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# Palladium(II)/Copper(II)-Catalyzed C-H Sulfidation or Selenation of Arenes Leading to Unsymmetrical Sulfides and Selenides

Kota Nishino,[a] Shouya Tsukahara,[a] Yohei Ogiwara,[a] and Norio Sakai*[a]

**Abstract:** We developed a novel palladium(II)/copper(II)-catalyzed sulfidation of the C–H bond in electron-rich arenes and in pentafluorobenzene with disulfides. This catalytic system can be used to efficiently produce various types of either unsymmetrical aryl sulfides or alkyl aryl sulfides. Also, the present protocol could be applied to the direct preparation of unsymmetrical aryl selenides via C–H selenation.

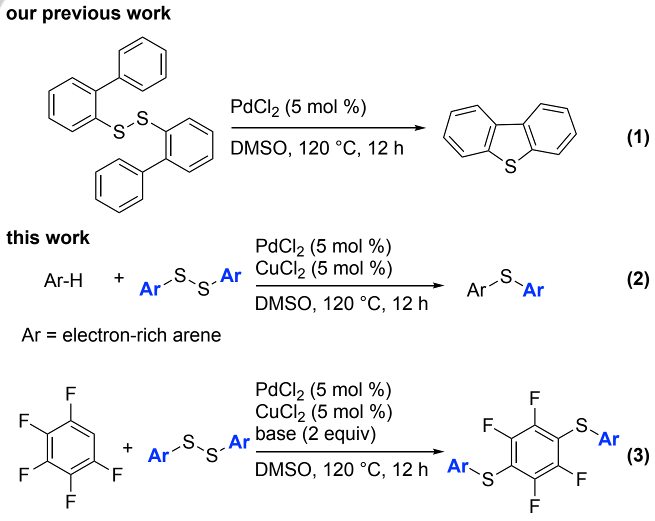
## Introduction

Aryl sulfides constitute a common framework for highly functional molecule, such as pharmaceuticals and organic materials.[1] The conventional preparation of an aryl sulfide involves a coupling reaction of aryl halides with sulfur sources as alkali sulfides and elemental sulfur, and organosulfur compounds, such as thiols and disulfides.[2]

The directly transition-metal-catalyzed formation of a C($sp^2$)–S bond from a C–H bond of arenes has recent received much attention, because this strategy enables to lead a target compound without extra functional group transformations. The synthetic protocols of aryl sulfides, Pd,[3] Ni,[4] Rh,[5] Cu,[6] Co,[7] or Ru,[8]-catalyzed C–H sulfidation have been demonstrated. Most of these sulfidations, however, have been limited to the use of starting materials bearing a directing group such as a pyridyl group,[3a,5a,6b] a pyrimidyl group,[4f,5b,6d,7a] and an 8-aminoquinolyl group,[4c,4d,4e,6a] which creates difficulties in expanding the substrate scope.

On the other hand, C–H sulfidation of electron-rich or electron-withdrawing group-substituted arenes have been investigated. Because these methods do not require substrates with a directing group, the development of this type of synthetic protocol is valuable and practical. For example, arenes such as an indole,[9] trimethoxybenzene,[10] a benzothiazole,[11] and pentafluorobenzene[12] have been subjected to C–H sulfidation with a transition metal catalyst. Recently, as other approaches, metal-free preparations of aryl sulfides through the reactions of either electron-rich arenes, such as trimethoxybenzene,[13] and *N*-heterocyclic arenes,[14] or electron-deficient arenes, such as pentafluorobenzene[15] with typical sulfur sources, such as thiols and disulfides, has been demonstrated. Also, the reactions of these arenes with electrophilic organosulfur reagents such as an *N*-thiosuccinimide[13d] and an aryl sulfinic acid derivative[13c,13e,14c] have led to the preparation of aryl sulfide derivatives. These methods, however, generally require either a catalytic or a stoichiometric amount of an oxidizing agent, molecular iodine, a strong acid or a base.

Our group reported a $PdCl_2$-catalyzed intramolecular cyclization of 2-biphenyl disulfides to dibenzothiophenes in DMSO (eq 1 in Scheme 1).[16] This protocol via C–H sulfidation was useful for the C–S bond formation of a variety of 2-biphenylyl disulfides because this synthetic method does not require extra additives, such as metal oxidant, a ligand, and a base. In the present study, we first attempted to apply the utility of the $PdCl_2$/DMSO catalytic system described in eq 1 to an intermolecular mode between electron-rich arenes and disulfides (eq 2 in Scheme 1). Second, we investigated the intermolecular bis-sulfidation of a C–H/C–F bond in an electron-deficient arene, pentafluorobenzene, (eq 3 in Scheme 1). Finally, we developed a direct and effective selenation of these arenes. Herein, we report the full details.



**Scheme 1**. $PdCl_2$-catalyzed construction of a C-S bond from a C–H bond.

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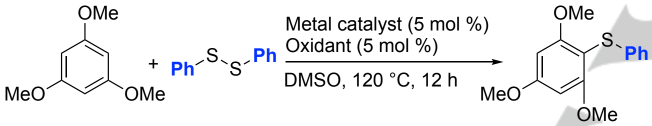
## Results and Discussion

Initially, we focused on optimizing the reaction conditions. When 1,3,5-trimethoxybenzene (**1**) as an electron-rich arene and diphenyl disulfide (**2a**) were treated with palladium dichloride, the desired sulfide **3a** was obtained in a low yield (Table 1, entry 1). Without a metal catalyst, however, the expected coupling product was not obtained (entry 2). Next, when adding a catalytic amount of $CuCl_2$ as an oxidant, the yield of **3a** was greatly improved to 93% (entry 3). When a thiol is formed through hydrolysis of a palladium thiolate species in a sulfidation series, one of the roles of $CuCl_2$ is believed to be the re-oxidization of the thiol to a disulfide.[17] Compared with the use of $PdCl_2$, however, other palladium catalysts such as $Pd(OAc)_2$, $Pd(dba)_2$, and $Pd(PPh_3)_4$ produce lower yields of **3a** (entries 4-6). Also, $NiCl_2$ did not show a highly catalytic activity for the sulfidation (entry 7). Lowering the reaction temperature led to a slight decrease in the product yield of **3a** (entry 8). When attempting the use of DMF as a solvent, the expected reaction did not proceed well (entry 9). Thus, DMSO played the role of an oxidant and was an essential agent in this reaction.[18] Moreover, when using only $CuCl_2$, sulfidation was not effective (entry 10).

**Table 1**. Examination of the reaction conditions.[a]



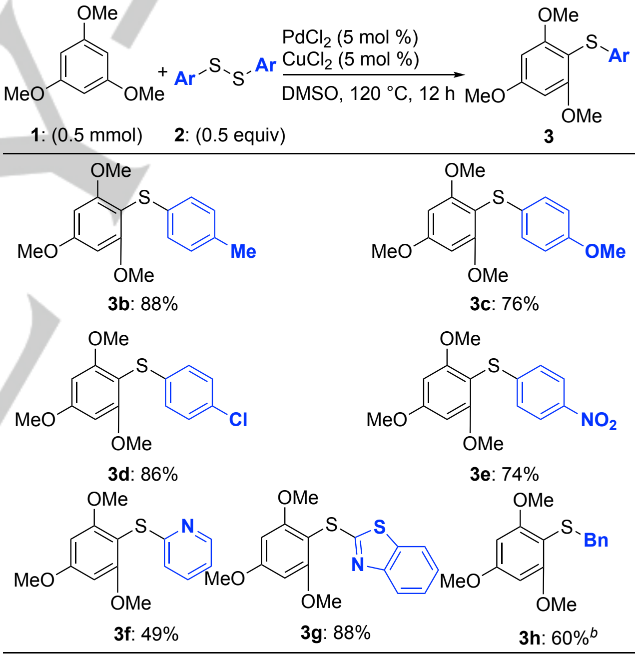
**1**: (0.5 mmol) **2a**: (0.5 equiv) **3a**

| Entry | Metal catalyst | Oxidant | Conversion | Yield [%][b] |
|---|---|---|---|---|
| 1 | $PdCl_2$ | ---- | 24 | 14 |
| 2 | ---- | ---- | 17 | 0 |
| 3 | $PdCl_2$ | $CuCl_2$ | >99 | 93 (84) |
| 4 | $Pd(OAc)_2$ | $CuCl_2$ | 85 | 76 |
| 5 | $Pd(dba)_2$ | $CuCl_2$ | 37 | 3 |
| 6 | $Pd(PPh_3)_4$ | $CuCl_2$ | 92 | 75 |
| 7 | $NiCl_2$ | $CuCl_2$ | 75 | 62 |
| 8[c] | $PdCl_2$ | $CuCl_2$ | 61 | 54 |
| 9[d] | $PdCl_2$ | $CuCl_2$ | 29 | 22 |
| 10 | ---- | $CuCl_2$ | 33 | 17 |

[a] Reaction conditions: trimethoxybenzene (**1**: 0.5 mmol), diphenyl disulfide (**2a**: 0.25 mmol), a metal catalyst (0.025 mmol), an additive (0.025 mmol), DMSO (0.5 mL), 120 °C, 12 h, under air. [b] GC yield; Isolated yield is given in parenthesis. [c] At 80 °C. [d] In DMF.

With the optimal conditions in hand, the synthesis of various unsymmetrical sulfides bearing a trimethoxybenzene moiety was then examined and the results are listed in Table 2. When using electron-donating substituted disulfides **2b** and **2c**, the corresponding sulfides **3b** and **3c** were obtained in high yields. Next, when examining the preparation of a sulfide bearing electron-withdrawing groups such as a chloro and a nitro group, the expected sulfides **3d** and **3e** were provided in high yields. Moreover, the synthesis of a heterocycle-substituted sulfide was attempted, and sulfide **3f** bearing a pyridinyl group was afforded in a moderate yield. We were pleased to discover that the preparation of sulfide **3g** bearing a benzothiazolyl group was achieved in a high yield. Consequently, this protocol revealed a relatively wide scope of disulfide substrates, which led to the production of various unsymmetrical diaryl sulfides. Furthermore, when applying dibenzyl disulfide to a dialkyl disulfide under our optimal conditions, the desired aryl benzyl sulfide **3h** was obtained in a relatively good yield.[19]

**Table 2**. Scope of the sulfidation of trimethoxybenzene with diaryl disulfides.[a]

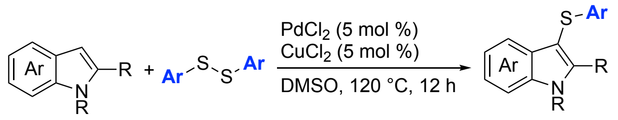


**3b**: 88% **3c**: 76% **3d**: 86% **3e**: 74% **3f**: 49% **3g**: 88% **3h**: 60%$^b$

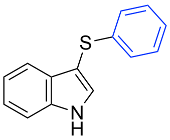
[a] Reaction conditions: trimethoxybenzene (**1**: 0.5 mmol), disulfide (**2**: 0.25 mmol), $PdCl_2$ (0.025 mmol), $CuCl_2$ (0.025 mmol) in DMSO (0.5 mL), 120 °C, 12 h, under air. [b] At 100 °C.

Subsequently, the substrate scope was extended to an electron-rich heterocycle (Table 3). In the reaction between indole and diphenyl disulfide, a thiophenyl group was selectively introduced at the C3 position of indole to produce unsymmetrical sulfide **5a** in a moderate yield. With di-(*p*-tolyl) disulfide, the corresponding product **5b** was given in a 60% yield. When using *N*-methyl indole and a disulfide bearing a benzothiazole ring, an interesting unsymmetrical sulfide **5c** that involved two different heterocyclic moieties was given in a practical yield. Additionally, in two cases with *N*-methylindole bearing a phenyl group at the C2 position, each sulfidation effectively proceeded to give **5d** and **5e** in good yields. This catalytic protocol shows a high effect for sulfidation of even 2-substituted indole, which generally shows a high degree of steric hindrance toward the C3 position. Fortunately, when using an indole bearing a bromo group at the C5 position, the group of which frequently reacts with a palladium catalyst, sulfide **5f** preserved the bromo group was provided in a good yield. Thus, the present catalytic system composed of palladium(II) with a copper(II) catalyst shows a relatively wide tolerance of functional groups.

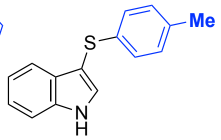
**Table 3**. Scope of the sulfidation of an indole.[a]



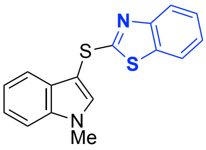
**4**: (0.5 mmol) **2**: (0.5 equiv) **5**



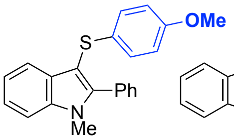
**5a**: 37%



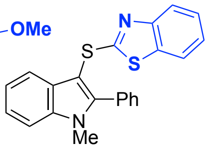
**5b**: 60%



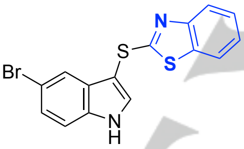
**5c**: 65%



**5d**: 83%



**5e**: 82%$^b$



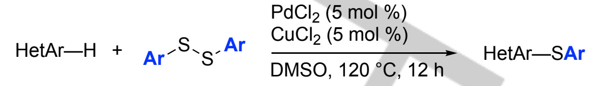
**5f**: 76%$^b$

[a] Reaction conditions: indole (**4**: 0.5 mmol), disulfide (**2**: 0.25 mmol), PdCl$_2$ (0.025 mmol), CuCl$_2$ (0.025 mmol) in DMSO (0.5 mL), 120 °C, 12 h, under air. [b] DMSO (0.5 M).

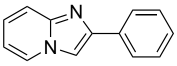
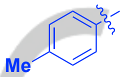
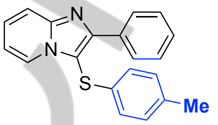
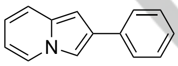
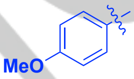
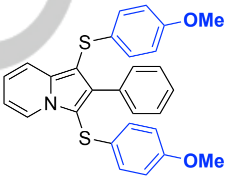
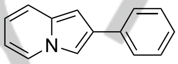
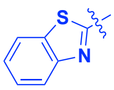
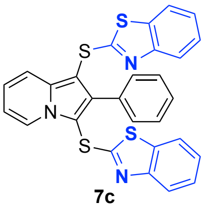
The present C–H sulfidation was further applied to two electron-rich heteroarenes (Table 4). When using 2-phenylimidazo[1,2-*a*]pyridine (**6a**) as a substrate, the expected sulfidated compound **7a** was afforded in a good yield. Also, under the optimal conditions, 2-phenylindolizine (**6b**) and 1.0 equiv of disulfide **2c** yielded a double-sulfidated product **7b** as the sole product, but the formation of a mono-sulfidated compound was not observed.[20] In a similar manner, heterocyclic disulfide **2g** afford a di-sulfidated indolizine in a moderate yield. Unlike previous studies at the bis-sulfidation of indolizines,[21] a primary feature of our C–H bis-sulfidation is that the reaction catalytically proceeds.

Next, sulfidation of a strong electron-deficient arene, pentafluorobenzene, with a disulfide was attempted using the PdCl$_2$/DMSO system. In this reaction, the optimal conditions required a further addition of 2 equiv of CsF to effectively promote bis-sulfidation of both a C–H bond and a C–F bond of pentafluorobenzene (Scheme 2).[22] We speculated that CsF, which cooperates with a palladium catalyst would function as a base to abstract an acidic proton of pentafluorobenzene.

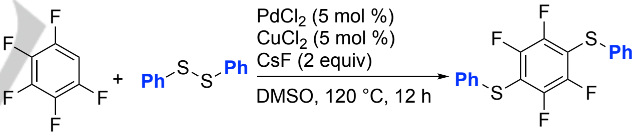
**Table 4**. Sulfidation of the imidazopyridine and the indolizine.[a]



**6**: (0.5 mmol) **2**: (0.5 equiv) **7**

| HetAr | Disulfide | Product | Yield (%) |
|---|---|---|---|
| <br>**6a** | <br>**2b** | <br>**7a** | 63% |
| <br>**6b** | <br>**2c**$^b$ | <br>**7b** | 62% |
| <br>**6b** | <br>**2g**$^b$ | <br>**7c** | 51% |

[a] Reaction conditions: *N*-heterocycles (**6**: 0.5 mmol), disulfide (**2**: 0.25 mmol), PdCl$_2$ (0.025 mmol), CuCl$_2$ (0.025 mmol) in DMSO (0.5 mL), 120 °C, 12 h, under air. [b] disulfide (1.0 equiv).



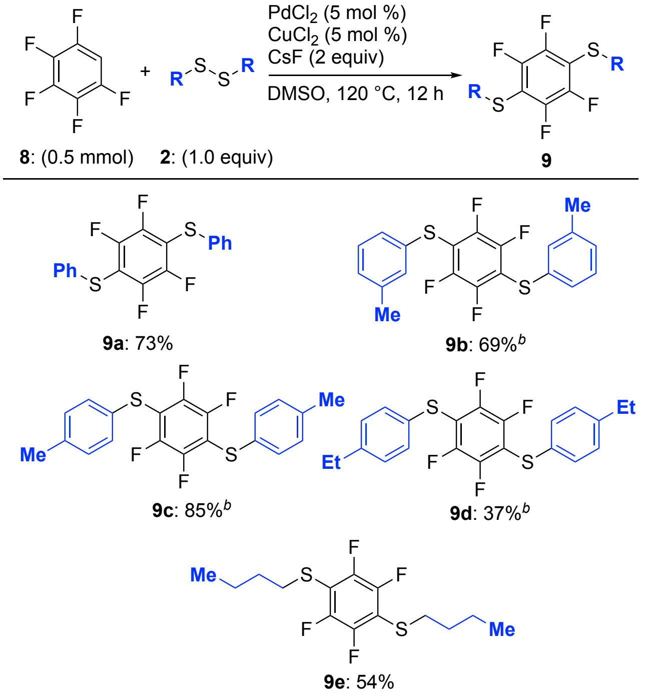
**8**: (0.5 mmol) **2a**: (1.0 equiv) **9a**

80% (GC yield)
Without CsF: 0%

**Scheme 2**. Bis-sulfidation of pentafluorobenzene with diphenyl disulfide by addition of CsF.

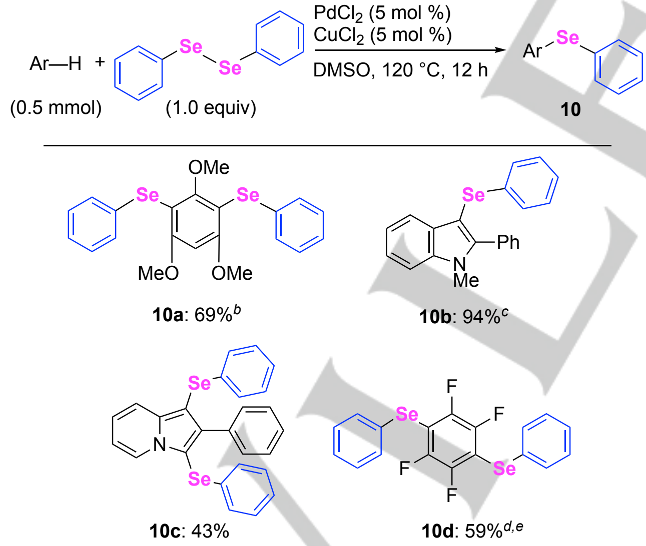
Based on the results shown in Scheme 2, the scope of the bis-sulfidation of pentafluorobenzene with several disulfides was investigated, and the results are summarized in Table 5. When using diphenyl disulfide with CsF, the corresponding product **9a** was isolated in a 73% yield. A methyl-substituted disulfide at either the *m*- or the *p*-position was also converted into the bis-sulfidated compounds **9b** and **9c** in good yields, and 4-ethylphenyl disulfide gave product **9d** in a 37% yield. Notably, an aliphatic disulfide, dibutyl disulfide, provided the corresponding product **9e** in a moderate yield.

**Table 5**. Scope of the bis-sulfidation of pentafluorobenzene with disulfides.[a]



[a] Reaction conditions: pentafluorobenzene (**8**: 0.5 mmol), disulfide (**2**: 0.5 mmol), PdCl$_2$ (0.025 mmol), CuCl$_2$ (0.025 mmol), CsF (1.0 mmol) in DMSO (0.5 mL), 120 °C, 12 h, under air. [b] At 140 °C.

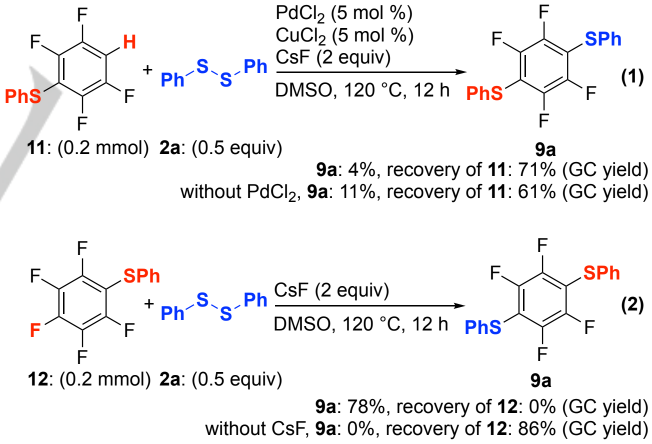
**Table 6**. Selenation of arenes with a PdCl$_2$/CuCl$_2$ catalyst.[a]



[a] Reaction conditions: arene (0.5 mmol), diphenyl diselenide (0.5 mmol), PdCl$_2$ (0.025 mmol), CuCl$_2$ (0.025 mmol) in DMSO (0.5 mL), 120 °C, 12 h, under air. [b] a little amount of mono-selenated compound was observed. [c] diphenyl diselenide (0.5 equiv). [d] At 140 °C. [e] added CsF (2 equiv).

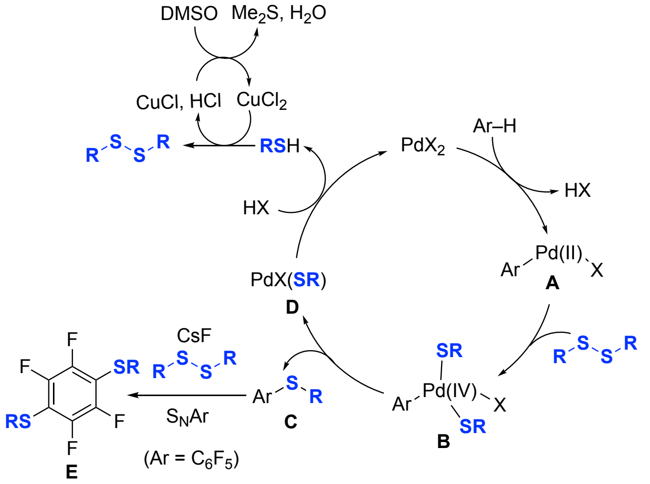
It was rewarding to find that the present reaction system was applicable to C–H selenation (Table 6). For example, when the reaction of trimethoxybenzene (**1a**) with 1.0 equiv of diphenyl diselenide was conducted in the presence of 5 mol % of PdCl$_2$ and CuCl$_2$ in DMSO, the corresponding di-selenated compound **10a** was obtained in a 69% yield.[23] Additionally, *N*-methyl-2-phenylindole gave the corresponding unsymmetrical selenide **10b** in an excellent yield. When using 2-phenylindolizine and diphenyl diselenide, as well as the reaction with diphenyl disulfide (vide Table 4), double C–H selenation proceeded to produce bis-selenated 2-phenylindolizine **10c** in a moderate yield. This process was also successful in the bis-selenation of pentafluorobenzene. This type of direct bis-selenation of either 2-phenylindolizine or pentafluorobenzene is unprecedented.

To gain preliminary insight into the sulfidation of pentafluorobenzene, control experiments were performed. Under the optimal conditions with or without PdCl$_2$, the initial reaction of prepared mono-sulfidated arene **11** with diphenyl disulfide (**2a**) resulted in a rather low conversion of **11** (eq 1 in Scheme 3). The reaction between prepared substrate **12** and diphenyl disulfide with only CsF (2 equiv), however, yielded bis-sulfidated compound **9a** in a 78% yield (eq 2 in Scheme 3). In the absence of CsF, product **9a** was not obtained. These results showed that, rather than the substitution of compound **11** at the C–H side, the substitution of compound **12** at the C–F bond is the major key step in the sulfidation series, and the mechanism of the C–S bond formation from the C–F bond of intermediate **12** proceeds through CsF-promoted aromatic nucleophilic substitution that involves neither PdCl$_2$ nor CuCl$_2$.



**Scheme 3**. Control experiments to clarify a key intermediate.

On the basis of these results, a plausible reaction mechanism for a series of sulfidation is outlined in Scheme 4. Initially, a palladium(II) catalyst reacts with an arene leading to palladium arene species **A** through C–H functionalization. Then, oxidative addition of **A** into a disulfide occurs to generate palladium(IV) complex **B**.[24] Subsequently, reductive elimination from complex **B** provides unsymmetrical sulfide **C** and palladium thiolate species **D**, the latter of which would be hydrolyzed by HX to reproduce PdX$_2$ and a thiol. Also, the role of CuCl$_2$ is assumed to be that of an oxidant to generate a disulfide from a formed thiol, and DMSO must function as a re-oxidant of CuCl. In the case of pentafluorobenzene, the C–F bond of unsymmetrical sulfide **C** (Ar = $C_6F_5$) again reacts with a disulfide in the presence of CsF via aromatic nucleophilic substitution, which finally yields bis-sulfidated compound **E**.[25, 26]



**Scheme 4**. Proposed reaction mechanism.

## Conclusions

In this study, C–H sulfidation of electron-rich arenes such as trimethoxybenzene and *N*-heterocyclic compounds was accomplished using the developed $PdCl_2/CuCl_2$ catalytic system. When using 2-phenylindolizine, the transformation of its double C–H bonds into a C–S bond proceeded. Also, in the case of pentafluorobenzene, the addition of 2 equiv of CsF to the catalytic system underwent the same bis-sulfidation with the transformation of both the C–H and C–F bonds to two C–S bonds. Moreover, the present catalytic system was applied to the direct selenation of various arenes such as trimethoxybenzene, an indole, an indolizine, and pentafluorobenzene. Further studies of the extension of derivatives and a mechanistic study are ongoing in this laboratory.

## Experimental Section

### General procedure A for the $PdCl_2$-catalyzed synthesis of sulfide 3

To a freshly distilled DMSO solution (0.5 mL) in a screw-capped test tube under an ambient atmosphere were successively added a magnetic stirrer, trimethoxybenzene (**1:** 84 mg, 0.50 mmol), a disulfide (**2:** 0.25 mmol), palladium dichloride (4.4 mg, 0.025 mmol), and copper dichloride (3.35 mg, 0.025 mmol). The test tube was sealed with a cap that contained a PTFE septum and was heated to 120 °C for 12 h. After the reaction, the resultant reaction mixture was diluted with ethyl acetate (3 mL). The solution was then filtered through a celite pad. The filtered solution was dried over anhydrous $Na_2SO_4$, filtered and then evaporated under reduced pressure. The crude material was purified by a silica gel column chromatography (hexane/EtOAc) to give the corresponding sulfide **3**.

## Acknowledgments

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**Keywords:** Palladium • Sulfidation • Selenation • C–H activation • Oxidation

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[20] When using 0.5 equiv of disulfide **2c**, only product **7b** was obtained in a 24% yield, and formation of a mono-sulfidated indolizine was not observed.

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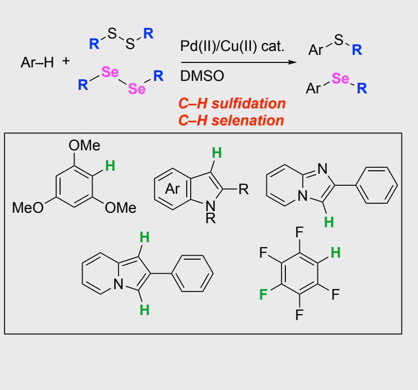
## Entry for the Table of Contents (Please choose one layout)

## FULL PAPER

**C–H sulfidation or selenation of arenes by a Pd(II)/Cu(II) catalytic system**: Preparation of unsymmetrical sulfides or selenides by C–H functionalization has been disclosed. This protocol could be applied a various of arenes. In the case of using an indolizine and pentafluorobenzene, bis-sulfidated product were obtained.



C–H sulfidation

*Kota Nishino, Shouya Tsukahara, Yohei Ogiwara, Norio Sakai**

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**Palladium(II)/Copper(II)-Catalyzed C–H Sulfidation or Selenation of Arenes Leading to Unsymmetrical Sulfides and Selenides**