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Mechanistic Studies of the Zirconium−Triisopropanolamine-Catalyzed Enantioselective Addition of Azide to Cyclohexene Oxide[†]

Brent W. McCleland,[1] William A. Nugent,*[,2] and M. G. Finn*[,1]

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901, and The DuPont Company, Central Research and Development, P.O. Box 80328, Wilmington, Delaware 19880-0328

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The mechanism of the enantioselective ring-opening of cyclohexene oxide by Me_3SiN_3, catalyzed by zirconium complexes of the C_3-symmetric ligand (+)-(*S*,*S*,*S*)-triisopropanolamine, has been investigated. Measurements of molecular weights of precatalyst species show that complexes are formed with average trimeric aggregation. Kinetics measurements reveal the overall process to be approximately half order in total zirconium, epoxide, and Me_3SiN_3 components. The reaction also shows a strong nonlinear relationship between enantiomeric excess of product azido ether vs the incorporation of (*R*,*S*,*S*)-triisopropanolamine ligand in the catalyst mixture. On the basis of these and other results, a preequilibrium interconversion of dimeric and tetrameric zirconium−triisopropanolamine species is proposed to occur rapidly with respect to the rate of epoxide ring-opening, with the dimeric form being the active catalyst. The reaction is accelerated by silyl ethers or by small amounts of water or alcohol, whereas larger amounts of protic additives inhibit the reaction. Enantioselectivity is eroded at catalyst concentrations less than 1 mole-percent and at high concentrations of cyclohexene oxide. Both enantioselectivity and rate are influenced to a small extent by the nature of the silyl azide employed for the first catalytic turnover, suggesting that a silyl fragment becomes irreversibly incorporated in the catalyst structure. It is proposed that catalytic activity requires the cooperative action of two zirconium centers for the binding and delivery of azide to epoxide.

The enantioselective ring-opening of *meso*-epoxides has emerged as a powerful methodology for the asymmetric synthesis of useful chiral amino alcohols and related compounds.[3] Enzymes,[4] early transition metal Lewis acid catalysts,[5] and chiral lithium amide bases,[6,5g] have been developed for this purpose. The current state of the nonenzymatic art (Scheme 1) is defined by two catalysts that mediate the delivery of silyl azide nucleophiles: zirconium complexes of the C_3-symmetric ligand (+)-(*S*,*S*,*S*)-triisopropanolamine (**1**),[7] and chiral salen complexes of chromium.[8] The titanium complexes of **1** and related ligands have also been employed for the catalytic asymmetric oxidation of sulfides.[9]

The mechanistic details of the Lewis acid catalyzed silyl azide opening of epoxides are intriguing from several perspectives. Enantiomeric discrimination is likely be the result of two events, which present a unique topological challenge: binding of the epoxide by the chiral catalyst, and attack of azide nucleophile in S_N2 fashion with selectivity for one of the resulting diastereotopic epoxide carbons. Silyl azides alone are unreactive and so must undergo an activation process, for which a metal center may also be required.

Here we report the results of kinetic and structural studies of the zirconium-triisopropanolamine system. Several precatalyst species are shown to be of average trimeric molecular weight, and the kinetic rate law for the catalytic process is reported. On the basis of these results, an equilibrium between dimeric and tetrameric zirconium complexes is proposed, with the dimer being much the more active and enantioselective catalyst. In addition, investigations of the effects of water, alcohol, and silyl ether additives are described, suggesting an interesting dependence of turnover rate on the rate of alkoxide−azide exchange.

[†] Dedicated to the memory of the late Dr. Maurice Caron.

[1] University of Virginia.

[2] DuPont Central Research.

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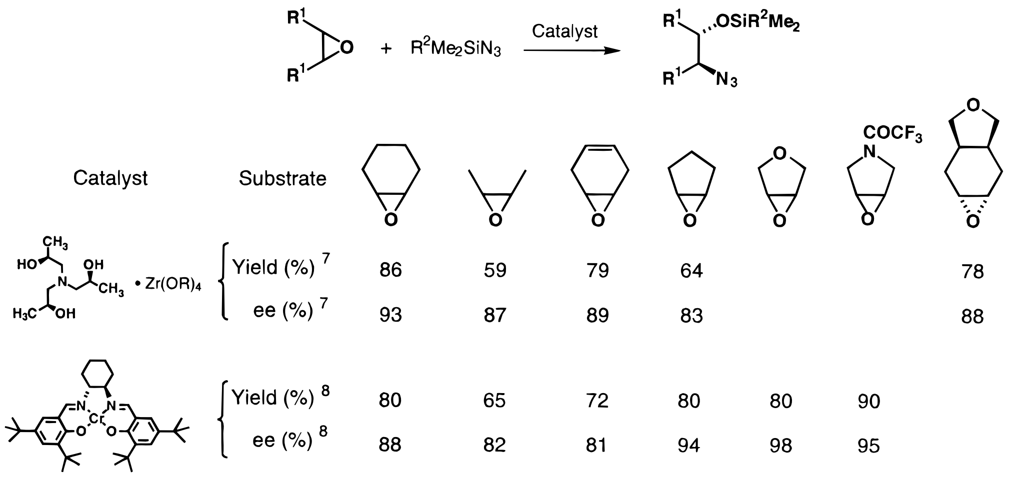
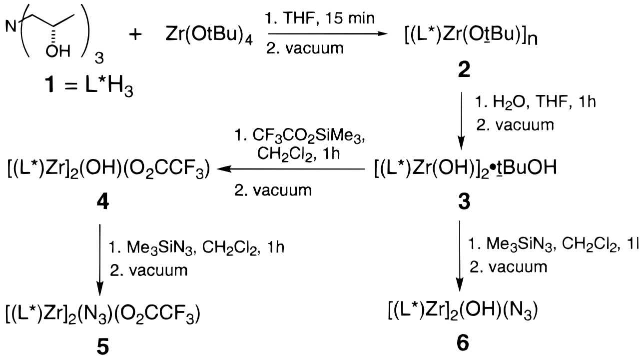
Scheme 1

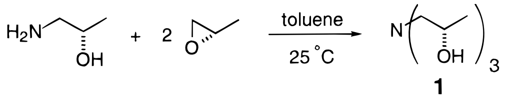


Scheme 2



Results

Precatalyst Preparation. (+)-(S,S,S)-Triisopropanolamine, **1**, was prepared by combining (S)-(+)-1-amino-2-propanol and (S)-(−)-propylene oxide according to eq 1.[7] Exposure of **1** to Zr(OtBu)$_4$ in THF followed by

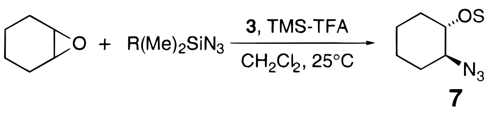


(1)

evaporation of the solvent gave a crystalline white powder, **2** (Scheme 2), in quantitative yield. As originally reported,[7a] the required treatment of **2** with approximately 1 equiv of water was performed in THF; evaporation of the solvent provided “precatalyst” **3**, a white solid in 83% yield. The composition of **3** is formulated on the basis of its elemental analysis.[7a]

Complex **3** was activated for use by treatment with 0.5 equiv of trimethylsilyl trifluoroacetate per zirconium, forming the species designated **4**, which may be used in situ or may be isolated by evaporation. Addition of the same amount of Me_3SiN_3 to **3** and **4** generates **6** and **5**, respectively. Complex **6** is not directly relevant to the catalytic process, since $Me_3SiOCOCF_3$ is required for high enantioselectivity. Elemental analyses and IR spectra of complexes **4** and **5** are consistent with the molecular compositions shown in Scheme 2, showing that hydroxide ligands are successively replaced by trifluoroacetate and azide, presumably with loss of Me_3SiOH in each case. Azide-for-alkoxide ligand substitution reactions are well-known,[10] although the involvement of a hydroxide ligand in such an exchange is unusual. Given the tendency for hydroxyl groups to bridge metal centers and the electron-withdrawing nature of the trifluoroacetate ligand, these modifications are likely to boost the Lewis acidity and perhaps the conformational flexibility of the catalyst. The NMR spectra of these complexes are complicated by the presence of more than one species in solution and therefore yield little information about structure. Spectroscopic data are included as Supporting Information.

All precatalyst batches were screened for activity in a standard ring opening of cyclohexene oxide with Me_3SiN_3 (eq 2), and only those which afforded high ee and yields were used for kinetic, molecular weight, and NMR studies. Reproducible rates and enantioselectivities are obtained when the triisopropanolamine ligand has the correct melting point (see Experimental Section). The standard reaction procedure consists of mixing precatalyst **3** with $Me_3SiOCOCF_3$, followed by addition of a solution of Me_3SiN_3 and cyclohexene oxide at ambient temperature. For convenience and relevance to molecular weight measurements, all studies except for the investigation of ee vs enantiomeric purity of the triisopropanolamine ligand were conducted in CH_2Cl_2 instead of the previously reported chlorobenzene and 1,2-dichlorobutane solvents, resulting in a loss of only 2−5% enantiomeric excess under standard conditions and no reduction in product yields.



(2)

Molecular Weight Measurements. The molecular weights of the zirconium complexes shown in Scheme 2 were determined by the Signer method[11] (a variation of vapor phase osmometry) in CH_2Cl_2 using Ti(OiPr)$_4$ as the

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Table 1. Molecular Weight Measurements

compd	obsd MW (g/mol)	calcd MW (g/mol)	molecularity
$Zr(OtBu)_4$	417	383.7	1.1
3	882	333.5[a]	2.6
3	968	333.5[a]	2.9
4	1165	344.5[a]	3.3
4	1230	344.5[a]	3.5
5	953	357.0[a]	2.7
6	1002	309.0[a]	3.2

[a] Calculated molecular weight per Zr atom based on formulation derived from elemental analysis (Scheme 2).

molecular weight standard; the results are collected in Table 1. The molecular weights of each of the trialkanolamine complexes indicate an approximate average trimeric aggregation state, within the 10−20% experimental error normally assigned to the technique.[12]

Complex **5** catalyzes the addition of azide to cyclohexene oxide in clean fashion, but with an enantiomeric excess that is both diminished and widely variable (49−72% ee for four runs). Thus, **5**, formed by pretreatment of the $Me_3SiOCOCF_3$ conditioned precatalyst (**4**) with 0.5 equiv of Me_3SiN_3 followed by removal of volatile components under vacuum, is somehow different than the catalyst species produced from **4** and an excess of Me_3SiN_3. A marked difference in the ^1H and ^{13}C NMR spectra of the two systems is evident, but the complexities of the spectra preclude detailed structural analysis. The latter mixture (**4** + excess Me_3SiN_3) can retain an active hydroxyl group, whereas evaporation in the synthesis of complex **5** can drive the loss of hydroxyl as Me_3SiOH. To test this hypothesis, a sample of complex **5** was divided into two portions. One was treated with excess Me_3SiN_3 and cyclohexene oxide in dry CH_2Cl_2 and found to catalyze the production of **7** in 72% ee. The second portion of **5** was treated with 0.5 equiv of water (with respect to total Zr) in the form of wet CH_2Cl_2 and then used as before, leading to the production of **7** in 83% ee, which matches the value obtained using precatalyst **4** and excess Me_3SiN_3 in dry solvent without evaporation. The mechanistic consequences of retaining a catalytic amount of active protic functionality are discussed below.

Effects of Diastereomeric Ligand Impurities. (*R*,*S*,*S*)-Triisopropanolamine, **8**, was prepared from (*R*)-(−)-1-amino-2-propanol and (*S*)-(−)-propylene oxide and was used to explore the effect of a stereochemical impurity in the catalyst system. Two sets of experiments were performed: (1) precatalysts **3** prepared separately from pure (*S*,*S*,*S*)- and (*R*,*S*,*S*)-triisopropanolamines were mixed in varying proportions prior to addition of $Me_3SiOCOCF_3$, Me_3SiN_3 and cyclohexene oxide; and (2) mixtures of (*S*,*S*,*S*)- and (*R*,*S*,*S*)-triisopropanolamine ligands were used to prepare and test the zirconium catalyst in the standard fashion.

$$2\,L^*{}_2Zr_2X_2 \xrightleftharpoons{K_{eq}} L^*{}_4Zr_4X_4 \qquad (3)$$

$$L^* = \mathbf{1},\ X = OR,\ N_3$$

In the first instance, product enantiomeric excess was remarkably insensitive to the presence of the (*R*,*S*,*S*)-isomer until approximately 80% of the catalyst mixture was composed of the system derived from **8** (Figure 1, squares). Note that pure (*R*,*S*,*S*)-catalyst gives essentially racemic product. When ligands are mixed prior to catalyst formation (Figure 1, circles), enantiomeric excess is substantially more sensitive to the presence of >50% (*R*,*S*,*S*)-triisopropanolamine **8**.[13]

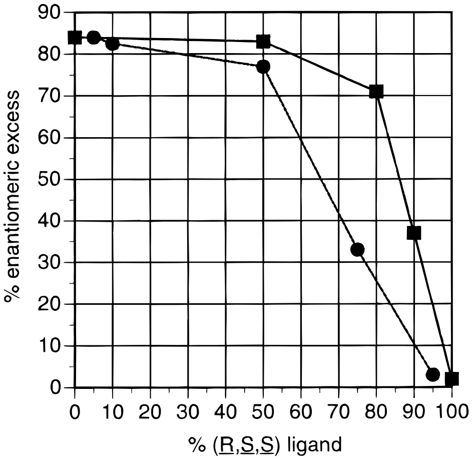

Figure 1. Results of mixed ligand studies (squares = mixtures of catalysts; circles = mixtures of ligands).

Kinetics. Reaction rates were measured under catalytic conditions either by following the disappearance of Me_3SiN_3 by IR spectroscopy or by monitoring the appearance of products in quenched aliquots by chiral capillary GC. Sample data and plots for the determination of rate constants using each technique appear as Supporting Information. When followed by IR spectroscopy, disappearance of Me_3SiN_3 and appearance of **7** occur in an isosbestic fashion. While less convenient, GC analysis is more informative: the use of an internal standard allowed for simultaneous determination of absolute rate as well as enantiomer ratios and demonstrated the overall clean nature of the reaction. Rate measurements were obtained by following each reaction from approximately 2% completion to between 10% and 25% completion. Interestingly, all reactions exhibited a gradual increase in rate and enantioselectivity over the first catalytic turnover,[14] and also showed rate accelerations to varying small degrees at greater than 25% completion. Complete kinetics results are collected in the Supporting Information.

By individually varying component concentrations over ranges of 10- to 45-fold, the rate order in each component

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[13] These observations closely resemble the phenomenon of “nonlinear” relationships between the enantiomeric composition of a chiral catalyst and the enantiomeric excess of its catalyzed process, first identified by Kagan and co-workers. For examples, see the following references. (a) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357. (b) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430−9439. (c) Zhang, S. Y.; Girard, C.; Kagan, H. B. *Tetrahedron: Asymmetry* **1995**, *6*, 2637−2640, and references therein. (d) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832−4842; see also ref 30b. (e) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363−2364. (f) Kitamoto, D.; Imma, H.; Nakai, T. *Tetrahedron Lett.* **1995**, *36*, 1861−1864. (g) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusagawa, F. *Organometallics* **1994**, *13*, 2218−2229. (h) Terada, M.; Mikami, T.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623−1624. (i) Rossiter, B. R.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; Vickers, D.; Fluckiger, E.; Patterson, G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965−986. (j) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 7624−7626. See also ref 28c.

[14] A typical reaction resulting in a final ee of 82% starts out at approximately 60−65% ee over the first 1−2% of the reaction (corresponding approximately to one-half the amount of total zirconium) and then rises quickly to the steady-state value. The reaction rate varies similarly.

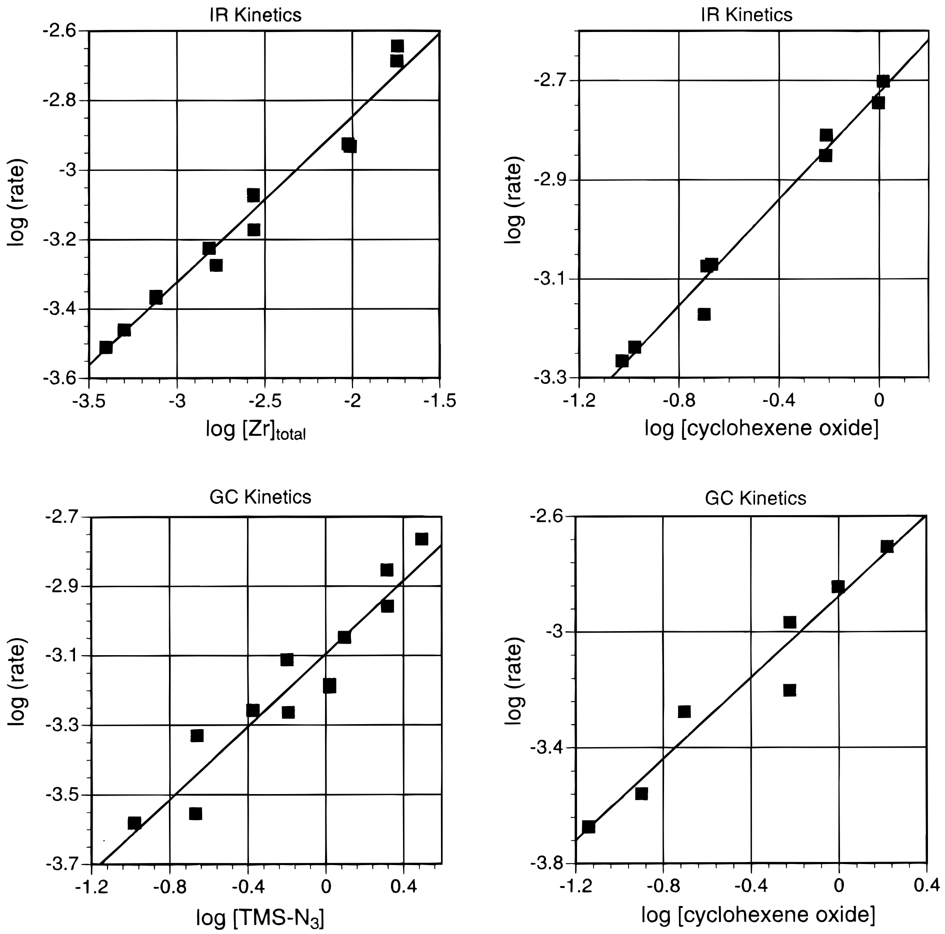


Figure 2. Determinations of kinetic rate order in each reaction component.

Table 2. Component Rate Orders from Kinetic Studies

component (technique)	rate order	R^2	concn range (M)
Zr_{total} (IR)	0.48 ± 0.06	0.97	0.000452−0.0203
epoxide (IR)	0.54 ± 0.06	0.98	0.105−1.035
epoxide (GC)	0.73 ± 0.10	0.98	0.072−1.661
$TMSN_3$ (GC)	0.53 ± 0.12	0.92	0.104−3.13

was found to be approximately 0.5 by plotting log(rate) vs log[component] (Figure 2 and Table 2). The two techniques used to measure rate dependence on cyclohexene oxide give roughly equivalent results.

Plots of enantiomeric excess at 20% consumption of epoxide vs component concentration (holding all other components at constant concentration) are shown in Figure 3. Enantioselectivity is very sensitive to catalyst concentration below approximately 1 mol % total Zr relative to substrate epoxide, but is invariant to Zr complex concentration above that level. Enantiomeric excess appears to increase over a modest range in direct proportion to Me_3SiN_3 concentration, although ee values are increasingly erratic as Me_3SiN_3 concentrations are increased. [The determination of rate order in Me_3SiN_3 is likewise the most erratic (Figure 2, Table 2).] Most striking is the drop in ee observed as the starting concentration of cyclohexene oxide is increased. Several attempts were made to improve enantioselectivity by manipulating the reaction according to the these trends. Thus, reactions were performed at high catalyst and Me_3SiN_3 concentrations and low levels of cyclohexene oxide, achieved by adding a solution of epoxide to a mixture of precatalyst **3**, $Me_3SiOCOCF_3$, and Me_3SiN_3 over 10−15 h by syringe pump. Although the ee was increased slightly under these conditions (from 78% to 81−84%), the results were not sufficiently promising to encourage additional optimization.

The aforementioned observation of increasing rate past 25% completion suggests that product azidosilyl ether may have an accelerating effect on the process. To probe this possibility, reactions performed in the presence of added silyl ethers, as well as alcohols, water, and molecular sieves, were followed by GC. Complete results of this study are collected in the Supporting Information and are summarized in Table 3 below. The reaction rate was found to increase by factors of 1.4−2.5 in the presence of these additives, with the following significant observations.

(1) Rate accelerations were observed upon the addition of large amounts (approximately 150 times the total zirconium concentration, or roughly equimolar with substrate) of silyl ethers (Table 3, entries 1−6, 8−10). The magnitude of rate acceleration is roughly proportional to the concentration of silyl ether additive over a small range of rates. An analogous dialkyl ether (*t*BuOMe) does not have the same effect: at a comparable concentration, as the reaction rate is slightly diminished (entry 7).

(2) Smaller amounts of cyclohexanol and water (approximately 10 times the total Zr concentration) boost the rate, but the reaction is strongly inhibited by larger amounts of these protic additives (Table 3, entries 11−12, 16−21). The magnitudes of the largest rate acceleration for each additive are similar. For the addition of

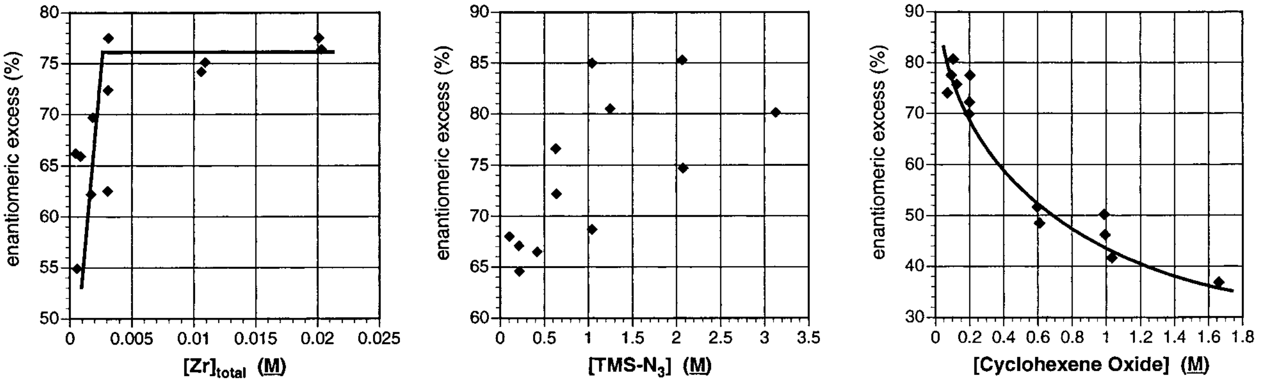


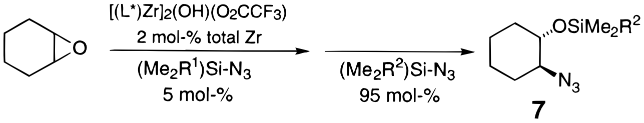
Figure 3. Plots of enantiomeric excess at 20% completion vs starting component concentration.

Table 3. Reaction Rate Variations with Additives

entry	additive^a	[additive]/ [epoxide]^b	relative rate	% ee
1	none	*c* or *d*	1.0	84
2	CyOSiMe$_3$	1.5^c	1.4 ± 0.1	86
3	CyOSiMe$_3$	4.6^c	1.6 ± 0.2	87
4	CyOSiMe$_2$*i*Pr	2.2^c	2.1 ± 0.2	86
5	CyOSiMe$_2$*t*Bu	1.4^c	1.6 ± 0.1	85
6	CyOSi(*i*Pr)$_3$	1.3^d	1.9 ± 0.1	78
7	*t*BuOMe	1.4^d	0.78 ± 0.1	79
8	*n*-C$_5$H$_{11}$OSiMe$_3$	0.30^c	1.3 ± 0.1	85
9	*n*-C$_5$H$_{11}$OSiMe$_3$	0.50^c	1.4 ± 0.1	85
10	*n*-C$_5$H$_{11}$OSiMe$_3$	2.60^c	1.8 ± 0.1	86
11	CyOH	0.19^d	2.5 ± 0.2	85
12	CyOH	1.2^d	very slow	35^e
13	*n*-C$_5$H$_{11}$OH	0.35^d	2.5 ± 0.2	83
14	CyOSiMe$_3$ + CyOH	3.9 + 0.0055^c	1.7 ± 0.1	86
15	CyOSiMe$_3$ + CyOH	3.5 + 0.046^c	1.9 ± 0.1	86
16	H_2O	0.63^d	0	–
17	H_2O	0.32^d	0.79 ± 0.1^f	79
18	H_2O	0.16^d	2.2 ± 0.2	88
19	H_2O	0.10^d	2.1 ± 0.2^f	85
20	H_2O	0.073^d	1.3 ± 0.1	85
21	H_2O	0.027^d	1.3 ± 0.1	82
22	4 Å sieves	–	0.2 ± 0.02	54

[a] Cy = cyclohexyl. [b] Equivalents of additive relative to starting concentration of cyclohexene oxide; $[Zr]_{total}$ = 1.4 mol % of starting epoxide concentration for all runs. [c] $[TMSN_3]$ = 4.7–5.0 times that of starting epoxide concentration. [d] $[TMSN_3]$ = [epoxide]. [e] After two weeks at room temperature. [f] Relative rate corrected for mismatch in $[TMSN_3]$ when compared to the analogous reaction without additive.

Table 4. Reactions Involving the Sequential Addition of Silyl Azides



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entry	azide no. 1	azide no. 2	solvent	temp, °C	% ee	rate (× 10^{-4} s^{-1})
1	none	Me$_3$SiN$_3$	CH_2Cl_2	24	82	7.9 ± 0.2
2	none	(*i*Pr)Me$_2$SiN$_3$	CH_2Cl_2	24	78	6.4 ± 0.3
3	(*i*Pr)Me$_2$SiN$_3$	Me$_3$SiN$_3$	CH_2Cl_2	24	75	6.6 ± 0.2
4	Me$_3$SiN$_3$	(*i*Pr)Me$_2$SiN$_3$	CH_2Cl_2	24	82	7.6 ± 0.2
5	none	Me$_3$SiN$_3$	C_6H_5Cl	0	88	
6	none	(*i*Pr)Me$_2$SiN$_3$	C_6H_5Cl	0	92	
7	(*i*Pr)Me$_2$SiN$_3$	Me$_3$SiN$_3$	C_6H_5Cl	0	93	

water, enantiomeric excess follows roughly the same trend as rate. The trimethylsilyl ether of cyclohexanol is not formed from the alcohol to an extent detectable by capillary GC analysis.

(3) The magnitude of the rate acceleration is insensitive to the steric nature of both the silyl (Table 3, entries 2–6) and alcohol (entries 2–6 vs 8–10) components of silyl ethers.

(4) Product azidosilyl ether **7** is formed exclusively with the SiMe$_3$ unit; no silyl group crossover is observed even in the presence of large amounts of other silyl ethers. (Note in this context that the SiMe$_2$*i*Pr group is a competent component of the catalytic process when its azide is employed; see below).[7a]

(5) When silyl ethers and cyclohexanol are both present, the observed rate enhancement is no greater than the effect produced by either additive alone (Table 3, entries 14 and 15).

(6) The increase in reaction rates observed in the absence of additives at greater than 20–30% completion is not observed in the presence of additives.

(7) The addition of 4 Å molecular sieves, which has been shown to increase the activity of other d^0 early metal alkoxide catalyst systems,[15] has a deleterious effect on both the rate and enantioselectivity in the present case (Table 3, entry 22). (Pretreating a solution of the precatalyst **3** with molecular sieves has no effect on the subsequent reaction.) This result is expected, since the anhydrous complex **5** was found to be a poor catalyst, as discussed above. We have also observed by IR spectroscopy that Me$_3$SiN$_3$ is removed from solution in the presence of sieves, presumably by entrainment of the azide functionality at the zeolite surface. This may also contribute to the reduction of both rate and enantioselectivity, the latter according to the trend observed in Figure 3.

Consistent with the data outlined above, the Zr-triisopropanolamine catalyst is not adversely affected by modest exposure to atmospheric moisture. Precatalyst **3** was stored as a solid in air for 3 days and then used in a standard reaction under nitrogen with no loss in yield or enantiomeric excess compared to freshly prepared catalyst under the same conditions. The same result was also obtained when precatalyst **3** (freshly prepared under nitrogen) was treated with Me$_3$SiOCOCF$_3$, Me$_3$SiN$_3$, and cyclohexene oxide in air and allowed to react under a short CaCl$_2$-packed drying tube.

Finally, the effect of the nature of the silyl group on rate and enantioselectivity was probed with the experiments shown in Table 4. When used in chlorobenzene solvent at 0 °C (entry 6), *i*PrMe$_2$SiN$_3$ and cyclohexene

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(15) (a) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922–1925. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940–1941. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949–3954.

oxide provide azido ether **7** in 92% ee, matching the published result.[7a] Under the same conditions, Me_3SiN_3 gives the analogous **7** in 88% ee (entry 5). In CH_2Cl_2 at 24 °C (the conditions of the kinetics experiments reported here), the opposite trend is observed: *i*$PrMe_2SiN_3$ gives **7** in 78% ee (entry 2), whereas Me_3SiN_3 engages in a slightly more enantioselective reaction (82% ee; entry 1). Furthermore, the bulkier azide shows a much longer "induction period" of approximately 14 h compared to 40 min for Me_3SiN_3, comprising one slow turnover cycle, during which the rate increases to a "steady-state" value slightly less than the $Me_3Si{-}N_3$ case. Thus, the nature of the silyl group plays a small but significant role in both enantioselectivity and rate.

If a mixture of epoxide and catalyst in CH_2Cl_2 is treated first with 5 mol % Me_3SiN_3 (with respect to epoxide) and the azide is allowed to react completely before the introduction of 95 mol % *i*$PrMe_2SiN_3$, the *i*$PrMe_2Si$-substituted product is formed in 82% ee (the characteristic value for Me_3SiN_3 under these conditions) at a rate that is very similar to the reaction performed with Me_3SiN_3 alone (Table 4, entry 4). The converse experiment, initial addition and reaction of 5 mol % *i*$PrMe_2SiN_3$, followed by 95 mol % Me_3SiN_3, gives the Me_3Si-containing product in 75% ee (the characteristic *i*$PrMe_2SiN_3$ value) at a rate that matches that of *i*$PrMe_2SiN_3$ alone (entry 3). In each case, no induction period is observed for the reaction of the second azide. Thus, enantioselectivity is modulated by the first silyl group to be introduced. The same observation is made in chlorobenzene solvent, in which a higher enantiomeric excess is achieved with Me_3SiN_3 by the preliminary reaction of a small amount of *i*$PrMe_2SiN_3$ (entry 7).[16]

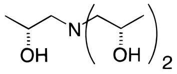
Discussion

Complex Molecularity and Ligand Exchange. The preservation of substantial enantioselectivity in reactions catalyzed by mixtures of highly enantioselective (*S*,*S*,*S*)- and nonselective (*R*,*S*,*S*)-triisopropanolamine complexes (Figure 1) shows that the enantioselective species is much more active. For example, a 4:1 mixture of catalysts derived from (*R*,*S*,*S*)-**8** and (*S*,*S*,*S*)-**1** affords azidosilyl ether **7** in approximately 70% ee, implying that the rate of reaction catalyzed by the (*S*,*S*,*S*)-species is approximately 20 times that of the (*R*,*S*,*S*)-system.[17] Furthermore, the fact that different results are obtained by mixing preformed catalysts vs preparing catalysts from the mixed ligands (Figure 1) shows that the active catalyst species is not a monomeric Zr·triisopropanolamine complex (in contrast to the titanium system using the same ligand),[7b,9] and that exchange of triisopropanolamine ligands among zirconium complexes is slow. From a practical standpoint, it is clear that a small amount of epimeric impurity in the form of an (*R*,*S*,*S*)-diastereomer is not detrimental to the enantioselectivity of the epoxide ring-opening process. Molecular weight measurements of a variety of Zr·**1** complexes show average trimeric aggregation states for each (Table 1), consistent with the conclusion that a catalyst of higher aggregation state is involved.

The kinetics experiments reported above comprise a determination of the following experimental rate equation, showing approximately half-order dependence of rate on each reaction component:

$$\text{rate} = k[\text{cyclohexene oxide}]^{0.63}[\mathrm{Me_3SiN_3}]^{0.53}[\mathrm{Zr_{total}}]^{0.48},$$

where $[Zr_{total}]$ denotes the total concentration of zirconium atoms in solution. Given the stoichiometry of the epoxide ring-opening transformation, such a rate equation is quite unexpected and requires that a proportion of zirconium atoms added at increasing concentration be removed from the catalytic cycle. An aggregation equilibrium in which the higher molecular weight species is inactive (or less active) than the lower molecular weight species can account for such an observation. In particular, the half-order dependence on total zirconium concentration suggests two important conclusions: (1) a rapid equilibrium interconversion of dimeric,[18,9b] and tetrameric complexes occurs to give the observed average trimeric molecular weight in solution (eq 3),[19] and (2) the dimeric species is the kinetically dominant catalyst. In this way, the concentration of active catalyst (dimer) increases as the square root of the amount of total Zr·**1** added.[20] To be consistent with the observed nonlinear relationship between ligand composition and ee (Figure 1), such a dimer−tetramer equilibrium must occur without exchange of aminotriol ligands among metal centers.



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The data are also consistent with the proposition that, *when considering only the active catalyst*, the epoxide ring-opening process is first order in epoxide, Me_3SiN_3, and catalyst, as expected.[21] The observed half-order dependence on substrate and azide concentrations can arise from the presence of interconverting inactive (tet-

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[16] In this case, the reported result is achieved when Me_3SiN_3 is added following the consumption of 2 mol % of the epoxide with $^iPrMe_2SiN_3$, corresponding to one turnover with respect to total zirconium. If Me_3SiN_3 is added after only 0.5 mol % reaction, the ee of the Me_3Si-containing product is 89%. In all cases involving sequential addition of silyl azides, enantiomeric excess for the first azide produced is 50−70%.

[17] Assuming that no exchange of propanolamine ligands occurs, let *x* and *y* represent the rates of reaction catalyzed by the (*S*,*S*,*S*)- and (*R*,*S*,*S*)-complexes, respectively. Noting that the pure (*S*,*S*,*S*)-catalyst gives approximately 84% ee (92: 8 mixture of enantiomers), and the (*R*,*S*,*S*)-catalyst gives nearly racemic product,

$$70\%\ \text{ee} = \frac{85}{15} = \frac{1x{\cdot}92 + 4y{\cdot}50}{1x{\cdot}8 + 4y{\cdot}50}, \quad \text{which gives} \quad \frac{x}{y} = 20.$$

[18] For an example of a binuclear Zr-alkoxide employing a simple diol ligand, see: Galeffi, B.; Simard, M.; Wuest, J. D.*Inorg. Chem.* **1990**, *29*, 955−958.

[19] Trimeric molecular weights were measured at total zirconium concentrations of approximately 0.24 M. At this concentration, the observation of equal amounts of dimeric and tetrameric species, accounting for all of the zirconium alkoxide complexes in solution, leads to a calculation of K_{eq} = [tetramer]/[dimer]^2 = (0.04 M)/(0.04 M)^2 = 25.

[20] In other words, for equilibria between species of differing molecularity, higher aggregates are favored disproportionately at higher overall concentrations. The system can be analyzed as follows. From eq 3, $K_{eq} = [L^*_4Zr_4X_4]/[L^*_2Zr_2X_2]^2$. Total Zr concentration is defined as $Zr_{total} = 4[L^*_4Zr_4X_4] + 2[L^*_2Zr_2X_2]$. Combining the two equations and solving for the concentration of dimer in terms of Zr_{total}, one obtains an expression for $[L^*_2Zr_2X_2]$ that is proportional to the square root of $[Zr_{total}]$.

$$[L^*{}_2Zr_2X] = \frac{1}{4K_{eq}}\left(\sqrt{1 + 4K_{eq}[Zr_{total}]} - 1\right)$$

rameric) and active (dimeric) forms that are equally capable of binding the reaction components, assuming that exchange of monodentate ligands among these sites is fast with respect to the rate of the turnover-limiting step in the catalytic cycle. In such a system, only a fraction of the sites available for binding of azide and epoxide during a catalytic cycle are potentially "productive". In a manner related to the analysis of active catalyst concentration,[20] the population of these active sites by the required components (and therefore the reaction rate) would be predicted to rise as the square root of total amount of azide or epoxide added to the solution.[22]

Proposed Mechanism. Figure 4 shows a simplified proposed catalytic cycle. Dimeric precatalyst **9** is activated by exchange of an alkoxide or hydroxide ligand for azide to give **10**. Dimeric species can be in equilibrium with kinetically ineffective tetramers or other oligomers at any point in the catalytic cycle (not shown). Coordination of epoxide to one metal center is followed by intramolecular delivery of azide from the other Zr site to afford the intermediate azidoalkoxide complex **11**. Activation of azide by coordination to zirconium, rather than attack of silyl azide on bound epoxide,[5a] is necessary to explain its kinetic rate order.[22] Azide complexes of early metal alkoxides have been previously reported to be active nucleophiles toward epoxides.[10] The delivery of coordinated azide to epoxide cannot occur on a single metal center to afford the observed relative trans stereochemistry. Thus, we believe this reaction requires a bimetallic system for rapid and effective catalysis.

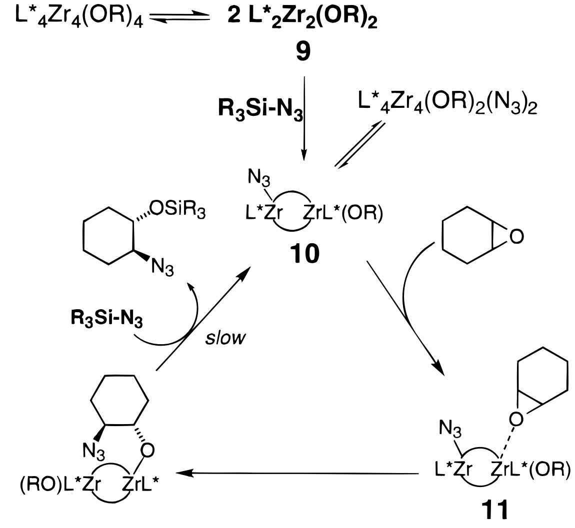

Figure 4. A proposed outline of the catalytic cycle.

Completion of the catalytic cycle requires exchange of azidoalkoxide for azide, releasing the silyl ether product. This is the only step in which added or product silyl ethers can have an impact on reaction rates without changing enantioselectivity (Table 3), and so ligand exchange is thereby identified as the turnover-limiting step. The independence of the accelerating effect of such additives on the size of the silyl and alkyl fragments makes the origin of the phenomenon difficult to probe. A direct reaction of R_3SiN_3 with Zr-alkoxide is the only route available for this step at early reaction times and in the absence of additives (the conditions under which the experimental rate law was determined). Additives may separately assist the ligand exchange process; for example, low concentrations of added alcohols or water may simply serve to maintain a small amount of HN_3 in solution, which is likely to participate in rapid ligand exchange.[23] (Alcohol and water in higher concentrations poison the process, presumably by competing with azide and epoxide for available ligand sites and/or irreversibly changing the catalyst structure.) However, we are presently unable to propose a mechanism for silyl ether-accelerated ligand exchange that does not require the transfer of silyl residues between alkoxides, which is not observed. The sensitivity of enantioselectivity to starting concentrations of epoxide (Figure 3) can be the result of several factors. One contributor could be an unselective

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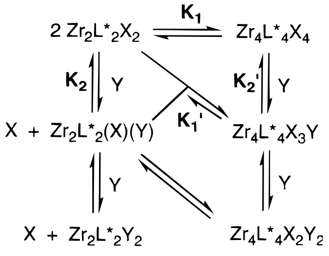
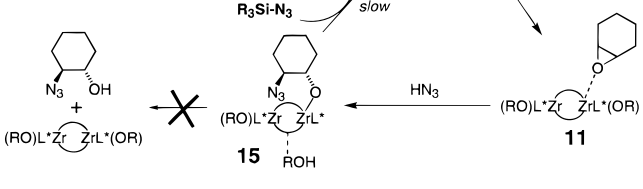
[21] An overall second-order rate law has been reported for the reaction of a titanium azide complex with styrene oxide: Blandy, C.; Gervais, D.; Suárez Cardenas, M. *J. Mol. Catal.* **1986**, *34*, 39–46.

[22] A simplified analysis follows. Suppose Y represents the monodentate component under consideration (azide or epoxide), which must exchange with a monodentate ligand X in order to bind to a metal center. $Zr_2L^*_2X_2$ and $Zr_4L^*_4X_4$ represent the "resting" forms of dimeric and tetrameric species, respectively. A set of equilibria governing some of the relevant ligand exchange events is represented below. If $Zr_2L^*_2(X)(Y)$, for example, is the "active" species, then the overall reaction rate will be proportional to its concentration, and an expression relating the total amount of added X to $[Zr_2L^*_2(X)(Y)]$ is desired.

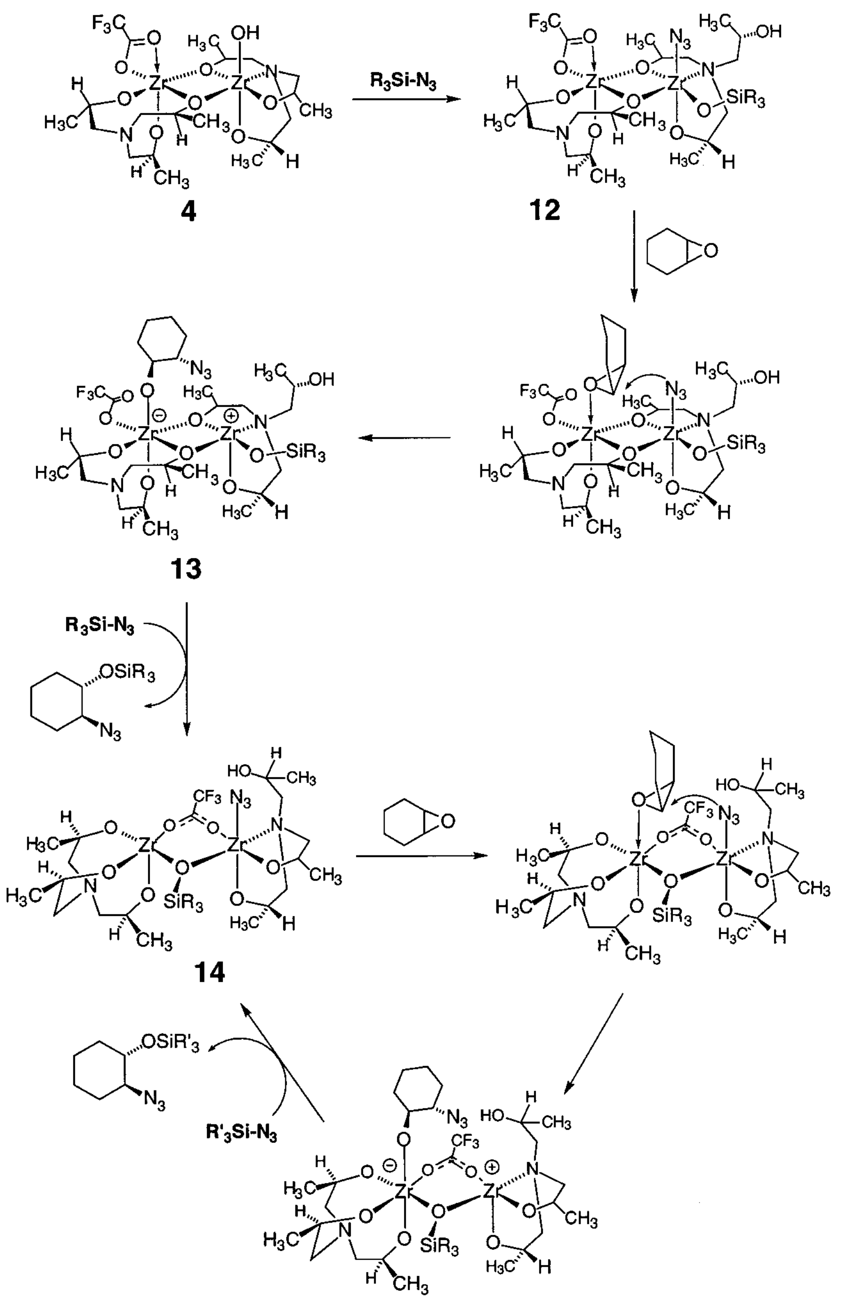


A simplified set of these interlocking equilibria involving the production of the monosubstituted complexes $Zr_2L^*_2(X)(Y)$ and $Zr_4L^*_4X_3Y$ was evaluated with the program MathCad. Using the four relevant equilibrium constant expressions (with $K_1 = K_{1'} = 25$,[19] and $K_2 = K_2' = 10^{-3}$) and expressions for total zirconium and total additive (X) concentrations as known quantities, the six unknowns in the system {$[Zr_2L^*_2X_2]$, $[Zr_4L^*_4X_4]$, $[Zr_2L^*_2(X)(Y)]$, $[Zr_4L^*_4X_3Y]$, $[X]_{free}$, and $[Y]_{free}$} were calculated for the concentrations employed in the catalytic experiments {$[Zr]_{total} = 0.028$ M, $[Y]_{added} = 0.05-3.5$ M}. A plot of log{$[Y]_{added}$} vs calculated log$[Zr_2L^*_2(X)(Y)]$ over this concentration range provides a nearly straight line ($R^2 = 0.9994$) with slope 0.47. This is consistent with the observed half-order dependence of reaction rate on total added epoxide or silyl azide, assuming that the dimer is the active catalyst. The mathematical model gives increasingly nonlinear plots over the latter portion of the concentration range for K_2 and $K_{2'}$ values greater than 0.01, but the slope of the log–log plot is very close to 0.5 no matter what the magnitude of K_2 and $K_{2'}$ below this value.

[23] A catalytic cycle employing HN_3, analogous to Figure 4, is shown below. The ROH moiety in structure **15** represents an alcohol ligand (an "arm" of the trialkanolamine, trifluoroacetate, hydroxide, silyloxide, or monodentate alkoxide) released from the metal center upon conversion of bound epoxide to azido alkoxide. The release of free azido alcohol from intermediate **15** is ruled out, since such a step would require the alcohol to be converted to the observed silyl ether product by silyl azide. This is not observed when cyclohexanol is used as an additive or when *trans*-2-azidocyclohexanol is added to a reaction mixture lacking cyclohexene oxide.



Scheme 3



reaction of free R_3SiN_3 or HN_3 with epoxide activated at any zirconium binding site, including those that are not productive in the enantioselective pathway.[22] Such a reaction would very likely be first order in epoxide, and thus would be increasingly favored at high epoxide concentration relative to the half-order Zr-catalyzed process.

The observation of a slow initial turnover of the catalyst and the role played by the silyl residue involved in that turnover in determining enantioselectivity and rate (Table 4) demand that a silyl fragment be added to the catalyst in the first catalytic cycle. This residue must not exchange with other silyl fragments during subsequent cycles. Scheme 3 shows a working, but highly speculative, hypothesis that accommodates these observations. The complexes shown are not meant to be interpreted as limiting proposals as they are unsupported by detailed structural data but are consistent with known trends of group 4 alkoxide chemistry and are presented only to illustrate certain mechanistic points.

The suggested dimeric structure shown for precatalyst **4** includes bridging alkoxide bonds from the unsymmetrically bound triisopropanolamine ligands,[9b] a terminal Zr-hydroxide fragment, and a bidentate trifluoroacetate ligand. The addition of silyl azide replaces the hydroxide group with an N_3 unit to give **12**, but without evaporation the system retains an active proton. In Scheme 3, this is represented by the combination of a terminal Zr−$OSiR_3$ group and a released alcohol "arm" of one of the tridentate ligands, although free silanol, HN_3, and trifluoroacetic acid could be produced instead. (Evaporation of volatile components of this mixture drives the removal of R_3SiOH to give the azide species **5**, as shown in Scheme 2.) Coordination of epoxide to **12** followed by intramolecular azide attack gives structure **13**, formally a zwitterionic species.

Completion of the first turnover by the addition of a second unit of silyl azide must then occur with a change in catalyst structure that “locks in” the first silyl residue and releases the first equivalent of product azido ether in lower enantiomeric excess than is produced subsequently. This is shown in complex **14**, in which one of the metal bridging positions is occupied by silyloxide from the first R_3SiN_3 molecule introduced. Such a bridging silyloxide ligand would resist exchange with other species present in the reaction mixture (such as silyl azides, silyl ethers, water, and/or alcohols) and would place the SiR_3 unit in a position to influence the enantioselectivity of the epoxide ring-opening event. For simplicity, the other bridging unit is shown to be trifluoroacetate, although other possibilities abound (such as triisopropanolamine alkoxide or hydroxide).

The possible presence of HN_3 in the reaction mixture suggests that free azide anion could be the active nucleophile, attacking epoxide bound to Zr in enantioselective fashion.[24] While this cannot be excluded by the data presently in hand, we consider it unlikely because it would be difficult to rationalize the observed half-order rate dependence on $[Me_3SiN_3]$ if the active nucleophile is not coordinated to a zirconium species.[22]

The important mechanistic conclusions reached thus far include the following points.

(1) An equilibrium interconversion of dimeric and tetrameric species occurs rapidly with respect to the rate of epoxide ring-opening. While ligand exchange among zirconium alkoxides is usually much slower than for analogous titanium systems, it is reasonable for the proposed dimerization process to be faster than the turnover rate for two reasons: (a) the equilibrium does not require an exchange of ligands (indeed, the data demand that the chiral aminotrialkoxide must remain in place), but merely an association/dissociation process involving bridging alkoxide, azide, or trifluoroacetate units; and (b) the catalytic turnover rate is fairly slow.

(2) The lower molecular weight species (dimer) is the active catalyst. Since aggregates of metal alkoxide complexes are often formed with bridging ligand interactions, and since Lewis acidic activity is generally enhanced by coordinative unsaturation, it is reasonable for d^0 metal centers in lower aggregation states to be more Lewis acidic. Such a correlation has been elegantly demonstrated by Seebach and co-workers with titanium complexes of the chiral TADDOL ligand,[24] and similar observations have been reported for other Ti-catalyzed processes.[25]

(3) Catalytic activity is proposed to require the cooperative action of two zirconium centers for the binding and delivery of azide to epoxide.

(4) Catalytic turnover is completed by rate-limiting alkoxide exchange with silyl azide in a process that is sensitive to the presence of silyl ethers or small amounts of alcohol and water in solution.

(5) A single turnover of the catalyst is required for its conversion to a more active and enantioselective form, in which a silyl group is incorporated.

(6) The catalyst is stable to small amounts of protic reagents, consistent with both the slow ligand exchange rates characteristic of zirconium alkoxides and the large binding constants expected of polydentate amino alcohol ligands.

(7) A variation of ligand-accelerated catalysis[26] is demonstrated here by the preservation of enantioselectivity as the Zr complex of (*S*,*S*,*S*)-**1** is increasingly diluted with the Zr complex of (*R*,*S*,*S*)-**1**: the catalyst that is more enantioselective also operates at a substantially higher rate.

(8) The cooperative action of two metal centers described above is also required for enantioselective epoxide ring-opening catalyzed by chiral Cr−salen complexes, brought about by an *intermolecular* association of monomeric catalyst species.[27] These examples contribute to what we regard as an emerging design principle for asymmetric catalysis, in which two or more metal centers engage in chemically distinct operations that are each necessary to achieve the overall transformation.[28] Other examples of bimetallic asymmetric catalysis include the contributions of Shibasaki and co-workers in a variety of addition reactions mediated by lanthanide−alkali−binaphthol complexes,[29] oxazaborolidine-catalyzed hydride reductions of ketones from the Corey group,[30] the mechanistic proposals of the Itsuno and Noyori groups regarding amino alcohol-mediated diethylzinc addition to aldehydes,[31] and several copper catalysts for enantioselective Michael additions to enones and other substrates.[32] We anticipate that other examples of binding and activation of substrates and reagents by multinuclear metal systems will prove effective for enantioselective organic transformations.

Experimental Section

General. Unless otherwise noted, all manipulations involving zirconium species were conducted under dry nitrogen atmosphere. Cyclohexene oxide, (*S*)- and (*R*)-(+)-1-amino-2-propanol, (*S*)-(−)-propylene oxide, and all other organic starting materials were purchased from Aldrich Chemical Co. and used as received. $Zr(OtBu)_4$ was purchased from Strem Chemical Co. and used without further purification. *i*PrMe$_2$-

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[24] (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99−101. (b) Seebach, D.; Behrendt, L.; Felix, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1008−1009. (c) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321. (d) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D.; Pettner, W. *Helv. Chim. Acta* **1992**, *75*, 2171. (e) von dem Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719−5730. (f) Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363−4384.

[25] (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837−8838. (b) Nowotny, S.; Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 4539−4540. In this instance, substitution of $Ti(OtBu)_4$ for $Ti(OiPr)_4$ gives dramatic enhancements of enantioselecitivty in dialkylzinc alkylation of aldehydes. The issue of titanium complex molecularity is not discussed, but we believe it to be an important part of the observed chemistry.

[26] Berrisford, D. J.; Bolm. C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.

[27] Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924−10925.

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[30] (a) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153−9156, and references therein. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.

[31] (a) Itsuno, S.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4142−4143. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69, and references therein.

[32] (a) van Koten, G. *Pure Appl. Chem.* **1994**, *66*, 1455−1462. (b) Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1995**, *36*, 4275−4278. (c) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467−4478. (d) van Klaveren, M.; Persson, E. S. M.; del Villar, A.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Tetrahedron Lett.* **1995**, *36*, 3059−3062. (e) van Klaveren; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D. M.; van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6135−6138.

SiN_3 was prepared by the literature method[33] and purified by careful vacuum distillation. Dichloromethane was either distilled under nitrogen from CaH_2 or purified by deoxygenation (done by purging with N_2 for 1 h) followed by passage through activated type A2 alumina (12 × 32 mm beads; Roche Industries) in the manner of Grubbs and co-workers.[34] Chlorobenzene was dried by distillation from CaH_2. Gas chromatography was performed on a Shimadzu GC-14A instrument equipped with an automatic injector and a cyclodex-B capillary column (30 m × 0.25 mm i.d., 0.25 μm film, J&W Scientific). IR kinetic studies were performed with 0.5 mm CaF_2 cells. Elemental analyses were performed at the University of Virginia on a Perkin-Elmer Model 2400 CHN Analyzer, using acetanilide as the calibration standard; samples were handled in air with no special precautions. Flash chromatography was carried out on 230−400 mesh silica gel.

Ligands **1** and **8** and precatalyst **3** were prepared as previously reported.[7] Samples of ligand **1** having melting points lower than 98 °C invariably produced catalysts of diminished enantioselectivity. Recrystallization of crude **1** obtained from toluene was usually necessary to achieve the proper melting point of 101−102 °C; yields of recrystallized **1** were generally 70−90%. Test reactions of the catalyst (eq 7) were conducted following the original procedure,[7a] except that CH_2Cl_2 was used as the solvent instead of chlorobenzene, resulting in an ee of 78−86% compared to 81−86%.

Complex 4. Precatalyst **3** (627 mg, 1.93 mg-atom Zr) was dissolved in CH_2Cl_2 (10 mL) followed by addition of $Me_3SiOCOCF_3$ (179 mg, 0.96 mmol). The mixture was allowed to stir for 70 min whereupon volatiles were removed at reduced pressure. The resulting solid was redissolved in CH_2Cl_2 (5 mL) and evaporated again to give **4** as a free-flowing white solid after drying under vacuum for several hours (630 mg, 95%). IR ($CDCl_3$, cm^{-1}) 1683 (trifluoroacetate). Anal. Calcd for $C_{20}H_{37}O_9F_3N_2Zr_2$: C, 34.87; H, 5.41; N, 4.07. Found: C, 34.89; H, 5.43; N, 4.47.

Complex 5. Complex **4** (501 mg, 1.45 mg-atom Zr) was dissolved in CH_2Cl_2 (10 mL) followed by addition of Me_3SiN_3 (292 mg, 2.41 mmol). The reaction was allowed to stand for 14 h, followed by evaporation, solvation in CH_2Cl_2, and repeat evaporation as above to afford **5** as a white solid after drying under vacuum (501 mg, 97%). IR ($CDCl_3$, cm^{-1}) before evaporation: 2139 (minor, free Me_3SiN_3), 2096 (major, bound azide), 1687 (trifluoroacetate); after evaporation: 2108, 2089 (bound azide), 1674 (trifluoroacetate). Anal. Calcd for $C_{20}H_{36}O_8F_3N_5Zr_2$: C, 33.65; H, 5.08; N, 9.81. Found C, 34.10; H, 5.23; N, 9.54.

Molecular Weight Measurements. A typical procedure involved placing 400 mg of zirconium complex in one bulb of the Signer flask,[11] and 300 mg (1.06 mmol) of distilled $Ti(OiPr)_4$ in the other. All studies were performed using approximately 7 mL of CH_2Cl_2 and were allowed to stand at room temperature for at least one week to reach equilibrium. Measured aliquots of each zirconium solution were removed before and after molecular weight measurement and tested for catalytic activity under standard conditions (eq 2). All except for complex **5** gave high yields of azido ether **7** in the normal 75−80% ee range, both before and after the molecular weight measurements, showing that the zirconium species do not decompose over the course of the study.

Kinetic Studies. A typical IR kinetics experiment was performed as follows. In the drybox, **3** (18 mg, 0.054 mmol Zr) was mixed with a CH_2Cl_2 stock solution of $Me_3SiOCOCF_3$ (0.3 mL solution containing 5.0 mg, 0.027 mmol) in CH_2Cl_2, followed by addition of CH_2Cl_2 (18.7 mL) and Me_3SiN_3 (507 mg, 4.40 mmol). This mixture was allowed to stand for 45−60 min, whereupon cyclohexene oxide (392 mg, 3.99 mmol) was added. The mixture was allowed to stand for about 5 min, and then a small amount was transferred into a CaF_2 IR cell and sealed with Teflon plugs. The cell was removed from the drybox and placed in the chamber of the IR instrument, the temperature of which was found to be sufficiently stable (27.0 ± 0.2 °C) that independent thermostating was unnecessary. Scans were taken at timed intervals (usually every 15−20 min), monitoring the disappearance of the Me_3SiN_3 azide resonance at 2140 cm^{-1} over the first 10% of the reaction (see Supporting Information). The rate constant was obtained by a plot of ln(peak height) vs time, as is appropriate for the pseudo-first order conditions of the experiment, assuming that peak height is directly proportional to concentration. After 4 days the bulk reaction mixture was exposed to air and filtered through a plug of silica gel to remove the zirconium species. The resulting solution was concentrated and purified by flash chromatography (98:2 light petroleum ether:diethyl ether) to afford azidosilyl ether **7** as a colorless liquid (0.81 g, 95% yield, 72.4% ee).

A typical GC kinetics experiment was performed as follows. In the drybox, a CH_2Cl_2 stock solution of **3** (containing 9.0 mg, 0.027 mmol Zr) was mixed with a stock solution of $Me_3SiOCOCF_3$ (containing 2.5 mg, 0.013 mmol) followed by the addition of CH_2Cl_2 (11.19 g), tetradecane (80 mg, 0.403 mmol), and Me_3SiN_3 (769 mg, 6.34 mmol). The mixture was allowed to stand for 1 h, whereupon cyclohexene oxide (208 mg, 2.11 mmol) was added and the reaction allowed to proceed in a closed vial in the drybox. All reactions were performed at 24 ± 0.5 °C. A 0.3 mL aliquot was removed every 75−90 min and filtered through a disposable pipet packed with a short plug of silica gel, using about 3 mL of CH_2Cl_2 as a wash. Each aliquot was analyzed directly by GC, and the reaction was followed by monitoring the appearance of **7** relative to the amount of tetradecane internal standard. Initial rates were obtained for the first 10% of reaction (excluding the first 1%, which invariably showed lower ee and a slower rate than the rest of the process) from the linear plots of product concentration vs time, demonstrating that the assumption of zero-order conditions in reactants over the initial reaction period is valid. After 20−30% of the reaction was complete, the remaining reaction mixture was allowed to stand for 4 days and then analyzed by GC to determine the final ee (73.7%) and product yields (112%). Yields at completion are calculated by converting the observed **7**/tetradecane ratio to a molar concentration of **7** using a calibration curve constructed with known mixtures of pure **7** and tetradecane. As precise figures for the yield at completion are not important to the analysis of each experiment, no effort was made to periodically update the calibration curve, and so a relatively large error can be expected for these numbers. It is only important to know whether the reactions proceeded with large or small absolute product yields. It was also determined that the concentration and ee of a sample of **7** was unchanged upon exposure to a mixture of catalyst and Me_3SiN_3 under otherwise normal reaction conditions for 7 days. Values obtained for reaction rate orders (Table 2) do not change significantly when rates are corrected for the small deviations from standard values for the two components held at constant concentration.

Rates of reactions performed in the presence of additives (Table 3) were measured using GC of aliquots as described above, except that the additive was introduced just before cyclohexene oxide and a little less CH_2Cl_2 was added to keep the total volume constant. The silyl ethers were prepared by reaction of cyclohexanol or pentanol with an equimolar amount of the silyl chloride in THF with triethylamine,[35] or in DMF with imidazole,[36] and were purified by distillation ($CyOSiMe_3$, n-C_5H_{11}-$OSiMe_3$) or column chromatography ($CyOSiMe_2iPr$, $CyOSiMe_2tBu$, $CyOSi(iPr)_3$). Water was introduced as an additive by the use of water-saturated CH_2Cl_2 (prepared by stirring excess water with CH_2Cl_2 for 12−24 h, and which contains 0.179 g of H_2O in 100 g of CH_2Cl_2 at 24 °C)[37] in place

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of some or all of the dry solvent. For reactions involving the sequential addition of azides (Table 4), the first azide (5 mol % with respect to epoxide) was allowed to react for 12−14 h prior to the addition of the second azide (95 mol %). This period was sufficient for all the Me_3SiN_3 to react as the first reagent, and for one catalytic turnover to be accomplished with *i*$PrMe_2SiN_3$. In the latter case, approximately half (2−3 mol %) of the *i*$PrMe_2SiN_3$ remained when Me_3SiN_3 was introduced but was not incorporated to a significant extent during the period of the subsequent rate measurement (10 mol % epoxide consumed). The GC analysis allows for the simultaneous monitoring of the amounts and enantiomeric compositions of Me_3Si- and *i*$PrMe_2Si$-containing products. Rates given in Table 4 are the average of two runs.

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Supporting Information Available: Tables of complete kinetics results, sample plots of GC- and IR-derived data, and NMR spectra of complexes **3**−**5** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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