

Palladium-catalyzed Cross-coupling of Unactivated Aryl Sulfides with Arylzinc Reagents under Mild Conditions

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Abstract: Cross-coupling of general aryl alkyl sulfides with arylzinc reagents proceeds smoothly, even at room temperature or below, with a palladium-NHC catalyst. When combined with reactions that are unique to organosulfurs, i.e., S_NAr sulfanylation or Pummerer reaction, the cross-coupling offers interesting transformations that are otherwise difficult to achieve. An alkylsulfanyl group is preferentially converted with leaving tosyloxy and chloro intact, which expands the variety of orthogonal cross-coupling.

Cross-coupling reactions are among the most important carbon-carbon bond formations in organic synthesis.^[1] Aryl bromides and iodides have played a central role as electrophilic partners for cross-coupling. Aryl sulfonates and phosphates are also good substrates thanks to the high leaving ability of their oxygen functionalities. Recent dramatic advances in transition metal catalysts have been expanding the scope of electrophiles. With very electron-rich transition metal complexes that undergo smooth oxidative addition, one can use less reactive aryl chlorides^[2] and fluorides^[2b,3] and usually inert phenol derivatives such as carbonates, esters, and even ethers^[4,5] as electrophilic substrates.

Less attention has been paid to the use of organosulfur compounds in cross-coupling reactions.^[6] Among them, aryl sulfides bearing a divalent sulfur atom constitute the most challenging substrates. Their $C(sp^2)-S$ bonds are rather strong^[7] to retard oxidative addition. Furthermore, starting aryl sulfides can poison transition metal catalysts and the resulting thiolate anions can even much more. Naturally, transmetalation would be slow because of the high affinity between a cationic transition metal and a thiolate anion.

Since Takei's and Wenkert's pioneering work,^[8] Grignard reagents are the choice of nucleophilic partners in cross-coupling of aryl sulfides,^[9] probably due to their high reactivity for efficient transmetalation. Because Grignard reagents have low functional group compatibility, organozinc, -stannane, and -boron reagents are preferable. However, cross-coupling of aryl sulfides with these mild organometallic species has severe limitations: (1) The leaving group must be neutral tetrahydrothiophene (aryltetramethylenesulfonium salts as substrates) or chelating thioglycolate derivatives that capture a

zinc ion to facilitate transmetalation.^[10] (2) Otherwise, aryl groups must be either activated heteroaryl such as thioester mimics^[11,12] (2-pyridyl, 2-pyrimidyl, 2-pyrazinonyl, etc.) and 2-benzofuryl^[9i,13] or aryl bearing an *ortho*-directing group (carbonyl or nitro).^[14] To the best of our knowledge, there are no reports on cross-coupling reactions of unactivated aryl alkyl sulfides with organozinc reagents despite their seeming simplicity. Here we report the first examples of such cross-coupling reactions.

We chose the reaction of methyl *p*-tolyl sulfide with *p*-ethoxycarbonylphenylzinc iodide•lithium chloride complex^[15] as a model reaction. Our success heavily depends on the choice of a palladium catalyst. We screened a variety of palladium salts and ligands to find that commercially available Pd-PEPPSI-SIPr^[16] is the best catalyst (See Supporting Information for the catalyst structure and optimization). Surprisingly, the reaction proceeded at room temperature (20 °C). Palladium complexes bearing phosphine ligand(s) were found to be almost inactive. Other palladium-NHC complexes exhibited moderate reactivities. A Ni-NHC complex NiCl₂(IPr)(PPh₃) is not effective. Acetonitrile has proved to be the best solvent and ethereal solvents such as THF, 1,2-dimethoxyethane, and diglyme also worked as well. Less polar toluene and diethyl ether were inferior.

Arylzinc reagents can contain electron-withdrawing ester, cyano, trifluoromethyl or electron-donating methoxy group (Table 1, entries 1–4).^[17] Heteroaromatic 2-thienylzinc reagent as well as sterically demanding 1-naphthylzinc reagent also participated smoothly (entries 5 and 6) although the latter required a higher temperature. Alkenylzinc bromide•lithium chloride complex prepared from α -bromostyrene reacted to yield alkenylated product **1g** (entry 7).

Interestingly, the presence of lithium chloride is crucial for the success of the arylation (Scheme 1).^[18] Gosmini's arylzinc reagent,^[19] prepared from ethyl 4-bromobenzoate and zinc powder in the presence of cobalt(II) bromide, did not undergo the coupling at all in the absence of lithium chloride. Dramatically, an addition of lithium chloride accelerated the arylation with Gosmini's reagent to afford **1a** in 92% yield. Deprotonation of benzofuran and *N*-methylindole by butyllithium followed by transmetalation with zinc chloride provided the corresponding benzoheteroarylzinc chloride•lithium chloride, which underwent smooth cross-coupling with thioanisole.

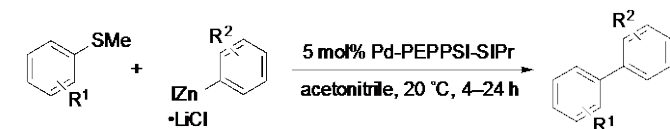
The scope of aryl sulfides is broad. Although electron-donating methoxy and *t*-butoxycarbonyloxy group slowed down the arylation, the reactions completed in 24 h to afford the corresponding products in high yields (Table 1, entries 8 and 9). Electron-withdrawing groups facilitated the arylation (entries 10–12). Notably, formyl and acetyl groups are compatible. A methyl group at the *ortho* position did not retard the reaction (entry 13). Not only 2-alkylsulfanylpyridine but also 3-alkylsulfanylpyridine, which is not a thioester mimic, reacted smoothly (entries 15 and 16). As a protecting group of NH₂, succinimido protection is suitable (entry 17). Other protections that leave acidic NH, such as acetoamido, inhibited the reaction.

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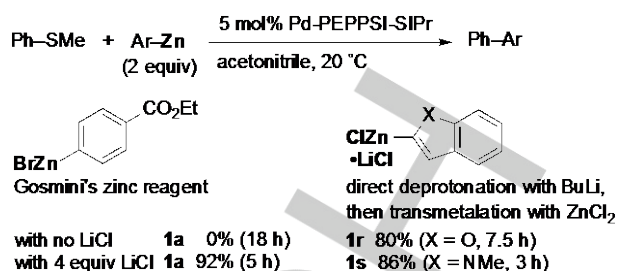
The leaving sulfanyl moiety is not limited to a methylsulfanyl group. Odorless dodecylsulfanyl^[20] and phenylsulfanyl are good leaving groups (99% yield of **1a** in both cases). However, the reaction of *t*-butyl phenyl sulfide was sluggish to afford **1a** in only 21% yield under the otherwise same conditions.

Table 1. Cross-coupling of aryl sulfides with arylzinc reagents^[a]



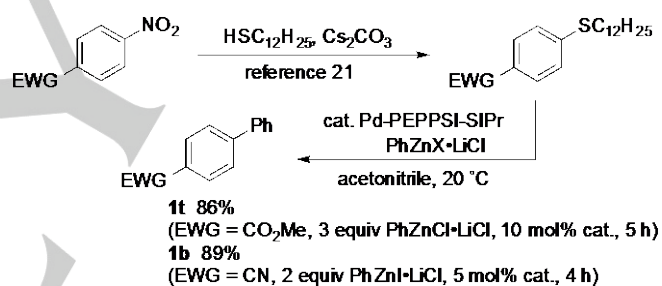
Entry	R ¹	R ²	Time [h]	Product	Yield [%]
1	H	4-CO ₂ Et	4	1a	99
2	H	4-CN	16	1b	83
3	H	4-CF ₃	24	1c	85
4	H	4-OMe	4	1d	91
5	H	(2-thienyl)	5	1e	91
6	4-Me	(1-naphthyl)	4.5	1f	95 ^[b]
7	H	(CPh=CH ₂) ^[c]	24	1g	62
8	4-OMe	4-CO ₂ Et	22	1h	77 ^[d]
9	4-OBoc	4-CO ₂ Et	16	1i	73
10	4-CHO	H	4	1j	96
11	4-COCH ₃	4-CO ₂ Et	4	1k	89 ^[d]
12	4-F	4-CO ₂ Et	2	1l	88
13	2-Me	4-CO ₂ Et	4	1m	87
14	(2-naphthyl)	4-CO ₂ Et	5	1n	93
15	(2-pyridyl)	4-CO ₂ Et	16	1o	91
16	(3-pyridyl) ^[e]	4-CO ₂ Et	4	1p	91
17	4-succinimido	4-CO ₂ Et	5	1q	75

[a] Conditions: aryl methyl sulfide (0.50 mmol), ArZn•LiCl (1.0 M in THF, 2 equiv), Pd-PEPPSI-SIPr (5 mol%), acetonitrile (1.5 mL). [b] 60 °C. [c] With CH₂=CPhZnBr•LiCl. [d] In diglyme. [e] 3-Dodecylsulfanylpyridine was used.



Scheme 1. Reactions with arylzinc species prepared through other methods.

Alkanethiols are nucleophilic enough to react with electron-deficient arenes by an S_NAr mechanism. The S_NAr reactions of methyl 4-nitrobenzoate and 4-nitrobenzotrile with dodecanethiol in the presence of cesium carbonate^[21] resulted in cleanly replacing the NO₂ groups with dodecylsulfanyl (Scheme 2). The sulfides thus generated underwent cross-coupling with an arylzinc reagent smoothly. These two-step transformations represent displacement of a nitro group with an aryl group taking advantage of the high nucleophilicity of a thiolate anion, which halide and alkoxide anions are unable to achieve.

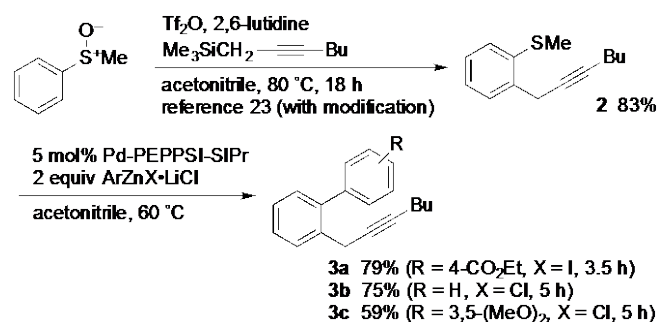


Scheme 2. S_NAr displacement of NO₂ with C₁₂H₂₅S followed by cross-coupling.

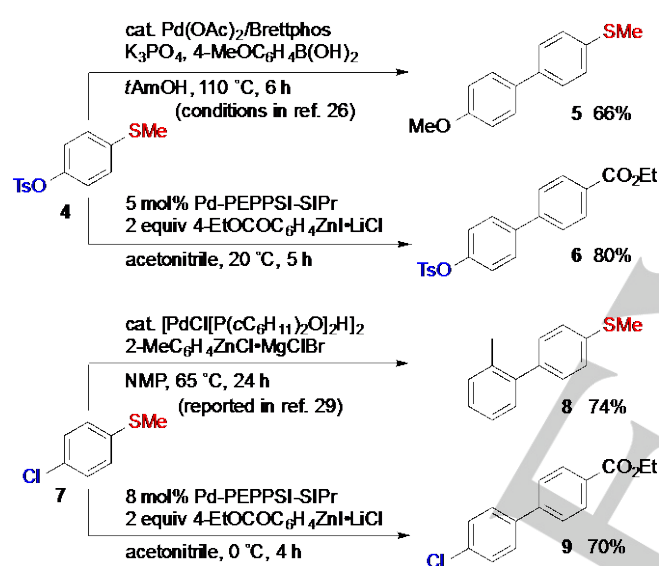
Another unique transformation of organosulfur compounds is the Pummerer reaction.^[22] According to Procter's protocol,^[23] methyl phenyl sulfoxide was converted to 2-propargylphenyl sulfide **2** (Scheme 3). After this *ortho*-functionalization that the corresponding aryl halides and pseudohalides cannot engage in, the following cross-coupling reaction afforded products **3a–c**. The overall transformations represent vicinal propargylation/arylation substitution to synthesize *o*-propargylbiaryls, potent precursors of phenanthrenes under Lewis acid catalysis,^[24] from very simple building blocks.

The emergence of this new cross-coupling option raised questions about orthogonality with other cross-coupling footholds.^[25] According to the procedure of Buchwald,^[26] Suzuki-Miyaura arylation of aryl tosylate **4** selectively substituted the tosyloxy group to yield methylsulfanylbiaryl **5**. In contrast, arylation of **4** under our conditions afforded **6** with replacing the methylsulfanyl group and leaving the tosyloxy moiety intact. Similarly, 4-chlorothiobanisole (**7**) underwent arylation under our conditions to yield **9** without touching the chloro group at 0 °C^[27,28] whereas selective arylation of **7** at the chlorinated

position was reported to form **8**.^[29] Our new protocol thus expands the variety of orthogonal functionalizations of arenes.



Scheme 3. Pummerer propargylation/arylation sequence.



Scheme 4. Controllable cleavage.

In summary, we have developed general and efficient protocol for accomplishing cross-coupling of unactivated aryl sulfides with arylzinc reagents under Pd-PEPPSI-SIPr catalysis. Electronically and sterically diverse aryl sulfides undergo cross-coupling, even at room temperature. Not only Knochel's ArZn•LiCl but also other arylzinc species are employable with the aid of lithium chloride. The cross-coupling can follow S_NAr displacement of a nitro group with an alkylsulfanyl or Pummerer *ortho*-propargylation, which eventually offers otherwise difficult transformations by taking advantage of the unique reactivity of organosulfurs. Our system exhibits intriguing orthogonal reactivity, leaving tosyloxy and chloro intact. Our current studies are directed to disseminate C–S-based organic synthesis that complements C–X-based synthesis.^[30]

Experimental Section

The reaction of thioanisole with 4-ethoxycarbonylphenylzinc reagent is representative (Table 1, entry 1). To Pd-PEPPSI-SIPr (17.0 mg, 0.025 mmol) in a 20-mL two-neck flask was added 4-ethoxycarbonylphenylzinc iodide•lithium chloride complex (1.0 mL, 1.0 mmol, 1.0 M in THF) at 20 °C under nitrogen. After 3 min, the solution turned black. Acetonitrile (1.5 mL) and phenyl methyl sulfide (62.1 mg, 0.50 mmol) were added and the resulting mixture was stirred at 20 °C for 4 h. Saturated NH₄Cl aq. (10 mL) was added and organic compounds were extracted with a mixture of *n*-hexane/EtOAc (3/1, 10 mL×3). The combined organic layer was passed through pads of anhydrous sodium sulfate and activated alumina. Concentration followed by purification on silica gel (*n*-hexane/EtOAc = 30/1) provided **1a** (112.0 mg, 0.49 mmol, 99%).

Acknowledgements

This work was supported by Grants-in-Aid from MEXT (Nos.: 24106721 “Reaction Integration” and 25107002 “Science of Atomic Layers”) and from JSPS (Nos.: 24685007 (Young Scientists (A)) and 26620081 (Exploratory Research)). D.F. and K.M. acknowledge JSPS for financial support.

Keywords: organosulfur compounds • cross-coupling • organozinc compounds • palladium • C–S bond activation

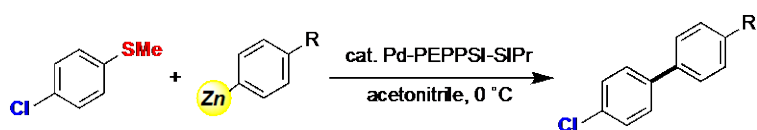
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A palladium-carbene complex has now made reluctant aryl sulfides reactive in the cross-coupling reactions with organozinc reagents. The cross-coupling is broad in scope and proceeds even at room temperature or below. When combined with sulfur-specific reactions, the cross-coupling offers useful transformations that are otherwise difficult to achieve. The cross-coupling converts an alkylsulfanyl group with leaving chloro intact, which expands the variety of orthogonal cross-coupling.

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Palladium-catalyzed Cross-coupling of Unactivated Aryl Sulfides with Arylzinc Reagents under Mild Conditions