

Stereoselective Ring-Opening Polymerization of Racemic Lactide Using Aluminum-Achiral Ligand Complexes: Exploration of a Chain-End Control Mechanism

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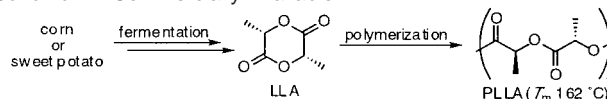
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Recent concerns with our environment call for the development of environmentally benign materials. One of the most promising and practical materials is polylactide (PLA). Because of its biodegradability and biocompatibility, PLA is recognized as an important material for medical and pharmaceutical applications as well as for industrial applications such as food packaging and paper coating.¹ Commercially available PLA is poly(L-lactide) (PLLA) mostly synthesized by the ring-opening polymerization of the homochiral (*S,S*)-lactide (LLA) prepared from fermentation of corn or sweet potato (Scheme 1).

The polymerizations of the racemic lactide (*rac*-LA) have recently been studied via stereoselective catalysis, although conventional catalysts such as Al(O^{*i*}Pr)₃ produce atactic PLA² which is amorphous and less attractive (Scheme 2a). Three distinctive synthetic studies of isotactic PLA³ are presented in Scheme 2b–d. Spassky originally introduced the Al–Schiff base complex and synthesized stereoblock [PLLA–PDLA]_{*n*}^{4,5} (Scheme 2b) using the achiral catalyst **1** (Chart 1). Synthesis of gradient PDLA–PLLA was reported using homochiral (*R*)-2^{6,7} (Scheme 2c), and this was the first success of the poly(*rac*-LA) from *rac*-LA, thermally more stable⁸ than homochiral PLLA (*T*_m 162 °C⁹) due to a stereocomplex formation.¹⁰ Baker and Smith then used the *chiral* but *racemic* complex *rac*-**2** and succeeded in the development of the living polymerization of *rac*-LA to form a mixture of enantiomerically pure (or enriched) polymer chains, PLLA and PDLA, in one step^{11–13} (Scheme 2d). The last two examples using (*R*)- or *rac*-**2** adopted a site control mechanism (SCM), whose key step is the consistent differentiation of LLA or DLA throughout the polymerization by the catalyst coordinated by a *chiral* binaphthyl auxiliary. From a scientific point of view, a chain-end control mechanism (CEM) remained unsuccessful, where the pre-catalyst such as **1** does not contain any chirality, and the stereogenic center of the last inserted monomer determines which enantiomer is entering the polymer terminal (Scheme 3). Although this CEM is conceptually simple,³ no catalysts have been reported to produce a poly(*rac*-LA) thermally more stable than the homochiral PLLA. We now report a simple and highly stereoselective living polymerization of *rac*-LA for thermally more stable [PLLA–PDLA]_{*n*} via an exploration of CEM.

We examined two series of substituted catalysts **3** and **4** (Chart 1), both of which were simply prepared in situ by mixing Et₃Al and each ligand.¹⁴ *rac*-LA was polymerized in the presence of **3** or **4** at 70 °C.^{15,16} The catalytic reactivity of **4** was much higher than

Scheme 1. Commercially Available PLLA



Scheme 2. Synthesis of Isotactic PLA from *rac*-LA

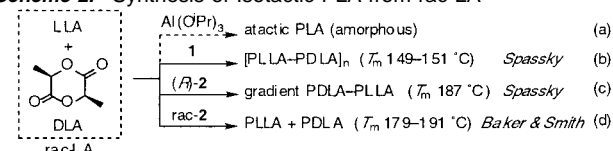
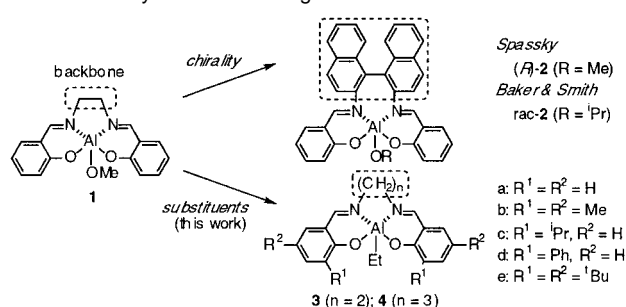
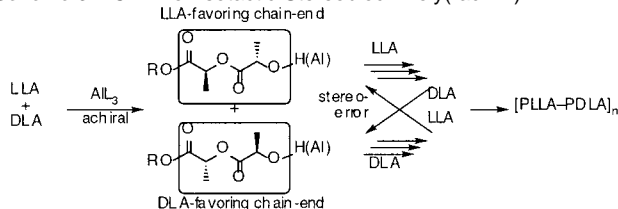


Chart 1. Catalysts for Stereoregular PLA from *rac*-LA



Scheme 3. CEM for Isotactic Stereoblock Poly(*rac*-LA)



that of **3**, and larger R¹ in the aromatic rings generally induced a higher isotacticity. Our extensive studies of the initiation reaction¹⁷ revealed that adventitious moisture from N₂ influenced the activities of the catalysts and *M*_n values of polymers, but it did not do the selectivity. Under a purified N₂ atmosphere, three notable results in the presence of 1 equiv of benzyl alcohol to the catalyst are shown in Table 1. The relationship between the *rac*-LA conversion to the polymer and *M*_n was linear with a narrow *M*_w/*M*_n (1.06–1.1) throughout the polymerization using both **4d** and **4e**. By introduction of Ph-substituents into the aromatic rings, the polymerization rate was accelerated with a high selectivity, probably because of electronic effects (entry 1). *T*_m of poly(*rac*-LA) was measured, for it is sensitive to the stereoregularity. *T*_m of the obtained poly(*rac*-LA) was at 170 °C (*P*_{meso} 0.81),^{2b} which was

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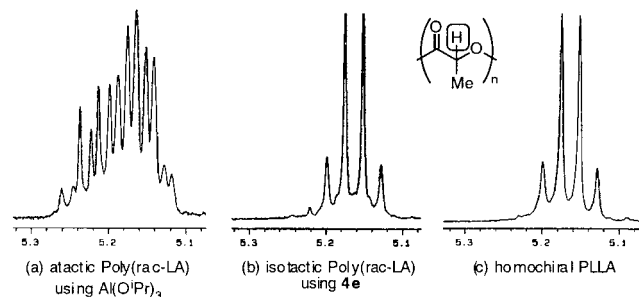
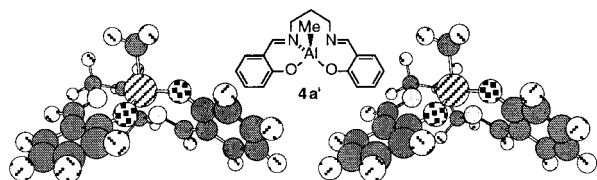
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Table 1. Polymerization of rac-LA Using **4d** or **4e**^a

entry	catalyst	[rac-LA]/[Al] ^b	time, h	conv., %	yield, ^d %	$M_n^e \times 10^{-3}$	PDI ^f
1	4d	100	1.3	94	91	20.0	1.11
2	4d	300	4.5	93	90	59.5	1.07
3	4e	100	14	95	93	22.4	1.06

^a See ref 15 for polymerization conditions. ^b The ratio of rac-LA/catalyst; 1 equiv of BnOH to the catalyst had been added to rac-LA. ^c The conversion of rac-LA to PLA was measured by ¹H NMR. ^d Isolated yield. ^e The number-average molecular weight estimated by SEC (polystyrene, CHCl₃). ^f Polydispersity index (M_w/M_n).

**Figure 1.** ¹H NMR spectra of the methine region of PLA.**Figure 2.** Stereoview of the most stable conformational enantiomer.

slightly higher than that of the homochiral PLLA. Compared with other reported isotactic polymerization catalysts,^{5,6,11} the polymerization using **4d** was quite fast, and poly(rac-LA) of the expected and higher M_n with a narrow polydispersity was easily prepared (entry 2). On the contrary, ^tBu-substituents slowed the polymerization rate (entry 3), while the highest selectivity was obtained. The thermal properties of PLA using **4e** indicated a high stereoregularity (T_m 192 °C, ΔH_{fus} 48 J/g, P_{meso} 0.91^{2b}), which was comparable or superior to those via SCM.^{11–13} The stereocomplex formation of poly(rac-LA) was confirmed by powder X-ray diffraction. The 300 MHz ¹H NMR spectrum of the methine region of poly(rac-LA) using **4e** is shown in Figure 1b with those of the atactic one (Figure 1a) and homochiral PLLA (Figure 1c).

There are two possibilities for isotactic selectivity: (1) highly selective CEM and (2) SCM from the conformational racemic chirality constructed by the achiral ligand. The most stable conformation of the simplistic complex **4a'** by the DFT(B3LYP/6-31G*)¹⁸ calculations is shown in Figure 2. It contained a twisted asymmetry, while the activation energy between each conformational enantiomer was estimated at 13.7 kJ/mol, which was smaller than that of the free rotation energy of C-2–C-3 about butane.¹⁹ It suggested the trimethylene-backbone itself in **4** be flexible. A microstructural analysis by the homonuclear decoupled 500 MHz ¹H NMR of poly(rac-LA) using **4e** indicated the formation of [PLLA–PDLA]_n, which could be obtained via CEM.^{12,15}

In conclusion, we have reported the living polymerization of rac-LA for highly isotactic poly(rac-LA) without any chiral auxiliaries

on the catalyst. The stereoselectivity in this catalysis via CEM was comparable to or higher than that of known polymerization via SCM. Further studies for practical synthesis of isotactic poly(rac-LA) from rac-LA as a thermally more stable material is in progress.

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Supporting Information Available: Experimental procedures, results using each complex, decoupled 500 MHz ¹H NMR spectra, DSC charts, and discussion of the initiation reaction of the catalysis (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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