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RESEARCH ARTICLE

Sulfonamide-Derived N,N,N-Ligand Enabled Copper-Catalyzed Radical 1,2-Trichloromethylthioesterification of Styrenes

Zhi-Chao Chen[1] | Fu Liu[1,2] | Derong Cao[2] | Peng-Fei Wang[1] | Yu Tian[1] | Xin-Yuan Liu[1]

[1]Shenzhen Grubbs Institute, Department of Chemistry, and Guangming Advanced Research Institute, Southern University of Science and Technology, Shenzhen, China | [2]State Key Laboratory of Luminescent Materials and Devices, School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou, China

Correspondence: Yu Tian (tiany3@sustech.edu.cn) | Xin-Yuan Liu (liuxy3@sustech.edu.cn)

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The copper-catalyzed radical difunctionalization of alkenes using readily accessible carbon tetrachloride (CCl_4) and potassium benzothioate offers an attractive approach for thioester synthesis. Major challenges stem from the weak reducing capacity of copper catalysts in their ground state and the facile atom transfer radical addition between CCl_4 and alkenes. In this work, we describe an efficient radical 1,2-trichloromethylthioesterification of styrenes conducted under mild thermal conditions. The effectiveness of this approach depends on the application of an anionic sulfonamide-derived N,N,N-ligand, which not only boosts the reducing capability of the copper catalyst to initiate the reaction but also promotes the formation of $C(sp^3)$–S bonds. This method exhibits a broad substrate scope, thus serving as a valuable complement to existing 1,2-carbothiolation of alkenes. Mechanistic investigations confirm that a radical mechanism is operative.

1 | Introduction

The radical-involved 1,2-difunctionalization of alkenes stands as a versatile strategy for accessing complex organic molecules, with two core advantages driving its utility: it enables the direct construction of complex structures from simple alkenes and the simultaneous, precise introduction of two vicinal functional groups [1–6]. For this transformation, copper catalysts are particularly outstanding, owing to their ease of operation, cost efficiency, commercial availability, and robust single-electron transfer (SET) ability [7–9]. A further critical advantage is that high-valent copper species tend to undergo facile reductive elimination or radical homolytic substitution [10, 11], which facilitates carbon–heteroatom bond formation. Given the widespread applications of organosulfur compounds in organic synthesis [12–14], pharmaceuticals [15–17], agrochemicals [18], and materials science [19–21], the copper-catalyzed radical three-component intermolecular 1,2-carbothiolation of alkenes with readily accessible alkyl halides has drawn considerable attention (Scheme 1A).

However, the weak reducing capability of ground-state copper [$E_{red}(Cu^{2+}/^{+})$ = 0.15 V vs. SCE] hinders the generation of carbon-centered radicals via SET reduction of alkyl halides. To address this challenge, Doyle [22] developed a halogen atom transfer (XAT) strategy: a highly reactive α-amino radical abstracts a halide atom from an alkyl halide to produce an alkyl radical, which then selectively adds to an alkene, the newly generated carbon-centered radical is subsequently trapped by a

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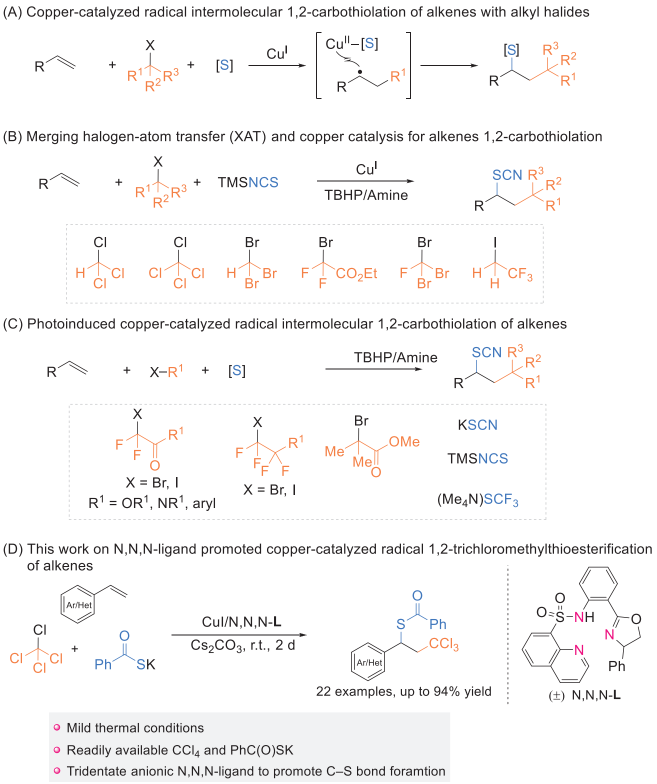
Zhi-Chao Chen and Fu Liu contributed equally to this work.

Dedicated to Prof. Armido Studer on the occasion of his Paracelsus Prize

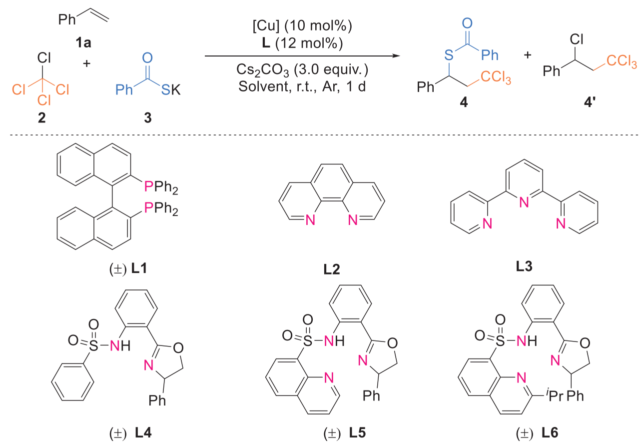


SCHEME 1 | Research background and our work on copper-catalyzed radical 1,2-trichloromethylthioesterification of styrenes.

Cu(II)–SCN complex to afford 1,2-carbothiocyanation products (Scheme 1B). Another approach leverages photoactive copper catalysts, whose enhanced reducing ability under light irradiation initiates radical generation. In this context, Peters, Fu, and others have demonstrated 1,2-carbotrifluoromethylthiolation [23] and 1,2-carbothiocyanation [24–27], respectively (Scheme 1C). Nevertheless, these existing protocols are restricted to SCN- or SCF_3-based nucleophiles, leaving other sulfur-containing nucleophiles largely unexplored. Given the operational simplicity of thermal reactions and the prevalence of thioesters in nature and biological systems [28–31], it is highly desirable to develop a copper-catalyzed alkene 1,2-difunctionalization strategy to synthesize thioesters under mild thermal conditions.

Our group has focused on radical reaction research and previously developed the “copper/anionic single-electron transfer catalyst” strategy [32]. This approach employs electron-rich anionic ligands to enhance the reducing ability of Cu(I) catalysts, enabling the conversion of alkyl halides to alkyl radicals. These radicals then participate in diverse cross-coupling [33–44] and alkene 1,2-difunctionalization reactions [45–48] under mild thermal conditions. Notably, we have recently reported a radical enantioconvergent $C(sp^3)$–S cross-coupling reaction of alkyl halides with sulfur nucleophiles [49, 50]. A key success factor was the use of Cu(I)/chiral multidentate anionic ligand catalysts, which mediate a biomimetic radical homolytic substitution pathway for $C(sp^3)$–S bond formation. Building on this work, we hypothesized that two widely used reagents—carbon tetrachloride (CCl_4) and potassium benzothioate—could enable a three-component radical 1,2-trichloromethylthioesterification of alkenes (Scheme 1D). However, the primary challenge stems from the inherently facile occurrence of atom transfer radical addition (ATRA) between CCl_4 and alkenes [51], which could compete with the desired reaction. Herein, we describe the development of a mild Cu(I)/sulfonamide-derived N,N,N-ligand catalytic system for the intermolecular three-component radical 1,2-trichloromethylthioesterification of styrenes with CCl_4 and potassium benzothioate. The success of this system hinges on the anionic N,N,N-ligand, which both enhances the copper catalyst’s reducing ability to initiate the reaction and facilitates $C(sp^3)$–S bond formation (Scheme 1D).

TABLE 1 | Optimization of reaction conditions[a].



Entry	L	Yield of 4 (%)	Yield of 4’ (%)
1	**L1**	Trace	Trace
2	**L2**	Trace	Trace
3	**L3**	Trace	Trace
4	**L4**	8	Trace
5	**L5**	60	10
6	**L6**	Trace	Trace
7[b]	**L5**	85	2

[a] Reaction conditions: **1a** (0.10 mmol), **2** (1.5 equiv.), **3** (1.0 equiv.), $Cu(MeCN)_4BF_4$ (10 mol%), **L** (12 mol%), and Cs_2CO_3 (3.0 equiv) in toluene (1.0 mL) at room temperature for 1 day under argon. Yield was based on ^1H NMR analysis of the crude product using mesitylene as an internal standard.

[b] CuI was used as copper salt, and run at 2 days.

2 | Results and Discussion

Based on the above assumption, we first investigated the ligand effect using the model reaction of styrene **1a**, CCl_4 **2**, and potassium benzothioate **3**, with $Cu(MeCN)_4BF_4$ and Cs_2CO_3 as base in toluene at room temperature under argon atmosphere (Table 1). Electron-neutral ligands—bisphosphine **L1**, 1,10-phenanthroline **L2**, and 2,2’:6’,2”-terpyridine **L3**—afforded only trace amounts of the carbothioesterification product **4** (Table 1, entries 1–3), likely due to their weak reducing ability. In contrast, the electron-rich sulfonamide-derived N,N-bidentate ligand **L4** improved reactivity, affording the desired product **4** in 8% yield (Table 1, entry 4). Our recent study on the radical cross-coupling of benzyl/propargyl halides with alkenylboronate esters provided further guidance: we observed that tridentate N,N,N-ligands effectively promoted the reaction, whereas bidentate N,N-ligands with the same backbone delivered significantly lower yields [37]. Motivated by this finding, we tested sulfonamide-derived N,N,N-ligands, and found that ligand **L5** outperformed **L4**, generating **4** in 60% yield, albeit with 10% yield of the ATRA byproduct **4'** (Table 1, entry 5). To confirm the importance of tridentate coordination, we modified **L5** by introducing an isopropyl group at the position vicinal to the additional nitrogen-coordinating site (affording **L6**); this modification resulted in almost no product formation. We attribute this to excessive steric hindrance from the isopropyl group, which restricts **L6** to bidentate coordination with the copper center—further highlighting that tridentate coordination is critical for enhancing reaction efficiency. After optimizing additional parameters, including copper salts, solvents, and reaction times (Table S1, Supporting Information), we identified the optimal conditions as follows: the reaction of **1a** (1.0 equiv.), CCl_4 **2** (1.5 equiv.), and potassium benzothioate **3** (1.0 equiv.) in the presence of CuI (10 mol%), **L5** (10 mol%), and Cs_2CO_3 (3.0 equiv.) in toluene at room temperature for 2 days afforded **4** in 85% NMR yield (Table 1, entry 7).

With the optimal condition established, we next explored the substrate scope of the reaction (Figure 1). Styrenes bearing electron-neutral, electron-donating, and electron-withdrawing groups at the *ortho*, *para*, or *meta* positions of the aryl ring were all compatible with the system, furnishing the corresponding target products **4**–**25** in 47%–94% yields. Notably, the reaction exhibited good functional group tolerance: methoxyl (**9**–**11**), phenoxyl (**12**), acetyl (**13**), thioether (**14**), phenyl (**15**), trifluoromethyl (**16**), and halide (**17**–**20**) substituents all remained intact under standard conditions. The system also accommodated structurally complex alkenes: alkenes featuring a bicyclic naphthalene ring served as viable substrates, affording product (**21**) in good yield.

More importantly, heteroarylated alkenes containing medicinally relevant heterocyclic cores, including benzo[*b*]thiophene (**22**) and pyridine (**23**), underwent the reaction smoothly, delivering the desired products in moderate to good yields (47%–73%). Moreover, more substituted styrenes, such as α-methylstyrene (**24**) and β-methylstyrene (**25**), also participated well in the reaction, affording the corresponding products in 85% and 46% yields, respectively Figure 1.

Evaluation of the reaction scalability is essential for demonstrating its practical applicability. Accordingly, the 1,2-trichloromethylthioesterification was performed on a gram scale under the standard conditions, affording the desired product **4** without any loss of efficiency (Scheme 2A). Thioesters are synthetically versatile intermediates that can undergo a wide range of transformations. To further showcase their synthetic utility, product **4** was smoothly converted into the corresponding sulfonyl fluoride **26** through a straightforward transformation (Scheme 2B), highlighting the potential of this method for downstream functionalization and late-stage diversification.

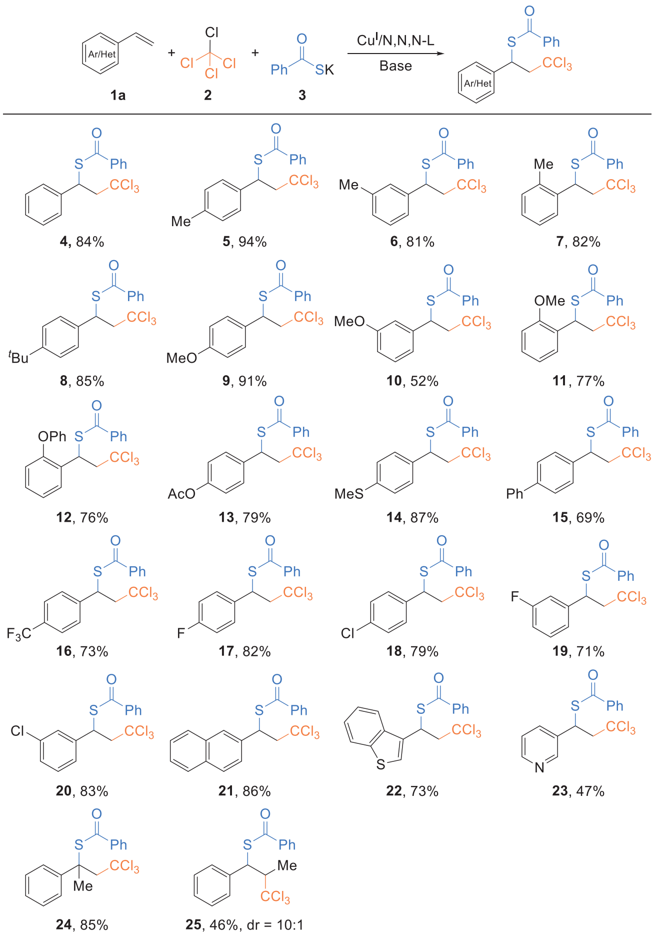
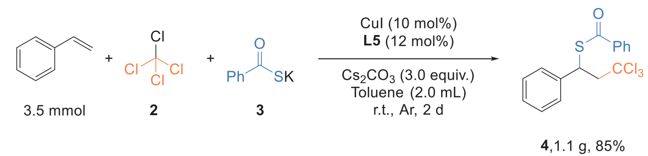
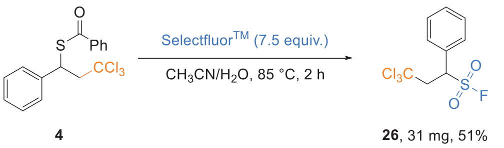


FIGURE 1 | Substrate scope for copper-catalyzed radical 1,2-trichloromethylthioesterification of styrenes. Standard reaction condition: **1** (0.20 mmol), CCl_4 **2** (0.30 mmol), potassium benzothioate **3** (0.20 mmol), CuI (10 mol%), **L5** (12 mol%), and Cs_2CO_3 (0.60 mmol) in toluene (2.0 mL) at room temperature for 2 days under argon. Isolated yields are shown.

(A) Gram-scale reaction

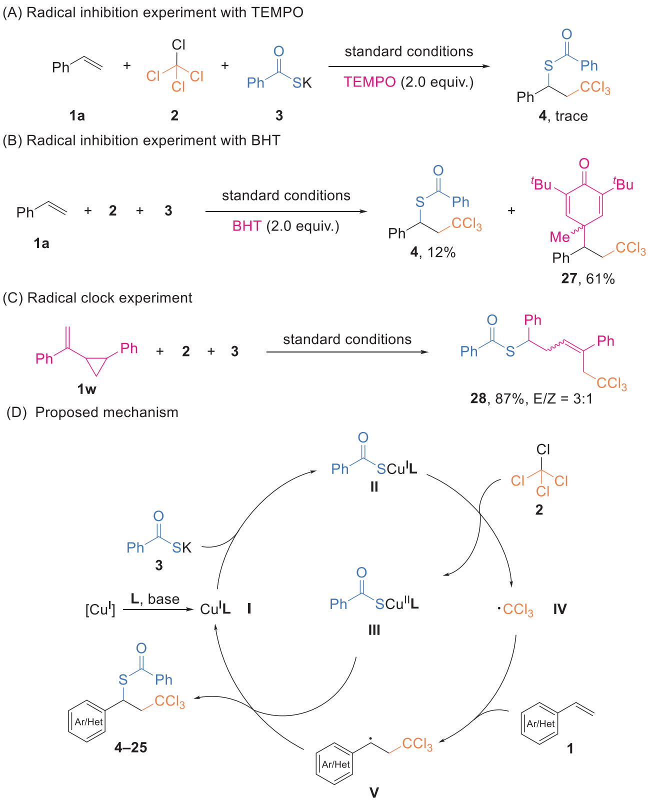


(B) Synthetic utility



SCHEME 2 | Synthetic application.

To gain insights into the reaction mechanism, we performed a series of control experiments. First, when 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was used as a radical trap reagent, a marked inhibition of the reaction was observed (Scheme 3A). Similarly, employing butylated hydroxytoluene (BHT) under typical reaction conditions greatly reduced the yield of **4** and led to the formation of the BHT-adducted product **27** (Scheme 3B). Furthermore, the reaction of the radical clock substrate **1w** with **2** and **3** failed to produce the target product, yielding only the ring-opened product **28** (Scheme 3C). Collectively, these outcomes provide evidence for the involvement of a radical mechanism. Drawing



SCHEME 3 | Mechanistic investigation and proposed mechanism.

on these results and our prior studies [32, 49, 50], a reasonable reaction mechanism was proposed (Scheme 3D): Initially, in the presence of a base, CuI interacted with sulfonamide-derived N,N,N ligand to form the **L5**Cu(I) complex **I**. This complex then underwent ligand exchange with potassium benzothioate **3** to generate the **L5**Cu(I)SC(O)Ph complex **II**, Complex **II** proceeds to SET reduce CCl_4 **2**, forming the **L5**Cu(II)SC(O)Ph complex **III** and a trichloromethyl radical **IV**. The trichloromethyl radical subsequently adds directly to styrenes **1** to form the alkyl radical **V**. The interaction between radical **V** and complex **III** produced the 1,2-trichloromethylthioesterification products **4–25** while regenerating the catalytically active species **I** to sustain the reaction cycle.

3 | Conclusion

In conclusion, we have successfully developed a copper-catalyzed radical 1,2-trichloromethylthioesterification of styrenes, utilizing easily accessible CCl_4 as the radical precursor and potassium benzothioate as the sulfur nucleophile. Employing an anionic sulfonamide-derived N,N,N-ligand is critical to the success, it not only triggers the initiation of the reaction but also promotes the formation of C(sp^3)–S bonds. This synthetic approach is highly compatible with readily available arylated and heteroarylated alkenes, thereby enabling the preparation of thioesters with diverse functional groups. Furthermore, the Cu(I)/N,N,N-ligand catalyst developed in this work enriches the library of SET catalysts established by our group, and we expect this catalyst will contribute to the achievement of additional radical transformation reactions in future studies.

4 | Experimental Section

4.1 | General Procedure for the Copper-Catalyzed Radical 1,2-trichloromethylthioesterification of Styrenes

Under argon atmosphere, an oven-dried resealable Schlenk tube equipped with a magnetic stir bar was charged with potassium benzothioate (35.2 mg, 0.2 mmol, 1.0 equiv.), CuI (3.8 mg, 0.02 mmol, 10 mol%), **L5** (10.3 mg, 0.024 mmol, 12 mol%), and Cs_2CO_3 (195.5 mg, 0.60 mmol, 3.0 equiv.). Then, (hetero)styrene (0.20 mmol, 1.0 equiv.), CCl_4 (29.0 μL, 0.3 mmol, 1.5 equiv.), and toluene (2.0 mL) were sequentially added to the mixture and the reaction mixture was stirred at room temperature for 2 days. Upon completion (monitored by TLC), the precipitate was filtered off and washed with CH_2Cl_2. The filtrate was evaporated, and the residue was purified by silica gel column chromatography to afford the desired product.

Author Contributions

Zhi-Chao Chen, Fu Liu, and Peng-Fei Wang carried out optimization reactions, substrate scope expansion, mechanism experiments, and data analysis. All authors contributed to the discussion of results and writing of the Supporting Information. Yu Tian and Xin-Yuan Liu drafted the manuscript, and Xin-Yuan Liu devised and supervised the project.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

The authors have cited additional references within the Supporting Information [52, 53].

Supporting File: hlca70038-sup-0001-SuppMat.pdf