Copper-Catalyzed Oxidative N−S Bond Formation for the Synthesis of *N*-Sulfenylimines
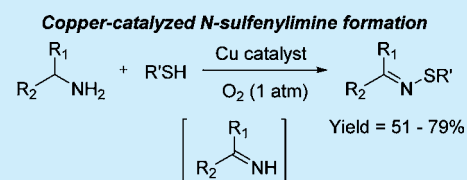
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S *Supporting Information*

ABSTRACT: Despite the remarkable success of the copper-catalyzed oxidative coupling reaction, direct cross-coupling of amines and thiols for the synthesis of *N*-sulfenylimines has not been previously reported. Using commercially available copper catalysts (CuI) and oxygen as an environmentally benign oxidant, synthetically useful *N*-sulfenylimines were prepared from amines and thiols in good yields without overoxidation of sulfur atoms.

Copper-catalyzed N-sulfenylimine formation

$$R_1R_2CHNH_2 + R'SH \xrightarrow[O_2 \ (1 \ atm)]{Cu \ catalyst} R_1R_2C{=}N{-}SR' \quad [R_1R_2C{=}NH]$$

Yield = 51 - 79%

N-Sulfenylimines are sulfur analogs of oximes possessing a nitrogen−sulfur bond and are also called thio-oximes and sulfenimines. Despite the utility of sulfenylimines in the preparation of *N*-sulfinylimines, *N*-sulfonylimines, β-lactams, vinyl formamides, and H₂S-releasing reagents, efficient and catalytic methods to prepare sulfenylimines have not yet been actively explored.[1−4] Based on the pioneering work by Davis, sulfenylimines were synthesized in a one-step process using disulfides, aldehydes, ammonia, and silver complexes, although the use of stoichiometric amounts of silver complexes and ammonia was required (Scheme 1, eq 1).[2d,e,3] *S*-Aroylthiohydroxylamine (SATHA) was also used to prepare sulfenylimines from aldehydes (Scheme 1, eq 2).[2g,h] The synthesis of SATHA requires the reaction of acyl chloride with H₂S followed by amination using hydroxylamine sulfonic acid. The combination of trimethylphosphine and *N*-(phenylthio)-phthalimide which is synthesized from thiophenol also

provided sulfenylimines from oximes (Scheme 1, eq 3).[4] Although various reaction conditions for the synthesis of sulfenylimines have been reported, there is no catalytic method to synthesize sulfenylimines directly from amines.

Copper-catalyzed aerobic oxidative coupling reactions have been successful for inducing C−C, C−N, C−P, C−S, N−P, P−S, and N−S bond formation without prefunctionalization of reactants.[5−7] As substrates in the oxidative coupling reaction, amines are known to be relatively susceptible under oxidation conditions (e.g., the oxidation of amines to imines and the oxidative α-functionalized tertiary amines); however, to the best of our knowledge, direct oxidative coupling of amines with thiols to afford *N*-sulfenylimines (N−S bond formation) has not yet been reported.[8,9] The reactions of amines and thiols often provided sulfonamides under oxidation conditions.[6i−k,10] In this study, we present the first copper-catalyzed aerobic oxidative coupling of amines and thiols to provide various *N*-sulfenylimines (Scheme 1, eq 4). Selective oxidation occurred to form *N*-sulfenylimines without *N*-sulfinyl- and *N*-sulfonyl-imines.
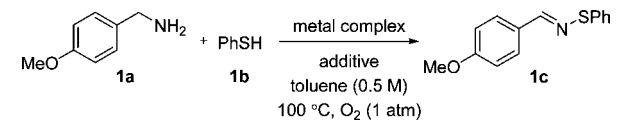
The optimization results are given in Table 1. Although disulfides are often used as electrophiles (e.g., sulfenylation of aromatic compounds), disulfides are formed from thiols under copper-catalyzed aerobic conditions.[11] Therefore, we decided to use benzenethiol **1b** instead of disulfides. For this process, *p*-OMe-benzyl amine **1a** (2 equiv) and benzenethiol **1b** (1 equiv) were subjected to copper-catalyzed aerobic oxidation conditions. In the presence of CuI (2 mol %), the solution of **1a** and **1b** in toluene (0.5 M) was stirred at 100 °C under 1 atm of oxygen to afford sulfenylimine **1c** in 42% yield (entry 1). We also screened several metal salts; CuBr, CuBr₂, FeCl₂, and FeCl₃ showed inferior catalytic activity compared to CuI (entries 2−5). Because the yield of the copper-catalyzed oxidation of amines is affected by ligand additives, we tested several ligands. The reactions with 2,2,6,6-tetramethyl-

Scheme 1. Synthesis of *N*-Sulfenylimines
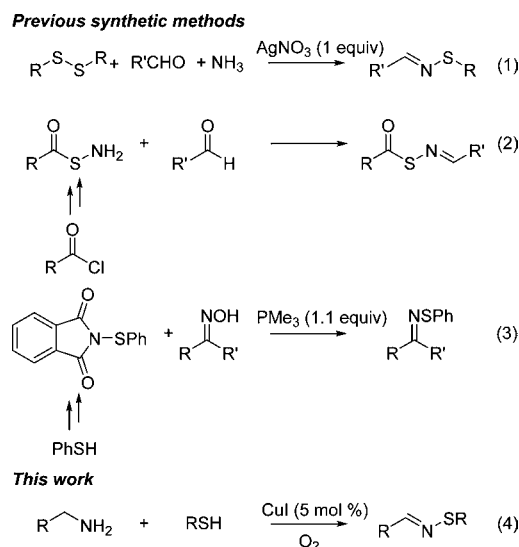
Table 1. Optimization of the Formation of Sulfenylimine 1c

entry	metal complex	additive	yield
1	CuI (2 mol %)	–	42%
2	CuBr (2 mol %)	–	9%
3	CuBr$_2$ (2 mol %)	–	6%
4	FeCl$_2$ (2 mol %)	–	–
5	FeCl$_3$ (2 mol %)	–	–
6	CuI (2 mol %)	TEMPO (2 mol %)	29%
7	CuI (2 mol %)	PPh$_3$ (2 mol %)	30%
8	CuI (2 mol %)	IMes (2 mol %)	31%
9	CuI (2 mol %)	1,10-phen (2 mol %)	33%
10	CuI (2 mol %)	TBD (1 equiv)	33%
11	CuI (2 mol %)	TBD (0.1 equiv)	68% (10%,[a] 39%[b])
12	CuI (2 mol %)	DBU (1 equiv)	53%
13	CuI (2 mol %)	DBU (0.1 equiv)	58%
14	CuI (2 mol %)	KO^{t}Bu (1 equiv)	--
15	TEMPO (5 mol %)	TBD (0.1 equiv)	--

[a]The reaction was run under nitrogen atmosphere. [b]The reaction was run in 1 M of toluene.

piperidinyloxy (TEMPO), PPh$_3$, 1,3-bis(2,4,6-trimethyl-phenyl)imidazol-2-ylidene (IMes), and 1,10-phenanthroline (1,10-phen) provided **1c** in lower yields (entries 6–9). To improve the deprotonation (α-proton) of the amines, a strong organic base, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), was added. By varying the amount of bases, the yield increased to 68% (entries 10 and 11). In the absence of oxygen, **1c** was formed in low yield (10%, entry 11). To avoid the large amount of solvents, the reaction was tested in toluene (1 M) to afford **1c** in 39% yield (entry 11). Addition of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) also improved the yield of **1c** to 58% (entries 12 and 13). Inorganic base KO^{t}Bu did not promote sulfenylimine formation (entry 14). In the absence of metal complexes, TEMPO was used as an organocatalyst, but **1c** was not formed (entry 15).[12]

To investigate the substrate scope of the reaction, diverse thiols and amines were subjected to aerobic oxidation conditions using CuI (2 mol %) and TBD (0.1 equiv) (Figure 1). First, benzyl amine derivatives were exposed to the optimized reaction conditions. As shown in Figure 1, benzyl amine was transformed to **2c** with a 74% yield. Then, F- and Cl-substituted benzyl amines were converted to the corresponding sulfenyl imines **3c** in 79% yield and **4c** in 75% yield. Electron-rich OMe- and Me-substituted benzyl amines participated in the reaction to afford the desired products **5c** and **6c** in good yields. Piperonyl amine was also incorporated in the sulfenylimine **7c** in 62% yield. Next, we carried out the reactions of thiophenol derivatives with benzyl amine. Fluoro-substituted thiophenol reacted with benzyl amine to give **8c** in 73% yield. Electron-rich thiophenols participated in the reaction to afford the corresponding sulfenylimines **9c** and **10c** in 76% and 75% yield, respectively. Next, amines forming thio-ketoximes were subjected to the reaction conditions. Thio-ketoximes possessing phenyl-ethyl **11c**, phenyl-methyl **12c**, diphenyl **13c**, and OMe-substituted phenyl-methyl group **14c** were synthesized in modest to good yields. As an aliphatic amine, octyl amine was subjected to the reaction conditions, but either desired sulfenylimines or octyl aldehydes formed
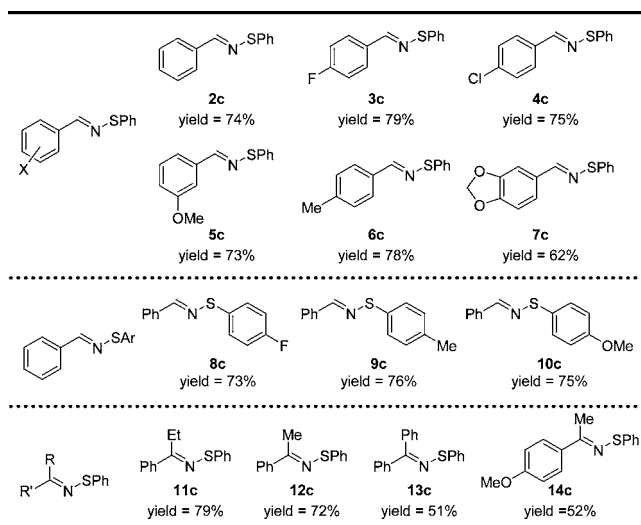

Figure 1. Examples of sulfenylimines.

from the oxidation of octyl amine followed by hydrolysis were not observed. The reactions of aliphatic thiol, octyl thiol with benzyl amine provided trace amounts of *N*-sulfenyl imines.

To investigate the reaction mechanism, the following experiments were carried out. As mentioned earlier, disulfide may be the key intermediate. With diphenyldisulfide **1b′**, sulfenylimine **1c** was obtained in 66% yield, a result comparable to that of the reaction of thiophenol **1b**. Next, the role of copper catalysts was examined. Copper catalysts oxidize thiols to disulfides, and amines to imines under oxidation conditions. In addition, copper catalysts might promote nitrogen–sulfur bond formation in **1a** and **1b′**. As shown in the second and third reactions of Scheme 2, in the absence of copper catalysts,

Scheme 2. Reactions of 1a with Disulfide 1b′
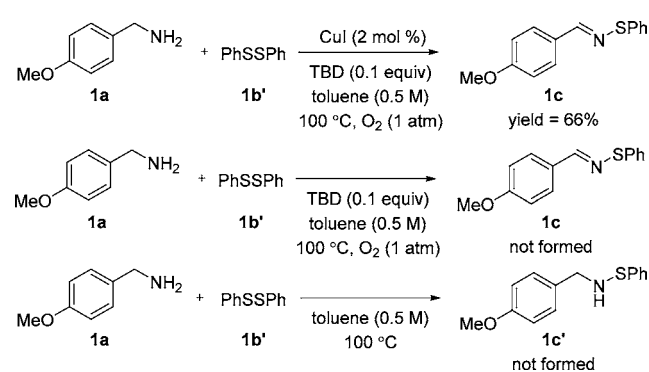
N–S bond formation did not occur, implying that N–S bonds were not formed via the simple nucleophilic addition of amines to disulfides. In other words, the copper catalyst is a prerequisite for N–S bond formation.

To identify the catalytically active species, CuSPh was subjected to the optimized conditions as both the catalyst and substrate (Scheme 3).[7d] As a catalyst, CuSPh was less efficient than CuI. The CuSPh-catalyzed reaction afforded **2c** in 14% yield. When CuSPh was used as a reactant in the absence of CuI, **2c** was obtained in only 29% yield. On the other hand, with 2 mol % of CuI, the reaction of benzyl amine and CuSPh afforded **2c** in 67% yield. These results indicate that CuSPh is not an active catalyst. Prior to the reaction of copper catalysts

Scheme 3. Reactions Using CuSPh as a Catalyst and a Substrate
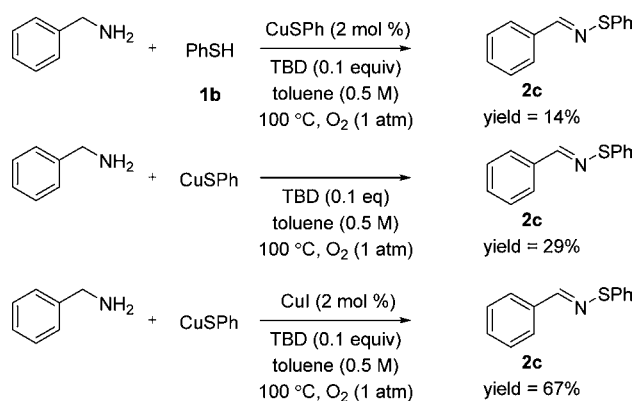
with phenylthioloates, the copper-catalyzed oxidation of amines to imines should occur. In the context of amine oxidation, CuI appears to be more reactive in forming **2c**. The observation that sulfenamides were not formed during the experiments also supports this hypothesis.

Based on the results of the control experiment, we propose a possible reaction mechanism (Scheme 4). Benzyl amine

Scheme 4. Proposed Reaction Mechanism
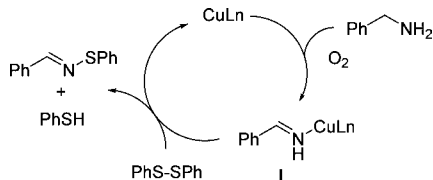
underwent aerobic oxidation by the Cu catalyst to form imine−Cu complex **I**.[9f] Intermediate **I** reacted with diphenyldisulfide formed from thiophenol to afford the desired sulfenylimines.[6i,7b]

In conclusion, we have reported an efficient copper-catalyzed aerobic coupling of amines and thiols to afford *N*-sulfenylimines in good yields. Under aerobic oxidation conditions, no overoxidation to form sulfinylimines or sulfonylimines was observed. This direct synthesis of *N*-sulfenylimines from amines and thiols would expand the utility of sulfenylimines in the synthesis of a range of sulfur-containing organic compounds. Based on control experiments, the reaction mechanism was proposed to involve selective amine oxidation, followed by N−S bond formation.

◼ ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures and spectra of **1c−14c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

◼ REFERENCES

(1) For reviews of sulfenylimines, see: (a) Davis, F. A.; Zhou, P.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13−18. (b) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993−9003.

(2) For the synthesis and applications of sulfenylimines, see: (a) Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2243−2252. (b) Baldwin, J. E.; Adlington, R. M.; Russell, A. T.; Smith, M. L. *J. Chem. Soc., Chem. Commun.* **1994**, 85−86. (c) Baldwin, J. E.; Adlington, R. M.; O'Neil, I. A.; Russell, A. T.; Smith, M. L. *Chem. Commun.* **1996**, 41−42. (d) Coantic, S.; Mouysset, D.; Mignani, S.; Tabart, M.; Stella, L. *Tetrahedron* **2007**, *63*, 3205−3216. (e) Coantic, S.; Mouysset, D.; Mignani, S.; Tabart, M.; Stella, L. *Tetrahedron Lett.* **2007**, *48*, 4301−4303. (f) Barman, P.; Bhattacharjee, S. K.; Bhattacharjee, T. *Synth. Commun.* **2011**, *41*, 2870−2875. (g) Foster, J. C.; Matson, J. B. *Macromolecules* **2014**, *47*, 5089−5095. (h) Foster, J. C.; Powell, C. R.; Radzinski, S. C.; Matson, J. B. *Org. Lett.* **2014**, *16*, 1558−1561. (i) Baldwin, J. E.; Aldous, D. J.; Chan, C.; Harwood, L. M.; O'Neil, I. A.; Peach, J. M. *Synlett* **1989**, 9−14.

(3) For articles on the synthesis of sulfenylimines from disulfides, see: (a) Davis, F. A.; Slegeir, W. A. R.; Evans, S.; Schwartz, A.; Goff, D. L.; Palmer, R. *J. Org. Chem.* **1973**, *38*, 2809−2813. (b) Davis, F. A.; Slegeir, W. A. R.; Kaminsky, J. M. *J. Chem. Soc., Chem. Commun.* **1972**, 634−635.

(4) For articles on the synthesis of sulfenylimines from oximes, see: (a) Lukin, K. A.; Narayanan, B. A. *Tetrahedron* **2002**, *58*, 215−219. (b) Lamy, E.; Lüthi, P.; Paturel, C.; Winkler, T.; Jung, P. M. *J. Tetrahedron Lett.* **2006**, *47*, 5657−5660. (c) Burés, J.; Isart, C.; Vilarrasa, J. *Org. Lett.* **2007**, *9*, 4635−4638. (d) Gillis, H. M.; Greene, L.; Thompson, A. *Synlett* **2009**, 112−116.

(5) For recent review articles on copper-catalyzed aerobic oxidative coupling reactions, see: (a) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011**, *40*, 2761−2776. (b) Hirano, K.; Miura, M. *Chem. Commun.* **2012**, *48*, 10704−10714.

(6) For selected articles on copper-catalyzed aerobic oxidative coupling reactions, see: (a) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833−835. (b) Guo, Y.; Wang, G.; Chen, L.; Xu, P.; Zhao, Y.; Zhou, Y.; Han, L.-B. *J. Am. Chem. Soc.* **2009**, *131*, 7956−7957. (c) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2010**, *132*, 7262−7263. (d) Guo, S.; Qoan, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522−525. (e) Jin, X.; Yamaguchi, K.; Mizuno, N. *Chem. Commun.* **2012**, *48*, 4974−4976. (f) Wang, L.; Huang, H.; Priebbenow, D. L.; Pan, F.-F.; Bolm, C. *Angew. Chem., Int. Ed.* **2013**, *52*, 3478−3480. N−P bond: (g) Fraser, J.; Wilson, L. J.; Blundell, R. K.; Hayes, C. J. *Chem. Commun.* **2013**, *49*, 8919−8921. P−S bond: (h) Kumaraswamy, G.; Raju, R. *Adv. Synth. Catal.* **2014**, *356*, 2591−2598. N−S bond: (i) Taniguchi, N. *Eur. J. Org. Chem.* **2010**, 2670−2673. (j) Tang, X.; Huang, L.; Qi, C.; Wu, X.; Wu, W.; Jiang, H. *Chem. Commun.* **2013**, *49*, 6102−6104. (k) Huang, X.; Wang, J.; Ni, Z.; Wang, S.; Pan, Y. *Chem. Commun.* **2014**, *50*, 4582−4584 (copper-mediated reaction).

(7) For articles on the sulfenylation of aromatic compounds using disulfides, see: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790−6791. (b) Fukuzawa, S.-i.; Shimizu, E.; Atsuumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374−2376. (c) Fang, X.-L.; Tang, R.-Y.; Zhong, P.; Li, J.-H. *Synthesis* **2009**, 4183−4189. (d) Zhang, S.; Qian, P.; Zhang, M.; Hu, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6732−6735. (e) Iwasaki, M.; Iyanaga, M.; Tsuchiya, Y.; Nishimura, Y.; Li, W.; Li, Z.; Nishihara, Y. *Chem.—Eur. J.* **2014**, *20*, 2459−2462. (f) Iwasaki, M.; Kaneshika, W.; Tsuchiya, Y.; Nakajima, K.; Nishihara, Y. *J. Org. Chem.* **2014**, *79*, 11330−11338.

(8) For selected reviews of oxidation of amines to imines: (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062−11087. (b) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464−3484.

(9) For metal-catalyzed aerobic oxidation of amines to imines, see: (a) Wilkins, R. G.; Burkin, A. R. *J. Chem. Soc.* **1950**, 132−136. (b) Maeda, Y.; Nishmura, T.; Uemura, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2399−2403. (c) Paine, T. K.; Weyhermüller, T.; Wieghardt, K.; Chaudhuri, P. *Dalton Trans.* **2004**, 2092−2101. (d) Samec, J. S. M.; Éll, A. H.; Bäckvall, J.-E. *Chem.—Eur. J.* **2005**, *11*, 2327−2334. (e) Lang, X.; Ji, H.; Chen, C.; Ma, W.; Zhao, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3934−3937. (f) Patil, R. D.; Adimurthy, S. *Adv. Synth. Catal.* **2011**, *353*, 1695−1700. (g) Hu, Z.; Kerton, F. M. *Org. Biomol. Chem.* **2012**, *10*, 1618−1624. (h) Zhang, E.; Tian, H.; Xu, S.; Yu, X.; Xu, Q. *Org. Lett.* **2013**, *15*, 2704−2707. (i) Damodara, D.; Arundhathi, R.; Likhar, P. R. *Adv. Synth. Catal.* **2014**, *356*, 189−198.

(10) (a) Bahrami, K.; Khodaei, M. M.; Soheilizad, M. *Tetrahedron Lett.* **2010**, *51*, 4843−4846. (b) Veisi, H.; Ghorbani-Vaghei, R.; Hemmati, S.; Mahmoodi, J. *Synlett* **2011**, 2315−2320. (c) Veisi, H. *Bull. Korean Chem. Soc.* **2012**, *33*, 383−386.

(11) (a) Wang, X.; Ji, M.; Lim, S.; Jang, H.-Y. *J. Org. Chem.* **2014**, *79*, 7256−7260. (b) Lim, S.; Ji, M.; Wang, X.; Lee, C.; Jang, H.-Y. *Eur. J. Org. Chem.* **2015**, 591−595.

(12) Studer reported the TEMPO-catalyzed aerobic oxidation of alkoxyamines to oximes: Wertz, S.; Studer, A. *Helv. Chim. Acta* **2012**, *95*, 1758−1772.