

## Oxidation of Symmetric Disulfides with Hydrogen Peroxide Catalyzed by Methyltrioxorhenium(VII)

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Organic disulfides with both alkyl and aryl substituents are oxidized by hydrogen peroxide when  $\text{CH}_3\text{ReO}_3$  (MTO) is used as a catalyst. The first step of the reaction is complete usually in about an hour, at which point the thiosulfinate,  $\text{RS(O)SR}$ , can be detected in nearly quantitative yield. The thiosulfinate is then converted, also by MTO-catalyzed oxidation under these conditions, to the thiosulfonate and, over long periods, to sulfonic acids,  $\text{RSO}_3\text{H}$ . In the absence of excess peroxide,  $\text{RS(O)SR}$  ( $\text{R} = p\text{-tolyl}$ ), underwent disproportionation to  $\text{RS(O)}_2\text{SR}$  and  $\text{RSSR}$ . Kinetics studies of the first oxidation reaction established that two peroxorhenium compounds are the active forms of the catalyst,  $\text{CH}_3\text{ReO}_2(\eta^2\text{-O}_2)$  (**A**) and  $\text{CH}_3\text{ReO}(\eta^2\text{-O}_2)_2(\text{OH}_2)$  (**B**). Their reactivities are similar; typical rate constants ( $\text{L mol}^{-1} \text{s}^{-1}$ ,  $25^\circ\text{C}$ , aqueous acetonitrile) are  $k_{\text{A}} = 22$ ,  $k_{\text{B}} = 150$  ( $\text{Bu}_2\text{S}_2$ ) and  $k_{\text{A}} = 1.4$ ,  $k_{\text{B}} = 11$  ( $\text{Tol}_2\text{S}_2$ ). An analysis of the data for  $(p\text{-XC}_6\text{H}_4)_2\text{S}_2$  by a plot of  $\log k_{\text{B}}$  against the Hammett  $\sigma$  constant gave  $\rho = -1.89$ , supporting a mechanism in which the electron-rich sulfur attacks a peroxy oxygen of intermediates **A** and **B**.

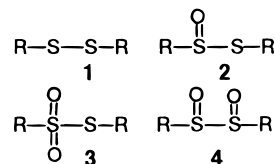
### Introduction

Oxidation of the disulfide functional group (**1**, Chart 1) has been studied quite extensively because of its important role in metabolism, via a variety of mechanistic paths.<sup>1</sup> With the use of different oxidants and well-controlled situations, various intermediate compounds have been obtained.<sup>2–6</sup> Among these are thiosulfonates, **2**, which can provide a sulfinyl group that acts as a removable source of diastereoselectivity in asymmetric syntheses.<sup>7</sup> Similarly, such reactions can produce thiosulfonates, **3**, which are powerful sulfenylating agents useful for the temporary blocking of mercapto groups in protein chemistry.<sup>8</sup>

Peracids are the reagents most commonly used to oxidize disulfides, although hydrogen peroxide in acetic acid also finds application. The hydrogen peroxide reactions, in the absence of a catalyst, often require a large excess and a higher temperature.<sup>1,3</sup> Oxometal complexes are catalysts for the oxidation; molybdates and tungstates are effective, especially under phase-transfer conditions.<sup>9–11</sup>

Methyltrioxorhenium,  $\text{CH}_3\text{ReO}_3$  or MTO, has been widely used as a catalyst for reactions that use hydrogen peroxide as a stoichiometric oxidant.<sup>12–15</sup> One can anticipate that either or both of the peroxorhenium species that

Chart 1. Disulfide and Oxidation Products; R = Alkyl, Aryl



exist in an equilibrium or a steady-state relation with MTO, as shown in Scheme 1, will be the active form of the catalyst. Since a sequence of oxidation steps will occur, the experiments were carried out. The principal objective of this research is the study of the reaction kinetics, of the first stage in particular, as written in eq 1.



The first reaction proved to be faster than the subsequent oxidations. This allowed, when hydrogen peroxide was taken in only 1:1 ratio to the disulfide, the detection of the thiosulfonates, otherwise difficult to realize owing to their transient nature. We also report, qualitatively, on the formation of thiosulfonates and sulfonic acids.

### Experimental Section

**Reagents.** Aqueous acetonitrile was used as the reaction solvent, the water being purified by a Millipore-Q water purification system. The disulfides were used as received from Aldrich, save for  $p$ -chlorophenyl disulfide, which was prepared

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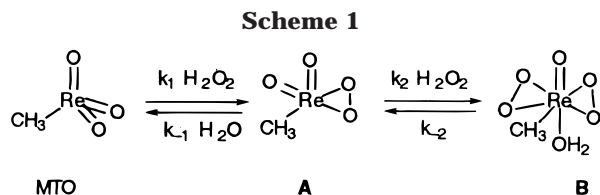
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by the literature method<sup>16</sup> and purified by recrystallization from ethanol–water, and for *tert*-butyl disulfide, which was vacuum distilled.

**Kinetics.** Both UV/visible and <sup>1</sup>H NMR methods were used. Quantitative measurements were made at 25 °C in 4:1 v/v acetonitrile–water at pH 1 (to stabilize MTO in peroxide-containing media)<sup>17</sup> maintained by trifluoromethanesulfonic acid. Owing to the large molar absorptivities of the diaryl disulfides, it was often necessary to use cuvettes of 0.01–0.05 cm optical path. One or more wavelengths were chosen for each compound to allow quantitative monitoring of the reaction progress. The conditions and wavelengths selected were such that the loss of ArSSAr was followed, although at other wavelengths not used for kinetics, a rise in absorbance accompanying the buildup of **2** could be seen. Under the conditions of the spectrophotometric determinations, principally that [ArSSAr] was quite low and [H<sub>2</sub>O<sub>2</sub>] effectively constant, the reactions followed pseudo-first-order kinetics. The absorbance–time data from each experiment were analyzed according to eq 2, from which a value of  $k_{\text{eff}}$  was obtained

$$\text{Abs}_t = \text{Abs}_\infty + (\text{Abs}_0 - \text{Abs}_\infty) \exp^{-k_{\text{eff}}t} \quad (2)$$

by nonlinear least-squares fitting. In the case of dialkyl disulfides, where there are no useful UV absorptions, the reaction kinetics was evaluated from NMR intensities. These values were converted by computer program<sup>18</sup> to concentrations based on the total intensity of the starting material. Certain data sets were analyzed by first-order kinetics according to eq 3. That was allowable at high concentrations of

$$C_t = C_0 e^{-k_{\text{eff}}t} \quad (3)$$

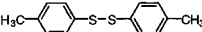
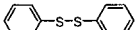
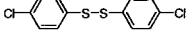
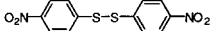
hydrogen peroxide, where (see later) the rate becomes peroxide-independent. However, at lower peroxide concentrations the data conform to the Michaelis–Menten form for catalytic reactions, and the data cannot be analyzed by an integrated rate law. In these circumstances the method of initial rates was used. To determine the value of the initial rate,  $v_i$ , the concentration was expressed as a polynomial function (eq 4)

$$C_t = C_0 - a_1 \cdot t - a_2 \cdot t^2 - a_3 \cdot t^3 - \dots \quad (4)$$

by least-squares fitting, from which it can be seen that  $v_i = a_1$ . For one compound, with R = *p*-tolyl, it was confirmed that both UV and NMR methods gave the same ultimate parameter value.

**Products.** The procedure used to identify the reaction products was based on chromatography and spectroscopy. A solution containing MTO (2.5 μmol) and hydrogen peroxide (1 mmol) was slowly added to 1 mmol *p*-ditolyl disulfide (for example) in 5.0 mL of acetonitrile. The reaction was allowed to run for 2 h, during which time its progress was monitored periodically by TLC. When this test showed that the reaction progress had nearly stopped, the mixture was separated by preparative TLC, using cyclohexanes–ethyl acetate (95:5) as the eluting agent. This gave *p*-tolyl *p*-toluenethiosulfinate, **2**, as the major product, along with a barely detectable amount of *p*-tolyl *p*-toluenethiosulfonate, **3**. These products were identified either by <sup>1</sup>H NMR and GC–MS techniques, in comparison with the values of the authentic compounds, or

**Table 1.** Rate Constants at 298 K for the Oxidation of Disulfides by Peroxorhenium Complexes A ( $k_3$ ) and B ( $k_4$ ) in Aqueous Acetonitrile<sup>a–c</sup> Containing 0.100 M CF<sub>3</sub>SO<sub>3</sub>H

Substrate	$k_3/\text{L mol}^{-1} \text{s}^{-1}$	$k_4/\text{L mol}^{-1} \text{s}^{-1}$
Bu <sup>L</sup> -S-S-Bu <sup>L</sup>	22.1 ± 0.8 <sup>a</sup> 6.44 ± 0.25 <sup>b</sup>	~150 <sup>a</sup>
H <sub>3</sub> C-S-S-CH <sub>3</sub>	5.57 ± 0.16 <sup>b</sup>	
	1.43 ± 0.20 <sup>b</sup>	10.1 ± 0.03 <sup>c</sup> 12.7 ± 0.01 <sup>b</sup>
		8.57 ± 0.00 <sup>c</sup>
		2.66 ± 0.01 <sup>c</sup>
		0.27 ± 0.00 <sup>c</sup>

<sup>a</sup> CD<sub>3</sub>CN/H<sub>2</sub>O (1:1 v/v), by NMR, <sup>b</sup> CD<sub>3</sub>CN/H<sub>2</sub>O (4:1 v/v) by NMR, <sup>c</sup> CH<sub>3</sub>CN/H<sub>2</sub>O (4:1 v/v) by UV.

literature values.<sup>7,19–21</sup> Adding excess hydrogen peroxide into the above solution eventually afforded the final product, *p*-toluenesulfonic acid. The reaction was also monitored by <sup>1</sup>H NMR, during which both the thiosulfinate **2** and thiosulfonate **3** were detected. No α,α'-disulfonate **4** was detected for any of the substrates used in this study.

## Results

**Preliminary Experiments.** No significant interaction was found between the disulfides and MTO on the basis of <sup>1</sup>H NMR results. This finding implies that the reaction does not proceed by way of a prior complex between these two. The result further suggests that the reaction, when it does occur as hydrogen peroxide is added, does not feature attack of the sulfur at the rhenium center, for there is no reason to believe that this interaction would occur then, when it did not do so on its own. All six substrates (see Table 1) were initially examined in the absence of a catalyst. Without MTO, there was no evidence for a reaction, even with excess hydrogen peroxide, as indicated either by a UV spectrum that remained nearly unchanged for several hours or by the absence of new peaks growing in the NMR spectrum.

Once MTO had been added, however, the spectra immediately began to show the buildup of the product. These determinations were also performed with equal initial concentrations of the disulfide and hydrogen peroxide. A certain small amount of the thiosulfonate was detected along with the major thiosulfinate for R = Ph, *p*-tolyl, and *p*-chlorophenyl. With three of the compounds, those with R = Me, <sup>t</sup>Bu, and *p*-nitrophenyl, the thiosulfinate was very nearly the only product. Isosbestic points were maintained during these reactions, even with a small excess of hydrogen peroxide. Such a series of repetitive scans is shown in Figure 1.

For this second group of disulfides, the further steps of oxidation beyond the thiosulfinate are a great deal slower, and for all of the disulfides studied there is a

(18) We are grateful to Dr. M. Englehardt of Bruker Corp. for supplying this program.

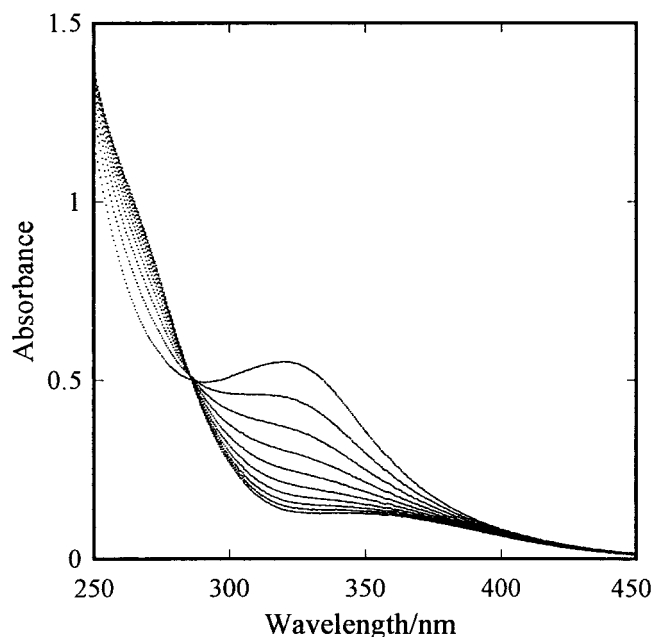
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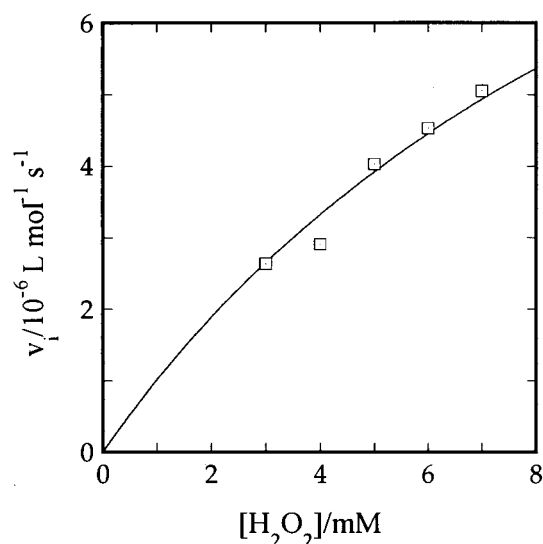
**Figure 1.** Spectral changes at 5.0 min intervals for the oxidation of *p*-nitrophenyl disulfide (0.5 mM) with  $\text{H}_2\text{O}_2$  (0.65 M) in the presence of 0.1 mM MTO at pH 1 in 4:1  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ .

considerable rate advantage found in the first stage of oxidation. This information was used to plan the quantitative studies of the kinetics, so that only the first oxidation stage was important during the data acquisition time.

**Kinetics Studies.** The first part of understanding the reaction scheme lies in the two kinetic steps shown in Scheme 1. In this solvent system, these are the relevant parameters at 298 K:  $k_1 = 15.5 \text{ L mol}^{-1} \text{ s}^{-1}$ ,  $k_{-1} = 0.17 \text{ s}^{-1}$ ,  $K_1 = 91 \text{ L mol}^{-1}$ ,  $K_2 = 347 \text{ L mol}^{-1}$ .<sup>22</sup> It is useful to differentiate studies at “low” and “high” concentrations of hydrogen peroxide, by which we mean experiments at  $<7 \text{ mM}$  and  $>0.5 \text{ M}$ , respectively. We start by presuming that **A** and **B** are separate participants in the oxidation and denote their respective rate constants as  $k_3$  and  $k_4$ . We further presumed, and later confirmed for two compounds, that  $k_3$  and  $k_4$  are of the same order of magnitude. If so, then the term in the rate law for the reaction of **B** with disulfide makes  $\leq 10\%$  contribution in experiments with “low” concentrations of hydrogen peroxide. Under those conditions, the reaction proceeds largely with the **A** form of the catalyst, and its velocity is given by

$$v = \frac{k_1 k_3 [\text{Re}]_{\text{T}} \cdot [\text{R}_2\text{S}_2] \cdot [\text{H}_2\text{O}_2]}{k_{-1} + k_3 [\text{R}_2\text{S}_2] + k_1 [\text{H}_2\text{O}_2]} \quad (5)$$

For purposes of data analysis, the values of  $k_1$  and  $k_{-1}$  were set at their known values.<sup>22</sup> With that, the only unknown in eq 5 is  $k_3$ . Its value could be determined for each experiment, whether the data were in the form of  $v_i$  or  $k_p$ . Under those conditions the variation in the initial rate with hydrogen peroxide concentration, at fixed concentrations of the disulfide and MTO, defines a rectangular hyperbola. Data from experiments with  $\text{Me}_2\text{S}_2$  are presented in Figure 2. A second method for



**Figure 2.** Variation of initial rate of reaction of dimethyl disulfide with the concentration of hydrogen peroxide. The curve is a fit to eq 5. This is applicable when **[B]** is negligible compared to **[A]**. The values of  $k_1$  and  $k_{-1}$  (Scheme 1) were fixed at  $15.5 \text{ L mol}^{-1} \text{ s}^{-1}$  and  $0.17 \text{ s}^{-1}$ . Conditions used: 0.5 mM MTO, 5 mM  $\text{Me}_2\text{S}_2$  in 4:1  $\text{CH}_3\text{CN}-\text{H}_2\text{O}$  at  $25.0 \text{ }^\circ\text{C}$  and pH 1.

data analysis, based on the same chemical mechanism, was used for di-*tert*-butyl disulfide. The concentration–time data for all of the experiments with  $\text{Bu}_2\text{S}_2$  were fit globally with the use of the program FitSim.<sup>23</sup>

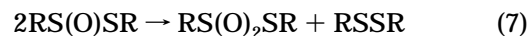
At high hydrogen peroxide, when  $[\text{B}] \gg [\text{A}]$ , the absorbance–time (UV–vis) or concentration–time (NMR) data fit first-order kinetics. Because  $[\text{B}] \cong [\text{Re}]_{\text{T}}$ , the rate law under this condition becomes

$$v = k_4 [\text{Re}]_{\text{T}} \cdot [\text{R}_2\text{S}_2] = k_p [\text{R}_2\text{S}_2] \quad (6)$$

For these determinations, a series of experiments was carried out with constant  $[\text{H}_2\text{O}_2]$  and  $[\text{R}_2\text{S}_2]$  in which  $[\text{Re}]_{\text{T}}$  was varied, typically 0.1–0.5 mM. The plot of  $k_p$  against  $[\text{Re}]_{\text{T}}$  was linear, as depicted for three compounds in Figure 3. The values of  $k_4$  given by the slopes of these lines are summarized in Table 1.

It should be noted that the various aspects of the data analysis presented are all different components of the same reaction scheme. The differences arise from the different ranges of concentration chosen for different sets of experiments and also because the relative rate constants are different from one disulfide to the next.

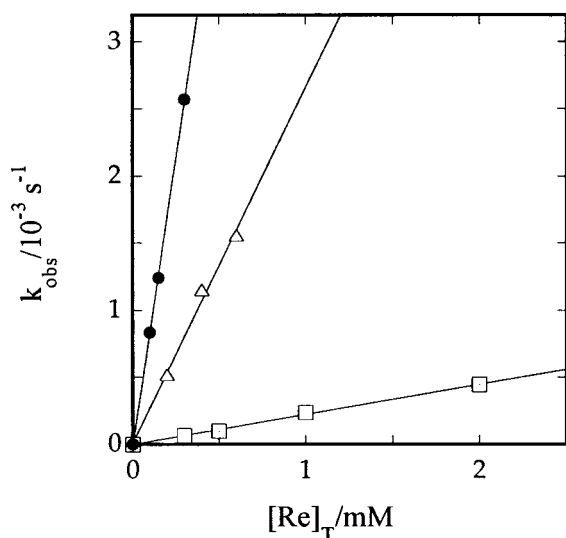
**Fate of the Thiosulfates.** Compounds of the formula  $\text{RS}(\text{O})\text{SR}$  tend to be unstable and usually cannot be isolated. Careful NMR measurements were made during the reaction between 20 mM di(*p*-tolyl) disulfide and a limited (10 mM) concentration of hydrogen peroxide. Once the thiosulfate had been formed, it slowly decomposed with the formation of the thiosulfonate,  $\text{RS}(\text{O})_2\text{SR}$ , and partial regeneration of the disulfide. This is compatible with a disproportionation process:



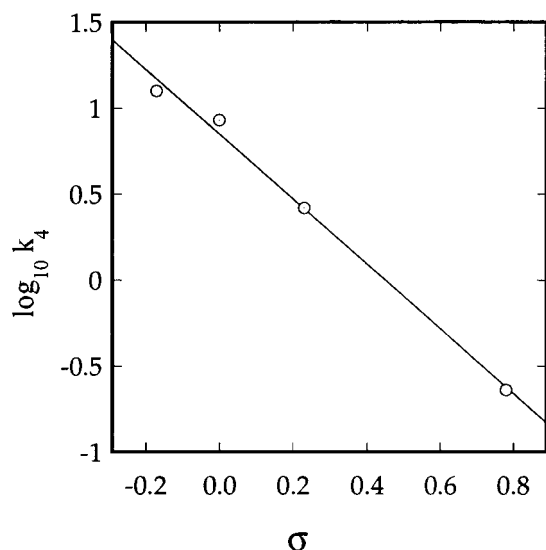
A companion experiment with di(*tert*-butyl) disulfide gave a thiosulfate that seemed stable for a much longer

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**Figure 3.** The pseudo-first-order rate constants (4:1 CH<sub>3</sub>CN–H<sub>2</sub>O at 25.0 °C and pH 1) for the oxidation of diaryl disulfides (0.5 mM) by H<sub>2</sub>O<sub>2</sub> (0.65 M) vary linearly with the total catalyst concentration, as shown in order of increasing slope for the para substituents NO<sub>2</sub>, Cl, and H. The slope of this line affords the values of  $k_4$ .



**Figure 4.** Hammett plot for the oxidation of substituted phenyl disulfides by the peroxorhenium compound **B**. The slope of the line gives  $\rho = -1.89$ .

period, suggesting that disproportionation is sterically impeded by the bulky R group.

### Discussion

To assess the extent to which electronic factors play a role in the transition state, the rate constants for the diaryl disulfides were examined by the Hammett correlation. The plot of  $\log(k_4)$  vs  $\sigma$ , the Hammett substituent constant, was constructed (Figure 4). The four points define a reasonable straight line; its slope is the reaction constant,  $\rho = -1.89$  (correlation coefficient 0.997). The negative value of  $\rho$  implies that the reaction center (the

sulfur atom) shows a buildup of positive charge relative to that in the free molecule. This effect, although in the same direction, is considerably larger than that found for RAr ( $\rho = -0.98$ ).<sup>24</sup> We argue that the enhanced  $\rho$  value arises principally from the conjugative effect caused by the para-conjugated phenylmercapto group. In this case, the electronic effect of this group seems comparable to that of a phenyl group. The electronic effect of the para substituent on the sulfur atom that is not being oxidized appears muted.

When these results are combined with the information already available about organic sulfides<sup>24</sup> and thioketones,<sup>22</sup> comparisons can be made to gain an understanding of these results. The disulfides are some  $10^3$ – $10^4$  less reactive than either of those families of compounds. This comparison does not require a precise one-to-one match of substituents, because the rate effects are quite large. This is one series that is reasonable for comparison: for Et<sub>2</sub>S, thiocamphor, and Me<sub>2</sub>S<sub>2</sub>, values of  $k_3$  are  $2 \times 10^4$ ,  $3 \times 10^3$ , and  $6.4 \text{ L mol}^{-1} \text{ s}^{-1}$ . This large difference can be ascribed to the substitution of an SR group for an R group. Despite the electron-releasing conjugative effect, the SMe group is electron-withdrawing; its Hammett  $\sigma$  value is +0.07 and the Taft  $\sigma_1$  value is +0.23. This effect may lower the nucleophilicity of the sulfur atom to which it is bound in the disulfide, thus lowering, relative to the sulfides and thioketones, the rate at which it attacks the peroxorhenium compound.

The reactivity of **B** as compared to **A** is given by the ratio  $k_4/k_3$ . With but the one exception of allyl alcohols,<sup>25</sup> clearly a special case, the reactivity of these two are comparable and often in favor of **A**. In the two cases examined here (and by extrapolation, likely all six) **B** is somewhat more reactive than **A** by a factor of ca. 7.

From the results obtained here and the general pattern set by other reagents with the MTO–H<sub>2</sub>O<sub>2</sub> system, we propose a transition state in which one sulfur atom of the substrate nucleophilically attacks the peroxy group of **A** or **B**. Probing more closely, we note that certain reactions show virtually no steric effect, such as observed for R<sub>2</sub>S<sub>2</sub>: the values of  $k_3$  are 6.4 (R = Me) and 5.6 (R = <sup>t</sup>Bu) L mol<sup>-1</sup> s<sup>-1</sup>. This insensitivity of rate to steric bulk is in accord with values for PAR<sub>3</sub>,<sup>26</sup> R<sub>2</sub>S,<sup>24</sup> and Br<sup>-</sup>.<sup>27</sup> In contrast, the epoxidation of olefins show an important steric effect.<sup>28</sup> Oxidation of MeSS<sup>t</sup>Bu by peracetic acid forms MeS(O)S<sup>t</sup>Bu and MeSS(O)<sup>t</sup>Bu in 1:2 yield,<sup>29</sup> showing that these reactions also have small steric effects.

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