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Direct Cross-Coupling Access to Diverse Aromatic Sulfide: Palladium-Catalyzed Double C−S Bond Construction Using $Na_2S_2O_3$ as a Sulfurating Reagent

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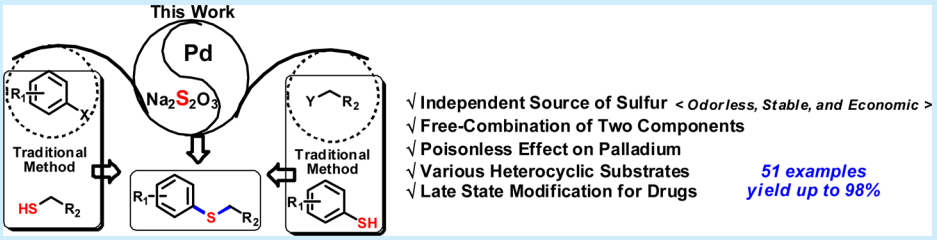
Supporting Information

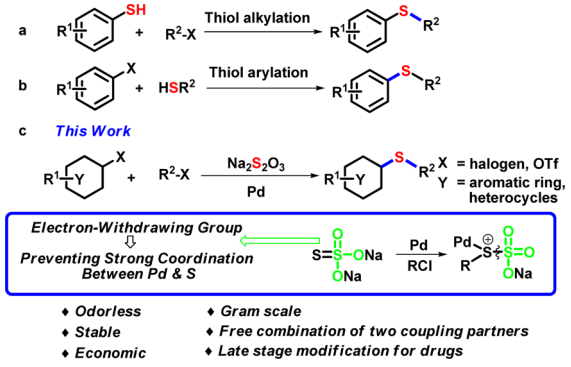


ABSTRACT: The Pd-catalyzed cross-coupling of aryl halides, alkyl halides, and $Na_2S_2O_3·5H_2O$ to deliver aromatic thioethers is described. Pyridine, furan, thiophene, benzofuran, benzoxazole, benzothiophene, benzothiazole, and pyrazine are all amenable to this protocol. The odorless and stable solid $Na_2S_2O_3·5H_2O$ was used as a convenient and environmentally friendly source of sulfur. Pd-catalyzed cross-couplings without thiols or thiophenols to build C−S bonds have not previously been achieved, which renders our observation more striking.

Organosulfur chemistry has gained attention because sulfur-containing building blocks serve important functions in general organic synthesis[1] as well as applications in the pharmaceutical industry,[2] material science,[3] and food chemistry.[4] Because of the significance of organosulfur compounds, the development of new, efficient, and environmentally benign synthetic methodologies for the incorporation of sulfur into organic frameworks is an important and challenging task.[5] Pd-catalyzed cross-coupling reactions have been developed into classical transformations for the construction of C−O and C−N bonds.[6] However, Pd-catalyzed C−S bond formation has been less studied due to the deactivation of the metal catalysts by strong coordinating properties.[7] Migita's group realized the first Pd-catalyzed Csp^2−S bond formation in 1980.[8] More recently, contributions by Hartwig,[9a−c] Lee,[9d] Kim,[9e] Stambuli,[9f] and Zheng[9g,h] have appeared in Pd-catalyzed cross-coupling with the help of special additives (ligands, indium, or zinc) for protecting palladium from sulfur poisoning. Other transition metals, such as Cu,[10] Ni,[11] Co,[12] Fe,[13] Au,[14] Rh,[15] and Pt,[16] have emerged as appealing catalysts for this reaction.

Generally, organometallic transformation methodologies for C−S bond formation involve thiophenol coupling with halide. The other method for C−S bond formation employs thiol as a coupling partner (Scheme 1, entries a and b). According to these two strategies, thiols or thiophenols function as sulfur sources, which are indispensable partners. However, the method generally suffers from preparation difficulties, unpleasent smell, easy oxidation, and toxicity during the entire process.

Scheme 1. Strategies for Cross Coupling



To overcome these problems, the key point is to look for different thiol surrogates as independent sulfur sources to realize a free combination of the two coupling partners (Csp^2−X and Csp^3−X halides) without thiol (Csp^2−SH) or thiophenol (Csp^3−SH). Very recently, our group has described Pd-catalyzed intramolecular double C−S bond formation by using $Na_2S_2O_3·5H_2O$.[17] We envisioned that the structural feature of thiosulfate anion could repress the notorious sensitivity of sulfur for late-transition-metal catalysts. In addition, we used $Na_2S_2O_3·5H_2O$ as the sulfur source instead

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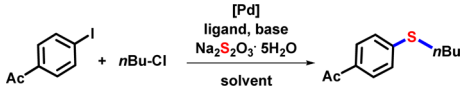
of prepared sulfide, a one-pot reaction, to avoid a series of problems in the process of raw material preparation. Base on this hypothesis and our previous work, we are eager to develop a new catalytic system to improve the practicality of aryl sulfide generation in cross-coupling reactions.

We commenced our study by investigating the cross-coupling of 4-iodoacetophenone and 1-chlorobutane under our aforementioned strategy. We were pleased to find that the desired product was isolated in 45% yield under $PdCl_2$(dppf) catalyst in a sealed tube (Table 1, entry 1). Different palladium

Table 1. Optimization of the Reaction Conditions[a]



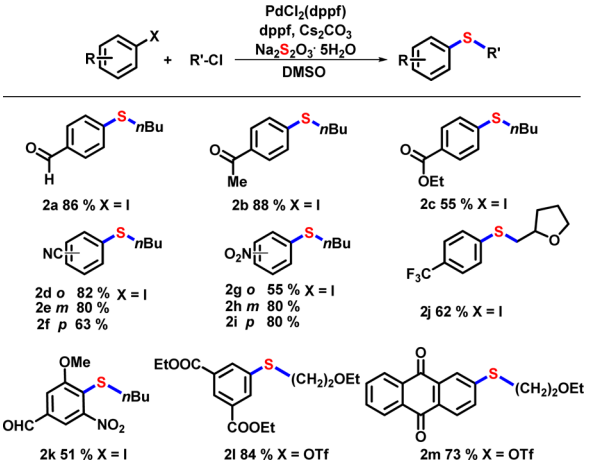
entry	[Pd] (10 mol %)	ligand (mol %)	base (3 equiv)	solvent	yield[b] (%)
1[c]	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	MeCN	45
2[c]		dppf (5)	Cs_2CO_3	MeCN	NR
3[c]	$PdCl_2$(dppf)		Cs_2CO_3	MeCN	35
4[c]	$PdCl_2$(dppf)	dppf (5)		MeCN	NR
5[c]	$PdCl_2$(dppf)	dppe (5)	Cs_2CO_3	MeCN	31
6[c]	$PdCl_2$(dppf)	dppp (5)	Cs_2CO_3	MeCN	46
7[c]	$PdCl_2$(dppf)	dppb (5)	Cs_2CO_3	MeCN	29
8[c]	$Pd(dba)_2$	dppp (15)	Cs_2CO_3	MeCN	trace
9	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	DMF	46
10	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	DMSO	47
11	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	CH_3NO_2	NR
12	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	NMP	NR
13	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	DMF	57[d]
14	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	DMSO	63[d]
15	$PdCl_2$(dppf)	dppf (5)	DBU	DMSO	ND[d]
16	$PdCl_2$(dppf)	dppf (5)	NaOAc	DMSO	ND[d]
17	$PdCl_2$(dppf)	dppf (5)	K_3PO_4	DMSO	ND[d]
18	$PdCl_2$(dppf)	dppf (5)	Cs_2CO_3	DMSO	40[e]
19	**$PdCl_2$(dppf)**	**dppf (15)**	**Cs_2CO_3**	**DMSO**	**88**[f]

[a]Reaction conditions: Ar-I (0.2 mmol), *n*-Bu-Cl (3.0 mmol), [Pd] (0.02 mmol), ligand (0.01 mmol), base (0.6 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (1.0 mmol), solvent (4.0 mL), 120 °C, Schlenk tube, 10 h. [b]Isolated yield. [c]H_2O (0.2 mL), 150 °C, sealed tube. [d]Glycol (0.2 mL). [e]Glycol (0.4 mL). [f]Glycol (0.1 mL).

catalysts and ligands were screened, which showed that $PdCl_2$(dppf) with dppf is a better choice (Table 1, entries 5−8). The system was much cleaner when DMSO was used as a solvent in a Schlenk tube and the temperature was lowered to 120 °C (Table 1, entry 10). When glycol was added as a cosolvent in DMSO, the yield was increased to 63% (Table 1, entry 14). The base played an important role in the transformation. No product was detected when DBU, NaOAc, and K_3PO_4 were used instead of Cs_2CO_3 (Table 1, entries 15−17). To our delight, when the ratio of DMSO to glycol was changed to 40:1, the yield was elevated to 88% (Table 1, entry 19).

Having identified the optimal conditions, the substrate scope of this reaction was investigated. As shown in Table 2, the aryl iodides bearing different electron-withdrawing groups, such as formyl (Table 2, **2a**), nitryl (Table 2, **2g**, **2h**, and **2i**), and cyano group (Table 2, **2d**, **2e**, and **2f**) substituted at the ortho-, para-, or meta-position, could proceed smoothly. However, target products could not be obtained in electron-rich aromatic systems. The method is compatible with not only single

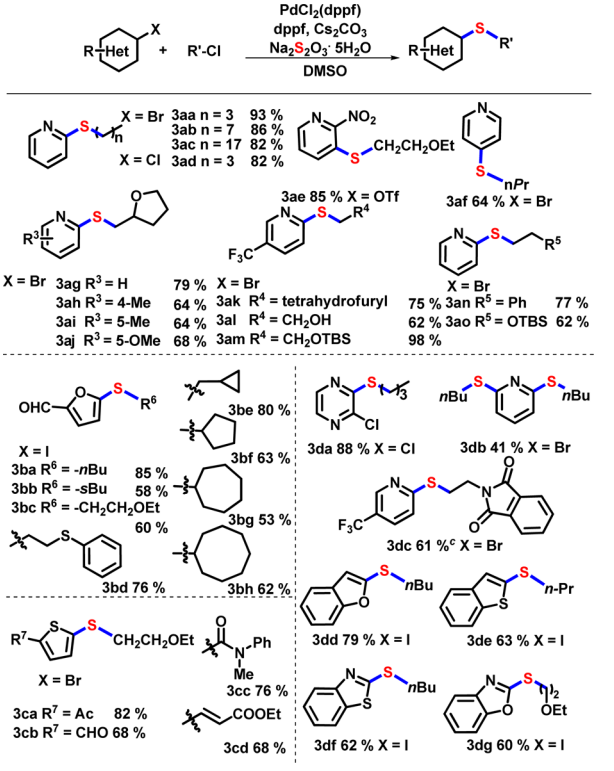
Table 2. Synthesis of Substituted Phenyl Sulfides[a,b]



substituted functional groups but also polysubstituted compounds (Table 2, **2k** and **2l**) and anthracene structures (Table 2, **2m**).

Considering the significance of heteroarenes in drug molecules, we were eager to test whether or not this protocol is compatible with heterocyclic substrates. Remarkably, various heterocyclic halides could be converted to the corresponding product in good to excellent yields (Table 3). Furan with free aldehyde exhibited very good tolerance with different halides (Table 3, **3b**). Hydroxyl-containing halide is of compatibility in this reaction (Table 3, **3al**). It is worth noting that secondary

Table 3. Synthesis of Substituted Heterocyclic Sulfides[a,b]



[a]Reaction conditions: Ar-X (0.2 mmol), alkyl-Cl (3.0 mmol), $PdCl_2$(dppf) (0.02 mmol), dppf (0.01 mmol), Cs_2CO_3 (0.6 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (1.0 mmol), DMSO (4.0 mL), glycol (0.1 mL), 120 °C. [b]Isolated yield. [c]Alkyl-Cl (1.0 mmol).

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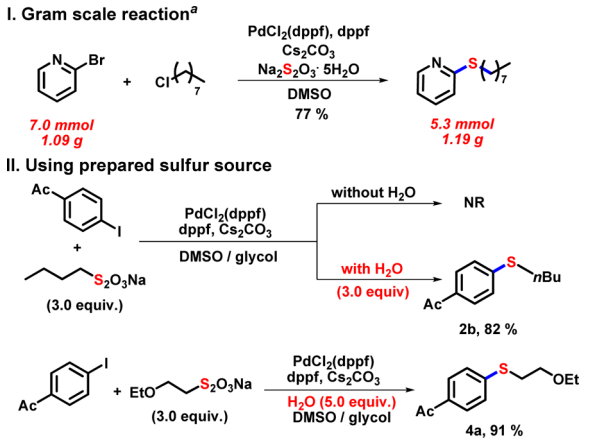
halides, such as cyclopentane, cycloheptane, and cyclooctane, showed great reactivity as well (Table 3, **3bf**, **3bg**, and **3bh**). Pyridine was also an efficient coupling partner with various halides (Table 3, **3a**). Dibromopyridine could give product **3db** in 44% yield with cross coupling twice. Pyrazine, benzofuran, benzothiophene, benzoxazole, and benzothiazoleare were all amenable to the reaction, which provided the possibilities for drug late-stage modification.

To test the reaction's practical utility, a gram-scale reaction was carried out by using 2-bromopyridine and 1-chlorooctane, which affords the desired product 1.19 g (Scheme 2, I).

Scheme 2. Further Exploration[a]

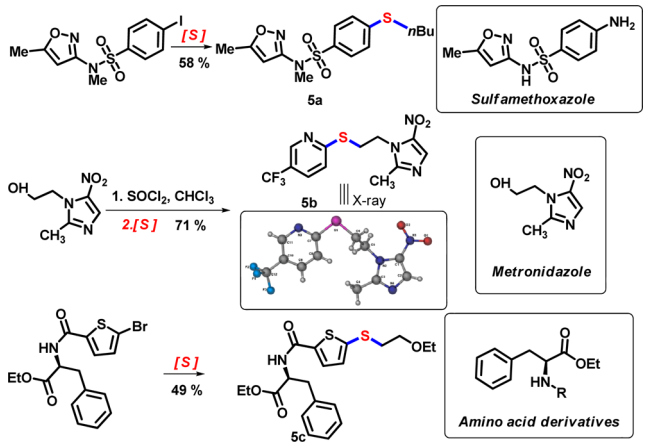


[a]Reaction conditions: 2-bromopyridine (7.0 mmol, 1.0 equiv), 1-chlorooctane (56.0 mmol, 8.0 equiv), $PdCl_2$(dppf) (0.35 mmol, 5.0 mol %), dppf (0.18 mmol, 2.5 mol %), Cs_2CO_3 (1.5 mmol, 2.1 equiv), $Na_2S_2O_3{\cdot}5H_2O$ (25.0 mmol, 3.6 equiv), DMSO (40.0 mL), glycol (1 mL), 120 °C.

Different prepared thiosulfate salts were viable substrates for this transformation when water was added to the system (Scheme 2, II). Further explorations of the application of this strategy by using an independent sulfur source have shown practicability, variability, and ease of operation. In addition, it is known that late-stage modification of drug candidates is valuable for structure–activity relationship studies. Various complex derivatives of pharmaceutical importance were examined to prove the synthetic potential of this strategy. We were pleased to find that derivatives of sulfamethoxazole, metronidazole, and amino acid (Scheme 3), biological active molecules with different kinds of heteroatoms, were all tolerant in this transformation. The structure of **5b** was confirmed by X-ray analysis.[18]

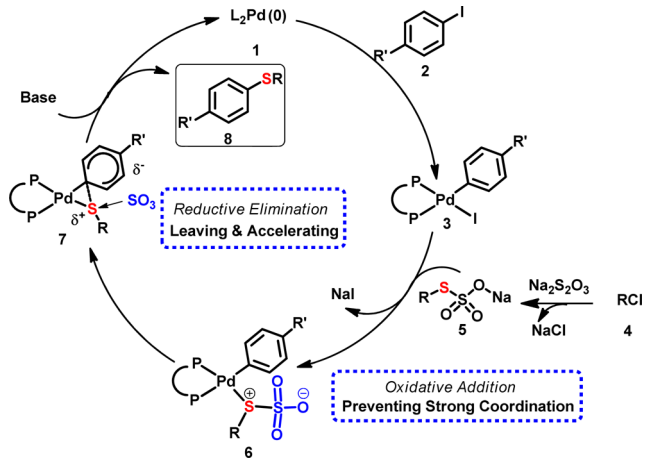
Although a precise reaction mechanism remains to be established, a plausible mechanism is outlined (Scheme 4). We assumed that palladium intermediate **3** could be generated via the oxidative addition of Pd(0) **1**. Csp^3–Cl reacted with thiosulfate to form thiosulfate-substituted organic salt **5**. Subsequent ligand exchange between intermediate **3** and **5** produced palladium thiosulfate **6**, which could transform to **7** via the release of SO_3. In that process, the electron-withdrawing effect of the sulfonic acid group weakened the strong coordinating properties of sulfur to palladium. Meanwhile, reductive elimination of Pd(II) was accelerated by sulfur trioxide leaving from the intermediate **7**. Then intermediate **7** gave the product thioether **8** and regenerated Pd(0).

Scheme 3. Modification of Drugs and Complex Substrates[a]



[a]Reaction conditions: Ar-X (0.1 mmol), X = I, Br or Cl, alkyl-Cl (15.0 mmol), $PdCl_2$(dppf) (0.01 mmol), dppf (0.005 mmol), Cs_2CO_3 (0.3 mmol), $Na_2S_2O_3{\cdot}5H_2O$ (0.5 mmol), DMSO (2.0 mL); glycol (0.05 mL), 120 °C.

Scheme 4. Proposed Mechanistic Cycle



In conclusion, we have developed a novel method for diverse aromatic sulfide by Pd-catalyzed cross coupling. The important feature of this method is using the odorless, stable, and environmentally friendly $Na_2S_2O_3{\cdot}5H_2O$ salt as a sulfurating reagent which is commercially available and easily handled. This method provides a free cross-coupling approach to aromatic sulfide, which is an important unit in biologically active molecules. Various pharmaceutical molecules were examined to prove the synthetic potential of this strategy. Further studies to deeply understand the reaction mechanism and synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Procedure, NMR spectra, X-ray data, and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) CCDC-980603 (**5b**): $C_{12}H_{11}F_3N_4O_2S$, MW = 332.31, monoclinic, space group $P2(1)/c$, final R indices $[I > 2\sigma(I)]$, R1 = 0.0661, wR2 = 0.1910, R indices (all data), R1 = 0.0750, wR2 = 0.2036, a = 9.7909(3) Å, b = 9.9299(3) Å, c = 15.0054(5) Å, α = 90°, β = 108.1950(10)°, γ = 90°, V = 1385.92(8) Å^3, T = 296(2) K, Z = 4, reflections collected/unique: 15637/2440 (R(int) = 0.0250). These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/ci