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COMMUNICATION

Direct C-H Heteroarylation of Azoles with 1,2-Di(pyrimidin-2-yl)disulfides through C-S Cleavage of Disulfides

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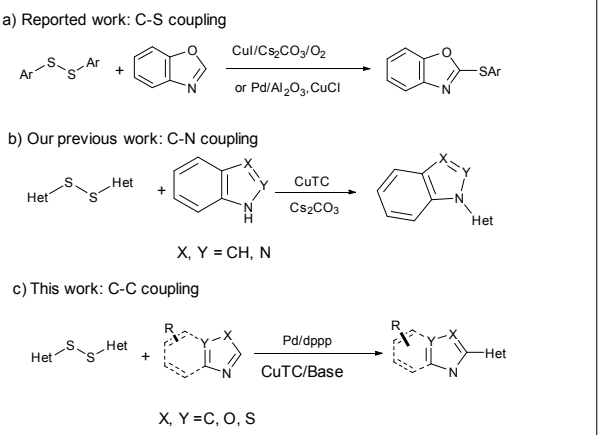
The C-C bond constructtion via C-H bond functionalization of oxazoles/thiazoles and C–S bond cleavage of di(hetero)aryl disulfides is described. Central to this strategy is the conversion of disulfides into 2-heterocyclic aryl oxazoles or thiazole by palladium-catalyzed copper-promoted chemoselectively C–S bond cleavage and generated the corresponding products in good yields.

The development of efficient methods to construct a C-C bond between two heteroarenes has been a topic of high scientific significance in chemical synthesis.[1] Especially, 2-aryl oxazoles or thiazoles are important structural units found in natural products, functional materials, agrochemicals, and pharmaceutically active compounds.[2,3] Considering of environmental and economical problems, direct C–H bond arylation of oxazoles or thiazoles is a significant alternative to traditional cross-coupling reactions.[4,5] In recent years, significant progress has been achieved in the development of the direct C–H bond arylation of oxazoles and thiazoles through oxidative coupling or using aryl electrophiles such as aryl halides and phenol derivatives.[6-10] Among the electrophiles, relatively expensive aryl iodides and triflates were largely employed because of their high reactivity. Searching for new aryl electrophiles and improving the catalytic efficiency of current systems are still active research topics.

To date, the use of organosulfur compounds such as sulfoether and diaryl disulfides as electrophiles in transition metal catalyzed cross coupling reactions has received less attention. This is presumably due to the poisoning effect on some reagents and transition metals by sulfur compounds.[11] Even so, some successful trials have been carried out. In 2015, Wang and co-workers developed palladium-catalyzed arylation of azoles and thiozaoles with aryl thioethers via C–H/C–S activation, however, it employed complicatedly preformed catalysts.[12] Further, Yu and co-workers developed the reaction mechanisms by density functional theory investigation.[13] Compared sulfoether, diaryl disulfides demonstrate more characteristic due to structurally symmetrical, and easily available. More recently, some groups independently developed the C-H arylation of heterocycles including benzoxazole, benzothiazole and 1-methylindole with diaryl disulfide and achieving C–S coupling products in the presence of catalyst such as $CuI/Cs_2CO_3/O_2$,[14] Cs_2CO_3/ionic liquids[15] and Pd/Al_2O_3, CuCl [16] (Scheme 1a). Meanwhile, our group reported the C-C bond formation through C–S bond cleavage of di(hetero)aryl disulfides with aryl boronic acids, terminal alkynes or Grignard reagents, nevertheless, the nucleophiles always need pre-functionalized.[17] In 2016, our group report C-N coupling reaction of disulfides with anilines, indoles, triazole, benzotriazole and benzoimidazole through C–S bond cleavage of di(hetero)aryl disulfides (Scheme 1b).[18]

Scheme 1. Cross coupling of disulfides with various nucleophiles



Herein, we explored the possibility of applying 1,2-di(pyrimidin-2-yl) disulfides in the C–C cross-coupling reaction with oxazoles or thiazoles giving a 2-heterocyclic aryl oxazoles or thiazoles under Pd catalyzed Cu accelerated conditions (Scheme 1c). To the best of our knowledge, this is the first example using disulfides as carbon-electrophile in the

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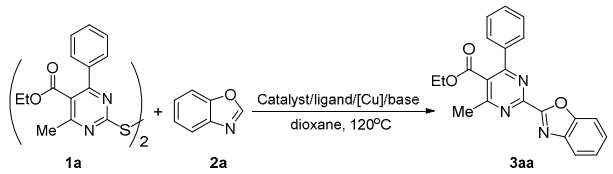
transition metal catalyzed C-H functionalization of heterocyclic compounds.

Table 1. Optimization of the cross-coupling reaction of disulfides **1a** and benzoxazole **2a**.[a]



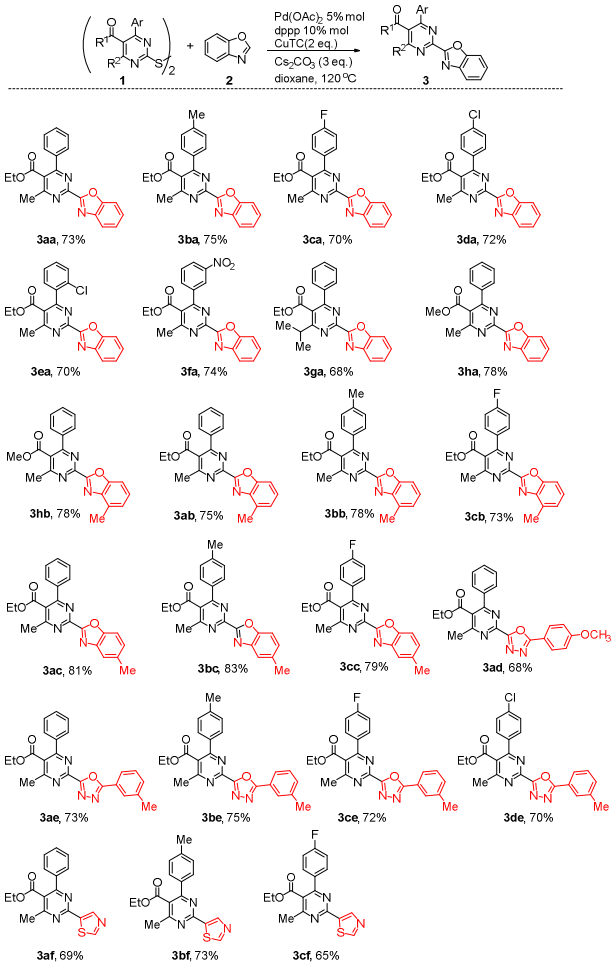
1a **2a** **3aa**

Entry	catalyst (5 mol%)	[Cu] (2 eq.)	Ligand (10 mol%)	Base (3eq.)	Yield/%[b]
1	$PdCl_2$	CuCl	dppp	Cs_2CO_3	Trace
2	$PdCl_2$	CuBr	dppp	Cs_2CO_3	Trace
3	$PdCl_2$	CuTC	dppp	Cs_2CO_3	48
4	$Pd(acac)_2$	CuTC	/	Cs_2CO_3	43
5	$Pd(dppf)Cl_2$	CuTC	/	Cs_2CO_3	56
6	**$Pd(OAc)_2$**	**CuTC**	**dppp**	**Cs_2CO_3**	**73**
7	$Pd(OAc)_2$	CuTC	dppb	Cs_2CO_3	69
8	$Pd(OAc)_2$	CuTC	X-phos	Cs_2CO_3	48
9	$Pd(OAc)_2$	CuTC	PPh_3	Cs_2CO_3	39
10	$Pd(OAc)_2$	CuTC	PCy_3	Cs_2CO_3	57
11	$Pd(OAc)_2$	CuTC	dppp	K_3PO_4	51
12	$Pd(OAc)_2$	CuTC	dppp	NaOAc	35
13	$Pd(OAc)_2$	CuTC	dppp	^{t}BuONa	59
14	$Pd(OAc)_2$	CuTC	dppp	^{t}BuOK	65
15	/	CuTC	dppp	Cs_2CO_3	N.R.
16	Pd(OAc)2	/	dppp	Cs_2CO_3	N.R.
17[c]	$Pd(OAc)_2$	CuTC	dppp	Cs_2CO_3	Trace

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), dioxane (3 mL). [b] Isolated yield after column chromatography (based on both pyrimidine groups from one molecule). [c]The reaction was carried out at air atmosphere. PPh_3 = Triphenylphosphine hydrobromide. dppb = 1,4-Bis(diphenylphosphino)butane, dppp = 3-Bis(diphenylphosphino)propane. CuTC = Copper(I) thiophene-2-carboxylate.

To optimize the reaction conditions, 1,2-di(pyrimidin-2-yl) disulfides **1a** with benzoxazole **2a** as a C-C coupling reaction was chosen as a model system. The influence on the model reaction of various parameters such as catalysts, copper salts, ligands and bases were examined, and the results are summarized in Table 1. Initially, we studied the effect of different copper salts on the C-C coupling reaction of **1a** with **2a**, using $PdCl_2$ as a catalyst, dppp as a ligand and Cs_2CO_3 as a base under nitrogen atmosphere (entries 1-3). When CuTC, CuCl, and CuBr were tested, CuTC promoted the reaction to give the desired product **3aa** in 48% yield (entries 3), whereas CuCl, CuBr did not give the desired product with starting material **1a** was recovered (entries 1-2). Next, we screened various palladium precursors and ligands to increase the yield of **3aa**, and it was found that a catalyst like $Pd(OAc)_2$ and a ligand like dppp gave **3aa** in good yield (entry 6). In contrast, $Pd(acac)_2$, $Pd(dppf)Cl_2$ and $Pd(OAc)_2$ with kinds ligands, such as dppb, X-phos, PPh_3 and PCy_3 provided **3aa** in moderate yields (entries 4-10). Furthermore, the effect of various bases was studied, and we found that the base plays a significant role on the reaction outcome (entries 11-14). Compared with t-BuONa, t-BuOK, K_3PO_4, NaOAc, Cs_2CO_3 performed better in 73% yield. Finally, the controlled experiments without $Pd(OAc)_2$ or CuTC shown no reaction (entry 15-16) and the reaction almost could not occur in the air (entry 17). Based on the above experiments, the reaction was best conducted with $Pd(OAc)_2$ as the catalyst, CuTC as the copper salt, dppp as the ligand, the Cs_2CO_3 as the base, and dioxane as the solvent at 120 ^{o}C for 18 h.

Scheme 2. The cross-coupling reactions of disulfides with oxazoles and thiazoles.



With these optimized reaction conditions, the general applicability of the developed protocol was examined for the C-C coupling reaction of disulfides with oxazoles and thiazole (Scheme 2). The process proved to be relatively broad in scope, tolerating a variety of steric and electronic changes to both reaction partners. In general, moderate to good yields (65-83%) were obtained under the standard reaction conditions (**3aa-3cf**). The reaction conditions were suitable for a variety of disulfides containing electron-donating group (Me) on the phenyl ring as well as electron-withdrawing (F, Cl and NO_2) on the phenyl ring (**3ba-3fa**). The steric effects were negligible and the 4-(2-chlorophenyl) substituted disulfide or 4-isopropyl substituted disulfide gave the target product **3ea**

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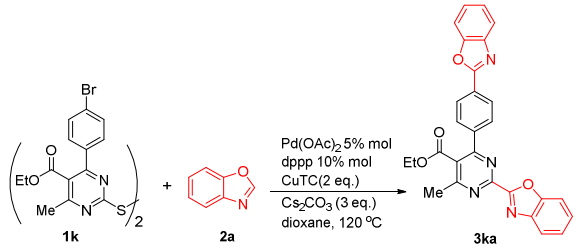
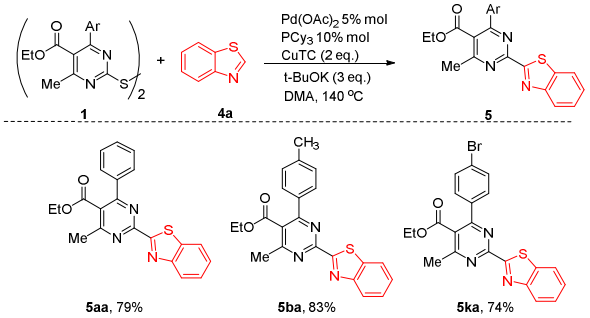
in 70% yield or **3ga** in 68% yield, respectively. As expected disulfides with Me group substituted on the phenyl ring of benzoxazole achieved corresponding products in good yield (**3hb-3cc**). The reaction conditions were suitable for a variety of disulfides and 2-phenyl-1,3,4-oxadiazole to give products (**3ad-3de**). And also, we attempted to disulfides with thiazole deliever corresponding products in modst yields (**3af-3cf**). To our surprise, the disulfides **1k** with 4-Br substituted on the phenyl ring coupled with benzoxazole **2a** giving the bi(1,3,4-oxadiazolo)-substituted pyrimidine **3ka** (Scheme 3). No matter how we decreased the equivalents of **2a** (**1k**:**2a** = **1**:**2**) or raising the equivalents of **1k** (**1k**:**2a** = **1**:**1**), the desired product **3ka** was obtained.

Scheme 3. The reaction of achieve bi-molecular substituted product.



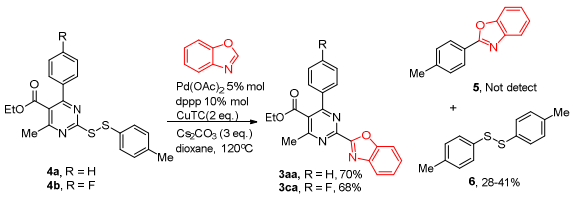
The coupling reaction of disulfides with benzothiazole was then examined. The previous optimized conditions were applied to the cross-coupling reaction, but the desired product was not detected. The choice of ligand was critical to the success of the reaction, and improved yields were obtained when PCy_3 was screened as ligand using $Pd(OAc)_2$ catalyst, *t*-BuOK as base DMA as a solvent at 140 °C, which gave up to 79% and 83% yield of cross-coupling products **5aa** and **5ba**, respectively (Scheme 4). Attempts to apply disulfide **1k** with benzothiazole, the corresponding product **5ka** was formed exclusively.

Scheme 4. The cross-coupling reactions of disulfides with benzothiazole.



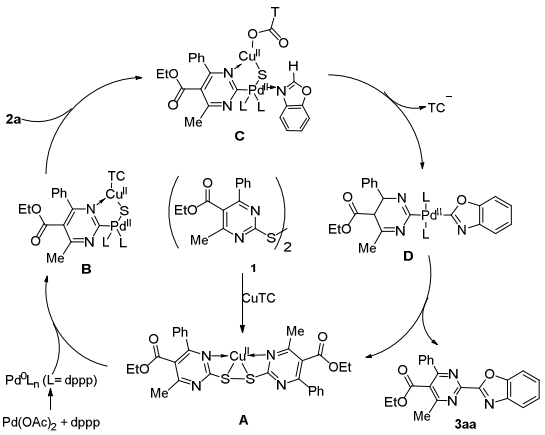
After the tests towards symmetrical diheteroaryl disulfides, two unsymmetrical disulfides **4a** and 4b as reaction substrates were examined. When the reaction of **4a** with **2a** was performed under optimized conditions, the corresponding **3aa** was obtained in a high yield of 70% with the formation of diaryl disulfide **6** (41%), but the 2-(p-tolyl)benzoxazole **5** was not detected. Similarly, using disulfide **4b** gave the corresponding **3ca** (68%) and **6** (28%) (Scheme 5). Unfortunately, reaction of 2,2'-dithiodipyridine or diphenyl disulfide with benzoxazole failed to achieve the desired product, but the starting materials were recovered. Compared with the active oxazoles and thiazoles, the 1-methylindole and 1-methylbenzimidazole were relative unactive and failed to coupling with disulfide to give the corresponding products.

Scheme 5. Cross-coupling of unsymmetrical disulfides.



On the basis of these results and previous literature, [17a, 19] a possible mechanism pathway for the Pd-catalyzed copper-promoted C-C coupling of azoles and thiazoles with 1,2-di(pyrimidin-2-yl) disulfides via C–H/C–S activation reagents is depicted in Scheme 6. Pyrimidine-containing disulfides are more efficient than aryl disulfides in the reaction, which may be due to the coordination of a soft basic atom (such as N atom) to the copper salt promoting C-S activation to give the C-C cross-coupling products. A formal oxidative addition of copper into the S-S bond affords Cu(II) dithiolato intermediate **A**.[20] Subsequent reductive cleavage of the S-S bond leads to the formation of the corresponding copper(II) species **B**. Then, oxidative addition of the Pd(0) to the Cu(II) thiolato intermediate B results in formation of complex **C**.[21] Transmetalation from boron to palladium next occurs, and then reductive elimination, giving the C-C cross-coupling product 3.[22]

Scheme 6. Possible mechanism for the C-C coupling reaction of disulfides with benzoxazole.



In summary, we developed an efficient method to construct C-C bond via direct C-H functionalization of oxazoles or thiazoles with C–S bond cleavage of di(hetero)aryl disulfides. The use of a copper salt such as CuTC was necessary for efficient formation of the C-C bond in this C-C coupling

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reaction. The reaction tolerated a wide substrate scopes and delivered good yields.

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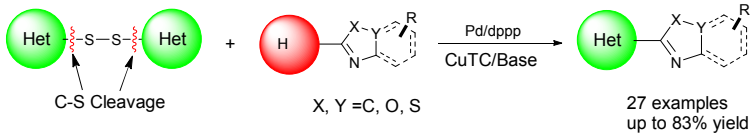
Graphical Abstracts

The C-C Cross-Coupling Reactions of 1,2-Di(pyrimidin-2-yl) disulfides with Azoles and Thiazoles through C-S Cleavage of Disulfides

Kai-Jie Wei, Zheng-jun Quan, Zhang Zhang, Yu-xia Da and Xi-cun Wang



Key words: benzoxazole, benzothiazole, Disulfides, CuTC, C-C coupling

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