Green Chemistry

Photochemical oxidation of benzylic primary and secondary alcohols utilizing air as the oxidant†

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A mild and green photochemical protocol for the oxidation of alcohols to aldehydes and ketones was developed. Utilizing thioxanthenone as the photocatalyst, molecular oxygen from air as the oxidant and cheap household lamps or sunlight as the light source, a variety of primary and secondary alcohols were converted into the corresponding aldehydes or ketones in low to excellent yields. The reaction mechanism was extensively studied.

Introduction

Carbonyl compounds are one of the most important functionalities in pharmaceuticals and their synthesis *via* alcohol oxidation is a key reaction in chemical science.[1] Among the traditional and most common methods for the oxidation of alcohols are the use of stoichiometric amounts of oxidants, such as MnO_2, hypochlorite, permanganate, osmium oxide, activated dimethylsulfoxide (DMSO), hypervalent iodine reagents, peroxide-based or salt-based protocols, corresponding to a number of named reactions in organic synthesis, that nowadays are common practice (Scheme 1A).[1,2] Unfortunately, these processes create large volumes of waste that deteriorate the climate on Earth, while most of them can be also considered quite toxic. In order to avoid the use of large amounts of toxic and hazardous reagents, a variety of homogeneous and heterogeneous catalytic systems have been reported. In an effort to make these reactions friendlier to the chemical industry and more environmentally-friendly, new, green and sustainable protocols have been developed utilizing air or oxygen as the oxidant (Scheme 1B).[3,4]

These catalytic systems use either metal-complexes or metal nanoparticles or Tempo-like radicals as catalysts which, unfortunately, lead to a variety of byproducts and wastes. For example, the group of Iwabuchi have elegantly demonstrated the oxidation of alcohols to carbonyl compounds, utilizing a balloon of oxygen or air as the oxidant and a synthetic catalyst, which is not commercially available (TEMPO-like reagent).[4d]
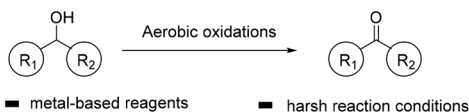
Unfortunately, the use of acetic acid as the solvent can be considered harsh for sensitive groups and not environmentally friendly. Moreover, biocatalysis has also provided significant advances in oxidation reactions.[5]

Over the past two decades, photocatalysis has made a powerful impact in the activation of molecules and its appli-
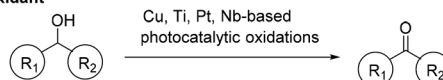
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Scheme 1 Different approaches for the oxidation of alcohols to carbonyl compounds.

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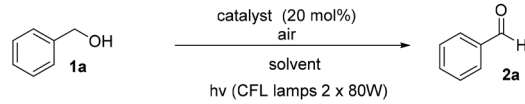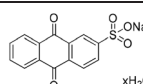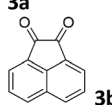
cations have increased significantly.[6] Inspired by the potential of photocatalysis, several metal-based photocatalysts have been reported, based on Cu, Ti, Pt, Nb, Pt-functionalized porphyrinic MOF, supported nanoparticles, *etc.* for the oxidation of alcohols (Scheme 1C).[7] Although most of these processes are very elegant, the requirement of a metal cluster can be considered as a disadvantage. In an effort to prevent the use of toxic metallic reagents in oxidation reactions, there is a strong requirement for alternative metal-free photocatalysts.[8] Photoorganocatalysis is a low-cost and environmentally friendly alternative.[9] Photocatalysis has already been used for the oxidation of alcohols to carbonyl compounds, utilizing various oxidants, such as DDQ or TBHP.[10] Small organic molecules have also shown their activity towards the activation of O_2 under visible light, and this concept has already shown powerful applications in organic synthesis.[11] A part of these applications constitutes the oxidation of alcohols to carbonyl compounds.[12]

We have a long interest in photocatalysis[13] and in sustainable processes for oxidations.[14] In an effort to develop a green catalytic protocol, herein, we report a mild photochemical system for the selective oxidation of alcohols, without the use of toxic metal clusters and 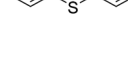complexes or the use of stoichiometric oxidation. The presented protocol herein, focuses on an eco-friendly metal-free process, which avoids the use of toxic and hazardous reagents, minimizing the need for energy consumption (since the reaction can be also performed by sunlight irradiation) and utilizes air, which is considered by green metrics the best source, as the oxidant (Scheme 1D).

Results and discussion

We initiated our study utilizing benzyl alcohol (**1a**) as the substrate and air as the oxidant. In the optimization of the reaction conditions, a variety of different catalysts and solvents were tested (Table 1). As shown in Table 1, aromatic ketones, in the role of the catalyst, such as sodium anthraquinone-2-sulfonate (**3a**) or acenaphthenquinone (**3b**) provided low yields (Table 1, entries 1 and 2). A common photocatalytic organic dye, eosin Y (**3c**), showed similar reactivity (Table 1, entry 3). Different type of catalysts, such as acetophenone (**3f**) or benzophenone (**3g**), which are usually used as photoinitiators, afforded the product in low yields (Table 1, entries 4–8). In contrast, the use of thioxanthenone (**3i**) as the photocatalyst, provided the desired aldehyde in 61% yield (Table 1, entry 9). Further increase in the reaction time dropped the yield in 55% (Table 1, entry 10). This result was very interesting, and by monitoring the reaction outcome by ^{1}H-NMR, it was possible to detect the production of benzoic acid. This meant that overoxidation to the corresponding carboxylic acid was occuring, a common problem in the selective oxidation of primary alcohols.[15] Therefore, we decided to reduce the reaction time and examine whether we could obtain a higher yield of the product. To our delight, when the reaction time dropped to 14 h, we managed to obtain the aldehyde in 85% yield

Table 1 Optimization of the reaction conditions for the photochemical oxidation of benzyl alcohol

Entry	Solvent	Catalyst	Time (h)	Yield[a] (%)
1	DMSO	**3a**	18	34
2	DMSO	**3b**	18	11
3[b]	DMSO	Eosin Y **3c**	18	29
4	DMSO	**3d**	18	6
5	DMSO	**3e**	18	12
6	DMSO	**3f**	18	26
7	DMSO	**3g**	18	5
8	DMSO	**3h**	18	4
9	DMSO	**3i**	18	61
10	DMSO		19	55
11	DMSO		14	85(82)[c]
12	MeCN		14	33
13	H_2O		14	0
14	DMF		14	25
15	Toluene		14	0
16	MeCN/DMSO		14	58

[a] All reactions were carried out with **1a** (0.20 mmol), catalyst (20 mol%) and solvent (0.6 mL) in an open-air vessel, under household bulb irradiation. [b] 5 mol% catalyst loading. [c] Isolated yield.

(Table 1, entry 11). For more details regarding the ratio of overoxidation, see ESI.† We also examined if benzaldehyde could act as the photocatalyst (autocatalytic reaction), which gave a poor 5% yield (Table 1, entry 8). Since DMSO is still considered a practical solvent for chemical industries, but it would be highly desirable if we could substitute it with a greener solvent, our next step was to examine the role of the solvent in the reaction. Acetonitrile provided the product in 33% yield (Table 1, entry 12), while other polar solvents, such as water or DMF, afforded lower results (Table 1, entries 13 and 14). When non-polar solvents, such as toluene, were used no product was detected (Table 1, entry 15). When a mixture of MeCN/DMSO (instead of MeCN alone) was used as the solvent, the yield was increased from 33% to 58%, which indicates that DMSO plays a significant role in the reaction outcome and cannot be replaced (Table 1, entry 16 *vs.* 12). Trying to determine the role of the solvent, it is known that DMSO can stabilize the excited state of diaryl ketones (of similar chemical type with **3i**), so it is rational to assume that the excited state of thioxanthene-9-

one (**3i**) has a prolonged lifetime in the presence of DMSO as the solvent, making it an important part of the reaction.[16]

Having in hand the optimized reaction conditions, we then explored the substrate scope (Scheme 2). Various mono- or di-substituted benzyl alcohols were used and provided the desired aldehydes **2a–2c** in good yields. Furthermore, *ortho*-substituted benzyl alcohols afforded the desired aldehydes **2d** and **2e** in lower yields, probably due to steric hindrance close to the center of the reaction. The electronics on the aromatic ring plays a significant role in the reaction outcome, since products **2f–i** were obtained in various yields (from 14 to 70%). Unfortunately, non-benzylic primary alcohols, like 3-phenyl-propanol and 1-hexanol, did not afford the oxidation. When the photochemical protocol was applied in an allylic alcohol (cinnamyl alcohol), the desired α,β-unsaturated aldehyde **2j** was formed in 36% yield. In the case of benzyl secondary alcohols, we determined that we could lower the catalyst
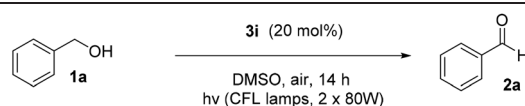
loading to 5 mol%, in order to highlight the green character of the protocol. In some cases we could purify the desired ketone just by an ice-water workup-extraction, in order to remove the DMSO from the reaction mixture. The best results were provided from the oxidation of substituted 1-phenylethan-1-ols. *para*-Substituted alcohols, with either electron-donating or electron-withdrawing groups, provided the desired ketones **2k–2s** in moderate to excellent yields. In the case of **2l**, it was possible to isolate the desired product by simple solvent evaporation, without the need of column chromatography. This also applies in all cases where the reaction reached completion (for example, compounds **2m–p**). *ortho*-Substituted alcohols, like **1r**, provided the desired product **2r** in 39% yield, presumably due to steric hindrance close to the center of the reaction. Double and triple bond-bearing alcohols also afforded the desired products **2u** and **2w** in very good yields, highlighting the chemoselectivity of the method. Aromatic substituted alcohols, such as benzhydrol, and xanthydrol, provided ketones **2t** and **2aa** in excellent yields. In order to expand the substrate scope, we attempted the oxidation of cyclic secondary alcohols, which gave the ketones **2ac–2ag** in very good yields. Aliphatic secondary alcohols, such as 2-pentanol, provided the carbonyl compound **2ab** in 49% yield, due to volatility issues. In order to examine the chemoselectivity of the method, we chose to oxidize an 1,3-diol to the corresponding β-hydroxy ketone (**2ah**), as the only product in 70% yield, showing the chemoselectivity of the method to the oxidation of the benzylic position *versus* the aliphatic one. In order to apply the oxidation in more complicated real-life examples, cholesterol (**1ai**) was employed as the substrate and the desired ketone **2ai** was obtained in 63% yield.

After substrate scope evaluation, we became interested in determining the actual role of the catalyst and the light source. Performing control experiments for the oxidation reaction of benzyl alcohol (**1a**) to benzaldehyde (**2a**), we extracted some very important results, in order to understand the different parameters of the reaction (Tables 2 and 3). These experiments showed that no product was obtained under dark (Table 2, entry 2) and thermal conditions (Table 2, entry 3), indicating a
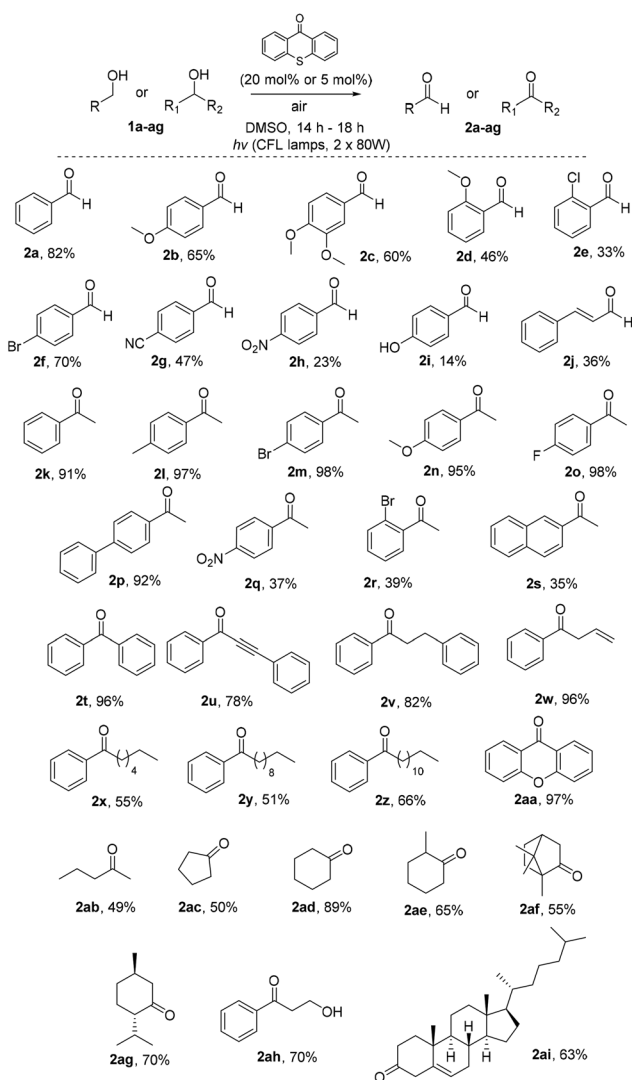
Scheme 2 Substrate scope for the photochemical oxidation of benzylic and secondary alcohols.

Table 2 Control experiments for the photochemical aerobic oxidation of benzyl alcohol

Entry	Reaction parameters	Yield[a] (%)
1	Standard conditions	85
2	No light	0
3	Heating, no light	0
4	No catalyst	0
5	Ar atmsphere	0

[a] All reactions were carried out with **1a** (0.20 mmol), **3h** (20 mol%), solvent (0.6 mL), air, under 2 × 80 W household lamps irradiation. Yields were determined by GC-MS.

Table 3 Quenching experiments for the photochemical aerobic oxidation of benzyl alcohol

Entry	Quencher (equiv.)	Note	Yield[a] (%)
1	Tempo (1)	Radical scavenger	0
2	BHT (1)	Radical scavenger	0
3	NaN₃ (1)	Singlet oxygen scavenger	35
4	DABCO (1)	Singlet oxygen scavenger	6
5	2,2,6,6-Tetramethyl-piperidine (1)	Singlet oxygen scavenger	5

[a] Yields were determined by GC-MS.

"clean" photochemical reaction, while in the absence of catalyst, no product was obtained (Table 2, entry 4). In addition, when the reaction was performed under argon atmosphere, no product was observed, which highlighted the importance of oxygen in the reaction (Table 2, entry 5). When Tempo was added in the reaction mixture as a radical trap, no oxidation product was formed (Table 3, entry 1). The intermediate compound formed between Tempo and alcohol **1k** was observed by GC-MS, hinting the generation of a benzyl radical.[17] Furthermore, quenching reagents were used, in order to recognize the oxygen species that take part in the reaction mechanism (Table 3). As an oxygen species quencher, NaN₃ was used and partially inhibited the process, which as a fact shows that the presence of singlet oxygen species in the reaction mechanism is strong (Table 3, entry 3). An additional experiment, that strongly indicates the association of singlet oxygen, is the use of anthracene and its derivatives as singlet oxygen traps, which was introduced in literature by Fukuzumi.[18] The addition of anthracene in the standard reaction mixture furnished the corresponding anthraquinone in 90% yield, which indicates the presence of singlet oxygen. The same conclusion can be drawn with the use of DABCO (Table 3, entry 4). Additionally, utilizing 2,2,6,6-tetramethylpiperidine, which is a known singlet oxygen quenching reagent,[19] no product was formed (Table 3, entry 5).

Another tool that contributes to the understanding of the reaction mechanism, is the determination of the quantum yield (Φ) of the photocatalytic reaction. Based on literature,[20] the quantum yield (Φ) of the photocatalytic reaction was calculated: $[\Phi = 12 \ (\Phi > 1)]$, which hints that a radical propagation mechanism is taking place.

In order to gather further information about the reaction mechanism, fluorescence quenching studies took place. Stern–Volmer plots for the fluorescence quenching experiments revealed that the excited photocatalyst does not interact directly with benzyl alcohol or benzhydrol, since the slope of the quenching is minimal (Scheme 3).[8e] Further support for this notion, that a direct single electron transfer between excited thioxanthenone and benzyl alcohol is not possible, is given by the comparison of the reduction potentials of the two
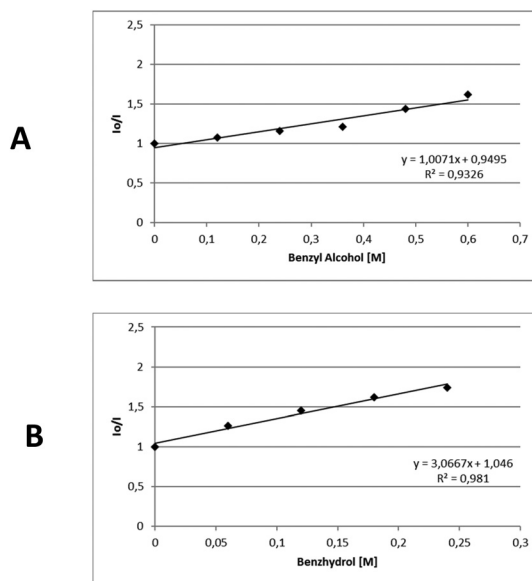
Scheme 3 Stern–Volmer plots for the fluorescence quenching of thioxanthenone (1 mM in DMSO) with A. Benzyl alcohol, B. Benzhydrol.

compounds ($E^*_{(red)}$ thioxanthenone = +1.52 eV *vs.* SCE,[6e] while $E_{(ox)}$ benzyl alcohol = +2.16 eV *vs.* SCE[21]). Furthermore, bubbling oxygen in a cuvette with a solution of thioxanthenone led to diminished fluorescence, validating that air quenches the catalyst.[17] Further control fluorescence quenching experiments with the quenchers of Table 3 were also performed.[17]

Based on literature, Orfanopoulos and coworkers performed a series of experiments, in order to distinguish between SET or HAT processes for the oxidation of alcohols.[22] In that work, a control experiment utilizing 1-(4-methoxyphenyl)-2,2-dimethyl-1-propanol (**1aj**) as the substrate was demonstrated. Due to its substitution pattern, when a SET process is occurring in the C_α–H of the hydroxyl group, a C_α–C_β bond cleavage follows, leading to the formation of the corresponding aldehyde and carboxylic acid. On the other hand, if the photooxidation of this substrate proceeds through a HAT event, then, the reaction furnishes the *tert*-butyl ketone (**2aj**), as the sole product.[22] Applying this test reaction in our method, we examined the photooxidation of 1-(4-methoxyphenyl)-2,2-dimethyl-1-propanol (Scheme 4, **1aj**). In our case, after 18 h of irradiation, the starting alcohol was converted completely in a mixture of **2aj** : benzaldehyde : benzoic acid in a ratio of 68 : 3 : 29, respectively. As we expected, the major product is ketone **2aj**, which indicates that our method does not involve a SET process, but mainly a HAT event (Scheme 4). Moreover,
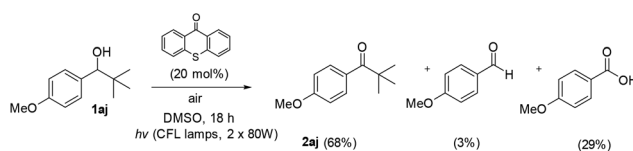
Scheme 4 Mechanistic test reaction for SET or HAT processes.

similar conclusions derived from quenching experiments with 1,3,5-trimethoxybenzene (TMB).[17] TMB has a relative low oxidation potential ($E_{(ox)}$ TMB = +1.12 eV vs. SCE)[22] and subsequently can act as an electron donor against the excited form of thioxathenone, quenching the excited state and as a result the termination of the radical procedure. We performed the oxidation of benzyl alcohol **1a** to aldehyde **2a** in the presence of TMB. The result of the reaction was, as we assumed, the oxidation of the alcohol to aldehyde, verifying that the reaction does not proceed through a SET pathway.[22]

Utilizing the above mechanistic studies, we can propose a plausible mechanism for the photochemical oxidation (Scheme 5). The first step is the excitation of the photocatalyst, thioxanthene-9-one, by light. Next, based on the results of the fluorescent quenching studies, excited thioxanthene-9-one interacts with molecular oxygen, generating singlet oxygen and returning thioxanthene-9-one to its ground state. This is in agreement with literature precedent, regarding excited thioxanthenone as singlet oxygen generator.[23] Then, singlet oxygen, as an activated form of oxygen, interacts with benzyl alcohol, either through a two-step mechanism, in which the first step is the abstraction of a hydrogen atom, leading to the formation of the benzylic radical **I** followed by a fast radical recombination,[24] leading, to the formation of peroxy hemiacetal **II** or through an one-step insertion in the C–H bond of the benzylic position, leading again to **II**. This activated compound decomposes with further irradiation, leading to benzaldehyde and hydroxy radicals, which can lead to propagation or can decompose to hydrogen peroxide. Indication for the presence of hydrogen peroxide in the reaction is the formation the corresponding dimethylsulfone, as a byproduct, the product of oxidation of the solvent (Scheme 6). In order to be sure for the origin of the oxidant source, we examined the power of hydrogen peroxide as the oxidation reagent, firstly for the oxidation of dimethylsulfoxide to dimethylsulfone and secondly for the oxidation of 1-phenylethanol (**1k**) to acetophenone (**2k**)
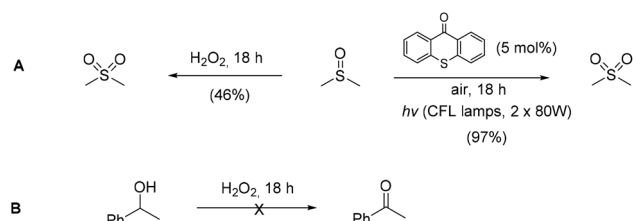
Scheme 6 Test reactions for the oxidant source.
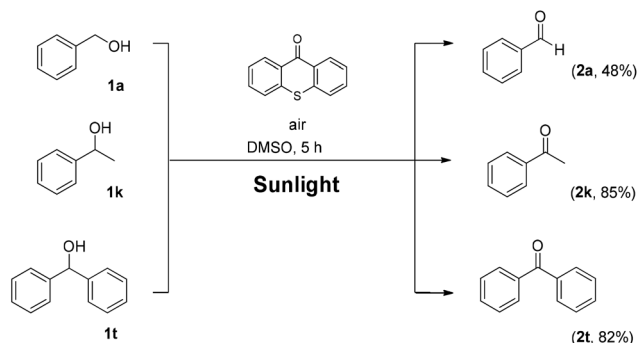
Scheme 7 Photochemical oxidation utilizing sunlight.

(Scheme 6). DMSO can be oxidized either by aqueous hydrogen peroxide solution itself or hydrogen peroxide-derived from singlet oxygen,[23b,25] the latter can be formed by thioxanthenone through a photocatalytic process (Scheme 6A). On the other hand, aqueous hydrogen peroxide solution cannot oxidize alcohol **1k**, confirming the hypothesis that singlet oxygen is the main oxidant source (Scheme 6B). Finally, the use of alternative energy source in our photochemical process was envisaged, in order to have a significant industrial applicability. Therefore, a variety of primary and secondary alcohols was tested as substrates, utilizing sunlight as the irradiation source, instead of CFL lamps, and the desired carbonyl compounds were formed in very good yields (Scheme 7). Secondary benzylic alcohol, like **1k** and **1t** afforded the desired ketones in similar yields as the household lamps. Unfortunately, the oxidation of **1a** under sunlight led to diminished yield (48%), since overoxidation to benzoic acid could not be controlled.

Conclusions

In conclusion, a green and sustainable photochemical protocol for the oxidation of alcohols was developed. Since a plethora of stoichiometric and catalytic systems have been used for this reaction, our approach was to find an environmentally friendly way to promote this transformation, by utilizing air as the oxidant and a cheap and commercially available organic molecule as the photocatalyst. After an extensive study, a variety of benzylic and secondary alcohols were transformed to the corresponding carbonyl compounds and mechanistic studies were performed in order to better understand our catalytic system.
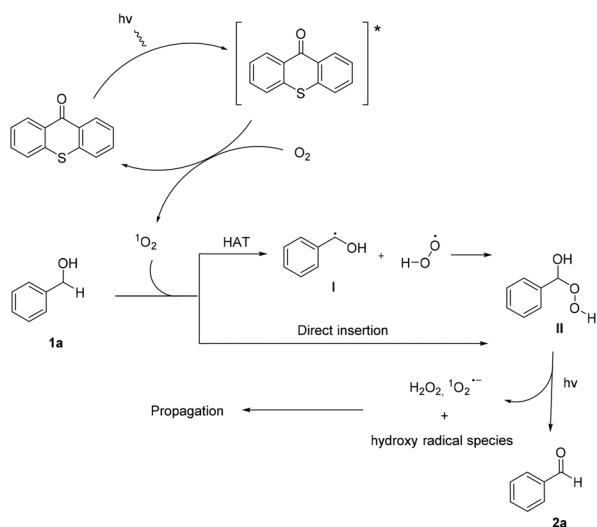
Scheme 5 Proposed reaction mechanism.

Experimental

General procedure for the oxidation of alcohols

In a glass vial containing thioxanthene-9-one (**3i**) (8.5 mg, 0.04 mmol) in DMSO (0.6 mL), benzyl alcohol or secondary alcohol (0.20 mmol) was added. The vial was left open in air and left stirring under household bulb irradiation (2 × 80 W household lamps) for 14–18 h. The desired product was isolated via purification of the crude mixture by flash column chromatography or just by ice-water workup-extractions.

Conflicts of interest

There are no conflicts to declare.

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