

Ring-Opening Polymerization of Cyclic Esters by an Enantiopure Heteroscorpionate Rare Earth Initiator**

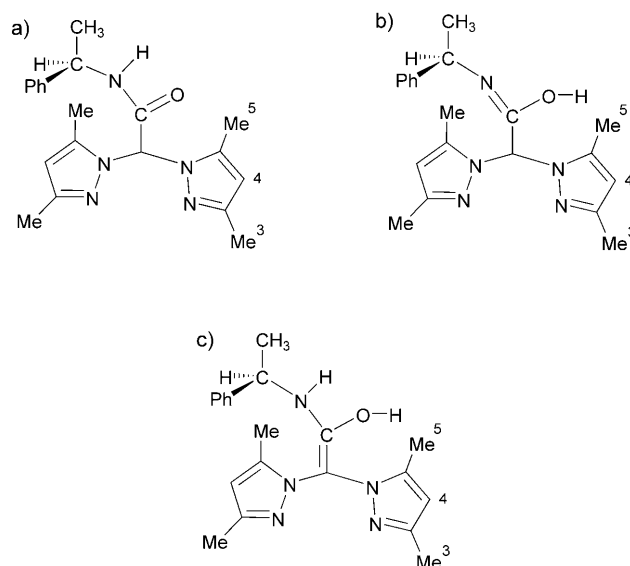
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Polyesters have been of great interest over the last three decades in applications in the medical field owing to their biodegradable, biocompatible, and permeable properties.^[1] Ring-opening polymerization (ROP) of cyclic esters has been the major method employed to synthesize this type of polymer.^[2] Of the wide variety of polyesters made for this way, poly-(D,L)-lactide is particularly significant because of the presence of a chiral carbon atom in the repeating unit.^[3] The stereochemical structure has a strong influence on the physical and mechanical properties of the resulting polymeric material. Polymers with a high degree of crystallinity have properties that make them useful for applications ranging from degradable packaging to surgical implants for drug delivery.^[4] Many efforts have been made in the last decade towards the preparation of discrete, well-defined single-site catalysts for controlling the stereochemistry of lactide polymerization.^[5] Among a wide variety of initiators, rare earth compounds and, in particular oxo isopropoxide derivatives, have proved to be highly efficient initiators for the living ring-opening polymerization of lactides.^[6] However, compared to other metals,^[7] structurally well-characterized rare-earth-metal complexes that initiate controlled ring-opening polymerization of lactides are scarce.^[2] Chiral amide yttrium and rare earth compounds have been described as active initiators for the ring-opening polymerization of *rac*-lactides, yielding isotactic-enriched polylactides.^[5c-d] However, the design of chiral Lewis acidic catalysts capable of promoting enantio-morphic site control requires a more detailed understanding of the nature of tacticity control in polylactides.^[8]

Herein, we describe our first results in the controlled and enantioasymmetric^[9] polymerization of *rac*-lactide by means of an enantiopure heteroscorpionate rare earth compound. Anionic heteroscorpionate ligands derived from bis(pyrazol-1-yl)methanes that containing an anionic “arm” group are

one of the most interesting polydentate nitrogen-containing donor ligands.^[10] These intriguing heteroscorpionate ligands present different types of functional groups, which successfully broadens the scope of their applications.^[11]

Following a simple and efficient synthetic methodology,^[12] a neutral enantiopure acetamide compound, namely (*S*)-(-)-*N*- α -methylbenzyl-2,2-bis(3,5-dimethylpyrazol-1-yl)acetamide ((*S*)-mbpamH; **1**) was isolated (see Experimental Section). From such a reaction, three tautomers are possible (Scheme 1). However, ¹H NMR spectroscopic data indicate that only tautomer (a) is present.



Scheme 1. Possible tautomers for compound **1**.

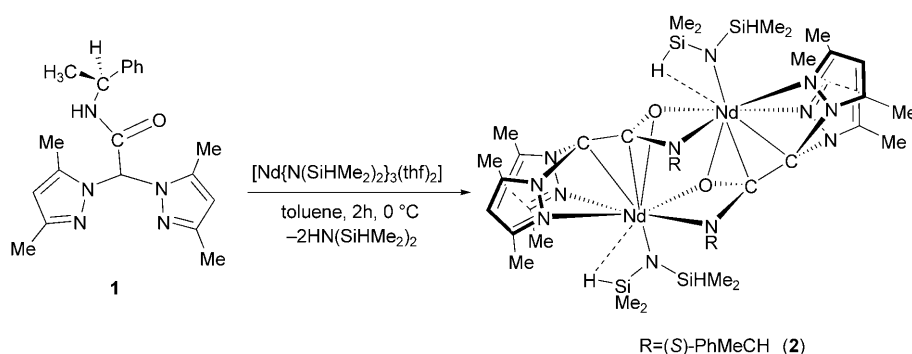
One effective route to prepare fnd metal compounds involves protonolytic reaction of metal alkyl or amide precursors with the protonated form of the desired ancillary ligand. Following this method, the versatile precursor [Nd{N-(SiHMe₂)₂}₃(thf)₂]^[13] has been chosen as starting material for the synthesis of the first enantiopure heteroscorpionate rare earth metal complex **2** (Scheme 2). An unexpected double deprotonation^[14] of the enantiopure acetamide results in a dianionic heteroscorpionate pseudoallyl ligand coordinated to the neodymium center. To our knowledge, this is the first example of a C–H activation of the bridge methine group by deprotonation and subsequent coordination to the metal center for this class of heteroscorpionates.

The ¹H and ¹³C{¹H} NMR spectra of **2** exhibit strong paramagnetic shifts, with the SiH proton signals appearing

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Scheme 2. Synthesis of the enantiopure neodymium complex **2**.

upfield at $\delta = -15.38$ and -16.48 ppm, which is evidence for a strong Nd $\cdots$ H-Si agostic interaction.

The structure of compound **2** determined by single-crystal X-ray diffraction (Figure 1), which shows the (*S,S*)-enantiomer as a dimeric structure in which two neodymium atoms are linked by two oxygen and two nitrogen atoms from acetamido groups. Additionally, each neodymium atom is bonded to

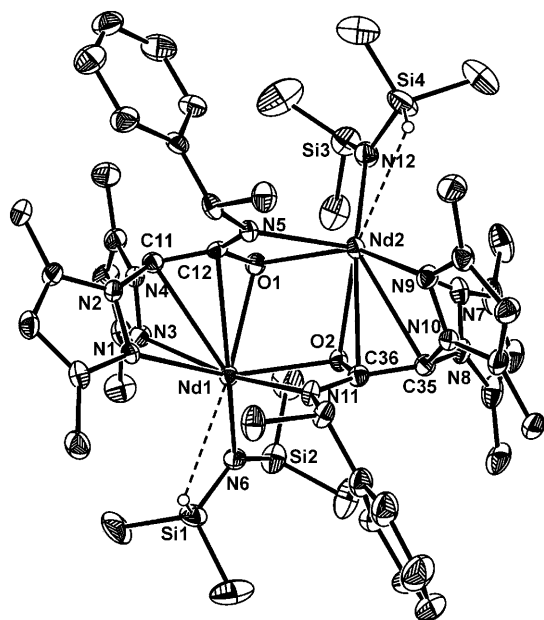


Figure 1. The structure of complex **2**. Thermal ellipsoids are set at 30% probability, and hydrogen atoms (except those attached to Si1 and Si4) are omitted for clarity.

two nitrogen atoms of pyrazole rings and to a π -pseudoallyl moiety (Nd1 is bound to C11-C12-O1, and Nd2 to C35-C36-O2), and to one nitrogen atom of the amide ligand. The peculiar bonding features of the N(SiHMe₂)₂ ligands comprising distinct Nd-N-Si angles (Nd1-N6-Si1: 104.1(3)°, Nd1-N6-Si2: 125.0(3)°) and relatively short Nd-Si contacts (3.200(3)–3.164(2) Å) are indicative of Nd $\cdots$ H-Si β -agostic interactions.^[13] The Nd–C bond lengths of 2.721(7) to 2.925(7) compare well with those observed in other neutral neodymium complexes^[15] in which the Nd–C π interaction exists

unambiguously. It is worth noting that there is a strong π interaction of the carbon atoms bridging pyrazole rings (C11 and C35) with the neodymium atoms Nd1 and Nd2, respectively (see Supporting Information).

To date, few examples of rare earth amides have been described as being successful catalysts for the ROP of cyclic esters.^[16] Under mild conditions (50 °C) with a ratio of *rac*-lactide/**2** of 200, 52% monomer conversion occurs in 15 h, with $M_n = 23\,000$ and a polydispersity index

PDI = 1.09. The molecular weight of the polymer increases linearly with the extent of conversion (Figure 2a), which indicates that a good control of polymerization is achieved. The low polydispersities obtained (PDI = 1.05–1.20) support a controlled propagation, and suggest that transesterifications take place to a small extent and that the initiation step is not very fast with respect to propagation.

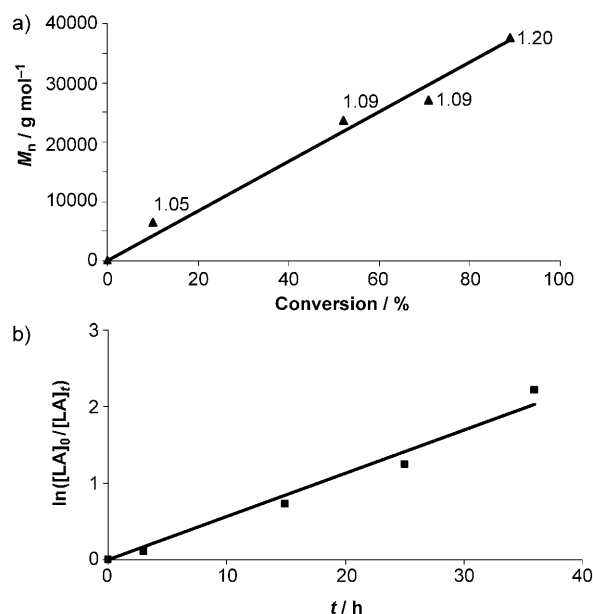


Figure 2. a) M_n vs *rac*-lactide conversion, with polydispersity index values indicated (linear fit, $R = 0.992$). b) Semilogarithmic plot of relative *rac*-lactide (LA) concentration against time. $k_{app} = 1.55 \times 10^{-5} \text{ s}^{-1}$ (linear fit, $R = 0.988$).

The homopolymerization by **2** strictly follows first-order kinetics with respect to racemic lactide (*rac*-LA) monomer concentration ($k_{app}(\text{rac-LA}) = 1.55 \times 10^{-5} \text{ s}^{-1}$) for the ratio of concentrations of lactide and of complex that were investigated (Figure 2b). End-group analysis indicates that the polymers obtained with the initiator **2** contain -NH(SiMe₃)₂ termini, which supports the proposition that the polymerization follows a nucleophilic route. Initiation may be by the transfer of an amide ligand to the monomer, with cleavage of the acyl oxygen bond and formation of a metal alkoxide

propagating species.^[17] Homonuclear-decoupled ¹H NMR spectra of the methine region of the polylactide samples at low conversion (10%) show a high enantiomeric enrichment in the polymer ($P_m=0.61$), although at high conversions a decrease in the probability of *meso* linkages was observed ($P_m=0.29$ at 52% conversion). Pronounced optical rotation is observed for the polymers, namely $[\alpha]_D=-85.3^\circ$ ^[15] and -16.2° for polylactides obtained at 10% and 52% conversion, respectively. The negative values are consistent with a preferential polymerization of L-lactide. Thus, complex **2**, being an enantiopure compound, exhibits a homosteric^[9] preference, polymerizing preferentially the L-lactide from the racemic mixture. This result is consistent with enantioasymmetric^[9] polymerization, and thus requires an enantiomorphic site-control mechanism. Alternative incorporation of L and D-lactide at high conversions is explained by the relative increase of the other isomer in the monomer pool, although one cannot rule out the possibility of a conflict between chain-end and site-control mechanisms, which has been observed in olefin polymerization.^[18]

In summary, we report the synthesis and characterization of the first enantiopure heteroscorpionate rare earth compound by double deprotonation of an enantiopure acetamide derivative. This process is the first example of activation of a C–H bridging methine group with the subsequent coordination of the carbon atom in this class of heteroscorpionates. The neodymium complex acts as an efficient single-site initiator for the controlled ring-opening polymerization of *rac*-lactide, which shows a homosteric preference for one of the two enantiomers at low conversions. Further studies are being carried out to thoroughly examine the effect of changes both to the metal center and the substituents of the ligand framework on the polymerization behavior of the complexes, as well as employing complex **2** for the synthesis of new polyester architectures.

Experimental Section

1: In a 250 mL Schlenk tube, bis(3,5-dimethylpyrazol-1-yl)methane^[19] (2.00 g, 9.79 mmol) was dissolved in dry THF (70 mL) and cooled to -70°C . A 1.6 M solution of *n*BuLi (6.12 mL, 9.79 mmol) in hexane was added, and the suspension was stirred for 1 h. The reaction mixture was allowed to warm to -10°C , and the resulting yellow suspension was added dropwise to a cool (-10°C) solution of (*S*)-(-)-*N*- α -methylbenzylisocyanate (1.44 g, 9.79 mmol). The reaction mixture was stirred for 1 h and was allowed to warm to room temperature. The product was hydrolyzed by adding saturated aqueous NH_4Cl (15 mL) dropwise. The organic layer was extracted, dried over MgSO_4 overnight, and filtered, and the solvent was removed under vacuum to give the product as yellow oil. The oil was treated with a mixture of THF/hexane to give **1** as white solid. Yield: 90%. $[\alpha]_D^{25}=-23.7^\circ\text{deg cm}^3\text{g}^{-1}\text{dm}^{-1}$ ($c=0.10\text{ g cm}^{-3}$, THF). ¹H NMR (500 MHz, CDCl_3 , 297 K): $\delta=8.15$ (brs, 1H, (PhCHCH₃)NHCO), 7.27–7.19 (m, 5H, (PhCHCH₃)NHCO), 6.62 (s, 1H, CH), 5.77, 5.72 (s, 2H, H^{4,4'}), 5.11 (m, 1H, (PhCHCH₃)NHCO), 2.30, 2.16 (s, 6H, Me^{5,5'}), 2.12 (s, 6H, Me^{3,3'}), 1.46 ppm (d, ³*J*_{HH}=6.9 Hz, 3H, (PhCHCH₃)NHCO). ¹³C{¹H} NMR (125 MHz, CDCl_3 , 297 K): $\delta=163.6$ [(PhCHCH₃)NHCO], 149.1, 149.0, 141.3, 141.2 (C^{3,3'} or ^{5,5'}), 143.6–126.5 [(PhCHCH₃)NHCO], 107.0, 106.9 (C^{4,4'}), 71.9 (CH), 49.9 [(PhCHCH₃)NHCO], 22.2 [(PhCHCH₃)NHCO], 13.6, 13.7 (Me^{3,3'}), 11.1, 11.0 ppm (Me⁵). Elemental analysis (%) calcd for $\text{C}_{20}\text{H}_{25}\text{N}_5\text{O}$: C 68.35, H 7.17, N 19.92; found: C 68.65, H 7.24, N 19.25.

2: In a 100 mL Schlenk tube, $[\text{Nd}(\text{N}(\text{SiHMe}_2)_2)_3(\text{thf})_2]$ (0.40 g, 0.58 mmol) and **1** (0.21 g, 0.58 mmol) were suspended in toluene (80 mL). The resulting solution was stirred for 2 h at 0°C . The solvent was removed under vacuum, and the solid was washed with hexane, and recrystallized from a mixture of toluene/hexane to give blue crystals. Yield 80%. $[\alpha]_D^{25}=-48.7^\circ\text{deg cm}^3\text{g}^{-1}\text{dm}^{-1}$ ($c=0.10\text{ g cm}^{-3}$, toluene). ¹H NMR (500 MHz, C_6D_6 , 297 K): $\delta=10.51$, 9.75 (brs, 12H, SiCH₃), 6.93, 6.91 (s, 2H, H^{4,4'}), 2.35, 1.59 (brs, 12H, Me^{3,3',5,5'}), -15.38 , -16.48 ppm (SiH); remaining signals ($\delta=19.76$, 11.53, 10.05 ppm) could not be assigned. ¹³C{¹H} NMR (125 MHz, C_6D_6 , 297 K): $\delta=173.8$, 167.0, 163.4, 160.3, 147.1, 135.1, 130.2, 123.1, 121.7, 74.3, 26.9, 26.2, 26.3, 25.9, 21.3, 20.2, 15.3, 1.4 ppm. Elemental analysis (%) calcd for $\text{C}_{48}\text{H}_{74}\text{N}_{12}\text{Nd}_2\text{O}_2\text{Si}_4$: C 46.05, H 5.96, N 13.42; found: C 46.58, H 6.24, N 13.01.

CCDC-713430 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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