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Unsymmetrical Diaryl Sulfones through Palladium-Catalyzed Coupling of Aryl Boronic Acids and Arylsulfonyl Chlorides

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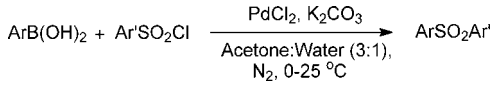
ABSTRACT



A simple and efficient method for the synthesis of unsymmetrical diaryl sulfones using the palladium-catalyzed coupling of aryl boronic acids and arylsulfonyl chlorides has been developed. High product yields, a short reaction time, and mild reaction conditions are important features of this method.

Organosulfones are important intermediates in organic synthesis[1] because of their chemical properties[2] and biological activities.[3] Diaryl sulfones are important synthetic targets and widely used synthons for synthetic organic chemists due to their many industrial applications.[4] These are useful in the practice of medicinal chemistry because the sulfone functional group is found in numerous drugs, including the recently developed selective COX-2 inhibitor Vioxx.[5] Diphenyl sulfone is used as an intermediate for the synthesis of 4,4′-diamino-diphenyl sulfone (DAPSONE), which is effective for leprosy treatment.[6] Recently, diaryl sulfones have been shown to inhibit HIV-1 reverse transcriptase and represent an emerging class of substances able to address the toxicity and resistance problems of nucleoside inhibitors.[7]

Sulfones are generally prepared by oxidation of the corresponding sulfides and sulfoxides or by a displacement

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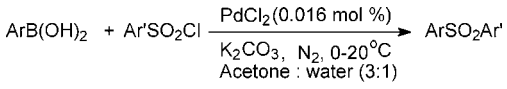
reaction of sodium arenesulfinate with an appropriate alkyl halide.[8] The electrophilic aromatic substitution of arenes with arenesulfonic acids in the presence of strong acids[9] or with arenesulfonyl halides[10] and the reaction of organomagnesium halides[11] or organolithium compounds[12] with sulfonate esters are known procedures for their preparation. Some metal halides,[1a] zeolites,[13] Bronsted acids,[14] bismuth triflate,[15] indium triflate,[16] and Fe(III)-exchanged montmorillonite clay[17] have been successfully used for catalytic sulfonylation of arenes. Lithium perchlorate[18] and sodium perchlorate[19] have been used as efficient catalysts under neutral conditions. More recently, sulfones were prepared from sulfinic acid salts and aryl iodides using copper[20] and palladium catalysts.[21] Each of the above methods has its own merit, while some of these methods are plagued by limitations. Most of the methods require drastic conditions. The electrophilic approach required strong protic or Lewis acids and suffers from the formation of mixtures of isomeric products and inefficiency with arenes bearing strongly electron-withdrawing substituents. The application of organometallic reagents does not tolerate the presence of many functional groups elsewhere in the molecule. The well-known Suzuki reaction[22] of aryl iodides with an aryl sulfinate required more than stoichiometric amounts of copper iodide (1.5 equiv) and arene sulfinate (1.6 equiv) in DMF at 110 °C. However, the use of an excess amount of copper complicates the workup of large-scale reactions. The recently developed copper-catalyzed method[20] for the coupling of aryl iodides and sulfinic acid salts required high temperatures (110 °C) and a longer reaction time (20 h) and afforded poor yields for heterocyclic substrates. The palladium-catalyzed coupling required not only drastic conditions but also addition of xantphos and $^{n}Bu_4NnCl$,[21] and the presence of substituents close to the C−I bond was found to hamper the reaction.[21] Consequently, there is an opportunity for further development toward mild conditions, increased variation of the substituents in the components, and better yields.

In this communication, we report that diaryl sulfones are prepared using palladium-catalyzed coupling of aryl boronic acids with arylsulfonyl chlorides under mild conditions (Scheme 1).

Scheme 1



1 **2** **3**

The catalytic activity of the $PdCl_2$ was investigated with respect to the loadings. After many studies on coupling reaction, we found that when less than 1.6 mol % $PdCl_2$ was applied, it resulted in no reaction or in low yield of the corresponding product (Table 1, entries 2−5), whereas use of more than 1.6 mol % did not improve the yield (Table 1, entries 7, 8). When attempts were made to carry out coupling reaction in the absence of catalyst ($PdCl_2$), it resulted in almost quantitative recovery of the substrate (Table 1, entry1). A wide variety of electronically and structurally diverse aryl boronic acids and aryl sulfonyl chlorides can be cross-coupled efficiently under mild reaction conditions[23] (Tables 2 and 3). The palladium-catalyzed coupling of aryl boronic acids with aryl sulfonyl chlorides was found to be an extremely efficient route for the synthesis of unsymmetrical diaryl sulfones. Various substituted aryl boronic

Table 1. Catalytic Effect of $PdCl_2$ in the Coupling Reaction of Phenyl Boronic Acid (1 mmol) with *p*-Toluenesulfonyl Chloride (1 mmol) at 25 °C

entry	$PdCl_2$ (mol %)	reaction time (min)	yield (%)
1	0	960	0
2	0.6	30	0
3	0.8	30	0
4	1.1	30	55
5	1.4	30	68
6	1.6	30	98
7	2.3	30	98
8	2.8	30	97

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(23) **Typical Procedure.** To a mixture of benzene boronic acid (121 mg, 1 mmol), *p*-toluene-sulfonyl chloride (190 mg, 1 mmol), and K_2CO_3 (276 mg, 2 mmol) in acetone/water (3:1, 10 mL) at 0 °C was added palladium chloride (3 mg, 0.016 mmol), and stirring was continued at room temperature under a N_2 atmosphere. The reaction was monitored by TLC. After completion of the reaction after 30 min, the solvent was removed under reduced pressure. Distilled water (10 mL) was added to the reaction mixture, and the product was extracted with petroleum ether (40−60 °C) and washed with water (2 × 10 mL). The removal of the solvent under reduced pressure yielded the product, which was found to be pure with no need for further purification. Phenyl *p*-tolyl sulfone: mp 120−121 °C (lit.[12] 119−122); IR (KBr) 1091, 1340, 1596, 2922, 3092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.5 (s, 3 H, Ar−CH_3), 6.95 (d, 2 H, J = 8.7 Hz, Ar−H), 7.4−7.43 (m, 5 H, Ar−H), 7.47 (d, 2 H, J = 8.7 Hz, Ar−H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 127.2, 127.5, 129.7, 129.9, 132.8, 138.5, 141.5, 143.7. Anal. Calcd for $C_{13}H_{12}O_2S$: C, 61.21; H, 5.21; S, 13.80. Found: C, 61.11; H, 5.26; S, 13.69.

Table 2. Palladium-Catalyzed Synthesis of Diaryl Sulfones from Aryl Boronic Acids and Aryl Sulfonyl Chlorides at 25 °C

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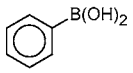
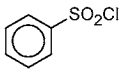
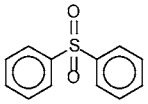
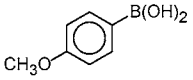
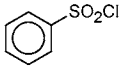
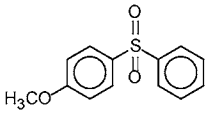
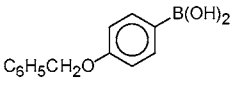
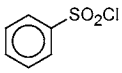
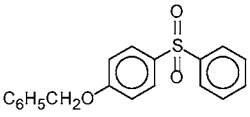
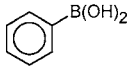
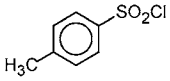
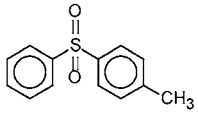
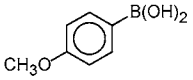
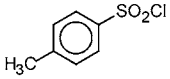
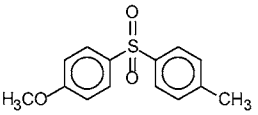
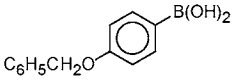
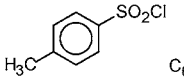
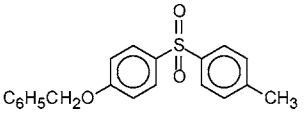
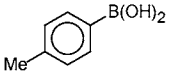
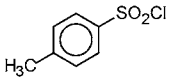
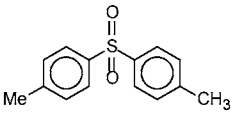
1				35	94
2				25	98
3				15	98
4				30	98
5				25	98
6				15	97
7				15	96

acids were subjected to coupling with arylsulfonyl chlorides, and the results are presented in Table 2. When boronic acids with electron-donating substituents were subjected to the coupling, the rate of the coupling process was increased (Table 2, entries 2, 3, 5, 6) as compared to unsubstituted aryl boronic acids (Table 2, entries 4, 6). It is important to mention that, in general, the time required for coupling in the present method is short as compared to the reported methods. It is worth mentioning that only cross-coupled products were obtained and that self-coupling of boronic acids or formation of diarylsulfide was not observed even in trace amounts under these reaction conditions, which demonstrates the superiority of this method over the existing methods.[24,25]

It is important to note that the coupling proceeds smoothly in the absence of ligand. The present procedure worked very well in the case of ortho-substituted boronic acids as well as heterocyclic boronic acids, resulting in excellent yields of products in a short reaction time (Table 3). Mild reaction conditions and short reaction times in an acetone−water cosolvent system are important advantages of this method over the reported ones. When acetone or water alone was used as a solvent, there was no reaction, even after stirring the reaction mixture for a longer time (16 h). All cross-coupling reactions have been carried out under a nitrogen atmosphere. When attempts were made to carry out reactions in the absence of the nitrogen atmosphere, the cross-coupling reactions did not proceed even after the reaction mixture was stirred for a longer period of time (16 h). However, the reaction mixture became black in color.

More recently, Dabbaka and Vogel reported palladium-catalyzed Suzuki−Miyaura cross-couplings of sulfonyl chlorides and boronic acids[25] as well as palladium-catalyzed Stille

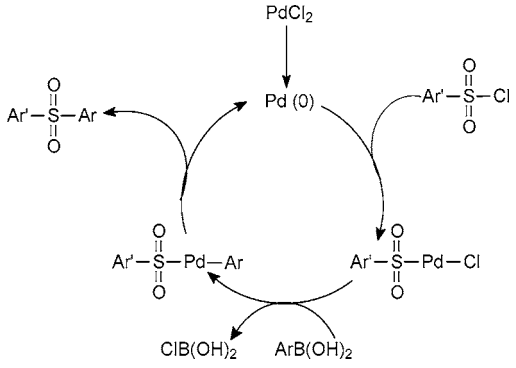
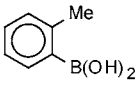
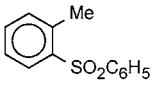
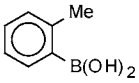
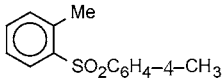
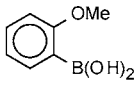
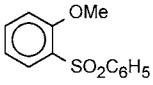
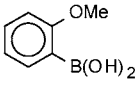
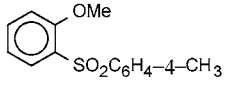
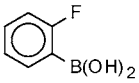
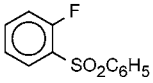
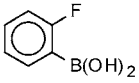
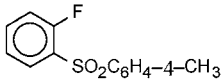
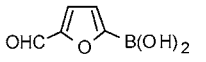
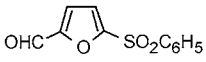
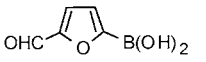
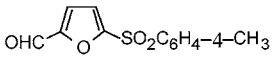
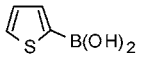
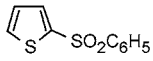
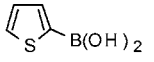
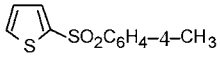
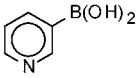
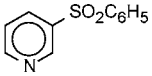
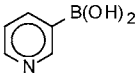
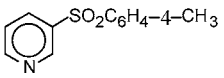


Figure 1.

Table 3. Palladium-Catalyzed Coupling of Ortho-Substituted Aryl Boronic Acids, Heteroaryl Boronic Acids, and Aryl Sufonyl Chlorides at 25 °C

entry	arylboronic acid	aryl sulfonyl chloride	diaryl sulfone	time (min)	yield (%)
1		$C_6H_5SO_2Cl$		50	94
2		$4\text{-}CH_3C_6H_4SO_2Cl$		60	93
3		$C_6H_5SO_2Cl$		55	91
4		$4\text{-}CH_3C_6H_4SO_2Cl$		70	88
5		$C_6H_5SO_2Cl$		60	85
6		$4\text{-}CH_3C_6H_4SO_2Cl$		65	90
7		$C_6H_5SO_2Cl$		60	82
8		$4\text{-}CH_3C_6H_4SO_2Cl$		75	80
9		$C_6H_5SO_2Cl$		50	85
10		$4\text{-}CH_3C_6H_4SO_2Cl$		55	87
11		$C_6H_5SO_2Cl$		60	88
12		$4\text{-}CH_3C_6H_4SO_2Cl$		70	82

cross-coupling of sulfonyl chlorides and organostannanes[26] at high temperatures and using long reaction times. However, the results were very interesting and contrast the results presented here. Vogel described both Stille and Suzuki-type cross-couplings of boronic acids with sulfonyl chlorides, but the products were biaryls after extrusion of SO_2. However, the present results demonstrate simple cross-couplings without extrusion of SO_2. Desulfitative coupling required higher temperatures than the simple coupling. After palladium insertion into the SO_2-Cl bond, if conditions are not adapted for a competitive desulfitation, the sulfur can be retained in the Suzuki coupling. The present procedure involved mild reaction conditions (0−25 °C) as compared to procedure applied by Vogel (110 °C).[25] A probable catalytic cycle for Suzuki−Miyaura cross-couplings of boronic acids and sulfonyl chlorides to prepare diaryl sulfones is given in Figure 1. Work is in progress in our laboratory to develop mild procedures for various Suzuki−Miyaura cross-couplings.

Supporting Information Available: Experimental procedures, characterization of unknown compounds, and references to known procedures and known physical constants of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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