Heterotactic Polymers

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A Germanium Alkoxide Supported by a C_3-Symmetric Ligand for the Stereoselective Synthesis of Highly Heterotactic Polylactide under Solvent-Free Conditions**

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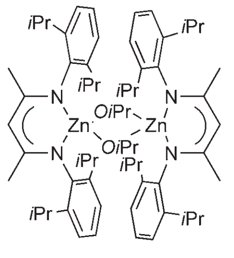
Polylactide (PLA) is a degradable aliphatic polyester that is obtainable economically from biorenewable resources and is of interest both as a commodity polymer and for use in biomedical applications such as medical implants and drug-delivery systems.[1] Commercially, ring-opening polymerization (ROP) of lactide (LA) is most commonly carried out without solvent in the melt by using tin carboxylate initiators, but a lack of control over polymer microstructure limits control over physical, mechanical, and degradation properties of PLA. This drawback, coupled with concerns over the toxicity of tin, have prompted the development of benign metal alkoxides as stereoselective single-site polymerization initiators.[1] It has been shown that metal complexes of achiral ligands can lead to either highly heterotactic [$(S,S,R,R)_n$] or highly isotactic [$(S,S)_n(R,R)_n$] PLA through a chain-end control mechanism (e.g., complexes **I**,[2] **II**,[3] **III**,[4] **IV**,[5a] and **V**[5b]; Bz = benzyl), whereas complexes of chiral ligands can lead to isotactic stereoblock PLA through an enantiomorphic site control mechanism (e.g., complexes **VI**[6] and **VII**[7]). Despite these impressive recent developments, major challenges remain. For example, mechanistic details are not well understood[8] and, although solvent-free melt polymerization is necessary for the practical bulk production of PLA and is highly desirable to eliminate solvent residues from biomedical-grade polymer, there is to date only one previous example of highly stereoselective solvent-free ROP of *rac*-LA. This advance was made by Feijen and co-workers who recently reported that complex **VII** afforded highly isotactic PLA in the melt at 130 °C ($P_i = 0.88$, where P_i is the probability of the formation of a new *i*-dyad).[7a]

Herein we report the synthesis of a new germanium alkoxide supported by a C_3-symmetric ligand and demonstrate its application to the solvent-free ROP of *rac*-LA, most notably, to provide for the first time highly heterotactic PLA in the bulk. Although germanium is less likely to undergo undesirable transesterification reactions than tin[9] and its organic compounds are generally nontoxic,[10] to our knowledge there are no previous reports of single-site germanium alkoxide initiators for the ROP of LA even though its potential has been demonstrated by the application of spirocyclic germanium tetraalkoxides for the ring-expansion polymerization of L-LA.[10] To provide steric and electronic control at the germanium center, we chose to use an amine (trisphenolate) ligand (**LH**$_3$, Scheme 1). This class of ligand has recently generated considerable interest in metal coordi-



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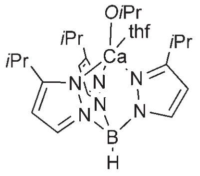

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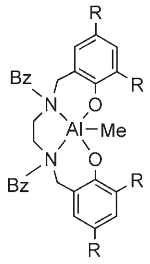

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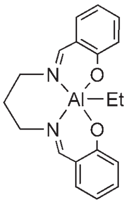

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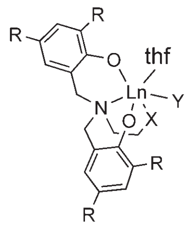

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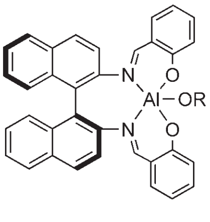

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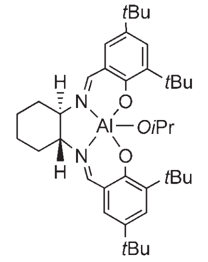

VII

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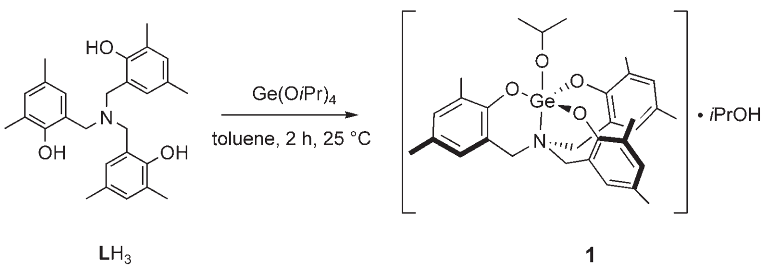


Scheme 1. Preparation of **1**.

nation chemistry for its ability to stabilize well-defined monomeric complexes for a wide range of reactive metal centers.[11–14] Encouragingly, titanium amine (trisphenolate)s have shown activity for ROP of LA, although they afforded only atactic PLA.[12]

Reaction of the ligand **L**H$_3$ with Ge(O*i*Pr)$_4$ in toluene yielded **L**Ge(O*i*Pr)·(HO*i*Pr) **1** in good yield (Scheme 1). The molecular structure of **1** was determined by X-ray crystallography and, like the related complexes **L**Si(OMe)[13] and **L**Ti(O*i*Pr),[14] the ligand adopts a C_3-symmetric, O_3N tetradentate, propeller-like arrangement around a trigonal-bipyramidal metal center (Figure 1). Somewhat surprisingly, to our knowledge, **1** is the first example of a mixed germanium alkoxide–aryloxide to be characterized structurally.[15] Even though the geometric parameters within the complex are unexceptional, an unexpected structural feature is the inclusion of isopropanol in the secondary coordination sphere of **1** through hydrogen bonding to the isopropoxide ligand.

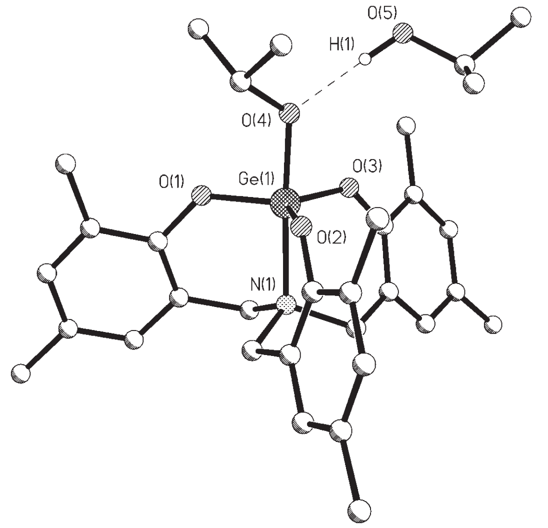


Figure 1. Molecular structure of **1**. Hydrogen atoms (except H(1)) and lattice toluene not shown for clarity. Selected distances [Å] and angles [°]: Ge(1)–O(1) 1.791(2), Ge(1)–O(2) 1.800(2), Ge(1)–O(3) 1.782(2), Ge(1)–O(4) 1.799(2), Ge(1)–N(1) 2.112(2), O(4)-Ge(1)-N(1) 176.38(7), O(3)-Ge(1)-O(2) 123.38(8), O(3)-Ge(1)-O(1) 117.51(8), O(2)-Ge(1)-O(1) 119.11(8). Hydrogen-bond parameters: O(5)···O(4), 2.810(2) Å; O(5)-H(1)-O(4), 170(3)°.

^{1}H NMR spectroscopy confirmed that the significant features of the solid-state structure are retained in solution. At −30 °C, an AX spin system is observed for the methylene protons of the ligand, which is consistent with retention of the C_3-symmetric structure, although at room temperature these resonances coalesce into a broad singlet, indicating rapid inversion between the *P* and *M* enantiomers of **1** on the NMR spectroscopic timescale. Two 1:1 septets owing to the methine protons of the isopropanol and isopropoxide moieties are observed in ^{1}H NMR spectra, even at elevated temperatures (85 °C), suggesting that rapid alcohol–alkoxide exchange does not take place.

Polymerization experiments were performed by using **1** as an initiator for ROP of *rac*-LA in the bulk at 130 °C. Over a range of initiator concentrations and reaction times, molecular weights were close to the calculated values with low-molecular-weight distributions; results that are consistent with well-controlled "living" polymerization (Table 1 and Figure 2). A MALDI-TOF mass spectrum of isolated PLA (Table 1, entry 2) displayed a major series corresponding to H[OC(Me)C(O)OC(Me)C(O)]$_n$O*i*Pr and only a minor series corresponding to H[OC(Me)C(O)]$_n$O*i*Pr, indicating that

Table 1: Ring-opening polymerization of *rac*-LA initiated by **1**.[a]

Entry	M/I	*t* [h]	Yield[b] [%]	M_n[c]	M_w/M_n[c]	P_r[d]
1	200	24	71	17700	1.15	0.78
2	300	3	30	12000	1.08	0.80
3	300	6	49	18700	1.13	0.80
4	300	18	65	24600	1.10	0.81
5	300	24	85	35700	1.15	0.79
6	600	24	70	52100	1.19	0.82
7[e]	200	48	95	24900	1.37	[f]

[a] Polymerization of 1.33, 2.00, or 4.00 g *rac*-LA in the absence of solvent at 130 °C. [b] Yield of isolated PLA. [c] Determined by gel permeation chromatography (GPC) in THF, relative to polystyrene standards. [d] P_r is the probability of heterotactic enchainment calculated by analysis of the homonuclear decoupled ^{1}H NMR spectra.[2] [e] Polymerization initiated by *rac*-**VII** for comparison.[7a] [f] $P_i = 0.88$.[7a]

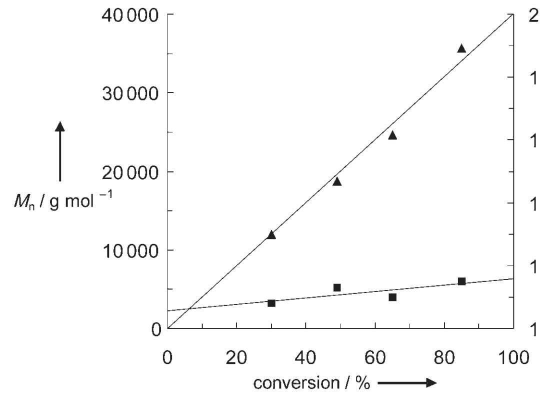
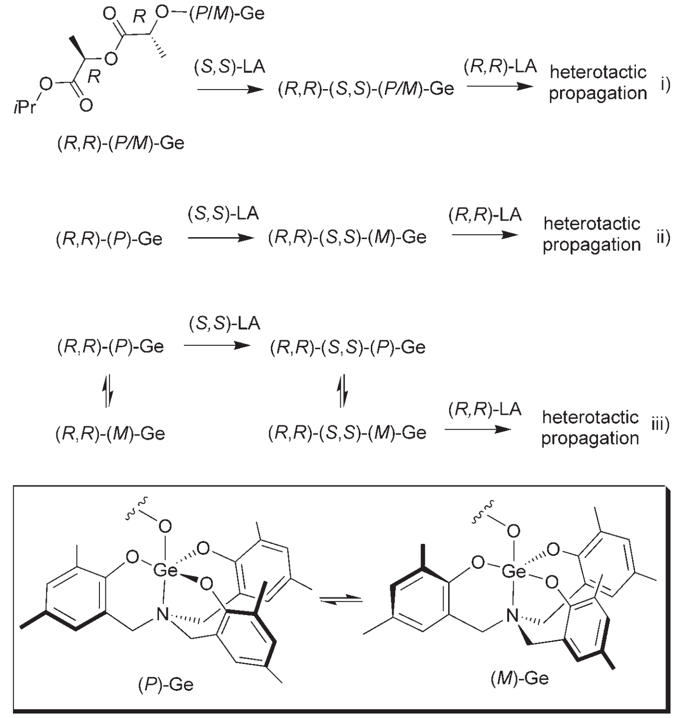


Figure 2. Plot of PLA M_n (▲) and molecular-weight distribution (■) as a function of conversion, highlighting the well-controlled nature of the polymerization (data from Table 1, entries 2–5). M_n = number-average molecular weight, PDI = polydispersity index.

neither intermolecular transesterification nor intramolecular "back-biting" occurs to an appreciable extent. Most interestingly, analysis of the microstructure of isolated polymers by homonuclear decoupled ^{1}H NMR spectra revealed a strong heterotactic bias in all cases ($P_r = 0.78$–0.82, Table 1). This represents, to our knowledge, the first example of a stereoselective initiator that is able to afford highly heterotactic PLA under such solvent-free conditions. As mentioned above, in the only previous example of stereoselective ROP of *rac*-LA in the bulk, initiator **VII** yielded highly isotactic material under similar conditions to ours (see Table 1, entry 7 for a comparison).[7a] Therefore, **1** and **VII** are complementary in providing routes to heterotactic and isotactic PLA, respectively.

Given the particularly robust stereoselective control displayed by **1**, the question arises as to the role played by the C_3 symmetry of the amine(trisphenolate) ligand. Initiation of polymerization by insertion of a chiral monomer (for example (*R*,*R*)-LA) into the metal alkoxide bond of *rac*-**1** can potentially generate two diastereoisomers (*R*,*R*)-(*P*)-Ge and (*R*,*R*)-(*M*)-Ge. Although mechanistic details of stereoselective ROP of LA are not well understood,[8] it is assumed that stereoselective chain propagation originates from the point of chirality of the growing polymer chain, or the axial chirality at the metal center, or a combination of both. This gives rise to three possible modes of heterotactic propagation (Scheme 2); 1) The chirality of the growing chain is dominant in determining selectivity and, although steric and/or electronic characteristics of the amine(trisphenolate) ligand may be significant, its axial chirality is unimportant. This is analogous to a chain-end control mechanism as observed for achiral bulky ligands such as **I**.[2] 2) The axial chirality at the metal center is controlled by the chirality of the growing chain such that only one diastereomer is present on the timescale of the next insertion [for example, (*R*,*R*)-(*P*)-Ge] and the axial chirality then plays a dominant role in selective enchainment of (*S*,*S*)-LA. Selective insertion of (*S*,*S*)-LA into (*R*,*R*)-(*P*-Ge) inverts the stereochemistry at Ge and heterotactic propagation will proceed through (*R*,*R*)-(*S*,*S*)-(*M*)-Ge. As the selective propagation is controlled by the dynamic chirality at Ge, such a mode could be termed "dynamic enantiomorphic site control".[16] 3) In an intermediate situation between the two extremes above, both the stereogenic centers of the growing chain and the axial chirality at the metal are important for selective enchainment, such that (*R*,*R*)-(*P*)-Ge, for example, reacts selectively with (*S*,*S*)-LA even in the presence of (*R*,*R*)-(*M*)-Ge, which is less reactive. This case does not require inversion at the metal center to be slow on the timescale of the subsequent insertion but instead relies on diastereocontrol over insertion. In other words, the chirality at the metal enhances the selectivity of (*S*,*S*)-LA over (*R*,*R*)-LA insertion. A similar form of chain propagation was proposed by Schrock and co-workers in the context of ring-opening metathesis polymerization of enantiomerically pure dienes and was termed "enhanced chain-end control".[18]



Scheme 2. Possible modes of heterotactic propagation of PLA mediated by **1**: i) chain-end control; ii) "dynamic" enantiomorphic site control; or iii) "enhanced" chain-end control. The inset shows inversion of chirality at Ge.

To distinguish between these three possibilities would require detailed mechanistic studies. Even with such information, as Chisholm et al. recently noted,[8b] the interplay between chirality at the metal and at the end group of the growing polymer chain is unpredictable, making it problematic to ascribe the origin of stereocontrol to either chain-end or enantiomorphic site control. However, it is noteworthy that the discussion above applies more generally to metal complexes that possesses dynamic axial chirality,[17] including many of the most successful stereoselective initiators reported to date (e.g., **II**–**IV**).

In conclusion, the synthesis and structural characterization of a new C_3-symmetric germanium amine(trisphenolate) has led to the development of the first single-site germanium alkoxide initiator for ROP of LA. This initiator has the unique ability to afford highly heterotactic PLA under solvent-free conditions. Currently, the coordination chemistry of germanium aryloxides is poorly developed relative to that of other metals used as initiators for ROP of LA, and our preliminary investigations suggest that Ge-O*i*Pr complexes of ligands related to **L** (for example, where aryl substituents are *t*Bu or Cl rather than Me) cannot be prepared in an analogous manner to **1**. However, other synthetic routes are currently under investigation with the aim of optimizing the selectivity and activity of Ge-based single-site initiators for ROP of LA and related monomers.

Experimental Section

Full synthetic and spectroscopic details including variable-temperature NMR spectra of **1**, homonuclear decoupled ^{1}H NMR and ^{13}C NMR spectra of PLA, and a MALDI-TOF mass spectrum of PLA are contained in the Supporting Information.

Synthesis of **1**: $\mathbf{L}H_3$ (0.84 g, 2 mmol) was dissolved in toluene (20 mL) and $Ge(OiPr)_4$ (0.62 g, 2 mmol) was added under dry argon and stirred at room temperature for 2 h. The volatile products were removed under vacuum and the product recrystallized from toluene at 0 °C. ^{1}H NMR ($CDCl_3$): $\delta = 1.21$ (6 H, d, $J = 6$ Hz, $2\times CH_3$ (O*i*Pr)), 1.41 (6 H, d, $J = 6$ Hz, $2\times CH_3$ (O*i*Pr)), 1.60 (1 H, br s, OH), 2.21 (9 H, s, Ar-CH_3), 2.30 (9 H, s, Ar-CH_3), 2.36 (1.5 H, s, CH_3 (toluene)), 3.64 (6 H, br s, NCH_2), 3.95 (1 H, sept, $J = 6$ Hz, CH (HO*i*Pr)), 4.73 (1 H, sept, $J = 6$ Hz, CH (O*i*Pr)), 6.57 (3 H, s, Ar-H), 6.93 (3 H, s, Ar-H), 7.1–7.3 ppm (2.5 H, m, Ar-H (toluene)). HRMS (FAB) *m*/*z* calcd for $C_{30}H_{37}N_1O_4Ge$ [M^+] 549.1929; found 549.1931.

Polymerization of *rac*-LA (typical experiment): The initiator **1** (30 mg, 0.046 mmol) and *rac*-lactide (2.0 g, 14 mmol) were stirred at 130 °C for 24 h. Methanol (20 mL) was then added and dichloromethane (50 mL) was added to dissolve the mixture. The volatiles were removed in vacuo and the white solid was washed with methanol (3×100 mL) and dried to afford polylactide as a white solid. Yield = 85 %, M_n (GPC) = 35 700, PDI = 1.15.

Crystal data for $\mathbf{1}\cdot 0.5(C_7H_8)$: $C_{36.5}H_{49}GeNO_5$, $M_n = 654.36$, $0.15\times 0.12\times 0.10$ mm^3, orthorhombic, space group *Pbcn* (No. 60), $a = 11.666(1)$, $b = 16.581(1)$, $c = 34.551(3)$ Å, $V = 6683.34(9)$ Å^3, $Z = 8$, $\rho_{\text{cald}} = 1.301$ g cm^{-3}, $F_{000} = 2776$, $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, $\mu = 0.959$ mm^{-1}, $T = 150(2)$ K, $2\theta_{\max} = 55.0°$, 56 003 reflections collected, 7620 unique ($R_{\text{int}} = 0.0575$). Final $GooF = 1.040$, $R1 = 0.0458$, $wR2 = 0.1105$, R indices based on 6527 reflections with $I > 2\sigma(I)$ (refinement on F^2), 427 parameters, 0 restraints. CCDC 621853 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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