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Visible light-mediated selective α-functionalization of 1,3-dicarbonyl compounds *via* disulfide induced aerobic oxidation†

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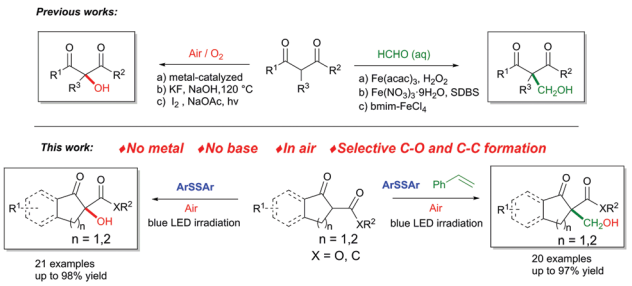
A visible light-mediated α-functionalization of 1,3-dicarbonyl compounds with switchable selectivity induced by disulfide is disclosed. Upon irradiation with visible light, the metal- and base-free α-hydroxylation or α-hydroxymethylation reaction proceeded smoothly through a disulfide-catalyzed oxidation under mild conditions. The combination of a continuous-flow strategy could further improve the reaction efficiencies.

Direct C–C and C–O bond formation *via* α-functionalization of 1,3-dicarbonyl compounds provides a powerful synthetic strategy for the construction of organic compounds.[1a] For many years, research in this field has largely focused on the invention of new catalysts and the optimization of their performance to achieve high conversions and/or selectivities.[1b] However, inspired by nature,[2] chemists are beginning to turn their attention to the development of a switchable selectivity chemical process.[3] Alternatively, metal-free visible light-mediated aerobic oxidation is an appealing environmentally friendly method which has offered an attractive and energy-saving platform in comparison to the traditional oxidation processes. Although a significant number of transition-metal-catalyzed hydroxylation and hydroxymethylation reactions of 1,3-dicarbonyl compounds have been developed,[4,5] practical and efficient α-functionalization with molecular oxygen as the terminal oxidant and oxygen source are still desirable. Recently, the field of disulfide and thiol catalysis has grown rapidly,[6] partly because these reagents can serve as a hydrogen-atom-transfer (HAT) cocatalyst in photo-redox catalysis.[7] Recently, disulfide-catalyzed visible light-mediated oxidative cleavage of C=C bonds has been reported by Wang and their experimental and computational studies suggested that an olefin-disulfide EDA complex exists.[7p] Therefore, as part of our studies on visible light-induced green chemical reactions and inspired by the reported results,[7,8] we audaciously envisioned visible light-mediated readily tunable and chemoselective transformations in the α-functionalization of 1,3-dicarbonyl compounds induced by disulfide (Scheme 1).



Scheme 1 Approaches to α-functionalization of 1,3-dicarbonyl compounds.

Initially, the visible light-mediated disulfide catalyzed hydroxylation protocol was probed with 1-indanone-derived β-keto ester (**1a**) as the model substrate. When diphenyl disulfide (**2a**) was present, the reaction proceeded smoothly and formed the desired α-hydroxylation product (**3a**) in 31% yield (Table 1, entry 1). Notably, we observed none of the desired products in the absence of disulfide or visible light (Table 1, entries 2 and 3), demonstrating the requirement of both components in this protocol. Various light sources were then applied to the model reaction. We chose a 10 W blue LED (450–455 nm) as the best light source. The substituent groups of the aromatic ring in the disulfides could influence the reaction results (Table S2, entries 1–8, ESI†). When the *para*-positions of the disulfides contain electron-withdrawing groups it will improve the yield; for example, bis(4-fluorophenyl)disulfide (**2d**) could afford a better 56% yield (Table 1, entry 4). Unexpectedly, when the reaction proceeded in DMF (with **1a** 0.025 M), 96% yield could be observed (Table 1, entry 6). We further investigated the application of this visible light-mediated disulfide-catalyzed activation of molecular oxygen for aerobic dehydrogenation coupling reactions. While examining the alkylation between β-keto esters and olefins in the presence of **1a** and 10 W blue LED irradiation, we serendipitously discovered that the presence of styrene leads predominantly to the α-hydroxymethyl β-keto ester rather

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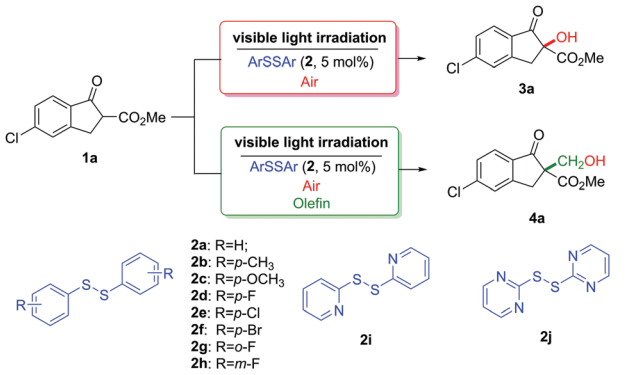
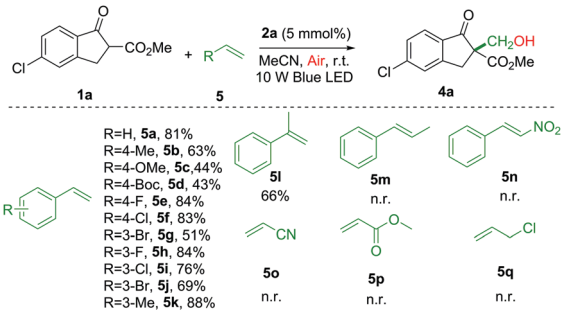
Table 1 Selected optimization of the reaction conditions[a]



Entry	Alteration	Yield[b] [%] 3a	4a
1[c]	None	31	N.R.
2	No light (dark) or no air	N.R.	N.R.
3[c]	No disulfide **2a**	Trace	N.R.
4[d]	**2d** instead of **2a**	56	N.R.
5[d]	**2d** instead of **2a**, DMF instead of PhMe	89	N.R.
6	**2d**, DMF, **1a** (0.025 M)	96	N.R.
7[e]	Styrene	N.R.	81[f], 88[g], 95[h]
8[c,e]	Styrene; no light, no **2a** or no air	N.R.	N.R.

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), disulfide **2a** (5 mol%), and 2.0 mL PhMe in a quartz tube at room temperature under the irradiation of a 10 W blue LED for a given time. Meanwhile, the solution was bubbled with an air pump. [b] Yield determined by ^{1}H-NMR. [c] 3 W white LED. [d] 3 W blue LED. [e] MeCN. [f] **5a** (1.5 equiv.), 24 h. [g] **5a** (1.5 equiv.), O_2 balloon, 24 h. [h] **5a** (10 equiv.), 4 h.

than the cross-dehydrogenative coupling product (Table 1, entry 7). As the amount of styrene **5a** increased, the yield of the reaction is increased while the reaction time is greatly shortened. We next evaluated the activity of some commonly employed olefins and a variety of solvents for the hydroxymethylation of the 1-indanone-derived β-keto ester **1a**. Unfortunately, due to the basic reaction conditions in combination with the disulfide and visible light irradiation, the hydroxylation product was observed (**5o**, **5p** and **5q**). Therefore, we recognized that judicious selection of a styrene would be necessary to suppress the formation of this unwanted byproduct without obstructing the desired photocatalytic hydroxymethylation reaction pathway. When the phenyl ring of the styrene has a halogen substitution on the *para*- or *meta*-position, the yields will fluctuate (**5e–5j**, 51–84% yield). When electron-donating methyl or methoxyl groups were introduced to the *para*-position of the aromatic ring, lower yields were observed (**5b–5c**, 44–63%). The yield declined to 43% when the Boc group was on the *para*-position of the styrene and the yield slightly fluctuated for the 3-methyl substituted styrene. 1,2-Disubstituted olefins, such as β-nitrostyrene and β-methylstyrene, were also examined; however, the desired hydroxymethylation product **4a** was not formed after 24 h (Scheme 2). A series of control experiments omitting each individual reaction component highlighted the importance of the disulfide, aromatic terminal alkenyl derivatives and visible light for achieving this general hydroxymethylation reaction protocol accomplished by the oxidative cleavage of C=C double bonds (Tables S4 and S5, ESI†).

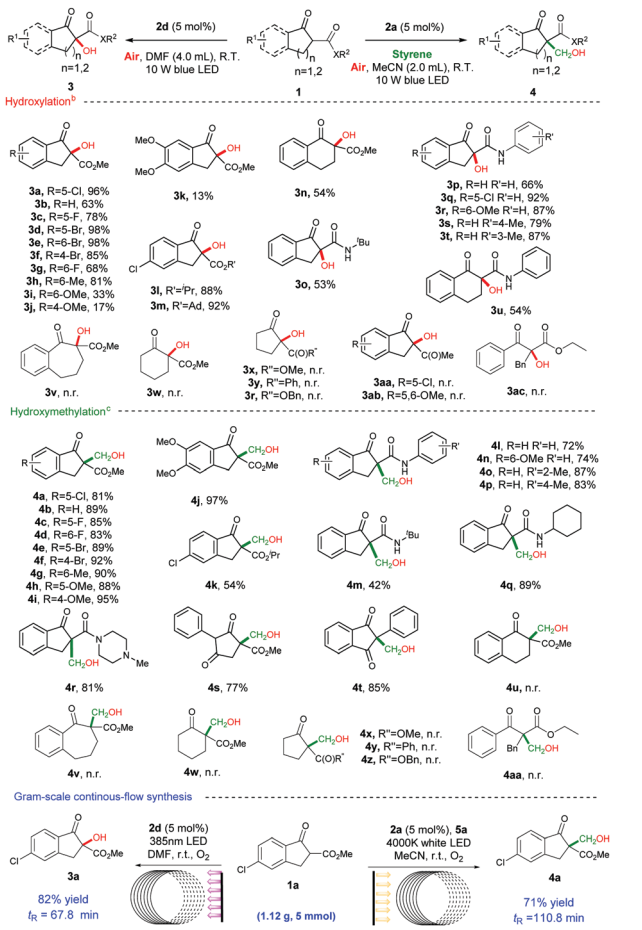


Scheme 2 Substrate scope of olefin.

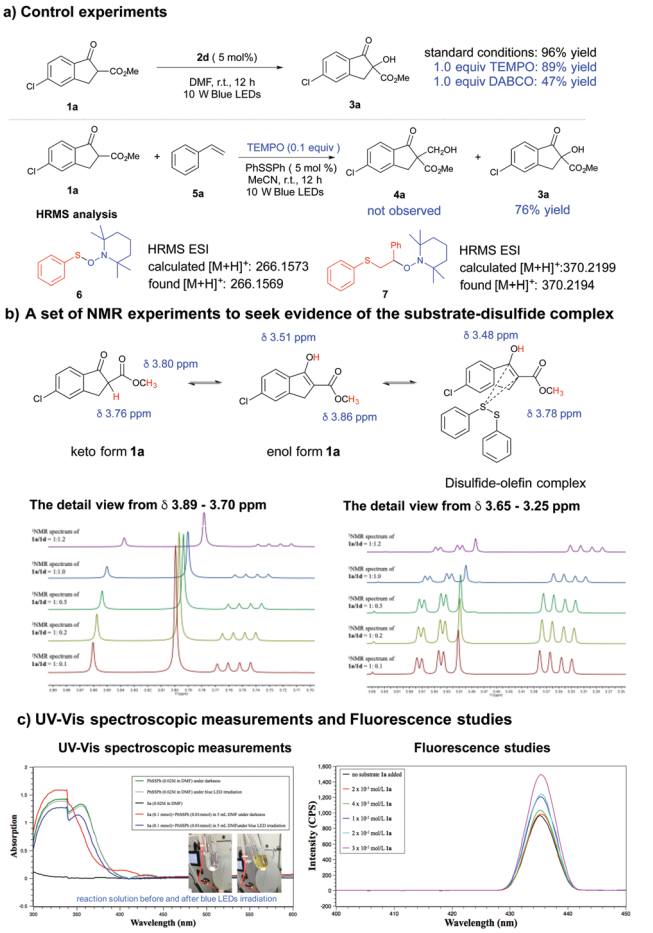
With the optimal conditions in hand, we sought to evaluate the generality of these transformations. As highlighted in Table 2, a wide range of 1,3-dicarbonyl substrates can be hydroxylated and hydroxymethylated under the developed reaction conditions. β-Keto esters and β-keto amides with electron-donating or electron-withdrawing substituents (such as methyl or halides) on the phenyl ring are hydroxylated in excellent efficiencies (**3a**, **3c–3h**, **3l–3m** and **3q**, 68–98% yield). They could also effectively react with styrene in the presence of **2a** (5 mol%) under blue LED irradiation to furnish hydroxymethylation products in good yield and selectivity (**4a**, **4c–4g** and **4k**, 54–92% yield). The unsubstituted indanone carboxylic methyl ester (**1b**) gave **3b** in 63% yield and **4b** in 89% yield. However, a sharp decrease in the yields was observed when electron-donating methoxyl groups were introduced into the aromatic ring of β-keto esters (**3i–3k**, 13–33% yield) while there was slight fluctuation in the yields of hydromethylation products (**4h–4j**, 88–97% yield). After investigation of the β-keto esters, the scope of β-keto amides was then examined. We found that the yields of hydroxylated and hydroxymethylated β-keto amides were related to the *N*-substituent groups (**3o–3p** and **3s–3t**, 53–87% yield; **4l–4m** and **4o–4r**, 42–89% yield). Further substrate expansion to 1-tetralone-derived 1,3-dicarbonyl substrates and carbonyl compounds was also investigated and the corresponding products were generated effectively (**3n**, **3u** and **4s–4t**, 54–85% yield). Efforts were made to expand the species scope of the substrate. However, some other 1,3-dione compounds such as open 1,3-dicarbonlyl compounds, functionalized five-, six- and seven-membered keto ester derivatives and carbonyl compounds did not react under identical reaction conditions. To further expand the utility of the reactions, we directed our efforts toward achieving a continuous-flow process. The disulfide-catalyzed aerobic oxidations were amenable to scale-up to gram quantities using continuous-flow reactors (Table 2).

A series of control experiments were further carried out to better understand the possible mechanism. When the transformation was performed under an N_2 atmosphere, no anticipated product **3a** and **4a** was obtained, confirming the crucial role of O_2 in the reaction (Schemes S3 and S4, ESI†). However, the model hydroxylation reaction worked very well even with the addition of one equivalent of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, a well-known radical scavenger), and afforded product **3a** in 89% yield. In contrast, when the singlet oxygen quencher DABCO (1,4-diazabicyclo[2.2.2]octane) was added to the hydroxylation reaction of **1a**, the yield of product decreased

Table 2 Switchable selectivity in the α-functionalization of 1,3-dicarbonyl compounds[a]



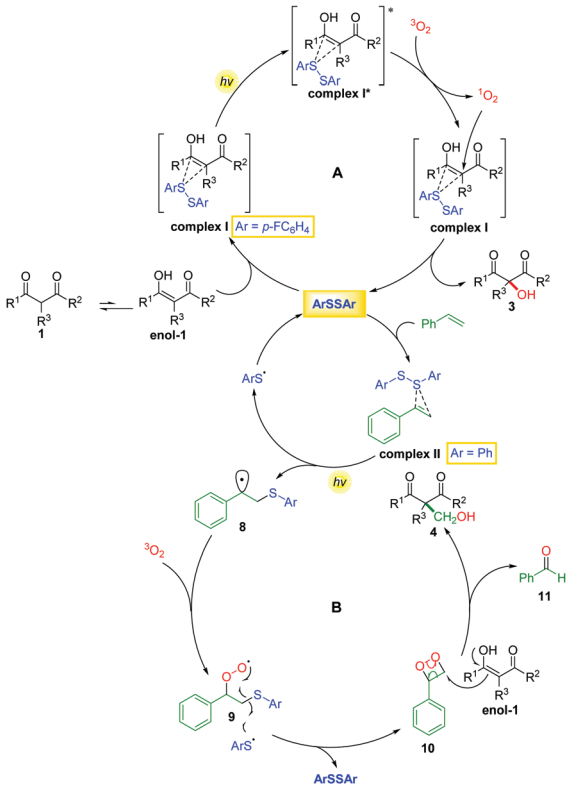
[a] Isolated yields. [b] Reaction conditions: **1a** (0.1 mmol), disulfide (5 mol%) and DMF (4.0 mL) in a quartz tube at room temperature under irradiation of a 10 W blue LED for a given time. In addition, the solution was bubbled with an air pump for 12 h. [c] Reaction conditions: **1a** (0.1 mmol), disulfide (5 mol%) and MeCN (2.0 mL) in a quartz tube at room temperature under irradiation of a 10 W blue LED for a given time. In addition, the solution was bubbled with an air pump for 24 h.



Scheme 3 Preliminary mechanistic investigations.

dramatically, affording product **3a** in 47% yield, suggesting that a singlet oxygen process might be involved in the present reaction. To provide some insight into the plausible radical mechanism for the hydroxymethylation reaction, TEMPO as a radical scavenger was subjected to our standard conditions. As expected, the hydroxymethylation reaction was significantly inhibited, and the system was prone to hydroxylation. In addition, the hydroxymethylation system in the presence of TEMPO afforded adducts **6** and **7** (Scheme 3a). These results suggest that an alkyl intermediate might be involved in this transformation. We carried out NMR experiments to confirm the formation of the disulfide–substrate enol complex. The ^{1}H NMR spectra are shown in Scheme 3b, and changes in the peaks and chemical shifts were observed at δ 3.90–3.30 ppm as the ratio of disulfide to **1a** increased. From Scheme 3b, the chemical shift of –COOCH$_3$ (δ 3.80 ppm, 3.86 ppm) from the keto form and enol form of **1a** shifted upfield, and the peak of α-H (–CH–) (δ 3.76 ppm) as well as β-H (–CH$_2$–) (δ 3.35 ppm) shifted upfield, which indicated that the electron density on the substrate had increased. To better understand this photochemical oxidation reaction and to elucidate the mechanism, we also performed UV-Vis spectroscopic measurements on a combination of **1a** and **2a**. Notably, we observed the formation of a new peak (λ_{max} = 410 nm) when **1a** and **2a** were combined; this peak is proposed to result from the absorption of disulfide–enol complex (Scheme 3c). Meanwhile, the photographs of the reaction solution before and after blue LED irradiation indicated that an EDA complex might exist. In addition, fluorescence experiments were also conducted to prove the complexation between **1a** and **2a** (Scheme 3c). The emission intensity of PhSSPh dramatically increased with the increasing amounts of **1a**. This complex may be photosensitive.

Based on the above results and considering previous studies, a preliminary mechanism is proposed in Scheme 4. (A) Irradiation of the disulfide–enol complex **I** yields a photoexcited disulfide–enol complex **I***, which then transferred energy to the triplet oxygen (^{3}O$_2$) to form reactive singlet oxygen (^{1}O$_2$). Then ^{1}O$_2$ reacts with complex **I** to afford hydroxylation product **3**.[8] (B) Upon the addition of a stoichiometric amount styrene, there is precedence for the disulfide to react with the styrene to form a disulfide–olefin complex **II**. The complex **II** would provide a S–S bond that is more



Scheme 4 Plausible reaction mechanism.

easily homolytically cleaved under visible light irradiation, and thus the generated thiyl radical would add to styrene to give intermediate **8**. We believed that the key intermediate was the dioxetane **10**, which was formed from intermediate **9** by the abstraction and substitution of the thiyl radical and alkyl radical.[7p] Then enol-form **1** attacked dioxetane **10** to afford benzaldehyde **11** and hydroxymethyl-adduct **4**.[9]

In conclusion, a visible light-mediated switchable selective α-functionalization of 1,3-dicarbonyl compounds using air as the oxidant and an oxygen source induced by disulfide is disclosed for the first time. Upon irradiation with visible light, the metal- and base-free α-hydroxylation or α-hydroxymethylation reactions proceeded smoothly through a disulfide-catalyzed oxidation under mild conditions. The combination of a continuous-flow strategy could further improve the reaction efficiencies. The application of this system to the synthesis of other compounds is currently underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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