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Electron rich (salen)AlCl catalysts for lactide polymerisation:
Investigation of the influence of regioisomers on the rate and initiation efficiency

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Graphical Abstract
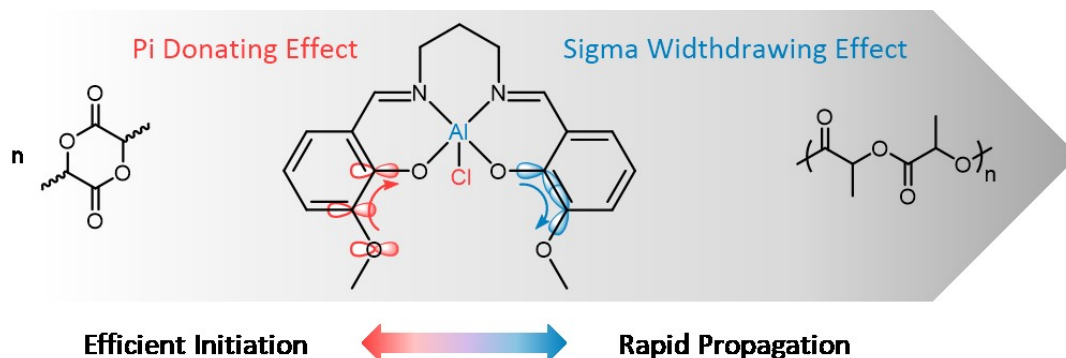
Abstract

Aluminium-alkyl complexes are well known as initiators for lactide ring-opening polymerisation, yet aluminium-chloride complexes remain underexplored despite benefits such as ease of synthesis and improved air-stability. While aluminium-chloride complexes are typically poor initiators, recent studies have shown that electron-rich amino-substituted (salen)AlCl complexes can efficiently initiate lactide polymerisation in the presence of an epoxide. Herein, we report eight ether-substituted complexes as efficient initiators for lactide polymerisation, where exchanging strongly electron-donating amino groups for weaker electron-donating methoxy substituents maintains efficient initiation and also improves the propagation rate by a factor of four. Investigation of *ortho*-, *meta*-, *para*- and *meta'*-methoxy-substituted regioisomers established that the *ortho*-substituted complex was twice as active as the other regioisomers. Kinetic and spectroscopic studies suggest that the initiation efficiency is influenced by the electronics (*ortho* and *para* > *meta* and *meta'*), with substituents closer to Al giving improved initiation (*ortho* > *para* and *meta'* > *meta*). While electron-donating *ortho*-substituents often decrease catalyst activity in lactone polymerisation, here we show that ether groups can act as σ-electron withdrawing groups and π-electron donors, to deliver improved propagation rates, initiation and tacticity control.

Introduction

The ring-opening polymerisation (ROP) of lactones is an efficient method of preparing polyesters with useful optical and material properties.[1] Poly(lactic acid) (PLA) is one of the most promising bioderived and biodegradable polyesters, and is typically prepared through ROP of lactide (LA)[2] for diverse applications including packaging, electronics and biomedical devices.[3–8] Lactide ROP requires a catalyst and some of the most promising are highly active organometallic complexes enabling excellent stereocontrol, targeted molecular weights and narrow dispersities.[9] Organometallic catalysts are generally proposed to operate *via* a coordination-insertion mechanism, where a key feature involves LA coordination to a Lewis acidic metal.[9–11] While a broad range of metal complexes have been investigated,[12–17] aluminium is a particularly attractive choice, as it is earth abundant, inexpensive and can generate polymers with well-controlled microstructure.[18–25] Salen-derived complexes have shown particular success,[9] and the ligand can be readily modified to alter the steric and electronic properties.[9,18,26] However, ligand substituents are often Janus-faced. For example, electron-withdrawing groups often help propagation, by enhancing the metal Lewis acidity thus monomer coordination, yet hinder initiation and stereocontrol. In contrast, bulky electron-donating *ortho*-phenol substituents generally reduce the polymerisation rate (e.g. by a factor of up to 60)[26] but give improved stereocontrol,[9,11] attributed to the steric obstruction of LA monomers coordinating to the metal centre and/or a key transition state associated with ring-opening. While substituents are broadly categorised as electron-donating or electron-withdrawing according to conventional organic classifications, many have dual properties and can act as σ-electron withdrawers yet π-electron donors.[27,28] The influence of regioisomeric ligand substituents upon initiation and propagation remains less systematically explored, in spite of evidence that the substituent position alters the catalyst activity and polymerisation control.[26,29]

Cyclic ester ROP is typically initiated by metal-alkoxide species, often formed *in situ* through alcoholysis of a metal-alkyl precursor. While metal-chloride complexes may offer benefits of improved air-stability compared to the metal-alkyl analogues, aluminium chloride complexes are typically poor initiators for LA ROP. Yet ring-opening a highly strained epoxide is an easier target than LA,[30–32] a phenomenon that has successfully been exploited in various polymerisations.[33–38] Thomas, Maron *et al.* demonstrated that the Jacobsen (salen)AlCl complex can initiate LA ROP *via* epoxide ring-opening (Figure 1, left) in the presence of an onium salt (PPNCl) and excess epoxide.[39] We recently showed that external Lewis bases can be avoided by incorporating electron-donating diamino-substituents into the salen scaffold (Figure 1 right). The electron-donating diamino-substituents improved the initiation efficiency by increasing the nucleophilicity of the Al-Cl bond and facilitating epoxide attack. However, strongly electron-donating ligand substituents may hamper propagation, by increasing the electron density at Al thus reducing the Lewis acidity and disfavouring LA (or epoxide) coordination. Herein, weaker electron donating ether-substituents were investigated as a route to improve propagation rate whilst maintaining efficient initiation. We reveal the influence of regioisomeric ether-substituted (salen)AlCl complexes upon the catalyst activity and stereocontrol.
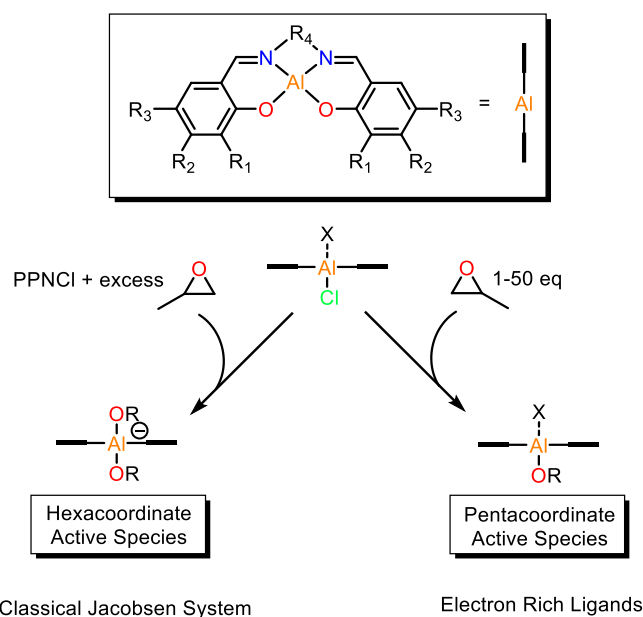
Figure 1: Comparison of the proposed initiation mechanisms with the classical Jacobsen system (left; $R_1=R_3=^tBu$, $R_2=H$; $R_4=Cy-C_6H_{10}$) and electron rich (salen)AlCl complexes (right; $R_2=NEt_2$, $R_1=R_3=H$, $R_4=C_3H_6$). (PPN$^+$ cation omitted for clarity, X = vacant coordination site).[39,40]

Results and Discussion

A series of methoxy-substituted (salen)AlCl complexes were synthesised in high yields *via* ligand metalation with Et$_2$AlCl (**C1**-**C6**, Scheme 1), and characterised by multinuclear NMR spectroscopy, mass spectrometry and elemental analysis. Complexes **C2** (*ortho*-OMe), **C3** (*para*-OMe) and **C6** (*ortho*-OEt) display almost identical imine proton shifts (HC=N: **C2**, δ = 8.18 ppm; **C3**, δ = 8.15 ppm; **C6**, δ = 8.17 ppm), attributed to the electronic similarity due to resonance delocalisation (refer to supporting information, Figure S25). The imine resonances of complexes **C1c** (*meta*-methoxy, 8.07 ppm) and **C4** (*meta'*-methoxy, 8.71 ppm) are noticeably different, with the significant downfield shift of **C4** attributed to the close proximity of the *meta'*-OMe substituent.[41]
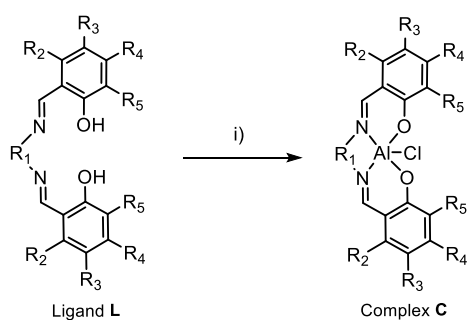
	R₁	R₂	R₃	R₄	R₅	Yield
C1a	$(CH_2)_2$	-	-	OMe	-	71%
C1b	$(CH_2)_3$	-	-	OMe	-	55%
C1c	$CH_2C(Me)_2CH_2$	-	-	OMe	-	89%
C2	$CH_2C(Me)_2CH_2$	-	-	-	OMe	70%
C3	$CH_2C(Me)_2CH_2$	-	OMe	-	-	83%
C4	$CH_2C(Me)_2CH_2$	OMe	-	-	-	91%
C5	$(CH_2)_3$	-	-	-	OEt	87%
C6	$CH_2C(Me)_2CH_2$	-	-	-	OEt	94%
C7a	$(CH_2)_2$	-	-	NEt_2	-	96%
C7b	$(CH_2)_3$	-	-	NEt_2	-	90%
C7c	$CH_2C(Me)_2CH_2$	-	-	NEt_2	-	29%

Scheme 1. Synthesis of electron-rich (salen)AlCl complexes **C1**-**C6**. i) Reaction conditions: [**L**]:[Et_2AlCl] = 1:1, toluene solvent at RT for 16 hrs.

Complexes **C1**-**C6** were tested for *rac*-LA ROP in toluene solvent at 120 °C, using a catalyst:PO:*rac*-LA ratio of 1:50:100. These conditions were selected as being optimum for related (salen)AlCl catalysts.[40] All eight complexes displayed good catalytic activities and controlled *rac*-LA ROP, with a linear relationship between M_n and conversion, reasonable dispersities and a first order dependence on the monomer concentration (Figures 2 – 3 and S26 – S33). To understand the influence of the electron donating substituent, complexes **C1a**, **C1b** and **C1c** were compared to previously reported NEt_2-substituted analogues (**C7a**, **C7b** and **C7c**, respectively, Scheme 1).[40] For all three systems, the ether-substituted complexes displayed significantly higher catalytic activities (Figure 2). The propagation rate quadrupled using *meta*-OMe-substituted **C1a** (k_{obs} = 0.3 x 10^{-3} s^{-1}) compared to the *meta*-NEt_2-substituted analogue **C7a** (k_{obs} = 7.0 x 10^{-5} s^{-1}). This activity increase is attributed to the weaker electron donating ether substituent increasing the Lewis acidity of the Al centre thus favouring monomer coordination, a key step in *rac*-LA ROP.[9] The kinetic studies showed no significant induction period using the ether-substituted complexes (or the amine-substituted complexes). ^{1}H NMR monitoring of the reaction between (salen)AlCl complexes and PO shows a correlation between the strength of the electron donating group and the rate of PO ring-opening (NEt_2, **C7a**, 1 h; OMe, **C1c**, 3 h; Jacobsen, 5 h; all in d_8-toluene at ambient temperature).[40] Our previous studies have shown that incorporating a Lewis basic amino-substituent into the salen ligand not only reduces the induction period but also alters the initiation mechanism, which avoids the need for external Lewis bases (onium salt and excess PO, Figure 1).[39,40] The ether-substituted complexes improve the propagation rate and achieve efficient initiation without external Lewis bases. Comparing the ^{1}H NMR spectra, the imine resonances of amino-substituted complexes **C7a**, **C7b** and **C7c** are significantly shielded (δ = 8.09, 8.07 and 7.84 ppm, respectively) compared to the analogous ether-substituted complexes (**C1a**, **C1b** and **C1c**, δ = 8.27, 8.14 and 8.04 ppm respectively). These observations suggest that the strength of the electron donating substituents influences the electronics of the conjugated ligand backbone. The

more electronegative (and poorer electron donating) methoxy-group results in a deshielded imine resonance, which in turn correlates with a reduced initiation rate (Table S3).[40] While drawing comparisons between **C1-C6** and related literature systems is limited by the range of different polymerisation conditions tested, the ether-substituted complexes are generally amongst the most active (salen)Al complexes reported for *rac*-LA ROP (Table S4). Complexes **C1a-c** all display a similar and moderate isotactic bias (**C1a** P_i = 0.62, **C1b** P_i = 0.66 and **C1c** P_i = 0.66), determined using the method proposed by Ovitt and Coates,[20] and no significant change in tacticity was observed over the course of the reaction. These P_i values were similar albeit slightly lower than those obtained using the NEt_2 analogues (**C7a-c**, P_i = 0.69-0.74).[40] The higher tacticity obtained using the amino-substituted catalysts is attributed to the slower propagation rate caused by the more sterically bulky and strongly electron-donating NEt_2 substituents.[9,42] While the diamino linker does not significantly influence the tacticity, it does have a powerful impact on the propagation rate (Table S6). In line with previous reports, complexes bearing longer linkers display greater catalytic activities, attributed to the increased flexibility facilitating access to key transition states involved in *rac*-LA ROP.[26]

In general, the molecular masses determined by GPC analysis ($M_{n,obs}$) gave good agreement with the theoretical values ($M_{n,calc}$), indicating a controlled polymerisation (Table S5). However, for complexes **C1a** and **C1c** the observed values are lower than expected (refer to Figures S26 and S28). With **C1a**, **C1b** and **C1c**, the dispersity broadened at high conversions. These observations indicate that chain transfer or transesterification reactions may become dominant in the late stages of the polymerisation,[43] a feature which has previously been reported for related (salen)Al systems.[9,27] Accordingly, MALDI-ToF analysis revealed that transesterification occurred at high conversion of *rac*-LA (Figures S35 – S38). Confirming initiation *via* epoxide opening from Al-*chloride*, the PLA produced was α-chloropropoxyl, ω-hydrogen end-capped. In the late stages of the polymerisation, some cyclic PLA was also observed.
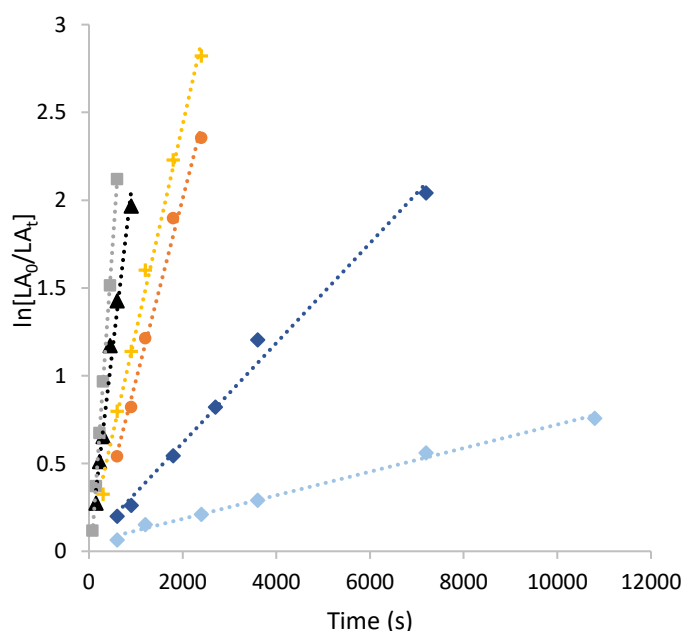

Figure 2: Kinetic plot of $\ln[LA_0/LA_t]$ vs time for *rac*-LA ROP catalysed by complexes: **C1a** (♦ k_{obs} = 0.3 x 10^{-3} s^{-1}, R^2 = 0.99), **7a** (♦ k_{obs} = 7.0 x 10^{-5} s^{-1}, R^2 = 0.99), **C1b** (▲ k_{obs} = 2.3 x 10^{-3} s^{-1}, R^2 = 0.98), **7b** (● k_{obs} = 1.1 x 10^{-3} s^{-1}, R^2 = 0.99), **C1c** (■ k_{obs} = 3.8 x 10^{-3} s^{-1}, R^2 > 0.99) and **C7c** (+ k_{obs} = 1.2 x 10^{-3} s^{-1}, R^2 = 0.99). Reaction conditions: [catalyst]:[PO]:[*rac*-LA] = 1:50:100, [*rac*-LA] = 1 M in toluene, 120°C.

To investigate the influence of the regiochemistry upon the catalyst activity, kinetic studies were performed using complexes **C1c**, **C2**, **C3** and **C4** (Figure 3). These complexes all feature a 2,2-dimethyl-1,3-diamino propyl backbone, which was selected for investigation as **C1c** and **C7c** outperformed the other catalyst species. *Ortho*-substituted **C2** displayed significantly higher catalytic activity (k_{obs} = 6.9 x 10^{-3} s^{-1}) than the *meta*-, *para*- and *meta'*-substituted regioisomers (3.8 x 10^{-3} s^{-1}, 3.9 10^{-3} s^{-1} and 3.8 x 10^{-3} s^{-1} respectively). It is generally accepted that electron-withdrawing groups enhance the Lewis acidity of the Al centre, facilitating LA ROP. Whilst ether-substituents are considered to be electron donating overall, there is a balance between the σ-inductive electron-withdrawing effect and mesomeric π-donation from the lone pair of electrons in the p orbital. With the *ortho*-substituted complex, the inductive effect appears to be the dominant influence, thus increasing the Lewis acidity of the nearby Al centre. The similar activities obtained for the *meta*-, *para*- and *meta'*-substituted complexes suggests that the electronic effect is less significant for these three complexes. Alternatively, the *ortho*-methoxy group may facilitate LA coordination through electrostatic interaction between the resonance delocalised ligand species with LA, in a similar manner to that proposed between PPNCl and LA (Figure S54).[40] To investigate this hypothesis, NMR spectroscopic studies of complex **C2** with LA in toluene solvent were performed, however no significant shift of the methylene LA resonance was observed in the ^{1}H NMR spectra. While these observations do not unequivocally rule out an electrostatic interaction between LA and **C2**, they suggest that the inductive effect of the *ortho*-substituent has a greater influence. Complexes **C1c**, **C2**, **C3** and **C4** all displayed moderate isotactic control; the P_i values range from 0.59 to 0.70 with *ortho*-substituted **C2** displaying the highest isotactic bias. This is in contrast with the literature, where an inverse relationship between polymerisation rate and the degree of isotacticity is generally observed. Bulky electron-donating *ortho*-substituents (e.g. ^{t}Bu) typically display reduced activities but improved stereocontrol,[11,26,44–47] whereas electron-withdrawing groups (e.g. Cl) generally increase the activity but reduce stereocontrol. Our results suggest that that the size and nature of the *ortho*-substituent are both important, as *ortho*-OMe substituents can simultaneously improve the polymerisation rate and stereocontrol. With all four complexes, the polymerisation was generally well controlled, however, in the late stages of the reaction $M_{n,obs}$ started to deviate from $M_{n,calc}$, and was lower than expected (Figures S28 - S31), which was attributed to transesterification and chain transfer processes. End-group analysis by MALDI-ToF mass spectrometry confirmed initiation *via* epoxide ring-opening by Al-Cl, while catalysts **C2** and **C4** also gave a series of α-hydrogen, ω-hydroxyl end-capped PLA initiated by propylene diol (Figure S39 and S41). Propylene diol can act as a mono- or bi-functional chain transfer agent, and is a known impurity in PO typically formed from the *in situ* reaction of PO with trace water.[48] Transesterification and cyclic PLA were also observed in the late stages of the ROP.

Extrapolation of the kinetic plots suggests that the rate of initiation decreases in the order *ortho* = *para* > *meta'* >> *meta* (refer to ESI, Table S3). Detailed NMR studies were also performed by monitoring the reaction of **C1c** and **C2**-**C4** with PO in d$_8$-toluene, which indicated the trend (*ortho* > *meta'* > *para* > *meta*) (refer to ESI, Figures S46 - 53). It is important to note that these studies were performed at ambient temperature to avoid inconsistencies with temperature variation upon transferring the Youngs NMR tube from the oil bath to the NMR instrument. While d$_8$-toluene solvent was selected to mimic the reaction solvent, the incomplete complex solubility at ambient temperature may potentially affect the rate of PO ring-opening. However, these studies also suggested that *ortho*-substituted **C2** is

the fastest initiator, where the electron-donating group is directly adjacent to Al. The kinetic studies show that the *para*- and *meta'*-substituted complexes are also efficient initiators, whereas the *meta*-substituted analogue is the least efficient. In general, the *ortho* and *para*-substituted complexes outperform the *meta'*- and *meta*-substituted complexes, suggesting that the resonance electronics influence the initiation efficiency (Figure S25). Both kinetic and NMR studies show that *meta'*-substituted **C4** is a better initiator than *meta*-substituted analogue **C1c**, which is attributed to the greater electronic influence of the *meta'* substituent adjacent to the C=N-Al group. While there is literature precedent for the ring-opening of PO to occur *via* nucleophilic attack at the methylene or methine position,[49] HSQC studies show that with **C1c** and **C2**-**C4**, attack occurs at the less sterically hindered methylene carbon (Figures S45 - 53).
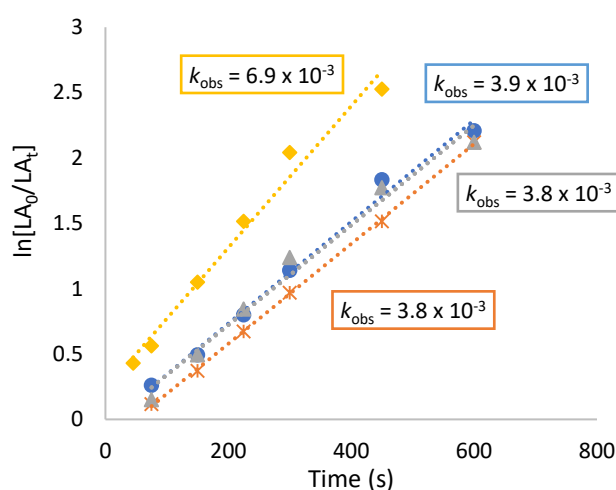

Figure 3: Kinetic plot of $\ln[LA_0]/[LA_t]$ vs time for *rac*-LA ROP catalysed by complexes*:* **C1c** (✕ k_{obs} = 3.8 x 10^{-3} s^{-1}, R^2 > 0.99), **C2** (◆ k_{obs} = 6.9 x 10^{-3} s^{-1}, R^2 = 0.98), **C3** (● k_{obs} = 3.9 x 10^{-3} s^{-1}, R^2 = 0.99) and **C4** (▲ k_{obs} = 3.8 x 10^{-3} s^{-1}, R^2 = 0.98). Reaction conditions: [catalyst]:[PO]:[rac-LA] = 1:50:100, [rac-LA] = 1 M in toluene, 120 °C.

As *ortho*-methoxy-substituted **C2** gave the highest catalyst activities, the influence of the steric bulk of the *ortho*-substituent was further investigated by testing the ethoxy-substituted analogue (**C6**) for *rac*-LA ROP. Based on the kinetic plots, the propagation rate increased slightly, from 6.9 x 10^{-3} s^{-1} to 7.9 x 10^{-3} s^{-1}, however the initiation period appears to be extended (Table 1). Whilst the electronic effect of the OMe and the OEt groups is similar, it is possible that the increased steric bulk of the ethoxy group hinders epoxide coordination and therefore slows down the initiation. This highlights the careful balance required between steric bulk, π-donating effects and σ-withdrawing effects which, when all optimised, can result in the most efficient polymerisation.

Table 1 Rate and initiation times of (salen)AlCl complexes

Complex	Rate (x10^{-3} s^{-1})	Initiation (s)
C1c	3.8 ± 0.04	49
C2	6.9 ± 0.4	7
C3	3.9 ± 0.2	7
C4	3.8 ± 0.3	11
C6	7.9 ± 0.5	24

Standard error calculated through least squares regression via LINEST function in excel, initiation time determined by backward extrapolation of the complex kinetic plot to determine x-intercept.

Conclusions

In conclusion, a series of ether-substituted (salen)AlCl complexes have been synthesised and characterised through a combination of multinuclear NMR spectroscopy, mass spectrometry and elemental analysis. In the presence of propylene oxide, all eight complexes display good catalytic activities and reasonable control towards LA ROP. The ether-substituted catalysts outperform the amino-substituted analogues, attributed to the enhanced Lewis acidity of Al through stronger σ-inductive and weaker π-donor effects of the methoxy substituents. The *ortho*-ether-substituted salens gave significantly faster initiation and propagation rates compared to the *meta*, *meta'* and *para* substituted regioisomers, as well as improved stereocontrol. Within LA ROP catalyst design, there is often a trade-off between fast propagation, effective initiation and good stereocontrol. Incorporating multifunctional ether-substituents in the *ortho*-position appears to enhance all three features: the rate of propagation through σ-electron-withdrawing effects; initiation through π-donation; and stereocontrol through increasing the steric bulk. These studies suggest that ether-substituents can be re-classified from electron-donating groups to multifunctional substituents, with the potential to improve initiation, propagation and stereocontrol in future ROP catalyst design.

Conflicts of Interest

There are no conflicts of interest to declare.

Acknowledgements

Electronic supplementary information (ESI) available.

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