

Short Communication

Addition of unactivated thiols to epoxides and oxetanes catalyzed by a rhenium-oxo complex



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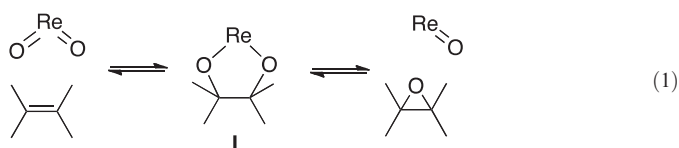
Thiols

ABSTRACT

A method for synthesizing β - and γ -hydroxy thioethers via addition of unactivated thiols to epoxides and oxetanes has been developed. This reaction is proposed to proceed through an unconventional mode of activation of the heterocycles. The transformation is catalyzed by $\text{ReO}_2(\text{PPh}_3)_2$ affording β - and γ -hydroxy thioethers in moderate to excellent yield with excellent regioselectivity.

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Regio-, stereo-, and chemoselective bond forming reactions are the key to efficient syntheses of organic compounds and materials. A frequently employed strategy for achieving selective reactivity is the use of transition metal catalysis. Often, transition metals can provide access to reaction pathways that may not be available to main group elements. One privileged class of transition metal catalysts is the metal-oxo complexes, which contain metal–oxygen multiple bonds [1]. The use of metal-oxo complexes as catalysts in the oxidation of unsaturated hydrocarbons to yield epoxides, diols, and carbonyl compounds is well documented [2]. Espenson and Gable have elegantly shown that, in the case of epoxidations catalyzed by high oxidation state rhenium-oxo complexes, the oxygen atom transfer is reversible [3]. They discovered that equilibrium is established between the epoxide and the corresponding olefin and proposed that the interconversion of these two compounds proceeded via the formation of a rhenium diolate **I** (Eq. (1)). The formation of **I** from the epoxide implies a variation from the traditional Lewis acidic activation of epoxides.

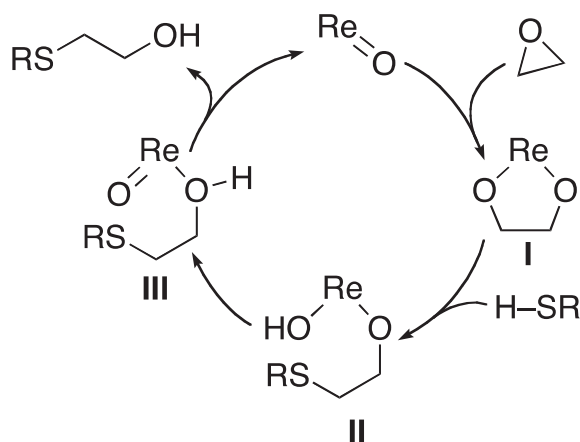


The deoxygenations of epoxides using rhenium-oxo complexes were rendered catalytic with the addition of triphenylphosphine as an oxygen acceptor [4]. We postulated that this non-traditional mode of activation could be incorporated into catalytic nucleophilic ring opening reactions by intercepting diolate **I** with a nucleophile before deoxygenation. These reactions would be complementary to existing Lewis acid reactions [5] and allow for controlled additions to strained heterocycles. Based on the results reported by Gable and coworkers in the deoxygenation reaction described above, we began examining rhenium(V)-oxo complexes in the catalytic activation of epoxides toward the addition of thiols [6]. It was envisioned that, after activation of the epoxide, diolate intermediate **I** could be intercepted with the addition of a thiol (Scheme 1). Nucleophilic substitution on the diolate and proton transfer would result in the formation of alkoxy rhenium hydroxide complex **II**. Tautomerization regenerates the metal-oxo ligand [7] and the cycle is closed after liberation of the functionalized product [8].

A number of rhenium(V)-oxo complexes were examined as potential catalysts in the reaction of 4-methylbenzenethiol with styrene oxide, **8** (Eq. (2)). A representative sampling, **1–7**, is shown in Fig. 1. Measureable amounts of the desired β -hydroxy thioether **9** were obtained in the presence of catalytic quantities of **1–7**; however, these reactions also showed significant amounts of styrene, **12**, via the competitive deoxygenation pathway. Also present in the reaction mixtures was the hydration product 1-phenylethanol, **10**. The reactions promoted by complexes **1–5** also lead to the formation of 2-chloro-2-phenylethanol, **11**, presumably through transfer of the chloride ligand from the metal. A similar iodinated product was not observed for reactions run in the presence of **6** or **7** [9]. Significant degradation of the starting material to unidentified, possibly polymeric byproducts was observed in the presence of **6**. Reactions catalyzed by **7** produced the

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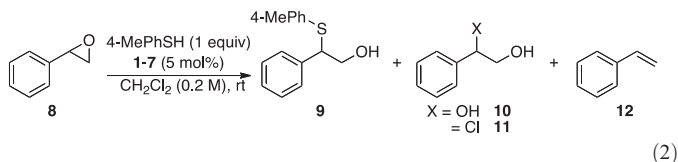


Scheme 1. Proposed catalytic cycle for addition of thiols to epoxides.

Table 1
Optimization studies.

Entry	Solvent	Temp (°C)	Time (h)	Conc (M)	% Cat	% Conv	Distribution of products (%)		
							9	10	11
1	CH ₂ Cl ₂	rt	19	0.2	5	70	70	22	3
2	CH ₃ CN	rt	19	0.2	5	8	75	17	0
3	hexanes	rt	19	0.2	5	64	86	4	6
4	EtOAc	rt	19	0.2	5	100	56	39	3
5	dry EtOAc	rt	19	0.2	5	100	76	19	0
6	dry EtOAc	4–7 °C	48	0.2	5	100	81	15	0
7	dry EtOAc	rt	4	1.0	5	100	85	9	0
8	dry EtOAc	rt	4	2.0	5	100	90	4	0
9	dry EtOAc	rt	20	2.0	1	100	90	2	0

highest conversion of starting material to **9** with **10** and **12** as the most notable byproducts. Therefore, reaction optimization was continued, employing **7** as the catalyst.



For the optimization studies, the addition of 1 equivalent of 4-methylbenzenethiol to styrene oxide in the presence of **7** was examined. The percent conversion and product distribution [10] were determined by ¹H NMR versus an internal standard. In the presence of 5 mol% of **1** at room temperature in CH₂Cl₂ (0.2 M), styrene oxide was transformed to a mixture of **9**, **10**, and **12** with a total conversion of 70% (Table 1, entry 1). Highly coordinating acetonitrile permitted very little reactivity with only 8% conversion of styrene oxide to **9** and **10** with no deoxygenation observed (entry 2). In hexanes, a decreased conversion, relative to CH₂Cl₂, was obtained; however, there was a notable decrease in hydration and deoxygenation products (entry 3). Gratifyingly, ethyl acetate showed complete conversion of the starting material to **9**, the major product; however, the reaction was prone to hydrolysis (entry 4). By using ethyl acetate that had been dried over activated molecular sieves, the relative amount of thioether **9** formed was markedly increased. Comparable yields were observed when the reaction was conducted at lower temperatures with extended reaction times (entry 6).

Increasing the concentration allowed for a further increase in the yield of **9** relative to diol **10** and decrease in the reaction times (entries 7–8). In addition, the catalyst loading could be decreased to 1.0% with negligible impact on the yield; however, extended reaction times were required (entry 9).

The reactivity of styrene oxide toward the addition of substituted thiophenols derivatives was probed for generality. The reactions were performed under the optimized conditions: 2.0 M in dry ethyl acetate at room temperature in the presence of 1 mol% of **7**. The reactions were quenched upon completion as determined by TLC (approximately 4–8 h). Electron-rich and electron deficient thiophenol derivatives were added to styrene oxide to produce the corresponding β-hydroxy thioethers in good yield (62–77%, Table 2, entries 1–4). For these reactions, only one regioisomer was observed. The observed regioselectivity, addition of the thiols to the benzylic position of styrene oxide, is attributed to the stabilizing ability of the aromatic ring toward charges developing in the transition state leading to the thiol addition. The regioselectivity was preserved with the reaction of styrene oxide derivatives **12** and **13** with 4-methylbenzenethiol (entries 5 and 6).

The reactivity of alkyl and benzyl substituted epoxides was examined for reactivity under the above described reaction conditions with a reaction time of 4–24 h. 1,2-Hexene oxide, **17**, was highly reactive toward the addition of electron-rich and electron-deficient thiophenol derivatives (49–95%, Table 3, entries 1–4). The reaction proceeded with excellent regioselectivity leading to the formation of the secondary alcohol. We postulate that regioselectivity is dictated by minimization of steric repulsion of the incoming thiol leading to opening of alkyl-

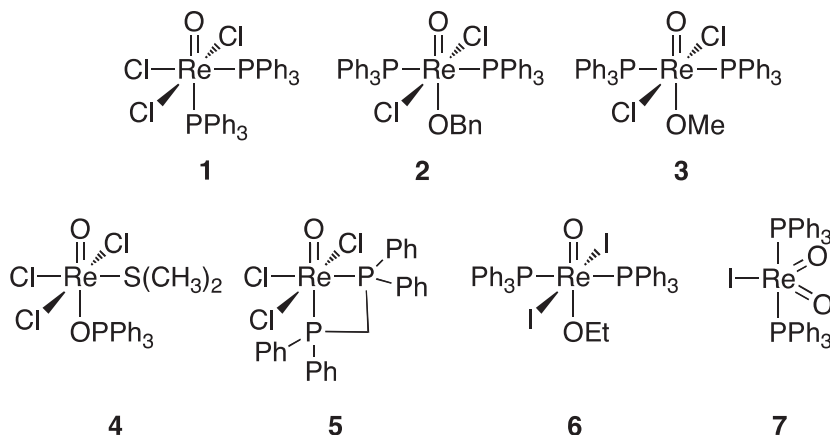


Fig. 1. Sampling of re-oxo complexes screened for catalytic activity.

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