Stereorechemistry of Lactide Polymerization with Chiral Catalysts: New Opportunities for Stereorecontrol Using Polymer Exchange Mechanisms

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Abstract: The synthesis of chiral alumina and yttrium alkoxydes and their application for lactide polymerization are reported. The complexes (SalBinap)MOR [4, M = Al, R = Pr; 5, M = Y, R = (CH2)2-NEt2] are synthesized by reacting the ligand (SalBinap)H2 [2,2′-[(1,1′-binaphthalene)-2,2′-diylbis(nitrilo- methylidyne)]bisphenol] with the appropriate metal trisalkoxide. While enantiomerically pure yttrium complex 5 did not effect stereorecontrol in the polymerization of either meso- or rac-lactide, homochiral 4 was found to exhibit excellent stereorecontrol in a range of lactide polymerizations. Enantiomerically pure 4 polymers meso-lactide to syndiotactic poly(lactic acid) (PLA), while rac-4 polymerizes meso- and rac-lactide to heterotactic and isotactic stereoblock PLA, respectively. On the basis of the absolute stereorechemistry of ring-opening of meso-lactide using (R)-4, a polymer exchange mechanism is proposed to account for the PLA microstructures resulting from rac-4.

Introduction

Stereochemistry is one of the main factors that determine the physical and mechanical properties of a polymeric material, as well as its rate of chemical and biological degradation. Polymers that have stereocenters in the repeat unit can exhibit two structures of maximum order, isotactic and syndiotactic. Isotactic polymers contain sequential stereocenters of the same relative configuration, while syndiotactic polymers contain sequential stereocenters of opposite relative configuration. These stereoregular polymers are typically crystalline and have found use in many applications. Homogeneous single-site catalysts have proven to be one of the most promising methodologies for the synthesis of stereoregular polymers. With single-site catalysts, enchainment of a monomer occurs at a metal center (M, the active site) that is bound by an organic ligand (L). This ancillary ligand remains bound throughout the catalytic reaction, modulating the reactivity of the metal center. Typical single-site catalysts for lactone polymerization are of the form Ln,MOR, where the alkoxide group (OR) is capable of propagation. These complexes are conceptually different from typical lactone polymerization catalysts of the form M(OR)n, which do not possess a permanent ancillary ligand. In contrast to conventional heterogeneous catalysts, homogeneous catalysts have been designed that can control polymer molecular weights, molecular weight distributions (MWDs), comonomer incorporation, and stereoregistry. Despite significant progress toward the development of well-defined catalysts for olefin polymerization, relatively few single-site catalysts have been reported for the ring-opening polymerization of heterocycles such as epoxides and lactones.

Poly(lactic acid)s (PLAs) are biocompatible and biodegradable materials with many potential medical, agricultural, and packaging applications.\(^{26-31}\) PLAs are formed by the ring-opening of lactide (LA), a cyclic diester of lactic acid, by various metal alkoxide species (Figure 1). The ring-opening occurs through a coordination-insertion mechanism by cleavage of the acyl-oxygen bond with retention of configuration.\(^{32-36}\) Prior to work in our laboratory, available microstructures were limited to atactic, partially heterotactic, and isotactic PLA. For example, amorphous atactic polymers are afforded from the polymerization of rac-lactide or meso-lactide with aluminum tris(alkoxide)\(^{34,35}\) or tin bis(carboxylate)\(^{36}\) catalysts. These atactic polymers possess random placements of -RR- and -SS- sequences for rac-lactide and -RS- and -SR- stereosequences for meso-lactide.

One of the most important advances in the control of PLA stereochmey was reported by Spassky and co-workers,\(^{3}\) who found the enantiomerically pure, chiral complex (R)-(SalBinap)-Al(OCH\(_3\))\(_3\) [(R)-2] (Scheme 1) exhibited high selectivity in the polymerization of rac-lactide or meso-lactide with aluminum tris(alkoxide) or tin bis(carboxylate) catalysts. These atactic polymers possess random placements of -RR- and -SS- sequences for rac-lactide and -RS- and -SR- stereosequences for meso-lactide.

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The complex exhibits cleft between the ligands is occupied by a methoxide group. Larger alkoxide group would favor the desired monometallic complexes because groups larger than an ethoxide are sterically close to the metal, we decided to synthesize complex (R)-4.

The synthesis of (R)-(SalBinap)AlO(i-Pr) [(R)-4] was achieved by adding freshly distilled Al(O(i-Pr))3 to a toluene solution of (R)-1. After the mixture was stirred at 70 °C for 2 days, the solvent was removed in vacuo to yield (R)-4 as a yellow solid. Despite repeated attempts, we were not able to obtain single crystals of (R)-4. The 1H NMR spectrum of (R)-4 suggests that the complex exhibits Cs symmetry as exhibited by analogous yttrium compounds (vide infra).

We decided to also investigate yttrium-based complexes due to the established relations between group 3 and 13 metals, as well as the high activity of yttrium alkoxide complexes for lactone polymerization.42 [(R)-(SalBinap)YO(CH2)2NMe2]2 [(R)-5] was synthesized by adding Y(O(CH2)2NMe2)3 to a toluene solution of (R)-1. After the mixture was stirred at 70 °C for 1 day, the solvent was removed in vacuo to yield (R)-5 as a crystalline yellow solid. A single crystal of this complex was subjected to X-ray structural analysis (Figure 4). (R)-5 is an alkoxy-bridged dimer, with seven-coordinate yttrium centers ligated by (R)-1 adopting a cis-β geometry and Δ chirality. We tentatively propose that the structure of (R)-4, for which no X-ray crystal structure could be obtained, is analogous to that of (R)-5.

Polymerization of meso-Lactide Using Enantiomerically Pure Catalysts. (R)-5 was examined for the polymerization of meso-lactide (LA).12 After 14 h at 70 °C, the reaction proceeded to 97% conversion ([LA] = 0.2 M in toluene, [LA]/{[(R)-5] = 100}). Analysis of the polymer microstructure using homonuclear decoupled 1H NMR revealed that (R)-5 forms atactic poly(lactic acid).

We then investigated (R)-4 for the polymerization of meso-lactide ([LA] = 0.2 M in toluene, [LA]/{[(R)-4] = 100}) (Figure 5).12 After 40 h at 70 °C, the reaction had proceeded to 94% conversion. Subsequently, the polymerization was performed at 70 °C for varying amounts of time (Table 1).44 Gel permeation chromatography revealed Mn values (relative to polystyrene) close to the theoretical values and narrow MWDs (Table 1).


(44) A polymerization was performed at 50 °C for 40 h ([M]/[I] = 100; [lactide] = 0.2 M in toluene). A conversion of 84% was achieved with a selectivity of 96%. Mn = 11 200, PDI = 1.06, and Tm = 149 °C. Because a lower temperature afforded no increase in selectivity, all subsequent reactions were performed at 70 °C.
is highly syndiotactic, while atactic polymer forms when R oxygen sites that can be ring-opened by (48). Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Munson, E. J.

As shown in Figure 5, meso-lactide at one of the enantiotopic acyl oxygen groups. Although it should be noted that the PLA literature often contains the ds notation (i = isotactic ("i"), s = syndiotactic ("s").

The low polydispersities and the linear correlation ($r^2 = 0.99$) between $M_n$ and conversion are indicative of a living polymerization as well as a single type of reaction site (Figure 6).45

According to enantiomorphic site control statistics, poly(lactic acid) derived from both rac- and meso-lactide can exhibit five tetrad sequences (Table 2). The relative proportions of the tetrad sequences depend on the extent to which the catalyst controls racemic (r-dyad) and meso (m-dyad) placement of monomer units. In the case of meso-lactide polymerization, the parameter $\alpha$ is the probability that a given enantiomer of a catalyst opens lactide at one of the two enantiotropic acyl–oxygen sites. As shown in Figure 5, meso-lactide has two enantiomorphic acyl–oxygen sites that can be ring-opened by (R)-4; $\alpha$ is then equal to $k_A/k_B$. When $\alpha$ approaches 0 or 1, the polymer formed is highly syndiotactic, while atactic polymer forms when $\alpha$ is 0.5.

(45) This assumes that if multiple active species are present, they do not exchange polymer chains on a time scale that is faster than propagation, and they exhibit different rates of polymerization.

(46) We prefer to use the standard mr nomenclature described by Bovey (Bovey, F. A.; Mirau, P. A. NMR of Polymers; Academic Press: San Diego, 1996) although it should be noted that the PLA literature often contains the ds notation (i = isotactic (“i”), s = syndiotactic (“s”)).

The tacticity of the polymers prepared with (R)-4 was determined by inspection of the homonuclear decoupled $^1$H NMR spectrum. $^1$H NMR analysis proves that the polymers formed were highly syndiotactic as evidenced by the large rrr tetrad peak. In addition, a small rrr impurity peak is observed. Assuming an enantiomorphic site control mechanism (vide infra), rrr, mmr, and mrr tetrads must also be present due to the -RSRSSRSRS- defect sequences, but are too small to be visible due to near chemical shift equivalence with the syndiotactic rrr tetrad peak. Further evidence for a high level of syndiotacticity is the presence of isolated absorptions in the $^{13}$C NMR at $\delta$ 169.2, 69.3, and 16.3 ppm. Close inspection of the $^{13}$C NMR in the methine region (Figure 8) reveals small peaks corresponding to the tetrad impurities noted above. The presence of the mmr tetrad as well as the [rrm]-[mmr]-[mrr]-[rrr] contents of approximately 1:1:1:2 confirm that the reaction occurs via an enantiomorphic (47) Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Lindgren, T. A.; Munson, E. J. Macromolecules 1997, 30, 2422–2428.


Figure 4. X-ray crystal structure of (R)-5.

Figure 5. Synthesis of syndiotactic PLA.

Table 1. Polymerization of meso-Lactide with (R)-4

<table>
<thead>
<tr>
<th>time (h)</th>
<th>conversion (%)</th>
<th>$P_\alpha$ (%)</th>
<th>$M_n$ ($\times 10^{-3}$)</th>
<th>MWD$^b$</th>
<th>$T_g$ (°C)</th>
<th>$T_m$ (°C)</th>
</tr>
</thead>
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<tr>
<td>5</td>
<td>46</td>
<td>95</td>
<td>6.28</td>
<td>1.05</td>
<td>38.5</td>
<td>153</td>
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<td>11</td>
<td>62</td>
<td>95</td>
<td>10.69</td>
<td>1.05</td>
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<td>81</td>
<td>96</td>
<td>12.26</td>
<td>1.04</td>
<td>47.3</td>
<td>149</td>
</tr>
<tr>
<td>30</td>
<td>90</td>
<td>96</td>
<td>14.39</td>
<td>1.06</td>
<td>44.0</td>
<td>149</td>
</tr>
<tr>
<td>40</td>
<td>92</td>
<td>96</td>
<td>15.44</td>
<td>1.06</td>
<td>50.7</td>
<td>149</td>
</tr>
</tbody>
</table>

$^a$ [meso-LA]/[(R)-4] = 100; $T_{mix} = 70$ °C; [m-LA] = 0.2 M in toluene.

$^b$ Determined via integration of the methine resonances of monomer units and is determined from the methine region of the $^{13}$C NMR at 169.2 ppm.

$^c$ Determined by differential scanning calorimetry with a heating rate of 10 °C/min.

$^d$ $M_n$ and conversion are indicative of a living polymerization as well as a single type of reaction site (Figure 6).

Figure 6. PLA $M_n$ (versus polystyrene standards) as a function of conversion using meso-lactide and (R)-4 (toluene, 70 °C, [LA]/[Al] = 100).

Table 2. Tetrad Probabilities Based on Enantiomorphic Site Control Statistics

<table>
<thead>
<tr>
<th>tetrad</th>
<th>meso-lactide</th>
<th>rac-lactide</th>
</tr>
</thead>
<tbody>
<tr>
<td>mmm</td>
<td>$\alpha^4 + (1 - \alpha)^4 + \alpha^0 + (1 - \alpha)^0/2$</td>
<td></td>
</tr>
<tr>
<td>mmr</td>
<td>$\alpha^3(1 - \alpha) + \alpha(1 - \alpha)^3/2$</td>
<td></td>
</tr>
<tr>
<td>rmm</td>
<td>$\alpha(1 - \alpha) + \alpha^3(1 - \alpha)^0/2$</td>
<td></td>
</tr>
<tr>
<td>mrr</td>
<td>$\alpha^3(1 - \alpha) + \alpha^0(1 - \alpha)^3/2$</td>
<td></td>
</tr>
<tr>
<td>rrr</td>
<td>$\alpha^0 + (1 - \alpha)^2 + \alpha^3 + (1 - \alpha)^0/2$</td>
<td></td>
</tr>
</tbody>
</table>

$\alpha$ is the probability that a given enantiomer of a catalyst opens lactide at one of its two enantiotropic acyl–oxygen sites.
the polymer exhibits a glass-transition temperature (T_g) of approximately 45 °C, and a peak melting temperature (T_m) as high as 153 °C. Although microstructural analysis of the 1H NMR spectrum (Figure 7) shows that (R)-4 forms highly syndiotactic PLA from meso-lactide, it is not possible to determine which enantiotropic acyl–oxygen bond of the monomer is opened with the (R)-enantiomer of the catalyst (Figure 5). Interestingly, selective opening at either site produces the same syndiotactic polymer (neglecting end groups); thus, the reaction is a rare example of the polymerization of a meso-

monomer with a chiral catalyst where an achiral polymer is produced (the polymer is however cryptochiral if the end groups are taken into consideration51). Since the absolute configuration of the opened site provides valuable information concerning the mechanism of stereocore, we decided to investigate the stereochemistry of the ring-opening process. Complex (R)-4 was reacted with approximately 1 equiv of meso-lactide; following hydrolysis of the resultant product, (S)-(+)methoxy-α-(trifluoromethyl)phenylacetyl chloride [(S)-MTPA(Cl)] was added to produce the Mosher ester (Figure 9).52,53 Following column chromatography, a diastereomeric mixture of the possible Mosher esters of the ring-opened adducts (6, 7) were isolated and analyzed using 1H NMR spectroscopy (Figure 10). Using the model compounds 8 and 9 (Figure 9), which have Mosher methoxy shifts at δ 3.65 and 3.57, respectively, we have assigned the minor peak at δ 3.65 to 6 and the major peak at δ 3.55 to 7. Therefore, (R)-4 opens meso-lactide preferentially at site B (Figure 9) to yield a syndiotactic polymer with an (S)-lactic acid unit at the active end bound to the metal. The relative ratio 6:7 is 3:97, which agrees well with the observed selectivity of (R)-4 for the polymerization of meso-lactide (4:96).54 Since the stereoselectivity of insertion of meso-lactide into the achiral isopropoxide of (R)-4 is not significantly enhanced or diminished, we propose that chain-end effects are not significant in these systems. On the basis of the observed absolute configuration of the ring-opening of meso-lactide using (R)-4, we propose a mechanism for ring-opening that embodies this information (Figure 11).

**Polymerization of meso-Lactide Using a Racemic Catalyst.**

The polymerization of meso-lactide with optically active 4

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54. The corresponding experiment with (S)-4 confirmed ring-opening at site A to form an R-chain end with a similar high selectivity.
afforded achiral syndiotactic PLA. Typically, a racemic catalyst is much less expensive than either of its optically active components. Therefore, we investigated the reaction of meso-lactide with rac-(SalBinap)AlOPr to determine whether syndiotacticity requires optically active catalyst. After 40 h at 70 °C the reaction of rac-4 with meso-lactide proceeded to 98% conversion ([LA]₀ = 0.212 M in toluene, [LA]/[rac-4] = 106). Gel-permeation chromatography (GPC) revealed a Mₙ = 13,600 (theoretical Mₙ = 15,000) and a MWD of 1.07. The polymer was amorphous and exhibited a T_g = 43.2 °C.

The most notable feature of the reaction using the racemic catalyst is that the polymer formed was unexpectedly heterotactic, where 80% of the linkages formed during the polymerization occurred between lactic acid units of identical stereochemistry (Figure 12). The methine region of the homonuclear decoupled ¹H NMR spectrum of the polymerization of meso-lactide by rac-4 is shown in Figure 13. The peaks were assigned to the appropriate tetrads in accordance with the correlations established in the literature. The major tetrad peaks correspond to those of the mrr and rrm tetrads, indicative of the heterotactic -RSSRRRS- sequence of the polymer (Figure 13). Also present were the rrr, rrm, and rrr tetrad impurities, corresponding to a -RSSRRRSSRS- defect sequence. We propose a polymer exchange mechanism to account for the formation of this heterotactic microstructure, whereby each individual polymer chain effectively switches between enantimeric aluminum centers before insertion of a subsequent monomer unit (Figure 14). Currently, we cannot rule out the possibility of a bimetallic active species bearing enantiomeric ligands, although current kinetic data is consistent with a monomeric enchainment mechanism (vide infra). The mechanism proposed in Figure 14 is conceptually related to an ancillary ligand exchange mechanism reported by Brookhart and Wagner to account for the formation of a syndiotactic polyketone when an optically active complex was used in the presence of an equivalent of enantiomeric ligand. The detailed nature of the switching process is not clear, however we propose exchange through -alkoxide or [L₆Al⁺][OP^-] ionic species result in polymer transfer. We have found that added alcohol results in an “immortal” polymerization (through rapid alcoholysis new polymer chains grow, resulting in decreased overall molecular weight for a given [LA]/[Al] ratio). Thus the possibility that trace protic impurities shuttle chains between enantiomeric aluminum centers cannot be ruled out at the current time. By studying the absolute stereochemistry of ring opening, we know that the (R)- and (S)-4 open meso-lactide to place S- and R-stereocenters, respectively, at the growing end of the polymer chain, respectively. Molecular modeling suggests that the (R)-catalyst prefers an R-center (and the (S)-catalyst prefers an S-center), assuming a C₂-symmetric ligand configuration. If polymer exchange is rapid, then the differences between the

Although the ¹C NMR spectrum shows an approximate 1:1:1 ratio of the rrr, rrm, and rrr tetrads, the ¹H NMR shows a 2:1 ratio of what has previously been assigned as the rrr and rrm+ rrr tetrads, respectively. Since the ratio should be 1:2, we propose that either the rrm or rrr tetrad must exhibit chemical shift equivalence with the rrr tetrad for this polymer.

Stereochemistry of Lactide Polymerization

Figure 10. ¹H NMR spectrum of the Mosher group methoxy region of the meso-lactide ring-opened adducts using (R)-4 (300 MHz, CDCl₃).

Figure 11. Proposed mechanism of ring-opening of meso-lactide using (R)-4.

Figure 12. Synthesis of heterotactic PLA.

Figure 13. Homonuclear decoupled ¹H NMR spectrum of the methine region of heterotactic PLA prepared with rac-4/meso-lactide at 70 °C (500 MHz, CDCl₃).

55 Although the ¹C NMR spectrum shows an approximate 1:1:1 ratio of the rrr, rrm, and rrr tetrads, the ¹H NMR shows a 2:1 ratio of what has previously been assigned as the rrr and rrm+ rrr tetrads, respectively. Since the ratio should be 1:2, we propose that either the rrm or rrr tetrad must exhibit chemical shift equivalence with the rrr tetrad for this polymer.

standard free energies of the transition states leading to syndiotactic and heterotactic PLA will determine stereochemistry. Hence we propose a polymer exchange/insertion sequence to account for the heterotactic structure of the polymer (A; B; Figure 14). The exact nature of sterechemical control is clearly very complex, and will be the subject of further study in our lab.

**Polymerization of rac-Lactide Using a Racemic Catalyst.** Isotactic PLA exhibits a peak melting temperature of 170–180 °C.\(^5\) However, when poly[(R)-(lactic acid)] and poly[(S)-(lactic acid)] are mixed, cococrystallization occurs and the \(T_m\) of the resulting stereocomplex is 230 °C.\(^5\) This observation motivates an attempt to use rac-lactide for the preparation of isotactic PLA directly from rac-lactide, where both enantiomers of the monomer are simultaneously incorporated into poly(R) segments and poly(S) segments. Stereocomplex PLA is an attractive target for several reasons, including the enhancement in melting temperature and the low cost of the rac-lactide monomer.

The polymerization of rac-lactide with (R)-2 afforded a tapered stereoblock PLA with a \(T_m\) much lower than the theoretical maximum of 230 °C.\(^5\) A gradient of stereogenic centers in the main chain was the apparent cause. One method of circumventing this problem is to sequentially polymerize (R,R)-lactide and then (S,S)-lactide with an achiral, living initiator.\(^5\) However, this strategy suffers from the fact that (R,R)-lactide is much more expensive than the (S,S)-enantiomer. An alternate approach is to employ a more selective catalyst to effect the kinetic resolution of rac-lactide (i.e., a catalyst with a propagation rate constant for the preferred enantiomer that is much higher than the corresponding rate constant for the unpreferred enantiomer). The disadvantage of this strategy is that an increase in the ratio of these rate constants will dramatically lengthen the reaction time, if the rate of enchainment of the preferred enantiomer is held constant.

An even more formidable synthetic accomplishment would be the polymerization of rac-lactide to form separate isotactic poly[(R)-(lactic acid)] and poly[(S)-(lactic acid)] chains in a “one-pot” reaction. On the basis of our previous findings, we speculated that this objective might be met with rac-(SalBinap)-AlOPr. It was expected that (R)-4 would produce pure chains of (R)-lactide, (S)-4 would produce pure chains of (S)-lactide, and the chains would cococrystallize to form a high-melting stereocomplex. Initial experiments on the polymerization of rac-lactide with rac-(SalBinap)AlOPr yielded highly crystalline, predominantly isotactic material, apparently consistent with the desired goal of simultaneously forming pure isotactic (R)-PLA and (S)-PLA (Figure 15). In fact, during the course of our work Baker and Smith reported exactly this finding, confirming our original results.\(^5\) However, on the basis of the observation of polymer exchange during the polymerization of meso-lactide using rac-4, we decided to investigate the detailed microstructure of the polymer formed from rac-lactide/rac-4 with the expectation that the polymer might not consist of enantiomerically enriched chains.\(^5\) In fact, further examination of our data revealed the formation of a stereoblock PLA instead (Figure 15).

The methine region of the homonuclear decoupled \(^1\)H NMR spectrum of the polymerization of rac-lactide by rac-4 is shown in Figure 16. The peaks were assigned to the appropriate tetrads in accordance with the literature.\(^5\)–\(^10\) The \(mmm\) tetrad, diagnostic of isotacticity, is the predominant peak in the spectrum. However, it is the defect tetrads that reveal the true structure of the polymer, and provide valuable information about the mechanism of stereocontrol. The \(rmn\), \(mnr\), and \(mmr\) tetrad are all present in approximately equal intensity, with an additional small \(rnm\) peak near 5.22 ppm. If the polymer sample consisted of isotactic PLA, where each chain was made by one molecule of

\[\text{Stereocomplex Poly(lactic acid)}\]
\[\text{Isotactic Poly((R)-lactic acid)} / \text{Isotactic Poly((S)-lactic acid)}\]

\[\text{Stereoblock Isotactic Poly(lactic acid)}\]

**Figure 15.** Stereocomplex and stereoblock PLAs.
exchange occurs and the wrong enantiomer of lactide is incorporated (B, C). At this point, propagation resumes with the favored lactide stereoisomer, creating a stereoblock structure. An alternative interpretation of the data is that, prior to polymer exchange, the disfavored lactide is enchained. This is followed by polymer exchange where the propagation resumes with the favored lactide enantiomers. Since both pathways give the same polymer, neither can be ruled out at the current time.

The stereoblock PLA prepared from the reaction of rac-lactide and rac-4 at 70 °C ([rac-lactide]/[Al]) = 100) exhibited a peak T_app at 179 °C, which was higher than that of isotactic poly([R]-lactide) or poly([S]-lactide). This is strong evidence that these block copolymers adopt a stereocomplex morphology in the solid state, and due to the shorter runs of enantiomerically pure blocks in the main chain, the melting points are lower than a 1:1 mix of the enantiopure homopolymers. The polymer was analyzed by GPC, revealing a M_n = 22 600 and a molecular weight distribution of 1.09. The polymerization exhibits living behavior, as evidenced by the correlation between the predicted and observed molecular weights and the narrow MWD. In addition, the narrow MWD suggests that no significant trans-esterification occurs. Indeed, for enantiomerically pure isotactic chains to form (Figure 15), transesterification cannot take place. It should be noted that, in our proposed mechanism, a type of transesterification does occur, but since the chains are not lengthened or shortened, the molecular weight distribution remains monodisperse.

**Kinetics of Lactide Polymerization with (SalBinap)AlO_iPr.** To determine the relative rates of reaction for the polymerization of lactide with (SalBinap)AlO_iPr, a series of consecutive reactions was run for each of the following monomer—initiator combinations: (i) (S,S)-lactide + (S)-(SalBinap)AlO_iPr, (ii) meso-lactide + rac-(SalBinap)AlO_iPr, (iii) rac-lactide + rac-(SalBinap)AlO_iPr, and (iv) meso-lactide + (R)-(SalBinap)AlO_iPr. All reactions were run under the same conditions at 70 °C in toluene ([LA]_o = 0.2 M; [Al] = 0.002 M; [LA]/[Al] = 100). Lactide conversion with time was monitored by 1H NMR spectroscopy until monomer consumption reached 90%. In each case, first-order kinetics in monomer were observed. At high conversion of monomer, slight deviation from first-order behavior occurs, which is proposed to be due to the formation of cyclic species (discovered using MALDI-TOF MS). Therefore, data collected at long reaction times were not used. The polymerization of lactide by (SalBinap)AlO_iPr obeys the first-order rate law

$$-d[LA]/dr = k_{app}[LA]^1$$  (1)

where \(k_{app} = k_p[Al]^1\), and where \(k_p\) is the propagation rate constant. To determine the order in aluminum, ln \(k_{app}\) versus ln [Al] was plotted for the polymerization of meso-lactide with (R)-4 at [LA]/[Al] = 50, 75, and 100. At higher [LA]/[Al] ratios, the kinetic data were irreproducible. From this plot, the order in initiator (slope) is 1.1 ± 0.3. Due to the limited data, though, the order in initiator must be considered preliminary.

(62) See the Supporting Information.
Therefore, we currently propose the polymerization of meso-lactide by \((R)\)-4 follows an overall kinetic law of the form

\[
-d[LA]/dt = k_{\text{app}}[A][LA]
\]  

(2)

At the current time we cannot rule out the presence of an alkoxide-bridged bimetallic resting state of the catalyst that reacts with lactide in a bimetallic pathway that would also yield first-order kinetics with respect to aluminum. Due to the stability of the chelate formed by the polymer chain end with the aluminum center (Figure 11), we favor a monomeric species as the active catalyst.

The first-order rate constant \((k_{\text{app}})\) for the polymerization of \((S,S)\)-lactide with \((S)\)-4 to form isotactic PLA is the largest of those studied \((5.5 \times 10^{-3} \text{ min}^{-1})\). Therefore, the formation of isotactic PLA has the fastest rate of reaction relative to the other systems. The system with the second fastest relative rate was the reaction of meso-lactide with \((R)\)-4 to form heterotactic PLA \((4.4 \times 10^{-3} \text{ min}^{-1})\). The relative rate of reaction of rac-lactide with \((R)\)-4 to form stereoblock PLA \((2.1 \times 10^{-3} \text{ min}^{-1})\) was approximately half the rate of formation of isotactic PLA from \((S)\)-4 and the preferred enantiomer. The magnitudes of these rate constants are reasonable considering that, in the case of the polymerization of \((S,S)\)-lactide with \((S)\)-4, all monomer molecules may be ring-opened by all catalyst molecules. In contrast, only half of the monomer molecules may be ring-opened by each catalyst enantiomer in the polymerization of rac-lactide with \((R)\)-4.

The polymerization of meso-lactide with \((R)\)-4 to form syndiotactic poly(lactic acid) exhibits a \(k_{\text{app}}\) of \(2.0 \times 10^{-3} \text{ min}^{-1}\). This is approximately half the rate of formation of heterotactic PLA from meso-lactide with \((R)\)-4. This result is reasonable on the basis of the fact that \((R)\)-4 can only open meso-lactide at one acyl–oxygen. In contrast, \((R)\)-4 has the kinetic advantage of rapid polymer exchange, followed by a lower energy pathway for ring-opening after the exchange occurs.

Summary and Conclusions

The synthesis of chiral aluminum and yttrium alkoxides and their application for lactide polymerization is reported. Although enantiomerically pure yttrium complex \((R)\)-5 did not effect stereocntrol in the polymerization of either meso- or rac-lactide, homochiral \((R)\)-4 was found to exhibit excellent stereocontrol in a range of lactide polymerizations. Enantiomerically pure \((R)\)-4 polymerizes meso-lactide to syndiotactic PLA with an enantiotopic ring-opening selectivity of 96%. Interestingly, \((R)\)-4 polymerizes meso-lactide to heterotactic PLA. On the basis of the absolute stereochemistry of ring-opening of meso-lactide using \((R)\)-4, a polymer exchange mechanism is proposed to account for the tacticity of this polymer. With this information in mind we reinvestigated the polymer made from rac-lactide using \((R)\)-4. Instead of producing the expected stereocomplex PLA consisting of enantiomerically pure strands of isotactic polymer, an isotactic stereoblock PLA was produced. We propose this novel microstructure again results from a polymer exchange mechanism, where runs of enantiomerically pure lactide are interrupted by periodic changes in stereochemistry due to interchange between enantiomeric catalyst species.

Due to the growing importance of lactic acid polymers in a range of biomedical, agricultural, and packaging applications, the results reported here are significant in that new routes to PLA architectures are now available. Subsequent work in our group will center on the study of the physical and mechanical properties of these polymers. However, perhaps the most important implication of the current work is that single-site catalysts offer new opportunities for microstructural control if new reaction pathways are accessed through catalyst design and control of reaction conditions. Our future research will be directed toward increasing the mechanistic complexity of polymerization catalysts to produce previously unattainable polymer architectures.

Experimental Section

General Considerations. All reactions with air- and/or water-sensitive compounds were carried out under dry nitrogen using a MBraun Labmaster drybox or standard Schlenk line techniques. NMR spectra were recorded on Bruker AF300 (\(\text{H}, 300 \text{ MHz}; ^{13}\text{C}, 75 \text{ MHz}\)) and Varian UNITY 500 (\(\text{H}, 500 \text{ MHz}; ^{13}\text{C}, 125 \text{ MHz}\)) spectrometers, and referenced versus shifts of solvents containing residual proton impurities. For \(^1\text{H} NMR\), coupling constants \(J\) are given in hertz. Gel permeation chromatography (GPC) analyses were carried out using a Waters instrument (M510 pump, U6K injector) equipped with Waters UV486 and Milton Roy differential refractive index detectors, and four 5 μm PL Gel columns (Polymer Laboratories; 100, 500, and 1000 Å, and mixed C porosities) in series. The GPC columns were eluted with tetrahydrofuran at 45 °C at 1 mL/min and were calibrated using 23 monodisperse polystyrene standards. Crystallographic data were col-
X-ray analysis of the crystals revealed that the complex exists as a 6-alkoxide-bridged dimer in the solid state.62

Polymer Synthesis. The following is a representative procedure using rac-(SalBinap)AIOPr (rac-4) and rac-lactide: In the drybox, a Schlenk tube was loaded with (R)-4 as a 0.0106 M solution in toluene (0.657 mL, 0.0069 mmol), (S)-4 as a 0.0117 M solution in toluene (0.592 mL, 0.0069 mmol), rac-lactide (0.199 g, 1.38 mmol), and toluene (6 mL). The system was heated to 70 °C and the mixture stirred for 40 h. An aliquot was taken for percent conversion analysis by 1H NMR. The solvent was removed in vacuo and the polymer dissolved in CH2Cl2 and precipitated from cold MeOH. The white crystalline solid was filtered and dried in vacuo to a constant weight. Yield: 0.165 g.

The following is a representative procedure using rac-4 and meso-lactide: In the drybox, a Schlenk tube was loaded with (R)-4 as a 0.0106 M solution in toluene (0.657 mL, 0.0069 mmol), (S)-4 as a 0.0117 M solution in toluene (0.592 mL, 0.0069 mmol), rac-lactide (0.199 g, 1.38 mmol), and toluene (6 mL). The system was heated to 70 °C and the mixture stirred for 40 h. The reaction was quenched via rapid cooling with liquid N2. The solvent was removed in vacuo, and the polymer dissolved in CH2Cl2 and precipitated from cold MeOH. The white crystalline solid was isolated and dried in vacuo to a constant weight. Yield: 0.19 g.

The following is a representative procedure using rac-4 and meso-lactide: In the drybox, a Schlenk tube was loaded with (R)-4 as a 0.0106 M solution in toluene (0.657 mL, 0.0069 mmol), (S)-4 as a 0.0117 M solution in toluene (0.592 mL, 0.0069 mmol), rac-lactide (0.214 g, 1.48 mmol), and toluene (6 mL). The system was heated to 70 °C and the mixture stirred for 40 h. The reaction was quenched via rapid cooling with liquid N2. The solvent was removed in vacuo, and the polymer dissolved in CH2Cl2 and precipitated from cold MeOH. The white crystalline solid was isolated and dried in vacuo to a constant weight. Yield: 0.169 g.

(2)-2-Methoxy-2-(trifluoromethyl)phenylacetae of Isopropyl Lactoylactate (from meso-Lactide/S)-4 (6). In the drybox, a dry NMR tube was loaded with (S)-4 (0.024 g, 0.041 mmol), toluene-d8 (0.7 mL), and meso-lactide (0.0047 g, 0.033 mmol). The tube was sealed with a rubber septum, shaken, and allowed to stand at room temperature overnight. H2O (1 µL) was added via syringe and the solution shaken. The solvent was removed in vacuo, yielding a yellow residue. Dry CDCl3 (0.3 mL), dry pyridine (0.3 mL), and (S)-(+)α-methoxy-α-(trifluoromethyl)phenylacety chloride (S)-MTPA(Cl); 8.5 µL, 0.046 mmol) were added via syringe. The reaction mixture was allowed to stand overnight. The tube was removed from the drybox, and N,N-dimethyl-1,3-propanediamine (7.8 µL, 0.062 mmol) was added via syringe to react with excess (S)-MTPA(Cl). The solution was shaken vigorously and allowed to stand at room temperature for at least 5 min. The solution was diluted with ether (15 mL) and washed with cold 1 N HCl (3 × 10 mL), saturated Na2CO3 (3 × 10 mL), and saturated NaCl (3 × 10 mL). The organic phase was dried over Na2SO4, filtered, and concentrated in vacuo, yielding a yellow oil. The product was purified via flash chromatography (CH2Cl2, Rf = 0.43). Yield: 0.0014 g. 1H NMR spectroscopic analysis revealed a 97:3 ratio of 6.7. 1H NMR (CDCl3, 300 MHz): δ 7.67–7.63 (2H, m), 7.38–7.43 (3H, m), 5.28–5.35 (1H, m), 5.07–5.13 (1H, m), 5.01–5.06 (1H, m), 3.65 (3H, br s), 1.56 (3H, d, J = 7.0), 1.48 (3H, d, J = 7.0), 1.26 (3H, d, J = 5.9), 1.22 (3H, d, J = 6.5). HRMS (FAB): m/z 421.1473 ([M + H]+). C16H16O2F3 requires 421.1474.

(R)-2-Methoxy-2-(trifluoromethyl)phenylacetae of Isopropyl Lactoylactate (from meso-Lactide/R)-4 (7). The method described for the synthesis of 6 from (S)-4 and meso-lactide was used for the synthesis of 7 from (R)-4 and meso-lactide. Yield: 0.0019 g. 1H NMR spectroscopic analysis revealed a 97:3 ratio of 7.6. 1H NMR (CDCl3, 300 MHz): δ 7.67–7.63 (2H, m), 7.38–7.43 (3H, m), 5.31–5.38 (1H, m), 4.99–5.10 (2H, m), 3.55 (3H, br s), 1.63 (3H, d, J = 7.0), 1.45 (3H, d, J = 7.0), 1.24 (3H, d, J = 7.0), 1.22 (3H, d, J = 7.0). HRMS (FAB): m/z 421.1477 ([M + H]+). C16H16O2F3 requires 421.1474.
(R)-2-Methoxy-2-(trifluoromethyl)phenylacetate of (R)-Methyl Lactate (8). A dry NMR tube under N₂ was loaded with pyridine (0.3 mL) and CDCl₃ (0.3 mL). In the drybox, the tube was loaded with (S)-(+)α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (26.2 μL, 0.14 mmol) and (R)-lactic acid methyl ester (9.55 μL, 0.10 mmol). The tube was shaken vigorously and allowed to stand overnight at room temperature. Excess N,N-dimethyl-1,3-propanediamine (24 μL, 0.20 mmol) was added and the mixture allowed to stand for 5 min. The mixture was diluted with ether (15 mL) and washed with cold 1 N HCl (3 × 10 mL), saturated Na₂CO₃ (3 × 10 mL), and brine (3 × 10 mL). The organic phase was dried (Na₂SO₄), filtered, and concentrated in vacuo, yielding a yellow oil. Yield: 0.029 g. ¹H NMR (CDCl₃, 300 MHz): δ 7.60–7.63 (2H, m), 7.38–7.43 (3H, m), 5.23–5.31 (1H, q), 3.78 (3H, s), 3.65 (3H, br s), 1.51 (3H, d, J = 7.5).

(R)-2-Methoxy-2-(trifluoromethyl)phenylacetate of (S)-Methyl Lactate (9). The method described for the synthesis of 8 was used for the synthesis of 9. from (S)-(++)α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and (S)-lactic acid methyl ester. Yield: 0.028 g. ¹H NMR (CDCl₃, 300 MHz): δ 7.55–7.60 (2H, m), 7.39–7.43 (3H, m), 5.26–5.34 (1H, q), 3.74 (3H, s), 3.57 (3H, br s), 1.58 (3H, d, J = 7.5).

General Procedure for Kinetics Studies. A series of 4 mL vials in the drybox were loaded with a small amount of lactide, catalyst from a stock solution in toluene ([lactide]/[Al] = 100), and dry toluene (lactide concentration in toluene was 0.2 M). The reaction vials were sealed tightly, removed from the drybox, and heated to 70 °C via an oil bath. After specified time intervals, each reaction was quenched via rapid cooling with liquid N₂. The solvent was removed in vacuo and the percent conversion determined by ¹H NMR. Each reaction was used as one data point.

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Supporting Information Available: X-ray crystal structures and crystallographic data for (R)-3 and (R)-5, plots of ln([Mₒ/Mₜ]) vs time (lactide/4) and ln k_app vs ln [Al] (meso-lactide/(R)-4), and ¹³C NMR spectra of heterotactic and stereoblock PLA (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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