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Novel C–H functionalization of arenes: palladium-catalyzed synthesis of diaryl sulfides†

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A novel protocol for the direct arylthiolation of electron-rich arenes is described. Applying arylsulfonyl cyanides in the presence of catalytic amounts of Pd allows for a straightforward synthesis of diaryl sulfides.

Arylsulfonyl motifs are widely used in organic synthesis as the protecting group, activating the leaving group, substrates for the introduction of sulfur, *etc.*¹ The conventional way of introducing sulfur *via* arylsulfonyl derivatives includes Lewis acid mediated arylsulfonylation of electron-rich arenes² and arylsulfonylation under strong acidic conditions.³ More recently, these traditional methods were complemented by Cu- and Pd-catalyzed arylsulfonylations.⁴ In general, in these reactions arylsulfonyl chlorides, anhydrides or amides are employed leading to the formation of diarylsulfones (Fig. 1, left side). Here, we disclose an alternative approach towards diaryl sulfides. To the best of our knowledge such direct synthesis of diaryl sulfides employing arylsulfonyl derivatives as sulfur source has not been described yet (Fig. 1, right side).

Diaryl sulfide (diaryl thioether) scaffolds are found in pharmaceutically important natural products such as the Lissoclinotoxin and Lissoclibadin class of natural products (Fig. 2).⁵ In addition, non-natural diaryl sulfides are also

interesting, *e.g.* as serotonin transporter (SERT) ligands (Fig. 2),⁶ and retinoid analogs for the specific binding and transactivation of retinoid X receptors (RXR).⁷

Most synthetic approaches to diaryl sulfides are based on the formation of C–S bonds through nucleophilic reaction of metal thiolates with aryl halides.⁸ On the other hand, the reduction of aryl sulfones or aryl sulfoxides was also adopted for their synthesis.⁹ However, these methods are often limited by their harsh conditions, low regioselectivity, narrow preparative scope, and use of toxic reagents. Therefore, the development of milder transition metal-catalyzed reactions for the synthesis of diaryl sulfides is of actual interest.¹⁰

In the last few years, we developed novel methodologies for the synthesis of functionalized arenes under electrophilic conditions.¹¹ During the course of our investigations on the direct cyanation of substituted benzenes with *p*-toluenesulfonyl cyanide in the presence of palladium salts,¹² serendipitously, we observed the formation of diaryl sulfide (Table 1).

Table 1 Optimization of reaction conditions for the synthesis of diaryl sulfide **A**^a

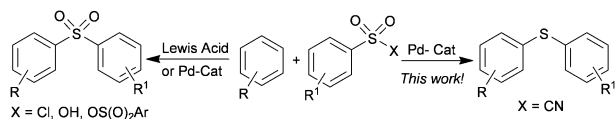
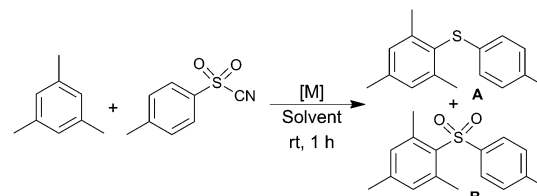


Fig. 1 Catalytic reactions of arylsulfonyl derivatives with arenes.

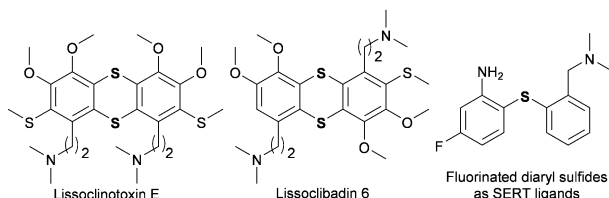


Fig. 2 Examples of therapeutically important diaryl sulfides.

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| Entry | Metal (mol%) | Solvent | Yield ^b (%) | Ratio of A : B |
|-------------------|---------------------------|-----------------------------------|------------------------|----------------|
| 1 | Pd(OAc) ₂ (10) | CF ₃ COOH | 47 | 3 : 1 |
| 2 | Pd(OAc) ₂ (10) | CH ₃ COOH | — | — |
| 3 | Pd(OAc) ₂ (10) | CF ₃ SO ₃ H | — | — |
| 4 | Pd(OAc) ₂ (10) | HCOOH | — | — |
| 5 | — | CF ₃ COOH | — | — |
| 6 | AuCl ₃ (10) | CF ₃ COOH | 6 | 5 : 1 |
| 7 | HAuCl ₄ (10) | CF ₃ COOH | 11 | 9 : 2 |
| 8 | FeCl ₃ (10) | CF ₃ COOH | 14 | 13 : 1 |
| 9 ^c | Pd(OAc) ₂ (10) | CF ₃ COOH | 61 | 2 : 1 |
| 10 ^d | Pd(OAc) ₂ (10) | CF ₃ COOH | 81 | 26 : 1 |
| 11 ^{d,e} | Pd(OAc) ₂ (10) | CF ₃ COOH | 47 | 6 : 1 |
| 12 | Pd(OAc) ₂ (5) | CF ₃ COOH | 78 | 51 : 1 |

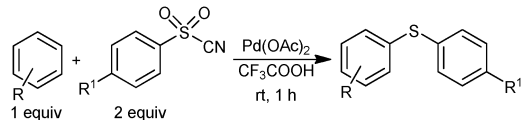

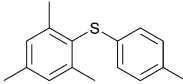

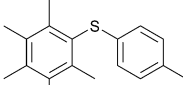

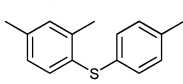

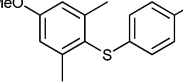

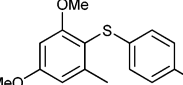

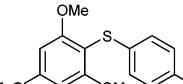

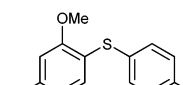

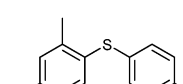

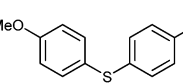

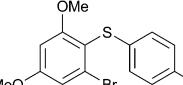

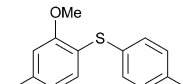

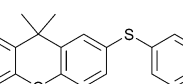

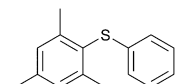

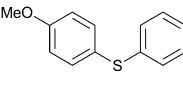
^a Reaction conditions: mesitylene (1 equiv.), TsCN (2 equiv.), metal (*x* mol%), solvent (1 mL), rt, 1 h. ^b GC yield. ^c 5 eq. of mesitylene was used and the yield is based on TsCN. ^d Mesitylene was added after 10 min. ^e 1.2 eq. of TsCN was used.

For this unusual reductive arylthiolation we found no precedent in the literature. Hence, we studied the reaction of mesitylene with *p*-toluenesulfonyl cyanide (TsCN) more closely. An initial screening of the influence of different solvents and palladium precursors revealed that the model reaction proceeded best in trifluoroacetic acid (TFA) with Pd(OAc)₂. Here, at room temperature a mixture of diaryl sulfide **A** and diaryl sulfone **B** is obtained in 47% yield in a ratio of 3 : 1 (Table 1, entry 1). To improve the selectivity and yield, various acids and metals as solvents and catalysts, respectively, were examined (Table 1, entries 2–8). Less acidic formic acid and acetic acid or more acidic trifluoro-methanesulfonic acid resulted in the decomposition of TsCN (Table 1, entries 2–4). Notably, no product is observed in the absence of Pd(OAc)₂ and the reaction resulted only in recovering the starting materials (Table 1, entry 5).

Replacement of Pd(II) with other metals such as Au(III) and Fe(III) afforded only small amounts of **A** and **B** (Table 1, entries 6–8).¹³ Alternatively, introduction of mesitylene into the reaction mixture after pre-formation of the reagents for 10 min increased the yield to 81%, along with a dramatically improved selectivity to 26 : 1 for **A** and **B**, respectively (Table 1, entry 10). Apparently, the reaction of TsCN with palladium in TFA generates a highly reactive species which then affords the observed diaryl sulfide in excellent yield and selectivity. Reducing the ratio of mesitylene to TsCN to 1 : 1.2 furnished the products in 47% yield with moderate selectivity (Table 1, entry 11). Interestingly, decreasing the loading of catalyst to 5 mol% also gave similar results (Table 1, entry 12).

Based on these results we envision the following mechanism for the direct arylthiolation of mesitylene with 4-tolylsulfonyl cyanide (Fig. 3): initially, palladium-mediated activation of TsCN proceeds in the acidic medium. Rearrangement and elimination of CF₃CO₂CN gave the respective sulfinic acid. Subsequent trifluoroacetylation forms a cationic sulfur species which can react either with mesitylene directly or with the palladated arene. Final reduction with the *in situ*-generated sulfinic acid leads to the observed diaryl sulfide.¹⁴ The present

Table 2 Synthesis of diaryl sulfides: scope and limitations^a

|  | | | |
|--|--|---|-------------------------|
| Entry | Arene | Product | Yield ^b (%) |
| 1 |  |  | 72 |
| 2 |  |  | 76 |
| 3 |  |  | 57 |
| 4 ^c |  |  | 43 (1 : 3) ^d |
| 5 |  |  | 58 |
| 6 |  |  | 44 |
| 7 |  |  | 39 |
| 8 ^e |  |  | 66 |
| 9 |  |  | 61 |
| 10 |  |  | 37 |
| 11 ^f |  |  | 55 |
| 12 |  |  | 57 |
| 13 |  |  | 33 |
| 14 |  |  | 41 |

^a Reaction conditions: arene (1 mmol), ArSO₂CN (2 mmol), Pd(OAc)₂ (5 mol%), TFA (1 mL), rt, 1 h. ^b Isolated yield. ^c 21% of diarylthiolated product. ^d *Ortho* : *para* ratio. ^e 10% of diarylthiolated product. ^f 6% of diarylthiolated product.

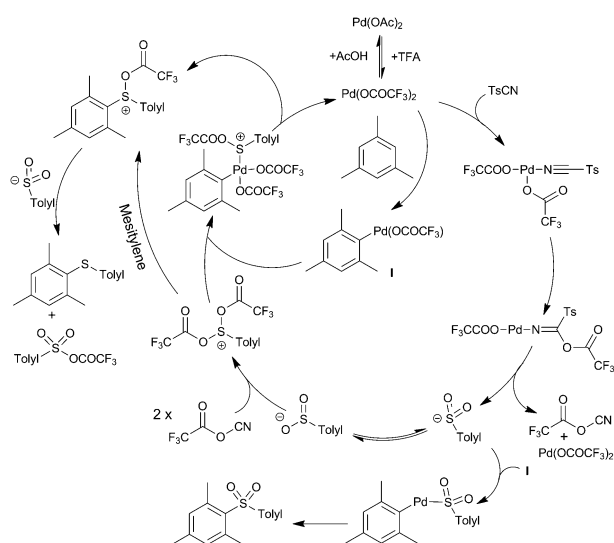


Fig. 3 Proposed mechanism.

proposal is supported by the following observations: (1) the presence of palladium in the reaction mixture is a prerequisite for the arylthiolation to occur; (2) addition of mesitylene after pre-formation of the active species increases the yield and selectivity; (3) in order to observe yields > 50% an arylsulfonyl cyanide to arene ratio > 1 : 1.2 is necessary. Furthermore, we were able to obtain the same products in good yield (> 70%) by replacement of the arylsulfonyl cyanide with sodium 4-tolylsulfinate in the presence of trifluoroacetic anhydride. Notably, no reaction is observed without this anhydride.¹⁴

After having identified suitable conditions for the model reaction (Table 1, entry 12), we tested a number of arenes with two arylsulfonyl cyanides to explore the scope of this new methodology (Table 2). Arylthiolation of mesitylene with TsCN yielded the corresponding diaryl sulfide in 72% isolated yield (Table 2, entry 1). A similar result is obtained with pentamethylbenzene (Table 2, entry 2). More simple substrates such as anisole and *m*-xylene underwent smooth reaction to afford the diaryl sulfides in 61% and 57% yield, respectively (Table 2, entries 9 and 3). It is interesting to note that the *ortho* to *para* selectivity in both cases is found to be excellent. However, arylthiolation of 3,5-dimethylanisole furnished a mixture of *ortho*- and *para*-arylthiolated products in a 1 : 3 ratio (Table 2, entry 4). Substituted diaryl sulfides (from 3,5-dimethoxytoluene and 1,3,5-trimethoxybenzene) were also readily synthesized employing the present conditions (Table 2, entries 5 and 6). Moreover, 1,3-dimethoxybenzene as well as 3-methylanisole are arylthiolated in 39% and 66% yield (Table 2, entries 7 and 8). From a synthetic point of view it is interesting to note that aryl bromides can be used as substrates for the arylthiolation reaction. Thus, arylthiolation of 5-bromo-1,3-dimethoxybenzene and 3-bromoanisole with TsCN gave a moderate yield of the corresponding brominated diaryl sulfide (Table 2, entries 10 and 11). Additionally, 9,9-dimethylxanthene, a heterocyclic arene was arylthiolated in 57% yield (Table 2, entry 12). Finally, benzenesulfonyl cyanide was utilized in place of TsCN.¹⁵ Consequently, arylthiolation of simple arenes such as mesitylene and anisole with benzenesulfonyl cyanide afforded the respective diaryl sulfides in moderate yield (Table 2, entries 13 and 14).

In summary, a novel C–H functionalization methodology for the synthesis of diaryl sulfides from arenes has been developed. This palladium-catalyzed reaction utilizes arylsulfonyl cyanide as sulfur source, which is the key for the success of the present strategy. Different mono- and diarylthiolations proceed under mild conditions with moderate to excellent chemo- and regioselectivity.

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