Organic dye photocatalyzed α-oxyamination through irradiation with visible light†‡

Hongjun Liu, Wei Feng, Choon Wee Kee, Yujun Zhao, Dasheng Leow, Yuanhang Pan and Choon-Hong Tan*

Received 23rd November 2009, Accepted 30th March 2010
First published as an Advance Article on the web 23rd April 2010
DOI: 10.1039/b924609f

Rose Bengal, an organic dye, was used as a visible light photocatalyst to investigate novel α-oxyamination reactions between 1,3-dicarbonyl compounds and a free radical (TEMPO). Compounds that are difficult to obtain such as quaternary fluorinated compounds were synthesized using this method. This visible light photocatalytic reaction can also be performed in water.

The call for sustainable development has led to increasing interest in green chemistry and minimizing energy consumption is an important aim of green chemistry.[1] The use of abundant sunlight as a clean source of energy in synthetic organic photochemistry dates back to the beginning of 20th century. However, this strategy has been widely ignored for a long time.[2] One fundamental obstacle is the lack of photoactive compounds absorbing in the emission maxima of the spectral distribution of the sunlight reaching Earth's surface. Another obstacle is the requirement for specialized photoreactors to generate high-intensity UV light or to concentrate natural sunlight.[3] Thus, it is particularly important to develop efficient visible light photocatalysts for synthetic transformations.

The ability of $Ru(bpy)_3Cl_2$ (tris(2,2′-bipyridine)-ruthenium(II) chloride, Fig. 1) to mediate electron transfer allows it to be a one-electron photoredox catalyst.[4] It has recently been shown by several groups to be an excellent photocatalyst in several reactions that are irradiated by visible light. An important concept developed in these works is the use of inexpensive household fluorescent bulbs as the photon source, thereby circumventing one obstacle in the use of sunlight – its variable irradiation strength and time. Nicewicz and MacMillan demonstrated that $Ru(byp)_3Cl_2$, when used in combination with an imidazolidinone organocatalyst, promotes a direct asymmetric alkylation reaction.[5] Subsequently, Yoon and co-workers utilized the same photocatalyst in both intramolecular and intermolecular of [2+2] enone cycloadditions.[6] A tin-free reductive dehalogenation reaction was reported by Stephenson *et al.* using a combination of $Ru(bpy)_3Cl_2$ and formic acid as the hydrogen atom source.[7] MacMillan *et al.* has also shown that an iridium complex is an efficient photocatalyst in enantioselective trifluoromethylation of aldehydes.[8]

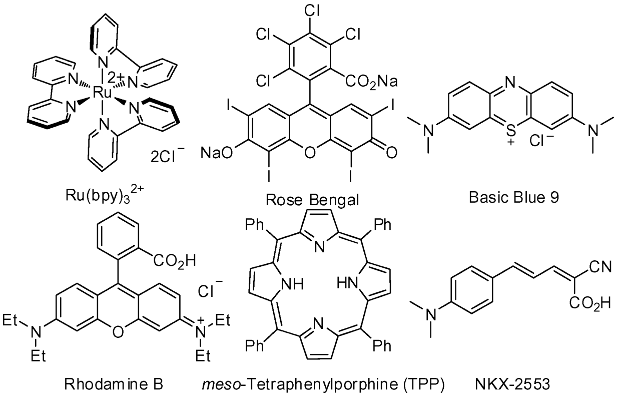


Fig. 1 Structures of photocatalysts.

Conversely, organic dyes, which are more environmentally friendly, cheaper and easier to prepare, present a viable alternative to inorganic photocatalysts. In fact, several industrial pilot studies had been conducted with organic dyes as photocatalyst.[9,10] For example, the photosensitized oxygenation (or Schenck ene reaction) of citronellol and 1,5-dihydroxynaphthalene were studied using Rose Bengal (Fig. 1).[10a] Concentrated sunlight from special solar collectors was needed in the development of these solar-chemical reactions. Organic dyes as photocatalysts can also be used in conjunction with ultraviolet light from 419 nm Rayonet lamps.[11] We are interested in the development of new reactions using organic dyes as photocatalyst in the presence of an inexpensive and convenient source of photon – household fluorescent bulbs.

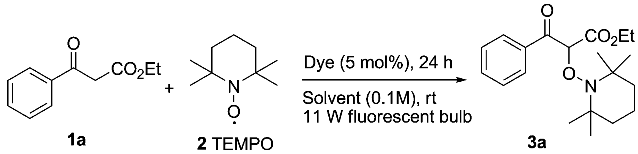
α-Oxyamination of aldehydes is a powerful transformation in organic synthesis.[12] This radical-mediated reaction involved cationic radical intermediates which were generated by either transition-metal oxidants (Fe^{3+})[12a] or electrochemical oxidation.[12b] α-Oxyamination between 1,3-dicarbonyl compounds and the free radical, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) has only been reported using a two step method.[13] Herein, we report a metal-free and environmentally friendly α-oxyamination reaction with organic dyes as visible light photocatalysts.

Department of Chemistry, 3 Science Drive 3, National University of Singapore, Singapore 117543. E-mail: chmtanch@nus.edu.sg

† Electronic supplementary information (ESI) available: [General procedures for organic dye photocatalyzed α-oxyamination, spectroscopic data and results of computational studies]. See DOI: 10.1039/b924609f

‡ *General experimental protocol for organic dye photocatalyzed α-oxyamination through irradiated with visible light*: To a clear vial, **2** TEMPO (7.8 mg, 0.05 mmol), Rose Bengal (2.5 mg, 0.00025 mmol), a stirring bar and distilled CH_3CN (0.5 mL) were added in this sequence. After stirring at room temperature for a while, ethyl benzoylacetate **1a** (9.0μL, 0.05 mmol) was added to the mixture in one portion. Subsequently, the vial was put under an 11 W household fluorescent bulb. After the reaction was completed in 24 h, the reaction mixture was concentrated and loaded onto a short silica gel column, followed by flash chromatography. Product **3a** (16.8 mg) was obtained as colorless oil in 97% yield.

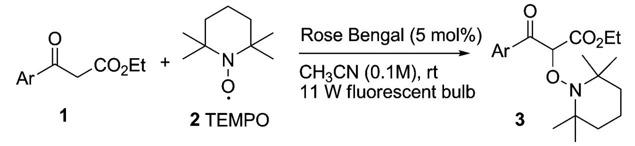
Table 1 α-Oxyamination reactions between β-ketoeseter **1a** and TEMPO



Entry	Dye	Solvent	Conv./%[a]
1	Rose Bengal	CH_2Cl_2	26
2	Rose Bengal	THF	30
3	Rose Bengal	Toluene	0
4	Rose Bengal	CH_3CN	100
5	Basic Blue 9	CH_3CN	9
6	Rhodamine B	CH_3CN	34
7	TPP	CH_3CN	4
8	NKX-2553	CH_3CN	7
9	$Ru[(bpy)_3]^{2+}$	CH_3CN	7
10	None	CH_3CN	0
11	Rose Bengal[b]	CH_3CN	0

[a] Conversion was determined by ^{1}HNMR. [b] Reaction was performed in dark.

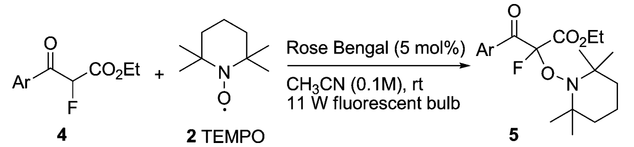
Table 2 Substrate scope of visible light irradiated α-oxyamination reactions



Entry	1	Ar	3	Time/h	Yield/%[a]
1	**1a**	Ph	**3a**	24	97
2	**1b**	4-MeOPh	**3b**	40	95
3	**1c**	3-MePh	**3c**	28	84
4	**1d**	3-NO_2Ph	**3d**	5	64
5	**1e**	4-ClPh	**3e**	18	64
6	**1f**	4-FPh	**3f**	19	67

[a] Isolated yield.

Table 3 Visible light photosyntheses of quaternary fluoro compounds



Entry	4	Ar	5	Time/h	Yield/%[a]
1	**4a**	Ph	**5a**	30	88
2	**4b**	4-MeOPh	**5b**	40	88
3	**4c**	3-NO_2Ph	**5c**	18	95
4	**4d**	4-ClPh	**5d**	27	91
5	**4e**	4-FPh	**5e**	19	90

[a] Isolated yield.

In our preliminary study, we utilized an 11 W household fluorescent light bulb as the visible light source, which operates within a wide spectral window (~400 to 700 nm). However, fluorescent light bulb provided a line-like spectral distribution, different from that of sunlight. Rose Bengal (RB), which has a strong absorption band in the range of 500–600 nm,[14] was efficient in catalyzing the α-oxyamination reaction between β-ketoester **1a** and TEMPO **2** to give the product **3a** (Table 1). During the optimization process, we found that solvents have a great effect on the reactivity of this reaction (Table 1, entries 1–4). Acetonitrile was shown to be the best solvent for the photocatalysis reaction (Table 1, entry 4).

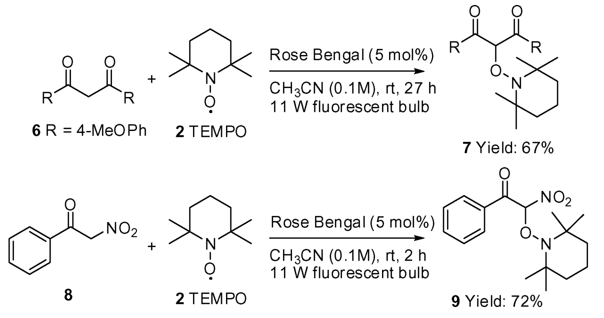
Further investigations were conducted using other organic dyes like Basic Blue 9, Rhodamine B and *meso*-tetraphenylporphine (TPP) (Fig. 1 and Table 1, entries 5–7). In most examples, only low conversions were observed. A polyene dye 2-cyano-5-(4-dimethylaminophenyl)penta-2,4-dienoic acid (NKX-2553) (Fig. 1),[15] which was demonstrated to be an efficient dye for dye-sensitized solar cells, also gave low conversion (Table 1, entry 8). Surprisingly, the common organometallic photocatalyst, $Ru(byp)_3Cl_2$, gave a low conversion of 7% (Table 1, entry 9). In the absence of either the photocatalyst or light source, no product was obtained (Table 1, entry 10 and 11).

Subsequently, the substrate scope of the α-oxyamination reactions was examined. Complete reactions were observed and excellent isolated yields were obtained for the coupling products **3a–c** (Table 2, entry 1–3). A strong electron donating group on the aromatic ring will lead to slower reaction rate (Table 2, entry 2). In contrast, a faster reaction was observed for a strong electron deficient aromatic β-ketoester **1d** (Table 2, entry 4). However, only 64% yield was obtained due to the decomposition of the product **3d**. Alkyl ketone esters did not give any products.

There is a strong demand for fluorinated compounds as they are often used as leads and building blocks in medicinal chemistry.[16] The preparation of quaternary fluorinated compounds is particularly difficult and interesting. As far as we know, a general method for the synthesis of α-fluorinated α-hydroxy acid derivatives is not available. We recently reported guanidine-catalyzed formation of highly enantioselective and diasteroselective chiral quaternary C–F bond through conjugate addition and Mannich reactions using α-fluoro-β-ketoesters as the fluorocarbon nucleophiles.[17] Using similar fluorocarbon nucleophiles, α-fluoro-β-ketoesters **4a–e**, a series of quaternary α-fluorinated α-hydroxy acid derivatives **5a–e** were synthesized with high yields using this new methodology (Table 3). The reaction rates of the electron deficient aromatic α-fluoro-β-ketoesters were faster than that of the electron rich ones. To our best knowledge, this is the first report on the synthesis of α-fluorinated α-hydroxy acid derivatives.

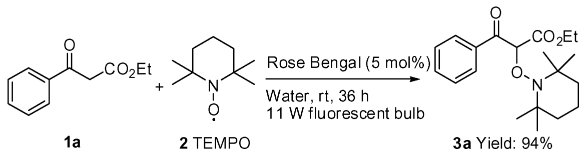
With the optimized condition, we screened other substrates for this photocatalytic α-oxyamination reaction. 1,3-Diketone **6** was efficiently converted to the corresponding adduct **7** with 67% yield (Scheme 1). Similarly, the nitro-ketone compound **8** exhibited an extremely fast reaction and gave adduct **9** with 72% yield (Scheme 1).

Interest in aqueous photochemistry generally revolved around these main themes: the photodegradation of aromatic compounds in the atmosphere, photocatalysis as a method to treat hazardous wastewater and more recently, photocatalytic splitting of water.[18] However, this can also potentially be an interesting technique for the selective and clean transformation of organic chemicals. So far the only example for aqueous photosynthesis of compounds utilized ultraviolet light. Excellent



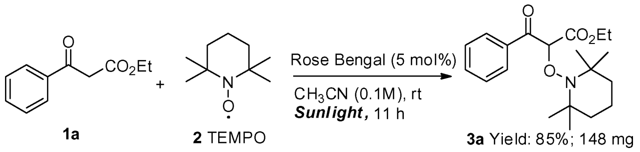
Scheme 1 Applications of photocatalysis of α-oxyamination reactions.

yield of adduct **3a** was obtained when the experiment was conducted in water (Scheme 2) and the reaction was essentially similar to the example in CH_3CN (Table 2, entry 1).



Scheme 2 Visible light mediated α-oxyamination in water.

As a demonstration of the scalability of this visible light driven photocatalytic process, we performed the α-oxyamination using the ambient sunlight on the roof of our laboratory building and obtained 150 mg of **3a** (Scheme 3). The same experiment was also conducted under laboratory condition using fluorescent light bulb with the same result.



Scheme 3 Ambient sunlight mediated α-oxyamination reaction.

As Rose Bengal is well known as a singlet oxygen sensitizer, we conducted control experiments in a glove box to verify the role of oxygen. It was clearly shown that oxygen was not essential for the visible light driven α-oxyamination reaction (see ESI†). Based on this result, we proposed a mechanism for the α-oxyamination reactions (Fig. 2).[19] Photoexcitated by visible light, Rose Bengal (RB) accepted a photon from the visible light to form RB*; as a reductant, it transferred an electron to the substrate **1** *via* a single electron transfer process (SET). Rose Bengal was recycled *via* another SET process from the electron rich intermediate **11**. The radical **12** was coupled with free radical TEMPO to give the product **3**.

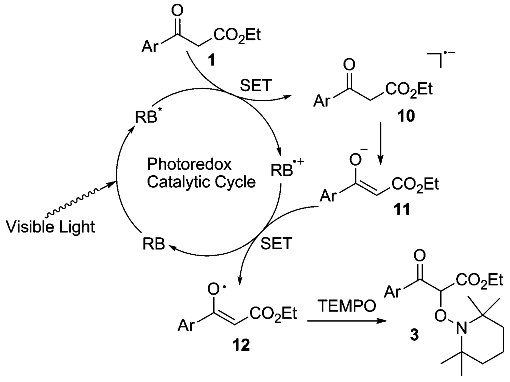


Fig. 2 Proposed mechanism for α-oxyamination reactions.

Using DFT calculations performed at M06-2X level of theory using Gaussian 09 program, we found that the electron affinity (EA) of aromatic β-ketoesters **1** was positive. The anion **10** can exist sufficiently long enough and the SET process was favorable.[19b] In contrast, the EA of alphatic β-ketoesters was negative in the SET process, suggesting alphatic keto-ester is not suitable for the α-oxyamination reaction which matches the experimental results. In addition, the LUMO's energy level of alphatic β-ketoesters was much higher than that of aromatic keto-ester. We are currently still investigating the detailed mechanism of this reaction.

In conclusion, we have developed an organic dye, Rose Bengal, photocatalyzed C–O coupling reaction through the irradiation of visible light. This method was applied to the synthesis of a variety of α-hydroxy acid derivatives with excellent yields and also to the synthesis of quaternary α-fluorinated α-hydroxy acid derivatives. We have also successfully demonstrated that this photocatalytic reaction can be conducted in water in the presence of visible light.

Acknowledgements

This work is supported by ARF grant (R-143-000-337-112), research scholarships (to H. L., D. L. and Y. P.) from the National University of Singapore. We thank the Medicinal Chemistry Program for their financial support.

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