Salan-Vanadium Catalyzed Enantioselective Desymmetrization of *meso*-Epoxides with Aromatic Thiols

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Abstract: The first example of salan-vanadium catalyzed enantioselective ring-opening of *meso*-epoxides has been reported, which furnished *β*-hydroxy sulfides in good yields and moderate enantioselectivities.

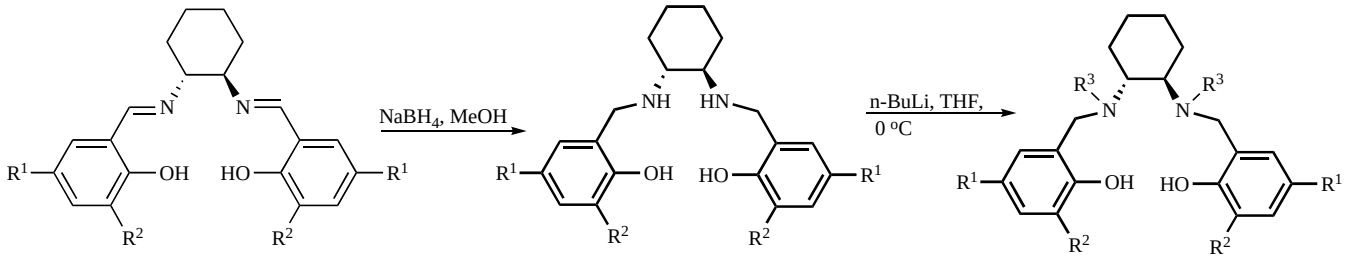
Keywords: Vanadium, Ring-opening, Thiols, Epoxides, Enantioselectivity, Asymmetric catalysis.

INTRODUCTION

Since vanadium can exist in oxidation states ranging from -3 to +5, this versatility permits vanadium compounds can be used in a wide range of organic reactions by controlling their redox potentials [1]. Generally, chiral vanadium complexes have been used mainly on asymmetric oxidation reactions, such as asymmetric epoxidation [2], asymmetric sulfoxidation [3] and kinetic resolutions of alcohols with molecular oxygen [4]. However, a few reports concerned enantioselective addition of thiols to *meso*-epoxides catalyzed by chiral salan-vanadium complexes.

RESULTS AND DISCUSSION

The synthesis of chiral ligands is straightforward as shown in Scheme **1**. The ligands can be easily prepared from commercially available salen ligands **1a** and **1b** in high chemical yields. Choosing cyclohexene oxide as the model



Scheme 1.

about other types of reactions [5]. On the other hand, although the enantioselective desymmetrization of *meso*-epoxides with nucleophiles has proven to be a valuable tool for the straightforward synthesis of enantiomerically highly enriched 1,2-difunctionalized organic compounds [6], the use of thiols as nucleophiles is still relatively unexplored and only a few of examples have been reported [7]. Recently, chiral salan [*N*,*N*'-alkyl-bis(salicylamine)] ligands have been widely investigated in various asymmetric reactions with high enantioselectivities [8, 9]. Herein we wish to report the substrate, we initially investigated the ring-opening reaction with thiophenol catalyzed by the *in situ* formation of chiral vanadium complexes (Table **1**). From the summarized results, we can find that $VO(O^iPr)_3$-**2a** afforded the best results in terms of reactivity and selectivity (entry 7) [11]. Among the five solvents investigated, toluene proved to be the best one. Further investigation on the reaction temperature showed that 0 °C was the preferred temperature. The reactions were finished in 36 h at 0 °C whereas -40 °C gave very low yield (entry 15). High yield but low enantioselectivity were obtained when the reaction was carried out at room temperature (entry 16).

Next, the ring-opening reactions of various *meso*-epoxides have been investigated under the optimized reac-

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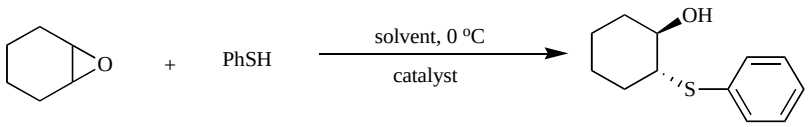
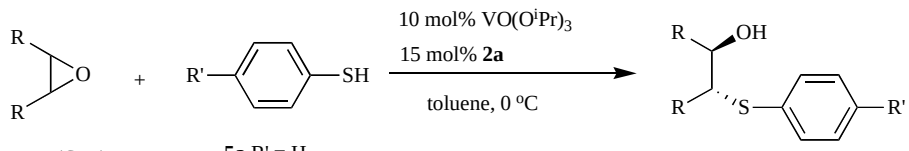
Table 1. Asymmetric Ring-Opening of Cyclohexene Oxide with Thiophenol[a]



Entry	Vanadium	Ligand	Solvent	Yield (%)[b]	Ee (%)[c]
1	$VO(acac)_2$	**1a**	Toluene	43	<5
2	$VO(acac)_2$	**1b**	Toluene	35	<5
3	$VO(acac)_2$	**2a**	Toluene	33	37
4	$VO(acac)_2$	**2b**	Toluene	27	24
5	$VO(O^iPr)_3$	**1a**	Toluene	51	16
6	$VO(O^iPr)_3$	**1b**	Toluene	46	8
7	$VO(O^iPr)_3$	**2a**	Toluene	85	71
8	$VO(O^iPr)_3$	**2b**	Toluene	67	23
9	$VO(O^iPr)_3$	**3a**	Toluene	63	42
10	$VO(O^iPr)_3$	**3b**	Toluene	52	26
11	$VO(O^iPr)_3$	**2a**	CH_2Cl_2	82	54
12	$VO(O^iPr)_3$	**2a**	CH_3CN	91	17
13	$VO(O^iPr)_3$	**2a**	THF	90	32
14	$VO(O^iPr)_3$	**2a**	Hexane	37	46
15[d]	$VO(O^iPr)_3$	**2a**	Toluene	24	69
16[e]	$VO(O^iPr)_3$	**2a**	Toluene	83	52

[a]Reaction conditions: 1 mmol cyclohexene oxide, 1.2 mmol PhSH, 10 mol% vanadium compounds, 15 mol% chiral ligand, 0 °C; [b]Isolated yield; [c]Determined by HPLC analysis using a Daicel Chiracel OD-H column or OB-H column; [d]The reaction was carried out at -40 °C; [e]The reaction was carried out at 25 °C.

Table 2. Asymmetric Ring-Opening of *meso*-Epoxides with Aromatic Thiols[a]



4a R = $-(CH_2)_4-$
4b R = $-(CH_2)_3-$
4c R = Ph

5a R' = H
5b R' = CH_3
5c R' = Cl

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Entry	Epoxide	Thiol	Product	Yield (%)[b]	Ee (%)[c]
1	**4a**	**5a**	**6aa**	85	71
2	**4b**	**5a**	**6ba**	82	66
3	**4c**	**5a**	**6ca**	68	52
4	**4a**	**5b**	**6ab**	84	72
5	**4b**	**5b**	**6bb**	76	74
6	**4c**	**5b**	**6cb**	64	38
7	**4a**	**5c**	**6ac**	72	67
8	**4c**	**5c**	**6cc**	77	56

[a]Reaction conditions: 1 mmol epoxide, 1.2 mmol aromatic thiol, 10 mol% $VO(O^iPr)_3$, 15 mol% **2a** , toluene, 0 °C, 36 h; [b]Isolated yield; [c]Determined by HPLC analysis using a Daicel Chiracel OD-H column or OB-H column.

tion conditions [10]. The results were summarized in Table **2**. All reactions proceeded smoothly to afford the desired hydroxy sulfides in moderate yields (from 54 to 84%) and moderate enantioselectivities (from 32 to 74%). The highest ee value was obtained when **4a** was used as substrate and thiol **5b** as nucleophile (entry 6). Amongst all of the three

aromatic thiols investigated, the *para*-methyl substituted thiol afforded the corresponding products in highest enantioselectivities.

CONCLUSION

In summary, the asymmetric ring-opening reaction of *meso*-epoxides with thiols catalyzed by salan-vanadium complexes has been realized. *β*-hydroxy sulfides were obtained in moderate yields (up to 85%) and moderate enantioselectivities (up to 74% ee). Currently we are extending the application of chiral vanadium compounds to other reactions and studying their synthetic applications.

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[10] A general procedure of the asymmetric ring-opening of *meso*-epoxide with thiol: To a stirred solution of **2a** (0.15 mmol) in toluene (3.0 mL) under argon was added $VO(O^iPr)_3$ (0.1 mmol). The resulting mixture was stirred at room temperature for 1 h, then cooled to 0°C, epoxide (1.0 mmol) and thiol (1.2 mmol) was added. After stirred at 0°C for 36 h, the reaction mixture was filtered through a silica gel and washed with CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography to furnish the corresponding hydroxyl sulfides. The enantiomeric purity was determined by HPLC analysis using a Daicel Chiracel OD-H column or OB-H column.

[11] Ligand **3b** was synthesized according to the following procedure: Under an argon atmosphere, 1.5 mL anhydrous DMF was added dropwise into a mixture of NaH (1.5 g, 25 mmol) and 15 mL anhydrous THF in a Schlenk tube. Then the mixture was stirred for 10 min and **2a** (1.62 g, 5 mmol) was added. After stirred for another 30 min, bromobenzyl (1.3 mL, 11 mmol) was added and the mixture was stirred for 8 h at 50 °C. Water (5 mL) was then added to quench the reaction and the aqueous layer was separated and extracted with ether (3 × 30 mL). The combined organic layer was dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product, which was further purified by flash chromatography (petroleum ether:ethyl acetate = 3:1) to give **3b** (1.16 g, 46% yield) as a yellow solid, mp: 52 °C; $[\alpha]_D^{20}$= -3.9 (c 0.05, CH_2Cl_2). ^{1}H-NMR (300MHz, $CDCl_3$): δ 1.10-1.37 (m, 4H), 1.69-1.82 (m, 2H), 2.07-2.10 (m, 1H), 2.23-2.29 (m, 1H), 2.60 (s, 2H), 3.41-3.46 (d, 1H), 3.55-3.59 (d, 1H), 3.75-3.82 (t, 3H), 3.98-4.02 (d, 1H), 4.96-5.11 (m, 4H), 6.91-6.93 (m, 4H), 7.21-7.27 (m, 3H), 7.29-7.34 (m, 3H), 7.40-7.47 (m, 10H). MS (EI): 505(M-1, 16), 399(26), 94(5), 213(3), 197(17), 107(4), 106(2), 91(100), 65(2).