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Synthesis, structure, and catalytic activity of a new zinc complex derived from a chiral hydroxyazetidine ligand

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ABSTRACT

A new chiral tetrameric zinc complex [(**1**)ZnEt]$_4$ (**2**) has been readily prepared *via* alkane elimination between ZnEt$_2$ and a chiral azetidine derivative, (2*R*,3*R*)-1-[(1*S*)-1-(4-methoxyphenyl)ethyl]-2-phenyl-3-hydroxyazetidine (**1**H). Complex **2** has been characterized by various spectroscopic techniques, elemental analyses, and X-ray diffraction analysis. Complex **2** has a cubane-like Zn$_4$O$_4$ core structure, and is an active catalyst for the polymerization of *rac*-lactide, leading to the heterotactic-rich polylactides.

Chiral zinc complexes have been widely studied for the past decades. One of the driving forces for this work is the growing interest in the development of catalysts for lactide polymerization [1–9], because the polylactide finds increasing use as a commodity polymer due to its biodegradability and the possibility of deriving the monomer from renewable resources [10,11]. The physical and mechanical properties of polylactides, as well as the rate of degradation, are intimately related to the chain stereochemistry [12,13]. For example, a stereocomplex polymer formed by an equivalent mixture of poly(L-lactide) and poly(D-lactide) has many advantages such as higher melting temperature (230 °C) comparing with the enantiopure polylactide (180 °C) [14,15]. Thus, the directing polymerization of *rac*-lactide *via* stereoselective catalysts offers a significative challenge and opportunity for chemists. To date, the chiral zinc catalysts have been shown to be promising for this transformation, however, even within this class, successful catalysts affording significant stereoselectivity are rare [1–9,16–19]. Thus, the preparation of polylactide remains an open area of research. The development of new zinc catalysts for polymerization of *rac*-lactide is still a desirable and challenging goal. Ligand modification plays a key role in the developing new catalyst precursors for optimizing polymerization activity as well as polymer properties such as stereoregularity, molecular weight, bulky and polar comonomer incorporation, and microstructure. In recent years, we have developed a series of chiral ligands, and their Ta(IV), Ti(IV), Zr(IV), Zn(II) and lanthanide complexes are useful catalysts for a range of transformations [20–31]. For example, the ligand (2*R*,3*R*)-1-[(1*S*)-1-(4-methoxyphenyl)ethyl]-2-phenyl-3-hydroxyazetidine (**1**H) is a useful auxiliary for the asymmetric diethylzinc addition to aldehydes, in some cases, the enantioselectivity is as high as 97% ee [31]. Encouraged by the attractive feature of this ligand, we have recently started exploring the **1**H in polymerization of *rac*-lactidine. Herein, we report on some observations concerning the chemistry of ligand **1**H with ZnEt$_2$, and the use of the resulting complex as catalyst in the polymerization of *rac*-lactidine.

The chiral ligand, (2*R*,3*R*)-1-[(1*S*)-1-(4-methoxyphenyl)ethyl]-2-phenyl-3-hydroxyazetidine (**1**H), can be easily prepared by a three-step procedure (Scheme 1) [31]. Condensation of (*S*)-1-(4-methoxyphenyl)ethylamine with the benzaldehyde in dichloromethane in the presence of anhydrous MgSO$_4$ affords the corresponding aldimine **I**. Subsequently, performing the Staudinger reaction of imine **I** with acetoxyketene, derived from acetoxyacetyl chloride and Et$_3$N, gives a crude mixture of *cis*-*β*-lactams **IIa** and **IIb**, which can be separated by recrystallization from an ethyl acetate solution. Reduction of *cis*-*β*-lactams **IIa** by AlH$_2$Cl, prepared from LiAlH$_4$ and AlCl$_3$ in ratio of 1:1 in dry THF, gives the 3-hydroxyazetidine **1**H after purification by recrystallization from an *n*-hexane and ethyl acetate mixture (2:3). The configuration of phenyl and hydroxyl groups in **1**H is assigned as *cis* by its crystal structure (Fig. 1). The hydroxyl group and electron lone pair on N atom are situated on the same side of the azetidine backbone, indicating that a metal ion would easily chelated/coordinate to both of them.

Organozinc complexes can be easily prepared by alkane elimination of dialkylzinc with protic reagents. For example, treatment of **1**H with 1 equiv of ZnEt$_2$ gives a desired chiral tetrameric zinc complex [(**1**)ZnEt]$_4$ (**2**) in 68% yield (Scheme 1) [32]. Complex **2** is stable in dry nitrogen atmosphere, while it is very sensitive to moisture. It is soluble in organic solvents such as THF, DME, pyridine, toluene, and benzene. Complex **2** has been characterized by various spectroscopic techniques, elemental analysis, and X-ray diffraction analysis [33].

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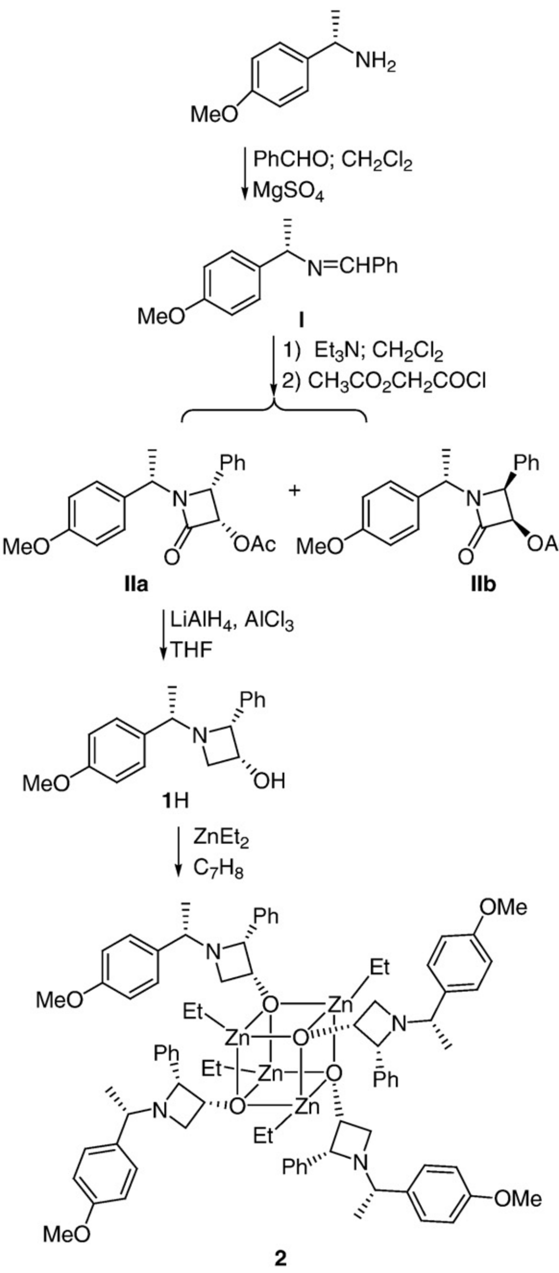


Scheme 1. Synthesis of complex **2**.

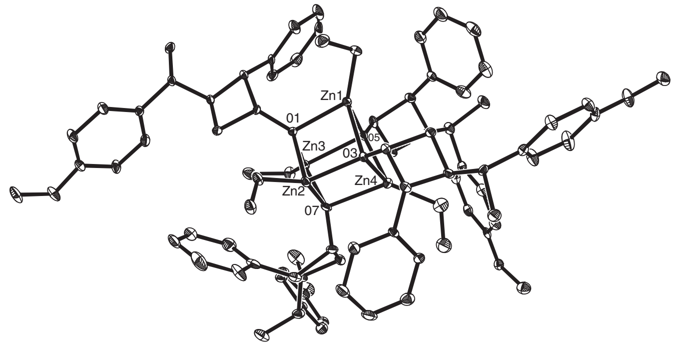


Fig. 2. Molecular structure of **2** (thermal ellipsoids drawn at the 35% probability level). Selected bond lengths (Å) and bond angles (deg): Zn–C (av.) 1.974(4), Zn–O (av.) 2.099(3), Zn···Zn (av.) 3.099(1), Zn–O–Zn (av.) 96.7(1), O–Zn–O (av.) 82.8(1).

The solid-state structure of **2** shows that each substituted azetidine group is far away from the metal center (Fig. 2). The main structural feature of **2** is the distorted Zn_4O_4 heterocubane central core which is topologically related to the structural fragments observed in NaCl-like metal oxide ZnO [34]. Each zinc atom possesses highly distorted tetrahedral coordination and lies at the corner of a tetrahedron. The atom arrangement in **2** is very close to the structures observed for related tetrameric alkylzinc alkoxides, such as $[MeZnO(CMe_3)]_4$ [35], and $[Me_3SiCH_2Zn(O\text{-}1\text{-}Ad)]_4$ [36]. The entire molecule shows S_4 quasi-symmetry with a symmetry axis passing through the centers of two parallel cube faces, Zn(1)-O(3)-Zn(2)-O(1) and Zn(3)-O(5)-Zn(4)-O(7). The distortion of the Zn_4O_4 heterocubane (the average Zn–O–Zn and O–Zn–O angles are 96.7(1)° and 82.8(1)°, respectively) can be described in terms of outward movements of zinc atoms along the S_4 axis, indicating that the atomic orbitals of zinc used in forming bonds to oxygen are mostly p character. The Zn···Zn distances are in the range of 3.061(1) to 3.146(1) Å, with an average value of 3.099(1) Å. The Zn–O distances range from 1.992(3) to 2.276(2) Å, with an average value of 2.099(3) Å. The Zn–C distances are equal within the experimental error and have an average value of 1.974(4) Å. These crystal data are comparable to those found in tetrameric alkylzinc alkoxides [35,36].

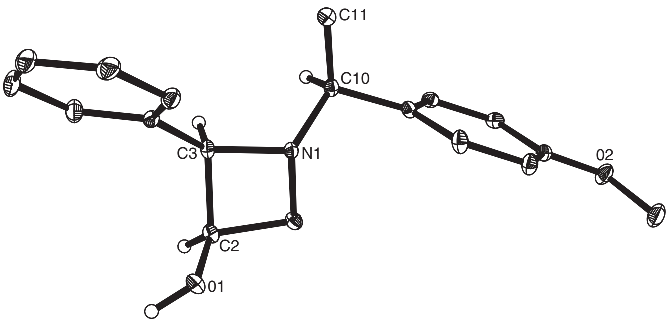
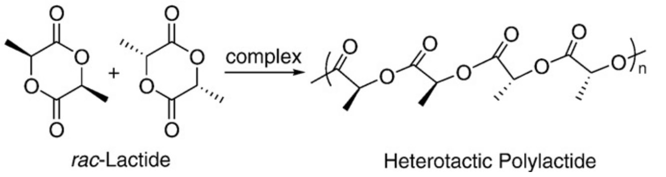


Fig. 1. Molecular structure of **1** (thermal ellipsoids drawn at the 35% probability level).

The polymerization data show that **2** can initiate the ring opening polymerization (ROP) of *racemic*-lactide [37] under mild conditions (Table 1). For example, it allows the complete conversion of 250 equiv

Table 1

Polymerization of *rac*-lactide catalyzed by complex **2** [a].



Entry	T (°C)	Solvent	Conv. (%)	M_n [b] (kg/mol)	M_w/M_n [b]	P_r [c] (%)
1	25	THF	100	35.8	1.15	66
2	70	Toluene	100	35.6	1.18	68
3	25	CH_2Cl_2	62	24.2	1.58	58
4	10	THF	85	29.7	1.22	71
5	10	CH_2Cl_2	28	11.5	1.96	54
6	40	THF	100	35.4	1.26	65
7	40	CH_2Cl_2	92	33.7	1.48	56
8[d]	40	THF	93	66.7	1.32	67
9[d]	40	CH_2Cl_2	56	39.5	1.72	59

[a] Conditions: [Zn]/LA (mol/mol) = 1/250; polymerization time, 12 h; solvent, 5 mL; [LA] = 0.5 mol/L.

[b] Measured by GPC (using polystyrene standards in THF).

[c] P_r is the probability of *racemic* linkages between monomer units and is determined from the methine region of the homonuclear decoupled ^1H NMR spectrum in $CDCl_3$ at 25 °C [2,3].

[d] Conditions: [Zn]/LA (mol/mol) = 1/500; polymerization time, 12 h; solvent, 5 mL; [LA] = 1.0 mol/L.

of lactide within 12 h at room temperature in THF at [*rac*-LA] = 0.5 mol L^{-1}, and the molecular weight distribution is very narrow (1.15) over the entire monomer-to-initiator ratio range (Table 1, entry 1), in agreement with a single-site catalyst system [38]. It also can produce a narrow molecular weight distribution polymer (1.18) in toluene at 70 °C (Table 1, entry 2). However, at room temperature in CH_2Cl_2 solution, the polymerization with this zinc initiator/catalyst proceeds much more slowly with a much broader molecular weight distribution (1.58) (Table 1, entry 3). This might be due to the coordination of CH_2Cl_2, which changes the steric environment and the Lewis acidity of the central metal. This difference between CH_2Cl_2 and THF solvent is more obvious at lower temperature (Table 1, entries 4 and 5) than at higher temperature (Table 1, entries 6 and 7). This difference is also observed in high monomer/catalyst ratio system (Table 1, entries 8 and 9). The resulting polylactides are all heterotactic rich under the conditions examined, and the molecular weights range from 11.5 to 66.7 kg mol^{-1}. Our results show that the catalytic activity of **2** resemble that of zinc complex [(*S*)-PhCH(Me)N(2-CH_2-4,6-$^tBu_2C_6H_2O)_2]Zn_2Et_2$ [2], while the microstructure of the resulting polylactides is similar to those initiated by [{(*S*)-PhCH(Me)(N=CMe)}$_2$CH]Zn(OPr^i) [3].

In conclusion, a new chiral tetrameric zinc complex [(**1**)ZnEt]$_4$ (**2**) has been readily prepared *via* alkane elimination reaction between $ZnEt_2$ and a chiral azetidine derivative, (2*R*,3*R*)-1-[(1*S*)-1-(4-methoxyphenyl) ethyl]-2-phenyl-3-hydroxyazetidine (**1**H). Complex **2** has a cubane-like Zn_4O_4 core structure, and is an active catalyst for the polymerization of *rac*-lactide, leading to the heterotactic-rich polylactides.

Acknowledgements

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Appendix A. Supplementary data

CCDC 865690 and 865691 contain the supplementary crystallographic data for **1**H and **2**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk. Supplementary data with this article can be found, in the online version, at doi: 10.1016/j.inoche.2012.03.015.

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[32] *Preparation of 2*. In a glovebox, a toluene solution of $ZnEt_2$ (0.49 g, 1.0 mmol, 25% in toluene) was slowly added into a toluene solution (10 mL) of **1**H (0.28 g, 1.0 mmol) with stirring at room temperature. After the solution was stirred at room temperature for one day, the solution was filtered. The volume of the filtrate was reduced to 5 mL, and colorless crystals of **2** were isolated when this solution was kept at −20 °C for one week. Yield: 0.25 g (68%). M.p.: 125–127 °C (dec.). ^1H NMR (C_6D_6): δ 7.68 (m, 2H, aryl), 7.26 (m, 3H, aryl), 6.93 (m, 4H, aryl), 4.01 (m, 2H, C*H*), 3.35 (s, 3H, OMe), 3.27 (m, 1H, C*H*), 3.05 (m, 1H, C*H*), 2.93 (m, 1H, C*H*), 1.59 (m, 3H, $ZnCH_2CH_3$), 1.01 (d, $J = 6.3$ Hz, 3H, Me), 0.65 (m, 2H, $ZnCH_2CH_3$). ^{13}C NMR (C_6D_6): δ 159.3, 138.6, 136.7, 129.0, 128.8, 127.9, 127.1, 113.9 (aryl *C*), 73.3 (CH), 70.2 (CH), 67.3 (CH), 61.4 (CH_2), 54.6 (OCH_3), 22.2 (CH_3), 13.0 ($ZnCH_2CH_3$), 0.80 ($ZnCH_2CH_3$). IR (KBr, cm^{-1}): ν 2964 (m), 1607 (m), 1508 (m), 1442 (m), 1376 (m), 1260 (s), 1091 (s), 1018 (s), 799 (s). Anal. Calcd for $C_{80}H_{100}N_4O_8Zn_4$: C, 63.75; H, 6.69; N, 3.72. Found: C, 63.68; H, 6.80; N, 3.92%.

[33] Crystal data for 1H: C18H21NO2, fw = 283.36, monoclinic, P21, a = 10.312(1) Å, b = 7.326(3) Å, c = 10.558(1) Å, β = 106.43(1)° V = 765.0(1) Å3, Z = 2, R1 = 0.030 for 8594 (I > 2σ(I)), wR2 = 0.075 (all data). Crystal data for 2: C80H100N4O8Zn4, fw = 1507.12, monoclinic, P21, a = 13.270(3) Å, b = 20.929(4) Å, c = 14.170(3) Å, β = 109.69(3)° V = 3705.2(13) Å3, Z = 2, R1 = 0.042 for 37105 (I > 2σ(I)), wR2 = 0.099 (all data).

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[37] *General procedure for polymerization of rac-lactide.* In a glovebox, a Schlenk flask was charged with a solution of **2** (typically 0.025 mmol) in CH_2Cl_2 (0.2 mL), THF (0.2 mL) or toluene (0.2 mL). To this solution was added rapidly a CH_2Cl_2, THF or toluene solution (5.0 mL) of *rac*-lactide (2.5 mmol), and the reaction mixture was vigorously stirred for 12 h at 10, 25, 40 or 70 °C. The polymerization was quenched by the addition of acidified methanol. The resulting precipitated polylactide was collected, washed with methanol several times, and dried in vacuum at 50 °C overnight. The molecular weight and the molecular weight distribution of the resulting polymer were determined by GPC. The tacticity of the polylactide was calculated according to the methine region of the homonuclear decoupled ^{1} H NMR spectrum [2,3].

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