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Palladium Catalyzed Diaryl Sulfoxide Generation from Aryl Benzyl Sulfoxides and Aryl Chlorides

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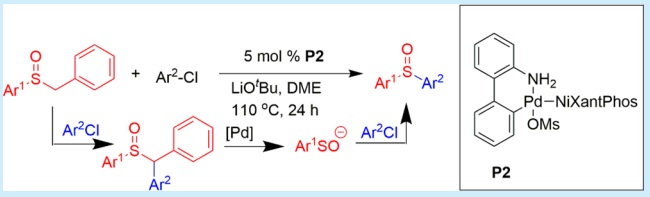
Supporting Information

ABSTRACT: Diaryl sulfoxides are synthesized from aryl benzyl sulfoxides and aryl chlorides via three sequential catalytic cycles all promoted by a NiXantPhos-based palladium catalyst. The key step is *S*-arylation of a sulfenate anion. An air- and moisture-stable precatalyst derived from NiXantPhos efficiently facilitates the transformation. Various functional groups, including those with acidic protons, were tolerated. This method can also be extended to methyl and dibenzyl sulfoxides substrates.



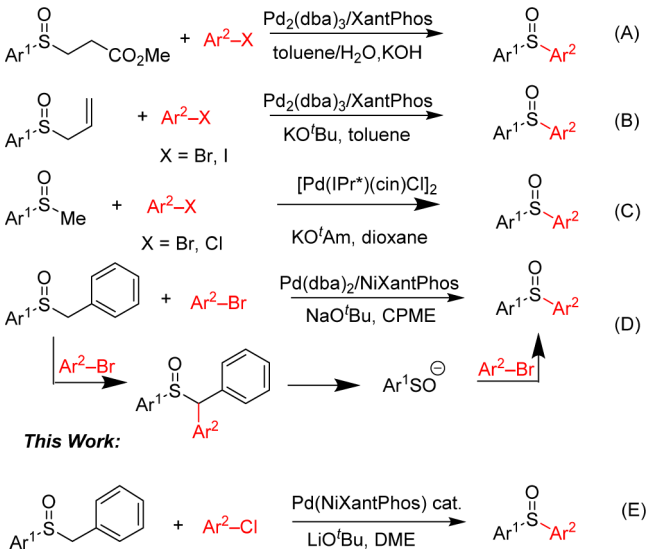
Aryl sulfoxides are important structural motifs in bioactive compounds[1] and marketed therapeutics.[2] They are also widely used as ligands in transition-metal catalysis.[3] Significant effort, therefore, has been devoted to their preparation. The most popular methods for the synthesis of sulfoxides are oxidation of sulfides and nucleophilic substitution of sulfinamides or sulfinate esters.[4]

Transition-metal catalyzed cross-coupling reactions are powerful methods to form C–S bonds[5] and offer an alternative approach to construct aryl sulfoxides. In 2007, Poli and Madec reported the first diaryl sulfoxide generation via palladium-catalyzed *S*-arylation between sulfenate anions[6] and aryl bromides and iodides.[7] Sulfenate anions were generated in situ via retro-Michael reaction (Scheme 1A). The same team subsequently employed the Mislow–Braverman–Evans rearrangement of allylic sulfoxides and generated sulfenate anions that were arylated in situ to provide diaryl sulfoxides (Scheme 1B).[8] Aryl chloride substrates were noticeably absent from these reports.

Very recently, the Nolan group reported an *N*-heterocyclic carbene-based palladium catalyst for the conversion of methyl sulfoxides to diaryl sulfoxides via a proposed Pd-carbene intermediate (Scheme 1C).[9] Although the reaction worked with aryl bromides and chlorides, the only functionalized aryl chloride employed was 4-chloro anisole.

Simultaneously, we communicated[10] diaryl sulfoxide formation from aryl benzyl sulfoxides and *aryl bromides* using a palladium catalyst based on van Lewueen's NiXantPhos ligand[11] (Scheme 1D). A systematic study revealed that this single palladium catalyst promoted three distinct transformations to generate diaryl sulfoxides (Figure 1), including α-arylation of benzyl sulfoxides (Cycle A), sulfenate anion generation (Cycle B), and *S*-arylation of sulfenate anions (Cycle C). Various diaryl sulfoxides and heteroaryl aryl sulfoxides were prepared from aryl bromides in good to excellent yields. Given the scarcity of aryl chlorides that have been successfully employed in the sulfenate anion arylation, and the reduced costs and greater abundance of aryl chlorides relative to aryl bromides, we viewed the inclusion of aryl chlorides in this reaction as important. Herein, we report a palladium-catalyzed diaryl sulfoxide formation from aryl benzyl sulfoxides and aryl chlorides (Scheme 1E).

Scheme 1. Aryl sulfoxides synthesis via palladium catalyzed C–S bond formation



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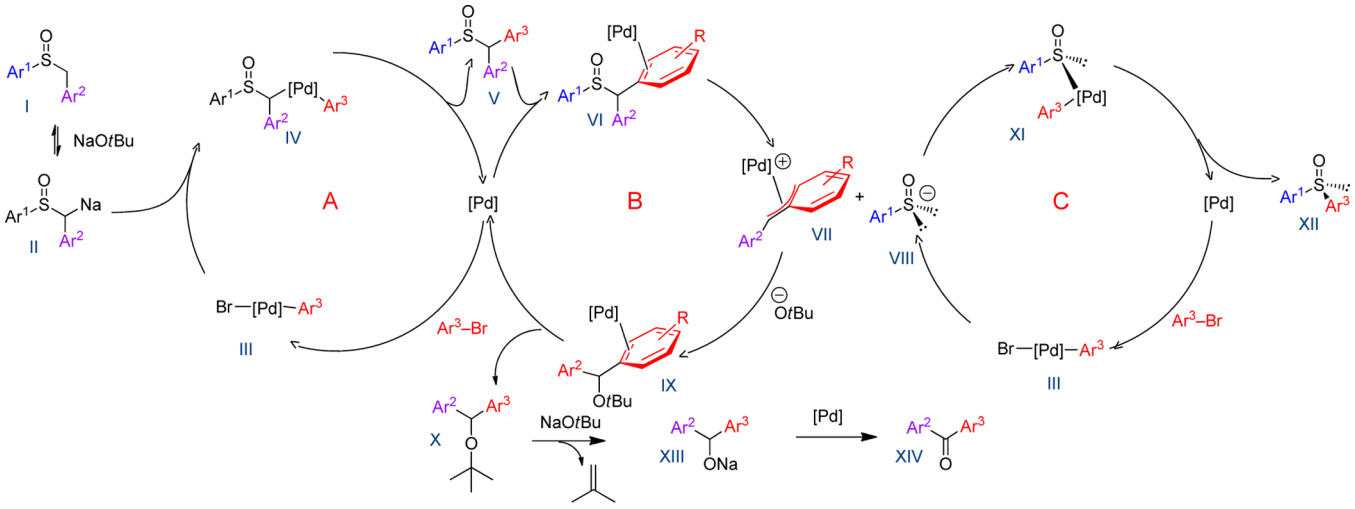


Figure 1. Palladium catalyzed diaryl sulfoxides formation from aryl benzyl sulfoxides and aryl bromides via a triple relay mechanism.

We employed coupling partners benzyl phenyl sulfoxide (**1a**) and 4-*tert*-butyl chlorobenzene (**2a**) as the model substrates to identify reaction conditions. The optimized conditions for coupling sulfoxide **1a** with *aryl bromides*, which involved 5 mol % $Pd(dba)_2$/7.5 mol % NiXantPhos ligand (Figure 2) and 3

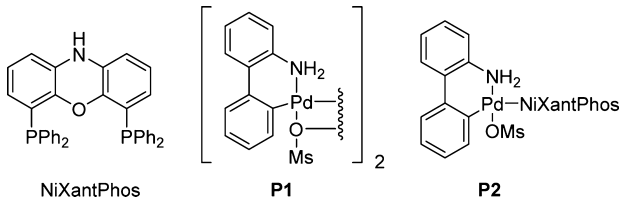
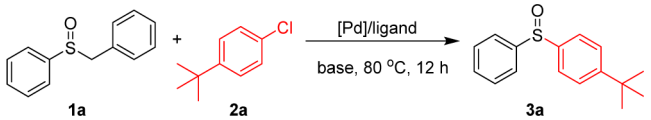


Figure 2. Structures of NiXantPhos and palladacyclic precursors **P1** and **P2**.

equiv of NaO^{t}Bu in CPME at 80 °C, were initially examined (Table 1, entry 1).[10] The desired diaryl sulfoxide product (**3a**) was formed in less than 5% assay yield. We were concerned that catalyst generation was an issue, so we used Buchwald's palladacyclic precatalysts,[12] which proved to be effective in the oxidative addition of aryl chlorides with NiXantPhos.[13] Two precatalysts (**P1** and **P2**, Figure 2) were prepared according to reported procedures[12f,13] and used under the conditions of the coupling reaction. When **P1** was used with NiXantPhos, the yield of **3a** improved to 15%. The yield of **3a** increased to 34% when the precatalyst bearing NiXantPhos (**P2**) was utilized. These low yields inspired us to screen bases that had been successfully applied to other deprotonative cross-coupling processes (DCCP). Thus, LiO^{t}Bu, KO^{t}Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$ were investigated. In this screen, LiO^{t}Bu gave the most promising result (43%, Table 1, entry 5 vs entries 3 and 6–9). Three additional ethereal solvents [DME (dimethoxyethane), dioxane, and THF) were surveyed with DME giving a better yield (51%, Table 1, entry 10 vs entries 5, 11 and 12). Increasing the temperature of the reaction from 80 to 110 °C led to a 61% yield of **3a** (Table 1, entry 13). Finally, doubling the reaction time to 24 h resulted in **3a** in 74% assay yield (^{1}H NMR) and 70% isolated yield (Table 1, entry 14). Further optimization did not lead to increased yields. Thus, the optimized conditions were 5 mol % palladacyclic **P2**, sulfoxide **1a** as the limiting reagent, 2 equiv

Table 1. Optimization of the Palladium-Catalyzed Diaryl Sulfoxide Formation[a]



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

entry	Pd/mol %	base	sol	assay yield[b] (%)
1[c]	$Pd(dba)_2$/5	NaO^{t}Bu	CPME	<5
2[c]	**P1**/2.5	NaO^{t}Bu	CPME	15
3	**P2**/5	NaO^{t}Bu	CPME	34
4[c]	**P2**/5	NaO^{t}Bu	CPME	29
5	**P2**/5	LiO^{t}Bu	CPME	43
6	**P2**/5	KO^{t}Bu	CPME	27
7	**P2**/5	$LiN(SiMe_3)_2$	CPME	11
8	**P2**/5	$NaN(SiMe_3)_2$	CPME	0
9	**P2**/5	$KN(SiMe_3)_2$	CPME	0
10	**P2**/5	LiO^{t}Bu	DME	51
11	**P2**/5	LiO^{t}Bu	dioxane	37
12	**P2**/5	LiO^{t}Bu	THF	28
13[d]	**P2**/5	LiO^{t}Bu	DME	61
14[e]	**P2**/5	LiO^{t}Bu	DME	74 (70[f])

[a]1 equiv of **1a**, 2 equiv of **2a**, and 3 equiv of base at 80 °C on 0.1 mmol scale for 12 h. [b]Assay yield determined by ^{1}H NMR by using 0.1 mmol of CH_2Br_2 as an internal standard. [c]7.5 mol % NiXantPhos used. [d]110 °C. [e]24 h. [f]Isolated yield.

of aryl chloride, and 3 equiv of LiO^{t}Bu in DME at 110 °C for 24 h.

With the optimized conditions for the palladium-catalyzed cross-coupling reaction of **1a** and **2a**, the substrate scope of aryl chlorides was investigated (Scheme 2). The parent diphenyl sulfoxide (**3b**) was generated from chlorobenzene (**2b**) in 72% yield. Aryl chlorides bearing electron-withdrawing groups, such as 4-F (**2c**) and 4-CN (**2d**), afforded the products in 85% and 63% yields, respectively. Both 1-chloronaphthalene (**2e**) and 3-chloroanisole (**2f**) were suitable cross-coupling partners, furnishing **3e** and **3f** in 70% and 87% yield, respectively. 4-Chlorobenzophenone was successfully coupled, delivering **3g** in 72% yield. Surprisingly, under the optimized conditions, acetamide **2h** and piperidine **2i** afforded products **3h** and **3i** both in 73% yield. Thus, the NiXantPhos ligated catalyst successfully promoted both C–C and C–S bond formations

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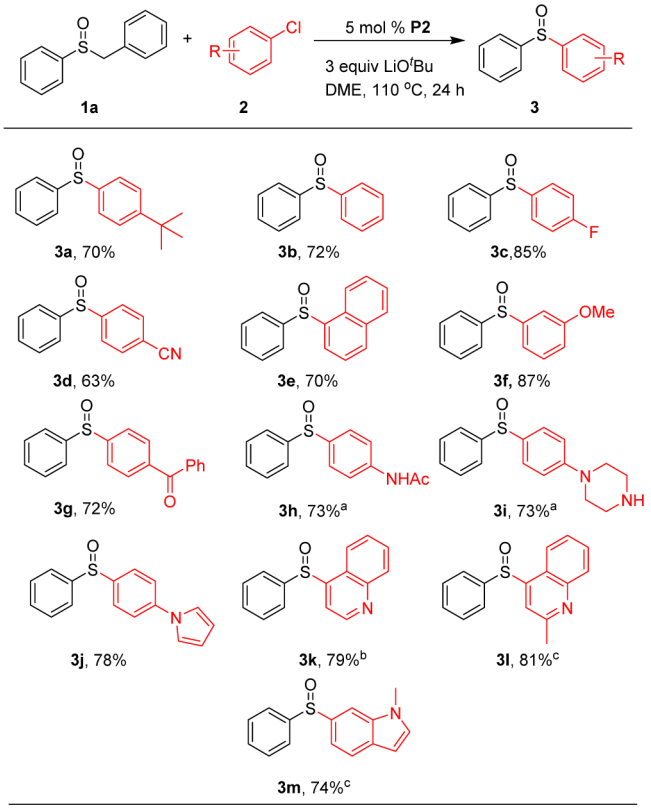
Scheme 2. Substrate Scope of Aryl Chlorides in Palladium-Catalyzed Diaryl Sulfoxides Synthesis with 1a

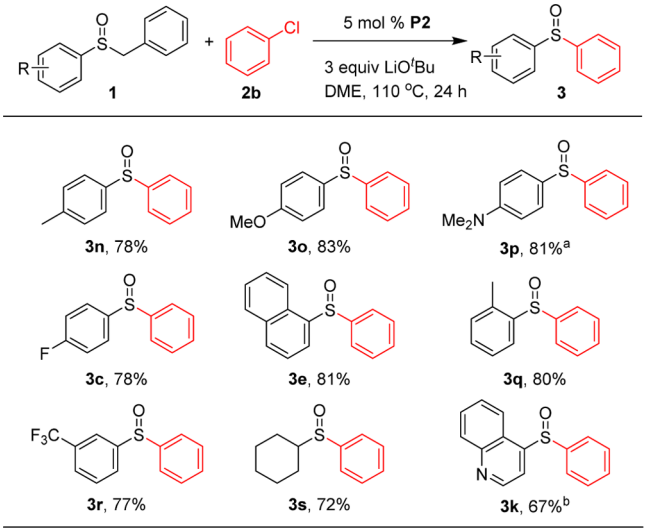


[a]Sequiv LiO^{t}Bu used. [b] 10 mol % **P2** used. [c] 48 h.

(Figure 2) faster than C–N bond formation (Buchwald–Hartwig coupling[14]), leaving the N–H's intact. Heterocyclic sulfoxides, which often exhibit bioactivities,[1] could also be prepared. Thus, 4-pyrrolephenyl phenyl sulfoxide (**3j**), 4-quinoline phenyl sulfoxide (**3k**), 2-methyl 4-quinoline phenyl sulfoxide (**3l**), and (*N*-methyl)-6-indolyl phenyl sulfoxide (**3m**) were generated in 74–81% yields. However, sterically hindered aryl chlorides, such as mesityl chloride, and some heteroaryl chlorides, such as 3-chloropyridine and 3-chlorothiophene, could not be coupled under our conditions.

A variety of aryl benzyl sulfoxides were next explored in the presence of 5 mol % NiXantPhos ligated precatalyst **P2** (Scheme 3). Aryl benzyl sulfoxides bearing electron-donating groups furnished diaryl sulfoxides **3n**–**3p** in 78–83% yields. For reasons that remain unclear, 1-(benzylsulfinyl)-4-methoxybenzene (**1o**) was not a viable substrate in our initial study.[10] In contrast, in the present case 4-chloroanisole afforded **1o** in 83% yield. Diaryl sulfoxides bearing 4-F or 3-CF_3 groups generated products in 77–78% yields. Sulfoxides bearing larger substituents, such as 1-naphthyl (**1e**) and 2-tolyl (**1q**), were also viable coupling partners, providing **3e** and **3q** in 80–81% yield. Alkyl benzyl sulfoxides are more challenging substrates, because their α-C–H's are less acidic than aryl benzyl sulfoxides.[15] Nonetheless, cyclohexyl benzyl sulfoxide reacted with chlorobenzene to generate cyclohexyl phenyl sulfoxide (**3s**) in 72% yield. Heteroaryl benzyl sulfoxides are potentially useful coupling partners. The quinoline benzyl sulfoxide underwent coupling to provide the heteroaryl aryl sulfoxide **3k** in 67% yield with 10 mol % catalyst.

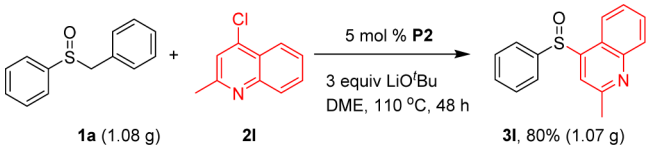
Scheme 3. Substrate Scope of Aryl Benzyl Sulfoxides in Palladium-Catalyzed Diaryl Sulfoxides Formation with 2b



[a]3 equiv PhCl used. [b] 10 mol % **P2** used.

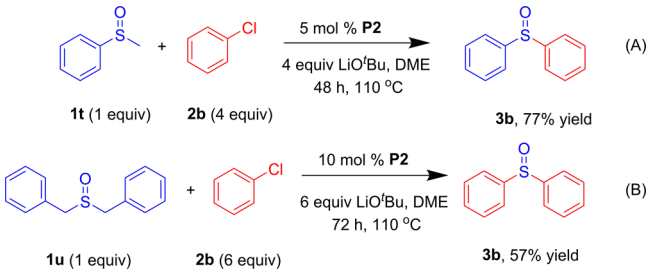
To demonstrate the potential utility of our method, we conducted a gram scale reaction with a heterocyclic aryl chloride (Scheme 4). Thus, phenyl benzyl sulfoxide (5 mmol, 1.08 g) was coupled with 4-chloro-2-methylquinoline (**2l**) in 80% yield (1.07 g).

Scheme 4. Gram Scale Synthesis of 3l via Palladium Catalyzed Diaryl Sulfoxide Generation



We next set out to evaluate different types of sulfoxides as precursors to diaryl sulfoxides. We previously demonstrated the arylation of aryl methyl sulfoxides to generate aryl benzyl sulfoxides,[12h] which are the substrates in the current study. Combining these two methods, we treated phenyl methyl sulfoxide with chlorobenzene under our standard conditions, giving diphenyl sulfoxide (**3b**) in 77% yield (Scheme 5A). Likewise, dibenzyl sulfoxide (**1u**) and chlorobenzene (**2b**) could also be converted to diphenyl sulfoxide in 57% yield (Scheme 5B). Considering four C(sp^2)–Cl bonds have to be

Scheme 5. Preparation of Diphenyl Sulfoxide (3b) from Methyl Phenyl Sulfoxide (1t) or Dibenzyl Sulfoxide (1u) and Chlorobenzene (2b)



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broken to generate each equivalent of **3b**, the moderate yield is reasonable.

In summary, aryl chlorides have been utilized as electrophiles in the cross-coupling reactions with aryl benzyl sulfoxides to produce diaryl sulfoxides. A variety of functional groups, including those which might be expected to participate in related coupling reactions (Buchwald−Hartwig) or undergo addition reactions (C═O, CN), were well tolerated. According to the proposed mechanism, two C(sp^2)−Cl bonds have to be cleaved to generate one molecule of product. In order to do so, an air and moisture stable NiXantPhos-derived palladacyclic precatalyst was employed.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, characterization data for all new 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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