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Palladium on Charcoal as a Recyclable Catalyst for C−S Cross-Coupling of Thiols with Aryl Halides under Ligand-Free Conditions

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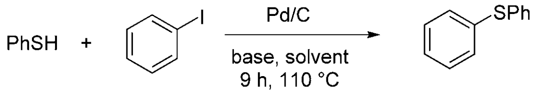
Abstract: *S*-Arylation of a wide variety of substituted aryl and aliphatic thiols with aryl halides using a catalytic amount of palladium on charcoal as a heterogeneous catalysis with potassium hydroxide as the base in dimethyl sulfoxide (DMSO) at 110 °C is accomplished in good yields. The C−S bond formation reaction functions under ligand-free conditions, and the palladium on charcoal catalyst can be is reused for five runs without any loss of activity.

Keywords: aryl sulfides; cross-coupling; heterogeneous catalysis; palladium on charcoal

Aryl sulfides are present in a large number of molecules with interest as pharmaceuticals and as useful polymeric materials.[1] For this reason, transition metal-catalyzed C−S bond formation has been a subject of intense study in organic chemistry over the past decade. Since Migita and co-workers first reported the $Pd(PPh_3)_4$-catalyzed C−S coupling of aryl iodides with thiols,[2] various palladium catalytic systems with different ligands[3] have realized some success and nickel-,[4] cobalt-,[5] copper-,[6] indium-,[7] and more recently iron-based[8] catalytic systems have also been studied. Still, the development of new, efficient catalytic systems for C−S cross-coupling is of great importance.

The heterogeneous palladium on charcoal (Pd/C) had been applied mostly only to hydrogenation before the 1990s,[9] recent research efforts have made organic chemists aware of various synthetically important coupling reactions that can also be catalyzed by Pd/C.[10] The heterogeneous catalysts are also attractive both from economic and industrial points of view as compared to homogeneous catalysts. To the best of our knowledge, however, until now there has been no report on Pd/C-catalyzed C−S cross-coupling reactions. In continuation of our efforts to develop new synthetic methods for important organic products,[11] herein we attempted C−S cross-coupling reactions with Pd/C under ligand-free conditions.

In our initial investigation, we chose the reaction of iodobenzene with benzenethiol as a model reaction (Scheme 1). As shown in Table 1, several solvents were first screened and we found that DMSO was more effective than the solvents such as DMF, diox-



Scheme 1. Model reaction.

Table 1. Screening for the reaction conditions.[a]

Entry	Pd/C (mol%)	Base	Solvent	Yield [%][b]
1	2	KOH	Toluene	trace
2	2	KOH	Dioxane	trace
3	2	KOH	DMF	8
4	**2**	**KOH**	**DMSO**	**96**
5	2	NaOMe	DMSO	16
6	2	K_2CO_3	DMSO	N.D.
7	2	K_3PO_4	DMSO	trace
8	1.5	KOH	DMSO	87
9	1	KOH	DMSO	79
10	0	KOH	DMSO	N.D.
11	2	KOH	DMSO	55[c]
12	0	KOH	DMSO	49[d]

[a] *Reaction conditions:* iodobenzene (2 mmol), thiophenol (2 mmol), Pd/C (5 wt%), base (3 mmol), and solvent (2 mL) were stirred under a nitrogen atmosphere for 9 h at 110 °C.

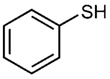
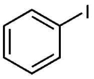
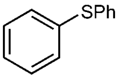
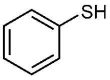
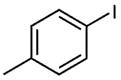
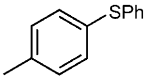
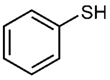
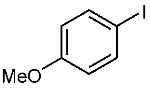
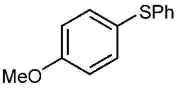
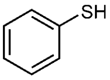
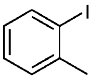
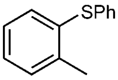
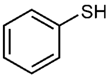
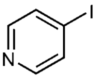
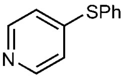
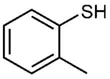
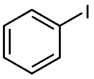
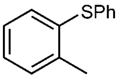
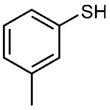
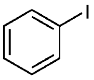
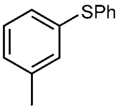
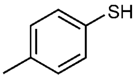
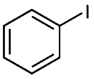
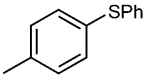
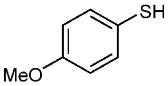
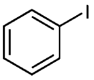
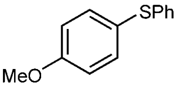
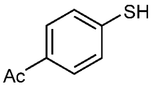
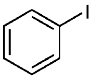
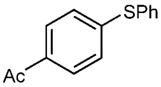
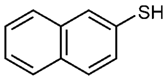
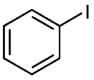
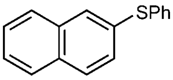
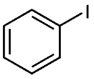
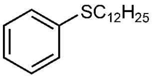
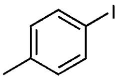
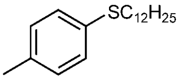
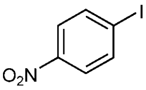
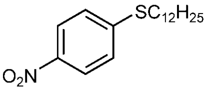
[b] Yield of the isolated product.

[c] At 80 °C for 15 h.

[d] 2 mol% Pd metal powder was used as the catalyst.

Table 2. Pd/C-catalyzed C–S cross-coupling of thiols and aryl iodides.[a]

$$\text{RSH} + \text{ArI} \xrightarrow[\text{KOH, DMSO}\\ \text{9 h, 110 °C}]{\text{Pd/C}} \text{ArSR}$$

Entry	Thiol	Aryl iodide	Product	Yield [%][b]
1				96
2				90
3				63
4				93
5				93
6				99
7				90
8				92
9				95
10				65
11				78
12	$C_{12}H_{25}SH$			70
13	$C_{12}H_{25}SH$			70
14	$C_{12}H_{25}SH$			93

[a] *Reaction conditions:* aryl iodide (2 mmol) , thiol (2 mmol), 2 mol% Pd/C (5 wt%), KOH (3 mmol), and DMSO (2 mL) were stirred under a nitrogen atmosphere for 9 h at 110 °C.

[b] Isolated yield.

ane and toluene (Table 1, entries 1–4). Then, we screened a variety of bases and found that KOH provided the diphenylsulfane in excellent yields and NaOMe gave low yields (Table 1, entries 4 and 5). Other bases such as K_2CO_3 and K_3PO_4 gave no product or only trace amounts of diaryl sulfide (Table 1, entries 6 and 7). The effect of the amount of Pd/C catalyst on this reaction was also evaluated. We found that reducing the amount of the catalyst loading from 2 mol% to 1.5 mol% or 1 mol% obviously decreased the yield (Table 1, entries 8 and 9). Furthermore, when the reaction was performed at 80 °C for 15 h, the expected coupling product was afforded in only 55% yield (Table 1, entry 11). When the model reaction was catalyzed by 2 mol% Pd metal powder instead of Pd/C, the desired diaryl sulfide was obtained in only 49% yield (Table 1, entry 12). It is possible that a critical role of the activated carbon is to help palladium disperse sufficiently on the solid support to form the active palladium complex without aggregating to inactive palladium black. Thus, the optimum reaction conditions for the desired C–S cross-coupling were found to be 2 mol% of Pd/C, 1.5 equiv. of KOH, 110 °C temperature with DMSO as the solvent under a nitrogen atmosphere for 9 h (Table 1, entry 4). To the best of our knowledge, this is the first demonstration of the catalyst Pd/C for C–S cross-coupling reaction.

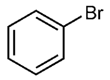
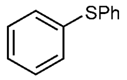
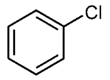
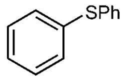
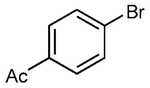
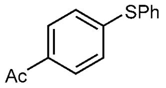
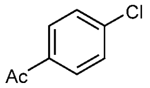
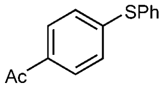
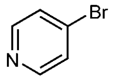
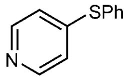
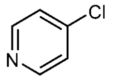
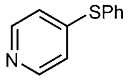
Next, we screened a range of commercially available aryl and heteroaryl iodides and aryl and alkyl thiols to explore the scope of the C–S coupling reaction. As shown in Table 2, in general, all reactions gave the aryl sulfide derivatives in high yields under the standard conditions. The protocol could tolerate electron-withdrawing and electron-donating functional groups and also to the presence of functional groups at the *ortho* position of the aryl iodide or thiol (Table 2, entries 4 and 6). It is observed that electron-withdrawing substituents in the thiol (Table 2, entry 10) or electron-donating substituents in the aryl iodides (Table 2, entries 2 and 3) decreased the yields of the products. A heteroaryl iodide (Table 2, entry 5) and alkyl thiols (Table 2, entries 12–14) were also applied to this coupling reaction. Thus, the scope of our protocol is quite broad.

We also attempted to extend the suggested method to the more inexpensive aryl bromides and aryl chlorides. Unfortunately, the corresponding diaryl sulfide was obtained in a very low yield using bromobenzene and chlorobenzene (Table 3, entries 1 and 2). However, an electron-withdrawing substituent in the aryl bromide and aryl chloride gave moderate yields of the product (Table 3, entries 3 and 4). A heteroaryl bromide and chloride were also applied to this coupling reaction with moderate yields (Table 3, entries 5 and 6).

In order to illustrate the recycling of the catalyst, the C–S cross-coupling of benzenethiol with iodobenzene in a scale of 10 mmol was tested under Pd/C with the optimum reaction conditions. After filtering off the product, Pd/C was washed with deionized water and CH_2Cl_2, and dried in the air at room temperature. The dried catalyst was then reused directly in the next reaction. The same procedure was repeated for all further cycles. Although the catalytic activity was gradually diminished, the yield was still 93% even in the fifth reuse (Table 4). Therefore, it is easy for the catalyst to be reused, and it has a potential application on an industrial scale.

Table 3. Pd/C-catalyzed C-S cross-coupling of thiophenol and various aryl halides.[a]

$$\text{PhSH} + \text{ArX} \xrightarrow[\text{KOH, DMSO}\\ \text{9 h, 110 °C}]{\text{Pd/C}} \text{ArSPh}$$

Entry	Aryl halide	Product	Yield [%][b]
1			30
2			trace
3			70
4			53
5			75
6			56

[a] *Reaction conditions:* aryl halide (2 mmol) , thiophenol (2 mmol), 2 mol% Pd/C (5 wt%), KOH (3 mmol), and DMSO (2 mL) were stirred under a nitrogen atmosphere for 9 h at 110 °C.

[b] Isolated yield.

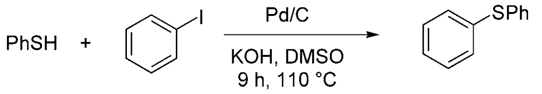
In summary, we propose a Pd/C-catalyzed method for the *S*-arylation of a wide variety of substituted aryl and aliphatic thiols with aryl halides. This protocol avoids the use of additives and expensive and/or air-sensitive ligands, and provides in most cases the desired sulfide in excellent yields. High catalytic activity was obtained using KOH with DMSO as the solvent at 110 °C. Furthermore, Pd/C can be recycled by simple filtration and washing sequences, even in the fifth reuse without the loss of activity.

Experimental Section

General Procedure for the Coupling Reaction

A mixture of aryl halide (2 mmol), thiol (2 mmol), 5 wt% Pd/C (2 mol%, 0.04 mmol), KOH (168 mg, 3 mmol), and DMSO (2 mL) were stirred under a nitrogen atmosphere for 9 h at 110 °C. After allowing the mixture to cool to room temperature, the mixture was diluted with ethyl acetate (30 mL) and filtered. The filtrate was washed with water (2 × 15 mL). The organic phase was dried with Na_2SO_4, filtered, and the solvent was removed under vacuum, and the residue was purified by chromatography on silica gel to give

Table 4. Recycling of the catalyst (without addition of fresh catalyst).[a]



Entry	Pd/C	Yield [%][b]
1	fresh	96
2	first reuse	96
3	second reuse	95
4	third reuse	94
5	fourth reuse	94
6	fifth reuse	93

[a] *Reaction conditions:* iodobeneze (10 mmol) , thiolphenol (10 mmol), KOH (15 mmol), and DMSO (10 mL), 9 h, 110 °C,under N_2. 2 mol% Pd/C (5 wt%) was used in the first run, then the recovered catalyst was used directly in the next runs.

[b] Isolated yield.

desired aryl sulfide. All products gave satisfactory spectroscopic and analytical data.

Typical Procedure for Recovering the Pd/C Catalyst

When the coupling reaction of benzenethiol with iodobenzene in a scale of 10 mmol was complete, the reaction mixture was cooled to room temperature. Then the mixture was filtered and the filter residue was washed with deionized water (5 mL) and CH_2Cl_2 (5 mL), and dried in air at room temperature to recover the Pd/C catalyst in quantitative yield. The dried Pd/C catalyst was then reused directly in the next reaction.

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