

# Synthesis of Sulfilimines Enabled by Copper-Catalyzed S-Arylation of Sulfenamides

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## Article

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# Abstract

Herein, an unprecedented synthetic route to sulfilimines via a copper-catalyzed Chan-Lam-type coupling of sulfenamides is presented. A key to success in this novel transformation is the chemoselective *S*-arylation of S(II) sulfenamides to form the S(IV) sulfilimines, overriding the competitive C-N bond formation that does not require a change in sulfur oxidation state. The mild and environmentally benign catalytic conditions enable broad functional group compability. A variety of diaryl or alkyl aryl sulfilimines could be efficiently prepared. The Chan-Lam coupling procedure could also tolerate alkenylboronic acids as coupling partners to afford alkenyl aryl sulfilimines, a class of scaffolds which cannot be directly synthesized via conventional imination strategies. The benzoyl protecting groups could be conveniently removed from the product which, in turn, could be readily transformed to several S(IV) and S(IV) derivatives.

## Introduction

Sulfilimines, the aza-analogues of sulfoxides, are a class of unique tetravalent sulfur-derived compounds. They find widespread applications in organic chemistry, serving as versatile intermediates, nitrene transfer reagents, directing groups, among others.<sup>1-3</sup> Chiral sulfilimines have also been developed as ligands for enantioselective transition-metal catalysis.<sup>4,5</sup> Recently, the biological significance of sulfilimines has drawn much attention. In 2009, Hudson and coworkers revealed that hydroxylysine-211 and methionine-93 in collagen IV was covalently cross-linked by a sulfilimine bond, which represents the first sulfilimine group identified in biomolecules.<sup>6,7</sup> This novel bond, which is an evolutionary adaptation to mechanical stress in metazoan evolution, is believed to play an important role in stabilizing the network of the basement membrane. In the field of chemical biology, Chang, Toste and coworkers have introduced a seminal methionine bioconjugation protocol by transforming methionines to the corresponding sulfilimine derivatives using oxaziridines under biocompatible conditions.<sup>8,9</sup> This powerful tagging method allows access to antibody-drug conjugates as well as identification of reactive methionine residues in whole proteomes.

Owing to the significant roles of sulfilimines in chemistry and biology, much effort has been devoted to their synthesis.<sup>10</sup> Conventionally, sulfilimines are prepared from the corresponding sulfides via a oxidative imination strategy wherein a sulfur-nitrogen double bond is generated (**Scheme 1a**).<sup>10</sup> This imination strategy suffers from limited compability with functional groups due to the requisite oxidation conditions. In addition, some commonly used imination reagents, such as the azide, are potentially explosive which jeopardizes their applications, especially in industry. Inspired by sulfur transferases, the Zhao group reported an elegant [2,3]-sigmatropic rearrangement of oxyacetamide derivatives to afford *ortho*-sulfiliminyll phenols (**Scheme 1b**).<sup>11,12</sup> This strategy again forms the sulfur-nitrogen double bond. To date, this novel strategy has not been expanded beyond the synthesis of *ortho*-hydroxylaryl sulfilimines. Willis and coworkers disclosed an innovative consecutive addition of two Grignard reagents to a bespoke sulfinylamine to afford sulfilimines (**Scheme 1c**).<sup>13</sup> While a redox neutral process, the application of this

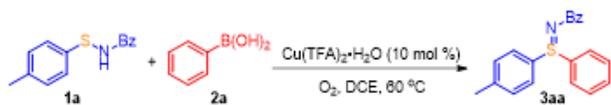
approach is limited to substrates that can tolerate the reactive Grignard reagents employed. Therefore, the development of mild and efficient synthetic methods to access to sulfilimines with broad functional groups tolerance remains a challenge.

Copper-catalyzed Chan-Lam coupling has emerged as one of the most powerful tools to construct C-N, C-O and C-S bonds in the past decades, attributed to cheap and abundant catalysts, an absence of elaborate ligands, mild and environmentally benign reaction conditions, as well as the excellent functional group compatibility.<sup>14, 15</sup> Very recently, our group reported an unprecedented photoredox dehydrogenative Chan-Lam coupling of diaryl sulfoximines under external-oxidant-free conditions.<sup>16</sup> We envisioned that sulfenamides (R-S-NH-R'), a class of stable and easily accessible sulfur(II)-derived molecules,<sup>17</sup> could undergo rearrangement to yield sulfiliminyll species, which could be utilized as a key intermediate to generate sulfilimines via a highly chemoselective *S*-arylation strategy. To the best of our knowledge, the *S*-arylation of sulfenamides has not been explored previously, most likely due to competitive reaction on the more nucleophilic nitrogen atom. Herein, we report a novel copper-catalyzed Chan-Lam-type *S*-arylation of sulfenamides and arylboronic acids to provide a facile access to diverse sulfilimines (**Scheme 1d**). In this process, S(II) compounds are converted to S(IV) compounds using only oxygen as the oxidant. In contrast to other oxidative routes (**Scheme 1a-b**), the substrate herein begins with an S-N single bond and the method creates a new S-C double bond.

## Results

**Reaction development.** We chose readily accessible sulfenamide (**1a**) and commercially available phenylboronic acid (**2a**) as the model substrates to optimize the catalytic conditions (**Table 1**). After the extensive studies, the optimal conditions were determined to be: sulfenamide (**1a**) as the limiting reagent, 1.2 equiv of phenylboronic acid (**2a**), 10 mol % of Cu(TFA)<sub>2</sub>·H<sub>2</sub>O as catalyst, in 1,2-dichloroethane (DCE, 0.2 mM), under an O<sub>2</sub> atmosphere (1 atm), at 60 °C for 12 h. The assay yield of the desired product **3aa** was 97%, with 94% isolated yield (**Table 1**, entry 1). For complete screening results, see Supporting Information (SI) for details. In addition, we conducted a series of control experiments. When the loading of copper catalyst was reduced to 5 mol %, the assay yield of **3aa** dropped dramatically to 34% (**Table 1**, entry 2). There was no desired product detected if no copper catalyst was employed, indicating its crucial role (**Table 1**, entry 3). When the oxygen atmosphere was replaced by argon atmosphere, **3aa** was only obtained in 13% assay yield due to the absence of external oxidant (**Table 1**, entry 4). Without the exposure to ambient light, the assay yield of **3aa** remained high (92%), which indicates that ambient light does not play a key role in the transformation (**Table 1**, entry 5). When a small amount of water (2.0 μL) was introduced to the standard conditions, the assay yield of **3aa** was somewhat diminished (85%) (**Table 1**, entry 6).

**Table 1.** Optimization of Sulfilimine Synthesis via a Copper-Catalyzed *S*-Arylation of Sulfenamide (**1a**) with Phenylboronic Acid (**2a**)<sup>a</sup>



entry	derivation from standard conditions	assay yield <sup>b</sup> /%
1	none	97/94 <sup>c</sup>
2	$\text{Cu}(\text{TFA})_2 \cdot \text{H}_2\text{O}$ (5 mol %)	34
3	without $\text{Cu}(\text{TFA})_2 \cdot \text{H}_2\text{O}$	0
4	$\text{O}_2$ replaced by Ar	13
5	without light	92
6	$\text{H}_2\text{O}$ (2.0 $\mu\text{L}$ ) added	85

**Substrate scope.** Having the optimal reaction conditions in hand, the scope of arylboronic acids in the coupling was investigated using **1a** (Table 2). The parent phenylboronic acid (**2a**) coupled successfully with **1a** to furnish **3aa** in 94% yield on small scale and was similarly effective on gram scale (4.1 mmol, 1.0 g) providing the product in 85% yield. Arylboronic acids bearing electron-donating groups, such as 4-Me (**2b**) or 4-OMe (**2c**), were compatible with the reaction conditions, providing **3ab** and **3ac** in 92% and 77% yield respectively. Electron-withdrawing groups, such as 4-F (**2d**), 4-Cl (**2e**), 4-Br (**2f**), or 4-CF<sub>3</sub> (**2g**), were well tolerated using the same conditions, and the corresponding products (**3ad-g**) were synthesized in yields ranging from 65% to 96%. The connectivity was unambiguously determined by X-ray crystallography of **3ae** (see SI for details). The sterically hindered 2-methylphenylboronic acid (**2h**) was also tolerated, affording **3ah** in 65% yield. 3-Substituted arylboronic acids were competent coupling partners, as evidenced by the formation of **3ai** in 79% yield. In accord with the mild reaction conditions, an array of functional groups could be incorporated on the arylboronic acid component. Aldehyde (**2j**), ketone (**2k**), ester (**2l**), unprotected hydroxyl (**2m**), and vinyl (**2n**) groups were well tolerated by our coupling protocol to provide the corresponding products (**3aj-n**) in 50–77% yields. Heteroarylboronic acids also exhibited good compatibility under the coupling conditions, and *N*-arylated products of the unprotected indolyl (**3ao**), 5-benzofuranyl (**3ap**) and 5-benzothiophenyl (**3aq**) sulfilimines were prepared in 42–89% yields. This method afforded novel sulfilimine-modified tyrosine (**3ar**), albeit in modest yield (63%). The coupling reactions of arylboronic acids bearing unprotected phenol (**2m**), free indole (**2o**), and secondary amide (**2r**) are particularly impressive, since they are known to afford the corresponding *O*- or *N*-arylated products by Chan-Lam couplings.<sup>14,15</sup> Of note, alkenyl aryl sulfilimines are challenging to prepare via the classical imination of sulfides, due to competitive addition of nitrenes to alkenes.<sup>18</sup> Remarkably, the couplings with vinylboronic acids formed of desired products (**3as-v**) in synthetically useful yields (33–55%), highlighting the power of this protocol.

Subsequently, we turned our attention to varying the sulfur substrate component coupling with phenylboronic acid **2a** (Table 2). The parent phenyl sulfenamide (**1b**) reacted successfully with **2a** to give

**4ba** in excellent yield. Aryl sulfenamides bearing electron-donating groups were amendable substrates for the coupling reaction, as evidenced by the formation of **4ca** in 84% yield. The electron-withdrawing groups appended on aryl sulfenamides, such as 4-F (**1d**), 4-Cl (**1e**), or 4-NO<sub>2</sub> (**1f**), were well tolerated, providing **4da-fa** in good yields. This coupling procedure also exhibited excellent compability with steric demanding 2-substituted aryl sulfenamides, and **4ga-ja** were prepared in 73-87% yield. The chemistry also accommodated aryl sulfenamides with 3-substituents, with **4ka** and **4la** being obtained in 80% and 64% yield, respectively. The coupling reaction between 2,4-difluorophenylboronic acids **1m** and **2a** proceeded smoothly to give **4ma** in 71% yield. A 2-thiophenyl substrate provided heteroaryl sulfilimine **4na** in moderate yield.

To determin if alkyl aryl sulfilimines could be formed, *S*-alkyl sulfenamides were evaluated (**Table 2**). The *S*-alkyl sulfenamides coupled very sluggishly when O<sub>2</sub> was employed as an oxidant. As such, we hypothesize that a stronger oxidant and higher temperatures would be effective. In line with this reasoning, 80 °C and DTBP as oxidant provided the product from linear *n*-heptyl sulfenamide (**1o**) in 81% yield (**5oa**). *S*-Alkyl sulfenamides bearing aromatic substituents could couple successfully with **2a**, exemplified by **5pa** (57%). The coupling procedure exhibited excellent compability toward *S*-alkyl sulfenamides containing a range of functional groups, including ester (**1q**, **1r**), nitrile (**1s**), ketone (**1t**) or amide (**1u**), with the corresponding products **5qa-ua** forming in 47-77% yield. The chemistry also accommodated sulfenamides bearing cyclic substituents leading to the formation of **5va** and **5wa** in 84% and 51% yield, respectively.

At the outset of this work, the mechanism for the transformation of a sulfenamide to sulfilimine was uncertain, and the factors that allowed *S*-coupling vs *N*-coupling were especially unclear. Several mechanisms were thus surveyed computationally. The initial ground states of the copper(II) species were surveyed using B3LYP/6-31G(d), Cu:SDD<sup>19, 20</sup> and pathways were calculated with PCM-DCE-M06-gd3/6-311+G(3d,p), Cu:SDD//B3LYP-GD3/6-311+G(3d,p), Cu:SDD<sup>21-24</sup> using Gaussian 16.<sup>25</sup> All graphics were made with Cylview.<sup>26</sup>

The bimolecular reductive elimination proposed by Stahl and coworkers<sup>27</sup> was investigated initially. In this proposed mechanism, the initial copper(I) is oxidized by O<sub>2</sub> which is followed by transmetalation with an arylboronic acid. Disproportionation with CuX<sub>2</sub> is invoked to generate a Cu(III) species along with a Cu(I) byproduct. A six-membered transition state can then be envisioned where the sulfur forms a carbon bond and the N-H hydrogen is abstracted by one of the X-groups on copper. Despite significant exploration, such a transition state could not be located computationally.

As such, we turned to possible pathways based on the proposed mechanism by Watson (**Figure 1a**).<sup>28</sup> Here, ligand exchange of the sulfenamide onto Cu(II) is followed by transmetalation of the arylboronic acid. Disproportionation with Cu(TFA)<sub>2</sub> is proposed to generate a Cu(III) species along with a Cu(I) byproduct. Reductive elimination then forms the S-C bond. Finally, the Cu(I) is reoxidized to Cu(II) by O<sub>2</sub>.

To begin exploring this pathway, the binding patterns for the deprotonated sulfenamide and Cu(II)OH species was investigated with different numbers of water molecules as ligands. To simplify calculations, a phenyl was used for Ar<sup>1</sup>/Ar<sup>2</sup> and *N*-acetyl was used in place of *N*-benzoyl. The two lowest energy geometries included copper complexes coordinating the sulfenamide at the nitrogen or at the sulfur (SI Scheme S2).

Notably, the initial complex binding through sulfur (**I**) is lower in energy than binding through nitrogen (**VI**) (**Figure 1b**). The structure of **I** is a more ideal square planar complex than **VI** contributing to the lower energy of that complex. Transmetalation of these initial complexes gave rise to **III** and **VIII** via transition states **II** and **VII**, respectively. Disproportionation with another Cu(II) provides to Cu(III) complexes **IV** and **IX**, along with copper(I) trifluoroacetate. Reductive elimination from these Cu(III) intermediates then forms aryl-heteroatom bond via transition states **V** and **X**.

For these pathways, the possible spin states for the disproportionation intermediates (**IV** and **IX**) and reductive elimination transition states (**V** and **X**) were explored since Cu(III) can exist as a singlet or triplet.<sup>29,30</sup> The triplet spin state for the nitrogen-bonded compounds **IX** and **X** was over 20 kcal/mol higher in energy than the singlet. No triplet reductive elimination transition state for the sulfur pathway would optimize. As such, the singlets became the focus and are shown in Figure 1b.

The reductive elimination transition state energy is lower for the C-N bond forming reaction (**X**) and proceeds through a classic three-membered transition state. In contrast, the C-S bond forming transition state (**V**) is 6.6 kcal/mol higher in energy. The hard Cu(III) avoids directly bonding with the soft sulfur center. Rather, the transition state involves coordination through the oxygen of the carbonyl while the sulfur adds to the carbon center via a six-membered transition.

Overall, the selectivity of the process appears to be determined during the transmetalation event which is the rate limiting step. Specifically, the *S*-transmetalation transition state (**II**) is 2.1 kcal/mol lower in energy than the *N*-transmetalation transition state (**VII**) accounting for the chemoselectivity observed in the reaction. The factor that leads to the lower energy of **I** vs **VI** and hence **II** vs **VII** appears to be the bidentate *S,O*-coordination. Similar bidentate coordination modes were higher in energy in the *N*-bonded complexes. The zwitterionic version illustrated in **I** better represents the computed charges and is consistent with the prior reports for similar compounds.<sup>31</sup>

According to the above calculations, the protecting group on nitrogen plays a key role by both stabilizing the negative charge on nitrogen via resonance and by coordinating the copper center. As such, other *N*-acyl groups which would be expected to exhibit a similar profile were explored (**table 2c**). Notably, the coupling reactions proceeded very well employing *N*-acyl sulfenamides as nucleophiles and led to the formation of **6xa-za** in good yields. The benzoxycarbamate was also well tolerated to produce **6baa** in modest yield under slightly modified conditions. On the other hand, phenyl (**1bb**) or 4-nitrophenyl protecting groups (**1bc**) on nitrogen were ineffective in the reaction consistent with our mechanistic

proposal. While this group would stabilize a negative charge on nitrogen as required the above mechanism, it would not be able to chelate which is also required the above mechanism.

**Synthetic applications.** To show the potential utility of our copper-catalyzed Chan-Lam coupling, deprotection of *N*-Bz-diphenyl sulfilimine **4ba** was performed. Treatment with sulfuric acid for 6 h readily generated the *N*H-diphenyl sulfilimine **7a** in 76% yield (condition **a**, **Scheme 2**). This free sulfilimine, is a versatile building block and allows access to diverse derivatives (**Scheme 2**). Oxidation of **7a** with  $\text{PhI}(\text{OAc})_2$  to afforded free sulfoximine **8a**,<sup>32</sup> a prevalent scaffold in medicinal chemistry (condition **b**).<sup>33</sup> Imination of **7a** by means of chloramine-T and  $\text{TsNHNa}$  generated sulfondiimine **8b**,<sup>34</sup> which represents a category of underexplored sulfur(VI)-derived compounds (condition **c**).<sup>35</sup> Leveraging the nucleophilicity of the free sulfilimine, **7a** could be subjected into Michael-type additions to either alkene (condition **d**) or alkyne (condition **e**) substrates, leading to the formation of **8c** and **8d** in 78% and 62% yield, respectively.<sup>36, 37</sup> As an example of sulfilimines which cannot be directly constructed by our Chan-Lam coupling procedure, **8e** could be easily prepared by installation of Boc group on **7a** in 87% yield (condition **f**).<sup>38</sup> Free sulfilimine **7a** could also be utilized as coupling partner with aryl iodide in palladium-catalyzed Buchwald-Hartwig amination, providing the arylated product **8f** in 85% yield (condition **g**).<sup>39</sup>

## Conclusion

In summary, we have developed a novel synthetic approach to form sulfilimines from stable and readily available sulfenamides and arylboronic acids via a copper-catalyzed Chan-Lam-type coupling strategy. A simple copper catalyst  $[\text{Cu}(\text{TFA})_2 \cdot \text{H}_2\text{O}]$  efficiently promotes the chemoselective *S*-arylation of sulfonamides, and a variety of diaryl, alkyl aryl, and even alkenyl aryl sulfilimines could be efficiently produced. Calculations indicate that the selectivity arises from a selective transmetallation event where bidentate sulfenamide coordination through the sulfur and oxygen atoms is key to the selectivity. This unprecedented protocol features excellent chemoselectivity, mild and environmentally benign conditions, broad functional group compatibility, and does not require an elaborate ligand or acid/base additives. The product is an entry point for a range of S(IV) and S(VI) product, further highlighting the strengths of this transformation. The concepts described herein also provide a basis for the development of novel methodologies to construct other organosulfur compounds, which are currently under investigation in our laboratory.

## Methods

**General Procedure for Catalysis.** To an oven-dried microwave vial equipped with a stir bar was added *N*-(*p*-tolylthio)benzamide (**1a**) (24.3 mg, 0.10 mmol), phenylboronic acid (**2a**) (14.6 mg, 0.12 mmol), and  $\text{Cu}(\text{TFA})_2 \cdot \text{H}_2\text{O}$  (2.9 mg, 10 mol %). Then, the microwave vial was sealed with a cap. Oxygen was purged/vacuumed three times through a three-way valve, and the microwave tube became an oxygen atmosphere. DCE (0.5 mL) was added to the microwave vial via syringe. The microwave vial was heated to 60 °C in an oil bath and stirred for 12 hours. Upon completion of the reaction, the sealed vial was

cooled to room temperature, and opened to air. The reaction solution was concentrated under reduced pressure. The crude product was purified by flash chromatography to afford the pure product.

### **Data availability**

Experimental procedure and characterization data of new compounds are available within Supplementary Information. Any further relevant data are available from the authors upon reasonable request.

## **Declarations**

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### **Author contributions**

T.J. and M.C.K. conceived and directed the project and wrote this paper. Q.J. and K.M., and S.F. performed the experiments. L.A. carried out computational study. M.C.K. directed the part of computational study. Q.J., K.M., and S.F. analyzed the data. All authors approved the submission of the manuscript. Q.J. and L.A. contributed equally.

### **Competing interests**

The authors declare no competing interests.

### **Additional information**

Supplementary information is available for this paper.

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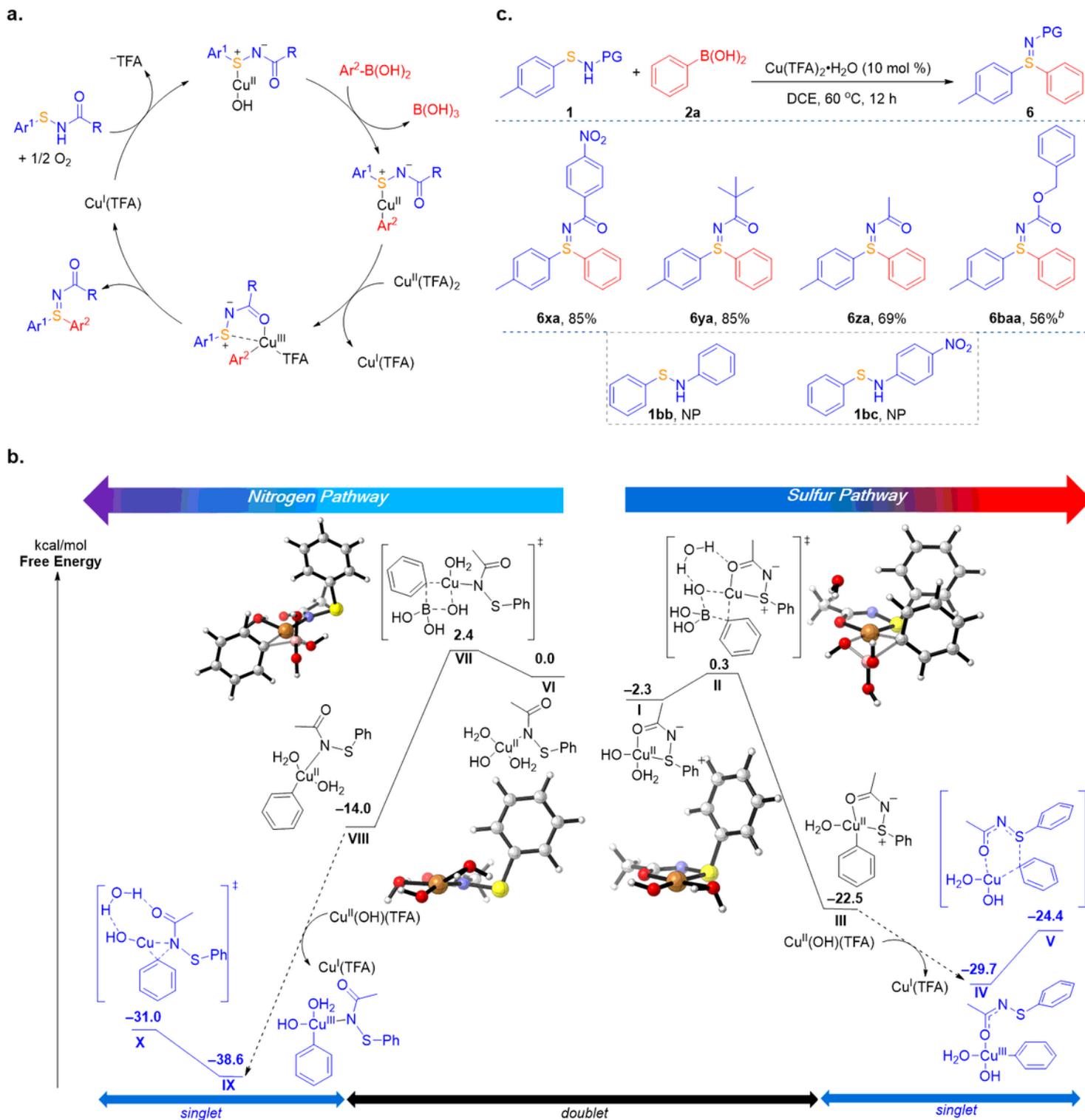
## Table 2

Table 2 is available in the Supplementary Files section

## Schemes

Schemes 1 and 2 are available in the Supplementary Files section

## Figures



**Figure 1**

Mechanistic investigations. a. Proposed catalytic cyclic for the formation of sulfilimine b. Energy profile for the formation of the sulfilimine. To the right is the pathway to form the S-aryl bond and to the left, the N-aryl bond. Free energies were computed using PCM-DCE-M06-gd3/6-311+G(3d,p), Cu:SDD//B3LYP-gd3/6-311+G(3d,p), Cu:SDD. Values are in kcal/mol. c. Protecting groups on nitrogen of sulfenamides.

Reaction conditions: 1 (0.1 mmol), 2a (1.2 equiv), Cu(TFA)<sub>2</sub>·H<sub>2</sub>O (10 mol %) and DCE (0.5 mL), stirred at 60 °C for 12 h under an O<sub>2</sub> atmosphere (1 atm). bDTBP (2.0 equiv) instead of O<sub>2</sub>. NP = No product.

## Supplementary Files

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- [Onlinefloatimage6.png](#)
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