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Salt additives as activity boosters: a simple strategy to access heterometallic cooperativity in lactide polymerisation†

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Inorganic salt additives can activate carbonyl groups towards organic addition reactions. Here, we translate this concept to ring-opening polymerisation for the first time, generating heterometallic ProPhenol catalysts *in situ*, which show similar activity enhancements to pre-formed heterometallic complexes. Extremely high activities are observed, with K/Mg and K/Ca combinations converting > 85 eq. lactide in 5 s at room temperature.

Heterometallic cooperativity can boost catalyst performance, yet heterometallic catalyst development lags behind homometallic analogues due to the synthetic challenge of preparing heterometallic complexes.¹ A simple and attractive route to heterometallic cooperativity involves the *in situ* addition of inorganic salts (e.g. LiCl) to homometallic reagents. This method has been exploited in nucleophilic addition, deprotonative metallation and metal–halogen exchange.² For example, Knochel's pioneering work combined RMgCl with stoichiometric LiCl to form “Turbo-Grignard” reagents such as (TMP)MgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidine), which generally showed improved functional-group tolerance and deprotonative power towards aromatic and heterocyclic substrates that are inert to conventional Grignard reagents.^{3–5}

Lewis acidic salt additives can activate carbonyl compounds towards addition reactions *via* carbonyl coordination.^{6,7} For example, lanthanide salts (LnCl₃·2LiCl, Ln = La, Ce or Nd) have facilitated 1,2-addition of Grignard reagents (Fig. 1).⁸ This concept is relevant to the ring-opening polymerisation (ROP) of carbonyl-containing *rac*-lactide (*rac*-LA), as Lewis acidic monomer activation *via* coordination to a metal is a key mechanistic step and promotes nucleophilic attack from a M-OR group (Fig. 1).⁹ *rac*-LA ROP is an efficient route to produce biodegradable and biocompatible poly(lactic acid)

(PLA),^{9,10} with packaging,¹¹ electronic and biomedical applications.¹² While the use of simple inorganic salts has not been explicitly explored in ROP, recent studies hinted that salts may act as activity boosters. Use of a silver salt with a non-coordinating anion (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) “switched on” the reactivity of a Ti(salen) complex;¹³ a 1 : 1 Ti(salen) : AgBARF mixture converted 76 eq. *rac*-LA in 1 h while the homometallic counterparts were inactive after 4 h (R.T., DCM). Our preliminary studies suggested that *in situ* addition of potassium benzoxide (KOBn) to a bis-Zn Trost ProPhenol complex gave significant activity enhancements in *rac*-LA ROP.¹⁴

Among isolated heterometallic ROP catalysts, the highest activities have generally been observed when a hard metal (M₁, e.g. Group 1/Ln) is paired with a softer, more carbophilic metal (M₂, e.g. Mg/Zn),^{14,15} with large and Lewis acidic M₁ proposed to provide additional monomer coordination sites and thus accelerate ROP. These heterometallic catalytic features could potentially also be accessed by combining inorganic salts with homometallic ROP catalysts. This would give access to a wide range of heterocombinations that can be more rapidly tested than isolated heterometallic catalysts. Herein, this concept is investigated in *rac*-LA ROP for the first time, comparing the activities using *in situ* salt additives to isolated heterometallic catalysts. The catalyst solution-state structures are investigated by NMR spectroscopy, highlighting the dynamic equilibria and complex nature of catalytic species in solution.

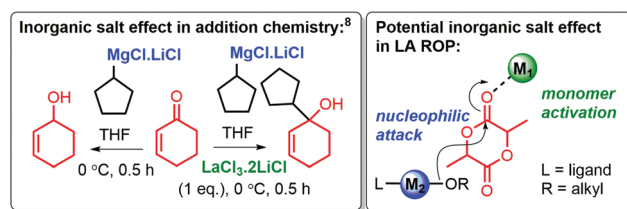
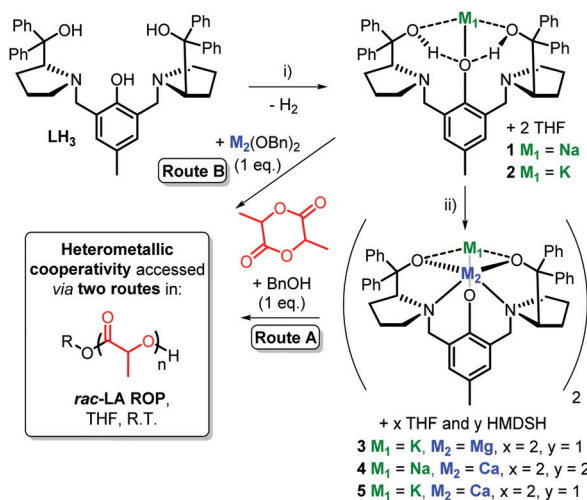


Fig. 1 The inorganic salt effect in addition chemistry and potential effect in LA ROP.

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Scheme 1 Synthesis of **1–5**. Reaction conditions: (i) 1.1 eq. M_1H ($M_1 = Na, K$), THF, R.T., 2 h; (ii) 1 eq. $M_2(HMDS)_2(THF)_n$ ($M_2 = Mg, n = 0$; $M_2 = Ca, n = 2$), THF, R.T., 1 h.

Starting from previously reported $[LH_2Na(THF)_2]$ (**1**) or $[LH_2K(THF)_2]$ (**2**),¹⁴ two routes towards heterometallic catalyst systems were explored (Scheme 1), one involving the isolation of heterometallic complexes (Route A) and the other exploiting the use of *in situ* salt additives (Route B). In Route A, heterometallic complexes $[LKMg]_2$ (**3**), $[LNaCa]_2$ (**4**) and $[LKCa]_2$ (**5**) were obtained *via* deprotonation of **1** or **2** with $Mg(HMDS)_2$ or $Ca(HMDS)_2(THF)_2$ (1 eq.). However, the synthesis of $[LNaMg]_2$ from **1** and 1 eq. $Mg(HMDS)_2$ was less selective, generating a product mixture that included $[LMg_2(HMDS)]$ as a major component. Complexes **3–5** were subsequently tested in *rac*-LA ROP using benzyl alcohol (BnOH) as an initiator. Route B featured *in situ* addition of a metal-benzoxide salt ($Mg(OBn)_2$ or $Ca(OBn)_2$) to **1** or **2**, and gave access to the Na/Mg heterocombination, highlighting a potential benefit of salt additives *vs.* the more synthetically challenging isolation of **3–5** (Route A). Heterometallic complexes **3–5** were characterised by NMR spectroscopy, mass spectrometry and elemental analysis (see ESI†). ¹H NMR analysis in THF-*d*₈ confirmed deprotonation of the benzylic OH moieties of **1** or **2** with $Mg(HMDS)_2$ or $Ca(HMDS)_2(THF)_2$, based on the disappearance of resonances at 9.96 (**4**, Fig. S6, ESI†) and 10.25 ppm (**3** and **5**, Fig. S2 and S9, ESI†). APPI-MS analysis confirmed heterometallic molecular ion peaks for **3–5**, and both APPI-MS and DOSY NMR analysis in THF-*d*₈ showed that **3–5** are dimeric (Fig. S3, S5, S7, S8, S10 and S11, ESI†).

Complexes **3–5** were extremely active initiators for *rac*-LA ROP with 1 eq. BnOH (R.T., THF, Table 1). Strikingly, K-based **3** and **5** converted 98 and 83 eq. *rac*-LA, respectively, in just 5 s. Na-based **4** was less active, converting 85 eq. *rac*-LA in 40 s. Notably, **3–5** all outperformed the previous heterometallic front-runners $[LNaZn_2Et_2(THF)_2]$ (**6**) and $[LKZn_2Et_2(THF)_2]$ (**7**) at R.T. in THF.¹⁴ **3** and **5** were too active to plot accurate kinetics, yet the slowest of the three catalysts, **4**/1 eq. BnOH, displayed $k_{obs} = 3.3 \times 10^{-2} s^{-1}$ (Fig. S16, ESI†), which is

Table 1 ROP of *rac*-LA catalysed by heterometallic **3–5**, homometallic **1–2**, **8–9**, $Mg(OBn)_2$, $Ca(OBn)_2$ and the 1 : 1 mixtures of **1** or **2** and $M(OBn)_2$ ($M = Mg, Ca$ or Zn)

Entry	Cat.	Time (s)	Conv. ^a (%)	$M_{n,obs}$ ^b (Da)	$M_{n,calc}$ ^c (Da)	\bar{D}^b
1 ^d	3	5	7	—	—	—
2	3	5	98	13 100	14 100	1.83
3 ^d	4	40	31	2100	4500	1.23
4	4	5	34	2900	4900	1.24
5	4	40	85	5600	12 300	1.56
6 ^d	5	5	7	—	—	—
7	5	5	83	6200	12 000	1.51
8 ^d	1	5	32	10 300	9200	2.50
9 ^d	2	5	59	29 700	8500	2.16
10 ^{de}	8	600	12	—	—	—
11 ^d	9	40	47	2800	6800	1.50
12 ^d	$Mg(OBn)_2$	5	8	—	—	—
13 ^d	$Ca(OBn)_2$	5	49	3000	3500 ^f	1.25
14 ^d	1 + $Ca(OBn)_2$	5	87	11 900	6300 ^f	1.77
15 ^d	2 + $Ca(OBn)_2$	5	88	13 900	6300 ^f	2.04
16 ^d	1 + $Mg(OBn)_2$	5	76	7500	5500 ^f	1.79
17 ^d	2 + $Mg(OBn)_2$	5	83	13 500	6000 ^f	1.40
18 ^d	$Zn(OBn)_2$	5	0	—	—	—
19 ^d	1 + $Zn(OBn)_2$	5	50	4400	3600 ^f	1.24
20 ^d	2 + $Zn(OBn)_2$	5	89	8900	6400 ^f	1.58

100 : 1 : 1 LA : cat : BnOH, $[LA] = 1$ M (THF). No stereocontrol was observed with **3–5**, **1**: $Ca(OBn)_2$, **2**: $Mg(OBn)_2$ or **2**: $Ca(OBn)_2$ as atactic PLA was generated ($P_i \approx 0.5$).²⁰ ^a Calculated by ¹H NMR spectroscopy. ^b Determined by SEC *vs.* polystyrene standards in THF using Mark-Houwink correction factor (0.58).²¹ ^c Calculated from monomer conversion $M_{n,calc} = M_0 \times ([M]/[I]) \times$ conversion assuming 1 chain per catalyst. ^d No BnOH. ^e Polymerisations run at 60 °C. ^f Calculated assuming 2 chains per catalyst.

10 times faster than **6**/2 eq. BnOH ($k_{obs} = 3.2 \times 10^{-3} s^{-1}$) and twice as fast as **7**/2 eq. BnOH ($k_{obs} = 1.7 \times 10^{-2} s^{-1}$). To the best of our knowledge, this makes **3–5**/BnOH the three fastest heterometallic *rac*-LA ROP catalysts reported to date. **3–5** maintained high activity at 0.33–0.5 mol% catalyst loadings (Table S1, ESI†) but were hindered at 0.1–0.2 mol% loadings, tentatively attributed to catalyst decomposition under dilute polymerisation conditions. At 0.33–0.5 mol% loadings, **5** outperformed **3**, converting 76 eq. *rac*-LA in 5 s *vs.* 53 eq. with **3** at 0.5 mol% catalyst loading. This suggests that the combination of large and Lewis acidic K^+ and Ca^{2+} gives superior activity by accelerating *rac*-LA coordination thus propagation.

The more active K-based complexes **3** and **5** displayed reduced polymerisation control *vs.* Na-based **4** ($\bar{D} = 1.83, 1.51$ and ~ 1.24 , respectively, Table 1). MALDI-ToF analysis indicated that **3** and **5** (+1 eq. BnOH) produced transesterified ($\Delta(m/z) = 72$ g mol⁻¹) α -benzoxy, ω -hydroxy (major) and α -hydroxy, ω -hydroxy capped or cyclic (minor) PLA (Fig. S18 and S22, ESI†). While the same end-groups were observed with **4**/BnOH, the improved polymerisation control suggested less transesterification occurs with this system. Indeed, with **4** the major series observed was non-transesterified PLA ($\Delta(m/z) = 144$ g mol⁻¹) but the non-quantitative nature of



MALDI-ToF should be noted (Fig. S19–S21, ESI†). Importantly, despite the presence of 1–2 eq. HMDSH with complexes 3–5 (Scheme 1), no HMDS-capped PLA was detected by MALDI-ToF analysis. We previously reported that no *rac*-LA ROP occurs with BnOH and HMDSH in the absence of a metal complex.¹⁶

BnOH was essential for the high activity of 3–5, as low *rac*-LA conversions were observed without it (entries 1, 3 and 6, Table 1). Combined with the relative stability of the Na/K-phenoxide unit towards BnOH,¹⁴ this initially suggested that 3–5 operate *via* an activated-monomer mechanism with BnOH.¹⁷ However, studying the reaction of 3–5 with 1 eq. BnOH in THF-*d*₈ by ¹H and DOSY NMR revealed that the *in situ* generated alcoholysis products (and thus the mechanism) are more complicated, as multi-component product mixtures are formed (see ESI†). While complex, some components of these mixtures could be identified, with the % product composition quantified based on the relative L resonances. The known products generated from 3/BnOH comprised of 2 (50%) and previously reported [LMg₂OBn] (8, 16%), whereas 4/BnOH gave 1 (13%) and previously reported [LCa₂OBn] (9, 13%), and 5/BnOH gave 2 (29%) and 9 (trace).^{14,16} *In situ* formation of unligated [Mg(OBn)₂]₂ and [Ca(OBn)₂]₂ salts from 3 and 5 with 1 eq. BnOH, respectively, was also proposed based on ¹H NMR and DOSY analysis, although the formation of heterometallic benzoxide salts cannot unequivocally be ruled out. No M(OBn)₂ species formed with 4/BnOH and instead, a greater proportion of asymmetric ligated products was generated. The complexity of the reaction mixtures formed here reflect the “black box” of multiple solution-state species observed with (TMP)MgCl-LiCl in THF-*d*₈, which were characterised using DOSY NMR several years after the initial report of this ground-breaking Turbo-Grignard.¹⁸ While many ROP catalysts involve alcohol co-initiators, most studies do not disclose the nature of the alcoholysis product(s). Our results highlight the importance of such investigations, as other systems are also likely to undergo *in situ* rearrangements in the presence of an alcohol to generate ligated and/or non-ligated homometallic species. In some cases, the presumed active catalyst species may actually not be present at all in a complex mixture of components.

Benchmarking 3–5 (+1 eq. BnOH) against 1–2,¹⁴ 8–9,¹⁶ Mg(OBn)₂ and Ca(OBn)₂ suggested that heterometallic complexes 3–5 generally outperform the homometallic counterparts (Table 1, entries 1–13). In particular, 3/BnOH showed significant activity enhancement, converting 98 eq. of LA in just 5 s vs. 2 (59 eq. in 5 s), 8 (12 eq. in 10 min) and Mg(OBn)₂ (8 eq. in 5 s, entries 2, 9, 10 and 12). It is worth noting that homometallic 2/BnOH (ESI†, Table S2, entry 2) gave comparable activity to heterometallic 3 and 5 (Table 1, entries 2 and 7), whereas 1/BnOH (ESI†, Table S2, entry 1) outperformed 4 (Table 1, entry 4). However, in the presence of BnOH, 1 and 2 likely catalyse *rac*-LA ROP through a different (activated-monomer) mechanism (AMM) to 3–5/BnOH, as 1–2 were previously shown to be unreactive towards BnOH.¹⁴ AMM typically operates in the presence of exogenous alcohol.¹⁹ In contrast, NMR analysis indicated that 3–5 rapidly react with BnOH to generate a

mixture of M–OBn species (*vide supra*), with no unreacted BnOH remaining (Fig. S25, S28 and S31, ESI†).

To probe whether some of the activity enhancements observed with 3–5 and 1 eq. BnOH can also be accessed *via* the *in situ* combination of 1 or 2 and Mg(OBn)₂ or Ca(OBn)₂, without pre-isolating a heterometallic complex, we investigated the use of salt additives in *rac*-LA ROP (Scheme 1 Route B and Table 1). Promisingly, the 1:1 2:Mg(OBn)₂ and 2:Ca(OBn)₂ mixtures displayed similar activities to 3 and 5 (+1 eq. BnOH), converting 83 and 88 eq. *rac*-LA in 5 s at R.T. (vs. 98 and 83 eq. with 3 and 5), respectively. The 1:1 1:Ca(OBn)₂ mixture was more active than 4/BnOH, converting 87 eq. *rac*-LA in 5 s (vs. 34 eq.). However, 4–5/BnOH showed improved polymerisation control vs. the 1:1 1 or 2:Ca(OBn)₂ mixtures. MALDI-ToF analysis of PLA generated with the 1:1 mixtures showed the same α-benzoxo, ω-hydroxyl (major) and α-hydroxy, ω-hydroxy capped or cyclic (minor) PLA as with 3–5/BnOH (Fig. S34, S35 and S37, ESI†). To showcase the versatility of Route B (Scheme 1), we also explored 1:1 combinations of 1:Mg(OBn)₂, 1:Zn(OBn)₂ or 2:Zn(OBn)₂ (Table 1), which displayed high activities in *rac*-LA ROP. Combining 1 or 2 with Zn(OBn)₂ improved the solubility of the latter. Heterometallic complexes often display improved solubility in organic solvents; here, this may open up access to polymerisations in a broader range of solvents.³

The 1:1 mixtures of 1 or 2 with M(OBn)₂ (M = Mg, Ca or Zn) generally outperformed the homometallic constituents (Table 1, entries 8–20), although the 1:Ca(OBn)₂ and 2:Ca(OBn)₂ heterocombinations only displayed significant reactivity enhancements at lower catalyst loadings (0.33–0.5 mol%, Table S2, ESI†). These results suggest the heterometals cooperate, with the large and Lewis acidic metal (Na or K) tentatively proposed to activate the LA carbonyl group towards nucleophilic attack from the M–OBn group (M = Mg, Ca or Zn, Fig. 1), based on the observation of OBn-capped PLA by MALDI-ToF spectrometry.

Combining 1 or 2 with 1 eq. Mg(OBn)₂ or Ca(OBn)₂ gave similar solution-state products to those observed *via* alcoholysis of 3–5 with BnOH, as evidenced by NMR analysis (refer to ESI†). For instance, 2:Mg(OBn)₂ gave the same three species as observed with 3/BnOH (2, 8 and an asymmetric product), albeit in a different ratio (33:27:40 vs. 50:16:34 with 3/BnOH; Fig. S26 and S41, ESI†). These results suggest that dynamic solution equilibria may generate similar catalytic species when isolated heterometallic ProPhenol complexes are reacted with BnOH (Route A) and when homometallic ProPhenol complexes are combined with M(OBn)₂ salts (Route B), explaining why similar activity enhancements were observed in LA ROP *via* both routes. This approach shows that heterometallic activity enhancements can be harnessed without isolating heterometallic complexes, and this concept may be applicable to other ROP systems.

In summary, our studies show that salt additives can boost the activity of homometallic ROP initiators, giving similar activity enhancements to isolated heterometallic complexes. With some heterocombinations (*e.g.* K/Mg, Na/Ca), the same species were formed *via* both routes, highlighting the importance of probing the solution-state catalyst structure after alcoholysis (which is often



not disclosed for heterometallic ROP catalysts). The salt additive approach is attractive as it allows rapid screening of different heterocombinations and avoids heterometallic complex syntheses enabling access to synthetically challenging heterometallic precursors. With both approaches, K/Mg and K/Ca combinations convert >85 eq. *rac*-LA in just 5 s at R.T., exhibiting the highest heterometallic LA ROP activities to date. The boosted activity is primarily attributed to enhanced LA activation, likely by the large and Lewis acidic K⁺ centre, as K/Mg and K/Ca systems outperform the Na/Ca analogue. These activity enhancements are somewhat analogous to organic addition reactions, where salt additives are assumed to activate Lewis acidic carbonyl groups. To the best of our knowledge, these results are the first example of employing simple salt additives in ROP. There is significant scope to explore other unstudied heterocombinations and activities with salt additives in ROP, as well as ring-opening copolymerisation and other polymerisations.

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Conflicts of interest

There are no conflicts to declare.

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