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A highly efficient metal-free, visible-light promoted aerobic sulfoxidation with remarkably simple workup protocols.

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ARTICLE TYPE

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A Simple Metal-free Catalytic Sulfoxidation under Visible Light and Air

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⁵ A metal-free aerobic selective sulfoxidation photosensitized by Rose Bengal or solid-supported Rose Bengal has been developed. The reaction utilizes visible light as the driving force and molecular oxygen as the oxidant. Highlighted by its high efficiency and selectivity, extremely simple operation and workup procedure, and minimal waste generation, the process is an excellent example of perfect green chemistry.

Introduction

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"Green chemistry" is one of the central topics both in academia and industry since early 1990's. The fundamental "Twelve Principles" have become the guidelines for the development of "green" chemical reactions or processes.¹ A "perfect chemical reaction", one that gives only the desired products with 100% ¹⁵ selectivity and 100% yield without unwanted wastes², is the ultimate goal for chemists. In addition to that, it is believed an ideal chemical reaction or process should be highly atomeconomical, environmentally benign, and energy-saving. Although most organic molecules do not absorb visible light, ²⁰ Nature has shown us through photosynthesis that visible light at ambient temperature is considered to be sustainable. The recent seminal work on photoredox catalysis by the MacMillan group³

²⁵ and the Yoon group⁴ have attracted significant attention to the applications of visible light photochemistry in organic synthesis. Several new exciting visible light photochemical processes sensitized by polybipyridyl metal complexes or organic dye photoredox catalysts were reported since then.⁵

Oxidation is a fundamental organic transformation and has been studied extensively. However, oxidation is also one of the most problematic reactions. Many classical oxidants are toxic and some heavy metal containing oxidants often generate large ³⁵ amounts of toxic waste. Moreover, many efficient but expensive oxidants have to be used stoichiometrically. Therefore, a catalytic, environmentally friendly, and economical oxidation process is

- always in demand. Among all the oxidants, molecular oxygen is an ideal reagent as it is "virtually unlimited" and free just as visible light. Numerous sophisticated oxidations occur in biological systems using molecular oxygen as the oxidant.
- However, molecular oxygen is not a reactive oxidant and in many cases the atom-economy is low (50% efficiency). Herein, we report our findings utilizing visible light and molecular oxygen
- ⁴⁵ for a selective sulfoxidation process. We believe this process meets the requirements of green chemistry and could be

considered a "near-perfect" reaction as it proceeds in a highly atom-economical and almost waste-free manner.

50 Results and discussion

The sulfoxidation of sulfides is important in many fields, such as pharmaceuticals,⁶ fossil fuels desulfurization,⁷ industrial wastewater treatment,⁸ and chemical warfare agent disposal.⁹ The main side reaction of sulfoxidation is the formation of sulfone 55 through over-oxidation. Many methods have been developed to achieve selective sulfoxidation.¹⁰ Among all the oxidants, hydrogen peroxide has been studied extensively as a "green oxidant" for sulfoxidation.^{10c} Nonetheless, a catalytic selective sulfoxidation using molecular oxygen as the terminal oxidant 60 would be more advantageous over existing methods. Although the mechanism of sulfoxidation by molecular oxygen via photochemical irradiation has been investigated in depth in physical chemistry,¹¹ the applications to organic synthesis have only been reported recently.¹² Our interest in practical synthetic 65 methods of sulfur-containing compounds under visible light photoredox conditions using molecular oxygen as the terminal oxidants,13 led us to investigate the selective sulfoxidation of thioanisole. Initial screening experiments examined the nature and effect of the photosensitizer and solvent. The results are 70 shown in Table 1. In the first round of catalyst screening, a solution of thioanisole in acetonitrile was added 2 mol% of various catalysts (entries 1-9). The reactions were carried out in open vessels under 14 W compact fluorescent lights for 24 hr. With the assistance of a catalytic amount of hydrochloric acid, 75 Rose Bengal appeared to be most efficient and selective catalyst (entry 4). Almost no over-oxidation was observed. Compared to the metal complex photoredox catalysts, Rose Bengal, an organic dye, is readily accessible and inexpensive. The reactivity of Rose Bengal in different solvents was then examined (entries 10-17), 80 with ethanol being the optimal solvent for this oxidation. The reaction was completed within 24 hr of light irradiation and the selectivity was excellent. Furthermore, the reaction time in EtOH could be shortened to 12 hr and selectivity was increased to > 99:1 in the presence of 0.2 equivalents of HCl. To ascertain that

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visible light was necessary for the reaction to proceed, a control reaction was carried out in the dark and no oxidation occurred (entry 18). Similarly, a control reaction in the absence of Rose Bengal did not proceed under identical conditions (entry 19).

5 Table 1. Screening of catalysts and solvent

	air <u>cat. (2 mol</u> Solvent, r	<u>%)</u> t 〔	0 	0
Entry	Catalyst	Solvent	GC yield	Selectivity ^b
1	Ru(bpy) ₃ Cl ₂ ·6H ₂ O	MeCN	50 %	>99:1
2	Ir(ppy) ₃	MeCN	N.R.	-
3	Rose Bengal	MeCN	16 %	>99:1
4 ^c	Rose Bengal	MeCN	80 %	98:2
5	Rodanmin B	MeCN	trace	-
6	Flourensin	MeCN	trace	-
7	Alizarin Red	MeCN	trace	-
8	Erosin B	MeCN	7.5 %	-
9°	Erosin B	MeCN	40 %	>99:1
10	Rose Bengal	DMF	19 %	>99:1
11	Rose Bengal	DMSO	7 %	>99:1
12	Rose Bengal	MeOH	75 %.	3:1
13	Rose Bengal	CH_2Cl_2	N.R.	-
14	Rose Bengal	EtOH	>99 %	98:2
15 ^c	Rose Bengal	EtOH	>99 % (12 h)	>99:1
16	Rose Bengal	NMP	N.R.	-
17	Rose Bengal	MeNO ₂	3 %	>99:1
18 ^{cd}	Rose Bengal	EtOH	N.R.	-
19 ^{ce}	-	EtOH	N.R.	

a: Reaction conditions: Thioanisole (1 mmol), catalysts (2 mol%), solvent (2 ml), opened to the air at room temperature, irradiating with 14 w fluorescent lamp for 24 hr. b: Based on GC area. c: 0.2 eq conc. HCl was 10 added. d: reaction was carried out in dark. e: no catalyst was added

The sulfoxidation of thioanisole was very clean and the only nonvolatile material besides the sulfoxide product was the catalyst. Therefore, an extremely simple workup/purification procedure 15 was developed by passing the crude reaction mixture through a short plug of basic alumina to remove the acidic Rose Bengal. Subsequent evaporation of the EtOH from the filtrate afforded a pure product without additional purification.

- ²⁰ This reaction and the workup process meet many requirements of green chemisty: a) the reaction is driven by visible light and occurs at ambient temperature; b) the reaction uses molecular oxygen from air as the oxidant; c) high atom-economy is achieved as no other reductant is involved; d) non-metal, cheap ²⁵ organic dye with relatively low loading is used as the catalyst; e)
- ²⁵ organic uye with relatively low loading is used as the catalyst; e) very low E-factor¹⁴ was achieved because minimal waste is generated; f) the reaction uses environmentally benign ethanol as the solvent that is easily recycled during workup.
- ³⁰ To test the generality of this reaction, a series of thioethers were subjected to the optimized reaction conditions (Table 2). The results demonstrate that dialkylthioethers and alkylarylthioethers almost uniformly afforded excellent yields and selectivity. Diphenylthioether gave a slow reaction possibly due to the low
- ³⁵ electron density on sulfur atom (entry 6). Phenylallylthioether only gave the desired sulfoxide in 73% yield along with an unknown byproduct (entry 8). Interestingly, the dithio derivative selectively gave mono-sulfoxidation in excellent yield and

selectivity (entry 12).¹⁵ Compared to arylalkylthioethers, the rate of dialkylthioether sulfoxidation was generally faster (entry 13-15). L-Methionine derivative was oxidized under the standard conditions as well, implying that the oxidation may be used in the sulfoxidation of biologically interesting methionine containing proteins or peptides.¹⁶ 1-(Methylsulfinyl)-4-nitrobenzene was not so oxidized because nitrobenzene is known to be a radical trap, which suggests that the oxidation may go through a radical pathway (entry 17).

Table 2. Homogeneous catalysis:	Visible light promoted aerobic
oxidation of various sulfides ^a	

Entry	Product	Reaction time	Yield ^b	Selectivity ^c
1	O=S	12 h	> 99%	>99:1
2	o S S	12 h	> 99%	>99:1
3	O S S	12 h	> 99%	>99:1
4	MeO	48 h	>99%	99:1
5	°≝s √	12 h	>99%	>99:1
6	S.Ph	48 h	67% ^{de}	>99:1
7	S_Ph	12 h	93%	98:2
8	S S S	12 h	73% ^e	99:1
9	CI S	18 h	99%	>99:1
10	Br	12 h	99%	>99:1
11	On S Br	24 h	99	>99:1
12		12 h	91% ^{ef}	>99:1
13	o S	6 h	> 99%	>99:1
14	o S S	6 h	> 99%	>99:1
15	S=O	6 h	98%	>99:1
16		8 h	>99%	>99:1 ^g
17	O-N	24 h	N.R.	-

⁵⁰ a: reaction conditions: thioether (1 mmol), Rose Bengal (2 mol%), 0.05 M HCl in EtOH (4 ml, 20 mol%), opened to the air at room temperature, using 14w fluorescent lamp as visible light source. b: isolated yield. c: selectivities were determined based on GC peak areas. d: GC conversion of sulfide is 67% after 48 h. e: isolated by silica gel chromatography. f: ⁵⁵ d.r.>99:1. g: selectivity was determined by HPLC peak areas.

To further demonstrate that the reaction is practical and scalable, a 50 mmol scale reaction was carried out in an Erlenmeyer flask under sunshine on the roof of the chemistry building (Figure 1). The reaction showed identical results as that carried out in the laboratory hood.



Figure 1. Reaction under sunshine

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The recycling of catalyst is a very important factor of green chemistry. To verify the catalyst could be reused, a thioanisole sulfoxidation reaction mixture was exposed to light and air for 12 10 hours after the reaction was completed, followed by the addition of a second equivalent of thioanisole. To our delight, the second sulfoxidation started without any problem and was completed within the same reaction timeframe, indicating the organic dye catalyst was not decomposed. This observation stimulated us to 15 seek a "greener" protocol to eliminate the catalyst waste and the waste generated during workup. The idea was to immobilize the catalyst so it could be easily recycled by a simple filtration. Attaching Rose Bengal on a resin with an ester linker was reported in the 1970's.¹⁷ Different types of heterogeneous 20 catalysts for sulfide oxidation were discovered in the last decades.^{12f, 18} It was decided to immobilize Rose Bengal onto Wang resin with a stronger amide linker (Figure 2).



²⁵ Figure 2. Preparation of solid-supported Rose Bengal.

The solid-supported catalyst was subjected to the sulfoxidation reaction. As shown in Table **3**, similar results were obtained except the rates of several heterogeneous reactions were ³⁰ somewhat slower. Nonetheless, the workup procedure was improved significantly with the use of a solid-support catalyst. Filtration to recover the catalyst, followed by evaporation/recovery of solvent, afforded the pure product.

 Table 3: Heterogeneous catalysis: Visible light promoted aerobic

 35 oxidation of various sulfides ^a

Entry	Product	Reaction time	yield ^b	Selectivity ^c
1	O S S	18 h	>99%	>99:1
2	S S S S S S S S S S S S S S S S S S S	24 h	>99%	>99:1
3	O S	24 h	> 99%	99:1
4	Meo	24 h	98%	97:3

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5	°≓S S V	48 h	>99%	98:2
6	S.Ph	48 h	53% ^{de}	99:1
7	O S Ph	24 h	78%	94:6
8	S S S	24 h	77% ^e	99:1
9	CI S	72 h	96%	98:2
10	Br	36 h	99%	98:2
11	O S Br	72 h	>99%	>99:1
12		24 h	87% ^{ef}	96:4
13	O S	12 h	98%	>99:1
14		12 h	>99%	>99:1
15	S=0	12 h	99%	>99:1

a: reaction conditions: thioether (1 mmol), polymer supported Rose Bengal (10 mol%), 0.05 M HCl in EtOH (4 ml, 20 mol%), opened to the air at room temperature, using 14 w fluorescent lamp as visible light source.
b: isolated yield. c: selectivities were determined based on GC 40 peak areas.
d: GC conversion of sulfide is 53% after 48 h. e: isolated by silica gel chromatography. f: d.r.>99:1.

To confirm the idea of catalyst recycling, the solid-supported catalyst was reused in the sulfoxidation of thioanisole for 10 ⁴⁵ times. As shown in Chart **1**, the oxidation results remained unchanged.



Chart 1. Solid-support catalyst recycling

Photosensitized sulfoxidation is generally accepted to occur via
⁵⁰ two main mechanisms, singlet oxygen oxidation through energy transfer and radical pathway through electron-transfer.^{11a, 11d, 11f} Diphenyl sulfide is known to be unreactive toward singlet oxygen. But under our optimized conditions, diphenyl sulfide was oxidized to diphenyl sulfoxide, albeit at a slower rate (Table 2, sentry 6 and Table 3, entry 6). 1-(Methylsulfinyl)-4-nitrobenzene containing a radical trap in the molecule did not participate in the reaction (Table 2, entry 17). These two results suggested that the

sulfoxidation might go through radical mechanism. It was consistant with that the oxidation of thioanisole was suppressed by benzoquinone, a radical quencher. Only 12% of PhS(O)Me was formed after 24 hours with 1 equivilent of benzoquinone ⁵ under otherwise identical conditions. Moreover, trace amount of

- diphenyl sulfone was observed when diphenyl sulfoxide was added to the reaction of thioanisole sulfoxidation. It indicated that the formation of persulfoxide, an intermediate in singlet oxygen pathway, was neglectable.¹⁹ All of the above evidence suggested to that the sulfoxidation went through electron-transfer pathway and
- superoxide anion might involved in the reaction. However, singlet oxygen oxidation through energy transfer mechanism could not be ruled out because it might operate with other thioether substrates, such as dialkyl sulfides.

15 Conclusions

In conclusion, a "near-perfect" sulfoxidation with excellent yields, selectivity, and without unwanted waste was developed. The protocol is very practical for the simple workup procedures in both homogeneous and heterogeneous reactions. Most ²⁰ importantly, the use of renewable feedstocks namely, visible light and air, and an environmentally benign solvent in a highly atom-economical and energy-efficient manner constitutes an ideal example of green chemistry.

Notes and references

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- † Electronic Supplementary Information (ESI) available: Experimental procedures, NMR and Mass spectra data of sulfoxides.
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