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Stereoselective Polymerization

C_3-Symmetric Lanthanide Tris(alkoxide) Complexes Formed by Preferential Complexation and Their Stereoselective Polymerization of *rac*-Lactide**

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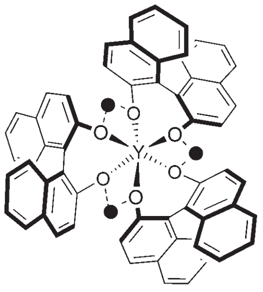
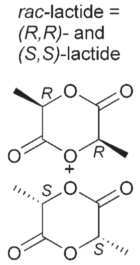
A great number and variety of homogeneous lanthanide catalysts are now used in industry and academia as low-cost, low-toxicity, Lewis acidic, and coordination catalysts.[1] In the search for new asymmetric catalysts, chiral C_3-symmetric complexes are emerging as interesting competitor systems to the ubiquitous C_2-symmetric systems.[2] Trivalent lanthanide cations are obvious candidates for the development of catalysts with threefold symmetry. However, the lability and the weak coordination geometry preferences of Ln^{III} centers make the synthesis of enantiopure lanthanide coordination compounds a difficult goal. One approach is to use pre-resolved, chiral polydentate ligands such as C_3-symmetric tris(oxazoline) adducts.[3] Another involves the coordination of three enantiopure, C_2-symmetric, biaryl ligands to make a homochiral $[LnL_3]$ complex.[4] The most successful asymmetric and bifunctional lanthanide catalysts are based on $Li_3[Ln(L)_3]$ (L = chiral enantiopure 1,1′-binaphtholate, binolate).[5] This latter class includes, to the best of our knowledge, the only example of spontaneous resolution of three molecules of a racemic ligand around a lanthanide center to date: the reaction of $[Y\{N(SiMe_3)_2\}_3]$ with *rac*-NaHbinol affords an equal mixture of the heterobimetallic (*RRR*)- and (*SSS*)-$Na_3[Y(binol)_3]$ complexes **A** (binol = 1,1′-bi-2-naphthyl). However, all other lanthanide/alkali-metal combinations give different combinations of (*RRS*)- and (*SSR*)- complexes.[6]

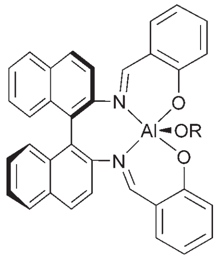
The polymerization of the biorenewable monomer *rac*-lactide (**B**) into the biodegradable polymer polylactide (PLA) provides an interesting challenge for new chiral catalysts,[7] since the physical properties of the lactide polymers are highly dependent on the polymer stereochemistry. It has been shown that when independently synthesized poly[(*R*)-(lactic acid)] and poly[(*S*)-(lactic acid)] are mixed, the chains cocrystallize to form a stereocomplex with a melting point of up to 230 °C, which is 50 °C higher than that of poly[(*S*)-(lactic acid)] (PLLA or poly[L-(lactic acid)]) alone.[8] However, the enantiopure *R*,*R* monomer is much more expensive than the *rac*-lactide.



A ● = Na(thf)$_2$



B



C

Thus, a one-pot catalytic process in which a racemic mixture of a chiral catalyst polymerizes (*R*,*R*)-(D-lactide) and (*S*,*S*)-(L-lactide) monomers separately into two, enantiomerically pure, isotactic polymer chains, which can then mix to form a stereocomplex, is an important goal.[9] Currently, highly selective, single-site catalysts based on the Al-salen framework **C** have been shown to promote the formation of polylactide with a high stereoblock content, in which the long, alternating chains of $(RRRRRR)_n$- and $(SSSSSS)_n$- PLA are formed, which subsequently form a stereocomplex polylactide with melting points up to 196 °C.[10] Both single-site [LLn(OR)] and homoleptic $[M(OR)_3]$ lanthanide alkoxides have been shown to be excellent initiators for the synthesis of PLA, but the products are normally heterotactic.[11]

Herein we show how a racemic mixture of a bidentate ligand L, which contains a single chiral carbon center, is resolved into a mixture of two homochiral C_3-symmetric complexes upon lanthanide complexation to form (*RRR*)-$[LnL_3]$ and (*SSS*)-$[LnL_3]$. The utility of this spontaneous resolution is demonstrated by the use of these chiral complexes as initiators for the formation of high-melting, stereoregular polylactides. HL is a chiral alcohol that is derived from a cheap, commercially available chiral (racemic or enantiopure) epoxide.

The colorless product **1** (HL, $(tBu)_2P(O)CH_2CH(tBu)OH$) was obtained by treatment of a mixture of racemic 3,3-dimethylepoxybutane and *n*-butyllithium with di-*tert*-

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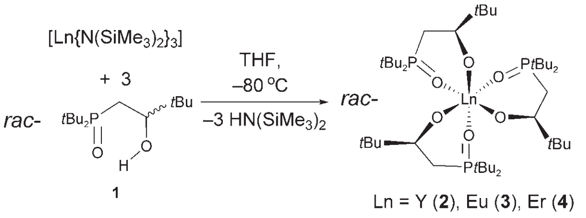
butylphosphine, and subsequent oxidation with peroxide. Treatment of [Ln{N(SiMe$_3$)$_2$}$_3$] (Ln = Y, Eu, Er) with three equivalents of **1** in THF at low temperature afforded [LnL$_3$] [Ln = Y (**2**), Eu (**3**), and Er (**4**)] in excellent yield after recrystallization from pentane [Eq. (1)]. Complex **2** is colorless, **3** is pale yellow, and **4** is pale pink. Chiral enantiopure **1** (**1a**) was also made from the *R* epoxide and used in the synthesis of diastereomerically pure [Y{(*R*)-L}$_3$],(i.e. (*RRR*)-[YL$_3$], **2a**, denoted *ep*-YL$_3$ herein for convenience).



(1)

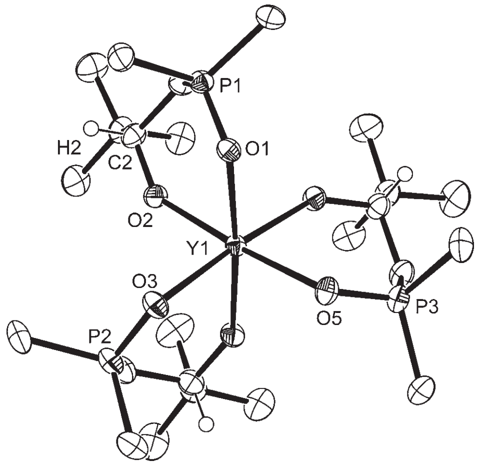


Figure 1. Displacement ellipsoid drawing of **2** (isostructural with **3** and **4**) 50% probability ellipsoids. P*t*Bu Me groups and all hydrogen atoms except the chiral CH group are omitted. Average distances [Å]: **2** Y–OR 2.1481, Y–OP2.3749; **3** Eu–OR 2.1981, Eu–OP 2.431; **4** Er–OR 2.1512, Er–OP 2.3675.

The ^{1}H and ^{31}P{^{1}H} NMR spectra of solutions of **2a** show a single ligand environment consistent with a single C_3-symmetric (*RRR*)-[YL$_3$] complex (see the Supporting Information). NMR spectra of solutions of **2** show that this homochiral isomer is present in 80% (although now as a mixture of *RRR*- and *SSS*- YL$_3$), and contain additional, minor set of resonances, which correspond to the diastereomer (*RRS*)-/(*SSR*)-[LnL$_3$], present in about 20% of the total yield. These samples are referred to as *rac*-YL$_3$ here for convenience. To the best of our knowledge, this is the only configurationally stable, monometallic lanthanide complex that is preferentially formed as a single diastereomer upon complexation.

The C_3-symmetric chirality of **2** is confirmed by a single-crystal X-ray diffraction study; Figure 1 shows the *RRR* diastereomer.[12] The paramagnetic complexes **3** (Eu) and **4** (Er) are isostructural with **2** (crystal structure data are shown in the Supporting Information), except for a small degree of disorder in one ligand, arising from a "contamination" by a ligand of the opposite chirality. Modeling studies of this disorder component show that 6.6% of the ligands in the structure of **4** are of the opposite chirality, and 10% in the structure of **3**. These three metals may all be regarded as small lanthanide cations (six-coordinate r_{cov} = 1.040 (Y), 1.087 (Eu), and 1.030 Å (Er)).[13]

The spontaneous formation of this racemic mixture of chiral complexes prompted us to look for asymmetric reactions that this complex might catalyze. The conversion of a racemic mixture of lactide monomer into a racemic mixture of two homochiral lactide polymers presents a suitable challenge to test the catalytic ability of these complexes. In 2004, Carpentier and co-workers demonstrated the first example of a Group 3 complex that rapidly polymerized *rac*-lactide into predominantly heterotactic PLA using a single-site Y^{III} initiator with a bulky bisphenolato ancillary ligand,[14] and more recently up to 71% isotactically enriched PLA from an enantiopure single-site Y^{III} initiator with a bulky C_2-symmetric diamido ligand.[15] Thus it is of interest to identify if these *rac*-[LnL$_3$] complexes can firstly act as stereoselective initiators, and, secondly, if a tris(ligand) complex can provide a sufficiently controlling environment for tacticity control in the initiation of the polymerization reaction.

The data from a series of reactions of the racemic [YL$_3$] initiator **2** and *rac*-lactide are collated in Table 1. Even at −18 °C, the polymerization is rapid and controlled (also see the Supporting Information). The polymer weights are high,[16] and the polydispersities (PDI) of the polymers are narrow. More than half of the monomer is consumed after four minutes, representing a very rapid polymerization. The melt polymerization also proceeds smoothly, but with poorer PDI control (full polymerisation data for all of these complexes are contained in the Supporting Information). Mass spectral analysis of the polymer indicates that each chain is terminated by a ligand L molecule (see the Supporting Information).

Table 1: Polymerization of *rac*-lactide using **2**.

Entry	Cat./monomer/solvent [a]	T [°C]	t [min]	Conv.[b] [%]	M_n[c] [g mol^{-1}]	M_w/M_n[d]	P_i[e]
1	1:100:10000	−18	0.33	5	2300	1.91	
2	1:100:10000	−18	2	35	47000	1.53	
3	1:100:10000	−18	4	60	80000	1.42	0.75
4	1:100:10000	−18	8	98	146000	1.38	0.78
5	1:200:10000	−18	5	60	130000	1.24	0.83
6	1:200:10000	−18	10	98	200000	1.23	0.81

[a] Solvent = dichloromethane. [b] Conversion of LA monomer (([LA]$_0$ −[LA])/[LA]$_0$). [c] Measured by GPC; values based on polystyrene standards, corrected by the Mark–Houwink equation [M_n(obsd) = 0.58M_n(GPC)].[17] [d] Polydispersity index (M_w/M_n) measured by GPC. [e] Probability of forming a new *i* dyad, determined by ^{1}H NMR spectroscopy [21].

The most notable property of these polymers is their very high degree of crystallinity and stereoregularity. The formation of a predominantly isotactic polymer, from the polymerization by *rac*-**2** of the D- and L-lactide monomers in parallel, is confirmed by ^{1}H and ^{13}C NMR spectroscopy.[10b]

The ^{1}H NMR spectrum of an isotactic polymer chain should resemble that of poly-L-lactide, with a single C*H*Me resonance (if the chains are infinitely long). If the polymerization is less selective, or if transesterification becomes a competing reaction at higher conversions, the original stereochemical control will be lost and the proton-decoupled spectra will show the different CH environments. Figure 2 shows the proton-decoupled methine region of the ^{1}H NMR spectra of three polylactide samples for comparison.[18]

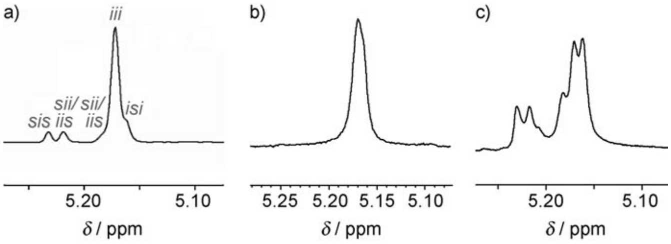


Figure 2. Methine region of homonuclear decoupled ^{1}H NMR spectra of a) highly isotactic PLA (Table 1 , entry 6) with tetrad resonances arising from insertion errors assigned; b) isotactic PLLA made from L-lactide by *ep*-[YL_3] initiator (0.5 %, CH_2Cl_2); c) atactic PLA made from by [$Y\{N(SiMe_3)_2\}_3$] (5 %, CH_2Cl_2, 1 h).

Sample (a) in Figure 2 shows the dominance of the *iii* tetrad in the polymer made by *rac*-[YL_3] from *rac*-lactide at complete conversion, which confirms the stereospecific control of the polymerization of D- and L-lactide into separate, isotactic chains. The smaller tetrad resonances are characteristic of the defects in the polymer. The ratio of the defect sizes is 1:2:1:1, corresponding to *iis*:*isi*:*sis*:*sii*. This ratio is only possible for a chain of the stereochemistry -*RRRRRRSSRRRRRR*- (and vice versa) containing single insertion defects. This type of polymer is most able to form a stereocomplex upon annealing to mix the chains together so the formation of high-melting polymers may be possible for this system.

If the polymer chains were stereoblock (of the form -*RRRRRRSSSSSSSSRRRR*-), the ratio of the defect resonances would be 1:1:1, corresponding to *iis*:*isi*:*sii*, and the *sis* resonance would be absent. This type of polymer would have arisen from a lower degree of stereocontrol, although it is still possible to form a stereocomplex from such a polymer.

For comparison, spectrum (b) is of poly-L-lactide polymerized by **2a** ((*RRR*)-[YL_3]) and (c) of poly-D,L-lactide, polymerized by [$Y\{N(SiMe_3)_2\}_3$]; spectrum (c) is comparable with that of poly-D,L-lactide polymerized with tin octanoate (see the Supporting Information).

It is interesting to compare the formation of isotactic polymers by complex **2** with the recent results reported by Davidson and co-workers, who showed that a *rac*-C_3-symmetric complex of a tetradentate aryloxide ([$Ge(OiPr)\{(O\text{-}Me_2\text{-}2,4\text{-}C_6H_2\text{-}6\text{-}CH_2)_3N\}$]), which interconverts rapidly between *P* and *M* isomers, affords highly heterotactic PLA.[19]

Analysis of the kinetics of the reaction suggests that only one ligand is displaced upon initiation of the polymerization, forming an [L_2Ln-O-P-L] propagating species (P = growing polymer chain), so the [L_2Ln] environment retains a degree of asymmetry so that further stereoselective monomer insertions can take place. This result suggests that even the *RRS* isomer impurity might give equally good stereocontrol in the polymerization if the *S* ligand was displaced by the initial monomer insertion.

In conclusion, the racemic phosphine oxide/alkoxide ligand HL is very effectively resolved into the diastereomeric *RRR*- and *SSS*-[LnL_3] complexes of the lanthanide trications, Y^{III}, Eu^{III}, or Er^{III} to afford a racemic mixture of homochiral, C_3-symmetric [LnL_3] complexes. The complexes provide a new class of very active initiators for the polymerization of *rac*-lactide into highly isotactic polylactic acid with retention of stereochemical control even at high monomer conversions and high molecular weights. This work also demonstrates that single site catalysts with one monodentate initiating ligand are not necessarily required to achieve good stereochemical control in polymerization. Work is under way to optimize the conversion of these polymer mixtures into stereocomplex PLA and to identify other organic transformations that these C_3-symmetric Lewis acid complexes can catalyze.

Experimental Section

HL was synthesized by a modification of the method of Cross et al.[20] ^{1}H NMR (C_6D_6): $\delta = 1.1$ (18 H, dd, $^{2}J_{PH} = 4.5$ Hz, $PC(CH_3)_3$); 1.15 (9 H, s, CCH_3); 1.7–1.9 (2 H, m, CH_2); 4.0–4.1 ppm (1 H, m, CH). ^{31}P NMR (C_6D_6): $\delta = 63.7$ ppm, (C_7D_8): $\delta = 63.8$ ppm. M.p.: 98 °C. Analysis (%) found: C 64.25, H 11.60; calcd. C 64.18, H 11.54.

[YL_3] (**2**): A solution of HL in THF (707 mg, 2.7 mmol, 10 mL) was added to a solution of [$Y\{N(SiMe_3)_2\}_3$] in THF (508 mg, 0.89 mmol, 10 mL) at −78 °C, was allowed to warm slowly to room temperature overnight with stirring. Workup afforded colorless **2**. Yield 705 mg (90 %). Integration of the resonances of the spectra of bulk **2** shows the major:minor ratio was 80:20. The pure *RRR*-diastereomer **2a** was synthesized as above, but by using enantiopure *R*-HL instead of racemic HL. ^{1}H NMR (C_6D_6) major diastereomer (minor diastereomer in parentheses): $\delta = 4.22$ (m, 3 H, CH); 1.78 (m, 6 H, CH_2); 1.24 (1.23) (d, 27 H, $^{2}J_{PC} = 11.4$ Hz, P*t*Bu); 1.19 (1.20) (s, 27 H, C*t*Bu); 1.14 ppm (1.12) (d, 27 H, $^{2}J_{PH} = 11.4$ Hz, P*t*Bu). ^{31}P NMR (C_6D_6): $\delta = 68.9$ ppm (68.6, 67.6). Analysis (%) found: C 57.48, H 10.25; calcd. C 57.78, H 10.39.

[EuL_3] (**3**): Yield 440 mg (94 %).^{1}H NMR (C_6D_6): $\delta = -7.6$ (3 H, CH); −6.1 (27 H, *t*Bu); −4.6 (3 H, CH_2); −1.4 (3 H, CH_2); 0.4 (27 H, *t*Bu); 9.1 ppm (27 H, *t*Bu). Analysis (%) found: C 53.78, H 9.48; calcd. C 53.9, H 9.6.

[ErL_3] (**4**): Yield 720 mg (93 %). ^{1}H NMR (C_6D_6): $\delta = -9.15$ (6 × *t*Bu H); 24.14 ppm (3 × *t*Bu H). Analysis (%) found: C 52.90, H 9.61; calc. C 53.0, H 9.5.

Polymerizations: Monomer (500 mg, 3.47 mmol) dissolved in the volume of solvent according to the table entry was addded to a Schlenk flask and the solution stirred at the temperature given in the table. A solution of initiator (**2**, **3**, or **4**: 2.5 mg (0.5 % initiator) or 5 mg (1 % initiator)) was added via cannula, according to the table entries. Aliquots were removed via syringe and quenched/precipitated with MeOH after the stated time. The resulting polymer was dissolved in dichloromethane, filtered through silica gel 60, and dried. The yield for each completed polymerization was quantitative.

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[12] Crystallographic data for **2**: $C_{43}H_{92}Cl_2O_6P_3Y$, $M = 957.89$, crystal dimensions $0.43 \times 0.24 \times 0.12$ mm^3, orthorhombic, space group $Pca2_1$, $a = 20.186(3)$, $b = 13.426(2)$, $c = 20.202(3)$ Å, $V = 5475.1(14)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.162$ g cm^{-3}, $\mu = 1.29$ mm^{-1}, $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), $T = 150(2)$ K. 31313 data (10864 unique, $R_{int} = 0.036$, $\theta < 27.6°$), ω scans, $wR_2 = 0.055$, $R = 0.027$, $S = 0.95$ for 523 parameters. Flack parameter $= -0.027(2)$. Final residual electron density extrema were 0.38 and -0.26 e Å^{-3}. CCDC 681262 (**1**), 681263 (**2**), 681264 (**3**), 681265 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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