Highly Stereoselective Polymerization of Racemic Lactide by Bimetallic Schiff Base Complexes

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ABSTRACT: A series of bimetallic Salen aluminum (III) complexes with different steric substituents were synthesized. These complexes were used as catalysts to produce polylactide in the ring-opening polymerization of racemic lactide. A kinetic research of polymerization demonstrated that the steric substituents on the phenolate ring of the complexes had remarkable influence on the stereoselectivity and the polymerization activity. The highest stereoselectivity was obtained with bulky substituent on the ortho position of the salicylidene moieties. Kinetic studies using all these complexes indicated that the polymerizations were first-ordered with respect to lactide monomers. All these complexes gave highly isotactic polylactides with controlled molecular weight and narrow molecular weight distributions.

KEYWORDS: Stereoselective polymerization, racemic lactide, bimetallic catalysts

1 INTRODUCTION

Since the start of the modern industrial revolution, the petrochemical-based polymers have achieved tremendous development. Although these materials have obvious advantages, due to the recent concerns about pollution of our environment, the investigation of substituents such as biodegradable polymers has aroused wide interest. Polylactide (PLA) is one of the most widely researched biodegradable materials which could be used as green plastics for textiles and packaging films, scaffolds for tissue engineering and drug controlled delivery systems [1–8]. Generally, the method for synthesizing PLA is ring-opening polymerization (ROP) of lactide. Because of the chiral carbon in lactide monomer, there are three stereoisomers of lactide, namely D-lactide (D-LA), L-lactide (L-LA) and *meso*-lactide. Therefore, PLA has different chain microstructures (Scheme 1). The chain microstructures of PLA are crucial for the physical, mechanical and degradation properties of the polymers [9–11]. An equivalent mixture of PLLA and PDLA could form stereocomplex polymers which have interesting thermal property: the melting temperature (T_m) of homochiral PLLA or PDLA is 162–180°C, while the stereocomplex polymer is ~230°C [12,13]. Because the mechanical properties of PLA are stable up to the melting temperature, it is an attractive challenge to produce the stereocomplex from racemic lactide (rac-LA, a 1:1mixture of L-LA and D-LA). Conventional catalysts such as tin (II) octanoate and Al(O*i*Pr)$_3$ produced PLA from rac-LA could not obtain crystalline stereocomplex, and the requirement for an enantiopure monomer places strict restrictions on the polymer synthesis [14,15].

Because of their excellent performance in the homogeneous catalytic reaction, Schiff base metal complexes are considered as very important catalysts. They have been successfully used in ROP of lactide [16–21]. Spassky and coworkers first reported an aluminum complex of a chiral binaphthyl Schiff base to polymerize rac-LA to stereoblock PLA. Due to the formation of stereocomplex, the mechanical properties of PLA were more stable than homochiral PLLA [16]. A series of excellent research has attempted to explore the relationship between the aluminum Schiff base complexes and stereoselectivity of polymerization. It was believed that achiral salen Schiff base catalysts took the chain-end control mechanism and chiral salen Schiff base catalysts took the enantiomorphic site control mechanism [17–21].

Much progress has been made in the preparation of highly stereoregular PLA materials by monometallic bis(salicylidene) Schiff base aluminum catalyst [22–24]. The effects of the phenolate substituents on

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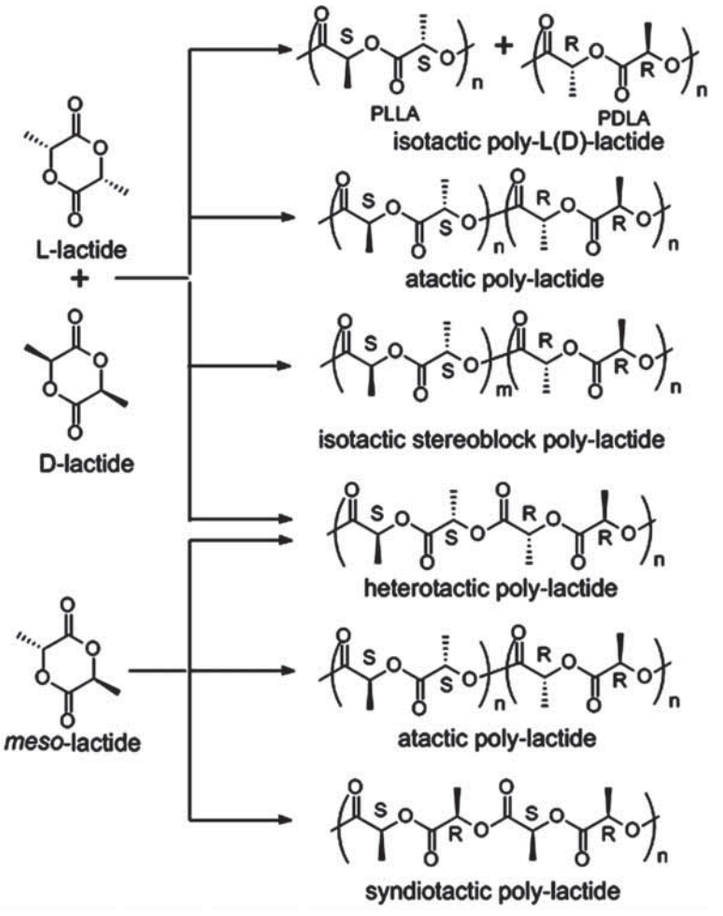


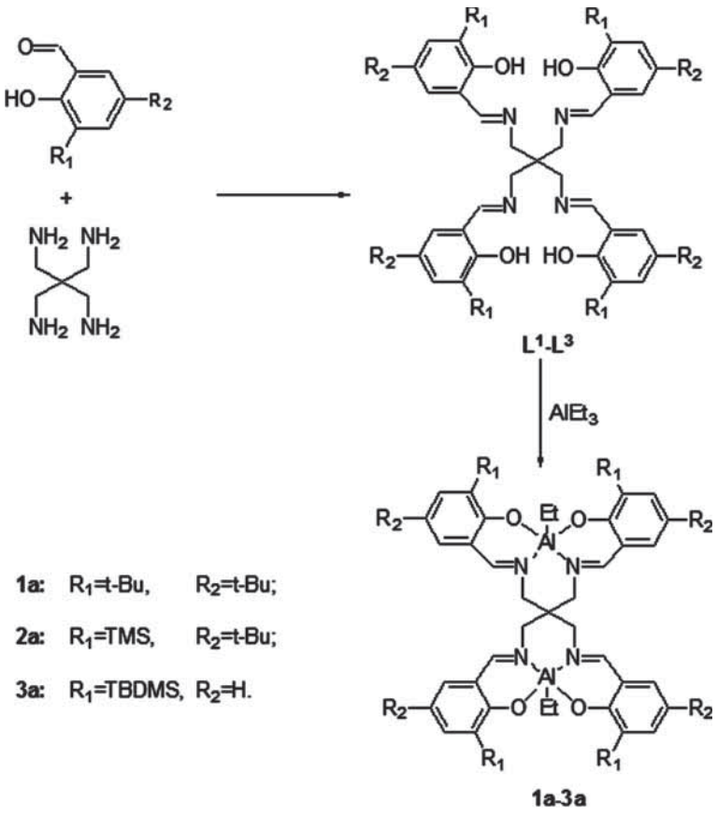
Scheme 1 Microstructure patterns of PLA.

the Schiff base ligands have been investigated in detail [22]. However, few studies about bimetallic Schiff base aluminum complex were reported despite their great potential structure varieties [25–28]. It is postulated that these complexes with bimetallic active centers might combine a high stereoselectivity and a high activity because of the synergetic effect of the two salicylidene moieties. Inspired by the successful preparation and application of symmetrical and unsymmetrical bimetallic salen complexes, we have been very interested in studies on the catalysis of bimetallic aluminum salen complexes. Recently, our research group has successfully developed some bimetallic aluminum salen complexes, which were used as catalysts to prepare isotactic enriched PLA from rac-LA [29–32]. Based on our previous work, it has been found that in the bimetallic Schiff base systems, the enhancement of stereoselectivity requires bulky substituents at the ortho positions for the stereoselective polymerization of rac-LA. In this article, we present a new series of bimetallic Schiff base ligand and their aluminum complexes with different bulky phenolate substituents (Scheme 2). A kinetic research of stereoselective polymerization was carried out to investigate the effect of these catalyst architectures on rac-LA polymerization behaviors. The results showed that complex **3**a with the bulkiest substituent at the ortho position exhibited highest stereoselectivity (Pm = 0.95) among all the complexes in the bimetallic Schiff base systems reported by our group [29–32] so far.

2 RESULTS AND DISCUSSION

2.1 Synthesis of Ligands and Complexes

As shown in Scheme 2, the Schiff base ligands $\mathbf{L^1}$-$\mathbf{L^3}$ were synthesized by reaction of tetraamine with substituented salicylidene. Ligands $\mathbf{L^1}$-$\mathbf{L^3}$ had different substituents at the ortho positions (R_1): tert-butyl (t-Bu) for $\mathbf{L^1}$, trimethylsilyl (TMS) for $\mathbf{L^2}$ and tert-butyldimethylsilyl (TBDMS) for $\mathbf{L^3}$. The ^{1}H NMR spectra of



Scheme 2 General synthetic route for **L**[1]-**L**[3] and **1a-3a.**

L[3] show signals at δ = 3.76 and 8.40, which were attributed to the NCH_2 and NCH protons of the pentaerythrityl tetramine, respectively. The intensity ratio of the signals at δ = 3.76 and 8.40 ppm was 2:1, which confirmed the structure of **L**[3]. And then reaction of ligands **L**[1]-**L**[3] with $AlEt_3$ in toluene produced bimetallic Schiff base aluminum complexes **1a-3a**, respectively. The ^{1}H NMR spectrum of complex compound **3a** shows signals at δ = –0.01 and 1.01 ppm, which were attributed to the methylene and methyl protons of the aluminum ethyl group, respectively. In comparison, with **L**[3], the corresponding signals of NCH_2 and NCH protons in complex **3a** moved to δ = 4.01 and 8.21, respectively. The intensity ratio of the signals at δ = -0.01, 1.01, 4.01 and 8.21 ppm was 2:3:4:2, which confirmed the structure of **3a**.

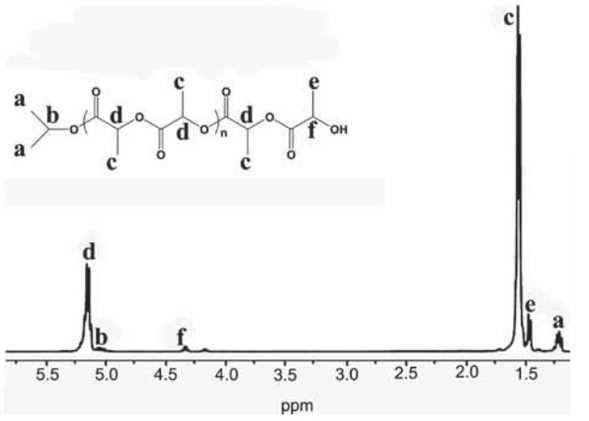


Figure 1 The ^{1}H NMR spectrum of oligomers of rac-LA.

2.2 Rac-LA Polymerization

To examine the influence of different steric substituents on their catalytic performance, polymerizations of rac-LA in toluene using **1a-3a** in the presence of 2-propanol were investigated. The levels of conversion were monitored by ^{1}H NMR by determination of samples withdrawn from the reaction mixtures. The ^{1}H NMR spectrum of the PLA oligomers (Figure 1) obtained with the ratio of [rac-LA]:[**2a**]:[2-propanol]=25:1:2 showed that the integral ratio of the two peaks at δ = 4.35 ppm (the methine proton neighboring the hydroxyl end group) and δ = 1.24 ppm (the methyl protons of the isopropoxycarbonyl end group) was close to 1:6. This

elucidated that the polymer chains were end-capped with a hydroxyl group and an isopropyl ester group and the ring-opening occurred through a so-called coordination-insertion mechanism [33,34].

2.3 Kinetics of Rac-LA Polymerization

The polymerization processes were investigated by kinetic studies using **1a-3a**. Polymerization data were collected in Table 1. The data of conversion versus time were collected for these three complexes in the presence of 2-propanol in toluene at 70°C, 90°C and 110°C, respectively (Figure 2). In all cases, first-order kinetics in monomer was observed.

The polymerization of rac-LA by using **1a-3a** proceeded according to:

$$-d[LA]/dt = k_{app}[LA] \quad (1)$$

Table 1 Polymerization data of rac-LA using complexes **1a–3a.**

Entry	Complex	*T*/°C	*t*[h]	$[M]_0/[Cat]$[a]	Conv%.[b]	M_n[c][10^3]	PDI[c]	P_m[d]
1	1a	70	12.5	200	86	14.2	1.14	0.91
2	1a	90	4.8	100	88	8.1	1.29	0.78
3	1a	110	3.2	100	90	8.4	1.35	0.68
4	2a	70	24	200	86	10.1	1.10	0.94
5	2a	90	16	200	92	11.2	1.13	0.83
6	2a	110	8	200	90	9.2	1.13	0.75
7	3a	70	24	200	71	3.5	1.11	0.95
8	3a	90	16	200	84	7.5	1.20	0.87
9	3a	110	8	200	89	10.2	1.20	0.80

[a]The polymerizations were were carried out in toluene solution. $[LA]_0 = 0.5$ mol/L. [b]Measured by ^{1}HNMR. [c]Obtained from GPC analysis and calibrated against polystyrene standard. The true value of Mn could be calculated according to formula Mn=0.58MnGPC. [d]The parameter *Pm* is the probability of meso linkages. According to chain-end control mechanism, the expressions for the terad probabilities of poly(rac-LA) are: $[mmm] = P_m^2 + (1-P_m)P_m/2$, $[mmr] = [rmm] = (1-P_m)P_m$, $[rmr] = (1-P_m)2$, $[mrm] = ((1-P_m)2 + P_m(1-P_m))/2$.

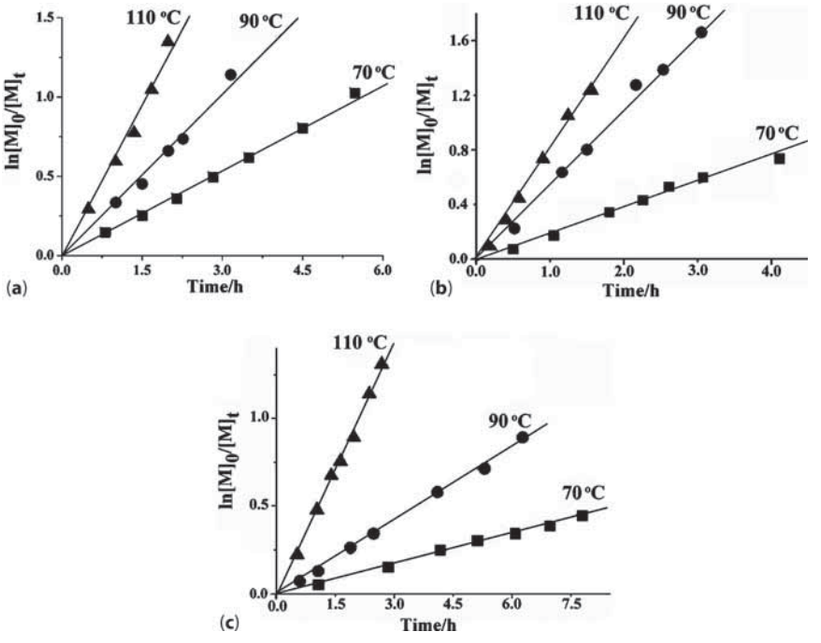


Figure 2 Kinetic plots of the rac-lactide conversion vs the reaction time at different tempratures: (a) complex **1a**, $[M]_0/[cat] = 100$; (b) complex **2a**, $[M]_0/[cat] = 200$; (c) complex **3a**, $[M]_0/[cat] = 200$.

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Table 2 Kinetic data of complex **1a-3a** for the ROP of *rac*-LA in toluene with $[LA]_0 = 0.5$ mol L^{-1}.

Entry	Complex	$[M]_0/[cat]$	T/°C	k_{app}/h^{-1}	k_p/Lmol^{-1} min^{-1}
1	1a	200	70	1.78	0.71
2	1a	100	90	8.05	1.61
3	1a	100	110	12.45	2.49
4	2a	200	70	0.18	0.60
5	2a	200	90	0.55	1.83
6	2a	200	110	0.85	2.83
7	3a	200	70	0.057	0.19
8	3a	200	90	0.14	0.47
9	3a	200	110	0.50	1.67

The linear relationship illustrated a first-order in monomer ($k_{app}=k_p$[cat]), the polymerization of rac-LA initiated and catalyzed by **1a-3a** followed a kinetic law as shown by Equation 2.

$$-d[LA]/dt = k_p[Al][LA] \quad (2)$$

All of k_{app} and k_p were calculated for **1a-3a**/2-propanol in toluene (Table 2). The polymerization data indicated that the introduction of substituent groups on the phenolate ring significantly affected the stereoselectivity and activity. Complexes **1a**, **2a** and **3a** had different phenolate substituents. Polymerization data (Table 1) revealed that **1a** had the highest activity among these three complexes. By changing the t-Bu substituent of **1a** into TMS in **2a**, the k_p value was reduced from 0.71 to 0.60. And for **3a** with even bigger instituent of TBDMS, the k_p value was reduced to less than a third of **1a**. It was consistent with previous results in monometallic [25,34] and bimetallic [30,31] Shiff base systems. The bulkier substituents with more steric hindrance, which might keep active species from being approached by lactide monomer, accordingly, would lead to slower polymerization rate.

2.4 Complex Structure and Stereochemistry of Rac-LA

The stereochemical microstructures of the isolated PLAs were determined from the methine region of the homonuclear decoupled ^{1}H NMR (Figure 3). Due to the bulky substituents at the ortho positions (R_1), complexes **1a-3a** showed high stereoselectivity in the polymerization of rac-LA, and the PLA material produced by **2a**/2-propanol in the ROP of rac-LA at 70°C in toluene is substantially isotactic with a P_m of 0.94. Since all ligands prepared were achiral, it was expected that the ROP of rac-LA by this catalyst

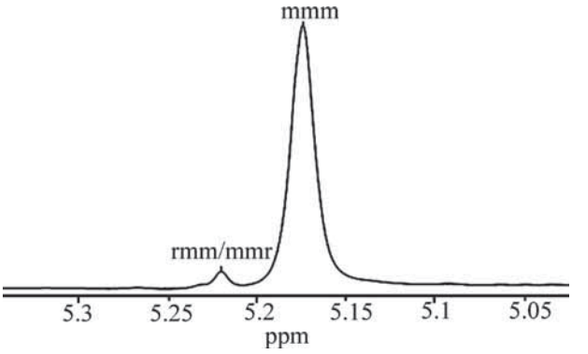

Figure 3 Methine region of homonuclear decoupled ^{1}HNMR spectra of isolated PLA materials using complex **2a**.

system took place via chain-end control mechanism [17,18]. In such a mechanism, the catalysts have the same effect between the two enantiomers, and the stereogenic center in the last unit would influence which monomers (D-LA or L-LA) would incorporate next.

It is obvious that the reaction was in accordance with first-order Markovian statistics [35,36]. According to first-order Markovian statistics and absolute reaction rate theory, the activation entropy difference ($\Delta S_m^{\neq} - \Delta S_r^{\neq}$) and activation enthalpy difference ($\Delta H_m^{\neq} - \Delta H_r^{\neq}$) between homo-propagation (k_m) and cross-propagation (k_r) would be determined by Equation 3.

$$P_m/(1-P_m) = k_m/k_r = \exp[(\Delta S_m^{\neq} - \Delta S_r^{\neq})/R - (\Delta H_m^{\neq} - \Delta H_r^{\neq})/RT] \quad (3)$$

If $k_m > k_r$ the formation of isotactic sequences were favored, otherwise syndiotactic sequences were produced. The ($\Delta S_m^{\neq} - \Delta S_r^{\neq}$) was the entropy difference between homo-propagation and cross-propagation, and the ($\Delta H_m^{\neq} - \Delta H_r^{\neq}$) was the enthalpy difference between homo-propagation and cross-propagation. Ln [$P_m/(1 - P_m)$] was plotted against $1/T$ (Figure 4)

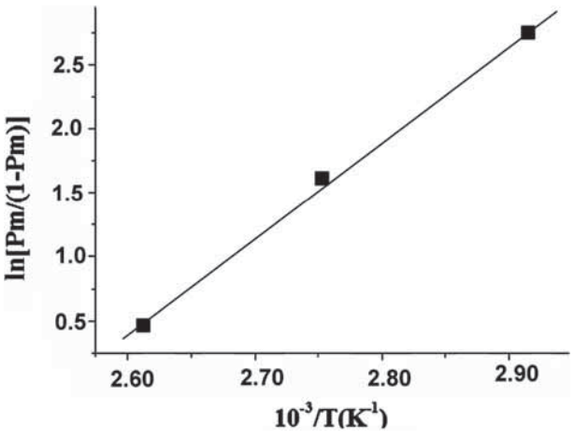

Figure 4 Relationship between polymerization temperature and stereochemistry of the resulting poly(rac-LA)s by using **2a**/2-propanol.

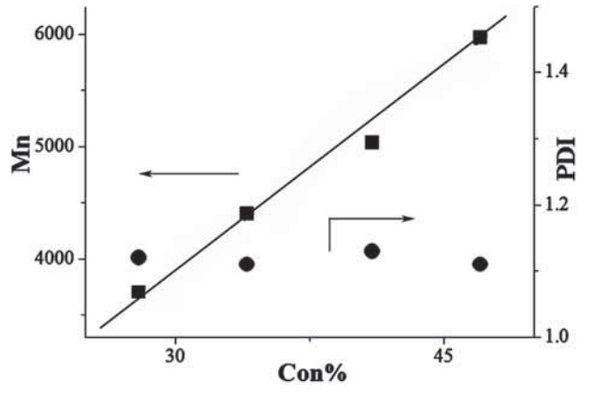

Figure 5 Plot of PLA Mn and polydispersity (Mw/Mn) as a function of rac-lactide conversion using complex **3a**/2-propanol T=70°C $[M]_0/[Cat]$=200.

to calculate the values of ($\Delta S_m^{\neq} - \Delta S_r^{\neq}$) and ($\Delta H_m^{\neq} - \Delta H_r^{\neq}$). The entropy and enthalpy differences of 2**a**/2-propanol were calculated as -10.81 cal $K^{-1}mol^{-1}$ and -26.27 cal $K^{-1}mol^{-1}$, respectively, which illustrate the preference of isotactic stereosequence.

As for **1a, 2a** and **3a**, a change of phenolate substituent to a bulkier one led to an increase in stereoselectivity. The P_m value was 0.91 for **1a,** 0.94 for **2a** and 0.95 for **3a**. This is consistent with a previous study in which the enhancement of stereoselectivity requires bulky substituents at the ortho positions for the stereoselective polymerization adopting chain-end control mechanism [30].

While increasing the polymerization temperature, P_m values of the resulting polymer decreased. As the temperature from 70°C to 90°C and 110°C using **3a** led to a reduction in P_m value of 8.4% and 15.8%, respectively (from 0.95 at 70°C to 0.87 at 90°C and 0.80 at 110°C. See Table 1, entries 7, 8 & 9).

Furthermore, the relation between the number-average molecular weight (Mn) and the monomer conversion also have been investigated. As shown by Figure 5, the linear relationship and the low polydispersity elucidated that the polymerization had a characteristic of controlled propagation.

2.5 Conclusion

In conclusion, we synthesized a series of dinuclear Salen ligands and their aluminum complexes, in which 3-position of the salicylidene moieties have bulky substituent groups. Their catalytic behavior in ROP of rac-LA has been investigated in detail. All of complexes have high stereoselective ROP of rac-LA. As the substituent group grows bulkier, the P_m value increases accordingly (P_m = 0.91 for **1a**, 0.94 for **2a** and 0.95 for **3a**), which is consistent with previous results in both of the monometallic and bimetallic Schiff base systems. Furthermore, the substituent groups affect the polymerization rate concurrently. Polymerization data revealed that **1a** had the highest activity: k_p value was 0.71 L mol^{-1} min^{-1} for **1a**, 0.60 L mol^{-1} min^{-1} for **2a** and 0.19L mol^{-1} min^{-1} for **3a**. Further investigation on the correlative mechanism of the bimetal centers interacted in stereoselective polymerization is in progress in our group.

3 EXPERIMENTAL SECTION

General: All experiments were carried out under argon using Schlenk techniques. Starting materials for the synthesis of ligand **L^1-L^3** were prepared according to the reported procedure [29,30]. Toluene was distilled from Na/benzophenone. Ethyl acetate and 2-propanol were distilled from CaH_2 under the protection of argon. Rac-LA (Purac) was purified by recrystallization from ethyl acetate and dried under vacuum at room temperature (RT) before use. NMR spectra were recorded on Bruker AV 300M and Bruker AV 400M in $CDCl_3$ at 25°C. Chemical shifts were given in parts per million from tetramethylsilane. Gel permeation chromatography (GPC) measurements were conducted with a Waters 515 GPC with $CHCl_3$ as the eluent (flow rate: 1 $mLmin^{-1}$, at 35°C). The molecular weights were calibrated against polystyrene (PS) standards.

3.1 Synthesis of Ligands and Complexes

General procedure for preparation of ligand **L^1-L^3**: A solution of tetraamine (0.1 $molL^{-1}$) in ethanol (40 mL)

was added dropwise to a stirred solution of substituent salicylidene (0.4 molL^{-1}) in ethanol (40 mL). The reaction mixture was refluxed for 12 h before cooling to RT. After removal of the solvent under vacuum a solid was produced and purified by recrystallization in ethanol/ dichloromethane.

L^1: ^{1}H NMR (300 MHz, $CDCl_3$): δ= 13.71(s, ArO*H* 4H), 8.55(s, NC*H* 4H), 7.46(s, Ar*H* 4H), 7.18(s, Ar*H* 4H), 3.84(s, CCH_2N 8H), 1.53(s, ArC(CH_3)$_3$ 36H), 1.35(s, ArC(CH_3)$_3$ 36H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.87(NCH), all benzene ring: 157.70, 139.96, 136.34, 126.93, 125.86, 117.32; 61.16(NCH_2), 43.79((CH$_2$)$_2$*C*(CH$_2$)$_2$), 34.74, 33.78(Ar*C*(CH$_3$)$_3$), 31.11(C(CH$_3$)$_3$), 29.11(C(*C*H$_3$)$_3$). Elem. Anal.: Calcd C 78.27, H 9.70, N 5.62%; Found C 78.30, H 9.68, N 5.67%.

L^2: ^{1}HNMR (300.00MHz, $CDCl_3$): δ=13.22(s, OH 4H), 8.50(s, NC*H* 4H), 7.52(d, Ar*H* 4H), 7.31(d, Ar*H* 4H), 3.82(s, CH_2N 8H), 1.35(s, CCH_3 36H), 0.41(s, SiCH_3 36H). ^{13}CNMR (100 MHz, $CDCl_3$): δ =167.75(NCH), all benzene ring: 163.60, 140.80, 135.25, 129.54, 126.59, 116.90; 61.54(CCH_2N), 46.18((CH$_2$)$_2$*C*(CH$_2$)$_2$), 34.19(Ar*C*(CH$_3$)$_3$), 31.49(C(*C*H$_3$)$_3$), -0.93(Si(CH$_3$)$_3$). MALDI-TOF (THF), m/z: 1061. Elem. Anal.: Calcd. C 69.00, H 9.11, N 5.28; Found C 68.93, H 9.09, N 5.25%.

L^3: ^{1}HNMR (300.00MHz, $CDCl_3$): δ=13.36(s, OH 4H), 8.40(s, NC*H* 4H), 7.45, 7.24, 6.91(m, Ar*H* 12H), 3.76(s, CH_2N 8H), 0.96(s, SiC(CH_3)$_3$ 36H), 0.37(s, Si(CH_3)$_2$ 24H). ^{13}CNMR (100 MHz, $CDCl_3$): δ=167.61(NCH), all benzene ring: 166.00, 139.77, 133.15, 124.93, 118.37, 117.71; 61.67(CCH_2N), 44.05((CH$_2$)$_2$*C*(CH$_2$)$_2$), 27.20 (SiC(CH_3)$_3$), 17.74(SiC(CH$_3$)$_3$, -4.65(Si(*C*H$_3$)$_2$). MALDI-TOF (THF), m/z: 1005. Elem. Anal.: Calcd. C68.07, H8.82, N 5.57; Found C67.95, H 8.85, N 5.57%.

For Schiff base aluminum complexes **1a–3a**: $AlEt_3$ (0.2 mmol) in toluene (5 mL) was added to the stirred 1mL toluene solution of ligand precursors **L^1-L^3** (0.1 mmol) at RT. The reaction was maintained at 70°C for 12 h. Despite our efforts, single crystals suitable for X-ray crystal structure determination were not obtained for **1a-3a**.

1a: ^{1}H NMR (300 MHz, $CDCl_3$): δ= 8.19(m, NC*H* 4H), 7.43(m, Ar*H* 4H), 6.91(m, Ar*H* 4H), 3.80(m, CCH_2N 8H), 1.50(m, ArC(CH_3)$_3$ 36H), 1.32(m, ArC(CH_3)$_3$ 36H), 0.70(m, (Al-CH$_2$)CH_3 6H), 0.19(m, AlCH_2 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 176.79(NCH), all benzene ring: 168.11, 157.96, 140.58, 136.57, 130.65, 127.00, 126.12, 117.81; 62.17(NCH$_2$), 45.11((CH$_2$)$_2$*C*(CH$_2$)$_2$), 35.09, 33.84(Ar*C*(CH$_3$)$_3$), 31.34(*C*(CH$_3$)$_3$), 29.35(*C*(CH$_3$)$_3$), 8.64(AlCH$_2$CH$_3$), 1.34(AlCH$_2$CH$_3$). Elem. anal.: Calcd C 74.96, H 9.30, N 5.07%; Found C 75.01, H 9.27, N 5.09%.

2a: ^{1}H NMR (400MHz, $CDCl_3$): δ=8.22(d NC*H* 4H), 7.68(m Ar*H* 4H), 7.05(d Ar*H* 4H), 3.74(d CH_2N 8H), 1.30(s CCH_3 36H), 0.96(m (Al-CH$_2$)CH_3 6H), 0.31(s SiCH_3 36H), -0.12(m Al-CH_2 4H). ^{13}C NMR (100MHz, $CDCl_3$): δ=177.26(NCH), all benzene ring: 170.84, 142.50, 140.72, 138.61, 132.47, 116.83; 61.18(CCH_2N), 44.14((CH$_2$)$_2$C(CH$_2$)$_2$),33.93(ArC(CH$_3$)$_3$),31.46(C(*C*H$_3$)$_3$), 9.12(Al-CH$_2$CH$_3$), 1.61(Al-CH$_2$CH$_3$), -0.97(Si(*C*H$_3$)$_3$). Elem. Anal.: Calcd. C 66.74, H 8.49, N 4.61%; Found C 66.71, H 8.45, N 4.58%.

3a: ^{1}H NMR (400MHz, $CDCl_3$): δ=8.21(s NC*H* 4H), 7.58, 6.91, 6.71(m Ar*H* 12H), 4.01(s CH_2N 8H), 1.01(m (Al-CH$_2$)CH_3 6H), 0.93(s SiC(CH_3)$_3$ 36H), 0.31(s Si(CH_3)$_2$ 24H), -0.01(m Al-CH_2 4H). ^{13}C NMR (100MHz, $CDCl_3$): δ=177.37(NCH), all benzene ring: 170.14, 146.59, 144.37, 137.19, 135.32, 130.26, 118.11; 62.87(CCH_2N), 45.09((CH$_2$)$_2$*C*(CH$_2$)$_2$), 27.28(SiC(*C*H$_3$)$_3$), 17.87(Si*C*(CH$_3$)$_3$), 9.04(Al-*C*H$_2$CH$_3$), 1.53(Al-CH$_2$CH$_3$), -4.55(Si(*C*H$_3$)$_2$). Elem. Anal.: Calcd. C 65.78, H 8.51, N 4.85%; Found C 65.77, H 8.56, N 4.91%.

3.2 Polymerization of Rac-LA

Under the protection of argon, the rac-LA (20 mmol, 2.88 g), complexes 1a–3a, (0.10 mmol in 5 mL of toluene), 2-propanol (0.10 mmol, in 2 mL of toluene), and toluene (33 mL) were added to a dried reaction vessel equipped with a magnetic stirring bar. The vessel was maintained at 70°, 90° or 110° in an oil bath. Conversion of the monomer was determined on the basis of ^{1}HNMR spectroscopic studies. The polymers were isolated by precipitation into cold ethanol, then centrifuged and dried under vacuum at RT for 24 h.

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