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Copper-Catalyzed Regioselective Intramolecular Electrophilic Sulfenoamination via Lewis Acid Activation of Disulfides under Aerobic Conditions

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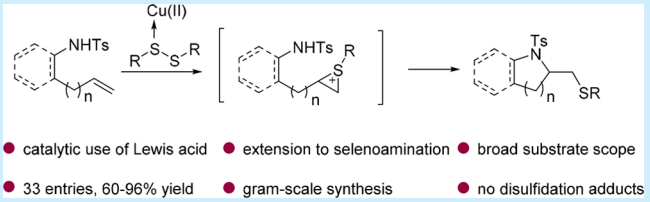
Supporting Information

ABSTRACT: The activation of disulfides by Cu(II) salts has been realized, which triggers a highly efficient electrophilic sulfenoamination of alkenes under aerobic conditions. Various sulfenyl N-heterocycles and their Selena counterparts were produced regioselectively, with no competing disulfidation products detected. Mechanistic studies suggest a profound influence of the counterions on the Lewis acidic copper center, and the important roles of oxygen and DMSO as co-oxidants for these cyclization processes.



Organosulfur compounds constitute an essential class of substances for life, as manifested in their frequent occurrence in nature and critical biochemical functions as amino acids, vitamins, and cofactors (e.g., cysteine, biotin, glutathione, etc.).[1] The unique biological properties of these molecules have inspired the innovation of a number of important pharmaceutical agents such as antibiotic penicillin. Importantly, a nitrogen-containing heterocycle motif is frequently found adjacent to the sulfur unit in these molecular frameworks (Figure 1).[2]

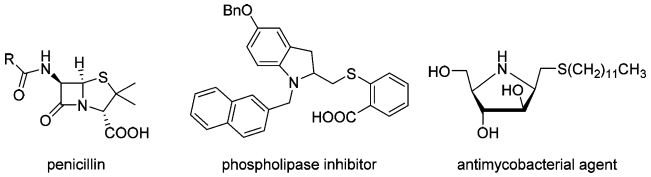
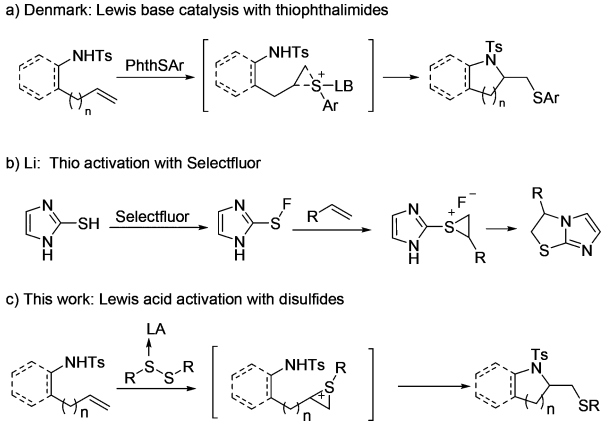


Figure 1. Selected examples of bioactive sulfenylated nitrogen-containing heterocycles.

In this context, synthetic methods allowing straightforward assembly of sulfenylated N-heterocycles are in high demand. Oxidative alkene sulfenofunctionalization has been established as a practical tool for the simultaneous introduction of sulfur and other functionalities;[3] however, direct sulfenoaminations are still rare. The majority of the known studies have focused on intermolecular acetamidosulfenylation via a Ritter-type reaction using stoichiometric acids or oxidants.[4] While other nitrogen nucleophiles have also been sporadically documented,[5] these protocols could not be easily amended in intramolecular settings for the preparation of sulfenylated N-heterocycles. In recent years, electrophilic activation of alkenes has been utilized to construct sulfenylated cyclic frameworks.[6] For instance, Denmark et al. have described that addition of arylthiophthalimides generates thiiranium ions and further leads to various ring systems upon capture by certain pendant nucleophiles (Scheme 1a).[6a−e] Such intermediates are conventionally accessed from

Scheme 1. Strategies for Intramolecular Electrophilic Alkene Sulfenoamination



reactive, but unstable sulfenyl halides,[7] thus stimulating researchers to seek alternative sulfur precursors that include ease of handling.[8] As such, the Li group recently disclosed an elegant alkene sulfenoamination reaction with sulfenyl fluoride in situ generated from thiobenzimidazoles and selectfluor (Scheme 1b).[8e] Despite advantages in terms of stability, availability, and ease of operation, drawbacks associated with these precursors,

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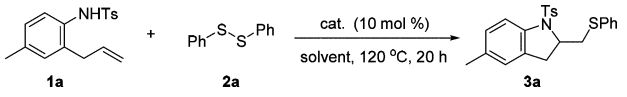
such as limited structural diversity and necessity of additional oxidants, restrict the practical applications of these protocols.

Disulfides are attractive sulfenylating reagents featuring modulable stability, ready availability, and biocompatibility.[9] The polarizability of the S−S bond renders it susceptible to scission by strong nucleophiles, as seen in thiol−disulfide exchange in biological protein contexts.[10] However, this functional group is not sufficiently polar to directly undergo electrophilic addition to alkenes, which requires activation by stoichiometric oxidants (e.g., $Pb(OAc)_4$, $Mn(OAc)_3$).[11] Fundamentally, coordination of Lewis acid to sulfur would enhance the polarization of disulfide bonds and facilitate electrophilic alkene sulfenoamination with nitrogen nucleophiles. Such a seemingly simple strategy is, however, hampered by the competitive disulfidation process and limited turnover of the metal catalyst inhibited by sulfur and other heteroatoms in the reaction mixture.[12] On the basis of our recent report on Lewis acid catalyzed synthesis of indolines via an oxidative [3 + 2] cyclization,[13] we reasoned that an appropriate selection of metal catalysts and pendant nitrogen nucleophiles with weak coordination properties might minimize poisoning of the Lewis acid center. As a result, intramolecular sulfenoamination might become possible that allows efficient assembly of valuable sulfenylated N-heterocycles (Scheme 1c).

Our study began with the search for a suitable Lewis acid catalyst for the model cyclization reaction of 2-alkenylaniline **1a** with disulfide **2a**. Pleasingly, the performance of commonly used Lewis acids, including $Zn(OTf)_2$, $Sc(OTf)_3$, $AlCl_3$, $InCl_3$, AgOTf, and $BF_3{\cdot}Et_2O$, indeed proved our hypothesis (Table 1, entries 1−5). A substantial amount of exocyclized product **3a** was regiospecifically produced (23%) with 10 mol % of $InCl_3$ at 120 °C under air. Notably, no reaction occurred in the absence of a catalyst (entry 7). Owing to the remarkable properties of copper salts as Lewis acid catalysts in organic synthesis,[14] various Cu(I) and Cu(II) compounds were also evaluated. $CuBr_2$ turned out to be highly effective, resulting in the isolation of indoline **3a** in 63% yield. The inability of $Cu(OTf)_2$ and $CuCl_2$ to mediate this process indicates the profound influence of the counterions (entries 8−10). CuBr and $FeBr_3$ were also competent catalysts, albeit less effective (entries 11−12). It is noteworthy that no disulfidation adducts were detected; employing excess disulfide **2a** was beneficial to reach complete consumption of **1a**. Solvent screening was subsequently performed, and DMSO was identified as being superior to other mediums, delivering product **3a** in 89% yield.

Having identified the optimal reaction conditions, we proceeded to explore the generality of this sulfenocyclization reaction (Scheme 2). Pleasingly, a wide range of diarylsulfides with different electronic and steric substitution patterns could be employed, and good to high yields (63−86%) were recorded for the respective adducts (**3b−o**). Aliphatic disulfides were tolerated as well, as seen in the effective production of indolines **3p−r** bearing a cyclohexyl, *n*-butyl, or benzyl group in equally good yields (64−71%). To the best of our knowledge, this case represents the only method available for the synthesis of alkylsulfenyl N-heterocycles in a single step. Apart from these, substrates **1** with different substituents on their aromatic rings were also readily processed to furnish the desired adducts **3s−v** (60−82%). Further efforts were made on the synthesis of N-heterocycles other than indolines. To our delight, tetrahydroquinoline **3w** was easily accessed (71%) as well by the same protocol from an alkenylaniline with a longer tether. Reactions with aliphatic sulfonamides also proceeded smoothly, leading to the formation of sulfenylated pyrrolines and piperidines **3x−z** with equal efficiency. Importantly, in all the cases described above, N-heterocycles were produced in a regiospecific fashion.

Table 1. Optimization of the Sulfenoamination Reaction[a]

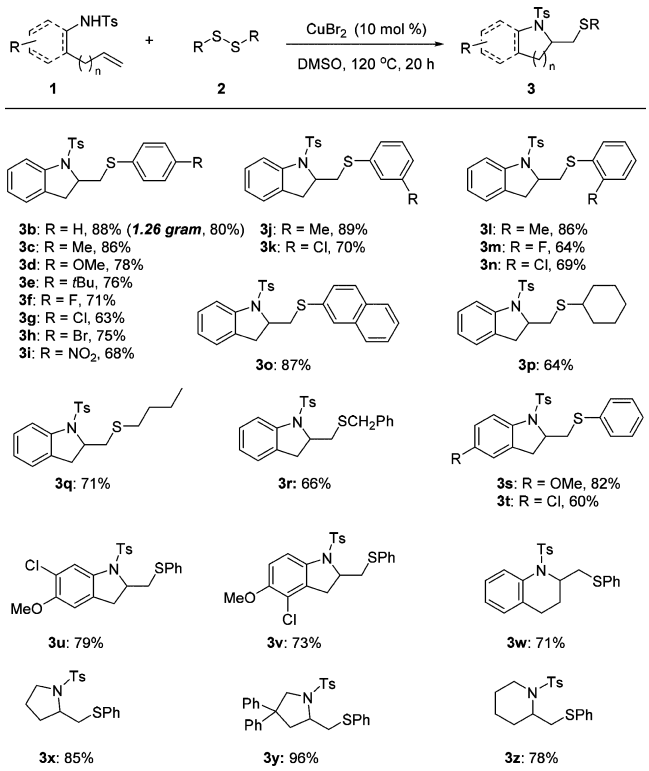


1a 2a 3a

entry	catalyst	solvent	yield[b] (%)
1	$Zn(OTf)_2$	toluene	<10
2	$Sc(OTf)_3$	toluene	<10
3	$AlCl_3$	toluene	12
4	$InCl_3$	toluene	23
5	AgOTf	toluene	11
6	$BF_3{\cdot}Et_2O$	toluene	<10
7	−	toluene	NR
8	$Cu(OTf)_2$	toluene	0
9	$CuBr_2$	toluene	63
10	$CuCl_2$	toluene	trace
11	CuBr	toluene	41
12	$FeBr_3$	toluene	38
13	$CuBr_2$	P-xylene	59
14	$CuBr_2$	DMF	85
15	$CuBr_2$	DCE	75
16	$CuBr_2$	DMSO	89
17	$CuBr_2$	1,4-dioxane	81

[a]Reactions were performed with **1a** (0.2 mmol), **2a** (0.2 mmol), and catalyst (10 mol %) in solvent (2.5 mL) at 120 °C for 20 h in a sealed tube under air. [b]Isolated yield.

Scheme 2. Scope of $CuBr_2$-Catalyzed Intramolecular Sulfenoamination of Alkenylaniline 1 with Disulfide 2[a,b]



[a]For reactions conditions, see Table 1, entry 16. [b]Isolated yield.

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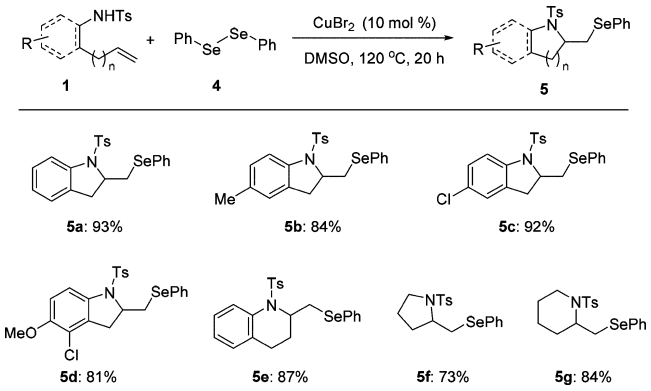
A scale-up preparation of compound **3b** (1.26 g, 80%) has been successfully performed, and we demonstrated the practicality of this synthetic method.

The success of the above-mentioned sulfenoamination reactions encouraged us to attempt an analogous synthesis of seleno-N-heterocycles owing to the strong bioactivity profiles of this class of compounds.[15] Gratifyingly, a quick examination of cyclization with diselenide **4** revealed that the desired selenylated products **5**, including indoline, tetrahydroquinoline, pyrroline, and piperidine derivatives,[16] could be efficiently prepared in higher yields (73−93%) under identical reaction conditions in comparison to their thia-counterparts (Scheme 3).

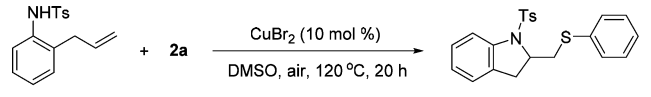
Scheme 3. Formation of Selenylated N-Heterocycles[a,b]



[a]For reactions conditions, see Table 1, entry 16. [b]Isolated yield.

To gain more insight into the reaction mechanism, additional controlled experiments were performed (Table 2). Strictly

Table 2. Controlled Experiments[a]



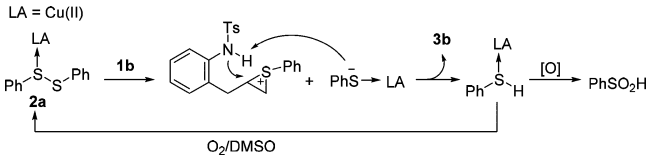
entry	changes made to standard conditions	yield[b] (%)
1	none	88
2	toluene was used instead of DMSO	69
3	in degassed DMSO under N_2	59
4	in degassed toluene under N_2	16
5	thiophenol was used instead of **2a**	80
6	thiophenol was used instead of **2a** in toluene	15
7	0.5 equiv of **2a** was used	54
8	1.5 equiv of BHT was added	44
9	5.0 equiv of BHT was added	42

[a]Reactions were performed with **1b** (0.2 mmol), **2a** (0.2 mmol), and catalyst (10 mol %) in DMSO (2.5 mL) at 120 °C for 20 h in a sealed tube under air. [b]Isolated yield.

deoxygenated reaction conditions resulted in substantially decreased reactivity in both DMSO and toluene (entries 3−4). However, the former still afforded **3b** in 59% yield, suggesting an oxidation process involving both molecular oxygen and DMSO is in operation.[17] This speculation was further evidenced by the fact that cyclization with thiophenol as a sulfur precursor also yielded product **3b**, and a higher yield was again recorded with DMSO than toluene (entries 5−6). The necessity of using excess disulfide might be attributable to the generation of sulfinic acid.[18]

Nevertheless, given that a 54% yield was obtained based on 0.5 equiv of **2a** (entry 7), it seems safe to conclude that both sulfur atoms of **2a** are incorporated into product **3b** in an atom-economic fashion under aerobic conditions. On the other hand, despite certain degrees of inhibition with BHT as an additive, the isolated yield of **3b** was, in reality, independent of the quantity of this radical scavenger. These observations suggest that a radical mechanism is not likely the case in the present catalytic system. Collectively, we propose a plausible reaction mechanism (Scheme 4). Complexation of copper with a sulfur atom

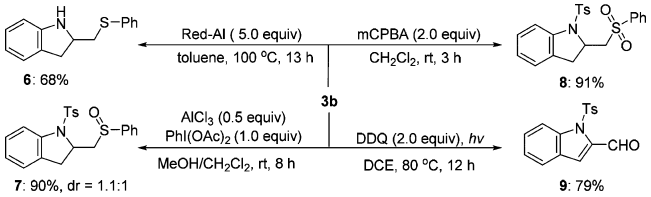
Scheme 4. Plausible Reaction Mechanism



polarizes the S−S bond of **2a** and triggers an electrophilic addition to the olefin moiety of **1b**, and the resulting thiiranium ion undergoes a regioselective ring-opening transformation to afford product **3b** and thiophenol. The latter is oxidized into disulfide **2a** to re-enter the catalytic cycle and is associated with partial overoxidation into the side product sulfinic acid. The thiophilic nature of copper and profound influence of the counterions on its Lewis acidity might account for the superior catalytic performance of $CuBr_2$ over others,[14] as showcased in Table 1.[19]

The removal of the tosyl group was readily accomplished by treating **3b** with Red-Al, and indoline **6** was obtained in 68% yield. The functionalized N-heterocycles produced herein are not only of potential biological interest but also synthetically useful (Scheme 5). For instance, compound **3b** could be

Scheme 5. Synthetic Manipulations Using Adduct 3b as a Precursor



selectively oxidized into sulfoxide **7** (with separable 1:1 diastereoisomers) or sulfone **8** in excellent yields under specific conditions. Moreover, upon treatment with DDQ in heated dichloroethane, adduct **3b** underwent a photochemical desulfenylative aromatization to give indole **9** (79%).[20] As such, our method provides a highly practical two-step conversion of alkenylaniline derivatives into indole-2-carboxaldehydes, a class of versatile synthon in organic chemistry.

In summary, we have developed a highly efficient copper-catalyzed intramolecular sulfenoamination reaction of alkenes. Notably, this is the first time that Lewis acid activation of disulfides has been realized successfully for in situ generation of electrophilic thiiranium intermediates for aminofunctionalization of alkenes. Diaryl and dialkyl sulfides as well as aryl and alkyl sulfonamides are compatible reaction partners in this protocol, allowing access to a broad range of synthetically and biologically valuable sulfenyl N-heterocycles. Detailed mechanistic investigations and attempts to apply this novel Lewis acid catalyzed

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sulfenylation process to other organic transformations are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01803.

Experimental procedures, analytical data for all new compounds, NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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(18) A substantial amount of sulfinic acid was detected in the reaction mixture, and the oxidation mechanism is still unclear. Further controlled experiments showed disulfide **2a** alone was also oxidized under the same conditions.

(19) These significantly lower yields obtained with redox-inactive Lewis acids in Table 1 also suggest that copper might function as both a Lewis acid and oxidant mediator. For relevant studies, see: (a) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074. (b) Hemric, B. N.; Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2016**, *138*, 5813. (c) Shen, K.; Wang, Q. *J. Am. Chem. Soc.* **2017**, *139*, 13110. (d) Wu, F.; Stewart, S.; Ariyarathna, J. P.; Li, W. *ACS Catal.* **2018**, *8*, 1921.

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