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Palladium Catalyzed Aryl(alkyl)thiolation of Unactivated Arenes

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Supporting Information

ABSTRACT: A general palladium-catalyzed aryl(alkyl)-thiolation of various substituted unactivated arenes is accomplished for the synthesis of diverse unsymmetrical diaryl(alkyl) sulfides in good yield employing electrophilic sulfur reagent **6** derived from succinimide. The developed strategy was coupled with intramolecular arylation of a C−H bond to afford dibenzothiophene derivatives, an important moiety in material science as organic semiconductors.

Diaryl sulfides (or arylalkyl sulfides) are potential scaffolds found in biologically important natural products such as the Lissoclibadin and Lissoclinotoxin family of natural products[1] and natural product inspired drug molecules such as AZD4407, a 5-lipoxygenase inhibitor (Figure 1).[2] In material science, dibenzothiophene derivatives, a fused form of diarylsulfides, are ubiquitous subunits present in a number of organic semiconductors.[3]

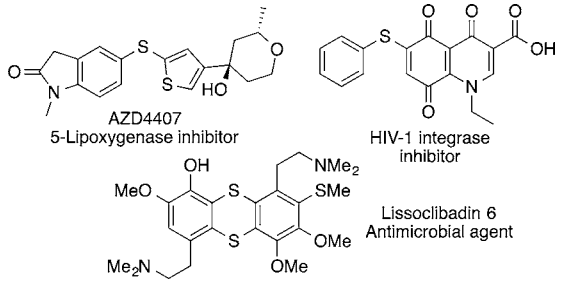
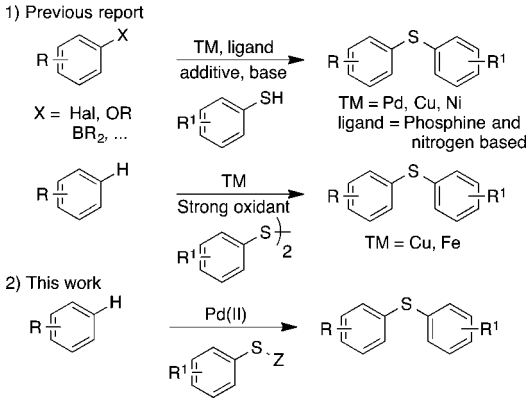


Figure 1. Representative examples of biologically important aryl sulfide.

While these diaryl sulfides can be synthesized through the reaction of arylmagnesium halides[4] or arylboronic acid derivatives[5] with a suitable electrophilic arylsulfur reagent and catalyst, the widely adopted method is the transition metal catalyzed/mediated C−S cross-coupling of aryl halides or its equivalent with thiols and its derivatives (Scheme 1).[6] Nonetheless, general problems associated with these reactions are the use of expensive aryl halides, high catalyst loading due to sulfide poisoning,[7] or addition of superstoichiometric amounts of additives (generally metal salts) and harsh reaction conditions.

Alternatively, most economic and benign routes to the synthesis of diaryl sulfides is the direct arylthiolation of widely present C−H bonds employing an appropriate thiolating reagent. The known examples includes copper mediated alkylthiolation of chelation assisted C−H with dimethyldisulfide[8] or dimethylsulfoxide[9] using air or $K_2S_2O_8$ as an oxidant,

Scheme 1. Approaches towards the Synthesis of Diaryl Sulfides



respectively, and copper catalyzed arylthiolation of the acidic C−H of heterocycles such as benzoxazole, benzothiazole, and indole with diaryldisulfides or arylthiols.[10] Furthermore, the direct aryl thiolation of unactivated arenes was also reported with transition metal catalyzed or metal-free arylthiolation with diaryldisulfides and oxidizing agent (Scheme 1).[11] However, these reactions also suffer from the requirement of specific to selected substrates, such as 2-phenylpyridine and trimethoxybenzene, and the need for a stoichiometric copper complex or highly oxidizing agent. Thus, the development of a mild and general direct arylthiolation of simple arenes is highly warranted. Due to the high importance of diaryl sulfides and our interest in the functionalization of C−H bonds,[12] we herein reveal the palladium-catalyzed direct arylthiolation of C−H bonds of unactivated arenes.[13]

The direct phenylthiolation of mesitylene **1** to mesitylphenyl sulfide **2** was chosen as a model reaction. Initially, the palladium-catalyzed phenylthiolation of mesitylene was investigated employing various readily accessible electrophilic

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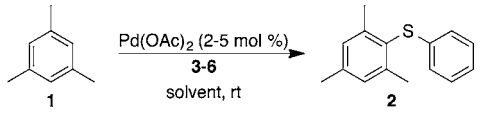
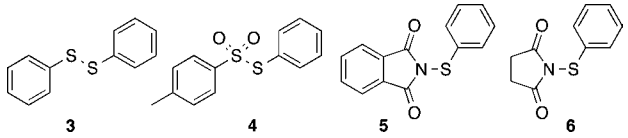
arylthiolation reagents (**3**–**6**).[14] The reaction of mesitylene **1** with palladium acetate (5 mol %) and diphenyldisulfide **3** in trifluoroacetic acid (TFA) at room temperature furnished the expected mesitylphenyl sulfide **2** in an isolable yield (Table 1, entry 1). A similar result was observed with reagent **5**. Interestingly, a high yield of **2** was obtained using reagents **4** and **6**; among them reagent **6**[15] was found to be superior to reagent **4** since the reaction with the former required only 45 min to give product **2** in 95% yield (Table 1, entries 2 and 4). In the absence of palladium acetate, the complete decomposition of **6** was observed after 12 h and product **2** was isolated in very low yield (Table 1, entry 5). Changing the reaction medium to acetic acid (AcOH), methanesulfonic acid (MsOH), or trifluoromethanesulfonic acid (TfOH) reduced the formation of sulfide **2** (Table 1, entries 6–8). Reducing the equivalents of mesitylene from 5 to 3 decreased the yield of **2** (Table 1, entry 9). Interestingly, the decrease in the catalyst loading to 2 mol % also afforded the sulfide **2** in comparable yield (Table 1, entries 4 and 10). Replacing palladium acetate with palladium chloride gave the sulfide **2**, but with a low yield (Table 1, entry 11). From the optimization studies, we chose the following conditions for studying the generality of the methodology: Arene (5 equiv), **6** (1 equiv), $Pd(OAc)_2$ (2 mol %), TFA, rt, 45 min.

Table 1. Palladium-Catalyzed Arylthiolation of Arenes: Optimization[a]



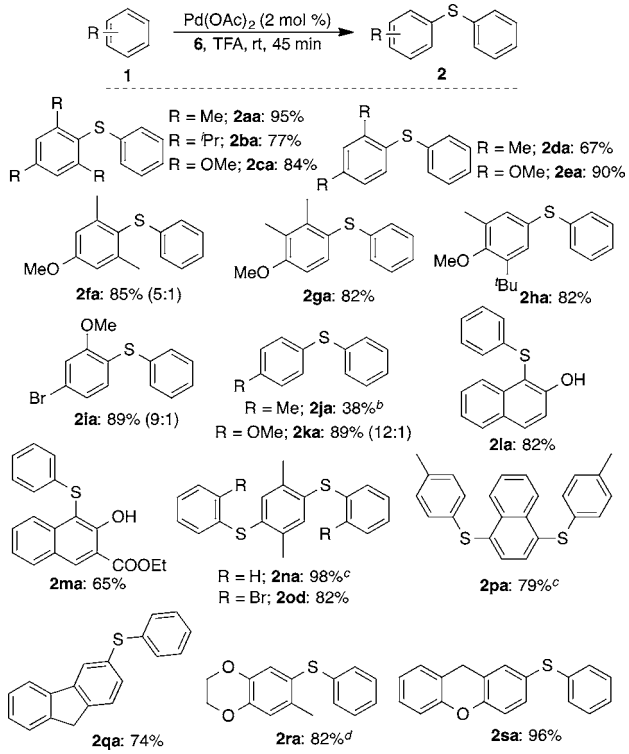
entry	PhS^+ source (**3**–**6**)	solvent	time (h)[b]	yield (%)[c]
1	**3**	TFA	6	18
2	**4**	TFA	6	87
3	**5**	TFA	24	19
4	**6**	TFA	45 min	95
5[d]	**6**	TFA	12	20
6	**6**	AcOH	48	11
7	**6**	MsOH	6	29
8[e]	**6**	TfOH	15 min	0
9[f]	**6**	TFA	45 min	67
10[g]	**6**	TFA	45 min	90
11[h]	**6**	TFA	45 min	79

[a]Reaction conditions: Mesitylene (5 equiv), **3**–**6** (1 equiv), $Pd(OAc)_2$ (5 mol %), solvent (1 mL), rt, time. [b]Time required for consumption of reagent **3**–**6**. [c]Isolated yield based on arylthiolating reagent. [d]Without $Pd(OAc)_2$. [e]Reagent decomposed quickly. [f]3 equiv of mesitylene. [g]2 mol % of $Pd(OAc)_2$. [h]5 mol % of $PdCl_2$ was used.



Next, various substituted arenes were subjected under the optimized conditions to reagent **6** to examine the generality of the developed strategy (Scheme 2). The arylthiolation of mesitylene gave the corresponding mesitylphenyl sulfide **2aa** in 95% isolated yield. A similar result was obtained with the formation of (trimethoxyphenyl)phenyl sulfide **2ca**. Sterically hindered 1,3,5-triisopropylbenzene also underwent a smooth reaction to afford **2ba** in 77% yield. The arylthiolation of 1,3-disubstituted and 1,2,3-trisubstituted arenes furnished the corresponding products (**2da**, **2ea**, **2ga**, and **2ha**) in good yield with excellent selectivity. 3,5-Dimethylanisole and 3-bromoanisole gave a mixture of *para*- and *ortho*-arylthiolated product in a 5:1 and 1:9 ratio, respectively. Interestingly, simple substrates such as anisole, naphthalene, and toluene and a carbocycle such as fluorene also furnished the corresponding arylthiolated product (**2ka**, **2pa**, **2ja**, and **2qa**) in moderate to good yield under the optimized conditions. The arylthiolation of *para*-xylene afforded the diarylthiolated compound (**2na** and **2od**) as the sole product. It is worth noting that the free hydroxyl group and electron withdrawing (carboxylate) group (*β*-naphthaol and ethyl 3-hydroxy-2-naphthoate) were also tolerated under the present arylthiolating conditions. Furthermore, arylthiolated heteroarenes (**2ra** and **2sa**) are also achieved in good yield.

Scheme 2. Palladium-Catalyzed Phenylthiolation of Arenes: Scope and Limitation[a]



[a]Reaction conditions: **6** (1 equiv), arene (5 equiv), $Pd(OAc)_2$ (2 mol %), TFA (0.5 mL), rt, 45 min. All are isolated yields. [b] 4 h. [c] 1 equiv of arene and 2 equiv of **6**. [d] Based on ^1H NMR.

The scope of reagent **6** with various arylthiol partners was also examined under the optimized arylthiolation conditions (Scheme 3). Reagent **6** with simple arylthiols such as *p*-tolylthiol and 2-naphthalenethiol furnished the arylthiolated product **2ab** and **2af** in 83% and 84% yield, respectively. Both electron donating (*p*-methoxybenzenethiol) and electron withdrawing group (*p*-nitrobenzenethiol and *p*-benzoylbenzenethiol) substitution on the arylthiol partner was tolerated well and afforded the products (**2ah**, **2cj**, and **2ak**) in excellent yield. Halogenated diaryl sulfides (**2ac**, **2ad**, and **2ag**), precursors for the synthesis of sulfur based heterocycles, were achieved in good yield from corresponding substituted reagent **6**. Interestingly, 4,6-dimethylpyrimidine-2-thiol substituted reagent **6**, a heterocycle based thiol, underwent a smooth

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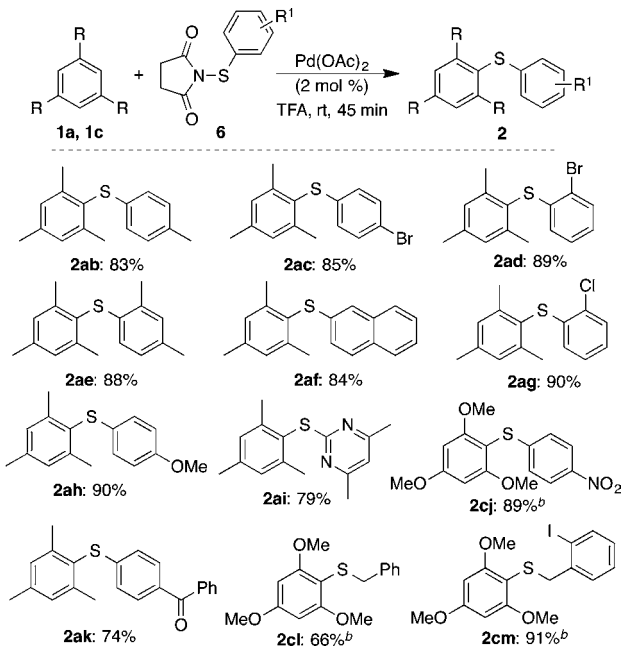
Scheme 3. Palladium-Catalyzed Arylthiolation of Mesitylene: Scope and Limitation[a]

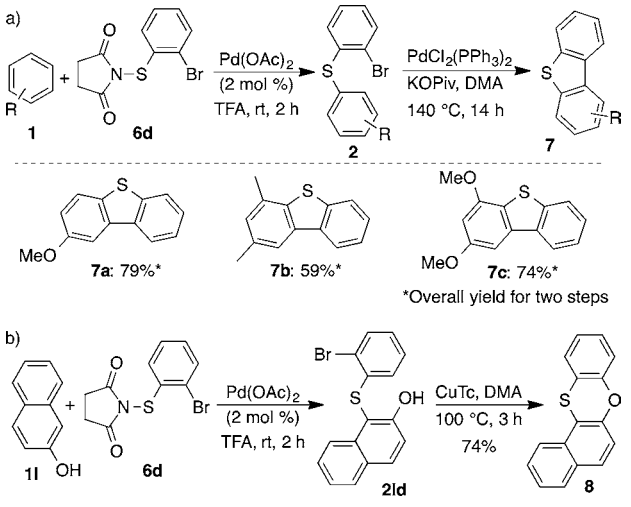


[a]Reaction conditions: **6** (1 equiv), arene (5 equiv), $Pd(OAc)_2$ (2 mol %), TFA (0.5 mL), rt, 45 min. All are isolated yields. [b] 4 h.

reaction to afford the aryl(heteroaryl) sulfide **2ai** in 79% yield. In addition to the arylthiols, alkyl thiols also can be employed to afford the arylalkyl sulfides. Arylalkyl sulfides (**2cl** and **2cm**) were achieved in good yield from corresponding reagent **6**.

After the synthesis of various diarylsulfides, the utility of the synthesized diaryl sulfides was demonstrated by converting them into sulfur based heterocycles. At first, we envisaged the synthesis of benzothiophenes, an important moiety present in various organic semiconductors, through intramolecular arylation of the C−H bond (Scheme 4a). The appropriate substrate **2kd** was synthesized employing the present strategy and subjected to the intramolecular arylation employing a palladium catalyst.[12,16] Based on the optimized conditions (see Supporting inforamtion) dibenzothiophene **7a** was isolated in

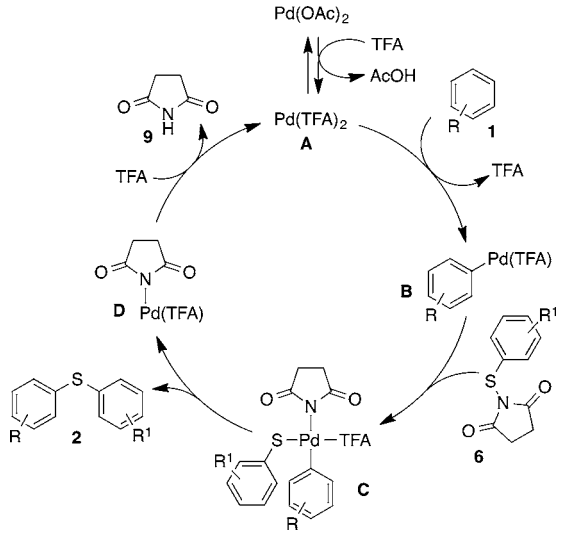
Scheme 4. Synthesis of Dibenzothiophene and Benzo[*a*]phenoxathiine Derivatives



79% overall yield over two steps. Subsequently, other substituted diaryl sulfides (**2dd** and **2ed**) were also examined under the optimized conditions to yield the corresponding dibenzothiophenes (**7b** and **7c**) in good yield. Thus, the developed intramolecular arylation of the C−H bond of a diaryl sulfide can be applied to synthesize the other substituted dibenzothiophenes as well. In addition, benzo[*a*]phenoxathiine **8** was also synthesized through the copper mediated C−O cross-coupling of **2ld** employing the reported protocol in 74% yield (Scheme 4b).

As shown in Scheme 5, we postulated the mechanism for the arylthiolation of arenes with **6** based on the earlier reports on

Scheme 5. Plausible Mechanism for the Formation of Diaryl Sulfide



the palladium-catalyzed C−H functionalization of arenes.[12,17] Initially, highly electrophilic palladium trifluoroacetate **A**, generated from palladium acetate and TFA, reacts with arenes **1** to afford the arylpalladium(II) species **B** through C−H functionalization. Oxidative insertion of **B** into the N−S bond of **6** would lead to the palladium(IV) species **C**. The formation of product **2** could be achieved *via* the reductive elimination of the aryl and arylthio moiety from **C**, which concomitantly produced the species **D**. Finally, ligand exchange will furnish the active palladium species **A** to complete the catalytic cycle and the same reacts with another arene to continue the subsequent cycle.

In conclusion, we have disclosed the direct palladium-catalyzed aryl(alkyl)thiolation of C−H bonds of unactivated arenes. The readily accessible succinimide based electrophilic reagent **6** enables the synthesis of diverse unsymmetrical diaryl or arylalkyl sulfides from readily available arenes in good yield and selectivity under mild conditions. Futhermore, reaction conditions were also optimized for the palladium-catalyzed intramolecular arylation of C−H bonds of diaryl sulfides to afford dibenzothiophene derivatives, a highly important framework in material science. The synthesis of benzophenoxathiine was also accomplished through C−O cross-coupling.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental methods, characterizations data, and ^{1}H and ^{13}C NMR spectra of isolated 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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