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Palladium-Catalyzed Arylation of Aryl Sulfenate Anions with Aryl Bromides under Mild Conditions: Synthesis of Diaryl Sulfoxides

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Supporting Information

ABSTRACT: A palladium-catalyzed arylation of aryl sulfenate anions generated from aryl 2-(trimethylsilyl)ethyl sulfoxides and CsF has been developed. This protocol is effective for the synthesis of diaryl sulfoxides and heteroaryl aryl sulfoxides under mild conditions employing aryl bromides. Various functional groups, including those with acidic protons, are well tolerated.

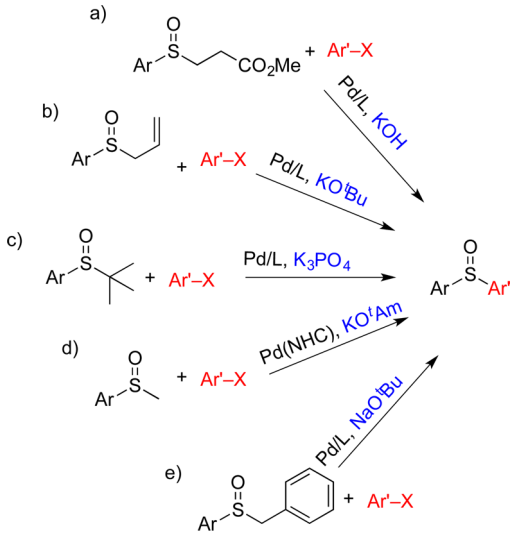
Aryl sulfoxides are important structural motifs in natural products,[1] bioactive compounds,[2] and marketed therapeutics, such as Nexium[3] and Provigil.[4] They are also used as ligands in transition-metal catalysis.[5] The two classic methods for sulfoxides synthesis are the oxidation of sulfides and nucleophilic substitution of sulfinate amides or esters.[6] Despite the utility of these two methods, they leave room for improvement. These approaches use either strong oxidants or reactive organolithium and Grignard reagents, which can limit their functional group compatibility.

In recent years, transition-metal-catalyzed reactions have been employed in the formation of sulfoxide C–S bonds (Scheme 1) via the arylation of sulfenate anions, $[RSO]^-$.[7] In pioneering work, Poli and Madec[8] reported a KOH-promoted retro-Michael reaction of β-sulfinyl esters to generate sulfenate anions followed by palladium-catalyzed arylation with aryl iodides and bromides to prepare aryl sulfoxides (Scheme 1a).[9] An enantioselective version of this reaction has also been introduced.[10] Subsequently, the same group reported a palladium-catalyzed C–O bond cleavage of allylic sulfenate esters by a Mislow–Braverman–Evans rearrangement of the allyic sulfoxides. The resulting aryl sulfenate anion underwent palladium-catalyzed coupling with aryl iodides or bromides to yield diaryl sulfoxides (Scheme 1b).[11]

In 2015, Perrio and co-workers utilized the thermal fragmentation of *tert*-butyl sulfoxides to generate sulfenate anions that underwent Pd-catalyzed arylation (Scheme 1c).[12] These reactions all employed Pd(XANTPHOS)-based catalysts. In 2013, Nolan and co-workers developed an *N*-heterocyclic carbene (NHC)-ligated palladium catalyst for the synthesis of diaryl sulfoxides from aryl methyl sulfoxides and aryl bromides or chlorides (Scheme 1d).[13] Simultaneously, our group reported a general, high-yielding method for the synthesis of diaryl sulfoxides from benzyl aryl sulfoxides (Scheme 1e).[14] In these latter two cases, the sulfoxide substrates undergo an initial α-arylation.

In general, the generation of alkyl sulfenate anions with β-hydrogens, $RCH_2CH_2SO^-$, under the basic conditions employed in Scheme 1, is challenging due to the instability of the precursors,[15] intermediates,[16] and/or products.[7a−c,16b,17] For these reasons, we recently developed a palladium-catalyzed arylation of *alkyl sulfenate anions*, which afforded alkyl aryl sulfoxides in high yield (Scheme 2a).[18] Key to success of this process was a fluoride-triggered elimination strategy with alkyl 2-(trimethylsilyl)ethyl sulfoxides[15,19] to liberate the requisite alkyl sulfenate anion intermediates. Given the mildly basic conditions that can be used with 2-(trimethylsilyl)ethyl

Scheme 1. Palladium-Catalyzed Arylation of Sulfenate Anions with Aryl Halides



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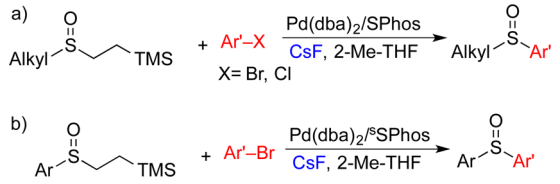
Scheme 2. Arylation of (a) Alkyl Sulfenate Anions and (b) Aryl Sulfenate Anions



sulfoxides, we envisioned that this approach would also be useful for the synthesis of diaryl sulfoxides. Herein, we present the palladium-catalyzed arylation of sulfenate anions with aryl bromides initiated with aryl 2-(trimethylsilyl)ethyl sulfoxides under mild conditions (Scheme 2b).

We initiated our studies using NIXANTPHOS/Pd(dba)$_2$ to catalyze cross-coupling of phenyl 2-(trimethylsilyl)ethyl sulfoxides (**1a**) and 4-*tert*-butylbromobenzene (**2a**, see Figure 1 for

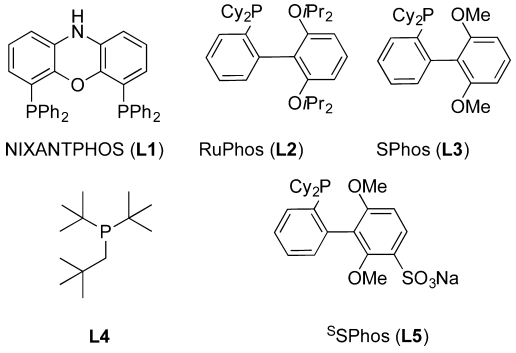
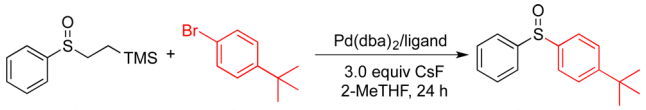


Figure 1. Ligand structures.

ligand structures). We previously used this catalyst for the arylation outlined in Scheme 1e.[14a] Four fluoride sources (LiF, NaF, KF, and CsF) and six commonly used solvents [THF, toluene, 2-Me-THF, DME (dimethoxyethane), CPME (cyclopentyl methyl ether), and dioxane] were screened (see the Supporting Information for details). The leading hit was CsF in 2-Me-THF with 67% assay yield (0.1 mmol scale, Table 1, entry 1). We next examined 44 sterically and electronically diverse mono- and bidentate ligands on microscale. Along with NIXANTPHOS (**L1**), RuPhos (**L2**), SPhos (**L3**), di-*tert*-butylneopentylphosphine·HBF$_4$ (**L4**), and ^{S}SPhos (**L5**) were the most promising hits. With 5 mol % of Pd(dba)$_2$ and 10 mol % of ligand loading (**L2**–**L5**), the microscale reactions were successfully translated to laboratory scale with similar high assay yields (>90%). When the palladium loading was reduced to 2 mol %, however, ^{S}SPhos outperformed the other ligands (entry 2–4 vs entry 5) and was, therefore, used for the duration of these studies. Attempts to decrease the temperature, catalyst loading, equivalents of aryl bromide (**2a**) or CsF led to diminished assay yields of **3a** (entries 6–9). Increasing the reaction concentration from 0.1 to 0.5 M increased assay yield to 96% with 93% isolated yield after purification (entry 10).

With optimized conditions for the arylation of sulfenate anions (Table 1, entry 10), we examined the scope of aryl bromides with trimethyl(2-(phenylsulfinyl)ethyl)silane (**1a**, Scheme 3). Aryl bromides bearing electron-donating groups, such as 4-*tert*-butyl and 4-methoxy, were well tolerated, providing **3a** and **3b** in 93% and 94% yield, respectively. Electron-withdrawing groups on the aryl bromides also exhibited good reactivity. 4-Fluorobromobenzene (**2c**) and 4-

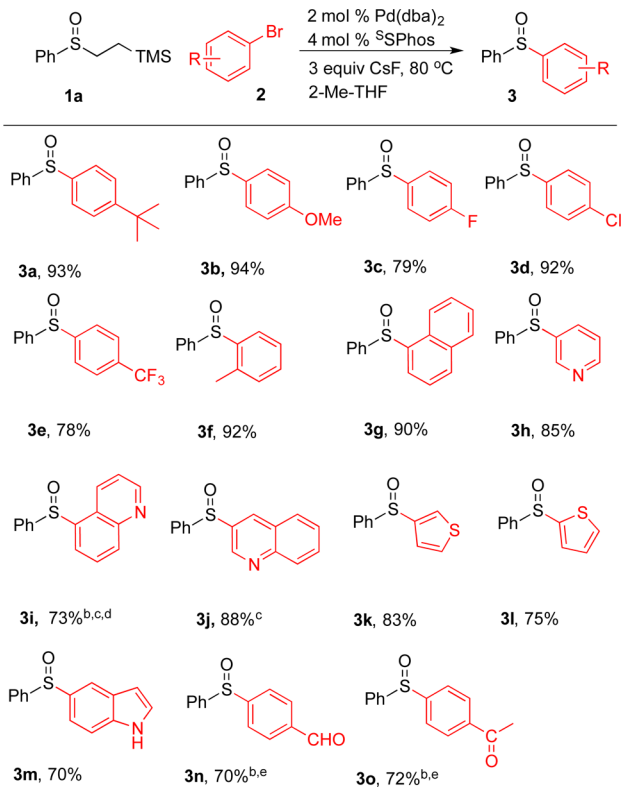
Table 1. Optimization of Palladium-Catalyzed Diaryl Sulfoxide Formation from 1a and 2a



entry	ligand	[Pd]/ligand (mol %)	concn (M)	**3a**[a] (%)
1	NIXANTPHOS	5/7.5	0.1	67
2	RuPhos	2/4	0.1	57
3	SPhos	2/4	0.1	71
4	P(*t*Bu)$_2$(CH$_2$*t*Bu)	2/4	0.1	75
5	^{S}SPhos	2/4	0.1	92
6[b]	^{S}SPhos	2/4	0.1	<5
7	^{S}SPhos	1/2	0.1	62
8[c]	^{S}SPhos	2/4	0.1	64
9[d]	^{S}SPhos	2/4	0.1	32
10	^{S}SPhos	2/4	0.5	96 (93[e])

[a]Assay yields determined by ^{1}H NMR using 0.1 mmol (7 μL) CH_2Br_2 as internal standard. [b]50 °C. [c]1.5 equiv of **2a**. [d]2.0 equiv of CsF. [e]Isolated yield.

Scheme 3. Substrate Scope of Aryl Bromides in Pd-Catalyzed Diaryl Sulfoxides Formation with 1a[a]



[a]Reaction conditions: **1a** (0.5 mmol), **2a**–**l** (1.0 mmol), CsF (1.5 mmol), Pd(dba)$_2$ (0.01 mmol), ^{S}SPhos (0.02 mmol), 2-Me-THF (1 mL), 80 °C, 24 h. [b]5 mol % of Pd(dba)$_2$, 10 mol % of ^{S}Sphos. [c]48 h. [d]2 mL of 2-Me-THF. [e]32 h.

trifluoromethyl bromobenzene (**2e**) afforded the corresponding products in 79% and 78% yield, respectively. We were pleased that good chemoselectivity in coupling at bromide over chloride was achieved with 4-chlorobromobenzene, affording **3d** in 92% yield. Further studies indicated that, although ^{S}SPhos

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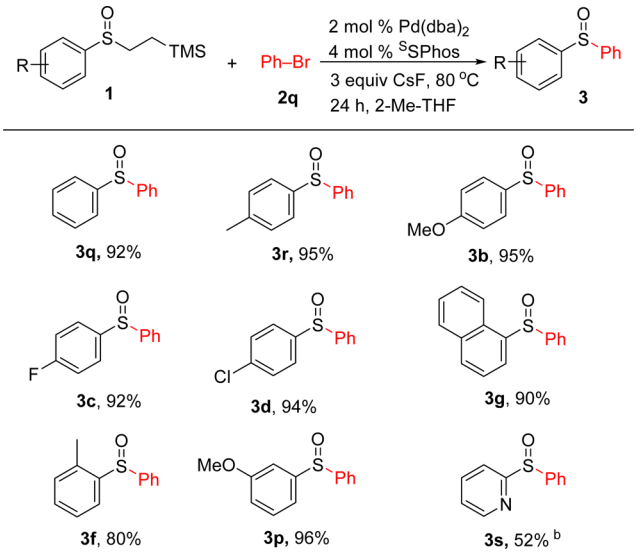
has been used in coupling of aryl chlorides,[20] these substrates are not viable under our conditions. Sterically hindered aryl bromides, such as 2-bromotoluene (**2f**) and 1-bromonaphthalene (**2g**), furnished the products **3f** and **3g** in 92% and 90% yield, respectively.

Heterocycle-containing sulfoxides exhibit a broad range of biological activities. Our protocol is effective for their synthesis. Thus, 3-(phenylsulfinyl)pyridine (**3h**), 5-quinoline phenyl sulfoxide (**3i**), 3-quinoline phenyl sulfoxide (**3j**), 3-thiophene phenyl sulfoxide (**3k**), and 2-thiophene phenyl sulfoxide (**3l**) were generated in 73−88% yields. Under the optimized conditions, 5-bromo-1*H*-indole (**2m**) afforded products **3m** in 70% yield. It is noteworthy that the ^{S}SPhos-ligated catalyst successfully promoted C−S bond formation faster than C−N bond formation (Buchwald−Hartwig coupling[21]), leaving the N−H intact. 4-Bromobenzaldehyde and 4-bromoacetophenone were also good substrates, providing the coupling products **3n** and **3o** in 70 and 72% yield, respectively.

Next, we turned our attention to the substrate scope of aryl 2-(trimethylsilyl)ethyl sulfoxides (Scheme 4). In general, various substituents on the aryl sulfoxide were compatible, affording the desired diaryl sulfoxides in high yields. Aryl 2-(trimethylsilyl)ethyl sulfoxides coupled with bromobenzene (**2q**) to give the parent diphenyl sulfoxide (**3q**) in 92% yield. 2-(Trimethylsilyl)ethyl sulfoxides bearing electron-donating groups such as 4-Me (**1r**) and 4-OMe (**1b**) both provided the products in 95% yield. 2-(Trimethylsilyl)ethyl sulfoxides bearing 4-F (**1c**) and 4-Cl (**1d**) furnished products in 92% and 94% yield, respectively. Hindered 1-naphthyl (**1g**) and 2-tolyl (**1f**) 2-(trimethylsilyl)ethyl sulfoxides provided the expected products in 90 and 80% yield, respectively. The 3-OMe derivative (**1p**) could also be used as a coupling partner, affording **3p** in 96% yield. 2-Pyridyl 2-(trimethylsilyl)ethyl sulfoxide underwent the coupling reaction, but the isolated yield was only 52%.

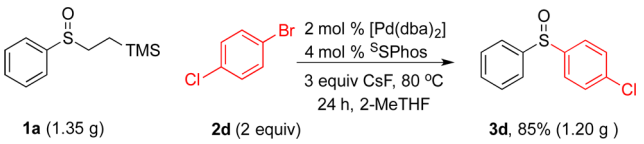
Scheme 4. Substrate Scope of Aryl 2-(Trimethylsilyl)ethyl Sulfoxides in Pd-Catalyzed Diaryl Sulfoxide Formation with Bromobenzene[a]



[a]Reaction conditions: **1** (0.5 mmol), **2q** (1.0 mmol), CsF (1.5 mmol), $Pd(dba)_2$ (0.01 mmol), ^{S}SPhos (0.02 mmol), 2-Me-THF (1 mL), 80 °C, 24 h. [b]**1** (0.1 mmol), **2q** (0.2 mmol), CsF (0.3 mmol), $Pd(dba)_2$ (0.005 mmol), ^{S}SPhos (0.01 mmol), 2-Me-THF (0.5 mL), 100 °C, 24 h.

To demonstrate the synthetic utility of this approach, we performed the coupling of 2-(trimethylsilyl)ethyl sulfoxide **1a** (6 mmol) with 4-chlorobromobenzene (**2d**) in 85% yield (1.20 g, Scheme 5).

Scheme 5. Gram-Scale Synthesis of 3d via Palladium-Catalyzed Diaryl Sulfoxide Generation



In summary, we introduce a palladium-catalyzed route to prepare diaryl sulfoxides from aryl 2-(trimethylsilyl)ethyl sulfoxides and aryl bromides. The aryl sulfenate anions were generated in situ by a fluoride-triggered elimination strategy under mildly basic conditions, enabling the synthesis of a wide range of functionalized diaryl sulfoxides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00073.

Procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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