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## Short communication

# A recyclable fluorous thiourea organocatalyst for the chemoselective oxidation of sulfides

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## ARTICLE INFO

## ABSTRACT

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*Keywords:* Fluorous thiourea Organocatalyst Oxidation Fluorous solid-phase extraction (F-SPE) As a kind of organocatalyst, 1-[4-(perfluorooctyl)phenyl]-3-phenylthiourea was employed to the chemoselective oxidation of sulfides in the presence of 30% H<sub>2</sub>O<sub>2</sub>. A variety of diaryl, dialkyl, alkyl aryl sulfides could be oxidized to sulfoxide under the mild condition. The catalyst could be easily recovered by fluorous solid-phase extraction for reuse.

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## 1. Introduction

Compared with the traditional metal-based catalyst, organocatalyst has drawn much attention, owing to its low toxicity, operational simplicity and high efficiency [1]. However, some drawbacks also gradually appear with the application of organocatalyst. The major disadvantages are the high loading (up to 20 mol%) and the difficulty of recovering the catalyst. As a result, some alternative strategies, i.e. immobilization technique [2,3] and fluorous tag technique [4] have been developed to recycle the organocatalysts.

Recently Curran's group have elaborated a recycling technique by the fluorous solid-phase extraction (F-SPE) methodology using fluorous silica gel [5]. Then some fluorous orgnocatalysts have been designed for a variety of reactions, and could be recovered by F-SPE. In our previous work, 1-[4-(perfluorooctyl)phenyl]-3-phenylthiourea **2** (Scheme 1) have been prepared and applied to the reductive amination [6]. Moreover, the fluorous thiourea catalyst could perform in the reactions as well as the Schreiner catalyst of N, N'-bis[3,5bis(trifluoromethyl)phenyl]thiourea **1** (Scheme 1) [7]. The most important one is that the catalyst **2** could be recovered much easier than the catalyst **1** by F-SPE. It was because that catalyst **2**  bearing long fluorous chain  $C_8F_{17}$ - had better retention behavior than catalyst **1** in the fluorous gel, which was favorable for the recovering the catalyst during F-SPE.

Organosulfur compounds, such as sulfoxides and sulfones, are useful synthetic agents in organic chemistry. In particular, sulfoxides are valuable synthetic intermediates for the production of therapeutic agents [8]. Generally, sulfoxides could be obtained by the oxidation of sulfides. Many oxidizing reagents could be used to accomplish this transformation [9]. Among them, hydrogen peroxide is the most attractive one because of its low cost and cleanness. In the previous reports, H<sub>2</sub>O<sub>2</sub>/acetone [10], H<sub>2</sub>O<sub>2</sub>/methanol [11], and H<sub>2</sub>O<sub>2</sub>/acetic acid [12] were employed to oxidize dialkyl sulfides and some aryl sulfides. In these methods, several fold equivalents of hydrogen peroxide were needed and longer time was demanded. In addition, these methods were unsuitable for the oxidation of diaryl sulfide [10,11] and some sensitive substrates [12]. Later, all kinds of the improved oxidation methods, especially by the use of transition metal (V, Mo, Ti) ion [9], were developed so as to overcome these drawbacks. But organocatalytic oxidative system was seldom reported [13,14].

As far as we know, all kinds of the substituted thiourea could effectively catalyze the organic reactions due to the double hydrogen bond activation [7]. In 2009, Lattanzi et al. [15] reported the first example of sulfoxidation with tert-butyl hydroperoxide (TBHP) mediated by the thiourea **1**. Inspired by their idea, we applied the fluorous thiourea **2** to the oxidation of sulfides with

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Scheme 1. Two kinds of thiourea catalyst

30% hydrogen peroxide. To our delight, the catalyst exhibited good catalytic activity and selectivity in the reaction.

## 2. Results and discussion

In our experiment, catalyst **2** could be easily prepared by phenyl isothiocyanate and perfluorooctyl aniline in THF [6]. At the beginning, we carried out a model reaction involving the sulfoxidation of methyl phenyl sulfide with 30% hydrogen peroxide.

As seen from Table 1, the solvent had a pronounced effect on the yield. In the absence of catalyst, the transformation of sulfides to sulfoxides was difficult to proceed under the above conditions (Table 1, entries 1–5). From these results, we found that the sulfoxides obtained in the solvent of  $CH_2Cl_2$  or  $CH_3OH$  were higher than those in the other solvents. When catalyst 1 or 2 was loaded to the reaction, the oxidation of sulfides proceeded smoothly in  $CH_2Cl_2$  (Table 1, entries 7 and 9). Unfortunately, the corresponding yields were not high with  $CH_3OH$  as a solvent (Table 1, entries 6 and 8), which could be explained by the inhibition of catalyst activity due to intermolecule hydrogen bonding [15].

Next, the effect of catalyst loading on the results was also evaluated. When catalyst loading was changed from 2 mol% to 5 mol%, the yields of sulfoxides were increased from 85% to 95% (Table 1, entries 10–12). When 10 mol% of catalyst was used, the yield did not increase significantly (Table 1, entry 9). In addition, methyl phenyl sulfone as a kind of by-product of over oxidation was not determined by GC–MS.

With the optimized reaction conditions in hand, we next examined the recovery of catalyst **2**. After the reaction was finished, the mixture was concentrated and then loaded onto a Fluoro*Flash*<sup>®</sup> silica gel cartridge for F-SPE. It was found that the catalyst **2** could be cleanly recovered (92–95%). The corresponding product purity was above 98.5% with HPLC analysis. Meanwhile, the organocatalyst **2** could be repeatedly reusable. In each run, the

#### Table 1

Oxidation of methyl phenyl sulfide to methyl phenyl sulfoxide with  $H_2O_2$  catalyzed by fluorous thiourea catalyst  ${\bf 1}$  or  ${\bf 2.}^a$ 

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%) <sup>b</sup>
1	None	CH₃OH	24	28
2	None	CH <sub>3</sub> CN	24	22
3	None	$CH_2Cl_2$	24	31
4	None	THF	24	13
5	None	Toluene	24	10
6	<b>1</b> (10)	CH <sub>3</sub> OH	12	76
7	<b>1</b> (10)	$CH_2Cl_2$	12	95
8	<b>2</b> (10)	CH₃OH	12	80
9	<b>2</b> (10)	$CH_2Cl_2$	12	97
10	<b>2</b> (5)	$CH_2Cl_2$	12	95
11	<b>2</b> (2)	$CH_2Cl_2$	12	85
12	<b>2</b> (2)	$CH_2Cl_2$	16	88

 $^a\,$  Reaction condition: methyl phenyl sulfide 2 mmol,  $H_2O_2$  4 mmol, solvent 2 mL, room temperature 25 °C.

<sup>b</sup> Isolated yield after column chromatography.

recovered **2** retained its catalytic activity for five cycles (Table 2) without further purification.

Next, oxidation of a variety of sulfides was examined in order to demonstrate the scope of reaction as revealed in Table 3, all the reactions could give the products in moderate to excellent yields. Initially, different phenyl substituted sulfides were examined under the optimized condition. The substrates bearing electron withdrawing group such as para-nitro, exhibit higher activity than the other ones, and the yield was 98% (Table 3, entry 4). However, for para-methyl and para-chloro substituents, longer time was required to obtain the products with high yields (Table 3, entries 2 and 3). As for entry 5, an equimolar amount of *para*-nitro (1 mmol) and para-methyl sulfides (1 mmol) is treated with 1 mmol of 30%  $H_2O_2$  in the presence of the thiourea catalyst, the product could be obtained with 4-nitrophenyl methyl sulfoxide (72%) and 4methylphenyl methyl sulfoxide (26%). It could be explained that substituent bearing electron withdrawing group was more active than it of electron donating group. In addition, we explored the processes with some steric substrates of diphenyl sulfide and thioxanthone. We found that the reaction rate slowed down significantly, and the reaction yields were not high (Table 3, entries 6 and 7). The results showed that the steric effects seemed to play an important role in the sulfoxidation.

In order to investigate the reactivity of the substrates with dialkyl group, diethyl sulfide was examined further. We found that the corresponding product was obtained in 97% yield (Table 3, entry 8). While one alkyl group was replaced with benzyl, the reaction was also proceeded efficiently in high yield (Table 3, entry 9). Furthermore, sulfides with functional group such as C=C were also found to be well tolerated during the oxidative process. A variety of sulfides were smoothly transformed into sulfoxides in our oxidative system. Meanwhile, the sulfones were not determined by GC–MS in the products.

As shown in entries 2, 6 and 8, the corresponding catalyst could be recycled more than three times with high reactivity. In addition, all products listed in Table 3 are known compounds. In addition, all products listed in Table 3 are known compounds and their structures were determined by <sup>1</sup>H NMR, <sup>13</sup>C NMR and by GC–MS, which were in accordance with the literatures.

Table 2
Recycling and reuse of the fluorous organocatalyst ${\bf 2}$ by F-SPE. <sup>a</sup>

Run	Recovered catalyst (%) <sup>b</sup>	Yield of product (%) <sup>c</sup>
Initial use	100	95
First reuse	95	93
Second reuse	95	92
Third reuse	93	90
Fourth reuse	92	90
Fifth reuse	90	89

 $^a\,$  Reaction condition: methyl phenyl sulfide 2 mmol,  $H_2O_2\,4$  mmol,  $CH_2Cl_2\,2\,mL$ , catalyst 2.5 mol%, reaction time 12 h, room temperature 25 °C.

<sup>b</sup> Recovered by F-SPE.

<sup>c</sup> Isolated yield after column chromatography.

## Table 3

Chemoselective oxidation of sulfides with fluorous thiourea/H2O2 system.<sup>a</sup>

Entry	Sulfide <b>3</b>	Sulfoxide <b>4</b>	Time (h)	Yield <b>4</b> (%) <sup>b</sup>
1	SS_	0 II S	12	95
	3a	<b>4a</b>		
2	SS	O II S	16 16	82 80
	3b	4b	16	79
3	SS_		16	90
	CI 3c	<b>ct 4c</b>		
4	SS		10	98°
	NO <sub>2</sub> 3d	NO <sub>2</sub> 4d		
5	SS_		16	26 <sup>d</sup>
	3b	4b		
	SS			72
NO <sub>2</sub>	NO <sub>2</sub> 3d	NO <sub>2</sub> 4d		
6	S S	0    5	24 24	78 78
	3e	4e	24	76
7	S S	O II S	32	76 <sup>c</sup>
	<sup>0</sup> 3f	↓ ↓ ↓ 0 4f		
8	<u>∕_s</u> ∕3g	S S S S S S S S S S S S S S S S S S S	8 8	97 <sup>e</sup> 95
9		<sup>0</sup> 4g	8	92
-	3h	S U U	-	
10		• <b>4h</b>	24	83
	31	<b>4i</b>		
11	<u>۶ مرکم میں</u>		8	92 <sup>e</sup>
		$\sim \sim \sim \leq 4j$		

<sup>a</sup> Reaction condition: sulfide 2 mmol, H<sub>2</sub>O<sub>2</sub> 4 mmol, catalyst 2.5 mol%, CH<sub>2</sub>Cl<sub>2</sub> 2 mL, room temperature 25 °C.
 <sup>b</sup> Isolated yield after column chromatography.
 <sup>c</sup> 5 mL CH<sub>2</sub>Cl<sub>2</sub> was required to ensure to dissolve substrates.
 <sup>d</sup> 1 mmol **3b** and 1 mmol **3d**, H<sub>2</sub>O<sub>2</sub> 1 mmol, catalyst 2.5 mol%, CH<sub>2</sub>Cl<sub>2</sub> 2 mL, room temperature 25 °C.
 <sup>e</sup> Yields were determined by GC.

## 3. Conclusions

In summary, a kind of fluorous organocatalyst was applied to the chemoselective oxidation of sulfides in presence of  $30\% H_2O_2$ . A variety of diaryl, dialkyl, alkyl aryl sulfides could be afforded to sulfoxide under the mild condition. The fluorous organocatalyst could be easily recovered by F-SPE for reuse.

## 4. Experimental

Sulfide **3** (2 mmol) and catalyst **2** (0.1 mmol, 64.5 mg) were dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 mL). H<sub>2</sub>O<sub>2</sub> (4 mmol, 30% H<sub>2</sub>O<sub>2</sub> 272.2 mg) was then added. The reaction process was monitored by TLC. When the reaction was finished, the solvent was removed under reduced pressure. The residue was loaded onto a Fluoro-*Flash*<sup>®</sup> silica gel cartridge (2 g), then eluted by 80% aqueous methanol 8–10 mL in order to separate non-fluorous organic components from the mixture. Then the cartridge was eluted by 100% methanol 15–20 mL so as to recover the catalyst. Meanwhile, the first elutant was evaporated to obtain the crude products. The remains was purified by flash chromatography on silica gel using mixtures of petroleum ether and ethyl acetate (80:20–20:80) as eluent to give the sulfoxides **4a–4j**. All compounds were characterized by MS, <sup>1</sup>H NMR and <sup>13</sup>C NMR, and were compared with the authentic samples.

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