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Facile Synthesis of 2-(Phenylthio)phenols by Copper(I)-Catalyzed Tandem Transformation of C−S Coupling/C−H Functionalization

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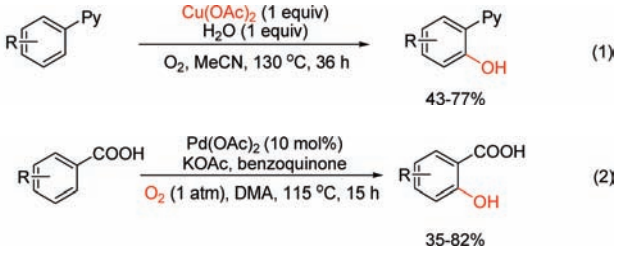
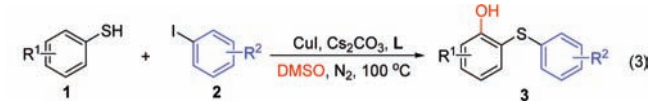
Abstract: 2-(Phenylthio)phenols were successfully synthesized from simple phenols and aromatic halides by using dimethyl sulfoxide as the oxidant. The transformation was accomplished via tandem copper(I)-catalyzed C−S coupling/C−H functionalization employing the CuI/L [L = (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one] catalyst system. The mechanism of the reaction was elucidated based on an isotope labeling strategy.

The development of selective hydroxylation of arenes is a challenging process in organic synthesis.[1] Transition-metal catalysis has been significantly promoted for this purpose via direct C−H functionalization of the arenes in the past decade. However, most of the present C−H bond functionalization methods rely on the use of noble metals such as palladium,[2] rhodium, platinum, gold, etc.[3] which restricts large scale application of these methods. Because of the good functional group tolerance and the economic attractiveness, copper catalysts have been extensively employed in the functionalization of C−H bonds and significant advancements in this area have been achieved. However, expanding the application scope of C−H bond functionalization is still highly desirable.[4] For example, exquisite methods have been developed for the oxidative hydroxylation of the aromatic motifs bearing N atom (eq 1) or carboxylic acid (eq 2) as an activation group, which are exemplified by the latest reports from Yu's group.[5] The S atom has a similar electronic profile pattern to that of the N atom; however, there are no reports on the capability of an S-containing group to promote the C−H bond functionalization.

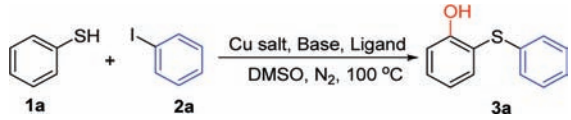


Considering the significance of developing a direct C−H functionalization reaction assisted by more diversified substituents, we focused our attention toward the studies on the copper-catalyzed C−H bond transformation of arenes. Here, we report our preliminary results on a new method for the synthesis of (2-hydroxylphenyl) aryl thioethers **3** via the tandem copper-catalyzed reaction of C−S coupling/C−H functionalization as shown in eq 3.

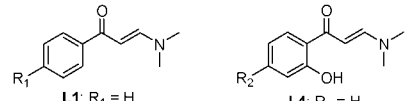


These reactions were mainly based on the employment of the ligand (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one (**L4**) which was previously discovered as an effective ligand for the copper-catalyzed Ullmann C−N coupling reactions between aryl halides and various azoles in our laboratories.[6] The reaction conditions were screened based on the model reaction of thiophenol (**1a**) and iodobenzene (**2a**) by employing various copper(I) species and ligands derived from **L1** in different solvents (Table 1). It was discovered that compound **L4** was the ideal choice for this transformation (entries 5−10). CuI exhibited superior catalytical efficiency over all other examined Cu(I) catalysts (entries 1−5),

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	Cu salt	base	yield (%)[b]
1	**L1**	$Cu(OAc)_2$	Cs_2CO_3	12
2	**L1**	$CuSO_4$	Cs_2CO_3	0
3	**L1**	CuBr	Cs_2CO_3	23
4	**L1**	$CuBr_2$	Cs_2CO_3	19
5	**L1**	CuI	Cs_2CO_3	38
6	**L2**	CuI	Cs_2CO_3	29
7	**L3**	CuI	Cs_2CO_3	36
8	**L4**	CuI	Cs_2CO_3	67
9	**L5**	CuI	Cs_2CO_3	46
10	**L6**	CuI	Cs_2CO_3	38
11	**L4**	CuI	K_2CO_3	42
12	**L4**	CuI	K_3PO_4	0
13	**L4**	CuI	Cs_2CO_3	31[c]
14	**L4**	CuI	Cs_2CO_3	49[d]
15	**L4**	CuI	Cs_2CO_3	0[e]
16	**L4**	CuI	Cs_2CO_3	0[f]



[a] Unless otherwise noted, reactions conditions were **1a** (0.5 mmol), **2a** (0.6 mmol), Cu salt (10 mol %), ligand (10 mol %), base (2 equiv), protected by N_2, in DMSO (2 mL) at 100 °C for 10 h. [b] Isolated yield. [c] Reaction time for 5 h. [d] 80 °C. [e] In pure CH_3CN (2 mL). [f] In pure DMF (2 mL).

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and Cs_2CO_3 turned out to be the proper base additive (entries 11−13). However, a reagent that played an indispensable role in the reaction appears to be dimethyl sulfoxide (entries 15, 16).

The scope of reaction was further investigated, and results are summarized in Table 2. A wide array of thiophenols **1** and aryl iodides **2** were subjected to the reaction, and the corresponding products were in moderate to good yields. Thiophenol derivatives bearing either an electron-withdrawing or -donating group reacted smoothly with **2** to afford corresponding products. This transformation is applicable for both *meta*- and *para*-substituted thiophenols. Aryl iodides bearing an electron-donating group showed better reactivity than those with an electron-withdrawing group.

Table 2. Copper-Catalyzed C−S Coupling/C−H Functionalization of Aryl Iodides with Thiols[a]

entry	R^1	R^2	product	yield (%)[b]
1	H	H	**3a**	67
2	H	4-Cl	**3b**	78
3	H	4-Br	**3c**	75
4	H	2-CH_3	**3d**	56
5	H	4-CH_3	**3e**	62
6	H	4-OCH_3	**3f**	69
7	H	2-CF_3	**3g**	76
8	4-CH_3	H	**3i**	68
9	4-CH_3	4-Cl	**3j**	82
10	4-CH_3	4-Br	**3k**	80
11	4-CH_3	2-CH_3	**3l**	66
12	4-CH_3	4-CH_3	**3m**	71
13	4-CH_3	4-OCH_3	**3n**	64
14	4-CH_3	2-CF_3	**3o**	84
15	3-CH_3	4-Br	**3p**	77
16	3-CH_3	4-OCH_3	**3q**	73
17	4-Br	H	**3u**	55
18	4-Br	4-CH_3	**3v**	63
19	4-Br	4-Br	**3w**	70
20	4-Br	4-Cl	**3x**	81

[a] Reactions conditions were **1** (0.5 mmol)**2** (0.6 mmol), CuI (10 mol %), **L4** (10 mol %), Cs_2CO_3 (2 equiv), protected by N_2, in DMSO (2 mL) at 100 °C for 10 h. [b] Isolated yield.

In addition, to our surprise, we found that aryl bromides were also able to react with **1** smoothly, at 110 °C, and some typical results are listed in Table 3. Interestingly, the aryl bromide containing an electron-donating group also gave the corresponding product in fair yield (entry 2).

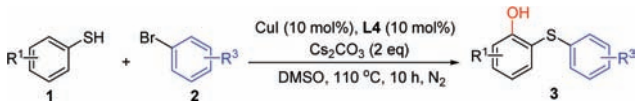


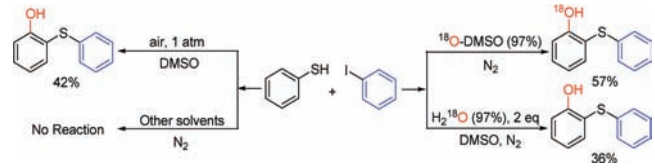
Table 3. Copper-Catalyzed C−S Coupling/C−H Functionalization of Aryl Bromides with Thiols[a]

entry	R^1	R^3	product	yield (%)[b]
1	H	H	**3a**	52
2	H	4-OCH_3	**3f**	45
3	H	3-CF_3	**3h**	63
4	4-CH_3	H	**3i**	47
5	4-CH_3	2-CF_3	**3o**	62
6	4-Cl	H	**3r**	51
7	4-Cl	4-Cl	**3s**	60
8	4-Cl	4-Br	**3t**	57
9	4-Br	H	**3u**	40
10	4-Br	4-Br	**3w**	55

[a] Reactions conditions were **1** (0.5 mmol), **2** (0.6 mmol), CuI (10 mol %), **L4** (10 mol %), Cs_2CO_3 (2 equiv), protected by N_2, in DMSO (2 mL) at 110 °C for 10 h. [b] Isolated yield.

As we found that the presense of dimethyl sulfoxide was critical to the reaction, we decided to further understand how it was involved. In most C−H functionalization reactions, the oxidants are either O_2 or other strong oxidative reagents. But in our reactions O_2 did not appear to be the oxidant because the reactions could be performed in either open air or in a N_2 atmosphere; in fact, the open air operation afforded evidently even lower yields when ^{18}O-DMSO was used as the reaction medium, and the ^{18}O labeled products were obtained (Scheme 1).[7] These results indicate that dimethyl sulfoxide served as the main oxidant in this novel transformation.

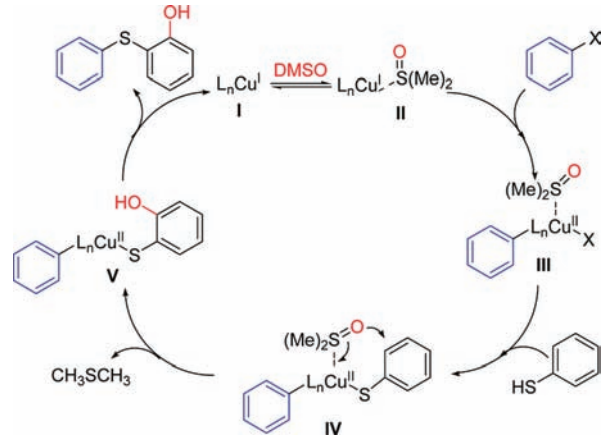
Scheme 1. Preliminary Mechanistic Studies[a]



[a] Unless otherwise noted, reactions conditions were CuI (10 mol %), **L4** (10 mol %), Cs_2CO_3 (2 equiv), at 100. °C for 10 h. Isolated yield. Isotope product yield based on GC.

Given this isotope labeling result, we tentatively proposed a reaction mechanism as shown in Scheme 2. The key intermediate is complex **II**.[8,9] Selective hydroxylation of the aromatic ring was determined by the transitional state, complex **IV**.[10] Reductive elimination of complex **IV** produces complex **V**, which regenerates complex **I** for the next catalytic cycle.[11] However, how the ligand promotes this transformation has not been made clear yet, and further studies on this are ongoing.

Scheme 2. Possible Mechanism



In conclusion, we have found a novel hydroxylation reaction of arenes at a position activated by an adjacent S group. The method involves tandem conversion of C−S cross-coupling/C−H functionalization. The preliminary investigation of the reaction mechanism suggests that dimethyl sulfoxide serves as the oxidant.

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

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