Highly active and stereoselective zirconium and hafnium alkoxide initiators for solvent-free ring-opening polymerization of *rac*-lactide†‡

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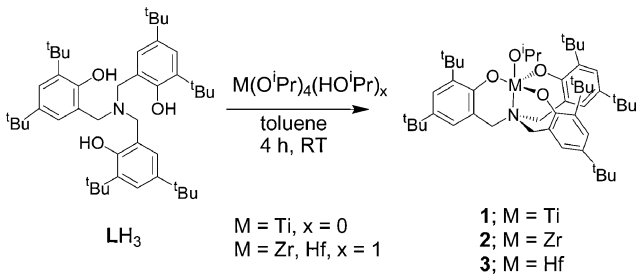
Under solvent-free conditions (at 130 °C), zirconium and hafnium amine tris(phenolate) alkoxides are extremely active, well-controlled, single-site initiators for the ring-opening polymerization of *rac*-lactide, yielding highly heterotactic polylactide.

The ring-opening-polymerization (ROP) of cyclic esters, such as *rac*-lactide (*rac*-LA), has received considerable attention in recent years. The resulting (bio)degradable polymers have found use in high value biomedical applications, and industrial production of polylactide (PLA) from renewable resources has made PLA a viable alternative to traditional petrochemical-based commodity polymers.[1–5] In order to increase the range of potential applications for these environmentally desirable polymers, PLAs with defined and controlled physical and mechanical properties are especially required. To this end, major advances have been made in the development of stereoselective metal alkoxide initiators for ROP of *rac*-LA which are able to achieve high degrees of isotactic or heterotactic enrichment using a range of metals.[6–10] However, in spite of the fact that solvent-free conditions are necessary for industrial-scale polymerizations, as well as being attractive for the laboratory scale preparation of highly pure PLA, to our knowledge, only a very limited number of initiators has been reported previously that are able to achieve highly stereoselective ROP of *rac*-LA at the high temperatures ($\geq$ 130 °C) required.[11–13] A major limitation of these Al- and Ge-based initiators is the prolonged reaction times required (up to 48 h) to reach high levels of conversion, which limits their potential utility. Herein, we report the stereoselective ROP of *rac*-LA under solvent-free conditions using Zr- and Hf-based initiators[14–16] supported by amine tris(phenolate) ligands which offer an unprecedented combination of high stereocontrol ($P_r > 0.90$) and high activity (95% conversion in $<$30 min).

Since the first report of group 4 amine tris(phenolate) complexes,[17] there has been considerable interest in their structure and reactivity.[13,18–21] Recent results have highlighted the potential of amine tris(phenolate)s in ROP[13,16,20] and have prompted us to investigate the potential utility of Group 4 complexes as stereoselective initiators for ROP of *rac*-LA. Ti, Zr and Hf complexes of the bulky amine tris(phenolate) precursor LH_3 were prepared and isolated as crystalline solids (**1–3**, respectively, Scheme 1).§‡



Scheme 1 Synthesis of Group 4 metal alkoxide initiators **1–3**.

A single crystal X-ray structure of **3**¶ (Fig. 1) reveals a five-coordinate, monomeric complex in which the ligand scaffold adopts a C_3-symmetric propeller-like arrangement

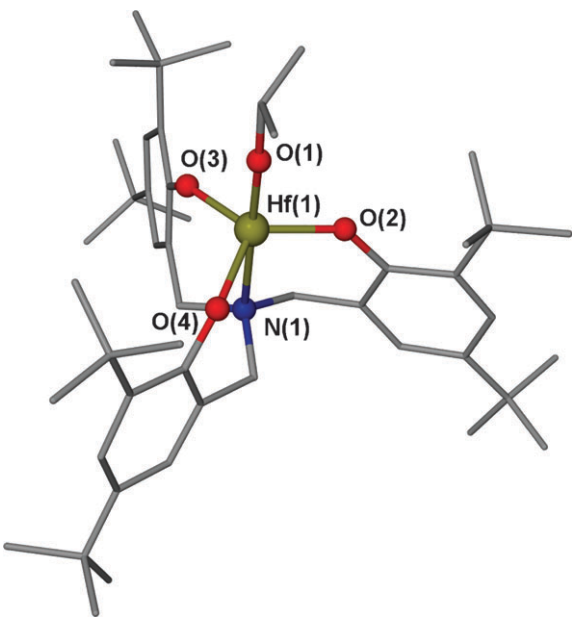


Fig. 1 Molecular structure of **3**: hydrogen atoms, lattice solvent and ligand disorder have been omitted for clarity. Selected bond lengths [Å] and angles [°]: Hf(1)–O(1) 1.920(2), Hf(1)–O(2) 1.949(3), Hf(1)–O(3) 1.944(3), Hf(1)–O(4) 1.999(3), Hf(1)–N(1) 2.406(2), O(1)–Hf(1)–N(1) 179.33(9), O(4)–Hf(1)–O(3) 116.31(13).

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around the metal center. The structure is racemic such that both *P* and *M* enantiomers are found in the crystal lattice. In solution, NMR data show that this structure is retained and that inversion is slow on the NMR timescale at −30 °C.‡ These observations are in accord with the previous characterizations of **1** and **2**.[17,19]

Complexes **1–3** were tested as initiators for the ROP of *rac*-LA under solvent-free conditions (Table 1, entries 1–3). The Ti complex, **1**, showed far higher activity than its Ge analogue,[13] but, in accord with previous results,[20] analysis of the polymer microstructure (by homonuclear decoupled ^{1}H NMR spectra, see ESI for details‡) revealed atactic PLA (Table 1, entry 1). For Zr and Hf complexes **2** and **3**, high levels of conversion were achieved very rapidly under melt conditions (Table 1, entries 2 and 3, respectively). Most interestingly, this rapid conversion is accompanied by a high degree of stereocontrol, with the isolated PLA possessing a high degree of heterotactic enrichment. To our knowledge, this combination of activity and stereoselectivity has not been achieved previously for any initiator under solvent-free conditions. For example, to our knowledge, the highest selectivity previously reported under similar conditions was achieved by Nomura *et al.* using an aluminium salen complex (130 °C, [M]/[I] = 300, 30 min, 25% yield, P_m = 0.84).[11] The unprecedented performance of **2** and **3** even under these non-ideal batch conditions (inefficient mixing, poor heat transfer, *etc.*) suggests their potential applicability to the production of PLA and related (co)polymers using continuous processes such as reactive extrusion, for which a significant further rate enhancement can be expected.[22,23]

For solvent-free polymerizations, analysis of molecular weights and molecular weight distributions are consistent with well-controlled polymerization. More detailed investigations using **2** as an initiator in solution further confirmed the living nature of the polymerization (Table 1, entries 4 and 5, and Fig. 2). Levels of stereocontrol are high and similar to those observed in the melt, polymer molecular weights are consistent with theoretical values, and molecular weight distributions are very narrow. MALDI-TOF mass spectra confirm that polymerization is initiated by isopropoxide groups and also indicate that competing side reactions such as transesterification are minimal.‡

Kinetic analyses for ROP of LA initiated by **2** were performed in $CDCl_3$ solution and reveal first order kinetics in monomer and rapid initiation of polymerization. The first order rate constants (k_{app}) for polymerization of *rac*-LA and (*S*,*S*)-LA are 4.2 × 10^{-3} min^{-1} and 0.6 × 10^{-3} min^{-1}, respectively. In other words, polymerization of (*S*,*S*)-LA to give isotactic PLA proceeds at a rate approximately seven times slower than the polymerization of *rac*-LA to give heterotactic PLA [(*R*,*R*)-LA polymerization proceeds at a very similar rate to (*S*,*S*)-LA, see ESI‡]. This is consistent with the observed heterotactic selectivity and is very similar to the relative rate difference previously found for a heteroselective zinc β-diiminate initiator.[6]

Factors governing stereocontrol of ROP initiators are subtle and remain poorly understood.[7] The dramatic switch from atactic to heterotactic selectivity between Ti to Zr could be accounted for by minor differences in the coordination mode of the growing polymer chain to the metal center which is known to be a significant factor in related systems.[10] In terms of the heteroselectivity of **2** and **3**, it has recently been proposed that inversion of axial chirality during chain propagation can lead to alternating stereochemistry at the metal center and therefore heterotactic selectivity *via* a dynamic enantiomorphic site control mechanism.[9,13] The C_3-symmetry of the amine tris(phenolate) ligand suggests that such a mechanism could be operating in this case, although a chain-end control mechanism, dependent on the steric bulk of the ligand rather than its chirality cannot be discounted at present. Work is ongoing to prepare model complexes of propagating species and enantiopure analogues[21] of **2** and **3** to probe these mechanistic aspects further. Regardless of precise details, it seems likely that the strongly bound, bulky trianionic ligand, leaving only a single site for chain propagation, provides a particularly robust platform for well-controlled ROP of PLA under solvent-free conditions. Since it has been shown that only minor changes in ligand substitution can lead to dramatic changes in stereoselectivity,[8] further investigation of amine tris(phenolate)s is warranted with the aim of developing similarly robust initiators for isotactic polymerization of *rac*-LA, which could be of considerable commercial utility for the facile preparation of high melting PLA stereocomplexes.

In summary, we have demonstrated for the first time that living and highly stereoselective ROP of *rac*-LA can be

Table 1 Polymerization data for *rac*-LA with initiators **1–3**

Entry	Initiator	Time/h	Yield (%)	M_n[c]	M_w/M_n[c]	P_r[d]
1[a]	**1**	0.5	50	37 100	1.38	0.50
2[a]	**2**	0.1	78	32 300	1.22	0.96
3[a]	**3**	0.5	95	71 150	1.19	0.88
4[b]	**2**	48	50	11 700	1.09	0.98
5[b]	**3**	48	30	8900	1.08	0.97

[a] [M]/[I] = 300, 130 °C, solvent-free. [b] [M]/[I] = 100, room temperature, toluene. [c] Determined by gel permeation chromatography (GPC) in THF, relative to polystyrene standards. [d] P_r is the probability of heterotactic enchainment, calculated from ^{1}H homonuclear decoupled NMR spectra.

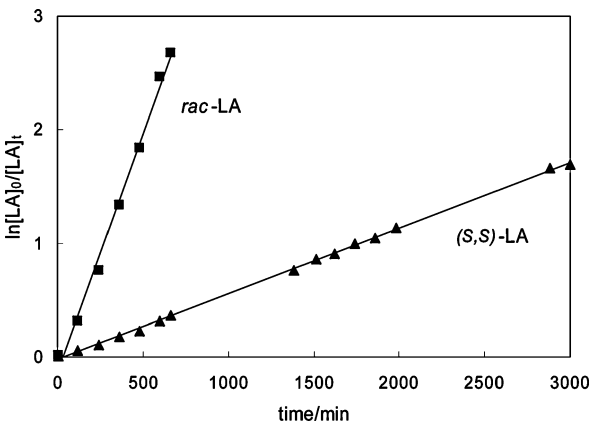

Fig. 2 First order plots for conversion of *rac*-LA (squares) and (*S*,*S*)-LA (triangles) *versus* time using **2** as an initiator ($CDCl_3$, 25 °C, $[LA]_0$ = 0.66 M, $[LA]_0/[\mathbf{2}]$ = 100).

achieved in the bulk with high conversion on a timescale compatible with continuous processing technologies such as reactive extrusion. This is an important development in the cost-effective production of PLA as a commodity polymer and in the quest for efficient routes to functional biocompatible materials with well-defined and tunable chemical and physical properties.

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Notes and references

§ *Synthesis of* **3**: $Hf(O^iPr)_4{}^iPrOH$ (0.71 g, 1.5 mmol) was dissolved in toluene (20 ml) to which the ligand (1.0 g, 1.5 mmol) was added. The solution was stirred for 2 h, after which time the solvent was removed *in vacuo* and product recrystallized from hexane at −20 °C, collected on a frit and dried *in vacuo*. Anal. calc. for $C_{54}H_{87}NO_4Hf$: C, 65.3; H, 8.83; N, 1.41. Found: C, 64.9; H, 8.79; N 1.18%. ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) 0.9 (m, 6H, CH_3 hexane), 1.29 (s, 35H, ^{t}Bu and CH_2 hexane), 1.40 (d J = 6.0 Hz, 6H, $CH(CH_3)_2$), 1.45 (s, 27H, ^{t}Bu), 2.96 (br s, 3H, CH_2), 4.01 (br s, 3H, CH_2), 4.73 (sept J = 6.0 Hz, 1H, $CH(CH_3)_2$), 6.98 (d J = 2.3 Hz, 3H, Ar–H), 7.27 (d J = 2.3 Hz, 3H, Ar–H). $^{13}C\{^1H\}$ NMR 14.1 (CH_3 hexane), 22.7 (CH_2 hexane), 27.4 ($CH(CH_3)_2$), 27.7 ($C(CH_3)_3$ *t*Bu), 31.6 ($C(CH_3)_3$ *t*Bu), 31.6 (CH_2 hexane), 34.2 ($C(CH_3)_3$ *t*Bu), 34.9 ($C(CH_3)_3$ *t*Bu), 59.5 (NCH_2), 72.3 ($CH(CH_3)_2$), 123.6 (Ar–C), 123.7 (Ar–H), 124.6 (Ar–H), 136.7 (Ar–C), 141.5 (Ar–C), 157.2 (Ar–O).

¶ *Crystal data for* **3**: $C_{54}H_{87}HfNO_4$, M = 992.74, colourless prism, 0.50 × 0.40 × 0.35 mm^3, tetragonal, space group $P4_3$ (No. 78), $a = b$ = 14.57000(10), c = 25.4100(2) Å, V = 5394.16(7) Å^3, Z = 4, D_c = 1.222 g cm^{-3}, F_{000} = 2088, MoKα radiation, λ = 0.71073 Å, T = 150(2) K, $2\theta_{max}$ = 55.0°, 81 147 reflections collected, 12 310 unique (R_{int} = 0.0362). Final GooF = 1.064, $R1$ = 0.0228, w$R2$ = 0.0504, R indices based on 11 451 reflections with $I > 2\sigma(I)$ (refinement on F^2), 762 parameters, 1 restraint. Lp and absorption corrections applied, μ = 1.974 mm^{-1}. Absolute structure parameter = 0.432(6):[24] structure refined as a racemic twin.

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