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Palladium-Catalyzed Arylation of Alkyl Sulfenate Anions

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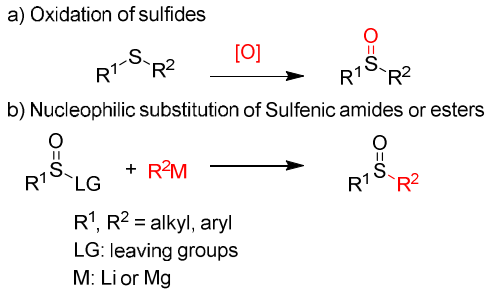
ABSTRACT: A unique palladium-catalyzed arylation of alkyl sulfenate anions is introduced that affords aryl alkyl sulfoxides in high yields. Due to the base sensitivity of the starting sulfoxides, sulfenate anion intermediates, and alkyl aryl sulfoxide products, the use of a mild method to generate alkyl sulfenate anions was crucial to the success of this process. Thus, a fluoride triggered elimination strategy was employed with alkyl 2-(trimethylsilyl)ethyl sulfoxides to liberate the requisite alkyl sulfenate anion intermediates. In the presence of palladium catalysts with bulky monodentate phosphines (SPhos and Cy-CarPhos) and aryl bromides or chlorides, alkyl sulfenate anions were readily arylated. Moreover, the thermal fragmentation and the base promoted elimination of alkyl sulfoxides was overridden. The alkyl sulfenate anion arylation exhibited excellent chemoselectivity in the presence of functional groups, such as anilines and phenols, which are also known to undergo palladium catalyzed arylation reactions.

INTRODUCTION

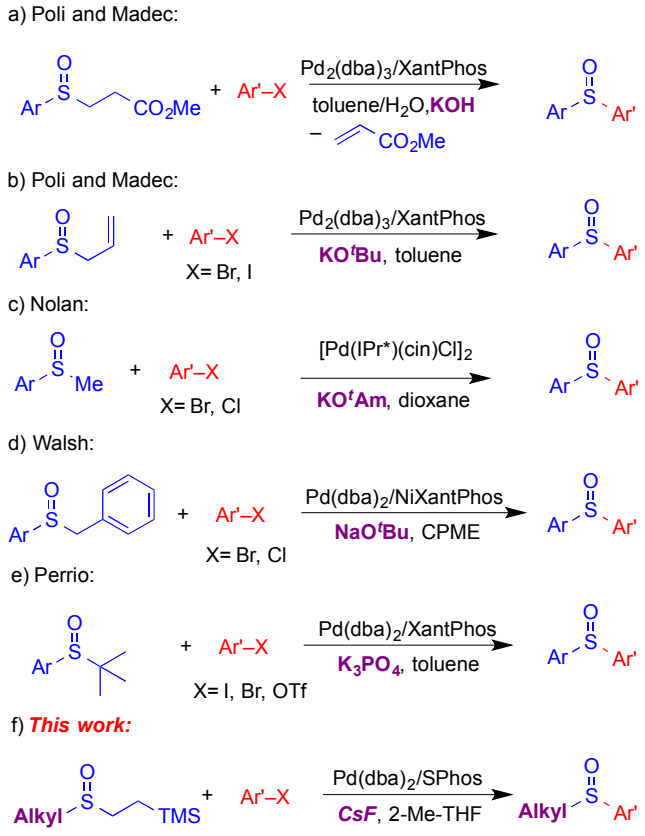
Sulfoxides are prevalent in medicinal chemistry,[1] natural products,[2] and marketed therapeutics such as Nexium[3] and Provigil.[4] They also find widespread applications in agricultural chemistry[5] and material science.[6] In recent years, sulfoxides have been successfully employed as ligands in transition metal catalyzed processes, including enantioselective transformations that take advantage of *S*-chirality.[7]

In general, sulfoxides are accessed by either oxidation of sulfides or nucleophilic substitution of sulfinate esters or amides (Scheme 1).[8] Despite the utility of these approaches, the use of either strong oxidizing agents or reactive lithium- or magnesium-based nucleophiles limits their functional group compatibility.



Scheme 1. Two major methods to prepare sulfoxides.

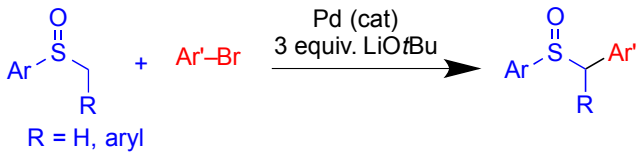
Recently, an alternative strategy to access diaryl sulfoxides has been developed involving generation and trapping of aryl sulfenate anions, $ArSO^-$.[9] To forge linkages between sulfenate anions and C(sp^2) centers, palladium catalyzed arylation of aryl sulfenate anions and aryl halides has been developed (Scheme 2). In pioneering work, Poli and Madec reported the palladium catalyzed arylation of aryl sulfenate anions that were generated by KOH triggered elimination of β-sulfinyl esters (Scheme 2a).[10] Subsequently, the same team achieved the C–S bond cleavage in route to sulfenate anions by a Mislow-Braverman-Evans rearrangement of allylic sulfoxides (Scheme 2b).[11] The resulting aryl sulfenate anions underwent palladium catalyzed coupling with aryl iodides in the presence of KO^{t}Bu to afford diaryl sulfoxides. Nolan and coworkers reported an *N*-heterocyclic carbene (NHC)-ligated palladium catalyst for diaryl sulfoxide formation from methyl aryl sulfoxides and aryl bromides or chlorides (Scheme 2c).[12] Simultaneously, we developed a method to generate a variety of diaryl sulfoxides from aryl benzyl sulfoxides and aryl bromides and chlorides via palladium catalyzed process (Scheme 2d).[13] The key intermediate is an aryl sulfenate anion, $ArSO^-M^+$. Earlier this year, Perrio and coworkers utilized the thermal fragmentation of *tert*-butyl sulfoxides to generate diaryl sulfoxides via palladium catalyzed arylation of aryl sulfenate anions (Scheme 2e).[14] No examples of alkyl sulfoxides bearing β-hydrogens were prepared with this method, although the weak base K_3PO_4 was employed.



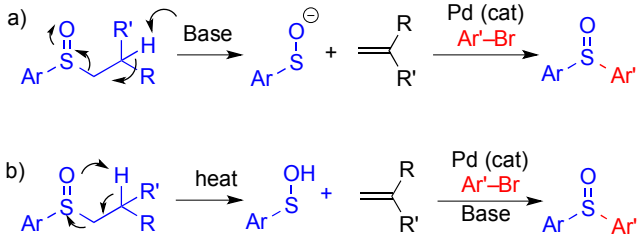
Scheme 2. Palladium catalyzed arylation of sulfenate anions with aryl halides and triflates.

Despite advances in palladium catalyzed arylation of aryl sulfenate anions, $ArSO^-$ to give diaryl sulfoxides, these methods are not suitable for arylation of *alkyl sulfenate anions*.[15] Therefore, the development of conditions to generate alkyl sulfenate anions and the identification of catalysts to promote their arylation is of central importance to the synthesis of alkyl-substituted sulfoxides. Furthermore, if a transition metal catalyzed arylation of alkyl sulfenate anions can be demonstrated, it will most likely also be possible to develop asymmetric catalysts to produce enantioenriched alkyl-substituted sulfoxides.

There are challenges that must be overcome to achieve coupling reactions with alkyl sulfenate anions. First, alkyl sulfenate anions are reported to be difficult to generate[16] and unstable under the basic conditions previously employed in palladium catalyzed cross-coupling reactions of aryl sulfenate anions (Scheme 2).[17] For example, alkyl sulfoxides bearing α-hydrogens are known to undergo Pd/base promoted α-arylation reactions[18] (Scheme 3). Furthermore, alkyl sulfoxides possessing β-hydrogens can undergo base promoted elimination (Schemes 4a and 2a) or thermal fragmentation at elevated temperatures[19] releasing olefin and sulfenic acids (Schemes 4b and 2e).[9a-c] By combining weakly basic CsF triggered fragmentation to liberate the alkyl sulfenate anion with an appropriate palladium/ligand combination at relatively low temperatures, we have achieved the first general arylation of alkyl sulfenate anions with aryl bromides (Scheme 2f).



Scheme 3. Pd/base promoted α-arylation of sulfoxides

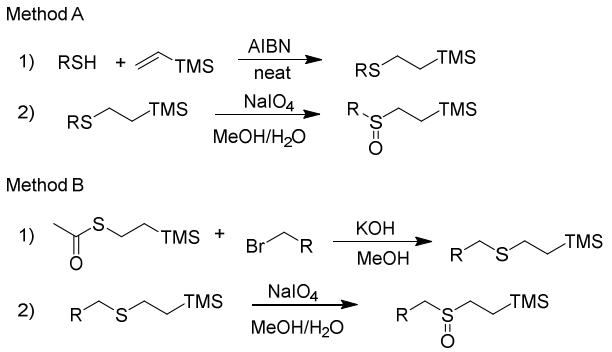


Scheme 4. a) Base induced E2 elimination and b) thermal fragmentation of alkyl sulfoxides leading to diaryl sulfoxides

RESULTS AND DISCUSSION

To systematically explore palladium catalyzed coupling of alkyl sulfenate anions containing α- or β-hydrogens, a different strategy to generate the sulfenate anions was needed. Considering the base- and heat-sensitivity of requisite substrates, intermediates, and products, we chose a fluoride-triggered elimination strategy with 2-(trimethylsilyl)ethyl substituted sulfoxides (Scheme 5).[16,20]

Alkyl 2-(trimethylsilyl)ethyl sulfoxides were prepared by a radical addition/oxidation sequence generally in 70-80% yield (Scheme 5, method A).[20d,e] This two-step procedure is operationally simple; the thioether products from radical addition can be used without purification in the oxidation. The scope of this method is very broad, and various functional groups are well tolerated. Olefin-containing substrates, however, undergo radical addition reactions under the conditions of method A. For such substrates, Schwan and co-workers described a substitution/oxidation protocol to prepare alkyl 2-(trimethylsilyl)ethyl sulfoxides bearing olefin subunits (Scheme 5, method B).[20e] Using these methods several alkyl 2-(trimethylsilyl)ethyl sulfoxides were successfully produced in 50-60% range of yields and applied in our cross-coupling reaction.

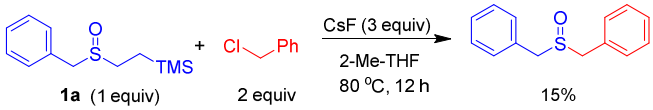


Scheme 5. Synthesis of alkyl 2-(trimethylsilyl)ethyl sulfoxides

To develop a useful arylation of alkyl sulfenate anions, conditions for the sulfenate anion generation must be established and paired with a suitable palladium precursor and ligand combination. To limit the number of variables simultaneously optimized, we initially examined the generation and trapping

of the sulfenate anion with benzyl chloride before turning to catalyst identification (Scheme 6).

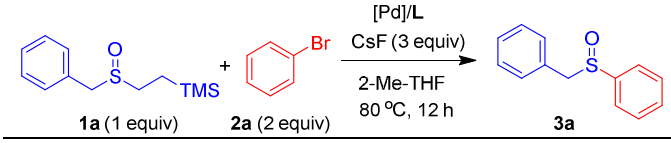
Employing 2-(trimethylsilyl)ethyl benzyl sulfoxide (**1a**)[20e] in the presence of benzyl chloride we examined four fluoride sources (LiF, NaF, KF and CsF) in six common solvents [THF, toluene, 2-Me-THF, DME (dimethoxyethane), CPME (cyclopentyl methyl ether), and dioxane] using microscale techniques. Of the four fluoride sources examined, only CsF led to sulfenate anion formation, as judged by generation of dibenzyl sulfoxide. When the experiments were scaled up to lab scale (0.1 mmol), the most promising lead to generate dibenzyl sulfoxide (3 equiv CsF in 2-Me-THF at 80 °C), gave only 15% yield. Nonetheless, CsF and 2-Me-THF were used to search for a palladium/ligand combination.



Scheme 6. Benzylation study with **1a** and benzyl chloride.

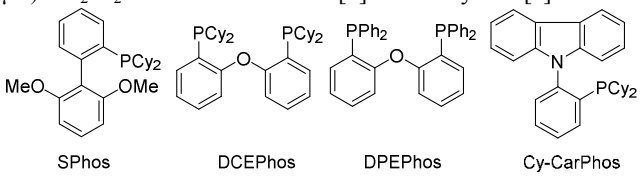
For the arylation, we employed 2-(trimethylsilyl)ethyl benzyl sulfoxide (**1a**) and bromobenzene (**2a**) and examined 44 ligands with $Pd(dba)_2$, which was the best palladium source in our diaryl sulfoxide synthesis[13a] (see Supporting Information for details). Among the ligands, SPhos,[21] DCEPhos,[22] DPEPhos[23] and Cy-CarPhos[24] (see Table 1 for structures) gave the highest assay yields (AY, as determined by HPLC) of benzyl phenyl sulfoxide (**3a**) on microscale (0.01 mmol). When the ligand screening results were translated to lab scale (0.1 mmol), SPhos resulted in the highest AY (^{1}H NMR) of **3a** (47% yield, Table 1, entry 1). Under the same conditions, the other three ligands generated **3a** in 11 to 41% AY (entries 2–4). Concentration was found to have a significant impact on the reaction outcome, with the yield of **3a** increasing to 60% when the concentration was increased from 0.1 to 0.2 M (entry 5). The assay yield of **3a** reached 86% at a concentration of 0.5 M (entry 6) but fell slightly at 1.0 M, probably due to solubility issues with CsF (82% AY, entry 7). Examination of palladium sources $Pd(OAc)_2$ and $[(allyl)PdCl]_2$ revealed that $[(allyl)PdCl]_2$ resulted in 98% AY of **3a** (entry 9 vs 6 and 8). Attempts to decrease the loading of the catalyst and the reaction temperature both led to lower AY (entries 10 and 11). The optimized reaction conditions for our palladium catalyzed alkyl aryl sulfoxide formation from sulfoxide **1a** (limiting reagent) and Ph–Br (2 equiv) are 2.5 mol % $[(ally)PdCl]_2$, 10 mol % SPhos, 3 equiv CsF at 0.5 M in 2-Me-THF at 80 °C for 12 h.

Table 1. Optimization of the palladium catalyzed cross-coupling with **1a** and **2a**.



Entry	Pd /mol %	Ligand /mol %	Conc. /M	NMR Yield[a] /%
1	$Pd(dba)_2$/5	SPhos/10	0.1	47
2	$Pd(dba)_2$/5	DCEPhos/10	0.1	41
3	$Pd(dba)_2$/5	DPEPhos/10	0.1	11
4	$Pd(dba)_2$/5	Cy-CarPhos/10	0.1	40
5	$Pd(dba)_2$/5	SPhos/10	0.2	60
6	$Pd(dba)_2$/5	SPhos/10	0.5	86
7	$Pd(dba)_2$/5	SPhos/10	1.0	82
8	$Pd(OAc)_2$/5	SPhos/10	0.5	15
9	$[(allyl)PdCl]_2$/ 2.5	SPhos/10	0.5	98(96[b])
10	$[(allyl)PdCl]_2$/ 1.25	SPhos/5	0.5	53
11[c]	$[(allyl)PdCl]_2$/ 2.5	SPhos/10	0.5	29

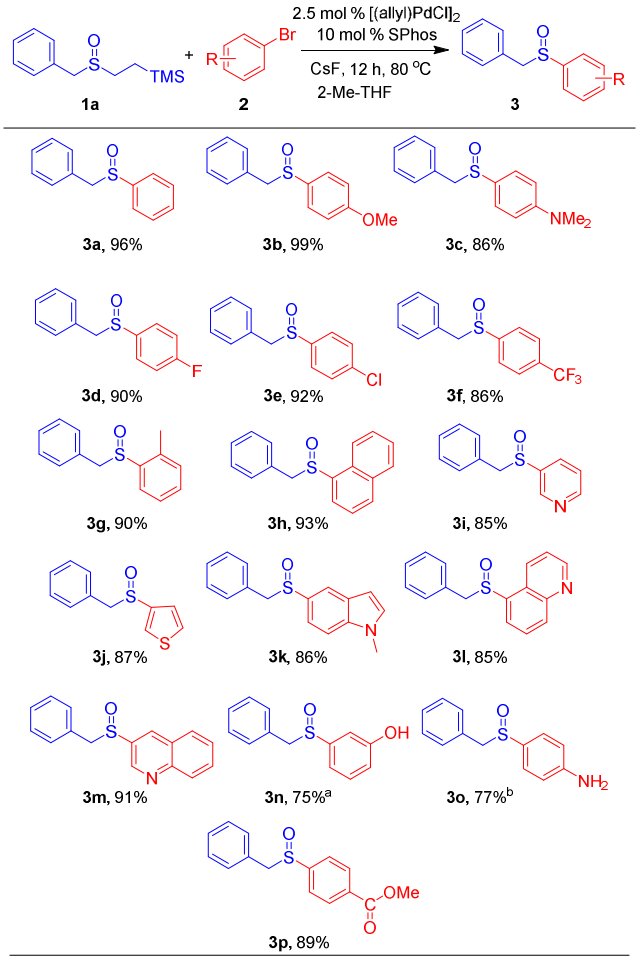
[a] Assay yields determined by ^{1}H NMR using 0.1 mmol (7 μL) CH_2Br_2 as internal standard. [b] Isolated yield. [c] 50 °C.



With reaction conditions established, the substrate scope of aryl bromides was examined with sulfoxide **1a** (Scheme 7). The parent benzyl phenyl sulfoxide (**3a**) was prepared in 96% isolated yield from bromobenzene (**2a**). Aryl bromides bearing electron-donating 4-OMe or 4-NMe_2 were successfully utilized as reaction partners, affording **3b** and **3c** in 99 and 86% yields, respectively. Aryl bromides with electron-withdrawing 4-F, 4-Cl or 4-CF_3 generated products **3d–f** in 86–92% yields. The sterically hindered 2-bromotoluene (**2g**) and 1-bromo naphthalene (**2h**) provided **3g** and **3h** in 90 and 93% yields, respectively. Heterocyclic sulfoxides exhibit anti-cancer, anti-fungi and anti-inflammatory activities[1,2d] and are, therefore, important targets. Fortunately, a variety of heterocyclic benzyl sulfoxides could be prepared in good yields under our standard conditions, as demonstrated using heteroaryl bromides possessing 3-pyridyl, 3-thienyl, 5-(*N*-methyl)indonyl, 5-quinolino, and 3-quinolino benzyl sulfoxides (**3i–m**, 85–91% yields). It is noteworthy that 3-pyridyl benzyl sulfoxide (**3i**) is a key structural motif with activity against hepatitis C.[1e] As outlined in Scheme 3, benzylic sulfoxides undergo palladium catalyzed α-arylation under basic conditions.[18] However, no such byproducts were formed under the mild conditions employed in Scheme 7.

Aryl bromides with base-sensitive functional groups that are known to participate in C–O and C–N bond-forming reactions[25] (3-OH, 4-NH_2) and carbonyl additions (4-CO_2Me), reacted smoothly, producing the corresponding products (**3n**, **3o** and **3p**) in 75, 77, and 89% yields, respectively. These results indicate that our catalyst system exhibits excellent chemoselectivity.

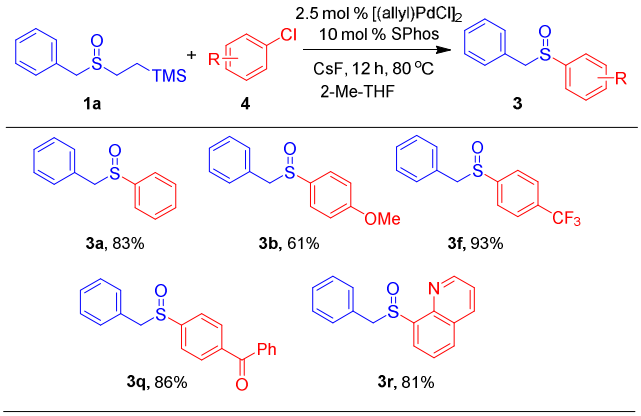
Scheme 7. Substrate scope of aryl bromides in palladium catalyzed alkyl aryl sulfoxide formation with **1a**.



[a] 24 h, 110 °C, at 0.25 M concentration, 5 equiv CsF used. [b] 24 h, 110 °C, at 0.17 M concentration, 7 equiv CsF used.

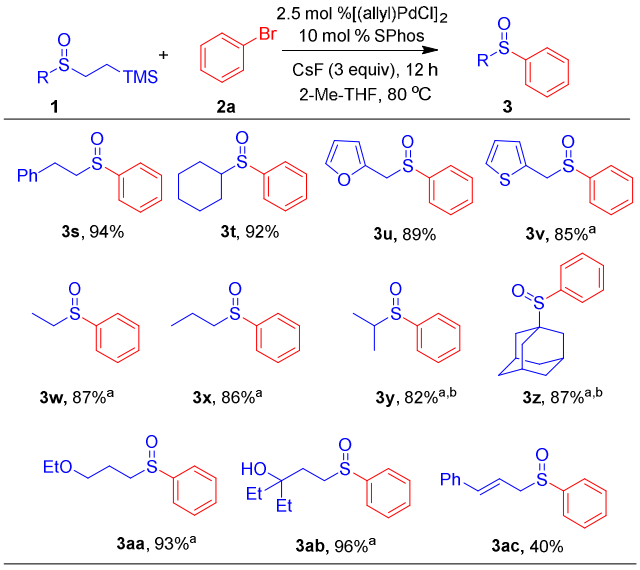
Aryl chlorides are desirable coupling partners because of their abundance and lower cost.[26] However, they can be more challenging substrates in cross-coupling reactions.[27] Gratifyingly, we observed that under our optimized conditions for aryl bromides, aryl chlorides could be successfully employed in the synthesis of alkyl aryl sulfoxides (Scheme 8). Five representative aryl chlorides were chosen to demonstrate the substrate scope in our cross-coupling protocol. Chlorobenzene (**4a**) reacted smoothly with **1a**, producing **3a** in 83% yield. 4-Chloroanisole (**4b**) is a relatively difficult substrate, because of its electron rich character. Nonetheless, the arylation product **3b** was formed in modest yield (61%). On the other hand, aryl chlorides bearing electron-withdrawing groups are easier to be oxidatively added. Thus, 1-chloro-4-(trifluoromethyl)benzene and 4-chlorobenzophenone were excellent cross-coupling partners providing 91 and 86% yields, respectively. Heterocyclic 8-chloroquinoline was a good substrate, undergoing reaction to furnish (benzylsulfinyl)quinoline (**3r**) in 81% yield.

Scheme 8. Substrate scope of aryl chlorides in palladium catalysed alkyl aryl sulfoxide formation with **1a**.



We next sought to examine the substrate scope of 2-(trimethylsilyl)ethyl alkyl sulfoxides in palladium catalyzed cross-coupling reactions with bromobenzene (**2a**) (Scheme 9). As mentioned, the 2-(trimethylsilyl)ethyl alkyl sulfoxides are precursors to alkyl sulfenate anions bearing β-hydrogens, and had not been previously developed. Our scope, therefore, was primarily focused on these challenging substrates. (2-Phenyl)ethyl phenyl sulfoxide (**3s**), itself an excellent precursor to sulfenate anions under basic conditions[9e] and cyclohexyl phenyl sulfoxide (**3t**) were prepared under our standard reaction conditions in 94 and 92% yield, respectively. Heterocycle-substituted alkyl sulfoxides acted as cross-coupling partners, as exemplified by 2-furanyl derivative **1u**, which afforded **3u** in 89% yield. Surprisingly, switching the heterocycle from 2-furanyl to 2-thienyl led to poor yield of **3v** (13%). We therefore revisited the other three promising ligands in the initial catalyst identification screen (DCEPhos, DPEPhos and Cy-CarPhos, Table 1). Using 5 mol % $Pd(dba)_2$ and 10 mol % Kwong's Cy-CarPhos in DME at 80 °C for 24 h led to a satisfactory yield of the desired product **3v** (85% yield). In the subsequent examination of the substrate scope, we observed that the use of Cy-CarPhos was complementary to use of SPhos with a wide range of 2-(trimethylsilyl)ethyl alkyl sulfoxides. We therefore examined both phosphines with the remaining substrates. Linear or branched alkyl substituted 2-(trimethylsilyl)ethyl sulfoxides were amenable to our protocol, providing **3w**–**y** in 82–87% yields. Not surprisingly, bulkier sulfenate anion precursors, such as the adamantyl derivative, required slight tweaking of the conditions, but ultimately furnished the desired product **3z** in 87% yield. In addition, functionalized alkyl substrates were also found to be suitable, as demonstrated by the synthesis of ether **3aa** and alcohol **3ab** in 93 and 96% yield, respectively. Surprisingly, sulfoxide possessing internal olefin subunit (**1ac**) could furnish the corresponding product (**3ac**) in modest yield under the optimized conditions. The reduced yield (40%) is most likely due to competitive Tsuji-Trost reaction.[11]

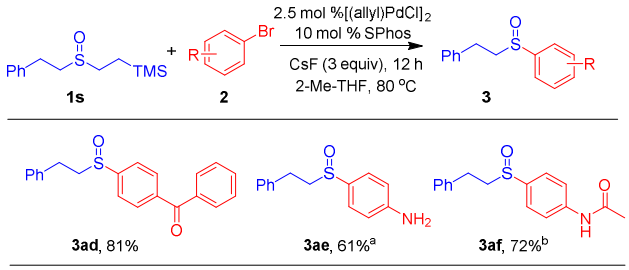
Scheme 9. Substrate scope of 2-(trimethylsilyl)ethyl alkyl sulfoxides in palladium catalysed alkyl aryl sulfoxide formation with **2a**.



[a] 5 mol % $Pd(dba)_2$, 10 mol % Cy-CarPhos in 1.0 mL DME for 24 h. [b] 48 h.

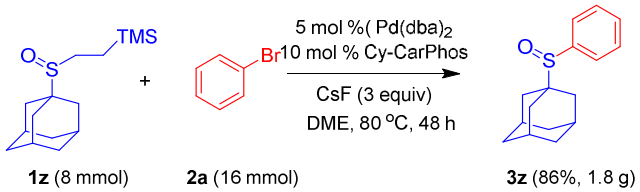
As noted earlier, sulfoxides bearing the (2-phenyl)ethyl group are excellent precursor to sulfenate anions under basic conditions.[9e] To broaden the substrate scope, and compare the reactivity to well-established palladium catalyzed reactions, more functionalized aryl bromides were examined. As shown in Scheme 10, 4-chlorobenzophenone underwent coupling in 81% yield to furnish the ketone-containing product (**3ad**). To compare our *S*-arylation to *N*-arylation (Buchwald-Hartwig cross-coupling[25]), 4-bromoaniline and 4-bromoacetanilide were coupled with **1s** in 61 and 72% yields under slightly modified conditions (Scheme 10). These results highlight the high degree of chemoselectivity displayed by the SPhos-based catalyst under our reaction conditions.[25b]

Scheme 10. Palladium catalysed alkyl aryl sulfoxide formation with **1s**.



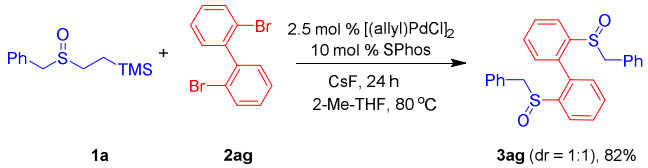
[a] 48 h, 7 equiv CsF used. [b] 48 h, 5 equiv CsF used.

Besides broad functional group tolerance, the method also must be scalable to be useful. A scale-up experiment (8 mmol **1x**) was conducted with adamantyl derivative **1z** and bromobenzene, providing 1.8 g of the product **3z** (86% yield, Scheme 11).



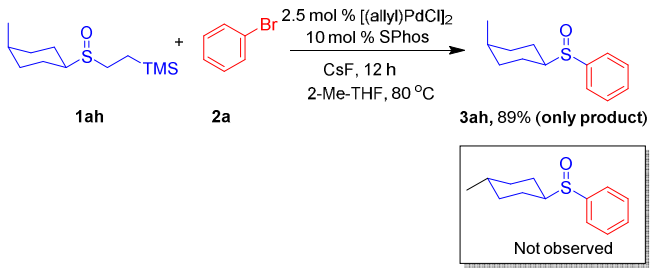
Scheme 11. Gram scale synthesis of 3**z** via palladium catalyzed arylation of alkyl sulfenate anions.

Bis-sulfoxides are widely utilized as ligands in transition metal catalyzed reactions.[7] Therefore, our cross coupling protocol was evaluated in the synthesis of bis-sulfoxides. Benzyl 2-(trimethylsilyl)ethyl sulfoxide (**1a**) was coupled with 2,2'-dibromobiphenyl (**2ag**) under our standard reaction conditions to afford **3ag** in 82% yield (dr = 1:1).



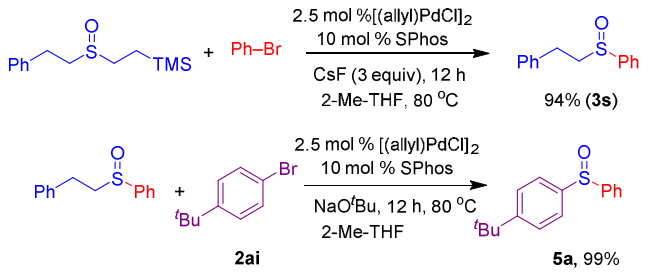
Scheme 12. Bis-sulfoxide **3ag** formation via palladium catalysed cross-coupling of **1a** and **2ag**.

Furthermore, to examine the stability of stereocenters α to the sulfoxide group, we employed the *cis*-diastereomer of **1ah** in coupling with bromobenzene **2a** under our standard reaction conditions (Scheme 13). The *cis*-diastereomer **3ah** was obtained in 89% yield with no epimerization to the thermodynamically favored *trans*-diastereomer.



Scheme 13. Palladium catalyzed reaction of *cis*-2-(trimethylsilyl)ethyl (4-methyl)cyclohexyl sulfoxides (**1ah**) and bromobenzene (**2a**).

Finally, to highlight the difference between previous procedures conducted under basic conditions (Schemes 2–3) and this fluoride induced elimination strategy, (2-phenyl)ethyl 2-(trimethylsilyl)ethyl sulfoxide was treated with CsF and bromobenzene in the presence of the Pd-catalyst (Scheme 14) to yield the phenyl sulfoxide **3s** in 94%. Coupling of **3s** with 4-*tert*-butyl bromobenzene in the presence of NaO^{t}Bu under otherwise identical conditions afforded diaryl sulfoxide **5a** in 99% yield.



Scheme 14. Palladium catalyzed diaryl sulfoxide (**5a**) formation in presence of NaO^{t}Bu.

CONCLUSION

In summary, a novel protocol to prepare alkyl aryl sulfoxides via palladium catalyzed C–S bond-formation between alkyl sulfenate anions and aryl bromides or chlorides is pre-

sented. This is the first general example of alkyl sulfenate anions employed in transition metal catalysis. The alkyl sulfenate anions were generated *in situ* by a fluoride triggered elimination strategy from 2-(trimethylsilyl)ethyl alkyl sulfoxides under weakly basic conditions. The key to success of this method is avoidance of strong bases and high temperature (>100 ^{o}C), as well as the utilization of highly selective catalysts for the arylation of alkyl sulfenate anions. Given the wide variety of aryl bromides or chlorides commercially available, this method enables the synthesis of a vast array of functionalized alkyl aryl sulfoxides. We anticipate that this approach will be adopted to prepare diverse aryl alkyl sulfoxides for use in medicinal chemistry.

ASSOCIATED CONTENT

Supporting Information. Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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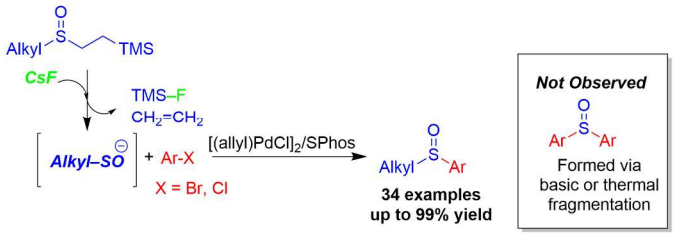
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