Inorganic Chemistry
·Communication

Diastereoisomerically Selective Enantiomerically Pure Titanium Complexes of Salan Ligands: Synthesis, Structure, and Preliminary Activity Studies

**Adi Yeori, Stanislav Groysman, Israel Goldberg, and Moshe Kol***

*School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences,
Tel Aviv University, Tel Aviv 69978, Israel*

The degree of diastereoselectivity in the wrapping of four new chiral Salan ligands to form chiral-at-metal titanium complexes ranged from mild to perfect as a function of the ligands' *N* substituents; the enantiomerically pure complexes catalyzed the addition of diethyl zinc to benzaldehyde in 73–76% enantiomeric excess.

Asymmetric catalysis is the preferred method for preparation of chiral compounds in an enantiomerically pure form. Various successful catalysts comprised of metal complexes of chiral chelating ligands have been introduced in the past few years, including BINOLs, TADDOLs, and Salens.[1] Notably, the chirality source of most such systems is the ligand backbone and not the ligand wrapping mode around the metal; that is, these complexes are not *chiral-at-the-metal*. In contrast, the isotactic polymerization catalysts *ansa*-metallocenes[2] and Salan complexes[3] are C_2 chiral as a result of the wrapping mode of the ligand around the group IV metal. However, the lack of chirality of the ligand backbone in these compounds leads to racemic catalyst mixtures.[4] Unraveling the factors that determine the wrapping tendencies of chiral ligands around metal centers may lead to asymmetric catalysts of *predetermined* chirality at the metal.[5] In this context, we describe herein the synthesis of enantiomerically pure diastereoisomerically specific Salan com-

Scheme 1. Two Possible *fac−fac* Wrapping Modes of Chiral Salan Ligands around an Octahedral Titanium Center
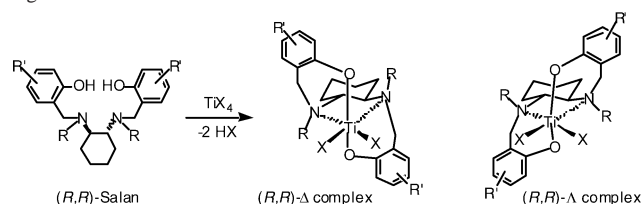
plexes of titanium and their preliminary application in asymmetric catalysis.

The preferred wrapping mode of achiral tetradentate Salan ligands around octahedral zirconium and titanium centers is *fac−fac*, leading to C_2 chiral complexes.[3,6] The introduction of chirality to the Salan backbone may lead to two C_2 chiral *fac−fac* isomers having a diastereoisomeric relationship (Scheme 1). Walsh and co-workers reported that a chiral Salan ligand featuring methyl substituents on the amine donors and *ortho,para-tert*-butyl substituents on the phenolate rings led to a ca. 1:1 mixture of these two diastereoisomers;[7] namely, no chiral induction from the ligand backbone to the metal was attained. The four chiral Salan ligands described in this work are assembled around *trans*-1,2-diaminocyclohexane, featuring either H or Me *N* substituents, and either dichloro- or dibromophenolate substituents (Lig$^{1−4}$H$_2$, Figure 1).

The synthesis of the ligand precursors Lig^{1,3}H$_2$ was accomplished by a two-step reaction. First, a condensation between *trans*-1,2-diaminocyclohexane and 2 equiv of the respective substituted salicylaldehyde yielded the Salen-type intermediates. Then, reduction of the imine functionalities with NaBH$_4$ yielded the unsubstituted (Y = H) Salan ligands. The corresponding *N*-Me-substituted ligand precursors, Lig^{2,4}H$_2$, were obtained by further condensation of Lig^{1,3}H$_2$ with formaldehyde and reduction. All ligand precursors

---

* Author to whom correspondence should be addressed. E-mail: moshekol@post.tau.ac.il.

(1) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; *Wiley-VCH*: New York, 2000.

(2) Brintzinger, H. H.; Fischer, D.; Mülhaupt, R.; Rieger, B.; Waymouth, R. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1143.

(3) (a) Tshuva, E. Y.; Goldberg, I.; Kol, M. *J. Am. Chem. Soc.* **2000**, *122*, 10706. (b) Segal, S.; Goldberg, I.; Kol, M. *Organometallics* **2005**, *24*, 200.

(4) For several examples of employing chiral metallocenes in asymmetric transformations following their resolution, see: (a) Waymouth, R. M.; Pino, P. *J. Am. Chem. Soc.* **1990**, *112*, 4911. (b) Troutman, M. V.; Appella, D. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4916. (c) Hansen, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713.

(5) (a) Knof, U.; von Zelewsky, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 302. (b) Mamula, O.; von Zelewsky, A. *Coord. Chem. Rev.* **2003**, *242*, 87.

(6) In contrast, *fac−mer* dinuclear complexes of Salan ligands around aluminum were reported: Wei, P.; Atwood, D. A. *Polyhedron* **1999**, *18*, 641.

(7) Balsells, J.; Carroll, P. J.; Walsh, P. J. *Inorg. Chem.* **2001**, *40*, 5568.
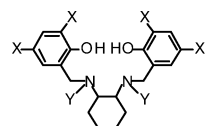
Lig¹H₂: X = Cl, Y = H; Lig²H₂: X = Cl, Y = Me
Lig³H₂: X = Br, Y = H; Lig⁴H₂: X = Br, Y = Me

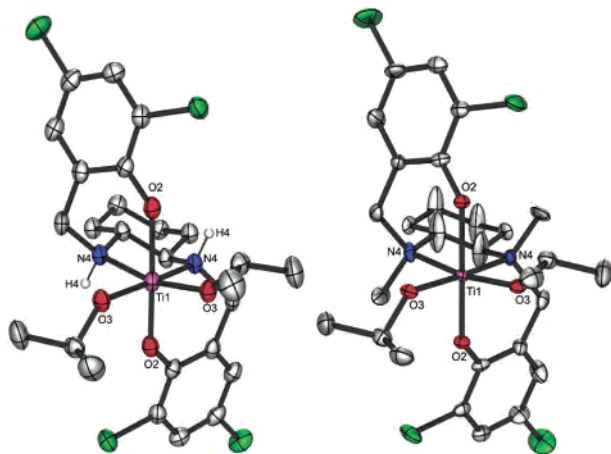**Figure 1.** Chiral Salan ligand precursors employed in this work.

Figure 2. Crystal structures of (R,R)-Lig¹Ti(OiPr)₂ (left) and Lig²Ti-(OiPr)₂ (right).

(except Lig⁴H₂) were synthesized both as racemic mixtures and in enantiomerically pure forms (see Supporting Information).

Titanium diisopropoxide complexes of all of the ligands were readily obtained by reacting the corresponding ligand precursors with titanium tetraisopropoxide at room temperature for 2 h. According to the ¹H NMR spectra, each of the racemic complexes rac-Lig¹Ti(OiPr)₂ and rac-Lig³Ti(OiPr)₂ formed as a single C_2-chiral-at-metal diastereoisomer. This signifies that, in contrast to Walsh's system, a perfect chiral induction from the ligand to the metal center had taken place. As expected, the enantiomerically pure ligands (R,R)-Lig¹,³H₂ ([α]D = −26, −23°) also led to single diastereoisomeric complexes ([α]D = −125, −46°). (R,R)-Lig¹Ti(OiPr)₂ crystallized in a chiral space group ($P4_32_12$), the unit cell containing a single diastereoisomer of crystallographic C_2 symmetry (Figure 2, left).[8] The chiral Salan wrapping mode around the octahedral metal center was fac−fac, as was previously observed for the achiral Salan ligands, forcing a cis disposition of the isopropoxide groups. The structure confirms the (R,R) assignment of the trans-diaminocyclohexane system[9] and reveals that the stereochemistry of the metal center is Δ.[5]

In a sharp contrast, the reaction of rac-Lig²H₂ with Ti(OiPr)₄ did not lead to a single diastereoisomer. Instead, a mixture consisting mostly of two C_2-symmetrical species, in a ratio of ca. 1.5:1, was observed, indicating that the

(8) Crystal data for (R,R)-Lig¹Ti(OiPr)₂: C₂₆H₃₄Cl₄N₂O₄Ti; M = 628.25; tetragonal; space group $P4_32_12$; a = 14.9470(5), b = 14.9470(5), c = 13.1990(3) Å; V = 2948.83(15) Å³; T = 106(2) K; Z = 4; Dc = 1.415 g cm⁻³; μ(Mo Kα) = 0.687 mm⁻¹; R₁ = 0.0408 and wR₂ = 0.0893 for 2493 reflections with I > 2σ(I); R₁ = 0.0717 and wR₂ = 0.1140 for all 3363 unique reflections.
(9) All crystallographic measurements were made with high precision at ca. 110 K, with a clear indication of the structures' chirality.

Scheme 2. Overlapping of Two Diastereoisomers that Feature the Same Chirality at the Metal and Opposite Chirality of the Diaminocyclohexane

(R,R)-Δ complex   complex overlap   (S,S)-Δ complex
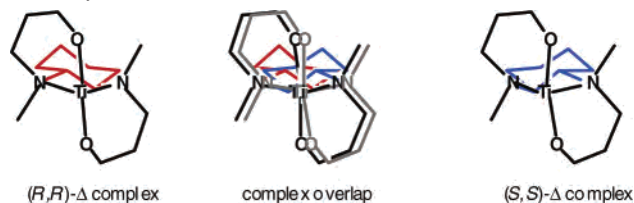
chiral induction from the N-methyl-substituted ligand backbone to the metal was weak.[10] Interestingly, even though Lig²Ti(OiPr)₂ exists as a mixture of four stereoisomers (a major and a minor diastereoisomer of each enantiomer), it yielded crystals suitable for X-ray analysis (Figure 2, right).[11] The analyzed crystal featured the same chiral space group ($P4_32_12$) and similar unit cell dimensions as those observed for (R,R)-Lig¹Ti(OiPr)₂, signifying a conglomerate rather than a racemate crystallization (a crystal featuring the opposite chiral space group could have been chosen from the crystallization mixture with the same probability). At first sight, the structure of Lig²Ti(OiPr)₂ seems analogous to the structure of (R,R)-Lig¹Ti(OiPr)₂, evident most clearly in the Δ stereochemistry around the metal center. However, a closer examination reveals elongated atomic displacements (even at the experimental temperature of 110 K) for four of the six carbon atoms of the cyclohexane ring as well as reduced cyclohexane puckering (root mean square deviation from planarity of 0.143 Å in contrast to the normal 0.235 Å in the former structure). We propose that this unusual structural feature is a consequence of the co-crystallization of two diastereoisomers featuring the same chirality at the metal and opposite chirality of the cyclohexane skeleton, that is, (R,R)-Δ and (S,S)-Δ, as demonstrated in Scheme 2. The orientation of the cyclohexane ring indicates that (R,R)-Δ is the major isomer. Possibly, this structure reflects the solution composition that is proposed to include the enantiomers (R,R)-Δ and (S,S)-Λ as major diastereoisomers and (S,S)-Δ and (R,R)-Λ as minor diastereoisomers.

In an attempt to obtain a resolved structure with a given metal chirality, we grew single crystals of the diastereoisomer mixture of Lig²Ti(OiPr)₂ that was prepared from the enantiomerically pure (R,R) ligand. The "normal" atomic displacements of this structure supported the expected crystallization of a single diastereoisomer. This arbitrarily chosen crystal was found isometric with the former ones and represents the (R,R)-Λ diastereoisomer, which had crystallized in the "opposite chirality" $P4_12_12$ group and is proposed to be the minor isomer in solution (Figure 3).[12]

The perfect chiral induction for Lig¹,³ in contrast to the low chiral induction for Lig²,⁴ may be rationalized by steric interactions between the N substituents and the axial

(10) A more complex diastereoisomer mixture was observed for Lig⁴H₂.
(11) Crystal data for rac-Lig²Ti(OiPr)₂: C₂₈H₃₈Cl₄N₂O₄Ti; M = 656.30; tetragonal; space group $P4_32_12$; a = 15.1060(4), b = 15.1060(4), c = 13.1100(3) Å; V = 2991.59(16) Å³; T = 110(2) K; Z = 4; Dc = 1.457 g cm⁻³; μ(Mo Kα) = 0.680 mm⁻¹; R₁ = 0.0756 and wR₂ = 0.1393 for 2551 reflections with I > 2σ(I); R₁ = 0.0859 and wR₂ = 0.1421 for all 2815 unique reflections.
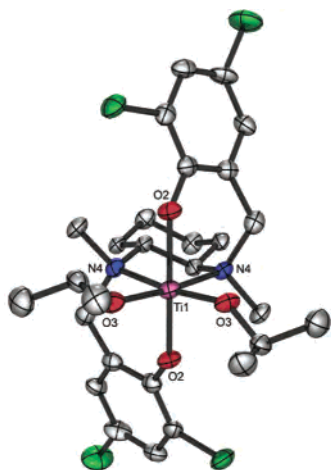
Figure 3. Crystal structure of (R,R)-Λ-Lig^{2}Ti(O^{i}Pr)$_2$ obtained from the enantiomerically pure ligand.

hydrogens of the adjacent cyclohexane carbons: For Lig^{1,3}, the considerable difference between H and CH$_2$ bound to the N donors places the CH$_2$ group away from these axial hydrogens, thus leading to a specific Δ wrapping of the (R,R) ligand. On the other hand, wrapping of Lig^{2,4} around the metal is less selective as a result of the similar size of the CH$_2$ and CH$_3$ N-bonded fragments, and both diastereoisomers are formed (Scheme 1).

To evaluate the potential of these chiral-at-metal complexes as asymmetric catalysts, we employed the diastereomerically pure complexes Lig^{1}Ti(O^{i}Pr)$_2$ and Lig^{3}Ti(O^{i}Pr)$_2$ as catalysts in the addition reaction of Et$_2$Zn to benzaldehyde (Scheme 3).[13,14] A total of 5 mol % of the catalysts were utilized, and the reactions were carried to practically full conversion. A chiral-GC analysis of the resulting products

Scheme 3. Asymmetric Catalytic Addition of Et$_2$Zn to Benzaldehyde
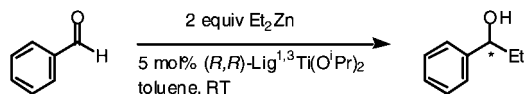
indicated that, for both catalysts, systematic enantiomeric excesses (ee's) in the range of 73−76% were obtained. Although higher ee's were reported for this reaction with other catalysts,[15] it should be stressed that, usually, stoichiometric quantities of Ti(O^{i}Pr)$_4$ are employed. More significantly, the attempted asymmetric catalysis of this reaction with a titanium complex of the Salen ligand featuring chloro phenolate substituents resulted in negligible %ee. It, thus, follows that, for certain reactions, chiral-at-metal Salan complexes may outperform the corresponding Salen complexes (having the same phenolate substituents) in promoting asymmetric catalysis. We are currently exploring the possible catalytic applications of such complexes.

Supporting Information Available: Experimental procedures and compound characterization data (pdf). Crystallographic data in cif format for the three structures. This material is available free of charge via the Internet at http://pubs.acs.org.

IC050745B

(12) Crystal data for (R,R)-Lig^{2}Ti(O^{i}Pr)$_2$: C$_{28}$H$_{38}$Cl$_4$N$_2$O$_4$Ti; $M = 656.30$; tetragonal; space group $P4_12_12$; $a = 15.0670(5)$, $b = 15.0670(5)$, $c = 13.1350(5)$ Å; $V = 2981.84(18)$ Å^3; $T = 110(2)$ K; $Z = 4$; $D_c = 1.462$ g cm^{-3}; μ(Mo Kα) = 0.682 mm^{-1}; $R_1 = 0.0585$ and $wR_2 = 0.1068$ for 1813 reflections with $I > 2\sigma(I)$; $R_1 = 0.1058$ and $wR_2 = 0.1220$ for all 2797 unique reflections.

(13) The ^{1}H NMR spectrum of Lig^{1}Ti(O^{i}Pr)$_2$ in d$_8$-toluene taken at 90 °C did not exhibit any new peaks, and upon cooling to room temperature, it was identical to the original spectrum. We thus propose that the diastereoisomeric purity of these complexes is not compromised during the catalytic reaction course.

(14) For asymmetric catalysis employing dinuclear $fac-mer$ Salan aluminum complexes, see: Ward, C. V.; Jiang, M.; Kee, T. P. *Tetrahedron Lett.* **2000**, *41*, 6181. For asymmetric catalysis employing a Salan titanium complex, see: Dai, Z.; Zhu, C.; Yang, M.; Zheng Y.; Pan, Y. *Tetrahedron: Assymetry* **2005**, *16*, 605.

(15) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233.