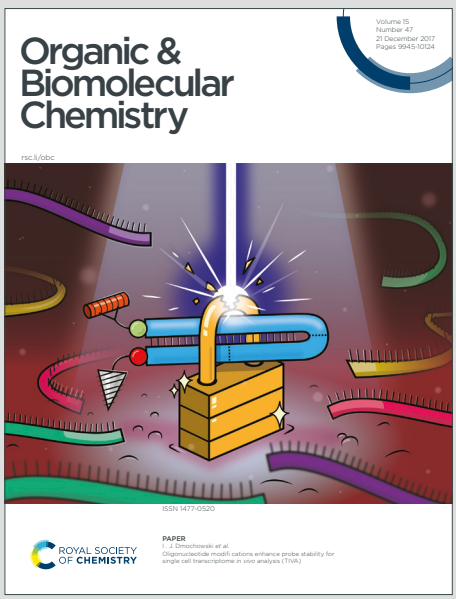
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. Ma, J. feng, K. Zhang, B. Zhang and D. Du, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB01349H.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/D0OB01349H

COMMUNICATION

Photoredox β-thiol-α-carbonylation of enones accompanied by unexpected Csp²-C(CO) bond Cleavage

Received 00th January 20xx,
Accepted 00th January 20xx

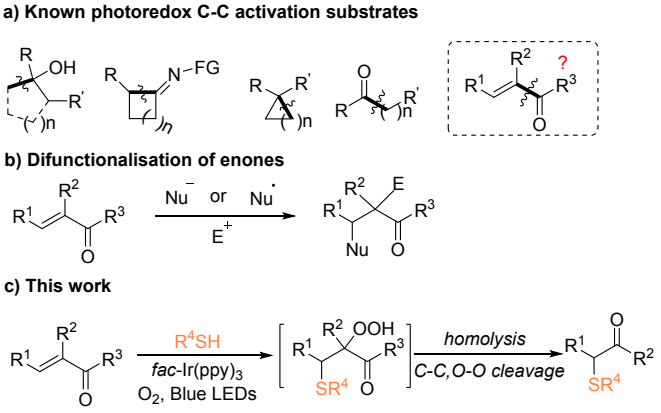
DOI: 10.1039/x0xx00000x

Rui Ma[a], Jie Feng,[a] Kuili Zhang[a], Beichen Zhang[a] and Ding Du[a]*

An olefinic difunctionalization method of enones was presented here via aerobic visible-light catalysis. A novel reactivity was showcased in conjunction with the selective Csp²-C(CO) bond activation of enones, which provided a convenient method for preparation of various β-thiolated-α-functionalized compounds. Moreover, preliminary mechanism investigation indicated that a β-peroxysulfides intermediate was formed under the promotion of visible light under oxygen atmosphere, which finally induced the unexpected C-C bond cleavage.

Olefin difunctionalization has been drawing much attention in the field of synthetic methodology, as it provides a synthetically useful route to introduce two functionalized substituents simultaneously[1]. Among them, α,β-vicinal difunctionalization of activated olefins, typically like enones (or enals), is a standard tactic in organic synthesis, which is utilized for multicomponent assembly of synthetic fragments in one single step.[2] Enones are well known as excellent Michael acceptors,[3] however, great advances have been achieved for radical-pathway or transition-metal-catalyzed difunctionalizations of enones, such as halofunctionalization,[2b] acyl-azidation,[4] hydroxysulfenylation[5] etc.,[6] affording various α,β-difunctionalized ketones (Scheme 1b).

Meantime, the C-C bond activation and subsequent functionalization are particularly important in simplifying the synthetic routes for assembling complex molecules and constructing functionalized compounds from readily-available starting materials.[7] In recent years, photo-redox C-C bond activation reactions have emerged as a versatile and powerful method, enabling the construction of targeted product under ambient conditions.[8] Until now, one of the common photo-redox strategies to facilitate C-C bond activation is the utilization of strained molecules, typically like 3-5 membered ring compounds.[8b,8d-8f] Besides that, radical reactions via hydrogen atom transfer (HAT) or proton-coupled electron transfer (PCET) strategies are always employed to promote the C–C bond cleavage (Scheme 1a).[8a,8g] Although great pioneering works have been made in this field, activation of specific C-C bonds remains largely underexplored. In Particular, for enone substrates, most previous literatures focused on olefinic difunctionalizations. Selective Csp²-C(CO) σ-bond cleavage of enones are rarely reported due to the existence of vinylogous reactivity and conjugated structure.[9] Therefore, a general solution to the challenging Csp²-C(CO) σ-bond activation of enones for further constructing functionalized molecules would be meaningful. Herein, we wished to report a visible-light and oxygen promoted method for β-thiol-α-carbonylation of enones accompanied by selective Csp³-C(CO) σ-bond cleavage (Scheme 1c).



Scheme 1. Enone difunctionalization and overview of this work

At the start of this work, the model reaction of thiophenol **1a** with benzalacetophenone **2a** was carried out under oxygen atmosphere (Figure 1). To our interest, unexpected β-thiolative-α-aldehyde **3a** was monitored in less than 10% yield (Figure 1, column 2, blue). As a comparison, no product **3a** was observed under argon conditions (Figure 1, column 1, blue). So, oxygen was crucial to this transformation. The addition of photo catalyst *fac*-Ir(ppy)$_3$ and conducting the reaction under

[a] State Key Laboratory of Natural Medicines, Department of Organic Chemistry, China Pharmaceutical University, No. 24 Tongjiaxiang Road, Nanjing, 210009, P.R. China. E-mail: ddmn9999@ cpu.edu.cn

† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

white LEDs irritation significantly improved the yield of **3a** (Figure 1, column 3, blue).

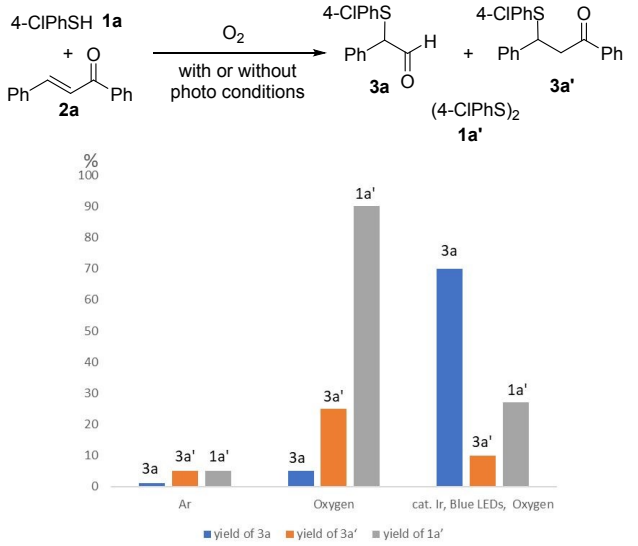
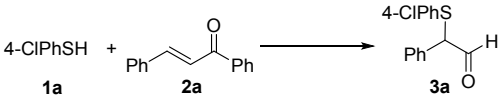


Figure 1. Primary reaction condition screening for *β*-thiol-*α*-carbonylation of enone **2a**. Reaction conditions: 4-chlorothiophenol (0.4 mmol), chalcone (0.2 mmol), photocatalyst (0.004 mmol), O_2 balloon, 23W white LEDs, solvent 4 mL, RT, 4 h. Yield was determined by ^{1}H NMR.

Next, Different photo-catalysts and light irradiations were screened successively (Table 1, entries 1-7). The NMR yield could boost to 82% using fac-Ir(ppy)$_3$ as photo-catalyst under blue LED irradiation (Table 1, entry 7). Other photocatalysts were inferior to *fac*-Ir(ppy)$_3$ (Table 1, entries 2-6). Further screening of the light wavelength identified the blue LEDs as the best light source (Table 1, entry 7). Next, solvent effect proved to be crucial for the observed reactivity, and CH_3CN emerged as the best choice (Table 1, entry 7). Moderate yields

Table 1 Optimal condition screening for β-thiol-α-carbonylation of enone **2a**[a]

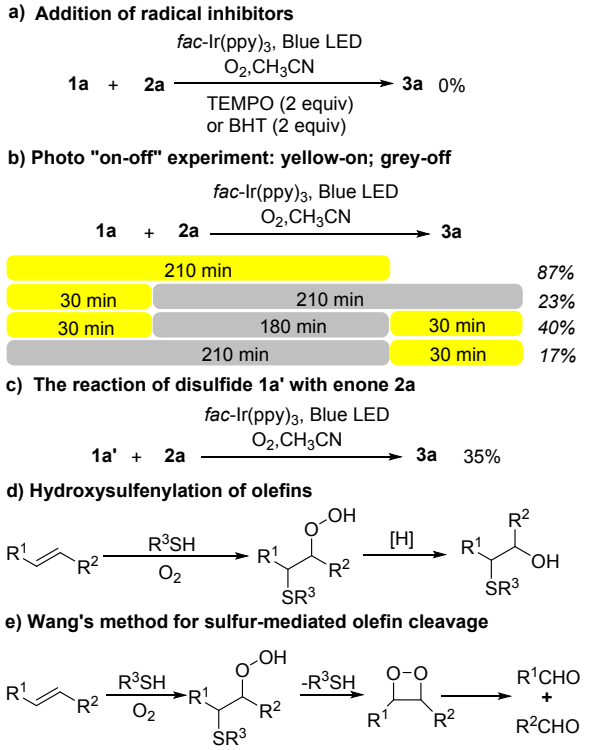


Entry	PC*	Light/LEDs	Solvent	Yield/%[b]
1	*fac*-Ir(ppy)$_3$	White LED	CH_3CN	68
2	Ru(bpy)$_3$Cl$_3$	White LED	CH_3CN	0
3	Eosin Y	Green LED	CH_3CN	Trace
4	Eosin B	Blue LED	CH_3CN	0
5	ACR-Mes	Blue LED	CH_3CN	Trace
6	Methylene Blue	Blue LED	CH_3CN	30
7	*fac*-Ir(ppy)$_3$	Blue LED	CH_3CN	82
8	*fac*-Ir(ppy)$_3$	Blue LED	Toluene	54
9	*fac*-Ir(ppy)$_3$	Blue LED	DCM	50
10	*fac*-Ir(ppy)$_3$	Blue LED	MeOH	Trace
11	*fac*-Ir(ppy)$_3$	Blue LED	THF	17

[a]Reaction conditions: 4-chlorothiophenol **1a** (0.4 mmol), chalcone **2a** (0.2 mmol), photocatalyst (0.004 mmol), O_2 balloon, light, solvent (4 mL), RT, 4 h. [b] Yield was determined by ^{1}H NMR using mesitylene as internal standard.

could be obtained with toluene and dichloromethane (Table 1, entries 8 and 9). When protic solvent MeOH was used, only hydrothiolation byproduct was obtained (Table 1, entry 10) .

Encouraged by these results, great interests have been aroused to understand the possible mechanism involved. Thiophenol is known to be " auto-oxidized " to form mercapto radical under aerobic conditions.[10] Alternatively, mercapto radical can also be initiated via photo-redox catalysis.[11] Radical inhibitors TEMPO and BHT were then added to the model reaction, respectively. As a result, product **3a** was not observed for both two reagents (Scheme 2a). After that, a photo "on-off" experiment was conducted (Scheme 2b). Model reaction with photocatalyst was firstly treated under Blue LEDs irradiation for 30 mins and then without the light irradiation for another 210 mins, and 23% yield was obtained. Reversely, if the reaction was irradiated for the last 30 mins, the yield would drop to 17%. As a comparison, when model reaction was irradiated at both the first and last 30 mins, 40% yield was obtained. It indicated that photocatalyst along with Blue LEDs was the main driving force to this reaction. Actually, in this reaction, thiophenol **1a** would be quickly transformed to disulfides **1a'** in the presence of oxygen (Figure 1, column 2, grey). While, in the presence of photocatalyst and light irradiation, the formed disulfides **1a'** can relay generating the product **3a** (Scheme 2c).

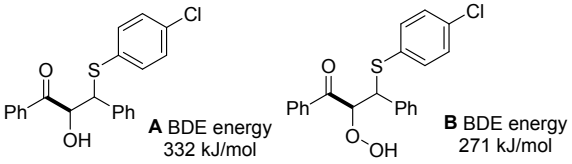


Scheme 2. Control experiments and relative literature reports

In classic enone hydrothiolation reactions, mercapto radical was added to *β*-position of enone to get Michael-addition product. In this work, similar pathway may occur with mercapto radicals adding to enones. Meantime, in some pioneering work[12] and our previous work,[13] hydroxysulfenylation of terminal olefins have proven to be an efficient pathway to afford *β*-hydroxysulfides (Scheme 2d).

DOI: 10.1039/D0OB01340H

These processes were considered to undergo through *β*-peroxysulfide radical intermediates which were subsequently reduced to *β*-hydroxysulfides. Likewise, for non-terminal olefins, Wang group reported that similar *β*-peroxysulfide intermediates could proceed olefinic C-C cleavage after the abandon of the thiophenol part (Scheme 2e)[12c]. Therefore, it can be anticipated that *β*-benzoyl-*β*-hydroxysulfides **A** or *β*-benzoyl-*β*-peroxysulfides **B** may be the potential reaction intermediate in this process (Scheme 3).



Scheme 3. Possible reaction intermediates and their C-C BDE energy

Comparatively, *β*-hydroperoxysulfide **B** is a preferred candidate as the calculated C-C BDE energy of *β*-hydroperoxysulfides is significantly weaker than its counterpart *β* -hydroxysulfide **A** (271 KJ/mol vs 332 KJ/mol, Scheme 3). Moreover, calculation using Gaussian 09 has been made to further support the assumption. As illustrated in Figure 2, the bold C-C bond of hydroperoxide **B** was extended to 2.07 Å and the energy barrier was only 5.7 kcal/mol. According to the calculation results, the homolytic C-C and O-O cleavage of hydroperoxide may occur to give the product **3a**, hydroxyl radical and benzoyl radical. In this reaction, both benzaldehyde and benzoic acid were observed. Benzaldehyde may come from the protonation of benzoyl radical and benzoic acid may come from the combination of hydroxyl radical with benzoyl radical.

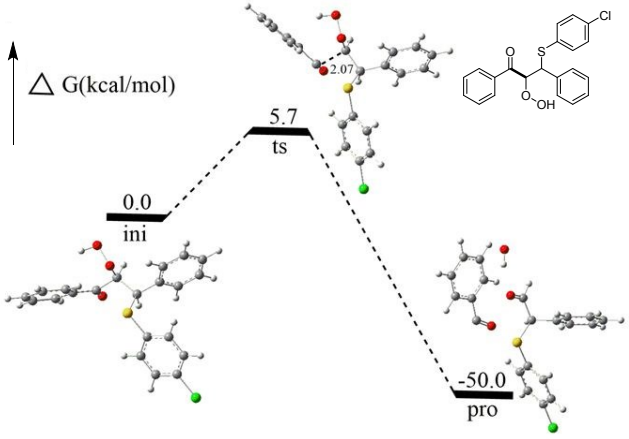


Figure 2. Theoretical calculation for the possible reaction intermediate **B**

Based on the above results, possible mechanism was shown in Figure 3. Mercapto radical was generated by auto-oxidation or photo oxidation of thiophenol **1a**. Along with the reaction process, the formed disulfide can be also transformed to mercapto radical with aid of photo-redox catalytic cycle. *β*-Peroxysulfide radical intermediate **D** was then formed via the addition of thiyl radical to enone **2a** followed by capturing oxygen under aerobic condition.[12d] Radical intermediate **D** was further protonated to give intermediate B, which undergoes homolysis C-C and O-O bond cleavage to yield product **3a** and some observed byproducts. As for the photo-redox cycle, Ir(III) was activated under the visible light irritation, activated Ir(III) was reduced to Ir(II) with thiopheol. Last, intermediate **D**, the formed H_2O_2 or disulfides **1a'** may oxidize Ir(II) to regenerate the Ir(III) photocatlyst. Another byproduct **3a'** was supposed to be generated through protonation of intermediate **C**.

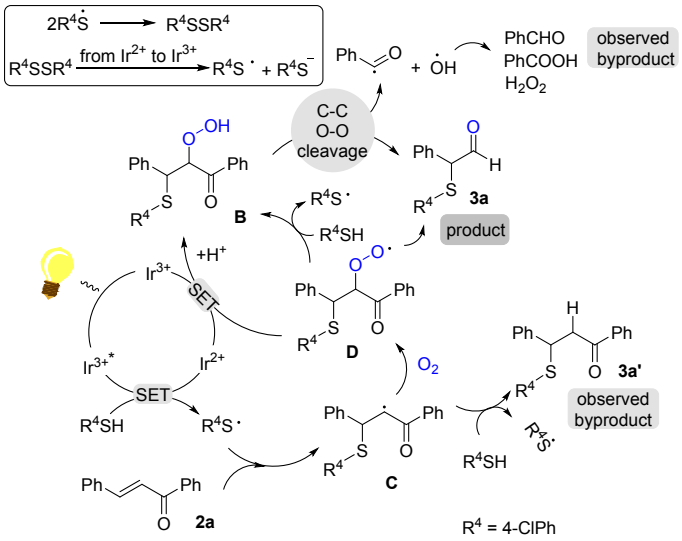
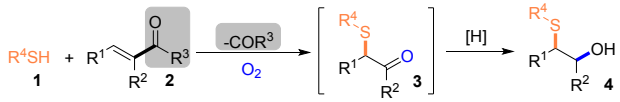


Figure 3. Possible reaction mechanism

With the optimal conditions in hand and preliminary understanding of the mechanism, the substrate scope was then investigated. During the research, although the α-thiolaldehyde **3a** could be isolated via flash column separation, **3a** was not stable under air atmosphere. It was difficult to store the sample and take test. Therefore, an extra reduction process with $NaBH_4$ was conducted to yield more stable β-hydroxysulfides **4** (Table 2). First, some commercially available thiophenols bearing various substituents were used to react with benzalacetophenone **2a.** Thiophenols with substituents at different positions showed good tolerance to give products **4a-e** in moderate to good yields (entries 1-5). However, representative alkyl thiols were not suitable for this reaction as hydrothiolation products **3f'** and **3g'** instead of the desired products were obtained without $NaBH_4$ reduction (entries 6 and 7). It may be explained that aliphatic thiols had higher S-H bond BDE energy, which would be more difficult to be initiated to form relative radicals. Meantime, competitive Michael addition to enones was in priority because the aliphatic thiols usually have higher nucleophilicity than thiophenols. As for heterocyclic thiophenol (entry 8), only trace of starting material was transformed to product. In terms of the enones **2**, similar high yields were given when R^3 was phenyl group or steric 2-methoxyl phenyl group (entry 9). However, a significantly decreased yield was obtained when R^3 was an alkyl group (entry 10). α,β-Unsaturated ester was also found to be unsuitable due to the low conversion of the substrate (entry 11). As the acyl group acts as a leaving group that has no influence on the product structure, R^3 was set as phenyl

group in the following screening process. The reaction was amenable to substituted benzalacetophenones, affording the corresponding products **4i**-**4o** in the average yield of 80% (entries 12-18). Interestingly, 4-Br and 3-CN substituted substrates showed significantly decreased yields under the standard conditions, but replacement of benzalacetophenone with 2-methoxyl benzalacetophenone could increase the yields of **4p** and **4q** to 69% and 76%, respectively (entries 19-22). Additionally, 2-naphthyl substituted substrate was also tested, and the desired product **4r** was obtained in 68% yield (entry 23). The product for the 4-pyridyl substrate can be tracked but failed to be isolated due to the low transformation efficiency and instability of product (entry 24). When 3-cyclohexyl-1-phenylprop-2-en-1-one was used as the enone substrate, the desired product **4t** was also obtained in a moderate yield (entry 25). Furthermore, two α-substituted benzalacetophenones were tested. The reaction of α-methyl benzalacetophenone afforded desired product **3u** in 60% yield without $NaBH_4$ work-up (entry 26).

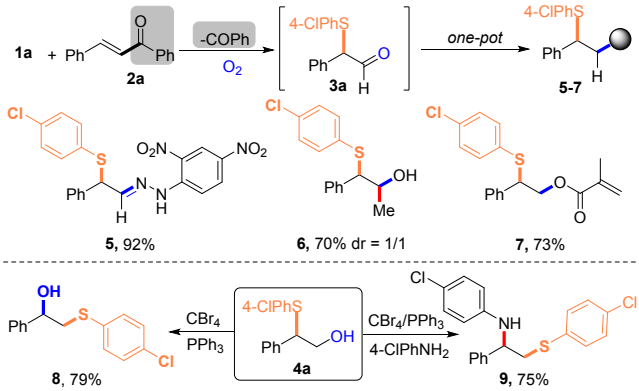
Table 2. Substrate scope for β-thiol-α-carbonylation of enone[a]



Entry	R^4	R^1	R^2	R^3	Product	Yield/%
1	4-ClPh	Ph	H	Ph	**4a**	82
2	3-MePh	Ph	H	Ph	**4b**	76
3	2-CO_2MePh	Ph	H	Ph	**4c**	62
4	4-MePh	Ph	H	Ph	**4d**	68
5	4-*t*BuPh	Ph	H	Ph	**4e**	80
6	Cyclohexyl	Ph	H	Ph	**3f'**	30[b,c]
7	*n*-Bu	Ph	H	Ph	**3g'**	25[b,c]
8	4-Pyridyl	Ph	H	Ph	**4h**	trace
9	4-ClPh	Ph	H	2-OMePh	**4a**	80
10	4-ClPh	Ph	H	Me	**4a**	38
11	4-ClPh	Ph	H	OMe	**4a**	trace
12	4-ClPh	4-FPh	H	Ph	**4i**	74
13	4-ClPh	4-MePh	H	Ph	**4j**	82
14	4-ClPh	4-*t*BuPh	H	Ph	**4k**	80
15	4-ClPh	4-ClPh	H	Ph	**4l**	84
16	4-ClPh	3-MePh	H	Ph	**4m**	86
17	4-ClPh	3-ClPh	H	Ph	**4n**	79
18	4-ClPh	2-ClPh	H	Ph	**4o**	83
19	4-ClPh	4-BrPh	H	Ph	**4p**	13
20	4-ClPh	4-BrPh	H	2-OMePh	**4p**	79
21	4-ClPh	3-CNPh	H	Ph	**4q**	46
22	4-ClPh	3-CNPh	H	2-OMePh	**4q**	76
23	4-ClPh	2-naphthyl	H	Ph	**4r**	68
24	4-ClPh	4-Pyridyl	H	Ph	**4s**	trace
25	4-ClPh	Cyclohexyl	H	Ph	**4t**	60
26	4-ClPh	Ph	Me	Ph	**3u**	60[c]

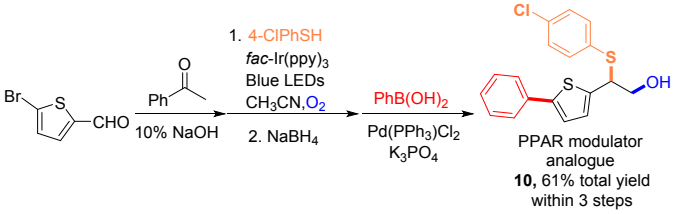
[a] Reaction conditions: thiols (0.4 mmol), enones (0.2 mmol), O_2 balloon, photocatalyst (0.004 mmol), CH_3CN (4 mL), blue LED, RT, 4 h, followed by $NaBH_4$ (0.6 mmol), isolated yield. [b] Yield of hydrothiolation product **3'**. [c]Without $NaBH_4$ workup.

The present method also provided a convenient pathway to synthesize various α-thiolaldehyde derivatives (Scheme 4). For example, one-pot condensation of **3a** with 2,4-dinitrophenylhydrazine afforded hydrazone **5** in overall 92% yield. Treatment of the reaction mixture with methyl Grignard regent can afforded higher order β-thiolative-α-alcohol **6**. Sequential reduction and esterification of intermediate **3a** in one pot afforded product **7** in overall 73% yield. Notably, additional separation process is not necessary for the above reactions. Additionally, treatment of **4a** with a brominating reagent and a nucleophilic reagent also allows for the 1,2-sulfur migration reaction. For instance, product **8** can be accessed with the addition of CBr_4 and PPh_3; dehydroxylated amination product **9** was achieved in the presence of CBr_4/PPh_3 and aniline. Thus, the developed method can serve as alternative access to α-thiolated derivatives, avoiding pre-synthesis of unstable α-thiolaldehyde.



Scheme 4. Functionalization of **3a** to afford α-thiolated derivatives

Another feature of this photo-catalyzed protocol is the opportunity for potential drug molecule skeleton synthesis (Scheme 5). For example, starting from commercially available 5-bromothiophene-2-carbaldehyde, synthesis of PPAR modulators molecule[14]could be easily accessed via sequential aldol condensation, this developed photo-catalysis reaction and Suzuki-Miyuara coupling to afford product **10** in 61% total yield.



Scheme 5. Synthesis of PPAR modulator analogue with the developed method.

In summary, a photoredox sulfenylcarbonylation method of enones is reported. This method fulfills the simultaneous C-S coupling, oxidation, C-O coupling and Csp^2–C(CO) σ-bond cleavage in one pot. Preliminary mechanistic studies indicate the potential radical pathway and highlight the potential homolytic C-C and O-O cleavage. Moreover, the procedure is

attractive from the application perspective, as evidenced by the ability for construction of various α-thiolated derivatives.

Acknowledgements

This work is funded by the National Natural Science Foundation of China (Nos. 21572270, 21702232), the "Double First-Class" University Project (CPU2018GY02 and CPU2018GY35).

Conflicts of interest

There are no conflicts to declare

Notes and references

1 a) Q. Fu, Z.Y. Bo, J. H. Ye, T. Ju, H. Huang, L. L. Liao, D. G. Yu, *Nature Commun*. 2019, **10**, 1; b) S. Y. Hong, S. Chang, *J. Am. Chem. Soc.* 2019, **141**, 10399; c) M. W. Campbell, J. S. Compton, C. B. Kelly, G. A. Molander. *J. Am. Chem. Soc.* 2019, **141**, 20069; d) J. Hou, A. Ee, H. Cao, H.-W. Ong, J.-H. Xu, J. Wu, *Angew. Chem. Int. Ed.* 2018, **57**, 17220; e) H. Mei, Z. Yin, J. Liu, H. Sun, J. Han, *Chin. J. Chem.*, 2019, **37**, 292; f) Z. Luo, Y. Meng, X. Gong, J. Wu, Y. Zhang, L. Ye, C. Zhu, *Chin. J. Chem.* 2020, **38**, 173; g) Z. Zhang, L. Gong, X.-Y. Zhou, S.-S. Yan, J. Li, D. G. Yu, *Acta Chim. Sinica,* 2019, **77**, 783; h) J.-J. Zhong, Q.-Y. Meng, B. Chen, C.-H. Tung, L.-Z. Wu, *Acta Chim. Sinica*, 2017, **75**, 34-40; i) Y. Chen, L.-Q. Lu, D.-G. Yu, C.-J. Zhu, W.-J. Xiao, *Sci. Chin. Chem.* **62**, 2019, 24.

2 a) Y. Cai, X. Liu, P. Zhou, X. Feng, *J. Org. Chem.* 2019, **84**, 1; b) H. Wang, L. Zhang, Y. Tu, R. Xiang, Y. Guo, J. Zhang, *Angew. Chem., Int. Ed.* 2018, **57**, 15787; c) Y. Lan, X.-H. Chang, P. Fan, C.-C. Shan, Z.-B. Liu, T.-P. Loh, Y.-H. Xu, *ACS Catal.* 2017, **7**, 7120. c) X. Sun, S. Yu, *Chin. J. Org. Chem.* 2016, **36**, 239.

3 a) J. L. Fulton, M. A. Horwitz, E. L. Bruske, J. S. Johnson, *J. Org. Chem.* 2018, **83**, 3385; b) A. Alexakis, J. E. Bäckvall, N. Krause, O. Pàmies, M. Diéguez, *Chem. Rev*. 2008, **10**, 2796.

4 L. Ge, Y. Li, H. Bao, *Org. Lett.* 2019, **21**, 256.

5 H. Xi, B. Deng, Z. Zong, S. Lu, Z.-P. Li *Org. Lett.* 2015, **17**, 1180.

6 a) S. R. Chemler, M. T. Bovino, *ACS Catal*. 2013, **3**, 1076; b) P. Zhou, X. Liu, W. Wu, C. Xu, X.-M. Feng, *Org. Lett.* 2019, **21**, 1170; c) T. Courant, G. Masson, *J. Org. Chem.* 2016, **81**, 6945;

7 a) Z. Nairoukh, M. Cormier, I. Marek, *Nat. Rev. Chem.* 2017, **1**, 35; b) S. P. Morcillo, *Angew. Chem., Int. Ed.* 2019, **58**, 14044; c) J. Zhu, J. Wang, G. B. Dong, *Nature Chem.* 2019, **11**, 45.

8 For selected recent references see: a) L. Huang, T. Ji, M. Rueping, *J. Am. Chem. Soc.* 2020, ***142***, 3532; b) S. Sakurai, S. Tsuzuki, R. Sakamoto, K. Maruoka, *J. Org. Chem.* 2020, **85**, 3973-3980; c) M. Lubbesmeyer, E. G. Mackay, M. A. R. Raycroft, J. Elfert, D. A. Pratt, A. Studer, *J. Am. Chem. Soc.* 2020, ***142***, 2609; d) E. M. A. Ahmed, A. M. Y. Suliman, T. J. Gong, Y. Fu, *Org. Lett.* 2020, **22**, 1414; e) J. X. Yu, F. Teng, J. N. Xiang, W. Deng, J. H. Li, *Org. Lett.* 2019, ***21***, 9434.

9 a) Y. Zhou, C. Rao, S. Mai, Q. Song, *J. Org. Chem.* 2016, **81**, 2027; b) T. W. Pouambeka, G. Zhang, G.-F. Zheng, G.-X. Xu, T. Xiong, Q. Zhang, *Org. Chem. Front.*, 2017, **4**, 1420.

10 S. Zhou, X. Pan, Z. Zhou, A. Shoberu, J. Zou, *J. Org. Chem.* 2015, **80**, 3682.

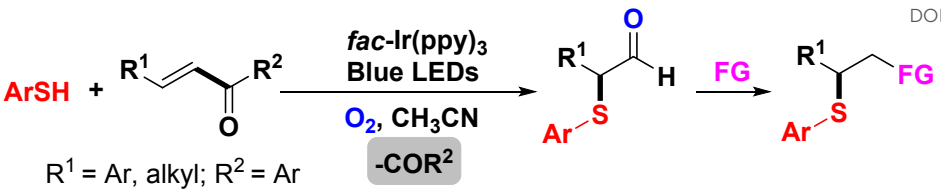
11 H. Wang, Q. Lu, C. Qian, C. Liu, W. Liu, K. Chen, A. W. Lei, *Angew. Chem. Int. Ed.* 2016, **55**, 1094.

12 a) R. He, X. Chen, Y. Li, Q. Liu, C. Liao, L. Chen, Y. Huang, *J. Org. Chem.*2019, **84**, 8750; b) B. Du, Y. Wang, H. Mei, J. Han, Y. Pan, *Adv. Synth. Catal.* 2017, **359**, 1684; c) Y. Deng, X.-J. Wei, H. Wang, Y. Sun, Ti. Noi, X. Wang, *Angew. Chem. Int. Ed.* 2017, **56**, 832.

13 B. Zhang, T. Liu, Y. Bian, T. Lu., J. Feng, *ACS Sustain. Chem. Eng*. 2018, **6**, 2651.

14 N. B. Mantlo, X. Wang, G. Zhu, *PCT Int. Appl.*, 2004, 2004063184.

View Article Online
DOI: 10.1039/D0OB01349H



R^1 = Ar, alkyl; R^2 = Ar

- Unexpected aerobic enone difunctionalization
- Method for α-thiolative-β-functions
- Homolytic C-C and O-O cleavage