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A General Copper-Catalyzed Sulfonylation of Arylboronic Acids

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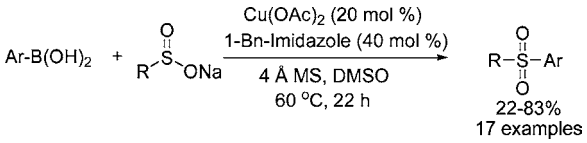
ABSTRACT



A general copper-catalyzed method for the sulfonylation of arylboronic acids with sulfinate salts is described. A variety of alkyl–aryl, diaryl, and alkyl–heteroaryl sulfones were synthesized in good yield.

The synthesis of sulfones has drawn much attention over the years since they constitute useful building blocks in organic chemistry as well as in medicinal chemistry. Because of their chemical properties[1] and promising biological activities,[2] especially, aryl and diaryl sulfones have emerged as important synthetic targets in recent years. As an example, aryl sulfones are the main constituent of many drugs, such as the selective COX-2 inhibitor Vioxx[3] (**1**) and the prostaglandin D_2 (DP) antagonist MK-0524 (**2**),[4] whereas the diaryl sulfones **3** 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 (Figure 1).[5]

Known procedures for aryl sulfone preparation are based on the oxidation of the corresponding sulfides,[6] the electro-

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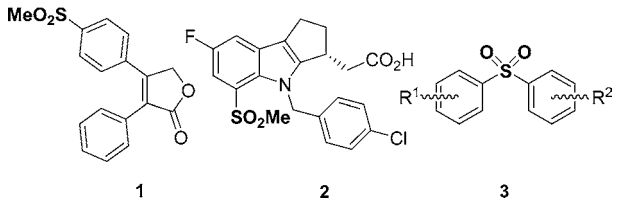
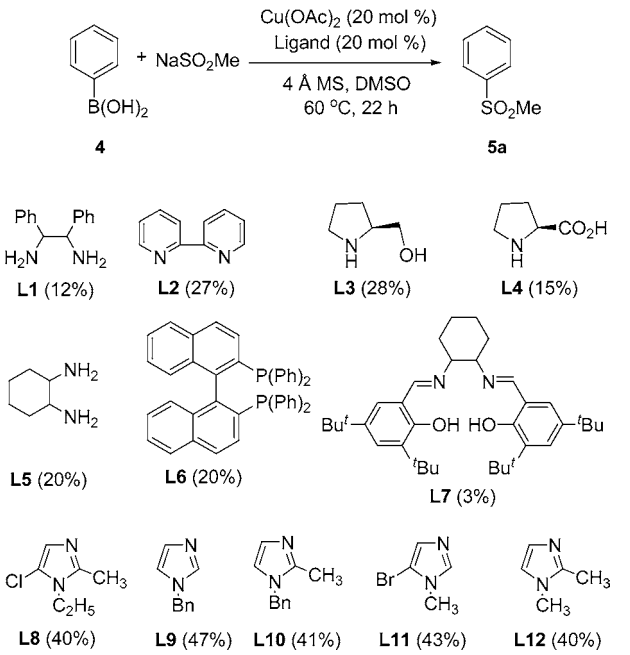


Figure 1. Structures of Vioxx (**1**), MK-0524 (**2**), and diaryl sulfones **3**.[3−5]

philic aromatic substitution of arenes with arenesulfonic acids in the presence of strong acids[7] or with arenesulfonyl halides,[8] the reaction of carbon electrophiles with sulfinate salts,[9] and the reaction of organomagnesium halides[10] or organolithium compounds[11] with sulfonate esters. All these simple and attractive procedures have their own drawbacks, mainly due to the incompatibility with numerous functional groups such as amines, olefins, and some nitrogen heterocycles. Over the past decade, there has been a significant improvement in metal-mediated coupling of sulfinic acid salts with aryl halides and triflates[12] as well as arylboronic acids with sulfonyl chlorides[13] as alternatives to these conventional methods. However, the scope is limited to aryl bromides/iodides or triflates, and the use of air- or moisture-sensitive reagents is sometimes not avoidable. Recently, a copper-mediated oxidative coupling reaction of arylboronic acid with sulfinic acid salt was described.[14] However, an excess of copper acetate (with respect to the arylboronic acid) was required. Hence, improved methods for the preparation of diaryl sulfones are therefore highly desirable. In recent years, we have applied catalytic reactions to the synthesis of new pharmacologically interesting compounds.[15] On the basis of our previous work on copper-catalyzed reactions,[16] we thought that the use of an appropriate ligand or additive would enable us to realize a catalytic version of the

Scheme 1. Catalytic Sulfonylation with Different Ligands (GC Yield)[a]



[a] Reaction conditions: see Supporting Information.

sulfonylation of boronic acids to synthesize aryl sulfones (Scheme 1). With the wide variety of commercially available boronic acids and esters as well as the metal-catalyzed direct C−H bond functionalization to the not easily accessible boronates,[17] catalytic sulfonylation of these boron-containing compounds should be very versatile for the preparation of sulfones. In light with these issues, here we report the first copper-catalyzed oxidative coupling of arylboronic acids with sulfinic acid salts. In our prototypical reaction, phenylboronic acid and sodium methanesulfinate were reacted at 60 °C in anhydrous DMSO in air in the presence of $Cu(OAc)_2$, a ligand, and K_2CO_3 as base. The initial screening of the

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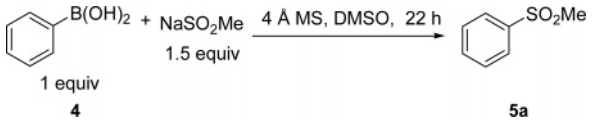
ligands clearly showed that the reaction can be performed catalytically with 20 mol % of $Cu(OAc)_2$. We have tested different ligand types in our model reaction. Among these ligands, tetradentate and bidentate N ligands gave poor results irrespective of their donor atom and capacity. We realized that only monodentate ligands can stabilize the generated copper species for the required transformation, and indeed, N-protected imidazoles were found to be the most suitable ligands for this reaction with a loading of 20 mol % with respect to the substrate.

In fact, when the ligand loading was increased to 40 mol %, a substantial amount of conversion was observed and the corresponding methyl sulfone was isolated in 64% yield (Table 1). Following a previously reported protocol using a

Table 1. Cross-Coupling Reaction between Arylboronic Acid and Sodium Methanesulfinate[a]



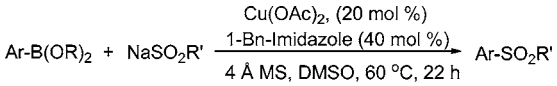
entry	$Cu(OAc)_2$	1-benzylimidazole	temp	GC yield (%)
1	1.1 equiv	–	rt	59
2	20 mol %	20 mol %	60 °C	47
3	20 mol %	40 mol %	60 °C	**64**

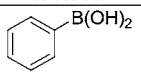
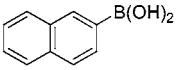
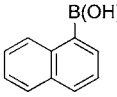
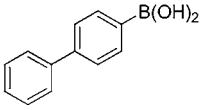
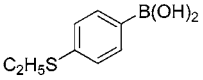
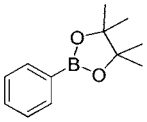
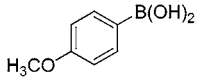
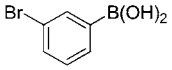
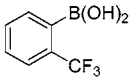
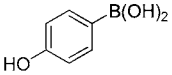
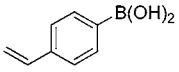
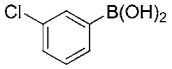
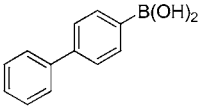
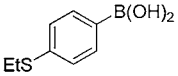
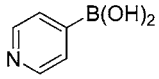
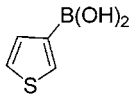
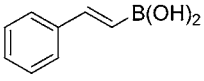
[a] Reaction conditions: see Supporting Information.

stoichiometric amount of copper at room temperature,[12] the same substrate gave only 59% of the desired product. These results indicate that our catalytic system is even slightly more efficient than the reported stoichiometric conditions. Reactions with different additives, such as $(CH_3)_4NBr$, CsF, chloramine-T, and 1,4-benzoquinone, were also performed in the presence or absence of ligand; however, none of them were able to improve the yield significantly. Further optimization showed the best catalytic system was defined as follows: 0.5 mmol of boronic acid, 1.5 equiv of sulfinic acid salt, 20 mol % of $Cu(OAc)_2$, 40 mol % of 1-benzylimidazole, 2 equiv of K_2CO_3, and 1.25 g of molecular sieves (4 Å) at 60 °C in anhydrous DMSO in a flask equipped with an air drying tube. To the best of our knowledge, this is the first example of copper-catalyzed sulfonylation of an arylboronic acid.

A variety of aryl sulfones have been prepared employing these reaction conditions, as shown in Table 2. This cross-coupling reaction is quite general and can be easily applied to a wide range of arylboronic acids. Both electron-rich and electron-deficient substrates reacted with almost similar ease, and the substrate variety indicates that the substitution pattern in the aromatic ring does not have significant influence in the reaction outcome. Bromo and chloro substituents on the boronic acid part are also tolerated under the reaction conditions, which could extend the scope of further functionalization on the aromatic ring. The reaction also proceeded with pinacol boronate ester with good yield (Table 2, entry 6). Reaction of the 2-trifluoromethylphenylboronic acid is noteworthy. In spite of the presence of a strong

Table 2. Catalytic Sulfonylation of Boronic Acids[a]



entry	substrate	R′	product	isolated yield (%)
1		Me	**5a**	64
2		Me	**5b**	70
3		Me	**5c**	64
4		Me	**5d**	69
5		Me	**5e**	83
6		Me	**5a**	71
7		Me	**5f**	68
8		Me	**5g**	70
9		Me	**5h**	43
10		Me	**5i**	27
11		Me	**5j**	50
12		Me	**5k**	52
13		Tol	**5l**	59
14		Ph	**5m**	44
15		Me	**5n**	22
16		Me	**5o**	54
17		Me	**5p**	65

[a] Reaction conditions: see Supporting Information.

electron-withdrawing group at the *ortho* position, it reacted smoothly to provide the corresponding sulfone (Table 2, entry 9). Of particular interest is the reaction with 4-vinylphenylboronic acid to the corresponding methyl sulfone. Although the starting material polymerized, we were able to obtain a moderate product yield (Table 2, entry 11). Under the same reaction conditions, we were able to couple 4-hydroxyphenylboronic acid to the corresponding methyl sulfone, but only with moderate yield, most probably because of the reduction of the in situ generated arylcopper species (Table 2, entry 10).[18]

The same method can also be extended to synthesize diaryl or heteroaryl substrates, which are of particular interest for potential drug applications. Arylsulfinate salts were efficiently coupled with arylboronic acids to provide diaryl sulfones in good yields following the same reaction procedure (Table 2, entries 13 and 14). Similarly, this reaction was also possible with heterocyclic substrates, such as thiophene-3-boronic acid and pyridine-4-boronic acid, though the yields were somewhat lower (Table 2, entries 15 and 16). This method is also applicable to a vinyl sulfone. As an example, phenylvinylboronic acid was coupled successfully to give the corresponding vinyl methyl sulfone in good yield (Table 2, entry 17).

In summary, we have developed an efficient and general method for a copper-catalyzed synthesis of methyl−aryl, aryl−aryl, and heteroaryl sulfones with various functional groups, which can also be extended to the preparation of vinyl sulfones. Further studies to increase the catalytic activity are currently underway in our laboratory.

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Supporting Information Available: A typical experimental procedure and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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