Palladium (II)-Catalyzed 2-(Phenylseleninyl) quinoxalines Synthesis via a Tandem Reaction of C-S Bond Direct Cross-Coupling/Sulfonylation

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Article

Palladium (II)-Catalyzed 2-(Phenylseleninyl) quinoxalines Synthesis via a Tandem Reaction of C-S Bond Direct Cross-Coupling/Sulfonylation

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Abstract: A palladium (II)-catalyzed tandem reaction of C-S bond direct cross-coupling/sulfonylation has been developed. Starting from substituted quinoxalines and substituted phenylthiophenols versatile biologically active 2-(phenylsulfinyl)-6,7-dihydroquinoxaline derivatives and 1-methyl-2-(phenylsulfinyl)-1H-pyrrole derivatives were efficiently synthesized. The reaction mechanism was studied by the deuterium isotope experiments. This protocol features were under mild reaction conditions, wider substrate scope and provides an economical approach toward C(sp^2)-sulfoxide bond formation.

Keywords: palladium(II)-catalyzed; C(sp^2)-sulfoxide bond; direct cross-coupling; quinoxalines; phenylthiophenols

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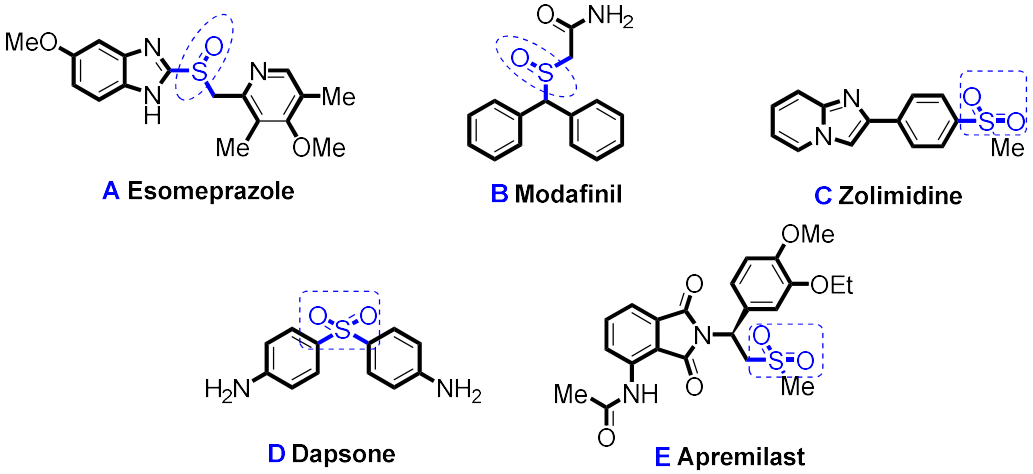
Organic sulfoxides and sulfone compounds have series most important applications in organic synthesis [1], medicines[2], functional materials[3,4]. For example, Scheme 1, Esomeprazole (**A**) can effectively inhibit gastric acid secretion and it is a most widely used effective drug for treating disease-related diseases such as duodenal ulcer. Since its listing in 1989, the global cumulative sales have exceeded 60 billion dollars [5]. Modafinil (**B**) is an excitatory α_1 receptor agonist, mainly used for the treatment of spontaneous hypersomnia and sleep disorders, and was commercialized in the 1990s [6]. Zolimidine (**C**) is an imidazole heterocyclic derivative drug, mainly used for the treatment of digestive system diseases [7]. Dapsone (**D**) is a prescription drug for external use, used to treat inflammatory and non-inflammatory acne. Apremilast (**E**) is the first oral phosphodiesterase-selective inhibitor used to treat active psoriasis and plaque psoriasis [8].



Scheme 1. The important clinical drugs of organic sulfoxides and sulfone compounds.

The synthesis of organic sulfoxides and sulfone compounds have attracted extensive attention of synthetic chemists. It is known that transition-metal catalyzed cross coupling reaction is the mostly

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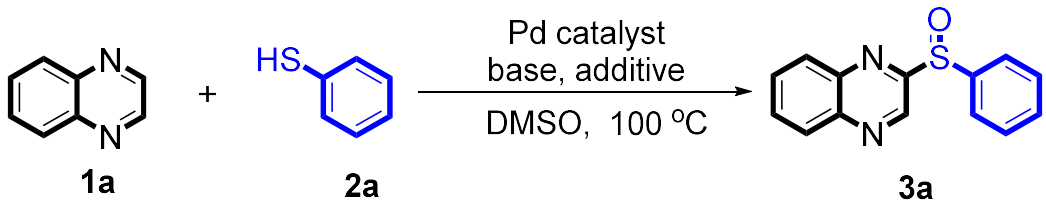
used methodology for the incorporation of a S atom into aromatic frameworks [9]. However, prefunctionalization of the substrate is generally requested. Similar methods of C(sp2)-sulfoxide bonds formation have been scarcely described [10–12]. Our group interesting are focuses on the tradition-metal catalyzed C-H bond functionizationals [13]. Herein, a apalladium(II)-catalyzed tandem C-S bond direct cross-coupling/sulfonylation reaction has been developed. Starting from substituted quinoxalines and substituted phenylthiophenols versatile biologically active 2-(phenylsulfinyl)-6,7-dihydroquinoxaline derivatives and 1-methyl-2-(phenylsulfinyl)-1H-pyrrole derivatives were efficiently synthesized. The reaction mechanism was studied by the deuterium isotope experiments. This protocols were under mild reaction conditions, wider substrate scope and provides an economical approach toward C(sp^2)-sulfoxide bond formation.

At first, the reaction conditions were screened based on the model reaction of quinoxaline **1a** and phenylthiophenol **2a** (Table 1). The palladium catalysts displayed a good catalytic activity (entries 1-7). In addition, $Pd(OAc)_2$ gave a 70% yield (entry 7), exhibited superior catalytic efficiency over all of the examined palladium catalysts. These results indicated that Cs_2CO_3 were the optimal base and additive, which produced the product **3a** with a 81% yield (entry 8). It was also noted that the product yield was decreased when the reaction temperature was lower or higher than 100 °C (entries 16 and 17). Furthermore, the results also show that DMSO as an essential solvent is higher than that of other solvents. Thus, the optimum reaction condition was determined as the **1** and **2** ratio of 1:1.5 in the presence of $Pd(OAc)_2$ (15 mol %), Cs_2CO_3 (2 equiv), at 100 °C (Table 1, entry 15).

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	Palladium catalyst	Base	Solvent	1a : 2a	Yield (%)[b]
1	$Pd(CO)_4$	Na_2CO_3	CH_3CN	1:1	0
2	$PdCl_2(PPh_3)_2$	Na_2CO_3	DMSO	1:1	13
3	$[PdCl(C_3H_5)]_2$	Na_2CO_3	DMSO	1:1	24
4	$PdCl_2$	Na_2CO_3	DMSO	1:1	29
5	$PdBr_2$	Na_2CO_3	DMSO	1:1	55
6	$PdSO_4$	Na_2CO_3	DMSO	1:1	39
7	$Pd(OAc)_2$	Na_2CO_3	DMSO	1:1	70
8	$Pd(OAc)_2$	Cs_2CO_3	DMSO	1:1	81
9	$Pd(OAc)_2$	NaOH	DMSO	1:1	51
10	$Pd(OAc)_2$	Na_2SO_4	DMSO	1:1	44
11	$Pd(OAc)_2$	NaOEt	DMSO	1:1	60
12	$Pd(OAc)_2$	Cs_2CO_3	DMSO	1:1	0
13	$Pd(OAc)_2$	Cs_2CO_3	DMSO	1:1	43
14	$Pd(OAc)_2$	Cs_2CO_3	DMSO	1:1	48
15	$Pd(OAc)_2$	Cs_2CO_3	DMSO	1:1.5	84
16	$Pd(OAc)_2$	Cs_2CO_3	DMSO	1:1.5	71[c]
17	$Pd(OAc)_2$	Cs_2CO_3	DMSO	1:1.5	79[d]

[a] Unless otherwise noted, reactions conditions were **1a** (0.5 mmol), **2a** (0.5 mmol), palladium catalyst (15 mol%), base (2 equiv), additive (2 equiv or under N_2 atmosphere), solvent (15 mL), 100 °C for 12 h. [b] Isolated yield. [c] 90 °C. [d] 110 °C.

Next, the reaction scope was been screened, a wide array of substituted quinoxalines **1** and substituted phenylthiophenols **2** were subjected to this reaction and given the products 2-(phenylsulfinyl)-6,7-dihydroquinoxalines **3** in good to excellent yields (64-93% yield, Scheme 2). It

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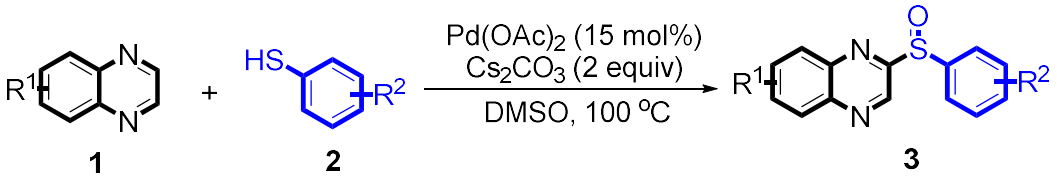
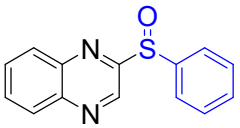
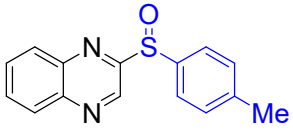
was found that both the electron-donating and electron-withdrawing quinoxaline derivatives **1** reacted smoothly with substituted phenylthiophenols **2**. Furthermore, quinoxaline derivatives **1** bearing electron-withdrawing groups showed better activity than bearing electron-donating groups. Substituted phenylthiophenols **2** bearing electron-donating groups showed better activity than bearing electron-withdrawing groups. To our delight, despite the electron-withdrawing effect of -NO_2 and -CF_3 group is so strong, the corresponding product**s 3h** and **3r** were still obtained in 78% and 89% yield.

Furthermore, we next focused on evaluating the generality of palladium (II)-catalyzed tandem reaction of C-S bond direct cross-coupling/sulfonylation by using a series of pyrroles **4** (Scheme 3). To our delight, N-methylpyrrole **4** with phenylthiophenols **2** successfully provided the corresponding products **5** (62-81% yield). For both substrates, this reaction was amenable when electroneutral group, electrondonating group, electron-withdrawing group, Moreover, the trifluoromethyl substituted delivered the product **5h** exclusively in 62% yield which bearing of storang strong electron-withdrawing group. Furthermore, reactants with more complex substituents also perform smoothly. Both the results demonstrated the good generality and high functional group tolerance of this method.

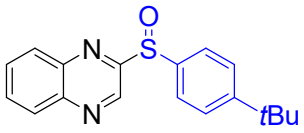




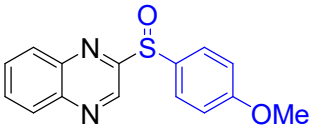
3a, 84%



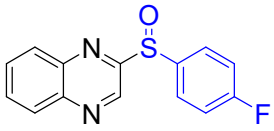
3b, 85%



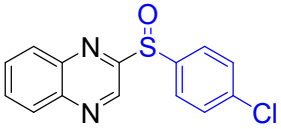
3c, 88%



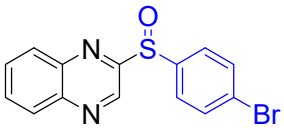
3d, 93%



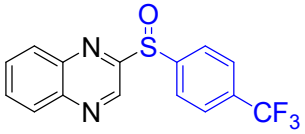
3e, 79%



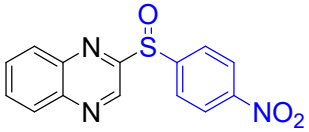
3f, 82%



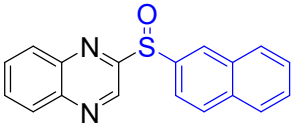
3g, 84%



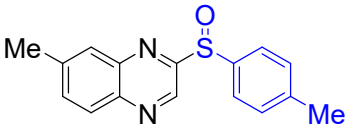
3h, 78%



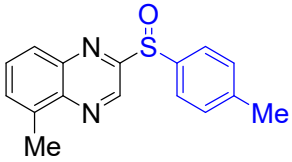
3i, 70%



3j, 77%



3k, 73%



3l, 74%

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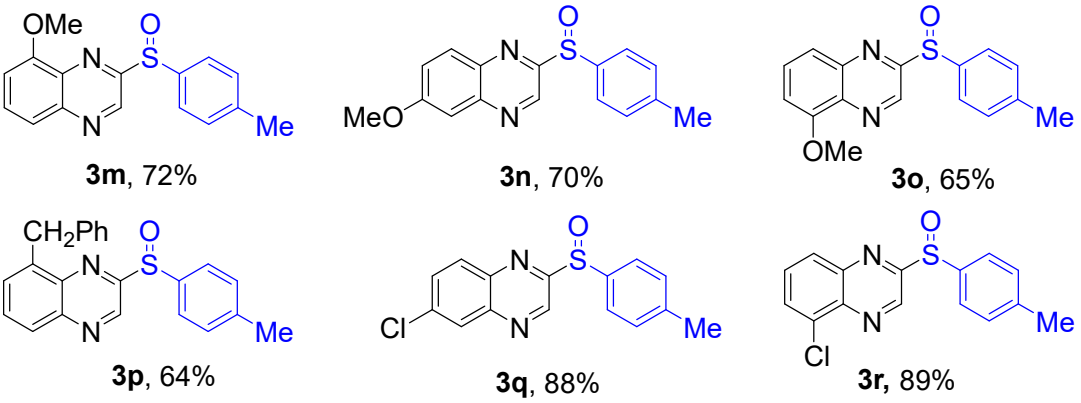
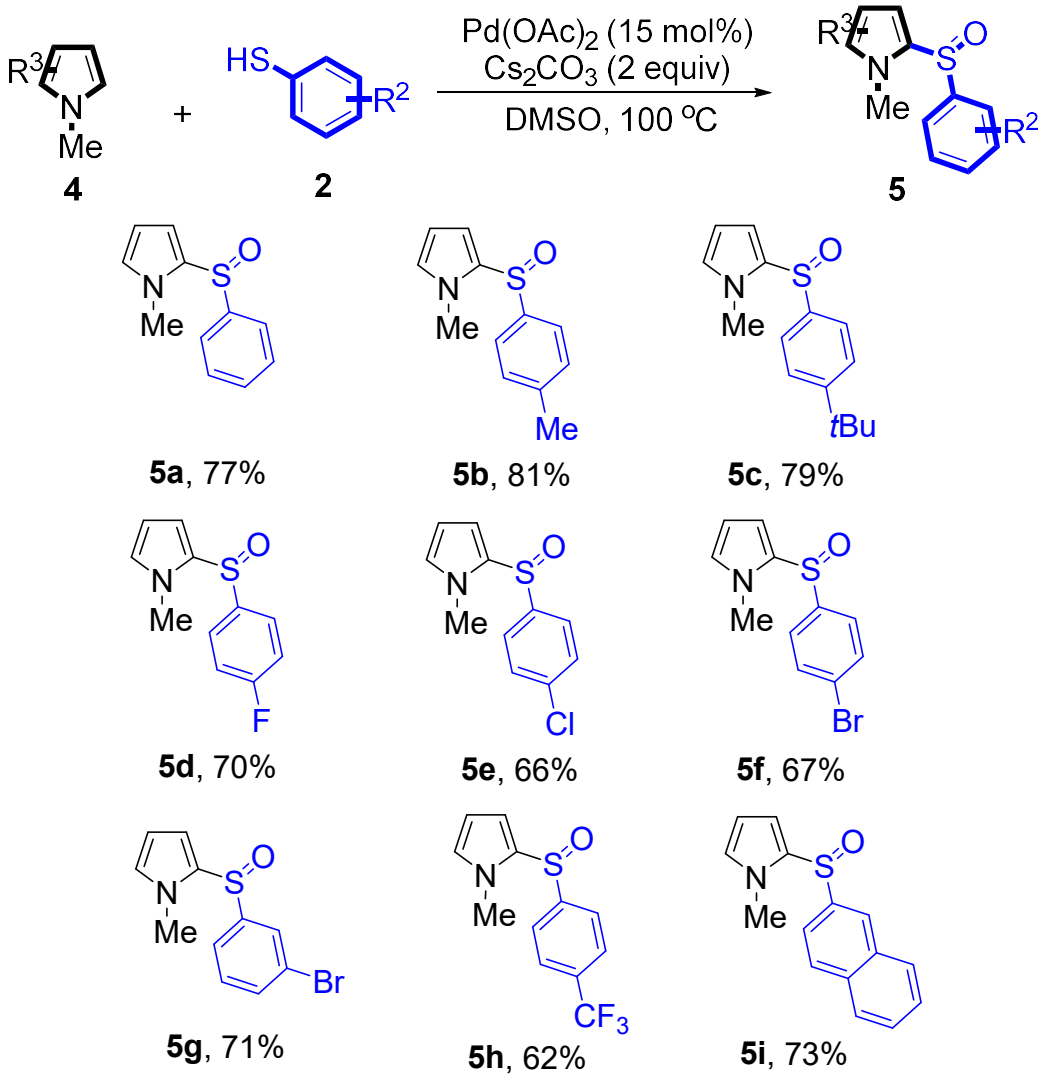


Scheme 2. Palladium (II)-catalyzed C-S bond direct cross-coupling/sulfonylation of quinoxalines with phenylthiophenols. [a, a] Unless noted, reaction conditions were **1** (0.5 mmol), **2** (0.75 mmol), $Pd(OAc)_2$ (15 mol%), Cs_2CO_3 (2 equiv), under a N_2 atmosphere, DMSO (15 mL), 100 °C for 12 h. [b] Isolated yield.



Scheme 3. Palladium (II)-catalyzed C-S bond direct cross-coupling/sulfonylation of N-methylpyrroles with phenylthiophenols. [a, a] Unless noted, reaction conditions were 1 (0.5 mmol), 2 (0.75 mmol), $Pd(OAc)_2$ (15 mol%), Cs_2CO_3 (2 equiv), under a N_2 atmosphere, DMSO (15 mL), 100 °C for 12 h. [b] Isolated yield.

To obtain the preliminary datas of the mechanism, some addition reactions were been done (Scheme 4). At first, the model reaction (4**I**) was conducted in two separate steps: palladium (II)-

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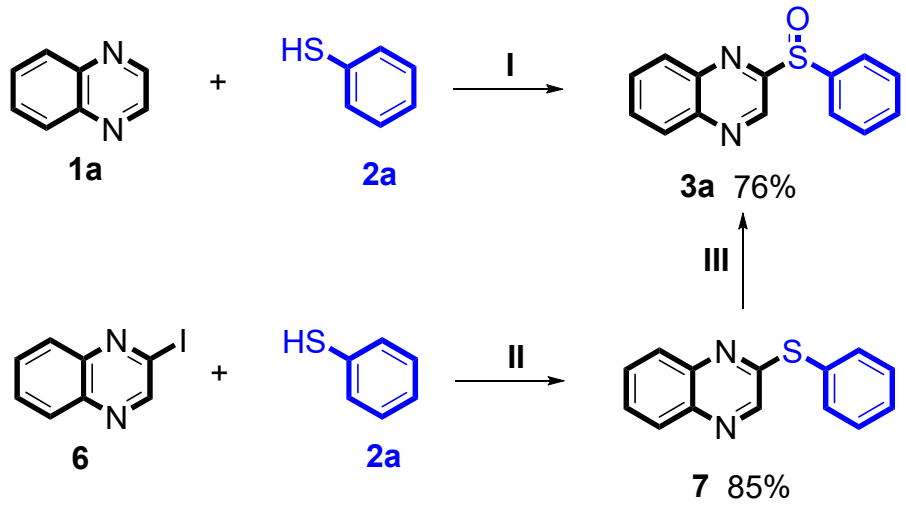
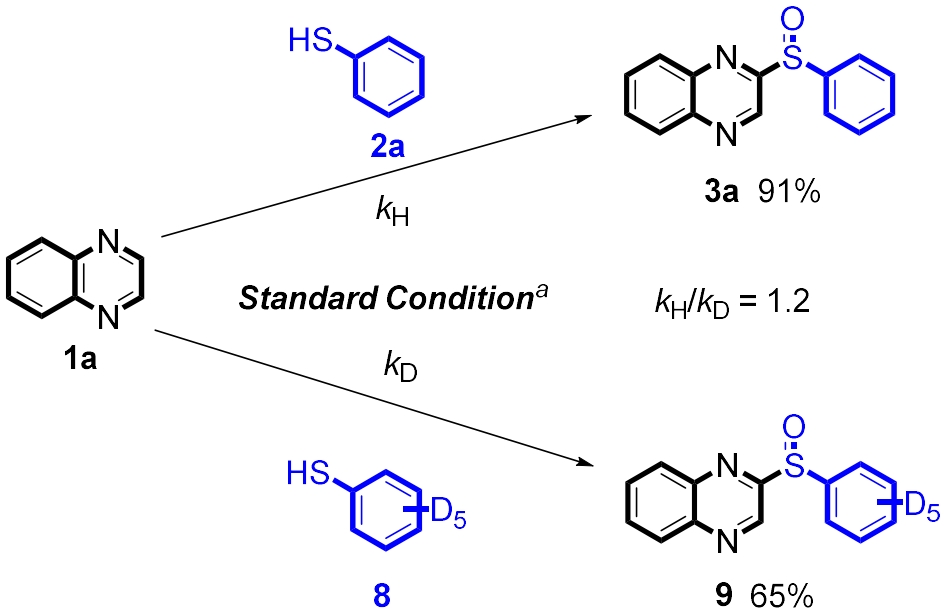
catalyzed C-S bond direct cross-coupling/sulfonylation of **6** with **2a** given a product **7** (4**II**, 85% yield) [13]. Next, **7** was reacted under our standard conditions, the reaction successfully obtained the target product **3a** (4**III** 76% yield), indicating that the intermediate **7** was involved in the reaction mechanism.



I **1a** (0.5 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (15 mol%), Cs_2CO_3 (2 equiv), under N_2.
II **6** (0.5 mmol), **2a** (0.75 mmol), CuI (10 mol%), *o*-Phen (10 mol%), 110 °C.
III **7** (0.5 mmol),$Pd(OAc)_2$ (15 mol%), Cs_2CO_3 (2 equiv), in N_2.

Scheme 4. Preliminary datas of the palladium (II)-catalyzed C-S bond direct cross-coupling/sulfonylation reaction mechanism.

Next, we used isotope experiments to further study the reaction mechanism (Scheme 5). The kinetic deuterium isotope effects [14] observed in the control experiments were indicated that the C(sp^2)-H cleavage being the rate-limiting step (k_H/k_D = 1.4, for detail information please see SI).



[a] **1a** (0.5 mmol), **2a** (0.75 mmol), $Pd(OAc)_2$ (15 mol%), Cs_2CO_3 (2 equiv), under N_2.

Scheme 5. The kinetic deuterium isotope effects of palladium (II)-catalyzed C-S bond direct cross-coupling/sulfonylation reaction.

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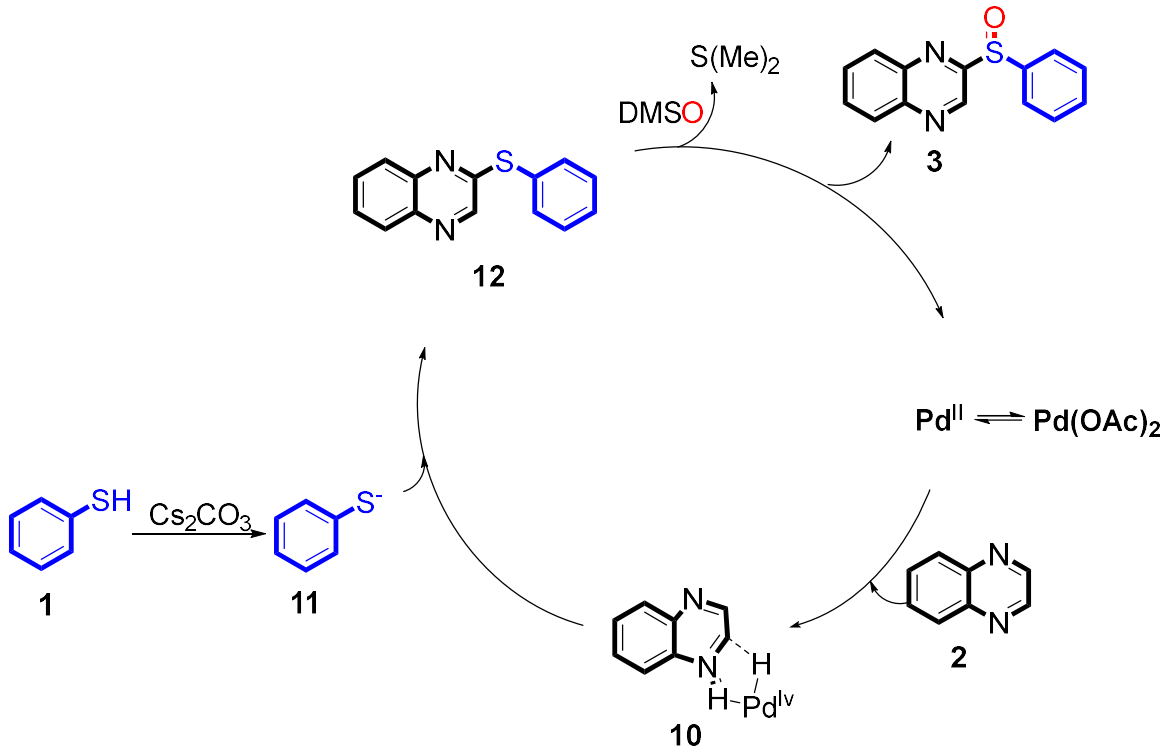
Based on the above results, a possible reaction mechanism was been proposed (Scheme 6) [15]. At the beginning, the coordination process of Pd^{II} and reactant **2** generated a Pd^{IV} intermediate **10**. Then, reactant **1** was converted to intermediate **11** by reacted with Cs_2CO_3. Next, intermediate **12** was provided from intermediate **10** with **11** via C-S bond cross coupling. At last, through the oxidation reaction by DMSO, intermediate **12** generated the desired products **3** and concomitantly formed a Pd^{II} intermediate, which re-entered the catalytic cycle.



Scheme 6. Proposed palladium (II)-catalyzed C-S bond direct cross-coupling/sulfonylation reaction mechanism.

Conclusions

In summary, in this paper a palladium (II)-catalyzed tandem reaction of C-S bond direct cross-coupling/sulfonylation has been developed. Starting from substituted quinoxalines and substituted phenylthiophenols versatile biologically active 2-(phenylsulfinyl)-6,7-dihydroquinoxaline and 1-methyl-2-(phenylsulfinyl)-1H-pyrrole derivatives were efficiently synthesized. The reaction mechanism was studied by the deuterium isotope experiments. This protocol features were under mild reaction conditions, wider substrate scope and provides an economical approach toward C(sp2)-sulfoxide bond formation.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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