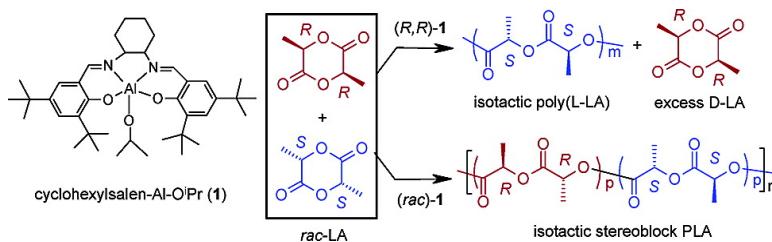


Controlled and Stereoselective Polymerization of Lactide: Kinetics, Selectivity, and Microstructures

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Controlled and Stereoselective Polymerization of Lactide: Kinetics, Selectivity, and Microstructures

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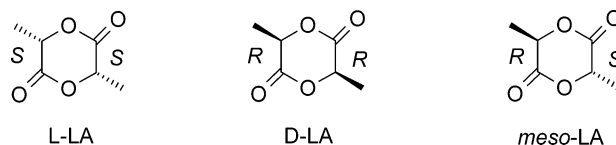
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Abstract: Chiral aluminum isopropoxides based on enantiopure or racemic cyclohexylsalen ligand (Jacobsen ligand) have been prepared and employed for stereoselective/stereoselective ring-opening polymerization of lactide in toluene at 70 °C. The kinetics, selectivity of the catalysts, and microstructure of the obtained polylactides, using different combinations of lactide enantiomers and catalysts, were determined. In all cases, polylactides of controlled molecular weight, low polydispersity, and defined end groups were obtained. The polymerizations are first-order in both monomer(s) and catalyst. (*R,R*)-CyclohexylsalenAlOⁱPr [(*R,R*)-1] polymerizes L-lactide significantly faster than D-lactide with a rate constant ratio k_L/k_D of ~14. The polymerization of *rac*-lactide using (*R,R*)-1 yields crystalline polymers, for which a selectivity factor of ~5.5 could be calculated up to 50% conversion based on the optical purity of the isolated polymers. The polymerization of a L-lactide/D-lactide (molar ratio: 80/20) mixture by (*R,R*)-1 furnishes an isotactic–atactic block copolylactide, which is highly crystalline with a $T_m = \sim 155$ °C. Polymerization of *rac*-lactide applying *rac*-cyclohexylsalenAlOⁱPr [*rac*-1] yields isotactic stereoblock polylactides with a high $T_m = \sim 185$ °C and a high degree of crystallinity.

Introduction

Poly(lactide) (PLA), a polymer derived from lactic acid, is one of the most important synthetic biodegradable polymers investigated for a wide range of biomedical and pharmaceutical applications such as controlled drug delivery, resorbable sutures, medical implants, and scaffolds for tissue engineering.^{1,2} On the basis of annually renewable resources, PLAs are also promising degradable substitutes for petrochemical-based polyolefins.^{3,4} Ring-opening polymerization of lactide (LA), the cyclic dimer of lactic acid, represents the most effective and versatile method to prepare PLAs.^{5,6} Moreover, lactide exists as three different stereoisomers (Scheme 1), which opens pathways to prepare amorphous to semicrystalline materials with a wide range of physical, mechanical, and degradation properties. Ring-opening polymerization of lactides is catalyzed by the addition of organometallic compounds such as stannous octoate⁷ and zinc lactate⁸ and high temperatures have to be

Scheme 1. Lactide Stereoisomers. *rac*-LA Is a 1:1 Mixture of L-LA and D-LA

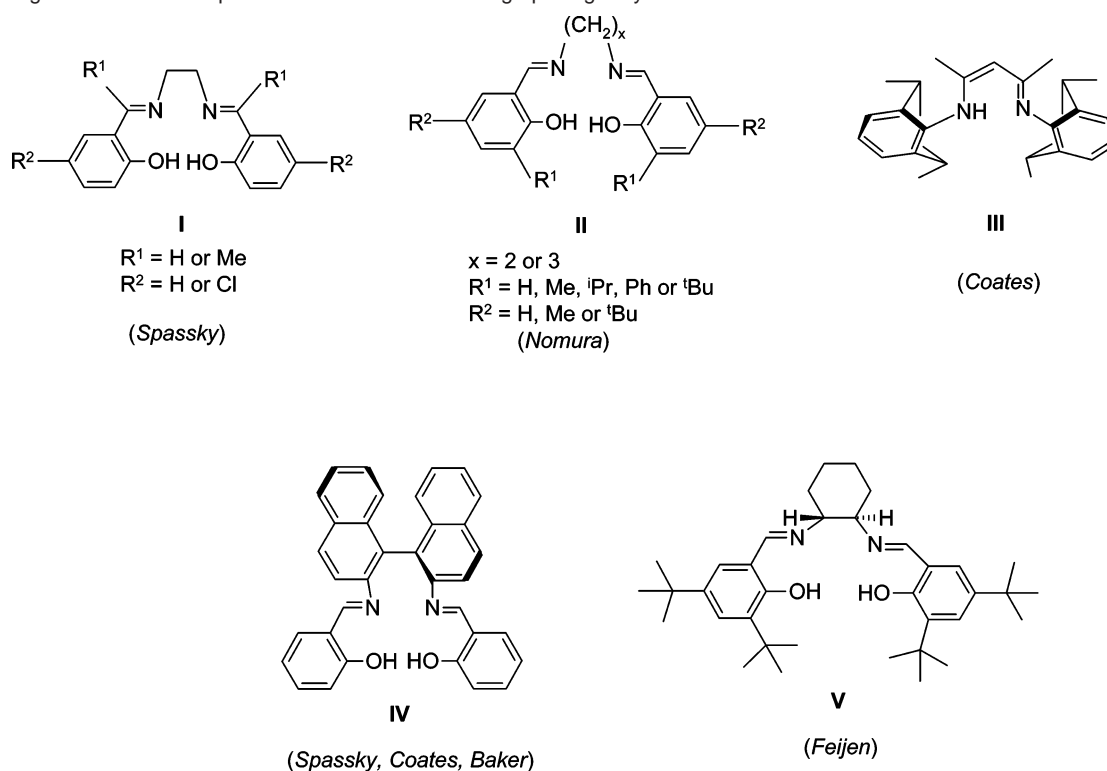


applied. Such conditions induce side reactions such as transesterification and racemization, which hampers the control over the polymerization process. The scientific interest in well-defined macromolecular architectures including telechelic-, block-, graft-, and star-shaped polymers has initiated major research efforts toward initiators that do yield well-defined polylactones and polylactides. Initiators such as aluminum alkoxides,⁹ yttrium and lanthanide alkoxides,¹⁰ and recently iron alkoxides¹¹ have been shown to give a controlled and living polymerization of LAs via a so-called coordination–insertion mechanism. Especially calcium-based initiating systems generated in situ by exchange of bis(trimethylsilyl)amide ligands with alcohols have shown to induce a fast living and highly controlled solution polymerization of lactide at room temperature.^{12,13} However, all above catalysts do not bias toward the different

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Scheme 2. Ligand Precursors Explored for Stereoselective Ring-opening Polymerization of Lactides

lactide stereoisomers. This implies that isotactic polylactides can be prepared only by the ring-opening polymerization of optically pure L-LA or D-LA, whereas *rac*-LA (a 1:1 mixture of L-LA and D-LA) or *meso*-LA will give an atactic polymer.

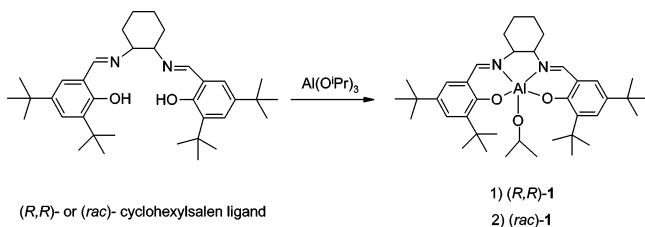
The physical and mechanical as well as degradation properties of PLAs are intimately dependent on the chain stereochemistry.^{14,15} For instance, isotactic poly(L-LA) is a highly crystalline material with a T_m of 170 °C.^{15,16} It has excellent mechanical properties and degrades rather slowly. Atactic poly(*rac*-LA) is amorphous and subject to a comparatively fast degradation. Therefore, it is of utmost importance to control chain stereochemistry for PLA homopolymers as well as their copolymers. Two different strategies, chain-end control and enantiomorphic site control of the catalyst, have been exploited.^{16–26} Scheme 2 presents known organic ligands that in combination with an appropriate metal center are capable of effecting stereoelectivity/stereoselectivity in lactide polymerization. Ligands **I**, **II**, and

III, which are achiral, induce stereoselectivity most probably via a chain-end control mechanism. Spassky et al showed that the aluminum complex of **I** imposes a moderate preference for isotactic addition in *rac*-LA polymerization.^{18–20} Nomura and co-workers used a different approach, in-situ generation of the initiating species from triethylaluminum, **II**, and an alcohol, and polylactides of notably high isotacticity can be obtained from *rac*-LA.²⁶ Coates and co-workers discovered that the β -diiminate (**III**) zinc alkoxide enables the preparation of mostly heterotactic (*-RRSSRRSS-*) PLA from *rac*-LA.^{21,24}

Indubitably, the most important breakthrough was Spassky's discovery of stereoelective lactide polymerization, applying aluminum complexes of a chiral binaphthyl Schiff's base (**IV**).¹⁷ At low conversion, the aluminum methoxide complex of (*R*)-**IV** demonstrated a preference for D-LA over L-LA to yield an optically active essentially isotactic D-LA polymer from *rac*-LA in toluene at 70 °C. The chiral ligand induces enantiomorphic site control in the LA ring-opening polymerization. This site control allows for the first time the synthesis of syndiotactic PLA from *meso*-LA applying the (*R*)-**IV**-AlO^{*i*}Pr catalyst.²² In a racemic mixture of L-LA and D-LA preferential polymerization can be achieved using a racemic mixture of (*R*)- and (*S*)-**IV**-AlO^{*i*}Pr, leading to enantiomeric poly(L-LA) and poly(D-LA) blocks that easily form stereocomplexes.^{16,23,25} These stereocomplexes have a much higher melting temperature than isotactic poly(L-LA). Therefore, enantiomorphic site control catalysts are highly versatile and provide many challenging synthetic opportunities.

Recently, we have shown that the cyclohexylsalen aluminum alkoxide, (*R,R*)-**V**-AlO^{*i*}Pr and *rac*-**V**-AlO^{*i*}Pr, provide a high isospecificity and excellent control in both solvent-based and solvent-free lactide polymerization.²⁷ The stereoselective polymerization of lactide in the bulk has not been reported before.

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Scheme 3. Synthesis of Cyclohexylsalen-Al-OⁱPr

In this paper, the polymerization kinetics and stereoselectivity of cyclohexylsalen aluminum alkoxide for lactide polymerization have been determined. We have also shown that by employing such a site-control catalyst poly(lactides) with many distinct microstructures and properties can be readily obtained.

Results and Discussion

Synthesis of (Cyclohexylsalen)Al Complexes. The stoichiometric reaction of (*R,R*)- or *rac*-cyclohexylsalen ligand (Jacobsen ligand) with aluminum isopropoxide in toluene at 80 °C afforded (*R,R*)-(cyclohexylsalen)AlOⁱPr [(*R,R*)-**1**] or *rac*-(cyclohexylsalen)AlOⁱPr [*rac*-**1**] as yellowish solids in high yield (Scheme 3). Elemental analysis revealed that species with a molecular formula of AlC₃₉H₆₁N₂O₃ had been formed. The ²⁷Al NMR spectrum of (*R,R*)-**1** using toluene-*d*₈/toluene (v/v: 1/2) displayed a single resonance at δ 35.45 (*w*_{1/2} = 954 Hz), in line with a monomeric five coordinate aluminum center.^{28,29} The ¹H NMR spectrum (Figure 1) of (*R,R*)-**1** (see for comparison the free (*R,R*)-cyclohexylsalen ligand) showed signals at δ 0.86 and 3.71 with an integral ratio of 6:1, which are attributed to the methyl protons and methine proton of the isopropoxide ligand, respectively. Notably, the isopropoxide methyl protons appeared as double doublets, indicating that the two methyl groups are chemically inequivalent. In addition, the protons of the cyclohexylsalen moiety in (*R,R*)-**1** are well resolved into two different chemical environments. The -N=CH- protons display chemical shifts at δ 8.36 and 8.15, and the α-protons of the cyclohexane moiety show resonances at δ 3.92 and 3.04. This spectroscopic inequivalence shows that (*R,R*)-**1** and *rac*-**1** adopt a distorted square-pyramidal geometry.^{28,30} The equal intensities of the signals at δ 3.92 and 3.71 confirmed the formation of the (cyclohexylsalen)AlOⁱPr complex.

Ring-Opening Polymerization Mechanism. To elucidate the ring-opening mechanism, a L-LA living oligomer was prepared and analyzed by ¹H NMR spectroscopy. The polymerization of L-LA with (*R,R*)-**1** in a 12:1 molar ratio was allowed to proceed for 1 day in toluene at 70 °C, and after removal of the solvent the residue was redissolved in CDCl₃. The ¹H NMR of the thus obtained living oligomer (see supporting information) showed that the protons of the cyclohexylsalen moiety had similar chemical shifts as observed for (*R,R*)-**1**, in accordance to our expectation that the cyclohexylsalen ancillary remains bound to the aluminum center during the ring opening. The signals of the Al isopropoxide ligand have completely disappeared. In combination with homonuclear COSY experiments, a double doublet centered at δ 1.24/1.26 is attributed to the methyl

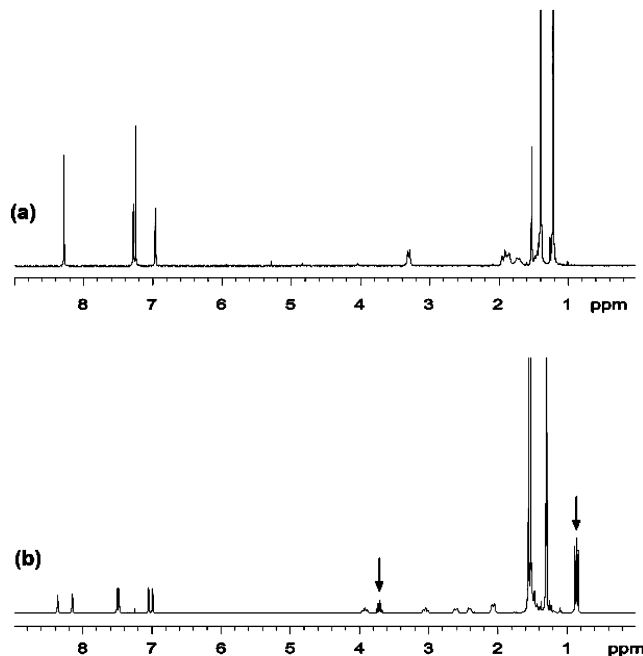


Figure 1. ¹H NMR spectra (300 MHz, CDCl₃) of (*R,R*)-cyclohexylsalen ligand (a) and (*R,R*)-(cyclohexylsalen)AlOⁱPr. (b) Arrows indicate signals arising from the isopropoxide unit.

protons of the formed isopropyl ester end group. Resonances at δ 4.22 (q) and 1.17 (d) correspond to the lactyl unit bound to the aluminum center, whereas the quartet at δ 4.82 and the doublet at δ 1.39 most probably arise from the penultimate lactyl unit. These differences in chemical shifts may be due to a shielding effect of the cyclohexylsalen ligand and/or the dative bond formation between the α-carbonyl oxygen and aluminum forming a five-membered species (Scheme 4).³¹ The disappearance of the above lactyl signals after quenching the active species with acetic acid confirms our hypothesis. Moreover, the -N=CH- protons gave a singlet at δ 8.26, the α-cyclohexane protons revealed a broad resonance at δ 3.31, and signals attributable to the living ends vanished. Instead, a quartet at δ 4.34 characteristic of the methine proton neighboring a hydroxyl group (-CH(Me)OH) emerged. Resonances at δ 5.16 (q) and 1.59 (d) belong to the methine and methyl protons of the polymer main chain. The conversion was determined from the integrals of signals at δ 1.65 (LA) and 1.59 (PLA) and is 92%.

The ¹H NMR of the purified oligomer (see supporting information) shows clearly that the PLA oligomer is systematically end-capped with one isopropyl ester group and one hydroxyl group. The *M_n* determined by end-group analysis is 1900, close to the theoretical value *M_n*(theory) = 1650. MALDI-TOF mass spectrometry (Figure 2) further corroborates the chain structure and afforded a *M_n* = 1800 and *M_w*/*M_n* = 1.05. Notably, peaks corresponding to molecular masses of (n + 1/2) lactide repeat units (marked with an asterisk in Figure 2) are also present. This unveils that intermolecular ester-exchange reactions are occurring to a certain extent.³² However, no peak attributable to transesterification, either intermolecular or intramolecular, is detected for polymers obtained from *rac*-**1** initiated *rac*-LA

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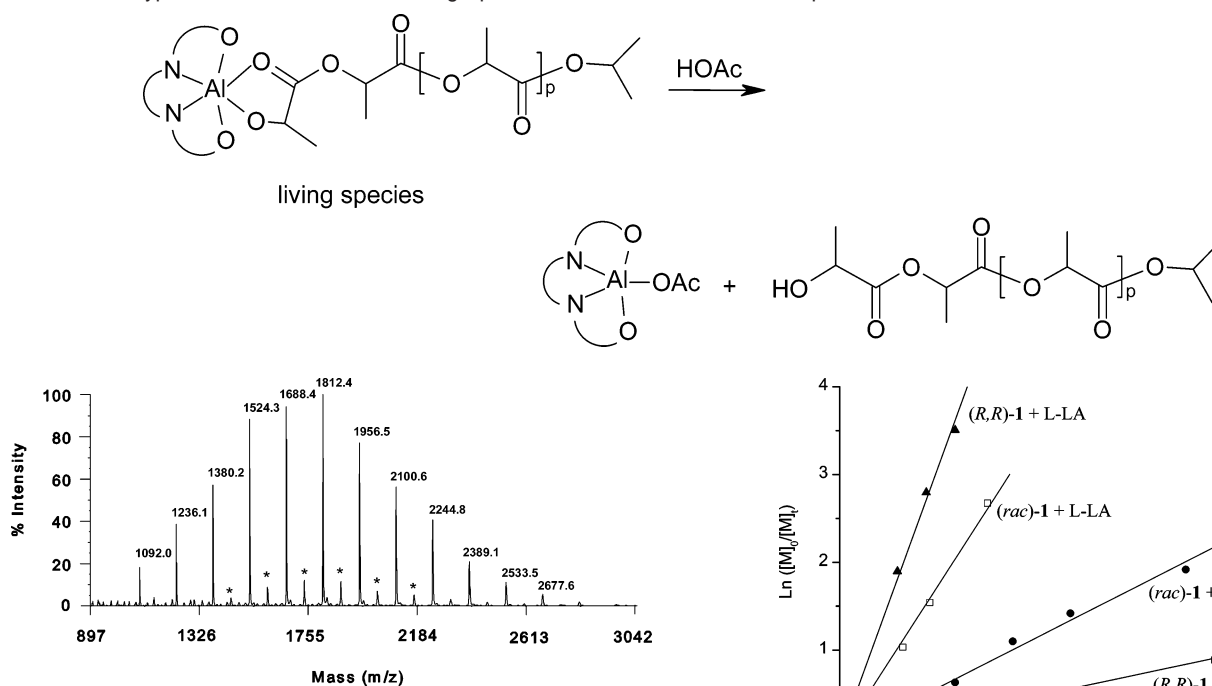
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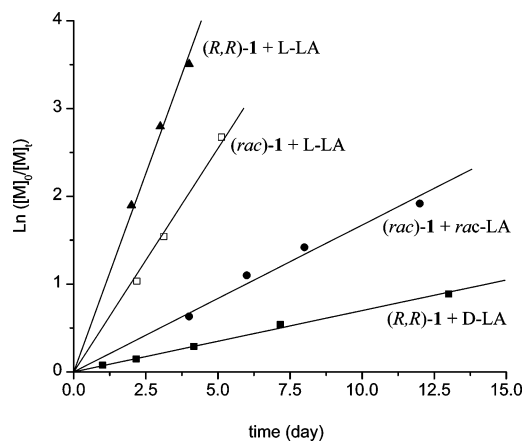
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Scheme 4. Hypothetic Structures of the Living Species as Well as the Quenched Species**Figure 2.** MALDI-TOF spectrum of L-LA oligomer. The signals marked with an asterisk have values corresponding to $(n + 1/2)$ repeating units and are due to polymer chains formed from intermolecular transesterifications. The polymer chains are adducted with a sodium ion.

polymerization over a time period of 12 days with a $[LA]_0/[Al]_0 = 62/1$ under otherwise similar polymerization conditions (see supporting information). Therefore, it appears that the rather high catalyst concentration in combination with a prolonged reaction time after high conversion in the preparation of oligomers might account for the observed transesterification reactions. The molecular mass of the polymers increases linearly with monomer conversion while retaining a low polydispersity (see supporting information). All the results are in accordance with a living polymerization.

It is evident that during the polymerization the cyclohexylsalen ancillary chelates the aluminum center in a defined geometry, which is believed the origin of the stereoselectivity/stereoselectivity. The initiation is quantitative and the polymerization proceeds exclusively through acyl-oxygen cleavage of the monomer.

Polymerization Kinetics. The polymerization kinetics were studied with $[LA]_0/[Al]_0 = 62/1$ and $[LA]_0 = 0.8$ M at 70 °C using toluene as a solvent. Different combinations of catalysts and lactide stereoisomers were used. In all cases, the polymerization obeyed first-order kinetics in monomer with instantaneous initiation (Figure 3). The fastest polymerization was observed for (R,R) -**1** initiated L-LA polymerization having a pseudo-first-order rate constant $k_{app} = 0.902$ day⁻¹. The polymerization rate for (R,R) -**1** and D-LA is the lowest ($k_{app} = 0.067$ day⁻¹), which is only 1/14 the rate for (R,R) -**1** and L-LA. Hence, it is clear that (R,R) -**1** has a marked preference for the L-isomer as compared to the D-isomer. The polymerization of L-LA using rac -**1** has a rate constant ($k_{app} = 0.509$ day⁻¹) slightly higher than half that of (R,R) -**1** and L-LA. This is in line with our expectation since only half of the rac -**1** has the (R,R) -configuration and the other half (S,S)-**1** can only slowly polymerize L-LA.

**Figure 3.** First-order kinetic plots for lactide polymerizations in toluene at 70 °C with $[M]_0/[I]_0 = 62$ and $[M]_0 = 0.8$ M. Different combinations of catalysts and lactide enantiomers were used.

The extent of the stereoselectivity of a chiral catalyst in an enantiomorphic site control polymerization of a racemic monomer mixture may be determined from the enantiomeric excess (ee) of the recovered unreacted monomer. It is difficult, however, to recover the unreacted lactide monomer quantitatively from the polymerization medium. Therefore, in this study the optical activities of polymers formed from (R,R) -**1** and rac -LA at different time intervals were measured by polarimetry and used for the calculation of the ee of the monomers. All the polymers displayed a pronounced optical rotation, e.g., $[\alpha]_D^{25} = -90.3^\circ$ and -22.2° for polylactides obtained at 21.1% and 87.8% conversion, respectively. The negative values are consistent with preferential polymerization of L-LA by (R,R) -**1**. The specific rotation of poly(L-LA) increases with increasing molecular mass and becomes constant when $M_n > 8000$. For example, poly(L-LA)s with $M_n = 1800$, 5600, and 8600 have $[\alpha]_D^{25} = -142^\circ$, -148° , and -152° , respectively. Therefore, M_n has to be taken into account when determining the enantiomeric excess (ee) of L-LA in polylactides obtained from (R,R) -**1** and rac -LA. The ee of LA units in the isolated polymer as well as the calculated ee of the unreacted monomer based on the optical purity of polymer and monomer conversion as a function of conversion is shown in Figure 4. This profile resembles the polymerization of rac -LA using enantiopure (R) -binaphthyl Schiff base aluminum methoxide¹⁷ as well as the kinetic resolution of organic reagents with a chiral catalyst.³³

The selectivity factor (s), which is quantified as the ratio of the relative rates of reaction for the two enantiomers ($s = k_{rel}$

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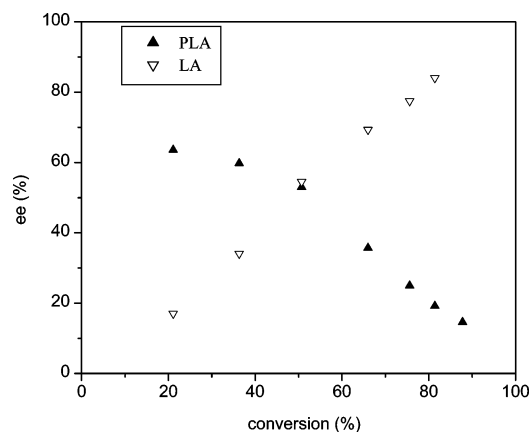


Figure 4. Enantiomeric excess (ee) of LA units in recovered polymer (▲) and the calculated ee of unreacted LA monomers (▽) based on the optical purity of the polymer versus conversion for *rac*-LA polymerization initiated with (*R,R*)-**1** ($[LA]_0/[Al]_0 = 62/1$, $[LA]_0 = 0.8$ M, toluene, 70 °C).

$= k_{fast}/k_{slow}$), is generally used for evaluation of the efficacy of stereoselective/stereoselective catalysts. Assuming a first-order kinetic dependence on the substrates, s can be determined by eq 1, where c represents the monomer conversion and ee the enantiomeric excess of L-LA units in the obtained polymer.

$$s = k_{rel} = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)] \quad (1)$$

Nearly constant s values of 5.5 are computed up to 50% LA conversion to polymer. At higher conversions, the measurement of the optical activity of the polymer becomes less accurate and therefore also the calculation of the s values. The stereoselectivity is intrinsically dictated by the magnitude of $\Delta\Delta G^\ddagger$ (eq 2), the difference in activation energies between the transition states for different enantiomers in the selectivity-determining step of the polymerization. Based on $s = 5.5$, a $\Delta\Delta G^\ddagger = \Delta G^\ddagger_L - \Delta G^\ddagger_D = 1.16$ kcal/mol could be calculated for the polymerization of *rac*-LA using (*R,R*)-**1** at 70 °C.

$$s = k_{rel} = k_{fast}/k_{slow} = e^{\Delta\Delta G^\ddagger/RT} \quad (2)$$

The polymerization of *rac*-LA applying *rac*-**1** revealed a $k_{app} = 0.167$ day⁻¹ (Figure 3), which is much lower than for L-LA polymerization with *rac*-**1** ($k_{app} = 0.509$ day⁻¹). The low reaction rate found with the system *rac*-LA and *rac*-**1** could possibly be explained by the interchange of growing chains between the *R,R* and *S,S* catalyst effectively decreasing the reaction rate because the coordination of (*R,R*)-**1** and poly(D-LA) chain leads to a very low rate of polymerization. In other words, the number of active sites for polymerization is decreased. In addition it has been shown that for asymmetric catalysis interaction between enantiomers could exert influences on the reaction rate.³⁴ Therefore, it can be imagined that such interaction will also influence the coordination of monomers with the catalyst, which may lead to lower reaction rates. Furthermore, stereocomplex formation between growing chains associated with the catalyst may also hinder the polymerization.

The polymers obtained from *rac*-**1** and *rac*-LA are all optically inactive, in line with our assumption that the chiral compounds (*S,S*)-**1** and (*R,R*)-**1** have identical stereoselectivity

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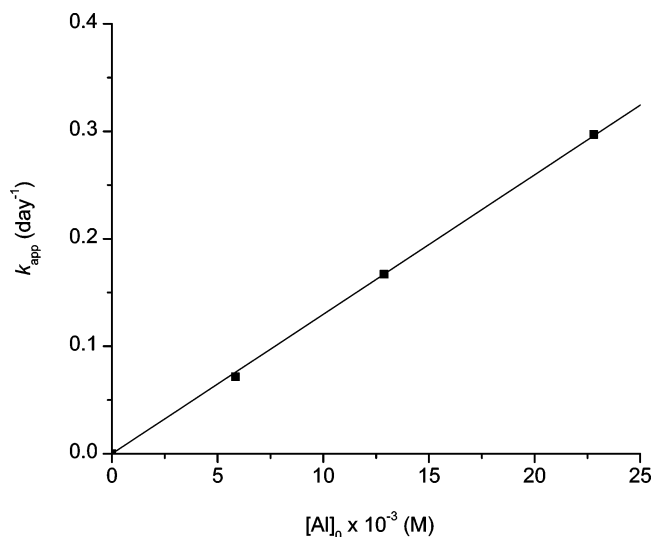


Figure 5. Plot of k_{app} versus $[Al]_0$ for the polymerization of *rac*-LA with *rac*-**1** in toluene at 70 °C using $[M]_0 = 0.8$ mol/L.

in lactide polymerization but with preference for enantiomers of the opposite configurations.

The polymerization kinetics for an enriched enantiomeric mixture of lactide, D20L80 (D-LA/L-LA: 20/80), using (*R,R*)-**1** was also examined. The conversions of L-LA and D-LA at different intervals were determined on the basis of the ee of L-LA units in the isolated polymers and the total monomer conversion (c). The first-order kinetics for L-LA and D-LA revealed a remarkably high relative polymerization rate $k_L/k_D = 25$ (see supporting information). The polymer obtained at 51.3% conversion consists essentially of L-LA units, and almost all L-LA has been converted to polymer at 86.8% conversion, while D-LA is enriched from initial 20% to 95% in the monomer pool. This is in sharp contrast with other catalyst systems, e.g., stannous octoate initiated polymerization of enantiomerically enriched lactides, where the minor component would be depleted with a higher pseudo rate constant than the major component due to a preference for syndiotactic enchainment.^{35,36} The important implication from this result is that when using an isospecific catalyst like (*R,R*)-**1**, it is not essential to start from optically extremely pure L-LA or D-LA in order to prepare isotactic poly(lactides).

To determine the kinetic dependence on the catalyst, the concentration of *rac*-**1** was varied from 5.84×10^{-3} to 22.8×10^{-3} M under otherwise identical conditions ($[rac-LA]_0 = 0.8$ M, toluene, 70 °C). In all cases, the polymerization follows first-order kinetics in monomer. The pseudo-first-order rate constant versus the concentration of *rac*-**1** is plotted in Figure 5. The k_{app} increases linearly with *rac*-**1**. Hence, the polymerization of *rac*-LA by *rac*-**1** obeys the following kinetic law:

$$-d[LA]/dt = k_p[LA][Al]$$

A k_p value of 9.02×10^{-3} L·mol⁻¹·min⁻¹ is determined for *rac*-**1** initiated *rac*-LA polymerization in toluene at 70 °C. This value is lower than that of *rac*-LA polymerization with Al(O^{*i*}-

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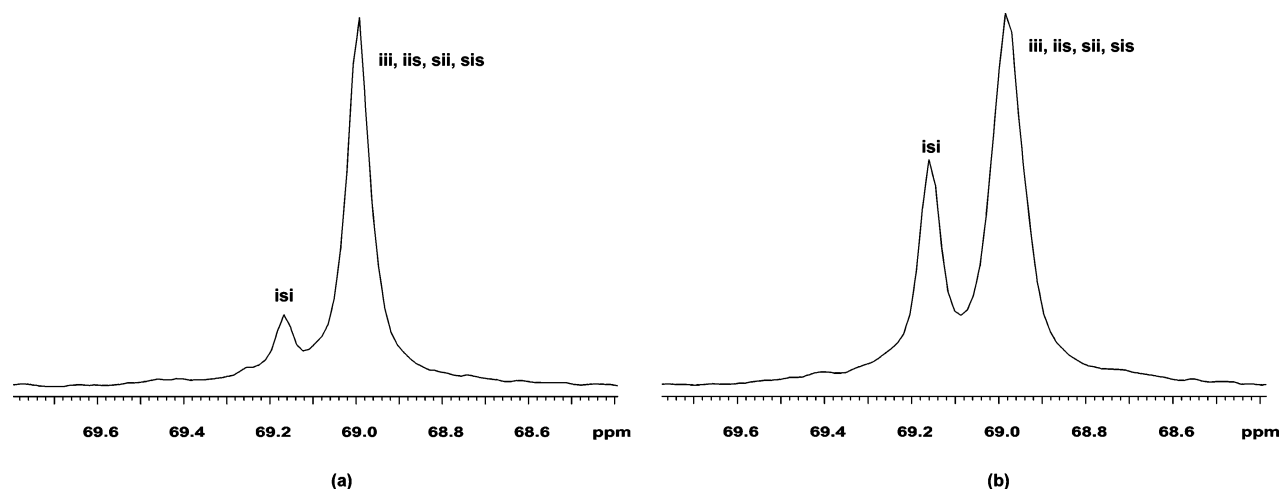


Figure 6. Methine carbon resonances in the ^{13}C NMR spectra (75 MHz, CDCl_3) for poly(*rac*-LA)s. (a) PLA sample obtained from *rac*-LA polymerization by (*R,R*)-**1** in toluene at 70 °C with $[\text{LA}]/[\text{Al}] = 62/1$ and conversion = 87.8%. (b) Poly(*rac*-LA) prepared by a nonselective catalyst $\text{Zn}(\text{OCH}(\text{Me})\text{COO}^i\text{-Pr})_2$.

$\text{Pr})_3$ ($k_p = 0.60 \text{ L}\cdot\text{mol}^{-1}\cdot\text{min}^{-1}$)³⁷ or achiral SalenAlOMe ($0.061 \text{ L}\cdot\text{mol}^{-1}\cdot\text{min}^{-1}$)²⁰ under similar conditions, which is most probably due to the rather rigid and bulky nature of the cyclohexylsalen ligand in *rac*-**1**. It is worth mentioning herein that *rac*-SALBinaphtAlO^{*i*}Pr brought about a much faster polymerization of *rac*-LA ($1.05 \text{ L}\cdot\text{mol}^{-1}\cdot\text{min}^{-1}$)²⁵ than *rac*-**1**. The higher activity of SALBinaphtAlO^{*i*}Pr as compared to *rac*-**1** might be due to the ability of binaphthyl moiety to delocalize electrons, the absence of bulky substituents in the aromatic rings in the ortho position, and a long diamino bridge (four carbons for SALBinaphtAlO^{*i*}Pr vs two carbons for *rac*-**1**). It has been shown that the replacement of ethylene diamino with trimethylene diamino in SalenAlOBz significantly increases the polymerization rate.²⁶

This overall kinetic law could in principle be extrapolated to other combinations of (cyclohexylsalen)AlO^{*i*}Pr catalysts and lactide enantiomers such as (*R,R*)-**1** or *rac*-**1** for L-LA or D-LA polymerization.

Polymer Microstructures and Thermal Properties. During the past decade, particularly ^{13}C NMR^{38–42} and homonuclear decoupled ^1H NMR^{35,36,42,43} have become powerful tools for elucidating the microstructure of polylactides. The methine carbon resonances in the ^{13}C NMR spectra can be assigned in terms of tetrad probabilities. Figure 6 presents a spectrum of PLA obtained from polymerization of *rac*-LA using (*R,R*)-**1** at 87.8% conversion (a) as well as a spectrum for poly(*rac*-LA) by a nonselective zinc alkoxide catalyst (b). Clearly, (*R,R*)-**1** favors the formation of isotactic sequences. On the basis of enantiomorphic site control statistics, PLAs obtained from *rac*-LA can exhibit five tetrad sequences, i.e., *iii*, *isi*, *iis*, *si*, and *sis*, where *i* denotes isotactic and *s* syndiotactic. The degree of stereoselectivity may be defined by the parameter P_i , which is

Table 1. Normalized Tetrad Intensities of PLAs Obtained from Polymerization of *Rac*-LA Using (*R,R*)-**1** or *rac*-**1** at Different Monomer Conversions^a

monomer conv, %	tetrad intensities (normalized) ^b		P_i^c
	<i>isi</i>	<i>iii</i> + <i>iis</i> + <i>sii</i> + <i>sis</i>	
<i>(R,R)</i> - 1 for <i>rac</i> -LA			
21.1	0.071	0.929	0.92
36.3	0.083	0.917	
50.7	0.106	0.894	
66.0	0.114	0.886	
75.6	0.121	0.879	
81.4	0.125	0.875	
87.8	0.120	0.880	
<i>rac</i> - 1 for <i>rac</i> -LA			
46.8	0.068	0.932	0.93
66.7	0.070	0.930	0.92
75.8	0.069	0.931	0.93
85.3	0.068	0.932	0.93

^a Polymerization was performed in toluene at 70 °C with $[\text{LA}]_0/[\text{Al}]_0 = 62/1$. ^b Tetrad intensities were determined from the methine resonances in the ^{13}C NMR spectra (75 MHz, CDCl_3). ^c P_i is the probability of forming a new *i*-dyad. The tetrad intensities for *rac*-LA polymerization in terms of P_i have been expressed as follows: $[iii] = [P_i^2 + (1 - P_i)^2 + P_i^3 + (1 - P_i)^3]/2$, $[isi] = [P_i(1 - P_i) + P_i(1 - P_i)^2]/2$, $[iis] = [sii] = [sis] = [P_i^2(1 - P_i) + P_i(1 - P_i)^2]/2$.

the probability of forming a new *i*-dyad. The relative proportions of the tetrad sequences are largely dependent on the P_i exerted by the catalyst, where $[iii] = [P_i^2 + (1 - P_i)^2 + P_i^3 + (1 - P_i)^3]/2$, $[isi] = [P_i(1 - P_i) + P_i(1 - P_i)^2]/2$, $[iis] = [sii] = [sis] = [P_i^2(1 - P_i) + P_i(1 - P_i)^2]/2$.²⁵ Hence, employing the methine carbon region of the ^{13}C NMR of the isolated polymers, the extent of stereoselectivity can be determined. However, it should be noted that the above relationship holds only at low conversion for (*R,R*)-**1** initiated polymerization of *rac*-LA, since the enantiomeric composition is continuously altered during the polymerization process. The tetrad proportions for polymers obtained from *rac*-LA polymerization initiated with (*R,R*)-**1** are listed in Table 1. The PLAs formed at low conversion have long isotactic sequences as revealed by the comparatively low intensity of *isi* sequence. The *isi* proportion, nevertheless, first increases and then starts to decrease with increasing conversion. This is in accordance with a tapered distribution of stereocenters from predominantly isotactic L-lactyl units to predominantly isotactic D-lactyl units. Based on the polymer sample obtained

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at 21.1% conversion, a P_i value as high as 92% is calculated for (*R,R*)-**1** initiated *rac*-LA polymerization in toluene at 70 °C. Thermal analysis revealed that all polymers are crystalline. For example, the PLA resulting after 87.8% conversion shows an $T_m = 161.5$ °C and $\Delta H_m = 31.1$ J/g in the first heating scan. No recrystallization takes place in the second heating after rapid cooling from the melt, in accordance with the literature.^{15,44}

Unlike (*R,R*)-**1** initiated *rac*-LA polymerization, the polymerization of *rac*-LA using *rac*-**1** affords polymers having microstructures which are conversion-independent, as revealed by the ¹³C NMR (Table 1). The P_i values (~93%) are nearly equal to that determined for *rac*-LA and (*R,R*)-**1** at low conversion. These results support the conclusion that the preferential propagation of L-LA enantiomer on (*R,R*)-**1** species parallels the preferential propagation of D-LA on (*S,S*)-**1** species. A polymer with a low $M_n = 4800$ displayed a high melting temperature of 185.8 °C [$\Delta H_m = 41.9$ J/g, $T_c = 96.8$ °C, $\Delta H_c = -35.4$ J/g, $T_g = 46.8$ °C], which is approximately 20 °C higher than that for the poly(L-LA) homopolymer with a $M_n = 9900$ [$T_m = 168.4$ °C, $\Delta H_m = 59.2$ J/g, $T_c = 98.1$ °C, $\Delta H_c = -37.3$ J/g, $T_g = 57.4$ °C]. At high monomer conversion the polymer ($M_n = 7800$) showed an analogous thermal behavior, except for a relatively higher $T_g = 54.4$ °C and $T_c = 112.4$ °C. The high melting temperatures of these polymers are due to the formation of stereocomplexes between isotactic blocks of opposite configurations.^{44,45} On the basis of an enantiomorphic site control mechanism, (*R,R*)-**1** preferentially polymerizes L-LA to produce a predominantly L-LA chain, while (*S,S*)-**1** preferentially polymerizes D-LA to produce a predominantly D-LA chain, and therefore -LLLLLDLLLL- and -DDDDDLDDDD- sequences are anticipated. Recently, Coates and co-workers reported that a stereoblock-type (-LLLLD-DDDD-) PLA is formed employing an analogous *rac*-binaphthyl Schiff base aluminum alkoxide catalyst to polymerize *rac*-LA, for which a polymer exchange mechanism where growing chains switch between (*R*)- and (*S*)-species was proposed.²⁵ The homonuclear decoupled ¹H NMR spectra (see supporting information) of the polymers prepared from *rac*-LA polymerization using *rac*-**1** revealed besides a major *iii* tetrad, three small resonances assignable to *sii*, *iis*, and *isi* tetrads with nearly identical integrals and an almost negligible *sis* peak. This result strongly suggests that a polymer exchange mechanism is operative for *rac*-**1** initiated *rac*-LA polymerization, yielding PLAs with an isotactic stereoblock microstructure.²⁵ The intensity of *sii*, *iis*, *isi*, and *sis* tetrads relative to *iii* tetrad does not change with conversion, indicating a homogeneous distribution of isotactic sequences in the polymer chain. Furthermore, additional signals at δ 5.195 and 5.225 were also observed. These two resonances are most probably due to the lactyl units placed at both ends, as shown by their systematically decreasing intensities with increasing degree of polymerization. The absence of a signal at δ 5.208 attributable to *iiiss* and *ssiii* hexads further confirms that no transesterification reactions took place.⁴³

A PLA obtained from a D-LA/L-LA mixture (ratio: 20/80) and (*R,R*)-**1** at 51.3% conversion is composed almost exclusively of isotactic L-lactyl units, as revealed by the barely discernible *isi* signals (see supporting information). This polymer is highly crystalline with thermal properties [$T_m = 156.7$ °C, $\Delta H_m = 43.0$

J/g, $T_c = 98.6$ °C, $\Delta H_c = -35.2$ J/g, $T_g = 51.3$ °C] much like those of isotactic poly(L-LA) of similar molecular weight ($M_n = 4600$). Polymer samples acquired at high monomer conversion (90.5%) contain more syndiotactic sequences, also readily crystallized ($T_c = 121$ °C, $\Delta H_c = -39.3$ J/g) after quenching from the melt. The polymer had a rather high melting temperature ($T_m = 155.1$ °C, $\Delta H_m = 40.6$ J/g) and a significant degree of crystallinity (38.3%). These results are unusual and might be attributed to a distinct microstructure comprising a long mostly isotactic L-lactyl block (crystalline) and a relatively short atactic block (amorphous).

Conclusions and Perspectives

In summary, a readily accessible chiral catalyst system that induces highly stereoselective yet controlled ring-opening polymerization of lactide has been reported. A marked preference for L-LA over D-LA isomer was imposed by enantiopure (*R,R*)-**1**, which contrasts analogous (*R*)-binaphthyl Schiff's base aluminum complex (preference for D-LA rather than L-LA). Poly lactides of distinct microstructures and properties could be obtained. The polymerization of *rac*-LA employing (*R,R*)-**1** affords crystalline polymers, although they are unable to crystallize after quenching from the melt. *rac*-**1** to polymerize *rac*-LA yields polymers of high melting point (~185 °C) and high crystallinity, due to the effective cocrystallization between poly(L-LA) blocks and poly(D-LA) blocks. Interestingly, the polymerization of L-LA / D-LA (molar ratio: 80/20) using (*R,R*)-**1** gives an isotactic-atactic stereoblock poly lactide which is highly crystalline with $T_m = \sim 155$ °C.

The recent developed stereoselective catalysts offer great potential in preparing new distinct polymers from conventional monomers. Through rational catalyst design especially assisted by, e.g., molecular modeling and combinatorial methods, we believe that even more efficient catalyst systems with better stereoselectivity might be developed.

Experimental Section

General. All experiments were carried out under argon using Schlenk techniques or under nitrogen in a glovebox. Toluene and hexane were distilled from sodium wire. Aluminum isopropoxide (>99.99%-Al, Strem Chemicals), (*1R, 2R*)-(-)-1,2-cyclohexanediamino-*N,N'*-bis(3,5-di-*tert*-butyl-salicylidene) [(*R,R*)-cyclohexylsalen ligand] and (*1S, 2S*)-(+)-1,2-cyclohexanediamino-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene) [(*S,S*)-cyclohexylsalen ligand] (98.0%, Acros Organics) were used without further purification. L-Lactide and D-lactide (Purac Biochem b.v., The Netherlands) were purified by recrystallization from toluene. All glassware for the polymerization was dried in an oven before use.

Measurements. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were recorded on a Varian Inova spectrometer using CDCl₃ solutions and were referenced to shifts of residual CHCl₃ (δ 7.25 for ¹H NMR and δ 77.0 for ¹³C NMR). Matrix assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry was performed using a Voyager-DE-RP MALDI-TOF mass spectrometer (Applied Biosystems/PerSeptive Biosystems, Inc., Framingham, MA) equipped with delayed extraction. A 337-nm UV nitrogen laser producing 3-ns pulses was used and the mass spectra were obtained in the linear and reflectron modes. Samples were prepared by mixing 10 μ L of poly lactide solution with 30 μ L of a solution of 1.0 mg/L of 2,5-dihydroxybenzoic acid (DHBA) or [2-(4-hydroxyphenylazo)benzoic acid] (HABA) in tetrahydrofuran. One microliter of the solution was loaded on a gold sample plate, the solvent was removed in warm air, and the sample was transferred to the mass spectrometer for analysis. GPC measurements were conducted with a Waters 6000A GPC apparatus equipped with a

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series of standard Waters Styragel HR columns and a H502 viscometer detector (Viscotek Corp.). Polystyrene standards were used for column calibration and the molecular weights were determined by universal calibration. Polymers were dissolved in chloroform (1.0 wt %) and eluted with chloroform at 25 °C at a flow rate of 1.5 mL/min. Differential scanning calorimetry (DSC) was carried out with a Perkin-Elmer DSC-7 apparatus calibrated with pure indium and gallium. The sample was heated from -50 to 220 °C at a rate of 20 °C/min, kept at 220 °C for 2 min, quenched to -50 °C (300 °C/min), kept at -50 °C for 2 min, and then heated to 220 °C for the second time at a rate of 20 °C/min. The maximum of the endothermic peak was taken as the melting temperature (T_m), the maximum of the exothermic peak during the second heating scan was considered as the crystallization temperature (T_c), and the temperature corresponding to half C_p was taken as the glass transition temperature (T_g). The specific rotation $[\alpha]_D^{25}$ was measured at a concentration of 10 mg/mL in CHCl_3 at 25 °C on a Perkin-Elmer 241 polarimeter equipped with Na lamp and a light pass length of 10 cm. The enantiomeric excess (ee) was calculated based on $\text{ee} (\%) = 100[\alpha]_D^{25}/([\alpha]_D^{25})_0$ where $([\alpha]_D^{25})_0$ is the specific rotation of optically pure poly(L-LA) with similar M_n .

(*R,R*)-(Cyclohexylsalen)AlO^tPr [(*R,R*)-1]. Aluminum isopropoxide (0.583 g, 2.85 mmol), (*R,R*)-cyclohexylsalen ligand (1.56 g, 2.85 mmol), and toluene (15 mL) were introduced into a dried reaction vessel equipped with a magnetic stirring bar. After the mixture was stirred for 3 days at 80 °C, the solvent and volatiles were removed in vacuo. The yellow solid was then washed with cold hexane, filtered, and dried in vacuo. Yield: 95.6%. Elemental analysis, found (calcd): C 73.94 (74.25), H 9.53 (9.43), N 4.52 (4.44), Al 4.24 (4.27). ¹H NMR (300 MHz, CDCl_3): δ 8.36 (s, 1 H), 8.15 (s, 1 H), 7.47–7.50 (dd, J 2.7, 8.0 Hz, 2 H), 6.98–7.05 (dd, J 2.7, 17.0 Hz, 2 H), 3.92 (t, J 9.6 Hz, 1 H), 3.71 (sep, J 5.7 Hz, 1 H), 3.04 (t, J 9.6 Hz, 1 H), 2.60 (b, 1 H), 2.40 (b, 1 H), 2.06 (b, 2 H), 1.55 (s, 9 H), 1.52 (s, 9 H), 1.47 (m, 4 H), 1.30 (s, 9 H), 1.29 (s, 9 H), 0.86 (dd, J 5.7, 7.5 Hz, 6 H). ²⁷Al NMR (104 MHz, toluene/ $[\text{D}_8]$ toluene (v/v : 2/1), $\text{Al}_2(\text{SO}_4)_3$ in D_2O): δ 35.45 ($w_{1/2}$ = 954 Hz).

***rac*-(cyclohexylsalen)AlO^tPr [*rac*-1].** Aluminum isopropoxide (0.583 g, 2.85 mmol), *rac*-cyclohexylsalen ligand (1.56 g, 2.85 mmol), and toluene (15 mL) were introduced into a dried reaction vessel equipped with a magnetic stirring bar. After the mixture was stirred for 3 days at 80 °C, the solvent and volatiles were removed in vacuo. The yellow

solid was then washed with cold hexane, filtered, and dried in vacuo. Yield: 94.3%. Elemental analysis, found (calcd): C 74.28 (74.25), H 9.42 (9.43), N 4.50 (4.44), Al 4.13 (4.27). ¹H NMR (300 MHz, CDCl_3): δ 8.36 (s, 1 H), 8.15 (s, 1 H), 7.47–7.50 (dd, J 2.4, 7.5 Hz, 2 H), 6.98–7.05 (dd, J 3.0, 17.1 Hz, 2 H), 3.92 (t, J 10.5 Hz, 1H), 3.71 (sep, J 5.7 Hz, 1 H), 3.04 (t, J 10.5 Hz, 1 H), 2.60 (b, 1H), 2.40 (b, 1 H), 2.06 (b, 2H), 1.55 (s, 9 H), 1.52 (s, 9 H), 1.47 (m, 4 H), 1.30 (s, 9 H), 1.29 (s, 9 H), 0.86 (dd, J 5.7, 7.5 Hz, 6 H).

Polymerizations. In a typical experiment, *rac*-1 (0.102 g, 0.162 mmol), *rac*-LA (1.44 g, 10 mmol), and toluene (12 mL) were introduced into a dried reaction vessel equipped with a magnetic stirring bar. The vessel was placed in an oil bath thermostated at 70 °C. At certain time intervals, about 1.2-mL aliquots were removed and reaction was terminated by adding acetic acid. After the solvent was evaporated, a sample was taken for determination of the conversion using ¹H NMR. The remaining residues were redissolved in CH_2Cl_2 and the polymer was precipitated from an excess of cold methanol. Filtration followed by drying at 40 °C in vacuo yielded a white crystalline polymer.

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Supporting Information Available: A table summarizing the polymerization results obtained from different combinations of catalysts and lactide stereoisomers; a table comparing the propagation rate constants for *rac*-LA polymerization initiated by various aluminum alkoxides, ¹H NMR spectra of L-LA living oligomer, after quenching with acetic acid and purified oligomer; MALDI-TOF spectra showing the evolution of M_n over time; kinetics for (*R,R*)-1 initiated D20L80 polymerization; DSC curves for some PLA samples; homonuclear decoupled ¹H NMR spectra (600 MHz, CDCl_3) of PLAs obtained from *rac*-LA polymerization using *rac*-1; and the ¹³C NMR of PLAs resulting from D20L80 using (*R,R*)-1. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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