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Developments in the use of rare earth metal complexes as efficient catalysts for ring-opening polymerization of cyclic esters used in biomedical applications

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Abstract:
Biodegradable polymers represent a class of particularly useful materials for many biomedical and pharmaceutical applications. Among these types of polyesters, poly(ε-caprolactone) and polylactides are considered very promising for controlled drug delivery devices. These polymers are mainly produced by ring-opening polymerization of their respective cyclic esters, since this method allows a strict control of the molecular parameters (molecular weight and distribution) of the obtained polymers. The most widely used catalysts for ring-opening polymerization of cyclic esters are tin- and aluminium-based organometallic complexes; however since the contamination of the aliphatic polyesters by potentially toxic metallic residues is particularly of concern for biomedical applications, the possibility of replacing organometallic initiators by novel less toxic or more efficient organometallic complexes has been intensively studied. Thus, in the recent years, the use of highly reactive rare earth initiators/catalysts leading to lower polymer contamination has been developed. The use of rare earth complexes is considered a valuable strategy to decrease the polyester contamination by metallic residues and represents an attractive alternative to traditional organometallic complexes.

Keywords: biodegradable polymers, catalysts, polymerization

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1 Biodegradable polymers

In the last decades, biodegradable polymers have become increasingly important in the development of drug delivery systems (DDS). Most of the polymers used in DDS are based on biodegradable and biocompatible materials, mainly aliphatic polyesters, polyanhydrides, polyethers, polyamides, polyorthoesters and polyurethanes [1].

Biodegradable polymers can be natural or synthetic. The synthetic polymers have many advantages over the natural ones since their structure can be tailored to meet specific requirements such as hydrophobicity, crystallinity, degradability, solubility, glass transition temperature and melting temperature, by changing the synthesis protocol. In contrast, natural biodegradable polymers lack versatility since they can only be modified. Among the various families of biodegradable polymers, aliphatic polyesters are of most interest since by their chain cleavage, compounds which are easily metabolized are formed.

Poly(lactides) (PLAs) (Figure 1) are the most used among the aliphatic polyesters for drug delivery as a result of their fast and adjustable degradation rate. Due to their versatile physical properties, PLAs are being widely used in medicine as surgical sutures and resorptable prostheses and in pharmaceutics and tissue engineering such as media for the controlled drugs release, scaffolds and delivery of antibodies and genes [2].

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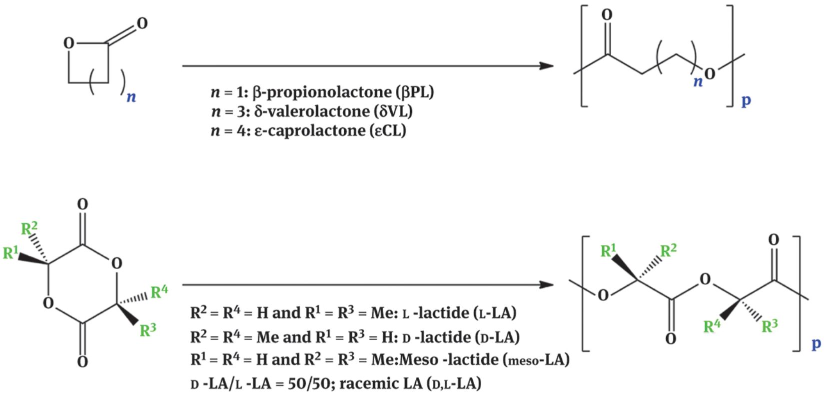


Figure 1: Ring-opening polymerization of unsubstituted lactones and lactides.

2 Polymerization mechanisms for polyester synthesis

Polyesters can be synthesized by two types of mechanisms:

- step-growth polymerization or polycondensation (PC);–ring-opening polymerization (ROP) of cyclic esters and related compounds.

The PC technique consists of condensation between hydroxy-acids or mixtures of diacids and diols (Figure 2).

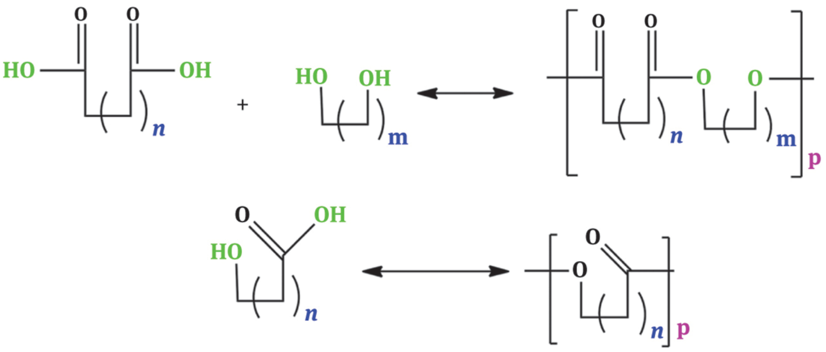


Figure 2: Synthesis of aliphatic polyesters by step-growth polycondensation.

The PC method may appear more direct than ROP, but with this technique it is difficult to obtain high-molecular-weight polymers with well-defined structure. Another major drawback of the PC mechanism is that it requires high temperatures and long reaction times, which ultimately favour the side reactions. Moreover, since they are equilibrium reactions, water must be removed from the polymerization medium in order to increase the conversion and the molecular weight of the obtained product.

On the other hand, the polymerization of lactides and lactones by the ROP process does not present these limitations. ROP mechanism allows a good control of the polymer characteristics; thus high-molecular-weight polyesters can be easily prepared under mild conditions from lactones of different ring size, substituted or not by functional groups [3, 4].

The ROP proceeds mainly via two major polymerization mechanisms depending on the used organometallics. Some of them act as catalysts and activate the monomer by complexation with the carbonyl group (Figure 3). Polymerization is then initiated by any nucleophile (water or alcohol) present in the polymerization medium as impurities or as added compound.

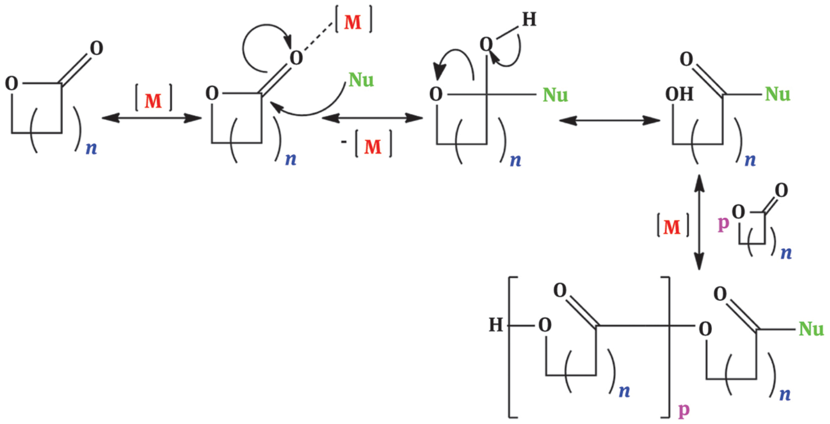


Figure 3: ROP of lactones catalyzed by organometallic species [M] in presence of nucleophiles (Nu).

In the second mechanism, the organometallic plays the role of initiator and the polymerization proceeds through an “insertion–coordination” mechanism (Figure 4).

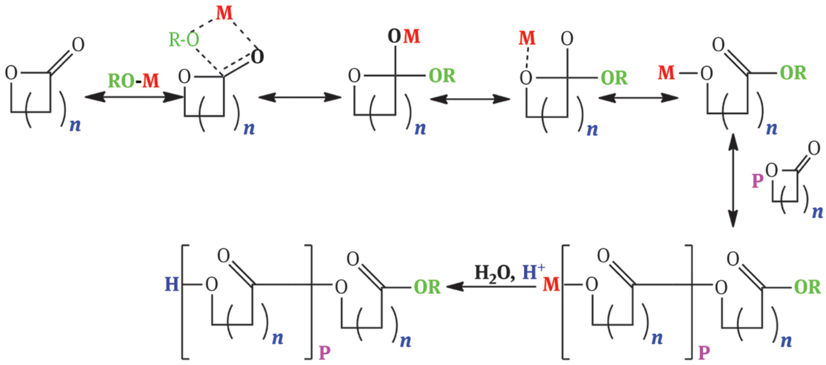
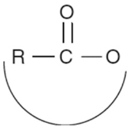


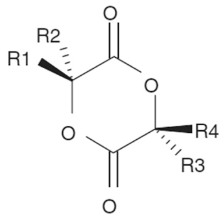
Figure 4: ROP of lactones by the “coordination–insertion” mechanism.

The initiator (typically metal alkoxides) first coordinates the carbonyl of the monomer, followed by the cleavage of the acyl–oxygen bond of the monomer and simultaneous insertion into the metal alkoxide bond [1].

Stridsberg et al. explored for the first time the ROP technique for lactones, cyclic anhydrides and carbonates [5]. Since then, this method has been applied to a wide range of monomers with a great variety of initiator and catalyst systems. Table 1lists some of the most commonly used monomers and their related polyester chains obtained by ROP which are currently used as biomaterials as well as ecological materials that preserve the environment.

Table 1: Monomer and polymer structures of the most common aliphatic polyesters obtained by ROP [6].

Monomer	Polymer
 R = -$(CH_2)_2$-βPL, β-propiolactone R = -$(CH_2)_3$-γBL, γ-butyrolactone R = -$(CH_2)_4$-δVL, δ-valerolactone R = -$(CH_2)_5$-εCL, ε-caprolactone R = -$(CH_2)_2$-O-$(CH_2)_2$-DXO, 1,5-dioxepan-2-one R= -(CH_2–CH(CH_3))–βBL, β-butyrolactone R = -(C$(CH_3)_2$–CH_2)-PVL, pivalolactone R = -CH_2-CH($CO_2C_7H_7$)–βMLABz, benzyl β-malolactonate	Polylactone poly(ω-hydroxy acid) PβPL PγBL PδVL PεCL PDXO PβBL isotactic PβBL atactic PPVL P(R,S)MLABz P(R)MLABz P(S)MLABz Polydilactone



Poly(α-hydroxyacid)
PGA
PL, L-LA
PD, D-LA
PmesoLA
PDLLA

R_1

= R_2 = R_3 = R_4 = H GA, glycolide
R_1 = R_4 = CH_3, R_2 = R_3 = H L,L-LA, L,L-lactide
R_1= R_4 = H, R_2 = R_3 = CH_3 D,D-LA, D,D-lactide
R_1 = R_3 = CH_3, R_2 = R_4 = H meso-LA, meso-lactide
D,D-LA/L,L-LA (50-50) D,L-LA, (D,L) racemic lactide

Nowadays, PLAs of high molecular weight are produced almost exclusively by ROP of the corresponding cyclic monomers.

3 Catalysts for ROP of PLAs

A broad range of catalysts have been reported for the ROP; most of them are organometallic derivatives of metals with d-orbitals of a favourable energy, such as Al, Sn, Nd, Y, Yb, Sm, La, Fe, Zn, Zr, Ca, Ti and Mg [7, 8].

Since the contamination of the aliphatic polyesters by potentially toxic metallic residues is particularly of concern for biomedical applications, the possibility to replace organometallic initiators by novel less toxic or more efficient organometallics has been studied. Thus, a large variety of rare earth (RE) derivatives have been used to initiate the ROP of lactones and lactides due to their high reactivity [9]. The use of a catalytic amount of lanthanide complexes is a valuable strategy to decrease the polyester contamination by metallic residues as compared to the previously described tin- and aluminum-based initiators which must be used in stoichiometric amount vs. alcohol to favour the polymerization kinetics [1].

On the other hand, lanthanide complexes have been of considerable interest in the recent years as a result of their implications in the optical imaging of cells, such as luminescent chemosensors for medical diagnostics and contrast reagents for medical magnetic resonance imaging, in bioorganic chemistry [10, 11] and in the manufacture of superconductors [12–15], ceramics [16] and glass for optical, electronic and medical applications [13].

RE metal oxides have also found numerous applications in the field of catalysis [17–20]. Thus, organolanthanide chemistry has registered a growing interest in the past decades; the design and application of organolanthanide complexes as catalysts for polymerization and organic synthesis have occupied an especially important place. Changing the ligand environment of a complex to modify its properties has been an important strategy for the development of more efficient or selective catalysts.

Initially, organolanthanide chemistry has been dominated mainly by metallocene complexes that bear two substituted or unsubstituted cyclopentadienyl ligands. In the following years, the search for new ligand systems to extend the lanthanide chemistry has increased considerably [21].

4 Rare earth-based catalysts for synthesis of PLAs

In 1995, Mortreux et al. patented a method for the synthesis of complexes of the type $[(C_5Me_5)_2LnCl_2Li(OEt_2)_2]$ with Ln-Sc, Y and lanthanides as initiators for the preparation of caprolactone–ethylene block copolymers [[22]]. One year later, Nomura et al. reported the block copolymerization of tetrahydrofuran (THF) with δ-valerolactone by alkylsamarium ($RSmI_2$) complex [23]. Polymerization of δ-valerolactone by butylsamarium gave the corresponding poly(valerolactone) in good yield, while the polymerization of δ-valerolactone with poly-THF led to the block copolymer of THF with δ-valerolactone.

In 1997, Boffa and Novak reported the synthesis of “link-functionalized” poly(ε-caprolactone) (LFP) using bimetallic complexes of the type $(C_5Me_5)_2Sm/R/Sm(C_5Me_5)_2$ [24].

LFPs are of special interest because:

- they may serve as building blocks to other architectures;
- are useful models for the environment experienced by the polymer backbone;

– their functionality may be used to influence the polymerization process itself [25].

Hultzsch et al. investigated the ROP of ε-caprolactone catalysed by the heterobimetallic complexes $\mathrm{Li[Ln(\eta^5{:}\eta^1\text{-}C_5R_4Si\text{-}Me_2NCH_2CH_2X)_2]}$ (Ln = Lu, Y) [26]. The product of this polymerization had a high molecular weight and moderate polydispersity. The initial step of the polymerization is a nucleophilic attack by one of the nucleophilic amido-nitrogen atoms at the lactone carbonyl–carbon atom, followed by acyl bond cleavage and formation of an alkoxide (Figure 5).

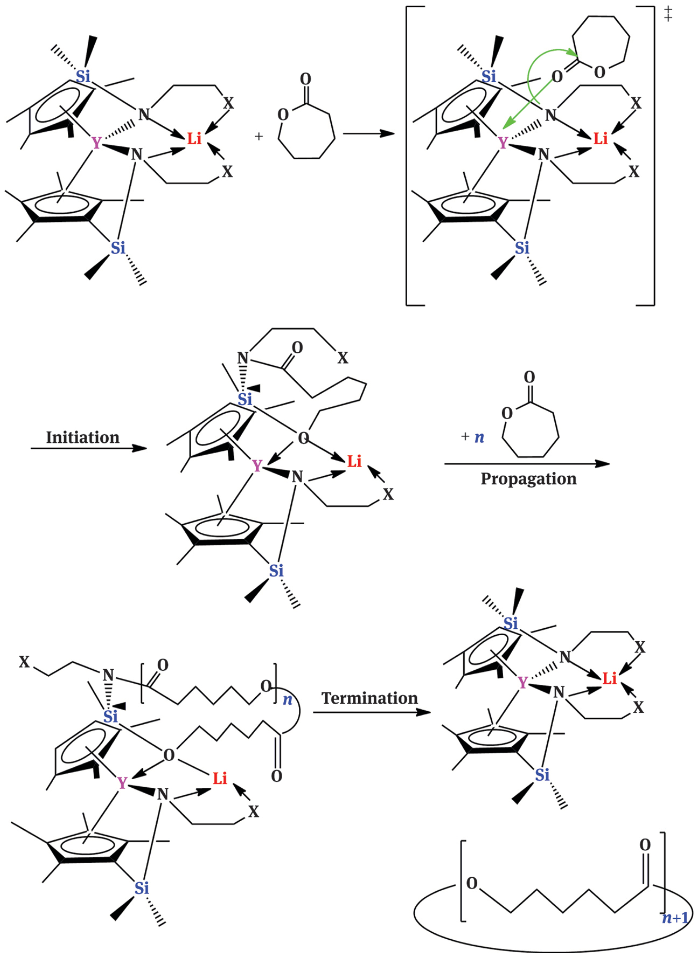


Figure 5: ROP of ε-caprolactone catalyzed by the heterobimetallic complexes $\mathrm{Li[Ln(\eta^5{:}\eta^1\text{-}C_5R_4Si\text{-}Me_2NCH_2CH_2X)_2]}$.

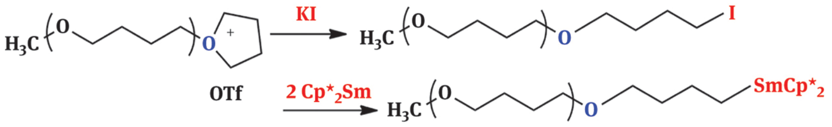


Figure 6: Transformation reaction of living poly(THF) with potassium iodide.

In 1998, Nomura et al. published a novel transformation reaction of living poly(THF) from cationic into anionic propagation species [27]. These species were formed by end-capping of living poly(THF) with potassium iodide (Figure 6) followed by the reduction with bis(pentamethyl cyclopentadienyl)samarium ($\mathrm{Cp^*{}_2Sm}$).

The formed terminal anionic carbanion was active for the polymerization of ε-caprolatone and δ-valerolactone and leads to the selective formation of unimodal block copolymers.

ROP of lactones using $\mathrm{Sm}X_2$ (X = I, Br, C_5H_5) catalysts was reported by Agarwal et al. [28]. Successful room temperature ROP of ε-caprolactone and δ-valerolactone has been carried out using the $\mathrm{SmX_2}$ catalysts. $\mathrm{SmI_2}$ in the presence of metallic Sm was found to enhance the reactivity at room temperature in ROP processes as compared to pure $\mathrm{SmI_2}$. $\mathrm{SmBr_2}$ and $\mathrm{Sm(C_5H_5)_2}$ showed increased reactivity compared with the $\mathrm{Sm/SmI_2}$ system owing to their higher reductive power [28].

Among other studies of other samarium (II) aryloxide complexes, Nishiura et al. showed that $\mathrm{[(C_5Me_5)Sm(\mu\text{-}OC_6H_2{}^tBu_2\text{-}2,6\text{-}Me\text{-}4)]_2}$ exhibited an extremely high activity for the ROP of ε-caprolactone and δ-valerolactone [29].

In the article of Yuan et al., it was shown that the homopolymerization and copolymerization of ε-caprolactone and lactides can be initiated efficiently by 2-methylphenyl samarium according to the mechanism of "coordination–deprotonation–insertion," by which the monomer is inserted on the Ln–O bond of RE enolate [30]. When the polymerizations are conducted in bulk, 2-methylphenyl samarium can give high yield and high-molecular-weight products.

Desurmont et al. described the first example of well-controlled block copolymerization of 1-olefins with ε-caprolactone using bridged $Me_2Si(C_5R_4)_2LnH$ (Ln =Y, Sm) type complexes [31]. These initiators are highly active in copolymerization processes without the presence of any cocatalyst (Figure 7).

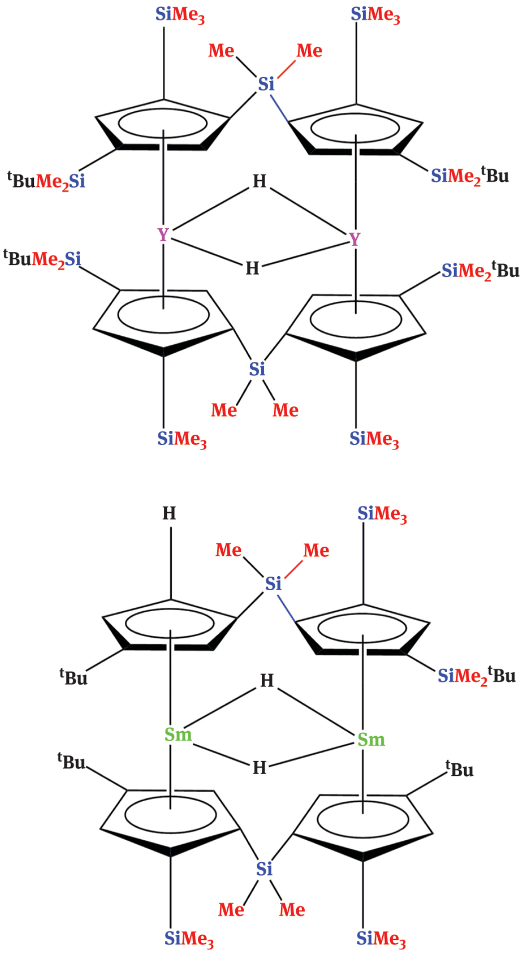


Figure 7: Bridged organolanthanide hydrides of yttrium and samarium.

The dimeric structure of the yttrium and samarium hydride complexes is converted into a monomeric structure in the first step of the reaction. Subsequent reactions lead to a chain elongation. The authors reported the preparation of block copolymers of hexene or pentene with ε-caprolactone [31].

In the study of Deng et al., ROP of D,L-lactide was initiated with RE phenyl compound in bulk and solution [32]. These RE phenyl initiators gave high yield and high-molecular-weight poly(D,L-lactide) products. The results showed that reaction conditions have a great influence on the yield and molecular weight of PLA. Thus, a high molecular weight of PLA was obtained in the case of lower M/I molar ratio.

The ROP of cyclic esters (ε-caprolactone and L-lactide) initiated with $LnCp_3$ complexes (Ln = Sm, Er, Pr, Gd and Ce) was reported by Agarwal and Puchner [33]. The size of the metal atom was found to have an effect on the catalytic activity. Thus, the order of reactivity was Er ~ Gd > Sm > Pr > Ce. Although the polymerization system was not living, the growing polymer chains were found to be active for the polymerization of second monomer, thus capable of synthesizing block copolymers.

In the work of Cui et al., the substituted indenyl ytterbium (II) complex $(C_9H_6C_5H_9)_2Yb(THF)_2$ showed high activity for ROP of lactones [34]. Scandium dialkyl complexes containing bulky iminophenolato ligands have been found to be efficient catalysts for the ROP of ε-caprolactone [35]. The ROP of cyclic esters (ε-caprolactone and L-lactide) is initiated by Cp_3Ln complexes (Ln = Ce, Pr, Sm, Gd, Er), and it was observed that the size of the metal ion had an effect on the catalytic activity. Other complexes which have been found to exhibit high catalytic activity in the ROP of ε-caprolactone include $Cp_3Dy_2(NPPh_3)_3$ [36].

ROP and block copolymerization of L-lactide has also been achieved with the divalent samarocene complexes $(C_5H_4C_5H_9)_2Sm(THF)_2$ as catalyst [37], while D,L-lactide was effectively polymerized using $Cp^*{}_2SmMe(THF)$ [38].

In their study, Satoh et al. showed that the complexes $[(C_5H_4SiMe_3)_2Sm(\mu\text{-}Me)]_2$ and $[\{C_5H_3(SiMe_3)2\text{-}1,3\}_2Ln(\mu\text{-}Me)]_2$ (Ln = Nd, Sm) performed the block copolymerization of L-lactide with ε-caprolactone with high yields in the absence of any cocatalysts [39]. The guanidinate lanthanide methyl complexes $[(Me_3Si)_2NC(NPr^i)_2]_2Ln(\mu\text{-}Me)_2Li(TMEDA)$ (Ln = Nd, Yb) have been established as effective single-component initiators for ε-caprolactone polymerization [40]. Other organolanthanide complexes reported to catalyse the (co-)polymerization of ε-caprolactone include homoleptic lanthanide guanidinate complexes [41], $Cp^*{}_2Sm(BH_4)(THF)$ [42] and sterically hindered lanthanide allyl complexes [43].

Single-component RE tris(4-tert-butylphenolate)s $[Ln(OTBP)_3]$ (Ln=La, Nd, Gd, Er, Y) were found to be effective initiators for the ROP of ε-caprolactone. Among them, $La(OTBP)_3$ has shown higher activity and gave higher-molecular-weight poly(ε-caprolactone) [44].

In the work of Fan et al., a novel single-component RE phenolate catalyst-lanthanide tris(2,4,6-trimethylphenolate)s $[Ln(OTMP)_3]$ (Ln=La, Nd, Sm, Er, Y) (Figure 8) initiated ROP of ε-caprolactone [45]. It was found that the polymerization activity of the compounds had the following order: La ≈ Sm > Nd > Er > Y. Among the studied complexes, $La(OTMP)_3$ exhibited the highest activity and the prepared poly(ε-caprolactone).

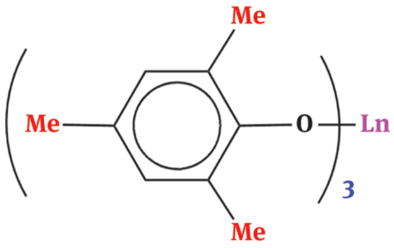


Figure 8: Structure of $Ln(OTMP)_3$ (Ln = La, Nd, Sm, Y, Er).

Single-component RE 2,6-dimethylaryloxide $[Ln(ODMP)_3]$ (Figure 9) was used as catalyst or initiator for the ROP of L-lactide, and it was shown that the catalytic activity of different RE compounds followed the order: La > Nd > Sm > Gd > Er > Y, which may result from different coordination abilities of these RE elements with the monomer [46].

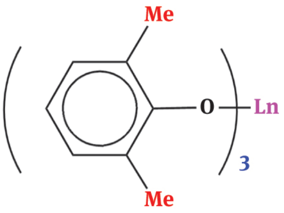


Figure 9: Structure of $Ln(ODMP)_3$ (Ln = La, Nd, Sm, Gd, Er, Y).

In the same work, ROP of ε-caprolactone was achieved by a novel RE initiator of scandium tris(2,6-di-tert-butyl-4-methylphenolat) producing poly(ε-caprolactone) under mild conditions [47].

Several tris(allyl) and bis(allyl)(diketiminato)lanthanide complexes have been demonstrated to be highly effective single-component catalysts for the ROP of ε-caprolactone and *rac*-LA. Polymer end-group analysis showed that the polymerization process was initiated by allyl transfer to the monomer [48]. Reactivity studies of amine–bis(phenolate) complexes of the type $[Me_2NCH_2CH_2N\{CH_2(2\text{-}OC_6H_2Bu_2t\text{-}3,5)\}_2]LnMe(THF)$ (Ln = Er, Yb) showed them to be efficient initiators for the ROP of ε-caprolactone [49].

A comparison of organolanthanide complexes $Cp^*{}_2SmMe(THF)$ and $(\mu\text{-}PhC{=}C{=}C{=}CPh)[Cp^*{}_2Sm]_2$, with tin compounds $Bu^n{}_2Sn(OMe)_2$ and $Bu^n{}_2Sn(OCH_2CH_2CH_2O)$ in the preparation of random diblock and triblock copolymers composed of L-lactide and D,L-lactide, has been described by Nakayama et al. [50].

In the same year, Wu et al. reported that lanthanide complexes containing silyl group-functionalized indenyl ligands exhibited high catalytic activities for ε-caprolactone polymerization [51]. Also, the organosamarium thiolate complex $[(MeC_5H_4)_2Sm(\mu\text{-}SPh)(THF)]_2$ has been reported to be an efficient initiator for the homo- and copolymerization of ε-caprolactone [52].

A Lewis acidic yttrium (III) complex of an anionic, metal-tethered carbene ligand (Figure 10) was reported to act as bifunctional catalyst for the polymerization of D,L-lactide, using a combination of Lewis acid and base functionalities to initiate the ROP of the cyclic monomer.

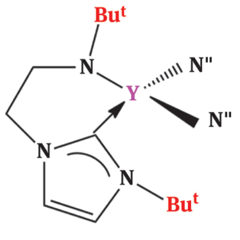


Figure 10: Structure of metal-tethered carbene ligand N″ = N $(SiMe_3)_2$.

The alcohol- and amino-functionalized carbenes from which the complexes derive provide models for the first insertion step and also display metal-free polymerization catalysts to generate polylactic acid [53].

In 2007, several articles dealing with the use of lanthanide complexes as catalysts for the ROP of lactide were published. For example, the lanthanide alkyl complexes bearing *N*,*O*-multidentate ligands shown in Figure 11 were successfully tested. It was found that the combination of aminoamine-modified bis(phenolate) ligands with lanthanide alkyl units generated unprecedented stereoselective initiators for the ROP of *rac*-LA to give heterotactic poly(lactide) [54].

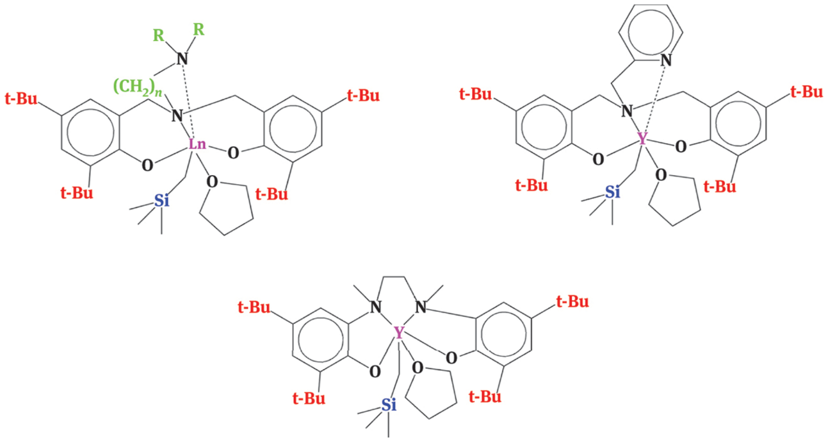


Figure 11: Structure of the lanthanide alkyl complexes with N,O-multidentate ligands.

The RE complexes shown in Figure 12 (R = H, Me, ^{t}Bu; R′ = Me, Et, pyridyl; R″ = alkyl, amino, phenoxy; Ln = Sc, Y, Lu) were also found to catalyse the stereoselective ROP of *rac*-LA.

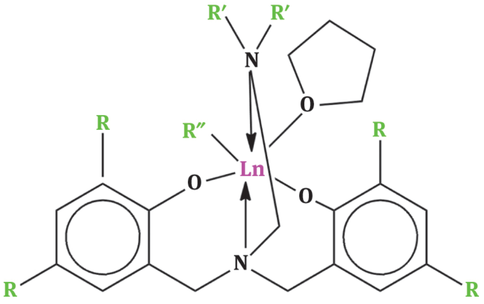


Figure 12: Structure of RE complexes (R = H, Me, ^{t}Bu; R′ = Me, Et, pyridyl; R″ = alkyl, amino, phenoxy; Ln = Sc, Y, Lu).

Bulk polymerizations were carried out with THF, dichloromethane or toluene as solvents, obtaining a conversion of 100%. The content of heterotactic polymer in the obtained poly(lactide) reached 0.99, which is higher than the highest value (0.96) previously reported [55].

The aminophenolate-supported lanthanide mono(alkyl) complexes shown in Figure 13 were found to be highly active initiators for the ROP of ʟ-lactide to give isotactic poly(lactide) with high molecular weight and narrow-to-moderate polydispersity [56]. RE metal alkyl complexes stabilized by anilido-phosphinimine and amino-phosphine ligands (Figure 14) were reported to initiate the ROP of ᴅ,ʟ-lactide with high activity to give atactic PLAs [57].

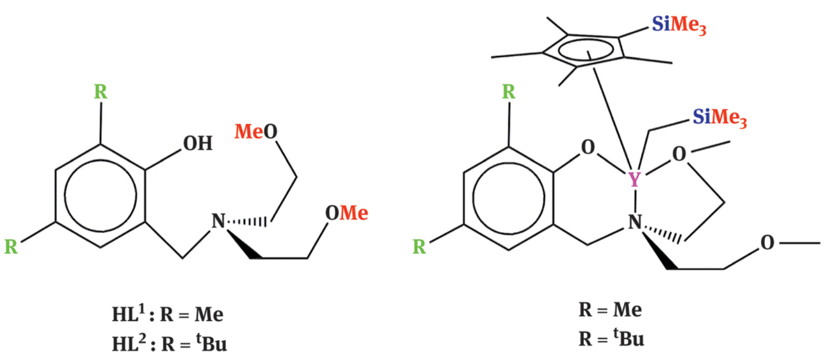


Figure 13: Structure of aminophenolate-supported lanthanide mono(alkyl) complexes.

Atactic PLAs were also obtained from D,L-lactide using as catalysts the pyrrolide–ligated organoyttrium complexes shown in Figure 15 [58].

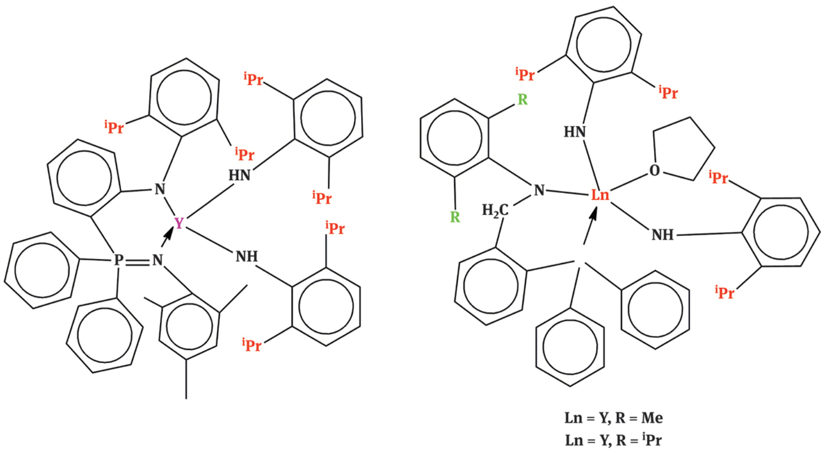


Figure 14: Structure of RE metal alkyl complexes stabilized by anilido phosphinimine and amino phosphine ligands.

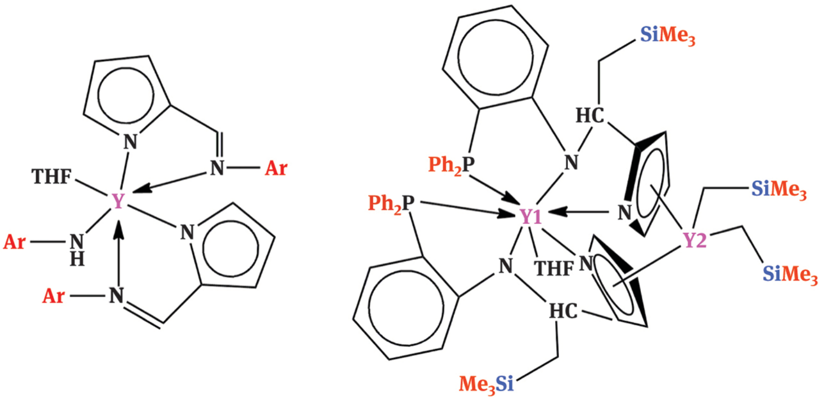


Figure 15: Structure of pyrrolide-ligated organoyttrium complexes.

Lanthanide (II) complexes containing tetrahydro-2H-pyranyl functionalized indenyl ligands (Figure 16) were reported to exhibit high catalytic activity in the polymerization of ε-caprolactone [59].

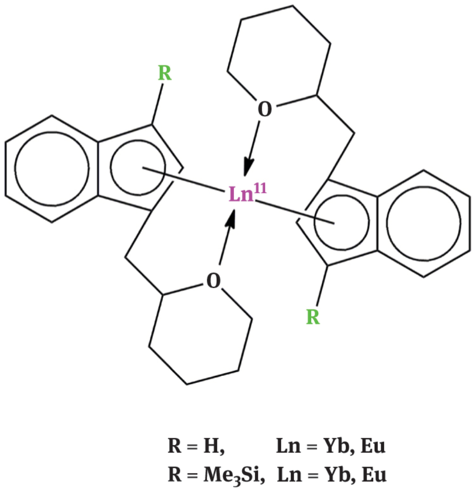


Figure 16: Structure of lanthanide (II) complexes containing tetrahydro-2H-pyranyl functionalized indenyl ligands.

ROP of ε-caprolactone was also achieved using [ethylene bis (η^5indenyl)][bis(trimethylsilyl)amido] lanthanide (III) complexes (EBI)LnN($SiMe_3$)$_2$ (Ln = Y, Sm, Yb) (Figure 17) [60].

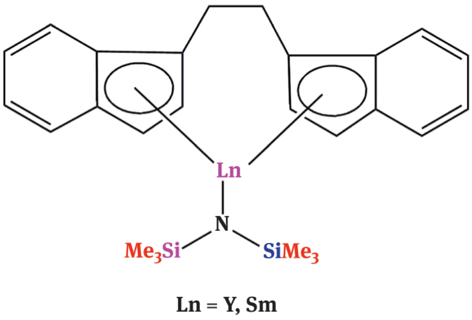
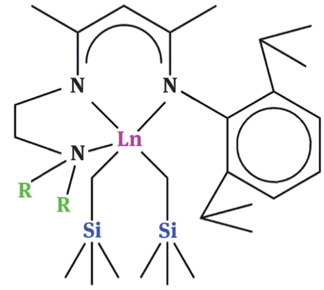


Figure 17: Structure of [ethylene-bis(η^5- indenyl)][bis(trimethylsilyl)amido]lanthanide(III) complexes (EBI)LnN($SiMe_3$)$_2$ (Ln = Y, Sm).

The polymerization mechanisms of ε-caprolactone initiated by either the RE hydride $Cp_2Eu(H)$ or the borohydrides $Cp_2Eu(BH_4)$ or (N_2NN')Eu(BH_4) (N_2NN'=(2-C_5H_4N)CH_2(CH_2CH_2NMe)$_2$) proceed in two steps: hydride transfer from the RE initiator to the carbonyl carbon of the lactone, followed by ring-opening of the monomer. In the last step, a difference was observed between the hydride and borohydride complexes, because for the latter, the ring-opening is induced by an additional B–H bond cleavage leading to a terminal –CH_2OBH_2 group. This corresponds to the reduction by BH_3 of the carbonyl group of ε-caprolactone. Upon reaction of $Cp_2Eu(H)$ with ε-caprolactone, the alkoxy–aldehyde complex produced $Cp_2Eu[O(CH_2)_5C(O)H]$ is the first-formed initiating specie. In contrast, for the reaction of ε-caprolactone with the borohydride complexes (L_x)Eu(BH_4) (L_x = Cp_2 or N_2NN'), an aliphatic alkoxide with a terminal –CH_2OBH_2 group, (L_x)Eu[O(CH_2)$_6$$OBH_2$] is formed and subsequently propagates the polymerization [61].

The dialkyllanthanide complexes shown in Figure 18 were found to display high activities for the ROP of ε-caprolactone, in which narrow-polydispersity polymers were produced.

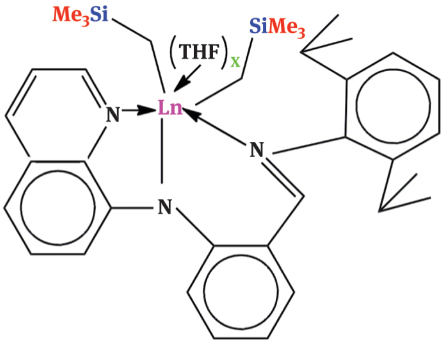


R = Me, Ln = Y
R = Me, Ln = Lu
R = Me, Ln = Sm
R = Me, Ln = Nd
R = Et, Ln = Y
R-R = -(CH_2)$_5$, L = Y

Figure 18: Structure of dialkyllanthanide complexes.

The size of the pendant arm has a significant effect on the molecular weight of the obtained polymer. In comparison to the Y complex with an $–NMe_2$ group, the Y complexes with NEt_2 and $–N((CH_2CH_2)_2CH_2)$ groups yield much higher-molecular-weight polymers (60,000 vs. 20,000) [62].

RE metal bis(alkyls) supported by a quinolinyl anilido-imine ligand (Figure 19) were reported to catalyse the ROP of ε-caprolactone with high activities; the Lu complex was proved to be more active than its Sc and Y analogues [63].



Ln = Sc; X = 0
Ln = Y; X = 1
Ln = Lu, X = 0

Figure 19: RE metal bis(alkyls) supported by a quinolinyl anilido-imine.

The scandium dimethylbenzyl complex Sc(fc[NSi(^{t}Bu)Me_2]$_2$)(CH_2Xy-3,5)(THF) and its adduct with $AlMe_3$ (Figure 20) were reported to polymerize ʟ-lactide [64].

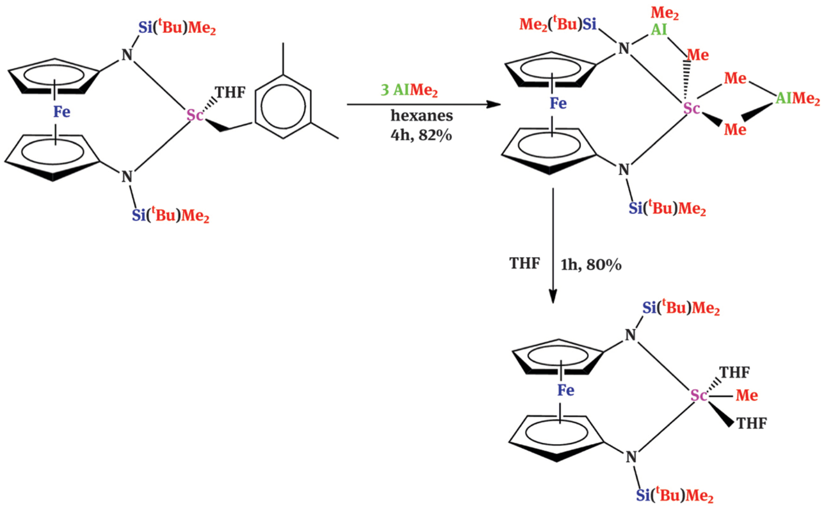


Figure 20: Synthesis route for scandium dimethylbenzyl complex Sc(fc[NSi(^{t}Bu)Me_2]$_2$)(CH_2Xy-3,5)(THF) and its adduct with $AlMe_3$.

RE metal complexes having piperazine-alkyl-bridged bis(aryloxy) ligands have been claimed in a patent as polymerization catalysts for ʟ-lactide [65]. In particular, the complexes [OArNNArO]Ln(CH_2SiMe_3)(THF), wherein Ln = heavy RE metals selected from Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu and Y([OArNNArO] = $C_4H_8N_2$[1,4-(2-O-5-R^1-3-R^2-$C_6H_2CH_2$)$_2$], $R^{1,2}$ = C1-C4 alkyl) were found to be useful as monocomponent catalysts for the ROP of ʟ-lactide under mild conditions with high catalytic activity, high poly(lactide) molecular weight, narrow poly(lactide) molecular weight distribution and good polymerization controllability [65].

In the work of Mahrova et al., the tertbutoxide and borohydride complexes (DAB)Y(O^{t}Bu)(THF)(DME) and [Li(DME)$_3$][(DAB)Y(BH_4)$_2$] shown in Figure 21 acted as monoinitiators for the room temperature ROP of *rac*-LA and β-butyrolactone (Figure 22). In these reactions, atactic polymers with controlled molecular weights and relatively narrow polydispersities were obtained [66].

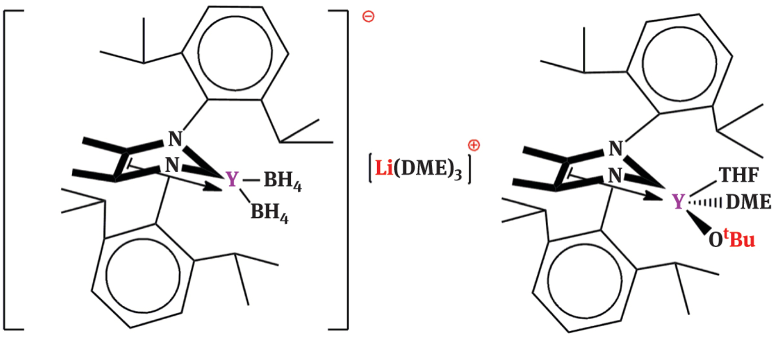


Figure 21: Structure of tertbutoxide and borohydride complexes (DAB)Y(O^{t}Bu)(THF)(DME) and [Li(DME)$_3$][(DAB)Y(BH_4)$_2$].

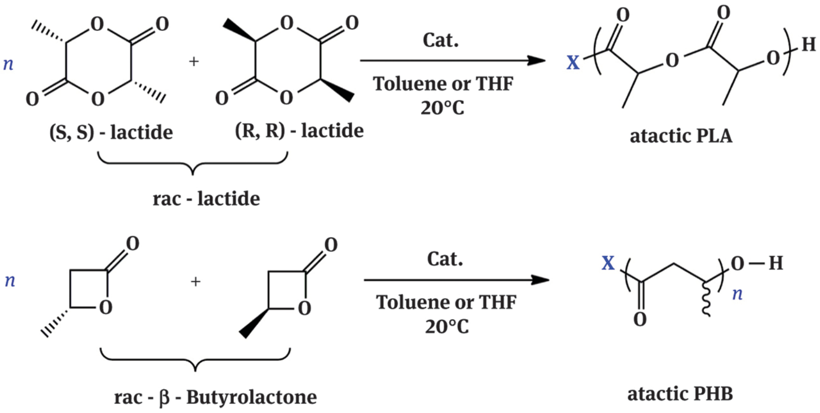
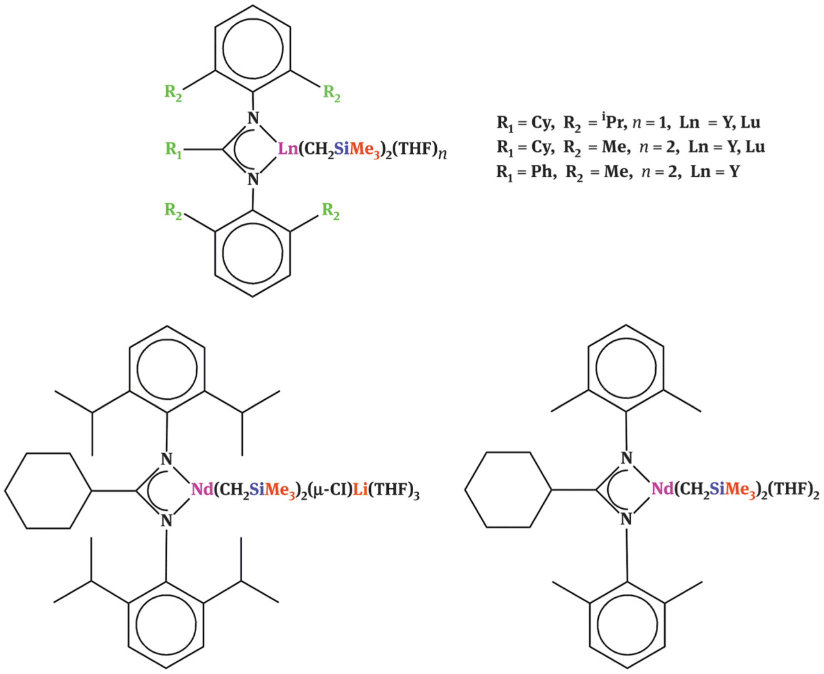


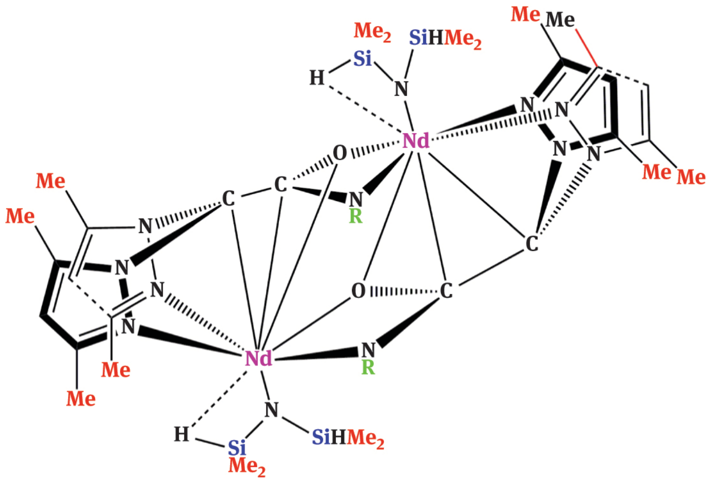
Figure 22: ROP of rac-LA and β-butyrolactone catalyzed by tertbutoxide and borohydride complexes (DAB)Y(O^{t}Bu)(THF)(DME) and [Li(DME)$_3$][(DAB)Y(BH_4)$_2$].

The neutral mono(amidinato) RE metal bis(alkyl) complexes shown in Figure 23 exhibited activity towards ʟ-lactide polymerization to give high-molecular-weight and narrow-molecular-weight distribution polymers [67]. The neodymium heteroscorpionate complex shown in Figure 24 acted as an efficient single-site initiator for the controlled ROP of *rac*-LA, which showed a homosteric preference for one of the two enantiomers at low conversions [68].



R_1 = Cy, R_2 = ^{i}Pr, n = 1, Ln = Y, Lu
R_1 = Cy, R_2 = Me, n = 2, Ln = Y, Lu
R_1 = Ph, R_2 = Me, n = 2, Ln = Y

Figure 23: Structure of mono(amidinato) RE metal bis(alkyl) complexes.



R = (S)-PhMeCH

Figure 24: Structure of neodymium heteroscorpionate complex.

Preliminary results of Otero et al. showed that heteroscorpionate complexes with acetamide and thioacetamide functionalities (Figure 25) can act as single-component living initiators for ROP reactions. Polymerization of ε-caprolactone occurred within minutes to give medium-molecular weight polymers and narrow polydispersities. Polymer end-group analysis showed that the polymerization process is initiated by alkyl transfer to the monomer [69].

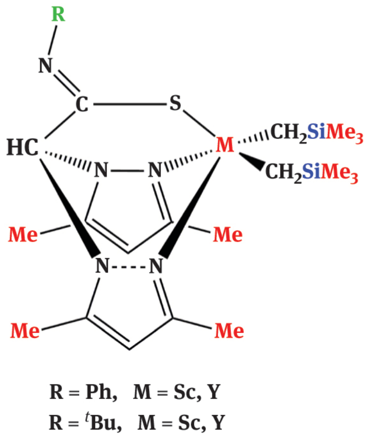


Figure 25: Structure of heteroscorpionate complexes with acetamide and thioacetamide functionalities.

The catalytic properties of the divalent lanthanide 2-pyridylmethyl-substituted fluorenyl complexes (η^5:η^1-$C_5H_4NCH_2C_{13}H_8)_2$Ln (Ln = Eu, Y) on the ROP of ε-caprolactone have been studied and the temperatures and solvent effects on the catalytic activities of the complexes examined [70]. It was reported that the lanthanide alkyl complexes supported by a piperazidine-bridged bis(phenolato) ligand shown in Figure 26 are highly efficient initiators for the controlled ROP of ʟ-lactide, giving polymers with high molecular weights and narrow-molecular-weight distributions.

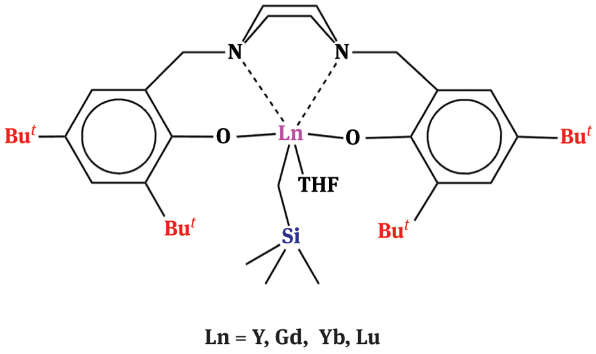


Figure 26: Structure of divalent lanthanide 2-pyridylmethyl substituted fluorenil complexes (η^5:η^1- $C_5H_4NCH_2C_{13}H_8)_2$Ln (Ln = Eu, Y).

It was found that the complex [ONNO]Y(CH_2SiMe_3)(THF) (Figure 26) can also initiate *rac*-LA polymerization with high activity, but the stereoselectivity was poor. In contrast, the dimeric gadolinium complex depicted in Figure 27 exhibited apparently low activity for this polymerization [71].

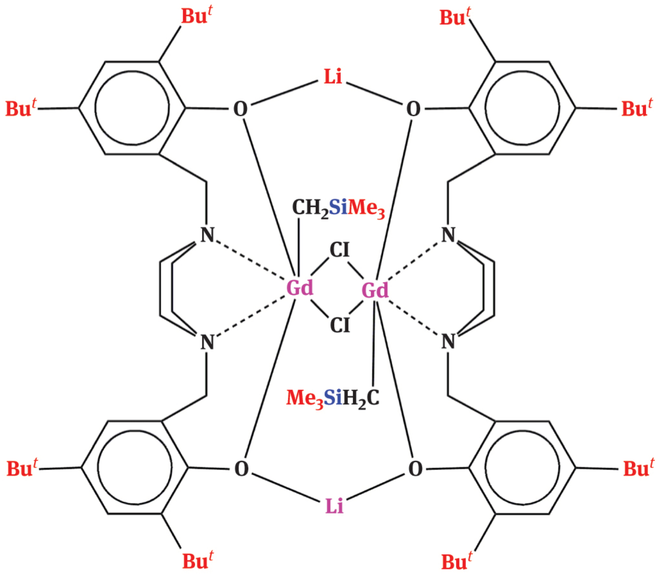


Figure 27: Structure of gadolinium alkyl complex, $\{[ONNO]Gd(CH_2SiMe_3)(\mu\text{-}Li)(\mu\text{-}Cl)\}_2$.

Several bimetallic lanthanide bis(alkyl)complexes bearing bridged amidinate ligands (Figure 28) also showed activity towards L-lactide polymerization in toluene [72].

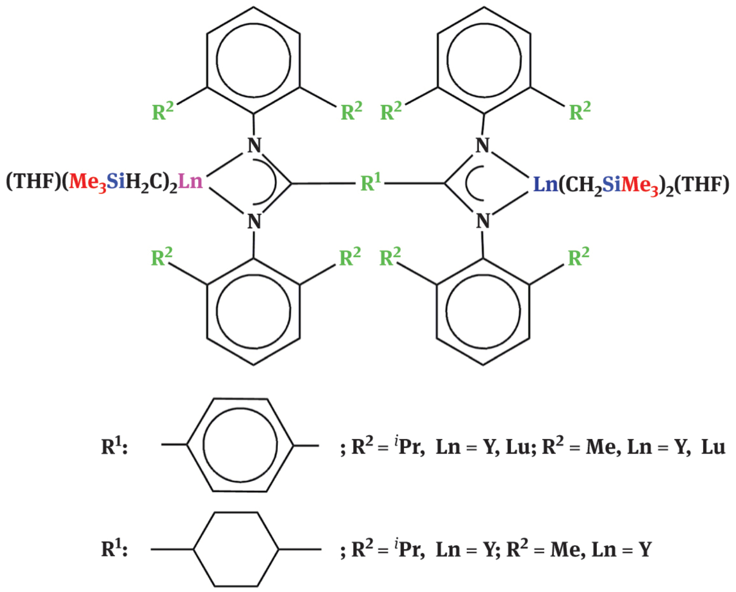


Figure 28: Structure of binuclear lanthanide bis(alkyl) derivatives with bridged amidinate ligands.

In another study, the behaviour of the samarium (II) borohydrides $Sm(BH_4)_2(THF)_2$ and $Cp^*Sm(BH_4)(THF)_2$ as initiators in the ROP of ε-caprolactone has been investigated [73]. ROP could be performed rapidly at room temperature with both initiators. The half-sandwich complex $Cp^*Sm(BH_4)(THF)_2$ led to narrow polydispersities and higher activity.

An initiating system comprising a rare neodymium–alkyl–carbene complex $Nd[C(PPh_2N^iPr)_2][CH(PPh_2N^iPr)_2]$ and externally added ^{i}PrOH was also proved to be an efficient catalyst for the ROP of lactide [74].

Dicationic and zwitterionic yttrium compounds, prepared according to Figure 29 from the tris(alkyl) precursors Ln, have been reported to act as catalysts for the primary or secondary amine-initiated immortal ROP of *rac*-LA [75]. Amine-terminated, highly heterotactic poly(*rac*-LA) with narrow polydispersities and well-controlled molecular weights have been obtained following this method.

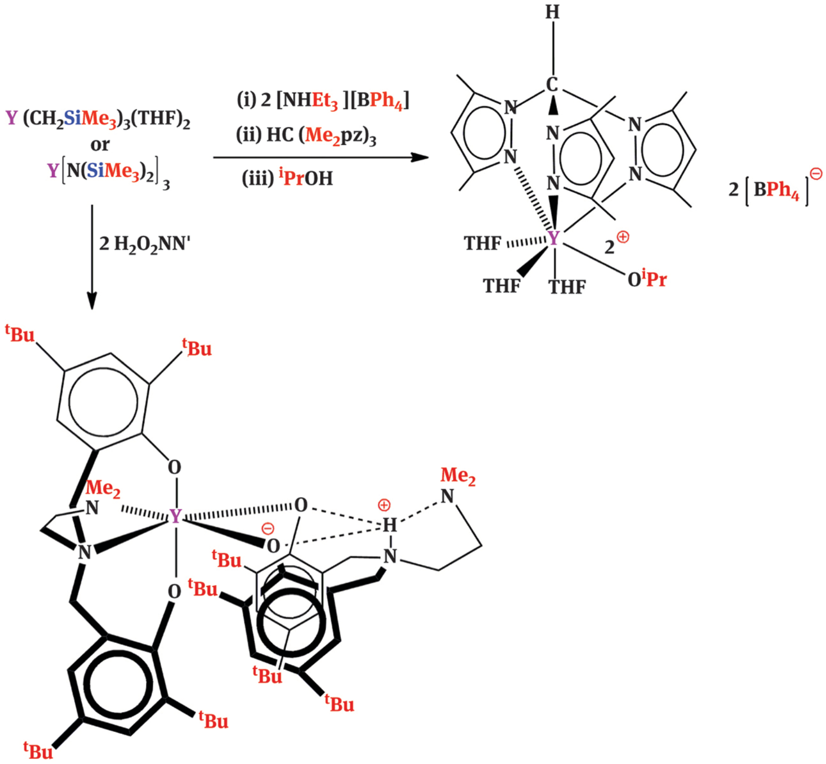


Figure 29: Synthesis route for dicationic and zwitterionic yttrium compounds.

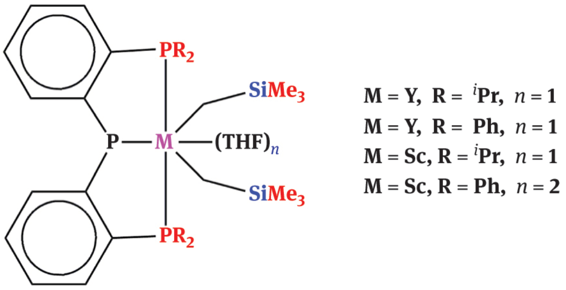
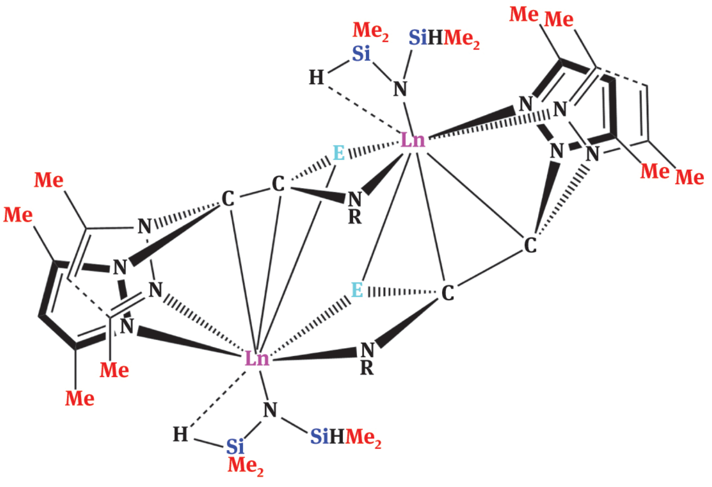


Figure 30: Structure of scandium and yttrium complexes of the type $LLn(CH_2SiMe_3)_2(THF)_n$ supported by the related tridentate phosphido-diphosphine pincer ligands $(o\text{-}C_6H_4PR_2)_2PH$ (L^1H: R =^{i}Pr, L^2H: R = Ph).

The scandium and yttrium complexes supported by tridentatephosphido-diphosphine ligands shown in Figure 30 have been studied as initiators for the ROP of lactide [76].

The yttrium complexes exhibited high activity and good polymerization control, while the analogous scandium complexes gave a good molar mass control but lower activities.

Neodymium complexes are known to be active initiators for the ROP of lactide and lactones, giving rise to medium–high molar mass polymers under mild conditions and with narrow polydispersities. The heteroscorpionate complexes depicted in Figure 31 were found to be well-suited for achieving well-controlled polymerization through an insertion–coordination mechanism.



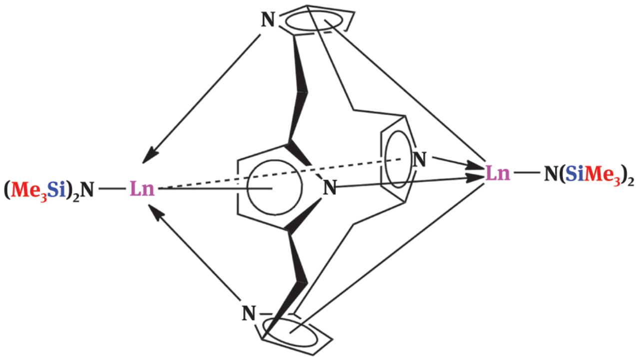
R = (S)-PhMeCH, E = O, Ln = Nd, Sm
R = ^{s}Bu, E = O, Ln = Nd, Sm
R = Ph, E = S, Ln = Nd, Sm
R = ^{t}Bu, E = S, Ln = Nd, Sm

Figure 31: Structure of complexes containing dianionic heteroscorpionate pseudoallyl ligands.

A chiral and racemic complexes did not affect stereocontrol in the polymerization of *rac*-LA, but the enantiomerically pure complex [Nd*{*N(SiHMe$_2$)$_2$*}*(NNE)]$_2$ was found to exhibit a homosteric preference for one of the two enantiomers of *rac*-LA at low conversions [77].

DAuria et al. reported the ROP of cyclic esters promoted by phosphido-diphosphine pincer Group 3 metal bis(alkyl) complexes [78]. The phosphido-diphosphine complexes [(*o*-C$_6$H$_4$PR$_2$)$_2$P]Ln(CH$_2$SiMe$_3$)$_2$ (Ln = Sc, Y; R = iPr, Ph) have been found to be very efficient catalysts for the ROP of ε-caprolactone, L-lactide and δ-valerolactone under mild polymerization conditions. In the ROP of ε-caprolactone, all four complexes promoted the quantitative conversion of high amounts of monomer with very high turnover frequencies showing a catalytic activity among the highest reported in the literature. In the ROP of δ-valerolactone, the catalysts showed the same activity observed for lactides (L- and D,L-lactide) producing high-molecular-weight polymers with narrow distribution of molar masses. The complexes also promoted the ROP of *rac*-β-butyrolactone affording at low-molecular-weight poly(hydroxybutyrate) bearing unsaturated end-groups probably generated by elimination reactions [78].

The bent-sandwiched calix[4]-pyrrolyl lanthanide amido complexes displayed in Figure 32 were found to exhibit high catalytic activities towards the ROP of L-lactide, using the dinuclear trivalent lanthanide amido complexes bearing a {(CH$_2$)$_5$}4-calix[4]-pyrrolyl ligand [79].



R = Me, Ln = Nd, Sm, Dy
R = { -(CH$_2$)$_5$- }$_{0.5}$, Ln = Nd, Sm
R groups were omitted for clearity

Figure 32: Structure of dinuclear alkali metal-free trivalent lanthanide amido complexes (5:1:5:1-R$_8$-calix[4]-pyrrolyl)[LnN(SiMe$_3$)$_2$]$_2$ (R =Me, Ln = Nd, Sm, Dy; R={ (CH$_2$)$_5$}$_{0.5}$, Ln = Nd, Sm).

The heterobimetallic oxo-bridged aluminum–RE metal complexes shown in Figure 33 have been investigated as lactide polymerization initiators. The heterobimetallic samarium alkoxide derivative (Figure 33 right) was found to be highly active, yielding high-molecular-weight PLs with over 91% conversion [80]. Reactions of LAl[C(Ph)CH(Ph)](μ-O)Ln(CH_2SiMe_3)[NN]$(THF)_2$ (Ln = Y, Sm) with 1 equiv. of ^iPrOH yielded the corresponding alkoxide complexes (Figure 33 left).

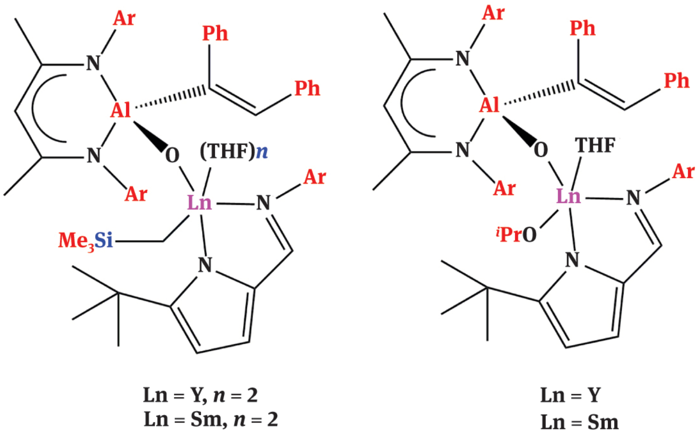


Figure 33: Structure of LAl[C(Ph)CH(Ph)](μ-O)Ln(CH_2SiMe_3)[NN]$(THF)_2$ (Ln = Y, Sm) (right) and its corresponding alkoxide complexes (left).

A germyl-bridged lanthanocene chloride, [$Me_2Ge(^tBuC_5H_3)_2$]NdCl, was prepared and successfully used as single catalyst to initiate the ROP of ε-caprolactone for the first time [81]. It was found that under mild conditions, [$Me_2Ge(^tBuC_5H_3)_2$]NdCl efficiently catalysed the polymerization of ε-caprolactone, giving high yield (> 95%) of poly(lactones) with high molecular weight. When the polymerization was carried out in bulk or in petroleum ether solution, it gave poly(lactones) with higher molecular weight and perfect conversion (100%). The higher catalytic activity of this neodymocene chloride could be attributed to the bigger atom (Ge) in the bridged ring ligands. It was also found that some activators, such as $NaBPh_4$, KBH_4, $AlEt_3$ and $Al(^iBu)_3$, can promote the polymerization of ε-caprolactone by [$Me_2Ge(^tBuC_5H_3)_2$]NdCl, which leads to an increase both in the polymerization conversion and in the molecular weight of poly(lactones) [81].

Zhao et al. developed a new strategy for the facile synthesis of fluorescent dye-labelled polyesters via immortal ROP of heterocyclic monomers (ε-caprolactone, racemic β-butyrolactone and *rac*-LA, etc.) by using a catalytic amount of metal-based complexes (including a lutetium alkyl derivative) with an excess of hydroxylated dye compounds (Figure 34) [82].

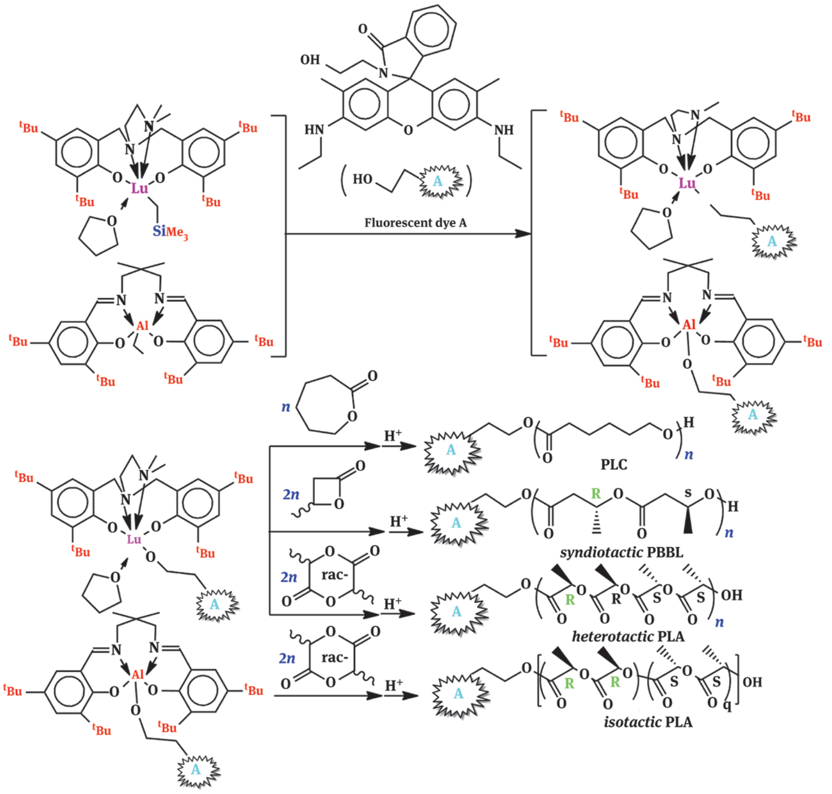


Figure 34: Synthesis of fluorescent dye-labeled polyesters via immortal ROP of heterocyclic monomers.

This strategy breaks the “one catalyst-one dye-labeled polymer chain” limitation in that a series of “clean” dye-labeled polyesters have been obtained in the form of low metal residue, designed molecular weight, narrow distributions, excellent α-dye labelled and *o*-hydroxyl fidelity and high stereoregularity [82].

Bis(imino)diphenylamido RE metal dialkyl catalysts $[o\text{-}(2,6\text{-}{}^{i}Pr_2C_6H_3N\ CC_6H_4)_2N]Ln(CH_2SiMe_3)_2$ (Ln = Sc, Y, Lu) have been synthesized according to Figure 35 in good yields. They served as highly efficient single-component catalysts for the living ROP of ε-caprolactone, with the activity being dependent on the steric hindrance around the metal centre [83].

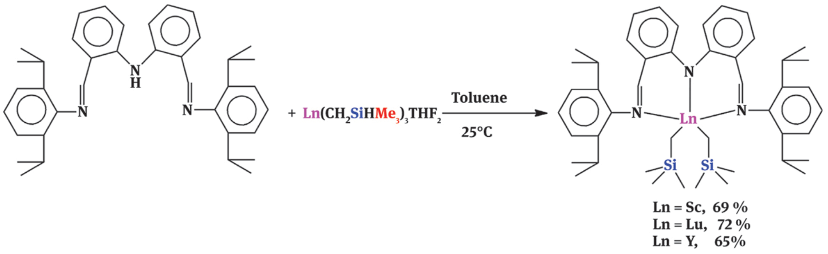


Figure 35: Synthesis of bis(imino)diphenylamido RE metal dialkyl catalysts $[o\text{-}(2,6\text{-}{}^{i}Pr_2C_6H_3N\ CC_6H_4)_2N]Ln(CH_2SiMe_3)_2$ (Ln = Sc, Y, Lu).

The neutral mono-indenyl-ligated RE metal bis(silylamide) complexes $(C_9H_6CMe_2CH_2C_5H_4N\text{-}\alpha)Ln[N(SiHMe_2)_2]_2$ (Ln = La, Sm, Er, Lu) shown in Figure 36 have been found to be highly active for the ROP of ʟ-lactide and *rac*-LA (Figure 37) [84].

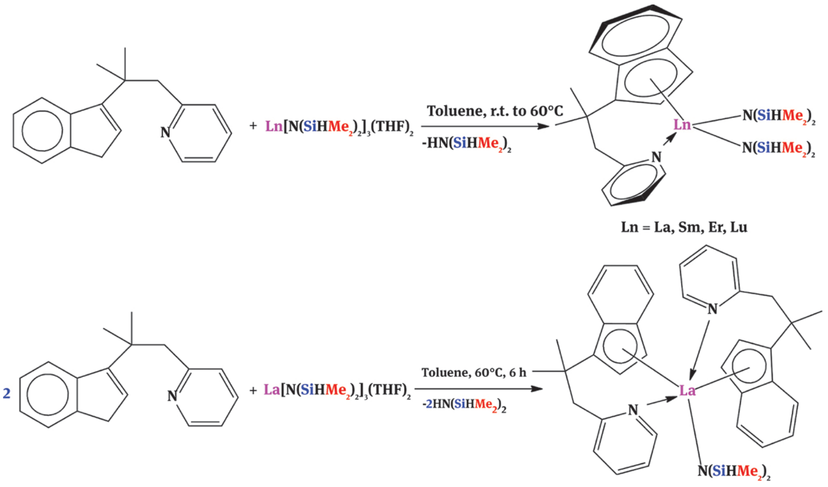


Figure 36: Synthesis route for $(C_9H_6CMe_2CH_2C_5H_4N\text{-}\alpha)Ln[N(SiHMe_2)_2]_2$ (Ln = La, Sm, Er, Lu) and $(C_9H_6CMe_2CH_2C_5H_4N\text{-}\alpha)2LaN(SiHMe_2)_2$.

Several dinuclear RE metal bis(o-aminobenzyl) complexes bearing a 1,4-phenylenediamidinate co-ligand (Figure 38) have also been reported to show high activity for *rac*-LA and ε-caprolactone polymerization. For *rac*-LA, a synergistic effect between two metal centres was observed [85].

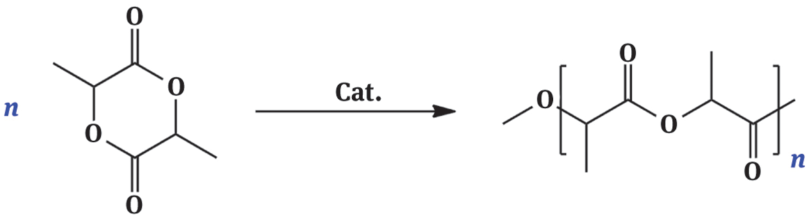


Figure 37: ROP of lactide.

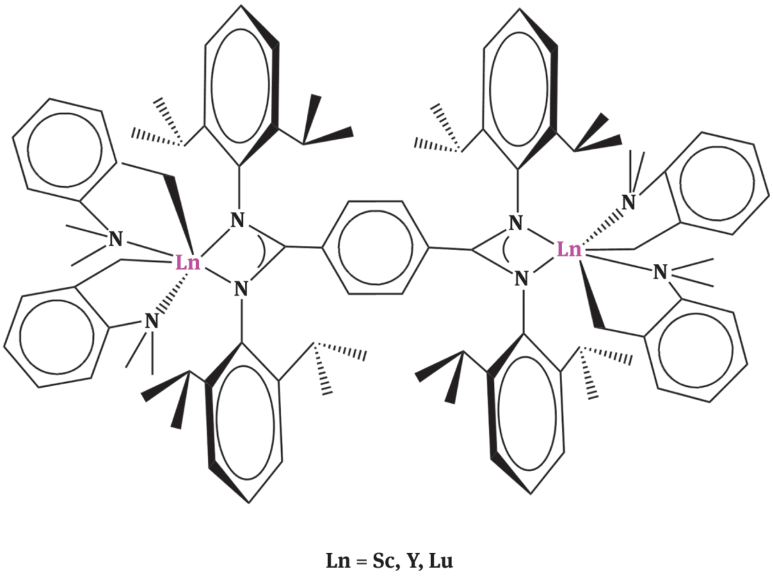


Figure 38: Structures of dinuclear RE metal bis(o-aminobenzyl)complexes with 1,4-$C_6H_4[C(NR)_2Ln(o\text{-}CH_2C_6H_4NMe_2)_2]_2$ (R = 2,6-$^iPr_2C_6H_3$, Ln = Sc, Y, Lu) catalysts.

The bis(oxazolinylphenyl)amide (BOPA) ligand-supported lanthanide alkyl complexes shown in Figure 39 have been successfully employed in the ROP of *rac*-LA [86].

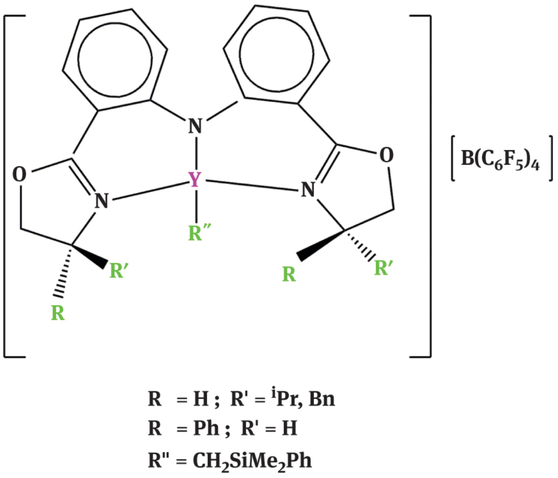
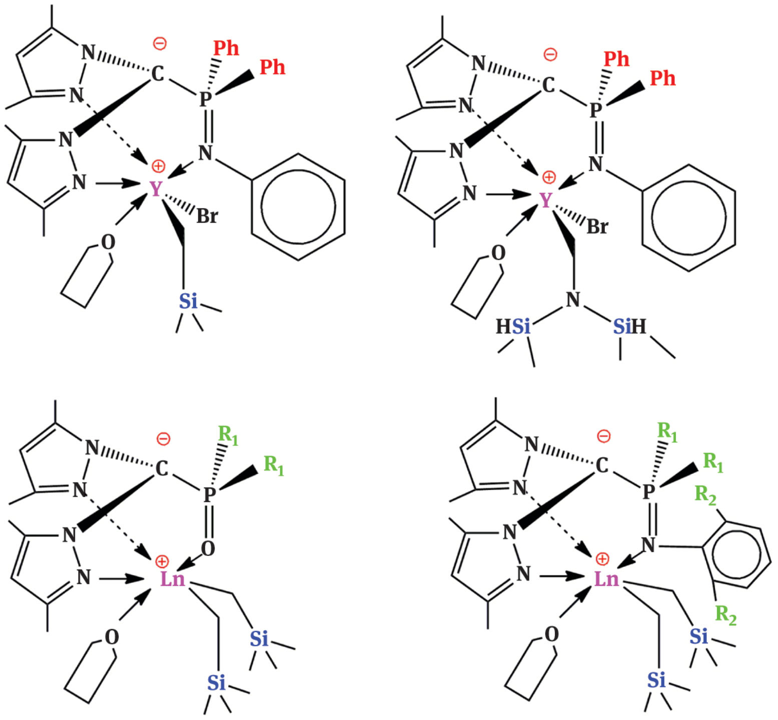


Figure 39: Bis(oxazolinylphenyl)amide (BOPA)-supported yttrium alkyl complexes.

A series of heteroscorpionate yttrium and lutetium zwitterionic initiators (Figure 40) all showed similar high activity towards the ROP of *rac*-LA at room temperature, and both the alkyl species participated in initiation, of which the lutetium complexes exhibited slightly higher selectivity than their yttrium analogues [87].



$R_1 = {}^tBu$, Ln = Y, Lu
R_1 = Cy, Ln = Y, Lu

R_1 = Cy, R_2 = H, Ln = Y, Lu
R_1 = Ph, R_2 = H, Ln = Y, Lu
R_1 = Ph, R_2 = Me, Ln = Y, Lu

Figure 40: Structures of zwitterionic bis(alkyl) complexes $L^{1-5}Ln(CH_2SiMe_3)_2(THF)$ (Ln = Y, Lu).

5 Conclusions

Biodegradable polymers represent a class of particularly useful materials for many biomedical and pharmaceutical applications. Among these types of polyesters, poly(ε-caprolactone) and polylactides are considered very promising for controlled drug delivery devices. These polymers are mainly produced by ROP of their respective cyclic esters, since this method allows a strict control of the molecular parameters (molecular weight and distribution) of the obtained polymers. The most widely used catalysts for ROP of cyclic esters are tin- and aluminium-based organometallic complexes; however, since the contamination of the aliphatic polyesters by potentially toxic metallic residues is particularly of concern for biomedical applications, the possibility of replacing organometallic initiators by novel less toxic or more efficient organometallics has been intensively studied. Thus, in the recent years, the use of highly reactive RE initiator/catalysts leading to lower polymer contamination has been developed. The use of RE complexes is considered a valuable strategy to decrease the polyester contamination by metallic residues and represents an attractive alternative to traditional organometallic complexes.

Acknowledgment

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References

[1] Jérôme C, Lecomte P. Recent advances in the synthesis of aliphatic polyesters by ring-opening polymerization. Adv Drug Deliver Rev. 2008;60:1056
[2] Edelmann FT. Lanthanides and actinides: Annual survey of their organometallic chemistry covering the year 2007. Coord Chem Rev. 2009;253:2515.
[3] Williams CK. Synthesis of functionalized biodegradable polyesters. Chem Soc Rev. 2007;36:1573.

[4] Lou X, Detrembleur C, Jérôme R. Novel aliphatic polyesters based on functional cyclic (di) esters. Macromol Rapid Commun. 2003a;24:161.

[5] Stridsberg K, Ryner M, Albertsson AC. Controlled ring-opening polymerization: polymers with designed macromolecular architecture. Adv Polym Sci. 2002;157:41.

[6] Coulembier O, Degée P, Hedrick JL, Dubois P. From controlled ring-opening polymerization to biodegradable aliphatic polyester: especially poly (β-malic acid) derivatives. Prog Polym Sci. 2006;31:723.

[7] Penczek S, Cypryk M, Duda A, Kubisa P, Slomkowski S. Living ring-opening polymerizations of heterocyclic monomers. Prog Polym Sci. 2007;32:247.

[8] Lecomte P, Jérôme R. New developments in the synthesis of aliphatic polyesters b ring-opening polymerization. In: Smith R, editors. Biodegradable polymers for polymer industrial applications. Cambridge: Woodhead Publishing Ltd. editor 2005:77–106.

[9] Agarwal S, Mast C, Dehnicke K, Greiner A. Rare earth metal initiated ring-opening polymerization of lactones. Macromol Rapid Commun. 2000;21:195.

[10] Bunzli JC. Benefiting from the unique properties of lanthanide ions. Acc Chem Res. 2006;39:53.

[11] Bunzli JC, Piquet C. Lanthanide-Containing Molecular and Supramolecular Polymetallic Functional Assemblies. Chem Rev. 2002;102:1897.

[12] Berry AD, Holm RT, Fatemi M, Gaskill DK. OMCVD of thin films from metal diketonates and triphenylbismuth. Mater Res. 1990;5:1169.

[13] Matsuzawa H. Novel magnetic applications of high-Tc bulk superconductors: Lenses for electron beams. J Appl Phys. 1994;74(12):111.

[14] Ilott DJ, Saiful Islam M. J Chem Soc Faraday Trans. 1993;89:3833.

[15] Schulte B, Maul M, Becker W, Schlosser EG, Haussler P, Adrain II. Carrier gas-free chemical vapor deposition technique for in situ preparation of high quality $YBa_2Cu_3O_{7-\delta}$ thin films. Appl Phys Lett. 1991;59:869.

[16] Uchikawa F, Mackenzi JD. Superconducting $YBa_2Cu_3O_{7-x}$ fibers from the thermoplastic gel method. J Mater Res. 1989;4:787.

[17] Tanabe K, Mismo K, Ono Y, Hattori H. New solid acids and bases. New York: Kodansha, Tokyo Elsevier, 1989:41–47.

[18] Arakawa H. Technol Jpn. 1988;21(11):32.

[19] Otsuka K, Jinn K, Morikawa A. Active and selective catalysts for the synthesis of C_2H_4 and C_2H_6 via oxidative coupling of methane. J Catal . 1986;100(2):353

[20] Okabe K, Sayarna K, Kusama H, Arakawa H. Effect of Catalyst Preparation on the Oxidative Coupling of Methane over $SrO–La_2O_3$. Bull Chem Soc Jpn. 1994;67:2894.

[21] Hou Z, Wakatsuki Y. Recent developments in organolanthanide polymerization catalysts. Coord Chem Rev. 2002;231:1.

[22] Pelletier J-F, Bujadoux K, Olonde X, Adisson E, Mortreux A. Eur. Pat. Appl. EP 736,536 (Cl.C07F3:02), 9 Oct. 1996, FR Appl. 95:4,203. 7 Apr 1995.

[23] Nomura R, Shibasaki Y, Endo T. Block copolymerization of tetrahydrofuran with δ-valerolactone by the samarium iodide-induced transformation. Polym Bull. 1996;37:597.

[24] Boffa LS, Novak BM. "Link-Functionalized" Polymers: An Unusual Macromolecular Architecture through Bifunctional Initiation. Macromolecules. 1997;30:3494.

[25] Hyeon J-Y, Edelmann FT. Lanthanides and actinides: annual survey of their organometallic chemistry covering the year 1997. Coord Chem Rev. 2003;241:249.

[26] Hultzsch KC, Spaniol TP, Okuda J. Chiral Lanthanocene Derivatives Containing Two Linked Amido— Cyclopentadienyl Ligands: Heterobimetallic Structure and Lactone Polymerization Activity. Organometallics. 1997;16:4845.

[27] Nomura R, Shibasaki Y, Endo T. Transformation of the cationic growing center of poly (tetrahydrofuran) into an anionic one by bis (pentamethylcyclopentadienyl) samarium. J Polym Sci A. 1998;36:2209.

[28] Agarwal S, Brandukova-Szmikowski NE, Greiner A. Reactivity of Sm (II) compounds as ring-opening polymerization initiators for lactones. Macromol Rapid Commun. 1999;20:274.

[29] Nishiura M, Hou Z, Koizumi T-A, Imamoto T, Wakatsuki Y. Ring-opening polymerization and copolymerization of lactones by samarium (II) aryloxide complexes. Macromolecules. 1999;32:8245.

[30] Yuan M, Li X, Xiong C, Deng X. Polymerization of lactides and lactones 5. Ring-opening polymerization of ε-caprolactone and dl-lactide by rare earth 2-methylphenyl samarium. Eur Polym J. 1999;35:2131.

[31] Desurmont G, Tokimitsu T, Yasuda H. First Controlled Block Copolymerizations of Higher 1-Olefins with Polar Monomers Using Metallocene Type Single Component Lanthanide Initiators. Macromolecules. 2000;33:7679.

[32] Deng X, Yuan M, Li X, Xiong C. Polymerization of lactides and lactones: VII. Ring-opening polymerization of lactide by rare earth phenyl compounds. Eur Polym J. 2000;36:1151.

[33] Agarwal S, Puchner M. Ring opening polymerisations of cyclic esters and carbonate by rare-earth LnCp 3. Eur Polym J. 2002;38:2365.

[34] Cui D, Tang T, Cheng J, Hu N, Chen W, Huang B. Synthesis and characterization of $(C_5H_9C_9H_6)_2Yb(THF)_2$(II) (1) and $[(C_5H_9C_5H_4)_2Yb(THF)]_2O_2$ (2), and ring-opening polymerization of lactones with 1. J Organomet Chem. 2002;650:84.

[35] Emslie DJ, Piers WE, Parvez M, McDonalds R. Organometallic complexes of scandium and yttrium supported by a bulky salicylaldimine ligand. Organometallics. 2002;21:4226.

[36] Ravi P, Grob T, Dehnicke D, Greiner A. Ring-Opening Polymerization of ε-Caprolactone by Phosphorane Iminato and Cyclopentadienyl Complexes of Rare Earth Elements. Macromol Chem Phys. 2001;202:2641.

[37] Cui D, Tang T, Bi W, Cheng J, Chen W, Huang B. Ring-opening polymerization and block copolymerization of L-lactide with divalent samarocene complex. J Polym Sci Part A Polym Chem. 2003;41:2667.

[38] Tsutsumi C, Nakagawa K, Shirahama H, Yasuda H. Biodegradations of statistical copolymers composed of D, L-lactide and cyclic carbonates. Polym Int. 2003;52:439.

[39] Satoh Y, Ikitake N, Nakayama Y, Okuno S, Yasuda H. Syntheses of bis- and tetra(trimethylsilyl) substituted lanthanocene methyl complexes and their catalyses for polymerizations of methyl methacrylate, ε-caprolactone and l-lactide. J Organomet Chem. 2003;667:42.

[40] Lou Y, Yao Y, Shen Q, Yu K, Weng L. Synthesis and Characterization of Lanthanide(III) Bis(guanidinate) Derivatives and the Catalytic Activity of Methyllanthanide Bis(guanidinate) Complexes for the Polymerization of ε-Caprolactone and Methyl Methacrylate. Eur J Inorg Chem. 2003;2003(2):318

[41] Chen J-L, Yao Y-M, Luo Y-J, Zhou L-Y, Zhang Y, Shen Q. Synthesis, characterization of homoleptic guanidino lanthanide complexes and their catalytic activity for the ring-opening polymerization of ε-caprolactone. J Organomet Chem. 2004;689:1019.

[42] Palard I, Soum A, Guillaume SM. Unprecedented Polymerization of ε-Caprolactone Initiated by a Single-Site Lanthanide Borohydride Complex,[Sm $(\eta\text{-}C_5Me_5)_2(BH_4)$(thf)]: Mechanistic Insights. Chem Eur J. 2004;10:4054.

[43] Kuehl CJ, Simpson CK, John KD, Sattelberger AP, Carlson CN, Hanusa TP. Monomeric f-element chemistry with sterically encumbered allyl ligands. J Organomet Chem. 2003;683:149.

[44] Yu C, Zhang L, Shen Z. Ring-opening polymerization of ε-caprolactone using rare earth tris (4-tert-butylphenolate) s as a single component initiator. Eur Polym J. 2003;39:2035.

[45] Fan L, Zhang L, Shen Z. Characteristics and kinetics of ring-opening polymerization of ε-caprolactone initiated by lanthanide tris (2, 4, 6-trimethylphenolate) s. Polym J. 2004;36(2):91.

[46] Zhang L, Shen Z, Yu C, Fan L. Characteristics and mechanism of L-lactide polymerization by lanthanide 2, 6-dimethylaryloxide. J Mol Catal A Chem. 2004;214:199.

[47] Zhu W, Ling J, Shen Z. Homopolymerization of ε-caprolactone Initiated by a Scandium Aryloxide. Polym Bull. 2004;52:185.

[48] Sanchez-Barba LF, Hughes DL, Humphrey SM, Bochmann M. New bis (allyl)(diketiminato) and tris (allyl) lanthanide complexes and their reactivity in the polymerization of polar monomers. Organometallics. 2005;24:3792.

[49] Yao Y, Ma M, Xu X, Zhang Y, Shen Q, Wong W-T. Synthesis, reactivity, and characterization of amine bis (phenolate) lanthanide complexes and their application in the polymerization of ε-caprolactone. Organometallics. 2005;24:4014.

[50] Nakayama Y, Yasuda H, Yamamoto K, Tsutsumi C, Jerome R, Lecomte P. Comparison of Sm complexes with Sn compounds for syntheses of copolymers composed of lactide and cyclic carbonates and their biodegradabilities. React Funct Polym. 2005;63:95.

[51] Wu Y, Wang S, Qian C, Sheng W, Xie M, Yang G, et al. Homolysis of the Ln–N bond: Synthesis, characterization and catalytic activity of organolanthanide(II) complexes with furfuryl- and tetrahydrofurfuryl-functionalized indenyl ligands. J Organomet Chem. 2005;690:4139.

[52] Li H, Yao Y, Yao C, Sheng H, Shen Q. You have free access to this contentHomo- and copolymerization of 2,2-dimethyltrimethylene carbonate promoted by samarium thiolate derivatives: Novel and versatile initiators. J Polymer Sci. 2005;43:1312.

[53] Patel D, Liddle ST, Mungur SA, Rodden M, Blake AJ, Arnold PL. Bifunctional yttrium(III) and titanium(IV) NHC catalysts for lactide polymerisation. Chem Commun. 2006;(10):1124

[54] Liu X, Shang X, Tang T, Hu N, Pei F, Cui D, et al. Achiral lanthanide alkyl complexes bearing N, O multidentate ligands. Synthesis and catalysis of highly heteroselective ring-opening polymerization of rac-lactide. Organomet. 2007a;26:2747.

[55] Miao W, Li S, Cui D, Huang B. Rare earth metal alkyl complexes bearing N,O,P multidentate ligands: Synthesis, characterization and catalysis on the ring-opening polymerization of l-lactide. J Organomet Chem. 2007a;692:3823.

[56] Miao W, Li S, Zhang H, Cui D, Wang Y, Huang B. Synthesis, characterization, and catalytic activity of divalent organolanthanide complexes with new tetrahydro-2H-pyranyl-functionlized indenyl ligands. J Organomet Chem. 2007;692:2099.

[57] Liu B, Cui D, Ma J, Chen X, Jing X. Synthesis and reactivity of rare earth metal alkyl complexes stabilized by anilido phosphinimine and amino phosphine ligands. Chem Eur J. 2007;13:834.

[58] Yang Y, Li S, Cui D, Chen X, Jing X. Pyrrolide-ligated organoyttrium complexes. Synthesis, characterization, and lactide polymerization behavior. Organometallics. 2007;26:671.

[59] Wang S, Wang S, Zhou S, Yang G, Luo W, Hu N, et al. Mixed ligands supported yttrium alkyl complexes:: Synthesis, characterization and catalysis toward lactide polymerization. J Organomet Chem. 2007;692:4828.

[60] Zhou S, Wang S, Yang G, Li Q, Zhang L, Yao Z, et al. Synthesis, Structure, and Diverse Catalytic Activities of [Ethylenebis(indenyl)]lanthanide(III) Amides on N—H and C—H Addition to Carbodiimides and ε-Caprolactone Polymerization. Organometallics. 2007;26:3755.

[61] Barros N, Mountford P, Guillaume SM, Maron L. A DFT Study of the Mechanism of Polymerization of ε-Caprolactone Initiated by Organolanthanide Borohydride Complexes. Chem Eur J. 2008;14:5507.

[62] Xu X, Xu X, Chen Y, Sun J. Dialkyllanthanide complexes containing new tridentate monoanionic ligands with nitrogen donors. Organometallics. 2008;27:758.

[63] Gao W, Cui D. Rare-earth metal bis (alkyl) s supported by a quinolinyl anilido-imine ligand: synthesis and catalysis on living polymerization of ε-caprolactone. Organometallics. 2008;27:5889.

[64] Carver CT, Monreal MJ, Diaconescu PL. Scandium alkyl complexes supported by a ferrocene diamide ligand. Organometallics. 2008;27:363.

[65] Chen Z-W, Dou J. U.S. Pat. Appl. Publ., US 2009315444 A1 20091224 2009.

[66] Mahrova TV, Fukin GK, Cherkasov AV, Trifonov AA, Ajellal N, Carpentier J-F. Yttrium complexes supported by linked bis (amide) ligand: synthesis, structure, and catalytic activity in the ring-opening polymerization of cyclic esters. Inorg Chem. 2009;48:4258.

[67] Luo Y, Wang X, Chen J, Luo C, Zhang Y, Yao Y. Mono(amidinate) rare earth metal bis(alkyl) complexes: Synthesis, structure and their activity for l-lactide polymerization. J Organomet Chem. 2009;694:1289.

[68] Otero A, Fernandez-Baeza J, Lara-Sanchez A, Alonso-Moreno C, Marquez-Segovia I, Sanchez-Barba LF, et al. Ring-Opening Polymerization of Cyclic Esters by an Enantiopure Heteroscorpionate Rare Earth Initiator. Angew Chem. 2009;121:2210.

[69] Otero A, Lara-Sanchez A, Fernandez-Baeza J, Martinez-Caballero E, Marquez-Segovia I, Alonso-Moreno C, et al. New achiral and chiral NNE heteroscorpionate ligands. Synthesis of homoleptic lithium complexes as well as halide and alkyl scandium and yttrium complexes. Dalton T. 2010;39:930

[70] Miao H, Wang S, Zhou S, Wei Y, Zhou Z, Zhu H, et al. Synthesis, characterization of some organolanthanide complexes containing 2-pyridylmethyl substituted fluorenyl ligand and catalytic activity of organolanthanide(II) complexes. Inorg Chim Acta. 2010;363:1325.

[71] Luo Y, Li W, Lin D, Yao Y, Zhang Y, Shen Q. Lanthanide Alkyl Complexes Supported by a Piperazidine-Bridged Bis(phenolato) Ligand: Synthesis, Structural Characterization, and Catalysis for the Polymerization of l-Lactide and rac-Lactide. Organometallics. 2010;29:3507.

[72] Yang J, Xu P, Luo Y. Bimetallic Rare Earth Alkyl Complexes Bearing Bridged Amidinate Ligands: Synthesis and Activity for L-Lactide Polymerization. Chin J Chem. 2010;28:457.

[73] Jaroschik F, Bonnet F, Le Goff X-F, Ricard L, Nief F, Visseaux M, et al. Synthesis of samarium (ii) borohydrides and their behaviour as initiators in styrene and ε-caprolactone polymerisation. Dalton T. 2010;39:6761

[74] Buchard A, Platel RH, Auffrant A, Le Goff XF, Le Floch P, Williams CK. Iminophosphorane neodymium (III) complexes as efficient initiators for lactide polymerization. Organometallics. 2010;29:2892.

[75] Clark L, Cushion MG, Dyer HE, Schwarz AD, Duchateau R, Mountford P. Dicationic and zwitterionic catalysts for the amine-initiated, immortal ring-opening polymerisation of rac-lactide: facile synthesis of amine-terminated, highly heterotactic PLA. Chem Commun. 2010;46:273.

[76] Mazzeo M, Lamberti M, DAuria I, Milione S, Peters JC, Pellecchia C. Phosphido-diphosphine pincer group 3 complexes as efficient initiators for lactide polymerization. J Polym Sci A Polym Chem. 2010;48:1374.

[77] Otero A, Lara-Sanchez A, Fernandez-Baeza J, Alonso-Moreno C, Marquez-Segovia I, Sanchez-Barba LF, et al. Heteroscorpionate rare-earth initiators for the controlled ring-opening polymerization of cyclic esters. Dalton T. 2011;40:4687

[78] DAuria I, Mazzeo M, Pappalardo D, Lamberti M, Pellecchia C. Ring-opening polymerization of cyclic esters promoted by phosphido-diphosphine pincer group 3 complexes. J Polym Sci A Polym Chem. 2011;49:403.

[79] Zhou S, Wu S, Zhu H, Wang S, Zhu X, Zhang L, et al. Synthesis, structure and catalytic activity of alkali metal-free bent-sandwiched lanthanide amido complexes with calix [4]-pyrrolyl ligands. Dalton T. 2011;40:9447

[80] Hao J, Li J, Cui C, Roesky HW. Synthesis and Characterization of Heterobimetallic Oxo-Bridged Aluminum–Rare Earth Metal Complexes. Inorg Chem. 2011;50:7453.

[81] Hou W, Chen J, Yan X, Shi Z, Sun J. A single active site metal center of neodymocene chloride for the ring-opening polymerization of ε-caprolactone. J Appl Polym Sci. 2012;123:1212.

[82] Zhao W, Wang Y, Liu X, Cui D. Facile synthesis of fluorescent dye labeled biocompatible polymers via immortal ring-opening polymerization. Chem Commun. 2012;48:4483.

[83] Du G, Wei Y, Zhang W, Dong Y, Lin Z, He H, et al. Bis(imino)diphenylamido rare-earth metal dialkyl complexes: synthesis, structure, and catalytic activity in living ring-opening ε-caprolactone polymerization and copolymerization with γ-butyrolactone. Dalton T. 2013;42:1278

[84] Wang Y, Lei Y, Chi S, Luo Y. Rare earth metal bis(silylamide) complexes bearing pyridyl-functionalized indenyl ligand: Synthesis, structure and performance in the living polymerization of L-lactide and rac-lactide. Dalton T. 2013;42:1862

[85] Li M, Hong J, Chen Z, Zhou X, Zhang L. Synthesis, structure and reactivity of dinuclear rare earth metal bis (o-aminobenzyl) complexes bearing a 1, 4-phenylenediamidinate co-ligand. Dalton T. 2013;42:8288

[86] Bennett SD, Core BA, Blake MP, Pope SJA, Mountford P, Ward BD, et al. Chiral lanthanide complexes: coordination chemistry, spectroscopy, and catalysis. Dalton T. 2014;43:5871

[87] Mou Z, Liu B, Liu X, Xie H, Rong W, Li L, et al. Efficient and Heteroselective Heteroscorpionate Rare-Earth-Metal Zwitterionic Initiators for ROP of rac-Lactide: Role of σ-Ligand. Macromolecules. 2014;47:2233.