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Enantioselective Ring Opening of Meso Aziridines Catalyzed by Tridentate Schiff Base Chromium(III) Complexes

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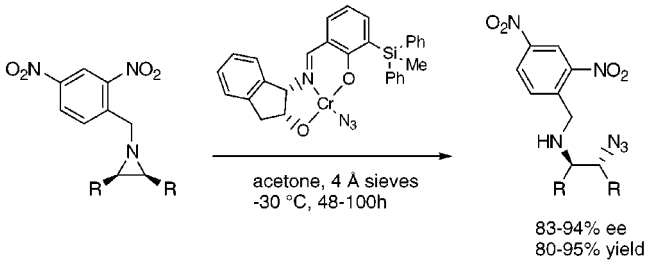
ABSTRACT



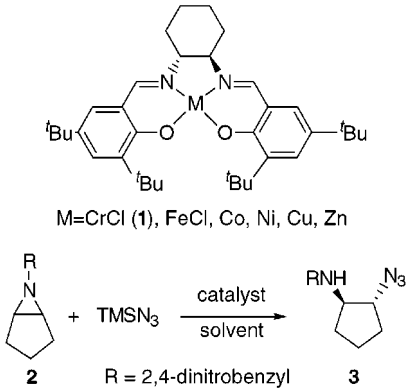
A catalytic method for the enantioselective ring opening of meso aziridines by $TMSN_3$ is described. Tridentate Schiff base chromium complexes derived from 1-amino-2-indanol were identified as the optimal catalysts.

Aziridines and their ring-opened products are valuable intermediates in organic synthesis.[1,2] Direct access to optically active amines by the nucleophilic ring opening of these electrophiles requires either the use of enantiomerically enriched aziridines or an enantioselective method for ring opening of appropriate meso compounds. Asymmetric catalytic approaches have been taken in both contexts with some success,[3,4] although existing methods are still quite limited with regard to scope and efficacy.

With the emergence of (salen)Cr(III) complexes as useful catalysts for the enantioselective ring opening of epoxides with $TMSN_3$,[5] we considered the possibility of using these or related complexes for aziridine ring opening. This has led us to the discovery that Cr(III) complexes of tridentate Schiff base ligands are highly effective catalysts for the ring opening of meso aziridines by $TMSN_3$. We report herein our preliminary results.

A series of chiral (salen)metal complexes were screened for catalysis for the model ring-opening reaction of cyclopentene-derived aziridine **2** with $TMSN_3$ (Scheme 1). While complexes of Zn, Ni, Fe, Cu, and Co were found to be

Scheme 1. Model Reaction



(1) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
(2) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.
(3) For a recent review of asymmetric aziridination, see: Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York; 1999; Chapter 17.
(4) For examples of desymmetrization of meso aziridines, see: (a) Matsubara, S.; Kodama, T.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6379. (b) Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *J. Chem. Soc., Chem. Commun.* **1994**, 2699. (c) Hayashi, M.; Ono, K.; Hoshimi, H.; Oguni, N. *Tetrahedron* **1996**, *52*, 7817. (d) Müller, P.; Nury, P. *Org. Lett.* **1999**, *1*, 439.

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inactive, the chromium(III) complex **1** did catalyze the reaction to a limited extent. A turnover frequency below 1 h^{-1} was measured and the ring-opened product **3** was obtained in 14% ee. While these results indicated that Cr(III) might be a competent metal ion for aziridine ring opening, we suspected that the steric requirements of the coordinated aziridine might be the cause for diminished enantioselectivity and reactivity with the salen complexes relative to that seen with epoxides and the same catalyst (Figure 1). Following

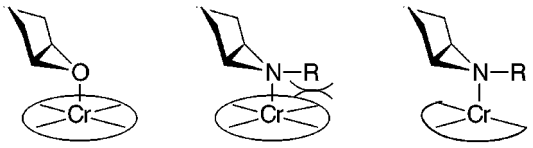
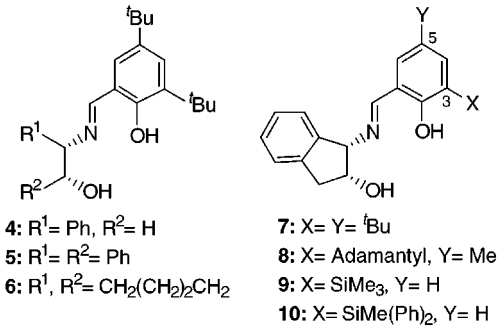


Figure 1. Schematic illustrating the possible advantage of tridentate ligands for the activation of aziridines.

this rationale, we evaluated chromium(III) complexes of tridentate ligands **4**−**10**, with the hope that a less sterically hindered coordination environment at the catalyst might lead to improved results (Figure 2).



4: R^1= Ph, R^2= H
5: R^1= R^2= Ph
6: R^1, R^2= $CH_2(CH_2)_2CH_2$

7: X= Y= ^{t}Bu
8: X= Adamantyl, Y= Me
9: X= $SiMe_3$, Y= H
10: X= $SiMe(Ph)_2$, Y= H

Figure 2. Ligands **4**−**10**.

Four different chiral amino alcohols were condensed with di-*tert*-butylsalicylaldehyde to provide ligands **4**−**7**. Of these, the aminoindanol-derived ligand (**7**) proved substantially more reactive and enantioselective in the model reaction (Table 1).[6] Variation of the substituents of the salicylidene aromatic group revealed a subtle-yet-clear trend toward

Table 1. Asymmetric Ring Opening of *N*-2,4-Dinitrobenzyl Cyclopentene Imine (**2**) Catalyzed by Cr(III) Complexes of Ligands **4**−**10**[a]

ligand	**4**	**5**	**6**	**7**	**8**	**9**	**10**
ee (%)[b]	4	7	24	66	64	69	70
convn (%)[c]	30	50	60	100	100	100	100

[a] Reactions were carried out at room temperature in acetone with 5 mol % of catalyst. [b] Enantiomeric excesses were determined by HPLC analysis of crude reaction mixtures. [c] Reaction time was 24 h for **4**−**6** and 3 h for **7**−**10**.

higher enantioselectivity with more sterically demanding 3-substituents.[7] In this manner, ligand **10** was identified as the most effective of those evaluated, and it was selected for further study.

The identity of the aziridine *N*-substituent was found to play an important role in the enantioselective ring opening. Sulfonyl-protected aziridines proved unreactive with any of the Cr Schiff base catalysts examined, while high conversions but low enantioselectivities were observed with amide and carbamate derivatives. *N*-Alkyl-substituted aziridines proved to be the most effective substrates by a wide margin, with those bearing the highly electron-deficient 2,4-dinitrobenzyl group giving the best results.[8]

Solvent was found to have an important effect on the reaction rate. In what might be considered an unexpected result for a Lewis acid-catalyzed process,[7] reactions carried out in acetone proceeded with the fastest rates, with reactions reaching complexion within 3 h at room temperature in the presence of 5 mol % of **10**. In contrast, use of solvents such as THF, CH_2Cl_2, and CH_3CN led to 27%, 83%, and 63% conversion, respectively, under the same conditions. On the other hand, product ee's were almost invariant in these different solvents.

The reactivity of the catalyst could be enhanced further by counterion methatesis to generate the corresponding azide complex.[9] Treatment of the complex derived from ligand **10** and $CrCl_3$ with $TMSN_3$ afforded a catalyst that displayed reasonable reactivity even at reduced temperatures. This allowed substantially higher enantioselectivities to be obtained in the ring opening of **2** (74% ee at 20 °C, 87% ee at −30 °C). Using the optimized catalyst and reaction condi-

(5) (a) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (b) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420. (c) Schaus, S. E.; Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1997**, *62*, 4197.

(6) **General Procedure for Aziridine Ring-Opening Reaction:** To a stirred solution of tridentate Cr(III) catalyst (5−10 mol %) in 1 mL of dry solvent was added the aziridine (0.50 mmol) under a nitrogen atmosphere at room temperature. After 15 min, the reaction temperature was stabilized as indicated (room temperature or −30 °C) and $TMSN_3$ (1.05 equiv) was added via syringe. The solution was stirred for the appropriate reaction time. Finally, the reaction mixture was concentrated in vacuo and isolation of the pure ring-opened product was accomplished by flash column chromatography on silica gel.

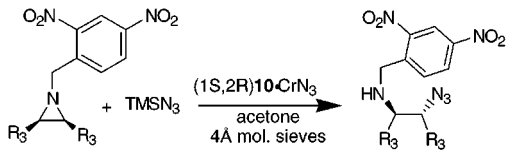
(7) For a similar trend in asymmetric hetero-Diels−Alder reactions, see: Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Intl. Ed. Engl.***1999**, *38*, 2398.

(8) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *11*, 1693.

(9) **Procedure for preparation of catalyst (1*S*,2*R*)-10·CrN$_3$:** In a flame-dried Schlenk flask under a nitrogen atmosphere, (*1S*,2*R*)-ligand **10** (763 mg, 1.70 mmol) was disolved in dry THF (30 mL). 2,6-Lutidine (0.79 mL, 6.81 mmol, freshly distilled from CaH_2) was added to the flask, followed by chromium(III) chloride tetrahydrofuran complex (1:3, 97%) (636 mg, 1.70 mmol). The resulting dark brown solution was stirred under nitrogen for 12 h and then diluted with *tert*-butylmethyl ether (200 mL) and washed with NH_4Cl and brine. The organic portion was dried over Na_2SO_4 and then concentrated under reduced pressure. The dark brown air-stable solid thus obtained was treated with $TMSN_3$ (2.25 mL, 17 mmol) and was stirred under a nitrogen atmosphere overnight at room temperature. Volatile materials were removed in vacuo. Flash column chromatography (13−20% acetone in hexane) afforded 459 mg (50% yield) of the complex as an air-stable brown solid.

tions outlined above, very good enantioselectivities were obtained in the ring opening of a variety of aziridines (Table 2).

Table 2. Enantioselective Ring Opening of Meso *N*-2,4-Dinitrobenzyl Aziridines Catalyzed by **10**·CrN_3[a]



entry	R_3	R_3	temp (°C)	time (h)	isolated yield (%)	ee (%)[b]
1	-$(CH_2)_4$-		−30	48	95	94
2	-CH_2CH=$CHCH_2$–		−30	100	75	88
3	-$(CH_2)_3$–		−30	72	87	87
4	-CH_2OCH_2-		−15	90	73	90
5	Me	Me	−30	96	80	83

[a] Reactions were carried out with 10 mol % catalyst and 4 Å molecular sieves (ca. 1:1 w/w relative to the aziridine substrate). [b] Enantiomeric excesses were determined by HPLC analysis of crude reaction mixtures.

The cyclohexene-derived aziridine underwent ring opening with higher enantioselectivity than that of the five-membered ring counterpart. The aziridine derived from *cis*-2-butene was slightly less efficient (entry 5).

The azido *N*-2,4-dinitrobenzyl amino products of the ring-opening reactions can be transformed into the corresponding C_2 symmetric 1,2-diamines under reductive conditions, and the present method thus provides an efficient route to these very useful chiral auxiliaries and ligand components. Even though such 1,2-diamines can usually be obtained in optically pure form by classical resolution, synthesis of the racemic materials is not always straightforward. The fact that the two functional groups of the ring-opened products are differentially protected amines allows straightforward access to useful non C_2 symmetric diamine or diimine ligands that are not otherwise easily prepared.[10] These types of ligands are likely to prove important in the development of new asymmetric reactions and the study of the mechanism of known transformations.

Tridentate Schiff base complexes of Cr(III) have now proven effective as catalysts for two very different asymmetric transformations: the hetero-Diels−Alder reaction of monoalkoxy dienes and aldehydes[7] and the ring-opening of meso aziridines with $TMSN_3$. The further optimization, scope, and mechanism of the new aziridine ring-opening reaction are under further investigation, as is the application of the new chromium catalysts to other important asymmetric transformations.

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Supporting Information Available: Procedure for the preparation of catalyst **10**·CrN_3 and full details of a representative ring-opening reaction (Table 2, entry 1) along with analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2580 and references cited herein.