Highly Enantioselective Ring Opening of Epoxides Catalyzed by (salen)Cr(III) Complexes

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Epoxides are valuable intermediates for the stereocontrolled synthesis of complex organic compounds, and their utility has expanded dramatically with the advent of practical asymmetric catalytic methods for their synthesis.[1] In addition to the epoxidation of prochiral and chiral olefins, approaches to the use of epoxides in the synthesis of enantiomerically enriched compounds include kinetic resolutions of racemic epoxides[2] and asymmetric ring openings of meso epoxides.[3,4] Substantial progress has been made recently in the development of catalytic methods for these latter types of reactions;[3g,5] however, neither has been developed to a level such that it has found widespread use in organic synthesis.

Given that chiral salen complexes are remarkably effective catalysts for the asymmetric epoxidation of simple olefins,[6] we considered whether similar systems could be useful in epoxide ring-opening reactions. Thus, the elements of stereochemical communication between substrate and ligand in olefin oxidation (Figure 1a)[7] might apply to epoxide activation by a metal(salen) complex (e.g., Figures 1, b or c). We report here that the chromium(salen) complex **1** is indeed a highly effective catalyst for the enantioselective ring opening of epoxides with Me_3SiN_3. This reaction is notable not only for its high enantioselectivity and the synthetic utility of its products but also for its remarkable efficiency as a catalytic process.

Metal complexes of the readily available chiral salen ligand **2**[8] were screened as catalysts for the model reaction of cyclohexene oxide with Me_3SiN_3 (eq 1).[3c] Complexes of Al, Ti, and Mn each were found to catalyze the reaction; however, the azido silyl ether product **4** was generated in racemic form. In contrast, the corresponding Cr complex **1** catalyzed ring opening to produce **4** in >80% yield and with >80% ee.[9,10] Highest enantioselectivities were obtained using ethereal solvents (e.g., *tert*-butyl methyl ether, THF, Et_2O). In addition to **4**, trace amounts of byproducts **5** and **6** were produced with low enantioselectivity (see discussion below).

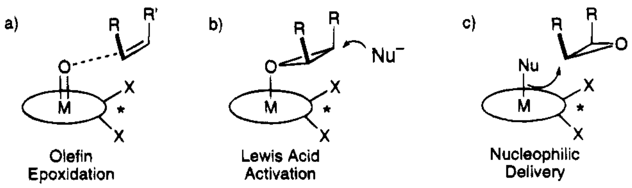
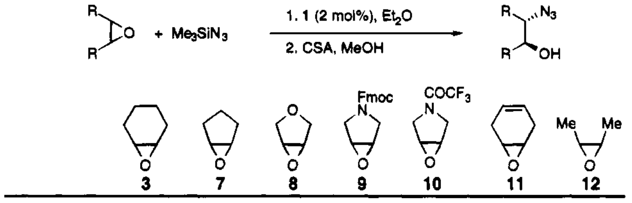


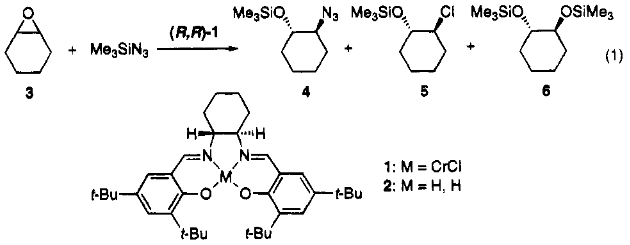
Figure 1.

Table 1. Enantioselective Opening of Meso Epoxides with (*R*,*R*)-**1**[a]



	3	7	8	9	10	11	12
Time (h)	18	28	18	36	16	46	30
Yield (%)[b]	80	80	80	80	90	72	65[d]
ee (%)[c]	88	94	98	95	95	81	82

[a] All reactions were run as described in ref 11. Absolute configurations for the products derived from **3**, **7**, and **12** were determined as in ref 3e. The absolute configurations of the remaining products were assigned by analogy. [b] Isolated yield of azido alcohol, unless noted otherwise. [c] All ee's correspond to those of the azido silyl ether product and were determined by chiral chromatography. Details of the procedures and conditions used for analysis are provided as supplementary material. [d] Isolated yield of the azido trimethylsilyl ether.



The reaction of a variety of meso epoxides with Me_3SiN_3 was screened using 2 mol % catalyst **1** (Table 1).[11] Epoxides fused to five-membered rings (e.g., **7–10**) underwent ring opening with very high levels of enantioselectivity, while six-membered-ring and acyclic substrates were slightly less effective. Ether, olefin, and carbonyl-containing functional groups were all tolerated. In fact, such functionalized epoxides were among the most reactive substrates examined in this study, indicating that Lewis basic groups do not inhibit catalytic activity.

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(10) The synthesis and characterization of **1** is provided as supplementary material.

(11) General procedure for the asymmetric ring-opening reactions in Table 1: A 5 mL flask is charged with 42 mg (0.060 mmol) of **1** and 1.0 mL of Et_2O. The epoxide (3.00 mmol) is added, and the mixture is stirred for 15 min, at which time Me_3SiN_3 (0.418 mL, 3.15 mmol) is added. The resulting brown solution is stirred at room temperature for the indicated time (Table 1). The solution is then concentrated *in vacuo*, and the residue is filtered through a 10 mL plug of silica gel with 100 mL of 5–20% EtOAc/hexanes. The filtrate is concentrated, and the resulting residue is subjected to analysis by GC or HPLC to determine the enantiomeric composition of silylated azido alcohol.

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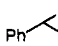
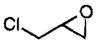
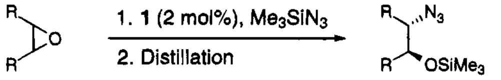
Table 2. Kinetic Resolution of Racemic Epoxides with Me_3SiN_3 Catalyzed by (*R*,*R*)-**1**[a]

Epoxide	Me_3SiN_3 (equiv)	Time (h)	Conversion (%)[b]	ee (%)[c]
	0.70	67	76	98 (*R*)
	0.60	21	80	97 (*S*)

[a] All reactions were run with 3.00 mmol of epoxide, 0.060 mmol of catalyst, and the indicated amount of Me_3SiN_3 in 1.0 mL of Et_2O. [b] Determined by GC employing nonane as internal quantitative standard. [c] Determined by chiral GC.

Table 3. Enantioselective Opening of Meso Epoxides under Solvent-Free Conditions with Catalyst Recycling[a]



Cycle	Epoxide	Time (h)	Isolated yield (%)[b]	ee (%)[c]
1	**3**	18	86	84
2	**3**	21	88	87
3	**3**	20	91	88
4	**7**	4	81	94
5	**11**	18	75	83

[a] Each cycle was carried out with 5.00 mmol of epoxide and 5.25 mmol of Me_3SiN_3. [b] Isolated yield of azido silyl ether. [c] Determined by chiral GC.

Preliminary experiments revealed that the ring-opening reaction catalyzed by **1** may also be extended to the kinetic resolution of chiral racemic epoxides (Table 2). For example, treatment of 3 mmol of styrene oxide with 0.70 equiv of Me_3SiN_3 and 2 mol % of catalyst **1** resulted in 76% conversion of the epoxide to a complex mixture of products. The ee of the unreacted styrene oxide was 98%. Similarly, epichlorohydrin proceeded to 80% conversion when treated with 0.60 equiv of Me_3SiN_3, and the ee of the remaining epoxide was 97%. Thus, despite the evident participation of multiple epoxide-decomposition pathways, remarkably effective kinetic resolutions of synthetically valuable terminal epoxides are possible using catalyst **1**.

Given that the condensation of epoxides with Me_3SiN_3 to produce azido silyl ethers is a transformation wherein all atoms from the reacting partners are incorporated into a single product,[12] a solvent-free process would constitute an asymmetric catalytic reaction with the highest possible volumetric productivity.[13] Furthermore, if catalyst could be recycled quantitatively, such a process would generate no waste whatsoever. The successful implementation of this strategy is illustrated in Table 3. Thus, reaction of 5 mmol of cyclohexene oxide with 2 mol % catalyst **1** and 5.25 mmol (1.05 equiv) of Me_3SiN_3 for 18 h, followed by short-path distillation under reduced pressure (**CAUTION!**[14]), afforded an 86% yield of the azido silyl ether **4** in 84% ee (cycle 1). As expected, this product was contaminated with small amounts (≤2% of each) of silylated chlorohydrin **5** and bis-silyl ether **6**. Treatment of the residual catalyst with additional portions of cyclohexene oxide (5 mmol) and Me_3SiN_3 (5.25 mmol) followed by distillation resulted in isolation of product **4** in 88% yield and 87% ee, with no detectable byproducts (cycle 2). An additional recycling of the catalyst afforded **4** in 91% yield and 88% ee (cycle 3). A fourth reaction was then performed with cyclopentene oxide, and the corresponding product was obtained in 81% yield and 94% ee Finally, 4,5-epoxycyclohexene was used for the fifth cycle (75% yield, 83% ee). In all cases, complete conversion of the epoxide was observed within the times indicated in Table 3.

In both the solvent-based and the solvent-free reactions, byproducts **5** and **6** were generated only during the initial stages, and in yields proportional to the amount of catalyst employed (i.e., ≈2 mol % relative to starting epoxide). The fact that these products do not appear in subsequent cycles of the solvent-free reactions indicates that **1** is in fact a precatalyst. Elemental analysis of the catalyst isolated after the first cycle revealed a nitrogen-to-chromium molar ratio of 5:1 and the absence of chlorine. In addition, the catalyst displayed a strong IR absorbance at 2058 cm^{-1}, consistent with a $Cr-N_3$ N=N stretch.[15] These data indicate that the active catalyst is in fact a (salen)CrN_3 complex. Although it remains to be established whether enantioselective epoxide ring opening involves Lewis acid activation by the chromium center (Figure 1b) or nucleophilic delivery of azide by a $Cr-N_3$ intermediate (Figure 1c), these results provide circumstantial support for the latter.

The epoxide ring-opening reactions outlined above may be exploited immediately for the practical synthesis of a wide range of interesting chiral amino alcohols and related compounds. In a broader sense, this work introduces a new role for chiral salen complexes in asymmetric catalysis. Such catalysts are well-defined and readily accessible, and they bear ligands that can be fine-tuned both sterically and electronically.[16] Application of this and related new catalyst systems to reactions between other classes of electrophiles and nucleophiles is likely to emerge.[17]

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Supplementary Material Available: Chromatographic analyses of all racemic and enantiomerically enriched azido silyl ethers from Table 1, full characterization of all new azido silyl ethers and azido alcohols, and synthesis and characterization of catalyst **1** (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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[14] **CAUTION!** Although these experiments have proceeded without incident, extreme caution should be excercised in the handling of organic and metal azides, particularly with manipulations that involve heating of neat liquids or solid residues.

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