

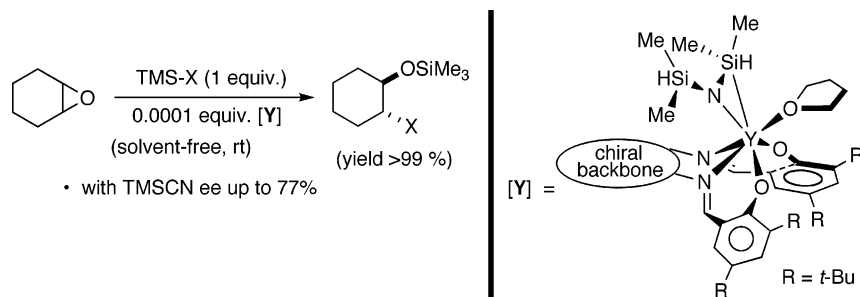
Exceptionally Active Yttrium–Salen Complexes for the Catalyzed Ring Opening of Epoxides by TMSCN and TMSN₃

Biswajit Saha, Mei-Huey Lin, and T. V. RajanBabu*

Department of Chemistry, 100 West 18th Avenue, The Ohio State University, Columbus, Ohio 43210

rajanbabu.1@osu.edu

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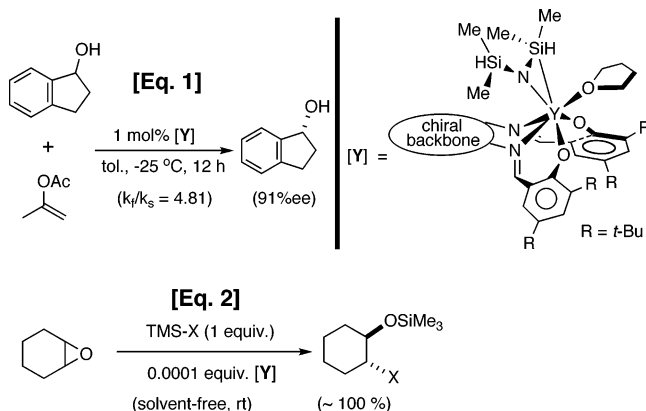


Halide or alkoxide free yttrium–salen complexes are excellent catalysts for the ring opening of epoxides mediated by TMSCN and TMSN₃. Substrate to catalyst ratios up to 10000 have been realized in these potentially useful reactions, which can be run under solvent-free conditions. Even though the enantioselectivities for the TMSCN-mediated reaction remains modest (best 77% ee), these studies with a highly tunable ligand system may provide further impetus for work in this important area of catalysis. Even though attempts to isolate a Y–cyanide complex, which was detected by in situ IR spectroscopy, failed, a related dimeric hydroxide complex was isolated. A kinetic study using in situ IR spectroscopy did not provide conclusive data to assign an order with respect to Y in this reaction.

Introduction

In previous publications,¹ we disclosed that Y(III)–alkoxides and salen complexes are excellent catalysts for acylation of secondary alcohols using enol esters. In selected cases, the Y–salen catalysts afford moderate enantioselectivity in kinetic resolution of secondary alcohols (for example, $k_f/k_s = 4.81$ for 1-indanol, eq 1). Based on the solid-state structure of the catalyst complex, we proposed a novel mechanism in which the yttrium center acts as a Lewis acid, activating the electrophile (the enol acetate) and the nucleophile (the putative alkoxide). We have been searching for other applications of such coordination catalysis and now find that Y–salen complexes serve as excellent catalysts for ring opening of epoxides by trialkylsilyl nitriles and azides.² The unusually high turnover efficiency

(substrate/catalyst = 10000) seen for the addition of TMSCN (eq 2) prompted us to examine the scope and limitations of this reaction.



(1) Lin, M.-H.; RajanBabu, T. V. *Org. Lett.* **2000**, 2, 997. (b) Lin, M.-H.; RajanBabu, T. V. *Org. Lett.* **2002**, 4, 1607.

(2) The initial results on the yttrium-catalyzed opening of epoxycyclohexane and epoxycyclopentane are extracted from: Lin, M.-H. Yttrium-Catalyzed Reactions: Transacylation, Secondary Alcohol Resolution, Cyanosilylation of Ketones and Epoxides. Ph.D. Dissertation, The Ohio State University, 2002.

Desymmetrization of *meso*-epoxides and aziridines by carbon nucleophiles such as cyanides or organometallic reagents is a reaction of great synthetic potential, and considerable effort has

been invested in this reaction.^{3,4} The best results in this area are represented by the works of Hoveyda, who used a combinatorial approach to discover Ti–imine complexes^{3a,5} to achieve modest to good enantioselectivities for this reaction, and of Jacobsen, who added TMSCN to *meso*-epoxides under catalysis by Yb(III)–pybox complexes.^{3b} The major limitation of both of these methods is the relatively large amount of the catalyst needed to complete the reaction. In order to obtain even modest yields (60–70%) in the Ti-catalyzed reaction, one needs to use 10–20 mol % of a high-molecular weight catalyst. The yields in the Yb-catalyzed reactions are better, yet it still requires 10 mol % of catalyst (4 days at –45 °C for 90% yield and 91% ee for epoxycyclohexane). The need for such large quantities of the catalyst in the [imine]Ti-mediated reaction is understandable in light of the large number of Lewis basic centers in the ligand, which could reduce the effective Lewis acidity of the metal. In the case of the Yb-catalyzed reaction there are two possible reasons why excessive catalyst is needed. This could be due to the residual chloride ions that are present which compete with the electrophilic activation of the epoxide and/or due to the termolecular nature of the reaction, in which the metal (Yb) serves dual roles, one, for activation of the epoxide and, two, for activation of the nitrile.^{3b,6} We reasoned that a catalyst devoid of extraneous Lewis basic centers (either on the ligand or present as free halide⁷ or alkoxide^{3a} ions during the catalyst generation) should be more effective in achieving this reaction. In addition, if the role of catalyst can be limited to that of a Lewis acid alone (i. e., unimolecular in the metal), significant kinetic advantages could be derived. We conjectured that the square-pyramidal yttrium-salen complex (eq 1) with Y in a low-coordinate environment⁸ might be a suitable candidate to test these ideas.

(3) For leading references, see, for TMSCN: (a) Cole, B. M.; 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) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, 2, 1001. (c) Addition of TMSCN to aziridines: Mita, T.; Fujimori, I.; Wada, R.; Wen, J.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, 127, 11252. For other notable results: (d) addition of an enolate: Crotti, P.; Di Bussolo, V.; Favero, L.; Macchia, F.; Pineschi, M. *Gazz. Chim. Acta* **1997**, 127, 273. (e) Addition of PhLi: Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, 39, 9023. (f) Addition of alkynyllithium reagents: Zhu, C.; Yang, M.; Sun, J.; Zhu, Y.; Pan, Y. *Synlett* **2004**, 465. (g) Addition of TMSCN with ephedrine Ga and In complexes gives isonitriles: Yuan, F.; Zhu, C.; Sun, J.; Liu, Y.; Pan, Y. *J. Organomet. Chem.* **2003**, 682, 102. (h) For a report of TMSCN-mediated ring opening of α,β -epoxy carboxamides catalyzed by Sm(III), see: Tosaki, S.; Tsuji, R.; Oshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, 127, 2147.

(4) For a review of asymmetric ring opening reactions of epoxides, see: Jacobsen, E. *Acc. Chem. Res.* **2000**, 33, 421. For a compilation of more recent references, see: Schneider, C.; Sreekanth, A. R.; Mai, E. *Angew. Chem., Int. Ed.* **2004**, 43, 5691.

(5) 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.

(6) Evidence for such dual activation by metal, and the attendant kinetic consequences have been documented in additions of TMSN₃ to epoxycyclohexane. (a) See: Jacobsen, E. *Acc. Chem. Res.* **2000**, 33, 421 and references cited therein. (b) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, 120, 10780. Footnote 7 of this paper is especially relevant to the present discussion.

(7) Anecdotal evidence for such inhibition by chloride ion can be found in the early experiments of Utimoto who showed that lanthanide chlorides are poor catalysts for the reaction between epoxycyclohexane and TMSCN. See: Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, 31, 6209.

(8) For a discussion of low coordinate Y-complexes, see: Schuetz, S. A.; Silvernail, C. M.; Incarvito, C. D.; Rheingold, A. L.; Clark, J. L.; Day, V. W.; Belot, J. A. *Inorg. Chem.* **2004**, 23, 6203.

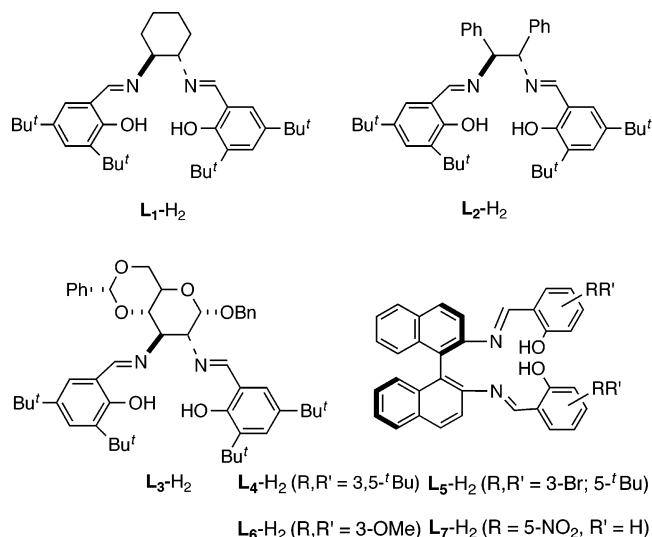


FIGURE 1. Prototypical salen ligands.

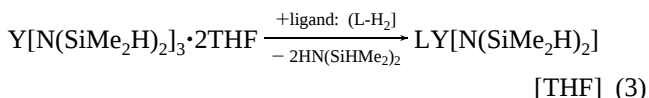
TABLE 1. Opening of Epoxycyclohexane with TMSCN in the Presence of Y Complexes of L1–L7^a

entry	ligand	solvent	time (h)	% ee ^b (config)
1	L1	CH ₂ Cl ₂	11	16 (1 <i>S</i> ,2 <i>R</i>)
2	L1	PhCH ₃	11	13 (1 <i>S</i> ,2 <i>R</i>)
3	L1	THF	10	8 (1 <i>R</i> ,2 <i>S</i>)
4	L1	hexane	10	7 (1 <i>S</i> ,2 <i>R</i>)
5	L2	CH ₂ Cl ₂	10	16 (1 <i>R</i> ,2 <i>S</i>)
6	L3 ^c	CH ₂ Cl ₂	8.5	15 (1 <i>R</i> ,2 <i>S</i>)
7	L4	CH ₂ Cl ₂	20	77 (1 <i>R</i> ,2 <i>S</i>)
8	L5	CH ₂ Cl ₂	10	<5
9	L6	CH ₂ Cl ₂	10	<5
10	L7	CH ₂ Cl ₂	10	<5
11	L4	THF	14	72 (1 <i>R</i> ,2 <i>S</i>)
12	L4	PhCH ₃	16	56 (1 <i>R</i> ,2 <i>S</i>)
13	L4	hexane	20	62 (1 <i>R</i> ,2 <i>S</i>)
14	L4	^t BuOMe	20	64 (1 <i>R</i> ,2 <i>S</i>)
15	L4	CH ₃ CN	23	15 (1 <i>R</i> ,2 <i>S</i>)

^a 1:1 epoxide/TMSCN 1 M; 2 mol % of catalyst; rt, 100% conversion except in entry 6. ^b Determined by GC analysis. ^c 88% conversion.

Results

Our investigations started with an examination of the reaction between epoxycyclohexane with TMSCN in the presence of salen complexes (Figure 1) of yttrium, and the results are shown in Table 1. The catalytically active complexes were prepared by the silylamide route⁹ (eq 3), and the reaction was run with 1–2 mol % of the catalyst in a 1 M solution of the epoxide and TMSCN in a molar ratio of 1:1. The reaction was followed by TLC or GC until all starting materials disappeared. The reaction mixture was quenched by the addition of water, and the product was isolated and analyzed by GC and NMR. Separation of the enantiomers was accomplished on a Cyclodex B or Chiraldex B–Ph column, which showed baseline separation of the two enantiomers (GC traces of the crude material are included in the Supporting Information).



(9) Runte, O.; Priemeier, T.; Anwender, R. *J. Chem. Soc., Chem. Commun.* **1996**, 1385.

TABLE 2. Effect of the Metal on the Opening of Epoxycyclohexane with TMSCN^a

metal	time (h)	conv (%)	% ee
Y	20	100	77
Yb	72	>98	28
La	5	100	33
Pr	47	100	47
Sc	72	0	NA
Al	72	0	NA
Ti	120	18	12
Zr	120	35	35

^a Catalyst generated as shown in eq 3 using ligand **L4**; 1 mol % of catalyst, CH₂Cl₂, rt.

TABLE 3. Effect of the Catalyst Concentration^a

entry	[Y] (mol %)	solvent	T (°C)	time (h)	% ee
1	2.0	CH ₂ Cl ₂	25	2	77 ^b
2	1.5	hex	−15	3	72
3	1.0	hex	−15	3	73
4	0.5	hex	−15	3	74
5	0.1	hex	−15	3	73
6	0.05	no solvent	25	4	56
7 ^b	0.01	no solvent	25	4	56

^a Catalyst generated as shown in eq 3 using ligand **L4**. See text for experimental procedure. ^b With 4 Å molecular sieves.

In early experiments, we identified CH₂Cl₂ as the best solvent for the reaction (entries 1–4, 7, 11–15 in Table 1). Among the ligands examined,^{1b,10} salen derivatives from vicinal diamines (**L1–L3**) and 2,2'-diamino-1,1'-binaphthyl (**L4–L7**) showed the most activity. For BINAP(NH₂)₂-derived ligands, in order to achieve high selectivity both the 3- and 5-Bu substituents on the salicylaldehyde from which these are derived are essential (entries 7–10). Thus, all BINAP ligands (**L4–L7**) gave nearly quantitative yields, but only ligand **L4** (3,5-*t*-Bu) showed good enantioselectivity (entries 7, 11–14). Others yielded nearly racemic products (entries 8–10). As with **L1**, the best solvent for the reactions catalyzed by complex from **L4** appears to be CH₂Cl₂ (entry 7).

Having identified **L4** as a suitable ligand, the effect of the metal was briefly examined and the results are shown in Table 2. In each case, the catalyst was prepared as described in eq 3 from the corresponding metal dimethylsilylamide (dms) salts¹¹ and the ligand **L4**. Yttrium and lanthanides (lanthanum, praseodymium, and ytterbium) were viable metals for the ring opening reaction, with the yttrium giving by far the best results. Surprisingly, Sc, Al, Ti, and Zr showed only low reactivity.

The efficacy of the catalyst derived from ligand **L4** was tested by examining the effect of its concentration on the reaction. The results are shown in Table 3. As shown in entries 1–5, a 20-fold decrease in the catalyst has very little effect on the enantioselectivity, suggesting that there are few deleterious side reactions including uncatalyzed background reaction. When the enantiomeric excess of the product was measured as a function of the conversion it was observed that, even for the slower reactions, the ee remains constant until the end of the reaction. This clearly suggests that the catalyst is robust under these

(10) For full experimental details, including the preparation and use of the ligands listed in Figure 1, see the Supporting Information. Details of the spectroscopic and chromatographic identification of compounds are also included there.

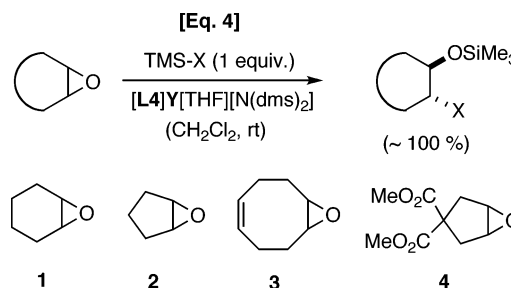
(11) For the synthesis of the amides, see: Anwender, R.; Runte, O.; Eppinger, J.; Gerstberger, G.; Herdtweck, E.; Spiegler, M. *J. Chem. Soc., Dalton Trans.* **1998**, 847.

TABLE 4. Epoxide Opening Reactions Catalyzed by [L4]Y(THF)(dms)^a

entry	TMSX	epoxide	S/C ratio	time (h)	% ee (config)
1	TMSCN	2	10000	44	--
2	TMSCN	2	100	20	54 (1R,2S)
3	TMSCN	3	100	40	<5
4	TMSCN	4	50	62 ^b	<5
5	TMSN ₃	1	10000	38	29 ^c (1R,2S)
6	TMSN ₃	1	100	24	32 (1R,2S)
7	TMSN ₃	2	50	72	12 (1R,2S)

^a See eq 4. ^b For 100% conversion except for entry 4. ^c With no solvent.

reactions conditions, and nonselective catalysis by adventitious Y or any other species is most likely not involved in the reaction. As the concentration of the catalyst is decreased to 0.05 mol % (0.0005 M in catalyst, S/C = 2000), there is a noticeable decrease in the enantioselectivity. Surprisingly the reaction can be carried to completion even with 0.01 mol % of catalyst (0.0001 M in catalyst, S/C 10000), even though under these conditions, the enantioselectivity is significantly lower. Note also that this highly catalytic reaction is carried out with stoichiometric amounts of the epoxide and TMSCN with *no solvent* added. We also noted that addition of molecular sieves improve the reproducibility of these reactions.



Other Epoxide Opening Reactions. Encouraged by the high turnovers in the reactions of epoxycyclohexane, we briefly examined other related reactions, and the results are shown in Table 4. Thus, the Y catalyst prepared from **L4** effects quantitative ring-opening reactions of epoxycyclopentane, epoxycyclooct-5-ene, and epoxy[4-bis(methoxycarbonyl)]cyclopentane, even though the enantioselectivities of these reactions are not satisfactory for preparative purposes. Note that reactions of epoxycyclohexane with both TMSCN and TMSN₃ can be run under exceptionally low catalyst loading (S/C = 10000) under solvent-free conditions.¹² A similar reaction of epoxycyclopentane with TMSCN is reported in entry 1. Substrates with medium-size rings and those carrying Lewis basic centers (e.g., −CO₂Me groups in **4**) react considerably slower than epoxycyclohexane and epoxycyclopentane (entries 3 and 4).

Geometry of the Y–Salen Complexes and Possible Relevance to High Efficiency of the Catalyst. We have determined structures of two yttrium complexes (**5** and **6**) that may be relevant to this highly catalytic reaction.¹³ They are shown in Figures 2 and 3. In connection with our work on the transacylation of secondary alcohols using enol acetates (eq 1), we had previously reported on the solid-state structure of the

(12) Jacobsen has reported that 1 mol % of a monomeric (salen)Cr–N₃ complex is needed effect the opening of epoxycyclopentane with TMS–N₃ under these conditions (see ref 6).

(13) Crystallographic details for **6** and a figure representing thermal ellipsoids are included in the Supporting Information.

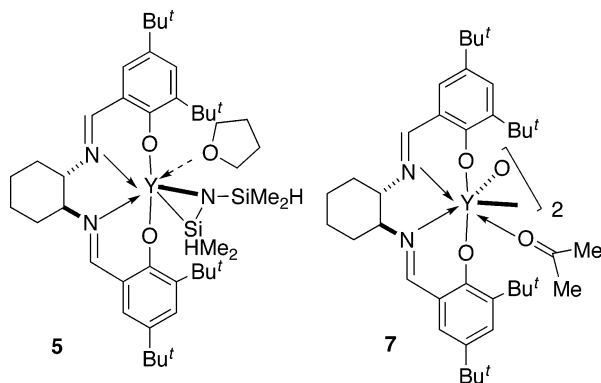


FIGURE 2. Monomeric and dimeric Y-salen complexes.

yttrium-salen complex $[\text{L1}]\text{Y}[\text{THF}][\text{N}(\text{dms})_2]$ (Figure 2).^{1b} Here, we report the structure of the complex $[(\text{L4})\text{Y}(\mu\text{-OH})_2]$ (Figure 3).¹⁴ The former incorporates one anionic ligand $[\text{-N}(\text{SiHMe}_2)_2]$ and one neutral ligand (THF), while the latter appears to be an adventitious hydrolysis product of a similar complex from BINAP(NH_2)₂-derived salen. This complex has a dimeric structure carrying a bridging OH ion. The structure of $[\text{L1}]\text{Y}[\text{THF}][\text{N}(\text{dms})_2]$ (eq 1) has distorted trigonal prismatic geometry while the latter (Figure 3) has a distorted octahedral geometry. The structure of L1-derived complex 5 also reveals an unusual agostic interaction between one of the Si atoms and Y, presumably brought about by the highly Lewis acidic nature of Y and the particular geometry of the backbone. In a related salen complex prepared from 1,2-ethylenediamine, this interaction is absent.^{14b} In 5, the large yttrium atom is placed 0.95 Å above the N_2O_2 plane. From a mechanistic perspective, such a structure would permit activation of either the epoxide (ligand substitution of THF) or of the cyanide (substitution of the silylamide ligand). A comparison of structures 6 and 7, a dimer prepared by Morken^{14a} from L1 and yttrium isopropoxide, seems to suggest that L1 is a sterically less demanding ligand (vis-à-vis L4) since the dimer 7 contains an additional acetone moiety coordinated to each of the Y atoms. Such an additional ligand is not seen in 6, prepared from L4. Thus, a tightly controlled ligand field in complexes of L4 might account for the improved selectivity of catalysts derived from BINAP(NH_2)₂.

An Attempt To Determine the Order of the Reaction in the Metal. The moderate enantioselectivity in the epoxycyclohexane opening (77% ee vs the best published result, 91%) notwithstanding, the Y-catalyzed reaction, which can be run under solvent-free conditions with 0.0001 equiv of the catalyst, is truly remarkable in its efficiency. Most relevant is the comparison to the Jacobsen protocol which uses an YbCl_3 -(pybox) complex, where, through kinetic studies, he has provided tentative evidence for the possible involvement of a bimetallic activation.^{3b} In a corresponding solvent-free TMSN₃ opening, Jacobsen reports that 0.01 equiv of a monomeric

salen-Cr catalyst (24 h) is needed to complete the reaction.⁶ In this better-understood TMS-N₃ reaction, it is known that the reactive nucleophile (LCr-N_3) is generated from initially formed HN_3 , which when used separately, can also initiate the reaction. We believe that the cyanide-opening reactions catalyzed by Y are mechanistically different. For example, in an early experiment we saw that no trace of the ring-opening product was formed when HCN was used in place of TMSCN. Also running the reaction with 5 fold excess (with respect to the catalyst) of a desiccant $\text{Cp}_2\text{Zr}(\text{Me})_2$ or activated molecular sieve has no effect on the reaction. A set of parallel reactions with either TMSCN or TMSN₃ with epoxycyclohexane proceed with the same rate and selectivity, whether 5 equiv of $\text{Cp}_2\text{Zr}(\text{Me})_2$ is present or not.

An examination of a possible nonlinear effect using catalyst $[\text{L4}]\text{Y}[\text{N}(\text{dms})_2][\text{THF}]$ of varying enantiomeric excess showed that there is no such effect operating in the Y-salen-mediated TMSCN opening of epoxides. Thus, between 0 and 100% ee of the catalyst, a plot of % ee of the ligand vs % ee of the product showed a nearly perfect linear fit ($R^2 = 0.9758$).¹⁰

With the structural information on the Y catalysts, and the early evidence suggesting an exceptionally fast reaction (Table 3), we wondered whether the dual-activation mechanism suggested by Jacobsen is plausible in such a highly efficient catalyst. We sought to clarify the mechanism of the TMSCN-mediated reaction by studying its kinetics by in situ IR spectroscopy. Four factors make this an almost ideal reaction for the use of this technique: (i) the total absence of any other side reactions (including the formation of the isonitrile adduct,¹⁵ $\nu_{\text{NC}} = 2140 \text{ cm}^{-1}$); (ii) the distinct and clearly resolved IR signatures of TMSCN ($\nu_{\text{CN}} = 2192 \text{ cm}^{-1}$) of and of the product cyanohydrin TMS ether ($\nu_{\text{CN}} = 2246 \text{ cm}^{-1}$); (iii) moderate and easily measurable reaction rates under near stoichiometric conditions of the reagents, using 0.10–0.50 mol % of catalyst at temperatures between -20 and $+25$ °C; and (iv) the fact that there is no deterioration of selectivity as a function of conversion, clearly suggesting that the catalyst is quite robust under these reaction conditions.

In initial blank experiments, it was observed that the addition of epoxide to a stoichiometric amount of the Y catalyst brought about very little change in either the IR (hexane) or NMR spectra (toluene-*d*₈) for 22 h. The characteristic peaks due to the coordinated epoxide [¹H NMR in tol-*d*₈: broad doublet δ 2.93 and 3.01; ¹³C NMR δ 53.84 (m), 24.46 (s) and 24.38(s)] are retained at least up to 22 h after mixing a stoichiometric amount of the catalyst $[\text{L4}]\text{Y}[\text{N}(\text{dms})_2][\text{THF}]$ and epoxycyclohexane. However, upon addition of an equivalent amount of cyanide, significant changes ensue, the most important being an immediate (<1 min) replacement in the IR of the peak due to TMSCN ($\nu_{\text{CN}} = 2192 \text{ cm}^{-1}$) by a strong signal at 2077 cm^{-1} , tentatively

(14) For recent examples of related structures of other salen metal complexes, see, Y: (a) $\text{Y}(\text{L1})(\mu\text{-OH})_2$: Mascarenhas, C. M.; Miller, S. P.; White, P. S.; Morken, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 601. (b) Runte, O.; Priemeier, T.; Anwander, R. *J. Chem. Soc., Chem. Commun.* **1996**, 1385. (c) Herrmann, W. A.; Anwander, R.; Munck, F. C.; Scherer, W.; Dufaud, V.; Huber, N. W.; Artus, G. R. J. *Z. Naturforsch., B* **1994**, *49*, 1789. (d) Evans, W. J.; Fujimoto, C. H.; Ziller, J. W. *J. Chem. Soc., Chem. Commun.* **1999**, 311. (e) An alkoxide bridged dimer: Oviatt, T. M.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1316. Al: (f) $\text{Al}(\text{L4})\text{X}$: Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884.

(15) In the ring-opening reaction of epoxycyclohexane by TMSCN, selective formation of a nitrile or an isonitrile product can be achieved by the choice of Lewis acids. Thus, Zn, Pd, Sn, In, and Ga salts give the isonitrile, whereas Ca, Mg, Zn, Y, Ti, and most lanthanide salts give the nitrile. Isonitrile: (a) Gassman, P. G.; Guggenheim, T. L. *J. Am. Chem. Soc.* **1982**, *104*, 5849. (b) Spessard, G. O.; Ritter, A. R.; Johnson, D. M.; Montgomery, A. M. *Tetrahedron Lett.* **1983**, *24*, 655. (c) Imi, K.; Yanagihara, N.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 1013. (d) Zhu, C.; Yuan, F.; Gu, W.; Pan, Y. *Chem. Commun.* **2003**, 692. Nitrile: (e) Lidy, W.; Sundemeyer, W. *Tetrahedron Lett.* **1973**, 1449. (f) Mullis, J. C.; Weber, W. P. *J. Org. Chem.* **1982**, *47*, 2873. (g) Hayashi, M.; Tamura, M.; Oguni, N. *Synlett* **1982**, 663. (h) Sugita, K.; Ohta, A.; Onaka, M.; Izumi, Y. *Chem. Lett.* **1990**, 481. (i) Matsubara, S.; Onishi, H.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6209. See also refs 3a,b,g.

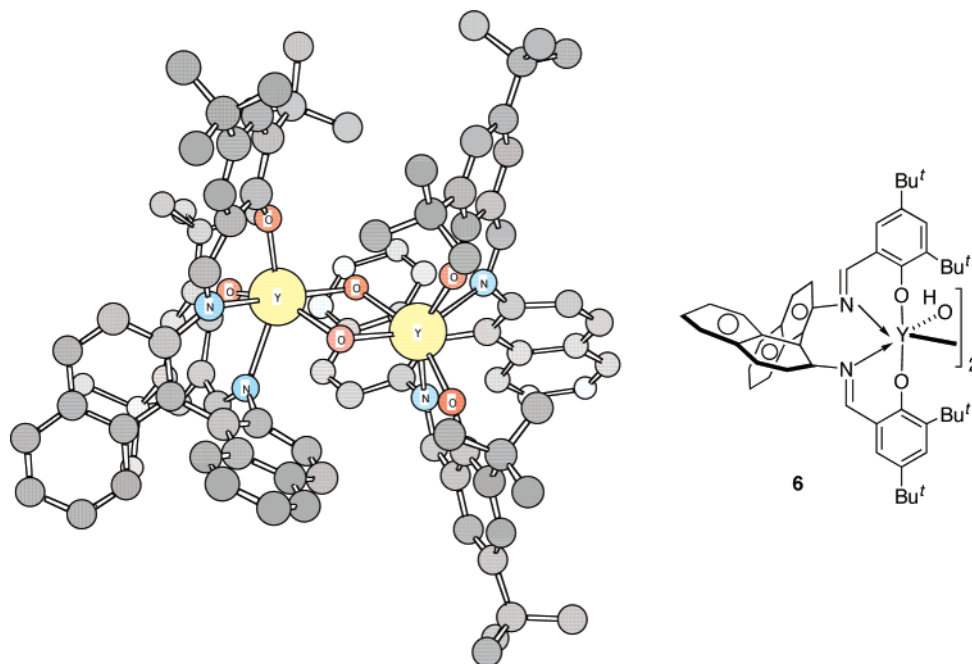


FIGURE 3. Solid-state structure of $\{[L_4]Y[\mu\text{-OH}]\}_2$ (**6**). Hydrogens omitted for clarity.

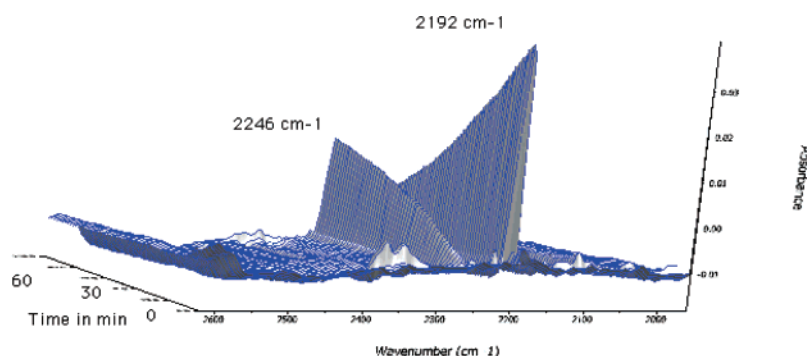


FIGURE 4. Typical kinetic run. Stacked IR spectra showing disappearance of TMSCN (2192 cm^{-1}) and appearance of the product (2246 cm^{-1}).

assigned as arising from a bridged Y–isonitrile intermediate.^{16,17} In the NMR, peaks due to the epoxide disappear. Even though the resulting NMR spectra are inscrutable, upon workup, the only product seen is the expected cyanohydrin trimethylsilyl ether.

A typical kinetic experiment was run as follows with TMSCN as the limiting reagent with excess of the epoxide. To a mixture of the epoxide (0.250 g, 0.257 mL, 2.5 mmol) and the catalyst $[L_4]Y[N(\text{dms})_2][\text{THF}]$ (0.005 g, 0.005 mmol) in 0.5 mL of hexane, under nitrogen, was added 5 μL (0.038 mmol) of TMSCN, and the mixture was stirred for 30 min. The ReactIR probe was introduced, and the mixture was cooled to 0°C in an ice bath where the temperature was rigorously maintained ($\pm 0.1^\circ\text{C}$) through out the experiment. After equilibration, TMSCN (0.05 g, 0.067 mL, 0.5 mmol) was added and the spectra were collected at 1 min intervals.

A typical stack of spectra obtained (0.1 mol % of catalyst, 1 M in substrate, 0.001 M in catalyst), showing the relevant peaks

for TMSCN (2192 cm^{-1}) and the product cyanohydrin–TMS ether (2246 cm^{-1}), is shown in Figure 4. The concentration profile of TMSCN and the product as a function of time is shown in Figure 5. Individual spectra at $t = 1, 53,$ and 85 min and at the end of the reaction are shown in Figure 6.

Kinetic runs were carried out with different concentrations of the catalyst, in a 10 fold range, between 0.1 and 1 mol %, with respect to TMSCN. Plots of $\ln[(a^0)/(a^0 - x)]$ versus time (min), where (a^0) is the initial absorbance of (TMSCN) and ($a^0 - x$) is the absorbance of remaining TMSCN as measured by the absorbance at time t] gives straight lines (Figure 1, Supporting Information), indicating a first-order reaction under these conditions. The relative values of k_{obs} were derived from the slope of these lines. A plot of k_{obs} vs $[\text{cat.}]^2$ and k_{obs} vs $[\text{cat.}]$ (Figure 2, Supporting Information) gave inconclusive results, with R^2 values of 0.995 for the former and 0.961 for the latter. We believe that this distinction is ambiguous even though very similar data ($R^2 = 0.997$ and 0.967 , respectively) was used by Jacobsen^{3b} to argue in favor of a bimetallic activation process in the (pybox)YbCl₃-mediated epoxide opening by TMSCN.

(16) For IR spectroscopy of bridged nitrile/isonitrile complexes, see: (a) Sheng, T.; H. Vahrenkamp, H. *Inorg. Chim. Acta* **2004**, 357, 1739. (b) Dixon, D. A.; Hertler, W. R.; Chase, D. B.; Farnham, W. B.; Davidson, F. *Inorg. Chem.* **1988**, 27, 4012.

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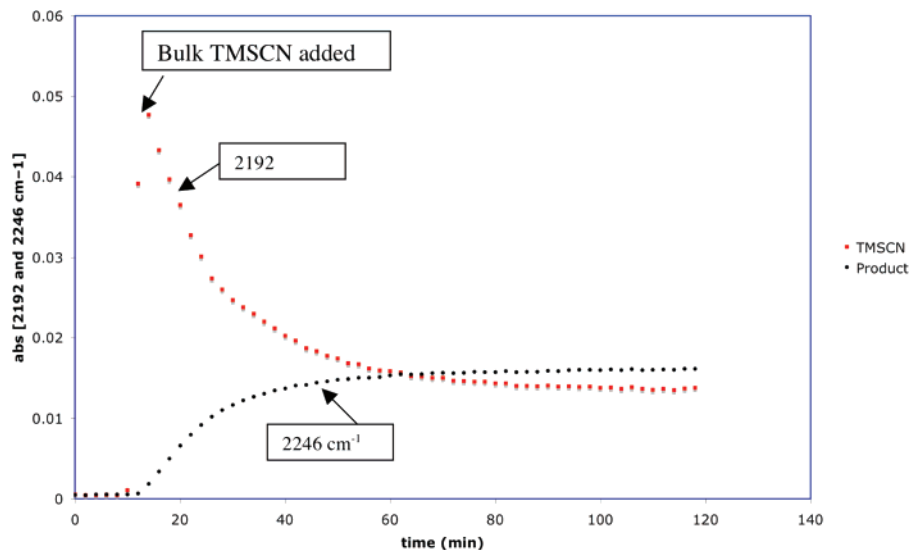


FIGURE 5. Profiles of absorbances for TMSCN and the cyanohydrin–TMS ether product as a function of time (conditions: 1 M TMSCN and epoxycyclohexane (1:1) in hexane, 0.1 mol % (0.001 M in catalyst) [L₄]Y[N(dms)₂][THF]).

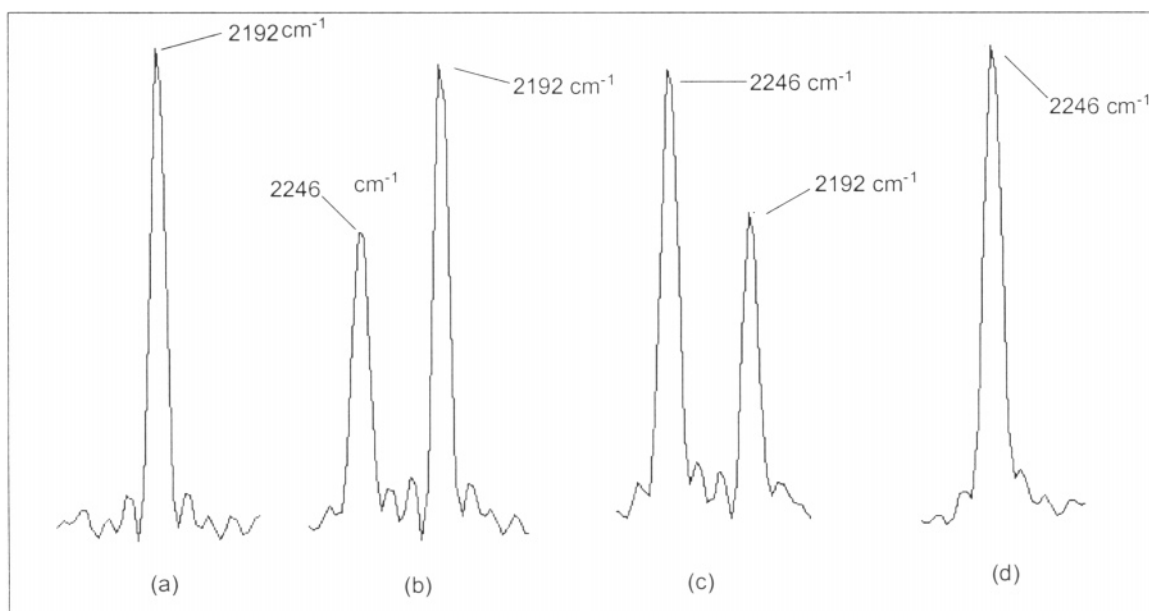


FIGURE 6. Individual spectra at $t = 1$ min (a), 53 min (b), and 85 min (c) using 0.1 mol % of catalyst at 0 °C and at the end of the reaction (d).

Discussion

The key features that distinguish the Y-catalyzed TMSCN-mediated opening from the well-studied Cr-catalyzed TMSN₃ opening are the following:

(i) There *appears* to be no induction period observed in the TMSCN-mediated reactions once the bulk of the TMSCN is added. However, since the addition of ~ 5 μ L of TMSCN at the beginning of the reaction before equilibration helps reproducibility of the runs, formation of an exceedingly reactive catalyst at this stage cannot be totally discounted. Obviously, if that is the case, no induction period would be observed.

(ii) We have not observed any nonlinear effects in the asymmetric induction process.

(iii) While the TMS-N₃ reaction is known to proceed through the initial generation of HN₃, and thus through a chromium azide, there is no indication that HCN is involved in the

Y-catalyzed reaction. *Indeed, attempting to carry out the reaction with HCN (2 M solution of HCN in toluene, see the Supporting Information for details of the experiment) instead of TMSCN yielded no product.* These reactions were done with rigorous exclusion of moisture in a drybox. Besides, addition of activated 4 Å molecular sieves or Cp₂ZrMe₂ to remove residual water has no effect on the ring-opening reaction with TMSCN (or TMSN₃). Indeed, highly reproducible reactions at the lowest concentrations of the catalyst (0.01 mol %) were carried out with molecular sieves present in the reaction medium. In a stoichiometric reaction with the catalyst, epoxide, and TMSCN in molar ratio of 1:1:1, the only isolated product is the product cyanohydrin–TMS ether.

At this stage, one can only speculate about the origin of the remarkable efficiency of the Y(III)-catalyzed reaction vis-à-vis the Yb(III)- or Ti(IV)-catalyzed reactions. One clear difference between these reactions is the absence of chloride or alkoxide

ions in solution in the (salen)Y[N(dms)₂]-catalyzed reactions. The instantaneous disappearance of absorbance of TMSCN (2192 cm⁻¹) upon mixing with stoichiometric amounts of the catalyst (vide supra) suggests the rapid formation of the reactive nucleophilic species. Likewise, activation of the epoxide involves a simple ligand displacement of neutral THF by the epoxide, which could be expected to be a more facile process than the corresponding one in the LYbCl₃ or L_nTi^{IV}(OR)_m mediated reactions since Cl⁻ or RO⁻ ligands are harder to displace.

Conclusions

In this paper, we report a highly efficient halide- or alkoxide-free yttrium complex that catalyzes the ring opening of epoxides mediated by TMSCN and TMSN₃. Substrate to catalyst ratios up to 10000 has been realized in these potentially useful reactions, which can be run under solvent-free conditions.

Experimental Section

See the Supporting Information for general descriptions of procedures, separations, and characterization of compounds. Details of the kinetic experiments are also reported there.

A Typical Procedure for Ring Opening of Epoxycyclohexane with TMSCN using Chiral Yttrium Complexes (Table 1): (1R,2S)-2-Trimethylsilyloxycyclohexane-1-carbonitrile. To a CH₂-Cl₂ solution (0.5 mL) of Y complex was added epoxide (0.049 g, 0.5 mmol), the yellow colored solution was stirred at room temperature for 10 min, and TMSCN (neat) (0.050 g, 0.50 mmol) was added slowly and dropwise to the stirred solution of epoxide and catalyst. The reaction was monitored by GC. After completion of the reaction, the mixture was passed through a short silica gel column, and evaporation of the solvent gave clean product nearly in quantitative yield in almost every case. Spectroscopic data were identical with what has been reported in the literature.^{3b} Enantiomer separation: chiral GC analysis (Cyclodex-B column, 110 °C isothermal for 50 min, *t_R* (minor) = 30.70 min, *t_R* (major, 1R,2S) = 31.63 min [*α*]_D = +25 (c 1, CH₂Cl₂), 77% ee [lit.^{3b} (1S,2R): [*α*]_D = -38.5 (c 4.52 CH₂Cl₂, 91% ee]. See the Supporting Information for chromatograms.

YbCl₃·2.7THF.¹⁸ Ytterbium trichloride (YbCl₃) (0.2 g, 0.72 mmol) in THF (4.2 mL) was charged in a 25 mL two-necked flask under an inert atmosphere and heated to reflux for 1.5 h. The mixture was cooled to room temperature and evaporated to dryness to give a white solid (0.34 g). By weight difference between YbCl₃ and the white THF adduct, the composition of the product was calculated as YbCl₃·2.7THF.

Preparation of Yb[N(SiMe₂H)₂]₃·2.7THF. To a hexane solution (7 mL) of YbCl₃·2.7THF (0.3 g, 0.63 mmol) was added LiN-(SiMe₂H)₂ (0.23 g, 1.64 mmol), and the mixture was stirred for 12 h at room temperature. The white precipitate of the reaction mixture was allowed settle down, and the solution was filtered through a pad of Celite to get clear solution. The residual solid was washed two times with hexanes (5 mL) and filtered as mentioned above. The solvent was removed under vacuum to give pale yellowish solid that was crystallized from pentane (352 mg) and directly used for chiral complex preparation.

PrCl₃·2THF.¹⁸ Praseodymium chloride (PrCl₃) (0.5 g, 2.02 mmol) in THF (12 mL) was charged in a 50 mL two-necked flask under an inert atmosphere and heated to reflux for 1.5 h. The mixture was cooled to room temperature and was evaporated to dryness to give white solid (0.78 g). By weight difference between PrCl₃ and the white THF adduct, the product was estimated to be PrCl₃·2THF.

Preparation of Pr[N(SiMe₂H)₃·2THF. To a hexane solution (7 mL) of PrCl₃·2THF (0.25 g, 0.64 mmol) was added LiN-(SiMe₂H)₂ (0.23 g, 1.66 mmol), and the mixture was stirred for 12 h at room temperature. The white precipitate of the reaction mixture was allowed settle, and the solution was filtered through a pad of Celite to get a clear solution. The residual solid was washed two times with hexanes (5 mL) and filtered as mentioned above. The solvent was removed under vacuum to give a pale yellowish solid which was crystallized from pentane (0.21 g) and directly used for chiral complex preparation.

Preparation of La[N(SiMe₂H)₃·3THF. A three-neck, round-bottom flask was charged with LiN(SiMe₂H)₂ (0.21 g, 1.52 mmol) and fitted with rubber septum, stopper, and solid addition funnel containing La(OTf)₃ (0.3 g, 0.51 mmol). The flask was removed from the glovebox and connected to N₂ line, and THF (11 mL) hexanes (5.5 mL) were introduced subsequently to the reaction flask. The glass stopper was replaced by a reflux condenser and connected to N₂, and then the septum was replaced by a glass stopper; at this point, La(OTf)₃ was added to the reaction mixture under stirring conditions. The reaction was refluxed for 14 h, cooled to room temperature, and taken inside the drybox, and the solvent was removed under vacuum to get a white solid. To that solid was added 10 mL of pentane. The mixture was stirred for 15 min, and the solvent was decanted and evaporated under vacuum to get a white solid (0.18 g). ¹H NMR (C₆D₆, 250 MHz NMR): δ 5.01 (sept, 6 H, -SiHMe₂, 3.68 (m, 12 H, THF), 1.36 (m, 12 H, THF), 0.38 (d, -SiHMe₂).

Synthesis of Chiral Lanthanide Complexes. To a mixture of chiral ligand **L**₄ (0.043 mmol) in THF (0.25 mL) was added La-[N(SiMe₂H)₂]₃·*n*THF [La = Yb, Pr, La] (0.043 mmol) in hexanes (0.25 mL). The reaction mixture was stirred for 4 days at room temperature, and finally, the solvent was removed under high vacuum to obtain a solid which was directly used for catalytic reactions without further purification.

Reaction of Epoxycyclohexane in the Absence of a Catalyst. A mixture of the epoxide (0.049 g, 0.5 mmol) and TMSCN (0.050 mg, 0.5 mmol) in 0.5 mL of hexane was stirred for 20 h, following the reaction by GC. No trace of the product was detected under these conditions.

Reaction of Epoxycyclohexane with TMSCN in the Presence of the Salen Ligand Only. A mixture of the epoxide (0.049 g, 0.5 mmol), TMSCN (0.050 g, 0.5 mmol), and the ligand **L**₄ (0.02 equiv) in 0.5 mL of hexane was stirred for 18 h, following the reaction by GC. No trace of the product was detected under these conditions.

Reaction of Epoxycyclohexane with TMSCN in the Presence of Y-Amide Only. A mixture of epoxycyclohexane (0.049 g, 0.5 mmol), TMSCN (0.05 g, 0.5 mmol), and Y[N(SiMe₂H)₂]₃·2THF (0.01 equiv) in CH₂Cl₂ (0.5 mL) was stirred, and the reaction was followed by GC. No trace of the expected product was detected up to 3 h.

Reaction of Epoxycyclohexane with TMSCN in the Presence of Stoichiometric Amount of the Catalyst. An NMR Study. In a nitrogen-filled drybox, the catalyst (**L**₄)Y[N(dms)₂](THF) (0.030 g, 0.03 mmol) was dissolved in 1 mL of toluene-*d*₈. Both ¹H and ¹³C NMR spectra of this sample were recorded. Among the most discernible lines are three sets of Si-Me's (three doublets between δ 0.06 and 0.16, *J* = 3 Hz in the proton NMR and three singlets at δ 0.17, 3.22, and 3.28 in the carbon NMR) and a broad doublet between δ 3.40 and 3.70, which has been assigned to the CH₂O protons of the coordinated THF. The Si-H protons appear as three distinct multiplets at δ 4.66, 4.79, and 4.93 in a ratio of 0.09:0.35:0.05, clearly suggesting that several geometric isomers maybe present in solution. The residual protons of toluene-*d*₈ appearing at δ 2.09 were used to calibrate the changes in intensities of the other protons. After 10 min, epoxycyclohexane (0.003 g, 0.03 mmol, 1 equiv) was added, and the NMR was recorded again after 10 min and 22 h. The spectra remain unchanged over this period of time. A new broad doublet in the ¹H NMR that appears at δ 2.93 and 3.01 is most likely from the epoxycyclohexane. In the ¹³C

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spectrum new peaks appear at δ 24.39, 24.46, and 53.84, and these are assigned to the epoxide. The Si-Me signals show some dispersion; now each of the three doublets appear at δ 0.103, 0.219, and 0.277. The corresponding ¹³C signals appear at δ 0.57, 3.95, and 4.11. Careful examination of the spectra revealed no changes in any of the major absorptions over the 22 h between the two recordings. The absence of any significant new peaks between δ 3 and 4 suggests that the coordinated amide most likely *does not* open the epoxide. Further GC analysis indicated no new products are formed under these conditions. Finally, the presence of unreacted epoxide in the mixture was confirmed by addition to the above solution of 1 equiv (0.003 g) of TMSCN. The broad signals at δ 2.905 and 2.975 gradually disappear, and new TMS peaks appear at δ 0.58 and δ -2.54 in the ¹³C NMR spectrum. Workup of the reaction and isolation of the major product confirms the structure of the product as the expected cyanohydrin-TMS ether by GC and NMR.

A Typical Procedure for Ring Opening of Epoxycyclohexane with TMSCN Using Lanthanide Complexes (Table 2). To a CH₂-Cl₂ solution (0.5 mL) of catalyst was added epoxide (0.049 g, 0.5 mmol), the solution was stirred at room temperature for 5 min, and TMSCN (0.05 g, 0.5 mmol) (neat) was added slowly and dropwise to the stirred solution of epoxide and catalyst. The reaction was monitored by GC and the stirring continued until completion (see Table 2 for the exact times). After completion of the reaction, the mixture was passed through a short silica column, and evaporation of the solvent gave clean product.

A Typical Procedure for Solvent-Free Ring Opening of Epoxycyclohexane with TMSCN Using [L₄]Y[N(SiMe₂H)₂]₂·[THF] (Table 3). In a 10 mL vial was dissolved [L₄]Y[N(SiMe₂H)₂]₂·[THF] (2.5 mg, 0.0025 mmol) in epoxycyclohexane (~5 mmol, 500 mg), the yellow solution was stirred for 5 min, and 50 mg of this mixture (~0.00025 mmol catalyst + 0.5 mmol epoxycyclohexane) was transferred to another vial. To this was added 200 mg (2 mmol) more of epoxycyclohexane (epoxide/catalyst 10000). To a 50 mg sample of this solution (0.5 mmol of epoxide and 0.00005 mmol of catalyst) was added TMSCN (50 mg, 0.5 mmol) slowly and dropwise at rt. The reaction mixture was stirred for 4 h to get complete conversion of epoxide to the desired product. The crude mixture was passed through a short silica gel column, and evaporation of the solvent gave the clean product in nearly quantitative yield (enantioselectivity 56%).

A Typical Procedure for Solvent-Free Ring Opening of Epoxycyclohexane with TMSN₃ Using [L₄]Y[N(HSiMe₂)₂]₂·[THF] (Table 4). To another 50 mg sample of epoxycyclohexane and the catalyst (0.5 mmol of epoxide and 0.00005 mmol of catalyst) from the above experiment was added TMSN₃ (58 mg, 0.5 mmol) slowly and dropwise at rt. The reaction mixture was stirred for 38 h to get complete conversion of epoxide to the desired product. The crude mixture was passed through a short silica gel column, and evaporation of the solvent gave the clean product in nearly quantitative yield (enantioselectivity 29%).

General Procedure for Ring-Opening of *meso*-Epoxides (2–4) with TMSCN Using Chiral Yttrium Complex [L₄]Y·[N(SiMe₂H)₂]₂·[THF] (Table 4). To a CH₂Cl₂ solution (0.5 mL) of catalyst was added epoxide (0.5 mmol), the yellow solution was stirred at room temperature for 10 min, and TMSCN (neat) (0.50

mmol) was added slowly and dropwise to the stirred solution of epoxide and catalyst. The reaction was monitored by GC. After completion of the reaction, the mixture was passed through a short silica gel column, and evaporation of the solvent gave clean product in nearly quantitative yield in almost every case.

(1R,2S)-2-Trimethylsilyloxycyclopentane-1-carbonitrile (from Epoxide 2). Spectroscopic data were identical with the literature value.^{3b} Enantiomer separation: chiral GC analysis (Cyclodex-B column, 90 °C for 25 min, 1 °C/min, *t_R* (minor) = 34.54 min, *t_R* (major) = 35.51 min).

Yttrium-Catalyzed Reaction of Epoxycyclohexane with 2 M HCN in Toluene. To a toluene solution of epoxycyclohexane (0.049 g, 0.5 mmol) and [L₄]Y[N(dms)₂]₂·[THF] (0.005 g, 0.005 mmol) was added 2 M HCN in toluene¹⁹ (0.28 mL, 0.56 mmol) slowly, in a dropwise manner, and the reaction mixture was stirred at room temperature. A small amount of the reaction sample was analyzed by GC periodically in every 2 h interval to determine the conversion of the reaction until 8 h. No ring opening of the epoxide with HCN was observed. The reaction mixture was stirred for another 10 h, and final analysis of the crude reaction mixture using GC and proton NMR also showed no ring opening with HCN.

Procedures for Yttrium-Catalyzed Reactions of Epoxycyclohexane with TMSCN and TMSN₃ in the Presence of Cp₂ZrMe₂. To a CH₂Cl₂ solution (0.5 mL) of epoxycyclohexane (0.05 g, 0.5 mmol) and TMSCN [or TMSN₃ (0.5 mmol)] was added Cp₂ZrMe₂ (0.01 mmol). The reaction mixture was stirred at rt for 10 min, yttrium complex [L₄]Y[N(dms)₂]₂·[THF] (0.0085 mg, 0.01 mmol) was added, and stirring was continued until the complete consumption of epoxide (based on GC analysis). No inhibition of the reaction was observed under these conditions.

Probing the Nonlinear Effect. For this experiment the two enantiomerically pure ligands L₄ and *ent*-L₄ were mixed in the appropriate ratios, and the catalysts were prepared as described earlier. The reaction was run under standard conditions using 1 mol % of catalyst. After all the starting material was consumed, the product was isolated and analyzed by gas chromatography to ascertain the enantiomeric excess. The ee of the product is plotted against the ee of the starting ligand (see the Supporting Information for the graph). A linear relationship (*R*² = 0.989) between the two ee's indicates the absence of nonlinear effects in this reaction.

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Supporting Information Available: Full experimental procedures, ORTEP representation of **6** with details of the X-ray analysis, and chromatographic data for enantiomeric mixtures listed. Details of the kinetic measurements and the graphical representations of data including the plots of *k*_{obs} vs [cat. concn] and *k*_{obs} vs [cat. concn]². This material is available free of charge via the Internet at <http://pubs.acs.org>.

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