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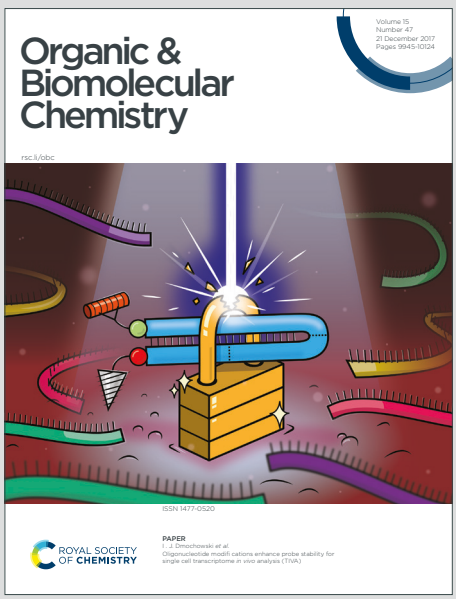

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ARTICLE

TCCA/PhSH-Mediated regioselective hydroethoxylation and hydromethoxylation of allenamides *via* a radical process.

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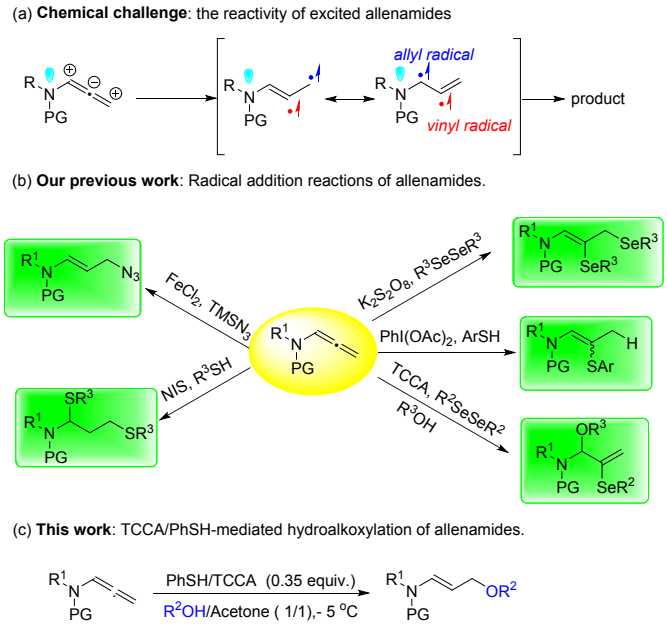
An efficient TCCA/PhSH-mediated regioselective hydroethoxylation and hydromethoxylation of allenamides *via* a radical process was developed to create a workable route to γ-oxygenated enamides. This process is highly regioselective, affording (*E*)-γ-oxygenated enamides in moderate to good yields. Mechanistic investigations indicated that the ethoxy radical was formed through the motivation of TCCA/PhSH, which subsequently added to the terminal carbon of allenamides to form the vinyl radical intermediate. The efficiency of the gram-scale reaction suggests the potential industrial application of this synthetic method. Notably, our approach eliminates the need for metal catalysts representing a significant advancement in greener chemistry practices.

Introduction

As readily available allene sources, *N*-allenamides bearing an electron-withdrawing group (EWG) on the nitrogen atom have emerged as powerful nitrogen-containing synthons in a variety of transformations.[1] In contrast to their well-established thermal reactivity, which depends on an electronic bias in their ground state (S0),[2] their properties and reactivity in the triplet excited state (T1) remain elusive (Scheme 1). So far, the transformation of allenamides *via* a radical approach has rarely been explored. Since Hsung and Yamashita reported AIBN [3] and SmI_2 [4] mediated radical cyclization of allenamides for the synthesis of isoquinoline, indole, Indane, and naphthalene derivatives, more sustainable catalytic processes have been recently developed. Kimber, Lombardo and Sarkar group reported an photoredox-catalyzed radical domino addition of allenamides to synthesis allylaminals, 2-aminofurans and indoles in the presence of Ir and Eosin Y photocatalyst.[5] Voskressensky group reported an photoredox catalysed hydrosulfonylation of allenamides using Eosin Y as the photocatalyst.[6] Maestri's group reported the visible-light-promoted cycloadditions of allenamides for the synthesis of complex polycyclic systems.[7] These radical annulations involving allenamides are governed in the majority by toxic and expensive transition metals, which restricted its application. In the most recent work in this field, Miesch group



Scheme 1 Radical addition reaction of allenamides.

reported a photocatalyst-free, visible-light-induced regio-and stereoselective synthesis of phosphorylated enamines from *N*-allenamides via [1,3]-sulfonyl shift at room temperature.[8] Nevertheless, the development of new methods for the radical reaction of allenamides is still highly desired.

γ-Oxygenated enamines and enamides are versatile scaffolds that have been extensively exploited as starting materials or synthetic intermediates for the construction of useful products,[9] in some cases showing interesting pharmacological properties (Figure 1).[10] The hydroalkoxylation of allenamides represents one of the most effective and atom-

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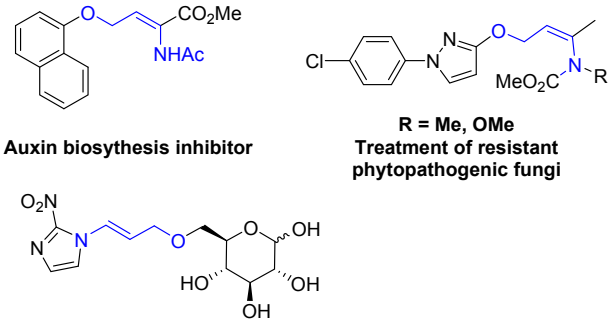
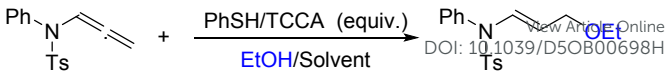


Figure 1 Examples of bioactive *γ*-oxygenated enamines and enamides.

economical methods to prepare γ-oxygenated enamides. Horino and co-workers reported a cationic gold(I) catalyzed intermolecular addition of alcohols at the α-position of the allenic double bond, wherein thermal conditions led to the γ-addition.[11] The reaction was limited to cyclic oxazolidinone derivatives containing an additional electron-withdrawing group on the nitrogen. Álvaro and coworkers reported an $AuCl_3$ catalyzed intermolecular hydroalkoxylation of allenamides with EtOH and MeOH, which was limited to low temperatures (- 78 °C) and expensive transition metals.[12] Croatt and coworkers reported an $AlCl_3$-catalyzed regioselective intermolecular mono- or bis-hydroalkoxylation of allenamides, but the low yields limit its applications.[13] Kuram and coworkers reported a fluorinated alcohol promoted hexafluoroisopropoxylation and trifluoroethoxylation of allenamides, which was limited to aryl-substituted allenaides. [14] Quintavalla and coworkers reported a CSA catalyzed hydrofunctionalization of allenamides to diverse heteroatom-containing enamides.[15] Nevertheless, developing and expanding more general and efficient strategies for the hydroalkoxylations of allenamides to synthesis *γ*-oxygenated enamides would still be highly desirable. Based on our previous reports on the intermolecular radical additton reactions of allenamides (Scheme 1b),[16] we report herein an efficient TCCA/PhSH-mediated regioselective hydroethoxylation and hydromethoxylation of allenamides *via* a radical process to create a workable route to γ-oxygenated enamides. (Scheme 1c).

Results and discussion

Our group recently developed an efficient TCCA/RSeSeR mediated selenoalkoxy of allenamides for the construction of selanyl-allylic N,O-aminal derivatives, we speculate on the possibility of TCCA/PhSH-mediated regioselective thioalkoxylation of allenamides under the similar reaction conditions. Surprisingly, a hydroethoxylation product was observed when PhSH was employed instead of PhSeSePh in our previous reaction conditions. Delightfully, the control experiments confirmed that the hydroethoxylation of allenamides were occurred through a radical procrss. Inspired by this result, optimization studies are performed by



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1a 2a

Table 1 Screening of optimal conditions [a]

Entry	PhSH (equiv.)	TCCA (equiv.)	EtOH/Solvent	*T* (°C)/t (min/h)	Yield (%)[b]
1	1.0	0.35	EtOH:DCM=1:1	25/5 min	30
2	0.5	0.35	EtOH:DCM=1:1	25/5 min	44
3	0.35	0.35	EtOH:DCM=1:1	25/15 min	49
4	0.25	0.35	EtOH:DCM=1:1	25/5 min	46
5	0.35	0.35	EtOH:DCM=1:1	50/10 min	28
6	0.35	0.35	EtOH:DCM=1:1	0/10 h	60
7	0.35	0.35	EtOH:DCM=1:1	-5/20 h	69
8	0.35	0.35	EtOH:DCM=1:1	-10/16 h	65
9	0.35	0.5	EtOH:DCM=1:1	-5/11 h	61
10	0.35	0.7	EtOH:DCM=1:1	-5/12 h	66
11	0.35	1	EtOH:DCM=1:1	-5/10 h	30
12	0.35	0.35	EtOH:DCM=2:1	-5/25 h	45
13	0.35	0.35	EtOH:DCM=3:1	-5/27 h	59
14	0.35	0.35	EtOH:DCM=1:2	-5/21 h	54
15	0.35	0.35	EtOH:DCM=1:3	-5/21 h	52
16	0.35	0.35	EtOH:THF=1:1	-5/2 h	62
17	0.35	0.35	EtOH:CH_3CN=1:1	-5/17 h	66
18	0.35	0.35	EtOH:Dioxane=1:1	-5/10 h	48
19	0.35	0.35	EtOH: Toluene =1:1	-5/10 h	87
20	0.35	0.35	EtOH:CH_3Cl =1:1	-5/12 h	57
21	0.35	0.35	EtOH:DCE =1:1	-5/12 h	84
22	0.35	0.35	EtOH:EtOAc =1:1	-5/6 h	68
23	0.35	0.35	EtOH:Acetone =1:1	-5/3 h	94

[a] Unless noted, all the reactions were carried out at 0.2 mmol of **1a** in 2 mL solvent. [b] Isolated yield.

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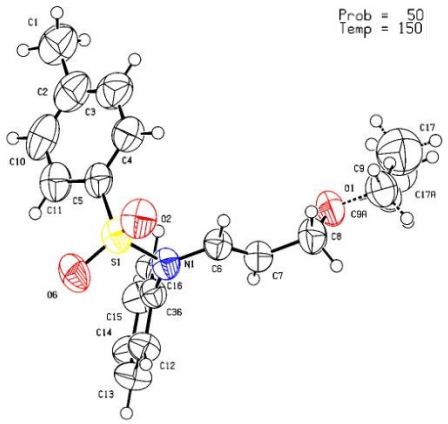
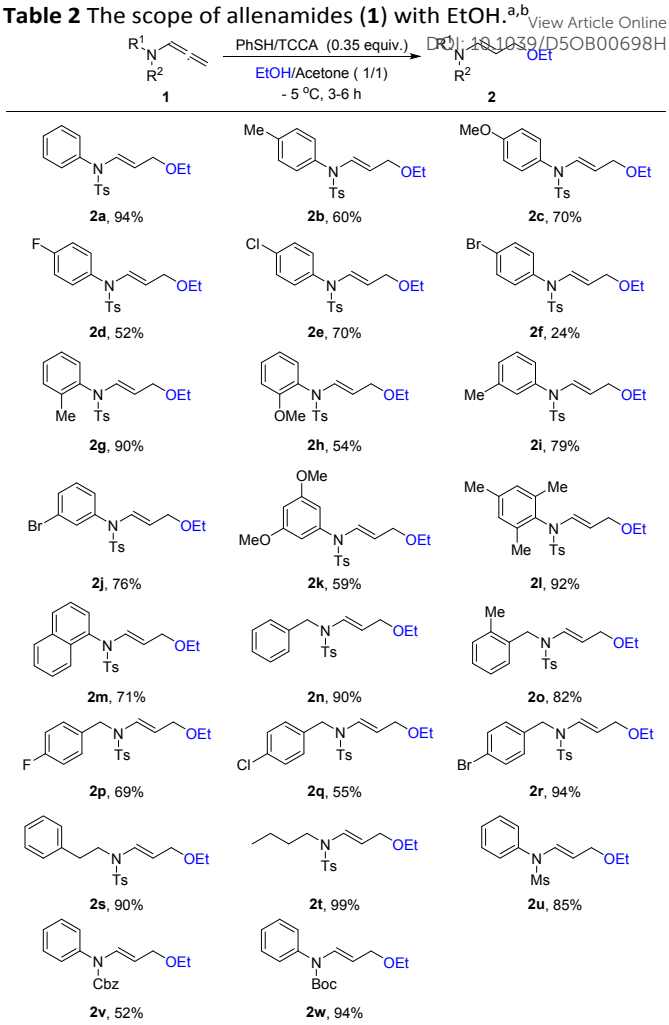


Figure 2 X-ray structure of **2a.**

investigating the reaction between 1 equiv. of allenamide **1a** and 1 equiv. of PhSH in the presence of 0.35 equiv. of TCCA, using EtOH/DCM (1/1) as a solvent. After 5 min at room temperature, total conversion of **1a** into the hydroethoxylation product **2a** was observed, and the product was obtained in 30% yield after column chromatography purification (Table 1, entry 1). Moreover, the molecular structure of the product **2a** was unambiguously determined by single-crystal X-ray diffraction (Figure 2).[17] Encouraged by this preliminary result, we intently evaluated various reaction parameters. The conversion of **2a** was increased to 49% by decreasing the loading of PhSH to 0.35 equiv. (Table 1, entries 2-4). The yield of **2a** could increase to 69% in 20 hours when lowering the reaction temperature to -5°C (Table 1, entries 5-8). Further studies demonstrated that the yield could not be improved upon increasing the amount of TCCA (Table 1, entries 9-11). Finally, we moved on to assess the impact of solvents on this reaction. The conversion of **2a** was slightly reduced by either increasing the ratio of EtOH or DCM (Table 1, entries 12-15). Subsequent screening of the solvents led to an increase in the yield to 94% in 3 hours when EtOH/Acetone (1/1) was used as the solvent (Table 1, entries 16-23).

With the optimized reaction conditions in hand, we first examined the substrate scope of allenamides (**1**) with EtOH (Table 2). Initially, the electron-rich compounds 4-methyl and 4-methoxyl substituted phenyl allenamides **1b** and **1c** were investigated, and the desired addition products **2b** and **2c** were obtained in 60% and 70% yields, respectively. Additionally, we also investigated the influence of electron-deficient substituents at the *para*- position of the aryl ring. 4-Fluoro and 4-chloro substituted phenyl allenamides **1d** and **1e** gave the corresponding products **2d** and **2e** in 52% and 70% yields, while 4-bromo substituted phenyl allenamide **1f** showed lower reactivity, giving the desired product **2f** in 24% yield. 2-Methyl and 2-meothyl substituted phenyl allenamides **1g** and **1h** could produce products **2g** and **2h** in 90% and 54% yields, respectively. 3-Methyl and 3-bromo substituted phenyl allenamides **1i** and **1j** produced products **2i** and **2j** in 79% and 76% yields, respectively. Both 3,5-dimethoxy and 2,4,6-trimethyl-substituted phenyl allenamides **1k** and **1l** efficiently

Table 2 The scope of allenamides (**1**) with EtOH.[a,b]

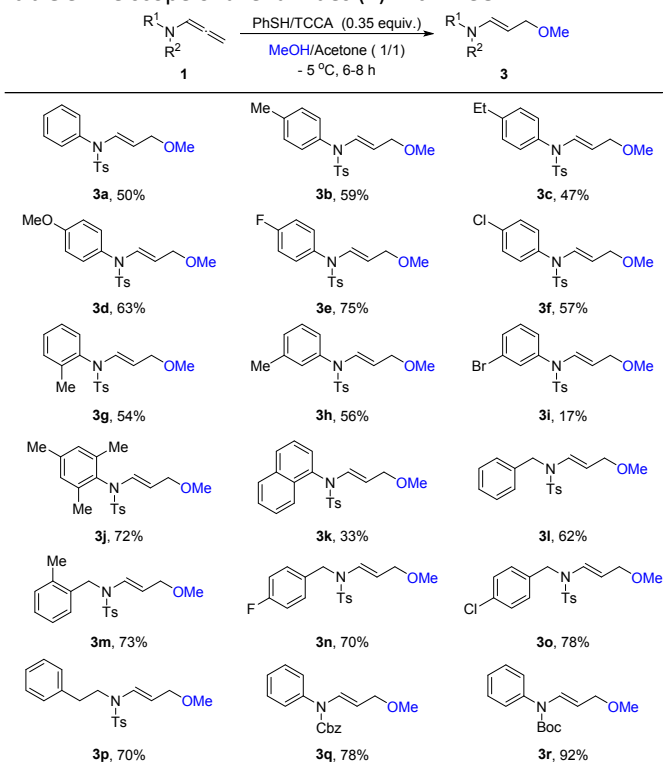


[a] Reaction conditions: **1** (0.2 mmol), PhSH/TCCA (0.07 mmol), EtOH/Acetone (1/1, 2 mL), - 5 °C, within 3 - 6 h. [b] Isolated yield.

reacted with EtOH to afford **2k** and **2l** in 59% and 92% yields, respectively. 1- Naphthyl-substituted allenamides **1m** could also produce product **2m** in 71% yield. Subsequently, we evaluated benzyl allenamide substrates. Benzyl allenamide **1n** and 2-methyl-substituted benzyl allenamide **1o** successfully isolated the desired products **2n** and **2o** in 92%, 90% and 82% yields, respectively. 4-Fluoro, 4-chloro and 4-bromo substituted phenyl allenamides **1p**, **1q** and **1r** also gave the corresponding products **2p**, **2q** and **2r** in good to mediate yields. Furthermore, the reactivity of different aliphatic substituted allenamides was also investigated. Phenethyl- and n-butyl-substituted allenamide **1s** and **1t** gave product **2s** and **2t** in good yields. Finally, the allenamides with Mesyl, Cbz and Boc-amino-protecting groups were tried, giving **2u**, **2v** and **2w** in 85%, 52% and 94% yields, respectively.

Next, MeOH is investigated as a cosolvent and substrate for the hydromethoxylation on the allenamides **1** (Table 3). Hydromethoxylation products containing electron-donating (Me, Et and OMe) and halogen (F and Cl) groups at the *para*-position of the aryl ring were obtained in moderate yields from the corresponding allenamides without significant electronic effects. 2- Methyl and 3-methyl substituted allenamides could

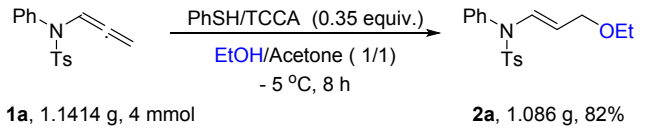
Table 3 The scope of allenamides (**1**) with MeOH.[a,b]



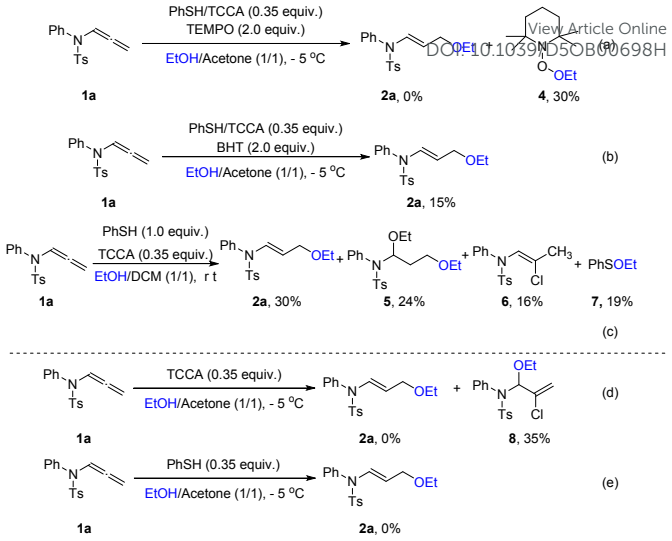
[a] Reaction conditions: **1** (0.2 mmol), PhSH/TCCA (0.07 mmol), MeOH/Acetone (1/1, 2 mL), - 5 °C, within 6 - 8 h. [b] Isolated yield.

also gave the corresponding products in moderate yields, while 3-bromo substituted phenyl allenamide **1i** showed lower reactivity, giving the desired product **3i** in 17% yield. 2,4,6-Trimethyl-substituted phenyl allenamides **1j** efficiently reacted with MeOH to afford **3j** in 72% yield. 1-Naphthyl-substituted allenamides **1k** gave product 3**k** in 33% yield. Benzyl allenamide **1l** and containing electron-donating (2-Me) and halogen (4-F and 4-Cl) groups could also obtain the desired products in moderate yields. Phenethyl-substituted allenamide **1p** gave product **3p** in 70% yield. Finally, the allenamides with Cbz and Boc-amino-protecting groups were tried, giving **3q** and **3r** in 78% and 92% yields, respectively.

To further exemplify the synthetic utility of this reaction, a gram-scale synthesis of the γ-oxygenated enamides **2a** was performed. When 1.14 g of allenamide **1a** (4 mmol) was used, 1.08 g of the desired product **2a** was obtained in 82% yield in 8 hours, indicating that this transformation is easy to scale up to the gram scale in efficiency (Scheme 2).



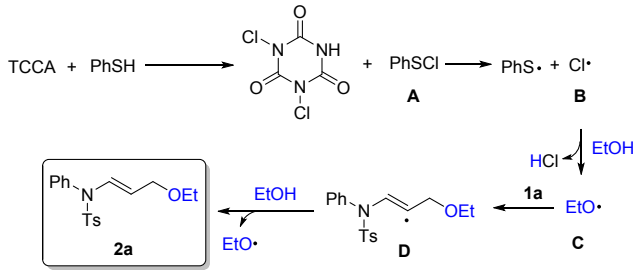
Scheme 2 Gram-scale synthesis.



Scheme 3 Control experiments.

Lastly, in order to gain further insights regarding the reaction and to tentatively propose a mechanism, some control experiments were conducted (Scheme 3). Firstly, we investigated the reaction in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), which is known as an effective radical scavenger. When 2.0 equiv of TEMPO was added in the reaction of **1a** under identical conditions, the reaction was shut down, while the TEMPO-OEt adduct was formed as estimated by HRMS analysis (See Supporting information) of the reaction mixture (Scheme 3a). This result indicates that the ethoxy radical may be involved in the transformation. Moreover, the 2,6-di-tert-butyl-4-methylphenol (BHT) also inhibited the reaction to afford the desired product **2a** in 15% yield (Scheme 3b), which further indicats the involvement of a radical intermediate in this reaction. In the optimized reaction conditions, we isolated diethoxy-substituted product **5**, chlorinated product **6** and ethoxy(phenyl)sulfane **7** when using 1 equiv. of PhSH with EtOH and DCM as the solvent in room temperature (Scheme 3c). This result indicates that the ethoxy, chlorine and thiophenol radical may be involved in the transformation. Finally, a reaction without PhSH or TCCA was carried out and we did not observe the formation of the desired product **2a**, while the chlorinated alkoxylative product **8** was observed in 35% yield, showing the necessity of the PhSH and TCCA for the protocol (Scheme 3d and 3e).

Based on the previous reports[18] and control experiments, we proposed a reaction mechanism for synthesizing **2a** as outlined in Scheme 4. The reaction initiates through the reaction of TCCA with PhSH to generate PhSCl intermediate **A**, followed by cleavage of unstable S–Cl bond to generate chlorine radical **B** that can abstract the strong EtO–H hydrogen atom to give ethenyloxy radical **C**. The ethenyloxy radical **C** immediately underwent an addition reaction with allenamide **1a** to form the corresponding vinyl radical intermediate **D**, which finally abstracts a hydrogen atom from ethanol to afford the desired product **2a**.



Scheme 4 Proposed reaction mechanism.

Author contributions

Qingsong Liu: methodology (synthesis), writing – original draft; Gele Jiri: methodology (synthesis), writing – original draft; Xingyao She: methodology (synthesis); Zhigang Zhao: supervision, review & editing; Xiaoxiao Li: writing – review & editing.

Conclusions

In summary, we have developed an efficient TCCA/PhSH-mediated regioselective hydroethoxylation and hydromethoxylation of allenamides *via* a radical process to create a workable route to γ -oxygenated enamides. This process is highly regioselective, affording (*E*)-γ-oxygenated enamides in moderate to good yields. Mechanistic investigations indicated that the ethoxy radical was formed through the motivation of TCCA/PhSH, which subsequently added to the terminal carbon of allenamides to form the vinyl radical intermediate. The efficiency of the gram-scale reaction suggests the potential industrial application of this synthetic method. Notably, our approach eliminates the need for metal catalysts representing a significant advancement in greener chemistry practices. The liminations of this transformation is that simple allene and other alcohols could bot be able to obtain the corresponding products. The potential utilization and extension of this interesting synthetic methodology are currently underway.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data underlying this study are available in the published article and its supporting information.

Acknowledgements

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17 **2a**'s molecular structure was confirmed by their X-ray diffraction. CCDC 2425797 contains the supplementary crystallographic data for **2a**.

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The data underlying this study are available in the published article and its supporting information.