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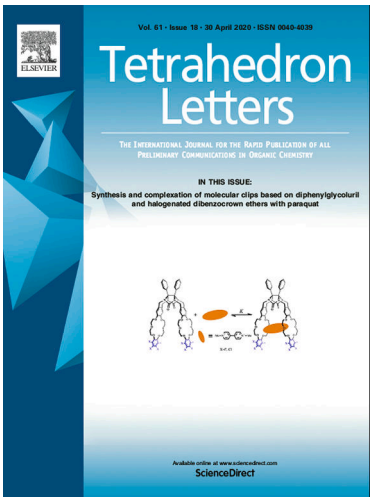

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Visible Light Photoredox-Catalyzed Hydrothiolation of Enamides and Enecarbamates

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Keywords
Photoredox
Hydrothiolation
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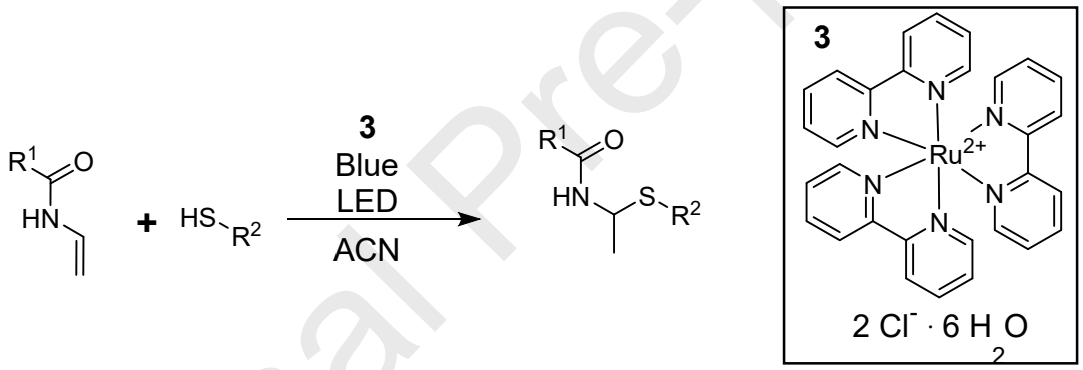
Enamides
Enecarbamates
N, *S*-Acetal

Graphical Abstract



Abstract

An efficient visible light photoredox-catalyzed, Markovnikov selective, hydrothiolation reaction of enamides and enecarbamates is presented. This protocol is mild and operationally simple. This process provides access to *N*, *S*-acetal products from available thiols and a variety of enamides and enecarbamates.

Introduction

Hydrothiolation reactions directly couple a thiol and an alkene, two common and abundant building blocks, to form a thioether via a new C−S and C−H bond.[1-3] This strategy toward C−S bond formation is highly valuable because organosulfur compounds are common synthetic intermediates and components of many sulfur-containing natural products.[4-7] Among various hydrothiolation reactions, the thiol–ene reaction, a radical addition of thiols to olefins, is

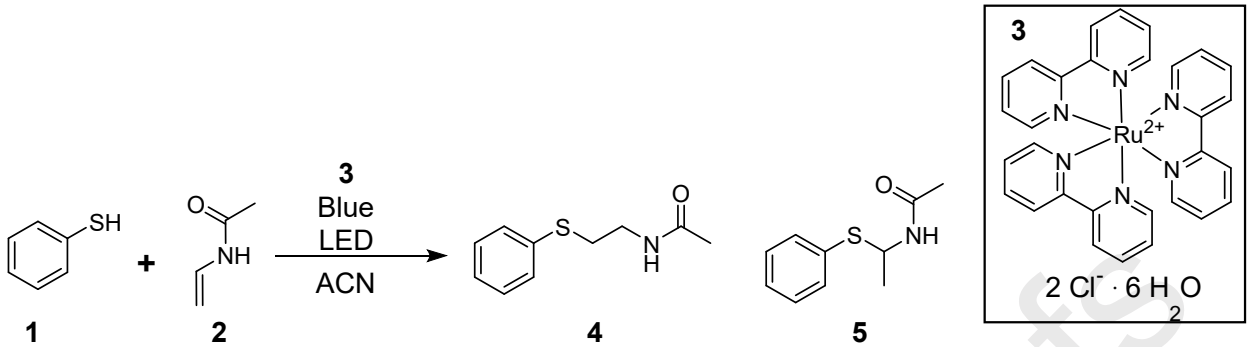
arguably one of the most powerful current methods because of its widespread employment in areas of bioconjugate chemistry, polymer science, and pharmaceutical chemistry.[8,9] Since the first transition metal-catalyzed hydrothiolation by Ogawa, organometallic chemists have designed catalytic systems capable of selectively synthesizing C−S bonds from alkynes and allenes.[10-12] On that note, transition metal-catalyzed hydrothiolations of alkenes is relatively underdeveloped.[13,14] Ogawa demonstrated the Pd-catalyzed hydrothiolation of alkenes bonded directly to heteroatoms, such as vinyl ethers and vinyl lactams.[15] This was followed by the recent disclosure of the Au-catalyzed anti-Markovnikov hydrothiolation of terminal olefins to afford linear C−S bonds.[16] Recently, Hull published a rhodium-catalyzed regiodivergent hydrothiolation of allyl amines and imines.[17] Compared to other hydrofunctionalization methods, visible-light mediated photoredox-catalyzed hydrothiolation reactions have been relatively underexplored. Yoon has employed photoredox catalysis to achieve the anti- Markovnikov hydrothiolation of alkenes via a thiol−ene reaction.[18] Using this protocol, the hydrothiolation of a variety of styrenes, simple alkenes, and alkynes could be performed.[18,19] Following this methodology, a handful of hydrothiolation reactions or thiol−ene reactions, employing photoredox catalysis have been presented in both functionalization of styrenes or terminal alkenes present in small molecules or polymers.[20-24] In addition, there have been reports of aqueous anti-Markovnikov addition of thiols to unactivated alkenes.[25] We demonstrate here a very simple hydrothiolation reactions of enamides and enecarbamates driven by visible light and a photoredox catalyst

Although many advances in the visible light photoredox-catalyzed thiol-ene reaction have been made, the we noticed that in general, the substrate scope with regards to alkenes were limited to the anti-Markovnikov hydrothiolation product.[26] This observation from the literature propelled our interest in determining if the use of enamides and enecarbamates, as unsymmetrical alkene substrates, would lead to regiodivergent visible light photoredox-catalyzed hydrothiolation products. More specifically, we grew interest in determining if we could develop regioselective visible light photoredox-catalyzed hydrothiolation reaction methodologies. We began to explore and develop a visible light-mediated photoredox-catalyzed hydrothiolation methodology to regioselectively functionalize enamides and enecarbamates.

Results and Discussion

In our preliminary studies, we chose to screen the reaction of thiophenol (**1**) and *N*-vinyl acetamide (**2**) with Tris(2,2'-bipyridyl)ruthenium(II) chloride hexahydrate (**3**) as the photoredox catalyst with a variety of organic and aqueous solvents (Table 1, entries 1-12). To our surprise we could identify and isolate the two regiodivergent thiol-ene addition products, **4** and **5** (Table 1). In all the reactions done in aqueous solutions thioether **4**, the expected anti-Markovnikov product was the only product and was isolated in moderate yields. We were able to further investigate these reaction conditions to develop a metal-free, anti-Markovnikov selective, hydrothiolation reaction of enamides and enecarbamates in an aqueous medium.[27] In contrast, we observed that when the reaction was done in acetonitrile or methylene chloride the only product was the *N*,*S*-acetal **5**, which was isolated in moderate to good yields. The *N*, *S*-acetal functionality in **5** is of interest because *N*, *S*-acetals are found in a number of biologically active compounds and natural products and overall their role as biologically active molecules have been underexplored (Figure 1).We subsequently decided to explore the reaction conditions associated with the Markovnikov, *N*,*S*-acetal product. During the process of optimizing the reactions conditions for the *N*, *S* -acetal product **5**, we saw that more efficient reactions could be produced when 1.1 equivalents of **1** was used and we discovered that the catalyst loading of **3** could be lowered to 1% without deviating from our best recorded isolated yield (Table 2, entries 1-4). We also determined that the visible light photoredox-catalyzed reaction to prepare **5**, can also be done on the 10 mmol scale with minimal change in efficiency (Table 2, entry 4). We were also able to determine that in the absence of catalyst, with and without Blue LED light, that there is a slower background reaction that favors the formation of anti-Markovnikov product **4** (Table 2, entry 5 and 6). Previous reactions were all done open to air, when the reaction was run with rigorously degassed solvent in an inert atmosphere we observed that the rate of the reaction with repsect to the formation of compound **5** decreased along with the formation of anti-Markovnkov product **4 (**Table 2, entry 7).

Table 1: Initial and optimized reaction conditions.



1 2 4 5

Entry[a]	% Catalyst 3	Solvent	% Yield 4[b]	% Yield 5[b]
1	5 %	ACN	0 %	75 %
2	5 %	DCM	0 %	45 %
3	5 %	THF	25 %	35 %
4	5 %	MeOH	25 %	25 %
5	5 %	10 X PBS	50 %	0 %
6	5 %	H_2O	55 %	0 %
7	2.5 %	ACN	0 %	60 %
8	2.5 %	H_2O	50 %	0 %
9	1%	ACN	0 %	80 %
10	1%	H_2O	55 %	0 %
11	0 %	ACN	0 %	0 %
12	0 %	H_2O	55 %	0 %

a.) Reactions run with 1 mmol of **1** and **2** in 0.2M solvent for 18 hr with Blue LED light and monitored by TLC. b.) Isolated yield after column chromatography.

Figure 1. Biologically active Sulfur-containing compounds.

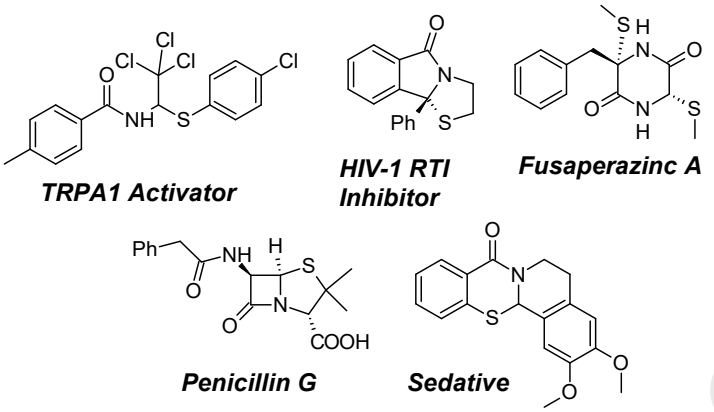
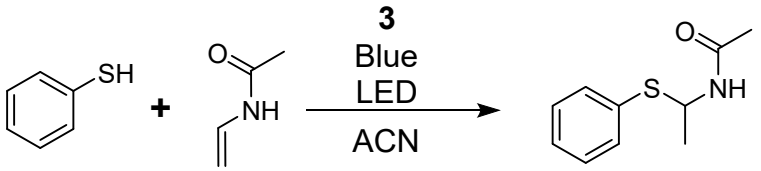


Table 2: Reaction optimization for compound **5**.



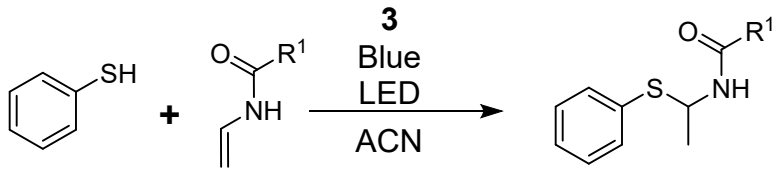
1 **2** **5**

Entry	% Catalyst 3	Equiv 1	Equiv 2	Rxn Time (Hr)	% Yield 4[a]	% Yield 5[a]
1	**1 %**	**1.1**	**1.0**	**2**	**0 %**	**90 %**
2	**1 %**	**2.0**	**1.0**	**2**	**0 %**	**88 %**
3	**1 %**	**4.0**	**1.0**	**2**	**0 %**	**84 %**
4[b]	**1 %**	**1.1**	**1.0**	**2**	**0 %**	**86 %**
5[c]	**0 %**	**1.1**	**1.0**	**24**	**25 %**	**0 %**
6[d]	**0 %**	**1.1**	**1.0**	**24**	**25 %**	**0 %**
7[e]	**1 %**	**1.1**	**1.0**	**24**	**35 %**	**50 %**

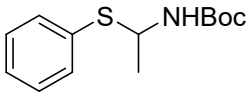
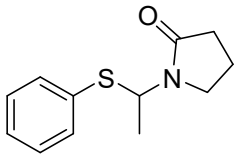
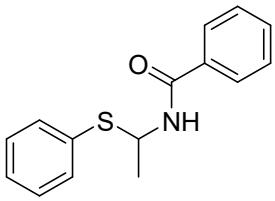
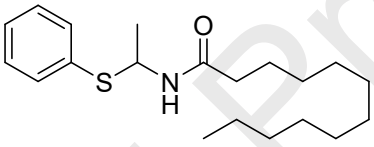
All reactions run in 0.2 M ACN and monitored by TLC. a.) Isolated yields after column chromatography. b.) Reaction run at 10 mmol scale. c.) Reaction run with Blue LED and no catalyst. d.) Reaction run with no catalyst in the dark. e.) Reaction run with degassed solvent under inert atmosphere.

Next, we proceeded to explore and expand the substrate scope of the currently optimized visible light photoredox-catalyzed Markovnikov hydrothiolation procedure. We discovered in the following experiments that thiophenol (**1**) was a suitable thiol for efficient Markovnikov hydrothiolation to a variety of enamides and enecarbamates (Table 3). In all examples, the Markovnikov hydrothiolation *N*,*S*-acetal products were isolated in moderate to very good yields.

Table 3. Results for the hydrothiolation of different enamides and enecarbamates with thiophenol (**1**).



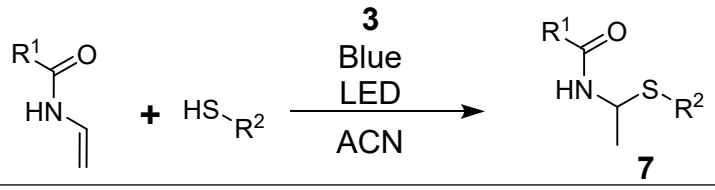
1 **6**

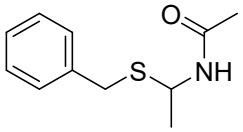
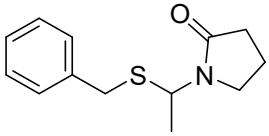
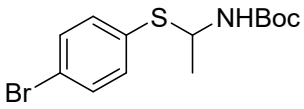
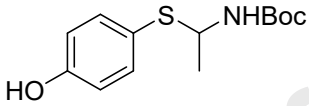
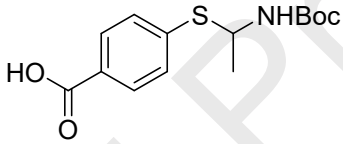
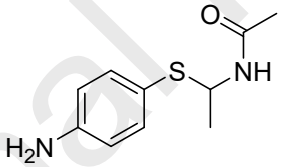
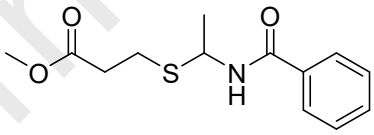
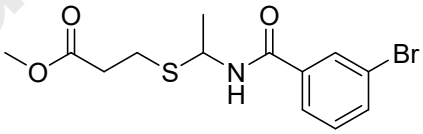
Entry	R	Product	% Yield
1		**6a**	**90 %**
2		**6b**	**93 %**
3		**6c**	**86 %**
4		**6d**	**75 %**

Reactions were run with 1.1 mmol of **1** and 1.0 mmol Enamide or Enecarbamate in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. Isolated yields after column chromatography.

Next, we turned our attention to explore the reaction substrate scope with respect to variations in thiols with varying encarbamates and enamides (Table 4). Benzyl mercaptan was determined to be a suitable thiol for the Markovnikov hydrothiolation reaction with various enamides (Table 4, **7a** and **7b**). Again, these *N*,*S*-acetal products can be isolated in very good yields. We then explored the use of para-functionalized aromatic thiols (Table 4, **7c-7f**), with an N-Boc derived enecarbamate. We were pleased to discover that the visible light photoredox-catalyzed Markovnikov hydrothiolation products could be isolated in moderate to very good yields (Table 4, **7a-f**). Although the initial thiols used in the reaction screening process were aromatic. The lab began to investigate the use of 3-mercaptopropionic acid methyl ester with benzoic acid derived enamides. (Table 4, **7e** and **7g**). Both Markovnikov hydrothiolation *N*,*S*-acetal products **7e** and **7g** are isolated in good yields. Again, we can demonstrate that this protocol is quite compatible with a varying degree of substrates that provide the possibility for further transformations. Unfortunately, when these conditions were applied to reactions using simple alkyl thiols, only the bis addition products **8a** and **8b** were isolated (Table 5).

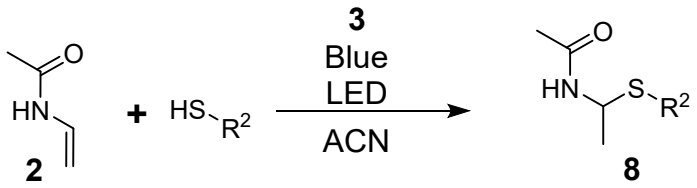
Table 4. Results for the hydrothiolation of different enamides and enecarbamates with various thiols.



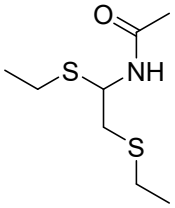
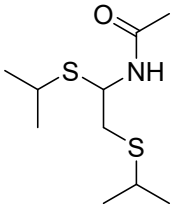
Entry	R	Product	% Yield[a]
1		7a	90 %
2		7b	92 %
3		7c	88 %
4		7d	80 %
5		7e	78 %
6		7f	70 %
7		7g	88 %
8		7h	85 %

Reactions were run with 1.1 mmol of Thiol and 1.0 mmol Enamide or Enecarbamate in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. a.) Isolated yields after column chromatography.

Table 5. Results for the hydrothiolation of **2** with alkyl thiols.



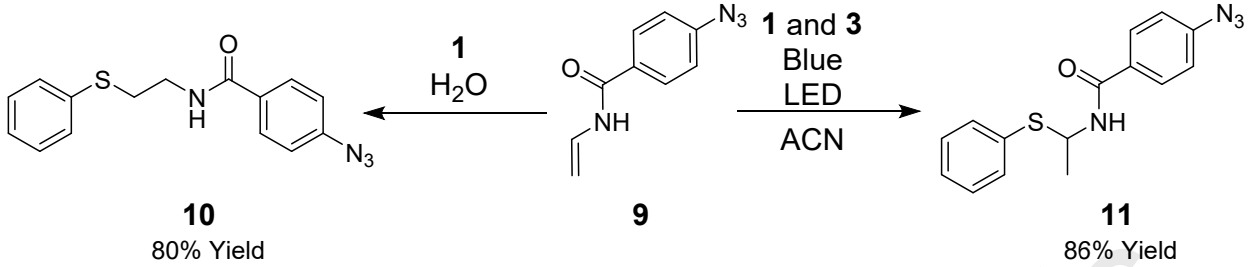
2 **8**

Entry	R	Product	% Yield[a]
1		**8a**	**40 %**
2		**8b**	**45 %**

Reactions were run with 1.1 mmol of Thiol and 1.0 mmol Enamide or Enecarbamate in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. a.) Isolated yields after column chromatography.

Having developed two different and regiodivergent hydrothiolation protocols, we looked to apply these procedures toward the regioselective hydrothiolation of N-vinyl amide **9** (Figure 1).[27] We found that the anti-Markovnikov hydrothiolation product (**10**) for the reaction of thiophenol (**1**) to N-vinyl amide (**9**) in water was isolated in 80% yield after 18 hours (Figure 2). When thiophenol (**1**) and N-vinyl amide (**9**) were reacted with photoredox catalyst **3** in acetonitrile with blue LED light, the Markovnikov hydrothiolation *N*,*S*-acetal product **11** was isolated in 85% yield after 18 hours (Figure 2).

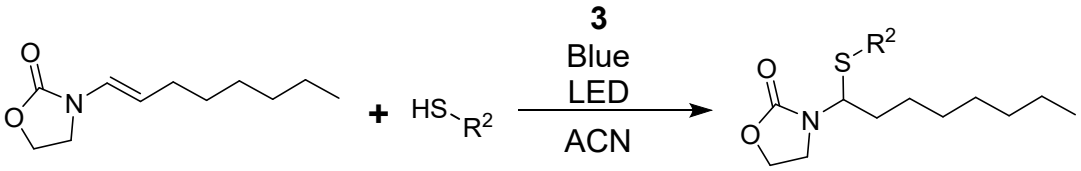
Figure 2. Regiodivergent hydrothiolation of enamide **3** with thiophenol (**1**).



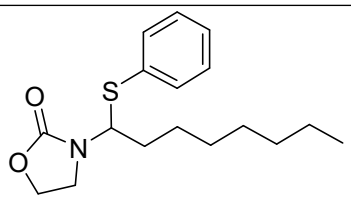
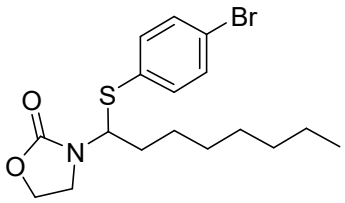
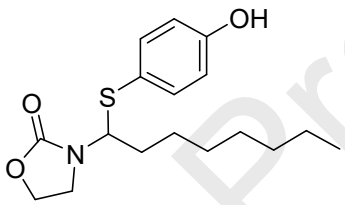
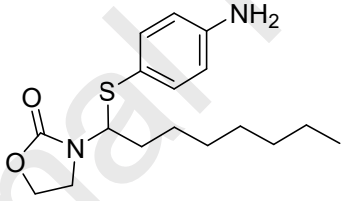
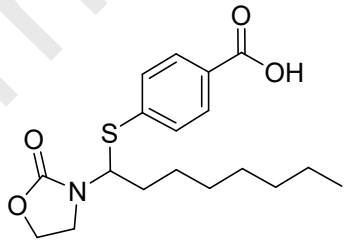
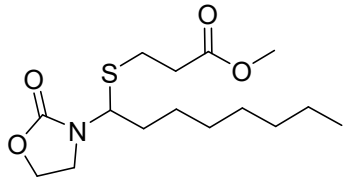
Reactions were run with 1.1 mmol of thiophenol (**1**) and 1.0 mmol enamide (**3**) in 0.2 M H_2O (**10**) for 18 hr or 0.2 M ACN with Blue LED light (**11**) for 18 hr and monitored by TLC. Isolated yields after column chromatography.

Next, disubstituted E-*N*-vinyl-enamide **12** was exposed to previously disclosed conditions with thiophenol (**1**) and photoredox catalyst **3**. Pleasingly, this gave the *N*,*S*-acetal product **13a** in 92% isolated yield. We then explored the use of para-functionalized aromatic thiols (**13b-13e**), with an E-*N*-vinyl-enamide **12**. We were pleased to discover that the visible light photoredox-catalyzed Markovnikov hydrothiolation products could be isolated in moderate to very good yields (Table 6, **13a-13e**). Unfortunately, there was no reaction when the thiol, 3-mercaptopropionic acid methyl ester, was used as the thiol substrate (Table 6, **13f**).

Table 6. Results for the hydrothiolation of different enamides and enecarbamates with various thiols.



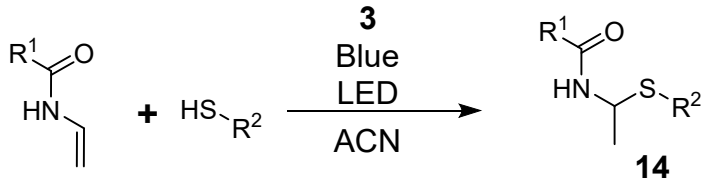
12 **13**

Entry	R	Product	% Yield[a]
1		**13a**	**92 %**
2		**13b**	**90 %**
3		**13c**	**80 %**
4		**13d**	**70 %**
5		**13e**	**73 %**
6		**13f**	**No Reaction**

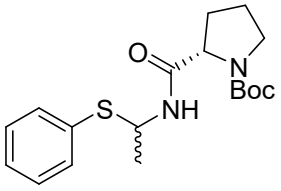
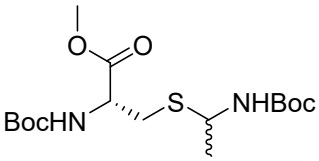
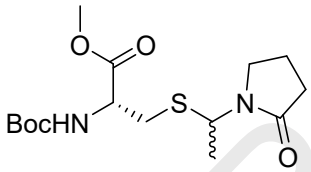
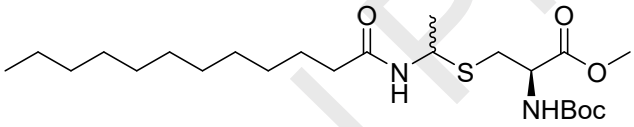
Reactions were run with 1.1 mmol of Thiol and 1.0 mmol Enamide in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. a.) Isolated yields after column chromatography.

Finally, we began to investigate the diastereoselectivity of the proposed visible light photoredox-catalyzed hydrothiolation reaction. Thiophenol (**1**) we exposed to chiral enamide derived Boc-proline with photoredox catalyst **3** in acetonitrile with blue LED light. NMR analysis of the crude hydrothiolation *N*,*S*-acetal product **14a** revealed a diastereomic ratio of 2:1. Following column chromatography the *N*,*S*-acetal product **14a** was isolated in 65% yield with no change in the diastereomeric ratio (Table 7, **14a**). Next, *N*-Boc-L-Cysteine methyl ester was reacted under the same conditions with a variety of enamide and enecarbamate substrates (Table 7, **14b**-**14d**). The diastereomeric ratio of the crude hydrothiolation *N*,*S*-acetal product **14b**-**14d** were determined by NMR. Again, isolated yields after column chromatography could be obtained but with no change in the diastereomeric ratio. Unfortunately, the lauric acid and pyrrolidinone derived enamides produced *N*,*S*-acetal products **14c** and **14d** with a 1:1 diastereomeric ratio. A slight increase in diastereoselectivity of 2:1 was observed when the *N*-Boc-derived enecarbamate substrate was used (Table 7, **14b**).

Table 7. Results for the hydrothiolation of chiral enamides and enecarbamates with various thiols.

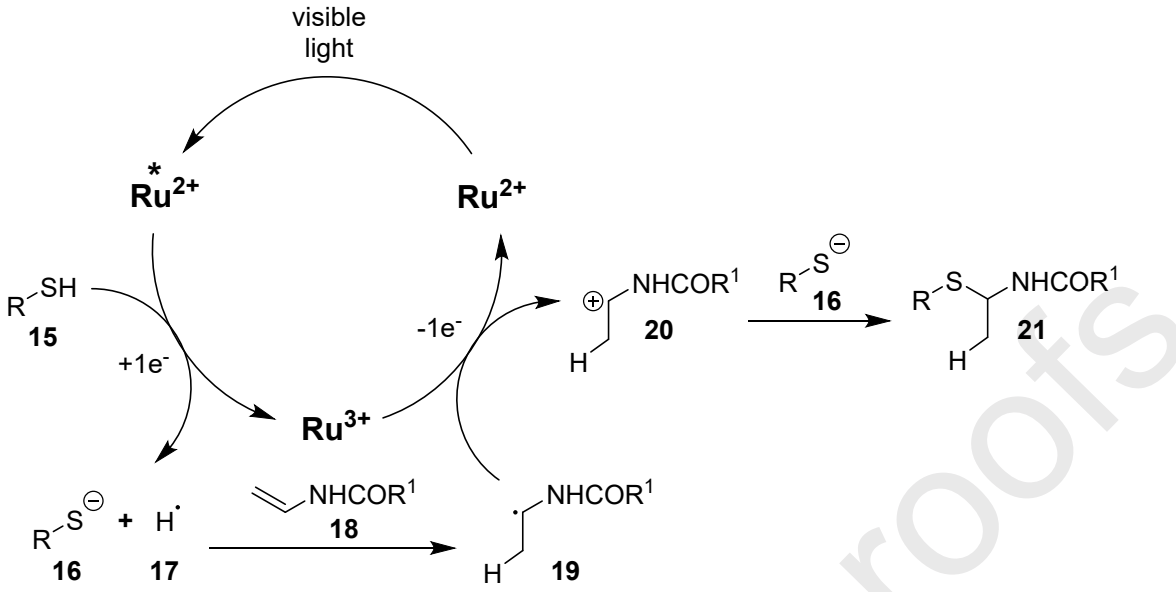


14

Entry	R	Product	Diastereomer Ratio[a]	% Yield[b]
1		**14a**	**2:1**	**65 %**
2		**14b**	**2:1**	**72 %**
3		**14c**	**1:1**	**80 %**
4		**14h**	**1:1**	**70 %**

Reactions were run with 1.1 mmol of Thiol and 1.0 mmol Enamide or Enecarbamate in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. a.) Diastereomer ratio of the crude product determined by NMR. b.) Isolated yields after column chromatography with no change in the diastereomer ratio.

A plausible mechanism (Scheme 1) that we propose begins with the visible-light irradiation of $Ru(bpy)_3^{2+}$ to form a strongly reducing species $*Ru(bpy)_3^{2+}$, which performs a single-electron transfer (SET) to generate a thiolate anion **16** and a hydrogen atom **17** which directly adds to the electron-rich β-position of enamide or enecarbamate (**18**). Hydrogen atom addition generates radical **19** which performs a single-electron transfer (SET) to oxidize and regenerate the $Ru(bpy)_3^{2+}$ from $Ru(bpy)_3^{3+}$. The resulting cation **20** can be directly trapped by thiolate anion **16** to provide the *N*,*S*-acetal product **21**.



Scheme 1. Proposed mechanism for the visible light photoredox-catalyzed hydrothiolation reaction.

Conclusion

In conclusion, we have developed a simple and efficient visible light photoredox-catalyzed methodology for the addition of thiols to enamides and enecarbamates producing the Markovnikov *N*,*S*-acetal products. The significant advantages offered by this method are simple operation and mild experimental conditions that are compatible with various functionalities, Markovnikov regioselectivity, and moderate to very good yields of isolated *N*,*S*-acetal products. This methodology thus provides a very convenient and synthetically useful approach to preparing chemically useful *N*,*S*-acetals. Further studies on the mechanism and application of this methodology to the thiol selective conjugation of enamides and enecarbamates to Cysteine containing peptides and proteins are currently in progress.

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Supplementary Data
Supplementary data associated with this article can be found, in the online version, at

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Visible Light Photoredox-Catalyzed Hydrothiolation of Enamides and Enecarbamates

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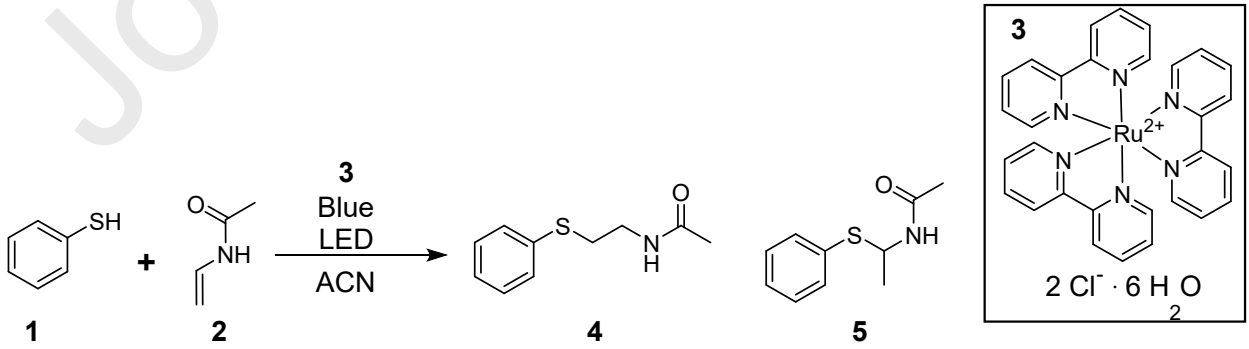
Highlights

- An efficient visible light photoredox-catalyzed thiol-ene reaction.
- Markovnikov selective thiole-ene reaction.
- Hydrothioaltion reaction of enamides and enecarbamates.
- This protocol is operationally simple, mild, and atom-economical.
- This process provides access to *N*,*S*-thioacetals from available thiols and a variety of enamides and enecarbamates.

Table 1: Initial and optimized reaction conditions.



Entry[a]	% Catalyst 3	Solvent	% Yield 4[b]	% Yield 5[b]
1	**5 %**	**ACN**	**0 %**	**75 %**
2	**5 %**	**DCM**	**0 %**	**45 %**
3	**5 %**	**THF**	**25 %**	**35 %**
4	**5 %**	**MeOH**	**25 %**	**25 %**
5	**5 %**	**10 X PBS**	**50 %**	**0 %**
6	**5 %**	**H_2O**	**55 %**	**0 %**
7	**2.5 %**	**ACN**	**0 %**	**60 %**
8	**2.5 %**	**H_2O**	**50 %**	**0 %**
9	**1%**	**ACN**	**0 %**	**80 %**
10	**1%**	**H_2O**	**55 %**	**0 %**
11	**0 %**	**ACN**	**0 %**	**0 %**
12	**0 %**	**H_2O**	**55 %**	**0 %**

b.) Reactions run with 1 mmol of **1** and **2** in 0.2M solvent for 18 hr with Blue LED light and monitored by TLC. b.) Isolated yield after column chromatography.

Figure 1. Biologically active Sulfur-containing compounds.

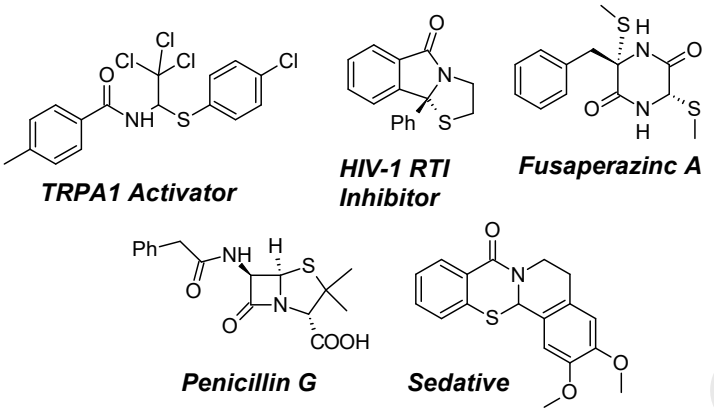
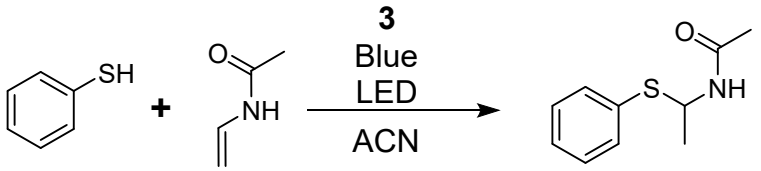


Table 2: Reaction optimization for compound **5**.

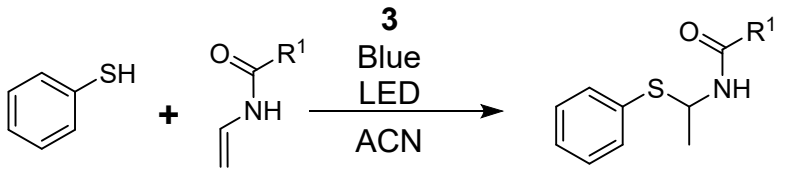


1 **2** **5**

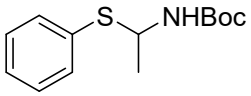
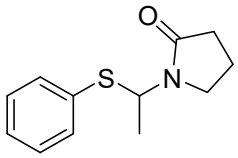
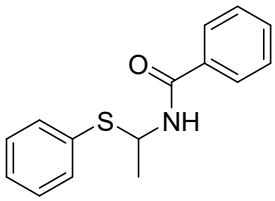
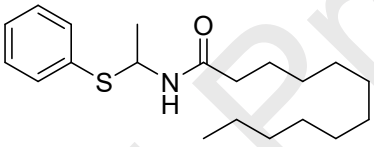
Entry	% Catalyst 3	Equiv 1	Equiv 2	Rxn Time (Hr)	% Yield 4[a]	% Yield 5[a]
1	**1 %**	**1.1**	**1.0**	**2**	**0 %**	**90 %**
2	**1 %**	**2.0**	**1.0**	**2**	**0 %**	**88 %**
3	**1 %**	**4.0**	**1.0**	**2**	**0 %**	**84 %**
4[b]	**1 %**	**1.1**	**1.0**	**2**	**0 %**	**86 %**
5[c]	**0 %**	**1.1**	**1.0**	**24**	**25 %**	**0 %**
6[d]	**0 %**	**1.1**	**1.0**	**24**	**25 %**	**0 %**
7[e]	**1 %**	**1.1**	**1.0**	**24**	**35 %**	**50 %**

All reactions run in 0.2 M ACN and monitored by TLC. a.) Isolated yields after column chromatography. b.) Reaction run at 10 mmol scale. c.) Reaction run with Blue LED and no catalyst. d.) Reaction run with no catalyst in the dark. e.) Reaction run with degassed solvent under inert atmosphere.

Table 3. Results for the hydrothiolation of different enamides and enecarbamates with thiophenol (**1**).

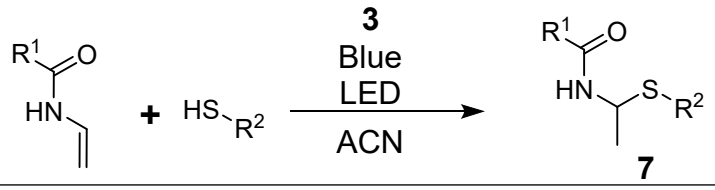


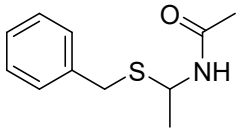
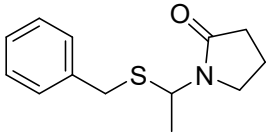
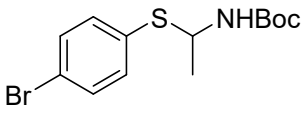
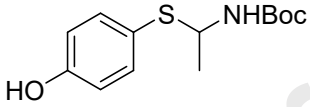
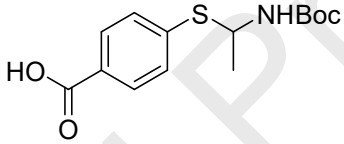
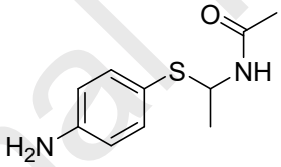
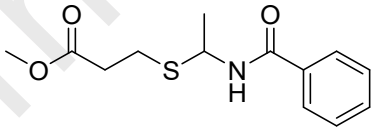
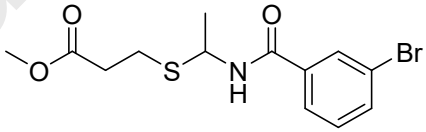
1 **6**

Entry	R	Product	% Yield
1		**6a**	**90 %**
2		**6b**	**93 %**
3		**6c**	**86 %**
4		**6d**	**75 %**

Reactions were run with 1.1 mmol of **1** and 1.0 mmol Enamide or Enecarbamate in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. Isolated yields after column chromatography.

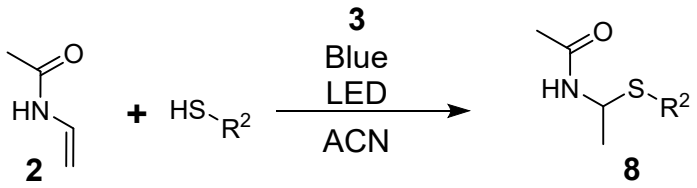
Table 4. Results for the hydrothiolation of different enamides and enecarbamates with various thiols.



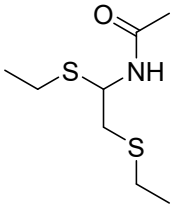
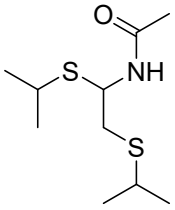
Entry	R	Product	% Yield[a]
1		7a	90 %
2		7b	92 %
3		7c	88 %
4		7d	80 %
5		7e	78 %
6		7f	73 %
7		7g	88 %
8		7h	85 %

Reactions were run with 1.1 mmol of Thiol and 1.0 mmol Enamide or Enecarbamate in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. a.) Isolated yields after column chromatography.

Table 5. Results for the hydrothiolation of **2** with alkyl thiols.

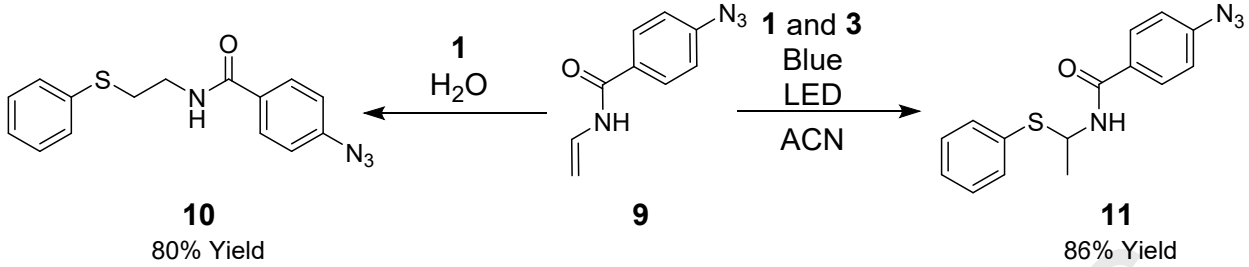


2 **8**

Entry	R	Product	% Yield[a]
1		**8a**	**40 %**
2		**8b**	**45 %**

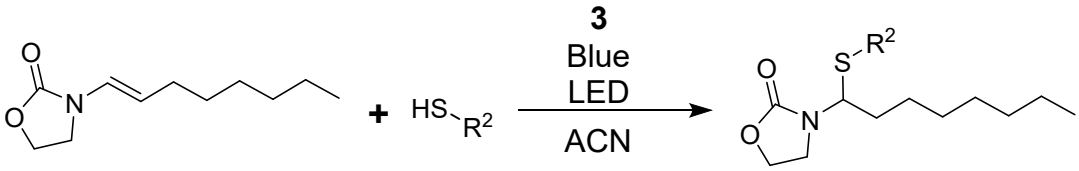
Reactions were run with 1.1 mmol of Thiol and 1.0 mmol Enamide or Enecarbamate in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. a.) Isolated yields after column chromatography.

Figure 2. Regiodivergent hydrothiolation of enamide **3** with thiophenol (**1**).

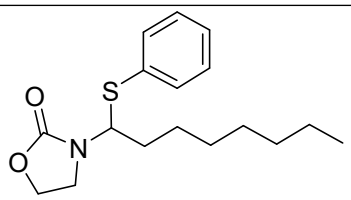
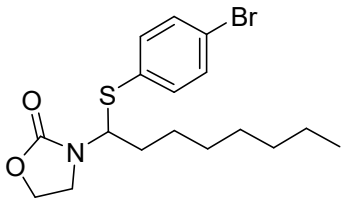
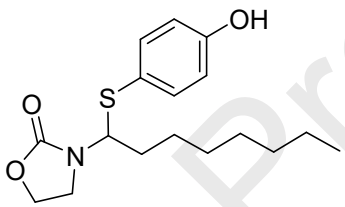
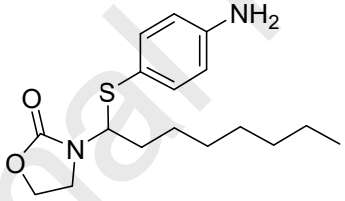
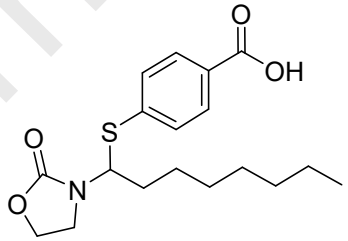
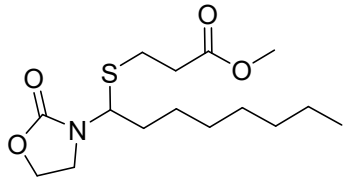


Reactions were run with 1.1 mmol of thiophenol (**1**) and 1.0 mmol enamide (**3**) in 0.2 M H_2O (**10**) for 18 hr or 0.2 M ACN with Blue LED light (**11**) for 18 hr and monitored by TLC. Isolated yields after column chromatography.

Table 6. Results for the hydrothiolation of different enamides and enecarbamates with various thiols.

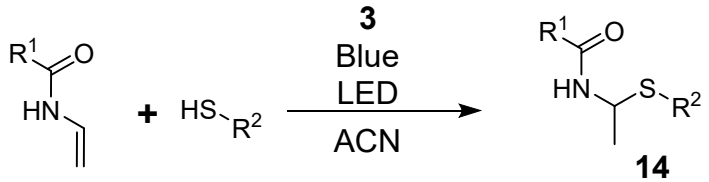


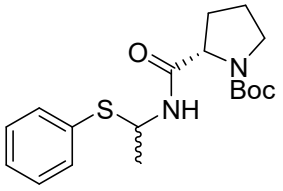
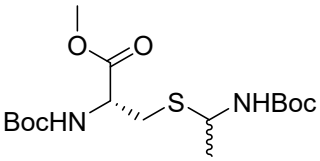
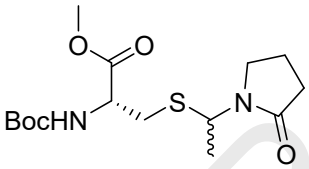
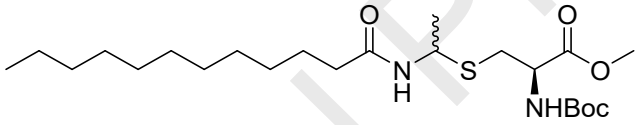
12 **13**

Entry	R	Product	% Yield[a]
1		**13a**	**92 %**
2		**13b**	**90 %**
3		**13c**	**80 %**
4		**13d**	**75 %**
5		**13e**	**78 %**
6		**13f**	**No Reaction**

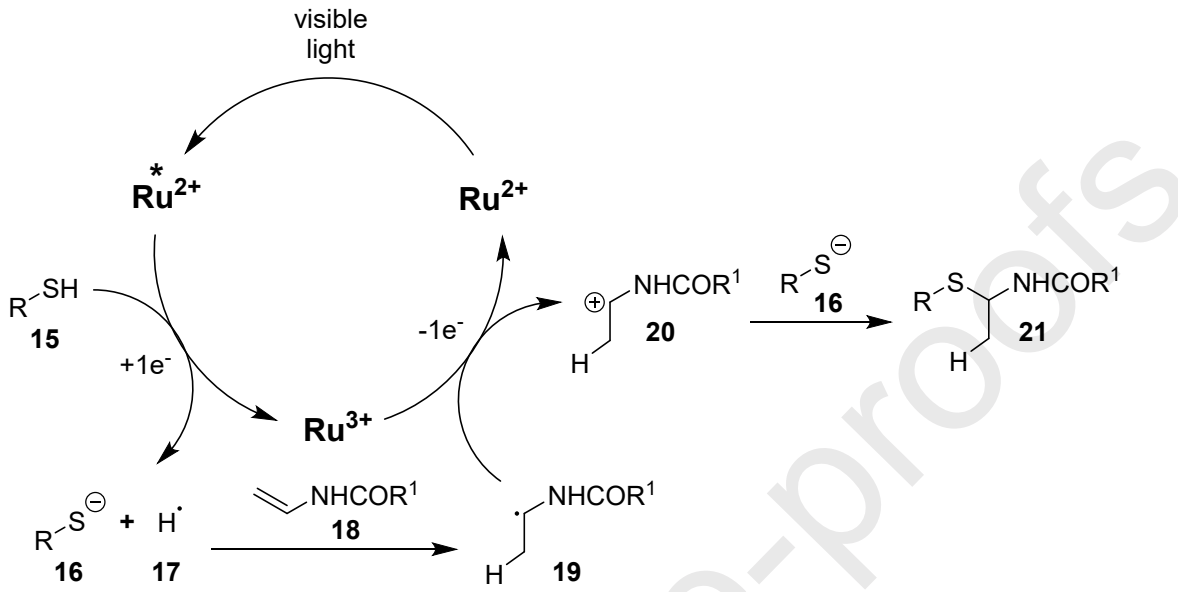
Reactions were run with 1.1 mmol of Thiol and 1.0 mmol Enamide in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. a.) Isolated yields after column chromatography.

Table 7. Results for the hydrothiolation of chiral enamides and enecarbamates with various thiols.



Entry	R	Product	Diasteriomer Ratio[a]	% Yield[b]
1		14a	2:1	65 %
2		14b	2:1	72 %
3		14c	1:1	80 %
4		14h	1:1	70 %

Reactions were run with 1.1 mmol of Thiol and 1.0 mmol Enamide or Enecarbamate in 0.2 M ACN with Blue LED light for 18 hr and monitored by TLC. a.) Diastereomer ratio of the crude product determined by NMR. b.) Isolated yields after column chromatography with no change in the diatereomer ratio.



Scheme 1. Proposed mechanism for the visible light photoredox catalyzed hydrothiolation reaction.

Graphical Abstract