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On the Mechanism of Asymmetric Nucleophilic Ring-Opening of Epoxides Catalyzed by (Salen)Cr^{III} Complexes

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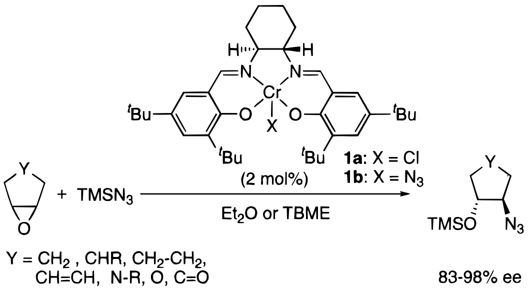
Enantioselective catalysis of reactions between nucleophiles and electrophiles is of synthetic interest since such processes can provide practical access to valuable chiral materials. Although effective catalysts for enantioselective nucleophilic additions to simple electrophiles such as carbonyl compounds,[1] imines,[2] and epoxides[3] have been developed over the past decade, in many cases a detailed mechanistic understanding of how these systems function is lacking. As a result, the ability to rationally develop new catalysts or improve existing ones remains limited.

We reported recently that chiral (salen)Cr^{III} complexes effectively catalyze the asymmetric ring opening of epoxides by trimethylsilyl (TMS) azide (eq 1).[3b,4] The efficiency of this process and the stability of the catalyst under the reaction conditions have enabled us to undertake a careful mechanistic study of this reaction. We disclose here several critical findings that have emerged from this investigation, including the characterization of the active catalyst, the identification of the initially-formed intermediate in the ring-opening reaction, and compelling kinetic and structural evidence that this transformation proceeds by catalyst activation of both the nucleophile and the electrophile in a bimetallic enantioselectivity-determining step.



(1)

Substantial evidence points to complex **1a** acting only as a precatalyst in the ring-opening reaction, with azide complex **1b** being the catalytically relevant species.[3b] Complex **1b** can be recovered cleanly from ring-opening reactions initiated with chloride complex **1a**, and **1b** has been recycled up to 10 times at the 1 mol % level with no measurable loss of activity or enantioselectivity. While the participation of a metal azide as the catalytically active species suggests that the mechanism of epoxide ring-opening involves azide delivery from the catalyst, epoxide activation by the (salen)Cr catalyst is still possible, either with or without azide dissociation. We addressed this issue through a series of structural and kinetic studies.

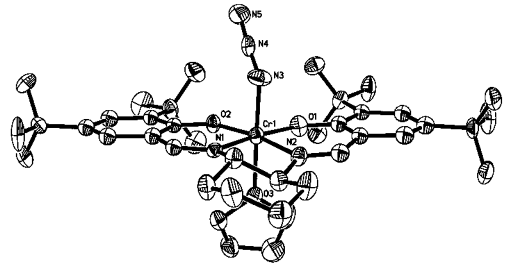
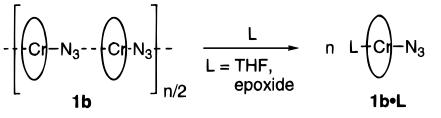


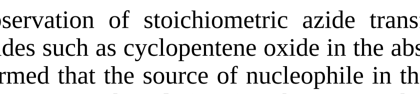
Figure 1. Structure of **1b·THF**. Thermal ellipsoids represent 50% electron probability. Hydrogen atoms are omitted for clarity.

Complex **1b** is a brown powder insoluble in all noncoordinating solvents but readily soluble in donor solvents such as THF. The solution IR spectrum of **1b** in THF displays a single sharp absorbance at 2053 cm^{-1}, similar to that of known chromium azide complexes.[5] Treatment of suspensions of **1b** in *tert*-butyl methyl ether (TBME) with a substrate such as cyclopentene oxide also leads to immediate dissolution of the complex and to the appearance of an azide stretching frequency at 2053 cm^{-1} in the solution IR spectrum. These solubilization effects by donor ligands are most likely due to dissociation of a polymeric network of bridging CrN$_3$ units in ligand-free **1b** by Lewis base coordination through the sixth coordination site on Cr (eq 2). This notion was supported by a single-crystal X-ray diffraction study of crystals of **1b** grown from THF (Figure 1).[6] The observed axial coordination of THF to the catalyst and the spectroscopic evidence that epoxides bind in a similar manner identify catalyst **1b** as being capable of epoxide activation via Lewis acid complexation. Thus, the structural characterization does not provide an answer as to whether **1b** is an azide delivery or epoxide activation agent, but rather it suggests that it could act in either manner.



(2)

Observation of stoichiometric azide transfer from **1b** to epoxides such as cyclopentene oxide in the absence of TMSN$_3$ confirmed that the source of nucleophile in the reaction is the chromium complex **1b** (eq 3). The IR stretch at 2053 cm^{-1} of a solution of the **1b**·cyclopentene oxide complex in TBME was replaced cleanly within 2 h by an absorbance at 2095 cm^{-1},[7] consistent with the formation of a new complex (**2**) bearing an



(3)

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(5) Prasad, D. R.; Ramasami, T.; Ramaswamy, D.; Santappa, N. *Synth. React. Inorg. Met.-Org. Chem.* **1981**, *11*, 431.

(6) Crystal data for **1a**: triclinic crystal system, space group *P*1 with $a = 9.8078(6)$ Å, $b = 13.8163(8)$ Å, $c = 17.119(1)$ Å, $\alpha = 87.235(1)°$, $\beta = 81.752(1)°$, $\gamma = 73.170(1)°$, $V = 2196.7(2)$ Å^3, and $Z = 2$. Data were collected on a Siemens SMART CCD diffractometer at −60 °C. A 2θ range from 2.4 to 46.6° gave 7655 independent reflections. The structure was solved using direct methods and refined to $R_1 = 0.050$, $wR_2 = 0.127$, and GOF = 1.07 for $I > 2\sigma(I)$ data.

(7) Relevant spectra are provided as Supporting Information.

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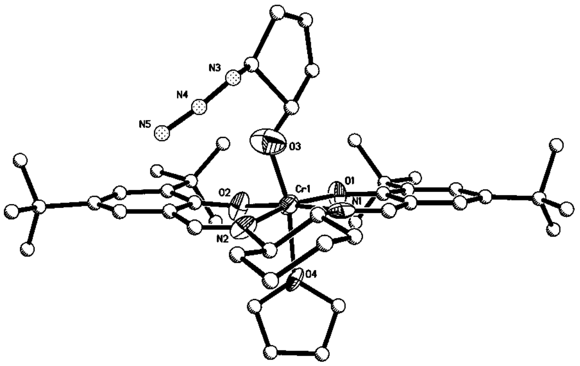


Figure 2. Structure of **2·THF**. The metal and coordination sphere are displayed as 40% ellipsoids. Hydrogen atoms are omitted for clarity.

organic azide.[8] Solutions of **2**, when exposed to HN_3, methanol, or wet silica gel, afforded the corresponding azido alcohol in identical enantioselectivity to the catalytic reaction (eq 3). Treatment of **2** with $TMSN_3$ in the presence of trace amounts of water also provided the azido silyl ether in identical enantioselectivity as well as regenerated **1b** as an insoluble brown precipitate. Analysis of crystals of **2** grown from THF/heptane by X-ray diffraction revealed a monomeric (salen)Cr–alkoxide complex (**2·THF**) bearing an axial THF ligand (Figure 2).[9]

The reaction in eq 1 is kinetically well-behaved but rates vary depending on the degree of hydration of **1b**. Reactions run in the presence of 5 mol % of Cp_2ZrMe_2, a highly efficient dessicant,[10] were immeasurably slow, with no detectable conversion after 24 h. Subsequent addition of 15 mol % of water relative to epoxide led to complete reaction within 9 h with the same enantioselectivity as in reactions carried out with “wet” catalyst. Catalytic activity of azeotropically dried complex **1b** was also fully reestablished upon addition of catalytic amounts of HN_3. These observations are consistent with $TMSN_3$ not playing a direct role in the catalytic cycle, but rather serving as a source of HN_3, the active reagent, in the presence of water. Indeed, catalytic reactions carried out with HN_3 proceeded smoothly to afford azido alcohol product with the same enantioselectivity to reactions run with $TMSN_3$ and wet catalyst.

Kinetic runs performed on the catalytic reaction of HN_3 with excess epoxide ($\geq$ 5 equiv relative to HN_3) in the presence of **1b** were reproducible and revealed a zero-order dependence on $[HN_3]$. This is consistent with rate-determining formation of **2** and its rapid cleavage by HN_3.[11] Rate constants (k_{obs}) were determined over a 7-fold range of catalyst concentrations. A linear correlation between k_{obs} vs $[\mathbf{1b}]^2$ was obtained (Figure 3), reflecting a second-order dependence on catalyst.

These kinetic data provide strong support for a mechanism involving catalyst activation of both nucleophile and electrophile in a bimetallic rate-determining step (Scheme 1). Consistent with this mechanism, significant nonlinear effects of catalyst enantiomeric composition on reaction enantioselectivity are observed in this reaction.[12] In the presence of donor ligands such as epoxides or THF, the resulting alkoxide intermediate exists as the monomeric complex **2·L**, which undergoes rapid reaction with HN_3 to afford azido alcohol and regenerate catalyst **1b**.

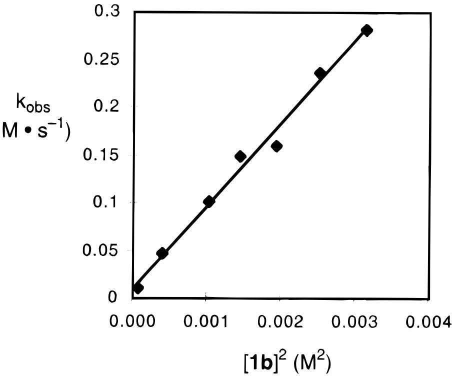
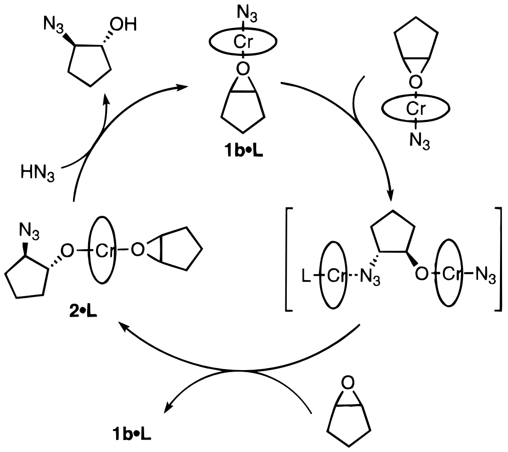


Figure 3. Plot of k_{obs} vs $[\mathbf{1b}]^2$ for the catalytic ring opening of cyclohexene oxide with HN_3. Individual runs were monitored for appearance of product by GC using an internal standard. Initial concentrations: [epoxide] = 2.0 M, $[HN_3]$ = 0.2 M in TBME.

Scheme 1



The critical features of the catalytic mechanism for (salen)-Cr-catalyzed ring-opening of epoxides by $TMSN_3$ have thus been elucidated and reveal an important design principle for this and almost certainly many other, nucleophile-electrophile reactions.[13] On the basis of these results, we are currently exploring the synthesis and application of bimetallic catalysts capable of simultaneous activation of both electrophile and nucleophile in enantioselective reactions.

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Supporting Information Available: IR spectra of **1b** in the presence of cyclohexene oxide; plot of catalyst ee vs product ee for the reaction of cyclohexene oxide with $TMSN_3$ catalyzed by **1b**; crystal data and details of the structure refinement for **1b·THF** and **2·THF**, including tables of atomic coordinates, bond lengths and angles, and anisotropic displacement parameters (29 pages). See any current masthead page for ordering and Internet access instructions.

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[8] The IR spectrum of *trans*-1-azido-2-cyclopentanol exhibits an azide absorbance at 2096 cm^{-1}.

[9] Crystal data for **2**: monoclinic crystal system, space group *P*2(1) with $\mathbf{a} = 45.5812(9)$ Å, $b = 10.6890(1)$ Å, $c = 18.6692(3)$ Å, $\beta = 89.432(1)°$, $V = 8949.4(2)$ Å^3, and $Z = 8$. Data were collected on a Siemens SMART CCD diffractometer at −60 °C. A 2θ range from 1.8 to 40.0° gave 8044 independent reflections. The structure was solved using direct methods and refined to $R_1 = 0.111$, w$R\mathbf{2} = 0.254$, and GOF = 1.07 for $I > 2\sigma(I)$ data.

[10] Proulx, G.; Bergman, R. G. *Organometallics* **1996**, *15*, 684.

[11] Kinetics measurments were carried out by monitoring azido alcohol appearance by GC against an internal quantitative standard.

[12] A plot of catalyst ee vs product ee is provided in the Supporting Information. For a detailed discussion of the principles underlying such nonlinear effects, see: Guillaneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.

[13] Bimetallic activation of nucleophile and electrophile has been proposed for several enantioselective systems. For example: Michael additions (a) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. Hydroboration (b) Masamune, S.; Kennedy, R. M.; Petersen, J. S.; Houk, K. N.; Wu, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7404. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. Diethylzinc addition to aldehydes (d) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. Epoxide ring-opening by Zr catalysts (e) see ref 3a. Finn, M. G.; Nugent, W. A. Personal communication.