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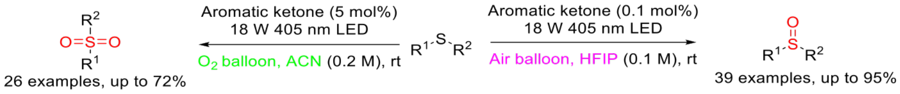

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Modulation of photochemical oxidation of thioethers to sulfoxides or sulfones using an aromatic ketone as the photocatalyst

Bin Zhao,† Gerald B. Hammond,, ‡ and Bo Xu*, †*

† Key Laboratory of Science and Technology of Eco-Textiles, Ministry of Education, College of Chemistry, Chemical Engineering and Biotechnology, Donghua University, Shanghai 201620, China.
‡ Department of Chemistry, University of Louisville, Louisville, Kentucky 40292, United States

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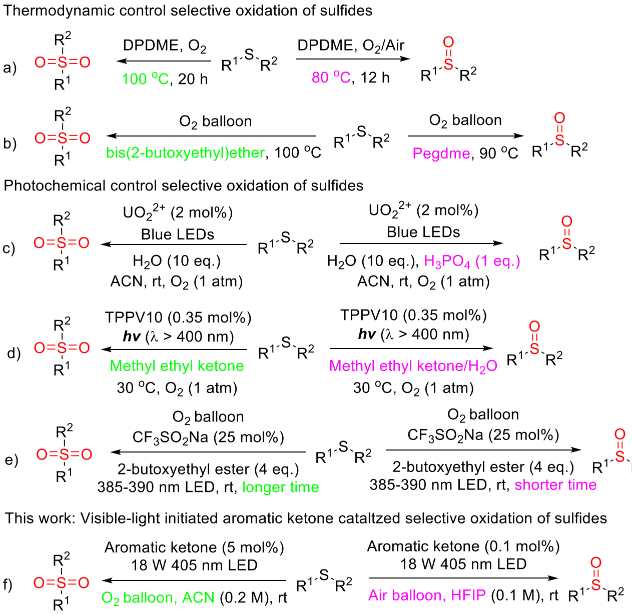
ABSTRACT

We have developed an eco-friendly and chemo-selective photocatalytic synthesis of sulfoxides or sulfones via oxidation of sulfides (thioethers) at ambient temperature using air or O_2 as the oxidant. An inexpensive thioxanthone was used as the photocatalyst. Our method offers excellent chemical yields and good functional group tolerance. The hydrogen bonding between hexafluoro-2-propanol (HFIP) and sulfoxides may play an important role in minimizing the over-oxidization of sulfoxides.

Sulfur-containing molecules are important fragments in natural products[1-5] and valuable building blocks in organic synthesis[6-11]. More specifically, sulfoxides (R^1SOR^2) and sulfones ($R^1SO_2R^2$) are essential intermediates in drugs [12-16] and biologically active molecules[17-19]. Consequently, the synthesis of sulfoxides[20, 21] and sulfones[22-26] has generated significant attention. The oxidation of sulfides or thioethers (R^1SR^2) is one of the most straightforward pathways for the synthesis of sulfoxides. Common oxidants for sulfide oxidation include hypervalent iodine reagents[27, 28], hydrogen peroxide(H_2O_2)[29], peroxycarboxylic acid[30], O_3[31], NaClO[21], $K_2S_2O_8$[32], Oxone[33]. Most of these oxidants are not eco-friendly. In addition, a common issue is the overoxidation of sulfoxides to sulfones if the conditions are not well controlled. Developing a tunable and eco-friendly synthesis of sulfoxides and sulfones through chemo-selective oxidation of the abundant and readily available sulfides is highly desired. Among chemical oxidants, molecular oxygen is the most abundant and sustainable oxidant.[34] In 2019, the Liu group[35] proposed the temperature-controlled selective oxidation of sulfides using molecular oxygen in ether solvent under heating conditions (Scheme 1a). In 2020, He's group[36] disclosed the oxidation of sulfides to sulfoxide or sulfones by molecular oxygen; the selectivity was modulated by different solvents (Scheme 1b). However, these reactions needed high temperatures and flammable organic solvents, which may create safety issues.

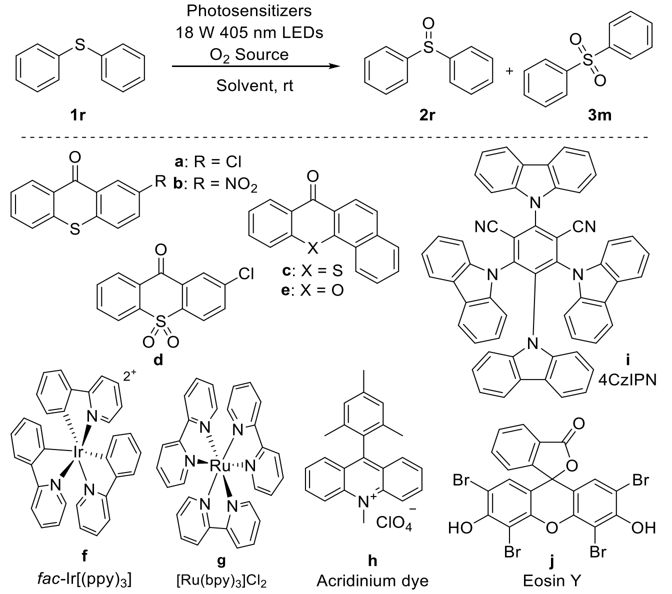


Scheme 1. Literature background.

Visible light has served as a clean and renewable chemical energy source in chemical transformations at ambient temperatures. In 2019, the Jiang group[37] described a uranyl photocatalyzed selective oxygenation of sulfides (thioethers) in the presence of O_2 with H_3PO_4 as the product-dependent additives (Scheme 1c). In 2020, Suzuki and Yamaguchi[38] reported the visible-light-responsive switchable oxygenation of sulfides using tetraphenylphosphonium decavanadate (TPPV10) as the photocatalyst in methyl ethyl ketone by simply adding water to control the product selectivity (Scheme 1d). Very recently, He's group[39] disclosed that time controlled visible-light-induced oxidation that synergistically catalyzed by CF_3SO_2Na and 2-butoxyethyl ether for the switchable preparation of sulfoxides and sulfones (Scheme 1e).

Recently, our group[40] developed electrochemical selective oxidation of sulfides using a hydrogen-bonding donor HFIP (hexafluoro-2-propanol) as the solvent. The formation of a strong hydrogen bond between HFIP and sulfoxides prevented the over oxidation of sulfoxides to sulfones. Based on published reports and our previous work, we were aware that a cheap and readily available aromatic ketone could be used as a photocatalyst to activate molecular oxygen. Herein, we disclose an eco-friendly and tunable protocol for the preparation of sulfoxides and sulfones via the oxidation of thioethers (Scheme 1f). The hydrogen bonding between HFIP and sulfoxides may play an essential role in minimizing the over-oxidization of sulfoxides.

Table 1. Optimization of reaction conditions for sulfoxide formation



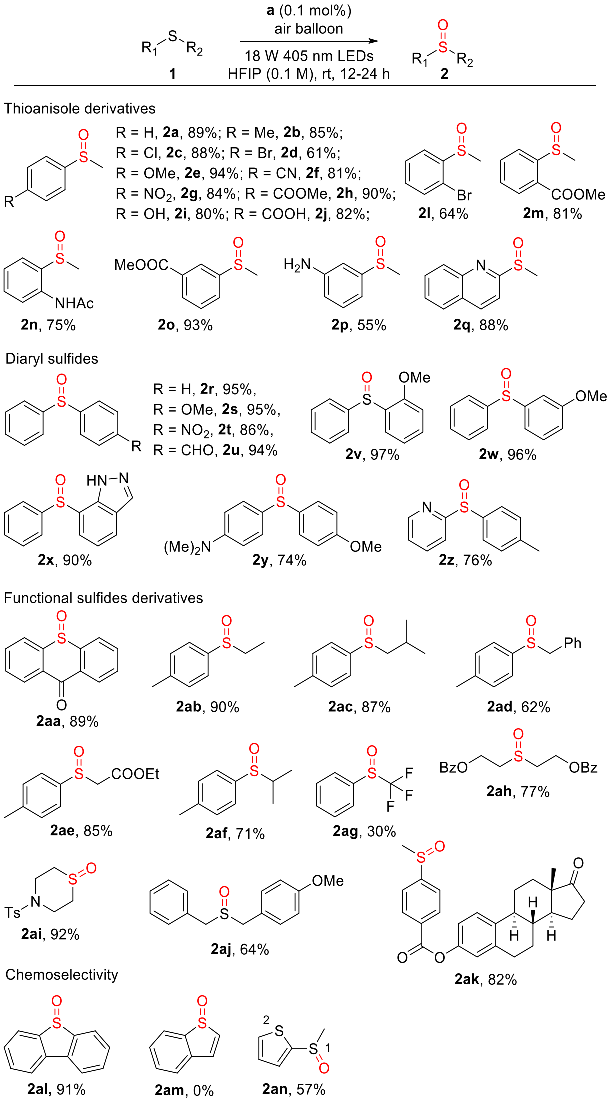
No.	Variations from standard conditions	Yields[a] (**2r**/**3m**)%
1	none	99% (99/1)
2	**b - e** as photocatalyst [b]	67% (99/1), 94% (97/3), 94% (96/4), 4%[c] (100/0)
3	**f - j** as photocatalyst [b]	36%[c] (86/14), 96% (98/2), 94% (97/3), 80%[c] (98/2), 82% (99/1)
4	DMSO, Acetone, Dioxane, *t*-BuOH, MeOH, THF as solvents [b]	0-55% [c]
5	ACN and DCM as solvents [b]	56% (79/21), 84% (87/13)
6	0.01 mol% photocatalyst loading	99% (99/1)
7	425 nm 18 W LEDs	99% (100/0)
8	No photocatalyst	0%
9	Dark	0%

Standard conditions: **1r** (0.1 mmol), **a** (0.1 mol%) HFIP (0.1 M), air balloon, 18 W 405 nm LEDs, rt, 12 h. [a] Yields determined by GC-MS with using 9H-fluorene as internal standard. [b] 5 mol% photocatalyst loading. [c] Conversions determined by GC-MS.

We selected the oxygenation of sulfide **1r** as our model reaction (Table 1). When the model reaction was carried out under the standard conditions, the reaction gave a good yield of sulfoxide **2r** (99%) with little over-oxidation (1%) (Table 1, entry 1). As the photocatalyst was changed from **a** to other aromatic ketone photocatalysts **b-d**, the conversions were comparable, but the selectivity was slightly reduced (Table 1, entry 2). Moreover, the reaction using photocatalyst **e** only gave a 4% conversion (Recently, our group40 developed electrochemical selective oxidation of sulfides using a hydrogen-bonding donor HFIP (hexafluoro-2-propanol) as the solvent. The formation of a strong hydrogen bond between HFIP and sulfoxides prevented the over oxidation of sulfoxides to sulfones. Based on published reports and our previous work, we were aware that a cheap and readily available aromatic ketone could be used as a photocatalyst to activate molecular oxygen. Herein, we disclose an eco-friendly and tunable protocol for the preparation of sulfoxides and sulfones via the oxidation of thioethers (Scheme 1f). The hydrogen bonding between HFIP and sulfoxides may play an essential role in minimizing the over-oxidization of sulfoxides.

Table 1, entry 2). Besides, some other commonly used photocatalysts, including Ir or Ru-based catalysts, organic dyes (Eosin Y, 4CzIPN), show less efficacy or selectivity (Table 1, entry 3). DMSO, acetone, dioxane, *t*-BuOH, MeOH, and THF were not suitable solvents as they gave lower yields (0% to 55%) (Table 1, entry 4). Reactions in both ACN and DCM gave 100% conversions, but over-oxidation was observed (21% and 13%, respectively) (Table 1, entry 5). We also investigated the effects of catalyst loading (see Table S2 in SI). Notably, the photocatalyst could be reduced to a very low level (0.01 mol% loading) (Table 1, entry 6). When longer wavelength light sources were employed, a compatible yield was found in the reaction under 425 nm LEDs (Table 1, entry 7). As expected, both photocatalyst and light are essential for the reaction (Table 1, entries 8-9). More detailed optimization attempts are shown in Tables S1-2 in the supporting information.

Table 2. Selective photochemical oxidation of thioethers to sulfoxides

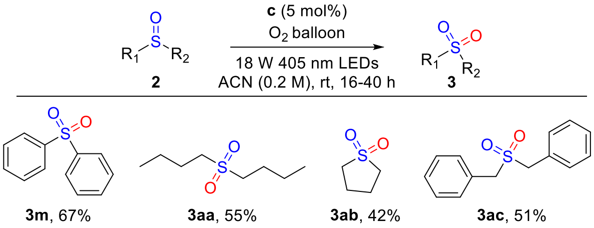


Conditions: **1** (0.2 mmol), **a** (0.1 mol%) HFIP (0.1 M), air balloon, 18 W 405 nm LEDs, rt, 12-24 h.

With the optimized conditions in hand, the scope of the model reaction was evaluated (Table 2). Firstly, diverse thioanisole derivatives (**2a**-**2q**) could be selectively oxidized to sulfoxides in good to excellent yields. Besides, various diaryl sulfides (**2r**-**2z**) also were suitable substrates and gave good yields in all cases. It should be noted that the substitution pattern (ortho, meta, para) and electronic properties of aromatic substituents (electron-deficient or rich) had little effect on this transformation. Functional groups such as alkyl (**2b**), halogens (**2c**, **2d**, **2l**), ether (**2e**, **2s**, **2v**, **2w**), ester (**2h**, **2m**, **2o**), amide (**2n**), -NO_2 (**2g**, **2t**), -CN (**2f**), -CHO (**2u**), amine (**2y**) and ketone (**2aa**) were all well tolerated, affording good to excellent isolated yields. It should be noted that the active hydrogens (-OH, -COOH, -NH_2) were well tolerated (**2i**, **2j**, and **2p**). Heterocycle compounds, such as quinoline (**2q**), 1H-indazole (**2x**), pyridine (**2z**), and thiophene (**2an**) worked well under the standard conditions. Sulfides containing various functional groups, such as primary, secondary, or tertiary alkyl groups bonded to the sulfur atom directly (**2ab** – **2ag**) were suitable substrates, except a trifluoromethyl containing sulfide (**2ag**, 30% yield). Additionally, our protocol also tolerated carbon chains (**2ah**, **2aj**) or ring (**2ai**) dialkyl sulfides and sulfides containing natural product skeletons (**2ak**). It should be noted that the benzyl group led to poor yields (**2ad** and **2aj**). Finally, the chemo-selectivity of this method was investigated in the oxidation of sulfides containing two different sulfur moieties (**2an**). The oxidation selectively occurred at the S-1 site, which may be due to this sulfur having high electron density and being more prone to oxidation. On the other hand, benzo[b]thiophene, in which the sulfur was located in the conjugated ring system, could not be oxidized in our conditions (**2am**, 0% conversion).

We speculated that sulfoxides could be further converted to sulfones using our protocol. Thus, we screened the photocatalyst loading in the sulfone-promoted formation solvent ACN (Table 1, entry 5) under higher oxygen concentration (oxygen balloon was utilized) with sulfoxide **2r**. The conversion was increased when more photocatalyst was added (conversion was up from 5% on 0.1 mol% loadings to 73% on 10 mol% loading) (Table S3 in SI). Then, the other photocatalysts were screened. The results showed that aromatic ketone photocatalyst **c** gave the highest conversion but with a low yield (91% conversion and 64% GC yield) (Table S4 in SI). Next, we investigated solvent effects, but no improvement was observed (Table S5 in SI). On the other hand, the reaction concentration seemed to affect the conversion, and 0.2 M was the optimal concentration (Table S6 in SI). Adding an additional portion of photocatalyst several hours after the start of the reaction slightly speeded up the reaction (Table S7 in SI). The formation of **2aa** from 9H-thioxanthen-9-one indicated that the aromatic ketone photocatalyst could be oxidated. The optimal conditions were catalyst **c** (5 mol%)/O_2 balloon/acetonitrile combination. Several sulfoxides were successfully oxidated to sulfones in satisfactory yields (Table 3).

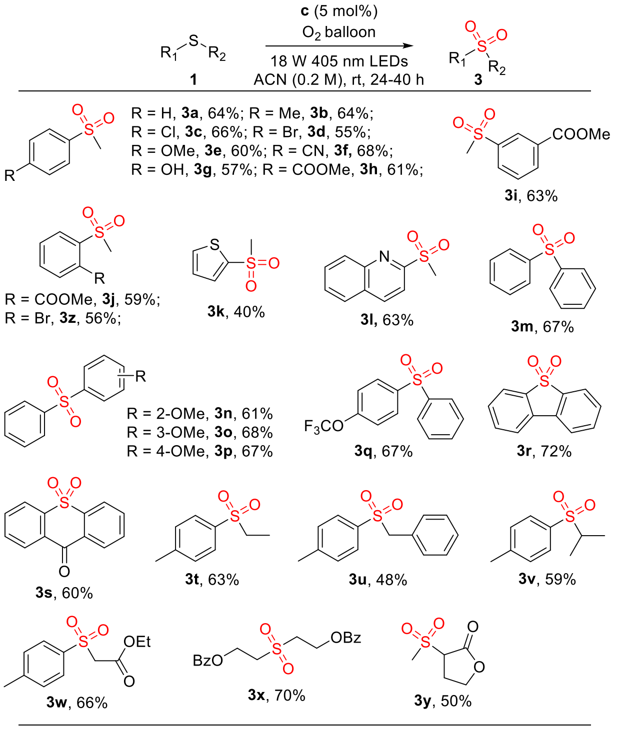
Table 3. Photochemical oxidation of sulfoxides to sulfones



Conditions: **2** (0.2 mmol), **c** (5 mol%) ACN (0.2 M), O_2 balloon, 18 W 405 nm LEDs, rt, 16-40 h.

Because sulfoxides could be oxidized to sulfones, we conjectured that sulfides could also be oxidized to sulfones directly. Indeed, sulfides successfully produced sulfones, albeit in slightly lower yields (Table 4, **3a** – **3z**). Similarly, the conditions worked well for diverse thioanisoles, diaryl sulfides, and dialkyl sulfides with functional groups. The substitution pattern (*ortho*, *meta*, *para*) and electronic property of substituents (electron-deficient or electron-rich) on aromatics had little effect on chemical yields.

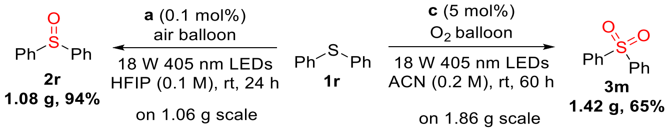
Table 4. Selective photochemical oxidation of thioethers to sulfones



Conditions: **1** (0.2 mmol), **c** (5 mol%) ACN (0.2 M), O_2 balloon, 18 W 405 nm LEDs, rt, 24-40 h.

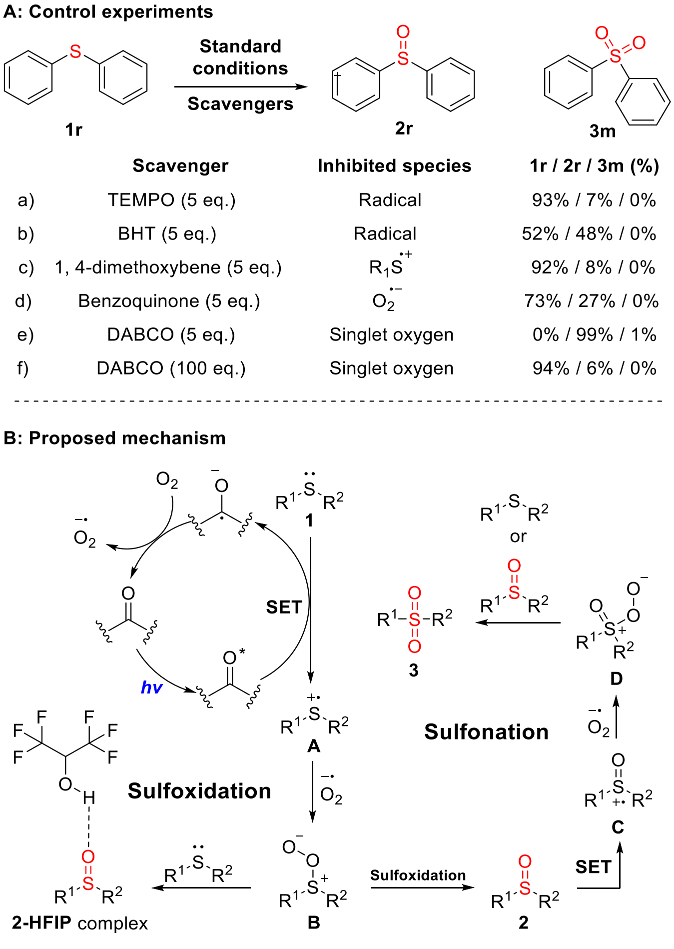
Our methodology could be used in larger-scale synthesis without complications. **1r** was selectively oxidized to **2r** in 94% yield or **3m** in 65% yield on a gram scale (Table 5).

Table 5. Gram scale reaction



Guo and coworkers[41] had suggested that the oxygenation of sulfoxides from sulfides catalyzed by a ketone might occur via both singlet oxygen involved energy transfer pathway and a superoxide radical anion involved electron transfer pathway. To gain insights into the reaction mechanism, we conducted several control experiments. The radical trapping experiment (Scheme 2A-a and Scheme 2A-b) with excess TEMPO or BHT dramatically inhibited the formation of sulfoxides and sulfones. These results suggested a radical pathway. Then, a well-known sulfide cation radical scavenger, 1,4-dimethoxybenzene, was added into the reaction under standard conditions. The reaction was depressed revealing that the sulfide cation radical might be a key intermediate for the transformation of sulfoxides (Scheme 2A-c). Next, the formation of a superoxide anion radical was confirmed by adding benzoquinone as a superoxide radical scavenger (Scheme 2A-d). Furthermore, the addition of five equivalents of a singlet oxygen quencher (1,4-diazabicyclo[2.2.2]octane, DABCO) did not inhibit the reaction (Scheme 2A-e), and even large excess of DABCO (100 equiv) could not inhibit the reaction completely (Scheme 2A-f). These combined results suggested to us that singlet oxygen may not play an essential role in our reaction.

All the above control experiments indicated a superoxide radical anion-involved electron transfer pathway (Scheme 2B). The excited ketone photocatalyst is a relatively strong oxidant; therefore, it should be able to transfer the sulfide **1** to the corresponding radical cation **A**, together with the formation of a ketyl radical anion. The ketyl radical anion reacts with oxygen to reproduce the ground state photocatalyst and generate the superoxide radical anion.[42] Next, the sulfide radical cation **A** reacts with the superoxide radical anion, and another molecule of sulfide to furnish the final product **2**.[41] In the process of sulfoxidation, the strong hydrogen bond between hydrogen donor solvent HFIP and hydrogen acceptor sulfoxide will deprive some electron density to the sulfoxide and make it less prone to be further oxidized. However, in the process of sulfonation, the formed **2** undergoes a second-round single electron transfer (SET) trapped by the excited photocatalyst to generate intermediate **C**, which reacts with the superoxide radical anion, delivering the persulfone intermediate **D**. Finally, **D** reacts with another sulfide or sulfoxide and produces sulfones **3**. However, the singlet oxygen-involved energy transfer pathway cannot be ruled out.



	Scavenger	Inhibited species	1r / 2r / 3m (%)
a)	TEMPO (5 eq.)	Radical	93% / 7% / 0%
b)	BHT (5 eq.)	Radical	52% / 48% / 0%
c)	1, 4-dimethoxybene (5 eq.)	$R_1S^{•+}$	92% / 8% / 0%
d)	Benzoquinone (5 eq.)	$O_2^{•-}$	73% / 27% / 0%
e)	DABCO (5 eq.)	Singlet oxygen	0% / 99% / 1%
f)	DABCO (100 eq.)	Singlet oxygen	94% / 6% / 0%

Scheme 2. Control experiments and proposed mechanism. [a] Standard condition: **1r** (0.1 mmol), **a** (0.1 mol%), HFIP (0.1 M), scavengers as indicated, air balloon, 18 W 405 nm LEDs, rt, 24 h. **1r** / **2r** / **3m** were detected by GCMS.

Conclusions

In summary, we have developed a chemo-selective photocatalytic protocol for the synthesis of sulfoxides or sulfones. This protocol is based on readily available sulfides using inexpensive aromatic ketone photocatalyst - thioxanthone. This mild and convenient reaction has selectively furnished the sulfoxides or sulfones in good product-selectivity and moderate to excellent yields.

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