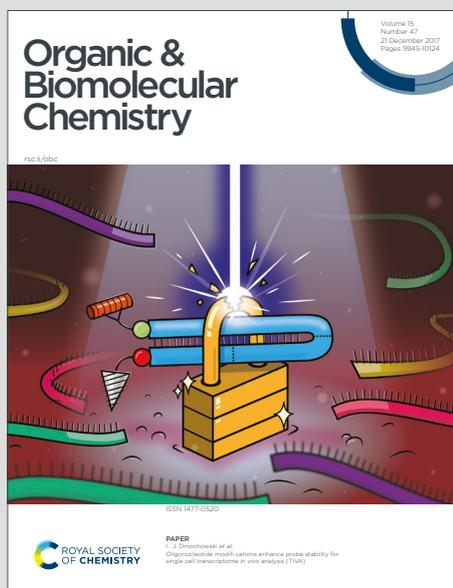


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Tungsten-catalyzed continuous-flow oxidation of sulfides to sulfones with hydrogen peroxide

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Abstract

Continuous-flow oxidation of sulfides to sulfones was achieved with hydrogen peroxide (H₂O₂) using a catalyst column, which was simply packed with a mixture of oxodiperoxotungstate–2,2'-bipyridine and commercially available activated carbon. Sulfones were continuously produced in more than 90% yield for up to 160 h by passing an acetonitrile solution of sulfides and H₂O₂ through the catalyst column. Activated carbon played a key role in immobilizing the tungsten catalyst while the other supports, Celite or silica gel did not have such an ability to catch the catalyst. Selective oxidation to sulfone took place under continuous-flow conditions even though the sulfide substrates contained other oxidizable functional groups, such as olefinic double bond, hydroxy group, and pyridyl and amino functional groups.

Introduction

Sulfones are useful synthetic intermediates due to their ability to stabilize α -carbanions, and sulfonyl moieties have been incorporated into various structures, such as agrochemicals, pharmaceuticals and polymers.¹ In general, sulfones can be synthesized through the oxidation of the corresponding sulfides.² Although oxidation of the sulfide to the corresponding sulfone has been performed using a wide variety of traditional oxidizing agents, such as KMnO₄,³ CrO₃,⁴ and RuO₄,⁵ there remains a demand for environmentally and economically viable synthetic routes that do not require expensive and toxic reagents. From these points of view, hydrogen peroxide (H₂O₂) is a superior oxidizing agent, as water is the sole coproduct after the oxidation.⁶ Recently, H₂O₂ in combination with a metal catalyst, such as tungsten,⁷ iron,⁸ cobalt,⁹ or titanium¹⁰ has been shown to be effective for the oxidation of sulfides to sulfones. For recovery of the oxidation catalyst, various processes have been proposed,



with immobilization of metal catalysts on a solid support being among the most promising.

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During the last few decades, organic reactions under flow conditions have attracted considerable interest in both academia and industry.¹¹ Especially in the field of oxidation processes, flow reactions have numerous advantages over the corresponding batch reactions, including environmental compatibility due to the closed vapor-tight system, efficiency due to the small reaction volume, and relatively safer reaction conditions.¹² Doherty et al. previously reported the continuous-flow oxidation of sulfides to sulfones using a fine-tuned organopolymer-immobilized peroxophosphotungstate catalyst, which was prepared from an imidazolium-based styrene monomer via multiple steps.¹³ They demonstrated that sulfones could be continuously provided over 8 h by the flow of sulfides and H₂O₂ through a catalyst-packed column. Subsequently, continuous-flow synthesis of sulfones was also achieved using electrochemical flow processes¹⁴ and microreactor systems.¹⁵ The main issue of continuous-flow reaction is the requirement of a tightly immobilized and highly efficient catalyst. With respect to oxidation catalysts, oxodiperotungsten and oxodiperotungsten molybdenum complexes have recently been shown to be efficient.¹⁶ In 2007, Li et al. reported that an oxodiperotungstate–1,10-phenanthroline complex efficiently catalyzed the oxidation of dibenzothiophene to the corresponding sulfone in an ionic liquid by a batch method.¹⁷

Recently, we reported the continuous-flow selective oxidation of sulfides to sulfoxides catalyzed by iron oxide on activated carbon with H₂O₂.¹⁸ The iron oxide on activated carbon catalyst was selective toward sulfoxide formation and no remarkable increase in sulfone formation was observed, even though the amount of iron-activated carbon composite catalyst increased. It should be also emphasized that oxidation could be successfully performed with commercially available and less expensive materials; iron salts, H₂O₂ and activated carbon. Building on our previous finding that activated carbon is an effective support for metal catalysts, we explored activated carbon-supported tungsten-based catalysts. In this paper, we report the continuous-flow oxidation of sulfides to sulfones catalyzed by oxodiperotungstate–2,2'-bipyridine (WO(O₂)₂-bpy) immobilized on activated carbon.

Results and discussion

Catalytic activity of a tungsten-based catalyst for continuous-flow oxidation of sulfides

Immobilized metal–ligand catalysts have often been prepared using metallic species and solid-supported ligands. For example, peroxotungstate ions (WO₄²⁻) supported on mesoporous silica were



prepared from Na_2WO_4 and ammonium salt-functionalized mesoporous silica by an ion-exchange process.¹⁹ On the other hand, activated carbon has recently been used as a solid support without specific ligands.²⁰ In our previous report, we showed that iron salts were introduced onto activated carbon and that the resulting composite catalyzed the oxidation of sulfides to sulfoxides in continuous-flow reactions.¹⁸ In this study, we further explored the potential of activated carbon by investigating flow oxidations using activated carbon as a solid support for other metal catalysts. We focused on oxodiperoxotungstate–2,2'-bipyridine ($\text{WO}(\text{O}_2)_2\text{-bpy}$) **1** as shown in Fig. 1 which was prepared from tungsten oxide WO_3 or the polyoxotungstate anion $\text{PW}_{12}\text{O}_{40}^-$ and 2,2'-bipyridine and has shown catalytic activity in the epoxidation of olefins.^{21,22}

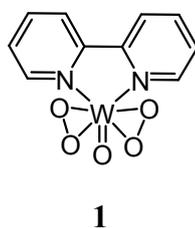


Fig. 1 Oxodiperoxotungstate–2,2'-bipyridine ($\text{WO}(\text{O}_2)_2\text{-bpy}$) **1**

In continuation of our studies of sulfide oxidation, we performed the continuous-flow oxidation of sulfides to sulfones with H_2O_2 by utilizing the tungsten complex **1** immobilized on activated carbon as a catalyst (Fig. 2). Preparation of the catalyst was straightforward. Powdered tungsten complex **1** was mixed with activated carbon, which was purchased from Strem Chemicals, Inc, and the mixture was packed into a glass column (5 mm inner diameter \times 50 mm length). An acetonitrile solution of diphenyl sulfide **2a** (0.1 M) containing H_2O_2 (2.2 eq. per **2a**) was introduced into a flow reactor equipped with the packed column.²³ The reaction was conducted at 40 °C under a back pressure of 0.2 MPa, with the flow rate set to 0.05 mL min^{-1} . The molar hourly space velocity (SV_{mol}) was 16 h^{-1} ,²⁴ which was calculated by multiplying the flow rate by the concentration of sulfide **2a** in acetonitrile, dividing by the amount of $\text{WO}(\text{O}_2)_2$ in the column, and correcting for time units.

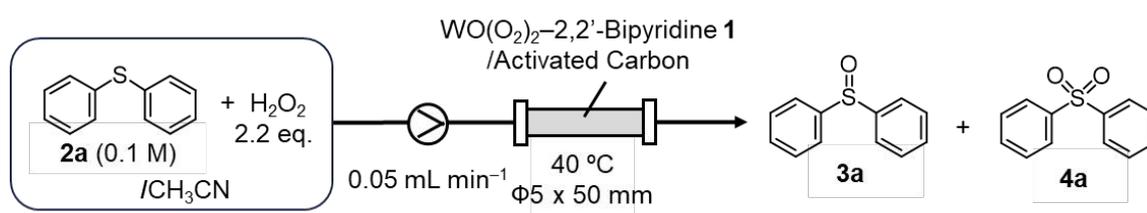
Fig. 2a shows the time-course curve of the continuous-flow oxidation after reaching a steady state, in which the total yields of sulfide **2a**, sulfoxide **3a**, and sulfone **4a** were over 95%, indicating that no other by-products were produced.²⁵ The effluent was collected every hour. The sample labeled “4 h” in the graph corresponds to the fraction collected from 3 h to 4 h (hereafter, “the 4 h fraction”).



In this flow reaction, sulfide **2a** was completely consumed. The gradual increase of yield of sulfone **4a** accompanying the gradual decrease of yield of sulfoxide **3a** was observed from 4 h to 20 h. After 10 h, over 90% yield of sulfone **4a** was continuously produced up to the 110 h fraction without a decrease in the yield of **4a**.^{26,27} At the early stage of flow reaction, fixation of catalyst **1** on activated carbon takes place. In addition, induction time may be needed to reach equilibrium stage between starting material **2a**, sulfoxide **3a**, sulfone **4a** and activated carbon. Therefore, it was suggested that some time was essential to reach maximum catalytic efficiency.

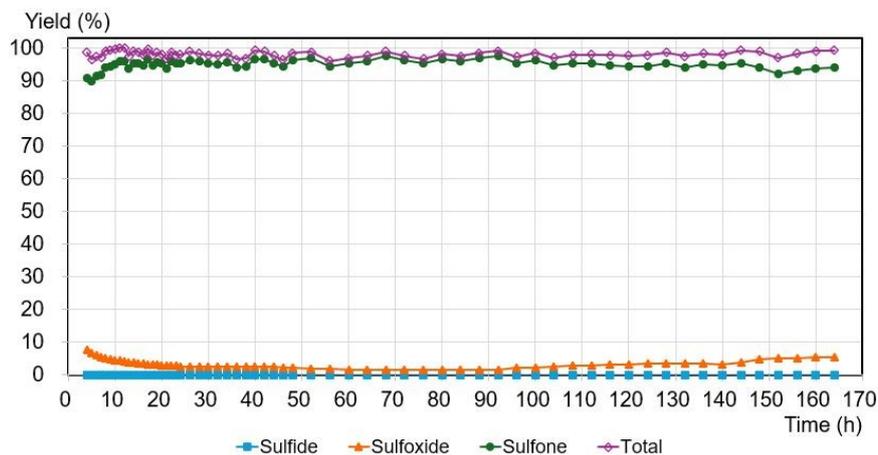
On the other hand, the yield of sulfone **4a** decreased slightly by the end of the 164 h fraction, accompanied by a slight increase in sulfoxide **3a**. To clarify the reason for the decrease in catalytic activity, we performed the following experiments. First, the 51 h to 100 h fractions were collected and subjected to quantitative ICP-MS analysis to evaluate tungsten leaching. Only 0.17% of tungsten, relative to the initial amount of tungsten complex **1** loaded in the column, was detected in the collected fractions. Therefore, the decrease in catalytic activity does not appear to be attributable to the leaching of the tungsten catalytic species.

Secondly, a washout experiment was performed. After flow oxidation for 164 h, the column was washed with acetonitrile at a flow rate of 0.05 mL min⁻¹ at 40 °C for 5 h. An acetonitrile solution of diphenyl sulfide **2a** and H₂O₂ was again introduced into the flow reactor for 24 h. As a result, the average yield of sulfone **4a** recovered to 97%, and the average yield of sulfoxide **3a** was suppressed to 2% (Fig. 2b). These results suggest that the gradual decrease in the yield of sulfone **4a** after 100 h (Fig. 2a) was caused by adsorption of sulfur-containing compounds on the catalytic species, namely deactivation of the catalyst. Overall, the results indicate that the decreased yield of sulfone **4a** at the end stage of Fig. 2a is unlikely to be due to leaching of tungsten catalytic species from the column.



a) $\text{WO}(\text{O}_2)_2\text{-bpy } \mathbf{1}$ /activated carbon





b) $\text{WO}(\text{O}_2)_2$ -bpy **1**/activated carbon (after flow reaction followed by washing the catalyst column)

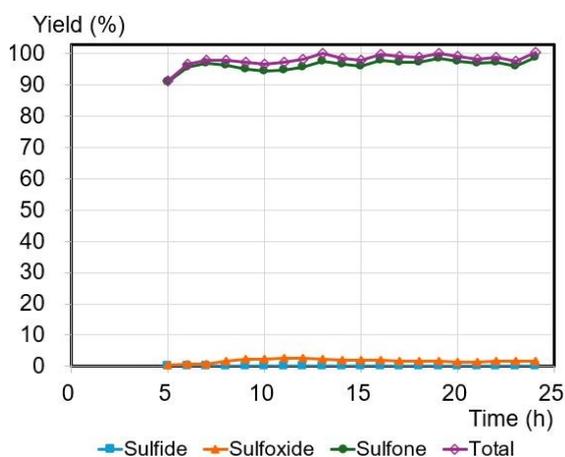


Fig. 2 Continuous-flow oxidation of diphenyl sulfide **2a** with H_2O_2 . a) Time course curve of oxidation using a mixture of $\text{WO}(\text{O}_2)_2$ -bpy **1**/activated carbon as a catalyst. b) Recovery of catalytic activity by washing the column with acetonitrile (0.05 mL min^{-1} at $40 \text{ }^\circ\text{C}$ for 5 h) after flow oxidation over 164 h.

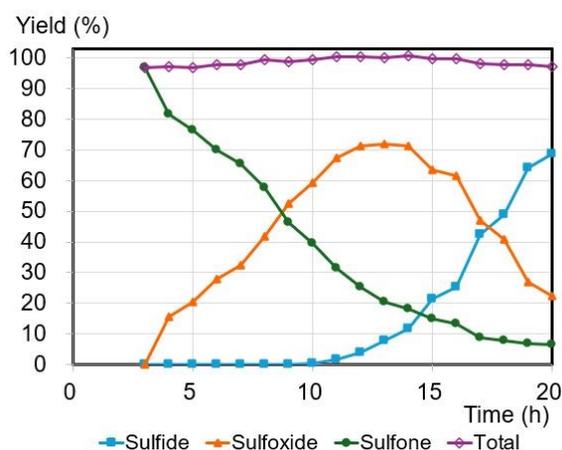
Role of activated carbon

In order to investigate the effect of activated carbon in the reaction, other solid supports were examined. The catalyst column was prepared using the same procedure, but with activated carbon replaced by Celite or silica gel. Continuous-flow oxidation reaction of diphenyl sulfide **2a** using a $\text{WO}(\text{O}_2)_2$ -bpy **1**/Celite column was carried out for 20 h. In contrast to the **1**/activated carbon catalyst, the yield of sulfone **4a** decreased significantly over time (Fig. 3a). When a mixture of tungsten complex **1** and silica gel was used as a catalyst, the yield of sulfone **4a** also decreased after 7 h (Fig.



3b), although the decrease was slower than in the $\text{WO}(\text{O}_2)_2$ -bpy **1**/Celite case. These unique results suggest that tungsten catalytic species were deactivated and/or leached from the column. As these results sharply contrast with those obtained using the $\text{WO}(\text{O}_2)_2$ -bpy **1**/activated carbon catalyst, we further investigated differences in tungsten leaching among the solid supports.

a) $\text{WO}(\text{O}_2)_2$ -bpy **1**/Celite



b) $\text{WO}(\text{O}_2)_2$ -bpy **1**/silica gel

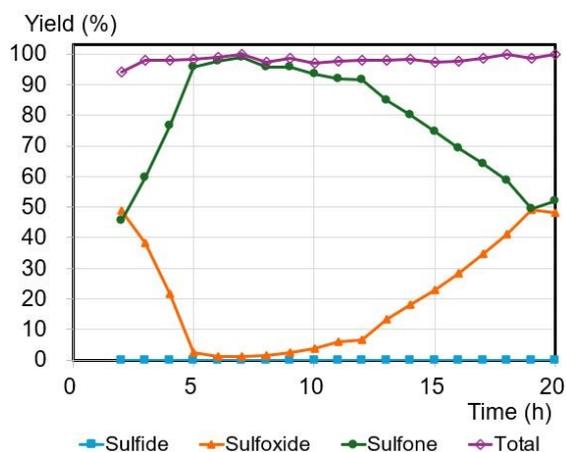


Fig. 3 Continuous-flow oxidation of diphenyl sulfide **2a** with H_2O_2 using a mixture of $\text{WO}(\text{O}_2)_2$ -bpy **1** and a solid support. a) Celite; b) silica gel.

To confirm whether leached tungsten species from each solid support exhibited catalytic activity in the oxidation of sulfide **2a**, we subsequently examined sulfide oxidation by a batch method using fractions collected from the flow reactions (Fig. 2a, Fig. 3a, and Fig. 3b), as shown in Fig. 4. Three fractions that gave a high yield of diphenyl sulfone **4a** were transferred to the reaction vessels (Fig.



2a: the 41–43 h fractions; Fig. 3a: the 4 h–6 h fractions, Fig. 3b: the 5 h–7 h fractions). Diphenyl sulfide **2a** (final concentration, 0.1 M) and H₂O₂ (2.2 eq. per **2a**) were added to each vessel, and the solution was stirred at 40 °C for 24 h. The yields of sulfone **4a** and sulfoxide **3a** were calculated based on the initial amount of sulfide **2a**, which was completely converted to sulfoxide **3a** and sulfone **4a** under flow oxidation.

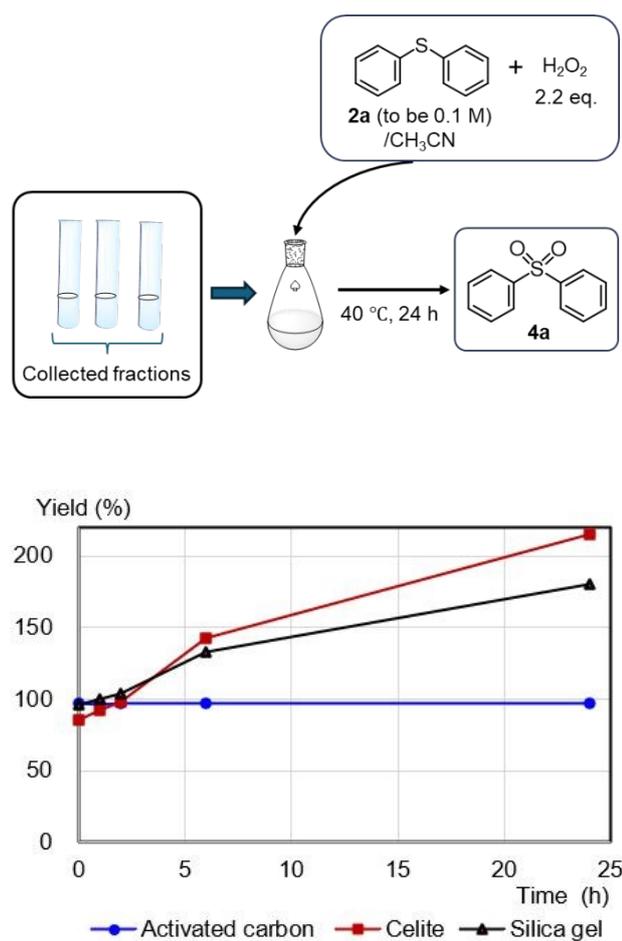


Fig. 4 Oxidation of diphenyl sulfide **2a** to diphenyl sulfone **4a** using fractions collected from the flow reactions by a batch method. The yields of **4a** at 0 h represent the average yields of **4a** in the collected fractions. The time-dependent increase in the yield of **4a** is shown as the accumulated yield from the collected fractions; thus, the yield of sulfone **4a** can exceed 100%.

As shown in the time-course curve for oxidation of diphenyl sulfide **2a** in Fig. 4, the yield of sulfone **4a** did not increase when the collected fraction from the continuous-flow reaction using the WO(O₂)₂-bpy **1**/activated carbon catalyst was subjected to further oxidation. On the other hand, a time-dependent increase in the yield of sulfone **4a** was observed for cases when fractions collected from



continuous-flow reactions using either $\text{WO}(\text{O}_2)_2$ -bpy **1**/Celite or $\text{WO}(\text{O}_2)_2$ -bpy **1**/silica gel were subjected to further oxidation. In particular, the increase in the yield of sulfone **4a** was pronounced for the $\text{WO}(\text{O}_2)_2$ -bpy **1**/Celite system. These increases can be explained by catalytic oxidation by leached tungsten species present in the collected fractions. These results further indicate again that the tungsten catalytic species is firmly immobilized on activated carbon, but not on Celite or silica gel.

Continuous-flow oxidation of various sulfides

Encouraged by the results that $\text{WO}(\text{O}_2)_2$ -bpy **1**/activated carbon is a suitable oxidation catalyst, we then performed continuous-flow oxidation of various sulfides **2** catalyzed by $\text{WO}(\text{O}_2)_2$ -bpy **1**/activated carbon (Table 1). Average yields were calculated after reaching a steady state, in which the total yields of sulfide **2**, sulfoxide **3**, and sulfone **4** reached 90%. The time windows used for yield calculation are indicated as "Fraction time" in Table 1. The procedures for catalyst preparation and the flow reaction were the same as in Fig. 2a. For diphenyl sulfide **2a** (Table 1, entry 1), the data in Fig. 2a are summarized in Table 1, indicating that diphenyl sulfide **2a** continuously provided sulfone **4a** in a 95% average yield, with no remaining sulfide **2a**, and with formation of 3% sulfoxide **3a**. In the oxidation of aliphatic sulfides (dibutyl sulfide **2b**, dibenzyl sulfide **2c**, dodecyl methyl sulfide **2d**, and thiacyclopentane **2e**), the sulfides were completely consumed and the corresponding sulfones **4b**–**4e** were continuously produced in nearly quantitative yields (Table 1, entries 2–5). Methyl phenyl sulfide **2f** and the chloro- or methoxy- substituted analogues **2g** and **2h** also produced the corresponding sulfones **4f**, **4g**, and **4h** in excellent average yields (>99%, >99% and 98%, respectively; Table 1, entries 6–8).

Subsequently, we performed continuous-flow oxidation of sulfides bearing easily oxidizable functional groups. In the oxidation of methyl 2-pyridyl sulfide **2i**, the corresponding sulfoxide **3i** and sulfone **4i** were produced without *N*-oxidation in 11% and 86% average yields, respectively (Table 1, entry 9). These results suggest that the catalytic activity of the $\text{WO}(\text{O}_2)_2$ -2,2'-bipyridine complex **1** was sustained without *N*-oxidation of the 2,2'-bipyridine ligand during flow oxidation. The oxidation of sulfides bearing other functional groups—2-(phenylthiol)ethanol **2j** and phenyl 2-propenyl sulfide **2k**—gave the corresponding sulfones **4j** and **4k** nearly quantitatively without oxidation of the hydroxy group or the olefinic double bond (98% and >99% yield; entries 10 and 11,

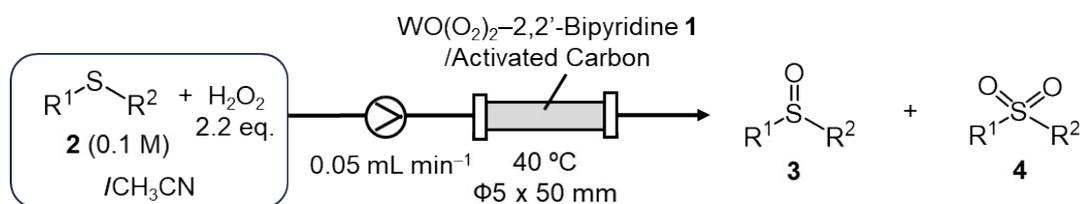


respectively). These results could be attributed to the short residence time under continuous-flow oxidation of sulfides (*ca.* 14.5 min).

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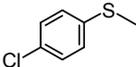
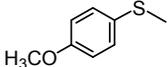
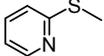
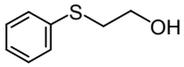
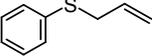
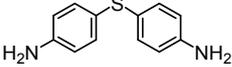
The flow oxidation of bis(4-aminophenyl) sulfide **2i** efficiently afforded bis(4-aminophenyl) sulfone **4i** (the antibacterial agent Dapsone) in a 91% average yield with 5% sulfoxide **3i** (Table 1, entry 12). It was recently reported that sulfone **4i** is synthesized by the oxidation of sulfide **2i** with H₂O₂ using silicopolyoxotungstovanadate as a catalyst in a batch method.²⁸ There are many reports and patents of synthetic procedures for Dapsone. One representative example starts from the coupling of 4-aminothiophenol and 4-chloro-nitrobenzene, followed by sulfide oxidation with sodium tungstate and reduction of the nitro groups.²⁹ The continuous-flow synthesis of bis(4-aminophenyl) sulfone **4i** by the oxidation of sulfide **2i** would be a potential alternative to large-scale industrial synthesis of Dapsone due to its simple and safe operation.

Table 1. Continuous-flow oxidation of various sulfides **2** with H₂O₂ using a mixture of WO(O₂)₂-bpy **1**/activated carbon as a catalyst.^a



| Entry | Substrate | Fraction time (h) | 3 Average yield (%) ^b | 4 Average yield (%) ^{b,c} | |
|-------|-----------|-------------------|---|---|-----|
| 1 | | 2a | 3–164 | 3 | 95 |
| 2 | | 2b | 3–24 | 1 | 97 |
| 3 | | 2c | 2–24 | 0 | >99 |
| 4 | | 2d | 2–24 | 0 | >99 |
| 5 | | 2e | 2–24 | 0 | 98 |
| 6 | | 2f | 2–24 | 0 | >99 |



| | | | | | |
|----|---|-----------|------|----|-----|
| 7 |  | 2g | 2–24 | 0 | >99 |
| 8 |  | 2h | 2–24 | 0 | 98 |
| 9 |  | 2i | 3–24 | 11 | 86 |
| 10 |  | 2j | 3–24 | 0 | 98 |
| 11 |  | 2k | 2–24 | 0 | >99 |
| 12 |  | 2l | 4–24 | 5 | 91 |

^a Reaction conditions: *ca.* 0.019 mmol **1**, *ca.* 400 mg activated carbon packed into a 50 mm catalyst column (5 mm inner diameter); a 0.1 M solution of **2** in acetonitrile; a 35% (w/w) aqueous solution of H₂O₂ (2.2 eq. per **2**); 1-tert-butyl-4-methoxybenzene as an internal standard (0.25–0.5 eq. per **2**); 40 °C; flow rate: 0.05 mL min⁻¹.

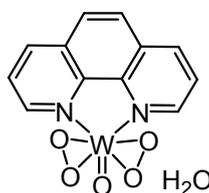
^b **a, b, e, f, g, h, i**: Determined by GC analysis using an internal standard method; **c, d, j, k, l**: Determined by ¹H NMR analysis using an internal standard method.

^c Isolated yields: **4a** 90% (100 h–106 h fraction); **4b** 93% (15 h–20 h fraction); **4c** 91% (14 h–20 h fraction); **4d** 92% (5 h–9 h fraction); **4e** 96% (13 h–18 h fraction); **4f** 90% (16 h–24 h fraction); **4g** 92% (16 h–24 h fraction); **4h** 93% (16 h–24 h fraction); **4i** 84% (4 h–16 h fraction); **4j** 95% (16 h–24 h fraction); **4k** 96% (16 h–24 h fraction); **4l** 89% (8 h–22 h fraction).

To evaluate the catalytic activity of WO(O₂)₂-bpy **1**/activated carbon, continuous-flow oxidation of dibenzothiophene **2m** was performed in comparison with WO(O₂)₂-1,10-phenanthroline·H₂O (WO(O₂)₂-phen·H₂O) **5** (Fig. 5). The catalyst WO(O₂)₂-phen·H₂O **5** has been reported to effectively catalyze the oxidation of dibenzothiophene **2m** to the corresponding sulfone **4m** in an ionic liquid under batch conditions.¹⁷ Dibenzothiophene is known to be a refractory sulfur compound for removal from fuels by catalytic oxidation.³⁰ Thus, we performed continuous-flow oxidation of **2m** using WO(O₂)₂-bpy **1**/activated carbon as the catalyst. The results are summarized in Table 2, together with



those obtained using $\text{WO}(\text{O}_2)_2\text{-phen}\cdot\text{H}_2\text{O}$ **5**/activated carbon as the catalyst. When $\text{WO}(\text{O}_2)_2\text{-bpy}$ **1**/activated carbon catalyst was used, oxidation of dibenzothiophene **2m** proceeded continuously, producing the corresponding sulfone **4m** in a 92% average yield with 7% sulfoxide **3m** (Table 2, entry 1). In contrast, when $\text{WO}(\text{O}_2)_2\text{-phen}\cdot\text{H}_2\text{O}$ **5** catalyst was used, sulfone **4m** was continuously produced in 67% yield, with 14% unreacted sulfide **2m** and 19% sulfoxide **3m** (Table 2, entry 2). These results suggest that $\text{WO}(\text{O}_2)_2\text{-bpy}$ **1**/activated carbon shows somewhat higher catalytic activity than $\text{WO}(\text{O}_2)_2\text{-phen}\cdot\text{H}_2\text{O}$ **5**/activated carbon under continuous-flow conditions. Therefore, continuous-flow oxidation utilizing the $\text{WO}(\text{O}_2)_2\text{-bpy}$ **1**/activated carbon catalyst, which maintains catalytic activity, may provide an efficient method for desulfurization.



5

Fig. 5 Oxodiperotungstate-1,10-phenanthroline·H₂O ($\text{WO}(\text{O}_2)_2\text{-phen}\cdot\text{H}_2\text{O}$) **5**Table 2. Continuous-flow oxidation of dibenzothiophene **2m** with H₂O₂ by $\text{WO}(\text{O}_2)_2\text{-bpy}$ **1**/activated carbon and $\text{WO}(\text{O}_2)_2\text{-phen}\cdot\text{H}_2\text{O}$ **5**/activated carbon as a catalyst.^a

| Entry | Substrate | Tungsten complex | Fraction time (h) | 2m Average yield (%) ^b | 3m Average yield (%) ^b | 4m Average yield (%) ^b |
|-------|-----------|------------------|-------------------|--|--|--|
| 1 | 2m | 1 | 5–24 | 0 | 7 | 92 ^c |
| 2 | 2m | 5 | 4–24 | 14 | 19 | 67 |

^a Reaction conditions are the same as those indicated in Table 1.

^b Determined by ¹H NMR analysis using an internal standard method.

^c Isolated yield of **4m**: 83% (5 h–20 h fraction)

Conclusions

Continuous-flow oxidation of sulfides to sulfones was achieved with H₂O₂ using catalyst columns



packed with a mixture of oxodiperoxotungstate–2,2'-bipyridine **1** and activated carbon. Sulfones were continuously produced by simply passing an acetonitrile solution of sulfides and H₂O₂ through the column in more than 90% yield for up to 160 h. The flow oxidation preferentially produced sulfones from sulfides, even though other functional groups, such as olefinic double bond, hydroxy group, and pyridyl and amino functional groups, were present in the substrates. It was also clarified that activated carbon was a superior solid support that firmly immobilized the tungsten catalytic species, whereas Celite and silica gel did not.

Considering that the oxidation with H₂O₂ provides only H₂O as a coproduct and less than 1% (w/w) H₂O₂ in the feed solution is sufficient for this continuous-flow oxidation of sulfides, the method we developed is an environmentally benign and safe system. In addition, preparation of the catalyst column is straightforward: the column is packed with a mixture of the tungsten complex and activated carbon. Therefore, the developed method is suitable for the continuous-flow oxidation of sulfides to sulfones.

Experimental

Materials and Equipment

Oxodiperoxotungstate–2,2'-bipyridine **1**^{22a} and oxodiperoxotungstate–1,10-phenanthroline·H₂O **5**³¹ were synthesized according to the literature. Activated carbon (Carbon powder, 99+%) was purchased from Strem Chemicals, Inc. Celite (Celite® No.545) was purchased from Fuji Film Wako Chemical Corporation. Silica gel (Silica Gel 60 (spherical), 40–50 μm diameter) was purchased from Kanto Chemical Co., Inc. Reagent grade acetonitrile was purchased from Fuji Film Wako Chemical Corporation. A 35% (w/w) H₂O₂ aqueous solution was purchased from Tokyo Chemical Industry Co. All commercial chemicals were used for all experiments without further treatment.

The flow synthesis system consisted of a degassing apparatus (Gastorr AG-42; Flom Inc.), an intelligent plunger pump (UI22-110P; Flom Inc.), a column flow reactor (MCR-1000; EYELA), a back pressure regulator (BPR-1000; EYELA), and a fraction collector (CHF100AA; Advantec Toyo Kaisha). An empty glass column (L = 50 mm, ID = 5 mm, and filter pore size = 10 μm) was purchased from EYELA.

For determination of the product yield during the continuous-flow reaction, a Shimadzu gas chromatography system GC-2014 (FID detector) was used. In some cases where GC analysis was not



suitable, yields were quantified by ^1H NMR analysis using a Bruker AV600 spectrometer.

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Continuous-flow oxidation of sulfide **2 to sulfone **4**: General procedure (Figs. 2 and 3 and Tables 1 and 2)**

The tungsten complex **1** or **5** (0.019 mmol) and activated carbon (*ca.* 400 mg) were mixed and packed in a glass reactor column ($L = 50$ mm and $ID = 5$ mm), and the column was placed in the flow reaction system. Then, an acetonitrile solution containing sulfide **2** (0.1 M), 1-tert-butyl-4-methoxybenzene (an internal standard; 0.25–0.5 eq. per **2**) and a 35% (w/w) aqueous H_2O_2 (2.2 eq. per **2**), which was cooled at 0°C to suppress the oxidation of **2** before introduction into the catalyst column, was passed through the column with a flow rate of 0.05 mL min^{-1} at 40°C .

The effluent was collected every hour. In the case of **2d**, **2l**, and **2m** as substrates, the effluent was directly collected into a dichloromethane solution without using a fraction collector due to the high crystallinity of these products. Yields were determined by GC analysis using an internal standard. In some cases where GC analysis was not suitable, ^1H NMR analysis was applied to determine yields, as shown in Tables 1 and 2 (note b), also using an internal standard.

Isolation of sulfone **4a from fractions of continuous-flow oxidation: Typical procedure (Table 1, Entry 1)**

The fractions collected from 100 h to 106 h were combined to obtain a mixed acetonitrile solution. Dodecane was added as an internal standard, and GC analysis was performed. The amount of 1-tert-butyl-4-methoxybenzene contained in the mixed solution was determined by an internal standard method using the GC peak area of dodecane. From the amount of 1-tert-butyl-4-methoxybenzene, the amount of diphenyl sulfide **2a** as a starting material was calculated.

After the addition of sodium thiosulfate aqueous solution to the mixed acetonitrile solution, the mixture was evaporated under reduced pressure, and the residue was purified by column chromatography (hexane/ethyl acetate = 9/1–7/3 as eluent) on silica gel to give sulfone **4a** (348.2 mg, 1.595 mmol) in a 90% chemical yield.

Oxidation of diphenyl sulfide **2a to diphenyl sulfone **4a** using collected fractions by a batch method: General procedure (Fig. 4)**

Fractions giving a high yield of diphenyl sulfone **4a** under flow oxidation of diphenyl sulfide **2a** (Figs. 2a, 3a, and 3b) were transferred to reaction vessels (Fig. 2a (**1**/activated carbon): the 41 h–43 h fractions; Fig. 3a (**1**/Celite): the 4 h–6 h fractions; Fig. 3b (**1**/silica gel): the 5 h–7 h fractions).



Diphenyl sulfide **2a** and H₂O₂ (2.2 eq. per **2a**) were added to each fraction, and the mixture was diluted with acetonitrile to give a 0.1 M solution of diphenyl sulfide **2a**. The solution was stirred at 40 °C. Yields of sulfone **4a** were determined by ¹H NMR analysis with reference to an internal standard at 1 h, 2 h, 6 h and 24 h.

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Data availability

The data supporting this article have been included as part of the ESI. Time course curves of oxidation of **2a** and ¹H NMR spectra of products. See DOI:

Conflicts of interest

There are no conflicts to declare.

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(23) When using 2.0 eq. of H₂O₂, the flow oxidation of sulfide **2a** did not completely proceed to produce sulfoxide **3a** and sulfone **4a** in 18% and 80% average yields over 24 h, respectively (Figure ESI 1a). Thus, 2.2 eq. of H₂O₂ was used as standard conditions.

(24) In the case of decreased amount of the catalyst where the catalyst WO(O₂)₂-bpy **1** was used under SV_{mol} value of 32 which corresponds to about half amount of **1**, average yield of sulfone **4a** was 78% over 24 h (Figure ESI 1b).

(25) At the initial stage of continuous-flow reactions, no compound was detected due to the dead volume of tube and reactor equipment (0 h–1 h) and the material balance (indicated as “Total” in Fig. 2a) was subsequently fluctuated due to the initial specific absorption of the reaction compounds (**2a**, **3a** and **4a**) and an internal standard on activated carbon (1 h–3 h).

(26) When using a catalyst column packed with activated carbon alone, sulfoxide **3a** and sulfone **4a** were continuously produced in 12% and 3% average yields over 24 h, respectively.

(27) When methanol was used as the alternative solvent in continuous-flow oxidation of sulfide **2a**, 4% of sulfone **4a** was continuously produced and the average yield of sulfoxide **3a** decreased from 51% to 16% over 24 h.

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Data availability

The data supporting this article have been included as part of the electronic supplementary information (ESI).

