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Copper-Catalyzed Aerobic Oxidative N–S Bond Functionalization for C–S Bond Formation: Regio- and Stereoselective Synthesis of Sulfones and Thioethers

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Abstract: A regio- and stereoselective synthesis of sulfones and thioethers by means of Cu^{I}-catalyzed aerobic oxidative N–S bond cleavage of sulfonyl hydrazides, followed by cross-coupling reactions with alkenes and aromatic compounds to form the C_{sp^2}–S bond, is described herein. N_2 and H_2O are the byproducts of this transformation, thus offering an environmentally benign process with a wide range of potential applications in organic synthesis and medicinal chemistry.

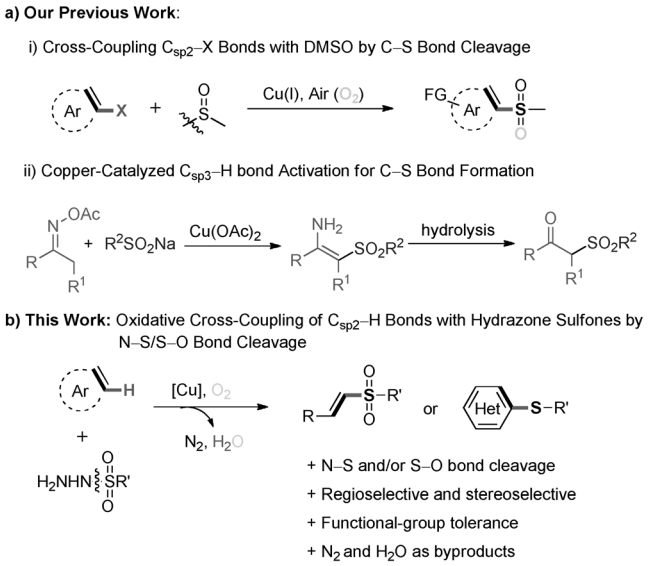
Owing to concerns about reserves of fossil fuels decreasing and environmental pollution increasing, an urgent demand for organic chemists is to find alternative sustainable processes to build privileged structures through selective functionalization of unreactive C–H bonds.[1] In this context, copper-catalyzed aerobic oxidative functionalization of organic molecules, with the advantage of low cost, abundance, and the versatility of a Cu/O_2 catalytic system, provide a new route towards these targets.[2] However, great challenges still remain with respect to synthetic scope, chemo-, regio-, and stereoselectivity; catalytic systems that are capable of performing selective C–H oxidation in substrates bearing electron-rich nitrogen functional groups are extremely scarce.

The last several decades have witnessed great advances in transition-metal-catalyzed C–C and C–heteroatom (N, O, P) bond formations,[3] however, the efficient construction of C–S bonds with high selectivity remains relatively unexplored, probably owing to the deactivation of the catalyst by the sulfur species.[4] On the other hand, sulfur-containing molecules, such as sulfones and thioethers, are of great demand in the pharmaceutical industry, in materials science, and they are also important synthetic building blocks.[5] Despite longstanding biological and synthetic interest, direct access to this important class of compounds is complicated by the lack of efficient, safe, and general methods for their synthesis.[6]

Sulfonyl hydrazides are readily accessible synthetic intermediates that can be used to construct hydrazones, heterocycles, and reductants, and can also be used as aryl sources by means of C–S bond cleavage. More significantly, they could also serve as sulfone or thioether sources by means of N–S and/or S–O bond cleavage.[7] Compared to other sulfenylation/sulfonation agents, sulfonyl hydrazides are not sensitive to air and moisture, they are easy to prepare, and more importantly, N_2 and water are the only byproducts.

Recently, we have developed a copper-catalyzed aerobic oxidative cross-coupling of C_{sp^2}–X bonds with DMSO to afford aryl/vinyl (methyl)sulfones by means of oxidative cleavage of the C–S bond of DMSO[8a] (Scheme 1). A copper-catalyzed aerobic oxidative C_{sp^3}–H bond functionalization of the α position of ketone derivatives, leading to β-ketosulfones, was also developed by our group.[8b] Lei et al. developed an elegant oxygen-triggered oxysulfonylation of alkenes and alkynes to furnish β-hydroxysulfones or β-ketosulfones.[8c,d] Willis et al. further utilized their palladium-catalyzed aminosulfonylation process in a three-component one-pot sulfone synthesis, compromising of C_{sp^2}–X bonds, a sulfonyl unit, and an electrophilic coupling partner.[8e,f]

Complementary to conventional synthetic strategies, based on C–X bond functionalization, we envisioned that these molecules could be expeditiously accessed by means of oxidative functionalization of C_{sp^2}–H bonds, therefore, reducing the reliance on existing functional groups. As part of our continuous



Scheme 1. Copper-catalyzed aerobic oxidative C_{sp^2}–S bond formation.

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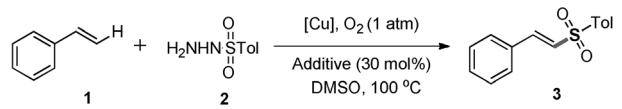
efforts towards dioxygen activation and copper-catalyzed aerobic oxidative functionalization of organic molecules,[9] herein, we report a copper-catalyzed aerobic oxidative cross-coupling of alkenes or aromatic compounds with sulfonyl hydrazides to construct C_{sp^2}–S bonds by means of N–S bond and/or S–O bond cleavage, affording vinyl sulfones and aromatic thioethers. This transformation features an inexpensive catalyst, a green oxidant from readily available starting materials, and N_2 and H_2O byproducts to afford the synthetically valuable intermediates and privileged drug scaffolds.

Our studies began by examining the oxidative functionalization of styrene (**1a**) and *p*-toluene sulfonohydrazide (**2a**) for C–S bond formation, in the presence of CuCl catalyst in DMSO, under air (Table 1, entry 1). With the use of 1,4-diazabicyclo-

Table 1. Optimization of reaction conditions.[a]



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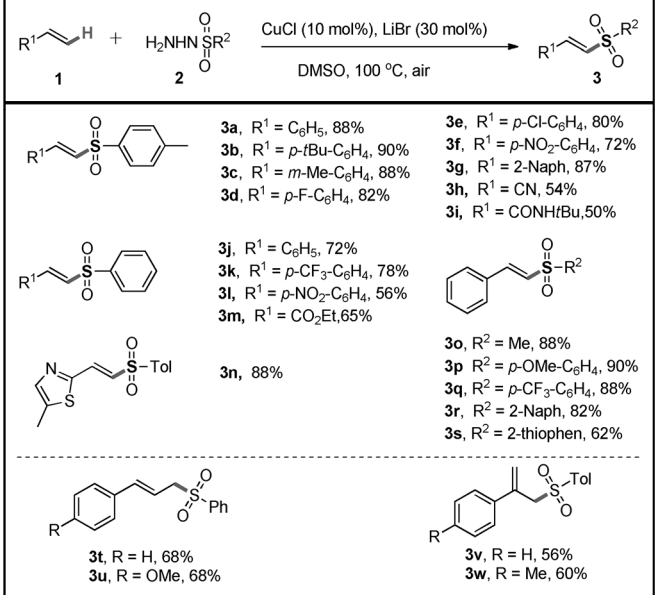
Entry	Cu source	Additive	Yield [%]
1	CuCl	DABCO	55
2	$CuCl_2$	DABCO	23
3	$Cu(OAc)_2$	DABCO	46
4	$Cu(OTf)_2$	DABCO	38
5	CuCl	phen	43
6	CuCl	bpy	28
7	CuCl	PPh_3	trace
8	CuCl	LiBr	92 (88)
9	CuCl	LiBr	trace
10	CuCl	LiBr	<10
11	CuCl	LiBr	18
12	–	–	trace

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), [Cu] (10 mol%), and additive (0.3 equiv) in 2.0 mL of solvent under O_2 (1 atm), at 80 °C for 12 h. [b] Determined by GC analysis. Number in parentheses is yield of isolated product. [c] Toluene was used as the solvent. [d] The reaction was conducted under N_2 atmosphere. OTf = triflate; phen = 1,10-phenanthroline; bpy = 2,2′-bipyridine.

octane (DABCO) as the additive, several copper catalysts were tested; CuCl showed superior reactivity towards this transformation (Table 1, entries 1–4). Further investigation of the additives revealed that LiBr was the best additive, whereas phosphorus ligands gave no desired product. It should be noted that β-keto sulfones, recently developed by Lei et al.,[8c] were also detected when nitrogen ligands were added to this catalytic system (Table 1, entries 5 and 6). With respect to solvents, DMSO was found to be important for this oxidative cross-coupling reaction. When DMSO was replaced by toluene, product **2a** could not be obtained. Control experiments suggested that copper and air were essential to this reaction. In their absence only trace amounts of the desired product could be detected.

With the optimized conditions in hand, we explored the generality of this methodology and the results are summarized in Table 2. The scope of the alkenes was first explored, and an array of alkenes bearing electron-withdrawing and electron-donating substituents on the phenyl ring (**3a**–**3f**), as well as

Table 2. Cu^{II}-catalyzed oxidative sulfonations of alkenes.[a]



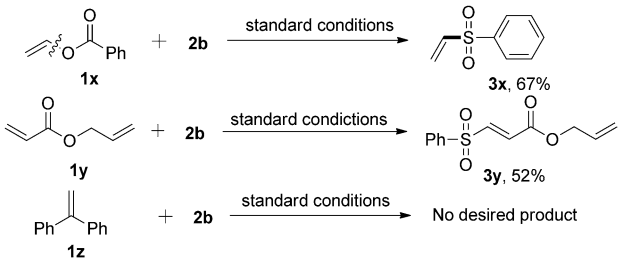
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), CuCl (5 mol%), and LiBr (0.5 mmol) in 2.0 mL of DMSO under air, at 100 °C for 12 h. Yields are those of the isolated product.

naphthalene (**3g**), could afford the desired products in moderate to high yields. The use of a heteroaromatic alkene (**3n**) also led to the cross-coupling product in good yield. The compatibility of nitrile (**3h**), amide (**3i**), ester (**3m**), chloride (**3e**), nitro (**3f** and **3l**), and trifluoromethyl (**3k**) functional groups means that this oxidative cross-coupling reaction has great potential for application in the late-stage modifications of advanced intermediates in medicines and materials. An electronic effect was not evident for the alkene partners in this C–H sulfonation, whereas the steric effect was critical for the reactivity. Unfortunately, increased substitution of the alkenes was not tolerated with the current catalytic system. However, allyl-type alkenes could deliver the allylic-substituted sulfonation products in moderate yield (**3t**–**3w**). It is worth noting that for all the C–H sulfonation products, only *trans*-1,2-disubstituted vinylsulfones were observed. No trace of the *cis*-vinyl isomer, nor 1,1-disubstituted regioisomeric sulfones have been detected.

With respect to sulfone hydrazides, various aliphatic and aromatic substituents were shown to be suitable cross-coupling partners (**3a**, **3j**, and **3o**–**3s**) for this oxidative transformation.

Substrate **1x** underwent C–O bond cleavage[10] under the standard conditions, affording **3x** as the product. The reaction also demonstrated great chemoselectivity when using **1y** bearing vinyl and allyl substituents, with **2b** as the substrate, under the standard conditions; **3y** was selectively formed and the allyl group remained intact. However, disubstituted alkene **1z** gave no desired product under the optimal conditions.

Inspired by the success of developing oxidative alkene C_{sp^2}–H sulfonations, we wondered whether we could further explore the C_{sp^2}–H bond of heteroaromatic rings, which have great synthetic potential in medicines and materials.



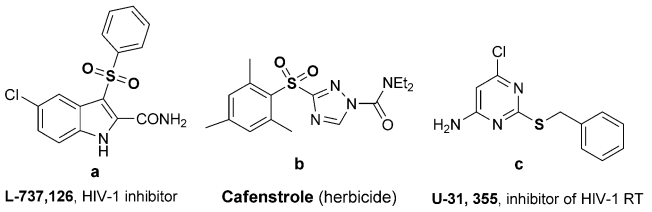


Figure 1. Sulfur-containing biologically active molecules.

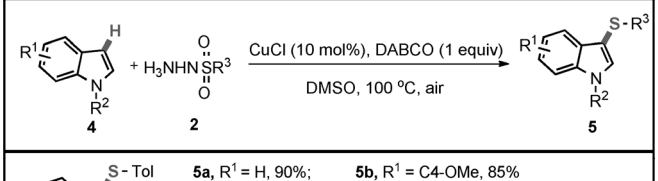
We first thought to investigate indoles[11] because of their wide existence in nature, important biological activities, and wide applications as pharmaceuticals and agricultural chemicals. Thus, selective functionalization of the C–H bonds of indoles has attracted much attention from both academia and industry.[12] To our delight, by slight modification of the additive in this oxidative transformation (see the Supporting Information for details), C3–H sulfenation of indoles **4**, which underwent N–S bond cleavage, S–O bond cleavage, and C–S bond formation, to obtain compounds **5** as the major product with great regioselectivity. Trace amounts of C2–H sulfonation products **5′** could also be detected (see the Supporting Information for details). It is noteworthy that even when the reactions were performed using oxidants, such as BQ (*p*-benzoquinone), DDQ (2,3-dicholro-5,6-dicyano-1,4-benzoquinone) H_2O_2 or $K_2S_2O_8$, the yield of **5′** did not increase. As summarized in Table 3, functional groups, such as ether (**5f**) and halide (**5c**–**5h**) groups at the C5-position of N–H indoles could be well tolerated in this process. Furthermore, N–Me, C2–Me, C3–Me, and C7–Me indole thioethers could also be obtained with moderate yield.

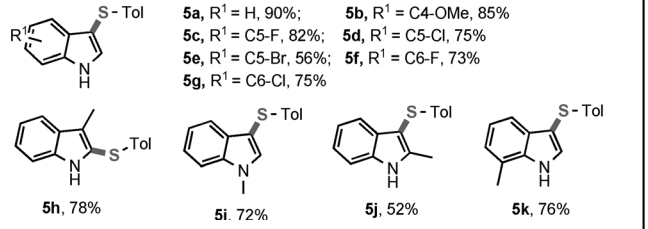
The heterocyclic aromatic sulfene skeleton has proven to be a useful building block in organic synthesis, medicinal chemistry, and natural-product synthesis. It exists widely in pharmaceutical molecules, such as enzyme inhibitors and biologically active antagonists, which are exemplified in Figure 1. Compound **a** is a novel, potent, and highly selective HIV-1 non-nucleoside reverse transcriptase inhibitor. Compounds **b** and **c** are potent and selective serotonin 5-HT6-receptor (5-HT6R) antagonists[13].

The success of oxidative-functionalized indole derivatives inspired us to investigate a variety of electron-rich (hetero)aromatic rings,[14] owing to their great significance in medicines and advanced materials. As depicted in Table 4, 1,3,5-trimethoxybenzene **6a** could be transformed into the corresponding thioether in good yield. Although mesitylene **6b** could undergo the cross-coupling reaction with low yield, the main byproducts were oxidative homocoupling isomers.[15a] N-Heterocycles, such as pyrimidine,[15b] 2-phenylpyridine,[15c] and imidazo[1,2-a]pyridine,[15d] could all be thiolated, regioselectively, in moderate yield. Furthermore, naphthols (**7f** and **7g**) were good coupling partners to afford the corresponding sulfenation products. The corresponding sulfamide could be detected when β-naphthylamine was used as substrate.[16] It should be noted that functionalized 2-naphthenols are precursors for dyes and the synthetically valuable ligand azobisisobutyronitrile (BINAP), and 1-naphthenols are important intermediates for insecticides and pharmaceuticals. *N*-Phenylacetamide could also undergo the C–H sulfenation reaction, however, with low efficiency.[15e]

To gain further insights into this reaction, firstly, we performed experiments with the addition of a radical scavenger (2,2,6,6-tetramethylpiperidine, TEMPO; butylated hydroxytoluene, BHT; and 1,4-nitrobenzene) under the optimized conditions. However, the reaction proceeded with a slightly de-

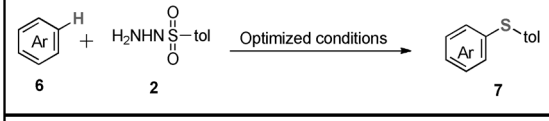
Table 3. Substrate scope of indoles.[a]

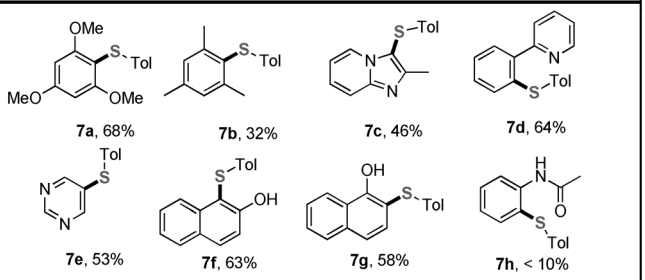




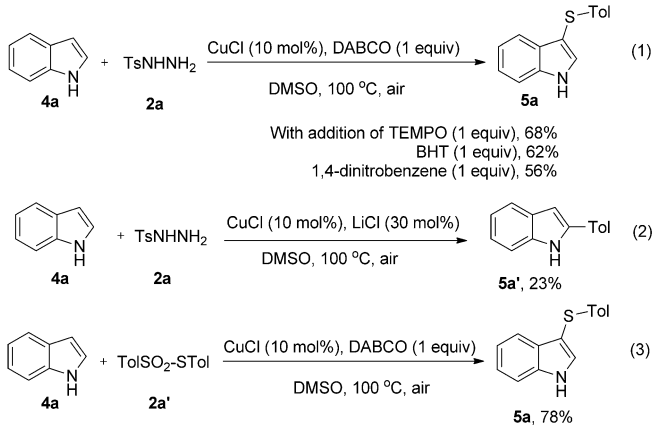
[a] Reaction conditions: **4** (0.5 mmol), **2** (0.5 mmol), CuCl (5 mol%), DABCO (0.5 mmol) in 2.0 mL of DMSO under air, at 100 °C for 12 h.

Table 4. Oxidative sulfenation of heterocycles.[a]





[a] Reaction conditions: **4** (0.5 mmol), **2** (0.5 mmol), CuCl (5 mol%), DABCO (0.5 mmol) in 2.0 mL of DMSO under air at 100 °C for 12 h.

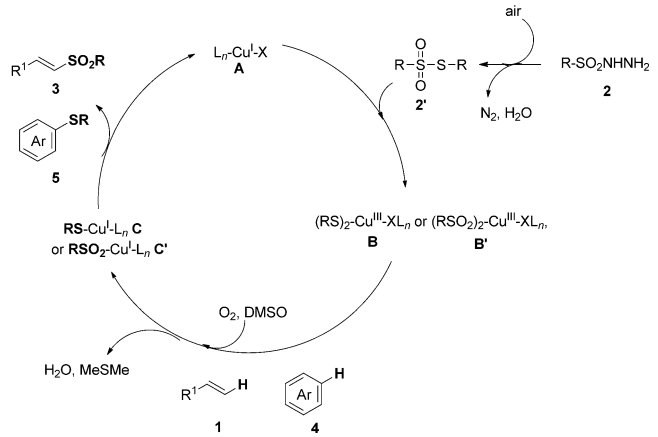


Scheme 2. Mechanistic studies.

creased yield [Scheme 2, Eq. (1)]. These results suggested that a radical process might not be involved in this transformation. Furthermore, during our optimization studies for the sulfenation of indoles, we observed that the addition of LiCl led to C2-arylated product [Scheme 2, Eq. (2)]. This C–H arylation result not only highlighted the rich chemistry of sulfone hydrazides in the cross-coupling reactions, complementing the copper-catalyzed C_{sp^2}–H sulfonations and sulfenations, but also demonstrated that an RCu intermediate could be generated in this process.

It is worth noting that sulfonothioate **2a**′, a byproduct observed in the reaction, could react with indole **2a** under the optimal conditions to afford **5a** in 78% yield. Thus, we speculated that **2a** was the active sulfenating agent. This observation was in accordance with findings by Yang and Tian[7a] and Cheng et al.[18a]

Although comprehensive studies are required to elucidate the mechanistic details of the present reaction, on the basis of the above results, a tentative mechanism for the oxidative N–S bond functionalizations for C–S bond cross-coupling is proposed (Scheme 3). It is envisioned that, initially, with the aid of a copper catalyst, air oxidative decomposition of sulfonyl hydrazides **2** into **2**′ takes place, with the release of N_2 and H_2O. Subsequently, **2**′ reacts with copper complex **A** to afford the active sulfenyl cuprate, **B**,[18] or sulfonyl cuprate **B**′, which reacts further with alkenes **1** or aromatic rings **4** to afford the corresponding sulfones **3** or sulfenes **5**, respectively, with the addition of different additives. It was speculated that DMSO might also serve as a co-oxidant in this process,[19] and dimethylsulfane was detected by GC-MS analysis. However, the precise mechanism regarding the chemoselectivity towards alkenes and aromatic rings, to afford sulfones or thioethers, is not clear currently.



Scheme 3. Proposed mechanism for the copper-catalyzed oxidative C_{sp^2}–H sulfenations/sulfonations.

In summary, we have developed a copper/air catalytic system for the regio- and stereoselective sulfonation, or sulfenation, of alkenes and (hetero)aromatic cycles through N–S and/or S–O bond cleavage of sulfonyl hydrazides. This transformation provides a general method to afford synthetically valuable sulfones and thioethers, and features sustainable chemistry while utilizing sulfonyl hydrazides as the versatile sulfur source, with N_2 and water as the byproducts. Further study the mechanism of this reaction, and efforts to develop significant utility in a variety of synthetic applications of this copper/air system, are the focus of current investigations.

Acknowledgements

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Keywords: C–H functionalization · copper · oxygen · sulfones · thioethers

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Synthetic Methods

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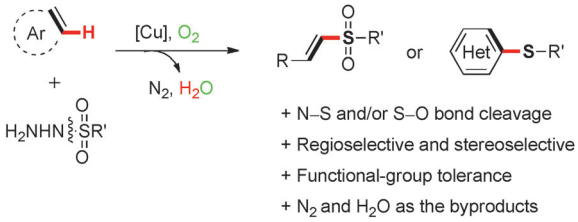
Copper-Catalyzed Aerobic Oxidative N–S Bond Functionalization for C–S Bond Formation: Regio- and Stereoselective Synthesis of Sulfones and Thioethers



First cleave, then cross-couple: A direct Cu-catalyzed aerobic oxidative C_{sp^2}–H functionalization and C–S bond coupling reaction has been developed (see scheme). By slight modification of the additive, sulfonyl hydrazides could serve as sulfonation, sulfenation, or arylation reagents to undergo cross-coupling reactions with alkenes and (hetero)aromatic cycles, affording sulfones, thioethers, and biaryl compounds with high regio- and stereoselectivities (see scheme).