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Single site catalysts for stereoselective ring-opening polymerization of lactides

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Poly(lactide) (PLA) is the most well known biodegradable and biocompatible material among the aliphatic polyesters nowadays explored for biomedical, pharmaceutical and environmental applications. Different poly(lactide)s are distinguished, namely stereoregular PLLA and PDLA, atactic, heterotactic, syndiotactic and stereoblock PLAs. Because the stereochemistry of the monomeric units in the polymer chains plays a decisive role in the mechanical, physical and degradation properties of PLA materials, stereospecific catalysts to prepare different polylactide architectures are a major topic. In this review, after a general introduction on metal catalyzed ring opening polymerization, we mainly focus on single site catalyst systems inducing stereoselective polymerization of lactides.

Introduction

Polymeric materials derived from petrochemical feedstock are widely used nowadays. However, these petrochemical resources will arguably be consumed in the near future. Thus, there is an urgent need to develop new polymeric materials using renewable resources. The production and utilization of biodegradable aliphatic polyesters, such as poly(lactic acid)s (PLAs), have been developed recently to meet this requirement. The most straightforward methods to prepare PLAs are (1) the polycondensation of lactic acid and (2) the ring-opening polymerization (ROP) of lactide. It seems that polycondensation of lactic acid is the commercially most attractive route to prepare PLAs. However, condensation polymerization to form PLAs is hampered by the typical limitations of step polymerization, like the difficulty in obtaining polymers with sufficiently high molecular weights. Since esterification reactions are equilibrium processes in a condensation polymerization, it is necessary to drive the polymerization by the removal of water to achieve high degrees of polymerization. The ROP of lactide circumvents this disadvantage and is the method nowadays used to prepare PLAs.

Ring-opening polymerization of lactide

Lactide, which is a cyclic dimer of lactic acid, is produced by the thermal degradation of poly(lactic acid) oligomers. A catalyst is required for the ROP of lactide and depending on the catalyst used, different mechanisms are involved, such as a cationic,^{1–4} anionic,^{5–8} or coordination–insertion mechanism.⁹

It is very difficult to obtain PLA materials with high molecular weights by using metal complexes which act *via* a cationic mechanism in the ROP of lactide.¹⁰ Moreover, the ROP of lactide following an anionic mechanism usually leads to problems in controlling the molecular weight and molecular weight distribution of the PLA product, which is mainly caused by side reactions such as epimerization, chain termination, and inter-/intra-molecular transesterification reactions.¹¹ Therefore, the

study of metal complexes that catalyze lactide polymerization *via* a coordination–insertion mechanism has become an important topic.

Metal alkoxides are known to catalyze the ROP of lactide *via* a coordination–insertion mechanism, which involves four steps as depicted in Fig. 1: (i) coordination of the lactide monomer to the Lewis-acid metal center, (ii) the lactide monomer inserts into the metal-alkoxide bond *via* nucleophilic addition, (iii) ring-opening of the lactide monomer *via* acyl-oxygen cleavage and (iv) continuous insertion of lactide monomers. Finally termination of the polymerization reaction by hydrolysis of the active propagation chain is performed before isolation of the PLA material.

Multivalent metal alkoxides

The most widely used catalyst for the industrial production of PLA materials is undoubtedly tin(II) bis(2-ethylhexanoate), usually referred to as tin(II) octanoate or Sn(Oct)₂. The mechanism of the ROP of lactones and lactides catalyzed by Sn(Oct)₂ has been a research subject for many years. Now it is generally accepted that protic reagents such as alcohols, or even impurities such as lactic acid present in the monomer may act as co-initiators^{12–14} (Fig. 2). Tin(II) alkoxides will be generated from the reaction between Sn(Oct)₂ and the protic reagents in the initiation step, and act as the true active species to initiate the ROP of lactides.

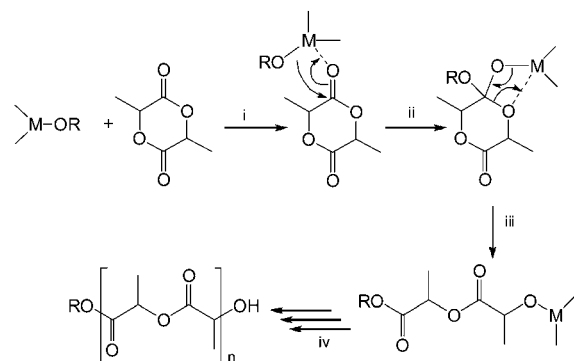


Fig. 1 Proposed mechanism of a coordination–insertion mechanism in the ROP of lactide.

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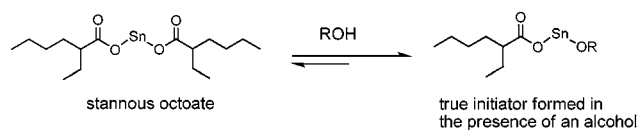


Fig. 2 Structure for the true initiator of Sn(Oct) formed in the presence of protic reagents.

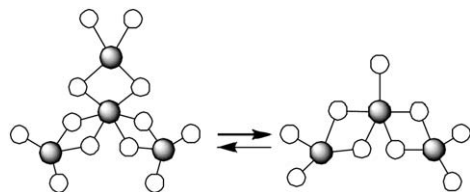


Fig. 3 Equilibrium between the tetramer and trimer of $\text{Al}(\text{O}^i\text{Pr})_3$. Only aluminium atoms (grey) and oxygen atoms (white) are shown for clarity.

Aluminium alkoxides have also been proven to be efficient initiator/catalysts for the ROP of lactide.^{15–17} The aluminium isopropoxide, $\text{Al}(\text{O}^i\text{Pr})_3$, turned out to be remarkably less active than $\text{Sn}(\text{Oct})_2$. Moreover, an induction period of a few minutes is observed when applying $\text{Al}(\text{O}^i\text{Pr})_3$ as an initiator in lactide polymerization. This feature was attributed to the presence of an equilibrium between the tetramer (A_4) and the trimer (A_3) (Fig. 3), of which A_3 was demonstrated to be more reactive than A_4 .¹⁸

Homoleptic metal alkoxide clusters were also studied in lactide polymerization. Feijen and coworkers¹⁹ have reported that $\text{Y}_5(\mu\text{-O})(\text{O}^i\text{Pr})_{13}$, with a core structure shown in Fig. 4, has a remarkable activity in (*S,S*)-LA polymerization, and a non-linear relationship between the apparent propagation rate and the cluster concentration is present, which is an indication that the propagating chains aggregate in the solution. Tolman and coworkers²⁰ reported that $\text{Fe}_5(\mu\text{-O})(\text{OEt})_{13}$, having an analogous cluster structure, displayed very high rates and excellent molecular weight control in lactide polymerization.

Although these metal alkoxides were proven to be efficient catalyst-initiators for the ROP of lactide, control of molecular weight is sometimes complicated by the clustered form of the active species. Molecular weight distributions will be broadened when more than one growing chain is connected to one metallic center. For these reasons, well-defined single-site catalysts have been designed and exploited in lactide polymerization.¹⁹

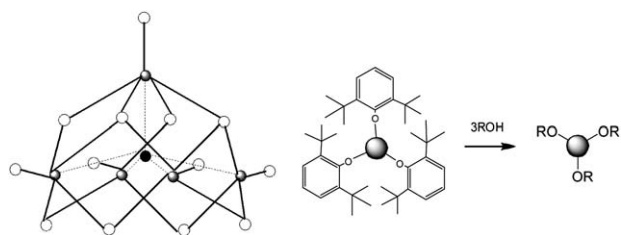
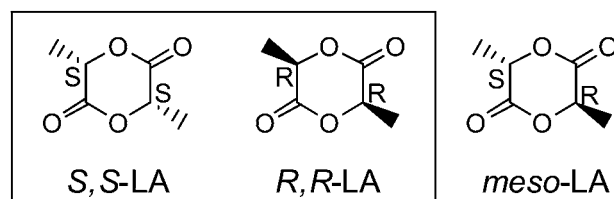


Fig. 4 Left: core structure of $\text{Fe}_5(\mu\text{-O})(\text{OEt})_{13}$ or $\text{Y}_5(\mu\text{-O})(\text{O}^i\text{Pr})_{13}$. Metal atoms are presented by grey circles and oxygen atoms by white circles. The filled circle in the center represents the $\mu\text{-5}$ oxygen atom connecting to all the metal atoms. All other atoms are left out for clarity. Right: *In situ* generation of an active yttrium alkoxide from a sterically hindered and non-active alkoxide.

Single-site metal catalysts for stereoselective polymerization of lactide

The last two decades have witnessed a tremendous development of single-site metal catalysts in the synthesis of polyolefins²¹ and polyesters. These single-site catalysts have a general formula of L_nMR , where M is a central metal atom surrounded by an ancillary ligand L_n . The steric and electronic properties of the ligand adjust the bonding of the metal center to the ligand, and therefore, influence the activity and stereoselectivity of the catalyst. R is the initiating group, which also affects the polymerization activity of the complexes. It is possible, by employing appropriate combinations of L_n with M and R, to generate efficient catalysts which can precisely control the polymerization rate, molecular weight, molecular weight distribution, comonomer incorporation, and even polymer stereochemistry in lactide polymerization. Spassky and coworkers²² were the first to discover that (*R*-SalBinap)AlOMe induced a highly stereocontrolled polymerization of *rac*-LA to form isotactic and crystalline PLAs with a higher melting temperature (T_m) than that of optically pure (*S,S*)-PLA or (*R,R*)-PLA. Since that time it was demonstrated that single-site metal alkoxides supported by various kinds of auxiliary ligand frameworks have unique advantages in carrying out well-controlled and in certain cases stereoselective polymerization of lactides. Because there are two stereogenic centers in one lactide molecule, different stereo-isomers of lactide are distinguished, (*S,S*)-LA, (*R,R*)-LA, and *meso*-LA (Fig. 5). An equivalent mixture of (*S,S*)-LA and (*R,R*)-LA is referred to as *rac*-LA. The alignment of *R* and *S* stereogenic centers in different modes along the polymer chain (Fig. 6) determines the mechanical and physical properties of the PLA materials. Stereoregular PLA materials can be prepared from *rac*- or *meso*-LA by using a variety of single-site metal complexes, which function *via* two different mechanisms (i) a chain-end-control mechanism, where the configuration of the next inserted monomer in *rac*-LA polymerization or the cleavage site of the monomer in *meso*-LA polymerization is determined by the stereogenic center in the last repeating unit along the propagating chain. If the stereogenic center in the last unit favors a *meso*-enchainment, isotactic PLA is obtained from *rac*-LA and heterotactic PLA will be obtained by using *meso*-LA.

However, if the stereogenic center in the last unit favors a *racemic*-enchainment, heterotactic PLA will be obtained from *rac*-LA and syndiotactic PLA from *meso*-LA; (ii) an enantiomorphic site-control mechanism, where the configuration of the inserted monomer in *rac*-LA polymerization or the cleavage site of the monomer in *meso*-LA polymerization is determined by the



1:1 mixture is *rac*-LA

Fig. 5 Structures of lactide stereoisomers.

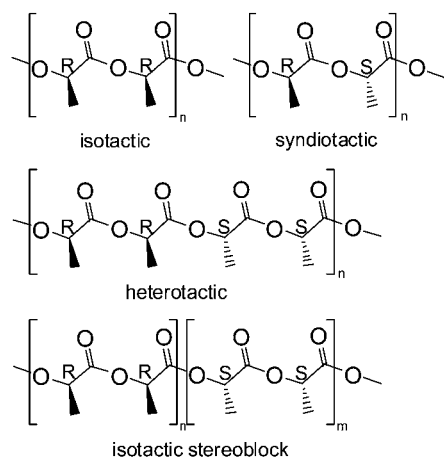


Fig. 6 Structures of stereoregular PLA materials.

configuration of the surrounding ligand. Thus, in the lactide polymerization following an enantiomorphic site control mechanism, only isotactic or syndiotactic PLA can be obtained from *rac*- or *meso*-LA, respectively.

Formation of isotactic/stereoblock PLAs from *rac*-LA

The most important breakthrough in the field of stereoselective polymerization of lactide was made by Spassky and co-workers.²² They discovered that in a *rac*-LA polymerization carried out at 70 °C initiated by the enantiomerically pure Schiff base aluminium methoxide (*R,R*)-**1**, the polymerization rate of (*R,R*)-LA is 19 times higher than that of (*S,S*)-LA. A living polymerization occurred as shown by the narrow molecular weight distributions of the polymers obtained. At conversions less than 50%, the polymer microstructure was predominantly isotactic, in this case (*R*)-PLA. At conversions higher than 60%, only (*S,S*)-LA remained. The reaction reached 100% conversion very slowly due to the fact that the polymerization rate of (*S,S*)-LA is much lower than that of (*R,R*)-LA. The resulting PLA had a tapered stereoblock microstructure, in which the stereoblock distribution was changing from all (*R,R*)-units to all (*S,S*)-units over the polymer chain (Fig. 7). This material exhibited a T_m of 187 °C, higher than that of the enantiopure isotactic (*S*)-PLA or (*R*)-PLA, which have T_m 's in between 170 and 180 °C.

Coates and Ovit^{23,24} discovered the presence of a bimetallic side product when preparing **1**. In order to eliminate the formation of this bimetallic side product, they prepared compound **2** with an isopropoxide group connected to the central aluminium. They reported that the polymerization of *rac*-LA using *rac*-**2** at 70 °C gave a stereoblock PLA material with a T_m of 179 °C. Inspecting the methine region of the homonuclear decoupled ¹H NMR spectrum of the resulting polymer revealed that the PLA is not a stereocomplex formed between enantiomerically pure strands of isotactic (*S,S*)-PLA and (*R,R*)-PLA previously reported

by Baker.²⁵ Instead, the true structure of the resulting PLA is a stereoblock copolymer.

Schiff base aluminium isopropoxides (*R,R*)-**3** and *rac*-**3** prepared from the commercially available Jacobsen ligand were reported by Feijen and co-workers.^{26,27} It was demonstrated that (*R,R*)-**3** has a moderate activity in *rac*-LA polymerization. Unlike (*R,R*)-**1** which exhibits a 20 : 1 preference for the polymerization of (*R,R*)-LA over (*S,S*)-LA ($k_{RR}/k_{SS} = 20$), (*R,R*)-**3** has a strong preference for the polymerization of (*S,S*)-LA ($k_{SS}/k_{RR} = 14$). *Rac*-**3** initiated and catalyzed the polymerization of *rac*-LA to form a stereoblock PLA material with a P_i value of 0.93 at 85% conversion of *rac*-LA. Notably, this excellent stereocontrol was still maintained even in a bulk polymerization. At 130 °C, the poly(*rac*-LA) prepared by using *rac*-**3** has a P_i value of 0.88. So far, this is the first time that a highly isotactic PLA is obtained under bulk polymerization conditions from *rac*-LA. Chisholm *et al.*^{28,29} have recently re-examined the *rac*-LA polymerization using (*R,R*)-**3**, revealing a combined influence of some factors on the stereoselectivity of the complex, which are the chirality of the complex, the initiating group, and the nature of the polymerization solvent. Thus, it is problematic to ascribe the high stereoselectivity of (*R,R*)-**3** either completely to a chain-end-control or to an enantiomorphic site-control mechanism.

Many achiral Schiff base aluminium alkyls were proven to be efficient stereoselective catalysts for lactide polymerization in the presence of an alcohol as initiator. Nomura and coworkers³⁰

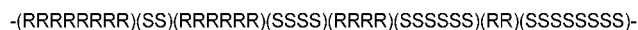
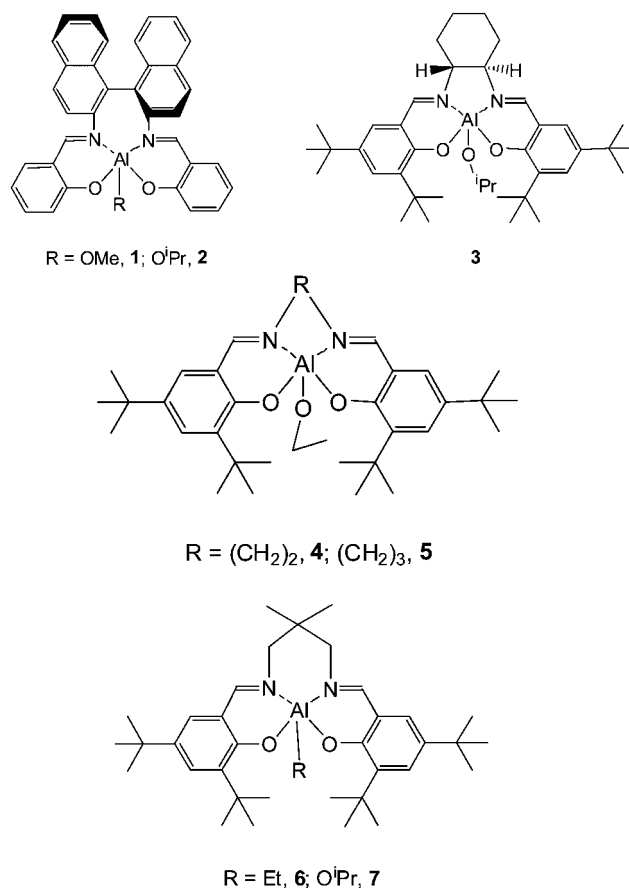
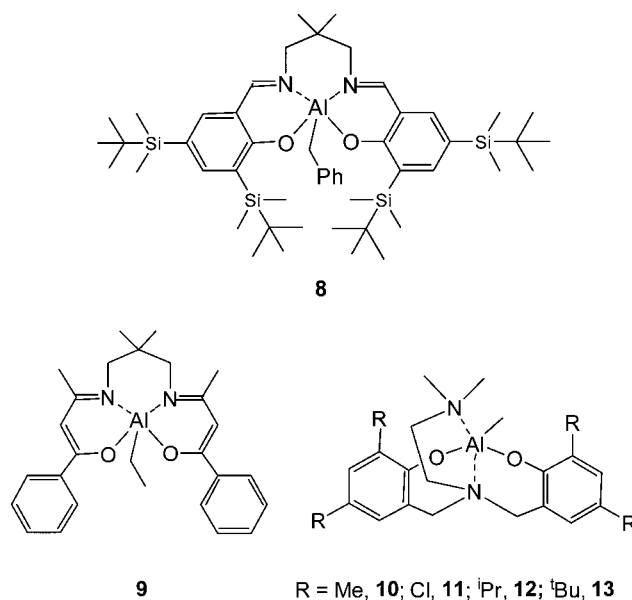


Fig. 7 Schematic structure of tapered isotactic PLA.

reported on the stereoselective polymerization of *rac*-LA by *in situ* formed aluminium alkoxides from the achiral Schiff base aluminium ethyls **4** and **5** with bulky *tert*-butyl groups at the *ortho* and *para* positions of the phenol group. In the presence of benzyl alcohol as an initiator, complexes **4** and **5** catalyzed *rac*-LA polymerization via a chain-end-control mechanism. Complex **5** with a propylene diimine bridge furnished PLA materials with an isotacticity ($P_m = 0.91$) higher than that of PLA obtained with complex **4** comprising of an ethylene diimine bridge. DFT(B3LYP/6-31G*) calculations of the most stable conformation of complex **5** revealed that the propylene diimine bridge is more flexible than the ethylene diimine bridge. The more flexible propylene diimine bridge in complex **5** may allow an easy adaptation for the lactide with a specific configuration, which will increase the difference in transition state energy between lactides with different configurations, leading to an enhanced isoselectivity of **5** in *rac*-LA polymerization.

In 2003, Chen and coworkers³¹ reported on the complex **6**/2-propanol as a catalyst/initiator system in *rac*-LA polymerization. In the presence of 2-propanol, complex **6** has a high isoselectivity in the polymerization of *rac*-LA generating a stereoblock PLA with a P_m value of 0.90. Thermal analysis revealed that this stereoblock PLA has a T_m of 201 °C. Kinetic data indicated that the *rac*-LA polymerization using complex **6**/2-propanol is first-order, both in monomer and catalyst. Subsequently, the aluminium isopropoxide **7** was synthesized by the reaction between **6** and 2-propanol.³² Complex **7** was structurally determined to be monomeric with a five-coordinated central aluminium both in the solid and solution state. Polymerization data revealed that complex **7** gave the same isoselectivity and polymerization rate constant as that of **6**/2-propanol, indicating that **7** is the true active species that initiates the lactide polymerization when using **6**/2-propanol as a catalyst/initiator system. Further polymerizations carried out by the group of Nomura *et al.*³³ illustrated that compound **7** maintains a high isoselectivity in bulk polymerization of *rac*-LA. At 130 °C, the obtained PLA showed a high T_m of 169 °C with a P_m value of 0.84. At 150 °C, the polymerization furnished PLA materials with a P_m value of 0.82 and a T_m of 158 °C. As the polymerization temperature increased to 180 °C, the P_m and T_m values of the resultant PLA decreased to 0.80 and 155 °C, respectively. In 2007, Nomura *et al.* have reported on a Schiff base aluminium complex **8** with flexible but bulky ^tBuMe₂Si substituents at the *ortho* and *para* positions of the phenol groups. This catalyst induced stereoblock PLA formation from *rac*-LA with a P_m value of 0.98 and a T_m of 210 °C.³⁴ Up to now, this is the highest isotactic stereoblock PLA material which has been prepared using an achiral catalyst/initiator system in *rac*-LA polymerization.

Schiff base aluminium catalysts which have been traditionally applied in lactide polymerizations are based on a bis(salicylidene) Schiff base ligand framework. Chen and co-workers^{35,36} reported the synthesis of a series of tetradentate enolic Schiff base aluminium ethyl complexes and their application as catalysts in *rac*-LA polymerization. Systematic research revealed that modifications on the auxiliary ligand exerted a dramatic influence on their catalytic performance, including activity and stereoselectivity. Lengthening the ethylene diimine bridge to a propylene diimine bridge and the presence of electron-withdrawing substituents at the 5-position in the diketone skeleton both resulted in a remarkable

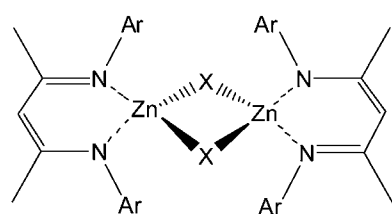


enhancement of stereoselectivity and polymerization rate. In the presence of 2-propanol as an initiator, complex **9** polymerized *rac*-LA to form isotactic enriched PLA materials with a P_m of 0.78.

A family of aluminium methyl complexes supported by tetradentate aminophenoxide ligands have been prepared by Gibson *et al.*³⁷ and exploited for the ROP of *rac*-LA. It was found that the catalytic behavior of these complexes is highly dependent on the substituents at the *ortho* and *para* positions of the phenol group. Complexes **10** and **12** with methyl and isopropyl groups at the *ortho* and *para* positions of the phenol group furnished isotactic-biased PLA materials with P_m values of 0.73 and 0.65, respectively. However, complex **13** with *tert*-butyl substituents at the *ortho* and *para* positions of the phenol group led to a slight heterotactic polymerization of *rac*-LA, affording PLA material with a P_r value of 0.57.

Complex **11** with chlorine substituents at the *ortho* and *para* positions of the phenol group only gave an atactic material from *rac*-LA.

In recent years metal free catalyst were discovered that induce stereoselective polymerization of lactides (also see next section). Most importantly, Wade *et al.* found that a dimeric phosphazene base polymerizes *rac*-LA with $P_m = 0.95$ at low temperatures.³⁸



Ar = 2,6-ⁱPr₂C₆H₃, X = OⁱPr, **14**
Ar = 2,6-ⁱPr₂C₆H₃, X = OAc lactate, **15**

Formation of heterotactic PLAs from *rac*-LA

The most notable feature for β -diketiminate zinc or magnesium complexes is that they furnish highly heterotactic PLAs in *rac*-LA polymerization. Coates and Oviatt^{39,40} reported the synthesis and characterization of the zinc isopropoxide **14** and zinc methyl lactate **15**. Structural characterization revealed that both compounds are dimeric in the solid as well as in solution. Polymerization data indicated that they are both efficient initiators for lactide polymerization, producing PLAs with predictable molecular weights and narrow molecular weight distributions. Notably, complex **14** initiated the stereoselective ROP of *rac*-LA via a chain-end-control mechanism, yielding highly heterotactic microstructures with a P_r value up to 0.90 at room temperature and 0.94 at 0 °C.

The monomeric zinc triphenylsilanoxide complex **16** supported by a β -diketiminate ligand⁴¹ with a THF molecule coordinated to the central zinc atom was shown to have the same heteroselectivity toward *rac*-LA in THF as that of the dinuclear zinc complex **14** in CH_2Cl_2 . Although the magnesium complexes **17** and **18** as reported by Chisholm *et al.*^{42,43} do not show stereoselectivity toward *rac*-LA either in CH_2Cl_2 or benzene, they have a similar heteroselectivity in THF as complex **14**. It seems that the coordinated THF molecule to the central metal atom plays an important role in enhancing the heteroselectivity of the β -diketiminate zinc or magnesium complexes.

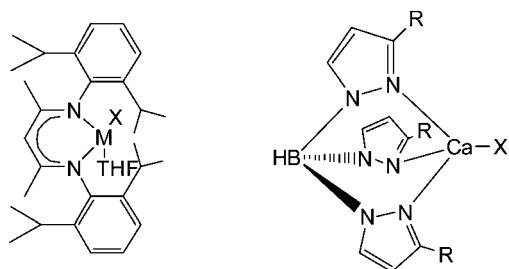
Chisholm and coworkers⁴⁴ have used trispindazolyl(Tp)-hydroborate ligands to coordinate calcium to form efficient initiators for lactide polymerization. The calcium amide complex **19** with bulky *tert*-butyl substituents on the Tp ligand was reacted with 200 equiv of *rac*-LA in THF. In all cases, polymerizations of *rac*-LA were very rapid, 90% conversion within 5 min was

achieved. Complex **20** with the less bulky isopropyl substituents on the Tp ligand revealed an extremely rapid *rac*-LA polymerization, achieving 90% conversion in less than 1 min. Moreover, under the protection of the bulky *tert*-butyl substituent on the Tp ligand, complex **21** furnished a heterotactic PLA material from *rac*-LA with a P_r value of 0.90.

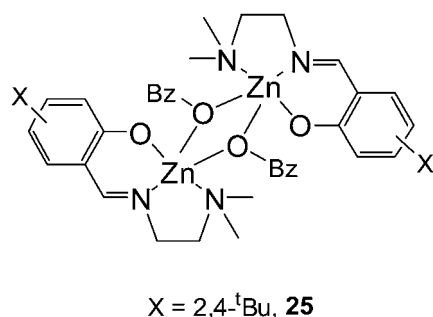
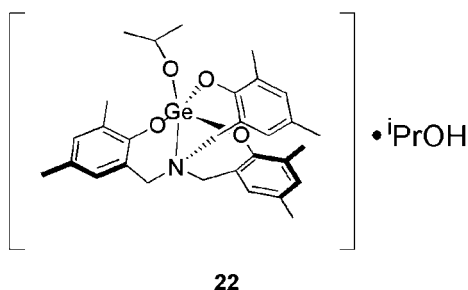
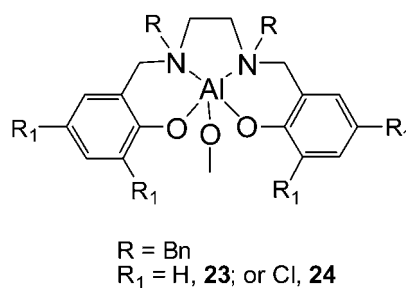
A new germanium alkoxide **22** supported by a C_3 -symmetric amine(trisphenolate) ligand was recently reported by Davidson *et al.*⁴⁵ This compound has been applied in the bulk polymerization of *rac*-LA at 130 °C. Analysis of the microstructure of the isolated polymers revealed a strong heterotactic bias ($P_r = 0.78$ – 0.82). So far, this is the first example of a highly heteroselective polymerization of *rac*-LA under solvent-free conditions at a relatively high temperature.

It must be emphasized that Gibson and coworkers⁴⁶ have found an interesting remarkable stereocontrol of achiral aminophenoxide aluminium methyl complexes in the polymerization of *rac*-LA. In the presence of benzyl alcohol as an initiator, these complexes catalyzed *rac*-LA polymerizations in a well-controlled and living manner, affording highly isotactic PLA materials with a P_m value of 0.88 by using **23**, and highly heterotactic PLAs with a P_r value of 0.96 by using **24**. So far, this is the first time that aluminium complexes have been found to furnish a highly heterotactic PLA, and the first time that a dramatic switch in tacticity of the resulting PLA has been observed upon changing the substituent pattern at the *ortho* and *para* positions of the phenol group in the complexes. Preliminary kinetic data indicated that the *rac*-LA polymerizations catalyzed by these complexes were both first-order in monomer and catalyst.

Lin and coworkers⁴⁷ synthesized a series of dinuclear zinc complexes supported by a N,N,O -tridentate Schiff base ligand framework. Polymerization data indicated that the reactivities of these complexes were dramatically affected by both the electronic and steric properties of the substituents at the *ortho* and *para*

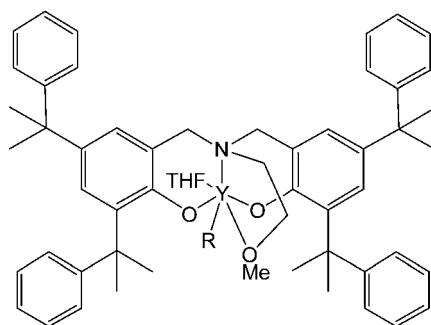
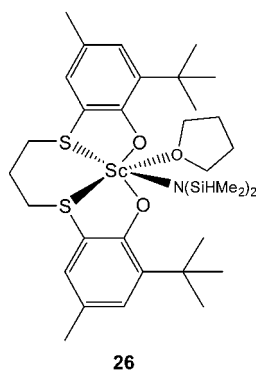


M = Zn, X = OSiPh₃, **16** R = *t*Bu, X = N(SiMe₃)₃, **19**
 M = Mg, X = NⁱPr₂, **17** R = *i*Pr, X = OC₆H₃-2,6-*i*Pr, **20**
 M = Mg, X = O^tBu, **18** R = *t*Bu, X = OC₆H₃-2,6-*i*Pr, **21**

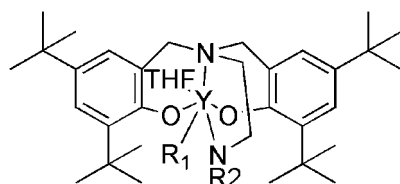


positions. Kinetic data showed that the polymerizations are both first-order in monomer and initiator. All these complexes furnish heterotactic PLA materials from *rac*-LA. It is worthwhile to note that a heterotactic PLA with a high P_r value up to 0.91 can be obtained at $-55\text{ }^\circ\text{C}$ by using complex **25**.

Exciting advances were made when rare earth metal complexes were applied in *rac*-LA polymerization. Okuda *et al.*^{48,49} synthesized a series of scandium complexes supported by 1,6-dithiaalkanediy-bridged bis(phenolate) ligands. These complexes showed excellent heterotactic-control in *rac*-LA polymerization. It was found that both THF as a solvent and bulky substituents at the *ortho* position of the phenol group largely improve the heterotacticity of the isolated PLAs. Moreover, polymerization data revealed that the complex with a propylene dithialkane bridge improved the heteroselectivity. At $25\text{ }^\circ\text{C}$ in THF, complex **26** afforded heterotactic PLA materials from *rac*-LA with a P_r up to 0.96. A scandium *tert*-butoxy-*R*-lactate complex was synthesized from complex **26** and isolated as a key model complex. Structural analysis revealed that this model complex has a dimeric structure



R = N(SiHMe₂)₂, **27**



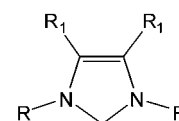
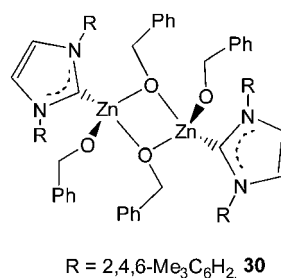
R₁ = CH₂SiMe₃;
R = Me, **28**; Et, **29**.

with a single ligand conformation of A,A^{50} in the solid state. ¹H NMR spectroscopy of this model complex revealed that the dimeric structure of the complex in the solid state is retained in solution, and the *R* configuration of the lactate ester has selectively induced the *A* conformation of the ligand in the complex because of steric repulsion, which additionally favors the insertion of (*S,S*)-LA.

Carpentier *et al.* discovered that yttrium amido complexes supported by an amine bis(phenolate) ligand have good heteroselectivity in the polymerization of *rac*-LA.^{51–53} By introducing bulky substituents at the *ortho* and *para* positions of the phenol group and changing the donor group on the pendent chain from methoxy ether to a dimethyl substituted amine group, the heteroselectivity in *rac*-LA polymerization of the complex is improved. Complex **27** with bulky and conformationally flexible α,α -dimethylbenzyl groups at the *ortho* and *para* positions of the phenol group produced substantially heterotactic PLAs with a P_r up to 0.90 at $20\text{ }^\circ\text{C}$.

Cui *et al.*⁵⁴ also reported a series of THF-solvated lanthanide (mono)alkyl complexes supported by *O,N,N,O*-tetradentate diamine bis(phenolate) ligands. Notably, complexes **28** and **29** displayed modest activity but high stereoselectivity in the polymerization of *rac*-LA to give highly heterotactic PLA materials with P_r values ranging from 0.95 to 0.99. An active oligomer connected to complex **28** prepared from *rac*-LA was characterized by ¹H NMR. The spectrum of the active oligomer demonstrated that the ligand and the pendent nitrogen atom remain coordinated to the metal ion, and the geometry around the central metal in complex **28** did not collapse but retained its structure in solution upon monomer coordination and insertion. The spatially steric environment in the resulting propagating sites will favor the incorporation of a configurationally opposite enantiomer to lower the transition state energy.

Tolman *et al.*^{55,56} discovered that the dinuclear zinc complex **30**, comprising monodentate *N*-heterocyclic carbenes (NHCs), gave heterotactic-biased PLA materials with a P_r value of 0.60 at room temperature in *rac*-LA polymerization. To address whether a free carbene was participating in lactide polymerization, the free carbene **31** was exploited as a catalyst in the presence of benzyl alcohol as initiator in *rac*-LA polymerization. A striking difference in the tacticity of the resulting polymers obtained by using the free carbene compared to using the zinc complex **30** was discovered. Free carbene **31** produced isotactic enriched PLA with a P_m value of 0.75 from *rac*-LA in CH₂Cl₂ at



R = 2,4,6-Me₃C₆H₂, R₁ = H, **31**
R = 2,4,6-Me₃C₆H₂, R₁ = Ph, **32**
R = CH(Me)Ph, R₁ = Ph, **33**

$-20\text{ }^{\circ}\text{C}$. Further studies using the more sterically hindered NHCs in lactide polymerization were carried out by Waymouth *et al.*⁵⁷ Most notably, achiral carbene **32** produced highly isotactic PLA material with a P_m value up to 0.90 from *rac*-LA at $-70\text{ }^{\circ}\text{C}$. Lactide polymerizations using chiral free carbene **33** were also investigated. The enantiomerically pure and racemic carbene **33** both furnished highly isotactic poly(*rac*-LA) material at $-70\text{ }^{\circ}\text{C}$ with a P_m value of 0.88.

Formation of stereoregular PLAs from *meso*-LA

Coates and Ovitt^{24,58} showed that the enantiomerically pure aluminium complex (*R,R*)-**2** affords syndiotactic PLA from *meso*-LA via an enantiomorphic site control mechanism. The polymerization data showed that when the polymerization proceeded at $70\text{ }^{\circ}\text{C}$ in toluene for 40 h, the syndiotacticity of the resulting PLA is 0.96. Due to the high degree of syndiotacticity, the PLA produced by *meso*-LA polymerization using (*R,R*)-**2** is crystalline. Following annealing at $95\text{ }^{\circ}\text{C}$ for 60 min, this polymer exhibits a glass-transition temperature (T_g) at approximately $45\text{ }^{\circ}\text{C}$, and a T_m as high as $153\text{ }^{\circ}\text{C}$. So far this is the only example of a PLA material with high syndiotacticity. Coates and Ovitt also investigated the ROP of *meso*-lactide using *rac*-**2**.²⁴ After 40 h at $70\text{ }^{\circ}\text{C}$, the polymerization reached 98% conversion. Although the resulting polymer has a heterotacticity of 0.80, it was amorphous and only exhibited a T_g at $43.2\text{ }^{\circ}\text{C}$. To explain the novel formation of the heterotactic structure from *meso*-LA by using *rac*-**2**, a polymer exchange mechanism (Fig. 8) was proposed, whereby each individual polymer chain effectively switches between enantiomeric aluminium centers before the insertion of the next monomer unit.

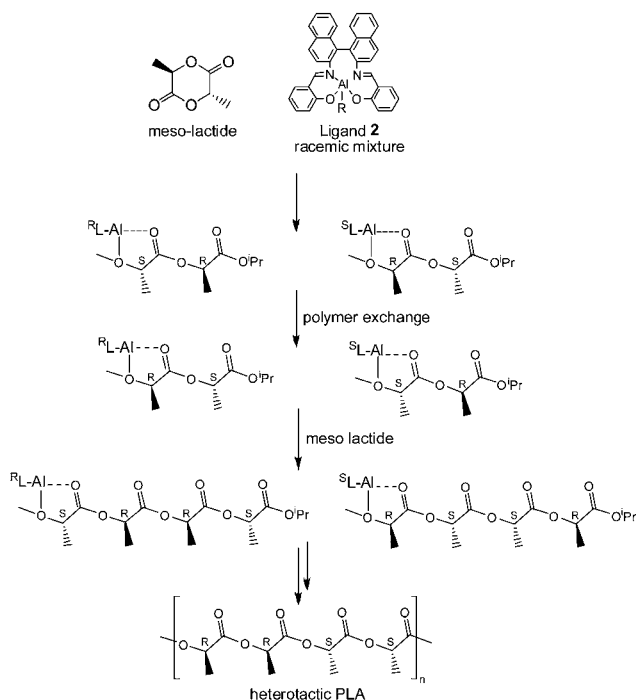


Fig. 8 Polymer exchange mechanism for the formation of heterotactic PLA from *meso*-LA by using *rac*-**2**.

Some other achiral metal complexes were also applied in *meso*-LA polymerization aiming for a chain-end-control mechanism. However, the chain-end-control of these complexes on the stereochemistry in *meso*-LA polymerization is very poor. Coates *et al.*⁴⁰ reported that the dinuclear zinc isopropoxide complex **14** supported by β -diketiminate ligand affords syndiotactic PLA with a P_r value of 0.76. The yttrium amido complex **24** supported by bulky bis(phenoxy) amine ligand reported by Carpentier *et al.*⁵² also furnished a moderate syndiotactic PLA material with a P_r value of 0.75.

Applying the free carbene **32** in the polymerization of *meso*-Lac afforded a heterotactic-biased material with a P_r value of 0.83 at $-40\text{ }^{\circ}\text{C}$.⁵⁷

Summary and perspectives

Remarkable advances have been made in the design and synthesis of various kinds of single-site metal complexes that exert excellent stereocontrol in lactide polymerization. So far, highly isotactic and heterotactic PLA materials are formed from *rac*-LA, while highly syndiotactic PLA is prepared from *meso*-LA. The metal employed, chirality of the ligand and introduction of bulky substituents are all parameters which influence the stereocontrol. The design of new efficient and stereoselective catalyst systems will depend on *e.g.* the way the monomer can be conformationally positioned at the active site, stereochemistry and rigidity of the ligand, kinetics of interchange of the metal active site to polymer chains.

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