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Palladium-catalyzed One-step Synthesis of Symmetrical Diaryl Sulfones from Aryl Halides and a Sulfur Dioxide Surrogate

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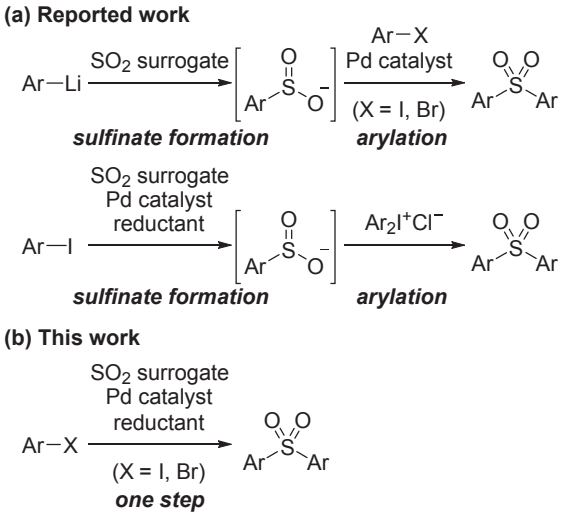
A convenient method for the one-step synthesis of symmetrical diaryl sulfones from aryl halides has been developed. A keystone of the method is the use of $K_2S_2O_5$, which can be easily and safely handled, as a sulfur dioxide surrogate. The palladium catalyst bearing P(*t*-Bu)$_3$ as a ligand enables formation of the desired sulfones without significant formation of byproducts.

Keywords: Sulfur dioxide | Palladium catalyst | Sulfone

Diaryl sulfones are an important class of compounds in various fields, including pharmaceuticals, electronic devices, and polymers.[1] Traditionally, these sulfones are synthesized via aromatic electrophilic substitution with arenesulfonyl halides or the oxidation of diaryl sulfides.[2] However, the former method requires handling of unstable sulfonyl halides, and the latter cannot be used for substrates with oxidation-sensitive functional groups. In addition, the sulfonyl halides or sulfides must first be prepared by methods in which the introduction of the sulfur groups is often tedious. Arylation of arenesulfinates with aryl halides is an alternative, emerging method that is useful for the synthesis of various diaryl sulfones,[3] although the preparation of the starting arenesulfinates, in many cases, also requires the use of sulfonyl halides or toxic sulfur dioxide (SO_2) gas.[4] Therefore, there is still a need to develop a convenient method for the synthesis of diaryl sulfones.

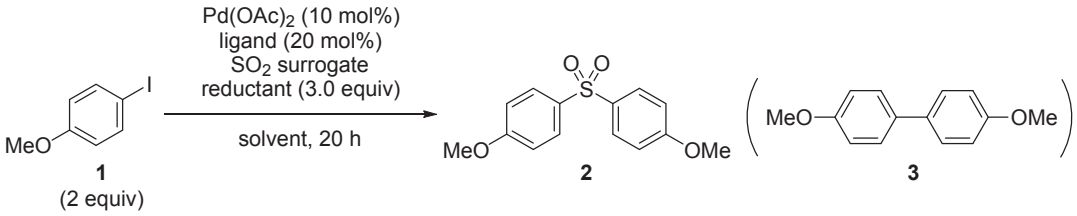
In the past decade, SO_2 surrogates,[5] such as DABSO (DABCO•2SO_2)[6] and potassium metabisulfite ($K_2S_2O_5$),[7] have been used for synthesis of sulfur-containing organic compounds. These surrogates are stable solids that are easily handled: SO_2 is generated by heating in the reaction vessel. Thus, the reaction can be set up without the need to handle toxic SO_2 gas. The use of SO_2 surrogates has also been reported for the synthesis of diaryl sulfones. In these reported examples, a two-step strategy that consisted of sulfinate formation and subsequent arylation was used (Scheme 1a).[8] The strategy can be conducted in one pot and applied for the synthesis of asymmetric sulfones, which have two different aryl groups. However, there are some drawbacks: strongly basic and nucleophilic organometals or expensive diaryliodonium salts have to be used. If both the sulfinate formation and the arylation steps are catalyzed by the same catalyst, diaryl sulfones could be synthesized from aryl halides in one step under relatively mild reaction conditions, without the use of organometals or iodonium salts (Scheme 1b). Recently, an excellent method for diaryl sulfone synthesis via sulfonylative Suzuki–Miyaura coupling was reported;[9] however, boronic acids must be used in this reaction. No methods have yet been reported for a one-step synthesis in which both the aryl groups of the diaryl sulfones are introduced directly using aryl halides. Herein, we report the Pd-catalyzed one-step synthesis of diaryl sulfones from aryl halides, using $K_2S_2O_5$ as an SO_2 surrogate. Although this method produces only symmetrical sulfones, the reaction can be conducted easily, and requires neither an organometallic substrate nor an iodonium salt.



Scheme 1. (a) Reported work on two-step synthesis of diaryl sulfones using an SO_2 surrogate. (b) One-step synthesis of diaryl sulfones (this work).

The reaction conditions of the sulfone synthesis were optimized by using 4-iodoanisole (**1**) as a model substrate (Table 1). Based on our previous work on the Pd-catalyzed synthesis of sulfonamides and sulfinamides,[13] we chose $K_2S_2O_5$ as an SO_2 surrogate and a tertiary amine as a reductant. When the reaction was conducted by using Pd(OAc)$_2$ as a catalyst, the HBF_4 salt of P(*t*-Bu)$_3$[14] as a ligand, $K_2S_2O_5$ as an SO_2 surrogate, and *i*Pr$_2$NEt as a reductant in toluene at 80 °C, a small amount (<15% yield) of the desired sulfone **2** was obtained (Entry 1). Among the solvents (Entries 2–5), DMSO and DMF were found to be promising. At higher temperatures, DMF produced better results than DMSO (Entry 6 vs. 7), and 100 °C was the optimal temperature (Entry 7 vs. 8). When the amount of $K_2S_2O_5$ was reduced, **2** was still obtained in good yields (Entries 9 and 10), suggesting that two equivalents of SO_2 are available from one equivalent of $K_2S_2O_5$. The optimal amount of $K_2S_2O_5$ was found to be 0.75 equivalent (Entry 9). Next, the effects of ligands were studied. In the absence of ligands, **2** was not obtained at all, and a significant amount of biaryl **3** was formed (Entry 11), indicating that the ligand plays an important role. Unexpectedly, the other ligands tested also failed to yield the sulfone, and **3** was obtained as the major product (Entries 12–20). It is of note that only P(*t*-Bu)$_3$ was effective for sulfone synthesis. We also tested other SO_2 surrogates, but better results were not obtained (Entries 21 and 22). Other reductants, such as NEt_3 and HCO_2Na, resulted in poorer yields (Entries 23 and 24); the

Table 1. Optimization of reaction conditions for diaryl sulfone synthesis.[a]



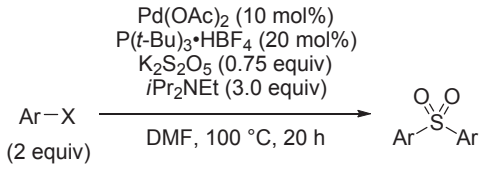
entry	ligand	SO_2 surrogate (equiv)	reductant	solvent	temperature (°C)	yield (%) $\mathbf{2}^b$	yield (%) $\mathbf{3}^c$
1	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (1.5)	*i*Pr$_2$NEt	Toluene	80	<15[d]	0
2	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (1.5)	*i*Pr$_2$NEt	*i*PrOH	80	<26[d]	trace
3	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (1.5)	*i*Pr$_2$NEt	MeCN	80	33	trace
4	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (1.5)	*i*Pr$_2$NEt	DMSO	80	49	2
5	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (1.5)	*i*Pr$_2$NEt	DMF	80	49	trace
6	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (1.5)	*i*Pr$_2$NEt	DMSO	100	51	6
7	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (1.5)	*i*Pr$_2$NEt	DMF	100	73	6
8	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (1.5)	*i*Pr$_2$NEt	DMF	110	72	9
9	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	81	7
10	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.50)	*i*Pr$_2$NEt	DMF	100	72	15
11	—	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	0	56
12	PPh_3	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	0	44
13	PCy_3	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	0	54
14	P(*c*-Pent)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	0	<52[d]
15	Ad_2PBu	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	5	64
16	JohnPhos	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	0	77
17	XPhos	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	trace	69
18	*t*-BuXPhos	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	7	69
19	DPPP (10 mol %)	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	0	51
20	SIPr·HCl	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	trace	59
21	P(*t*-Bu)$_3$·HBF$_4$	$Na_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	40	18
22	P(*t*-Bu)$_3$·HBF$_4$	DABSO (0.75)	*i*Pr$_2$NEt	DMF	100	6	42
23	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	NEt_3	DMF	100	14	29
24	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	HCO_2Na	DMF	100	21	3
25	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	—	DMF	100	trace	0
26[e]	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	89	trace
27[f]	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	0	0
28[g]	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	0	0
29[h]	P(*t*-Bu)$_3$·HBF$_4$	$K_2S_2O_5$ (0.75)	*i*Pr$_2$NEt	DMF	100	79	6

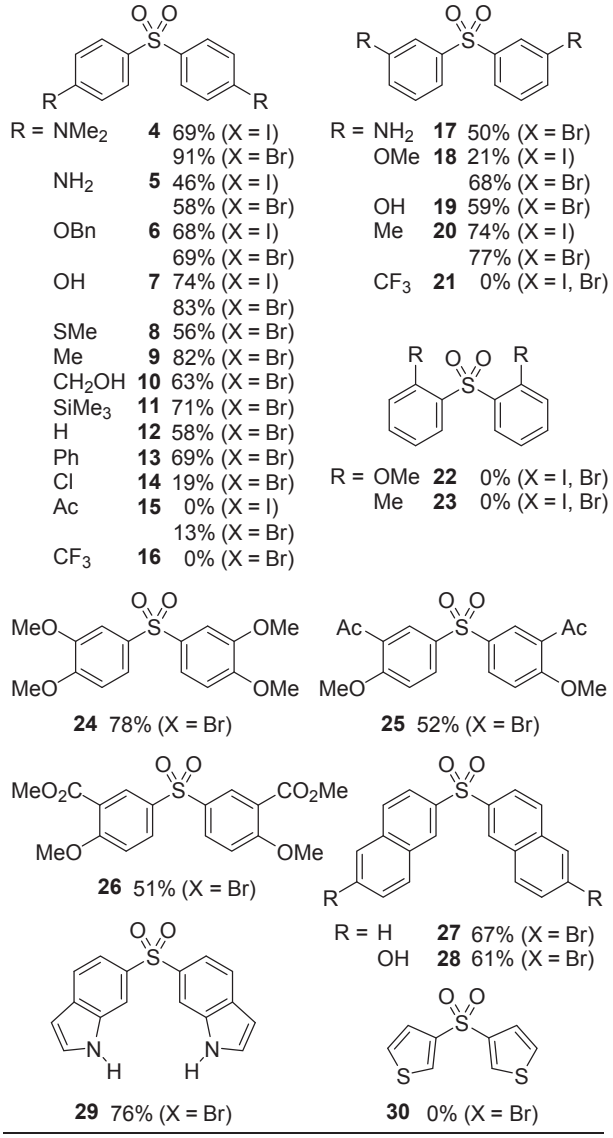
[a]The reaction was conducted using 0.4 mmol of **1** unless otherwise noted. [b]Isolated yield calculated as {2 × (moles of **2**)/(moles of **1** used)} × 100. [c]NMR yield. [d]Trace amounts of byproducts were present. [e]4-Bromoanisole was used instead of **1**. [f]4-Chloroanisole was used instead of **1**. [g]4-Methoxyphenyl triflate was used instead of **1**. [h]10 mmol of **1** was used. JohnPhos: 2-(di-*t*-butylphosphino)-biphenyl,[10] XPhos: 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl,[11] *t*-BuXPhos: 2-di-*t*-butylphosphino-2′,4′,6′-triisopropyl-biphenyl,[11] DPPP: 1,3-bis(diphenylphosphino)propane, SIPr·HCl: 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride.[12]

reaction hardly proceeded without reductant (Entry 25). To our delight, 4-bromoanisole also reacted to give **2**, with a higher yield under the best conditions (Entry 26), whereas the aryl chloride and triflate did not react (Entries 27 and 28). The optimized reaction conditions (Entry 9) were successfully applied to a 10 mmol-scale reaction (Entry 29).

With the optimized conditions determined, the scope of substrates for the sulfone synthesis was studied (Table 2). In most cases, the use of aryl bromides resulted in higher yields than aryl iodides, because the aryl iodides tended to form by-products such as the biaryls more than the aryl bromides did. The substrates with electron-donating and neutral substituents at the *para*-position gave the desired sulfones (**4**–**13**) in good yields. It should be mentioned that free amino and hydroxy groups were compatible with the conditions. Unfortunately, electron-withdrawing substituents, such as chloro, acetyl, and trifluoromethyl groups, significantly reduced the yield of the sulfones (**14**–**16**). These poor substrates mainly produced biaryl byproducts. This electronic effect of substituents was also observed for *meta*-substituted substrates; the sulfones with elec-

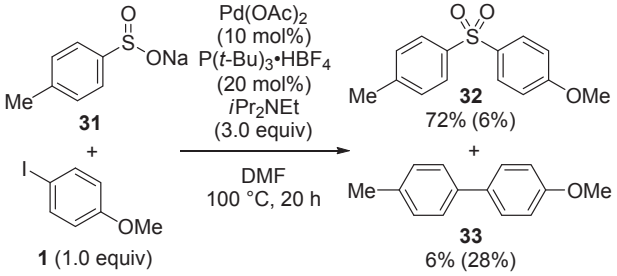
Table 2. Substrate scope for diaryl sulfone synthesis.



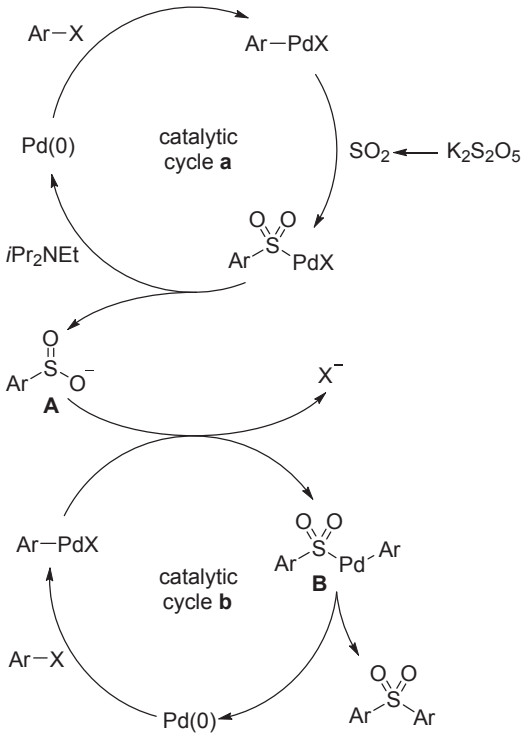


tron-donating groups (**17**–**20**) were obtained in good yields, whereas the trifluoromethylated sulfone **21** was not formed. Substituents at the *ortho*-position were detrimental, and the corresponding sulfones (**22** and **23**) were not obtained. Bromobenzenes with substituents at both the *para*- and *meta*-positions reacted without difficulty when the electron-donating methoxy group was located at the *para*-position (**24**–**26**). Naphthalene and indole derivatives successfully afforded the desired sulfones (**27**–**29**), whereas a thiophene derivative did not (**30**).

We assume that the reaction proceeds via an arenesulfinate as an intermediate. To support this hypothesis, the cross-coupling of sulfinate **31** with **1** was conducted under the reaction conditions without using the SO_2 surrogate (Scheme 2). The reaction indeed proceeded to give the desired sulfone **32** in good yield (72%). Interestingly, when JohnPhos[10] instead of P(*t*-Bu)$_3$ was used as the ligand, **32** was obtained in a very low yield (6%) and biaryl **33** was formed as the main byproduct (28%). These results suggest that both sulfones and biaryls are formed via the corresponding arenesulfinates.



Scheme 2. Reaction of sulfinate **31** with **1**. The yields in the reaction using JohnPhos instead of P(*t*-Bu)$_3$ are shown in parentheses.



Scheme 3. Proposed mechanism of sulfone formation.

The proposed reaction mechanism is shown in Scheme 3. Oxidative addition of the aryl halide and the subsequent insertion of SO_2, which is generated by heating of $K_2S_2O_5$, produce sulfinate **A** through catalytic cycle **a**. The Pd(II) species is finally reduced with *i*Pr$_2$NEt to afford Pd(0).[15] Sulfinate **A** then enters catalytic cycle **b** to undergo Pd-catalyzed arylation with another molecule of the aryl halide. Reductive elimination from the Pd species **B** gives the desired sulfone and Pd(0), completing catalytic cycle **b**. Biaryl byproducts, mainly observed in the reactions using ligands other than P(*t*-Bu)$_3$ or

substrates with electron-withdrawing groups, are presumably formed via desulfinylative coupling[16] between sulfinate **A** and the aryl halide. Therefore, it is assumed that the arylation of **A** without desulfinylation predominantly occurs only when P(*t*-Bu)$_3$ and substrates with electron-donating or neutral groups are used. Electron-withdrawing groups are likely to retard the reductive elimination from **B**, which has electron-withdrawing arenesulfonyl and aryl groups on the Pd atom. As a consequence, elimination of SO_2 gradually occurs from **B** to form diarylpalladium, which can now undergo reductive elimination to form the biaryl. Although further studies are needed to clarify the reasons for the unexpected effect of P(*t*-Bu)$_3$, it is clear that the successful sulfone formation is realized by a subtle balance between the steric and electronic properties of the ligands and substrates.

In summary, a one-step synthesis of symmetrical diaryl sulfones from aryl halides was achieved by using a Pd catalyst bearing P(*t*-Bu)$_3$. In addition to aryl iodides, bromides can also be used. The reaction is assumed to proceed via Pd-catalyzed sulfinate formation and arylation steps, both of which are facilitated only by using P(*t*-Bu)$_3$ as the ligand. Although the scope of substrates described at present is limited, the findings presented here will contribute to further progress in metal-catalyzed reactions with SO_2 surrogates.

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