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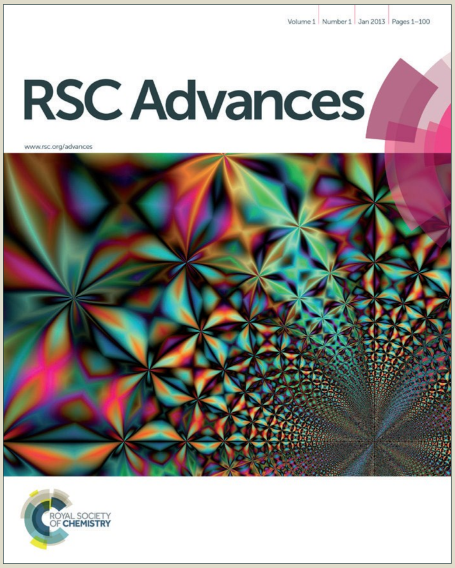

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Graphic Abstract

(2-Chlorobenzoyloxy)copper(I) catalyzed C-S cross-coupling of di(hetero)aryl disulfides with aryl boronic acids under base-free conditions

Yan Guo, Zheng-Jun Quan, Yu-Xia Da, Zhang Zhang, and Xi-Cun Wang

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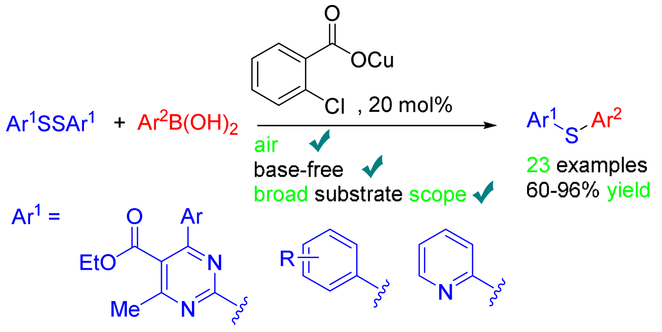

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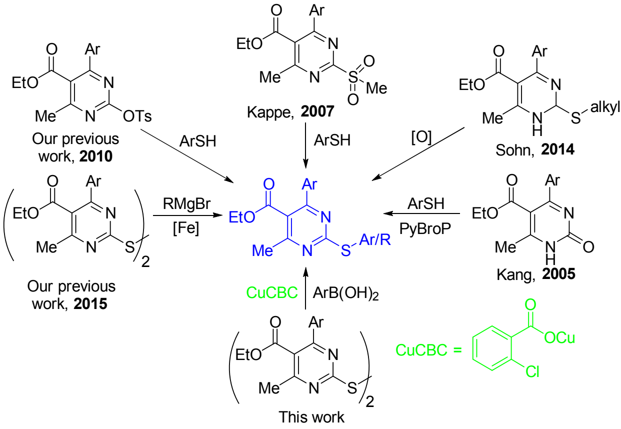
(2-Chlorobenzoyloxy)copper(I) exhibited high activity towards the challenging C-S cross-coupling of di(hetero)aryl disulfides with aryl boronic acids. Herein, diheteroaryl as well as diaryl thioethers were produced with good to excellent yields under base-free conditions.

Currently, organosulfur compounds, present in many biologically active compounds, are widely used as building blocks in organic synthesis and receive considerable attention.[1] To date, many methods for the construction of C-S bonds have been developed using a variety of aromatic moieties and sulfur-containing reagents. Generally, such procedures involve the coupling of an organic halide reacting with boronic acid or thiols using a palladium, nickel, copper catalyst, and other transition metals as catalysts under basic conditions.[2]

Alternatively, the transition metal-catalyzed construction of C-S bonds through S-S cleavage of disulfides (R_2S_2), and various nucleophilic reagents were employed to react with disulfides to construct C-S bonds, has been developed. Up to now, the C-S cross-coupling reaction of diaryl disulfides with aryl halides catalyzed by different transition-metal-system including palladium,[3] nickel[4] and copper[5] have been reported. However, in some cases of copper-catalyst, a stoichiometric metal such as Fe, Zn or Mg as an additive was needed.[6] In addition, Liu and coworkers reported the CuI-catalyzed selective bis-sulfenylation of dihaloaryls by using disulfides as bis-thiolating agents and 2-hydroxylphenyl functionalized enaminone as the ligand.[7] Importantly, copper-catalyzed cross-coupling reactions between diaryl disulfides (dichalcogenides) and aryl boric acids or silicones -catalyst have been developed for diaryl thioethers.[8] Another approach to the formation of C-S bonds was the addition reaction of S-S bonds to the triple bond of alkynes.[1a] Iron[9] and $InBr_3$[10] were also used in the C-S bond formation through the reaction of diaryl disulfides (dichalcogenides) and aryl boric acids. The reaction of aryl diazonium fluoroborates and diaryl dichalcogenides in the presence of zinc dust has been reported.[11]

Among the used transition metal catalysis, copper catalysts have proven not only cheaper and more readily available but also superior in terms of efficiency and functional group tolerance. One important advantage of copper systems concerns the involvement of less toxic nitrogen or oxygen ligands. Palladium-based catalytic systems usually require phosphines. In particular, copper-catalyzed C–S bond formation reactions are valuable in organic synthesis because of their tolerance to sulfur unlike other metal-catalyzed reactions, in addition to the low cost with no need of ligands.[1a]

In most cases, however, both the electrophiles used in the C-S bond formation usually require a combination of a transition metal with a ligand and/or additive for efficient reaction. Although Cu- or Fe-catalyzed ligand-free cross-coupling reaction of diaryl diselenides, diaryl disulfides, ditellurides with aryl halides or aryl boronic acids has been disclosed.[9,10,12] The development of new types of cheaper, less toxic, base-free and more readily available catalysis and ligand is still in high demand.



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† Electronic supplementary information (ESI) available: Experimental procedures, 1H, 13C, spectral data and analytical data for the products. See DOI: 10.1039/c4ra

Scheme 1. Strategies for synthesis of pyrimidin-2-yl thioethers.

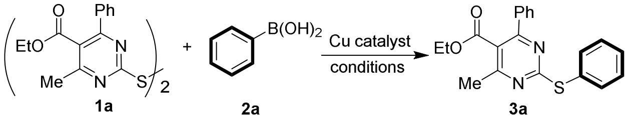
Our group recently developed the palladium- or iron-catalyzed cross-coupling reaction between dipyrimidin-yl disulfides with an aryl boronic acid, alkyne or Grignard reagent to generate the C-C and C-S bonds (Scheme 1).[13] More recently, we have found that (2-chlorobenzoyloxy)copper(I) exhibited high activity towards the challenging amination of 2-amino pyrimidines with aryl halides to give the C-N coupling products.[14] Inspired from our previous works as well as our continuous interest in the synthesis of novel pyrimidine derivatives,[15] we would like to further explore the (2-chlorobenzoyloxy)copper(I)-catalyzed C-S cross-coupling of di(hetero)aryl disulfides with aryl boronic acids. Notably, the reaction delivered the 2-(arylthio)-4-aryl-pyrimidines under mild reaction conditions, which no requirement for additives or bases and easy-to-handle procedure make this method more attractive.

To our best knowledge, few examples have been reported for preparation of 2-(arylthio)-4-aryl-pyrimidines. Synthetic procedures, for instances, through the condensation of enones with corresponding sulfur-containing guanidine,[16] the substitution of 2-methylsulfonyl-pyrimidines with *p*-thiocresol[17] or via the Kappe dehydrogenation the PyBroP-mediated coupling of pyrimidin-2(1*H*)-one with thiophenol have been reported.[18] More recently, Sohn *etal*[19] demonstrated the Cu-catalyzed oxidative dehydrogenation of dihydropyrimidyl thioether to produce 2-(alkylthio)pyrimidine. Generally, these reports were limited to the use of few *S*-nucleophiles, which limited the diversity of the products. In 2010, we expanded the synthesis method for the pyrimidin-2-yl thioethers by cross-coupling reaction of pyrimidin-2-yl sulfonates with S nucleophiles at room temperature (Scheme 1).[20]

Initially, in order to optimize the C-S coupling reaction, the Cu-catalyzed reaction between 1,2-di(pyrimidin-2-yl) disulfide **1a** and phenylboronic acid **2a** was chosen as a model (Table 1). We have recently demonstrated that (2-chlorobenzoyloxy)copper(I) (CuCBC) is an effective catalyst for the amination of 2-amino pyrimidines with aryl halides.[13] Thus, we expected to perform the reaction using CuCBC as catalyst. As expected, the C-S coupling of substrate **1a** with **2a** was conducted successfully using CuI as the catalyst in DMSO under air atmosphere. Initially, ligands such as 1,10-phenanthroline (phen), 2,2'-bipyridine (bpy) were examined, and both the catalytical-system could afford the product **3a** in 92-94% yield with complete consumption of **1a** (entries 1-2). The presence of water decreased the production of **3a** (entry 3). Without ligands, the reaction also gave a satisfactory yield in 92% (entry 4). It was possible to run the C-S coupling reaction with a lower catalyst loading, but lower yield of product was obtained (entries 5 and 6). Lowering temperature resulted in a poor product yield (entries 7 and 8).

However, other tested copper(I) carboxylates, such as copper(I) 2-hydroxybenzoyloxylate and copper(I) thiophenecarboxylate (CuTC) delivered **3a** in a slightly lower yield (entries 9-10). The CuI, which was widely used in the C-S coupling reaction, was also tested. However, the combinations of CuI with ligands, for example CuI with bpy, phen, PPh_3 or TMEDA gave lower yields (entries 7-12). Other copper catalyst systems [$Cu(OAc)_2$-phen, $Cu(OAc)_2$-D-glouse, $CuSO_4$-Vitamin C (VC) and $Cu(CH_3CN)_4BF_4$] in different solvents did not work effectively (entries 13-16). Finally, with respect to its outstanding performance and lower price, CuCBC without using ligand was chosen as a better catalyst for the C-S coupling reaction (entry 4), although CuCBC-phen system was also efficient favoring **3a** (entry 1).

Table 1 Optimization of reaction conditions for the C-S coupling of di(pyrimidin-2-yl) disulfide and phenylboronic acid[a]



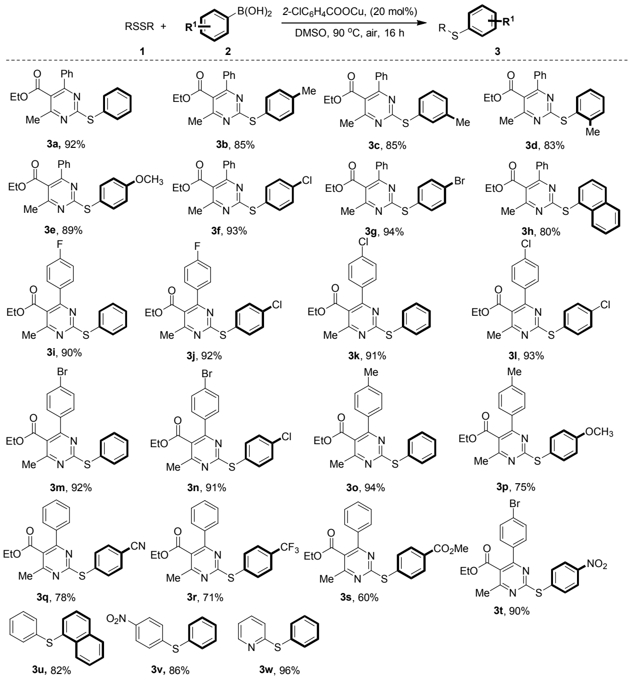
Entry	Catal. (mol%)	Ligand (mol%)	Solvent	Yield[b] (%)
1	2-ClC_6H_4COOCu (20)	Phen (20)	DMSO	94
2	2-ClC_6H_4COOCu (20)	Bpy (20)	DMSO	92
3	2-ClC_6H_4COOCu (20)	Phen (20)	DMSO/H_2O	60
4	**2-ClC_6H_4COOCu (20)**	**–**	**DMSO**	**92**
5	2-ClC_6H_4COOCu (10)	-	DMSO	89
6	2-ClC_6H_4COOCu (5)	-	DMSO	20
7[c]	2-ClC_6H_4COOCu (20)	–	DMSO	trace
8[d]	2-ClC_6H_4COOCu (20)	–	DMSO	20
9	2-OHC_6H_4COOCu (20)	–	DMSO	82
10	CuTC	-	DMSO	56
11	CuI (20)	PPh_3 (30)	dioxane	trace
12	CuI (20)	Phen (20)	DMSO/H_2O	68
13	CuI (20)	Phen (20)	DCE	30
14	CuI (20)	Phen (20)	dioxane	5
15	CuI (20)	Bpy (20)	DMSO/H_2O	79
16	CuI (20)	TMEDA	DMSO/H_2O	35
17	$Cu(OAc)_2$ (20)	Phen (20)	DMSO/H_2O	10
18	$Cu(OAc)_2$ (20)	D-glouse (40)	DMSO/H_2O	10
19	$CuSO_4$ (20)	VC (40)	DMSO/H_2O	trace
20	$Cu(CH_3CN)_4BF_4$ (20)	–	dioxane	15

[a] Catalytic conditions: **1a** (0.2 mmol), **2a** (0.6 mmol) and cat. (20 mol %), solvent (3 mL), 90 °C, 20 h, air. [b] Isolated yield based on disulfide **1a** (2 mol). [c] Reaction was carried out at rt. [d] Reaction was carried out at 50 °C.

On the basis of the previously described experimental results, we next examined the generality of this C-S cross-coupling using CuCBC as catalyst in DMSO. In general, dipyrimidin-2-yl disulfide **1a** smoothly reacted with various arylboronic acids, leading to the C-S cross-coupling products (Scheme 2). Both electron-rich arylboronic acids, such as methyl- and methoxyphenyl, and electron-poor arylboronic acids, such as 4-chloro-, 4-bromo-, and 4-florophenyl, underwent C-S cross-coupling to deliver the products **3b**-**3g** in excellent yields. 1-Naphthyl group could also be tolerated in this reaction (**3h**).

Under similar reaction conditions, a series of dipyrimidin-2-yl disulfides with various arylboronic acids (**2**) generated C-S-coupled products **3i**-**3p** in 75-95% yield. Disulfides containing methyl, floro, chloro and bromo substitution on the phenyl ring were well tolerated.

Furthermore, phenylboronic acids containing a stronger electron withdrawing group such as CN-, F_3C-, MeO_2C-, O_2N-, MeCO-, or OHC- were tested in this reaction. The reaction of cyano-, trifluoromethyl-, methoxy formyl- or nitrosubstituted phenylboronic acids with 1,2-di(pyrimidin-2-yl) disulfide derivatives resulted in the formation of **3q-3t** in 60-90% yield, respectively. Unfortunately, the reaction of **1a** with carboxyl-, acetyl-, or formylsubstituted phenylboronic acids did result in trace of product (Figure 1).



Scheme 2. CuCBC-catalyzed C-S coupling of disulfides with aryl boronic acids

Then, we explored the reaction using other di(hetero)aryl disulfides. According to the previously developed procedure, the CuCBC catalyzed coupling of diaryl disulfides or di(pyridin-2-yl)disulfide with arylboronic acids was carried out (Scheme 2). As expected, the unsymmetrical aryl thioethers **3u-3w** were obtained in good yields, and the present reaction was not affected by substrates. However, compared with the tested di(hetero)aryl disulfides, alkyl disulfides showed much lower reactivity. For example, the reaction of 1,2-diallyldisulfide and 1,2-di(tert-butyl)disulfide with phenylboronic acid **2a** did not result in any C-S coupled product under the similar reaction conditions, but the homo-coupled product of phenylboronic acid was obtained as unique product, showing a lower activity in this process (Figure 1).

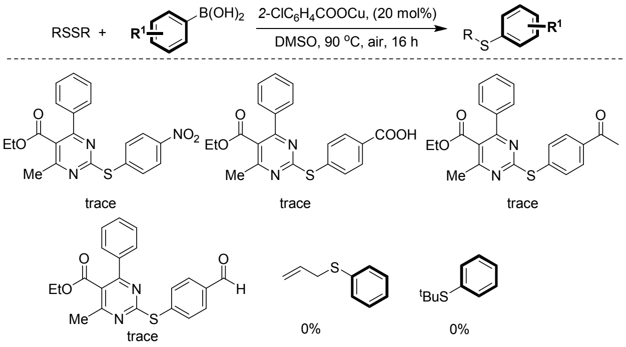
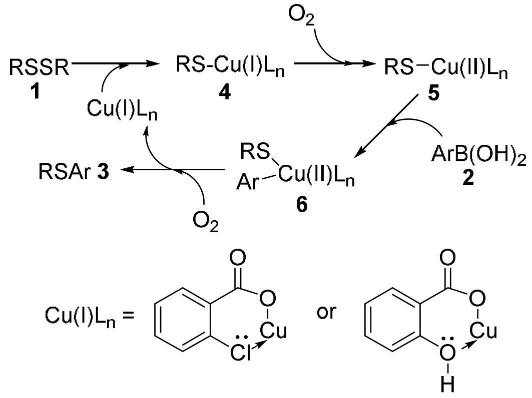


Figure 1. Limitations of the C-S coupling of disulfide with boronic acids.

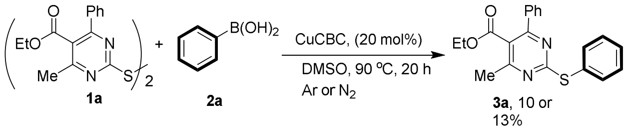
A possible mechanism is depicted in Scheme 3. Herein, 2-chloro- or 2-hydroxybenzoyloxy itself acts also as a ligand like other as bipyridine (bpy) or 2-thiophenecarboxylic acid (TC). The $RSCu(I)L_n$ **5** produced by the reaction of ligated copper-catalyst ($Cu()L_n$) react with $(RS)_2$ **1**. Sequentially, $(RS)(Ar)Cu(II)$ **6** is formed *via* the oxidation of **5** with $ArB(OH)_2$ **2**. Finally, RSAr **3** is produced through the oxidation of **6** with delivering copper-catalyst ($Cu(I)L_n$) the in the presence of oxygen.[8d,8j,8m]



Scheme 3. The possible mechanism for the C-S coupling.

For the purpose of investigation of the reaction mechanism, we examined a reaction in the absence of oxygen. When the CuCBC-catalyzed reaction of 1,2-di(pyrimidin-2-yl) disulfide **1a** and phenylboronic acid **2a** was carried out under Ar or N_2 atmosphere, the corresponding sulfide **3a** was obtained in only 10% (Ar) or 13% (N_2) production (Scheme 4).

Both the copper cation and the carboxylate anion with an ortho functionalized phenyl are critical to the reaction. CuI, $Cu(OAc)_2$ and $Cu(CH_3CN)_4BF_4$ were ineffective. Since CuI halides and $Cu(CH_3CN)_4BF_4$ are ineffective, the carboxylate counterion is clearly important in facilitating transmetalation from boron, possibly through direct coordination to trivalent boron.[21] Low yield of the desired product was observed in the presence of CuTC. O_2 is also essential for efficient reaction. Furthermore, both copper(I) 2-hydroxybenzoyloxylate and copper(I) 2-chlorobenzoyloxylate are effective catalysts may be due to the more strong coordination between the copper cation with Cl or O atom.



Scheme 4. Reaction of 1,2-di(pyrimidin-2-yl) disulfide **1a** and phenylboronic acid **2a** (PhS)2 in the absence of oxygen.

In conclusion, we have developed simple and efficient copper-catalyzed cross-couplings of di(hetero)aryl disulfides with arylboronic acids, providing C-S bond with excellent yields under base-free conditions. The method allows the synthesis of pyrimidin-yl thioethers as well as other aryl/pyridyl containing thioethers with general satisfactory results. And it is worth raising that the cheaper and stable copper(I) carboxylate, (2-chlorobenzoyloxy)copper(I), was introduced, which shown an extraordinary catalytically activity.

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