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Stereoelective polymerization of D,L-lactide using N-heterocyclic carbene based compounds†

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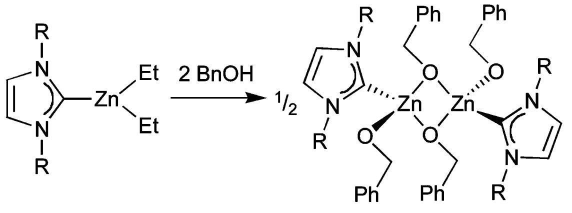
Received (in Columbia, MO, USA) 21st April 2004, Accepted 5th August 2004
First published as an Advance Article on the web 8th September 2004

A new Zn alkoxide catalyst supported by an N-heterocyclic carbene rapidly polymerizes D,L-lactide (D,L-LA) to heterotactic enriched poly(lactide) (PLA), while the free carbene and analogs instead yield highly isotactic enriched PLA.

Polylactide (PLA) is an attractive alternative to petrochemically derived polyolefins due to its utility (*e.g.*, in biomedical and packaging applications), biodegradation characteristics, and facile synthesis from lactide (LA), a monomer synthesized from renewable resources.[1] An ideal LA polymerization catalyst would exhibit high activity, allow for precise molecular weight control, give polymers with narrow molecular weight distributions, and show a high degree of stereoelectivity in the polymerization of stereochemically impure monomer feeds. This combination of attributes has not been fully realized, although single site metal alkoxides are the most promising candidates.[2] For example, aluminium alkoxides with various salen-type ligands have produced PLA from racemic D,L-LA with tacticities ranging from highly isotactic to heterotactic, and have yielded highly syndiotactic PLA from *meso*-LA.[3] While excellent stereocontrol was achieved with these Al systems, they suffer from inherently low activity; reasonable conversions are generally attained only at high temperatures (> 70 °C) over long times (hours). Zinc complexes have been shown to be more active, although less versatile from a control of tacticity standpoint.[4,5] Notwithstanding these advances, our understanding of the origin of stereocontrol and high activity in LA polymerizations by metal alkoxides is rudimentary and improvements in catalyst versatility are warranted. As part of an ongoing effort to address these issues,[6] we explored Zn complexes of N-heterocyclic carbenes, ligands with readily tuned steric properties important for stereoselective reactions.[7] Herein we report the preparation of such a complex, demonstration of its efficient and selective LA polymerization behavior, and discovery of the stereoelective polymerization of D,L-LA by free achiral N-heterocyclic carbenes.

Addition of benzyl alcohol (BnOH) to the previously reported complex (1,3-dimesitylimidazol-2-ylidene)ZnEt$_2$[8] in toluene produced **A** in 92% yield (Scheme 1). The X-ray structure‡ of **A** (Fig. 1) shows each Zn in a distorted tetrahedral geometry bound to a carbene and three benzyloxides, two bridging and one terminal. The Zn–carbene bond distance (2.054 Å) falls between those of the two other reported examples (2.022 Å[9] and 2.096 Å). The ^{1}H NMR spectrum in CD$_2$Cl$_2$ shows only two mesityl CH$_3$ resonances and one benzylic resonance, suggesting that in solution **A** either cleaves into C_2-symmetric monomers or remains dimeric but is highly fluxional *via* a process(es) that involves terminal/bridging benzyloxide ligand exchange.



A R = 2,4,6-trimethylphenyl

Scheme 1

Complex **A** is an efficient catalyst for the polymerization of D,L-LA in CH$_2$Cl$_2$ at 25 °C (Table 1). Polymerization control was demonstrated by a linear relationship between conversion and M_n (ESI).† Kinetics measurements (ReactIR) showed a first order dependence on [D,L-LA], with $k_{obs} = 1.9 \times 10^{-3}\ s^{-1}$ for $[\mathbf{A}]_0 =$ 2.7 mM ($[Zn]_0$ = [carbene ligand] = 5.3 mM). This value is only slightly less than that of the fastest reported Zn catalyst at the same catalyst loading ($k_{obs} = 1.2 \times 10^{-2}\ s^{-1}$ at $[Zn]_0$ = 5.3 mM).[6a] In a reaction performed at $[\text{D,L-LA}]_0/[\mathbf{A}]_0 = 290$ and terminated at 7.4% conversion, the PLA produced had M_n = 2840 g mol^{-1} by MALDI MS in good agreement with the value predicted (M_n = 3090 g mol^{-1}) under the assumption of initiation by all four benzyl alkoxides. Incorporation of benzyl alcohol end groups is consistent with the MALDI MS data (ESI, Fig. S2). ^{1}H NMR spectroscopic analysis[10] showed heterotactic enrichment of PLA (Fig. 2, i) consistent with chain-end control (P_r = 0.6).[11] Similarly heterotactic enriched PLA also was obtained from polymerizations of D,L-LA performed in the melt (140–180 °C).

Although N-heterocyclic carbenes are generally considered to be nonlabile (*e.g.*, relative to phosphines on late transition metals), their known efficacy as LA polymerization catalysts (in the presence of alcohol initiator)[12] raised concerns that the free carbene **B** was responsible for the observed high activity. In support of

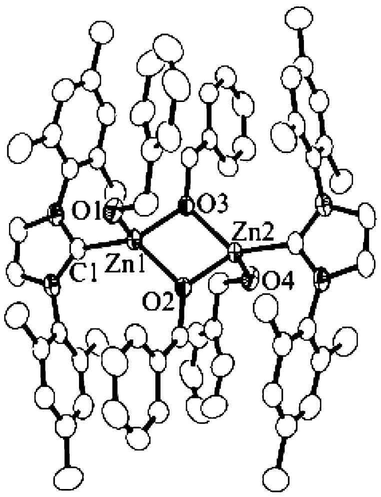


Fig. 1 Representation of the X-ray crystal structure of **A**, showing non-hydrogen atoms as 50% thermal ellipsoids. Selected bond distances (Å) and angles (°): Zn1–O1, 2.0135(14); Zn1–O2, 1.9198(15); Zn1–C1, 2.054(2); Zn1–Zn2, 3.0211(6); O1–Zn1–O2, 112.31(7); O2–Zn1–O3, 81.98(6); Zn1–O2–Zn2, 98.02(6); O2–Z1–C1, 124.80(8); O1–Zn1–C1, 107.75(7).

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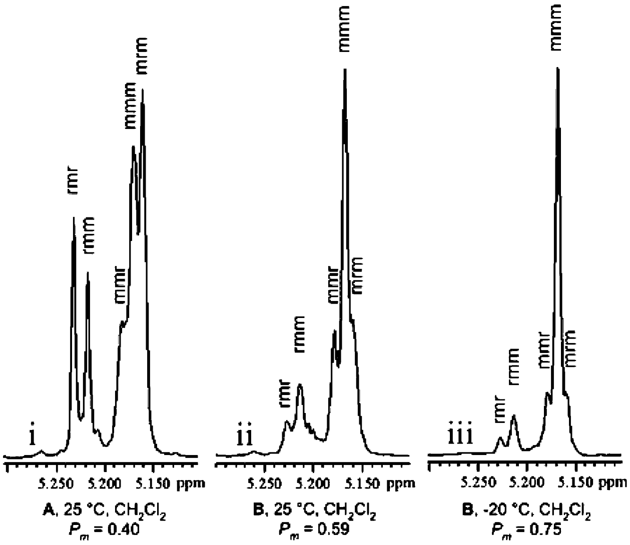
† Electronic supplementary information (ESI) available: full experimental details and crystallographic data for **A**. See http://www.rsc.org/suppdata/cc/b4/b405362a/

DOI: 10.1039/b405362a

Table 1 Polymerization of D,L-LA by compounds **A–D** ($[LA]_0 = 1$ M, CH_2Cl_2)

Entry	Catalyst	$[LA]_0$/ $[Init.]_0$	T (°C)	t (min)	% conv.[a]	M_n (kg mol^{-1})[b]	PDI (M_w/ M_n)[b]	P_m[c]
1	**A**	130	25	20	96	17.2	1.25	0.40
2	**B**[d]	130	25	30	98	16.9	1.23	0.59
3[e]	**B**[d]	150	−20	20	71	15.9	1.26	0.75
4	**C**[d]	75	25	20	92	8.42	1.39	0.60
5	**D**[d]	75	25	20	95	7.01	1.36	0.55

[a] Determined by ^1H NMR spectroscopy. [b] SEC (relative to polystyrene in THF). [c] See ref. 11. [d] Benzyl alcohol added. [e] $[LA]_0 = 0.1$ M.



A, 25 °C, CH_2Cl_2 $P_m = 0.40$

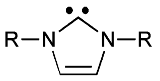
B, 25 °C, CH_2Cl_2 $P_m = 0.59$

B, -20 °C, CH_2Cl_2 $P_m = 0.75$

Fig. 2 ^1H NMR spectra (500 MHz, $CDCl_3$) of PLA methine resonances with selective decoupling of PLA methyl resonances; (i) heterotactic enriched PLA, Table 1, entry 1; (ii) isotactic enriched PLA, Table 1, entry 2; (iii) isotactic enriched PLA, Table 1, entry 3.

possible carbene ligand dissociation in **A**, attempts to synthesize an analog of **A** with a more hindered carbene *via* treatment of (**C**)$ZnEt_2$ with BnOH (⩾ 1 equiv.) resulted in generation of free **C** (> 70% by ^1H NMR spectroscopy).

To address whether free carbene **B** was participating in polymerizations using **A**, we compared the polymerization kinetics obtained using **B** (with 0.5–2 equiv. added BnOH) to the data obtained for **A**. With $[\mathbf{B}]_0/[BnOH]_0 = 0.54$, the PLA formation rate was first-order in [D,L-LA], with a value ($k_{obs} = 3.1 \times 10^{-3}$ s^{-1} at $[\mathbf{B}]_0 = 5.3$ mM) slightly greater than for **A** (1.9×10^{-3} s^{-1}) under the same conditions. On the basis of this data, one cannot rule out catalysis by some level of pure **B** when using **A** as the precatalyst.



B R = 2,4,6-trimethylphenyl
C R = 2,6-diisopropylphenyl
D R = t-butyl

However, we discovered a striking difference in the tacticity of the product polylactide when using **B**. In contrast to the heterotactic material produced when using **A** (Fig. 2, i), the combination of **B** and BnOH produced isotactic enriched PLA from D,L-LA under similar conditions (CH_2Cl_2, 25 °C, Fig. 2, ii).§ In fact, carbenes **C** and **D** also produced PLA with isotactic enrichment (Table 1). The highest isotacticity PLA we obtained was with **B** and 0.67 equiv. BnOH at −20 °C in CH_2Cl_2 ($P_m = 0.75$, Table 1, entry 3; Fig. 2, iii). That material, produced in 71% yield from racemic D,L-LA, showed a melting point by differential scanning calorimetry of 153 °C ($\Delta H_{fus} \cong 0.8$ J g^{-1}) consistent with the presence of a small amount of semicrystalline material (supporting information).[13] In addition to implicating intriguing mechanistic differences between polymerizations by **A** and free **B**, these findings provide motivation for the development both of new Zn–carbene complexes and N-heterocyclic carbenes for the controlled, rapid, and stereoelective polymerization of lactide, particularly in view of the wide range of N-heterocyclic carbene structures available.¶

Financial support from the NSF (CHE9975357) is gratefully acknowledged, and we thank K. A. Switek for assistance with the MALDI-MS experiments.

Notes and references

‡ CCDC 237615. See http://www.rsc.org/suppdata/cc/b4/b405362a/ for crystallographic data in .cif or other electronic format.

§ This difference in tacticity bias between **A** and **B** persists even in the melt polymerization of D,L-LA at 140 °C.

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