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Synthesis of Aryl Sulfonamides via Palladium-Catalyzed Chlorosulfonylation of Arylboronic Acids

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Abstract

A palladium-catalyzed method for the preparation of sulfonamides is described. The process exhibits significant functional group tolerance and allows for the preparation of a number of arylsulfonyl chlorides and sulfonamides under mild conditions.

The medical significance of aryl sulfonamides can be traced to the 1930's, with the discovery and development of the first commercially available antibiotics, the so-called sulfa drugs.[1] Today, the presence of sulfonamides in medicinal agents is widespread; close to ten percent of the top 100 pharmaceuticals prescribed in 2011 either bear a sulfonamide subunit or are co-administered with a sulfonamide-containing drug.[2] In general, aryl sulfonamides can be prepared by the straightforward reaction of a sulfonyl chloride with an amine.[3] However, the difficulties associated with sulfonamide synthesis stem not from the amination reaction, but from the preparation of sulfonyl chlorides themselves. Two types of processes represent the current state of the art in arylsulfonyl chloride synthesis: (1) electrophilic aromatic substitution (EAS) with chlorosulfonic acid[4] and (2) oxidative chlorination of organosulfur compounds.[5–9] The use of both approaches suffers from significant limitations. In particular, the acidic conditions required for EAS processes (and most oxidative chlorination methods) impose severe restrictions on substrate scope. Furthermore, desired substitution patterns may be inaccessible via EAS because the regioselectivity is dictated by the intrinsic properties of the parent arene. Traditionally, oxidative chlorination involves the use of hazardous reagents (e.g., aqueous chlorine)[6] or strong chlorinating agents (e.g., $SOCl_2$[7] and SO_2Cl_2).[8] Although milder conditions have been reported,[9] oxidative chlorination of thiophenol derivatives ultimately requires prior formation of a carbon–sulfur bond. [10–11]

In principle, a transition metal catalyst could obviate the need for such reagents and permit the convergent synthesis of sulfonamide analogs, allowing variation of both sulfonyl (–SO_2–) substituents. Unfortunately, success in this area of catalysis is limited to a single Pd-catalyzed aminosulfonylation process, initially reported by Willis in 2010, to prepare *N*-amino-sulfonamides (**1**) from aryl iodides and hydrazines (Eq. 1).[12] While this example represents an important achievement in sulfonylation chemistry, amine nucleophiles remain incompatible with these types of couplings.[12–13] To address this limitation, we devised an alternative strategy (Eq. 2), which involves oxidative addition of LPd(0) to an electrophile of the type X–SO_2–X′ (**A**), where X and X′ represent leaving groups of different reactivity.

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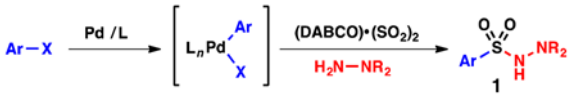
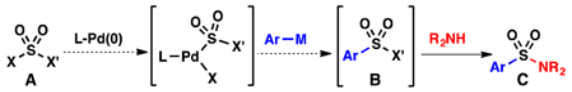
Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare the following competing financial interest(s): MIT has patents on ligands that are described in the paper from which S.L.B. receives royalty payments.

Subsequent coupling with an organometallic nucleophile would afford electrophilic species **B**, which, in turn, would serve as a direct precursor to the sulfonamide product (**C**).



Willis and coworkers (Eq. 1)



Our approach (Eq. 2)

Early in the investigation, we selected arylboronic acids as coupling partners due to their compatibility with other functional groups, ready availability, and ease of handling. Upon examining the reaction sequence from a retrosynthetic perspective, we envisioned exploiting arylsulfonate esters (**3**, Scheme 1)[14] as the immediate precursors to sulfonamides, and thus potential targets for Suzuki-Miyaura cross-coupling. In turn, we proposed that sulfonate esters (**3**) could be prepared from an aryl chlorosulfate derivative (**2**)[15] via Pd-catalysis. However, contrary to our expectations, we discovered serendipitously that this coupling process generates arylsulfonyl chlorides (**4**) in preference to **3**, and we describe herein the development and scope of a Pd-catalyzed chlorosulfonylation reaction.

Initial experiments focused on identifying conditions to prepare **3a** from the simplest aryl chlorosulfate, phenyl chlorosulfate (**2a**, Table 1), which is an easy to prepare, easily handled liquid.[16] Results from a preliminary survey of bases are outlined in Table 1, utilizing 4-methoxyphenylboronic acid in combination with a catalyst derived from Pd(OAc)$_2$ and *tert*-BuBrettPhos (**L8**) or DavePhos (**L1**). Unexpectedly, we observed mixtures of **3a** and the corresponding sulfonyl chloride (**4a**) when excess oxygen base was used (entries 1–3). More importantly, we discovered that **4a** could be formed exclusively in the absence of base (entries 4 & 5), and that neither product is formed in the absence of Pd or phosphine ligand.[17] Additional control experiments verified that aryl sulfonate esters (**3**) are not converted to the corresponding sulfonyl chlorides (**4**) under the reaction conditions;[18] conversely, ester **3a** is generated when crude reaction mixtures of **4a** are treated with excess K_3PO_4 or K_2CO_3 (following complete consumption of **2a** in the absence of base).

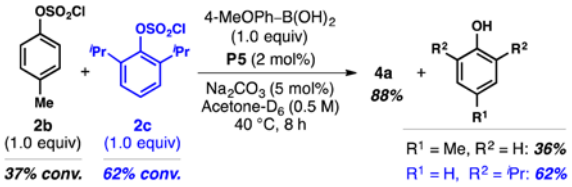
The above results suggest a catalytic cycle in which Pd(0) inserts into the SO_2–OPh bond of **2a** in preference to the SO_2–Cl bond (Figure 1).[19] The phenoxy substituent of the resulting Pd-sulfinate complex (**6**) would be expected to facilitate transmetallation without the aid of an oxygen base;[20] subsequent reductive elimination from **7** would yield **4** and regenerate the active Pd(0) catalyst. Oxygen bases likely promote the release of phenoxide, which in turn would react with the sulfonyl chloride to provide **3**. Examination of the chemical literature revealed that Buncel and coworkers have also observed the displacement of aryloxide from aryl chlorosulfate derivatives (**2**), but in the context of direct nucleophilic additions.[15,21] Nonetheless, this precedent demonstrates the lability of the SO_2–OPh bond, as we have observed for the transfer of –SO_2Cl in the analogous Pd-catalyzed process.

In light of these results, we focused our efforts on the preparation of sulfonyl chlorides as they represent ideal precursors to sulfonamides. However, the system represented in Table 1, entry 5 proved ineffective for both electron-deficient and *ortho*-substituted substrates. For example, subjecting 2-methoxyphenylboronic acid to these conditions resulted in near complete recovery of phenyl chlorosulfate (**2a**). Further optimization revealed that yields of aryl-sulfonyl chlorides could be increased by employing anhydrous acetone as solvent in combination with a catalytic amount of Na_2CO_3 (5 mol %). Although $Pd(OAc)_2$ proved to be a competent palladium source, the use of palladacyclic precatalysts[22] (**P1**–**P7**) allowed for these experiments to be conducted at lower temperatures. As exemplified in the coupling of **2a** with 2-methoxyphenylboronic acid (Figure 2), precatalysts based on diphenyl-(**L3** and **L5**) and di-*tert*-butylbiaryl phosphine ligands (**L2** and **L7**) proved to be the most effective. In particular, the PhCPhos precatalyst (**P5**) afforded **4b** in the highest yield (82%), albeit with only a slight improvement over that derived from *tert*-BuDavePhos, **L2** (80%). In contrast, the use of XPhos (**L6**),[23] previously reported to be an excellent ligand for Suzuki-Miyaura reactions, provided little product.[24]

With this improved protocol, utilizing 2 mol % **P5** and 5 mol % of Na_2CO_3 in acetone, we prepared and isolated a number of sulfonyl chlorides in good yields (Table 2). In general, electron-rich, -neutral and -deficient arylboronic acid reagents represent compatible substrates. Couplings with electron-rich substrates can be conducted at 50 °C, while reactions with electron-deficient substrates are typically slower and require higher temperatures.[25–26] While most of the sulfonyl chlorides are stable to chromatography, electron-deficient compounds, such as **4h** and **4j**, were found to decompose to varying degrees upon attempted purification.[27] Thus to circumvent this problem, the sulfonyl chloride intermediates were converted to sulfonamides (**5a–m**) directly by simply adding a primary or secondary amine to the crude reaction mixtures of **4** (Table 3).[28] Weakly nucleophilic aniline derivatives may also be incorporated into the sulfonamide moiety, but pyridine is required to facilitate amination in these cases. As illustrated in Tables 2 and 3, the chlorosulfonylation reaction tolerates chloro-, bromo-, and iodo-substituted arylboronic acids as well as substrates containing TBS-ethers, ester and acetyl functional groups. Heteroaryl substrates, such as 3-thiophene and 2-dibenzofuran boronic acid, also represent suitable coupling partners.[29]

Several additional features of this chemistry are noteworthy. First, Pd(0) reacts with phenyl chlorosulfate (**2a**) in preference to aryl iodide groups bearing electron-withdrawing sulfonyl groups *para* to the iodo-substituents (*e.g.*, **4e** and **5i**). Second, while others have demonstrated that arylsulfonyl chlorides *themselves* are efficient cross-coupling partners for various Pd-catalyzed processes,[30–32] these intermediates are essentially unreactive under the chlorosulfonylation conditions. Third, palladium typically catalyzes the *desulfonylation* of arylsulfonyl chlorides; as a result, these substrates (**4**) are often used as aryl halide equivalents for carbon–carbon bond-forming processes.[32] In contrast, the Pd-catalyst derived from **L5** promotes carbon– sulfur bond formation, thus enabling the installation of a sulfonyl chloride ($–SO_2Cl$) functional group.[33] Finally, regarding the oxidative addition step, we surmised that the sp^3 oxygen atom of **2a** might direct the insertion of Pd(0) into the proximal $PhO–SO_2$ bond; however, results from a competition experiment between **2b** and the bulkier **2c** (Eq. 3) revealed that **2c** is slightly more reactive than **2b** (ratio of recovered **2b**/**2c** = 1.7:1).[34] Moreover, this counterintuitive trend in reactivity is not specific to Pd-catalysis. For example, reacting a 1:1 mixture of **2b** and **2c** with piperidine (Eq. 4) resulted in a comparable ratio of recovered **2b**/**2c** (1.6:1) along with formation of the sulfamoyl chloride (**8**) derived from piperidine. To explain the displacement of phenoxide from non-catalyzed nucleophilic additions to **2**, Buncel has invoked an S_N2 mechanism in which elongation of the S–O bond relieves considerable strain in the bipyramidal transition state;

according to the authors, such relief of strain would not accompany partial rupture of the S–Cl bond.[21] In this regard, increasing the size of the aryloxy substituent of **2** may intensify this stereoelectronic effect and further weaken the S–O bond.



(Eq. 3)

(Eq. 4)

In summary, we demonstrated that phenyl chlorosulfate (**2a**) represents an excellent $[SO_2Cl]^+$ synthon in the context of Pd-catalyzed Suzuki-Miyaura cross-coupling. The chlorosulfonylation reaction exhibits considerable functional group tolerance and the transformation is inherently regioselective; the substitution patterns of many of the products shown (such as **4h**–**4j**) cannot be accessed by EAS processes. Furthermore, the sulfonyl chloride intermediates can be derivatized *in situ* and isolated as the corresponding sulfonamides. Therefore, both the aryl and amine components of arylsulfonamides can be installed in a single synthetic operation from readily available reagents. Investigations aimed at broadening the scope of this transformation and further delineating the mechanism of sulfur-oxygen bond scission are currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. Alternatively, sulfonyl compounds can be prepared in one-pot from Grignard additions to SO_2 (see refs 8a-b), but subsequent chlorination requires SO_2Cl_2, which readily chlorinates aromatic rings.
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16. Phenyl chlorosulfate is prepared by reacting phenol SO_2Cl_2 and pyridine at −78 °C. Compound **2a** is stable in neat form for at least one year when stored at 4 °C.
17. No reaction was observed when solutions of 4-methoxyphenylboronic acid (1.5 equiv) and **2a** (1.0 equiv) in toluene or 1,4-dioxane were stirred at 110 °C for 24 h.
18. Subjecting a phenyl sulfonate ester (**3**) to the reaction conditions in the presence of **2a** and $ArB(OH)_2$ resulted in complete recovery of **3**. See Supporting Information for details.
19. An alternative mechanism might involve reversible oxidative addition to **2a**, with transmetallation occurring at the –OPh group of **7** in preference to the –Cl group of the related Pd-Cl species. Oxidative addition is typically considered an irreversible process, although examples of reductive elimination of aryl halides have been reported. See: Roy AH, Hartwig JF. Organometallics. 2004; 23:1533.Newman SG, Lautens M. J Am Chem Soc. 2010; 132:11416. [PubMed: 20681622]
20. Alkoxo- and (phenoxo)Pd(II) complexes are known to undergo efficient transmetallation without the aid of base. For reviews and discussions, see: Miyaura N. J Organomet Chem. 2002; 653:54.Miyaura N, Suzuki A. Chem Rev. 1995; 95:2457.
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24. Similarly, little to no product was observed using SPhos or RuPhos ligands. For a review of Suzuki–Miyaura reactions employing dialkylbiaryl phosphine ligands, see: Martin R, Buchwald SL. Acc Chem Res. 2008; 41:1461. [PubMed: 18620434]
25. Both Pd(0) and phosphine ligands can potentially react with **4**; thus to limit product decomposition and promote complete conversion of **2a**, we chose to increase the reaction temperatures accordingly rather than adjust the respective catalyst loadings.
26. Electron-poor arylboronic acids typically undergo transmetallation at a slower rate than electron-neutral and electron-rich arylboronic acids.
27. The volatility of **4d–4i** may also contribute to lower yields.
28. The stoichiometry of the amine can be reduced to 1.2 equivalents if DIPEA is used as a sacrificial base. See conditions for product **5d** (Table 3).
29. Currently, boronic acids derived from nitrogen heterocycles do not couple in useful yields. This inefficiency is due to deboronation of the starting material and/or the instability of the corresponding sulfonyl chlorides. See: Caldwell WT, Kornfeld EC. J Am Chem Soc. 1950; 72:4890.
30. The order of reactivity of electrophiles for Suzuki-Miyaura cross-coupling is: ArI > **$ArSO_2Cl$** > ArBr ≫ ArCl (see ref 32c).
31. Aryl sulfonyl chlorides have been used as precursors to diaryl sulfones. See: Bandgar BP, Bettigeri SV, Phopase J. Org Lett. 2004; 6:2105. [PubMed: 15200296]
32. For examples of desulfonylative cross-couplings of sulfonyl chlorides to form C—C bonds, see: Miura M, Itoh K. Chem Lett. 1989; 18:77.Dubbaka SR, Vogel P. J Am Chem Soc. 2003; 125:15292. [PubMed: 14664564] Dubbaka SR, Vogel P. Org Lett. 2004; 6:95. [PubMed: 14703359] Dubbaka SR, Vogel P. Tetrahedron Lett. 2006; 47:3345.
33. We observe homocoupling (< 15% biaryl) of certain electron-deficient and *ortho*-substituted arylboronic acids (e.g. corresponding to **5f** and **5j**). This side reaction may occur at the expense of **2a** via an oxidative addition/desulfonylation pathway.
34. A control experiment in which **2c** is introduced after complete conversion of **2b** verified that **2c** is not converted to **2b**. See Supporting Information for details.

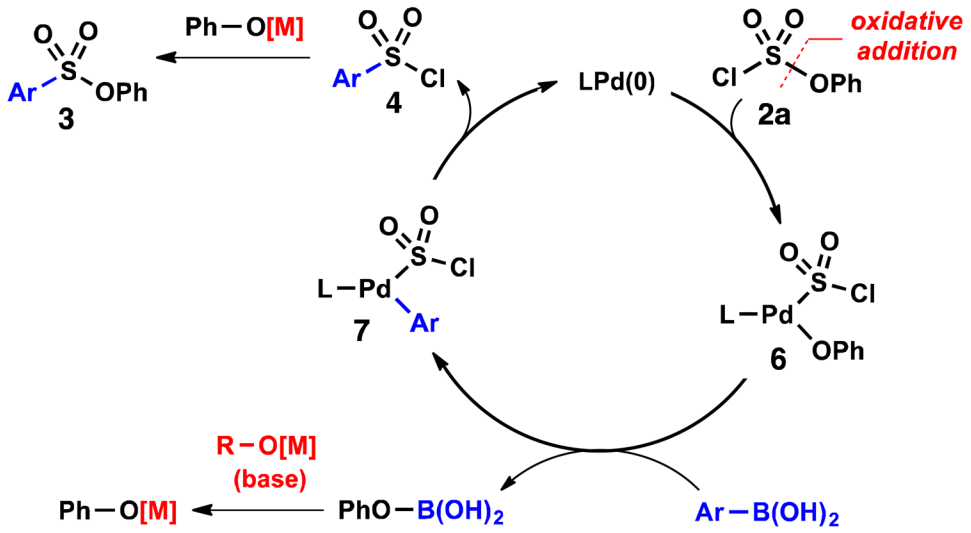


Figure 1.
Proposed Catalytic Cycle

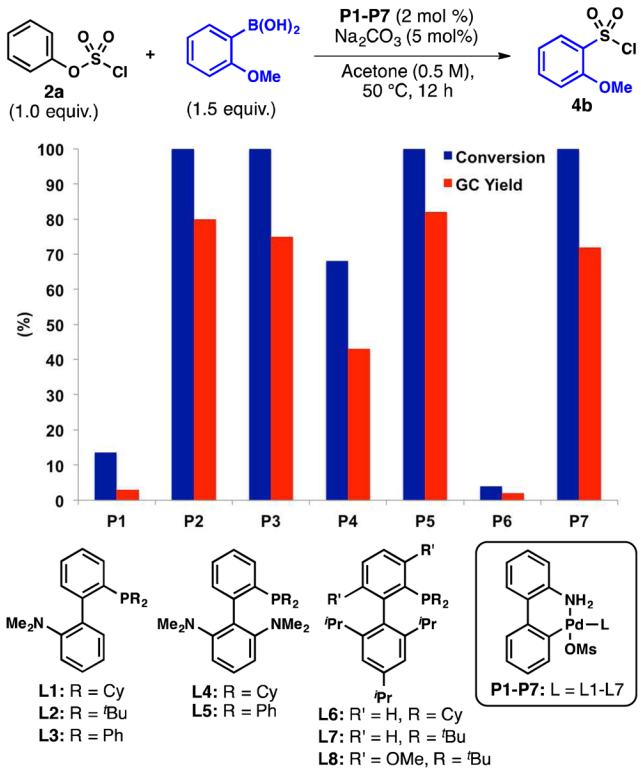
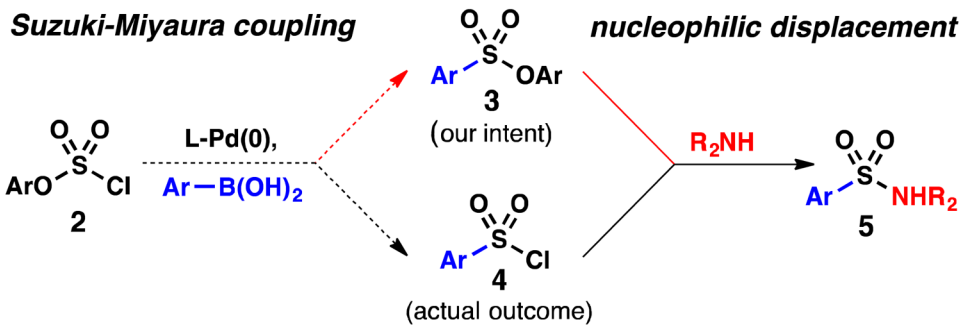


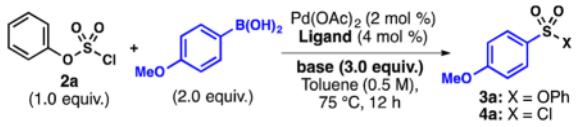
Figure 2.
Ligand Effects



Scheme 1.
Sulfonylation of Arylboronic Acids

Table 1

Pd-Catalyzed Chlorosulfonylation[a]



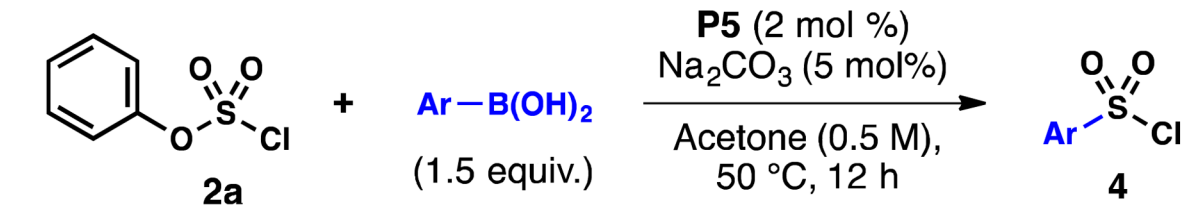
Entry	Ligand	Base	3a (%)[b]	4a (%)[b]
1	**L8**	K_3PO_4	31	4
2	**L8**	K_2CO_3	15	22
3	**L8**	Na_2CO_3	4	36
4	**L8**	none	0	59
5	**L1**	none	0	87

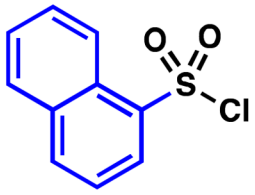
[a]Performed on a 0.5 mmol scale with respect to **2a**.

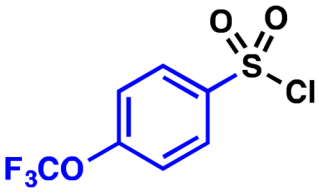
[b]GC yields.

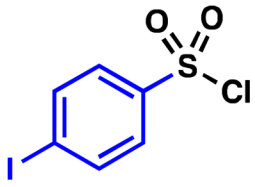
Table 2

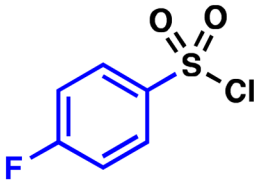
Chlorosulfonylation of Boronic Acids[a]

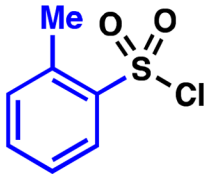


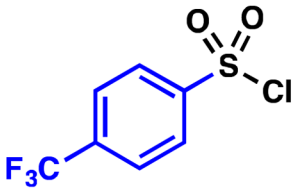


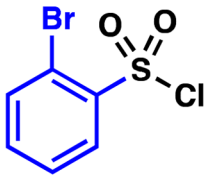


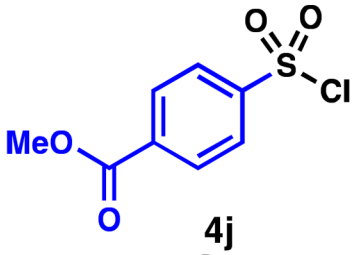








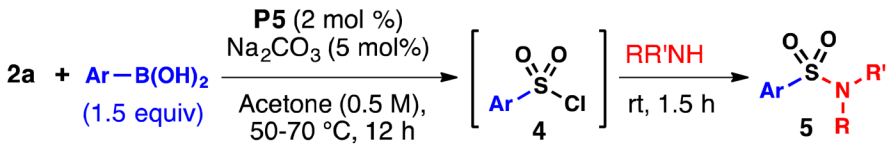


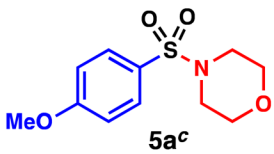


[a]Yields represent isolated yields (average of two runs): **2a** (1 mmol), $ArB(OH)_2$ (1.5 mmol), Na_2CO_3 (5 mol %), **P5** (2 mol %), degassed, anhydrous acetone (2 mL), 50–70 °C, 12 h.

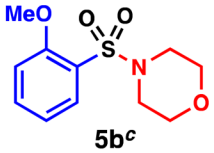
Table 3

Preparation of Sulfonamides

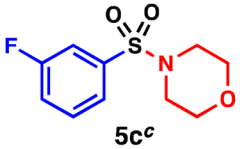




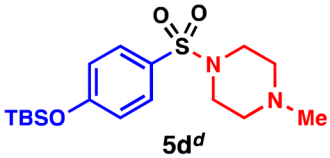
5a[c]
50 °C, 95%



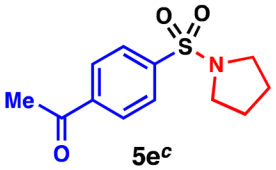
5b[c]
50 °C, 84%



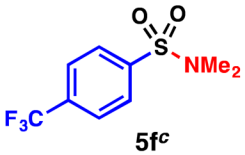
5c[c]
70 °C, 66%



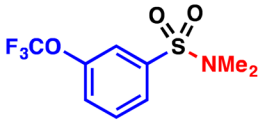
5d[d]
50 °C, 80%



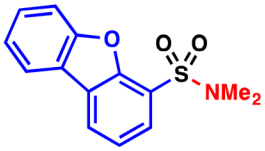
5e[c]
60 °C, 74%



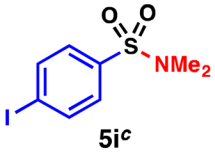
5f[c]
70 °C, 65%



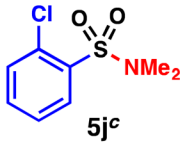
5g[c]
65 °C, 77%



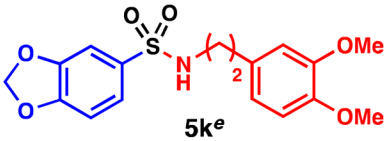
5h[c]
60 °C, 71%



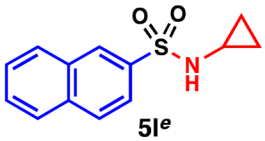
5i[c]
55 °C, 75%



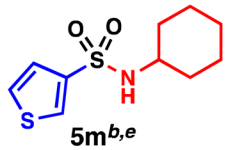
5j[c]
60 °C, 66%



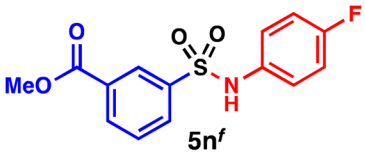
5k[e]
50 °C, 75%



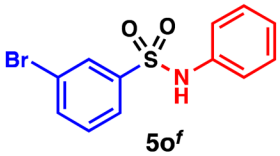
5l[e]
50 °C, 81%



5m[b,e]
55 °C, 70%



5n[f]
60 °C, 80%



5o[f]
55 °C, 83%

[a] Isolated yields (average of two runs). **Step 1:** See conditions in Table 2.

[b] **P4** (2 mol %) was used. **Step 2:**

[c] R_2NH (2.2 mmol), rt, 1.5 h.

[d] 1-methylpiperazine (1.2 equiv.) and DIPEA (2.0 equiv.) were used.

[e] RNH_2 (3.0 equiv.), rt, 1.5 h.

[f] $ArNH_2$ (1.2 equiv.), pyridine (3.0 equiv.), rt, 5 h.