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# Cooperative Heterometallic Catalysts for Lactide Ring-Opening Polymerisation: Combining Aluminium with Divalent Metals

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KEYWORDS: poly(lactic acid) heterometallic catalysis aluminum salen

While homometallic (salen)Al catalysts display excellent performance in lactide ring-opening polymerisation (ROP), heterometallic (salen)Al complexes have yet to be reported. Herein, we describe four heterobimetallic (salen)Al catalysts, and show that the choice of the heterometal is key. Cooperative Al/Mg and Al/Zn combinations improved the catalyst activity by a factor of up to 11 compared to the mono-Al analogue, whereas the mono-Mg and mono-Zn analogues were completely inactive. In contrast, Al/Li and Al/Ca heterocombinations stunted the polymerisation rate. Kinetic and computational studies suggest that Al/Mg and Al/Zn cooperativity arises from the close intermetallic proximity facilitating chloride bridging (thus enhancing initiation), which promotes a rigid square pyramidal geometry around the Al centre and further increases the available monomer coordination sites. This work also translates the use of ab initio molecular dynamics calculations to ROP, introducing a useful method of investigating catalyst flexibility and

revealing that ligand strain and molecular rigidity can enhance heterometallic catalyst performance.

## **Introduction**

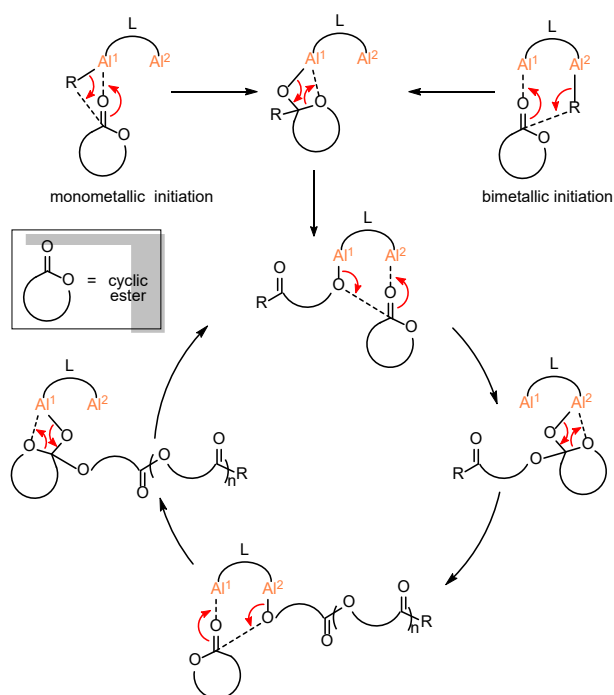
Heterometallic (mixed-metal) cooperativity is an emerging means of improving catalyst activity in small and macro-molecular transformations, and many heterometallic catalysts significantly outperform the monometallic analogues in terms of activity and selectivity.<sup>1</sup> This concept has been well-established in C-H activation,<sup>2</sup> metal-halogen exchange,<sup>3</sup> and olefin polymerisation<sup>4,5</sup> and has shown good promise in ring opening copolymerisation.<sup>6,7</sup> However, within the ring-opening polymerisation (ROP) of cyclic esters, the vast majority of catalyst development has focused on tailored ligand design. Heterometallic reactivity enhancement is an equally promising yet much less explored method of improving ROP catalyst performance, and many of the overarching design principles are still not well understood.<sup>8,9-11</sup>

Poly(lactic acid) (PLA) is a promising degradable alternative to some conventional engineering polymers, with applications ranging from commodity plastics to biomedicine.<sup>12-16</sup> While many monometallic ROP catalysts have been reported, aluminium salen catalysts are particularly notable as they provide excellent stereocontrol,<sup>17-22</sup> yet often suffer from low activity and thus require high temperatures or long reaction times to achieve high conversions. Aluminium salen complexes have been exploited in a range of transformations,<sup>23</sup> including cyclic carbonate synthesis,<sup>24</sup> epoxide resolution,<sup>25</sup> photoredox catalysis,<sup>26</sup> and polycarbonate synthesis,<sup>27</sup> and the salen ligand flexibility has been identified as a key factor in improving the catalyst activity.<sup>17,28,29</sup> On the basis of experimental and computational modelling studies, conventional wisdom in cyclic ester ROP suggests that increasing the length (and therefore the flexibility) of the diamino bridge increases the catalyst activity by enabling access to key transition states. This concept can be further explored

using ab initio molecular dynamics (AIMD), which offer a route to capturing the time-averaged geometry, thus giving a more quantifiable insight into the importance of dynamic atomic movements around the catalytic active site, applicable to a variety of transformations.

Homobimetallic catalysts are often highly active and can outperform the monometallic analogues in cyclic ester ROP,<sup>30–33</sup> with some bis-Al catalysts displaying activities eight times higher than the monometallic analogues, attributed to a proposed bimetallic mechanism (Figure 1).<sup>34,35</sup> Heterobimetallic complexes can further increase polymerisation activity, as electronic communication between the two metals can simultaneously alter the metal Lewis acidity and metal-R bond polarity hence nucleophilicity (where R is alkyl, alkoxy, carbonate or halide).<sup>36,37</sup> To the best of our knowledge only three LA ROP studies have reported heterometallic reactivity enhancements with salen complexes (Ni/La and Cu/Nd), none containing Al.<sup>38–40</sup> Indeed, very few heterobimetallic Al complexes have been reported for LA ROP (based on Li, Na or K/Al, Sm/Al and Y/Al),<sup>41–43</sup> and these have not always led to activity enhancements. Developing new heterometallic aluminium salen complexes not only offers a novel method of improving catalyst activity within LA ROP (as well as other catalytic transformations) but also an opportunity to understand which catalyst features are important in exploiting heterometallic cooperativity.

Heterometallic cooperativity between earth abundant and biocompatible metals is a particularly attractive goal.<sup>44,45</sup> In LA ROP, some of the most active systems are homobimetallic complexes based on magnesium and zinc,<sup>31,46–49</sup> and designing heterometallic complexes offers a route to combine the high activity of Mg or Zn with the control of (salen)Al systems. Herein we report four heterobimetallic complexes supported by an asymmetric salen ligand and reveal the influence of different heterometallic combinations on the structure and catalyst performance.



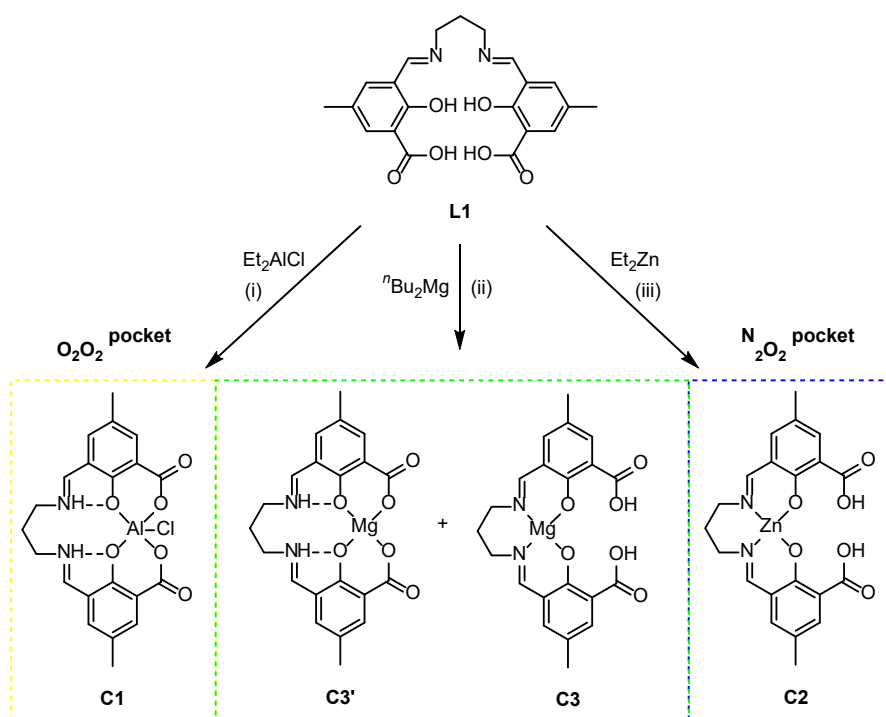
**Figure 1** Proposed chain shuttling mechanism for cyclic ester ROP initiated by homobimetallic Al complexes (L = piperazine-bridged bis(phenolato) / alkyl bridged salen ligand).<sup>34,35</sup>

## Results and Discussion

The acid-functionalised salen ligand, **L1** (Figure 2, Figure S1), can be tetra-deprotonated and contains two distinct metallation sites (imine-phenol,  $N_2O_2$ ; phenol-acid pocket  $O_2O_2$ ). While both trivalent (Al) and divalent metals (Mg and Zn) were successfully incorporated into the ligand scaffold to form monometallic complexes, the location depended on the metal valency, hardness and electropositivity (refer to ESI for details).

Di-deprotonation of **L1** with  $Et_2AlCl$  (Figure 2) gives Al coordination in the  $O_2O_2$  binding pocket. The  $^1H$  NMR resonance of the phenolic protons (12.36 ppm in  $d_6$ -DMSO, Figure S3) is in a similar range to both phenolic and iminium protons in comparable complexes,<sup>50,51</sup> perhaps indicating a bridged or transient proton state. Conservation of these protons is further evidenced

through unchanged integration and coupling to both imine and backbone proton resonances (Figure S15). Preferential deprotonation and metal coordination within the O<sub>2</sub>O<sub>2</sub> pocket can be rationalised by the relative acidity of the carboxylic acid protons ( $pK_a \approx 3.0$ ) *versus* the phenol protons ( $pK_a \approx 13.6$ ) of salicylic acid.<sup>52</sup> Subsequent or simultaneous addition of a second equivalent of Et<sub>2</sub>AlCl to **C1** gave no further reaction under the conditions tested. The acidity of the phenolic protons, Brønsted basicity of Et<sub>2</sub>AlCl and the well-documented metallation of salen Schiff-base N<sub>2</sub>O<sub>2</sub> ligands<sup>29</sup> suggests that bis-metallation with Al may be possible, however the presence of the Al-Cl unit may stabilise the product and lead to electrostatic repulsion or steric hindrance that prevents bis-metallation. This selectivity for mono-metallation of **L1** is a benefit of using Et<sub>2</sub>AlCl to prepare heterometallic complexes. While zinc complex **C2** shows exclusive phenol-OH deprotonation, both magnesium isomers (**C3** and **C3'**) were present in a 5:2 ratio (Figures 2, S4-S5). Heating the product mixture in *d*<sub>6</sub>-DMSO changed the **C3**:**C3'** ratio to 10:1, suggesting that proton exchange occurs to give **C3** as the thermodynamic product (Figure S5). The relative metal hardness (Al > Mg > Zn) and metal oxophilicities ( $\theta_{Al} = 0.8 > \theta_{Mg} = 0.6 > \theta_{Zn} = 0.2$ ) reflects the trend for chelation within the O<sub>2</sub>O<sub>2</sub> pocket,<sup>53</sup> which contains harder oxygen Lewis donors (*vs* nitrogen).<sup>54</sup> The similar ionic radii of Mg<sup>2+</sup> (72 pm) and Zn<sup>2+</sup> (74 pm) suggests that size is not a major factor.<sup>55,56</sup> Rather, the increased conformational flexibility and oxygen bonding afforded by the outer pocket may contribute to the preference for O<sub>2</sub>O<sub>2</sub> coordination of Mg and Al (Figure S2).<sup>57-59</sup>



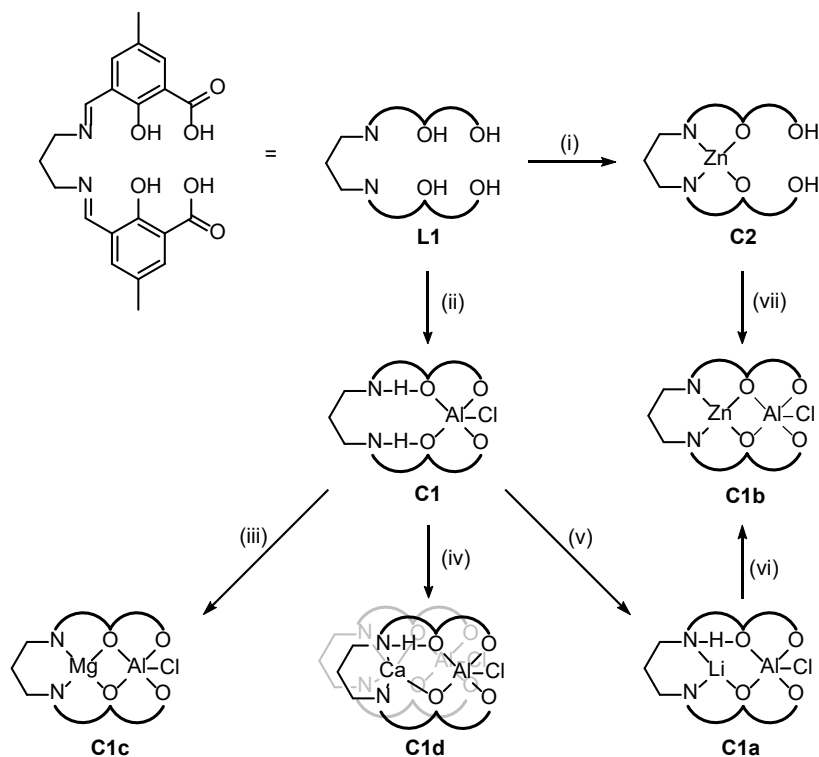
**Figure 2** Synthesis of complexes **C1**, **C2** and **C3** highlighting the different metallation sites. Optimised reaction conditions: (i): 1 eq  $\text{Et}_2\text{AlCl}$  in THF at  $-78^\circ\text{C}$ ; (ii): 1 eq  ${}^n\text{Bu}_2\text{Mg}$  in THF at RT; (iii): 1 eq  $\text{Et}_2\text{Zn}$  in THF at RT.

Most of the heterometallic catalysts reported for LA ROP are based on symmetric ligands,<sup>60</sup> yet asymmetric ligands offer potential benefits in simplifying heterometallic complex synthesis, with distinct binding pockets tailored for different metals (thus helping to avoid mixtures of homo- and hetero-metallic complexes). Heterometallic complexes were selectively obtained by incorporating a second metal (Li, Mg or Ca) into the  $\text{N}_2\text{O}_2$  binding pocket of **C1** through deprotonation with LiHMDS (**C1a**),  ${}^n\text{Bu}_2\text{Mg}$  (**C1c**) or  $\text{CaHMDS}_2$  (**C1d**) (Figure 3, iii-v). Direct metallation of **C1** with  $\text{Et}_2\text{Zn}$  generated a mixture of products, and so complex **C1b** was selectively prepared through two alternative routes (Figure 3, vi-vii). Sequential metallation using  $\text{Et}_2\text{Zn}$  then  $\text{Et}_2\text{AlCl}$  (Figure 3, i/vii) was deemed preferable over transmetallation from LiAl complex **C1a** (Figure 3, v/vi), as

this avoided the production of LiCl by-products which were challenging to remove (Figures S47-S48).

With complexes **C1b** (ZnAl) and **C1c** (MgAl), tetra-deprotonation of **L1** was supported by the absence of phenol and carboxylic acid ligand protons, as well as complete reaction of all Zn-Et/Mg-*n*Bu groups evidenced by <sup>1</sup>H NMR spectroscopy (Figure S8). Using 2 equivalents of LiHMDS (**C1a**) or a single equivalent of CaHMDS<sub>2</sub> (**C1d**) resulted in the formation of multiple products. Interestingly, reducing the heterometal stoichiometry to 1 or 0.5 equivalents of LiHMDS or CaHMDS<sub>2</sub> respectively, gave a single product in the <sup>1</sup>H NMR spectrum for each complex (Figures S9 and S10). The absence of phenol protons in these product <sup>1</sup>H NMR spectra, despite the reaction stoichiometry, is ascribed to the increased phenol proton acidity and hydrogen bonding/proton fluxionality causing peak broadening. With both **C1a** and **C1d**, incomplete deprotonation of **C1** is likely due to the steric hindrance within the N<sub>2</sub>O<sub>2</sub> pocket. The ionic radius of Li<sup>+</sup> (76 pm) is significantly larger than the atomic radius of H (37 pm),<sup>55,56</sup> and whilst it is similar to Mg<sup>2+</sup> (72 pm) and Zn<sup>2+</sup> (74 pm), the inclusion of two Li<sup>+</sup> in the N<sub>2</sub>O<sub>2</sub> pocket would greatly increase steric congestion. Similarly, the ionic radius of Ca<sup>2+</sup> (100 pm) is significantly larger than either magnesium or zinc. Instead of di-deprotonation of **C1** and coordination of calcium in the N<sub>2</sub>O<sub>2</sub> pocket, NMR studies suggest that **C1d** comprises two mono-deprotonated **C1** units bridged by calcium. This observation aligns with structural studies on related (salen)Ca and (aminophenol)Ca complexes, where Ca is situated above the ligand plane to reduce steric hindrance around the metal centre enabling coordination to two ligands.<sup>61,62</sup> Complex **C1d** was also analysed using ICP-OES, which confirmed the 2:1 Al:Ca ratio. <sup>1</sup>H NMR spectroscopy showed complete loss of the Ca-HMDS ligand resonance at -0.12 ppm, as well as the formation of HMDSH ( $\delta = 0.01$  ppm, Figures S10, S37).





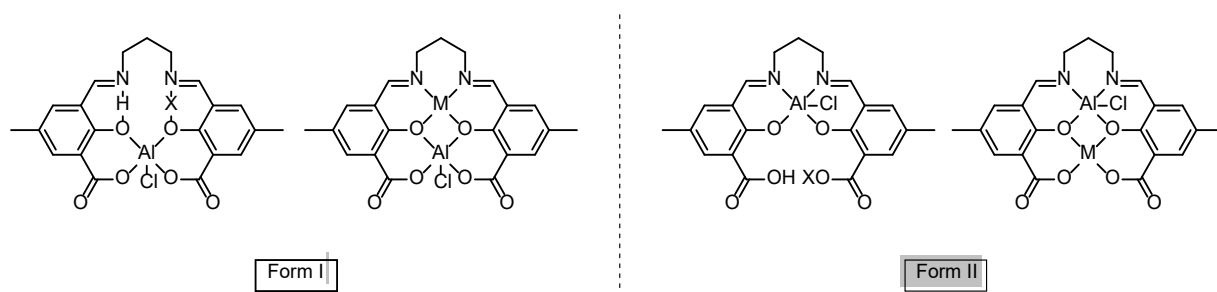
**Figure 3** Reactivity scheme for **L1** and complexes **C1**, **C2** and **C1a-d**. Reaction conditions: (i): 1 eq  $\text{Et}_2\text{Zn}$  in THF at  $-78\text{ }^\circ\text{C}$ ; (ii): 1 eq  $\text{Et}_2\text{AlCl}$  in THF at  $-78\text{ }^\circ\text{C}$ ; (iii): 1 eq  $n\text{Bu}_2\text{Mg}$  in DMSO at RT; (iv): 0.5 eq  $\text{CaHMDS}_2$  in DMSO at RT; (v): 1 eq  $\text{LiHMDS}$  in DMSO at RT; (vi): 1 eq  $\text{ZnCl}_2$  in DMSO at RT; (vii): 1 eq  $\text{Et}_2\text{AlCl}$  in DMSO at RT.

The  $^1\text{H}$  imine resonances of **C1a-C1d** correlate with the heterometal electropositivity (Figure S8), with an upfield shift relative to monometallic **C1** ( $\delta = 8.81$  ppm; **C1b**, 8.43 ppm,  $\chi_{\text{Zn}} = 1.65$ ; **C1c**, 8.40 ppm,  $\chi_{\text{Mg}} = 1.31$ ; **C1d**, 8.24 ppm,  $\chi_{\text{Ca}} = 1.00$ ; **C1a**, 8.20 ppm  $\chi_{\text{Li}} = 0.98$ ). Incorporating a heterometal can thus modify the electronics of the complex, akin to the better explored use of electron withdrawing/electron donating ligand substituents to modulate catalyst activity in

ROP.<sup>28,29,63</sup> Unfortunately, crystals of complexes **C1** and **C1a-d** suitable for X-ray diffraction studies could not be obtained due to limited complex solubility.

To explore the structural effect of incorporating a heterometal within the ligand, a series of geometry optimisation calculations were performed for complexes **C1** and **C1a-C1c**, at the B3LYP/6-311G\* level (see ESI). In heterobimetallic complexes **C1a-C1c**, DFT simulations support the metal arrangement predicted by <sup>1</sup>H NMR analysis, with Al in the O<sub>2</sub>O<sub>2</sub> binding pocket and Li/Zn/Mg within the N<sub>2</sub>O<sub>2</sub> pocket (form I, Table 1). Conversely, DFT models of homometallic **C1** determined the lower energy conformation is form II, albeit with a difference of just 9.2 kJ mol<sup>-1</sup> (Table S2). These calculations suggest that the **C1-I** (form I) structure observed experimentally is likely to be the kinetic, rather than the thermodynamic, metallation product. The low energy difference between **C1-I** and **C1-II** indicates that experimental conditions and solvent effects may influence the product distribution. The geometry around Al was investigated to determine the  $\tau_5$  character (where 0.00 represents an ideal square pyramidal geometry and 1.00 represents an ideal trigonal bipyramidal geometry).<sup>64</sup> For each complex, form I displayed greater square pyramidal character and a reduced inter-metal separation (by c.a. 0.1 – 0.4 Å, Table 1). For all heterometallic complexes, the Cl atom resides closer to the heterometal in form I (*vs* form II), as demonstrated by shorter M-Cl distances and increased Al-Cl bond lengths (Table 1). The short M-Cl distances observed for **C1a** and **C1c** suggest a  $\mu^2$ -Cl binding motif.

**Table 1** Top: Structural comparison of form I and form II of complexes **C1** (X = H), **C1a** (X = Li), **C1b** (M = Zn) and **C1c** (M = Mg). Bottom: Comparison of Al metal geometry, internal strain, intermetallic separation and Al-Cl bond length of complexes **C1** and **C1a-C1c**, calculated at the B3LYP/6-311G\* level.

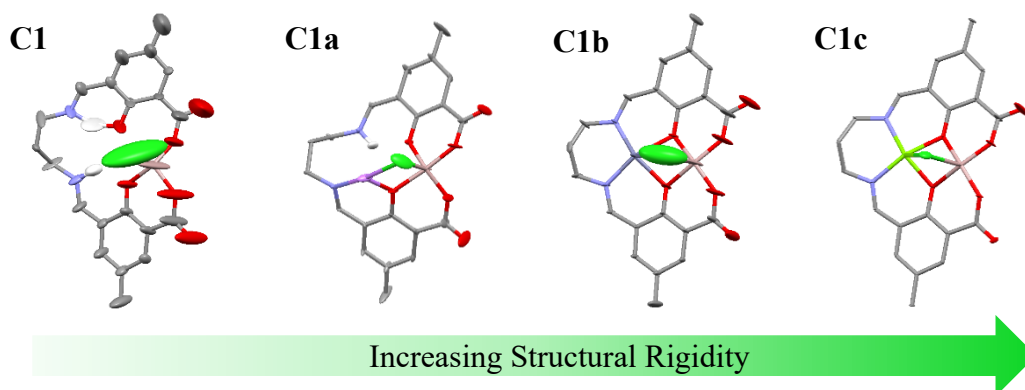


Complex	$\tau_5$ character <sup>[a]</sup>	$\Delta G_{\text{strain}}$ (kJ mol <sup>-1</sup> )	Intermetallic separation (Å)	Al – Cl bond length (Å)	M – Cl bond length / distance (Å)
<b>C1-I</b>	0.71	82.5	-	2.20	-
<b>C1-II</b>	0.87	120.4	-	2.18	-
<b>C1a-I</b>	0.57	159.9	2.93	2.27	2.32
<b>C1a-II</b>	0.83	152.1	3.32	2.17	4.20
<b>C1b-I</b>	0.15	188.0	3.04	2.20	3.46
<b>C1b-II</b>	0.53	166.5	3.14	2.17	4.23
<b>C1c-I</b>	< 0.01	197.2	2.83	2.32	2.60
<b>C1c-II</b>	0.54	170.2	3.08	2.17	4.13

[a]  $\tau_5$  character determined according to the method published by Addison, Reedijk *et al.*<sup>64</sup>

To investigate the structure and dynamics of **C1-I** and **C1a-C1c-I** in more detail, AIMD simulations were performed to calculate the thermal motion of all atoms at room temperature over a 6 ps timescale (see ESI).<sup>65,66</sup> The resulting time averaged structures (Figure 4), with atomic displacement parameters (ADPs) expressed at the crystallographic standard 50% probability

ellipsoidal level, capture significant functional group movement and provide insight into the structure-activity trends expressed by these complexes. Complex **C1** has a high degree of structural mobility, which is particularly noticeable at the chloride and aromatic carbon centres. Multiple proton transfer events were observed along the N...H...O hydrogen bond linkage in the N<sub>2</sub>O<sub>2</sub> pocket, resulting in the bridging time-averaged ellipsoidal model shown in Figure 4. Incorporating a heterometal increases the rigidity through the formation of additional six-membered ring(s), with MgAl complex **C1c** displaying the highest rigidity of all (Figure 4). All three heterobimetallic structures show a bridging Cl-heterometal interaction. The identity of the heterometal appears to directly affect the Cl mobility: the small Cl ADP observed in rigid **C1c** contrasts markedly with the larger ADP of the ZnAl **C1b** structure, which suggests a high degree of flux between a bridged and non-bridged state in **C1b**. This increased flux in **C1b** (vs **C1a** and **C1c**) is likely due to the Lewis acidity of the heterometal, with shorter M-Cl distances observed for the most electropositive metals ( $\chi_{\text{Li}} = 0.98$ , M-Cl = 2.30 Å;  $\chi_{\text{Mg}} = 1.31$ , M-Cl = 2.63 Å;  $\chi_{\text{Zn}} = 1.65$ , M-Cl = 2.80 Å). The increased Al-Cl bond length in complexes **C1a** (2.28 Å), **C1b** (2.22 Å) and **C1c** (2.30 Å) relative to monometallic **C1** (2.03 Å) is attributed to the dative M-Cl bond lengthening, thereby weakening the Al-Cl bond.



**Figure 4** AIMD time-averaged structures of complexes **C1** (left), **C1a** (middle left), **C1b** (middle right) and **C1c** (right).

Complexes **C1-3** and **C1a-C1d** were tested for their activity toward *rac*-lactide (*rac*-LA) ROP. The complex, initiator (propylene oxide, PO) and monomer (*rac*-LA) were mixed in a 1:50:100 ratio in toluene at 120 °C, conditions chosen as optimised for homometallic (salen)AlCl initiators (Table 2, Table S1 and Figure 5).<sup>28</sup> The polymerisation was also tested with a 1:1 catalyst:PO ratio, however this significantly reduced the catalyst activity, likely due to inefficient initiation reflected by higher than predicted  $M_n$  values (Table S1, entry 20). In line with previously reported (salen)AlCl complexes, monometallic **C1** was inactive towards *rac*-LA ROP; however, *in situ* ring-opening of PO generated an active aluminium alkoxide initiator (Table S1, entries 1-6). Complexes **C1b** (ZnAl,  $k_{\text{obs}} = 1.8 \times 10^{-3} \text{ s}^{-1}$ ) and **C1c** (MgAl,  $k_{\text{obs}} = 8.8 \times 10^{-3} \text{ s}^{-1}$ ) both displayed marked reactivity enhancements, outperforming homometallic **C1** by respective factors of 2 and 11 (Al,  $k_{\text{obs}} = 0.8 \times 10^{-3} \text{ s}^{-1}$ , Figure 5) and forming atactic PLA. MALDI-ToF end-group analysis confirmed initiation *via* PO ring-opening (Figure S57). Both complexes **C1b** and **C1c** produced PLA with a similar degree of control to monometallic **C1** ( $\mathcal{D} \approx 1.2$ ). PLA with increased dispersity and poor  $M_n$  agreement was obtained at high conversions using **C1b** (Table 2, entry 8,  $\mathcal{D} = 1.63$ ), which is attributed to post polymerisation transesterification reactions such as the formation of cyclic PLA as evidenced by MALDI-ToF analysis (Figure S58). It is also possible that the zinc complex may catalyse some depolymerisation in the late stages of the reaction, as has been reported for some other zinc-based catalysts.<sup>67,68</sup> **C1b** was also tested with higher lactide loading (300-1000 eq, Table S1 entries 21-23) displaying good activity and similar polymerisation control, albeit with a slight reduction in catalyst activity. In contrast to **C1b**, **C1c** yields good  $M_n$  agreement; the improved propagation rate of catalyst **C1c** may outcompete transesterification to give greater control over the resultant PLA.

**Table 2** *Rac*-lactide ROP mediated by catalysts **C1** and **C1a-C1d**.<sup>[a]</sup>

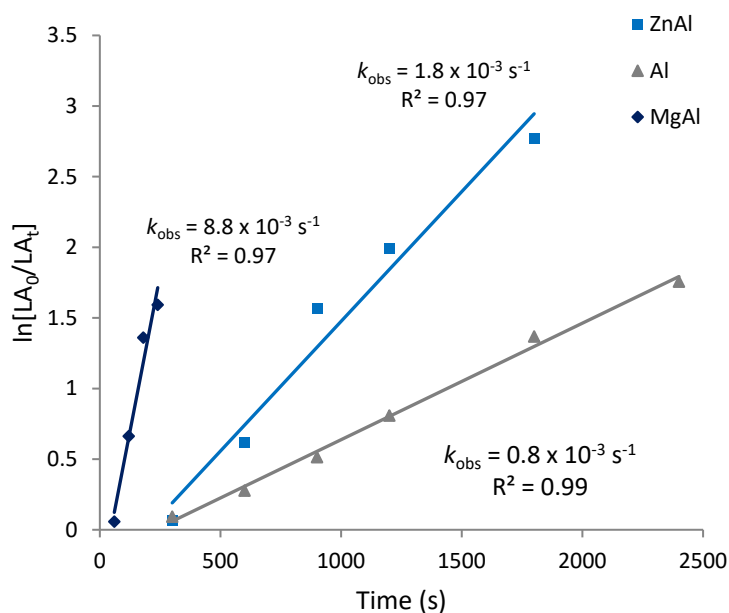
Entry	Catalyst	Time (min)	% Conversion <sup>[b]</sup>	$M_{n,calc} / Da$ <sup>[c]</sup>	$M_{n,obs} / Da$ <sup>[d]</sup>	$\bar{D}$ <sup>[d]</sup>
1 <sup>[e]</sup>		30	-	-	-	-
2	<b>C1</b>	5	9	1270	810	1.25
3		10	24	3490	2710	1.10
4		40	83	11910	7640	1.21
5		<b>C1a</b>	5	3	400	390
6	30		24	3490	1600	1.35
7	<b>C1b</b>	5	6	900	670	1.10
8		30	94	13500	5610	1.63
9	<b>C1c</b>	2	48	6980	7190	1.14
10		5	80	11550	8930	1.22
11		10	90	13020	10140	1.25
12	<b>C1d</b>	5	3	-	-	-
13		15	7	-	-	-
14	<b>C2</b>	30	-	-	-	-
15	<b>C3</b>	30	-	-	-	-

[a] Reaction conditions: 0.0212 mmol catalyst [catalyst]/[PO]/[*rac*-LA] = 1:50:100, [*rac*-LA] = 1 M in toluene, 120 °C. [b] Determined by <sup>1</sup>H NMR spectroscopy. [c] Calculated as ([*rac*-LA]/[catalyst])×(%conversion/100)×MW of lactide, assuming that only one chain grows per catalyst system. [d] Determined by size-exclusion chromatography (SEC) in THF, universal calibration relative to polystyrene standards,  $M_n$  was calculated considering Mark–Houwink’s corrections for  $M_n$  ( $M_n(\text{calc}) = 0.58[M_n(\text{SEC})]$ ).<sup>73</sup> [e] No PO added.

Previously reported Al-salen catalysts have been tested under a range of conditions, with reported  $k_{\text{obs}}$  values typically ranging from  $1.9 \times 10^{-6}$  to  $6.9 \times 10^{-3} \text{ s}^{-1}$ .<sup>19,20,28,35,63,69–72</sup> While the different conditions limit direct comparison, to the best of our knowledge the incorporation of Mg within complex **C1c** gives the fastest (salen)Al-chloride catalyst reported for *rac*-LA ROP to date ( $k_{\text{obs}} = 8.8 \times 10^{-3} \text{ s}^{-1}$ , Figures S55 and S56). While these heterometallic (salen)Al catalysts are

slower than the fastest homometallic Mg and Zn catalysts for *rac*-lactide ROP, they display good activities compared to state-of-the-art Al systems albeit under different reaction conditions (Figure S64, Table S4), and provide insight into the features underpinning heterometallic cooperativity.

The reactivity enhancement observed with complexes **C1b** and **C1c** is partly attributed to the presence of the second, Lewis acidic metal providing additional monomer coordination sites. The cooperative bimetallic mechanism proposed by Yao *et al.* (Figure 1) highlights the importance of monomer coordination in close proximity to the metal-O(polymer) chain, which may, in part, rationalise the reactivity enhancements observed with heterometallic **C1b-c**.<sup>34</sup> Catalysts **C1b** and **C1c** each feature a single initiating group per catalyst as an important feature. The lack of catalytic activity observed with homometallic **C2** and **C3** (Table 2) emphasizes the importance of initiating groups. Bimetallic catalysts with two initiating groups can produce two growing polymer chains;<sup>35</sup> in some cases, the two metal centres operate independently thus creating a misleading appearance of improved catalyst activity compared to the monometallic analogues. Further, close proximity between two propagating (metal-coordinated) polymer chains can result in enhanced chain transfer and transesterification, thus reducing polymerisation control.<sup>74</sup> Bimetallic catalysts with a single initiating group offer a means to improve control and reduce steric congestion around the metal centres, facilitating monomer access to key transition states involved in ROP.



**Figure 5** Kinetic plot of  $\ln[LA]_0/\ln[LA]_t$  versus time for the ROP of *rac*-LA catalysed by complexes **C1b** (■), **C1c** (◆) and **C1** (▲). Reaction conditions: [catalyst]/[PO]/[*rac*-LA] = 1:50:100, [*rac*-LA] = 1 M in toluene, 120 °C.

Enhancing the metal Lewis acidity through salen ligand modification often improves propagation but reduces the initiation efficiency.<sup>17,29,75</sup> Heterometallic cooperativity may overcome this dichotomy: enhancing monomer coordination by providing additional Lewis acid sites, whilst also lengthening and weakening the Al-Cl bond to boost initiation. Heterometallic **C1b** and **C1c** outperform monometallic **C1** in both initiation efficiency and propagation rate. Computational modelling simulations performed on **C1** indicate that dynamic proton transfer occurs in the  $N_2O_2$  pocket, with the optimised structure favouring the proton bound to the nitrogen atom. Elegant studies by Romain *et al.* on related (salen)Al complexes have shown that ligand N-H groups can facilitate LA coordination and activation through noncovalent interactions (NCIs).<sup>76</sup> However, with our bimetallic systems, tetra-deprotonated **C1b** and **C1c** outperform **C1** in LA



ROP, suggesting that any beneficial NCIs are outweighed by the Lewis acidic heterometal providing additional LA coordination sites or cooperative metal-metal effects, although the hindered accessibility of equatorial N-H groups in **C1** may also restrict LA coordination.<sup>77</sup>

The activity enhancements demonstrated by **C1b** and **C1c** correlate with literature reports showing that increased metal electropositivity can enhance LA polymerisation rate,<sup>78</sup> (Mg > Zn vs **C1**), whereas **C1a** (LiAl) and **C1d** (CaAl) contradict this trend. However, **C1a** and **C1d** both retain highly acidic phenolic protons, which may quench the polymerisation. Unlike conventional chain transfer agents, reactions with the phenolic protons would form resonance stabilised metal-phenoxide species as poor initiators, which may reduce the catalyst activity.

Extrapolation of the kinetic plots for catalysts **C1**, **C1b**, **C1a** and **C1c** gave polymerisation induction periods of 4 min, 3 min, 2.5 min and 1 min, respectively. Longer (and weaker) Al-Cl bonds (determined from the AIMD time-averaged structure) suggest a greater chloride nucleophilicity, which in turn drives a faster initiation step (Al-Cl bond lengths: **C1** 2.03 Å, **C1b** 2.22 Å, **C1a** 2.28 Å, **C1c** 2.30 Å, Table S3). Structures **C1b** and **C1c** suggest that magnesium acts as a better Cl lone pair electron acceptor than zinc, as evidenced by a shorter M-Cl bond length and reduced intermetallic separation (Figure 4 and Table 1). The longer Al-Cl bond in **C1c** may also indicate some “ate” behaviour, where the more electronegative metal (Zn > Al > Mg, *vide supra*) can adopt a formal negative charge, stabilised by the counter-cation formed from the electropositive metal.<sup>36</sup> For example, heterobimetallic combinations of metal halides AlCl<sub>3</sub>, MgCl<sub>2</sub> and ZnF<sub>2</sub> have been shown to form aluminium zincates and magnesium aluminates through halide transfer to generate an ion pair.<sup>79,80</sup> Complexes **C1b** and **C1c** may therefore display some aluminium zincate and magnesium aluminate character, each containing a bridging halide due to

intermetal proximity. The formation of ate species could partially account for the improved reactivity of **C1c** and **C1b** by increasing the Lewis acidity of Mg/Al, as well as enhancing the nucleophilicity of the Al-OR/Zn-OR bond, respectively; monomer coordination and nucleophilic attack are both key steps in *rac*-LA ROP. A limited number of Al-Cl complexes have been reported for LA ROP, and the examples reported to date require an external or internal Lewis base (e.g. PPnCl<sup>81</sup> or electron donating ligand substituents) to increase the nucleophilicity of the Al-Cl bond towards initiation.<sup>28</sup> The use of onium salts such as PPnCl have been proposed to transfer a chloride ion to the Al metal centre to form an active aluminate species. Here, incorporation of a second Lewis acidic metal may mimic this effect, not only forming an active ate complex but providing the secondary benefit of additional metal coordination sites for monomer activation.

The introduction of divalent metals and consequent chloride bridging causes a distortion to square pyramidal geometry at the adjacent Al metal centre, correlating with increased ROP rates (Figure S62). Square pyramidal geometry provides a larger vacant site at Al relative to a trigonal bipyramidal coordination; an effect highlighted by comparing the Spacefill model of **C1c-I** (Gaussian calculations,  $\tau_5 = < 0.01$ ) to **C1a-II** (Gaussian calculations,  $\tau_5 = 0.83$ ) (Table 1, Figure S61). The vacant site provides an accessible surface for epoxide coordination during initiation and lactide coordination during propagation, thus avoiding long induction periods and low polymerisation activity. The tetra-anionic ligand scaffold prevents coordinative saturation at the metal centres, as only one co-ligand (initiator) is required for charge balance.<sup>82</sup> Studies on monometallic catalysts for cyclic ester ROP have suggested that trigonal bipyramidal geometries require lower framework distortion energies to access key octahedral transition states compared to the square pyramidal analogues; this reactivity trend appears to be less relevant or completely reversed with heterometallic complexes **C1b-c**.<sup>83–85</sup>

Within monometallic Al-salen complexes, increased ligand flexibility is generally accepted to improve cyclic ester polymerisation rates; this observation has been borne out by multiple experimental and computational studies.<sup>28,29,84,85</sup> Molecular dynamic DFT calculations can provide deeper insight into this key aspect of polymerisation catalysis. In contrast to monometallic literature systems, AIMD studies show that for heterobimetallic systems, reduced structural mobility (**C1c** << **C1b** < **C1a** < **C1**) generally corresponds to increased polymerisation rate (**C1c** > **C1b** > **C1** > **C1a**). Similarly, the ligand strain DFT calculations suggest that increased strain correlates with an increased rate of polymerisation (**C1c-I**: 197.2 kJ mol<sup>-1</sup>,  $k_{\text{obs}} = 8.8 \times 10^{-3} \text{ s}^{-1}$  > **C1b-I**: 188.0 kJ mol<sup>-1</sup>,  $k_{\text{obs}} = 1.8 \times 10^{-3} \text{ s}^{-1}$  > **C1a-I**: 159.9 kJ mol<sup>-1</sup>,  $k_{\text{obs}} = 0.8 \times 10^{-3} \text{ s}^{-1}$ ) (Table 1). With complexes **C1b** and **C1c**, the proximity of the heterometallic coordination site appears to overcome the need for ligand flexibility. Indeed, the increased strain in **C1b** and **C1c** may facilitate access to octahedral transition states previously proposed in cyclic ester ROP.<sup>83</sup> In contrast to monometallic salen systems,<sup>84</sup> our observations suggest that square pyramidal Al geometry facilitates monomer-metal coordination, and hence rapid polymerisation.

These observations suggest that the conventional design parameters established for monometallic (salen)Al ROP catalysts should be revisited for heterometallic analogues, which offer a promising method of improving catalyst performance. These studies also highlight the opportunity to use AIMD calculations within future catalyst development, showcasing the power of this method to capture time-averaged catalyst geometries and gain a deeper understanding of structure-activity relationships and the origins of heterobimetallic cooperativity. These insights provide underpinning methodologies for future heterometallic ROP catalyst design, which may also apply to other catalytic transformations, as aluminium salen catalysts have wide-reaching applications spanning small molecule transformations and ring-opening (co)polymerisation.

## **Conclusion**

A series of mono- and bi-metallic complexes were derived from an acid salen ligand scaffold, characterised and tested for *rac*-LA ROP. The heterobimetallic MgAl and ZnAl catalysts significantly outperform the analogous monometallic Al complex, whereas the LiAl and CaAl catalysts do not. These studies emphasize that the heterometal must be carefully chosen as ionic radius, charge and electronegativity can all affect the complex structure and polymerisation activity. Previous studies with monometallic (salen)Al catalysts have shown that increased ligand flexibility improves catalyst activities in cyclic ester ROP, yet our studies show that this conventional wisdom does not hold true for heterometallic systems. Indeed, molecular dynamic simulations suggest that rigidity can be an important characteristic in heterobimetallic salen systems. This work unveils the potential of AIMD simulations in polymerisation catalysis, to understand structural flexibility and test experimental design methodology, leading to a deeper understanding of which catalyst features influence activity. Future heterometallic catalyst design should consider the introduction of a secondary metal as a promising method to simultaneously increase Lewis acidity and M-OR nucleophilicity as well as rigidity. These studies suggest that ROP catalyst design principles that are widely accepted for monometallic catalysts may need to be revisited for heterometallic systems, to exploit the exciting potential of cooperative heterometallic catalysis within cyclic ester ROP, as well as other fields.

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## Abbreviations

AIMD, ab initio molecular dynamics; ADP, atomic displacement parameters; COSY, homonuclear correction spectroscopy; DFT, density functional theory; DMSO, dimethyl sulfoxide;  $\epsilon$ -CL,  $\epsilon$ -caprolactone; HMDS, bis(trimethylsilyl)amine; HSQC, heteronuclear single quantum correlation spectroscopy; ICP-OES, inductively coupled plasma optical emission spectrometry; LA, lactide; MALDI-ToF, matrix-assisted laser desorption/ionisation – time of flight; NCI, noncovalent interaction; PO, propylene oxide; PLA, poly(lactic acid); ROP, ring-opening polymerisation; RT, room temperature; TBP, trigonal bipyramidal.

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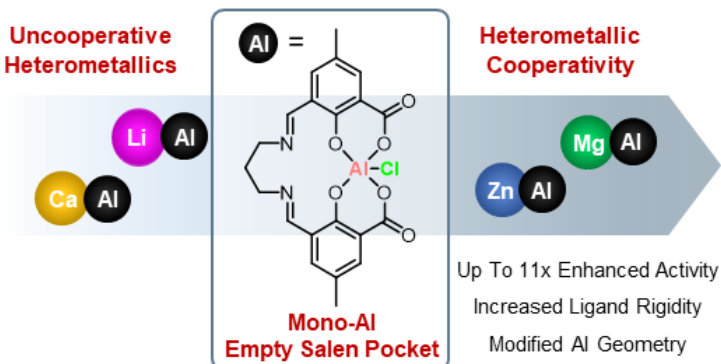
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## Table of Contents



### Synopsis:

Careful choice of the heterometal is key in determining whether or not heterometallic Al salen complexes exhibit cooperative catalysis in lactide ring-opening polymerisation. Experimental studies combined with *ab initio* molecular dynamic simulations reveal that metal-metal proximity, chloride bridging, aluminium centre geometry and ligand rigidity are important parameters underpinning cooperative catalysis, all of which are influenced by the heterometal.