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Synthesis of α,β-unsaturated carbonyl compounds *via* a visible-light-promoted organocatalytic aerobic oxidation†

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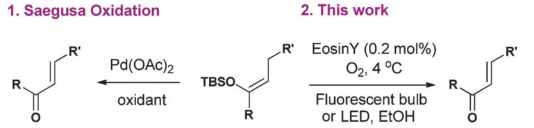
α,β-Unsaturated ketones and aldehydes have been synthesized from their corresponding silyl enol ethers in a straightforward protocol involving a visible-light promoted organocatalytic, aerobic oxidation reaction. A cheap organic dye was used catalytically in these reactions as the photosensitizer.

α,β-Unsaturated carbonyl subunits are important structural motifs and arguably one of the most versatile synthetic intermediates for the construction of structurally diverse natural products, as well as a variety of other functional molecules.[1] Compounds containing these structural units can participate in a large number of highly privileged organic transformations, which lead to formation of products of pronounced structural diversity. Several representative approaches using some of the more readily available saturated carbonyl feedstock have been reported in the literature. For example, Nicolaou *et al.*[2] developed a convenient method for the oxidation of ketones and aldehydes to their α,β-unsaturated derivatives using stoichiometric IBX. More recently, Stahl *et al.*[3] as well as our own group[4] reported the direct aerobic catalytic dehydrogenation of aldehydes and ketones *via* a palladium enolate intermediate. In practice, the Saegusa–Ito oxidation is frequently used as an effective method for the introduction of a C═C double bond next to an aldehyde or a ketone, especially in the context of natural product synthesis (Scheme 1).[5,6]

The benefit of using silyl enol ethers is that they enable convenient control of the regiochemical outcome of the reaction.[7] The Saegusa reaction requires palladium as the catalyst to mediate the oxidation in the presence of an external oxidant.[8] Metal-free protocols using molecular oxygen as the sole oxidant remain scarce. Herein we report for the first time a transition-metal-free, photocatalytic, aerobic system for the synthesis of α,β-unsaturated aldehydes and ketones from structurally diverse silyl enol ethers.



Scheme 1 Representative strategies for the oxidation of carbonyl compounds to their corresponding α,β-unsaturated derivatives.

We initially attempted to use the oxidation of a cyclohexanone-derived TBS enol ether **1a** as a model reaction using a variety of different photosensitizers and O_2 under different visible light sources. All of these reactions were carried out at room temperature in DMF (Table 1). The desired cyclohexenone product **2a** was observed when $Ru(bpy)_3Cl_2$ (5 mol%) was used as a metallic sensitizer under several household light sources.

Energy-saving compact fluorescent light bulbs (Philips, Tornado-24 W) were found to be the most efficient of the household light sources for promoting the desired oxidation, affording the desired product **2a** in 41% yield after 15 hours (Table 1, entry 3). We then proceeded to investigate the effect of several organic dyes. While rhodamine B and alizarin failed to catalyze this oxidation (Table 1, entries 4 and 5), TPP and Eosins B and Y were found to be quite effective (Table 1, entries 6–8). In the absence of a photocatalyst or light, no enone product was observed. In addition, when the reaction was conducted in a glovebox, no reaction occurred.

We then proceeded to investigate the effect of solvents on this aerobic oxidation reaction (Table 2). In most of the nonpolar and polar aprotic solvents tested, except for DMSO, low conversions of the starting material were observed, with the saturated ketones being isolated as the major side-product. In contrast, the use of polar protic solvents, such as methanol and ethanol, as well as the polar aprotic solvent DMSO, led to reasonable yields of the desired cyclohexenone products. The major side reaction was the ozonolysis-like oxidative cleavage of the enol ether double bond.

The reaction scope was then studied using different silyl enol ethers, and the results are summarized in Table 3.

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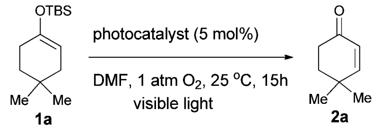
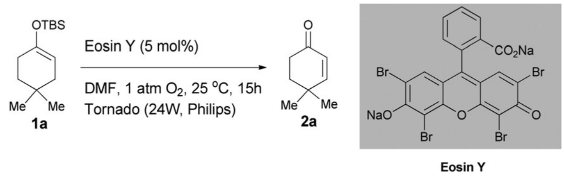
Table 1 Initial investigation of different light sources and photosensitizers for the oxidation of **1a**[a]



Entry	Light source	Photocatalyst	Yield[b] (%)
1	LED corn light (12 W)	$Ru(bpy)_3Cl_2$	9
2	LED green light (9 W)	$Ru(bpy)_3Cl_2$	13
3	Fluorescent bulb (24 W)	$Ru(bpy)_3Cl_2$	41
4	Fluorescent bulb (24 W)	Rhodamine B	0
5	Fluorescent bulb (24 W)	Alizarin	0
6	Fluorescent bulb (24 W)	TPP	32
7	Fluorescent bulb (24 W)	Eosin B	33
8	Fluorescent bulb (24 W)	Eosin Y	45
9	—	Eosin Y	0
10	Fluorescent bulb (24 W)	—	0

[a] The reaction was carried out on a 1 mmol scale. Conditions: 1 (0.2 M); 1 atm O_2; r.t.; 15 hours. [b] Yields were determined by GC using biphenyl as the internal standard.

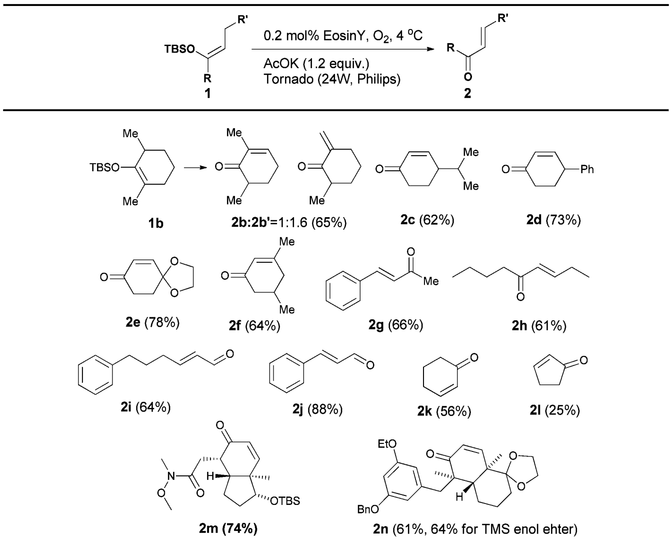
Table 2 Solvent effects and the influence of additives[a]



Entry	Cat. (mol%)	Solvent	Additive[a]	Yield[b] (%)
1	5.0	Toluene	—	5
2	5.0	THF	—	19
3	5.0	DCM	—	10
4	5.0	DME	—	12
5	5.0	Dioxane	—	16
6	5.0	CH_3CN	—	35
7	5.0	Acetone	—	20
8	5.0	DMSO	—	52
9	5.0	MeOH	—	59
10	0.2	EtOH	—	59
11[c]	0.2	EtOH	AcOK	65

[a] The reaction was carried out on a 1 mmol scale. [b] Yields were determined by GC using biphenyl as the internal standard. [c] The reaction was carried out for 4 hours at +4 °C; isolated yield.

Table 3 Substrate scope[a]

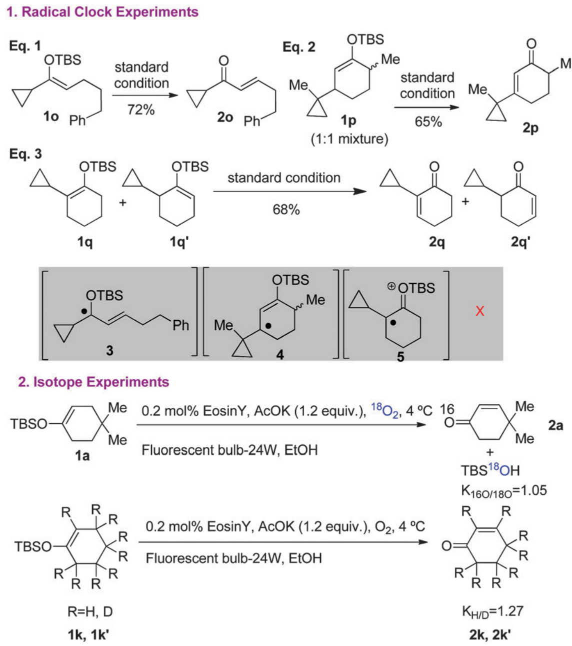


[a] Isolated yield.

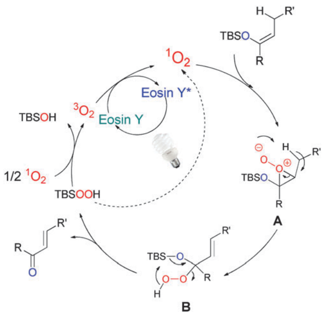
The overall utility of our new protocol was then evaluated using the structurally sophisticated intermediates **1m** and **1n**, which have been used as building blocks in the total syntheses of dysidavarones A–D and solanoeclepin A.[9] Despite the multiple functionalities present in these molecules, our oxidation reactions proceeded smoothly to give enones **2m** and **2n** in good yields. A TMS analogue of **1n** showed similar reactivity, while the corresponding TIPS substrate led to low conversion. A gram scale reaction using **2k** afforded a similar yield, while using 1.0 mol% photosensitizer.

We then moved on to investigate the mechanism of this transformation. MacMillan *et al.*[10] recently reported a visible light photoredox protocol for the functionalization of the β-carbon atoms of saturated ketones and aldehydes. This particular reaction was reported to proceed *via* a stabilized amino allyl radical intermediate, which was supported by the experimental evidence, as well as theoretical calculations. We therefore attempted to trap a similar oxygenated allylic radical using cyclopropane substituted substrates (Scheme 2, eqn (1) and (2)).

To this end, silyl enol ethers **1o** and **1p** were prepared, and oxidized under the optimized conditions. Interestingly, **2o** and **2p** were formed as the cyclopropane substituted α,β-unsaturated ketones, excluding that the TBSO-substituted allylic radicals were intermediates for the reaction. An α-cyclopropyl silyl enol ether (as a mixture of regioisomers: **1q** and **1q′**) was synthesized and subjected to our standard conditions. The isolation of the cyclopropane bearing products only strongly disfavoured an α-keto radical pathway (Scheme 2).[11] The rate of the photocatalytic aerobic oxidation reaction



Scheme 2 Radical clock and isotope experiments.



Scheme 3 Proposed reaction mechanism.

was zero order with respect to the catalyst and first order to the substrate concentration (see the ESI† for detailed kinetic studies). A reaction under an $^{18}O_2$ balloon did not result in the incorporation of any ^{18}O in the product. Instead, TBS ^{18}OH was detected as the major silicon by-product by HRMS, with a negligible isotope effect ($K_{16O/18O}$ = 1.05). No ^{18}O was found within the catalyst framework. A further experiment involving the use of a fully deuterated substrate yielded an isotope effect of $K_{H/D}$ = 1.27, suggesting that the C–H bond cleavage was not involved in the rate limiting step.

Based on the experimental data provided above and information from the literature, we speculate a singlet oxygen mechanism for this transformation. Eosins are known to excite molecular oxygen from its triplet state to its singlet state under light radiation.[12] An ene reaction between the singlet oxygen and the silyl enol ether through intermediate **A** (Scheme 3) to generate a hydroperoxy silyl hemiacetal **B** has been reported.[13] This intermediate **B** might undergo an intramolecular silyl transfer to release the desired product together with hydroperoxysilane, which would decompose to form O_2 and silanol. It is noteworthy that in contrast to conventional photosensitized singlet oxygen protocols, which require intense light sources (such as 300 W Hg lamps or photoreactors), the current oxidation reaction relies on simple exposure to a household light source to initiate the oxidation, possibly due to direct conversion of the hydroperoxysilane to singlet oxygen catalyzed by Eosin Y*. An in-depth mechanistic study is currently underway in our laboratories to fully elucidate the mechanism of this reaction.

In summary, we have developed a novel method for the synthesis of α,β-unsaturated ketones and aldehydes from their corresponding silyl enol ethers in a straightforward manner involving a visible-light organocatalytic, aerobic oxidation reaction. This protocol has several practical advantages over the existing procedures for the synthesis of α,β-unsaturated carbonyl compounds: it is metal-free, uses an inexpensive commercial catalyst, requires only ultralow catalyst loading, operates under aerobic conditions, uses ethanol as a low toxicity solvent, and operates effectively at ambient or even lower temperatures.

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