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Atom Transfer Radical Addition to Styrenes with Thiosulfonates Enabled by Synergetic Copper/Photoredox Catalysis

Xin Zhou, Zhiyuan Peng, Peng George Wang, Qingchao Liu,* and Tiezheng Jia*



radicals as the key intermediate in the transformation.

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E ver since the pioneering works by Kharasch and coworkers,¹ atom transfer radical addition (ATRA) has provided a facile and straightforward tool to install two functional groups across an unsaturated C—C bond in a single step, and thus has found widespread applications in organic synthesis² and polymer science.³ Traditionally initiated by radical initiators⁴ or transition-metal catalysts,⁵ ATRA enables the rapid difunctionalization of alkenes or alkynes with increasing the molecular complexity. Since photoredox catalysis is considered to be mild, efficient, and environmentally benign,^{2,6} much effort has been devoted to the development of visible-light photoredox catalyzed ATRA reactions in recent years.⁷

derivatize bioactive natural products in late stage, and to install

fluorophores across alkenes. The mechanistic studies reveal sulfonyl

Sulfones and sulfides are prevailing scaffolds in natural products,⁸ bioactive synthetic molecules,⁹ and marketed therapeutics.¹⁰ Consequently, methods for the construction of sulfones and sulfides have been intensively studied. In this regard, ATRA reactions of thiosulfonates¹¹ with alkenes or alkynes are particularly attractive, primarily due to the incorporation of sulfonyl group (RSO_2-) and thiyl group (RS-) into vicinal carbons of unsaturated C-C bonds simultaneously. In 2007, Xu's group disclosed a seminal photoredox ATRA protocol of thiosulfonates with styrenes enabled by dual gold and ruthenium-based photocatalyst in the presence of $AgSbF_6$ (Scheme 1a).¹² Though representing the breakthrough of thiosulfonates in ATRA reactions, Xu's protocol required the employment of three precious metal salts. Later on, the same group succeeded in reversing the regioselectivity of additions between thiosulfonates and styrenes in the assistance of a Lewis acid catalyst (Scheme 1b).¹³ Of note, the method was demonstrated to operate in an ionic pathway rather than a radical process. The first ATRA of thiosulfonates with unactivated alkenes catalyzed by silver nitrate employing stoichiometric potassium persulfate as oxidant was developed by Shen's group (Scheme 1c).¹⁴ Unfortunately, only monofluoromethyl and difluoromethyl-

Scheme 1. Difunctionalization of Alkenes with Thiosulfonates

Fluorescent probe labeling Late-stage modification of natural products

(a) Dual Au/Ru catalysis (Xu, 2017)



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benzenethiosulfonate (PhSO₂SCH₂F and PhSO₂SCHF₂) were utilized as coupling partners, which jeopardized its further application. Very recently, Maes and co-workers described an efficient and environmentally benign photocatalyzed ATRA protocol of thiosulfonates with unactivated alkenes, employing 9-mesityl-10-methylacridinium perchlorate as photocatalyst under the irradiation of visible light (Scheme 1d).¹⁵ A vast array of unactivated alkenes could be successfully utilized as coupling partners, whereas *styrenes* were not tolerated by their protocol due to their low oxidation potentials. Therefore, a general and practical ATRA of thiosulfonates and styrenes with broad functional group compability, especially tolerating α and/or β -substituted styrenes as well as *alkyl*thiosulfonates, is still a highly desirable but unmet task.

Following our continuous interests regarding the development of sulfones' synthetic methods via difunctionalization of alkenes¹⁶ and alkynes¹⁷ employing thiosulfonates, herein we report a highly regioselective ATRA procedure of styrenes with thiosulfonates enabled by synergetic photoredox and copper catalysts (Scheme 1e).

We chose styrene (1a) and S-(p-tolyl)-4-methyl-benzenesulfonothioate (2a) as the model reactants (Table 1). After

Table 1. Optimization of ATRA of Styrene 1a with 2aEnabled by Synergetic Copper/Photoredox Catalysis^a

1a	$\begin{array}{c} & \underset{Cu(CH_3CN)_4PF_6}{\text{Ru}(phen)_3(PF_6)_2(1 \text{ fmol } \%)} \\ & \underset{Cu(CH_3CN)_4PF_6}{\text{Cu}(CH_3CN)_4PF_6(5 \text{ fmol } \%)} \\ & \underset{DIPEA (1 \text{ equiv})}{\text{DIPEA} (1 \text{ equiv})} \\ & \underset{2a}{\text{Me}_{DMF}, \text{rt}, 12 \text{ h}, \text{ blue LED}} \end{array}$	s + + + + + + + + + + + + + + + + + + +
entry	derivation from standard conditions	assay yield ^b /%
1	none	97(93 ^c)
2	without light	0
3	without $Ru(phen)_3(PF_6)_2$	0
4	without DIPEA	trace
5	without Cu(CH ₃ CN) ₄ PF ₆	56
6	without L4	65
7	L1 instead of L4	87
8	L2 instead of L4	85
9	L3 instead of L4	56

^{*a*}Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), Ru-(phen)₃(PF₆)₂, DIPEA (0.1 mmol), Cu(CH₃CN)₄PF₆ (5 mol %), **L4** (7.5 mol %), DMF (3.0 mL) at room temperature under the irradiation of 11 W blue LED under an argon atmosphere for 12 h. ^{*b*}Assay yield determined by ¹H NMR using 0.1 mmol of CH₂Br₂ (7.0 μ L) as internal standard. ^{*c*}Isolated yield.



intensive optimization studies, the synergetic conditions were as follows: styrene (1a) as the limiting reagent, 2.0 equiv of thiosulfonate (2a) as addition partner, 5 mol % Cu- $(CH_3CN)_4PF_6$ and 7.5 mol % L4 as the copper catalyst, 1 mol % Ru(phen)_3(PF_6)_2 as the photocatalyst, 1.0 equiv DIPEA as base, under the irradiation of 11 W blue LED in DMF at room temperature for 12 h (for complete screening results, see Supporting Information). The assay yield of the desired product 3aa was 97%, with 93% isolated yield (Table 1, entry 1). In a series of control experiments, the light source, DIPEA, and Ru(phen)_3(PF_6)_2 were demonstrated to be essential for the catalytic reaction. No or only a trace amount of desired product was observed in the absence of any of these components (Table 1, entries 2–4). Furthermore, when the reactions were performed in the absence of $Cu(CH_3CN)_4PF_6$ or L4, the yields of 3aa dramatically dropped to 56% and 65%, respectively (Table 1, entries 5 and 6), with emphasis on the synergetic catalysis of copper and photoredox. Ligand L4 outperformed other three structurally similar ligands (L1–L3) screened in the transformation (Table 1, compare entry 1 vs entries 7–9). The structure, especially the regioselectivity, of 3aa was unambiguously assigned by X-ray crystallography (Table 1).

With the optimal conditions established, the substrate generality of styrenes was evaluated in synergetic copper/photoredox catalyzed ATRA with 2a (Scheme 2). The parent styrene (1a) reacted with 2a to produce 3aa in 93% yield. Styrenes possessing electron-donating groups, such as 4-Me





^aReaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), Ru-(phen)₃(PF₆)₂ (1 mol %), DIPEA (0.1 mmol), Cu(CH₃CN)₄PF₆ (5 mol %), **L4** (7.5 mol %), DMF (3.0 mL) at room temperature under the irradiation of 11 W blue LED under an argon atmosphere for 12 h. ^b**1u** (1.0 mmol), **2a** (2.0 mmol), Ru(phen)₃(PF6)₂ (1 mol %), DIPEA (1.0 mmol), Cu(CH₃CN)₄PF₆ (5 mol %), **L4** (7.5 mol %), DMF (30.0 mL).

(1b) or 4-OMe (1c), were suitable substrates, giving 3ba and 3ca in 90% and 84% yield, respectively. Electron-withdrawing groups on styrenes exert a negligible effect on the outcome of the catalysis, affording 3da-3fa in 83-90% yields. Sterically demanding 2-methylstyrene could be well tolerated by our method, providing 3ga in 85% yield. Various functional groups, including hydroxyl (1j), amide (1k), ketone (1l), and aldehyde (1m), could be well tolerated by our ATRA strategy, owing to the mild reaction conditions, furnishing 3ja-3ma in 58-91% yields. Heterocycles are a class of structural motifs of great value in medicinal chemistry and marketed drugs. Our ATRA strategy was proven to be applicable to a variety of heteroaryl alkenes, and pyridyl (1n, 1o), indolyl (1p), benzofuranyl (1q), and benzothiophenyl (1r) alkenes reacted smoothly with 2a to deliver the desired products (3na-3ra) in good to excellent yields. The internal styrene derivatives, exemplified by linear β methylstyrene (cis-/trans- mixtures, 1s) and cyclic indene (1t), were compatible with the optimal catalytical conditions, providing 3sa and 3ta as a single diastereomer, albeit in modest yields. Though representing a facile and atomeconomical access to benzylic quaternary carbon center, ATRA of α -substituted styrenes remains underexplored, presumably due to the related steric hindrance as well as the competitive elimination pathway of benzylic cation intermediates.¹⁸ Remarkably, the chemistry is well accommodated with the α -substituted styrenes, independent of the electronic or steric effects of the substituents. Styrenes bearing an aromatic α -substituent, exemplified by 1,1-diphenylethylene (1u), proceeded smoothly under the optimal conditions to deliver **3ua** in near-quantitative yield. Styrenes with α -alkyl substituents, either linear (1v, 1w) or cyclic (1x), were amenable for the newly devised method, providing the desired products (3va-3xa) in good yields. Of note, the substrates feathered with exocyclic alkene, such as 1y, were also tolerated by our catalytical conditions, giving 3ya in 82% yield. However, our protocol finds its limitation, as unactivated aliphatic alkenes, such as 1-hexene, cannot be tolerated. Encouraged by the broad functional group tolerance as well as the mild reaction conditions, our synergetic ATRA strategy was applied to the late-stage functionalization of bioactive natural products derivatives. Aryl ethylenes derived from the prevalent pharmacores, such as flavone (1z), estrone (1aa), estradiol (1ba), and tocol (1ca), reacted effectively with 2a to generate **3za-caa** in modest to good yields, which displays the synthetic utility of our protocol. The synergetic ATRA proceeded smoothly with 1u and 2a to generate 3ua in 98% yield (1.0 mmol scale), demonstrating the synthetic utility of our protocol.

Next, we turned our attention to the substrate scope of Saryl-4-methylbenzenesulfonothioates in synergetic copper/ photoredox catalyzed ATRA with 1a (Scheme 3). The parent S-phenyl-4-methylbenzenesulfonothioate (2b) reacted with 1a to afford 3ab in 86% yield. Substrates possessing electronwithdrawing substituents, such as *para*-F (2c) or Cl (2d) were well-suited under the optimal conditions, generating 3ac and 3ad in 84% and 72% yield, respectively. S-Aryl thiosulfonates with electron-donating groups were compatible substrates, as evidenced by 3ae obtained in 95% yield. The sterically demanding 2-tolylthiosulfonate (2f) underwent ATRA with 1a smoothly to provide 3af in 75% yield. It is noteworthy that Sheteroaryl thiosulfonates (2g-i) could be utilized as addition partners with 1a under the optimal conditions to prepare the corresponding products (3ag-i) in good yields. Arylsulfonyl Scheme 3. Substrate Scope of S-Aryl-4-Methylbenzenesulfonothioates in Synergetic Copper/Photoredox Catalyzed ATRA with $1a^{a}$



^aReaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), Ru-(phen)₃(PF₆)₂ (1 mol %), DIPEA (0.1 mmol), Cu(CH₃CN)₄PF₆ (5 mol %), **L4** (7.5 mol %), DMF (3.0 mL) at room temperature under the irradiation of 11 W blue LED under an argon atmosphere for 12 h.

groups bearing electron-withdrawing groups could be efficiently installed on styrene via our ATRA strategy to prepare 3aj-l in the yields ranging from 75% to 80%. Electrondonating para-OMe group on S-(p-tolyl)-arylsulfonothioate exhibited little effect on the outcome of the catalytical transformation, giving 3am in 85% yield. We were delighted to observe that our synergetic ATRA protocol could even be applied to label styrene with l-dimethylaminonaphthalene-5sulfonyl group, a powerful and widely used fluorescent probe named dansyl,¹⁹ as evidenced by the generation of 3an, albeit in slightly diminished yield. In sharp contrast to arylsulfonothioates, alkyl-sulfonothioates are a category of challenging addition partners primarily due to the inferior stability of alkyl sulfonyl radicals to their aryl counterparts. To date, only a single substrate of this class (S-phenylmethylsulfonothioate) has been employed in ATRA reactions.¹⁵ Nevertheless, the tested alkylsulfonothioates (2o-q)with varied substitution patterns could undergo effective

transformation under the standard conditions to deliver the desired products (3ao-q) in synthetic useful yields, highlighting the expediency and breadth of the newly devised method. Unfortunately, S-alkyl-arylthiosulfonates are not compatible by our protocol.

To shed light on the mechanism of the synergetic ATRA, a light "on–off" experiment was carried out (Figure S1). It is revealed that occurrence of the ATRA reaction between 1a and 2a required the continuous irradiation of the blue LED light. In addition, the photochemical quantum yield (Φ) ($\lambda_{ex} = 457$ nm) of the reaction between 1u and 2a was determined to be $\Phi = 0.1$ (see SI for details), implying the reaction more likely performed through a photoredox-catalysis pathway rather than a radical chain process.

Furthermore, when 1i and 2a were subjected to the otherwise standard catalytical conditions along with 1,4-dinitrobezene (2 equiv), a commonly used radical scavenger (Scheme 4a), the formation of 3ia was completely inhibited,

Scheme 4. Synergetic Copper/Photoredox Catalyzed ATRA Interfered with Radical Scavengers

a) Catalytic ATRA Interfered with 1,4-dinitrobenzene



1i was completely recovered determined by ¹H NMR

b) EPR Studies with DMPO



and the reactant **1i** could be quantitatively recovered based on the analysis of ¹H NMR. As we expected, introduction of 1 equiv of 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) led to the generation of tosyl radical trapped product **4** (Scheme 4b), which was characterized by electron paramagnetic resonance spectroscopy (EPR) (Figure S2)²⁰ and HRMS analysis (Figure S3). These results coincidentally supported the key role of *tosyl radical* in the transformation. Subsequently, we performed the fluorescence quenching experiments of Ru(phen)₃(PF₆)₂ by styrene **1a**, thiosulfonates **2a** and DIPEA (Figure S4). The Stern–Volmer plots indicate that the excited state of Ru(phen)₃(PF₆)₂ was quenched by DIPEA, whereas **1a** and **2a** exhibited no quenching effect at all.

Based on the aforementioned observations, a plausible mechanism is proposed in Figure 1. The photocatalytic cycle commences with the reductive quenching of the excited state $Ru(phen)_3(PF_6)_2$ ($[Ru^{II}]^*$) with DIPEA to yield the radical cation of DIPEA and $[Ru^I]$ species. A single electron transfer (SET) from the latter species to 2a yields the tosyl radical A and the thiyl anion B. The Cu^I species D is oxidized by radical cation of DIPEA to provide Cu^{II} species E, initiating the copper catalysis cycle. Thiyl anion B binds to E to generate the intermediate F. Simultaneously, A undergoes addition to 1a to afford the benzylic radical intermediate C, which subsequently reacts with F in a single-electron oxidation manner to provide G. The copper(III) species G undergoes rapidly reductive



Figure 1. Proposed mechanism of synergetic copper/photoredox catalyzed ATRA.

elimination to afford the final product **3aa**, and regenerates **D** to close the overall catalytical cycle. Another possible mechanism without the copper catalyst is also provided in SI as Figure S5.

In summary, a general and practical synergetic copper/ photoredox catalyzed ATRA of styrenes with thiosulfonates is reported. A vast array of functional groups, especially medically relevant heteroaryl scaffolds, could be well tolerated by the newly devised method. By leveraging the high level of substrate compability as well as the mild reaction conditions, our protocol can be used to introduce fluorophores across the olefin moieties, and to derivatize bioactive natural products in late stage. The mechanistic studies support the pivotal role of sulfonyl radicals in the transformation, and corroborate a synergetic copper/photoredox catalysis process.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04254.

Detailed experimental procedures, characterization data, and NMR spectra of new compounds (PDF)

Accession Codes

CCDC 2023810 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

- Qingchao Liu Department of Pharmaceutical Engineering, College of Chemical Engineering, Northwest University, Xi'an, Shanxi 710069, P. R. China; Email: liuqc21@nwu.edu.cn
- Tiezheng Jia Shenzhen Grubbs Institute, Department of Chemistry and Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong S18055, P. R. China; State Key Laboratory of Elemento-Organic Chemistry, Nankai University, 300071 Tianjin, China; orcid.org/0000-0002-9106-2842; Email: jiatz@sustech.edu.cn

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Authors

- Xin Zhou Department of Pharmaceutical Engineering, College of Chemical Engineering, Northwest University, Xi'an, Shanxi 710069, P. R. China; Shenzhen Grubbs Institute, Department of Chemistry and Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, P. R. China
- Zhiyuan Peng Shenzhen Grubbs Institute, Department of Chemistry and Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, Guangdong 518055, P. R. China
- Peng George Wang School of Medicine, Southern University of Science and Technology, Shenzhen 518055, P. R. China; orcid.org/0000-0003-3335-6794

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c04254

Author Contributions

T.J. designed and supervised the project. X.Z. and Z.P. performed the experiments. T.J., P.G.W., and Q.L. analyzed the results. T.J. wrote the paper.

Notes

The authors declare no competing financial interest.

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