1, entries 3–5). Moreover, the result of the blank experiment was disappointing in the absence of ligand (Table 1, entry 6), which shows that NaAsc played a key role in this reaction for help generating copper(I) in situ from  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ .

Next, we had a screening of bases<sup>19</sup> by using different bases such as  $\text{NaO}^t\text{Bu}$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{K}_3\text{PO}_4$ , and NaOH and we found that KOH was most suitable for this reaction (Table 1, entries 7–10). It is intriguing that the mixed solvent systems of DMSO, and  $\text{H}_2\text{O}$  in a 1:1 (v/v) ratio were the best choice yielding a good yield (Table 1, entries 11–13). When the amount of the catalysts and ligands was increased, the lower yields and by-products were obtained. (Table 1, entry 14). Finally, this revealed that the reaction was best conducted with  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (5 mol %) as catalyst, NaAsc (10 mol %) as ligand, KOH (3 equiv) as base in DMSO/ $\text{H}_2\text{O}$  (v/v=1:1) at 120 °C for 24 h, which afforded the desired product in the highest isolated yield.

With the optimized reaction conditions in hand, the scope of aryl halides was then explored. As shown in Scheme 1, drawing our great attention is that different aryl halides such as aryl iodides, aryl

bromides and even aryl chlorides were transformed into the corresponding phenols in excellent to low yield ranging from 92% to 9%. From the above results, we can get the following conclusions, which showed an order of reactivity of  $\text{PhI} > \text{PhBr} > \text{PhCl}$  by using  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  and NaAsc as catalyst systems (Scheme 1). On the other hand, we found that aryl halides with electron-withdrawing groups provided higher yield than those with electron donating groups. For example, 1-iodo-4-methylbenzene and 1-iodo-4-methoxybenzene could afford the corresponding products 4-cresol **2b** and 4-methoxyphenol **2c** in 82% and 86% yield, respectively, and 4-iodobenzoic acid could afford the corresponding product 4-hydroxybenzoic acid **2h** in 92% yield. However, the steric effect has a little influence on the reaction. For example, 1-iodo-4-methylbenzene and 1-iodo-2-methylbenzene could afford the corresponding products 4-cresol **2b** and 2-cresol **2k** in 82% and 80% yield, respectively. Moreover, functional groups such as methyl, methoxyl, nitro, and carboxyl are well tolerated in this catalytic system. Additionally, the synthesis of 4-hydroxybenzoic acid **2h** and 3-hydroxybenzoic acid **2i** need 6 equiv KOH.

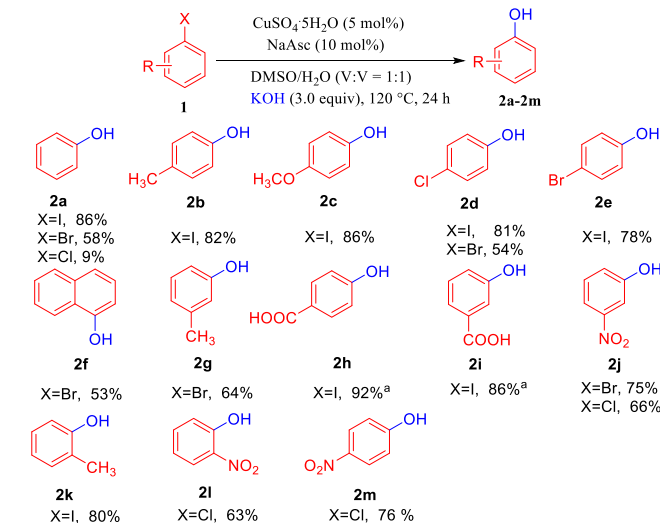
**Table 1**  
Optimization of reaction conditions<sup>a</sup>

	<b>1a</b>	$\xrightarrow[\text{Base, Solvent, 120 } ^\circ\text{C, 24h}]{\text{CuSO}_4 \cdot 5\text{H}_2\text{O, Ligand}}$	<b>2a</b>	
	<b>L1</b>		<b>L2</b>	<b>L3</b>
	<b>L4</b>		<b>L5</b>	<b>L6</b>
	<b>L7</b>			
Entry	Ligand	Solvent (v/v)	Base	Yield (%) <sup>b</sup>
1	<b>L1</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	KOH	86
2	<b>L2–L4</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	KOH	Trace
3	<b>L5</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	KOH	37
4	<b>L6</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	KOH	49
5	<b>L7</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	KOH	35
6	—	DMSO: $\text{H}_2\text{O}$ (1:1)	KOH	Trace
7	<b>L1</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	$\text{NaO}^t\text{Bu}$	67
8	<b>L1</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	$\text{K}_2\text{CO}_3$	—
9	<b>L1</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	$\text{K}_3\text{PO}_4$	Trace
10	<b>L1</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	NaOH	72
11	<b>L1</b>	DMSO	KOH	23
12	<b>L1</b>	DMSO: $\text{H}_2\text{O}$ (2:1)	KOH	48
13	<b>L1</b>	PEG-400: $\text{H}_2\text{O}$ (1:1)	$\text{K}_2\text{CO}_3$	46
14 <sup>c</sup>	<b>L1</b>	DMSO: $\text{H}_2\text{O}$ (1:1)	KOH	68

<sup>a</sup> Reaction conditions: iodobenzene (1.0 mmol), base (3.0 equiv), ligand (10 mol %),  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (5 mol %), in 3.0 mL solvent at 120 °C for 24 h.

<sup>b</sup> Isolated yields.

<sup>c</sup>  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (20 mol %), **L1** (40 mol %).



**Scheme 1.** Coupling products from various aryl halides. [a] 6.0 equiv KOH were used for the synthesis of **2h** and **2i**.

Further, in order to exploit this new catalytic system, we expand the scope of C–O cross coupling for the formation of the diaryl ethers, alkyl aryl ethers. As a model study for the optimization of the reaction conditions, we first chose the coupling of iodobenzene **1a** and 4-methoxyphenol **2a** to give 1-methoxy-4-phenoxybenzene **3a** (see the details in SI Table 1). The screening shows that the choice of appropriate base is the key to the reaction: the desired 1-methoxy-4-phenoxybenzene **3a** could be obtained in yields were 26% and 89%, respectively when  $\text{K}_3\text{PO}_4$  and  $\text{Cs}_2\text{CO}_3$  was employed. The best result was achieved when the reaction was performed in the presence of  $\text{Cs}_2\text{CO}_3$  consisting  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$  (5 mol %), NaAsc (10 mol %) in DMSO at 120 °C. In addition, it is worth noting that blank experiments screening led to disappointing results in the absence of ligand, which confirmed that NaAsc played a crucial role in this reaction.

To demonstrate the generality of this optimized protocol, we tested a series of alkyl aryl halides as electrophiles for the synthesis of aryl alkyl ethers. The aryl alkyl ether structure is often found in pharmaceuticals, agrochemicals, and fine organic chemicals. The use and functionalization of aryl alkyl ether based molecules is also an important tactical tool in medicinal chemistry.<sup>20</sup> In addition, for aryl alkyl ethers synthesis, copper-catalyzed Ullmann-type C–O bond formation has been an attractive alternative, however, sometimes the possibility of a competing  $\beta$ -H elimination side-reaction might

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