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#### Letter

# One-Pot Sulfonamide Synthesis Exploiting the Palladium-Catalyzed Sulfination of Aryl Iodides

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Dedicated, with best wishes, to Professor Steven Ley on the occasion of his 70th birthday



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Abstract Aryl ammonium sulfinates, conveniently prepared from aryl iodides and the sulfur dioxide surrogate DABSO, under the action of a palladium(0) catalyst, are transformed in a one-pot process to a variety of functionalized sulfonamides. The sulfinate to sulfonamide transformation is achieved by simple treatment with an aqueous solution of the relevant amine and sodium hypochlorite (bleach). A broad range of amines, including anilines, and amino acid derivatives, are combined efficiently with a variety of aryl iodides, leading to sulfonamides in high yields.

Key words sulfonamides, palladium catalysis, sulfinates, amines, aryl halides

Some of the features that contribute to sulfonamide groups finding wide application in pharmaceuticals and agrochemicals include their chemical and metabolic stability, three-dimensional structure, polarity, and connectivity. These properties have resulted in sulfonamide-containing molecules being developed as treatments for a broad range of indications (Figure 1).<sup>1</sup> Aryl and heteroaryl sulfonamides are prominent amongst these molecules and are usually prepared from the combination of an aryl (or heteroaryl) sulfonyl chloride and an amine.<sup>2</sup> This is an effective and reliable process, although it does have limitations. For example, certain heteroaryl sulfonyl chlorides are unstable, and ready access to the desired sulfonyl chloride is also needed.

Sulfonyl chlorides are most often prepared from the electrophilic sulfonylation of an arene, using either [HSO<sub>3</sub>]<sup>+</sup> or [ClSO<sub>2</sub>]<sup>+</sup> synthons as the electrophile.<sup>3</sup> Again, these are well-established reactions, but the products accessible can be limited by the inherent characteristics of aromatic elec-





trophilic substitution reactions, in that only certain substrates are sufficiently reactive to undergo the reactions, and only certain substitution patterns are straightforward to achieve. An alternative approach relies on the preparation of an aryl thiol, followed by exhaustive oxidation of the thiol to the corresponding sulfonyl chloride.<sup>4</sup> This approach avoids the limitations imposed by aromatic electrophilic substitution reactivity, but instead involves the preparation of a potentially odorous thiol and the use of strong oxidizing conditions, which can often limit functional-group compatibility. A conceptually different approach involves transforming a pre-activated, nucleophilic arene into a sulfinate, and then directly converting the sulfinate into the desired sulfonamide. Such an approach would avoid both electrophilic aromatic substitution chemistry, and the need to prepare thiol intermediates. By careful choice of the type of nucleophilic arenes used, it should be possible to employ readily available substrates such as Grignard reagents, potentially allowing access to different areas of chemical space to those achievable using sulfonyl chloride chemistry.5,6

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We have recently shown that a variety of metal sulfinates can be readily obtained from the combination of a preformed organometallic reagent and the sulfur dioxide surrogate (DABCO)(SO<sub>2</sub>)<sub>2</sub>,<sup>7</sup> DABSO (Scheme 1, a).<sup>8</sup> Organolithium, organozinc, and Grignard reagents could all be successfully used. The metal sulfinates could then be treated with an aqueous solution of an amine and sodium hypochlorite (bleach) to provide the corresponding sulfonamide.<sup>9</sup> The method is straightforward to perform and was used to prepare a broad range of sulfonamides, and was also adapted to an array format. However, the need to use a preformed organometallic reagent does impose limitations on compatible functional groups, with base-sensitive and highly electrophilic functionalities not being suitable. To address the limitations imposed by the use of preformed organometallics, we have also explored methods starting from benign substrates such as aryl halides and then catalytically generating reactive organometallic intermediates for reaction with SO<sub>2</sub>-surrogates.<sup>10,11</sup> In this context, we have shown that it is possible to access a wide range of aryl ammonium sulfinates from the combination of aryl iodides and DABSO using palladium(0) catalysis (Scheme 1, b).<sup>12</sup> We were able to demonstrate that the ammonium sulfinate intermediates could be converted into a range of derivatives, mostly sulfone based, but including a single sulfonamide example. The sulfonamide was obtained by treatment of the ammonium sulfinate with sulfuryl chloride, followed by addition of an amine. The need to employ sulfuryl chloride, a notoriously sensitive reagent that requires frequent purification, represents a significant limitation to this method. Shavnya and Mascitti have described related chemistry,<sup>13</sup> in which catalytically generated sodium sulfinates are converted into sulfonamides by treatment with NBS and an amine.<sup>14</sup> In these cases the sulfonamides were obtained in only moderate (37-65%) yields. Given our convenient and high-vielding sulfonamide synthesis starting from preformed organometallics, and our success in producing ammonium sulfinates from aryl iodides using palladium catalysis, we were attracted to the merger of the two methods, to deliver a general sulfonamide synthesis that uses aryl halides as substrates (Scheme 1, c). This Letter documents the successful realization of this goal.

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The main issue in merging the two DABSO-based methods was reconciling the different solvents used in the two transformations: the palladium-catalyzed ammonium sulfinate formation was performed in isopropanol,<sup>11</sup> while the Grignard addition to DABSO had employed THF as solvent,<sup>8</sup> before addition of an aqueous amine/hypochlorite solution. Using the coupling of 4-iodotoluene, DABSO and morpholine as a test reaction we evaluated different solvent combinations (Scheme 2). Pleasingly, the simplest experimental conditions proved effective, as performing the initial catalytic sulfinate formation in isopropanol and then adding an aqueous solution of morpholine and sodium hypochlorite directly to this allowed the target sulfonamide 3a to be isolated in 90% yield. Experiments that removed the isopropanol after the first step, and then added a second solvent with the amine, were uniformly less successful. For example, using only water for the second step resulted in <5% of the sulfonamide, while employing CH<sub>2</sub>Cl<sub>2</sub> delivered the sulfonamide in 73% yield.

We next explored the variation that was possible for the aryl iodide substrate, using morpholine as the constant amine component (Table 1). A variety of neutral and electron-donating substituents performed well, with *ortho*, *meta*, and *para* substitution all possible (entries 1–5). The successful inclusion of the *para*-SMe derivative is notable (en-



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try 5), as the preparation of products featuring *S* functionality at differing oxidation levels can be challenging using traditional methods.





<sup>a</sup> Reaction conditions:  $Pd(OAc)_2$  (5 mol%),  $PAd_2Bu$  (7.5 mol%), DABSO (0.6 equiv),  $Et_3N$  (3.0 equiv), *i*-PrOH (0.2 M), 75 °C, 16 h, then morpholine (3 equiv), NaOCl (10.3% aq solution, 2 equiv), r.t., 90 min. <sup>b</sup> NCS (2 equiv) used in place of NaOCl.

A para-hydroxyl substituent was successfully incorporated into the sulfonamide product, providing a good illustration of a substrate that would likely be incompatible with the Grignard-based method (entry 6). Electron-withdrawing substituents, including halides, were also efficient substrates, providing sulfonamides in good yields (entries 7–12). Amongst these examples are several substrates that are potentially susceptible to nucleophilic addition from preformed organometallics (ester, nitrile, ketone; entries 10–12). It should be noted that NCS was employed as the oxidant with the ketone example, as hypochlorite delivered only a poor yielding reaction. A simple heterocycle (entry 13) and a 1-naphthyl (entry 14) example are also shown to work well.

Variation of the amine component is shown in Scheme 3. Primary amines generally performed well (**4a–d**); notable amongst this group are several that feature potentially sensitive functionality, including an acetal (**4b**), a trisubstituted alkene (**4c**), and a pyridyl group (**4d**). Cyclopropane and cyclobutane-substituted amines delivered the targeted sulfonamides, although in slightly reduced yields (**4e,f**). Aniline derivatives could also be successfully employed as substrates (**4g,h**). Finally, amino acid derivatives could be employed, allowing the corresponding sulfonamides to be isolated in reasonable yields (**4i***j*). The reactions to prepare sulfonamides **4d** and **4j** were both performed on a 4.23 mmol scale (1.0 g of aryl iodide), demonstrating that synthetically useful scales are not problematic.

In conclusion, we have shown that a variety of aryl sulfonamides can be prepared from aryl iodides, the SO<sub>2</sub> surrogate DABSO, and amines. The aryl iodide substrates first undergo conversion to an ammonium sulfinate intermediate using a palladium(0)-catalyzed sulfination. Addition of an aqueous solution of the amine and sodium hypochlorite then provides the desired sulfonamides. The reactions are straightforward to perform, tolerate a variety of acidic and

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electrophilic functional groups on the arene, as well as encompassing the use of both primary and secondary amines, anilines, and amino acid derivatives.



**Scheme 3** Scope of the amine component in one-pot sulfonamide formation. *Reagents and conditions*:  $Pd(OAc)_2$  (5 mol%),  $PAd_2Bu$  (7.5 mol%), DABSO (0.6 equiv), Et<sub>3</sub>N (3.0 equiv), *i*-PrOH (0.2 M), 75 °C, 16 h, then amine (3 equiv), NaOCl (10.3% aq solution, 2 equiv), 0 °C to r.t., 45 min to 3.5 h. <sup>a</sup> The reaction was performed on 4.23 mmol scale (1.0 g) of starting aryl iodide. <sup>b</sup> Additional amine (3.0 equiv) and NaOCl (2.0 equiv) added after 2 h. <sup>c</sup> The solvent from first step was removed and replaced by water. The ee of the methyl ester derivative was confirmed by chiral HPLC to be >99%.

#### General Procedure for the Formation of Sulfonamides Using Morpholine, Exemplified by the Preparation of 4-Tosylmorpholine 3a

An oven-dried glass reaction tube was charged with the relevant aryl iodide (4-iodotoluene) (87 mg, 0.40 mmol, 1 equiv), DABSO (58 mg, 0.24 mmol),  $Pd(OAc)_2$  (5.0 mg, 20.0 µmol, 5 mol%), and CataCXium A (11.0 mg, 31.6 µmol, 7.5 mol%), sealed with a rubber septum and flushed with nitrogen. Under positive pressure of nitrogen, Et<sub>3</sub>N (168 µL, 1.20 mmol, 3 equiv), and anhydrous 2-PrOH (1.5 mL) were added sequentially through the septum. The reaction mixture was then immersed in a preheated oil bath at 75 °C for 16 h. The formation of the ammonium sulfinate and the disappearance of the aryl iodide are easily followed by HPLC. After cooling to r.t., the relevant amine (morpholine) (104 µL, 1.20 mmol, 3 equiv) and previously titrated 10.31% w/w aq NaOCI (0.47 mL, 0.80 mmol, 2 equiv) were added sequentially through the septum and stirred at r.t. for 90 min until consumption of the sulfinate was observed by HPLC. Upon completion, the reaction

mixture was filtered through Celite and the filter washed with acetone until disappearance of the brown color. The organic solution was then concentrated and the residue purified by flash chromatography with silica gel under standard eluent mixtures [typically EtOAc in PE (40–60 °C bp PE)]. The products were dried under high vacuum and analyzed by NMR and IR spectroscopy and MS.

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## Supporting Information

Supporting information for this article is freely available online at http://dx.doi.org/10.1055/s-0035-1560578 and includes experimental procedures and associated characterization data.

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