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Letter

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Synthesis of Alkynyl Sulfides by Copper-Catalyzed Thiolation of Terminal Alkynes Using Thiosulfonates

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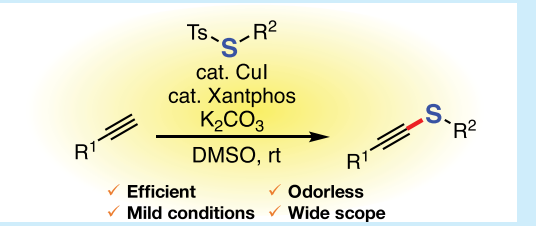
Supporting Information

ABSTRACT: A mild and odorless copper-catalyzed thiolation of terminal alkynes with thiosulfonates is described. The broad substrate scope provides convenient access to a wide variety of sulfur-containing heterocycles. In particular, divergent benzoheteroles are efficiently prepared in a simple manner by thiolation of ethynylbenzenes bearing *ortho*-nucleophilic functional groups followed by iodocyclization.



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Organosulfur compounds have a broad range of applications, particularly in the fields of medicinal chemistry[1] and materials science.[2] Recent advances in the transformations of thio groups have further enhanced the synthetic utility of organosulfurs, enabling the preparation of a wide variety of compounds via C−S bond cleavage including cross-coupling reactions.[3] In particular, alkynyl sulfides have attracted attention as useful synthetic intermediates because they are transformable into various organosulfur compounds through diverse types of reactions including addition,[4a,b,h] iodocyclization,[4f,g] cycloaddition,[4d,e,i] and cross-coupling reactions.[4c] In spite of their utility, C(sp)−S bond forming reactions[5] have been less studied than C(sp^2)−S and C(sp^3)−S bond formations,[6] and thus, an efficient method to prepare alkynyl sulfides by thiolation of terminal alkynes is still required.

In recent years, several facile methods to prepare alkynyl sulfides from simple terminal alkynes employing thiols or disulfides have been developed (Figure 1A and 1B).[7] However, during our work on drug discovery based on organosulfur compounds,[1c] we found that these approaches suffer from a series of practical limitations. For example, the copper-catalyzed thiolation of terminal alkynes **1a** and **1b** bearing amino or acetyl groups, respectively, with 2-phenethylthiol (**2a**) under an oxygen atmosphere[7e] resulted in failure due to the low conversion of **1a** and undesired addition reaction of the nucleophilic thiol **2a** to the electron-deficient alkyne **1b** (Figure 1D). Another attempt to achieve the thiolation using thiosulfonate **3a** in the presence of *t*-BuOLi, which was recently reported by Xu and co-workers as a part of their mechanistic study of the interrupted click reaction (Figure 1C),[7g] was also unsuccessful, and the desired alkynyl sulfides **4a** and **4b** were obtained only in low yields (Figure 1E). Moreover, using K_2CO_3 instead of *t*-BuOLi to avoid the decomposition of the products resulted in lower yields.

To develop an efficient catalytic system for the synthesis of alkynyl sulfides, we focused our attention on thiosulfonates,

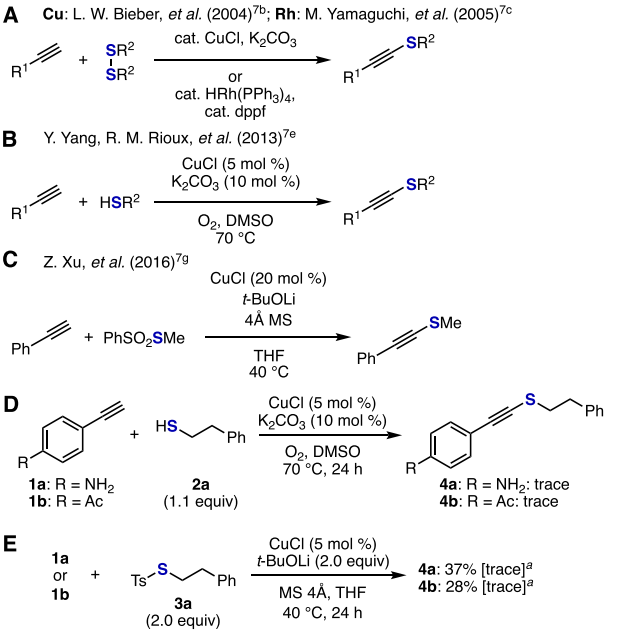

Figure 1. Reported methods for catalytic formation of alkynyl sulfides (A−C) and our attempts to synthesize alkynyl sulfides **4** by these methods (D and E). [a] K_2CO_3 (2.0 equiv) was used instead of *t*-BuOLi. Yields were determined by HPLC.

since they had been previously demonstrated to offer great advantages in copper-[8a,c] and rhodium-catalyzed[8b] deborylthiolation reactions that proceed efficiently under mild and odorless conditions and have a wide substrate scope. Considering the good leaving ability of the sulfonyl group and the lower nucleophilicity of the liberated sulfinic acids compared with thiols, we conceived that the catalytic thiolation

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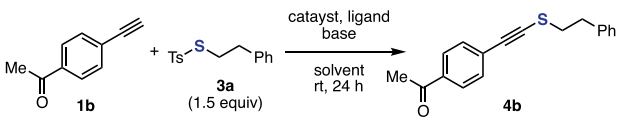
of terminal alkynes using thiosulfonates could enable the efficient preparation of alkynyl sulfides even with substrates bearing sensitive functional groups. Herein, we report an efficient and odorless copper-catalyzed C−S bond forming reaction between terminal alkynes and thiosulfonates that exhibits a dramatically expanded substrate scope.

After an extensive screening using terminal alkyne **1b** and thiosulfonate **3a** (1.5 equiv), we found the conditions suitable for the desired thiolation at room temperature (Table 1).

Table 1. Optimization of the Reaction Conditions



entry	catalyst/ligand (mol %)	base (equiv)	solvent	yield (%)[a]
1	$CuSO_4$ (5)	K_2CO_3 (4.0)	DMSO	10
2	CuCl (5)	K_2CO_3 (4.0)	DMSO	18
3	CuI (5)	K_2CO_3 (4.0)	DMSO	22
4	CuI (5)/bpy (6)	K_2CO_3 (4.0)	DMSO	14
5	CuI (5)/TMEDA (6)	K_2CO_3 (4.0)	DMSO	18
6	CuI (5)/PPh_3 (12)	K_2CO_3 (4.0)	DMSO	9
7	CuI (5)/dppp (6)	K_2CO_3 (4.0)	DMSO	43
8	CuI (5)/DPEphos (6)	K_2CO_3 (4.0)	DMSO	21
9	CuI (5)/Xantphos (6)	K_2CO_3 (4.0)	DMSO	74
10	CuI (5)/Xantphos (6)	$NaHCO_3$ (4.0)	DMSO	25
11	CuI (5)/Xantphos (6)	Cs_2CO_3 (4.0)	DMSO	trace
12	CuI (5)/Xantphos (6)	K_2CO_3 (1.5)	DMSO	90[b]
13	CuI (5)/Xantphos (6)	K_2CO_3 (1.5)	DMF	83[b]
14	CuI (5)/Xantphos (6)	K_2CO_3 (1.5)	toluene	trace

[a]Yields were determined by HPLC analysis, unless otherwise noted. [b]Isolated yield.

Although several copper salts catalyzed the phenethylthiolation of **1b** in the presence of K_2CO_3 (4.0 equiv) in DMSO, these reactions resulted in low conversions (entries 1−3). A screening of ligands (entries 4−9) revealed that the combined use of Xantphos and CuI dramatically improved the efficiency of the reaction (entry 9). Although the use of other bases such as $NaHCO_3$ and Cs_2CO_3 instead of K_2CO_3 proved ineffective (entries 10 and 11), reducing the amount of K_2CO_3 to 1.5 equiv was found to further improve the yield of the desired alkynyl sulfide **4b** (entry 12). The thiolation also proceeded efficiently in other polar solvents such as DMF (entry 13), clearly ruling out the role of DMSO as an oxidant.

The optimized conditions (Table 1, entry 12) were successfully applied to the thiolation of a wide range of terminal alkynes with *S*-methyl thiosulfonate **3b** (Figure 2). Considering the utility of alkynyl methyl sulfides as synthetic intermediates,[4b,g,i] our method using stable and odorless thiosulfonate as the methylthio source presents an advantage over conventional methods that require volatile methanethiol with an unpleasant odor. Arylacetylenes bearing an electron-donating or -withdrawing group on the benzene ring at the *ortho*-, *meta*-, or *para*-position participated in this transformation to afford alkynyl sulfides **4c**−**m**. Notably, arylacetylenes bearing an unprotected amino group or an ester moiety and heteroarylacetylenes such as 3-pyridylacetylene, which were unfavorable substrates under the previously reported conditions,[9] were successfully thiolated using our method, affording alkynyl sulfides **4e**, **4f**, and **4l**, respectively, in high yields. Furthermore, methylthiolation of alkylacetylenes

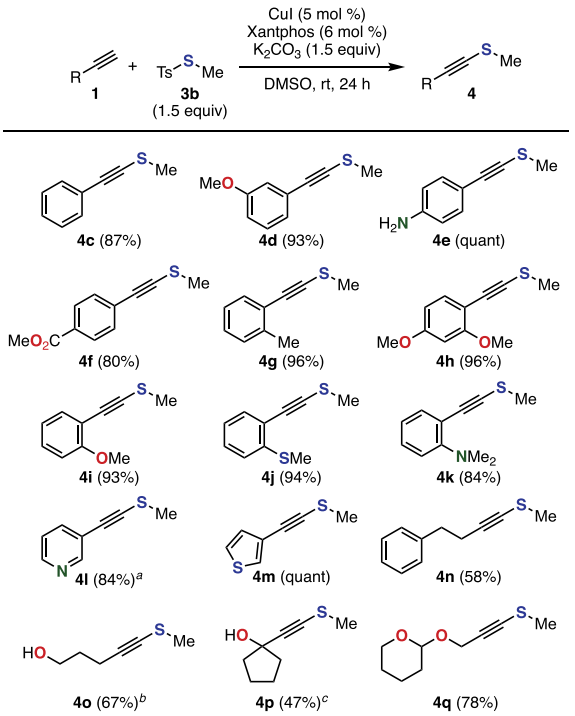


Figure 2. Thiolations of various terminal alkynes with *S*-methyl thiosulfonate **3b**. [a] CuI (10 mol %) and Xantphos (12 mol %) were used. [b] The reaction was performed using 3.0 equiv of **3b** at 100 °C for 1 h. [c] The reaction was performed using 3.0 equiv of **3b** at 50 °C for 12 h.

bearing a hydroxy group or acetal moiety also proceeded under modified conditions to afford the corresponding alkynyl sulfides **4n**−**q** in moderate to good yields leaving these functional groups untouched.

Various thiosulfonates including *S*-alkyl and *S*-(hetero)aryl thiosulfonates were also applicable to this thiolation method, as demonstrated in the reaction with 4-ethynylanisole (**1q**) (Figure 3). Not only the methylthiolation of **1q** with *S*-methyl thiosulfonate (**3b**) but also arylthiolations using *S*-aryl thiosulfonates bearing electron-donating or electron-withdrawing groups on the benzene ring proceeded smoothly under the standard conditions to afford alkynyl aryl sulfides **4t**−**y** in high yields. Noteworthily, sulfides containing further transformable groups such as chloro, bromo, and methoxycarbonyl groups were also obtained. Furthermore, alkyl alkynyl sulfides were easily prepared from alkyl halides, potassium thiosulfonate, and terminal alkynes following a one-pot procedure. For example, substitution of alkyl bromide **5** with the readily available potassium thiosulfonate **6** in DMSO, followed by direct addition of K_2CO_3, CuI, Xantphos, and alkyne **1q** to the reaction mixture, afforded **4s** in moderate yield (Scheme 1).

To gain insights into the mechanism of the copper-catalyzed thiolation of terminal alkynes, we conducted several control experiments (Figure 4). As shown in Figure 3, the thiolation of alkyne **1q** with thiosulfonate **3c** proceeded smoothly under the standard conditions using catalytic amounts of CuI and Xantphos (redescribed in Figure 4A, top scheme). In contrast, employment of disulfide **7** or thiol **2b** instead of thiosulfonate **3c** resulted in almost complete recovery of alkyne **1q** (Figure 4A, middle and bottom schemes). These results indicate that the catalytic cycle of the thiolation does not involve a C−S

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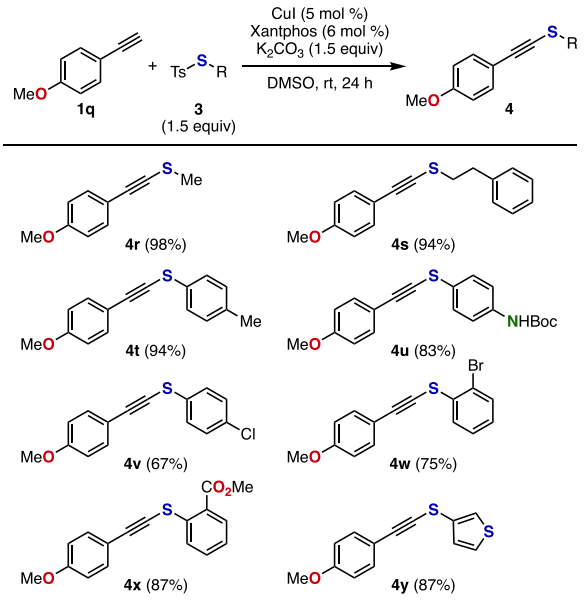
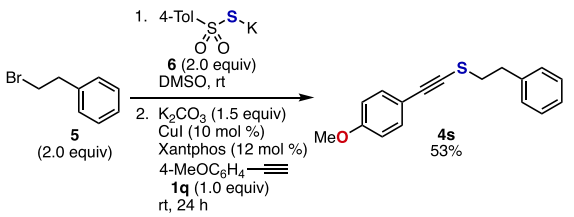


Figure 3. Thiolations of terminal alkyne **1q** with various thiosulfonates.

Scheme 1. One-Pot Synthesis of Alkynyl Sulfide 4s from Phenethyl Bromide 5



bond formation with disulfide **7** or thiol **2b**, which are potential intermediates. In addition, conducting the reaction between **1q** and **3c** in the presence of 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO) did not affect significantly the formation of alkynyl sulfide **4t**, which suggests that the involvement of radical intermediates can be ruled out (Figure 4B). Furthermore, treatment of copper acetylide **8**, which was prepared in situ from the reaction between alkyne **1c**, CuI, and K_2CO_3 according to the reported method,[10] with Xantphos and a stoichiometric amount of thiosulfonate **3b** afforded alkynyl sulfide **4c** with similar efficiency to that of the reaction between alkyne **1c** and **3b** conducted using stoichiometric amounts of CuI and Xantphos (Figure 4C). These results indicate that the copper acetylide intermediate is likely involved in the catalytic thiolation. On the basis of these results, we propose the catalytic cycle depicted in Figure 4D, which starts with the generation of copper acetylide intermediate **II** by ligand exchange between terminal alkyne and copper catalyst **I** coordinated with Xantphos with the assistance of a base and the copper catalyst. Subsequently, either *σ*-bond metathesis of copper acetylide **II** with thiosulfonate (path a) or oxidative addition of thiosulfonate to copper acetylide **II** followed by reductive elimination (path b) would afford the alkynyl sulfide and regenerate the catalyst.[11]

The wide substrate scope of the alkynyl sulfide synthesis provides easy access to a variety of sulfur-containing heterocycles. For example, thiolation of terminal alkynes bearing *o*-

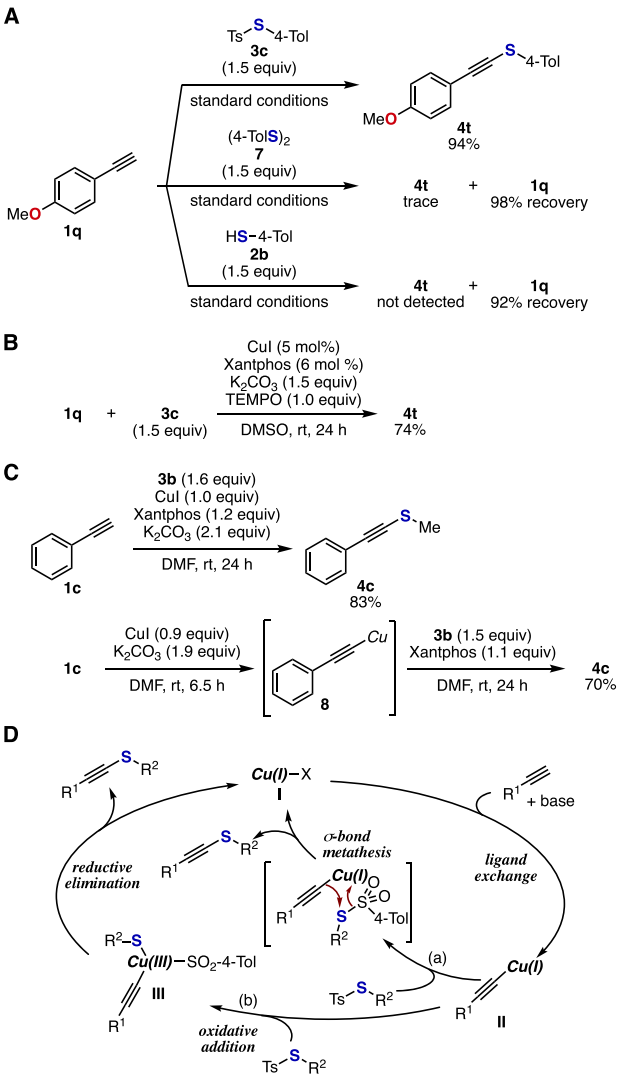


Figure 4. Mechanistic studies. (A) Thiolation of alkyne **1q** using different sulfur surrogates (thiosulfonate **3c**, disulfide **7**, and thiol **2b**) under the standard conditions; thiolation reagent (1.5 equiv), CuI (5 mol %), Xantphos (6 mol %), K_2CO_3 (1.5 equiv), DMSO, rt, 24 h. (B) Thiolation of alkyne **1q** in the presence of TEMPO. (C) Reaction of copper acetylide **8** with thiosulfonate **3b** and reaction of alkyne **1c** with **3b** using stoichiometric amounts of CuI and Xantphos. (D) Plausible reaction mechanisms. Yields were determined by HPLC analysis.

methoxy-, *o*-methylthio-, and *o*-dimethylaminophenyl groups proceeded efficiently to afford alkynyl sulfides **4z–af** with various substitutions including base-sensitive functional groups (Table 2). Subsequent iodocyclization[4f,g,12] of the resulting alkynyl sulfides **4z–af** successfully afforded benzo[*b*]furans **9a–e**, benzo[*b*]thiophene **9f**, and indole **9g** having various functional groups. Following this approach, we also achieved the efficient synthesis of the tricyclic heteroaromatic compound **12** from diyne **10** by a double-thiolation/iodocyclization sequence (Figure 5A).[13]

The synthetic utility of the thiolation of terminal alkynes developed in this study was further demonstrated by performing derivatizations of the cyclized product containing both iodo and methylthio groups. For example, tetracyclic 2-chlorobenzofuro[2,3-*b*]benzofuran (**15**) was successfully prepared from 5-chloro-3-iodo-2-methylthiobenzo[*b*]furan (**9d**)

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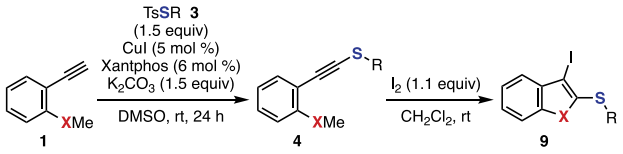
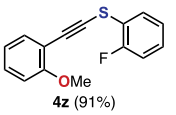
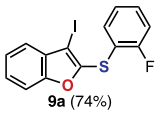
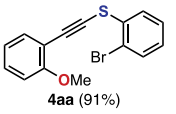
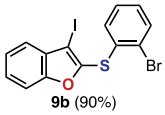
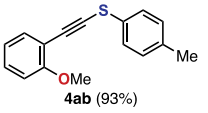
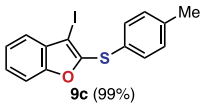
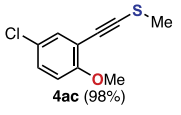
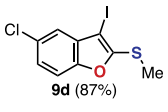
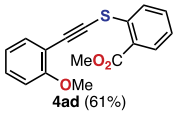
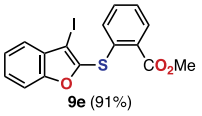
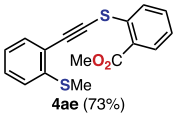
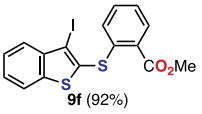
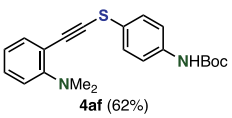
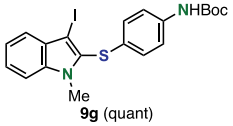
Table 2. Thiolation and Subsequent Iodocyclization of Terminal Alkynes



entry	yield of **4** (%)	yield of **9** (%)
1	 **4z** (91%)	 **9a** (74%)
2	 **4aa** (91%)	 **9b** (90%)
3	 **4ab** (93%)	 **9c** (99%)
4	 **4ac** (98%)	 **9d** (87%)
5	 **4ad** (61%)	 **9e** (91%)
6	 **4ae** (73%)	 **9f** (92%)
7	 **4af** (62%)	 **9g** (quant)

by selective Suzuki−Miyaura cross-coupling at the iodo group, followed by oxidation of the methylthio group to methanesulfonyl and subsequent base-mediated cyclization[14] (Figure 5B). Furthermore, benzofuran **9d** was successfully subjected to a sequential three-step selective arylation[15] that involved a palladium-catalyzed Suzuki−Miyaura cross-coupling at the iodo group,[16] a nickel-catalyzed Kumada−Tamao−Corriu cross-coupling at the methylthio group,[3e] and a palladium-catalyzed Suzuki−Miyaura cross-coupling at the remaining chloro group (Figure 5C).[17] These transformations took place smoothly with high selectivity and efficiency, clearly showing the utility of benzofuran **9d** as a platform molecule for the synthesis of diverse multifunctionalized benzofurans.

In summary, we have developed an odorless thiolation reaction of terminal alkynes with thiosulfonates by a catalytic CuI/Xantphos system. The method showed a wide substrate scope owing to the mild conditions, providing ready access to various alkynyl sulfides. We also achieved the facile synthesis of a variety of sulfur-containing heterocycles by thiolation of alkynes, followed by iodocyclization and further transformations including sequential cross-coupling reactions. These results highlight the utility of this alkynyl sulfide

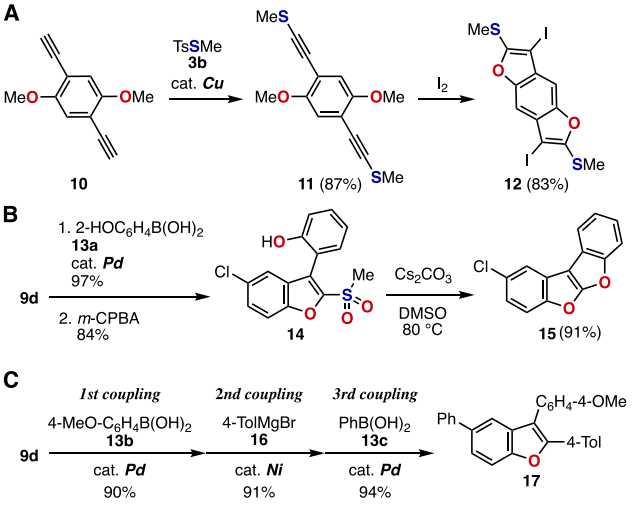


Figure 5. Synthesis of diverse benzoheterole derivatives. (A) Synthesis of π-conjugated heteroacene **12** from diyne **10** via a double-thiolation/iodocyclyzation sequence. (B) Derivatization of benzofuran **9d** via cross-coupling, oxidation, and cyclization. (C) Sequential three-step coupling from **9d**. See the Supporting Information for details.

synthesis, which enables rapid access to privileged scaffolds that are useful for developing new drugs and materials.[18] Further studies including application toward the synthesis of bioactive sulfur-containing molecules and detailed mechanistic studies are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00875.

Experimental procedures, characterization for new compounds including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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