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Unsymmetrical Diaryl Sulfones through Palladium-Catalyzed Coupling of Aryl Iodides and Arenesulfinates

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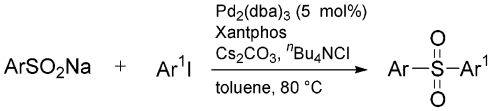
ABSTRACT



The palladium-catalyzed coupling of aryl iodides and arenesulfinates provides a simple and extremely efficient new route to unsymmetrical diaryl sulfones, usually isolated in high yield. The reaction tolerates a variety of functionalized aryl iodides, including those containing ether, ester, and nitro groups. The best results have been obtained by using Pd$_2$(dba)$_3$, Xantphos, Cs$_2$CO$_3$, and ^{n}Bu$_4$NCl in toluene at 80 °C.

Because of their chemical properties[1] and biological activities,[2] diaryl sulfones are important synthetic targets. Recently, diaryl sulfones have been shown to inhibit the HIV-1 reverse transcriptase and represent an emerging class of substances able to address the toxicity and resistance problems of nucleoside inhibitors.[3]

Known procedures for their preparation are based on the oxidation of the corresponding sulfides,[4] the electrophilic aromatic substitution of arenes with arenesulfonic acids in the presence of strong acids[5] or with arenesulfonyl halides,[6] and the reaction of organomagnesium halides[7] or organolithium compounds[8] with sulfonate esters. All these procedures have their own drawbacks: the oxidation process is limited by the availability of sulfides; the electrophilic approach suffers from the formation of mixtures of isomeric products and inefficiency with arenes bearing strongly electron-withdrawing substituents, and employment of organometallic reagents does not tolerate many functionalities. Recently, a copper-mediated displacement reaction of non-activated aryl iodides with arenesulfinates has been described.[9] However, an excess of copper iodide is required. Improved methods for the preparation of diaryl sulfones is therefore highly desirable.

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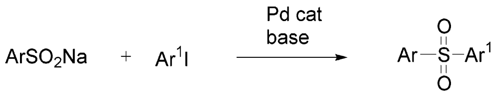
Here we report that aryl iodides form diaryl sulfones through a novel palladium-catalyzed reaction employing a straightforward procedure (Scheme 1).

Scheme 1



1 2 3

Direct palladium-catalyzed replacement of the aryl C−I bond by a C−SO$_2$ bond is, to our knowledge, unprecedented. This is in sharp contrast to analogous processes involving the substitution of the aryl C−I bond with an aryl C−heteroatom bond such as C−N,[10] C−PR$_2$,[11] C−PO(OR)$_2$[11c,12] and C−SR[13] bonds, which have been used extensively in organic synthesis. We discovered that the palladium-catalyzed coupling of aryl iodides and arenesulfinates provides an extremely efficient route to unsymmetrical diaryl sulfones.

Initial attempts focused on exploring the feasibility of the transformation. *p*-Iodoanisole and the commercially available sodium *p*-toluenesulfinate were used as the model system. Reactions were carried out using Pd$_2$(dba)$_3$ as the precatalyst, K$_2$CO$_3$, Rb$_2$CO$_3$, or Cs$_2$CO$_3$ as the bases, and a variety of phosphine and carbene ligands at temperatures ranging from 40 to 80 °C. However, no sulfone product was formed with PPh$_3$, (*o*-tol)$_3$P, (2-furyl)$_3$P, (*p*-MeO−C$_6$H$_4$)$_3$P, [2,4,6-(MeO)$_3$−C$_6$H$_2$]$_3$P, (*p*-Cl−C$_6$H$_4$)$_3$P, BINAP, MOP, dppp, dppb, and 1,3-bis-(2,4,6-trimethylphenyl)imidazolium chloride.[14]

Only after switching to Xantphos [9,9-dimethyl-4,6-bis-(diphenylphosphino)xanthene][15] did the desired sulfone product form in satisfactory yield within 8 h (Table 1, entry 1). The yield increased to 90% in 1 h by adding 1.2 equiv of ^{n}Bu$_4$NCl (Table 1, entry 3). Lower reaction rate and yield were observed with K$_2$CO$_3$ (Table 1, entry 6) and Rb$_2$CO$_3$ (Table 1, entry 7) or upon substituting LiCl for ^{n}Bu$_4$NCl (Table 1, entry 8). Use of more polar solvents such as DMSO, DMF, and DME proved to be unsuccessful. In DMF, formation of small amounts of toluenesulfinic acid 4-methoxyphenyl ester (derived from the competing O-arylation process) was observed.

Table 1. Bases and Salts in the Reaction of *p*-Iodoanisole and Sodium *p*-Toluenesulfinate **1** in the Presence of Pd$_2$(dba)$_3$ and Xantphos to Give *p*-Methoxyphenyl Tolyl Sulfone.[a]

entry	Xantphos	Cs$_2$CO$_3$	salt	*T* (°C)	time (h)	yield (%)[b]
1	+	Cs$_2$CO$_3$		80	8	70
2	+		^{n}Bu$_4$NCl	80	24	49
3	+	Cs$_2$CO$_3$	^{n}Bu$_4$NCl	80	1	90[c]
4	−	Cs$_2$CO$_3$		80	36	
5	−			80	48	
6	+	K$_2$CO$_3$	^{n}Bu$_4$NCl	80	6	58
7	+	Rb$_2$CO$_3$	^{n}Bu$_4$NCl	80	6	76
8	+	Cs$_2$CO$_3$	LiCl	80	48	31
9	+	Cs$_2$CO$_3$	^{n}Bu$_4$NCl	40	24	80
10	+	Cs$_2$CO$_3$	^{n}Bu$_4$NCl	60	4	81

[a] Reactions were conducted on a 0.350 mmol scale in starting aryl iodides in toluene (2 mL) under argon using the following molar ratio: **1**:*p*-iodoanisole:Pd$_2$(dba)$_3$:Xantphos:base:^{n}Bu$_4$NCl or LiCl (when added) = 1.2:1:0.025:0.05:1.5:1.2. [b] Yields are given for isolated products. [c] *p*-Methoxyphenyl tolyl sulfone was isolated in 81% yield (6 h) by using lithium *p*-toluenesulfinate.

Under the best conditions developed so far [Pd$_2$(dba)$_3$, Xantphos, Cs$_2$CO$_3$, ^{n}Bu$_4$NCl, toluene, 80 °C],[16] the reaction proceeds very smoothly and, as shown in Table 2, appears to tolerate a variety of functional groups in the aryl iodides, including ether, ester, and nitro groups. Unsymmetrical diaryl sulfones were isolated usually in high yields with many neutral, electron-rich, and electron-poor aryl iodides. Only *p*-iodoacetophenone, among the substrates that we have investigated, produced a complex reaction mixture (most probably as a result of ketone arylation processes)[17] that we have not further investigated. The presence of substituents

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(16) **Typical Procedure for the Preparation of Unsymmetrical Diaryl Sulfones.** In a Carousel Tube Reaction (Radley Discovery), to a solution of sodium *p*-toluenesulfinate (0.075 g, 0.420 mmol) and *p*-iodoanisole (0.082 g, 0.350 mmol) in 2.0 mL of toluene under argon were added Pd$_2$(dba)$_3$ (0.008 g, 0.009 mmol), Xantphos (0.010 g, 0.018 mmol), Cs$_2$CO$_3$ (0.171 g, 0.525 mmol), and ^{n}Bu$_4$NCl (0.117 g, 0.420 mmol). The mixture was warmed at 80 °C and stirred for 1 h. After cooling, the reaction mixture was diluted with ethyl acetate, washed with water, dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The reaction mixture was purified by chromatography (silica gel, 35 g; 80/20 v/v *n*-hexane/ethyl acetate) to give 0.0825 g of *p*-methoxyphenyl *p*-tolyl sulfone (90% yield): mp 103−4 °C; IR (KBr) 2925, 1320, 1152; ^{1}H NMR (CDCl$_3$) δ 7.57−7.44 (m, 4H), 7.25 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H); 3.86 (s, 3H); 2.40 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 159.0, 138.1, 136.4, 133.8, 129.5, 128.0, 126.7, 114.2, 55.4, 21.1. Anal. Calcd for C$_{14}$H$_{14}$O$_3$S: C, 64.10; H, 5.38. Found: C, 64.01; H, 5.36.

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Table 2. Palladium-Catalyzed Synthesis of Diaryl Sulfones from Aryl Iodides **2** and Sodium *p*-Toluenesulfinate **1**

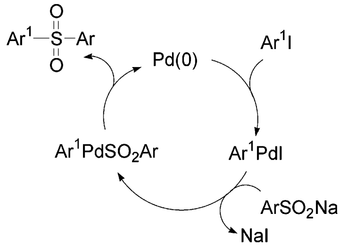
entry	Ar^1I **2**	time (h)	diaryl sulfone **3** yield (%)
1	p-MeO−C_6H_4−I	1	90
2	m-MeO−C_6H_4−I	1	88
3	o-MeO−C_6H_4−I	24	
4	p-Me−C_6H_4−I	6	96
5	m-Me−C_6H_4−I	1	93
6	o-Me−C_6H_4−I	24	
7	3,5-Me_2−C_6H_3−I	1	85
8	PhI	1	90
9	p-F−C_6H_4−I	1	89
10	m-F−C_6H_4−I	5	90
11	o-F−C_6H_4−I	24	
12	p-Cl−C_6H_4−I	3	81
13	m-CF_3−C_6H_4−I	24	46
14	p-Br−C_6H_4−I	1	67
15	p-EtO_2C−C_6H_4−I	6	65
16	p-O_2N−C_6H_4−I	1	72

[a] Reactions were conducted on a 0.350 mmol scale in starting aryl iodides in toluene (2 mL) at 80 °C under argon using the following molar ratio: **1**:**2**:$Pd_2(dba)_3$:Xantphos:Cs_2CO_3:$^nBu_4NCl$ = 1.2:1:0.025:0.05:1.5:1.2. [b] Yields are given for isolated products.

close to the C−I bond was found to hamper the reaction (Table 2, entries 3, 6, and 11).

A possible rationale for the presented synthesis of diaryl sulfones involves the following basic steps (the ligand has been omitted for clarity): (a) oxidative addition of aryl iodide to Pd(0), (b) nucleophilic displacement of iodide to give an arylsulfonylpalladium intermediate, and (c) reductive elimination of a Pd(0) species to give the sulfone product (Scheme 2).

Scheme 2



In conclusion, we have developed an efficient and straightforward procedure for the preparation of unsymmetrical diaryl sulfones. The methodology can tolerate many important functional groups, and diaryl sulfones are usually isolated in high yield. Further work is in progress along this line.

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Supporting Information Available: Experiments conducted to evaluate the influence of ligands and solvents on the reaction outcome, typical experimental procedure for the preparation of unsymmetrical diaryl sulfones, and characterization data for all compounds listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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