

Chemoselective Carbon-Carbon Cross-Coupling *via* Palladium-Catalyzed Copper-Mediated C–S Cleavage of Disulfides

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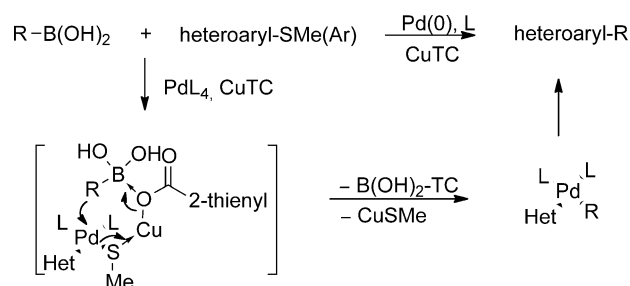
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Abstract: An efficient method for carbon-carbon bond formation is described. The process employs the palladium-catalyzed copper-mediated cross-coupling of diheteroaryl disulfides with arylboronic acids or alkynes to deliver C–C coupling products through unreactive C–S bond cleavage. The scope of the coupling reactions, including both the disulfides and arylboronic acids or alkynes, are documented.

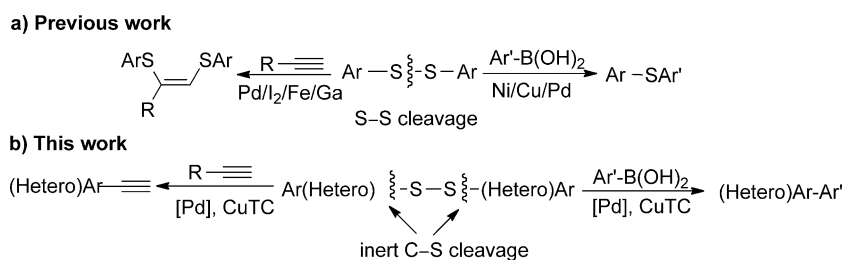
Keywords: alkynes; arylboronic acids; C–S bond cleavage; diheteroaryl disulfides; Liebeskind–Srogl cross coupling

Transition metal-catalyzed cross-couplings are some of the most dependable and effectual methods for forming C–C bonds.^[1] The Suzuki–Miyaura^[2] or the Sonogashira^[3] couplings have become one of the most useful tools to construct Csp^2 – Csp^2 (Csp) bonds. Alkenyl/aryl halides are frequently used as the electrophiles due to their relatively high reactivity and spectacular achievements have been made in recent decades. However, some disadvantages have to be accepted.^[4] For example, aryl halides are not always easily available. Thus, the search for alternative electrophiles as novel substrates to organic halides for the cross-coupling reactions has been the focus of much attention.^[4a] Among these, O- and S-based electrophiles as alternatives for the halides are particularly attractive due to the ubiquitous presence of the O- and S-based starting materials in both the natural world and synthetic systems.^[5] Transition metal-catalyzed selective cleavage of C–S bonds is a particularly attractive route to C–C bond formation.^[6] Cu(I) carboxylate-mediated, Pd-catalyzed cross-coupling reac-

tions of boronic acid with different sulfur compounds, which is well known as the Liebeskind–Srogl cross-coupling reaction, have attracted extensive interest in the organic chemistry community.^[7] The cross-couplings of thioamide with boronic acids or alkynes as a variant of the non-basic Liebeskind–Srogl reaction have been studied by others,^[8] most notably Kappe and co-workers.^[9] The Liebeskind–Srogl cross-coupling implies a Cu ion pair with the thiolate in a thermodynamically strong Cu–SMe bond and the formation of an intermediate from the oxidative addition of the $C(sp^2)$ –S bond, rather than of the $C(sp^3)$ –S bond, to palladium (Scheme 1). We hypothesized that an sp^2 hybridized disulfide-boronic acid cross-coupling carried out under Liebeskind–Srogl reaction conditions in the presence of a second sacrificial equivalent of the Cu(I) would achieve the desired two C–C coupling products. Furthermore, the successful development of such a reaction would demonstrate for the first time that disulfide activation is subject to selective C–C bond formation. Here, we reveal the unique attributes of the Liebeskind–Srogl coupling system applied to the cross-coupling of disulfides with arylboronic acids and terminal alkynes (Scheme 2).



Scheme 1. Proposed mechanism for the Liebeskind–Srogl reaction.



Scheme 2. Strategy to construct heterobiaryl compounds and heteroalkynes *via* cleavage of C–S bonds.

In 2007, Liebeskind reported the first catalytic CuI-3-methylsalicylate (CuMeSal)-catalyzed coupling of thiol esters with an excess of the boronic acids under aerobic conditions without using a Pd catalyst.^[10] A few successful examples of Pd- and/or Cu,Ni-catalyzed cross-coupling of thioethers or thioesters with arylboronic acids, and organometallic reagents were developed under aerobic conditions.^[11–14] The Rh(I)-catalyzed cross-coupling of boronic acid derivatives or terminal alkynes with aryl methyl sulfides by C–SMe cleavage to construct C–C bonds has been developed by Willis's^[15] and Zhang's^[16] groups. At the same time, O. Kwon et al reported the Pd(0)-catalyzed and copper(I)-thiophene-2-carboxylate-(CuTC)-mediated desulfurative couplings of nitrothioethers with boronic acids.^[17]

Diaryl disulfides are structurally symmetrical, air stable, and easy to handle. They are useful sulfenylating reagents and were widely used as sulfenyl and sulfinyl reagents through S–S cleavage with various reagents.^[18–23] However, there is a notable absence of examples of couplings of disulfides for the formation of C–C bonds between arylboronic acids and disulfides (Scheme 2).^[24,25]

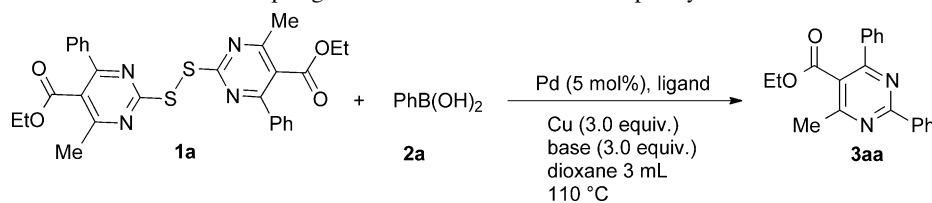
Based on the wide ranging biological activity of 3,4-dihydropyrimidinones^[26] and their utilization as important precursors in the synthesis of pyrimidine bases,^[27] combined with our previous experience on the synthesis of 3,4-dihydropyrimidinone derivatives,^[28] we selected the coupling of 1,2-di(pyrimidin-2-yl) disulfide **1a** (for the preparation, see the Supporting Information) and phenylboronic acid (**2a**) as the model reaction. Gratifyingly, the reaction generated the C–C coupling product **3aa** in 55% yield in the presence of CuTC and K₃PO₄ using Pd(OAc)₂ as the catalyst (Table 1, entry 1). In an attempt to find a more favored Cu source, we evaluated a number of Cu additives including CuI, CuBr, copper(I) acetate [Cu(OAc)] and copper(II) acetate [Cu(OAc)₂]. The use of CuI or CuBr resulted in trace of the target product, but with formation of the homo-coupling product biphenyl (entries 2 and 3). Although Cu(OAc) gave almost complete conversion, a low yield (50%) of **3aa** was obtained (entry 4). When we investigated Cu(OAc)₂ as copper source, undesired products were detected by TLC, LC-MS and ¹H NMR

without the desired product **3aa** (entry 5). Continuing with CuTC, we investigated the influence of different Pd sources, ligands and solvents, PdCl₂, and PdCl₂(PPh₃)₂, respectively, giving lower yield or being inactive compared with the Pd(PPh₃)₄ (entries 6–13). Among the tested bases, K₃PO₄ was the best to give product. Generally, 5 mol% of Pd(PPh₃)₄ and 3 equiv. of CuTC with 3 equiv. of K₃PO₄ were sufficient to achieve a good yield in 1,4-dioxane within 12 h at 110 °C (entry 7). In THF, the reaction gave a lower yield (entry 10). In the absence of Cu additive, no reaction was detected (entry 14). Without Pd the reaction gave a mixture and **3aa** in 25% yield (entry 15), but no **3aa** was detected under an O₂ atmosphere (entries 16 and 17).

Next, the optimized conditions developed for the coupling of **1a** and **2a** were applied to a wide range of arylboronic acid substrates (Table 2). The process proved to be broad in scope, tolerating a variety of steric and electronic changes to both reaction partners. Both electron-rich methyl- and 2-methoxyphenylboronic acid and electron-poor 4-fluoro- and 4-chlorophenylboronic acid underwent cross-couplings to deliver the products **3ab–3ag** in good yields. In addition, the electron-deficient boronic acids, i.e., thiopheneboronic acid and 1-naphthaleneboronic acid were also successful substrates delivering the products (**3ah**, **3ai**, **3ch** and **3ci**), although in these cases long reaction times (24 h) were required to ensure full conversion. An *ortho*-substituted phenylboronic acid underwent cross-coupling with relatively moderate efficiency to form the product **3ad**.

Various pyrimidine functionalized-disulfides (**1b–g**) were also suitable partners for the coupling reaction giving the cross-coupling products (**3ba–3ga**) in good yields. Notably, couplings of 4-fluoro-, 4-chloro-, and 4-bromophenyl-substituted disulfides proceeded with phenylboronic acid with equally high efficiency to yield the C–C coupling products (**3ca**, **3da**, **3ea**, **3ch**, **3ci**). These results are particularly striking because these aryl halides are typical substrates for Suzuki–Miyaura cross-couplings, demonstrating the orthogonal reactivity of disulfides with arylboronic acids.^[29]

To further expand the scope of the nucleophilic coupling partners, we explored the couplings of the pyrimidine -functionalized disulfides **1** with terminal

Table 1. Optimization of the C–C cross-coupling reaction of disulfide **1a** with phenylboronic acid **2a**.^[a]

Entry	Catalyst	Ligand/[mol%]	Cu	Base	Yield ^[b] [%]
1	Pd(OAc) ₂	PPh ₃ /20	CuTC	K ₃ PO ₄	55
2	Pd(OAc) ₂	PPh ₃ /20	CuI	K ₃ PO ₄	trace ^[c]
3	Pd(OAc) ₂	PPh ₃ /20	CuBr	K ₃ PO ₄	trace
4	Pd(OAc) ₂	PPh ₃ /20	Cu(OAc)	K ₃ PO ₄	50
5	Pd(OAc) ₂	PPh ₃ /20	Cu(OAc) ₂	K ₃ PO ₄	trace
6	Pd(OAc) ₂	DPE-Phos/6	CuTC	K ₂ CO ₃	60
7	Pd(PPh ₃) ₄	–	CuTC	K ₃ PO ₄	88
8	Pd(PPh ₃) ₄	–	CuTC	CS ₂ CO ₃	56
9	Pd(PPh ₃) ₄	–	CuTC	K ₂ CO ₃	75
10	Pd(PPh ₃) ₄	–	CuTC	K ₃ PO ₄	81 ^[d]
11	PdCl ₂	DPE-Phos/6	CuTC	K ₃ PO ₄	65
12	PdCl ₂ (PPh ₃) ₂	DPE-Phos/6	CuTC	K ₃ PO ₄	70
13	Pd(PPh ₃) ₄	–	CuTC	–	63
14	Pd(PPh ₃) ₄	–	–	K ₃ PO ₄	–
15	–	–	CuTC	K ₃ PO ₄	25 ^[e]
16	Pd(PPh ₃) ₄	–	CuTC	K ₃ PO ₄	0 ^[f]
17	–	–	CuTC	–	0 ^[g]

^[a] Conditions: **1** (0.25 mmol), **2** (0.75 mmol), Pd(PPh₃)₄ (5 mol%), Cu (3.0 equiv.), base (3.0 equiv.), 1,4-dioxane (4 mL), argon atmosphere, 12 h unless otherwise noted.

^[b] Isolated yield (based on both pyrimidine groups from one molecule).

^[c] Determined by LC-MS and TLC.

^[d] THF was used as solvent at 80 °C for 12 h.

^[e] Undesired products were detected.

^[f] Under an O₂ atmosphere.

^[g] 20% mol of CuTC was used under an O₂ atmosphere.

alkynes **4**. These desulfurative coupling reactions smoothly proceeded under the optimal reaction conditions using Et₃N replace the K₃PO₄ as the base, with complete conversion observed. The cross-couplings of disulfides **1a–d** and **1f** with both aryl- and alkylalkynes selectively proceeded to deliver the C–C cross-coupling products **5aa–5fa** in good yields (Table 3).

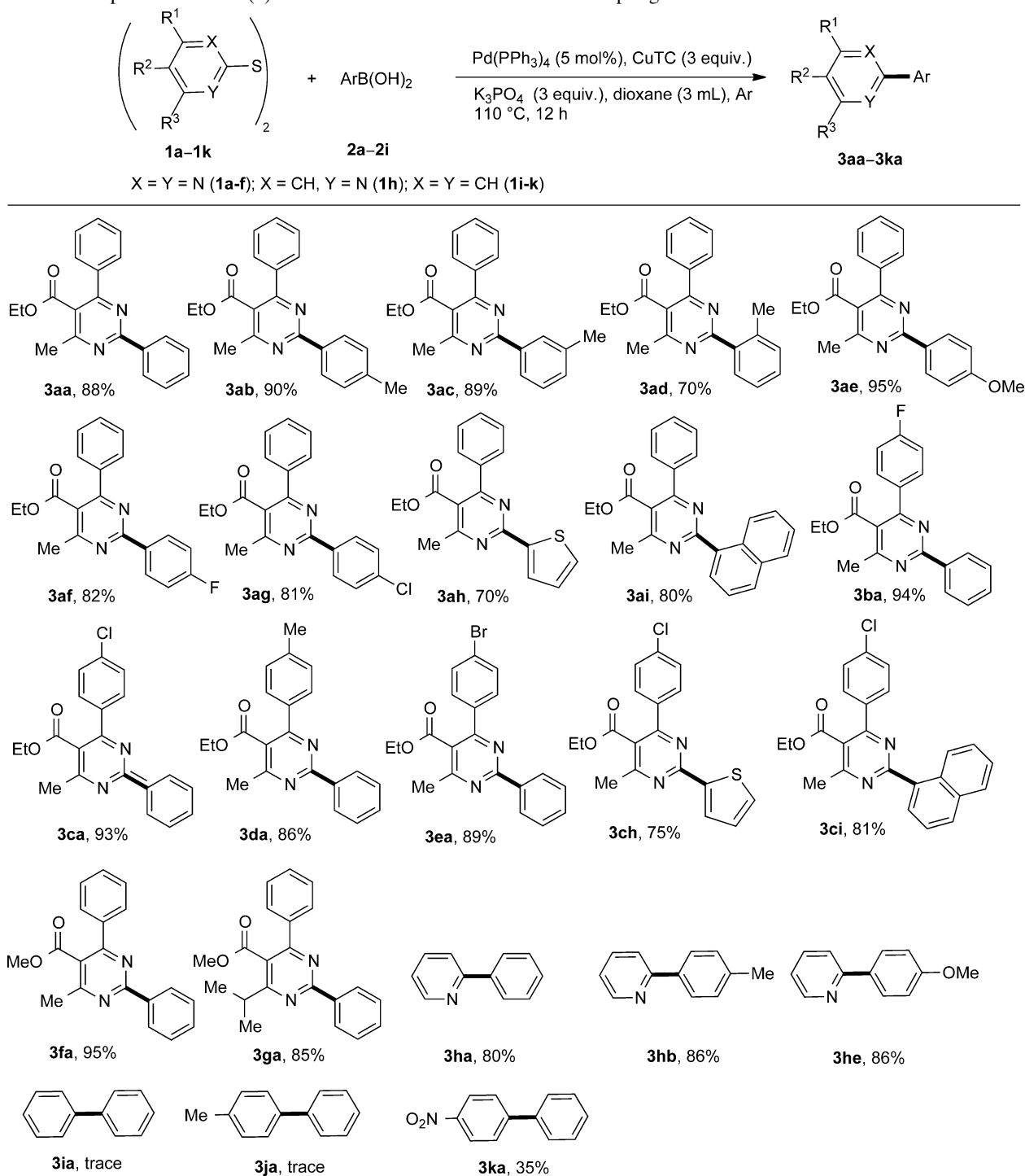
To fully delineate the inherent power of C–C cross coupling protocols, 1,2-di(pyridin-2-yl) disulfide and aryl disulfides were exposed to the C–C cross-coupling reaction. The reactivity of 1,2-di(pyridin-2-yl)disulfane **1h** also induced the C–C cross-coupling with arylboronic acids **2b**, **2e** and alkyne **4b** to form desired products **3hb**, **3he** (Table 2) and **5hb** (Table 3), respectively. In fact, the cross-coupling reaction of mercaptopyrindine **6** with **2a** also gave the desired C–C coupling product **3ha** under the optimal conditions. With (pyridin-2-yl-sulfanylidene)copper (PySCu) **7** and **2a**, the desired product **3ha** was also obtained (Scheme 3). Then, compound **1l** was tested as substrate. It reacted with **2a** smoothly generating prod-

ucts **3aa** and **3ha**. Subsequently, we subjected the compound **1l** to the C–C cross-coupling with 1-octyne **4b** successfully giving both the desired products **5ab** and **5hb**. In each case, the cleavage reaction occurred at the two C–S bonds (Scheme 4).

Compared with the tested nitrogen-containing disulfides, aryl disulfides showed much lower efficiency. For example, 1,2-bis(4-nitrophenyl) disulfide **1k** reacted with **2a** and **4a** to deliver the products **3ka** (Table 2) and **5ka** (Table 3), respectively, albeit in lower yields. In addition, 1,2-diphenyldisulfane **1i** and 1,2-di-*p*-tolyl disulfide **1j** failed to produce the desired product under the same conditions. Alternatively, the homo-coupling of boronic acid or alkyne was significantly increased.

On the basis of these observations, we propose that the reaction mechanism is similar to that for the modified Liebeskind–Srogl cross-coupling reaction as shown in Scheme 5.^[9] Nitrogen-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

Table 2. Scope of disulfides (**1**) and boronic acids in the C–C cross-coupling reaction.^[a]

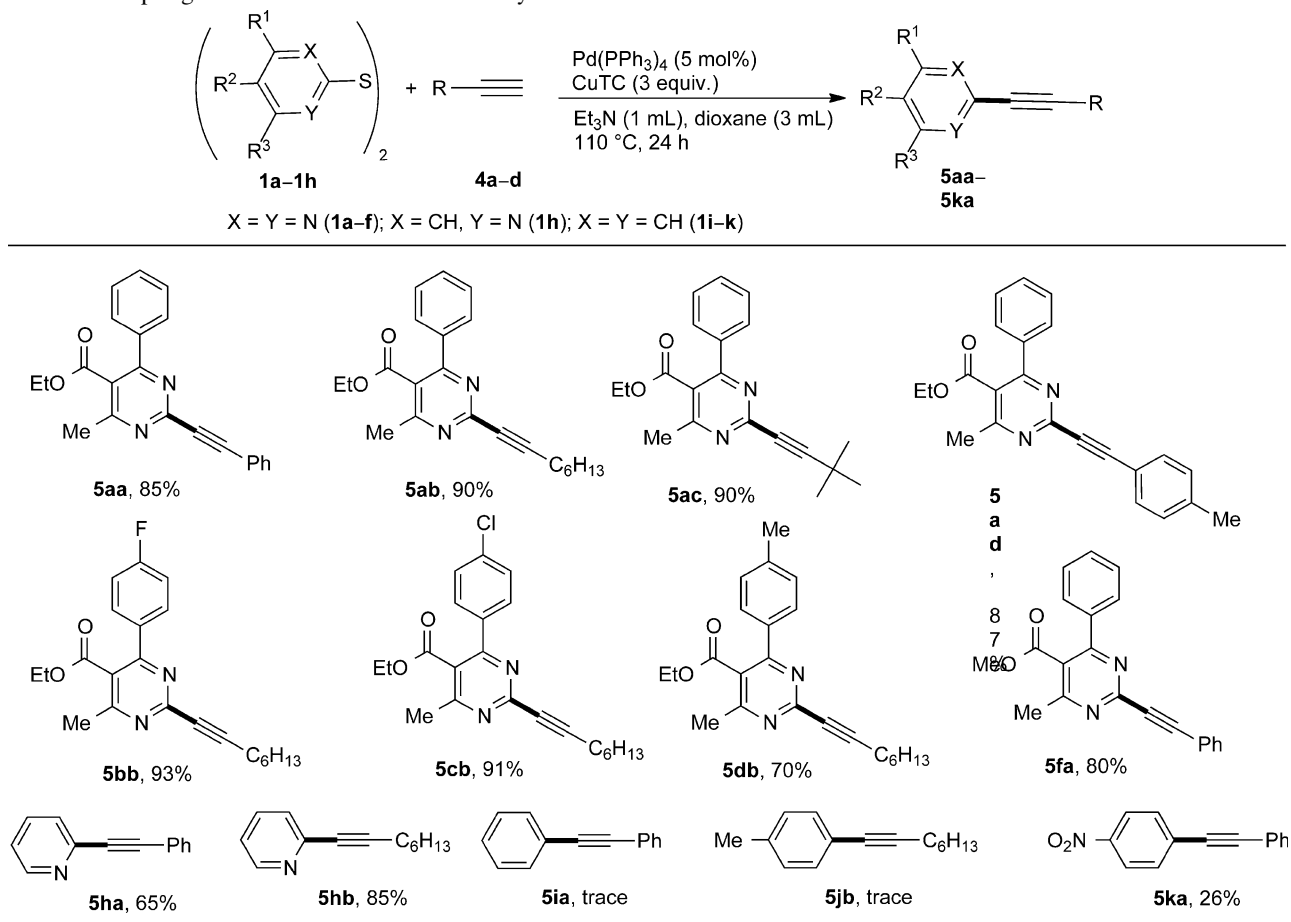


^[a] Conditions: **1** (0.25 mmol), **2** (0.75 mmol), Pd(PPh₃)₄ (5 mol%), CuTC (3.0 equiv.), K₃PO₄ (3.0 equiv.), 1,4-dioxane (4 mL), argon atmosphere, 12 h. Isolated yields.

C–S activation to give the C–C cross-coupling product. A formal oxidative addition of copper into the S–S bond affords Cu(II) dithiolato intermediate **A**.^[30] Subsequent reductive cleavage of the S–S bond leads to the formation of the corresponding copper(II) species **B**. In fact, the ESI-MS analysis of the reaction

mixture for **3aa** gave a set of prominent peaks with a mass that is consistent with the molecular formulation of compound [Cu(II)(**1a**)] (**A** or **B**) (ESI-MS: *m/z* = 609). Then, oxidative addition of the Pd(0) to the Cu(II) thiolato intermediate **B** results in formation of complex **C**.^[22] Transmetalation^[1a] from boron

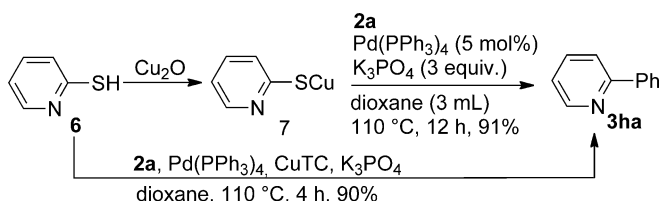
Table 3. Coupling of disulfides with terminal alkynes.^[a]



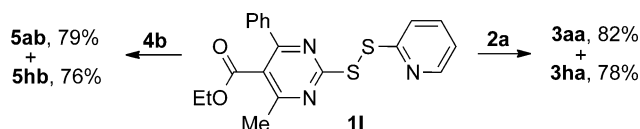
^[a] *Conditions:* **1** (0.25 mmol), **4** (0.75 mmol), Pd(PPh₃)₄ (5 mol%), CuTC (3.0 equiv.), Et₃N (1.0 mL), argon atmosphere, 24 h. Isolated yields.

to palladium next occurs, and then reductive elimination, giving the C–C cross-coupling products **3aa**.

In conclusion, we reported a C–C bond forming reaction *via* a Liebeskind–Srogl-type cross-coupling involving the cleavage of the C–S bond of di(hetero)aryl disulfides by arylboronic acids or 1-alkynes. The use of a thiophilic additive such as Cu(OAc) or CuTC was necessary for efficient formation of the C–C bond in these reactions. The reaction using nitrogen-containing disulfides as substrates typically proceeds with high efficiency and chemoselectivity. This protocol exhibits broad substrate scope with



Scheme 3. Coupling of pyridine-2-thiol with **2a**.



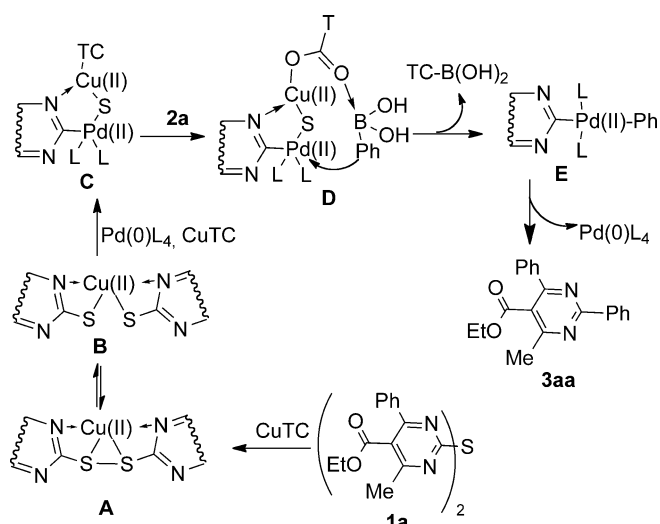
Scheme 4. Couplings of 2-(pyridin-2-ylsulfanyl)pyrimidine.

respect to arylboronic acids and alkynes, providing products in good to excellent yields.

Experimental Section

General Procedure for the Synthesis of C-2-Arylpyrimidines (**3aa–3he**)

A sealed tube (15 mL) initially fitted with a septum containing Pd(PPh₃)₄ (19.3 mg, 0.05 equiv.) was evacuated and purged with argon gas three times. Pyrimidin-2-yl disulfide (**1**, 0.25 mmol), arylboronic acid (**2**, 0.75 mmol, 3.0 equiv.), K₃PO₄ (0.75 mmol, 3.0 equiv.) and 1,4-dioxane (3 mL) were added to the system and the reaction mixture was stirred at 110 °C for 12 h until complete consumption of **1** (based on TLC monitoring). After completion of reaction, the mixture



Scheme 5. Possible mechanism for the cross coupling of disulfides and boronic acids.

was cooled to room temperature and quenched with saturated aqueous NH_4Cl solution (3 mL), then extracted with ethyl acetate (2×10 mL). The organic solvents were combined and washed with aqueous NaOH solution (2 mmol mL^{-1} , 2 mL), brine and dried over MgSO_4 . Purification *via* silica gel column chromatography using petroleum ether/EtOAc (90:1) as eluent gave the corresponding products **3**.

General Procedure for the Synthesis of C-2-Alkynylpyrimidines (**5aa–5hb**)

A sealed tube (15 mL) initially fitted with a septum containing $\text{Pd}(\text{PPh}_3)_4$ (19.3 mg, 0.05 equiv) was evacuated and purged with argon gas three times. Pyrimidin-2-yl disulfide (**1**, 0.25 mmol), alkyne (**4**, 0.75 mmol, 3.0 equiv.), Et_3N (1 mL) and 1,4-dioxane (3 mL) were added to the system and the reaction mixture was stirred at 110°C for 24 h until complete consumption of **1** (based on TLC monitoring). After completion of the reaction, the mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl solution (3 mL), then extracted with ethyl acetate (2×10 mL). The organic solvents were combined and washed with NaOH aqueous solution (2 mmol mL^{-1} , 2 mL), brine and dried over MgSO_4 . Purification *via* silica gel column chromatography using petroleum ether/EtOAc (30:1) as eluent gave the corresponding C–C coupling products **5**.

Acknowledgements

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