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Copper-Catalyzed Synthesis of *gem*-Bisarylthio Enamines under Redox-Neutral Conditions

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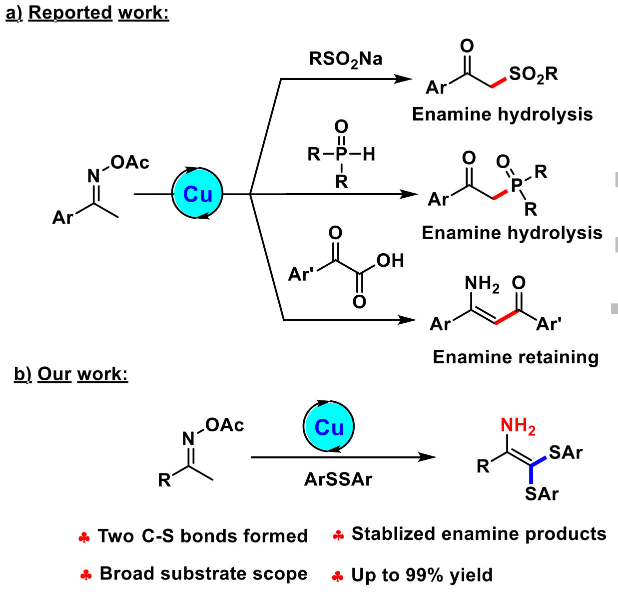
Abstract: An efficient approach for the construction of *gem*-bisarylthio enamines via coupling of oxime acetates with diaryl disulfides is developed. This process involved copper-catalyzed N-O/S-S bond cleavages and formation of two new C-S bonds. A broad range of substrates with diverse functional groups were tolerated.

Keywords: copper; oxime acetates; disulfides; redox-neutral; *gem*-bisarylthio enamines

Transition-metal-catalyzed reactions using ketone oxime esters as internal oxidants have attracted more and more attention in organic synthesis.[1] Specifically, oxime acetates represent a class of useful synthons that are widely applied in the field of transition-metal-catalyzed oxime N-O bond transformations.[2,3] In general, the conversion of oxime acetates triggered by transition-metals occurs through iminyl radical intermediates, which are then converted to carbon radicals or metal-enamine intermediates.[1f] Recently, such radical transformation strategy[4] using copper as the catalyst and oxime acetates as substrates has been achieved by the Jiang group[2b,d] and Lei group[2c] (Scheme 1a). In these cases, copper-catalyzed radical cross-couplings of oxime acetates with sodium sulfonates[2b] or phosphine oxides[2c] were accomplished. More recently, the Jiang group[2d] further reported a copper-catalyzed α-C(sp^3)-H bond acylation of oxime acetates with α-oxocarboxylic acids to afford enamine products that are generally unstable and readily rearranged to imine tautomers.

Inspired by the Jiang group and Lei group's elegant work in copper-catalyzed oxidative coupling of oxime acetates and in view of the limited structures bearing the arylthio function, we envisioned that an arylthio radical[5] generated from diaryl disulfides might react with oxime acetates in this copper-catalyzed oxidative coupling system thus leading to arylthio substituted ketones.



Scheme 1. Cu-catalyzed C(sp^3)-H oxidative coupling of oxime acetates.

To our surprise, we found that treatment of acetophenone *O*-acetyl oxime with diphenyl disulfide under Cu catalysis provided an unexpected *gem*-bisphenylthio enamine, which represents a unique and barely reported thio-containing architecture (Scheme 1b).[6,7] A literature research disclosed that there was only one report (Scheme 2) ever describing the formation of such *gem*-bisarylthio enamines[8] by the Davis group, who found that the sulfenamide enolate equivalent **II** which were prepared by treatment of sulfenime **I** with LDA, could react with diaryl disulfides to afford the α-arylthiosulfenimine **III**, together with the *gem*-bisarylthio enamine **IV** as

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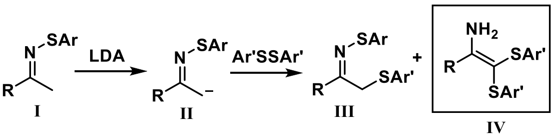
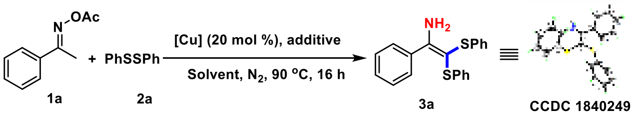
a side product. Although this was reported in 1980, the harsh reaction conditions restricted it for further investigation. Herein, we report a copper-catalyzed method allowing for rapid and efficient construction of *gem*-bisarylthio enamines from oxime acetates and diarylthio disulfides.



Scheme 2. Reported Synthesis of *gem*-bisarylthio enamines.

Initially, we commenced our investigation using acetophenone oxime acetate (**1a**) and diphenyl disulfide (**2a**) as model substrates (Table 1). Among the copper(I) salts, CuI showed the best catalytic reactivity, giving 45% yield of the *gem*-bisphenylthio enamine product **3a**,[9] while CuCl, CuBr and CuOAc showed lower reactivity (entries 1-4). In addition, commonly used copper(II) salts such as Cu(OAc)$_2$ and Cu(TFA)$_2$ did not catalyze this conversion (entries 5 and 6). Subsequently, different solvents such as toluene, 1,4-dioxane, DCE and DMF were screened, but no improvements were obtained (entries 7-10). Pleasantly, the yield of **3a** was significantly enhanced to 95% in the presence of 1 equiv of NaI (entry 11).[10] Replacement of NaI with KI provided inferior result (entry 12). In addition, reducing the loading of CuI to 10 mol % slightly decreased the yield (entry 13). It was found that the absence of CuI catalyst led to no product (entry 14). Furthermore, when one equivalent of **2a** was used, the yield **3a** was decreased to 83% (entry 15).

Table 1. Optimization of Reaction Conditions.[a]

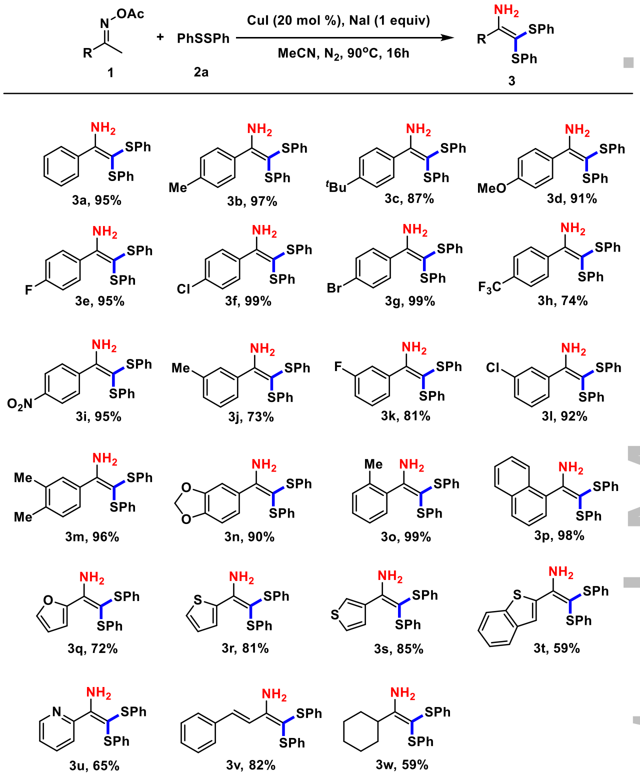


Entry	[Cu]	Additive	Solvent	Yield[%][b]
1	CuCl	/	MeCN	0
2	CuBr	/	MeCN	0
3	CuI	/	MeCN	45
4	CuOAc	/	MeCN	Trace
5	Cu(OAc)$_2$	/	MeCN	0
6	Cu(TFA)$_2$	/	MeCN	Trace
7	CuI	/	PhMe	0
8	CuI	/	1,4-dioxane	9
9	CuI	/	DCE	21
10	CuI	/	DMF	7
11	CuI	NaI	MeCN	95(85[c])
12	CuI	KI	MeCN	85
13	CuI[d]	NaI	MeCN	90
14	/	NaI	MeCN	0
15	CuI	NaI	MeCN	83[e]

[a] Reactions were carried out by using **1a** (0.10 mmol), **2a** (0.20 mmol), Cu catalyst (20 mol%), additive (0.10 mmol), solvent (1.0 ml), 90°C, N$_2$, 16h. [b] Isolated yield. [c] 1 mmol scale. [d] CuI(10 mol%). [e] 2a (0.10 mmol).

To validate the optimum reaction condition in entry 11, a 1.0 mmol-scale reaction was performed and compound **3a** was produced in 85% yield, demonstrating the good scalability of this protocol. Therefore, the optimum reaction condition was determined as those in entry 11.

Table 2. Reactions with various oxime acetates.[a,b]



[a] Reactions were carried out by using **1** (0.10 mmol), **2a** (0.20 mmol), CuI (0.02 mmol, 20 mol%), NaI (0.10 mmol), MeCN (1.0 ml), 90°C, N$_2$, 16h. [b] Isolated yield.

With the optimized reaction conditions in hand, we then evaluated the versatility and limitations of the current copper-catalyzed synthesis of *gem*-bisarylthio enamines by using various oxime acetates **1** (Table 2). Generally, this reaction proceeded smoothly and gave the desired products **3** in good to excellent yields. Acetophenone oxime acetates bearing a variety of *para*- or *meta*-substituents that are either electron-donating groups (Me, ^{t}Bu, MeO) or electron-withdrawing groups (F, Cl, Br, CF$_3$, NO$_2$) showed good compatibility, and the corresponding products **3b-l** were obtained in 73-99% yields. The tolerance of fluoro, chloro and bromo groups provides a complementary platform for further synthetic transformations via classic cross-coupling reactions. It is worth noting that the disubstituted acetophenone

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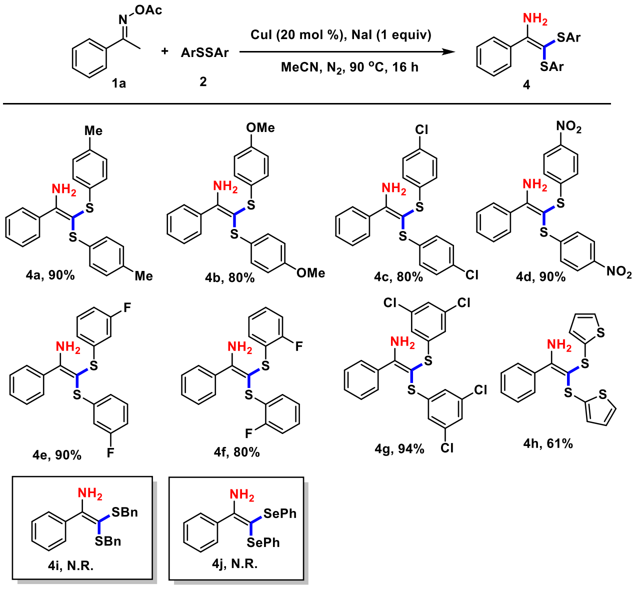
oxime acetates were suitable substrates, and the corresponding products were obtained in 96% and 90% yields (**3m**, **3n**) respectively. Notably, the *ortho*-substituted substrate **1o** was converted to the corresponding product **3o** as well in 99% yield, implying that the steric hindrance had little effect on the reaction. Also 1-acetylnaphthalene oxime acetate was found to be a suitable substrate for this reaction, affording the desired product **3p** in 98% yield. Furthermore, a series of oxime acetates containing a heterocyclic component, including furan (**1q**), thiophene (**1r, 1s**), benzothiophene (**1t**), and pyridine (**1u**), took part in this reaction smoothly to generate the desired products **3q-u** in 59-85% yields. More appealingly, the oxime acetate of 4-phenylbut-3-en-2-one was also transformed to the corresponding product **3v** in 82% yield, indicating the double bond in the substrate has no effect on either copper chelation or radical attack. In addition, methylcyclohexyl ketone oxime acetate also participated in the reaction very well and the corresponding product **3w** was obtained in 59% yield.

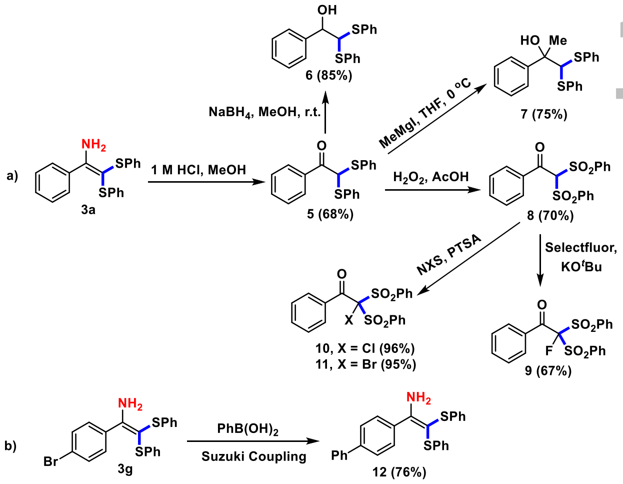
Table 3. Reactions with various diaryl disulfides.[a,b]



[a] Reactions were carried out by using **1a** (0.10 mmol), **2** (0.20 mmol), CuI (0.02 mmol, 20 mol%), NaI (0.10 mmol), MeCN (1.0 ml), 90°C, N_2, 16h. [b] Isolated yield.

For a thorough evaluation of the utility of this protocol, we then turned our attention to investigate the scope of diaryl disulfides **2**. Irrespective of the nature of the substituents and their position in the arene ring, the disulfides were well suited for the present transformation, affording satisfactory yields of the desired products **4a-h** (Table 3). Diaryl disulfides with Me-, MeO-, Cl- and NO_2- substituents at the *para*-position efficiently participated in the reaction, rendering corresponding *gem*-bisarylthio enamines products **4a−d** in 80−90% yields. Diaryl disulfides with substituent such as fluoro at the *meta*- or *ortho*-position also reacted smoothly with substrate **1a** and provided corresponding products **4e−f** in good yields. It is worth noting that the reaction tolerates 3,5-dichlorophenylthio substituent (**4g**), which are handy synthetic tools for further functionalization to complex molecules. Besides aromatic disulfides, the heteroaromatic disulfides such as 2,2′-dithienyl disulfide showed good reactivity, and the heteroarene substituted product **4h** was obtained in 61% yield. At last, alkyl disulfides (BnSSBn) was explored in this method. But the result (**4i**) shows that the alkyl disulfide was incompatible, which may result from the unstable alkylthio radical. We also tested the reactivity of PhSeSePh, but no reaction (N.R.) occurred (**4j**), suggesting that selenation was incompatible in current reaction system.

Inspired by this unique coupling reaction, we explored its transformations (Scheme 5).[11] Hydrolysis of **3a** with 1M HCl gave 1-phenyl-2,2-bis(phenylthio)ethan-1-one **5** in 68% yield, which could be used for further functional transformations such as ketone-reduction by $NaBH_4$ or nucleophilic addition by Grignard reagent or oxidation of sulfides, thus leading to compounds **6-8** in 70-85% yields. Furthermore, the bis(phenylsulfonyl) methine of **8** could be halogenated to generate quaternary products **9-11** in 67-96% yields (Scheme 3a). In addition, the classic Suzuki coupling strategy was used for further functionalization of **3g**, and the corresponding coupling product **12** was obtained in 76% yield (Scheme 3b).



Scheme 3. Transformations of **3a** and **3g**.

To gain more insight into the mechanism of this transformation, a series of control experiments were performed (Scheme 4). First, we envisioned that only one phenylthio group would be stalled if 2-methyl-1-phenylpropan-1-one (**1x**) was used as the substrate. As expected, although quite sluggish, the reaction of **1x** with **2a** afforded **13** in 39% yield as the major product (Scheme 4a). Second, the reaction of oxime with only one alpha-methyl group under standard conditions could also produce one arylthio-equipped

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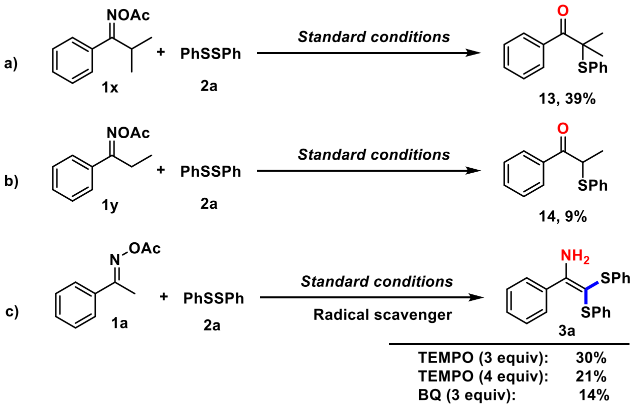
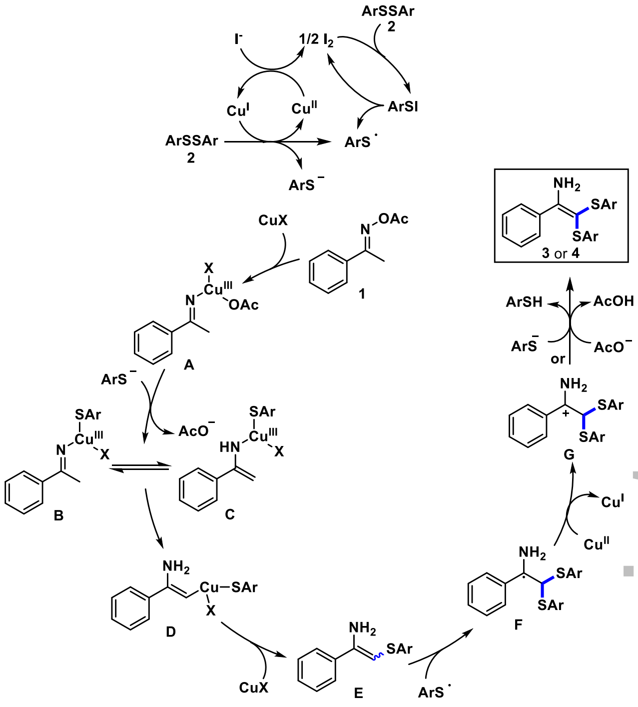
ketone in 9% yield, which means the steric effect of methyl group inhibit the second C-S bond formation (Scheme 4b). Subsequently, we added radical scavengers, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 1,4-benzoquinone (BQ) to our standard reaction (Scheme 4c). We found that this conversion was partially inhibited, giving product **3a** in significantly reduced yield (14-30%), indicating that both a radical process and an organometallic pathway might be involved in this transformation, phenomena similar to that in Jiang's report.[12]



Scheme 4. Mechanistic studies.

Based on the experiments above and the literature reports,[2,3,5] a plausible reaction mechanism is proposed in Scheme 5. The mechanism may involve organo-copper(III) species as the key intermediates. First, the copper(III) intermediate **A** was formed by oxidative addition of **1** to Cu(I).[13] Meanwhile, an arylthio radical and an arylthio anion were generated from diaryl disulfide **2** by Cu(I) in a single-electron-transfer reaction.[5] Alternatively, iodine ions were oxidized by Cu(II) to generate I_2, which reacted with **2a** to yield ArSI. Then ArSI underwent homolytic cleavage to afford arylthio radicals.[14] Subsequent coordination of arylthio anion to **A** formed the intermediate **B** that was then tautomerized to the copper(III) species **D.**[2b] Reductive elimination of CuX from the intermediate **D** afforded the key intermediate **E**. Attack of a second equivalent of arylthio radical to the intermediate **E** formed the radical intermediate **F**, which then underwent a single electron transfer to generate a carbocation species **G**. The *gem*-bisaryl enamines **3** or **4** were finally formed from intermediate **G** via a β-H abstraction by ArS^- or AcO^-.



Scheme 5. Proposed reaction mechanism.

In conclusion, we have developed a copper-catalyzed oxidative cross-coupling of oxime acetates with diaryl disulfides leading to a unique class of *gem*-bisarylthio enamines in high yields. This process involves copper-catalyzed N-O/S-S bond cleavage and formation of two new C-S bonds. This transformation possesses a broad substrate scope with good functional group compatibility.

Experimental Section

General procedure for the synthesis of *gem*-bisarylthio enamines. To an oven-dried 10 mL sealed tube was added substrate **1** (0.10 mmol), diaryl disulfides **2** (0.20 mmol), CuI (3.8 mg, 0.020 mmol), NaI (15 mg, 0.10 mmol) and acetonitrile (1.0 mL) under a nitrogen atmosphere. The mixture was stirred for 16 h at 90 °C. The mixture was then cooled to room temperature, and concentrated *in vacuo*. The desired product *gem*-bisarylthio enamines **3** and **4** were purified by silica-gel column chromatography in moderate to good yields.

Acknowledgements

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Copper-Catalyzed Synthesis of *gem*-Bisarylthio Enamines under Redox-Neutral Conditions

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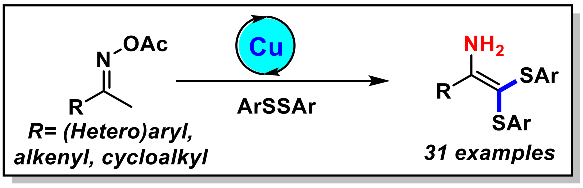
Jiabin Ni, Xiaokang Mao, Ao Zhang*



- **Two C-S bonds formed**
- **Stablized enamine products**
- **Broad substrate scope**
- **Up to 99% yield**

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