Enantioselective Ring-Opening

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Enantioselective Desymmetrization of *meso*-Aziridines with $TMSN_3$ or TMSCN Catalyzed by Discrete Yttrium Complexes**

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Ever since Nugent first reported a practical, catalytic method for the enantioselective opening of *meso*-epoxides with trimethylsilyl azide ($TMSN_3$),[1] such desymmetrization reactions of epoxides[2] and aziridines[2e,3] using a variety of nucleophiles have been the subject of extensive research. The less developed ring-opening reactions, those of *meso*-aziridines by carbon and nitrogen nucleophiles, give direct access to enantiopure β-amino acids and 1,2-diamines—two classes of compounds which have broad chemical and pharmaceutical relevance. Li, Fernández, and Jacobsen first reported enantioselective ring-opening of *meso*-aziridines with $TMSN_3$, which were catalyzed by Cr^{III} complexes of tridentate Schiff bases.[3f] Then Shibasaki et al. reported Y and Gd complexes as catalysts for related reactions with $TMSN_3$[3g] and TMSCN.[3h] The opening of aziridine rings with $TMSN_3$ under Brønsted acid catalysis,[3i] and a similar reaction with aryl amines catalyzed by Nb^{V} complexes[2e] are also noteworthy. Herein we report the synthesis and application of readily available, discrete dimeric yttrium–salen complexes that catalyze highly enantioselective desymmetrization of *meso*-aziridines with both $TMSN_3$ and TMSCN. For comparable substrates, the enantioselectivity in the $TMSN_3$-mediated reactions exceed the highest values reported to date.

In previous work, we reported that Y^{III} alkoxides and salen complexes are exceptionally efficient catalysts for transacylation of secondary alcohols[4a] and for ring-opening of epoxides by TMSCN or $TMSN_3$:[4c,5] only 0.01 mol% catalyst is required (substrate/catalyst ratio of 10000:1) in the epoxide ring-opening reactions. Even though the enantioselectivity in these reactions [Eq. (1) in Figure 1; up to 77% *ee* for TMSCN-mediated ring-opening of epoxycyclohexane] never matched the best reported results[6] (91% *ee* at a substrate/catalyst ratio of about 9:1), the catalytic efficiency is unparalleled among epoxide ring-opening reactions, and may require a different model to describe the transition state. To explain the second-order dependence of the catalyst on Cr- and Yb-catalyzed ring-opening reactions, Jacobsen has quite convincingly suggested the involvement of two molecules of the catalyst: one each for the activation of the nucleophile and the electrophile.[2a] However, by looking at the structure of our yttrium catalyst (a distorted trigonal bipyramid with yttrium at the apex, see Figure 1),[4b] it is difficult to envision how two individual molecules of the yttrium complex can be involved (as indicated by the transition state suggested by Jacobsen) in a reaction that proceeds with such high efficiency. An attractive alternative would be to invoke a dimeric catalyst along the lines of one suggested by McCleland, Nugent, and Finn[7] to explain the observations related to the (alkanolamine)Zr-mediated ring-opening of epoxides by $TMSN_3$ (Scheme 1). Anecdotal support for such a hypothesis comes from the ease with which early transition metals, inclusive of yttrium, form anion-bridged dimers,[8] including an OH-dimer from **2a** which we have isolated and characterized.[5] Changes seen in the IR spectrum of a mixture the yttrium–salen complex **2a** (Figure 1) and excess TMSCN are also indicative of bridged CN-structures. Kinetic studies based on in situ IR spectroscopy, though tentative, do not rule out such a possibility.[5] The veracity of such an idea notwithstanding, we decided to examine the ring-opening reactions of *N*-4-nitrobenzoylaziridines[3c] catalyzed by fully characterized dimeric yttrium–salen complexes.

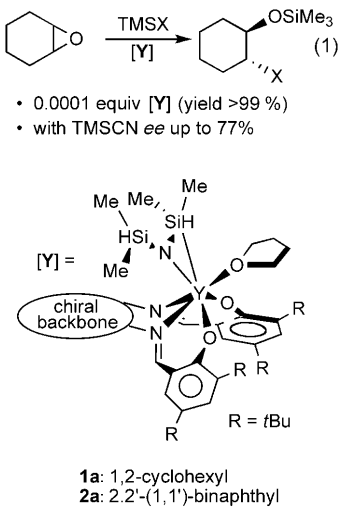

Figure 1. Epoxide ring-opening reaction and structures of yttrium catalysts.

A variety of yttrium compounds, among them monomeric complexes **1a, 1b, 2a, 2b**, and **2c** (Figure 2),[9] were prepared from $Y[N(SiHMe_2)_2]_3 \cdot 2THF$ and the corresponding ligands, as previously described[4b,10] [Eq. (2)]. The dimeric complexes

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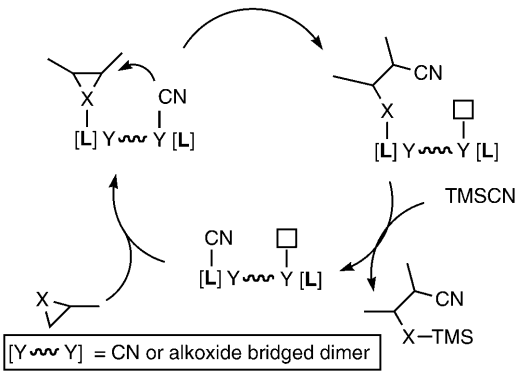


Scheme 1. A proposed mechanism. [L] = lanthanoid complex.

3a, 3b, 4a, 4b, and **4c** were prepared by treating $Y(OCH_2CH_2NMe_2)_3$[11] with a solution of salen ligand in toluene at 70 °C for 24 hours [Eq. (3)] and isolated by

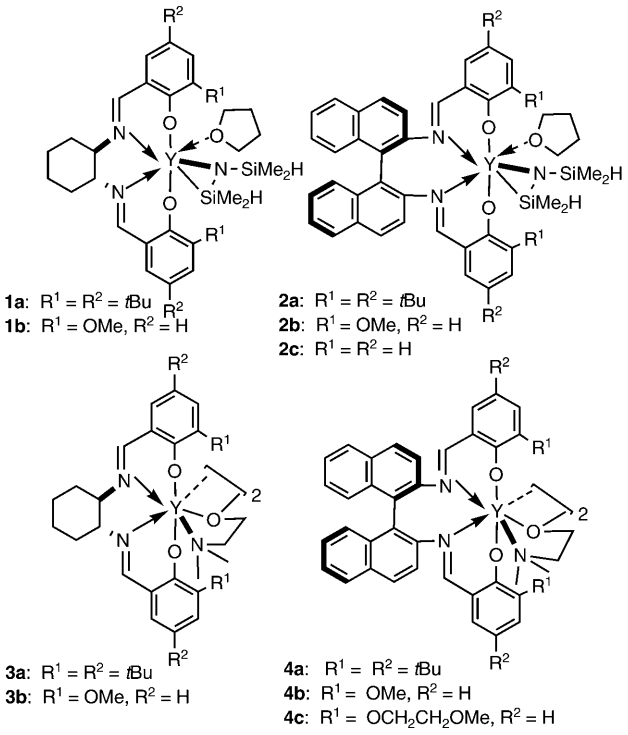


Figure 2. Yttrium complexes as catalysts for the asymmetric ring-opening of *meso*-aziridines with TMSCN and $TMSN_3$.

subsequent removal of the solvent.[8d] The resulting products were recrystallized to give the active catalysts. In preliminary experiments, the cyclohexane-derived aziridine **5** was treated with TMSCN in the presence of catalytic amounts (0.05 equiv) of yttrium complexes [Eq. (4)], and the results are shown in Table 1.

Among the monomeric complexes,[9] **1a**[12] and **2b** gave the best selectivity (Table 1, entries 1 and 5). In keeping with our conjecture, the highest selectivity was recorded for a dimeric complex (**4b**) with a binaphthyl scaffolding. Importantly, the substituents on the aryl imine part of the complex are critical. Only the 3-methoxy substituent gave acceptable enantioselectivity (Table 1, entry 10). Recrystallization of the catalyst is important to achieve high selectivity. We noticed that before recrystallization, **4b** gave an *ee* value of only 77 % in the ring-opening of **5**. Ring-opening reactions of prototypical *N*-acylaziridines by TMSCN were examined under the optimized reaction conditions (0.1 equiv of **4b**, $ClCH_2CHCl$, RT, 3 days) and the results are shown in Table 2.

Although the cyanide adducts **6–9** were formed in acceptable yields and selectivity, these readily available dimeric catalysts were especially suited for reactions of aziridines with $TMSN_3$ and gave the best yields and selectivity under almost identical reaction conditions (0.1 equiv of catalyst). These results are shown in Table 3. Although the products were formed with excellent selectivity in most cases, the reaction was very sensitive to steric effects. Notably, the sterically demanding substrates (Table 3, entries 6 and 7) gave lower yields under the standard reaction conditions. The corresponding eight-membered aziridine failed to react. A control experiment demonstrated that the observed lack of reactivity

Table 1: Catalyst screening for ring-opening of *meso*-aziridine **5** with TMSCN.[a]

Entry	Catalyst	Yield [%][b]	*ee* [%] (*RR*)[c]
1	**1a**[d]	>99	52
2	**1a**[e]	>99	−43[f]
3	**1b**	58	−18
4	**2a**	77	<5
5	**2b**	85	55
6	**2c**	>99	30
7	**3a**	79	37
8	**3b**	56	−6
9	**4a**[g]	>99	8
10	**4b**[g]	>99	88 (94)[h]
11	**4c**	64	30

[a] See Equation (4) for the procedure. [b] Yield of isolated product. [c] Configuration and *ee* values were determined by HPLC on a chiral stationary phase. For the synthesis of racemic products, see the Supporting Information. The absolute configuration was determined by comparison with authentic samples.[3h] [d] Catalyst was prepared in *n*-hexane. [e] Catalyst was prepared in THF. [f] The *SS* configuration. [g] 0.1 equivalents of catalyst was used. [h] Reaction was carried out at −3 °C, 5 d.

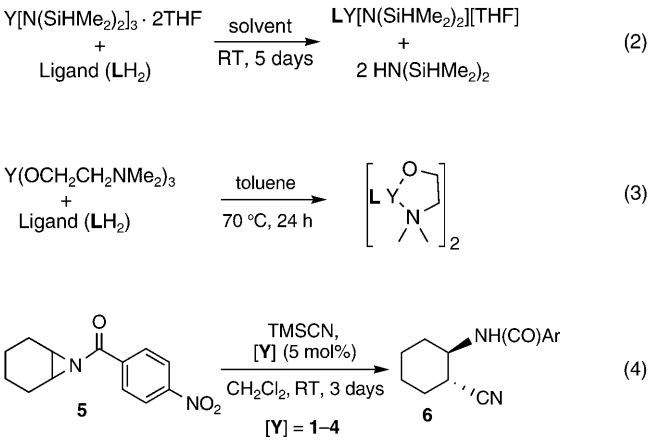
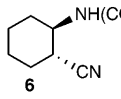
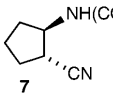
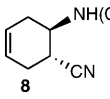
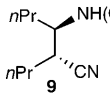
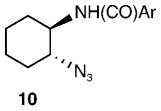
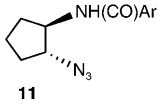
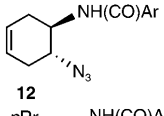
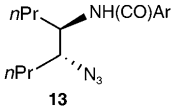
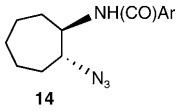
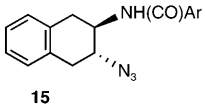


Table 2: Ring-opening reaction of *N*-acylaziridines with TMSCN catalyzed by **4b**[a].

	 **6**	 **7**	 **8**	 **9**
Yield [%][a]	87	85	86	47
ee [%][b]	94	99	92	82

[a] Yield of isolated product. [b] The *ee* values were determined by HPLC methods with a chiral stationary phase.

Table 3: Ring-opening reaction of *N*-acylaziridines with $TMSN_3$ catalyzed by **4b**[a].

Entry	Product[a]	Yield [%][b]	*ee* [%][c]
1	 **10**	>99	97
2	*ent*-**10**	>99	96
3	 **11**	>99	98
4	*ent*-**11**	>99	94
5	 **12**	>99	99
6	 **13**	73	92[d]
7	 **14**	47	97[d]
8	 **15**	>99	90[e]

[a] Ar = 4-$NO_2C_6H_4$. [b] Yield of isolated product. [c] The *ee* values were determined by HPLC methods with a chiral stationary phase. [d] Reaction time was 5 d. [e] Reaction time was 7 days.

is not due to deterioration of the catalyst (see the Supporting Information). Based on relative rates studies, the cyclohexane derivative **10** is formed at least four times faster than the cycloheptane analogue **14**. Given that both enantiomers of $BINAP(NH_2)_2$ (BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), and consequently the corresponding yttrium complexes are readily available, products with the opposite configuration can also be prepared readily (Table 3, entries 2 and 4).

For insight into the asymmetric induction process, we examined the solid-state structure of the yttrium–salen complex **4b**.[13] Single crystals of **4b** suitable for X-ray analysis were obtained by the addition of *n*-hexane to a solution of the complex in CH_2Cl_2 (Figure 3). In this highly organized C_2-symmetric structure, the bottom of the Y_2O_2 core is completely blocked by the OMe and NMe_2 groups. Thus the yttrium centers, approachable only from the opposite face, are buried in a well-defined chiral cavity. The lack of reactivity of the larger substrates and the exceptional selectivity in the ring-opening reactions are indicative of an asymmetric induction process. This process results from an initial coordination of the substrate and subsequent metal-assisted diastereoselective additions within the confines of a well-defined chiral cavity. The details of this heuristic model and the processes that are invoked remain highly speculative. We plan to seek further validation of the model while exploring other applications of these yttrium complexes in organic synthesis.

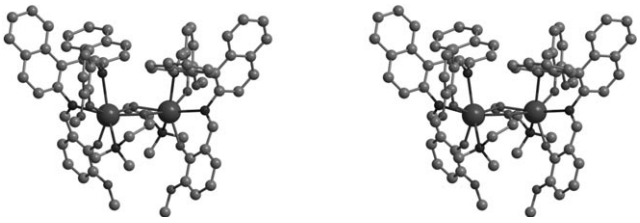


Figure 3. Stereoview of the solid-state structure of **4b**.

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[1] W. A. Nugent, *J. Am. Chem. Soc.* **1992**, *114*, 2768.
[2] a) E. N. Jacobsen, *Acc. Chem. Res.* **2000**, *33*, 421; b) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668; c) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307; d) C. Schneider, A. R. Sreekanth, E. Mai, *Angew. Chem.* **2004**, *116*, 5809; *Angew. Chem. Int. Ed.* **2004**, *43*, 5691; e) K. Arai, S. Lucarini, M. M. Salter, K. Ohta, Y. Yamashita, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 8103, and references therein.
[3] a) S. Matsubara, T. Kodama, K. Utimoto, *Tetrahedron Lett.* **1990**, *31*, 6379; b) Z. Zhang, R. Scheffold, *Helv. Chim. Acta* **1993**, *76*, 2602; c) M. Hayashi, K. Ono, H. Hoshimi, N. Oguni, *J. Chem. Soc. Chem. Commum.* **1994**, 2699; d) M. Hayashi, K. Ono, H. Hoshimi, N. Oguni, *Tetrahedron* **1996**, *52*, 7817; e) P. Müller, P. Nury, *Org. Lett.* **1999**, *1*, 439; f) Z. Li, M. Fernández, E. N. Jacobsen, *Org. Lett.* **1999**, *1*, 1611; g) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 6312; h) I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, S. Furusho, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 16438; i) E. B. Rowland, G. B. Rowland, E. Rivera-Otero, J. C. Antilla, *J. Am. Chem. Soc.* **2007**, *129*, 12084.
[4] a) M.-H. Lin, T. V. RajanBabu, *Org. Lett.* **2000**, *2*, 997; b) M.-H. Lin, T. V. RajanBabu, *Org. Lett.* **2002**, *4*, 1607; c) M.-H. Lin, PhD Thesis, Ohio State University (USA), **2002**.
[5] B Saha, M.-H. Lin, T. V. RajanBabu, *J. Org. Chem.* **2007**, *72*, 8648.
[6] S. E. Schaus, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 1001.
[7] a) B. W. McCleland, W. A. Nugent, M. G. Finn, *J. Org. Chem.* **1998**, *63*, 6656; similar models have been invoked by others to

rationalize asymmetric induction in other metal-catalyzed transformations, for reviews, see: b) M. Kanai, N. Kato, E. Ichikawa, M. Shibasaki, *Synlett* **2005**, 1491; c) T. R. J. Achard, L. A. Clutterbuck, M. North, *Synlett* **2005**, 1828.

[8] a) For titanium examples, see: G. Boche, K. Möbus, K. Harms, M. Marsch, *J. Am. Chem. Soc.* **1996**, *118*, 2770; for yttrium examples, see: b) $(\mathbf{L}_n)Y(m\text{-Cl})]_2$ (several chloride bridged dimers): W. J. Evans, C. H. Fujimoto, J. W. Ziller, *Chem. Commun.* **1999**, 311; c) $Y(\mathbf{L})(m\text{-OH})]_2$ (an hydroxide bridged dimer): C. M. Mascarenhas, S. P. Miller, P. S. White, J. P. Morken, *Angew. Chem.* **2001**, *113*, 621; *Angew. Chem. Int. Ed.* **2001**, *40*, 601; d) $Y(\mathbf{L})(\text{m-OR})]_2$ (an alkoxide bridged dimer): T. M. Ovitt, G. W. Coates, *J. Am. Chem. Soc.* **2002**, *124*, 1316; for CN-bridged complexes, see: e) C. E. Plecnik, S. Liu, S. S. Shore, *Acc. Chem. Res.* **2003**, *36*, 499; f) S. Tanase, J. Reedijk, *Coord. Chem. Rev.* **2006**, *250*, 2501.

[9] For a more complete list of complexes and the corresponding selectivities observed in the reaction shown in [Eq. (4)], see the Supporting Information.

[10] O. Runte, T. Priermeier, R. Anwander, *Chem. Commun.* **1996**, 1385.

[11] S. L. McLain, T. M. Ford, N. E. Drysdale, *Polym. Prep.* **1992**, *33*, 463 (Am. Chem. Soc. Div. Polym. Chem.).

[12] Curiously, when using catalyst **1a** the enantioselectivity in the ring-opening reaction was depend on the solvent used for its preparation (see Table 1, entries 1 and 2). For example, the reaction carried out with the catalyst prepared in *n*-hexane gave an enantioselectivity of 52% *ee* (*RR*), whereas the catalyst prepared in THF gave 43% *ee* (*SS*), thus suggesting very subtle effects of aggregation.

[13] See the Supporting information for the details of the X-ray crystallographic analysis of **4b**. CCDC 701484 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. As the crystals form very thin plates, it was necessary to collect a data set by using a synchrotron. This data set was collected by Dr. Jeanette Krause through the SCrALS (Service Crystallography at Advanced Light Source) program at the Small-Crystal Crystallography Beamline 11.3.1 at the Advanced Light Source (ALS). The ALS is supported by the U.S. Department of Energy, Office of Energy Sciences, Materials Sciences Division, under contract DE-AC02-05CH11231 at Lawrence Berkeley National Laboratory.

