



## Visible-light-activated selective synthesis of sulfoxides via thiol-ene/oxidation reaction cascade

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### ABSTRACT

A convenient, highly selective and metal-free synthesis of sulfoxides from alkenes and thiols using NHPI as an inexpensive and reusable organophotoredox catalyst is reported. The protocol involves radical thiol-ene/oxidation reaction cascade and utilizes visible light and air (O<sub>2</sub>) as inexpensive, readily available, non-toxic and eco-sustainable reagents to afford up to 96% yields of the product at room temperature.

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Posner in 1905 reported the radical hydrothiolation of alkenes with thiols,<sup>1</sup> which was later termed as the thiol-ene click (TEC) reaction by Schlaad<sup>2</sup> due to its efficiency, atom economy and regioselectivity.<sup>3</sup> The reaction is synthetically very useful for the formation of carbon-sulfur bonds in various pharmaceuticals and natural products,<sup>4</sup> polymers and organic materials<sup>5</sup> as well as ligands and chiral auxiliaries.<sup>6</sup> The TEC reaction involves the anti-Markovnikov radical addition of thiols to alkenes and provides one of the most common methods for the synthesis of thioethers.<sup>3,7</sup> Owing to its high efficiency and desired functional groups compatibility, the reaction is of particular importance in biological and material sciences.<sup>8</sup>

Recently, the research groups of Yoon<sup>9</sup> and Stephenson<sup>10</sup> have demonstrated novel applications of visible light for the activation of radical thiol-ene reactions employing Ru(bpy)<sub>3</sub>(PF<sub>6</sub>) and Ru(bpy)<sub>3</sub>Cl<sub>2</sub>, respectively as the photoredox catalysts. Although these transition metal based complexes are highly efficient visible light photoredox catalysts, they suffer from disadvantages such as high cost, potential toxicity and problematic removal of their undesired traces from products. Alternatively, we have very recently used benzophenone as an inexpensive visible light organophotocatalyst in radical thiol-ene reactions.<sup>11</sup>

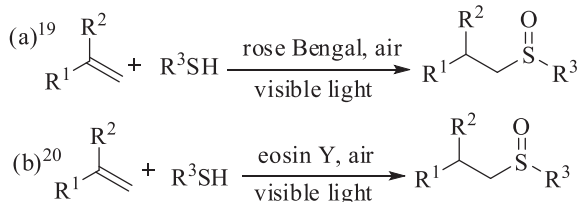
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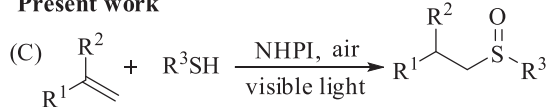
Sulfoxides constitute a class of sulfur compounds that are significantly important in natural products, medicinal chemistry and organic synthesis.<sup>12</sup> Traditional synthetic approaches to sulfoxides rely on the oxidation of sulfides with stoichiometric amounts of oxidants such as peroxides<sup>13</sup> and hypervalent<sup>14</sup> iodine reagents in the presence of a variety of transition metal catalysts.<sup>15</sup> A few reports are also available on the application of visible light photocatalysis to the oxidation of sulfides to sulfoxides.<sup>16</sup> All these methods require at least two operationally separate steps, that is, the preparation of sulfides and their oxidation. In addition, most of them use hazardous oxidants and some toxic metal reagents, and also suffer from overoxidation of sulfoxides to sulfones.

Recently, Klusmann<sup>17</sup> and Chi<sup>18</sup> have reported one-pot synthesis of sulfoxides from alkenes and thiols using methanesulfonic acid (MsOH) and *N*-fluorobenzene sulfonimide (NFSI), respectively. In continuation of this advancement, the research groups of Wang<sup>19</sup> and Aleman<sup>20</sup> have demonstrated the elegant synthesis of sulfoxides via thiol-ene/oxidation tandem reaction using rose Bengal (Scheme 1a) and eosin Y (Scheme 1b), respectively as visible light photocatalysts. Although the reactions are efficient and performed under an air atmosphere, both the photocatalysts are unstable and they decompose under visible light irradiation,<sup>21</sup> hence their recovery from the reaction mixture for reutilization is problematic. This prompted us to go for a stable, more efficient and reusable photocatalyst suitable for thiol-ene/oxidation tandem reaction. Based on the effectiveness of recently reported<sup>22</sup> visible

## Previous work



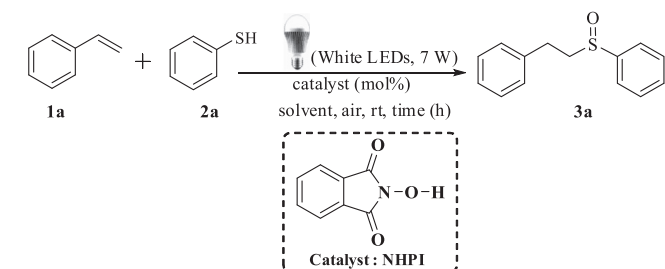
## Present work



Scheme 1. Visible-light-promoted synthesis of sulfoxides.

light organophotoredox catalyst, NHPI (*N*-hydroxyphthalimide), we opted to use it throughout the present study. NHPI generates PINO (phthalimide-*N*-oxyl) radicals under visible light irradiation.<sup>22</sup>

In view of the above points and our current focus on the development of visible light organophotoredox catalyzed new synthetic routes,<sup>22,23</sup> we assumed that the thiyl radicals could be easily generated photochemically from thiols using NHPI as the catalyst, which would lead to the formation of sulfoxides through thiolene reaction and subsequent oxidation with atmospheric oxygen under the same reaction conditions (Scheme 1c). To the best of our knowledge, this is the first example to generate thiyl radicals employing NHPI under visible light irradiation.

Table 1  
Optimization of reaction conditions.<sup>a</sup>

Entry	Reaction conditions	Time (h)	Yield (%) <sup>b</sup>
1	NHPI (10 mol%), CH <sub>3</sub> CN, white LEDs	8	89
2	NHPI (10 mol%), CH <sub>3</sub> CN, in the dark	12	n.d.
3	No catalyst, CH <sub>3</sub> CN, white LEDs	12	n.d.
4	NHPI (10 mol%), DCE, white LEDs	8	58
5	NHPI (10 mol%), DMF, white LEDs	8	68
6	NHPI (10 mol%), DMSO, white LEDs	8	73
7	NHPI (10 mol%), THF, white LEDs	8	65
8	NHPI (5 mol%), CH <sub>3</sub> CN, white LEDs	8	54
9	NHPI (15 mol%), CH <sub>3</sub> CN, white LEDs	8	89
10	NHPI (10 mol%), CH <sub>3</sub> CN, 80 °C	8	53 <sup>c</sup>
11	NHPI (10 mol%), CH <sub>3</sub> CN, white LEDs	8	89 <sup>d</sup>
12	NHPI (10 mol%), CH <sub>3</sub> CN, white LEDs	8	89 <sup>e</sup>

<sup>a</sup> Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), NHPI (5–15 mol%), in 3 mL solvent irradiated under an air atmosphere at rt using white LEDs (7 W) for 8–12 h.

<sup>b</sup> Isolated yield of the pure product **3a** (For general procedure, see experimental section); n.d. = not detected.

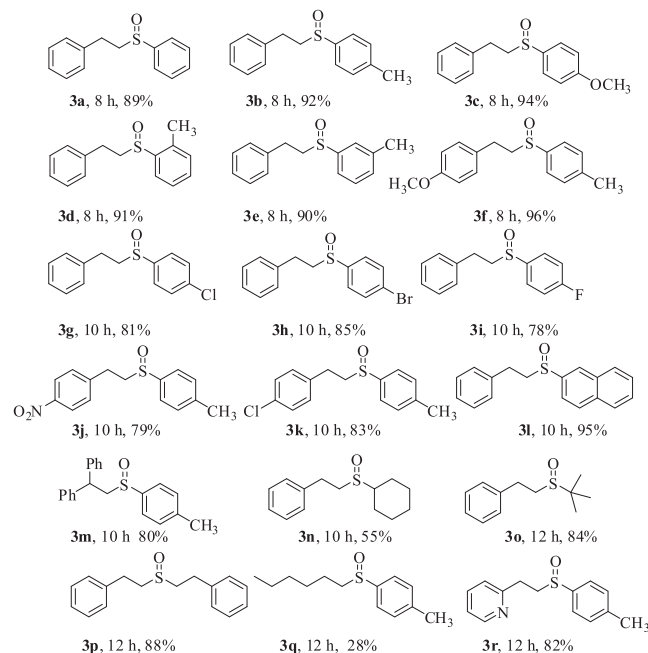
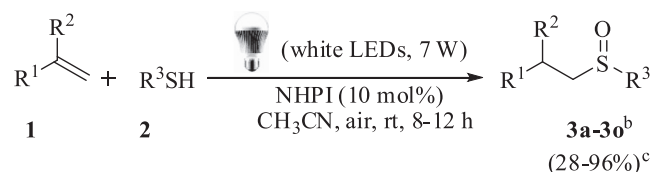
<sup>c</sup> Reaction was conducted at 80 °C in the dark.

<sup>d</sup> Catalyst was recovered in 93% yield.

<sup>e</sup> Recovered catalyst was used.

To realize our assumed protocol and optimize the reaction conditions, a model reaction was performed with a mixture of styrene **1a** (1 mmol) and thiophenol **2a** (1 mmol) in acetonitrile (3 mL) in the presence of catalytic amount of NHPI (10 mol%) under an air atmosphere and irradiation with 7 W white LEDs (white light emitting diodes) at room temperature (Table 1). We were delighted to get the desired product sulfoxides **3a** in 89% yield (Table 1, entry 1). We demonstrated that there was no product formation when the reaction was conducted in the dark (Table 1, entry 1 versus 2). Then, the control experiments were carried out, which show that a photocatalyst, NHPI and visible light are essential for the reaction because in the absence of NHPI the desired product was not detected (Table 1, entry 1 versus 3).

Next, we optimized the reaction for a suitable solvent. It was found that acetonitrile was the best among the tested solvents, viz. DCE, DMF, DMSO and THF to afford the desired product in excellent yield (Table 1, entry 1 versus 4, 5, 6 and 7), hence it was used throughout the present study. The optimum amount of the photocatalyst NHPI required for the reaction was 10 mol%. On decreasing the amount of the catalyst NHPI from 10 mol% to 5 mol%, a significant decrease in the yield of **3a** was observed (Table 1, entry 1 versus 8), while an increase in the amount of the photocatalyst from 10 mol% to 15 mol% does not affect the yield of the product (Table 1, entry 1 versus 9). Moreover, the catalyst NHPI also works under thermal conditions but gives a considerably lower yield of the desired product **3a** (Table 1, entry 1 versus 10). Advantageously, the catalyst was recovered in high

Table 2  
Substrate scope for the synthesis of sulfoxides.<sup>a</sup>

<sup>a</sup> For experimental procedure, see Ref. 24.

<sup>b</sup> All compounds are known and were characterized by comparison of their spectral data with those reported in the literature.<sup>17–19</sup>

<sup>c</sup> Yields of isolated pure compounds **3**.

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