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Short Communication

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

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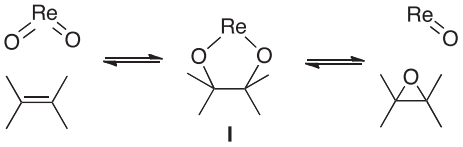
ABSTRACT

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 $ReO_2I(PPh_3)_2$ affording β- and γ-hydroxy thioethers in moderate to excellent yield with excellent regioselectivity.

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 oxidization 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.



I (1)

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-phenylethanediol, **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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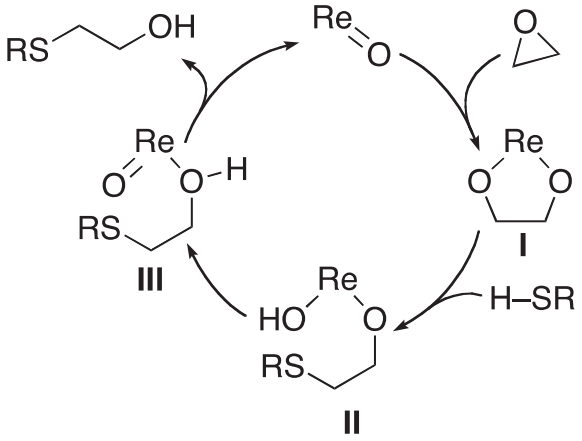
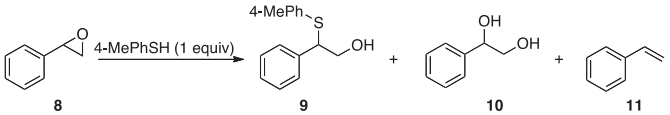


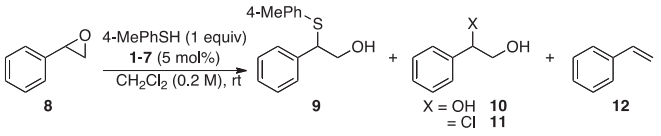
Scheme 1. Proposed catalytic cycle for addition of thiols to epoxides.

Table 1
Optimization studies.



Entry	Solvent	Temp (°C)	Time (h)	Conc (M)	%Cat	%Conv	Distribution of products (%)		
							9	10	11
1	CH_2Cl_2	rt	19	0.2	5	70	70	22	3
2	CH_3CN	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.



(2)

For the optimization studies, the addition of 1 equivalent of 4-methylbenezenethiol to styrene oxide in the presence of **7** was examined. The percent conversion and product distribution [10] were determined by ^{1}H NMR versus an internal standard. In the presence of 5 mol% of **1** at room temperature in CH_2Cl_2 (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 CH_2Cl_2, 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-

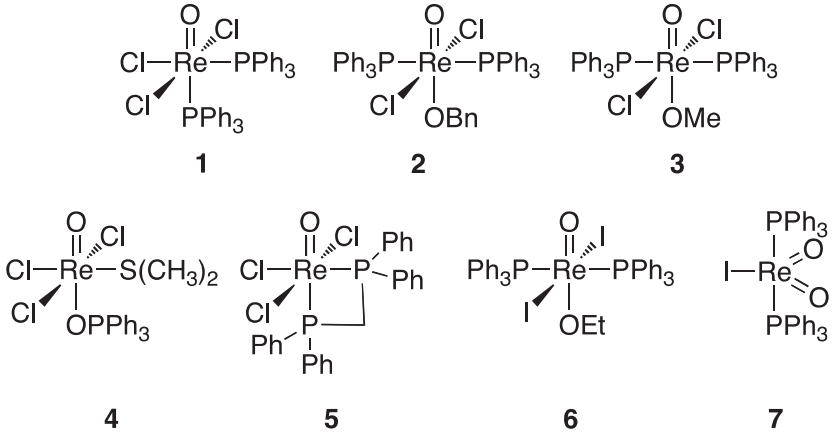
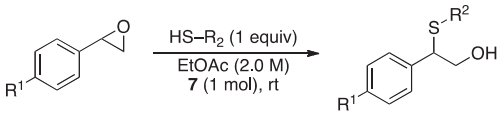
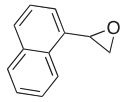


Fig. 1. Sampling of re-oxo complexes screened for catalytic activity.

Table 2
Reaction of styrene oxides with thiophenol derivatives.



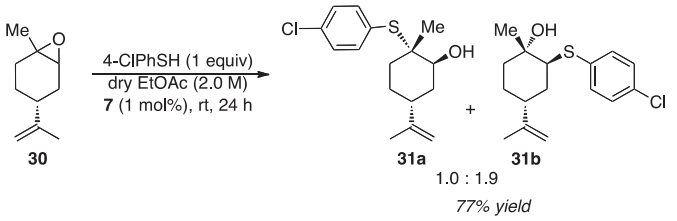
8, 12, 13 **9, 14a-c, 15, 16**

Entry	R^1		R^2	% Yield	
1	H	**8**	4-(OMe)Ph	68	**14a**
2	H	**8**	4-MePh	77	**9**
3	H	**8**	Ph	62	**14b**
4	H	**8**	4-ClPh	70	**14c**
5	Cl	**12**	4-MePh	52	**15**
6		**13**	4-MePh	55	**16**

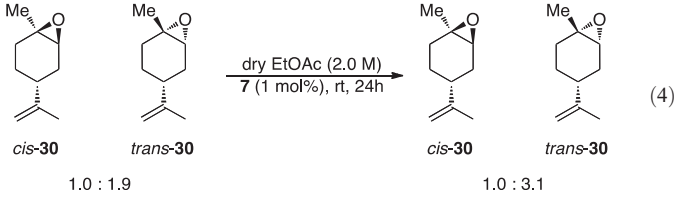
substituted epoxides at the less substituted position. Under standard conditions, the opening of benzylic epoxide **18** also proceeded in good to excellent yield, 56–93%, with excellent regioselectivity (Table 3 entries 5–8). With both epoxides, measurable amounts of the minor regioisomer were formed from the addition of the more electron rich thiophenol derivatives (entries 1, 5, and 6).

The scope of the reaction was further probed for the tolerance of various functional groups. Moderate to good yields were obtained from the reaction of epoxides bearing α-alkoxy substitution (56–81%, Table 4, entries 1 and 2). The presence of the phenoxy functionality did not influence the regioselectivity of the reaction; the only regioisomer obtained resulted from the addition to the less substituted position of the epoxide. However, glycidyl butyrate, **22**, was reacted to form a 15.8:1.0 inseparable mixture of the regioisomers. This addition reaction is not limited to mono-substituted epoxides. Tetra substituted epoxide **23** provided tertiary thioether **27** in moderate yield (42%, entry 3). The reaction of 1,2-epoxy-9-decene, **24**, with 4-chlorothiophenol provided an 85% yield of an 86:14 mixture of regioisomers with β-hydroxy thioether **28** as the major product (entry 4). Higher yields, 91%, were obtained when **24** was reacted with 4-methoxythiophenol. Thioether **29** was obtained as a 7.1:1.0 mixture of regioisomers (entry 5). Gratifyingly, no oxidation of the terminal alkene was observed in either reaction.

The addition of 4-chlorothiophenol to (+)-limonene oxide, **30**, provided our first insight into the mechanism of the reaction. The reaction produced a 1.0:1.9 mixture of **31a** and **31b** as single diastereomers of each regioisomer with an overall yield of 77% (Eq. (3)). Past studies have shown that the opening of cyclic epoxides will proceed through the axial attack of the nucleophile [11]. Based on this precedence, regioisomer **31a** would be formed from the opening of *cis*-(+)-limonene oxide (*cis*-**30**) and **31b** from *trans*-(+)-limonene oxide (*trans*-**30**). The initial *cis*:*trans* ratio of (+)-limonene oxide was 1.0:1.3. The enriched regioselectivity of the addition products, 1.0:1.9, relative to the starting ratio of the *cis*:*trans* isomers, 1.0:1.3, suggests that an isomerization of the epoxide was taking place. To test this, a sample of (+)-limonene oxide was reacted with **7** in the absence of thiol. After 24 h, the reaction was quenched and the ratio of the diastereomers was determined by ^{1}H NMR and found to be a 1.0:3.1 mixture of *cis*:*trans* isomers (Eq. (4)). An isomerization to *trans*-**30** proceeding concurrently with the addition reactions would enable for an enrichment of **31b** in the product distribution. It is envisioned that such an isomerization could be accomplished through a deoxygenation/epoxidation sequence. Such a process would mirror the observations of Gable and coworkers.

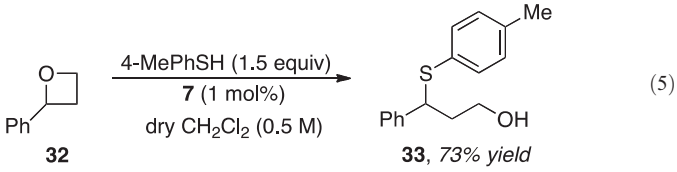


(3)



(4)

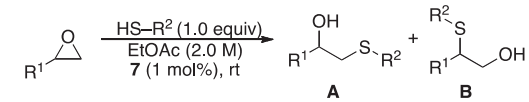
Having successfully activated epoxides, we looked to extend this methodology to the addition of thiols to oxetanes. It was expected that oxetanes could also be activated in a manner analogous to the postulated mechanism (Scheme 1) to form a six-membered diolate intermediate. Gratifyingly, 2-phenyloxetane underwent addition of 4-clorothiophenol in the presence of 1 mol% of **7** under the conditions used for the epoxide reactions. A brief optimization study identified that a 0.5 M reaction solution in dry CH_2Cl_2 produced the highest conversion of **32** to the thioether **33**. One regioisomer of thioether **33** was isolated in a 73% yield (Eq. (5)). It is of note that no polymerization of the oxetane was observed [12].



(5)

Rhenium(V)-oxo complex **7** was shown to be an effective catalyst for the addition of unactivated thiols to differentially substituted epoxides and 2-phenyloxetane. The reaction proceeded in moderate to excellent yield with excellent regioselectivity. Elaboration of this reaction and elucidation of the mechanism are underway in our laboratory and will be reported in due time.

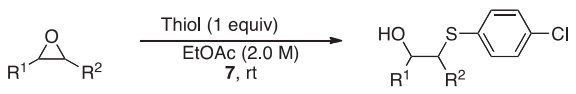
Table 3
Addition of thiols to alkyl and benzyl epoxides.

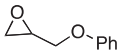
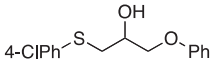
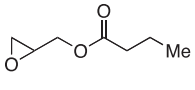
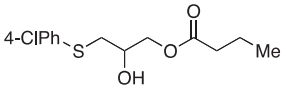
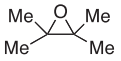
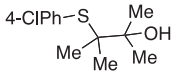
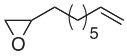
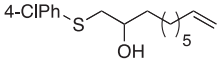
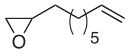
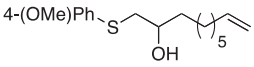


17, 18 **19a-d, 20a-d**

Entry	R^1		R^2	% yield		A:B
1	*n*-butyl	**17**	4-(OMe)Ph	89	**19a**	98:2
2	*n*-butyl	**17**	4-MePh	95	**19b**	>99:1
3	*n*-butyl	**17**	Ph	49	**19c**	>99:1
4	*n*-butyl	**17**	4-ClPh	88	**19d**	>99:1
5	$PhCH_2$	**18**	4-(OMe)Ph	93	**20a**	96:4
6	$PhCH_2$	**18**	4-MePh	90	**20b**	98:2
7	$PhCH_2$	**18**	Ph	56	**20c**	>99:1
8	$PhCH_2$	**18**	4-ClPh	89	**20d**	>99:1

Table 4
Extension of substrate scope.



Entry	Epoxide		Thiol	Thioether		Yield (%)
1		**21**	4-ClPhSH		**25**	56[a]
2		**22**	4-ClPhSH		**26**	81[b]
3		**23**	4-ClPhSH		**27**	42[b]
4		**24**	4-ClPhSH		**28**	85[a]
5		**24**	4-(OMe)PhSH		**29**	91[a]

Acknowledgements

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