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Highly regioselective synthesis of aryl chalcogenides through C–H functionalization of arenes†

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We report here the regioselective synthesis of aryl chalcogenides through the iridium-catalyzed *meta* C–H borylation followed by copper-catalyzed C–S coupling reaction with chalcogenide sources in one pot, giving the 3,5-disubstituted aryl chalcogenides with high regioselectivity and good yields.

Aryl chalcogenides are important building blocks in organic synthesis, materials science and in the pharmaceutical industry.[1] Transition-metal-catalyzed cross-coupling reaction of thiols and disulfides with aryl halides and pseudo halides is one of the most powerful approaches for preparing aryl thioethers.[2–9] Palladium,[3] copper,[4] cobalt,[5] indium,[6] gold,[7] rhodium[8] and iron[9] have all been reported as the catalysts for the coupling reaction of aryl halides with thiols. Additionally, transition metals such as palladium, nickel and copper have also been reported as the catalysts for C–Se and C–Te bond forming reactions.[1,10]

Direct C–H functionalization of arenes is an important consideration from the atom economy standpoint.[11] Many reliable and efficient protocols have been developed for making C–C,[12] C–N,[13] and other C-heteroatom bonds[14] through metal-catalyzed activation of arene C–H bonds; C–S bond formation by this approach is relatively less studied.[15–19] Yu *et al.* reported the copper-catalyzed *ortho*-thiolation of 2-phenylpyridine with thiophenols and methyl disulfide.[15] Dong *et al.* reported the palladium-catalyzed *ortho*-sulfonylation of 2-phenylpyridine with $ArSO_2Cl$.[16] These methods enabled the highly regioselective *ortho*-C–S bond formation; however, pyridine is required as a directing group for such systems. Cheng *et al.* reported the copper-catalyzed C–H functionalization of arenes, giving the corresponding aryl thioethers in moderate yields; however, only very electron-rich arenes such as 1,3,5-trimethoxybenzene and 1,2,4-trimethoxybenzene are suitable as the coupling partners.[17] Recently, Beller *et al.* reported the palladium-catalyzed coupling of arylsulfonyl cyanides with arenes, giving the diaryl thioethers in moderate yields.[18] However, some limitations remained by this system. First, the system employs trifluoroacetic acid as a solvent and acid sensitive functional groups may react under these conditions. Second, *ortho* and *para* C–S formation is observed in most cases. Third, the mixtures of *ortho*- and *para*-arylthiolated products were found in some cases. Notably, these two systems prefer the *ortho* and *para* rather than *meta* C–S formation. Very recently, Frost *et al.* reported the ruthenium-catalyzed *meta* sulfonation of 2-phenylpyridines with sulfonyl chlorides; however, pyridine is required as a directing group.[19] To the best of our knowledge, the direct *meta* C–H functionalization of arenes with sulfur surrogates in the absence of a directing group is not well-documented.

The combination of iridium-catalyzed C–H and sequential functionalization of the resulting aryl boronic esters is an excellent approach for regioselective *meta* C–H functionalization of arenes.[20] It should be possible to prepare aryl chalcogenides with high regioselectivity using iridium-catalyzed C–H activation followed by C–S, C–Se and C–Te cross-coupling reactions. Here, we report the *meta* C–H functionalization of arenes with chalcogenide sources, giving the aryl chalcogenides with high regioselectivity and good to excellent yields.

The coupling of the resulting arylboronic esters from iridium-catalyzed C–H activation with sulfur nucleophiles is the key step for preparing aryl thioethers from arenes. Although the coupling of arylboronic acids with sulfur sources including aryl disulfide is known,[10d,21] the C–S bond formation between arylboronic esters and sulfur surrogates is undocumented. Initially, 3,5-dimethylphenyl boronic ester was selected as a substrate to screen the optimal reaction conditions with 0.55 equiv. of aryl disulfide as a sulfur surrogate. The results are summarized in Table 1. The control experiments showed that no product was obtained when the reaction was carried out in the absence of the catalyst (Table 1, entry 1), and only a trace amount of product was observed when the reaction was performed without a ligand (Table 1, entry 2). The combination of CuI with bpy (2,2′-dipyridyl) in the solvent of DMSO–H_2O showed good reactivity,[10d] giving the target in 78% isolated yield (Table 1, entry 3). A low yield was observed when the reaction was carried out in the absence of water (Table 1, entry 4); this phenomenon has also been recognized in the copper-catalyzed coupling of nucleophiles with arylboronic esters.[20f,g] Other solvent systems, including the comb!ination of EtOH, DMF, or dioxane with water, could not provide satisfactory results (Table 1, entries 5–7). Interestingly, lower and higher temperatures diminished the yield of the product (Table 1, entries 8 and 9, respectively). We studied the effect of ligands (Table 1, entries 10–13), and the results

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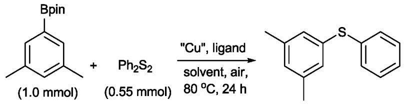
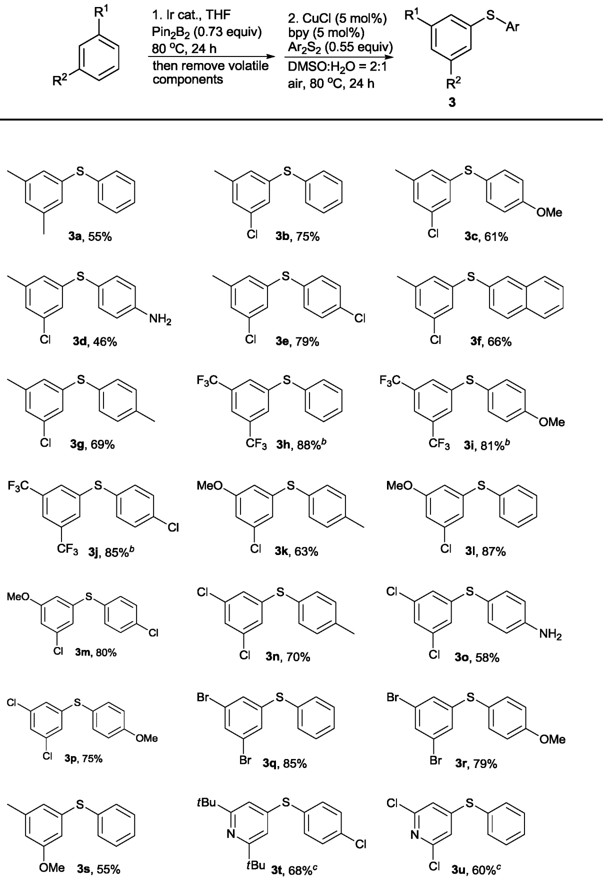
Table 1 Optimized reaction conditions[a]



Entry	"Cu"	Ligand	Solvent	Yield[b] (%)
1	—	—	DMSO/H_2O (2 : 1)	—
2	CuI	—	DMSO/H_2O (2 : 1)	Trace
3	CuI	bpy	DMSO/H_2O (2 : 1)	78
4	CuI	bpy	DMSO	29
5	CuI	bpy	EtOH/H_2O (2 : 1)	54
6	CuI	bpy	DMF/H_2O (2 : 1)	49
7	CuI	bpy	Dioxane/H_2O (2 : 1)	21
8[c]	CuI	bpy	DMSO/H_2O (2 : 1)	64
9[d]	CuI	bpy	DMSO/H_2O (2 : 1)	58
10	CuI	dmphen	DMSO/H_2O (2 : 1)	Trace
11	CuI	dmbpy	DMSO/H_2O (2 : 1)	75
12	CuI	dtbpy	DMSO/H_2O (2 : 1)	74
13	CuI	phen	DMSO/H_2O (2 : 1)	70
14	CuCl	bpy	DMSO/H_2O (2 : 1)	88
15	CuBr	bpy	DMSO/H_2O (2 : 1)	54
16	CuO	bpy	DMSO/H_2O (2 : 1)	Trace
17[e]	Cu_2O	bpy	DMSO/H_2O (2 : 1)	37
18[f]	CuCl	bpy	DMSO/H_2O (2 : 1)	51

[a] Reaction conditions: Cu source (0.05 mmol, 5 mol%), ligand (0.05 mmol, 5 mol%), 3,5-dimethylphenyl boronic ester (1.0 mmol) and diphenyl disulfide (0.55 mmol) in 0.6 mL solvent. [b] Isolated yield. [c] 70 °C. [d] 110 °C. [e] Cu_2O: 2.5 mol%. [f] CuCl (3.0 mol%) and bpy (3.0 mol%).

Table 2 Synthesis of diaryl thioethers through tandem C–H borylation and copper-catalyzed C–S coupling reactions[a]



[a] Reaction conditions unless otherwise stated: arene (1.0 mmol), $[Ir(cod)OMe]_2$ (0.0015 mol, 0.15 mol%), dtbpy (0.003 mmol, 0.3 mol%) in 1.5 mL THF for the first step; CuCl (0.05 mmol, 5.0 mol%), bpy (0.05 mmol, 5.0 mol%), disulfide (0.55 mmol) in 0.4 mL DMSO and 0.2 mL H_2O for the second step. [b] Borylation with 0.1 mol% $[Ir(cod)OMe]_2$ and 0.2 mol% dtbpy. [c] Borylation with 3.0 mol% $[Ir(cod)OMe]_2$ and 6.0 mol% dtbpy.

revealed that other ligands such as dmphen (2,9-dimethyl-1,10-phenanthroline), dmbpy (4,4′-dimethyl-2,2′-bipyridine), dtbpy (4,4′-di-*tert*-butyl-2,2′-dipyridyl) and phen (1,10-phenanthroline) could not provide the product in a good yield. The screening of copper sources (Table 1, entries 14–17) showed that CuCl is the best (Table 1, entry 14), giving the product in 88% isolated yield under air at 80 °C. Lower catalyst loading will reduce the product yield (Table 1, entry 18).

Based on the optimized reaction conditions in hand, we then studied the tandem regioselective *meta* C–H borylation followed by C–S bond formation in one pot. As demonstrated in Table 2, a variety of 1,3-disubstituted arenes and thiophenols bearing electron-donating and electron-withdrawing substituents were reacted with B_2Pin_2 in the presence of iridium catalyst to give the arylboronates,[20f,g,i,j] after removing the volatile components, the reaction mixtures were further conducted with aryldisulfides using copper catalysis, giving the corresponding diaryl thioethers in good yields. Meanwhile, free amine (**3d**, **3o**), chloro (**3b–3g**, **3k–3p** and **3u**), trifluoromethyl (**3h–3j**), bromo (**3q** and **3r**) and nitrogen-containing moieties (**3t** and **3u**) all tolerate the reaction conditions employed. The halogen-containing products are particularly amenable to further modification.

We next turned our attention to the regioselective *meta* C–Se and C–Te bond formations. The results are summarized in Table 3, the diaryl selenides (**4a–4f**) and diaryl tellurides (**4g–4k**) were obtained when the reactions were conducted with diselenides and ditellurides, respectively. In general, the diaryl selenides and tellurides are obtained in moderate to good yields. Although good results are observed by the reactions of diaryl chalcogenides, unfortunately, the dialkyl chalcogenides are not suitable as the coupling partners for the synthesis of aryl–alkyl chalcogenides under the catalysis shown above. Indeed, we have tried many dialkyl chalcogenides including *n*Bu–S–S–*n*Bu, *t*Bu–S–S–*t*Bu, $C_{12}H_{25}$–S–S–$C_{12}H_{25}$ and Me–Se–Se–Me as the coupling partners. Unfortunately, only trace amounts of the targets were detected by GC-MS analysis. The corresponding arylboronic esters and the starting dialkyl chalcogenides were both observed as the major materials in such cases.

In conclusion, we have developed a general method for the regioselective synthesis of diaryl chalcogenides through the iridium-catalyzed *meta* C–H borylation followed by copper-catalyzed C–S coupling reaction with aryl dichalcogenides in one pot allowing for the direct synthesis of 3,5-disubstituted diaryl chalcogenides. Preparation of diaryl chalcogenides for bioactive tests and improvement for the synthesis of aryl–alkyl chalcogenides are underway in our laboratory.

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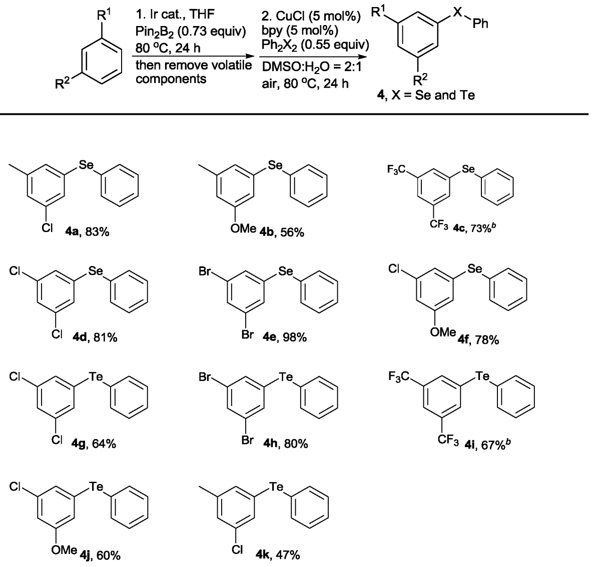
Table 3 Tandem C–H borylation and copper-catalyzed C–Se, C–Te coupling reactions[a]



[a] Reaction conditions unless otherwise stated: arene (1.0 mmol), $[Ir(cod)OMe]_2$ (0.0015 mol, 0.15 mol%), dtbpy (0.003 mmol, 0.3 mol%) in 1.5 mL THF for the first step; CuCl (0.05 mmol, 5.0 mol%), bpy (0.05 mmol, 5.0 mol%), diaryl selenide or diaryl telluride (0.55 mmol) in 0.4 mL DMSO and 0.2 mL H_2O for the second step. [b] Borylation with 0.1 mol% $[Ir(cod)OMe]_2$ and 0.2 mol% dtbpy.

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