Aryl, heteroaryl, and alkenyl sulfones play a prominent role in organic and medicinal chemistry. Not only are they versatile intermediates in organic synthesis,[1] but they are also of particular pharmaceutical relevance, and exhibit an extensive and broad range of biological activities (Scheme 1).[2] In addition, sulfone-containing polymers display novel properties as materials.[3] Although there are a variety of methods known for the preparation of sulfones, the majority of these processes feature associated limitations. For example, oxidation of the corresponding sulfide relies on functional-group compatibility with oxidizing agents and the availability of catalysts to promote selectivity for sulfone formation over sulfoxide formation; in addition, the preparation of the required sulfide substrate often involves the use of foul-smelling thiols.[4, 5] Friedel–Crafts-type sulfonylation of arenes is limited not only by the generally harsh reaction conditions, but also by the inherent regioselective bias imposed by the electronic and steric properties of the arene substrate.[5, 6]

In response to these limitations, the use of transition-metal-catalyzed cross-coupling has been exploited as a route to sulfones.[7] The most utilized has been copper catalysis, in which sodium sulfinates couple with aryl, heteroaryl, or alkenyl halides,[8] or boronic acids.[9] However, the requirement for stoichiometric phase-transfer additives, high temperatures, and the use of undesirable solvents or ionic liquids, are significant drawbacks. An analogous palladium-catalyzed approach has also been developed using (pseudo)halides as coupling partners, although it too features the use of stoichiometric additives and high temperatures, and consequently suffers from limited scope.[10, 11] In addition to these problems, the variety of sulfones prepared by these metal-catalyzed methods is poor; only a small number of sodium sulfinates (typically methyl, phenyl, and p-tolyl) have been used to demonstrate the scope. This reflects the very limited commercial availability of sodium sulfinates, perhaps as a result of impractical or limited synthetic routes. Organo-metallic addition to sulfur dioxide gas[12] (followed by cation exchange) and reduction of the sulfonyl chloride[12, 13] are two such examples, but both have shortcomings such as the harsh reaction conditions, but also by the inherent regioselective bias.

We have recently developed DABSO (1), which is a solid, bench-stable complex formed between 1,4-diazabicyclo-[2.2.2]octane (DABCO) and two sulfur dioxide molecules.[15] Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201303569. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited. 

**Scheme 1.** Pharmaceuticals featuring an aryl sulphone unit.

**Scheme 2.** A convergent three-component sulfone synthesis exploiting DABSO, an easy-to-handle solid replacement for sulfur dioxide gas.
a broad range of aryl, heteroaryl, and alkenyl sulfones, employing palladium catalysis and DABSO (Scheme 2).

Given our previous demonstration of the efficient addition of Grignard reagents to DABSO to form magnesium halide sulfinate salts,\(^{16}\) we envisioned that these would couple with (pseudo)halides to form sulfones in a similar fashion to the reported sodium salt examples using transition metal catalysis. Unfortunately, after testing a variety of catalytic conditions, we were not able to achieve this. Suspecting that this was due to the difference in the nature of the counter ions, we elected to study the addition of organolithiums to form the more closely related lithium sulfinites. We chose to explore palladium rather than copper catalysis because the reported conditions for sodium salts were the most amenable to our organolithium proposal.\(^{10,11}\)

We were mindful, however, of the precedent for certain metal sulfinates to undergo palladium-catalyzed desulfonylative cross-couplings, whereby extrusion of \(\text{SO}_2\) from the palladium-bound sulfinate ultimately leads to a biaryl product.\(^{18}\)

We began our investigations with the addition of PhLi solution to a suspension of DABSO in THF at \(-40^\circ\text{C}\). Pleasingly, HPLC analysis revealed that quantitative conversion to the lithium sulfinate \(2\) was achieved; only traces of benzene from deleterious protonation were detected. This crude sulfinate suspension was then combined with \(\text{[Pd}_2(\text{dba})_3]\) (\(\text{dba} = \text{dibenzylideneacetone}\)), XantPhos, \(\text{Cs}_2\text{CO}_3\), \(\text{nBu}_4\text{NCl}\), and \(p\)-tolyliodide; the conditions reported for sodium sulfinate coupling.\(^{10}\) Analysis of the crude \(^1\text{H}\) NMR spectrum indicated the presence of the desired sulfone \(3\text{a},\) albeit at a low conversion (see the Supporting Information). However, by switching to \(\text{Pd(OAc)}_2\), conversion increased to 65\% and it was also found that the \(\text{nBu}_4\text{NCl}\) additive was effectively redundant. Postulating that the incomplete conversion was a result of the lower temperature used relative to that for the sodium salt, the solvent was switched from THF to 1,4-dioxiane, and the reaction heated at \(85^\circ\text{C}\). Gratifyingly, a quantitative conversion was achieved (Scheme 3).

Unfortunately, upon purification, two different sulfone products were isolated. Desired sulfone \(3\text{a}\) was present in 70\% yield together with 23\% of diphenylsulfone. From the observation that a phenyl group was always incorporated in the arylation of ureas,\(^{20}\) gave similar or a small increase in selectivity whilst maintaining good conversion of starting material was observed.\(^{22}\) Finally, variation of the phosphine ligand was undertaken. We found that, in agreement with the work of Cacchi et al., the XantPhos backbone was key to reactivity.\(^{10}\) many other ligands, including those with similar structures, such as DPPEPhos, as well as alkyl phosphines (which cannot undergo this exchange process), demonstrated little or no activity.\(^{23}\)

With the XantPhos architecture established as optimal, we next explored electronic and steric variations of this unique backbone.\(^{23}\) These ligands were evaluated under the cross-coupling conditions previously established (Table 1). Aryl (entries 3–5) and sterically hindering aryl substituents (entries 3 and 7) on the XantPhos backbone led only to recovered starting material. As expected, a more electron-rich phosphine gave more aryl–aryl exchange.\(^{18}\) Electron-poor phosphines, which have been reported to suppress transfer for alkyl substituted arylation of ureas,\(^{20}\) gave similar or a small increase in selectivity as hoped, but for the more selective reaction, the conversion was poor (entries 8–10). However, by switching to the aryl bromide substrate in place of the iodide substrate, full conversion was achieved with high selectivity when using the 3,5-bis(CF\(_3\))-substituted XantPhos \(5\text{f}\) (entry 13). Using these optimized conditions, the scope of the aryl bromide coupling partner was next investigated (Scheme 4).

\(m\)-Tolylithium \(6\text{a}\) was chosen to demonstrate the synthesis of sulfones that have not been prepared through
sodium sulfinate coupling. A stock solution was readily synthesized by using lithium–halogen exchange between butyllithium and 3-bromotoluene in dibutylether, which is a Lewis-basic solvent in which lithium–halogen exchange is kinetically facile and yet aryl lithiums are more stable to storage than in Et₂O or THF. [24] A wide range of aryl and heteroaryl bromides coupled in good to excellent yields (Scheme 4). Electron-rich substrates performed well, with C-, O-, S-, and N-based functionality all tolerated. Electron-poor aryl bromides also proved to be compatible, with ester, amide, aldehyde, chloro, and trifluoromethyl functional groups retained. The use of unprotected anilines, aryl fluoride, and napthyl derivatives demonstrated further scope. We established additional versatility by using heteroaromatic pyridyl, thiophenyl, and benzofuryl bromides, as well as using iodide or triflate substrates in place of bromide. Unfortunately, ketones and arenes bearing ortho substituents led to no reaction. Provided that K₃PO₄ was used in place of Cs₂CO₃, alkenyl tosylates could be successfully employed as the electrophilic coupling partner and allowed access to the corresponding aryl–alkenyl sulfone products. [11]

Next, we investigated the scope of the organolithium species (Scheme 5). Using 3-bromoanisole as the standard coupling partner, a range of aryl lithums were successfully subjected to the optimized conditions. Pleasingly, all the organolithiums prepared added, as expected, to DABSO to form the corresponding lithium sulfinate, and the subsequent palladium-catalyzed coupling worked well for a broad range of aryl sulfinates, including those with electron-donating, neutral, and electron-withdrawing functionality; trifluoromethyl, chloro, and silane functional groups were all successfully tolerated. Unfortunately, heterocyclic lithium 2-thienyl sulfinate led to biaryl formation from desulfonylative coupling through SO₂ extrusion, [18] while ortho-substituted lithium 2-anisyl sulfinate resulted in the recovery of aryl bromide starting material.

A limitation of our presented methodology was the inability to include functionality positioned ortho to the sulfone moiety. To address this issue, we exploited the capacity of the sulfone functional group to direct ortho metalation. [25] We demonstrated this through two regioselective ortho functionalizations of sulfone 8d by using the cooperative effect of meta-disposed directing groups to give 1,2,3-trisubstituted aryl sulfones 9 and 10 in good yields (not optimized, Scheme 6).

As a proof of the versatility and applicability of the presented methodology, we sought to demonstrate the synthesis of a significant target molecule. GSK-742457 (11) is a quinoline-based drug molecule that is currently under development for treating Alzheimer’s disease. [26] We envisaged disconnection to the known bis-halogenated quinoline derivative 12 [27] In the forward direction, palladium-catalyzed sulfonylation of 12 would generate chloro derivative 13, and a subsequent palladium-catalyzed Buchwald–Hartwig amination would produce the target medicinal agent (Scheme 7). The proposed sequence was successfully achieved, with the
sulfonation being realized in 70% yield, and the amination in 68% yield (both not optimized). This is an attractive route to the target system via the bis-halogenated quinoline 12, which provides a suitable branch point for the rapid preparation of analogues.

In summary, we have demonstrated the synthesis of a broad range of aryl, heteroaryl, and alkenyl sulfones through a convergent three-component palladium-catalyzed coupling approach. This method allows the straightforward production of varied sulfones through the union of two readily available coupling partners; an aryl lithium species and aryl, heteroaryl, or alkenyl (pseudo)halides; with SO₂ provided by the easy-to-handle bench-stable solid surrogate DABSO. The use of an electron-poor XantPhos-type ligand offers much improved yields over XantPhos itself. In addition, ortho functionality can be introduced by exploiting the ability of the sulfone group to direct ortho metatalation. A demonstration of the utility of the methodology was achieved through the synthesis of a medicinal agent that is currently in development, utilizing a versatile bis-halogenated quinoline as the starting material. Finally, evidence for the nontrivial nature of the preparation of aryl-aryl (and related) sulfones is found in the observation that of the 36 sulfone products reported herein, more than 90% are novel compounds.

Keywords: aryl lithium reagents · palladium · sulfones · sulfur dioxide · synthetic methods

[22] See the Supporting Information for proposed mechanism, and associated conditions screened.  
[23] These were all prepared through double *ortho* lithiation of 9,9-dimethylxanthene, followed by trapping with the appropriate chlorophosphine, according to reported procedures (see the Supporting Information).  
[27] This bis-halogenated quinoline was synthesized from commercially available 8-chloroquinoline through an NIS iodination (see Ref. [26].  