Cu(II)-Catalyzed Aerobic Synthesis of Sulfinamidines from Sulfenamides

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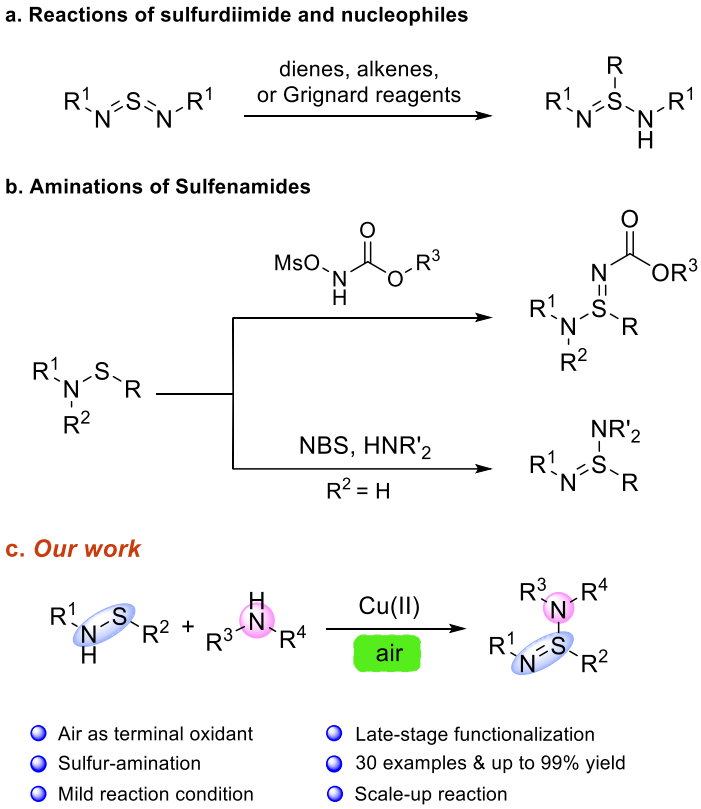
Herein, we present the pioneering example of copper-catalyzed oxidative amination of sulfenamides for the synthesis of sulfinamidines. By employing air as the terminal oxidant, a diverse array of secondary and primary amines can be efficiently transformed into their corresponding products. This method is well-suited for last-stage functionalization, and the underlying mechanism has been investigated. The transformation is characterized by exceptional chemoselectivity, mild conditions, facile operation, and broad substrate compatibility, which holds significant implications for the fields of pharmaceuticals and organic synthesis.

Within the sphere of drug discovery, burgeoning attention is directed toward devising cutting-edge synthetic methodologies for the incorporation of sulfur-bearing functional moieties.[1] The pharmacological realm of trivalent sulfur architectures is primarily typified by the prevalence of sulfoxides.[2] Notwithstanding, the synthesis of other potentially consequential trivalent sulfur aza analogs, such as sulfinamidines, persists as an under-explored domain in scientific inquiry. Sulfinamidines, a unique class of organosulfur compounds characterized by an S=N double bond, have attracted considerable attention in recently due to their potential applications in medicinal chemistry and as versatile building blocks in organic synthesis.[3] Despite the growing interest in these compounds, the current synthetic strategies for accessing sulfinamidines remain limited, often suffering from drawbacks such as stringent reaction conditions, complex starting materials, or the need for stoichiometric amounts of reagents, which can affect the scalability and sustainability of these approaches. For instance, early methods involving the reaction of sulfurdiimides with conjugated dienes, [4] alkenes, [5]and Grignard reagents[6] necessitate stringent reaction conditions and complex starting materials, hindering their synthetic utility and scalability (Scheme 1a).
Sulfenamides synthesized from a variety of starting materials, such as thiols, amines, and halogenated compounds, offers a flexible platform for generating diverse structures and reactivity profiles, drawing increased attention from chemists very recently.[7] Sulfenamides, especially those featuring an S-NH bond, have gained prominence as valuable intermediates in organic synthesis. Possessing excellent sulfur nucleophilicity, these compounds have recently become the subject of extensive research among chemists. For instance, Ellman achieved S-alkylation of carbenes with sulfenamides using a Rh(II) catalyst,[8] while Li[9] and our group [10] accomplished S-alkylation

under metal-free conditions. Moreover, we have recently reported on S-arylation [11] and S-esterification [12] reactions involving sulfenamides. However, methods for transforming sulfenamides into sulfinamidines have been relatively underexplored. In a significant advancement, Luisi and colleagues presented a streamlined approach for synthesizing sulfinamidines, utilizing sulfenamides and sulfonyloxycarbamates as nitrogen sources (Scheme 1b). [13] This method demonstrated improved efficiency and broader substrate scope compared to the previous approaches. However, the reliance on sulfonyloxycarbamates, which can be challenging to prepare and handle, remains a drawback of this strategy. More recently, Li and co-workers described a tandem oxidative bromination and amination process of sulfenamides for constructing sulfinamidines (Scheme 1c).[14] This innovative method leverages the benefits of a tandem reaction sequence, allowing for the formation of the desired sulfinamidines in a single synthetic operation. Nevertheless, the requirement for stoichiometric amounts of brominating reagents raises concerns about the environmental impact and cost-effectiveness of this approach. In addition to the aforementioned strategies, a few other methods have been reported in the literature with limited supporting documentation. [15] Despite the variety of methods available, there remains a need for the development of efficient, sustainable, and broadly applicable synthetic strategies for accessing sulfinamidines. Inspired by Jia's and Ellman's recent research on Cu-catalyzed S-arylation of sulfenamides, [16] we introduce a novel Cu(II)-catalyzed aerobic synthesis of sulfinamidines derived from sulfenamides. This method employs both sulfenamides and amines as substrates, facilitating the formation of the S=N bond through an oxidative amination process under an air atmosphere (Scheme 1c).

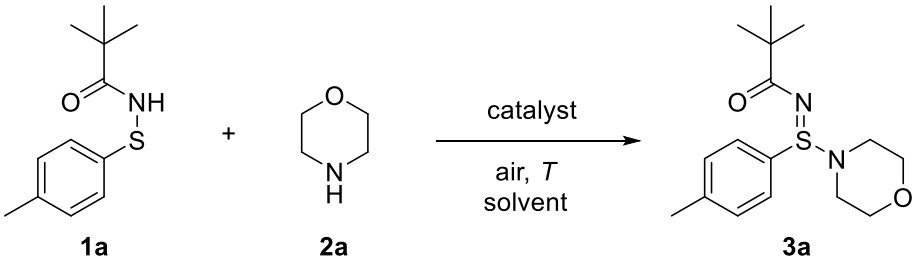


Scheme 1. Representative Methods for the Synthesis of Sulfinamidines

We initiated our research utilizing NH-monosubstituted sulfenamides **1a** and morpholine **2a** as

model substrates to determine the ideal reaction conditions (Table 1). Sulfenamides **1a** underwent a streamlined oxidation process, successfully synthesizing sulfinamidine **3a** in the presence of an earth-abundant Cu compound in toluene. However, the yield remained moderate, necessitating a reaction period of 48 hours (Table 1, entry 1). We subsequently investigated alternative transition metal catalysts, revealing that Cu compounds exhibited appreciable reactivity, while Fe compounds displayed negligible catalytic activity. Furthermore, incorporating MnO_2 as an equivalent proved unproductive in generating the target compound. In subsequent analyses, we scrutinized the effects of temperature and solvent parameters. Experimental results demonstrated that the reaction yielded superior performance in DCM. Temperature played a crucial role in the reaction dynamics, with elevated temperatures inversely affecting yield, likely attributable to the compromise of the air atmosphere above the reaction solution due to solvent vapor at higher temperatures. Lastly, we optimized catalyst and morpholine stoichiometry. Diminishing the catalyst proportion to 15 mol% exerted a minimal influence on yield, while augmenting the morpholine equivalent resulted in an NMR yield of 93% and an isolated yield of 85%. The impact of reaction duration on yield is notably significant. Extending the reaction time contributes to increased reaction conversion; however, it may occasionally result in a decline in yield. This phenomenon can be attributed to the partial transformation of the sulfenamide into a sulfoxide structure during the process.

Table 1 Reaction optimization [a]



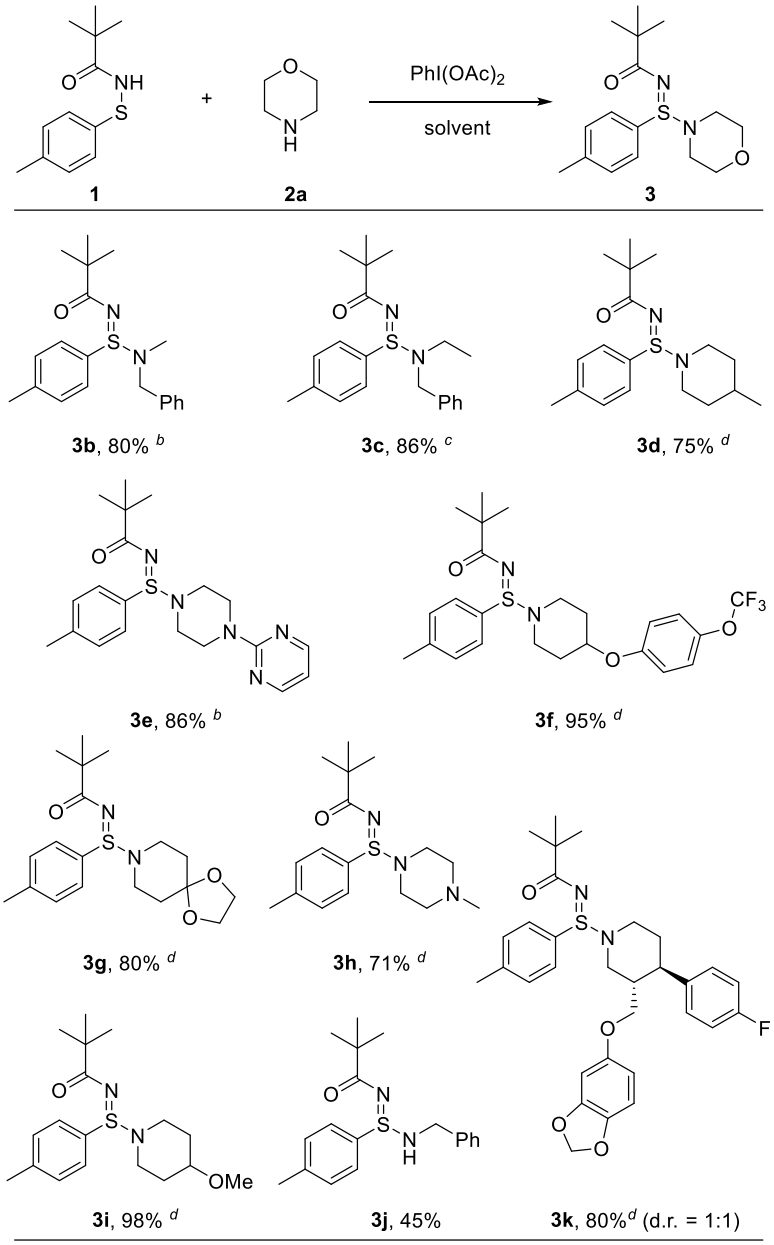
1a **2a** **3a**

Entry	Cat.	Solvent	Temp	Yield(%) [b]
1 [c]	$CuBr_2$	Toluene	r.t.	75 [c]
2 [d]	$Cu(OTf)_2$	Toluene	r.t.	45
3	CuI	Toluene	r.t.	40
4	$FeCl_2$	Toluene	r.t.	Trace
5	$CuBr_2$	DCM	50 ℃	79
6	$CuBr_2$	EtOAc	50 ℃	77
7	$CuBr_2$	DMF	50 ℃	63
8	$CuBr_2$	THF	50 ℃	76
9	$CuBr_2$	MeCN	50 ℃	72
10	$CuBr_2$	DCM	60 ℃	73
11	$CuBr_2$	DCM	90 ℃	18
12 [d,e]	$CuBr_2$	DCM	50 ℃	93 (85) [c]
13 [d]	$CuBr_2$	DCM	50 ℃	88
14 [d,f]	$CuBr_2$	DCM	50 ℃	89

a. Unless otherwise noted, reactions were performed with sulfonamide **1a** (1.0 equiv, 0.10 mmol), morpholine **2a** (2.0 equiv, 0.2 mmol), 20 mol% $CuBr_2$ (1.5 equiv, 0.3 mmol), and solvent (2.0 mL), for 2 days. b. ^1H NMR yields were determined using mesitoxybenzene as an internal standard. c. Isolated yield.

d. The reactions were conducted for a duration of 12 hours. e. 2.5 equiv. of morpholine **2a** was utilized. f. 15 mol% $CuBr_2$ was employed in the process.

Scheme 2. Substrate scope of amines [a]



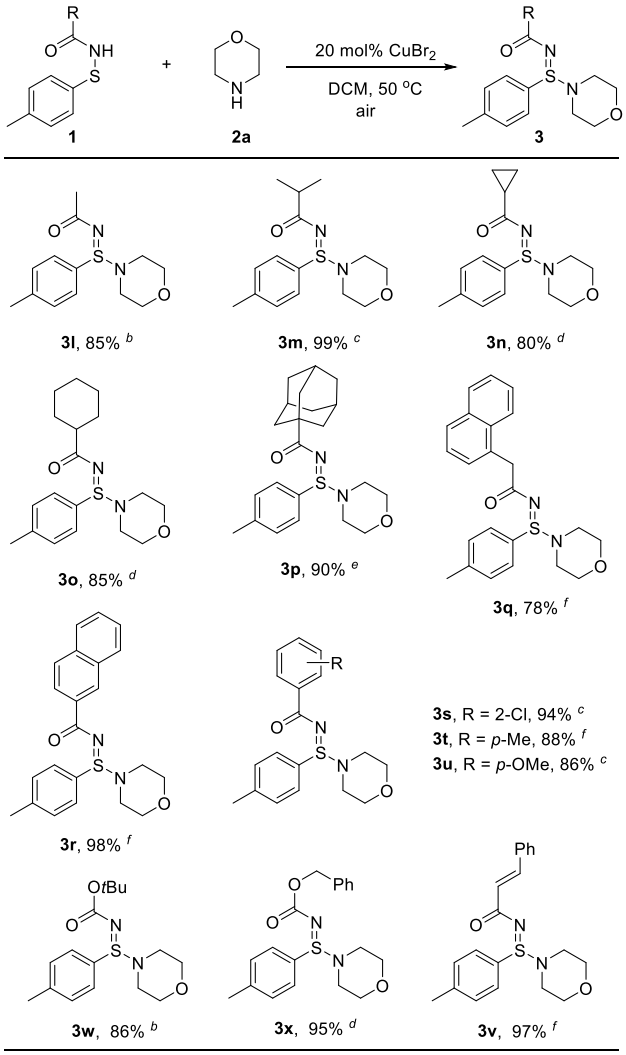
a Reaction conditions: Sulfenamides (0.15 mmol, 1.0 equiv.), morpholine (2.5 equiv.), $CuBr_2$ (20 mol%), DCM, 50 °C, air atmosphere. b Reactions proceeded for 3 days. c Reactions proceeded for 6.5 days. d Reactions proceeded for 4 days.

Under the optimal reaction conditions, we initially explored the substrate scope of amines with NH-monosubstituted sulfenamides **1a** under $CuBr_2$/air conditions (Scheme 2). Generally, both linear and cyclic amines yielded the corresponding target products in moderate to high yields under standard conditions. Straight-chain amines, such as *N*-methylbenzylamine (**3b**) and *N*-ethylbenzylamine (**3c**), achieved target product yields of 80% and 86% under the optimal reaction conditions. However, N-diethylamine cannot produce the desired product and 60% sulfoxide product was obtained (See the

Supporting Information for more details). Conversely, a significantly lower yield was obtained when *N*-dibenzylamine was employed as the starting material. These findings suggest that the steric hindrance of amines plays a pivotal role in influencing reactivity. 1-Methylpiperazine (**3h**) and substituted piperidines (**3d,3f, 3i**) were well tolerated under standard conditions, yielding 71-98% of the product, with the 4-substituted alkoxy group exhibiting exceptional activity. The ketal structure, which exhibits good tolerance under standard conditions, was incorporated at the 4-position of piperidine, enabling the successful synthesis of product **3g** with a yield of 80%. Notably, when an N atom susceptible to Lewis acid coordination is present in the substrate amine, the reaction can still progress smoothly, yielding 86% of **3e**. Finally, we assessed the reactivity of primary amines under standard conditions. The target compound **3j** was successfully obtained after a two-day reaction period, albeit with a modest yield.

Motivated by the preceding results, we further probed the impact of diverse acyl substitutions in sulfenamides. Sulfenamides showcasing alkanoyl substituents, including linear formyl (**3l**), branched isobutyryl (**3m**), cyclic cyclopropanecarbonyl (**3n**), and cyclohexanecarbonyl (**3o**) groups, exhibited good tolerance under optimized conditions, delivering corresponding products with yields ranging from 80-99%. Moreover, we were delighted to find that sterically encumbered adamantane-1-carbonyl and 2-(naphthalen-1-yl)acetyl produced products **3p** and **3q** with yields of 90% and 78%, respectively. Thereafter, various aryloyl substituents in sulfenamides were investigated. Under standard conditions, the reactivity of the sterically demanding 2-naphthoyl (**3r**) and 2-chlorobenzoyl (**3s**) was maintained, achieving 98% and 94% yields, respectively. Sulfenamides bearing both methyl and methoxy substituents at the para position of the benzoyl ring were examined, resulting in products with moderate to appreciable yields (**3t** and **3u**). Impressively, the current oxidative system demonstrated proficiency in accommodating the C=C double bond, as illustrated by the efficient synthesis of product **3v** at an 97% yield. Furthermore, sulfenamides originating from *tert*-butyl carbamate and benzyl carbamate yielded the desired products in good to excellent yields (**3w** and **3x**).

Scheme 3. The impact of diverse acyl substitutions in sulfenamides. [a]

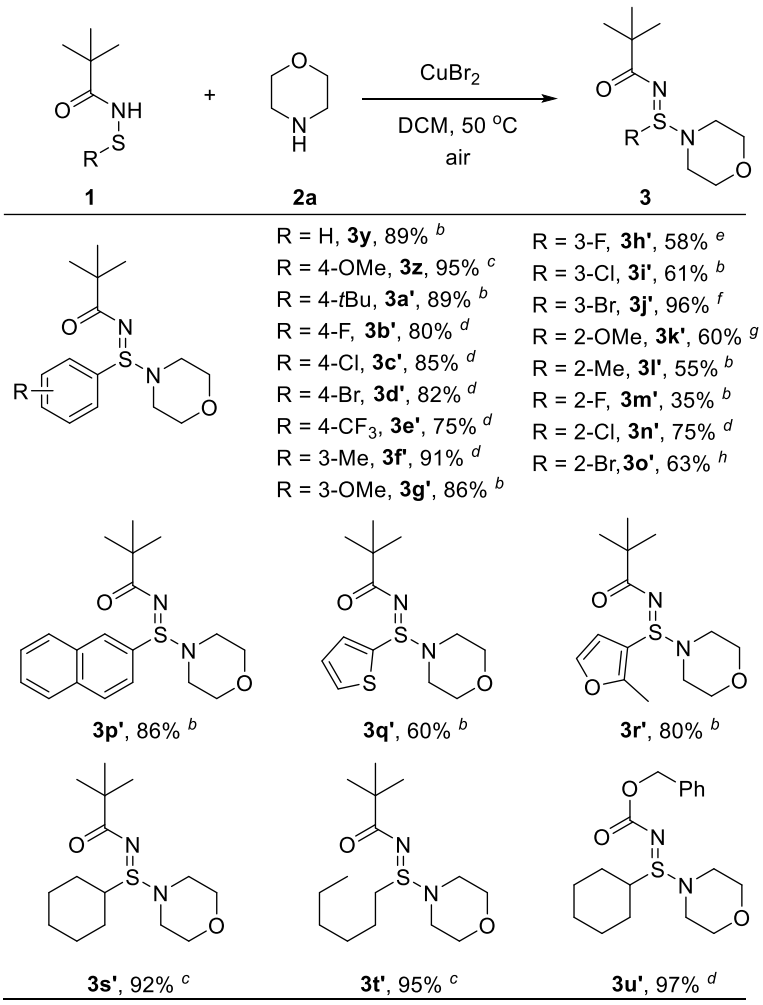


a Reaction conditions: Sulfenamides (0.15 mmol, 1.0 equiv.), morpholine (2.5 equiv.), $CuBr_2$ (20 mol%), DCM, 50 °C, air atmosphere. b Reactions proceeded for 2 days. c Reactions proceeded for 1 days. d Reactions proceeded for 3 days. e Reactions proceeded for 1.5 days. f Reactions proceeded for 4 days.

Finally, we investigated the impact of various substituents on the reactivity of phenylsulfenamides, thereby expanding the range of substrates under examination (Scheme 4). Our findings clearly indicate that the substitutions on the benzene ring is a crucial determinant of reactivity in phenylsulfenamide-based reactions. While para- and meta-substituted derivatives exhibited minimal impact on product yield, the ortho-substituted counterparts, whether electron-rich or electron-poor, severely impeded reactivity. We attribute this observation to the ortho effect, which likely influences the coordination between the copper compound and the sulfur atom at the reaction center, thereby modulating the reaction pathway. In addition, our results highlight the pronounced impact of electronic effects on reaction outcomes. Specifically, electron-donating substituents were found to promote product formation, whereas electron-withdrawing groups led to diminished reactivity and often necessitated prolonged reaction times to achieve desired conversion rates. These findings underscore the intricate interplay between steric and electronic factors that govern the reactivity of sulfenamides and provide valuable insights into the design of more efficient catalysts.

Notably, heteroatom aryl-substituted sulfenamides were suitable for the transformation, affording sulfinamidines **3q'** and **3r'** in 60% and 80% yields, respectively. We were pleased to find that both straight and branched chain alkanethiols gave rise to sulfenamides that displayed exceptional reactivity under standard reaction conditions, whether the thiol partner was an amide or benzyl carbamate derivative (**3s'**-**3u'**).

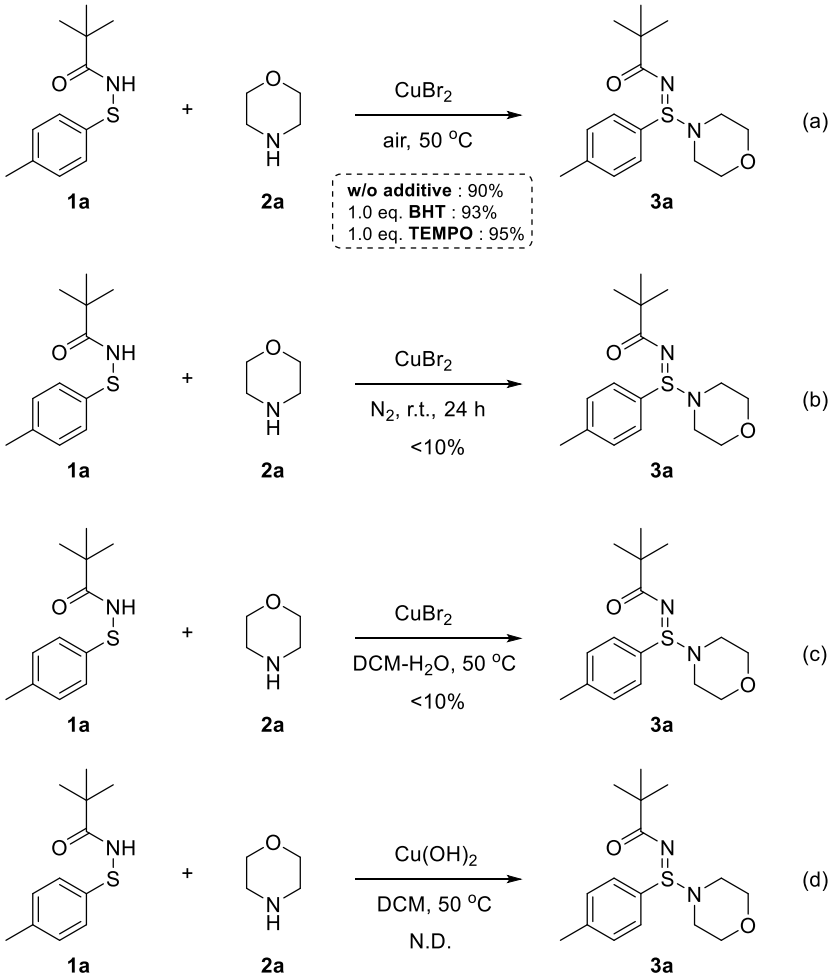
Scheme 4. Substrate scope of sulfenamides from diverse thiols.



a Reaction conditions: Sulfenamides (0.1 mmol, 1.0 equiv.), morpholine (2.0 equiv), $CuBr_2$ (20 mol%), DCM, 50 °C, air atmosphere. b Reactions proceeded for 2.5 days. c Reactions proceeded for 1 days. d Reactions proceeded for 3 days. e Reactions proceeded for 2 days. f Reactions proceeded for 4.5 days. g Reactions proceeded for 3.5 days. h Reactions proceeded for 7 days.

To gain insights into the oxidation mechanism governing the present protocol, we carried out a series of control experiments. We began by introducing radical scavengers, such as butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), as additives in the model reaction involving substrate **1a** (Scheme 5). Based on the findings, it is evident that the additives do not have a significant impact on the yields compared to the case without any additives. It may be necessary to exclude free radical reaction pathways. When the reaction is carried out under

a nitrogen atmosphere, the yield declines drastically, signifying that oxygen is essential for the reaction to progress. Based on the above control experiments, we proposed a possible reaction process (See the Supporting Information for more details).



Scheme 5. Control experiments.

In conclusion, we have successfully developed a copper-catalyzed aerobic oxidative amination process for sulfenamides, culminating in a variety of sulfinamidines. This method exhibits extensive substrate compatibility, efficiently converting sulfenamides derived from amides and carbamates, and incorporating primary and secondary amines as partners, into their respective sulfinamidines under remarkably mild conditions. Additionally, this operationally straightforward technique relies solely on air as a terminal oxidant, rendering it highly accessible and well-suited for potential industrial-scale applications. Regarding the practical applications of these products, our research team is currently conducting additional experiments and expects to disclose our findings at a later date.

ACKNOWLEDGMENT

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