Zinc-Catalyzed Highly Isoselective Ring Opening Polymerization of rac-Lactide

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Supporting Information

ABSTRACT: A family of chiral zinc amido-oxazolinate complexes are shown to be highly active and isoselective initiators for the ring-opening polymerization (ROP) of rac-lactide, yielding isotactic stereoblock polylactides (PLA) with $P_m$ up to 0.91. This represents the highest isoselectivity observed with zinc-based catalysts for ROP of rac-lactide.

As one of the leading sustainable materials, polylactides (PLAs) have attracted considerable interest due to their outstanding properties such as biodegradability, biocompatibility, and renewability. Synthetically, PLAs can be produced from lactic acids through condensation polymerization; or more preferably, from the ring opening polymerization (ROP) of lactide (LA), because the latter approach offers advantages such as higher molecular weight, narrower distribution, and better stereocontrol. Depending on the stereochemistry of the LA monomer, the selectivity of catalysts, and the reaction conditions, an array of microstructures can be obtained. Among them, the isotactic PLA is the most valuable due to its high melting point.

In principle, polymerization of homochiral lactides (L-LA or D-LA) can produce isotactic polymers in the absence of epimerization; however, the use of rac-lactide is advantageous because it opens up the possibility that stereocomplex PLA or stereoblock copolymer of PLA may be obtained, resulting in a melting point higher than PLLA or PDLA alone. Therefore, intensive efforts have been devoted to the discovery of new stereoselective initiators, particularly those that can produce isotactic PLAs from rac-LA.

Since the pioneering work that demonstrated a chiral salen aluminum complex exhibits high isoselectivity for rac-LA, a number of stereoselective initiators have been developed. Compared to the available heteroselective catalysts, isoselective catalysts are relatively scarce, and most of them are derived from aluminum complexes supported by salen-type ligands and their derivatives. However, Al catalysts often suffer from low activity in ROP of LA, typically requiring a prolonged time (24 h or longer) at elevated temperatures ($70−100$ °C). Other examples include those based on heavier group 13 elements, particularly indium, group 3 and lanthanides, and group 4 elements.

We have been interested in the amido-oxazolinate ligands (HL, Scheme 1) as a chiral variation of the conventional $\beta$-diketiminate ligands, because they allow opportunity for facile introduction of stereogenic groups. In analogy to the zinc-diketiminate complexes in alternating copolymerization of CO$_2$ and epoxides, we have shown the zinc complexes are viable initiators for asymmetric alternating copolymerization of CO$_2$ and cyclohexene oxide with modest stereocontrol.

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Herein we report their application for ROP of rac-lactide, in which they exhibit fast rates and high isoselectivity. Although zinc compounds have been extensively studied, to our knowledge, these are the highest isoselectivity achieved by zinc-based catalysts from rac-LA to date. In contrast, analogous zinc complexes supported by conventional β-diketiminate ligands induce high level of heterotacticity (Pm up to 0.94). Very recently, moderate to high preference toward isoselectivity has been obtained with zinc-based catalysts. However, the highest Pm (0.84) was achieved at very low temperature (−38 °C), and 

We initially examined compound 2a for ROP of rac-lactide under various conditions, which were conveniently monitored by 1H NMR spectroscopy. Selected results are summarized in Table 1. The reaction was first carried out in toluene at ambient temperature with 1 mol % catalyst, leading to a 91% conversion after 13 h. At 50 °C, the conversion was nearly complete within 30 min. At higher temperature (75 °C), low molecular weight PLA was produced (run 3). The reactions could be carried out in other solvents such as THF or dichloromethane with slightly lower conversions or without solvent under melt conditions (run 6). The catalyst loading can be decreased to 0.5 mol % without much change in conversion. No epimerization of lactide was observed during the catalysis, as [L-L]_aw a sp o l y m e r i z e dt o a purely isotactic PLA (run 7).

The molecular weights of the resulting PLAs appear to be significantly higher than the theoretical Mm calculated from the initial catalyst loading and conversion, assuming a single chain for each initiator. This can be attributed to a slow initiation step vs propagation, possibly due to the bulky initiating group [N(SiMe3)2]. However, in the presence of an alcohol, benzyl alcohol (BnOH, 1 equiv vs Zn), the polymerization became slower and low molecular weight PLA was produced (entry 9, Table S1). We attribute this lowered activity to the deactivation of Zn complex by alcohols, which is supported by the observation that stoichiometric reaction of BnOH and 2a leads mostly to free ligand. On the other hand, despite the slow initiation with 2a, the molecular weights increase with the progress of the reaction, and the dispersities are relatively narrow (1.03–1.30), suggestive of controlled behavior of the polymerization. Investigation by MALDI TOF mass spectrometry of a PLA sample (Figure S3) revealed the presence of a N(SiMe3)2 end group, as well as transesterification indicated by the cluster of peaks separated by 72 mass units.

The microstructure of the PLA was evaluated by the homonuclear-decoupled 1H NMR spectra, and the tetrad peaks were assigned according to the literature. The most notable feature is that catalyst 2a exhibits a high level of isoselectivity, as indicated by the dominant peak around 5.17 ppm attributed to the nnnn tetrad (Figure 1a). A Pm value of 0.81 was achieved at ambient temperature for 2a, which was further improved to 0.90 at 0 °C. The observed tetrads distribution for the methine carbon in the 13C NMR of the resulting PLA (Figure 1b) confirmed the high isotacticy. This represents the highest isoselectivity obtained with a zinc based initiator from ROP of rac-lactide thus far. Under bulk conditions (130 °C), the isotactic preference by 2a was maintained (Pm = 0.77). It is noted that a number of aluminum systems maintain high stereoselectivity under solvent-free conditions, which is often preferred in order to minimize generation of waste.

The reaction progress was monitored with compound 2a by periodically taking samples for 1H NMR determination. The conversion–time profile indicates approximately first order kinetics in monomer, as linear plot of ln([LA]0/[LA]t) versus time was observed with up to 85% conversion. The dependence on catalyst concentration was determined to be 0.93 (±0.14) from

### Table 1. ROP of rac-Lactide by Catalysts 2a–g

| run | cat | T (°C) | t (min) | conv. (%) | Mm (kg/mol) | Mm,calc (kg/mol) | Dr | Pm | Tm † (°C) |
|-----|-----|-------|--------|----------|-------------|----------------|----|----|----------|
| 1   | 2a  | 23    | 13 h   | 91       | 49.0        | 13.1           | 1.29 | 0.81 | 189     |
| 2   | 2a  | 50    | 30     | 98       | 30.0        | 14.1           | 1.30 | 0.77 | 176     |
| 3   | 2a  | 75    | 15     | 93       | 3.6         | 13.4           | 1.14 | 0.76 | 179     |
| 4   | 2a  | 0     | 3 d    | 94       | 59.2        | 13.5           | 1.19 | 0.90 (0.87)| 214     |
| 5*  | 2a  | 50    | 30     | 95       | 40.1        | 27.4           | 1.13 | 0.80 | 208     |
| 6** | 2a  | 130   | 8      | 91       | 45.5        | 13.1           | 1.15 | 0.77 |         |
| 7*  | 2a  | 50    | 125    | 91       | 34.5        | 13.1           | 1.12 | 1.0  | 168     |
| 8   | 2b  | 50    | 30     | 96       | 18.0        | 13.8           | 1.07 | 0.76 (0.76)| 184     |
| 9   | 2c  | 50    | 30     | 96       | 30.2        | 13.8           | 1.10 | 0.80 | 195     |
| 10  | 2d  | 50    | 30     | 97       | 28.0        | 14.0           | 1.18 | 0.67 (0.70)| 170     |
| 11  | 2e  | 50    | 30     | 80       | 29.4        | 11.5           | 1.05 | 0.72 | 194     |
| 12  | 2f  | 50    | 30     | 95       | 21.2        | 13.7           | 1.37 | 0.78 | 196     |
| 13  | 2g  | 50    | 30     | 93       | 37.4        | 13.4           | 1.23 | 0.86 (0.82)| 204     |
| 14  | 2g  | 23    | 44 h   | 96       | 52.2        | 13.8           | 1.32 | 0.91 (0.89)| 212     |

*Reactions were carried out using 1 mol % of catalyst at 50 °C in toluene, unless noted otherwise. 
**Determined by 1H NMR. 
13 Determined from the second heating cycles of DSC. The values are averages of three duplicates. 
4 Calculated molecular weight based on conversion and catalyst loading. 
5 Probability of meso enchainment, determined by the integration of methine region of the homonuclear decoupled 1H NMR. The Pm values in the parentheses were determined on the basis of 13C NMR. 
15 Determined from the 1H NMR of the resulting PLA (Figure 1b) con. 
16 The microstructure of the PLA was evaluated by the homonuclear-decoupled 1H NMR spectra, and the tetrad peaks were assigned according to the literature.

Figure 1. Methine region of (a) the homonuclear decoupled 1H NMR (500 MHz) and (b) 13C NMR (125 MHz) spectra of PLA generated with 2a (Table 1, run 4).

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the plot of ln(k_{m,rac}) versus ln[2a] (Figure S10), thus, the overall rate law can be written as rate = k[cat][LA]. Activation parameters of the polymerization were obtained from the Eyring plot (Figure S11) at 23–55 °C: ΔH^f = 54 (±7) kJ mol\(^{-1}\) and ΔS^f = −112 (±21) J mol\(^{-1}\) K\(^{-1}\). These values are comparable with the literature reports\(^{16,18}\) and suggest an ordered transition state that is in agreement with a coordination–insertion mechanism.

With established reaction conditions, we next examined a series of related zinc amido-oxazolinate complexes (2b–g) with varying steric and electronic substituents. At 50 °C in toluene with 1 mol % catalyst, the conversion of rac-lactide reacted >93% within 20–30 min for most of the catalysts tested. All of them showed good control of the polymerization process, as judged by the narrow molecular weight dispersions despite the molecular weight being higher than the theoretical values. Invariably this series of zinc catalysts exhibited a distinct preference for isotactic PLAs, and the highest P_m value of 0.86 (at 50 °C) was obtained with catalyst 2g that incorporates strong electron withdrawing groups (−CF\(_3\)). At 23 °C, the selectivity was improved to P_m = 0.91. The high isotacticity was further verified by the observed tetrads distribution for the methine carbon in the \(^{13}\)C NMR of the resulting PLA (Figures S6–7).

The thermal properties of the resulting PLAs were further investigated with differential scanning calorimetry (DSC). Distinctive melting transitions (T_m) abstracted from the second heating cycle were observed in a range of 170–215 °C. This can be roughly correlated with the P_m values of the polymers (Figure S16), in agreement with the literature report.\(^{19}\) In particular, the T_m value for PLA prepared from 2a at 0 °C with P_m = 0.90 (run 4, Table 1) was determined to be 214 °C (Figure 2), representing one of the highest T_m for PLA derived directly from rac-LA. As a comparison, T_m of a purely isotactic PLA is determined to be 168 °C (Table 1, run 7), in line with the literature value.\(^{18}\) The unusually high T_m may be attributed in part to the high molecular weights and supports the formation of stereoblock or stereocomplex PLAs due to the cocrystallization of isotactic segments of opposite configuration, which is expected from highly isospecific ROP of rac-LA.

As noted earlier, the iso-selectivity of ROP of rac-LA is mostly observed with Al-based catalysts, and their analogues in group 13 and group 3. It is worth noting that the metal alone is not the only factor determining the stereoselectivity, and the steric and electronic features of the supporting ligands may have a major effect on the stereo outcome. For example, with a slight modification of ligands, Al compounds have been tuned from highly isospecific (P_m = 0.79) to highly heterotactic (P_r = 0.96) in ROP of rac-LA.\(^{20}\) In this context, we also note that use of chiral catalysts does not necessarily ensure stereoccontrol in ROP of rac-LA, as a number of chiral zinc catalysts have demonstrated.\(^{21}\)

For metal-catalyzed ROP of cyclic esters, two pathways are often invoked to explain the observed stereoselectivity: chain end control and enantionomorphic site control. Since the present zinc catalysts are chiral, we thought that it may entail an enantionomorphic site control mechanism, that is, the chirality of the catalyst determines which monomer gets inserted favorably. This seems to agree with the result of an analogous, nonchiral Zn catalyst 3, in which only atactic PLA was produced for the ROP of rac-LA. However, the tacticities of the PLA obtained with 2a, as judged by P_{rr}, remained essentially unchanged versus conversion during the ROP of rac-LA (Figure S12). Though rac-LA reacted faster than l-LA under the same conditions with 2a, the rate difference, k_{rac-LA}/k_{l-LA} ~ 1.6 (Figure S13), is not large enough to account for the observed high isotacticity. The roughly first order dependence on rac-LA monomer also indicated little supposed differentiation between the two stereoisomers of rac-LA. Furthermore, the tetrads signals (particularly mmn and rrr; Figure S5) resulting from the stereomers showed unusual relative intensities that are not easily accounted for by a purely enantionomorphic site control or chain end control mechanism alone.\(^{22}\) A possible explanation is that there are significant contributions of chain end control mechanism after a chain transfer/transfation event leading to stereocomers. This gives rise to an isotactic multiblock stereocopolymer. The presence of both mechanisms has been proposed in other systems to account for the stereoselectivity during the ROP of rac-LA.\(^{15a,23}\)

In summary, we have described a family of amido-oxazolinate zinc catalysts that show fast rate and high isoiselectivity for ROP of rac-lactide, producing isotactic PLA with P_m up to 0.91, the highest so far by a zinc-based system. These findings demonstrate the ability of zinc catalysts to produce highly isotactic PLA from rac-lactide by proper selection of ancillary ligands. Given that zinc catalysts are generally more active than the aluminum catalysts in ROP of lactides and the present catalysts feature an easily modifiable ligand framework for improvement and interrogation, it is reasonable to expect that more active and stereoselective catalysts would be discovered. Efforts aimed at improving the stereocontrol and understanding the origin of isoselectivity and detailed reaction mechanisms are underway in our lab.

**ASSOCIATED CONTENT**

**Supporting Information**
Experimental details, representative NMR, GPC, MALDI MS, and DSC data and figures, and kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Gupta, A. P.; Kumar, V. Eur. Polym. J. 2007, 43, 4033–4074. (b) Nampoothiri, K. M.; Nimisha, R. N.; Rojan, P. J. Bioresour. Technol. 2010, 101, 8493–8501. (c) Tschan, M. J.-L.; Brule, E.; Haquette, P.; Thomas, C. M. Polym. Chem. 2012, 3, 836–851.

(2) (a) Dechy-Cabaret, O.; Martin-Vaca, B.; Bourissant, D. Chem. Rev. 2004, 104, 6147–6176. (b) Wu, J.; Yu, T.-L.; Chen, C. T.; Liu, C.-C.; Lin, C.-C. Coord. Chem. Rev. 2006, 200, 602–621.

(3) (a) Tsuji, H. Macromol. Biosci. 2005, 5, 569–597. (b) Sodergard, A.; Stolt, M. Prog. Polym. Sci. 2002, 27, 1123–1163.

(4) (a) Spasny, N.; Wisniewski, M.; Pluta, C.; Le Borgne, A. Macromol. Chem. Phys. 1996, 197, 2627–2637. (b) Wisniewski, M.; Le Borgne, A.; Spasny, N. Macromol. Chem. Phys. 1997, 198, 1227–1238.

(5) (a) Stanford, M. J.; Dove, A. P. Chem. Soc. Rev. 2010, 39, 486–494. (b) Thomas, C. M. Chem. Soc. Rev. 2010, 39, 165–173.

(6) (a) Dijkstra, P. J.; Du, H.; Feijen, J. Polym. Chem. 2011, 2, 520–527.

(7) (a) Normand, M.; Dorcet, V.; Kirillov, E.; Carpentier, J.-F. Macromol. Mater. Eng. 2010, 295, 1694–1709.

(8) (a) Wang, H.; Ma, H. Chem. Commun. 2013, 49, 8868–8868. (b) Horndro, M.; Otero, A.; Fernandez-Baeza, J.; Sanchez-Barba, L. F.; Lara-Sanchez, A.; Tejeda, J.; Carrion, M. P.; Martinez-Ferrer, J.; Gaces, A.; Rodriguez, A. M. Organometallics 2013, 32, 3473–3440.

(9) Song, S.; Zhang, M.; Ali, M.; Yang, Y. Dalton Trans. 2012, 41, 3266–3277.

(10) Zell, M. T.; Padden, B. E.; Paterick, A. J.; Thakur, K. A. M.; Kean, R. T.; Hillmyer, M. A.; Munson, E. J. Macromolecules 2002, 35, 7700–7707.

(11) Kasperczyk, J. E. Macromolecules 1995, 28, 3937–3939.

(12) Douglas, A. F.; Patrick, B. O.; Mehrkhodavandi, P. Angew. Chem. Int. Ed. 2008, 47, 2290–2293.

(13) Chisholm, M. H.; Eilers, N. W. Chem. Commun. 1996, 853–854.

(14) Nomura, N.; Hasegawa, J.; Ishii, R. Macromolecules 2009, 42, 4907–4909.

(15) Horndro, M.; Marshall, E. L.; Gibson, V. C.; White, A. J. Polym. Mater. Sci. Eng. 2014, 94, 2290–2293.

(16) Chisholm, M. H.; Eilers, N. W. Chem. Commun. 1996, 853–854.

(17) Dijkstra, P. J.; Feijen, J. Am. Chem. Soc. 2004, 126, 2688–2689.

(18) (a) Wang, H.; Ma, H. Chem. Commun. 2013, 49, 8868–8868. (b) Horndro, M.; Otero, A.; Fernandez-Baeza, J.; Sanchez-Barba, L. F.; Lara-Sanchez, A.; Tejeda, J.; Carrion, M. P.; Martin-Ferrer, J.; Gaces, A.; Rodriguez, A. M. Organometallics 2013, 32, 3473–3440.

(19) Song, S.; Zhang, M.; Ali, M.; Yang, Y. Dalton Trans. 2012, 41, 3266–3277.

(20) Zell, M. T.; Padden, E. B.; Paterick, A. J.; Thakur, K. A. M.; Kean, R. T.; Hillmyer, M. A.; Munson, E. J. Macromolecules 2002, 35, 7700–7707.

(21) Kasperczyk, J. E. Macromolecules 1995, 28, 3937–3939.

(22) Douglas, A. F.; Patrick, B. O.; Mehrkhodavandi, P. Angew. Chem. Int. Ed. 2008, 47, 2290–2293.

(23) Chisholm, M. H.; Eilers, N. W. Chem. Commun. 1996, 853–854.

(24) Nomura, N.; Hasegawa, J.; Ishii, R. Macromolecules 2009, 42, 4907–4909.

(25) Horndro, M.; Marshall, E. L.; Gibson, V. C.; White, A. J. Polym. Mater. Sci. Eng. 2014, 94, 2290–2293.

(26) Chisholm, M. H.; Eilers, N. W. Chem. Commun. 1996, 853–854.

(27) (a) Wang, H.; Ma, H. Chem. Commun. 2013, 49, 8868–8868. (b) Horndro, M.; Otero, A.; Fernandez-Baeza, J.; Sanchez-Barba, L. F.; Lara-Sanchez, A.; Tejeda, J.; Carrion, M. P.; Martin-Ferrer, J.; Gaces, A.; Rodriguez, A. M. Organometallics 2013, 32, 3473–3440.

(28) Song, S.; Zhang, M.; Ali, M.; Yang, Y. Dalton Trans. 2012, 41, 3266–3277.

(29) Zell, M. T.; Padden, B. E.; Paterick, A. J.; Thakur, K. A. M.; Kean, R. T.; Hillmyer, M. A.; Munson, E. J. Macromolecules 2002, 35, 7700–7707.

(30) Kasperczyk, J. E. Macromolecules 1995, 28, 3937–3939.

(31) Douglas, A. F.; Patrick, B. O.; Mehrkhodavandi, P. Angew. Chem. Int. Ed. 2008, 47, 2290–2293.

(32) Horndro, M.; Marshall, E. L.; Gibson, V. C.; White, A. J. Polym. Mater. Sci. Eng. 2014, 94, 2290–2293.

(33) Chisholm, M. H.; Eilers, N. W. Chem. Commun. 1996, 853–854.

(34) Nomura, N.; Hasegawa, J.; Ishii, R. Macromolecules 2009, 42, 4907–4909.