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Metal-free C–H thioarylation of arenes using sulfoxides: a direct, general diaryl sulfide synthesis†

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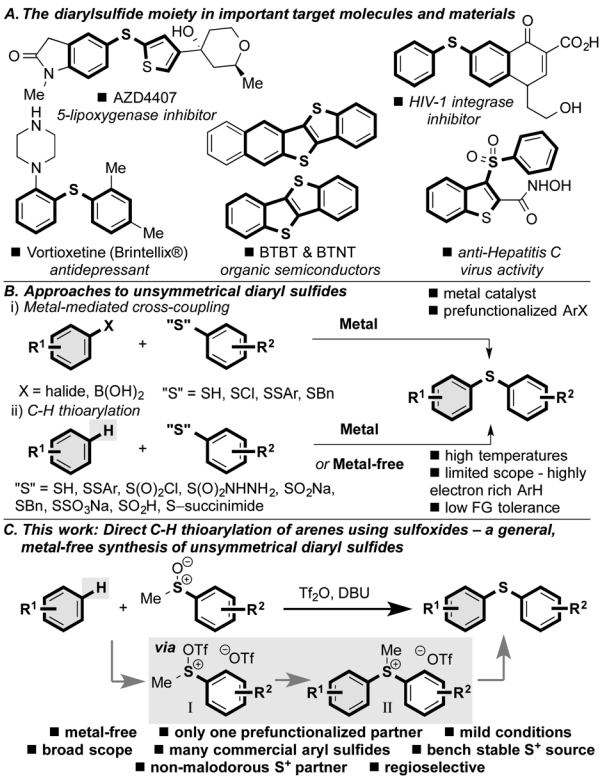
Metal-free C–H thioarylation of arenes and heteroarenes using methyl sulfoxides constitutes a general protocol for the synthesis of high value diaryl sulfides. The coupling of arenes and heteroarenes with *in situ* activated sulfoxides is regioselective, uses readily available starting materials, is operationally simple, and tolerates a wide range of functional groups.

Diaryl sulfides are prevalent in important and high value chemical structures such as biologically active compounds,[1] organic materials[2] and ligands[3] that mediate an array of chemical transformations (Scheme 1A). In addition, they are precursors to other higher oxidation state sulfur containing compounds that are found in similarly important chemicals.[4]

Due to the importance of unsymmetrical diaryl sulfides, their synthesis has garnered much attention. For example, in transition metal-mediated processes,[5] using Pd,[6] Ni,[7] Rh,[8] Cu,[9] In,[10] Fe[11] and Co,[12] the coupling of aryl halides (or pseudohalides) with various sulfur based partners has been described (Scheme 1Bi).[13,14] In an attempt to improve reaction efficiency by abolishing the need for a prefunctionalized arene (*e.g.* aryl halide), C–H thioarylation mediated by transition metals has received significant attention (Scheme 1Bii).[15] However, the use of metals raises issues of supply risk[16] and contamination of products.[17] In addition, these metal-catalyzed procedures for the synthesis of diaryl sulfides typically require elevated temperatures, that limit their general applicability. More recently, metal-free[18] C–H thioarylation of highly electron rich arenes and heteroarenes using electrophilic sulfur reagents and precursors, including *N*-(thio)succinimides,[19] sulfonyl hydrazines,[20] sulfonyl chlorides,[21] sodium sulfinates,[22] thiols,[23] disulfides,[24] and others[25] has emerged, and circumvents some of the problems associated with transition metal-mediated transformations (Scheme 1Bii). In these reactions the active sulfur electrophile, which is often formed *in situ*, is at the sulfide oxidation level and therefore has poor electrophilicity, limiting these methods to electron rich aryl coupling partners (typically indole or phenol/aniline derivatives) and the requirement for high temperatures.



Scheme 1 (A) The importance of unsymmetrical diaryl sulfides. (B) Conventional metal-mediated and metal-free approaches. (C) The metal-free C–H thioarylation of arenes provides convenient and general access to unsymmetrical diarylsulfides. Tf_2O = trifluoromethanesulfonic anhydride, DBU = 1,8-diazabicycloundec-7-ene.

Herein, we report the development of a simple, general, metal-free method for the synthesis of unsymmetrical diaryl sulfides that exploits a bench-stable, convenient sulfur electrophile, which has broad scope and high functional group tolerance (Scheme 1C).

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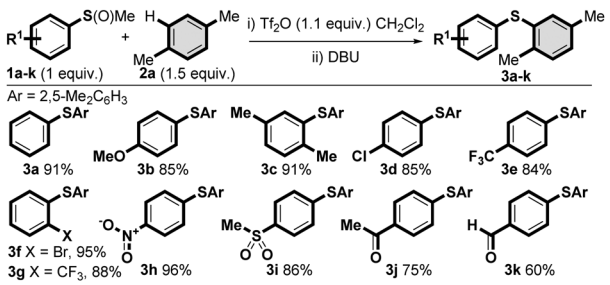
The method exploits the reactivity of activated sulfoxides, which we show to be excellent electrophiles, and as such allows the straightforward reaction to proceed under mild conditions with a variety of arene coupling partners in a highly regioselective manner.

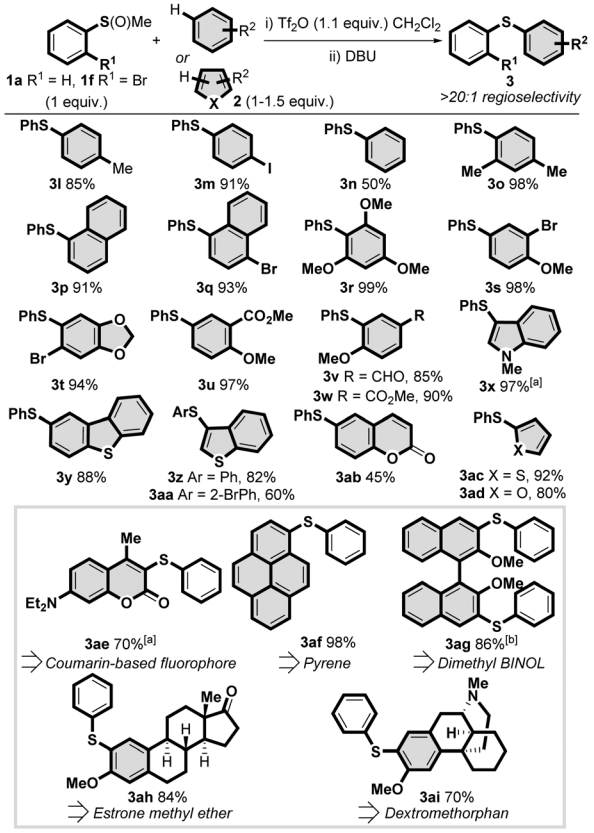
Based on the seminal studies by Balenkova[26] and recent work by us[27] and others[28] on the reactivity of sulfoxonium salts with a variety of nucleophiles,[29] we postulated that activated aryl methyl sulfoxides (**I**) would serve as efficient sulfur based electrophiles for the C–H thioarylation of arenes to afford sulfonium salts **II** (Scheme 1C). The intermediates **II** could then be demethylated *in situ* to afford a straightforward, metal-free synthesis of unsymmetrical diaryl sulfides. Thus, we treated methyl phenyl sulfoxide **1a** with trifluoromethanesulfonic anhydride, which formed the activated sulfoxide (*cf.* **I**). Addition of *p*-xylene **2a** led to the formation of an isolable sulfonium salt (*cf.* **II**),[30] that smoothly underwent demethylation with DBU to yield diaryl sulfide **3a** in 91% isolated yield (Scheme 2).[31]

We furthered investigated the scope of the metal-free C–H thioarylation process with regard to the aryl methyl sulfoxide partner (Scheme 2). A range of methyl sulfoxides **1**, commercially available or readily prepared from the corresponding commercial sulfides, were employed in the study. Electron-donating (**3b** and **3c**) and electron-withdrawing (**3d-k**) substituents were well tolerated and diaryl sulfides were obtained in excellent isolated yields. More hindered *ortho* substituted sulfoxides (forming **3c**, **3f** and **3g**), as well as a variety of important and/or functionalizable groups, such as methoxyl (**3b**), chloro (**3d**), trifluoromethyl (**3e** and **3g**), bromo (**3f**), nitro (**3h**), sulfone (**3i**), ketone (**3j**) and aldehyde (**3k**) were amenable to the process. It is important to note that the presence of halides would typically be incompatible with metal-mediated diaryl sulfide syntheses.

Next we turned to investigating the scope with regards to the aryl–H partner **2** and found that the metal-free C–H thioarylation embraced a variety of aromatics with complete regioselectivity observed in all cases (Scheme 3). Less activated arenes, such as toluene (**3l**), iodobenzene (**3m**) and even benzene (**3n**) underwent smooth C–H thioarylation, in stark contrast to other metal-free C–H thioarylation approaches to diaryl sulfides. More hindered *m*-xylene (**3o**), naphthalene (**3p**) and 1-bromo naphthalene (**3q**) were well tolerated, as well as arenes containing oxygen substitution (**3r-w** and **3ab**), including those with versatile bromo (**3s** and **3t**), acetal (**3t**), alkenyl (**3ab**), ester (**3u**, **3w** and **3ab**) and aldehyde (**3v**) functionality. Heteroaromatics, such as indole (**3x**), dibenzothiophene (**3y**), benzothiophene (**3z** and **3aa**), thiophene (**3ac**) and furan (**3ad**) were also successfully applied. We have used benzothiophene **3z** in a formal synthesis of an anti-hepatitis-C drug candidate (see Scheme 1A for structure).[32] Also of note, **3aa** is a known precursor[15a] to BTBT organic semiconductors (see Scheme 1A for structure).



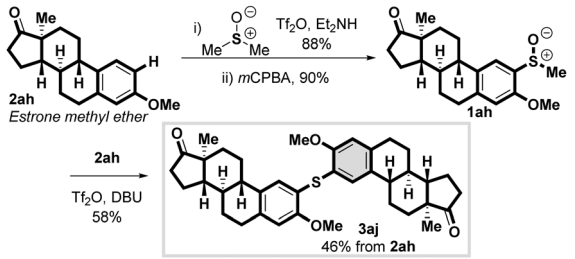
Scheme 2 Scope of the methyl aryl sulfoxide coupling partner in the metal-free C–H thioarylation approach to diaryl sulfides. Isolated yields stated.



Scheme 3 Scope of the arene and heteroarene coupling partner in the metal-free C–H thioarylation approach to diaryl sulfides and metal-free C–H thioarylation for scaffold construction and late-stage modification. Isolated yields stated. [a] TFAA used as activator. [b] 2 equiv. of **1a** and 2.1 equiv. of Tf_2O.

We further evaluated the efficacy of the process in the late-stage diversification of a range of molecular scaffolds. Aryl sulfide **3ae** was formed from an established coumarin based fluorophore, useful in the study of biological systems.[33] Pyrene, a common motif in dyes, also efficiently formed diaryl sulfide **3af**, an intermediate in the synthesis of fluorescent chemosensors.[34] Dimethyl BINOL, bearing the ubiquitous binaphthyl chiral scaffold, smoothly underwent a one-pot double C–H thioarylation with two equivalents of activated sulfoxide without reduction in efficiency (**3ag**). The metal-free protocol was applied to estrone methyl ether, an estrogenic hormone derivative, leading selectively to sulfide **3ah**. In addition, dextromethorphan,[35] a drug of the morphinan class commonly sold in over-the-counter cold and cough medicines, led to the corresponding diaryl sulfide **3ai** in good yield.

These late stage modifications (**3ae-ai**), general scope of the sulfoxide **1** (**3a-k**) and aryl–H coupling partner **2** (**3l-ad**) underscore



Scheme 4 Metal-free, iterative C–H thioarylation in the synthesis of diaryl sulfides from the union of two aryl–H coupling partners and DMSO as the sulfur source.

some key features of this metal-free C–H thioarylation protocol: (1) the reaction has broad functional group tolerance, including halides, methoxy, carbonyl derivatives, nitro, sulfone, and basic nitrogen atoms; (2) electron withdrawing groups on the aryl–H partner and electron neutral aryl–H partners are well tolerated in contrast to other metal-free protocols; (3) the reaction yields diaryl sulfides with complete regioselectivity; and (4) over C–H thioarylation is impossible due to intermediate sulfonium salt **II** being deactivated to further S_EAr with another molecule of activated sulfoxide **I**. These facets are made possible by the superior reactivity of activated sulfoxides as sulfur electrophiles, meaning the reaction does not require harsh conditions and elevated temperatures.

The chemical union of two biologically active molecules is of significant interest to medicinal chemists.[36] We reasoned that we could use our approach in an iterative C–H thioarylation to link two biologically active aryl–H partners *via* a sulfur atom (Scheme 4). In order to explore iterative C–H thioarylation we reacted estrone methyl ether **2ah** with activated DMSO,[26] which after dealkylation and oxidation gave estrone derived methyl sulfoxide **1ah** in high yield over two steps (79%). The generated sulfoxide **1ah** then served as the sulfur partner in the metal-free C–H thioarylation of another molecule of estrone methyl ether **2ah**, giving dimeric estrone methyl ether **3aj** in a convenient three-step, metal-free procedure from two non-prefunctionalized aryl–H coupling partners and DMSO[37] as the sulfur source. This strategy would also be useful when the required methyl aryl sulfoxide **1** (or corresponding methyl sulfide) is not commercially available.[38]

In summary, we have developed a general, operationally simple metal-free synthesis of diaryl sulfides that proceeds under mild conditions. The C–H thioarylation process is made possible by the use of readily available sulfoxides that once activated, form sulfoxonium salts that serve as excellent sulfur electrophiles for coupling with a variety of aryl–H partners, including those that are not electronically biased, with universally high regioselectivity. The method allows the incorporation of a variety of functional groups in either coupling partner, and as such is suitable for the construction of complex diaryl sulfides that have broad applications. In addition, we have described an iterative C–H thioarylation approach to complex diaryl sulfides utilising two aryl–H partners and DMSO as the sulfur source.

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