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Asymmetric Ring Opening of Meso Epoxides with TMSCN Catalyzed by (pybox)lanthanide Complexes

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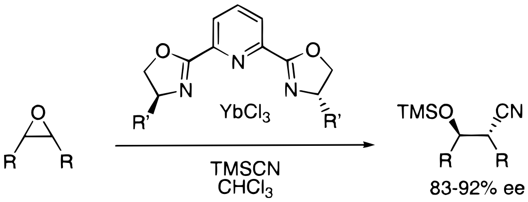
ABSTRACT



The asymmetric ring opening of meso epoxides with TMSCN is catalyzed by (pybox)YbCl$_3$ complexes, yielding the β-trimethylsilyloxy nitrile ring-opened products with good enantioselectivities (83–92% ee). The reaction exhibits a second-order kinetic dependence on catalyst concentration and a first-order dependence on epoxide concentration, consistent with a bimetallic pathway involving simulataneous activation of epoxide and cyanide.

The asymmetric ring opening (ARO) of meso epoxides catalyzed by chiral metal complexes has emerged as an important synthetic strategy for the preparation of valuable chiral building blocks.[1] A variety of nucleophiles have been employed successfully in ARO reactions, with the majority of these being heteroatom-based. These methodologies have provided practical access to enantioenriched 1,2-azido alcohols,[2] 1,2-halohydrins,[3] 1,2-hydroxy sulfides,[4] 1,2-benzoyloxy alcohols,[5] and 1,2-aryloxy alcohols.[6] In contrast, the number of methods for effecting catalytic ARO reactions with carbon-based nucleophiles remains quite limited. Two important advances have been made in this area: Snapper and Hoveyda applied a novel solid-phase ligand optimization approach to the discovery of titanium-based catalysts for the ARO of meso epoxides with TMSCN[7] and Oguni made the striking discovery that uncomplexed salen ligands catalyze ARO reactions with organolithium reagents.[8]

Cyanide is a particularly interesting carbon-based nucleophile for epoxide desymmetrization reactions because of its low cost and the synthetic versatility of the nitrile ring-opened products. We were intrigued by the possibility of effecting cyanide ARO reactions with lanthanide-based catalysts, drawing on the seminal observation by Kagan et al. that lanthanide chloride salts effectively promote the ring opening

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[1] For reviews, see: (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361. (b) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 35.

[2] (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (b) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (c) Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197.

[3] (a) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428. (b) Nugent W. A. *J. Am. Chem. Soc.* **1998**, *120*, 7139.

[4] (a) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783. (b) Wu, M. H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252.

[5] Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.

[6] Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223.

[7] (a) Cole, M. B.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1668. (b) Shimizu, K. D.; Cole, M. B.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1704.

[8] (a) Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 9023. (b) See also: Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Gazz. Chim Acta* **1997**, *127*, 273.

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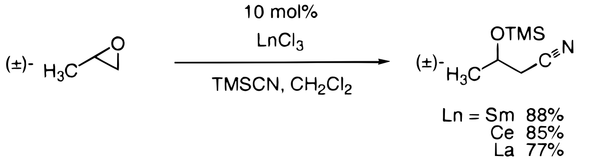
of propylene oxide with TMSCN.[9] In particular, they reported that treatment of racemic propylene oxide with TMSCN and $LnCl_3$ (Ln = Sm, Ce, La) yielded the desired trimethylsilylcyanohydrin in good yields (eq 1).

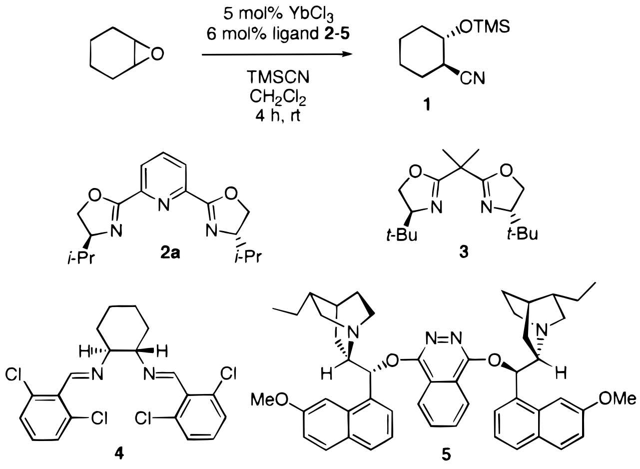


(1)

It was later disclosed by Utimoto that ytterbium salts also catalyze the reaction of TMSCN with epoxides, with the active catalyst for the reaction identified as $Yb(CN)_3$.[10] In both reports, the lanthanide catalysts were found to be selective for the formation of the nitrile product,[11] with minimal production of the isomeric isonitrile.[12]

Recognizing that the multiple coordination sites available to lanthanide salts might allow coordination of ancillary chiral ligands in these ring-opening reactions, we evaluated a series of neutral chiral additives (e.g., **2**−**5**) in the TMSCN addition to cyclohexene oxide catalyzed by $YbCl_3$ (Scheme 1). Formation of the (ligand)$YbCl_3$ complexes was conducted in THF and was discernible by dissolution of the otherwise insoluble salt. The complex was isolated by concentration of the THF solution and redissolved in CH_2Cl_2, and reaction was then initiated by sequential addition of TMSCN and cyclohexene oxide. After 4 h at rt, GC analysis indicated formation of the desired cyanide ring-opened product **1** in all four cases, with formation of ca. 5% of the corresponding *O*-trimethylsilylchlorohydrin as a side product. While reactions with ligands **3**−**5** afforded the cyanide ring-opened product in racemic form, the *i*-Pr-pybox ligand **2a** led to formation of **1** in 47% ee.[13]

Scheme 1



A systematic evaluation of $LnCl_3$ hydrates in the ARO of cyclohexene oxide with pybox ligand **2a** revealed a consistent increase in enantioselectivity as a function of the lanthanide atomic number, with the highest ee of 51% obtained with $LuCl_3$ (Table 1, Figure 1). If one makes the rather substantial assumption that all of the complexes mediate the ARO by a common mechanism, then this trend can be ascribed to more effective stereochemical communication resulting from the smaller ionic radius of the metals with higher atomic numbers.

Table 1. Asymmetric Ring Opening (ARO) of Cyclohexene Oxide Catalyzed by $2 \cdot LnCl_3 \cdot 6H_2O$. Reactions Were Run at Room Temperature for 12 h with 5 mol % of Catalyst

	Ce	Pr	Nd	Eu	Dy	Er	Yb	Lu
yield (%)[a]	68	96	88	91	89	88	96	94
ee (%)[b]	0	2	10	25	31	40	47	51

[a] Crude yield of **1** determined by GC analysis. [b] Determined by chiral GC analysis (see Supporting Information).

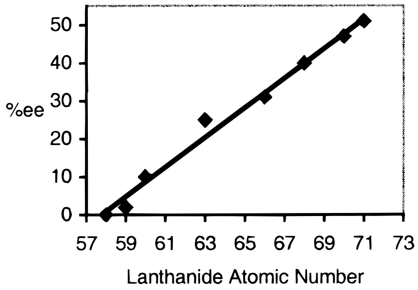


Figure 1. Plot of ee as a function of lanthanide atomic number in the ARO of cyclohexene oxide with TMSCN.

A series of different pybox ligands (**2a**−**e**) was evaluated in association with $YbCl_3$ in order to identify the most enantioselective system for the ARO of cyclohexene oxide

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(9) Vougioukas, A. E.; Kagan, H. B. *Tetrahedron Lett.* **1987**, *28*, 5513.

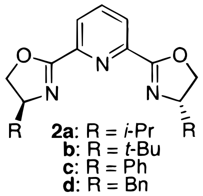
(10) Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209.

(11) For other metal-catalyzed methods for the ring opening of epoxides with TMSCN, see: (a) Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1995**, *36*, 1649. (b) Choudry, B. M.; Narender, N.; Bhuma, V. *Synth. Commun.* **1971**, *25*, 2829. (c) Ohno, H.; Mori, A.; Inoue, S. *Chem. Lett.* **1993**, 975. (d) Mitchell, D.; Koenig, T. M. *Tetrahedron Lett.* **1992**, *33*, 3281. (e) Hayashi, M.; Tamura, M.; Oguni, N. *Synlett* **1992**, 663. (f) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *32*, 4775. (g) Sassaman, M. B.; Surya Prakash, G. K.; Olah, G. A. *J. Org. Chem.* **1990**, *55*, 2016. (h) Imi, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 1013.

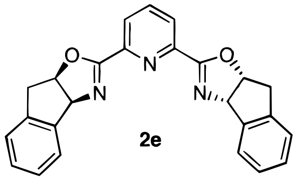
(12) For selective synthesis of isonitrile via epoxide ring opening, see: (a) Imi, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 1013. (b) Gassman, P. G.; Guggenheim, T. L. *J. Am. Chem. Soc.* **1982**, *104*, 1849. (c) Gassman, P. G.; Guggenheim, T. L. *Org. Synth.* **1985**, *64*, 39.

(13) Chiral pybox (2,6-bis[4′-phenyloxazolin-2′-yl]pyridine) derivatives have emerged over the past decade as among the most useful and versatile ligands for asymmetric catalysis. First developed by Nishiyama in 1989 for the Rh-catalyzed hydrosilylation of aryl ketones,[14] they have been used effectively in a wide range of asymmetric carbon−carbon bond-forming reactions.[15] Most relevant to the present study, Aspinall and Greeves disclosed very recently that a complex of Ph-pybox and $YbCl_3$ catalyzed the addition of TMSCN to benzaldehyde to yield the corresponding trimethylsilylcyanohydrin adduct in 89% ee and 61% yield.[16]

with TMSCN. The (*S*,*S*)-Ph-pybox ligand **2c** afforded the highest enantioselectivity, yielding the product in 67% ee (Table 2). Moreover, the product obtained with (*S*,*S*)-**2c** was of opposite configuration to that obtained with the other (*S*,*S*)-pybox ligands.[17]



2a: R = *i*-Pr
b: R = *t*-Bu
c: R = Ph
d: R = Bn



2e

Table 2. Effect of Ligand in the ARO of Cyclohexene Oxide with TMSCN Catalyzed by $YbCl_3{\cdot}6H_2O$. Reactions Were Run at Room Temperature for 4 h with 5 mol % of Catalyst

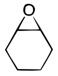
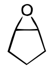
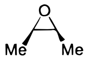
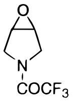
ligand	yield (%)[a]	ee (%)[b]	config[c]
(*S*,*S*)-**2a**	95	47	1*S*,2*R*
(*S*,*S*)-**2b**	93	57	1*S*,2*R*
(*S*,*S*)-**2c**	96	−67	1*R*,2*S*
(*S*,*S*)-**2d**	96	28	1*S*,2*R*
(*S*,*S*)-**2e**	93	28	1*S*,2*R*

[a ,b]See Table 1. [c] Absolute configuration of the predominant enantiomer of **1** generated with (*S*,*S*)-ligand.

The reaction conditions for the ARO of cyclohexene oxide with $\mathbf{2c}{\cdot}YbX_3{\cdot}6H_2O$ were optimized systematically with respect to both enantioselectivity and yield. While all ytterbium salts that were studied catalyzed formation of **1** in good yield, the complex derived from $YbCl_3$ afforded substantially higher enantioselectivity than those derived from the corresponding bromide, triflate, or alkoxide salts. A strong solvent dependence was observed, with halogenated solvents providing best results and nonpolar solvents such as toluene or TBME leading to low conversions and ee's. Chloroform proved to be the optimal solvent, providing ring-opened product **1** in 92% yield and 72% ee at room temperature. Decreased reaction temperatures led to improvement in ee's, although at the expense of reaction rate. Thus, at −40 °C, the ARO could be carried out with 10 mol % of catalyst, affording **1** in 91% ee and 90% isolated yield after 4 days.

Investigation of the scope of the ARO was conducted under the optimized conditions outlined above (Table 3).

Table 3. ARO of Meso Epoxides with TMSCN Catalyzed by $(pybox)YbCl_3$ Complexes[a]

entry	substrate	ligand	temp (°C)	time (d)	yield (%)[b]	ee (%)[c] (conf.)
1		(*S*,*S*)- **2c**	–45	4	90	91 (1*S*,2*R*)
2		(*S*,*S*)- **2b**	–10	7	83	92 (1*R*,2*S*)
3		(*S*,*S*)- **2c**	–40	7	80	90 (2*S*,3*R*)
4		(*S*,*S*)- **2b**	0	7	86	83 (1*R*,3*S*, 4*R*)
5		(*S*,*S*)- **2b**	–10	7	72	87 (3*R*,4*R*)

[a] All reactions were carried out in $CHCl_3$ (1.0M) using 1.2 equiv. TMSCN, 10 mol% $YbCl_3$, and 12 mol% ligand. [b] Isolated yield. [c]Enantiomeric excess of isolated product as determined by chiral GC analysis. Absolute configurations in parenthesis.

While it was possible to achieve good yield and enantioselectivity for a variety of meso epoxides, the optimal ligand and reaction temperature proved to be highly substrate-dependent. For example, the ARO of cyclopentene oxide carried out at room temperature proceeded in 33% ee with ligand **2c** but in 63% ee with the *t*-Bu-pybox ligand **2b**. At −10 °C, the enantioselectivity was improved to 92%. For those substrates examined, epoxides fused to five-membered rings (entries 2, 4, and 5) performed best with the *t*-Bu-pybox ligand **2b**, whereas the Ph-pybox ligand **2c** proved superior with cyclohexene oxide and *cis*-2-butene oxide. As was observed in the ARO of cyclohexene oxide (see above), these two ligands consistently afforded product of opposite absolute configuration.

While the results summarized in Table 3 compare favorably with the state-of-the-art for ARO of meso epoxides with TMSCN,[7] it is clear that the reaction is by no means ideal from a practical standpoint. In particular, the reactions must be carried out at reduced temperature in order to achieve high enantioselectivity, and as a result several days are required to attain optimal yields. To glean some insight into this process as a first step toward the design of improved catalysts, we have carried out a set of preliminary mechanistic investigations that are summarized below.

As noted above, a chloride transfer byproduct was obtained in the initial stages of the ARO of cyclohexene oxide in yields roughly equal to the amount of catalyst employed. This, in combination with the observations made by Utimoto with achiral ytterbium catalysts,[10] is consistent with the requisite formation of a cyanoytterbium species as the active catalyst.[18] While this might suggest a role of nucleophile-delivery agent for the catalyst, the observation of significant

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[14] (a) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846. (b) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1991**, *10*, 500. (c) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *Organometallics* **1992**, *11*, 4306.

[15] Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 1, 669. For a recent review of chiral bis(oxazoline)-metal catalyzed reactions, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.

[16] Aspinall, H. C.; Greeves, N.; Smith, P. S. *Tetrahedron Lett.* **1999**, *40*, 1763.

[17] A reversal of the absolute sense of selectivity from (*S*,*S*)-*tert*-butyl- to (*S*,*S*)-phenyl-bis(oxazoline) ligands has been observed previously in asymmetric bis(oxazoline)-Cu(II) catalyzed hetero-Diels−Alder and ene reactions. Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879.

rate inhibition with coordinating solvents such as THF and CH_3CN suggested that the Lewis acidity of the catalyst is also important. The observation of a significant positive nonlinear effect (Figure 2) provided the first concrete indication that a bimetallic mechanism of catalysis might be involved. A nonlinear effect is symptomatic of catalyst aggregation at some point in the catalytic cycle[19,20] and is consistent with the catalyst playing a dual role of cyanide-delivery agent and Lewis acid (Figure 3).[21]

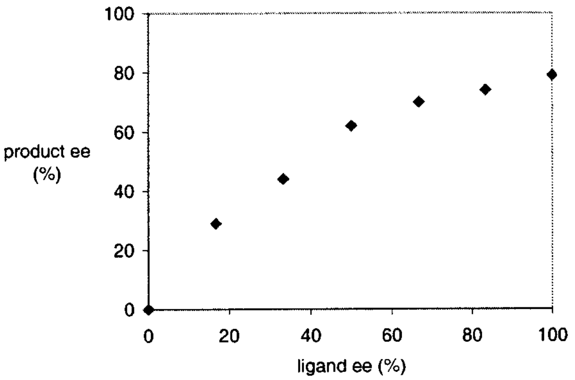

Figure 2. Plot of product ee vs catalyst ee for the ARO of cyclohexene oxide with TMSCN using 5 mol % of catalyst **2b·** $YbCl_3$. Reactions were carried out at 0 °C in $CHCl_3$.

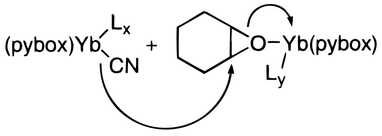

Figure 3. Proposed bimetallic mechanism for the ARO.

Kinetic studies provided additional insight into the nature of the ring-opening reaction.[22] Measurements were carried out at five different catalyst loadings over an 8-fold concentration range, and the rate constants thus obtained correlated in a linear manner with the square of catalyst concentration (Figure 4). This second-order dependence on catalyst is again consistent with a bimetallic rate-limiting ring-opening reaction.

In summary, the ARO of several meso epoxides was accomplished with good enantioselectivity and yield by employing $(pybox)YbCl_3$ catalysts. Preliminary kinetic studies point to a bimetallic mechanism of catalysis, indicating that it may be possible to construct more effective and reactive catalysts by covalent linkage of (pybox)lanthanide units. Efforts in this direction are ongoing and will be reported in due course.

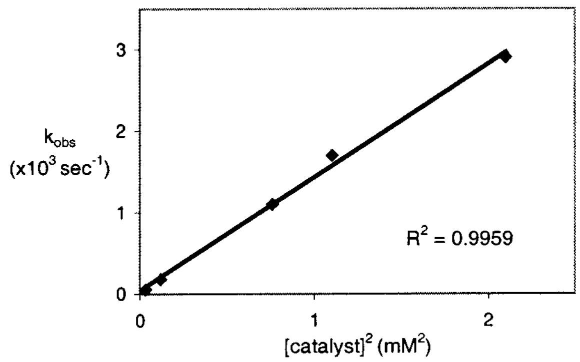

Figure 4. Plot of first-order rate constant k_{obs} vs the square of catalyst concentration for the ARO of cyclohexene oxide with TMSCN. Reactions were carried out at 23 °C in $CHCl_3$.

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Supporting Information Available: Complete experimental procedures, analytical data, and chiral chromatographic analyses of hydrocyanation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) On the other hand, the observation of a significant counterion effect on ee (see above) provides strong evidence that at least one chloride remains associated with the active catalyst.

(19) (a) Puchot, C.; Samuel, O.; Duñach, Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353. (b) Guillaneux, D.; Zhao, S.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430.

(20) For a recent, definitive review, see: Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923.

(21) A similar effect has been observed in bimetallic epoxide ARO reactions catalyzed by (salen)Cr complexes: (a) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1996**, *118*, 10924. (b) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780.

(22) Rates were determined by monitoring the appearance of the cyanide ring-opened product **1** as a function of time by GC analysis. An induction period was observed corresponding to the formation of chlorohydrin byproduct. First-order rate constants (pseudo-first-order conditions, 5-fold excess TMSCN, and limiting epoxide) were extracted by plotting ln [**1**] vs time after the induction period was complete (ca. 15% conversion of epoxide) and over >2 half-lives.