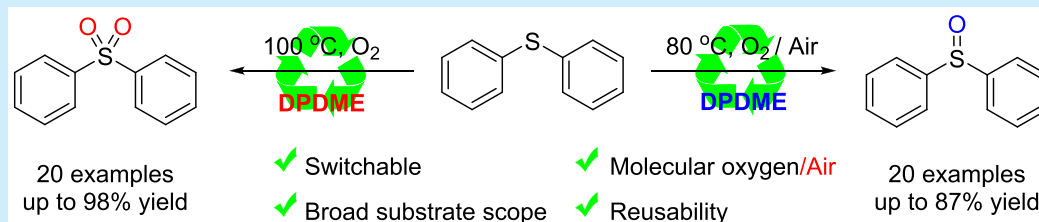


Switchable Synthesis of Aryl Sulfones and Sulfoxides through Solvent-Promoted Oxidation of Sulfides with O₂/Air

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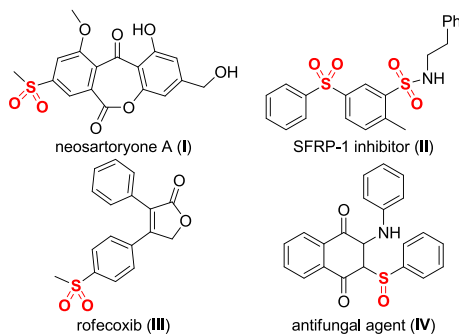
S Supporting Information



ABSTRACT: A practical and switchable method for the synthesis of aryl sulfones and sulfoxides via sulfide oxidation was developed. The chemoselectivities of products were simply controlled by reaction temperature using O₂/air as the terminal oxidant and oxygen source. The broad substrate scope, easy realization of gram-scale production, and the simplification of a sulfide oxidation system render the strategy attractive and valuable.

Oxidation reaction is one of the most elementary and significant organic reactions in both chemistry textbooks and industrial scale production.¹ Sulfones and sulfoxides are important oxygen-containing organic compounds which widely exist in natural products² and pharmaceutical active molecules³ and also function as versatile structural units⁴ and organic mono/bidentate ligands⁵ in synthetic chemistry. For example, neosartoryone A (I), as a modification of the natural product which comes from *Neosartorya udagawae*, has provided decreased lipid activity in vitro. Diphenylsulfone sulfonamide derivative (II), rofecoxib (III), and amino sulfoxide quinone (IV) can be used as a protein (sFRP-1) inhibitor, a cyclooxygenase-2 (COX-2) inhibitor, and an antifungal agent, respectively (Scheme 1).^{2,3}

Scheme 1. Representative Natural Products and Biologically Active Molecules Containing Sulfone and Sulfoxide Fragments



Driven by their rich biological activities, many elegant synthetic methods for the construction of sulfones and sulfoxides through indirect cross-coupling reactions have been well-established.⁶ Compared to cross-coupling reactions, the direct oxidation of sulfides is undoubtedly the most straightforward, atom-economical, and reliable way to form sulfones and sulfoxides. However, stoichiometric quantities of toxic and/or strong oxidants such as peroxy acids, prevalent iodine reagents, or inorganic periodates are usually indispensable.⁷ Moreover, these methods are often accompanied by harsh reaction conditions, poor chemoselectivities, over oxidation, and environmental contamination problems. Consequently, further exploration of green and sustainable methods for the controllable transfer of sulfides to sulfones and sulfoxides under mild reaction conditions is still highly desirable.

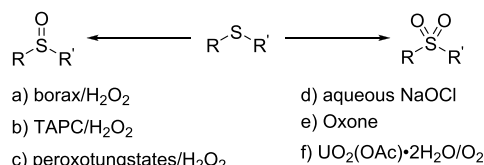
O₂ (air) is an eco-friendly, easily available, low-cost, and sustainable oxidant which has been widely used in oxygenation reactions during recent years.⁸ Along this line, remarkable progress has been made on homo/heterogeneous aerobic oxidation of sulfides employing dioxygen/air as the terminal oxidant and oxygen source in the past few decades.⁹ However, most of those developed oxidation systems could only chemoselectively form sulfones or sulfoxides, independently. To overcome the shortage, many adjustable sulfide oxidative systems were sequentially developed using H₂O₂, aqueous NaOCl, and oxone as oxidants, in which the product distributions were controlled by different reaction parameters such as pH value,^{10a} oxidant,^{10b,c} additive,^{10d} or solvent^{10e}

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(Scheme 2a–e). Very recently, during the preparation of this paper, an unprecedented selective late-stage oxygenation of

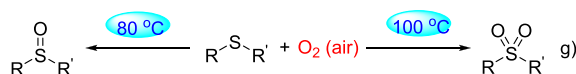
Scheme 2. Switchable Oxidation of Sulfides to Sulfones and Sulfoxides

Previous work



TAPC: 1,3,5-triazo-2,4,6-triphosphorine-2,2,4,4,6,6-tetrachloride

Our work



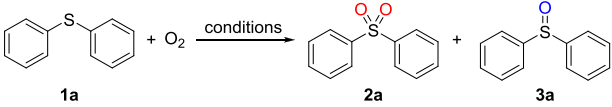
sulfides with ground-state oxygen as oxidant and uranyl acetate as photocatalyst was successfully presented by Jiang and co-workers (Scheme 2f).¹¹ Despite this progress, switchable oxidation of sulfides to sulfones and sulfoxides in the presence of 1 atm dioxygen or air under concise metal-free conditions is still very limited.

As part of our continuous research interests devoted to aerobic oxidation with O₂ under metal-free conditions¹² and green organic synthesis,¹³ we present herein a dipropylene glycol dimethyl ether (DPDME)-promoted, temperature-controlled oxidation of sulfides with molecular oxygen and air at atmospheric pressure for the selective synthesis of aryl sulfones and sulfoxides (Scheme 2g).

Diphenyl sulfide (**1a**) was selected as the starting material to screen the reaction conditions under 1 atm dioxygen atmosphere for the formation of diphenylsulfone (**2a**) and diphenylsulfoxide (**3a**) (Table 1). According to the literature, NMP and O₂ at 105 °C can in situ generate the peroxide, which can function as the key intermediate to initiate the oxidation reaction.¹⁴ We wondered whether this combination could be applied to oxidize the sulfur-containing compounds. To our delight, the oxidative products **2a** and **3a** were obtained in 27 and 59% yields at 100 °C within 13 h, respectively (entry 1). Although the yields of sulfone can be increased by prolonging the reaction time, the product distributions were not satisfactory (entries 2 and 3). It was found that the reaction medium had a significant effect on the reaction efficiency. Other solvents such as DMSO, CH₃CN, H₂O, Et₂O, THF, and 1,2-dimethoxyethane were ineffective for this reaction (entries 4–9). The high boiling point solvents involving ether linkage took effect to varying degrees (entries 10–13).¹⁵ Among them, DPDME achieved almost quantitative conversion and total chemoselectivity (entry 13, **2a**, 93% isolated yield). A blank experiment proved that oxygen atmosphere was essential, and only poor isolated yield was obtained when the reaction was performed under an argon atmosphere (entry 14). Decreasing the temperature to 80 °C delivered **3a** in 72% isolated yield (entry 15). However, two of the target products were not detected when the reaction temperature was further decreased to 60 °C (entry 16). Note that DPDME could be reused at least three times in 74–86% yields due to its good reusability performance.

Having established the optimal reaction conditions, the scope and limitations of sulfones **2** were initially investigated. As shown in Scheme 3, a wide range of diaryl sulfides and aryl(heteroaryl) alkyl sulfides **1** with both electron-donating and

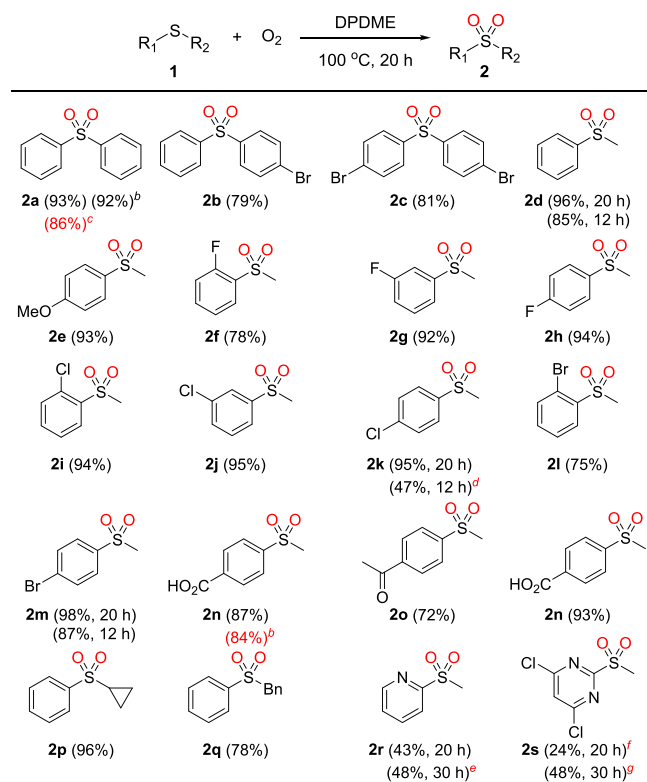
Table 1. Optimization of the Reaction Conditions^a



entry	solvent	temp (°C)	t (h)	yield of 2a (%) ^b	yield of 3a (%) ^b
1	NMP	100	13	27	59
2	NMP	100	20	39	55
3	NMP	100	24	48	49
4	DMSO	100	20	NR	NR
5	CH ₃ CN	100	20	NR	NR
6	H ₂ O	100	20	NR	NR
7	Et ₂ O	100	20	NR	NR
8	THF	100	20	NR	NR
9	1,2-dimethoxyethane	100	20	NR	NR
10	dioxane	100	20	7	36
11	diglyme	100	20	98	2
12	diethyldigol	100	20	>99	<1
13	DPDME	100	20	>99 (93) ^c	<1
14 ^d	DPDME	100	20	NR	NR
15	DPDME	80	20	16	74 (72) ^c
16	DPDME	60	20	NR	NR

^aReaction conditions: **1a** (0.5 mmol), solvent (0.5 mL), O₂ balloon, 100 °C, 20 h. ^bDetermined by GC analysis. ^cIsolated yields in parentheses. ^dUnder Ar. NR: no reaction.

Scheme 3. Substrate Scope of Sulfone **2** at 100 °C^a



^aReaction conditions: **1** (0.5 mmol), DPDME (0.5 mL, 6.4 equiv), O₂ balloon, 100 °C, 20 h. Isolated yields. Unless stated otherwise, no sulfoxides were obtained. ^b10 mmol, under air. ^c20 mmol, under air, 30 h, 86% sulfoxide was isolated. ^d58% sulfoxide was isolated. ^e7% sulfoxide was isolated. ^f29% sulfoxide was isolated. ^g11% sulfoxide was isolated.

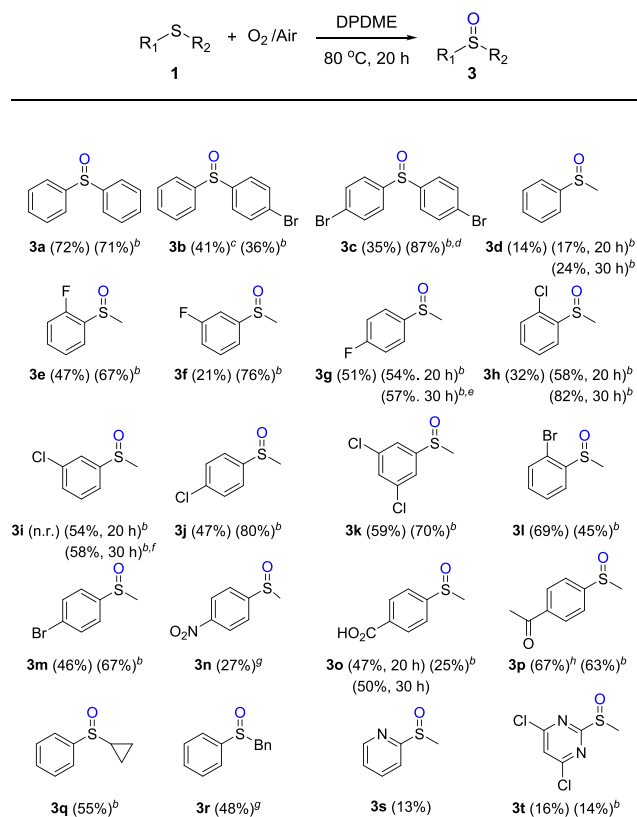
electron-withdrawing groups were compatible to generate the desired sulfone products **2a–2s** in moderate to excellent yields (up to 98% yield). For model substrate **1a** and substituted diphenyl thioether, the oxidative products were generated in very satisfactory yields. The thioanisole and its derivatives attached various substituents on the phenyl ring including $-\text{OMe}$, $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, $-\text{CHO}$, $-\text{COCH}_3$, and $-\text{COOH}$ groups worked very well with O_2 under standard conditions to produce sulfones **2d–2n** in 72–98% yields. It is worth noting that all of the above-mentioned functional groups could be easily applied for further transformation to various synthetically important compounds (for details, see the [Supporting Information, S4](#)). It was observed that the reaction efficiency of some substrates was sensitive to the steric hindrance (e.g., **2f–2h** and **2l**, **2m**). Treatment of 4-(methylthio)benzaldehyde, which contains an easily oxidized formyl group, led to the oxygenation product 4-(methylsulfonyl)benzoic acid **2n** in 87% yield. In the case of cyclopropyl phenyl sulfide, the desired product **2p** was also furnished in 96% yield. Replacing the cyclopropyl with a benzyl group, **2q** was obtained with a yield of 78%. Importantly, the heteroaryl sulfide derivatives also reacted smoothly with molecular oxygen to give the corresponding sulfones **2r** and **2s**, albeit with relatively low yields. The current oxidation process can be easily scaled up to 10 mmol in good yields (92% of **2a** and 84% of **2n**). When the model reaction was further magnified to 20 mmol scale, the sulfoxide product **3a** was preferentially formed.

Subsequently, the universality of this selective oxidation of sulfides **1** to sulfoxides **3** was examined ([Scheme 4](#)). In general, under optimal conditions, a variety of sulfoxide products **3a–3t** with similar substituent groups as shown in the sulfonation reactions were produced in 13–87% yields. Interestingly, the oxidation of sulfides to sulfoxides under air behaved comparatively or with even much better efficiency than that under dioxygen.

To shed some light on the reaction mechanism of this switchable oxidation process, several mechanistic experiments were executed. Adding 2 equiv of the widely used radical scavengers, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), or 1,1-diphenylethylene, completely suppressed the model reaction ([Scheme 5a](#)). The results revealed that a possible free radical process might be involved in the developed oxidation process. However, the electron paramagnetic resonance spectrum with an absorption maximum at $g = 2.0046$ further demonstrated the involvement of the free radical in the reaction system (for details, see the [Supporting Information, S9](#)). To track the source of the oxygen atom, the model reaction was first carried out in an $^{18}\text{O}_2$ atmosphere. The corresponding ^{18}O -labeled products **2a** and **3a** were obtained in 47 and 57% yields, respectively ([Scheme 5b](#)). However, when 10 equiv of H_2^{18}O was added to the model reaction, only the ^{16}O -labeled sulfone **2a** was formed in 96% yield, which further shows that the oxygen atom of the product originates from molecular oxygen rather than from water ([Scheme 5c](#)). Under standard conditions, diphenyl sulfoxide **3a** could be converted into diphenyl sulfone **2a** in 95% yield, showing that the oxidative formation of sulfones might go through via sulfoxide intermediate ([Scheme 5d](#)).

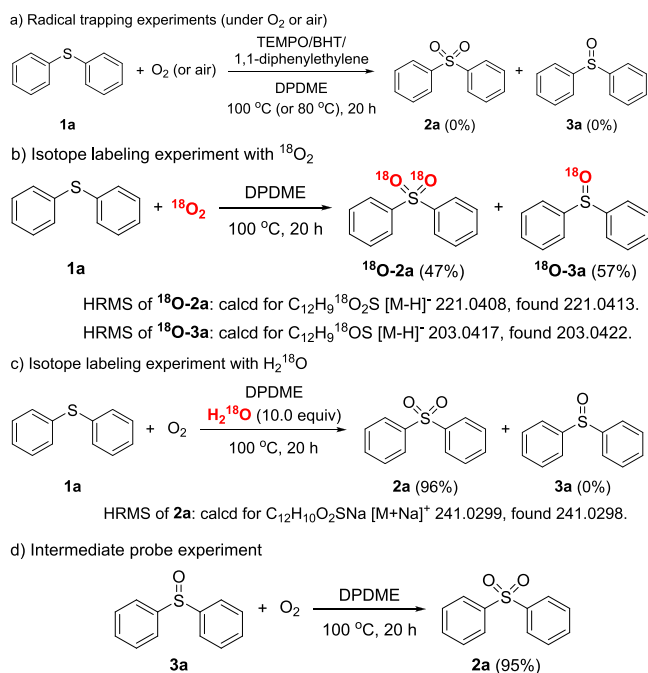
The in situ IR experiment was adopted to monitor the oxidative process at 100°C for 12 h under air (for details, see the [Supporting Information, S9](#)). Two new peaks of the sulfone **2a** and sulfoxide **3a** were formed at 730 and 1051 cm^{-1} , respectively. The kinetic profiles clearly showed that, with the

Scheme 4. Substrate Scope of Sulfoxide **3** at 80°C ^a



^aReaction conditions: **1** (0.5 mmol), DPDME (0.5 mL, 6.4 equiv), O_2 balloon, 80°C , 20 h. Isolated yields. Unless stated otherwise, no sulfones were obtained. ^bUnder air. ^c6% **2b** was isolated. ^d14% **2c** was isolated. ^e38% **2h** was isolated. ^f37% **2j** was isolated. ^gAt 98°C , O_2 balloon. ^h9% **2o** was isolated.

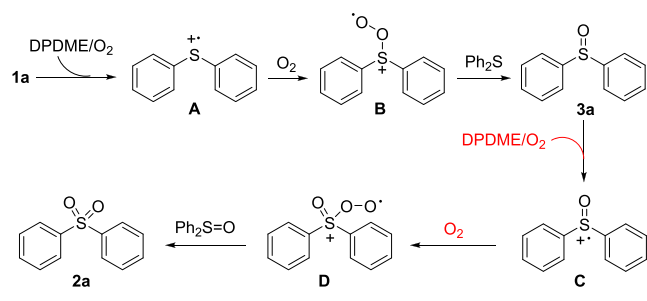
Scheme 5. Mechanistic Studies



consumption of the starting material **1a**, the oxidation products **2a** and **3a** were formed and their intensities increased gradually.

In view of the results mentioned above and literature reports,^{11,15} a possible reaction mechanism is proposed in Scheme 6. Originally, the DPDME/O₂ system is prone to form

Scheme 6. Proposed Mechanism



solvent-free radicals under heating to initiate the formation of sulfur radical cation **A**.^{14,16a} Then, radical addition of **A** to molecular oxygen generates the persulfide radical **B**, which is subsequently caught by another molecule of sulfide **1a** to provide the sulfoxide product **3a**.^{16b} Overoxidation of sulfoxide **3a** through a similar procedure gave the final sulfone **2a**.

In summary, we have developed an efficient and switchable methodology for the chemoselective synthesis of sulfones and sulfoxides via oxidation of sulfides. The reaction takes advantage of dioxygen or air as the green oxidant and exclusive oxygen source. A wide variety of diaryl sulfides and aryl(heteroaryl) alkyl sulfides were compatible to assemble the desired products in moderate to excellent yields. DPDME had a dual role of solvent and promoter.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03192.

Experimental materials and procedures, NMR of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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