Radical Reactions

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Solvent-Enabled Radical Selectivities: Controlled Syntheses of Sulfoxides and Sulfides

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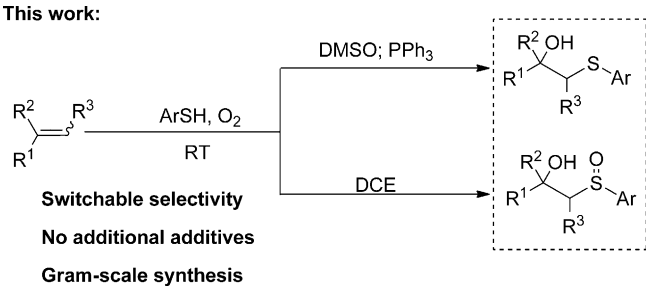
Abstract: *Controlling selectivity is of central importance to radical chemistry. However, the highly reactive and unstable radical intermediates make this task especially challenging. Herein, a strategy for taming radical redox reactions has been developed, in which solvent-bonding can alter the reactivity of the generated radical intermediates and thereby drastically alter the reaction selectivity at room temperature. Various β-oxy sulfoxides and β-hydroxy sulfides can be facilely obtained, some of which are difficult to synthesize by existing methods. Notably, neither a metal catalyst nor any further additives are necessary in these processes.*

Radical chemistry has been vibrant and alive for more than one century, yet controlling selectivity in radical reactions has always been an essential issue. The fast reaction rates, highly reactive and unstable radical intermediates make this task especially challenging.[1] Recently, attention has been shifted towards the use of milder radical initiators, such as transition metal catalysts and photosensitizers, to tune the reaction selectivity.[1,2] Despite the significance of these developments, the successful application of these strategies often relies on creative substrate design. Until now, switching product selectivity from the same starting materials still remains a fundamental challenge.[3] Seeking efficient and sustainable alternatives to achieve this goal is an appealing, yet difficult, task.

β-Oxy sulfoxides and β-hydroxy sulfides are widely featured in natural products, pharmaceuticals, and biologically active compounds.[4] They are also important building blocks and have versatile synthetic applications in asymmetric synthesis and total synthesis of natural products.[4] Despite the intriguing properties of the sulfoxide and sulfide groups, facile synthesis of these molecules from simple starting materials is still underdeveloped,[5] especially for the valuable β-oxy sulfoxides.[6] In this regard, thiol–oxygen co-oxidation (TOCO) reactions, which are traditionally free-radical-mediated hydroxysulfenylation reactions, have provided a promising process for preparation of β-hydroxy sulfides and β-hydroxy sulfoxides.[7] However, the diversity of these transformations is often constrained to electron-rich olefins and suffers from low regioselectivity, chemical inefficiency, and requires assistance in the form of UV irradiation, peroxides, and/or transition metals.[1b,d,5e,7,8] Until now, only a handful of methods have been developed for the synthesis of β-hydroxy sulfides, and the efficient approach towards β-oxy sulfoxides from simple starting materials is still very limited.[5,6] Herein, a method to control radical selectivity through solvent-bonding is presented, which can dictate reaction selectivity without outside assistance. Various β-oxy sulfoxides and β-hydroxy sulfides can be facilely obtained featuring switchable selectivity, mild conditions, and gram-scale synthesis (Scheme 1).



Scheme 1. Switchable synthesis of β-oxy sulfoxides and β-hydroxy sulfides.

Radical redox reactions of thiols and alkenes in the presence of dioxygen have been a fundamental research area in synthetic community, and the final products obtained from these reactions largely depend on the reaction concentration, temperature, structure of reactant, solvent, initiator, catalyst, and other conditions.[1b,d,7,8] Consequently, the product distribution remains difficult to predict, even today. In principle, the H-abstraction products or the oxygenation products, hydroperoxy sulfides, can be generated after the reversible addition of the thiyl radical to the alkene (Scheme 2). However, hydroperoxy sulfides are simultaneously a combination of an oxidant and reductant, which can easily undergo rearrangement to sulfoxides, sulfides, hemithioacetals, aldehydes, and ketones, resulting in low reaction selectivity.[9] As shown in Scheme 2, the redox reactivity of the hydroperoxy sulfide may directly determine the self- or intermolecular redox processes, leading to the β-hydroxy sulfoxide or β-hydroxy sulfide, respectively. Accordingly, the ability to tune the redox reactivity of the unstable hydroperoxy sulfide would be the key to achieve high reaction selectivity. Spurred by the unique structure of the hydroperoxy sulfide, we envisioned that the solute–solvent interaction might have an

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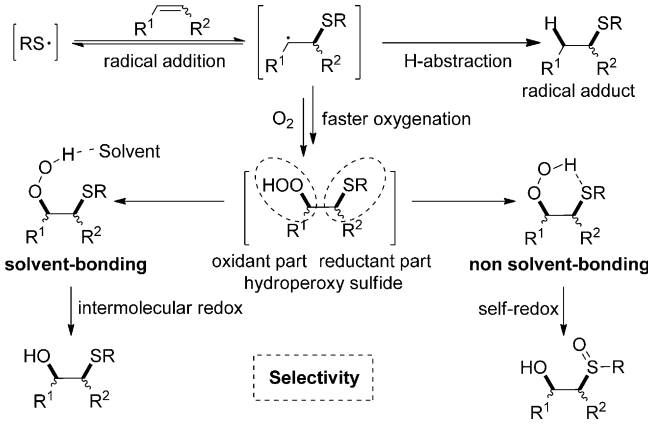


Scheme 2. Solvent bonding for selectivity control in radical redox processes.

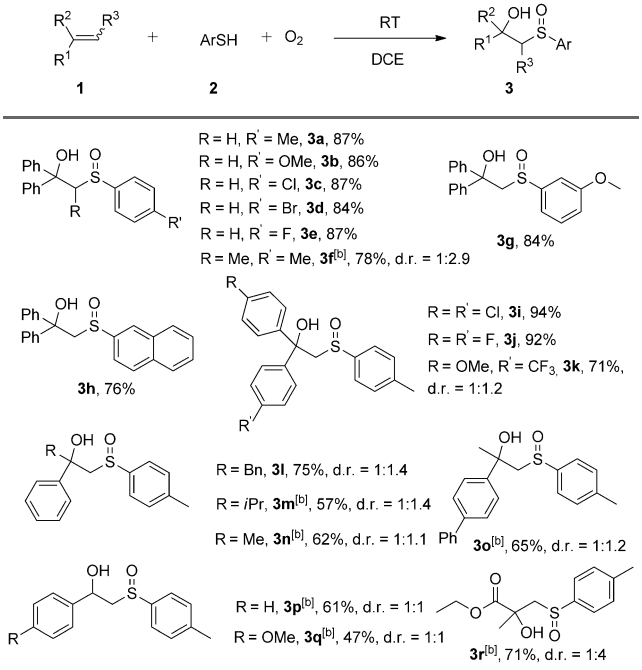
impact on the redox reactivity of the hydroperoxy sulfide through solvent-bonding, thus providing a possible way to steer the redox processes to the corresponding sulfoxide or sulfide under metal-free conditions.

To test whether the solvent-bonding could influence the redox selectivity, we chose the abundant and commonly used 1,1-diphenylethylene (**1a**) and *p*-toluenethiol (**2a**) as the starting materials to test different solvents (Supporting Information, Table S1). Indeed, β-hydroxy sulfoxide **3a** could be furnished in good to excellent yields (up to 90% NMR yield) at room temperature in weakly hydrogen-bonding solvents, including $CHCl_3$, dichloroethane (DCE), and toluene. Conversely, when DMSO was used as the solvent, the selectivity was reversed, as expected, and 89% NMR yield of β-hydroxy sulfide **4a** was obtained after PPh_3 workup. Notably, no **3a** or **4a** was observed when the reaction was carried out under N_2 atmosphere, which was also consistent with proposed reaction routes in Scheme 2.

Furthermore, $^{18}O_2$-labeling experiments were conducted to elucidate the origin of the oxygen atom of the β-hydroxy sulfoxide and β-hydroxy sulfide. The corresponding ^{18}O-labeled **3a** and **4a** could be isolated in 90% and 89% yields under optimized conditions, which confirmed that dioxygen took part in this transformation and was incorporated into the final products (Supporting Information).[10]

Subsequently, the substrate scope for the highly selective synthesis of tertiary β-hydroxy sulfoxides was investigated (Table 1), this substrate class was selected because they are normally difficult to synthesize by existing methods. Thiophenols bearing not only electron-donating groups, such as methoxy and methyl, but also electron-withdrawing groups, such as F, Cl, and Br, could react smoothly with **1a**, affording the corresponding products in 84–87% yields (**3a–e** and **3g**). To our delight, non-terminal styrene derivatives, such as 2-methyl-1,1-diphenylethylene, were amenable to this method (**3f**). 2-Naphthalenethiol also reacted efficiently with **1a** to give the product in 76% yield (**3h**). Furthermore, a variety of α-substituted styrene derivatives were suitable partners in this procedure, and an array of tertiary β-hydroxy sulfoxides could be facilely obtained in moderate to excellent yields (**3i–o**). Encouraged by these promising results, we further applied this method to prepare secondary β-hydroxy sulfoxides using

Table 1: Synthesis of β-hydroxy sulfoxides.[a]



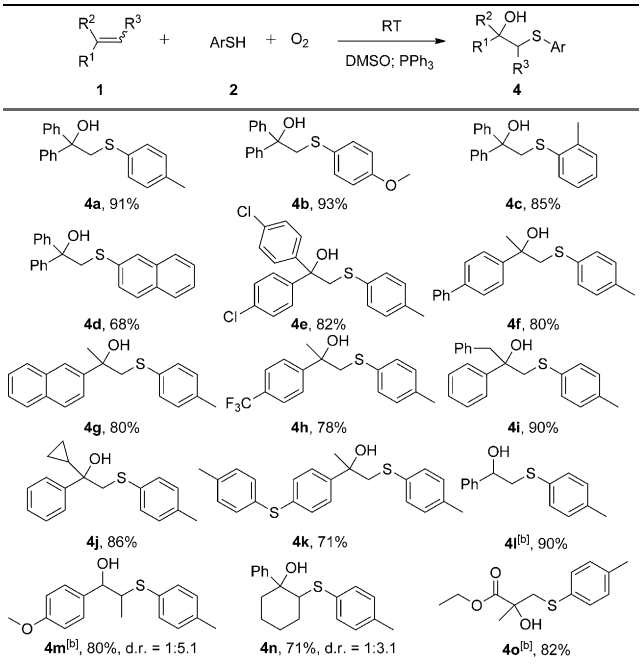
[a] Unless otherwise specified, all of the reactions were carried out using **1** (0.2 mmol) and **2** (0.2 mmol) in DCE (0.1 mL) at room temperature for 2 h under O_2. Isolated yield (%). [b] 3 h.

styrene derivatives as substrates. As exemplified by styrene and *p*-methoxystyrene, the desired secondary β-hydroxy sulfoxides (**3p–q**), were furnished in 61% and 45% yields, respectively. Importantly, activated aliphatic alkene also performed well, generating **3r** in 71% yield with high selectivity, probably owing to the directional selectivity from the steric hindrance. Nevertheless, non-activated aliphatic alkenes, such as 1-butene, were not amenable to this procedure, probably owing to the lower stability of the corresponding radical intermediates.

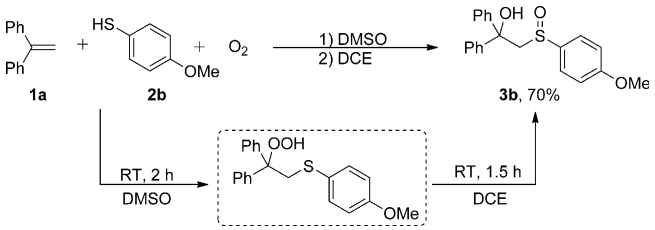
Additionally, a series of tertiary and secondary β-hydroxy sulfides could be obtained in good to excellent yields from the corresponding alkenes and thiophenols (Table 2). Notably, α-cyclopropylstyrene reacted smoothly with **2a** without ring opening rearrangement, providing the desired product **4j** in 86% yield. Secondary β-hydroxy sulfides, exemplified by **4l**, could also be readily prepared by using styrene as reactant. Pleasingly, non-terminal and cyclic styrene derivatives with steric hindrance, such as *trans*-anethole and 1-phenyl-1-cyclohexene, were able as well to give the expected products **4m** and **4n** in good yields, respectively. Furthermore, ethyl methacrylate, a widely used Michael acceptor, effectively outcompeted the Michael addition of thiophenol to the electron-deficient alkene, generating **4o** in 82% yield.

The efficiency of this method on a larger scale was next investigated. It is noteworthy that this procedure can be scaled up to gram quantities of the desired β-hydroxy sulfoxides and β-hydroxy sulfides without sacrificing yield. For instance, 1.39 g of **3a** and 1.41 g of **4a** could be isolated in 83% and 88% yields, highlighting the synthetic utility of this method (Supporting Information).

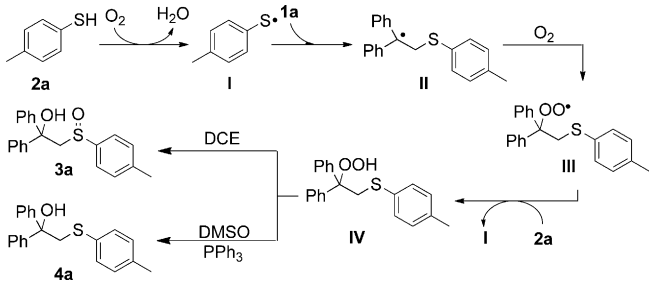
Table 2: Synthesis of β-hydroxy sulfides.[a]



[a] Unless otherwise specified, all of the reactions were carried out using **1** (0.2 mmol) and **2** (0.2 mmol) in DMSO (2.0 mL) at room temperature for 2 h under O_2. Isolated yield after PPh_3 workup (%). [b] 3 h.



Scheme 3. Switchable synthesis of β-hydroxy sulfoxide **3b**.



Scheme 4. Proposed mechanism.

To gain insight into the reaction mechanism, radical trapping experiments were conducted. The reaction between **1a** and **2a** was extremely inhibited by the radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), either using DCE or DMSO as the solvent (Supporting Information), supporting the proposed radical pathway for this reaction.

Additionally, the reaction of **1a** and **2a** in DCM was monitored by in situ IR. The signal of **3a** increased gradually in intensity with the consumption of **2a**, and no inductive period and obvious reaction intermediate were observed (Supporting Information). In contrast, the hydroperoxy sulfide could be confirmed as the vital reaction intermediate for β-hydroxy sulfide formation. The consumption of **2a** and **1a**, generation of hydroperoxy sulfide **IV** and **4a** could all be well tracked in sequence (^{1}H NMR experiments; Supporting Information).

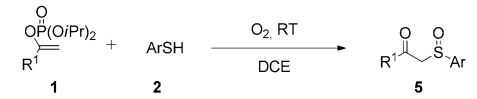
With these results in hand, we wondered whether the β-hydroxy sulfoxide also originates from the hydroperoxy sulfide under the current conditions. Interestingly, **3b** can be isolated in 70% yield by reacting the hydroperoxy sulfide (generated in DMSO without isolation; Supporting Information) in DCE for 1.5 h (Scheme 3). These results suggested that the hydroperoxy sulfide might be formed predominantly in both transformations. This result also indirectly demonstrated that solvent-bonding stabilizes the unstable hydroperoxy sulfide and induces an intermolecular redox, whereas a self-rearrangement would occur easily.[11]

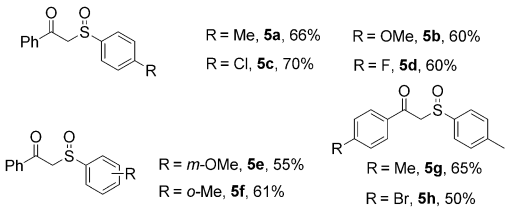
Based on these results and on previous works,[7,10] a mechanism for this reaction is proposed in Scheme 4. Firstly, arenethiyl radical **I** is generated from autoxidation of 4-methylthiophenol (**2a**). Then, radical addition of **I** to alkene (**1a**) affords carbon-centered radical **II**, which would further react quickly with dioxygen and be transformed into peroxyl radical **III**. Subsequently, an intermolecular hydrogen abstraction process occurs between **2a** and **III**, delivering arenethiyl radical **I** and the key intermediate, hydroperoxy sulfide **IV**. Finally, **IV** undergoes a redox process with or without assistance of solvent-bonding, providing β-hydroxy sulfoxides and β-hydroxy sulfides, respectively.

On the basis of this mechanistic proposal, we further attempted to apply the present method in the synthesis of β-keto sulfoxides by introducing a good leaving group at the α-position of the alkene. As shown in Table 3, a range of β-keto sulfoxides could be successfully synthesized in moderate yields by employing α-substituted alkenes. Intriguingly, these reactions were also performed at room temperature under metal-free conditions, highlighting the practical utility of this method. Furthermore, because the reaction intermediate, β-hydroperoxy sulfide, easily undergoes decomposition, a thiophenol-catalyzed radical cleavage of 1,1-diphenylethylene was further developed under irradiation by a 3 W Blue LED, in which benzophenone could be selectively obtained in 78% yield (Supporting Information).[12,13]

In summary, we have developed a practical strategy for the highly selective construction of β-oxy sulfoxides and β-hydroxy sulfides from readily available starting materials.[14] This reaction features simple operation, switchable selectivity, green reagents, and gram-scale synthesis. Crucially, neither metal catalyst nor any additional additive was necessary in these transformations. Mechanistic investigations demonstrated that hydroperoxy sulfide might be the same intermediate for both of the redox processes, and solvent-bonding enables tuning of the redox reactivity of the unstable hydroperoxy sulfide, which is the key to achieve switchable selectivity. Ongoing research, including further mechanistic details and expanding the substrate scope, are currently underway.

Table 3: Synthesis of β-keto sulfoxides.[a]





[a] All of the reactions were carried out using **1** (0.2 mmol) and **2** (0.24 mmol) in DCE (0.5 mL) at room temperature for 5 h under 1 atm O_2. Isolated yield (%).

Acknowledgements

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[14] Aliphatic thiols are not amenable to this procedure. These transformations are addition of aromatic thiols to styrenes and its derivatives.

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