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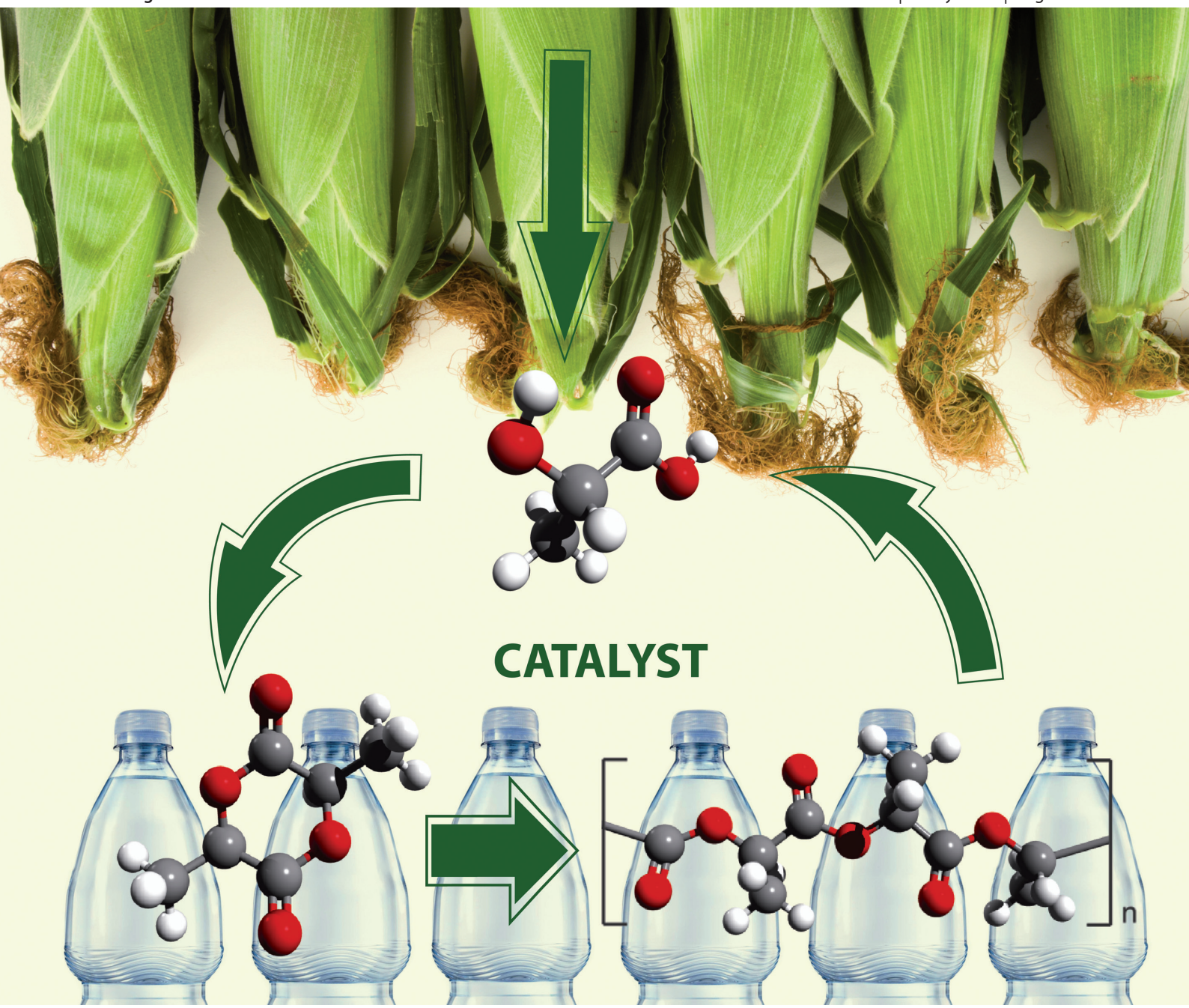

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Complexes of Mg, Ca and Zn as homogeneous catalysts for lactide polymerization

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Interest in the utility of polylactide as a commodity polymer has increased significantly in recent years due to numerous environmental advantages over conventional petrochemically derived plastics. As such, the development of novel catalyst systems for the ring opening polymerization of lactide has seen tremendous progress in the past decade. In particular, divalent metals (*i.e.* Mg, Ca and Zn) supported by monoanionic ancillary scaffolds are appealing because of their low toxicity and cost. A much less common approach involves the use of neutral ligands in combination with the aforementioned divalent metal centres. The additional valence thus renders it possible, upon reaction with traditional Lewis or Brønsted acid activators, to generate sterically and electronically unsaturated species, akin to the most widely employed olefin polymerization catalysts. This Perspective is not intended as a comprehensive review, but rather a systematic highlight of key contributions, which have served to extend the forefront of this exciting field.

1. Introduction

In the present era of depleting petrochemical feedstocks and increasing environmental awareness, polylactide (PLA) has become an attractive alternative to conventional polyolefins.[1] PLA is produced *via* ring opening polymerization of lactide, which in turn may be generated from renewable resources such as beets and corn. Its production would thus help to reduce the consumption of non-renewable petrochemical resources, of which 150 million tonnes are consumed annually as raw material for plastic production.[2] In addition, PLAbased plastics maintain many of the desirable properties of traditional plastics with the added bonus that they are also biocompatible, readily biodegradable, and easily recycled.

While polylactide has found use as a speciality polymer for medical applications, such as slow release drug delivery and biodegradable sutures,[3] its use as a commodity polymer has remained limited because of high production cost compared with conventional plastics, as well as poor activity and stereochemical control of available catalyst systems.

PLA is becoming increasingly economically viable as reduced production costs arising from technological advances have been magnified by concomitant increases in the price of petrochemical feedstocks. In 2002, Natureworks LLC, presently a joint venture between Cargill and Teijen Limited, opened a 300 million lb per year PLA production plant, marking the first commodity polymer to be derived from corn instead of fossil fuel. This industrially produced PLA, fabricated in isotactic form, has physical properties similar to polyolefins and polystyrene, and has found use in materials applications such as bulk packaging and fibers (trade name Ingeo™). By purchasing sufficient wind energy certificates, Natureworks LLC has demonstrated that this process can be carbon neutral.[4]

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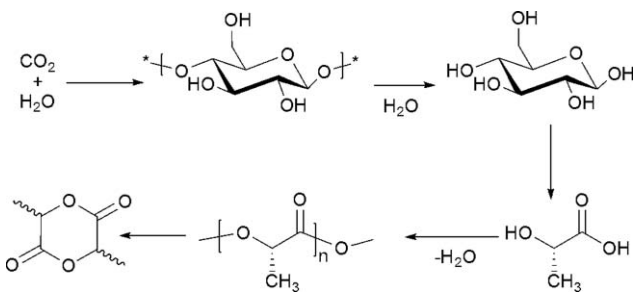
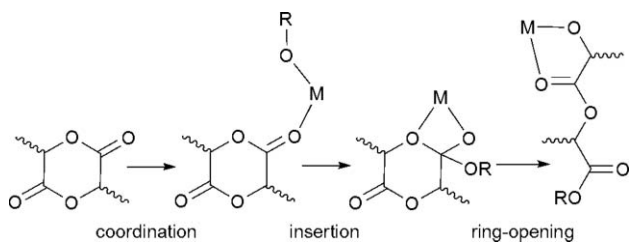
The production of PLA starts from a starch or sugar feedstock, which is processed to yield D-glucose. Optically pure L-lactic acid is then generated by a fermentation process using bacteria of the genera *Lactobacillus*, *Streptococcus* and *Pediococcus*.[5] Poly(L-lactic acid) can be produced as a low molecular weight pre-polymer (MW = 1000–5000) directly from lactic acid through condensation polymerization. The synthesis of lactide is then achieved by a depolymerization process to afford the lactide monomer (Scheme 1). Generation of higher molecular weight PLA can then be accomplished by ring opening polymerization using a suitable homogeneous metal catalyst (Scheme 2).



Scheme 1 Synthesis of lactide monomer from natural resources.



Scheme 2 General coordination–insertion mechanism for the metal–catalysed ring-opening polymerization of lactide.

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This depolymerization process used in the commercial synthesis of lactide results in a loss of optical purity,[6] generating a mixture of isomers which must be separated prior to polymerization. Lactide possesses two stereocenters, and thus there exist three stereoisomers; L-lactide, its enantiomer D-lactide, and the diastereomer *meso*-lactide (Fig. 1a). As such, there are a plethora of ordered polymer microstructures, the most simple of which are depicted in Fig. 1b. Isotactic L-PLA is the most easily prepared, requiring no polymerization stereocontrol when pure L-lactide is utilized as the monomer. Syndiotactic PLA, however, can only be synthesized from *meso*-lactide and requires that the catalyst selectively insert at only one stereocenter of the monomer. Meanwhile, heterotactic PLA is produced from *rac*-lactide by selective insertion of the lactide isomer with opposite configuration to the previously inserted monomer. Catalysts which generate isotactic PLA from *rac*-lactide are also an important target, as a mixture of *iso*tactic L-PLA and D-PLA has bulk properties much different than that of pure L-PLA.[7]

The most desirable features for lactide polymerization catalysts are high activity, ability to controllably produce high molecular

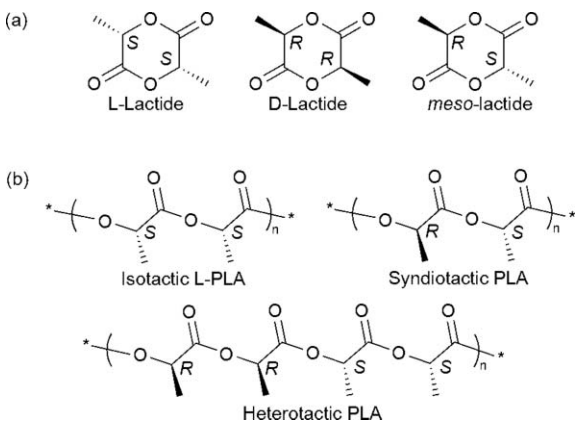
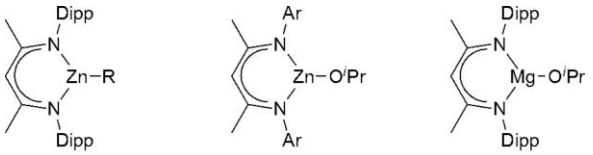


Fig. 1 (a) Lactide monomer stereoisomers. (b) Microstructures of polylactide which can be achieved either through polymerization of optically pure L-lactide (L-PLA) or by stereochemically selective polymerization of *rac*-lactide or *meso*-lactide (hetereotactic and syndiotactic PLA, respectively).



1 R = $N(SiMe_3)_2$
2 R = O^{i}Pr
3 R = $OCHMeCO_2Me$
4 R = Et
5 R = OAc

6 Ar = 2,6-diethylphenyl
7 Ar = 2,6-di-^{n}propylphenyl

8

Fig. 2 General structure of single-site catalysts prepared from the BDI ligand framework.

weight, low polydispersity polymers and stereochemical control. In addition to these qualities, low toxicity, low cost, and minimal colour and odour are also desirable features. A number of single-site homogeneous catalyst systems incorporating many of these features have been reported over the past decade, and several excellent reviews are available.[8] Single-site homogeneous catalysts are particularly useful because rational fine-tuning of their steric and electronic properties is possible. A wide array of ligand frameworks have been employed, generating a library of catalysts with substantial variation in both steric environment and Lewis acidity. The effect of Lewis acidity on the activity of cyclic ester polymerization, however, is still not well understood,[9] and is further complicated by the potentially chelating nature of the growing polymer chain.[10] This Perspective will highlight the most significant developments in the use of biocompatible metals in groups 2 and 12. While there has been significant progress with stereoselective group 3 and 13 initiators,[11,12] we believe that calcium, magnesium, and zinc hold the most promise for industrial application owing to their low cost, remarkably high activities and minimal toxicity. Several such catalyst systems which exhibit good stereochemical control have revealed two unique and possibly competing mechanisms: chain-end control and enantiomorphic site-control.[12h] A chain-end control mechanism occurs when the stereochemistry of the most recently inserted monomer influences the stereochemistry of the subsequent insertion. Such control is typically observed in systems which exploit sterically bulky ligands to crowd the active site. Alternatively, the enantiomorphic site-control mechanism relies on the chirality of the ancillary ligand, and hence, the catalyst itself is the source of stereochemical selectivity due to steric interactions between the incoming monomer and the catalyst framework. When a chiral catalyst is used, stereochemical control may arise from a complicated interplay between these two mechanisms.[12h]

Herein, we aim to examine progress that has been made in calcium, magnesium, and zinc-based catalyst systems with the aforementioned key features. The first portion of the Perspective will focus on important metal complexes featuring monoanionic ligands while the latter sections will address systems supported by neutral ligand frameworks. The reader will see that the chemistry of divalent metals supported by monoanionic ancillary ligands has been well studied, while the development of lactide polymerization catalysts stabilized by neutral ancillary ligands is in its infancy. It is our hope that other researchers in the field may be enticed to use this strategy to pursue cationic, single-site catalysts for this important transformation.

2. Anionic ligand families

While single-site metal catalysts have been successfully exploited for olefin polymerization,[13] prior to the turn of the century very few such catalysts were applied to the polymerization of lactones. The pioneering work of Coates and co-workers in the development of β-diiminate (BDI) supported catalysts, and of Chisholm in the preparation of tris(pyrazolyl)borate (TPB) systems was largely responsible for breaking the field wide open.

2-1. β-Diiminate complexes

An initial report by Coates and co-workers utilized the bulky 2,6-diisopropylphenyl (Dipp) substituted β-diiminate ligand (BDI-1), which they proposed may be capable of stereocontrol in the polymerization of *rac*-lactide *via* a chain-end control mechanism.[14] Zinc complex **1** (Fig. 2) was readily generated in quantitative yield by reaction of $Zn(N(SiMe_3)_2)_2$ with the requisite proteo ligand. This complex features a single amide initiating group, and was found to slowly polymerize lactide. The alkoxide bridged dimer $[(BDI\text{-}1)Zn(O^iPr)]_2$ (**2**), which has an initiating group that is a closer mimic of the propogating alkoxide polymer chain, was generated by reaction of **1** with isopropanol. Reactivity studies revealed **2** to be a highly active catalyst for polymerization of *rac*-lactide at 20 °C, giving high conversion to polymer after only 20 min (Table 1, entry 2). Notably, polymerization with this complex is highly controlled, affording a narrow molecular weight distribution (PDI = 1.10). Most interestingly, however, is the degree of stereocontrol incurred by this catalyst, yielding a highly heterotactic polymer (P_r = 0.90).[15] The stereoregularity could be even further enhanced by conducting the polymerization at lower temperature, yielding almost exclusively heterotactic polymers (P_r = 0.94) at 0 °C (Table 1, entry 3). Complex **2** represents the first group 12 metal complex to initiate lactide polymerization with substantial stereochemical control. β-diiminate systems have since been studied with great enthusiasm.

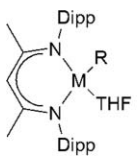
A subsequent report by Coates and co-workers considered the same ligand framework in more detail, studying a greater breadth of initiating groups (R = $OCH(Me)CO_2Me$, Et, OAc, O^{i}Pr), and reduced steric bulk on the ligand (BDI-2, Ar = 2,6-diethylphenyl; BDI-3, Ar = 2,6-di-^{n}propylphenyl) (Table 1, entries 4–8).[16] Initiating group effects were systematically inspected through the preparation of complexes **3**, **4**, and **5**, which confirmed the utility of alkoxide functionalities as initiators (as seen with **2**). Utilization of a methyl lactate initiator (**3**) gave little change in activity, while amide (**1**) and alkyl (**4**) initiators were significantly less active, and acetate (**5**) initiators were even worse. This report also established that the reduced steric bulk of the ancillary ligand (demonstrated by **6** and **7**, complexes of BDI-2 and BDI-3, respectively) caused diminished stereocontrol, thereby supporting the proposed chain-end control mechanism. A dimeric magnesium alkoxide complex (**8**) of BDI-1 was also reported in the same study (Table 1, entry 9). While this complex is more active than the zinc analogue, giving complete conversion of *rac*-lactide to PLA under similar conditions in only 2 min, the resulting microstructure is atactic and the molecular weight distribution is broad (PDI = 1.59). Thus, the increase in activity comes at the expense of both molecular weight and stereocontrol.

Table 1 Polymerization of *rac*-lactide or L-lactide by BDI and related catalysts. (T_{rxn} = 20 °C and CH_2Cl_2 is the solvent except where noted)

Entry	Catalyst	$[LA]_o$/mol L^{-1}	Loading (mol%)	*t*/min	Conv. (%)[a]	PDI	P_r
1	**1**	0.40	0.5	600	97	2.95	—
2	**2**	0.40	0.5	20	95	1.10	0.90
3[b]	**2**	0.40	0.5	120	95	1.09	0.94
4	**3**	0.40	0.5	20	97	1.14	—
5	**4**	0.40	0.5	1200	97	1.83	—
6	**5**	0.40	0.5	4200	92	2.07	—
7	**6**	0.40	0.5	480	97	1.10	0.79
8	**7**	0.40	0.5	1140	97	1.09	0.76
9	**8**	0.40	0.5	2	>99	1.59	Atactic
10	**9**	0.46	1	4200	91	1.45	—
11	**10**	0.46	1	2	97	1.49	—
12[c]	**11**	0.46	1	5	94	1.60	—
13[c]	**12**	0.46	0.5	120	90	—	Atactic
14[d,e]	**13**	—	1	300	78	1.5	Atactic
15[e]	**14**	2.8	1	8	81	1.78	Atactic
16[f]	**15**	2.8	1	10	85	1.10	—
17[f]	**16**	2.8	1	30	90	1.15	—
18[c]	**17**	0.46	1	10	91	1.19	0.67
19[c]	**18**	0.46	1	90	90	1.70	0.85
20[f]	**19**	—	1	150	61	1.44	—
21[f]	**20**	—	1	120	>99	1.74	—
22[d]	**21**	1.25	0.33	100	98	1.06	—
23[d]	**22**	1.25	0.33	90	97	1.06	—

[a] Determined by ^{1}H NMR. [b] T_{rxn} = 0 °C. [c] THF solvent. [d] T_{rxn} = 50 °C. [e] Benzene solvent. [f] Chloroform solvent.

The labour of Chisholm *et al.* has produced an analogous series of BDI-1 complexes, which are monomeric THF adducts rather than dimers (Fig. 3).[17] Polymerizations were carried out in methylene chloride solvent, and the overall trends reported are similar to those previously discussed by Coates *et al.* (Table 1, entries 10–13). Magnesium complex **9** shows much higher activity than the zinc analogue **10** while exhibiting poor molecular weight control and no stereoselectivity whatsoever. Further studies by Chisholm explored a range of initiating groups, including amide derivative **11** (polymerization rates: $O^tBu > N^iPr > N(SiMe_3)_2 > OSiPh_3$). Most interestingly, however, is the report of solvent dependence on stereoselectivity, whereby **10** was found to generate 90% heterotactic PLA from *rac*-lactide if the polymerization was carried out in THF rather than methylene chloride. In separate accounts, Chisholm and co-workers have recounted the synthesis and reactivity of the related Calcium complex [(BDI-1)CaN$(SiMe_3)_2$] (**12**).[18] Notably, NMR studies indicated that **12** exists as a complex equilibrium between a variety of species in solution, and polymerization of *rac*-lactide with this complex afforded atactic polylactide exclusively.

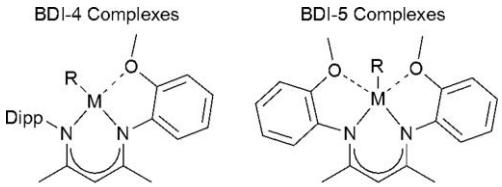


9 M = Zn, R = $OSiPh_3$
10 M = Mg, R = O^tBu
11 M = Mg, R = N^iPr
12 M = Ca, R = $N(SiMe_3)_2$
13 M = Mg, R = $CH_2CH{=}CH_2$

Fig. 3 Solvated magnesium, calcium, and zinc complexes of the BDI ligand.

An additional solvated magnesium complex of BDI-1 was prepared by Bochmann *et al.* using a vastly different synthetic route.[19] The magnesium allyl complex **13** was generated by reaction of mixed-metal lanthanide–magnesium allyl complexes with proteo BDI-1. For example, reaction of $[Mg(THF)_6][Ln(\eta^3\text{-allyl})_4]_2{\cdot}2THF$ (Ln = Nd or Sm) with proteo BDI-1 yielded **13**, with propene and neutral tris-allyl lanthanide afforded as side products. The rate of catalysis achieved using this complex was slower than that observed for either complexes **10** or **11**, requiring an elevated temperature of 50 °C to reach 78% conversion in 5 h (Table 1, entry 14). The resulting polymer had a rather broad molecular weight distribution (PDI = 1.5), and analysis of the polymer microstructure revealed no stereochemical control. Overall, the results suggest that the allyl functionality is not a desirable initiating group.

There have been several attempts to improve the BDI catalyst system by substantial modification to the ligand framework. One prominent strategy has involved the installation of one or two ether appendages to generate the second generation tridentate (BDI-4) and tetradentate (BDI-5) ancillary ligands, respectively. Magnesium and zinc complexes have been been examined by Gibson and co-workers for BDI-4,[20] and by Chisholm in the case of BDI-5. (Fig. 4).[21] It was anticipated that these hemilabile ether sites would serve to moderate the reactivity of magnesium complexes, thereby potentially improving molecular weight and stereochemical control.



14 M = Mg, R = N^iPr_2
15 M = Zn, R = $N(SiMe_3)_2$
16 M = Zn, R = $OSiPh_3$
17 M = Zn, R = O^iPr
18 M = Mg, R = O^tBu

Fig. 4 Magnesium and zinc complexes prepared from modified BDI ligands bearing ether substituents.

While the solid-state structure of **14** revealed a distinct, albeit relatively long M–O interaction (Mg–O = 2.486(5) Å), no such coordination was found in zinc complexes **15** or **16**. As a general trend, it was established that the BDI-4 complexes of zinc were significantly more active catalysts for lactide polymerization than their first generation counterparts, but they suffered from limited stereo- and polydispersity control (Table 1, entries 16–17).[20] These findings are likely due to the reduced steric protection offered by this scaffold. Similarly, magnesium complex **14** maintained high activity with 81% conversion of *rac*-lactide to PLA in 8 min at room temperature. As with zinc, no improvement in molecular weight or stereochemical control was achieved. It has been suggested that the ether functionality dissociates from the metal in solution, and is thereby unable to assist in moderating the reactivity.

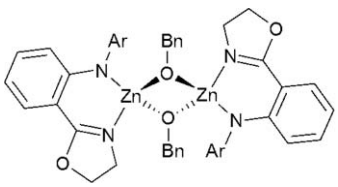
For the investigation of the potentially tetradentate BDI-5 ligand, Chisholm *et al.* synthesized zinc alkoxide **17** and the similar magnesium alkoxide **18**.[21] While an X-ray crystal structure was not obtained for the zinc complex, the magnesium species was established to be a dimer in the solid state with no coordination of the pendent ether groups. Lactide polymerization studies were performed under ambient conditions in THF with a 1% catalyst loading (Table 1, entries 18–19). As with the analogous BDI-4 species, **17** exhibits higher polymerization activity than its first generation counterpart, while maintaining polymerization control (PDI = 1.19). Unfortunately stereochemical control is substantially diminished (P_r = 67%). Conversely, magnesium complex **18** is plagued with severely hampered activity and broad polydispersity (PDI = 1.70), but exhibits notable stereoselectivity (P_r = 0.85). As with homogeneous olefin polymerization catalysis, overcoming the intricate inverse relationship between activity and selectivity remains a significant challenge.[22] A calcium complex of BDI-5 has also been investigated, but no polymerization data were provided.[18b]

A more substantial modification of the BDI backbone was recently detailed by Chivers and colleagues.[23] The general ligand architecture deviates from those previously discussed by the placement of an electron accepting boron atom in the backbone of a boraamidinate/amidinate (bamam) framework. Magnesium alkyl and aryl complexes **19** and **20** were synthesized by reaction of the appropriate Grignard reagents with the proteo bamam ligand (Scheme 3).[23b] The solid-state structures of a variety of these complexes were obtained, and all were found to be monomeric, with a single THF or ether solvent molecule coordinated to the metal. Complexes bearing alkoxide or amide functionalities were not developed and only preliminary polymerization data were reported for the alkyl and aryl complexes. Unfortunately, these studies demonstrated poor molecular weight and stereochemical control, as well as lower activity than the comparable BDI complexes (Table 1, entries 20–21).

19 R = Me, L = OEt_2
20 R = Ph, L = THF

Scheme 3 Preparation of magnesium complexes of the "bamam" ligand.

Zinc complexes of an anilido-oxazolinate ligand framework, which is structurally and electronically similar to the BDI ligand, have been the subject of investigation by Chen *et. al.*.[24] Sequential reaction of the proteo ligand with diethylzinc followed by benzyl alcohol gave rise to the alkoxy bridged dimers **21** and **22** (Fig. 5). These complexes differ only in the nature of the amide substituent, which for **22** is a potentially donating alkoxy group. Both complexes exhibited similar polymerization activity, requiring a temperature of 50 °C to reach near complete conversion in a period of 100 and 90 min, respectively (Table 1, entries 22–23). The molecular weights of the resultant polymers were nearly monodisperse (PDI = 1.06), and correspond well to the monomer to initiator ratio, suggesting living character in the polymerization. No studies were undertaken to determine if the catalysts are able to impart any stereochemical control.

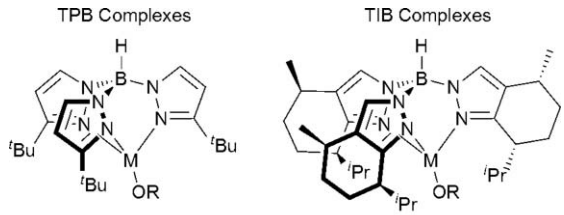


21 Ar = Mes
22 Ar = 2-methoxyphenyl

Fig. 5 Dimeric zinc alkoxide complexes of an anilido-oxazolinate ligand framework.

2-2. Tris(pyrazolyl)borate and related ligands

Bulky tripodal ligands based on a substituted tris(pyrazolyl)borate (TPB) skeleton were shown by Parkin in the early 1990's to be useful ligands for stabilizing magnesium and zinc alkyl and hydroxide species;[25] however, it was not until Chisholm's ground breaking work that these were considered as useful ligands for lactide polymerization catalysts.[26] The initial report was quite comprehensive and detailed both zinc and magnesium complexes, chiral and achiral derivatives of the ligand, and variation on the sterically bulky substituents. As catalysts, the TPB complexes **23** and **24**, and the TIB complexes **25** and **26** (Fig. 6) exhibited good molecular weight control (PDI = 1.1–1.25). Magnesium analogues **24** and **26** once again displayed notably higher reactivity than their respective zinc analogues. This was attributed by the authors to be a result of the significant polarization of the M–OR bond by the more electropositive Mg centre.



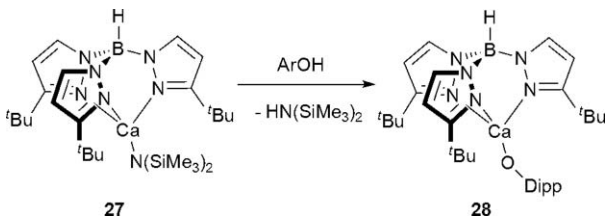
23 M = Zn, R = $SiMe_3$
24 M = Mg, R = Et
25 M = Zn, R = $SiMe_3$
26 M = Mg, R = Ph

Fig. 6 Complexes featuring tris(pyrazolyl)borate (TPB) and tris-(indazolyl)borate (TIB) ligands.

While none of these catalyst systems demonstrated high enantioselectivity, their diastereoselectivities were tested in the polymerization of 1 : 1 mixtures of *meso*- and *rac*-lactide. All of the

tested complexes exhibited some preference for polymerization of *meso*-lactide, with the selectivity of the chiral magnesium complex **26** being the most notable. Impressively, when the polymerization was catalyzed by **26** and conducted at –40 °C in methylene chloride, complete and selective consumption of *meso*-lactide was observed, leaving the *rac*-lactide unconsumed. Examination of the resulting polymer also indicated a modest preference for a syndiotactic microstructure.

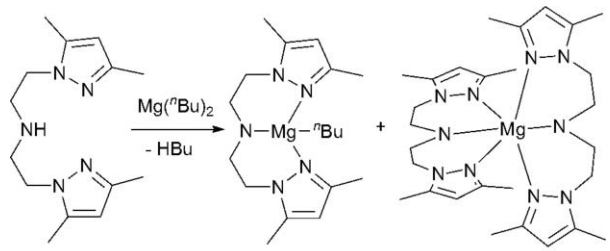
The excellent properties of magnesium and zinc TPB based catalysts prompted an investigation of their analogous calcium chemistry.[18b] Chisholm *et al.* prepared and structurally characterized both amide (**27**) and aryloxide derivatives (**28**) of the calcium TPB compounds (Scheme 4). As was the case for the BDI derivatives, these species exhibited a marked improvement in polymerization activity over zinc and magnesium counterparts (Table 2, entries 1 and 2). A 0.5% catalyst loading resulted in 90% monomer conversion within 1 min under ambient conditions. While these catalysts afforded only modest control over molecular weight (PDI = 1.74 and 1.68, for **27** and **28**, respectively), they showed remarkable stereoselectivity, producing heterotactic PLA almost exclusively (P_r > 90%). It has been proposed that the improved stereocontrol of these calcium complexes relative to analogous BDI species (*vide supra*) is a result of increased steric protection, which is not necessary for the smaller magnesium and zinc centres.



27 **28**

Scheme 4 Synthesis of a calcium aryloxide complex of the TPB ligand.

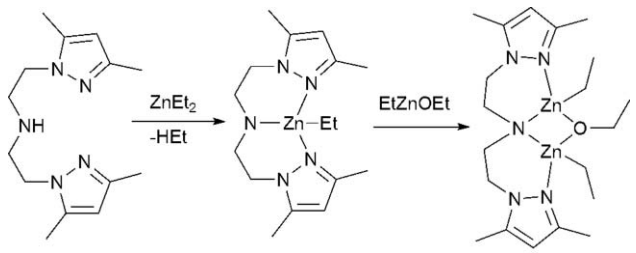
The success of this early work by Chisholm has prompted a number of other researchers to study related tripodal frameworks bearing pyrazole donor groups. One example is a bis(pyrazolyl)amide (BPA) ligand, which has been investigated by Carpentier and colleagues.[27] The reaction of BPA with one equivalent of dibutylmagnesium led to concomitant production of the targeted heteroleptic complex **29** and the homoleptic sandwich species **30** (Scheme 5). Adjustment of the reaction parameters failed to generate the heteroleptic species selectively, and attempts to separate the two components were unsuccessful. However, pure **30** could be obtained by reaction of dibutylmagnesium with two equivalents of BPA. Intriguingly, even though **30** lacks a traditional initiating group, it is highly active for the polymerization of *rac*-lactide, giving 97% monomer conversion in 60 min at a catalyst loading of 0.5% (Table 2, entry 3). Under these conditions, a relatively narrow polydispersity of 1.33 was observed. It is important to note that in this situation it is almost certain that the ligands themselves act as initiating groups, and thus, the complex does not represent a single-site catalyst in the usual sense.



29 **30**

Scheme 5 Reaction of BPA with 1 equivalent of dibutylmagnesium yielding a mixture of target heteroleptic complex **29** and the homoleptic sandwich by-product **30**.

Further efforts by Carpentier *et al.* have resulted in the isolation of several zinc complexes of the same ligand (Scheme 6).[27b] The ethylzinc complex **31** was generated simply by reaction of one equivalent of diethylzinc with the proteo BPA ligand. Reaction of this complex with one equivalent of [(EtO)ZnEt] yielded the



31 **32**

Scheme 6 Synthesis of the BPA supported mononuclear zinc ethyl complex **31** and the binuclear zinc alkoxide **32**.

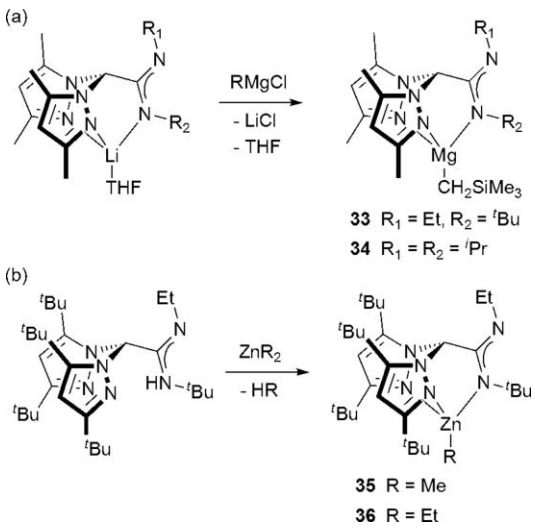
Table 2 Polymerization of *rac*-lactide by TPB, BPA and HSC catalysts. (T_{rxn} = 20 °C and THF was the solvent except where noted)

Entry	Catalyst	$[LA]_o$/mol L^{-1}	Loading (mol%)	*t*/min	Conv. (%)	PDI	P_r
1	**27**	—	0.5	1	90	1.74	>0.9
2	**28**	—	0.5	1	90	1.68	>0.9
3	**30**	0.8	0.5	60	97	1.33	Atactic
4	**31**	0.4	1	1800	93	1.71	Atactic
5	**32**	0.4	1	1800	95	1.23	Atactic
6[a]	**32**	1.6	0.25	1800	>99	1.40	Atactic
7[b]	**33**	—	1	4320	31	1.09	Atactic
8[b]	**34**	—	1	4320	42	1.09	Atactic
9[c]	**35**	—	1	2880	71	1.13	0.50
10[c]	**36**	—	1	2880	63	1.11	0.68
11[c,d]	**36**	—	1	2880	89	1.23	0.60

[a] CH_2Cl_2 solvent. [b] T_{rxn} = 70 °C, Toluene solvent. [c] T_{rxn} = 110 °C, Toluene solvent. [d] Addition of 1 equivalent of isopropanol to the pre-catalyst.

corresponding binuclear complex **32**, which bears a bridging ethoxide initiating group. Polymerization data were obtained for both complexes, with **32** consistently demonstrating superior activity and polydispersity (Table 2, entries 4–6). Even at an extremely low catalyst loading of 0.25%, complex **32** achieved complete conversion in 30 h at room temperature, while **31** reached only 93% conversion in the same time frame with 1% catalyst loading.

A family of ligands more closely resembling the tris-(pyrazolyl)borate framework has been developed by Sànchez-Barba and colleagues. These so-called "heteroscorpionate" (HSC) ligands are based on a bis(pyrazolyl)methane system, but feature a third donor arm which can incorporate one of a variety of monoanionic functionalities. The HSC system used for lactide polymerization catalysis bears an amidinate donor arm.[28] Sanchez-Barba *et al.* have successfully isolated a wide array of magnesium alkyl complexes supported by this heteroscorpionate framework *via* reaction of LiL with the appropriate Grignard reagent (Scheme 7). Complexes **33** and **34** differ in steric bulk at the amidinate arm (HSC-1: $R_1 = Et$, $R_2 = {}^tBu$; HSC-2: $R_1 = R_2 = {}^iPr$), and only those bearing a hefty alkyl initiating group were investigated as lactide polymerization catalysts. Polymerization experiments were carried out at an elevated temperature of 70 °C in toluene with a catalyst loading of 1%, and it was determined that consumption of *rac*-lactide proceeded at a relatively slow rate (Table 2, entries 7 and 8). Specifically, the more sterically encumbered complex **33** required 72 h to reach 31% conversion, while **34** achieved 42% conversion in the same time frame. It was established that despite their poor activity, the catalysts yielded polymer with a narrow molecular weight distribution (PDI = 1.09), though no stereocontrol was noted.

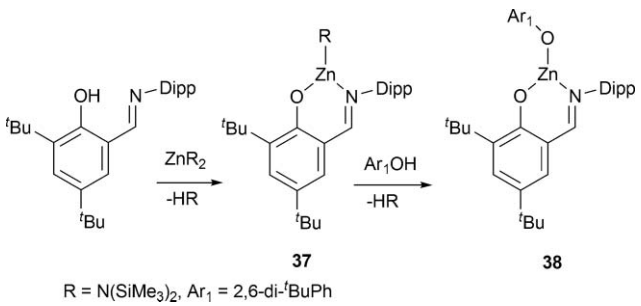


Scheme 7 Preparation of (a) magnesium and (b) zinc complexes of HSC scaffolds.

Heteroscorpionate zinc alkyl complexes of HSC-1 (**35** and **36**) have more recently been investigated (Scheme 7b).[28b] As with their magnesium analogues **33** and **34**, these complexes exhibited poor activity and stereochemical control. Complexes **35** and **36** required long reaction times and elevated temperatures to produce high conversion to polymer (Table 2, entries 9–11), though excellent polydispersities were obtained under these conditions. Slightly better activity was noted when one equivalent of isopropanol was added to the pre-catalyst. Polymerization of *rac*-lactide using these catalysts gave a slight heterotactic bias. A less bulky analogue of **35**, in which the *tert*-butyl groups on the pyrazole rings were replaced with methyl groups, was also studied. This did not have substantially improved activity, and not surprisingly, resulted in a complete loss of stereochemical control.

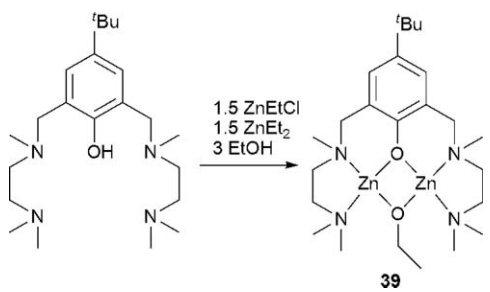
2-3. Phenolate and analogous ligands

Phenolate ligands bearing a variety of pendant nitrogen-donor groups have recently garnered interest for their ability to stabilize magnesium and zinc amides and alkoxides. Early zinc complexes of a Schiff base ligand bearing bis(trimethylsilyl)amide (**37**) and 2,6-*tert*-butylphenoxide (**38**) initiating groups (Scheme 8) have been described.[29] These species were reportedly catalytically active for the polymerization of both L-lactide and *rac*-lactide (Table 3, entries 1 and 2). At a relatively high catalyst loading of 5 mol% both **37** and **38** lacked remarkable activity at 25 °C (**37** resulted in 90% conversion to polymer after 3 h while **38** required approximately 72 h to reach the same point). The lower rate of polymerization observed with **38** was attributed to the large steric demands associated with the initiating group. Neither catalyst displayed any appreciable stereoselectivity.



Scheme 8 Synthesis of zinc amide (**37**) and aryloxide (**38**) complexes of a Schiff base ligand.

Within the past 6 years, Hillmyer and Tolman have demonstrated a notably more successful use of a phenoxy based ancillary, which possesses two ethylenediamine tethers installed at the *ortho* sites of the phenoxy ring.[30] Highly active zinc alkoxide catalysts were prepared by reaction of the proteo ligand with a mixture of EtZnCl and $ZnCl_2$, followed by treatment with ethanol, to ultimately afford the binuclear monoalkoxide complex (**39**) in good yield (Scheme 9). At a catalyst loading of 0.33%, complex **39** controllably polymerized *rac*-lactide to 90% conversion in only 30 min (Table 3, entry 3). This highly active catalyst also generated



Scheme 9 Preparation of the highly active dinuclear zinc alkoxide **39**.

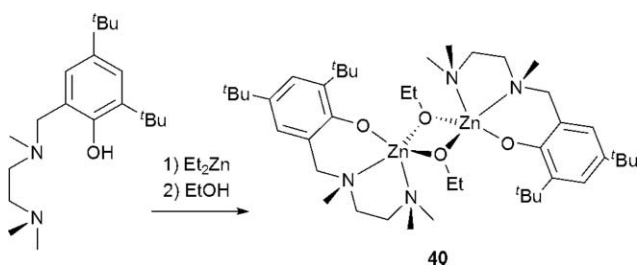
Table 3 Polymerization of *rac*-lactide or L-lactide by complexes supported by phenolate and related ancillary ligands (T_{rxn} = 25 °C, CH_2Cl_2 solvent except where noted)

Entry	Catalyst	$[LA]_o$/mol L^{-1}	Loading (mol%)	*t*/min	Conv. (%)	PDI	P_r
1[a,b]	**37**	0.83	5	180	90	—	Atactic
2[a]	**38**	0.83	5	4320	90	—	Atactic
3	**39**	1	0.33	30	90	1.19	—
4	**40**	1	0.15	5	96	1.42	—
5	**40**	1	0.10	13	96	1.40	—
6	**40**	1	0.067	18	93	1.34	—
7	**41**	2.5	1	120	98	1.09	N.A.[d]
8	**42**-BnOH	2.5	1	60	99	1.16	N.A.[d]
9[b,c]	**43**	1–2	1	15	>99	3.6	Atactic
10[b,c]	**44**	1–2	1	1440	>99	1.9	Atactic
11[b,c]	**45**	1–2	1	180	>99	1.7	Atactic
12[b]	**46**	0.5	0.5	240	97	1.26	0.59
13[b]	**47**	0.5	0.5	240	98	1.14	0.65
14[b]	**49**	0.5	0.5	240	95	1.07	0.65
15[b]	**50**	0.5	0.5	360	98	1.13	0.74
16[e]	**51**	0.25	1	4	93	1.15	N.A.[d]
17[e]	**52**	0.25	1	4	87	1.13	N.A.[d]
18[e]	**53**	0.25	1	4	90	1.07	N.A.[d]
19[e]	**54**	0.25	1	4	92	1.16	N.A.[d]
20[e]	**55**	0.25	1	4	>99	1.12	N.A.[d]
21[e]	**56**	0.25	1	4	88	1.08	N.A.[d]
22[c]	**57**	—	0.5	90	>99	1.31	N.A.[d]
23[c]	**58**	—	0.5	120	>99	1.33	N.A.[d]
24[e]	**59**	0.5	0.5	4	98	1.08	N.A.[d]
25[e]	**60**	0.5	0.5	5	97	1.08	N.A.[d]
26[e]	**61**	0.5	0.5	5	94	1.06	N.A.[d]
27[e]	**62**	0.5	0.5	5	97	1.05	N.A.[d]
28[e]	**63**	0.5	0.5	5	92	1.05	N.A.[d]
29[e]	**64**	0.5	0.5	5	93	1.09	N.A.[d]
30[c]	**65**	0.5	0.5	8	97	1.13	N.A.[d]
31[c,e]	**66**	0.5	0.5	2	>99	1.46	N.A.[d]
32[c]	**67**	0.5	0.5	4	89	1.08	N.A.[d]
33[f]	**68**	—	0.14	30	69	1.04	N.A.[d]
34[c,g]	**69**	0.49	1.67	400	92	1.03	Atactic

[a] Benzene solvent. [b] T_{rxn} = 20 °C. [c] Toluene solvent. [d] Not applicable. [e] T_{rxn} = 0 °C. [f] Melt polymerization, 110 °C. [g] T_{rxn} = 80 °C.

aproximately monodisperse polymer (PDI = 1.19) and exhibited living catalyst behaviour.

The aforementioned promising results prompted further studies by Hillmyer and Tolman. Particularly noteworthy are the family of mononuclear zinc complexes supported by a phenoxy ligand bearing a single ethylenediamine tether at the *ortho* position (Scheme 10).[31] Such complexes were produced by reaction of the substituted phenol with diethylzinc and subsequent derivatization to the corresponding alkoxide by treatment with ethanol. Complex **40** was established to exist as an alkoxy bridged dimer in the solid state. In addition, pulsed gradient spin-echo (PGSE) NMR measurements demonstrated that the complex is monomeric in solution. It was reported that **40** has an incredibly high catalytic



Scheme 10 Preparation of zinc alkoxide **40**.

activity for the polymerization of *rac*-lactide, and exhibits narrow polydispersities (PDI = 1.34–1.42) even with very low quantities of catalyst (Table 3, entries 4–6). At 0.15% catalyst loading, 96% conversion was obtained in 5 min. High molecular weight PLA was yielded (130 kg mol^{-1}) at 0.067% catalyst loading, with 93% conversion to polymer in a mere 18 min. Indeed, **40** represents the most active zinc based lactide polymerization catalyst known to date, and maintains effective activity at the lowest known concentration of any zinc catalyst. The only drawback of this remarkable catalyst system appears to be its lack of stereochemical control.

Both the hetero and homoleptic zinc complexes of a simple bidentate aminophenolate ligand have been the subject of study by Sobota and co-workers.[32] The reaction of one equivalent of the ligand with diethylzinc, followed by one equivalent of benzyl alcohol yielded the corresponding heteroleptic alkoxy bridged dimer **41**, while reaction of diethylzinc with two equivalents of the ligand afforded complex **42** (Fig. 7). Both species were found to effectively initiate the polymerization of L-lactide at room temperature (Table 3, entries 7 and 8). Complex **41** achieved 98% polymerization in two hours, while complex **42**, upon addition of one equivalent of benzyl alcohol as a co-catalyst, required only one hour for near quantitative conversion. The molecular weight distributions were small for both

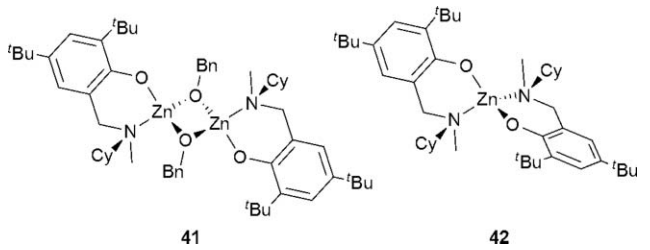


Fig. 7 Heteroleptic (**41**) and homoleptic (**42**) zinc complexes of an aminophenolate ligand.

(PDI = 1.09, 1.16), and neither catalyst has been employed for stereoselective polymerization.

A similar series of aminophenolate ligands bearing one or two additional nitrogen donor functionalities (pyridyl or pyrazolyl) have been used to synthesize the monomeric zinc amide species **43**, **44**, and **45** (Fig. 8).[33] These complexes were generated through an amine elimination route *via* reaction of the proteo ligand with the requisite zinc precursor. While all three complexes were determined to be reactive toward *rac*-lactide at room temperature, their activities varied dramatically (Table 3, entries 9–11). Catalyst **43** is by far the most active, giving complete conversion within 15 min at 1% catalyst loading. However, analysis of the polymer revealed a rather broad molecular weight distribution (PDI = 3.6), suggesting a poorly controlled polymerization process. Complex **44** gave an improvement in the molecular weight distribution (PDI = 1.9), but at a price of significantly lower activity (24 h was required for total monomer consumption). Finally, complex **45** demonstrated the most desirable catalytic properties of the group, generating polymer with moderately narrow polydispersity (PDI = 1.7), while retaining notable activity. Unfortunately, no evidence for stereochemical control was observed with any of these catalysts.

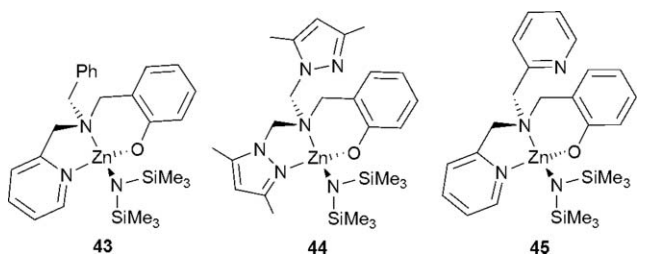
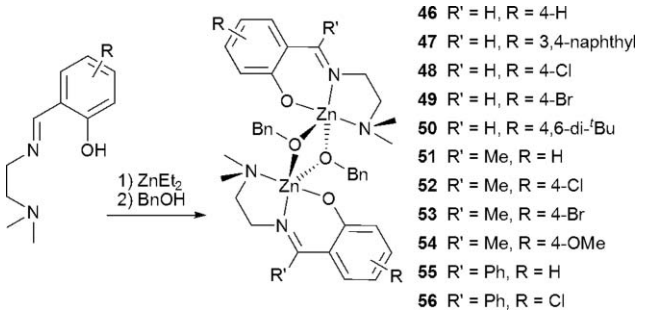


Fig. 8 Zinc amide complexes of multidentate aminophenolate ligands.

The incredible catalytic activity associated with zinc alkoxide complexes of phenolate ancillary ligands has prompted further investigation by several groups. Among these, Lin and co-workers[34] have attempted to combine the best features of Chisholm's bidentate Schiff base framework and Tolman's tridentate phenoxy(diamine) ligand (Scheme 11). Although a range of ligand variants have been explored (**46**, **47**, **48**, **49** and **50**), a zinc alkoxide complex (**46**) of the most simple derivative, which contains an unsubstituted backbone ring, has been most thoroughly studied. Data for the polymerization of *rac*-lactide were obtained for all derivatives, and under the conditions chosen, the catalysts gave between 95% and 98% conversion to polymer after 4 or 6 h (Table 3, entries 12–15), with the exception of **48**, which was found to be completely inactive. The polymerization was



Scheme 11 Preparation of zinc alkoxide complexes of a tridentate Schiff base ligand.

well controlled (PDI = 1.07–1.26) and a modest selectivity for heterotactic microstructure was observed (P_r = 0.59–0.74). The bulkier derivative bearing *tert*-butyl substituents (**50**) showed superior molecular weight and stereochemical control (PDI = 1.13; P_r = 0.74) but reduced activity, requiring 6 h to achieve 98% conversion under identical conditions.

Further modifications of this Schiff base catalyst system have been undertaken by Lin and co-workers, differing only in the placement of substituents at the imine carbon.[35] Specifically, compounds **51–54** all bear a methyl group at this position, while **55**, **56** bear a phenyl ring instead. This modification of the ligand backbone proved to be very successful in improving the activity of the resulting zinc alkoxide catalysts. All are extremely active at a reduced temperature of 0 °C, giving between 87% and 100% conversion in only 4 min (Table 3, entries 16–21). As previously described for **46–50**, those complexes which have an unsubstituted phenyl ring in the ligand backbone are most active, while those bearing electron withdrawing substituents exhibit reduced activity. In addition, these catalysts produced nearly monodisperse polymer (PDI = 1.07–1.16), suggesting a living polymerization. The authors did not probe the stereochemical control of these catalysts; however, this exciting new study clearly indicates that modification of the imine carbon substituent can significantly enhance the catalytic competence of Schiff base supported catalysts.

The homoleptic magnesium complexes **57** and **58** (Fig. 9) were prepared by reaction of two equivalents of the appropriate aminophenolate ligand with $MgBu_2$. The two ligands differ in the nature of the amine substituent, which is the potentially coordinating oxolane in **57** and the non-coordinating cyclohexyl group in **58**. As with the homoleptic magnesium complex **30**, **57**

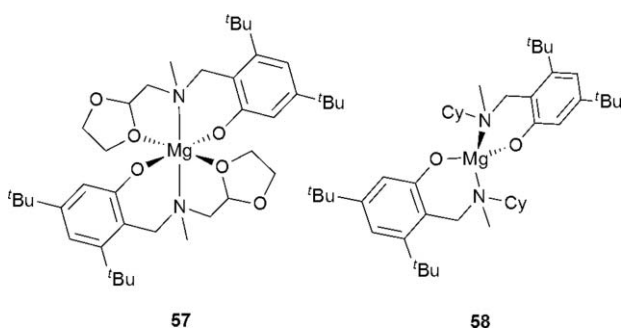


Fig. 9 Homoleptic magnesium complexes of related tridentate (**57**) and bidentate (**58**) aminophenolate ligands.

and **58** lack a traditional initiating group, and thus it is expected that the first turnover will require insertion of lactide into the metal–oxygen bond, thereby incorporating one ligand from each complex as the terminal group in each polymer chain. Regardless, these complexes do exhibit reasonable polymerization activity at ambient temperature (Table 3, entries 22 and 23). Intriguingly, the molecular weight distributions of the corresponding polymers are only slightly broad (1.31–1.33).

While important work is being performed by several research groups with bis(phenolate) frameworks, ligands of this type are generally dianionic and thus outide the scope of this discussion.[36] One study, however, has changed this divalent ancillary into a monovalent analogue by conversion of the alkoxide group into a sulfonate functionality.[37] These alkoxide-bridged magnesium dimers **59–64** (Fig. 10) differ only in the benzenesulfonate substiuent. All of the complexes are remarkably active at 0 °C; after only 5 min complete consumption of monomer was observed when 0.5 mol% catalyst was added (Table 3, entries 24–29). Excellent molecular weight control was also achieved (PDI = 1.05–1.08), though no substantial stereochemical control was found.

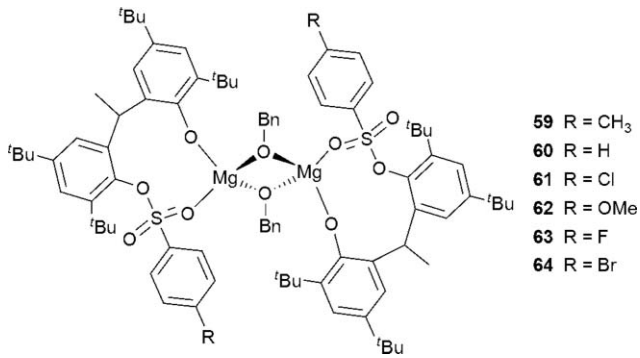
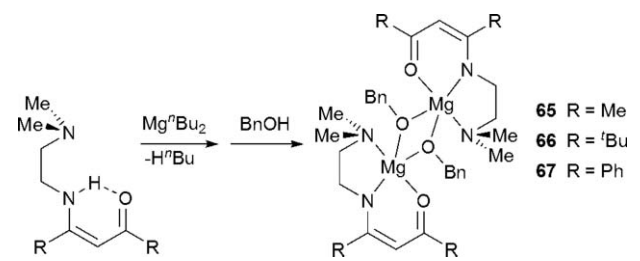


Fig. 10 Dimeric magnesium alkoxide complexes of a mononionic bis(phenolate) ligand.

While few phenolate-supported magnesium complexes have been reported as catalysts for the polymerization of lactide, magnesium complexes of the structurally analogous ketiminate ligand are known.[38] These species were constructed *via* a standard alkane elimination protocol followed by reaction of the resulting complexes with benzyl alcohol to afford the alkoxy bridged dimers (Scheme 12). Complexes **65**, **66** and **67** differ only in the degree of steric bulk in the ligand backbone. Their activity toward L-lactide polymerization was studied (Table 3, entries 30–32), and it was determined that complex **66** is by far the most active, generating complete conversion to PLA in two minutes at 0 °C. It should be noted, however, that the molecular weight distribution was relatively broad (PDI = 1.46). Complexes **65** and **67** are highly active at room temperature, completely consuming lactide monomer in under 10 min (PDI = 1.13 and 1.08, respectively). Variable-temperature ^{1}H NMR studies suggested that these complexes exist in solution as an equilibrium between dimeric and monomeric species; the dramatically higher activity of **66** is attributed to greater steric bulk, which enhances the tendency of this complex to dissociate to a monomer in solution. On the basis of these observations, it was proposed that the monomeric complexes possess substantially greater activities than their respective dimers.



Scheme 12 Synthesis of magnesium alkoxide complexes supported by a ketiminate ancillary ligand.

A single example of Schiff base supported calcium lactide polymerization catalysts has been described.[39] Reaction of the Schiff base ligand with calcium iodide in THF in the presence of two equivalents of $NaN(SiMe_3)_2$ yielded the solvated calcium amide complex **68** (Fig. 11). Melt polymerization experiments were conducted at 110 °C and even with a catalyst loading as low as 0.14%, 69% conversion was achieved within 30 min. (Table 3, entry 33) Furthermore, the polymer polydispersity approached unity (PDI = 1.04). While no significant stereochemical control was achieved with this calcium complex, it is notable for such low catalyst loading to display such excellent molecular weight control.

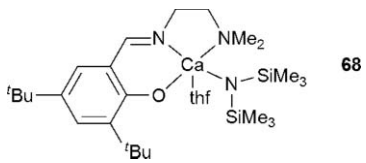


Fig. 11 Monomeric calcium amide complex of a simple Schiff base ligand.

The standard Schiff base framework has been incorporated into the ligand design of Wang and co-workers, such that a pendant pyrazole ring is incorporated into the system.[40] A zinc complex of this ligand bearing an ethyl initiating group has been isolated (**69**, Fig. 12), but the authors were unable to prepare an alkoxide analogue. Nonetheless, complex **69** demonstrated catalytic competence for lactide polymerization; at 80 °C in toluene, although a relatively high catalyst loading and long reaction times were required to achieve high conversion of *rac*-lactide to polymer (Table 3, entry 34). No stereochemical control was realized; however, the resulting polymer has an extremely narrow molecular weight distribution (PDI = 1.03). It is anticipated that the polymerization activity of **69** could be improved by installing a more suitable initiating group, and we look forward to future reports of improvements on this catalyst system.

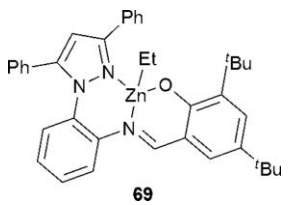
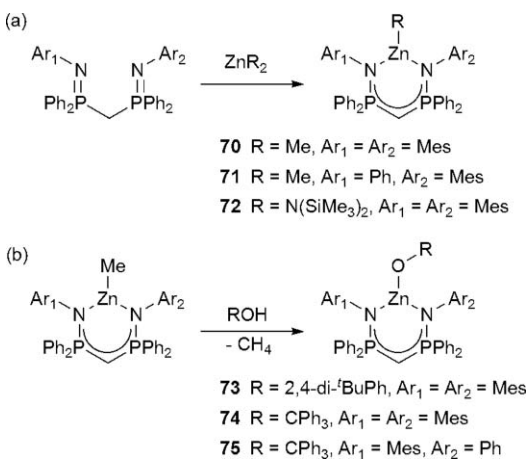


Fig. 12 Zinc complex of a Schiff base ligand with a pendant pyrazole arm.

2-4. Bis(phosphinimino)methanide ligand complexes

The bis(phosphinimino)methanide (BPM) scaffold, which is extremely electronically versatile and bears a significant structural resemblance to the BDI ligands (*vide supra*), has recently demonstrated promise for supporting a plethora of metal complexes. Upon deprotonation of the methylene backbone this ligand serves as a bidentate monoanionc ancillary. Initial attempts to prepare lactide polymerization catalysts from this ligand focused on the preparation of zinc alkoxides analogous to the most successful BDI species.[41] The authors targeted three-coordinate zinc complexes with C_2 (BPM-1) or C_s (BPM-2) symmetric ligands. The corresponding zinc alkyl compounds **70** and **71**, and the amido compound **72** were prepared by reaction of bis(alkyl) or bis(amido) zinc precursors with the appropriate neutral ligand (Scheme 13a). Zinc alkoxide derivatives were subsequently generated by reaction of **70** or **71** with a suitable alcohol (Scheme 13b). Unlike the BDI alkoxides, all of these species are monomeric in the solid state. This may be attributed to the enhanced steric bulk of the alkoxide initiating groups. Unfortunately, none of the BPM complexes were found to be catalytically active for lactide polymerization at room temperature; however, the alkoxide derivatives **73**, **74** and **75** exhibited varying degrees of activity at 60 °C (Table 4, entries 1–3). Not surprisingly, higher polymerization activities were observed for the less sterically encumbered **75**. Polydispersities of the resulting polymers were broad and somewhat erratic, suggesting a poorly controlled polymerization. Likewise, polymer molecular weights are much higher than the theoretical value calculated from the monomer to initiator ratio. It has been suggested by the authors that the large initiating groups may be effectively inhibiting monomer coordination, and that the carbanionic character of the ligand backbone may be modifying the behaviour of the system in unpredictable ways. This illustrates the need for further study to better understand the fundamental chemistry inherent to this type of catalyst.



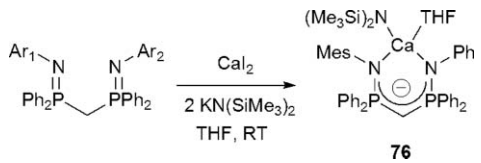
Scheme 13 Synthesis of zinc complexes supported by the BPM ligand.

Table 4 Polymerization of lactide by BPM supported catalysts

Entry	Catalyst	$[LA]_o$/mol L^{-1}	Loading (mol%)	t/h	Conv. (%)[a]
1[b]	**73**	0.29	1	4	>95
2[b]	**74**	0.29	1	5	>95
3[b]	**75**	0.29	1	2	>95
4[c]	**76**	—	0.5	<1 min	>99

[a] Determined by ^{1}H NMR Spectroscopy. [b] T = 60 °C, toluene solvent [c] T_{rxn} = room temperature, THF solvent.

Details regarding a calcium complex of the symmetric BPM ligand (**76**) were recounted seperately by Hill *et al.* (Scheme 14).[42] A single THF molecule is bound to the calcium centre and the complex is monomeric in the solid state. While only preliminary polymerization studies were undertaken, the complex is dramatically more reactive than the analogous zinc complexes, reportedly giving quantitative polymerization under the same conditions in less than a minute (Table 4, entry 4).



Scheme 14 Preparation of calcium complex **76**.

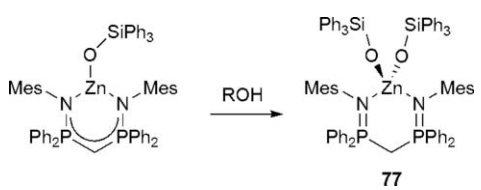
3. Neutral ligands and activated complexes

While the majority of lactide polymerization catalysts involve monoanionic ligands, several researchers have recently been exploring the use of neutral ligands for stabilization of divalent metals. We believe that exploration of neutral ligands has the potential to generate novel chemical reactivity which may differ from that achieved through the use of anionic ligands.

The following section will highlight examples of neutral ligands employed for stabilizing lactide polymerization catalysts with an analysis of some of the problems encountered thus far. This will be followed by a discussion of the ongoing work in our laboratory and the strategy we have made use of in an attempt to generate highly active cationic organozinc catalysts.

3-1. Neutral bis(phosphinimine)methane

It has been shown that alkoxy-zinc complexes featuring neutral BPM supports may be prepared from analogous species supported by anionic BPM ligands when the bulky triphenylsiloxide group is utilized.[41] The reaction of one equivalent of silanol with **70** yielded the expected three-coordinate zinc complex of the anionic BPM ligand. However, addition of a second equivalent resulted in ligand protonolysis, affording the corresponding dialkoxyzinc complex **77** (Scheme 15). Complex **77** was not catalytically active for the polymerization of lactide, even at 60 °C. This inactivity is likely due to excessive steric bulk of the triphenylsiloxide initiating group, which has been shown by Chisholm *et al.* to dramatically decrease activity.[17]



Scheme 15 Preparation of a zinc bis(alkoxide) bound to a neutral bis(phosphinimine) ligand (**77**).

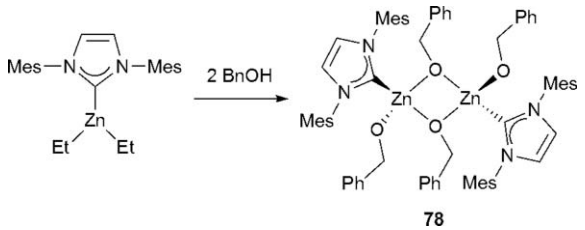
Table 5 Polymerization of *rac*-lactide by NHC complex **78** and the free parent carbene. ($T = 25$ °C, 0.77 mol% catalyst, [LA] = 1 M, CH_2Cl_2)

Catalyst	t/h	Conv. (%)	PDI	P_r
78	0.33	96	1.25	0.60
Carbene[a]	0.50	98	1.23	0.41

[a] In the presence of benzyl alcohol.

3-2. *N*-heterocyclic carbenes

While *N*-heterocyclic carbene (NHC) complexes of zinc have been known for a considerable time, their first described use as lactide polymerization catalysts appeared only 4 years ago.[43] Alkoxy bridged dimer **78** was synthesized *via* the straightforward reaction between a previously known diethylzinc complex,[44] and two equivalents of benzyl alcohol (Scheme 16). Complex **78** is an effective catalyst for the polymerization of *rac*-lactide, with an impressive rate only marginally less than the most active zinc complex which was previously reported by the same group (Table 5).[31] At 25 °C, 96% monomer consumption occurred after only 20 min, and the resultant polymer had a relatively narrow polydispersity of 1.25.

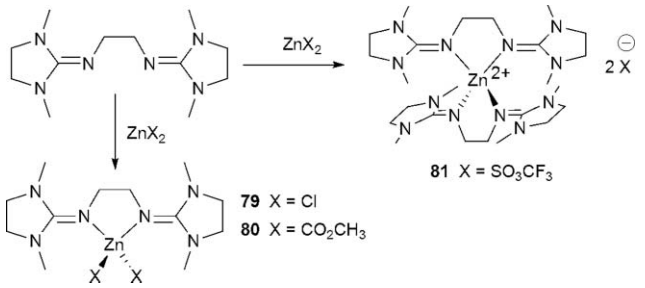


Scheme 16 Preparation of an NHC supported zinc alkoxide (**78**).

Free carbenes are known to be excellent organocatalysts for the ring-opening polymerization of lactide,[45] and though these ligands are generally considered to be non-labile, the possibility exists that ligand dissociation may occur, and that the free ligand may be responsible for the observed activity of **78**. This concern was addressed by the authors, but never fully disproven. Zinc complex **78** is only slightly more active than the free carbene (Table 5); however, notably different polymer microstructures were obtained from each, as the zinc complex generated heterotactic-enriched PLA ($P_r = 0.60$), and the free carbene generated isotactic enriched PLA ($P_r = 0.41$) (Table 5). This would suggest that at least a substantial portion of the catalytic activity of **78** is due to polymerization by the intended complex.

3-3. Bis(guanidine) complexes of zinc

While relatively few guanidine complexes of the group 2 and 12 metals are known, the use of neutral bidentate bis(guanidine) ligands to stabilize other transition metals has been well established.[46] An interesting family of bis(guanidine) ligands has been explored in detail by Herres-Pawlis and co-workers.[47] Specifically, several zinc complexes of the bis(guanidine)ethyl (BGE) ligand have been prepared and tested as catalysts for the bulk polymerization of lactide. The production of heteroleptic complexes **79** and **80** was achieved by reaction of BGE with zinc dichloride and zinc acetate, respectively, while reaction with zinc triflate selectively afforded homoleptic complex **81** (Scheme 17).[48]

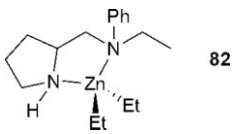


Scheme 17 Complexes prepared from the BGE ligand.

Though none of these complexes contained an alkoxide initiating group, all were moderately active in the neat polymerization of *rac*-lactide. At temperatures ranging from 135–165 °C, and with catalyst loadings of 0.1% and 0.2%, moderate yields of polymer (46% to 93%) with relatively broad polydispersities (PDI = 1.54–1.88) were achieved within a 24 h period (Table 6). While these results appear promising, the nature of the active catalyst and the mechanism of polymerization remains unclear. The possibility of dissociation of zinc from BDE, as for NHC complex **78** was not addressed.

3-4. Zinc complexes featuring other neutral ligands

A noteworthy account by Jeong *et al.* describes the use of the chiral (*S*)-*N*-ethyl-*N*-phenyl-2-pyrrolidinemethanamine (S-EPP) ligand (Fig. 13).[49] The pyrrolidine N–H has an exceptionally high pK_a value (~44 in DMSO),[50] which will not easily undergo protonolysis, thereby rendering S-EPP a neutral donor. Although only the zinc dichloride complex of S-EPP was isolated, polymerization of *rac*-lactide was investigated using the *in situ* generated diethylzinc species (**82**). Unfortunately, the desired stereochemical control was not imparted by the system. This may be due to ligand dissociation, which would necessarily render the catalyst achiral. Additional work is required to unambiguously identify the active catalyst.



82

Fig. 13 Proposed structure of a diethylzinc complex (**82**) of the neutral pyrrolidine ligand.

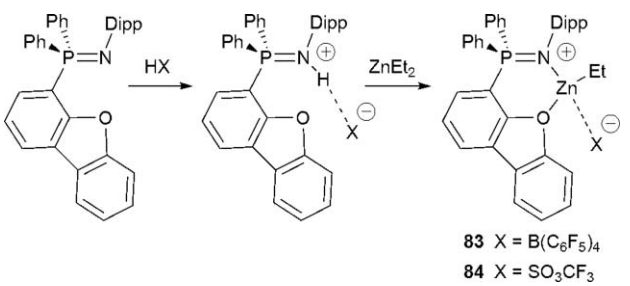
Table 6 Selected data for melt polymerization of *rac*-lactide by BGE complexes of zinc ($t = 24$ h)

Catalyst	Loading (mol%)	T_{rxn}/°C	Conv. (%)	PDI
79	0.2	135	82	1.74
79	0.1	150	70	1.55
79	0.2	165	61	1.62
80	0.2	135	63	1.63
80	0.1	150	86	1.77
80	0.2	165	46	1.54
81	0.2	135	82	1.74
81	0.1	150	93	1.88
81	0.2	165	51	1.58

3-5. Cationic/activated complexes of zinc

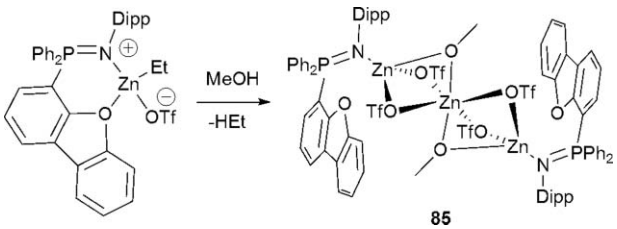
We have been inspired by the pioneering work of Bochmann's cationic alkyl and amido zinc species,[51] and have developed zinc complexes bearing weakly coordinating anions for utilization as activated lactide polymerization catalysts. The premise that cationic zinc centers may give improved polymerization activity arises from the observation that tris(pyrazolyl)borate complexes, which are formally zwitterionic in nature, have very high polymerization activities. Also, in numerous direct comparisons between magnesium and zinc initiators, the more electropositive magnesium centre tends to have substantially greater activity. We believe that the development of zinc catalysts with an even greater electropositive nature could give rise to highly active catalysts while maintaining the polymerization control of traditional species stabilized by anionic ligands. While this discussion represents a brief initial foray into the field, significant progress has already been made.[52,53]

Effort thus far has been directed toward development of novel neutral phosphinimine based ligands, and the subsequent preparation of various zinc complexes supported by these ligands.[52] Specifically, the included work has been devoted to complexes of a dibenzofuran backbone containing a modular phosphinimine subunit (DBF). It has been observed that a highly electron-deficient metal centre is required for the zinc to bind tightly to this neutral scaffold. Attempts to isolate neutral complexes of the ligand with ZnE_2 (E = alkyl, amido, alkoxy) were unsuccessful because the zinc precursors would not coordinate strongly to the ligand, and the components existed in equilibrium between associated and dissociated states.[53] Initial progress towards our ultimate goal of synthesizing activated zinc complexes bearing a suitable alkoxide initiating group have been realized by following a route similar to that utilized by Bochmann. Specifically, the nitrogen donor of DBF can be readily protonated, and the resultant protonated ligand can then be reacted directly with diethylzinc to afford the desired cationic or "activated" complex (depending on the coordinating strength of the counterion, Scheme 18). Complexes with $B(C_6F_5)_4^-$ (**83**) and $SO_3CF_3^-$ (**84**) counterions have been prepared in this manner.[52] Preliminary polymerization experiments have been conducted using a catalyst loading of 1% and an initial L-lactide concentration of 1M in 1 : 1 benzene–bromobenzene at 100 °C. Under these conditions, **83** produced 90% polymer in 6 h, while **84** resulted in only 85% monomer consumption after 9 h.[52] It is notable that **84** has reduced activity compared with $B(C_6F_5)_4^-$ analogue **83**, and we suggest that this difference arises as a direct result of competitive coordination of the more strongly coordinating $SO_3CF_3^-$ anion.



Scheme 18 Synthesis of activated zinc ethyl complexes by protonation of the DBF ligand followed by reaction with diethylzinc.

The synthesis of simple alkoxide derivatives by reaction of **83** or **84** with one equivalent of an alcohol has thus far been fraught with difficulty. The reaction of **84** with methanol in aromatic solvents yielded the activated trinuclear alkoxide **85**, which could be isolated from a mixture of other poorly defined species (Scheme 19).[53] Although the reactivity of **85** has not yet been fully explored, it has the potential to be highly active for the catalytic polymerization of lactide, given the success of dinuclear alkoxide **39**. The design and production of more simple zinc alkoxides bearing weakly coordinating anions is currently being pursued.[53]



Scheme 19 Synthesis of the trinuclear activated zinc alkoxide complex **89**.

4. Conclusions

The development of single-site homogeneous catalysts for the ring-opening polymerization of lactide has undergone tremendous growth in the past decade. Of particular importance has been the development of several classes of sterically encumbered monoanionic ligands. While the chemistry of such zinc complexes has generally been thoroughly explored, some progress has also been made on the development of analogous magnesium and calcium catalysts. Such complexes generally exhibit higher activities but offer poor control over the polymerization process. It has been well established that the nature of the initiating group plays a large role in activity and control, with simple alkoxides generally being most effective. In addition, it has been demonstrated that the steric bulk associated with the chelating ligand is a crucial factor in controlling polymer stereochemistry; several examples of catalyst systems, which generate exclusively heterotactic PLA through a chain-end control mechanism have been reported. We hope that future work will afford a chiral catalyst system capable of producing isotactic PLA from *rac*-lactide, a goal towards which the group 3 and 13 catalysts have seen marked success.[11,12]

While there are several examples of zinc complexes supported by neutral chelating ligands, it has been shown that these tend to be unstable unless the zinc precursor is sufficiently electron deficient. Likewise, complexities may arise when coordination of the lactide monomer proves to be competitive with the ancillary ligand. This ultimately raises questions about the nature of the active catalyst. A possible means to overcome this obstacle may be realized through the design and construction of sterically and electronically unsaturated cationic complexes.

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