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Synthesis of Cyclic Sulfilimines and Sulfoximines via Copper-Mediated C(sp^2)–H Sulfanylation of Benzylamines with a Catalytic Transient Directing Group

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C—H functionalization presents opportunities to streamline the synthesis of valuable molecular structures. This study details the development of a copper-mediated, transient C(sp^2)–H sulfanylation of benzylamines with a transient directing group (TDG). Subsequent oxidative cyclization forms novel cyclic sulfilimines and sulfoximines, emerging heterocyclic scaffolds with attractive properties for drug discovery. Crucially, sulfenamides are identified as effective sulfanylating reagents for the C—H sulfanylation with catalytic 2-hydroxynicotinaldehyde as the TDG. Unconventionally, sulfenamides provided a slow release of the essential sulfanyl radicals through a thermally induced homolytic cleavage of the N—S bond, supported by mechanistic studies including electron paramagnetic resonance spectroscopy and radical quenching experiments. The sulfide products are then readily diversified at sulfur and nitrogen, including through cyclization.

1. Introduction

Sulfur-containing functional groups in various oxidation states serve as valuable scaffolds in medicinal chemistry and are frequently found in bioactive natural products and pharmaceutical compounds.[1,2] For example, thioethers, sulfoxides, sulfones, and sulfonamides are well-established functional groups present in agrochemicals and FDA-approved drugs (**Figure 1**A).[3] Vortioxetine is a notable thioether derivative discovered as an effective antidepressant for treating major depressive disorder.[4] Meanwhile, the aza-analogs of sulfones and sulfoxides, such as sulfoximines and sulfilimines, are emerging as new, important design elements for drug discovery. The additional N-vector enables the flexible modulation of physicochemical properties.[5–7] Recent advancements have highlighted sulfoximines as key components in the development of advanced drug candidates and agrochemicals.[8]

Driven by the potential of sulfur-containing compounds as promising pharmacophores in drug design, there is a growing demand for the development of more atom-efficient and effective synthetic methodologies to introduce these motifs, particularly with the potential for late-stage incorporation. In this regard, C—H functionalization presents a highly attractive strategy for accessing the key thioether functional group, which can also serve as a diversification point to generate a wide range of S(IV) and S(VI) stereogenic centers via oxidative transformations (Figure 1B).[9–11] In 2006, Yu and coworkers reported the first example of copper(II)-mediated C(sp^2)–H sulfanylation, using pyridine as an innate directing group and thiols or disulfides as sources of thiolate ions (Figure 1B).[12] In 2012, Daugulis demonstrated the use of cleavable amide-linked aminoquinoline and picolinamide directing groups to facilitate copper-mediated sulfanylation of benzoic acids and benzylamines with disulfides as reagents.[13] Liu and coworkers employed a similar strategy to develop the sulfanylation of benzoic acid derivatives using aliphatic thiols and thiophenols with aminoquinoline as the directing group, while Maiti reported a similar transformation using 2-pyridone as the directing group in 2024.[14,15] Additionally, Ackermann developed a C(sp^2)–H sulfanylation of indolines and indoles, using a 2-pyrimidyl directing group with disulfides.[16] More recently, Shi reported an enantioselective C(sp^2)–H sulfanylation of ferrocenes with disulfides.[17]

Although the use of amide-linked directing groups has proven to be an effective strategy for introducing the thioether moiety via C—H functionalization, this approach remains inefficient as additional steps are required for directing group installation and cleavage. The TDG strategy, involving dynamic in situ formation of imine-derived directing group, has recently emerged as a promising alternative to overcome these limitations to achieve efficient C—H functionalization reactions, predominantly with palladium catalysis.[18–20] We recently extended this strategy to copper-mediated C(sp^2)–H sulfonylation of aldehydes and benzylamines.[21,22] Nucleophilic coupling partners pose additional challenges to this approach, as undesired competitive addition to either the aldehyde substrate or the TDG can interfere with imine formation. Thiols in particular also present challenges of over-coordination. Very recently, Zhang and coworkers

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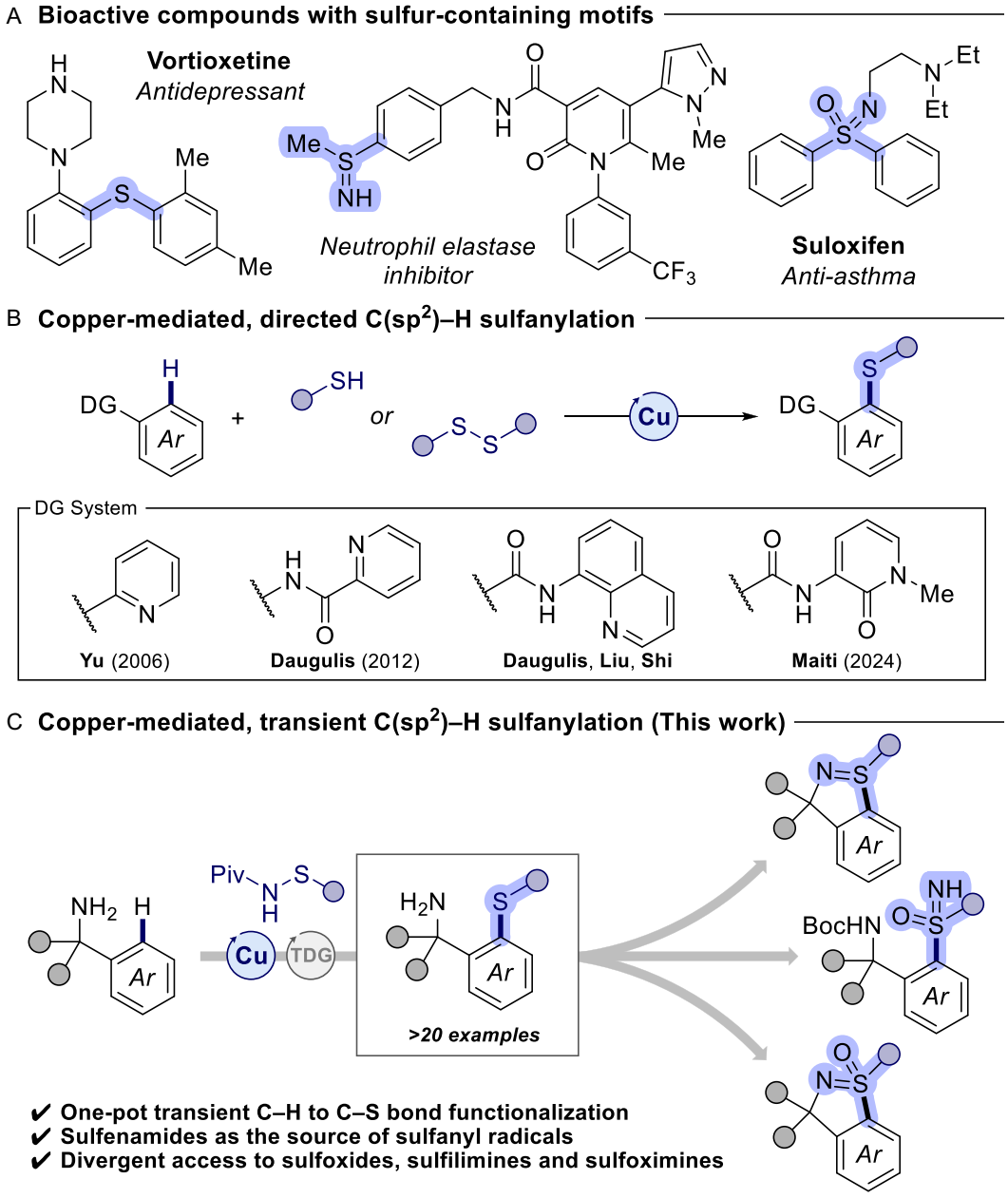

Figure 1. a) Examples of sulfur-containing bioactive compounds, b) previous work on copper-mediated, directed C(sp^2)–H sulfanylation, and c) the transient C(sp^2)–H sulfanylation of benzylamines and approach to sulfilimines and sulfoximines (this work).

reported transient C(sp^2)–H thiolation reactions with disulfides.[23] Here, we report a copper-mediated, TDG-catalyzed C(sp^2)–H sulfanylation of benzylamines with sulfenamides to generate thioethers. These 3-aminothioethers present valuable intermediates, which can be transformed into a range of synthetically under-explored cyclic sulfilimine and sulfoximines (Figure 1C).

The study commenced with an evaluation of different sulfanylating reagents using cumylamine **1** and a catalytic amount of 2-hydroxynicotinaldehyde (**TDG1**) as the TDG in a mixture of hexafluoroisopropanol and *N*-methyl-2-pyrrolidone (HFIP): N-methyl-2-pyrrolidone (NMP), 3:1) at 80 °C under an argon atmosphere with K_2CO_3 as the base (**Scheme 1**).[24] Reactions with thiophenol **2a**, disulfide **2b**, and the succinimide derivative **2c** provided the desired thioether product **3** in low yields (17–24%). The use of thiosulfonate **2d** resulted in a mixture of thioether **3** (32%) and sulfone **3′** (44%). Gratifyingly, a moderate yield of the thioether **3** (34%) was obtained with *N*-(*p*-tolylthio) benzamide **2e**, without the formation of the undesired sulfone **3′**. Further investigation into the electronic effects of the N-group on the sulfenamide improved the yield considerably. The use of methyl carbamate on the sulfenamide **2f** led to a slight yield improvement to 44%, and the use of the pivaloyl group on the sulfenamide **2g** significantly enhanced the yield of the desired thioether **3** to 69%. Interestingly, the use of sulfinamide

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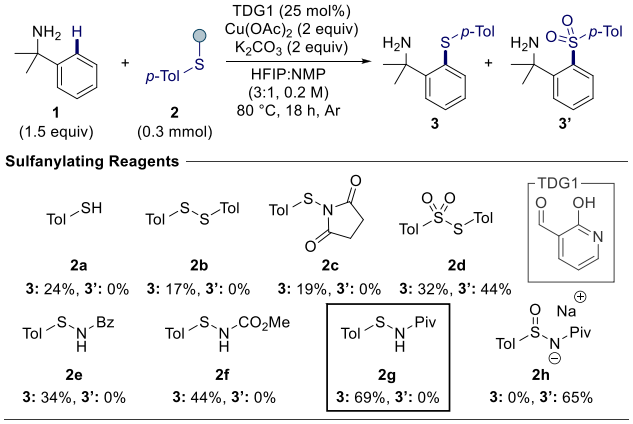


Scheme 1. Evaluation of different sulfanylating reagents. Reactions were conducted on 0.30 mmol scale.

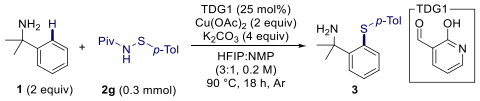
sodium salt **2h** as the coupling partner produced the sulfone **3'** product exclusively in 65% yield with unexpected S—N cleavage.

The reaction parameters were then optimized using a sequential design of experiment approach (see Supporting Information for details). A six-factor definitive screening design optimization was initially employed to determine the optimal amine equivalents (2 equiv), concentration (0.20 M), and reaction temperature (90 °C). A follow-up response surface model (Box–Behnken) design was then utilized to finalize the optimal loading of **TDG1** (25 mol%), copper(II) acetate (2 equiv), and base (4 equiv) to conclude the optimization process to achieve 82% yield of the thioether **3**. Attempts to use substoichiometric copper with additional oxidants were unsuccessful due to the formation of disulfide as the major product. A series of control experiments demonstrated the requirement for the TDG, copper(II) acetate, base, and heat (**Table 1**, entries 1–5). Notably, only 2% yield was observed in the absence of the TDG, supporting the role of the bidentate imine. The use of HFIP:NMP (3:1) solvent mixture was also essential, as a diminished yield of 58% was observed when the reaction was carried out in HFIP only (Table 1, entry 6). No product formation was observed when NMP alone was used as the solvent (Table 1, entry 7). These results indicate that the use of HFIP as the major component of the solvent mixture is essential, presumably aiding in maintaining the dynamic imine equilibrium to turn over the TDG during the reaction.[18]

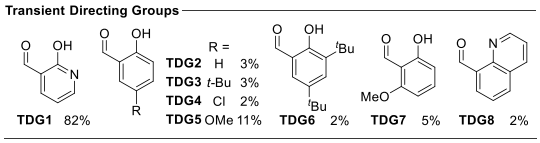
A broad range of copper salts, bases, and TDGs was also systematically evaluated. The use of copper(I) acetate, or other copper (II) salts, was less effective, affording thioether **3** in 69% yield (Table 1, entries 8–11), compared to $Cu(OAc)_2$. Other potassium bases, including KOAc, KOPiv, and KO^{t}Bu, and other metal carbonates gave reduced yields (Table 1, entries 12–17). Among the TDGs tested, 2-hydroxynicotinaldehyde **TDG1** was highly effective, whereas other salicylaldehydes (**TDG2**–**7**) and quinoline-8-carbaldehyde **TDG8** as TDG resulted in poor yields of 2–11% (Table 1, bottom).[25,26]

With the optimal conditions established, the reaction scope was explored by varying the amine and sulfenamide reactants (**Scheme 2**). The benzylic position of the benzylamines was not restricted to a gem-dimethyl group, as a tert-butyl group,

Table 1. Optimization of C(sp^2)–H sulfanylation conditions.



Entry[a]	Deviation from standard conditions	Yield [%][b]
Control experiments		
1	None	82 (82)
2	No TDG	2
3	No $Cu(OAc)_2$	0[c]
4	No K_2CO_3	35
5	Room temperature	0
Solvent		
6	HFIP	58
7	NMP	0
Copper salts		
8	CuOAc	69
9	$Cu(OTf)_2$	56
10	CuF_2	31
11	$Cu(TFA)_2$	58
Base		
12	KOAc	60
13	KOPiv	53
14	KO^{t}Bu	18
15	Li_2CO_3	61
16	Na_2CO_3	32
17	Cs_2CO_3	59



[a]Reactions were conducted on 0.30 mmol scale with respect to the sulfenamide. [b]Yield determined by analysis of crude ^{1}H NMR with using CH_2Br_2 as internal standard. Isolated yield in parenthesis. [c]*p*-Tolyl disulfide was formed in 68% yield.

and cyclopentane derivative were tolerated to afford thioethers **4** (54%) and **5** (60%), respectively. Other less substituted amines, such as (±)-1-phenylethylamine, were unsuccessful, presumably due to undesired oxidation at the benzylic position. Benzylamines bearing an electron-donating group (OMe) at the *para*- and *meta*-positions to the target C—H bond gave the corresponding thioether **6** and **7** in 71% and 41% yield, respectively. The limiting sulfanamide was fully consumed in both cases. The electronic properties of the benzylamines were varied without affecting the efficiency of the functionalization process. For example, benzylamines with a methyl or trifluoromethyl substituent at the *para*-position gave the desired thioethers **8** and **9** in 65% yield. Halogenated benzylamines were also compatible with this reaction to produce the corresponding thioethers **10**–**12** (22–74%) with different halogens and at different positions.

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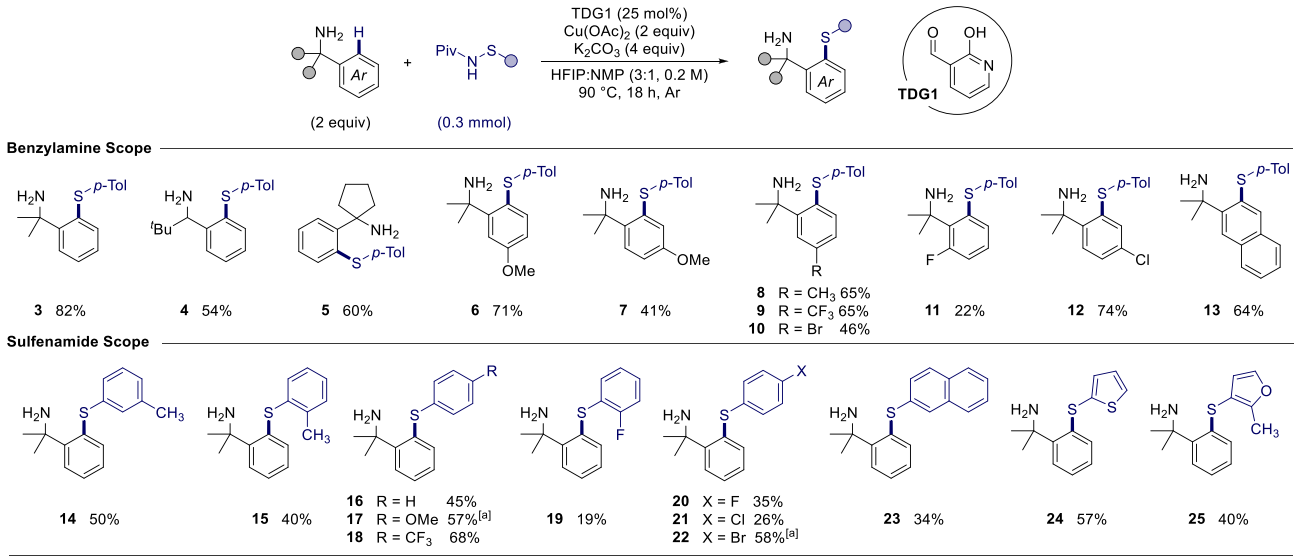
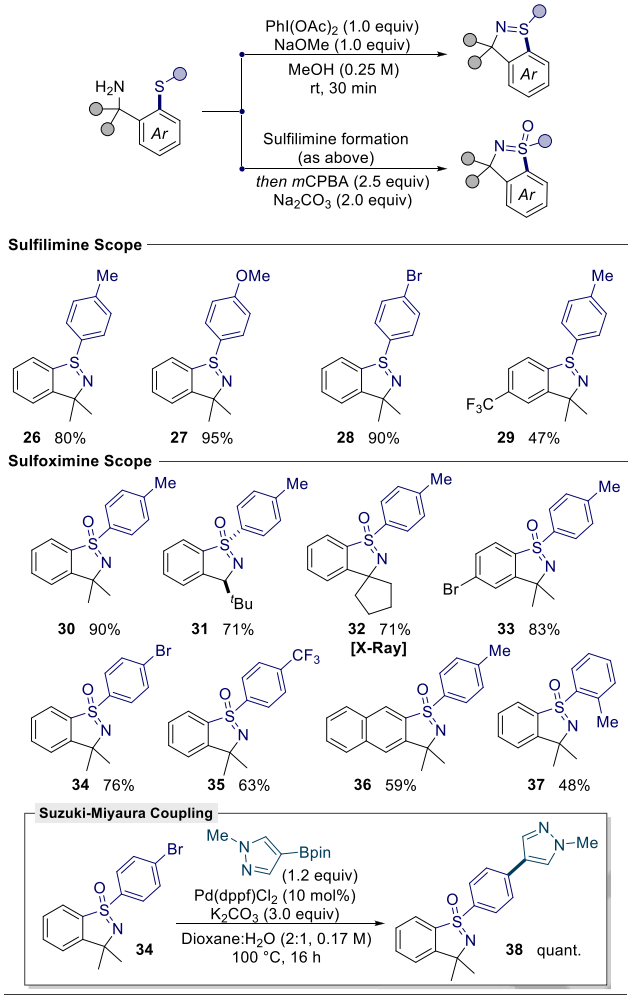


Scheme 2. Reaction scope varying the benzylamine and sulfenamide. Reactions were conducted on a 0.30 mmol scale with isolated yield reported. [a] Reactions were conducted at 0.90 mmol scale.

A naphthalene derivative was functionalized in good yield (**13**, 64%). Amines such as 1-indanylamine, 1-aminotetralin, and containing furan and thiophene heterocycles were unsuccessful. A wide variety of sulfenamides were also compatible with the optimized conditions with cumylamine **1**. A trend of decreasing yield was observed when the methyl group on the tolyl substituent of the sulfenamides was shifted from the *para*- (**3**, 82%) to *meta*- (**14**, 50%) and *ortho*-positions (**15**, 40%), due to steric hindrance. Sulfanylation with *N*-(phenylthio)pivalamide provided thioether **16** in 45% yield. Sulfenamides with electron-rich (OMe) and electron-deficient (CF_3) functional groups were well tolerated, affording thioethers **17** and **18** in 57% and 68%, respectively. Halogenated sulfenamides were also compatible to produce the thioethers **19**–**22** in 19–58% yield. Other (hetero) aromatic sulfenamides were tolerated in moderate yield, including naphthalene-thioether **23** (34%), thiophene **24** (57%), and furan **25** (40%). Sulfenamides with alkyl substituents were incompatible with the developed conditions. Di-sulfanylation was not observed in any examples, presumably due to the unfavorable steric clash between the *gem*-dimethyl group and the thioether in the orientation required for a second C—H functionalization.

Sulfoximines have become an established functional group in medicinal chemistry programs, whereas sulfilimines remain less explored and of emerging interest.[5,6] However, synthetic protocols for synthesizing endocyclic variants remain scarce, and consequently, cyclic sulfilimines and sulfoximines remain underexplored yet highly attractive heterocyclic scaffolds.[27–31] We envisaged that the developed transient C—H sulfanylation strategy, which leveraged the benzylamine functionality to introduce the key thioether moiety, would also correctly locate the necessary functionality for oxidative S—N cyclization (**Scheme 3**). Treatment of thioether **3** with $PhI(OAc)_2$ (1 equiv) in the presence of NaOMe (1 equiv) in MeOH resulted in the oxidative imination to give cyclic sulfilimine **26** in excellent yield



Scheme 3. Reaction scope for the synthesis of cyclic sulfilimines and sulfoximines. Reactions were conducted on a 0.20 mmol scale with isolated yield reported.

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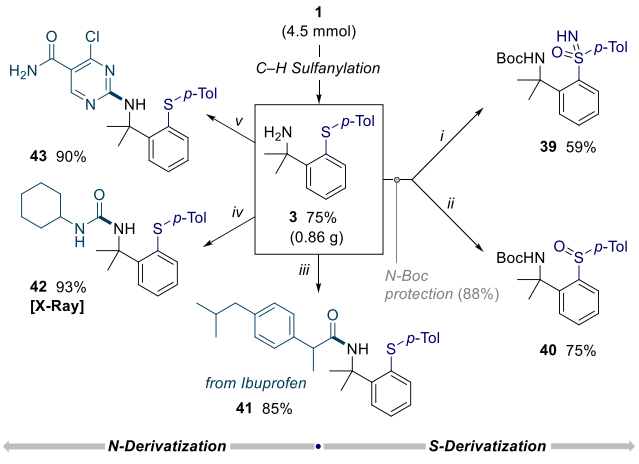
(80%).[30,32] Other thioethers **17** and **22** were also successfully cyclized, providing the corresponding cyclic sulfilimines **27** and **28** with excellent yields of 95% and 90%, respectively. A lower yield of sulfilimine **29** (47%) was observed with electron-deficient thioether **9**. Cyclic sulfoximines were prepared through a one-pot sequential sulfilimine formation, followed by *m*CPBA oxidation. Cyclic sulfoximine **30** was synthesized in 90% yield from thioether **3**, and the reaction conditions were compatible with all thioethers examined. Benzylamine **4** was successfully converted into sulfoximine **31** in 71% yield as a single diastereomer, assigned as *trans*- on the basis of nuclear Overhauser effect studies (see Supporting Information for further details).

Spirocyclic sulfoximine **32** was obtained from thioether **5** in 71% yield. Thioethers **10** and **22** with a bromine substituent on different arenes were also cyclized to the corresponding sulfoximine with excellent yields of 83% and 76%, respectively. Additionally, thioether **18** with an electron-deficient (CF_3) group and the naphthalene derivative **13** were also compatible with the conditions to give sulfoximines **35** (63%) and **36** (59%). A lower yield of sulfoximine **37** (48%) was observed due to steric effects when the methyl group was at the *ortho*-position with thioether **15**. The bromide substituent on the arene of sulfoximine **34** could serve as the point of further derivatization with transition metal catalysis, which was well demonstrated with a Suzuki-Miyaura cross-coupling reaction to give pyrazole **38** in quantitative yield.

Both the amine and sulfide functional groups could also be independently functionalized (**Scheme 4**). The C—H sulfanylation of amine **1** was successfully performed on a gram-scale (4.5 mmol), affording thioether **3** in 75% yield. Following N-Boc protection (88%), one-pot N- and O-transfer reaction with $PhI(OAc)_2$ and ammonium carbamate gave sulfoximine **39** in



Scheme 4. Gram-scale C—H sulfanylation, N- and S-derivatization of the product. N-Boc protection was carried out on a 1 mmol scale. Derivatization reactions were conducted on a 0.20 mmol scale with isolated yield reported. Reaction conditions: (i) $PhI(OAc)_2$, $NH_2CO_2NH_4$, MeOH, room temperature, 3 h; (ii) H_2O_2, AcOH, room temperature, 2 h; (iii) ibuprofen acid chloride, Et_3N, CH_2Cl_2, room temperature, 18 h; (iv) CyNCO, MeCN, room temperature, 2 h; (v) 2,4-dichloropyrimidine-5-carboxamide, Et_3N, tetrahydrofuran, room temperature, 24 h.

59% yield.[33,34] Oxidation of thioether **3** with H_2O_2 in AcOH provided sulfoxide **40** in 75% yield. The amine functionality of **3** was directly used in amide formation with ibuprofen-derived acid chloride (**41**, 85%) and in urea formation with cyclohexyl isocyanate (**42**, 93%).

The amine group readily underwent nucleophilic aromatic substitution (S_NAr) reaction with a chloropyrimidine derivative, yielding pyrimidine **43** in 90% yield.

Mechanistic investigations into imine formation by ^{1}H NMR in the absence of $Cu(OAc)_2$ revealed that the **TDG1** readily condenses with both the cumylamine and product amines, forming imines in high yields (84–96%) across different solvent systems (HFIP, HFIP:NMP (3:1), and NMP; Table S10, Supporting Information). Notably, product **3** formed an imine with **TDG1** preferentially over the substrate amine **1**, with a ratio of 7:3 (Table S11, Supporting Information), presumably due to the thermodynamically stabilizing role of the neighboring chalcogen bonding available in the product imine.[35] This preferred product imine formation also provides an explanation for the use of the substrate amine in slight excess to favor the productive imine equilibrium. ^{1}H NMR studies also confirmed that there was no reaction between sulfenamide **2g** and **TDG1,** whereas thiol **2a** showed reaction with **TDG1** to form a hemithioacetal, diminishing the reaction efficiency (Table S12, Supporting Information).

We hypothesized that the sulfenamide provided a sulfanyl radical, an unprecedented role of this reagent for C—H functionalization. Using copper catalysis, sulfenamides are increasingly well-documented substrates for the synthesis of sulfilimines, retaining the S—N bond.[36–40] To probe for the involvement of radical intermediates, various radical scavengers were introduced under the standard reaction conditions using cumylamine **1** and sulfenamide **2g** (**Figure 2**A). The yield of the desired sulfanylated amine **3** was significantly reduced (38–52% vs. 82%) in the presence of 1 equivalent of butylated hydroxytoluene, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), or galvinoxyl free radical. Increasing the concentration of TEMPO to 5 equivalents completely suppressed the productive process, suggesting the involvement of a sulfanyl radical in the transformation. Notably, in the absence of $Cu(OAc)_2$, the standard reaction using sulfamide **2g** gave pivalamide and disulfide **2b** as the major product (68%; Table 1, entry 3), presumed to be from radical dimerization. Attempts to observe the sulfanyl radical by electron paramagnetic resonance (EPR) spectroscopy using nitrone spin traps (DMPO, PBN) gave limited support, presumably due to instability of the adducts under the elevated temperatures of the reaction. Therefore, to demonstrate the thermal generation of radicals from sulfenamide **2g**, a 10 mM solution of **2g** (HFIP:NMP) was heated at 90 °C in the presence of TEMPO (50 mM), and the TEMPO concentration was monitored over time by EPR spectroscopy (Figure 2B). The concentration of TEMPO steadily decreased in the presence of sulfenamide **2g** by ≈8 mM over 24 h, consistent with radical quenching of the resulting sulfanyl radical. Control experiments without **2g** showed that a solution of TEMPO was stable at 90 °C over 24 h in the presence or absence of K_2CO_3. These findings support the hypothesis that the sulfenamides undergo thermolysis via

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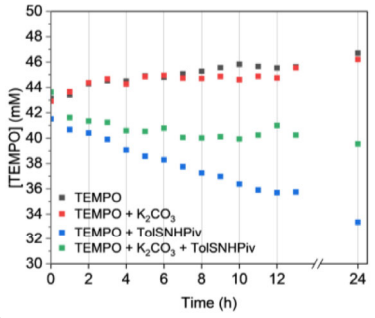
A **Radical Scavengers**[a]

Entry	Radical Scavenger	Yield*
1	None	82%
2	BHT (1 equiv)	38%
3	TEMPO (1 equiv)	41%
4	TEMPO (5 equiv)	0%
5	Galvinoxyl, free radical (1 equiv)	52%

* Determined by ^{1}H NMR using CH_2Br_2 as internal standard.

B **TEMPO Quenching**[b]



C **Proposed Reaction Mechanism**

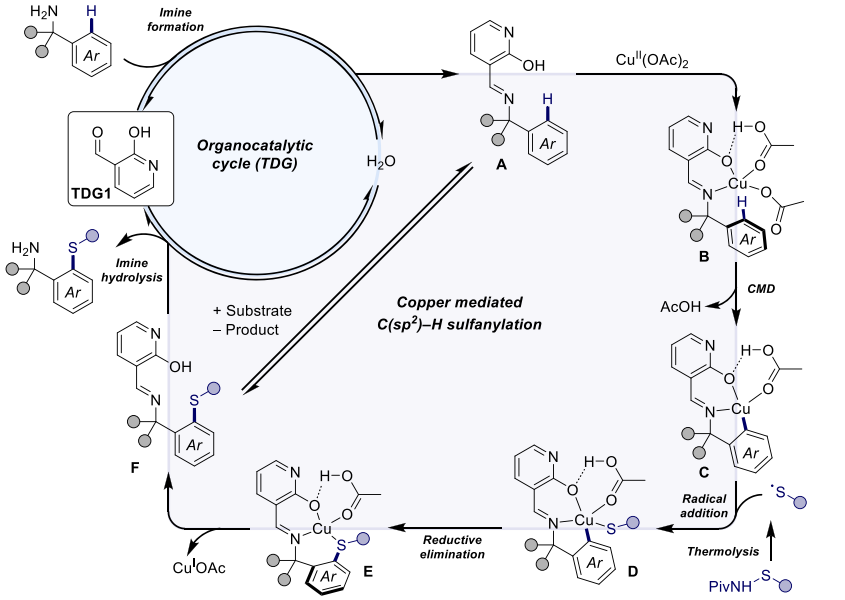


Figure 2. Mechanistic investigations and proposed reaction mechanism. [a] Reactions between cumylamine and sulfenamide **2g** under standard conditions in the presence of a radical scavenger. [b] TEMPO quenching experiment monitoring the TEMPO concentration in following mixture in HFIP:NMP (3:1) at 90 °C by EPR spectroscopy: i) TEMPO (50 mM), ii) TEMPO (50 mM) + K_2CO_3 (40 mM), iii) TEMPO (50 mM) + TolSNHPiv (**2g**, 10 mM), and iv) TEMPO (50 mM) + TolSNHPiv (**2g**, 10 mM) + K_2CO_3 (40 mM).

homolytic cleavage of the N—S bond, providing the sulfanyl radicals necessary for the sulfanylation process.[41–44]

Based on these findings and previous density functional theory calculations, a reaction mechanism was proposed (Figure 2C).[22] The substrate amine condenses with a catalytic amount of **TDG1** to form imine **A**, which then coordinates to $Cu(OAc)_2$ to generate intermediate **B**. This complex undergoes a concerted metalation–deprotonation step to form complex **C**, which subsequently reacts with the sulfanyl radical generated via the homolytic cleavage of the sulfenamide, affording the Cu(III) intermediate **D**. The resulting aminyl radical reacts with HFIP to produce pivalamide as the side product. The Cu(III) complex then undergoes reductive elimination to give Cu(I) complex **E**. The product imine **F** subsequently undergoes hydrolysis to regenerate the TDG and deliver the desired thioether product. Direct transimination of imine **F** with the substrate amine to form imine **A** would also be a feasible reaction pathway.

In conclusion, a copper-mediated, transient C(sp^2)–H sulfanylation of benzylamines has been developed using sulfenamides and catalytic 2-hydroxynicotinaldehyde as the TDG. The conditions were compatible with a wide range of benzylamines and sulfenamides. Mechanistic studies by ^{1}H NMR and EPR spectroscopy provided evidence that the sulfenamide undergoes thermally induced homolytic cleavage of the N—S bond to generate the necessary sulfanyl radical required for the process. The unprecedented use of sulfenamides as sulfanyl group donors is compatible with the transient C—H functionalization strategy, mitigating undesired hemithioacetal formation between the aldehyde TDG with conventional sulfanyl radical sources such as thiols and disulfides. This transient process leverages the amine functionality to introduce the thioether moiety, which can subsequently be transformed into a range of underexplored cyclic sulfilimines and sulfoximines without requiring further manipulation of a directing group. Further investigations into other copper-mediated C—H functionalization processes are ongoing in our laboratory.

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Conflict of Interest

The authors declare no conflict of interest.

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Data Availability Statement

The data that support the findings of this study are openly available in Imperial College London Research Data Repository at https://doi.org/10.14469/hpc/15167.

Keywords: C—H functionalization · copper · sulfanylation · Sulfenamides · transient directing group

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