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Copper-Catalyzed Coupling Reactions of Cyclobutanone Oxime Esters with Sulfur Nucleophiles at Room Temperature

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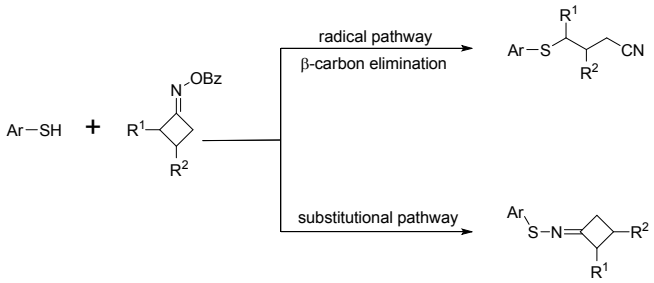
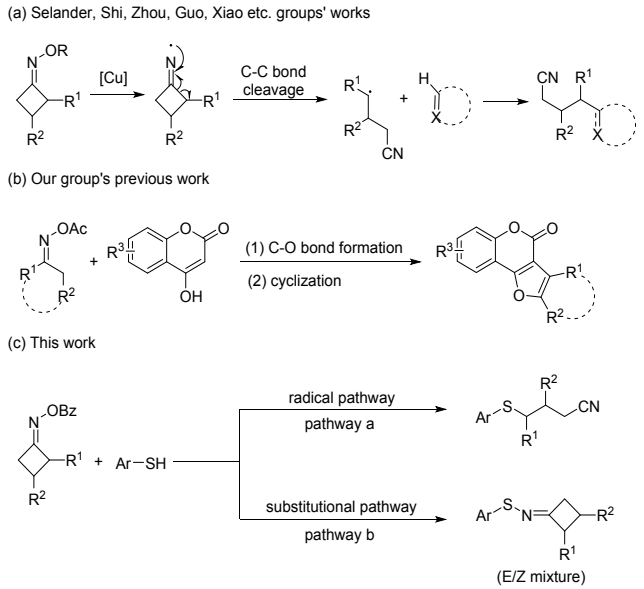


ABSTRACT: A copper-catalyzed iminyl radical-mediated C-C bond cleavage/cross-coupling tandem reaction of cyclobutanone oxime esters with aryl thiols in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature was developed and aryl cyanopropyl sulfides were smoothly synthesized in 20-88% yields. By altering copper reagent and the molar ratio of cyclobutanone oxime ester/aryl thiol/DBU, substitutional product *N*-arylthio cyclobutanone imines were selectively generated in 50-91% yields. Using this protocol, C-S bond and N-S bond formations using aryl thiols as sulfur sources were realized under very mild conditions without the use of photocatalysis and electrocatalysis techniques.

INTRODUCTION

Cyclobutanone oxime esters have received considerable attention from organic chemists.[1] Over the past decades, many research groups have investigated the application of aryl ketone oxime esters in the synthesis of pyridines,[2] pyrroles,[3] pyrazoles,[4] pyrrolines,[5] thiazoles,[6] etc. However, research on the use of alkyl ketone oxime esters has always been neglected. In 1991 Zard group[7] first used cyclobutanone sulfenylimines and carboxymethyl oximes to achieve selective C-C bond cleavage and produce γ-cyanoalkyl radicals. However, until two years ago, the application value of cyclobutanone *O*-acyl oximes in organic synthesis was revived through several research groups' extensive exploration (Scheme 1a). In 2017, Selander and other groups respectively applied transition-metal and photoredox catalysis to realize iminyl radical-mediated C-C bond cleavage/cross-coupling tandem reaction of cyclobutanone oxime esters with olefins and (hetero)arenes providing efficient approaches for the synthesis of complex and multifunctionalized nitriles.[1] However, among these transtion-metal catalyzed cross-coupling reactions, the elevated temperature was



Scheme 1. Cross-Coupling Reaction of Ketone Oximes

required to trigger the generation of radical species from cyclobutanone oxime esters.

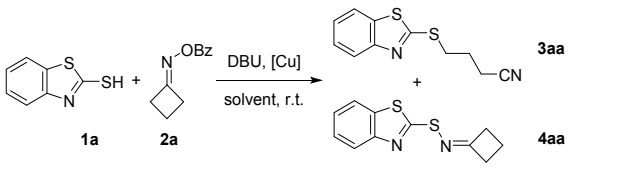
Sulfur-containing compounds play important roles in medicinal chemistry and functional materials, and some of them are often widely employed as versatile synthetic building blocks.[8] The traditional strategy for the C-S bond construction used metal catalysts and complex reaction conditions.[9] Recently, the use of diverse sulfur sources, photocatalysis and electrocatalysis has been successfully developed for the elegant construction of C-S bond.[10] In view of the importance of organosulfur compounds in organic synthesis, seeking simple and effective strategies for the synthesis of sulfur-containing compounds under mild conditions has always been an active and hot topic for organic chemists.

Cyano-containing organosulfur compounds can be easily transformed into diverse multifunctionalized molecules, for example, sulfoxides, sulfones, ketones, amino acids, and *N*-heterocycles, etc.[11] The strategy for the synthesis of cyano-containing organosulfur compounds in one single step is undoubtedly a challenging task for organic chemists. To the best of our knowledge, the cross-coupling reaction of γ-cyanoalkyl radicals resulted from β-scission of cyclobutanone oxime esters with organosulfur compounds has been rarely reported.[12] Very recently, we disclosed a copper-catalyzed radical/radical cross-coupling of ketoxime carboxylates with 4-hydroxycoumarins providing an easy access to furo[3,2-*c*]-coumarins,[13] as a continuation of project towards the synthetic application of ketoximes, herein, we disclosed a copper-catalyzed iminyl radical-mediated C-C bond cleavage/cross-coupling tandem reaction and a substitutional reaction of cyclobutanone oxime esters with aryl thiols under very mild conditions, in which alternate methods for the synthesis of aryl cyanopropyl sulfide derivatives and *N*-arylthio cyclobutanone imines were provided.

RESULTS AND DISCUSSION

To initiate our studies, we selected 2-mercaptobenzothiazole **1a** and cyclobutanone *O*-benzoyl oxime **2a** as model substrates and copper(II) trifluoromethanesulfonate as a catalyst to investigate the feasibility of C-S bond formation via iminyl radical-mediated C-C single bond cleavage. Pleasingly, when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added as a base and 1,4-dioxane was used as solvent, the desired product **3aa** was obtained in 31% yield, nevertheless a substitutional product **4aa** was also unexpectedly gained in 40% yield (Table 1, Entry 1). Finally, after screening of

Table 1. Optimization of Reaction Conditions[a]



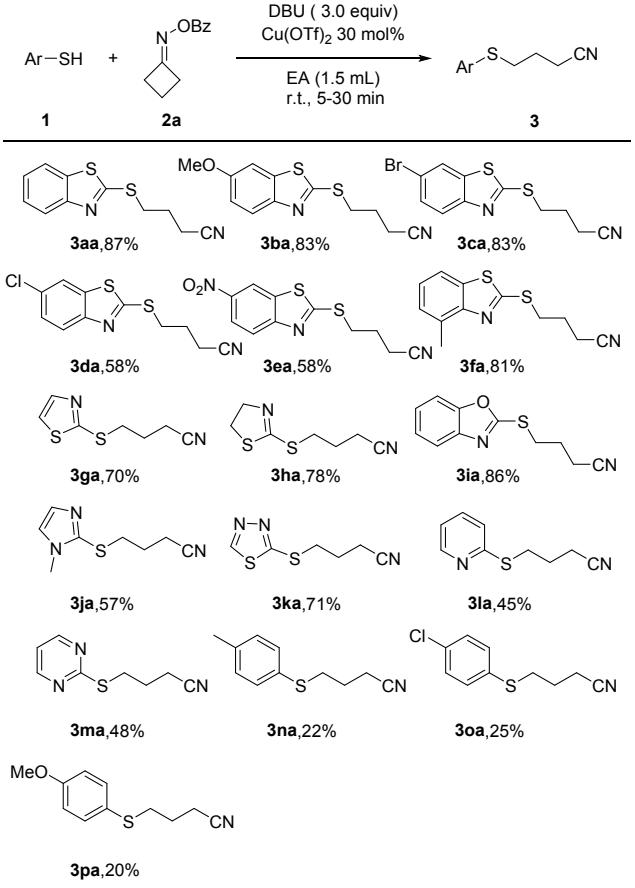
Entry	1a	2a	DBU	[Cu]/mol %	[S]/mL	Yield[b] (%) 3aa/4aa
1	0.2 mmol	0.2 mmol	2.0 equiv	$Cu(OTf)_2$ /15%	1,4-dioxane/2	31/40
2	0.2 mmol	0.4 mmol	3.0 equiv	$Cu(OTf)_2$ /30%	EtOAc/1.5	87/trace
3	0.3 mmol	0.2 mmol	3.0 equiv	$CuBr_2$ /15%	toluene/1	trace/85

[a]Reaction conditions: To a 10-mL single-necked flask was added **1a**, **2a** and [Cu] (mol% of **2a**), to a 4.5-mL sample tube was added DBU (equiv of **1a**) and solvent, then transfer the solution in the sample tube to flask and stirred for 5 - 60 min at room temperature. [b]Isolated yields.

reaction conditions including copper reagent, solvent, the molar ratio of **1a**/**2a**/DBU, and the amount of solvent, the optimum reaction conditions for selectively synthesizing **3aa** and **4aa** were respectively obtained (Table 1, Entry 2 and 3; for details, see supporting information).

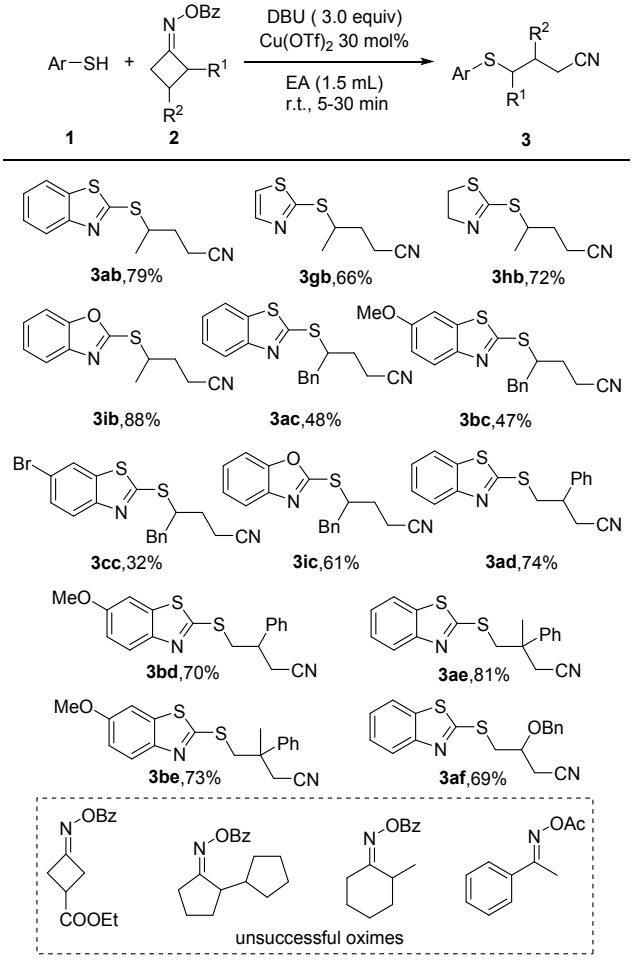
With the optimal conditions established, we then investigated the application scope of aryl thiols **1** for selective formation of products **3** by reacting with cyclobutanone *O*-benzoyl oxime **2a** (Table 2). First, substituted 2-mercaptobenzothiazoles were evaluated. As a result, both 6-methoxy and 6-bromo substituents on benzene ring worked well to give the coupling products **3ba** and **3ca** with good yields. 6-Chloro and 6-nitro substituents also proceeded smoothly to give products **3da** and **3ea** in moderate yields. 4-Methy-2-mercaptobenzothiazole showed good tolerance to deliver the corresponding product **3fa** in 81% yield. 2-mercaptobenzothiazoles with electron-withdrawing groups on the benzene ring gave lower yields than those with electron-donating groups on benzene ring. Next, various heteroaromatic sulfur nucleophiles were tested. And cheerfully, results in Table 2 showed that all of them are suitable for this transformation. 2-Mercaptothiazole, 2-thiazoline-2-thiol and 2-mercaptobenzoxazole provided the desired products **3ga-3ia** in 70-86% yields. 1-Methylimidazole-2-thiol and 2-mercapto-1,3,4-thiadiazol furnished the corresponding products **3ja** and **3ka** in 57% and 71% yields, respectively. 2-Mercaptopyridine and 2-mercapropyrimidine also worked well to offer products **3la** and **3ma** with moderate yields. It is worth noting that the reactions of *p*-substituted thiophenols (4-methy, 4-chloro, 4-methoxy) with **2a** provided **3na-3pa** in comparatively lower yields of 20-25%, and the corresponding disulfides being major products. Finally, a gram-scale reaction of **1a** (4 mmol) with **2a** (6 mmol, 1.135 g) was explored, and

Table 2. Scope of Thiolaromatics for Product **3**.[a]



[a]Reaction conditions: To a 10-mL single-necked flask was added **1**, **2a** and [Cu] (30 mol% of **2a**), to a 4.5-mL sample tube was added DBU (3 equiv of **1**) and solvent, then transfer the solution in the sample tube to flask and stirred for 5-30 min at room temperature. Isolated yields.

Table 3. Scope of Cyclobutanone Oximes for Product **3**.[a]



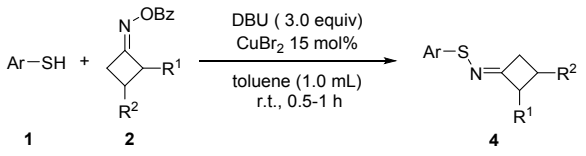
[a]Reaction conditions: To a 10-mL single-necked flask was added **1**, **2** and [Cu] (30 mol% of **2**), to a 4.5-mL sample tube was added DBU (3 equiv of **1**) and solvent, then transfer the solution in the sample tube to flask and stirred for 5-30 min at room temperature. Isolated yields.

the product **3aa** could be produced in 63% yield, which confirmed that this protocol possessed practical application value in organic synthesis.

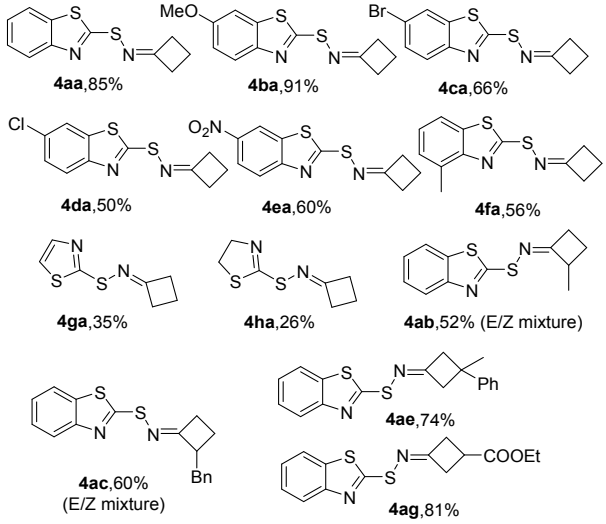
After the above works, the substrate scope of cyclobutanone oxime esters was inspected (Table 3). Delightedly, when 2-methycyclobutanone *O*-benzoyl oxime **2b** was reacted with 2-mercaptobenzothiazole, 2-mercaptothiazole, 2-thiazoline-2-thiol and 2-mecaptobenzoxazole, the corresponding products **3ab**, **3gb**, **3hb**, and **3ib** were smoothly produced with yields ranging from 66% to 88%. Encouraged by these results, 2-benzylcyclobutanone oxime **2c** was also applied to react with four sulfhydryl heteroaromatics. Although the efficiency was not as good as 2-methycyclobutanone oxime, the desired products **3ac**, **3bc**, **3cc**, and **3ic** could also be obtained in yields of 32-61%. Next, 3-substituted cyclobutanone oximes, including 3-phenyl, 3-methyl-3-phenyl, 3-benzyloxy and 3-carboxylate, were employed to test the tolerability of functional groups. As expected, 3-phenyl and 3-methyl-3-phenyl cyclobutanone oximes (**2d** and **2e**) could also react with 2-mercaptobenzothiazole and 6-methoxyl-2-mercaptobenzothiazole to give the products **3ad**, **3bd**, **3ae** and **3be** with good yields (70-81%). Finally, 3-benzyloxy cyclobutanone oximes (**2f**) were treated with 2-mercaptobenzothiazole, the desired product **3af** was furnished in 69% yield. Disappointedly, 3-ethoxycarbonyl cyclobutanone *O*-benzoyl oxime, 2-cyclopentylcyclopentanone *O*-benzoyl oxime, 2-methylcyclohexanone *O*-benzoyl oxime and acetophenone *O*-acyl oxime did not work for this conversion. These results indicated that cyclobutanone oxime with electron-withdrawing substituent on cyclobutane ring and aromatic ketoxime are not suitable substrates. The reason might result from the failure of ring-opening of these substrates in mild reaction conditions.

Next, we evaluated the substrate scope for product **4** under the corresponding optimum conditions (Table 4). Several products (**4ba**-**4fa**) with substituents (6-methoxy, 6-bromo, 6-chloro, 6-nitro and 4-methy) on benzene ring could be successful

Table 4. Substrate Scope for Product **4**.[a]



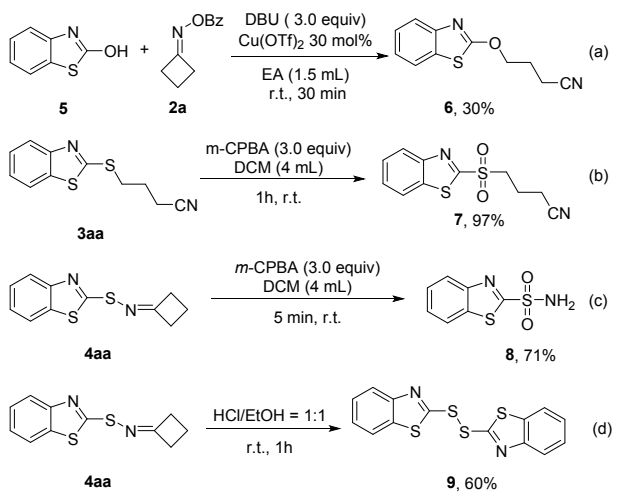
1 2 4



[a]Reaction conditions: To a 10-mL single-necked flask was added **1** (0.3 mmol), **2** (0.2 mmol) and [Cu] (15 mol% of **2**), to a 2.0-mL sample tube was added DBU (3.0 equiv of **1**) and solvent, then transfer the solution in the sample tube to flask and stirred for 0.5-1 h at room temperature. Isolated yields.

synthesized by reacting with cyclobutanone *O*-benzoyl oxime in moderate to excellent yields. These results showed that the effects of different substituents on benzene ring varied. However, 2-mercaptothiazole and 2-thiazoline-2-thiol exhibited lower reactivity with **4ga** and **4ha** prepared in 35% and 24% yield, respectively. The reactions of substituted cyclobutanone oximes (**2b**, **2c**, **2e**, and **2g**) with 2-mercaptothiazole proceeded very well to deliver thecorresponding products **4ab**, **4ac**, **4ae**, and **4ag** in 52-81% yields.

Scheme 2. C-O Bond Formation and Derivatization of Products.[a]

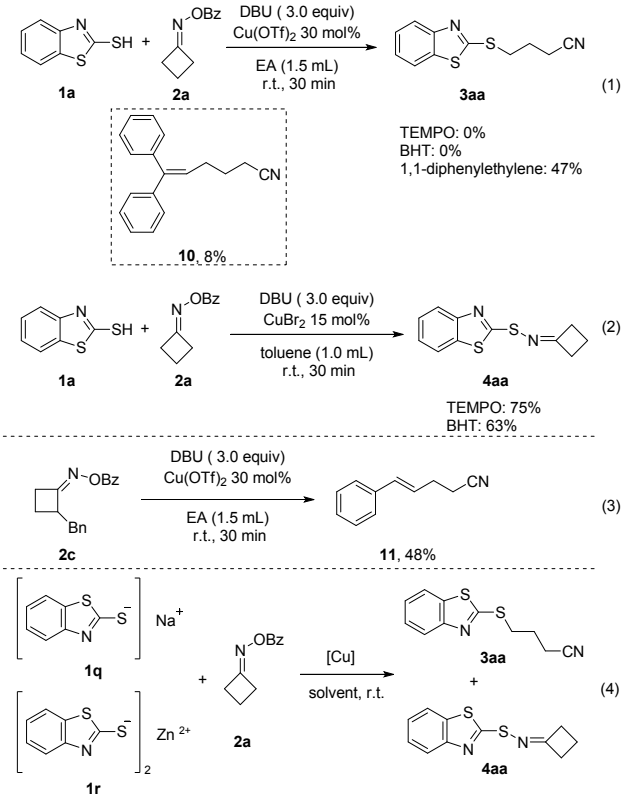


[a]Reaction conditions: (a) Refer to standard condations for the synthesis of prouct **3**. (b) and (c) To a 10-mL flask was added **3aa** or **4aa** (0.2 mmol), *m*-CPBA (3.0 equiv) and DCM (4 mL), stirred for 5 min or 1 h at room temperature. (d) To a 10-mL flask was added **4aa** (0.2 mmol), EtOH (1 mL) and 1 N HCl (1 mL), stirred for 1 h at room temperature.

Furthermore, the construction of C-O bond could be achieved by our procedure under standard conditions (Scheme 2, a). Derivatization or application of product **3aa** and **4aa** was studied. **3aa** could almost totally be transformed into sulfone **7** via oxidization with *m*-chloroperoxybenzoic acid (Scheme 2, b). Similarly, **4aa** could easily be oxidized to sulfonamide **8** (Scheme 2, c). Disulfide **9** was generated when product **4aa** was treated with 1 N HCl aqueous solution (Scheme 2, d).

To gain more insight into the mechanism of these two processes, several control experiments were carried out (Scheme 3). Several radical scavengers, such as TEMPO, BHT, and 1,1-diphenylethylene were respectively added to the reaction mixture under the separate optimal conditions for **3aa** and **4aa**. On one hand, **3aa** was not detected or was obtained in a reduced yield when TEMPO or BHT was added. The

Scheme 3. Mechanistic Studies.[a]

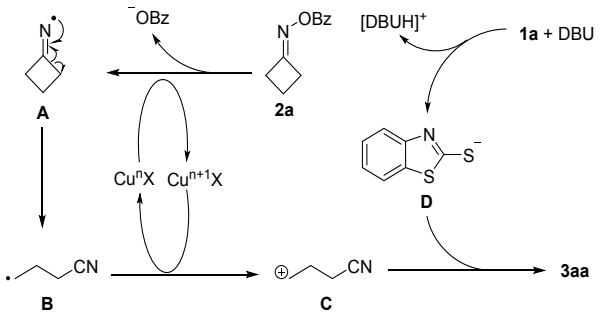


	1	DBU	[Cu]	solvent	3aa	4aa
(a)	1q	no add	$Cu(OTf)_2$	EtOAc	0%	trace
(b)	1q	no add	$CuBr_2$	toluene	0%	80%
(c)	1r	no add	$Cu(OTf)_2$	EtOAc	trace	0%
(d)	1r	no add	$CuBr_2$	toluene	38%	10%
(e)	1q	3.0 equiv	$Cu(OTf)_2$	EtOAc	59%	trace

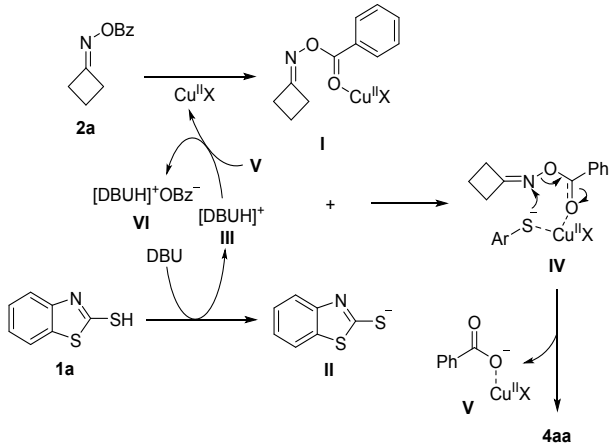
[a]Reaction conditions: see **Experimental Section**.

addition of 1,1-diphenylethylene resulted in the formation of a trapped product **10** (Scheme 3, 1). On the other hand, **4aa** was less influenced by TEMPO or BHT (Scheme 3, 2). Then benzyl substituted cyclobutanone oxime **2c** was selected to further explore the transformational pathway to **3**. When none of sulfur nucleophiles existed, a ring-opening elimination product **11** was observed (Scheme 3, 3). These results suggested that a radical process may be involved in the formation of **3**, but not for **4**. Besides, we conjectured that the sulfur nucleophiles may participate in reactions as a sulfur anion, therefore, two kinds of thiol salts, 2-mercaptothiazole sodium salt and 2-mercaptothiazole zinc salt, were used instead of 2-mercaptothiazole in the absence of DBU to react with cyclobutanone *O*-benzoyl oxime **2a** through four different methods (Scheme 3, 4a-4d). The product **3aa** and **4aa** still could be furnished under these conditions. **3aa** was not formed smoothly under the conditions (4a) and (4c) of scheme 3, which perhaps was due to the pool solubility of 2-mercaptothiazole sodium salt in ethyl acetate. In order to improve the solubility of sodium salt in solvent, DBU was added, and **3aa** was found to be easily produced (Scheme 3, 4e). These results indicated that sulfur nucleophiles may participate in reactions via a sulfur anion for the formation of both **3** and **4**.

Formation of Product 3



Formation of Product 4



Scheme 4. Plausible Reaction Mechanism

Based on the experimental results along with the previous reports, two possible mechanisms were proposed (Scheme 4). For the formation of **3aa**, a cyclobutylideneiminyl radical **A** was first generated from **2a** in the presence of Cu(II) catalyst, which immediately isomerized to γ-cyanoalkyl radical **B** via a *β*-carbon scission process. Subsequently, species **B** lost an electron by Cu(III) to give a cation **C** and Cu(II). Meanwhile, **1a** lost a proton to afford sulfur anion **D** which directly coupled with **C** to furnish product **3aa**. The exact mechanism for the formation of **4aa** is unknown at this time. Species **I** might form resulting from the coordination of **2a** with Cu(II) salt. Then species **I** reacted with sulfur anion **II** to generate a transition state species **IV** which subsequently gave the desired product **4aa** via a substitutional process. The combination of species **V** with species **III** released Cu(II)X to terminate the catalytic cycle. In the whole procedure, the valence of [Cu] species did not change. The reason why the two discrepant generation of **3** and **4** occurred under different conditions is not clear. However, results disclosed that the molar ratio of **2** to **1** and solvent polarity play the most important roles in determining the reaction pathway into **3** or **4**.

CONCLUSION

In conclusion, two different cross-coupling reactions of cyclobutanone oxime esters with sulfur nucleophiles were developed at room temperature. These transformations can be triggered under very mild conditions without heat and the use of photocatalysis or electrocatalysis techniques. A novel manner for C-S bond was achieved through this simple process providing aryl cyanopropyl sulfides in 20-88% yields. Another kind of substitutional product *N*-arylthio cyclobutanone imines were selectively generated in 50-91% yields under slightly different reaction conditions. These obtained products are expected to have potential application in organic synthesis and the investigation are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reactions were performed under air atmosphere at room temperature (20-35 °C) used a 10-mL single neck flask. Unless otherwise noted, all reagents were obtained from commercial suppliers (Adamas, TCI and Alfa) and used without further purification. NMR-spectra were recorded on Agilent DD2 400 HMz. ^{1}H NMR spectra were recorded on 400 MHz and ^{13}C NMR spectra were recorded on 101 MHz, and

tetramethylsilane as an internal standard. The chemical shifts are referenced to signals at 7.26 and 77.0 ppm ($CDCl_3$). Column chromatography was carried out on silica gel with petroleum ether/ethyl acetate as the eluent. All new compounds were further measured by high resolution mass spectra (HRMS).

General Procedure for the Preparation of Cyclobutanone *O*-Benzoyl Oximes 2a, 2d, 2e, 2f, and 2g.[1] Cyclobutanone *O*-benzoyl oximes were obtained from the corresponding cyclobutanones, which were commercially available or produced by the reduction of α,α-dichlorocyclobutanones. α,α-Dichlorocyclobutanones can be synthesized from the corresponding alkenes by the reported procedure with slight modification. (1) To a 50-mL three-necked flask under argon were added alkene derivative (1 equiv), zinc-copper couple (3.0 equiv), and anhydrous ether (0.5 M), to this was added a solution of trichloroacetyl chloride (2.0 equiv) and phosphorus oxychloride (1.1 equiv) in ether (0.5 M) over 1 h through an addition funnel. The suspension was stirred overnight at reflux. The resulting mixture was filtered through a pad of Celite and was washed with ether (20 mL). The organic solution was successively washed with water (30 mL), saturated aqueous solution of $NaHCO_3$ (30 mL) and brine (30 mL), and dried over $MgSO_4$. Then the solution was filtered, concentrated and used in the next step without further purification. (2) A mixture of 2,2-dichlorocyclobutanones (1.0 equiv) and zinc dust (4.0 equiv) in acetic acid (0.5 M) was stirred in room temperature for 2 h and then heated at 80 °C for 5 h. The resulting mixture was allowed to cool to room temperature, then, the solution was diluted with water (30 mL) and extracted with ether (3×20 mL). The organic phase was successively washed with saturated $NaHCO_3$ aqueous solution (3×30 mL), water (30 mL) and brine (30 mL), then dried over $MgSO_4$ and concentrated *in vacuum*. The crude material was then purified by flash chromatography with a mixture of petroleum ether and ethyl acetate to afford various cyclobutanones (PE/EA= 600/1). (3) To a solution of cyclobutanone (1.0 equiv) in anhydrous ethyl alcohol (1 M) was added hydroxylamine hydrochloride (2.0 equiv) in a single-necked flask, under stirring a saturated aqueous solution of Na_2CO_3 was added to the mixture slowly until pH = 8-9. Upon completion of the reaction monitored by TLC, the suspension was diluted with water and extracted twice with ethyl acetate. The combined organic extracts was wished with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give the crude materials, which were used in next step without further purification. (4) To a stirred solution of cyclobutanone oxime (1.0 equiv) in a mixed solvent of pyridine and dichloromethane (1:1, 0.5 M), DMAP (10 mol%) was added followed by benzoyl cholide at 0 °C. After 1 h, water was added to the above solution and extracted with ethyl acetate twice, the combined organic phase was washed with hydrochloric acid solution (1 N) and brine, dried over $MgSO_4$. The solvent was removed under vacuum and the residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford various cyclobutanone O-benzoyl oximes (PE/EA = 25:1).

Cyclobutanone O-Benzoyl Oxime (2a).[1b] According to the general procedure, **1a** was prepared from the commercially available cyclobutanone as a colorless solid (3.2 g, 58%): ^{1}H NMR (400 MHz, Chloroform-d) δ 7.99 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.8 Hz, 2H), 3.21 – 2.94 (m, 4H), 2.05 (pd, J = 8.2, 2.4 Hz, 2H).

3-Phenylcyclobutanone O-Benzoyl Oxime (2d).[1b] According to the general procedure, **2d** was prepared from the corresponding styrene (10 mmol) as a pale yellow oil (1.655 g, 62%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 – 7.93 (m, 2H), 7.62 – 7.54 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.14 (m, 3H), 3.76 – 3.51 (m, 3H), 3.32 – 3.17 (m, 2H).

3-Methyl-3-Phenylcyclobutanone O-Benzoyl Oxime (2e).[1b] According to the general procedure, **2e** was prepared from the corresponding prop-1-en-2-ylbenzene (15 mmol) as a pale yellow oil (1.519 g, 36%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 – 7.94 (m, 2H), 7.62 – 7.53 (m, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.41 – 7.30 (m, 2H), 7.28 – 7.21 (m, 3H), 3.46 (ddd, *J* = 16.6, 13.2, 2.9 Hz, 2H), 3.31 – 3.16 (m, 2H), 1.57 (s, 3H).

3-(Benzyloxy)cyclobutanone O-Benzoyl Oxime (2f).[1b] According to the general procedure, **2f** was prepared from the commercially available 3-(benzyloxy)cyclobutan-1-one (3 mmol) as a colorless oil (420 mg, 50%): ^{1}H NMR (400 MHz, Chloroform-d) δ 8.02 (dd, J = 8.3, 1.5 Hz, 2H), 7.60 – 7.54 (m, 1H), 7.54 – 7.25 (m, 7H), 4.49 (d, J = 2.0 Hz, 2H), 4.27 (tt, J = 6.8, 5.3 Hz, 1H), 3.46 – 3.30 (m, 2H), 3.11 (tddd, J = 17.0, 4.7, 3.0, 1.5 Hz, 2H).

Ethyl 3-((Benzoyloxy)imino)cyclobutanecarboxylate (2g).[1b] According to the general procedure, **2g** was prepared from the commercially available 3-oxocyclobutane-1-carboxylate (3 mmol) as a colorless oil (409 mg, 52%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 – 7.93 (m, 2H), 7.60 – 7.53 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.43 – 3.34 (m, 4H), 3.24 (p, *J* = 8.0 Hz, 1H), 1.26 (t, *J* = 7.2 Hz, 3H).

General Procedure for the Preparation of Cyclobutanone *O*-Benzoyl Oximes 2b, 2c.[1] (1) To a solution of cyclobutanone (1.0 equiv) in anhydrous ethyl alcohol (1 M) was added hydroxylamine hydrochloride (2.0 equiv) in a single-necked flask, then a saturated aqueous solution of Na_2CO_3 was added to the mixture slowly until pH = 8-9. Upon completion of the reaction monitored by TLC, the suspension was diluted with water and extracted with ethyl

acetate for two times, the combined organic phase was combined and washed with brine, dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was used in the next step without further purification. (2) To a solution of cyclobutanone (1.0 equiv) in dry THF was added n-BuLi (2.0 equiv) slowly at 0 °C, then continued to stir for another 15 minutes at this temperature for the formation of syn dianion. RX (1.0 equiv) was added dropwise at 0 °C, then the mixture was warmed to room temperature for 2 h. Subsequently, the reaction was quenched by cold water, the mixture was extracted with ether twice, the combined organic layer was washed with water and brine, dried over $MgSO_4$, and solvent was removed under reduced pressure. The residue was subjected to column chromatography on silica gel with a mixture of petroleum ether and EtOAc as eluent to give α-substituted cyclobutanone oximes (PE/EA = 8/1). (3) To a stirred solution of cyclobutanone oxime (1.0 equiv), DMAP (10 mol%) and a mixed solvent of pyridine and dichloromethane (1:1, 0.5 M) in a single-necked flask was added benzoyl cholide slowly at 0 °C. After 1 h, water was added to the above solution and extracted with ethyl acetate twice, the combined organic phase was wished with hydrochloric acid solution (1 N) and brine, dried over $MgSO_4$. The solvent was removed under vacuum and the residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford α-substituted cyclobutanone *O*-benzoyl oximes (PE/EA = 25:1).

2-Methylcyclobutanone O-Benzoyl Oxime (2b). [1b] According to the general procedure, **2b** (E/Z mixture) was prepared from the corresponding cyclobutanone (10 mmol) as a colorless solid (908 mg, 48%): ^{1}H NMR (400 MHz, Chloroform-d) δ 8.03 (dd, J = 30.3, 7.5 Hz, 2H), 7.57 – 7.47 (m, 1H), 7.44 – 7.35 (m, 2H), 3.42 (dqd, J = 10.0, 7.0, 3.0 Hz, 1H), 3.17 – 2.85 (m, 2H), 2.30 – 2.14 (m, 1H), 1.64 (tt, J = 10.5, 7.1 Hz, 1H), 1.44 – 1.26 (m, 3H).

2-Benzylcyclobutanone O-Benzoyl Oxime (2c). [1b] According to the general procedure, **2c** (E/Z mixture) was prepared from the corresponding cyclobutanone (25 mmol) as a colorless solid (2.181g, 31%): ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 7.95 (m, 2H), 7.57 (dd, *J* = 8.7, 6.5 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.11 (m, 5H), 3.68 (ddt, *J* = 7.2, 4.9, 2.4 Hz, 1H), 3.32 – 3.22 (m, 1H), 3.05 – 2.87 (m, 3H), 2.14 (dtd, *J* = 11.5, 9.3, 6.0 Hz, 1H), 1.86 (ddt, *J* = 11.6, 9.9, 7.0 Hz, 1H).

General Procedure for the Preparation of Products 3. Without other special note, all products of **3** were synthesized according to the following procedure: To a 10-mL single-necked flask was added **1** (0.2 mmol), **2** (0.4 mmol) and $Cu(OTf)_2$ (30 mol% of **2**). To a 4.5-mL sample tube was added DBU (3.0 equiv of **1**) and ethyl acetate (1.5 mL). Then transfer the solution in sample tube to the flask and stirred for 5-30 min at room temperature. Upon completion of the reaction monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford various products **3** (PE/EA = 25/1 – 10/1).

4-(Benzo[d]thiazol-2-ylthio)butanenitrile (3aa). Colorless oil; isolated yield = 87%, 40.6 mg; a larger scale reaction was also performed: To a 50-mL single-necked flask was added **1a** (4 mmol, 0.669 g), **2a** (6 mmol, 1.135 g) and $Cu(OTf)_2$ (30 mol% of **2a**). To a 50-mL beaker was added DBU (3.0 equiv of **1a**) and ethyl acetate (30 mL). Then transfer the solution in the beaker to the flask and stirred for 1 h at room temperature. Upon completion of the reaction monitored by TLC, the solution was diluted with water (30 mL) and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic phase was washed with brine (50 mL), then dried over $MgSO_4$ and concentrated *in vacuum*. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent (PE/EA = 25/1) to afford product **3aa** in 63% yield, 0.588 g. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 – 7.82 (m, 1H), 7.79 – 7.70 (m, 1H), 7.42 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.35 – 7.27 (m, 1H), 3.48 (t, *J* = 6.8 Hz, 2H), 2.57 (t, *J* = 7.1 Hz, 2H), 2.24 (p, *J* = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.2, 153.0, 135.3, 126.1, 124.5, 121.6, 121.0, 118.8, 31.7, 25.4, 16.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_2S_2$ 235.0358; Found: 235.0362.

4-((6-Methoxybenzo[d]thiazol-2-yl)thio)butanenitrile (3ba). Pale yellow oil; isolated yield = 83%, 43.7 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 – 7.70 (m, 1H), 7.21 (d, *J* = 2.6 Hz, 1H), 7.03 – 6.96 (m, 1H), 3.83 (d, *J* = 1.2 Hz, 3H), 3.45 – 3.39 (m, 2H), 2.55 (td, *J* = 7.0, 1.7 Hz, 2H), 2.24 – 2.16 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.9, 157.2, 147.6, 136.6, 122.1, 119.0, 115.0, 104.1, 55.8, 31.9, 25.4, 16.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}N_2OS_2$ 265.0464; Found: 265.0462.

***4-((6-Bromobenzo[d]thiazol-2-yl)thio)butanenitrile* (3ca).** Colorless solid; mp: 93-94 °C; isolated yield = 83%, 51.8 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (t, *J* = 1.7 Hz, 1H), 7.68 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.49 (dt, *J* = 8.7, 2.2 Hz, 1H), 3.46 (td, *J* = 7.0, 2.2 Hz, 2H), 2.55 (td, *J* = 7.1, 1.8 Hz, 2H), 2.22 (td, *J* = 7.0, 2.1 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 166.1, 151.9, 136.8, 129.6, 123.6, 122.6, 118.9, 117.9, 31.7, 25.3, 16.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{10}BrN_2S_2$ 312.9463; Found: 312.9456.

4-((6-Chlorobenzo[d]thiazol-2-yl)thio)butanenitrile (3da). Colorless solid; mp: 75-76 °C; isolated yield = 58%, 31.0 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.63 (m, 2H), 7.36 (dd, *J* = 8.7, 2.1 Hz,

1H), 3.46 (t, *J* = 6.9 Hz, 2H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.22 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 166.0, 151.6, 136.4, 130.3, 126.8, 122.2, 120.7, 118.9, 31.7, 25.3, 16.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{10}ClN_2S_2$ 268.9968; Found: 268.9966.

4-((6-Nitrobenzo[d]thiazol-2-yl)thio)butanenitrile (3ea). Colorless solid; mp: 104-105 °C; isolated yield = 58%, 32.2 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.65 (d, *J* = 2.3 Hz, 1H), 8.28 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 1H), 3.54 (t, *J* = 7.0 Hz, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.26 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 172.6, 156.7, 144.2, 135.6, 121.9, 121.4, 118.7, 117.5, 31.8, 25.2, 16.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{10}N_3O_2S_2$ 280.0209; Found: 280.0209.

4-((4-Methylbenzo[d]thiazol-2-yl)thio)butanenitrile (3fa). Pale yellow oil; isolated yield = 81%, 40.1 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.58 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 2H), 3.47 (t, *J* = 6.9 Hz, 2H), 2.68 (s, 3H), 2.56 (t, *J* = 7.1 Hz, 2H), 2.24 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 163.8, 152.3, 135.1, 131.7, 126.8, 124.4, 119.0, 118.5, 31.8, 25.5, 18.4, 16.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}N_2S_2$ 249.0515; Found: 249.0513.

4-(Thiazol-2-ylthio)butanenitrile (3ga). Colorless oil; isolated yield = 70%, 25.7 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 3.4 Hz, 1H), 7.23 (d, *J* = 3.4 Hz, 1H), 3.32 (t, *J* = 6.8 Hz, 2H), 2.53 (t, *J* = 7.1 Hz, 2H), 2.13 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 163.1, 142.8, 119.5, 118.9, 32.7, 25.2, 16.0. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_7H_9N_2S_2$ 185.0202; Found: 185.0201.

4-((4,5-Dihydrothiazol-2-yl)thio)butanenitrile (3ha). Pale yellow oil; isolated yield = 78%, 28.9 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 4.17 (t, *J* = 8.0 Hz, 2H), 3.38 (t, *J* = 8.0 Hz, 2H), 3.17 (t, *J* = 6.9 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.08 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 164.4, 119.0, 64.1, 35.6, 31.0, 25.4, 16.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_7H_{11}N_2S_2$ 187.0358; Found: 187.0358.

4-(Benzo[d]oxazol-2-ylthio)butanenitrile (3ia). Colorless oil; isolated = 86%, 37.6 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.57 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.47 – 7.38 (m, 1H), 7.32 – 7.19 (m, 2H), 3.38 (t, *J* = 7.1 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.24 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 151.8, 141.6, 124.43, 124.1, 118.7, 118.5, 110.0, 30.6, 25.2, 16.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_2OS$ 219.0587; Found: 219.0591.

***4-((1-Methyl-1H-imidazol-2-yl)thio)butanenitrile* (3ja).** Colorless oil; isolated yield = 57%, 20.5 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.01 (d, *J* = 1.4 Hz, 1H), 6.92 (d, *J* = 1.3 Hz, 1H), 3.60 (s, 3H), 3.10 (t, *J* = 6.8 Hz, 2H), 2.52 (t, *J* = 7.1 Hz, 2H), 2.03 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 129.3, 122.6, 119.1, 33.3, 32.3, 25.4, 15.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_{12}N_3S$ 182.0746; Found: 182.0746.

4-((1,3,4-Thiadiazol-2-yl)thio)butanenitrile (3ka). Colorless oil; isolated yield = 71%, 26.3 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 9.01 (s, 1H), 3.47 (t, *J* = 6.9 Hz, 2H), 2.54 (t, *J* = 7.1 Hz, 2H), 2.23 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 164.6, 151.8, 118.7, 32.2, 25.0, 16.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_6H_8N_3S_2$ 186.0154; Found: 186.0165.

4-(Pyridin-2-ylthio)butanenitrile (3la). Colorless oil; isolated yield = 45%, 15.9 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.47 – 8.34 (m, 1H), 7.46 (td, *J* = 7.7, 1.9 Hz, 1H), 7.15 (dt, *J* = 8.2, 1.1 Hz, 1H), 6.97 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 1H), 3.28 (t, *J* = 6.8 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.07 (p, *J* = 7.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 157.6, 149.5, 136.1, 122.5, 119.7, 119.4, 28.3, 25.6, 16.1. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_9H_{11}N_2S$ 179.0637; Found: 179.0647.

4-(Pyrimidin-2-ylthio)butanenitrile (3ma). Colorless oil; isolated yield = 48%, 17.2 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.50 (d, *J* = 4.8 Hz, 2H), 6.98 (t, *J* = 4.8 Hz, 1H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.11 (p, *J* = 7.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 171.4, 157.4, 119.2, 116.8, 29.3, 25.3, 16.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_8H_{10}N_3S$ 180.0593; Found: 180.0593.

4-(p-Tolylthio)butanenitrile (3na). Pale yellow oil; isolated yield = 22%, 8.4 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.27 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.49 (t, *J* = 7.1 Hz, 2H), 2.32 (s, 3H), 1.91 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 137.1, 131.0, 130.9, 129.9, 119.0, 33.3, 24.9, 21.0, 15.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{14}NS$ 192.0841; Found: 192.0842.

4-((4-Chlorophenyl)thio)butanenitrile (3oa). Pale yellow oil; isolated yield = 25%, 10.5 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.27 (s, 4H), 3.00 (t, *J* = 6.9 Hz, 2H), 2.49 (t, *J* = 7.0 Hz, 2H), 1.93 (p, *J* = 6.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 133.3, 132.9, 131.4, 129.3, 118.8, 32.8, 24.8, 15.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{10}H_{11}ClNS$ 212.0295; Found: 212.0295.

4-((4-Methoxyphenyl)thio)butanenitrile (3pa). Pale yellow oil; isolated yield = 20%, 8.3 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.34 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 2.90 (t, *J* = 6.8 Hz, 2H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.87 (p, *J* = 7.0 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 159.4, 133.9, 124.8, 119.1, 114.8, 55.35, 55.33, 34.6, 24.9, 15.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{14}NOS$ 208.0791; Found: 208.0784.

4-(Benzo[d]thiazol-2-ylthio)pentanenitrile (3ab). Colorless oil; isolated yield = 79%, 39.0 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.41 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.30 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 4.16 – 4.01 (m, 1H), 2.66 – 2.48 (m, 2H), 2.23 – 2.08 (m, 2H), 1.53 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.6, 153.1, 135.3, 126.2, 124.6, 121.8, 121.0, 119.2, 42.8, 32.5, 21.0, 15.1. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{13}N_2S_2$ 249.0515; Found: 249.0518.

4-(Thiazol-2-ylthio)pentanenitrile (3gb). Pale yellow oil; isolated yield = 66%, 26.3 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 3.4 Hz, 1H), 7.28 (d, *J* = 3.4 Hz, 1H), 3.70 (h, *J* = 6.9 Hz, 1H), 2.67 – 2.48 (m, 2H), 2.09 – 2.00 (m, 2H), 1.45 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.3, 143.3, 120.6, 119.2, 43.8, 32.2, 21.0, 15.0. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_8H_{11}N_2S_2$ 199.0358; Found: 199.0358.

4-((4,5-Dihydrothiazol-2-yl)thio)pentanenitrile (3hb). Colorless oil; isolated yield = 72%, 28.8 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.18 (t, *J* = 8.0 Hz, 2H), 3.82 (h, *J* = 7.0 Hz, 1H), 3.35 (t, *J* = 8.0 Hz, 2H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.08 – 1.96 (m, 2H), 1.40 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.1, 119.3, 64.3, 41.7, 35.3, 32.5, 20.9, 14.9. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_8H_{13}N_2S_2$ 201.0515; Found: 201.0513.

4-(Benzo[d]oxazol-2-ylthio)pentanenitrile (3ib). Colorless oil; isolated yield = 88%, 40.8 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 6.8 Hz, 1H), 7.50 – 7.35 (m, 1H), 7.35 – 7.15 (m, 2H), 3.95 (h, *J* = 7.0 Hz, 1H), 2.56 (t, *J* = 7.3 Hz, 2H), 2.26 – 2.10 (m, 2H), 1.56 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 163.0, 151.6, 141.7, 124.4, 124.2, 119.0, 118.6, 110.0, 42.0, 32.2, 21.1, 15.0. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{13}N_2OS$ 233.0743; Found: 233.0747.

4-(Benzo[d]thiazol-2-ylthio)-5-phenylpentanenitrile (3ac). Colorless oil; isolated yield = 48%, 30.9 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.38 – 7.18 (m, 6H), 4.23 (dddd, *J* = 10.1, 8.4, 6.2, 4.1 Hz, 1H), 3.31 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.99 (dd, *J* = 14.0, 8.3 Hz, 1H), 2.64 – 2.47 (m, 2H), 2.22 (dddd, *J* = 13.1, 8.8, 7.1, 4.2 Hz, 1H), 2.05 (dtd, *J* = 14.6, 8.9, 5.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 164.5, 153.1, 137.6, 135.3, 129.3, 128.7, 127.1, 126.2, 124.6, 121.8, 121.0, 119.2, 49.2, 41.3, 29.6, 15.2. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{17}N_2S_2$ 325.0828; Found: 325.0828.

4-((6-Methoxybenzo[d]thiazol-2-yl)thio)-5-phenylpentanenitrile (3bc). Colorless oil; isolated yield = 47%, 33.1 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 (d, *J* = 8.9 Hz, 1H), 7.52 – 7.12 (m, 6H), 7.02 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.11 (dddd, *J* = 9.9, 8.0, 6.0, 4.1 Hz, 1H), 3.85 (s, 3H), 3.29 (dd, *J* = 14.0, 6.2 Hz, 1H), 2.97 (dd, *J* = 14.0, 8.3 Hz, 1H), 2.68 – 2.47 (m, 2H), 2.25 – 2.14 (m, 1H), 2.02 (dtd, *J* = 14.6, 8.9, 5.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 160.8, 157.3, 147.7, 137.6, 136.8, 129.3, 128.7, 127.0, 122.4, 119.2, 115.1, 103.9, 55.8, 49.5, 41.4, 29.6, 15.2. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{19}H_{19}N_2OS_2$ 355.0933; Found: 355.0935.

4-((6-Bromobenzo[d]thiazol-2-yl)thio)-5-phenylpentanenitrile (3cc). Pale yellow oil; isolated yield = 32%, 26.1 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 2.0 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.52 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.43 – 7.03 (m, 5H), 4.24 (tdd, *J* = 8.3, 6.4, 4.2 Hz, 1H), 3.29 (dd, *J* = 14.0, 6.3 Hz, 1H), 3.00 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.64 – 2.47 (m, 2H), 2.28 – 2.17 (m, 1H), 2.11 – 1.99 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.4, 151.9, 137.4, 136.9, 129.6, 129.2, 128.7, 127.1, 123.5, 122.8, 119.1, 118.0, 49.4, 41.3, 29.6, 15.2. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{16}BrN_2S_2$ 402.9933; Found: 402.9932.

4-(Benzo[d]oxazol-2-ylthio)-5-phenylpentanenitrile (3ic). Colorless oil; isolated yield = 61%, 37.4 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (dd, *J* = 7.3, 1.7 Hz, 1H), 7.44 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.41 – 7.08 (m, 7H), 4.13 – 4.04 (m, 1H), 3.30 (dd, *J* = 14.0, 6.5 Hz, 1H), 3.05 (dd, *J* = 14.0, 8.1 Hz, 1H), 2.65 – 2.48 (m, 2H), 2.30 – 2.20 (m, 1H), 2.11 (dtd, *J* = 14.7, 8.9, 5.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.8, 151.7, 141.7, 137.3, 129.3, 128.7, 127.2, 124.5, 124.3, 119.0, 118.7, 110.0, 48.5, 41.2, 29.5, 15.2. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{17}N_2OS$ 309.1056; Found: 309.1057.

4-(Benzo[d]thiazol-2-ylthio)-3-phenylbutanenitrile (3ad). Colorless oil; isolated yield = 74%, 45.7 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.26 (m, 7H), 3.73 (d, *J* = 7.3 Hz, 2H), 3.56 (p, *J* = 7.4 Hz, 1H), 2.95 – 2.81 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.2, 152.9, 139.7, 135.3, 129.1, 128.2, 127.3, 126.2, 124.5, 121.6, 121.1, 118.0, 41.7, 37.7, 23.3. HRMS (ESI-TOF) *m/z*: [M+K]$^+$ calcd for $C_{17}H_{14}N_2S_2K$ 349.0230; Found: 349.0224.

4-((6-Methoxybenzo[d]thiazol-2-yl)thio)-3-phenylbutanenitrile (3bd). Colorless oil; isolated yield = 70%, 47.7 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (d, *J* = 8.9 Hz, 1H), 7.45 – 7.27 (m, 5H), 7.22 (d, *J* = 2.5 Hz, 1H), 7.02 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.84 (s, 3H), 3.75 – 3.62 (m, 2H), 3.53 (qd, *J* = 7.6, 5.3 Hz, 1H), 2.95 – 2.80 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 161.9, 157.2, 147.5, 139.8, 136.7, 129.1, 128.1, 127.3, 122.1, 118.0, 115.0, 104.1, 55.8, 41.7, 37.9, 23.3. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{17}N_2OS_2$ 341.0777; Found: 341.0774.

4-(Benzo[d]thiazol-2-ylthio)-3-methyl-3-phenylbutanenitrile (3ae). Colorless oil; isolated yield = 81%, 52.3 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.73 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.45 – 7.36 (m, 5H), 7.30 (dddd, *J* = 9.2, 7.0, 3.1, 1.5 Hz, 2H), 3.99 (d, *J* = 13.5 Hz, 1H), 3.86 (d, *J* = 13.5 Hz, 1H), 2.98 (d, *J* = 16.7 Hz, 1H), 2.89 (d, *J* = 16.7 Hz, 1H), 1.70 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.9, 152.7, 142.3, 135.3, 128.9, 127.7, 126.2, 125.8, 124.5, 121.5, 121.0, 117.6, 44.4, 41.6, 29.6, 24.8. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{18}H_{17}N_2S_2$ 325.0828; Found: 325.0824.

4-((6-Methoxybenzo[d]thiazol-2-yl)thio)-3-methyl-3-phenylbutanenitrile (3be). Colorless oil; isolated yield = 73%, 50.9 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (d, *J* = 8.7 Hz, 1H), 7.48 – 7.33 (m, 4H), 7.32 – 7.25 (m, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 7.01 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.95 – 3.78 (m, 5H), 2.92 (q, *J* = 16.7 Hz, 2H), 1.68 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 162.6, 157.2, 147.3, 142.3, 136.7, 128.9, 127.7, 125.8, 122.0, 117.7, 114.9, 104.1, 55.8, 44.7, 41.6, 29.6, 24.8. HRMS (ESI-TOF) *m/z*: [M+K]$^+$ calcd for $C_{19}H_{18}N_2OS_2K$ 393.0492; Found: 393.0491.

4-(Benzo[d]thiazol-2-ylthio)-3-(benzyloxy)butanenitrile (3af). Colorless oil; isolated yield = 63%, 46.9 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.85 (d, *J* = 8.2 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.46 – 7.26 (m, 7H), 4.79 – 4.71 (m, 2H), 4.22 – 4.12 (m, 1H), 3.77 (dd, *J* = 14.1, 5.2 Hz, 1H), 3.47 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.80 – 2.71 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 165.1, 152.8, 137.0, 135.3, 128.6, 128.2, 128.0, 126.2, 124.6, 121.5, 121.1, 117.1, 73.3, 72.5, 35.7, 22.8. HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ calcd for $C_{18}H_{16}N_2OS_2Na$ 363.0596; Found: 363.0589.

General Procedure for the Preparation of Products 4. Without other special note, all products of **4** were synthesized according to the following procedure: To a 10-mL single-necked flask was added **1** (0.3 mmol), **2** (0.2 mmol) and $CuBr_2$ (15 mol% of **2**). To a 2.0-mL sample tube was added DBU (3.0 equiv of **1**) and toluene (1.0 mL), then transfer the solution in the sample tube to the flask and stirred for 0.5-1.0 h at room temperature. Upon completion of the reaction monitored by TLC, the solvent was evaporated under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford various products **4** (PE/EA = 100/1).

S-(Benzo[d]thiazol-2-yl)-N-cyclobutylidenethiohydroxylamine (4aa). Colorless solid; mp: 118-119 °C; isolated yield = 85%, 40.1 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 17.3, 8.0 Hz, 2H), 7.49 – 7.34 (m, 1H), 7.28 (t, *J* = 8.9 Hz, 1H), 3.12 (t, *J* = 8.1 Hz, 2H), 2.98 (t, *J* = 8.1 Hz, 2H), 2.16 – 2.03 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 176.6, 154.1, 134.9, 125.9, 123.7, 121.7, 120.9, 38.8, 37.7, 12.7. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_{11}N_2S_2$ 235.0358; Found: 235.0366.

N-Cyclobutylidene-S-(6-methoxybenzo[d]thiazol-2-yl)thiohydroxylamine (4ba). Colorless solid; mp: 99-100 °C; isolated yield = 91%, 48.0 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 (d, *J* = 8.9 Hz, 1H), 7.28 (d, *J* = 2.6 Hz, 1H), 6.99 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.83 (s, 3H), 3.09 (tt, *J* = 7.8, 1.7 Hz, 2H), 2.98 – 2.92 (m, 2H), 2.06 (p, *J* = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 176.3, 168.6, 156.7, 148.6, 136.3, 122.2, 114.7, 104.2, 55.8, 38.8, 37.7, 12.7. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{13}N_2OS_2$ 265.0464; Found: 265.0468.

S-(6-Bromobenzo[d]thiazol-2-yl)-N-cyclobutylidenethiohydroxylamine (4ca). Colorless solid; mp: 131-132 °C; isolated yield = 66%, 41.1 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 3.5, 1.9 Hz, 1H), 7.68 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.49 (ddd, *J* = 8.7, 3.4, 1.9 Hz, 1H), 3.18 – 3.04 (m, 2H), 3.04 – 2.88 (m, 2H), 2.16 – 2.00 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 177.3, 173.0, 153.0, 136.6, 129.3, 123.5, 122.7, 117.2, 38.8, 37.8, 12.7. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_{10}BrN_2S_2$ 312.9463; Found: 312.9459.

S-(6-Chlorobenzo[d]thiazol-2-yl)-N-cyclobutylidenethiohydroxylamine (4da). Colorless solid; mp: 136-137 °C; isolated yield = 50%, 26.8 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 – 7.53 (m, 2H), 7.35 (dt, *J* = 8.7, 1.7 Hz, 1H), 3.16 – 3.06 (m, 2H), 2.96 (t, *J* = 8.0 Hz, 2H), 2.14 – 2.03 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 177.3, 172.8, 152.6, 136.1, 129.6, 126.6, 122.4, 120.7, 38.8, 37.8, 12.7. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_{10}ClN_2S_2$ 268.9968; Found: 268.9969.

N-Cyclobutylidene-S-(6-nitrobenzo[d]thiazol-2-yl)thiohydroxylamine (4ea). Pale yellow solid; mp: 131-132 °C; isolated yield = 60%, 33.4 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.69 (d, *J* = 2.3 Hz, 1H), 8.27 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.85 (d, *J* = 9.0 Hz, 1H), 3.19 – 3.09 (m, 2H), 3.04 – 2.94 (m, 2H), 2.11 (p, *J* = 8.1 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 179.4, 178.7, 158.0, 143.6, 135.2, 121.8, 121.5, 117.4, 38.9, 37.9, 12.7. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{11}H_{10}N_3O_2S_2$ 280.0209; Found: 280.0206.

N-Cyclobutylidene-S-(4-methylbenzo[d]thiazol-2-yl)thiohydroxylamine (4fa). Colorless solid; mp: 145-146 °C; isolated yield = 56%, 28.0 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.5 Hz, 1H), 7.24 – 7.13 (m, 2H), 3.11 (t, *J* = 7.9 Hz, 2H), 2.96 (t, *J* = 8.2 Hz, 2H), 2.68 (s, 3H), 2.07 (p, *J* = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 176.6, 170.6, 153.4, 134.7, 126.6, 123.6, 118.4, 38.8, 37.7, 18.3, 12.7. HRMS (ESI-TOF) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{13}N_2S_2$ 249.0515; Found: 249.0515.

N-Cyclobutylidene-S-(thiazol-2-yl)thiohydroxylamine (4ga). Colorless solid; mp: 75-76 °C; isolated yield = 35%, 13.0 mg; ^{1}H

NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 3.4 Hz, 1H), 7.30 (d, *J* = 3.4 Hz, 1H), 3.09 (tq, *J* = 7.8, 2.2 Hz, 2H), 2.94 (ddq, *J* = 9.4, 5.7, 2.1 Hz, 2H), 2.12 – 2.01 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 176.1, 169.3, 143.1, 119.0, 38.8, 37.6, 12.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_7H_9N_2S_2$ 185.0202; Found: 185.0201.

N-Cyclobutylidene-S-(4,5-dihydrothiazol-2-yl)thiohydroxylamine (4ha). Colorless solid; mp: 61-63 °C; isolated yield = 26%, 9.6 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 4.36 (t, *J* = 8.2 Hz, 1H), 3.30 (t, *J* = 8.2 Hz, 1H), 3.08 – 3.01 (m, 1H), 2.88 (tq, *J* = 7.3, 1.7 Hz, 1H), 2.08 – 1.97 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 175.5, 170.8, 65.4, 38.8, 37.5, 32.6, 12.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_7H_{11}N_2S_2$ 187.0358; Found: 187.0359.

S-(Benzo[d]thiazol-2-yl)-N-(2-methylcyclobutylidene)thiohydroxylamine (4ab). Colorless solid; mp: 110-111 °C; isolated yield (E/Z mixture) = 52%, 25.8 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.74 (m, 2H), 7.40 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.27 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 3.43 – 3.26 (m, 1H), 3.12 – 2.87 (m, 2H), 2.33 – 2.20 (m, 1H), 1.66 (dtd, *J* = 11.0, 8.6, 6.7 Hz, 1H), 1.34 (dd, *J* = 27.7, 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 180.8, 172.7, 154.1, 134.9, 126.0, 125.9, 123.7, 123.7, 121.68, 121.64, 121.0, 120.9, 46.6, 45.8, 35.8, 35.3, 21.7, 20.8, 16.7, 15.4. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}N_2S_2$ 249.0515; Found: 249.0515.

S-(Benzo[d]thiazol-2-yl)-N-(2-benzylcyclobutylidene)thiohydroxylamine (4ac). Colorless oil; isolated yield (E/Z mixture) = 60%, 39.2 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.85 (dd, *J* = 14.1, 8.0 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 1H), 7.27 (ttd, *J* = 18.6, 8.8, 8.3, 4.5 Hz, 6H), 3.61 (dddd, *J* = 15.9, 13.1, 7.8, 4.9 Hz, 1H), 3.27 – 3.14 (m, 1H), 2.94 – 2.79 (m, 3H), 2.25 – 2.12 (m, 1H), 1.84 (ddt, *J* = 11.2, 9.2, 7.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 178.9, 172.5, 154.1, 138.9, 135.0, 129.0, 128.9, 128.7, 128.5, 126.7, 126.3, 125.99, 125.96, 123.8, 123.7, 121.74, 121.68, 120.99, 120.97, 52.5, 52.0, 37.6, 36.2, 35.2, 35.0, 19.6, 18.2. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{16}N_2S_2Na$ 347.0647; Found: 347.0639.

(Benzo[d]thiazol-2-yl)-N-(3-methyl-3-phenylcyclobutylidene)thiohydroxylamine (4ae). Colorless oil; isolated yield = 74%, 48.0 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.84 (dd, *J* = 18.5, 8.2 Hz, 2H), 7.45 – 7.12 (m, 7H), 3.48 (dd, *J* = 16.8, 3.0 Hz, 1H), 3.33 (dd, *J* = 16.9, 3.0 Hz, 1H), 3.20 (dt, *J* = 16.8, 3.5 Hz, 1H), 3.06 (dt, *J* = 16.9, 3.5 Hz, 1H), 1.58 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 172.7, 171.8, 154.0, 148.0, 134.9, 128.6, 126.3, 126.0, 125.3, 123.8, 121.7, 121.0, 51.5, 50.3, 36.5, 31.1. HRMS (ESI-TOF) *m/z*: $[M+K]^+$ calcd for $C_{18}H_{16}N_2S_2K$ 363.0386; Found: 363.0377.

Ethyl 3-((Benzo[d]thiazol-2-ylthio)imino)cyclobutanecarboxylate (4ag). Colorless solid; mp: 87-88 °C; isolated yield = 81%, 49.8 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.83 (dd, *J* = 17.0, 8.1 Hz, 2H), 7.41 (td, *J* = 7.6, 1.2 Hz, 1H), 7.31 – 7.24 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.44 – 3.14 (m, 5H), 1.28 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 173.6, 170.8, 154.0, 134.9, 126.0, 123.9, 121.8, 121.0, 61.4, 42.6, 41.3, 29.7, 14.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{15}N_2O_2S_2$ 307.0569; Found: 307.0568.

General Procedure for the Preparation of Products 6-11.

4-(Benzo[d]thiazol-2-yloxy)butanenitrile (6). To a 10-mL single-necked flask was added **5** (0.2 mmol), **2a** (0.4 mmol) and [Cu] (30 mol% of **2a**). To a 4.5-mL sample tube was added DBU (3.0 equiv of **5**) and ethyl acetate (1.5 mL). Then transfer the solution in sample tube to the flask and stirred for 5-30 min at room temperature. Upon completion of the reaction monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **6** (PE/EA = 10/1). Colorless oil; isolated yield = 30%, 12.9 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 7.44 (d, *J* = 7.3 Hz, 1H), 7.34 (td, *J* = 7.8, 1.3 Hz, 1H), 7.18 (td, *J* = 7.7, 1.2 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 4.08 (t, *J* = 6.9 Hz, 2H), 2.45 (t, *J* = 7.1 Hz, 2H), 2.13 (p, *J* = 7.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 170.2, 136.4, 126.7, 123.5, 123.0, 122.7, 118.7, 110.2, 41.1, 23.9, 14.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_2OS$ 219.0587; Found: 219.0583.

4-(Benzo[d]thiazol-2-ylsulfonyl)butanenitrile (7). To a 10 mL flask was added **3aa** (0.2 mmol), m-CPBA (3.0 equiv) and DCM (4 mL), stirred for 5 min at room temperature. Upon completion of reaction monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **7** (PE/EA = 2/1). White solid; mp: 82-83 °C; isolated yield = 97%, 93.4 mg; ^1H NMR (400 MHz, Chloroform-*d*) δ 8.29 – 8.10 (m, 1H), 8.00 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.73 – 7.48 (m, 2H), 3.64 (t, *J* = 7.4 Hz, 2H), 2.63 (t, *J* = 7.1 Hz, 2H), 2.29 (p, *J* = 7.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, Chloroform-*d*) δ 164.8, 152.5, 136.7, 128.4, 127.9, 125.5, 122.4, 118.0, 52.9, 19.1, 16.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{11}N_2O_2S_2$ 267.0256; Found: 267.0249.

Benzo[d]thiazole-2-sulfonamide (8).[14] To a 10-mL flask was added **4aa** (0.2 mmol), m-CPBA (3.0 equiv) and DCM (4 mL), stirred for 1 h at room temperature. Upon completion of reaction monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **8** (PE/EA = 1/1). White solid; isolated yield = 71%, 30.5 mg;

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 2H), 8.23 (dd, J = 7.8, 1.6 Hz, 1H), 8.19 – 8.09 (m, 1H), 7.62 (dtd, J = 18.8, 7.4, 1.4 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 169.8, 152.2, 136.6, 128.0, 127.9, 124.6, 123.7.

1,2-Bis(benzo[d]thiazol-2-yl)disulfane (9).[15] To a 10-mL flask was added **4aa** (0.2 mmol), EtOH (1 mL) and 1 N HCl (1 mL), stirred for 1 h at room temperature. Upon completion of reaction monitored by TLC, the solvent was removed under reduced pressure. The crude material was recrystallized to afford product **9**. White solid; isolated yield = 60%, 39.9 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 – 7.83 (m, 2H), 7.83 – 7.67 (m, 2H), 7.49 – 7.41 (m, 2H), 7.38 – 7.31 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 154.5, 136.1, 126.6, 125.3, 122.6, 121.3.

6,6-Diphenylhex-5-enenitrile (10).[1b] To a 10-mL single-necked flask was added **1a** (0.2 mmol), **2a** (0.4 mmol), 1,1- diphenylethylene (3.0 equiv) and [Cu] (30 mol% of **2a**). To a 4.5-mL sample tube was added DBU (3.0 equiv of **1a**) and ethyl acetate (1.5 mL). Then transfer the solution in the sample tube to the flask and stirred for 30 min at room temperature. The solvent was removed under reduced pressure and the residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **10** (PE/EA = 400/1). Colorless oil; isolated yield = 8%, 4.1 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.45 – 7.09 (m, 10H), 6.00 (t, J = 7.5 Hz, 1H), 2.27 (dt, J = 22.0, 7.4 Hz, 4H), 1.79 (p, J = 7.4 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, Chloroform-*d*) δ 143.7, 142.1, 139.6, 129.7, 128.3, 128.2, 127.23, 127.15, 126.6, 119.5, 28.7, 25.7, 16.7.

5-Phenylpent-4-enenitrile (11).[16] To a 10-mL single-necked flask was added **2c** (0.4 mmol), and [Cu] (30 mol% of **2c**). To a 4.5 mL-sample tube was added DBU (0.6 mmol) and ethyl acetate (1.5 mL). Then transfer the solution in the sample tube to the flask and stirred for 30 min at room temperature. Upon completion of reaction monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **11** (PE/EA = 25/1). Colorless oil; isolated yield = 48%, 15.2 mg; ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.43 – 7.27 (m, 4H), 7.27 – 7.18 (m, 1H), 6.51 (d, J = 15.8 Hz, 1H), 6.17 (dt, J = 15.5, 6.7 Hz, 1H), 2.55 (q, J = 6.9, 6.3 Hz, 2H), 2.48 (dd, J = 8.1, 5.0 Hz, 2H). 13C{^{1}H} NMR (101 MHz, Chloroform-d) δ 136.6, 132.9, 128.6, 127.7, 126.3, 125.5, 119.2, 28.8, 17.6.

The Procedure of Mechanistic Study. (1) To a 10-mL single-necked flask was added **1a** (0.2 mmol), **2a** (0.4 mmol), TEMPO (or BHT, 1,1- diphenylethylene, 3.0 equiv) and [Cu] (30 mol% of **2a**), to a 4.5-mL sample tube was added DBU (3.0 equiv of **1a**) and ethyl acetate (1.5 mL), then transfer the solution in the sample tube to the flask and stirred for 30 min at room temperature. Upon completion of reaction monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **10** (PE/EA = 400/1). (2) To a 10-mL single-necked flask was added **1a** (0.3 mmol), **2a** (0.2 mmol), TEMPO (or BHT, 3.0 equiv) and [Cu] (15 mol% of **2a**), to a 2.0-mL sample tube was added DBU (3.0 equiv of **1a**) and toluene (1.0 mL), then transfer the solution in the sample tube to the flask and stirred for 1 h at room temperature. Upon completion of reaction monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **4aa** (PE/EA = 200/1). (3) To a 10-mL single-necked flask was added **2c** (0.4 mmol), and [Cu] (30 mol% of **2c**), to a 4.5-mL sample tube was added DBU (3.0 equiv of **2c**) and ethyl acetate (1.5 mL), then transfer the solution in the sample tube into the flask and stirred for 30 min at room temperature. Upon completion of reaction monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **11** (PE/EA = 25/1). (4) (4a): to a 10-mL single-necked flask was added **1q** (0.2 mmol), **2a** (0.4 mmol) [Cu] (30 mol% of **2a**) and ethyl acetate (1.5 mL), stirred for 3 h at room temperature. (4b): to a 10-mL single-necked flask was added **1q** (0.3 mmol), **2a** (0.2 mmol) [Cu] (15 mol% of **2a**) and toluene (1.0 mL), stirred for 3 h at room temperature. (4c): to a 10-mL single-necked flask was added **1r** (0.1 mmol), **2a** (0.4 mmol) [Cu] (30 mol% of **2a**) and ethyl acetate (1.5 mL), stirred for 3 h at room temperature. (4d): to a 10-mL single-necked flask was added **1r** (0.15 mmol), **2a** (0.2 mmol) [Cu] (15 mol% of **2a**) and toluene (1.0 mL), stirred for 3 h at room temperature. (4e): to a 10-mL single-necked flask was added **1q** (0.2 mmol), **2a** (0.4 mmol), and [Cu] (30 mol% of **2a**), to a 4.5-mL sample tube was added DBU (3.0 equiv of **1q**) and ethyl acetate (1.5 mL), then transfer the solution in the sample tube to the flask and stirred for 30 min at room temperature. Upon completion of reactions (4a, 4b, 4c, 4d, 4e) monitored by TLC, the solvent was removed under reduced pressure. The residue was then purified by flash chromatography on silica gel with a mixture of petroleum ether and ethyl acetate as eluent to afford product **3aa** or **4aa**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

The details of reaction optimization;

^{1}H NMR and ^{13}C NMR spectra for all the products.

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