

Mechanistic Insight into the Stereochemical Control of Lactide Polymerization by Salan–Aluminum Catalysts**

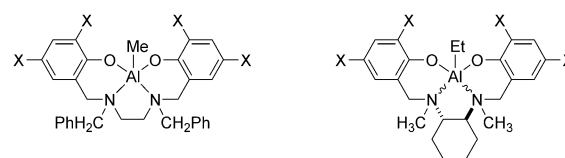
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Dedicated to Professor Benzion Fuchs on the occasion of his 85th birthday

Abstract: Alkyl aluminum complexes of chiral salan ligands assembled around the 2,2'-bipyrrrolidine core form as single diastereomers that have identical configurations of the N donors. Active catalysts for the polymerization of lactide were formed upon the addition of benzyl alcohol. Polymeryl exchange between enantiomorphous aluminum species had a dramatic effect on the tacticity of the poly(lactic acid) (PLA) in the polymerization of racemic lactide (rac-LA): The enantiomerically pure catalyst of the nonsubstituted salan ligand led to isotactic PLA, and the racemic catalyst exhibited lower stereocontrol. The enantiomerically pure catalyst of the chloro-substituted salan ligand led to PLA with a slight tendency toward heterotacticity, whereas the racemic catalyst led to PLA of almost perfect heterotacticity following an insertion/auto-inhibition/exchange mechanism.

Poly(lactic acid) (PLA) has attracted considerable attention in recent years as an environmentally friendly alternative to petroleum-derived plastics such as polyethylene or polystyrene in packaging applications, in addition to its established biomedical applications.^[1,2] PLA is generally produced by the catalyzed ring-opening polymerization (ROP) of its cyclic dilactone lactide (LA).^[3] The ROP by metal-based catalysts^[4,5] typically propagates by an insertion of the lactide carbonyl group to a metal–alkoxo group, followed by breaking of the bond between the acyl carbon atom and the endocyclic oxygen atom to form a new metal–alkoxo bond. The stereogenic centers of lactide are not affected by this process, so polymerization of the homochiral L-LA or D-LA can only lead to isotactic PLA. Polymerization of racemic lactide (rac-LA) may produce either isotactic PLA (chiral,^[6] diblock,^[7] or multiblock^[8,9]) or heterotactic PLA,^[10] following a homochiral or a heterochiral preference, respectively, in addition to stereoirregular PLA.^[11] The structure of the ligand, the character of the metal, and the identity of the proximal stereogenic center of the polymeryl group may all

be involved in selecting which lactide enantiomer would coordinate and insert. Polymeryl exchange between propagating species^[12] and catalyst fluxionality^[10b,e,13] may further diversify the stereocontrol. Arguably the most intriguing family of catalysts reported to date is Gibson's salan aluminum complexes (Scheme 1, left).^[14,15] Depending on



Scheme 1. Previously known aluminum complexes of achiral and diaminocyclohexane-based chiral salan ligands.

subtle ligand variations, these complexes led to a remarkable opposite stereocontrol in the polymerization of rac-LA: a complex of a salan ligand bearing no phenolate substituents gave isotactic PLA ($P_m = 0.79$), whereas a complex bearing chloro phenolate substituents gave highly heterotactic PLA ($P_r = 0.96$). Catalysts bearing other phenolate substituents afforded PLA with a tendency toward heterotacticity as well. While isoselectivity for aluminum-based catalysts is typical, the heteroselectivity for aluminum-based catalysts was unprecedented. Binding of these achiral salan ligands to aluminum renders the N donors stereogenic. A crystallographic structure of a methyl aluminum precatalyst showed an overall C_1 -symmetric trigonal-bipyramidal geometry with opposite (*R* and *S* centers) configurations of the two N donors, which was averaged to a symmetric species (presumably C_s) in solution, according to the NMR data. A chiral variety of these salan ligands based on the 1,2-*trans*-diaminocyclohexane core was described by Chen, Feijen, and co-workers (Scheme 1, right).^[16] These ligands led to mononuclear ethyl aluminum complexes as mixtures of nonresolvable diastereomers: major stereoisomers of C_1 symmetry featuring N donors of opposite configuration and minor stereoisomers of C_2 symmetry featuring N donors of identical (but unknown) configuration. These complexes exhibited stereoselectivity trends consistent with those found for Gibson's catalysts, and showed the occurrence of polymeryl exchange events. However, their stereoselectivity induction was low, possibly because of the presence of multiple catalytic species. We have previously introduced salan ligands assembled around the chiral 2,2'-bipyrrrolidine core, and demonstrated that, in contrast to the corresponding ligands assembled around the diaminocyclo-

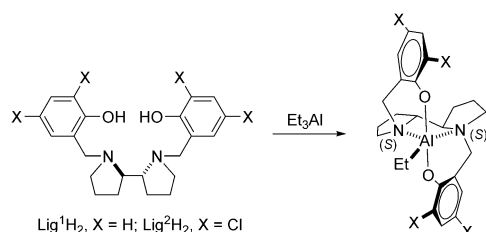
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hexane core, they led to single diastereomers of predetermined chirality of the N donors when wrapping around octahedral Group 4 transition-metal centers as well as around tetrahedral zinc centers.^[17,18] We hypothesized that such a high diastereoselectivity would be attained around the pentacoordinate aluminum as well.

Two bipyrrrolidine-centered salan ligand precursors that feature either nonsubstituted phenolates (Lig¹H₂) or dichloro-substituted phenolates (Lig²H₂)^[17] were targeted in accordance with Gibson's ligands (see the Supporting Information). Lig¹H₂ and Lig²H₂ reacted cleanly with Et₃Al, giving complexes of the form [[ONNO]Al-Et]. Similar results were obtained with Me₃Al. ¹H NMR data indicated that, in contrast to the diaminocyclohexane-based salan ligands,^[16] single diastereomers had formed, supporting, once again, the ability of the chiral 2,2'-bipyrrrolidine core to induce a specific helical wrapping. Moreover, variable temperature NMR spectroscopy (Figure S1 in the Supporting Information) indicated that these complexes were of high symmetry at higher temperatures, consistent with identical configurations of the two N donors, in contrast to the salan aluminum systems described above (Scheme 2).



Scheme 2. Chiral 2,2'-bipyrrrolidine-based salan ligands employed in this work and their aluminum complexes ((*R,R*)-ligand enantiomer is shown).

Single crystals of an ethyl aluminum complex of a related salan ligand bearing *tert*-butyl phenolate substituents (and an (*R,R*) configuration) were grown from cold ether and the structure was solved (Figure 1), showing a mononuclear pentacoordinate aluminum complex. The geometry around

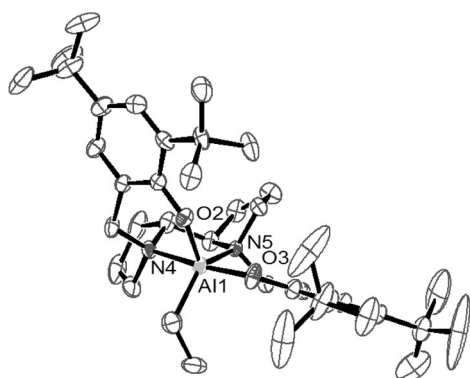


Figure 1. ORTEP representation of an Et-Al complex of (*R,R*)-salan ligand bearing *tert*-butyl phenolate groups. Selected bond lengths (Å): Al–O2 1.759(2); Al–O3 1.816(2); Al–N4 2.210(2); Al–N5 2.054(2); Al–C32 1.966(3).^[27]

the aluminum center is intermediate between square-pyramidal and trigonal-bipyramidal ($\tau = 0.56$),^[19] and the bond lengths are unexceptional. The bond between the pseudo-apical N4 donor and Al is 7% longer than the bond between the pseudo-equatorial N5 donor and Al: 2.210 and 2.054 Å, respectively, supporting a similar binding strength.^[20] Consistently with the NMR data, the configurations around the two N donors were identical: (*S,S*) for this (*R,R*) ligand, as can be predicted from simple ball-and-stick models (Scheme 2). We propose that an identical correlation between the configuration of the stereocenters of the bipyrrrolidine core and the configuration of the N donors is obtained for the complexes Lig¹Al-Et and Lig²Al-Et.

We investigated the catalytic activity of these complexes in the polymerization of *rac*-LA.^[21] Active catalysts were formed by reacting the [[ONNO]Al-Et] complexes with one equivalent of benzyl alcohol. Polymerizations were run in toluene at 70 °C or 50 °C with a LA/Al ratio of 100:1. Most of the polymer samples that were obtained had narrow molecular-weight distributions, and their molecular weights were consistent with their calculated values, thus supporting the full activation of the catalysts and controlled polymerizations. The polymerization of *rac*-LA with (*R,R*)-Lig¹Al-Et at 70 °C gave isotactic PLA with $P_m = 0.72$ (P_m = probability of isotactic enchainment determined by ¹H NMR spectroscopy). PLA with an identical degree of isotacticity was obtained with (*S,S*)-Lig¹Al-Et, thus supporting the reproducibility of the polymerization conditions (Table S1, entries 1 and 2). Lowering the polymerization temperature to 50 °C led to PLA of a higher degree of isotacticity of $P_m = 0.79$. Polymerization of *rac*-LA with *rac*-Lig¹Al-Et led to a considerable reduction in the isotacticity of PLA ($P_m = 0.56$ at 70 °C; $P_m = 0.59$ at 50 °C). The lower tacticity is associated with an enantiomorph-site control of tacticity, which is compromised by polymeryl-exchange events between enantiomorphous active species when a racemic catalyst is employed.^[12] To investigate the correlation between the chirality of the catalyst and the lactide enantiomer, we followed the consumption of L-LA and D-LA by (*R,R*)-Lig¹Al-Et by NMR experiments at 70 °C in [D₈]toluene. A strong preference for L-LA over D-LA was evident by a relative ratio of k_{app} 's of 11.3:1 (Figure S2). Following the consumption of *rac*-LA by (*R,R*)-Lig¹Al-Et, we observed a nonlinear dependence of $\ln([LA]_{t=0}/[LA]_t)$, thus supporting a polymerization under kinetic resolution.^[7] These findings are consistent with a clear role of the enantiomorph-site control mechanism. The enantiomerically pure catalysts (*R,R*)-Lig¹Al-Et or (*S,S*)-Lig¹Al-Et are proposed to give isotactic PLA of a diblock microstructure, whereas their racemic mixture gives isotactic PLA of a multiblock microstructure (and lower overall tacticity) as a result of polymeryl-exchange.^[22]

The polymerization results with Lig²Al-Et are summarized in Table S2. Polymerization of *rac*-LA with either (*R,R*)-Lig²Al-Et or (*S,S*)-Lig²Al-Et at 70 °C led to an almost atactic PLA having a slight heterotactic tendency of $P_r = 0.64$ (Table S-2, entries 1,2). Lowering the polymerization temperature to 50 °C gave PLA with an identical degree of tacticity. Partial conversions of about 50% were noted after 20 h for the polymerizations at both temperatures, thus signifying slow

reactions.^[23] On the other hand, employing the racemic variety of $\text{Lig}^2\text{Al-Et}$ for the polymerization of *rac*-LA at 70 °C led to a highly heterotactic PLA with a $P_r = 0.86$, and lowering the polymerization temperature to 50 °C gave PLA with a $P_r \geq 0.98$! The dramatic change of tacticity is clearly apparent in the homo-decoupled ^1H NMR spectra (Figure 2;

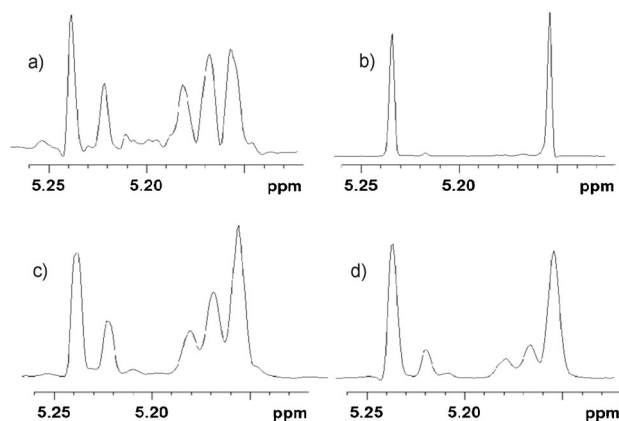


Figure 2. Homo-decoupled ^1H NMR spectra of PLA prepared from *rac*-LA employing $\text{Lig}^2\text{Al-Et}$. a) (R,R) - $\text{Lig}^2\text{Al-Et}$. b) *rac*- $\text{Lig}^2\text{Al-Et}$. c) 90:10 $(R,R)/(S,S)$ - $\text{Lig}^2\text{Al-Et}$ mixture. d) 65:35 $(R,R)/(S,S)$ - $\text{Lig}^2\text{Al-Et}$ mixture.

a versus b). This is one of the highest heterotacticities ever reported for any catalyst,^[10] and appears to exceed that reported for Gibson's original salan aluminum catalyst. Higher conversions (and correspondingly PLAs of higher molecular weights) were obtained through polymerizations catalyzed by *rac*- $\text{Lig}^2\text{Al-Et}$ relative to (R,R) - $\text{Lig}^2\text{Al-Et}$. Following the consumption of *rac*-LA by NMR spectroscopy at 70 °C in $[\text{D}_8]$ toluene showed first-order rates in lactide and a high relative k_{app} ratio of 7:1 for *rac*- $\text{Lig}^2\text{Al-OBn}$ versus (R,R) - $\text{Lig}^2\text{Al-OBn}$ (Figure 3).^[24]

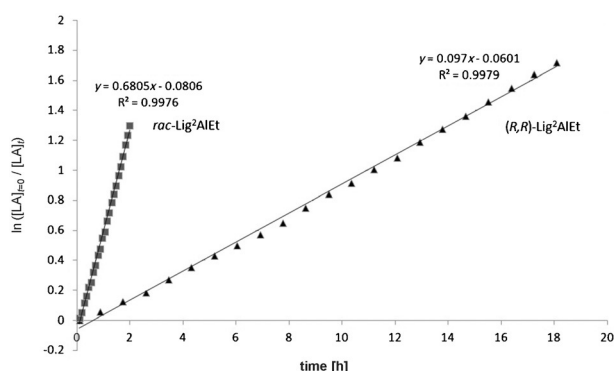
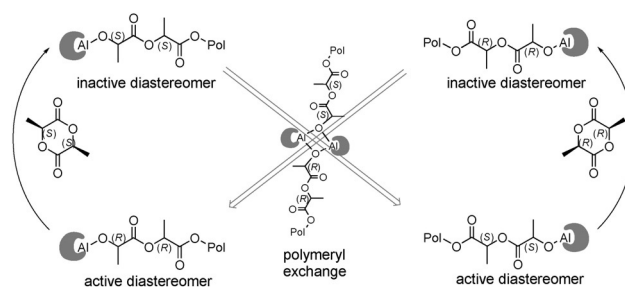


Figure 3. First-order kinetic plots for the consumption of *rac*-LA by (R,R) - $\text{Lig}^2\text{Al-OBn}$ and *rac*- $\text{Lig}^2\text{Al-OBn}$ in $[\text{D}_8]$ toluene at 70 °C. $[\text{LA}]_0 = 0.500 \text{ M}$; $[\text{LA}]_0/[\text{Al}] = 50$.

The proposed mechanism for this stereocontrol is depicted in Scheme 3. Insertion of a given lactide enantiomer is “allowed” only for a specific combination of salan chirality and last-inserted lactide enantiomer (of opposite chirality to the one being inserted). This insertion gives a diastereomeric combination of salan/last inserted lactide which is inactive



Scheme 3. Proposed mechanism for the high heteroselectivity induced by *rac*- $\text{Lig}^2\text{Al-Et}$. The two salan ligand enantiomers are schematically represented as opposite chiral environments.

towards insertion of either of the lactide enantiomers. Transfer of the polymeryl group to an aluminum complex that has the opposite salan chirality (via a presumable bridging-alkoxo dinuclear species)^[25] regenerates a diastereomer that has an active combination of salan/last inserted lactide chiralities, which can now insert the opposite lactide enantiomer. A key step in this stereocontrol mechanism is the unique auto-inhibition, namely: the blocking of the catalytic site after each insertion, which can only be released by an exchange with the opposite polymeryl chain bound to the opposite salan aluminum enantiomer. To our knowledge, such an accurate cooperation between two enantiomers of a given catalyst for affording a highly stereoregular polymeric microstructure is unprecedented.^[26]

This catalytic system represents a unique case of stereoselective synthesis in which a higher degree of product stereoregularity is obtained by increasing the enantiomeric impurity of the catalyst. To explore whether heterotacticity could still be observed when the degree of enantiomeric impurity of the catalyst was decreased, we polymerized *rac*-LA employing (R,R) - and (S,S) - $\text{Lig}^2\text{Al-Et}$ mixtures having enantiomer ratios of 65:35 and 90:10 at 50 °C. In both cases, the PLA obtained was heterotactically enriched, showing P_r values of 83 % and 72 %, respectively (Table S2, entries 6 and 7 and Figure 2, c and d). Consistently, slower rates for *rac*-LA consumption were recorded as the enantiomeric impurity of the catalyst decreased (Figure S7). We conclude that a minor chiral impurity in the catalyst can account for a visible increase in polymer stereoregularity and reaction rate.

In conclusion, by employing the 2,2'-bipyrrrolidine-based chiral salan ligands, well-defined aluminum complexes were obtained as single diastereomers of high symmetry. While it is still unclear at this point which catalyst stereoisomers were responsible for the (high) stereocontrol of lactide polymerization in Gibson's system and the (low) stereocontrol in the system of Feijen and Chen, the clear restraints of the bipyrrrolidine skeleton strongly support the involvement of well-defined ‘chiral-at-metal’ catalytic species in our system. Polymeryl exchange between enantiomorphous catalytic species were shown to play a significant role in reducing the stereoselectivity control in polymerizations catalyzed by $\text{Lig}^1\text{Al-Et}$ and a dramatic role in enhancing the stereocontrol in polymerizations catalyzed by $\text{Lig}^2\text{Al-Et}$. We are currently exploring the generality of these findings and developing related catalyst systems.

Keywords: aluminum complexes · chiral salan ligands · poly(lactic acid) · polymerization · stereoselective catalysis

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- [20] For comparison, in Gibson's complex, bonds of 2.452 and 2.055 Å between the Al center and the apical and equatorial N donors, respectively (16% difference) were found.^[14]
- [21] The polymerization of *meso*-LA by these catalysts will be described elsewhere.
- [22] A kinetic-resolution profile was also demonstrated for the 1,2-diaminocyclohexane-based chiral salan aluminum complexes.^[16]
- [23] Following the polymerization kinetics of D-LA and L-LA by (*R,R*)-Lig²Al-OBn showed slow and practically identical rates, namely a *meso*-dyad is disfavored for both lactide enantiomers by this catalyst. See also Figure S4 in the Supporting Information.
- [24] In comparison, the highest heterotacticity obtained by the racemic diastereomer mixtures of the 1,2-diaminocyclohexane salan aluminum complexes was $P_r = 73\%$, and the k_{app} 's ratio was 1.5:1 (at 70 °C).^[16]
- [25] Assuming that the polymeryl exchange event is the rate-determining step, the highly heteroselective polymerization is expected to exhibit second-order dependence on aluminum concentration. Measurements of kinetics by ¹H NMR spectroscopy at 70 °C showed $k_{app} = k_p[Al]^{1.75}$ consistent with this hypothesis. See Figures S5 and S6 in the Supporting Information.
- [26] Polymerization of *meso*-LA by the isoselective Spassky catalyst gave syndiotactic PLA ($P_r = 0.96$) for the enantiomerically pure catalyst, which shifted to heterotactic PLA (80% homochiral linkages) for the racemic catalyst following a related mechanism including an *allo*-inhibition step.^[12c]
- [27] CCDC 1055912 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.

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